Synthesis and Pharmacological Studies of Densely Functionalized Indole Derivatives

A Thesis Submitted to
University of Hyderabad
For the Degree of

DOCTOR OF PHILOSOPHY
In Chemistry

By

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September 2014

Dedicated

To

My Parents

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STATEMENT

I hereby declare that the matter embodied in the thesis is the result of investigation carried out by me in the Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Hyderabad, India, under the supervision of **Prof. Manojit Pal**.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted.

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Dr. Reddy's Institute of Life Sciences
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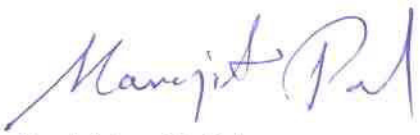
September 2014

DR. REDDY'S
INSTITUTE OF LIFE SCIENCES

CERTIFICATE

This is to certify that the thesis entitled ***"Synthesis and pharmacological studies of densely functionalized indole derivatives"*** being submitted by ***Mr. B. Prasad*** to University of Hyderabad for the award of Doctor of Philosophy in Chemistry has been carried out by him under my supervision and the same has not been submitted elsewhere for a degree. I am satisfied with that the thesis has reached to the standard fulfilling the requirements of the regulations relating to the nature of the degree.



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Whatever I am and whatever I intend to be in future is because of the good will and unstinted support that I have received from my family. I am very grateful to my Parents Govindamma (Mother), Ramappa (Father) for showing faith in me and giving me liberty to choose what I desired. I would like to thank Nirmala (Sister), Nagabhushana (Brother-in-law), K. Mallikarjuna (Cousin), E. Anjineyulu (Brother-in-laws) for their moral support and motivation, which drives me to give my best. I also thanks to my grandparents, my uncles, especially B. Venkataramana, E. Venkataramana, my aunts, all my cousins, brother-in-laws, and sister-in-laws for their continuous support and encouragement. Finally my special thanks and best wishes to my sweet niece Gahnavi, and nephew Govardhan for making memorable and joyful moments.

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Biography

Mr. B. Prasad was born in D. Chekkavari Palli, Anantapur Dist., Andhra Pradesh, India, on 26th March, 1986. He received his B.Sc. Degree in Maths, Physics and Chemistry from Sri Sai Degree College, Sri Krishnadevaraya University, Anantapur, Andhra Pradesh, India in 2006. In 2009 he received M.Sc. degree in Chemistry with specialization in Organic Chemistry from Sree Vidyanikethan Degree College, Sri Venkateswara University, Tirupati, Andhra Pradesh, India. Then, he qualified in CSIR-UGC NET and awarded a Junior Research Fellowship (JRF) from the CSIR, Government of India in June 2009. He also qualified in GATE 2009. In 2010 he started his doctoral research at Dr.Reddy's Institute of Life Sciences, University of Hyderabad under the guidance of Prof. Manojit Pal. During his doctoral programme at Dr.Reddy's Institute of Life Sciences, he has published number of papers in International Journals and presented two posters at national/international symposiums. He also delivered oral presentation at 9th Junior National Organic Symposium (J-NOST) in 2013. His areas of research interest include Synthetic Organic Chemistry, Metal catalysed Cascade/Multi Component Reactions and Medicinal Chemistry.

SYNOPSIS

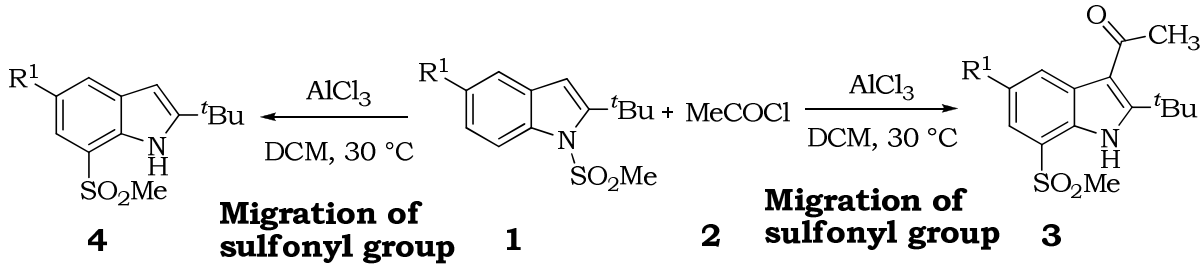
Investigations embodied in this thesis entitled "**Synthesis and Pharmacological Studies of Densely Functionalized Indole Derivatives**" have been presented in five chapters as follow:

Chapter 1

$AlCl_3$ mediated synthesis of 7-sulfonyl indoles as chorismate mutase inhibitors

(*Chem. Commun.*, **2012**, *48,* 10434-10436)

The substituted indole framework being integral part of many bioactive molecules is considered as one of the privileged structures in drug discovery. This chapter describes a novel methodology for the synthesis of 7-sulfonyl indoles *via* $AlCl_3$ mediated unexpected migration of sulfonyl group from *N*-sulfonyl indoles (Scheme 1). It represents a regioselective, straightforward and easy introduction of sulfonyl groups at C-7 of an indole ring. The molecular structure of one of the representative compound was confirmed unambiguously by single crystal X-ray diffraction study. Some of the compounds synthesized were tested for chorismate mutase inhibitory properties *in vitro* that was further supported by *in silico* studies.



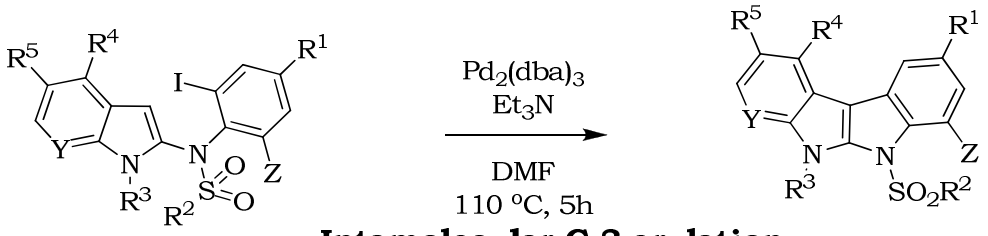
Scheme 1 Synthesis of 7-sulfonyl indoles *via* regioselective migration of sulfonyl group.

Chapter 2

Pd-catalyzed synthesis of indolo[2,3-*b*]indole based Sir 2 inhibitors

(*Chem. Commun.,* **2013**, *49,* 3970-3972)

The unique structural features and versatile biological activities of fused indoles have made them an attractive target for the development of novel pharmacological lead compounds. In this chapter we demonstrated design of novel inhibitors of Sir 2 from a known inhibitor using *in silico* studies. Thus, functionalized indolo[2,3-*b*]indoles were designed and synthesized first time as novel and unique class of heteroaromatics. In fact, the synthesis of indolo[2,3-*b*]indoles were carried out using an efficient, versatile Pd-catalysed intramolecular C-3 arylation reaction (Scheme 2). The molecular structure of one of the representative compound was confirmed unambiguously by single crystal X-ray diffraction study. Some of the synthesized compounds were then tested for sir 2 *in vitro*. Thus the unique class of indolo[2,3-*b*]indoles described here can be useful as potential inhibitors of sirtuins.



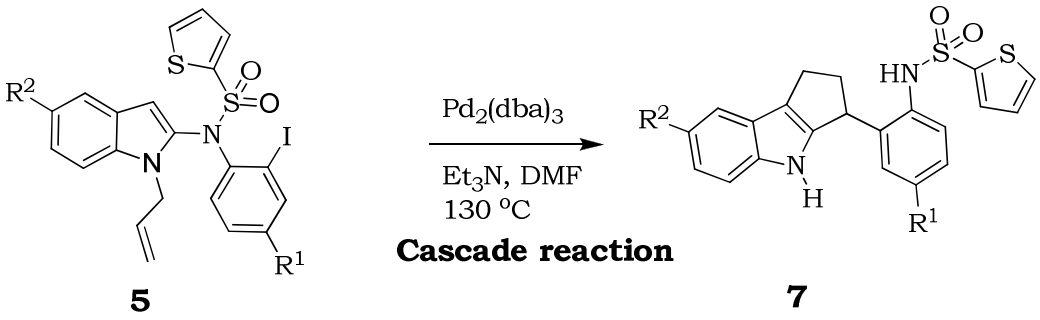
Scheme 2 Pd-catalyzed synthesis of novel indolo[2,3-*b*]indoles.

Chapter 3

Pd-catalyzed synthesis of cyclopenta[*b*]indole based PDE4 inhibitors

(*Chem. Commun.*, **2013**, *49*, 6716–6718)

This chapter deals with the continuation of work presented in chapter 2. We have demonstrated a Pd-mediated novel and diverse cascade reaction which involved intramolecular Heck coupling followed by the construction of a fused cyclopentane ring in a single pot. Thus, the present methodology provided a direct access to cyclopenta[*b*]indoles in a single pot (Scheme 3). The cascade reaction involved two C-N bonds cleavage whereas three new C-C bonds were formed in the same reaction. The molecular structure of one of the representative compound was confirmed unambiguously by single crystal X-ray diffraction study. Some of the compounds synthesized were tested for PDE4B inhibitory properties *in vitro* when several of them showed promising inhibition of PDE4B.

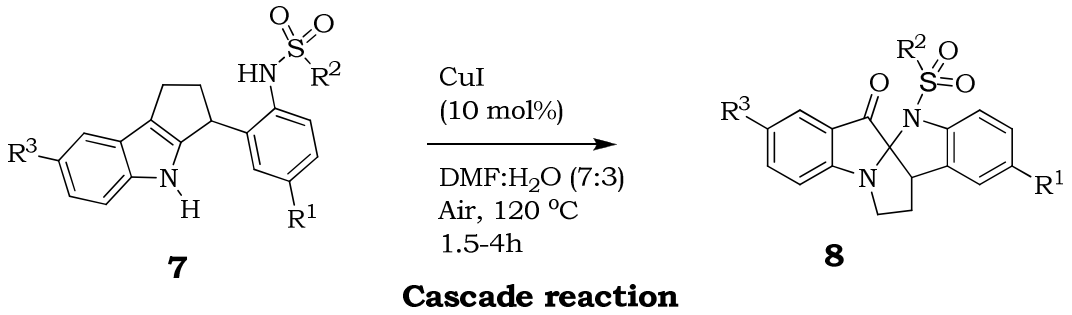


Scheme 3 Pd-catalyzed synthesis of novel cyclopenta[*b*]indoles.

Chapter 4

Cu- catalyzed synthesis of 2,2′-spiroindole derivatives

This chapter describes the details of further continuation of work presented in chapter 3. Thus a Cu-mediated unprecedented cascade reaction of cyclopentaindoles in the presence of air is described to furnish an array of 2,2'-spirobi[indolin]-3-one based novel and complex molecules (Scheme 4). This operationally simple, straightforward and inexpensive yet innovative method involved the rearrangement of several bonds in which Cu played a key role. The molecular structure of one of the representative compound was confirmed unambiguously by single crystal X-ray diffraction study. One-step and direct synthesis of a paullone like compound highlighted the potential of this method. Being not known in the literature the present research results could be a new and useful addition to the indole chemistry.



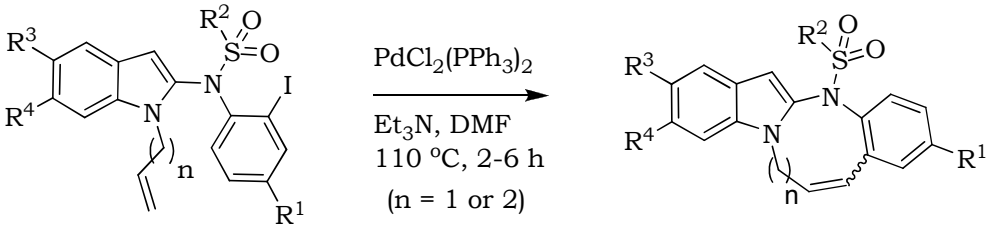
Scheme 4 Cu-catalyzed cascade reaction of **7** leading to novel 2,2'-spirobi[indolin]-3-one derivatives **8**.

Chapter 5

Pd- catalyzed synthesis of indole-1,2-fused 8 and 9 membered rings and their evaluation against apoptosis

(*Org. Biomol. Chem.*, **2014**, *12*, 2864-2868)

In this chapter we have described a strategy based on Pd-catalyzed intramolecular endo-trig ring closure of 1,2-disubstituted indoles leading to indole-1,2-fused 8 and 9 membered rings (Scheme 5). The methodology involved the use of unactivated olefin and proceeded with regioselective formation of an endocyclic doule bond the geometry of which was assigned as *cis* in case of compounds containing indole-1,2-fused 8 membered rings. A large number of fused indole derivatives were synthesized using this robust methodology and a representative compound showed promising apoptotic properties when tested in zebrafish embryos. As most of the cytotoxic anticancer agents are known to induce apoptosis the present class of indoles seemed to possess potential medicinal value. The strategy presented here therefore could be useful for the design and discovery of potential new drugs.



5 **Intramolecular Heck reaction** **9**

n = 1 (8 membered)
n = 2 (9 membered)

Scheme 5 Synthesis of Indole fused 8 or 9 membered rings.

Abbreviations

^{13}C NMR	:	carbon-13 nuclear magnetic resonance spectroscopy
^{1}H NMR	:	hydrogen-1 nuclear magnetic resonance spectroscopy
Ac_2O	:	acetic anhydride
AcOH	:	acetic acid
Ag_2CO_3	:	Silver(I) carbonate
$AlCl_3$	:	aluminium chloride
aq	:	aqueous
Ar	:	aryl
Arg	:	arginine
Asn	:	asparagine
Asp	:	aspartic acid
$AuBr_3$	:	Gold(III) bromide
Boc	:	tert-butoxycarbonyl
Br	:	bromo
bs	:	broad singlet
Bu_4NBr	:	tetra-*n*-butyl ammonium bromide
Bu_4NCl	:	tetra-*n*-butyl ammonium chloride
Bu_4NSO_4	:	tetra-*n*- butyl ammonium sulfate
$CaCl_2$	:	calcium chloride
cAMP	:	cyclic adenosine mono phosphate
CCDC	:	Cambridge Crystallographic Data Centre
$CDCl_3$	:	chloroform-*d*
$CHCl_3$	:	chloroform
CH_3CN/ACN/MeCN	:	acetonitrile
CH_3COCl	:	acetyl chloride
CH_3COOH	:	acetic acid
Cl	:	chloro
CM	:	chorismate mutase
CN	:	cyano

CO	:	carbon monoxide
COMe	:	acetyl
COPD	:	chronic obstructive pulmonary desease
COSY	:	correlation spectroscopy
$(C_pRhCl_2)_2$	:	bicyclopentadienyl rhodium chloride
Cs_2CO_3	:	cesium carbonate
CsOAc	:	caesium acetate
Cu	:	copper
CuCl	:	copper chloride
CuI	:	copper iodide
$Cu(OAc)_2$	:	copper acetate
$Cu(OAc)_2$. H_2O	:	copper acetate mono hydrate
$Cu(OTf)_2$	:	copper triflate
d	:	doublet
DBU	:	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	:	dichloromethane
DEPT	:	distortionless enhancement by polarization transfer
DIPEA	:	*N*, *N*'-diisopropylethylamine
DMA	:	*N,N*-dimethylacetamide
DME	:	dimethoxyethane
DMF	:	*N,N*-dimethylformamide
DMSO	:	dimethyl sulfoxide
DMSO-d_6	:	dimethyl sulfoxide-d_6
dppp	:	1,3-Bis(diphenylphosphino)propane
Et	:	ethyl
Et_3N	:	triethylamine
EtOH	:	ethanol
Gln	:	glycine
h	:	hour(s)
HCl	:	hydrochloric acid
His	:	histidine
HMBC	:	Heteronuclear multiple-bond correlation

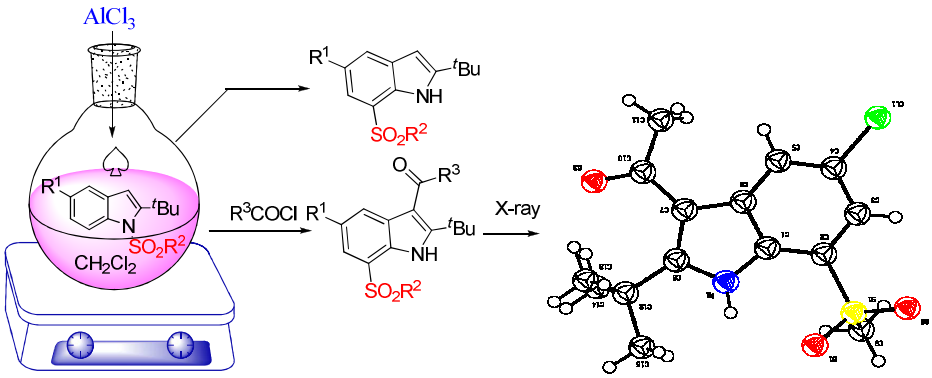
		spectroscopy
H_2O	:	water
HPLC	:	High performance liquid chromatography
HSQC	:	Hetero nuclear single quantum coherence spectroscopy
H_2SO_4	:	sulfuric acid
hv	:	Reaction in presence of light
Hz	:	Hertz
$InBr_3$	:	indium tribromide
I_2	:	iodine
IC_{50}	:	half maximal inhibitory concentration
i-PrOH	:	isopropanol
J	:	coupling constant in Hz
K_2CO_3	:	potassium carbonate
KNO_3	:	potassium nitrate
KOAc	:	potassium acetate
KOH	:	potassium acetate
$LiAlH_4$	:	lithium aluminiumhydride
LiCl	:	lithium chloride
m	:	multiplet
m-CPBA	:	*meta*-Chloroperoxybenzoic acid
Me	:	methyl
MeCOCl	:	acetyl chloride
MeOH	:	methanol
mg	:	milligram
mL	:	milliliter
mmol	:	mill mole
µM	:	Micro molar
MW	:	Micro wave
N_2	:	nitrogen
$NaAlH_4$	:	sodium aluminium hydride
NaCl	:	sodium chloride
Na_2CO_3	:	sodium carbonate

NaH	:	sodium hydride
$NaHCO_3$	:	sodium bicarbonate
NaDH	:	Nicotinamide adenine dinucleotide
NaOH	:	sodium hydroxide
NaOMe	:	sodium methoxide
Na_2SO_4	:	sodium sulphate
$NbCl_5$	:	niobium(V) chloride
NBS	:	*N*-bromo succinamide
NCE	:	new chemical entity
NH_4Cl	:	ammonium chloride
NOE	:	Nuclear Over hauser Effect
NO_2	:	nitrogen dioxide
OMe	:	methoxy
O_2	:	Oxygen
PCy_3	:	tricyclohexylphosphine
Pd	:	palladium
Pd/C	:	palladium on carbon
$PdCl_2(PPh_3)_2$	:	Bis(triphenylphosphine)palladium(II) dichloride
$Pd_2(dba)_3$	:	tris(dibenzylideneacetone)dipalladium(0)
$Pd(PPh_3)_4$	:	tetrakis(triphenylphosphine)palladium(0)
PDE	:	phosphodiesterase
$Pd(OAc)_2$	:	palladium acetate
PEG	:	polyethylene glycol
Ph	:	phenyl
$PhCh_3$	:	toluene
Phe	:	phenyl alanine
$PhI(TFA)_2$	:	phenyliodinebis(trifluoroacetate)
P(*o*-tol)$_3$	:	Tri(*o*-tolyl)phosphine
PPh_3	:	triphenyl phosphine
R_f	:	retention factor
RT (or) rt	:	room temperature
s	:	singlet

SiO_2	:	Silicon dioxide
$SnCl_4$	:	Tin(IV) chloride
t	:	triplet
^{t}Bu	:	tertiary butyl
TFA	:	Trifluoroacetic acid
Tyr	:	tyrosine
UV	:	ultra violet
X-Phos	:	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
$ZnBr_2$	:	Zinc bromide
δ	:	chemical shift in parts per million

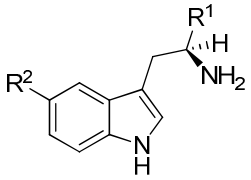
CHAPTER 1

$AlCl_3$ mediated synthesis of 7-sulfonyl indoles as chorismate mutase inhibitors

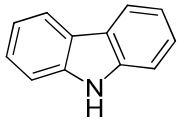


1.1 Introduction

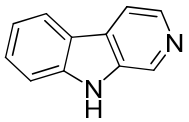
Indole derivatives have attracted enormous attention in the area of medicinal/pharmaceutical chemistry due to their natural occurrence and pharmacological activities[1] such as anti-tumor[2], anti-inflammatory[3], anti-convulsant[4], cardiovascular[5], and anti-bacterial.[6] Functionalised indoles have been referred to as "privileged structures" since they are capable of binding to many receptors with high affinity.[7] Indole derivatives also occur widely in many natural products such as those from plants[8], fungi[9] and marine organisms.[10] At present, there are approximately 1500 alkoloids has been described,[11] which includes simple and more complexy functionalised indole derivatives. For example, tryptophan (**F1.1**, Figure 1.1)**,** tryptamine (**F1.2**, Figure 1.1) and serotonin (**F1.3**, Figure 1.1) essential amino acids having simple indole skeleton. Whereas, cabazole (**F1.4**, Figure 1.1) and β-carbolines (**F1.5**, Figure 1.1) alkaloids possess complex fused indoles skeleton.



F1.1 $R^1 = CO_2H$, $R^2 = H$
F1.2 $R^1 = R^2 = H$
F1.3 $R^1 = H$, $R^2 = OH$



F1.4 Carbazole



F1.5 β-Carboline

Figure 1.1 Simple indole amino acids and complex indole alkaloids.

Indole derivatives that carry substituents, especially a hydroxy group, on the benzene ring are also of considerable interest. For example, serotonin[12] (**F1.6**, Figure 1.2) is a vasoconstrictor hormone and plays a key role in conducting impulses to the brain. Bufotenine (**F1.7**, Figure 1.2) is found in the skins of toads, toxic mushrooms, and West Indian snuff whereas psilocybin (**F1.8**, Figure 1.2) occurs in certain mushrooms. Both are known for their psychotropic effects.[13] Other complex bioactve indole alkoloids include strychinine (**F1.9**, Figure 1.2) which is used for eye disorders and optic nerve atrophy[8] and reserpine (**F1.10**, Figure 1.2) is a key drug in the treatment of hypertensive, nervous and mental disordes.[8] Interestingly, the sulfonyl substituted indoles such as sumatriptan[14] (**F1.11**, Figure 1.2) is used for the treatment of migraine and 3-arylmethylindole

(**F1.12**, Figure 1.2) is a COX-2 inhibitor.[15] Delavirdine (**F1.13,** Figure 1.2), an inhibitor of cytochrome P450 isozyme CYP3A4, is also an indole based drug possessing a sulfonyl substitutent has been developed for the treatment of HIV type 1.[16]

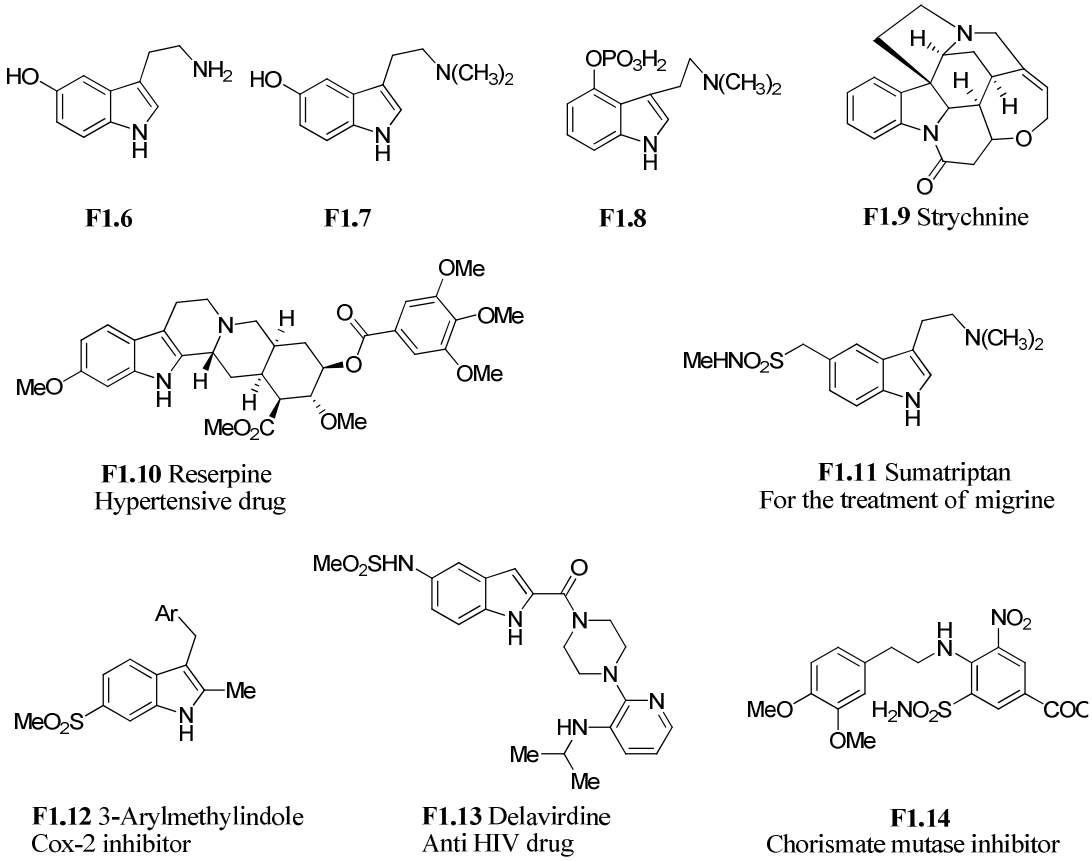
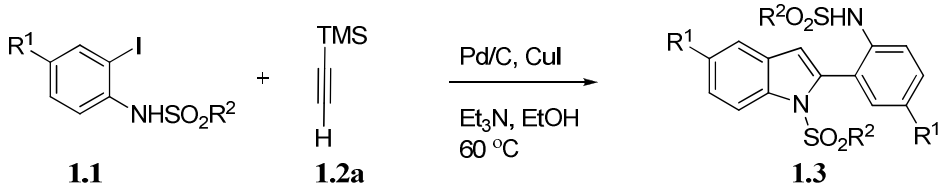


Figure 1.2 Representative examples for biologically active indole dervatives.

On other hand Tuberculosis (TB), though curable but deadly diseases that kills more than two million people a year worldwide. The growing incidences of multi-drug-resistance TB and its synergism with HIV is an emerging threat which requires immediate attention. Thus characterization of new enzyme targets and the identification of new drugs are highly desirable. Shikimate pathway for the biosynthesis of aromatic amino acids such as phenylalanine and tyrosine involve the Claisen rearrangement of chorismate to prephenate in the presence of chorismate mutase or CM (EC 5.4.99.5). Due to the absence of this pathway in animals but not in bacteria CM is considered as a promising target for the identification of new and potential antitubercular agents.[17] However, to our knowledge only few small molecules[18] have been reported to posses inhibitory

activity against CM including a sulfonamide[18a] derivative **F1.14**. In our endeavor, we have designed a novel scaffold i.e. 2(-*o*-($RSO_2NH)C_6H_4$)-indole[19] (**1.3)** from **F1.14**. The reaction of **1.1** with **1.2a** afforded target compound **1.3** *via* Pd/C-mediated Sila-Sonogashira based strategy[19] in a single-pot [Scheme 1.1]. Thus, as a part of our continuous interest on identification of novel indole based[20] inhibitors of CM we undertook the synthesis of compound **1.25**. Accordingly, we carried out Friedel-Crafts acylation reaction on *N*-alkyl/aryl/heteroarylsulfonyl indoles (**1.23**) in the presence of $AlCl_3$. Intrestingly we found regioselective migration of sulfonyl group from the nitrogen to the C-7 position of indole ring along with acylation at C-3 position.



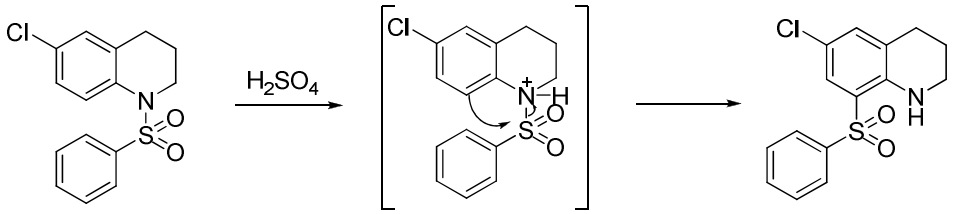
1.1 **1.2a** **1.3**

Scheme 1.1 Pd/C-mediated one-pot synthesis of 2-arylindoles.

1.2 Previous work

The precedensy in literature for synthesis of sulfonyl substituted compounds *via* migration of sulfonyl group discussed below.

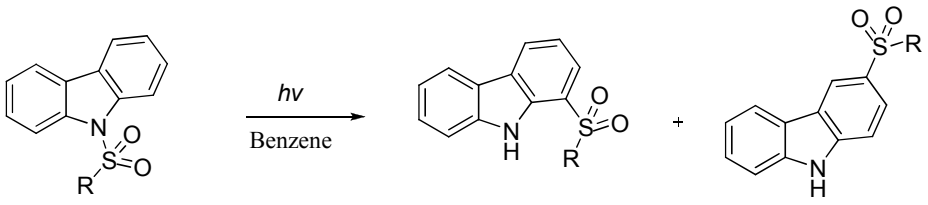
In 1970, Gennaro and co-workers reported acid mediated rearrangement of 6-chloro-1-(phenylsulfonyl)-1,2,3,4-tetrahydroquinoline (**1.4**) to 6-chloro-8-(phenylsulfonyl)-1,2,3,4-tetrahydroquinoline (**1.6**) via sulfitoamine (**1.5**) as an intermediate (Scheme 1.2).[21]



1.4 **1.5** **1.6**

Scheme 1.2 Acid mediated synthesis of 6-chloro-8-(phenylsulfonyl)-1,2,3,4-tetrahydroquinoline.

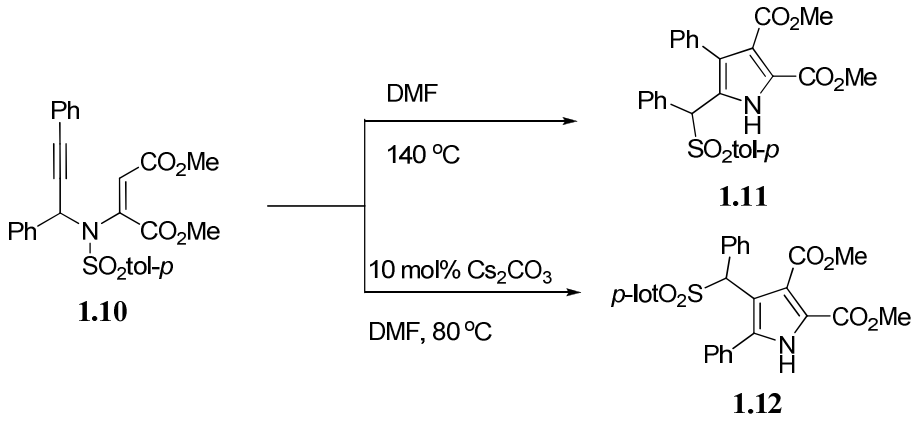
In 1989, Chakraborty and co-workers reported the Photo-Fries rearrangement of *N*-sulphonylcarbazoles (**1.7**) leading to l-sulphonylcarbazoles (**1.8**) and 3-sulphonylcarbazoles (**1.9**) in benzene (Scheme 1.3).[22] The migration of sulfonyl group was observed from nitrogen to C-1 or C-3 of the carbazole ring.



1.7 **1.8** **1.9**

Scheme 1.3 Photo-Fries rearrangement of *N*-sulphonylcarbazole.

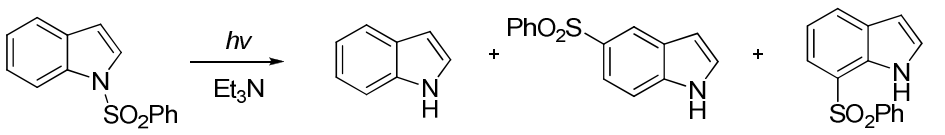
In 2012, Wan and co-workers reported an unexpected regio-selective sulfonyl group migration of *N*-sulfonyl-protected azaenyne (**1.10**) derivatives leading to the formation of functionalized pyrroles (Scheme 1.4). The migration of sulfonyl group was depending on reaction conditions.[23]



1.10 **1.11** **1.12**

Scheme 1.4 The new routes for synthesis of functionalized pyrroles.

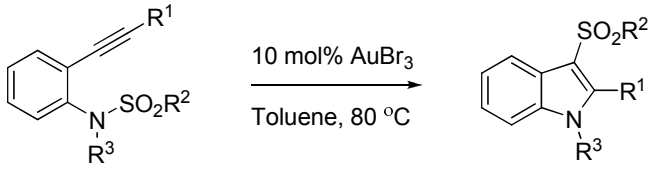
In 2007, Padwa and co-workers described the formation of both the *ortho* and *para* photo Fries rearrangement like products **1.15** (11%) and **1.16** (8%) as minor products during photo desulfonylation of *N*-sulfonylindoles (**1.13**) (Scheme 1.5).[24]



1.13 **1.14** (48%) **1.15** (11%) **1.16** (8%)

Scheme 1.5 Photo desulfonylation of indoles.

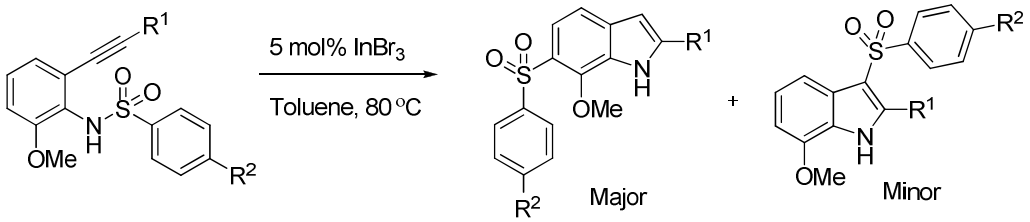
In 2007, Nakamura and co-workers reported that the reaction of the ortho-alkynyl-*N*-sulfonylaniline (**1.17**) affording the corresponding 3-sulfonyl indole (**1.18**) in good to excellent yields in the presence of a catalytic amount of $AuBr_3$ (Scheme 1.6).[25]



1.17 **1.18**

Scheme 1.6 $AuBr_3$-catalyzed synthesis of 3-sulfonylindoles.

In addition to that the cyclization of 2-alkynyl-6-methoxy-N-sulfonylanilines (**1.17a**) proceeded by an unprecedented 1,7-migration of the sulfonyl group to produce the 6-sulfonylindoles (**1.19**) as the major product in good to high yields in presence of $InBr_3$ (Scheme1.7).[25]

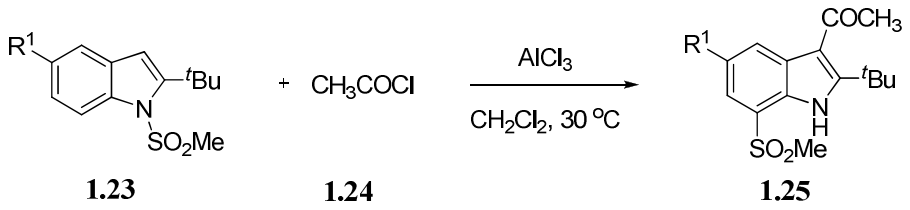


1.17a **1.19** **1.20**

Scheme 1.7 $InBr_3$-catalyzed synthesis of sulfonylindoles.

1.3 Present work

Most of these above mentioned reactions are involved the migration of sulfonyl group leading to sulfonyl substituted compounds. However, little has been explored for the synthesis of 3-sulfonylindoles particularly *via* migration of sulfonyl group. Thus, the development of new reactions for regioselective synthesis of sulfonylindoles is highly desirable. It is evident from the earlier reports that lewis acid catalysts can be used for the migration of sulfonyl group on indoles. Herein, we reported $AlCl_3$ mediated regioselective migration of sulfonyl group from nitrogen to C-7 of indole followed by the C-3 acylation starting from *N*-alkyl/aryl/heteroarylsulfonyl indoles in the presence of acetyl chloride in dry dichloromethane (Scheme 1.8).



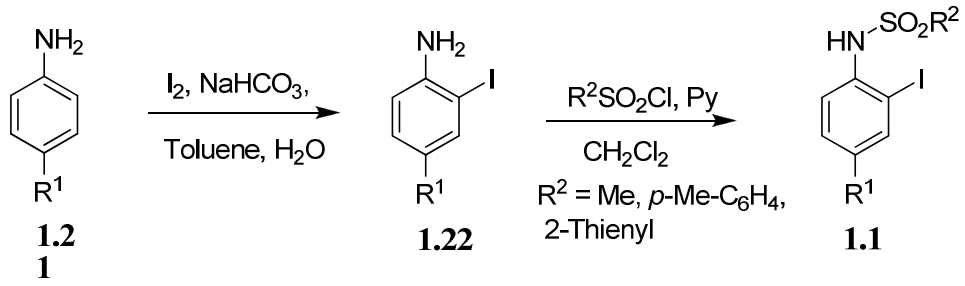
1.23 **1.24** **1.25**

Scheme 1.8 Synthesis of 3-acyl-7-sulfonyl indoles.

1.4 Results and discussion

1.4.1 Preparation of starting materials

The key starting material indole **1.23** required for our study was obtained from *N*-sulphonated-iodo-anilide **1.1** as shown in Table1.1. The requisite *N*-sulphonated-iodo-anilide was prepared *via* the conversion of anilines (**1.21**) to the corresponding iodo derivatives[26] **1.22** in the presence of elemental iodine and sodium bicarbonate in toluene-water (1:3). In the next step, the amine group of **1.22** was functionalized with mesyl or tosyl or 2-thiophenesulfonyl group by treatment of **1.22** with mesyl/tosyl/2-thiophene-sulfonyl chloride in CH_2Cl_2 using pyridine as a base to afford **1.1** (Scheme 1.9).[27]

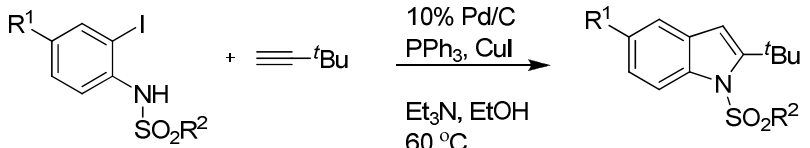


1.2 1 **1.22** **1.1**

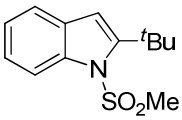
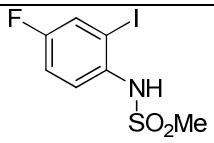
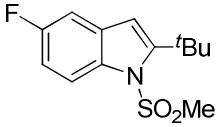
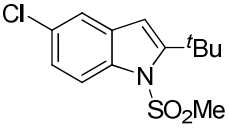
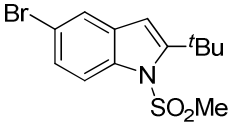
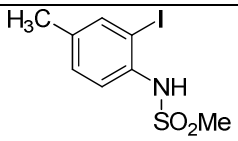
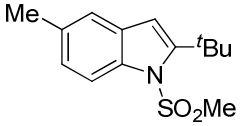
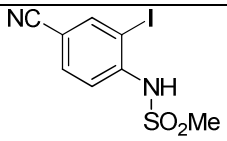
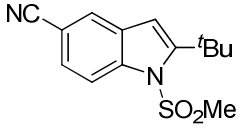
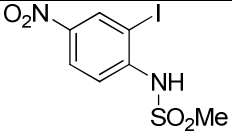
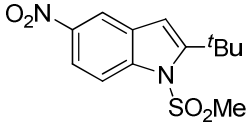
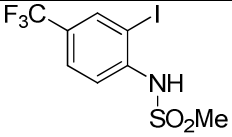
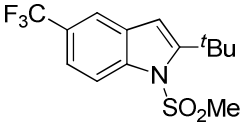
Scheme 1.9 Synthesis of *N*-sulfonylated *o*-iodoanilides.

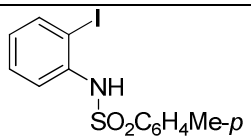
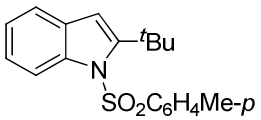
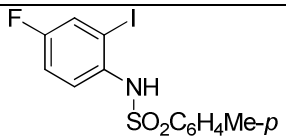
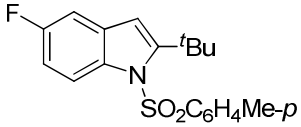
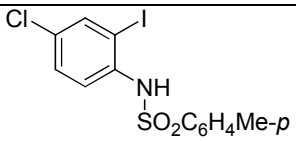
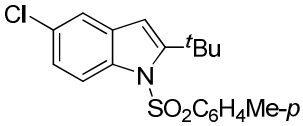
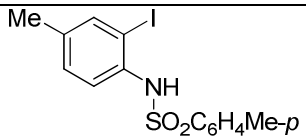
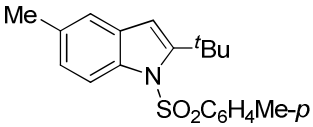
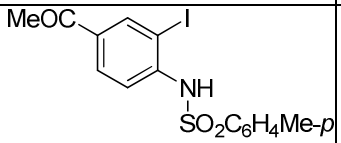
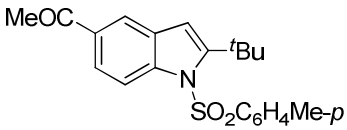
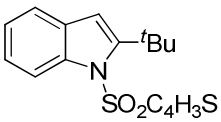
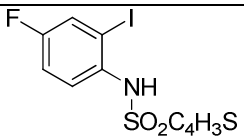
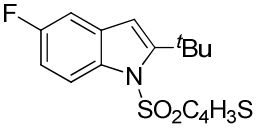
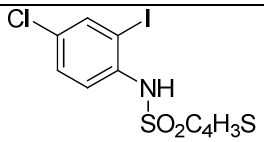
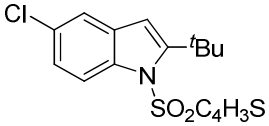
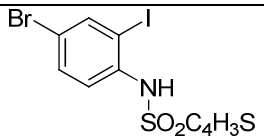
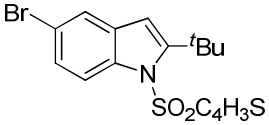
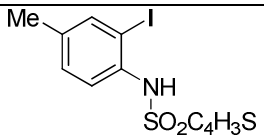
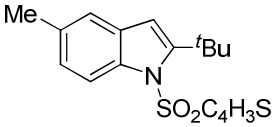
The synthesis of indole **1.23** was carried out using a palladium catalyzed coupling cyclization reaction. Due to our long term interest in the Pd/C-mediated alkynylation reactions,[28] we performed coupling cyclization reaction between *t*-butylalkyne **1.2b** with iodo anilides **1.1** in the presence of Pd/C, CuI and a base in ethanol at 60 °C to afford a variety of indoles **1.23a-r** in high yields (Table 1.1).

Table 1.1 synthesis of *N*-sulfonylindoles.



1.1 **1.2b** **1.23**

Entry	*o*-Iodo anilide (**1.1**)	*N*-sulphonyl indoles (**1.23**)	Time[b]/h	Yield[c] (%)
1	 **1.1a**	 **1.23a**	3.5	92
2	 **1.1b**	 **1.23b**	4.0	85
3	 **1.1c**	 **1.23c**	3.5	90
4	 **1.1d**	 **1.23d**	4.0	96
5	 **1.1e**	 **1.23e**	4.5	82
6	 **1.1f**	 **1.23f**	5.0	80
7	 **1.1g**	 **1.23g**	5.0	91
8	 **1.1h**	 **1.23h**	4.5	83

9	 **1.1i**	 **1.23i**	4.0	94
10	 **1.1j**	 **1.23j**	4.5	88
11	 **1.1k**	 **1.23k**	4.0	85
12	 **1.1l**	 **1.23l**	4.5	81
13	 **1.1m**	 **1.23m**	5.0	85
14	 **1.1n**	 **1.23n**	4.5	88
15	 **1.1o**	 **1.23o**	5.0	84
16	 **1.1p**	 **1.23p**	5.0	85
17	 **1.1q**	 **1.23q**	5.0	90
18	 **1.1r**	 **1.23r**	4.5	80

[a]All the reactions were carried out using *o*-iodoanilide **1.1** (0.31 mmol), alkyne **1.2b** (0.68 mmol), 10% Pd/C (0.03 mmol), PPh_3 (0.12 mmol), CuI (0.06 mmol) and Et_3N (0.62 mmol) in EtOH (5.0 mL), at 60 °C.

[b]After adding alkyne **1.2b**.

[c]Isolated yield.

All the indole derivatives **1.23** synthesized were characterized by spectral (NMR, IR and MS) data. This was further supported by the molecular structures of representative compounds **1.23b** (Figure 1.3) and **1.23c** (Figure 1.4) being confirmed unambiguously by single crystal X-ray diffraction study.

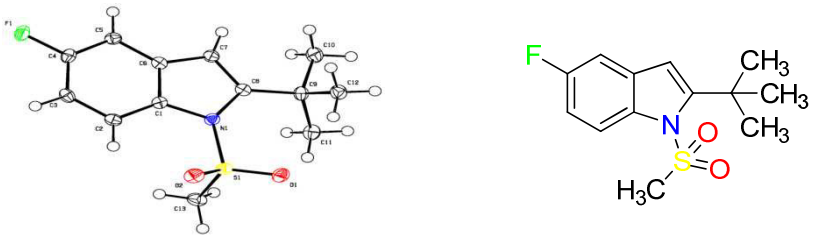


Figure 1.3 ORTEP representation of the **1.23b** (Thermal ellipsoids are drawn at 50% probability level).

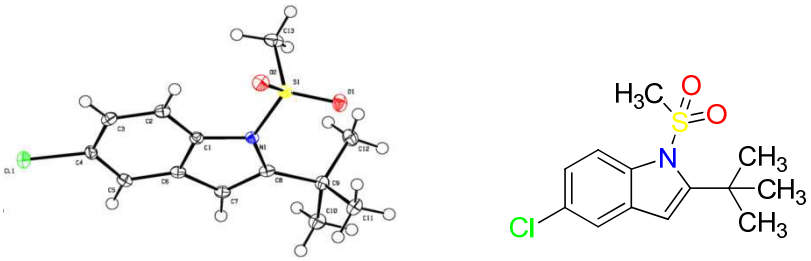


Figure 1.4 ORTEP representation of the **1.23c** (Thermal ellipsoids are drawn at 50% probability level).

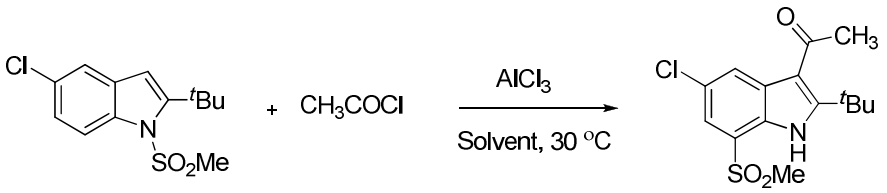
Having prepared indoles, we then performed further functionalisation of indole **1.23** using Friedal-Crafts acylation reaction with Acetyl chloride (**1.24a**) in the presence of $AlCl_3$. Interestingly, we found the formation 3-acetyl-7-sulfonyl indole (**1.25**) where unusual migration of sulfonyl group along with acetylation occurred leading to functionalized novel sulfonylindoles.

1.4.2 Reaction optimisation

The unusual migration of sulfonyl group prompted us to examine acylation reaction of compound **1.23c** with acetyl chloride **1.24a** in presence of various amounts (mmol) of $AlCl_3$ in a range of solvents (Table 1.2) to afford good yield of

compound **1.25c**. Initially, **1.23c** was treated with 1.0 and 1.5 equiv of $AlCl_3$ and **1.24a** respectively in dry CH_2Cl_2 for 6 h when **1.25c** was isolated in low yield (entry 1, Table 1.2). Systematic increase in equivalent of both $AlCl_3$ and **1.24a** increased the yield of **1.25c** (entries 2-4, Table 1.2). However, increase in reaction time did not improved the product yield (entry 5, Table 1.2). The use of other solvents such as chloroform and 1,2-dichloroethane was found to be less effective (entry 6 and 7, Table 1.2). Thus a combination of $AlCl_3$ (2 equiv) and **1.24a** (3 equiv) in dry CH_2Cl_2 was found to be optimum for the preparation of **1.25c** (entry 4, Table 1.2).

Table 1.2 Optimization of reaction conditions for synthesis of **1.25c**[a].



1.23c **1.24a** **1.25c**

Entry	No. of equiv. of $AlCl_3$	No. of equiv. of **1.24a**	Solvent	Time[b]/h	Yield[c](%)
1	1.0	1.5	CH_2Cl_2	6	28[d]
2	1.5	2.0	CH_2Cl_2	6	41[d]
3	1.5	3.0	CH_2Cl_2	6	45[d]
4	2.0	3.0	CH_2Cl_2	6	70
5	2.0	3.0	CH_2Cl_2	8	68
6	2.0	3.0	$CHCl_3$	6	44[d]
7	2.0	3.0	$ClCH_2CH_2Cl$	6	32[d]

[a]All the reactions were carried out using compound **1.23c** (0.5 mmol), $AlCl_3$, acetyl chloride **1.24a** in solvent (5.0 mL) at 30 °C.

[b]After adding **1.24a**.

[c]Isolated yield.

[d]**1.23c** was recovered.

1.4.3 Scope of the reaction

To examine the generality and scope of the present method the treatment of indoles was further assessed by reacting them with acetyl and propionyl chloride

under optimized conditions (Table 1.3). It is evident that indoles **1.23** containing *N*-alkyl (entries 1-8, Table 1.3), aryl (entries 9-12, Table 1.3) and heteroaryl (entries 13-16, Table 1.3) sulfonyl group were well participated affording the desired compound **1.25**. Further, the sulfonyl group migration occured smoothly in the presence of halogens e.g. F, Cl, Br and an electron releasing group e.g. Me at C-5. All the 1-(2-*tert*-butyl-5-substituted-7-sulfonyl-1*H*-indol-3-yl)alkanone **1.25** synthesized were characterized by spectral (NMR, IR and MS) data and this was supported by the molecular structure of a representative compound **1.25c** being confirmed unambiguously by single crystal X-ray diffraction study (Figure 1.5).

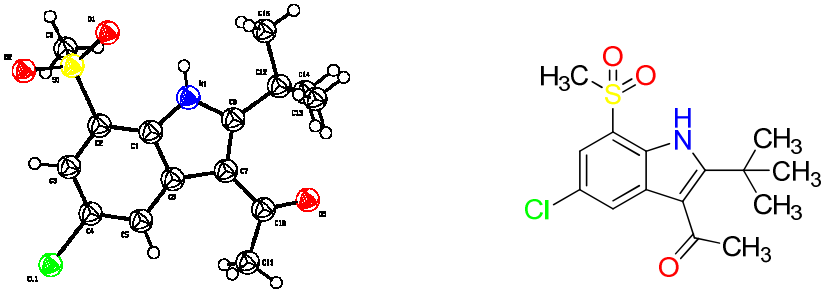
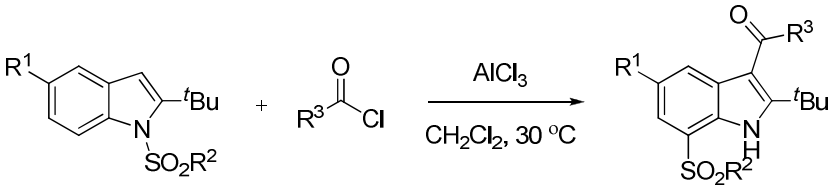
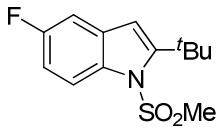
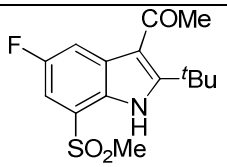
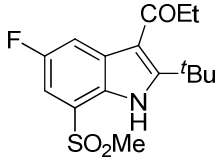


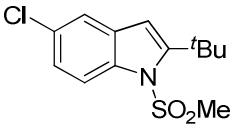
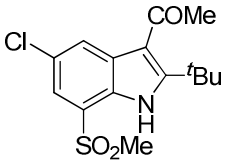
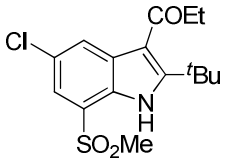
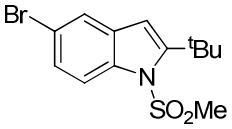
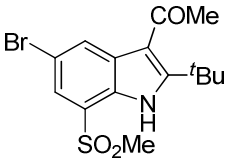
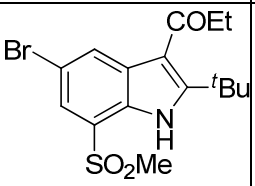
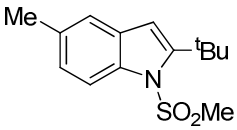
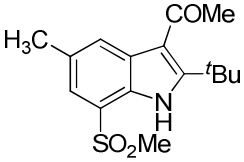
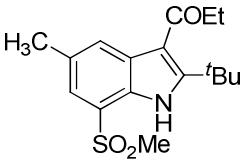
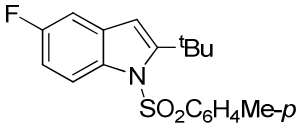
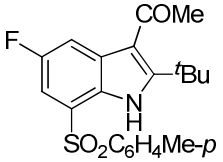
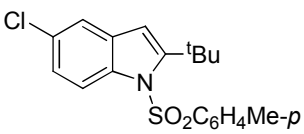
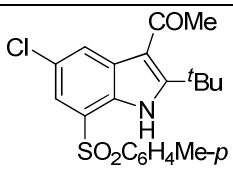
Figure 1.5 ORTEP representation of the compound **1.25c** (thermal ellipsoids are drawn at 50% probability level)

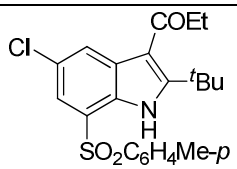
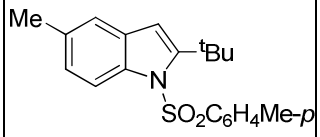
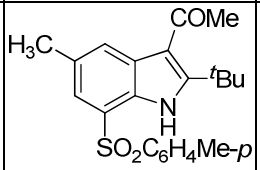
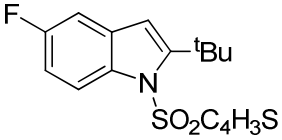
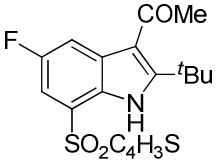
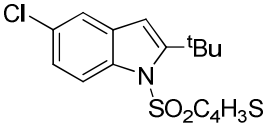
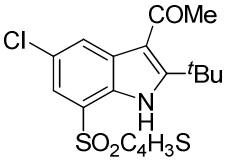
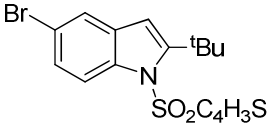
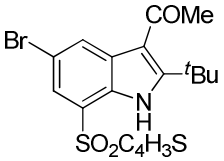
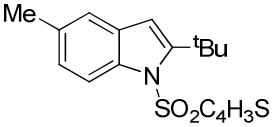
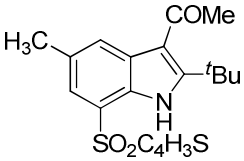
Table 1.3 $AlCl_3$ mediated synthesis of 3-acyl-7-sulfonyl indoles **1.25**.[a]



1.23 **1.24** **1.25**

Entry	indole (**1.23**)	**1.24**; R^3 =	Product (**1.25**)	Time[b] (h)	Yield[c] (%)
1	 **1.23b**	**1.24a**; Me	 **1.25a**	7.0	68
2	**1.23b**	**1.24b**; Et	 **1.25b**	6.5	65

3	 **1.23c**	**1.24a**	 **1.25c**	6.0	70
4	**1.23c**	**1.24b**	 **1.25d**	6.5	67
5	 **1.23d**	**1.24a**	 **1.25e**	6.5	66
6	**1.23d**	**1.24b**	 **1.25f**	7.5	65
7	 **1.23e**	**1.24a**	 **1.25g**	6.5	60
8	**1.23e**	**1.24b**	 **1.25h**	7.0	58
9	 **1.23j**	**1.24a**	 **1.25i**	7.5	56
10	 **1.23k**	**1.24a**	 **1.25j**	7.5	58

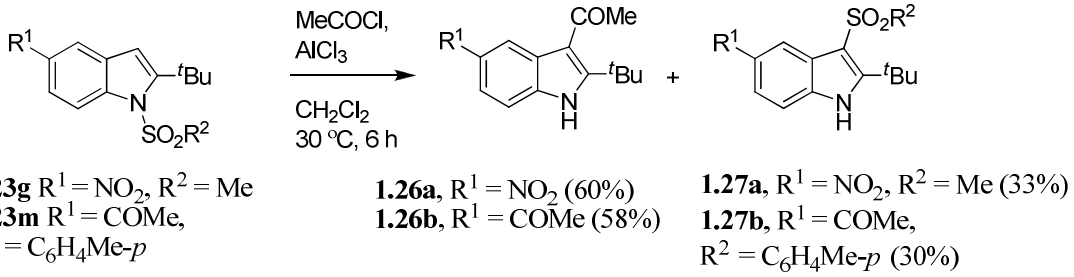
11	**1.23k**	**1.24b**	 **1.25k**	8.0	55
12	 **1.23l**	**1.24a**	 **1.25l**	8.0	52
13	 **1.23o**	**1.24a**	 **1.25m**	8.0	58
14	 **1.23p**	**1.24a**	 **1.25n**	8.0	55
15	 **1.23q**	**1.24a**	 **1.25o**	7.5	55
16	 **1.23r**	**1.24a**	 **1.25p**	8.0	54

[a]All the reactions were carried out using compound **1.23** (0.5 mmol), $AlCl_3$ (1.0 mmol), acid chloride **1.24** (1.5 mmol) in dry CH_2Cl_2 (5.0 mL) at 30 °C.

[b]After adding compound **1.23**.

[c]Isolated yield.

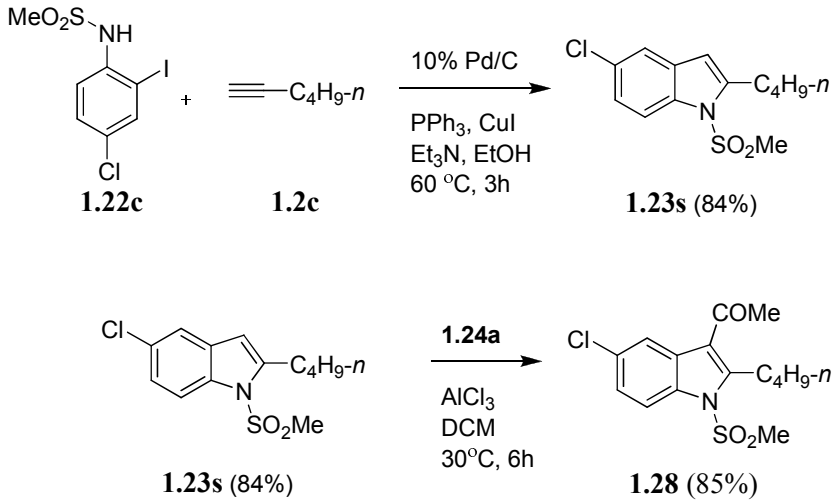
To examine the effect of an electron withdrawing or deactivating group in the present reaction conditions we have performed the reaction with nitro and acetyl substituted at C-5 of indoles. However, these reactions afforded the corresponding 3-acetyl indole **1.26** along with 3-sulfonyl indole **1.27** (Scheme 1.10) as a minor product due to deactivation of benzene part of indole system.



Scheme 1.10 Effect of electron withdrawing group at C-5 of indole ring.

1.4.4 Role of *tert*-butyl group at C-2 of indole

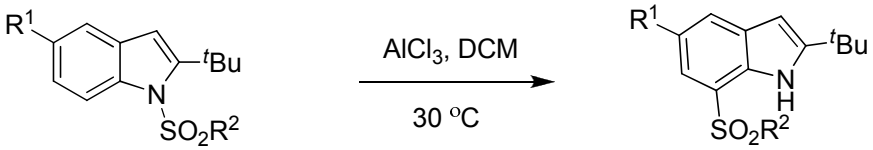
To know the role of bulky *tert*-butyl group at C-2 of indole in the present migration of *N*-sufonyl group we have synthesized 2-(*n*-butyl)-5-chloro-1-(methylsulfonyl)-1*H*-indole (**1.23s**) from *o*-iodoanilide using 1-hexyne **1.2c** by using the same procedure (Table 1.1). Then we carried out the acylation reaction using optimised conditions afforded the normal C-3 acylated product **1.28** (scheme 1.11). It clearly indicates that N-S bond cleavage seemed to be aided by the bulky *tert*-butyl group resulting in migration of the *N*-sufonyl group.



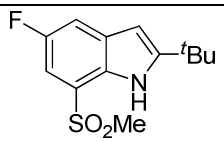
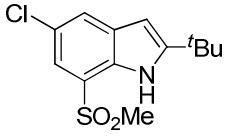
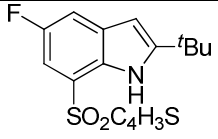
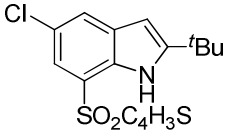
Scheme 1.11 Effect of *n*-butyl group at C-2 position of indole.

Additionally, the observation that a number of indoles e.g. **1.23b-c, 1.23k and 1.23o-r** underwent smooth N-S bond cleavage in the absence of acyl chloride leading to the C-7 sulfonyl substituted indoles **1.29** indicated the key role played by $AlCl_3$ in this transformation (Table 1.4).

Table 1.4 $AlCl_3$ mediated migration of *N*-sulfonyl group leading to 7-sulfonyl indoles[a].



1.23 **1.29**

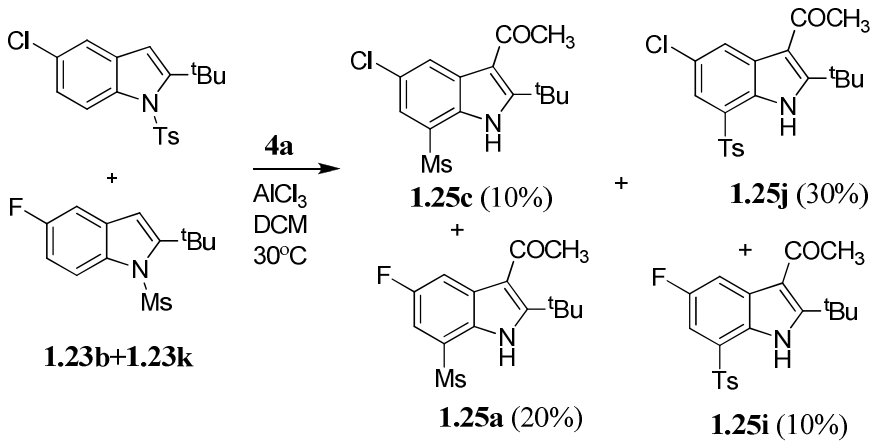
Entry	*N*-sulfonylindoles **1.23**	Product (**1.29**)	Time (h)	Yield[b] (%)
1	**1.23b**	 **1.29a**	4.5	68
2	**1.23c**	 **1.29b**	4.0	70
3	**1.23k**	 **1.29c**	5.0	65
4	**1.23o**	 **1.29d**	5.0	65
5	**1.23p**	 **1.29e**	4.5	68
6	**1.23q**	 **1.29f**	5.0	58
7	**1.23r**	 **1.29g**	4.5	60

[a]All the reactions were carried out using compound **1.23** (0.5 mmol) and $AlCl_3$ (1.0 mmol) in dry CH_2Cl_2 (5.0 mL) at 0 °C to room temperature.

[b]Isolated yield.

1.4.5 Cross over Experiment

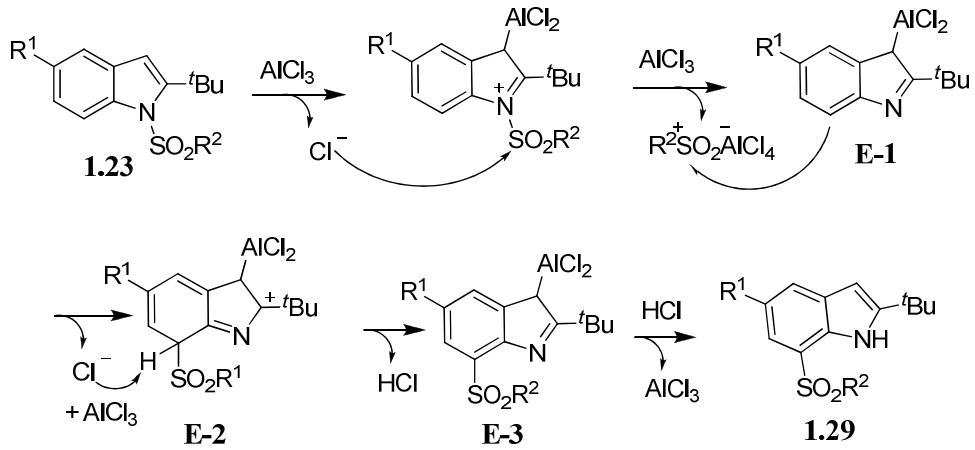
To understand the mode of migration of the sulfonyl group a cross over experiment was performed using a 1:1 mixture of **1.23b** and **1.23k** under the optimized condition. The isolation of cross over products *i.e.* **1.25c** and **1.25i** (Scheme 1.12) clearly suggested the involvement of a non-concerted process for the observed sulfonyl group migration.



Scheme 1.12 Cross over experiment between **1.23b** and **1.23k**.

1.4.6 Proposed mechanism

Based on the above observations we proposed the following mechanism for this reaction.



Scheme 1.13 Proposed mechanism for the $AlCl_3$ mediated migration of sulfonyl group.

The reaction seemed to proceed (Scheme 1.13) *via* $AlCl_3$-assisted activation of the indolyl double bond followed by N-S bond cleavage to give **E-1** which underwent

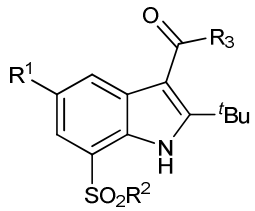
sufonylation at C-7 to give **E-3** *via* **E-2**. In addition to its steric bulk that perhaps aided the departure of *N*-sulfonyl group the *t*-Bu group facilitated the C-7 sulfonylation. The reaction followed a similar pathway in the presence of an acyl chloride when C-3 acylation facilitated the migration of *N*-sulfonyl group to C-7.

1.5 Pharmacology

1.5.1 *In vitro* data

Some of the compounds synthesized were tested for their inhibitory potential against CM *in vitro*.[29] The assay involved determination of activity of enzyme CM which catalyzes the conversion of chorismate to prephenate. A known inhibitor of CM *i.e.* 4-(3,5-dimethoxyphenethylamino)-3-nitro-5-sulfamoylbenzoic acid[18a] was used as a reference compound (IC_{50} < 10 µM).

Table 1.5 Inhibition of chorismate mutase by indole.



1.25

Entry	Indole **1.25** R^1; R^2; R^3 =	% of inhibition[a] @50µM
1	F, Me, Me (1.**25a**)	27.47
2	Cl, Me, Me (**1.25c**)	45.01
3	Br, Me, Me (**1.25e**)	26.91
4	Br, Me, Et (**1.25f**)	-18.04
5	F, C_6H_4Me-*p*, Me, (1.**25i**)	1.63
6	Cl, C_6H_4Me-*p*, Me, (1.**25j**)	-1.33
7	Me, C_6H_4Me-*p*, Me (1.**25l**)	13.43
8	F, 2-C_4H_3S, Me (1.**25m**)	18.09
9	Cl, 2-C_4H_3S, Me (1.**25n**)	29.65
10	Br, 2-C_4H_3S, Me (1.**25o**)	23.35
11	Me, 2-C_4H_3S, Me (1.**25p**)	22.18

[a]Average of three experiments.

Compounds **1.25a**, **1.25e, 1.25n, 1.25o** and **1.25p** showed 22-30% inhibition whereas **1.25c** showed 45% inhibition of CM when tested at 30 µM (Table 1.5).

1.5.2 *In silico* studies

The docking studies were performed to predict the interactions and binding mode of *in vitro* active molecules **1.25c** and **1.25n** with the binding site of chorismate mutase enzyme.

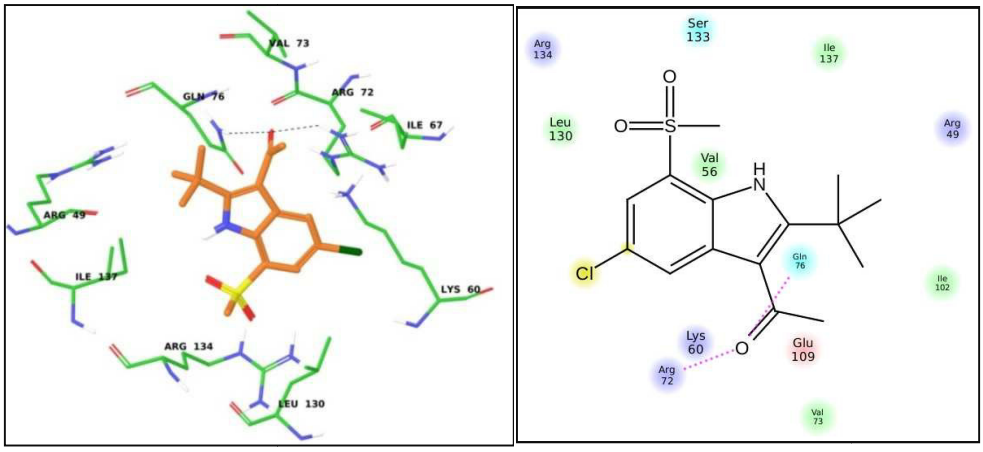


Figure 1.6 Binding pose and interaction of compound **1.25c** at the binding site of chorismate mutase enzyme.

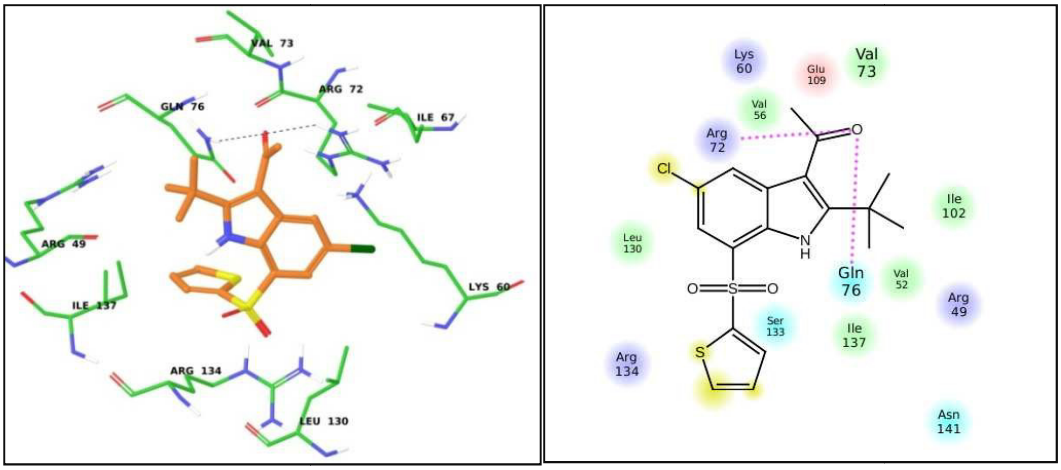


Figure 1.7 Binding pose and interaction of compound **1.25n** at the binding site of chorismate mutase enzyme.

In both molecules **1.25c** and **1.25n** carbonyl-group interacted well with the binding site residues of protein. The carbonyl oxygen of molecules made perfect hydrogen bond bridge with Glutamine-76 and Arginine-72 (Figure 1.6), but in case of **1.25n**, the thiophene ring was aligned towards the highly charged surface (Figure 1.7) of the binding pocket (Asp-138, Arg-

134), which requires a complementary features in ligand (H-Bond donor/acceptor). The lack of these complementary features in case of **1.25n** might be the reason for its relatively inferior *in vitro* activity compared to **1.25c**. Figure 1.8 represents the hydrophobic and hydrophilic mapping of molecules and reflecting their chemical nature. Overall, since tuberculosis is a leading cause of death worldwide hence the present class of compounds is of further interest.

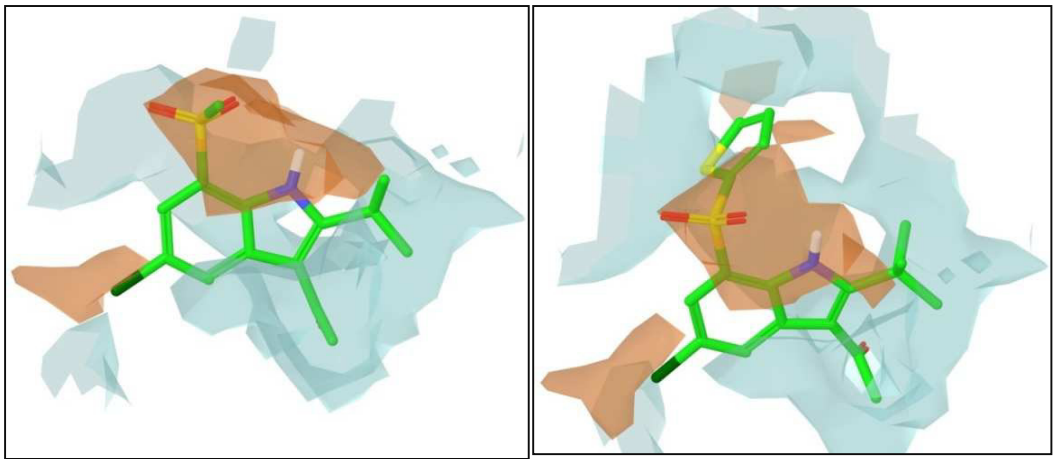


Figure 1.8 Hydrophobic/hydrophilic (Orange: hydrophilic region, Turquoise: Hydrophobic region) mapping of **1.25c** and **1.25n.**

1.6 Conclusions

In conclusion, we have demonstrated a novel methodology for synthesis of 7-sulfonyl indoles. It has been developed *via* $AlCl_3$ mediated unexpected sulfonyl group migration of *N*-sulfonyl indoles followed by acylation leading to new 7-sulfonyl indoles for the first time as potential inhibitors of CM. This represents a regioselective, straightforward and easy introduction of sulfonyl groups at C-7 of an indole ring. A representative compound **1.25c** the molecular structure of which was confirmed unambiguously by single crystal X-ray diffraction study. Compound **1.25c** showed moderate inhibition towards chorismate mutase *in vitro* and interacted well with the binding site residues of protein in *in silico* studies.

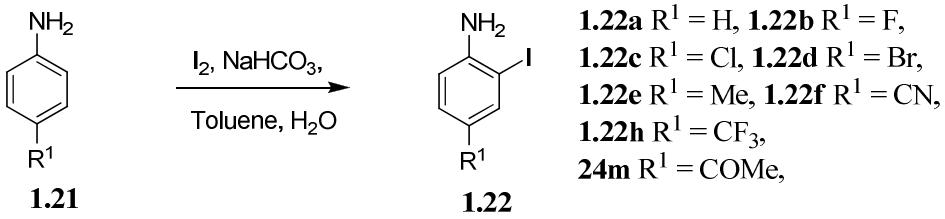
1.7 Experimental Section

1.7.1 Chemistry

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with

ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were recodred in $CDCl_3$ solution by using 400 MHz spectrometer. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT- IR spectrometer. MS spectra were obtained on a Agilent 6430 series Triple Quard LC-MS/MS spectrometer. Melting points (mp) were by using Buchi B-540 melting point appratus. Chromatographic purity by HPLC (Agilent 1200 series Chem Station software) was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention times.

1.7.1.1 General procedure for the preparation of 2-iodo-4-sustitutedaniline 1.22[27]

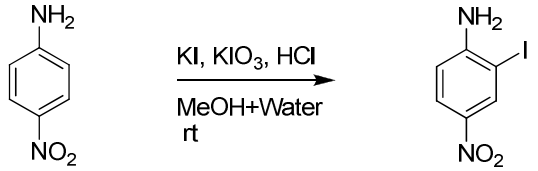


1.21 **1.22**

1.22a R^1 = H, **1.22b** R^1 = F,
1.22c R^1 = Cl, **1.22d** R^1 = Br,
1.22e R^1 = Me, **1.22f** R^1 = CN,
1.22h R^1 = CF_3,
24m R^1 = COMe,

A mixture of 4-substitutedaniline **1.21** (1.0 mmol), iodine (1.0 mmol) and sodium bicarbonate (1.5 mmol) in toluene and H_2O (10 mL, 3:7) was stirred at room temperature for 3h. After completion of reaction, the reaction mixture diluted with ethyl acetate (30 mL), washed with sodium thiosulphate solution (2 x 20 mL), followed by brine solution (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate – hexane to give desired compound **1.22**.

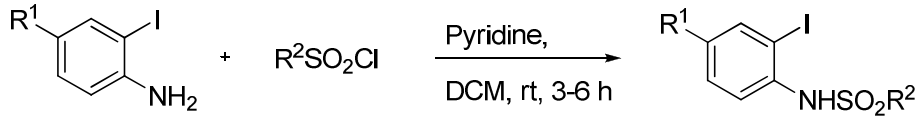
1.7.1.1.1 Typical procedure for the preparation of 2-iodo-4-nitroaniline 1.22g



1.21g **1.22g**

A solution of anisole **1.21g** (9.26 mmol), potassium iodide (6.22 mmol) and potassium iodate (3.08 mmol) was prepared in methanol (5 mL) and water (30 mL). This mixture was treated at room temperature with dilute hydrochloric acid (9.5 mmol) over 40 to 45 minutes and stirred for an additional 2-3 h, diluted with water (50 mL) and extracted with dichloromethane (25 diluted with water (50 mL) and extracted with dichloromethane (25 to give a thick oil (90%). Further purification was carried out by crystallization from cold hexane to afford a white crystalline product. m.p 52-54 °C (Lit[30] 53-54 °C), which showed satisfactory analytical and sectroscopic properties.

1.7.1.2 General procedure for preparation of 4-substituted *N*-(2-iodophenyl)sulfonamide (1.1)



R^1 = H, F, Cl, Br, Me, CN, CF_3

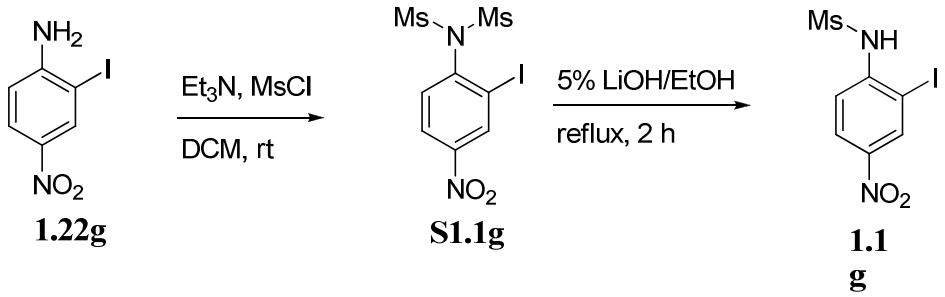
1.22 **1.1**

Sufonyl chloride (1.2 mmol) was slowly added to compound **1.22** (1 mmol) and pyridine (1.5 mL) in DCM (10 mL) at 0 °C under nitrogen atmosphere. Then, the reaction mixture stirred at rt for 4 h. After completion of reaction monitored by TLC, the reaction mixture was diluted with ethyl acetate (30 mL), washed with 2N HCl solution (25 mL) followed by brine solution (25 mL) and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-hexane to give the desired product [27] **1.1**.

1.7.1.2.1 Typical procedure for preparation of compound 1.1g

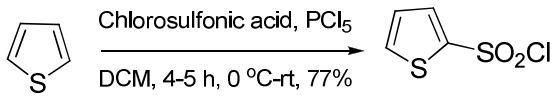
Step 1: To a solution containing 2-iodo-4-nitroaniline (95 mmol) and triethylamine (312 mmol) in CH_2Cl_2 (250 mL), a solution containing methanesulphonyl chloride (312 mmol) was added drop wise. The reaction mixture was left under stirring at room temperature for 18 hours, then NH_4Cl (saturated solution) was added (250 ml).

The biphasic solution was transferred into a separating funnel, the organic phase was separated, dried over Na_2SO_4 and the solvent was removed by evaporation under reduced pressure. The residue was suspended in EtOH (200 ml) and heated under stirring until a yellow solid precipitated (**S1.1g**).



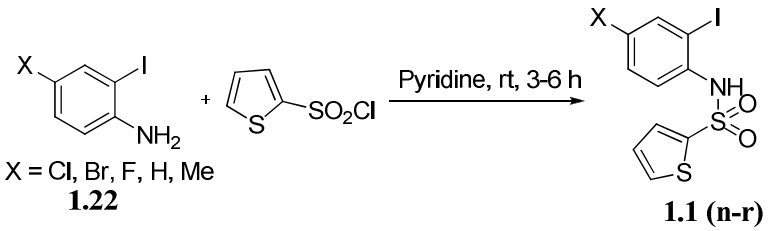
Step 2: To a mixture containing N-(2-iodo-4-nitrophenyl)-N-(methylsulfonyl) methane- sulfonamide (75 mmol) in EtOH (230 ml), water (115 ml) and LiOH (375 mmol) were added. The reaction mixture was refluxed for 2 hours and then cooled to room temperature, the solvent evaporated under reduced pressure. NH_4Cl (saturated solution, 250 ml) was added and the mixture was stirred until a yellow solid precipitated. The crude product was filtered and dried under vacuum to give N-(2-iodo-4-nitrophenyl)methanesulfonamide (24 g) which was used in the following reaction without any further purification.[31]

1.7.1.3 Typical procedure for preparation of thiophene-2-sulfonyl chloride



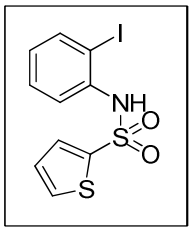
Chlorosulfonic acid (4.7 mL, 71.4 mmol) was slowly added to thiophene (2.8 mL, 35.7 mmol) in dry DCM (25 mL) at 0 °C under nitrogen atmosphere. Then, phosphorus pentachloride (0.75 g, 3.57 mmol) was added slowly to the reaction mixture and stirred at room temperature for 4-5 hours. After completion of reaction, saturated $NaHCO_3$ solution (100 mL) was slowly added to reaction mixture. Then, the residue was diluted with water (100 mL) and extracted with DCM (150 mL). The organic layers were collected, combined, washed with brine solution (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the desired product **13** (5 mL, 77%) which was used further without any purification.

1.7.1.4 General procedure for preparation of 4-substituted *N*-(2-iodophenyl)thiophene-2-sulfonamide (1.23n-r):



Thiophene-2-sulfonyl chloride (1.2 mmol) was slowly added to compound **1.22** (1 mmol) in pyridine (5mL) at 0 °C under nitrogen atmosphere. Then, the reaction mixture stirred at rt for 3-6 h. After completion of reaction monitored by TLC, the reaction mixture was diluted with ethyl acetate (30 mL), washed with 2N HCl solution (25 mL) followed by brine solution (25 mL) and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-hexane to give the desired product **1.1**.

1.7.1.4.1 *N*-(2-iodophenyl)thiophene-2-sulfonamide (1.1n)

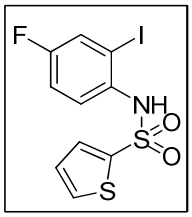


1.1n was prepared according to the above general procedure from **1.22a**.

White solid; yield: 89%; mp: 88-90 °C; R_f (5% EtOAc/*n*-Hexane) 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72-7.68 (m, 2H), 7.56 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.47 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.37-7.33 (m, 1H), 7.02-7.00 (m, 1H), 6.90-6.88 (m, 1H), 6.86 (bs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 139.1, 139.0, 137.1, 133.0, 132.9, 129.5, 127.4 (2C), 123.3, 92.9; HPLC: 96.6%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 5mM NH_4OAc in water mobile phase B: CH_3CN (gradient) T/B%: 0/40, 2/40, 9/95, 14/95, 16/40, 18/40; flow rate: 1.0 mL/min; UV 210 nm, retention time 6.99 min; IR (KBr) 3249, 3108, 1574, 1393 cm^{-1}; MS (ES mass): *m/z* 363.8 (M-1).

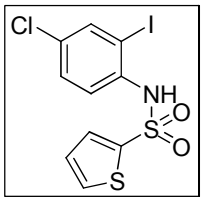
1.7.1.4.2 *N*-(4-fluoro-2-iodophenyl)thiophene-2-sulfonamide (1.1o)

1.1o was prepared according to the above general procedure from **1.22b**.



White floppy solid; yield: 87%; mp: 110-112 °C; R_f (10% EtOAc/*n*-Hexane) 0.72; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99-7.66 (m, 1H), 7.58 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.44-7.40 (m, 2H), 7.14-7.09 (m, 1H), 7.04-7.02 (m, 1H), 6.68 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.9 (C-F *J* = 250.3 Hz), 138.8, 133.6, 133.1 (C-F *J* = 4.7 Hz), 127.5 (2C), 125.7 (C-F *J* = 24.9 Hz), 125.4 (C-F *J* = 8.3 Hz), 116.6 (C-F *J* = 22.0 Hz), 93.4 (C-F *J* = 8.5 Hz); HPLC: 99.3%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 5mM NH_4OAc in water mobile phase B: CH_3CN (gradient) T/B%: 0/50, 2/50, 9/95, 14/95, 16/50, 18/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.09 min; IR (KBr) 3259, 3083, 1588, 1481 cm^{-1}; MS (ES mass): *m*/*z* 381.8 (M-1).

1.7.1.4.3 *N*-(4-chloro-2-iodophenyl)thiophene-2-sulfonamide (1.1p)

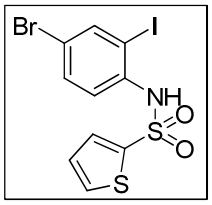


1.1p was prepared according to the above general procedure from **1.22c**.

White solid; yield: 85%; mp: 115-117 °C; R_f (10% EtOAc/*n*-Hexane) 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 3.4 Hz, 1H), 7.47 (d, *J* = 3.6 Hz, 1H), 7.34 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.03 (t, *J* = 4.2 Hz, 1H), 6.79 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.7, 138.2, 135.9, 133.2 (2C), 132.0, 129.6, 127.5, 124.0, 93.0; HPLC: 98.9%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 14/98, 16/50, 18/50; flow rate: 01.0 mL/min; UV 220 nm, retention time 6.91 min; IR (KBr) 3251, 3093, 1567, 1466 cm^{-1}; MS (ES mass): *m*/*z* 397.7 (M-1).

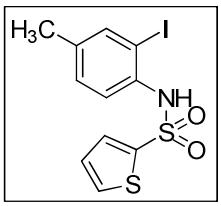
1.7.1.4.4 *N*-(4-bromo-2-iodophenyl)thiophene-2-sulfonamide (1.1q)

1.1q was prepared according to the above general procedure from **1.22d**.



White solid; yield: 71%; mp: 125-127 °C; R_f (10% EtOAc/*n*-Hexane) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, *J* = 2.0 Hz, 1H), 7.59-7.56 (m, 2H), 7.49-7.46 (m, 2H), 7.05-7.02 (m, 1H), 6.80 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.9, 138.7, 136.4, 133.2 (2C), 132.6, 127.6, 124.3, 119.5, 93.4; HPLC: 97.3%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 5mM NH_4OAc in water mobile phase B: CH_3CN (gradient) T/B%: 0/40, 2/40, 9/95, 14/95, 16/40, 18/40; flow rate: 1.0 mL/min; UV 230 nm, retention time 7.01 min; IR (KBr) 3250, 3102, 1581, 1398 cm^{-1}; MS (ES mass): *m/z* 443.7 (M-1).

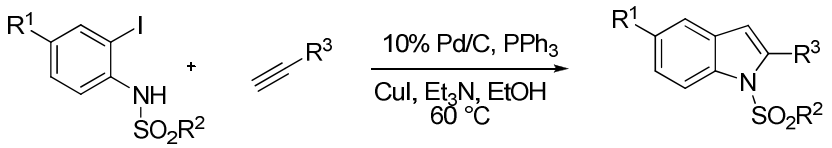
1.7.1.4.5 *N*-(2-iodo-4-methylphenyl)thiophene-2-sulfonamide (1.1r)



1.1r was prepared according to the above general procedure from **1.22e**.

White floppy solid; yield:83%; mp: 72-74 °C; R_f (5% EtOAc/*n*-Hexane) 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57-7.54 (m, 2H), 7.51 (s, 1H), 7.43 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.02-6.99 (m, 1H), 6.73 (bs, 1H), 2.26 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 139.3, 139.0, 137.8, 134.5, 133.0, 132.8, 130.3, 127.4, 123.8, 93.4, 20.3; HPLC: 99.7%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 5mM NH_4OAc in water mobile phase B: CH_3CN (gradient) T/B%: 0/40, 2/40, 9/95, 14/95, 16/40, 18/40; flow rate: 1.0 mL/min; UV 230 nm, retention time 7.85 min; IR (KBr) 3249, 3079, 1589, 1486 cm^{-1}; MS (ES mass): *m/z* 377.8 (M-1).

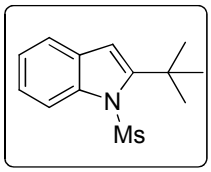
1.7.1.5 General procedure for the synthesis of 2-alkyl-1-(alkyl/aryl/heteroaryl sulfonyl)-1*H*-indole (1.23):



1.1 **1.2b** **1.23**

To a solution of 4-substituted ortho iodoanilides **1.1** (0.31 mmol) in ethanol (5.0 ml), 10% Pd/C (0.03 mmol), CuI (0.06 mmol), PPh_3 (0.12 mmol) and triethylamine (0.62 mmol) was added under nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 15 min, and then added corresponding alkyne **1.24** (0.68 mmol). The mixture was refluxed for 3-6 hr. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with saturated NH_4Cl solution (15 mL) and the product was extracted with ethyl acetate (3 x 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate–hexane to give desired product **1.23**.

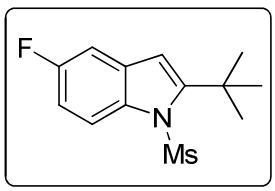
1.7.1.5.1 2-*Tert*-butyl-1-(methylsulfonyl)-1*H*-indole (1.23a)



1.23a was prepared according to the above general procedure from **1.1a** and *tert*-butylacetylene (**1.2b)**.

Semi solid; yield: 92%; R_f (10% EtOAc/*n*-Hexane) 0.90; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 8.00 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.32-7.25 (m, 2H), 6.63 (s, 1H), 2.94 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.8, 138.5, 129.4, 124.4, 123.8, 120.5, 115.3, 110.1, 39.4, 34.6, 30.8 (3C); HPLC: 99.1%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 13/98, 15/50, 18/50; flow rate: 1.0 mL/min; UV 255 nm, retention time 8.38 min; IR (KBr) 3030, 2987, 1521, 1355, 1186 cm^{-1}; MS (ES mass): *m/z* 251.9 (M+1).

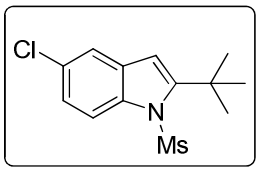
1.7.1.5.2 2-*Tert*-butyl-5-fluoro-1-(methylsulfonyl)-1*H*-indole (1.23b)



1.23b was prepared according to the above general procedure from **1.1b** and **1.2b**.

White solid; yield: 85%; mp: 50-52 °C; R_f (10% EtOAc/*n*-hexane) 0.82; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (dd, *J* = 9.2, 3.6 Hz, 1H), 7.13 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.00 (td, *J* = 9.2, 2.4 Hz, 1H), 6.58 (s, 1H), 2.92 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5 (C-F *J* = 239 Hz), 153.6, 134.7, 130.6, 116.6 (C-F *J* = 8.5 Hz), 112.1 (C-F *J* = 24.8 Hz), 110.0 (C-F *J* = 3.7 Hz), 106.0 (C-F *J* = 24.0 Hz), 39.5, 34.8, 30.8 (3C); HPLC: 96.2%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/60, 2/60, 9/98, 13/98, 15/60, 18/60; flow rate: 0.8 mL/min; UV 220 nm, retention time 8.02 min; IR (KBr) 3024, 2962, 1609, 1480, 1460, 1361 cm^{-1}; MS (ES mass): *m/z* 270.1 (M+1).

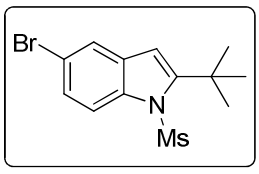
1.7.1.5.3 2-*Tert*-butyl-5-chloro-1-(methylsulfonyl)-1*H*-indole (1.23c)



1.23c was prepared according to the above general procedure from **1.1c** and **1.2b**.

White solid; yield: 90%; mp 105-107 °C; R_f (10% EtOAc/*n*-Hexane) 0.78; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 9.2 Hz, 1H), 7.45 (s, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 6.55 (s, 1H), 2.94 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.4, 136.8, 130.7, 129.6, 124.5, 120.0, 116.5, 109.3, 39.7, 34.8, 30.7 (3C); HPLC: 99.6%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/70, 2/70, 8/98, 13/98, 15/70, 18/70; flow rate: 1.0 mL/min; UV 260 nm, retention time 6.12 min; IR (KBr) 3022, 2953, 1598, 1452, 1361, 1328 cm^{-1}; MS (ES mass): *m/z* 286.5 (M+1).

1.7.5.4 5-Bromo-2-*tert*-butyl-1-(methylsulfonyl)-1*H*-indole (1.23d)

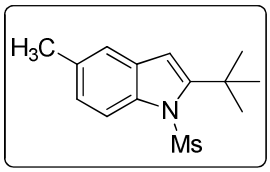


1.23d was prepared according to the above general procedure from **1.1d** and **1.2b**.

Brown solid; yield: 96%; mp: 110-112 °C; R_f (5% EtOAc/*n*-Hexane) 0.80; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.54 (s, 1H), 2.94 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ: 153.3, 137.3, 131.2, 127.2, 123.1, 117.3, 116.8, 109.2, 39.8, 34.8, 30.8 (3C); HPLC: 98.7%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/75, 2/75, 10/98, 14/98, 17/75, 20/75; flow rate: 01.0 mL/min; UV 260 nm, retention time 5.48 min; IR (KBr) 3019, 2949, 1591, 1453, 1361, 1186 cm^{-1}; MS (ES mass): *m/z* 251.0 (M-SO_2Me+1).

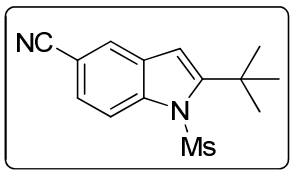
1.7.5.1.5 2-*Tert*-butyl-5-methyl-1-(methylsulfonyl)-1*H*-indole (1.23e)



1.23e was prepared according to the above general procedure from **1.1e** and **1.2b**.

Semi solid; yield: 82%; R_f (10% EtOAc/*n*-Hexane) 0.85; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 8.8 Hz, 1H), 7.27 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 1H), 2.90 (s, 3H), 2.42 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.9, 136.8, 133.5, 129.7, 125.8, 120.4, 115.1, 110.1, 39.4, 34.6, 30.8; HPLC: 98.7, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/70, 2/70, 9/98, 13/98, 15/70, 18/70; flow rate: 1.0 mL/min; UV 260 nm, retention time 5.82 min; IR (KBr) 3024, 2962, 1609, 1480, 1460, 1361 cm^{-1}; MS (ES mass): *m/z* 266.1 (M+1).

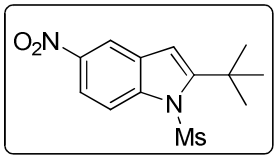
1.7.1.5.6 2-*Tert*-butyl-5-cyano-1-(methylsulfonyl)-1*H*-indole (1.23f)



1.23f was prepared according to the above general procedure from **1.1f** and **1.2b**.

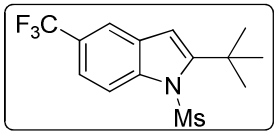
White solid; yield: 80%; mp: 193-195 °C; R_f (10% EtOAc/*n*-Hexane) 0.82; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, *J* = 8.8 Hz, 1H), 7.82 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 6.65 (s, 1H), 3.05 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.4, 140.2, 129.4, 127.4, 125.1, 123.7, 115.9, 108.9, 107.3, 40.7, 34.9, 30.7 (3C); HPLC: 98.7%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 13/98, 15/50, 18/50; flow rate: 1.0 mL/min; UV 235 nm, retention time 7.56 min; IR (KBr) 3011, 2957, 2258, 1582, 1455, 1333 cm^{-1}; MS (ES mass): *m/z* 277.1 (M+1).

1.7.1.5.7 2-*Tert*-butyl-5-nitro-1-(methylsulfonyl) -1*H*-indole (1.23g)



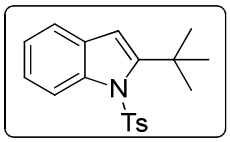
1.23g was prepared according to the above general procedure from **1.1g** and **1.2b**. White solid; yield: 91%; mp: 165-167 °C; R_f (10% EtOAc/*n*-Hexane) 0.85; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, *J* = 1.6 Hz, 1H), 8.28-8.10 (m, 2H), 6.73 (s, 1H), 3.08 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.2, 144.4, 141.4, 129.2, 119.5, 116.5, 115.4, 109.5, 40.9, 35.0, 30.7 (3C); HPLC: 99.8%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/60, 2/60, 9/98, 13/98, 15/60, 18/60; flow rate: 0.8 mL/min; UV 255 nm, retention time 7.59 min; IR (KBr) 3027, 2955, 1598, 1517, 1174 cm^{-1}; MS (ES mass): *m*/*z* 251.8 (M-NO_2).

1.7.1.5.8 2-*Tert*-butyl-1-(methylsulfonyl)-5-(trifluoromethyl)-1*H*-indole (1.23h)



1.23h was prepared according to the above general procedure from **1.1h** and **1.2b**. Brown solid; yield: 83%; mp: 60-62 °C; R_f (10% EtOAc/*n*-Hexane) 0.75; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, *J* = 9.2 Hz, 1H), 7.77 (s, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 6.68 (s, 1H), 3.01 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.8, 140.0, 129.1, 121.2, 117.9 (2C), 117.8, 115.5, 109.5, 40.3, 34.9, 30.7 (3C); HPLC: 92.2%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/60, 2/60, 9/98, 13/98, 15/60, 18/60; flow rate: 0.8 mL/min; UV 220 nm, retention time 9.4 min; IR (KBr) 3023, 2965, 1555, 1455, 1369, 1339 cm^{-1}; MS (ES mass): *m*/*z* 320.1 (M+1).

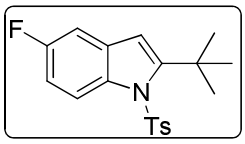
1.7.1.5.9 2-*Tert*-butyl-1-tosyl-1*H*-indole (1.23i)



1.23i was prepared according to the above general procedure from **1.1i** and **1.2b**. Semi solid; yield: 94%; R_f (30% EtOAc/*n*-Hexane) 0.80; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02-8.00 (m, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.40-7.38 (m, 1H), 7.17-7.15 (m, 2H),

7.09 (d, *J* = 8.0 Hz, 2H), 6.60 (s, 1H), 2.28 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.7, 143.9, 138.9, 136.8, 129.4 (2C), 129.2, 125.9 (2C), 124.1, 123.6, 120.3, 116.1, 110.7, 34.9, 31.3 (3C), 21.5; HPLC: 96.4%, column: Zorbax XDB C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/90, 2/90, 9/98, 12/98, 15/90, 18/90; flow rate: 0.8 mL/min; UV 222 nm, retention time 4.75 min; IR (KBr) 3019, 2956, 1465, 1363, 1184 cm^{-1}; MS (ES mass): *m*/*z* 327.5 (M+1).

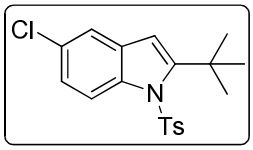
1.7.1.5.10 2-*Tert*-butyl-5-fluoro-1-tosyl-1*H*-indole (1.23j)



1.23j was prepared according to the above general procedure from **1.1j** and **1.2b**.

Semi solid; yield: 88%; R_f (10% EtOAc/*n*-Hexane) 0.87; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (dd, *J* = 9.1, 4.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.03 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.91-6.86 (m, 1H), 6.56 (s, 1H), 2.30 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 154.2, 144.2, 136.5, 135.2, 130.4, 129.5 (2C), 125.9 (2C), 117.3, 11.9, 110.6, 105.6, 35.1, 31.3 (3C), 21.5; HPLC: 97.0%, column: Zorbax XDB C-18 150*4.6 mm 5µ, mobile phase A: 0.05 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/80, 2/80, 9/98, 12/98, 15/80, 18/80; flow rate: 1.0 mL/min; UV 222 nm, retention time 6.74 min; IR (KBr): 2932, 2868, 1462, 1365, 1303 cm^{-1}; MS (ES mass): *m*/*z* 346.1 (M+1).

1.7.1.5.11 2-*Tert*-butyl-5-chloro-1-tosyl-1*H*-indole (1.23k)

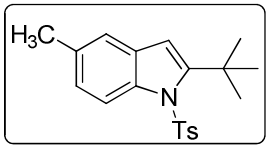


1.23k was prepared according to the above general procedure from **1.1k** and **1.2b**.

Semi solid; yield: 85%; R_f (30% EtOAc/*n*-Hexane) 0.80; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.36-7.35 (m, 1H), 7.13-7.10 (m, 3H), 6.54 (s, 1H), 2.31 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.3, 144.3, 137.2, 136.6, 130.5, 129.6 (2C), 129.3, 125.9 (2C), 124.2, 119.8, 117.1, 109.8, 35.1, 31.2 (3C), 21.5; HPLC: 98.9%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.05 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/90, 2/90, 9/95, 12/95, 15/90, 18/90; flow rate: 0.8 mL/min; UV 222 nm, retention

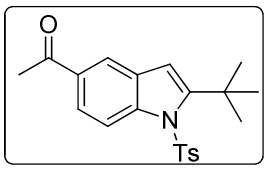
time 5.18 min; IR (KBr) 3032, 2963, 1455, 1363, 1184 cm^{-1}; MS (ES mass): *m/z* 362.1 (M+1).

1.7.1.5.12 2-*Tert*-butyl-5-methyl-1-tosyl-1*H*-indole (1.23l)



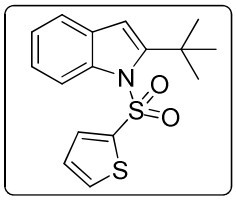
1.23l was prepared according to the above general procedure from **1.1l** and **1.2b**. Yellow solid; yield: 81%; mp: 88-90 °C; R_f (10% EtOAc/*n*-Hexane) 0.82; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.17 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.53 (s, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.7, 143.9, 137.2, 136.9, 133.1, 129.4 (3C), 125.9 (2C), 125.5, 120.2, 115.8, 110.6, 34.9, 31.1 (3C), 21.4, 21.1; HPLC: 96.1%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/80, 2/80, 9/98, 13/98, 15/80, 18/80; flow rate: 1.0 mL/min; UV 220 nm, retention time 6.31 min; IR (KBr): 2956, 2911, 1601, 1465, 1363 cm^{-1}; MS (ES mass): *m/z* 342.1 (M+1).

1.7.1.5.13 1-(2-*Tert*-butyl-1-tosyl-1*H*-indol-5-yl)ethanone (1.23m)



1.23m was prepared according to the above general procedure from **1.1m** and **1.2b**. Semi solid; yield: 85%; R_f (10% EtOAc/*n*-Hexane) 0.86; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (dd, *J* = 9.1, 1.8 Hz, 2H) 7.79 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.68 (s, 1H), 2.59 (s, 3H), 2.29 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.8, 154.5, 144.5, 141.5, 136.6, 132.9, 129.7 (2C), 128.9, 125.9 (2C), 124.2, 121.3, 115.8, 110.5, 35.1, 31.2 (3C), 26.6, 21.5; HPLC: 94.5%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 13/98, 15/50, 18/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 7.82 min; IR (KBr) 3014, 2943, 1656, 1454, 1342 cm^{-1}; MS (ES mass): *m/z* 370.0 (M+1).

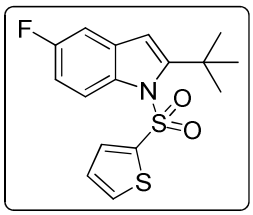
1.7.1.5.14 2-*Tert*-butyl-1-(thiophen-2-ylsulfonyl)-1*H*-indole (1.23n)



1.23n was prepared according to the above general procedure from **1.1n** and **1.2b**.

Brown color solid; yield: 88%; mp: 78-80 °C; R_f (3% EtOAc/*n*-Hexane) 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, J = 8.2 Hz, 1H), 7.45-7.44 (m, 1H), 7.40-7.38 (m, 2H), 7.28-7.26 (m, 1H), 7.22-7.20 (m, 1H), 6.88-6.86 (m, 1H), 6.60 (s, 1H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.2, 138.7, 132.5, 132.3, 129.9, 126.5, 124.3, 124.1, 120.4, 116.5, 112.1, 112.0, 340.9, 31.3 (3C); HPLC: 95.6%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 5mM NH_4OAc in water mobile phase B: CH_3CN (gradient) T/B%: 0/60, 2/60, 9/95, 14/95, 16/60, 18/60; flow rate: 1.0 mL/min; UV 220 nm, retention time 8.57 min; IR (KBr) 3101, 2922, 1455, 1371 cm^{-1}; MS (ES mass): *m/z* 319.8 (M+1).

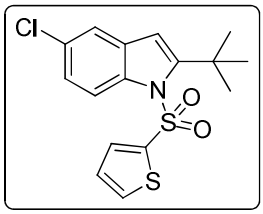
1.7.1.5.15 2-*Tert*-butyl-5-fluoro-1-(thiophen-2-ylsulfonyl)-1*H*-indole (1.23o)



1.23o was prepared according to the above general procedure from **1.1o** and **1.2b**.

White solid; yield: 84%; mp: 105-107 °C; R_f (10% EtOAc/*n*-Hexane) 0.85; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12-8.08 (m, 1H), 7.45-7.41 (m, 1H), 7.04 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.97-6.94 (m, 1H), 6.89 (t, *J* = 4.8 Hz, 1H), 6.56 (s, 1H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.1 (C-F *J* = 340.0 Hz), 154.1, 134.9, 132.6 (C-F *J* = 15.1 Hz), 131.0, 126.6 (2C), 117.7 (C-F *J* = 9.1 Hz), 111.9, 111.8 (C-F *J* = 24.8 Hz), 109.9, 106.0 (C-F *J* = 23.5 Hz), 35.1, 31.2 (3C); HPLC: 98.5%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 5mM NH_4OAc in water mobile phase B: CH_3CN (gradient) T/B%: 0/50, 2/50, 9/95, 16/95, 18/50, 20/50; flow rate: 1.0 mL/min; UV 254 nm, retention time 10.52 min; IR (KBr) 3099, 2957, 1605, 1458 cm^{-1}; MS (ES mass): *m/z* 337.8 (M+1).

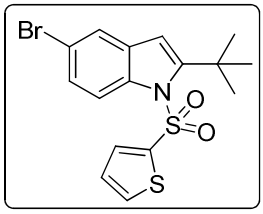
1.7.1.5.16 2-*Tert*-butyl-5-chloro-1-(thiophen-2-ylsulfonyl)-1*H*-indole (1.23p)



1.23p was prepared according to the above general procedure from **1.1p** and **1.2b**.

Light brown solid; yield: 85%; mp: 105-107 °C; R_f (5% EtOAc/*n*-Hexane) 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 8.6 Hz, 1H), 7.47-7.43 (m, 2H), 7.36 (d, *J* = 1.1 Hz, 1H), 7.21 (dd, *J* = 8.6, 1.2 Hz, 1H), 6.92-6.90 (m, 1H), 6.54 (s, 1H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.7, 138.3, 137.0, 132.7, 132.6, 131.1, 129.8, 126.6, 124.4, 119.9, 117.5, 111.2, 35.1, 31.1 (3C); HPLC: 97.8%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 5mM NH_4OAc in water mobile phase B: CH_3CN (gradient) T/B%: 0/50, 2/50, 9/95, 16/95, 18/50, 20/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 11.52 min; IR (KBr) 3110, 2965, 1596, 1451 cm^{-1}; MS (ES mass): *m*/*z* 353.8 (M+1).

1.7.1.5.17 5-Bromo-2-*tert*-butyl-1-(thiophen-2-ylsulfonyl)-1*H*-indole (1.23q)

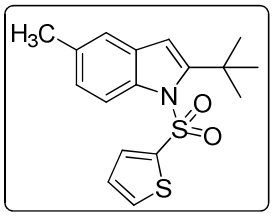


1.23q was prepared according to the above general procedure from **1.1q** and **1.2b**.

Light brown solid; yield: 90%; mp: 125-127 °C; R_f (8% EtOAc/*n*-Hexane) 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.46-7.43 (m, 2H), 7.35 (dd, *J* = 8.8, 1.8 Hz, 1H), 6.92-6.90 (m, 1H), 6.53 (s, 1H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.6, 138.2, 137.3, 132.8, 132.7, 131.6, 127.1, 126.7, 123.0, 117.9, 117.6, 111.0, 35.0, 31.1 (3C); HPLC: 98.5%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 5mM NH_4OAc in water mobile phase B: CH_3CN (gradient) T/B%: 0/50, 2/50, 9/95, 16/95, 18/50, 20/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 11.78 min; IR (KBr) 3100, 2965, 1592, 1450 cm^{-1}; MS (ES mass): *m*/*z* 399.7 (M+1).

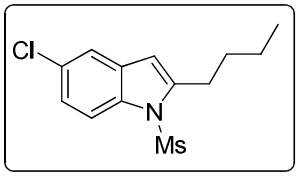
1.7.1.5.18 2-*Tert*-butyl-5-methyl-1-(thiophen-2-ylsulfonyl)-1*H*-indole (1.23r)

1.23r was prepared according to the above general procedure from **1.1r** and **1.2b**.



Light yellow solid; yield: 80%; mp: 102-104 °C; R_f (4% EtOAc/*n*-Hexane) 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 8.6 Hz, 1H), 7.43 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.37 (d, *J* = 8.6, 1.2 Hz, 1H), 7.17 (s, 1H), 7.07 (dd, *J* = 8.6, 1.2 Hz, 1H), 6.88-6.86 (m, 1H), 6.53 (s, 1H), 2.38 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.2, 138.5, 136.8, 133.8, 132.4, 132.2, 130.1, 126.4, 125.6, 120.3, 116.2, 112.0, 34.9, 31.2 (3C), 21.1; HPLC: 98.8%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 5mM NH_4OAc in water mobile phase B: CH_3CN (gradient) T/B%: 0/40, 2/40, 9/95, 18/95, 22/40, 25/40; flow rate: 1.0 mL/min; UV 255 nm, retention time 11.52 min; IR (KBr) 3097, 2963, 1465, 1364 cm^{-1}; MS (ES mass): *m*/*z* 333.9 (M+1).

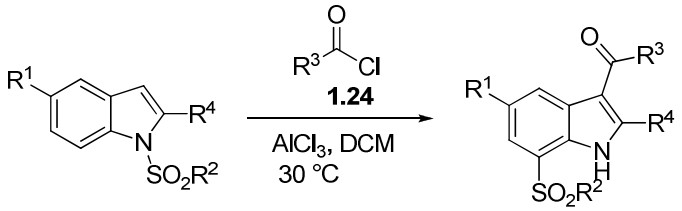
1.7.1.5.19 2-Butyl-5-chloro-1-(methylsulfonyl)-1H-indole (1.23s)



1.23s was prepared according to the above general procedure from **1.1c** and *n*-butyl acetylene (**1.2c**).

Semi solid; yield: 85%; R_f (10% EtOAc/*n*-Hexane) 0.85; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 9.2 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.18 (dd, *J* = 9.2, 2.0 Hz, 1H), 6.36 (s, 1H), 2.96 (s, 3H), 2.90 (t, *J* = 7.6 Hz, 2H), 1.74-1.66 (m, 2H), 1.46-1.37 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.9, 135.1, 131.0, 129.4, 124.0, 119.8, 115.2, 107.7, 40.6, 30.8, 28.5, 22.4, 13.9; HPLC : 99.1%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/70, 2/70, 9/98, 14/98, 16/70, 18/70; flow rate: 1.0 mL/min; UV 225 nm, retention time 6.59 min; IR (KBr, cm^{-1}): 3026, 2948, 2932, 1448, 1354; MS (ES mass): *m*/*z* 285.9 (M+1).

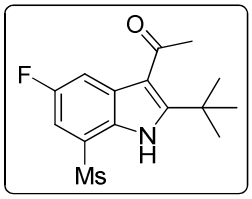
1.7.1.6 General procedure for preparation of 1-(2-*tert*-butyl-5-substituted-7-(alkyl/aryl/heteroaryl sulfonyl)-1*H*-indol-3-yl)alkanone (1.25):



1.23 **1.25**

A mixture of $AlCl_3$ (0.5 mmol) and acid chloride **1.24** (0.75 mmol) was stirred at 0 ºC in dry DCM (5 mL) for 10 min. To this indole **1.23** (0.25 mmol) in DCM (3 mL) was added and the reaction mixture was stirred at room temperature for 6-8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with DCM (20 ml), washed with water (10 mL) and brine solution (10 mL). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-hexane to give the desired product **1.25**.

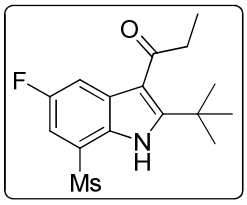
1.7.1.6.1 1-(2-*Tert*-butyl-5-fluoro-7-(methylsulfonyl)-1*H*-indol-3-yl)ethanone (1.25a)



Compound **1.25a** was prepared from **1.23b** and acetyl chloride (**1.24a**) according to the above general procedure.

White solid; yield: 68%; mp: 143-145 ^oC; R_f (10% EtOAc/*n*-Hexane) 0.32; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.10 (s, 1H), 7.79 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.43 (dd, *J* = 8.0, 2.2 Hz, 1H), 3.18 (s, 3H), 2.69 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.4, 157.5 (C-F *J* = 240.1 Hz), 156.8, 131.0, 130.9 (C-F *J* = 25.1 Hz), 126.4, 122.6, 112.5 (C-F *J* = 25.1 Hz), 109.6 (C-F *J* = 27.9 Hz), 45.2, 34.3, 32.4, 28.3 (3C); HPLC: 98.5%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 10/95, 15/95, 18/50, 20/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 6.41 min; IR (KBr, cm^{-1}): 3446, 3069, 2965, 1652, 1429, 1317 ; MS (ES mass): *m/z* 311.9 (M+1).

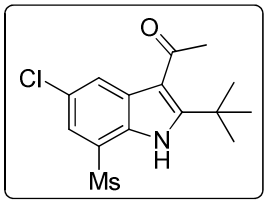
1.7.1.6.2 1-(2-*Tert*-butyl-5-fluoro-7-(methylsulfonyl)-1*H*-indol-3-yl)propan-1-one (1.25b)



Compound **1.25b** was prepared from **1.23b** and propanoyl chloride (**1.24b**) according to the above general procedure.

White solid; yield: 65%; mp: 115-117 ^{o}C; R_f (15% EtOAc/*n*-Hexane) 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.06 (bs, 1H), 7.76 (dd, *J* = 9.7, 1.5 Hz, 1H), 7.43 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.18 (s, 3H), 2.99 (q, *J* = 7.2 Hz, 2H), 1.54 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.4, 157.4 (C-F *J* = 240.0 Hz), 156.2, 130.5 (C-F *J* = 9.0 Hz), 126.4, 122.4 (C-F *J* = 8.1 Hz), 114.5 (C-F *J* = 27.9 Hz),112.5 (C-F *J* = 25.3 Hz), 109.6 (C-F *J* = 25.3 Hz), 45.2, 37.4, 34.3, 28.5 (3C), 8.6; HPLC: 99.6%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 5mM NH_4OAC in water B: CH_3CN (gradient) T/B% : 0/50,3/50, 12/95, 16/95, 18/50, 20/50; flow rate: 1.0 mL/min; UV 225 nm, retention time 8.72 min; IR (KBr, cm^{-1}): 3425, 3012, 2966, 1659, 1477, 1305; MS (ES mass): *m/z* 324.7 (M-1).

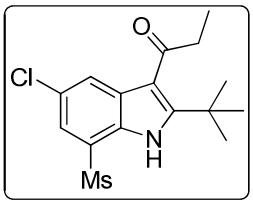
1.7.1.6.3 1-(2-*Tert*-butyl-5-chloro-7-(methylsulfonyl)-1*H*-indol-3-yl)ethanone (1.25c)



Compound **1.25c** was prepared from **1.23c** and **1.24a** according to the above general procedure.

White solid; yield: 70%; mp: 168-170 ^{o} C; R_f (10% EtOAc/*n*-Hexane) 0.65; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.10 (bs, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 3.18 (s, 3H), 2.70 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.5, 156.2, 131.2, 128.1, 127.3, 125.8, 123.1, 121.7, 114.2, 45.3, 34.3, 32.6, 28.4 (3C); HPLC: 99.7%, column: X Bridge C-18 150*4.6 mm 5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/95, 12/95, 15/15, 18/50; flow rate: 1.0 mL/min; UV 229 nm, retention time 7.28 min; IR (KBr, cm^{-1}): 3001, 2958, 1599, 1452, 1358, 1176; MS (ES mass): *m/z* 327.4 (M+1).

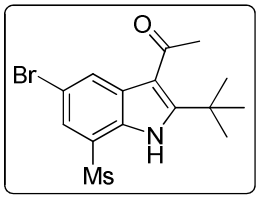
1.7.1.6.4 1-(2-*Tert*-butyl-5-chloro-7-(methylsulfonyl)-1*H*-indol-3-yl)propan-1-one (1.25d)



Compound **1.25d** was prepared from **1.23c** and **1.24b** according to the above general procedure.

White solid; yield: 67%; mp: 150-152 ºC; R_f (20% EtOAc/*n*-Hexane) 0.42; ^{1}H-NMR (400 MHz, $CDCl_3$): 10.06 (s, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 7.65 (d, *J* = 1.5 Hz, 1H), 3.19 (s, 3H), 3.01 (q, *J* = 7.2 Hz, 2H), 1.54 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.7, 155.5, 130.8, 128.1, 127.1, 125.8, 123.0, 121.6, 114.1, 45.3, 37.6, 34.2, 28.6 (3C), 8.5; HPLC: 94.5%, column: X Bridge C-18 150*4.6 mm 5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/95, 12/95, 15/15, 18/50; flow rate: 1.0 mL/min; UV 229 nm, retention time 8.95 min; IR (KBr, cm^{-1}): 3004, 2950, 1588, 1435, 1358, 1166; MS (ES mass): *m*/*z* 340 (M-1).

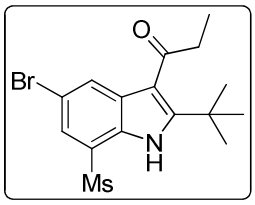
1.7.1.6.5 1-(5-Bromo-2-*tert*-butyl-7-(methylsulfonyl)-1*H*-indol-3-yl)ethanone (1.25e)



Compound **1.25e** was prepared from **1.23d** and **1.24a** according to the above general procedure.

White solid; yield: 66%; mp: 148-150 ^{o}C; R_f (15% EtOAc/*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.11 (bs, 1H), 8.20 (d, *J* = 1.4 Hz, 1H), 7.78 (d, *J* = 1.4 Hz, 1H), 3.19 (s, 3H), 2.70 (s, 3H), 1.54 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.6, 156.0, 131.7, 128.8, 128.4, 124.3, 123.5, 114.4, 114.1, 45.3, 34.3, 32.6, 28.4 (3C); HPLC: 99.4%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 10/95, 15/95, 18/50, 20/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 7.60 min; IR (KBr, cm^{-1}): 3423, 3079, 2915, 1644, 1423, 1308; MS (ES mass): *m*/*z* 372.8 (M+1).

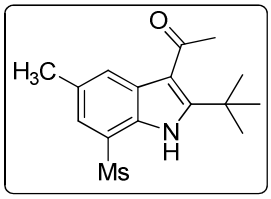
1.7.1.6.6 1-(5-Bromo-2-*tert*-butyl-7-(methylsulfonyl)-1*H*-indol-3-yl)propan-1-one (1.25f)



Compound **1.25f** was prepared from **1.23d** and **1.24b** according to the above general procedure.

White solid; yield: 65%; mp: 145-147 ºC; R_f (10% EtOAc/*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.05 (s, 1H), 8.16 (d, *J* = 1.2 Hz, 1H), 7.76 (d, *J* = 1.5 Hz, 1H), 3.18 (s, 3H), 3.00 (q, *J* = 7.2 Hz, 2H), 1.53 (s, 9H), 1.27 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.7, 155.2, 131.3, 128.7, 128.4, 124.2, 123.4, 114.0, 109.9, 45.3, 37.7, 34.2, 28.6 (3C), 8.5; HPLC: 99.1%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 10/95, 15/95, 18/50, 20/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 8.92 min; IR (KBr, cm^{-1}): 3424, 3074, 2918, 1654, 1412, 1312; MS (ES mass): *m/z* 385.8 (M-1).

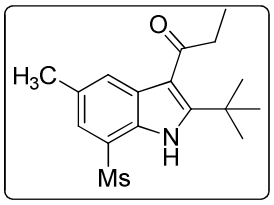
1.7.1.6.7 1-(2-*Tert*-butyl-5-methyl-7-(methylsulfonyl)-1*H*-indol-3-yl)ethanone (1.25g)



Compound **1.25g** was prepared from **1.23e** and **1.24a** according to the above general procedure.

White solid; yield: 60%; mp: 115-117 ºC; R_f (10% EtOAc/*n*-Hexane) 0.37; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.02 (s, 1H), 7.88 (s, 1H), 7.49 (s, 1H), 3.15 (s, 3H), 2.72 (s, 3H), 2.55 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.2, 155.0, 131.4, 130.4, 127.9, 126.5, 122.8, 121.8, 114.0, 45.3, 32.6, 29.8, 28.4 (3C), 21.6; HPLC: 95.6%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/10, 2/10, 9/95, 16/95, 17/10, 20/10; flow rate: 1.0 mL/min; UV 210 nm, retention time 9.77 min; IR (KBr, cm^{-1}): 3442, 2967, 2932, 1652, 1479; MS (ES mass): *m/z* 307.9 (M+1).

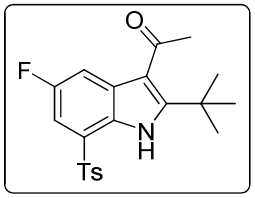
1.7.1.6.8 1-(2-*Tert*-butyl-5-methyl-7-(methylsulfonyl)-1*H*-indol-3-yl)propan-1-one (1.25h)



Compound **1.25h** was prepared from **1.23e** and **1.24b** according to the above general procedure.

White solid; yield: 58%; mp: 110-112 ºC; R_f (10% EtOAc/*n*-Hexane) 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.96 (s, 1H), 7.84 (s, 1H), 7.48 (s, 1H), 3.15 (s, 3H), 3.03 (q, *J* = 7.2 Hz, 2H), 2.54 (s, 3H), 1.53 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.3, 154.2, 131.1, 130.0, 128.1, 126.5, 122.7, 121.7, 113.9, 45.2, 37.6, 34.1, 28.6 (3C), 21.6, 8.6; HPLC: 97.6%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/10, 2/10, 9/95, 16/95, 17/10, 20/10; flow rate: 1.0 mL/min; UV 210 nm, retention time 10.38 min; IR (KBr, cm^{-1}): 3423, 2955, 2924, 1665, 1458; MS (ES mass): *m*/*z* 322.3 (M+1).

1.7.1.6.9 1-(2-*Tert*-butyl-5-fluoro-7-tosyl-1*H*-indol-3-yl)ethanone (1.25i)

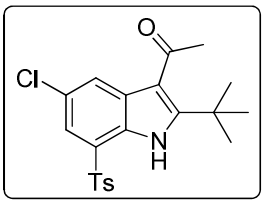


Compound **1.25i** was prepared from **1.23j** and **1.24a** according to the above general procedure.

White solid; yield: 56%; mp: 128-130 ºC; R_f (10% EtOAc/*n*-Hexane) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.21 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.68 (dd, *J* = 9.9, 2.1 Hz, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.65 (s, 3H), 2.41 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.3, 157.6 (C-F *J* = 240.0 Hz), 156.6, 145.1, 138.1, 130.8 (C-F *J* = 9.1 Hz), 130.2 (2C), 127.1 (2C), 126.2, 124.2 (C-F *J* = 8.2 Hz), 114.5, 111.9 (C-F *J* = 25.2 Hz), 110.0 (C-F *J* = 28.1 Hz), 34.3, 32.4, 28.3 (3C), 21.6; HPLC: 96.3%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/70, 2/70,

9/98, 14/98, 15/70, 18/70; flow rate: 1.0 mL/min; UV 215 nm, retention time 5.91 min; IR (KBr, cm^{-1}): 3430, 2925, 1665, 1458, 1309; MS (ES mass): *m/z* 387.8 (M+1).

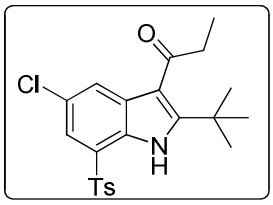
1.7.1.6.10 1-(2-*Tert*-butyl-5-chloro-7-tosyl-1*H*-indol-3-yl)ethanone (1.25j)



Compound **1.25j** was prepared from **1.23k** and **1.24a** according to the above general procedure.

White solid; yield: 58%; mp: 120-122 ºC; R_f (10% EtOAc/*n*-Hexane) 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.22 (s, 1H), 7.94 (d, *J* = 1.4 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 1.6 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 2.66 (s, 3H), 2.41 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.5, 156.1, 145.2, 138.2, 131.2, 130.2 (2C), 127.9, 127.3, 127.1 (2C), 125.3, 124.7, 121.9, 114.1, 34.3, 32.5, 28.4 (3C), 21.6; HPLC: 99.1%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 10/98, 15/98, 18/50, 20/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 10.59 min; IR (KBr, cm^{-1}): 3430, 2925, 1665, 1458, 1309; MS (ES mass): *m/z* 404.8 (M-1).

1.7.1.6.11 1-(2-*Tert*-butyl-5-chloro-7-tosyl-1*H*-indol-3-yl)propan-1-one (1.25k)

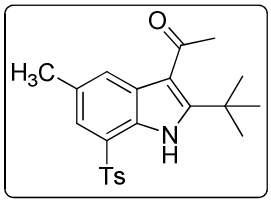


Compound **1.25k** was prepared from **1.23k** and **1.24b** according to the above general procedure.

White solid; yield: 55%; mp: 110-112 ºC; R_f (10% EtOAc/*n*-Hexane) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.17 (s, 1H), 7.91 (d, *J* = 1.4 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 2.96 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.56 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.6, 155.3, 145.2, 138.1, 130.7, 130.2 (2C), 128.0, 127.2, 127.1, 127.0, 125.3, 124.6, 121.9, 113.9, 37.5, 34.2, 28.6 (3C), 21.6, 8.5; HPLC: 98.6%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B:

CH_3CN (gradient) T/B% : 0/70, 2/70, 9/95, 15/95, 18/70, 20/70; flow rate: 1.0 mL/min; UV 210 nm, retention time 9.73 min; IR (KBr, cm^{-1}): 3430, 2956, 2925, 1669, 1457; MS (ES mass): *m/z* 418.4 (M+1).

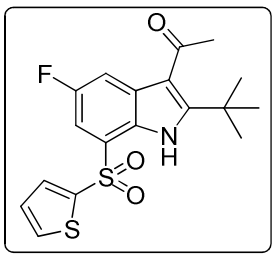
1.7.1.6.12 1-(2-*Tert*-butyl-5-methyl-7-tosyl-1*H*-indol-3-yl)ethanone (1.25l)



Compound **1.25l** was prepared from **1.23l** and **1.24a** according to the above general procedure.

White solid; yield: 52%; HPLC mp: 140-142 ºC; R_f (10% EtOAc/*n*-Hexane) 0.41; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.13 (s, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.78 (s, 1H), 7.43 (s, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 2.68 (s, 3H), 2.48 (s, 3H), 2.39 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.1, 154.8, 144.5, 138.9, 131.3, 130.3, 129.9 (2C), 129.3, 127.9, 126.9 (2C), 126.1, 123.2, 113.9, 34.2, 32.6, 29.9, 28.4 (3C), 21.7; HPLC : 98.6%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/70, 2/70, 9/98, 14/98, 15/70, 18/70; flow rate: 1.0 mL/min; UV 215 nm, retention time 5.99 min; IR (KBr, cm^{-1}): 3430, 2925, 1665, 1458, 1309; MS (ES mass): *m/z* 383.9 (M+1).

1.7.1.6.13 1-(2-*Tert*-butyl-5-fluoro-7-(thiophen-2-ylsulfonyl)-1*H*-indol-3-yl)ethanone (1.25m)

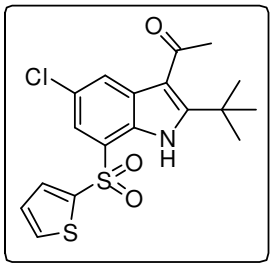


Compound **1.25m** was prepared from **1.23o** and **1.24a** according to the above general procedure.

White solid; yield: 58%; mp: 138-140 ºC; R_f (25% EtOAc/*n*-Hexane) 0.65; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.09 (s, 1H), 7.75-7.67 (m, 3H), 7.48 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.13-7.10 (m, 1H), 2.67 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.3, 158.8, 156.6, 142.2, 134.3, 133.4, 130.9, 128.2, 125.8, 112.4, 112.2, 109.9, 109.6, 34.3, 32.4, 28.3 (3C); HPLC : 95.8%, column: X Bridge C-18 150*4.6 mm 5µ,

mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 16/98, 18/50, 18/50, 20/50; flow rate: 1.0 mL/min; UV 270 nm, retention time 8.53 min; IR (KBr, cm^{-1}): 3425, 3091, 2950, 1659, 1426; MS (ES mass): *m*/*z* 379.8 (M+1).

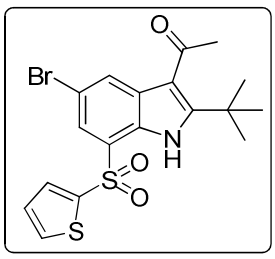
1.7.1.6.14 1-(2-*Tert*-butyl-5-chloro-7-(thiophen-2-ylsulfonyl)-1*H*-indol-3yl)-ethanone (1.25n)



Compound **1.25n** was prepared from **1.23p** and **1.24a** according to the above general procedure.

White solid; yield: 55%; mp: 112-115 °C; R_f (20% EtOAc/*n*-Hexane) 0.35; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.0 (bs, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.70-7.64 (m, 2H), 7.12 (t, *J* = 4.4 Hz, 1H), 2.67 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.8, 153.1, 131.6, 131.2, 131.0 (2C), 128.3, 126.9, 123.8, 122.9, 119.9, 112.2, 111.3, 34.0, 32.2, 30.0 (3C); HPLC: 97.2%; column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 14/98, 16/50, 18/50; flow rate: 01.0 mL/min; UV 230 nm, retention time 5.85 min; IR (KBr) 3228, 2957, 1673, ;427 cm^{-1}; MS (ES mass): *m*/*z* 394.8 (M-1).

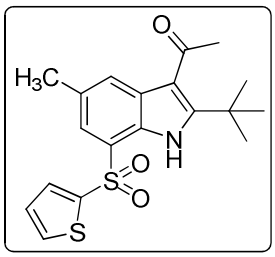
1.7.1.6.15 1-(5-Bromo-2-*ter*t-butyl-7-(thiophen-2-ylsulfonyl)-1*H*-indol-3-yl)-ethanone (1.25o)



Compound **1.25o** was prepared from **1.23q** and **1.24a** according to the above general procedure.

White solid; yield: 55%; mp: 145-147 °C; R_f (20% EtOAc/*n*-Hexane) 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (bs, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 2.2 Hz, 1H), 7.37-7.30 (m, 2H), 7.00 (t, *J* = 4.8 Hz, 1H), 2.64 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.9, 154.5, 145.2, 134.2, 133.5, 131.8, 129.7, 128.3, 124.9, 123.2, 123.1, 115.3, 112.7, 34.1, 32.7, 28.3 (3C); HPLC: 96.3%; column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 14/98, 16/50, 18/50; flow rate: 1.0 mL/min; UV 245 nm, retention time 11.21 min; IR (KBr) 3343, 3013, 1675, 1354 cm^{-1}; MS (ES mass): *m/z* 439.6 (M-1).

1.7.1.6.16 1-(2-*Tert*-butyl-5-methyl-7-(thiophen-2-ylsulfonyl)-1*H*-indol-3-yl) ethanone (1.25p)



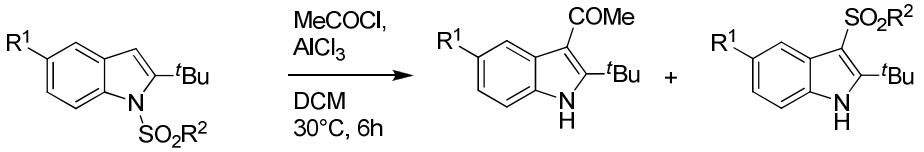
Compound **1.25p** was prepared from **1.23r** and **1.24a** according to the above general procedure.

White solid; yield: 54%; mp: 180-182 °C; R_f (20% EtOAc/*n*-Hexane) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (bs, 1H), 7.99 (s, 1H), 7.77 (s, 1H), 7.68 (dd, *J* = 4.6, 1.0 Hz, 1H), 7.48 (dd, *J* = 4.8, 1.0 Hz, 1H), 7.00-6.98 (m, 1H), 2.64 (s, 3H), 2.60 (s, 3H), 1.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.0, 154.6, 146.3, 133.1, 132.4, 131.5, 131.1, 130.5, 129.6, 126.9, 122.7, 113.6, 111.2, 34.6, 29.9 (3C), 29.5, 22.4; HPLC: 95.6%; column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 14/98, 16/50, 18/50; flow rate: 1.0 mL/min; UV 250 nm, retention time 10.12 min; IR (KBr) 3325, 2963, 1673, 1315 cm^{-1}; MS (ES mass): *m/z* 373.9 (M-1).

1.7.1.7 Procedure for preparation of compounds (1.26-1.27):

A mixture of $AlCl_3$ (0.5 mmol) and acetyl chloride **1.24a** (0.75 mmol) was stirred at 0 °C in dry DCM (5 mL) for 10 min. To this mixture of indoles **1.23g** or **1.23m** (0.25 mmol) in DCM (3 mL) was added and the reaction mixture was stirred at room temperature for 8h. After completion of the reaction, the reaction mixture was diluted

with DCM (3x10 mL), washed with water (3x10 mL) and brine solution (3x10 mL). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-hexane to give the desired products **1.26** and **1.27**.

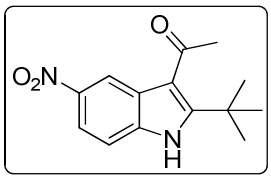


1.23g $R^1 = NO_2$, R^2 = Me
1.23m R^1 = COMe, $R^2 = C_6H_4Me$-*p*

1.26a, $R^1 = NO_2$ (60%)
1.26b, R^1 = COMe (58%)

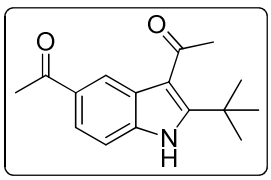
1.27a, $R^1 = NO_2$, R^2 = Me (33%)
1.27b, R^1 = COMe, $R^2 = C_6H_4Me$-*p* (30%)

1.7.1.7.1 1-(2-*Tert*-butyl-5-nitro-1*H*-indol-3-yl)ethanone (1.26a)



White solid; yield: 60%; mp: 183-185 °C; R_f (10% EtOAc/*n*-Hexane) 0.59; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86 (s, 1H), 8.80 (d, *J* = 1.6 Hz, 1H), 8.14 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.45 (d, *J* = 89.2 Hz, 1H), 2.79 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.5, 155.2, 144.4, 141.4, 129.2, 119.5, 116.5, 115.4, 109.5, 34.3, 32.6, 28.3 (3C); HPLC : 98.9%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/95, 14/95, 17/50, 19/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 6.12 min; IR (KBr, cm^{-1}): 3402, 2992, 2942, 1652, 1453; MS (ES mass): *m/z* 261.2 (M+1).

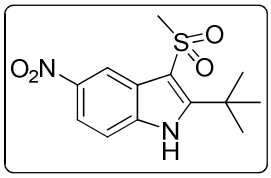
1.7.1.7.2 1,1'-(2-*Tert*-butyl-1*H*-indole-3,5-diyl)diethanone (1.26b)



White solid; yield: 58%; mp: 182-184 °C; R_f (10% EtOAc/*n*-Hexane) 0.52; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.79 (s, 1H), 8.52 (s, 1H), 7.86 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 2.78 (s, 3H), 2.69 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.2, 195.4, 154.5, 135.8, 131.3, 127.6, 122.7, 121.9, 115.2, 110.9, 34.1, 28.4, 26.8 (3C), 26.7; HPLC : 96.9%, column: X Bridge C-18 150*4.6 mm 5µ,

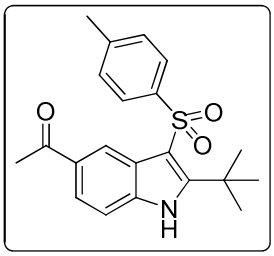
mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 14/98, 16/50, 18/50; flow rate: 1.0 mL/min; UV 245 nm, retention time 4.08 min; IR (KBr, cm^{-1}): 3391, 2967, 2930, 1685, 1642, 1482; MS (ES mass): *m/z* 258.1 (M+1).

1.7.1.7.3 2-*tert*-butyl-3-(methylsulfonyl)-5-nitro-1*H*-indole (1.27a)



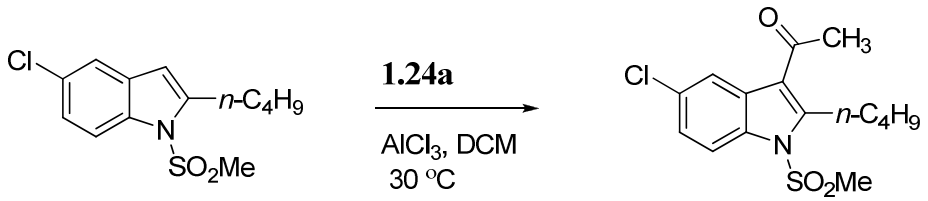
White solid; yield: 33%; mp: 215-217 °C; R_f (10% EtOAc/*n*-Hexane) 0.23; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.03 (s, 2H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 3.19 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.7, 143.7, 135.5, 127.3, 126.9, 118.9, 117.1, 113.2, 34.5, 29.6 (3C), 22.7; HPLC : 97.1%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/95, 14/95, 16/50, 18/50; flow rate: 1.0 mL/min; UV 255 nm, retention time 6.09 min; IR (KBr, cm^{-1}): 3409, 2977, 2924, 1444; MS (ES mass): *m/z* 297.2 (M+1).

1.7.1.7.4 1-(2-*tert*-butyl-3-tosyl-1*H*-indol-5-yl)ethanone (1.27b)



White solid; yield: 30%; mp: 179-181 °C; R_f (10% EtOAc/*n*-Hexane) 0.23; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.79 (s, 1H), 8.52 (s, 1H), 7.86 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H) 7.42 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 2.78 (s, 3H), 2.69 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.2, 153.3, 143.2, 141.6, 135.3, 131.9, 129.6, 129.3, 127.1, 126.2, 125.9, 123.1, 122.9, 122.7, 111.9, 34.5, 30.0, 26.9 (3C), 22.7; HPLC : 96.9%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 14/98, 16/50, 18/50; flow rate: 1.0 mL/min; UV 245 nm, retention time 4.08 min; IR (KBr, cm^{-1}): 3411, 2979, 2927, 1681, 1455; MS (ES mass): *m/z* 370.1 (M+1).

1.7.1.8 Preparation of 1-(2-butyl-5-chloro-1-(methylsulfonyl)-1*H*-indol-3-yl)-ethanone (1.28):

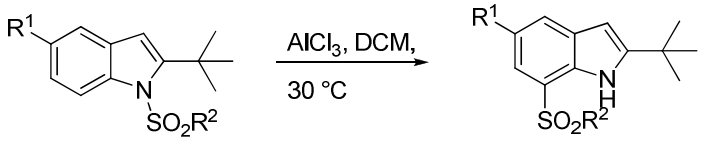


1.23s **1.28**

Compound **1.28** was prepared from **1.23s** and **1.24a** according to the above general procedure.

White solid; yield: 85%; mp: 120-122 °C; R_f (10% EtOAc/*n*-Hexane) 0.52; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.31 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.33-3.29 (m, 2H), 3.15 (s, 3H), 2.67 (s, 3H), 1.75-1.68 (m, 2H), 1.53-1.44 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.0, 149.4, 133.8, 130.6, 128.5, 125.1, 120.8, 119.6, 115.3, 41.8, 32.9, 31.9, 26.8, 22.9, 13.6; HPLC : 99.1%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/70, 2/70, 9/98, 14/98, 16/70, 18/70; flow rate: 0.8 mL/min; UV 220 nm, retention time 6.29 min; IR (KBr, cm^{-1}): 3008, 2961, 1645, 1379; MS (ES mass): *m/z* 327.8 (M+1).

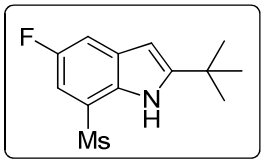
1.7.1.9 General procedure for preparation of 2-*Tert*-butyl-5-substituted-7-(alkyl/ary/heteroaryl sulfonyl)-1*H*-indole (1.31):



1.23 **1.29**

A mixture of $AlCl_3$ (2.10 mmol) and indole **1.23** (1.75 mmol) stirred at 0 ºC in dry DCM (5 mL) for 10 min. Then, the reaction mixture was stirred at room temperature for 4-5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with DCM (20 ml), washed with water (10 mL) and brine solution (10 mL). The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-hexane to give the desired product **1.29**.

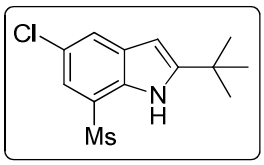
1.7.1.9.1 2-*Tert*-butyl-5-fluoro-7-(methylsulfonyl)-1*H*-indole (1.29a)



1.29a was prepared according to the above general procedure from **1.23b**.

White solid; yield: 68%; R_f (10 % EtOAc/*n*-Hexane) 0.72; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.29 (s, 1H), 7.45 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.33 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.34 (s, 1H), 3.15 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6 (C-F *J* = 237.3 Hz), 153.3, 131.6 (C-F *J* = 9.2 Hz), 128.9, 111.6 (C-F *J* = 23.3 Hz), 108.6, 108.3, 97.8, 44.9, 32.1, 30.1 (3C); HPLC : 98.1%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/60, 2/60, 9/95, 14/95, 16/60, 18/60; flow rate: 0.8 mL/min; UV 225 nm, retention time 6.74 min; IR (KBr, cm^{-1}): 3383, 2967, 2930, 1486; MS (ES mass): *m/z* 269.8 (M+1).

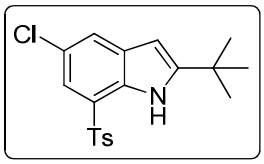
1.7.1.9.2 2-*Tert*-butyl-5-chloro-7-(methylsulfonyl)-1*H*-indole (1.29b)



1.29b was prepared according to the above general procedure from **1.23c**.

White solid; yield: 70%; R_f (10% EtOAc/*n*-Hexane) 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.34 (s, 1H), 7.73 (d, *J* = 1.6 Hz, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 6.32 (s, 1H), 3.15 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.0, 131.7, 128.8, 128.3, 124.3, 123.5, 114.3, 114.1, 45.3, 32.6, 28.4 (3C); HPLC: 96.4%; column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/95, 14/95, 16/50, 18/50; flow rate: 1.0 mL/min; UV 265 nm, retention time 9.12 min IR (KBr, cm^{-1}): 3441, 2962, 2920, 1652, 1451; MS (ES mass): *m/z* 286.0 (M+1).

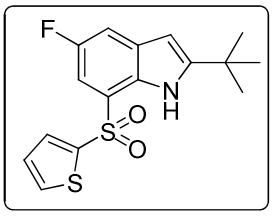
1.7.1.9.3 2-*Tert*-butyl-5-chloro-7-tosyl-1*H*-indole (1.29c)



1.29c was prepared according to the above general procedure from **1.23k**.

White solid; yield: 65%; R_f (15% EtOAc/*n*-Hexane) 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (s, 1H), 8.11 (d, *J* = 1.2 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.28-7.25 (m, 3H), 6.32 (s, 1H), 2.36 (s, 3H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.3, 145.2, 138.1, 130.7, 130.2 (2C), 128.0, 127.2, 127.1, 127.0, 125.3, 124.6, 121.9, 113.9, 34.2, 28.6 (3C), 21.6; HPLC : 99.1%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/70, 2/70, 9/95, 14/95, 16/70, 17/70; flow rate: 1.0 mL/min; UV 245 nm, retention time 10.09 min; IR (KBr, cm^{-1}): 3441, 2962, 2920, 1652, 1451; MS (ES mass): *m*/*z* 362.4 (M+1).

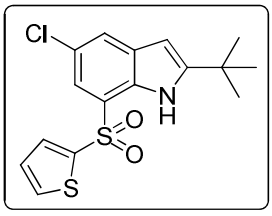
1.7.1.9.4 1-(2-*Tert*-butyl-5-fluoro-7-(thiophen-2-ylsulfonyl)-1*H*-indol-3-yl)propan-1-one (1.29d)



1.29d was prepared according to the above general procedure from **1.23o**.

White solid; yield: 65%; mp: 105-107 ºC; R_f (25% EtOAc/*n*-Hexane) 0.37; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (s, 1H), 7.82 (dd, *J* = 9.1, 2.0 Hz, 1H), 7.68 (d, *J* = 2.6 Hz, 1H), 7.48 (d, *J* = 5.2 Hz, 1H), 7.31-7.28 (m, 1H), 7.01-6.94 (m, 2H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 157.9, 153.2, 146.3, 131.4, 131.1, 129.1, 126.9, 112.4, 111.8, 111.6, 106.1, 34.4, 29.9 (3C); HPLC : 98.5%, column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 16/98, 18/50, 18/50, 20/50; flow rate: 1.0 mL/min; UV 280 nm, retention time 6.77 min; IR (KBr, cm^{-1}): 3372, 3104, 2962, 1478, 1448; MS (ES mass): *m*/*z* 337.9 (M+1).

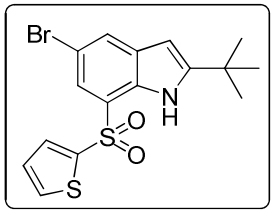
1.7.1.9.5 2-*Tert*-butyl-5-chloro-7-(thiophen-2-ylsulfonyl)-1*H*-indole (1.29e)



1.29e was prepared according to the above general procedure from **1.23p**.

Off white solid; yield: 68%; mp: 95-97 °C; R_f (20% EtOAc/*n*-Hexane) 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (bs, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.48 (d, *J* = 2.2 Hz, 1H), 7.22-7.15 (m, 2H), 7.01-6.99 (m, 1H), 6.49 (s, 1H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.8, 131.4, 131.3, 131.0, 128.0, 127.0, 123.7, 123.6, 120.0, 112.2, 111.1, 96.9, 34.4, 29.9 (3C); HPLC: 95.9%; column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 14/98, 16/50, 18/50; flow rate: 1.0 mL/min; UV 280 nm, retention time 5.48 min; IR (KBr) 3251, 2985, 1545, 1466 cm^{-1}; MS (ES mass): *m*/*z* 353.9 (M-+1).

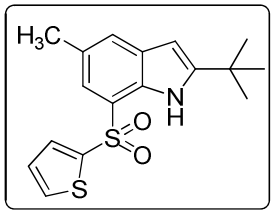
1.7.1.9.6 5-Bromo-2-*tert*-butyl-7-(thiophen-2-ylsulfonyl)-1*H*-indole (1.29f)



1.29f was prepared according to the above general procedure from **1.23q**.

Light red solid; yield: 58%; mp: 198-200 °C; R_f (20% EtOAc/*n*-Hexane) 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.37 (bs, 1H), 7.81 (d, *J* = 1.0 Hz, 1H), 7.72-7.71 (m, 2H), 7.61(dd, *J* = 5.8, 1.0 Hz, 1H), 7.08 (t, *J* = 4.8 Hz, 1H), 6.28 (s, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.6, 142.9, 133.7, 132.9, 132.6, 130.4, 128.2, 127.9, 123.7, 123.1, 111.9, 97.3, 32.1, 30.0 (3C); HPLC: 93.9%; column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 14/98, 16/50, 18/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 10.45 min; IR (KBr) 3364, 2986, 1521, 1432 cm^{-1}; MS (ES mass): *m*/*z* 399.8 (M+1).

1.7.1.9.7 2-*Tert*-butyl-5-methyl-7-(thiophen-2-ylsulfonyl)-1*H*-indole (1.29g)



1.29g was prepared according to the above general procedure from **1.23r**.

Light green solid; yield: 60%; mp: 170-172 °C; R_f (20% EtOAc/*n*-Hexane) 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (bs, 1H), 7.98 (s, 1H), 7.79-7.75 (m, 2H), 7.66-7.64

(m, 1H), 7.06-7.04 (m, 1H), 6.40 (s, 1H), 2.61 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.4, 132.0, 131.6, 130.9, 130.1, 124.4, 123.0 (2C), 122.3, 113.9, 113.6, 96.8, 32.7, 28.3 (3C), 22.8; HPLC: 98.9%; column: X Bridge C-18 150*4.6 mm 5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 2/50, 9/98, 14/98, 16/50, 18/50; flow rate: 1.0 mL/min; UV 245 nm, retention time 6.24 min; IR (KBr) 3334, 3012, 1532, 1387 cm^{-1}; MS (ES mass): *m/z* 333.8 (M+1).

1.7.2 Single crystal X-ray data

Single crystals suitable for X-ray diffraction of **1.23b, 1.23c** and **1.25c** were grown from methanol. The crystals were carefully chosen using a stereo zoom microscope supported by a rotatable polarizing stage. The data was collected at room temperature on Bruker's KAPPA APEX II CCD Duo with graphite monochromated Mo-Kα radiation (0.71073 Å). The crystals were glued to a thin glass fibre using FOMBLIN immersion oil and mounted on the diffractometer. The intensity data were processed using Bruker's suite of data processing programs (SAINT), and absorption corrections were applied using SADABS.[32] The crystal structure was solved by direct methods using SHELXS-97 and the data was refined by full matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms, using SHELXL-97.[33]

1.7.2.1 Crystal data of 1.23b: Molecular formula = $C_{13}H_{16}FNO_2S$, Formula weight = 269.34, Crystal system = Monoclinic, space group = P2(1)/n, a = 12.776 (15) Å, b = 7.860 (9) Å, c = 13.154 (15) Å, V = 1277.0 (3) Å^3, T = 296 K, Z = 4, D_c = 1.401 Mg m^{-3}, µ(Mo-Kα) = 0.26 mm^{-1}, 12623 reflections measured, 2784 independent reflections, 2527 observed reflections [I > 2.0 σ (I)], R_1_obs = 0.030, Goodness of fit =1.003. Crystallographic data (excluding structure factors) for **1.23b** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 859364.

1.7.2.2 Crystal data of 1.23c: Molecular formula = $C_{13}H_{16}ClNO_2S$, Formula weight = 285.79, Crystal system = Orthorhombic, space group = Pbca, a = 10.947 (14) Å, b = 9.428 (12) Å, c = 25.263 (3) Å, V = 2607.6 (6)Å^3, T = 296 K, Z = 8, D_c = 1.456 Mg m^{-3}, µ(Mo-Kα) = 0.45 mm^{-1}, 25387 reflections measured, 2835 independent reflections, 2660 observed reflections [I > 2.0 σ (I)], R_1_obs = 0.031, Goodness of fit

= 0.956. Crystallographic data (excluding structure factors) for **1.23c** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 859366.

1.7.2.3 Crystal data of 1.25c: Molecular formula = $C_{15}H_{18}ClNO_3S$, Formula weight = 327.81, Crystal system = Monoclinic, space group = P2(1)/n, a = 10.815 (5) Å, b = 9.725 (4) Å, c = 14.935 (7) Å, V = 1570.22 (12) $Å^3$, T = 296 K, Z = 4, Dc = 1.387 Mg m^{-3}, μ(Mo-Kα) = 0.39 mm^{-1}, 19884 reflections measured, 3429 independent reflections, 2873 observed reflections [I > 2.0 σ (I)], R1_obs = 0.032, Goodness of fit = 0.876. Crystallographic data (excluding structure factors) for **1.25c** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 859365.

1.7.3 Pharmacology

1.7.3.1 Chorismate mutase activity assay[29]

Mycobacterium *tuberculosis* chorismate mutase (MtCM) gene was PCR amplified and cloned into expression vector pET22b. MtCM was purified from over expressed culture of BL21 (DE3) harboring pET22b/ MtCM by Ni-NTA affinity chromatography.

Activity of chorismate mutase enzyme is based on the direct observation of conversion of chorismate to prephenate Spectrophotometrically at OD_{274}. The reaction volume of 100 µl contained 50 mM Tris-HCl (pH 7.5), 0.5 mM EDTA, 0.1 mg/ml bovine serum albumin, and 10 mM β-Mercaptoethanol, and chorismic acid 4 mM. The reaction was started by adding 180 pmol of purified protein to the pre-warmed chorismic acid solution. Inhibitory screening of the test compounds against chorismate mutase activity was measured at 30 µM concentration of the effectors. The reaction was allowed to proceed at 37 °C and was terminated after 5 min with 100 µl of 1 N HCl. A blank with no enzyme for every reaction was kept as a control to account for the non enzymatic conversion of chorismate to prephenate.

The percentage of enzyme inhibition caused by the test compound is calculated by the following formula

% inhibition = 100 – residual activity of CM

$$\left[\text{Residual activity of CM} = \frac{A_{274}(S + E' + C) - A_{274}(S + C)}{A_{274}(S + E) - A_{274}(S)} \times 100\right]$$

S = Absorbance of the substrate (chorismic acid) at 274 nm

E' = Absorbance of the enzyme (CM) at 274 nm with compound

E = Absorbance of the enzyme (CM) at 274 nm without compound

C = Test compound

(A_{274} indicates absorbance at 274 nm)

1.7.3.2 Docking study

Method: Docking simulations of molecules were performed using the Schrodinger software suite (Maestro, version 9.2).[34] The compounds were sketched in 3D format using build panel and were prepared for docking using ligprep application. The Protein (Chorismate mutase; PDB ID: 2F6L)[29a] for docking study was retrieved from protein data bank (PDB). The protein was prepared by giving preliminary treatment like adding hydrogen, adding missing residues, refining the loop with prime and finally minimized by using OPLS-2005 force field. Grids for molecular docking were generated by selecting 15 Å residues, around the binding site of protein. Compounds were docked using Glide in extra-precision mode,[35] with up to three poses saved per molecule.

1.8 Reference

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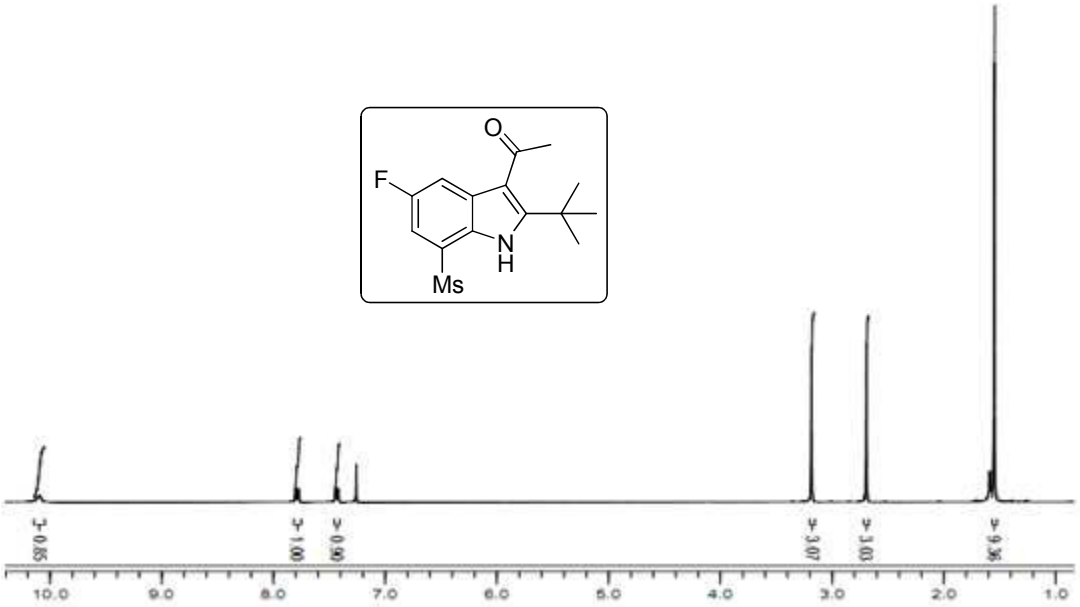
Appendix

1.25a ^{1}H NMR (400 MHz, $CDCl_3$)



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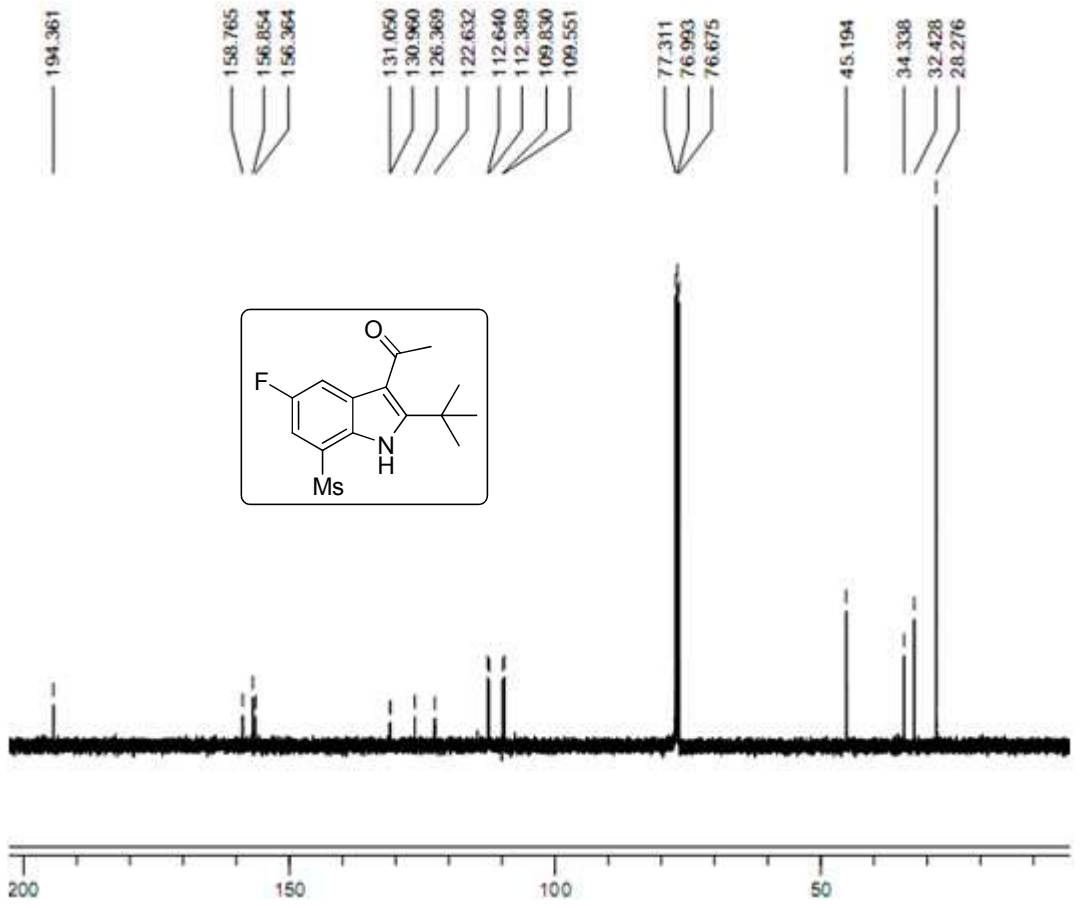

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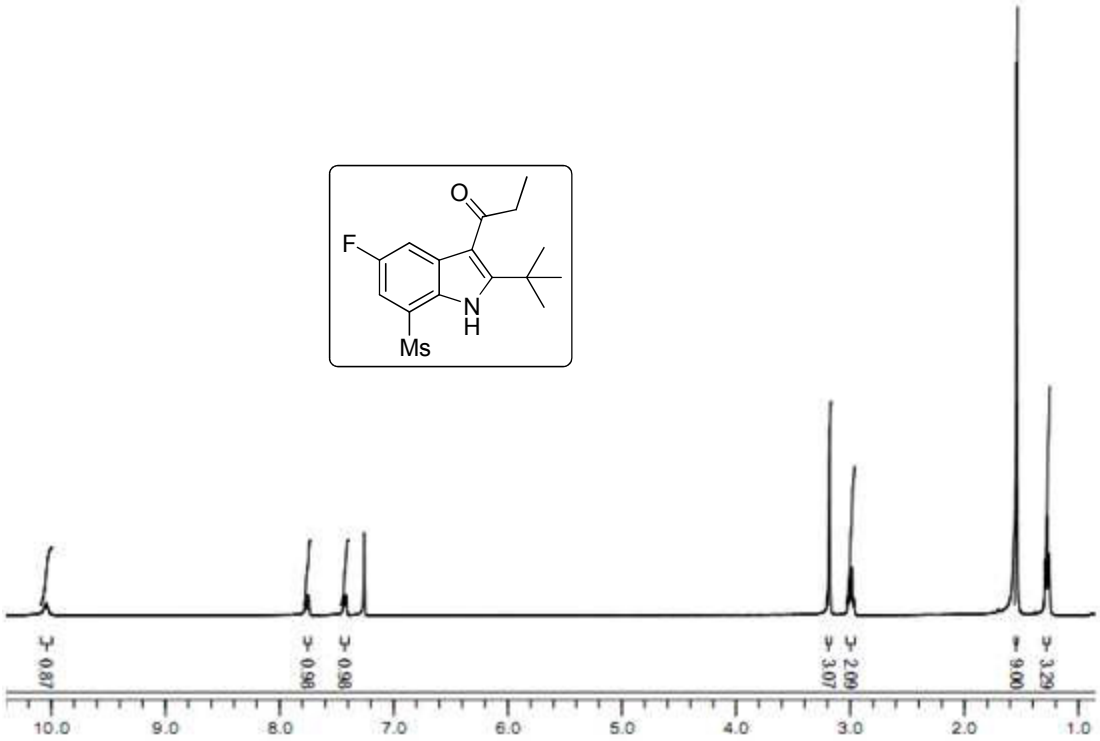
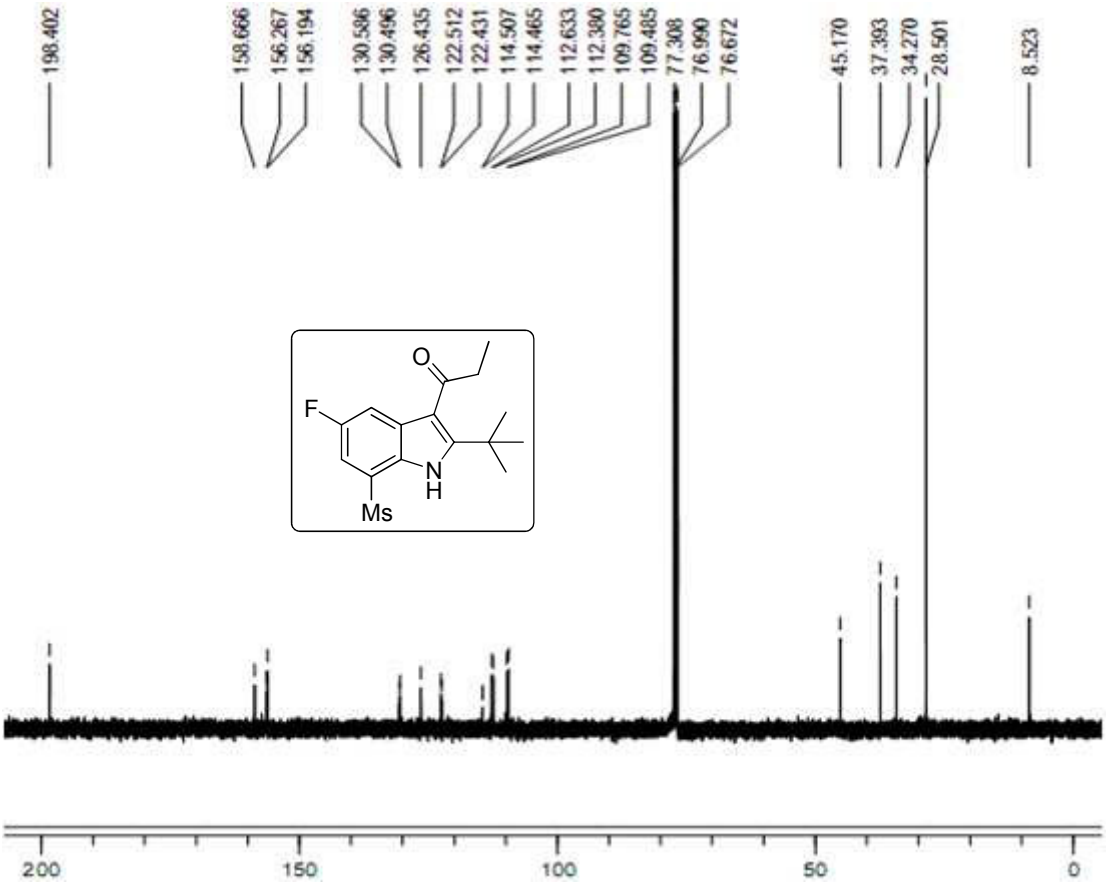


1.25b ^{13}C NMR (100 MHz, $CDCl_3$)



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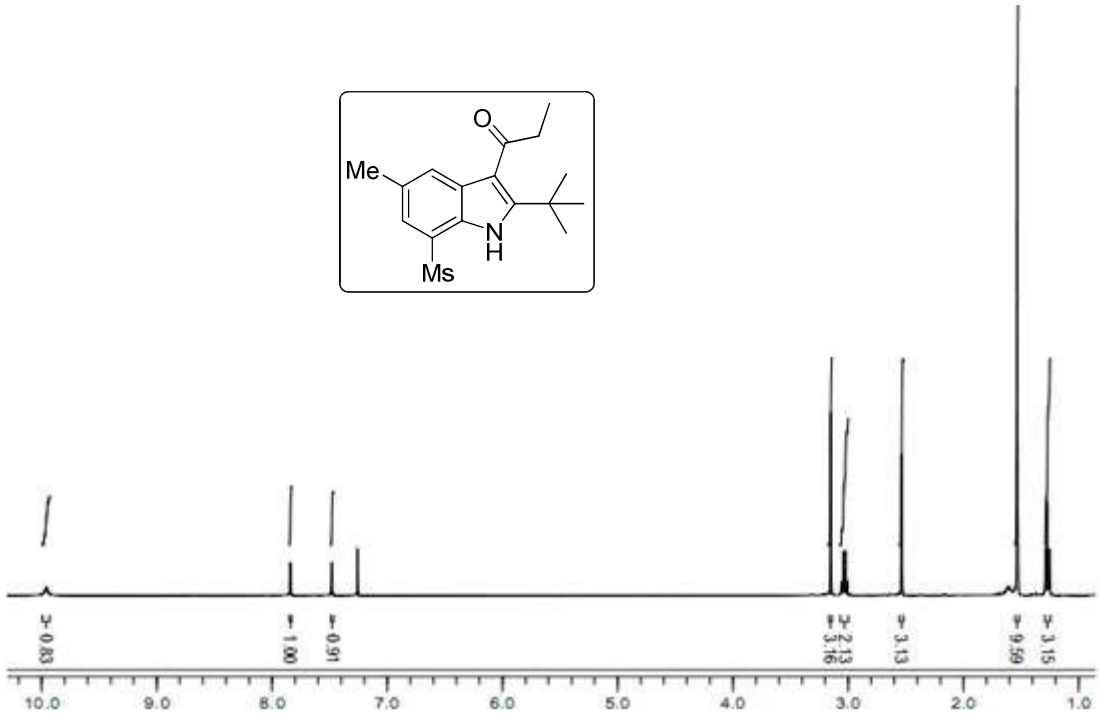

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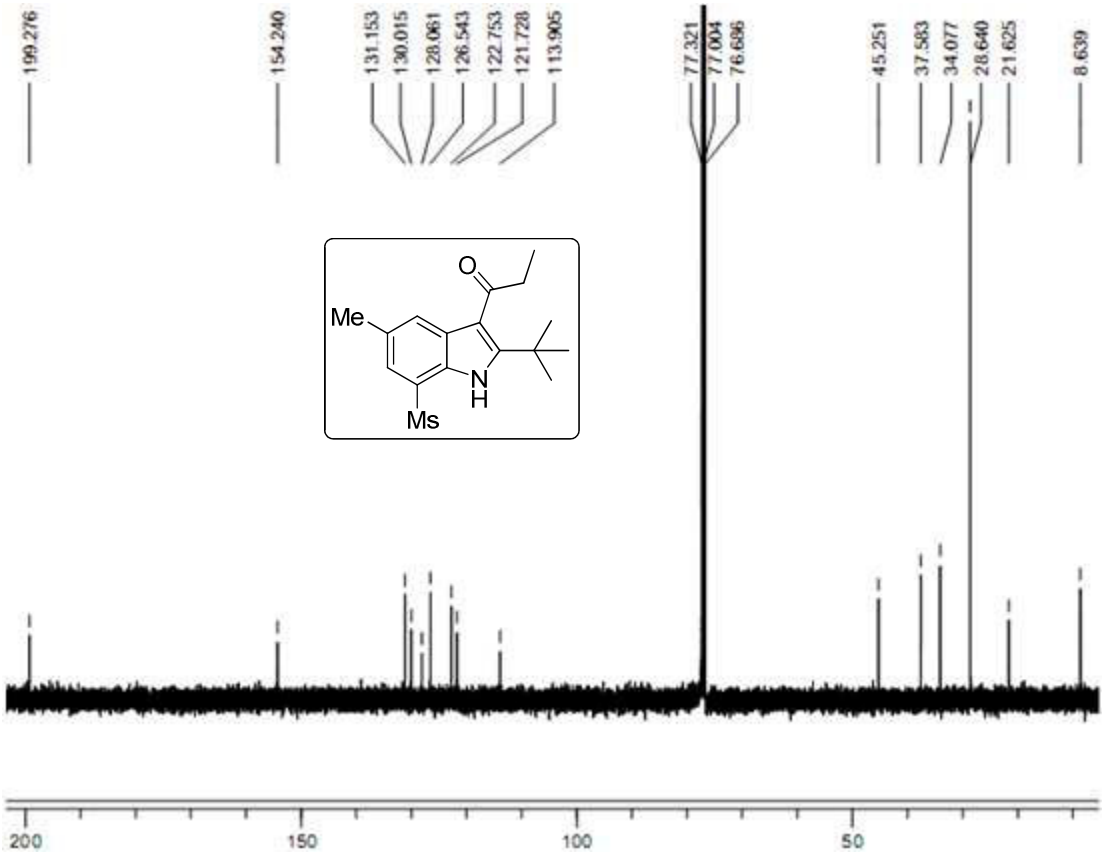

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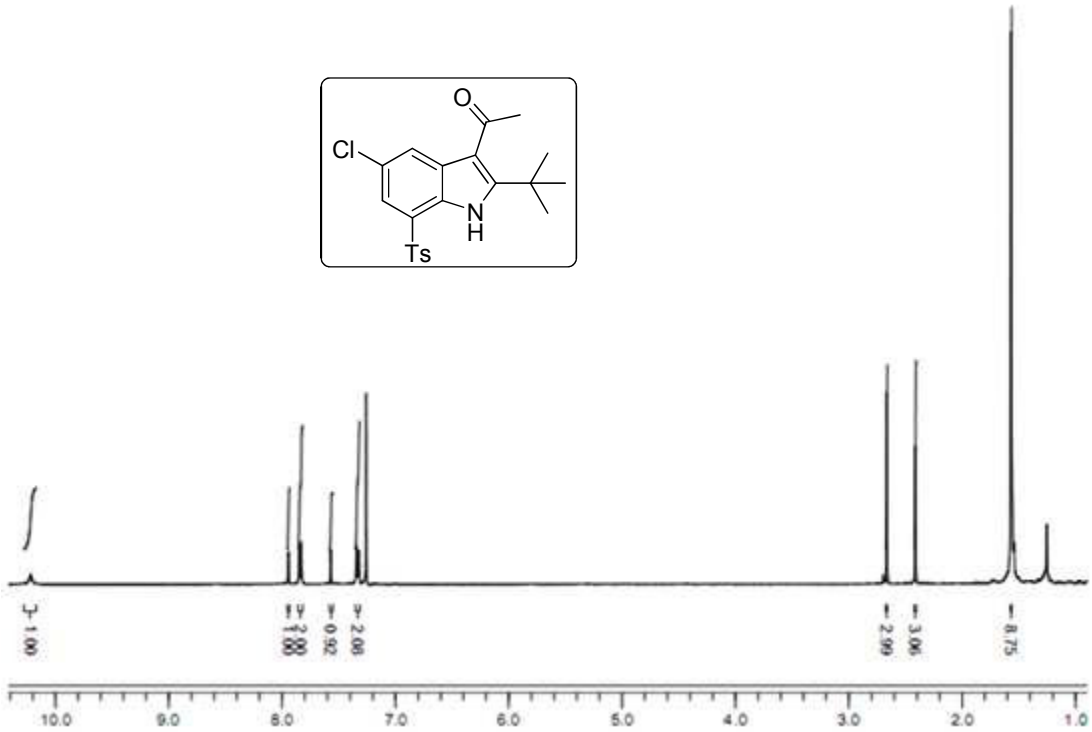
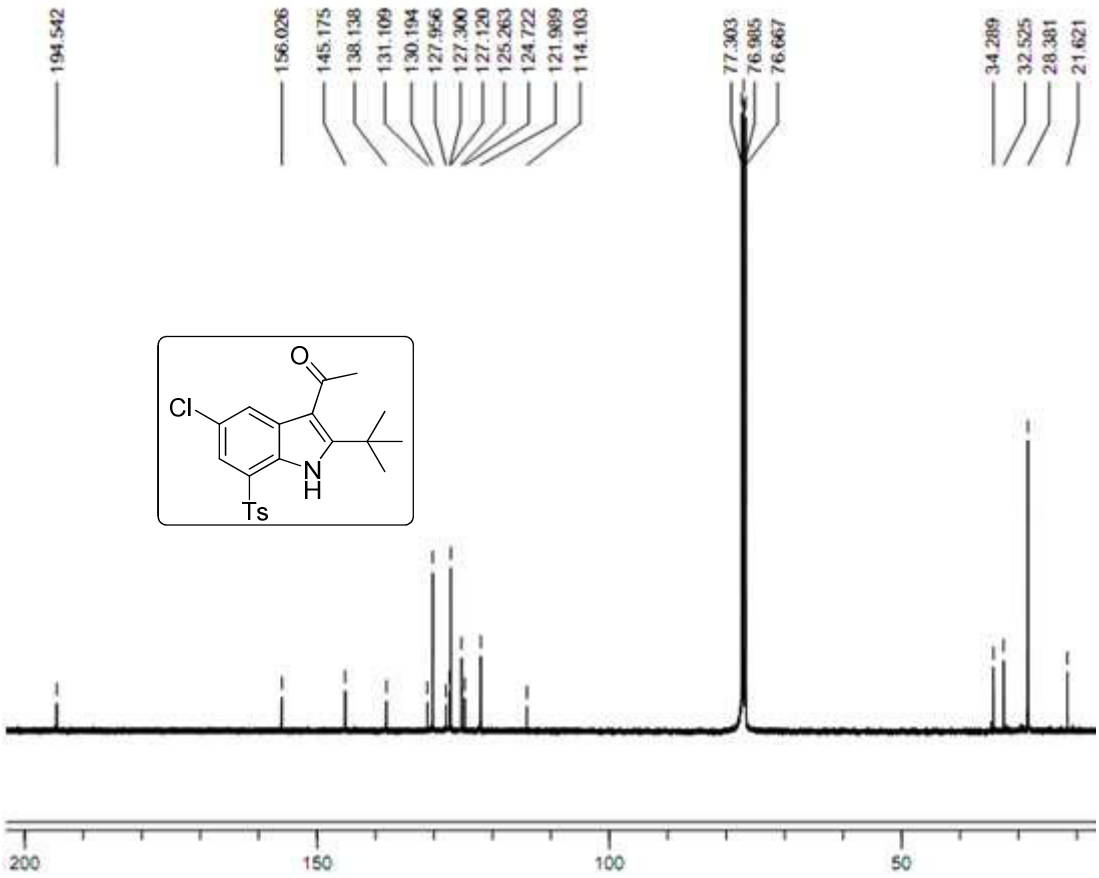
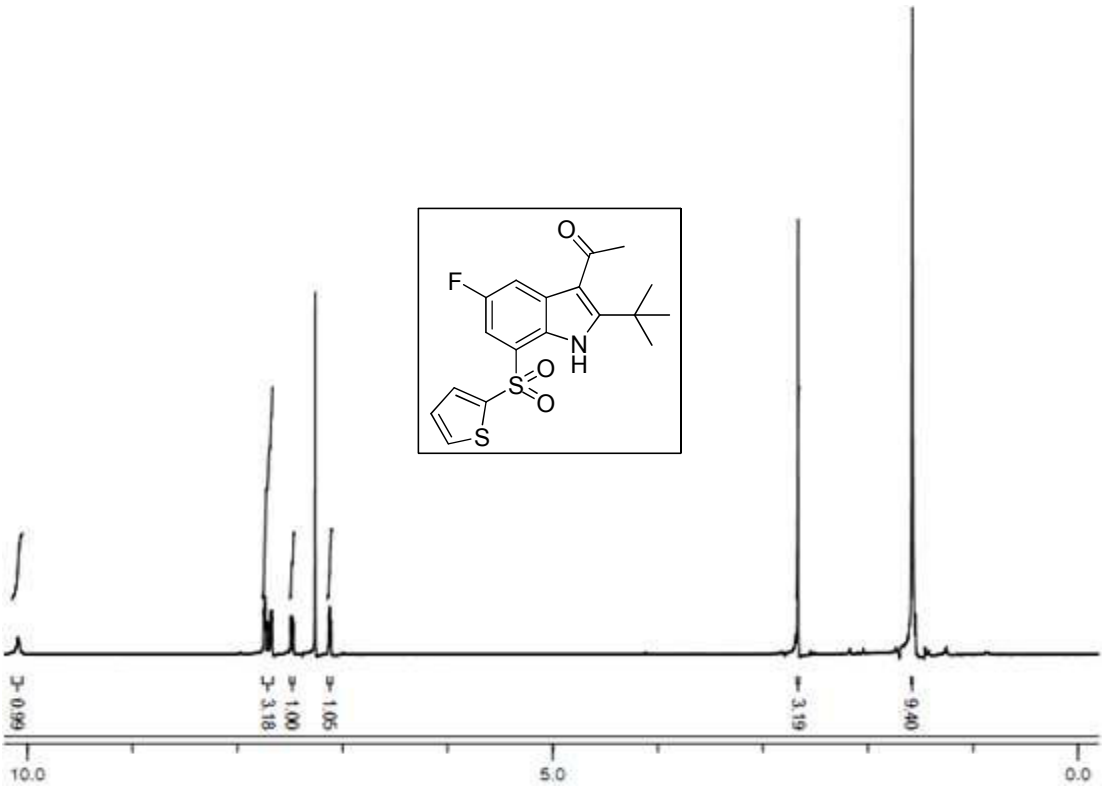


1.25j ^{13}C NMR (100 MHz, $CDCl_3$)



1.25m ^{1}H NMR (400 MHz, $CDCl_3$)



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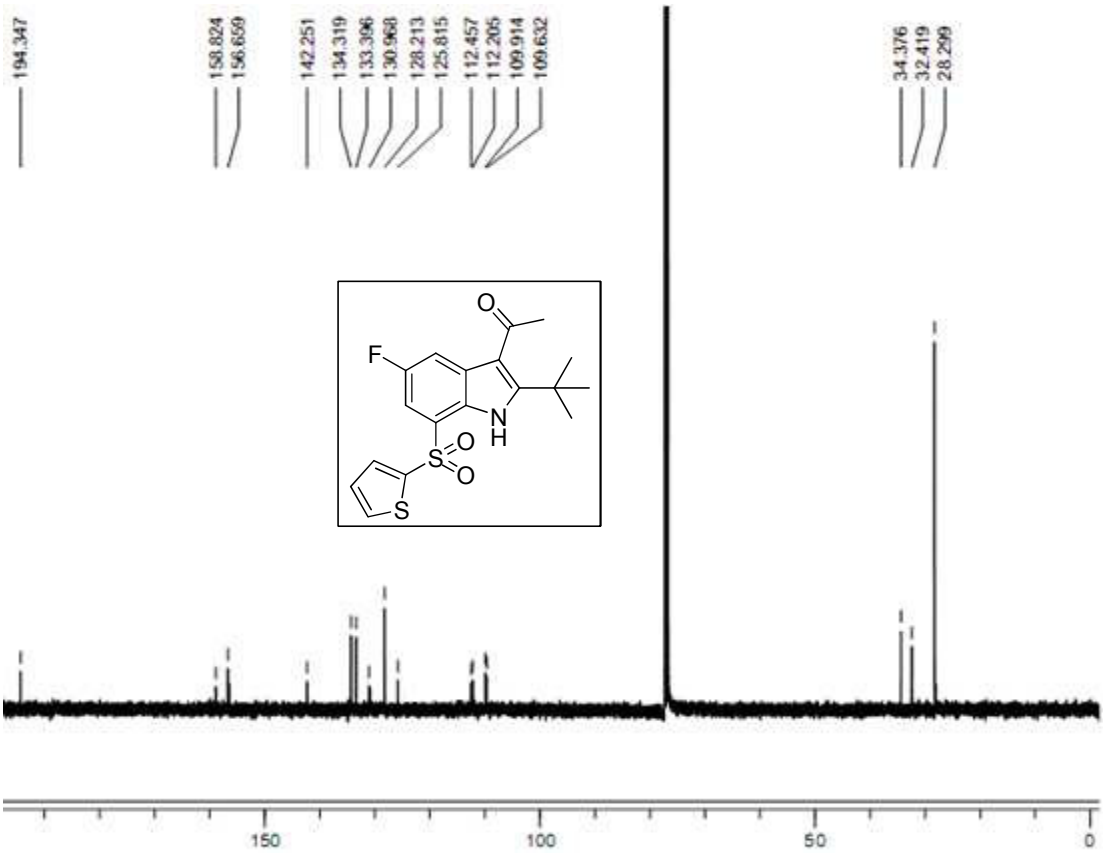
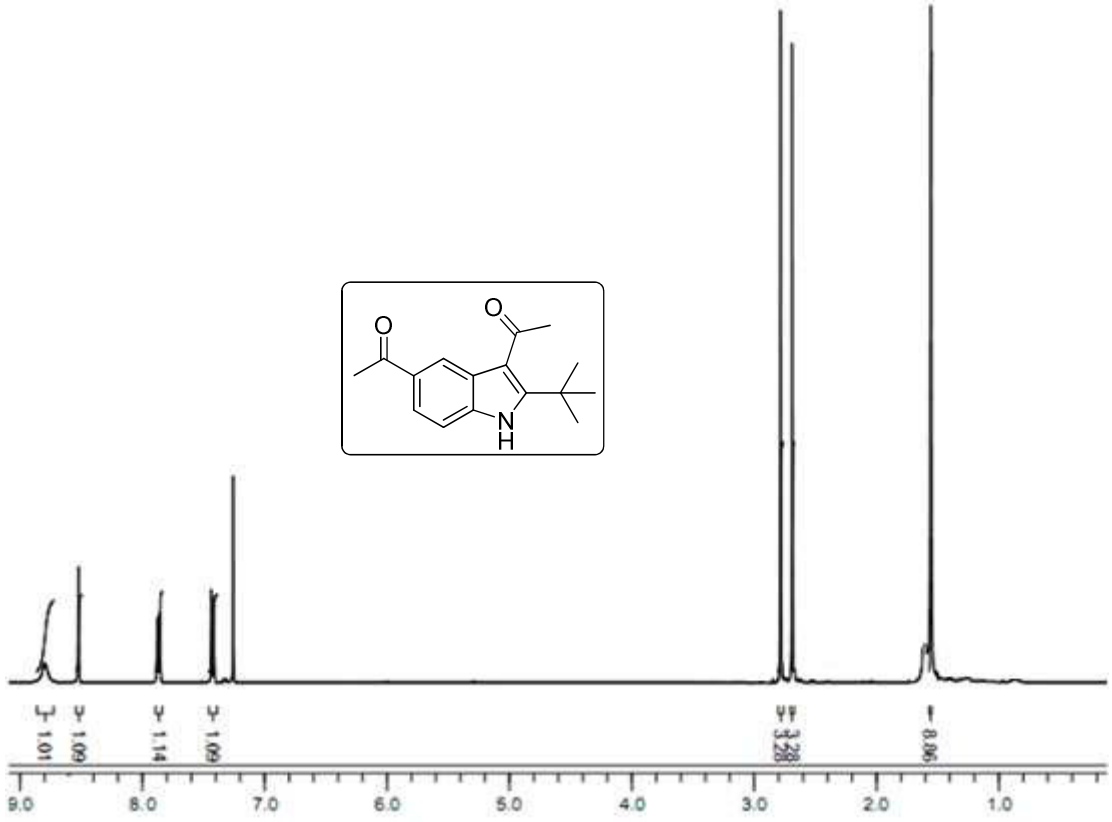
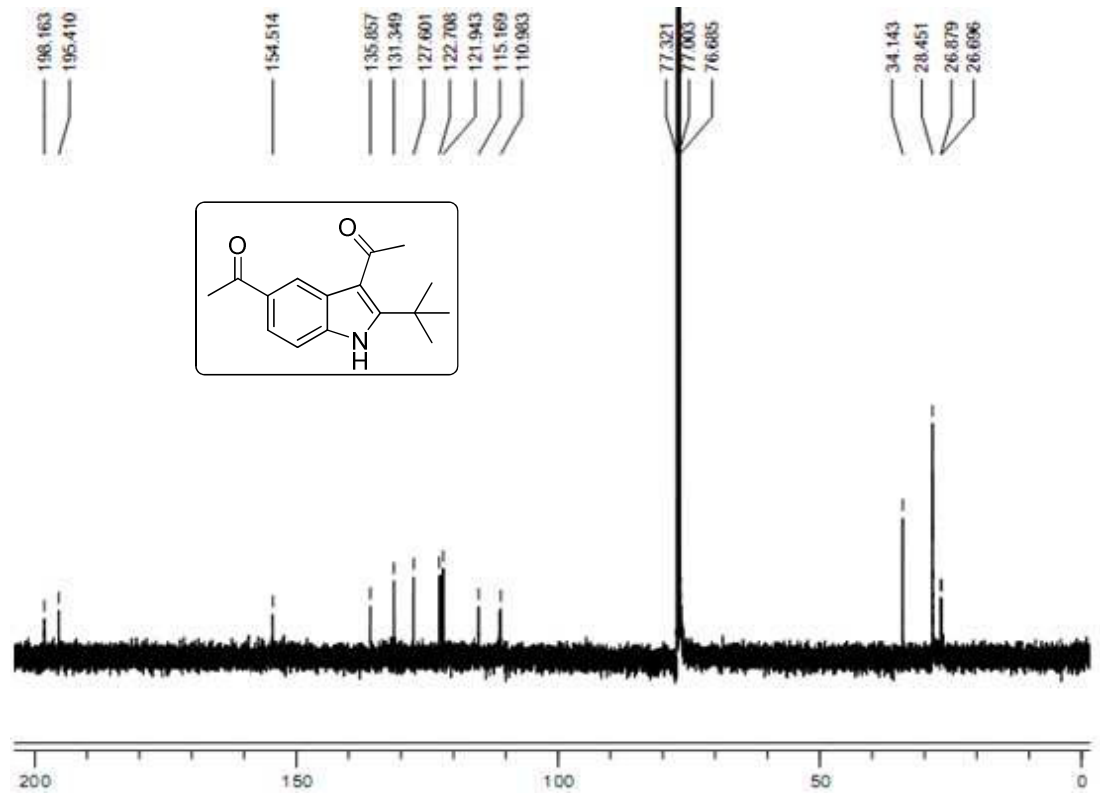


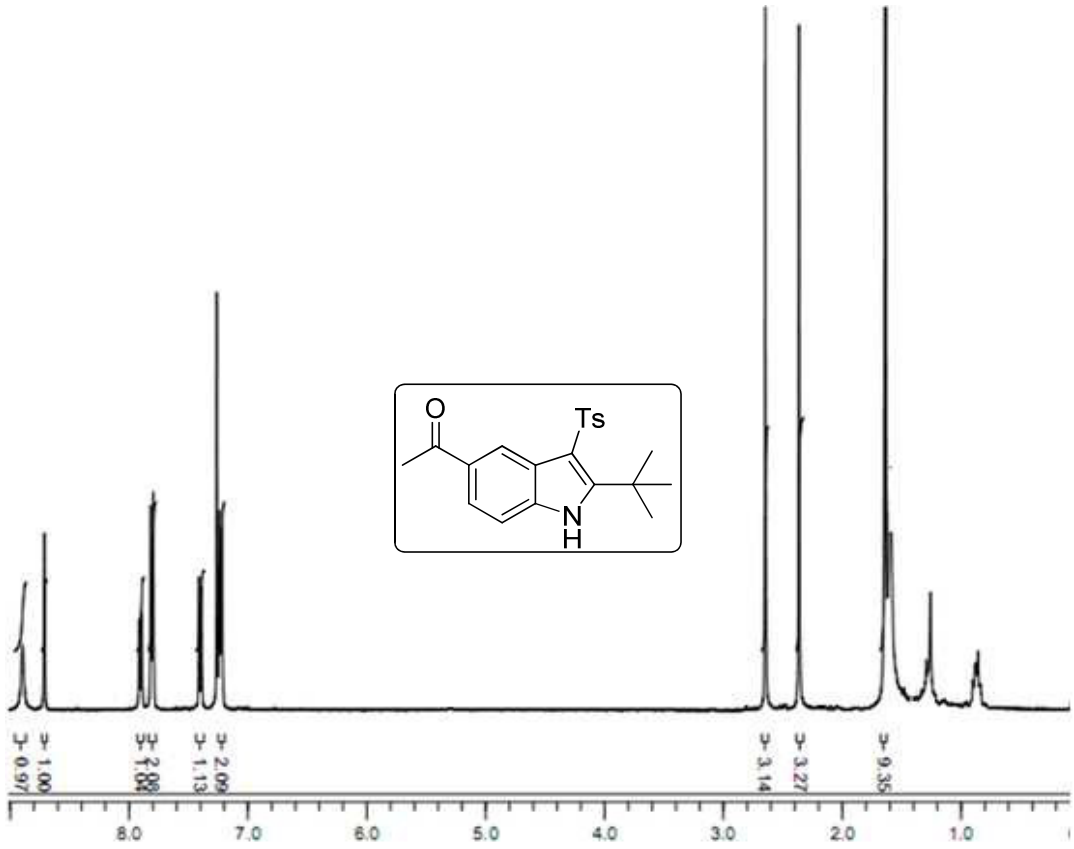
1.26b ^{1}H NMR (400 MHz, $CDCl_3$)



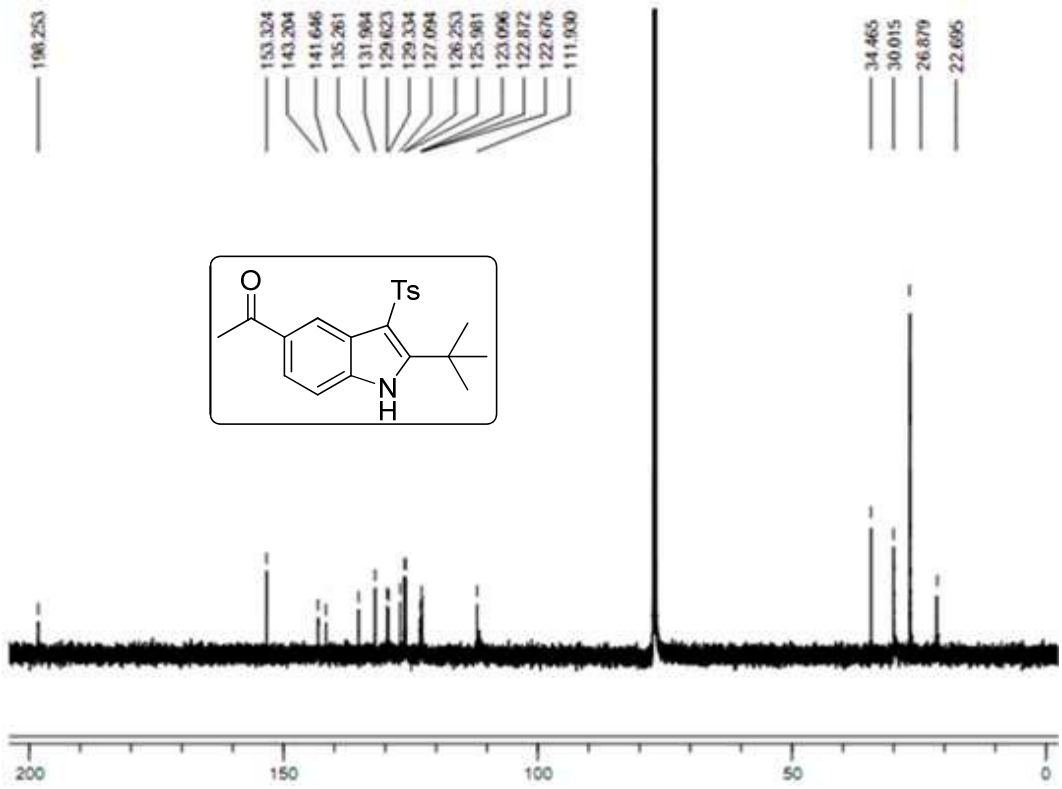
1.26b ^{13}C NMR (100 MHz, $CDCl_3$)



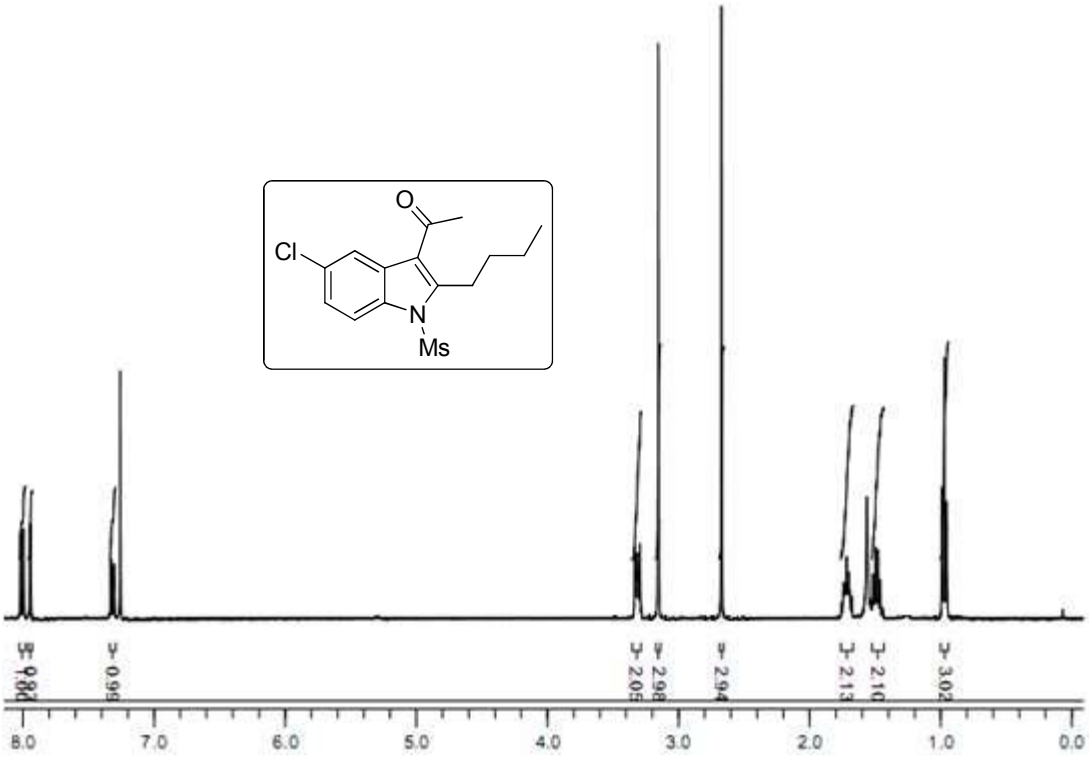
1.27b ^{1}H NMR (400 MHz, $CDCl_3$)



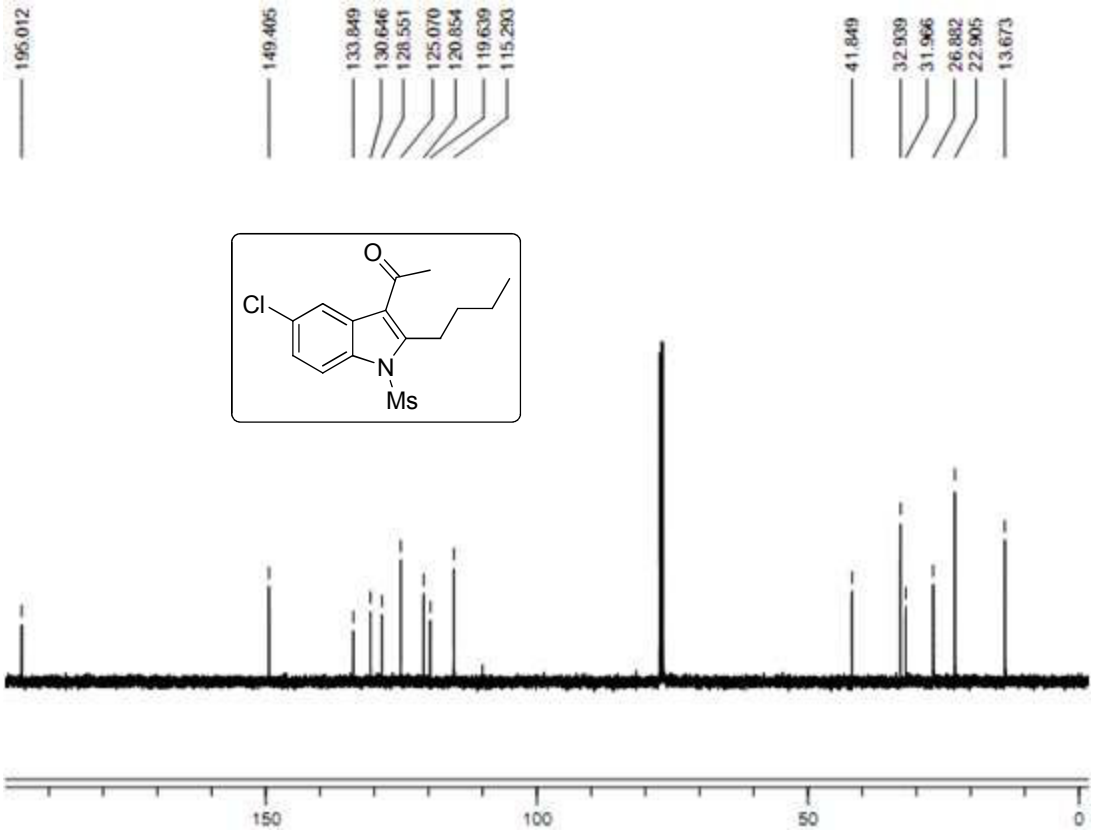
1.27b ^{13}C NMR (100 MHz, $CDCl_3$)



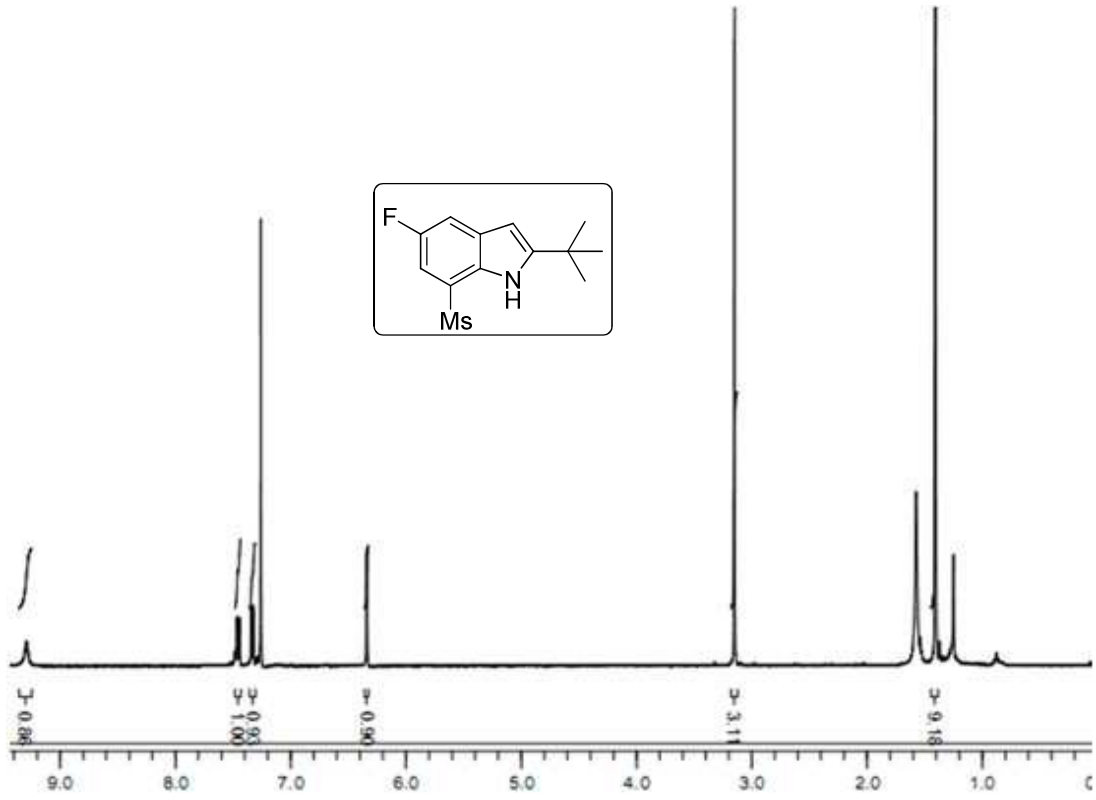
1.28 ^{1}H NMR (400 MHz, $CDCl_3$)



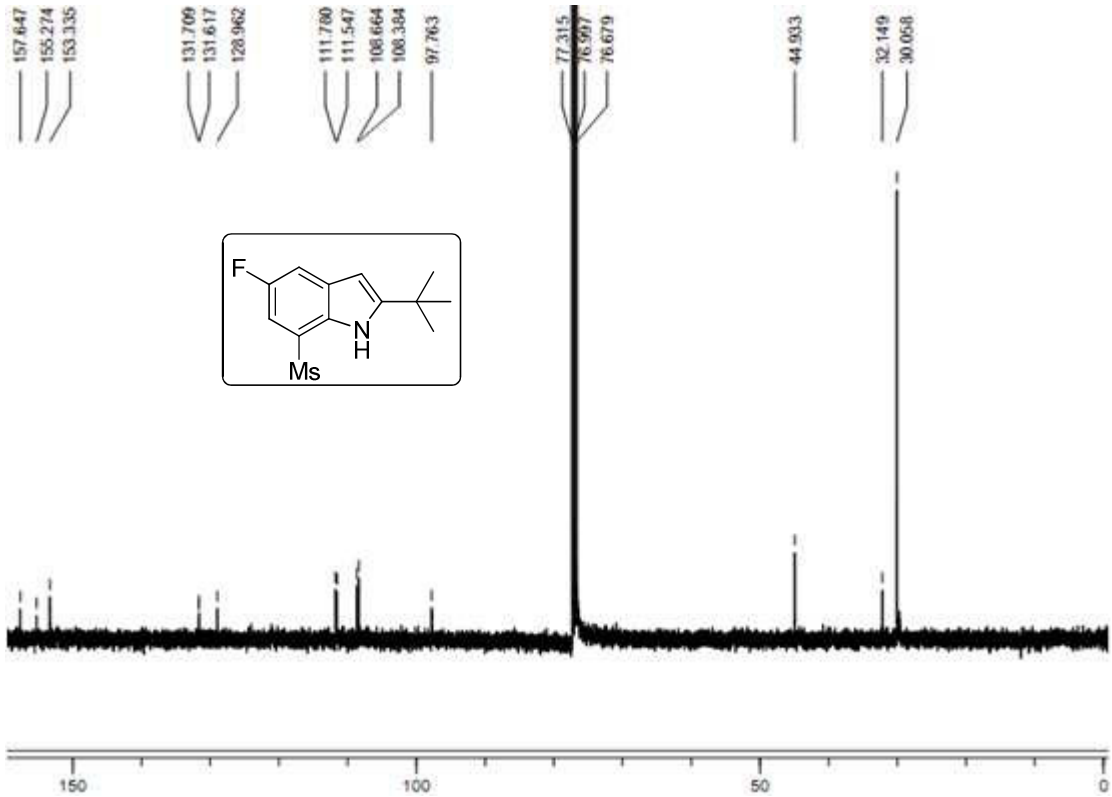
1.28 ^{13}C NMR (100 MHz, $CDCl_3$)



1.29a ^{1}H NMR (400 MHz, $CDCl_3$)

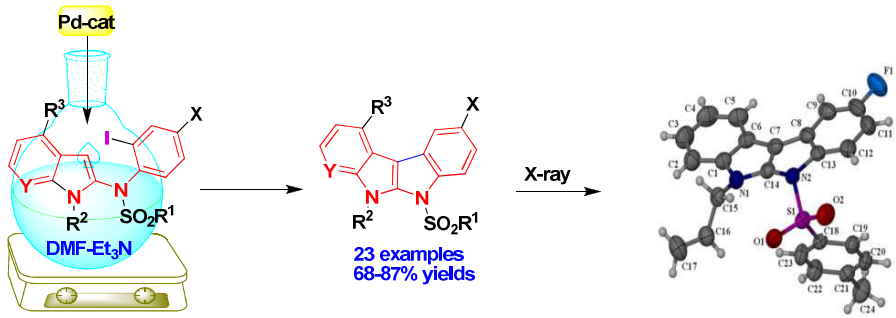


1.29a ^{13}C NMR (100 MHz, $CDCl_3$)



CHAPTER 2

Pd-catalyzed synthesis of indolo[2,3-*b*]indole based *Sir2* inhibitors



2.1 Introduction

The unique structural features and versatile biological activities of fused indoles have made them an attractive target for the development of novel pharmacological lead compounds. Indole alkaloids show different type of biological activities such as cytotoxic, antitumor, antiviral, antimicrobial, antiparasitics, antiserotonin and anti-inflammatory activities.[1,2] The dimeric indole alkaloids with a fused six, seven, or eight-membered ring between two indole rings are known and some of them possessed anticancer activity. The indolo[3,2-*a*]carbazole[3] (**F2.1**, Figure 2.1) with a bis-annelated six-membered ring, displayed antitumor properties. The other examples of bioactive indole fused alkaloids include ellipticine and olivacine. Ellipticine (**F2.2**, Figure 2.1) and olivacine (**F2.3**, Figure 2.1) which contain a pyrido[4,3-*b*]carbazole nucleus, have remarkable antitumour activities.[4] The tetracyclic indoles (**F2.4**, Figure 2.1) and (**F2.5**, Figure 2.1) were found to exhibit *in vitro* activity against human nasopharyngeal carcinoma (HONE-1) and gastricadeno carcinoma (NUGC-3) cell lines.[5] The pyrrolo[2,3-*e*]indole derivative **F2.6** showed *in vitro* cytotoxic activity in PC-3(prostate) cell line (Figure 2.1).[6]

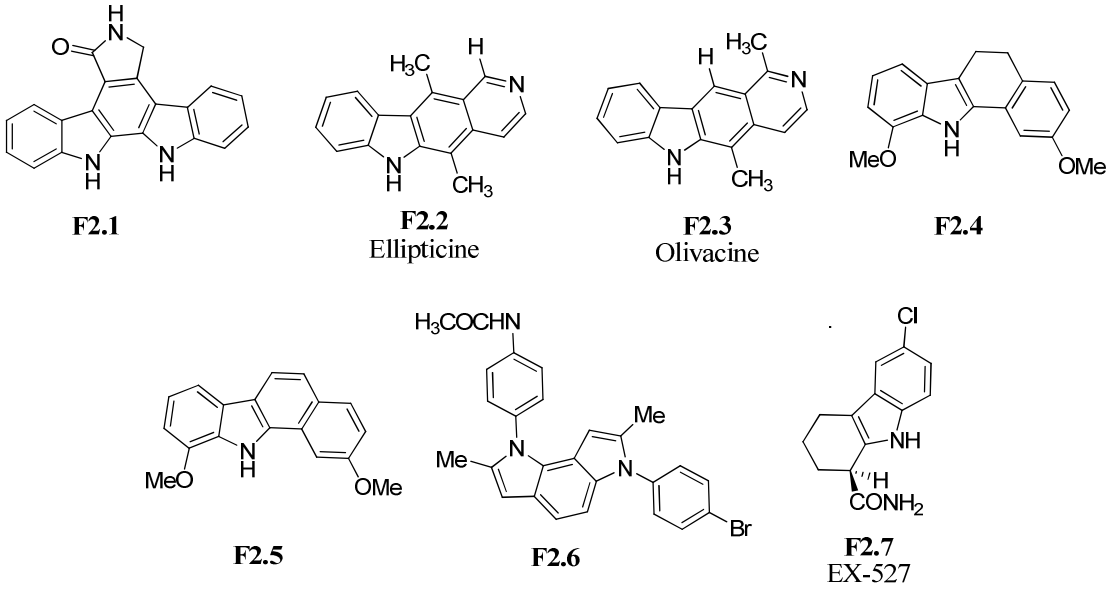
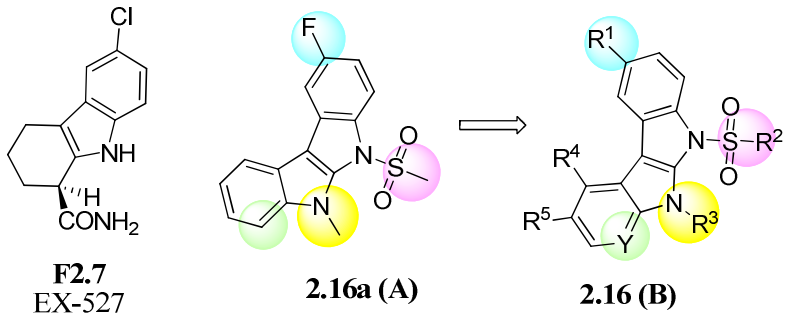


Figure 2.1 Biologically active fused indoles.

The fused indole EX- 527 (**F2.7**) was found to show inhibitory activities against sirtuins (Figure 2.1).[7] The silent information regulator *Sir2* and *Sir2*-like proteins (SIRT1-7, sirtuins) belong to the category of classIII histone deacetylases (HDACs). Their function has been suggested to be related to the aging process[8,9,

[10] and some cancers.[11,12] The sirtuins are known to be up-regulated in various types of cancer and are considered as promising targets for cancer therapeutics.[7,13] Inhibition of sirtuins allows re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells. However, till date only few small molecule inhibitors of *Sir2* have been identified. Thus, more inhibitors are needed to improve the understanding of biological function of SIRT2 and also to explore its possible therapeutic indications. Based on our long term interest for the identification of novel sirtuin inhibitors and the importance of indoles as privileged structural motifs in medicinal chemistry, we designed our target molecule **2.16** (containing indolo[2,3-*b*]indoles) (Figure 2.2) from a known inhibitor EX-527. The designing was based on the *in silico* binding studies of a representative compound **2.16a** in the catalytic pocket of yeast *Sir2* (Figure 2.3). The study showed binding of **2.16a** deep into the active site (docking score -5.8) along with an H-bond interaction of sulfonyl oxygen with the side chain amino group of ASN 35. We envisioned that transition metal mediated intramolecular C-3 arylation of indole **2.15** may lead to our target compounds **2.16/2.16a**.



F2.7
EX-527

2.16a (A)

2.16 (B)

Figure 2.2 Design of **A/B** as novel inhibitors of sirtuins.

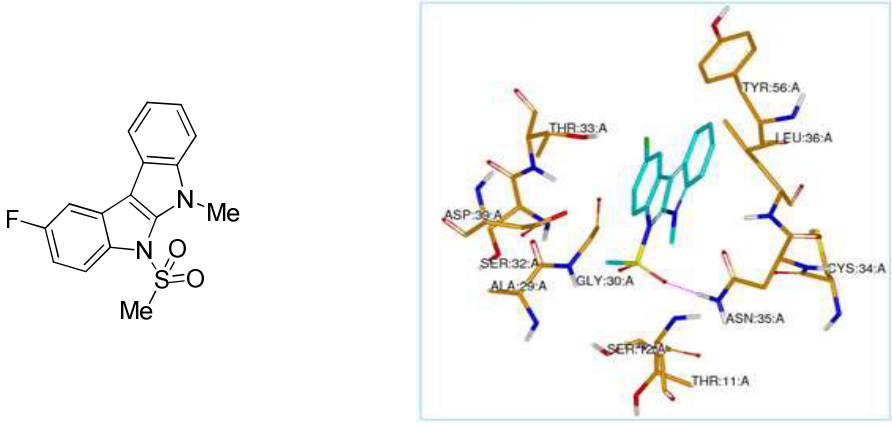
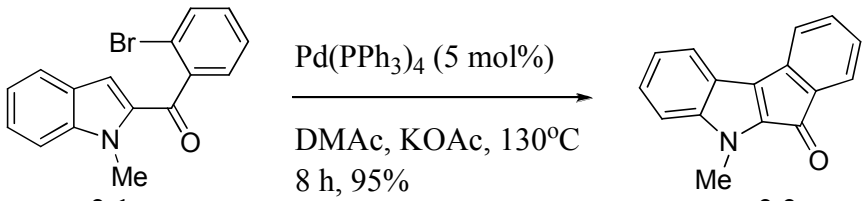


Figure 2.3 Binding mode of **2.16a** in yeast Sir2 (PDBID: 1Q1A).

2.2 Previous work on arylation reaction

In recent years, the intramolecular direct arylation leading to fused heteroaromatics, *via* a radical pathway[14] or transition metal-catalyzed single[15] or double C-H bond activation[16] has attracted particular attention. These methodologies offer a quick access to diverse and complex molecular structures *via* C-C bond forming reactions. Particularly, transition metal catalyzed functionalization of hydrocarbons has emerged as a versatile strategy for C-C bond formation on arene motifs. Among them, palladium catalyzed intramolecular direct C-3 arylation of hetero aromatic compounds with aryl halides by C-H bond activation has become a popular method for generating C–C bonds leading to complex polycyclic ring systems.

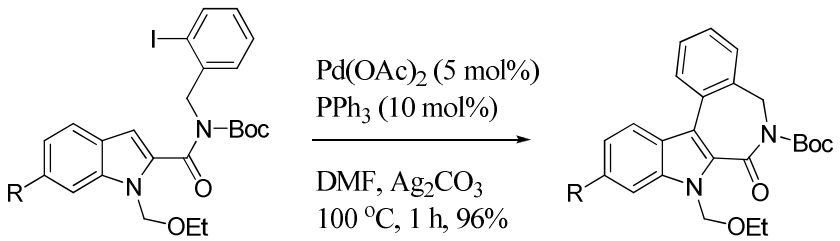
In 1991, Ma and Kozikowski reported the intramolecular cyclization/arylation of an indole substituted by 2-bromo benzoyl at C-2 in the presence of $[Pd(PPh_3)_4]$ as a catalyst and KOAc as a base affording tetracyclic product in 95% yield (Scheme 2.1).[17]



2.1 **2.2**

Scheme 2.1 Synthesis of 5-methylindeno[2,1-*b*]indol-6(5*H*)-one.

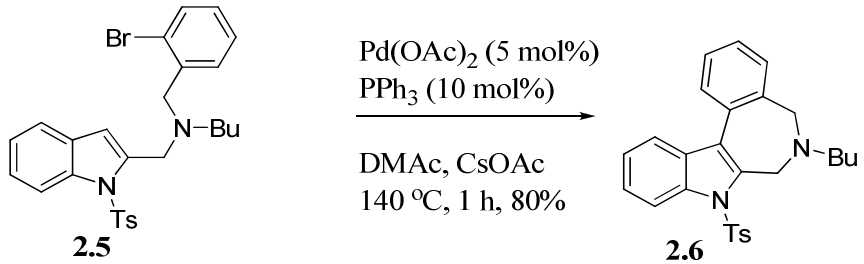
In 2007, Joseph and co-workers reported similar intramolecular cyclization of an indole substituted by 2-iodobenzylcarbamate at C-2 using 5 mol% $Pd(OAc)_2$ and 10 mol% PPh_3 with Ag_2CO_3 as a base resulting in the formation of seven membered ring in 90-96% yield (Scheme 2.2).[18]



2.3 **2.4**

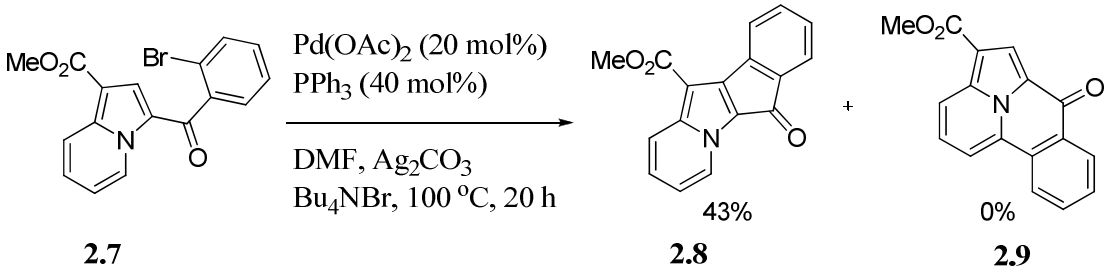
Scheme 2.2 Synthesis of azapine-1-carboxylate.

In 2007, Fujii and co-workers reported another intramolecular arylation using a similar catalyst and CsOAc as base, an indole with a (2-bromobenzyl)-butylamine derivative as 2-substituent gave the dihydrobenzoazepine fused indole in high yield (Scheme 2.3).[19]



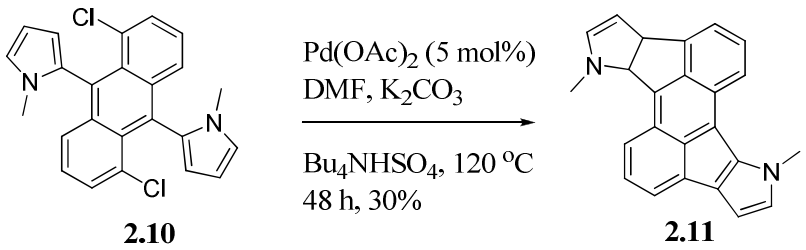
Scheme 2.3 Synthesis of dihydrobenzoazepine.

In 2003, Matsuda and co-workers reported intra molecular cyclization of an indolizine substituted by a 2-bromobenzoyl group at C-2 to give a tetracyclic compound in 43% yield in the presence of $Pd(OAc)_2/PPh_3$ catalyst and Ag_2CO_3 as a base (Scheme 2.4).[20]



Scheme 2.4 Synthesis of indeno[1,2-*b*]indolizine.

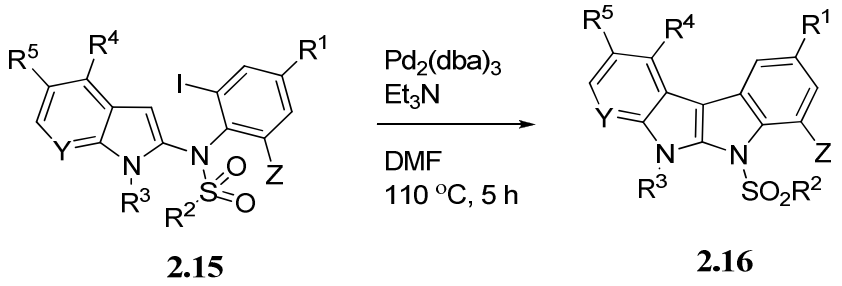
In 1999, Smet and co-workers reported an intramolecular cyclization of 1,5-dichloroanthracene substituted at C-9 and C-10 by two 1-methylpyrrol-2-yl substituents allowed the synthesis of substituted rubicenes (Scheme 2.5).[21]



Scheme 2.5 Synthesis of rubicenes.

2.3 Present work

Though several examples have been reported previously on intramolecular C-3 arylation of indoles leading to polycyclic compounds to the best of our knowledge the use of this strategy leading to indoloindoles is unprecedented. Herein we report Pd-mediated intramolecular cyclization of *N*-(2-iodoaryl)-*N*-(1-alkyl-1*H*-indol-2-yl)alkane/arene/heteroarenesulfonamide **2.15** leading to indolo[2,3-*b*]indoles **2.16** (Scheme 2.6).



2.15 **2.16**

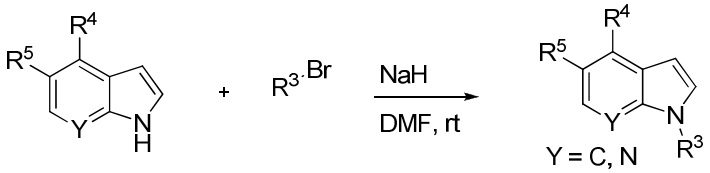
Scheme 2.6 Pd-mediated synthesis of novel indolo[2,3-*b*]indoles.

2.4 Results and discussion

2.4.1 Preparation of starting compounds

The requisite *N*-sulphonated-iodo-anilide **1.1**, derivatives were synthesized as described[22] in Chapter 1.

The other *N*-substituted indole **2.14** derivatives were prepared by reaction of indoles **2.12** with appropriate alkyl bromide/iodides **2.13** in the presence of a base (Scheme 2.7).[23]



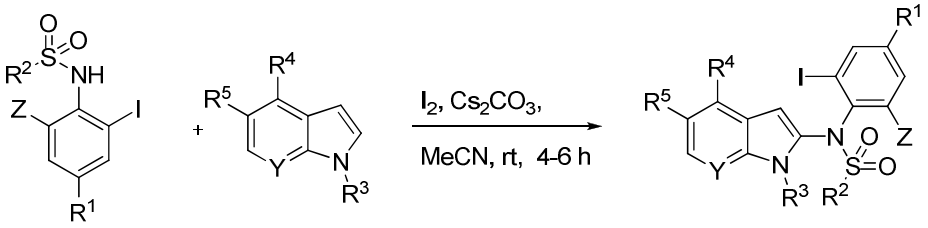
2.12 **2.13** **2.14**

Scheme 2.7 Synthesis of *N*-substituted indoles.

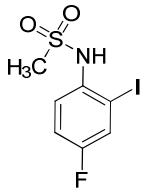
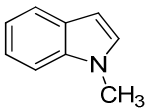
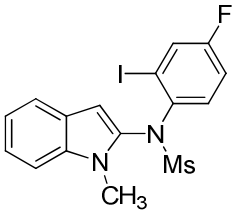
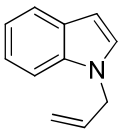
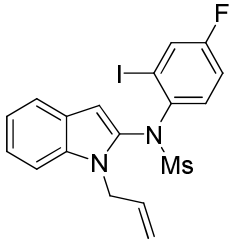
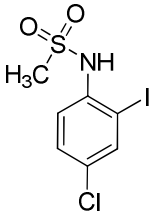
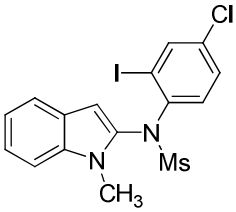
The key starting material **2.15** required for our study was prepared by direct C-2 amination of *N*-substituted indoles (**2.14**) with *N*-sulfonyl arylamines (**1.1**) in the presence of molecular iodine and a base at room temparature. The mild conditions

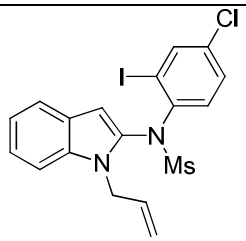
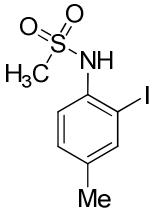
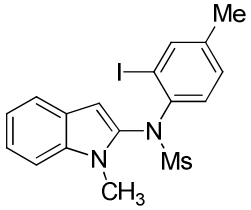
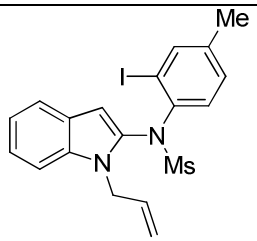
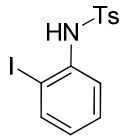
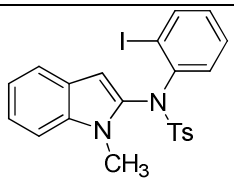
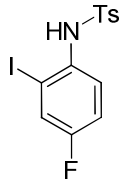
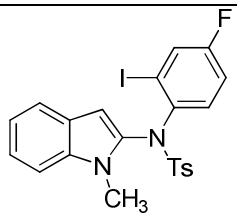
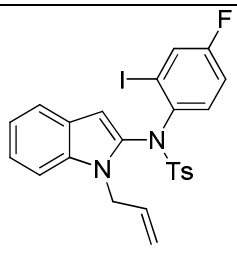
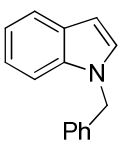
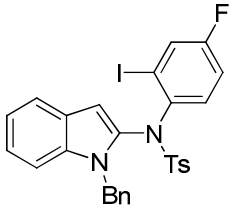
permit a broad set of functionalities both in the indoles and in the *N*-sulfonylbenzenamines. The reaction afforded a variety of indole derivatives **2.15** in moderate to good yields (Table 2.1).

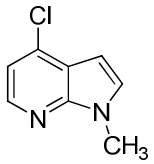
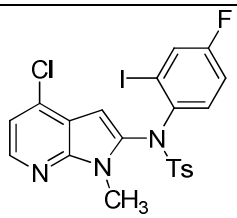
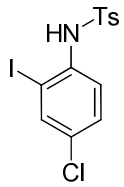
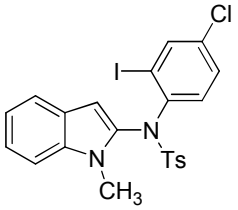
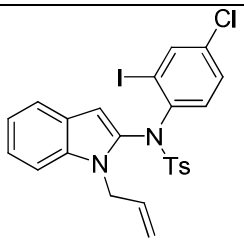
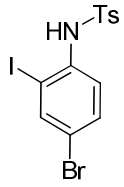
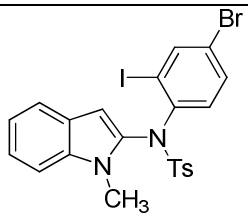
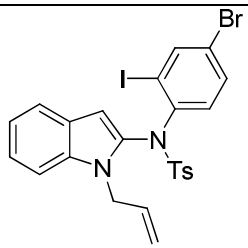
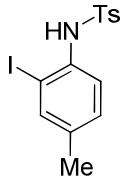
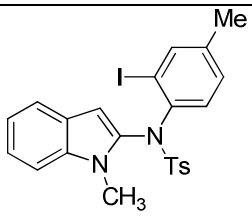
Table 2.1: Iodine mediated synthesis of *N*-(4-substituted-2-iodophenyl)-*N*-(1-alkyl-1*H*-indol-2-yl)alkane/arene/heteroarene sulfonamide.[a]

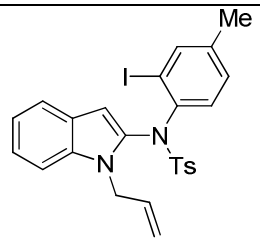
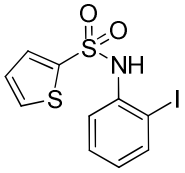
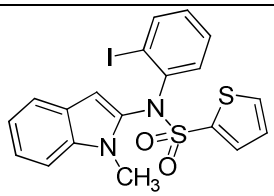
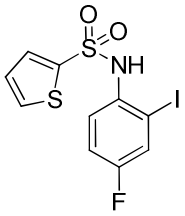
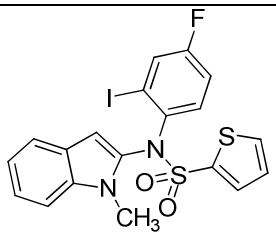
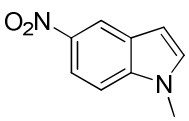
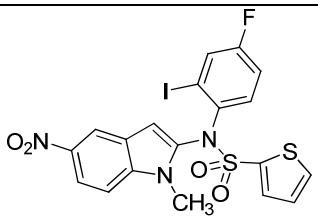
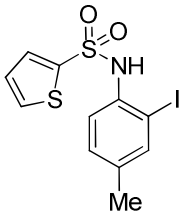
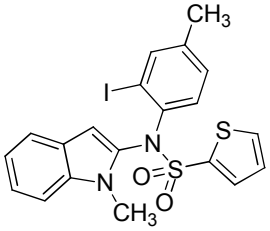
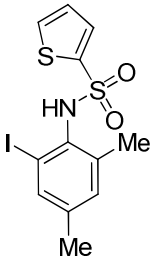
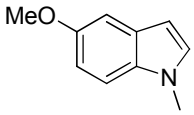
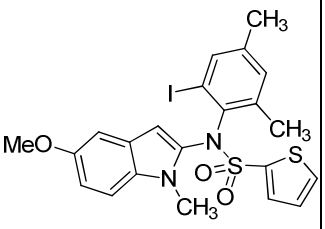


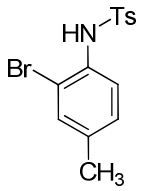
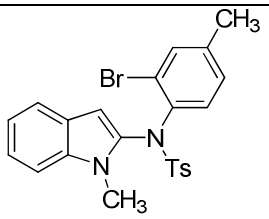
1.1 **2.14** **2.15**

Entry	Iodoanilides (**1.1**)	Indole (**2.14**)	Time[b] /h	Product (**2.15**)	Yield [c](%)
1	 **1.1b**	 **2.14a**	6	 **2.15ba**	60
2	**1.1b**	 **2.14b**	6	 **2.15bb**	61
3	 **1.1c**	**2.14a**	6	 **2.15ca**	62

4	**1.1c**	**2.14b**	6	 **2.15cb**	65
5	 **1.1e**	**2.14a**	4	 **2.15ea**	70
6	**1.1e**	**2.14b**	5	 **2.l5eb**	62
7	 **1.1i**	**2.14a**	4.5	 **2.15ia**	74
8	 **1.1j**	**2.14a**	5	 **2.15ja**	72
9	**1.1j**	**2.14b**	5	 **2.15jb**	64
10	**1.1j**	 **2.14c**	6		58

				2.15jc	
11	**1.1j**	 **2.14k**	6	 **2.15jk**	66
12	 **1.1k**	**2.14a**	4.5	 **2.15ka**	63
13	**1.1k**	**2.14b**	5	 **2.15kb**	58
14	 **1.1s**	**2.14a**	4.5	 **2.15sa**	62
15	**1.1s**	**2.14b**	6	 **2.15sb**	61
16	 **1.1l**	**2.14a**	4	 **2.15la**	75

17	**1.1l**	**2.14b**	6	 **2.15lb**	61
18	 **1.1n**	**2.14a**	5	 **2.15na**	76
19	 **1.1o**	**2.14a**	5	 **2.15oa**	75
20	**1.1o**	 **2.14i**	6	 **2.15oi**	55
21	 **1.1r**	**2.14a**	5	 **2.15ra**	75
22	 **1.1t**	 **2.14h**	6	 **2.15th**	65

23	 **1.1u**	**2.14a**	6	 **2.15ua**	80

[a]All the reactions were carried out using **1.1** (1.0 mmol), **2.14** (1.2 mmol), I_2 (1.0 mmol) and Cs_2CO_3 (1.5 mmol) in acetonitrile (5.0 mL), at room temperature under nitrogen.

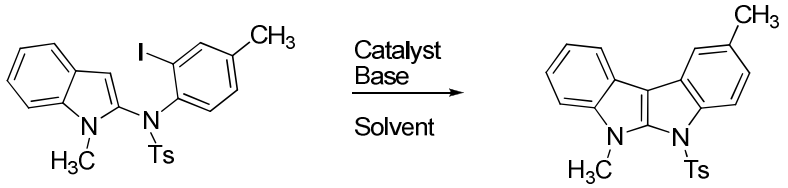
[b]After adding indole **2.14**.

[c]Isolated yield.

2.4.2 Reaction optimisation

Initially, we examined the intramolecular cyclization of *N*-(2-iodoaryl)indole derivative **2.15lb** in the presence of $Pd_2(dba)_3$ and K_2CO_3 in various solvents like MeCN, 1,4-dioxane and toluene when the desired product **2.16p** was isolated in low yield (entries 1-3, Table 2.2). The yield was improved when DMF was used (entries 4 and 5, Table 2) along with Et_3N (entry 5, Table 2.2). The use of lower quantity of catalyst decreased the product yield (entry 6, Table 2.2). The use of other Pd-catalyst e.g. $Pd(OAc)_2$ along with a ligand also afforded **2.16p** in good yield (entries 7-9, Table 2.2) whereas the use of Cu-catalysts was found to be ineffective (entries 10 and 11, Table 2.2). The use of 2-bromo derivative instead of **2.15lb** was less effective (entry 12, Table 2.2). Even though entries 5, 7, 8 and 9 gave desired product in good yields, we chosen entry 5 ($Pd_2(dba)_3$ catalyst and Et_3N as base in DMF) as the optimum condition to avoid additional use of ligands.

Table 2.2. Effect of conditions on intramolecular cyclization of **2.15lb**.



2.15lb **2.16p**

Entry	Catalyst	Base	Solvent	Time (h)	Yield[b] (%)
1	$Pd_2(dba)_3$	K_2CO_3	MeCN	10	25[c]
2	$Pd_2(dba)_3$	K_2CO_3	1,4dioxane	10	40[d]
3	$Pd_2(dba)_3$	K_2CO_3	Toulene	10	40[e]

4	$Pd_2(dba)_3$	K_2CO_3	DMF	5	75
5	$Pd_2(dba)_3$	Et_3N	DMF	5	85
6	$Pd_2(dba)_3$	Et_3N	DMF	5	50[f]
7	$Pd(OAc)_2$, X-Phos	Et_3N	DMF	4	80
8	$Pd(OAc)_2$, P(*o*-tol)$_3$	Et_3N	DMF	4	82
9	$Pd(OAc)_2$, PPh_3	Et_3N	DMF	4	81
10	$Cu(OAc)_2$	Et_3N	DMF	10	0
11	CuI	Et_3N	DMF	10	0
12	$Pd_2(dba)_3$	Et_3N	DMF	12	38[g]

[a]Reaction conditions: **2.15lb** (1.0 mmol), Pd-catalyst (5.0 mol%) and Et_3N (2.5 mmol) in solvent (2.0 mL) at 130 °C.

[b]Isolated yield.

[c]The reaction was performed at 80 °C.

[d]The reaction was performed at 100 °C.

[e]The reaction was performed at 110 °C.

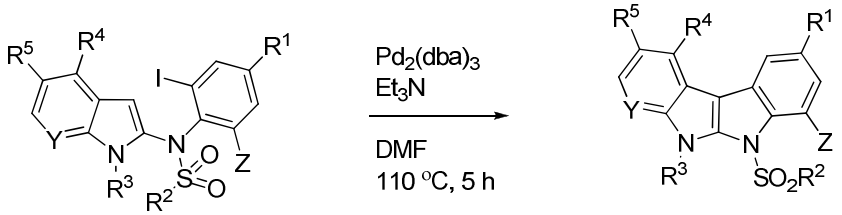
[f]2.5 mol% catalyst was used.

[g]*N*-(2-bromo-4-methylphenyl)-4-methyl-*N*-(1-methyl-1*H*-indol-2-yl)benzenesulfonamide (**2.15ua**) was used in place of **2.15lb**.

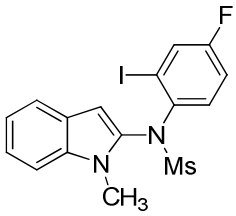
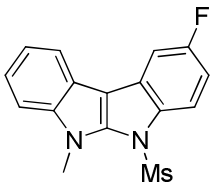
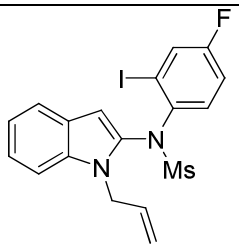
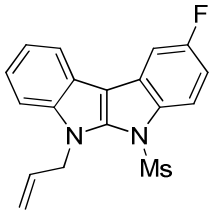
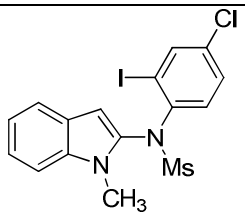
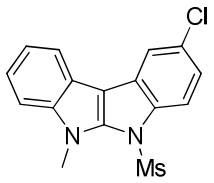
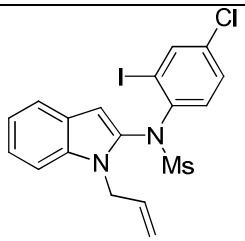
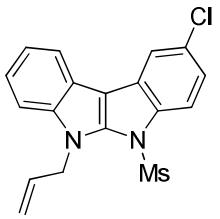
2.4.3 Scope of the reaction

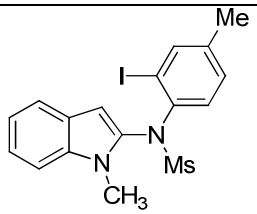
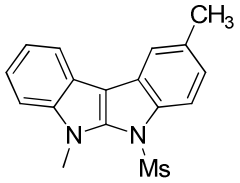
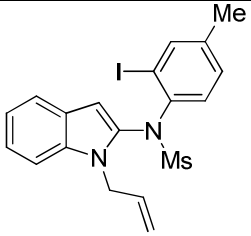
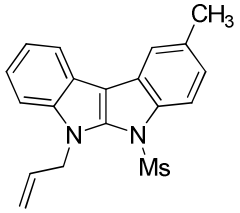
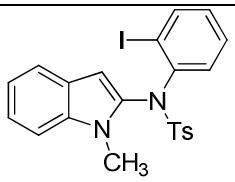
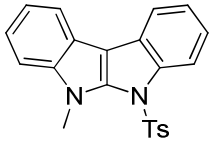
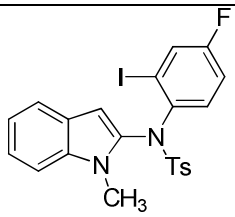
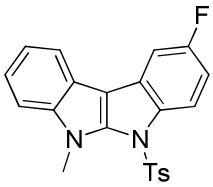
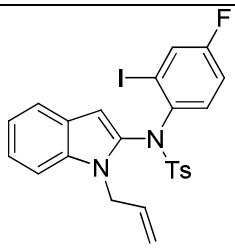
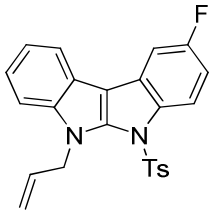
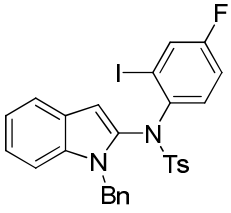
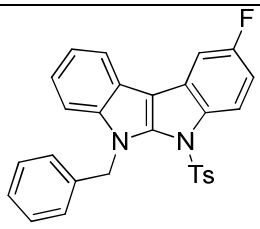
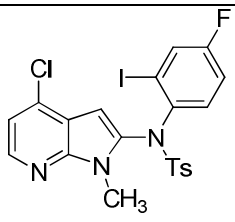
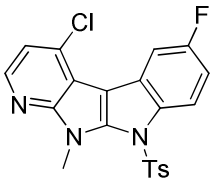
We then investigated the substrate scope and generality of this methodology (Table 2.3). Substituents like Me, allyl, and benzyl on the indole nitrogen and Me, F, Cl and Br on the *N*-aryl ring of **2.15** were well tolerated. Additionally, compound **2.15** containing *N*-alkyl (entries 1-6, Table 2.3), aryl (entries 7-17, Table 2.3), and heteroaryl (entries 18-22, Table 2.3) sulfonyl groups participated well in the present reaction afforded good yields. The Cl and Br present in **2.15** were also well tolerated (entries 3, 4, 12-15, Table 2.3) and the reaction was successful with azaindole **2.15jk** (entry 11, Table 2.3). The generality of this methodology was demonstrated further by synthesizing 8-methoxy-1,3,5-trimethyl-2-(thiophen-2-ylsulfonyl)-1,2-dihydroindolo [2,3-*b*]indole (**2.16v**) and 5-fluoro-1-methyl-8-nitro-2-(thiophen-2-ylsulfonyl)-1,2-dihydroindolo[2,3-*b*]indole (**2.16t**) in 74 and 68% yield, respectively.

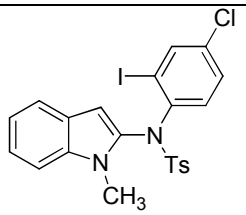
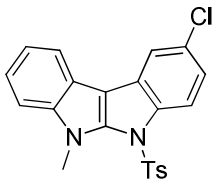
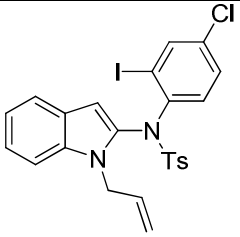
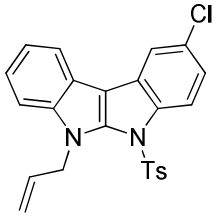
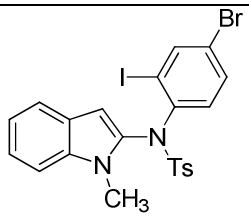
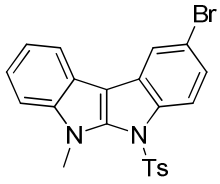
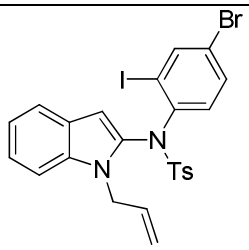
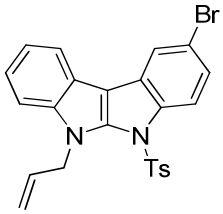
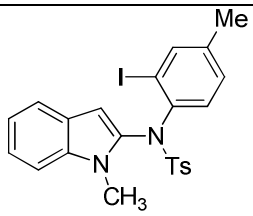
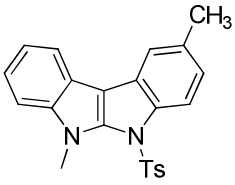
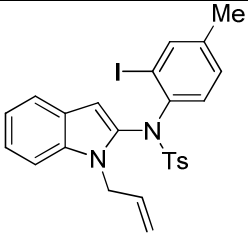
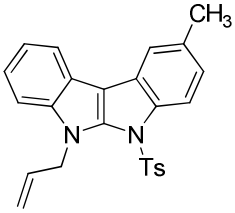
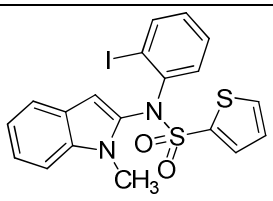
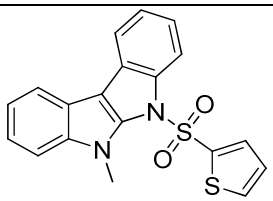
Table 2.3 Pd catalyzed synthesis of 2-substituted-6-methyl-5-(alkyl/aryl/hetero-aryl sulfonyl)-5,6-dihydroindolo[2,3-*b*]indole[a].

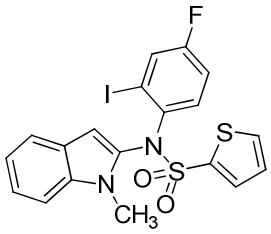
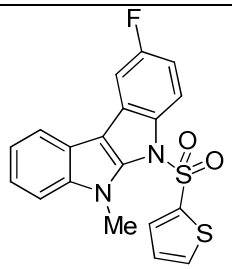
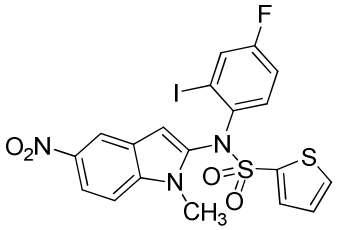
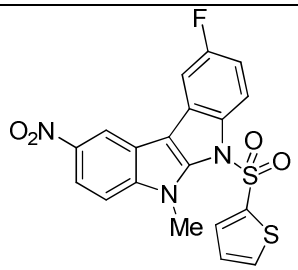
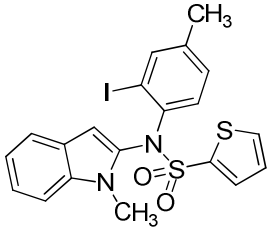
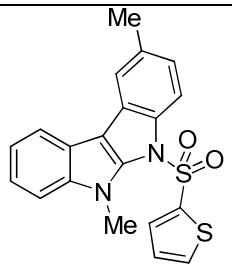
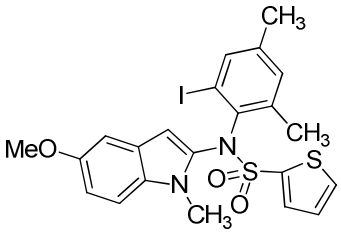
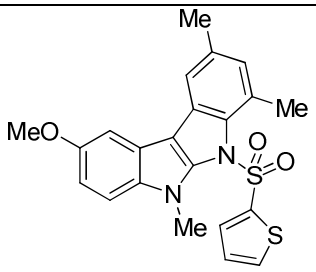
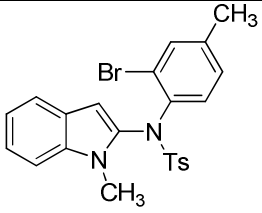


2.15 2.16

Entry	Iodo compound (**2.15**)	Product (**2.16**)	Yield[b](%)
1	 **2.15ba**	 **2.16a**	78
2	 **2.15bb**	 **2.16b**	70
3	 **2.15ca**	 **2.16c**	76
4	 **2.15cb**	 **2.16d**	78

5	 **2.15ea**	 **2.16e**	80
6	 **2.l5eb**	 **2.16f**	74
7	 **2.15ia**	 **2.16g**	83
8	 **2.15ja**	 **2.16h**	85
9	 **2.15jb**	 **2.16i**	76
10	 **2.15jc**	 **2.16j**	75
11	 **2.15jk**	 **2.16k**	70

12	 **2.15ka**	 **2.16l**	81
13	 **2.15kb**	 **2.16m**	70
14	 **2.15sa**	 **2.16n**	68
15	 **2.15sb**	 **2.16o**	69
16	 **2.15la**	 **2.16p**	85
17	 **2.15lb**	 **2.16q**	78
18			80

	2.15na	**2.16r**	
19	 **2.15oa**	 **2.16s**	84
20	 **2.15oi**	 **2.16t**	68
21	 **2.15ra**	 **2.16u**	87
22	 **2.15th**	 **2.16v**	74
23	 **2.15ua**	**2.16p**	45[c]

[a]Reaction conditions: **2.15** (1.0 mmol), $Pd_2(dba)_3$ (5 mol%) and Et_3N (2.5 mmol) in DMF (5 mL) at 130 °C for 5 h under N_2.

[b]Isolated yield.

[c]after 12 h 60% conversion.

All the compounds synthesized were well characterized by spectral (NMR, IR and MS) data and the molecular structure of a representative compound **2.16i** was confirmed unambiguously by single crystal X-ray diffraction study (Figure 2.4).[24]

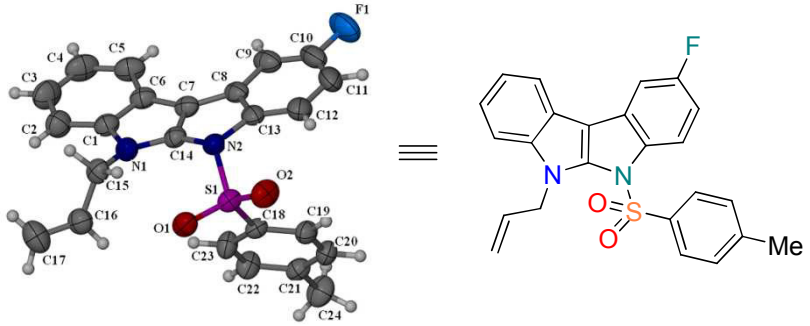
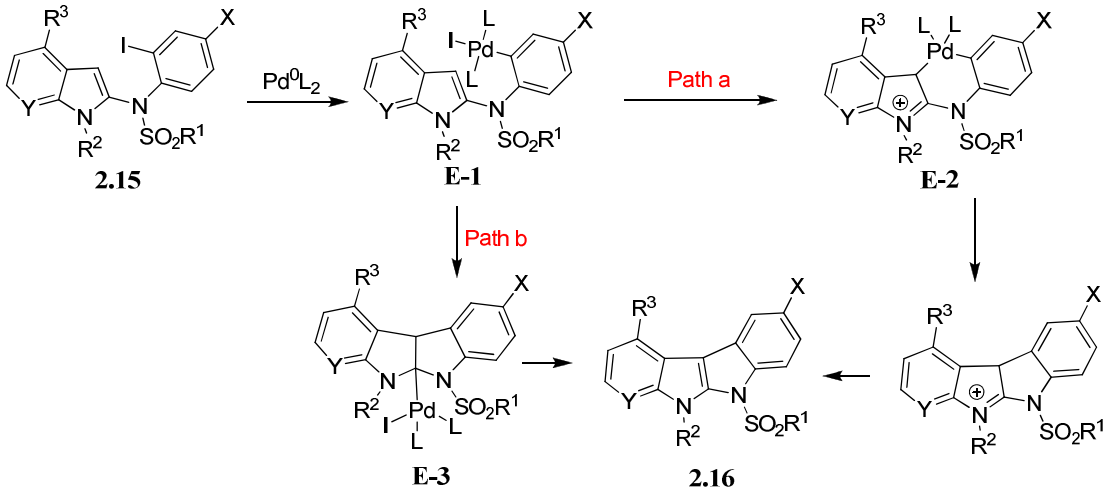


Figure 2.4 ORTEP representation of the **2.16i** (Thermal ellipsoids are drawn at 50% probability level).

2.4.4 Proposed mechanism

Based on our observations a proposed reaction mechanism is presented in Scheme 2.8. The first step of the catalytic cycle was the oxidative addition of palladium (0) into the aryl halide bond to afford the organo-Pd(II) species **E-1**. Then, the intramolecular cyclization reaction might follow one of two pathways e.g. Path a or Path b. The Path a involved electrophilic aromatic substitution (SEAr) at the metal[25] to give the **E-2** complex. A reductive elimination of Pd from **E-2** followed by aromatization afforded **2.16.** The path b i.e. Heck coupling seems less likely[26] as the syn-carbopalladation of the indole double bond would lead to the trans-fused intermediate **E-3** possessing unfavorable ring-strain.



Scheme 2.8 The proposed reaction mechanism.

2.5 Pharmacology

2.5.1 *Invitro* data

All the compounds synthesized were tested at 50 µM initially for their ability to inhibit yeast sirtuin family NAD-dependent histone deacetylase (HDAC) *Sir2* protein. A known inhibitor Splitomicin was used as a reference compound in this yeast cell based reporter silencing assay. The compounds (**2.16**) were tested for the inhibition of growth of yeast cells containing Ura3 gene at telomeric locus, in presence of 5-fluoroorotic acid (5-FOA).[27] A compound having the sirtuin inhibitory effect would inhibit the *Sir2* protein, and thus the URA3 gene would be de-repressed resulting the death of the yeast cell inpresence of 5-FOA. A parallel screen was performed in the absence of 5-FOA to check the cytotoxicity of the compounds. Among all the compounds tested **2.16a**, **2.16h** (or **A**, Fig. 1) and **2.16p** showed significant inhibition (> 40%) in the presence of 5-FOA and no significant toxic effect in the absence of 5-FOA.

2.5.2 *In silico* studies

The binding pose of inhibitors **2.16a** in the catalytic pocket of yeast *Sir2* was shown in Figure 2.3. In its docked conformation oxygen from sulfonyl group of inhibitor **2.16a** makes hydrogen bond interaction with the side chain amino group of ASN 35. This same kind of interaction was observed between inhibitor **2.16p** and yeast *Sir2* (Figure 2.5). Due to the presence of smaller substituent (N-Ms), inhibitor **2.16a** was found entering deep into the active site (Figure 2.6). Whereas, the presence of bulky group (N-Ts) group had restricted the entry of inhibitors **2.16p** and therefore it enters partially in to the catalytic site (Figure 2.6). The docking results for the compounds are given in Table 2.4, which are ranked on the basis of their chemguass4 docking scores.

Table 2.4 Docking results

Molecules	Dock score[a]	Steric	Protein desolvation	Ligand desolvation H-bond	Clash	Ligand desolvation	Hydrogen bond
2.16p	-6.0	-11.7	4.8	-0.18	0.54	1.02	-0.62
2.16a	-5.8	-10.6	4.2	-0.23	0.24	0.97	-0.44

[a] FRED Chemgauss4 score

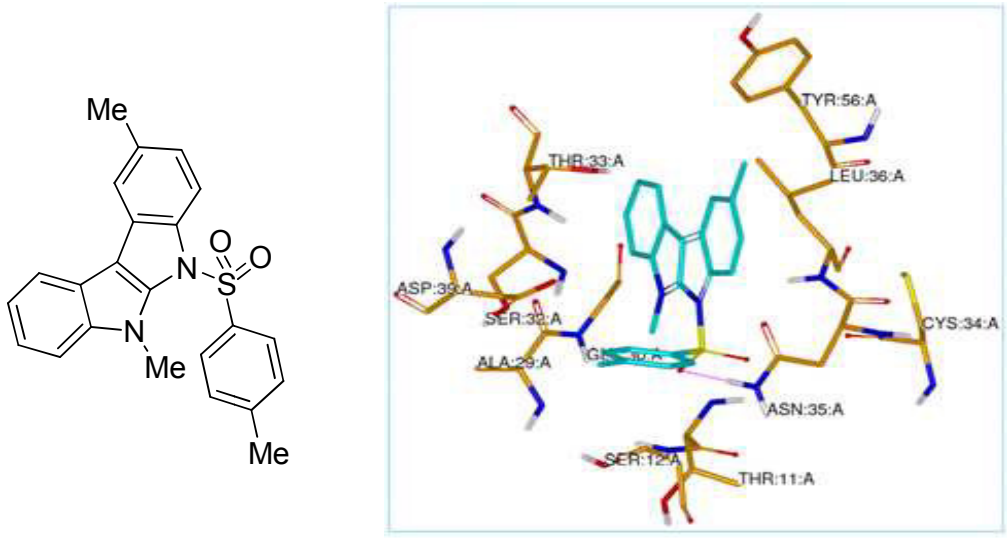
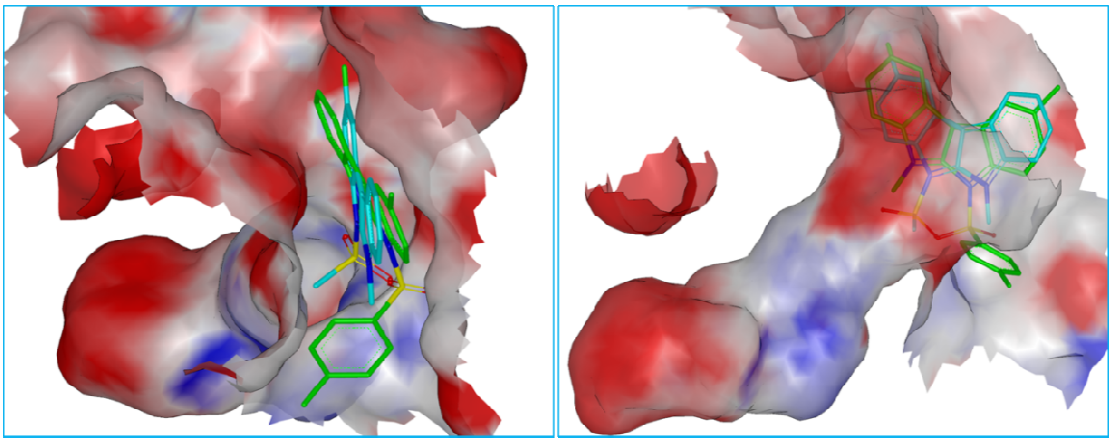


Figure 2.5 Binding mode of **2.16p** in yeast Sir2 (PDBID: 1Q1A), showing hydrogen bonding with ASN 35



a b

Figure 2.6: a) Front view of inhibitor **2.16a** (cyan) and **2.16p** (green)bound at yeast Sir2 active site b) Lateral view of inhibitor bound **2.16a** (cyan) and **2.16p** (green)bound at yeast Sir2 active site. The protein was represented as surface and mapped with electrostatic property (blue = positive potential, red = negative potential)

2.6 Conclusions

In this study, we have designed novel inhibitors of *Sir2* from a known inhibitor using *in silico* studies. Thus, functionalized indolo[2,3-*b*]indoles were designed and synthesized first time as novel and unique class of heteroaromatics. In fact, the synthesis of indolo[2,3-*b*]indoles were carried out using an efficient, new and versatile Pd-mediated intermolecular C-3 arylation reaction. The synthesized

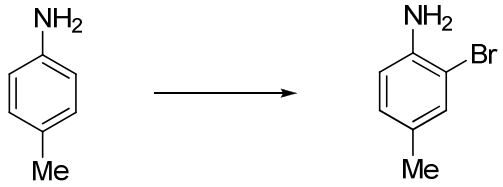
compounds were then tested for *sir2* in vitro. Thus the unique class of indolo[2,3-*b*]indoles described here can be useful as potential inhibitors of sirtuins.

2.7 Experimental Section

2.7.1 Chemistry

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution by using a 400 MHz spectrometer. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT- IR spectrometer. MS spectra were obtained on a Agilent 6430 series Triple Quard LC-MS / MS spectrometer. Melting points (mp) were by using BuchiB-540 melting point apparatus.

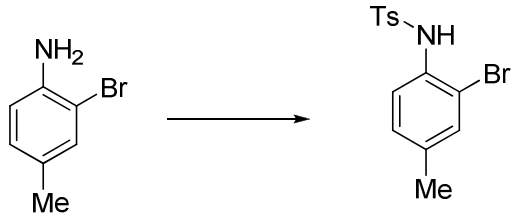
2.7.1.1 Procedure for the preparation of 2-bromo-4-methylaniline:[28]



1.21 **1.22**

To a suspension of activated aromatic compound (**1.21**) (1 mmol) in PEG-400 (2 mL), NBS (1.05 mmol) was added slowly, and the mixture was stirred at room temperature. The reaction was monitored by thin-layer chromatography (TLC). After completion, the mixture was poured onto water (10 ml) and extracted with EtOAc (3x10 ml). The combined extract was concentrated, and the residue was subjected to column chromatography (silicagel, hexane–EtOAc) to obtain pure mono brominated product (**1.22**).

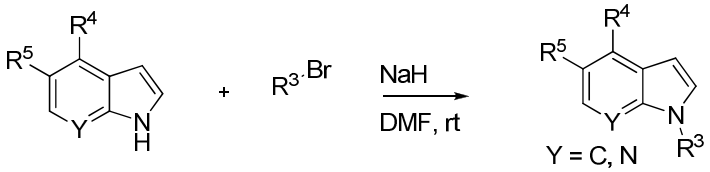
2.7.1.2 Procedure for the preparation of *N*-(2-bromo-4-methylphenyl)-4-methyl-benzenesulfonamide:[23]



1.22 **1.1u**

To a mixture of aniline (**1.22**) (1 equiv) and pyridine (6 equiv) in dichloromethane was added *p*-toluensulfonyl chloride portion wise under ice-bath. The mixture was warmed to room temperature and stirred overnight, then diluted with DCM, washed with dilute hydrochloric acid (3 M) and brine (100 mL), dried over Na_2SO_4 and volatiles were removed and purified by flash chromatography on silica gel to give the product (**1.1u**).

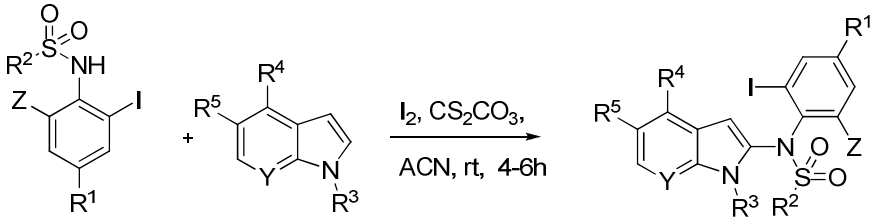
2.7.1.3 General Procedure for the preparation of *N*-substituted indole 2.14:



2.12 **2.13** **2.14**

To a solution of indole (1.0 mmol) in DMF (10 mL) was added NaH (1.5 mmol) at 0 °C. The reaction mixture was stirred for 10 min then corresponding halide (1.2 mmol) was added and stirred for 3 h at room temperature. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with ice cold water (5 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate–hexane to give the desired product (**2.14**).[23]

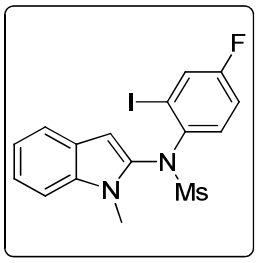
2.7.1.4 General procedure for the preparation of *N*-(4-substituted-2-iodophenyl)-*N*-(1-alkyl-1*H*-indol-2-yl)alkane/arene/heteroarene sulfonamide (2.15):



1.1 **2.14** **2.15**

To a mixture of *N*-(2-iodophenyl)methane/4-methylbenzene/thiophene-2-sulfonamide derivative **1.1** (1.0 mmol)**,** Cs_2CO_3 (1.5mmol), I_2 (1mmol) in acetonitrile (2.5 mL) was added indole derivative **2.14** (1.2 mmol). Then the mixture was stirred at room temperature under nitrogen for 4-6 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with a saturation solution of $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate–hexane to give the desired product (**2.15)** with 58-76% yields.

2.7.1.4.1 *N*-(4-fluoro-2-iodophenyl)-*N*-(1-methyl-1*H*-indol-2-yl)methane-sulfonamide (2.15ba)

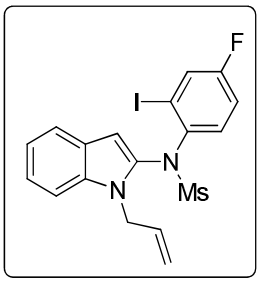


2.15ba was prepared *via* the reaction of **1.1b** with **2.14a** according to the general procedure as mentioned above.

Off white solid; yield: 60%; mp: 165-167 °C; R_f (10% EtOAc-*n*-Hexane) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.67 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.32-7.28 (m, 2H), 7.17-7.10 (m, 2H), 6.92 (s, 1H), 3.97 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5 (d, C-F *J* = 253.8 Hz), 138.6 (d, C-F *J* = 3.4 Hz), 135.5, 134.1, 131.7 (d, C-F *J* = 8.9 Hz), 128.1 (d, C-F *J* = 24.4 Hz), 125.7, 123.1, 121.0, 120.3, 116.6 (d, C-F *J* = 22.3 Hz), 109.9, 100.9, 100.8 (d, C-F *J* = 8.6 Hz), 39.2, 31.5; HPLC: 98.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV

210 nm, retention time 4.25 min; IR (KBr, cm^{-1}): 3065, 2960, 1473, 1343; MS (ES mass): *m/z* 444.8 (M+1).

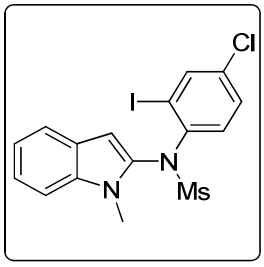
2.7.1.4.2 *N*-(1-allyl-1*H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)methanesulfonamide (2.15bb)



2.15bb was prepared *via* the reaction of **1.1b** with **2.14b** according to the general procedure as mentioned above.

Semi solid; yield: 61%; R_f (7% EtOAc-*n*-Hexane) 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66-7.61 (m, 3H), 7.27-7.25 (m, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.11-7.07 (m, 2H), 5.83-5.74 (m, 1H), 5.03-5.00 (m, 3H), 4.76 (d, *J* = 17.2 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5 (d, C-F *J* = 253.3 Hz), 137.8, 135.1, 133.9, 133.2, 131.8 (d, C-F *J* = 8.4 Hz), 127.9 (d, C-F *J* = 24.6 Hz), 125.9, 123.2, 121.2, 120.5, 116.5 (d, C-F *J* = 22.0 Hz), 116.3, 110.7, 101.5, 100.1 (d, C-F *J* = 7.5 Hz), 46.1, 39.5; HPLC: 98.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.41 min; IR (KBr, cm^{-1}): 3072, 2924, 1586, 1470, 1348; MS (ES mass): *m/z* 470.8 (M+1).

2.7.1.4.3 *N*-(4-chloro-2-iodophenyl)-*N*-(1-methyl-1*H*-indol-2-yl)methane-sulfonamide (2.15ca)

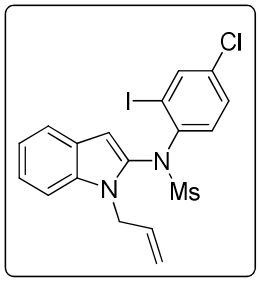


2.15ca was prepared *via* the reaction of **1.1c** with **2.14a** according to the general procedure as mentioned above.

Off white solid; yield: 62%; mp: 168-170 °C;R_f (10% EtOAc-*n*-Hexane) 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 2.0 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.60

(d, *J* = 7.6 Hz, 1H), 7.40 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.32-7.28 (m, 2H), 7.16-7.12 (m, 1H), 6.92 (s, 1H), 3.95 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.5, 140.8, 139.6, 135.5, 134.5, 130.4, 130.2, 125.8, 122.9, 120.9, 120.2, 109.9, 100.8, 100.5, 39.1, 31.6; HPLC: 94.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.53 min; IR (KBr, cm^{-1}): 3073, 2932, 1355, 1463, 1166; MS (ES mass): *m/z* 461.2 (M+1).

2.7.1.4.4 *N*-(1-allyl-1*H*-indol-2-yl)-*N*-(4-chloro-2-iodophenyl)methanesulfonamide (2.15cb)

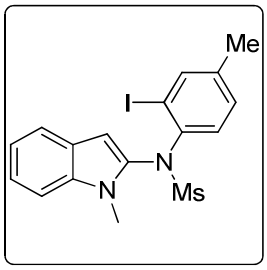


2.15cb was prepared *via* the reaction of **1.1c** with **2.14b** according to the general procedure as mentioned above.

Semi solid; yield: 65%; R_f (20% EtOAc-*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (d, *J* = 2.4 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.34 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.28 (s, 1H), 7.24-7.22 (m, 1H), 7.17-7.13 (m, 1H), 7.08 (s, 1H), 5.83-5.74 (m, 1H), 5.03-5.02 (m, 3H), 4.76 (d, *J* = 17.2 Hz, 1H), 3.26 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.3, 140.2, 135.1, 135.0, 133.7, 133.1, 131.4, 129.5, 125.9, 123.3, 121.2, 120.6, 116.4, 110.7, 101.7, 101.2, 46.1, 39.6; HPLC: 98.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.64 min; IR (KBr, cm^{-1}): 3073, 2932, 1355, 1463, 1166; MS (ES mass): *m/z* 487.2 (M+1).

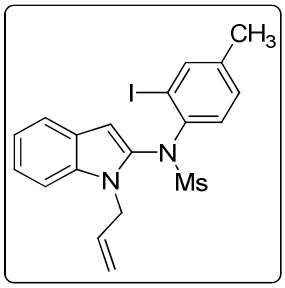
2.7.1.4.5 *N*-(2-iodo-4-methylphenyl)-*N*-(1-methyl-1*H*-indol-2-yl)methane-sulfonamide (2.15ea)

2.15ea was prepared *via* the reaction of **1.1e** with **2.14a** according to the general procedure as mentioned above.



Off white solid; yield: 70%; mp: 201-203 °C; R_f (10% EtOAc-*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, *J* = 0.8 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.31-7.28 (m, 2H), 7.24-7.21 (m, 1H), 7.14-7.10 (m, 1H), 6.92 (s, 1H), 3.98 (s, 3H), 3.27 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.5, 140.8, 139.6, 135.5, 134.5, 130.4, 130.2, 125.8, 122.9, 120.9, 120.2, 109.9, 100.8, 100.5, 39.1, 31.6, 20.4; HPLC: 98.9%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.39 min; IR (KBr, cm^{-1}): 3129, 3020, 2938, 1469, 1347, 1155; MS (ES mass): *m*/*z* 440.9 (M+1).

2.7.1.4.6 *N*-(1-allyl-1*H*-indol-2-yl)-*N*-(2-iodo-4-methylphenyl)methane-sulfonamide (2.15eb)

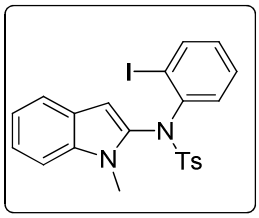


2.15eb was prepared *via* the reaction of **1.1e** with **2.14b** according to the general procedure as mentioned above.

Light yellow semi solid; yield: 62%; R_f (20% EtOAc-*n*-Hexane) 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.28-7.27 (m, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.18-7.11 (m, 2H), 7.06 (s, 1H), 5.84-5.75 (m, 1H), 5.07-5.02 (m, 3H), 4.85 (d, *J* = 17.2 Hz, 1H), 3.26 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.4, 140.6, 138.9, 135.1, 134.2, 133.5, 130.5, 130.1, 126.0, 122.9, 121.1, 120.3, 116.4, 110.8, 101.4, 100.6, 46.3, 39.4, 20.4; HPLC: 98.5%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98,

10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.54 min; IR (KBr, cm^{-1}): 3078, 3026, 2924, 1472, 1345; MS (ES mass): *m/z* 466.9 (M+1).

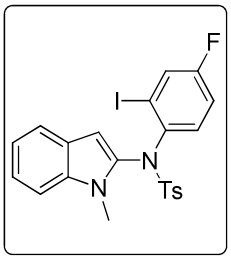
2.7.1.4.7 *N*-(2-iodophenyl)-4-methyl-*N*-(1-methyl-1*H*-indol-2-yl)benzene-sulfonamide (2.15ia)



2.15ia was prepared *via* the reaction of **1.1i** with **2.14a** according to the general procedure as mentioned above.

Brown solid; yield: 74%; mp: 190-192 °C; R_f (10% EtOAc-*n*-Hexane) 0.37; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.29-7.26 (m, 3H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz,1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.22 (s, 1H), 4.12 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.5, 141.4, 140.7, 140.5, 135.4, 135.3, 134.3, 129.7, 129.5, 129.4 (2C), 129.2 (2C), 125.6, 122.6, 120.8, 119.9, 109.9, 101.4, 100.1, 32.1, 21.7; HPLC: 99.3%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.84 min; IR (KBr, cm^{-1}): 3072, 2961, 1491, 1155; MS (ES mass): *m/z* 503.2 (M+1).

2.7.1.4.8 *N*-(4-fluoro-2-iodophenyl)-4-methyl-*N*-(1-methyl-1*H*-indol-2-yl)benzene-sulfonamide (2.15ja)

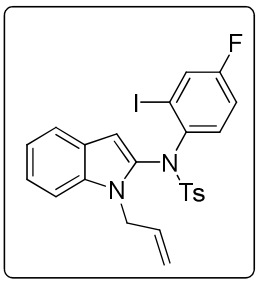


2.15ja was prepared *via* the reaction of **1.1j** with **2.14a** according to the general procedure as mentioned above.

Light pink color solid; yield: 72%; mp: 150-152 °C; R_f (10% EtOAc-*n*-Hexane) 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.54 (d, *J* = 8.4 Hz,

2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.35-7.27 (m, 4H), 7.14-7.08 (m, 2H), 7.00 (dd, *J* = 7.2, 2.4 Hz, 1H), 6.19 (s, 1H), 4.11 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5 (d, C-F *J* = 253.6 Hz), 144.8, 139.7, 135.3 (d, C-F *J* = 23.6 Hz), 133.9, 130.9 (d, C-F *J* = 8.9 Hz), 129.4 (2C), 129.3 (2C), 128.4, 127.9 (d, C-F *J* = 24.4 Hz), 125.6, 125.8, 122.8, 120.8, 120.0, 115.9 (d, C-F *J* = 22.2 Hz), 110.0, 100.1, 32.1, 21.7; HPLC: 90.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.91 min; IR (KBr, cm^{-1}): 3072, 2961, 1421, 1354; MS (ES mass): *m/z* 521.1 (M+1).

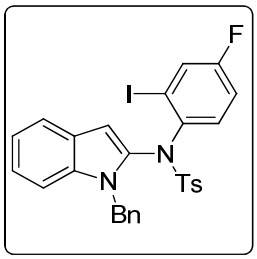
2.7.1.4.9 *N*-(1-allyl-1H-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)-4-methylbenzene-sulfonamide (2.15jb)



2.15jb was prepared *via* the reaction of **1.1j** with **2.14b** according to the general procedure as mentioned above.

Light pink solid; yield: 64%; mp: 167-169 °C; R_f (10% EtOAc-*n*-Hexane) 0.67; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (dd, *J* = 8.0, 2.8 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.32-7.29 (m, 3H), 7.27-7.21 (m, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.04-6.98 (m, 1H), 6.31 (s, 1H), 5.95-5.85 (m, 1H), 5.19 (d, *J* = 0.4 Hz, 2H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.89 (d, *J* = 17.6 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5 (d, C-F *J* = 253.4 Hz), 144.9, 139.2 (d, C-F *J* = 3.6 Hz),134.8, 134.6, 134.1, 133.9, 131.1 (d, C-F *J* = 8.9 Hz), 129.5 (2C), 129.4 (2C), 127.9 (d, C-F *J* = 24.3 Hz), 125.7, 122.9, 120.9, 120.2, 116.2, 115.9 (d, C-F *J* = 22.1 Hz), 111.1, 101.8 (d, C-F *J* = 8.4 Hz), 100.9, 46.7, 21.7; HPLC: 99.7%; column: Symmetry C-1875*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.91 min; IR (KBr, cm^{-1}): 3357, 3072, 2923, 1567, 1465, 1368; MS (ES mass): *m/z* 546.9 (M+1).

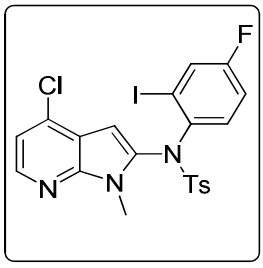
2.7.1.4.10 *N*-(1-benzyl-1*H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)-4-methyl-benzene-sulfonamide (2.15jc)



2.15jc was prepared *via* the reaction of **1.1j** with **2.14c** according to the general procedure as mentioned above.

Light pink solid; yield: 58%; mp: 181-183 °C; R_f (10% EtOAc-*n*-Hexane) 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 8.0 Hz, 2H), 7.56-7.54 (m, 2H), 7.29-7.24 (m, 3H), 7.14-7.07 (m, 5H), 6.97-6.92 (m, 2H), 6.77 (d, *J* = 6.4 Hz, 2H), 6.47 (s, 1H), 5.74 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4 (d, C-F *J* = 252.6 Hz), 144.9, 138.8, 137.3, 135.3, 134.8, 133.9, 131.3 (d, C-F *J* = 8.1 Hz), 129.5 (2C), 129.4 (2C), 128.3 (2C), 127.8, 127.6, 126.8, 126.1 (2C), 125.8, 123.0, 120.9, 120.3, 115.8 (d, C-F *J* = 22.2 Hz), 111.2, 101.2, 47.6, 21.7; HPLC: 98.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.00 min; IR (KBr, cm^{-1}): 3164, 2978, 1431, 1356; MS (ES mass): *m/z* 596.9 (M+1).

2.7.1.4.11 *N*-(4-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-*N*-(4-fluoro-2-iodophenyl)-4-methylbenzenesulfonamide (2.15jk)

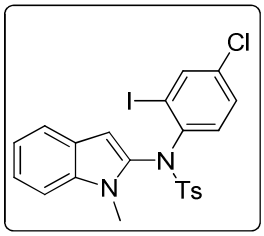


2.15jk was prepared *via* the reaction of **1.1j** with **2.14k** according to the general procedure as mentioned above.

White solid; yield: 66%; mp: 232-234 °C; R_f (10% EtOAc-*n*-Hexane) 0.51; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 4.8 Hz, 1H), 7.67 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.59 (d, *J* = 8. 4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.26-7.23 (m, 1H), 7.11 (d, *J* = 5.2 Hz, 1H), 7.09-7.04 (m, 1H), 6.36 (s, 1H), 4.18 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 162.7 (d, C-F *J* = 254.3 Hz), 146.6, 145.3, 144.4, 138.7 (d, C-F *J* = 3.7 Hz), 136.3, 135.9, 133.8, 131.4 (d, C-F *J* = 8.9 Hz), 129.6 (2C), 129.3 (2C), 128.1 (d, C-F *J* = 24.3 Hz), 127.8, 118.1, 116.6, 116.1, 115.9, 101.6 (d, C-F *J* = 8.4 Hz), 97.2, 31.3, 21.7; HPLC: 99.8%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.98 min; IR (KBr, cm^{-1}): 3077, 2987, 1584, 1476, 1368;MS (ES mass): *m/z* 582.3 (M+1).

2.7.1.4.12 *N*-(4-chloro-2-iodophenyl)-4-methyl-*N*-(1-methyl-1*H*-indol-2-yl)benzene-sulfonamide (2.15ka)

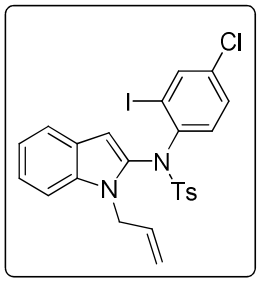


2.15ka was prepared *via* the reaction of **1.1k** with **2.14a** according to the general procedure as mentioned above.

Light pink solid; yield: 63%; mp: 152-154 °C; R_f (10% EtOAc-*n*-Hexane) 0.51; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 2.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.35-7.28 (m, 4H), 7.23 (d, *J* = 2.0 Hz,1H), 7.13-7.08 (m, 2H), 6.19 (s, 1H), 4.10 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.9, 142.0, 140.3, 135.3, 135.1, 134.8, 133.9, 130.6, 129.4 (2C), 129.3 (2C), 128.9, 125.5, 122.9, 120.8, 120.1, 110.0, 102.0, 100.3, 32.0, 21.7; HPLC: 97.9%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.23 min; IR (KBr, cm^{-1}): 3132, 3059, 2938, 1463, 1356, 1165; MS (ES mass): *m/z* 537.8 (M+1).

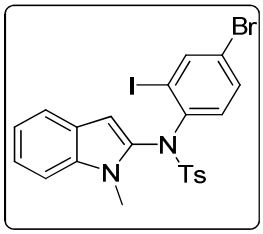
2.7.1.4.13 *N*-(1-allyl-1*H*-indol-2-yl)-*N*-(4-chloro-2-iodophenyl)-4-methylbenzene-sulfonamide (2.15kb)

2.15kb was prepared *via* the reaction of **1.1k** with **2.14b** according to the general procedure as mentioned above.



Light pink solid; yield: 58%; mp: 160-162 °C; R_f (10% EtOAc-*n*-Hexane) 0.48; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 3H), 7.24-7.23 (m, 1H), 7.19 (t, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.27 (s, 1H), 5.91-5.82 (m, 1H), 5.15 (d, *J* = 2.0 Hz, 2H), 5.05 (d, *J* = 11.2 Hz, 1H), 4.85 (d, *J* = 17.2 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.9, 141.6, 140.3, 134.9, 134.8, 134.3, 134.0, 133.9, 130.7, 129.5 (2C), 129.4 (2C), 128.9, 125.7, 122.9, 120.9, 120.2, 116.3, 111.1, 102.0, 101.1, 46.7, 21.7; HPLC: 99.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.20 min; IR (KBr, cm^{-1}): 3066, 2920, 1458, 1363, 1165; MS (ES mass): *m/z* 563.4 (M+1).

2.7.1.4.14 *N*-(4-bromo-2-iodophenyl)-4-methyl-*N*-(1-methyl-1*H*-indol-2-yl)benzene-sulfonamide (2.15sa)

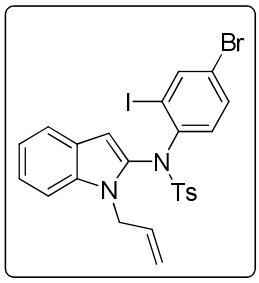


2.15sa was prepared *via* the reaction of **1.1s** with **2.14a** according to the general procedure as mentioned above.

Light brown solid; yield: 62%; mp: 163-165 °C; R_f (10% EtOAc-*n*-Hexane) 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.34-7.27 (m, 4H),7.10 (t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.17 (s, 1H), 4.09 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.9, 143.0, 142.5, 135.3, 134.7, 133.9, 131.9, 131.0, 129.4 (2C), 129.3 (2C), 125.5, 123.2, 122.9, 120.8, 120.1, 110.0, 102.5, 100.3, 32.0, 21.7; HPLC: 98.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98,

10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.22 min; IR (KBr, cm^{-1}): 3123, 2987, 1453, 1395, 1154; MS (ES mass): *m*/*z* 582.7 (M+1).

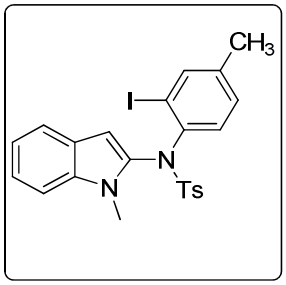
2.7.1.4.15 *N*-(1-allyl-1H-indol-2-yl)-*N*-(4-bromo-2-iodophenyl)-4-methylbenzene-sulfonamide (2.15sb)



2.15sb was prepared *via* the reaction of **1.1s** with **2.14b** according to the general procedure as mentioned above.

White solid; yield: 62%; mp: 173-175 °C; R_f (10% EtOAc-*n*-Hexane) 0.54; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 3H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.12-7.13 (m, 2H), 6.27 (s, 1H), 5.92-5.82 (m, 1H), 5.17-5.15 (m, 2H), 5.06-5.04 (m, 1H), 4.86 (d, *J* = 17.2 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.9, 143.1, 142.1, 134.8, 134.3, 134.0, 133.9, 131.9, 131.1, 129.5 (2C), 129.4 (2C), 125.7, 123.0, 122.9, 120.9, 120.2, 116.3, 111.1, 102.5, 101.1, 46.7, 21.7; HPLC: 99.1%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.35 min; IR (KBr, cm^{-1}): 3078, 2972, 1435, 1352; MS (ES mass): *m*/*z* 608.7 (M+1).

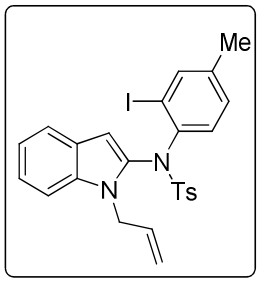
2.7.1.4.16 *N*-(2-iodo-4-methylphenyl)-4-methyl-*N*-(1-methyl-1*H*-indol-2-yl)benzene-sulfonamide (2.15la)



2.15la was prepared *via* the reaction of **1.1l** with **2.14a** according to the general procedure as mentioned above.

Light brown solid; yield: 75%; mp: 173-175 °C; R_f (15% EtOAc-*n*-Hexane) 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.29-7.24 (m, 3H), 7.10 (d, *J* = 8.4 Hz,1H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.21 (s, 1H), 4.13 (s, 3H), 2.48 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.5, 141.4, 140.7, 140.5, 135.4, 135.3, 134.3, 129.7, 129.5, 129.4 (2C), 129.2 (2C), 125.6, 122.6, 120.8, 119.9, 109.9, 101.4, 100.1, 32.1, 21.7, 20.4; HPLC: 95.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.07 min; IR (KBr, cm^{-1}): 3041, 2923, 1476, 1358, 1166; MS (ES mass): *m/z* 516.9 (M+1).

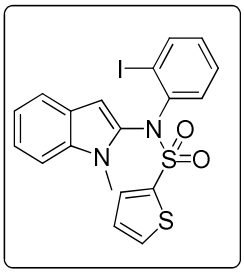
2.7.1.4.17 *N*-(1-allyl-1*H*-indol-2-yl)-*N*-(2-iodo-4-methylphenyl)-4-methylbenzene-sulfonamide (12lb)



2.15lb was prepared *via* the reaction of **1.1l** with **2.14b** according to the general procedure as mentioned above.

semisolid; yield: 61%; R_f (10% EtOAc-*n*-Hexane) 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.30-7.27 (m, 3H), 7.21-7.17 (m, 1H), 7.13-7.04 (m, 3H), 6.28 (s, 1H), 5.93-5.83 (m, 1H), 5.20 (s, 2H), 5.06 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.93 (dd, *J* = 17.2, 1.2 Hz, 1H), 2.46 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.6, 141.5, 140.4, 140.2, 134.9, 134.8, 134.3, 129.8, 129.6, 129.5 (2C), 129.2 (2C), 127.5, 125.8, 122.6, 120.8, 119.9, 116.3, 111.1, 101.4, 100.8, 46.9, 21.7, 20.4; HPLC: 95.8%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 5.11 min; IR (KBr, cm^{-1}): 2956, 1464, 1362, 1155; MS (ES mass): *m/z* 542.8 (M+1).

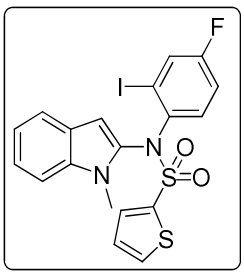
2.7.1.4.18 *N*-(2-iodophenyl)-*N*-(1-methyl-1*H*-indol-2-yl)thiophene-2-sulfonamide (2.15na)



2.15na was prepared *via* the reaction of **1.1n** with **2.14a** according to the general procedure as mentioned above.

Light brown solid; yield: 76%; mp: 185-187 °C; R_f (10% EtOAc-*n*-Hexane) 0.23; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 7.6 Hz, 1H), 7.70 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.35-7.29 (m, 4H), 7.16-7.08 (m, 2H), 7.06-7.01 (m, 1H), 6.39 (s, 1H), 4.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.9, 141.2, 137.3, 135.4, 135.2, 134.5, 133.8, 130.3, 130.2, 128.9, 127.4, 125.6, 122.9, 120.9, 120.1, 110.0, 101.4, 100.4, 32.1; HPLC: 99.0%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.52 min; IR (KBr, cm^{-1}): 3076, 2931, 1492, 1351, 1176; MS (ES mass): *m/z* 494.9 (M+1).

2.7.1.4.19 *N*-(4-fluoro-2-iodophenyl)-*N*-(1-methyl-1*H*-indol-2-yl)thiophene-2-sulfonamide (2.15oa)

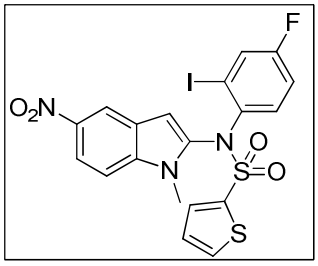


2.15oa was prepared *via* the reaction of **1.1o** with **2.14a** according to the general procedure as mentioned above.

Off white solid; yield: 75%; mp: 168-170 °C; R_f (15% EtOAc-*n*-Hexane) 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72-7.71 (m, 1H), 7.67 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.49-7.48 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 6.8 Hz, 1H), 7.16-7.09 (m, 2H), 7.05-7.00 (m, 1H), 6.35 (s, 1H), 4.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.7 (d, C-F *J* = 253.8 Hz), 139.3 (d, C-F *J* = 3.7 Hz), 136.9, 135.4, 135.3, 134.4, 133.9, 130.8 (d, C-F *J* = 8.9 Hz), 128.0

(d, C-F *J* = 24.5 Hz), 127.5, 125.5, 123.0, 120.9, 120.1, 116.0 (d, C-F *J* = 22.2 Hz), 110.0, 101.6 (d, C-F *J* = 8.6 Hz), 100.2, 32.0; HPLC: 98.4%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.89 min; IR (KBr, cm^{-1}): 3057, 2951, 1504, 1368, 1176; MS (ES mass): *m*/*z*512.9 (M+1).

2.7.1.4.20 *N*-(4-fluoro-2-iodophenyl)-*N*-(1-methyl-5-nitro-1*H*-indol-2-yl)thiophene-2-sulfonamide (2.15oi)

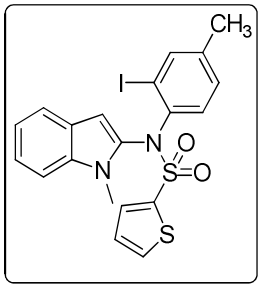


2.15oi was prepared *via* the reaction of **1.1o** with **2.14i** according to the general procedure as mentioned above.

Light yellow solid; yield: 55%; mp: 215-217 °C; R_f (15% EtOAc-*n*-Hexane) 0.31; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.52 (d, *J* = 1.6 Hz, 1H), 8.20 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.80 (d, *J* = 4.8 Hz, 1H), 7.71 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.50 (d, *J* = 3.6 Hz, 1H), 7.41 (d, *J* = 9.2 Hz, 1H), 7.24-7.20 (m, 2H), 7.14-7.06 (m, 1H), 6.55 (s, 1H), 4.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.9, 142.0, 138.6, 138.1, 137.6, 136.3, 135.6, 135.0, 134.5, 130.7 (d, C-F *J* = 9.0 Hz), 128.2, 127.9, 127.7, 124.5, 118.5 (d, C-F *J* = 28.5 Hz), 116.2 (d, C-F *J* = 22.1 Hz), 110.2, 102.6, 32.7; HPLC: 97.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.84 min; IR (KBr, cm^{-1}): 3081, 2924, 2860, 1475, 1326, 1160; MS (ES mass): *m*/*z* 555.7 (M-1).

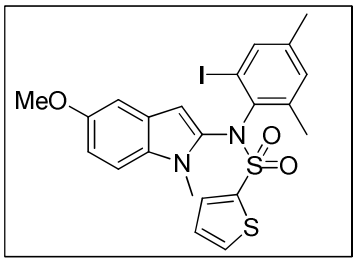
2.7.1.4.21 *N*-(2-iodo-4-methylphenyl)-*N*-(1-methyl-1*H*-indol-2-yl)thiophene-2-sulfonamide (2.15ra)

2.15ra was prepared *via* the reaction of **1.1r** with **2.14a** according to the general procedure as mentioned above.



White solid; yield: 75%; mp: 180-182 °C; R_f (10% EtOAc-*n*-Hexane) 0.57; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (s, 1H), 7.70 (d, *J* = 5.2 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 2.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.28-7.25 (m, 1H), 6.38 (s, 1H), 7.16-7.13 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 4.12 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.4, 140.6, 140.2, 137.3, 135.2, 134.9, 134.6, 133.5, 129.5, 129.4, 127.2, 125.5, 122.6, 120.7, 119.8, 109.9, 101.0, 100.0, 31.9, 20.3; HPLC: 99.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.75 min; IR (KBr, cm^{-1}): 3083, 2935, 1475, 1364; MS (ES mass): *m*/*z* 508.9 (M+1).

2.7.1.4.22 *N*-(2-iodo-4,6-dimethylphenyl)-*N*-(5-methoxy-1-methyl-1*H*-indol-2-yl)thiophene-2-sulfonamide (2.15th)

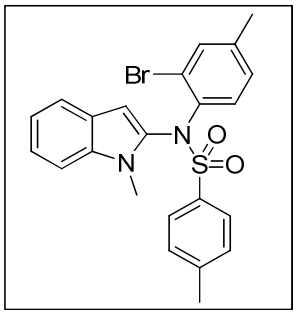


2.15th was prepared *via* the reaction of **1.1t** with **2.14h** according to the general procedure as mentioned above.

Off white solid; yield: 65%; mp: 100-102 °C; R_f (12% EtOAc-*n*-Hexane) 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 4.0 Hz, 1H), 7.72 (s, 1H), 7.58 (d, *J* = 4.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.06-7.02 (m, 3H), 6.99 (s, 1H), 6.86 (dd, *J* = 9.2, 2.0 Hz, 1H), 3.86 (s, 3H), 3.53 (s, 3H), 2.48 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.2, 141.2, 140.3, 140.1, 138.8, 137.0, 135.5, 134.3, 133.5 (2C), 130.5, 126.6, 126.0, 112.3, 110.0, 102.8, 102.2, 100.4, 55.7, 31.9, 21.4, 20.3; HPLC: 96.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98,

10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.20 min; IR (KBr, cm^{-1}): 3099, 2930, 1614, 1473, 1349, 1161; MS (ES mass): *m/z* 553.0 (M+1).

2.7.1.4.23 *N*-(2-bromo-4-methylphenyl)-4-methyl-*N*-(1-methyl-1*H*-indol-2-yl)benzenesulfonamide (2.15ua)



2.15ua was prepared *via* the reaction of **1.1u** with **2.14a** according to the general procedure as mentioned above.

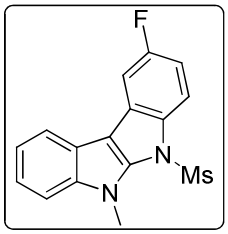
Off white solid; yield: 80%; mp: 148-150 °C; R_f (10% EtOAc-*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.32-7.25 (m, 4H), 7.12-7.09 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.24 (s, 1H), 4.04 (s, 3H), 2.49 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.4, 140.5, 137.1, 135.2, 135.0, 134.7, 134.6, 130.4, 129.3 (2C), 129.2 (2C), 128.7, 125.6, 124.9, 122.6, 120.8, 119.8, 109.9, 100.2, 30.8, 21.7, 20.7; HPLC: 99.4%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.57 min; IR (KBr, cm^{-1}): 3046, 2932, 1476, 1357, 1163; MS (ES mass): *m/z* 471.0 (M+1).

2.7.5 General procedure for preparation of 2-substituted-6-methyl-5-(alkyl/aryl/hetero arylsulfonyl)-5,6-dihydroindolo[2,3-*b*]indole (2.16):

A mixture of *N*-(4-substituted-2-iodophenyl)-*N*-(1-alkyl-1*H*-indol-2-yl) alkane/arene/ heteroarene sulfonamide (**2.15**) (0.4 mmol), $Pd_2(dba)_3$ (5 mol%), Et_3N (1.0 mmol), and anhydrous DMF (1 mL) was stirred at 130 °C under nitrogen atmosphere for 5 h. The progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature, and filtered to remove the solid materials. The filtrate was extracted with ethyl acetate (3 x 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under a

reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate–hexane to give the desired product **2.16**.

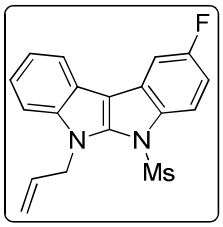
2.7.1.5.1 2-Fluoro-6-methyl-5-(methylsulfonyl)-5,6-dihydroindolo[2,3-*b*]indole (2.16a)



2.16a was prepared from **2.15ba** according to the general procedure as presented above.

Floppy white solid; yield: 78%; mp: 148-150 °C; R_f (5% EtOAc-*n*-Hexane) 0.71; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (dd, *J* = 9.2, 4.8 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.48-7.43 (m, 2H), 7.40-7.31 (m, 2H), 6.95 (td, *J* = 8.8, 1.2 Hz, 1H), 4.06 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3 (d, C-F *J* = 241.5 Hz), 143.6, 141.3, 136.6, 128.4, 122.7, 121.3, 119.9, 119.3, 118.3 (d, C-F *J* = 9.6 Hz), 110.9, 109.6 (d, C-F *J* = 24.4 Hz), 108.0, 105.4 (d, C-F *J* = 25.1 Hz), 36.1, 29.7; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.45 min; IR (KBr, cm^{-1}): 3018, 2928, 1449, 1365, 1168; MS (ES mass): *m*/*z* 317.2 (M+1).

2.7.1.5.2 6-Allyl-2-fluoro-5-(methylsulfonyl)-5,6-dihydroindolo[2,3-*b*]indole (2.16b)

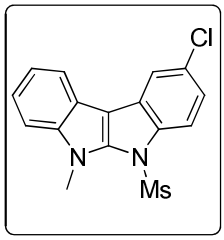


2.16b was prepared from **2.15bb** according to the general procedure as presented above.

Floppy white solid; yield: 70%; mp: 175-177 °C; R_f (7% EtOAc-*n*-Hexane) 0.54; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.88 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.47 (dd, *J* = 7.6, 2.4 Hz, 2H), 7.37-7.31 (m, 2H), 6.97 (td, *J* = 9.2, 2.8 Hz, 1H),

6.11-6.01 (m, 1H), 5.22-5.2 (m, 3H), 5.06 (d, *J* = 17.7 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4 (d, C-F *J* = 241.5 Hz), 142.6, 140.9, 136.3, 133.6, 128.0 (d, C-F *J* = 10.7 Hz), 122.6, 121.3, 120.1, 119.1, 118.8 (d, C-F *J* = 9.5 Hz), 116.5, 111.6, 109.4 (d, C-F *J* = 24.5 Hz), 108.2, 105.2 (d, C-F *J* = 25.0 Hz), 48.7, 36.2; HPLC: 99.5%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.63 min; IR (KBr, cm^{-1}): 2928, 1443, 1356, 1165; MS (ES mass): *m/z* 343.2 (M+1).

2.7.1.5.3 2-Chloro-6-methyl-5-(methylsulfonyl)-5,6-dihydroindolo[2,3-*b*]indole (2.16c)

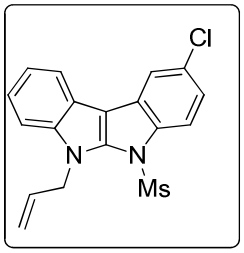


2.16c was prepared from **2.15ca** according to the general procedure as presented above.

Floppy white solid; yield: 76%; mp: 161-163 °C; R_f (10% EtOAc-*n*-Hexane) 0.69; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 1.6 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.41-7.31 (m, 2H), 7.22 (dd, *J* = 8.8, 1.6 Hz, 1H), 4.07 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.1, 141.4, 138.8, 131.8, 128.3, 122.7, 122.4, 121.3, 119.9, 119.3, 118.6, 118.0, 110.9, 107.5, 36.4, 33.7; HPLC: 99.9%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 235 nm, retention time 4.75 min; IR (KBr, cm^{-1}): 3054, 2932, 1564, 1152; MS (ES mass): *m/z* 333.8 (M+1).

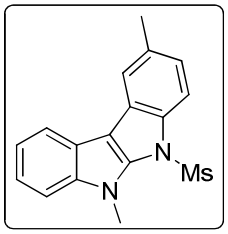
2.7.1.5.4 6-Allyl-2-chloro-5-(methylsulfonyl)-5,6-dihydroindolo[2,3-*b*]indole (2.16d)

2.16d was prepared from **2.15cb** according to the general procedure as presented above.



White solid; yield: 78%; mp: 188-190 °C; R_f (10% EtOAc-*n*-Hexane) 0.61; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 8.8 Hz, 1H), 7.91 (dd, *J* = 6.8, 3.2 Hz, 1H), 7.79 (d, *J* = 1.6 Hz, 1H), 7.50-7.48 (m, 1H), 7.39-7.33 (m, 2H), 7.25 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.12-6.03 (m, 1H), 5.23-5.21 (m, 3H), 5.03 (d, *J* = 17.2 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.3, 141.1, 138.6, 133.8, 131.6, 127.9, 122.8, 122.6, 121.5, 120.1, 119.3, 118.5, 117.9, 116.6, 111.7, 107.9, 48.8, 36.7; HPLC: 97.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.89 min; IR (KBr, cm^{-1}): 3057, 2951, 1504, 1368, 1176; MS (ES mass): *m*/*z* 359.2 (M+1).

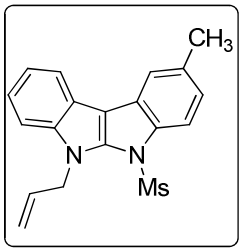
2.7.1.5.5 2,6-Dimethyl-5-(methylsulfonyl)-5,6-dihydroindolo[2,3-*b*]indole (2.16e)



2.16e was prepared from **2.15ea** according to the general procedure as presented above.

Light brown solid; yield: 80%; mp: 165-167 °C; R_f (10% EtOAc-*n*-Hexane) 0.65; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90-7.87 (m, 2H), 7.59 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.36-7.28 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 4.05 (s, 3H), 2.59 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.7, 141.3, 138.8, 135.8, 127.3, 123.7, 122.3, 120.9, 120.2, 119.4, 119.2, 116.8, 110.7, 108.4, 35.8, 33.6, 21.5; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.49 min; IR (KBr, cm^{-1}): 3057, 2951, 1504, 1368, 1176; MS (ES mass): *m*/*z* 313.9 (M+1).

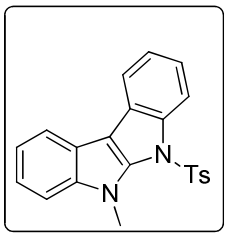
2.7.1.5.6 6-Allyl-2-methyl-5-(methylsulfonyl)-5,6-dihydroindolo[2,3-*b*]indole (2.16f)



2.16f was prepared from **2.15eb** according to the general procedure as presented above.

Floppy white solid; yield: 74%; mp: 170-172 °C; R_f (20% EtOAc-*n*-Hexane) 0.56; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 8.2 Hz, 2H), 7.62 (s, 1H), 7.47-7.45 (m, 1H), 7.34-7.29 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.10-6.00 (m, 1H), 5.21-5.17 (m, 3H), 5.06 (d, *J* = 16.8 Hz, 1H), 2.64 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.9, 141.1, 138.7, 135.7, 133.9, 126.9, 123.8, 122.4, 121.1, 120.5, 119.4, 119.2, 116.8, 116.5, 111.6, 108.7, 48.8, 36.1, 21.5; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.49 min; IR (KBr, cm^{-1}): 3057, 2951, 1504, 1368, 1176; MS (ES mass): *m/z* 338.8 (M+1).

2.7.1.5.7 5-Methyl-6-tosyl-5,6-dihydroindolo[2,3-*b*]indole (2.16g)

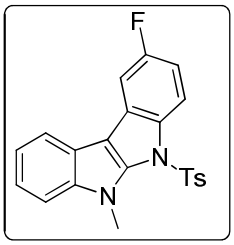


2.16g was prepared from **2.15ia** according to the general procedure as presented above.

Light brown solid; yield: 83%; mp: 160-162 °C; R_f (10% EtOAc-*n*-Hexane) 0.62; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.36-7.24 (m, 5H) 7.20 (t, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 4.21 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.8, 142.8, 141.5, 140.5, 132.2, 129.2 (2C), 127.1, 126.8 (2C), 125.4, 122.2, 122.1, 120.7, 120.3, 119.3, 118.3, 117.7, 110.7, 108.9, 33.8, 21.5; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in

water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.49 min; IR (KBr, cm^{-1}): 3057, 2951, 1504, 1368, 1176; MS (ES mass): *m/z* 374.8 (M+1).

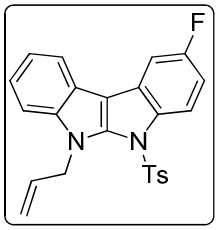
2.7.1.5.8 2-Fluoro-6-methyl-5-tosyl-5,6-dihydroindolo[2,3-*b*]indole (2.16h)



2.16h was prepared from **2.15ja** according to the general procedure as presented above.

Off white solid; yield: 85%; mp: 140-142 °C; R_f (10% EtOAc-*n*-Hexane) 0.72; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.07 (dd, *J* = 8.8, 4.4 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.28-7.25 (m, 3H), 7.21 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.87 (td, *J* = 9.2, 2.8 Hz, 1H), 4.19 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3 (d, C-F *J* = 240.7 Hz), 145.0, 143.9, 141.4, 136.4 , 136.3, 131.8, 129.3 (2C), 128.5 (d, C-F *J* = 10.7 Hz), 126.8 (2C), 122.4, 121.0, 120.1, 119.2, 118.8 (d, C-F *J* = 9.6 Hz), 110.8, 109.1 (d, C-F *J* = 24.6 Hz), 105.0 (d, C-F *J* = 25.0 Hz), 33.8, 21.5; HPLC: 99.8%; column: Symmetry C-18 75*4.6 mm 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 8/98, 10/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.55 min; IR (KBr, cm^{-1}): 3005, 2954, 1604, 1444, 1175; MS (ES mass): *m/z* 392.9 (M+1).

2.7.1.5.9 6-Allyl-2-fluoro-5-tosyl-5,6-dihydroindolo[2,3-*b*]indole (2.16i)

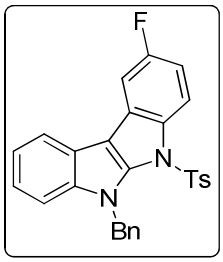


2.16i was prepared from **2.15jb** according to the general procedure as presented above.

Yellowish white solid; yield: 76%; mp: 133-135 °C; R_f (10% EtOAc-*n*-Hexane) 0.68; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.08 (dd, *J* = 9.2, 4.8 Hz, 1H), 7.75 (d, *J* = 7.6 Hz,

1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.35-7.27 (m, 4H), 7.23 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.89 (td, *J* = 9.2, 2.8 Hz, 1H), 6.21-6.11(m, 1H), 5.31 (d, *J* = 5.2 Hz, 2H), 5.29 (d, *J* = 10.4 Hz, 1H), 5.22 (d, *J* = 17.2 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2 (d, C-F *J* = 240.8 Hz), 145.0, 143.5, 141.4, 136.4, 133.5, 131.9, 129.2 (2C), 128.4 (d, C-F *J* = 10.7 Hz), 126.9 (2C), 122.5, 121.2, 120.4, 119.2, 118.8 (d, C-F *J* = 9.6 Hz), 117.1, 111.8, 109.9, 109.2 (d, C-F *J* = 24.5 Hz), 105.0 (d, C-F *J* = 25.0 Hz), 49.3, 21.5; HPLC: 99.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.14 min; IR (KBr, cm^{-1}): 3070, 2950, 1474, 1442, 1176; MS (ES mass): *m/z* 418.8 (M+1).

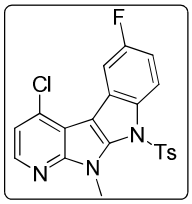
2.7.1.5.10 6-Benzyl-2-fluoro-5-tosyl-5,6-dihydroindolo[2,3-*b*]indole (2.16j)



2.16j was prepared from **2.15jc** according to the general procedure as presented above.

Light yellow solid; yield: 75%; mp: 150-152 °C; R_f (10% EtOAc-*n*-Hexane) 0.55; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (dd, *J* = 9.2, 4.8 Hz, 1H), 7.78-7.76 (m, 1H), 7.40 (dd, *J* = 7.6, 3.2 Hz, 1H), 7.28-7.23 (m, 6H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 6.8 Hz, 2H), 6.92-6.87 (m, 3H), 5.99 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2 (d, C-F *J* = 240.8 Hz), 145.0, 143.4, 141.4, 137.4, 136.4, 132.2, 129.2 (2C), 128.6 (2C), 128.2 (d, C-F *J* = 10.5 Hz), 127.3, 126.9 (2C), 126.4 (2C), 122.7, 121.3, 120.5, 119.3, 118.8 (d, C-F *J* = 9.5 Hz), 111.9, 109.4 (d, C-F *J* = 24.6 Hz), 109.3, 105.1(d, C-F *J* = 24.9 Hz), 49.8, 21.5; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.49 min; IR (KBr, cm^{-1}): 3057, 2951, 1504, 1368, 1176; MS (ES mass): *m/z* 469.1 (M+1).

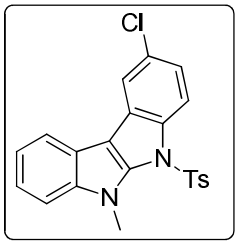
2.7.1.5.11 Compound 2.16k



2.16k was prepared from **2.15jk** according to the general procedure as presented above.

Off white solid; yield: 70%; mp: 203-205 °C; R_f (10% EtOAc-*n*-Hexane) 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, *J* = 5.2 Hz, 1H), 8.14 (dd, *J* = 9.2, 4.8 Hz, 1H), 7.67 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 5.2 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.95 (td, *J* = 8.8, 2.4 Hz, 1H), 4.32 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7, 151.9, 145.5, 143.4, 142.8, 135.6, 135.6, 134.3, 132.2, 129.6 (2C), 127.1 (d, C-F *J* = 11.0 Hz), 126.8 (2C), 118.4 (d, C-F *J* = 9.6 Hz), 117.5, 113.5, 110.3 (d, C-F *J* = 24.5 Hz), 107.1 (d, C-F *J* = 25.8 Hz), 32.9, 21.5; HPLC: 99.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.40 min; IR (KBr, cm^{-1}): 3029, 2959, 1481, 1349, 1173; MS (ES mass): *m*/*z* 428.0 (M+1).

2.7.1.5.12 2-Chloro-6-methyl-5-tosyl-5,6-dihydroindolo[2,3-*b*]indole (2.16l)

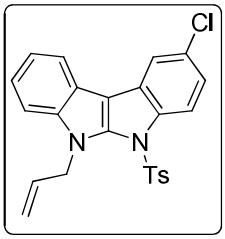


2.16l was prepared from **2.15ka** according to the general procedure as presented above.

White solid; yield: 81%; mp: 178-180 °C; R_f (10% EtOAc-*n*-Hexane) 0.68; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.31-7.27 (m, 3H), 7.14 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 4.20 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.1, 143.5, 141.5, 138.6, 132.1, 131.2, 129.4 (2C), 128.3, 126.8 (2C), 122.5, 121.9, 121.1, 119.9, 119.3, 118.5, 118.2, 110.8, 108.0, 29.7, 21.5; HPLC: 99.4%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50,

3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.31 min; IR (KBr, cm^{-1}): 3059, 2929, 1530, 1367, 1171; MS (ES mass): *m/z* 409.5 (M+1).

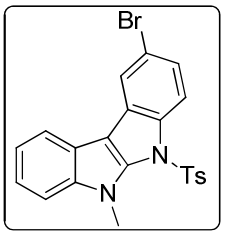
2.7.1.5.13 6-Allyl-2-chloro-5-tosyl-5,6-dihydroindolo[2,3-*b*]indole (2.16m)



2.16m was prepared from **2.15kb** according to the general procedure as presented above.

White solid; yield: 70%; mp: 155-157 °C; R_f (10% EtOAc-*n*-Hexane) 0.51; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.35-7.25 (m, 4H), 7.15 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.20-6.10 (m, 1H), 5.32-5.27 (m, 3H), 5.21 (d, *J* = 17.2 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.2, 143.1, 141.5, 138.7, 133.5, 132.1, 131.2, 129.4 (2C), 128.2, 126.9 (2C), 122.6, 122.1, 121.3, 120.4, 119.3, 118.6, 118.2, 117.1, 111.9, 108.5, 49.4, 21.5; HPLC: 99.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.44 min; IR (KBr, cm^{-1}): 3026, 2923, 1491, 1332, 1176; MS (ES mass): *m/z* 435.3 (M+1).

2.7.1.5.14 2-Bromo-6-methyl-5-tosyl-5,6-dihydroindolo[2,3-*b*]indole (2.16n)

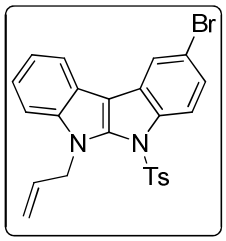


2.16n was prepared from **2.15sa** according to the general procedure as presented above.

White solid; yield: 68%; mp: 193-195 °C; R_f (10% EtOAc-*n*-Hexane) 0.58; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.36 (td, *J* = 8.4, 1.0 Hz, 1H), 7.32-7.28 (m, 4H), 6.98 (d, *J* = 8.4 Hz, 2H), 4.20 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ: 145.2, 143.4, 141.5, 139.1, 132.1, 129.4 (2C), 128.7, 126.8 (2C), 124.8, 122.5, 121.1, 121.0, 119.9, 119.3, 119.1, 118.9, 110.8, 109.9, 33.8, 21.5; HPLC: 96.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.46 min; IR (KBr, cm^{-1}): 3063, 2943, 1529, 1366, 1171; MS (ES mass): *m/z* 454.8 (M+1).

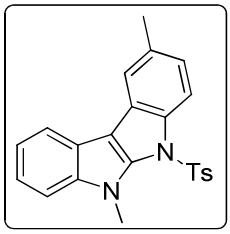
2.7.1.5.15 6-Allyl-2-bromo-5-tosyl-5,6-dihydroindolo[2,3-*b*]indole (2.16o)



2.16o was prepared from **2.15sb** according to the general procedure as presented above.

White solid; yield: 69%; mp: 160-162 °C; R_f (10% EtOAc-*n*-Hexane) 0.61; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 8.8 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 3H), 7.30-7.27 (m, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.20-6.10 (m, 1H), 5.32 (d, *J* = 4.8 Hz, 2H), 5.28 (d, *J* = 10.8 Hz, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.2, 142.9, 141.5, 139.1, 133.5, 132.1, 129.4 (2C), 128.6, 126.9 (2C), 124.9, 122.6, 121.3, 121.2, 120.4, 119.3, 119.1, 118.9, 117.1, 111.8, 108.4, 49.4, 21.5; HPLC: 98.4%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.53 min; IR (KBr, cm^{-1}): 3053, 2919, 1430, 1370, 1175; MS (ES mass): *m/z* 479.9 (M+1).

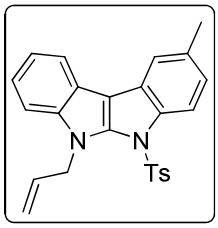
2.7.1.5.16 2,6-dimethyl-5-tosyl-5,6-dihydroindolo[2,3-*b*]indole (2.16p)



2.16p was prepared from **2.15la** according to the general procedure as presented above.

White solid; yield: 85%; mp: 165-167 °C; R_f (15% EtOAc-*n*-Hexane) 0.62; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.31 (s, 1H), 7.28-7.22 (m, 3H), 7.19-7.16 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.12 (s, 3H), 2.35 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.7, 142.9, 141.4, 138.4, 135.1, 132.3, 129.2 (2C), 127.2, 126.8 (2C), 123.2, 121.9, 120.6, 120.3, 119.2, 118.7, 117.3, 110.7, 108.8, 33.7, 29.7, 21.5; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µ, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 8/98, 10/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.72 min; IR (KBr): 3051, 2947, 1528, 1367, 1174 cm^{-1}; MS (ES mass): *m/z* 388.8 (M+1).

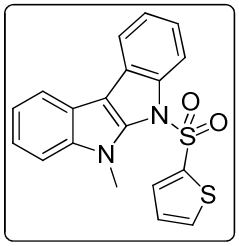
2.7.1.5.17 6-Allyl-2-methyl-5-tosyl-5,6-dihydroindolo[2,3-*b*]indole (2.16q)



2.16q was prepared from **2.15lb** according to the general procedure as presented above.

Light brown solid; yield: 78%; mp: 140-142 °C; R_f (10% EtOAc-*n*-Hexane) 0.62; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.39 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.26-7.23 (m, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.20-6.10 (m, 1H), 5.32 (d, *J* = 4.8 Hz, 2H), 5.26 (d, *J* = 10.4 Hz, 1H), 5.19 (d, *J* = 20.4 Hz, 1H), 2.42 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.7, 142.4, 141.4, 138.5, 137.5, 135.1, 133,7, 131.9, 129.8, 129.2, 126.9, 126.4, 124.2, 123.4, 122.1, 120.8, 119.3, 118.8, 117.4, 116.8, 111.7, 109.4, 49.3, 29.7, 21.5; HPLC: 96.4%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 235 nm, retention time 5.28 min; IR (KBr, cm^{-1}): 3014, 2967, 1514, 1342, 1167; MS (ES mass): *m/z* 415.2 (M+1).

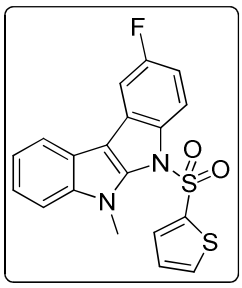
2.7.1.5.18 5-Methyl-6-(thiophen-2-ylsulfonyl)-5,6-dihydroindolo[2,3-*b*]indole (2.16r)



2.16r was prepared from **2.15na** according to the general procedure as presented above.

Light yellow solid; yield: 80%; mp: 162-164 °C; R_f (10% EtOAc-*n*-Hexane) 0.48; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.36-7.31 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.26-7.21 (m, 2H), 7.19 (d, *J* = 3.2 Hz, 1H), 6.73 (t, *J* = 4.4 Hz, 1H), 4.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.4, 141.4, 140.6, 134.2, 133.5, 133.2, 127.7, 126.8, 125.9, 122.5, 122.3, 120.8, 120.2, 119.4, 118.4, 118.1, 110.7, 109.5, 33.7; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.49 min; IR (KBr, cm^{-1}): 3057, 2951, 1504, 1368, 1176; MS (ES mass): *m/z* 367.1 (M+1).

2.7.1.5.19 2-Fluoro-6-methyl-5-(thiophen-2-ylsulfonyl)-5,6-dihydroindolo[2,3-*b*]indole (2.16s)

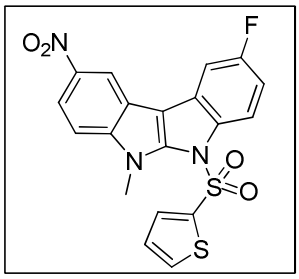


2.16s was prepared from **2.15oa** according to the general procedure as presented above.

Light yellow solid; yield: 84%; mp: 188-190 °C; R_f (15% EtOAc-*n*-Hexane) 0.61; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (dd, *J* = 9.2, 4.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.38-7.33 (m, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.25-7.23 (m, 1H), 7.18 (d, *J* = 3.2 Hz, 1H), 6.92 (td, *J* = 8.8, 2.4 Hz, 1H), 6.76 (t, *J* = 4.8 Hz, 1H), 4.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.6 (d, C-F *J* = 241.4 Hz), 143.5, 141.4, 136.5, 133.9, 133.7, 133.3, 129.1(d, C-F *J* = 10.7 Hz), 126.9, 122.6, 121.1, 119.9, 119.3, 119.2, 119.1, 110.8, 109.3 (d, C-F *J* = 24.5 Hz), 105.2 (d, C-F *J* = 25.1

Hz), 33.7; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.49 min; IR (KBr, cm^{-1}): 3057, 2951, 1504, 1368, 1176; MS (ES mass): *m/z* 385.0 (M+1).

2.7.1.5.20 2-Fluoro-6-methyl-9-nitro-5-(thiophen-2-ylsulfonyl)-5,6-dihydroindolo [2,3-*b*]indole (2.16t)

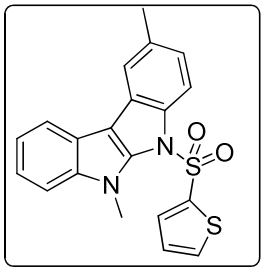


2.16t was prepared from **2.15oi** according to the general procedure as presented above.

Light yellow solid; yield: 68%; mp: 245-247 °C; R_f (15% EtOAc-*n*-Hexane) 0.56; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.70 (d, *J* = 2.4 Hz, 1H), 8.27 (dd, *J* = 9.2, 2.4, 1H), 8.13 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.41 (d, *J* = 4.8 Hz, 1H), 7.36 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.24 (d, *J* = 4.0 Hz, 1H), 7.03 (td, *J* = 8.8, 2.4 Hz, 1H), 6.82 (d, *J* = 4.4 Hz, 1H), 4.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.7 (d, C-F *J* = 243.6 Hz), 145.2, 143.9, 142.5, 136.6 (d, C-F *J* = 1.7 Hz), 134.1, 133.7, 127.2, 127.1, 120.5, 119.4 (d, C-F *J* = 9.9 Hz), 119.1, 118.0, 115.9, 110.7 (d, C-F *J* = 22.0 Hz), 110.8, 105.8 (d, C-F *J* = 25.1 Hz), 34.3, 29.6; HPLC: 98.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 5.02 min; IR (KBr, cm^{-1}): 3082, 2924, 1475, 1326, 1170; MS (ES mass): *m/z* 430.4 (M+1).

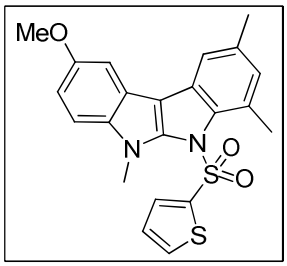
2.7.1.5.21 2,6-Dimethyl-5-(thiophen-2-ylsulfonyl)-5,6-dihydroindolo[2,3-*b*]indole (2.16u)

2.16u was prepared from **2.15ra** according to the general procedure as presented above.



Light green solid; yield: 87%; mp: 213-215 °C; R_f (10% EtOAc-*n*-Hexane) 0.67; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.31-7.23 (m, 2H), 7.19 (d, *J* = 4.1 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.76-6.73 (t, *J* = 4.4 Hz, 1H), 4.15 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.6, 141.4, 138.6, 135.7, 134.3, 133.3, 133.1, 127.7, 126.8, 123.4, 122.1, 120.7, 120.2, 119.4, 118.9, 117.7, 110.7, 109.4, 33.6, 21.5; HPLC: 99.9%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 235 nm, retention time 4.89 min; IR (KBr, cm^{-1}): 3098, 2953, 1532, 1368, 1173; MS (ES mass): *m/z* 380.8 (M+1).

2.7.1.5.22 9-methoxy-2,4,6-trimethyl-5-(thiophen-2-ylsulfonyl)-5,6-dihydroindolo [2,3-*b*]indole (2.16v)



2.16v was prepared from **2.15th** according to the general procedure as presented above.

Light yellow solid; yield: 74%; mp: 184-186 °C; R_f (10% EtOAc-*n*-Hexane) 0.51; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 4.0 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 7.06 (s, 1H), 6.95 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.82 (s, 1H), 6.80-6.79 (m, 1H), 6.67 (t, *J* = 4.0 Hz, 1H), 4.06 (s, 3H), 3.90 (s, 3H), 2.71 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.7, 145.7, 139.7, 136.7, 135.9, 133.6 (2C), 131.2, 131.3, 131.1, 126.6, 126.4, 120.5, 116.3, 11.4, 111.3, 110.5, 101.9, 55.8, 33.3, 21.3, 20.4; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (gradient) T/B% : 0/50,

0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.51 min; IR (KBr, cm^{-1}): 3098, 2928, 1453, 1372, 1171; MS (ES mass): *m/z* 425.1 (M+1).

2.7.2 Single crystal X-ray data

Single crystals suitable for X-ray diffraction of **2.16i** were grown from methanol. The crystals were carefully chosen using a stereo zoom microscope supported by a rotatable polarizing stage. The data were collected at room temperature on Bruker's KAPPA APEX II CCD Duo with graphite monochromated Mo-Kα radiation (0.71073 Å). The crystals were glued to a thin glass fibre using FOMBLIN immersion oil and mounted on the diffractometer. The intensity data were processed using Bruker's suite of data processing programs (SAINT), and absorption corrections were applied using SADABS.[29] The crystal structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms, using SHELXL-97.[30]

Crystal data of 2.16i: Molecular formula = $C_{24}H_{19}FN_2O_2S$, formula weight = 418.48, crystal system = Triclinic, space group = *P*-1, a = 8.4548 (9) Å, b = 11.3819 (12) Å, c = 11.7256 (12) Å, V = 1021.48 (19) $Å^3$, T = 296 K, Z = 2, D_c = 1.361 Mg m^{-3}, μ(Mo-Kα) = 0.19 mm^{-1}, 18280 reflections measured, 4932 independent reflections, 3687 observed reflections [I > 2.0 σ (I)], R_1_obs = 0.028, Goodness of fit =1.04. Crystallographic data (excluding structure factors) for **2.16i** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 903580.

2.7.3 Pharmacology

A yeast cell based assay[27] for identification of potential inhibitors of HDAC *Sir2*.

2.7.3.1 Reporter silencing assay: In this assay a yeast strain (TEL::URA3 strain (MATα ura3-52 lys2-801 ade2-101 trpΔ63 his3Δ200 leu3Δ200 leu2-Δ1 TEL adh4::URA) was used in which, a reporter gene URA3 was inserted in the silenced telomeric region where it is silenced by yeast *Sir2* protein. A compound having the *Sir2* protein inhibitory effect will inhibit the *Sir2* protein, and thus the URA3 gene will be expressed and this will result in the death of the yeast cell in presence of 5-

fluoro orotic acid (5-FOA) through formation of toxic 5-fluorouracil. This assay can also test the toxicity of compounds. The cells when grown in absence of 5-FOA should grow if the compound is not toxic. However in case of a toxic compound yeast cells would die.

The yeast strain was inoculated in 5.0 mL of YPDA media. The cells growing at the exponential phase were dispensed in the round bottom 96-well plate using cell dispenser. A Stock concentration of 10% 5-FOA was used to make a final concentration of 0.3% 5-FOA in the wells of 96-well plate. The compounds at a concentration of 50 uM were added to each well and the plates were incubated at 30 °C. Absorbance at 590 was measured using 96 well plate reader after 24 and 48 h. The inhibitory effect of compounds was analyzed after plotting the OD vs concentration of the compound in Excel data sheet. Splitomicin was used as a control (data not shown).

2.7.3.2 Molecular Docking Studies

The crystal structure of yeast *Sir2* protein in ternary complex with 2'-O-acetyl ADP ribose and histone peptide (PDB ID: 1Q1A)[31] was chosen for the present docking studies. In order to understand the binding modes of **2.16p** and **2.16a** at the catalytic site of yeast *Sir2*, molecular docking studies were performed by FRED v3.0[32] implemented from Open Eye Scientific Software. The multi-conformer database of the inhibitors was generated through OMEGA v1.7.7.[33]

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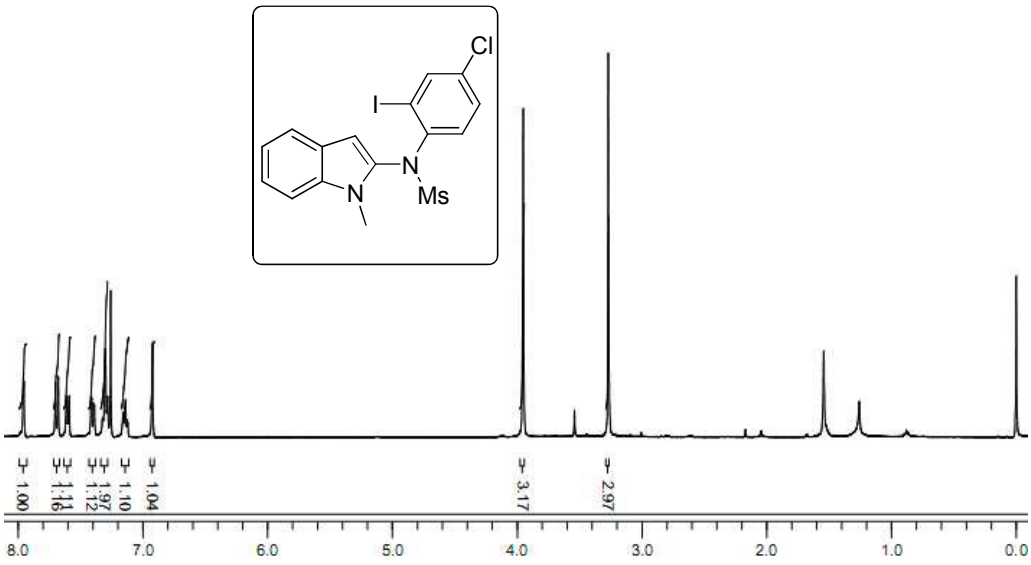
Appendix

2.15ca ^{1}H NMR (400 MHz, $CDCl_3$)



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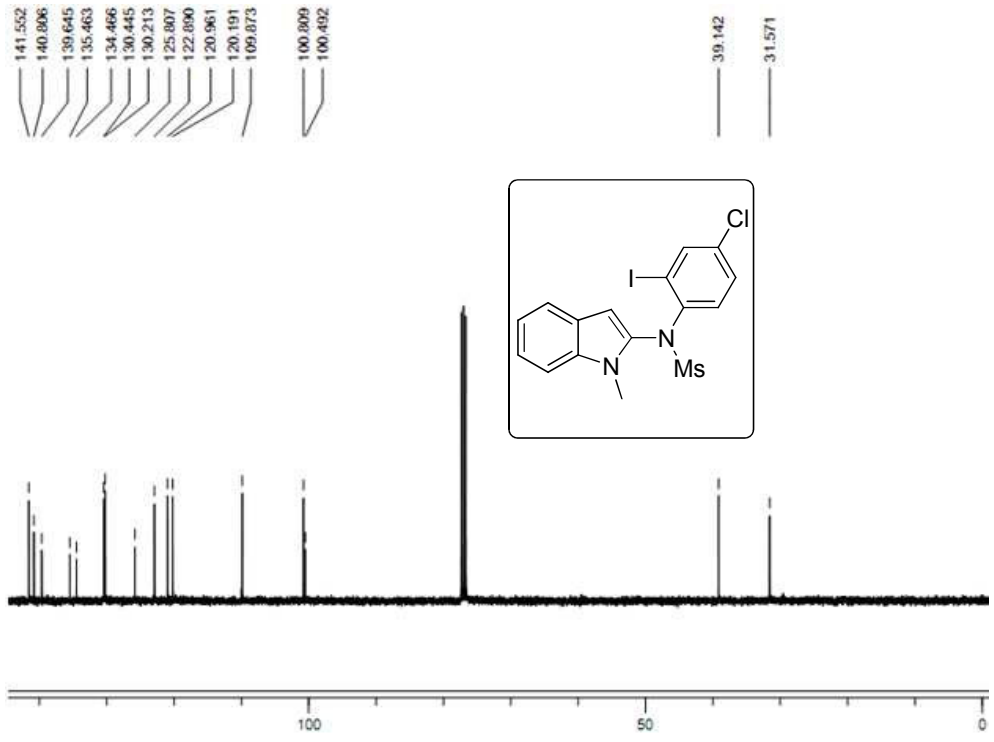

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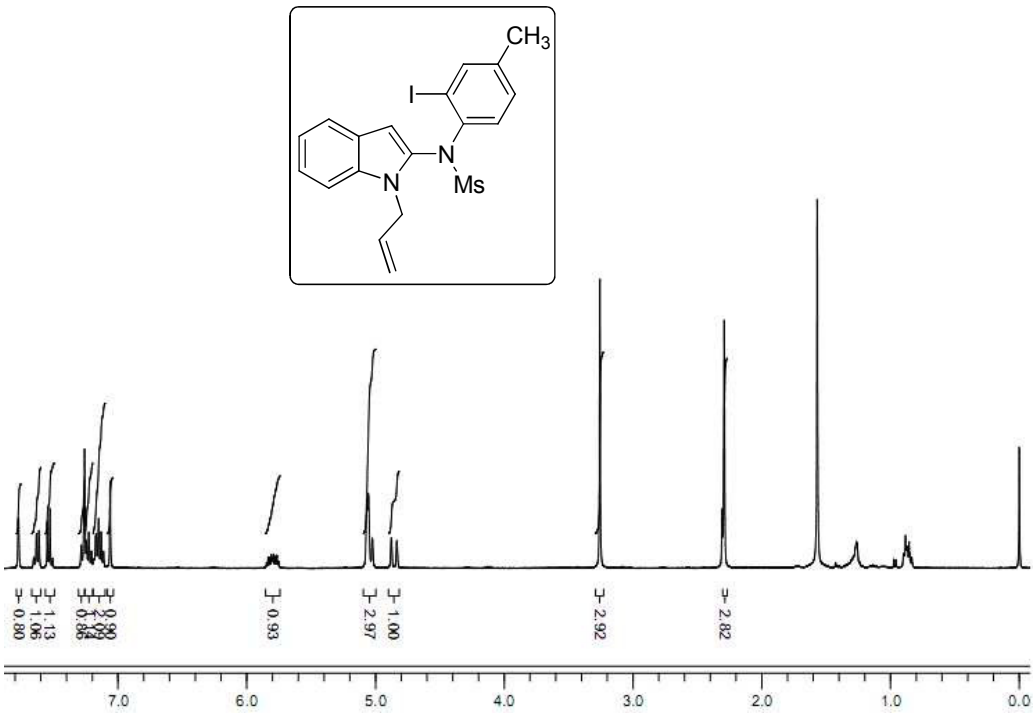

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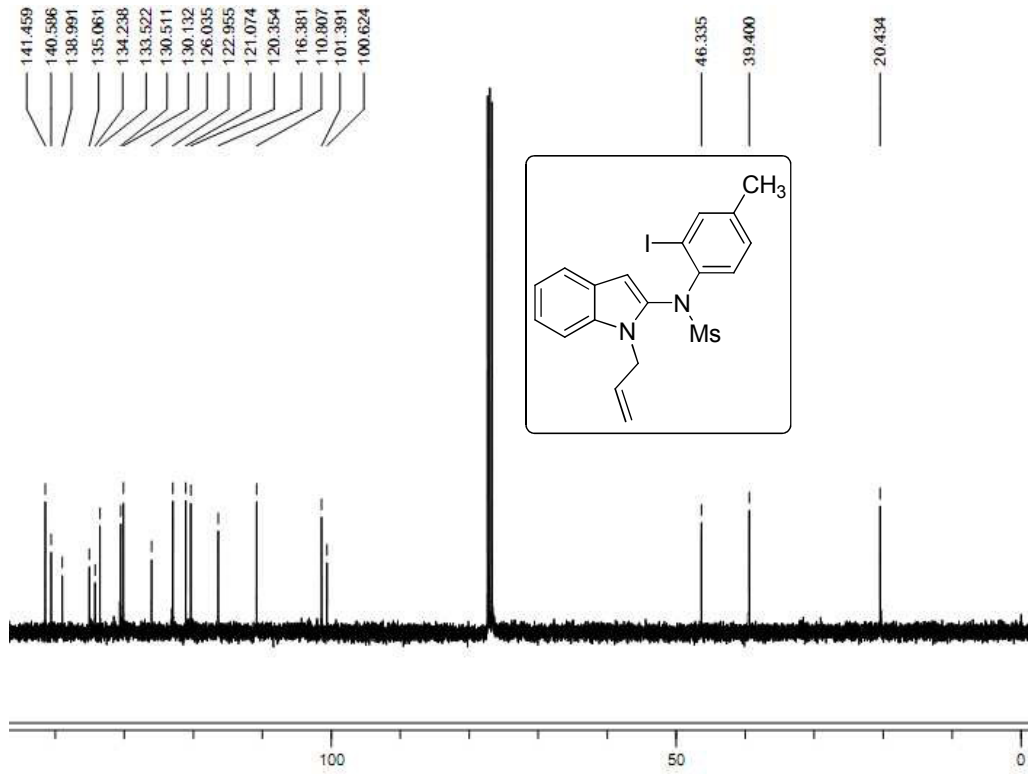

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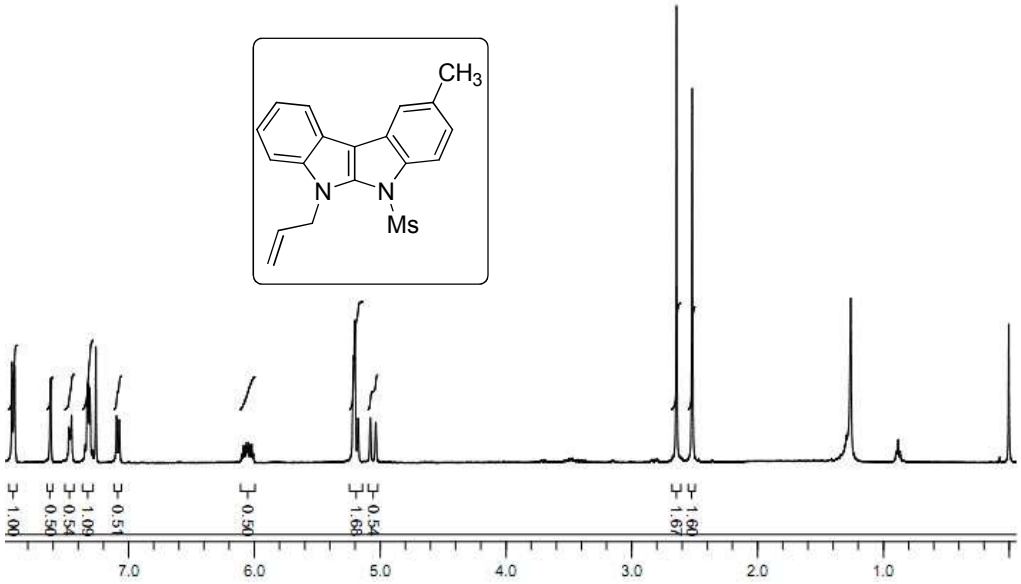

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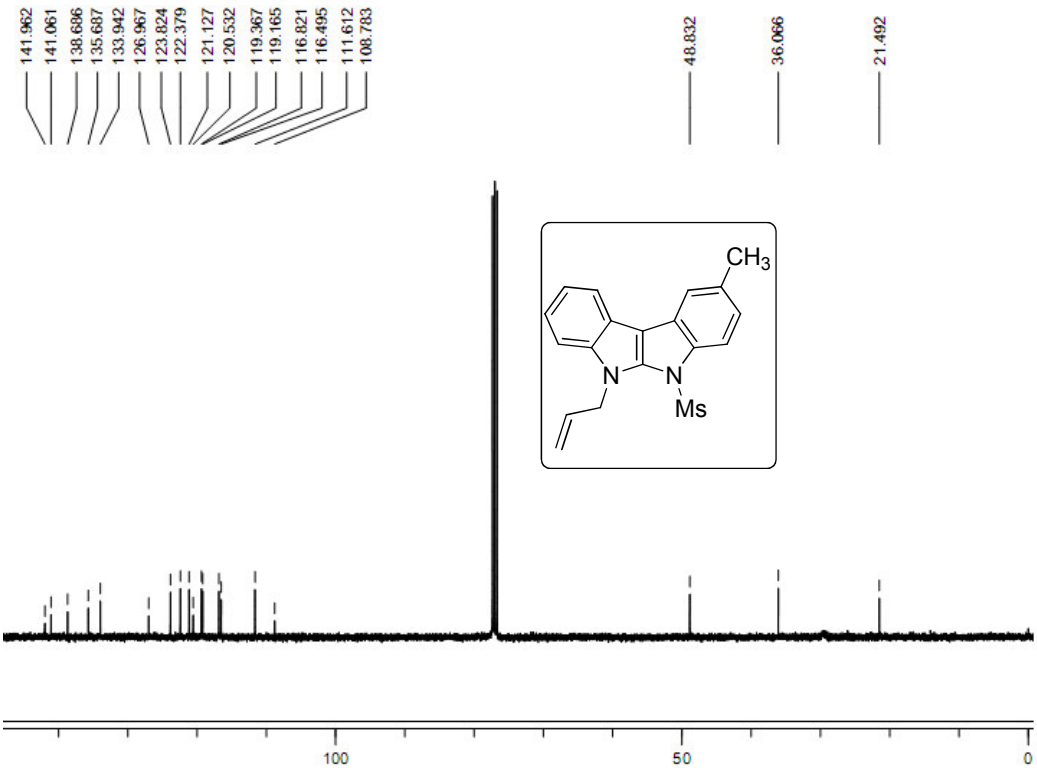

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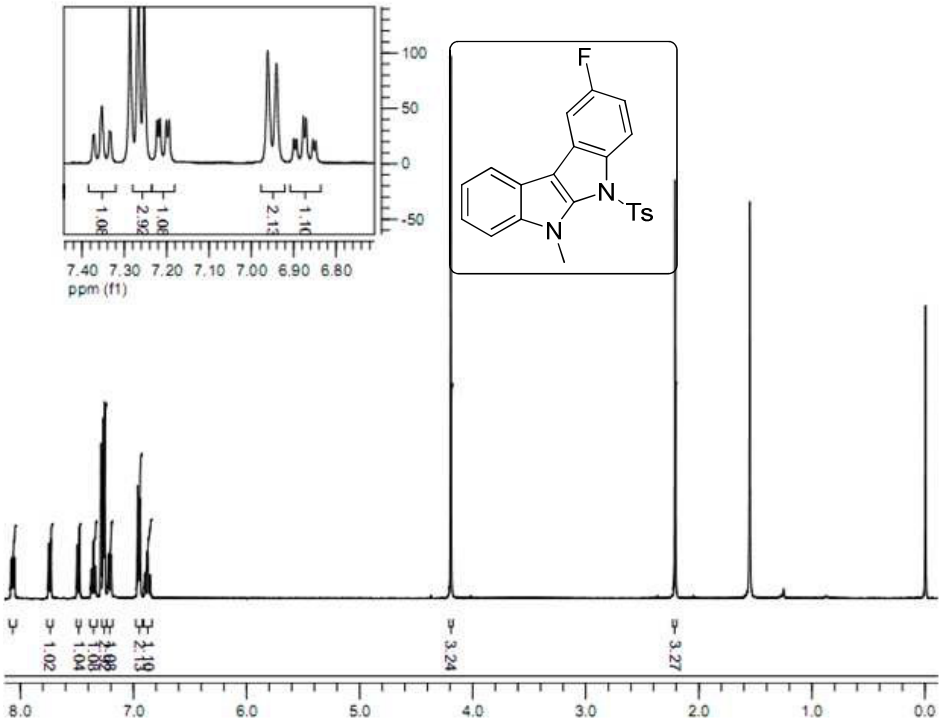

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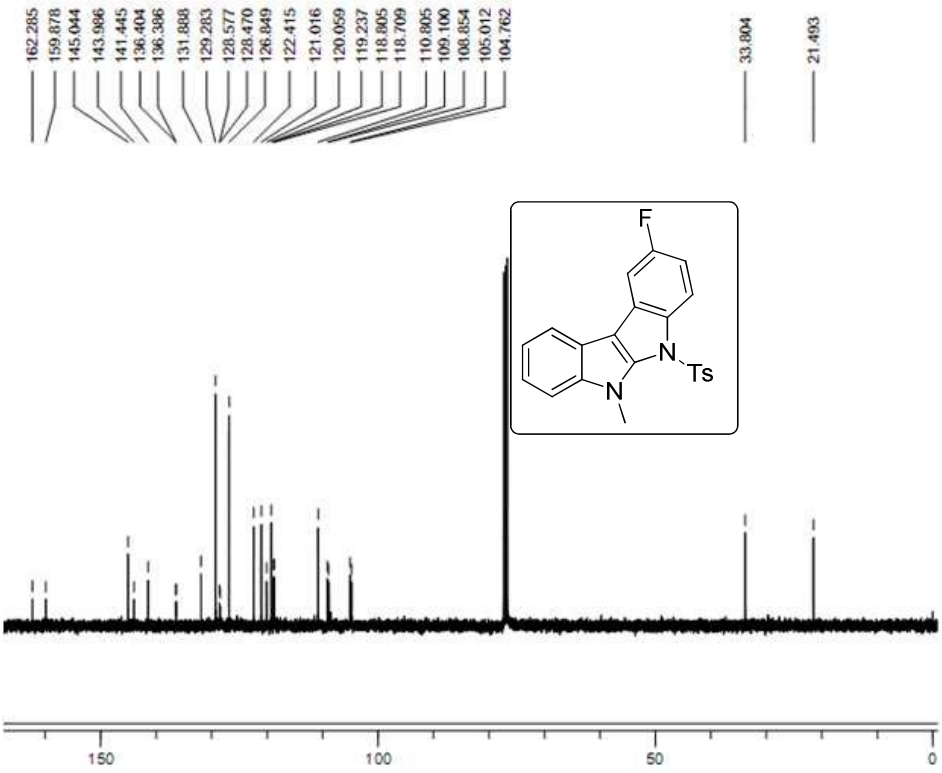

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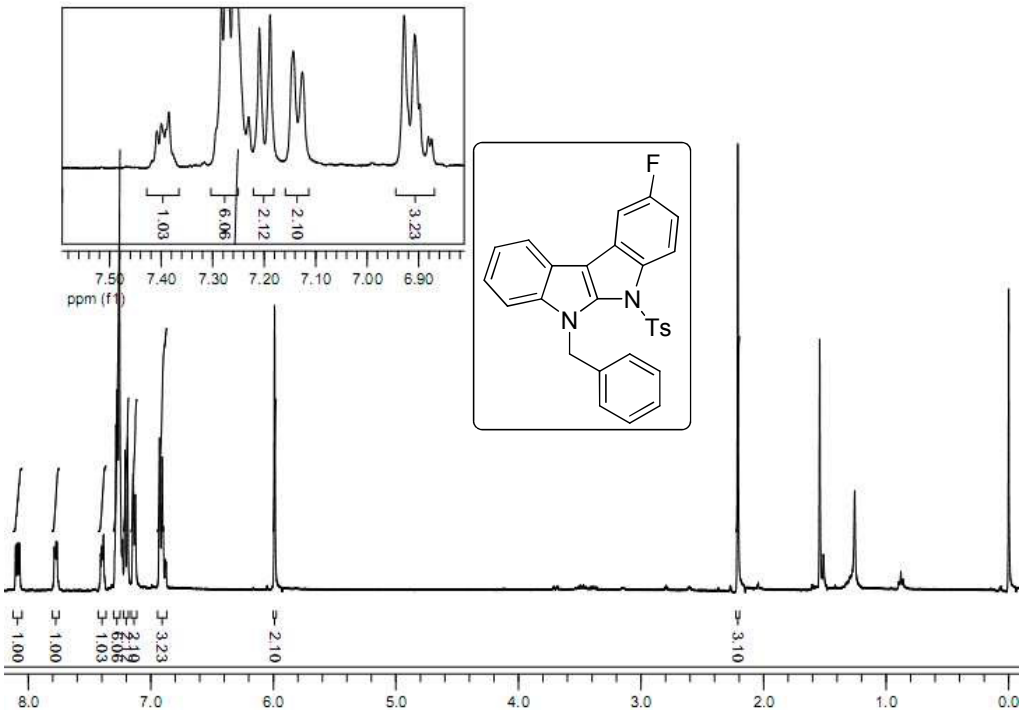

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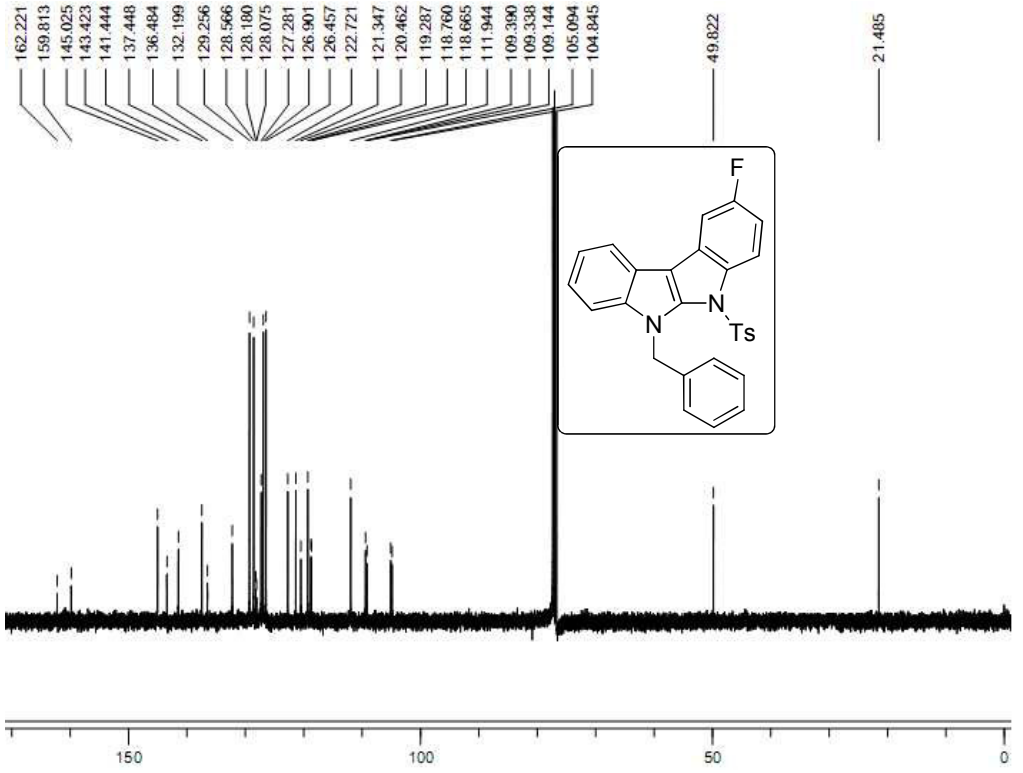

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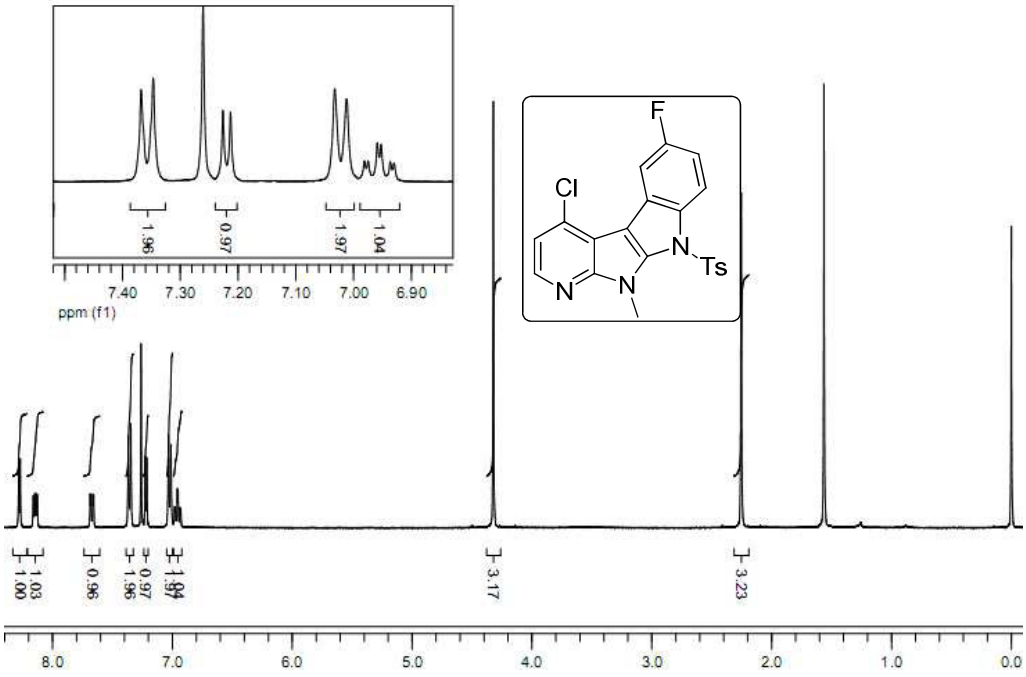

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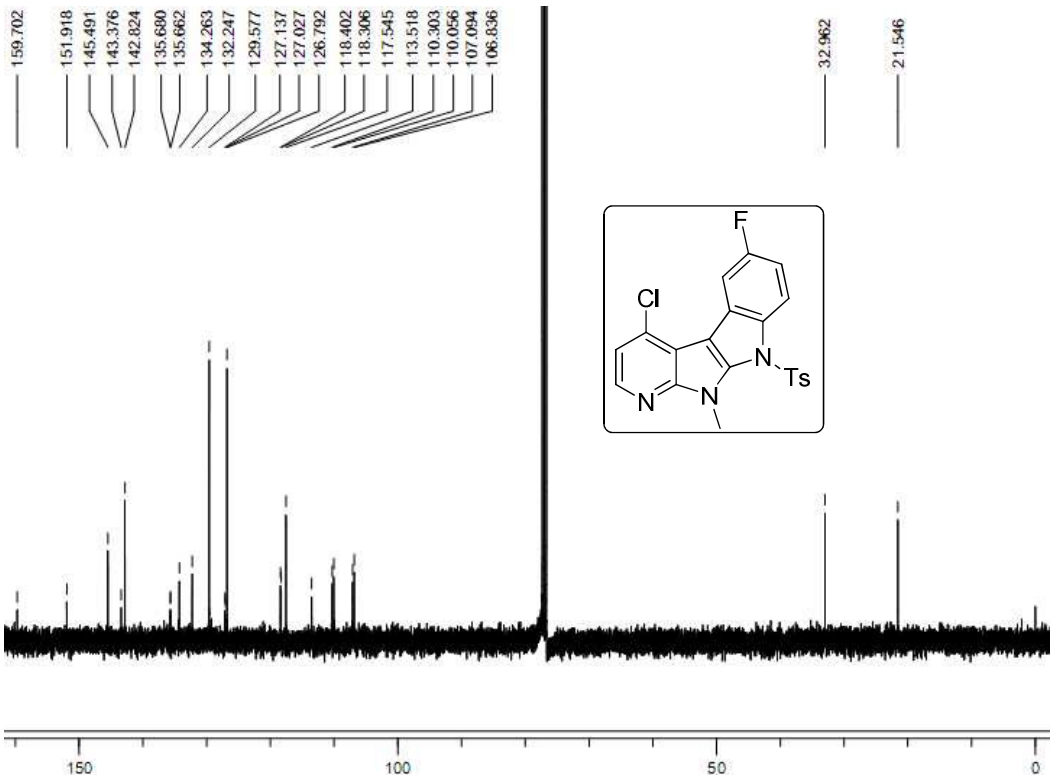

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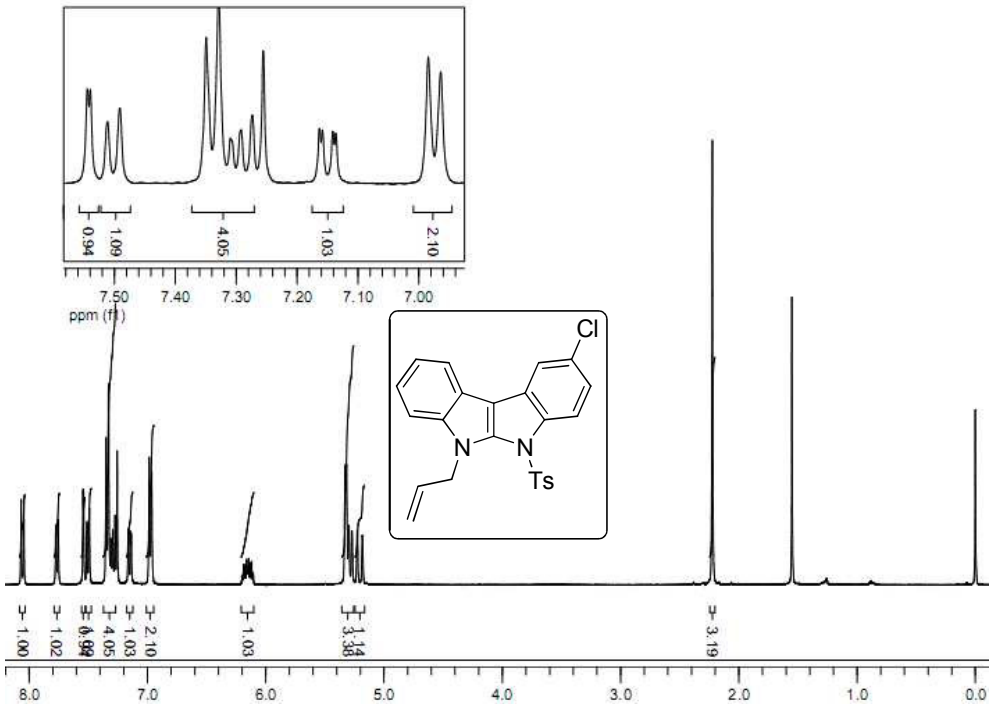
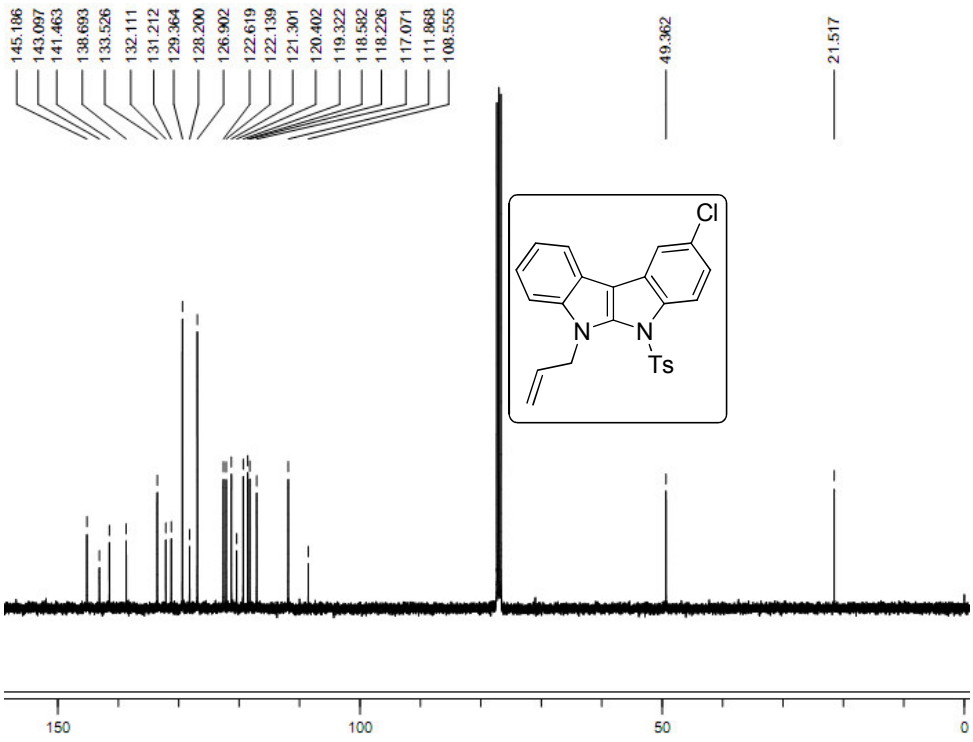


2.16m ^{13}C NMR (100 MHz, $CDCl_3$)



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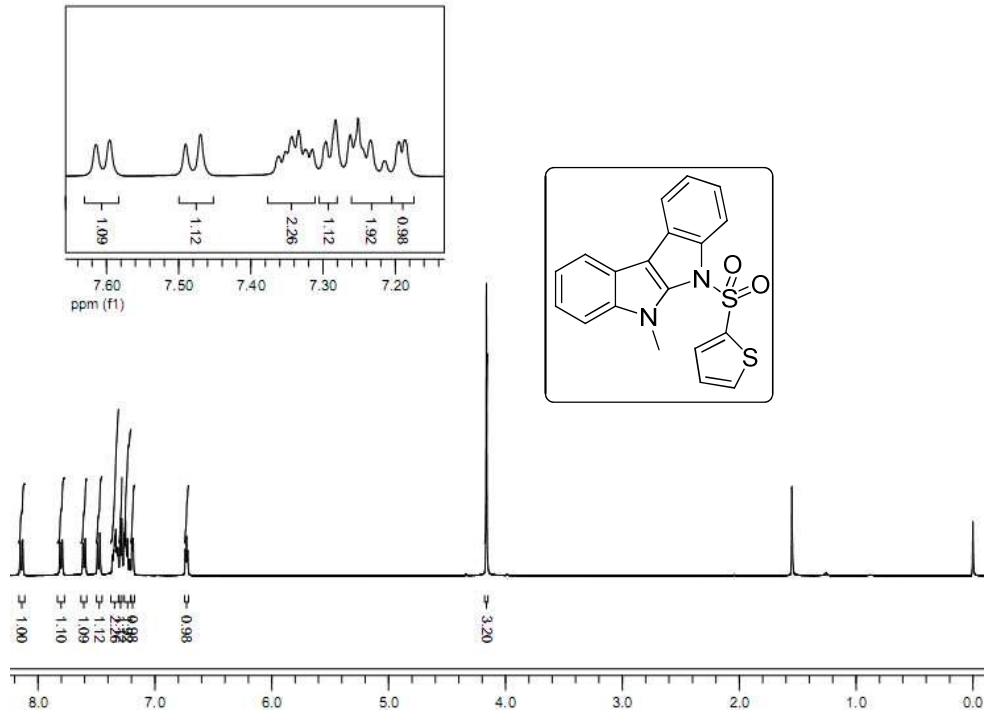
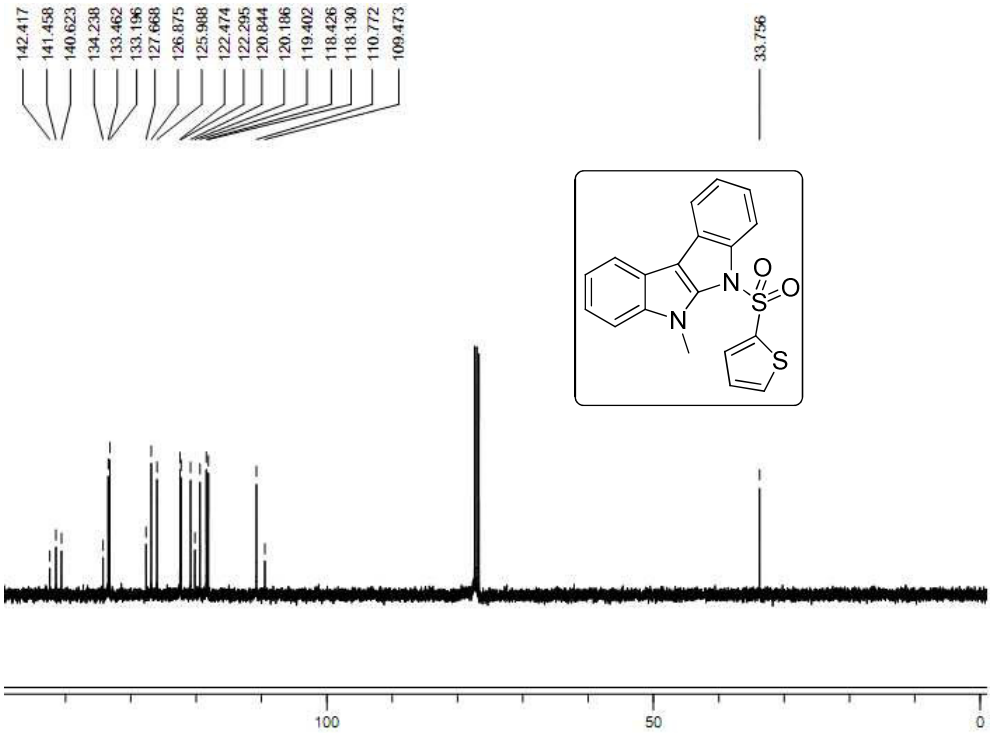
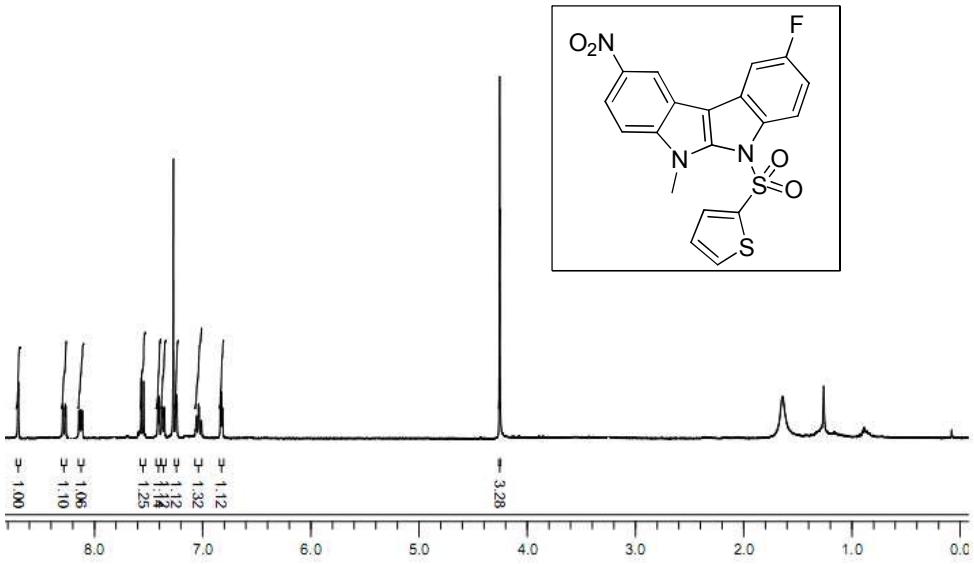


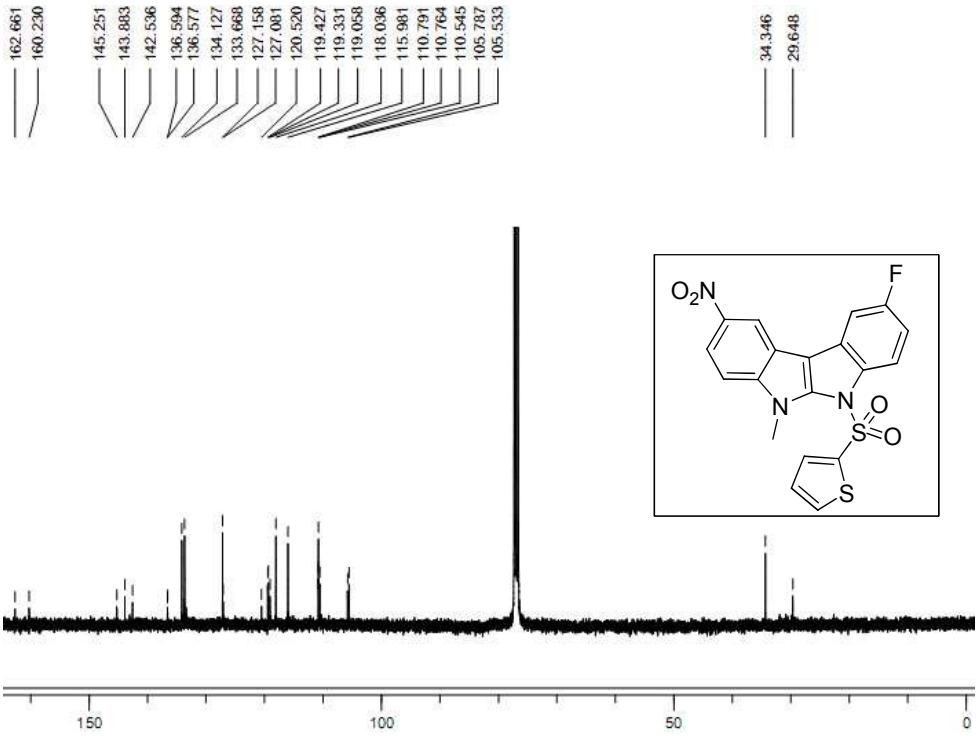
2.16r ^{13}C NMR (100 MHz, $CDCl_3$)



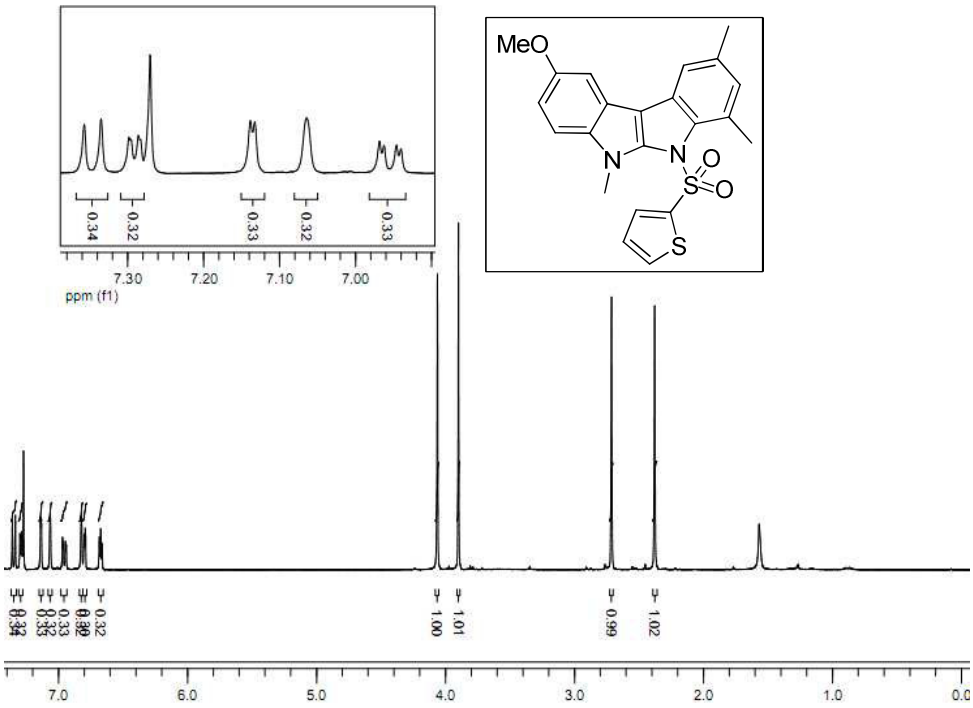
2.16t ^{1}H NMR (400 MHz, $CDCl_3$)



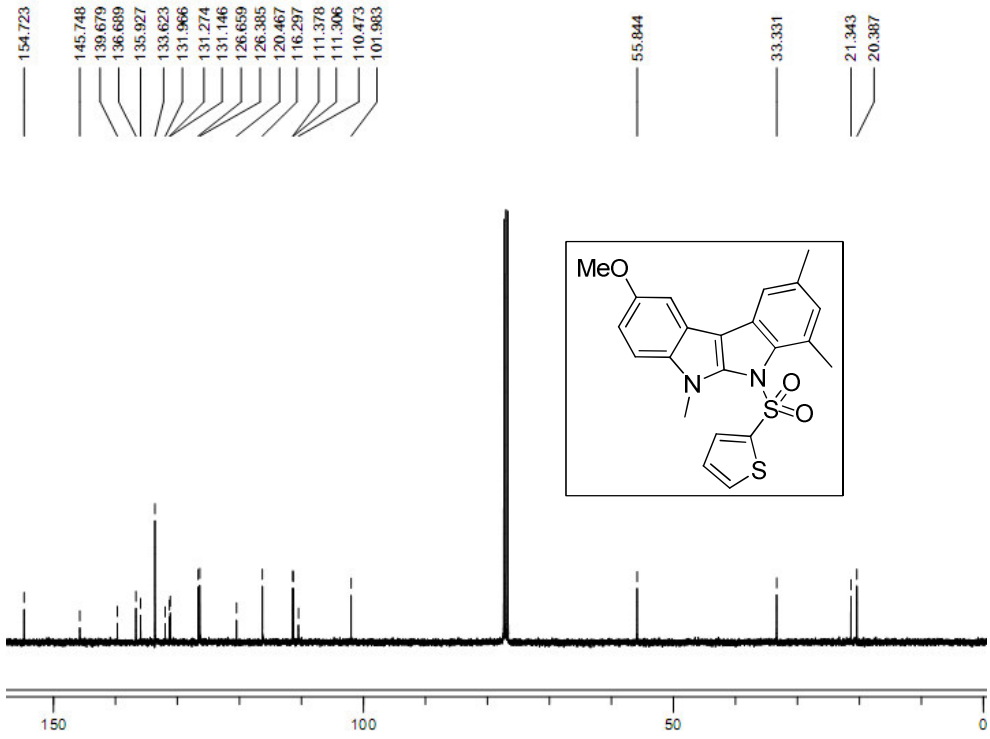
2.16t ^{13}C NMR (100 MHz, $CDCl_3$)



2.16v ^{1}H NMR (400 MHz, $CDCl_3$)

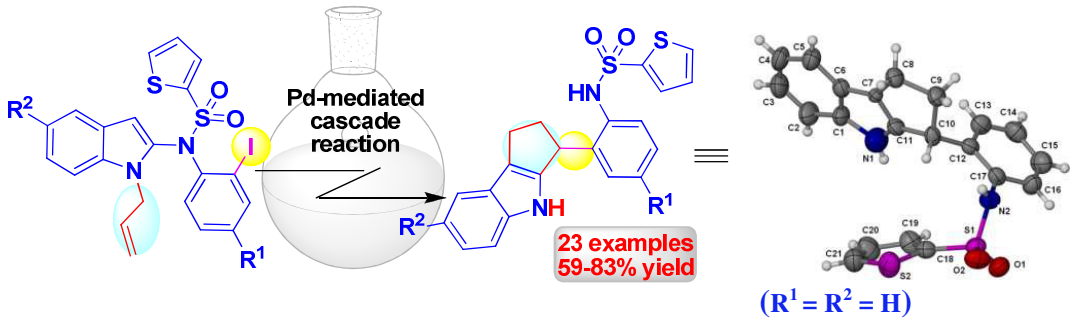


2.16v ^{13}C NMR (100 MHz, $CDCl_3$)



CHAPTER 3

Pd-catalyzed synthesis of cyclopenta[*b*]indole based PDE4 inhibitors



3.1 Introduction

As we discussed in Chapter 2 the unique structural features and versatile biological activities of fused indoles have made them an attractive target for the development of novel pharmacological lead compounds. For example, a fused indole *i.e.* 1,2,3,4-tetrahydrocyclopenta[*b*]indole is an integral part of natural product bruceollines[1], the tremorgenicmycotoxins[2] such as Paspaline (**F3.2**, Figure 3.1), Paxilline (**F3.3**, Figure 3.1) and Paspalitrem A (**F3.4**, Figure 3.1). A drug laropiprant (**F3.5**, Figure 3.1) is used in combination with niacin to reduce blood cholesterol contains 1,2,3,4-tetrahydrocyclopenta[*b*]indole skeleton (Figure 3.1).[3]

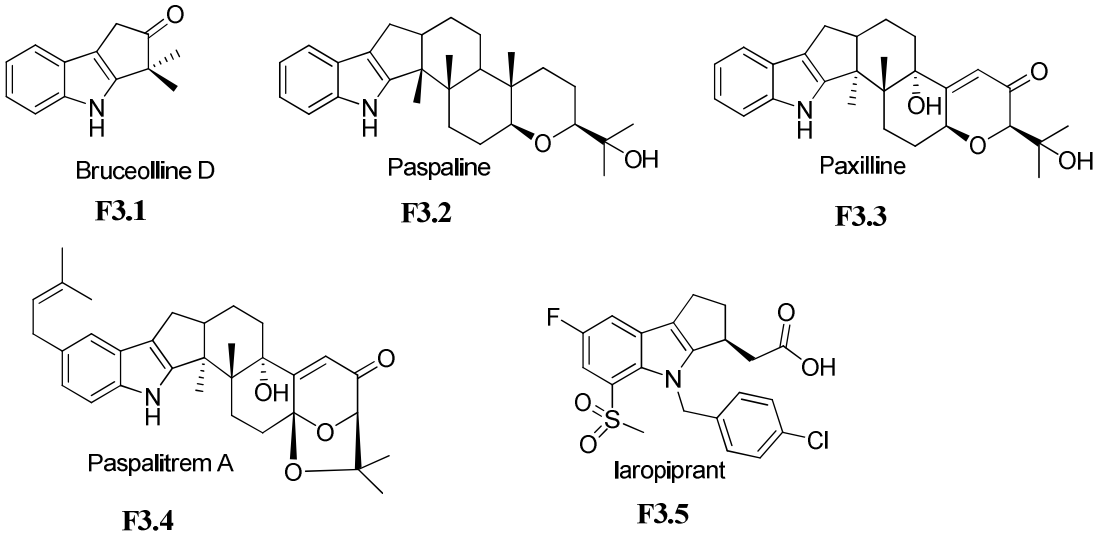


Figure 3.1 Biologically active 1,2,3,4-tetrahydrocyclopenta[*b*]indole compounds.

The presence of 1,2,3,4-tetrahydrocyclopenta[*b*]indole system in several biologically active natural products prompted us to explore cyclopenta[*b*]indole **3.14** (Figure3.2) as a new class of potential inhibitors of phosphodiesterase 4 (PDE4).

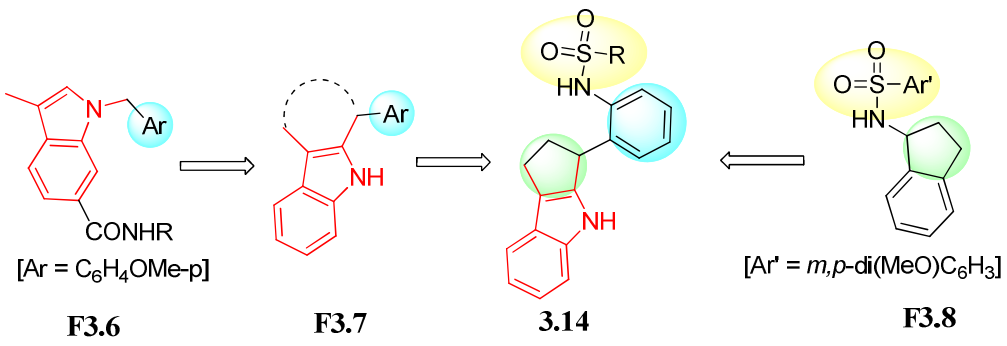
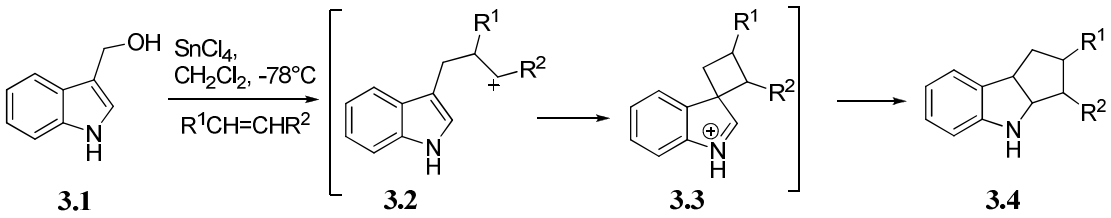


Figure 3.2 Design of **3.14** as novel inhibitors of PDE4.

PDE4 inhibitors are proved to be promising anti-inflammatory agents for the potential treatment of chronic obstructive pulmonary disease (COPD) and asthma.[4] Our target molecule **3.14** (Figure 3.2) derived from a known PDE4 inhibitor **F3.6** *via* **F3.7**[5] (Figure 3.2) and incorporating some of the structural features of another known inhibitor **F3.8**[6] (Figure 3.2) were designed based on the *in silico* docking studies of a representative compound **3.15a** in the active site of PDE4B. The synthesis of 1,2,3,4-tetrahydrocyclopenta[*b*]indole system has been reported in literature which are described below.

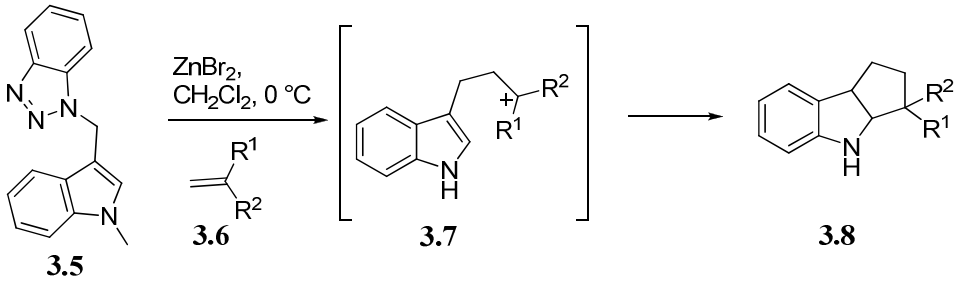
3.2 Previous work

In literature the synthesis of cyclopenta[*b*]indoles were reported using various methods. For example, in 1993, Moody and co-workers reported the synthesis of cyclopenta[*b*]indoles by the treatment of indole-2- or 3-methanols with tin (IV) chloride as a lewis acid in the presence of styrenes (Scheme 3.1). The reaction resulted in formal [3+2] cycloaddition of the indole stabilised cation to the alkene to give cyclopenta[*b*]indoles.[7]



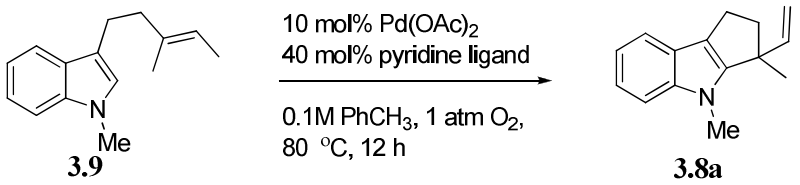
Scheme 3.1 Synthesis of cyclopenta[*b*]indoles.

Three years later in 1996, Katritzky and co-workers also reported a similar kind of [3 + 2] cycloaddition on treatment of **3.5** with styrenes in the presence of zinc bromide resulted in the formation of cyclopenta[*b*]indoles (Scheme 3.2).[8]



Scheme 3.2 Synthesis of cyclopenta[*b*]indoles.

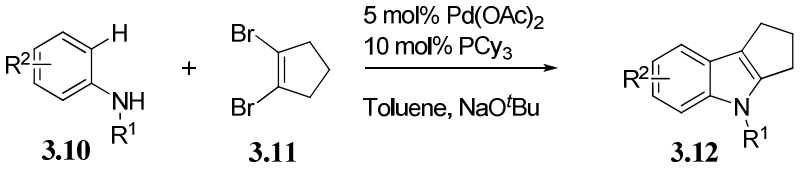
In 2003, Stoltz and co-workers reported a Pd catalysed aerobic oxidative annulation of indoles leading to cyclopenta[*b*]indoles (Scheme 3.3).[9]



3.9 **3.8a**

Scheme 3.3 Synthesis of cyclopenta[*b*]indoles.

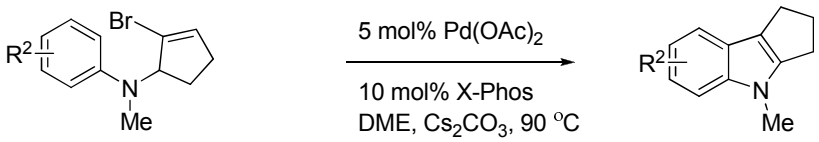
In 2007, Ackermann and co-workers reported a novel palladium-catalyzed domino reaction consisting of amination and a direct C-H bond arylation of compound **3.10** (Scheme 3.4). This allowed a general synthesis of annulated heterocycles starting from readily available 1,2-dibromo compounds and primary as well as secondary anilines.[10]



3.10 **3.11** **3.12**

Scheme 3.4 Synthesis of cyclopenta[*b*]indoles.

In 2010, Willis and co-workers reported palladium catalyzed intramolecular direct arylation reaction combined with an isomerization step provided a straight forward synthetic route to indoles (Scheme 3.5).[11]



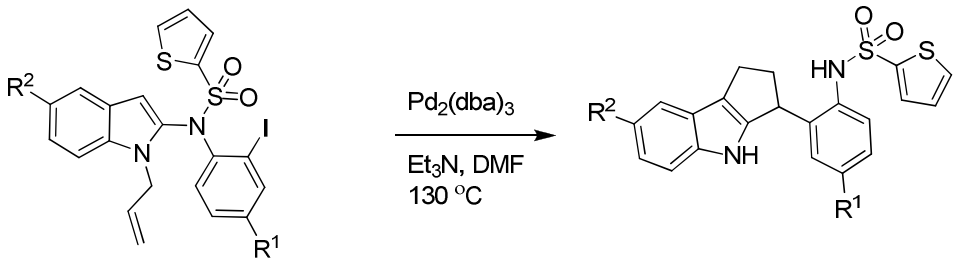
3.13 **3.12a**

Scheme 3.5 Synthesis of cyclopenta[*b*]indoles.

2.3 Present work

Though several methods have been reported in literature for the synthesis of cyclopenta[*b*]indoles, however diversity oriented synthetic approach for the quick generation of a library of molecules around this class is always desirable. Here we describe a novel, convenient method for a quick access to cyclopenta[*b*]indoles **3.14**. As part of our ongoing studies on newer synthesis of functionalized heteroaromatics[12]

including fused indoles[13] we further investigated the reactivity of *N*-(1-allyl-1*H*-indol-2-yl)-*N*-(2-iodoaryl)thiophene-2-sulfonamides towards Pd catalysts. To our surprise the reaction followed an unusual path with the formation of novel cyclopenta[*b*]indoles *i.e.* *N*-(2-(7-substituted-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-aryl)thiophene-2-sulfonamides as unexpected products (Scheme 3.6). Herein we describe a conceptually new synthesis of functionalized cyclopenta[*b*]indoles *via* a Pd-mediated cascade reaction[14] involving an intramolecular Heck coupling followed by the construction of a fused cyclopentane ring as a result of two C-N bonds cleavage and several C-C bond formations in a single pot.



2.15 **3.14**

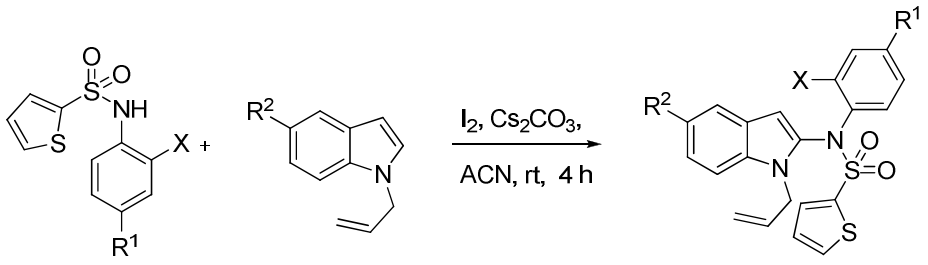
Scheme 3.6 Pd-mediated synthesis of novel cyclopenta[*b*]indoles.

3.4 Results and discussion

2.4.1 preparation of starting compounds

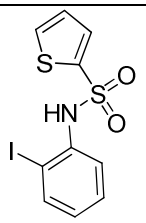
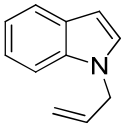
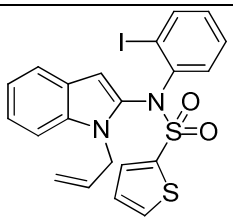
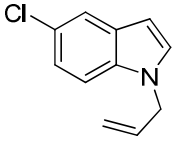
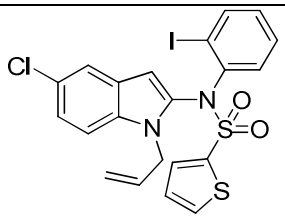
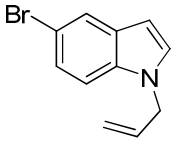
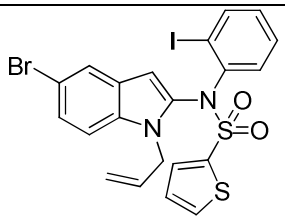
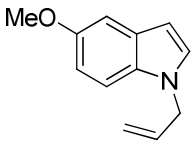
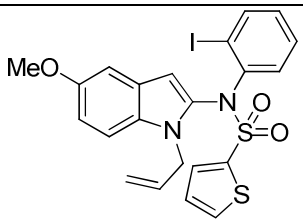
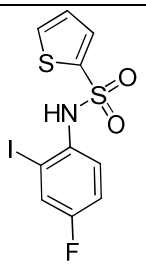
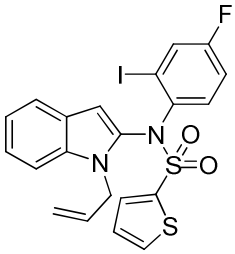
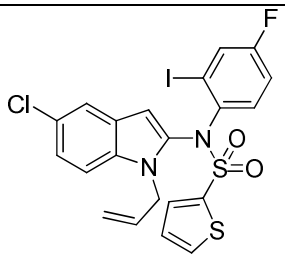
The synthesis of requisite starting material **2.15** was carried out according to the procedure described in Chapter 2 (Table 3.1).

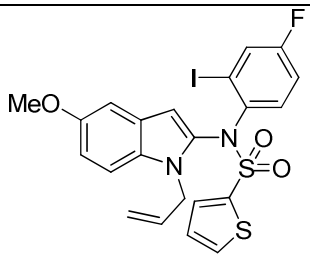
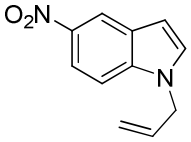
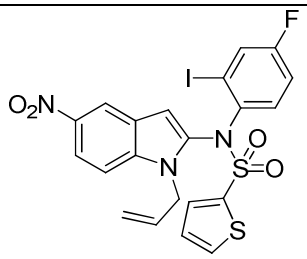
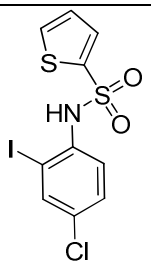
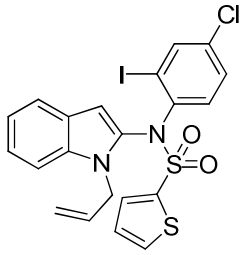
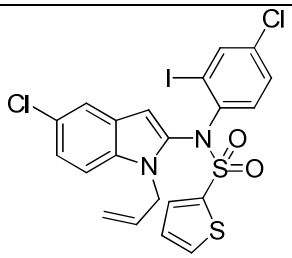
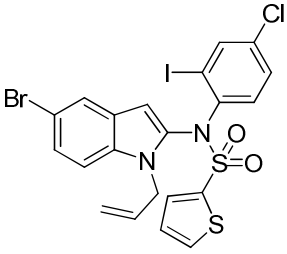
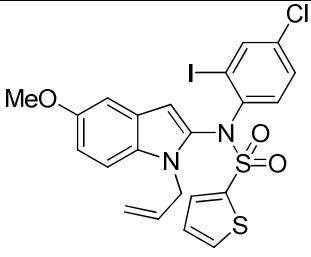
Table 3.1 Iodine mediated synthesis of *N*-(1-allyl-5-substituted-1*H*-indol-2-yl)-*N*-(2-iodo-4-substitutedphenyl)thiophene-2-sulfonamide.[a]

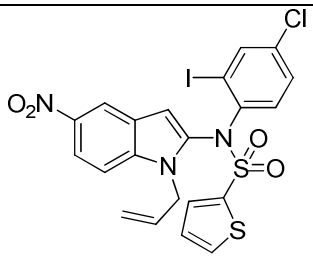
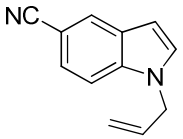
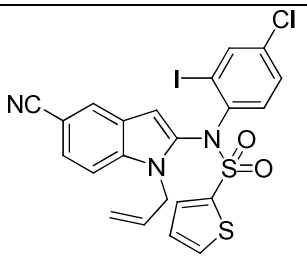
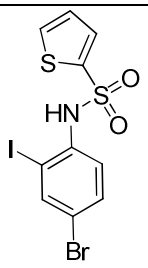
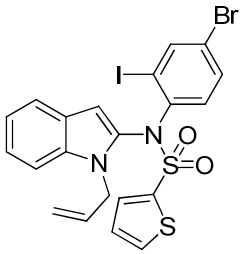
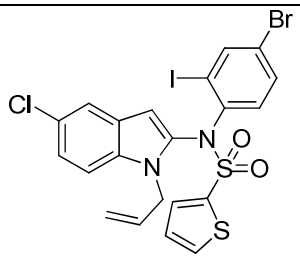
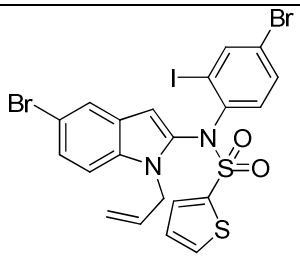
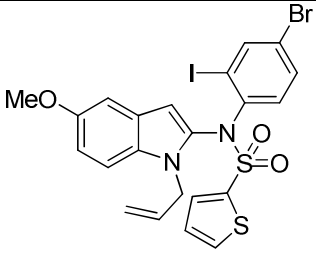


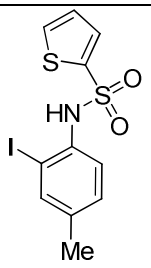
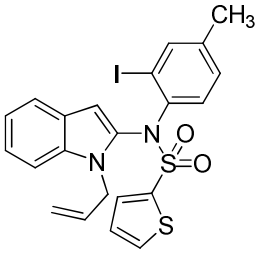
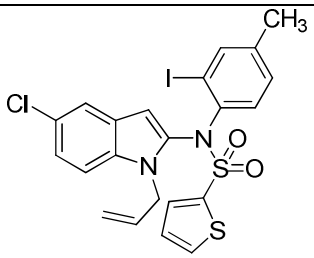
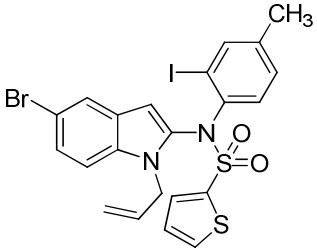
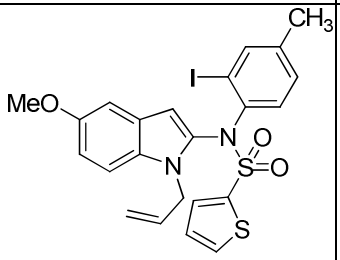
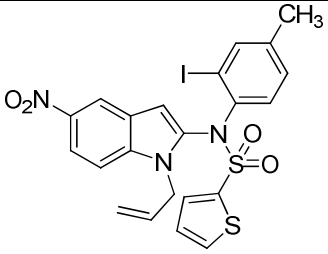
1.1 **2.14** **2.15**

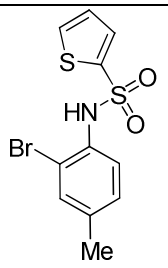
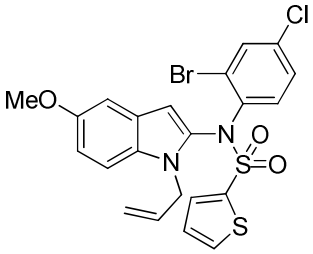
Entry	Iodo anilides (**1.1**)	Indole (**2.14**)	Product (**2.15**)	Yield[b] (%)

1	 **1.1n**	 **2.14b**	 **2.15nb**	58
2	**1.1n**	 **2.14f**	 **2.15nf**	58
3	**1.1n**	 **2.14h**	 **2.15nh**	47
4	**1.1n**	 **2.14m**	 **2.15nm**	50
5	 **1.1o**	**2.14b**	 **2.15ob**	56
6	**1.1o**	**2.14f**	 **2.15of**	45

7	**1.1o**	**2.14m**	 **2.15om**	46
8	**1.1o**	 **2.14o**	 **2.15oo**	48
9	 **1.1p**	**2.14b**	 **2.15pb**	52
10	**1.1p**	**2.14f**	 **2.15pf**	50
11	**1.1p**	**2.14h**	 **2.15ph**	48
12	**1.1p**	**2.14m**	 **2.15pm**	48

13	**1.1p**	**2.14o**	 **2.15po**	45
14	**1.1p**	 **2.14p**	 **2.15pp**	48
15	 **1.1q**	**2.14b**	 **2.15qb**	42
16	**1.1q**	**2.14f**	 **2.15qf**	46
17	**1.1q**	**2.14h**	 **2.15qh**	51
18	**1.1q**	**2.14m**	 **2.15qm**	43

19	 **1.1r**	**2.14b**	 **2.15rb**	60
20	**1.1r**	**2.14f**	 **2.15rf**	55
21	**1.1r**	**2.14h**	 **2.15rh**	44
22	**1.1r**	**2.14m**	 **2.15rm**	48
23	**1.1r**	**2.14o**	 **2.15ro**	43

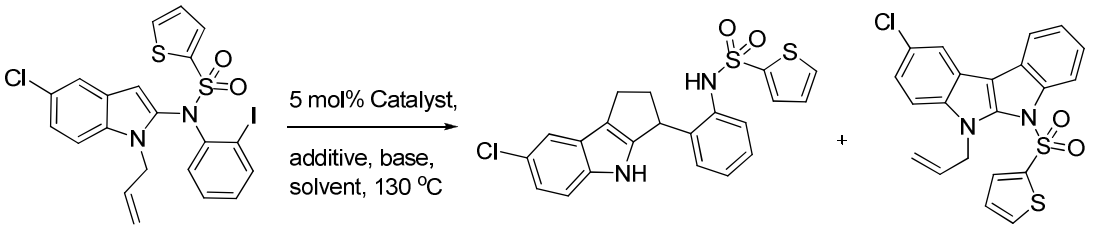
24	 **1.1u**	**2.14m**	 **2.15um**	60

[a]All the reactions were carried out using **1.1** (1.0 mmol), **2.14** (1.2 mmol), I_2 (1.0 mmol) and Cs_2CO_3 (1.5 mmol) in acetonitrile (5.0 mL), at room temperature under nitrogen.

[b]Isolated yield.

3.4.2 Reaction optimization

Table 3.2 Optimization of reaction conditions.[a]



2.15nf **3.14b** **2.16w**

Entry	Catalyst/additive	Base/solvent	time (h)	Yield (%)[b]	
				3.14b	**2.16w**
1	$Pd_2(dba)_3$	Et_3N/ EtOH	15	48	12[c]
2	$Pd_2(dba)_3$	Et_3N/ PEG	7	67	25
3	$Pd_2(dba)_3$	Et_3N/ DMF:H_2O (8:2)	7	63	28
4	$Pd_2(dba)_3$	Et_3N/ DMF	7	80	16
5	$Pd_2(dba)_3$	DBU/ DMF	7	58	36
6	$Pd_2(dba)_3$	K_2CO_3/ DMF	7	-	63[d]
7	$Pd(OAc)_2$	Et_3N/ DMF	4	-	84
8	$Pd(PPh_3)_2Cl_2$	Et_3N/ DMF	7	52	-[e]
9	$Pd(PPh_3)_4$	Et_3N/ DMF	7	46	-[e]
10	Pd/C / PPh_3	Et_3N/ DMF	12	44	-[e]
11	$Pd(OAc)_2$/ PPh_3	Et_3N/ DMF	5	-	84
12	$Pd(OAc)_2$/X-Phos	Et_3N/ DMF	4	22	70
13	$Pd(OAc)_2$/X-Phos	Et_3N/ DMF	4	-	83[f]

14	$Pd(PPh_3)_2Cl_2/Cu(OAc)_2$	Et_3N/ DMF	4	-	81
15	$Pd_2(dba)_3/Cu(OAc)_2$	Et_3N/ DMF	4	-	83
16	$Pd_2(dba)_3$	Et_3N/ DMF	7	47	48
17	$Cu(OAc)_2$	Et_3N/ DMF	8	-	-[g]

[a]Reaction conditions: **2.15nf** (1.0 mmol), catalyst (5.0 mol%) and base (2.5 mmol) in solvent (2.0 mL) at 130 °C.

[b]Isolated yield.

[c]The reaction was performed at 80 °C.

[d]The starting material was not consumed.

[e]Formation of unidentified and complex products was observed.

[f]The reaction was performed at room temperature.

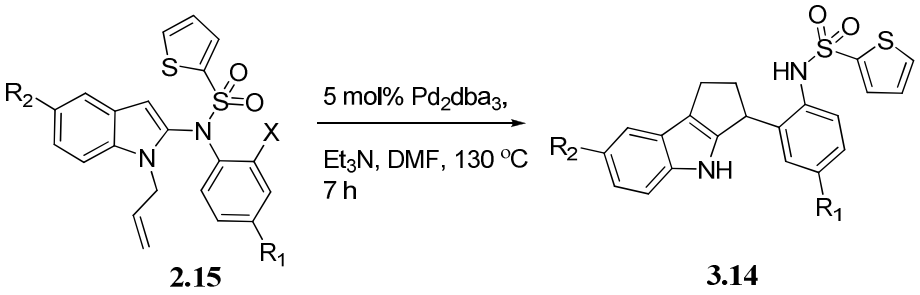
[g]1 mmol of catalyst was used.

The Pd-mediated cascade reaction of **2.15nf** was performed under a variety of conditions (Table 3.2) to establish the optimized reaction conditions. Initially, **2.15nf** was treated with Pd_2dba_3 and Et_3N in EtOH at 75 °C for 15 h, when **3.14b** was obtained as a major product (48% yield) along with indolo[2,3-*b*]indole **2.16w** (12%) and some unreacted **2.15nf** (entry 1**,** in Table 3.2**)**. Though the yield of **3.14b** was increased when the reaction was performed in PEG or DMF-H_2O (entry 2 and 3, Table 3.2) a significant improvement was observed when DMF was used as a solvent (entry 4, Table 3.2). The use of other base e.g. DBU or K_2CO_3 was not effective (entry 5 and 6, Table 3.2). Indeed, formation of **3.14b** was suppressed completely when K_2CO_3 was used. The **3.14b** was also not obtained when $Pd(OAc)_2$ was used as a catalyst (entry 7, Table 3.2), whereas the use of $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ or Pd/C-PPh_3 afforded **3.14b** in moderate to poor yield (entries 8-10, Table 3.2). The combination of $Pd(OAc)_2$with PPh_3 or X-Phos (entries 11-13, Table 3.2) or the use of $Cu(OAc)_2$ as a co-catalyst (entry 14 and 15, Table 3.2) mainly provided **2.16w** as a major or the only product. The use of LiCl as an additive afforded a 1:1 mixture of **3.14b** and **2.16w** (entry 16, Table 3.2) whereas $Cu(OAc)_2$ in place of Pd-catalyst was found to be ineffective (entry 17, Table 3.2). Overall, the combination of $Pd_2(dba)_3$ and Et_3N in DMF (entry **4** in Table 3.2**)** was found to be optimum for the preparation of **3.14b**.

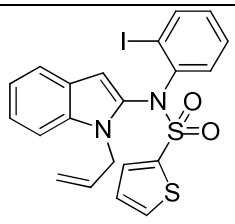
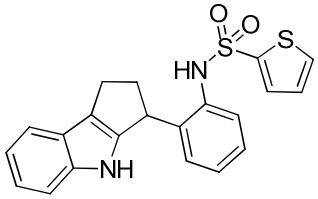
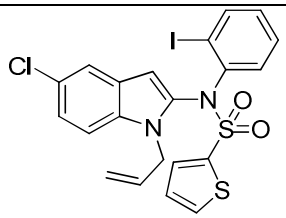
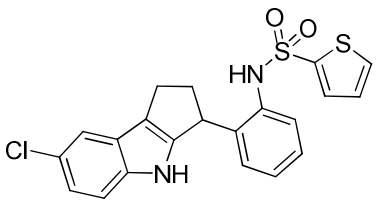
3.4.3 Scope of the reaction

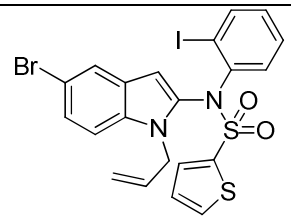
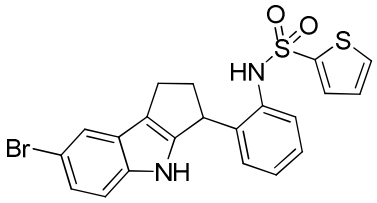
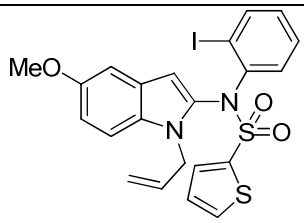
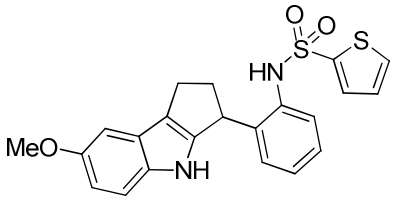
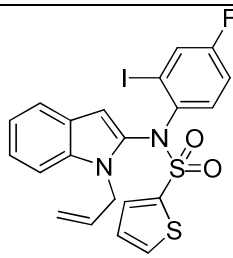
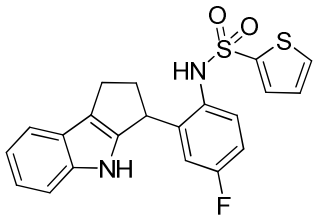
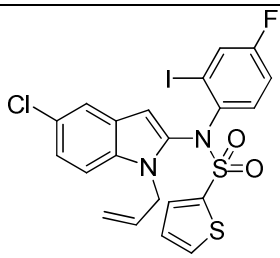
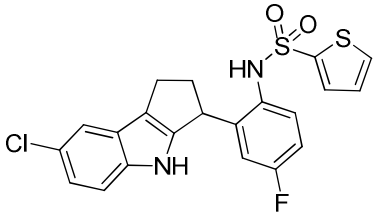
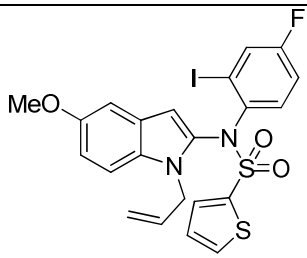
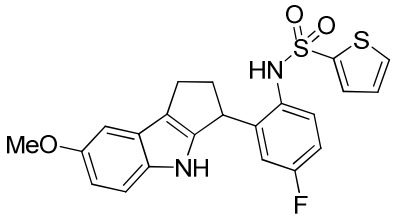
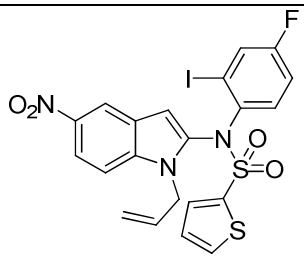
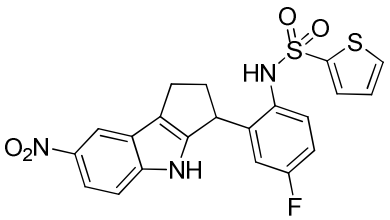
To examine the generality and further scope of this method we performed the Pd-mediated cascade reaction using various indole derivatives **3.14** (Table 3.3). Substituents like F (entries 5-8, Table 3.3), Cl (entries 2, 6, 9-14 and 20, Table 3.3) and Br (entries 3, 11, 15-18 and 21, Table 3.3), electron donating Me (entries 19-23, Table 3.3) and OMe (entries 4, 7, 12, 18 and 22, Table 3.3) groups or electron withdrawing NO_2 (entries 8, 13 and 23, Table 3.3) and CN (entry 14, Table 3.3) groups were well tolerated and a range of cyclopenta[*b*]indoles were prepared in good to acceptable yields. Notably, unlike **2.15** its bromo analogue *i.e.* *N*-(1-allyl-5-methoxy-1*H*-indol-2-yl)-*N*-(2-bromo-4-methylphenyl)thiophene-2-sulfonamide **2.15um** failed to participate in the present reaction to afford the corresponding cyclopenta[*b*]indole derivative (entry 24, Table 3.3).

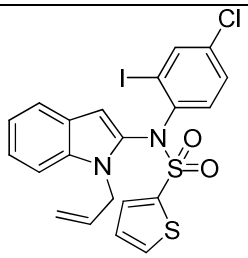
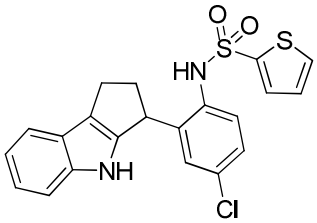
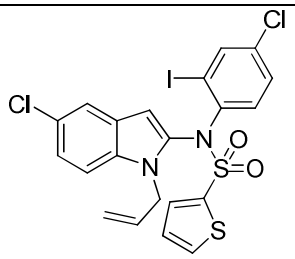
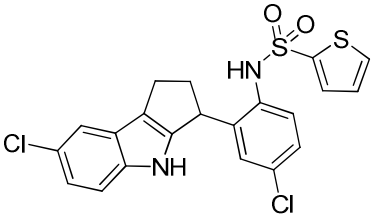
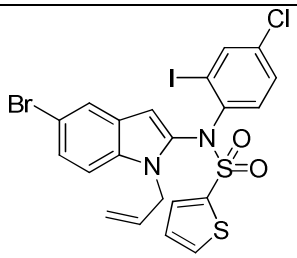
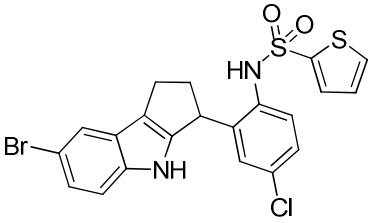
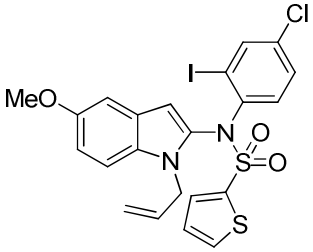
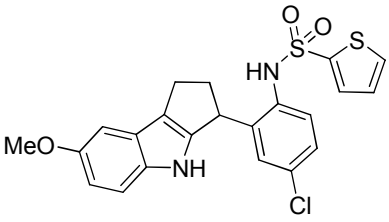
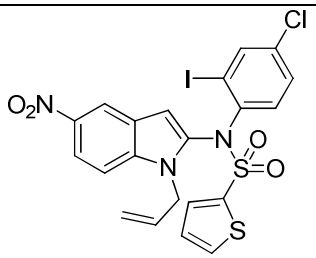
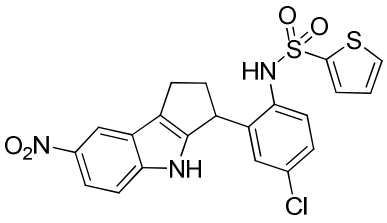
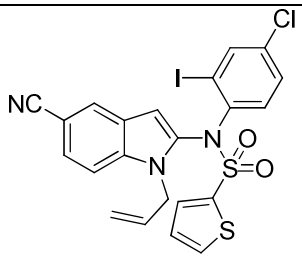
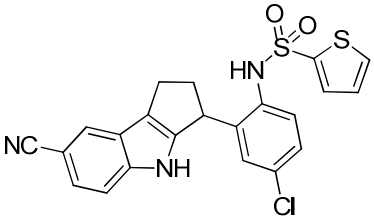
Table 3.3 Pd catalyzed synthesis of *N*-(2-(7-substituted-1,2,3,4-tetrahydrocyclo-penta[*b*]indol-3-yl)-4-substitutedphenyl)thiophene-2-sulfonamide.[a]

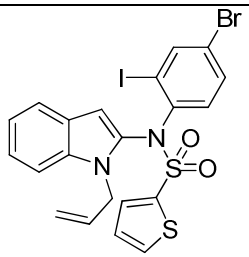
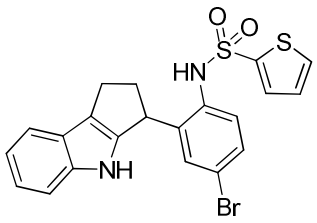
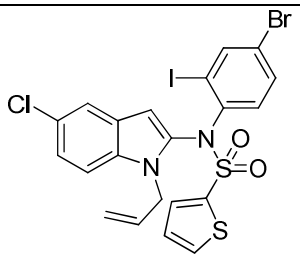
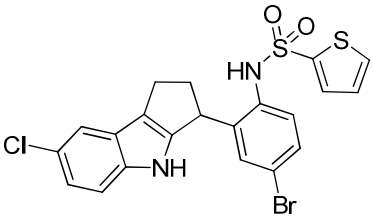
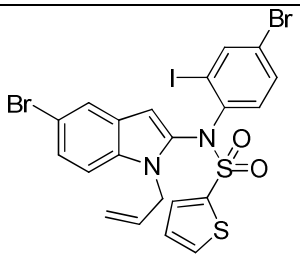
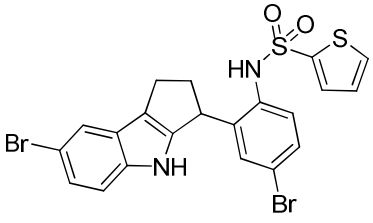
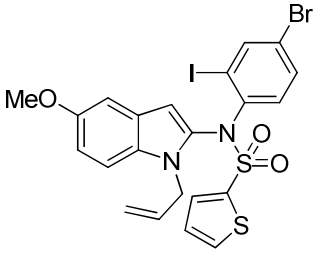
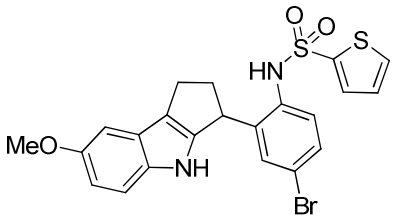
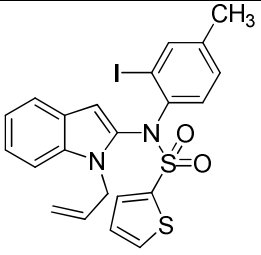
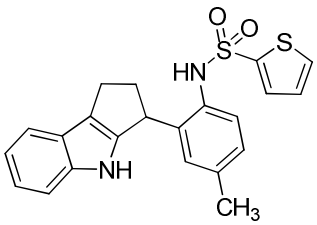
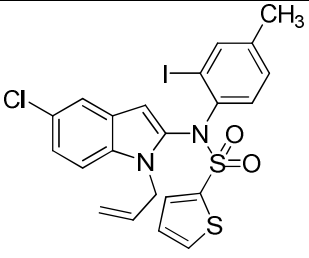
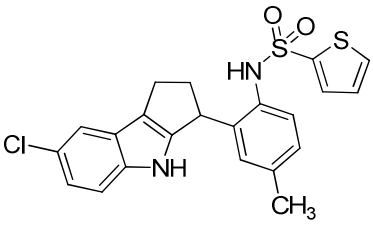


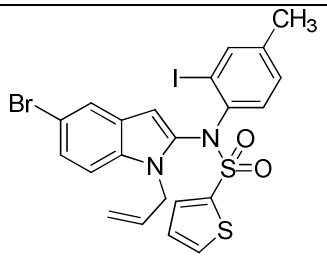
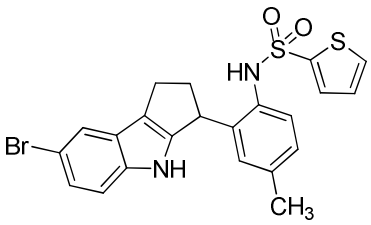
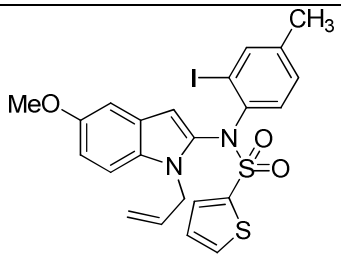
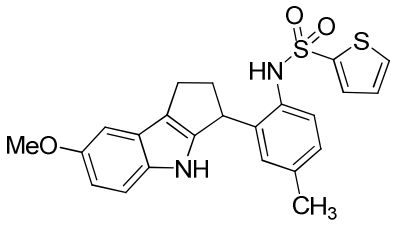
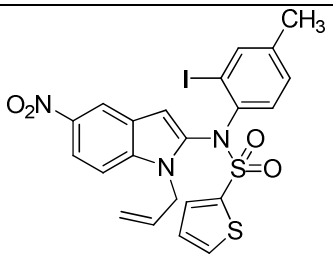
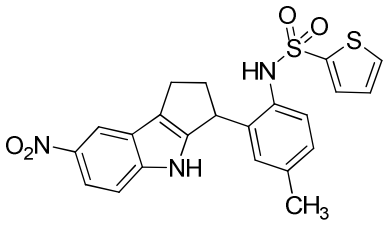
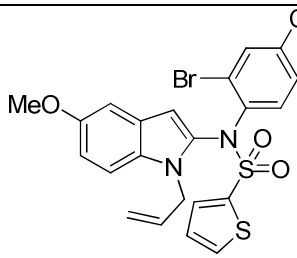
2.15 **3.14**

Entry	Compound (**2.15**)	Product (**3.14**)	Yield[b](%)
1	 **2.15nb**	 **3.14a**	81
2	 **2.15nf**	 **3.14b**	80

3	 **2.15nh**	 **3.14c**	72
4	 **2.15nm**	 **3.14d**	70
5	 **2.15ob**	 **3.14e**	71
6	 **2.15of**	 **3.14f**	68
7	 **2.15om**	 **3.14g**	62
8	 **2.15oo**	 **3.14h**	62

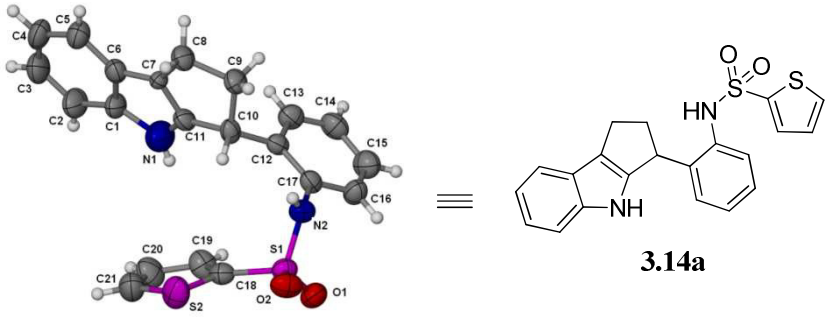
9	 **2.15pb**	 **3.14i**	78
10	 **2.15pf**	 **3.14j**	71
11	 **2.15ph**	 **3.14k**	68
12	 **2.15pm**	 **3.14l**	69
13	 **2.15po**	 **3.14m**	66
14	 **2.15pp**	 **3.14n**	59

15	 **2.15qb**	 **3.14o**	78
16	 **2.15qf**	 **3.14p**	70
17	 **2.15qh**	 **3.14q**	83
18	 **2.15qm**	 **3.14r**	68
19	 **2.15rb**	 **3.14s**	76
20	 **2.15rf**	 **3.14t**	68

21	 **2.15rh**	 **3.14u**	80
22	 **2.15rm**	 **3.14v**	81
23	 **2.15ro**	 **3.14w**	73
24	 **2.15um**	No product	-

[a]All the reactions were performed using **2.15** (0.4 mmol), $Pd_2(dba)_3$ (5 mol%) and Et_3N (1.2mmol) in DMF (2 mL) at 130 °C for 7 h under N_2.

[b]Isolated yield.



3.14a

Figure 3.3 ORTEP representation of **3.14a** (Thermal ellipsoids are drawn at 50% probability level.)

All the compounds synthesized were well characterized by spectral (NMR, IR and MS) data and the molecular structure of a representative compound **3.14a** was confirmed unambiguously by single crystal X-ray diffraction study (Figure 3.3).[15]

3.4.4 Proposed mechanism

3.4.4.1 Reaction performed in support of the mechanism

To explain the present cascade reaction we assumed that reaction might proceed *via* **E-3** intermediate leading to product (Figure 3.4).

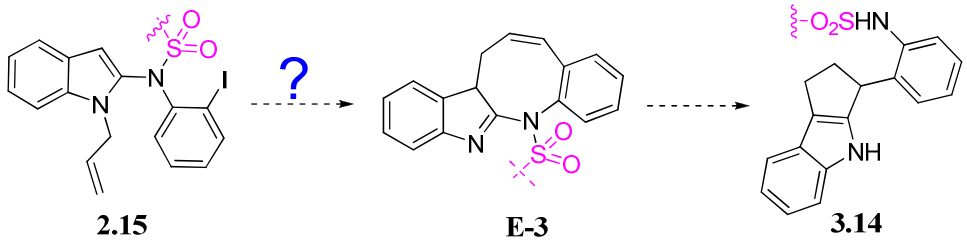


Figure 3.4 The possible intermediate in reaction.

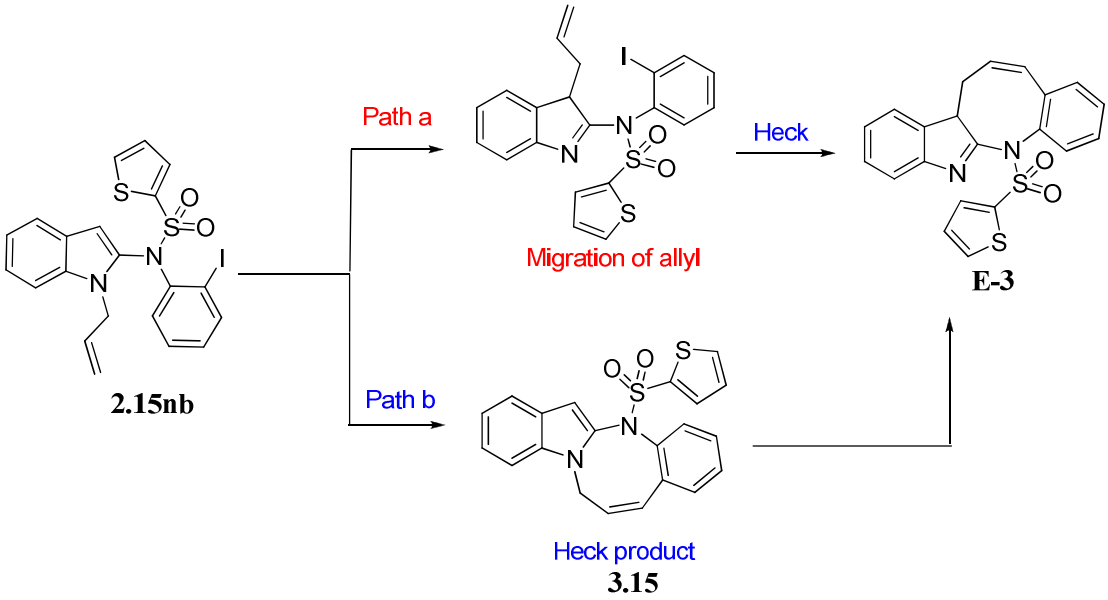
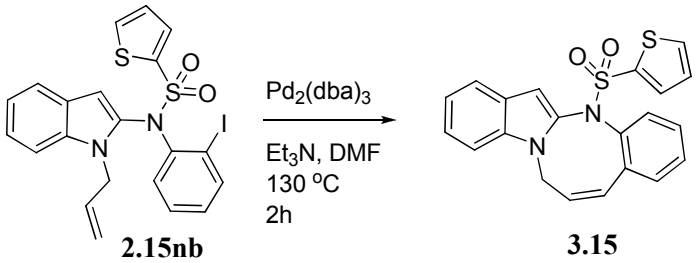


Figure 3.5 The possible paths to reach **E-3** intermediate in reaction.

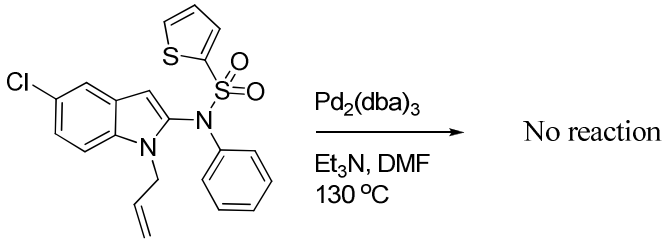
There were two possible path ways for the formation of **E-3** intermediate (Figure 3.5). In path a, the reaction proceeds *via* allyl migration from *N*-allyl to C-3 indole followed by Heck reaction. The other possibility was heck reaction followed by ring opening and ring closing electro cyclizations as showed in path b. Indeed we isolated

Heck product **3.15** (Scheme 3.7) during the course of reaction indicated that intramolecular Heck reaction might be the initial step. It was further supported by the reaction did not proceed with a deiodinated analogue of **3.14** *i.e. N*-(1-allyl-5-chloro-1*H*-indol-2-yl)-*N*-phenylthiophene-2-sulfonamide under the optimized conditions [Scheme 3.8].



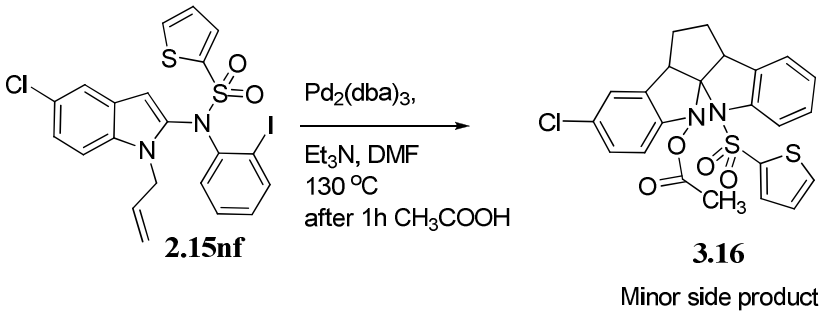
2.15nb **3.15**

Scheme 3.7 The Heck product **3.15** isolated from the reaction of **2.15nb**



2.15nf

Scheme 3.8 the reaction of a deiodinated analogue of **2.15nf**.

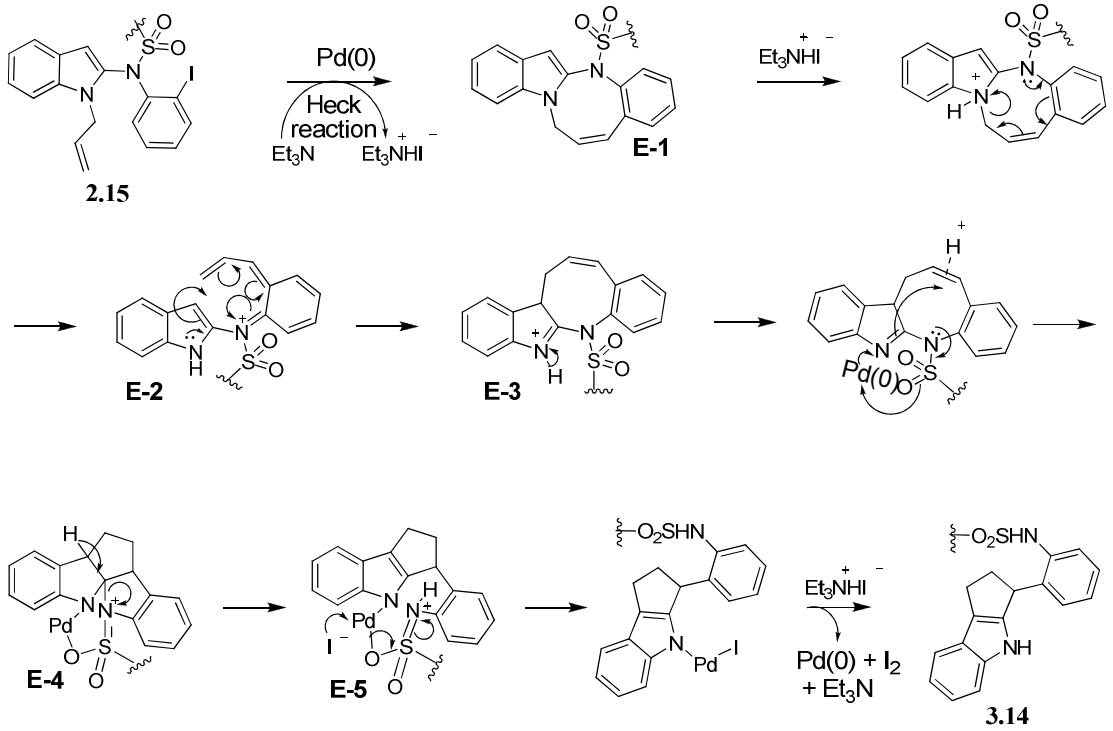


2.15nf **3.16**

Minor side product

Scheme 3.9 The side product **3.16** isolated from **2.15nf**.

While all our attempts to isolate any other intermediates were not successful however, we were able to isolate a side product **3.16** [Scheme 3.9] along with **3.14b** from the conversion of **2.15nf** under the condition of entry 4 of Table 3.2 in the presence of catalytic acetic acid. The compound **3.16** seemed to have formed *via* a nucleophilic attack on the iminium nitrogen of the intermediate obtained from **E-3** by the acetate ion (Scheme 3.9).



Scheme 3.10 The proposed reaction mechanism.

Based on the above observations, the reaction seemed to proceed *via* generation of **E-1** *in situ via* an intramolecular Heck reaction (*cf* **3.15**, Scheme 3.7) which then undergoes a C-N bond cleavage near the indole nitrogen to give **E-2**. A subsequent intramolecular attack of the indole ring *via* C-3 position on the C-C double bond provides **E-3**. Activation of the -C=N- of **E-3** in the presence of Pd(0) aided by the proximate sulfonamide moiety facilitated a further intramolecular attack on the olefinic double bond leading to **E-4** (instead of acetate ion, *cf* (**3.16**) Scheme 3.9). The six-membered Pd-containing ring of **E-4** then undergoes a C-N bond cleavage to give **E-5** which after following few more steps including the reductive elimination of Pd(0) completed the catalytic cycle affording the product **3.14**. It is evident that the sulfonamide moiety played a key role in the present cascade reaction the electron releasing property of which towards Pd was greatly facilitated by the electron rich thienyl moiety. This perhaps provides some explanations to the observation that replacing thienyl moiety of **2.15** by a benzene ring did not provide **3.14** as a major product.[16a] Nevertheless, it is evident from Table 3.2 that the formation of **3.14** was also dependent on the nature of catalyst/solvent used.

3.5 Pharmacology

3.5.1 *In vitro* data

Some of the compounds synthesized were tested against PDE4B along with a known inhibitor rolipram as a reference compound using an *in vitro* enzyme assay.[16] The compounds **3.14a, 3.14b, 3.14c, 3.14d, 3.14m, 3.14o, 3.14q, 3.14u** and **3.14v** showed 43, 42, 64, 41, 58, 45, 40, 40 and 49% inhibition respectively at 30 μM and **3.14v** (IC_{50} > 5 μM vs rolipram's IC_{50} ~ 1 μM) being the best among them. Since COPD and asthma are major health burden worldwide hence the present class of new chemical entities is of further interest.

3.5.2 *In silico* studies

The binding pose of inhibitor **3.14a** in the catalytic pocket of PDE4B protein is shown in Figure 3.5. In its docked conformation indole nitrogen of inhibitor **3.14a** makes hydrogen bond interaction with the side chain amino group of Gln 443(docking score -22.94). Rolipram makes hydrogen bond with the side chain of His234, Gln443 (Figure 3.6). The docking results of the **3.14a** and rolipram (a known inhibitor of PDE4B) are given in Table 3.4, which are ranked on the basis of their MOE Docking scores.

Table 3.4 Molecular interactions summary of top-ranked docking poses of rolipram and the molecule **3.14a**.

H-bond interactions	
Compounds	**PDE4B**
Rolipram	His234, Gln443
Molecule **3.14a**	Gln443

MOE Dockscore (K.cal/mol)	
Compounds	PDE4B
Rolipram	-22.94
Molecule **3.14a**	-18.22

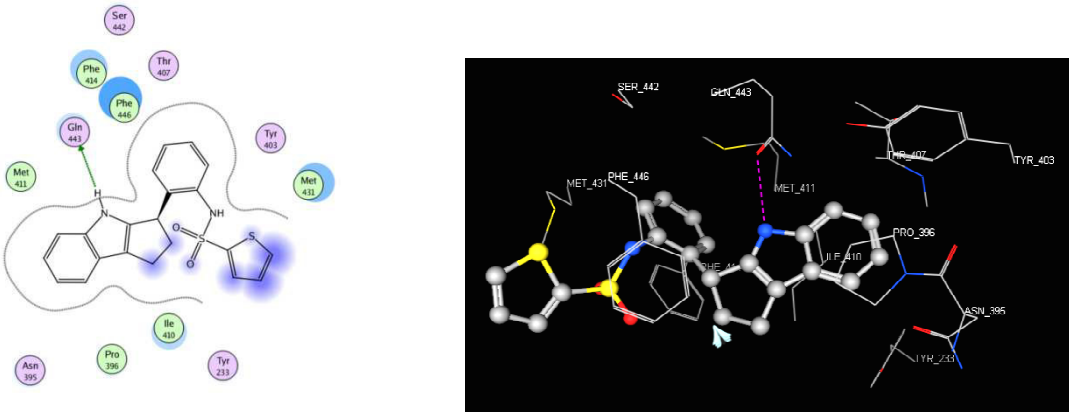


Figure 3.5 Binding mode of **3.14a** in PDE4B (PDBID: 1XMY), showing hydrogen bonding with GLN 443

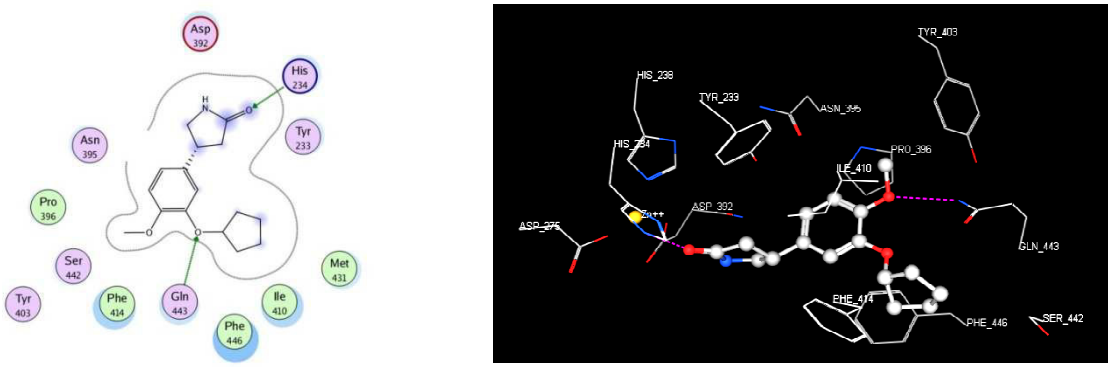


Figure 3.6 Binding mode of rolipram in PDE4B (PDBID: 1XMY), showing hydrogen bonding with GLN 443 and His234.

3.6 Conclusions

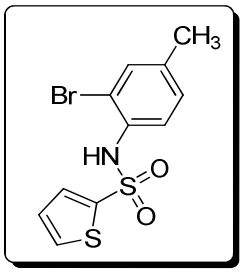
In this study, we have demonstrated a Pd-mediated novel and diverse cascade reaction which involved intramolecular heck coupling followed by the construction of a fused cyclopentane ring in a single pot. Thus, the present methodology provided a direct access to cyclopenta[*b*]indoles in a single pot. The cascade reaction involved two C-N bonds cleavage whereas three new C-C bonds were formed in the same reaction. The molecular structure of a representative compound **3.14a** was confirmed unambiguously by single crystal X-ray diffraction study. Some of the compounds synthesized were tested for PDE4B inhibitory properties *in vitro* when some of them showed promising inhibition of PDE4B.

3.7 Experimental Section

3.7.1 Chemistry

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were recodred in $CDCl_3$ solution by using 400 MHz spectrometer. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT- IR spectrometer. Melting points were determined using melting point apparatus and are uncorrected. MS spectra were obtained on a Agilent 6430 series Triple Quard LC-MS / MS spectrometer. Melting points (mp) were by using Buchi B-540 melting point appratus. Chromatographic purity by HPLC (Agilent 1200 series Chem Station software) was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention times.

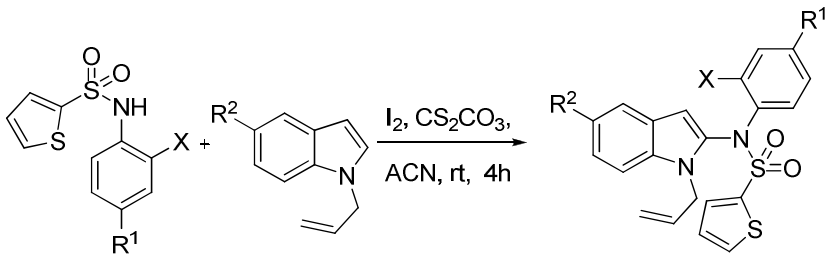
3.7.1.1 Procedure for the preparation of *N*-(2-bromo-4-methylphenyl)thiophene-2-sulfonamide (1.1v)



Thiophene-2-sulfonyl chloride (1.2 mmol) was slowly added to compound **1.22** (1 mmol) in pyridine (5mL) at 0 °C under nitrogen atmosphere. Then, the reaction mixture stirred at rt for 3-6 h. After completion of reaction monitored by TLC, the reaction mixture was diluted with ethyl acetate (30 mL), washed with 2N HCl solution (25 mL) followed by brine solution (25 mL) and dried over anhydrous

Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-hexane to give the desired product **1.1v**. White solid; yield: 87%; mp: 78-80 °C; R_f(10% EtOAc-*n*-Hexane) 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 8.4 Hz, 1H), 7.56 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.46 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.27 (s, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.02 (t, *J* =4.0 Hz, 1H), 6.90 (bs, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.4, 132.9, 132.8, 132.8, 131.6, 129.3, 127.3, 123.9, 123.8, 116.6, 20.6; IR (KBr, cm^{-1}): 3263, 3099, 2919, 1492, 1338, 1162; MS (ES mass): *m*/*z* 329.4 (M-1).

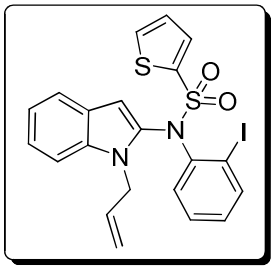
3.7.1.2 General procedure for the preparationof *N*-(1-allyl-5-substituted-1*H*-indol-2-yl)-*N*-(2-iodo-4-substitutedphenyl)thiophene-2-sulfonamide (2.15):



To a mixture of *N*-(2-iodophenyl)methane/4-methylbenzene/thiophene-2-sulfonamide derivative **1.1** (1.0 mmol)**,** Cs_2CO_3 (1.5mmol), I_2 (1 mmol) in acetonitrile (2.5 mL) was added indole derivative **2.14** (1.2 mmol). Then the mixture was stirred at room temperature under nitrogen for 4-6 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with a saturation solution of $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate–hexane to give the desired product (**2.15)** with 58-76% yields.

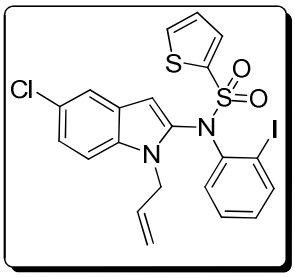
3.7.1.2.1 *N*-(1-Allyl-1*H*-indol-2-yl)-*N*-(2-iodophenyl)thiophene-2-sulfonamide (2.15nb)

2.15nb was prepared *via* the reaction of **1.1n** with **2.14b** according to the general procedure as mentioned above.



Off white solid; yield: 58%; mp: 160-162 °C; R_f (15% EtOAc-*n*-Hexane) 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.70 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.57-7.52 (m, 2H), 7.39 (dd, *J* = 8.05, 1.2 Hz, 1H), 7.32-7.29 (m, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.12 (td, *J* = 13.9, 5.5 Hz, 2H), 7.04-7.00 (m, 1H), 6.49 (s, 1H), 5.92-5.82 (m, 1H), 5.19 (s, 2H), 5.05 (dd, *J* = 10.3, 1.2 Hz, 1H), 4.91 (d,*J* = 17.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.2, 141.2, 137.3, 135.3, 134.9, 134.2, 134.0, 133.8, 130.3, 130.1, 128.9, 127.3, 125.8, 122.9, 121.0, 120.1, 116.3, 111.1, 101.5, 101.1, 46.8; HPLC: 99.9%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.66 min; IR (KBr, cm^{-1}): 3087, 1458, 1362, 1163; MS (ES mass): *m/z* 520.9 (M-+1).

3.7.1.2.2 *N*-(1-Allyl-5-chloro-1*H*-indol-2-yl)-*N*-(2-iodophenyl)thiophene-2-sulfonamide (2.15nf)

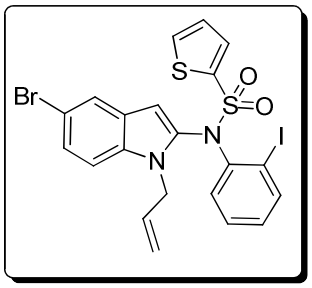


2.15nf was prepared *via* the reaction of **1.1n** with **2.14f** according to the general procedure as mentioned above.

Off white solid; yield: 58%; mp: 132-134 °C; R_f (10% EtOAc-*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ:7.97 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 4.8 Hz, 1H), 7.51 (d, *J* = 6.1 Hz, 2H), 7.36-7.30 (m, 2H), 7.25-7.21 (m, 1H), 7.17-7.13 (m, 2H), 7.07-7.00 (m, 1H), 6.42 (s, 1H), 5.90-5.80 (m, 1H), 5.19 (s, 2H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.89 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.2, 141.3, 137.1, 135.4, 135.3, 134.0, 133.7, 133.2, 130.3, 130.2, 128.9, 127.4, 126.7, 125.9, 123.3, 120.3,

116.6, 112.3, 101.5, 100.6, 47.1; HPLC: 96.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 0.5/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 235 nm, retention time 4.84 min; IR (KBr, cm^{-1}): 3097, 2921, 1457, 1372, 1102; MS (ES mass): *m*/*z* 554.7 (M+1).

3.7.1.2.3 *N*-(1-Allyl-5-bromo-1*H*-indol-2-yl)-*N*-(2-iodophenyl)thiophene-2-sulfonamide (2.15nh)

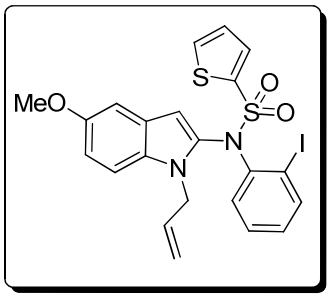


2.15nh was prepared *via* the reaction of **1.1n** with **2.14h** according to the general procedure as mentioned above.

Off white solid; yield: 47%; mp: 138-140 °C; R_f (10% EtOAc-*n*-Hexane) 0.31; ^1H NMR (400 MHz, $CDCl_3$) δ:7.97 (d, *J* = 7.6 Hz, 1H), 7.72 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.52-7.51 (m, 1H), 7.34 (d, *J* = 2.0 Hz, 1H),7.32 (dd, *J* = 6.8, 0.8 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H),7.18 (d, *J* = 8.8 Hz, 1H), 7.14(t, *J* = 4.8 Hz, 1H), 7.04 (td, *J* = 8.0, 2.0 Hz, 1H), 6.42 (s, 1H), 5.90-5.80 (m, 1H), 5.18 (d, *J* = 2.40 Hz, 2H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.88 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.2, 141.3, 137.1, 135.4, 135.2, 134.0, 133.7, 133.5, 130.3, 130.2, 128.9, 127.4, 127.3, 125.8, 123.4, 116.6, 113.5, 112.7, 101.5, 100.5, 47.0; HPLC: 99.5%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 3/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 220 nm, retention time 5.13 min; IR (KBr, cm^{-1}): 3089, 2928, 1458, 1366, 1160; MS (ES mass): *m*/*z* 599.7 (M+1).

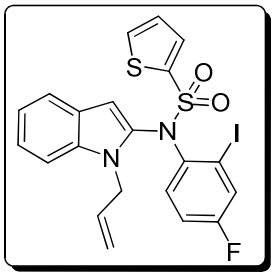
3.7.1.2.3 *N*-(1-Allyl-5-methoxy-1*H*-indol-2-yl)-*N*-(2-iodophenyl)thiophene-2-sulfonamide (2.15nm)

2.15nm was prepared *via* the reaction of **1.1n** with **2.14m** according to the general procedure as mentioned above.



Off white solid; yield: 50%; mp: 165-167 °C; R_f (15% EtOAc-*n*-Hexane) 0.32; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 8.03 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.76 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.61-7.60 (m, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.20 (t, *J* = 4.8 Hz, 1H), 7.09 (t, *J* = 8.4 Hz, 1H), 7.06-7.05 (m, 1H), 6.94 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.48 (s, 1H), 5.96-5.87 (m, 1H), 5.22 (dd, *J* = 2.8, 1.2 Hz, 2H), 5.12 (d, *J* = 10.0 Hz, 1H), 4.96 (d, *J* = 18.0 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.4, 142.4, 141.2, 137.4, 135.3, 134.3, 134.2, 133.8, 130.3, 130.2, 130.1, 128.9, 127.3, 126.1, 116.3, 113.5, 112.0, 102.4, 101.5, 100.8, 55.8, 46.9; HPLC: 99.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 3/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.75 min; IR (KBr, cm^{-1}): 3093, 2920, 1467, 1366, 1162; MS (ES mass): *m/z* 551.0 (M+1).

3.7.1.2.4 *N*-(1-Allyl-1*H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)thiophene-2-sulfonamide (2.15ob)

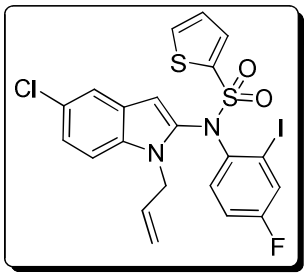


2.15ob was prepared *via* the reaction of **1.1o** with **2.14b** according to the general procedure as mentioned above.

Off white solid; yield: 56%; mp: 150-152 °C; R_f (15% EtOAc-*n*-Hexane) 0.48; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.67 (dd, *J* = 8.0, 2.8 Hz, 1H), 7.55-7.53 (m, 2H), 7.35 (dd, *J* = 8.9, 5.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.25-7.20 (m, 1H), 7.15-7.09 (m, 2H), 7.05-7.00 (m, 1H), 6.46 (s, 1H), 5.92-5.82 (m, 1H), 5.17 (s, 2H), 5.06 (dd, *J* = 10.3, 0.9 Hz, 1H), 4.87 (dd, *J* = 17.2, 0.9 Hz, 1H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ: 162.5 (d, C-F *J* = 253.6 Hz), 138.8 (d, C-F *J* = 3.4 Hz), 137.0, 135.4, 134.9, 134.1, 134.0, 133.9, 131.0 (d, C-F *J* = 9.0 Hz), 128.0, 127.8, 127.4, 125.7, 123.0, 120.9, 120.2, 116.3, 116.0 (d, C-F *J* = 22.2 Hz), 111.1, 100.9, 46.7; IR (KBr, cm^{-1}): 3082, 2944, 1498, 1356, 1176; MS (ES mass): *m/z* 538.9 (M+1).

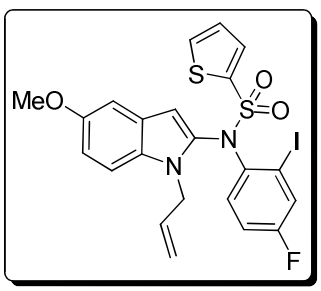
3.7.2.5 *N*-(1-Allyl-5-chloro-1H-indol-2-yl)-N-(4-fluoro-2-iodophenyl)thiophene-2-sulfonamide (2.15of)



2.15of was prepared *via* the reaction of **1.1o** with **2.14f** according to the general procedure as mentioned above.

Off white solid; yield: 45%; mp: 168-170 °C; R_f (15% EtOAc-*n*-Hexane) 0.38; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69-7.64 (m, 1H), 7.61 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.48-7.43 (m, 2H), 7.23 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.18-7.15 (m, 1H), 7.13-7.07 (m, 2H), 7.01-6.95 (m, 1H), 6.32 (s, 1H), 5.84-5.74 (m, 1H), 5.10 (s, 2H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.79 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.6 (d, C-F *J* = 254.2 Hz), 138.5 (d, C-F *J* = 4.5 Hz), 136.7, 135.5, 135.0, 134.2, 133.5, 133.4, 130.8 (d, C-F *J* = 7.0 Hz), 128.1 (d, C-F *J* = 24.5 Hz), 127.5, 127.2, 125.9, 123.4, 116.6, 116.1 (d, C-F *J* = 22.2 Hz), 113.5, 112.7, 101.7 (d, C-F *J* = 8.5 Hz), 100.3, 46.8; HPLC: 99.1%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.89 min; IR (KBr, cm^{-1}): 3084, 2921, 1452, 1348, 1152; MS (ES mass): *m/z* 573.0 (M+1).

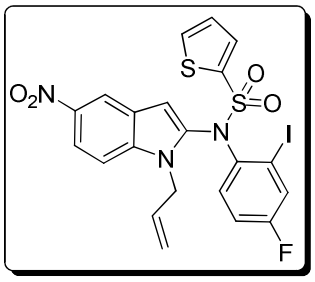
3.7.1.2.6 *N*-(1-Allyl-5-methoxy-1*H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl) thiophene-2-sulfonamide (2.15om)



2.15om was prepared *via* the reaction of **1.1o** with **2.14m** according to the general procedure as mentioned above.

Off white solid; yield: 46%; mp: 158-160 °C; R_f (15% EtOAc-*n*-Hexane) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.66 (dd, *J* = 8.0, 2.8 Hz, 1H), 7.53 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.34 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 5.2, 4.0 Hz, 1H), 7.05-6.98 (m, 2H), 6.89 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.38 (s, 1H), 5.90-5.81 (m, 1H), 5.13 (s, 2H), 5.04 (d, *J* = 10.0 Hz, 1H), 4.87 (dd, *J* = 17.2, 1.0 Hz, 1H), 3.81(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5 (d, C-F *J* = 253.7 Hz), 138.6 (d, C-F *J* = 3.5 Hz), 137.1, 135.4, 134.2, 134.0, 131.0 (d, C-F *J* = 8.9 Hz), 130.1, 128.0 (d, C-F *J* = 24.4 Hz), 127.4, 126.0, 121.0, 120.3, 116.3, 116.0 (d, C-F *J* = 22.1 Hz), 113.6, 112.0, 102.3, 101.6 (d, C-F *J* = 8.4 Hz), 100.6, 55.7, 46.8; HPLC: 99.8%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.02 min; IR (KBr, cm^{-1}): 3089, 2989, 1473, 1358, 1164; MS (ES mass): *m/z* 568.9 (M+1).

3.7.1.2.7 *N*-(1-Allyl-5-nitro-1H-indol-2-yl)-N-(4-fluoro-2-iodophenyl)thiophene-2-sulfonamide (2.15oo)

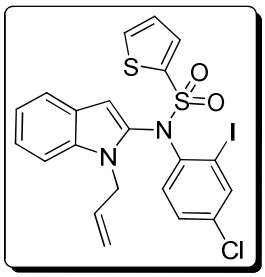


2.15oo was prepared *via* the reaction of **1.1o** with **2.14o** according to the general procedure as mentioned above.

Light yellow solid; yield: 48%; mp: 192-194 °C; R_f (20% EtOAc-*n*-Hexane) 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (d, *J* = 1.6 Hz, 1H), 8.19 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.84 (d, *J* = 4.8 Hz, 1H), 7.76 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.59 (d, *J* = 4.0 Hz, 1H), 7.43 (d, *J* = 9.2 Hz, 1H), 7.37 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.25 (t, *J* = 4.4 Hz, 1H), 7.19-7.11 (m, 1H), 6.70 (s, 1H), 6.01-5.91 (m, 1H), 5.33 (s, 2H), 5.21 (d, *J* = 10.4 Hz, 1H), 4.97 (d, *J* = 17.1 Hz, 1H); ^{13}C NMR (100 MHz,$CDCl_3$) δ: 162.8 (d, C-F *J* = 254.9 Hz), 142.0, 138.1 (d, C-F *J* = 3.9 Hz), 137.6, 137.2, 136.3, 135.7, 134.6, 132.9, 130.9 (d, C-F *J* = 9.0 Hz), 128.2 (d, C-F *J* = 24.4 Hz), 127.7, 124.7, 118.4, 118.2, 117.2, 116.2 (d, C-F *J* = 22.2 Hz), 111.3, 103.1, 101.6 (d, C-F *J* = 9.1 Hz), 47.3; HPLC: 93.1%;

column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 270 nm, retention time 5.57 min; IR (KBr, cm^{-1}): 3079, 1520, 1343, 1160; MS (ES mass): *m*/*z* 583.7 (M+1).

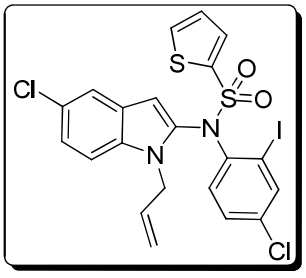
3.7.1.2.8 *N*-(1-Allyl-1*H*-indol-2-yl)-*N*-(4-chloro-2-iodophenyl)thiophene-2-sulfonamide (2.15pb)



2.15pb was prepared *via* the reaction of **1.1p** with **2.14b** according to the general procedure as mentioned above.

Off white solid; yield: 52%; mp: 158-160 °C; R_f (15% EtOAc-*n*-Hexane) 0.41; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.72 (d, *J* = 5.2 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.30-7.27 (m, 3H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.16-7.08 (m, 2H), 6.44 (s, 1H), 5.91-5.82 (m, 1H), 5.16 (s, 2H), 5.06 (d, *J* = 10.5 Hz, 1H), 4.86 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.1, 140.4, 137.0, 135.5, 135.1, 134.9, 134.0, 133.9, 133.8, 130.6, 129.0, 127.4, 125.7, 123.0, 121.0, 120.2, 116.3, 111.1, 101.8, 101.1, 46.6; HPLC: 99.0%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 0.5/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.92 min; IR (KBr, cm^{-1}): 3087, 2920, 1458, 1367, 1159; MS (ES mass): *m*/*z* 554.8 (M+1).

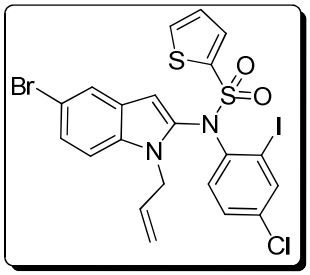
3.7.1.2.9 *N*-(1-Allyl-5-chloro-1*H*-indol-2-yl)-*N*-(4-chloro-2-iodophenyl)thiophene-2-sulfonamide (2.15pf)



2.15pf was prepared *via* the reaction of **1.1p** with **2.14f** according to the general procedure as mentioned above.

Light brown solid; yield: 50%; mp: 178-180 °C; R_f (10% EtOAc-*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 2.0 Hz, 1H), 7.74 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.52-7.50 (m, 2H), 7.32-7.26 (m, 2H), 7.24-7.18 (m, 2H), 7.16-7.14 (m, 1H), 6.38 (s, 1H), 5.91-5.80 (m, 1H), 5.16 (s, 2H), 5.08 (d, *J* = 10.2 Hz, 1H), 4.85 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.9, 140.5, 136.7, 135.6, 135.3, 134.9, 134.3, 133.6, 133.2, 130.5, 129.2, 127.5, 126.6, 126.0, 123.5, 120.3, 116.6, 112.3, 101.9, 100.6, 46.9; HPLC: 98.4%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.89 min; IR (KBr, cm^{-1}): 3090, 2923, 1459, 1361, 1159; MS (ES mass): *m*/*z* 589.8 (M+1).

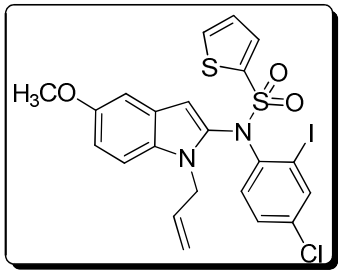
3.7.1.2.10 *N*-(1-Allyl-5-bromo-1*H*-indol-2-yl)-*N*-(4-chloro-2-iodophenyl) thiophene-2-sulfonamide (2.15ph)



2.15ph was prepared *via* the reaction of **1.1p** with **2.14h** according to the general procedure as mentioned above.

Light brown solid; yield: 48%; mp: 146-148 °C; R_f (15% EtOAc-*n*-Hexane) 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.68-7.65 (m, 2H), 7.52 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.32-7.28 (m, 2H), 7.20-7.14 (m, 2H), 7.07-7.02 (m, 1H), 6.39 (s, 1H), 5.90-5.81 (m, 1H), 5.16 (s, 2H), 5.08 (d, *J* = 10.2 Hz, 1H), 4.85 (d, *J* = 17.2 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 136.6, 135.5, 135.0, 134.2, 133.5, 133.4, 130.8, 130.7, 128.1, 127.8, 127.5, 127.2, 125.9, 123.4, 116.6, 116.1, 115.9, 113.5, 112.7, 100.3, 46.8; HPLC: 93.1%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 0.5/50, 3/95, 10/95, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 5.12 min; IR (KBr, cm^{-1}): 3071, 2922, 1462, 1348, 1153; MS (ES mass): *m*/*z* 634.2 (M+1).

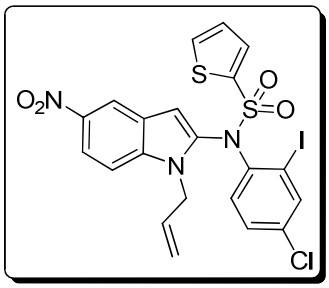
3.7.1.2.11 *N*-(1-Allyl-5-methoxy-1*H*-indol-2-yl)-*N*-(4-chloro-2-iodophenyl)-thiophene-2-sulfonamide (2.15pm)



2.15pm was prepared *via* the reaction of **1.1p** with **2.14m** according to the general procedure as mentioned above.

Off white solid; yield: 48%; mp: 171-173 °C; R_f (15% EtOAc-*n*-Hexane) 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (s, 1H), 7.72 (d, *J* = 4.9 Hz, 1H), 7.54 (d, *J* = 3.6 Hz, 1H), 7.30-7.28 (m, 2H), 7.20 (d, *J* = 9.2 Hz, 1H), 7.15 (t, *J* = 3.8 Hz, 1H), 6.99 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.37 (s, 1H), 5.90-5.81 (m, 1H), 5.13 (s, 2H), 5.06 (d, *J* = 10.4 Hz, 1H), 4.86 (d, *J* = 17.2 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.5, 141.2, 140.5, 137.1, 135.6, 135.2, 134.2, 134.1, 134.0, 130.7, 130.2, 129.2, 127.5, 126.1, 116.4, 113.8, 112.1, 102.4, 102.0, 100.8, 55.8, 46.9; HPLC: 99.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.80 min; IR (KBr, cm^{-1}): 3085, 2923, 1466, 1360, 1160; MS (ES mass): *m/z* 585.0 (M+1).

3.7.1.2.12 *N*-(1-Allyl-5-nitro-1*H*-indol-2-yl)-*N*-(4-chloro-2-iodophenyl)thiophene-2-sulfonamide (2.15po)

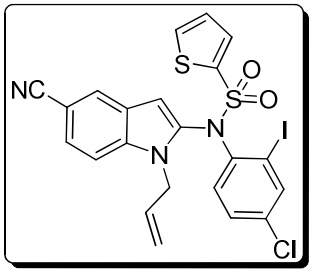


2.15po was prepared *via* the reaction of **1.1p** and **2.14o** according to the general procedure mentioned above.

Light yellow solid; yield: 45%; mp: 175-177 °C; R_f (15% EtOAc-*n*-Hexane) 0.29; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (d, *J* = 2.0 Hz, 1H), 8.13 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.97 (d, *J* = 2.2 Hz, 1H), 7.78 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.54-7.53 (m, 1H), 7.37-7.32

(m, 2H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.20-7.17 (m, 1H), 6.62 (s, 1H), 5.94-5.85 (m, 1H), 5.25-5.24 (m, 2H), 5.14 (d, *J* = 10.8 Hz, 1H), 4.89 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.1, 140.6, 140.5, 137.6, 136.9, 135.8, 135.7, 134.6, 132.9, 130.4, 129.2, 127.7, 124.7, 118.5, 118.2, 117.2, 111.3, 109.9, 103.2, 101.8, 47.2; HPLC: 99.5%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 3/95, 10/95, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.72 min; IR (KBr, cm^{-1}): 3093, 2933, 1528, 1433, 1345, 1159; MS (ES mass): *m/z* 599.7 (M+1).

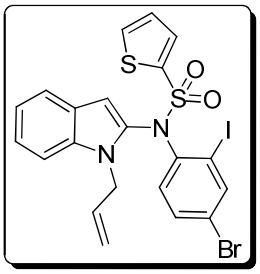
3.7.1.2.13 *N*-(1-Allyl-5-cyano-1*H*-indol-2-yl)-*N*-(4-chloro-2-iodophenyl) thiophene-2-sulfonamide (2.15pp)



2.15pp was prepared *via* the reaction of **1.1p** with **2.14p** according to the general procedure as mentioned above.

Off white solid; yield: 48%; mp: 142-144 °C; R_f (15% EtOAc-*n*-Hexane) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 2.4 Hz, 1H), 7.90 (s, 1H), 7.77 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.53-7.51 (m, 1H), 7.45 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.33 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.19-7.17 (m, 1H), 6.54 (s, 1H), 5.93-5.83 (m, 1H), 5.22 (s, 2H), 5.13 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:140.6, 140.5, 136.4, 136.3, 136.2, 135.7, 135.6, 134.5, 133.0, 130.5, 129.2, 127.6, 126.6, 125.7, 125.3, 120.2, 117.1, 112.1, 103.5, 101.8, 101.7, 47.1; HPLC: 91.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 240 nm, retention time 5.70 min; IR (KBr, cm^{-1}): 3093, 2921, 2222, 1466, 1364, 1165; MS (ES mass): *m/z* 579.8 (M+1).

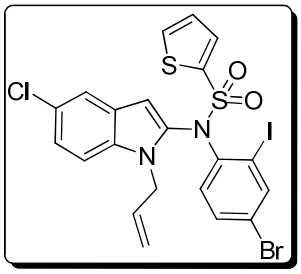
3.7.1.2.14 *N*-(1-Allyl-1*H*-indol-2-yl)-*N*-(4-bromo-2-iodophenyl)thiophene-2-sulfonamide (2.15qb)



2.15qb was prepared *via* the reaction of **1.1q** with **2.14b** according to the general procedure as mentioned above.

Off white solid; yield: 42%; mp: 148-150 °C; R_f (10% EtOAc-*n*-Hexane) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 2.1 Hz, 1H), 7.72 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.55-7.53 (m, 2H), 7.43 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.24-7.21 (m, 2H), 7.15-7.09 (m, 2H), 6.43 (s, 1H), 5.92-5.81 (m, 1H), 5.16 (d, *J* = 2.4 Hz, 2H), 5.04 (d, *J* = 10.4 Hz, 1H), 4.83 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.1, 141.6, 136.9, 135.5, 134.8, 134.1, 133.8, 133.7, 132.0, 131.0, 127.4, 125.7, 123.2, 123.0, 121.0, 120.2, 116.3, 111.1, 102.3, 101.1, 46.6; HPLC: 96.5%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.62 min; IR (KBr, cm^{-1}): 3087, 2914, 1460, 1359, 1160; MS (ES mass): *m*/*z* 598.1 (M-1).

3.7.1.2.15 *N*-(1-Allyl-5-chloro-1*H*-indol-2-yl)-*N*-(4-bromo-2-iodophenyl)-thiophene-2-sulfonamide (2.15qf)

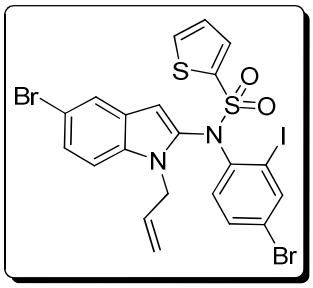


2.15qf was prepared *via* the reaction of **1.1q** with **2.14f** according to the general procedure as mentioned above.

Off white solid; yield: 46%; mp: 160-162 °C; R_f (15% EtOAc-*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 7.73 (d, *J* = 4.8 Hz, 1H), 7.52-7.50 (m, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.23-7.14 (m, 4H), 6.37 (s, 1H), 5.88-5.80(m, 1H), 5.14 (s, 2H), 5.07 (d, *J* = 10.3 Hz, 1H), 4.84 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.2, 141.3, 136.7, 135.6, 134.8, 134.3, 133.5, 133.2, 132.1, 130.9, 127.5,

126.5, 126.0, 123.5, 123.4, 120.3, 116.6, 112.3, 102.3, 100.6, 46.9; HPLC: 97.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98,10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 6.22 min; IR (KBr, cm^{-1}): 3086, 2924, 1457, 1364, 1159; MS (ES mass): *m/z* 634.9 (M+1).

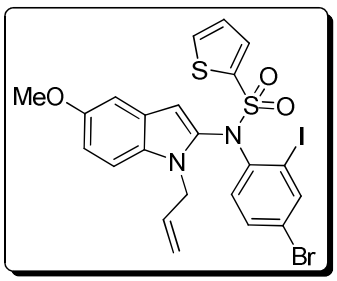
3.7.1.2.16 *N*-(1-Allyl-5-bromo-1*H*-indol-2-yl)-*N*-(4-bromo-2-iodophenyl)-thiophene-2-sulfonamide (2.15qh)



2.15qh was prepared *via* the reaction of **1.1q** with **2.14h** according to the general procedure as mentioned above.

Light green solid; yield: 51%; mp: 180-182 °C; R_f (10% EtOAc-*n*-Hexane) 0.42; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 7.73 (d, *J* = 4.2 Hz, 1H), 7.67 (s, 1H), 7.52 (d, *J* = 1.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.21-7.15 (m, 3H), 6.37 (s, 1H), 5.88-5.81 (m, 1H), 5.14 (s, 2H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.84 (d, *J* = 17.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.2, 141.3, 136.7, 135.5, 134.7, 134.3, 134.2, 133.4, 132.1, 130.9, 127.5, 127.2, 126.0, 123.5, 123.4, 116.6, 113.6, 112.7, 102.3, 100.5, 46.8; HPLC: 92.4%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/20, 0.5/20, 3/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 220 nm, retention time 5.55 min; IR (KBr, cm^{-1}): 3087, 2925, 1457, 1364, 1160; MS (ES mass): *m/z* 678.7 (M+1).

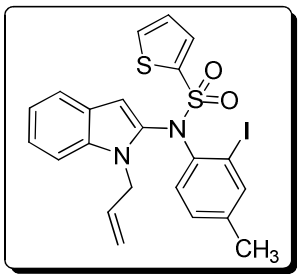
3.7.1.2.17 *N*-(1-Allyl-5-methoxy-1*H*-indol-2-yl)-*N*-(4-bromo-2-iodophenyl)-thiophene-2-sulfonamide (2.15qm)



2.15qm was prepared *via* the reaction of **1.1q** with **2.14m** according to the general procedure as mentioned above.

Off white solid; yield: 43%; mp: 157-159 °C; R_f (15% EtOAc-*n*-Hexane) 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 2.2 Hz, 1H), 7.71 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.54 (dd, *J* =4.0, 1.2 Hz, 1H), 7.43 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.23-7.18 (m, 2H), 7.14 (dd, *J* = 4.8, 3.6 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.36(s, 1H), 5.89-5.80 (m, 1H), 5.10 (s, 2H), 5.05 (d, *J* = 10.4 Hz, 1H), 4.86 (d, *J* = 17.2 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.4, 143.1, 141.6, 137.0, 135.4, 134.1, 134.0, 133.8, 132.0, 131.0, 130.6, 127.4, 126.0, 123.2, 116.3, 113.6, 112.0, 109.9, 102.3, 100.7, 55.7, 46.8; HPLC: 99.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 5.49 min; IR (KBr, cm^{-1}): 3087, 2924, 1466, 1358, 1160; MS (ES mass): *m/z* 629.7 (M+1).

3.7.1.2.18 *N*-(1-Allyl-1*H*-indol-2-yl)-*N*-(2-iodo-4-methylphenyl)thiophene-2-sulfonamide (2.15rb)

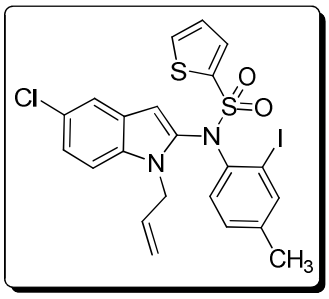


2.15rb was prepared *via* the reaction of **1.1r** with **2.14b** according to the general procedure as mentioned above.

White solid; yield: 60%; mp: 170-172 °C; R_f (12% EtOAc-*n*-Hexane) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ:7.80 (s, 1H), 7.70 (dd, *J* = 4.6, 1.2 Hz, 1H), 7.55-7.52 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 8.4 Hz, 2H), 7.14-7.09 (m, 3H), 6.46 (s, 1H), 5.94-5.84 (m, 1H), 5.21 (s, 2H), 5.08 (d, *J* = 10.4 Hz, 1H), 4.95 (d, *J* = 17.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.5, 140.6, 139.8, 137.3, 135.3, 134.8, 134.4, 134.2, 133.7, 129.7 (2C), 127.3, 125.8, 122.8, 120.9, 116.3, 111.1, 101.2, 100.8, 46.9, 20.4; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm,

retention time 5.84 min; IR (KBr, cm^{-1}): 3091, 2916, 1466, 1367, 1159; MS (ES mass): *m/z* 534.2 (M+1).

3.7.1.2.19 *N*-(1-Allyl-5-chloro-1*H*-indol-2-yl)-*N*-(2-iodo-4-methylphenyl)-thiophene-2-sulfonamide (2.15rf)

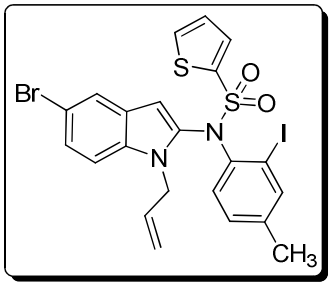


2.15rf was prepared *via* the reaction of **1.1r** with **2.14f** according to the general procedure as mentioned above.

Off white solid; yield: 55%; mp: 150-152 °C; R_f (10% EtOAc-*n*-Hexane) 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (s, 1H), 7.71 (d, *J* = 4.4 Hz, 1H), 7.59-7.55 (m, 1H), 7.52-7.50 (m, 2H), 7.24-7.20 (m, 1H), 7.17-7.10 (m, 3H), 6.39 (s, 1H), 5.92-5.82 (m, 1H), 5.19 (s, 2H), 5.11 (d, *J* = 10.4 Hz, 1H), 4.93 (d, *J* = 17.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.6, 140.8, 139.3, 137.1, 135.3, 133.9, 133.8, 133.2, 130.3, 129.7, 129.6, 127.3, 126.7, 125.8, 123.7, 123.2, 120.2, 116.6, 112.3, 100.4, 47.1, 20.4; HPLC: 93.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 0.5/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 235 nm, retention time 5.09 min; IR (KBr, cm^{-1}): 3094, 2922, 1465, 1370, 1161; MS (ES mass): *m/z* 568.9 (M+1).

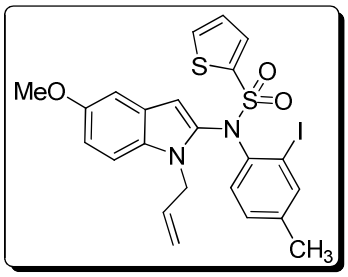
3.7.1.2.20 *N*-(1-Allyl-5-bromo-1*H*-indol-2-yl)-*N*-(2-iodo-4-methylphenyl)-thiophene-2-sulfonamide (2.15rh)

2.15rh was prepared *via* the reaction of **1.1r** with **2.14h** according to the general procedure as mentioned above.



Off white solid; yield: 44%; mp: 148-150 °C; R_f (10% EtOAc-*n*-Hexane) 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, *J* = 0.8 Hz, 1H), 7.70 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.65 (d, *J* = 1.6 Hz, 1H), 7.50 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.28 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.20-7.17 (m, 2H), 7.14-7.09 (m, 2H), 6.39 (s, 1H), 5.90-5.81 (m, 1H), 5.19 (s, 2H), 5.08 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.91 (d, *J* = 16.4 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.6, 140.8, 139.6, 137.2, 135.4, 135.3 (2C), 133.9, 133.8, 133.4, 129.8, 129.6, 127.4, 125.8, 123.4, 116.6, 113.4, 112.7, 101.2, 100.4, 47.1, 20.5; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 3/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 220 nm, retention time 5.34 min; IR (KBr, cm^{-1}): 3085, 2922, 1468, 1365, 1158; MS (ES mass): *m/z* 613.9 (M+1).

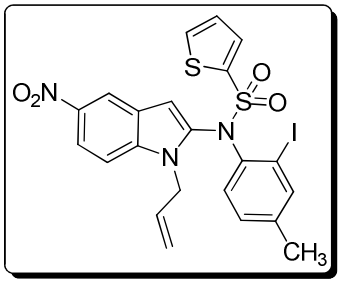
3.7.1.2.21 *N*-(1-Allyl-5-methoxy-1*H*-indol-2-yl)-*N*-(2-iodo-4-methylphenyl)-thiophene-2-sulfonamide (2.15rm)



2.15rm was prepared *via* the reaction of **1.1r** with **2.14m** according to the general procedure as mentioned above.

Off white solid; yield: 48%; mp: 150-152 °C; R_f (15% EtOAc-*n*-Hexane) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.69 (d, *J* = 4.8 Hz, 1H), 7.52 (d, *J* = 3.6 Hz, 1H), 7.21 (t, *J* = 8.4 Hz, 2H), 7.14-7.08 (m, 2H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.38 (s, 1H), 5.91-5.82 (m, 1H), 5.16 (s, 2H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.94 (d, *J* = 17.2 Hz, 1H), 3.82 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.3, 141.6, 140.6, 139.9, 137.5, 135.2, 134.5, 134.3, 133.7, 130.1, 129.7 (2C), 127.3, 126.2, 116.4, 113.4, 112.1, 102.4, 101.3, 100.6, 55.8, 47.0, 20.5; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 3/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.90 min; IR (KBr, cm^{-1}): 3091, 2918, 2022, 1476, 1363, 1163; MS (ES mass): *m/z* 564.7 (M+1).

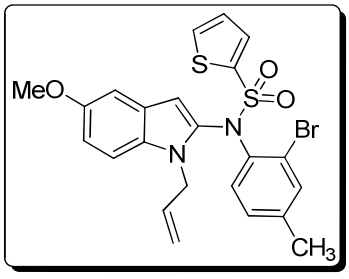
3.7.1.2.22 *N*-(1-Allyl-5-nitro-1*H*-indol-2-yl)-*N*-(2-iodo-4-methylphenyl)thiophene-2-sulfonamide (2.15ro)



2.15ro was prepared *via* the reaction of **1.1r** with **2.14o** according to the general procedure as mentioned above.

Light yellow solid; yield: 43%; mp: 150-152 °C; R_f (20% EtOAc-*n*-Hexane) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (d, *J* = 2.4 Hz, 1H), 8.12 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.82 (s, 1H), 7.76 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.54-7.52 (m, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.21-7.13 (m, 3H), 6.64 (s, 1H), 5.95-5.87 (m, 1H), 5.29 (s, 2H), 5.17 (d, *J* = 10.2 Hz, 1H), 4.99 (d, *J* = 17.3 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.9, 141.7, 141.2, 139.1, 137.6, 137.5, 136.7, 135.5, 134.3, 133.2, 129.8, 129.5, 127.5, 124.8, 118.2, 118.1, 117.2, 111.3, 103.0, 101.1, 47.3, 20.4; HPLC: 93.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.68 min; IR (KBr, cm^{-1}): 3098, 2927, 1516, 1336, 1160; MS (ES mass): *m*/*z* 580.0 (M+1).

3.7.1.2.23 *N*-(1-Allyl-5-methoxy-1*H*-indol-2-yl)-*N*-(2-bromo-4-methylphenyl)-thiophene-2-sulfonamide (2.15um)

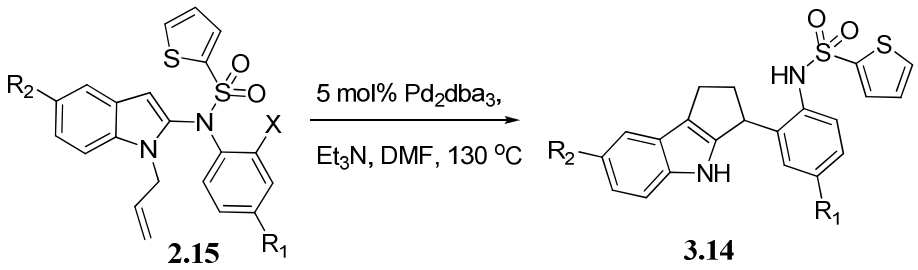


2.15um was prepared *via* the reaction of **1.1u** with **2.14m** according to the general procedure as mentioned above.

Off white solid; yield: 60%; mp: 100-102°C; R_f (15% EtOAc-*n*-Hexane) 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.53 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.49 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.14 (t, *J* = 4.0

Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.37 (s, 1H), 5.88-5.79 (m, 1H), 5.09 (d, *J* = 4.0 Hz, 2H), 5.05 (d, *J* = 10.4 Hz, 1H),4.92 (d,*J* = 17.2 Hz, 1H), 3.82 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.2, 140.7, 136.3, 134.9, 134.8 (2C), 134.1, 134.0, 133.6, 130.4, 130.1, 128.8, 127.3, 126.1, 124.9, 116.3, 113.4, 111.9, 102.3, 100.5, 55.7, 46.2, 20.7; HPLC: 94.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.68 min; IR (KBr, cm^{-1}): 3082, 2917, 1441, 1370, 1156; MS (ES mass): *m*/*z* 518.3 (M+1).

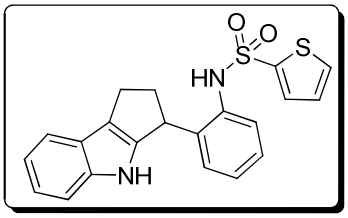
3.7.1.3 General procedure for preparation of *N*-(2-(7-substituted-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)-4-substitutedphenyl)thiophene-2-sulfonamide (3.14):



A mixture of *N*-(1-allyl-5-substituted-1*H*-indol-2-yl)-*N*-(2-iodo-4-substitutedphenyl) thiophene-2-sulfonamide **2.15**, (0.4mmol), $Pd_2(dba)_3$ (5mol%), and Et_3N (1.2 mmol), in anhydrous DMF (2 mL) was stirred at 130 °C for 7h under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature and filtered to remove the solid seperated. The filtrate was extracted with ethyl acetate (3 x 10 mL).The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate-hexane to give the desired product **3.14**.

Note: In most of the cases a minute quantity of the ligand (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one (**L**) dissociated from $Pd_2(dba)_3$ was isolated.

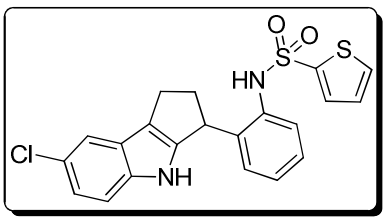
3.7.1.3.1 *N*-(2-(1,2,3,4-Tetrahydrocyclopenta[*b*]indol-3-yl)phenyl)thiophene-2-sulfonamide (3.14a)



3.14a was prepared from **2.15nb** according to the general procedure as presented above.

Light brown solid; yield: 81%; mp: 158-160 °C; R_f (20% EtOAc-*n*-Hexane) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 4.8 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.46 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.22-7.14 (m, 5H), 7.10-7.04 (m, 2H), 6.67 (s, 1H), 5.93 (s, 1H), 4.68 (t, *J* = 8.0 Hz, 1H), 4.25-4.19 (m, 1H), 4.07-4.00 (m, 1H), 3.01-2.93 (m, 1H), 2.39-2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.8, 139.9, 138.6, 133.3, 132.9, 132.9, 132.7, 132.6, 128.9, 127.7 (2C), 127.5, 126.0, 120.7 (2C), 119.4, 109.6, 93.5, 43.1, 38.7, 37.7; HPLC: 98.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.15 min; IR (KBr, cm^{-1}): 3337, 3087, 2923, 1851, 1458, 1358, 1162; MS (ES mass): *m/z* 395.0 (M+1).

3.7.1.3.2 *N*-(2-(7-Chloro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)phenyl)-thiophene-2-sulfonamide (3.14b):

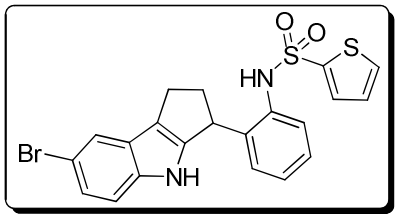


3.14b was prepared from **2.15nf** according to the general procedure as presented above.

Off white solid; yield: 80%;mp: 152-154 °C; R_f (15% EtOAc-*n*-Hexane) 0.23; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 4.8 Hz, 1H), 7.48-7.46 (m, 2H), 7.21-7.10 (m, 6H), 7.07 (t, *J* = 4.0 Hz, 1H), 6.46 (s, 1H), 5.89 (s, 1H), 4.75 (t, *J* = 8.4 Hz, 1H), 4.23 (td,*J* = 9.6, 3.6 Hz, 1H), 4.06 (q, *J* = 7.6 Hz, 1H), 3.06-2.97 (m, 1H), 2.44-2.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.4, 139.9, 138.7, 133.8, 133.2, 133.1, 132.6, 131.1, 128.9, 127.9, 127.8, 127.5, 126.2, 125.2, 121.0, 120.1, 110.4, 93.3, 43.4, 38.8, 37.7; HPLC: 98.9%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase

A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 0.5/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 235 nm, retention time 4.21 min; IR (KBr, cm^{-1}): 3246, 2933, 2885, 1457, 1341, 1156; MS (ES mass): *m/z* 429.0 (M+1).

3.7.1.3.3 *N*-(2-(7-Bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)phenyl)-thiophene-2sulfonamide (3.14c)

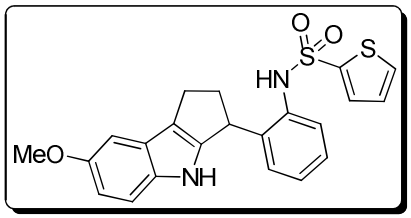


3.14c was prepared from **2.15nh** according to the general procedure as presented above.

Light yellow solid; yield: 72%; mp: 171-173 °C; R_f (15% EtOAc-*n*-Hexane) 0.21; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 1.6 Hz, 1H), 7.61 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.48-7.45 (m, 1H), 7.25-7.23 (m, 1H), 7.20-7.17 (m, 3H), 7.13-7.11 (m, 2H), 7.09-7.05 (m, 1H), 6.48 (s, 1H), 5.88 (s, 1H), 4.76 (t, *J* = 7.8 Hz, 1H), 4.26-4.20 (m, 1H), 4.08-4.02 (m, 1H), 3.06-2.97 (m, 1H), 2.44-2.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.3, 138.8, 134.4, 133.2, 133.1, 132.6, 131.3, 128.8, 128.0, 127.8, 127.5, 126.3, 123.5, 123.1, 112.7, 110.9, 109.9, 93.2, 43.4, 38.7, 37.8; HPLC: 93.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.79 min; IR (KBr, cm^{-1}): 3243, 3098, 1455, 1338, 1157; MS (ES mass): *m/z* 473.9 (M+1).

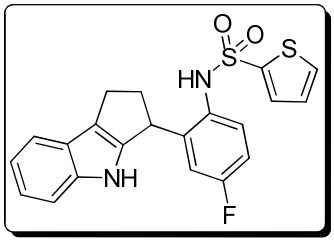
3.7.1.3.4 *N*-(2-(7-Methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)phenyl)-thiophene-2-sulfonamide (3.14d)

3.14d was prepared from **2.15nm** according to the general procedure as presented above.



Off white solid; yield: 70%; mp: 135-137 °C; R_f (20% EtOAc-*n*-Hexane) 0.23; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 4.4 Hz, 1H), 7.46 (d, *J* = 2.9 Hz, 1H), 7.24-7.13 (m, 5H), 7.07-7.05 (m, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.83 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.56 (s, 1H), 5.86 (s, 1H), 4.65 (t, *J* = 7.7 Hz, 1H), 4.22-4.15 (m, 1H), 4.05-3.97 (m, 1H), 3.84 (s, 3H), 2.99-2.91 (m, 1H), 2.37-2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.0, 146.2, 140.0, 138.4, 133.3, 133.2, 132.9, 132.5, 128.9, 128.1, 127.7, 127.6, 127.4, 125.9, 110.8, 110.2, 102.8, 93.2, 55.9, 43.3, 39.0, 37.6; HPLC: 96.0%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.01 min; IR (KBr, cm^{-1}): 3257, 3092, 2913, 1482, 1336, 1159; MS (ES mass): *m/z* 425.0 (M+1).

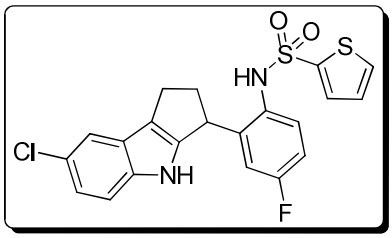
3.7.1.3.5 *N*-(4-Fluoro-2-(1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)phenyl)-thiophene-2-sulfonamide (3.14e)



3.14e was prepared from **2.15ob** according to the general procedure as presented above.

Off white solid; yield: 71%;mp: 145-147 °C; R_f (20% EtOAc-*n*-Hexane) 0.29; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.19-7.06 (m, 4H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.60 (s, 1H), 5.93 (s, 1H), 4.70 (t, *J* = 7.9 Hz, 1H), 4.22 (td, *J* = 10.0, 3.6 Hz,1H), 4.03 (q, *J* = 7.6 Hz,1H), 3.04-2.96 (m, 1H), 2.38-2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2 (d, C-F *J* = 247.0 Hz), 145.1, 142.7 (d, C-F *J* = 7.6 Hz), 139.7, 135.1, 133.1, 132.8, 132.7, 128.9 (d, C-F *J* = 3.0 Hz), 128.8 (d, C-F *J* = 8.7 Hz), 127.5, 124.9, 120.9 (d, C-F *J* = 9.1 Hz), 119.5, 115.6 (d, C-F *J* = 23.4 Hz), 114.7 (d, C-F *J* = 22.7 Hz), 109.5, 93.7, 43.1, 38.7, 37.7; HPLC: 94.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.19 min; IR (KBr, cm^{-1}): 3324, 3091, 2921, 1439, 1344, 1169; MS (ES mass): *m/z* 413.0 (M+1).

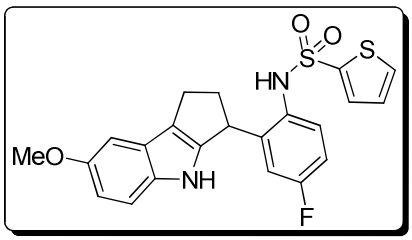
3.7.1.3.6 *N*-(2-(7-Chloro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-4-fluoro phenyl)thiophene-2-sulfonamide (3.14f)



3.14f was prepared from **2.15of** according to the general procedure as presented above.

Off white solid; yield: 68%; mp: 149-151 °C; R_f (20% EtOAc-*n*-Hexane) 0.29; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, *J* = 4.7 Hz, 1H), 7.43 (s, 1H), 7.40 (d, *J* = 3.6 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.06-7.02 (m, 2H), 6.96 (dd, *J* = 8.4, 5.2 Hz, 1H), 6.83-6.76 (m, 2H), 6.32 (s, 1H), 5.82 (s, 1H), 4.71 (t, *J* = 7.8 Hz, 1H), 4.19-4.13 (m, 1H), 4.01-3.95 (m, 1H), 3.01-2.93 (m, 1H), 2.35-2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.1 (d, C-F *J* = 163.2 Hz), 148.1, 137.6, 134.6, 133.3, 132.8 (d, C-F *J* = 3.0 Hz), 131.7, 127.6 (d, C-F *J* = 6.3 Hz), 126.8, 124.6, 122.5, 121.1, 120.3, 120.1, 115.6 (d, C-F *J* = 23.0 Hz), 114.9 (d, C-F *J* = 22.4 Hz), 110.9, 93.4, 44.1, 38.7, 37.4; HPLC: 91.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.13 min; IR (KBr, cm^{-1}): 3298, 2921, 1452, 1342, 1148; MS (ES mass): *m/z* 447.4 (M+1).

3.7.1.3.7 *N*-(4-Fluoro-2-(7-methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl) phenyl)thiophene-2-sulfonamide (3.14g)

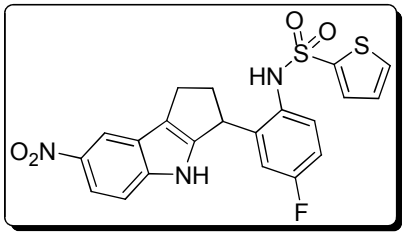


3.14g was prepared from **2.15om** according to the general procedure as presented above.

Light yellow solid; yield: 62%; mp: 125-127 °C; R_f (20% EtOAc-*n*-Hexane) 0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 4.4 Hz, 1H), 7.47-7.46 (m, 1H), 7.34-7.31 (m, 2H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.13-7.08 (m, 2H), 7.02 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.47 (s, 1H), 5.88 (s, 1H), 4.59 (t, *J* = 8.2 Hz, 1H), 4.24-4.19 (m, 1H), 4.04-

3.98 (m, 1H), 3.85 (s, 3H), 2.99-2.90 (m, 1H), 2.36-2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2 (d, C-F *J* = 246.7 Hz), 154.1, 142.8 (d, C-F *J* = 7.3 Hz), 139.7, 133.3, 133.2, 132.8, 128.9, 128.8, 128.1, 127.6, 115.7 (d, C-F *J* = 2.1 Hz), 115.5, 114.8 (d, C-F *J* = 22.5 Hz), 111.0, 110.3, 102.8, 93.3, 55.9, 43.3, 38.9, 37.7; HPLC: 93.1%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.09 min; IR (KBr, cm^{-1}): 3037, 2921, 1467, 1339, 1152; MS (ES mass): *m/z* 442.9 (M+1).

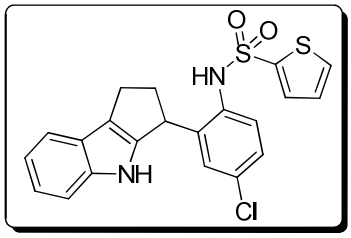
3.7.1.3.8 *N*-(4-Fluoro-2-(7-nitro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl) phenyl) thiophene-2-sulfonamide (3.14h)



3.14h was prepared from **2.15oo** according to the general procedure as presented above.

Light yellow solid; yield: 62%; mp: 145-147 °C; R_f (25% EtOAc-*n*-Hexane) 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (d, *J* = 2.0 Hz, 1H), 8.08 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.10 (t, *J* = 4.0 Hz,1H), 6.94-6.85 (m, 3H), 6.44 (s, 1H), 6.15 (s, 1H), 4.97 (t, *J* = 8.2 Hz, 1H), 4.36-4.29 (m, 1H), 4.14 (td, *J* = 10.2, 7.8 Hz, 1H), 3.18-3.11 (m, 1H), 2.51-2.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5 (d, C-F *J* = 247.9 Hz), 149.2, 143.1, 141.5, 139.3, 135.4, 133.4, 133.0, 131.9, 129.5 (d, C-F *J* = 8.8 Hz), 128.9 (d, C-F *J* = 3.0 Hz), 127.6, 117.9, 116.7, 115.6 (d, C-F *J* = 23.7 Hz), 115.1 (d, C-F *J* = 22.8 Hz), 109.3, 96.5, 43.6, 38.6, 38.0; HPLC: 95.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 4.09 min; IR (KBr, cm^{-1}): 3297, 3078, 2922, 1453, 1323, 1157; MS (ES mass): *m/z* 455.9 (M-1).

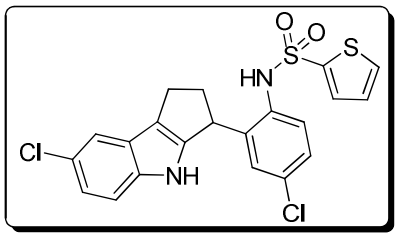
3.7.1.3.9 *N*-(4-Chloro-2-(1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)phenyl)-thiophene-2-sulfonamide (3.14i)



3.14i was prepared from **2.15pb** according to the general procedure as presented above.

Off white solid; yield: 78%; mp: 160-162 °C; R_f (20% EtOAc-*n*-Hexane) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 8.0 Hz, 1H), 7.55(d, *J* = 7.6 Hz, 1H), 7.47(d, = 2.8 Hz, 1H), 7.30(d, *J* = 8.4 Hz, 1H), 7.20-7.16 (m, 4H), 7.12-7.07 (m, 2H), 6.44 (s, 1H), 5.95 (s, 1H), 4.63 (t, *J* = 8.2 Hz, 1H), 4.24 (td, *J* = 10.2, 3.6 Hz, 1H), 4.04 (q, *J* = 7.6 Hz, 1H), 3.01-2.93 (m, 1H), 2.38-2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.7, 140.6, 139.6, 133.5, 133.1, 132.9, 132.8, 132.7, 131.8, 128.9, 127.9, 127.5, 127.4, 121.0, 120.8, 119.6, 109.6, 93.8, 43.1, 38.6, 37.5; HPLC: 98.8%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 0.5/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 220 nm, retention time 4.25 min; IR (KBr, cm^{-1}): 3361, 3091, 2922, 1474, 1335, 1159; MS (ES mass): *m*/*z* 428.9 (M+1).

3.7.1.3.10 *N*-(4-Chloro-2-(7-chloro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl) phenyl)thiophene-2-sulfonamide (3.14j)

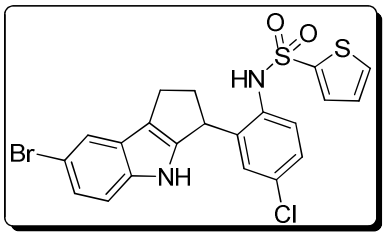


3.14j was prepared from **2.15pf** according to the general procedure as presented above.

Light brown solid; yield: 71%; mp: 146-148 °C; R_f (20% EtOAc-*n*-Hexane) 0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 4.8 Hz, 1H), 7.51 (s, 1H), 7.48 (d, *J* = 4.0 Hz, 1H), 7.21-7.18 (m, 1H), 7.16-7.12(m, 3H), 7.10-7.07 (m, 2H), 6.41 (s, 1H), 5.91 (s, 1H), 4.71 (t, *J* = 8.2 Hz, 1H), 4.28-4.21 (m, 1H), 4.08-4.02 (m, 1H), 3.03-2.98 (m, 1H), 2.40-2.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.6, 140.9, 139.5, 133.8, 133.3, 132.9, 131.8, 131.1, 128.9, 128.0, 127.8, 127.6 (2C), 125.2, 121.2, 120.2,

110.5, 93.5, 43.4, 38.7, 37.7; HPLC: 91.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.62 min; IR (KBr, cm^{-1}): 3280, 2923, 1720, 1467, 1337, 1159; MS (ES mass): *m/z* 463.0 (M+1).

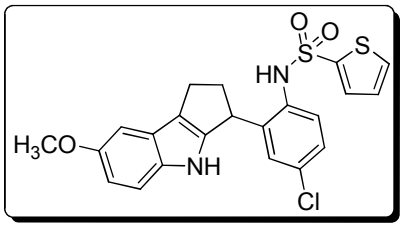
3.7.1.3.11 *N*-(2-(7-Bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-4-chloro phenyl)thiophene-2-sulfonamide (3.14k)



3.14k was prepared from **2.15ph** according to the general procedure as presented above.

Off white solid; yield: 68%; mp: 155-150 °C; R_f (20% EtOAc-*n*-Hexane) 0.26; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 1.5 Hz, 1H), 7.61 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.47-7.46 (m, 1H), 7.23-7.11 (m, 5H), 7.08-7.06 (m, 1H), 6.48 (s, 1H), 5.88 (s, 1H), 4.76 (t, *J* = 7.8 Hz, 1H), 4.25-4.20 (m, 1H), 4.08-4.02 (m, 1H), 3.05-2.97 (m, 1H), 2.44-2.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.3, 138.8, 134.4, 133.2, 133.1, 132.6, 131.3, 128.8, 128.0, 127.8, 127.5, 126.3, 123.5, 123.1, 112.7, 110.9, 109.9, 93.2, 43.4, 38.7, 37.8; HPLC: 97.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.73 min; IR (KBr, cm^{-1}): 3268, 3072, 2932, 1455, 1338, 1155; MS (ES mass):*m/z* 508.2 (M+1).

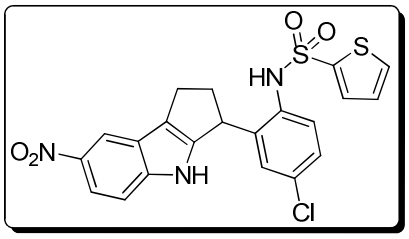
3.7.1.3.12 *N*-(4-Chloro-2-(7-methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl) phenyl)thiophene-2-sulfonamide (3.14l)



3.14l was prepared from **2.15pm** according to the general procedure as presented above.

Off white solid; yield: 69%; mp: 153-155 °C; R_f (20% EtOAc-*n*-Hexane) 0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.45 (dd, *J* = 4.2, 1.2 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.10-7.05 (m, 1H), 7.03-7.00 (m, 2H), 6.99-6.96 (m, 2H), 6.83 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.44 (s, 1H), 5.87 (s, 1H), 4.68 (t, *J* = 8.2 Hz, 1H), 4.23-4.17 (m, 1H), 4.05-3.97 (m, 1H), 3.84 (s, 3H), 2.98-2.90 (m, 1H), 2.37-2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.0, 146.7, 139.1, 138.0, 133.3, 132.9, 132.4, 130.4, 129.4, 128.4, 128.0, 127.4, 126.4, 110.7, 110.2, 109.9, 102.7, 93.1, 55.9, 43.4, 38.8, 37.8; HPLC: 96.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.57 min; IR (KBr, cm^{-1}): 3424, 2953, 1478, 1333, 1160; MS (ES mass): *m*/*z* 458.9 (M+1).

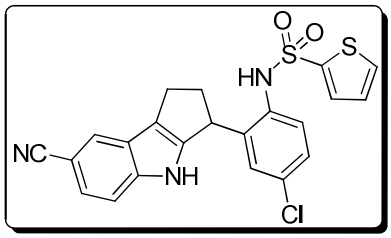
3.7.1.3.13 *N*-(4-Chloro-2-(7-nitro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl) phenyl)thiophene-2-sulfonamide (3.14m)



3.14m was prepared from **2.15po** according to the general procedure as presented above.

Light yellow solid; yield: 66%; mp: 142-144 °C; R_f (25% EtOAc-*n*-Hexane) 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (d, *J* = 1.9 Hz, 1H), 8.10 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.66 (d, *J* = 4.0 Hz, 1H), 7.50 (d, *J* = 2.6 Hz, 1H), 7.30 (d, *J* = 8.9 Hz, 1H), 7.19-7.14 (m, 2H), 7.13 (t, *J* = 4.4 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.60 (s, 1H), 6.15 (s, 1H), 4.91 (t, *J* = 8.0 Hz, 1H), 4.37-4.31 (m, 1H), 4.17-4.11 (m, 1H), 3.17-3.09 (m, 1H), 2.51-2.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:149.0, 141.5, 141.4, 139.2, 135.4, 134.2, 133.4, 133.0, 131.9, 131.7, 128.7, 128.3, 128.1, 127.6, 117.9, 116.7, 109.3, 96.5, 43.6, 38.4, 37.9; HPLC: 90.8%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 3.99 min; IR (KBr, cm^{-1}): 3271, 3032, 2932, 1456, 1321, 1149; MS (ES mass): *m*/*z* 474.0 (M+1).

3.7.1.3.14 *N*-(2-(7-Cyano-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-4-fluoro phenyl)thiophene-2-sulfonamide (3.14n)

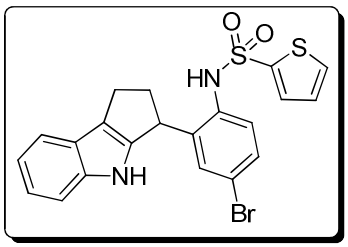


3.14n was prepared from **2.15pp** according to the general procedure as presented above.

Light yellow solid; yield: 59%; mp: 171-173 °C; R_f (20% EtOAc-*n*-Hexane) 0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.30 (d,*J*= 8.4 Hz, 1H), 7.20-7.16 (m, 3H), 7.12-7.07 (m, 2H), 6.44 (s, 1H), 5.95 (s, 1H), 4.63 (t, *J* = 8.2 Hz, 1H), 4.24 (td, *J* = 10.2, 3.6 Hz, 1H), 4.04 (q, *J* = 7.6 Hz, 1H), 3.01-2.93 (m, 1H), 2.38-2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.7, 140.6, 139.6, 133.5, 133.1, 132.9, 132.8, 132.7, 131.8, 128.9, 127.9, 127.5, 127.4, 121.0, 120.8, 119.6, 109.6, 102.2, 93.8, 43.1, 38.6, 37.5;HPLC: 94.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.01 min; IR (KBr, cm^{-1}): 3293, 2922, 2223, 1437, 1333, 1167; MS (ES mass): *m/z* 454.4 (M+1).

3.7.1.3.15 *N*-(4-Bromo-2-(1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)phenyl) thiophene-2-sulfonamide (3.14o)

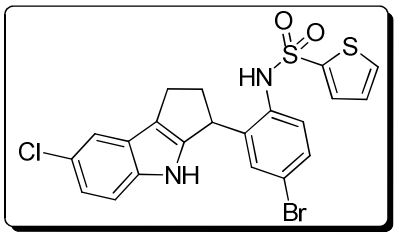
3.14o was prepared from **2.15qb** according to the general procedure as presented above.



Off white solid; yield: 78%; mp: 185-187 °C; R_f (15% EtOAc-*n*-Hexane) 0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63-7.61 (m, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.34-7.29 (m, 3H), 7.19 (t, *J* = 7.4Hz, 1H), 7.14-7.07 (m, 3H), 6.49 (s, 1H), 5.96 (s, 1H), 4.63 (t, *J* = 8.0 Hz, 1H), 4.25 (dt, *J* = 9.8, 3.4 Hz, 1H), 4.08-4.00

(m, 1H), 3.01-2.93 (m, 1H), 2.38-2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.6, 140.6, 133.2, 132.9, 132.8, 132.7, 132.4, 131.8, 130.9, 127.6, 127.5, 121.4, 121.0, 120.8, 119.6, 109.9, 109.6, 93.8, 43.1, 38.6, 37.6; HPLC: 96.9%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.85 min; IR (KBr, cm^{-1}): 3363, 3294, 3084, 2883, 1477, 1332, 1161; MS (ES mass): *m*/*z* 473.9 (M+1).

3.7.1.3.16 *N*-(4-Bromo-2-(7-chloro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)phenyl)thiophene-2-sulfonamide (3.14p)

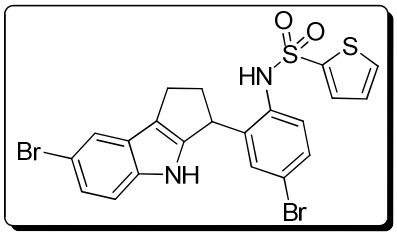


3.14p was prepared from **2.15qf** according to the general procedure as presented above.

Off white solid; yield: 70%; mp: 166-167 °C; R_f (20% EtOAc-*n*-Hexane) 0.23; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 4.5 Hz, 1H), 7.50-7.47 (m, 2H), 7.33-7.28 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.13-7.07 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 1H), 5.89 (s, 1H), 4.70 (t, *J* = 8.0 Hz, 1H), 4.23 (td, *J* = 8.8, 2.8 Hz, 1H), 4.06-4.00 (m, 1H), 3.05-2.97 (m, 1H), 2.41-2.31 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.4, 140.8, 139.4, 133.7, 133.3, 132.9, 132.3, 131.8, 131.1, 131.0, 127.8, 127.6, 125.3, 121.7, 121.2, 120.2, 110.5, 93.5, 43.3, 38.7, 37.6; HPLC: 96.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.69 min; IR (KBr, cm^{-1}): 3074, 2921, 1455, 1343, 1161; MS (ES mass): *m*/*z* 508.4 (M+1).

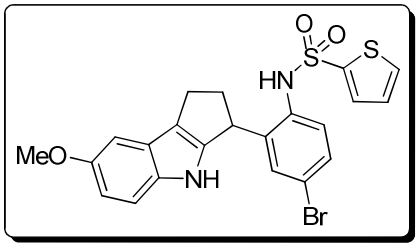
3.7.1.3.17 *N*-(4-Bromo-2-(7-bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl) phenyl)thiophene-2-sulfonamide (3.14q)

3.14q was prepared from **2.15qh** according to the general procedure as presented above.



White solid; yield: 83%; mp: 183-185 °C; R_f (15% EtOAc-*n*-Hexane) 0.27; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (s, 1H), 7.65 (d, *J* = 4.8 Hz, 1H), 7.50 (d, *J* = 3.6 Hz, 1H), 7.34 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.30-7.29 (m, 2H),7.17 (d, *J* = 8.8 Hz, 1H), 7.10 (t,*J* = 4.0 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.44 (s, 1H), 5.92 (s, 1H), 4.72 (t, *J* = 8.0 Hz, 1H), 4.26 (td, *J* = 10.0, 3.2 Hz, 1H), 4.09-4.02 (m, 1H), 3.06-2.98 (m, 1H), 2.44-2.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.2, 140.8, 139.5, 134.4, 133.2, 132.9, 132.3, 131.8, 131.4, 131.0, 127.8, 127.6, 123.8, 123.2, 121.7, 112.9, 110.9, 93.5, 43.3, 38.7, 37.6; HPLC: 99.8%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.27 min; IR (KBr, cm^{-1}): 3258, 2938, 2885, 1465, 1394, 1159; MS (ES mass): *m/z* 552.8 (M+1).

3.7.1.3.18 *N*-(4-Bromo-2-(7-methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl) phenyl)thiophene-2-sulfonamide (3.14r)

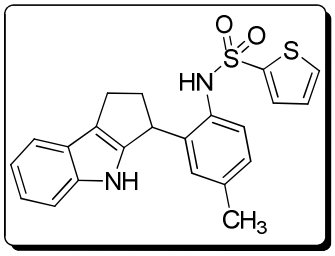


3.14r was prepared from **2.15qm** according to the general procedure as presented above.

Off white solid; yield: 68%; mp: 149-150 °C; R_f (20% EtOAc-*n*-Hexane) 0.17; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 4.4 Hz, 1H), 7.49-7.46 (m, 1H), 7.36-7.29 (m, 2H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.13-7.06 (m, 2H), 7.02 (s, 1H), 6.85 (d, *J* = 8.8Hz, 1H), 6.47 (s, 1H), 5.89 (s, 1H), 4.59 (d, *J* = 8.2Hz, 1H), 4.25-4.18 (m, 1H), 4.06-3.98 (m, 1H), 3.85 (s, 3H), 2.99-2.90 (m, 1H), 2.35-2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.2, 145.1, 140.3, 139.7, 133.3, 133.1, 132.7, 132.5, 131.9, 130.9, 128.2, 127.5, 127.3, 121.2, 111.2, 110.2, 102.9, 93.5, 55.9, 43.3, 39.0,37.4; HPLC: 95.5%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in

water mobile phase B: CH_3CN (Isocratic) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.57 min; IR (KBr, cm^{-1}): 3424, 2953, 1478, 1333, 1160; MS (ES mass): *m*/*z* 504.0 (M+1).

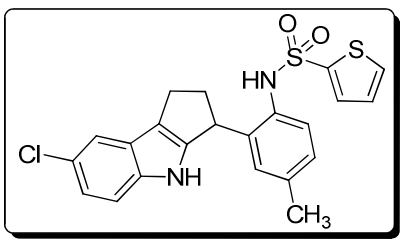
3.7.1.3.19 *N*-(4-Methyl-2-(1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)phenyl)-thiophene-2-sulfonamide (3.14s)



3.14s was prepared from **2.15rb** according to the general procedure as presented above.

White solid; yield: 76%; mp: 133-135 °C; R_f (20% EtOAc-*n*-Hexane) 0.29; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 5.2 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.46-7.45 (m, 1H), 7.30 (d, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.10-7.05 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.99-6.96 (m, 2H), 6.46 (s, 1H), 5.93 (s, 1H),4.69 (t, *J* = 8.0 Hz, 1H), 4.26-4.21 (m, 1H), 4.07-4.01 (m, 1H), 3.01-2.93 (m, 1H), 2.40-2.30 (m, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.2, 140.1, 139.2, 138.1, 132.9, 132.9, 132.7, 132.5, 130.5, 129.3, 128.4, 127.4, 126.5, 120.7, 120.6, 119.4, 109.6, 93.4, 43.2, 38.5, 37.9, 21.1; HPLC: 95.9%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Isocratic) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.28 min; IR (KBr, cm^{-1}): 3300, 3091, 2901, 1706, 1482, 1372, 1162; MS (ES mass): *m*/*z* 409.0 (M+1).

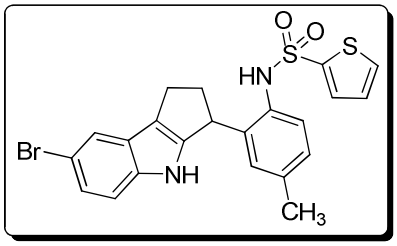
3.7.1.3.20 *N*-(2-(7-Chloro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-4-methyl phenyl)thiophene-2-sulfonamide (3.14t)



3.14t was prepared from **2.15rf** according to the general procedure as presented above.

Off white solid; yield: 68%; mp: 125-127 °C; R_f (15% EtOAc-*n*-Hexane) 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 4.4 Hz, 1H), 7.49 (s, 1H), 7.47 (d,*J* = 1.6 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.13-7.10 (m, 1H), 7.07 (t,*J* = 4.4 Hz, 1H), 6.97-6.95 (m, 3H), 6.35 (s, 1H), 5.89 (s, 1H), 4.77 (t,*J* = 8.0 Hz, 1H), 4.25 (td, *J* =9.6, 3.6 Hz, 1H), 4.08-4.01 (m, 1H), 3.06-2.96 (m, 1H), 2.45-2.35 (m, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.8, 140.0, 139.3, 138.3, 133.9, 133.0, 132.5, 131.1, 130.4, 129.3, 128.5, 127.4, 126.7, 125.1, 120.9, 120.1, 110.4, 93.2, 43.4, 38.7, 37.9, 21.1; HPLC: 95.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.88 min; IR (KBr, cm^{-1}): 3254, 2925, 1459, 1399, 1159; MS (ES mass): *m/z* 443.0 (M+1).

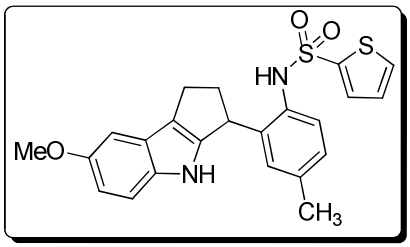
3.7.1.3.21 *N*-(2-(7-Bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-4-methyl phenyl)thiophene-2-sulfonamide (3.14u)



3.14u was prepared from **2.15rh** according to the general procedure as presented above.

Off white solid; yield: 80%; mp: 193-195 °C; R_f (15% EtOAc-*n*-Hexane) 0.19; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 1.4 Hz, 1H), 7.61 (d, *J* = 4.0 Hz, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.25 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.09-7.06 (m, 1H), 7.00-6.96 (m, 2H), 6.94 (s, 1H), 6.39 (s, 1H), 5.88 (s, 1H), 4.77 (t, *J* = 8.0 Hz, 1H), 4.27-4.19 (m, 1H), 4.07-4.00 (m, 1H), 3.05-2.97 (m, 1H), 2.40-2.32 (m, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.8, 139.8, 139.4, 138.3, 134.5, 133.0, 132.5, 131.2, 130.4, 129.2, 128.5, 127.5, 126.7, 123.3, 123.0, 112.6, 110.9, 93.1, 43.4, 38.5, 38.0, 21.1; HPLC: 97.9%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.03 min; IR (KBr, cm^{-1}): 3255, 2884, 1335, 1158; MS (ES mass): *m/z* 486.8 (M-1).

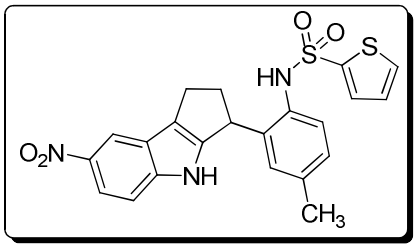
3.7.1.3.22 *N*-(2-(7-Methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-4-methyl phenyl)thiophene-2-sulfonamide (3.14v)



3.14v was prepared from **2.15rm** according to the general procedure as presented above.

Light green solid; yield: 81%; mp: 141-143 °C; R_f (20% EtOAc-*n*-Hexane) 0.23; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.46 (dd, *J* = 3.6, 0.8 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.07-7.04 (m, 1H), 7.02-7.00 (m, 2H), 6.99-6.96 (m, 2H), 6.83 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.46 (s, 1H), 5.85 (s, 1H), 4.66 (t, *J* = 8.0 Hz, 1H), 4.23-4.16 (m, 1H), 4.05-3.94 (m, 1H), 3.84 (s, 3H), 2.98-2.90 (m, 1H), 2.36-2.29 (m, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.0, 146.7, 139.1, 138.0, 133.3, 132.9, 132.4, 130.4, 129.4, 128.4, 128.0, 127.4, 126.4, 110.7, 110.2, 109.9, 102.7, 93.1, 55.9, 43.4, 38.8, 37.8, 21.0; HPLC: 95.5%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 0.5/50, 4/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.25 min; IR (KBr, cm^{-1}): 3266, 3092, 2926, 1484, 1333, 1156; MS (ES mass): *m/z* 439.1 (M+1).

3.7.1.3.23 *N*-(4-Methyl-2-(7-nitro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl) phenyl)thiophene-2-sulfonamide (3.14w)

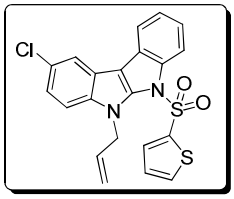


3.14w was prepared from **2.15ro** according to the general procedure as presented above.

Light yellow solid; yield: 75%; mp: 125-127 °C; R_f (25% EtOAc-*n*-Hexane) 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (d, *J* = 1.6 Hz, 1H), 8.11 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.65 (d, *J* = 4.8 Hz, 1H), 7.51 (d, *J* = 3.6 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.11-7.09

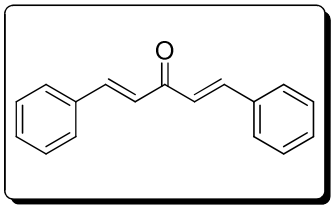
(m, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.46 (s, 1H), 5.03 (t, *J* = 8.0 Hz, 1H), 4.45-4.39 (m, 1H), 4.24-4.16 (m, 1H), 3.27-3.18 (m, 1H), 2.64-2.56 (m, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.3, 139.9, 139.3, 138.9, 136.4, 133.5, 132.8, 130.6, 129.6, 129.4, 128.9, 127.7, 118.1, 117.7, 116.6, 110.0, 109.3, 96.4, 44.6, 38.6, 38.4, 21.3; HPLC: 91.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 5.29 min; IR (KBr, cm^{-1}): 3268, 2930, 1732, 1509, 1326, 1156; MS
(ES mass): *m*/*z* 453.9 (M+1).

3.7.1.3.24 5-Allyl-2-chloro-6-(thiophen-2-ylsulfonyl)-5,6-dihydroindolo[2,3-*b*] indole (2.16w)



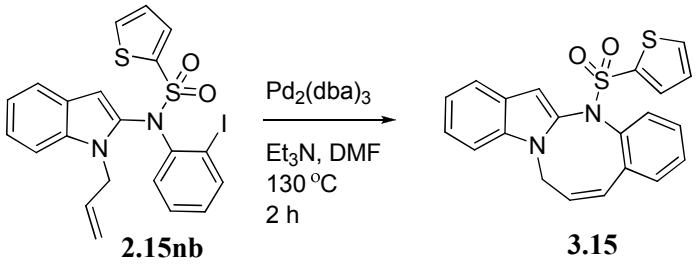
White solid; mp: 180-182 °C; R_f (10% EtOAc-*n*-Hexane) 0.68; ^{1}H NMR (400 MHz, $CDCl_3$) δ:8.15 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.38-7.33 (m, 2H), 7.29-7.27 (m, 1H),7.25-7.24 (m, 2H), 6.77 (t, *J* = 4.8 Hz,1H), 6.17-6.08 (m, 1H), 5.30-5.25 (m, 3H), 5.19 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.6, 140.6, 139.6, 133.9, 133.6, 133.4, 133.3, 126.9, 126.8, 126.7, 126.1, 125.6, 122.9, 122.5, 121.3, 118.9, 118.5, 118.1, 117.2, 112.8, 49.5; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 240 nm, retention time 6.15 min; IR (KBr, cm^{-1}): 3097, 2897, 1439, 1375, 1173; MS (ES mass): *m*/*z* 427.4 (M+1).

3.7.1.3.25 (1*E*,4*E*)-1,5-Diphenylpenta-1,4-dien-3-one (L)



Off white solid; mp: 110-112 °C; R_f (20% EtOAc-*n*-Hexane) 0.82; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, *J* = 15.6 Hz, 1H), 7.64-7.62 (m, 2H), 7.43-7.41 (m, 3H), 7.10 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:188.9, 143.3, 134.7, 130.5, 128.9 (2C), 128.4 (2C), 125.4.

3.7.1.4 Procedure for preparation of compound 3.15:



2.15nb **3.15**

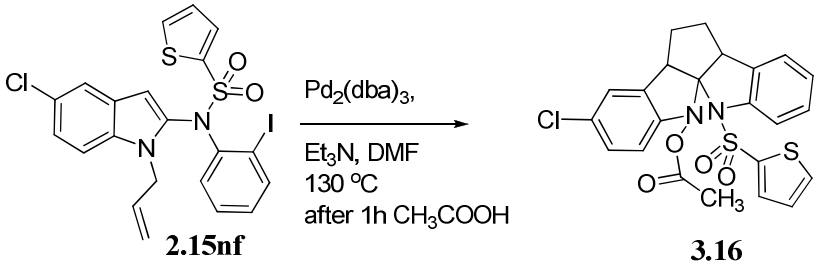
A mixture of *N*-(1-allyl-1H-indol-2-yl)-*N*-(2-iodophenyl)thiophene-2-sulfonamide **2.15nb**, (0.4mmol), $Pd_2(dba)_3$ (5mol%), and Et_3N (1.2 mmol), in anhydrous DMF (2 mL) was stirred at 130 °C for 2h under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. The mixture was cooled to room temperature and filtered to remove the solid separated. The filtrate was extracted with ethyl acetate (3 x 10 mL).The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate-hexane to give the desired product **3.15** in 20% yield.

White solid; mp: 156-158 °C; R_f (15% EtOAc-*n*-Hexane) 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.57-7.55 (m, 2H), 7.39-7.35 (m, 2H), 7.33 (s, 1H), 7.32-7.28 (m, 2H), 7.25-7.22 (m, 1H), 7.11-7.09 (m, 2H), 6.79 (d, *J* = 11.2 Hz, 1H), 6.62 (s, 1H), 6.04-5.97 (m, 1H), 4.92-4.87 (m, 1H), 4.07 (dd, *J* = 15.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.6, 138.1, 136.8, 135.1, 133.7 (2C), 132.7, 132.6, 130.0, 129.5, 129.3, 129.2, 127.1, 126.6, 125.8, 122.4, 121.1, 120.2, 109.3, 99.7, 41.7; MS (ES mass): *m*/*z* 392.5 (M+1).

3.7.1.5 Procedure for preparation of compound 3.16:

A mixture of *N*-(1-allyl-5-chloro-1*H*-indol-2-yl)-*N*-(2-iodophenyl)thiophene-2-sulfonamide **2.15nf**, (0.4mmol), $Pd_2(dba)_3$ (5mol%), and Et_3N (1.2 mmol), in anhydrous DMF (2 mL) was stirred at 130 °C for 1h under a nitrogen atmosphere. Then catalytic amount of acetic acid was added to reaction mixture. The progress of

the reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature and filtered to remove the solid separated. The filtrate was extracted with ethyl acetate (3 x 10 mL).The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate-hexane to give the desired product **3.16** in 14% yield.



2.15nf **3.16**

Off white solid; R_f (15% EtOAc-*n*-Hexane) 0.46; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, *J* = 2.9 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 4.4 Hz, 1H), 7.33-7.29 (m, 2H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.99-6.96 (m, 2H), 6.67 (d, *J* = 8.4 Hz, 1H),4.27 (d, *J* = 8.4 Hz, 1H), 3.32 (dd, *J* = 11.3, 6.9 Hz, 1H), 2.56 (td, *J* = 12.4,5.2 Hz, 1H), 2.15 (s, 3H), 2.11-2.03 (m, 2H), 1.96-1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4(C=O), 149.6, 141.1, 139.5, 133.9, 133.0, 130.2, 129.8, 128.5, 126.3, 126.2, 125.8, 124.6, 124.5, 123.9, 113.6, 111.7, 104.9, 79.6, 51.8, 47.0 (-CH_2-), 33.3 (-CH_2-), 20.9 (CH_3); IR (KBr, cm^{-1}): 2927, 1729, 1466, 1358, 1167; MS (ES mass): *m*/*z* 487.0 (M+1).

3.7.2 Single crystal X-ray data

Single crystals suitable for X-ray diffraction of **3.14a** were grown from methanol. The crystals were carefully chosen using a stereo zoom microscope supported by a rotatable polarizing stage. The data were collected at room temperature on Bruker'sKAPPA APEX II CCD Duo with graphite monochromated Mo-Kα radiation (0.71073 Å).The crystals were glued to a thin glass fibre using FOMBLIN immersion oil and mounted on the diffractometer. The intensity data were processed using Bruker's suite of data processing programs (SAINT), and absorption corrections were applied using SADABS.[17] The crystal structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms, using SHELXL-97.[18]

Crystal data of 3.14a: Molecular formula = $C_{21}H_{20}N_2O_2S_2$, formula weight = 396.10, crystal system = Triclinic, space group = *P*-1,*a* = 8.814 (5) Å, *b* = 10.987 (6) Å, *c* = 11.7256 (12) Å,*V* = 947.9 (9) $Å^3$, *T* = 298 K, *Z* = 2, D_c = 1.382 Mg m^{-3}, μ(Mo-Kα) = 0.30 mm^{-1}, 6911 reflections measured, 4456 independent reflections, 1925 observed reflections [I > 2.0 σ (I)], R_1_obs = 0.045, Goodness of fit =1.11.Crystallographic data (excluding structure factors) for **3.14b** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 918746.

3.7.3 Pharmacology

3.7.3.1 PDE4B protein production and purification

PDE4B1 cDNA was sub-cloned into pFAST Bac HTB vector (Invitrogen) and transformed into DH10Bac (Invitrogen) competent cells. Recombinant bacmids were tested for integration by PCR analysis. Sf9 cells were transfected with bacmid using Lipofectamine 2000 (Invitrogen) according to manufacturer's instructions. Subsequently, P3 viral titer was amplified, cells were infected and 48 h post infection cells were lysed in lysis buffer (50 mM Tris-HCl pH 8.5, 10 mM 2-mercaptoethanol, 1 % protease inhibitor cocktail (Roche), 1 % NP40). Recombinant His-tagged PDE4B protein was purified as previously described elsewhere.[19a] Briefly, lysate was centrifuged at 10,000 rpm for 10 min at 4 ºC and supernatant was collected. Supernatant was mixed with Ni-NTA resin (GE Life Sciences) in a ratio of 4:1 (v/v) and equilibrated with binding buffer (20 mM Tris-HCl pH 8.0, 500 mM-KCl, 5 mM imidazole, 10 mM 2-mercaptoethanol and 10 % glycerol) in a ratio of 2:1 (v/v) and mixed gently on rotary shaker for 1 hour at 4 ºC. After incubation, lysate-Ni-NTA mixture was centrifuged at 4,500 rpm for 5 min at 4 ºC and the supernatant was collected as the flow-through fraction. Resin was washed twice with wash buffer (20 mM Tris-HCl pH 8.5, 1 M KCl, 10 mM 2-mercaptoethanol and 10% glycerol). Protein was eluted sequentially twice using elution buffers (Buffer I: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 250 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol, Buffer II: 20 mM Tris-HCl pH 8.5, 100 mM KCl, 500 mM imidazole, 10 mM 2-mercaptoethanol, 10% glycerol). Eluates were collected in four fractions and analyzed by SDS-PAGE. Eluates containing PDE4B protein were pooled and stored at -80 ºC in 50% glycerol until further use.

PDE4 enzymatic assay

The inhibition of PDE4 enzyme was measured using PDElight HTS cAMP phosphodiesterase assay kit (Lonza) according to manufacturer's recommendations. Briefly, 10 ng of in house purified PDE4B1 or 0.5 ng commercially procured PDE4D2 enzyme was pre-incubated either with DMSO (vehicle control) or compound for 15 min before incubation with the substrate cAMP (5 µM) for 1 hour. The reaction was halted with stop solution and reaction mix was incubated with detection reagent for 10 minutes in dark. Dose response studies were performed at 13 different concentrations ranging from 200 µM to 0.001 µM. Luminescence values (RLUs) were measured by a Multilabel Plate Reader (PerklinElmer 1420 Multilabel Counter). The percentage of inhibition was calculated using the following formula and the IC_{50} values were determined by a nonlinear regression analysis from dose response curve using Graphpad Prism software (San Diego, U.S.A). IC_{50} values are presented as mean ± SD.

$$\%\ inhibition = \frac{(RLU of vehicle control - RLU of inhibitior)}{RLU of vehicle control} X\ 100$$

Some of the synthesized compounds were tested for their PDE4B inhibitory potential *in vitro* at 30 μM using PDE4B enzyme[16] and rolipram as a reference compound.

3.7.3.1 Molecular Modeling Studies

The molecular docking Simulation was performed using Chemical Computing Group's Molecular Operating Environment (MOE) software 2008.10 Version, "DOCK" application Module. The purpose of the Dock application was to search for favorable binding configurations in macromolecular target, which is usually a protein. For each ligand, a number of configurations called *poses* are generated and scored in an effort to determine favorable binding modes.

The Dock workflow involves Conformational Analysis, Placement, scoring, and Force field method of Refinement.

Procedure: The PDE4B protein in complex with Rolipram (PDB code-1XMY) was used for our docking studies.[19,20,21] The original PDE Protein's PDB file containing crystallized Zn and Mn metal ions were retrieved from PDB Database and Protonated (Addition of Hydrogen atoms) with Protonation 3D application in MOE. Connolly

Molecular surface was generated around the ligand site of the protein, Gasteiger Partial charges was added to the protein and finally energy was minimized to relieve bad crystallographic contacts. The "Active site finder" function of the MOE software was used to denote potential docking pockets within the Protein crystal structure. The test molecule was placed in the active site pocket of the protein by the "Triangle Matcher" Method, which generates poses by aligning the ligand triplet of atoms with the triplet of alpha spheres in cavities of tight atomic packing. The Dock scoring was carried out with London dG method after retaining and scoring the best 10 poses of the molecule. The Preparation of ligand for Docking Simulation involves the Energy minimization with Molecular Mechanics Force-field MMFF94x (Merck Molecular Force Field 94×) and then the molecule was subjected to conformational search in MOE using the Conformational Stochastic search module to find the lowest energy conformers.

The docking results appeared as docking score in which the docking poses are ranked by the Molecular Mechanics and Generalized Born solvation model (MM/GBVI) binding free energy.

For all scoring functions, lower scores indicate more favorable binding poses. The unit for all scoring functions is K.cal/mol. The final energy was calculated using the Generalized Born solvation model. Poses for each ligand were scored based on complementarity with binding pocket.

The London dG scoring function estimates the free energy of binding of the ligand from a given pose. The functional form is a sum of terms:

$$\Delta G = c + E_{flex} + \sum_{h-bonds} c_{HB} f_{HB} + \sum_{m-lig} c_M f_M + \sum_{atoms\ i} \Delta D_i$$

where c represents the average gain/loss of rotational and translational entropy; E_{flex} is the energy due to the loss of flexibility of the ligand (calculated from ligand topology only); f_{HB} measures geometric imperfections of hydrogen bonds and takes a value in [0,1]; c_{HB} is the energy of an ideal hydrogen bond; f_M measures geometric imperfections of metal ligations and takes a value in [0,1]; c_M is the energy of an ideal metal ligation; and D_i is the desolvation energy of atom i.

To validate the Docking accuracy of the program used, the native co-crystallized Rolipram ligand was docked back into its binding site of PDE4B protein.

3.8 References

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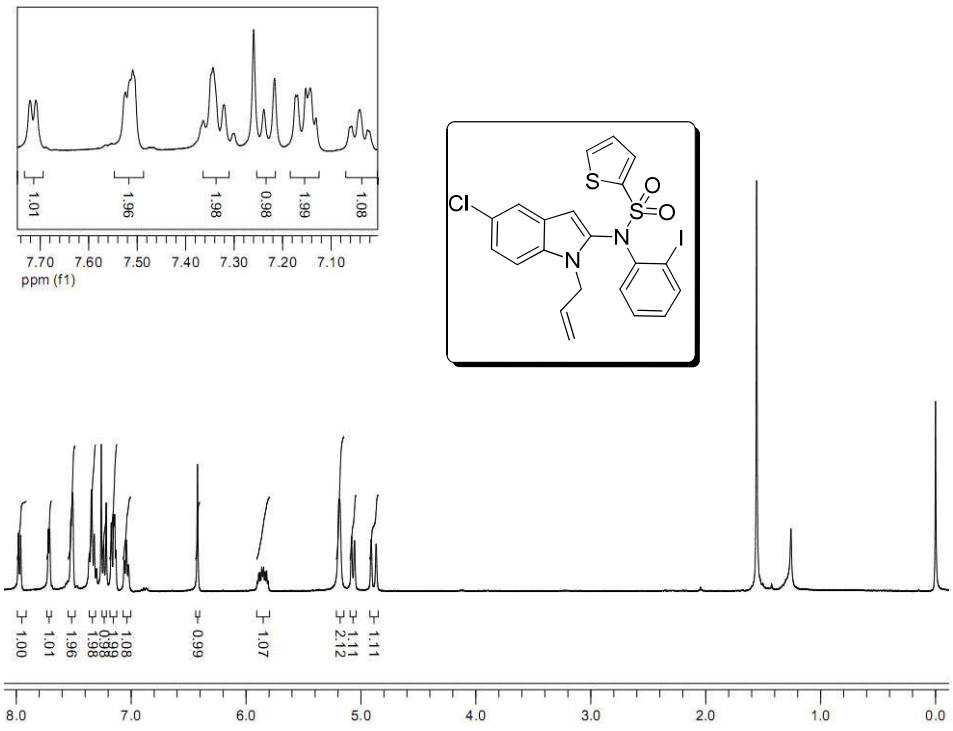
Appendix

^{1}H NMR (Varian, 400 MHz) spectrum of compound **2.15nf** in $CDCl_3$



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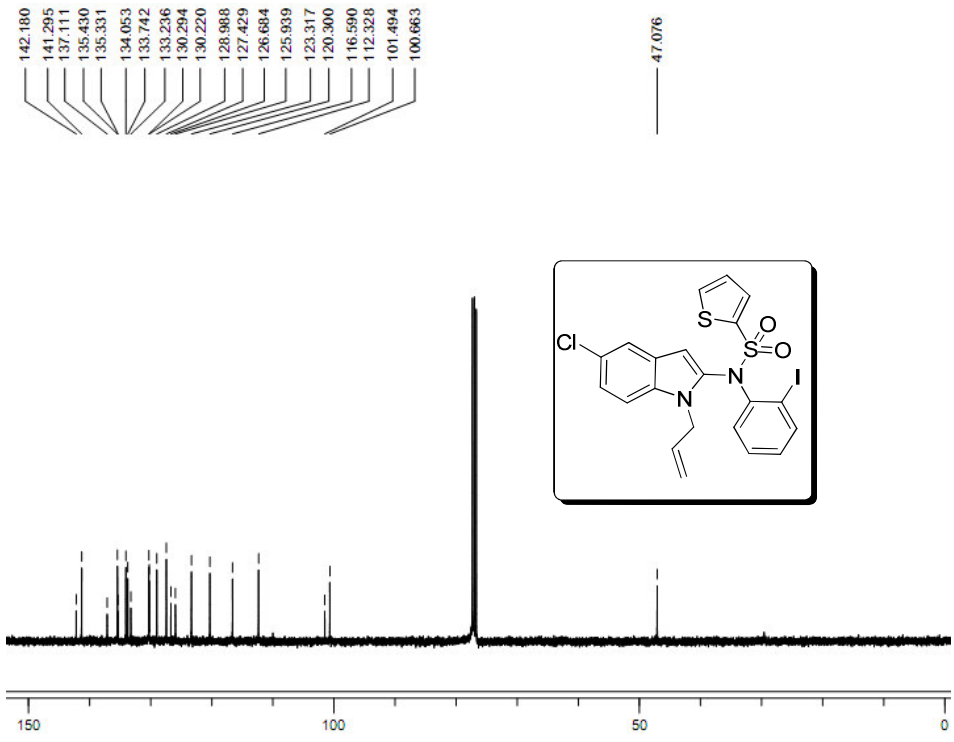
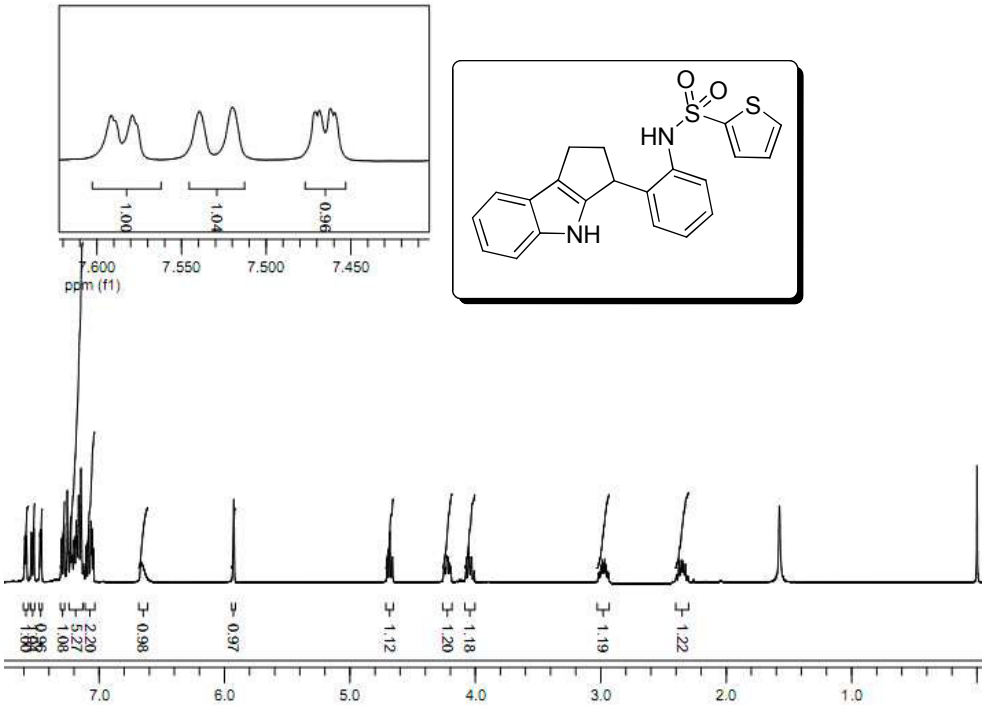


^{1}H NMR (Varian, 400 MHz) spectrum of compound **3.14a** in $CDCl_3$



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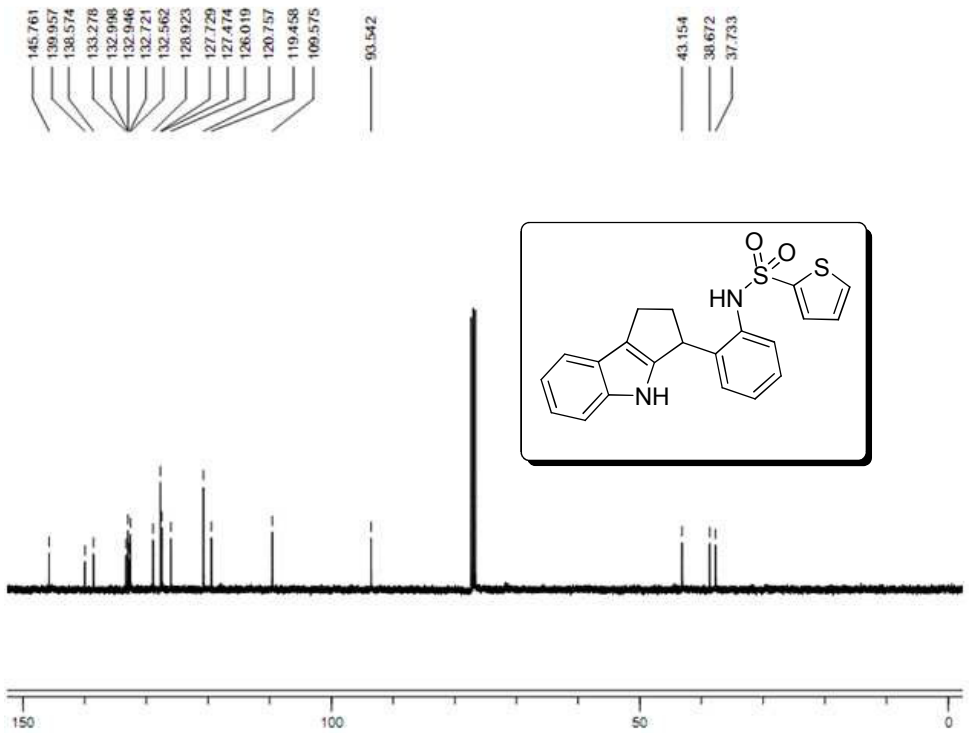

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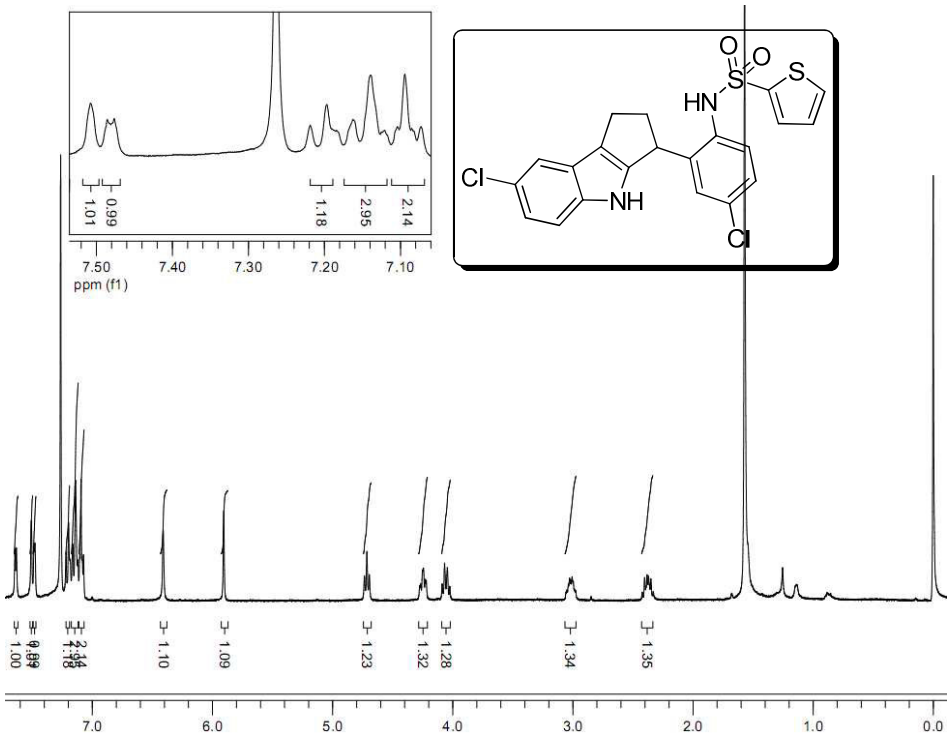

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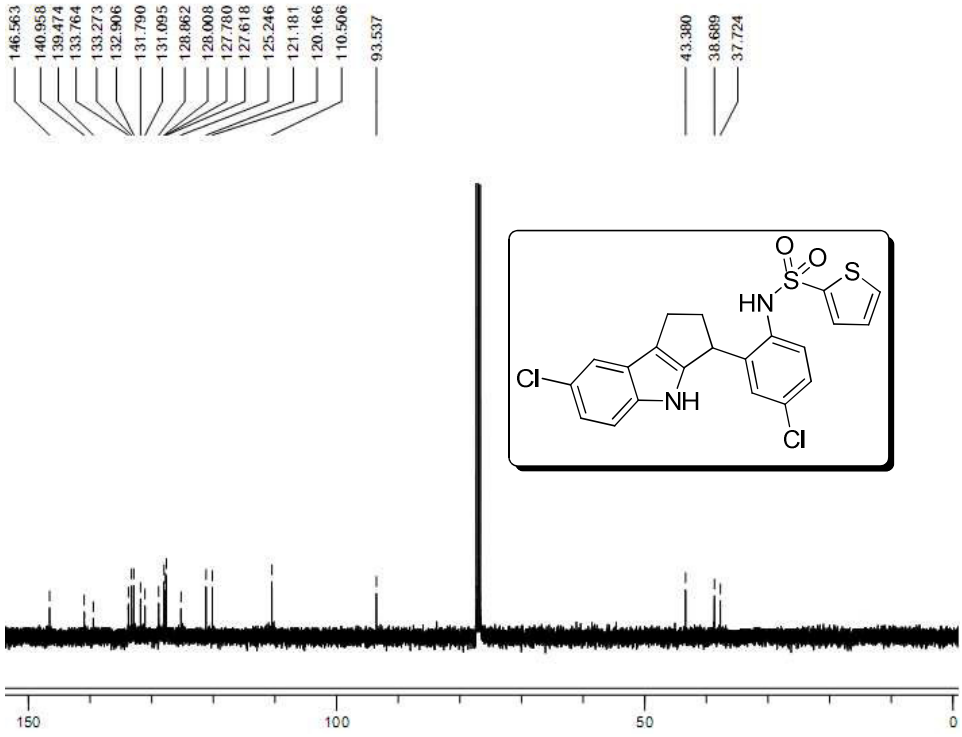

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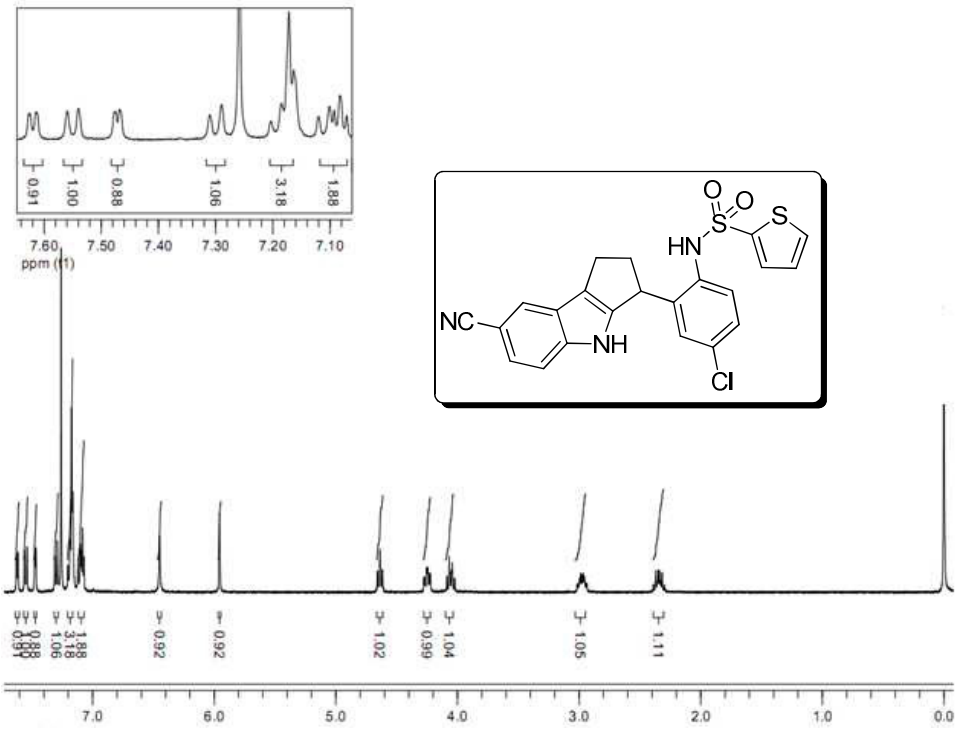
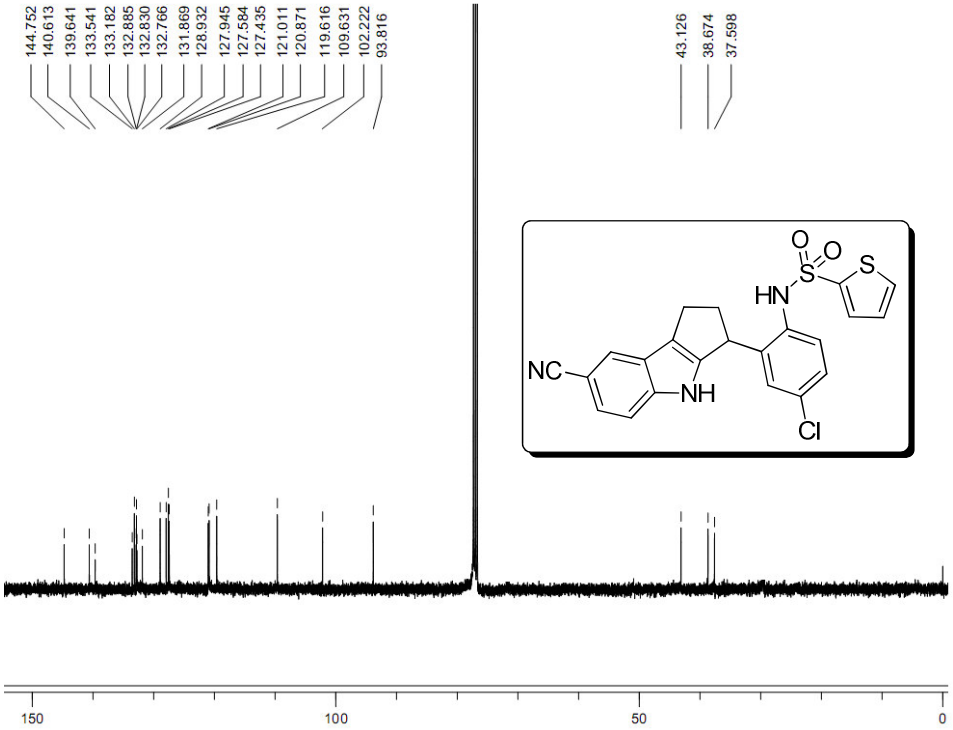


^{13}C NMR spectrum (Varian, 100 MHz) of compound **3.14n** in $CDCl_3$



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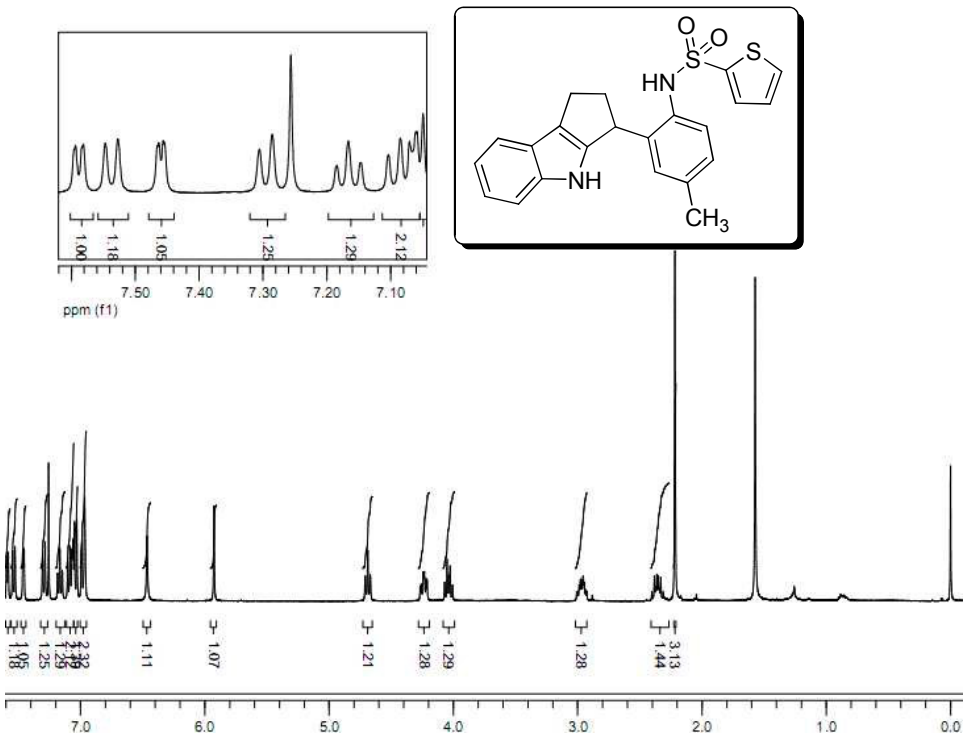

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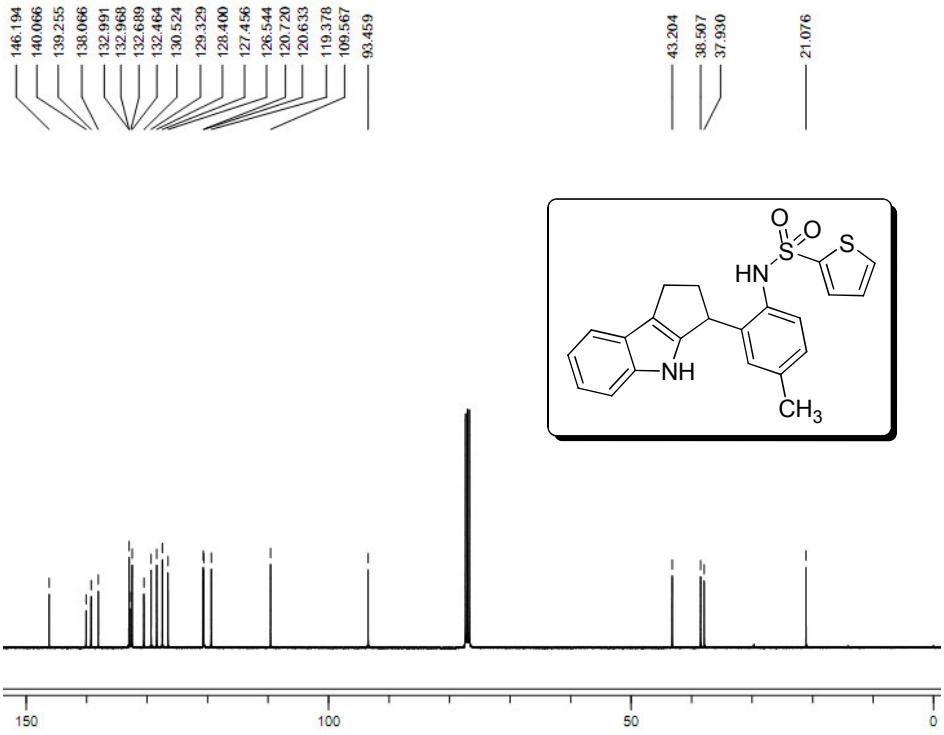

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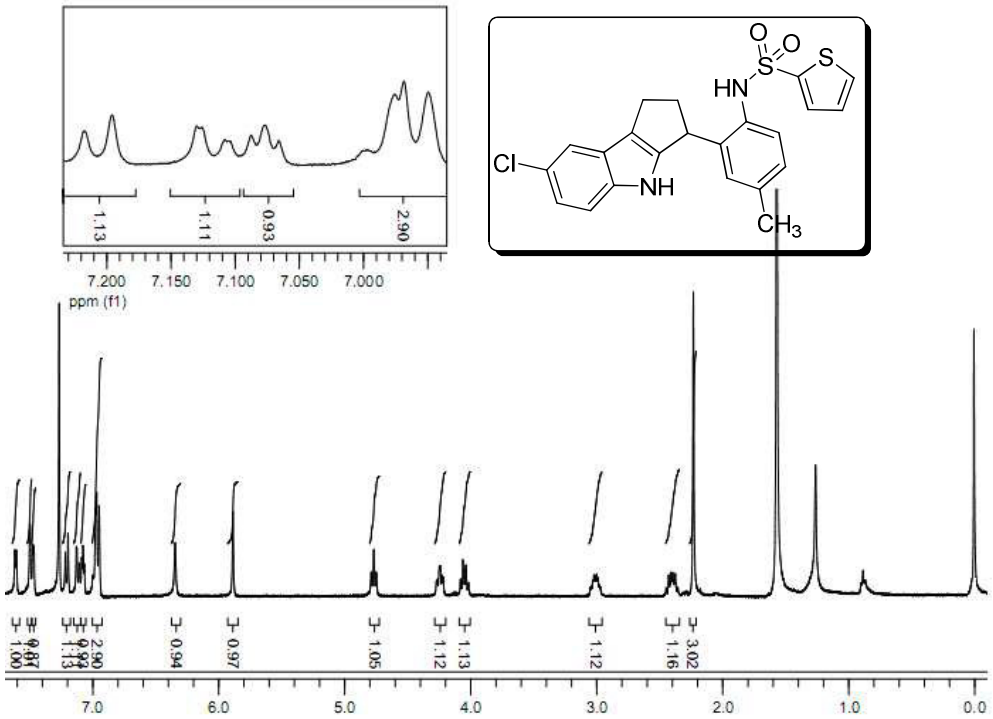
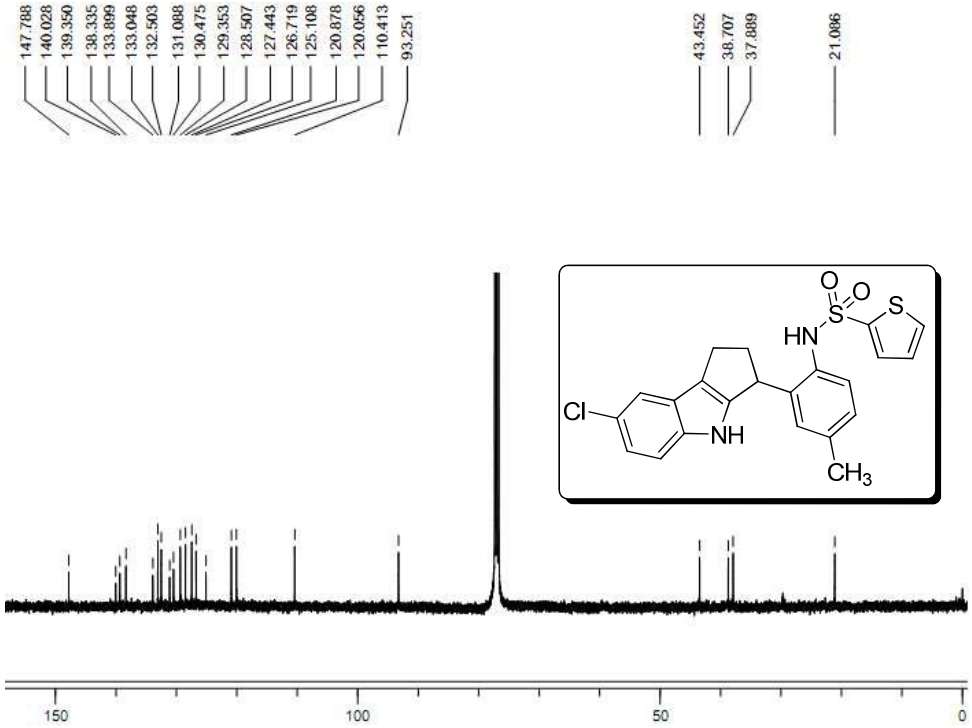
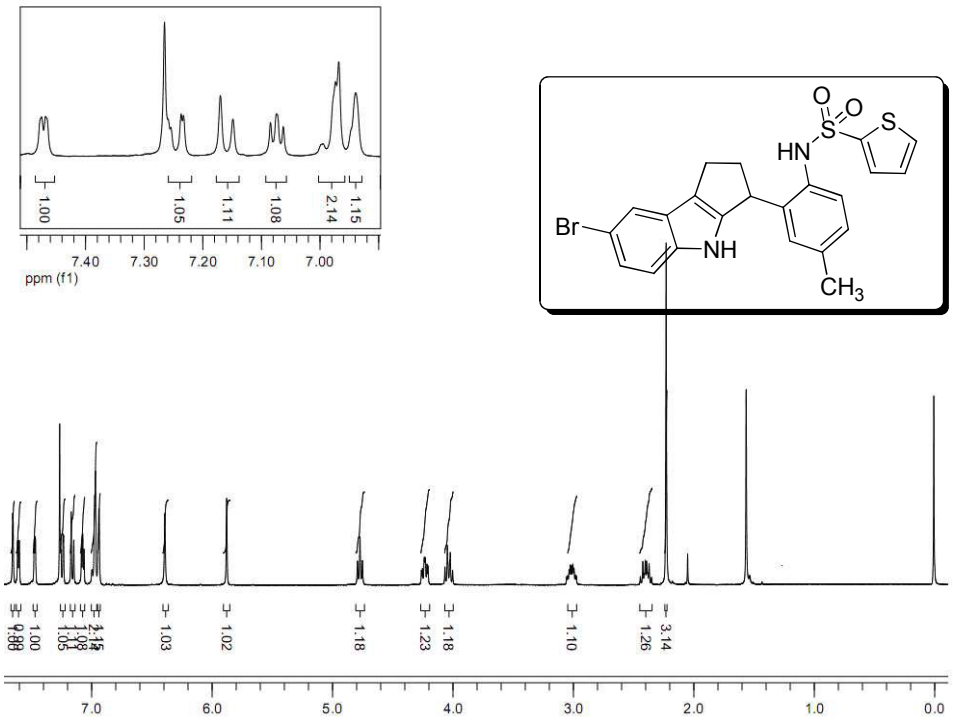


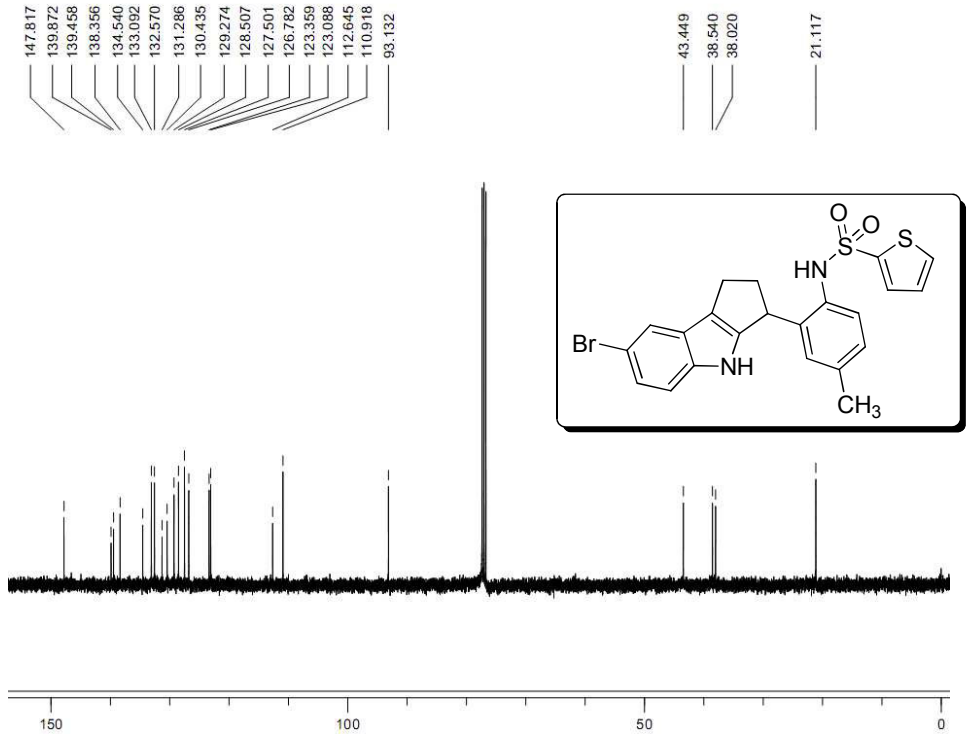
^{13}C NMR spectrum (Varian, 100 MHz) of compound **3.14t** in $CDCl_3$



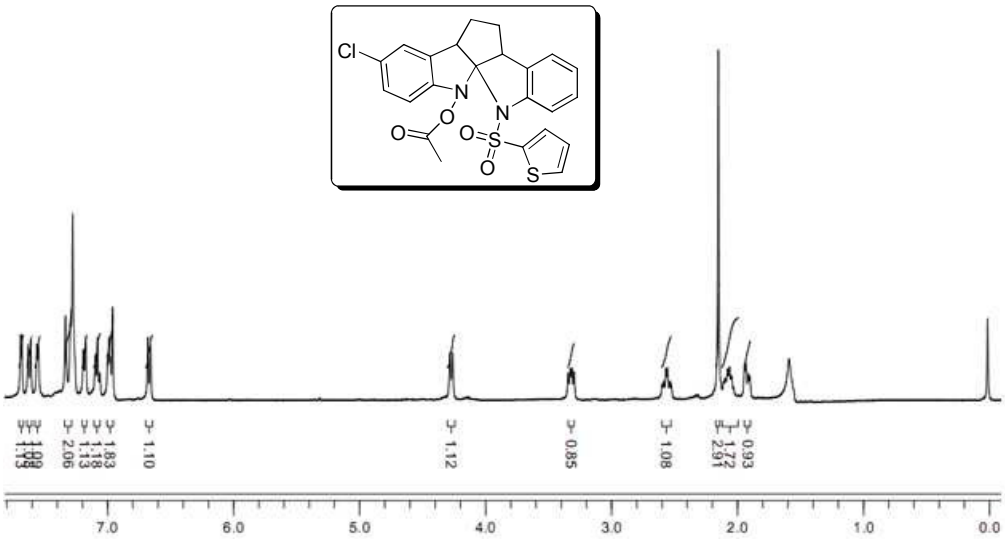
^{1}H NMR (Varian, 400 MHz) spectrum of compound **3.14u** in $CDCl_3$



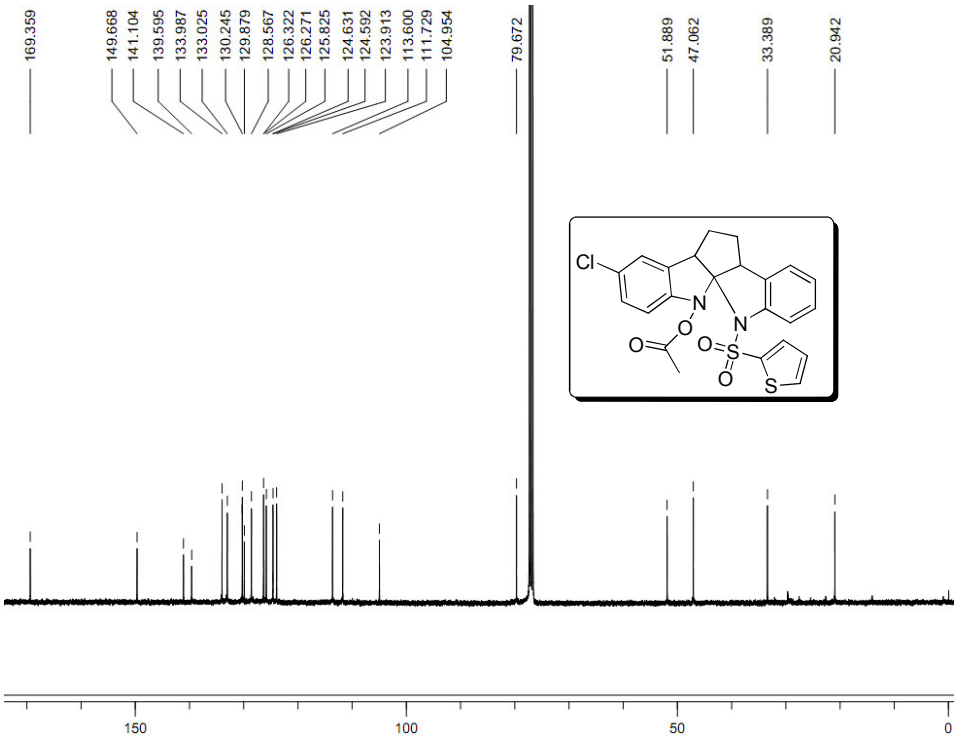
^{13}C NMR spectrum (Varian, 100 MHz) of compound **3.14u** in $CDCl_3$



^{1}H NMR (Varian, 400 MHz) spectrum of compound **3.16** in $CDCl_3$

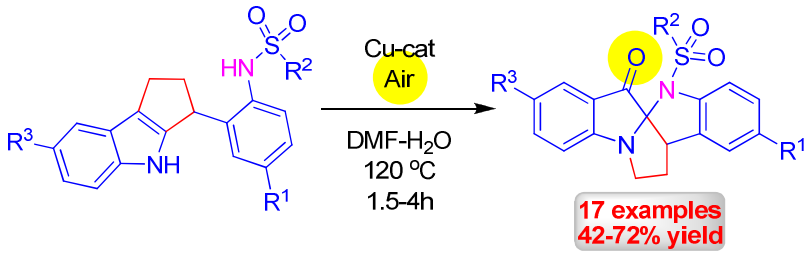


^{13}C NMR spectrum (Varian, 100 MHz) of compound **3.16** in $CDCl_3$



CHAPTER 4

Cu- catalyzed synthesis of 2,2′-spiroindole derivatives



4.1 Introduction

The unique structural features of spirooxindoles and the presence of spiro linkage as a basic skeleton in several natural products have increased their importance to a great extent. Normally, the naturally occurring spiroxindoles (with five membered nitrogen containing ring) exist in two forms. The spiroxindoles [3,3-disubstituted indolin-2-one] present in Horsfiline (**F4.1**, Figure 4.1)[1] showed analgesic activity, Spirotryprostatin A (**F4.2**, Figure 4.1)[2] acts as inhibitors of mammalian cell cycle at G2/M phase, and Elacomine (**F4.3**, Figure 4.1)[3] showed interesting biological properties. Mitraphylline (**F4.4**, Figure 4.1) containing the spiroxindole framework possesses anti-tumor activity against human brain cancer cell lines and malignant glioma GAMG.[4] Rhynchophylline (**F4.5**, Figure 4.1) is used as antipyretic, anti-hypertensive and anti convulsant medications for the treatment of headache, vertigo and epilepsy.[5]

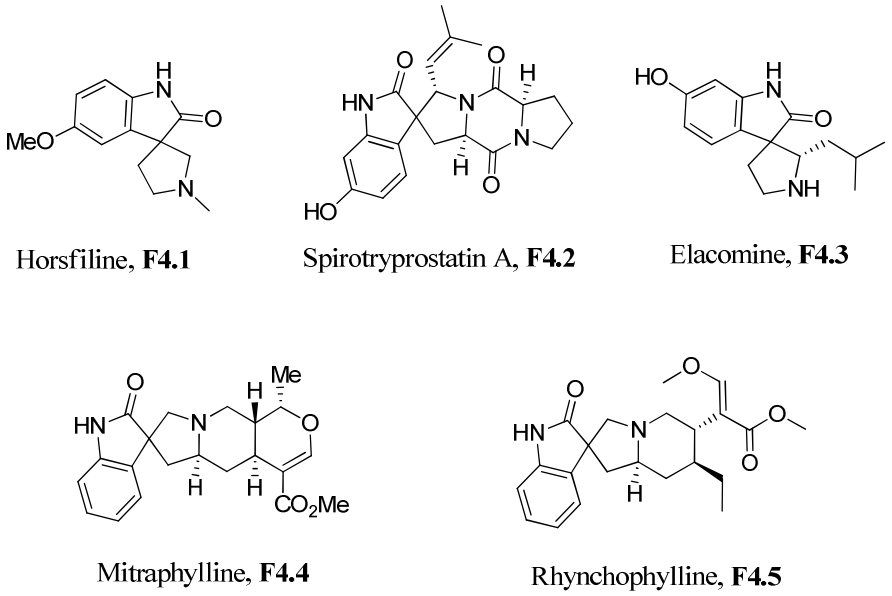


Figure 4.1 Biologically active spiroxindoles.

Another class of oxindole is pseudoindoxyl [2,2-disubstituted indolin-3-one] which is also a common structural feature of some of the indole alkaloids (Figure 5.2).[6] The Austamide[7] **F4.6** (toxic metabolite of *Aspergillus ustus*), Brevianamide A[8] **F4.7**, (induce cytoxicity in cells), Isatisine A[9] **F4.8**, (promising anti-HIV activity) and Notoamide O[10] **F4.9** are some of the representative natural products (Figure 4.2).

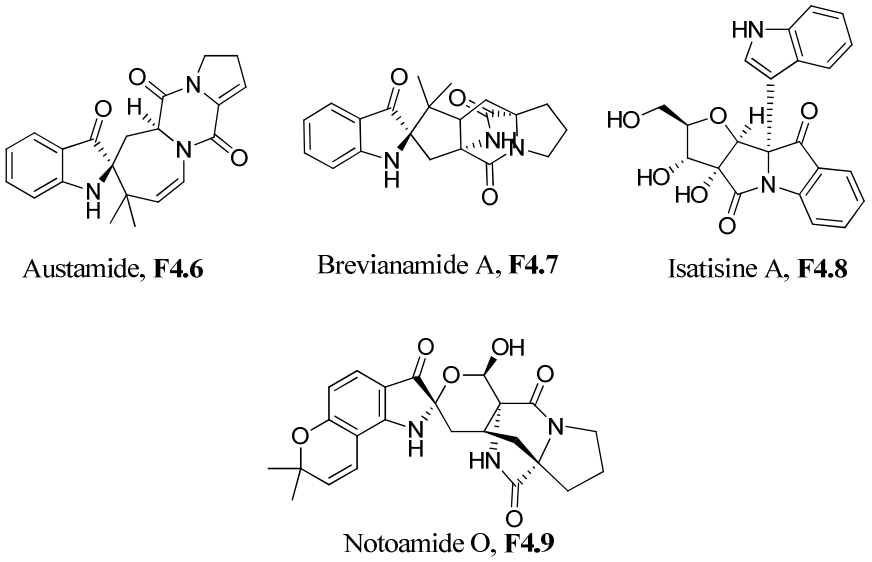
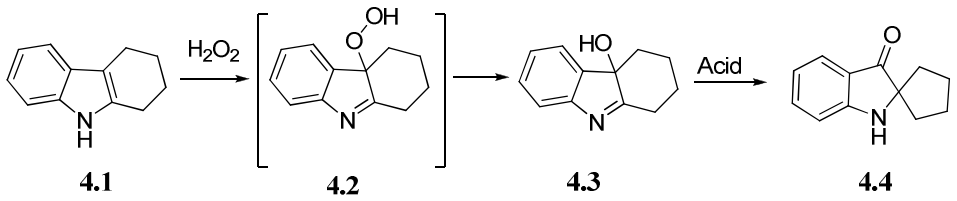


Figure 4.2 Natural products having pseudoindoxyl moiety.

Notably, despite their potential usefulness not much attention has been paid to pseudoindoxyl [2,2-disubstituted spiroindolin-3-one] derivatives perhaps due to their non accessibility and consequently as a class they are rather uncommon in the literature. In our effort on identification of novel small molecules of potential biological significance we have described in Chapter 2 and Chapter 3 the synthesis of densely functionalized indoles *via* two unique single-step reactions.[11] In further continuation of Chapter 3 work we are going to discuss a Cu-mediated cascade reaction for the synthesis of pseudoindoxyl moiety.

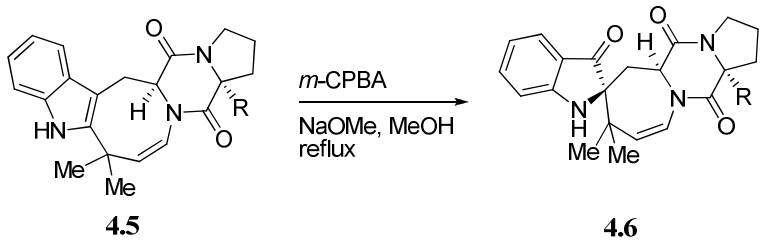
4.2 Previous work

In literature, the C-3 oxidations of indoles/intramolecular cyclization followed by the intra-molecular nucleophilic attack of the iminiumion by the nucleophiles leading to spiro indolines were reported. For example, in 1951 Patrick and coworkers reported the catalytic oxidation of tetrahydrocarbazole (**4.1**) in ethyl acetate with platinum catalyst and subsequent gentle hydrogenation leading to synthesis of 11-Hydroxytetrahydrocarbazolenine (**4.3**) *via* generation of 4a-hydroperoxy-2,3,4,4a-tetrahydro-1*H*-carbazole (**4.2**) (Scheme 4.1). The compound **4.3** undergoes acid-catalyzed Wagner-Meerwein rearrangement leading to spiro[cyclopentane-1,2'-indolin]-3'-one (**4.4**).[12]



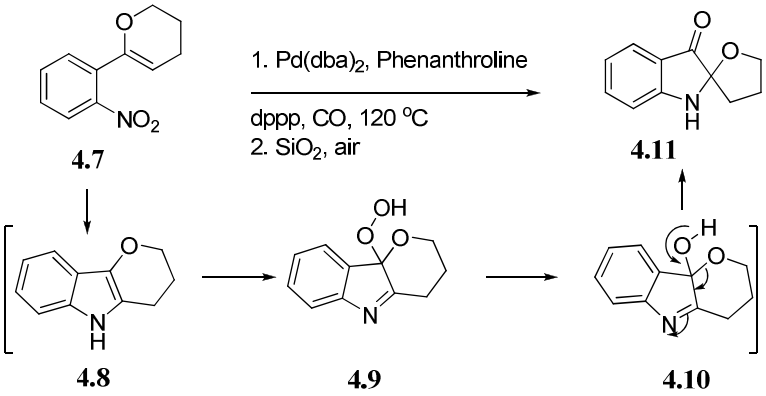
Scheme 4.1 Synthesis of spiro[cyclopentane-1,2'-indolin]-3'-one.

In 2002, Corey and coworkers reported the epoxidation of the 2,3-bond of the indole subunit in **4.5** with subsequent C-O cleavage to form a 3-hydroxyindoline that was then converted diastereo selectively to the spirocyclicoxindole **4.6** by heating with NaOMe in methanol (Scheme 4.2).[7a]



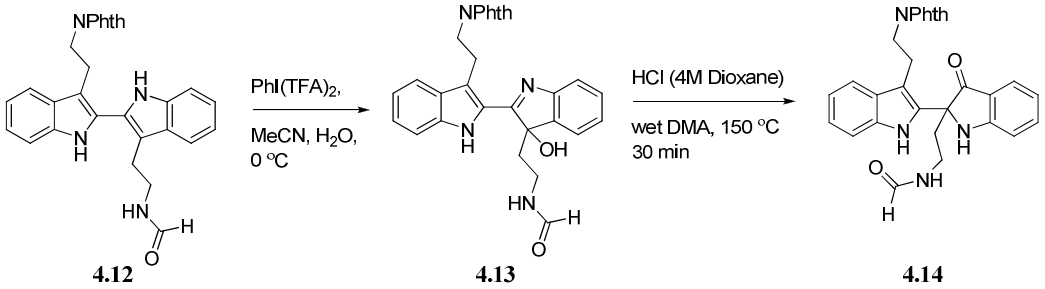
Scheme 4.2 Synthesis of spirocyclicoxindole.

In 2006, Soderberg and coworkers reported the conversion of nitro compound **4.7** to spiroindolone (**4.11**) by using $Pd(dba)_2$ and SiO_2 (Scheme 4.3). The spiroindolone **4.11** is probably formed via the peroxide **4.9** and the alcohol **4.10** though oxidative-rearrangements in air.[13]



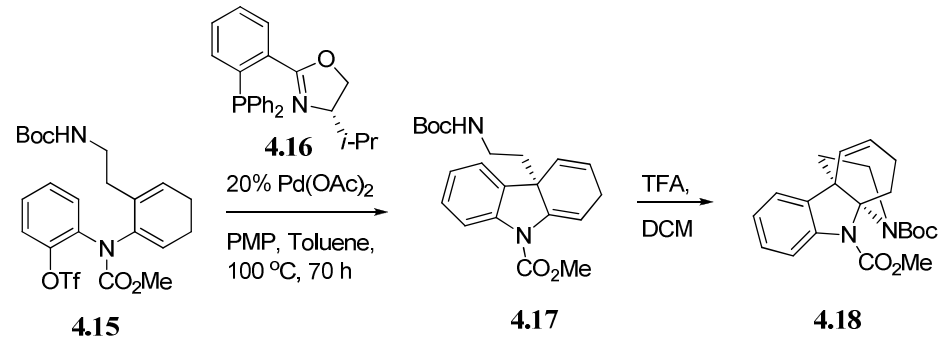
Scheme 4.3 Synthesis of spiroindolone.

In 2011, Tambar and coworkers reported the facile mono-oxidation of **4.12** under $PhI(TFA)_2$ preferentially produced hydroxyl indolenine **4.13** which underwent rearrangement to form the indoxyl **4.14** under the acidic conditions (Scheme 4.4).[14]



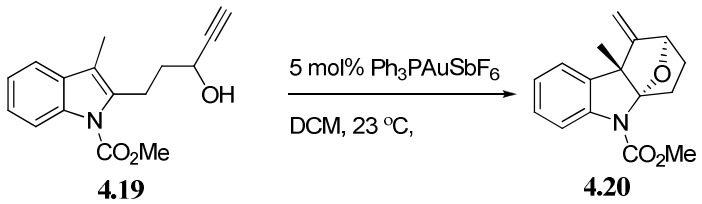
Scheme 4.4 Synthesis of indoxyl compound.

In 2008, Overman and coworkers reported a catalytic asymmetric intramolecular Heck coupling of **4.15** afforded **4.17** which was rapidly underwent iminium cyclization provided high enantiomeric 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazoles (**4.18**) (Scheme 4.5) in presence of TFA.[15]



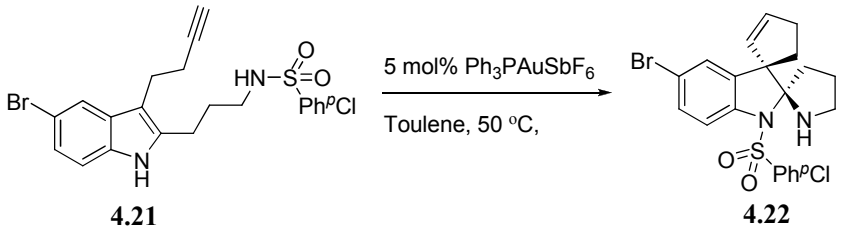
Scheme 4.5 Synthesis of 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazoles.

In 2010, X. Wang and coworkers reported $Ph_3PAuSbF_6$ mediated regio selective cyclization of **4.19** which afforded the diastereomer **4.20** (Scheme 4.6).[16]



Scheme 4.6 Synthesis of indoline **4.20**.

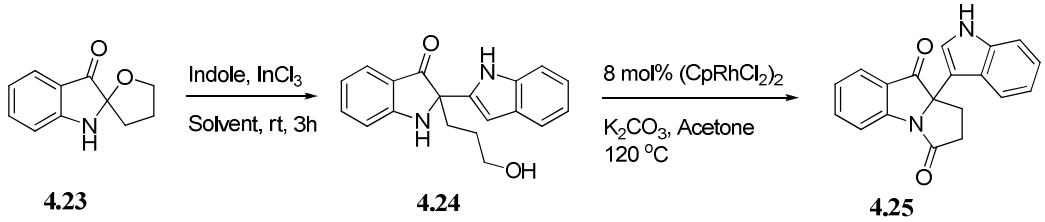
In 2013, same group reported that alkynyl indoles (**4.21**) underwent the tandem cyclization to produce the corresponding indolines (**4.22**) by the exo-dig cyclizations followed by the intra-molecular nucleophilic attack of the iminiumion by the nitrogen nucleophiles (Scheme 4.7).[17]



4.21 **4.22**

Scheme 4.7 Synthesis of induline **4.22** .

In 2014, Ramana and coworkers reported two sequential metal-catalysed transformations, (i) In-catalysed Friedel-crafts type addition of spiroaminol carbon (**4.23**) to C-3 of indole leading to 2-(3-hydroxypropyl)-2,2'-biindolin-3-one (**4.24**) (ii) Rh-catalyzed dehydrogenative cyclization of **4.24** afforded tricyclic γ-lactam (**4.25**) (Scheme 4.8).[18]



4.23 **4.24** **4.25**

Scheme 4.8 Synthesis of tricyclic γ-lactam.

4.3 Present work

Though several methods were reported in literature for synthesis of pseudoindoxyl like systems, but no direct one pot cascade reaction leading to 2,2'-spirobi[indolin]-3-one system was reported. However, one pot casacade reactions leading to complex spiro systems were highly desirable. Here we have describe a novel and convenient Cu-mediated unprecedented cascade reaction for the synthesis of spirobi[indolin]-3-one derivatives (Scheme 4.9). The present cascade reaction consists of (i) C-3 oxidation of indole (C-O bond formation) (ii) C-C bond cleavage and (iii) formation of two new C-N bonds (Figure 4.3).

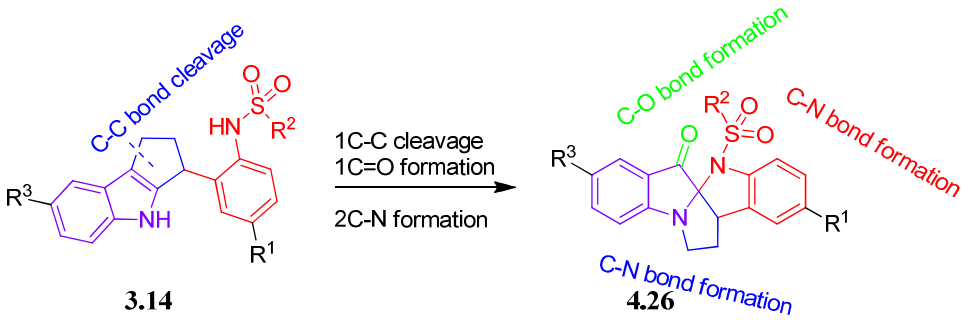
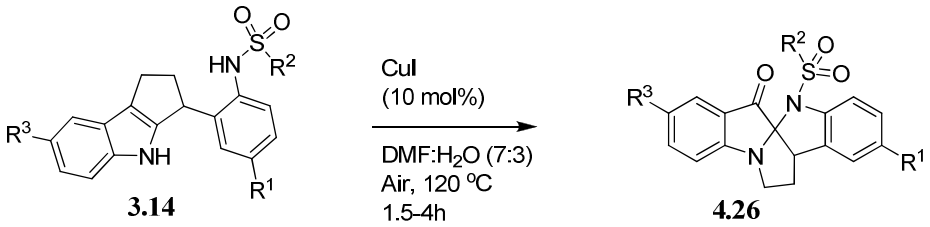


Figure 4.3 Bond events involved in cascade reaction.

Here we have describe a novel, convenient methode for spirobi[indolin]-3-one derivatives (**4.26**) by treatment of CuI with cyclopentaindoles (**3.14**) (Scheme 4.9).



Scheme 4.9 Cu-mediated cascade reaction of **3.14** leading to novel 2,2'-spirobi[indolin]-3-one derivatives **4.26**.

4.4 Results and discussion

4.4.1 Synthesis of Cyclopenta[*b*]indoles

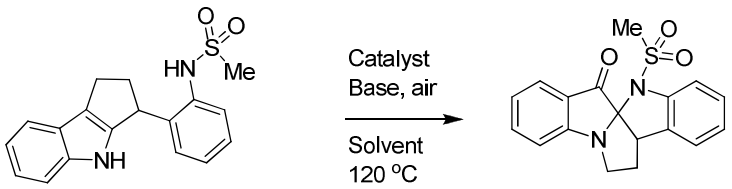
The synthesis of requisite starting materials **3.14** described in Chapter 3 (Table 3.3).

4.4.2 Reaction optimisation

We initiated our study by examining the expected cascade reaction of **3.14aa** in the presence of various catalysts, bases, and solvents and the results are summarized in Table 4.1. Initially the reaction was performed using **3.14aa,** $Cu(OAc)_2$ (1 equiv.) and Et_3N in DMF at 120 °C under air when the desired product **4.26a** was obtained in 25% yield after 3h (entry 1**,** in Table 4.1). The use of other catalyst e.g. $Cu(OTf)_2$ (entry 2**,** in Table 4.1) and base Cs_2CO_3 (entry 3**,** in Table 4.1) afforded **4.26a** in 30 and 56% yield respectively. While the combination of $Cu(OTf)_2$ / Cs_2CO_3 afforded **4.26a** in 60% yield (entry 4**,** in Table 4.1) the product formation was almost suppressed in the presence of benzoquinone (entry 5**,** in Table 4.1). An unidentified

polar material was obtained as a side product in this case. Until this we were not aware of the role of base in the present cascade reaction. However, we observed that the reaction proceeded well in the absence of base when performed in the presence of $Cu(OTf)_2$ (entry 6**,** in Table 4.1).

Table 4.1 Optimization of reaction conditions.[a]



3.14aa **4.26a**

Entry	Catalyst	Solvent/base	Time (h)	Yield[b](%)
1	1 eq. $Cu(OAc)_2$	DMF/Et_3N	3	25
2	1 eq. $Cu(OTf)_2$	DMF/Et_3N	3	30
3	1 eq. $Cu(OAc)_2$	DMF/Cs_2CO_3	2	56
4	1 eq. $Cu(OTf)_2$	DMF/Cs_2CO_3	2	60
5	1 eq. $Cu(OTf)_2$	DMF/Cs_2CO_3	3	10[c]
6	1 eq. $Cu(OTf)_2$	DMF	3	60
7	20 mol% $Cu(OTf)_2$	DMF	6	58
8	20 mol% $Cu(OTf)_2$	DMF + H_2O (7:3)	1.5	70
9	10 mol% $Cu(OAc)_2.H_2O$	DMF + H_2O (7:3)	1.5	65
10	5 mol% CuI	DMF + H_2O (7:3)	4	56
11	5 mol% CuI	DMF + H_2O (1:1)	4	50
12	10 mol% CuI	DMF + H_2O (7:3)	2	66
13	No catalyst	DMF/Cs_2CO_3	6	0

[a]All the reactions were performed using **3.14aa** (0.5 mmol) and catalyst in the presence/ absence of a base (1 equiv) in a solvent (2 mL) at 120 °C under air.

[b]Isolated yield.

[c]1 equiv of benzoquinone was added.

Next, to avoid the use of stoichiometric amount of catalyst we wanted to make this method truly a catalytic one. Accordingly, the reaction was performed using 20 mol% of $Cu(OTf)_2$. To our satisfaction, the reaction proceeded well to afford the expected product in 58% yield (entry 7**,** in Table 4.1) though the reaction time was

a bit longer i.e. 6 h. We then examined the use of aqueous DMF in place of DMF alone. To our surprise the reaction was completed within 1.5 h affording a better yield of **4.26a** (entry 8**,** in Table 4.1). Indeed, the use of lower quantity of $Cu(OAc)_2.H_2O$ also provided the similar outcome (entry 9, Table 4.1). These observations clearly indicated that the reaction is not a moisture sensitive one. To make the process more economic without affecting the product yield significantly we examined the use of a cheaper catalyst i.e. CuI in aqueous DMF (entries 10-12, Table 4.1). We found that 10 mol% CuI in 7:3 DMF-H_2O afforded **4.26a** in 66% yield within 2h (entry 12**,** in Table 1). Finally, the role of catalyst was also established by performing the reaction in absence of it when no product was formed (entry 13**,** in Table 4.1). Overall, we preferred conditions of entry 12 over entry 8 (Table 4.1) due to the comparable reaction time and yield in addition to the involvement of inexpensive catalyst.

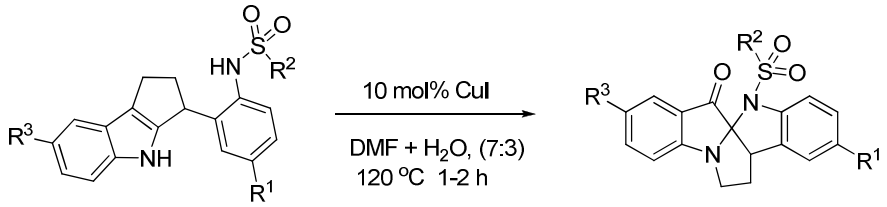
4.4.3 Scope of the reaction

With the optimized conditions in hand, we further investigated the substrate scope of this new cascade reaction. Thus a variety of cyclopentaindoles (**3.14**) were employed in this Cu-mediated reaction (Table 4.2). The presence of halogens e.g. F, Cl, Br (entries 2, 3, 5-13, 15 and 16, Table 4.2) and electron donating groups e.g. Me and OMe (entries 7, 10 and 12-17, Table 4.2) and electron with drawing group e.g. NO_2 (entry 17, Table 4.2) on the indole ring of **3.14** was tolerated and the reaction proceeded well in all these cases affording the desired product in good to acceptable yields. In general better yields of **4.26** were observed when an electron donating group was present. We also examined the effect of nature of sulfonamide moiety present in **3.14**. Accordingly, cyclopentaindole **3.14** containing alkyl (entries 1 and 2, Table 4.2), aryl (entry 3, Table 4.2) and heteroaryl (entries 14-17, Table 4.2) sulfonamide group was employed and the reaction proceeded as usual to afford the corresponding products.

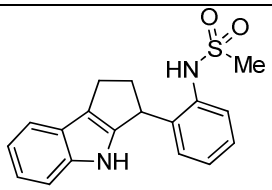
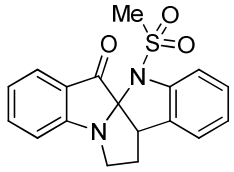
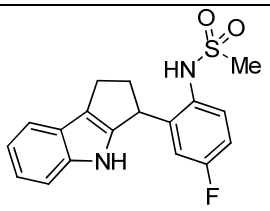
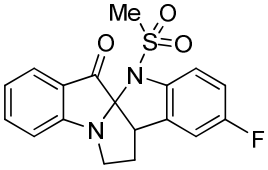
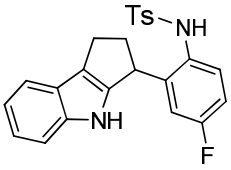
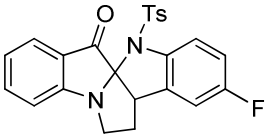
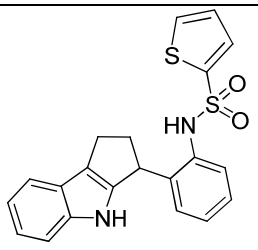
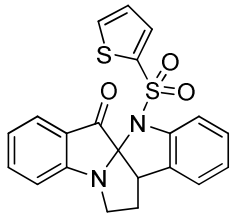
All the synthesized compounds were well characterized by spectral (NMR, IR and MS) data. For example, the IR (1718 cm^{-1}) and ^{13}C NMR [δ_C 197.2 (C_f)] of **4.26d** (Figure 4.4) indicated the presence of –C=O group. Its ^1H NMR signals in the aliphatic region at δ 3.90 (d, $1H_a$), 3.55 (dd, $1H_b{}^1$), 2.88 (td, $1H_b$), 2.08-2.00 (m, $1H_c{}^1$), 1.93 (dd, $1H_c$) clearly identified the respective protons whereas the ^{13}C NMR signals

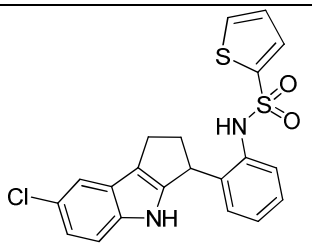
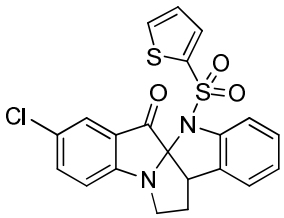
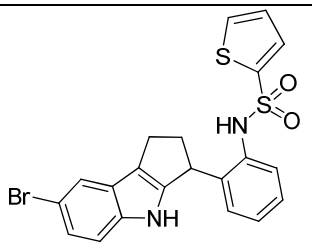
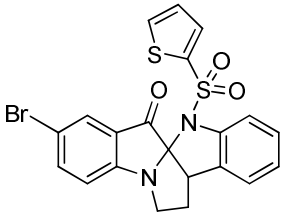
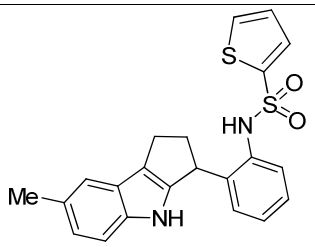
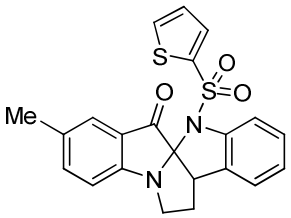
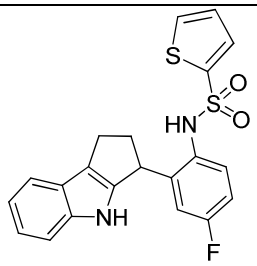
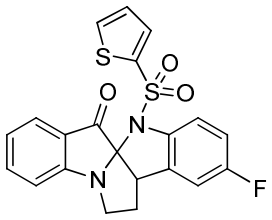
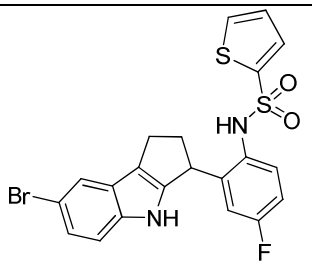
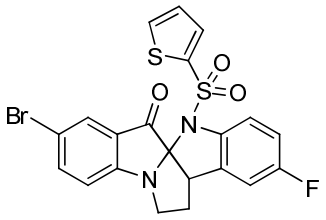
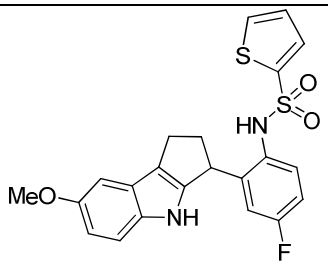
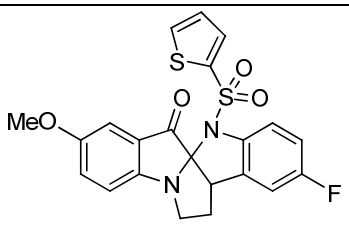
at δ_c 50.2 (C_c), 49.7 (C_a), 32.6 (C_b) and 95.9 (C_g) identified three aliphatic and one sp^3 quaternary carbon respectively (Figure 4.4).

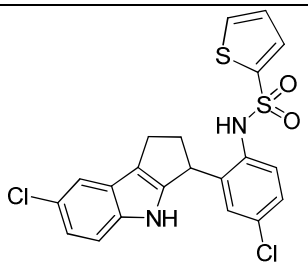
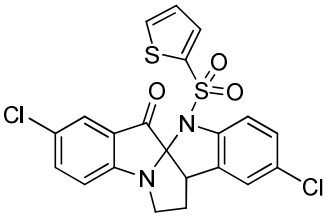
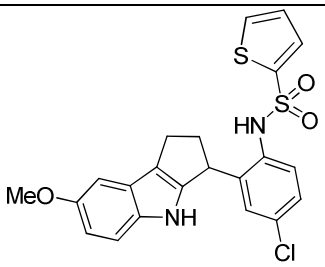
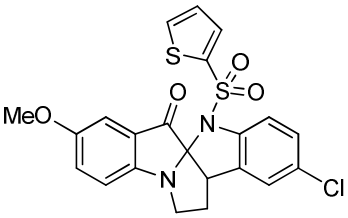
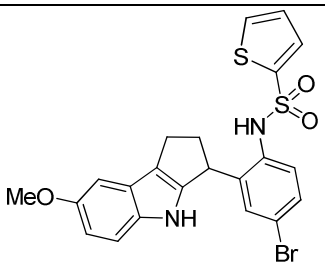
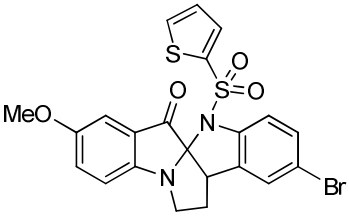
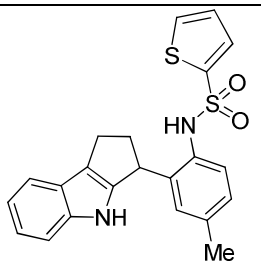
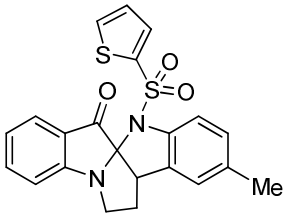
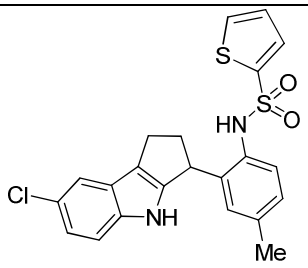
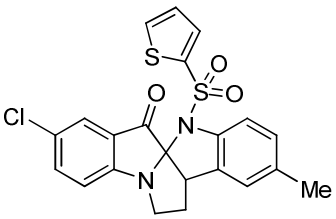
Table 4.2 Synthesis of 2,2'-spirobi[indolin]-3-one derivatives (**4.26**) from cyclopentaindoles (**3.14**).[a]

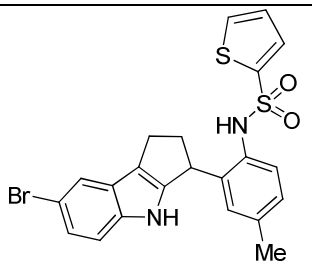
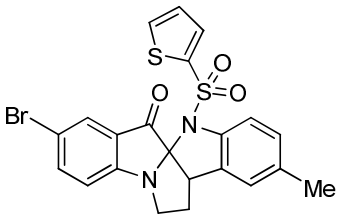
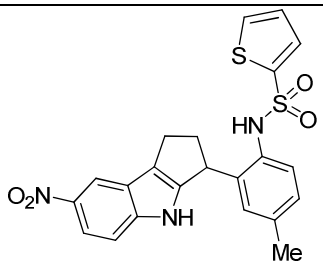
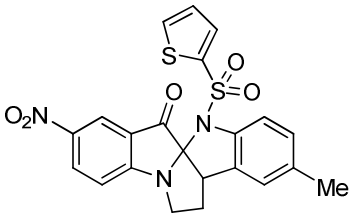


3.14 **4.26**

Entry	Compound (**3.14**)	Product (**4.26**)	Time (h)	Yield[b] (%)
1	 **3.14aa**	 **4.26a**	2	66
2	 **3.14ab**	 **4.26b**	1.5	54
3	 **3.14ac**	 **4.26c**	2	65
4	 **3.15a**	 **4.26d**	1.5	66

5	 **3.14b**	 **4.26e**	1.5	72
6	 **3.14c**	 **4.26f**	2	59
7	 **3.14x**	 **4.26g**	2	63
8	 **3.14e**	 **4.26h**	1.5	64
9	 **3.14y**	 **4.26i**	2	60
10		 **4.26j**	1.5	66

	3.14g			
11	 **3.14j**	 **4.26k**	2	52
12	 **3.14l**	 **4.26l**	1.5	62
13	 **3.14r**	 **4.26m**	1.5	64
14	 **3.14s**	 **4.26n**	2	61
15	 **3.14t**	 **4.26o**	1.5	63

16	 **3.14u**	 **4.26p**	2	57
17	 **3.14w**	 **4.26q**	4	42

[a]All the reactions were performed using **3.14** (0.5 mmol), 10 mol% of CuI in DMF+H2O (7:3) (1.5 mL) at 120 °C for 1.5-4h in air.

[b]Isolated yield.

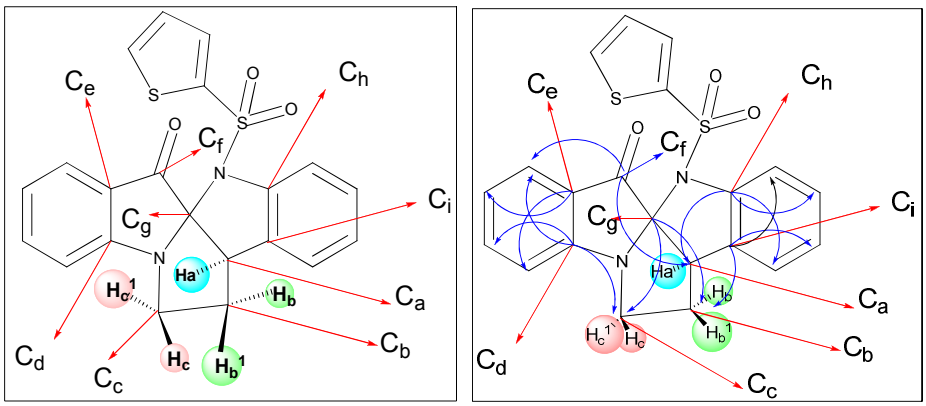


Figure 4.4. Compound **4.26d** and its HMBC correlations.

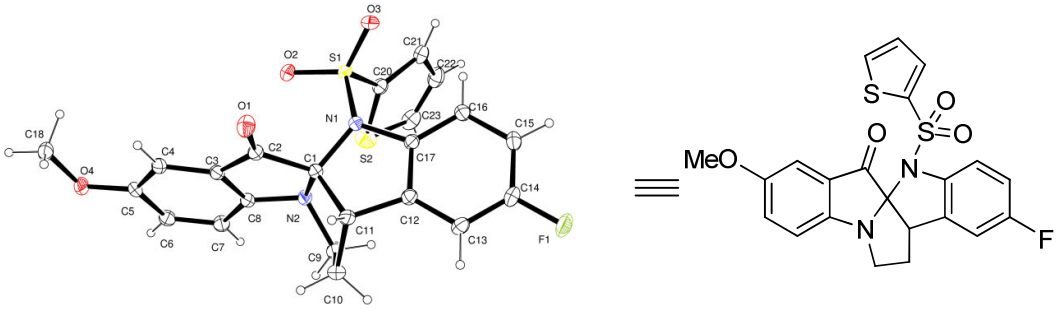
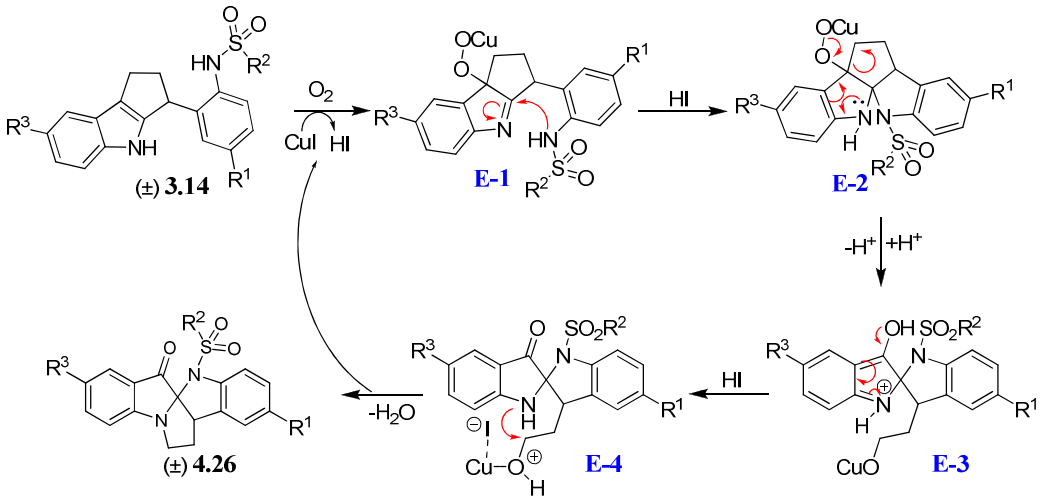


Figure 4.5 ORTEP representation of **4.26j.** Thermal ellipsoids are drawn at 50% probability level.

The ^{1}H-^{1}H COSY spectra of **4.26d** indicated that (i) H_a coupled with H_b and H_b^1, (ii) H_b coupled with H_b^1, H_c, H_c^1 and H_a (iii) H_b^1 coupled with H_b, H_c, H_c^1 and H_a (iv) H_c coupled with H_b^1, H_b and Hc^1 and (v) H_c^1 coupled with H_b^1, H_b and Hc. The ^{1}H-^{13}C HMQC spectra revealed that (i) C_a coupled with H_a (ii) C_b coupled with H_b and H_b^1 and (iii) C_c coupled with H_c and H_c^1. The DEPT spectrum of **4.26d** showed the presence of 7 quaternary, 2 CH_2 and 12 CH carbons. Moreover, the proposed arrangement was confirmed by HMBC correlations (Figure 4.4). Finally, the molecular structure of a representative compound **4.26j** was confirmed unambiguously by single crystal X-ray diffraction study (Figure 4.5).

4.4.4 Proposed mechanism

A proposed reaction mechanism involving the reaction of **3.14** with aerial oxygen in the presence of CuI in the first step leading to the intermediate **E-1** is shown in Scheme 3.[13] An intramolecular ring[12] closure aided by HI involving the –C=N- moiety and the proximate amidic nitrogen of **E-1** affords **E-2**. The subsequent ring opening of the fused cyclopentane ring of **E-2** followed by the cleavage of peroxide bond furnishes the spiro intermediate **E-3**. This step is facilitated by the participation of the fused indoline moiety of **E-2** which after being a charged species in **E-3** undergoes subsequent aromatization to give **E-4**. A further intramolecular ring closure of **E-4** aided by HI furnished the desired product **4.26** with the regeneration of CuI to complete the catalytic cycle. This ring closure thereby product yield can be influenced by the nature of R^3 *i.e.* electron donating or withdrawing group present (see Table 4.2). A similar pathway can be presented with $Cu(II)X_2$ (X = OAc, OTf etc) catalysts by replacing the –OCu moiety with –OCuX. It is evident that the presence of a base added externally is not necessary in this pathway. However, the catalyst is required to facilitate the initial step thereby the entire process. It appears that benzoquinone perhaps can compete with oxygen in the first step affording an adduct similar to **E-1** thereby decreasing the yield of desired product (entry 5, Table 4.1). While the precise reason for faster reaction observed in aqueous DMF in compared to DMF alone (entry 7 *vs* 8 and 12, Table 4.1) was not clearly understood the ability to absorb and retain a higher volume of oxygen by aqueous DMF perhaps was enhanced to a great extent due to the presence of water. However, the presence of a larger volume of water did not improve the reaction time or yield (entry 10 *vs* 11, Table 4.1) due to the lesser solubility of **3.14** in 1:1 aqueous DMF (Scheme 4.10).

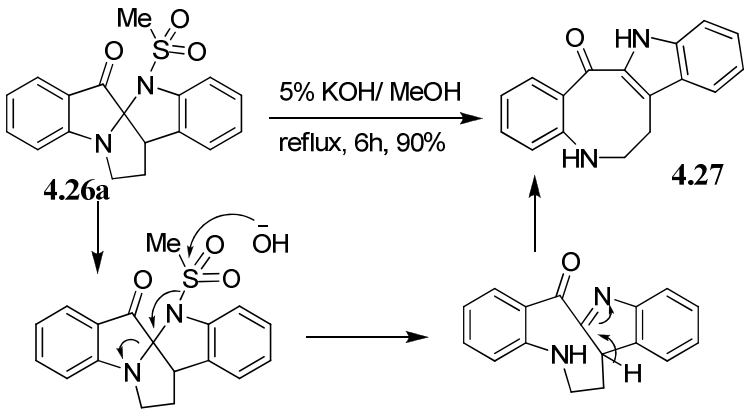


Scheme 4.10 The proposed reaction mechanism.

It is worthy to mention that the each cyclopentaindole derivative (**3.14**) used in the present reaction (Table 4.2) is a ~1:1 mixture of enatiomers that was confirmed by chiral HPLC analysis of a representative compound **3.14b**. Notably, each 2,2'-spirobi[indolin]-3-one derivative (**4.26e**) obtained from **3.14** was also found to be a 1:1 mixture of enatiomer (confirmed by chiral HPLC of **4.26e**) indicating that the present cascade reaction is a facial selective one.

4.5 Application of methodology

To demonstrate the potential of this method the compound **4.26a** was converted to the compound **4.27** possessing a paullone[19] like structural framework in a single step (Scheme 4.11). Thus, compound **4.26a** when treated with methanolic KOH participated in a sequential demesylation followed by ring opening and subsequent aromatization to afford the compound **4.27**. The presence of two -NH groups and a -CH_2CH_2- moiety in compound **4.27** was confirmed by the appearance of two D_2O exchangeable signals at δ 9.42 (bs, 1H) and 3.85 (bs, 1H) along with two triplets at δ 3.36 (t, J = 6.0 Hz, 2H) and 2.86 (t, J = 6.0 Hz, 2H) in the ^{1}H NMR spectra. Moreover, the ^{13}C NMR including DEPT experiments showed the presence of 7 quaternary carbons along with 8 CH and 2 aliphatic -CH_2 groups that corroborated with the structure of **4.27**.



Scheme 4.12 One-step synthesis of paullone like compound **4.27.**

4.6 Conclusions

In conclusion, we have described a Cu-mediated unprecedented cascade reaction of cyclopenta[*b*]indoles in the presence of air to furnish an array of 2,2'-spirobi[indolin]-3-one based novel and complex molecules useful for academic and industrial R&Ds. This operationally simple, straightforward and inexpensive yet innovative method involved the rearrangement of several bonds in which Cu played a key role. One-step and direct synthesis of a paullone like compound highlighted the potential of this method. Being not known in the literature the present research results could be a new and useful addition to the indole chemistry.

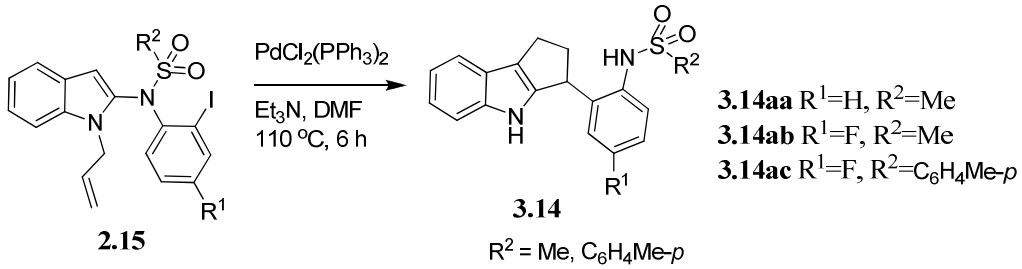
4.7 Experimental

4.7.1 Chemistry

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution by using a 400 MHz spectrometer. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT- IR spectrometer. MS spectra were obtained on aAgilent 6430 series Triple Quard LC-

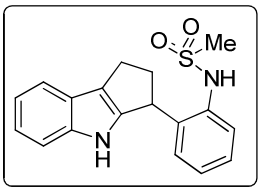
MS/MS spectrometer. High-resolution mass spectra (HRMS) were recorded using a Waters LCT Premier XE instrument. Melting points (mp) were by using BuchiB-540 melting point appratus. Chromatographic purity by HPLC (Agilent 1200 series Chem Station software) was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention times.

4.7.1.1 General procedure for the preparation of *N*-(2-(7-substituted-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-4-substitutedphenyl)alkyl/aryl-sulfonamide (3.14):



A mixture of sulfonamide **2.15**, (0.2 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol%), Et_3N (0.4 mmol) in anhydrous DMF (2 mL) was stirred at 110 °C for 6 h under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature, diluted with ethyl acetate (20 mL) and passed through celite. The filtrate was washed with water (2 x 10 mL), followed by brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate-hexane to give the desired product **3.14**.

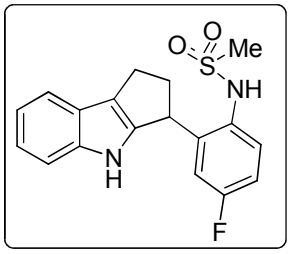
4.7.1.1.1 *N*-(2-(1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-3-yl)phenyl)methane sulfonamide (3.14aa)



3.14aa was prepared from **2.15ab** according to the general procedure presented above.

Off white solid; yield: 45%; mp: 187-189 °C; R_f (15% EtOAc-*n*-Hexane) 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 7.8 Hz, 1H), 7.42 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.32-7.27 (m, 2H), 7.26-7.24 (m, 1H), 7.22-7.16 (m, 2H), 7.11-7.07 (m, 1H), 6.44 (s, 1H), 6.07 (s, 1H), 4.87 (t, *J* = 7.9 Hz, 1H), 4.33-4.28 (m, 1H), 4.13-4.06 (m, 1H), 3.17-3.09 (m, 1H), 3.07 (s, 3H), 2.6-2.5 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.7, 137.8, 133.9, 132.9, 132.8, 129.4, 128.0, 127.4, 125.0, 120.8, 120.7, 119.5, 109.6, 93.5, 43.2, 40.2, 39.0, 37.6; MS (ES mass): *m*/*z* 327.1 (M+1);

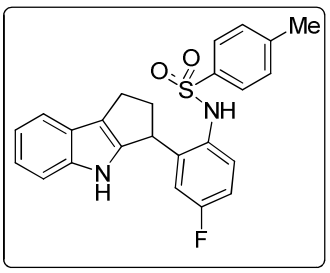
4.7.1.1.2 *N*-(4-fluoro-2-(1,2,3,4-tetrahydrocyclopenta[*b*]indol-3yl)phenyl)methane sulfonamide (3.14ab)



3.14ab was prepared from **2.15bb** according to the general procedure presented above.

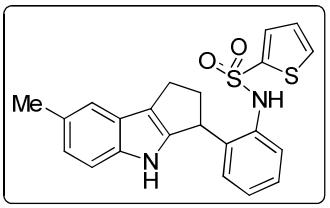
Off white solid; yield: 43%; mp: 160-162 °C; R_f (15% EtOAc-*n*-Hexane) 0.23; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (dd, *J* = 9.2, 4.8 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.48-7.43 (m, 2H), 7.40-7.31 (m, 2H), 6.95 (td, *J* = 8.8, 1.2 Hz, 1H), 6.18 (bs, 1H), 5.98 (bs, 1H), 4.92 (t, *J* = 8.0 Hz, 1H), 4.3 (td, *J* = 10.0, 3.2 Hz, 1H), 4.08 (dd, *J* = 17.2, 7.6 Hz, 1H), 3.15-3.09 (m, 1H), 3.07 (s, 3H), 2.59-2.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3 (d, C-F *J* = 241.5 Hz), 143.6, 141.3, 136.6, 128.4, 122.7, 121.3, 119.9, 119.3, 118.3 (d, C-F *J* = 9.6 Hz), 110.9, 109.6 (d, C-F *J* = 24.4 Hz), 105.4 (d, C-F *J* = 25.1 Hz), 92.7, 43.4, 40.2, 39.0, 37.8; MS (ES mass): *m*/*z* 345.1 (M-+1);

4.7.1.1.3 *N*-(4-fluoro-2-(1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)phenyl)-4-methylbenzene-sulfonamide (3.14ac)



3.14ac was prepared from **2.15jb** according to the general procedure presented above. Off white solid; yield: 30%; mp: 120-122 °C; R_f (15% EtOAc-*n*-Hexane) 0.24; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.28-7.27 (m, 3H), 7.18-7.14 (m, 1H), 7.10-7.08 (m, 1H), 7.07-7.02 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.35 (s, 1H), 5.86 (s, 1H), 4.63 (t, *J* = 8.0 Hz, 1H), 4.23-4.17 (m, 1H), 4.05-3.99 (m, 1H), 3.00-2.92 (m, 1H), 2.43 (s, 3H), 2.38-2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.9 (d, C-F *J* = 246.3), 145.3, 144.2, 142.4 (d, C-F *J* = 7.3), 136.1, 132.9, 132.6, 129.8 (2C), 129.3 (d, C-F *J* = 3.1), 128.9 (d, C-F *J* = 8.8), 127.3 (2C), 120.8, 120.7, 119.5, 115.5 (d, C-F *J* = 23.5), 114.6 (d, C-F *J* = 22.5), 109.6, 93.6, 43.1, 38.6, 37.7, 21.6; MS (ES mass): *m*/*z* 421.2 (M+1).

4.7.1.2 Procedure for the preparation of *N*-(2-(7-methyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-phenyl)thiophene-2-sulfonamide (3.14x)

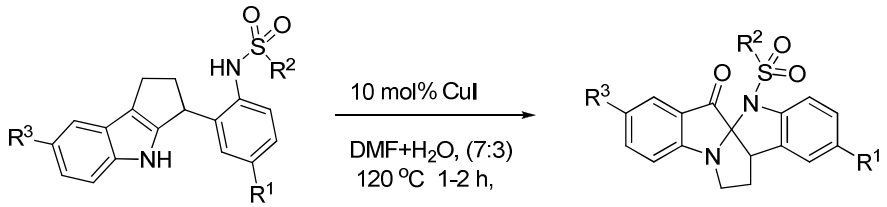


A mixture of *N*-(1-allyl-5-methyl-1*H*-indol-2-yl)-*N*-(2-iodophenyl)thiophene-2-sulfonamide (**2.15ka**), (0.4 mmol), $Pd_2(dba)_3$ (5 mol%), Et_3N (1.2 mmol), and anhydrous DMF (2 mL) was stirred at 130 °C for 7h under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature and filtered to remove the solid separated. The filtrate was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate-hexane to give the desired product **3.14x**.

Off white solid; yield: 68%; mp: 165-167 °C; R_f (15% EtOAc-*n*-Hexane) 0.26; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.32 (s, 1H), 7.24-7.22 (m, 1H), 7.20-7.18 (m, 2H), 7.16-7.11 (m, 2H), 7.06 (t, *J* = 4.2 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 1H), 5.85 (s, 1H), 4.64 (t, *J* = 8.0 Hz, 1H), 4.23-4.17 (m, 1H), 4.06-3.99 (m, 1H), 2.99-2.91 (m, 1H), 2.44 (s, 3H), 2.37-2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.5, 140.1, 138.2, 133.3, 133.2, 132.9, 132.5,

131.1, 129.0, 128.7, 127.7, 127.6, 127.4, 125.8, 122.4, 120.5, 109.2, 93.0, 43.2, 38.9, 37.5, 21.5; MS (ES mass): *m/z* 409.1 (M+1).

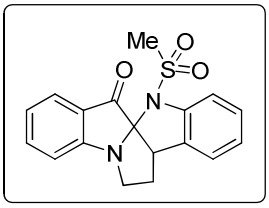
4.7.1.3 General procedure for preparation of Product (4.26)



3.14 **4.26**

To the solution compound **3.14**, in DMF:H_2O (7:3) was added 10 mol% of CuI. The reaction mixture was stirred for 1.5-4 h at 120 °C in the presence of air. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature and filtered to remove the solid separated. The filtrate was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate-hexane to give the desired product **4.26**.

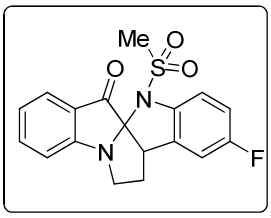
4.7.1.3.1 Compound 4.26a



4.26a was prepared from **3.14aa** according to the general procedure presented above. Light yellow solid; yield: 66%; mp: 201-203 °C; R_f (15% EtOAc-*n*-Hexane) 0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7. 6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.10-7.02 (m, 3H), 3.97 (d, *J* = 8.0 Hz, 1H), 3.70 (dd, *J* = 12. 4, 6.0 Hz, 1H), 3.26-3.20 (m, 1H), 3.18 (s, 3H), 2.15-2.07 (m, 1H), 2.03 (dd, *J* = 12.8, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.2, 161.5, 142.4, 137.8, 129.6, 129.1, 125.3, 124.9, 123.6, 123.3, 122.4, 113.9, 111.9, 95.9, 50.3, 49.9, 39.7, 32.6; HPLC: 96.4%; column: Symmetry C-18 250*4.6 mm, 5µm, mobile phase A: 5mm Ammonium Acetate in water mobile phase

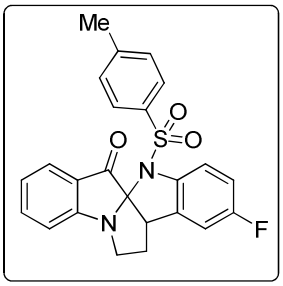
B: CH_3CN (Gradient) T/B% : 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 12.23 min; MS (ES mass): *m/z* 341.0 (M+1).

4.7.1.3.2 Compound 4.26b



4.26b was prepared from **3.14ab** according to the general procedure presented above. Light yellow solid; yield: 54%; mp: 188-190 °C; R_f (20% EtOAc-*n*-Hexane) 0.24; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.38-7.35 (m, 1H), 7.10-6.99 (m, 3H), 6.94 (d, *J* = 7.6 Hz, 1H), 3.95 (d, *J* = 8.0 Hz, 1H), 3.75-3.70 (m, 1H), 3.27-3.20 (m, 1H), 3.16 (s, 3H), 2.19-2.08 (m, 1H), 2.03-2.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:196.9, 161.4, 160.8 (d, C-F *J* = 241.1), 138.4 (d, C-F *J* = 2.1), 137.9, 125.0, 123.2, 122.6, 116.6 (d, C-F *J* = 22.7), 115.7 (d, C-F *J* = 23.3), 113.9, 112.8 (d, C-F *J* = 8.2), 112.7 (d, C-F *J* = 24.3), 96.3, 50.3, 49.7, 39.6, 32.5; HPLC: 96.8%; column: Symmetry C-18 250*4.6 mm, 5µm, mobile phase A: 5mm Ammonium Acetate in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 12.34 min; MS (ES mass): *m/z* 358.6 (M+1).

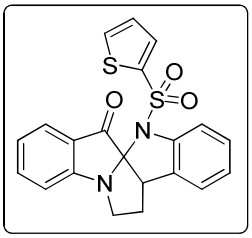
4.7.1.3.3 Compound 4.26c



4.26c was prepared from **3.14ac** according to the general procedure presented above. Off white solid; yield: 65%; mp: 228-230 °C; R_f (20% EtOAc-*n*-Hexane) 0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.30-7.27 (m, 3H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.90 (td, *J* = 8.8, 2.8 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 3.88 (d, *J* = 8.4 Hz, 1H), 3.54 (dd, *J* = 12.4, 6.4 Hz, 1H), 2.80 (td, *J* = 12.8, 5.2 Hz, 1H), 2.41 (s, 3H), 2.09-

2.01 (m, 1H), 1.91 (dd, *J* = 8.0, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:197.2, 161.1, 144.1, 138.2 (d, C-F *J* = 2.5), 137.7, 136.2, 129.3 (2C), 128.2 (2C), 125.1, 123.3, 122.3, 115.3 (d, C-F *J* = 23.3), 113.4, 113.0, 112.9, 112.3, 112.1, 96.1, 49.7, 49.5, 32.7, 21.6; HPLC: 99.3%; column: Symmetry C-18 250*4.6 mm, 5µm, mobile phase A: 5mm Ammonium Acetate in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 13.71 min; IR (KBr, cm^{-1}): 3072, 2938, 1732, 1474, 1361, 1161; MS (ES mass): *m/z* 435.2 (M+1).

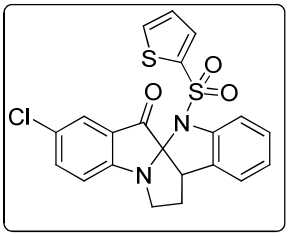
4.7.1.3.4 Compound 4.26d



4.26d was prepared from **3.14a** according to the general procedure presented above. Light yellow solid; yield: 66%; mp: 217-219 °C; R_f (20% EtOAc-*n*-Hexane) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 8.00 Hz, 1H), 7.58 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.25-7.23 (m, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.07-7.02 (m, 3H), 3.95 (d, *J* = 8.4 Hz, 1H), 3.58 (dd, *J* = 12.4, 6.8 Hz, 1H), 2.90 (td, *J* = 12.4, 6.8 Hz, 1H), 2.12-2.04 (m, 1H), 1.96 (dd, *J* = 12.4, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.2, 161.4, 141.6, 139.1, 137.6, 134.6, 133.4, 129.7, 128.7, 126.7, 125.1, 124.9, 123.7, 123.6, 122.3, 113.6, 112.7, 95.9, 50.2, 49.7, 32.6; HPLC: 97.8%; column: Symmetry C-18 250*4.6 mm, 5µm, mobile phase A: 0.1 % 5mm Ammonium Acetate in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 13.14 min; IR (KBr, cm^{-1}): 3399, 2926, 1718, 1604, 1469, 1356, 1163; MS (ES mass): *m/z* 409.1 (M+1); HRMS: *m/z* calcd for $C_{21}H_{17}O_3N_2S_2$ $[M + H]^+$ 409.06751, found 409.06598.

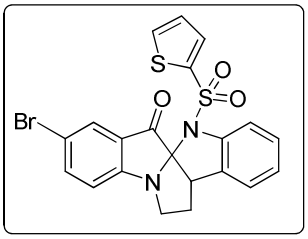
4.7.1.3.5 Compound 4.26e

4.26e was prepared from **3.14b** according to the general procedure presented above.



Light yellow solid; yield: 72%; mp: 231-233 °C; R_f (20% EtOAc-*n*-Hexane) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 2.8 Hz, 1H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.59-7.55 (m, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.25-7.22 (m, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.06-6.99 (m, 3H), 3.94 (d, *J* = 8.0 Hz, 1H), 3.53 (dd, *J* = 12.4, 6.8 Hz, 1H), 2.90 (td, *J* = 12.4, 5.2 Hz, 1H), 2.12-2.02 (m, 1H), 1.97 (dd, *J* = 12.8, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.1, 159.6, 141.4, 138.9, 137.4, 134.6, 133.5, 129.4, 128.8, 127.9, 126.8, 124.9, 124.7, 124.5, 123.8, 114.9, 112.6, 96.1, 50.3, 49.7, 32.7; HPLC: 99.1%; column: Symmetry C-18 250*4.6 mm, 5µm, mobile phase A: 5mm Ammonium Acetate in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 13.8 min; IR (KBr, cm^{-1}): 2927, 1729, 1607, 1466, 1358, 1167; MS (ES mass): *m/z* 442.3 (M+1).

4.7.1.3.6 Compound 4.26f

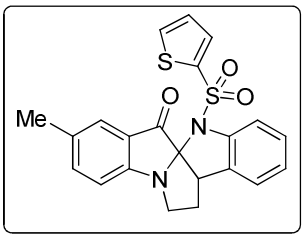


4.26f was prepared from **3.14c** according to the general procedure presented above.

Light yellow solid; yield: 59%; mp: 219-221 °C; R_f (15% EtOAc-*n*-Hexane) 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 2.0 Hz, 1H), 7.81 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.70 (dd, *J* = 8.4, 2.00 Hz, 1H), 7.59 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.25-7.23 (m, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 4.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.94 (d, *J* = 8.0 Hz, 1H), 3.53 (dd, *J* = 12.4, 6.4 Hz, 1H), 2.94-2.88 (m, 1H), 2.11-2.01 (m, 1H), 1.98 (dd, *J* = 12.8, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.8, 159.9, 141.5, 140.1, 139.1, 134.5, 133.4, 129.4, 128.8, 127.6, 126.8, 125.2, 124.9, 123.8, 115.2, 114.9, 112.6, 95.9, 50.2, 49.7, 32.7; HPLC: 99.0%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A:

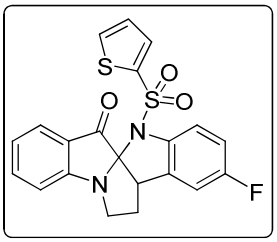
0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.16 min; IR (KBr, cm^{-1}): 2967, 1725, 1467, 1353, 1157; MS (ES mass): *m/z* 488.3 (M+1).

4.7.1.3.7 Compound 4.26g



4.26g was prepared from **3.14x** according to the general procedure presented above. Light yellow solid; yield: 63%; mp: 145-147 °C; R_f (15% EtOAc-*n*-Hexane) 0.24; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, *J* = 3.2 Hz, 1H), 7.57 (d, *J* = 4.8 Hz, 1H), 7.54 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.24-7.22 (m, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.06-7.01 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 3.92 (d, *J* = 8.0 Hz, 1H), 3.52 (dd, *J* = 12.0, 6.4 Hz, 1H), 2.86 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.37 (s, 3H), 2.09-2.01 (m, 1H), 1.94 (dd, *J* = 13.2, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.4, 159.6, 141.7, 139.2, 138.9, 134.6, 133.4, 132.1, 129.8, 128.7, 126.7, 124.9, 124.7, 123.7, 123.6, 113.5, 112.7, 96.2, 50.3, 49.7, 31.9, 29.7; HPLC: 90.4%; column: Symmetry C-18 250*4.6 mm, 5µm, mobile phase A: 0.1 % 5mm Ammonium Acetate in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 13.49 min; MS (ES mass): *m/z* 423.1 (M+1).

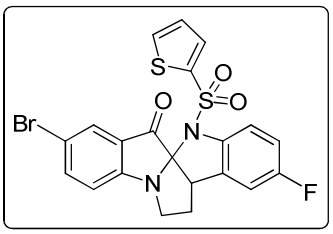
4.7.1.3.8 Compound 4.26h



4.26h was prepared from **3.14e** according to the general procedure presented above. Light yellow solid; yield: 64%; mp: 208-210 °C; R_f (20% EtOAc-*n*-Hexane) 0.29; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.81 (s, 1H), 7.76 (d, *J* = 6.8 Hz, 1H), 7.67-7.61 (m, 2H), 7.41 (d, *J* = 7.6, 4.0 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.08-7.06 (m, 2H), 6.99-6.94 (m, 1H), 6.89 (d, *J* = 6.4 Hz, 1H), 3.93 (d, *J* = 8.0 Hz, 1H), 3.62-3.57 (m, 1H), 2.92-2.85 (m, 1H), 2.10-2.06 (m, 1H), 1.97-1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ:196.9, 161.3, 160.8 (d, C-F *J* = 241.2), 138.8, 137.8, 137.6 (d, C-F *J* = 2.1), 134.6, 133.5, 131.6 (d, C-F *J* = 8.1), 126.8, 125.2, 123.4, 122.5, 115.5 (d, C-F *J* = 23.3), 113.5, 113.5 (d, C-F *J* = 8.2), 112.7 (d, C-F *J* = 24.2), 96.2, 50.2, 49.5, 32.5; HPLC: 97.9%; column: Symmetry C-18 250*4.6 mm, 5µm, mobile phase A: 0.1 % 5mm Ammonium Acetate in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 13.24 min; MS (ES mass): *m/z* 427.1 (M+1).

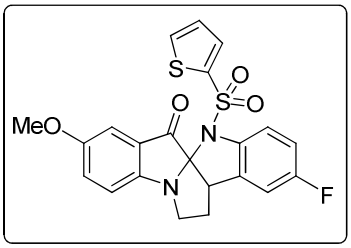
4.7.1.3.9 Compound 4.26i



4.26i was prepared from **3.14y** according to the general procedure presented above. Light yellow solid; yield: 60%; mp: 220-222 °C; R_f (15% EtOAc-*n*-Hexane) 0.19; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 1.9 Hz, 1H), 7.78 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.70 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.61 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.39 (dd, *J* = 8.8, 4.0 Hz, 1H), 7.04 (t, *J* = 4.4 Hz, 1H), 6.97-6.92 (m, 2H), 6.87 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.92 (d, *J* = 8.4 Hz, 1H), 3.54 (dd, *J* = 12.4, 6.8 Hz, 1H), 2.92-2.84 (m, 1H), 2.12-2.02 (m, 1H), 1.95 (dd, *J* = 12.8, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.5, 159.8, 140.2, 138.6, 137.4, 134.6, 133.6, 131.2 (d, C-F *J* = 7.9), 127.7, 126.8, 125.0, 115.6, 115.4, 115.2, 115.1, 113.4 (d, C-F *J* = 8.4), 112.4 (d, C-F *J* = 24.3), 96.2, 50.2, 49.5, 32.5; HPLC: 95.9%; column: Symmetry C-18 75*4.6 mm, 3µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/50, 1/50, 3/98, 10/98, 10.5/50, 12/50; flow rate: 1.0 mL/min; UV 235 nm, retention time 3.96 min; IR (KBr, cm^{-1}): 2918, 1732, 1434, 1335, 1163; MS (ES mass): *m/z* 504.9 (M+1); HRMS: *m/z* calcd for $C_{21}H_{14}O_3N_2BrFS_2$ $[M + H]^+$ 504.96860, found 504.96989.

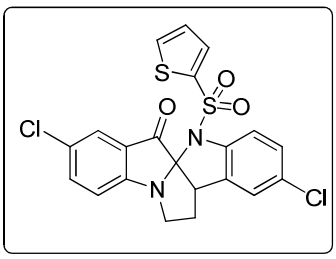
4.7.1.3.10 Compound 4.26j

4.26j was prepared from **3.14g** according to the general procedure presented above.



Light yellow solid; yield: 66%; mp: 200-202 °C; R_f (20% EtOAc-*n*-Hexane) 0.27; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.60 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.40 (dd, *J* = 8.8, 4.4 Hz, 1H), 7.28-7.26 (m, 1H), 7.18 (d, *J* = 2.8 Hz, 1H), 7.03 (t, *J* = 4.0 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.94 (td, *J* = 8.8, 2.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.90 (d, *J* = 8.0 Hz, 1H), 3.82 (s, 3H), 3.50 (dd, *J* = 12.4, 6.4 Hz, 1H), 2.85 (td, *J* = 12.8, 5.0 Hz, 1H), 2.10-2.01 (m, 1H), 1.92 (dd, *J* = 12.8, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:197.1, 160.8 (d, C-F *J* = 241.3), 156.3, 155.7, 138.8, 137.7, 134.7, 133.6, 131.6 (d, C-F *J* = 8.0), 127.7, 126.7, 123.8, 115.5 (d, C-F *J* = 23.4), 115.0, 113.5 (d, C-F *J* = 8.3), 112.4 (d, C-F *J* = 24.2), 105.4, 96.9, 55.8, 50.5, 49.7, 32.2; HPLC: 94.2%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 4.93 min; IR (KBr, cm^{-1}): 3064, 2935, 1735, 1465, 1365, 1159; MS (ES mass): *m/z* 457.0 (M+1); HRMS: *m/z* calcd for $C_{22}H_{17}O_4\ N_2FS_2$ $[M + H]^+$ 457.06865, found 457.06889.

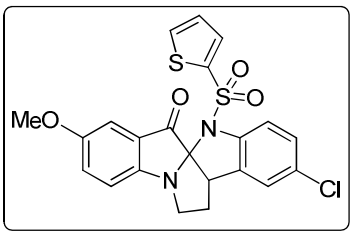
4.7.1.3.11 Compound 4.26k



4.26k was prepared from **3.14j** according to the general procedure presented above. Light yellow solid; yield: 52%; mp: 284-286 °C; R_f (20% EtOAc-*n*-Hexane) 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80-7.79 (m, 1H), 7.70 (d, *J* = 2.00 Hz, 1H), 7.62 (d, *J* = 5.2 Hz, 1H), 7.58 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.14 (s, 1H), 7.05 (t, *J* = 4.0 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 3.92 (d, *J* = 12.8, 6.8 Hz, 1H), 2.93-2.85 (m, 1H), 2.89 (s, 1H), 2.12-2.03 (m, 1H), 1.98 (dd, *J* = 12.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.6, 159.5, 140.2,

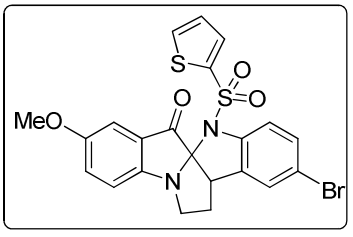
137.6, 134.8, 133.8, 131.4, 129.1, 128.9, 128.1, 126.9, 125.2, 124.6, 124.5, 122.9, 114.9, 113.6, 96.4, 50.3, 49.4, 32.6; HPLC: 96.5%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.20 min; IR (KBr, cm^{-1}): 2967, 1746, 1452, 1342, 1144; MS (ES mass): *m/z* 476.9 (M+1); HRMS: *m/z* calcd for $C_{21}H_{14}O_3N_2Cl_2S_2$ $[M + H]^+$ 476.98957, found 476.99155.

4.7.1.3.12 Compound 4.26l



4.26l was prepared from **3.14l** according to the general procedure presented above. Light yellow solid; yield: 62%; mp: 226-228 °C; R_f (20% EtOAc-*n*-Hexane) 0.22; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.81 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.61 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.29-7.27 (m, 1H), 7.22-7.20 (m, 1H), 7.18 (d, *J* = 2.8 Hz, 1H), 7.13 (s, 1H), 7.05-7.03 (m, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 3.91 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H), 3.51 (dd, *J* = 12.4, 7.2 Hz, 1H), 2.89-2.81 (m, 1H), 2.10-2.02 (m, 1H), 1.93 (dd, *J* = 12.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.9, 156.3, 155.7, 140.4, 138.8, 134.8, 133.7, 131.7, 128.9, 128.8, 127.7, 126.7, 125.1, 123.8, 114.9, 113.6, 105.5, 96.9, 55.8, 50.5, 49.6, 32.2; HPLC: 99.3%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 2/20, 10/95, 20/95, 22/20, 25/20; flow rate: 1.0 mL/min; UV 235 nm, retention time 9.37 min; MS (ES mass): *m/z* 473.0 (M+1).

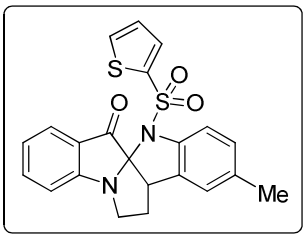
4.7.1.3.13 Compound 4.26m



4.26m was prepared from **3.14r** according to the general procedure presented above.

Light yellow solid; yield: 64%; mp: 235-237 °C; R_f (20% EtOAc-*n*-Hexane) 0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.61 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.37-7.32 (m, 2H), 7.28-7.27 (m, 2H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.04 (t, *J* = 4.8 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 3.91 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H), 3.51 (dd, *J* = 12.4, 6.8 Hz, 1H), 2.89-2.81 (m, 1H), 2.12-2.02 (m, 1H), 1.94 (dd, *J* = 12.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.9, 156.3, 155.7, 140.9, 138.6, 134.8, 133.7, 132.0, 131.6, 127.9, 127.7, 126.7, 123.8, 116.2, 114.9, 114.1, 105.4, 96.8, 55.8, 50.5, 49.5, 32.2; HPLC: 97.6%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 2/20, 10/95, 20/95, 22/20, 25/20; flow rate: 1.0 mL/min; UV 235 nm, retention time 9.52 min; IR (KBr, cm^{-1}): 3087, 2943, 1732, 1454, 1342, 1161; MS (ES mass): *m/z* 518.8 (M+1).

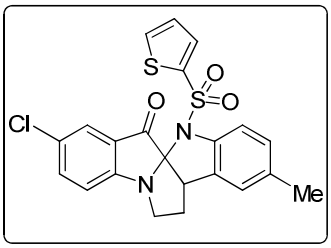
4.7.1.3.14 Compound 4.26n



4.26n was prepared from **3.14s** according to the general procedure presented above.

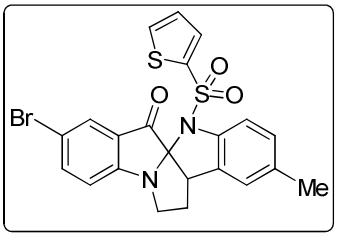
Light yellow solid; yield: 61%; mp: 262-264 °C; R_f (20% EtOAc-*n*-Hexane) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 8.4 Hz, 1H), 7.56 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.07-7.00 (m, 3H), 6.96 (s, 1H), 3.90 (d, *J* = 8.4 Hz, 1H), 3.55 (dd, *J* = 12.4, 6.4 Hz, 1H), 2.88 (td, *J* = 12.4, 5.2 Hz, 1H), 2.29 (s, 3H), 2.08-2.00 (m, 1H), 1.93 (dd, *J* = 12.8, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.2, 161.4, 139.4, 137.5, 134.3, 133.4, 133.0, 129.7, 129.2, 126.6, 125.4, 125.0, 123.6, 122.2, 113.4, 112.4, 109.9, 95.9, 50.2, 49.7, 32.6, 20.8; HPLC: 99.7%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.05 min; IR (KBr, cm^{-1}): 3094, 2922, 1722, 1611, 1477, 1362, 1161; MS (ES mass): *m/z* 422.4 (M+1).

4.7.1.3.15 Compound 2o



4.26o was prepared from **3.14t** according to the general procedure presented above. Light yellow solid; yield: 63%; mp: 282-284 °C; R_f (15% EtOAc-*n*-Hexane) 0.24; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.58-7.55 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.06-7.02 (m, 2H), 7.01-6.98 (m, 1H), 6.96 (s, 1H), 3.91 (d, *J* = 8.0 Hz, 1H), 3.52 (dd, *J* = 12.4, 6.4 Hz, 1H), 2.93-2.85 (m, 1H), 2.30 (s, 3H), 2.09-2.00 (m, 1H), 1.96 (dd, *J* = 12.4, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:196.2, 159.6, 139.2, 139.1, 137.4, 134.5, 133.6, 133.4, 129.5, 129.4, 127.9, 126.7, 125.5, 124.7, 124.5, 114.9, 112.4, 96.2, 50.3, 49.7, 32.6, 20.8; HPLC: 98.5%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 0.5/20, 4/98, 10/98, 10.5/20, 12/20; flow rate: 1.0 mL/min; UV 230 nm, retention time 5.28 min; IR (KBr, cm^{-1}): 2942, 1736, 1475, 1354, 1156; MS (ES mass): *m/z* 457.0 (M+1); HRMS: *m/z* calcd for $C_{22}H_{17}O_3N_2ClS_2$ $[M + H]^+$ 457.04419, found 457.04469.

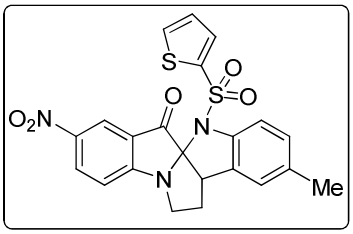
4.7.1.3.16 Compound 2p



4.26p was prepared from **3.14u** according to the general procedure presented above. Light yellow solid; yield: 57%; mp: 256-258 °C; R_f (20% EtOAc-*n*-Hexane) 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 1.6 Hz, 1H), 7.79 (d, *J* = 3.6 Hz, 1H), 7.69 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.57 (d, *J* = 5.2 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.06-7.01 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 3.90 (d, *J* = 8.0 Hz, 1H), 3.52 (dd, *J* = 12.4, 6.7 Hz, 1H), 2.92-2.84 (m, 1H), 2.29 (s, 3H), 2.07-2.01 (m, 1H), 1.96 (dd, *J* = 12.4, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.9, 159.9, 140.1, 139.1, 139.0, 134.4, 133.6, 133.3, 129.4, 129.3, 127.6, 126.7, 125.5, 125.2, 115.2, 114.9, 112.4, 96.0, 50.2, 49.7, 32.6, 29.7; HPLC: 93.5%; column: Symmetry C-18 75*4.6 mm, 3.5µm, mobile

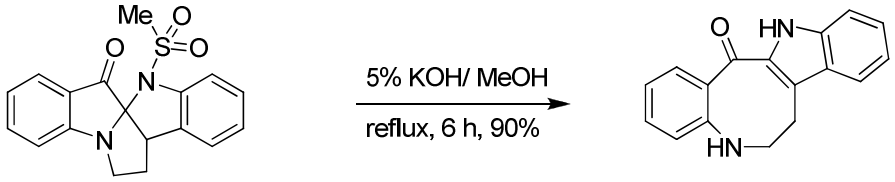
phase A: 0.1 % Formic Acid in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 1/20, 6/98, 10/98, 12/20, 15/20; flow rate: 1.0 mL/min; UV 235 nm, retention time 6.88 min; IR (KBr, cm^{-1}): 3095, 2953, 1736, 1452, 1371, 1148; MS (ES mass): *m/z* 502.8 (M+1).

4.7.1.3.17 Compound 2q



4.26q was prepared from **3.14w** according to the general procedure presented above. Light yellow solid; yield: 42%; mp: 294-296 °C; R_f (25% EtOAc-*n*-Hexane) 0.15; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (d, *J* = 2.0 Hz, 1H), 8.51 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.77 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.60 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.10-7.04 (m, 3H), 6.98 (s, 1H), 3.96 (d, *J* = 8.0 Hz, 1H), 3.65 (dd, *J* = 12.4, 6.0 Hz, 1H), 3.03-2.95 (m, 1H), 2.31 (s, 3H), 2.12-2.07 (m, 1H), 2.03 (dd, *J* = 12.4, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.3, 164.1, 142.7, 138.9, 134.4, 133.9, 133.4, 132.5, 129.6, 129.1, 127.9, 126.9, 125.6, 123.4, 121.6, 113.1, 112.4, 96.1, 49.7, 49.3, 33.5, 20.8; MS (ES mass): *m/z* 468.0 (M+1).

4.7.1.4 Procedure for the preparation of compound 4.27:



4.26a **4.27**

Compound **4.26a** (0.0mol) was dissolved in 10 mL of 5% methanolic potassium hydroxide [20] and refluxed for 6 h. The solvent removed by vaccume then dilution with water and extraction with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate-hexane to give the desired product **4.27**.

Off white solid; yield: 90%; mp: 226-228 °C; R_f (15% EtOAc-*n*-Hexane) 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.42 (bs, 1H), 7.80 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.56-7.52 (m, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.42-7.38 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28-7.24 (m, 1H), 7.19-7.15 (m, 1H), 3.85 (bs, 1H), 3.36 (t, *J* = 6.0 Hz, 2H), 2.86 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 184.5, 147.4, 136.8, 135.3, 135.2, 132.9, 130.2, 127.4, 126.9, 126.3, 124.5, 120.9, 120.5, 119.2, 111.9, 53.3, 23.5; HPLC: 99.5%; column: Symmetry C-18 250*4.6 mm, 5µm, mobile phase A: 5mm Ammonium Acetate in water mobile phase B: CH_3CN (Gradient) T/B% : 0/20, 3/20, 12/95, 23/95, 25/20, 30/20; flow rate: 1.0 mL/min; UV 210 nm, retention time 12.36 min; MS (ES mass): *m/z* 263.1 (M+1).

4.7.2 Single crystal X-ray data:

Single crystals suitable for X-ray diffraction of **4.26j** were grown from methanol. The crystals were carefully chosen using a stereo zoom microscope supported by a rotatable polarizing stage. The data were collected at room temperature on Bruker's KAPPA APEX II CCD Duo with graphite monochromated Mo-Kα radiation (0.71073 Å). The crystals were glued to a thin glass fibre using FOMBLIN immersion oil and mounted on the diffractometer. The intensity data were processed using Bruker's suite of data processing programs (SAINT), and absorption corrections were applied using SADABS.[21] The crystal structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms, using SHELXL-97.[22]

Crystal data of 4.26j: Molecular formula = $C_{22}H_{17}FN_2O_4S_2$, formula weight = 456.50, crystal system = Monoclinic, space group = *P2(1)/c*, *a* = 9.0012 (2) Å, *b* = 11.6897 (3) Å, *c* = 19.0204 (5) Å, *V* = 1999.06 (9) Å^3, *T* = 296 K, *Z* = 4, D_x = 1.517 Mg m^{-3}, µ(Mo-Kα) = 0.31 mm^{-1}, 14591 reflections measured, 3409 independent reflections, 2957 observed reflections [I > 2.0 σ (I)], R_{int} = 0.027, Goodness of fit = 1.05. Crystallographic data (excluding structure factors) for **2j** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 993261.

4.8 References:

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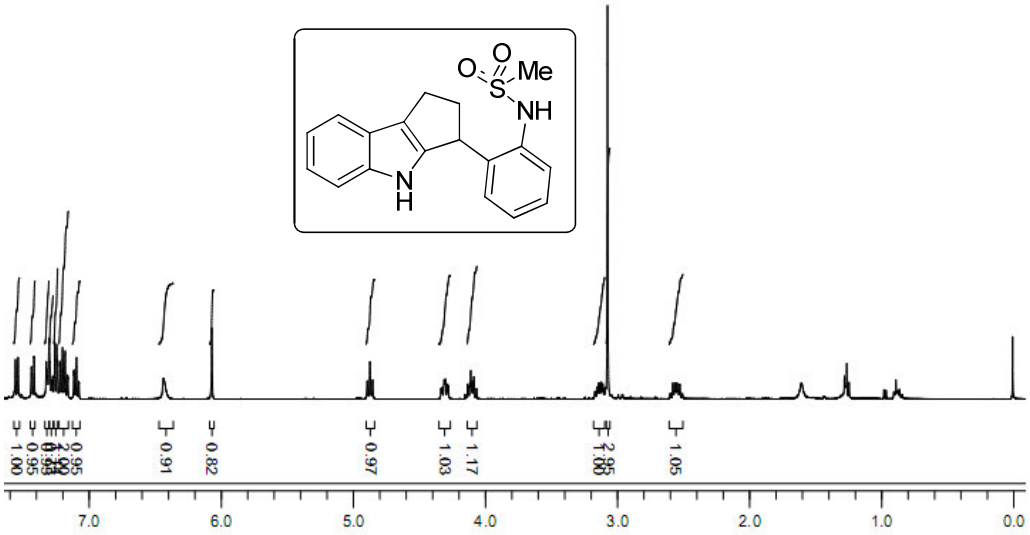
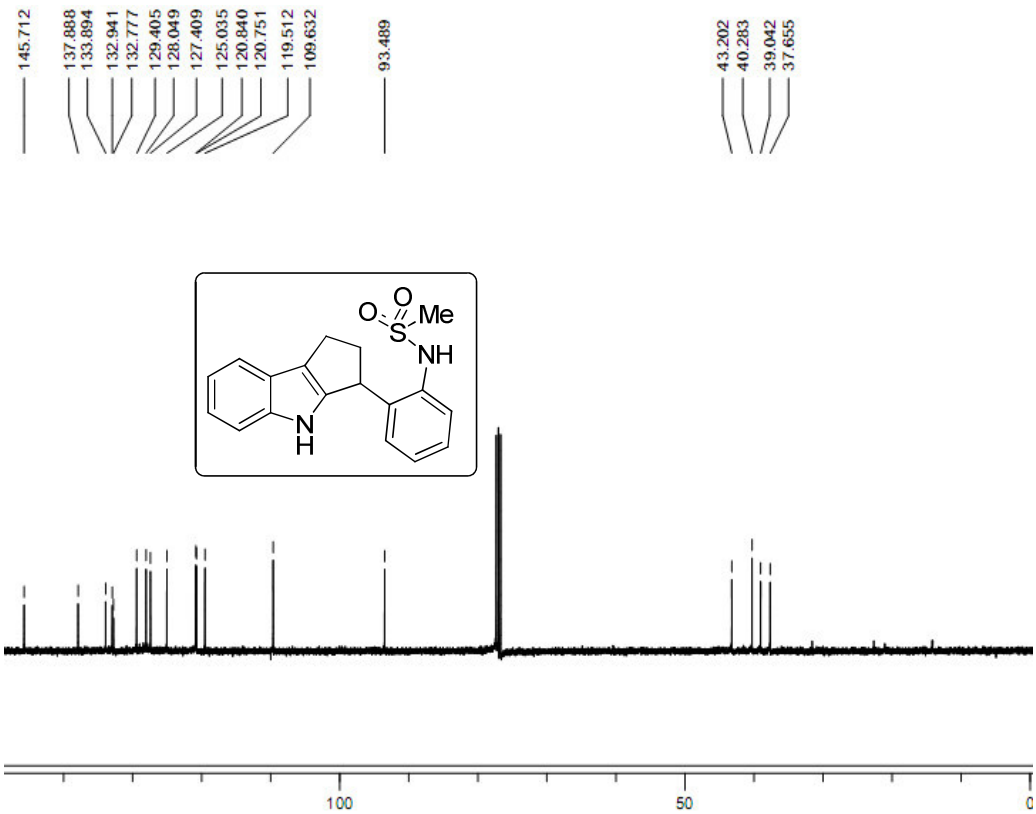
Appendix

^{1}H NMR (Varian, 400 MHz) spectrum of compound **3.14aa** in $CDCl_3$



^{13}C NMR spectrum (Varian, 100 MHz) of compound **3.14aa** in $CDCl_3$



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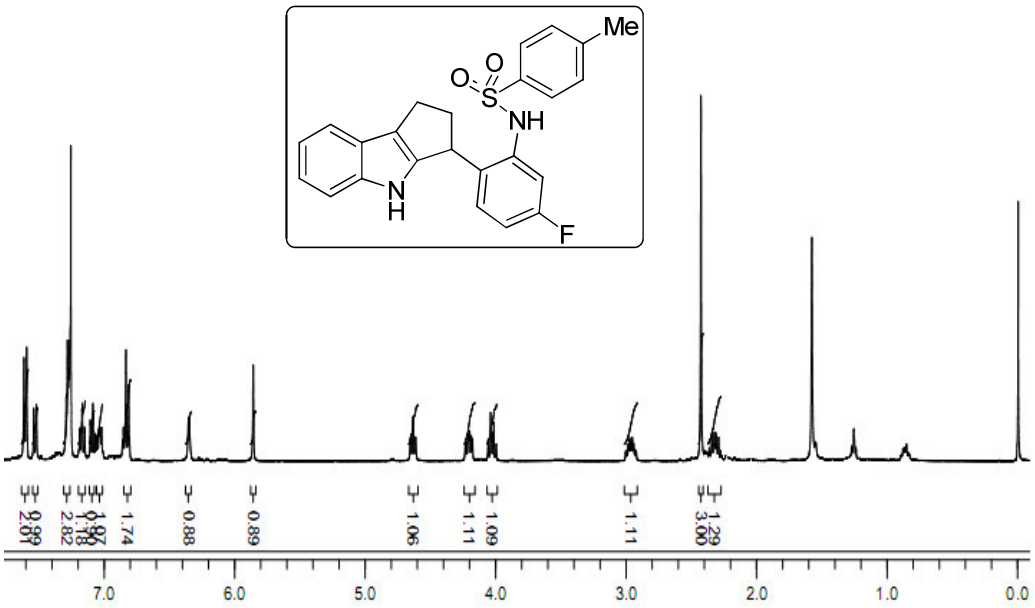

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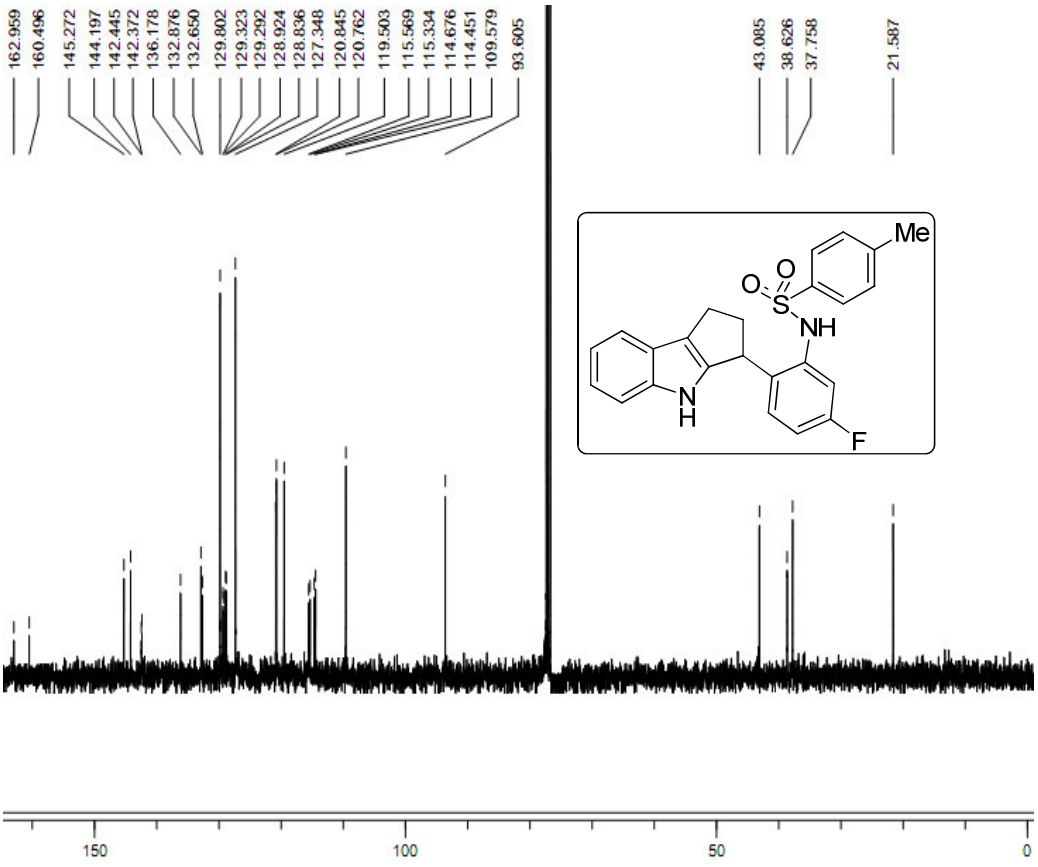
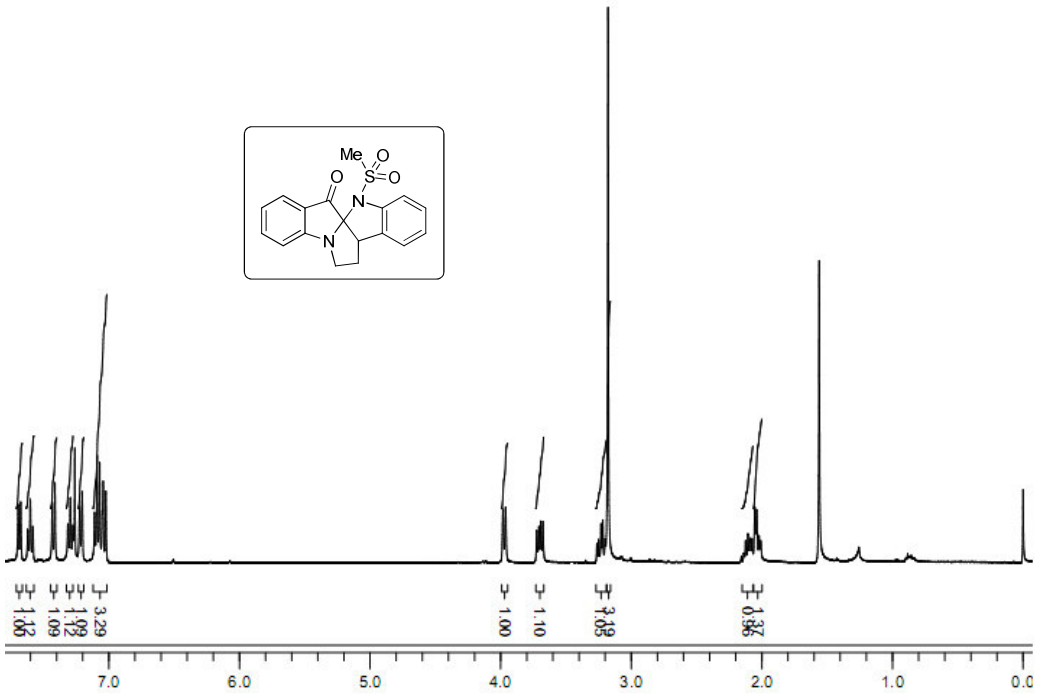


^{1}H NMR (Varian, 400 MHz) spectrum of compound **4.26a** in $CDCl_3$



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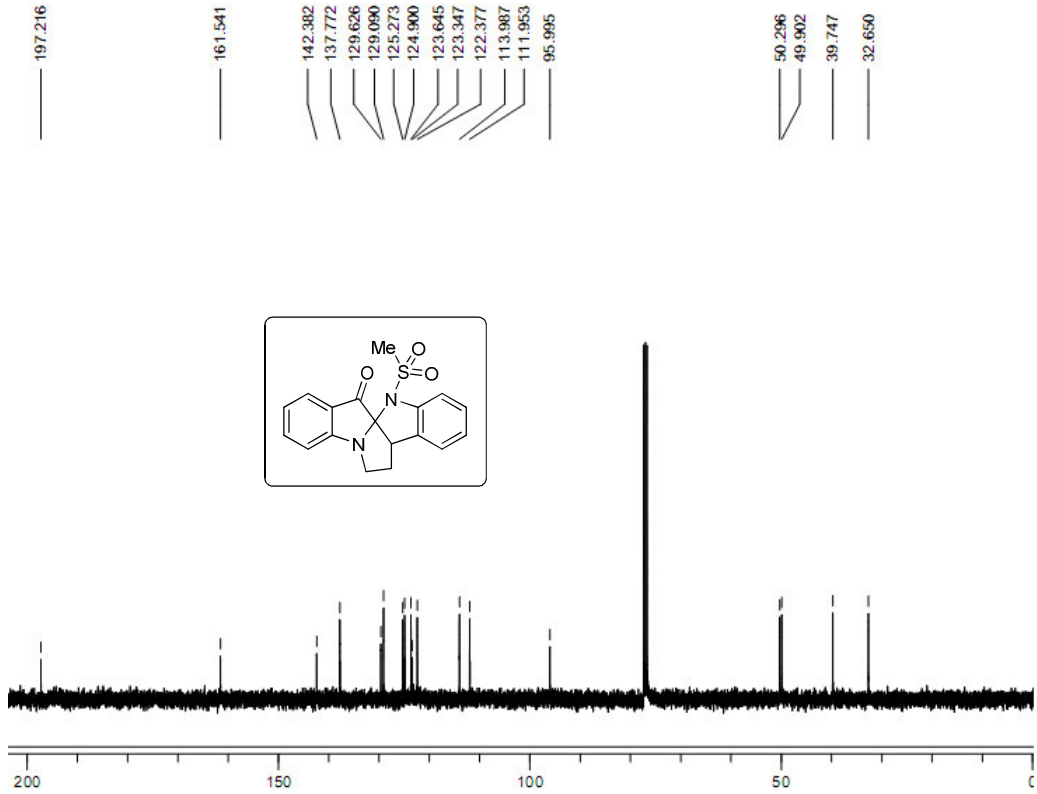

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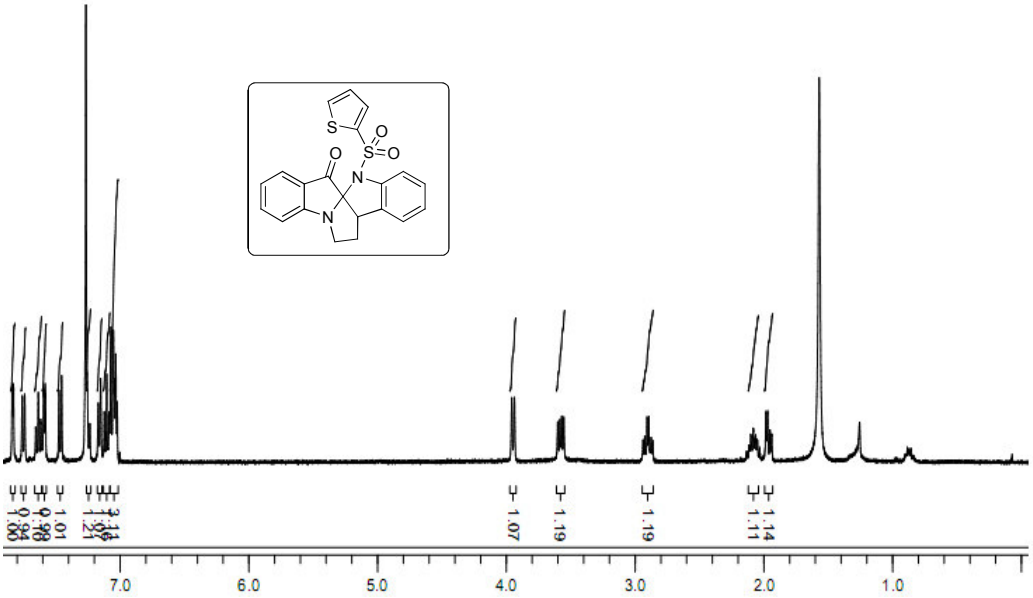

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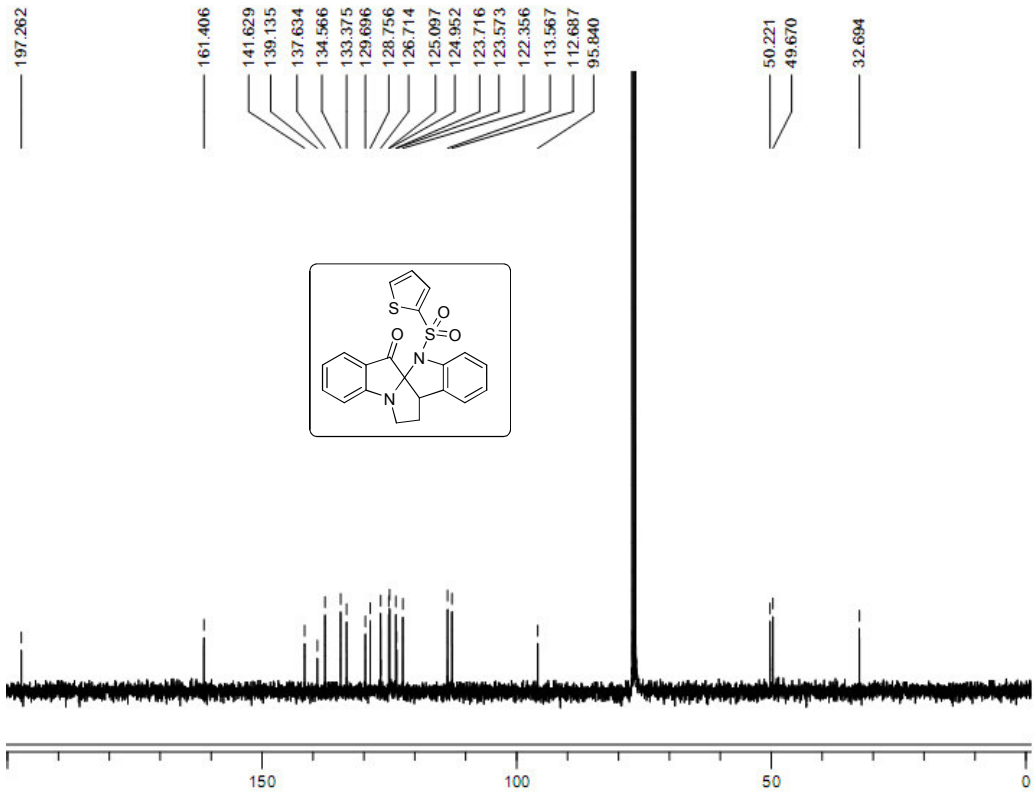
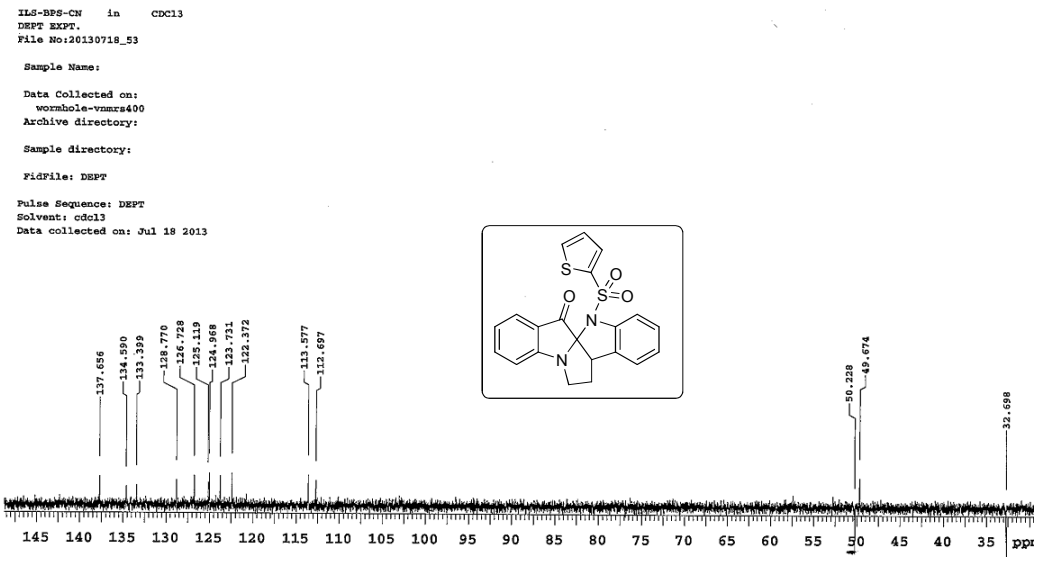
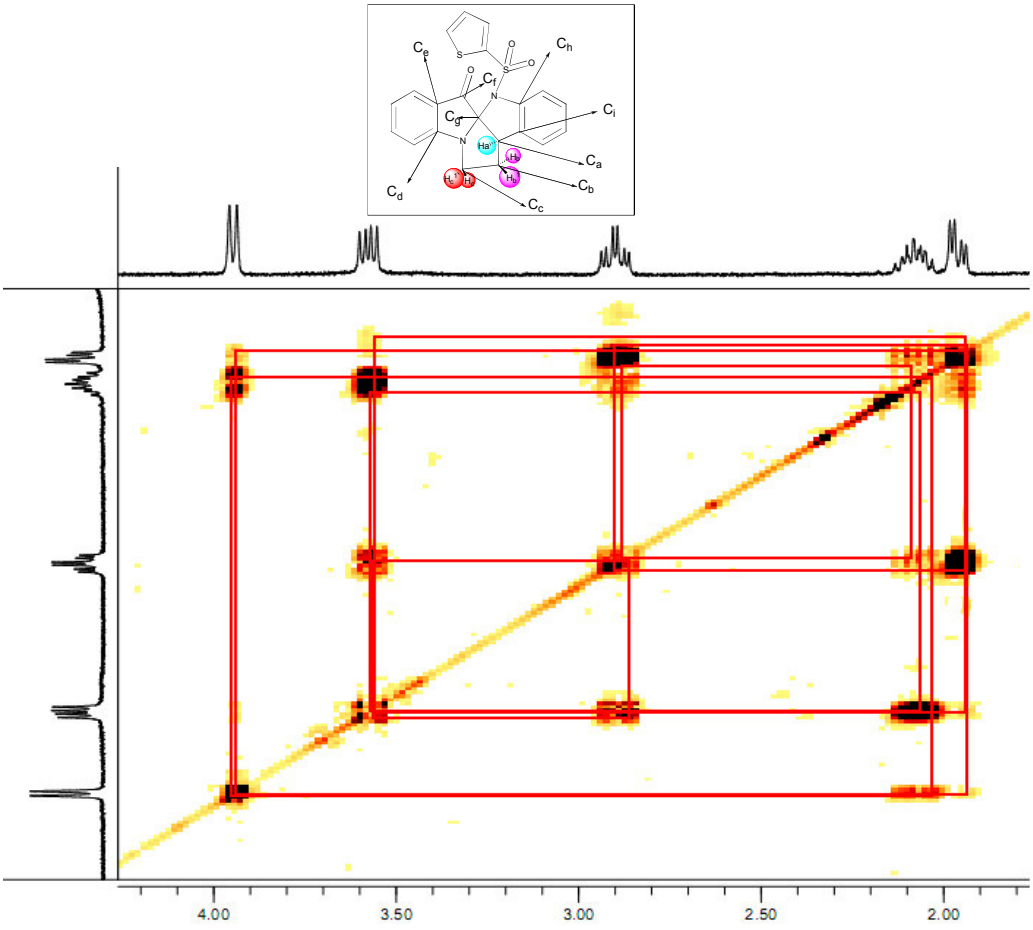


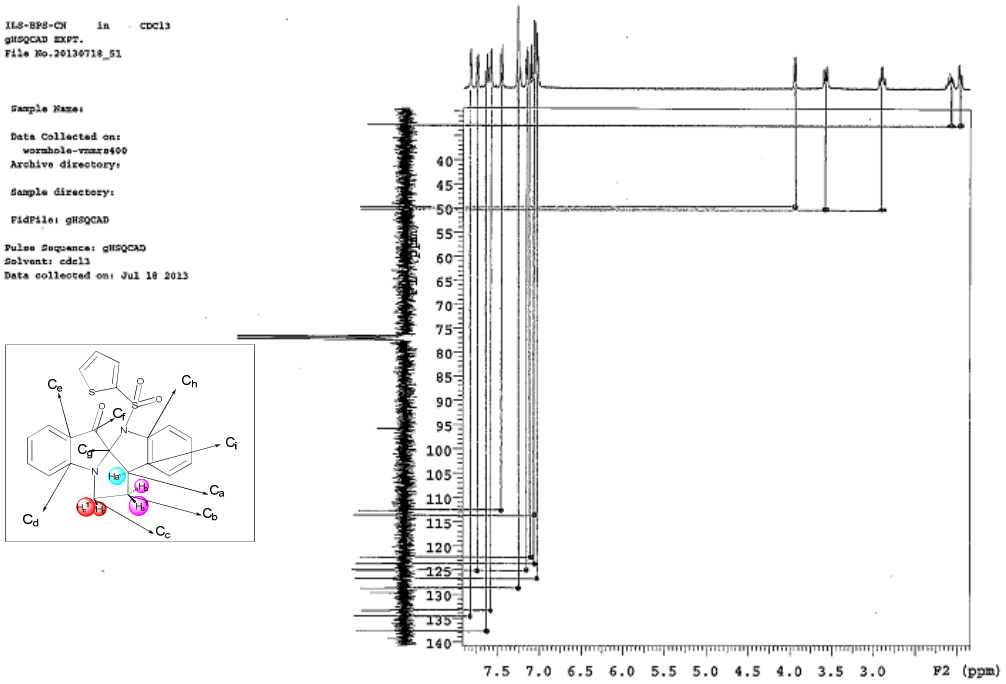
DEPT of compound **4.26d**



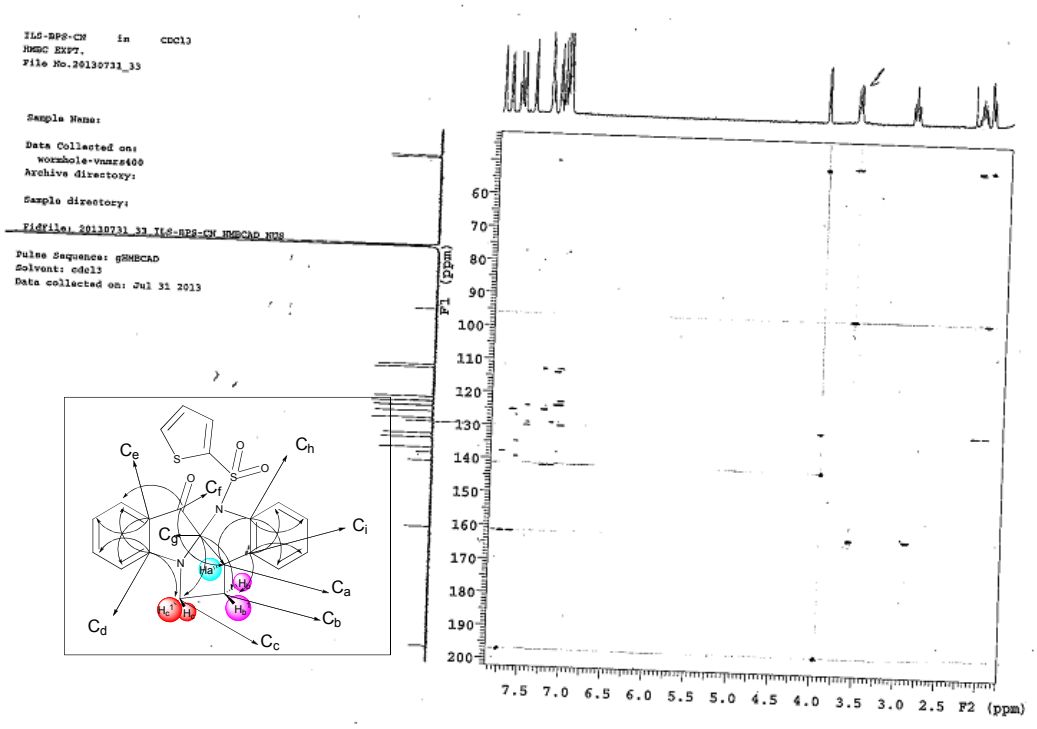
^{1}H-^{1}H COSY of compound **4.26d**



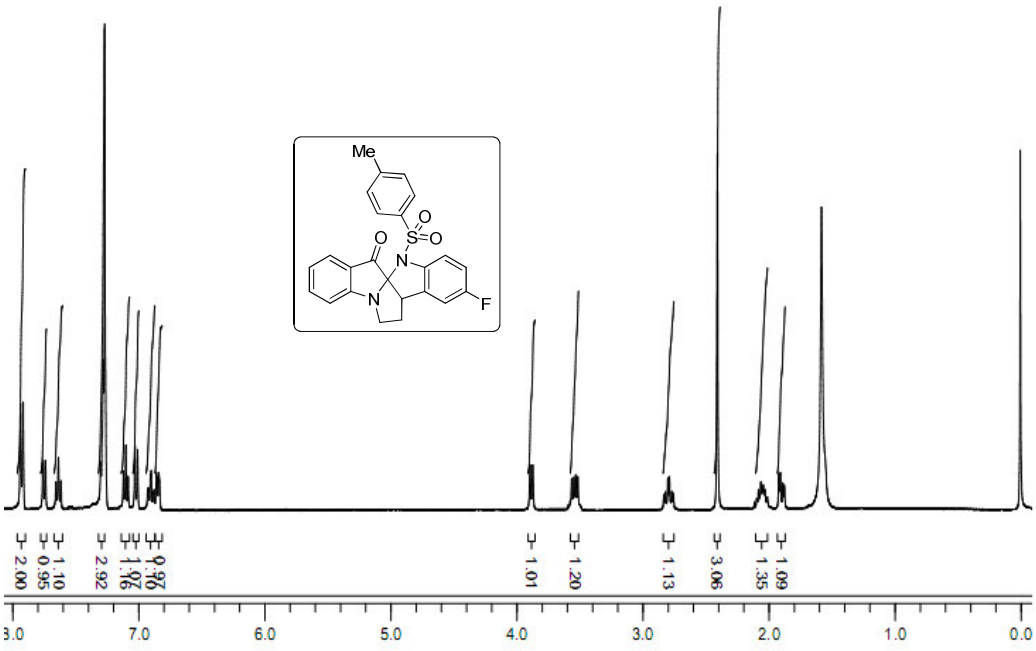
HSQC of compound **4.26d**



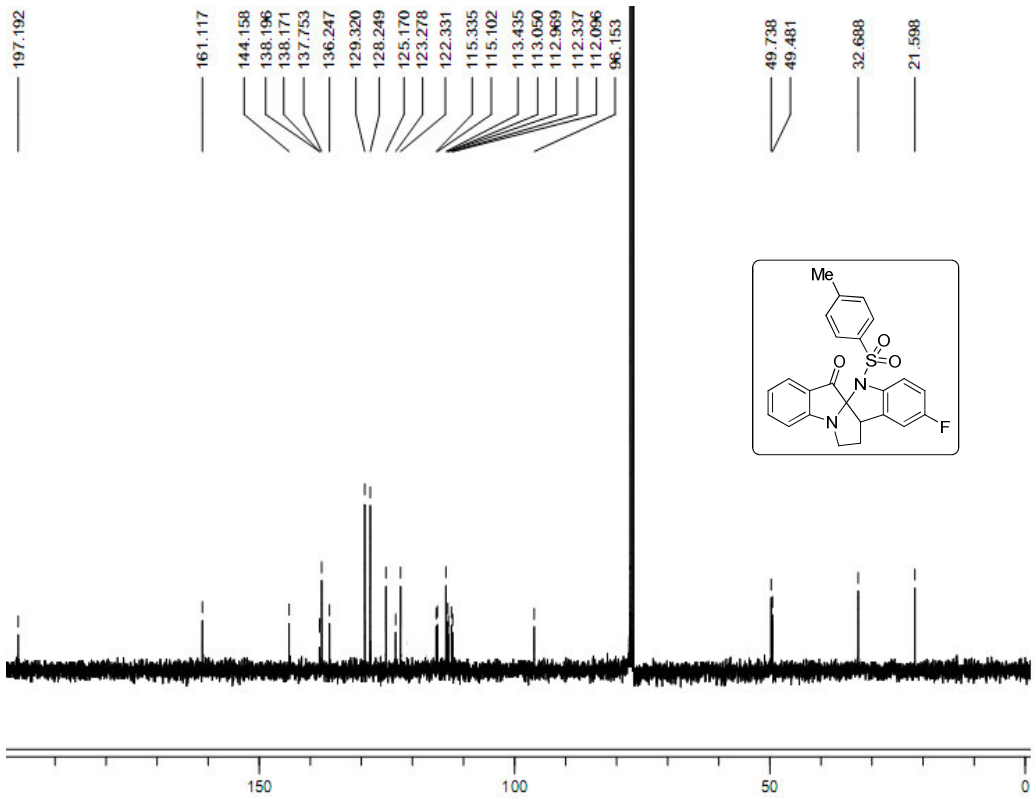
HMBC of compound **4.26d**



^{1}H NMR (Varian, 400 MHz) spectrum of compound **4.26c** in $CDCl_3$



^{13}C NMR spectrum (Varian, 100 MHz) of compound **4.26c** in $CDCl_3$



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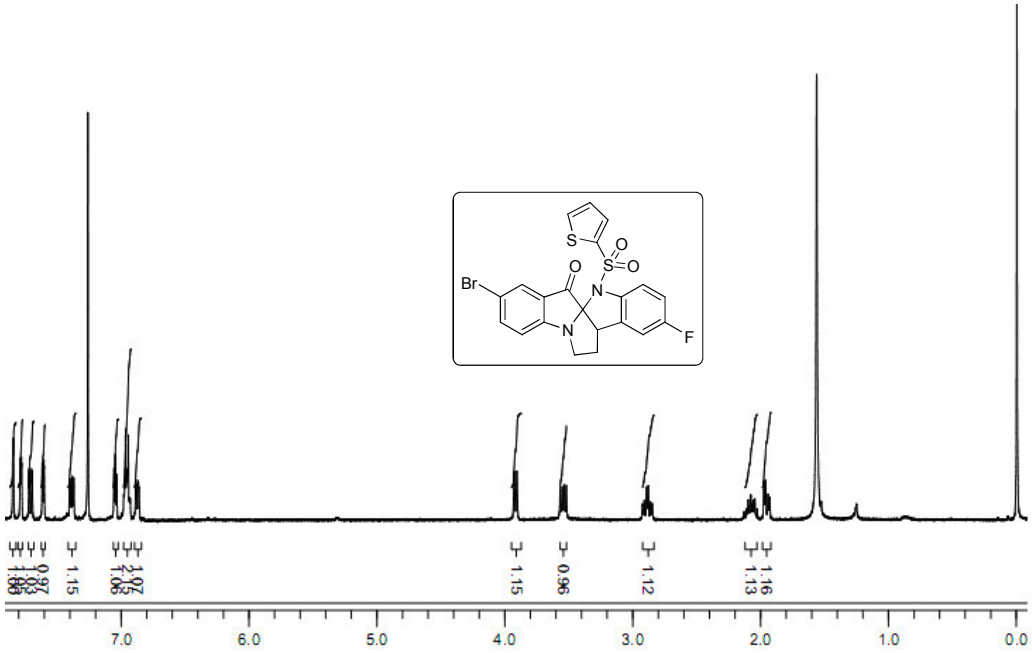
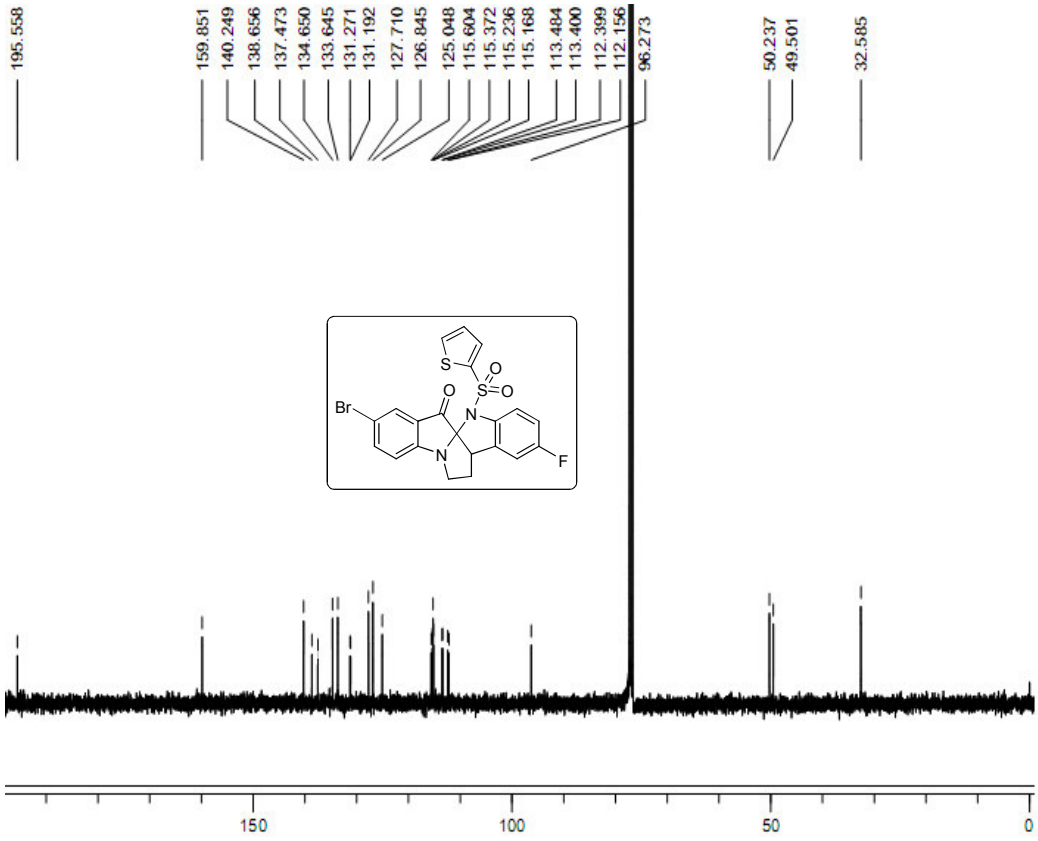
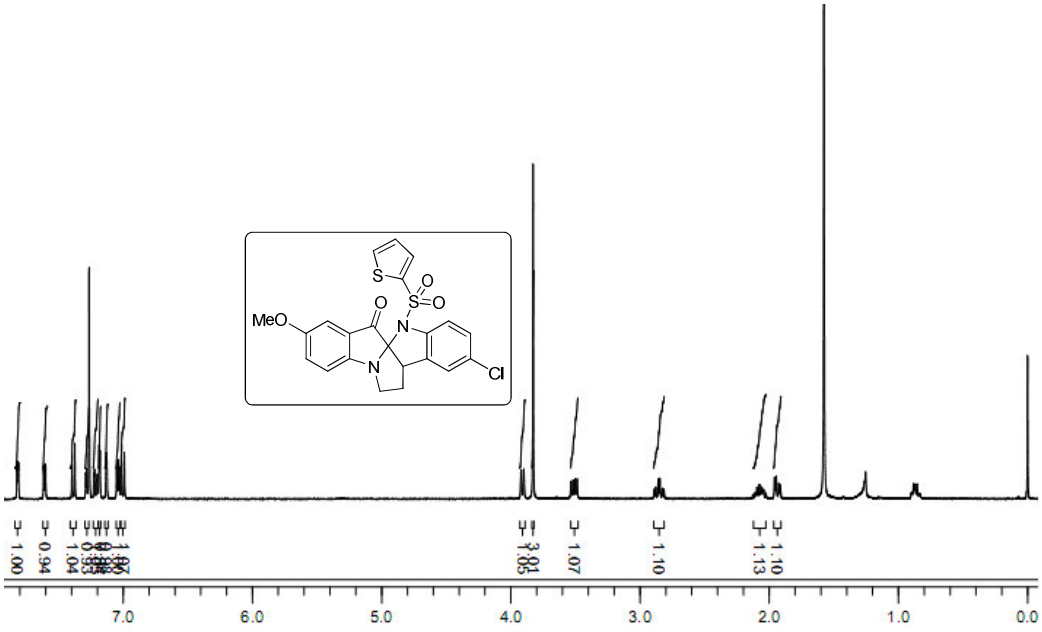


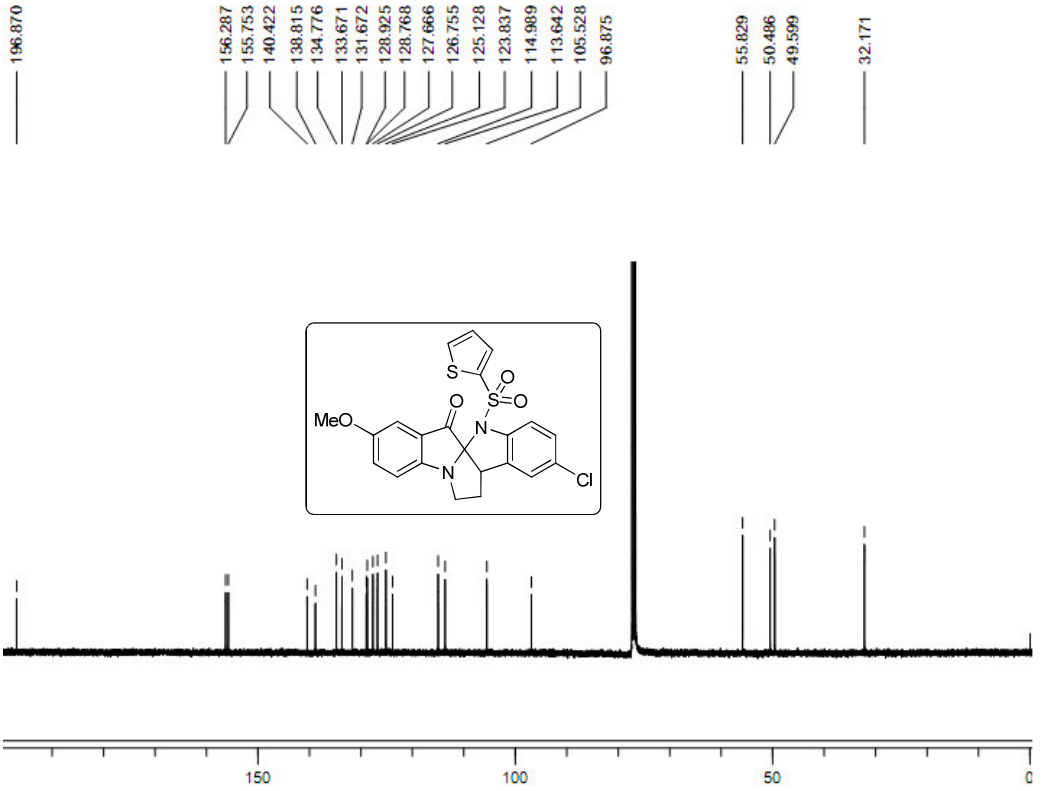
^{13}C NMR spectrum (Varian, 100 MHz) of compound **4.26i** in $CDCl_3$



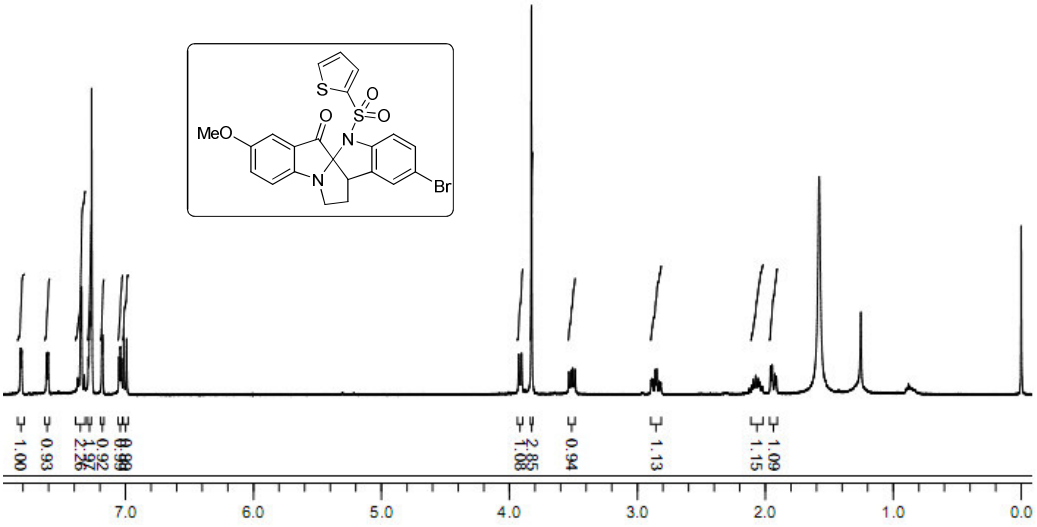
^{1}H NMR (Varian, 400 MHz) spectrum of compound **4.26l** in $CDCl_3$



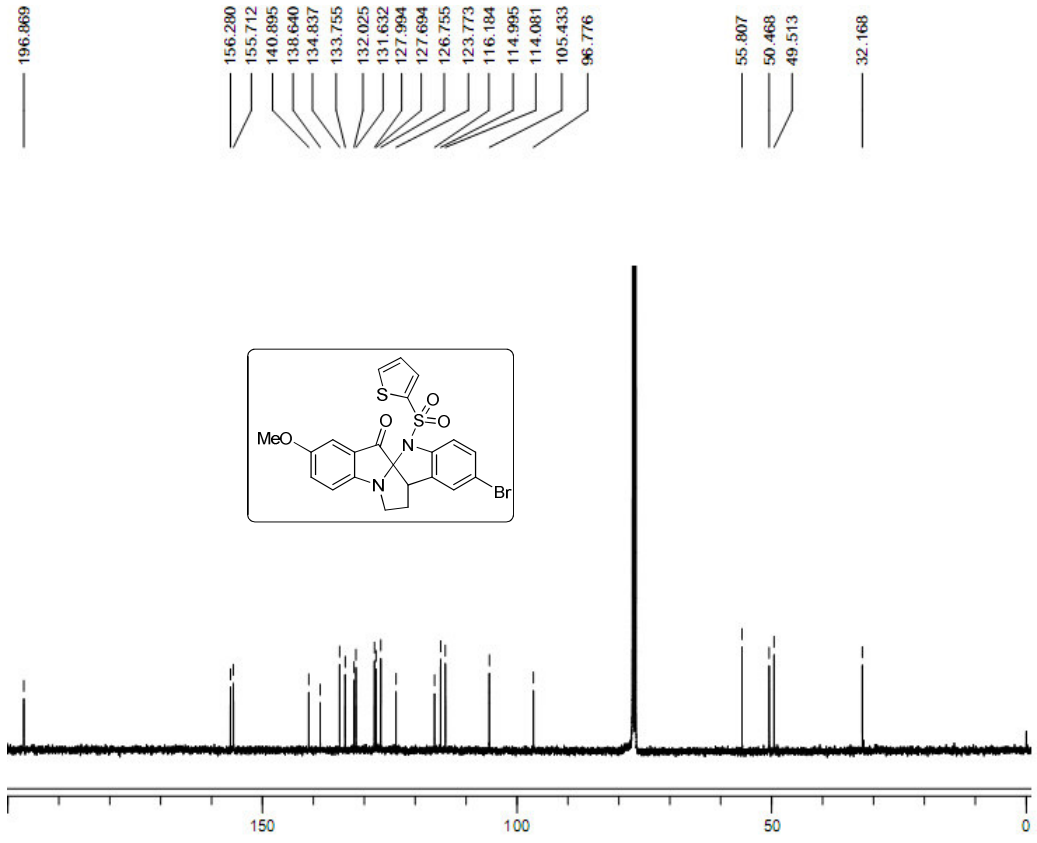
^{13}C NMR spectrum (Varian, 100 MHz) of compound **4.26l** in $CDCl_3$



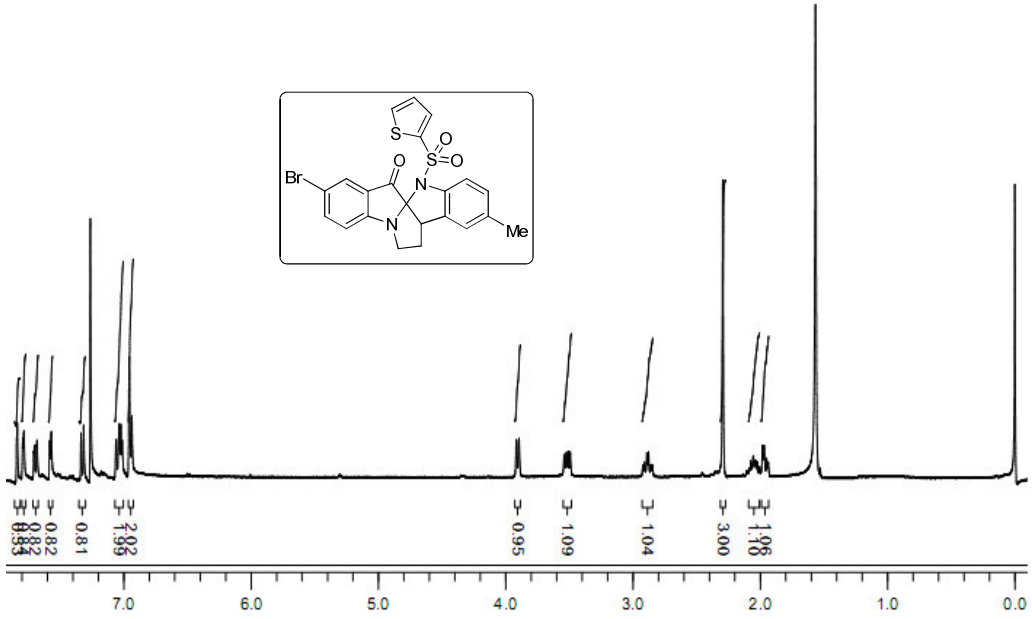
^{1}H NMR (Varian, 400 MHz) spectrum of compound **4.26m** in $CDCl_3$



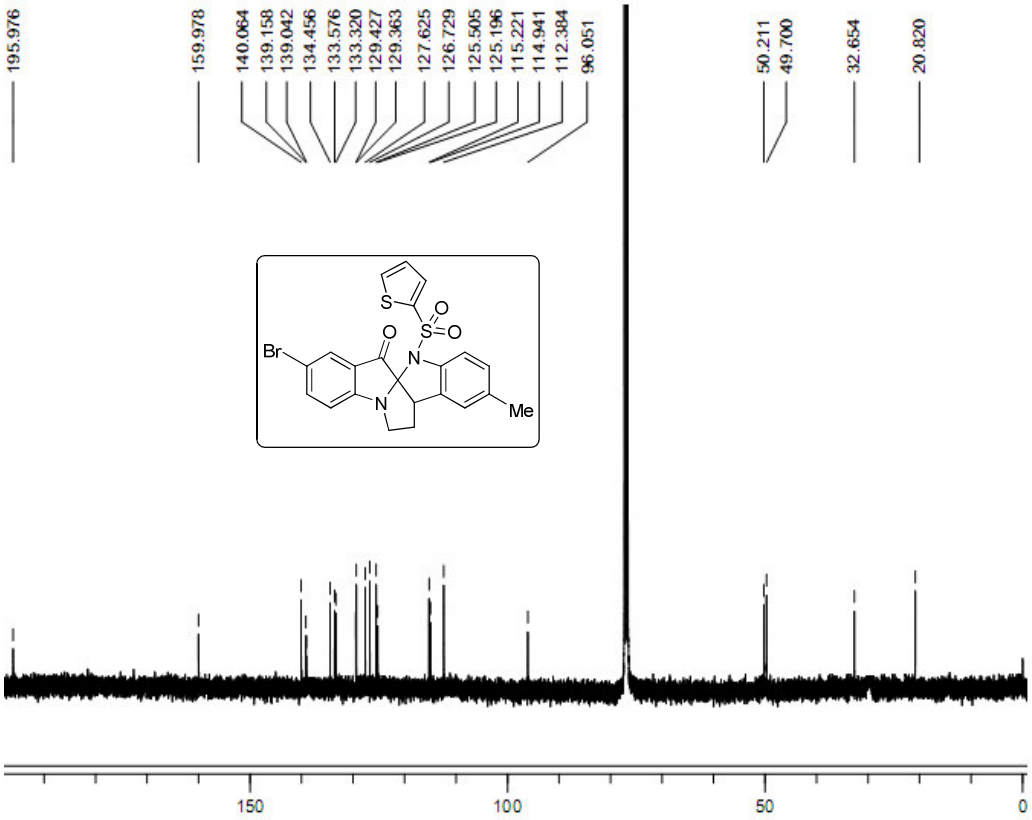
^{13}C NMR spectrum (Varian, 100 MHz) of compound **4.26m** in $CDCl_3$



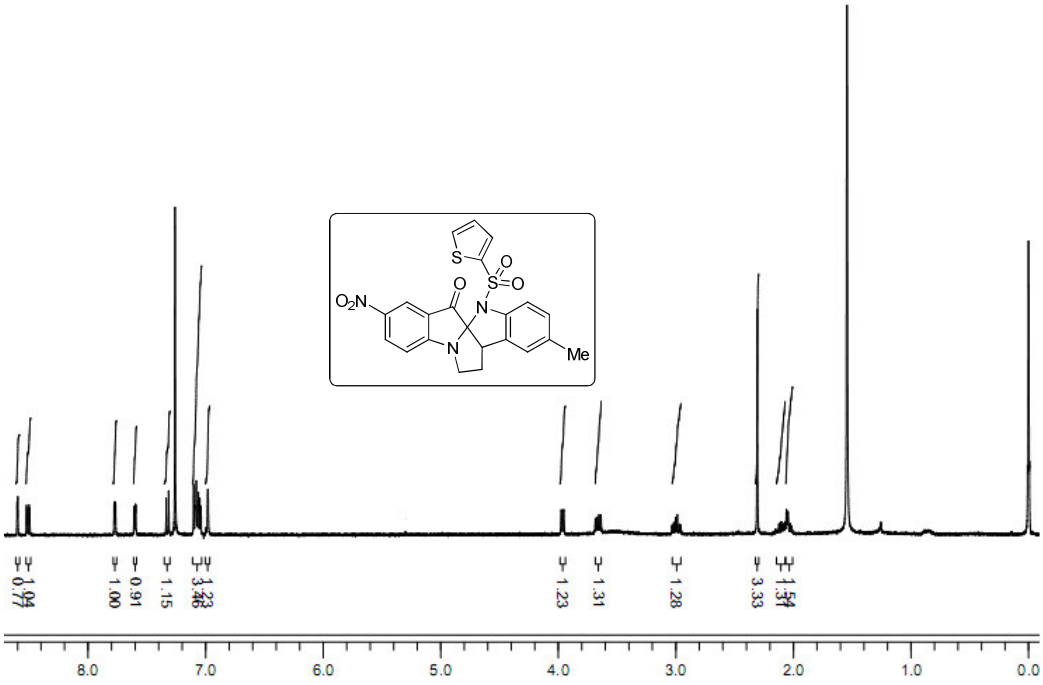
^{1}H NMR (Varian, 400 MHz) spectrum of compound **4.26p** in $CDCl_3$



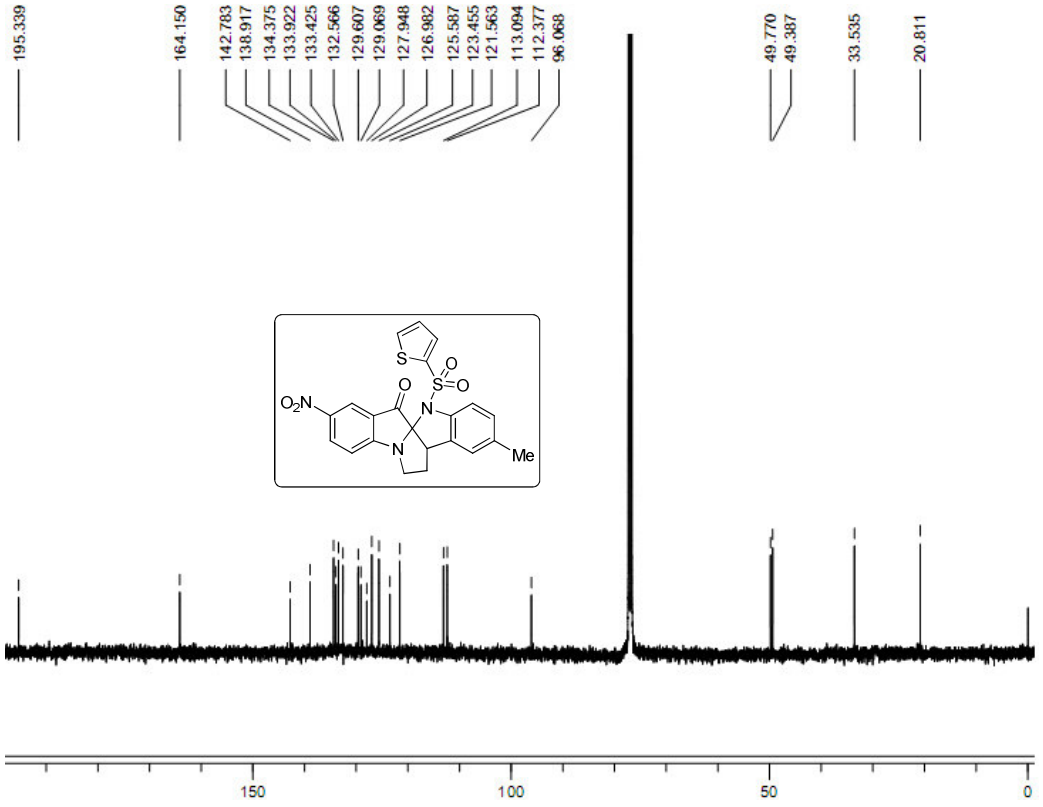
^{13}C NMR spectrum (Varian, 100 MHz) of compound **4.26p** in $CDCl_3$



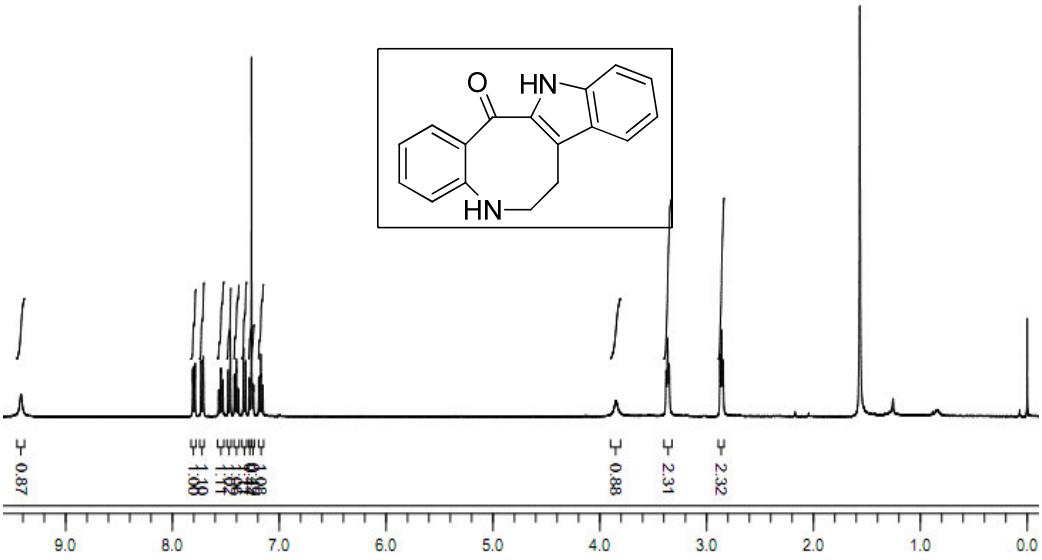
^{1}H NMR (Varian, 400 MHz) spectrum of compound **4.26q** in $CDCl_3$



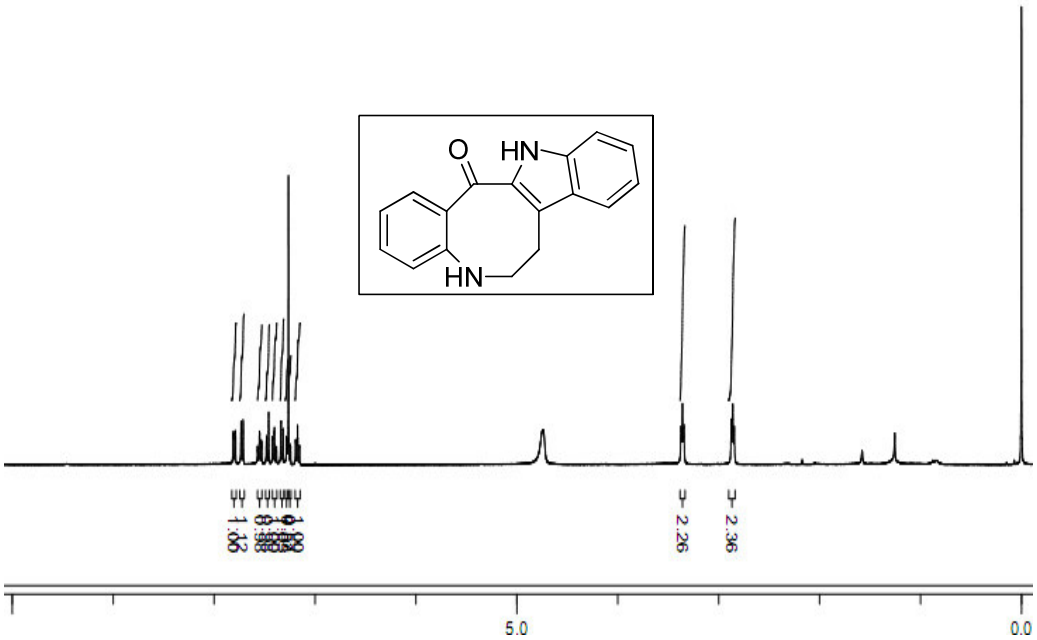
^{13}C NMR spectrum (Varian, 100 MHz) of compound **4.26q** in $CDCl_3$



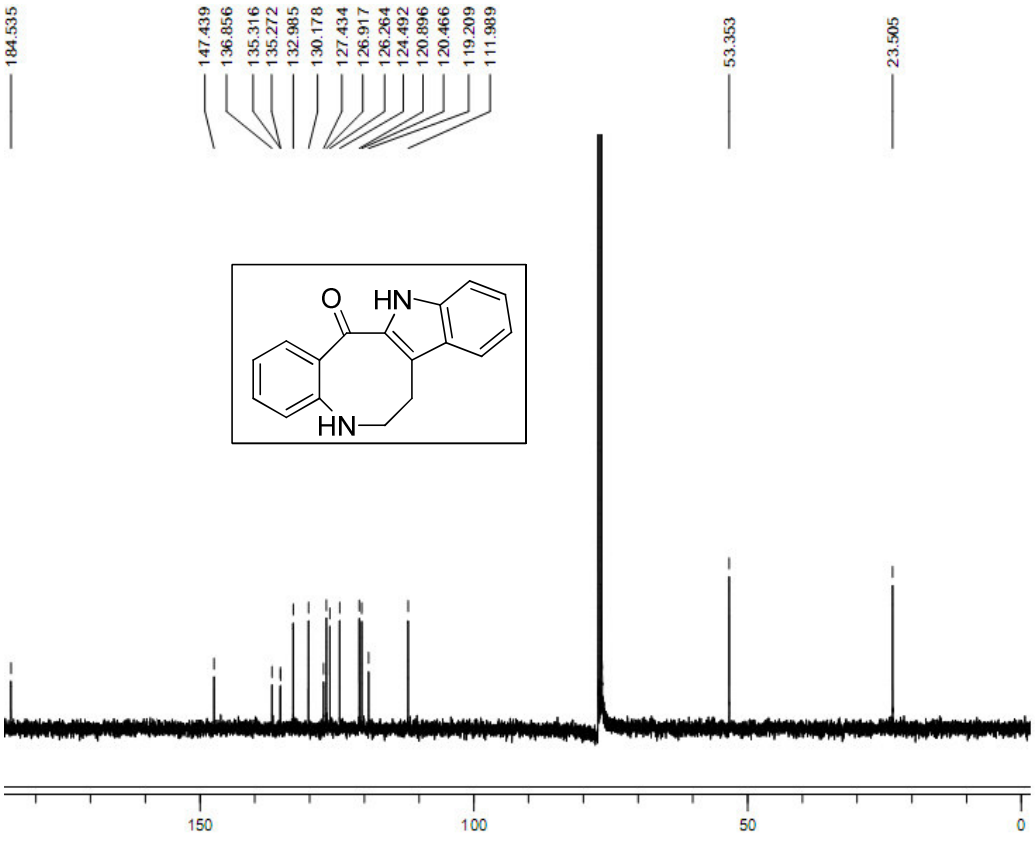
^{1}H NMR (Varian, 400 MHz) spectrum of compound **4.27** in $CDCl_3$



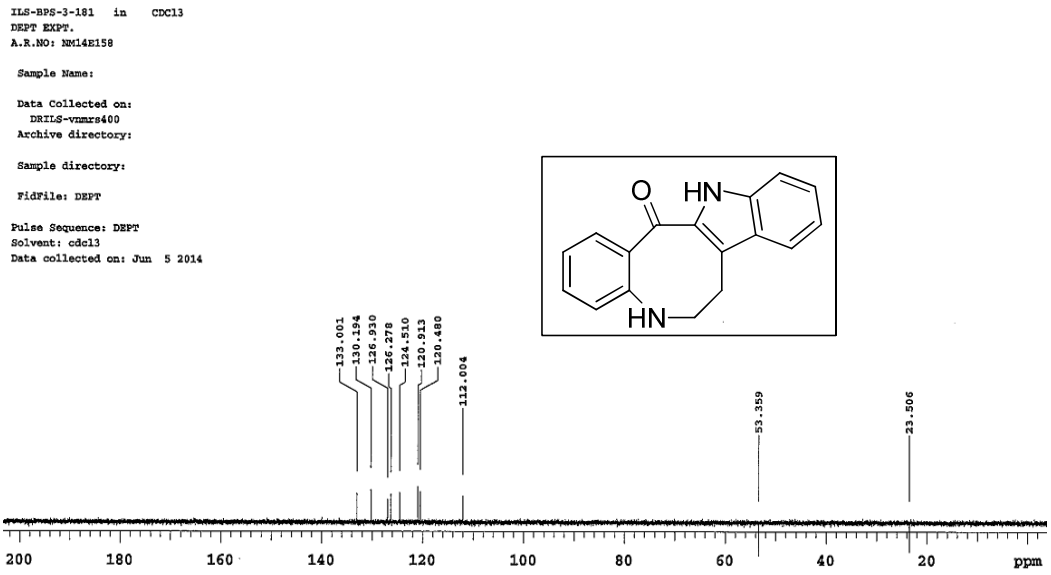
D_2O exchange spectrum of compound **4.27** in $CDCl_3$



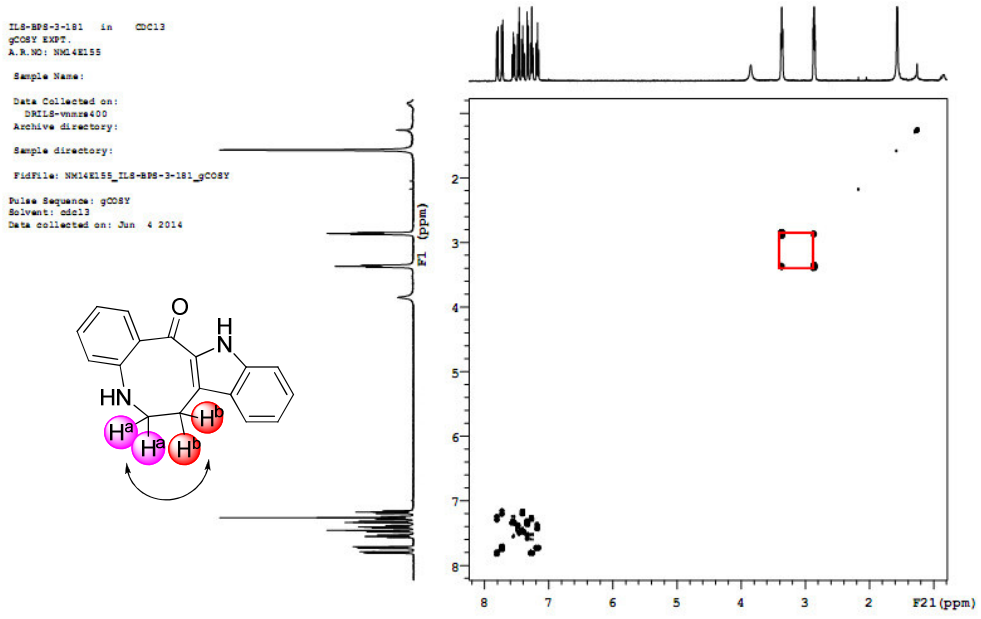
^{13}C NMR spectrum (Varian, 100 MHz) of compound **4.27** in $CDCl_3$



DEPT of compound **4.27**

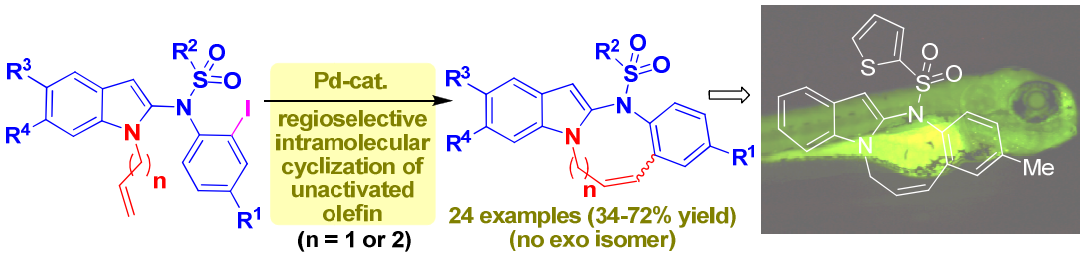


^{1}H-^{1}H COSY of compound **4.27**



CHAPTER 5

Pd- catalyzed synthesis of indole-1,2-fused 8 and 9 membered rings and their evaluation against apoptosis



5.1 Introduction

Increased structural complexity in indole-based compounds is seen in recent time where the fusion of the indolic moiety to other rings has been reported. These indole based compounds possess a wide variety of biological properties. Compounds containing 6 or 7 or 8-membered ring fused with indole framework at 1,2-position (**F5.1**, Figure 5.1) are not only of immense importance in medicinal chemistry and pharmacology but also common targets in synthetic organic chemistry. For example, synthesis of indolo-diazepines (**F5.2**, Figure 5.1) possessing antiserotonin activities,[1] 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]indole (**F5.3**, Figure 5.1) possessing antipressant[2] and CNS activities,[3] indolo-1,5-benzodiazocine possessing (**F5.4**, Figure 5.1) CNS activities,[4] 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indole (**F5.5**, Figure 5.1) possessing 5-HT antagonistic properties,[5] etc are mention worthy.

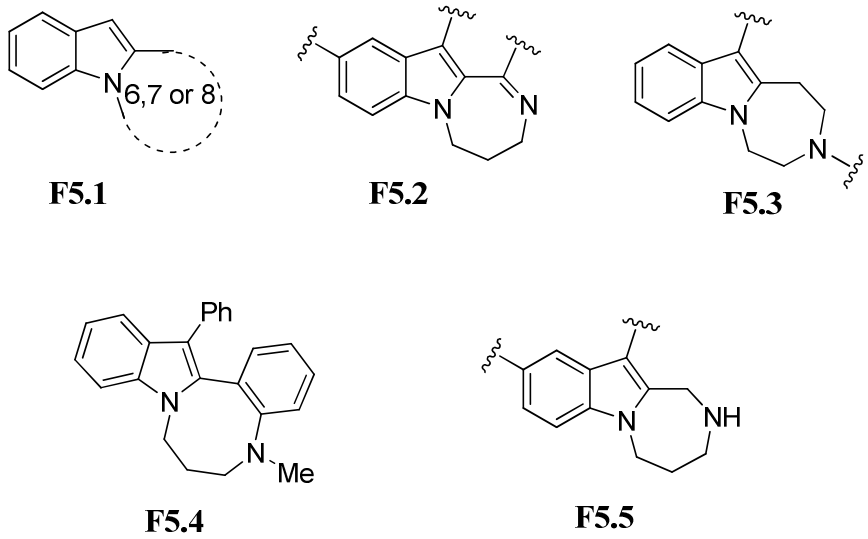


Figure 5.1 Compounds containing 6 or 7 or 8-membered ring fused with indole at 1,2-position.

Interestingly, compounds containing indole-2,3-fused 7 or 8 membered ring system have been explored for potential anticancer/antitumor activities.[6,7,8,9] Cancer is associated with lower degree of apoptosis and most of the cytotoxic anticancer agents are known to induce apoptosis. Apoptosis[10] that occurs in physiological and pathological conditions is an ordered and orchestrated cellular process. The complex mechanism of apoptosis involves many pathways. Defects in apoptotic pathways are thought to contribute to a number of human diseases, ranging from neurodegenerative disorders to malignancy.[10] Surprisingly, indole-1,2-fused 7 or 8 membered analogues

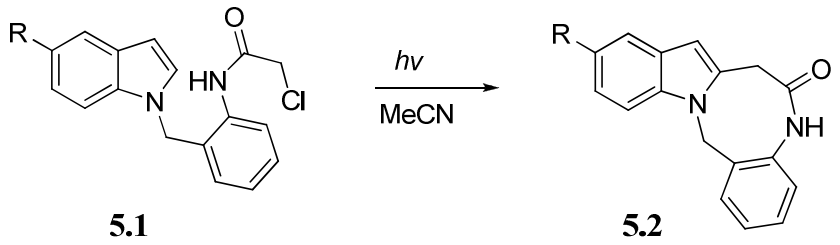
remained less or unexplored for potential anticancer/antitumor activities. More importantly, reports describing the pharmacological properties of compounds containing indole-2,3-fused 9 membered ring system are not common in the literature perhaps due to the cumbersome or non accessibility of this class of indoles. This prompted us to explore a suitable methodology for the quick access of compounds containing indole-1,2-fused 8 or 9 membered ring for their potential anticancer especially apoptotic properties.

5.2 Previous work

A number of methods have been reported in the literature for the synthesis of indole-fused 8 or 9-membered rings at the 1,2 position that can be classified according to the substrates used and the bond formed in the ring-closing step.

5.2.1 Ring closure of *N*-substituted indoles *via* bond formation to C-2 position

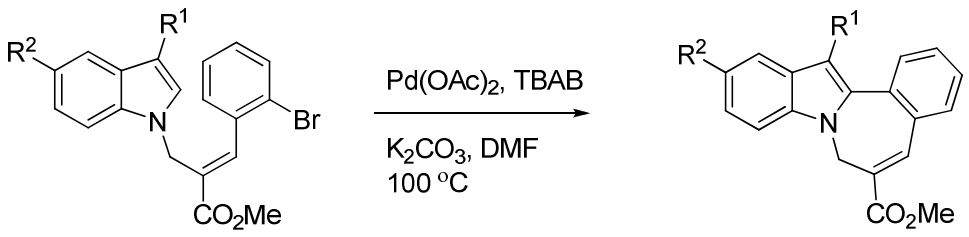
White and coworkers reported the photo cyclisation of chloro acetamides (**5.1**) affording Indolo[1,2-*d*][1,5]diazocinone (**5.2**) derivatives in low yields (Scheme 5.1).[11]



5.1 **5.2**

Scheme 5.1 Synthesis of indolodiazocinone.

Kim and coworkers reported the palladium-mediated intramolecular Heck reaction of indole containing Baylis–Hillman adducts (**5.3**) leading to formation of tetracyclic indole derivatives (**5.4**) (Scheme 5.2).[12]

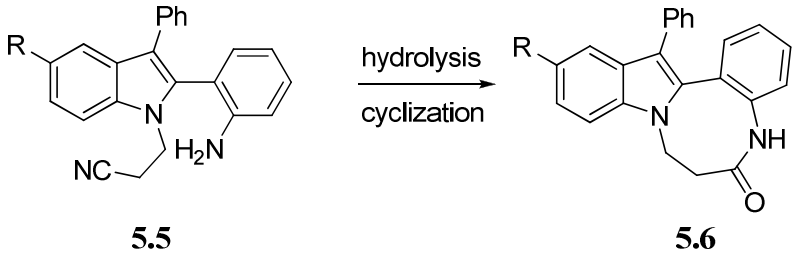


5.3 **5.4**

Scheme 5.2 Synthesis of indole based tetracyclic compounds.

5.2.2 Ring closure *via* 1, 2-disubstituted indoles

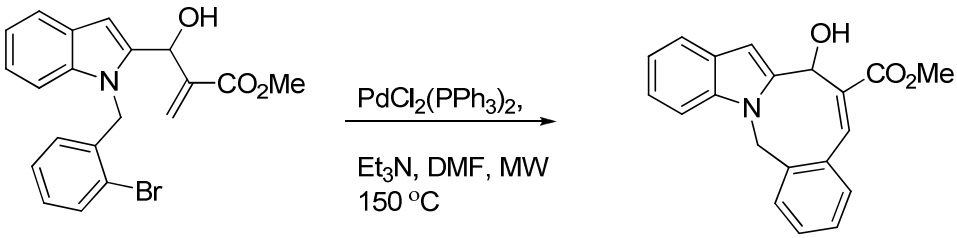
In 1981, Gatta and coworkers reported the hydrolysis cyano group of **5.5** gave the corresponding acid which underwent cyclization affording indolodiazocinone derivative **5.6** (Scheme 5.3).[13]



5.5 **5.6**

Scheme 5.3 Synthesis of indolodiazocinone.

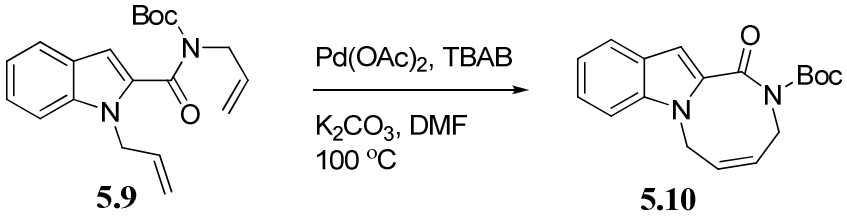
In 2010, Batra and coworkers reported the intramolecular Heck coupling reaction of **5.7** in the presence of palladium complex under microwave condition affording indole-fused benzoazocines (**5.8**) in moderate yields (Scheme 5.4).[14]



5.7 **5.8**

Scheme 5.4 Synthesis of indole fused compound.

In 2008, Me´rour reported the synthesis of indole fused with an eight-membered ring (**5.10**) *via* the ring closing metathesis of *N*-allyl-1-*H*-indole-2-carboxamide derivative **5.9** (Scheme 5.5).[15]

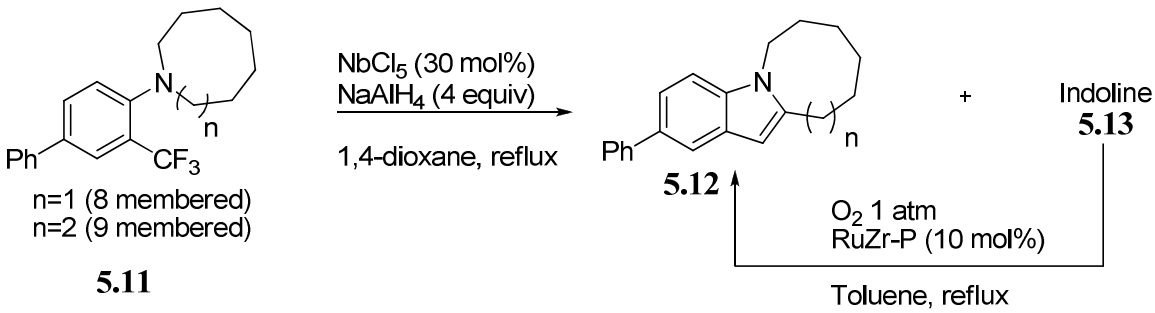


5.9 **5.10**

Scheme 5.5 Synthesis of indole fused with an eight membered ring.

5.2.3 Indole ring formation on a preformed 8 or 9-membered ring

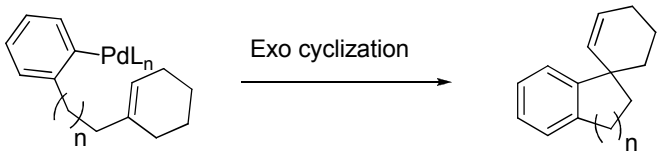
Akiyama and coworkers reported the synthesis of 1,2-fused indole skeletons (**5.11**) *via* a niobium-catalyzed C-F activation and C-H insertion approach from trifluoromethyl compound (**5.12**). Dehydrogenation of the isolated side product indoline (**5.13**) proceeded smoothly in the presence of a ruthenium catalyst under oxygen at atmospheric pressure (Scheme 5.6).[16]



Scheme 5.6 Synthesis of 1,2-fused indoles.

5.3 Present work

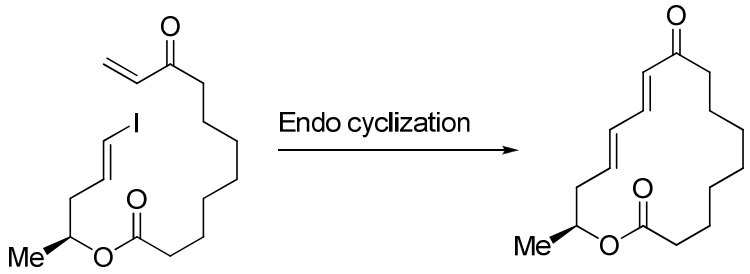
While many of the reported methods are very effective and elegant to access a particular class of fused indole derivatives some of them suffer from being not general and versatile in nature. Additionally, construction of indole-fused 9-membered ring at 1,2 position appeared as difficult or not feasible by using some of these methodologies. We therefore required a general and robust method to prepare indole-fused 8 and 9 membered ring compounds. Herein we report an elegant and effective method for the direct access to indole-fused 8 and 9 membered ring compounds *via* Pd-mediated intramolecular ring closure of 1,2-disubstituted indoles. Since its discovery in 1977,[17] the intramolecular Heck reaction has become a powerful tool for the quick construction of carbocyclic/heterocyclic rings.[18] The intramolecular Heck reactions are generally more efficient and regiochemistry in insertion step is highly sensitive to the electronics of the substrate, the reaction manifold and steric congestion. As a result regioselectivity can be poor for certain classes of substrates. The ring closure was found to be highly exo selective for 5, 6 and 7 membered rings (Scheme 5.7).



5.14 **5.15**

Scheme 5.7 Exo selective ring closure of Heck reaction (5, 6 and 7 membered rings).

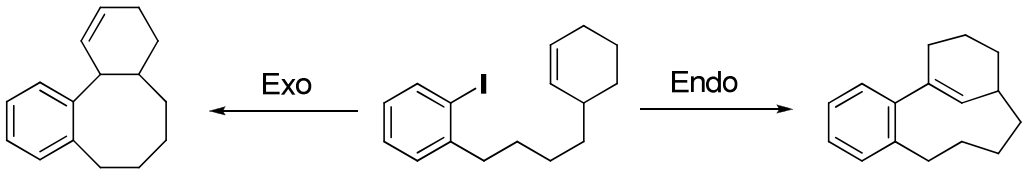
For large ring formation (13 and greater) the Heck reactions becomes endo selective and can be used as a macrocyclization strategy (Scheme 5.8).[19]



5.16 **5.17**

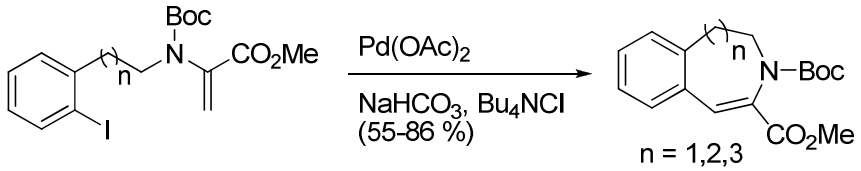
Scheme 5.8 Endo selective ring closure of Heck reaction (13 and greater).

A mixture of exo and endo products were formed in the closure of medium sized *i.e.* 8-12 membered rings (Scheme 5.9).[20]



5.19 **5.18** **5.20**

Scheme 5.9 Both exo and endo ring closure of Heck reaction (8-12 membered rings).

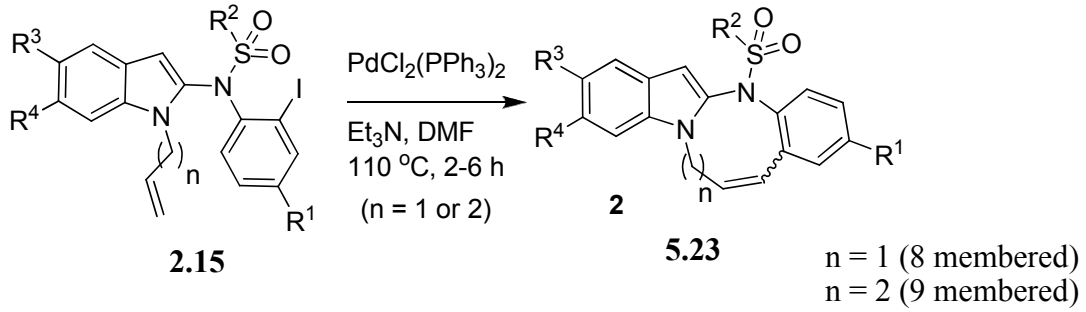


5.21 **5.22**

Scheme 5.10 Endo selective ring closure of Heck reaction (Michael-type olefinic fragment).

However, the endo mode of intramolecular Heck cyclization has been reported to be favoured for substrates that contain a Michael-type olefinic fragment (termed as electronic reasons)[18a] leading to 7, 8 or 9-membered rings (Scheme 5.10).[21]

It is in sharp contrast to our observations where no such electronic reasons aided the endo cyclization. Additionally, we were able to achieve this mode of cyclization using non-activated olefin as one of the reactant moieties. Thus an elegant and effective method for the synthesis of indole fused 8 or 9 membered ring derivatives (**5.23**) has been developed by treating the unactivated olefin substituents of compound **2.15** with $Pd[Cl_2(PPh_3)_2]$ (Scheme 5.11).



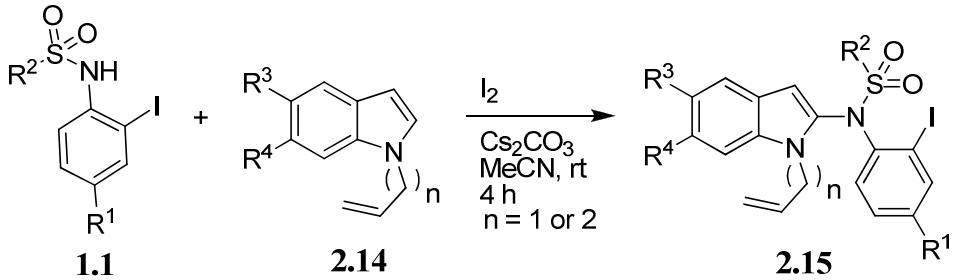
Scheme 5.11 Synthesis of indole fused 8 or 9 membered ring.

5.4 Results and discussion

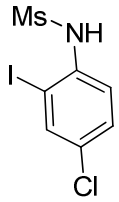
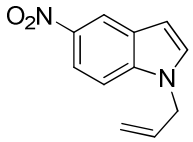
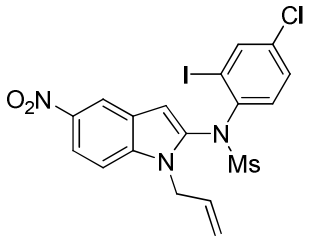
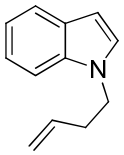
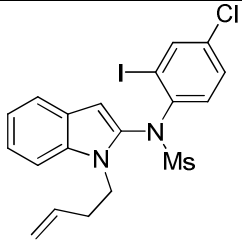
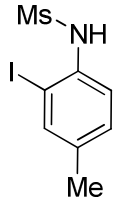
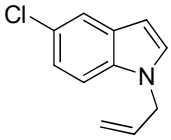
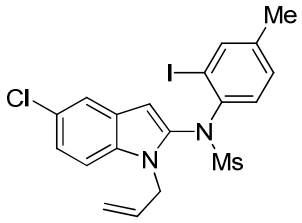
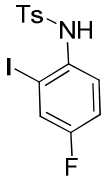
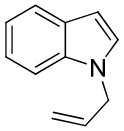
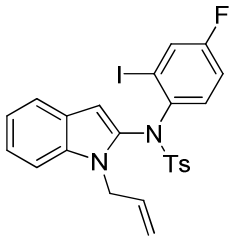
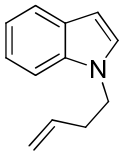
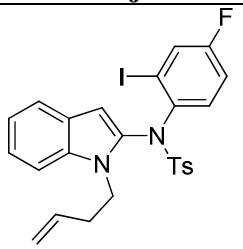
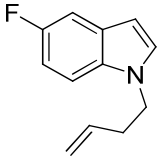
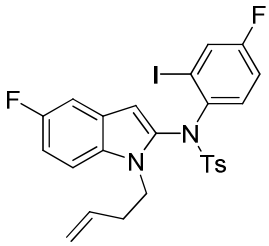
5.4.1 Synthesis of starting compound 2.15

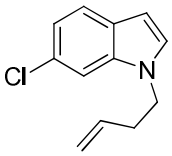
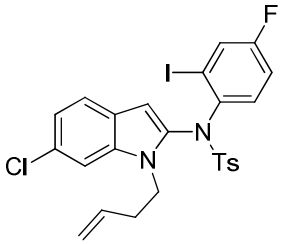
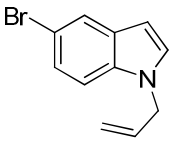
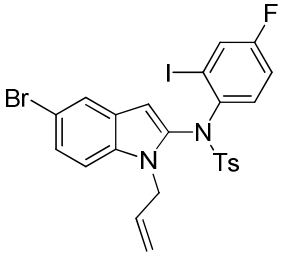
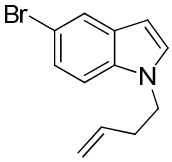
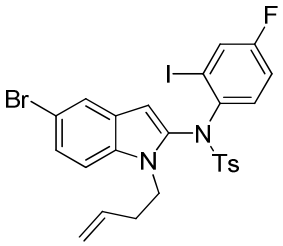
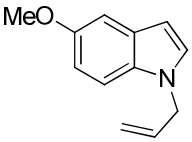
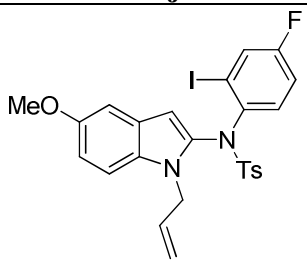
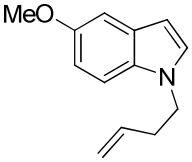
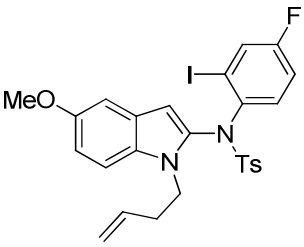
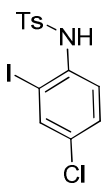
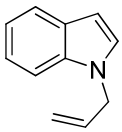
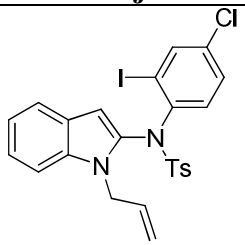
The synthesis of requisite starting materials **2.15** is described in Chapter 2 (Table 5.1).

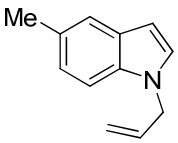
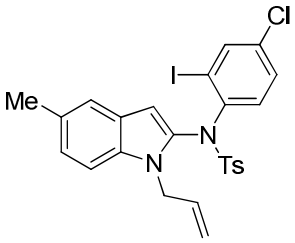
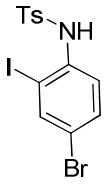
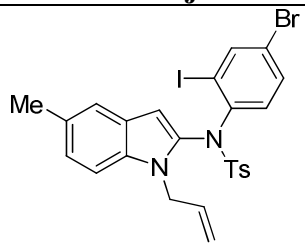
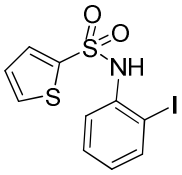
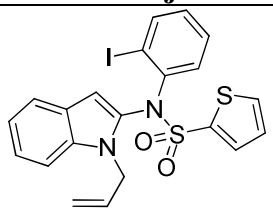
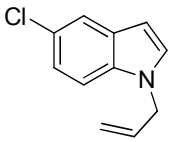
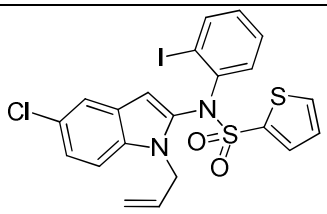
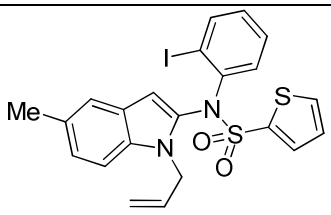
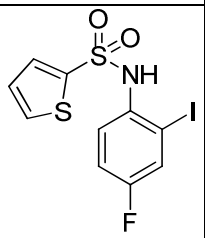
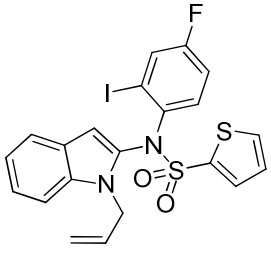
Table 5.1 Iodine mediated synthesis of *N*-(4-substituted-2-iodophenyl)-*N*-(1-alkyl-1*H*-indol-2-yl)alkane/arene/heteroarene sulfonamide.[a]

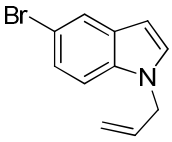
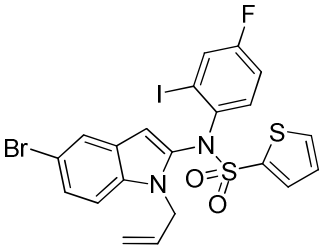
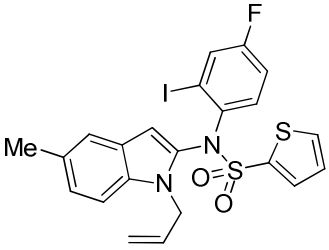
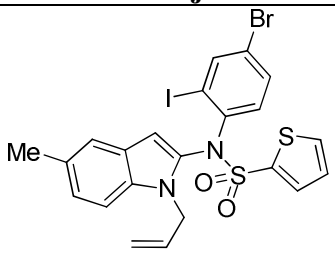
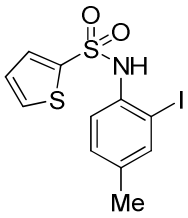
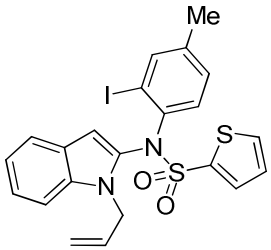
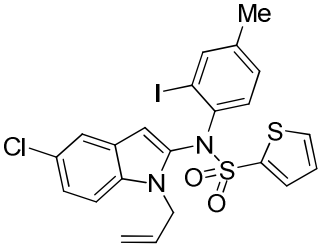
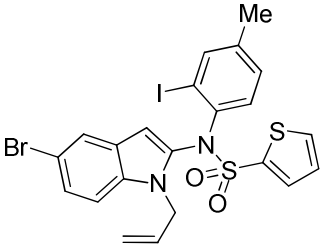


Entry	Iodoanilides (**1.1**)	Indole (**2.14**)	Time[b]/ h	Product (**2.15**)	Yield [c](%)

1	 **1.1c**	 **2.14o**	6	 **2.15co**	52
2	**1.1c**	 **2.14c**	6	 **2.15cc**	65
3	 **1.1e**	 **2.14f**	4	 **2.15ef**	45
4	 **1.1j**	 **2.14b**	5	 **2.15jb**	64
5	**1.1j**	 **2.14c**	5	 **2.15jc**	55
5	**1.1j**	 **2.14e**	5	 **2.15je**	47

6	**1.1j**	 **2.14g**	5	 **2.15jg**	51
7	**1.1j**	 **2.14h**	5	 **2.15jh**	47
8	**1.1j**	 **2.14i**	5	 **2.15ji**	51
10	**1.1j**	 **2.14m**	5	 **2.15jm**	57
9	**1.1j**	 **2.14r**	5	 **2.15jr**	55
11	 **1.1k**	 **2.14b**	5	 **2.15kb**	58

13	**1.1k**	 **2.14j**	6	 **2.15kj**	52
14	 **1.1s**	**2.14j**	5	 **2.15sj**	55
15	 **1.1n**	**2.14b**	4	 **2.15nb**	58
16	**1.1n**	 **2.14f**	4	 **2.15nf**	58
17	**1.1n**	**2.14j**	5	 **2.15nj**	52
18	 **1.1o**	**2.14b**	4	 **2.15ob**	56

19	**1.1o**	 **2.14h**	4	 **2.15oh**	55
20	**1.1o**	**2.14j**	5	 **2.15oj**	51
21	**1.1q**	**2.14j**	5	 **2.15qj**	53
22	 **1.1r**	**2.14b**	4	 **2.15rb**	60
23	**1.1r**	**2.14f**	5	 **2.15rf**	55
24	**1.1r**	**2.14h**	5	 **2.15rh**	44

[a]All the reactions were carried out using **1.1** (1.0 mmol), **2.14** (1.2 mmol), I_2 (1.0 mmol) and Cs_2CO_3 (1.5 mmol) in acetonitrile (5.0 mL), at room temperature under nitrogen.

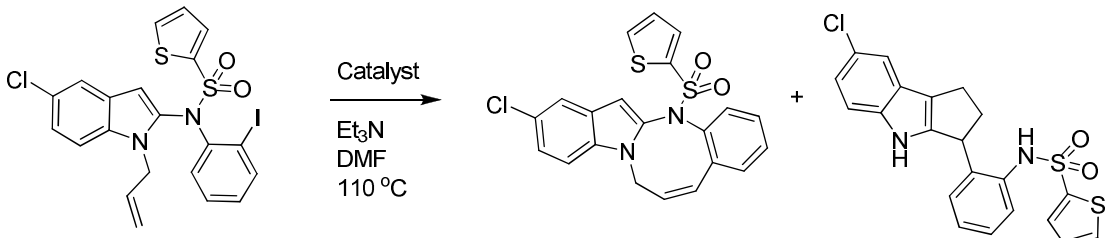
[b]After adding indole **2.14**.

[c]Isolated yield.

5.4.2 Reaction optimisation

To obtain the best reaction condition for the synthesis of desired product we have performed the Pd-mediated intramolecular Heck reaction of **2.15nf** under a variety of conditions (Table 5.2). Initially, **2.15nf** was treated with $Pd(PPh_3)_2Cl_2$ and Et_3N in DMF at 110 °C for 4h, when the desired product **5.23j** containing endocyclic double bond was isolated in 63% yield (entry 1, Table 5.2). While the cyclopenta[*b*]indole[21] **3.14b** was isolated as a side product in this case the formation of no isomeric product containing exocyclic double bond was detected. The use of other palladium catalysts e.g. $Pd(PPh_3)_4$ (entry 2, Table 5.2), Pd/C and PPh_3 (entry 3, Table 5.3) did not improve the yield of desired product. Also, the reaction did not proceed when $Cu(OAc)_2$ was used as a catalyst (entry 4, Table 5.4). From the above observations we concluded that the use of $Pd(PPh_3)_2Cl_2$ and Et_3N in DMF at 130 °C was optimum for the reaction.

Table 5.2 Optimization of reaction conditions.[a]



2.15nf **5.23j** **3.14b**

Entry	Catalyst/additive	Time (h)	Yield[b] (%)	
			5.23j	**3.14b**
1	$Pd(PPh_3)_2Cl_2$	4	63	30
2	$Pd(PPh_3)_4$	4	54	32
3	10%Pd/C / PPh_3	12	51	30
4[c]	$Cu(OAc)_2$	12	0	0

[a]Reactions were carried out using **2.15nf** (0.2 mmol), catalyst (5 mmol%) and Et_3N (0.4 mmol) in DMF (2 mL) at 110 ºC.

[b]Isolated yield.

[c]1 mmol of catalyst used.

5.4.3 Scope of the reaction

To check the generality of the intramolecular Heck reaction we carried out reaction with optimised condition using various iodo compounds (**2.15**) (Table 5.3). The presence of halogens e.g. F, Cl, Br (Table 5.3) and electron donating groups e.g. Me and OMe (Table 5.3) and electron withdrawing group e.g. NO_2 (Table 5.3) in **2.15** was tolerated and the reaction proceeded well in all these cases affording the desired product in acceptable yields. In general better yields of **5.23** were observed when an electron donating group was present. We also examined the effect of nature of sulfonamide moiety present in **2.15**. Accordingly, the iodo compound **2.15** containing alkyl (**5.23a-b**, Table 5.3), aryl (**5.23c-h**, Table 5.3) and heteroaryl (**5.23i-5.23r**, Table 5.3) sulfonamide group was employed and the reaction proceeded as usual to afford the corresponding product. All the synthesized compounds were well characterized by spectral data (NMR, IR & MS). The *cis* geometry of double bond in these compounds was assigned based on the coupling constant (J = 11.2-11.5 Hz) of H^b proton that appeared in the region 6.8-6.9 ppm in the ^{1}H NMR spectra of compounds **5.23a-r.** This was further supported by the interaction of H^a proton (6.00 ppm) with H^b (6.8 ppm) (being at the same side of the double bond) upon irradiation in a 1D NOE experiment performed using the compound **5.23i** (Figure 5.2).

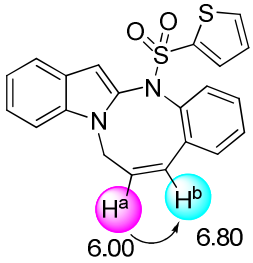
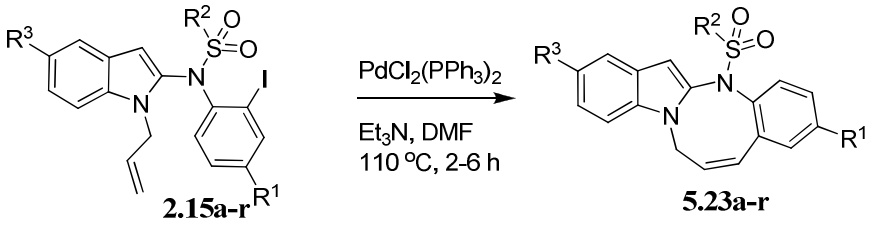


Figure 5.2 1D NOE experiment of compound **5.23i**

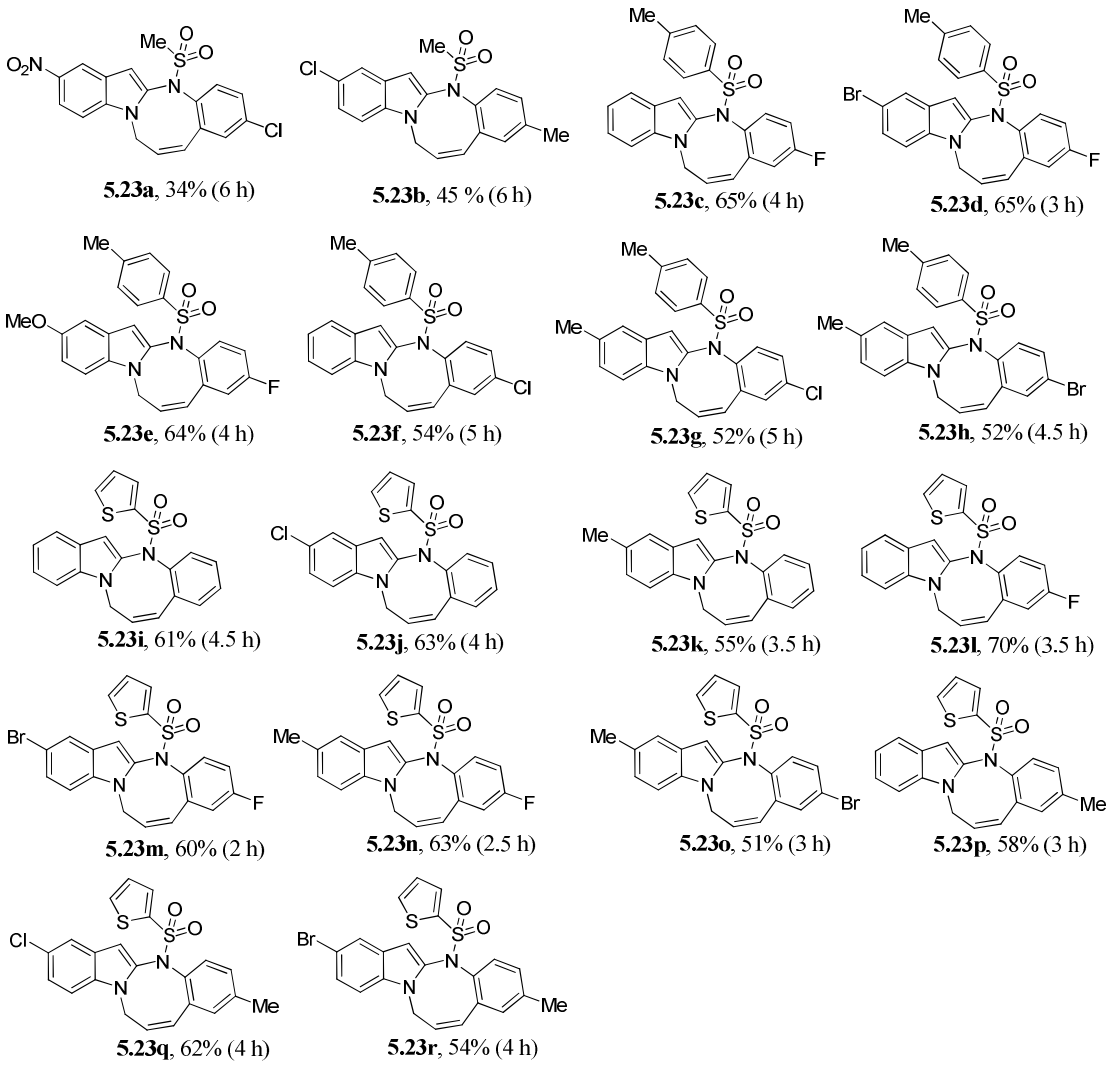
To check further scope and generality of this method we also made a number of analogues containing indole-1,2-fused 9 membered rings (Table 5.4) successfully by using homoallyl substituted starting compounds **2.15**. All the synthesized compounds were well characterized by spectral data (NMR, IR & MS). However, the coupling constants of olefinic protons could not be calculated in case of compounds **5.23s-x** (nor the 1D NOE experiment could be performed in these cases) due to the complex nature of these signals in their ^{1}HNMR spectra. Notably, the DEPT experiment (^{13}C

NMR) of compound **5.23x** confirmed the presence of endocyclic (not exocyclic) double bond in the 9-membered ring.

Table 5.3 Pd-mediated synthesis of indole-1,2-fused 8 membered rings (**5.23a-r**).[a]

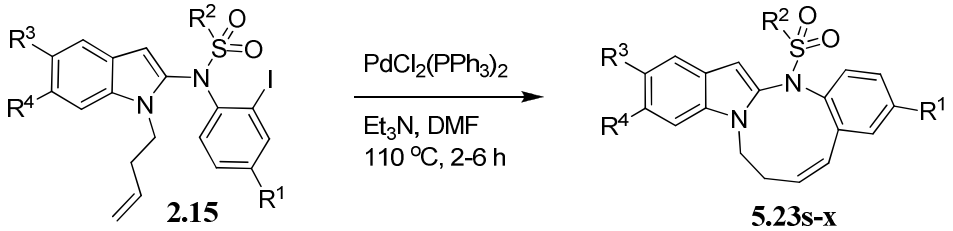


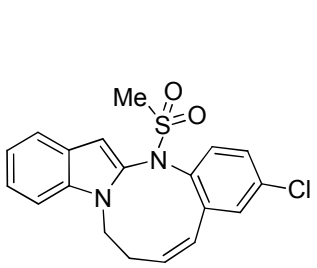
2.15a-r **5.23a-r**



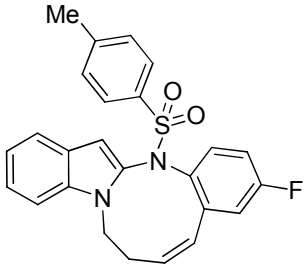
[a]All the reactions were performed using **2.15** (0.2 mmol), $PdCl_2(PPh_3)_2$ (5 mol%) and Et_3N (0.6 mmol) in DMF (2 mL) at 110 °C for 2-6 h under N_2.

Table 5.4 Pd-mediated synthesis of indole-1,2-fused 9 membered rings (**5.23s-x**).[a]

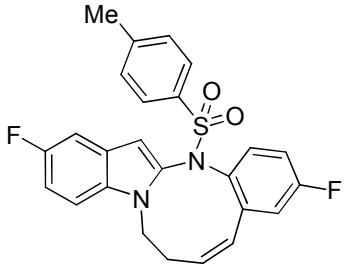




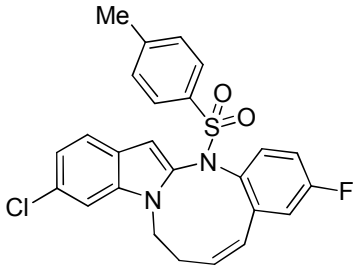
5.23s, 54% (6 h)



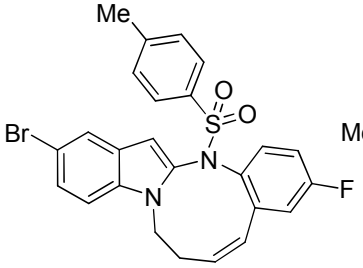
5.23t, 61% (4 h)



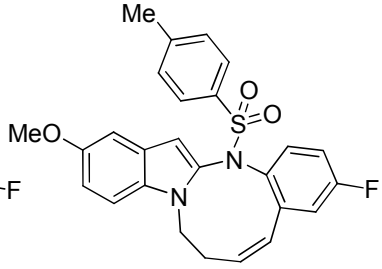
5.23u, 72% (2 h)



5.23v, 65% (3 h)



5.23w, 68% (3 h)



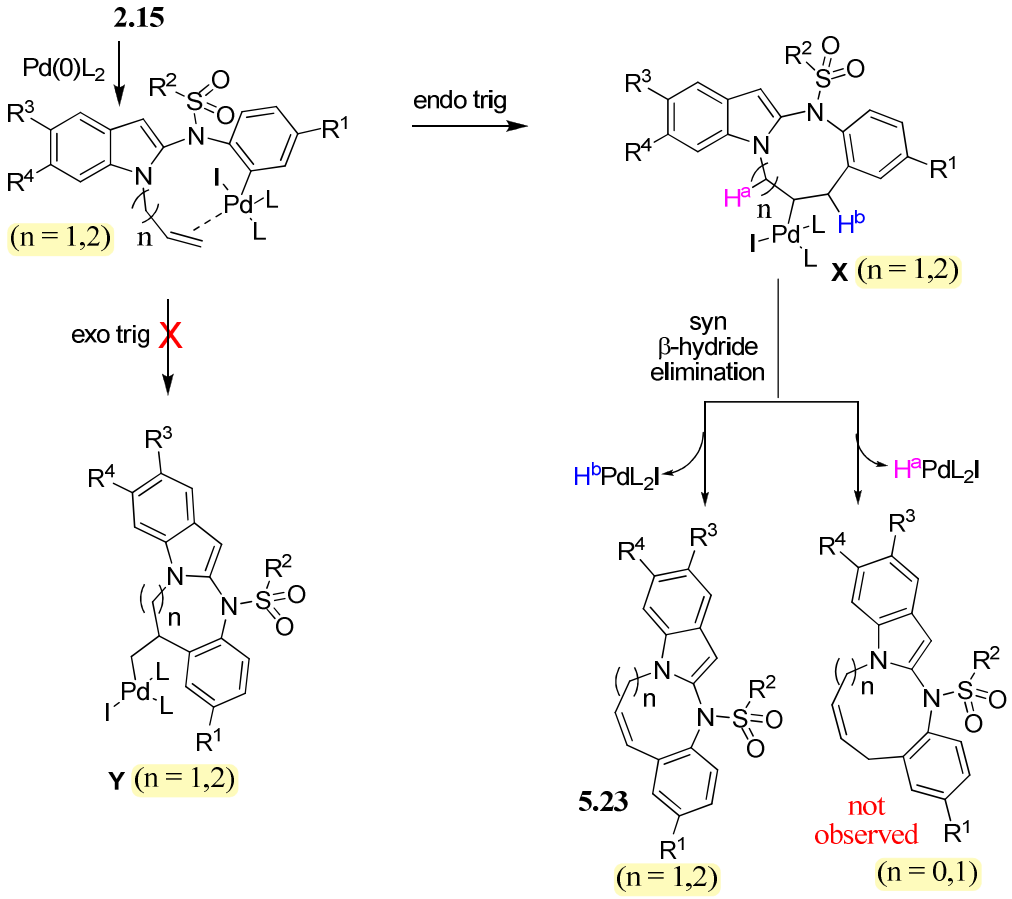
5.23x, 70% (2 h)

[a]All the reactions were performed using **2.15** (0.2 mmol), $PdCl_2(PPh_3)_2$ (5 mol%) and Et_3N (0.6 mmol) in DMF (2 mL) at 110 °C for 2-6 h under N_2.

5.4.4 Proposed mechanism

Based on our experimental observations a proposed reaction mechanism is presented in Scheme 5.12. While the reaction seems to follow a classical Heck coupling pathway[22] *i.e. via* the generation of intermediate **X** (but not **Y**). The regioselectivity of the double bond formation is the key feature of the present process. The higher stability of the resultant conjugated double bond (*i.e.* the styrene moiety) over the isolated one perhaps aided the regioselective elimination of H-Pd species from **X** leading to the product **5.23**. The flexible geometry due to the large ring size of **X**

could be the other reason for affording the *cis* olefin rather than the *trans* product usually observed in the case of intermolecular Heck reaction.[16b]

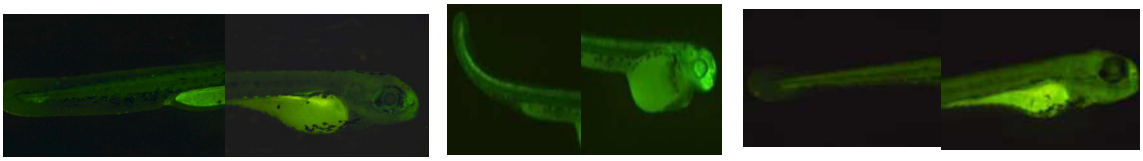


Scheme 5.12 The proposed reaction mechanism leading to **5.23**.

5.5 Pharmacology

All the synthesized compounds were tested for their apoptotic activities initially at 30 µM using Zebrafish embryos. Zebrafish (or *Danio rerio*), a small pet-shop fish, is being explored as a tool for enhancing interdisciplinary studies in biology and chemistry as well as in drug discovery.[23] Indeed, Zebrafish provides an inexpensive, reliable and efficient first-level screening model for testing toxicity, efficacy, and tissue-targeting for a large number of new chemical entities (NCEs). Our continued interest[24] in Zebrafish as a screening model for NCEs prompted us to assess the potential pharmacological effects of the present class of molecules in Zebrafish and/or their embryos. The most active compounds e.g. **5.23p** was tested at 1, 3, 10, and 30 µM along with a standard drug methotrexate. The percentage induction of apoptosis caused by the compound **5.23p** at different concentrations

along with methotrexate is shown in Figure 5.4 and the representative images of embryos are shown in Figure 5.3 The compound **5.23p** showed dose dependent increase in apoptotic activity along with promising activities both at 10 and 30 µM. The EC_{50} and the percentage induction of apoptosis of the compounds were calculated. The EC_{50} of compound **5.23p** was found to be 8.88µM. Since pro-apoptotic chemotherapeutic drugs provide an approach to overcoming the clinical problem of drug resistance[25] hence the present class of molecules may have potential medicinal value.



Control Methotrexate (30 µM) Compound **5.23p** (30 µM)

Figure 5.3 Representative images of the embryos treated with methotrexate and compound **5.23p** assayed for apoptosis.

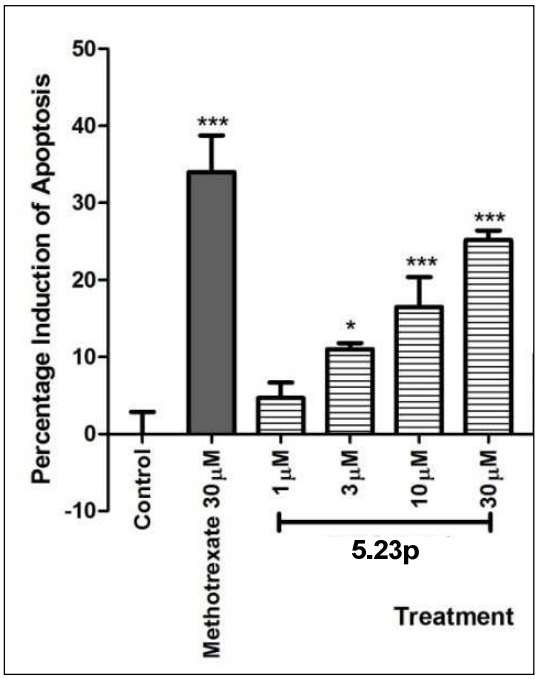


Figure 5.4 The percentage induction of apoptosis caused by compound **5.23p** at different concentrations along with methotrexate.

5.6 Conclusions

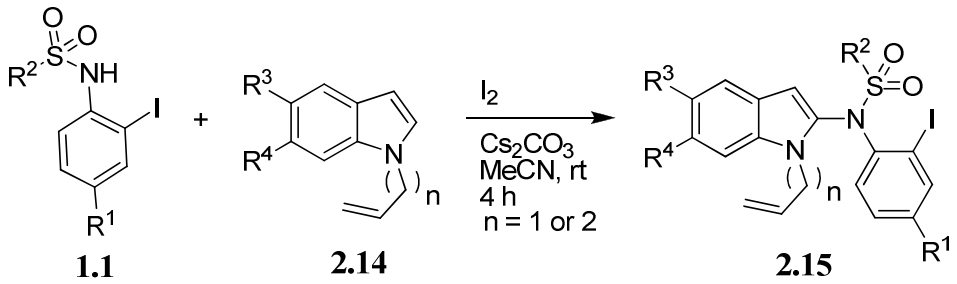
In conclusion, we have described a strategy based on Pd-mediated intramolecular endo-trig ring closure of 1,2-disubstituted indoles leading to indole-1,2-fused 8 and 9 membered rings for the identification of new and potential scaffolds for apoptosis. The methodology involved the use of unactivated olefin and proceeded with regioselective formation of an endocyclic doule bond the geometry of which was assigned as *cis* in case of compounds containing indole-1,2-fused 8 membered rings. A large number of fused indole derivatives were synthesized using this robust methodology and a representative compound showed promising apoptotic properties when tested in zebrafish embryos. As most of the cytotoxic anticancer agents are known to induce apoptosis the present class of indoles seemed to possess potential medicinal value. The strategy presented here therefore could be useful for the design and discovery of potential new drugs.

5.7 Experimental Section

5.7.1 Chemistry

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution by using a 400 MHz spectrometer (VARIAN 400 MR). Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), td (triplet of doublet) and m (multiplet) as well as bs (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer (FT/IR-4200, JASCO). Melting points were determined by using melting point apparatus (Buchi melting point B-540) and are uncorrected. MS spectra were obtained on a mass spectrometer (AGILENT 6430 triple quardrupole LC-MS).

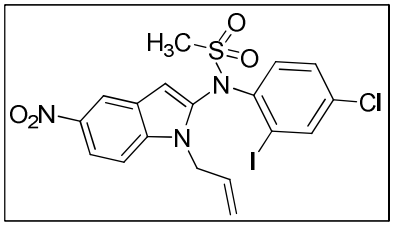
5.7.1.1 General procedure for the preparation of *N*-(1-allyl-5-substituted-1*H*-indol-2-yl)-*N*-(2-iodo-4-substitutedphenyl)alkyl/aryl/heteroarylsulfonamide (2.15)



1.1 **2.14** **2.15**

To a mixture of *N*-(2-iodophenyl)methane/4-methylbenzene/thiophene-2-sulfonamide derivative **1.1** (1.0 mmol)**,** Cs_2CO_3 (1.5 mmol), I_2 (1 mmol) in acetonitrile (2.5 mL) was added indole derivative **2.14** (1.2 mmol). Then the mixture was stirred at room temperature under nitrogen for 4-6 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with a saturation solution of $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate–hexane to give the desired product (**2.15)** with 58-76% yields.

5.7.1.1.1 *N*-(1-Allyl-5-nitro-1*H*-indol-2-yl)-*N*-(4-chloro-2-iodophenyl)methane sulfonamide (2.15co)

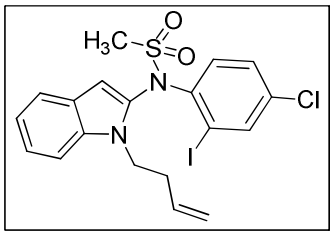


2.15co was prepared via the reaction of **1.1c** with **2.14o** according to the general procedure as mentioned above.

Light yellow solid; yield: 52%; mp: 116-118 °C; R_f (15% EtOAc-*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (d, *J* = 2.4 Hz, 1H), 8.15 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.96 (d, *J* = 2.3 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.40 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.25 (s, 1H), 5.84-5.76 (m, 1H), 5.11-5.07 (m, 3H), 4.78 (d, *J* = 17.3 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.3, 140.6, 139.7,

137.9, 136.7, 135.7, 132.2, 131.5, 129.7, 125.0, 118.6, 118.3, 117.2, 111.0, 103.8, 100.9, 46.7, 39.8; MS (ES mass): *m/z* 529.5 (M-1).

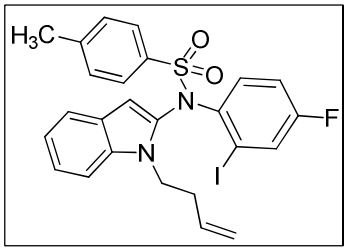
5.7.1.1.2 *N*-(4-Chloro-2-iodophenyl)-*N*-(1-(but-3-enyl)-*1H*-indol-2-yl)methane sulfonamide (2.15cc)



2.15cc was prepared *via* the reaction of **1.1c** with **2.14c** according to the general procedure as mentioned above.

Light red semi solid; yield: 65%; R_f (15% EtOAc-*n*-Hexane) 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, *J* = 2.4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.38-7.35 (m, 1H), 7.33-7.29 (m, 2H), 7.18 (t, *J* = 6.8 Hz, 1H), 7.09 (s, 1H), 5.87-5.77 (m, 1H), 5.13-5.06 (m, 2H), 4.40 (t, *J* = 8.0 Hz, 2H), 3.28 (s, 3H), 2.34-2.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.4, 140.1, 135.0, 134.5, 134.1, 133.5, 131.2, 129.5, 125.9, 123.2, 121.3, 120.4, 117.4, 110.2, 101.6, 101.1, 42.7, 39.3, 34.0; MS (ES mass): *m/z* 500.7 (M+1).

5.7.1.1.3 *N*-(1-(But-3-enyl)-1*H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)-4-methyl benzene-sulfonamide (2.15jc)

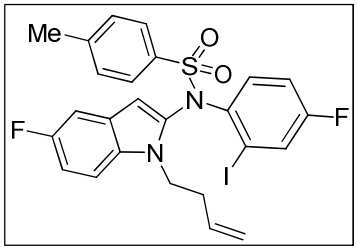


2.15jc was prepared *via* the reaction of **1.1j** with **2.14c** according to the general procedure as mentioned above.

Light brown solid; yield: 55%; mp: 138-140 °C; R_f (15% EtOAc-*n*-Hexane) 0.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (dd, *J* = 7.7, 2.8 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.32-7.27 (m, 4H), 7.25-7.22 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.03-6.98 (m, 1H), 6.25 (s, 1H), 5.91-5.79 (m, 1H), 5.13 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 4.50-4.49 (m, 2H), 2.47 (s, 3H), 2.45-2.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3 (d, C-F *J* = 253.5 Hz), 144.9, 139.1 (d, C-F *J* =

3.6 Hz), 134.6, 134.3, 134.2, 133.8, 131.1 (d, C-F *J* = 37.6 Hz), 129.5 (2C), 129.3 (2C), 128.0 (d, C-F *J* = 24.2 Hz), 125.7, 122.9, 121.0, 120.0, 117.0, 115.9 (d, C-F *J* = 22.1 Hz), 110.4, 101.7 (d, C-F *J* = 8.5 Hz), 101.1, 42.8, 33.9, 21.7; MS (ES mass): *m*/*z* 561.3 (M+1).

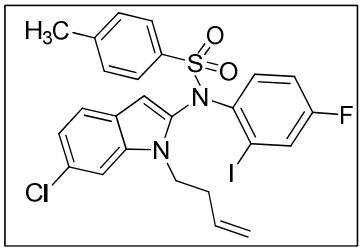
5.7.1.1.4 *N*-(1-(But-3-enyl)-5-fluoro-*1H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)-4-methyl-benzenesulfonamide (2.15je)



2.15je was prepared *via* the reaction of **1.1j** with **2.14e** according to the general procedure as mentioned above.

Light brown solid; yield: 47%; mp: 140-142 °C; R_f (15% EtOAc-*n*-Hexane) 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.25-7.22 (m, 2H), 7.16 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.04-6.97 (m 2H), 6.21 (s, 1H), 5.88-5.78 (m, 1H), 5.12 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 4.52-4.48 (m, 2H), 2.47 (s, 4H), 2.43-2.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4 (d, C-F *J* = 253.7 Hz), 159.1 (d, C-F *J* = 234.3 Hz), 145.0, 138.9 (d, C-F *J* = 3.6 Hz), 135.5, 134.4, 133.7, 131.0 (d, C-F *J* = 8.9 Hz), 130.8, 129.4 (2C), 129.3 (2C), 128.1 (d, C-F *J* = 24.4 Hz), 125.7 (d, C-F *J* = 10.4 Hz), 117.1, 116.0 (d, C-F *J* = 22.0 Hz), 111.6 (d, C-F *J* = 35.4 Hz), 111.4, 105.8 (d, C-F *J* = 23.3 Hz), 101.7 (d, C-F *J* = 8.5 Hz), 101.0 (d, C-F *J* = 4.4 Hz), 43.0, 33.9, 21.7; MS (ES mass): *m*/*z* 578.9 (M+1).

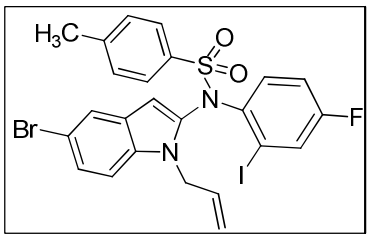
5.7.1.1.5 *N*-(1-(But-3-enyl)-6-chloro-1*H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)-4-methyl-benzenesulfonamide (2.15jg)



2.15jg was prepared *via* the reaction of **1.1j** with **2.14g** according to the general procedure as mentioned above.

Light red solid; yield: 51%; mp: 116-118 °C; R_f (15% EtOAc-*n*-Hexane) 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.29-7.24 (m, 4H), 7.08-7.00 (m, 2H), 6.27 (s, 1H), 5.88-5.77 (m, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 5.06 (d, *J* = 10.2 Hz, 1H), 4.46-4.42 (m, 2H), 2.47 (s, 3H), 2.46-2.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4 (d, C-F *J* = 253.7 Hz), 145.0, 138.8 (d, C-F *J* = 3.4 Hz), 134.9, 134.5, 134.2, 133.7, 131.0 (d, C-F *J* = 8.8 Hz), 129.4 (2C), 129.3 (2C), 128.8, 128.1, 127.9, 124.1, 122.0, 120.8, 117.3, 116.0 (d, C-F *J* = 22.2 Hz), 110.3, 101.3, 42.9, 33.7, 21.7; MS (ES mass): *m/z* 594.8 (M+1).

5.7.1.1.6 *N*-(1-Allyl-5-bromo-1*H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)-4-methyl benzene-sulfonamide (2.15jh)

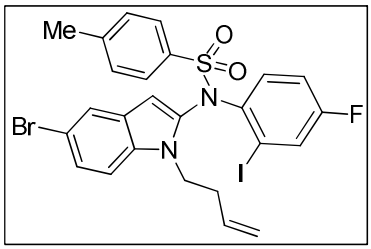


2.15jh was prepared *via* the reaction of **1.1j** with **2.14h** according to the general procedure as mentioned above.

Off white solid; yield: 47%; mp: 146-148 °C; R_f (15% EtOAc-*n*-Hexane) 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 8.0, 2.8 Hz, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 3H), 7.21-7.15 (m, 2H), 7.03-6.98 (m, 1H), 6.22 (s, 1H), 5.90-5.81 (m, 1H), 5.16 (d, *J* = 1.2 Hz, 2H), 5.07 (d, *J* = 11.2 Hz, 1H), 4.84 (d, *J* = 17.2 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5 (d, C-F *J* = 253.8 Hz), 145.1, 138.9 (d, C-F *J* = 3.7 Hz), 135.6, 134.3, 133.7, 133.4, 130.9 (d, C-F *J* = 9.1 Hz), 129.4 (2C), 129.4 (2C), 127.9, 127.7, 127.3, 125.8, 123.3, 116.5, 115.9 (d, C-F *J* = 22.1 Hz), 113.5, 112.7, 100.3, 46.9, 21.7; MS (ES mass): *m/z* 624.7 (M+1).

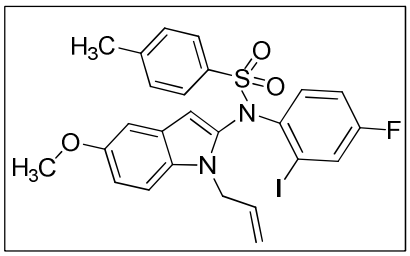
5.7.1.1.7 *N*-(5-Bromo-1-(but-3-enyl)-*1H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)-4-methyl-benzenesulfonamide (2.15ji)

2.15ji was prepared *via* the reaction of **1.1j** with **2.14i** according to the general procedure as mentioned above.



Light brown solid; yield: 51%; mp: 135-137 °C; R_f (15% EtOAc-*n*-Hexane) 0.46; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (dd, *J* = 8.0, 3.2 Hz, 1H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.34-7.29 (m, 3H), 7.26-7.24 (m, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.06-7.01 (m, 1H), 6.21 (s, 1H), 5.87-5.77 (m, 1H), 5.11 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.05 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.51-4.47 (m, 2H), 2.48 (s, 3H), 2.43 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4 (d, C-F *J* = 253.6 Hz), 145.1, 138.8 (d, C-F *J* = 3.4 Hz), 135.3, 134.3, 133.7, 132.9, 131.0 (d, C-F *J* = 8.9 Hz), 129.5 (2C), 129.4 (2C), 128.1 (d, C-F *J* = 24.4 Hz), 127.2, 125.8, 123.5, 117.3, 116.0 (d, C-F *J* = 22.2 Hz), 113.3, 112.0, 101.6, 100.6, 43.0, 33.9, 21.7; MS (ES mass): *m/z* 640.1 (M-+1).

5.7.1.1.8 *N*-(1-Allyl-5-methoxy-1*H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)-4-methylbenzene-sulfonamide (2.15jm)

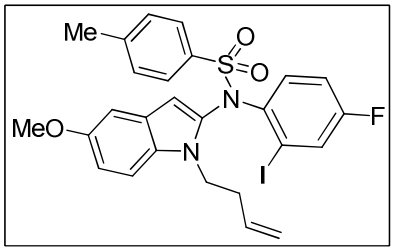


2.15jm was prepared *via* the reaction of **1.1j** with **2.14m** according to the general procedure as mentioned above.

Light red solid; yield: 57%; mp: 154-156 °C; R_f (15% EtOAc-*n*-Hexane) 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 8.0, 3.2 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.23-7.18 (m, 2H), 7.01-6.97 (m, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 6.88 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.21 (s, 1H), 5.91-5.81 (m, 1H), 5.14 (bs, 2H), 5.05 (d, *J* = 10.4 Hz, 1H), 4.87 (d, *J* = 17.4 Hz, 1H), 3.82 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4 (d, C-F *J* = 253.5 Hz), 154.3, 144.8, 139.1 (d, C-F *J* = 3.7 Hz), 134.7, 134.2, 133.9, 131.1 (d, C-F *J* = 8.9 Hz), 129.9, 129.4 (2C), 129.3 (2C), 127.8 (d, C-F *J* = 24.3 Hz), 126.0, 116.3, 115.7 (d, C-F *J* = 22.1 Hz), 113.4,

112.0, 102.3, 101.8 (d, C-F *J* = 8.3 Hz), 100.5, 55.7, 46.8, 21.7; MS (ES mass): *m/z* 577.2 (M+1).

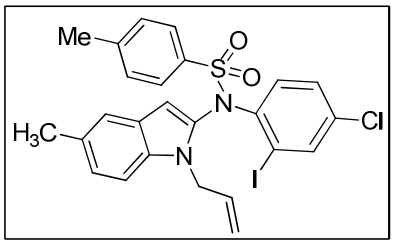
5.7.1.1.9 *N*-(1-(But-3-enyl)-5-methoxy-*1H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)-4-methyl-benzenesulfonamide (2.15jr)



2.15jr was prepared *via* the reaction of **1.1j** with **2.14r** according to the general procedure as mentioned above.

Light brown semi solid; yield: 55%; R_f (15% EtOAc-*n*-Hexane) 0.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.29-7.27 (m, 3H), 7.20 (d, *J* = 9.2 Hz, 1H), 7.03-6.98 (m, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.19 (s, 1H), 5.88-5.77 (m, 1H), 5.11 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.04 (dd, *J* = 10. 4, 1.6 Hz, 1H), 4.52 (t, *J* = 8.0 Hz, 2H), 3.82 (s, 3H), 2.46 (s, 3H), 2.43-2.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4 (d, C-F *J* = 253.4 Hz), 154.3, 144.8, 139.1 (d, C-F *J* = 3.6 Hz), 134.6, 134.4, 133.9, 131.1 (d, C-F *J* = 9.1 Hz), 129.5 (2C), 129.4, 129.3, 128.0 (d, C-F *J* = 24.4 Hz), 127.7, 127.4, 125.9, 117.0, 115.9 (d, C-F *J* = 22.0 Hz), 113.5, 111.4, 102.3, 100.7, 55.7, 42.9, 34.1, 21.7; MS (ES mass): *m/z* 574.8 (M-Me).

5.7.1.1.10 *N*-(1-Allyl-5-methyl-1*H*-indol-2-yl)-*N*-(4-chloro-2-iodophenyl)-4-methyl benzene-sulfonamide (2.15kj)

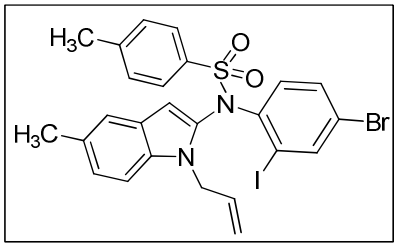


2.15kj was prepared *via* the reaction of **1.1k** with **2.14j** according to the general procedure as mentioned above.

Off white solid; yield: 52%; mp: 136-138 °C; R_f (15% EtOAc-*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, *J* = 2.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.41

(dd, *J* = 8.8, 2.4 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 3H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.18 (s, 1H), 5.92-5.82 (m, 1H), 5.15 (s, 2H), 5.05 (d, *J* = 10.4 Hz, 1H), 4.84 (d, *J* = 16.0 Hz, 1H), 2.49 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.9, 143.0, 142.1, 134.5, 134.1, 133.9, 131.9, 131.1, 129.4 (2C), 129.3 (2C), 125.8, 124.6, 122.9, 120.4, 116.1, 115.9, 115.6, 110.8, 102.5, 100.5, 46.6, 21.7, 21.4; MS (ES mass): *m*/*z* 577.4 (M+1).

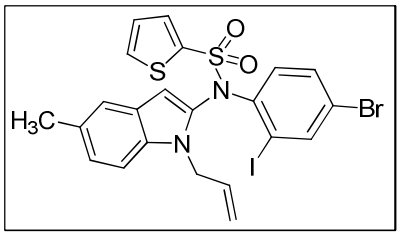
5.7.1.1.11 *N*-(1-Allyl-5-methyl-1*H*-indol-2-yl)-*N*-(4-bromo-2-iodophenyl)-4-methylbenzene-sulfonamide (2.15sj)



2.15sj was prepared *via* the reaction of **1.1s** with **2.14j** according to the general procedure as mentioned above.

Light brown solid; yield: 55%; mp: 108-110 °C; R_f (15% EtOAc-*n*-Hexane) 0.46; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, *J* = 2.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.41 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.31-7.29 (m, 3H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.07-7.05 (m, 1H), 6.18 (s, 1H), 5.92-5.82 (m, 1H), 5.15 (bs, 2H), 5.05 (d, *J* = 10.3 Hz, 1H), 4.85 (d, *J* = 17.2 Hz, 1H), 2.49 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.9, 143.0, 142.1, 134.1, 133.9, 133.1, 131.9, 131.0, 129.4 (2C), 129.3 (2C), 125.9, 124.6, 124.5, 122.9, 120.4, 116.1, 115.9, 110.8, 102.5, 100.5, 46.6, 21.7, 21.4; MS (ES mass): *m*/*z* 620.5 (M+1).

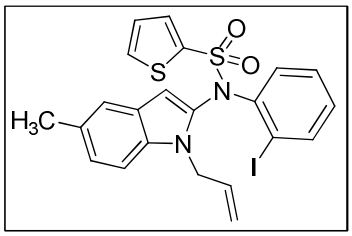
5.7.1.1.12 *N*-(1-Allyl-5-methyl-1*H*-indol-2-yl)-*N*-(4-bromo-2-iodophenyl) thiophene-2-sulfonamide (2.15qj)



2.15qj was prepared *via* the reaction of **1.1q** with **2.14j** according to the general procedure as mentioned above.

Light brown solid; Yield: 53%; mp: 132-134 °C; R_f (15% EtOAc-*n*-Hexane) 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J* = 2.2 Hz, 1H), 7.71-7.70 (m, 1H), 7.52 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.42 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.32 (s, 1H), 7.22 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.12 (t, *J* = 4.8 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.33 (s, 1H), 5.89-5.79 (m, 1H), 5.12 (bs, 2H), 5.03 (d, *J* = 10.3 Hz, 1H), 4.82 (d, *J* = 17.2 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.1, 141.6, 136.9, 135.5, 134.0, 133.9, 133.6, 133.2, 132.0, 130.9, 129.6, 127.4, 125.9, 124.8, 123.2, 120.5, 116.2, 110.8, 102.4, 100.6, 46.6, 21.4; IR (KBr, cm^{-1}): 3088, 2914, 1563, 1458, 1365, 1162; MS (ES mass): *m/z* 614.1 (M+1).

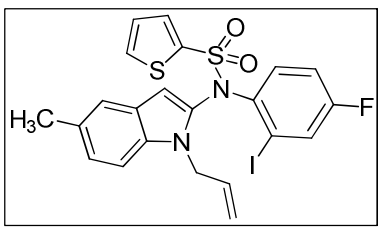
5.7.1.1.13 *N*-(1-Allyl-5-methyl-1*H*-indol-2-yl)-*N*-(2-iodophenyl)thiophene-2-sulfonamide (2.15nj)



2.15nj was prepared *via* the reaction of **1.1n** with **2.14j** according to the general procedure as mentioned above.

Off white solid; yield: 52%; mp: 108-110 °C; R_f (15% EtOAc-*n*-Hexane) 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 4.8 Hz, 1H), 7.54 (d, *J* = 4.0 Hz, 1H), 7.38 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.33-7.29 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.13 (t, *J* = 4.4 Hz, 1H), 7.06-7.01 (m, 2H), 6.39 (s, 1H), 5.89-5.80 (m, 1H), 5.17 (s, 2H), 5.03 (d, *J* = 10.4 Hz, 1H), 4.87 (d, *J* = 17.2 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.4, 141.2, 137.3, 135.3, 134.1, 134.0, 133.8, 133.2, 130.2, 130.1, 129.4, 128.9, 127.3, 125.9, 124.6, 120.5, 116.2, 110.8, 101.5, 100.6, 46.8, 21.4; MS (ES mass): *m/z* 534.5 (M+1).

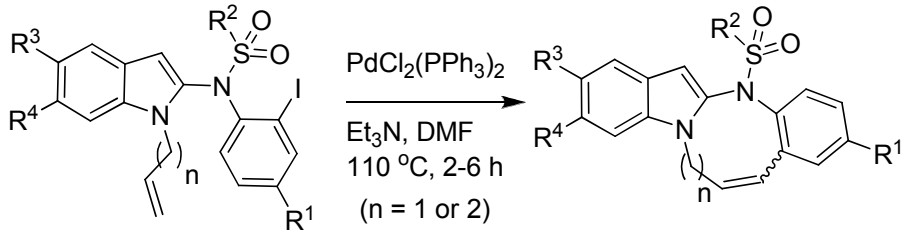
5.7.1.1.14 *N*-(1-Allyl-5-methyl-1*H*-indol-2-yl)-*N*-(4-fluoro-2-iodophenyl)-thiophene-2-sulfonamide (2.15oj)



2.15oj was prepared *via* the reaction of **1.1o** with **2.14j** according to the general procedure as mentioned above.

Light pink solid; yield: 51%; mp: 170-172 °C; R_f (15% EtOAc-*n*-Hexane) 0.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74-7.73 (m, 1H), 7.68 (dd, *J* = 8.0, 2.8 Hz, 1H), 7.56-7.55 (m, 1H), 7.38-7.35 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.17-7.15 (m, 1H), 7.09-7.07 (m, 1H), 7.06-7.03 (m, 1H), 6.39 (s, 1H), 5.93-5.83 (m, 1H), 5.17 (s, 2H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.87 (d, *J* = 17.6 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5 (d, C-F *J* = 253.6 Hz), 138.8 (d, C-F *J* = 3.4 Hz), 137.0, 135.4, 134.9, 134.1, 134.0, 133.9, 131.0 (d, C-F *J* = 9.0 Hz), 128.0, 127.8, 127.4, 125.7, 123.0, 120.9, 120.2, 116.3, 116.0 (d, C-F *J* = 22.2 Hz), 111.1, 100.9, 46.7, 21.7; MS (ES mass): *m/z* 552.8 (M+1).

5.7.1.2 General procedure for preparation of indole-1,2-fused 8 and 9 membered rings (5.23):



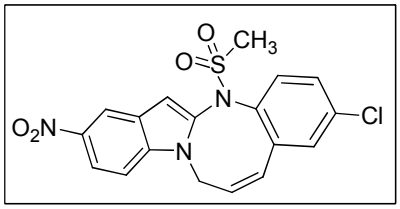
2.15 **5.23**

n = 1 (8 membered)
n = 2 (9 membered)

A mixture of *N*-(1-allyl-5-substituted-1*H*-indol-2-yl)-*N*-(2-iodo-4-substitutedphenyl) sulfonamide **2.14**, (0.2 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol%), Et_3N (0.4 mmol) in anhydrous DMF (2 mL) was stirred at 110 °C for 2-6 h under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (20 mL) and passed through celite. The filtrate was washed with water (2 x 10 mL), followed by brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by column chromatography over silica gel using ethyl acetate-hexane to give the desired product **5.23**.

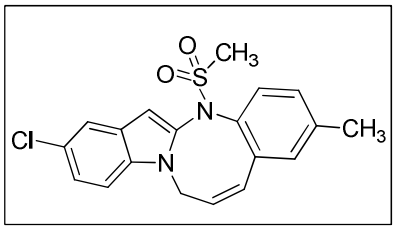
5.7.1.2.1 Compound 5.23a

5.23a was prepared from **2.15co** according to the general procedure as presented above.



Light yellow solid; yield: 34%; mp: 168-170 °C; R_f (20% EtOAc-*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, *J* = 2.0 Hz, 1H), 8.15 (dd, *J* = 9.2, 2.1 Hz, 1H), 7.50-7.46 (m, 1H), 7.41-7.35 (m, 3H), 7.04 (d, *J* = 10.8 Hz, 1H), 6.96 (s, 1H), 6.30-6.23 (m, 1H), 4.93 (dd, *J* = 14.8, 6.8 Hz, 1H), 4.03 (dd, *J* = 14.5, 8.4 Hz, 1H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.1, 139.7, 137.7, 135.9, 135.7, 134.0, 133.9, 131.5, 130.0, 129.5, 125.7, 125.6, 118.1, 118.0, 109.3, 101.1, 40.7, 29.6; MS (ES mass): *m*/*z* 404.2(M+1).

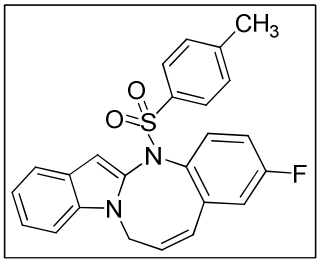
5.7.1.2.2 Compound 5.23b



5.23b was prepared from **2.15ef** according to the general procedure as presented above.

Light brown solid; yield: 45%; mp: 120-122 °C; R_f (20% EtOAc-*n*-Hexane) 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (s, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 5.6 Hz, 2H), 7.02 (d, 1H), 6.74 (s, 1H), 6.22-6.16 (m, 1H), 4.82(dd, *J* = 14.4, 6.8 Hz, 1H), 3.94 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.07 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.6, 137.8, 134.8, 134.5, 133.4, 133.2, 130.4, 129.9, 129.8, 127.6, 125.8, 124.9, 122.5, 120.3, 110.2, 98.6, 41.6, 40.4, 21.1; MS (ES mass): *m*/*z* 373.3 (M+1).

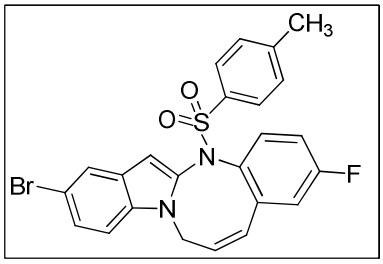
5.7.1.2.3 Compound 5.23c



5.23c was prepared from **2.15jb** according to the general procedure as presented above.

Off white solid; yield: 65%; mp: 151-153 °C; R_f (20% EtOAc-*n*-Hexane) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 8.4 Hz, 2H), 7.53 (t, *J* = 6.6 Hz, 1H), 7.33-7.25 (m, 5H), 7.23-7.20 (m, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 11.4 Hz, 1H), 6.46 (s, 1H), 6.04-5.98 (m, 1H), 4.87 (dd, *J* = 15.6, 5.7 Hz, 1H), 4.05 (dd, *J* = 15.5, 8.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3 (d, C-F *J* = 248.9 Hz), 144.0, 140.4 (d, C-F *J* = 9 Hz) 137.2, 135.0, 134.0, 133.2 (d, C-F *J* = 3.3 Hz), 131.7, 131.4 (d, C-F *J* = 9.2 Hz), 129.5 (2C), 128.1 (2C), 127.7, 126.8, 126.6, 122.4, 121.0 (d, C-F *J* = 85.4 Hz), 116.6 (d, C-F *J* = 22.6 Hz), 116.2 (d, C-F *J* = 22.6 Hz), 109.3, 99.6, 41.7, 21.6; IR (KBr, cm^{-1}): 3064, 2918, 2885, 1578, 1402, 1350, 1162; MS (ES mass): *m/z* 419.2 (M+1).

5.7.1.2.4 Compound 5.23d

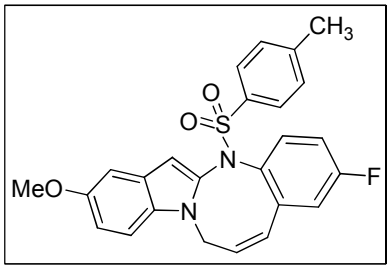


5.23d was prepared from **2.15jh** according to the general procedure as presented above.

White solid; yield: 65%; mp: 155-157 °C; R_f (15% EtOAc-*n*-Hexane) 0.23;^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66-7.64 (m, 3H), 7.31-7.27 (m, 4H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.03-6.99 (m, 2H), 6.70 (d, *J* = 11.6 Hz, 1H), 6.42 (s, 1H), 6.04-5.97 (m, 1H), 4.81 (dd, *J* = 15.6, 6.4 Hz, 1H), 3.98 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4 (d, C-F *J* = 249.2 Hz), 144.2, 140.5 (d, C-F *J* = 8.9 Hz), 136.9, 134.8, 133.6, 132.7 (d, C-F *J* = 3.3 Hz), 132.3, 131.6 (d, C-F *J* = 9.2 Hz), 129.5 (2C), 128.1, 128.0 (2C), 126.2, 125.2, 123.4, 116.5 (d, C-F *J* = 6.1 Hz), 116.2 (d, C-F *J* = 6.0 Hz), 113.3, 110.7, 98.8, 41.7, 21.6; IR (KBr, cm^{-1}): 2923, 2871, 1582, 1460, 1346, 1161; MS (ES mass): *m/z* 496.3 (M+1).

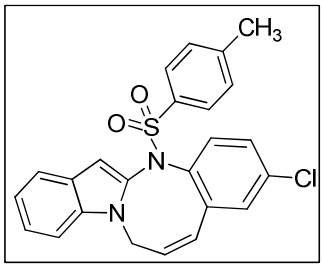
5.7.1.2.5 Compound 5.23e

5.23e was prepared from **2.15jm** according to the general procedure as presented above.



Off white solid; yield: 64%; mp: 164-166 °C; R_f (20% EtOAc-*n*-Hexane) 0.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 3H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.00-6.98 (m, 3H), 6.87 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.65 (d, *J* = 11.2 Hz, 1H), 6.41 (s, 1H), 6.02-5.96 (m, 1H), 4.79 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.98 (dd, *J* = 15.2, 8.0 Hz, 1H), 3.82 (s, 3H) 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3 (d, C-F *J* = 248.7 Hz), 154.3, 144.0, 137.3, 134.3, 133.1 (d, C-F *J* = 3.0 Hz), 131.7, 131.5 (d, C-F *J* = 9.3 Hz), 130.3, 129.5 (2C), 128.1 (2C), 127.7, 126.9, 126.7, 116.5 (d, C-F *J* = 22.8 Hz), 116.2 (d, C-F *J* = 22.6 Hz), 112.6, 110.2, 102.6, 99.4, 55.8, 41.9, 21.6; MS (ES mass): *m/z* 449.2 (M+1).

5.7.1.2.6 Compound 5.23f

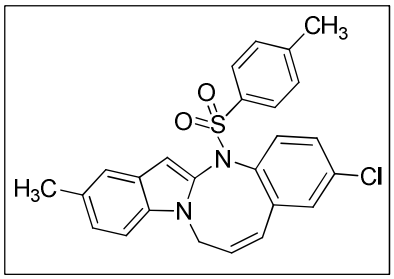


5.23f was prepared from **2.15kb** according to the general procedure as presented above.

Off white solid; yield: 54%; mp: 119-121 °C; R_f (20% EtOAc-*n*-Hexane) 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68-7.64 (m, 3H), 7.34-7.29 (m, 3H), 7.28-7.27 (m, 2H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.03-6.99 (m, 2H), 6.70 (d, *J* = 11.0 Hz, 1H), 6.42 (s, 1H), 6.02-5.95 (m, 1H), 4.83 (dd, *J* = 15.6, 6.4 Hz, 1H), 3.95 (dd, *J* = 15.4, 8.2 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.2, 140.5, 136.9, 134.8, 133.5, 132.7, 132.3, 131.6, 131.5, 129.5 (2C), 128.1, 128.0 (2C), 126.1, 125.1, 123.4, 116.4, 116.2, 113.2, 110.7, 98.8, 41.7, 21.6; MS (ES mass): *m/z* 434.9 (M+1).

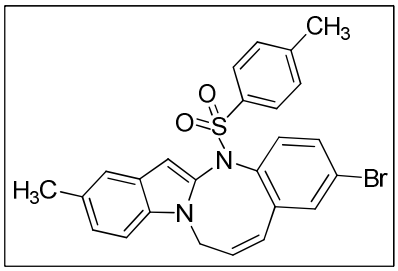
5.7.1.2.7 Compound 5.23g

5.23g was prepared from **2.15kj** according to the general procedure as presented above.



White solid; yield: 52%; mp: 152-154 °C; R_f (20% EtOAc-*n*-Hexane) 0.37; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.40-7.39 (m, 2H), 7.37-7.36 (m, 2H), 7.32-7.31 (m, 2H), 7.24 (d, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 11.5 Hz, 1H), 6.45 (s, 1H), 6.12-6.05 (m, 1H), 4.91(dd, *J* = 16.4, 5.6 Hz, 1H), 4.17-4.11 (m, 1H), 2.55 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.0, 139.6, 137.4, 134.7, 133.9, 133.5, 131.0, 130.8, 129.9, 129.6, 129.5 (2C), 129.2, 128.1 (2C), 127.8, 127.2, 124.0, 120.7, 117.9, 108.9, 99.4, 41.9, 21.6, 21.3; MS (ES mass): *m*/*z* 448.9 (M+1).

5.7.1.2.8 Compound 5.23h

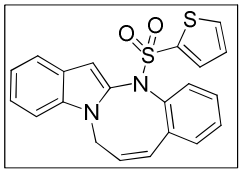


5.23h was prepared from **2.15sj** according to the general procedure as presented above.

Off white solid; yield: 52%; mp: 150-152 °C; R_f (25% EtOAc-*n*-Hexane) 0.44; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 3.8 Hz, 2H), 7.31-7.29 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.6 Hz, 2H), 6.62 (d, *J* = 11.5 Hz, 1H), 6.37 (s, 1H), 6.04-5.96 (m, 1H), 4.83 (dd, *J* = 15.6, 5.6 Hz, 1H), 4.05 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.2, 136.9, 134.8, 133.5, 132.3, 131.5, 131.2, 129.6, 129.5 (2C), 129.4, 128.0 (2C), 126.1, 125.1, 123.4, 116.4, 116.2, 116.1, 113.2, 110.7, 98.8, 41.7, 29.6, 21.5; MS (ES mass): *m*/*z* 492.8 (M+1).

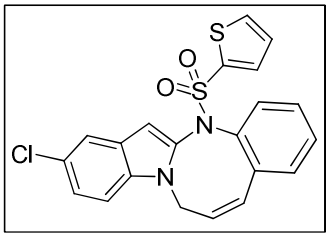
5.7.1.2.9 Compound 5.23i

5.23i was prepared from **2.15nb** according to the general procedure as presented above.



White solid; yield: 61%; mp: 156-158 °C; R_f (15% EtOAc-*n*-Hexane) 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.57-7.55 (m, 2H), 7.39-7.35 (m, 2H), 7.33 (s, 1H), 7.32-7.28 (m, 2H), 7.25-7.22 (m, 1H), 7.11-7.09 (m, 2H), 6.79 (d, *J* = 11.2 Hz, 1H), 6.62 (s, 1H), 6.04-5.97 (m, 1H), 4.92-4.87 (m, 1H), 4.07 (dd, *J* = 15.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.6, 138.1, 136.8, 135.1, 133.7 (2C), 132.7, 132.6, 130.0, 129.5, 129.3, 129.2, 127.1, 126.6, 125.8, 122.4, 121.1, 120.2, 109.3, 99.7, 41.7; IR (KBr, cm^{-1}): 3097, 2897, 1511, 1439, 1375, 1173; MS (ES mass): *m/z* 392.5 (M+1).

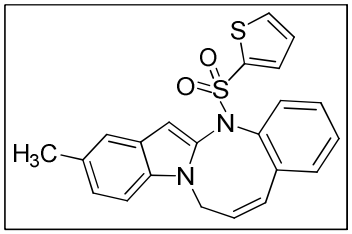
5.7.1.2.10 Compound 5.23j



5.23j was prepared from **2.15nf** according to the general procedure as presented above.

Off white solid; yield: 63%; mp: 152-154 °C; R_f (20% EtOAc-*n*-Hexane) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.56 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.53 (d, *J* = 1.2 Hz, 1H), 7.39 (d, *J* = 1.2 Hz, 1H), 7.37 (s, 1H), 7.35-7.32 (m, 2H), 7.19-7.16 (m, 2H), 7.11-7.09 (m, 1H), 6.82 (d, *J* = 11.4 Hz, 1H), 6.57 (s, 1H), 6.02-5.96 (m, 1H), 4.86-4.80 (m, 1H), 4.03-3.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.2, 140.5, 137.0, 135.5, 135.2, 134.9, 134.1, 133.9, 133.8, 130.6, 129.0, 127.4, 125.7, 123.1, 121.0, 120.2, 116.3, 111.1, 101.8, 101.1, 46.6; IR (KBr, cm^{-1}): 3100, 2924, 2875, 1554, 1457, 1352, 1161; MS (ES mass): *m/z* 427.4 (M+1).

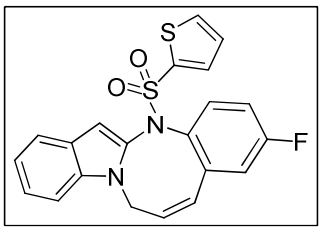
5.7.1.2.11 Compound 5.23k



5.23k was prepared from **2.15nj** according to the general procedure as presented above.

Off white solid; yield: 55%; mp: 158-160 °C; R_f (25% EtOAc-*n*-Hexane) 0.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 5.1 Hz, 1H), 7.57 (d, *J* = 3.0, 1H), 7.40-7.31 (m, 5H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.10-7.03 (m, 2H), 6.78 (d, *J* = 11.6 Hz, 1H), 6.54 (s, 1H), 6.02-5.95 (m, 1H), 4.83 (dd, *J* = 14.8, 6.4 Hz, 1H), 4.04 (dd, *J* = 15.2, 8.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.0, 136.9, 133.6, 133.5, 133.3, 132.5, 132.4, 130.0, 129.5, 129.4, 129.2, 129.0, 128.5, 126.9, 126.8, 125.8, 123.9, 120.7, 108.9, 99.3, 41.8, 21.2; IR (KBr, cm^{-1}): 2922, 2853, 1547, 1482, 1360, 1163; MS (ES mass): *m*/*z* 406.4 (M+1).

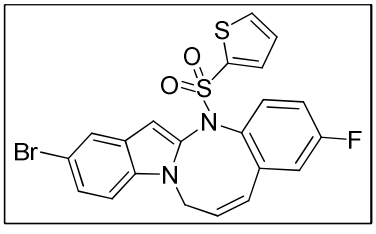
5.7.1.2.12 Compound 5.23l



5.23l was prepared from **2.15ob** according to the general procedure as presented above.

Light brown solid; yield: 70%; mp: 120-122 °C; R_f (20% EtOAc-*n*-Hexane) 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.60 (m, 2H), 7.40-7.37 (m, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.25 (dd, *J* = 11.8, 4.5 Hz, 1H), 7.16-7.10 (m, 2H), 7.08-7.00 (m, 2H), 6.76 (d, *J* = 11.3 Hz, 1H), 6.63 (s, 1H), 6.10-6.02 (m, 1H), 4.90 (dd, *J* = 15.3, 6.3 Hz, 1H), 4.06 (dd, *J* = 15.3, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3 (d, C-F *J* = 249.0 Hz), 140.4 (d, C-F *J* = 8.9 Hz), 133.6, 133.5, 133.4 (d, C-F *J* = 5.6 Hz), 132.9, 132.7, 131.6, 131.5 (d, C-F *J* = 9.2 Hz), 129.5, 127.3, 127.0 (d, C-F *J* = 30.4 Hz), 126.8, 124.1, 120.7, 118.1, 116.5 (d, C-F *J* = 21.2 Hz), 116.0, 108.9, 99.5, 41.7; IR (KBr, cm^{-1}): 3099, 2918, 1576, 1462, 1358, 1160; MS (ES mass): *m*/*z* 410.4 (M+1).

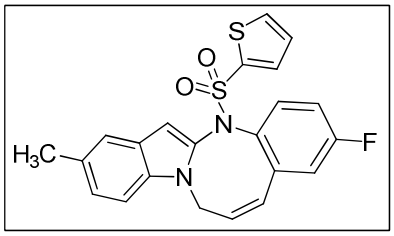
5.7.1.2.13 Compound 5.23m



5.23m was prepared from **2.15oh** according to the general procedure as presented above.

Off white solid; yield: 60%; mp: 168-170 °C; R_f (20% EtOAc-*n*-Hexane) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (dd, *J* = 15.1, 3.3 Hz, 2H), 7.61 (d, *J* = 4.0 Hz, 1H), 7.44-7.41 (m, 1H), 7.38 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.17 (dd, *J* = 5.7, 3.0 Hz, 1H), 7.13-7.08 (m, 2H), 6.83 (d, *J* = 11.0 Hz, 1H), 6.63 (s, 1H), 6.11-6.05 (m, 1H), 4.88 (dd, *J* = 14.9, 6.0 Hz, 1H), 4.04 (dd, *J* = 15.1, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5 (d, C-F *J* = 249.5 Hz), 140.5 (d, C-F *J* = 9.0 Hz), 140.0, 134.2, 133.9, 133.6, 133.0, 132.4 (d, C-F *J* = 2.5 Hz), 131.7(d, C-F *J* = 9.3 Hz), 128.0 127.2, 126.0, 125.3, 123.5, 116.5 (d, C-F *J* = 8.0 Hz), 116.3 (d, C-F *J* = 8.3 Hz), 113.3, 110.7, 109.9, 99.1, 41.6; MS (ES mass): *m*/*z* 490.8 (M+1).

5.7.1.2.14 Compound 5.23n

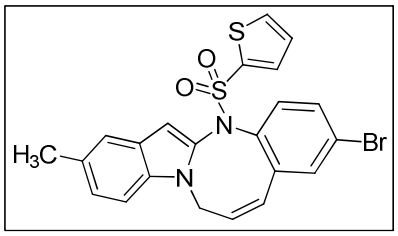


5.23n was prepared from **2.15oj** according to the general procedure as presented above.

Off white solid; yield: 63%; mp: 168-170 °C; R_f (20% EtOAc-*n*-Hexane) 0.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 4.8 Hz, 1H), 7.55 (d, *J* = 2.7 Hz, 1H), 7.36 (d, *J* = 8.0Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.11-6.99 (m, 4H), 6.73 (d, *J* = 11.2 Hz, 1H), 6.54 (s, 1H), 6.06-5.98 (m, 1H), 4.85-4.80 (m, 1H), 4.03-3.97 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3 (d, C-F *J* = 249.0 Hz), 140.4 (d, C-F *J* = 8.9 Hz), 133.6, 133.5, 133.4 (d, C-F *J* = 5.6 Hz), 132.9, 132.7, 131.6, 131.5 (d, C-F *J* = 9.2 Hz), 129.5, 127.3, 127.0 (d, C-F *J* = 30.4 Hz), 126.8, 124.1, 120.7, 118.1, 116.5 (d, C-F *J* = 21.2 Hz), 116.0, 108.9, 99.5, 41.7, 21.2; IR (KBr, cm^{-1}): 2933, 2885, 1532, 1457, 1324, 1158; MS (ES mass): *m*/*z* 425.2 (M+1).

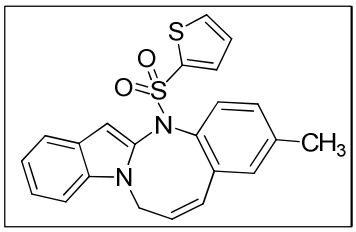
5.7.1.2.15 Compound 5.23o

5.23o was prepared from **2.15qj** according to the general procedure as presented above.



Off white solid; yield: 51%; mp: 148-150 °C; R_f (20% EtOAc-*n*-Hexane) 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.53-7.54 (m, 1H), 7.49-7.43 (m, 2H), 7.35 (d, *J* = 9.2 Hz, 1H), 7.25 (d, *J* = 9.5 Hz, 1H), 7.16 (t, *J* = 8.4 Hz, 1H), 7.11-7.09 (m, 1H), 7.06-7.03 (m, 1H), 6.69 (d, *J* = 11.4 Hz, 1H), 6.51 (s, 1H), 6.04-5.98 (m, 1H), 4.86-4.79 (m, 1H), 4.04 (dd, *J* = 15.4, 8.2 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.3, 139.9, 135.9, 133.8, 133.5, 133.1, 132.9, 132.3, 132.1, 131.3, 313.1, 129.6, 127.4, 127.1, 126.7, 124.2, 123.0, 120.8, 109.0, 99.6, 41.8, 29.7; IR (KBr, cm^{-1}): 3097, 2925, 2858, 1550, 1482, 1362, 1163; MS (ES mass): *m*/*z* 486.3 (M+1).

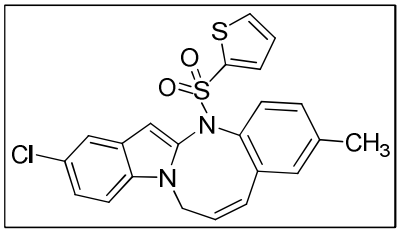
5.7.1.2.16 Compound 5.23p



5.23p was prepared from **2.15rb** according to the general procedure as presented above.

Off white solid; yield: 58%; mp: 148-150 °C; R_f (20% EtOAc-*n*-Hexane) 0.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.57-7.56 (m, 1H), 7.55 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.26-7.25 (m, 1H), 7.22 (t, *J* = 6.8 Hz, 1H), 7.12 (d, *J* = 5.4 Hz, 2H), 7.10-7.07 (m, 2H), 6.76 (d, *J* = 11.2 Hz, 1H), 6.62 (s, 1H), 6.01-5.94 (m, 1H), 4.86 (dd, *J* = 15.2, 6.1 Hz, 1H), 4.03 (dd, *J* = 15.3, 8.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.7, 139.3, 137.8, 135.0, 134.1, 133.8, 133.6, 132.9, 132.6, 130.4, 130.0, 129.3, 127.0, 126.6, 125.5, 122.3, 121.1, 120.1, 109.9, 99.5, 41.6, 21.2; IR (KBr, cm^{-1}): 3092, 3038, 2930, 1546, 1459, 1354; MS (ES mass): *m*/*z* 406.4 (M+1).

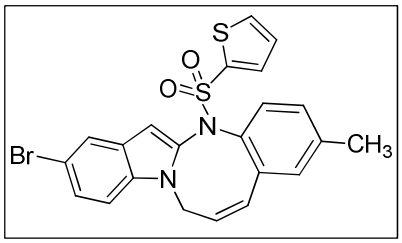
5.7.1.2.17 Compound 5.23q



5.23q was prepared from **2.15rf** according to the general procedure as presented above.

Light brown solid; yield: 62%; mp: 120-122 °C; R_f (20% EtOAc-*n*-Hexane) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 3.9 Hz, 1H), 7.72 (d, *J* = 4.8 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.44-7.41 (m, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 1.9 Hz, 1H), 7.32 (d, *J* = 5.6 Hz, 2H), 7.27 (t, *J* = 4.0 Hz, 1H), 6.97 (d, *J* = 11.2 Hz, 1H), 6.75 (s, 1H), 6.18-6.11 (m, 1H), 4.97 (dd, *J* = 15.2, 6.8 Hz, 1H), 4.18-4.12 (m, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.5, 139.5, 137.9, 134.7, 133.7, 133.6, 133.4, 133.3, 132.7, 130.3, 130.1, 129.4, 127.4, 127.1, 125.7, 124.9, 122.5, 120.3, 110.3, 98.9, 41.7, 21.2; IR (KBr, cm^{-1}): 2922, 2859, 1734, 1460, 1165; MS (ES mass): *m*/*z* 440.3 (M+1).

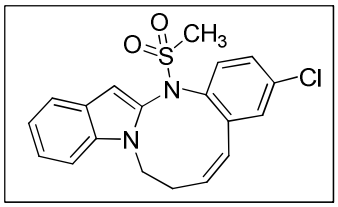
5.7.1.2.18 Compound 5.23r



5.23r was prepared from **2.15rh** according to the general procedure as presented above.

Light brown solid; yield: 54%; mp: 115-117 °C; R_f (20% EtOAc-*n*-Hexane) 0.37; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, *J* = 1.6 Hz, 1H), 7.64 (d, *J* = 4.9 Hz, 1H), 7.54 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.31-7.27 (m, 2H), 7.17-7.14 (m, 3H), 7.09 (t, *J* = 4.8 Hz, 1H), 6.80 (d, *J* = 11.2 Hz, 1H), 6.58 (s, 1H), 6.00-5.93 (m, 1H), 4.81 (dd, *J* = 15.2, 6.4 Hz, 1H), 3.98 (dd, *J* = 15.6, 8.3 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.4, 139.6, 137.9, 134.6, 133.7 (2C), 133.6, 133.4, 132.8, 130.3, 130.2, 129.4, 128.1, 127.1, 125.1, 124.9, 123.4, 113.2, 110.7, 98.8, 41.7, 21.2; IR (KBr, cm^{-1}): 3100, 2924, 2875, 1554, 1457, 1352, 1161; MS (ES mass): *m*/*z* 484.2 (M+1).

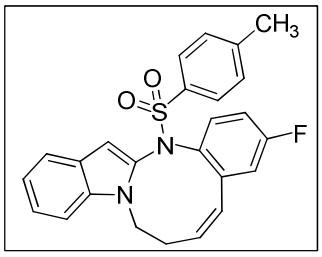
5.7.1.2.19 Compound 5.23s



5.23s was prepared from **2.15cc** according to the general procedure as presented above.

Off white solid; yield: 54%; mp: 240-242 °C; R_f (20% EtOAc-*n*-Hexane) 0.32; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.31-7.28 (m, 2H), 7.26-7.24 (m, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.63 (s, 1H), 5.80-5.69 (m, 2H), 5.63 (dd, *J* = 14.6, 10.2 Hz, 1H), 4.76-4.71 (m, 1H), 4.54 (dd, *J* = 14.6, 5.6 Hz, 1H), 3.27 (s, 3H), 3.01 (dd, *J* = 13.2, 6.4 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.5, 138.2, 135.3, 134.3, 134.1, 132.7, 130.9, 130.0, 128.1, 125.7, 125.1, 123.3, 121.1, 120.2, 109.6, 99.5, 37.9, 37.4, 30.7; MS (ES mass): *m/z* 372.9.

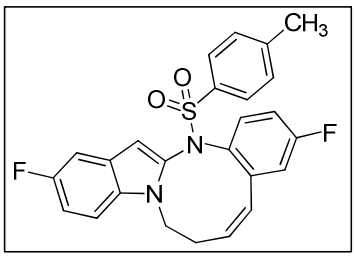
5.7.1.2.20 Compound 5.23t



5.23t was prepared from **2.15jc** according to the general procedure as presented above.

Light brown solid; yield: 70%; mp: 170-172 °C; R_f (15% EtOAc-*n*-Hexane) 0.37; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.28-7.27 (m, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.01 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.82-6.81 (m, 2H), 6.12 (s, 1H), 5.78-5.70 (m, 3H), 4.92-4.87 (m, 1H), 4.59 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.05 (dd, *J* = 12.3, 6.0 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5 (d, C-F *J* = 250.1 Hz), 144.5, 135.8 (d, C-F *J* = 3.3 Hz), 135.0, 134.7, 134.1, 132.7, 130.9 (d, C-F *J* = 10.0 Hz), 130.3, 129.4 (2C), 128.9 (2C), 125.7, 125.1, 122.9, 121.0, 119.9, 117.3 (d, C-F *J* = 22.2 Hz), 114.3 (d, C-F *J* = 22.5 Hz), 109.5, 99.5, 37.9, 30.9, 21.6; MS (ES mass): *m/z* 432.6 (M+1).

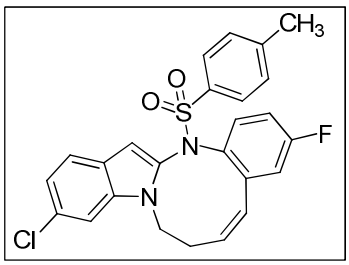
5.7.1.2.21 Compound 5.23u



5.23u was prepared from **2.15je** according to the general procedure as presented above.

Off white solid; yield: 61%; mp: 204-206 °C; R_f (15% EtOAc-*n*-Hexane) 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.32 (dd, *J* = 8.8, 4.4 Hz, 1H), 7.14 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.03-6.98 (m, 2H), 6.79 (d, *J* = 6.8 Hz, 2H), 6.08 (s, 1H), 5.76-5.69 (m, 3H), 4.90-4.84 (m, 1H), 4.56-4.49 (m, 1H), 3.04 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5 (d, C-F *J* = 249.0 Hz), 158.9 (d, C-F *J* = 233.9 Hz), 144.6, 144.3 (d, C-F *J* = 8.2 Hz), 136.1 (d, C-F *J* = 56.5 Hz), 134.6, 132.9, 130.9 (d, C-F *J* = 9.2 Hz), 130.7, 129.5 (2C), 129.3, 128.8 (2C), 125.8 (d, C-F *J* = 10.4 Hz), 124.8, 117.4 (d, C-F *J* = 22.2 Hz), 114.3 (d, C-F *J* = 22.6 Hz), 111.7 (d, C-F *J* = 26.2 Hz), 110.4 (d, C-F *J* = 9.5 Hz), 105.9 (d, C-F *J* = 23.5 Hz), 99.5 (d, C-F *J* = 4.8 Hz), 38.2, 30.9, 21.7; MS (ES mass): *m*/*z* 450.9 (M+1).

5.7.1.2.22 Compound 5.23v

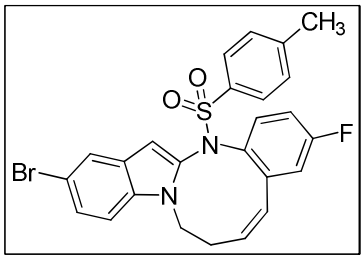


5.23v was prepared from **2.15jg** according to the general procedure as presented above.

Light yellow solid; yield: 72%; mp: 210-212 °C; R_f (15% EtOAc-*n*-Hexane) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.29-7.27 (m, 1H), 7.05-6.99 (m, 2H), 6.79 (d, *J* = 6.8 Hz, 1H), 6.09 (s, 1H), 5.76-5.69 (m, 3H), 4.88-4.82 (m, 1H), 4.51-4.47 (m, 1H), 3.04 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5 (d, C-F *J* =

250.1 Hz), 144.5, 135.8 (d, C-F *J* = 3.3 Hz), 135.0, 134.7, 134.1, 132.7, 130.9 (d, C-F *J* = 10.0 Hz), 130.3, 129.4 (2C), 128.9 (2C), 125.7, 125.1, 122.9, 121.0, 119.9, 117.3 (d, C-F *J* = 22.2 Hz), 114.3 (d, C-F *J* = 22.5 Hz), 109.5, 99.5, 37.9, 30.9, 21.6; MS (ES mass): *m*/*z* 466.5 (M+1).

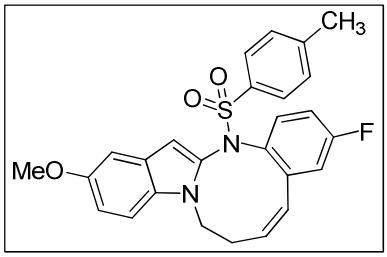
5.7.1.2.23 Compound 5.23w



5.23w was prepared from **2.15ji** according to the general procedure as presented above.

Off white solid; yield: 65%; mp: 238-240 °C; R_f (20% EtOAc-*n*-Hexane) 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61-7.58 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.33-7.29 (m, 2H), 7.02 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.81-6.79 (m, 2H), 6.05 (s, 1H), 5.75-5.71 (m, 3H), 4.89-4.83 (m, 1H), 4.54-4.49 (m, 1H), 3.06-3.02 (m, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2 (d, C-F *J* = 237.0 Hz), 144.7, 135.6 (d, C-F *J* = 38.3 Hz), 134.5, 133.1, 132.7, 130.9 (d, C-F *J* = 9.4 Hz), 129.5 (2C), 129.3, 128.9 (2C), 127.3, 125.9, 124.7, 123.5, 117.5 (d, C-F *J* = 22.5 Hz), 114.4 (d, C-F *J* = 22.2 Hz), 113.0 (d, C-F *J* = 25.3 Hz), 111.1, 109.9, 99.1, 38.2, 30.9, 21.7; MS (ES mass): *m*/*z* 512.9 (M-+1).

5.7.1.2.24 Compound 5.23x



5.23x was prepared from **2.15jr** according to the general procedure as presented above.

Off white solid; yield: 68%; mp: 232-234 °C; R_f (20% EtOAc-*n*-Hexane) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.93-6.90 (m, 2H), 6.79 (d, *J* = 6.4 Hz,

2H), 6.03(s, 1H), 5.75-5.65 (m, 3H), 4.89-4.83 (m, 1H), 4.53-4.49 (m, 1H), 3.80 (s, 3H), 3.02 (dd, *J* = 12.4, 6.0 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4 (d, C-F *J* = 250.0 Hz), 154.1, 144.4, 144.3 (d, C-F *J* = 8.1 Hz), 135.5 (d, C-F *J* = 3.2 Hz), 135.1, 134.7, 132.6, 130.9 (d, C-F *J* =9.1 Hz), 129.4 (2C), 129.3, 128.9 (2C), 125.9, 125.1, 117.3 (d, C-F *J* =22.2 Hz), 114.2 (d, C-F *J* = 22.5 Hz), 113.4, 110.4, 102.5, 99.0, 55.7, 38.0, 30.9, 21.7; MS (ES mass): *m/z* 462.5 (M+1).

5.7.2 Zebrafish embryo study (apoptotic assay):

Materials and Methods:

Husbandry:

Zebrafish obtained from a local vendor were maintained in in-house built recirculatory system under 14-10hrs light dark cycle and 28˚C temperature.[26] Breeding was carried out using females and males in ratio of 2:3 and the embryos obtained were collected in petridishes and maintained at 28°C.[24b,27]

Apoptosis Assay:

24hpf embryos were de-chorinated manually. 6 embryos were distributed as two sets in each well of 24 well plates with 250 µl of 0.1% DMSO. The working stock solutions were prepared by serial dilution as described earlier. Each well was added with 250µl of respective concentration to obtain final working concentration. Embryos were incubated at 28˚C for 24hrs and 48hrs.

The apoptotic effect was checked at 24 hrs and 48 hrs by washing drug exposed embryos thrice with E3 medium. Acridine orange (2µg/ml) solution of dye in E3 medium was added and incubated for 30 mins. The embryos were rinsed thoroughly twice in fresh E3 medium to wash the acridine orange solution. Stained embryos were anesthetized with tricaine and photographed under UV illumination using Zeiss AxioCamMR camera attached to a Zeiss florescence microscope (GFP filter set : excitation 473,emission 520) under 5X magnification. The Images were taken and analyzed using Image J software.

5.8 References

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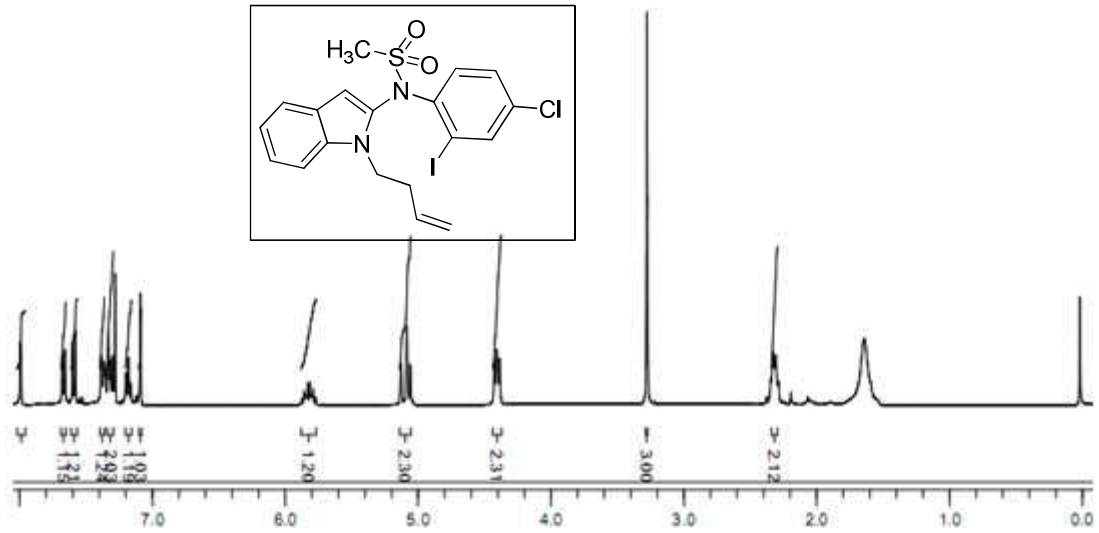
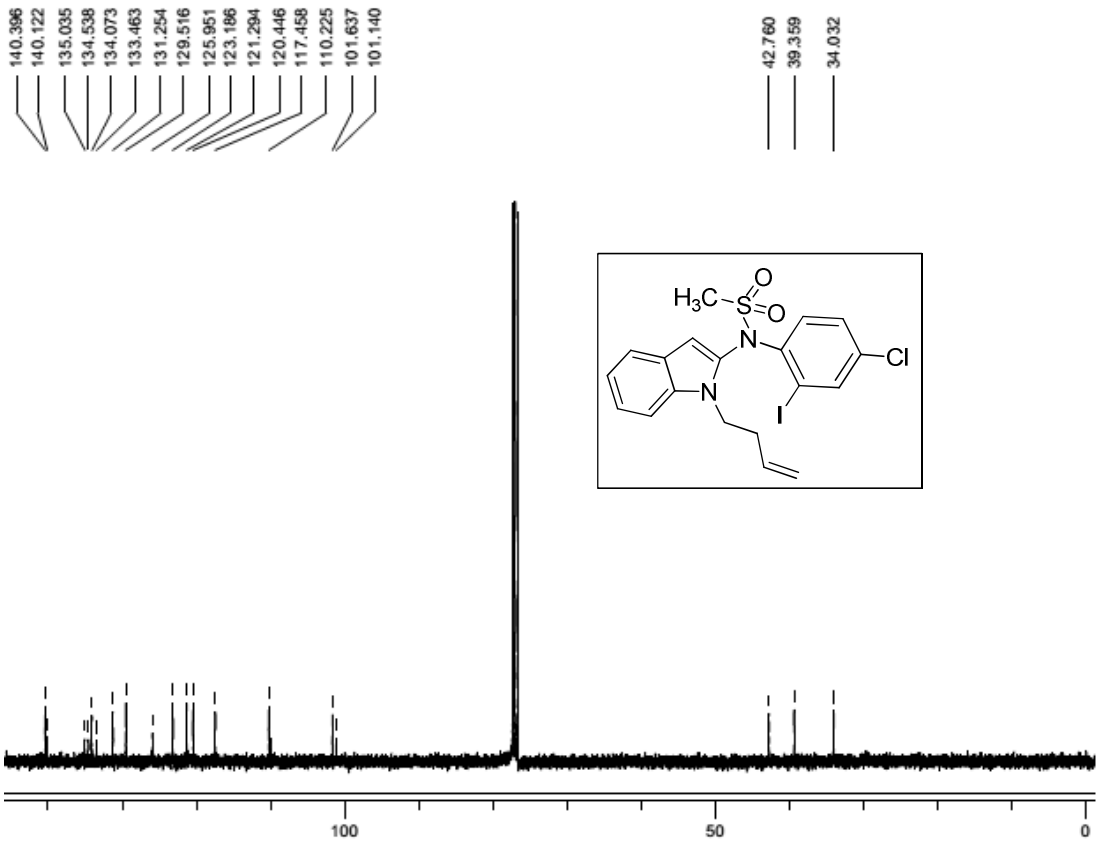
Appendix

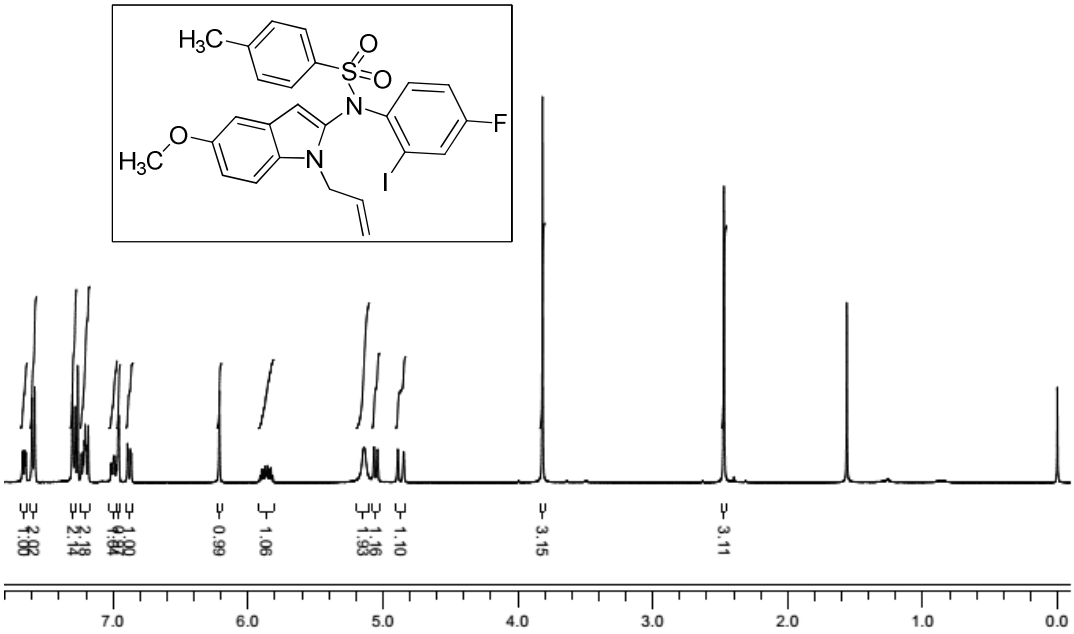
^{1}H NMR (Varian, 400 MHz) spectrum of compound **2.15cc** in $CDCl_3$



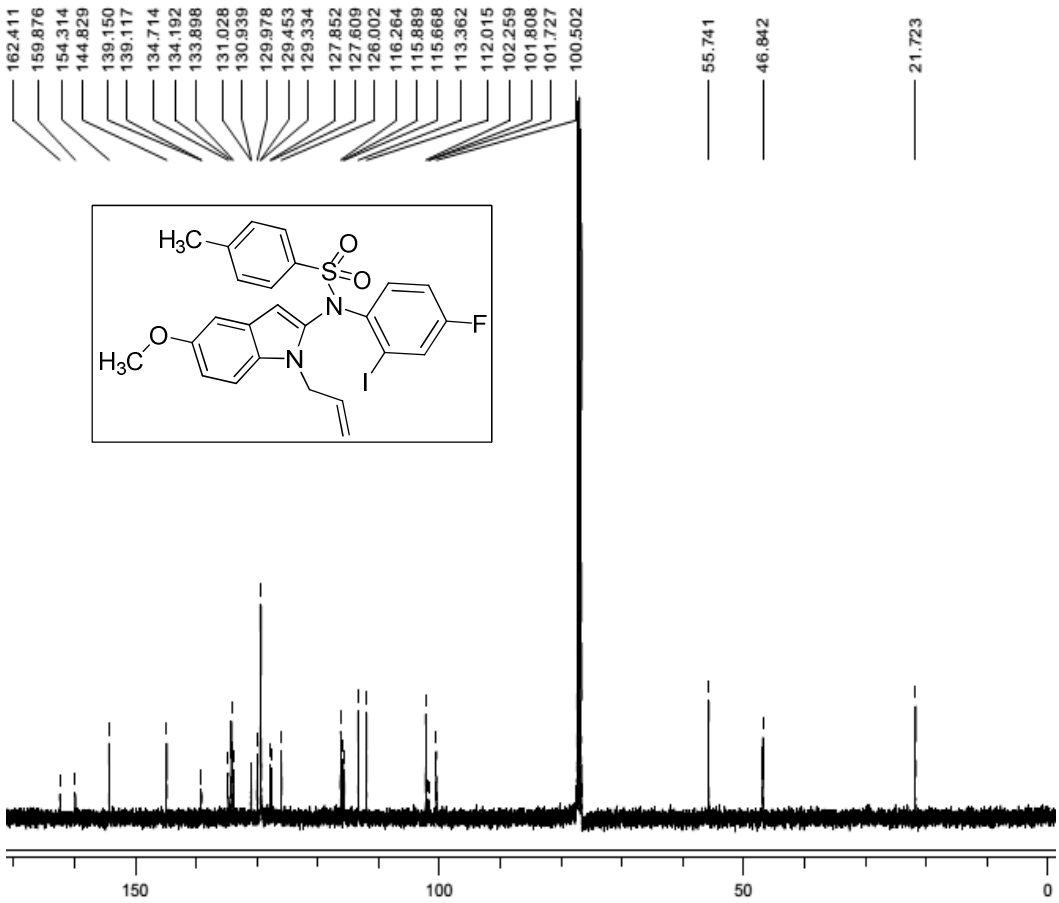
^{13}C NMR spectrum (Varian, 100 MHz) of compound **2.15cc** in $CDCl_3$



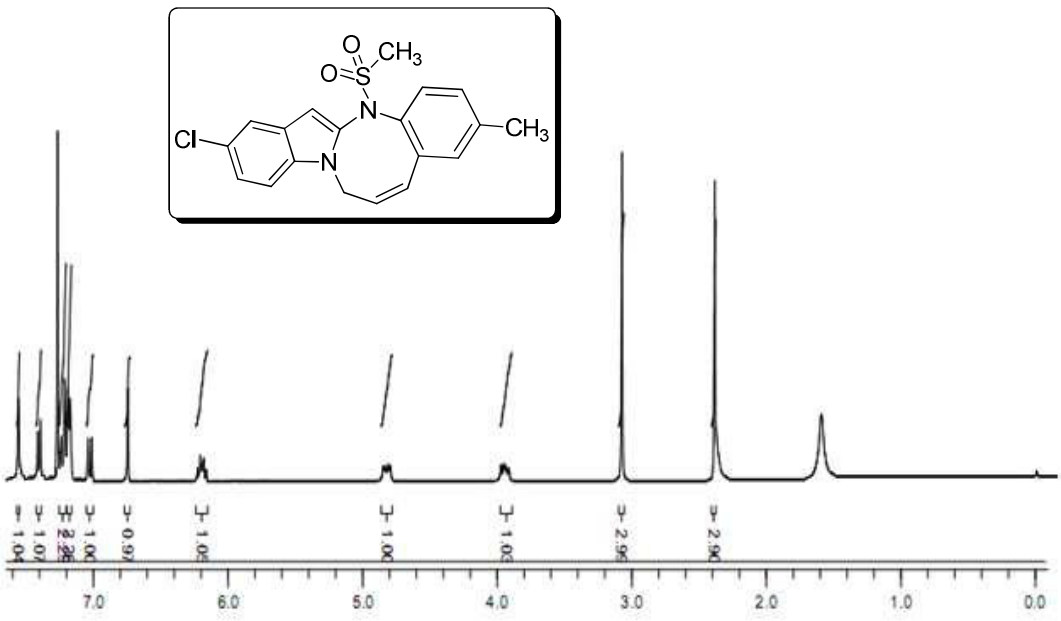
^{1}H NMR (Varian, 400 MHz) spectrum of compound **2.l5jm** in $CDCl_3$



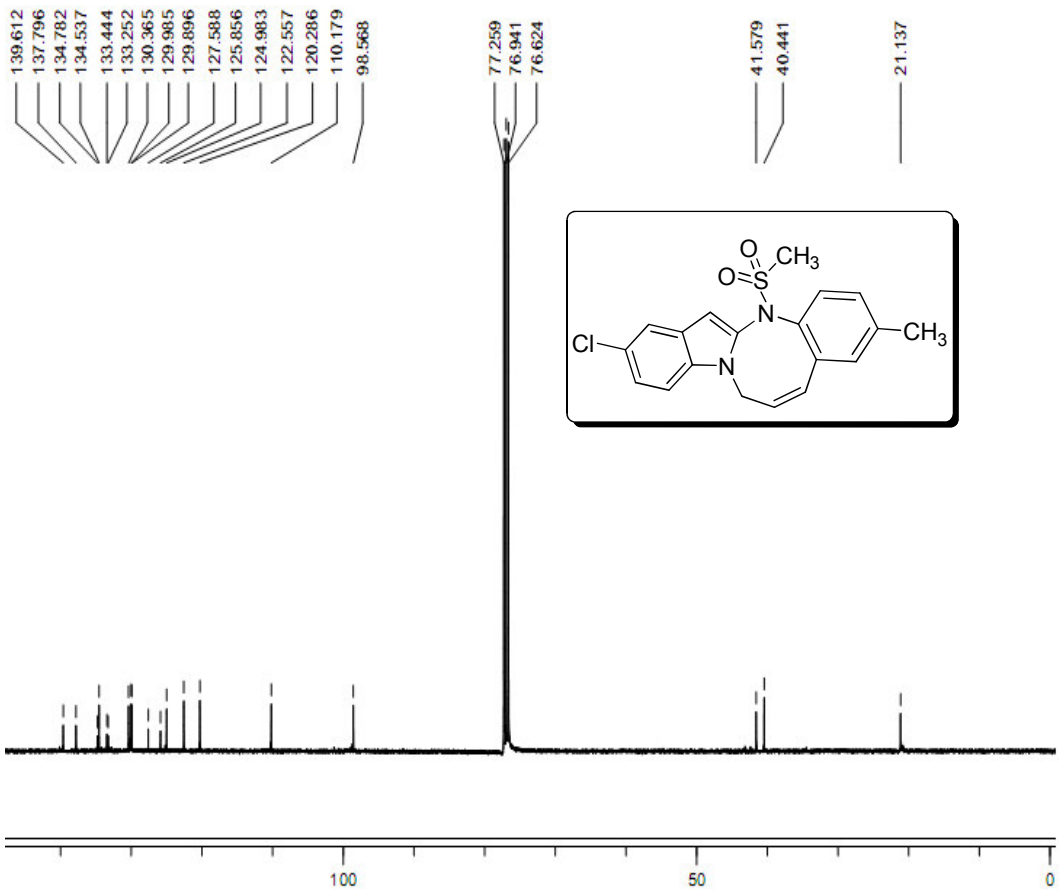
^{13}C NMR spectrum (Varian, 100 MHz) of compound **2.l5jm** in $CDCl_3$



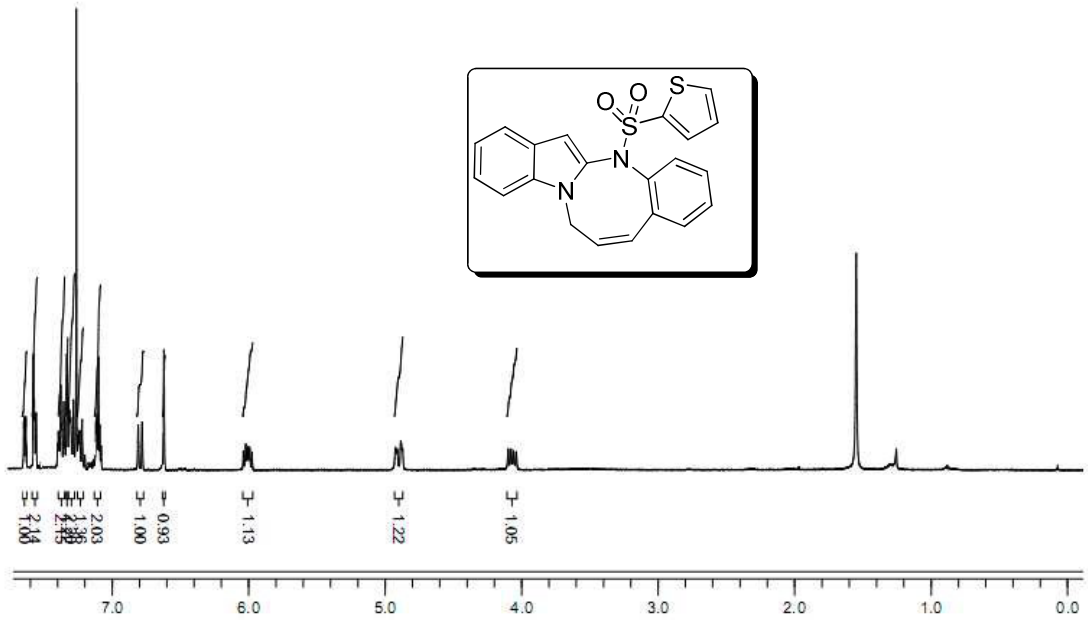
^{1}H NMR (Varian, 400 MHz) spectrum of compound **5.23b** in $CDCl_3$



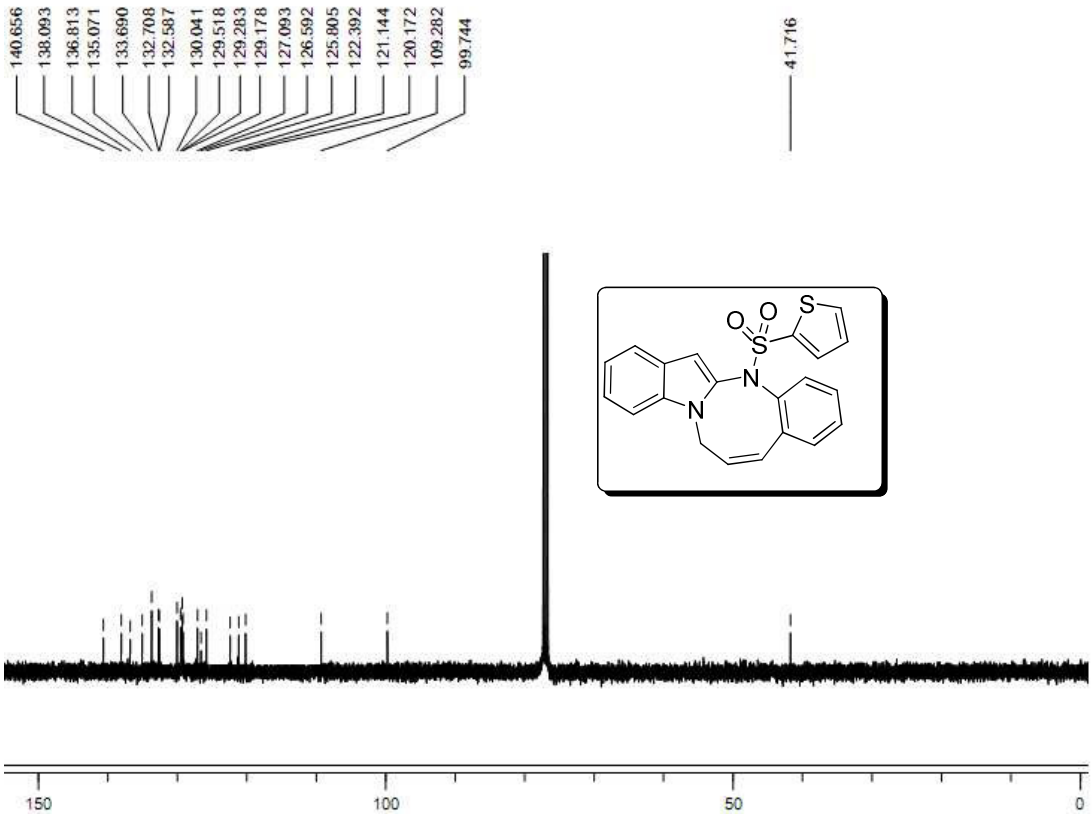
^{13}C NMR spectrum (Varian, 100 MHz) of compound **5.23b** in $CDCl_3$



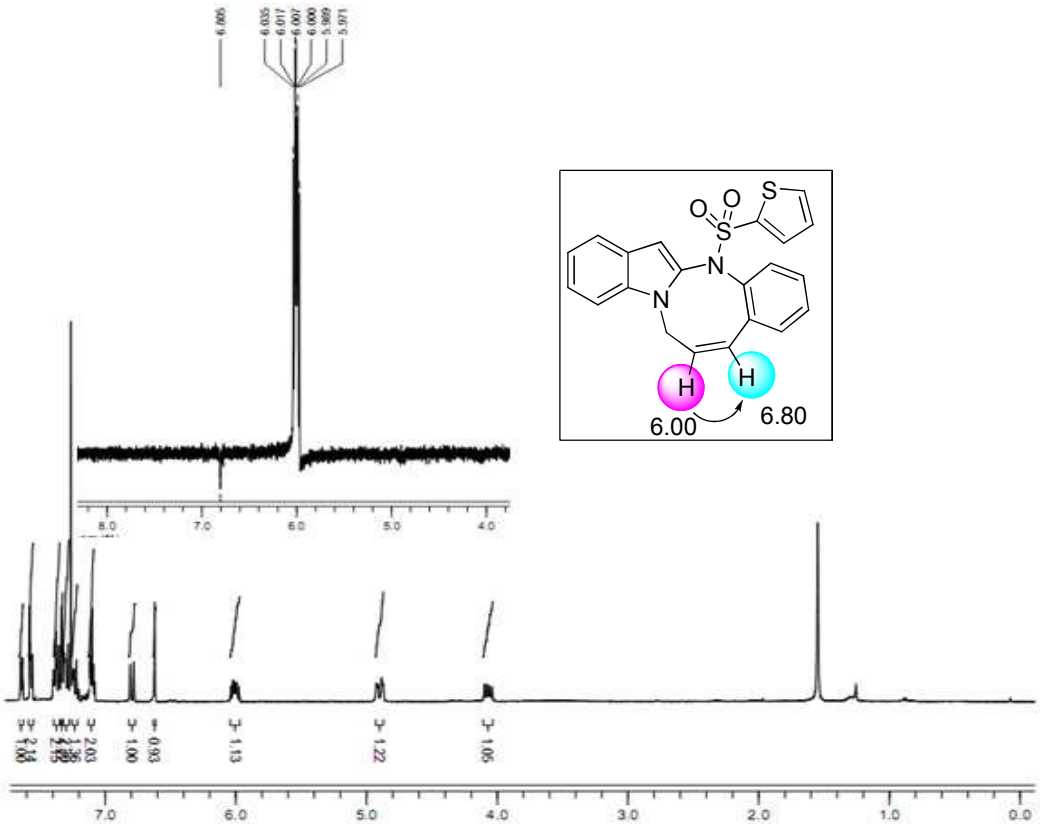
^{1}H NMR (Varian, 400 MHz) spectrum of compound **5.23i** in $CDCl_3$



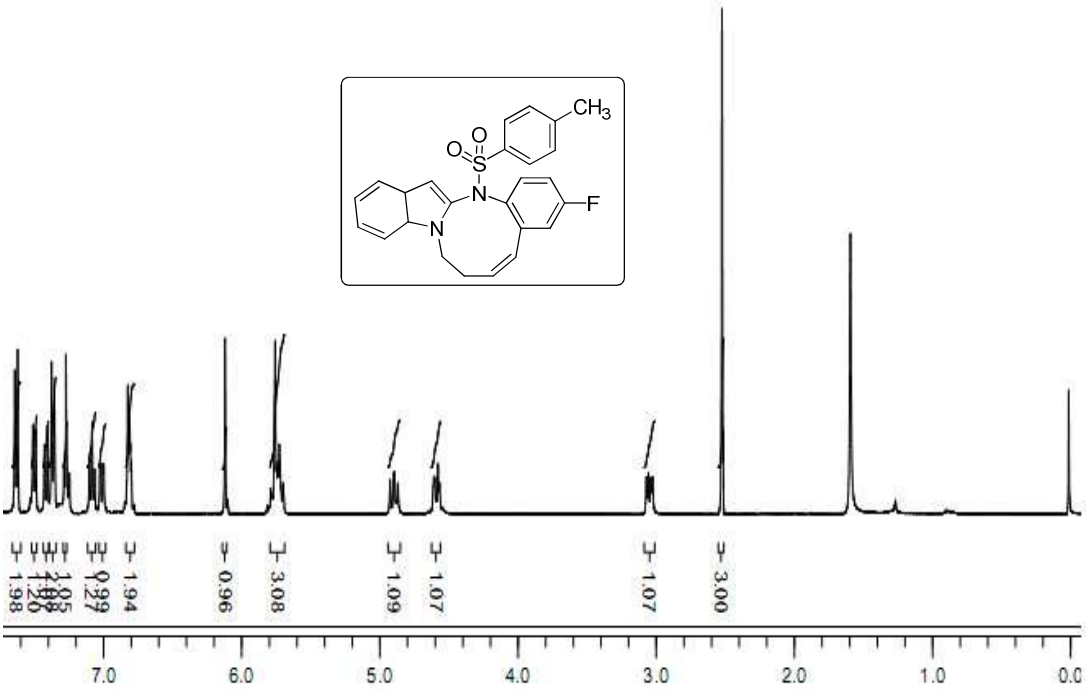
^{13}C NMR spectrum (Varian, 100 MHz) of compound **5.23i** in $CDCl_3$



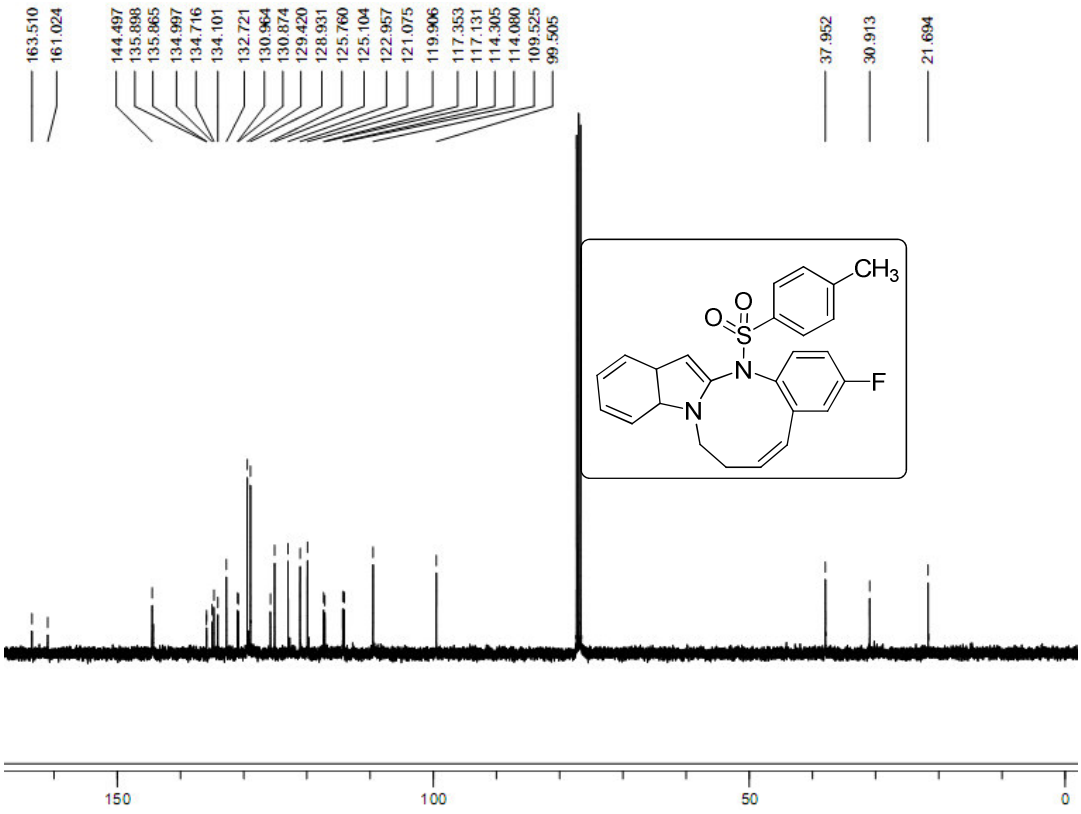
^{1}H NMR and 1D NOE (Varian, 400 MHz) spectrum of compound **5.23i** in $CDCl_3$



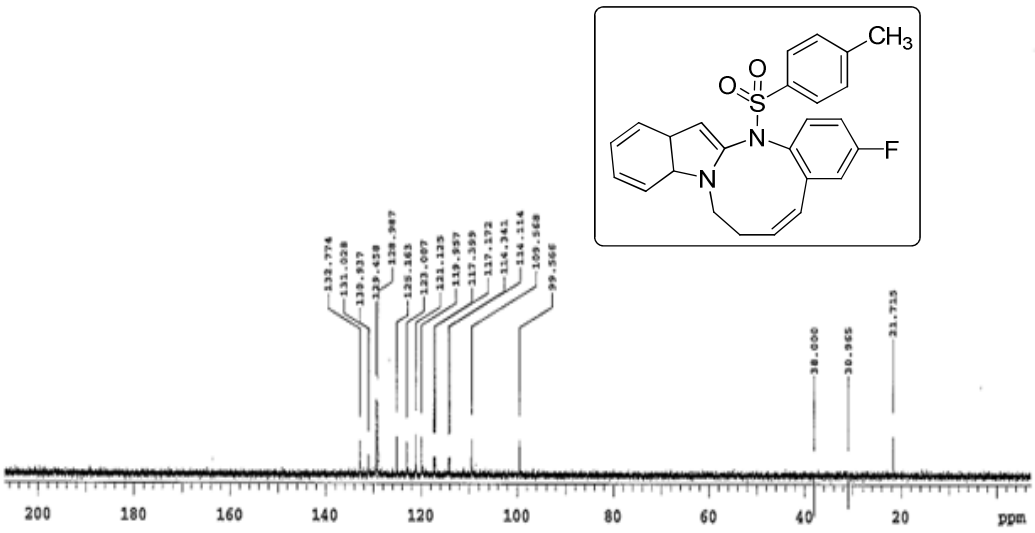
^{1}H NMR (Varian, 400 MHz) spectrum of compound **5.23t** in $CDCl_3$



^{13}C NMR spectrum (Varian, 100 MHz) of compound **5.23t** in $CDCl_3$



DEPT spectrum of compound **5.23t** in $CDCl_3$



List of Publications

a. Publications included in the thesis

1. "$AlCl_3$ mediated unexpected migration of sulfonyl group: regioselective synthesis of 7-sulfonyl indoles of potential pharmacological interest", **Prasad**, **B**.; Adepu, R.; Sandra, S.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Deora, G. S.; Misra P.; Pal, M.*, *Chem. Commun.*, **2012,** *48,* 10434-10436.

2. "Conformationally restricted functionalized heteroaromatics: A direct access to novel indoloindoles via Pd-mediated reaction", **Prasad**, **B**.; Sreenivas, B. Y.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Kumar, K. L.; Pal, M.* *Chem. Commun.*, **2013**, *49,* 3970-3972.

3. "Pd-mediated construction of a cyclopentane ring fused with indoles", **Prasad**, **B**.; Sreenivas, B. Y.; Krishna, G. R.; Kapavarapu, R.; Pal, M.* *Chem. Commun.*, **2013**, *49,* 6716-6718. (Cover Page and Most Read Article)

4. "A Pd-based regioselective strategy to indole-1,2-fused 8- and 9-membered rings: their evaluation as potential scaffolds for apoptosis in zebrafish", **Prasad**, **B**.; Sreenivas, B. Y.; Sushma, A.; Yellanki, S.; Medisetti, R.; Kulkarni, P.; Pal, M.* *Org. Biomol. Chem.*, **2014**, *12*, 2864-2868.

5. "Cu-catalyzed intramolecular cascade reaction under air: synthesis of novel small molecules based on 2,2'-spirobi[indolin]-3-one", **Prasad**, **B**.; Pal, M.* *Manuscript under preparation,* **2014**.

b. Publications not included in the thesis

1. "A new route to indoles *via in situ* desilylation Sonogashira strategy: identification of novel small molecules as potential anti-tuberculosis agents", Nakhi, A.; **Prasad**, **B**.; Rao, R. M.; Reddy, U.; Sandra, S.; Kapavarapu, R. K.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Kishore, R.; Misra, P.; Iqbal, J.*; Pal, M.* *Med. Chem. Commun.*, **2011**, *2*, 1006-1010.

2. "A new approach to construct fused 2-ylidene chromene ring: Highly regioselective synthesis of novel chromeno quinoxalines", Kumar, K. S.; Rambabu, D.; **Prasad**, **B**.; Mujahid, M.; Krishna, G. R.; Rao, M. V. B.; Reddy, C. M.; Vanaja, G. R.; Kalle, A. M.; Pal, M.* *Org. Biomol. Chem.*, **2012**, *10*, 4774–4781.

3. "Novel thieno[2,3-*d*]pyrimidines: their design, synthesis, crystal structure analysis and pharmacological evaluation", Adepu, R.; Rambabu, D.; **Prasad**, **B**.; Meda, C. L. T.; Kandale, A.; Krishna, G. R.; Reddy, C. M.; Chennuru, L. N.; Parsa K. V. L.; Pal, M.* *Org. Biomol. Chem.*, **2012**, *10*, 5554-5569.

4. "$AlCl_3$ induced C-N bond formation followed by Pd/C-Cu mediated coupling-cyclization strategy: synthesis of pyrrolo[2,3-*b*]quinoxalines as anticancer agents", **Prasad**, **B**.; Kumar, K. S.; Babu, P. V.; Anusha, K.; Rambabu, D.; Kandale, A.; Vanaja, G. R.; Kalle, A. M.; Pal, M.* *Tet. Lett.*, **2012**, *53*, 6059-6066.

5. "TFAA/H_3PO_4 mediated unprecedented *N*-acylation of carbazoles leading to small molecules possessing anti-proliferative activities against cancer cells", Kolli, S. K.; **Prasad, B**.; Babu, P. V.; Ashfaq, M. A.; Ehtesham, N. Z.; Raju, R. R.; Pal, M.* *Org. Biomol. Chem.*, **2014**, *12*, 6080-6084.

Oral and Poster Presentations

- **Oral presentation** on "Pd-mediated new cascade reaction: A direct access to functionalized cyclopenta[*b*]indoles", **B. Prasad** and M. Pal, 9th *J-NOST* Conference, IISER Bhopal, Madhya Pradesh, India, Dec 4th-6th, 2013.

- **Poster presentation** on "$AlCl_3$ mediated regioselective synthesis of 7-sulfonyl indoles of potential pharmacological interest", **B. Prasad** and M. Pal, 8th *J-NOST* Conference, IIT Guwahati, Assam, India, Dec 15th-17th, 2012.

- **Poster presentation** on "Pd-mediated new cascade reaction: A direct access to functionalized cyclopenta[*b*]indoles", **B. Prasad** and M. Pal, *International Symposium on Nature Inspired Initiatives in Chemical Trends* (NIICT), IICT Hyderabad, India, Mar 2nd-4th, 2014.

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COMMUNICATION

$AlCl_3$ mediated unexpected migration of sulfonyl groups: regioselective synthesis of 7-sulfonyl indoles of potential pharmacological interest†

Bagineni Prasad,[a] Raju Adepu,[a] Sandhya Sandra,[a] D. Rambabu,[a] G. Rama Krishna,[b] C. Malla Reddy,[b] Girdhar Singh Deora,[a] Parimal Misra[a] and Manojit Pal*[a]

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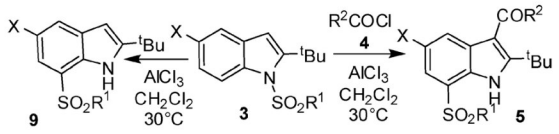
A conceptually new and straightforward introduction of sulfonyl groups at the C-7 position of an indole ring has been achieved *via* $AlCl_3$ mediated unexpected regioselective sulfonyl group migration for *N*-alkyl/aryl/heteroarylsulfonyl indoles affording potential inhibitors of *Mycobacterium tuberculosis* H37Rv chorismate mutase.

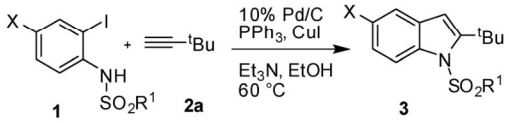
The discovery of new and efficient reactions leading to the novel and diversity based carbocyclic/heterocyclic structures is of enormous importance. The indole framework being an integral part of many bioactive molecules[1] is considered as one of the privileged structures in drug discovery. The development of new synthetic methods for indoles therefore has immense impact and value.

Due to its absence in animals but not in bacteria *Mycobacterium tuberculosis* H37Rv chorismate mutase (CM) is considered as a promising target for the identification of new and potential antitubercular agents.[2] However, only few small molecules are known as inhibitors of CM.[3] In pursuance of our research on the identification of indole based inhibitors[3a] of CM we required new routes to access our target indole derivatives. Accordingly, we unexpectedly observed a regioselective sulfonyl group migration for *N*-alkyl/aryl/heteroarylsulfonyl indoles in the presence of $AlCl_3$ leading to functionalized new indoles in which the nitrogen atom was unprotected and the sulfonyl group shifted to C-7 of an indole ring (Scheme 1). The migration of the sulfonyl group[4] was found to be highly selective and allowed the straightforward introduction of sulfonyl groups at C-7 of an indole ring. To the best of our knowledge no effective route was known earlier leading to 7-sulfonyl indoles[4c] of potential medicinal value. Herein, we report our preliminary results on the synthesis, crystal structure analysis and *in vitro* pharmacological evaluation of 7-sulfonyl indoles against CM.



Scheme 1 Synthesis of 7-sulfonyl indoles *via* regioselective migration of the sulfonyl group.

The key starting material *i.e.* indole **3** required for our study was prepared in high yields *via* a Pd/C-mediated coupling–cyclization reaction[5] (Scheme 2). We then examined the acylation of indole **3a** under Friedel–Crafts conditions using MeCOCl (**4a**)–$AlCl_3$. To our surprise the reaction proceeded well affording 3-acetyl-7-sulfonyl indole (**5a**) as a result of unusual migration of the sulfonyl group along with acetylation. Compound **5a** was characterized by spectral (NMR, IR and MS) data and its molecular structure was confirmed unambiguously by a single crystal X-ray diffraction study (Fig. 1).[6] This prompted us to investigate the reaction further under various conditions (Table 1). Initially, **3a** was treated with 1.0 and 1.5 equiv. of $AlCl_3$ and **4a**, respectively, in dry dichloromethane (DCM) for 6 h when **5a** was isolated in low yield (entry 1, Table 1). Systematic increase in equivalent of both $AlCl_3$ and **4a** increased the yield of **5a** (entries 2–4, Table 1).



1	X, R^1	3	T (h)	Yield (%)
1a	Cl, Me	3a	3.5	90
1b	F, Me	3b	4.0	85
1c	Br, Me	3c	4.0	96
1d	H, Me	3d	3.5	92
1e	CH_3, Me	3e	4.5	82
1f	CN, Me	3f	5.0	80
1g	NO_2, Me	3g	5.0	91
1h	CF_3, Me	3h	4.5	83
1i	Cl, C_6H_4Me-*p*	3i	4.0	85
1j	F, C_6H_4Me-*p*	3j	4.5	88
1k	H, C_6H_4Me-*p*	3k	4.0	94
1l	Me, C_6H_4Me-*p*	3l	4.5	81
1m	COMe, C_6H_4Me-*p*	3m	5.0	85
1n	Cl, 2-Thienyl	3n	5.0	85
1o	F, 2-Thienyl	3o	5.0	84
1p	Br, 2-Thienyl	3p	5.0	90
1q	H, 2-Thienyl	3q	4.5	88
1r	Me, 2-Thienyl	3r	4.5	80

Scheme 2 Synthesis of 2-*tert*-butyl-*N*-sulfonyl indole (**3**).

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[b] *Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, West Bengal 741252, India*

† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, results of docking study. CCDC 859365. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc35757g

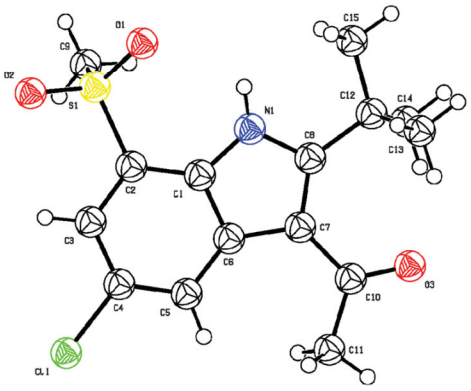
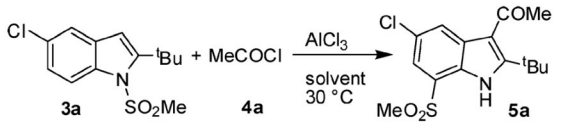


Fig. 1 ORTEP representation of compound **5a** (thermal ellipsoids are drawn at the 50% probability level).

Table 1 Effect of conditions on the reaction of **3a** with **4a**[a]



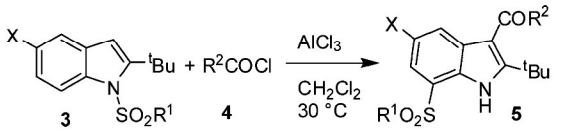
Entry	Equiv. of $AlCl_3$	Equiv. of **4a**	Solvent	Time[b]/h	Yield[c] (%)
1	1.0	1.5	CH_2Cl_2	6	28[d]
2	1.5	2.0	CH_2Cl_2	6	41[d]
3	1.5	3.0	CH_2Cl_2	6	49[d]
4	2.0	3.0	CH_2Cl_2	6	70
5	2.0	3.0	CH_2Cl_2	8	68
6	2.0	3.0	$CHCl_3$	6	44[d]
7	2.0	3.0	$ClCH_2CH_2Cl$	6	32[d]

[a] Reactions were carried out using **3a** (1 equiv.), **4a** and $AlCl_3$ in a solvent (5.0 mL). [b] After adding **3a**. [c] Isolated yield. [d] Unreacted **3a** was recovered.

However, increase in the reaction time did not improve the product yield (entry 5, Table 1) and the use of other solvents such as $CHCl_3$ and 1,2-dichloroethane was found to be less effective (entries 6 and 7, Table 1). Thus a combination of $AlCl_3$ (2 equiv.) and **4a** (3 equiv.) in dry DCM was found to be optimum for the preparation of **5a** (entry 4, Table 1).

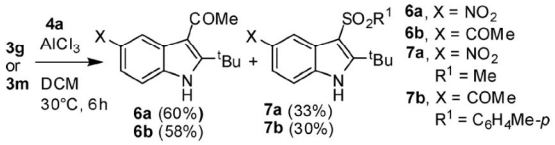
To test the generality of the present method other indoles were reacted with acetyl and propionyl chloride under optimized conditions (Table 2). Indoles **3** containing *N*-alkyl (entries 1–8, Table 2), aryl (entries 9–12, Table 2) and heteroaryl (entries 13–16, Table 2) sulfonyl groups were employed to give **5**. The sulfonyl group migration occurred smoothly in the presence of an electron donating group *e.g.* F, Cl, Br or Me at C-5. An electron withdrawing or deactivating group *e.g.* $-NO_2$ or –COMe at C-5 however afforded the corresponding 3-acetyl indole (**6**) along with 3-sulfonyl indole (**7**) as a minor product (Scheme 3). The N–S bond cleavage seemed to be aided by the bulky *tert*-butyl group at C-2 resulting in the migration of the *N*-sulfonyl group. This was supported by the fact that acetylation of 2-(*n*-butyl)-5-chloro-1-(methylsulfonyl)-1*H*-indole (**3s**) under the optimized conditions afforded the normal acylation product (Scheme 4) without migration of the *N*-sulfonyl group to the other position. Additionally, the observation that a number of

Table 2 $AlCl_3$ mediated synthesis of 3-acyl-7-sulfonyl indoles (**5**)[a]

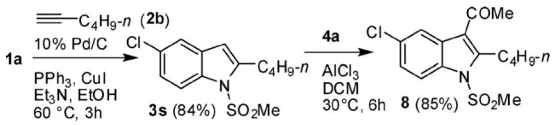


Entry	Indole (**3**)	**4**; R^2 =	Product (**5**)	Time[b]/h	Yield[c] (%)
1	**3a**	**4a**; Me	**5a**	6.0	70
2	**3a**	**4b**; Et	**5b**	6.5	67
3	**3b**	**4a**	**5c**	7.0	68
4	**3b**	**4b**	**5d**	6.5	65
5	**3c**	**4a**	**5e**	6.5	66
6	**3c**	**4b**	**5f**	7.5	65
7	**3e**	**4a**	**5g**	6.5	60
8	**3e**	**4b**	**5h**	7.0	58
9	**3i**	**4a**	**5i**	7.5	58
10	**3i**	**4b**	**5j**	8.0	55
11	**3j**	**4a**	**5k**	7.5	56
12	**3l**	**4a**	**5l**	8.0	52
13	**3n**	**4a**	**5m**	8.0	55
14	**3o**	**4a**	**5n**	8.0	58
15	**3p**	**4a**	**5o**	7.5	55
16	**3r**	**4a**	**5p**	8.0	54

[a] Reactions were carried out using **3** (1.75 mmol), **4** (5.25 mmol) and $AlCl_3$ (3.5 mmol), in dry DCM (5.0 mL). [b] After adding **3**. [c] Isolated yield.



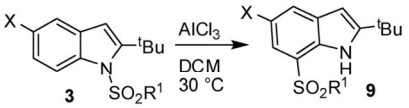
Scheme 3 Effect of the electron withdrawing group at C-5 of an indole ring.



Scheme 4 Preparation and acetylation of the 2-(*n*-butyl)indole derivative.

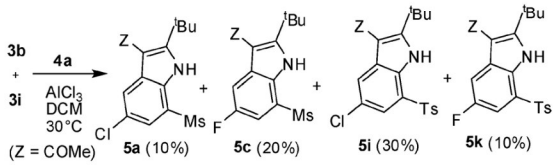
indoles *e.g.* **3a–b**, **3i**, **3n–p** and **3r** underwent smooth N–S bond cleavage in the absence of acyl chloride leading to the C-7 sulfonyl substituted indoles (**9**) indicated the key role played by $AlCl_3$ in this transformation (Scheme 5).

To understand the mode of migration of the sulfonyl group a cross over experiment was performed using a 1 : 1 mixture of **3b** and **3i** under the optimized conditions. The isolation of cross over products *i.e.* **5a** and **5k** (Scheme 6) clearly suggested a non-concerted process for the observed sulfonyl group migration.[7] Thus, the reaction seemed to proceed (Scheme 7) *via* $AlCl_3$-assisted activation of the indolyl double bond followed by N–S bond cleavage to give **E-1** which underwent sufonylation at C-7 to give **E-3** *via* **E-2**. In addition to its steric bulk that perhaps aided the departure of the *N*-sulfonyl group the *t*-Bu group facilitated the C-7 sulfonylation *via* stabilizing the carbocation **E-2**. The reaction follows a similar pathway in the presence of an acyl chloride when C-3 acylation facilitated the migration of the *N*-sulfonyl group to C-7.

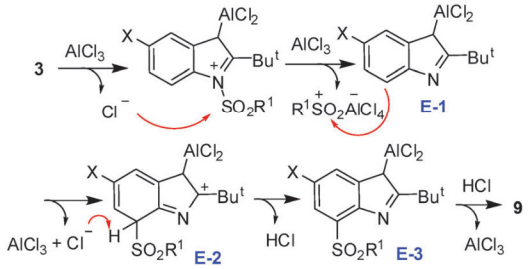


3	X, R^1	9	T (h)	Yield (%)
3a	Cl, Me	**9a**	4.0	70
3b	F, Me	**9b**	4.5	68
3i	Cl, C_6H_4Me-*p*	**9c**	5.0	65
3n	Cl, 2-Thienyl	**9d**	4.5	68
3o	F, 2-Thienyl	**9e**	5.0	65
3p	Br, 2-Thienyl	**9f**	5.0	58
3r	Me, 2-Thienyl	**9g**	4.5	60

Scheme 5 $AlCl_3$ mediated migration of the *N*-sulfonyl group leading to 7-sulfonyl indoles.



Scheme 6 Cross over experiment between **3b** and **3i**.



Scheme 7 Proposed mechanism for the $AlCl_3$ mediated migration of the sulfonyl group.

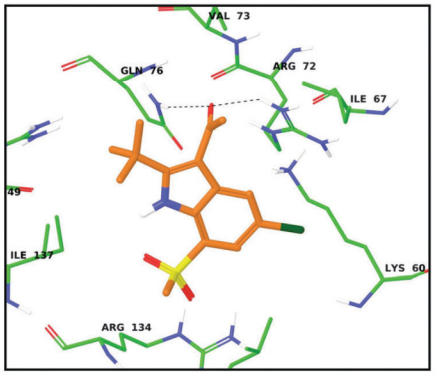


Fig. 2 Docking of compound **5a** at the active site of CM.

Some of the compounds synthesized were tested for their inhibitory potential against CM *in vitro*.[8] The assay involved determination of the activity of enzyme CM which catalyzes the conversion of chorismate to prephenate. A known inhibitor of CM *i.e.* 4-(3,5-dimethoxyphenethylamino)-3-nitro-5-sulfamoylbenzoic acid[3a] was used as a reference compound (IC_{50} < 10 μM). Compounds **5c**, **5e**, **5m**, **5o** and **5p** showed 22–30% inhibition whereas **5a** showed 45% inhibition of CM when tested at 30 μM. The docking of **5a** at the active site of CM (Fig. 2, see ESI†) indicated a perfect H-bond bridge between the carbonyl oxygen of **5a** and Glutamine-76 as well as Arginine-72 residue of the protein. Overall, since tuberculosis is a leading cause of death worldwide hence the present class of compounds is of further interest.

In conclusion, a novel methodology has been developed *via* an $AlCl_3$ mediated unexpected sulfonyl group migration for *N*-sulfonyl indoles leading to new 7-sulfonyl indoles as potential inhibitors of CM. This represents a regioselective, straightforward and easy introduction of sulfonyl groups at C-7 of an indole ring. A representative compound, the molecular structure of which was confirmed unambiguously by a single crystal X-ray diffraction study, showed inhibition and interactions with CM both in *in vitro* and *in silico* studies.

BP and RA thank CSIR, for Research Fellowships. The authors thank Prof. J. Iqbal and DBT (Grant BT/01/COE/07/02) for support.

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Conformationally restricted functionalized heteroaromatics: a direct access to novel indoloindoles *via* Pd-mediated reaction†

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A new, versatile and direct Pd-mediated method involving intramolecular cyclization of *N*-(2-iodoaryl)-*N*-(1-alkyl-1*H*-indol-2-yl)alkane/arene/heteroarene sulfonamide has been developed leading to a diverse and unique class of indolo[2,3-*b*]indoles for the potential inhibition of sirtuins.

The development of straightforward, versatile and new chemical approaches leading to densely functionalized heteroaromatics is of enormous importance as it allows the exploration of a diverse region of chemical space useful for pharmaceutical/medicinal chemistry efforts. Conformational restriction of heteroaromatics on the other hand has provided valuable insight into the early stage of drug discovery on several occasions.[1] This[2] and the importance of indoles as privileged structural motifs in medicinal chemistry/drug discovery prompted us to explore a new route to indolo[2,3-*b*]indoles (**B**, Fig. 1) as potential inhibitors of sirtuins. The sirtuins (class III NAD-dependent deacetylases) shown to be up-regulated in various types of cancer are considered promising targets for cancer therapeutics.[3] Inhibition of sirtuins allows re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells. Our target molecules derived from a known inhibitor,[3b] EX-537, were designed based on the *in silico* binding studies of the representative compound **A** (Fig. 1) in the catalytic pocket of yeast Sir2 (Fig. 2). The study showed binding of **A** deep into the active site (docking score −5.8) along with an H-bond interaction of sulfonyl oxygen with the side chain amino group of ASN 35 (see ESI†).

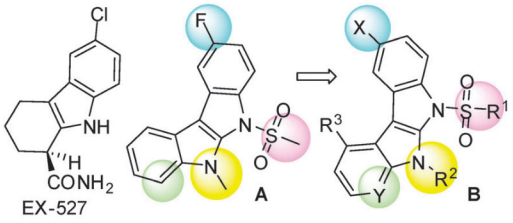


Fig. 1 Design of **A**/**B** as novel inhibitors of sirtuins.

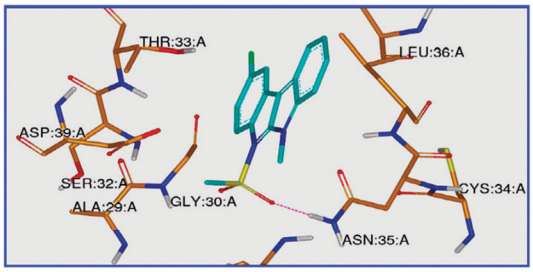
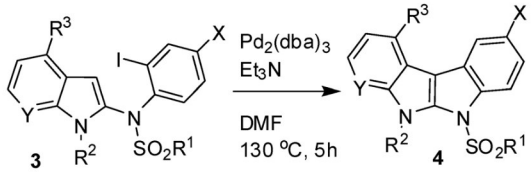


Fig. 2 Binding mode of **A** in yeast Sir2 (PDBID: 1Q1A).

In recent years, the intramolecular direct arylation leading to fused heteroaromatics, *via* a radical pathway[4] or transition metal-catalyzed single[5] or double C–H bond activation,[6] has attracted particular attention. These methodologies offer a quick access to diverse and complex molecular structures *via* C–C bond forming reactions. We envisioned that transition metal mediated C-3 arylation of indole in an intramolecular fashion could lead to our target compounds **A**/**B**. Herein we report our preliminary results on Pd-mediated intramolecular cyclization of *N*-(2-iodoaryl)-*N*-(1-alkyl-1*H*-indol-2-yl)alkane/arene/heteroarene sulfonamide **3** leading to indolo[2,3-*b*]indoles **4** (or **B**, Scheme 1). To the best of our



Scheme 1 Pd-mediated synthesis of novel indolo[2,3-*b*]indoles.

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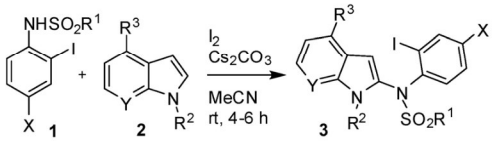
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, results of *in vitro* and docking study. CCDC 903580. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc38342j

Table 1 Iodine-mediated synthesis of sulfonamide **3**[a]



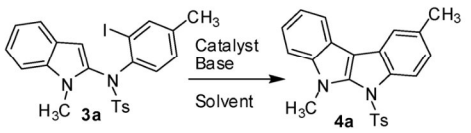
Entry	Anilides (**1**) X, R^1	Indole (**2**) R^2, R^3, Y	T^b/ h	Product (**3**) R^2, R^3, R^1, X, Y	Yield[c] (%)
1	Me, C_6H_4Me-*p*	Me, H, CH	4	Me, H, C_6H_4Me-*p*, Me, CH	75
	1a	**2a**		**3a**	
2	F, CH_3	**2a**	6	Me, H, CH_3, F, CH	60
	1b			**3b**	
3	Cl, CH_3	**2a**	6	Me, H, CH_3, Cl, CH	62
	1c			**3c**	
4	Me, CH_3	**2a**	4	Me, H, Me, CH_3, CH	70
	1d			**3d**	
5	F, C_6H_4Me-*p*	**2a**	5	Me, H, C_6H_4Me-*p*, F, CH	72
	1e			**3e**	
6	H, C_6H_4Me-*p*	**2a**	4.5	Me, H, C_6H_4Me-*p*, H, CH	74
	1f			**3f**	
7	Cl, C_6H_4Me-*p*	**2a**	4.5	Me, H, C_6H_4Me-*p*, Cl, CH	63
	1g			**3g**	
8	Br, C_6H_4Me-*p*	**2a**	4.5	Me, H, C_6H_4Me-*p*, Br, CH	62
	1h			**3h**	
9	CH_3, 2-thienyl	**2a**	5	Me, H, 2-thienyl, CH_3, CH	75
	1i			**3i**	
10	F, 2-thienyl	**2a**	5	Me, H, 2-thienyl, F, CH	75
	1j			**3j**	
11	H, 2-thienyl	**2a**	5	Me, H, 2-thienyl, H, CH	76
	1k			**3k**	
12	**1d**	Allyl, H, CH	5	Allyl, H, CH_3, CH_3, CH	62
		2b		**3l**	
13	**1b**	**2b**	6	Allyl, H, CH_3, F, CH	61
				3m	
14	**1c**	**2b**	6	Allyl, H, CH_3, Cl, CH	65
				3n	
15	**1a**	**2b**	6	Allyl, H, C_6H_4Me-*p*, CH_3, CH	61
				3o	
16	**1e**	**2b**	5	Allyl, H, C_6H_4Me-*p*, F, CH	64
				3p	
17	**1g**	**2b**	5	Allyl, H, C_6H_4Me-*p*, Cl, CH	58
				3q	
18	**1h**	**2b**	6	Allyl, H, C_6H_4Me-*p*, Br, CH	61
				3r	
19	**1e**	Benzyl, H, CH	6	Benzyl, H, C_6H_4Me-*p*, F, CH	58
		2c		**3s**	
20	**1e**	Me, Cl, N	6	Me, Cl, C_6H_4Me-*p*, F, N	66
		2d		**3t**	

[a] All the reactions were carried out using **1** (1.0 mmol), **2** (1.2 mmol), I_2 (1.0 mmol) and Cs_2CO_3 (1.5 mmol) in acetonitrile (5.0 mL) at room temperature under nitrogen. [b] After adding indole **2**. [c] Isolated yield.

knowledge use of this strategy leading to **4** is unprecedented. The key starting material **3** required was prepared *via* C-2 amination of indoles (**2**) using *N*-sulfonyl arylamines (**1**) (Table 1).[7]

Initially we examined the intramolecular cyclization of *N*-(2-iodoaryl)indole derivative **3a** in the presence of $Pd_2(dba)_3$ and K_2CO_3 in MeCN, 1,4-dioxane and toluene when the desired product **4a** was isolated in low yield (entries 1–3, Table 2). The yield was

Table 2 Effect of conditions on intramolecular cyclization of **3a**[a]



Entry	Catalyst	Base	Solvent	Time (h)	Yield[b] (%)
1	$Pd_2(dba)_3$	K_2CO_3	MeCN	10	25[c]
2	$Pd_2(dba)_3$	K_2CO_3	1,4-Dioxane	10	40[d]
3	$Pd_2(dba)_3$	K_2CO_3	Toluene	10	40[e]
4	$Pd_2(dba)_3$	K_2CO_3	DMF	5	75
5	$Pd_2(dba)_3$	Et_3N	DMF	5	85
6	$Pd_2(dba)_3$	Et_3N	DMF	5	50[f]
7	$Pd(OAc)_2$, X-Phos	Et_3N	DMF	4	80
8	$Pd(OAc)_2$, P(*o*-tol)$_3$	Et_3N	DMF	4	82
9	$Pd(OAc)_2$, PPh_3	Et_3N	DMF	4	81
10	$Cu(OAc)_2$	Et_3N	DMF	10	0
11	CuI	Et_3N	DMF	10	0
12	$Pd_2(dba)_3$	Et_3N	DMF	12	38[g]

[a] Reaction conditions: **3a** (1.0 mmol), catalyst (5.0 mol%) and base (2.5 mmol) in solvent (2.0 mL) at 130 °C. [b] Isolated yield. [c] The reaction was performed at 80 °C. [d] The reaction was performed at 100 °C. [e] The reaction was performed at 110 °C. [f] 2.5 mol% catalyst was used. [g] *N*-(2-Bromo-4-methylphenyl)-4-methyl-*N*-(1-methyl-1*H*-indol-2-yl)benzenesulfonamide was used in place of **3a**.

improved when DMF was used (entries 4 and 5, Table 2) along with Et_3N (entry 5, Table 2). The use of lower quantity of catalyst decreased the product yield (entry 6, Table 2). The use of other Pd-catalyst *e.g.* $Pd(OAc)_2$ along with a ligand also afforded **4** in good yield (entries 7–9, Table 2) whereas the use of Cu-catalysts was found to be ineffective (entries 10 and 11, Table 2). The use of the 2-bromo derivative instead of **3a** was less effective (entry 12, Table 2). Overall, we preferred $Pd_2(dba)_3$ to avoid the use of additional ligands.

We then investigated the substrate scope and generality of this method (Table 3). Substituents like Me, allyl, and benzyl on the indole nitrogen and Me, F, Cl and Br on the *N*-aryl ring of **3** were well tolerated. Additionally, compound **3** containing *N*-alkyl, aryl and heteroaryl sulfonyl groups participated well in the present reaction. The Cl and Br present in **3** were also well tolerated and the reaction was successful with azaindole **3t**. The generality of this methodology was demonstrated further by synthesizing 8-methoxy-1,3,5-trimethyl-2-(thiophen-2-ylsulfonyl)-1,2-dihydroindolo[2,3-*b*]indole (**4u**) and 5-fluoro-1-methyl-8-nitro-2-(thiophen-2-ylsulfonyl)-1,2-dihydroindolo[2,3-*b*]indole (**4v**) in 74 and 68% yield, respectively (see ESI†). All the compounds synthesized were well characterized by spectral (NMR, IR and MS) data and the molecular structure of **4p** was confirmed unambiguously by single crystal X-ray diffraction study (Fig. 3).[8]

Mechanistically (Scheme 2), the reaction proceeds *via* formation of Pd(II) species **E-1** [generated *via* oxidative addition of **3** to Pd(0)] which may undergo intramolecular cyclization following the path a or b. The path b *i.e.* Heck coupling seems less likely as the *syn*-carbopalladation of the indole double bond would lead to the *trans*-fused intermediate **E-3** possessing unfavorable ring-strain.

All the compounds synthesized were tested at 50 μM initially for their ability to inhibit the yeast sirtuin family NAD-dependent histone deacetylase (HDAC) Sir2 protein. A known inhibitor Splitomicin was used as a reference compound in this yeast cell based reporter silencing assay. The compounds (**4**) were tested

Table 3 Pd-mediated synthesis of indolo[2,3-*b*]indoles (Scheme 1)[a]

Entry	Indole (3)	Product (4) R^2, R^3, R^1, X, Y	Yield[b] (%)
1	**3a**	Me, H, C_6H_4Me-*p*, Me, CH **4a**	85
2	**3b**	Me, H, CH_3, F, CH **4b**	78
3	**3c**	Me, H, CH_3, Cl, CH **4c**	76
4	**3d**	Me, H, Me, CH_3, CH **4d**	80
5	**3e**	Me, H, C_6H_4Me-*p*, F, CH **4e**	85
6	**3f**	Me, H, C_6H_4Me-*p*, H, CH **4f**	83
7	**3g**	Me, H, C_6H_4Me-*p*, Cl, CH **4g**	81
8	**3h**	Me, H, C_6H_4Me-*p*, Br, CH **4h**	68
9	**3i**	Me, H, 2-thienyl, CH_3, CH **4i**	87
10	**3j**	Me, H, 2-thienyl, F, CH **4j**	84
11	**3k**	Me, H, 2-thienyl, H, CH **4k**	80
12	**3l**	Allyl, H, CH_3, CH_3, CH **4l**	74
13	**3m**	Allyl, H, CH_3, F, CH **4m**	70
14	**3n**	Allyl, H, CH_3, Cl, CH **4n**	78
15	**3o**	Allyl, H, C_6H_4Me-*p*, CH_3, CH **4o**	78
16	**3p**	Allyl, H, C_6H_4Me-*p*, F, CH **4p**	76
17	**3q**	Allyl, H, C_6H_4Me-*p*, Cl, CH **4q**	70
18	**3r**	Allyl, H, C_6H_4Me-*p*, Br, CH **4r**	69
19	**3s**	Benzyl, H, C_6H_4Me-*p*, F, CH **4s**	75
20	**3t**	Me, Cl, C_6H_4Me-*p*, F, N **4t**	70

[a] Reaction conditions: **3** (1.0 mmol), $Pd_2(dba)_3$ (5 mol%) and Et_3N (2.5 mmol) in DMF (5 mL) at 130 °C for 5 h under N_2. [b] Isolated yield.

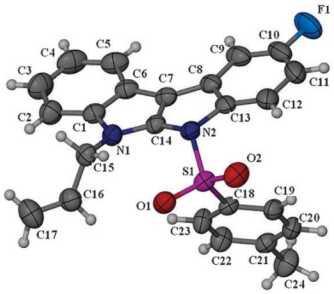
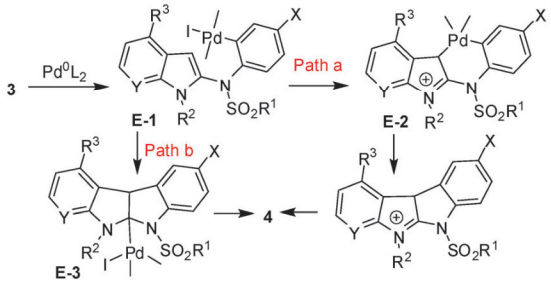


Fig. 3 ORTEP representation of the compound **4p**. Thermal ellipsoids are drawn at 50% probability level.

for their ability to inhibit Sir2 protein by estimating inhibition of growth of the yeast strain containing the Ura3 gene at the telomeric locus, in the presence of 5-fluoroorotic acid (5-FOA) (see ESI†).[9] A compound having the sirtuin inhibitory effect would inhibit the Sir2 protein, and thus the URA3 gene would be de-repressed resulting in the death of the yeast cell in the



Scheme 2 The proposed reaction mechanism.

presence of 5-FOA. A parallel screening was performed in the absence of 5-FOA to check the cytotoxicity of the compounds. Among all the compounds tested **4a**, **4b** (or **A**, Fig. 1) and **4e** showed significant inhibition[10] (>40%) in the presence of 5-FOA and no significant toxic effect in the absence of 5-FOA.

In conclusion, functionalized indolo[2,3-*b*]indoles have been synthesized for the first time as a novel and unique class of heteroaromatics *via* a new and versatile Pd-mediated method for the potential inhibition of yeast sirtuins.

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10 **4b** showed superior inhibition than **4a** which corroborated with the results of docking studies (see ESI†).

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Bagineni Prasad,[a] B. Yogi Sreenivas,[a] G. Rama Krishna,[b] Ravikumar Kapavarapu[c] and Manojit Pal*[a]

Unprecedented synthesis of functionalized indoles of potential pharmacological interest has been developed *via* a Pd-mediated cascade reaction involving an intramolecular Heck coupling followed by the construction of a fused cyclopentane ring in a single pot.

Rigid conformation *via* restriction of three dimensional relationships of multiple functional groups present on a polycyclic–heterocyclic system often renders specific and promising pharmacological properties, highly desirable for medicinal chemistry/drug discovery efforts. Cascade reactions[1] involving formation of several bonds and stereogenic centers in a single synthetic operation on the other hand are considered as powerful tools for the construction of such polycyclic–heterocyclic structures. Thus the development of cascade reactions especially those catalyzed by transition metals is of remarkable interest.

Indoles are prevalent in Nature and considered as valuable building blocks in organic synthesis[2] as well as privileged pharmacophores in drug discovery. For example, a fused indole *i.e.* 1,2,3,4-tetrahydrocyclopenta[*b*]indole is an integral part of natural product bruceollines[3a] and a known drug laropiprant.[3b] This prompted us to explore cyclopenta[*b*]indole **D** as a new class of potential inhibitors of phosphodiesterase 4 (PDE4). PDE4 inhibitors are proved to be promising anti-inflammatory agents for the potential treatment of chronic obstructive pulmonary disease (COPD) and asthma.[4] Our target molecules **D** derived from a known PDE4 inhibitor **A** *via* **B**[5a] and incorporating some of the structural features of another known inhibitor **C**[5b] (Fig. 1) were designed based on the *in silico* docking studies of a representative compound **E** in the active site of PDE4B (see **4b** in the ESI†).[5c]

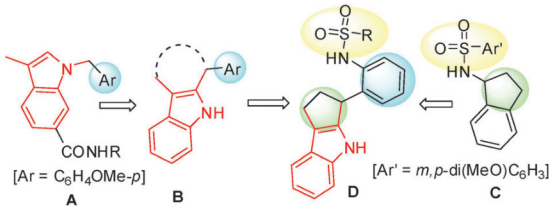
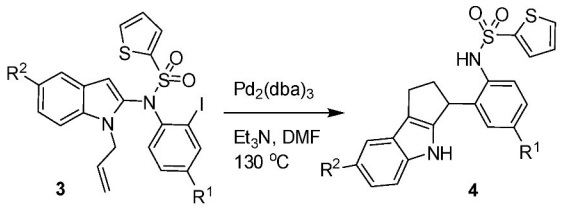


Fig. 1 Design of **D** as novel inhibitors of PDE4.

While elegant methods leading to cyclopenta[*b*]indoles *via* Lewis acid catalyzed formal [3+2] addition of indolylmethyl cations to alkenes[6a,b] or Pd-mediated approaches *e.g.* aerobic oxidative annulations of indoles[6c] or domino N–H/C–H bond activation[6d,e] are known none of them appeared to be handy for the quick access to **D**. As part of our ongoing studies on newer synthesis of functionalized heteroaromatics[7] including fused indoles[8] we further investigated the reactivity of *N*-(1-allyl-1*H*-indol-2-yl)-*N*-(2-iodoaryl)thiophene-2-sulfonamides towards Pd catalysts. To our surprise the reaction followed an unusual path affording novel cyclopenta[*b*]indoles *i.e.* *N*-(2-(7-substituted-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)-aryl)thiophene-2-sulfonamides as unexpected products (Scheme 1). We were delighted with this timely observation as this appeared to have potential to become a methodology for the direct access to a library of small molecules based on **D**. Herein we report conceptually new synthesis of functionalized cyclopenta[*b*]indoles *via* a Pd-mediated cascade reaction involving an intramolecular Heck coupling followed by the construction of a fused cyclopentane ring as a result of



Scheme 1 Pd-mediated synthesis of novel cyclopenta[*b*]indoles.

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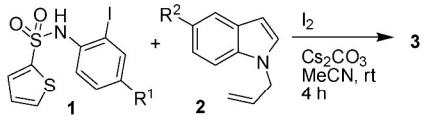
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, results of *in vitro* and docking study. CCDC 918746. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc42309c

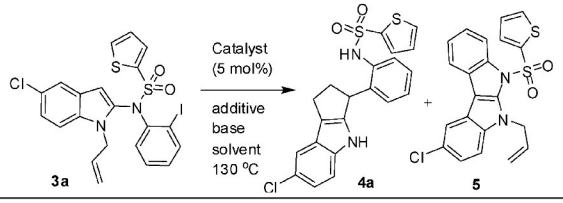


Scheme 2 Iodine-mediated synthesis of sulfonamide **3**.

cleavage of two C–N bonds and formation of several C–C bonds in a single pot.

The key starting material **3** required was prepared *via* C-2 amination of indoles (**2**) using *N*-sulfonyl arylamines (**1**) (Scheme 2).[9] The Pd-mediated cascade reaction of **3a** was then performed under a variety of conditions (Table 1) to establish the optimized reaction conditions. Initially, **3a** was treated with Pd_2dba_3 and Et_3N in EtOH at 80 °C for 15 h, when **4a** was obtained as a major product (48%) along with indolo[2,3-*b*]indole **5** (12%) and some unreacted **3a** (entry 1, in Table 1). Though the yield of **4a** was increased when the reaction was performed in PEG or DMF–H_2O (entries 2 and 3, Table 1) a significant improvement was observed when DMF alone was used (entry 4, Table 1). The use of other bases *e.g.* DBU or K_2CO_3 was not effective (entries 5 and 6, Table 1). **4a** was also not obtained when $Pd(OAc)_2$ was used as a catalyst (entry 7, Table 1), whereas the use of $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ or Pd/C-PPh_3 afforded **4a** in poor yield (entries 8–10, Table 1). The combination of $Pd(OAc)_2$ with PPh_3 or X-Phos (entries 11–13, Table 1) or the use of $Cu(OAc)_2$ as a co-catalyst (entries 14 and 15, Table 1) mainly

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst/additive	Base/solvent	Time (h)	Yield[b] (%) 4a	5
1[c,d]	$Pd_2(dba)_3$	Et_3N/EtOH	15	48	12
2	$Pd_2(dba)_3$	Et_3N/PEG	7	67	25
3	$Pd_2(dba)_3$	Et_3N/DMF : H_2O (8 : 2)	7	63	28
4	$Pd_2(dba)_3$	Et_3N/DMF	7	80	16
5	$Pd_2(dba)_3$	DBU/DMF	7	58	36
6	$Pd_2(dba)_3$	K_2CO_3/DMF	7	—	75
7	$Pd(OAc)_2$	Et_3N/DMF	4	—	84
8[e]	$Pd(PPh_3)_2Cl_2$	Et_3N/DMF	7	30	—
9[e]	$Pd(PPh_3)_4$	Et_3N/DMF	7	32	—
10[e]	Pd/C/PPh_3	Et_3N/DMF	12	30	—
11	$Pd(OAc)_2$/PPh_3	Et_3N/DMF	5	—	84
12	$Pd(OAc)_2$/X-Phos	Et_3N/DMF	4	22	70
13[f]	$Pd(OAc)_2$/X-Phos	Et_3N/DMF	4	—	83
14	$Pd(PPh_3)_2Cl_2$/ $Cu(OAc)_2$	Et_3N/DMF	4	—	81
15	$Pd_2(dba)_3$/$Cu(OAc)_2$	Et_3N/DMF	4	—	83
16	$Pd_2(dba)_3$/LiCl	Et_3N/DMF	7	47	48
17[g]	$Cu(OAc)_2$	Et_3N/DMF	8	—	—

[a] All the reactions were performed using **3a** (0.4 mmol), catalyst (5.0 mol%) and base (1.2 mmol) in a solvent (2.0 mL) at 130 °C. [b] Isolated yield. [c] The reaction was performed at 80 °C. [d] The starting material was not consumed completely. [e] Formation of an additional unidentified product was observed. [f] The reaction was performed at room temperature. [g] 1.0 mmol of catalyst was used.

Table 2 Synthesis of cyclopenta[*b*]indoles (**4**) (Scheme 1)[a]

Entry	Compound (3); R^1, R^2, X	Product (4); R^1, R^2	Yield[b] (%)
1	H, Cl, I (**3a**)	H, Cl (**4a**)	80
2	H, H, I (**3b**)	H, H (**4b**)	81
3	F, H, I (**3c**)	F, H (**4c**)	71
4	CH_3, H, I (**3d**)	CH_3, H (**4d**)	76
5	Cl, H, I (**3e**)	Cl, H (**4e**)	78
6	CH_3, Cl, I (**3f**)	CH_3, Cl (**4f**)	68
7	Br, Br, I (**3g**)	Br, Br (**4g**)	83
8	H, Br, I (**3h**)	H, Br (**4h**)	72
9	H, OMe, I (**3i**)	H, OMe (**4i**)	70
10	CH_3, OMe, I (**3j**)	CH_3, OMe (**4j**)	81
11	CH_3, Br, I (**3k**)	CH_3, Br (**4k**)	80
12	Br, OMe, I (**3l**)	Br, OMe (**4l**)	68
13	F, OMe, I (**3m**)	F, OMe (**4m**)	62
14	Br, H, I (**3n**)	Br, H (**4n**)	78
15	Br, Cl, I (**3o**)	Br, Cl (**4o**)	70
16	Cl, Cl, I (**3p**)	Cl, Cl (**4p**)	71
17	Cl, NO_2, I (**3q**)	Cl, NO_2 (**4q**)	66
18	Cl, Br, I (**3r**)	Cl, Br (**4r**)	68
19	F, Cl, I (**3s**)	F, Cl (**4s**)	68
20	Cl, CN, I (**3t**)	Cl, CN (**4t**)	59
21	F, NO_2, I (**3u**)	F, NO_2 (**4u**)	62
22	CH_3, NO_2, I (**3v**)	CH_3, NO_2 (**4v**)	73
23	Cl, OMe, I (**3w**)	Cl, OMe (**4w**)	69
24	CH_3, OMe, Br (**3x**)	No reaction	-

[a] Reactions were performed using **3** (0.4 mmol), $Pd_2(dba)_3$ (5 mol%) and Et_3N (1.2 mmol) in DMF (2 mL) at 130 °C for 7 h under N_2. [b] Isolated yield.

provided **5** as a major or the only product. The use of LiCl additive afforded a **1 : 1** mixture of **4a** and **5** (entry 16, Table 1) whereas $Cu(OAc)_2$ in place of the Pd-catalyst was found to be ineffective (entry 17, Table 1). Overall, $Pd_2(dba)_3$ and Et_3N in DMF (entry 4, Table 1) were found to be optimum for the preparation of **4a**.

We then performed the Pd-mediated cascade reaction using various indole derivatives **3** (Table 2). Substituents like F, Cl, Br, and OMe or electron withdrawing NO_2 and CN groups were well tolerated and afforded **4** in good to acceptable yields. Notably, unlike **3** its bromo analogue *i.e.* *N*-(1-allyl-5-methoxy-1*H*-indol-2-yl)-*N*-(2-bromo-4-methylphenyl)thiophene-2-sulfonamide **3x** failed to participate in the present reaction (entry 24, Table 2). All the compounds synthesized were well characterized by spectral (NMR, IR and MS) data and the molecular structure of a representative compound **4b** was confirmed unambiguously by single crystal X-ray diffraction study (Fig. 2).[10]

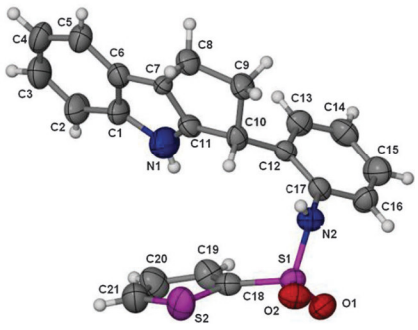
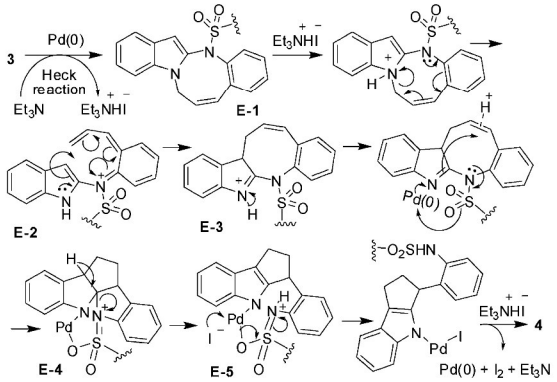


Fig. 2 ORTEP representation of **4b**. Thermal ellipsoids are drawn at the 50% probability level.



Scheme 3 The proposed reaction mechanism.

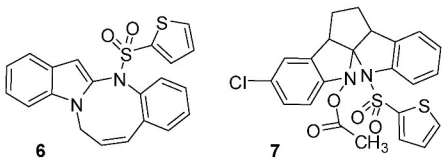


Fig. 3 The Heck product **6** isolated from the reaction of **3b** and the side product **7** isolated from **3a**.

Mechanistically, the reaction seemed to proceed *via* generation of **E-1** *in situ* as a result of an intramolecular Heck reaction which then undergoes a C–N bond cleavage near the indole nitrogen to give **E-2** (Scheme 3). A subsequent intramolecular attack of the indole ring *via* its C-3 position on –C=C– provides **E-3**. Activation of –C=N– of **E-3** in the presence of Pd(0) aided by the proximate sulfonamide moiety facilitated a further intramolecular attack on the olefinic bond leading to **E-4**. The six-membered Pd-containing ring of **E-4** then undergoes C–N bond cleavage to give **E-5** which after following a few more steps including the reductive elimination of Pd(0) to complete the catalytic cycle afforded product **4**. It is evident that the sulfonamide moiety played a key role in the present cascade reaction, the electron releasing property of which towards Pd was greatly facilitated by the electron rich thienyl moiety. This perhaps provides some explanations to the observation that replacing the thienyl moiety of **3** by a *p*-tolyl ring did not provide **4** as a major product.[8a] Nevertheless, it is evident from Table 1 that the formation of **4** was also dependent on the nature of catalyst/solvent used.

The initial Heck type coupling was supported by the fact that the corresponding Heck product **6** (*cf.* **E-1**, Fig. 3) was isolated from the reaction of **3b** (see ESI† for spectral data).[11] While all our attempts to isolate any other intermediates **E-2-5** were not successful we, however, were able to isolate a side product **7** (analogous to **E-4**) (Fig. 3) along with **4a** from the conversion of **3a** under the condition of entry 4 of Table 1 in the presence of catalytic acetic acid. Compound **7** seemed to have formed *via* a nucleophilic attack on the iminium nitrogen of the intermediate obtained from **E-3** by the acetate ion (instead of Pd, *cf.* Scheme 3). This suggests that the present cascade reaction arguably proceeds *via* **E-4**.

Some of the compounds synthesized were tested against PDE4B *in vitro*[12] when **4b**, **4e**, **4g**, **4i**, **4j**, **4k**, **4h**, **4n** and **4q** showed 43, 41, 40, 74, 49, 40, 42, 45 and 58% inhibition, respectively, at 30 μM and **4i** (IC_{50} > 5 μM *vs.* rolipram's IC_{50} ~ 1 μM) being the best among them.

In conclusion, novel cyclopenta[*b*]indoles have been synthesized as potential inhibitors of PDE4 *via* a Pd-mediated new cascade reaction involving an intramolecular Heck coupling followed by the construction of a fused cyclopentane ring in a single pot.

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A Pd-based regioselective strategy to indole-1,2-fused 8- and 9-membered rings: their evaluation as potential scaffolds for apoptosis in zebrafish†

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A strategy based on Pd-mediated ring closure of 1,2-disubstituted indoles containing an unactivated olefin leading to indole-1,2-fused 8- and 9-membered rings has been developed for the identification of new and potential scaffolds for apoptosis. A large number of fused indole derivatives containing an endocyclic double bond were synthesized using this robust methodology. A representative compound showed promising apoptotic properties in zebrafish embryos.

Compounds containing 6-, 7- or 8-membered ring fused with an indole framework at the 1,2-position (**A**, Fig. 1) are not only of immense importance in medicinal chemistry and pharmacology but also common targets in synthetic organic chemistry. For example, synthesis of indolo-diazepines (**B**, Fig. 1) possessing antiserotonin activities,[1] 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,7-*a*]indole (**C**, Fig. 1) possessing antipressant[2] and CNS related activities,[3] indolo-1,5-benzodiazocine (**D**, Fig. 1) having CNS related activities,[4] 2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[1,2-*a*]indole (**E**, Fig. 1) possessing 5-HT antagonistic properties[5] are mention worthy.

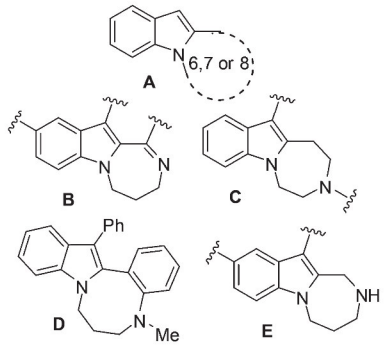

Fig. 1 Compounds containing 6- or 7- or 8-membered ring fused with indole at the 1,2-position.

Surprisingly, while compounds containing an indole-2,3-fused 7- or 8-membered ring system have been explored for potential anticancer/antitumor activities[6–9] their indole-1,2-fused analogues remain less or unexplored for this purpose. More importantly, reports describing the pharmacological properties of compounds containing indole-2,3-fused 9 membered ring system are not common in the literature perhaps due to the cumbersome or non accessibility of this class of indoles. It was therefore necessary to access and evaluate compounds containing indole-1,2-fused 8- or 9-membered ring for their potential anticancer especially apoptotic properties. Notably, cancer is associated with a lower degree of apoptosis and most of the cytotoxic anticancer agents are known to induce apoptosis. Apoptosis[10] that occurs in physiological and pathological conditions is an ordered and orchestrated cellular process. The complex mechanism of apoptosis involves many pathways. Defects in apoptotic pathways are thought to contribute to a number of human diseases, ranging from neurodegenerative disorders to malignancy.[10] The design of our target molecules **I** was prompted by known cytotoxic agents **F** containing an indole-2,3-fused 7-membered ring system[6] (Fig. 2). Thus the generic structure **I** was drawn from **F** *via* some necessary structural manipulations through **G** and then **H** as shown in Fig. 2.

A number of methods have been reported for the synthesis of indole-fused 7- and 8-membered rings at the 1,2 position that can be classified according to the substrates used and the bond formed in the ring-closing step.[11] These includes either indole ring formation on a preformed 7- or 8-membered ring or ring closure of (i) *N*-substituted indoles *via* bond formation to C-2 position, (ii) 2-substituted indoles *via* bond formation to N-1 position and (iii) 1,2-disubstituted indoles *via* bond formation between the substituents. While many of these methods are very effective and elegant to access a particular class of fused indole derivatives some of them suffer from

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[b]*Zephase Therapeutics (an incubated company at the Dr Reddy's Institute of Life Sciences), University of Hyderabad Campus, Gachibowli, Hyderabad 500046, India*

†Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, copies of spectra. See DOI: 10.1039/c4ob00140k

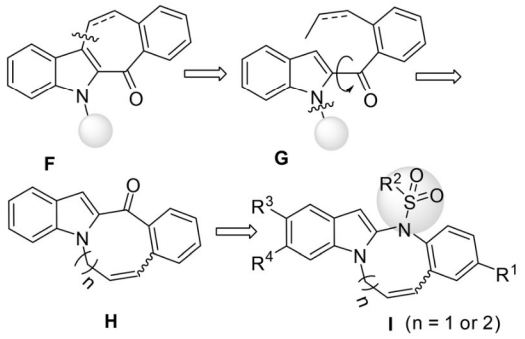
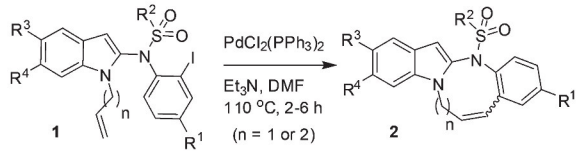


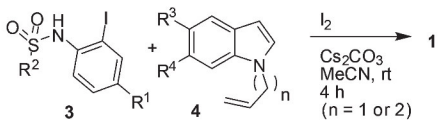
Fig. 2 Design of novel and potential apoptotic agents **I** from **F**.

being not general and versatile in nature. Additionally, construction of an indole-fused 9-membered ring at the 1,2 position appeared as difficult or not feasible by using some of these methodologies. We therefore required a general and robust method to prepare our target compound **I**. Herein, we report an effective method for the direct access to **I** (or **2**) *via* Pd-mediated intramolecular ring closure of 1,2-disubstituted indoles **1** (Scheme 1).

Since its discovery in 1977,[12] the intramolecular Heck reaction has become a powerful tool for the quick construction of carbocyclic/heterocyclic rings.[13] Intramolecular[12a] Heck reactions are generally more efficient and regioselective than their intermolecular[12b] version. While ring closure was found to be highly *exo* selective for 5-, 6- and 7-membered rings and *endo* selective for 13-membered and larger rings a mixture of *exo* and *endo* products were formed in the closure of medium sized, *i.e.* 8–12 membered, rings. Nevertheless, we adopted a similar Pd-mediated strategy to prepare our target compound **2**. The key starting material **1** required was prepared *via* C-2 amination of indoles **3** using *N*-sulfonyl arylamines **4** (Scheme 2).[14] We then performed the Pd-mediated intramolecular reaction of **1a** under a variety of conditions (Table 1) to establish the optimized reaction conditions. Initially, **1a** was

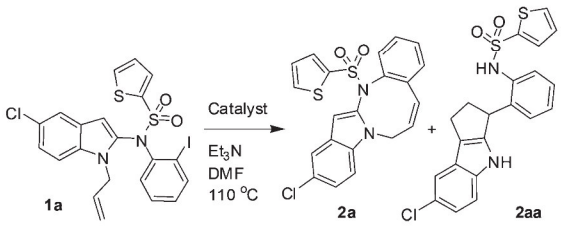


Scheme 1 Synthesis of compound **2** *via* Pd-mediated intramolecular ring closure of 1,2-disubstituted indoles **1**.



Scheme 2 Iodine-mediated synthesis of sulfonamide **1**.

Table 1 Optimization of reaction conditions[a]



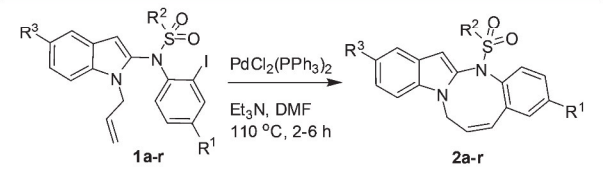
Entry	Catalyst/additive	Time (h)	Yield[b] (%) 2a	2aa
1	$Pd(PPh_3)_2Cl_2$	4	63	30
2	$Pd(PPh_3)_4$	4	54	32
3	$Pd/C/PPh_3$	12	51	30
4[c]	$Cu(OAc)_2$	12	0	0

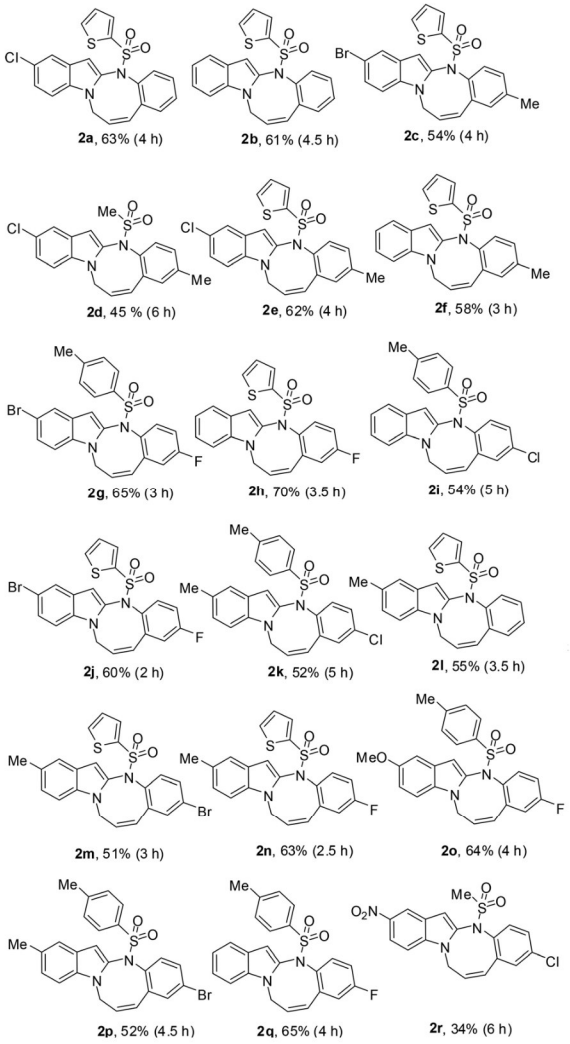
[a] Reactions were carried out using **1a** (0.2 mmol), catalyst (5 mmol%) and Et_3N (0.4 mmol) in DMF (2 mL) at 110 °C. [b] Isolated yield. [c] 1 mmol of catalyst used.

treated with $Pd(PPh_3)_2Cl_2$ and Et_3N in DMF at 110 °C for 4 h, when the desired product **2a** containing an endocyclic double bond was isolated in 63% yield (entry 1, Table 1). While the cyclopenta[*b*]indole[15] **2aa** was isolated as a side product in this case the formation of no isomeric product containing exocyclic double bond was detected. The use of other catalysts *e.g.* $Pd(PPh_3)_4$ (entry 2, Table 1), $Pd/C/PPh_3$ (entry 3, Table 1) and $Cu(OAc)_2$ (entry 4, Table 1) was examined when yield of **2a** was not improved in first two cases and the reaction did not proceed in the last case.

A variety of compounds containing indole-1,2-fused 8-membered rings were prepared by using the optimized reaction conditions in acceptable yields (Table 2). A number of analogues containing indole-1,2-fused 9-membered rings were also prepared using this methodology (Table 3). All the synthesized compounds were well characterized by spectral data (NMR, IR & MS). The coupling constant (J = 11.2–11.5 Hz) of the H^b proton appeared in the region 6.8–6.9 ppm in the ^{1}HNMR spectra of compounds **2a–r** and this indicated that a *cis* geometry of the double bond was present in these compounds. This was further supported by the interaction of H^a proton (6.00 ppm) with H^b (6.8 ppm) (being at the same side of the double bond) upon irradiation in a 1D NOE experiment performed using the compound **2b** (Fig. 3). However, the coupling constants of the olefinic protons could not be measured in the case of compounds **2s–x** due to the complex nature of these signals in their ^{1}H NMR spectra (see ESI†). The 1D NOE experiment performed in the case of compound **2s** was not conclusive (see ESI†). Notably, the DEPT experiment (^{13}C NMR) of **2s** confirmed the presence of an endocyclic (not exocyclic) double bond in the 9-membered ring. It is worthy to mention that the *endo* mode of the intramolecular Heck cyclization has been reported to be favored for substrates that contain a Michael-type olefinic fragment (termed as electronic

Table 2 Pd-mediated synthesis of indole-1,2-fused 8-membered rings (**2a–r**)[a,b]

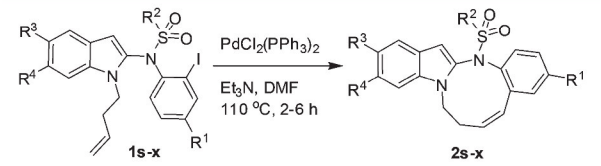


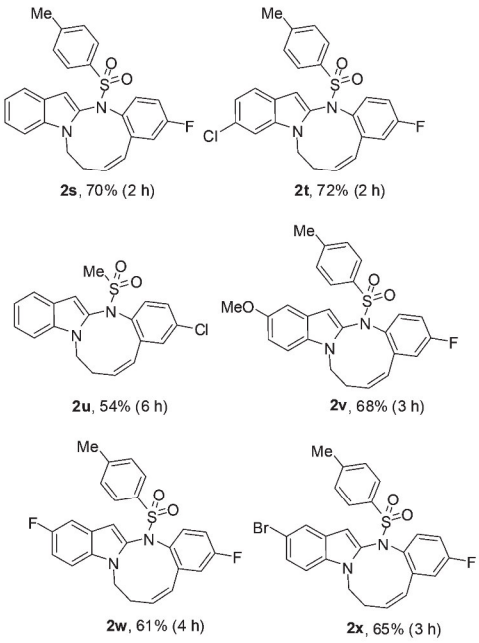


[a] All the reactions were performed using **1a–r** (0.2 mmol), $PdCl_2(PPh_3)_2$ (5 mol%) and Et_3N (0.4 mmol) in DMF (2 mL) at 110 °C for 2–6 h under N_2. [b] Figures indicate % yield and reaction time.

reasons)[13a] leading to 7-, 8- or 9-membered rings.[16a] This is in sharp contrast to our observations where such electronic reasons did not aid the endocyclization process. Additionally, we were able to achieve this mode of cyclization using unactivated olefin as one of the reactant moieties.

Table 3 Pd-mediated synthesis of indole-1,2-fused 9-membered rings (**2s–x**)[a,b]





[a] All the reactions were performed using **1s–x** (0.2 mmol), $PdCl_2(PPh_3)_2$ (5 mol%) and Et_3N (0.4 mmol) in DMF (2 mL) at 110 °C for 2–6 h under N_2. [b] Figures indicate % yield and reaction time.

Based on our experimental observations a proposed reaction mechanism is presented in Scheme 3. While the reaction seems to follow a classical Heck coupling pathway[12b] *i.e. via* the generation of intermediate **X** (but not **Y**) the regioselectivity of the double bond formation is the key feature of the present process. The higher stability of the resultant conjugated double bond (*i.e.* the styrene moiety) over the isolated one perhaps aided the regioselective elimination of H-Pd species from **X** leading to the product **2**. The flexible geometry due to

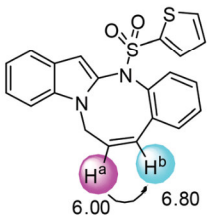
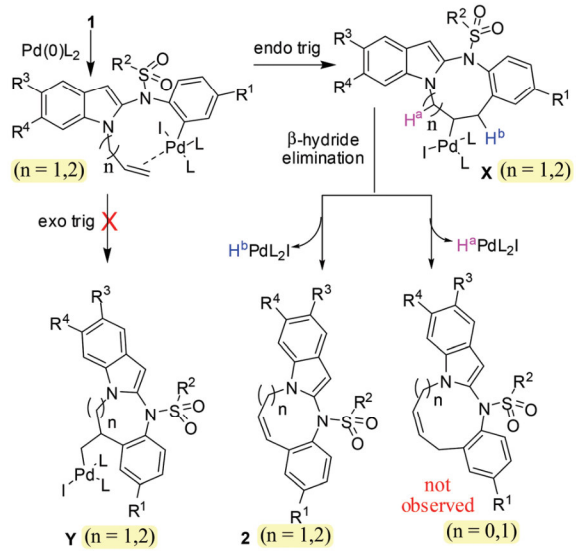


Fig. 3 1D NOE experiment of compound **2b**.



Scheme 3 The proposed reaction mechanism leading to **2**.

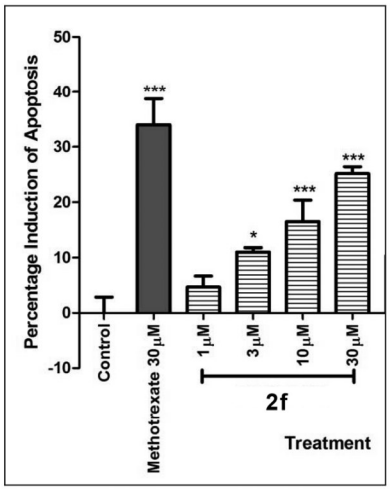


Fig. 4 The percentage induction of apoptosis caused by compound **2f** at different concentrations along with methotrexate. All the statistical analyses were performed using GraphPad Prism® software.

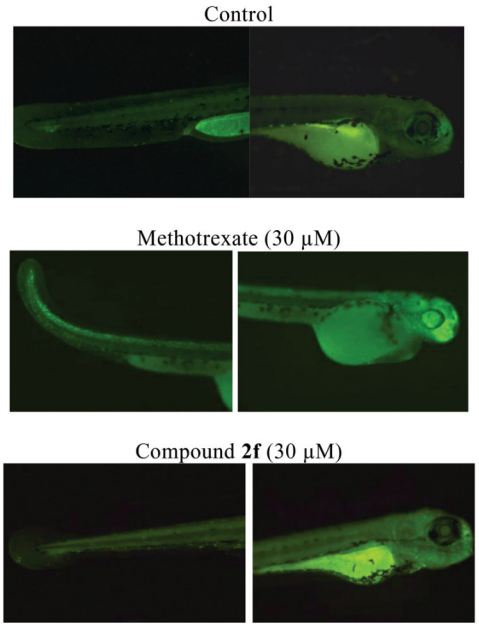


Fig. 5 Representative images of the embryos treated with methotrexate and compound **2f** assayed for apoptosis.

the large ring size of **X** could be the other reason for affording the *cis* olefin rather than the *trans* product usually observed in the case of intermolecular Heck reaction.[16b]

All the synthesized compounds were tested for their apoptotic activities initially at 30 μM using Zebrafish embryos. Zebrafish (or *Danio rerio*), a small pet-shop fish, is being explored as a tool for enhancing interdisciplinary studies in biology and chemistry as well as in drug discovery.[17] Indeed, Zebrafish provides an inexpensive, reliable and efficient first-level screening model for testing toxicity, efficacy, and tissue-targeting for a large number of new chemical entities (NCEs). Our continued interest[18–24] in Zebrafish as a screening model for NCEs prompted us to assess the potential pharmacological effects of the present class of molecules in Zebrafish and/or their embryos. The most active compound *e.g.* **2f** was tested at 1, 3, 10, and 30 μM along with a standard drug methotrexate. The percentage induction of apoptosis caused by compound **2f** at different concentrations along with methotrexate is shown in Fig. 4 and the representative images of embryos are shown in Fig. 5. Compound **2f** showed dose-dependent increase in apoptotic activity along with promising activities both at 10 and 30 μM. The EC_{50} and the percentage induction of apoptosis of the compounds were calculated. The EC_{50} of compound **2f** was found to be 8.88. Pro-apoptotic chemotherapeutic drugs provide an approach to overcoming the clinical problem of drug resistance[25] and hence the present class of molecules may have potential medicinal value.

In conclusion, we have described a strategy based on Pd-mediated intramolecular *endo*-trig ring closure of 1,2-disubstituted indoles leading to indole-1,2-fused 8- and 9-membered rings for the identification of new and potential scaffolds for apoptosis. The methodology involved the use of unactivated olefin and proceeded with regioselective formation of an endocyclic double bond, the geometry of which was assigned as *cis* in the case of compounds containing indole-1,2-fused 8-membered rings. A large number of fused indole derivatives were synthesized using this robust methodology and a representative compound showed promising apoptotic properties when tested in zebrafish embryos. As most of the cytotoxic anticancer agents are known to induce apoptosis the present class of indoles seemed to possess potential medicinal value. The

strategy presented here could therefore be useful for the design and discovery of potential new drugs.

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