Investigations on the Reactions of Acetoxy Allenoates and Indolyl-iodoarylsulfonamides in Cyclization or C-C Bond Formation

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

By

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MAY 2023

I dedicate this thesis to

My Family,

Teachers, and

Friends……

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PART A

DIVERGENT REACTIVITY OF *δ*-ACETOXY ALLENOATES WITH THIOAMIDES, *N*-SULFONYL HYDRAZIDES, AND 1,3-DICARBONYL COMPOUNDS

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of Prof. K. C. Kumara Swamy.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the finding of other investigators.

Hyderabad

May, 2023

Shabbir Ahmed Khan

DECLARATION

I, Shabbir Ahmed Khan hereby declare that this thesis entitled **"Investigations on the Reactions of Acetoxy Allenoates and Indolyl-iodoarylsulfonamides in Cyclization or C-C Bond Formation"** submitted by me under the guidance and supervision of **Professor K. C. Kumara Swamy** is a bonafide research work which is also free from plagiarism. I also declare that it has not been submitted previously in part or in full to this University or any other University or Institution for the award of any degree or diploma. I hereby agree that my thesis can deposited in Shodganga/INFLIBNET.

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Signature of the supervisor:

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CERTIFICATE

This is to certify that the thesis entitled "Investigations on the Reactions of Acetoxy Allenoates and Indolyl-iodoarylsulfonamides in Cyclization or C-C Bond Formation" submitted by Mr. Shabbir Ahmed Khan bearing registration number 17CHPH13 in partial fulfillment of the requirements for award of Doctor of Philosophy in the School of Chemistry is a bonafide work carried out by him under my supervision and guidance.

This thesis is free from plagiarism and has not been submitted previously in part or in full to this or any other University or Institution for award of any degree or diploma. Further the student has three publications before the submission of his thesis.

Part of this thesis has been published in the following publications:

1. **Khan, S. A**$^{\#}$.; Kumar, A. S$^{\#}$.; Kumara Swamy, K. C. *J. Org. Chem.* **2022**, *87*, 1285
2. Sunke, R$^{\#}$.; **Khan, S. A**$^{\#}$. Kumara Swamy, K. C. *Org. Biomol. Chem.* **2022**, *20*, 9148.
3. **Khan, S. A**$^{\#}$.; Kumar, A. S$^{\#}$.; Kumara Swamy, K. C. *Org. Lett.* **2023**, 0000. DOI: https://doi.org/10.1021/acs.orglett.3c01166

The following papers are to be communicated.

4. **Khan, S. A.**; Kumara Swamy, K. C. (*to be communicated*).

He has also made presentations in the following conferences:

1. Poster presentation in the 27th CRSI National Symposium in Chemistry Organized by IISER Kolkata, INDIA, 27-29 September 2021.

2. Oral and Poster presentation in the *Chemfest-2022* (annual in-house symposium), School of Chemistry, University of Hyderabad, INDIA, April 2022.

Further, the student has passed the following courses towards the fulfillment of the coursework requirement for Ph. D:

Sl. No	Course No	Title of the course	No of Credits	Grade
1.	CY801	Research proposal	4	Pass
2.	CY805	Instrumental methods-A	4	Pass
3.	CY806	Instrumental methods-B	4	Pass

Final Result: Passed.

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I would like to express my sincere gratitude to *all my childhood friends, BSc and MSc friends and my friends in School of Chemistry* for their support in many ways. All of them have been very kind, generous, affectionate and helpful.

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I thank the University Grants Commission (UGC, New Delhi) for financial support. I also thank Department of Science and Technology (New Delhi; under FIST and PURSE) and UGC (New Delhi; under UPE and CAS) for setting up many equipment facilities at the University of Hyderabad.

Family is the backbone for my success. During my whole journey they were always there to support me. Without my parents Md Imtiaz Khan and Mosarrat Jahan, it was impossible for me to stand in this platform and achieve something. I would also like to mention my sister Farzana Khatoon for enormous love and encouragement.

Shabbir...

LIST OF PUBLICATIONS

(A) ***Published papers:***

1. Reactions of alkynes copper-catalyzed cyclization of functionalized alkynes with elemental sulfur/selenium to form oxathiines/oxaselenines
   D. Gattaiah, Alla Siva Reddy, **Shabbir Ahmed Khan,** and K.C. Kumara Swamy
   J. Organomet. Chem. **2019**, *889*, 33.

2. Pyridine vs DABCO vs TBAB in annulations of δ-acetoxy allenoates with thioamides leading to dihydrothiophene, thiopyran, and thiazole Scaffolds
   Shabbir Ahmed Khan, [#] A. Sanjeeva Kumar, [#] and K. C. Kumara Swamy*
   J. Org. Chem. **2022**, *87*, 1285.

3. Pd-catalyzed intramolecular transformations of indolyl-iodobenzenesulfonamides: *ortho*-sulfonamido-bi(hetero)aryls *via* C2-arylation and polycyclic sultams *via* C3 arylation
   Rajnikanth Sunke, [#] **Shabbir Ahmed Khan**,[#] and K. C. Kumara Swamy*
   Org. Biomol. Chem. **2022**, *20*, 9148.

4. DBU-catalyzed ring expansion or ene-amine formation involving *δ*-acetoxy allenoates and *N*-sulfonyl hydrazides
   Shabbir Ahmed Khan, [#] A. Sanjeeva Kumar, [#] and K. C. Kumara Swamy*
   Org. Lett. **2023**, 0000. DOI: https://doi.org/10.1021/acs.orglett.3c01166

(B) ***The following paper is to be communicated.***

5. Lewis base catalyzed (3 + 3) annulation of acetoxy allenoates with 1,3-dicarbonyl compounds: Synthesis of pyran scaffolds. (*to be communicated*).
   Khan, S. A and K. C. Kumara Swamy*

Participation in Conferences/ Symposia

1. Pyridine vs DABCO vs TBAB in annulations of δ-acetoxy allenoates with thioamides leading to dihydrothiophene, thiopyran, and thiazole scaffolds
   Shabbir Ahmed Khan, [#] A. Sanjeeva Kumar, [#] and K. C. Kumara Swamy*
   Poster presentation in the 27th CRSI National Symposium in Chemistry Organized by IISER Kolkata, INDIA, 27-29 September 2021.

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   Oral and Poster presentation in the *Chemfest-2022* (annual in-house symposium), School of Chemistry, University of Hyderabad, INDIA, April 2022.

Synopsis

This thesis is divided into two parts: **Part-A** and **Part-B**. **Part-A** deals with the following topics: (i) Pyridine vs DABCO vs TBAB in annulation of *δ*-acetoxy allenoates with thioamides leading to dihydrothiophene, thiopyran, and thiazole scaffolds, (ii) DBU-catalyzed ring-expansion or ene-amine formation involving *δ*-acetoxy allenoates and *N*-sulfonyl hydrazides (iii) DMAP and DBU-catalyzed annulation of *δ*-acetoxy allenoates with 1,3-dicarbonyl compounds leading to dihydropyrans and 4*H*-pyrans. **Part-B** deals with the palladium-catalyzed intramolecular transformations of indolyl-iodoarylsulfonamides that lead to *ortho*-**s**ulfonamido-bi(hetero)aryls *via* C2-arylation or polycyclic sultams *via* C3 arylation.

Compounds synthesized in the present study are, in general, characterized by melting point, IR, and NMR [^{1}H, ^{13}C{^{1}H} and ^{19}F] techniques in conjunction with LC-MS/ HRMS/ elemental (CHN) analyses. X-ray structure determination has been undertaken wherever required. A summary and, as well as references, are given at the end of each part.

PART A

In Chapter 1, a review of the literature on aspects relevant to this part is presented. In Chapter 2, the results obtained are discussed while in Chapter 3, the experimental details are described. The precursors used in the present study are shown in Chart 1. The compound numbers given here are different from that in the main part of the thesis.

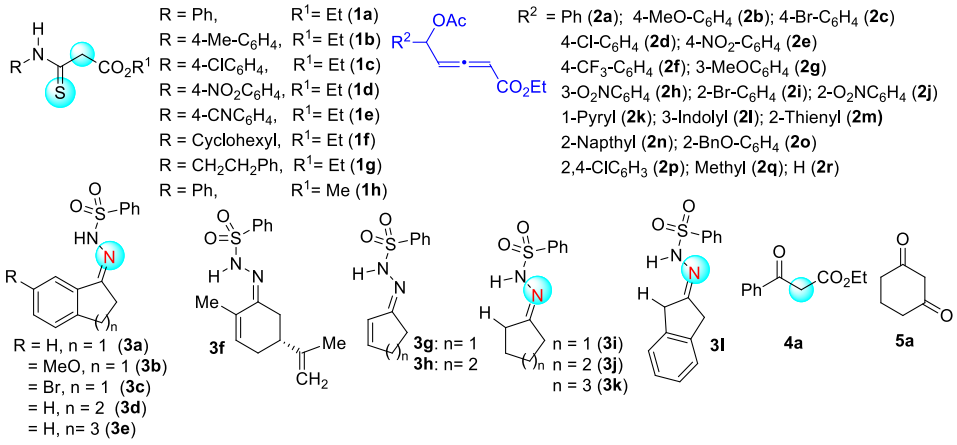
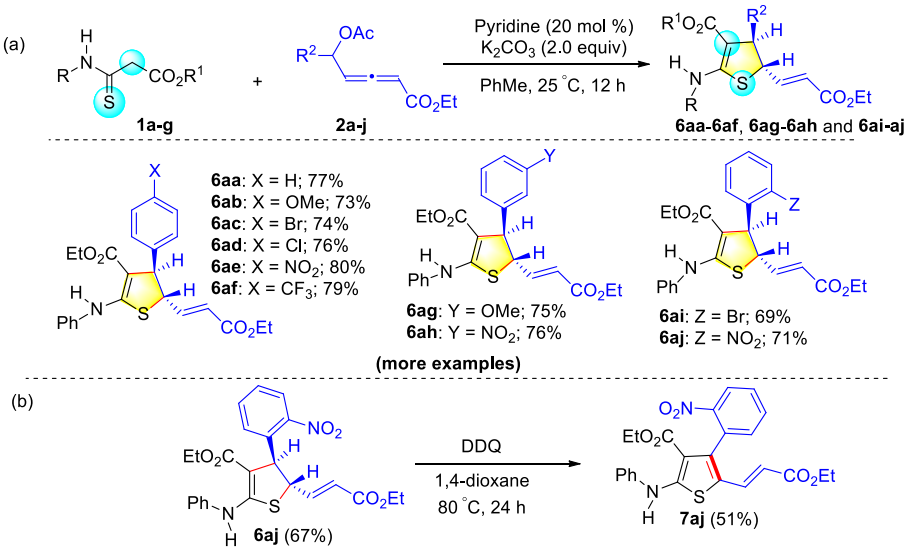


Chart 1. Precursors used in the present study (Part A)

(i) Reaction of δ-acetoxy allenoates with thioamides: Pyridine-catalyzed (3 + 2) annulation leading to dihydrothiophene motifs and synthetic utility

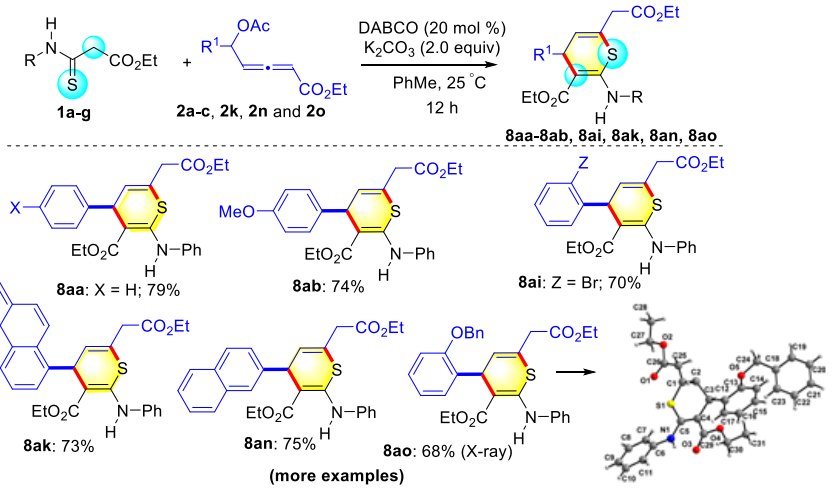
In the present work, we wanted to explore the reactivity of *δ*-acetoxy allenoates with thioamides under Lewis base catalysis. Thus pyridine catalyzed (3+2) annulation offered dihydrothiophene motifs **6** with excellent stereoselectivity (Scheme 1)**.** Here, δ-acetoxy allenoate functions as a 2C synthon. Upon treatment with DDQ, **6aj** could be oxidized to thiophene **7aj** in 51% yield. Mechanistic details are discussed in a later section.



Scheme 1. Synthesis of highly substituted dihydrothiophenes from δ-acetoxy allenoates and their synthetic utility

(ii) DABCO-catalyzed (3 + 3) annulation of δ-acetoxy allenoates with thioamides: Formation of thiopyrans via *6-exo-dig* cyclization

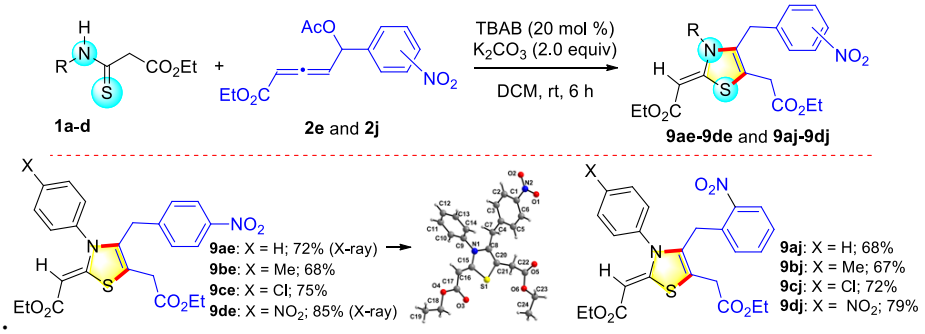
In contrast to the above, DABCO catalyzed (3 + 3) annulation of thioamide **1a** with *δ*-acetoxy allenoate **2a** at rt gave *thiopyran* **8aa** in high yield. This protocol is also accommodated by a variety of substrates including polyaryl substituted allenoates to generate products **8** in good yields (Scheme 2). Thus, in the case of DABCO, δ-acetoxy allenoate functions as a 3C synthon.



Scheme 2. DABCO-Catalyzed synthesis of substituted thiopyrans from δ-acetoxy allenoates

(iii) TBAB catalyzed (3 + 2) annulation of δ-acetoxy allenoates with thioamides: Formation of thiazoles

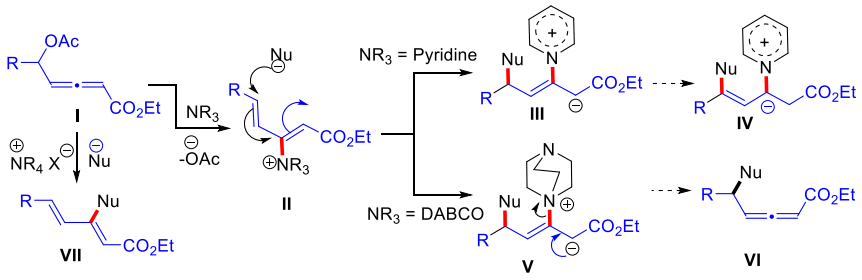
We have also explored the reactivity of δ-acetoxy allenoates in the presence of quaternary ammonium salts. Although tetra-*n*-butyl ammonium bromide (TBAB) is primarily used as a phase transfer catalyst, in our reactions it exhibited a slightly different role. Thus, TBAB-catalyzed (3+2) annulation led to thiazoles cores, rather than thiopyrans or dihydrothiophenes *via* 5-*exo*-trig cyclization. These thiazoles possess a *Z*-isomeric exocyclic double bond and are formed with excellent stereoselectivity (Scheme 3).



Scheme 3. TBAB catalyzed synthesis of highly substituted thiazoles from allenoates

The above reactions of δ-acetoxy allenoates have been explained by utilizing the intermediates shown in Scheme 4. δ-Acetoxy allenoate **I** can undergo S_N2'-attack with an amine to give diene-ammonium intermediate **II**. In the case of pyridine, the positive charge on the nitrogen atom is stabilized by the aromatic ring in the formation of ylide **IV**, an analogue of

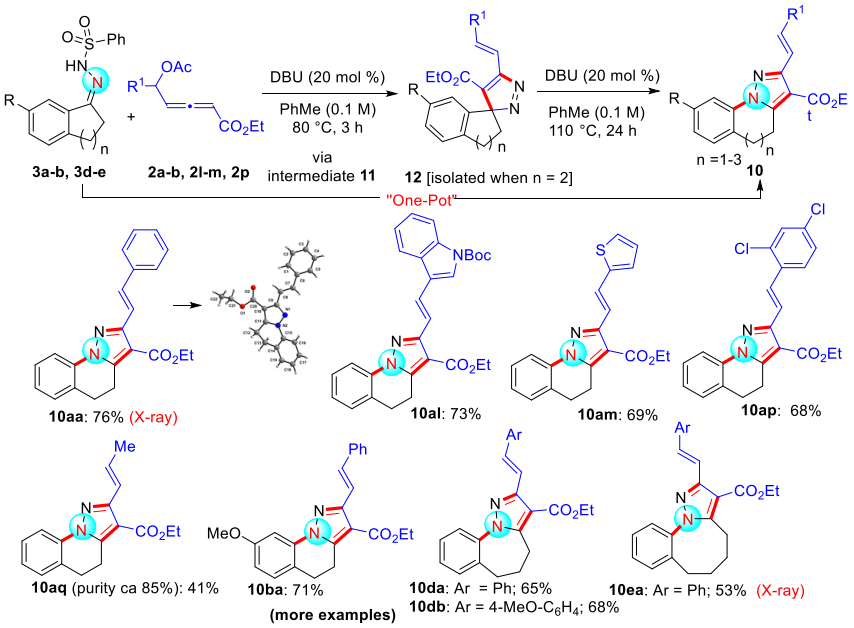
phosphonium ylide. In sharp contrast, DABCO intermediate **V** readily gives allenoate **VI** because of the absence of the delocalization effect. In the case of quaternary ammonium salt (TBAB), allenoate **I** is involved in an addition elimination reaction with a nucleophile to offer dienoate **VII**. Such a distinction led ultimately to vastly different products (Scheme 4).



Scheme 4. Possible intermediates in the reaction of δ-acetoxy allenoate in the presence of pyridine, DABCO and TBAB

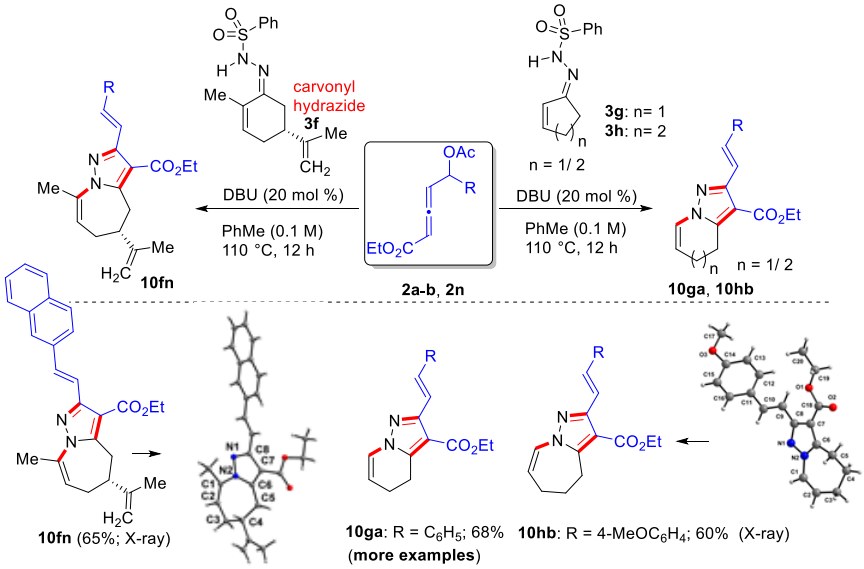
(iv) DBU-catalyzed ring-expansion reaction of fused cyclene sulfonyl hydrazides with δ-acetoxy allenoates

Cyclene sulfonyl hydrazides can serve as versatile building blocks when reacted with allenoates. With the suitable parameters in hand, the reaction of a variety of *δ*-acetoxy allenoates **2** and *N*-sulfonohydrazides **3** was examined to evaluate the flexibility and limitations of the ring-expansion (5→6, 6→7, and 7→8) protocol **10**. As depicted in Scheme 5, this novel ring-expansion protocol was compatible with a wide range of δ-acetoxy allenoates and *N*-sulfonohydrazides.



Scheme 5. Ring expansion (5→6, 6→7, and 7→8) reaction of δ-acetoxy allenoate with fused cyclene sulfonyl hydrazides.

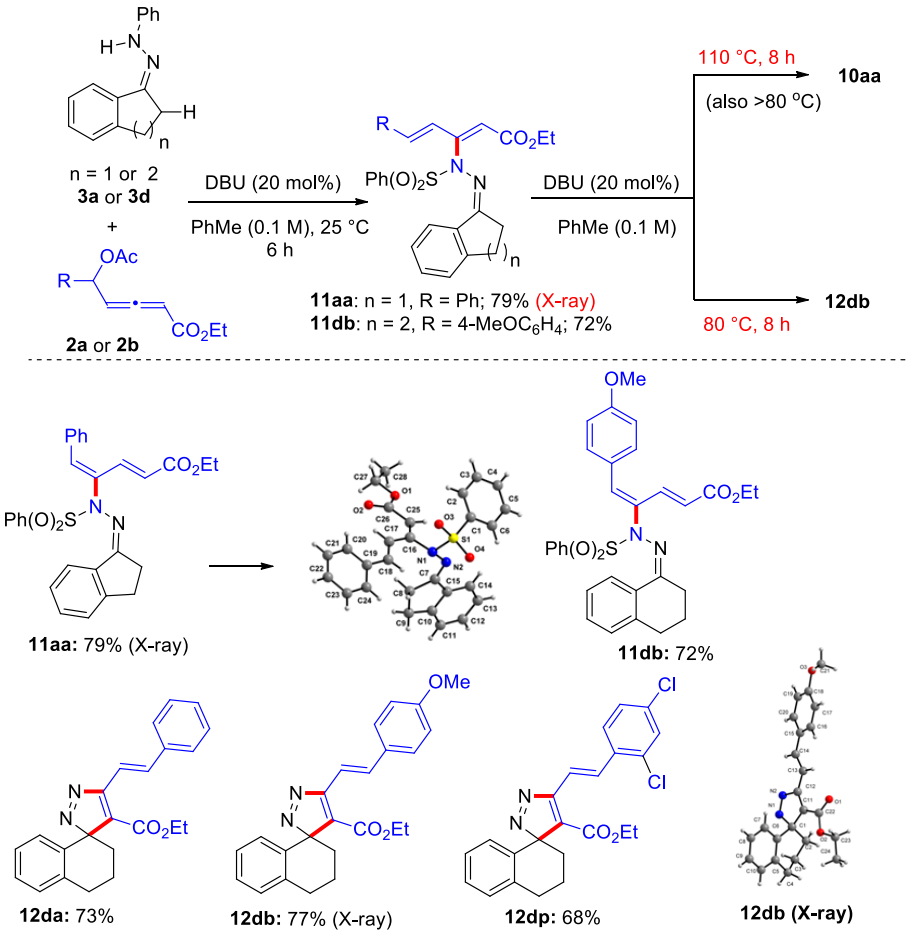
To diversify the domino reaction, ali-cyclene sulfonohydrazides (**3f-h**) were also subjected to the above organocatalytic protocol. Importantly, *R*-(−)-carvone-derived nucleophilic core **3f** gave the ring expanded product **10fn** in moderate yield of 65%. The reaction of other alicyclene substrates **3g** and **3h** resulted in products (**10ga** and **10hb**) with acceptable yields (60-68%) (Scheme 6).



Scheme 6. The reaction of alicyclene sulfonohydrazides with δ-acetoxy allenoates

(v) Isolation of diene-intermediates and spirocyclic products from the reaction of *N*-sulfonyl hydrazones with δ-acetoxy allenoates

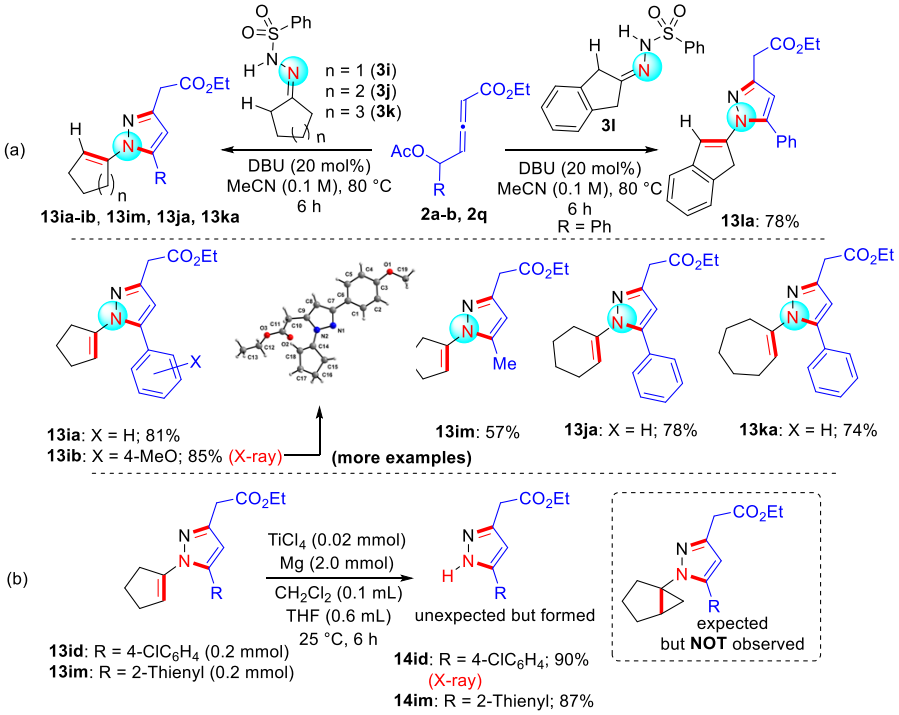
We have isolated diene-intermediates **11aa** and **11db** in good yields (79% and 72%) by performing the reaction between **3a**/ **3d** and **5a**/ **5b** at rt for 6 h. It is worth mentioning that spirocyclic products **12da**, **12db,** and **12dp** were also obtained in good yields under similar conditions but with the reaction time restricted to 3h at 80 °C (oil bath). Based on this finding, we concluded that ring-expanded products might have formed through spirocyclic intermediates. To substantiate this claim, we performed a reaction with **12db** using DBU and obtained **10db** in 98% yield (Scheme 7).



Scheme 7. Synthesis of diene-intermediates and spirocyclic products

(vi) Reaction of δ-acetoxy allenoates with cycl-3-ene-*N*-sulfonyl hydrazides: Synthesis of multisubstituted pyrazoles

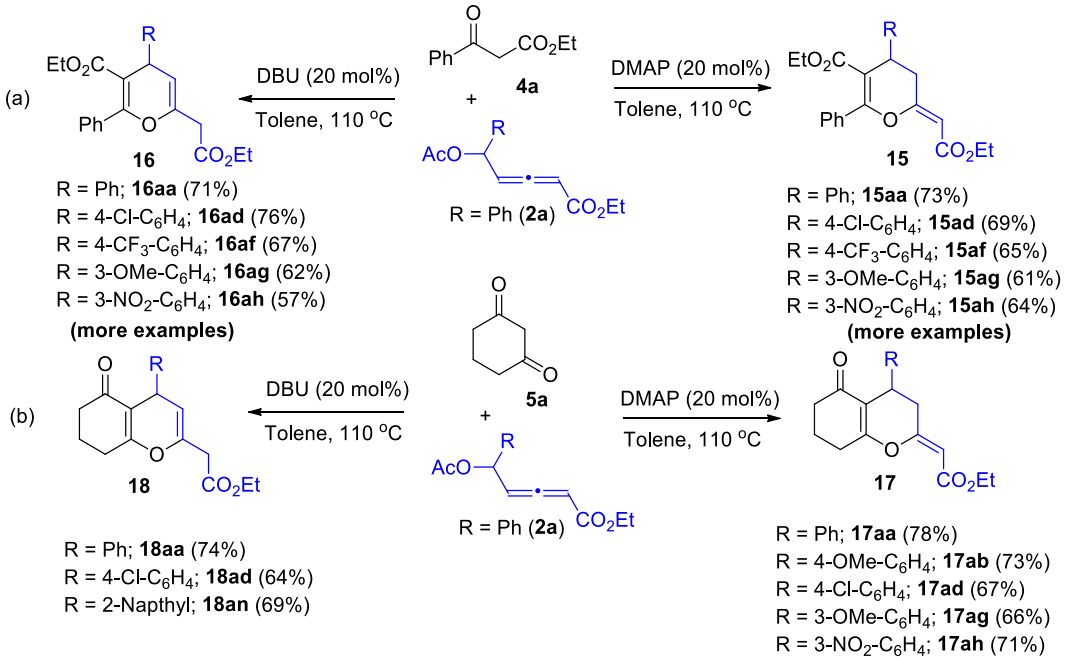
Next, we focused on the sulfonohydrazides derived from non-fused alicyclic ketones under identical conditions. Initially, we examined a reaction between **3i** and **2a** and obtained **13ia** in 81% yield and identified it as 1,2-pyrazole *via* (3 + 2) annulation (Scheme 8a). We performed a reaction of **13id**/ **13im** using $TiCl_4$-Mg in CH_2Cl_2 based on a literature procedure to obtain a fused cyclopropane product. Surprisingly, we observed C-N bond cleaved products (**14id**, **14im**), rather than the fused cyclopropanes, in excellent yields (87-90%) (Scheme 8b).



Scheme 8. Synthesis of multisubstituted pyrazoles (from δ-acetoxy allenoates) and their synthetic utility

(vii) Lewis-base dependent (3 + 3) annulation of acetoxy allenoates with 1C,3O-bisnucleophiles: Synthesis of novel pyran scaffolds

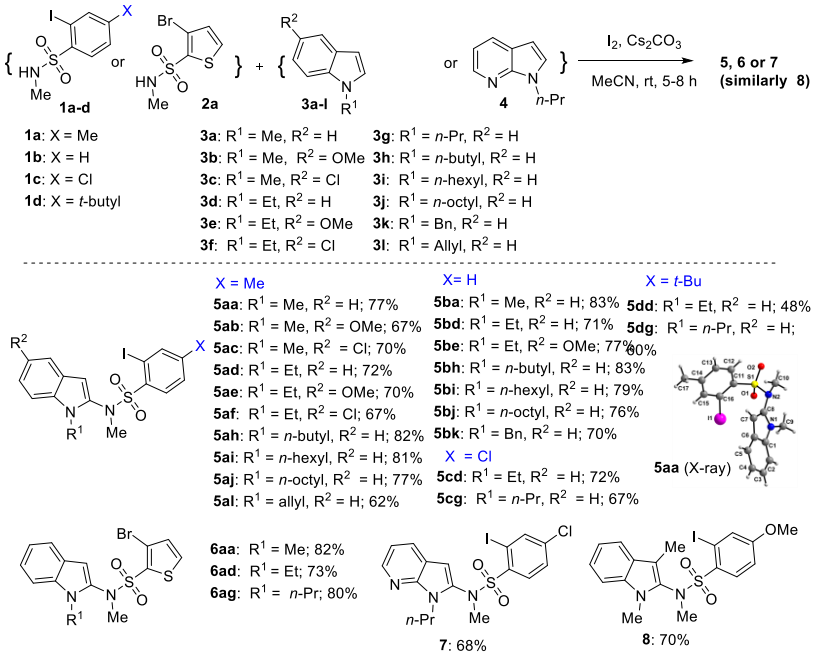
The presence of an active methylene group in the nucleophile plays a crucial role in the annulation reactions with allenoates. Thus in the presence of Lewis bases such as DBU or DMAP, allenoates can undergo (3 + 3) annulation reaction with ethyl benzoylacetate or cyclohexane-1,3-dione leading to the formation of pyrans (Scheme 9).



Scheme 9. Reaction of *δ*-acetoxy allenoates with ethyl benzoylacetate or cyclohexane-1,3-dione

PART B

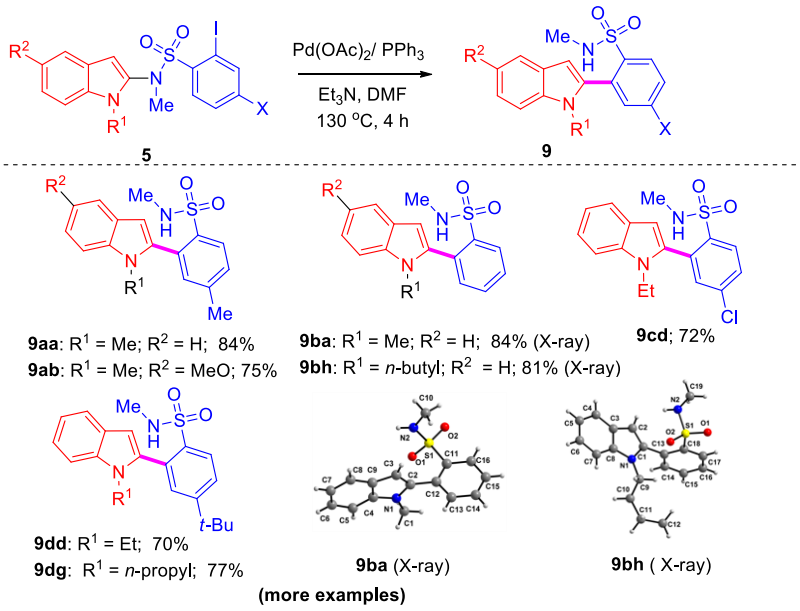
This part of the work deals with palladium-catalyzed intramolecular transformations of indolyl-benzenesulfonamides. In Chapter 4, a review of the literature on aspects relevant to this part is presented. In Chapter 5, the results obtained are discussed while in Chapter 6, the experimental details are described. The precursors used in this part are shown in Scheme 10.



Scheme 10: Precursors used in the present study (Part B)

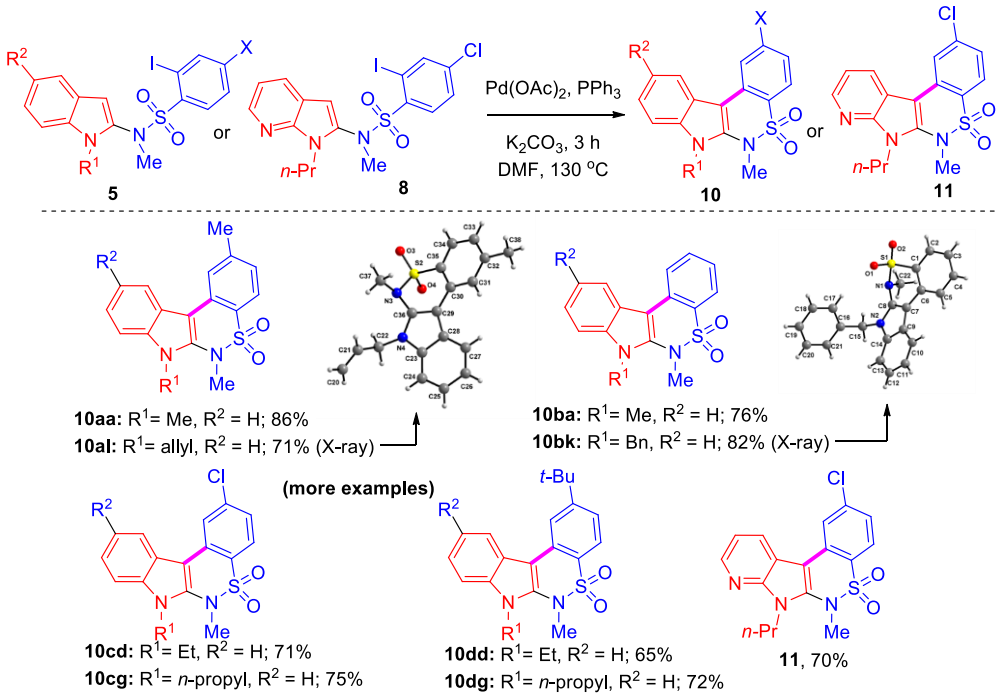
(i) [Pd]-catalyzed intramolecular transformations of indolylbenzenesulfonamides: Formation of *ortho*-sulfonamido-bi(hetero)aryls and polycyclic sultams

The precursors in this study possess (i) an indole moiety with unsubstituted 3-position and (ii) an arylsufonamide moiety with iodo-substitution at the *ortho* position of the aryl group. Hence intramolecular coupling is a feasible reaction. We have developed [Pd]-catalyzed intramolecular reaction of these substrates for the formation of 2-aryl indole products rather than the cyclized products with the C-N bond at the indole 2-position being replaced with a C-C bond using $Pd(OAc)_2/Ph_3P/Et_3N$ in DMF solvent (Scheme 11).



Scheme 11. [Pd]-catalyzed synthesis of 2-aryl indoles

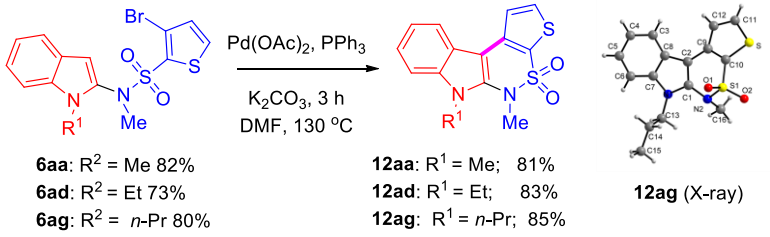
In continuation of the above, we have also developed Pd-catalyzed one-pot method for the construction of indole-fused sultams from indolyl iodo-benzenesulfonamide. Indoles possessing different alkyl substituents on nitrogen atom furnished the desired products in moderate to good yields of 65-86%. Similarly, 4-chloro-2-iodo-*N*-methyl-*N*-(1-propyl-pyrrolopyridinyl)benzenesulfonamide also delivered the corresponding product **11** in 70% yield. Among the Pd-catalysts, $Pd(OAc)_2$ was the most effective for this transformation. Among the phosphines PPh_3, P(*o*-tol)$_3$, PCy_3, P(*t*-Bu)$_3$ and P(*n*-Bu)$_3$, PPh_3 was found to be the most appropriate for this reaction (Scheme 12).



Scheme 12. [Pd]-catalyzed synthesis of tetracyclic sultams **10** or **11**

(ii) [Pd]-catalyzed reaction of indolyl bromothiophene sulfonamides: Formation of thiophene fused indolyl sultams

[Pd]-catalyzed synthesis of tetracyclic sultams *via* intramolecular cyclization of indolyl bromothiophene sulfonamides has been developed. This reaction takes place by coupling the *ortho*-position of the thienyl sulfonyl group with the C-3 position of the indole. Thus, we utilized the sulfonyl attached heteroaromatic substrates **6aa**, **6ad**, and **6ag** under standard conditions and were successful in obtaining the corresponding cyclized products **12aa**, **12ad**, and **12ag** in 81-85% yield (Scheme 13). Details on the mechanistic pathways are also discussed.



Scheme 13. [Pd]-catalyzed synthesis of thiophene fused indolyl sultams

PART A

DIVERGENT REACTIVITY OF *δ*-ACETOXY ALLENOATES WITH THIOAMIDES, *N*-SULFONYL HYDRAZIDES, AND 1,3-DICARBONYL COMPOUNDS

PART-A

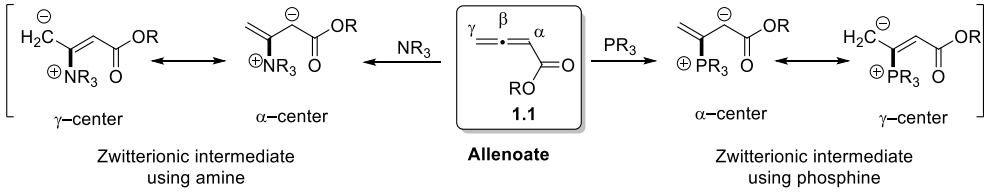
Chapter 1

INTRODUCTION

We have disclosed the previous reports related to our work on the reactivity of *N*-sulfonyl hydrazones and 1,3-dicarbonyl compounds with *δ*-acetoxy allenoates in Chapter 2. The introduction of allene and allenoate chemistry is elucidated in 1.1-1.3. The latest developments in the area of *δ*-acetoxy allenoates are considered in section 1.4. Whereas the reactivity of thioamides and *N*-sulfonyl hydrazides explored in sections 1.5-1.6

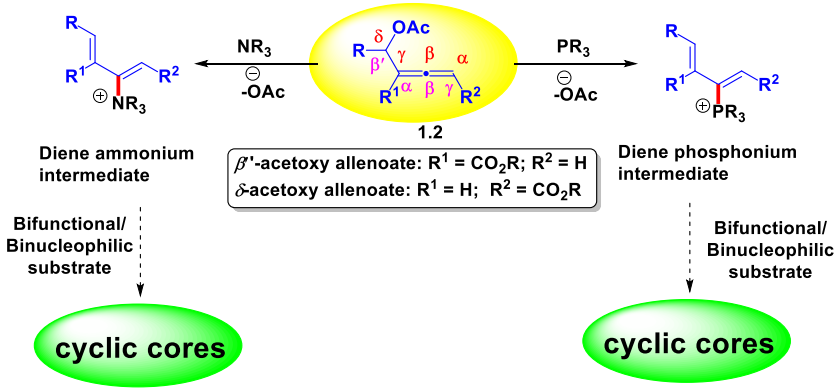
1.1 General Introduction: Allene Chemistry

Allene chemistry has received significant attention over the past few decades thanks to the presence of highly reactive adjacent *sp* and sp^2 carbon atoms.[1,2] Using their unique structure, numerous valuable reactions for generating diverse cyclic scaffolds have been developed, particularly in the last two decades. Appending another functional group to allene moiety would make the system more intriguing in terms of the versatile reactivity patterns in both catalytic and non-catalytic processes. Allenoates (butadienoates), that have an ester group attached to a terminal carbon of allenes, generate zwitterionic intermediates with Lewis bases and participate as one-,[3a] two-,[3b] three-,[3c] four-[3d] or five-[3e] carbon synthons for the rapid construction of diverse cyclic cores. Lewis bases, such as tertiary amine and phosphine, will attack the reactive sp-hybridized center of the allenoate to generate the carbanion at the α- and γ-position of the allenoate intermediate, which the neighboring ester group stabilizes. The resulting zwitterionic intermediate behaves as an electrophilic species (Scheme 1.1). It is important to note that due to the larger size (and some contribution from the d-orbitals), stabilization of the zwitterionic intermediate by phosphines tends to direct the reactivity in a manner different from that by amines.



Scheme 1.1: Resonance forms of zwitterions generated from allenoates and a base.

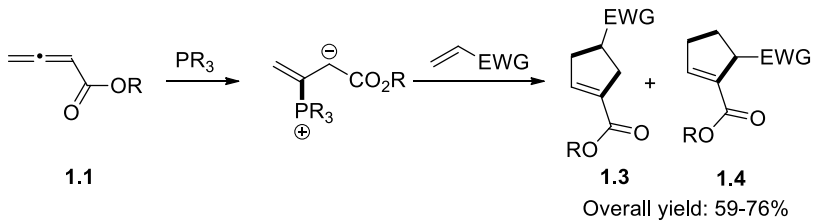
Since the pioneering report of Lu's (3 + 2) annulation between butadienoate with electron-deficient olefins,[4] a variety of annulations/cyclizations involving allenoates using Lewis bases have been widely used to construct a broad range of carbocyclic and heterocyclic cores.[5,6] To explore the allenoate chemistry, an acetoxy group is introduced in the allenoate moiety which makes the reactions more fascinating. Out of these two *δ*- and *β*-acetoxy allenoates, we have explored more on the reactivity of *δ*-acetoxy allenoates (cf. **1.2**). Here, most of the reactions are facilitated by the addition of Lewis base at the *sp* carbon of allenoate *via* addition-elimination manner to generate reactive ammonium or phosphonium dienyl-intermediate after the acetoxy group is removed. At the same time, annulation takes place with a suitable bi-nucleophilic substrate for constructing cyclic cores (Scheme 1.2).



Scheme 1.2: Formation of diene ammonium/phosphonium intermediates from acetoxy allenoates

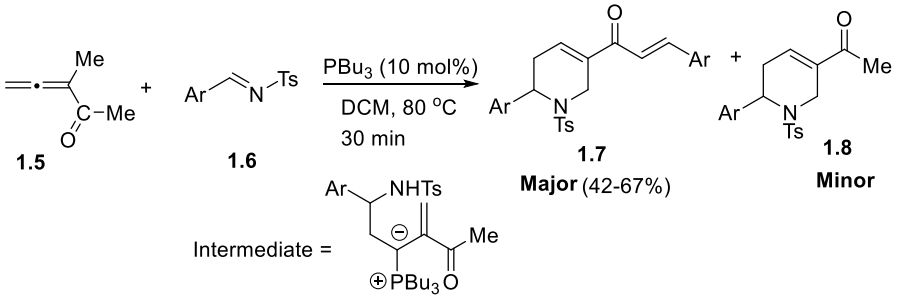
1.2. Phosphine catalyzed/mediated reactions of allenoates

Lu and their colleagues disclosed a novel (3 + 2) cycloaddition reaction between the allylic carbanion and allene with low electron density that resulted in the construction of cyclopentenes **1.3** or **1.4** involving ester allenoate **1.1** that is catalyzed by phosphine. This finding inspired the following types of reactions involving allenoates (Scheme 1.3).[4a]



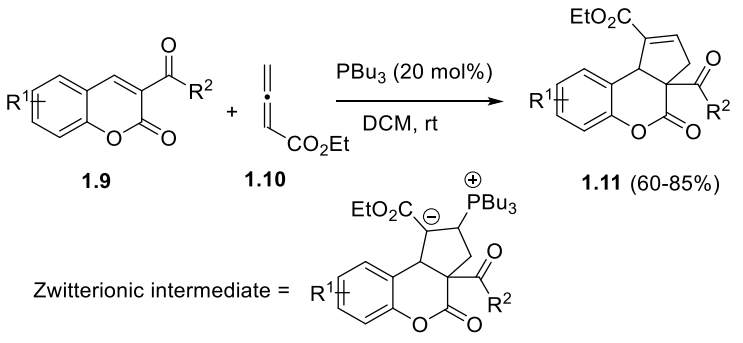
Scheme 1.3: Synthesis of cyclopentenes from allenoates by phosphine catalysis

Shi *et al.* reported Baylis–Hillman reactions of *N*-tosyl aldimines **1.6** and 3-methylpenta-3,4-dien-2-one **1.5**. The (4 + 2) annulation occurs *via* 1,4-dipolar cycloaddition for the construction of uncommon six-membered rings **1.7** and **1.8** *via* a zwitterionic intermediate (Scheme 1.4).[7] Compound **1.7** is the major product with selective *E*-configuration. Tributylphosphine was used as the catalyst (Scheme 1.4).



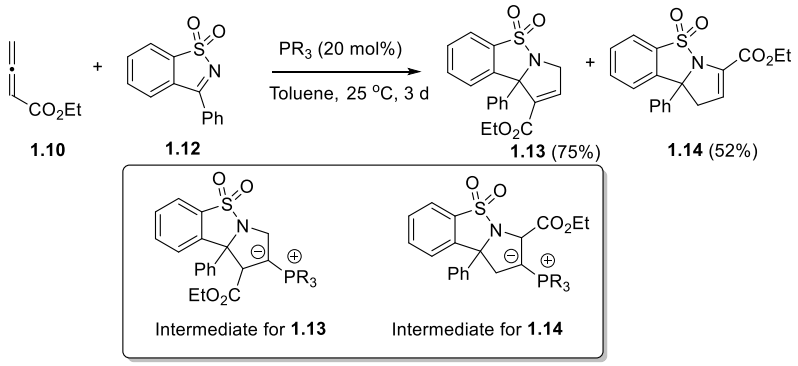
Scheme 1.4: Synthesis of tetrahydropyridine from allenoates by phosphine catalysis

Wang and coworkers reported an extremely regio-selective and stereo-selective (3+2) cycloaddition of 3-acetyl coumarin **1.9** with allenoate **1.10** under phosphine catalysis for the construction of cyclopentene-fused 1,2-benzopyrone motifs **1.11** in good to high yields by γ-addition of the allenoate via a zwitterionic intermediate using PBu3 (Scheme 1.5).[8] Using the same starting materials, the authors differentiated this outcome with triethylenediamine-catalyzed (4+2) annulations (discussed in a later section).



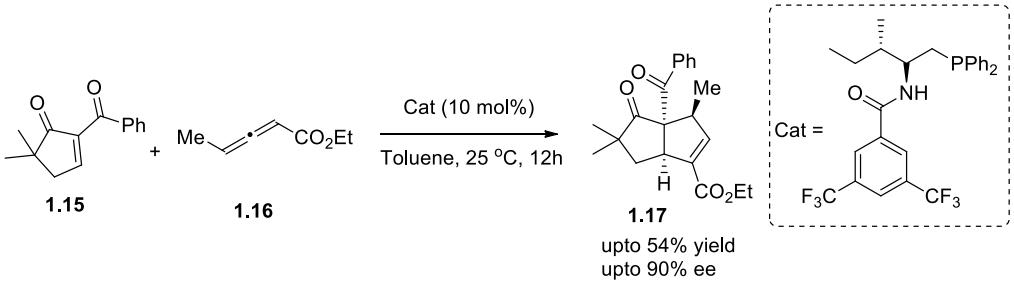
Scheme 1.5: Synthesis of (6,6,5)-fused ring systems from allenoates by phosphine catalysis

Ye and coworkers developed the reaction between cyclic ketimines **1.12** and allenoates **1.10** for the synthesis of *N*-heterocyclic motifs under phosphine mediated (3+2) cycloaddition that delivered to fused (6,5,5)-ring systems in moderate to high yields. They found that distinct products were produced under various phosphine-catalyzed processes. Thus triphenylphosphine functions as an electron-poor nucleophile, resulting in the formation of a compound through a zwitterionic intermediate **1.13**, while PBu3 functions as an electron-rich nucleophile, resulting in product. (Scheme 1.6).[9]



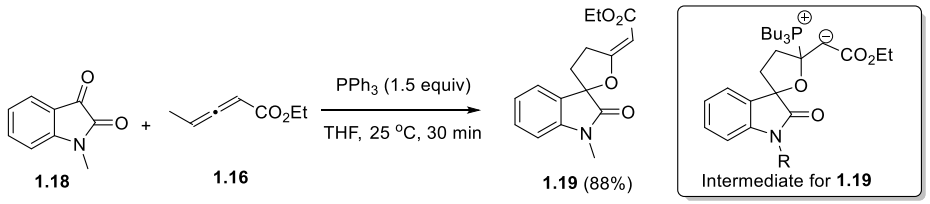
Scheme 1.6: Synthesis of (6,5,5)-ring system from allenoates by phosphine catalysis

In the year 2013, Waldmann *et al.* developed (3+2) cycloaddition involving cyclopentenones **1.15** and allenic esters **1.16** using a chiral phosphine for the construction of products **1.16** containing pyridyl ketones.[10] Interestingly, α, β, and γ-carbon atoms of the allenoate were involved in the formation of substituted cyclopentenones (Scheme 1.7).



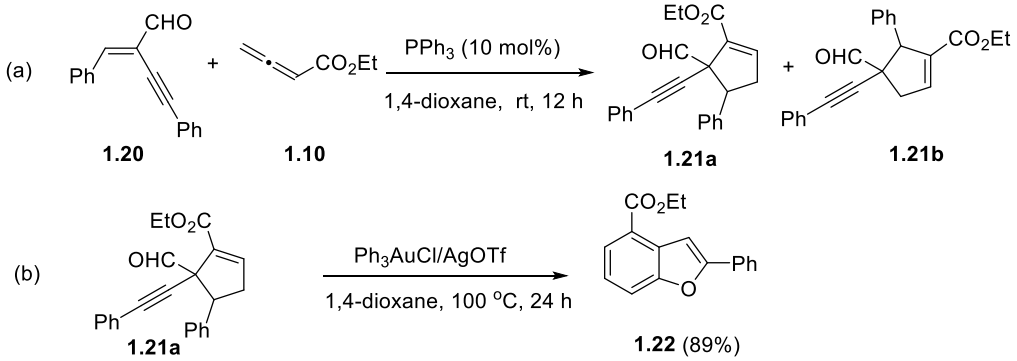
Scheme 1.7: Synthesis of cyclopentenones **1.17** from allenoates by chiral phosphine catalysis

Jose and co-workers developed the reaction between isatins **1.18** and 3-alkyl allenoate **1.16**. Surprisingly, phosphine-catalyzed (3+2) cycloaddition leads to spiro-furan oxindoles **1.19** *via* proton shift followed by cyclization (Scheme 1.8).[11]



Scheme 1.8 Synthesis of spirofuran oxindoles **1.19** from allenoates

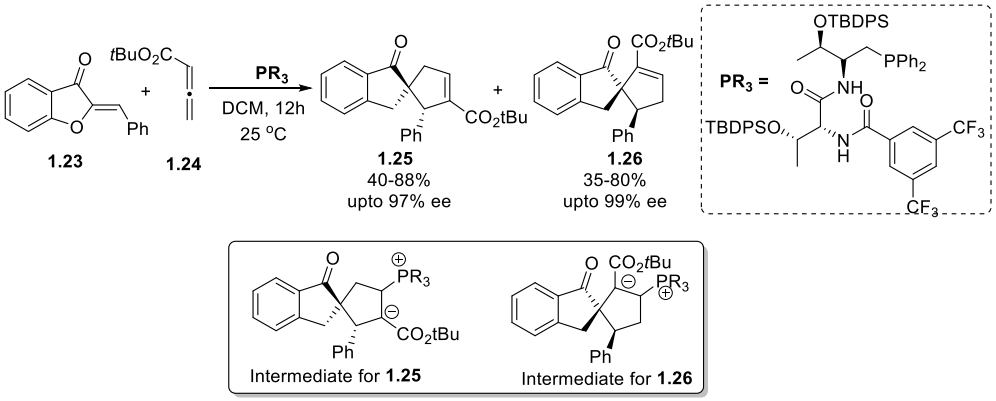
In the year 2015, the cycloaddition of ethyl allenoate **1.10** and enynals **1.20** by the phosphine catalyst to obtain functionalized cyclopentenes **1.21a** and **1.21b** was reported by our research group. Two target compounds were formed with good yields. Since γ-addition is preferred over α-addition, the major product **1.21a** containing both aldehyde and alkyne functional groups undergoes intramolecular gold-catalyzed cyclization to generate benzofurans in moderate yields (Scheme 1.9).[12]



Scheme 1.9: Synthesis of (a) functionalized cyclopentenes from allenoates and (b) gold-catalyzed cyclization leading to benzofurans

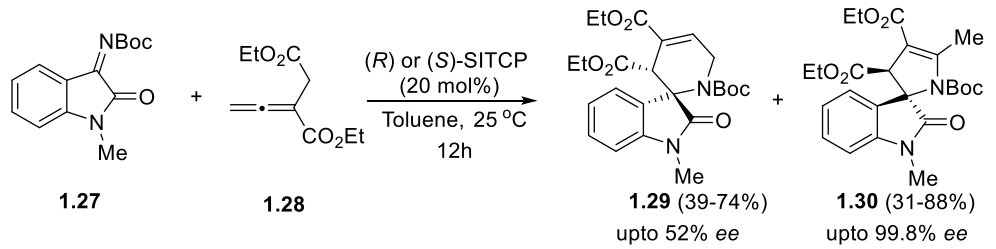
Lu *et al*. have developed regio-divergent chiral phosphine catalyst (3 + 2) annulations of substituted benzofuran **1.23** with allenoate **1.24**.[13] Therefore, it was simple to make *α*-selective annulation products with excellent regio- and enantioselectivities using a dipeptide phosphine catalyst. Phosphines containing L-L dipeptide might be used to yield *α*-selective annulation products with high enantioselectivities. Changing the catalyst design allows a wide range of aryl

or alkyl substituted α-selective **1.25** or γ-selective **1.26** spirocyclic benzofuranones to be easily generated (Scheme 1.10).



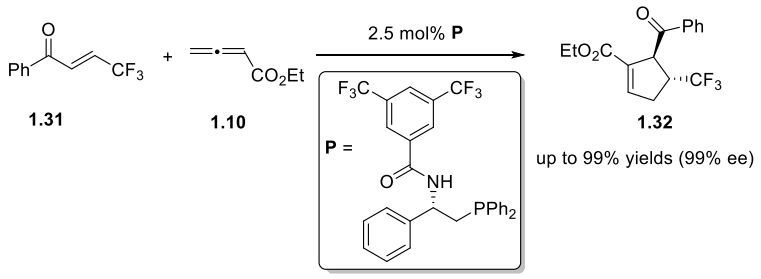
Scheme 1.10: Synthesis of benzofuranones from aurone and allenoate

Kumar's group reported a unique asymmetric annulation reaction of allenyl esters **1.28** and isatin-derived ketimines **1.27** to deliver spirocyclic pyrrolinyl compounds **1.29** and **1.30** in good yields and outsanding enantioselectivity. This annulation is catalyzed by the highly efficient and enantioselective catalytic addition of chiral phosphine (SITCP) to generate a zwitterionic dipole to *α*-substituted allenoate **1.28**. This dipole could interact with *N*-Boc-ketimines **1.27** generated by isatin (Scheme 1.11).[14]



Scheme 1.11: Synthesis of pyrrolinyl-spirooxindoles from *N*-Boc-ketimines and allenoate **1.28**

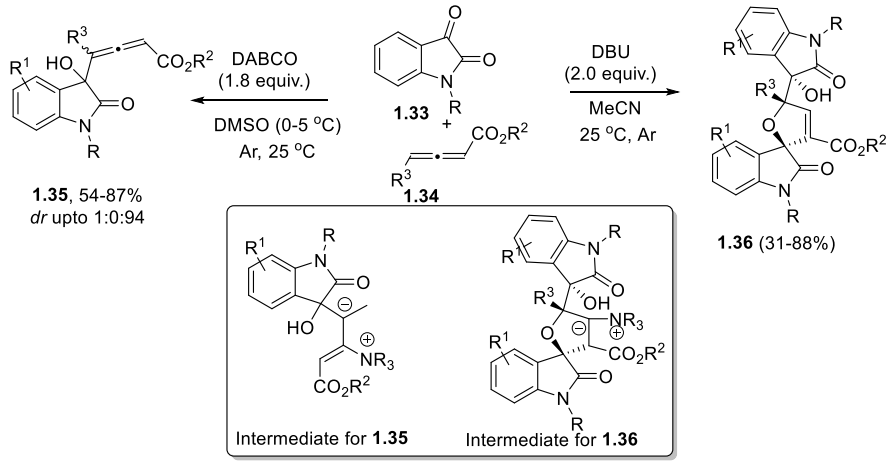
Zhou and co-workers developed a highly enantio- and diastereoselective phosphine-catalyzed (3+2) cycloaddition reaction to synthesize trifluoromethylated cyclopentenes **1.32** through β-perfluoroalkyl α,β-enones **1.31**. The authors performed their cycloaddition involving intramolecular Michael addition followed by proton transfer of terminal allenoate **1.10** with (*E*)-4,4,4-trifluoro-1-phenylbut-2-en-1-one **1.31** to give the cyclopentene **1.32** in the presence of amino acid derived phosphine in high yields and high enantioselective excess (Scheme 1.12).[15]



Scheme 1.12: Synthesis of cyclopentene **1.32**

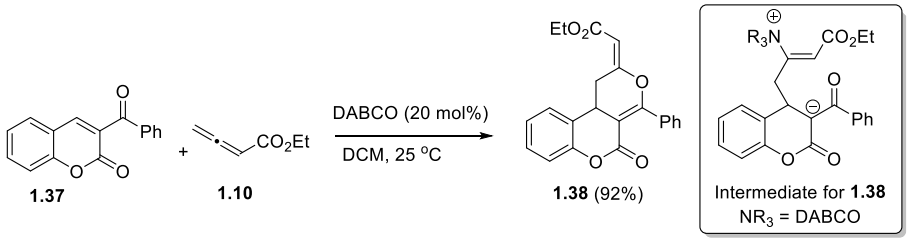
1.3. Amine catalyzed/mediated reactions of allenoates

Somappa *et al.* have designed and developed a reaction to synthesize 5-membered spiro-furan oxindoles **1.36** involving *N*-substituted isatin **1.33** and allenoate **1.34** effected by the DBU-mediated MBH reaction proceeds through a cascade process *via* the ammonium ion intermediate. Surprisingly, triethylenediamine delivered five-membered spiro-furan oxindole where the reaction of allenoates only involved the γ-carbon (Scheme 1.13).[16]



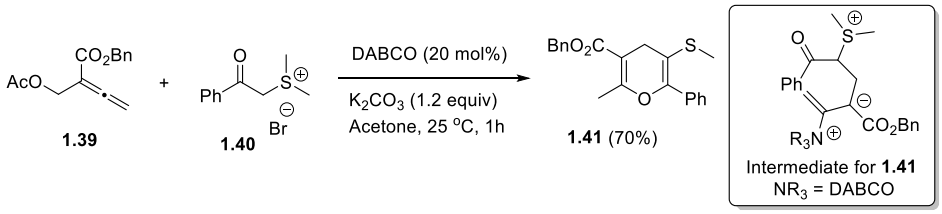
Scheme 1.13: Synthesis of 5-membered spiro-furan oxindoles **1.36** and γ-functionalized allenoates **1.35**

Wang *et al.* utilized the DABCO-catalyzed (4+2) cycloaddition reaction of 3-acetyl-coumarin **1.37** with allenoate **1.10** to obtain fused six-membered dihydropyran scaffolds in moderate to high yields with an *E*-isomeric exocyclic double bond. This reaction involves an attack from the γ-carbon of allenoate followed by ring construction from the enolate through a zwitterionic intermediate (Scheme 1.14).[8]



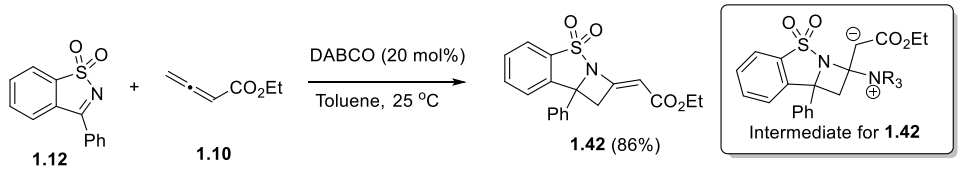
Scheme 1.14: Synthesis of dihydropyran **1.38** from 3-acyl-chromen-one **1.37** and allenoate **1.10**

Li and coworkers reported amine-catalyzed (3+3) annulations that utilize sulfur ylides **1.40** and 2-(acetoxymethyl)buta-2,3-dienoate **1.39** for the synthesis of 4*H*-pyrans **1.41** consisting of a vinyl sulfide group in good to high yields through 6-*endo*-dig cyclization. To facilitate this reaction, an aromatic group adjacent to the ketone is required (Scheme 1.15).[17]



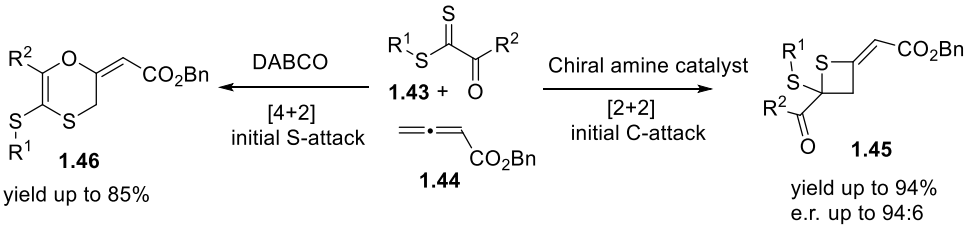
Scheme 1.15: Synthesis of substituted pyrans **1.41** from sulfur ylides **1.40**

In the year 2012, Ye's group described a DABCO-catalyzed (2+2) cycloaddition reaction of *N*-sulfonyl ketimine **1.12** with allenic ester **1.10** for the construction of multicyclic azetidine **1.42** in moderate to high yields with an *E*-isomeric exocyclic double bond *via* a zwitterionic intermediate (Scheme 1.16).[9]



Scheme 1.16: Synthesis of azetidine **1.42**

Min Shi *et al*. found that acetoxy allenoate **1.44** and dithioesters **1.43** undergo different cycloadditions when catalyzed by DABCO or β-IDC, giving chemoselective routes to 2,3-dihydro-1,4-oxathiines **1.46** and enantio-enriched thietane **1.45** motifs. Using DABCO [4+2] cycloaddition, 2,3-dihydro-1,4-oxathiines were obtained. By contrast, under chiral amine catalysis, acetoxy allenoates delivered thietanes in good to high yields (Scheme 1.17).[18]



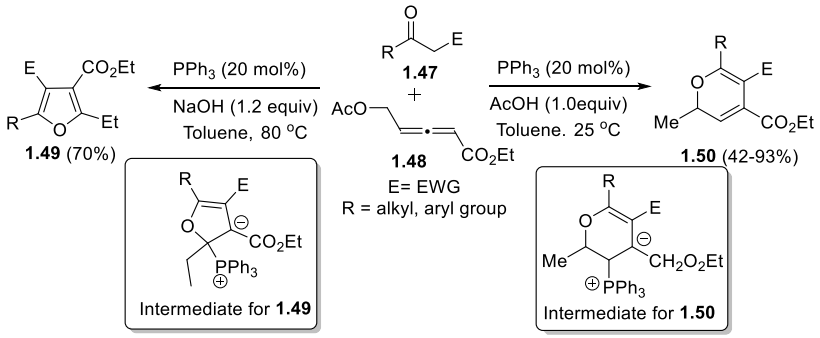
Scheme 1.17: Synthesis of 2,3-dihydro-1,4-oxathiines **1.46** and thietane **1.45**

1.4. Reactions of acetoxy allenoates

In various annulations, both δ- and β'-acetoxy allenoates have been employed as synthons, as shown in the scheme 1.2[19] above. These annulations are reliable techniques in organic synthesis, providing a diverse range of carbocycles and heterocycles. This part discusses the reactivity of δ-acetoxy allenoates.

1.4.1 Reaction of δ-acetoxy allenoate chemistry

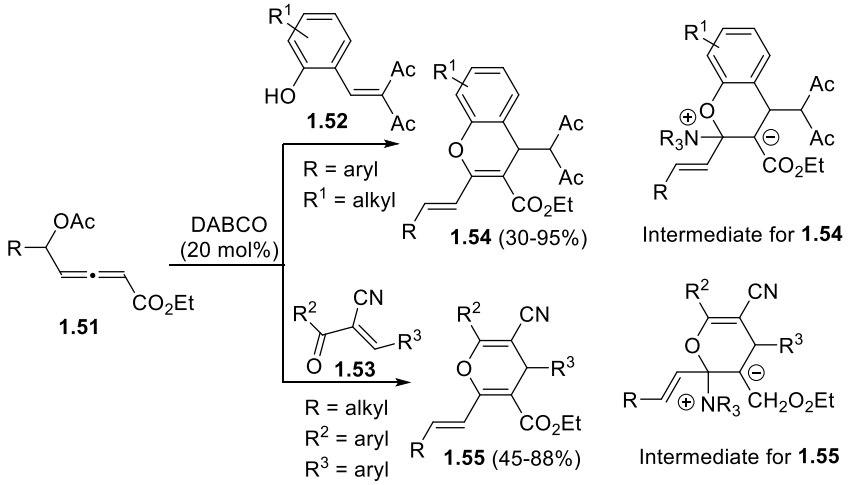
A very efficient method for the synthesis of five-membered fully substituted furans **1.49** and six-membered dihydropyrans **1.50** involving acetoxy allenoate **1.48** (*via* diene-phosphonium intermediate) and methyl that is active substrates **1.47** which function as 1C-3O bifunctional substrate was described by Tong and co-workers.[20] In contrast to (3 + 3) annulation, which performed effectively under an acidic medium, this PPh3-catalyzed (3 + 2) annulation needed basic conditions (Scheme 1.18).



Scheme 1.18: Synthesis of furans **1.49** and dihydropyrans **1.50** from acetoxy allenoate **1.48**

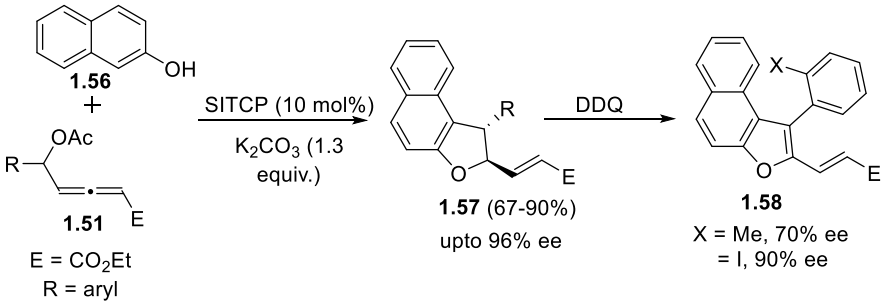
Tong's group published a diverse (4 + 2) annulation involving δ-acetoxy allenoate **1.51** and bifunctional substrates **1.52** or α-cyano carbonyls **1.53** in the presence of DABCO catalyst, which produced tetrahydro heterocycles chromenes **1.54** or pyrans **1.55** respectively *via* diene

ammonium ion.[21] Chromenes **1.54** are produced when R = Ar and pyrans **1.55** are produced when R = alkyl group (Scheme 1.19).



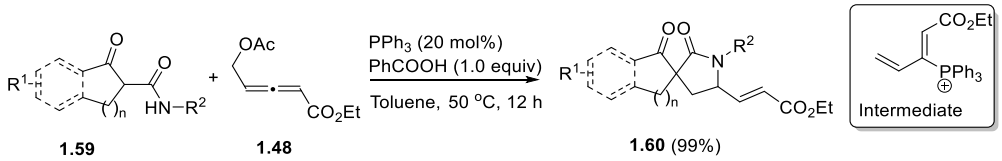
Scheme 1.19: Synthesis of 4*H*-chromenes **1.54** and 4*H*-pyrans **1.55** *via* diene-ammonium species

Tong *et al*. reported chiral phosphine catalyzed (3 + 2) annulation of *β*-naphthols **1.56** with *δ*-acetoxy allenoate **1.51** resulting in the formation of 1,2-dihydronaphtho-[2,1-*b*]napthols **1.57** in moderate to high yields with excellent enantiomeric excess.[22] The (*R*)-SITCP chiral phosphine catalyst rendered good enantioselectivity. Through DDQ oxidation, dihydrofuran was transformed to completely substituted furan **1.58** (Scheme 1.20).



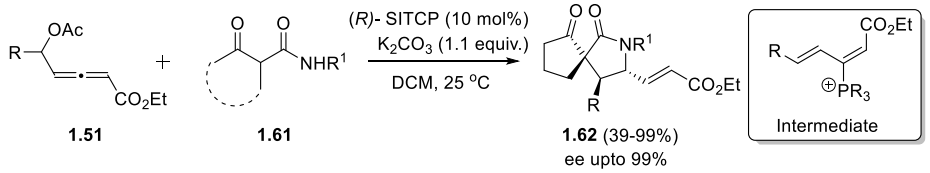
Scheme 1.20: Synthesis of dihydrofurans **1.57** from allenoates **1.51**

In 2017, Shi's group presented a highly enantioselective and diastereoselective (3+2) annulation to generate highly functionalized five-membered spiro-*N*-heterocyclic compounds **1.60** *via* diene-phosphonium ion intermediate with 1*C*,3*N*-bisnucleophile **1.59** and *δ*-acetoxy allenoate **1.48** by using phosphine catalyst. The authors were successful in producing various examples with high yields and enantiomeric excess (Scheme 1.21).[23]



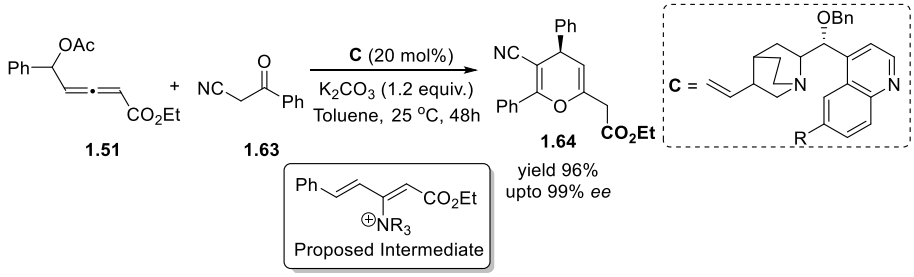
Scheme 1.21: Synthesis of spiro-heterocycles **1.60** from δ-acetoxy allenoates **1.48**

Zhou *et al.* utilized the asymmetric (3 + 2) annulation of δ-acetoxy allenoates **1.51** and substituted 3-oxobutanamide **1.61** to produce chiral -lactams **1.62**. It is uncommon for lactams to undergo chiral phosphine-catalyzed annulation reactions. For this reaction, they selected (*R*)-SITCP as the chiral phosphine catalyst (Scheme 1.22).[24]



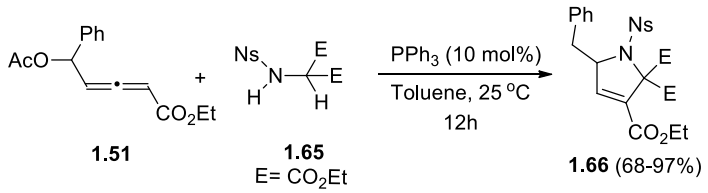
Scheme 1.22: Synthesis of chiral *γ*-lactams **1.62** from δ-acetoxy allenoates **1.51**

Tong *et al.* have reported the asymmetric (3 + 3) annulations of 1*C*,3*O*-bisnucleophiles **1.63** with δ-acetoxy allenoate **1.51** for the construction of 4*H*-pyran **1.64** with good enantioselectivity by using a sterically hindered bifunctional amine catalyst.[25] This reaction is distinguished by its broad substrate scope and mild reaction conditions (Scheme 1.23).



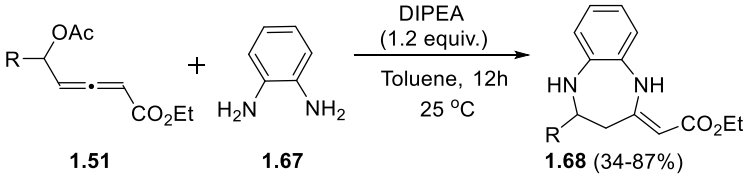
Scheme 1.23 Synthesis of 4*H*-pyran **1.64** from δ-acetoxy allenoate **1.51**

In the year 2018, Tong *et al.* reported phosphine-catalyzed (3 + 2) annulations for the formation of 3-pyrrolines **1.66** from *δ*-acetoxy allenoate **1.51** and 2-sulfonamide malonates **1.65**. They successfully produced various examples with good enantiomeric selectivity and higher yields by involving (*R*)-SITCP as the catalyst (Scheme 1.24).[26]



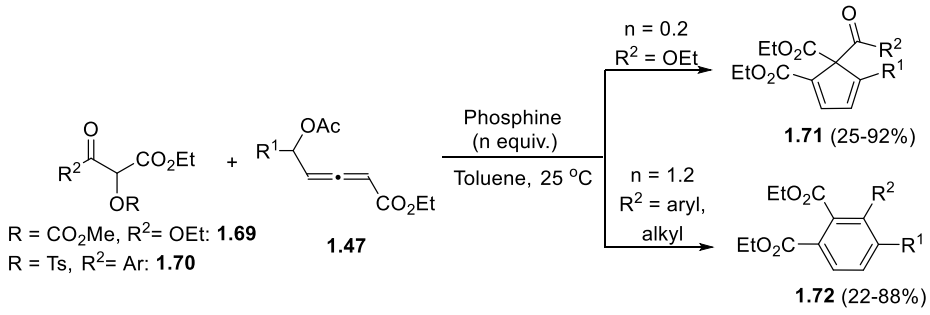
Scheme 1.24: Synthesis of polysubstituted 3-pyrrolines **1.66** from δ-acetoxy allenoates **1.51**

Tong's group demonstrated the reaction between *δ*-acetoxy allenoate **1.51** and *o*-diaminobenzene **1.67** using diisopropylamine as a catalyst. The ensuing (4 + 3) annulation leads to the formation of 1,5-benzodiazepines **1.68** in good to high yields with *Z*-isomeric exocyclic double bond (Scheme 1.23).[27] This method involves mild reaction conditions, has wide substrate scope, and utilizes easily available starting materials (Scheme 1.25).



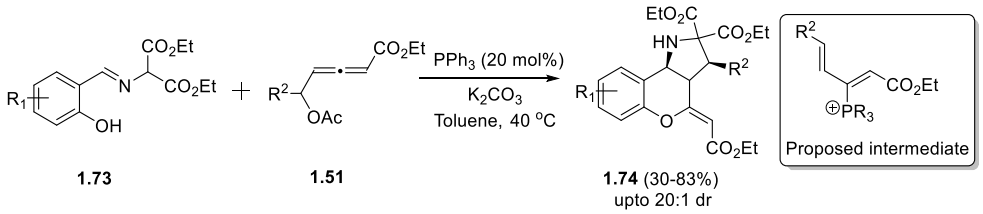
Scheme 1.25: Synthesis of 1,5-benzodiazepines **1.68** from δ-acetoxy allenoate **1.51** and *o*-diaminobenzene **1.67**

In the year 2019, Tong's group presented PPh_3-catalyzed (4+1) annulation reaction of unsymmetrical malonates with δ-acetoxy allenoate **1.47** affording highly substituted cyclopentadienes **1.67** in good yields. However, the same starting materials in the presence of 1.2 equiv of phosphine and base underwent (4+2) annulation, resulting in tetrasubstituted benzenes **1.68**. This protocol enabled the authors to produce a large number of examples with high yields (Scheme 1.26).[19b]



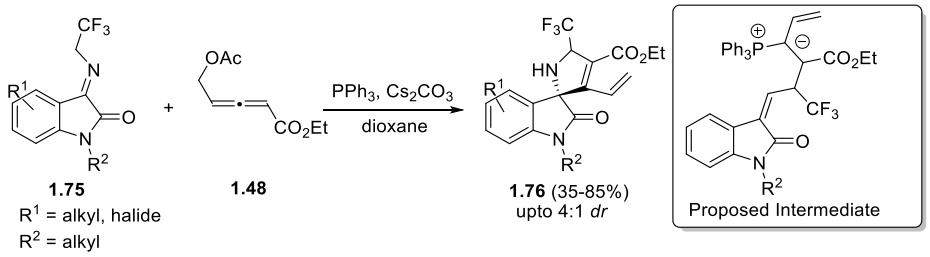
Scheme 1.26: Synthesis of multi-substituted cyclopentadienes **1.71** and aryls **1.72** from acetoxy allenoates **1.51**

Zhou and co-workers reported tandem cyclization using aldimine ester **1.73** and *δ*-acetoxy allenoate **1.51** with a variety of substrates catalyzed by phosphine for the synthesis of substituted tetrahydrochromen pyrrole derivatives **1.74** comprising three successive stereocenters in high yield and stereoselectivity.[28] the reaction occurs under mild conditions and has very efficient as well as excellent chemo- and diastereoselectivity (Scheme 1.27).



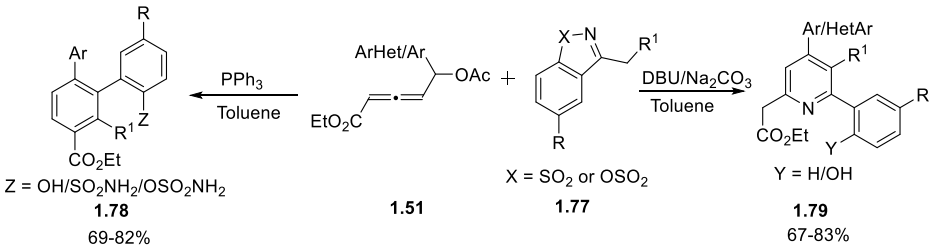
Scheme 1.27: Synthesis of compounds **1.74** from δ-acetoxy allenoates **1.51**

Min Shi's group reported (3 + 2) annulation involving *δ*-acetoxy allenoate **1.51** and isatin-derived *N*-2,2,2-trifluoroethyl ketimines **1.75** for the construction of spirocyclic oxindole scaffolds **1.76** using phosphine as a catalyst. The method applies to a wide range of substrates and can be used exclusively for the synthesis of spiro-oxindoles containing a CF_3 moiety with five-membered cyclic scaffolds (Scheme 1.28).[29]



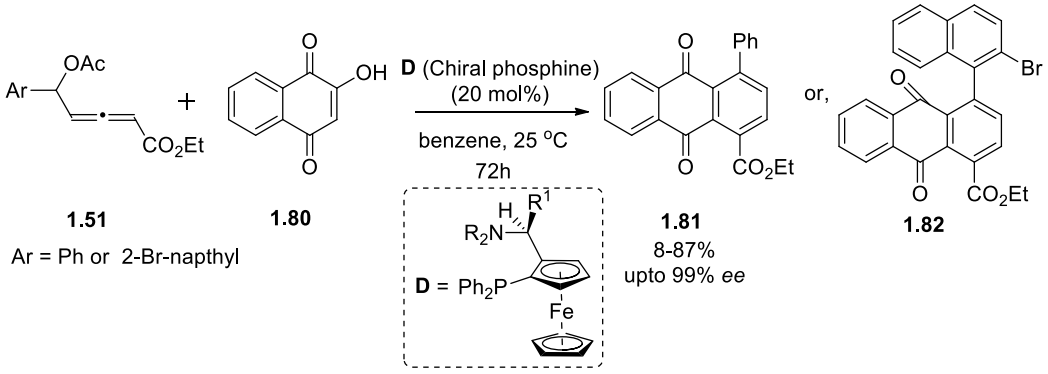
Scheme 1.28 Synthesis of spiro[indoline-3,2' pyrroles] **1.76**

In the year 2020, our group compared the phosphine and amine catalysts for the formation of 2-pyridinyl acetates **1.78**, and *o*-teraryl motifs **1.79**. The phosphine catalysts led to (4+2) annulation between δ-acetoxy allenoate **1.51** and *N*-sulfonyl ketimines **1.77** to form *o*-teraryl motifs **1.79**. When DBU/Na_2CO_3 combination was utilised as the catalyst, a novel (3+3) annulation was detected with moderate yields of the products (Scheme 1.29).[19c]



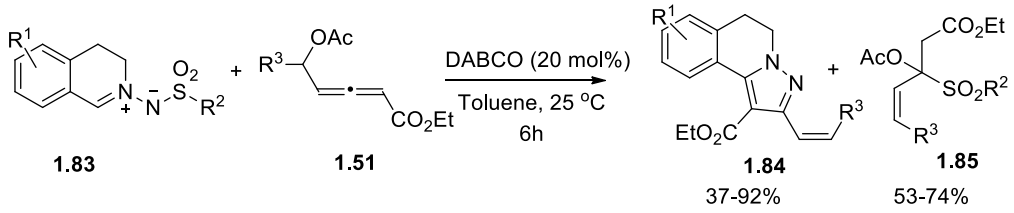
Scheme 1.29 Synthesis of compounds **1.78** and **1.79**

Tong *et al*. developed Lewis base catalyzed (4 + 2) annulation of 2-hydroxy-1,4-benzoquinone **1.80** involving δ-acetoxy allenoate **1.51** for the synthesis of compounds **1.81** or **1.82** using a chiral phosphine catalyst. In this process, a new benzene ring is added while simultaneously generating axial chirality, resulting in the production of the high enantioselectivity aryl naphthaquinone atropisomers (Scheme 1.30).[30]



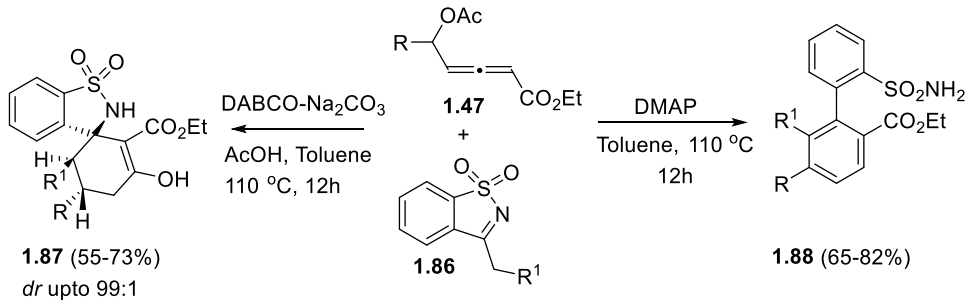
Scheme 1.30: Synthesis of aryl naphtha-quinones *via* δ-acetoxy allenoates

With the help of *δ*-acetoxy allenoate, Min Shi and their colleagues described (3 + 2) annulation of azomethine imine **1.83.** The DABCO-catalyzed reaction produced distinct compounds of pyrazoles **1.84** and substituted sulfonyl **1.85** in the presence of a tertiary amine. (Scheme 1.31).[31]



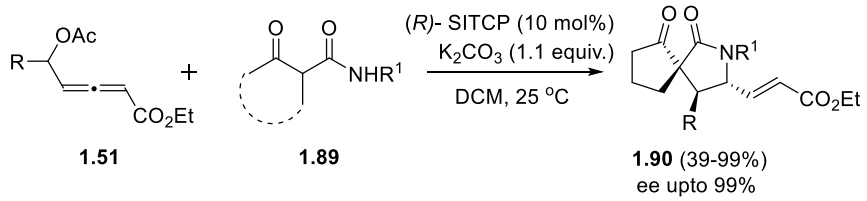
Scheme 1.31: Synthesis of pyrazole derivatives **1.84** and ethyl (*Z*)-3-acetoxy-3-tosylpent-4-enoates **1.85** using δ-acetoxy allenoates **1.51**

In 2021, our research team reported essentially single diastereomerisc products *via* chemo- and regio-specific (4+2)-carbo-annulation involving δ-acetoxy allenoates **1.51** and *N*-sulfonyl ketimines **1.86** initiated by the combination of DABCO and $MeCO_2H$. On the other hand, DMAP-catalyzed benzannulation with the same reactants produced unsymmetrical *m*-teraryls **1.88** *via* Mannich coupling where δ-acetoxy allenoates **1.51** served as a 4-carbon synthon (Scheme 1.32).[19d]



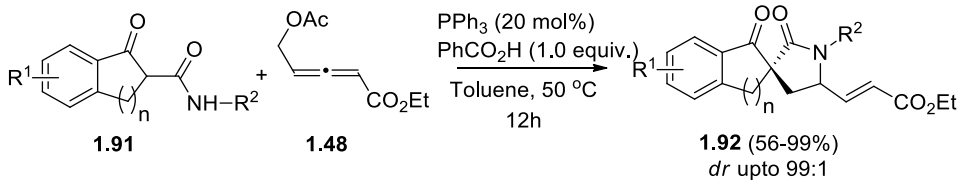
Scheme 1.32: Synthesis of compounds **1.87** and **1.88** from δ-acetoxy allenoates

According to Zhu *et al.* chiral *γ*-lactams were produced by asymmetric (3 + 2) annulation of *δ*-acetoxy allenoate **1.51** and *β*-carbonyl amides **1.89**. It's rare for lactams to undergo chiral phosphine-catalyzed annulation reactions. Here, they selected (R)-SITCP as the catalyst for chiral phosphine (Scheme 1.33).[32]



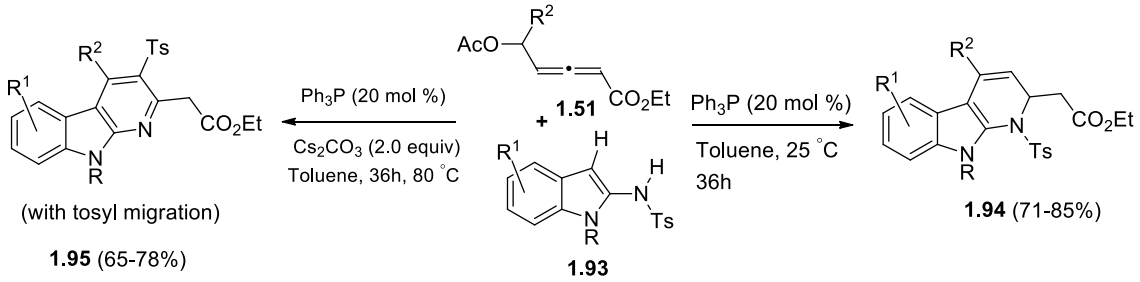
Scheme 1.33: Synthesis of chiral *γ*-lactams **1.90** from δ-acetoxy allenoates **1.51**

Min Shi and co-workers synthesized the five-membered heterocycles **1.92** that have a quaternary stereocenter *via* (3 + 2) annulation of *δ*-acetoxy allenoate **1.48** with *α*-substituted secondary *β*-keto amides **1.91** under phosphine catalysis.[33] Here, *β*-keto amides **1.91** acted as bis-nucleophiles (Scheme 1.34).



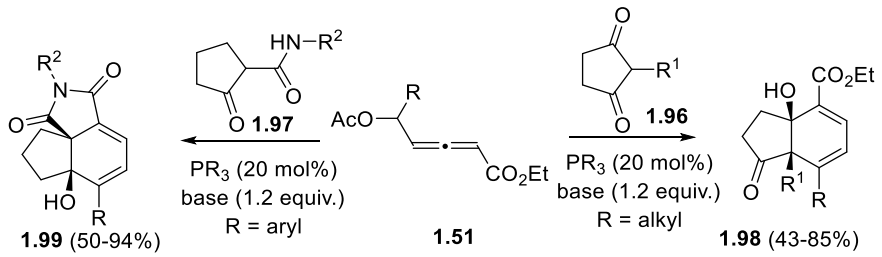
Scheme 1.34: Synthesis of spiro-heterocycles **1.92** from δ-acetoxy allenoate **1.48**

Our group has recently synthesized phosphine-catalyzed divergent annulations using acetoxy allenoate **1.51** and 2-sulfonamidoindoles **1.93**. "Aacetoxy allenoates **1.51** act as *β, γ* and *δ*-carbon donors" with substituted indole 2-sulfonamide **1.93** in temperature-dependent phosphine catalyzed (3 + 3) annulations. The migration of the tosyl group and its aromatization take place at a higher temperature (80 °C) to produce *α*-carboline derivatives with a tosyl functional group at the *γ*-carbon **1.95** (Scheme 1.35).[19f]



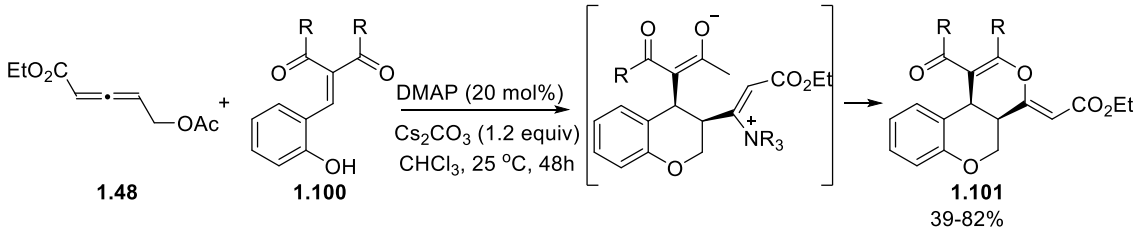
Scheme 1.35: Synthesis of 1,2-dihydro carbolines **1.94** and α-carboline **1.95** by starting with acetoxy allenoates **1.51**

Tong *et al*. discovered an effective method to obtain cyclohexane-1,3-dienes **1.98** and **1.99** between ketones and *δ*-acetoxy allenoate **1.51** by using phosphine-catalyzed (4+2) annulations, which are structurally complex but functionally rich. Allenoates with the *δ*-carbon alkyl group exhibit *δ*-carbon electrophilicity and *α*-carbon nucleophilicity when exposed to cyclic 1,3-dicarbonyl . On the other hand, allenoates containing an aryl group exhibit reverse reactivity when exposed to cyclic 1,3-dicarbonyl amides (Scheme 1.36).[34]



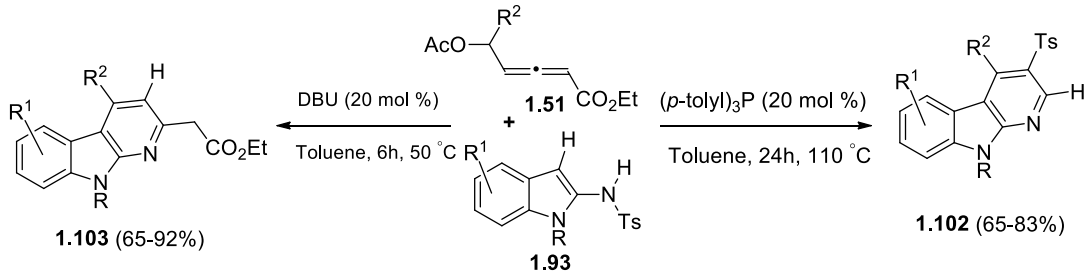
Scheme 1.36: Synthesis of fused 1,3-cyclohexadienes **1.98** and **1.99**

Tong's group disclosed a Lewis base catalyzed domino reaction to form polycyclic motifs **1.101**. The authors constructed these rings *via* addition/(4 + 2) annulation of acetoxy allenoate **1.48** to bifunctional substrate **1.100** *via* 4-dimethylaminopyridine catalysis (Scheme 1.37).[35]



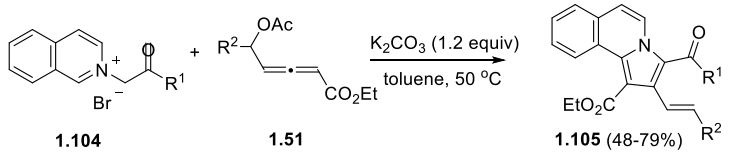
Scheme 1.37: Synthesis of hetero-polycyclic frameworks **1.101** from δ-acetoxy allenoate

In the year 2022, our research team reported the reaction of *δ*-acetoxy allenoate **1.51** with 2-sulfonamidoindoles **1.93** catalyzed by phosphine *via* diene phosphonium ion intermediate for the synthesis of tosyl-migrated α-carbolines **1.102**. By contrast, DBU-catalyzed (3+3) annulations delivered α-carbolines **1.103** *via* C-H and N-S bond cleavage using the same starting materials (Scheme 1.38).[36]



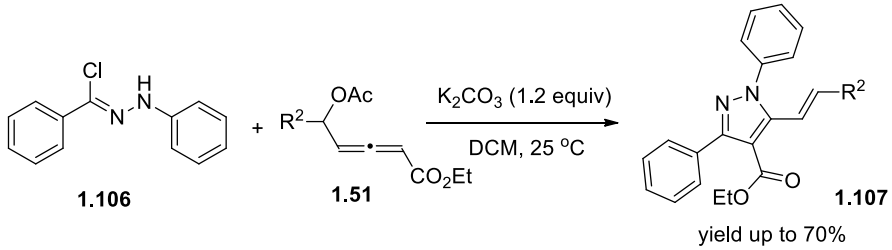
Scheme 1.38: Synthesis of tosyl-migrated α-carbolines **1.100** and α-carbolines **1.101**

In the year 2015, Tong *et al.* reported the use of K_2CO_3 as a base in the thermal 1,3-dipolar cycloaddition of δ-acetoxy allenoate **1.51** with pyridinium salts **1.104**. This method yielded cycloaddition products **1.105** with an endocyclic double bond in good to high yields (Scheme **1.39).**[37]



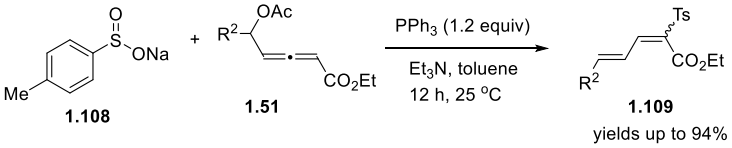
Scheme 1.39: Synthesis of pyridine derivatives **1.105** from δ-acetoxy allenoate

Zhou *et al.* reported a fast and effective method for producing 1,3,5-trisubstituted pyrazoles **1.107** from nitrilimines **1.106** and *δ*-acetoxy allenoate **1.51** in the presence of K_2CO_3 as a base *via* 1,3-dipolar cycloaddition (Scheme **1.40**).[38] The presence of electron-withdrawing nitro group on the benzene ring of nitrilimines caused a decrease in the yield while nitrilimines containing methoxy group increased the yield of the product.



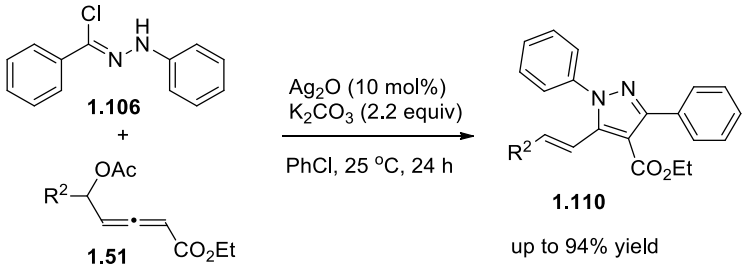
Scheme 1.40: Synthesis of trisubstituted pyrazoles **1.107** from δ-acetoxy allenoate

Tong *et al.* demonstrated the Lewis base catalyzed α-umpolung addition of sodium *p*-tolylsulfinate **1.108** to *δ*-acetoxy allenoate leading to the formation of conjugated *trans*-diene product **1.109** with good to excellent stereoselectivity. This reaction proceeds *via* 3-phosphonium-2,4-dienoate which is stabilized by the electrophilicity of the α-carbon atom of the acetoxy allenoate. The electron-withdrawing chloro substituent on the phenyl ring of sodium benzenesulfinate increased the yield of the product. On the other hand, the electron-donating substituent such as methoxy reduced the yield of the product (Scheme **1.41)**.[39]



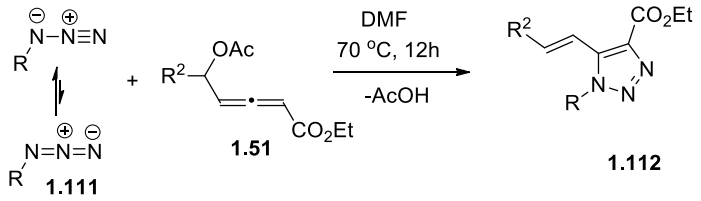
Scheme 1.41: Synthesis of conjugated *trans*-diene **1.109**

Li *et al.* reported the Huisgen cycloaddition in the reaction of hydrazonoyl chlorides **1.106** with δ-acetoxy allenoate in the presence of K_2CO_3 by using Ag_2O as the additive which produced substituted pyrazoles **1.110** in a highly efficient and selective manner (Scheme **1.42)**.[40]



Scheme 1.42: Synthesis of substituted pyrazoles **1.110** from δ-acetoxy allenoates

Recently, our research group developed a stereo- and regio-selective (3+2) cycloaddition involving δ-acetoxy allenoate **1.51** and azides **1.111** for the synthesis of tri-substituted 1,2,3-triazoles **1.112** motifs in good to high yields under metal-free conditions. Interestingly, α and β-carbons of δ-acetoxy allenoate were involved to deliver fully substituted triazole cores in good to high yields (Scheme **1.43**).[41]



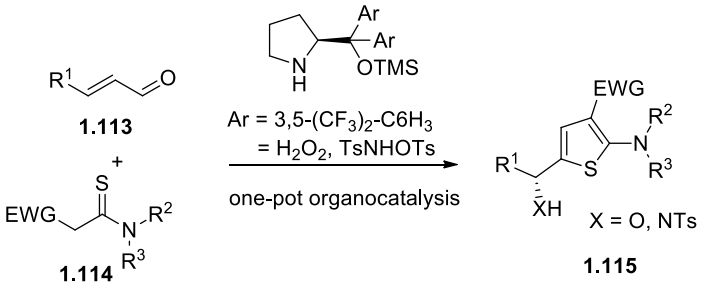
Scheme 1.43: Synthesis of triazole **1.112**

To the best of our knowledge, ring expansion reactions involving *δ*-acetoxy allenoates using a Lewis base has not appeared in the literature.

1.5 Reactions of thioamides

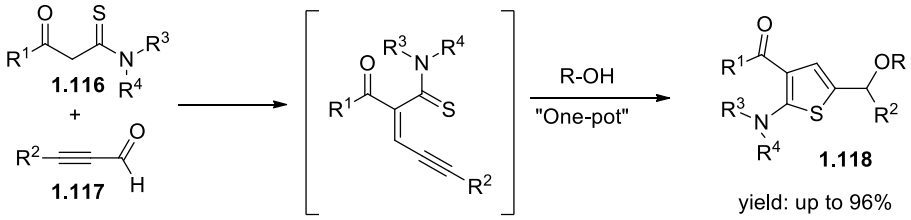
Thioamides are the other reacting partners that we have selected for the construction of five/ six-membered heterocyclic scaffolds. Due to the availability of lone pairs of electrons on nitrogen and sulfur atoms and an active methylene group, they can serve as useful nucleophiles to target the electrophilic center for the construction of heterocyclic scaffolds in the presence of a base.[42] Ransborg and co-workers reported a useful and very efficient stereoselective one-pot

method for the construction of optically active thiophenes **1.115** *via* an organocatalytic route from the easily available thioamides **1.114** and α,β-unsaturated aldehyde **1.113** (Scheme 1.44).[42a]



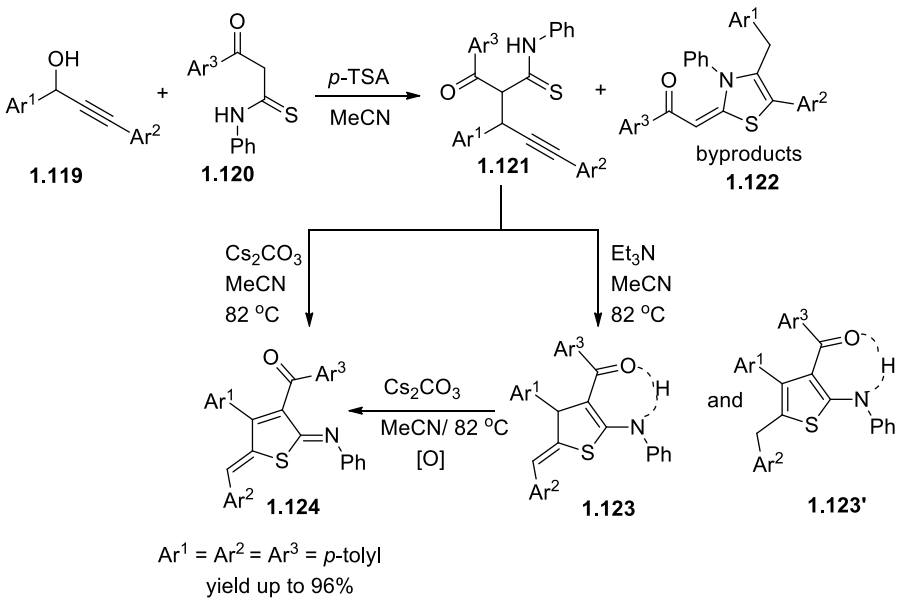
Scheme 1.44: Synthesis of substituted thiophenes **1.115** through organocatalysis

A study on the regioselective reaction toward the synthesis of functionalized 2-aminothiophenes **1.118** by concurrent intramolecular cyclization, conjugate addition, and aldol condensation was published by Deng's group. With good to outstanding yields, 2-ynals **1.117** with thioamides **1.116** could be used in a variety of alcohols without the use of any metal catalyst (Scheme 1.45).[42b]



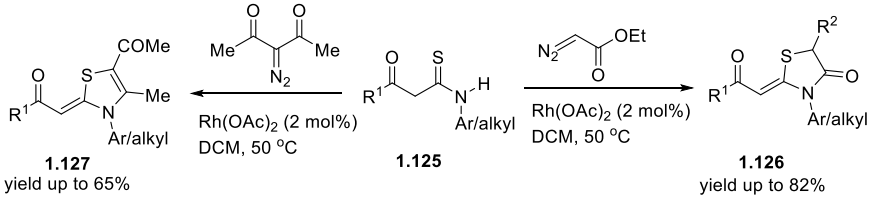
Scheme 1.45: Synthesis of functionalized 2-aminothiophenes **1.118** from thioamides **1.116**

In the year 2016, M. S. Singh's group disclosed a unique new metal-free methodology for the sythesis of fully substituted thiophenes **1.124** *via* a base-promoted intramolecular cycloisomerization in the presence of PTSA (Scheme 1.46).[42c]



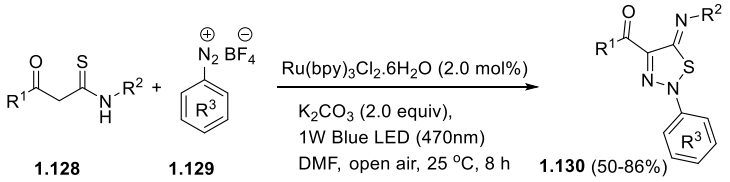
Scheme 1.46: Synthesis of substituted thiophenes **1.124** using organocatalysis

Singh's group has also reported Rh(II)-catalyzed intermolecular annulation of β-keto-thioamides **1.125** with diazo compounds leading to highly functionalized thiazolidine-4-ones **1.126** and thiazolines **1.127** in good to outstanding yields under favorable reaction conditions (Scheme 1.47).[42d]



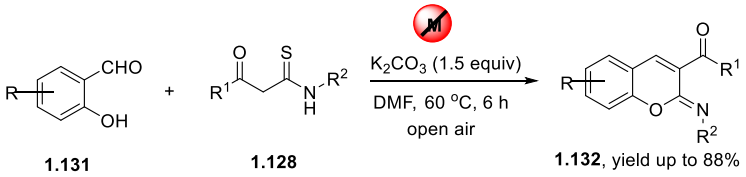
Scheme 1.47: Synthesis of thiazolidine-4-ones **1.126** and thiazolines **1.127**

Photocatalytic methods mediated by visible light have become efficient synthetic methods for constructing C-C and C-heteroatom bonds. Interestingly, photocatalysis offers the chance to produce intermediates with novel reactivity. In the year 2021, Singh's group explored a new type of radical cyclization reaction between thioamides **1.128** and diazonium salts **1.129** using UV-visible light for the synthesis of substituted thiadiazoles **1.130** *via* S-N bond formation at 25 °C. (Scheme 1.48).[42e]



Scheme 1.48: Synthesis of substituted thiadiazoles **1.130**

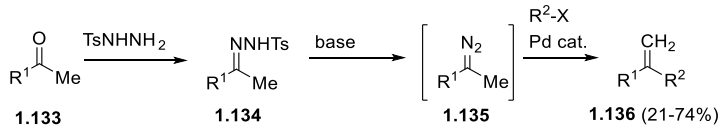
Singh's group demonstrated a methodology for the reaction of salicylaldehydes **1.131** with thioamides **1.128** in air to obtain 2*H*-chromene derivatives **1.132** *via* [4+2] annulation by using the simple base K_2CO_3 (Scheme 1.49).[42f]



Scheme 1.49: Synthesis of 2*H*-chromene derivatives **1.132**

1.6 Reactions of *N*-sulfonyl hydrazides

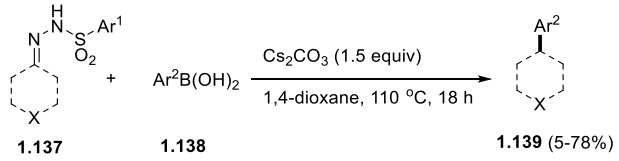
N-Sulfonyl hydrazides as key participants in annulations can be used for the construction of cyclic as well as acyclic *N*-inserted cores. Thus *N*-sulfonyl hydrazides have a significant impact on a variety of chemical processes. Sulfonyl hydrazides are noncorrosive, stable, simple to handle, moisture-compatible, and possess easy to donate nitrogen atoms serving as nitrogen sources to form C–N bonds.[43] A palladium-catalyzed cross-coupling reaction of tosyl hydrazones **1.134** with diazo compounds **1.135** for the production of polysubstituted alkenes **1.136** in the presence of base has been reported by Barluenga and Valdes (Scheme 1.50).[43a]



Scheme 1.50: Synthesis of polysubstituted alkenes **1.136** *via* tosylhydrazones

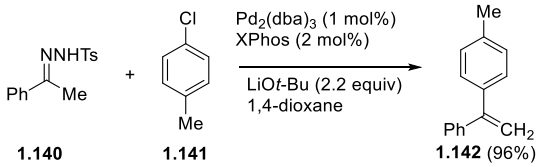
Sekar's group reported the boronic-coupling reaction with heteroaryl tosyl hydrazones **1.137** for the synthesis of bicyclic compounds **1.139** *via* a new C-C bond formation in the presence of inorganic base Cs_2CO_3. The reaction occurred through base-mediated thermolysis of

the *N*-tosyl hydrazones, resulting in the generation of the diazo intermediate, which then reacted with boronic acid to produce compound **1.139** (Scheme 1.51).[43b]



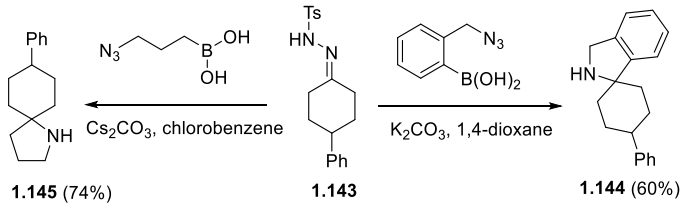
Scheme 1.51: Synthesis of compounds **1.139** using *N*-tosyl hydrazones

Wang and their colleagues discovered the palladium-catalyzed coupling reaction of *N*-tosyl hydrazone **1.140** with 4-chlorotoluene **1.141** to produce compound **1.142** in the presence of the base LiO*t*-Bu (Scheme 1.52).[43c]



Scheme 1.52: Synthesis of compound **1.142**

By combining *N*-sulfonylhydrazones **1.143** obtained from cyclic ketones with azido-substituted phenylboronic acid using a base in 1,4-dioxane as the solvent, [4+1] cyclizations result in the formation of spiro-isoindolines **1.144**.[43d] Valdes and their colleagues presented related cyclizations utilizing the same starting materials in the presence of γ-azido boronic acid that led to the formation of spirocyclic pyrrolidines **1.145** (Scheme 1.53).



Scheme 1.53: Synthesis of spirocyclic compounds **1.144** and **1.145**

OBJECTIVES OF THE PRESENT WORK-PART A

The main aim of this investigation was to investigate the reactivity of *δ*- acetoxy allenoates with thioamides, *N*-sulfonyl hydrazones, and 1,3-dicarbonyl compounds in the presence of nitrogen-containing Lewis bases. More specifically, it was intended to investigate

(i) Base switchable annulations of *δ*-acetoxy allenoates with thioamides that may provide access to novel dihydrothiophene, thiopyran, and thiazole frameworks,

(ii) Spiro-annulation ring expansion or ene-amine formation involving *δ*-acetoxy allenoates and cyclene-*N*-sulfonohydrazides, and

(iii) DMAP and DBU-catalyzed annulation of *δ*-acetoxy allenoates with 1,3-dicarbonyl compounds leading to dihydropyrans and 4*H*-pyrans.

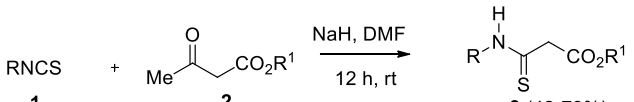
RESULTS AND DISCUSSION

This chapter deals with various transformations involving acetoxy allenoates and thioamides leading to dihydrothiophene, thiopyran, and thiazole scaffolds. It also deals with the reactivity of *N*-sulfonyl hydrazones and 1,3-dicarbonyl compounds with *δ*-acetoxy allenoates. Final compounds were initially analyzed by NMR spectroscopy, and molecular weight was confirmed by mass spectrometry followed by infrared spectroscopy. Further melting points were recorded for solid compounds. The ascribed regiochemistry and stereochemistry of the final compounds are based on X-ray crystallographic studies on exemplified compounds.

2.1 Synthesis of precursors

2.1.1 *Thioamides 3a-h*

The starting materials **3a-h** were prepared from isothiocyanatobenzene (**1a-h**) and ethyl acetoacetate **2a-h** by using the literature procedure in the presence of NaH, and DMF for 12 h (Scheme 1).[42a]

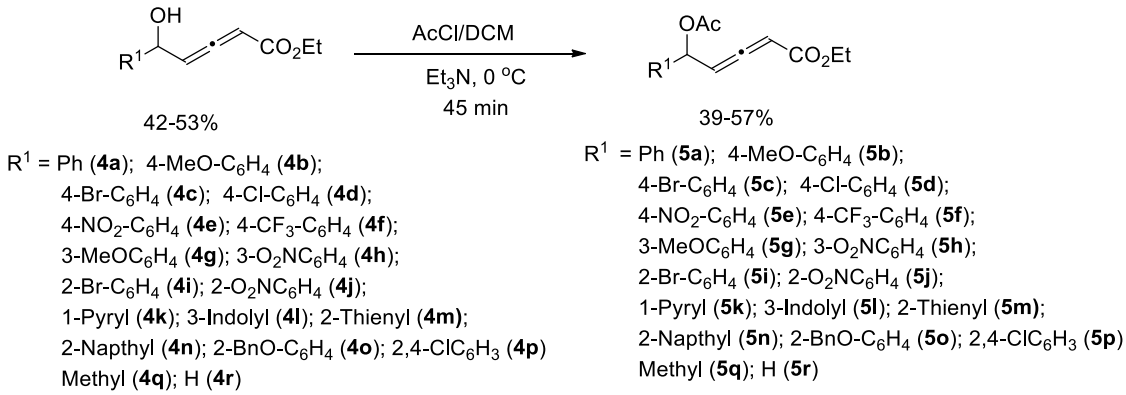


R = Ph, (**1a**)	R^1 = Et, (**2a**)	R = Ph, R^1= Et (**3a**)
R = 4-Me-C_6H_4, (**1b**)	R^1 = Et, (**2b**)	R = 4-Me-C_6H_4, R^1= Et (**3b**)
R = 4-ClC_6H_4, (**1c**)	R^1 = Et, (**2c**)	R = 4-ClC_6H_4, R^1= Et (**3c**)
R = 4-$NO_2C_6H_4$, (**1d**)	R^1 = Et, (**2d**)	R = 4-$NO_2C_6H_4$, R^1= Et (**3d**)
R = 4-CNC_6H_4, (**1e**)	R^1 = Et, (**2e**)	R = 4-CNC_6H_4, R^1= Et (**3e**)
R = Cyclohexyl, (**1f**)	R^1 = Et, (**2f**)	R = Cyclohexyl, R^1= Et (**3f**)
R = CH_2CH_2Ph, (**1g**)	R^1 = Et, (**2g**)	R = CH_2CH_2Ph, R^1= Et (**3g**)
R = Ph, R^1= Me (**1h**)	R^1 = Me, (**2h**)	R = Ph, R^1= Me (**3h**)

Scheme 1: Synthesis of thioamides **3a-h**

2.1.2 *δ-Acetoxy allenoates 5a-p*

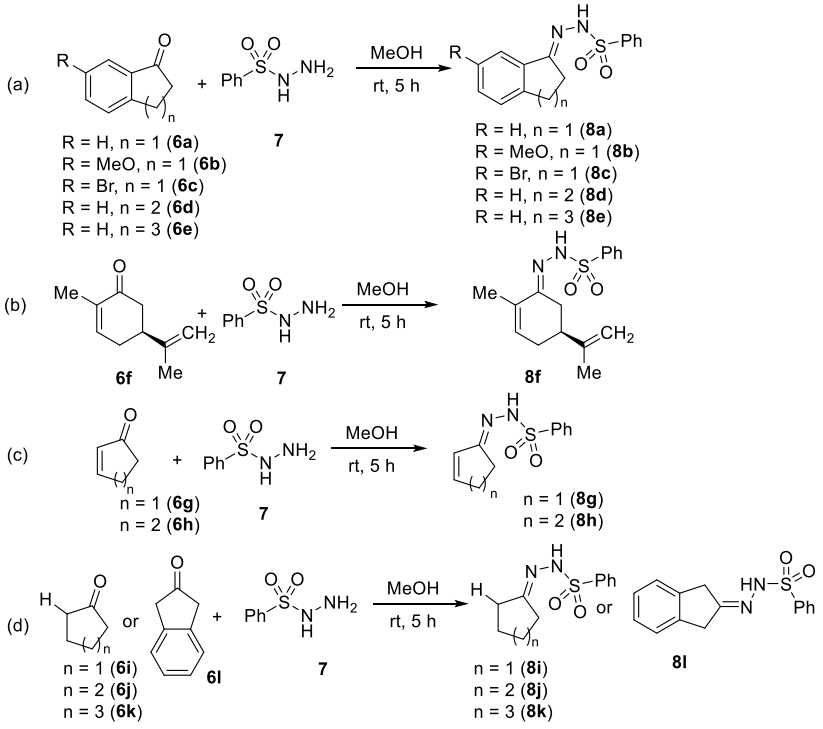
Substituted *δ*-acetoxy allenoates **5a-r** were obtained by treating the corresponding hydroxyl substituted allenes **4a-r**[19d] with acetyl chloride and Et_3N in DCM at 0 °C for 45 min using a literature procedure (Scheme 2).[19d]



Scheme 2. Synthesis of *δ*-acetoxy allenoates **5a-r** from *δ*-hydroxy allenoates **4a-r**

2.1.3 *Fused N-sulfonyl hydrazones, β-carvone N-sulfonyl hydrazone, Ali-cyclene N-sulfonyl hydrazones, and non-fused / β-fused N-sulfonyl hydrazones*

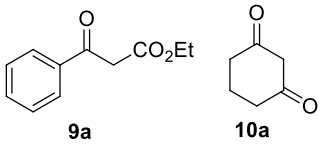
The precursors cycl-2-ene-*N*-sulfonyl hydrazides **8a-c** and **8e-f** are new and are synthesized from fused ketone **6a-c** and **6e-f** with benzenesulfonyl hydrazide **7**; precursors such as cycl-3-ene-*N*-sulfonyl hydrazides **8d**, and **8g-l** were prepared by a method reported in the literature (Scheme 3).[44]



Scheme 3: Synthesis of hydrazones **8a-8l**.

2.1.4 *1,3-dicarbonyl compounds*

The 1,3-dicarbonyl precursors **9a** and **10a** are commercially available.[20]



9a **10a**

2.2 Annulation reactions of *δ*-acetoxy allenoates with thioamides: Access to dihydrothiophene, thiopyran, and thiazole scaffolds

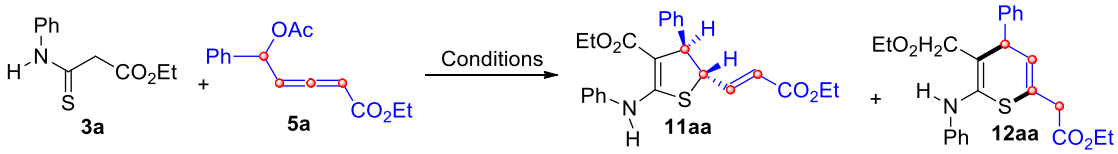
In the present work, we wanted to explore the reactivity of *δ*-acetoxy allenoates with thioamides under Lewis base catalysis. Interestingly, pyridine catalyzed (3+2) annulations offered dihydrothiophene motifs with excellent stereoselectivity whereas thiopyran cores were obtained by using DABCO via (3+3) annulations. Use of similar starting materials under TBAB-catalyzed (3+2) annulations led to thiazole cores. Details are presented below.

2.2.1 *Reaction of δ-acetoxy allenoates with thioamides: Synthesis of dihydrothiophenes and thiopyrans*

We have selected thioamide **3a** and *δ*-acetoxy allenoate **5a** as model substrates. As depicted in Table 1, we tested the reaction of **3a** (0.20 mmol) with **5a** (0.24 mmol) in the presence of DMAP (0.04 mmol) in toluene at rt (25 ^{o}C). We isolated **11aa** in 58% yield and identified it as (3 + 2) annulated product using its $^{1}H/^{13}C\{^{1}H\}$ NMR, HRMS, and IR data. We did not get a better yield by using 50 mol% (entry 2) of DMAP or at a higher temperature (entry 3). The addition of Na_2CO_3 (2.0 equiv) improved the yield of **11aa** to 71% (entry 4); other additives ($NaHCO_3$ and K_2CO_3) were also evaluated (entries 5-6). Among these, K_2CO_3 gave a better yield (74%, entry 6). Organic bases such as pyridine, DIPEA, Et_3N, and DABCO were examined as catalysts (entries 7-10) and pyridine was the best choice for **11aa** (entry 7). The solvent study (entries 8-13) revealed that toluene was still the best for giving **11aa** in high yield (entry 7). Interestingly, aliphatic (DIPEA and Et_3N) and alicyclic (DABCO) tertiary amines delivered [3 + 3] annulated product **12aa** (entries 17-19) with the exclusion of **11aa**. For optimizing conditions to get **12aa**, we examined several solvents (entries 20-25) and found that the DABCO-K_2CO_3 combination in toluene solvent at rt was the best condition to get **12aa** in high yield (entry 19). A lower catalyst loading (5 mol % or 10 mol %) resulted in the incomplete

consumption of starting materials (entries 14-15 and 26-27) but higher loading (100 mol %) of the organic base did not have any considerable impact on the yield (entries 16 and 28). The use of Ph_3P did not give a better yield of **11aa** at the rt as well as 80 ^oC (entries 29 and 30). Thus we concluded to utilize entry 7 for **11aa** and entry 19 for **12aa** as optimal conditions.

Table 1. Optimization of reaction conditions for the synthesis of 11aa and 12aa[a,b]



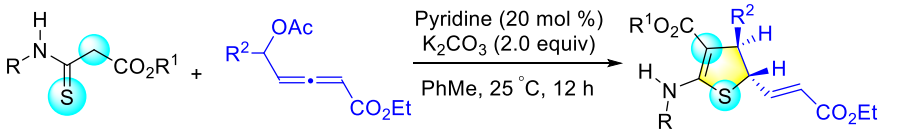
Entry	Base	Solvent	Additive	Yield (%)[b] **11aa**:**12aa**	dr for **11aa**[c]
1	DMAP	$PhCH_3$	-	58:00	20:1
2	DMAP	$PhCH_3$	-	58:00	20:1
3	DMAP	$PhCH_3$	-	58:00	20:1
4	DMAP	$PhCH_3$	Na_2CO_3	71:00	20:1
5	DMAP	$PhCH_3$	$NaHCO_3$	65:00	20:1
6	DMAP	$PhCH_3$	K_2CO_3	74:00	20:1
7	**Pyridine**	**$PhCH_3$**	K_2CO_3	**77:00**	**20:1**
8	Pyridine	DMF	K_2CO_3	43:00	20:1
9	Pyridine	MeCN	K_2CO_3	51:00	20:1
10	Pyridine	DCE	K_2CO_3	55:00	20:1
11	Pyridine	THF	K_2CO_3	48:00	20:1
12	Pyridine	MeOH	K_2CO_3	27:00	20:1
13	Pyridine	H_2O	K_2CO_3	-	-

14	Pyridine	$PhCH_3$	K_2CO_3	37:00	20:1
15	Pyridine	$PhCH_3$	K_2CO_3	48:00	20:1
16	Pyridine	$PhCH_3$	K_2CO_3	77:00	20:1
17	DIPEA	$PhCH_3$	K_2CO_3	00:34	-
18	Et_3N	$PhCH_3$	K_2CO_3	00:25	-
19	**DABCO**	**$PhCH_3$**	K_2CO_3	**00:79**	-
20	DABCO	DMF	K_2CO_3	00:45	-
21	DABCO	MeCN	K_2CO_3	00:53	-
22	DABCO	DCE	K_2CO_3	00:59	-
23	DABCO	THF	K_2CO_3	00:51	-
24	DABCO	MeOH	K_2CO_3	00:32	-
25	DABCO	H_2O	K_2CO_3	-	-
26	DABCO	$PhCH_3$	K_2CO_3	00:41	-
27	DABCO	$PhCH_3$	K_2CO_3	00:49	-
28	DABCO	$PhCH_3$	K_2CO_3	00:79	-
29	Ph_3P	$PhCH_3$	K_2CO_3	33:00	20:1
30	Ph_3P	$PhCH_3$	K_2CO_3	47:00	20:1

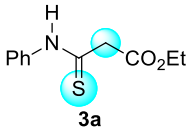
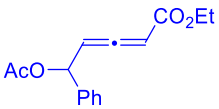
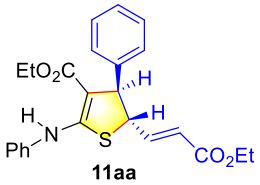
[a]Reaction conditions: **3a** (0.20 mmol) and **5a** (0.24 mmol) with base (5 mol % for entries 14 and 26; 10 mol % for entries 15 and 27; 20 mol % for entries 1, 3, 4-13, 17-25 and 29-30; 50 mol % for entry 2; 100 mol % for entries 16 and 28) and additive (0.40 mmol in solvent (2.0 mL); temperature (25 ^oC for entries 1, 2 and 4-28; 80 ^oC for entry 3 and 30). [b]Isolated yield. [c]Diastereomeric ratio.

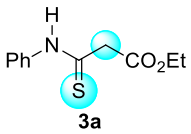
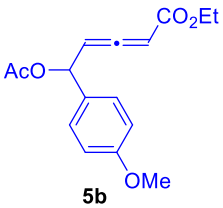
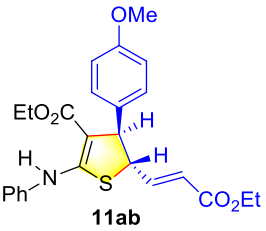
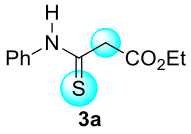
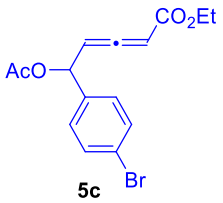
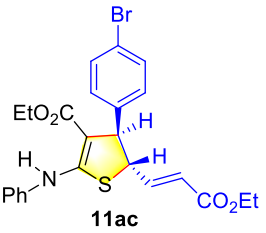
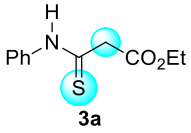
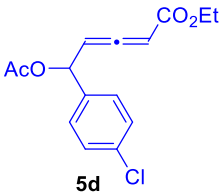
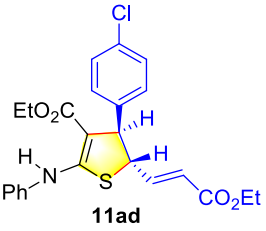
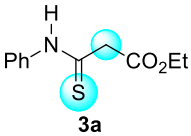
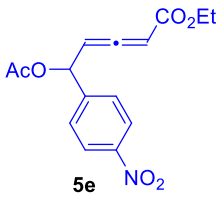
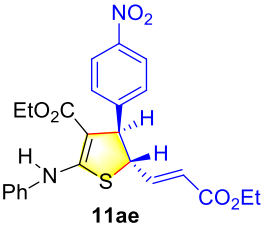
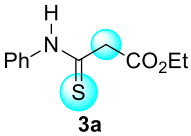
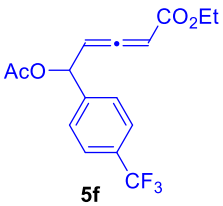
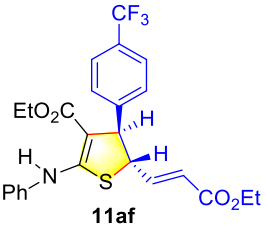
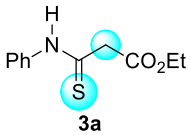
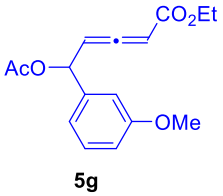
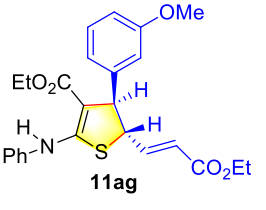
As shown in Table 2, a wide variety of allenoates smoothly underwent this (3 + 2) annulation to afford 4,5-dihydro-5-*E*-alkenyl thiophene carboxylates with excellent stereoselectivity (dr ≥20:1). Allenoates having different functionalities such as OMe, Br, Cl, NO_2, and CF_3 at the 4th position of the phenyl ring (**5b-5f**) were tolerated well and gave the corresponding products (**11ab-11af**) in high yields (73-80%). 3-Substituted allenoates **5g** and **5h** also furnished **11ag** and **11ah** in acceptable yields (75% and 76%). Due to steric factors, somewhat lower yields were obtained in the case of 2-substituted allenoates **5i** and **5j** when compared to 4 or 3-substituted allenoates (**11ai** in 69% and **11aj** in 71%). The polyaryl allenoate **5k** also was viable and delivered the desired product **11ak** in good yield (71%). Replacement of aryl groups with hetero-aryl functions such as 3-indolyl **5l** and 2-thienyl **5m** did not hamper the reactivity (**11al** in 68% and **11am** in 65%) and selectivity (dr ≥20:1). This annulation was also compatible with thioamides (**3b-3h**) possessing aromatic, alicyclic and aliphatic moieties to afford **11ba-11ha** in good to high yields (68-81%) with excellent selectivity (dr ≥ 20:1). Likewise, **11be**, **11db**, and **11dl** were also obtained in good yields. The relative configuration of substituents in **11da** and **11ea** was corroborated by single crystal X-ray structures (Figure 1).

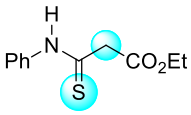
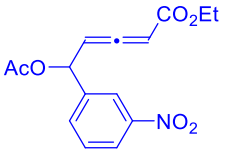
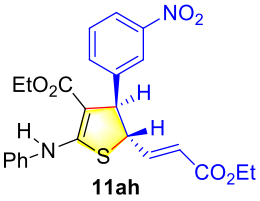
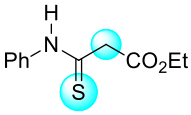
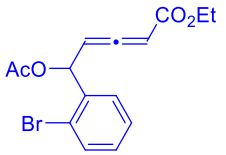
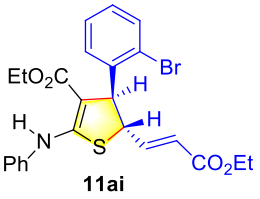
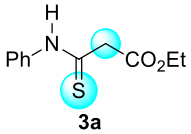
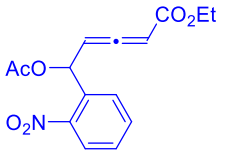
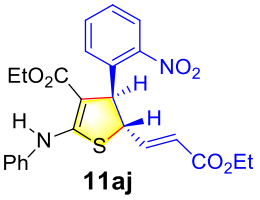
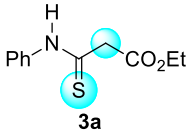
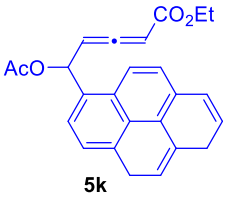
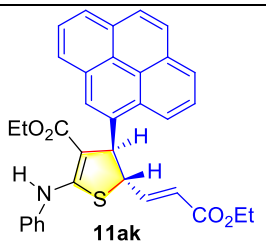
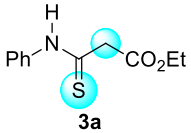
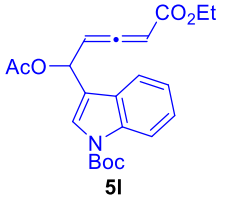
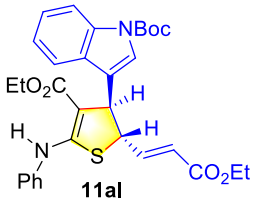
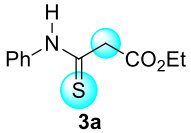
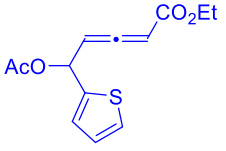
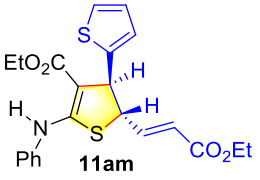
Table 2. Substrate scope for the synthesis of dihydrothiophene from thioamides and *δ*-acetoxy allenoates[a]

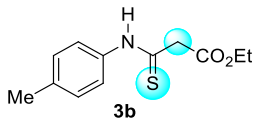
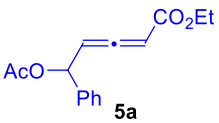
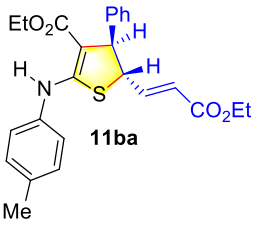
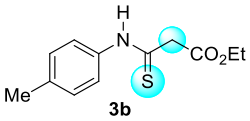
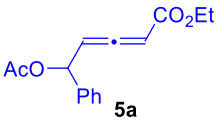
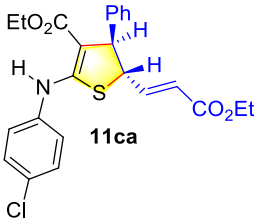
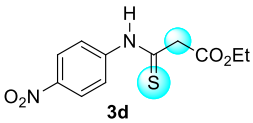
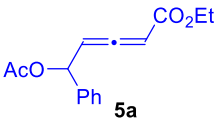
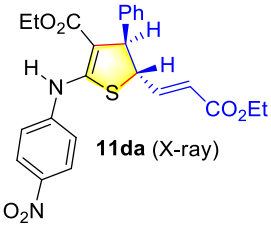
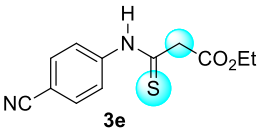
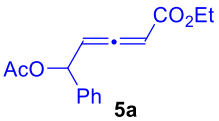
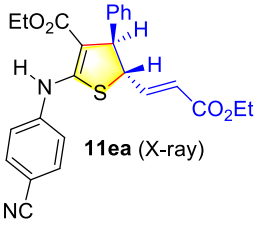
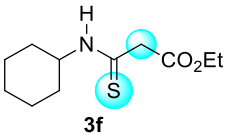
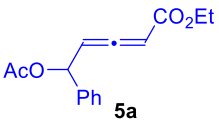
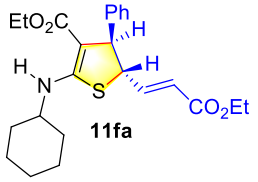
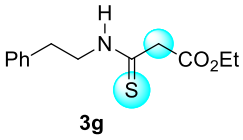
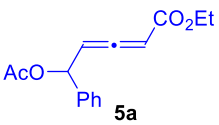
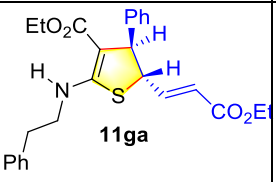


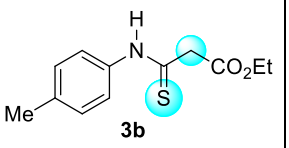
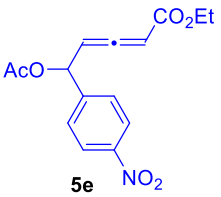
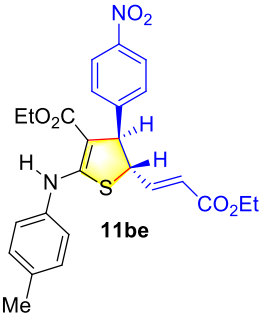
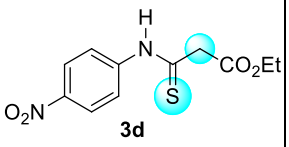
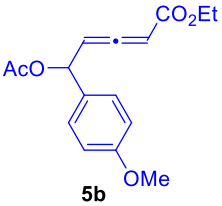
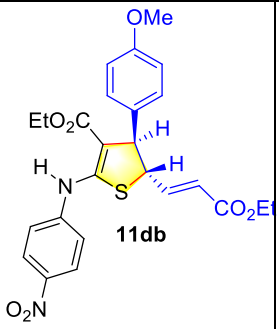
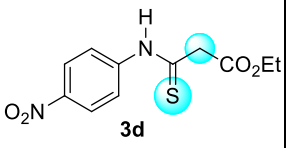
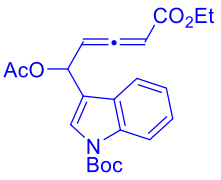
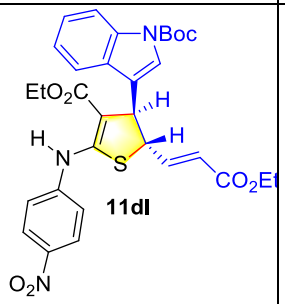
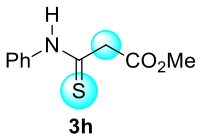
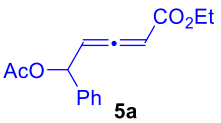
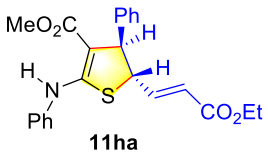
3a-h **5a-m** **11aa-11am**, **11ba-11ga** **11be, 11db, 11dl** and **11ha**

Entry	Thioamides	*δ*-Acetoxy allenoate	Dihydrothiophene	Yield (%)[b]
1	 **3a**	 **5a**	 **11aa**	77

2	 **3a**	 **5b**	 **11ab**	73
3	 **3a**	 **5c**	 **11ac**	74
4	 **3a**	 **5d**	 **11ad**	76
5	 **3a**	 **5e**	 **11ae**	80
6	 **3a**	 **5f**	 **11af**	79
7	 **3a**	 **5g**	 **11ag**	75

8	 **3a**	 **5h**	 **11ah**	76
9	 **3a**	 **5i**	 **11ai**	69
10	 **3a**	 **5j**	 **11aj**	71
11	 **3a**	 **5k**	 **11ak**	71
12	 **3a**	 **5l**	 **11al**	68
13	 **3a**	 **5m**	 **11am**	65

14	 **3b**	 **5a**	 **11ba**	75
15	 **3b**	 **5a**	 **11ca**	78
16	 **3d**	 **5a**	 **11da** (X-ray)	81
17	 **3e**	 **5a**	 **11ea** (X-ray)	77
18	 **3f**	 **5a**	 **11fa**	70
19	 **3g**	 **5a**	 **11ga**	68

20	 **3b**	 **5e**	 **11be**	71
21	 **3d**	 **5b**	 **11db**	73
22	 **3d**	 **5l**	 **11dl**	71
23	 **3h**	 **5a**	 **11ha**	75

[a]Reaction conditions: **3a-h** (0.20 mmol), **5a-m** (0.24 mmol), pyridine (0.04 mmol) and K_2CO_3 (0.40 mmol) in toluene (0.1 M) at 25 °C. [b]Isolated yield. [c]Diastereomeric ratio ≥ 20:1.

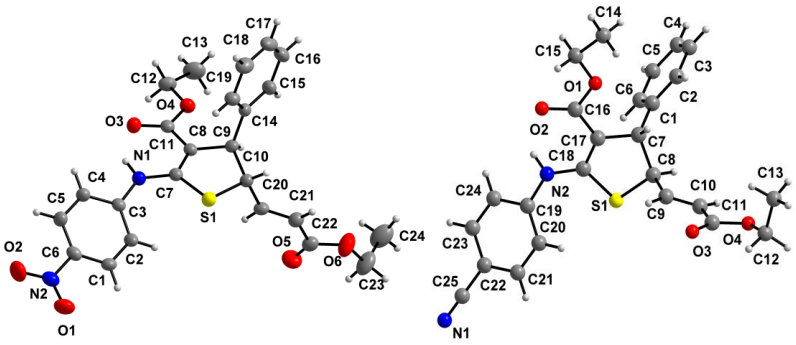
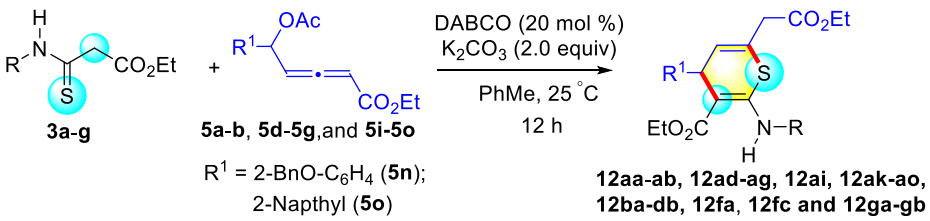
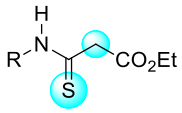
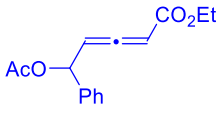
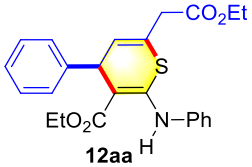
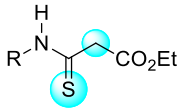
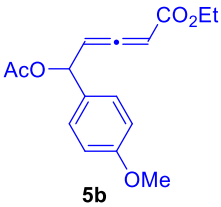
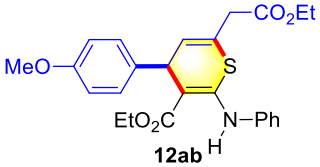
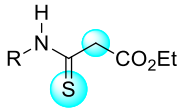
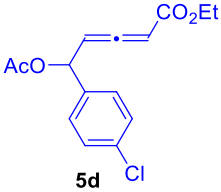
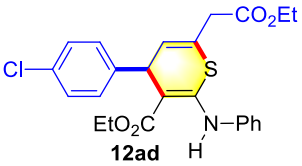
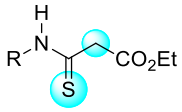
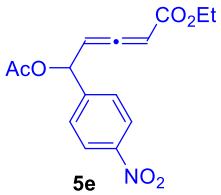
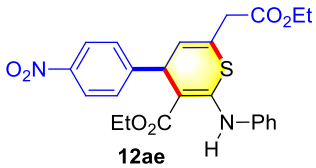
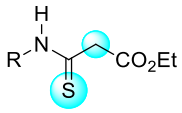
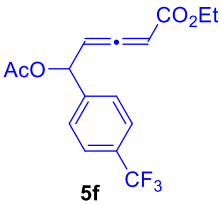
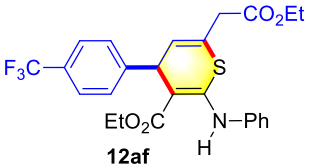
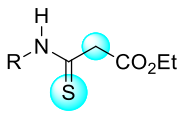
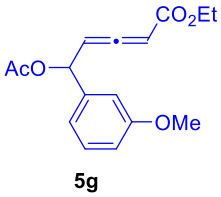
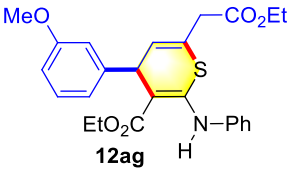


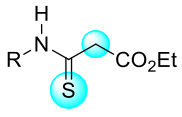
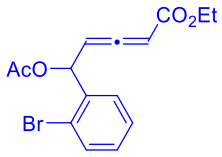
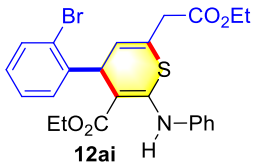
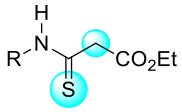
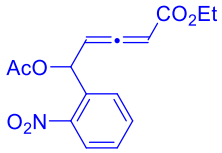
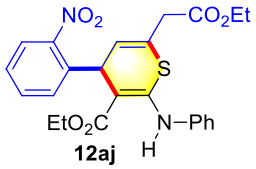
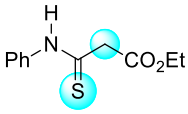
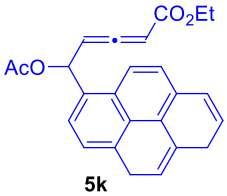
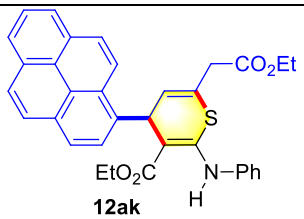
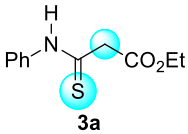
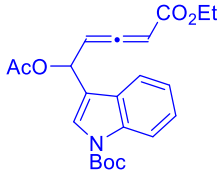
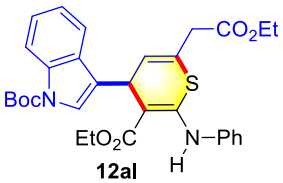
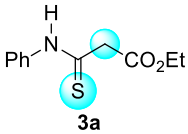
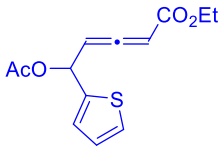
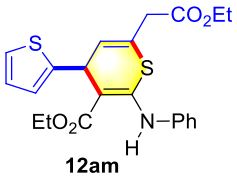
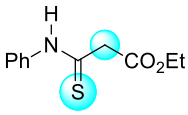
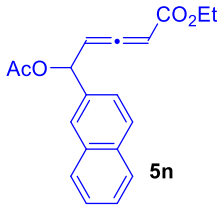
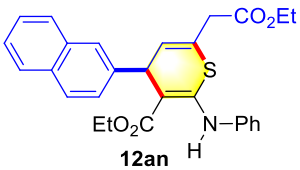
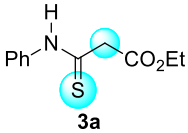
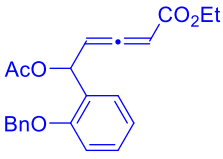
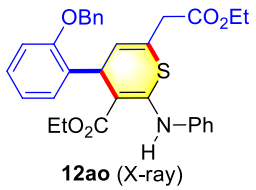
Figure 1: Molecular structures of compounds **11da** (left, CCDC No. 2110597) and **11ea** (right, CCDC No. 2110598).

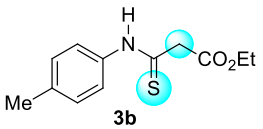
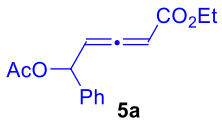
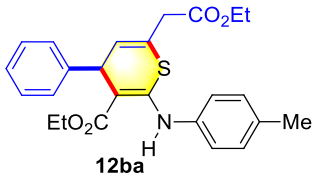
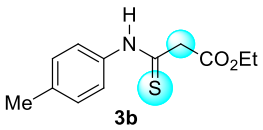
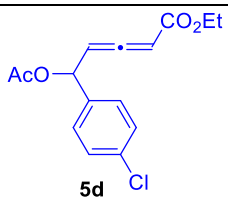
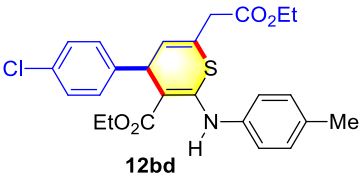
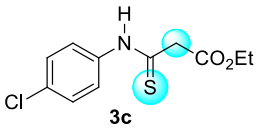
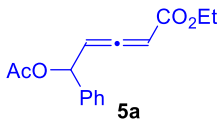
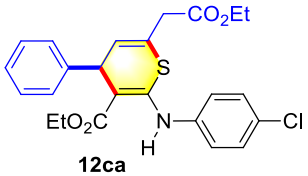
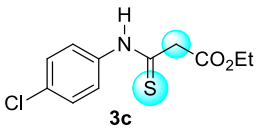
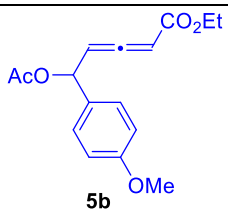
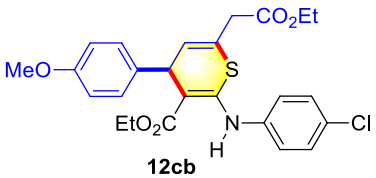
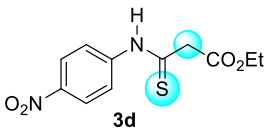
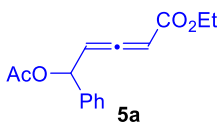
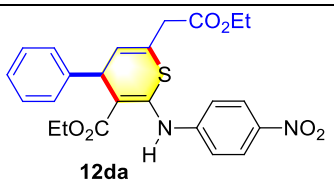
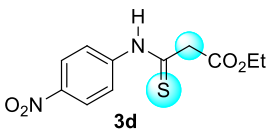
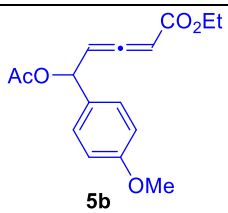
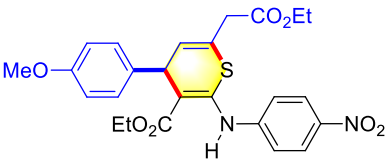
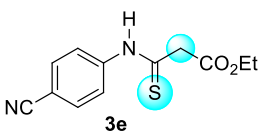
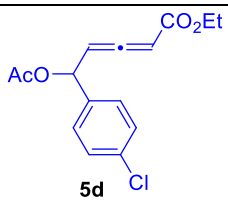
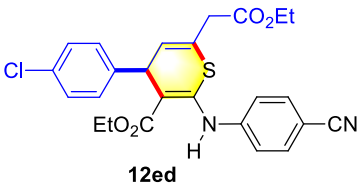
In contrast to the above, DABCO catalyzed (3 + 3) annulation of thioamide **3a** with *δ*-acetoxy allenoate **5a** at rt gave *thiopyran* **12aa** in high yield (79%; Table 1, entry 19). The substrate scope for this annulation is summarized in Table 3. As can be noted, this reaction is also quite general with respect to *δ*-acetoxy allenoates and thioamides. Thus unsubstituted (**5a**) and substituted (**5b**, **5d-5g**, **5i**, **5j**, and **5n**) allenoates delivered the thiopyran scaffolds (**12ab**, **12ad-12ag**, **12ai**, **12aj**, and **12an**) in good to high yields (68-84%). This protocol also accommodated polyaryl substituted allenoates (**5k** and **5o**) to generate the products **12ak** and **12ao** in 73% and 75% yields, respectively. Heteroaryl allenoates **5l** and **5m** were also found as effective substrates in offering **12al** and **12am** with good yields (69-71%). Different thioamides (**3b**-**3g**) also delivered the required thiopyran cores **12ba**-**12ed**, **12fa**, **12fd**, **12ga**, and **12gb** in satisfactory yields (77-85%, 71%, 66%, 70%, and 67%). Molecular structures of **12an** and **12db** are depicted in Figure 2.

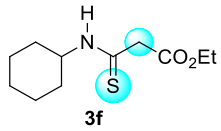
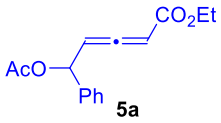
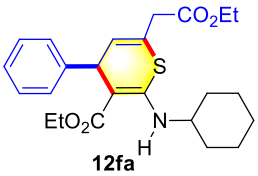
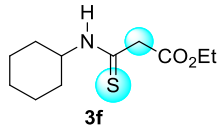
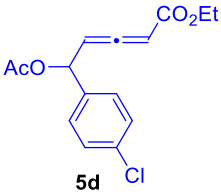
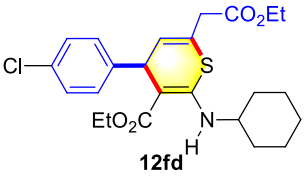
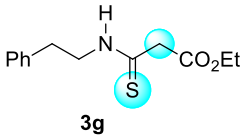
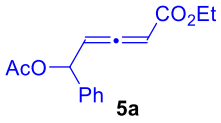
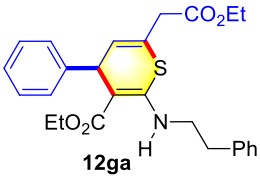
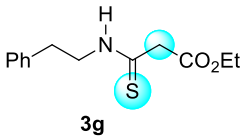
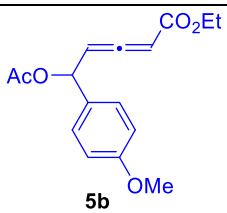
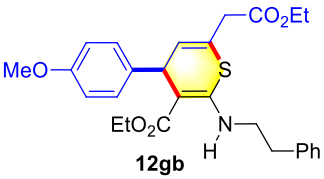
Table 3. Substrate scope for the synthesis of thiopyran from thioamides and *δ*-acetoxy allenoate[a]



Enty	Thioamides	δ-Acetoxy allenoate	Thiopyran	Yield (%)[b]
1	 **3a**	 **5a**	 **12aa**	79
2	 **3a**	 **5b**	 **12ab**	74
3	 **3a**	 **5d**	 **12ad**	77
4	 **3a**	 **5e**	 **12ae**	84
5	 **3a**	 **5f**	 **12af**	82
6	 **3a**	 **5g**	 **12ag**	76

7	 **3a**	 **5i**	 **12ai**	70
8	 **3a**	 **5j**	 **12aj**	72
9	 **3a**	 **5k**	 **12ak**	73
10	 **3a**	 **5l**	 **12al**	71
11	 **3a**	 **5m**	 **12am**	69
12	 **3a**	 **5n**	 **12an**	68
13	 **3a**	 **5o**	 **12ao** (X-ray)	75

14	 **3b**	 **5a**	 **12ba**	77
15	 **3b**	 **5d**	 **12bd**	79
16	 **3c**	 **5a**	 **12ca**	81
17	 **3c**	 **5b**	 **12cb**	78
18	 **3d**	 **5a**	 **12da**	85
19	 **3d**	 **5b**	 **12db** (X-ray)	80
20	 **3e**	 **5d**	 **12ed**	77

21	 **3f**	 **5a**	 **12fa**	71
22	 **3f**	 **5d**	 **12fd**	66
23	 **3g**	 **5a**	 **12ga**	70
24	 **3g**	 **5b**	 **12gb**	67

[a]Reaction conditions: **3a-g** (0.20 mmol), **5a-b, 5d-5g** and **5i-5o** (0.24 mmol), DABCO (0.04 mmol) and K_2CO_3 (0.40 mmol) in toluene (0.1 M) at 25 °C. [b]Isolated yield.

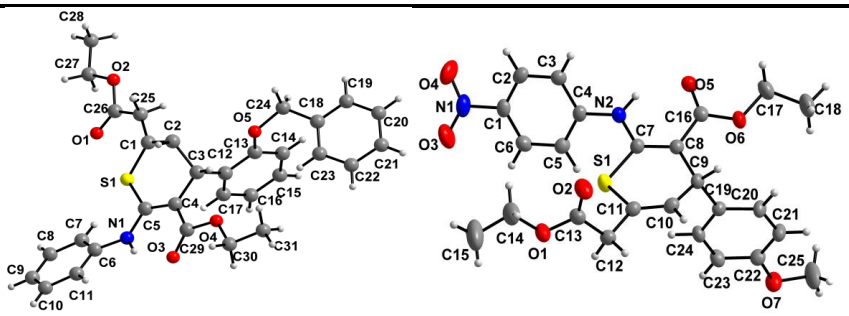


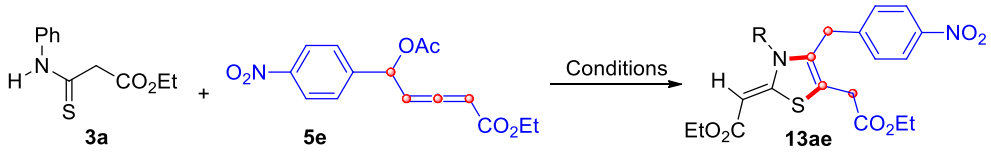
Figure 2: Molecular structures of compounds **12an** (left, CCDC No. 2110599) and **12db** (right, CCDC No. 2110600).

2.2.2 *Formation of thiazoles from δ-acetoxy allenoates mediated by TBAB*

We explored several conditions for the reaction between **3a** and **5e** as indicated in Table 4. Initially, we tested a reaction using tetra-*n*-butyl ammonium bromide (TBAB)-K_2CO_3

combination at rt as well as higher temperature (80 ^{o}C) but did not observe any reaction in either case (entries 1-2). However, the reaction in DCM proceeded nicely and afforded **13ae** with a *Z*-isomeric exocyclic double bond and containing sulfur and nitrogen inserted thiazole core (entry 3). After checking various solvents (MeCN, THF, and DCE) (entries 4-6) and other quaternary ammonium salts (TBAI, TBAF, and Triton-B) (entries 7-9), we concluded that DCM-TBAB was the best combination for this protocol (entry 3). No desired product was obtained using only K_2CO_3 (entry 10); hence the presence of quaternary ammonium salt is essential for this transformation.

Table 4. Optimization of reaction conditions for the thiazole 13ae

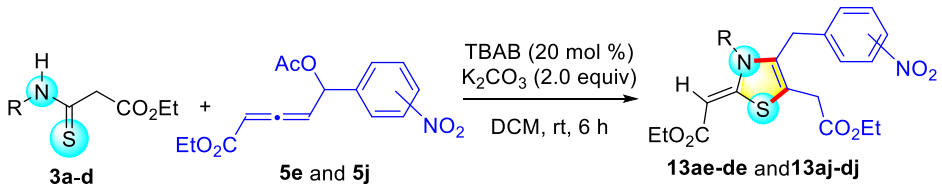


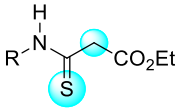
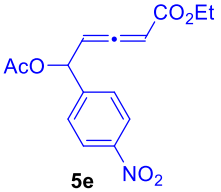
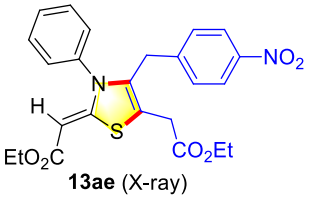
Entry	Base	Solvent	Yield (%)[b]	dr[c]
1	TBAB	$PhCH_3$	nr	-
2	TBAB	$PhCH_3$	nr	-
3	**TBAB**	**DCM**	**72**	**99:1**
4	TBAB	MeCN	63	99:1
5	TBAB	THF	65	99:1
6	TBAB	DCE	59	99:1
7	TBAF	DCM	57	99:1
8	TBAI	DCM	61	99:1
9	Triton-B	DCM	48	99:1
10	-	DCM	nr	-

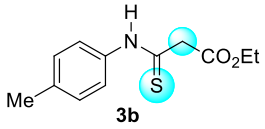
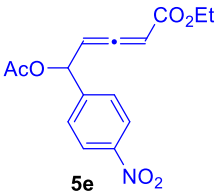
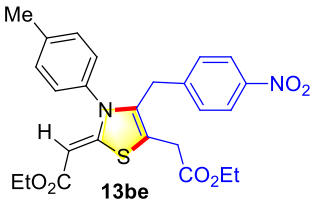
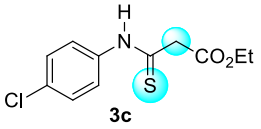
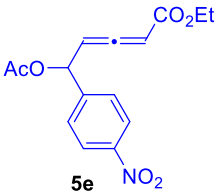
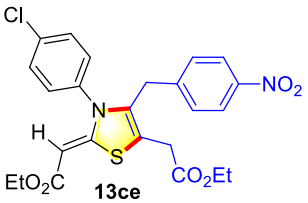
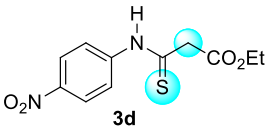
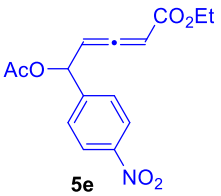
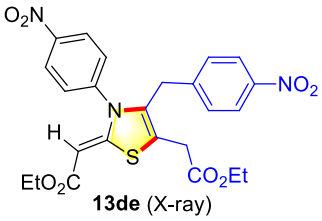
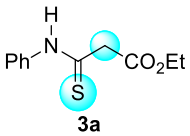
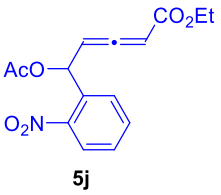
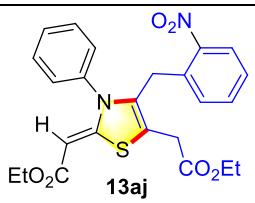
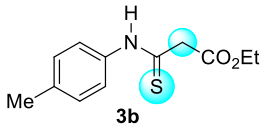
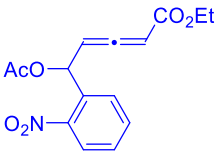
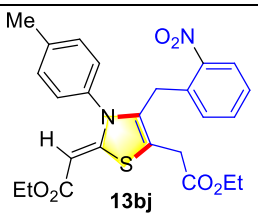
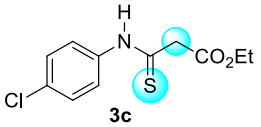
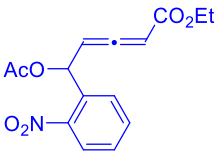
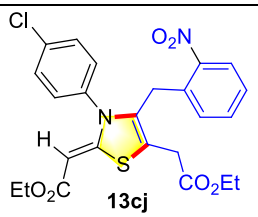
[a]Reaction conditions: **3a** (0.20 mmol) and **5e** (0.24 mmol) with quaternary ammonium salt (20 mol % for entries 1 and 3-10; 50 mol % for entry 2) and K_2CO_3 (0.40 mmol) in solvent (2.0 mL); temperature (25 °C for entries 1 and 3-10; 80 °C for entry 2). [b]Isolated yield. [c]Diastereomeric ratio.

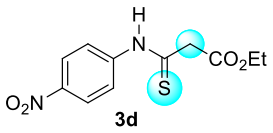
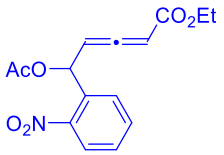
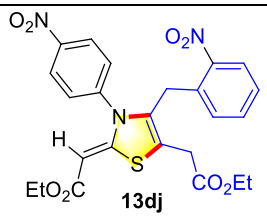
Tetra-*n*-butyl ammonium bromide (TBAB) as a phase transfer catalyst is well-documented.[45] Remarkably, the test reaction of **3a** with **5e** using TBAB (20 mol %) and K_2CO_3 (2.0 equiv) combination offered thiazole **13ae** via (3 + 2) annulation (Table 4, entry 3). A variety of allenoates (**5a-5o**) were examined, but this reaction worked well only with *ortho*/ *para* nitro-substituted allenoates **5e** and **5j** and other substituted allenoates (**5a-5d**, **5f-5i** and **5k-5o**) led only to decomposition and the expected products were not obtained. Based on this finding, we discerned that the electron-withdrawing function on the phenyl ring plays a key role in this cyclization. Thus, we synthesized thiazole motifs **13ae-de** and **13aj-dj** in good to high yields (68-85%, and 67-79%) with excellent stereoselectivity (dr ≥99:1). The relative configuration in **13ae** and **13de** was determined to be *Z* by single-crystal X-ray diffraction data (Figure 3).

Table 5. Substrate scope for the synthesis of thiazoles from thioamides and *δ*-acetoxy allenoate[a]



Entry	Thioamides	*δ*-Acetoxy allenoate	Thiazole	Yield (%)
1	 **3a**	 **5e**	 **13ae** (X-ray)	72

2	 **3b**	 **5e**	 **13be**	68
3	 **3c**	 **5e**	 **13ce**	75
4	 **3d**	 **5e**	 **13de** (X-ray)	85
5	 **3a**	 **5j**	 **13aj**	68
6	 **3b**	 **5j**	 **13bj**	67
7	 **3c**	 **5j**	 **13cj**	72

8	 3d	 5j	 13dj	79

[a]Reaction conditions: **3a-d** (0.20 mmol), **5e** and **5j** (0.24 mmol), tetra-*n*-butyl ammonium bromide (0.04 mmol) in DCM (0.1 M) at 25 °C. [b]Isolated yield. [c]Diastereomeric ratio ≥ 99:1.

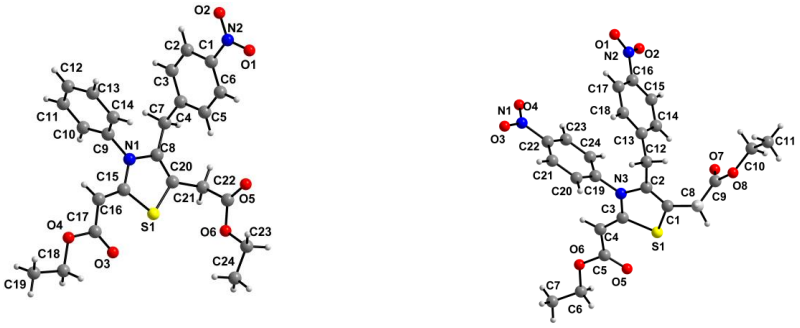
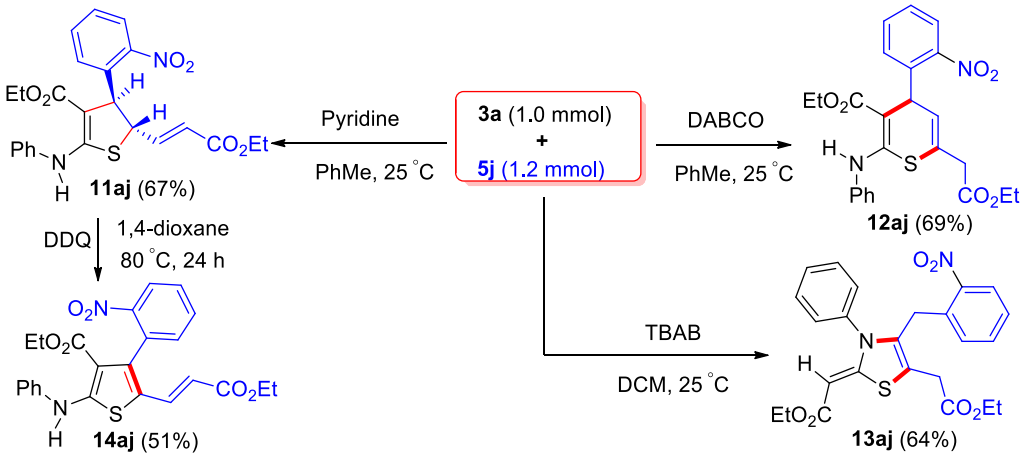


Figure 3: Molecular structures of compounds **13ae** (left, CCDC No. 2110601) and **13de** (right, CCDC No. 2110602).

2.2.3 *Scale-up experiments and synthetic utility*

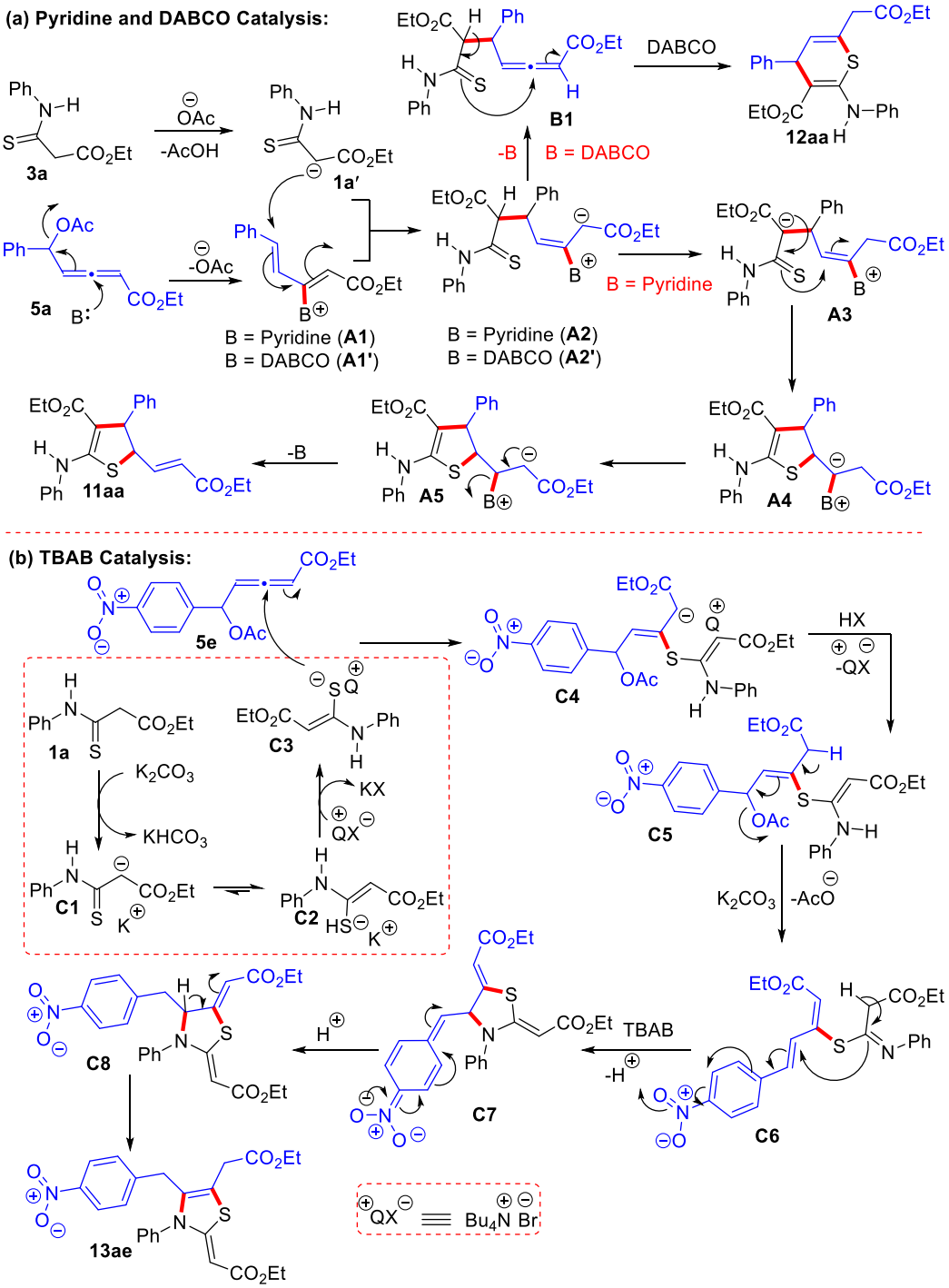
The 1.0 mmol scale reactions of thioamide **3a** with allenoate **5j** (1.2 mmol) under the above three optimized conditions led to **11aj**, **12aj**, and **13aj** in good yields (Scheme 4). Upon treatment with DDQ, **11aj** could be oxidized to the fully-substituted thiophene **14aj** in 51% yield.



Scheme 4: Scale up experiments and synthetic utility

2.2.4 *Proposed pathways for (3 + 2) and (3 + 3) annulations*

Plausible pathways for the above divergent annulations are shown in Scheme 5. These Lewis base-catalyzed annulations are initiated by an addition-elimination reaction of *δ*-acetoxy allenoate **5a** with an amine to give the cationic intermediate {**A1**: B = pyridine $[M]^+$ 280.1334; **A1′**: B = DABCO $[M + H]^+$ 313.1916} (Scheme 5a). In the [3 + 2] annulation, the addition of **1a′** to the *δ*-carbon of the cationic intermediate **A1** gives zwitterionic intermediate **A2** {B = pyridine $[M + H]^+$ 503.2013}. Species **A2** undergoes 1,5-proton transfer and affords **A3**. Subsequently, **A3** upon thia-Michael addition (*5-exo-trig cyclization*), 1,2-proton transfer, and pyridine elimination leads to dihydro-thiophene **11aa**. For the formation of dihydro-thiopyran **12aa**, intermediate **A2′** {B = DABCO $[M + H]^+$ 536.2598} readily undergoes base (DABCO) elimination to generate allenoate **B1**. Next, in the presence of DABCO, **B1** is involved in *6-exo-dig cyclization* for the formation of **12aa**. It is worth-mentioning that in pyridine catalyzed [3 + 2] annulation, the positive charge on the nitrogen atom might be weakened by the aromatic ring and such an effect is not possible in the case of DABCO. Hence, [3 + 2] annulation is achieved in the case of pyridine via ylide intermediate **A4**. In sharp contrast to these, in the TBAB catalyzed [3 + 2] annulation (Scheme 5b), thioamide is involved in deprotonation and delivers the intermediate **C3**. Next, arylnitro-substituted allenoate **2e** undergoes addition-elimination with **C3** to provide intermediate **C6** via **C4** and-**C5** {$[M + H]^+$ 529.1641}. Finally, **C6** leads to **13ae** by *5-exo-trig cyclization* and isomerization.[46] This annulation is compatible with only *o* or *p*-nitro substituted allenoates; this feature may be attributed to intermediate **C7**, which is not feasible in the case of other allenoates.



Scheme 5: Plausible mechanistic pathways for the formation of **11aa**, **12aa**, and **13ae**

2.3 DBU-catalyzed ring expansion or ene-amine formation involving *δ*-acetoxy allenoates and *N*-sulfonyl hydrazides

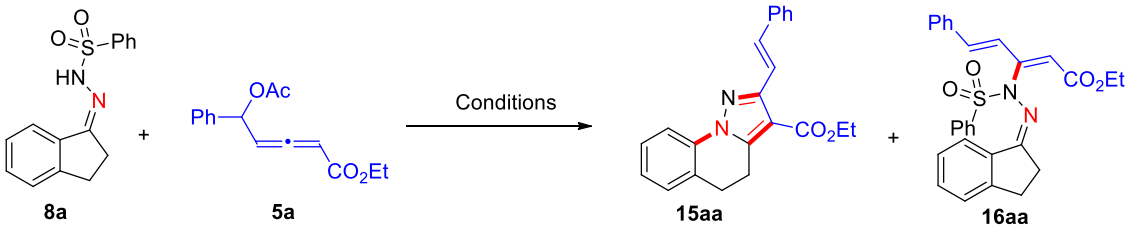
A general DBU-catalyzed spiro-annulation and concomitant ring expansion/ domino reaction of *δ*-acetoxy allenoates with cycl-2-ene-*N*-sulfonyl hydrazides affords ring expanded (5→6, 6→7, and 7→8) products. A distinctive *N*-insertion is involved in the process. By contrast, cycl-3-ene/ane-*N*-sulfonyl hydrazides under similar conditions deliver pyrazole cores with the same allenoate that involves allylic elimination as the key step in which *δ*-acetoxy allenoate serves as 3C-synthon. These organocatalytic annulations are initiated by the attack at *ipso*-carbon, but not on *δ*-carbon, in the diene-ammonium intermediate derived from the allenoate. The key spirocyclic intermediate as well as dienyl-amine intermediate are isolated and characterized by X-ray crystallography. Extension to (*R*)-(-)-carvone-derived sulfonyl hydrazide also led to ring expansion and gave pyrazolo-azepine. These results are discussed in the following sections.

2.3.1 *Reaction of δ-acetoxy allenoates with cycl-2-ene-N-sulfonyl hydrazides: Synthesis of hydroquinoline via 5→6 ring expansion*

The main aim was to check the reaction between *N*-sulfonyl hydrazide and *δ*-acetoxy allenoate using a Lewis base. In this regard, several reactions were performed between *N*-sulfonyl hydrazide **8a** and *δ*-acetoxy allenoate **5a,** and the results are collected in Table 6. The preliminary reaction was conducted between **8a** (0.20 mmol) and **5a** (0.24 mmol) in the presence of DBU (0.20 mmol) in acetonitrile solvent at 80 ^{o}C and observed an unexpected product **15aa** in 33% yield (entry 1). The structure of **15aa** was confirmed as nitrogen inserted and ring expanded product by its spectroscopic and crystallographic data (*vide infra*). This unusual result encouraged us to investigate the reaction systematically by changing the parameters to get better results with respect to yield. Thus, we examined a similar reaction in toluene solvent at the same temperature (80 °C) and isolated **15aa** in 61% yield (entry 2). Amazingly, the reaction nicely proceeded at 110 °C and afforded **15aa** in a slightly higher yield (entry 3). Inspired by this promising result, several other nitrogen-containing Lewis bases (DMAP, TBD, and DABCO) were screened. It was found that none of them are effective as DBU (entries 4-6). We have performed the reactions between **8a**/ **8i** and **5a** using strong bases such as KOH, ^{t}BuOK and LDA also, but did not observe any fruitful results; there was the decomposition of allenoate and

sulfonyl hydrazide (tlc evidence). In the case of triphenylphosphine and cesium carbonate, the reactants were intact even after 12 h (entries 7 and 8). To improve the yield, we examined several solvents such as DMSO, MeOH, and DCE; they gave inferior results (entries 9-11). Surprisingly, at room temperature, we observed a completely different product **16aa** in 70% yield (entry 12), and identified it as a product of an S_N2' attack followed by Michael-addition; more details on this compound will be discussed in a later section. No reaction was detected in the absence of DBU at 25 °C as well as 110 °C (entries 13 and 14).

Table 6. Optimization of reaction conditions for 15aa and **16aa**



Entry	Base[b]	Solvent	Temperature/ °C	Time/ h	Yield	
					15aa	**16aa**
1	DBU	MeCN	80	12	33	<5
2	DBU	PhMe	80	12	61	<5
3	**DBU**	**PhMe**	**110**	**12**	**76**	**<5**
4	DMAP	PhMe	110	12	51	<5
5	TBD	PhMe	110	12	48	<5
6	DABCO	PhMe	110	12	37	<5
7	Ph_3P	PhMe	110	12	-	-
8	CS_2CO_3	PhMe	110	12	-	-
9	DBU	DMSO	110	12	43	<5
10	DBU	MeOH	80	12	27	-

11	DBU	DCE	80	12	40	<5
12	DBU	PhMe	25	12	-	70
13	-	PhMe	110	24	-	-
14	-	PhMe	25	24	-	-

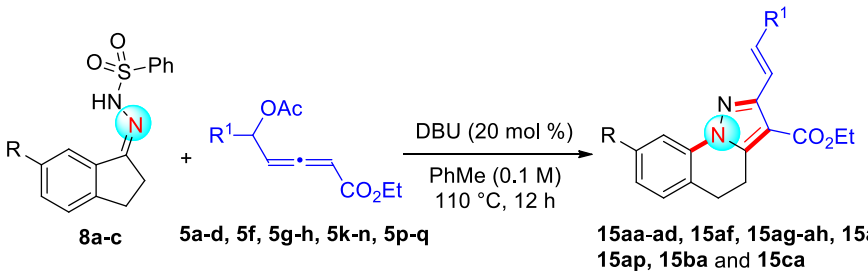
[a]Reaction conditions: **8a** (0.20 mmol), **5a** (0.24 mmol), base (20 mol%) in solvent (2.0 mL); temperature is that of the oil bath. [b]Isolated yield.

2.3.2 *Formation of hydroquinolines via 5→6 ring expansion from the reaction of cycl-2-ene-N-sulfonyl hydrazides with δ-acetoxy allenoates*

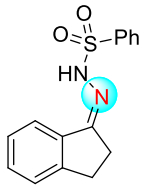
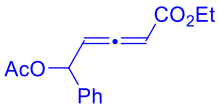
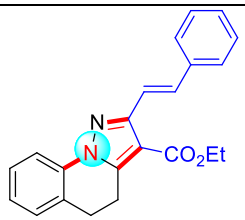
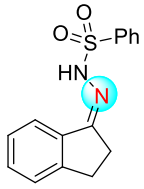
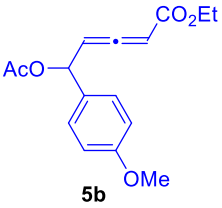
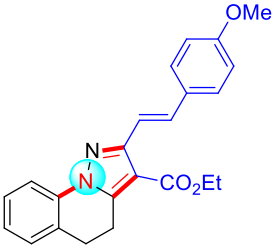
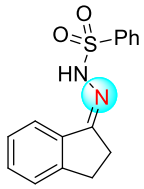
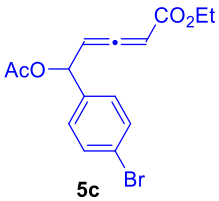
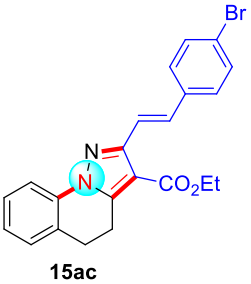
Various bases and solvents were examined for the ring expansion strategy. As mentioned above, our optimization studies revealed that the reaction of **8a** (0.20 mmol) with **5a** (0.24 mmol) in the presence of DBU (20 mol %) occurred smoothly in toluene at 110 ^{o}C (oil bath; 12h) affording product **15aa** in 76% yield. With optimal conditions in hand, a variety of acetoxy allenoates and sulfonohydrazides were examined to evaluate the flexibility and limitations of the ring expansion protocol. As shown in Table 7, this ring-expansion protocol was compatible with a variety of δ-acetoxy allenoates and sulfonohydrazides. The electronic properties of the functional groups (MeO, Br, Cl, NO_2, and CF_3) at the 4th position of the phenyl ring of allenoate (**5a-e**) had little effect on the ring-expansion reactivity in giving the ring expanded products (**15aa-ae**) in 70%-81% yields. The *meta*-aryl substituted allenoates (**5f** and **5g**) delivered **15af** (71%) and **15ag** (67%) in lower yields as compared to the *para*-substituted ones (**5b-e**). This reaction is compatible with the dichloro substituted allenoate **5p** also and leads to **15ap** in 68% yield. Heterocyclic allenoates (**5l-m**) served as successful partners in giving the **15al** and **15am** 73% and 69%, respectively. Polycyclic-substituted allenoates **5k** and **5n** also offered **15ak** and **15an** in acceptable yields (68% and 65%). Furthermore, the switch of the nucleophile species from **8a** to **8b** and **8c** showed fine reactivity in the 5→6 ring expansion reaction to give **15ba-ca** in good yields (71%-77%). Allenoate **5q** with a δ-methyl substituent also gave the product **15aq** in 41% yield; however, in the reaction of the unsubstituted allenoate **5n** and **8a** under these conditions, we could not isolate any product (the allene underwent decomposition). Molecular

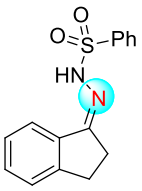
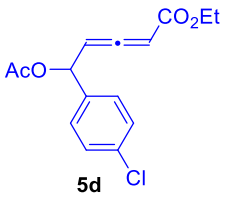
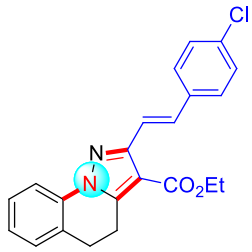
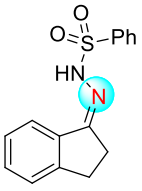
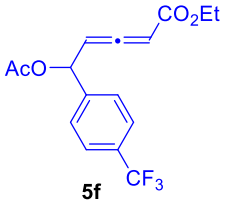
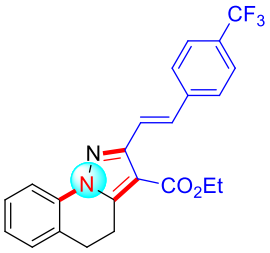
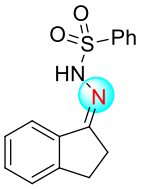
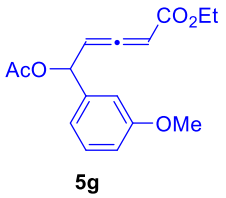
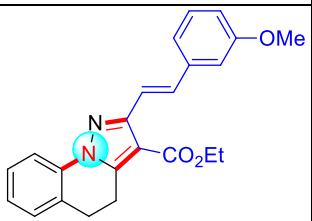
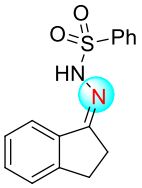
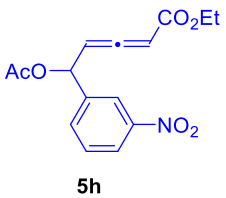
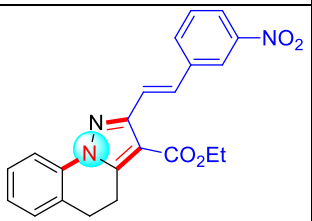
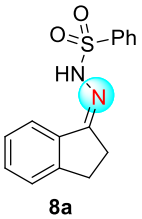
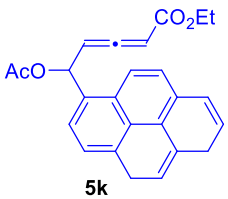
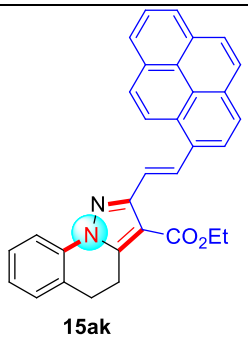
structures of **15aa** and **15ad**, as determined by single crystal X-ray crystallography, are shown in Figure 4.

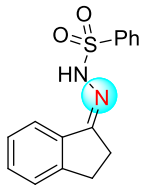
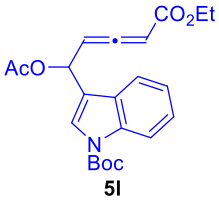
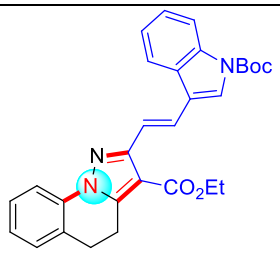
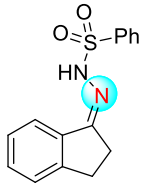
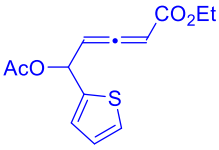
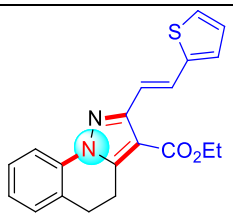
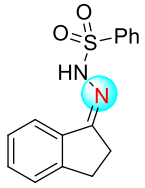
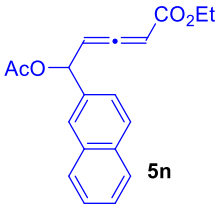
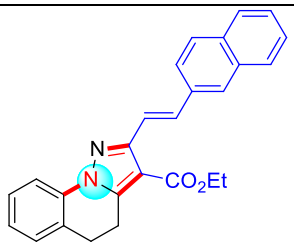
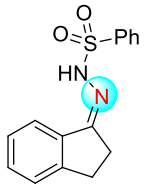
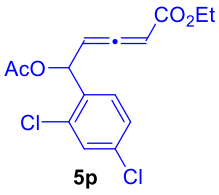
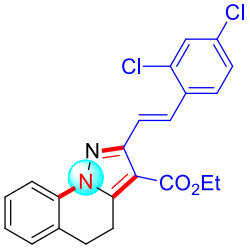
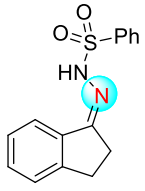
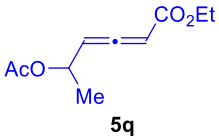
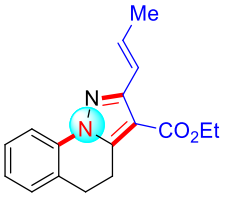
Table 7. Substrate scope for the synthesis of hydroquinoline via 5→6 ring expansion

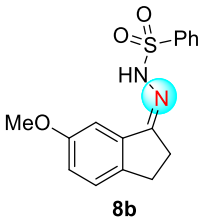
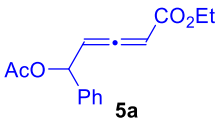
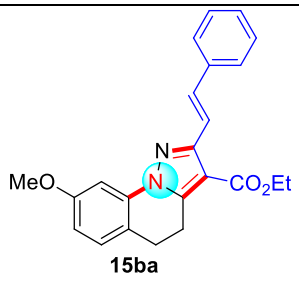
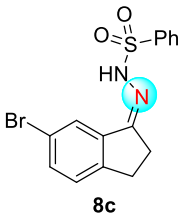
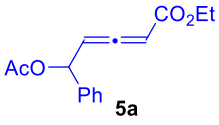
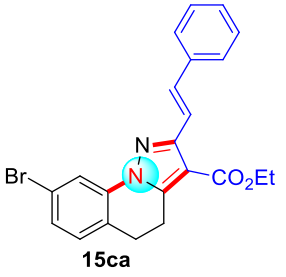


8a-c + **5a-d, 5f, 5g-h, 5k-n, 5p-q** → **15aa-ad, 15af, 15ag-ah, 15ak-an, 15ap, 15ba** and **15ca**

Entry	cycl-2-ene-*N*-sulfonyl hydrazides	*δ*-Acetoxy allenoate	Hydroquinoline 5→6 Ring Expansion	Yield (%)[b]
1	 **8a**	 **5a**	 **15aa** (X-ray)	76
2	 **8a**	 **5b**	 **15ab**	81
3	 **8a**	 **5c**	 **15ac**	75

4	 **8a**	 **5d**	 **15ad** (X-ray)	74
5	 **8a**	 **5f**	 **15af**	70
6	 **8a**	 **5g**	 **15ag**	71
7	 **8a**	 **5h**	 **15ah**	67
8	 **8a**	 **5k**	 **15ak**	65

9	 8a	 5l	 15al	73
10	 8a	 5m	 15am	69
11	 8a	 5n	 15an	68
12	 8a	 5p	 15ap	68
13	 8a	 5q	 15aq	41

14	 **8b**	 **5a**	 **15ba**	71
15	 **8c**	 **5a**	 **15ca**	77

[a]Reaction conditions: **8** (0.20 mmol), **5** (0.24 mmol) and DBU (0.04 mmol) in toluene (2.0 mL) at 110 °C. [b]Isolated yield.

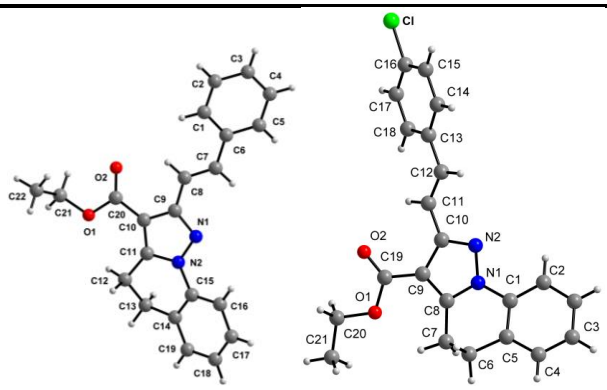


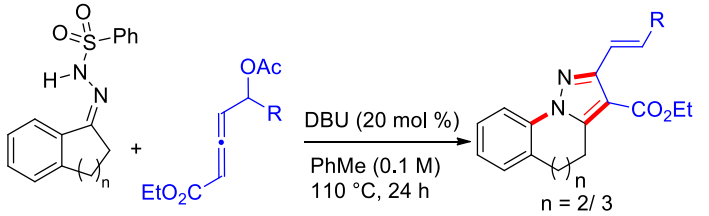
Figure 4: Molecular structures of compounds **15aa** (left, CCDC No. 2236876) and **15ad** (right, CCDC No. 2236877).

2.3.3 *Synthesis of azepines and azocines via 6→7 and 7→8 ring expansion from the reaction of α-fused N-sulfonyl hydrazones with δ-acetoxy allenoates*

To extend the generality of the above work, we explored the same strategy to synthesize fused hydro-azepine and azocine scaffolds by-6→7 and 7→8 ring expansion using sulfonohydrazides derived from tetralone and benzoannuleneone. As depicted in Table 8, this strategy worked well using hydrazide **8d** and allenoates to provide the corresponding 6→7 ring expansion products **15da-db**, **15dm**, and **15dn** (65%-68%, 55%, and 48%) but required slightly

longer time as compared to the 5→6 ring-expansion protocol. Delightedly, we isolated azocine structural frameworks (**15ea**, **15em**, **15en, and 15ep**) also in moderate yields (53%, 42%, 39% and 57%) *via* 7→8 ring expansion, which substantiates the utility of the developed protocol. Molecular structures of **15db** and **15ea** as determined by single crystal X-ray crystallography are shown in Figure 5.

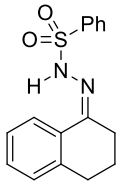
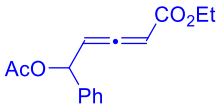
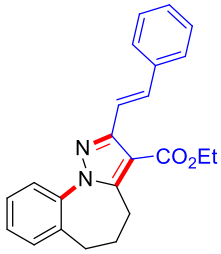
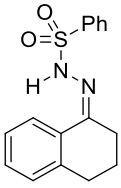
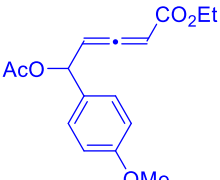
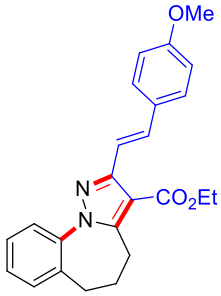
Table 8. Substrate scope for the synthesis of fused azepines and azocines via 6→7 and 7→8 ring expansion: Isolation of spirocyclics 17da-db and 17dh[a,b]

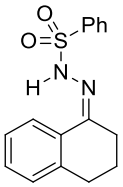
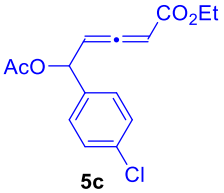
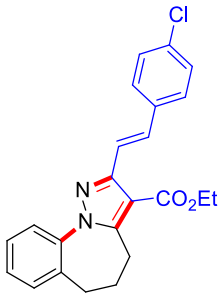
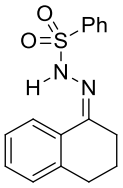
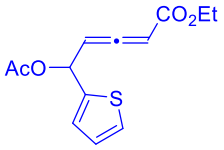
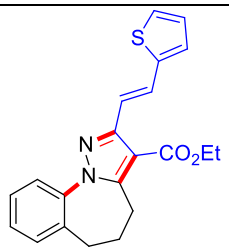
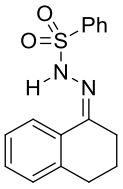
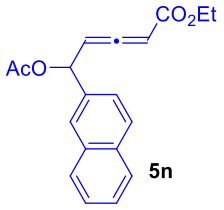
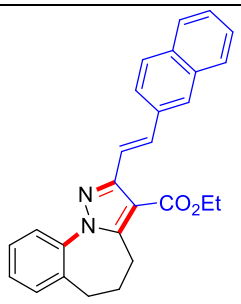
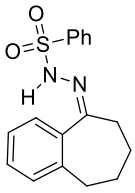
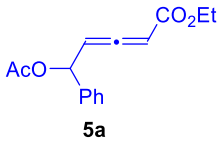
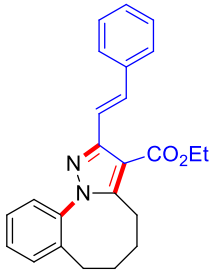


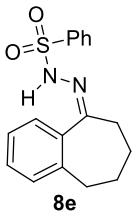
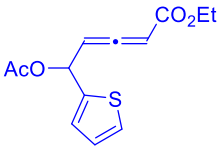
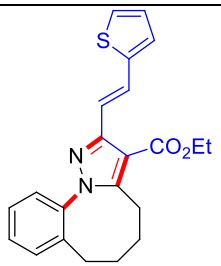
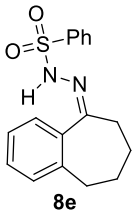
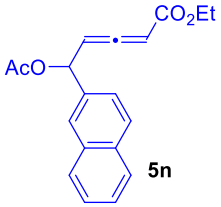
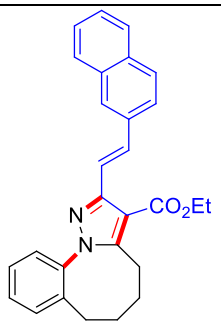
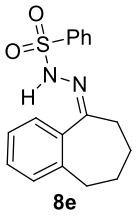
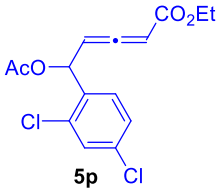
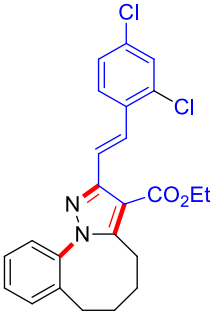
8d: n = 2
8e: n = 3

5a-b, 5m-n, 5p

15da-dc, 15dm-dn, 15ea
15ea, 15em-en, 15ep

Entry	α-fused *N*-sulfonyl hydrazones	*δ*-Acetoxy allenoate	Azepine(6→7) / Azocine(7→8)	Yield (%)[b]
1	 **8d**	 **5a**	 **15da**	65
2	 **8d**	 **5b**	 **15db** (X-ray)	68

3	 **8d**	 **5c**	 **15dc**	63
4	 **8d**	 **5m**	 **15dm**	55
5	 **8d**	 **5n**	 **15dn**	48
6	 **8e**	 **5a**	 **15ea** (X-ray)	53

7	 8e	 5m	 15em	42
8	 8e	 5n	 15en	39
9	 8e	 5p	 15ep	57

[a]Reaction conditions: **8d-e** (0.20 mmol), **5a-b**, **5m-n** and **5p** (0.24 mmol) and DBU (0.04 mmol) in toluene (2.0 mL) at 110 °C. [b]Isolated yield.

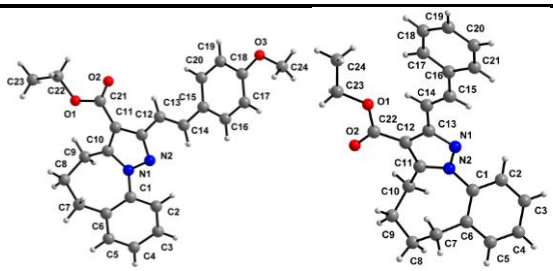
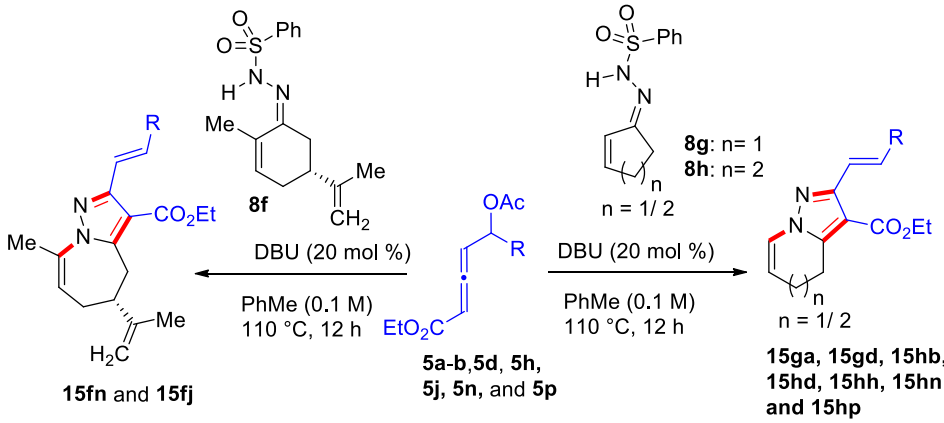


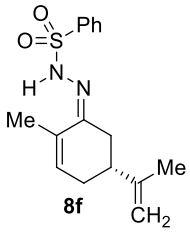
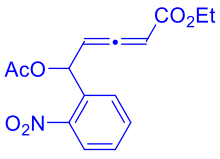
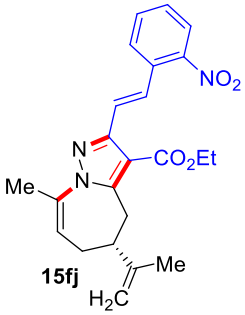
Figure 5: Molecular structures of compounds **15db** (left, CCDC No. 2236878), **15ea** (right, CCDC No. 2236879)

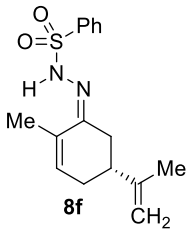
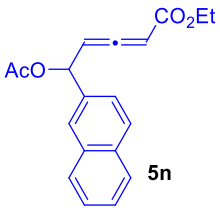
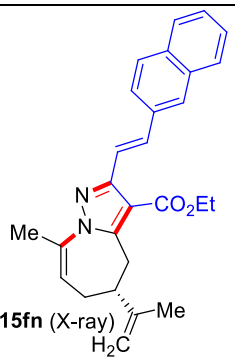
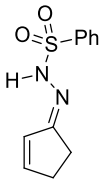
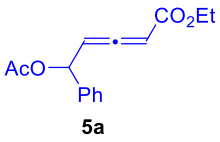
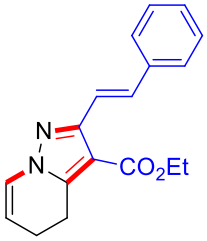
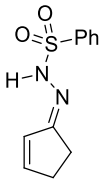
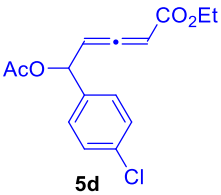
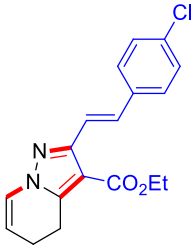
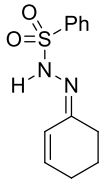
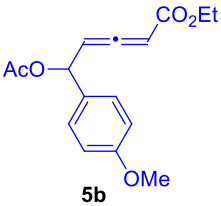
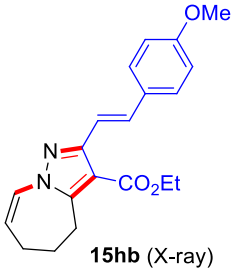
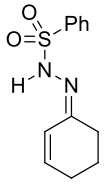
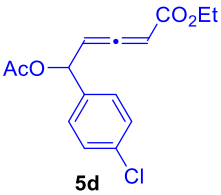
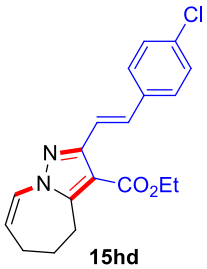
2.3.4 *Synthesis of fused pyridines and azepines via 5→6, 6→7 and 6→7 Ring expansion from the reaction of alicyclene sulfonohydrazides and β-carvone with δ-acetoxy allenoates*

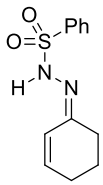
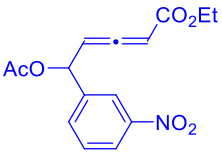
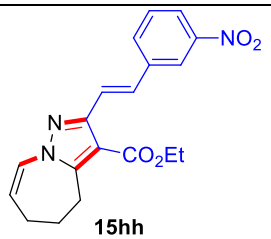
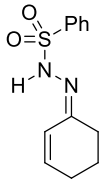
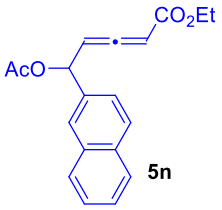
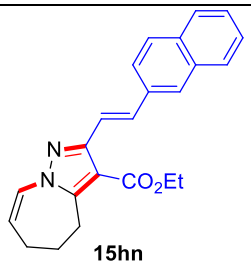
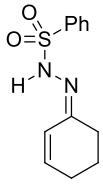
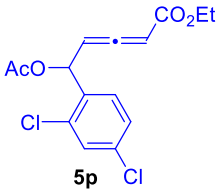
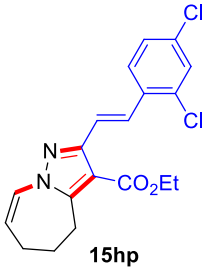
To diversify the above domino reaction, alicyclene sulfonohydrazides **8g-h** were also subjected to this catalytic methodology (Table 9). Importantly, *R*-(−)-carvone-derived nucleophilic core **8f** gave the ring expanded products **15fn** and **15fj** in moderate yields (65%-53%). The reaction of other ali-cyclene substrates **8g** and **8h** resulted in products **15ga**, **15gd**, **15hb, 15hd, 15hh, 15hn** and **15hp** with acceptable yields (52%-68%). The molecular structures of **15hb** and **15fn** are shown in Figure 6.

Table 9. Substrate scope for the synthesis of fused azepines and pyridines *via* 5→6 and 6→7 ring expansion from the reaction of (*R*)-(-)-carvone-derived sulfonyl hydrazide and ali-cyclene sulfonohydrazides with δ-acetoxy allenoates



Entry	Alicyclene sulfonohydrazides	δ-Acetoxy allenoate	5→6 and 6→7 ring expansion	Yield (%)[b]
1	 **8f**	 **5j**	 **15fj**	53

2	 **8f**	 **5n**	 **15fn** (X-ray)	65
3	 **8g**	 **5a**	 **15ga**	63
4	 **8g**	 **5d**	 **15gd**	55
5	 **8h**	 **5b**	 **15hb** (X-ray)	60
6	 **8h**	 **5d**	 **15hd**	53

7	 **8h**	 **5h**	 **15hh**	42
8	 **8h**	 **5n**	 **15hn**	39
9	 **8h**	 **5p**	 **15hp**	57

[a]Reaction conditions: **8f** and **8g-h** (0.20 mmol), **5a-b,5d, 5h, 5j, 5n, and 5p** (0.24 mmol) and DBU (0.04 mmol) in toluene (2.0 mL) at 110 °C. [b]Isolated yield.

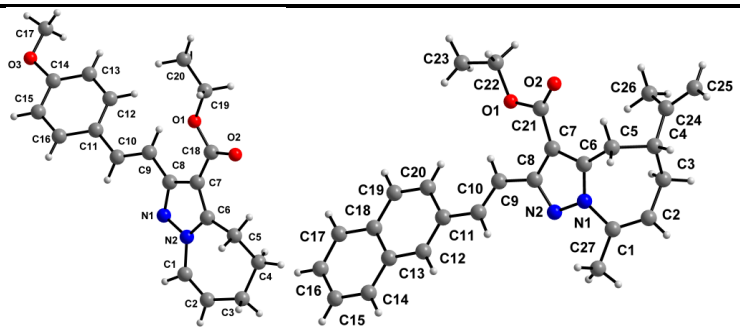
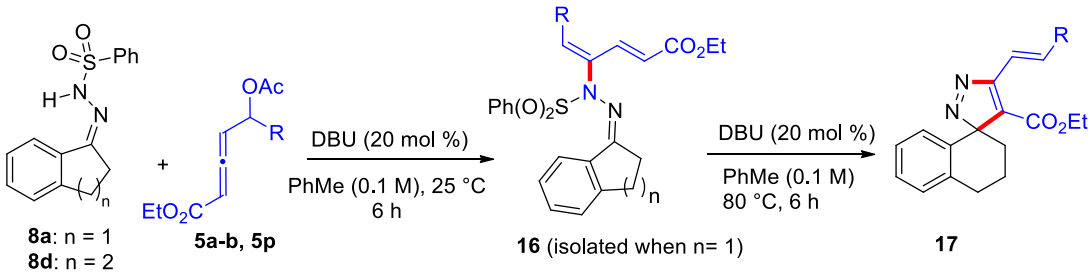


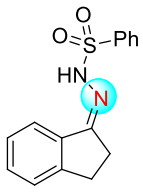
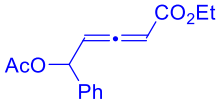
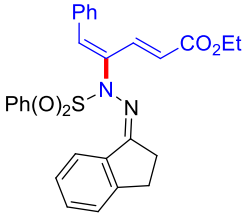
Figure 6: Molecular structures of compounds **15hb** (left, CCDC No. 2236881) and **15fn** (right, CCDC No. 2236880).

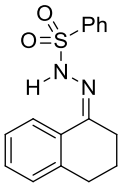
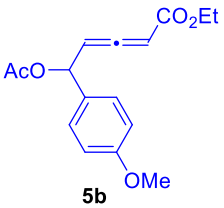
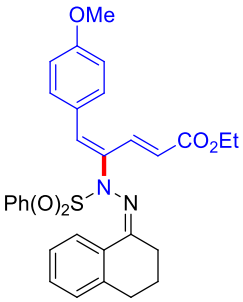
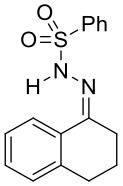
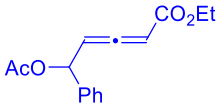
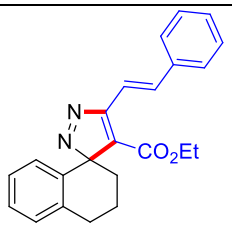
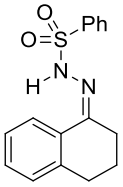
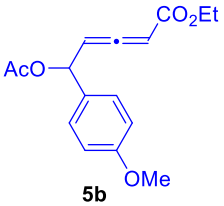
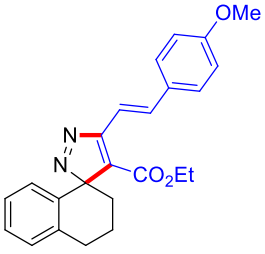
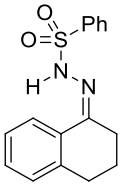
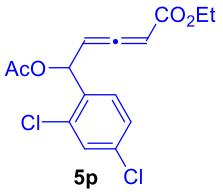
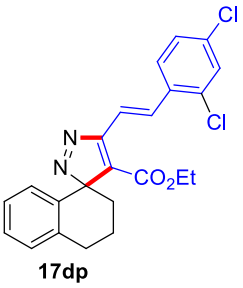
2.3.5 *Isolation of diene-intermediates and spirocyclic products from the reaction of N-sulfonyl hydrazones with δ-acetoxy allenoates*

We have isolated diene-intermediates **16aa** and **16db** in good yields (79% and 72%) by performing the reaction between **8a**/ **8d** and **5a**/ **5b** at rt for 6 h. It is worth mentioning that spirocyclic products **17da**, **17db,** and **17dh** were obtained in good yields under similar conditions but with the reaction time restricted to 3h at 80 °C (oil bath). Based on this finding, we concluded that ring-expanded products might have formed through spirocyclic intermediates. To substantiate this claim, we performed a reaction with **17db** using DBU and obtained **15db** in 68% yield. Molecular structures of **16aa** and **17db**, as determined by single crystal X-ray crystallography, are shown in Figure 7.

Table 10. Isolation of diene-intermediates and spirocyclic products



Entry	α-fused *N*-sulfonyl hydrazones	*δ*-Acetoxy allenoate	Diene intermediate/ Spirocyclics	Yield (%)[b]
1	 **8a**	 **5a**	 **16aa** (X-ray)	79

2	 **8d**	 **5b**	 **16db**	72
3	 **8d**	 **5a**	 **17da**	73
4	 **8d**	 **5b**	 **17db** (X-ray)	77
5	 **8d**	 **5p**	 **17dp**	68

[a]Reaction conditions: **8a-d** (0.20 mmol), **5a-b** and **5p** (0.24 mmol) and DBU (0.04 mmol) in toluene (2.0 mL) at rt for **16**, 80 °C for **17**. Isolated yield.

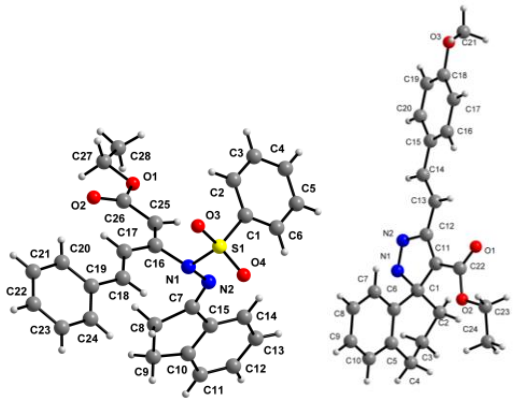
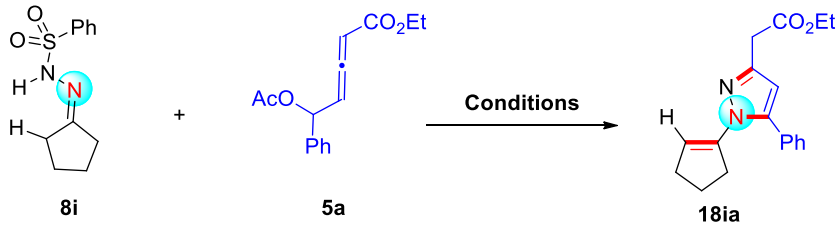


Figure 7: Molecular structures of compounds **16aa** (right, CCDC No. 2236882) and **17db** (left, CCDC No. 2236883)

2.3.6 *Reaction of δ-acetoxy allenoates with cycl-3-ene-N-sulfonyl hydrazides: Synthesis of multisubstituted pyrazoles*

Next, we intended to check the reactivity of *δ*-acetoxy allenoate **5a** with non-fused *N*-sulfonyl hydrazide **8i** under identical conditions (Table 11, entry 3) and observed an ene-amine type product via (3 + 2) annulation. To identify the best reaction parameters, we explored the reaction between **5a** and **8i** using different tertiary amines and solvents (entries 1-2 and 4-10), and the results are collated in Table 11. Finally, we identified that DBU in acetonitrile solvent at 80 °C was the optimal condition in terms of yield (entry 3).

Table 11. Optimization of reaction conditions for 18ia



Entry	Base	Solvent	Temp/ °C	Time/ h	Yield of **18ia** **(%)**
1	DBU	PhMe	110	12	56%
2	DBU	PhMe	80	12	56%

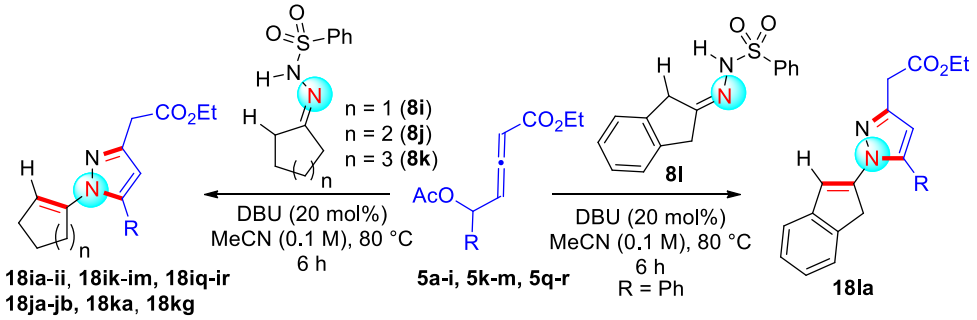
3	**DBU**	**MeCN**	**80**	**12**	**81**
4	DMAP	MeCN	80	12	67
5	DABCO	MeCN	80	12	51
6	TBD	MeCN	80	12	43
7	DBU	DMSO	80	12	55
8	DBU	$MeNO_2$	80	12	23
9	DBU	MeOH	80	12	33
10	DBU	Dioxane	80	12	19

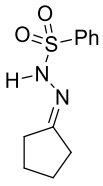
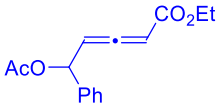
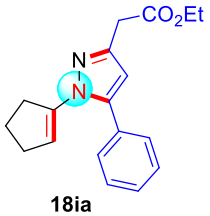
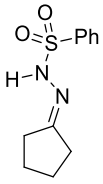
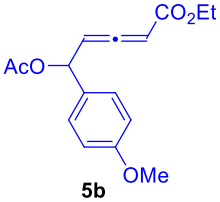
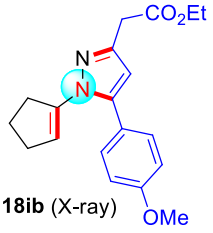
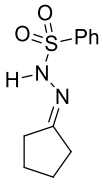
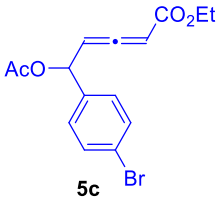
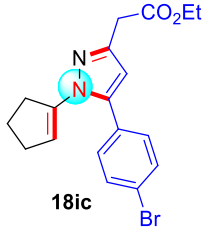
[a]Reaction conditions: **8i** (0.20 mmol), **5a** (0.24 mmol), base (20 mol%) in solvent (2.0 mL); temperature is that of the oil bath. [b]Isolated yield.

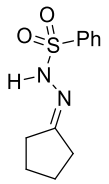
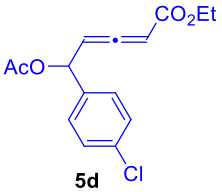
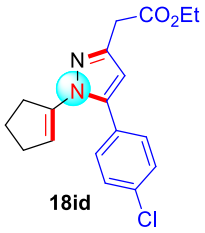
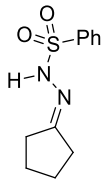
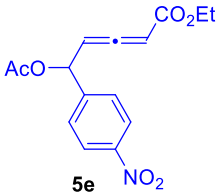
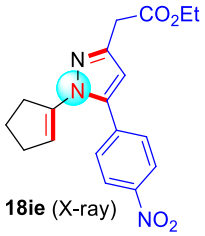
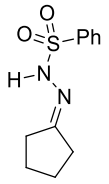
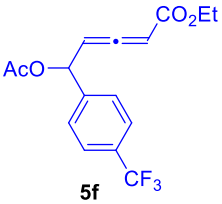
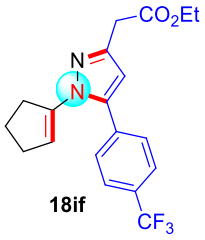
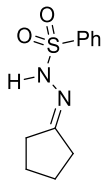
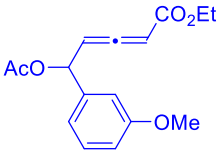
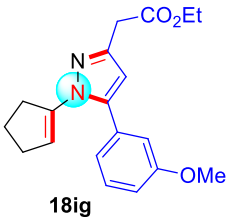
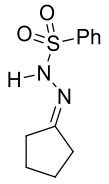
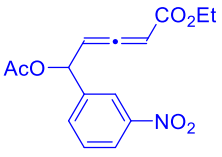
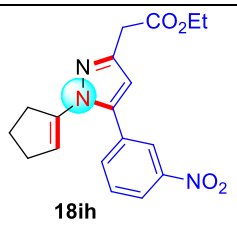
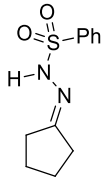
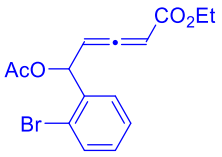
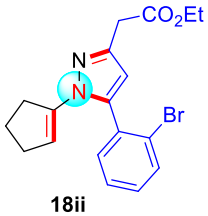
2.3.7 *Synthesis of multisubstituted pyrazoles from the reaction of cycl-3-ene-N-sulfonyl hydrazides with δ-acetoxy allenoates*

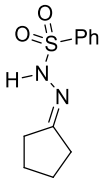
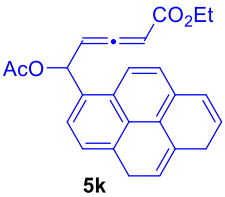
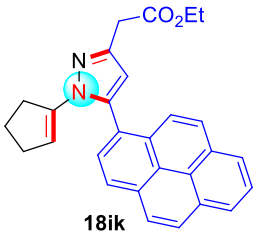
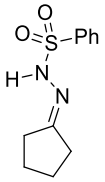
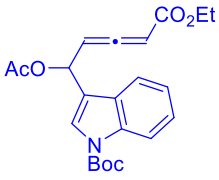
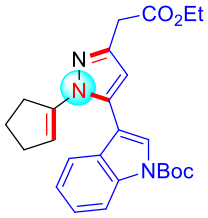
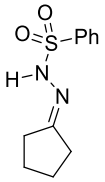
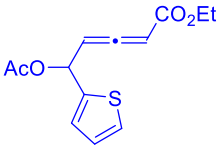
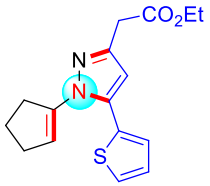
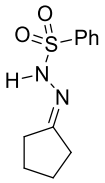
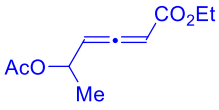
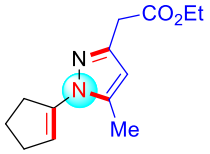
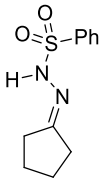
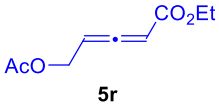
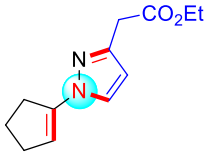
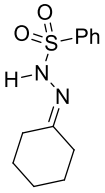
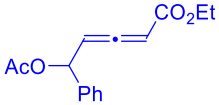
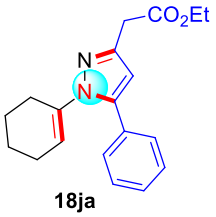
The above optimized conditions were applied to a series of allenoates, and the results are summarized in Table 12. Allenoates with electronic disparate groups at the *p*/*m*/ *o*-positions were involved nicely to offer corresponding cyclic cores **18ia-ii** in good to high yields (73%-85%). Allenoates having polyaryl and heteroaryl groups at the δ-position exhibited similar reactivity and generated **18ik-im** in 70-75% yields. As expected, other sulfonyl hydrazones **8j** and **8k** also proved as effective substrates in giving the desired multi-substituted pyrazoles **18ja**, **18jb**, **18ka**, and **18kg** in yields of 78%, 82%, 74%, and 69%, respectively. The molecular structures of **18ib** and **18ie** are shown in Figure 8.

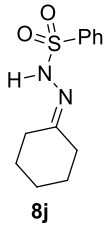
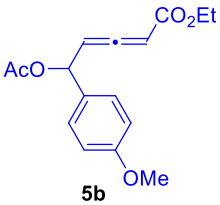
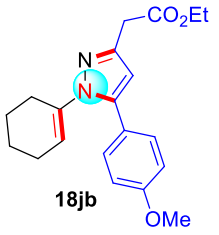
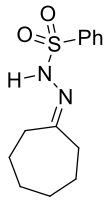
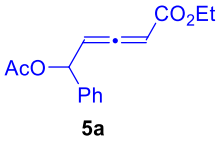
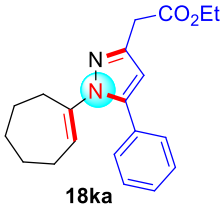
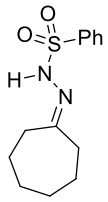
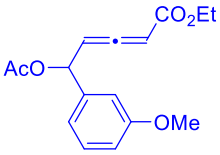
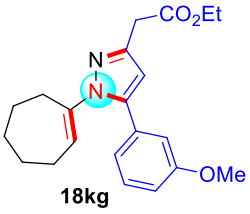
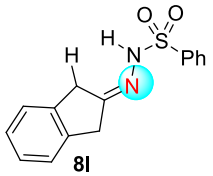
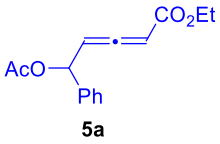
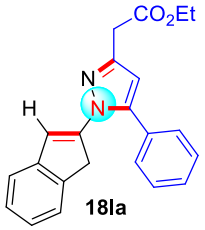
Table 12. Substrate scope for the synthesis of multisubstituted pyrazoles non-fused *N*-sulfonyl hydrazones with δ-acetoxy allenoates



Entry	Non-fused-sulfonyl hydrazones	δ-Acetoxy allenoate	Multisubstituted pyrazoles	Yield (%)[b]
1	 **8i**	 **5a**	 **18ia**	81
2	 **8i**	 **5b**	 **18ib** (X-ray)	85
3	 **8i**	 **5c**	 **18ic**	77

4	 **8i**	 **5d**	 **18id**	79
5	 **8i**	 **5e**	 **18ie** (X-ray)	73
6	 **8i**	 **5f**	 **18if**	76
7	 **8i**	 **5g**	 **18ig**	74
8	 **8i**	 **5h**	 **18ih**	78
9	 **8i**	 **5i**	 **18ii**	75

10	 8i	 5k	 18ik	67
11	 8i	 5l	 18il	75
12	 8i	 5m	 18im	72
13	 8i	 5q	 18iq	57
14	 8i	 5r	 18ir	49
15	 8j	 5a	 18ja	78

16	 8j	 5b	 18jb	82
17	 8k	 5a	 18ka	74
18	 8k	 5g	 18kg	69
19	 8l	 5a	 18la	78

Reaction conditions: **8i-l** (0.20 mmol), **5a-I, 5k-m** and **5q-r** (0.24 mol), and DBU (0.04 mmol) in acetonitrile (2.0 mL) at 80 °C. Yields given are after isolation.

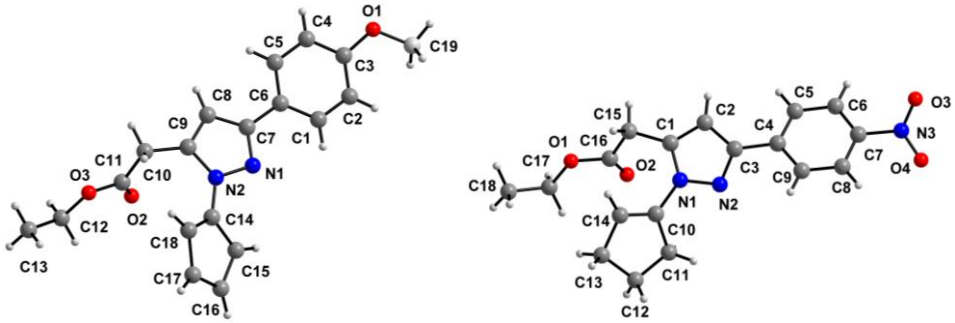
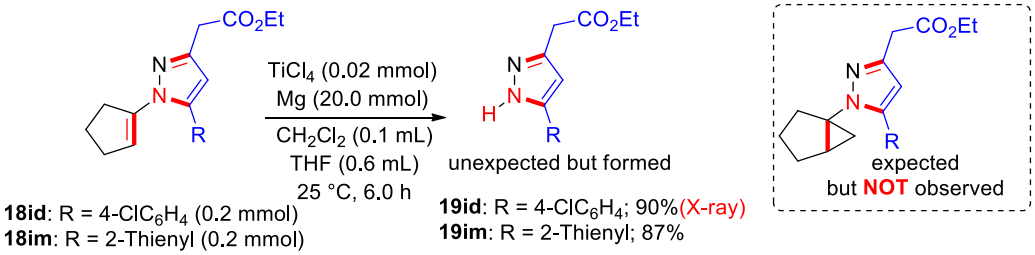


Figure 8: Molecular structures of compounds **18ib** (left, CCDC No. 2236884) and **18ie** (right, CCDC No. 2236885).

2.3.8 *Synthetic utility*

To highlight the synthetic utility of the developed protocol, we envisioned that the synthesized enamine cores can be utilized for the synthesis of fused cyclopropanes using dichloromethane as the carbon source based on a literature procedure.[47] Thus we performed a reaction of **18id**/ **18im** using $TiCl_4$-Mg in dichloromethane. Surprisingly, we observed C-N bond cleaved products [**19id** (X-ray, Figure 9)/ **19im**] in excellent yield (90%/ 87%) rather than the fused cyclopropanes (Scheme 7).



Scheme 6: Synthetic Utility of **18id** and **18im**.

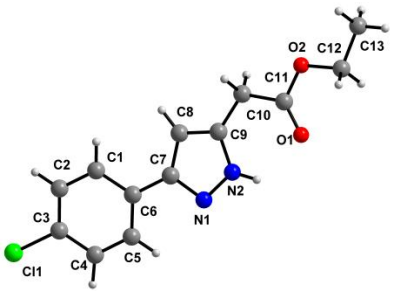
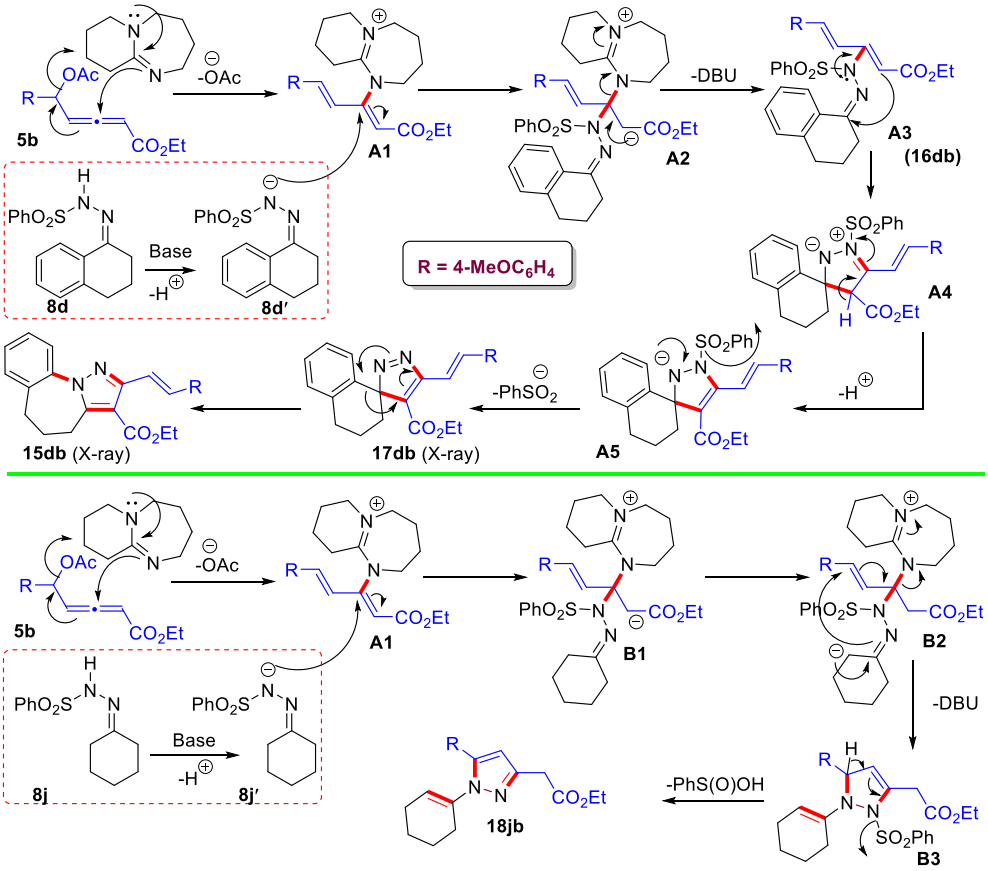


Figure 9: Molecular structure of compound **19id** (CCDC NO: 2236886)

2.3.9 *Proposed pathways for (3 + 2) annulation and ring expansion reactions*

Plausible pathways for ring expansion and (3 + 2) annulation are proposed in Scheme 9. These organocatalytic reactions are initiated by the addition of DBU to the *β*-carbon of the *δ*-acetoxy allenoate **5b** *via* allylic elimination (S_N2') to give the diene-ammonium ion intermediate **A1**. Next, Michael-addition with the anion **8d′/ 8j′** provides zwitterionic intermediate **A2/ B1**. In the case of spiro-annulation and ring-expansion strategy, 1,2-elimination is faster than Mannich coupling (**A2′**). Hence, **A2** upon elimination gives **A3** (**16db**) which is followed by Mannich coupling, isomerization, and sulfinic acid elimination offers the spirocyclic motif **17db** (X-ray). Finally, ring expansion in **17db** through nitrogen atom insertion/ C-C bond cleavage leads to the fused aza-heterocyclic scaffold **15db**. By contrast, with β′-/ non-fused sulfonohydrazide and **8i-**

k, **B1** rapidly undergoes a 1,6-proton shift and delivers intermediate **B2**. Subsequently, **B2** is involved in intramolecular allylic elimination to give cyclic intermediate **B3**. Then aromatization/ sulfonic acid exclusion in **B3** leads to trisubstituted pyrazole scaffold **18jb** exclusively. The driving force for compound **15** is 1,2-elimination but the proton shift is faster than 1,2-elimination in the case of compound **18**. Hence compounds **15** and **18** may be formed in entirely different pathways at later stages.



Scheme 7: Plausible mechanistic pathways for the formation of **15db, 16db, 17db** and **18jb**

2.4 Lewis-base dependent (3 + 3) annulation of acetoxy allenoates with 1C,3O-bisnucleophiles: Synthesis of novel pyran scaffolds

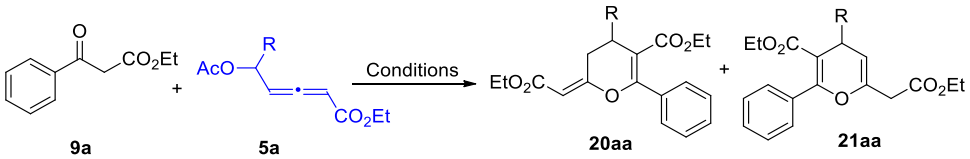
The presence of an active methylene group in the nucleophile plays a crucial role in the annulation reactions with allenoates. Allenoates can therefore undergo the (3 + 3) annulation process, resulting in the creation of pyran scaffolds, in the presence of Lewis bases like DBU or DMAP. One of the reasons for pursuing this part of the work was to check whether the products obtained are the same (or not) as those obtained earlier by Tong *et al.*[25]

We have not checked the chiral version in our work and use of other similar active methylene group containing substrates has been concurrently performed in our laboratory. The results of our reactions are discussed below.

2.4.1 *Synthesis of dihydropyrans and 4H-pyrans from δ-acetoxy allenoates and 1C,3O-bisnucleophiles*

We started with the reaction of *δ*-acetoxy allenoate **5a** (0.24 mmol) with 1,3-dicarbonyl compound **9a** (0.20 mmol) in the presence of 4-dimethylaminopyridine (20 mol %; 0.04 mmol) at 110 ^{o}C for 12 h (Table 13, entry 1). Dihydropyran was produced in high yield (73%). Several additional solvents, including DMF, 1,4-dioxane, THF, and DCE, were tested (entry 2-5), but toluene performed better in both situations. This result prompted us to investigate other nitrogen-containing bases, including DBU, TBD, DABCO, and Et_3N (entries 6-9). DABCO did not generate a distinct product, but using TBD and Et_3N, we were able to extract the products in yields of **47%** and **35%**, respectively. Surprisingly, we produced 4*H*-pyran when we employed DBU as a base. These results are similar to those obtained by my colleague but are slightly different from that reported by Tong *et al*.[25]

Table 13. Optimization of reaction conditions for 20aa and 21aa[a]



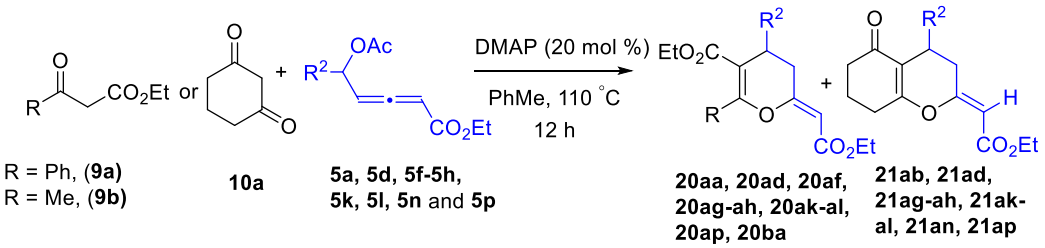
Entry	Base	Solvent	Temp (^{o}C)	Time (h)	Yield[b] **20aa:21aa**
1	**DMAP**	**PhMe**	**110**	**12**	**73:00**
2	DMAP	DMF	110	1	65:00
3	DMAP	Dioxane	110	1	56:00
4	DMAP	THF	110	1	42:00
5	DMAP	DCE	110	1	43:00

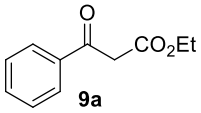
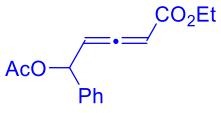
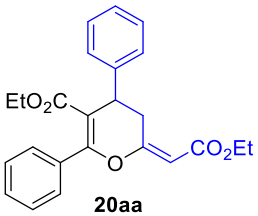
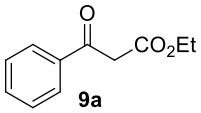
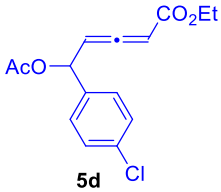
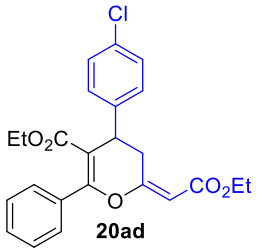
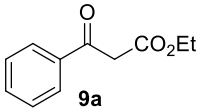
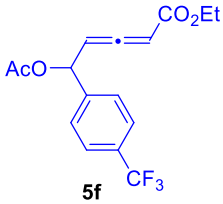
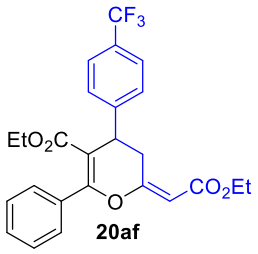
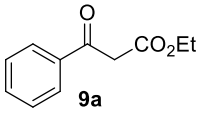
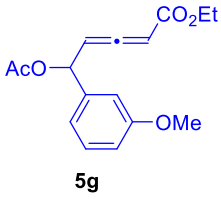
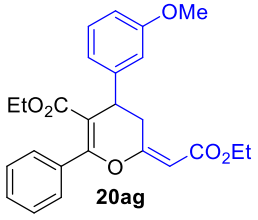
6	**DBU**	**PhMe**	**110**	**12**	**00:68**
7	TBD	PhMe	110	12	00:47
8	DABCO	PhMe	110	12	00:00
9	Et_3N	PhMe	110	1	00:35
10	DBU	THF	110	1	00:38
11	DBU	DCE	110	1	00:41
12	DBU	PhMe	25	1	00:52
13	DMAP	PhMe	25	1	46:00

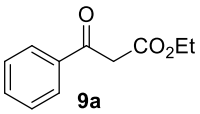
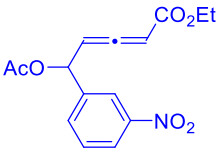
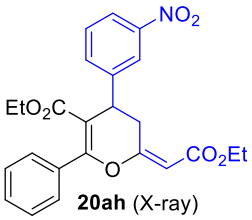
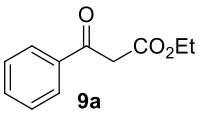
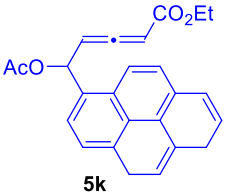
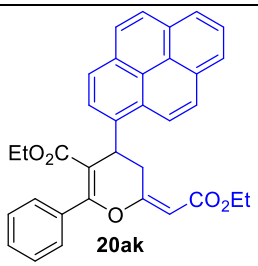
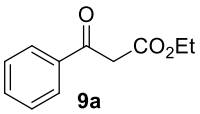
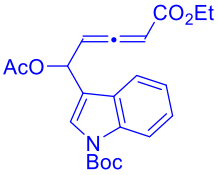
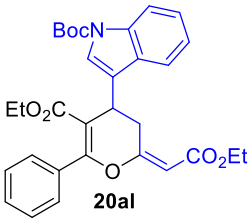
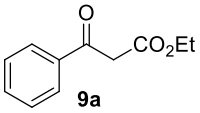
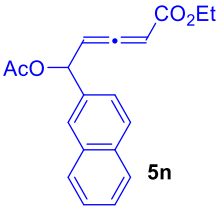
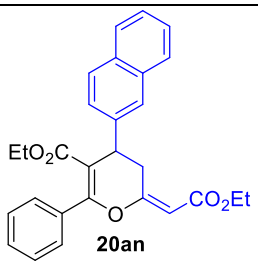
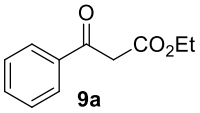
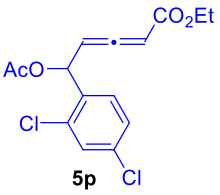
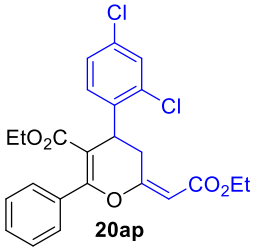
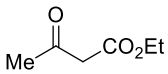
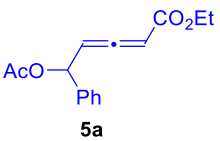
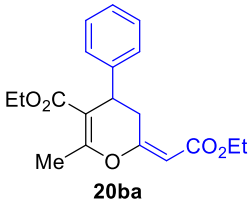
[a]Reaction conditions: **9a** (0.20 mmol), **5a** (0.24 mmol), DBU or DMAP (0.04 mmol in solvent (2.0 mL), . [b]Isolated yield.

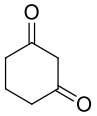
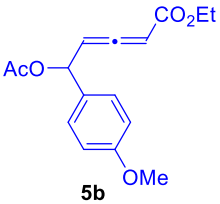
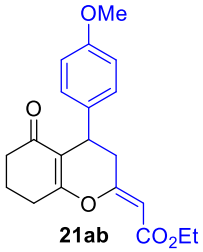
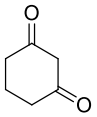
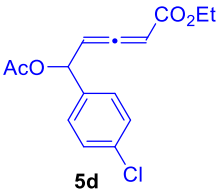
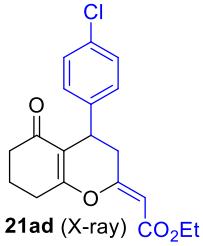
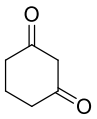
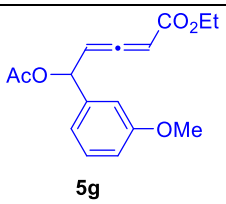
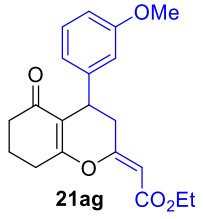
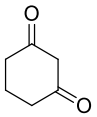
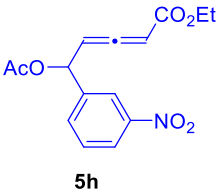
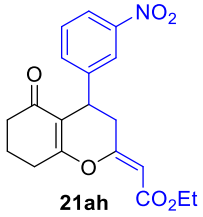
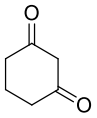
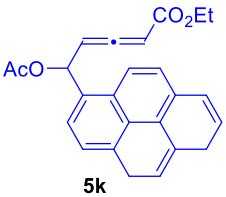
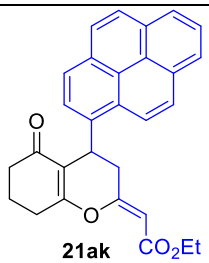
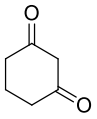
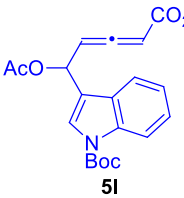
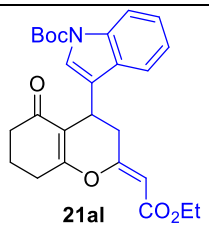
The scope and limits of the (3 + 3) annulation leading to dihydropyrans were examined using the optimised reaction conditions (cf. Table 13, entry 1). The results are shown in Table 14. The reaction efficiency is unaffected by the electrical parameters at the *p*-position (H, Cl, CF3) of the aryl ring of the allenoate moiety, and the corresponding products **20aa, 20ad, 20af** were isolated in yields of 73-65%. Under the present method, the precursors with *meta*-substitution (3-OMe, 3-NO_2) are also feasible and provide the products **20ag** and **20ah** (X-ray, Figure 10) in 61-64% yield. The polyaryl and indolyl substituted allenoates worked well to offer **20ak, 20al** and **20an** in good yields (69-75%). The reaction also worked well with the cyclohexane-1,3-dione. Allenoates having different functionalities such as OMe and Cl at the 4th position of the phenyl ring (**5b**, **5d**) were tolerated well and gave the corresponding products **21ab**-**21ad** (X-ray, Figure 10) in high yields (73-67%). 3-Substituted allenoates **5g** and **5h** also furnished **21ag** and **21ah** in acceptable yields (66% and 71%). The polyaryl allenoate **5k** also was viable and delivered the desired product **21ak** in good yield (65%). Replacement of aryl groups with heteroaryl functions such as 3-indolyl **5l** did not hamper the reactivity of **21al** in 70%.

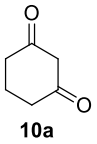
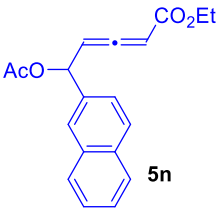
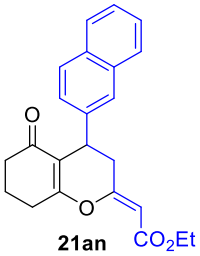
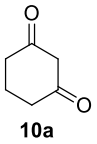
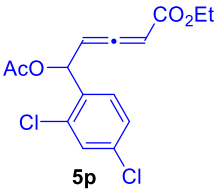
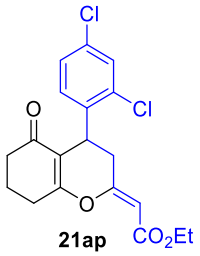
Table 14. Substrate scope for the synthesis of dihydropyrans from 1,3-dicarbonyl compounds and *δ*-acetoxy allenoates[a]



Entry	1C,3O-bisnucleophiles	*δ*-Acetoxy Allenoate	Dihydropyran	Yield (%)[b]
1	 **9a**	 **5a**	 **20aa**	73
2	 **9a**	 **5d**	 **20ad**	69
3	 **9a**	 **5f**	 **20af**	65
4	 **9a**	 **5g**	 **20ag**	61

5	 **9a**	 **5h**	 **20ah** (X-ray)	64
6	 **9a**	 **5k**	 **20ak**	69
7	 **9a**	 **5l**	 **20al**	75
8	 **9a**	 **5n**	 **20an**	70
9	 **9a**	 **5p**	 **20ap**	67
10	 **9a**	 **5a**	 **20ba**	62

11	 **10a**	 **5b**	 **21ab**	73
12	 **10a**	 **5d**	 **21ad** (X-ray)	67
13	 **10a**	 **5g**	 **21ag**	66
14	 **10a**	 **5h**	 **21ah**	71
15	 **10a**	 **5k**	 **21ak**	65
16	 **10a**	 **5l**	 **21al**	70

17	 10a	 5n	 21an	68
18	 10a	 5p	 21ap	62

[a]Reaction conditions: **9a-b** and **10a** (0.20 mmol), **5a, 5d, 5f-h, 5k, 5l, 5n** and **5p** (0.24 mmol), base (20 mol%) in solvent (2.0 mL) at 110 °C (oil bath). [b]Isolated yield.

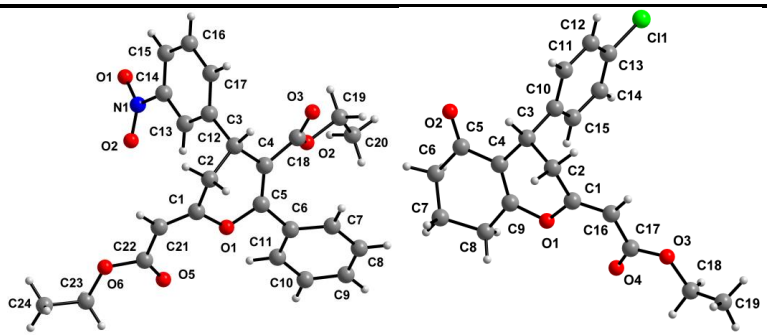
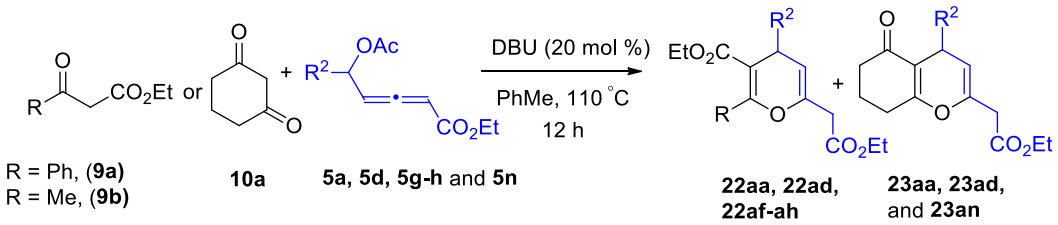
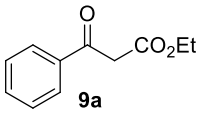
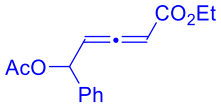
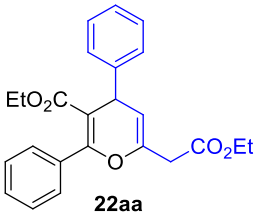
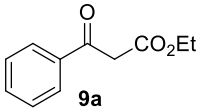
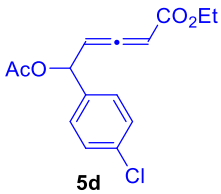
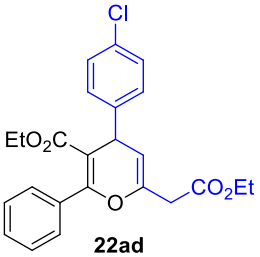
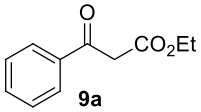
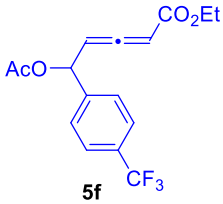
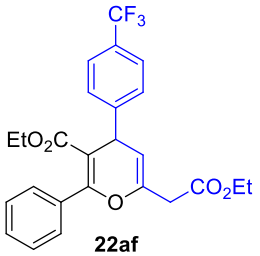
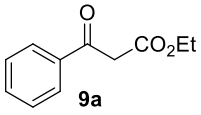
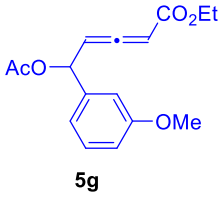
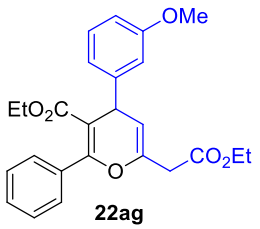


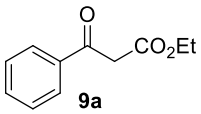
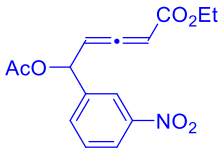
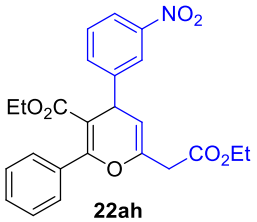
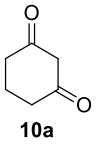
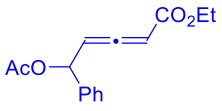
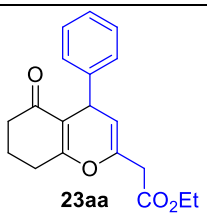
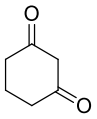
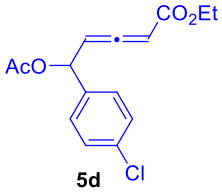
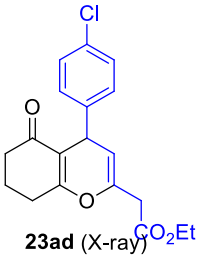
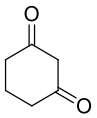
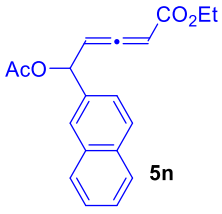
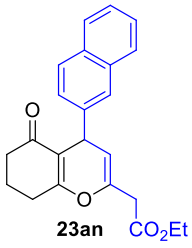
Figure 10: Molecular structures of compounds **20ah** (left) and **21ad** (right)

Next, the synthesis of 4*H*-pyran using 1,8-diazabicyclo[5.4.0]undec-7-ene catalysis was the subject of our next study. The δ-acetoxy allenoates with various functional groups on the phenyl ring delivered the desired annulated products successfully (Table 15). The reactivity and yield of allenoates (cf. **5d**, **5g**, and **5e**) were not significantly impacted by the position of the substituents on the aryl ring. High yields (62%-76%) were achieved for the annulated products **22aa**, **22ad**, **22af-ah**, **23aa**, **23ad** (X-ray, Figure 11) and **23an**.

Table 15. Substrate scope for the synthesis of 4*H*-pyrans from 1,3-dicarbonyl compounds and *δ*-acetoxy allenoates[a]



Entry	1C,3O-bisnucleophiles	*δ*-Acetoxy Allenoate	Dihydropyran	Yield (%)[b]
1	 **9a**	 **5a**	 **22aa**	71
2	 **9a**	 **5d**	 **22ad**	76
3	 **9a**	 **5f**	 **22af**	67
4	 **9a**	 **5g**	 **22ag**	62

5	 **9a**	 **5h**	 **22ah**	57
6	 **10a**	 **5a**	 **23aa**	74
7	 **10a**	 **5d**	 **23ad** (X-ray)	64
8	 **10a**	 **5n**	 **23an**	69

[a]Reaction conditions: **9a-b** and **10a** (0.20 mmol), **5a**, **5d, 5g-h** and **5n** (0.24 mmol), base (20 mol%) in solvent (2.0 mL); temperature is that of the oil bath. [b]Isolated yield.

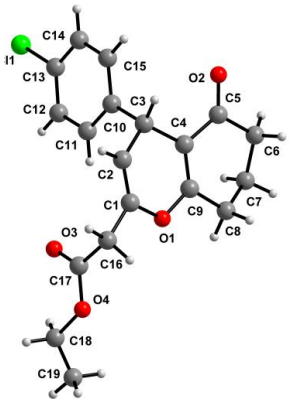
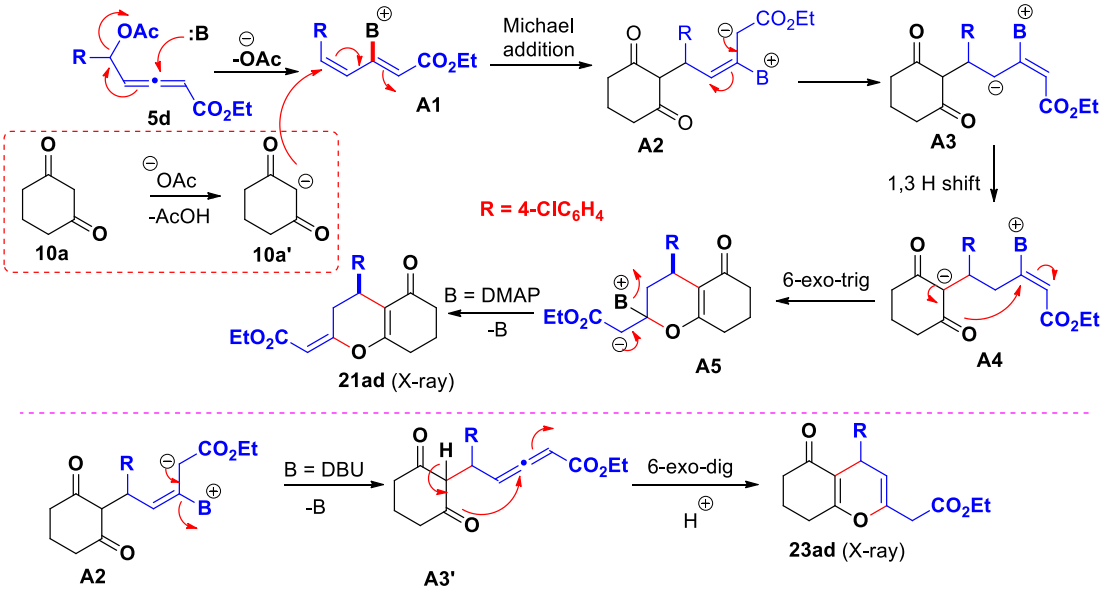


Figure 11: Molecular structure of compound **23ad**

2.4.2 *Proposed mechanistic pathways for DMAP and DBU catalysis*

Plausible pathways for the (3 + 3) annulations are shown in Scheme 8. These hetero-annulations may be initiated through the formation of diene-ammonium intermediate **A1** *via* the addition-elimination process between Lewis base (tertiary amine) and **5d** {**A1**: B = DMAP}. Next, the addition of **10a′** (*in situ* generated from **10a**) to **A1** at the *δ*-carbon gives zwitterionic intermediate **A2** {**A2**: B = DMAP}. Next, the base will be eliminated leading to the formation of allenic intermediate **A3**. In the case of DMAP catalysis, 1,3-proton shift followed by 6-*exo*-trig cyclization will occur for the ring closure to form the final compound **21ad** whereas, in DBU catalysis, it will lead to product **23ad** *via* 6-*exo*-dig cyclization.



Scheme 8: Plausible mechanistic pathways for the formation of **21ad** and **23ad**

Summary (PART-A)

(1) We have discovered distinct modes of Lewis base catalyzed chemoselective annulation between acetoxy allenoates with thioamides affording dihydrothiophene or thiopyran scaffolds under mild conditions. Thus, pyridine-catalyzed [3 + 2] annulation delivered dihydrothiophene motifs as *essentially single diastereomers* where amine behaves in a manner similar to phosphine in the catalytic reaction. Rather surprisingly, DABCO catalyzed [3 + 3] annulation affords thiopyrans by involving addition-elimination and *6-exo-dig* cyclization.

(2) In contrast to the above, TBAB catalyzed [3 + 2] annulation gives a novel class of thiazole motifs with a *Z-isomeric exocyclic double bond*, in which thioamide acts as sulfur and nitrogen source; the *β,* and *γ*-carbons of allenoate are involved in the cyclization.

(3) We have discovered two distinct modes of chemo-, regio-, and stereo-selective organocatalytic hetero-annulation involving *δ*-acetoxy allenoates and *N*-sulfonyl hydrazides. In the first one comprising spiro-annulation and ring-expansion (5→6, 6→7, and 7→8) strategy, *δ*-acetoxy allenoates delivered ring-expanded heterocyclic frameworks *via* vinyl amine-imine coupling. This ring expansion (6→7) could be extended to the natural product *R*-(−)-carvone-derived substrates.

(4) We have discovered the Lewis base-dependent and mutually exclusive (3 + 2) annulation strategy for the synthesis of *N*-alkenyl 1,2-pyrazole scaffolds *via* sequential allylic eliminations from *δ*-acetoxy allenoates and non-fused *N*-sulfonyl hydrazones. Furthermore, unlike a literature report, *N*-alkenyl pyrazoles were converted to *N*-H pyrazoles using $TiCl_4$/Mg.

(5) Additionally, we have developed a (3 + 3) annulation that is tertiary amine catalysed for the synthesis of pyran scaffolds from *δ*-acetoxy allenoates and 1C,3O-bisnucleophiles under metal-free conditions. Thus, in the reaction of *δ*-acetoxy allenoates with 1,3-dicarbonyl compounds, dihydropyran was produced when a catalytic quantity of DMAP was used, whereas 4*H*-pyran scaffold was produced when DBU was used.

Chapter 3

EXPERIMENTAL SECTION

General Methods. All the reactions were carried out either under an inert atmosphere or air. All required chemicals were procured from Aldrich or local manufacturers and used as such without further purification unless noted.[48]

Melting point: Melting points were determined using a SUPERFIT hot stage apparatus and are uncorrected.

Elemental analyses: Elemental analyses were carried out on a Perkin-Elmer 240C CHN or Thermo Finnigan EA1112 CHNS analyzer.

Infrared spectroscopy: IR spectra were recorded on a JASCO FT/IR 5300 spectrophotometer.

NMR spectroscopy: NMR spectra were recorded using 5 mm tubes on a Bruker 400 MHz [^{1}H and ^{13}C{^{1}H} operating at 400 and 100 MHz, respectively] or 500 MHz [^{1}H, ^{13}C{^{1}H} and ^{19}F operating at field strengths: 500, 125 and 470 MHz, respectively] NMR spectrometer in $CDCl_3$ solution (unless specified otherwise) with shifts referenced to $SiMe_4$ (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F) (δ = 0), respectively. All *J* values are in Hz.

LC-MS and HRMS: LC-MS equipment was used to record mass spectra for isolated compounds where appropriate. LC-MS data were obtained using electrospray ionization (positive mode) on a C-18 column. Mass spectra were recorded using HRMS (ESI-TOF and ESI-EXACTIVE ORBITRAP analyzer) equipment.

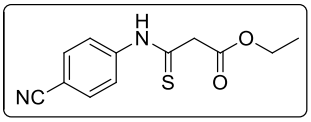
3.1 Synthesis of starting materials

The starting materials, ethyl 3-(phenylamino)-3-thioxopropanoates (**3a-h**) were prepared by using the literature procedure.[42a] Allenoate precursors **5a-p** were synthesized using the procedure reported earlier using **4a-p**.[19c-d] Of these, **3e** and **5h** are new. The solvent/s of crystallization for all the products was ethyl acetate-hexane (ca 4:1 v/v).

3.1.1 ***Synthesis of ethyl 3-((4-cyanophenyl)amino)-3-thioxopropanoate (3e).*** Following a literature procedure,[42a] a 25 mL RB flask equipped with a magnetic stir bar was charged with

EtOH (25.0 mL) and solid sodium (200.0 mg, 8.70 mmol, 1.05 equiv). After sodium being fully reacted, ethyl acetoacetate (1.05 mL, 8.25 mmol, 1.0 equiv) was added, and the mixture was allowed to stir for 15 min. 4-Isothiocyanatobenzonitrile (1.320 g, 8.25 mmol, 1.0 equiv) was added drop-wise over a period of 20 min, the mixture was stirred for 48 h, diluted using EtOAc (100.0 mL), and acidified with 1 M HCl (aq) (100.0 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/hexane (1:9) as the eluent to obtain **3e** as a yellow solid.

Compound 3e



Yield: 0.737 g (36%), Yellow solid

Mp: 89-91 ºC.

IR (neat): ν_{max} 3288, 2969, 2923, 2227, 1737, 1602, 1507, 1421, 1377, 1215, 1025, 840 cm^{-1}

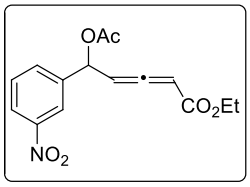
^1H NMR (500 MHz, $CDCl_3$): δ 11.38 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.70-7.68 (m, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.99 (s, 2H), 1.34 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 193.0, 170.6, 142.4, 133.1, 123.0, 118.5, 109.8, 62.4, 50.3, 14.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{12}H_{13}N_2O_2S$ $[M + H]^+$: *m/z* 249.0692, found: 249.0693.

3.1.2 ***Synthesis of ethyl 5-acetoxy-5-(3-nitrophenyl)penta-2,3-dienoate (5h).*** Following literature procedure,[19c-d] to a solution of ethyl 5-hydroxy-5-(3-nitrophenyl)penta-2,3-dienoate (10.0 mmol, 1.0 equiv) in dry dichloromethane (20 mL) at 0 °C was added triethylamine (20.0 mmol, 2.0 equiv), and then the mixture stirred for 30 min at the same temperature. After that, acetyl chloride (12.0 mmol, 1.2 equiv) was slowly added into the mixture over 5 min, and the contents were stirred for 40 min at 0 °C. After completion of the reaction (TLC), the aqueous layer was extracted with dichloromethane (3 × 25 mL). Then, the combined organic layer was washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/hexane (1:9) as the eluent to obtain **5h** as a gummy liquid {in the ^1H NMR spectrum for the minor isomer corresponding protons is indicated by the prime (′) symbol}.

Compound 5h



Yield: 1.74 g (57%).

IR (neat): ν_{max} 3012, 2969, 1967, 1742, 1716, 1529, 1349, 1217, 1158, 1025, 799 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.29-8.28 (m, 2H), 8.19-8.17 (m, 2H′), 7.77-7.75 (m, 2H′), 7.56-7.56 (m, 2H), 6.46-6.42 (m, 1H + 1H′), 5.91 (t, *J* = 6.0 Hz, 1H′), 5.86 (t, *J* = 6.0 Hz, 1H), 5.74-5.70 (m, 1H + 1H′), 4.23-4.15 (m, 2H + 2H′), 2.16 (s, 3H), 2.13 (s, 3H′), 1.29-1.25 (m, 3H + 3H′) ppm.

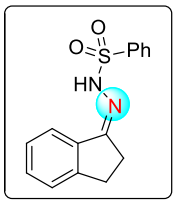
^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ (major isomer) 212.6, 169.6, 164.7, 148.5, 140.3, 133.2, 129.7, 123.6, 122.0, 96.1, 91.6, 71.5, 61.4, 21.1, 14.2; (minor isomer) 212.2, 169.6, 164.7, 148.5, 140.0, 133.4, 129.7, 123.7, 122.3, 96.3, 92.0, 70.9, 61.4, 21.0, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{15}H_{15}NNaO_6$ $[M + Na]^+$ *m/z* 328.0792, found: 328.0799.

3.2 Synthesis of sulfonohydrazides 8a-l and dicarbonyls 9a/ 10a: The sulfonohydrazides **8a-l** were synthesized by starting with the corresponding ketones **6a-l** and benzenesulfonyl hydrazide **7** using literature procedures.[44] Of these, compounds **8d**, **8g**-**h** and **8i**-**8k** are known; precursors **8a**-**c** and **8e**-**f** are new. The 1,3-dicarbonyl precursors **9a** and **10a** are commercially available.[20]

3.2.1 ***General procedure for the synthesis of compounds 8a-c and 8e-f.*** An oven-dried round-bottom flask was charged with phenylsulfonyl hydrazide (11.0 mmol, 1.1 equiv) in methanol (100.0 mL) at 25 °C. Subsequently, ketone (10.0 mmol, 1.0 equiv) was added drop-wise at room temperature and the mixture was stirred until the complete disappearance of the ketone. Then the reaction mixture was concentrated under reduced pressure at 40-45 °C. The crude product was purified by column chromatography using ethyl acetate and hexane mixture (40:60) as the eluent, the crude product was purified.

Compound 8a



Yield: 2.52 g (88%), White solid

Mp: 190-192 °C.

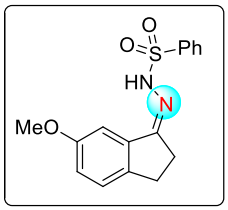
IR (neat): ν_{max} 3210, 3014, 2969, 2945, 1739, 1439, 1367, 1228, 1216, 1164, 1093, 754 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06-8.04 (m, 2H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.61-7.57 (m, 1H), 7.54-7.51 (m, 2H), 7.47 (s, 1H), 7.35-7.32 (m, 1H), 7.28-7.23 (m, 2H), 3.09-3.07 (m, 2H), 2.67-2.64 (m, 2H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.6, 148.5, 138.6, 137.1, 133.3, 131.1, 129.1, 128.2, 127.2, 125.5, 122.3, 28.5, 26.7 ppm.

HRMS (ESI-TOF): Calcd for $C_{15}H_{15}N_2O_2S$ $[M + H]^+$ *m/z* 287.0849, found 287.0849.

Compound 8b



Yield: 2.85 g (90%), White solid

Mp: 173-175 °C.

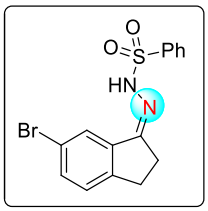
IR (neat): ν_{max} 3195, 2919, 2853, 1449, 1333, 1307, 1159, 1064, 1011, 755 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.41 (s, 1H), 7.95 (d, *J* = 7.0 Hz, 2H), 7.66-7.62 (m, 3H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.02-6.94 (m, 2H), 3.76(s, 3H), 2.93 (s, 2H), 2.76 (s, 2H) ppm.

^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6): δ 162.7, 159.1, 141.3, 139.7, 138.8, 133.3, 129.5, 128.0, 127.0, 118.9, 104.6, 55.8, 28.5, 27.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{16}H_{17}N_2O_3S$ $[M + H]^+$ *m/z* 317.0954, found 317.0953.

Compound 8c



Yield: 3.1 g (85%), White solid

Mp: 130-132 °C.

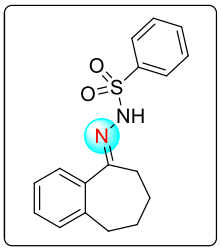
IR (neat): ν_{max} 3185, 3013, 2969, 2944, 1739, 1448, 1369, 1228, 1216, 1164, 1072, 1010, 918, 722 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.60 (s, 1H), 8.01-7.92 (m, 2H), 7.64-7.51 (m, 5H), 7.31 (d, *J* = 7.5 Hz, 1H), 2.97 (s, 2H), 2.77 (s, 2H) ppm.

^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6): δ 161.1, 148.3, 140.0, 139.6, 133.7, 133.4, 129.6, 129.4, 128.4, 127.9, 123.7, 120.6, 28.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{15}H_{14}{}^{79}BrN_2O_2S$ $[M + H]^+$ *m/z* 364.9954, found 364.9955.

Compound 8e



Yield: 2.58 g (82%), White solid

Mp: 108-110 °C.

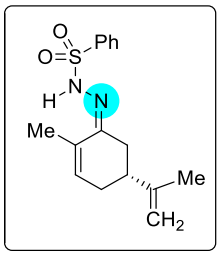
IR (neat): ν_{max} 3197, 3014, 2969, 2945, 1738, 1448, 1228, 1216, 1165, 1074, 636 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.63-7.60 (m, 1H), 7.55-7.52 (m, 2H), 7.29-7.26 (m, 2H), 7.21-7.18 (m, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.41-2.38 (m, 2H), 1.77-1.72 (m, 2H), 1.63-1.58 (m, 2H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.8, 138.9, 138.5, 137.3, 133.3, 129.7, 129.1, 128.6, 128.2, 128.0, 126.6, 31.3, 27.6, 25.5, 20.9 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{18}N_2NaO_2S$ $[M + Na]^+$ *m/z* 337.0981, found 337.0981.

Compound 8f



Yield: 2.71 g (89%), White solid

Mp: 156-158 °C.

IR (neat): ν_{max} 3204, 2999, 2969, 2937, 1738, 1447, 1405, 1367, 1228, 1216, 1163, 1028, 744 cm^{-1}.

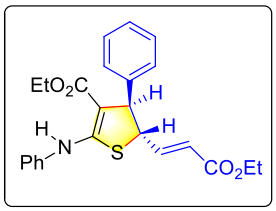
^1H NMR (500 MHz, $CDCl_3$): δ 8.01-7.99 (m, 2H), 7.62-7.58 (m, 1H), 7.53-7.50 (m, 2H), 7.38 (s, 1H), 6.09-6.07 (m, 1H), 4.79-4.71 (m, 2H), 2.60 (dd, *J* = 16.0, 4.5 Hz, 1H), 2.40-2.33 (m, 1H), 2.28-2.22 (m, 1H), 2.07-2.00 (m, 1H), 1.92 (dd, *J* = 16.0, 13.0 Hz, 1H), 1.78 (t, *J* = 1.5, Hz, 3H), 1.72 (s, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 155.2, 147.2, 138.3, 133.8, 133.2, 132.5, 128.8, 128.3, 110.5, 40.5, 30.1, 29.3, 20.7, 17.7 ppm.

HRMS (ESI-TOF): Calcd for $C_{16}H_{20}N_2O_2SNa$ $[M + Na]^+$ *m/z* 327.1138, found 327.1137.

3.3 General procedure for the synthesis of compounds 11aa-11am, 11ba-11ga, 11be, 11db, 11dl and 11ha. A Schlenk tube was charged with *δ*-acetoxy allenoate **5** (0.24 mmol), pyridine (0.04 mmol), K_2CO_3 (0.4 mmol), and toluene (1.0 mL). Subsequently, thioamide **3** (0.20 mmol) in toluene (1.0 mL) was added at 25 °C and the mixture was stirred at the same temperature for 12 h. The progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was quenched by adding water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). Then, the combined organic layer was washed with brine solution (20.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/ hexane (5:95) as the eluent.

Compound 11aa



Yield: 65.2 mg (77%).

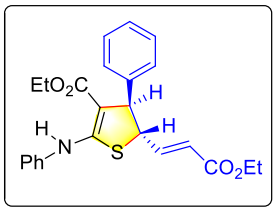
IR (neat): ν_{max} 3232, 2978, 2931, 1717, 1643, 1593, 1565, 1460, 1410, 1367, 1236, 1155, 1030, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.34 (s, 1H), 7.36-7.30 (m, 6H), 7.27-7.25 (m, 3H), 7.16-7.13 (m, 1H), 7.08 (dd, *J* = 15.0, 9.5 Hz, 1H), 5.89 (d, *J* = 15.0 Hz, 1H), 4.33 (d, *J* = 1.5 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.03(qd, *J* = 7.0, 1.5 Hz, 2H), 4.00-3.98 (m, 1H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.07 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 167.0, 166.4, 161.0, 146.2, 143.1, 140.2, 129.4, 128.7, 127.3, 127.1, 124.9, 121.7, 121.3, 95.9, 60.8, 59.4, 55.8, 55.3, 14.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{26}NO_4S$ $[M + H]^+$ *m/z* 424.1577, found: 424.1584.

Compound 11ab



Yield: 66.2 mg (73%).

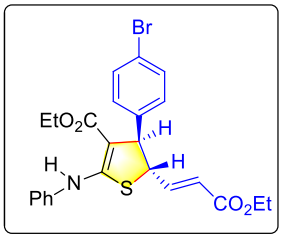
IR (neat): ν_{max} 3254, 2986, 2923, 1717, 1643, 1593, 1566, 1461, 1410, 1367, 1238, 1172, 1031, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.25 (s, 1H), 7.28-7.25 (m, 2H), 7.19-7.17 (m, 4H), 7.08-7.05 (m, 1H), 7.00 (dd, *J* = 15.5, 9.5 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.82 (dd, *J* = 15.5, 0.5 Hz, 1H), 4.22 (d, *J* = 1.0 Hz, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 4.01-3.94 (m, 2H), 3.87 (d, *J* = 9.5 Hz, 1H), 3.73 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.02 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 167.0, 166.3, 160.7, 158.8, 146.3, 140.2, 135.1, 129.4, 128.1, 124.8, 121.6, 121.2, 114.0, 96.2, 60.8, 59.4, 56.0, 55.4, 54.5, 14.4_1, 14.3_6 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{28}NO_5S$ $[M + H]^+$ *m/z* 454.1683, found: 454.1691.

Compound 11ac



Yield: 74.2 mg (74%).

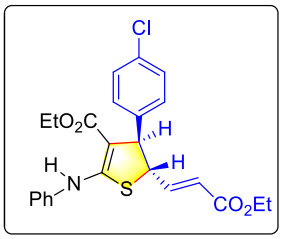
IR (neat): ν_{max} 3327, 2979, 2934, 1717, 1641, 1594, 1566, 1485, 1411, 1240, 1032, 694 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 10.25 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.29-7.26 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 7.09-7.07 (m, 1H), 6.98 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.82 (d, *J* = 15.5 Hz, 1H), 4.21 (s, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 4.00-3.94 (m, 2H), 3.86 (d, *J* = 9.0 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.01 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 166.8, 166.2, 161.2, 145.8, 142.1, 140.1, 131.8, 129.4, 128.8, 125.1, 121.7, 121.6, 121.0, 95.4, 60.9, 59.5, 55.5, 54.8, 14.4_0, 14.3_6 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}BrNO_4S$ $[M + H]^+$ *m/z* 502.0682, found: 502.0687.

Compound 11ad



Yield: 69.5 mg (76%).

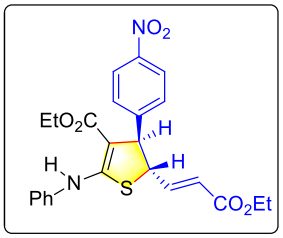
IR (neat): ν_{max} 3248, 2979, 2928, 1716, 1643, 1593, 1565, 1461, 1410, 1367, 1238, 1156, 1030, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.22 (s, 1H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.20-7.14 (m, 6H), 7.06-7.04 (m, 1H), 6.95 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.78 (d, *J* = 15.5 Hz, 1H), 4.20 (d, *J* = 1.5 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.94 (q, *J* = 7.0 Hz, 2H), 3.83 (d, *J* = 9.0 Hz, 1H), 1.19 (t, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 166.8, 166.2, 161.1, 145.8, 141.6, 140.1, 132.9, 129.4, 128.8, 128.5, 125.0, 121.7, 121.6, 95.5, 60.9, 59.5, 55.6, 54.8, 14.3_9, 14.3_6 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}ClNO_4S$ $[M + H]^+$*m/z* 458.1187, found: 458.1197.

Compound 11ae



Yield: 75.0 mg (80%), White solid.

Mp: 102-104 ºC

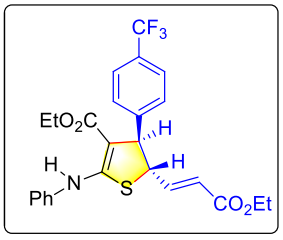
IR (neat): ν_{max} 3286, 2980, 2902, 1717, 1645, 1593, 1566, 1461, 1407, 1368, 1239, 1155, 1029, 694 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.33 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.38-7.35 (m, 2H), 7.27-7.25 (m, 2H), 7.20-7.17 (m, 1H), 7.07 (dd, *J* = 15.5, 9.5 Hz, 1H), 5.91 (d, *J* = 15.5 Hz, 1H), 4.42 (d, *J* = 1.5 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 4.06-4.02 (m, 2H), 3.97 (d, *J* = 9.5 Hz, 1H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.06 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 166.5, 166.0, 161.6, 150.5, 147.3, 145.1, 139.8, 129.5, 125.4, 124.0, 122.0, 121.9, 94.7, 61.0, 59.6, 55.1, 55.0, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_6S$ $[M + H]^+$ *m/z* 469.1428, found: 469.1432.

Compound 11af



Yield: 77.6 mg (79%).

IR (neat): ν_{max} 3254, 2992, 2922, 1718, 1645, 1594, 1567, 1461, 1412, 1368, 1238, 1160, 1031, 695 cm^{-1}.

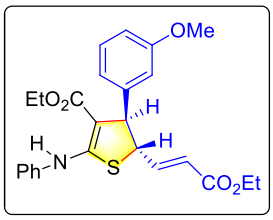
^1H NMR (500 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.29-7.26 (m, 2H), 7.19-7.18 (m, 2H), 7.10-7.07 (m, 1H), 7.00 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.83 (dd, *J* = 15.5, 1.0 Hz, 1H), 4.31 (d, *J* = 2.0 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.98-3.94 (m, 2H), 3.89 (dd, *J* = 9.0, 2.0 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.1, 161.4, 147.1, 145.5, 140.0, 129.8 (q, $^{2}J_{C\text{-}F}$ = 32.0 Hz), 129.7, 129.4, 127.5, 125.7 (q, $^{3}J_{C\text{-}F}$ = 3.4 Hz), 125.2, 124.3 (q, $^{1}J_{C\text{-}F}$ = 270.4 Hz), 121.8, 121.7, 95.1, 60.9, 59.5, 55.3, 55.1, 14.3 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ -62.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{25}F_3NO_4S$ $[M + H]^+$ *m/z* 492.1451, found: 492.1457.

Compound 11ag



Yield: 68.0 mg (75%).

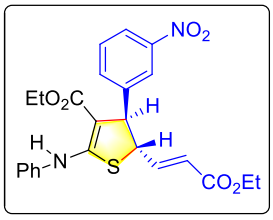
IR (neat): ν_{max} 3251, 2979, 2941, 1716, 1643, 1593, 1565, 1461, 1410, 1367, 1236, 1155, 1030, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.38 (s, 1H), 7.39-7.36 (m, 2H), 7.29-7.28 (m, 3H), 7.19-7.17 (m, 1H), 7.11 (dd, *J* = 15.5, 9.0 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.93_4-6.93_0 (m, 1H), 6.84 (dd, *J* = 8.5, 2.0 Hz, 1H), 5.93 (d, *J* = 15.5 Hz, 1H), 4.34 (d, *J* = 1.0 Hz, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 4.12-4.06 (m, 2H), 4.03 (d, *J* = 9.0 Hz, 1H), 3.84 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.8, 166.2, 160.9, 159.9, 146.1, 144.7, 140.1, 129.6, 129.3, 124.8, 121.6, 121.2, 119.4, 113.0, 112.1, 95.7, 60.7, 59.3, 55.6, 55.2, 14.3_3, 14.2_8 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{28}NO_5S$ $[M + H]^+$ *m/z* 454.1683, found: 454.1689.

Compound 11ah



Yield: 71.2 mg (76%).

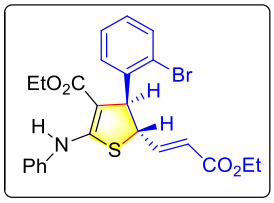
IR (neat): ν_{max} 3242, 2980, 1717, 1646, 1594, 1566, 1461, 1411, 1368, 1239, 1170, 1032, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.34 (s, 1H), 8.23 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.54-7.51 (m, 1H), 7.40-7.37 (m, 2H), 7.29-7.28 (m, 2H), 7.21-7.19 (m, 1H), 7.09 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.93 (dd, *J* = 15.5 Hz, 1H), 4.44 (s, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 4.06 (q, *J* = 7.0 Hz, 2H), 4.01 (d, *J* = 9.0 Hz, 1H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.5, 166.1, 161.6, 148.6, 145.2$_2$, 145.1$_5$, 139.8, 133.2, 129.6, 129.4, 125.3, 122.4, 122.2, 121.9, 94.8, 60.9, 59.6, 55.1, 54.9, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_6S$ $[M + H]^+$ *m/z* 469.1428, found: 469.1432.

Compound 11ai



Yield: 69.1 mg (69%).

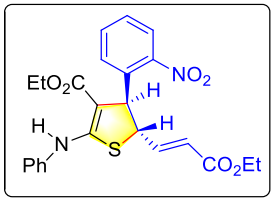
IR (neat): ν_{max} 3254, 2982, 2923, 1718, 1644, 1593, 1561, 1461, 1410, 1367, 1235, 1139, 1030, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.35 (s, 1H), 7.54-7.53 (m, 1H), 7.29-7.26 (m, 2H), 7.21-7.18 (m, 4H), 7.10-7.05 (m, 3H), 5.95 (dd, *J* = 15.5, 1.0 Hz, 1H), 4.70 (d, *J* = 1.0 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 4.01-3.94 (m, 2H), 3.86 (d, *J* = 9.0 Hz, 1H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.9, 166.5, 162.4, 146.0, 140.5, 140.1, 133.2, 129.4, 128.8, 128.4, 127.6, 125.0, 124.4, 121.6$_4$, 121.6$_0$, 94.1, 60.8, 59.5, 54.8, 53.6, 14.4$_2$, 14.3$_8$ ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}BrNO_4S$ $[M + H]^+$ *m/z* 502.0682, found: 502.0677.

Compound 11aj



Yield: 66.5 mg (71%).

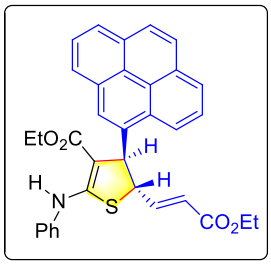
IR (neat): ν_{max} 3261, 2966, 2925, 1735, 1719, 1658, 1569, 1469, 1366, 1232, 1030, 762 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.37 (s, 1H), 7.93 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.61-7.54 (m, 2H), 7.45-7.41 (m, 1H), 7.38-7.35 (m, 2H), 7.28-7.26 (m, 2H), 7.19-7.16 (m, 1H), 7.13 (dd, *J* = 15.5, 9.0 Hz, 1H), 6.05 (dd, *J* = 15.5, 0.5 Hz, 1H), 4.77 (s, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 4.10 (d, *J* = 9.0 Hz, 1H), 4.00-3.96 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 166.4, 162.6, 148.9, 145.3, 139.9, 136.9, 133.3, 129.5, 129.3, 129.2, 128.2, 125.2, 124.6, 122.0, 121.7, 94.5, 60.8, 59.6, 54.9, 49.8, 14.3, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_6S$ $[M + H]^+$ *m/z* 469.1428, found: 469.1419.

Compound 11ak



Yield: 77.7 mg (71%).

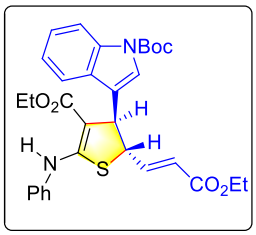
IR (neat): ν_{max} 3235, 2922, 2852, 1719, 1644, 1594, 1568, 1460, 1412, 1367, 1239, 1155, 1033, 694 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.59 (s, 1H), 8.29 (d, *J* = 9.0, 1.0 Hz, 1H), 8.23-8.15 (m, 4H), 8.06-8.01 (m, 4H), 7.39-7.32 (m, 5H), 7.18-7.15 (m, 1H), 6.04 (d, *J* = 15.0 Hz, 1H), 5.51 (s, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 4.10 (d, *J* = 9.5 Hz, 1H), 4.04-3.98 (m, 1H), 3.96-3.89 (m, 1H), 1.36 (t, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 167.2, 166.5, 162.0, 146.2, 140.2, 135.6, 131.5, 130.8, 130.7, 129.4, 128.3, 128.1, 127.7, 127.2, 126.1, 125.5, 125.4, 125.2, 125.1, 124.9, 124.3, 122.6, 121.7, 121.6, 120.5, 94.8, 61.0, 59.5, 56.0, 14.4_1, 14.3_5 ppm.

HRMS (ESI-TOF): Calcd for $C_{34}H_{30}NO_4S$ $[M + H]^+$ m/z 548.1890, found: 548.1898.

Compound 11al



Yield: 76.5 mg (68%).

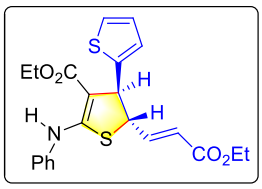
IR (neat): ν_{max} 3245, 2978, 2925, 1721, 1645, 1594, 1568, 1451, 1411, 1367, 1240, 1154, 1033, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.30 (s, 1H), 8.04 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.38 (s, 1H), 7.26-7.24 (m, 3H), 7.20-7.16 (m, 3H), 7.10-7.04 (m, 2H), 5.89 (d, *J* = 15.5 Hz, 1H), 4.54 (s, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 4.05-3.95 (m, 3H), 1.59 (s, 9H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.03 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 167.0, 166.4, 160.9, 150.0, 146.0, 140.1, 136.0, 129.4, 124.9, 124.6, 123.4, 122.7, 121.7, 121.5, 121.4, 120.0, 119.1, 115.7, 93.8, 84.0, 60.9, 59.6, 54.1, 46.4, 28.4, 14.5, 14.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{31}H_{35}N_2O_6S$ $[M + H]^+$ *m/z* 563.2210, found: 563.2217.

Compound 11am



Yield: 55.8 mg (65%).

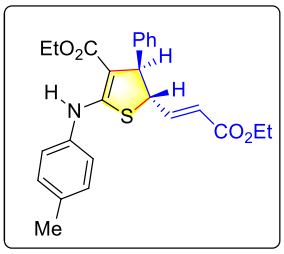
IR (neat): ν_{max} 3296, 2969, 2925, 1750, 1723, 1646, 1590, 1566, 1427, 1365, 1216, 1092, 693 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$):): δ 10.27 (s, 1H), 7.35-7.32 (m, 2H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.16-7.13 (m, 2H), 7.05 (dd, *J* = 15.5, 9.5 Hz, 1H), 6.98 (d, *J* = 3.5 Hz, 1H), 6.94 (dd, *J* = 5.0, 3.5 Hz, 1H), 5.94 (d, *J* = 15.5 Hz, 1H), 4.63 (s, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.14-4.08 (m, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 166.7, 166.3, 160.7, 146.6, 145.4, 140.0, 129.4, 126.7, 125.0, 124.0, 123.8, 121.8, 121.7, 96.2, 60.9, 59.6, 55.9, 50.2, 14.5, 14.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{24}NO_4S_2$ $[M + H]^+$ *m/z* 430.1141, found: 430.1145.

Compound 11ba



Yield: 65.6 mg (75%).

Mp: 94-96 ºC.

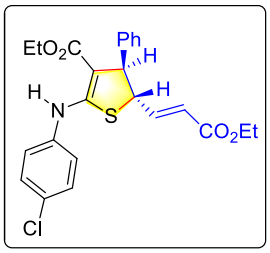
IR (neat): ν_{max} 3254, 3034, 2980, 1720, 1646, 1594, 1566, 1401, 1241, 1170, 1034, 699 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$):): δ 10.20 (s, 1H), 7.34-7.30 (m, 4H), 7.27-7.26 (m, 1H), 7.16-7.13 (m, 4H), 7.07 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.88 (d, *J* = 15.5 Hz, 1H), 4.34 (d, *J* = 1.0 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.03 (q, *J* = 7.0 Hz, 2H), 3.97 (d, *J* = 9.0 Hz, 1H), 2.33 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.06 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 167.0, 166.4, 161.6, 146.3, 143.2, 137.7, 134.9, 129.9, 128.6, 127.2, 127.1, 122.1, 121.2, 95.2, 60.8, 59.3, 55.7, 55.4, 21.0, 14.3_8, 14.3_7 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{28}NO_4S$ $[M + H]^+$ *m/z* 438.1734, found: 438.1719.

Compound 11ca



Yield: 71.3 mg (75%), yellow solid.

Mp: 83-85 ºC.

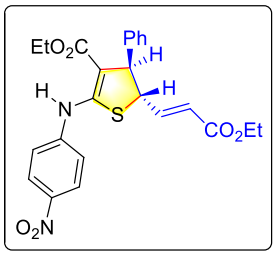
IR (neat): ν_{max} 3258, 2961, 2920, 1723, 1640, 1602, 1592, 1565, 1439, 1368, 1229, 1150, 1028, 702 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.32 (s, 1H), 7.32-7.26 (m, 7H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.07 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.90 (d, *J* = 15.5 Hz, 1H), 4.33 (s, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.04-4.00 (m, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.07 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.0, 166.3, 160.4, 146.0, 142.8, 138.8, 130.2, 129.4, 128.7, 127.3, 127.0, 122.9, 121.4, 96.5, 60.9, 59.6, 55.9, 55.3, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}ClNO_4S$ *m/z* $[M + H]^+$ 458.1187, found: 458.1197.

Compound 11da



Yield: 76.0 mg (81%), brown solid.

Mp: 96-98 ºC.

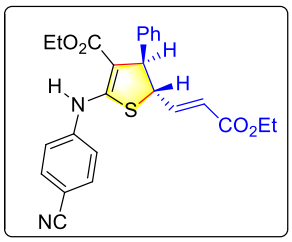
IR (neat): ν_{max} 3252, 2986, 2923, 1722, 1649, 1581, 1513, 1454, 1324, 1280, 1149, 1026, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.96 (s, 1H), 8.22 (d, *J* = 9.0 Hz, 2H), 7.37-7.27 (m, 7H), 7.09 (dd, *J* = 15.5, 9.5 Hz, 1H), 5.95 (d, *J* = 15.5 Hz, 1H), 4.34 (d, *J* = 1.5 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 4.11 (d, *J* = 9.5 Hz, 1H), 4.08-4.03 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.9, 166.1, 157.4, 145.8, 145.3, 143.2, 142.1, 128.9, 127.6, 127.0, 125.6, 122.0, 119.0, 100.4, 61.0, 60.1, 56.4, 55.0, 14.4, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_6S$ $[M + H]^+$*m/z* 469.1428, found: 469.1432.

Compound 11ea



Yield: 69.0 mg (77%), brown solid.

Mp: 122-124 ºC.

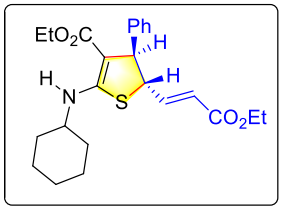
IR (neat): ν_{max} 3235, 2992, 2966, 2224, 1723, 1650, 1591, 1564, 1452, 1406, 1324, 1225, 1174, 1020, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.79 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.34-7.29 (m, 7H), 7.08 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.93 (d, *J* = 15.5 Hz, 1H), 4.33 (s, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 4.10-4.04 (m, 3H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.07 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.9, 166.2, 157.9, 145.4, 144.0, 142.2, 133.6, 128.8, 127.5, 127.0, 121.8, 119.9, 106.6, 99.5, 60.9, 60.0, 56.3, 55.0, 14.4, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{25}N_2O_4S$ $[M + H]^+$ *m/z* 449.1530, found: 449.1535.

Compound 11fa



Yield: 60.1 mg (70%).

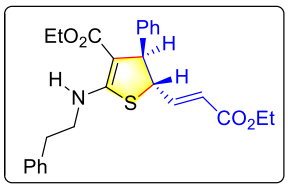
IR (neat): ν_{max} 3267, 2989, 2927, 1719, 1644, 1570, 1450, 1416, 1367, 1233, 1157, 1033, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.23-7.18 (m, 4H), 7.16-7.13 (m, 1H), 7.00 (dd, *J* = 15.5, 9.5 Hz, 1H), 5.82 (dd, *J* = 15.5, 1.0 Hz, 1H), 4.21 (d, *J* = 1.5 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.91-3.85 (m, 3H), 3.18-3.14 (m, 1H), 1.98-1.94 (m, 2H), 1.72-1.68 (m, 2H), 1.55-1.52 (m, 1H), 1.32-1.23 (m, 8H), 0.95 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.9, 166.3, 164.2, 146.6, 143.6, 128.4, 126.9$_4$, 126.9$_1$, 120.9, 90.9, 60.7, 58.7, 56.8, 55.6, 55.5, 34.2, 33.9, 25.4, 24.6, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{32}NO_4S$ $[M + H]^+$ *m/z* 430.2047, found: 430.2051.

Compound 11ga



Yield: 61.4 mg (68%).

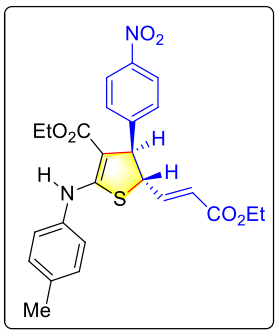
IR (neat): ν_{max} 3270, 2979, 2938, 1719, 1647, 1577, 1420, 1367, 1231, 1169, 1035, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.37-7.23 (m, 10H), 7.06 (ddd, *J* = 15.5, 9.5, 3.5 Hz, 1H), 5.89 (dd, *J* = 15.5, 1.0 Hz, 1H), 4.30-4.29 (m, 1H), 4.25 (qd, *J* = 7.0, 3.0 Hz, 2H), 3.98 (qd, *J* = 7.0, 3.0 Hz, 2H), 3.93 (d, *J* = 9.5 Hz, 1H), 3.56-3.50 (m, 2H), 2.98-2.94 (m, 2H), 1.34 (td, *J* = 7.0, 3.0 Hz, 3H), 1.07 (td, *J* = 7.0, 3.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.8, 166.4, 165.2, 146.5, 143.4, 138.2, 128.9, 128.8, 128.5, 127.0, 126.8, 121.0, 91.6, 60.8, 58.9, 55.8, 55.5, 49.3, 37.2, 14.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{26}H_{30}NO_4S$ $[M + H]^+$ *m/z* 452.1890, found: 452.1897.

Compound 11be



Yield: 61.4 mg (68%).

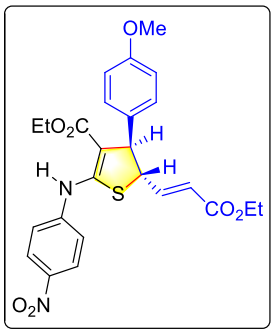
IR (neat): ν_{max} 3270, 2979, 2938, 1719, 1647, 1577, 1420, 1367, 1231, 1169, 1035, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.37-7.23 (m, 10H), 7.06 (ddd, *J* = 15.5, 9.5, 3.5 Hz, 1H), 5.89 (dd, *J* = 15.5, 1.0 Hz, 1H), 4.30-4.29 (m, 1H), 4.25 (qd, *J* = 7.0, 3.0 Hz, 2H), 3.98 (qd, *J* = 7.0, 3.0 Hz, 2H), 3.93 (d, *J* = 9.5 Hz, 1H), 3.56-3.50 (m, 2H), 2.98-2.94 (m, 2H), 1.34 (td, *J* = 7.0, 3.0 Hz, 3H), 1.07 (td, *J* = 7.0, 3.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.8, 166.4, 165.2, 146.5, 143.4, 138.2, 128.9, 128.8, 128.5, 127.0, 126.8, 121.0, 91.6, 60.8, 58.9, 55.8, 55.5, 49.3, 37.2, 14.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{26}H_{30}NO_4S$ $[M + H]^+$ *m/z* 452.1890, found: 452.1897.

Compound 11db



Yield: 72.7 mg (73%).

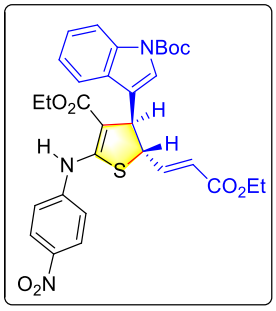
IR (neat): ν_{max} 3267, 2966, 2923, 1720, 1650, 1577, 1511, 1445, 1332, 1241, 1111, 1031, 694 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.94 (s, 1H), 8.21 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.07 (dd, *J* = 15.5, 9.5 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.94 (d, *J* = 15.5 Hz, 1H), 4.30 (s, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 4.09-4.04 (m, 3H), 3.80 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 166.9, 166.2, 159.1, 157.1, 145.8, 145.4, 143.1, 134.1, 128.0, 125.6, 121.8, 119.0, 114.2, 100.7, 61.0, 60.1, 56.6, 55.4, 54.2, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{27}N_2O_7S$ $[M + H]^+$ *m/z* 499.1533, found: 499.1538.

Compound 11dl



Yield: 86.2 mg (71%).

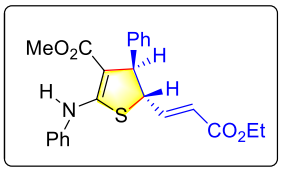
IR (neat): ν_{max} 3258, 2979, 2926, 1721, 1648, 1576, 1514, 1450, 1367, 1237, 1151, 1029, 746 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.99 (s, 1H), 8.22 (d, *J* = 9.0 Hz, 2H), 8.11 (s, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.46 (s, 1H), 7.37-7.29 (m, 4H), 7.16 (dd, *J* = 15.5, 9.5 Hz, 1H), 6.03 (d, *J* = 15.5 Hz, 1H), 4.64 (s, 1H), 4.27-4.17 (m, 3H), 4.16-4.04 (m, 2H), 1.67 (s, 9H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.9, 166.2, 157.5, 150.0, 145.7, 145.1, 143.2, 136.0, 129.3, 125.6, 124.8, 123.3, 122.9, 122.2, 120.5, 119.1, 118.9, 115.8, 98.4, 84.3, 61.1, 60.2, 54.8, 46.1, 28.4, 14.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{31}H_{34}N_3O_8S$ $[M + H]^+$ *m/z* 608.2061, found: 608.2069.

Compound 11ha



Yield: 61.4 mg (75%).

IR (neat): ν_{max} 3304, 2947, 2832, 1749, 1668, 1625, 1437, 1396, 1187, 1120, 1017, 698 cm^{-1}.

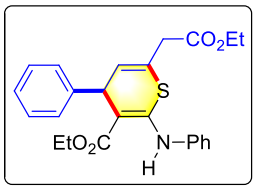
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.36 (s, 1H), 7.37-7.33 (m, 6H), 7.29-7.25 (m, 3H), 7.17-7.14 (m, 1H), 7.08 (dd, *J* = 15.5, 9.5 Hz, 1H), 5.90 (d, *J* = 15.5 Hz, 1H), 4.35 (d, *J* = 1.0 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.94 (d, *J* = 9.5 Hz, 1H), 3.59 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.4, 166.4, 161.6, 146.2, 142.6, 140.1, 129.4, 128.8, 127.4, 127.0, 125.0, 121.7, 121.2, 95.2, 60.9, 56.1, 54.9, 50.9, 14.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{24}NO_4S$ $[M + H]^+$ *m/z* 410.1421, found: 410.1422.

3.4 General procedure for the synthesis of compounds 12aa-ab, 12ad-ag, 12ai, 12ak-ao, 12ba-db, 12fa, 12fc, and 12ga-gb. A Schlenk tube was charged *δ*-acetoxy allenoate **5** (0.24 mmol), DABCO (0.04 mmol), K_2CO_3 (0.40 mmol) and toluene (1.0 mL). Subsequently, thioamide **3** (0.20 mmol) in toluene (1.0 mL) was added at 25 °C, and the mixture was stirred at the same temperature for 12 h, and the progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was quenched by adding water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). Then, the combined organic layer was washed with brine solution (20.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/ hexane (5:95) as the eluent.

Compound 12aa



Yield: 67.0 mg (79%), white solid.

Mp: 93-95 ºC.

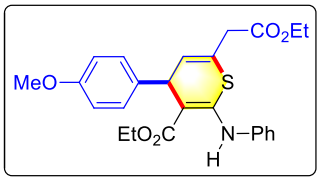
IR (neat): ν_{max} 3232, 2983, 2931, 1691, 1644, 1599, 1495, 1369, 1234, 1183, 1039, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$ δ 11.23 (s, 1H), 7.39-7.36 (m, 2H), 7.32-7.28 (m, 4H), 7.24-7.18 (m, 4H), 5.58 (s, 1H), 4.48-4.47 (m, 1H), 4.18-4.02 (m, 4H), 3.05 (dd, *J* = 14.0, 3.0 Hz, 1H), 2.91 (dd, *J* = 14.0, 3.0 Hz, 1H), 1.20-1.17 (m, 6H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.7, 165.6, 155.3, 151.1, 142.9, 138.7, 129.2, 128.4, 127.6, 126.5, 126.1_3, 126.1_1, 115.0, 95.1, 60.3, 59.9, 41.3, 37.9, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{26}NO_4S$ $[M + H]^+$*m/z* 424.1577, found: 424.1589.

Compound 12ab



Yield: 67.1 mg (74%), white solid.

Mp: 101-103 ºC.

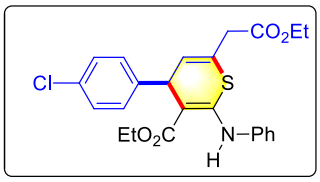
IR (neat): ν_{max} 3256, 2981, 2929, 1693, 1637, 1560, 1403, 1367, 1244, 1164, 1031, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.08 (s, 1H), 7.37-7.34 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.22-7.19 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 5.57 (s, 1H), 4.41-4.40 (m, 1H), 4.17-4.00 (m, 4H), 3.77 (s, 3H), 2.99 (dd, *J* = 14.0, 3.0 Hz, 1H), 2.85 (dd, *J* = 14.0, 3.0 Hz, 1H), 1.19-1.15 (m, 6H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.7, 165.6, 158.2, 155.0, 151.4, 138.7, 134.9, 129.2, 128.5, 126.0_4, 126.0_2, 114.9, 113.8, 95.5, 60.3, 59.9, 55.3, 41.4, 37.0, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{28}NO_5S$ $[M + H]^+$*m/z* 454.1683, found: 454.1685.

Compound 12ad



Yield: 70.4 mg (77%), white solid.

Mp: 130-132 ºC.

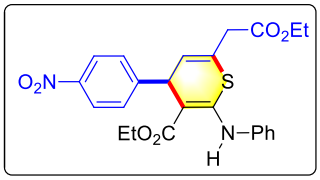
IR (neat): ν_{max} 3237, 2979, 2929, 1694, 1643, 1592, 1484, 1371, 1231, 1196, 1042, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.12 (s, 1H), 7.38-7.34 (m, 2H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.23-7.21 (m, 3H), 7.14 (d, *J* = 8.5 Hz, 2H), 5.55 (d, *J* = 1.5 Hz, 1H), 4.43-4.41 (m, 1H), 4.16-4.04 (m, 4H), 3.01 (ddd, *J* = 14.0, 5.0, 2.0 Hz, 1H), 2.83 (dd, *J* = 14.0, 3.0 Hz, 1H), 1.19-1.14 (m, 6H) ppm.

^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 168.5, 165.5, 155.4, 150.2, 141.3, 138.4, 132.2, 129.2, 128.9, 128.6, 126.3, 126.2, 115.2, 94.4, 60.4, 60.0, 41.1, 37.4, 14.4, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}ClNO_4S$ $[M + H]^+$*m/z* 458.1187, found: 458.1192.

Compound 12ae



Yield: 78.6 mg (84%), white solid.

Mp: 176-178 ºC.

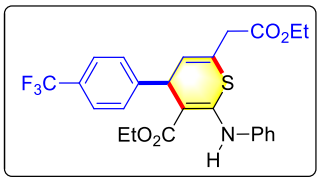
IR (neat): ν_{max} 3282, 2980, 2923, 1686, 1652, 1590, 1493, 1371, 1247, 1170, 1033, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.18 (s, 1H), 8.14-8.12 (m, 2H), 7.39-7.36 (m, 4H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.25-7.23 (m, 1H), 5.55 (d, *J* = 1.5 Hz, 1H), 4.55-4.54 (m, 1H), 4.14-4.03 (m, 4H), 3.09 (ddd, *J* = 14.0, 5.0, 2.0 Hz, 1H), 2.87 (dd, *J* = 14.0, 3.5 Hz, 1H), 1.18-1.12 (m, 6H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.3, 165.3, 156.1, 150.9, 149.5, 147.0, 138.2, 129.3, 128.4, 126.6, 123.8, 115.7, 93.3, 60.5, 60.1, 40.8, 38.1, 14.4, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_6S$ $[M + H]^+$*m/z* 469.1428, found 469.1437.

Compound 12af



Yield: 80.5 mg (80.5%), white solid.

Mp: 176-178 ºC.

IR (neat): ν_{max} 3457, 2990, 2945, 1738, 1691, 1642, 1590, 1498, 1370, 1230, 1199, 1040, 698 cm^{-1}.

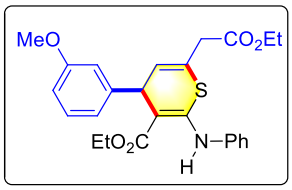
^1H NMR (500 MHz, $CDCl_3$) δ 11.15 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.39-7.35 (m, 2H), 7.33-7.29 (m, 4H), 7.25-7.22 (m, 1H), 5.56 (d, *J* = 1.5 Hz, 1H), 4.51-4.49 (m, 1H), 4.16-4.02 (m, 4H), 3.06 (ddd, *J* = 14.5, 5.0, 2.0 Hz, 1H), 2.87 (dd, *J* = 14.5, 3.5 Hz, 1H), 1.19-1.13 (m, 6H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.5, 165.5, 155.7, 150.2, 147.1, 138.3, 129.3, 128.8 (q, $^2J_{C\text{-}F}$ = 31.9 Hz), 127.9, 126.4, 126.3, 125.4 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.4 (q, $^1J_{C\text{-}F}$ = 270.1 Hz), 115.4, 93.9, 60.5, 60.0, 40.9, 37.9, 14.4, 14.2 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ -62.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{25}F_3NO_4S$ $[M + H]^+$ *m/z* 492.1451, found: 492.1452.

Compound 12ag



Yield: 69.0 mg (76%), white solid.

Mp: 91-93 ºC.

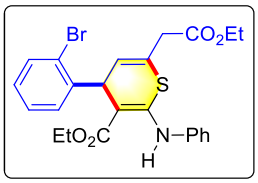
IR (neat): ν_{max} 3158, 2990, 2969, 1738, 1688, 1646, 1585, 1484, 1372, 1223, 1181, 1033, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.11 (s, 1H), 7.37-7.34 (m, 2H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.22-7.16 (m, 2H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.77 (s, 1H), 6.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.57 (s, 1H), 4.43-4.41 (m, 1H), 4.17-4.11 (m, 1H), 4.08-4.00 (m, 3H), 3.77 (s, 3H), 3.01 (dd, *J* = 14.0, 3.0 Hz, 1H), 2.89 (dd, *J* = 14.0, 3.0 Hz, 1H), 1.18-1.15 (m, 6H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.6, 165.6, 159.6, 155.3, 151.1, 144.5, 138.6, 129.3, 129.2, 126.1, 126.0, 120.0, 115.0, 113.6, 111.5, 95.0, 60.3, 59.9, 55.2, 41.2, 37.8, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{28}NO_5S$ [M + H]$^+$ *m/z* 454.1683, found: 454.1688.

Compound 12ai



Yield: 70.1 mg (70%), white solid.

Mp: 168-170 ºC.

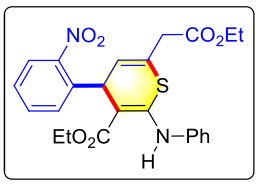
IR (neat): ν_{max} 3222, 2977, 2936, 1738, 1689, 1646, 1598, 1494, 1369, 1228, 1191, 1041, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.13 (s, 1H), 7.53 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.38-7.35 (m, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.22-7.15 (m, 3H), 7.06-7.03 (m, 1H), 5.53 (s, 1H), 4.89-4.87 (m, 1H), 4.13-3.96 (m, 4H), 2.99-2.92 (m, 2H), 1.18-1.11 (m, 6H) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.5, 165.6, 155.9, 150.3, 141.4, 138.4, 132.8, 129.3, 129.2, 128.2, 127.5, 126.3, 126.2, 123.5, 115.4, 94.6, 60.3, 60.0, 38.7, 37.6, 14.3, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}BrNO_4S$ [M + H]$^+$ *m/z* 502.0682, found: 502.0687.

Compound 12aj



Yield: 67.4 mg (72%), white solid.

Mp: 210-212 ºC.

IR (neat): ν_{max} 3463, 2969, 2945, 1738, 1689, 1648, 1600, 1494, 1367, 1226, 1200, 1039, 699 cm^{-1}.

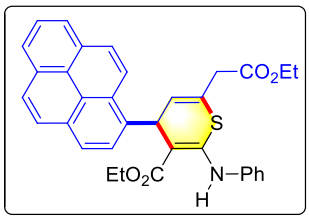
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.13 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.47-7.44 (m, 1H), 7.41-7.36 (m, 3H), 7.34-7.30 (m, 3H), 7.25-7.23 (m, 1H), 5.64 (s, 1H), 4.88-4.86 (m,

1H), 4.14-4.04 (m, 2H), 4.03-3.92 (m, 2H), 3.10-3.09 (m, 2H), 1.18 (t, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.2, 165.6, 156.1, 149.8, 149.5, 138.2, 132.7, 130.3, 129.3, 127.5, 126.6, 126.4, 124.1, 116.2, 94.5, 60.5, 60.1, 39.4, 33.7, 14.2, 14.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_6S$ $[M + H]^+$ *m/z* 469.1428, found: 469.1434.

Compound 12ak



Yield: 80.0 mg (73%), white solid.

Mp: 192-194 ºC.

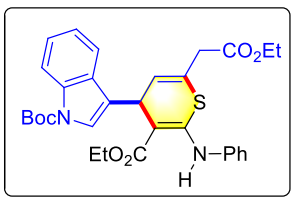
IR (neat): ν_{max} 3453, 3031, 2969, 1739, 1695, 1652, 1599, 1497, 1366, 1228, 1198, 1032, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.27 (s, 1H), 8.45 (d, *J* = 9.5 Hz, 1H), 8.22-8.18 (m, 4H), 8.06 (d, *J* = 8.0 Hz, 1H), 8.03-8.00 (m, 3H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.41-7.40 (m, 4H), 5.65-5.64 (m, 1H), 5.25 (s, 1H), 4.08-4.01 (m, 1H), 4.00-3.90 (m, 2H), 3.87-3.80 (m, 1H), 3.27 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.11 (dd, *J* = 14.0, 3.0 Hz, 1H), 1.05 (t, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 165.5, 156.1, 150.5, 138.7, 136.5, 131.6, 130.9, 130.2, 129.3, 127.8, 127.7, 127.6, 126.9, 126.2_1, 126.1_8, 125.9, 125.6, 125.4, 125.3, 125.2, 125.1, 124.9, 122.5, 115.4, 95.5, 60.2, 59.9, 40.8, 34.1, 14.2, 14.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{34}H_{30}NO_4S$ $[M + H]^+$ *m/z* 548.1890, found: 548.1894.

Compound 12al



Yield: 80.0 mg (71%), white solid.

Mp: 118-120 ºC.

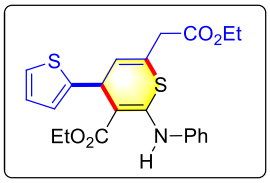
IR (neat): ν_{max} 3225, 2988, 2971, 2936, 1729, 1696, 1649, 1596, 1453, 1371, 1255, 1179, 1035, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.10 (s, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.37-7.34 (m, 2H), 7.33-7.27 (m, 5H), 7.24-7.20 (m, 1H), 5.50 (d, *J* = 1.5 Hz, 1H), 4.73-4.72 (m, 1H), 4.22-4.15 (m, 1H), 4.07-3.97 (m, 3H), 3.12 (dd, *J* = 14.0, 3.5 Hz, 1H), 3.00 (ddd, *J* = 14.0, 5.0, 2.0 Hz, 1H), 1.66 (s, 9H), 1.16-1.13 (m, 6H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.4, 165.5, 154.9, 151.3, 149.9, 138.5, 135.9, 129.5, 129.2, 126.1, 126.0, 124.2, 124.0, 122.4, 121.0, 118.8, 115.5, 115.1, 94.9, 83.7, 60.2, 60.0, 39.1, 29.2, 28.3, 14.4, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{31}H_{35}N_2O_6S$ $[M + H]^+$*m/z* 563.2210, found: 563.2215.

Compound 12am



Yield: 59.2 mg (69%), gummy liquid.

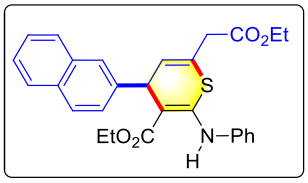
IR (neat): ν_{max} 3267, 2977, 2938, 1735, 1703, 1647, 1596, 1496, 1370, 1230, 1178, 1037, 694 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.07 (s, 1H), 7.36-7.33 (m, 2H), 7.27-7.25 (m, 2H), 7.22-7.19 (m, 1H), 7.10 (dd, *J* = 5.0, 1.5 Hz, 1H), 6.88 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.83-6.82 (m, 1H), 5.73 (s, 1H), 4.74-4.72 (m, 1H), 4.23-4.14 (m, 2H), 4.13-4.02 (m, 2H), 3.01-3.00 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.3, 165.6, 155.2, 151.1, 146.6, 138.3, 129.2, 126.8, 126.3, 126.2, 124.3, 123.6, 115.4, 95.5, 60.4, 60.1, 41.1, 33.2, 14.5, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{24}NO_4S_2$ $[M + H]^+$*m/z* 430.1141, found: 430.1149.

Compound 12an



Yield: 71.0 mg (75%), white solid.

Mp: 86-88 ºC.

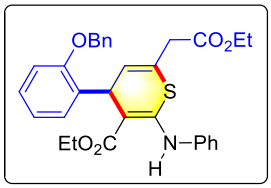
IR (neat): ν_{max} 3264, 2986, 2924, 1717, 1643, 1596, 1496, 1369, 1233, 1176, 1033, 695 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.62 (s, 1H), 7.46-7.33 (m, 7H), 7.24-7.21 (m, 1H), 5.52 (s, 1H), 4.63 (s, 1H), 4.16-4.10 (m, 1H), 4.06-3.94 (m, 3H), 3.10 (dd, *J* = 14.0, 3.0 Hz, 1H), 3.01 (dd, *J* = 14.0, 2.5 Hz, 1H), 1.13-1.11 (m, 6H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.7, 165.6, 155.5, 150.9, 140.3, 138.6, 133.6, 132.5, 129.2, 128.1, 127.6, 126.2, 126.1_4, 126.0_8, 126.0_2, 125.9, 125.5, 115.0, 94.8, 60.3, 60.0, 41.2, 38.0, 14.4, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{28}H_{28}NO_4S$ $[M + H]^+$ *m/z* 474.1734, found: 474.1738.

Compound 12ao



Yield: 72.0 mg (68%), white solid.

Mp: 116-118 ºC.

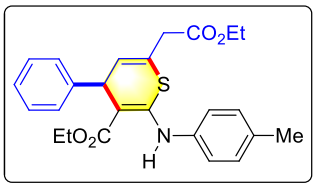
IR (neat): ν_{max} 3242, 2970, 2922, 1737, 1697, 1592, 1496, 1367, 1232, 1199, 1042, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.12 (s, 1H), 7.49-7.47 (m, 2H), 7.43-7.40 (m, 2H), 7.37-7.34 (m, 3H), 7.32-7.30 (m, 2H), 7.22-7.18 (m, 1H), 7.16-7.13 (m, 2H), 6.92-6.90 (m, 1H), 6.86-6.83 (m, 1H), 5.48 (d, *J* = 1.5 Hz, 1H), 5.20-5.13 (m, 2H), 4.98-4.96 (m, 1H), 4.15-4.09 (m, 1H), 4.08-3.97 (m, 3H), 3.06 (dd, *J* = 14.0, 3.5 Hz, 1H), 2.88 (ddd, *J* = 14.0, 5.0, 2.0 Hz, 1H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.11 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.7, 165.7, 155.8, 155.6, 152.0, 138.7, 137.6, 130.5, 129.2, 128.8, 128.7, 128.0, 127.5, 127.2, 126.0, 120.9, 114.6, 111.8, 95.1, 70.1, 60.2, 59.8, 39.0, 31.7, 14.4, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{31}H_{32}NO_5S$ $[M + H]^+$ *m/z* 530.1996, found: 530.2001.

Compound 12ba



Yield: 67.3 mg (77%), white solid.

Mp: 98-100 ºC.

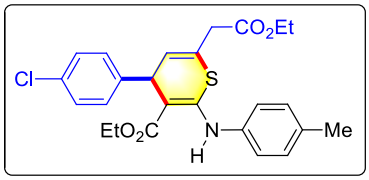
IR (neat): ν_{max} 3296, 3002, 2954, 2906, 1697, 1639, 1585, 1509, 1367, 1231, 1167, 1029, 690 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.03 (s, 1H), 7.25-7.24 (m, 2H), 7.21-7.18 (m, 3H), 7.17-7.14 (m, 4H), 5.54 (d, *J* = 1.5 Hz, 1H), 4.45-4.43 (m, 1H), 4.15-4.10 (m, 1H), 4.09-3.99 (m, 3H), 3.02 (ddd, *J* = 14.0, 5.0, 2.0 Hz, 1H), 2.88 (dd, *J* = 14.0, 3.5 Hz, 1H), 2.35 (s, 3H), 1.18-1.13 (m, 6H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.7, 165.6, 155.8, 151.4, 143.0, 136.2, 135.8, 129.8, 128.4, 127.6, 126.4_3, 126.3_9, 114.9, 94.1, 60.3, 59.8, 41.3, 37.8, 21.2, 14.4, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{28}NO_4S$ $[M + H]^+$ *m/z* 438.1734, found: 438.1740.

Compound 12bd



Yield: 74.4 mg (79%), white solid.

Mp: 107-109 ºC.

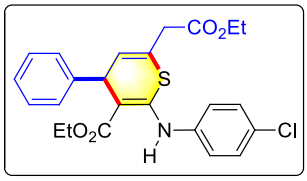
IR (neat): ν_{max} 3287, 2978, 1715, 1643, 1593, 1565, 1410, 1367, 1236, 1167, 1089, 1031, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.03 (s, 1H), 7.22-7.21 (m, 2H), 7.16-7.13 (m, 6H), 5.54 (d, *J* = 1.5 Hz, 1H), 4.41-4.40 (m, 1H), 4.13-4.02 (m, 4H), 3.00 (ddd, *J* = 14.5, 5.0, 2.0 Hz, 1H), 2.82 (dd, *J* = 14.5, 3.5 Hz, 1H), 2.35 (s, 3H), 1.19-1.14 (m, 6H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.6, 165.5, 156.1, 150.7, 141.6, 136.4, 135.7, 132.1, 129.9, 129.0, 128.5, 126.5, 115.2, 93.6, 60.4, 59.9, 41.2, 37.4, 21.2, 14.5, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{27}ClNO_4S$ $[M + H]^+$ *m/z* 472.1344, found: 472.1349.

Compound 12ca



Yield: 74.1 mg (81%), white solid.

Mp: 128-130 ºC.

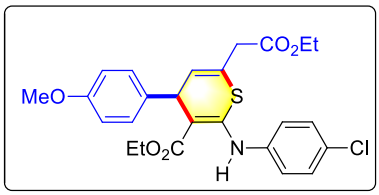
IR (neat): ν_{max} 3277, 2980, 2941, 1696, 1641, 1596, 1491, 1367, 1240, 1184, 1037, 692 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.06 (s, 1H), 7.32-7.31 (m, 2H), 7.27-7.25 (m, 1H), 7.24-7.23 (m, 2H), 7.22-7.16 (m, 4H), 5.58 (d, *J* = 1.5 Hz, 1H), 4.45-4.44 (m, 1H), 4.16-4.02 (m, 4H), 3.01 (ddd, *J* = 14.0, 5.0, 2.0 Hz, 1H), 2.89 (dd, *J* = 14.0, 3.5 Hz, 1H), 1.19-1.13 (m, 6H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.6, 165.6, 154.8, 150.7, 142.6, 137.2, 131.6, 129.3, 128.4, 127.5, 127.2, 126.5, 115.9, 95.9, 60.4, 60.1, 41.1, 37.8, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}ClNO_4S$ $[M + H]^+$ *m/z* 458.1187, found: 458.1194.

Compound 12cb



Yield: 76.0 mg (78%), white solid.

Mp: 141-143 ºC.

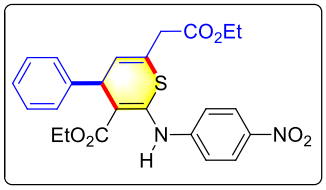
IR (neat): ν_{max} 3265, 2980, 1698, 1640, 1561, 1509, 1493, 1369, 1239, 1167, 1037, 815 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 11.03 (s, 1H), 7.32-7.30 (m, 2H), 7.22-7.21 (m, 2H), 7.12-7.10 (m, 2H), 6.80-6.78 (m, 2H), 5.58 (d, *J* = 1.5 Hz, 1H), 4.41-4.39 (m, 1H), 4.16-4.01 (m, 4H), 3.77 (s, 3H), 2.98 (ddd, *J* = 14.0, 5.0, 2.0 Hz, 1H), 2.86 (dd, *J* = 14.0, 3.5 Hz, 1H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.6, 165.6, 158.2, 154.5, 151.0, 137.3, 134.7, 131.5, 129.3, 128.5, 127.1, 115.1, 113.8, 96.4, 60.4, 60.1, 55.3, 41.3, 37.0, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{27}ClNO_5S$ [M + H]$^+$*m/z* 488.1293, found: 488.1298.

Compound 12da



Yield: 79.6 mg (85%), white solid.

Mp: 88-90 ºC.

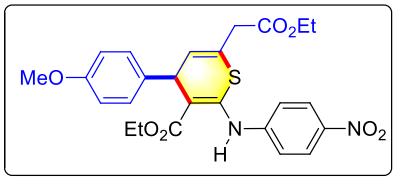
IR (neat): ν_{max} 3380, 2980, 2927, 1721, 1596, 1512, 1449, 1339, 1233, 1201, 1032, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.27 (s, 1H), 8.21 (d, *J* = 9.0 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 2H), 7.29-7.27 (m, 2H), 7.22-7.18 (m, 3H), 5.64 (d, *J* = 1.5 Hz, 1H), 4.50-4.49 (m, 1H), 4.16-4.05 (m, 4H), 3.05 (ddd, *J* = 14.5, 5.0, 2.0 Hz, 1H), 2.95 (dd, *J* = 14.5, 3.5 Hz, 1H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.16 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.1, 165.7, 151.6, 149.7, 145.6, 143.4, 141.7, 128.6, 127.5, 126.9, 125.2, 122.2, 115.7, 101.9, 60.7, 60.6, 40.6, 37.9, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_6S$ [M + H]$^+$*m/z* 469.1428, found: 469.1436.

Compound 12db



Yield: 79.7 mg (80%), white solid.

Mp: 108-110 ºC.

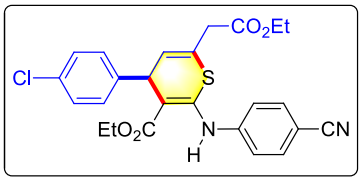
IR (neat): ν_{max} 3228, 2923, 2852, 1730, 1599, 1511, 1376, 1304, 1252, 1180, 1028, 654 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 2H), 7.33-7.28 (m, 4H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.11 (d, *J* = 7.5 Hz, 1H), 4.87 (d, *J* = 7.5 Hz, 1H), 4.19-4.15 (m, 4H), 3.78 (s, 3H), 3.28 (s, 2H), 1.29-1.24 (m, 6H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.6, 168.2, 158.7, 151.2, 145.9, 143.3, 135.8, 128.8, 128.0, 125.2, 122.2, 121.7, 114.1, 99.9, 61.5, 60.7, 55.4, 41.3, 41.2, 14.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{27}N_2O_7S$ [M + H]$^+$ *m/z* 499.1533, found: 499.1538.

Compound 12ed



Yield: 74.2 mg (77%), white solid.

Mp: 141-143 ºC.

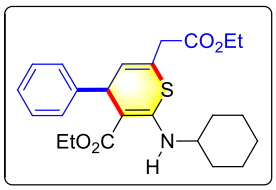
IR (neat): ν_{max} 3240, 2973, 2223, 1681, 1660, 1578, 1506, 1487, 1369, 1229, 1167, 1092, 1026, 836 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.24 (s, 1H), 7.62-7.61 (m, 2H), 7.353-7.34 (m, 2H), 7.24-7.22 (m, 2H), 7.12-7.10 (m, 2H), 5.62 (d, *J* = 1.5 Hz, 1H), 4.46-4.44 (m, 1H), 4.15-4.05 (m, 4H), 3.02 (ddd, *J* = 14.0, 5.0, 2.0 Hz, 1H), 2.88 (dd, *J* = 14.0, 3.5 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.16 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.1, 165.6, 152.5, 149.3, 143.3, 140.5, 133.3, 132.5, 128.8$_4$, 128.7$_6$, 123.6, 119.0, 115.8, 107.5, 99.7, 60.7, 60.6, 40.6, 37.4, 14.2$_9$, 14.2$_5$ ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{24}ClN_2O_4S$ [M + H]$^+$ *m/z* 483.1140, found: 483.1146.

Compound 12fa



Yield: 61.0 mg (71%).

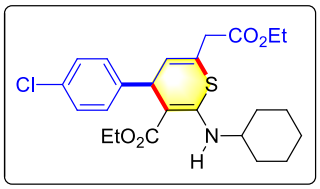
IR (neat): ν_{max} 3187, 2980, 2930, 1699, 1638, 1597, 1491, 1370, 1210, 1186, 1037, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (d, *J* = 9.0 Hz, 1H), 7.24-7.21 (m, 2H), 7.16-7.14 (m, 3H), 5.60 (d, *J* = 1.5 Hz, 1H), 4.38-4.37 (m, 1H), 4.18-4.03 (m, 3H), 4.01-3.95 (m, 1H), 3.77-3.71 (m, 1H), 2.96 (ddd, *J* = 14.5, 5.0, 2.0 Hz, 1H), 2.88 (dd, *J* = 14.5, 3.5 Hz, 1H), 2.05-2.02 (m, 2H), 1.79-1.73 (m, 2H), 1.61-1.58 (m, 1H), 1.43-1.33 (m, 5H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.11 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.8, 165.9, 156.6, 151.7, 143.2, 128.2, 127.5, 126.2, 114.6, 90.5, 60.3, 59.3, 52.4, 41.3, 37.5, 34.3, 34.1, 25.6, 24.7, 24.6, 14.5, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{32}NO_4S$ [M + H]$^+$ *m/z* 430.2047, found: 430.2055.

Compound 12fd



Yield: 61.1 mg (66%), white solid.

Mp: 86-88 ºC.

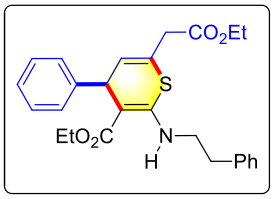
IR (neat): ν_{max} 3184, 2975, 2930, 1697, 1639, 1595, 1485, 1370, 1213, 1186, 1040, 709 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (d, *J* = 9.0 Hz, 1H), 7.20-7.18 (m, 2H), 7.09-7.08 (m, 2H), 5.59 (d, *J* = 1.5 Hz, 1H), 4.35-4.33 (m, 1H), 4.19-4.10 (m, 2H), 4.08-4.03 (m, 1H), 4.01-3.95 (m, 1H), 3.76-3.69 (m, 1H), 2.95 (ddd, *J* = 14.0, 5.0, 2.0 Hz, 1H), 2.83 (dd, *J* = 14.5, 3.5 Hz, 1H), 2.03-2.01 (m, 2H), 1.78-1.73 (m, 2H), 1.61-1.59 (m, 1H), 1.43-1.32 (m, 5H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.6, 165.8, 156.6, 151.0, 141.8, 131.9, 128.9, 128.4, 114.9, 90.0, 60.4, 59.4, 52.4, 41.1, 37.1, 34.3, 34.0, 25.5, 24.6_1, 24.5_6, 14.5, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{31}ClNO_4S$ [M + H]$^+$ *m/z* 464.1657, found: 464.1662.

Compound 12ga



Yield: 63.2 mg (70%).

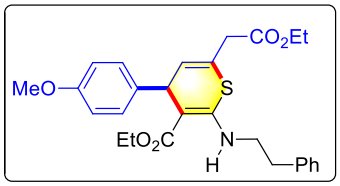
IR (neat): ν_{max} 3226, 2986, 2924, 1735, 1698, 1639, 1599, 1566, 1411, 1371, 1187, 1041, 730 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$)): δ 9.58 (t, *J* = 5.5 Hz, 1H), 7.35-7.28 (m, 2H), 7.25-7.21 (m, 5H), 7.16-7.13 (m, 3H), 5.60 (d, *J* = 2.0 Hz, 1H), 4.37-4.36 (m, 1H), 4.18-4.03 (m, 3H), 4.01-3.95 (m, 1H), 3.72-3.67 (m, 2H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.92 (dd, *J* = 4.5, 2.0 Hz, 1H), 2.88 (dd, *J* = 14.5, 3.5 Hz, 1H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.11 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.6, 165.8, 157.4, 151.1, 143.1, 138.5, 129.0, 128.7, 128.3, 127.5, 126.7, 126.3, 114.9, 91.2, 60.3, 59.4, 45.5, 41.1, 37.5, 36.9, 14.5, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{26}H_{30}NO_4S$ $[M + H]^+$ *m/z* 452.1890, found: 452.1897.

Compound 12gb



Yield: 64.5 mg (67%), white solid.

Mp: 148-150 ºC.

IR (neat): ν_{max} 3213, 2986, 2929, 1737, 1699, 1600, 1568, 1462, 1372, 1239, 1190, 1043, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (t, *J* = 6.0 Hz, 1H), 7.32-7.29 (m, 2H), 7.27-7.24 (m, 3H), 7.22-7.20 (m, 2H), 6.79-6.78 (m, 2H), 6.07 (d, *J* = 7.5 Hz, 1H), 4.76 (d, *J* = 7.0 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.14-4.03 (m, 2H), 3.77 (s, 3H), 3.61-3.48 (m, 2H), 3.29-3.22 (m, 2H), 2.95-2.87 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H) ppm.

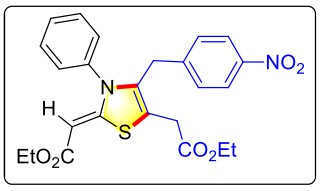
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.8, 168.6, 158.3, 157.7, 138.7, 137.6, 128.9, 128.7, 128.3, 126.7, 121.3, 113.7, 89.5, 61.3, 59.4, 55.4, 45.9, 41.8, 41.0, 37.0, 14.6, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{27}H_{32}NO_5S$ $[M + H]^+$ *m/z* 482.1996, found: 482.2002.

3.5 General procedure for the synthesis of compounds 13ae-de and **13aj-dj.** A Schlenk tube was charged *δ*-acetoxy allenoate **5** (0.24 mmol), TBAB (0.04 mmol), K_2CO_3 (0.40 mmol) and DCM (1.0 mL). Subsequently, thioamide **3** (0.20 mmol) in DCM (1.0 mL) was added at 25

°C, the mixture was stirred at the same temperature for 6 h, and the progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was quenched by adding water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). Then, the combined organic layer was washed with brine solution (20.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/ hexane (30:70) as the eluent.

Compound 13ae



Yield: 67.4 mg (72%), light brown solid.

Mp: 142-144 ºC.

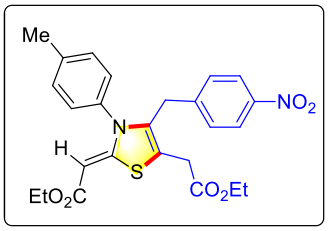
IR (neat): ν_{max} 2983, 2925, 2850, 1732, 1649, 1596, 1519, 1492, 1345, 1241, 1149, 1049, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 9.0 Hz, 2H), 7.38-7.35 (m, 1H), 7.31-7.28 (m, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 7.5 Hz, 2H), 4.60 (s, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.70 (s, 2H), 3.60 (s, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.5, 168.8, 163.3, 146.9, 144.1, 137.2, 133.5, 130.1, 129.6, 128.9_4, 128.8_6, 123.6, 111.4, 79.2, 61.8, 59.1, 32.8, 31.7, 14.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_6S$ $[M + H]^+$ *m/z* 469.1428, found: 469.1434.

Compound 13be



Yield: 65.6 mg (68%), light brown solid.

Mp: 122-124 ºC.

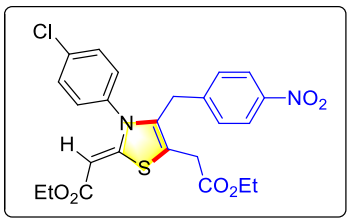
IR (neat): ν_{max} 2977, 2925, 1731, 1646, 1599, 1505, 1343, 1275, 1143, 1049, 707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 4.60 (s, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.70 (s, 2H), 3.58 (s, 2H), 2.35 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.6, 168.9, 163.5, 147.0, 144.2, 139.9, 134.5, 133.7, 130.7, 129.0, 128.6, 123.6, 111.3, 79.2, 61.9, 59.1, 32.8, 31.7, 21.3, 14.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{27}N_2O_6S$ $[M + H]^+$ *m/z* 483.1584, found: 483.1589.

Compound 13ce



Yield: 75.3 mg (75%), light brown solid.

Mp: 84-86 ºC.

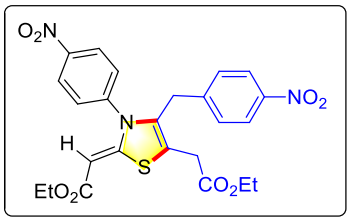
IR (neat): ν_{max} 2964, 2925, 1734, 1649, 1597, 1521, 1490, 1346, 1260, 1151, 1050, 798 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.57 (s, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.70 (s, 2H), 3.59 (s, 2H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.5, 168.8, 163.1, 147.1, 143.8, 135.9, 135.6, 133.0, 130.4, 130.3, 128.9, 123.8, 111.9, 79.7, 61.9, 59.3, 32.7, 31.7, 14.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{24}ClN_2O_6S$ $[M + H]^+$ *m/z* 503.1038, found: 503.1042.

Compound 13de



Yield: 87.2 mg (85%), light brown solid.

Mp: 162-164 ºC.

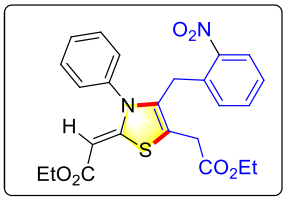
IR (neat): ν_{max} 2962, 1721, 1644, 1595, 1521, 1488, 1347, 1259, 1147, 1014, 770 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 4.55 (s, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.72 (s, 2H), 3.60 (s, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.3, 168.6, 162.4, 148.1, 147.2, 143.3, 142.7, 132.1, 130.4, 128.8, 125.5, 124.0, 112.9, 80.4, 62.0, 59.4, 32.6, 31.6, 14.7, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{24}N_3O_8S$ $[M + H]^+$ *m/z* 514.1279, found: 514.1285.

Compound 13aj



Yield: 63.7 mg (68%), light brown solid.

Mp: 143-145 ºC.

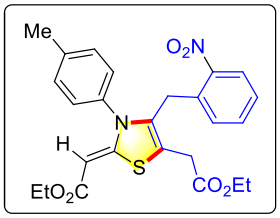
IR (neat): ν_{max} 2919, 2849, 1731, 1649, 1595, 1522, 1492, 1346, 1149, 1029, 696 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.51-7.48 (m, 1H), 7.34-7.30 (m, 2H), 7.28-7.26 (m, 2H), 7.24-7.22 (m, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 4.59 (s, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.95 (s, 2H), 3.57 (s, 2H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.5, 168.9, 163.4, 148.8, 136.9, 133.2, 131.7, 130.6, 130.1, 129.7, 128.5, 127.9, 124.8, 112.1, 79.2, 61.7, 59.1, 32.6, 28.4, 14.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_6S$ $[M + H]^+$ *m/z* 469.1428, found: 469.1435.

Compound 13bj



Yield: 64.6 mg (67%), light brown solid.

Mp: 135-137 ºC.

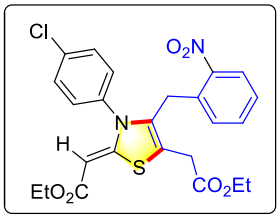
IR (neat): ν_{max} 2980, 2925, 1734, 1648, 1522, 1370, 1347, 1146, 1046, 722 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.51-7.48 (m, 1H), 7.34-7.31 (m, 1H), 7.27 (d, *J* = 6.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 2H), 4.60 (s, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.94 (s, 2H), 3.56 (s, 2H), 2.31 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.5, 168.9, 163.5, 148.8, 139.9, 134.1, 133.5, 133.2, 131.9, 130.6, 128.1, 127.8, 124.8, 111.8, 79.0, 61.7, 59.0, 32.6, 28.3, 21.2, 14.8, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{27}N_2O_6S$ $[M + H]^+$ *m/z* 483.1584, found: 483.1593.

Compound 13cj



Yield: 72.3 mg (72%), light brown solid.

Mp: 93-95 ºC.

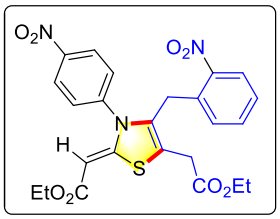
IR (neat): ν_{max} 2980, 2928, 1734, 1649, 1523, 1488, 1347, 1150, 1050, 770 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.52-7.49 (m, 1H), 7.37-7.34 (m, 1H), 7.24-7.22 (m, 3H), 6.77 (d, *J* = 8.5 Hz, 2H), 4.56 (s, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.95 (s, 2H), 3.55 (s, 2H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.5, 168.8, 163.2, 148.9, 136.0, 135.3, 133.3, 132.8, 131.4, 130.6, 130.4, 129.9, 128.2, 125.0, 112.4, 79.5, 61.8, 59.3, 32.6, 28.4, 14.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{24}ClN_2O_6S$ $[M + H]^+$*m/z* 503.1038, found: 503.1045.

Compound 13dj



Yield: 81.1 mg (79%), light brown solid.

Mp: 145-147 ºC.

IR (neat): ν_{max} 3107, 3088, 2980, 1732, 1648, 1596, 1516, 1490, 1346, 1277, 1146, 1048, 752 cm^{-1}.

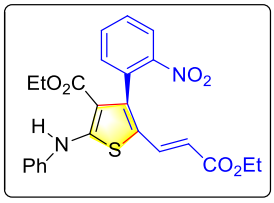
^1H NMR (500 MHz, $CDCl_3$) δ 8.15-8.12 (m, 2H), 7.72 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.53-7.50 (m, 1H), 7.39-7.35 (m, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.08-7.06 (m, 2H), 4.53 (s, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.96 (s, 2H), 3.56 (s, 2H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.3, 168.5, 162.4, 148.9, 147.9, 142.4, 133.4, 132.0, 130.8, 130.5, 130.0, 128.4, 125.4, 124.9, 113.2, 80.1, 61.8, 59.4, 32.4, 28.2, 14.7, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{24}N_3O_8S$ $[M + H]^+$ *m/z* 514.1279, found: 514.1283.

3.6 Procedure for the synthesis of ethyl (*E*)-5-(3-ethoxy-3-oxoprop-1-en-1-yl)-4-(2-nitrophenyl)-2-(phenylamino)thiophene-3-carboxylate (14aj). A 10 mL RB flask was charged DDQ (227.0 mg, 1.0 mmol) and 1,4-dioxane (2.0 mL). Subsequently, **11aj** (93.6 mg, 0.20 mmol) in 1,4-dioxane (2.0 mL) was added at 80 °C, and the mixture was stirred at the same temperature for 48 h, and the progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was quenched by adding $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). Then, the combined organic layer was washed with brine solution (20.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/ hexane (5:95)

Compound 14aj



Yield: 47.5 mg (51%), white solid.

Mp: 122-124 ºC.

IR (neat): ν_{max} 3315, 2925, 2851, 1697, 1657, 1604, 1552, 1515, 1408, 1345, 1240, 1193, 1029, 781 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.68-7.65 (m, 1H), 7.60-7.57 (m, 1H), 7.45-7.37 (m, 4H), 7.30 (d, *J* = 7.0 Hz, 1H), 7.21-7.18 (m, 2H), 5.91 (d, *J* = 15.5 Hz, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.94-3.88 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 3H), 0.79 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 167.0, 165.4, 160.8, 149.1, 140.6, 139.9, 135.5, 133.0, 132.6, 131.8, 129.9, 129.1, 125.0, 124.6, 120.4, 118.3, 114.6, 107.7, 60.4, 60.3, 14.4_0, 14.4_1 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{23}N_2O_6S$ $[M + H]^+$ *m/z* 467.1271, found 467.1278.

3.7 Scale-up experiments for 11aj, 12aj and 13aj

Synthesis of 11aj*:* A 25 mL RB flask was charged with *δ*-acetoxy allenoate **5j** (366.1 mg, 1.2 mmol), pyridine (16.0 mg, 0.20 mmol), K_2CO_3 (276.4 mg, 2.0 mmol) and toluene (5.0 mL). Subsequently, thioamide **3a** (223.1 mg, 1.0 mmol) in toluene (5.0 mL) was added at 25 °C, and the mixture was stirred at the same temperature for 12 h. The progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was quenched by adding water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). Then, the combined organic layer was washed with brine solution (25.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (5:95) as the eluent to obtain **11aj** (314.0 mg; 67%).

Synthesis of 12aj*:* A 25 mL RB flask was charged with *δ*-acetoxy allenoate **5j** (366.1 mg, 1.2 mmol), DABCO (22.4 mg, 0.20 mmol), K_2CO_3 (276.4 mg, 2.0 mmol) and toluene (5.0 mL). Subsequently, thioamide **3a** (223.1 mg, 1.0 mmol) in toluene (5.0 mL) was added at 25 °C and the mixture was stirred at the same temperature for 12 h. The progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was quenched by adding water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). Then the combined organic layer was washed with brine solution (25.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel

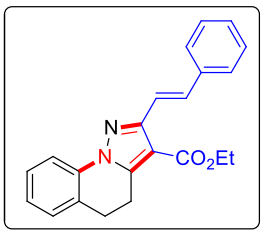
column chromatography using ethyl acetate/hexane (5:95) as the eluent to obtain **12aj** (323.0 mg; 69%).

Synthesis of 13aj*:* A 25 mL RB flask was charged with *δ*-acetoxy allenoate **5j** (366.1 mg, 1.2 mmol), TBAB (64.5 mg, 0.20 mmol), K_2CO_3 (276.4 mg, 2.0 mmol) and DCM (5.0 mL). Subsequently, thioamide **3a** (223.1 mg, 1.0 mmol) in DCM (5.0 mL) was added at 25 °C and the mixture was stirred at the same temperature for 6 h. The progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was quenched by adding water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). Then, the combined organic layer was washed with brine solution (25.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (5:95) as the eluent to obtain **13aj** (300.0 mg; 64%).

3.8 General procedure for the synthesis of compounds 15aa-ad, 15af, 15ag-ah, 15ak-an, 15ap, 15aq, 15ba, 15ca, 15da-dc, 15dm-dn, 15ea, 15em-en, 15ep, 15ga, 15gd, 15hb, 15hd, 15hh, 15hn,

and **15hp.** A Schlenk tube was charged with one of sulfonohydrazides **8** (0.20 mmol), DBU (0.20 mmol), and 1.0 mL of toluene. Subsequently, *δ*-acetoxy allenoate **5** (0.24 mmol) in toluene (1.0 mL) was added gradually over a period of 15 min at 110 °C (oil bath) and the mixture was stirred for the stipulated time (12.0-24.0 h) and progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was quenched by adding water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). Then the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/hexane (5:95) as the eluent.

Compound 15aa



Yield: 52.0 mg (76%), white solid.

Mp: 130-132 °C.

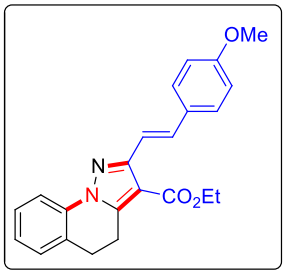
IR (neat): ν_{max} 3021, 2979, 2900, 1704, 1639, 1548, 1464, 1398, 1284, 1148, 1076, 749 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 16.5 Hz, 1H), 7.65 (d, *J* = 16.5 Hz, 1H), 7.61-7.59 (m, 2H), 7.39-7.36 (m, 3H), 7.30-7.27 (m, 2H), 7.22-7.19 (m, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.37 (t, *J* = 7.5 Hz, 2H), 3.00 (t, *J* = 7.5 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.1, 151.1, 143.8, 137.4, 135.9, 132.2, 128.8, 128.4, 128.1, 128.0, 127.1, 127.0, 126.3, 118.9, 116.9, 109.5, 60.3, 24.8, 21.6, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{21}N_2O_2$ $[M + H]^+$ *m/z* 345.1598, found 345.1599.

Compound 15ab



Yield: 61.0 mg (81%), white solid.

Mp: 120-122 °C.

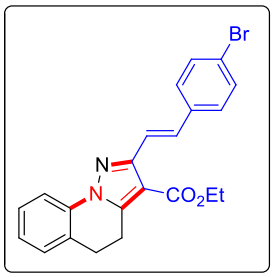
IR (neat): ν_{max} 3021, 2973, 2838, 1708, 1600, 1547, 1458, 1365, 1285, 1147, 1017, 749 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.60 (s, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.37-7.34 (m, 1H), 7.26-7.25 (m, 1H), 7.20-7.17 (m, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.36 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 3H), 3.35 (t, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.5 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.2, 159.7, 151.5, 143.7, 135.9, 131.8, 130.2, 128.4, 128.0, 126.9, 126.2, 116.8, 116.7, 114.2, 109.2, 60.2, 55.4, 24.8, 21.6, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}N_2O_3$ $[M + H]^+$ *m/z* 375.1703, found 375.1701.

Compound 15ac



Yield: 63.0 mg (75%), white solid.

Mp: 124-126 ºC.

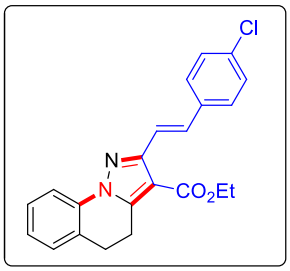
IR (neat): ν_{max} 2975, 2854, 1700, 1546, 1491, 1398, 1289, 1007, 811 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 16.5 Hz, 1H), 7.57 (d, *J* = 16.5 Hz, 1H), 7.50-7.44 (m, 4H), 7.39-7.36 (m, 1H), 7.28-7.26 (m, 1H), 7.23-7.20 (m, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.36 (t, *J* = 7.5 Hz, 2H), 3.00 (t, *J* = 7.5 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.1, 150.9, 143.8, 136.4, 135.9, 131.9, 130.9, 128.6, 128.5, 128.1, 127.0, 126.4, 121.9, 119.6, 116.9, 109.5, 60.3, 24.8, 21.7, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{20}{}^{79}BrN_2O_2$ $[M + H]^+$ *m/z* 423.0703, found 423.0706.

Compound 15ad



Yield: 56.0 mg (74%), white solid.

Mp: 136-138 ºC.

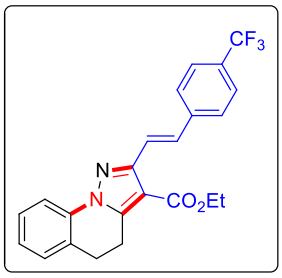
IR (neat): ν_{max} 3022, 2970, 1702, 1547, 1476, 1366, 1227, 1148, 1023, 759 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 16.5 Hz, 1H), 7.59 (d, *J* = 16.5 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.38-7.35 (m, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.27-7.26 (m, 1H), 7.22-7.19 (m, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 3.36 (t, *J* = 7.5 Hz, 2H), 3.00 (t, *J* = 7.5 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.0, 150.9, 143.8, 135.9, 135.8, 133.7, 130.8, 128.9, 128.5, 128.3, 128.0, 127.0, 126.4, 119.5, 116.9, 109.5, 60.3, 24.8, 21.6, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{20}ClN_2O_2$ [M + H]$^+$ *m/z* 379.1208, found 379.1202.

Compound 15af



Yield: 58.0 mg (70%), white solid.

Mp: 115-117 ºC.

IR (neat): ν_{max} 2923, 2851, 1706, 1613, 1553, 1479, 1324, 1227, 1162, 1016, 757 cm^{-1}.

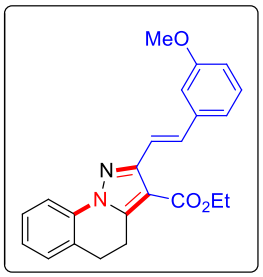
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 16.5 Hz, 1H), 7.69-7.67 (m, 3H), 7.64-7.60 (m, 2H), 7.39-7.36 (m, 1H), 7.28-7.27 (m, 1H), 7.23-7.20 (m, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.37 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.0, 150.6, 143.8, 140.9, 135.8, 130.5, 129.7 (q, $^{2}J_{C-F}$ = 33.0 Hz), 128.5, 128.1, 127.2, 127.0, 126.5 (q, $^{3}J_{C-F}$ = 4.1 Hz), 125.7, 124.4 (q, $^{1}J_{C-F}$ = 270.0 Hz), 121.3, 116.9, 109.7, 60.4, 24.7, 21.6, 14.6 ppm.

^{19}F NMR (475 MHz, $CDCl_3$): δ -62.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{20}F_3N_2O_2$ [M + H]$^+$ *m/z* 413.1471, found 413.1475.

Compound 15ag



Yield: 53.0 mg (71%), white solid.

Mp: 98-100 ºC.

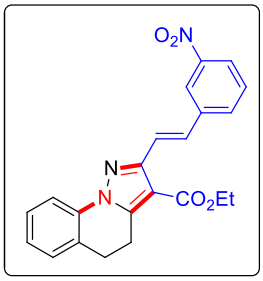
IR (neat): ν_{max} 2976, 2924, 1694, 1635, 1575, 1477, 1389, 1266, 1151, 1020, 752 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 16.5 Hz, 1H), 7.62 (d, *J* = 16.5 Hz, 1H), 7.39-7.36 (m, 1H), 7.30-7.27 (m, 2H), 7.22-7.19 (m, 2H), 7.14-7.11 (m, 1H), 6.84 (dd, *J* = 8.0, 2.5 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 3.37 (t, *J* = 7.5 Hz, 2H), 3.00 (t, *J* = 7.5 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.1, 160.0, 151.0, 143.8, 138.8, 135.8, 132.1, 129.7, 128.4, 128.0, 127.0, 126.3, 119.8, 119.2, 116.8, 114.0, 112.1, 109.5, 60.3, 55.4, 24.8, 21.6, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}N_2O_3$ $[M + H]^+$ *m/z* 375.1703, found 375.1701.

Compound 15ah



Yield: 52.0 mg (67%), white solid.

Mp: 156-158 ºC.

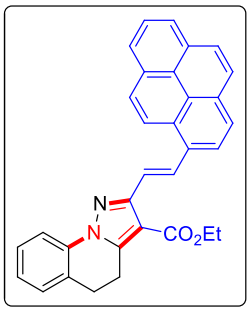
IR (neat): ν_{max} 2979, 2902, 1701, 1527, 1492, 1397, 1349, 1267, 1109, 1019, 758 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.88-7.85 (m, 2H), 7.67 (d, *J* = 16.5 Hz, 1H), 7.54-7.51 (m, 1H), 7.39-7.36 (m, 1H), 7.29-7.27 (m, 1H), 7.24-7.21 (m, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 3.37 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 1.46 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 163.9, 150.2, 148.9, 143.9, 139.2, 135.7, 132.7, 129.6, 129.5, 128.5, 128.1, 127.0, 126.6, 122.5, 121.9, 121.6, 116.9, 109.8, 60.5, 24.7, 21.6, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{20}N_3O_4$ $[M + H]^+$ *m/z* 390.1448, found 390.1444.

Compound 15ak



Yield: 61.0 mg (65%), white solid.

Mp: 150-152 ºC.

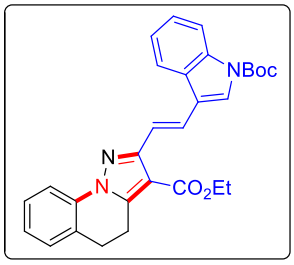
IR (neat): ν_{max} 2969, 2924, 1738, 1548, 1477, 1367, 1228, 1151, 1079, 756 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.78 (d, *J* = 16.5 Hz, 1H), 8.64 (d, *J* = 9.5 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.20-8.15 (m, 5H), 8.07-7.99 (m, 4H), 7.45-7.42 (m, 1H), 7.31-7.23 (m, 2H), 4.42 (q, *J* = 7.0 Hz, 2H), 3.42 (t, *J* = 7.5 Hz, 2H), 3.05 (t, *J* = 7.5 Hz, 2H), 1.46 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.2, 151.4, 143.9, 135.9, 131.9, 131.7, 131.3, 131.2, 129.0, 128.9, 128.5, 128.0, 127.7, 127.6, 127.5, 127.0, 126.4, 126.1, 125.4, 125.3, 125.2_1, 125.1_6, 125.1, 124.0, 123.5, 121.6, 117.0, 109.6, 60.3, 24.8, 21.7, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{32}H_{25}N_2O_2$ $[M + H]^+$ *m/z* 469.1911, found 469.1907.

Compound 15al



Yield: 70.5 mg (73%), white solid.

Mp: 122-124 ºC.

IR (neat): ν_{max} 2974, 2938, 1746, 1683, 1640, 1551, 1493, 1392, 1289, 1150, 1024, 752 cm^{-1}.

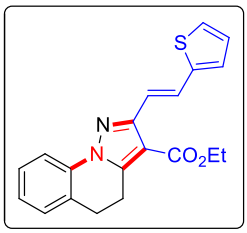
^1H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 6.5 Hz, 1H), 8.06-8.03 (m, 2H), 7.85 (d, *J* = 16.5 Hz, 1H), 7.78 (d, *J* = 16.5 Hz, 1H), 7.39-7.33 (m, 3H), 7.28-7.26 (m, 2H), 7.22-7.19

(m, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 3.38 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 1.69 (s, 9H), 1.48 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.2, 151.4, 149.6, 143.9, 136.4, 135.9, 128.8, 128.4, 128.0, 127.0, 126.3, 125.6, 124.9, 123.9, 123.2, 120.6, 119.2, 118.9, 116.9, 115.5, 109.2, 84.0, 60.3, 28.4, 24.8, 21.6, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{29}H_{30}N_3O_4$ $[M + H]^+$ *m/z* 484.2231, found 484.2233.

Compound 15am



Yield: 48.0 mg (69%), white solid.

Mp: 88-90 ºC.

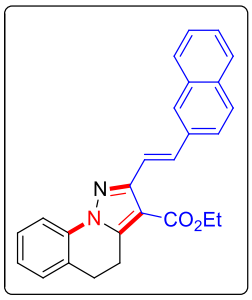
IR (neat): ν_{max} 2969, 29.24, 1703, 1591, 1550, 1477, 1367, 1286, 1149, 1022, 755 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 16.5 Hz, 1H), 7.53 (d, *J* = 16.5 Hz, 1H), 7.38-7.35 (m, 1H), 7.27-7.26 (m, 1H), 7.23 (d, *J* = 5.0 Hz, 1H), 7.22-7.19 (m, 1H), 7.15 (d, *J* = 3.5 Hz, 1H), 7.02 (dd, *J* = 5.0, 3.5 Hz, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 3.36 (t, *J* = 7.5 Hz, 2H), 2.99 (t, *J* = 7.5 Hz, 2H), 1.45 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.0, 150.7, 143.9, 143.0, 135.8, 128.5, 128.0, 127.8, 127.1, 127.0, 126.3, 125.3, 125.2, 118.4, 116.8, 109.4, 60.3, 24.8, 21.6, 14.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{20}H_{19}SN_2O_2$ $[M + H]^+$ *m/z* 351.1162, found 351.1155.

Compound 15an



Yield: 54.0 mg (68%), white solid.

Mp: 168-170 ºC.

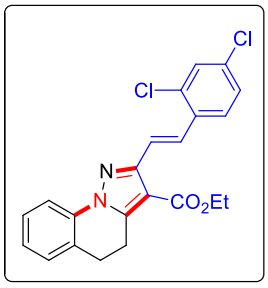
IR (neat): ν_{max} 3015, 2970, 2947, 1739, 1693, 1537, 1477, 1367, 1269, 1153, 1083, 742 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H), 7.89-7.80 (m, 6H), 7.49-7.44 (m, 2H), 7.40-7.37 (m, 1H), 7.29-7.27 (m, 1H), 7.23-7.21 (m, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 3.38 (t, *J* = 7.5 Hz, 2H), 3.02 (t, *J* = 7.5 Hz, 2H), 1.47 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.1, 151.2, 143.7, 135.9, 134.9, 133.8, 133.4, 132.2, 128.4, 128.3$_4$, 128.2$_6$, 128.0, 127.8, 127.5, 126.9, 126.4, 126.3, 126.1, 123.9, 119.2, 116.9, 109.4, 60.3, 24.7, 21.6, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{26}H_{23}N_2O_2$ $[M + H]^+$ *m/z* 395.1754, found 395.1753.

Compound 15ap



Yield: 56.0 mg (68%), white solid.

Mp: 128-130 ºC.

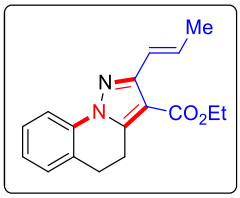
IR (neat): ν_{max} 2969, 1737, 1586, 1550, 1476, 1367, 1260, 1152, 1021, 756 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 16.5 Hz, 1H), 7.73-7.69 (m, 2H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.39-7.36 (m, 1H), 7.28-7.26 (m, 1H), 7.24-7.20 (m, 2H), 4.37 (q, *J* = 7.0 Hz, 2H), 3.36 (t, *J* = 7.5 Hz, 2H), 3.00 (t, *J* = 7.5 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.0, 150.5, 143.7, 135.7, 134.4, 134.1, 133.9, 131.2, 129.7, 128.4, 128.0, 127.8, 127.4, 126.9, 126.5, 121.9, 117.0, 109.7, 60.3, 24.7, 21.6, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{19}Cl_2N_2O_2$ $[M + H]^+$ *m/z* 413.0818, found 413.0815.

Compound 15aq



Yield: 23.0 mg (41%), yellow colored liquid.

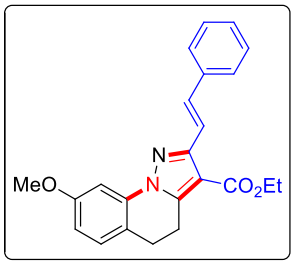
IR (neat): ν_{max} 2969, 2928, 1738, 1548, 1492, 1366, 1230, 1149, 1076, 755 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): (purity ca 85%) δ 7.97 (d, *J* = 7.5 Hz, 1H), 7.37-7.34 (m, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.21-7.18 (m, 1H), 7.01-6.97 (m, 1H), 6.82-6.76 (m, 1H), 4.38-4.34 (m, 2H), 3.35 (t, *J* = 7.5 Hz, 2H), 2.99 (t, *J* = 7.5 Hz, 2H), 1.96 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.42 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.2, 151.5, 143.5, 135.9, 130.6, 128.4, 127.9, 126.8, 126.1, 121.7, 116.7, 108.6, 60.1, 24.8, 21.6, 18.8, 14.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{19}N_2O_2$ $[M + H]^+$ *m/z* 283.1441, found 283.1440.

Compound 15ba



Yield: 53.0 mg (71%), white solid.

Mp: 102-104 ºC.

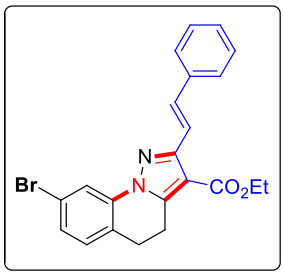
IR (neat): ν_{max} 3011, 2969, 2939, 1738, 1627, 1578, 1446, 1369, 1229, 1159, 1040, 762 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 16.5 Hz, 1H), 7.65 (d, *J* = 16.5 Hz, 1H), 7.61-7.60 (m, 3H), 7.39-7.36 (m, 2H), 7.30-7.27 (m, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.76 (dd, *J* = 8.0, 2.5 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.91 (s, 3H), 3.34 (t, *J* = 7.5 Hz, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.1, 159.6, 151.1, 144.0, 137.4, 136.5, 132.2, 129.2, 128.7, 128.1, 127.1, 118.9, 112.7, 109.6, 102.3, 60.3, 55.8, 24.0, 21.9, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}N_2O_3$ $[M + H]^+$ *m/z* 375.1703, found 375.1702.

Compound 15ca



Yield: 65.0 mg (77%), white solid.

Mp: 102-104 ºC.

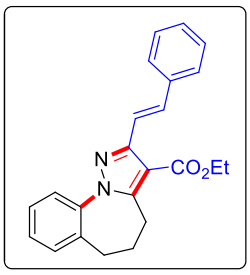
IR (neat): ν_{max} 3011, 2969, 2939, 1738, 1627, 1578, 1446, 1369, 1229, 1159, 1040, 762 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 16.5 Hz, 1H), 7.65 (d, *J* = 16.5 Hz, 1H), 7.61-7.60 (m, 3H), 7.39-7.36 (m, 2H), 7.30-7.27 (m, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.76 (dd, *J* = 8.0, 2.5 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.91 (s, 3H), 3.34 (t, *J* = 7.5 Hz, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.1, 159.6, 151.1, 144.0, 137.4, 136.5, 132.2, 129.2, 128.7, 128.1, 127.1, 118.9, 112.7, 109.6, 102.3, 60.3, 55.8, 24.0, 21.9, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}N_2O_3$ $[M + H]^+$ *m/z* 375.1703, found 375.1702.

Compound 15da



Yield: 46.6 mg (65%), white solid.

Mp: 82-84 ºC.

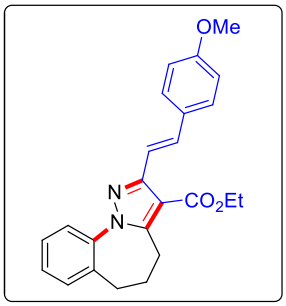
IR (neat): ν_{max} 2970, 2923, 2865, 1738, 1545, 1431, 1366, 1238, 1178, 1013, 760 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.76-7.71 (m, 2H), 7.61-7.57 (m, 3H), 7.45-7.42 (m, 1H), 7.37-7.27 (m, 5H), 4.39 (q, *J* = 7.0 Hz, 2H), 3.03 (t, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 7.0 Hz, 2H), 2.32-2.27 (m, 2H), 1.45 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.4, 150.9, 147.9, 139.1, 137.5, 134.4, 131.8, 129.8, 128.7, 128.3, 128.1, 128.0, 127.1, 124.0, 119.1, 109.7, 60.2, 30.8, 30.7, 22.2, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}N_2O_2$ [M + H]$^+$ *m/z* 359.1754, found 359.1758.

Compound 15db



Yield: 53.0 mg (68%), white solid.

Mp: 118-120 ºC.

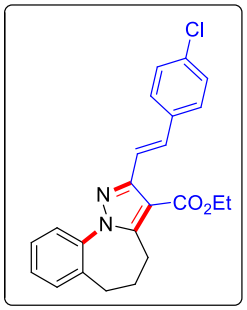
IR (neat): ν_{max} 2961, 1739, 1532, 1454, 1327, 1256, 1172, 1013, 790 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 16.5 Hz, 1H), 7.56-7.51 (m, 3H), 7.45-7.41 (m, 1H), 7.35-7.30 (m, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 3H), 3.02 (t, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 7.0 Hz, 2H), 2.32-2.26 (m, 2H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.5, 159.7, 151.2, 147.8, 139.1, 134.4, 131.4, 130.3, 129.7, 128.3, 128.2, 128.0, 124.0, 116.9, 114.2, 109.5, 60.2, 55.4, 30.7, 30.6, 22.2, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_3$ [M + H]$^+$ *m/z* 389.1860, found 389.1857.

Compound 15dc



Yield: 49.0 mg (63%), white solid.

Mp: 95-97 ºC.

IR (neat): ν_{max} 2961, 1739, 1532, 1454, 1327, 1256, 1172, 1013, 790 cm^{-1}.

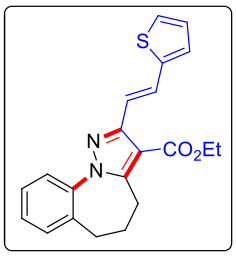
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 16.5 Hz, 1H), 7.56-7.51 (m, 3H), 7.45-7.41 (m, 1H), 7.35-7.30 (m, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.38 (q, *J* =

7.0 Hz, 2H), 3.83 (s, 3H), 3.02 (t, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 7.0 Hz, 2H), 2.32-2.26 (m, 2H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.4, 159.7, 151.2, 147.8, 139.1, 134.4, 131.4, 130.3, 129.7, 128.3, 128.2, 128.0, 124.0, 116.9, 114.2, 109.5, 60.2, 55.4, 30.7, 30.6, 22.2, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{22}ClN_2O_2$ $[M + H]^+$ *m/z* 393.1364, found 393.1368.

Compound 15dm



Yield: 40.0 mg (55%), white solid.

Mp: 106-108 ºC.

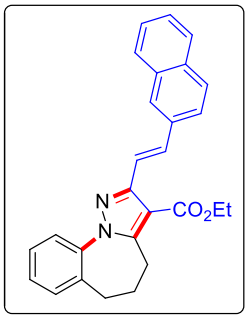
IR (neat): ν_{max} 3064, 2931, 2864, 1683, 1630, 1581, 1491, 1363, 1244, 1142, 1014, 763 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72-7.69 (m, 2H), 7.54 (d, *J* = 16.5 Hz, 1H), 7.44-7.41 (m, 1H), 7.34-7.32 (m, 2H), 7.22 (d, *J* = 3.5 Hz, 1H), 7.11-7.09 (m, 1H), 6.99-7.00 (m, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.02 (t, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.30-2.28 (m, 2H), 1.47 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.4, 150.5, 148.1, 143.1, 139.1, 134.4, 129.8, 128.3, 128.0, 127.7, 127.0, 125.0, 124.9, 123.9, 118.7, 109.6, 60.3, 30.7, 30.6, 22.1, 14.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{21}H_{21}N_2O_2S$ $[M + H]^+$ *m/z* 365.1318, found 365.1317.

Compound 15dn



Yield: 39.0 mg (48%), white solid.

Mp: 115-117 ºC.

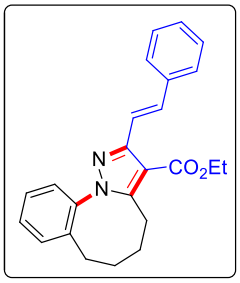
IR (neat): ν_{max} 3050, 2982, 2864, 1698, 1635, 1469, 1399, 1269, 1140, 1016, 751 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.91-7.74 (m, 8H), 7.48-7.44 (m, 3H), 7.37-7.32 (m, 2H), 4.42 (q, *J* = 7.0 Hz, 2H), 3.04 (t, *J* = 7.0 Hz, 2H), 2.64 (t, *J* = 7.0 Hz, 2H), 2.323-2.29 (m, 2H), 1.47 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 163.5, 150.0, 146.9, 138.1, 134.0, 133.4, 132.8, 132.4, 130.9, 128.8, 127.3_4, 127.2_8, 127.0, 126.8, 126.4, 125.4, 125.1, 123.0, 122.9, 118.4, 108.7, 59.3, 29.7, 29.6, 21.3, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{27}H_{25}N_2O_2$ $[M + H]^+$ *m/z* 409.1911, found 409.1912.

Compound 15ea



Yield: 39.0 mg (53%), white solid.

Mp: 104-106 ºC.

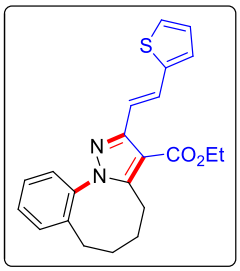
IR (neat): ν_{max} 3056, 2925, 2850, 1681, 1536, 1497, 1344, 1277, 1133, 1016, 742 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 16.5 Hz, 1H), 7.58-7.55 (m, 3H), 7.51 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.44-7.40 (m, 1H), 7.39-7.33 (m, 3H), 7.27-7.24 (m, 2H), 4.41-4.34 (m, 2H), 3.59 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.82 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.12-1.98 (m, 4H), 1.72-1.64 (m, 1H), 1.54-1.48 (m, 1H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.4, 151.1, 150.7, 140.2, 137.5, 137.1, 131.8, 130.5, 129.8, 128.7, 128.0, 127.4, 127.0, 126.7, 119.1, 108.9, 60.1, 30.9, 29.0, 27.3, 24.3, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_2$ $[M + H]^+$ *m/z* 373.1911, found 373.1910.

Compound 15em



Yield: 32.0 mg (42%), white solid.

Mp: 125-127ºC.

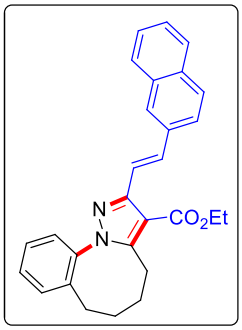
IR (neat): ν_{max} 2933, 2854, 1702, 1535, 1469, 1277, 1133, 1105, 763 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 16.0 Hz, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 7.51 (d, *J* = 6.5 Hz, 1H), 7.45-7.43 (m, 1H), 7.40-7.38 (m, 1H), 7.37-7.35 (m, 1H), 7.23 (d, *J* = 5.0 Hz, 1H), 7.12 (d, *J* = 3.5 Hz, 1H), 7.02-7.00 (m, 1H), 4.42-4.38 (m, 2H) 3.62 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.84 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.17-2.00 (m, 4H), 1.74-1.65 (m, 1H), 1.53-1.48 (m, 1H) 1.47 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.3, 150.8, 150.7, 143.1, 140.1, 137.0, 130.5, 129.8, 127.7, 127.4, 127.0, 126.6, 125.0, 124.9, 118.7, 108.7, 60.2, 30.8, 29.0, 27.2, 24.2, 14.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{23}N_2O_2S$ $[M + H]^+$ *m/z* 379.1475 found 379.1479.

Compound 15en



Yield: 33.0 mg (39%), white solid.

Mp: 102-104 ºC.

IR (neat): ν_{max} 3053, 2923, 2852, 1701, 1637, 1530, 1469, 1365, 1265, 1133, 1017, 769 cm^{-1}.

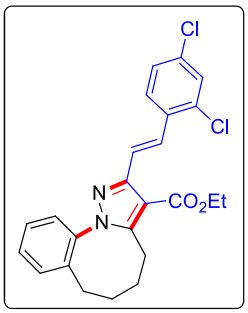
^1H NMR (500 MHz, $CDCl_3$): δ 7.94-7.90 (m, 2H), 7.85-7.81 (m, 4H), 7.76 (d, *J* = 16.5 Hz, 1H), 7.56-7.55 (m, 1H), 7.50-7.37 (m, 5H), 4.47-4.39 (m, 2H), 3.63 (dd, *J* = 13.5, 7.5

Hz, 1H), 2.86 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.20-2.03 (m, 4H), 1.76-1.68 (m, 1H), 1.55-1.51 (m, 1H), 1.48 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.4, 151.2, 150.7, 140.2, 137.1, 135.1, 133.8, 133.4, 131.9, 130.5, 129.8, 128.3_2, 128.2_8, 127.8, 127.4, 127.3, 126.7, 126.3, 126.1, 124.0, 119.5, 108.9, 60.1, 30.9, 29.0, 27.3, 24.3, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{28}H_{27}N_2O_2$ $[M + H]^+$ *m/z* 423.2067, found 423.2066.

Compound 15ep



Yield: 38.0 mg (43%), white solid.

Mp: 124-126 ºC.

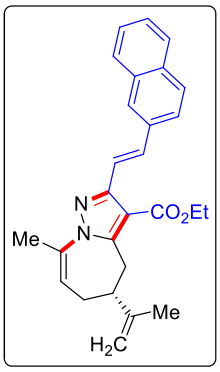
IR (neat): ν_{max} 2927, 2854, 1701, 1544, 1492, 1384, 1263, 1140, 1048, 762 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 16.0 Hz, 1H), 7.74 (d, *J* = 16.0 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H) 7.44-7.41 (m, 1H), 7.39-7.37 (m, 1H), 7.35-7.33 (m, 1H), 7.25 (d, *J* = 1.5 Hz, 1H), 7.23 (d, *J* = 1.5 Hz, 1H), 4.39-4.32 (m, 2H), 3.57 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.82 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.16-1.99 (m, 4H), 1.71-1.63 (m, 1H), 1.54-1.46 (m, 1H), 1.41 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.3, 150.7, 150.6, 140.1, 137.0, 134.4, 134.3, 133.8, 130.5, 129.9, 129.7, 127.9, 127.4 (2 s), 126.7 (2 s), 122.4, 109.1, 60.2, 30.9, 29.0, 27.3, 24.4, 14.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{23}Cl_2N_2O_2$ $[M + H]^+$ *m/z* 441.1131, found 441.1135.

Compound 15fn



Yield: 54.0 mg (65%), white solid.

Mp: 96-94 ºC.

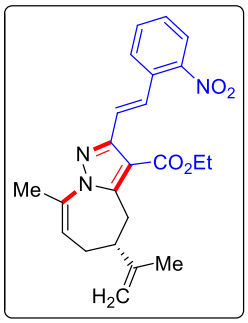
IR (neat): ν_{max} 2961, 2923, 2852, 1736, 1703, 1444, 1372, 1240, 1104, 1044, 746 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.85-7.78 (m, 5H), 7.68 (d, *J* = 16.5 Hz, 1H), 7.48-7.43 (m, 2H), 5.79 (t, *J* = 14.0 Hz, 1H), 4.81-4.77 (m, 2H), 4.38 (q, *J* = 6.5 Hz, 2H), 3.39 (dd, *J* = 14.0, 6.5 Hz, 1H), 3.07-3.02 (m, 1H), 2.92 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.33 (s, 3H), 2.11 (t, *J* = 6.5 Hz, 2H), 1.80 (s, 3H), 1.44 (t, *J* = 7.0 Hz 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.4, 150.2, 148.1, 147.9, 136.8, 135.0, 133.8, 133.3, 131.7, 128.3 (2 s), 127.8, 127.3, 126.4, 126.1, 123.9, 119.6, 119.0, 110.2, 109.4, 60.2, 51.3, 29.9, 28.5, 21.2, 20.0, 14.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{27}H_{29}N_2O_2$ $[M + H]^+$ *m/z* 413.2224, found 413.2223.

Compound 15fj



Yield: 43.0 mg (53%), gummy liquid.

IR (neat): ν_{max} 2976, 2923, 2862, 1701, 1604, 1521, 1481, 1440, 1343, 1228, 1105, 894, 784 cm^{-1}.

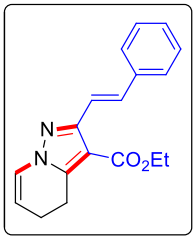
^1H NMR (500 MHz, $CDCl_3$): δ 7.94-7.91 (m, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 16.0 Hz, 1H), 7.60-7.57 (m, 1H), 7.42-7.39 (m, 1H), 5.78 (t, *J* = 6.0 Hz, 1H), 4.81-4.76

(m, 2H), 4.34 (q, *J* = 7.0 Hz, 2H) 3.36 (dd, *J* = 13.5, 6.0 Hz, 1H), 3.04-3.01 (m, 1H), 2.91 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.30 (s, 3H), 2.10 (t, *J* = 6.5 Hz, 2H), 1.79 (s, 3H), 1.39 (t, *J* = 7.0 Hz 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.3, 149.3, 148.4, 148.1, 147.9, 136.9, 133.1 (2 s), 128.6, 128.2, 126.2, 124.7, 124.5, 119.1, 110.3, 109.7, 60.2, 51.2, 29.9, 28.6, 21.1, 20.0, 14.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{26}N_3O_4$ $[M + H]^+$ *m/z* 408.1918, found 408.1919.

Compound 15ga



Yield: 40.0 mg (68%), white solid.

Mp: 83-85 °C.

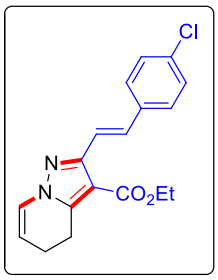
IR (neat): ν_{max} 3056, 2978, 2929, 1704, 1465, 1253, 1132, 1096, 789 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 16.5 Hz, 1H), 7.58 (d, *J* = 6.5 Hz, 2H), 7.50 (d, *J* = 16.5 Hz, 1H), 7.37-7.29 (m, 3H), 7.03 (d, *J* = 6.5 Hz, 1H), 5.62 (s, 1H), 4.38-4.36 (m, 2H), 3.27 (t, *J* = 8.0 Hz, 2H), 2.45 (s, 2H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.0, 150.4, 142.2, 137.3, 131.6, 128.7, 128.1, 127.1, 126.5, 118.7, 113.8, 109.2, 60.2, 20.9, 19.2, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{19}N_2O_2$ $[M + H]^+$ *m/z* 295.1441, found 295.1442.

Compound 15gd



Yield: 40.0 mg (61%), white solid.

Mp: 89-91 °C.

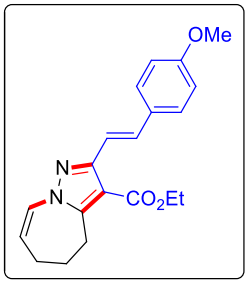
IR (neat): ν_{max} 3073, 2972, 2938, 1691, 1548, 1468, 1315, 1257, 1222, 1095, 734 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 16.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 16.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H) 7.01-6.99 (m, 1H), 5.62-5.59 (m, 1H), 4.34 (q, *J* = 7.0 Hz, 2H), 3.25 (t, *J* = 8.5 Hz, 2H), 2.45-2.40 (m, 2H), 1.41 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.0, 150.2, 142.1, 135.9, 133.7, 130.3, 128.9, 128.2, 126.4, 119.3, 114.0, 109.2, 60.3, 20.9, 19.2, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{18}ClN_2O_2$ $[M + H]^+$ *m/z* 329.1051, found 329.1053.

Compound 15hb



Yield: 41.0 mg (60%), white solid.

Mp: 96-98 °C.

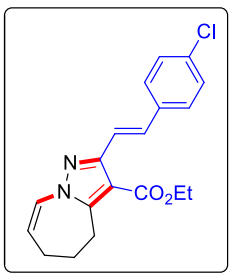
IR (neat): ν_{max} 2999, 2935, 2831, 1689, 1510, 1468, 1292, 1272, 1131, 1088, 792 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.46 (m, 3H), 7.39 (d, *J* = 16.5 Hz, 1H), 6.97-6.95 (m, 1H), 6.89 (d, *J* = 8.5 Hz, 2H) 5.42-5.38 (m, 1H), 4.35 (q, *J* = 7.0 Hz, 2H), 3.82 (s, 3H), 3.33-3.31 (m, 2H), 2.47-2.45 (m, 2H), 2.01-1.98 (m, 2H), 1.43 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 164.5, 159.7, 150.5, 149.0, 131.3, 130.2, 128.3, 128.1, 117.3, 117.0, 114.2, 109.8, 60.2, 55.4, 30.2, 25.4, 23.8, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{20}H_{23}N_2O_3$ $[M + H]^+$ *m/z* 339.1703, found 339.1703.

Compound 15hd



Yield: 39.0 mg (57%), white solid.

Mp: 118-120 °C.

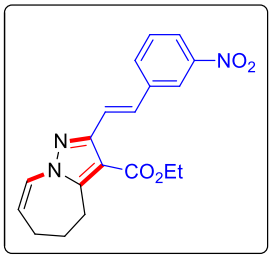
IR (neat): ν_{max} 3082, 2974, 2930, 1700, 1527, 1467, 1349, 1274, 1128, 1087, 737 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 16.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 16.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.97-6.94 (m, 1H), 5.44-5.40 (m, 1H) 4.35 (q, *J* = 7.0 Hz, 2H), 3.33-3.31 (m, 2H), 2.49-2.45 (m, 2H), 2.02-1.97 (m, 2H), 1.42 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.3, 149.9, 149.0, 135.9, 133.6, 130.4, 128.9, 128.1, 128.0, 119.7, 117.7, 110.0, 60.3, 30.3, 25.3, 23.7, 14.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{19}ClN_2O_2$ $[M + H]^+$ *m/z* 343.1208, found 343.1211.

Compound 15hh



Yield: 42.0 mg (59%), white solid.

Mp: 102-104 °C.

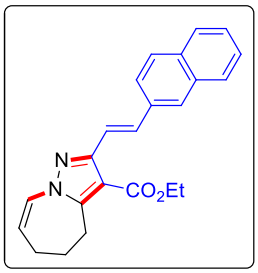
IR (neat): ν_{max} 3079, 2980, 2930, 1700, 1527, 1467, 1349, 1274, 1128, 1087, 737 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.11-8.10 (m, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 16.5 Hz, 1H), 7.53-7.46 (m, 2H), 6.98-6.96 (m, 1H), 5.47-5.43 (m, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 3.35-3.33 (m, 2H), 2.49-2.48 (m, 2H), 2.03-1.98 (m, 2H), 1.45 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.1, 149.2, 149.1, 148.8, 139.2, 132.7, 129.6, 129.0, 128.0, 122.4, 122.2, 121.3, 118.0, 110.2, 60.5, 30.3, 25.3, 23.7, 14.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{20}N_3O_4$ $[M + H]^+$ *m/z* 354.1448, found 354.1448.

Compound 15hn



Yield: 40.0 mg (55%), white solid.

Mp: 108-110 °C.

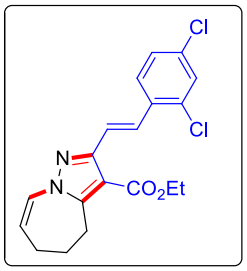
IR (neat): ν_{max} 2932, 2870, 1689, 1509, 1464, 1332, 1176, 1132, 1090, 851 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.83-7.80 (m, 3H), 7.77-7.73 (m, 2H), 7.61 (d, *J* = 16.5 Hz, 1H), 7.48-7.43 (m, 2H), 7.01-6.99 (m, 1H), 5.45-5.42 (m, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.36-3.33 (m, 2H), 2.49-2.47 (m, 2H), 2.03-1.98 (m, 2H), 1.46 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.4, 150.2, 149.0, 134.9, 133.8, 133.3, 131.8, 128.3, 128.2, 128.1, 127.8, 127.4, 126.4, 126.1, 123.8, 119.4, 117.5, 110.0, 60.3, 30.2, 25.4, 23.7, 14.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}N_2O_2$ $[M + H]^+$ *m/z* 359.1754, found 359.1754.

Compound 15hp



Yield: 39.0 mg (52%), white solid.

Mp: 110-112 °C.

IR (neat): ν_{max} 2926, 2856, 1702, 1471, 1446, 1384, 1148, 1086, 1048, 811 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 16.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 16.5 Hz, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 8.5, 2.0 Hz 1H), 7.00-6.97 (m, 1H), 5.45-5.41 (m, 1H), 4.34 (q, *J* = 7.0 Hz, 2H), 3.33-3.31 (m, 2H), 2.49-2.45 (m, 2H), 2.02-1.97 (m, 2H), 1.40 (t, *J* = 7.0 Hz, 3H) ppm.

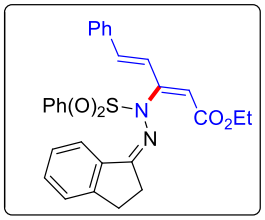
^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 164.2, 149.6, 149.0, 134.4, 134.2, 133.8, 129.7, 128.1, 127.7, 127.4, 126.6, 122.2, 117.7, 110.1, 60.3, 30.3, 25.4, 23.7, 14.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{19}Cl_2N_2O_2$ *m/z* $[M + H]^+$377.0818, found 377.0817.

3.9 General procedure for the synthesis of compounds 16aa and 16db. A Schlenk tube was charged with one of the sulfonohydrazides **8** (0.20 mmol), DBU (0.20 mmol) and 1.0 mL of toluene. Subsequently, *δ*-acetoxy allenoate **5** (0.24 mmol) in toluene (1.0 mL) was added

gradually over a period of 15 min at the 25 °C (oil bath), the mixture was stirred for the stipulated time (6.0 h), and the progress of the reaction was monitored using TLC. After consumption of sulfonohydrazide, the mixture was quenched by adding water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). Then the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/hexane (5:95) mixture as the eluent.

Compound 16aa



Yield: 77.0 mg (79%), white solid.

Mp: 125-127 ºC.

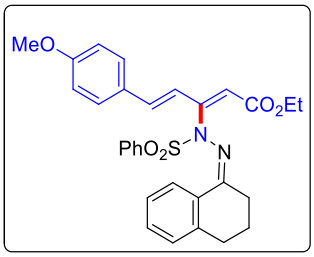
IR (neat): ν_{max} 3066, 2962, 1700, 1635, 1581, 1470, 1373, 1260, 1171, 1041, 759 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 16.0 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.70-7.67 (m, 1H), 7.59-7.56 (m, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.44-7.40 (m, 2H), 7.37-7.28 (m, 5H), 5.22 (s, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.04-3.02 (m, 2H), 2.91-2.88 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 176.7, 166.1, 154.1, 150.4, 139.5, 137.4, 136.2, 133.8_3, 133.7_5, 132.4, 130.5, 129.4, 128.9, 128.4, 128.1, 127.3, 125.8, 123.0, 122.4, 116.2, 60.5, 30.4, 28.9, 14.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{28}H_{27}N_2O_4S$ [M + H *m/z*]$^+$487.1686, found 487.1684.

Compound 16db



Yield: 76.0 mg (72%), gummy liquid.

IR (neat): ν_{max} 3059, 2929, 2840, 1734, 1606, 1510, 1445, 1370, 1250, 1172, 1124, 1028, 729 cm^{-1}.

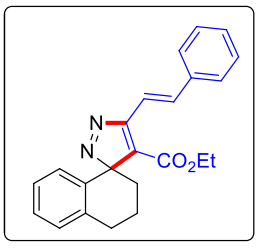
^1H NMR (500 MHz, $CDCl_3$): δ 8.06-7.98 (m, 4H), 7.69-7.66 (m, 1H), 7.58-7.54 (m, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 16.5 Hz, 1H), 7.35-7.32 (m, 1H), 7.23-7.22 (m, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.09 (s, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 3H), 2.78-2.75 (m, 4H), 1.89-1.87 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 168.6, 166.3, 160.8, 155.1, 141.6, 139.3, 133.8, 133.7, 131.6, 131.1, 130.5, 129.7, 129.1, 128.9, 128.3, 126.6, 126.0, 120.0, 114.5, 114.3, 60.4, 55.5, 29.6, 29.2, 22.1, 14.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{30}H_{31}N_2O_5S$ $[M + H]^+$ *m/z* 531.1948, found 531.1947.

3.10 General procedure for the synthesis of compounds 17da-db and **17dh.** A Schlenk tube was charged with one of sulfonohydrazides **8** (0.20 mmol), DBU (0.20 mmol) and 1.0 mL of toluene. Subsequently, *δ*-acetoxy allenoate **5** (0.24 mmol) in toluene (1.0 mL) was added gradually over a period of 15 min at the 80 °C (oil bath), the mixture was stirred for the stipulated time (3.0 h), and progress of the reaction was monitored using TLC. After consumption of sulfonohydrazide, the mixture was quenched by adding water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). Then the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/hexane (5:95) as the eluent.

Compound 17da



Yield: 52.0 mg (73%), white solid.

Mp: 101-103 ºC.

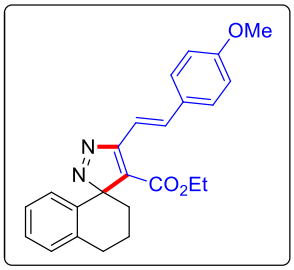
IR (neat): ν_{max} 2929, 2862, 1699, 1622, 1587, 1491, 1390, 1273, 1189, 1033, 745 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (d, *J* = 16.5 Hz, 1H), 7.87 (d, *J* = 16.5 Hz, 1H), 7.70 (d, *J* = 7.0 Hz, 2H), 7.47-7.39 (m, 3H), 7.28-7.27 (m, 1H), 7.22-7.20 (m, 1H), 7.00-6.97 (m, 1H), 6.30 (d, *J* = 7.5 Hz, 1H), 4.22-4.18 (m, 2H), 3.11-3.06 (m, 2H), 2.64-2.54 (m, 2H), 2.20-2.13 (m, 1H), 1.70-1.64 (m, 1H), 1.20 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.5, 157.6, 141.4, 138.3, 137.0, 136.3, 130.4, 129.8, 129.1, 128.4, 128.3, 127.9, 126.4, 125.4, 117.8, 101.5, 61.0, 31.6, 30.0, 21.8, 14.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}N_2O_2$ $[M + H]^+$ *m/z* 359.1754, found 359.1759.

Compound 17db



Yield: 60.0 mg (77%), white solid.

Mp: 113-115 ºC.

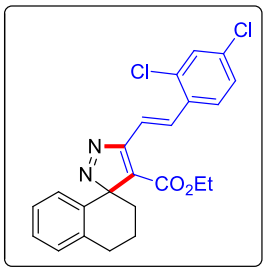
IR (neat): ν_{max} 2926, 2834, 1696, 1591, 1440, 1371, 1275, 1187, 1032, 759 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, *J* = 16.5 Hz, 1H), 7.71 (d, *J* = 16.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.26-7.24 (m, 1H), 7.19-7.17 (m, 1H), 6.97-6.94 (m, 3H), 6.28 (d, *J* = 7.5 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 3.11-3.05 (m, 2H), 2.57-2.51 (m, 2H), 2.15-2.11 (m, 1H), 1.64-1.62 (m, 1H), 1.17 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.7, 161.2, 158.2, 141.1 138.3, 135.5, 130.4, 129.5, 129.2, 128.6, 128.3, 126.4, 125.5, 115.7, 114.6, 101.4, 60.8, 55.5, 31.7, 30.0, 21.8, 14.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}N_2O_3$ $[M + H]^+$ *m/z* 389.1860, found 389.1859.

Compound 17dh



Yield: 58.0 mg (68%), white solid.

Mp: 105-107 ºC.

IR (neat): ν_{max} 2968, 2924, 2852, 1738, 1580, 1442, 1368, 1228, 1102, 965, 760 cm^{-1}.

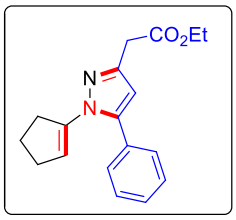
^1H NMR (500 MHz, $CDCl_3$): δ 8.71 (d, *J* = 16.5 Hz, 1H), 7.82 (d, *J* = 16.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 1.5 Hz, 1H), 7.32 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.26-7.25 (m, 1H), 7.21-7.18 (m, 1H), 6.98-6.95 (m, 1H), 6.26 (d, *J* = 8.0 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.12-3.04 (m, 2H), 2.58-2.50 (m, 2H), 2.16-2.14 (m, 1H), 1.65-1.63 (m, 1H), 1.15 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 162.3, 157.1, 138.7, 138.3, 135.8, 135.7, 135.5, 133.1, 130.5, 130.2, 128.5, 128.1, 127.7, 126.3, 125.4, 120.5, 101.8, 61.1, 31.2, 30.0, 21.8, 14.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{21}Cl_2N_2O_2$ $[M + H]^+$ *m/z* 427.0975, found 427.0978.

3.11 General procedure for the synthesis of compounds 18ia-ii, 18ik-im, 18iq-ir, 18ja-jb, 18ka, 18kg and **18la.** A Schlenk tube was charged with one of sulfonohydrazides **8** (0.20 mmol), DBU (0.20 mmol), and 1.0 mL of acetonitrile. Subsequently, *δ*-acetoxy allenoate **5** (0.24 mmol) in acetonitrile (1.0 mL) was added gradually over a period of 15 min at 80 °C (oil bath) and the mixture was stirred for 6 h, and progress of the reaction was monitored using TLC. After the consumption of sulfonohydrazide, the mixture was quenched by adding water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). Then the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/hexane (10:90) as the eluent.

Compound 18ia



Yield: 48.0 mg (81%), white solid.

Mp: 54-56 ºC.

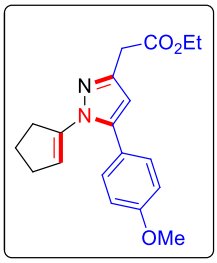
IR (neat): ν_{max} 2970, 2920, 1733, 1601, 1558, 1465, 1373, 1192, 1027, 767, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.84-7.82 (m, 2H), 7.42-7.39 (m, 2H), 7.33-7.30 (m, 1H), 6.62 (s, 1H), 5.72-5.70 (m, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 2H), 2.97-2.93 (m, 2H), 2.61-2.56 (m, 2H), 2.11-2.05 (m, 2H), 1.30 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.4, 151.0, 141.0, 136.8, 133.3, 128.6, 127.9, 125.8, 119.5, 105.3, 61.5, 33.8, 33.0, 31.4, 22.0, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{21}N_2O_2$ $[M + H]^+$ *m/z* 297.1598, found 297.1600.

Compound 18ib



Yield: 55.4 mg (85%), white solid.

Mp: 50-52 ºC.

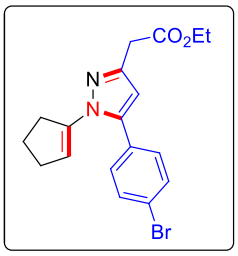
IR (neat): ν_{max} 2928, 2843, 1732, 1613, 1523, 1451, 1246, 1174, 1027, 835, 796 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.52 (s, 1H), 5.67 (s, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 2H), 2.96-2.88 (m, 2H), 2.59-2.51 (m, 2H), 2.08-2.04 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.4, 159.6, 150.8, 141.1, 136.7, 127.1, 126.1, 119.3, 114.1, 104.8, 61.5, 55.4, 33.8, 33.0, 31.4, 22.0, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{23}N_2O_3$ $[M + H]^+$ *m/z* 327.1703, found 327.1704.

Compound 18ic



Yield: 59.0 mg (79%), gummy liquid.

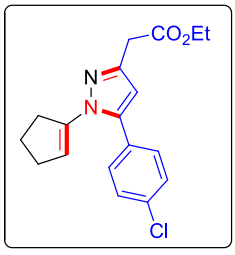
IR (neat): ν_{max} 2925, 2851, 1736, 1649, 1503, 1410, 1367, 1258, 1164, 1009, 832, 721 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 6.57 (s, 1H), 5.70-5.69 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.80 (s, 2H), 2.93-2.90 (m, 2H), 2.58-2.54 (m, 2H), 2.09-2.03 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.3, 149.9, 140.9, 137.0, 132.2, 131.8, 127.4, 121.8, 119.9, 105.2, 61.6, 33.8, 32.9, 31.4, 22.0, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{20}BrN_2O_2$ $[M + H]^+$ *m/z* 375.0703, found 375.0701.

Compound 18id



Yield: 51.0 mg (77%), gummy liquid.

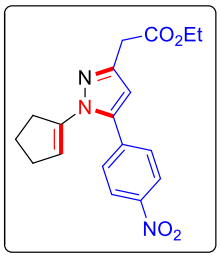
IR (neat): ν_{max} 2977, 2928, 1735, 1604, 1507, 1439, 1370, 1257, 1193, 1014, 836, 737 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.75-7.73 (m, 2H), 7.35-7.34 (m, 2H), 6.57 (s, 1H), 5.70-5.68 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.80 (s, 2H), 2.94-2.89 (m, 2H), 2.59-2.54 (m, 2H), 2.09-2.03 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.3, 149.9, 140.9, 137.0, 133.6, 131.8, 128.8, 127.1, 119.9, 105.2, 61.6, 33.8, 32.9, 31.4, 22.0, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{20}ClN_2O_2$ $[M + H]^+$ *m/z* 331.1208, found 331.1203.

Compound 18ie



Yield: 64.0 mg (78%), white solid.

Mp: 49-51ºC.

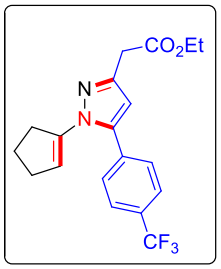
IR (neat): ν_{max} 2963, 2853, 1731, 1651, 1516, 1414, 1369, 1260, 1187, 1023, 852, 753 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.5 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H), 6.70 (s, 1H), 5.77-5.71 (m, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 2H), 2.94-2.92 (m, 2H), 2.60-2.57 (m, 2H), 2.11-2.05 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.1, 148.5, 147.2, 140.7, 139.5, 137.6, 126.2, 124.1, 120.7, 106.1, 61.7, 33.8, 32.8, 31.5, 21.9, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{20}N_3O_4$ $[M + H]^+$ *m/z* 342.1448, found 342.1441.

Compound 18if



Yield: 53.0 mg (73%), gummy liquid.

IR (neat): ν_{max} 2968, 2854, 1738, 1649, 1552, 1417, 1370, 1259, 1107, 1016, 848, 798 cm^{-1}

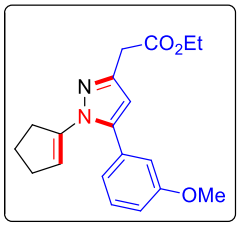
^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 6.65 (s, 1H), 5.72-5.71 (m, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.82 (s, 2H), 2.95-2.91 (m, 2H), 2.60-2.55 (m, 2H), 2.10-2.04 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.3, 149.5, 140.8, 137.2, 136.7, 129.6 (q, $^2J_{C-F}$ = 31.8 Hz), 125.9, 125.6 (q, $^3J_{C-F}$ = 3.9 Hz), 124.4 (q, $^1J_{C-F}$ = 270.0 Hz), 120.3, 105.6, 61.6, 33.8, 32.9, 31.4, 21.9, 14.3 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{20}F_3N_2O_2$ $[M + H]^+$ *m/z* 365.1471, found 365.1474.

Compound 18ig



Yield: 50.0 mg (76%), gummy liquid.

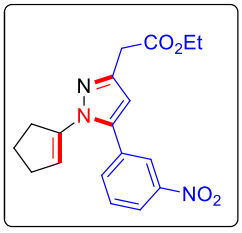
IR (neat): ν_{max} 2959, 2851, 1733, 1603, 1472, 1434, 1320, 1284, 1163, 1034, 869, 784 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H), 7.31-7.28 (m, 1H), 6.85 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.58 (s, 1H), 5.69-5.68 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 2H), 2.95-2.91 (m, 2H), 2.58-2.55 (m, 2H), 2.10-2.03 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.3, 159.9, 150.8, 140.9, 136.7, 134.6, 129.6, 119.5, 118.4, 113.9, 110.9, 105.4, 61.5, 55.4, 33.8, 32.9, 31.4, 21.9, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{23}N_2O_3$ $[M + H]^+$ *m/z* 327.1703, found 327.1703.

Compound 18ih



Yield: 50.5 mg (74%), white solid.

Mp: 56-58 ºC.

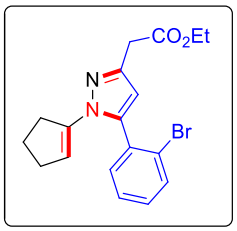
IR (neat): ν_{max} 2925, 2850, 1722, 1650, 1530, 1425, 1345, 1226, 1162, 1028, 803, 696 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.15 (d, *J* = 6.0 Hz, 2H), 7.56-7.53 (m, 1H), 6.69 (s, 1H), 5.73 (s, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 2H), 2.94 (s, 2H), 2.59 (s, 2H), 2.11-2.05 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.2, 148.8, 148.6, 140.8, 137.5, 135.1, 131.5, 129.6, 122.4, 120.6, 120.4, 105.5, 61.7, 33.8, 32.9, 31.4, 21.9, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{20}N_3O_4$ $[M + H]^+$ *m/z* 342.1448, found 342.1450.

Compound 18ii



Yield: 56.0 mg (75%), gummy liquid.

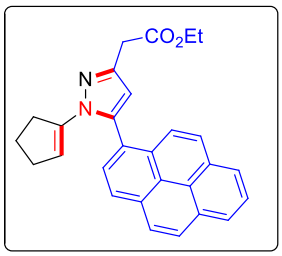
IR (neat): ν_{max} 2925, 2851, 1736, 1649, 1503, 1410, 1367, 1258, 1164, 1009, 832, 721 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.35-7.32 (m, 1H), 7.18-7.15 (m, 1H), 6.80 (s, 1H), 5.71-5.69 (m, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.84 (s, 2H), 2.95-2.90 (m, 2H), 2.59-2.54 (m, 2H), 2.08-2.02 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.4, 150.1, 140.9, 135.7, 134.4, 133.6, 131.3, 129.2, 127.5, 122.2, 119.5, 109.1, 61.5, 33.9, 33.0, 31.5, 22.0, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{20}BrN_2O_2$ $[M + H]^+$ *m/z* 375.0703, found 375.0702.

Compound 18ik



Yield: 56.0 mg (67%), gummy liquid.

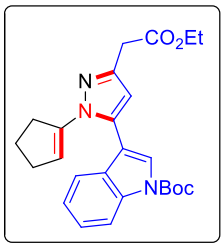
IR (neat): ν_{max} 2967, 2847, 1732, 1583, 1446, 1392, 1262, 1181, 1152, 1027, 847, 732 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.88 (d, *J* = 9.5 Hz, 1H), 8.25 (d, *J* = 7.5 Hz, 1H), 8.21-8.17 (m, 3H), 8.11-8.08 (m, 3H), 8.02-7.99 (m, 1H), 6.77 (s, 1H), 5.79-5.78 (m, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 3.94 (s, 2H), 3.08-3.04 (m, 2H), 2.65-2.60 (m, 2H), 2.14-2.08 (m, 2H), 1.32 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.5, 151.3, 141.1, 136.3, 131.6, 131.2, 128.8, 128.6, 127.8, 127.6$_1$, 127.5$_7$, 127.5, 126.0, 125.9, 125.3, 125.2, 125.0, 124.9, 119.2, 109.5, 61.6, 34.0, 33.1, 31.5, 22.0, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{28}H_{25}N_2O_2$ $[M + H]^+$ *m/z* 421.1911, found 421.1909.

Compound 18il



Yield: 65.0 mg (75%), gummy liquid.

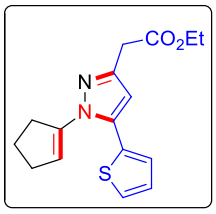
IR (neat): ν_{max} 2973, 2932, 2847, 1730, 1649, 1449, 1389, 1248, 1149, 1015, 801, 748 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 7.5 Hz, 1H), 8.19-8.16 (m, 1H), 7.90 (s, 1H), 7.37-7.29 (m, 2H), 6.62 (s, 1H), 5.69-5.67 (m, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 2H), 3.02-2.99 (m, 2H), 2.61-2.56 (m, 2H), 2.10-2.05 (m, 2H), 1.69 (s, 9H), 1.29 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.4, 149.8, 145.6, 141.0, 136.2, 135.9, 128.6, 124.7, 123.2, 123.1, 122.0, 118.3, 115.1, 114.6, 106.1, 83.9, 61.5, 33.9, 32.9, 31.5, 28.3, 21.9, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{30}N_3O_4$ $[M + H]^+$ *m/z* 436.2231, found 436.2235.

Compound 18im



Yield: 44.0 mg (72%), gummy liquid.

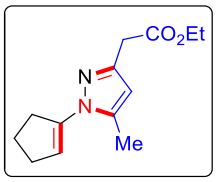
IR (neat): ν_{max} 2969, 2852, 1738, 1649, 1445, 1368, 1228, 1028, 846, 703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 3.5, 1 Hz, 1H), 7.24 (dd, *J* = 5, 1 Hz, 1H), 7.04 (dd, *J* = 5, 3.5 Hz, 1H), 6.50 (s, 1H), 5.69-5.68 (m, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.78 (s, 2H), 2.92-2.88 (m, 2H), 2.57-2.53 (m, 2H), 2.08-2.03 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.2, 146.4, 140.7, 136.8, 136.5, 127.5, 124.7, 124.1, 120.0, 105.3, 61.6, 33.8, 32.8, 31.4, 21.9, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{16}H_{19}N_2O_2S$ *m/z* $[M + H]^+$303.1162, found 303.1161.

Compound 18iq



Yield: 27.0 mg (57%), gummy liquid.

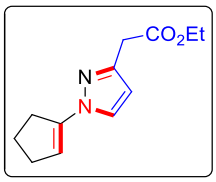
IR (neat): ν_{max} 2969, 2845, 1738, 1555, 1441, 1368, 1228, 1215, 1028, 897, 775 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.05 (s, 1H), 5.58-5.56 (m, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.72 (s, 2H), 2.85-2.81 (m, 2H), 2.53-2.48 (m, 2H), 2.26 (s, 3H), 2.04-1.85 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.5, 148.5, 140.7, 136.0, 118.6, 107.7, 61.3, 33.6, 32.7, 31.1, 22.0, 14.2, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{13}H_{19}N_2O_2$ *m/z* $[M + H]^+$235.1441, found 235.1444.

Compound 18ir



Yield: 22.0 mg (49%), gummy liquid.

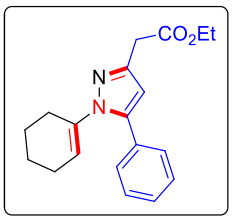
IR (neat): ν_{max} 3014, 2969, 1738, 1443, 1368, 1228, 1215, 1152, 1028, 897 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, *J* = 1.5 Hz, 1H), 6.27 (d, *J* = 1.5 Hz, 1H), 5.63-5.61 (m, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 3.78 (s, 2H), 2.87-2.85 (m, 2H), 2.56-2.52 (m, 2H), 2.06-2.00 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.4, 140.8, 139.3, 135.4, 118.9, 107.8, 61.4, 33.7, 32.8, 31.3, 21.9, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{12}H_{17}N_2O_2$ *m/z* $[M + H]^+$221.1285, found 221.1287.

Compound 18ja



Yield: 48.0 mg (78%), gummy liquid.

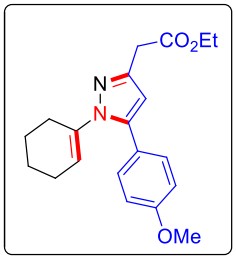
IR (neat): ν_{max} 2926, 2856, 1736, 1674, 1549, 1463, 1373, 1258, 1028, 764, 693 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81-7.80 (m, 2H), 7.39-7.36 (m, 2H), 7.30-7.28 (m, 1H), 6.55 (s, 1H), 5.83-5.81 (m, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.73 (s, 2H), 2.50-2.47 (m, 2H), 2.26-2.22 (m, 2H), 1.87-1.82 (m, 2H), 1.72-1.67 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.6, 151.0, 137.3, 136.2, 133.5, 128.6, 127.8, 125.8, 125.0, 104.0, 61.5, 32.5, 28.7, 24.7, 22.6, 21.7, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{23}N_2O_2$ $[M + H]^+$ *m/z* 311.1754, found 311.1758.

Compound 18jb



Yield: 56.0 mg (82%), white solid.

Mp: 53-55ºC.

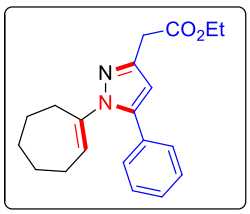
IR (neat): ν_{max} 2928, 2854, 1736, 1673, 1521, 1436, 1370, 1245, 1029, 836, 799 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.47 (s, 1H), 5.81-5.80 (m, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.83 (s, 3H), 3.72 (s, 2H), 2.49-2.46 (m, 2H), 2.24-2.21 (m, 2H), 1.86-1.81 (m, 2H), 1.71-1.66 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.6, 159.4, 150.8, 137.4, 136.1, 127.0, 126.3, 124.9, 114.0, 103.6, 61.4, 55.4, 32.5, 28.7, 24.7, 22.7, 21.7, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{20}H_{25}N_2O_3$ $[M + H]^+$ *m/z* 341.1860, found 341.1865.

Compound 18ka



Yield: 48.0 mg (74%), gummy liquid.

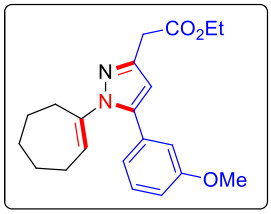
IR (neat): ν_{max} 2922, 2851, 1736, 1668, 1547, 1462, 1370, 1259, 1163, 1026, 763, 693 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81-7.80 (m, 2H), 7.38-7.35 (m, 2H), 7.29-7.28 (m, 1H), 6.53 (s, 1H), 5.95 (t, *J* = 6.5 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.73 (s, 2H), 2.65-2.63 (m, 2H), 2.31-2.27 (m, 2H), 1.85-1.80 (m, 2H), 1.79-1.74 (m, 2H), 1.71-1.67 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.6, 150.8, 142.2, 136.1, 133.5, 129.9, 128.6, 127.7, 125.8, 103.8, 61.4, 33.9, 32.6, 31.2, 27.0, 26.7, 26.0, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{20}H_{25}N_2O_2$ $[M + H]^+$ *m/z* 325.1911, found 325.1914.

Compound 18kg



Yield: 49.0 mg (69%), gummy liquid.

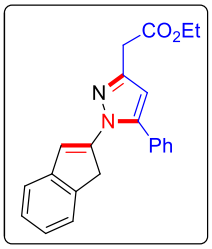
IR (neat): ν_{max} 2923, 2850, 1735, 1604, 1548, 1470, 1369, 1250, 1157, 1030, 779, 690 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.37 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.85-6.83 (m, 1H), 6.52 (s, 1H), 5.92 (t, *J* = 6.5 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 3.73 (s, 2H), 2.65-2.63 (m, 2H), 2.30-2.27 (m, 2H), 1.84-1.80 (m, 2H), 1.78-1.74 (m, 2H), 1.71-1.66 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.6, 160.0, 150.8, 142.2, 136.1, 134.9, 130.0, 129.6, 118.5, 113.9, 110.9, 104.0, 61.5, 55.5, 34.0, 32.6, 31.2, 27.0, 26.8, 26.0, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{21}H_{27}N_2O_3$ $[M + H]^+$ *m/z* 355.2016, found 355.2017.

Compound 18la



Yield: 54.0 mg (78%), white solid.

Mp: 105-107ºC.

IR (neat): ν_{max} 2924, 2852, 1736, 1603, 1577, 1463, 1378, 1260, 1159, 1027, 799, 695 cm^{-1}

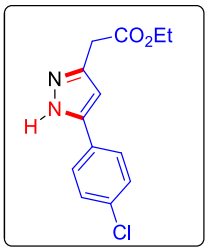
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87-7.86 (m, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.44-7.41 (m, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.35-7.32 (m, 1H), 7.31-7.28 (m, 1H), 7.23-7.20 (m, 1H), 6.71 (s, 2H), 4.22 (q, *J* = 7.0 Hz, 2H), 4.11 (s, 2H), 3.97 (s, 2H), 1.26 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.2, 151.8, 144.8, 143.5, 139.5, 137.0, 132.9, 128.8, 128.3, 126.9, 125.9, 125.0, 123.7, 121.3, 117.2, 106.7, 61.7, 40.2, 33.3, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{21}N_2O_2$ $[M + H]^+$ *m/z* 345.1598, found 345.1596.

3.12 General procedure for the synthesis of compounds 19id and 19im. A Schlenk tube was charged with **18id** or **18im** (0.20 mmol; 1.0 equiv.) and 0.1 mL of dichloromethane. Subsequently, magnesium (2.0 mmol; 10.0 equiv.), $TiCl_4$ (0.02 mmol; 0.1 equiv.), and THF (0.6 mL) were added at 25 °C, the mixture was stirred for the stipulated time and the progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was quenched by adding water (5.0 mL) and passed through celite bed. The aqueous layer was extracted with ethyl acetate (3 × 5 mL). Then the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/hexane (30:70) as the eluent.

Compound 19id



Yield: 48.0 mg (90%), white solid.

Mp: 130-132 °C.

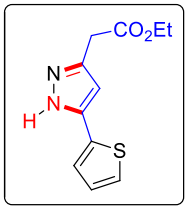
IR (neat): ν_{max} 3321, 2978, 2926, 1730, 1506, 1477, 1398, 1201, 1140, 1033, 800 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66-7.64 (m, 2H), 7.38-7.36 (m, 2H), 6.47 (s, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.78 (s, 2H), 1.32 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 170.3, 148.7, 140.0, 133.9, 130.7, 129.1, 127.0, 102.8, 61.7, 32.6, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{13}H_{14}ClN_2O_2$ $[M + H]^+$ *m/z* 265.0738, found 265.0727.

Compound 19im



Yield: 41.0 mg (87%), gummy liquid.

IR (neat): ν_{max} 3301, 3099, 2970, 1733, 1579, 1445, 1368, 1256, 1149, 1021, 794 cm^{-1}.

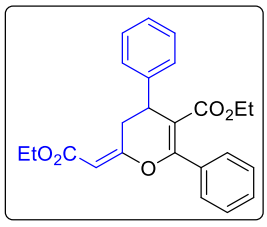
^1H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 3.0 Hz, 1H), 7.26 (d, *J* = 6.0 Hz, 1H), 7.05-7.04 (m, 1H), 6.41 (s, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.75 (s, 2H), 1.29 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 170.1, 144.9, 139.6, 135.1, 127.7, 125.0, 124.2, 102.9, 61.6, 32.4, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{11}H_{13}N_2O_2S$ *m/z* $[M + H]^+$237.0692, found 237.0685.

3.13 General procedure for the synthesis of compounds 20aa, 20ad, 20af, 20ag-ah, 20ak-al, 20ap, 20ba, 21ab, 21ad, 21ag-ah, 21ak-al, 21an, 21ap, 22aa, 22ad, 22af-ah, 23aa, 23ad, and **23an.** A Schlenk tube was charged with one of 1,3-bisnucleophiles (0.20 mmol), DMAP (0.20 mmol), and 1.0 mL of toluene. Subsequently, *δ*-acetoxy allenoate **5** (0.24 mmol) in toluene (1.0 mL) was added gradually over a period of 15 min at 110 °C (oil bath) and the mixture was stirred for 12 h and progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was quenched by adding water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL). Then the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using ethyl acetate/hexane (25:75) as the eluent.

Compound 20aa



Yield: 57.0 mg (73%), white solid.

Mp: 102-104 °C.

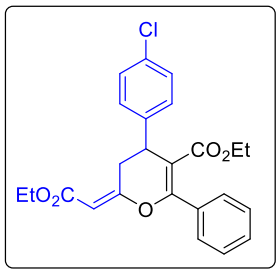
IR (neat): ν_{max} 2980, 1699, 1664, 1448, 1341, 1213, 1193, 1071, 1044, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 3.5 Hz, 2H), 7.42-7.40 (m, 3H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.23-7.19 (m, 3H), 4.93 (s, 1H), 4.32 (d, *J* = 5.5 Hz, 1H), 4.18-4.15 (m, 2H), 3.90-3.87 (m, 2H), 2.98-2.94 (m, 1H), 2.54 (d, *J* = 14.5 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.84 (t, *J* = 6.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 167.4, 164.4, 158.8, 158.4, 141.8, 134.1, 130.0, 129.2, 128.8, 128.0, 127.6, 127.3, 109.1, 100.6, 60.7, 60.0, 38.3, 35.1, 14.4, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{24}NaO_5$ $[M + Na]^+$ *m/z* 415.1516, found 415.1518.

Compound 20ad



Yield: 59.0 mg (69%), white solid.

Mp: 82-84 °C.

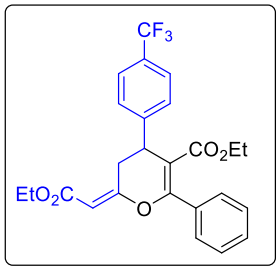
IR (neat): ν_{max} 2980, 2924, 1698, 1664, 1490, 1369, 1211, 1190, 1069, 1043, 793 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 5.5 Hz, 2H), 7.43-7.42 (m, 3H), 7.28-7.26 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), , 4.94 (s, 1H), 4.31 (d, *J* = 6.0 Hz, 1H), 4.19-4.16 (m, 2H), 3.91-3.88 (m, 2H), 2.98-2.93 (m, 1H), 2.49 (d, *J* = 14.0 Hz, 1H), 1.27 (t, *J* = 6.5 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 167.2, 164.2, 158.8, 158.2, 140.4, 133.9, 133.1, 130.2, 129.2, 129.0, 128.0, 108.6, 101.0, 60.8, 60.1, 37.7, 35.0, 14.4, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{24}ClO_5$ $[M + H]^+$ *m/z* 427.1307, found 427.1307.

Compound 20af



Yield: 60.0 mg (65%), white solid.

Mp: 115-117 °C.

IR (neat): ν_{max} 2982, 1697, 1664, 1446, 1323, 1213, 1195, 1158, 1066, 1044, 767 cm^{-1}.

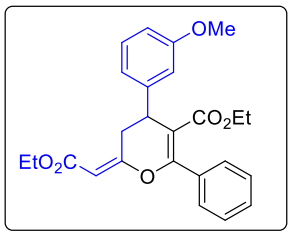
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.66 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 2H) 7.45-7.41 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.94 (d, *J* = 1.0 Hz, 1H), 4.39 (d, *J* = 6.0 Hz, 1H), 4.24-4.12 (m, 2H), 3.94-3.87 (m, 2H), 3.00-2.98 (m, 1H), 2.52 (dd, *J* = 14.5, 1.5 Hz, 1H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.84 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.1, 164.2, 159.2, 157.9, 146.0, 133.8, 130.3, 129.9 (q, $^{2}J_{C-F}$ = 32.2 Hz), 129.3, 128.0 (2 s), 125.8 (q, $^{3}J_{C-F}$ = 4.2 Hz), 124.4 (q, $^{1}J_{C-F}$ = 270.0 Hz), 108.2, 101.1, 60.9, 60.1, 38.1, 34.7, 14.4, 13.6 ppm.

^{19}F NMR (475 MHz, $CDCl_3$): δ -62.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{24}F_3O_5$ $[M + H]^+$ *m/z* 461.1570, found 461.1575.

Compound 20ag



Yield: 52.0 mg (61%), white solid.

Mp: 94-96 °C.

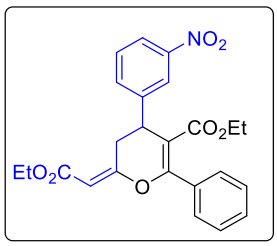
IR (neat): ν_{max} 2979, 1696, 1662, 1599, 1446, 1248, 1209, 1176, 1139, 1067, 1042, 733 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 5.5 Hz, 2H), 7.47-7.37 (m, 3H), 7.23-7.20 (m, 1H), 6.80-6.74 (m, 3H), 4.94 (s, 1H), 4.30 (d, *J* = 6.0 Hz, 1H), 4.18-4.15 (m, 2H), 3.91-3.88 (m, 2H), 3.78 (s, 3H), 2.97-2.93 (m, 1H), 2.55 (d, *J* = 14.0 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 6.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.3, 164.3, 159.8, 158.7, 158.4, 143.4, 134.1, 130.0, 129.8, 129.2, 127.9, 119.9, 113.3, 112.6, 109.0, 100.6, 60.7, 59.9, 55.2, 38.2, 35.0, 14.4, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{27}O_6$ $[M + H]^+$ *m/z* 423.1802, found 423.1800.

Compound 20ah



Yield: 52.0 mg (61%), white solid.

Mp: 94-96 °C.

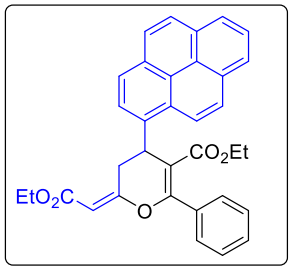
IR (neat): ν_{max} 2979, 1696, 1662, 1599, 1446, 1248, 1209, 1176, 1139, 1067, 1042, 733 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 5.5 Hz, 2H), 7.47-7.37 (m, 3H), 7.23-7.20 (m, 1H), 6.80-6.74 (m, 3H), 4.94 (s, 1H), 4.30 (d, *J* = 6.0 Hz, 1H), 4.18-4.15 (m, 2H), 3.91-3.88 (m, 2H), 3.78 (s, 3H), 2.97-2.93 (m, 1H), 2.55 (d, *J* = 14.0 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 6.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.3, 164.3, 159.8, 158.7, 158.4, 143.4, 134.1, 130.0, 129.8, 129.2, 127.9, 119.9, 113.3, 112.6, 109.0, 100.6, 60.7, 59.9, 55.2, 38.2, 35.0, 14.4, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{24}NO_7$ $[M + H]^+$ *m/z* 438.1547, found 438.1545.

Compound 20ak



Yield: 71.0 mg (69%), white solid.

Mp: 182-184 °C.

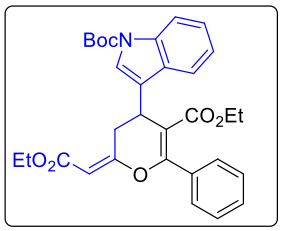
IR (neat): ν_{max} 3053, 2980, 1707, 1665, 1340, 1230, 1204, 1183, 1142, 1069, 753 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (d, *J* = 9.0 Hz, 1H), 8.23-8.19 (m, 3H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.12-8.01 (m, 3H), 7.83-7.79 (m, 3H), 7.49-7.48 (m, 3H) 5.54 (d, *J* = 6.0 Hz, 1H), 4.72 (d, *J* = 1.0 Hz, 1H) 4.19-4.08 (m, 2H), 3.85-3.78 (m, 2H), 3.25-3.20 (m, 1H), 2.75 (dd, *J* = 14.5, 2.0 Hz, 1H), 1.23 (t, *J* = 7.0 Hz, 3H), 0.74 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.4, 164.3, 159.3, 158.6, 134.9, 134.1, 131.5, 130.8, 130.7, 130.2, 129.3, 128.3, 128.1, 127.9, 127.6, 127.4, 126.1, 125.5, 125.2 (2 s), 125.1 (2 s), 122.2, 109.1, 101.0, 60.8, 59.9, 35.0, 34.4, 14.4, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{34}H_{29}O_5$ *m/z* $[M + H]^+$517.2010, found 517.2015.

Compound 20al



Yield: 72.0 mg (68%), white solid.

Mp: 120-122 ºC.

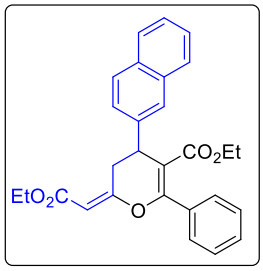
IR (neat): ν_{max} 2979, 2932, 1721, 1451, 1368, 1308, 1253, 1213, 1151, 1072, 1023, 764 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.67-7.59 (m, 3H), 7.43-7.40 (m, 3H), 7.34-7.31 (m, 3H), 4.92 (s, 1H), 4.60 (d, *J* = 6.5 Hz, 1H), 4.16-4.14 (m, 2H), 3.93-3.90 (m, 2H), 2.98-2.94 (m, 1H), 2.74 (d, *J* = 14.0 Hz, 1H), 1.65 (s, 9H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 167.6, 164.3, 158.9, 158.1, 149.8, 135.9, 134.0, 130.0, 129.1, 129.0, 128.0, 124.7, 123.9, 122.7, 120.8, 118.8, 115.6, 108.5, 100.9, 83.9, 60.9, 60.0, 33.2, 29.4, 28.3, 14.4, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{31}H_{33}NNaO_7$ *m/z* $[M + H]^+$554.2149, found 554.2144.

Compound 20an



Yield: 62.0 mg (70%), white solid.

Mp: 92-94 °C.

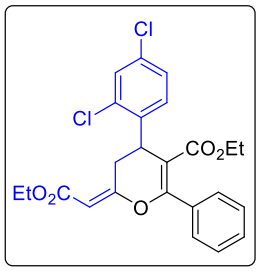
IR (neat): ν_{max} 2976, 1707, 1664, 1620, 1367, 1231, 1213, 1179, 1159, 1062, 744 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.81-7.79 (m, 3H), 7.74-7.72 (m, 2H), 7.63 (s, 1H), 7.48-7.34 (m, 5H), 7.35 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.91 (d, *J* = 2.0 Hz, 1H), 4.50 (dd, *J* = 7.0, 2.0 Hz, 1H) 4.22-4.10 (m, 2H), 3.92-3.84 (m, 2H), 3.06-3.01 (m, 1H), 2.64 (dd, *J* = 14.5, 2.0 Hz, 1H), 1.25 (t, *J* = 7.5 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 167.4, 164.3, 158.7, 158.5, 139.3, 134.1, 133.5, 132.8, 130.1, 129.3, 128.7, 128.1, 128.0, 127.7, 126.3, 126.2, 125.9, 125.8, 109.0, 100.7, 60.8, 60.0, 38.4, 35.1, 14.4, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{28}H_{27}O_5$ $[M + H]^+$ *m/z* 443.1853, found 443.1855.

Compound 20ap



Yield: 62.0 mg (67%), white solid.

Mp: 122-124 °C.

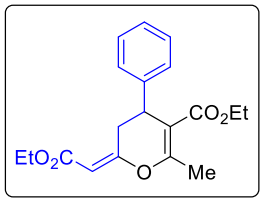
IR (neat): ν_{max} 2969, 1721, 1661, 1626, 1493, 1369, 1193, 1215, 1101, 1064, 1047, 744 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.70-7.68 (m, 2H), 7.47-7.41 (m, 4H), 7.18 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 4.90 (d, *J* = 1.5 Hz, 1H), 4.80 (dd, *J* = 7.0, 1.5 Hz, 1H), 4.21-4.11 (m, 2H), 3.96-3.88 (m, 2H), 2.95-2.91 (m, 1H), 2.54 (dd, *J* = 14.5, 2.0 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.7, 164.1, 160.1, 157.9, 137.4, 133.9, 133.7, 133.6, 130.3, 129.8, 129.7, 129.3, 128.0, 127.4, 107.6, 101.3, 60.9, 60.1, 34.8, 33.1, 14.4, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{23}Cl_2O_5$ [M + H]$^+$ *m/z* 461.0917, found 461.0921.

Compound 20ba



Yield: 41.0 mg (62%), white solid.

Mp: 92-94 °C.

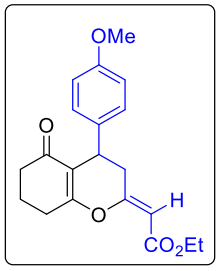
IR (neat): ν_{max} 2982, 1717, 1697, 1661, 1623, 1481, 1375, 1225, 1175, 1071, 1042, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.25 (m, 2H), 7.21-7.18 (m, 1H), 7.09 (d, *J* = 7.0 Hz, 2H), 4.83 (s, 1H), 4.17-4.12 (m, 2H), 4.09-4.04 (m, 3H), 2.85-2.81 (m, 1H), 2.54 (s, 3H), 2.44 (dd, *J* = 14.5, 1.5 Hz, 1H), 1.26 (t, *J* = 7.5 Hz, 3H), 1.13 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.7, 164.3, 161.1, 159.0, 142.5, 128.6, 127.4, 127.0, 107.6, 99.8, 60.5, 59.8, 36.8, 35.2, 19.4, 14.4, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{22}NaO_5$ [M + Na]$^+$ *m/z* 353.1359, found 353.1362.

Compound 21ab



Yield: 50.0 mg (73%), white solid.

Mp: 98-100 °C.

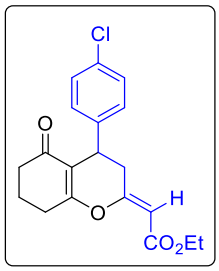
IR (neat): ν_{max} 2925, 1717, 1510, 1378, 1302, 1224, 1196, 1176, 1137, 1062, 1035, 830 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.96 (s, 1H), 4.18-4.12 (m, 2H), 4.08 (d, *J* = 6.5 Hz, 1H), 3.75 (s, 3H), 2.82-2.76 (m, 2H), 2.73-2.67 (m, 1H), 2.48 (d, *J* = 15.0 1H), 2.42-2.39 (m, 2H), 2.09-2.05 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.5, 167.1, 164.1, 159.8, 158.2, 134.1, 128.3, 116.0, 114.0, 101.2, 59.9, 55.3, 36.9, 35.3, 32.0, 27.8, 20.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{20}H_{23}O_5$ $[M + H]^+$ *m/z* 343.1540, found 343.1542.

Compound 21ad



Yield: 51.0 mg (73%), white solid.

Mp: 108-110 °C.

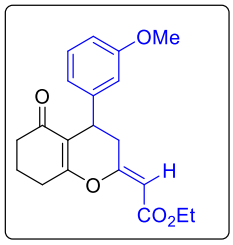
IR (neat): ν_{max} 2953, 1708, 1651, 1629, 1380, 1230, 1197, 1141, 1061, 1031, 877 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 4.96 (s, 1H), 4.16-4.14 (m, 2H), 4.10 (d, *J* = 6.0 Hz, 1H), 2.85-2.69 (m, 3H), 2.47-2.40 (m, 3H), 2.09-2.08 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.4, 167.6, 163.9, 158.2, 140.6, 132.8, 128.8, 128.7, 115.3, 101.6, 60.1, 36.9, 35.0, 32.4, 27.8, 20.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{20}ClO_4$ $[M + H]^+$ *m/z* 347.1045, found 347.1041.

Compound 21ag



Yield: 42.0 mg (66%), white solid.

Mp: 105-107 °C.

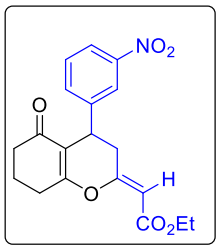
IR (neat): ν_{max} 2948, 1715, 1655, 1631, 1484, 1380, 1226, 1199, 1170, 1138, 1041, 789 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.19-7.15 (m, 1H), 6.73 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 6.66-6.65 (m, 1H), 4.96 (d, *J* = 2.0 Hz, 1H), 4.17-4.12 (m, 2H), 4.11 (d, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 2.84-2.76 (m, 2H), 2.73-2.67 (m, 1H), 2.51 (dd, *J* = 15.0, 1.5 Hz, 1H), 2.44-2.40 (m, 2H), 2.11-2.04 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 196.5, 167.4, 164.0, 159.8, 158.6, 143.6, 129.6, 119.6, 115.5, 113.4, 112.1, 101.3, 59.9, 55.2, 36.9, 35.0, 32.8, 27.8, 20.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{20}H_{23}O_5$ $[M + H]^+$ *m/z* 343.1540, found 343.1542.

Compound 21ah



Yield: 51.0 mg (71%), white solid.

Mp: 96-98 °C.

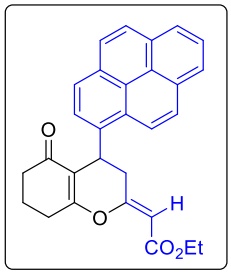
IR (neat): ν_{max} 2968, 1718, 1656, 1629, 1526, 1368, 1350, 1277, 1216, 1156, 1047, 739 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.46-7.42 (m, 1H), 5.09 (d, *J* = 4.5 Hz, 1H), 4.51 (d, *J* = 4.5 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.26-3.19 (m, 2H), 2.62-2.49 (m, 2H), 2.35-2.33 (m, 2H), 2.06-1.96 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 197.3, 169.0, 166.9, 148.6, 147.2, 144.2, 134.8, 129.2, 123.3, 121.8, 112.8, 106.6, 61.5, 38.8, 37.0, 35.2, 27.6, 20.3, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{19}NNaO_6$ $[M + Na]^+$ *m/z* 380.1105, found 380.1102.

Compound 21ak



Yield: 57.0 mg (65%), white solid.

Mp: 190-192 °C.

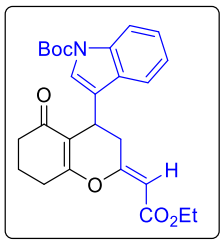
IR (neat): ν_{max} 2970, 1713, 1680, 1653, 1630, 1490, 1378, 1228, 1199, 1170, 1130, 1034, 879 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.44 (d, *J* = 9.5 Hz, 1H), 8.21-8.17 (m, 3H), 8.04-7.98 (m, 4H), 7.51 (d, *J* = 8.0 Hz, 1H), 5.30 (d, *J* = 6.5 Hz, 1H), 4.69 (d, *J* = 1.0 Hz, 1H) 4.12-4.06 (m, 2H), 3.11-3.07 (m, 1H), 3.02-2.96 (m, 1H), 2.88-2.82 (m, 1H), 2.71 (d, *J* = 14.5 Hz, 1H), 2.52-2.48 (m, 2H), 2.25-2.19 (m, 2H), 1.19 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 196.4, 168.5, 163.9, 158.5, 134.9, 131.5, 130.8, 130.6, 128.1, 127.8, 127.5, 127.2, 126.0, 125.5, 125.3, 125.1, 124.8, 124.2, 122.4, 115.6, 101.6, 59.9, 37.0, 35.3, 29.2, 28.0, 21.0, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{19}Cl_2O_4Na$ $[M + H]^+$ *m/z* 437.1747, found 437.1743.

Compound 21al



Yield: 63.0 mg (70%), white solid.

Mp: 128-130 °C.

IR (neat): ν_{max} 2972, 1718, 1654, 1634, 1369, 1340, 1197, 1153, 1135, 1074, 1040, 746 cm^{-1}.

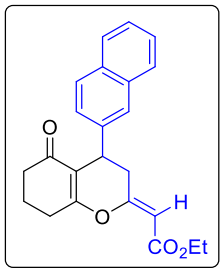
^1H NMR (500 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.32-7.29 (m, 1H), 7.23 (d, *J* = 7.0 Hz, 1H), 7.12 (s, 1H), 4.92 (s, 1H) 4.40 (d, *J* = 6.0 Hz, 1H), 4.13 (q, *J* =

6.5 Hz, 2H), 2.84-2.78 (m, 2H), 2.75-2.69 (m, 2H), 2.53-2.40 (m, 2H), 2.14-2.08 (m, 2H), 1.65 (s, 9H), 1.24 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.4, 167.8, 163.9, 158.6, 149.8, 135.9, 129.0, 124.6, 123.2, 122.6, 121.0, 119.0, 115.5, 115.0, 101.5, 83.8, 60.0, 36.9, 33.4, 28.3, 27.9, 24.1, 20.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{26}H_{30}NO_6$ $[M + H]^+$ *m/z* 452.2068, found 452.2064.

Compound 21an



Yield: 49.0 mg (68%), white solid.

Mp: 95-97 °C.

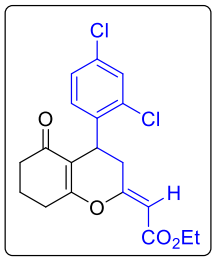
IR (neat): ν_{max} 2934, 1716, 1665, 1635, 1386, 1341, 1224, 1199, 1131, 1094, 1063, 852 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78-7.74 (m, 3H), 7.51 (s, 1H), 7.45-7.40 (m, 2H), 7.27 (d, *J* = 1.5 Hz, 1H), 4.94 (d, *J* = 1.5 Hz, 1H), 4.31 (d, *J* = 7.0 Hz, 1H), 4.17-4.12 (m, 2H), 2.93-2.84 (m, 2H), 2.79-2.73 (m, 1H), 2.60 (dd, *J* = 15.0, 2.0 Hz, 1H), 2.49-2.39 (m, 2H), 2.15-2.10 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 196.5, 167.6, 164.0, 158.6, 139.4, 133.4, 132.6, 128.5, 128.0, 127.6, 126.1, 125.8, 125.7, 115.5, 101.3, 59.9, 36.9, 35.2, 33.0, 27.8, 20.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}O_4$ $[M + H]^+$ *m/z* 363.1591, found 363.1593.

Compound 21ap



Yield: 47.0 mg (62%), white solid.

Mp: 130-132 °C.

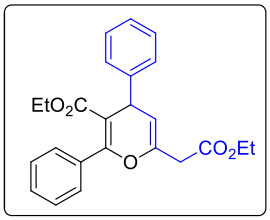
IR (neat): ν_{max} 2955, 1713, 1656, 1637, 1375, 1224, 1196, 1179, 1139, 1101, 1043, 856 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 2.0 Hz, 1H), 7.09 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 4.90 (d, *J* = 1.5 Hz, 1H), 4.52 (d, *J* = 7.0 Hz, 1H), 4.16-4.11 (m, 2H), 2.87-2.72 (m, 3H), 2.52 (dd, *J* = 14.5, 1.5 Hz, 1H), 2.43 (t, *J* = 6.0 Hz, 2H), 2.15-2.10 (m, 2H), 1.25 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 195.9, 168.8, 163.8, 157.8, 137.2, 134.0, 133.4, 129.9, 128.9, 127.2, 114.4, 101.9, 60.1, 36.8, 33.3, 29.9, 27.8, 20.8, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{19}Cl_2O_4Na$ $[M + Na]^+$ *m/z* 381.0655, found 381.0652.

Compound 22aa



Yield: 56.0 mg (71%), white solid.

Mp: 125-127 °C.

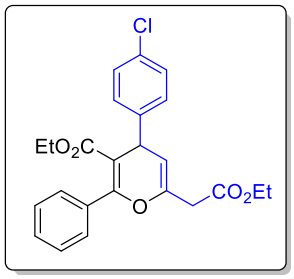
IR (neat): ν_{max} 2979, 1737, 1714, 1640, 1492, 1368, 1273, 1153, 1109, 1070, 759 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.41-7.38 (m, 4H), 7.36-7.33 (m, 2H), 7.26-7.23 (m, 2H), 5.12 (d, *J* = 4.5 Hz, 1H), 4.53 (d, *J* = 4.5 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.84 (q, *J* = 7.0 Hz, 2H), 3.27-3.19 (m, 2H), 1.30 (t, *J* = 7.0 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 169.2, 167.3, 157.8, 145.5, 143.6, 135.1, 129.3, 128.6, 128.5, 128.2, 127.8, 126.8, 106.8, 106.1, 61.1, 60.1, 39.5, 38.8, 14.2, 13.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{25}O_5$ $[M + H]^+$ *m/z* 393.1697, found 393.1694.

Compound 22ad



Yield: 65.0 mg (76%), white solid.

Mp: 74-76 °C.

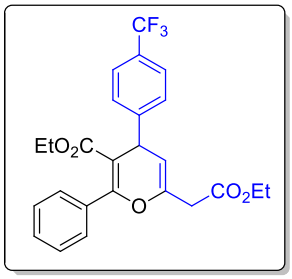
IR (neat): ν_{max} 2980, 1721, 1595, 1491, 1371, 1259, 1153, 1091, 1016, 834 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.36 (m, 5H), 7.33-7.26 (m, 4H), 5.07 (d, *J* = 5.0 Hz, 1H), 4.48 (d, *J* = 4.5 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.82 (q, *J* = 7.0 Hz, 2H), 3.24-3.17 (m, 2H), 1.27 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.3, 167.3, 158.2, 144.1, 144.0, 135.0, 132.7, 129.7, 129.6, 128.7(2 s), 127.9, 106.5, 105.8, 61.3, 60.3, 39.0, 38.8, 14.3, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{24}ClO_5$ $[M + H]^+$ *m/z* 427.1307, found 427.1303.

Compound 22af



Yield: 62.0 mg (67%), white solid.

Mp: 114-116 °C.

IR (neat): ν_{max} 2969, 1738, 1369, 1325, 1216, 1162, 1123, 1068, 1019, 846 cm^{-1}.

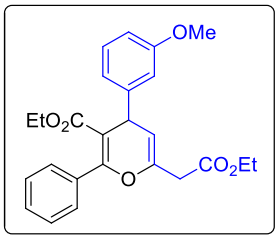
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H) 7.44-7.37 (m, 5H), 5.11 (d, *J* = 4.5 Hz, 1H), 4.60 (d, *J* = 5.0 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.84 (q, *J* = 7.0 Hz, 2H), 3.28-3.20 (m, 2H), 1.30 (t, *J* = 7.0 Hz, 3H), 0.83 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.1, 167.1, 158.6, 149.4, 144.2, 134.8, 129.5 (q, $^{2}J_{C-F}$ = 32.2 Hz), 129.6, 128.7, 128.6, 127.7 (q, $^{3}J_{C-F}$ = 4.2 Hz), 127.8, 125.5 (q, $^{1}J_{C-F}$ = 270.0 Hz), 106.0, 105.4, 61.2, 60.3, 39.4, 38.6, 14.2, 13.4 ppm.

^{19}F NMR (475 MHz, $CDCl_3$): δ -62.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{24}F_3O_5$ $[M + H]^+$ *m/z* 461.1570, found 461.1575.

Compound 22ag



Yield: 53.0 mg (62%), gummy liquid.

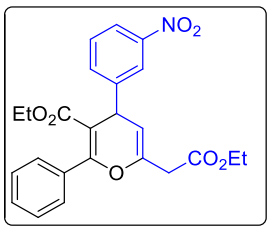
IR (neat): ν_{max} 2979, 2934, 1712, 1598, 1486, 1257, 1108, 1069, 1045, 766, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.42-7.36 (m, 3H), 7.28-7.25 (m, 1H), 7.00-6.96 (m, 2H), 6.80-6.78 (m, 1H), 5.12 (d, *J* = 4.5 Hz, 1H), 4.51 (d, *J* = 4.5 Hz, 1H), 4.21 (q, *J* = 7.5 Hz, 2H), 3.87-3.85 (m, 2H), 3.83 (s, 3H), 3.23-3.21 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.2, 167.3, 159.8, 157.8, 147.1, 143.6, 135.1, 129.4, 129.3, 128.6, 127.8, 120.5, 114.0, 112.1, 106.6, 106.1, 61.1, 60.1, 55.2, 39.5, 38.7, 14.2, 13.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{25}H_{27}O_6$ $[M + H]^+$ *m/z* 423.1802, found 423.1805.

Compound 22ah



Yield: 50.0 mg (57%), white solid.

Mp: 109-111 °C.

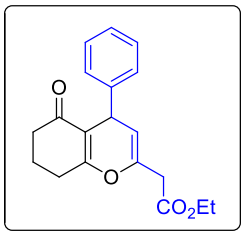
IR (neat): ν_{max} 2969, 1737, 1530, 1447, 1373, 1351, 1229, 1216, 1094, 1023, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.55-7.52 (m, 1H), 7.44-7.40 (m, 5H), 5.14 (d, *J* = 5.0 Hz, 1H), 4.67 (d, *J* = 4.0 Hz, 1H), 4.23 (q, *J* = 6.5 Hz, 2H), 3.85 (q, *J* = 7.0 Hz, 2H), 3.31-3.23 (m, 2H), 1.30 (t, *J* = 7.5 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 166.8, 164.0, 159.8, 158.7, 158.4, 148.6, 144.3, 133.7, 133.6, 130.4, 129.9, 129.3, 128.0, 122.8, 107.7, 101.5, 60.9, 60.2, 38.0, 34.6, 14.4, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{24}NO_7$ $[M + H]^+$ *m/z* 438.1547, found 438.1546.

Compound 23aa



Yield: 58.0 mg (74%), white solid.

Mp: 108-110 °C.

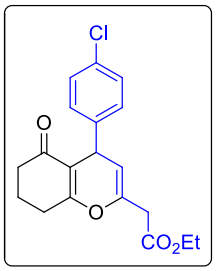
IR (neat): ν_{max} 2930, 1737, 1705, 1659, 1588, 1491, 1375, 1216, 1182, 1158, 1028, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.28 (m, 4H), 7.20-7.18 (m, 1H), 5.13 (d, *J* = 4.5 Hz, 1H), 4.40 (d, *J* = 4.0 Hz, 1H), 4.22 (q, *J* = 7.5 Hz, 2H), 3.25-3.12 (m, 2H), 2.60-2.48 (m, 2H), 2.40-2.30 (m, 2H), 2.07-1.92 (m, 2H), 1.31 (t, *J* = 14.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.3, 169.2, 166.1, 145.2, 143.0, 128.3, 128.2, 126.5, 113.7, 107.9, 61.2, 38.8, 37.0, 35.1, 27.6, 20.3, 14.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{21}O_4$ $[M + H]^+$ *m/z* 313.1434, found 313.1431.

Compound 23ad



Yield: 55.0 mg (64%), white solid.

Mp: 116-118 °C.

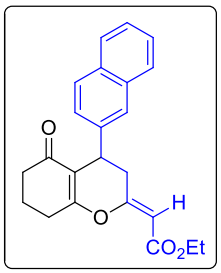
IR (neat): ν_{max} 3014, 2969, 1738, 1629, 1440, 1367, 1232, 1216, 1092, 525 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.27 (m, 2H), 7.25-7.23 (m, 2H), 5.07 (d, *J* = 4.5 Hz, 1H), 4.35 (d, *J* = 4.5 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.20-3.19 (m, 2H), 2.58-2.48 (m, 2H), 2.37-2.28 (m, 2H), 2.05-1.89 (m, 2H), 1.30 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.4, 169.3, 166.3, 143.7, 143.4, 132.3, 129.8, 128.5, 113.5, 107.5, 61.3, 38.8, 37.1, 34.6, 27.6, 20.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{20}ClO_4$ $[M + H]^+$ *m/z* 347.1045, found 347.1044.

Compound 23an



Yield: 61.0 mg (69%), white solid.

Mp: 89-90 °C.

IR (neat): ν_{max} 2969, 1735, 1658, 1624, 1368, 1339, 1215, 1245, 1169, 1135, 1025, 733 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83-7.78 (m, 4H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.47-7.41 (m, 2H), 5.19 (d, *J* = 4.5 Hz, 1H), 4.58 (d, *J* = 4.0 Hz, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.29-3.21 (m, 2H), 2.65-2.52 (m, 2H), 2.37-2.35 (m, 2H), 2.06-1.96 (m, 2H), 1.96 (t, *J* = 6.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.5, 169.4, 166.3, 143.2, 142.6, 133.5, 132.5, 128.1, 128.0, 127.6, 126.8 (2 s), 125.9, 125.5, 113.7, 107.9, 61.3, 38.9, 37.1, 35.3, 27.7, 20.4, 14.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{23}O_4$ $[M + H]^+$ *m/z* 363.1591, found 363.1595.

3.14 X-ray crystallography

A suitable crystal was mounted on a glass fiber (for **11da**, **11ea**, **12ao**, **12db**, **13ae, 13de**, **15aa**, **15ad, 15db**, **15ea**, **15fn**, **15hb**, **16aa**, **17db**, **18ia, 18ie**, **19id**, **20ah**, **21ad**, **23ad**) and X-ray data were collected at 298 K on a Bruker AXS-SMART or on an OXFORD diffractometer [Mo-Kα (λ = 0.71073 Å) or Cu- Kα (λ = 1.54184 Å)]. Structures were solved and refined using standard methods.[49] Crystal data are summarized in Tables 16-20.

Table 16: Crystal data for compounds **11da**, **11ea**, **12ao,** and **12db**

Compound	**11da**	**11ea**	**12ao**	**12db**
Emp. formula	$C_{24}H_{24}N_2O_6S$	$C_{25}H_{24}N_2O_4S$	$C_{31}H_{31}NO_5S$	$C_{25}H_{26.50}N_2O_{7.25}S$
Formula weight	468.51	448.52	529.63	503.04
Crystal system	Triclinic	Triclinic	Triclinic	Monoclinic
Space group	P-1	$P\bar{1}$	P-1	C 1 2/c 1
a /Å	9.9325(3)	9.9617(2)	7.6274(3)	28.6098(8)
b /Å	10.8550(5)	10.4885(3)	11.7869(5)	7.5809(2)
c /Å	11.6232(4)	11.7892(3)	16.6678(6)	25.1015(8)
α/deg	71.681(4)	72.279(2)	70.166(4)	90
β/deg	88.434(3)	88.343(2)	79.450(3)	109.894 (3)
γ/deg	76.249(3)	77.892(2)	89.967(4)	90
V /Å^3	1154.05(8)	1146.42(5)	1382.70(10)	5119.3(3)
Z	2	2	2	8
*D*calc /g cm^{-3}]	1.384	1.299	1.272	1.305
μ /mm^{-1}	0.183	0.175	0.158	0.174
F(000)	492.0	472.0	560.0	2116.0
Data/ restraints/ parameters	4055/0/300	4021/0/292	4033/0/358	4490/2/333
S	1.090	1.047	1.041	1.054
R1 [I>2σ(I)]	0.0585	0.0387	0.0756	0.0656
wR2 [all data]	0.1827	0.1034	0.2295	0.2297
Max./min. residual electron dens. [eÅ^{-3}]	0.301/-0.330	0.398/-0.299	0.356/-0.417	0.458/-0.233

[a]$R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $wR2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

Table 17: Crystal data for compounds **13ae**, **13de**, **15aa,** and **15ad**

Compound	**13ae**	**13de**	**15aa**	**15ad**
Emp. formula	$C_{24}H_{24}N_2O_6S$	$C_{24}H_{23}N_3O_8S$	$C_{22}H_{20}N_2O_2$	$C_{22}H_{19}ClN_2O_2$
Formula weight	468.51	513.51	344.40	378.84
Crystal system	Triclinic	Monoclinic	Monoclinic	Triclinic
Space group	P-1	P 1 21/c 1	P 1 21/c 1	$P\bar{1}$
a /Å	10.4628(11)	15.4857(10)	7.7602(3)	7.7212(2)
b /Å	10.5169(8)	7.4695(3)	18.1771(5)	11.1694(5)
c /Å	12.3713(12)	22.8213(16)	13.0701(3)	11.7336(3)
α/deg	88.373(7)	90	90	94.179(3)
β/deg	76.896(9)	108.918(7)	105.663(3)	107.705(3)
γ/deg	64.067(9)	90	90	100.577(3)
V /Å^3	1188.4(2)	2497.2(3)	1775.18(10)	938.62(6)
Z	2	4	4	2
*D*calc /g cm^{-3}]	1.309	1.366	1.289	1.340
μ /mm^{-1}	0.178	0.183	0.083	0.223
F(000)	492.0	1072.0	728.0	396.0
Data/ restraints/ parameters	4179/0/301	4367/0/327	3702/0/105	4018/0/245
S	0.926	0.897	1.056	1.047
R1 [I>2σ(I)]	0.0623	0.0710	0.0471	0.0636
wR2 [all data]	0.1820	0.2292	0.1293	0.2169
Max./min. residual electron dens. [eÅ^{-3}]	0.388/-0.331	0.407/-0.286	0.146/-0.239	0.308/-0.278

[a] $R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $wR2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

Table 18: Crystal data for compounds **15db**, **15ea**, **15fn** and **15hb**

Compound	**15db**	**15ea**	**15fn**	**15hb**
Emp. formula	$C_{24}H_{24}N_2O_3$	$C_{24}H_{24}N_2O_2$	$C_{27}H_{28}N_2O_2$	$C_{20}H_{22}N_2O_3$
Formula weight	388.45	372.45	412.51	338.39
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic
Space group	P-1	P-1	P 1 21 1	P 1 21/c 1
a /Å	9.6344(2)	10.3894(2)	19.6988(7)	15.2491(8)
b /Å	9.6501(2)	15.4809(3)	5.8442(2)	16.1792(9)
c /Å	12.2018(5)	26.3072(7)	20.8257(7)	7.2348(3)
α/deg	101.844(3)	102.463(2)	90	90
β/deg	90.201(2)	100.060(2)	105.564(4)	91.610(4)
γ/deg	111.579(2)	90.455(2)	90	90
V /Å^3	1028.57(6)	4063.37(16)	2309.62(14)	1784.25(16)
Z	2	8	4	4
*D*calc /g cm^{-3}]	1.254	1.218	1.186	1.260
μ /mm^{-1}	0.083	0.078	0.075	0.085
F(000)	412.0	1584.0	880.0	720.0
Data/ restraints/ parameters	4412/0/264	16908/0/1013	9137/10/553	3776/0/228
S	1.066	1.056	1.008	0.964
R1 [I>2σ(I)]	0.0610	0.0829	0.0707	0.0696
wR2 [all data]	0.1654	0.2511	0.2286	0.2172
Max./min. residual electron dens. [eÅ^{-3}]	0.152/-0.266	0.237/-0.222	0.449/-0.360	0.237/-0.301

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 19: Crystal data for compounds **16aa**, **17db**, **18ia** and **18ie**

Compound	**16aa**	**17db**	**18ia**	**18ie**
Emp. formula	$C_{28}H_{26}N_2O_4S$	$C_{24}H_{24}N_2O_3$	$C_{19}H_{22}N_2O_3$	$C_{18}H_{19}N_3O_4$
Formula weight	486.57	388.45	326.38	341.36
Crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	I 1 2/a 1	P-1	P 1 21/c 1	P 1 21/c 1
a /Å	16.0766(4)	9.0743(3)	6.7921(6)	14.0632(7)
b /Å	16.6712(4)	11.2346(3)	7.5593(9)	12.0092(5)
c /Å	19.2809(4)	12.0008(5)	34.241(3)	10.4688(4)
α/deg	90	113.289(3)	90	90
β/deg	99.128(2)	110.762(3)	92.634(7)	108.022(5)
γ/deg	90	91.021(2)	90	90
V /Å^3	5102.2(2)	1032.85(7)	1756.2(3)	1681.31(13)
Z	8	2	4	4
*D*calc /g cm^{-3}]	1.267	1.249	1.234	1.349
μ /mm^{-1}	0.163	0.083	0.084	0.097
F(000)	2048.0	412.0	696.0	720.0
Data/ restraints/ parameters	5349/0/317	4430/0/264	3672/0/219	2960/0/227
S	1.105	1.025	0.981	1.026
R1 [I>2σ(I)]	0.0496	0.0537	0.0736	0.0650
wR2 [all data]	0.1503	0.1647	0.2311	0.2160
Max./min. residual electron dens. [eÅ^{-3}]	0.151/-0.348	0.223/-0.209	0.208/-0.234	0.180/-0.324

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 20: Crystal data for compounds **19id**, **20ah**, **21ad** and **23ad**

Compound	**19id**	**20ah**	**21ad**	**23ad**
Emp. formula	$C_{13}H_{13}ClN_2O_2$	$C_{24}H_{23}NO_7$	$C_{19}H_{19}ClO_4$	$C_{19}H_{19}ClO_4$
Formula weight	264.71	437.43	346.79	346.79
Crystal system	Monoclinic	Triclinic	Triclinic	Monoclinic
Space group	P 1 21/c 1	P-1	P-1	P 1 21/c 1
a /Å	14.3294(17)	8.4988(2)	12.7297(3)	8.3051(6)
b /Å	15.1851(18)	12.3560(4)	12.8261(4)	23.4826(16)
c /Å	6.0108(7)	12.5322(4)	12.9349(3)	9.4132(9)
α/deg	90	63.027(3)	79.005(2)	90
β/deg	94.959(10)	80.888(2)	68.430(2)	109.650(9)
γ/deg	90	89.088(2)	65.172(3)	90
V /Å^3	1303.0(3)	1155.72(7)	1780.83(9)	1728.9(3)
Z	4	2	4	4
*D*calc /g cm^{-3}]	1.349	1.257	1.293	1.332
μ /mm^{-1}	0.289	0.093	0.233	0.240
F(000)	552.8	460.0	728.0	728.0
Data/ restraints/ parameters	2285/0/168	4960/0/291	7434/0/429	2967/2/218
S	1.031	1.017	1.203	0.918
R1 [I>2σ(I)]	0.0721	0.0617	0.0838	0.0612
wR2 [all data]	0.2560	0.1999	0.2756	0.1667
Max./min. residual electron dens. [eÅ^{-3}]	0.4263/-0.5005	0.183-0.192	1.067/-1.096	0.173/-0.216

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

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PART B

PALLADIUM-CATALYZED INTRAMOLECULAR TRANSFORMATIONS OF INDOLYL-IODOARYLULFONAMIDES: *ortho*-SULFONAMIDO-BI(HETERO)ARYLS *via* C2 ARYLATION AND POLYCYCLIC SULTAMS *via* C3 ARYLATION

PART B

Chapter 4

INTRODUCTION

This chapter includes work that is related to the topics that will be covered in Chapter 5. Sections 4.1 and 4.2 provide a brief introduction to the chemistry of sulfonamides as relevant to the present study. Current reports on reactions of indole substrates with sulfonamides are explained in section 4.3, whereas transition metal-catalyzed benzosultam synthesis is explored in section 4.4

4.1 General introduction: Sulfonamides

Sulfonamide functional group has been recognized as a significant structural motif in drug development. Sulfamethoxazole (antibacterial) and almotriptan (antimigraine agent) are two familiar drugs.[1] Bi(hetero)aryl subunits containing an *ortho*-sulfonamide group are important scaffolds in drug discovery due to their promising bioactivities and diverse medicinal uses. For example, compound **MK-996** and its analogues such as **L-159,894** (Figure 1) are potent angiotensin II antagonists for treating hypertension.[2] The compound **PF4455242** has been developed as a selective, short-acting antagonist of the κ-Opioid receptor; it was pursued in phase I clinical trial for the treatment of bipolar disorder.[3] Compound **BPBTS** is a potent sodium channel blocker that may be used as a template for the development of analgesic agents.[4] Recently, biaryls that contain an *ortho*-sulfonamide functionality have been identified as endothelin-A (ET_A) selective antagonists.[5] In addition to serving as a pharmacophore, the bulky sulfonamide group at the *ortho*-position restricts the rotation of aryl groups along the biaryl C-C axis resulting in atropisomerism.[6a-b] 2-Arylindoles (heterobiaryls) are also important structural units in many pharmaceuticals.[7a-c] Historically, 2-arylindoles have most often been prepared by methods developed by Fischer,[8a-b] Bischler-Mohlau,[9a-b] Larock,[10a-b] and Hegedus.[11] Considering the significance of this class of compounds, developing more efficient and sustainable methods to access them is still desirable. In recent years, several transition-metal-catalyzed C-H activation/annulation[12a-k] and the tandem reactions[13a-c] have been developed to access 2-

arylindoles. However, *ortho*-sulfonamido-bi(hetero)aryls like 2-(1*H*-indol-2-yl)benzenesulfonamides (e.g., **A** in Figure 1) are not common. Cyclic sulfonamides (sultams), are widely present in both natural products and therapeutic agents, and their application in organic synthesis and pharmaceutical chemistry has been well-demonstrated (e.g. Figure 1: **B** and **C**).[14-15] In particular, 1,2-benzothiazine-S,S-dioxide is a pharmacophore found in several marketed anti-inflammatory drugs such as meloxicam, piroxicam (Pfizer), sultiame (Bayer), and brinzolamide. Therefore, the development of new synthetic methodologies to access sultams has attracted much attention.[16]

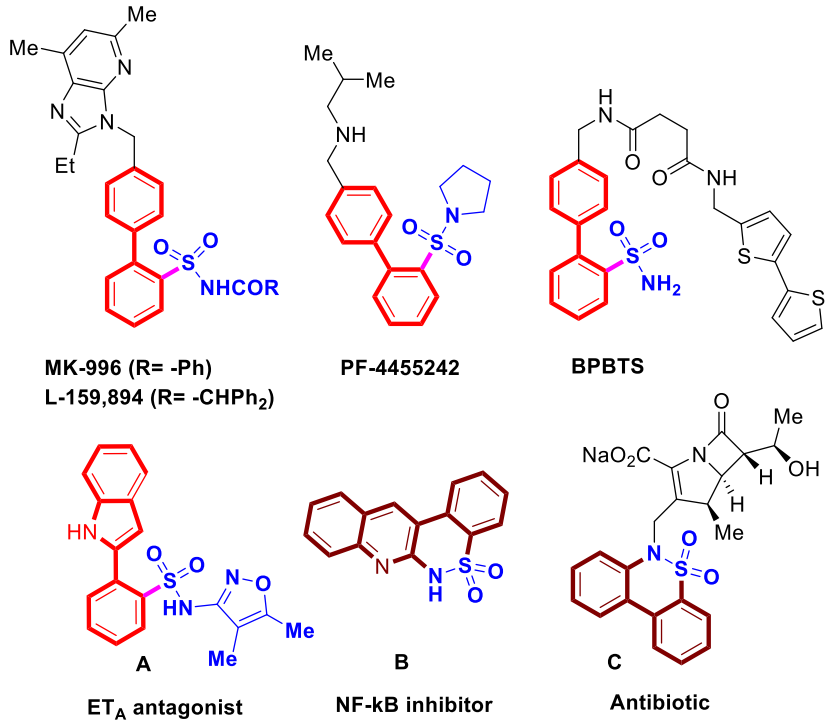
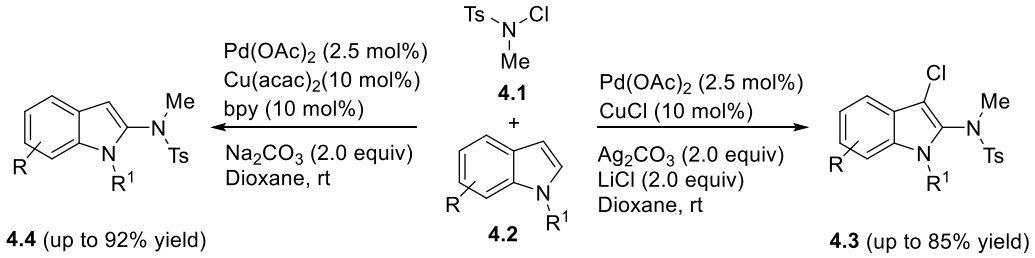


Figure 4.1. Selected examples of pharmaceutically active (i) bi(hetero)aryls with-sulfonamide group and (ii) polycyclic sultams.

4.2 Reaction of sulfonamides with indole substrates

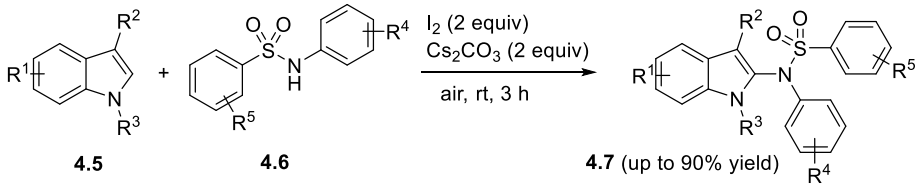
Sulfonamides are precursors that generate a variety of heterocycles by intramolecular or intermolecular cyclization as well as addition reactions because they are significant for pharmacological purposes.[17] Liang's group developed palladium-/copper-catalyzed intermolecular reaction between substituted indoles **4.2** and *N*-Chloro-*N*,4-dimethyl benzenesulfonamide **4.1** for the formation of chloroamination products **4.3** with the C-N and C-Cl bond construction in the absence of bipyridine. On the other hand, amination products **4.4**

could be obtained by using the same starting materials with the construction of only C-N bond in the presence of bipyridine (Scheme 4.1).[18]



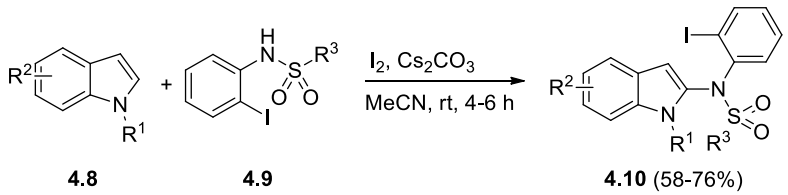
Scheme 4.1: Synthesis of chloroamination product **4.3** and amination product **4.4**

Liang *et al.* developed a technique for the direct C2-amination of indole with substituted *N*-phenyl benzenesulfonamide **4.6** that is extremely effective for the synthesis of substituted 2-aminated indoles **4.7** in the presence of iodine and Cs_2CO_3 at room temperature. The reaction occurs when an indole double bond is coordinated with iodine to form a cyclic iodonium ion. In the presence of a base, the tosylated amino group attacks on the C2 position of indole followed by the elimination of the HI molecule to give 2-aminated indole **4.7** (Scheme 4.2).[19]



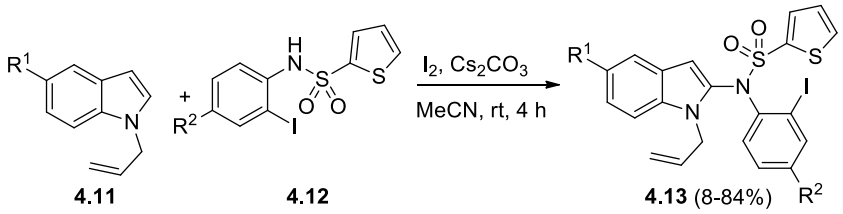
Scheme 4.2: Synthesis of substituted 2-aminated indoles **4.7**

Pal and co-workers reported the reaction between substituted indoles **4.8** and *ortho*-iodo-*N*-sulfonyl arylamine **4.9** for the synthesis of substituted *N*-(2-iodoaryl)indole **4.10** *via* iodine-mediation in the presence of Cs_2CO_3 in MeCN at room temperature (Scheme 4.3).[20] To produce indolyl benzenesulfonamide, cyclic three-membered iodonium ion is formed, which is then attacked by a reactant *ortho*-iodobenzene sulfonamide at the C2-position of the substituted indole.



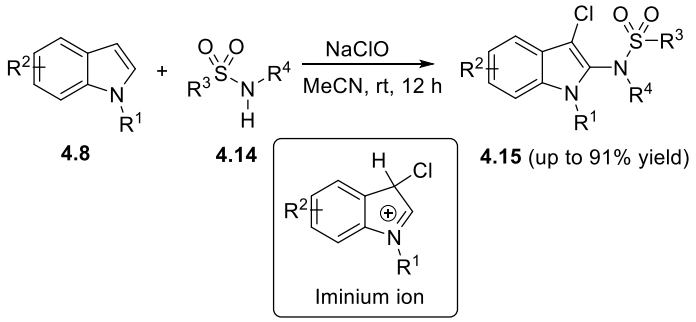
Scheme 4.3: Synthesis of substituted *N*-(2-iodoaryl)indole **4.10**

Pal and their colleagues also disclosed direct synthesis of sulfonamides *via* C2-amination of indole by using *N*-sulfonyl arylamines in the presence of iodine and cesium carbonate in acetonitrile solvent at room temperature for 4 h (Scheme 4.4).[21] This reaction also occurs *via* the formation of cyclic three-membered iodonium ion followed by the attack of a reactant at the C2-position of indole to afford indolyl benzenesulfonamide.



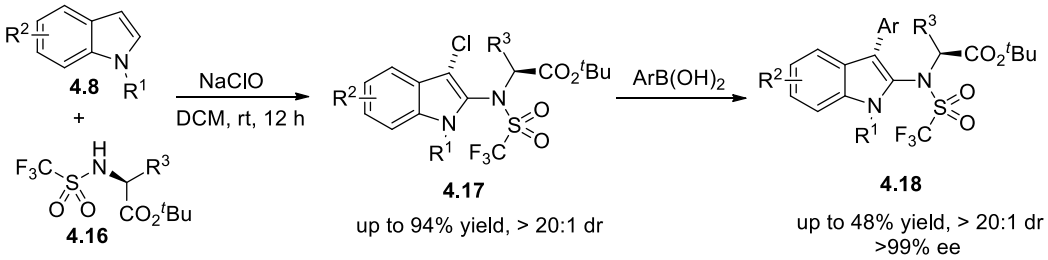
Scheme 4.4: Synthesis of indolo-sulfonamides **4.13**

In the year 2017, Yu's group developed a transition metal-free route for the construction of chloroamidation of indole **4.15** in good to excellent yields from substituted indole **4.8** by using unactivated sulfonamides **4.14** in the presence of NaClO in MeCN solvent at room temperature (Scheme 4.5).[22] Here, the sulfonamide **4.14** is first chlorinated by NaClO. This is followed by the reaction with substituted indole to give the final product *via* the iminium ion intermediate.



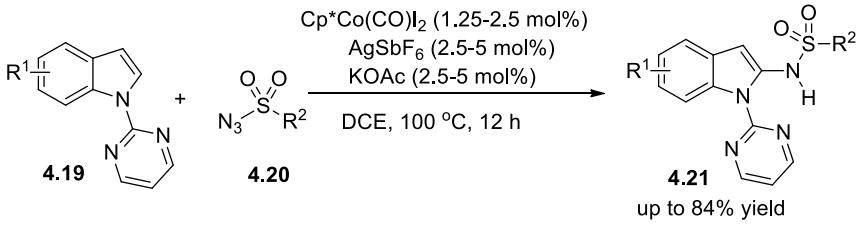
Scheme 4.5: Synthesis of chloroamidation product **4.15**

Yu and co-workers continued their work on hypohalide-mediated atroposelective coupling of substituted indoles **4.8** with chiral amino acid-based sulfonamides **4.16** for the synthesis of 2-amido-3-chloroindoles **4.17** containing the chiral axis of C-N bond with excellent diastereoselectivity (> 20:1). The C3 chlorine atom can allow other transformations, which can introduce various functionalities such as carbonyl, aryl, or alkenyl to afford the final product **4.18** (Scheme 4.6).[23]



Scheme 4.6: Synthesis of 2-substituted indoles **4.18** by atroposelective coupling

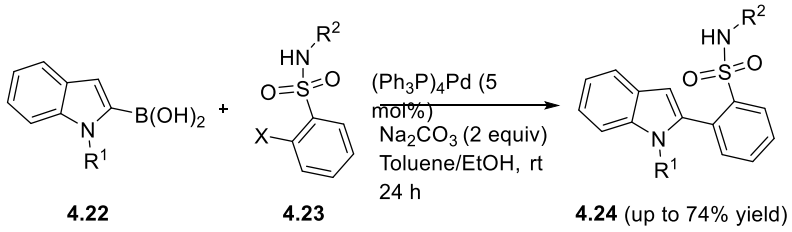
Vessally and co-workers reported cobalt-catalyzed direct sulfonamidation of aromatic C-H bonds between sulfonyl azides **4.20** and indoles **4.19** with a pyrimidine moiety that acts as a directing group. Selective sulfonamidation in the presence of $Cp^*Co(CO)I_2/AgSbF_6/KOAc$ combination gave the C2-amidated product **4.21** in good to excellent yields (Scheme 4.7).[24]



Scheme 4.7: Synthesis of indole C2-amidated product **4.21**

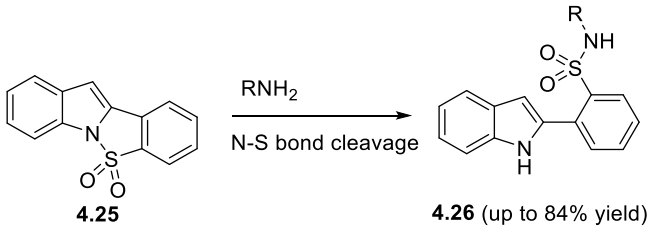
4.3 *ortho*-sulfonamido-bi(hetero)aryl scaffolds

Biaryls with an *o*-sulfonamide group are powerful, all-around active selective endothelin-A (ETA) antagonists. Murugesan and co-workers reported palladium-catalyzed coupling reaction between indole boronic acids with *ortho*-iodobenzenesulfonamide for the formaton of substituted indole 2-arylbenzene with the installation of an *ortho*-sulfonamide pharmacophore (Scheme 4.8).[5]



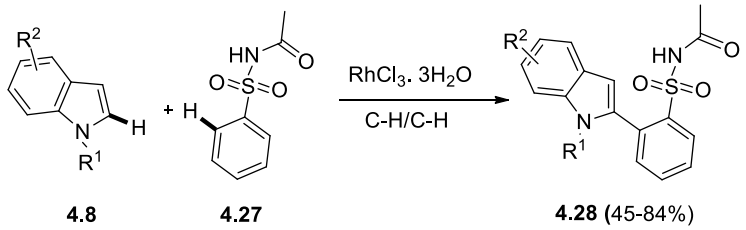
Scheme 4.8: Synthesis of indole 2-arylbenzenesulfonamide derivatives **4.24**

Laha *et al.* disclosed the reaction of heterobiaryl sultam **4.25** with an amine at 40 ^{o}C for 1.5 h in which there was a cleavage of N-S bond to give 2-arylindoles **4.26**, with the installation of an *ortho*-sulfonamide pharmacophore, in good to high yield (Scheme 4.9).[25]



Scheme 4.9: Synthesis of 2-arylindoles **4.26**

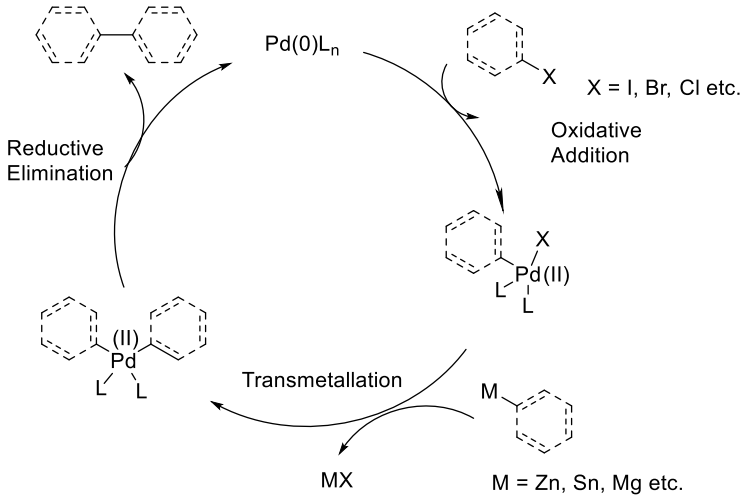
Jingsong and their colleagues disclosed an efficient rhodium-catalyzed oxidative C-H/C-H cross-coupling for the formation of *ortho*-sulfonamido bi(hetero)aryls **4.28** from aromatic sulfonamide **4.27** and substituted indoles **4.8** (Scheme 4.10).[26] This reaction was not observed in the absence of the transition metal catalyst.



Scheme 4.10: Synthesis of *ortho*-sulfonamido bi(hetero)aryls **4.28**

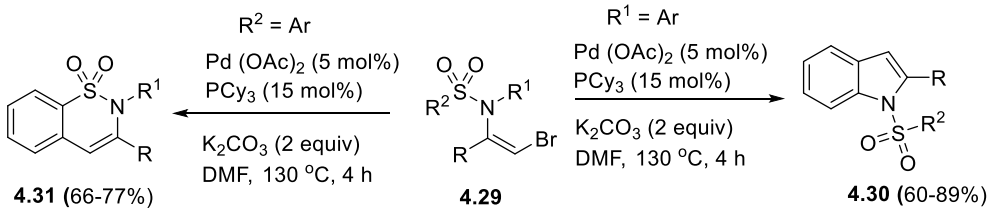
4.4 Transition metal catalyzed synthesis of benzosultam motifs

Transition metal-catalyzed C-H activation and subsequent functionalization (Ni, CO, Fe, Pt, Pd, Rh, Ir, and Ru) has been extensively studied during the last few decades and have become powerful tools for the formation of different skeleton heterocycles (Scheme 4.11).[27] The catalytic cycle is initiated by the oxidative addition of palladium(0) into aryl halide to afford the aryl-palladium halide intermediate, followed by transmetallation between palladium(II) intermediate with metal compound to afford the diaryl intermediate. Subsequent reductive elimination furnishes the biaryl product and regenerates the co-catalyst.[28]



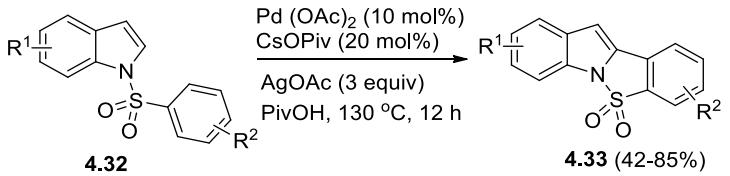
Scheme 4.11: Catalytic cycle for Pd-catalyzed cross-coupling reactions

Urabe and their colleagues reported C-H activation of bromoalkenes in 2010 for the synthesis of nitrogen heterocycles such as sultams by using a palladium catalyst. Thus when *Z*-bromoalkene **4.29** was treated with $Pd(OAc)_2$ in DMF solvent at 130 ^oC, *N*-sulfonyl indole **4.30** was obtained. On the other hand, 1,2-benzothiazine-1,1-dioxides **4.31** can be synthesized by the palladium-catalyzed cyclization involving aromatic C-H bond activation (Scheme 4.12).[29]



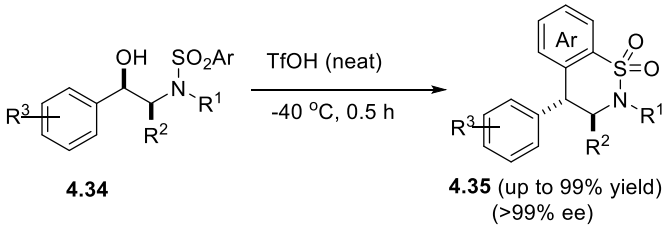
Scheme 4.12: [Pd]-Catalyzed synthesis of *N*-sulfonyl indole **4.30** and 1,2-benzothiazine 1,1-dioxide **4.31**

Laha and co-workers disclosed a novel palladium-catalyzed intramolecular oxidative coupling that utilized two C(sp^2)–H bonds in *N*-arylsulfonyl indoles for the construction of heterobiaryl sultams **4.33** in the presence of $Pd(OAc)_2$ (10 mol %), CsOPiv (20 mol %), AgOAc (3 equiv), and PivOH at 130 °C. This reaction takes place by coupling the *ortho*-position of the aryl-sulfonyl group with the C-2 position of the indole **4.32** and is catalyzed by Pd(II) (Scheme 4.13).[25]



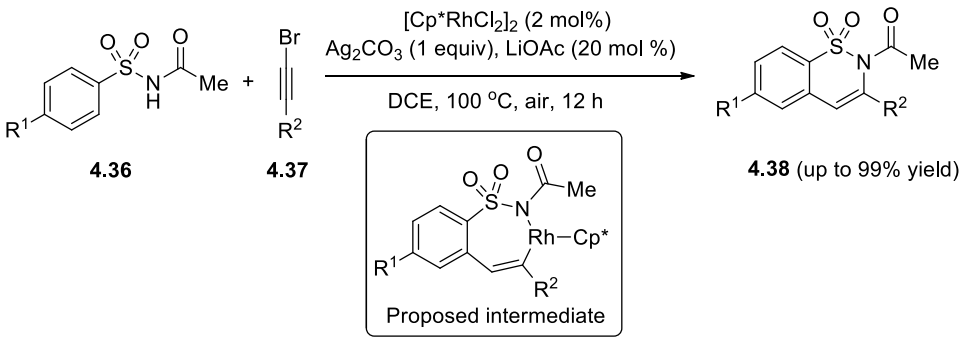
Scheme 4.13: [Pd]-Catalyzed synthesis of heterobiaryl sultam **4.33**

In the year 2020, Michelet and co-workers disclosed the formation of enantiopure benzosultams **4.35** from the easily available ephedrines **4.34** that undergo an intramolecular Friedel-Crafts reaction in the presence of triflic acid at -40 °C. This reaction proceeds through the formation of benzyl carbocation. Ephedrine derivatives, which have alkyl electron-donating groups on the aromatic ring, were easily converted to the corresponding enantiopure benzosultams **4.35** in good to outstanding yields. The strong deactivating substituents CF_3, C(O)Me, and NO_2 groups prevented cyclization. The authors chose to use neat trifluoromethanesulfonic acid at -40 °C to prevent the production of any regioisomeric by-products and to improve the reproducibility (Scheme 4.14).[15f]



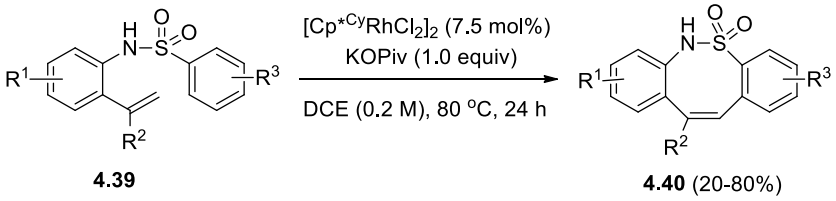
Scheme 4.14: Synthesis of enantiopure benzosultams **4.35**

Cramer and their colleagues discovered the C-H activation of substituted *N*-tosylacetamide and bromo alkynes **4.37** by using Rh(III) catalyst that leads to the formation of fused benzosultams **4.38** in moderate to high yields through the formation of a cyclo-methylated intermediate. In this reaction, aryl sulfonamides **4.36** containing electron-rich or electron-deficient groups are effective for this transformation by Rh-catalyst, Ag_2CO_3, and LiOAc in DCE solvent at 100 °C (Scheme 4.15).[30]



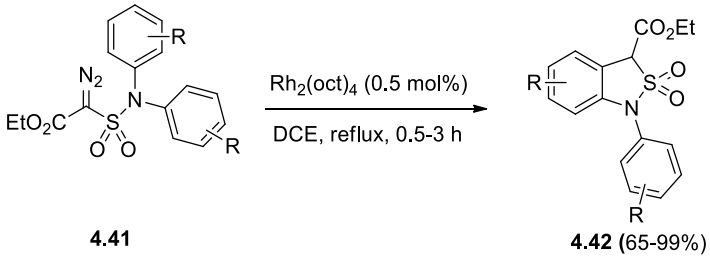
Scheme 4.15: [Rh]-Catalyzed synthesis of benzosultams with a six-membered ring

Zhou and Yi *et al*. found an interesting C-H activation of *N*-(2-(prop-1-en-2-yl) phenyl) benzenesulfonamide **4.39** in the presence of Rh(III) catalyst that produces eight-membered benzosultams **4.40** with good chemoselectivity. The C-H activation and hydrogen transfer were assisted by KOPiv. It was discovered that using $[Cp^{*Cy}RhCl_2]_2$/ KOPiv catalysts together could work well for this transformation (Scheme 4.16).[31]



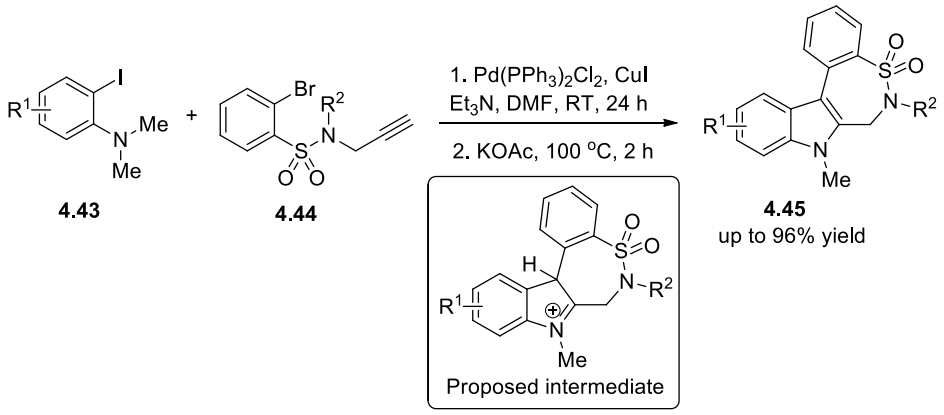
Scheme 4.16: [Rh]-catalyzed synthesis of benzosultams with an eight-membered ring

In the year 2014, Xu *et al*. reported an intramolecular aromatic C-H functionalization of *N*,*N*–diaryl diazosulfonamides **4.41** with 0.5 mol% $Rh_2(oct)_4$ [oct = octanoate] as the catalyst in DCE solvent under reflux conditions for the formation of five membered benzosultams **4.42** (Scheme 4.17).[32]



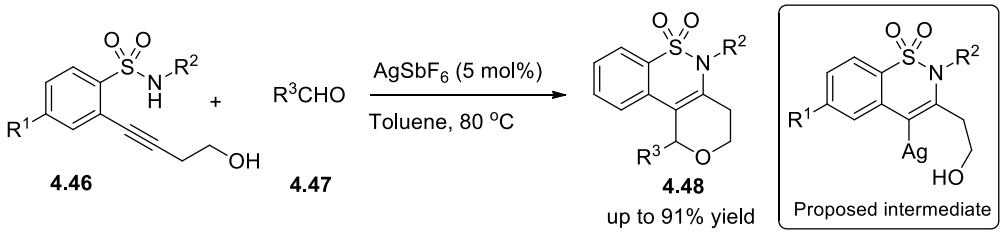
Scheme 4.17: [Rh]-catalyzed synthesis of *N*-aryl-benzo-γ-sultams **4.42**

In the year 2018, Mondal and their colleagues reported a one-pot method for the synthesis of unique cyclic benzosultams **4.45** in good to excellent yields by using readily available starting materials. This coupling reaction proceeds involving 2-iodophenylamine **4.43** with propargyl sulfonamides **4.44** in the presence of DMF solvent by using Et_3N as a base at rt for 24 h to produce an intermediate followed by addition of KOAc at 100 ^oC for 2 h to afford the aromatized product (Scheme 4.18).[33]



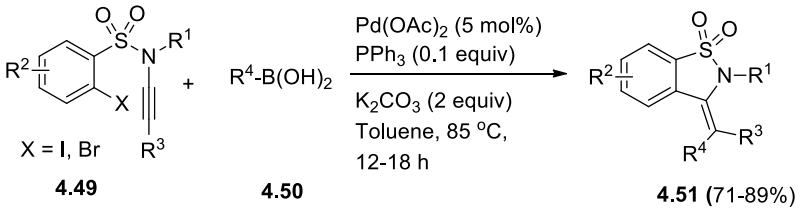
Scheme 4.18: [Pd]/[Cu]-Catalyzed **s**ynthesis of indole-fused benzosultams **4.45**

Reddy and coworkers reported a cyclized sultams **4.48** through C-N, C-O and C-C bond formation from alkynols **4.46** and aldehyde **4.47** *via* silver-promoted cyclization. The catalyst $AgSbF_6$ was the best option for this reaction, whereas Lewis acids like *p*-TSA, TFA, $FeCl_3$ etc. failed to give the same reaction. The reaction proceeds through the interaction of silver-catalyst with hydroxy alkynes generating an Ag-π bonded complex followed by cyclization involving 6-*endo*-dig to give a transition state intermediate, which leads to the formation of the final product (Scheme 4.19).[34]



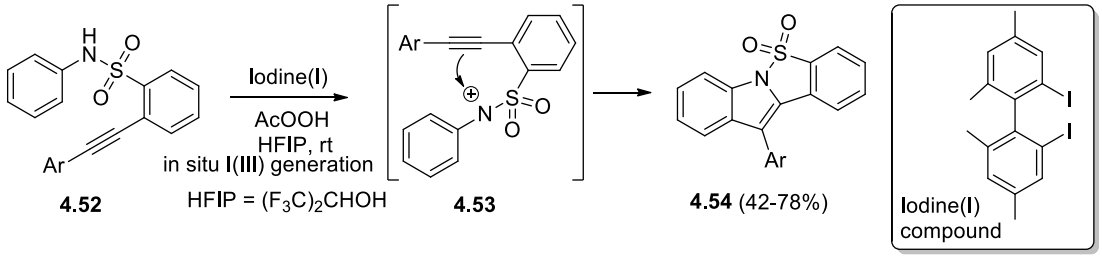
Scheme 4.19: [Ag]-Catalyzed synthesis of fused benzo-δ-sultams **4.48**

Very recently, our group has developed a palladium-catalyzed reaction of boronic acids **4.50** with ynamides **4.49** for the synthesis of benzosultams **4.51**. Among the Pd-catalysts, $Pd(OAc)_2$ was found to be the most suitable for this conversion. Among the phosphines tris(*o*-tolyl)phosphine, triphenylphosphine, tri-tert-butylphosphine, tricyclohexylphosphine, and tributylphosphine that were checked, PPh_3 was found to be the most appropriate for this reaction (Scheme 4.20).[35]



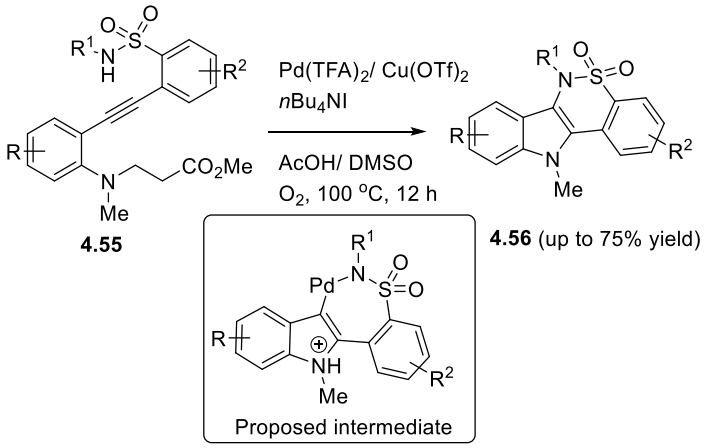
Scheme 4.20: [Pd]-Catalyzed synthesis of benzosultam **4.51**

Laura's group reported an iodine(III)-catalyzed regioselective synthesis of tetracyclics **4.54**. They used *N*-phenyl-benzene alkynyl sulfonamide **4.52** for this transformation. The reaction proceeds through intramolecular oxidative electrophilic N-H and C-H bond functionalization involving 5-*exo-dig* cyclization (Scheme 4.21).[36]



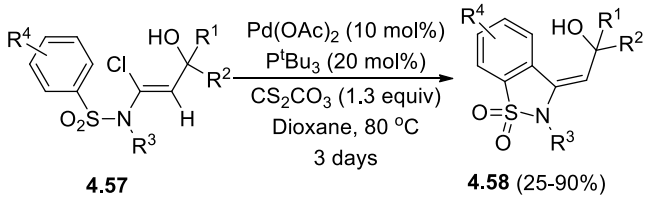
Scheme 4.21: I(III) Catalyzed synthesis of tetracyclic **4.54**

Zhu *et al*. reported the oxidative double cyclization of 1,2-diarylethynes with an *N*-methyl-N(2-methoxycarbonyl)ethylamino and an aminosulfonyl group catalyzed by Pd(II) that yielded indolobenzothiazine S,S-dioxide in good to high yields (Scheme 4.22).[16] The reaction of compound **4.55** with $Pd(TFA)_2$ in DMSO gave an intermediate (cf. Scheme 4.22).which was converted to the final product through the Pd(II)/Pd(0) catalytic cycle.



Scheme 4.22: [Pd]/[Cu]-Catalyzed synthesis of indole-fused benzosultams

To produce (*E*)-2,3-dihydrobenzoisothiazole 1,1-dioxides **4.58**, Suzuki reaction of both (*E*)- and (*Z*)-chloro-hydroxyenamides **4.57** was described by Matsuo *et al*. in 2018. Only trisubstituted enamides **4.58** were stereoselectively produced by the reaction (Scheme 4.23).[37] It was discovered that the γ-hydroxy group in chloroenamides accelerates and affects the geometry at the exocyclic double bond of the products. The products have dual activity as enamide and allylic alcohol which make them excellent intermediates for the synthesis of substituted amines.



Scheme 4.23: [Pd]-Catalyzed synthesis of trisubstituted enamides **4.58**

Zhang *et al.* reported catalytic C-H amination of arylsulfonyl azides **4.59** in the presence of a nonoxidative and neutral medium for the formation of cyclic sultams **4.60** (Scheme 4.24).[38] The EPR experiments are carried out to confirm the presence of α-Co(III)-aminyl radical as an intermediate. The greater value of kinetic isotopic effect (KIE) indicated carbon-hydrogen bonds were broken by *α*-Co(III)-aminyl complex through H-atom abstraction.

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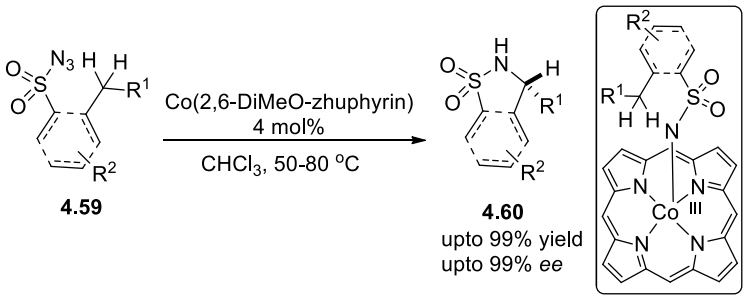
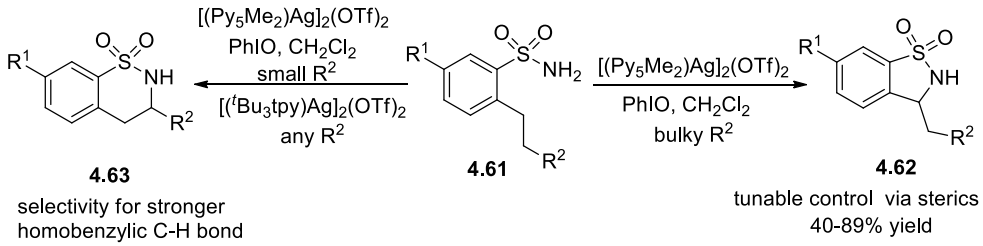


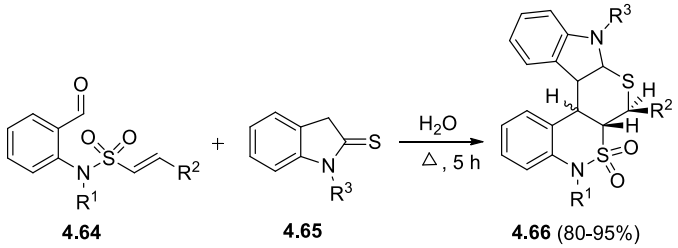
Scheme 4.24: [Co]-Catalyzed synthesis of cyclic sulfonamides **4.60**

Schomaker *et al.* reported that an electronically and sterically controllable transfer of the nitrine group for the amination was initiated by the silver catalyst, resulting in a variety of five- and six-membered benzosultams **4.62** and **4.63**. Thus benzosultams **4.63** with a six-membered ring were produced when alkyl-substituted benzenesulfonamide precursors were used (Scheme 4.25).[39]



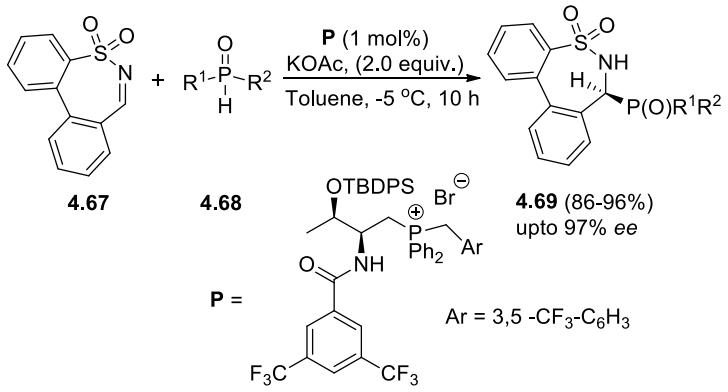
Scheme 4.25: [Ag]-Catalyzed synthesis of five- and six-membered benzosultams

Very recently, Langer's group reported domino Knoevenagel/intramolecular hetero-Diels-Alder reaction of highly substituted sulfonamides **4.64** with substituted indoline-2-thiones **4.65** in water. The protocol involves the high-yielding with catalyst free regioselective formation of pentacyclic benzosultam-annulated thiopyranoindole derivatives **4.66** (Scheme 4.26).[40]



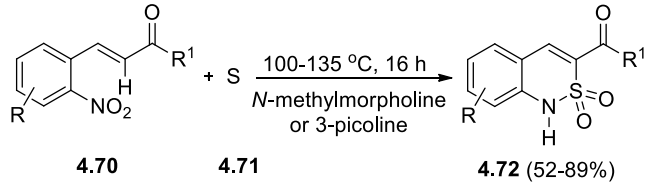
Scheme 4.26: Catalyst-free synthesis of compound **4.66**

Wang's and their colleagues recently reported the first seven-membered cyclic benzosultams **4.69** which were produced by enantioselective hydrophosphonylation of seven-membered cyclic imines **4.67** with substituted phosphine oxides **4.68**. The highly enantioselective benzosultams **4.69** were isolated in excellent yields with minimal catalyst loading (1 mol%). A nucleophilic attack of phosphorous from the Si face on cyclic imine takes place in the transition state (Scheme 4.27).[41]



Scheme 4.27: Synthesis of benzosultams **4.69**

Using 2-nitrochalcones **4.70** and elemental sulfur **4.71**, Nguyen and their colleagues presented a simple and atom-efficient construction of six-membered sultams **4.72** in 2017. This was done by using 3-methylpyridine (Scheme 4.28).[42]. A new bond formation of sulfur-nitrogen, carbon-sulfur, and sulfoxide bonds of the sulfonamides takes place between *ortho*-substituted nitro chalcone and elemental sulfur.



Scheme 4.28: Catalyst-free synthesis of benzosultams **4.72**

It is clear from the above survey that indolyl-based sultams are of sufficient current interest for organic chemists and hence exporing new synthetic routes to this class of compounds is worth investigating.

OBJECTIVES OF THE PRESENT WORK-PART B

The primary goal of this section of the endeavour was to investigate the reactivity of indolyl substituted iodo-sulfonamides under [Pd]-catalyzed conditions in the presence of different bases. More specifically, it was planned to investigate

(i) Palladium-catalyzed intramolecular transformations of indolyl-iodobenzenesulfonamides to check possible C2-N bond cleavage and C2-arylation, and

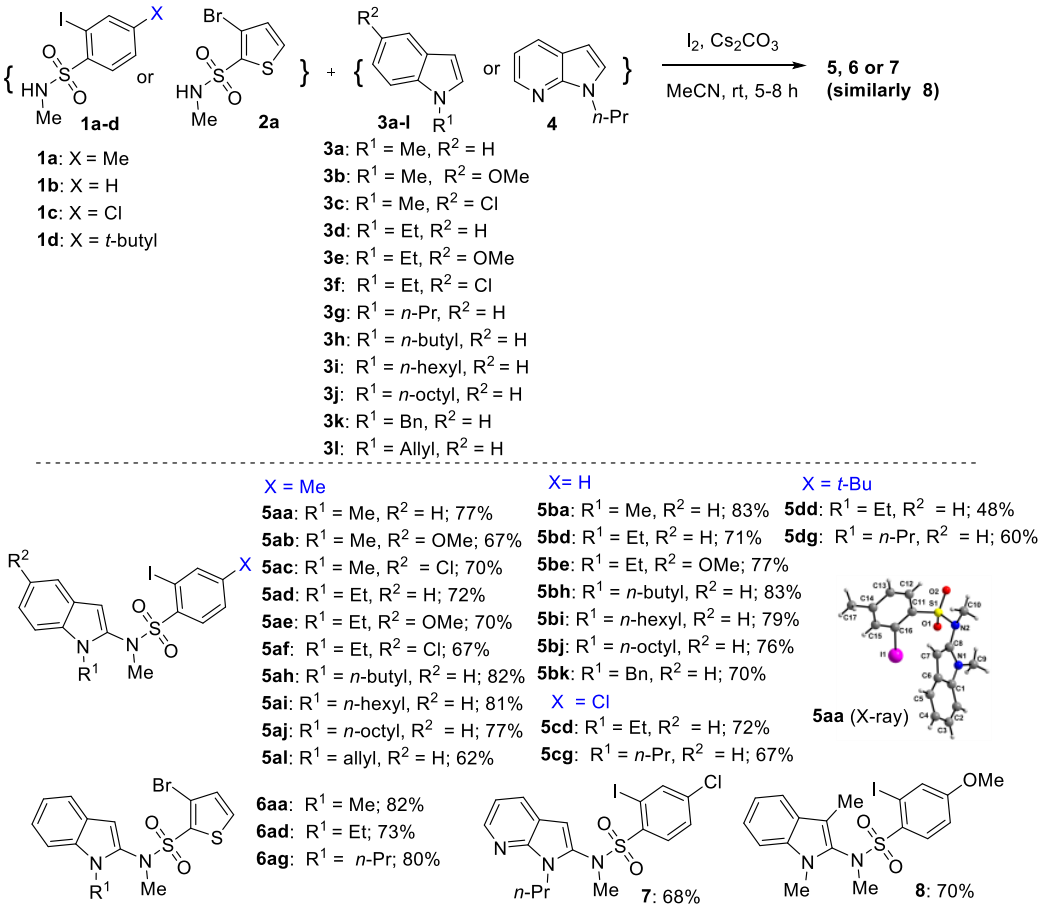
(ii) Possible intramolecular transformation of indolyl-iodobenzenesulfonamides using [Pd]-catalysis leading to polycyclic sultams *via* C3 arylation.

RESULTS AND DISCUSSION

This chapter deals with [Pd]-catalyzed reactions of indole-appended *ortho*-iodo-benzenesulfonamides or *ortho*-bromo-thoiophenesulfonamides. Details are presented below.

5.1 Precursors used in the present study

The precursors **1a-d, 2a, 3a-l**, and **4** used in the present study have been prepared by using standard literature procedures.[43] The substrates **5-7** were obtained from the reaction of indoles **3** and **4** with *N*-methyl sulfonamides **1** and **2** using I_2/ Cs_2CO_3 in acetonitrile at 60 ^oC/ 12 h (Scheme 1). A similar procedure was used to prepare compound 8.



Scheme 1. Synthesis of sulfonamide precursors

5.2 [Pd]-catalyzed intramolecular transformations of indolyl-iodoarylsulfonamides: Formation of *ortho*-sulfonamido-bi(hetero)aryls and polycyclic Sultams

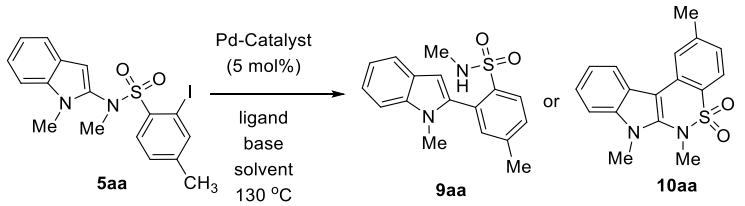
Palladium-catalyzed and base-dependent intramolecular *ipso*-substitution and cyclization strategies involving *N*-indolyl-substituted aryl-sulfonamides for the rapid construction of 2-aryl indole and indole-fused six-membered sultams are described herein. The $Pd(OAc)_2/Ph_3P/Et_3N$ combination delivers indolyl C(2)-arylated motifs *via* C(2)-N bond cleavage followed by C-C bond formation. In sharp contrast to this, the $Pd(OAc)_2/Ph_3P/K_2CO_3$ catalyzed intramolecular-Heck cross-coupling affords sultams exclusively. Details are presented below.

5.2.1 *Synthesis of ortho-sulfonamido-bi(hetero)aryls and polycyclic sultams from indolyl-iodoarylsulfonamides*

Initially, we examined the reaction of 2-iodo-*N*,4-dimethyl-*N*-(1-methyl-1*H*-indol-2-yl)benzenesulfonamide **5aa** using $Pd(OAc)_2$ (5.0 mol %), Ph_3P (10 mol%) and Et_3N (2.5 equiv) in DMF. Surprisingly, we obtained the C(2)-aryl bonded product **9aa**. This interesting C(2)-arylation prompted us to explore this reaction further to identify optimal conditions and the results are collated in Table 1. The screening of catalysts such as $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2/PPh_3$, $Pd(OAc)_2$/X-Phos, $Pd(OAc)_2/P(o\text{-tol})_3$, $Cu(OAc)_2$, and CuI with Et_3N as the base was performed in DMF (entries 1-8). The results revealed that $Pd(OAc)_2/PPh_3$ was the most suitable catalytic system and drove the reaction efficiently to give **9aa** in high yield (84%; entry 4). The combination of $Pd(OAc)_2$ with other ligands like X-phos and $P(o\text{-tol})_3$ also afforded **9aa** in moderate to good yields (entries 5-6). In the absence of palladium catalyst, product **9aa** was not observed (entry 9). Lowering of catalyst loading to 2.5 mol % decreased the yield whereas increasing the catalyst loading to (10 mol %) did not improve the yield of the reaction (entry 10). Among the solvents, DMSO, *N*,*N*-dimethylacetamide (DMA), 1,4-dioxane, toluene, and CH_3CN (entries 4, 11-15) were tested, DMF was found to be the solvent of choice. Conducting the reaction at 70 ^oC/12h or 150 ^oC/ 4 h afforded **9aa** in nearly the same yield (entry 16). Among the bases tested, Et_3N provided the best result (entries 4, 17-22). Surprisingly, the bases Na_2CO_3, Cs_2CO_3, and K_2CO_3 offered the C(3)-arylated cyclization product **10aa** in good yield (entries 19-22). The use of other [Pd]-catalysts and solvents did not improve the yield of

10aa (entries 23-27). Hence conditions in entries 4 and 21 were determined as optimal for the **9** and **10** series, respectively.

Table 1. Screening of reaction conditions for the synthesis of 9aa and 10aa[a,]



Entry	Catalyst/ligand	Base	Solvent	yield of **9aa** (%)[b]	yield of **10aa** (%)[b]
1	$Pd_2(dba)_3$	Et_3N	DMF	64	nd
2	$Pd(PPh_3)_2Cl_2$	Et_3N	DMF	47[c]	nd
3	$Pd(PPh_3)_4$	Et_3N	DMF	42	nd
4	**$Pd(OAc)_2/PPh_3$**	**Et_3N**	**DMF**	**84**	**nd**
5	$Pd(OAc)_2$/X-Phos	Et_3N	DMF	80	nd
6	$Pd(OAc)_2/P(o\text{-tol})_3$	Et_3N	DMF	82	nd
7	$Cu(OAc)_2$	Et_3N	DMF	nd	nd
8	CuI	Et_3N	DMF	nd	nd
9	-	Et_3N	DMF	nd[c]	nd
10	$Pd(OAc)_2/PPh_3$	Et_3N	DMF	(58)83[d]	nd
11	$Pd(OAc)_2/PPh_3$	Et_3N	DMSO	65	nd
12	$Pd(OAc)_2/PPh_3$	Et_3N	DMA	46	nd
13	$Pd(OAc)_2/PPh_3$	Et_3N	Toluene	52	nd
14	$Pd(OAc)_2/PPh_3$	Et_3N	1,4 dioxane	39	nd
15	$Pd(OAc)_2/PPh_3$	Et_3N	MeCN	25	nd
16	$Pd(OAc)_2/PPh_3$	Et_3N	DMF	(78)84[e]	nd
17	$Pd(OAc)_2/PPh_3$	DABCO	DMF	65	nd
18	$Pd(OAc)_2/PPh_3$	DIPEA	DMF	54	nd

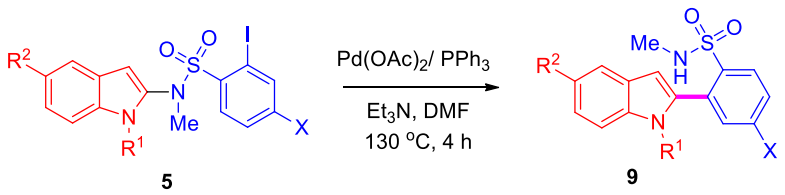
19	$Pd(OAc)_2/PPh_3$	Na_2CO_3	DMF	nd	78
20	$Pd(OAc)_2/PPh_3$	KO*t*-Bu	DMF	nd	10
21	**$Pd(OAc)_2/PPh_3$**	**K_2CO_3**	**DMF**	**nd**	**86**
22	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	DMF	nd	80
23	$Pd_2(dba)_3$	K_2CO_3	DMF	nd	78
24	$Pd(OAc)_2/P(o\text{-tol})_3$	K_2CO_3	DMF	nd	83
25	$Pd(OAc)_2/PPh_3$	K_2CO_3	MeCN	nd	36
26	$Pd(OAc)_2/PPh_3$	K_2CO_3	1,4 dioxane	nd	42
27	$Pd(OAc)_2/PPh_3$	K_2CO_3	Toluene	nd	47

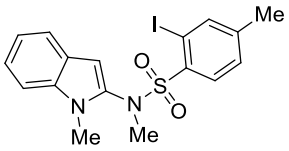
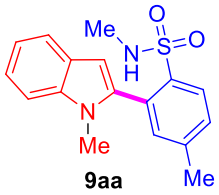
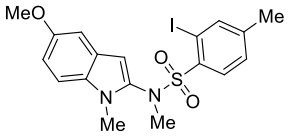
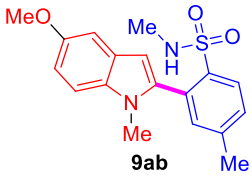
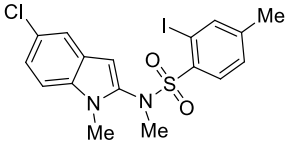
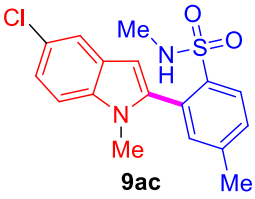
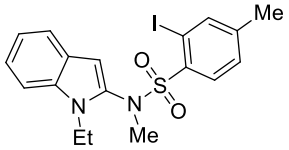
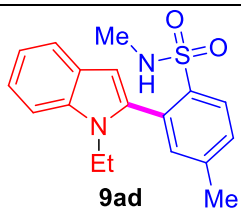
[a]Reaction conditions for **9aa**: **5aa** (0.23 mmol), catalyst (5.0 mol%), ligand (10 mol%) and base (0.57 mmol) in solvent (2.0 mL) at 130 ^oC (oil bath) for 4h. [b]Isolated yield of **9aa**. [c]No catalyst was added. [d]2.5 mol % and 10 mol % of catalyst was used. [e]The yields are for the reaction performed at 70 ^oC/10 h (78%) and 150 ^oC/ 3 h (84%). nd=not detected.

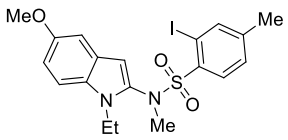
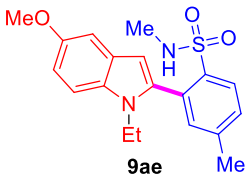
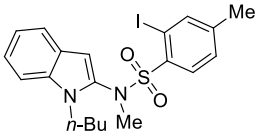
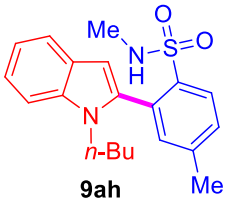
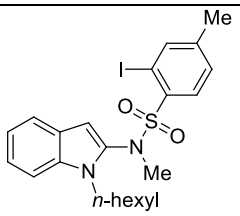
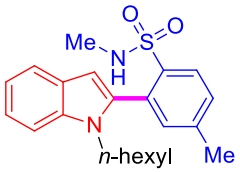
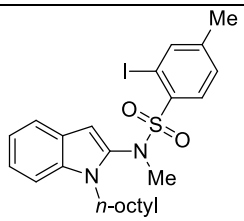
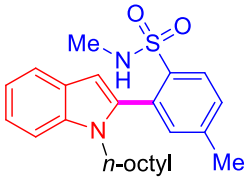
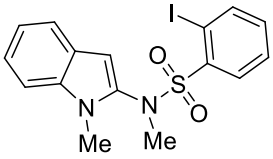
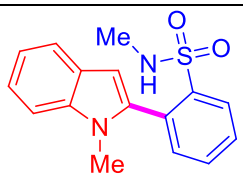
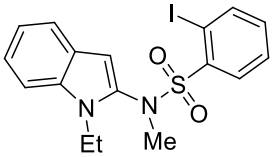
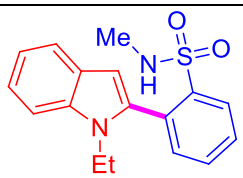
[a]Reaction conditions for **10aa**: **5aa** (0.23 mmol), catalyst (5.0 mol%), ligand (10 mol%) and base (0.57 mmol) in solvent (2.0 mL) at 130 ^oC (oil bath) for 3h.

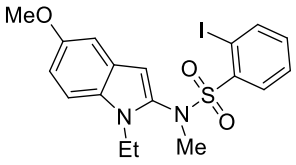
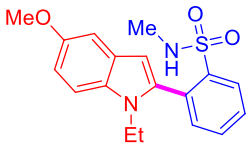
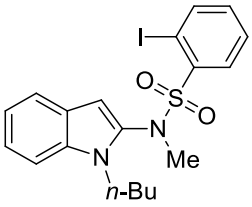
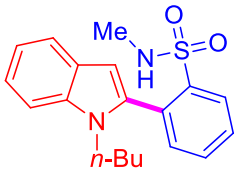
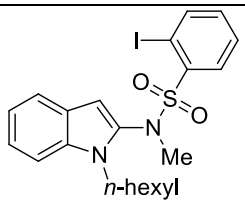
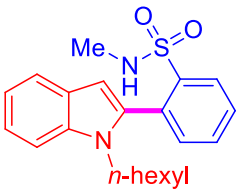
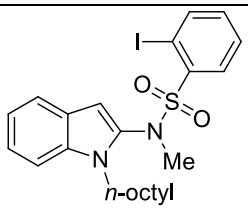
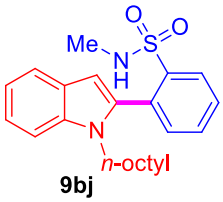
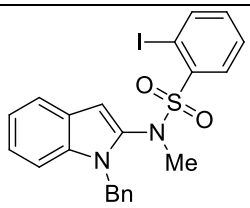
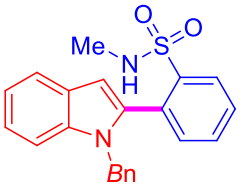
The results on substrate scope are summarized in Table 2. We tested a reaction using $Pd(OAc)_2$-PPh_3 combination in the presence of pyridine at higher temperature (130 ^oC) but did not observe any reaction. Substituents like methyl, ethyl, *n*-propyl, *n*-butyl, *n*-hexyl, *n*-octyl), and benzyl on the indole nitrogen furnished the desired products in moderate to good yields of 67-85% (Scheme 3). Indoles bearing electron-donating (OMe; **9ab, 9ae and 9be**) or electron-withdrawing group (Cl; **9ac**) gave moderate to good yields to afford the corresponding products**.** Substituents like Me, Cl, and *t*-butyl on the *N*-aryl ring of **5** were well tolerated. The molecular structures of **9ba** (X-ray, Figure I) and **9bh** (X-ray, Figure 1) were confirmed unambiguously by single crystal X-ray diffraction.

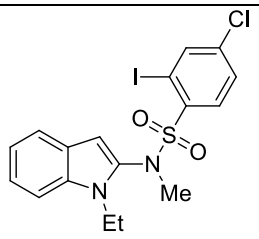
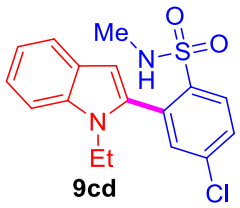
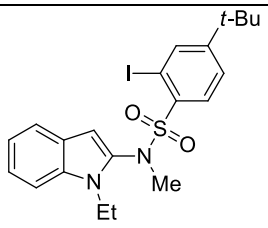
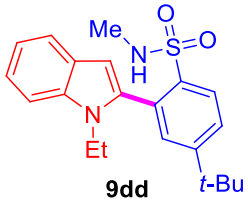
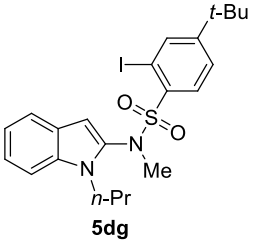
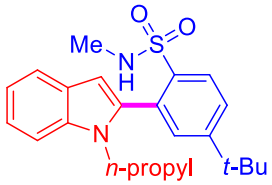
Table 2. Substrate scope for [Pd]-catalyzed synthesis of 2-(indol-2-yl)benzenesulfonamides 9[a,b]



Entry	2-iodo-*N*,4-dimethyl-*N*-(1-methyl-1*H*-indol-2-yl)benzenesulfonamide	2-(indol-2-yl)benzenesulfonamides	Yield **9** (%)[b]
1	 **5aa**	 **9aa**	84
2	 **5ab**	 **9ab**	75
3	 **5ac**	 **9ac**	69
4	 **5ad**	 **9ad**	85

5	 **5ae**	 **9ae**	75
6	 **5ah**	 **9ah**	73
7	 **5ai**	 **9ai**	67
8	 **5aj**	 **9aj**	70
9	 **5ba**	 **9ba**	84
10	 **5bd**	 **9bd**	77

11	 **5be**	 **9be**	74
12	 **5bh**	 **9bh**	81
13	 **5bi**	 **9bi**	72
14	 **5bj**	 **9bj**	71
15	 **5bk**	 **9bk**	75

16	 **5cd**	 **9cd**	72
17	 **5dd**	 **9dd**	70
18	 **5dg**	 **9dg**	77

[a]Reaction conditions : **5aa** (0.23 mmol), Pd-catalyst (5.0 mol%), ligand (10 mol%) and Et_3N (2.5 mmol) in DMF (2.0 mL) at 130 ^oC (oil bath) for 3h. [b]Isolated yield of **9**.

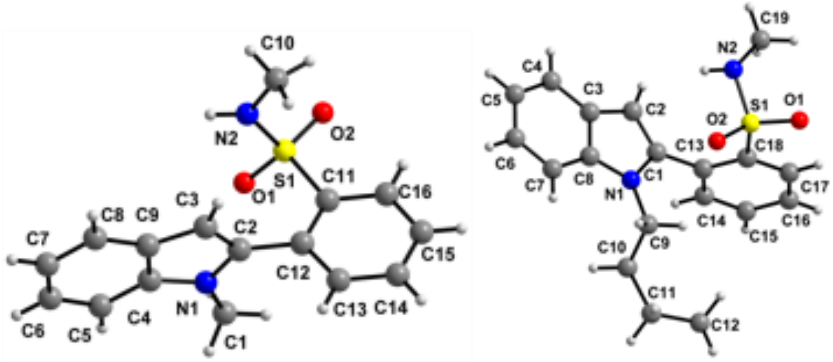
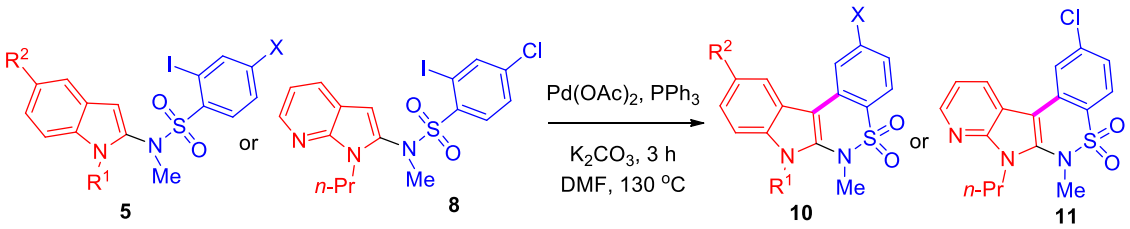


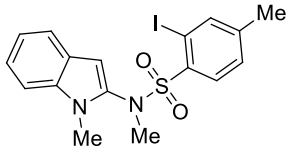
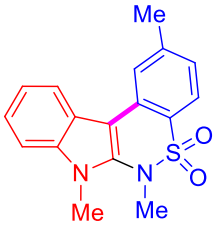
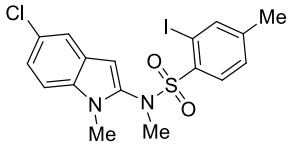
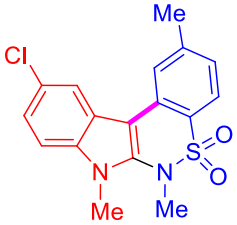
Figure 1: Molecular structures of compounds **9ba** (left, CCDC No. 2202001) and **9bh** (right, CCDC No. 2202002).

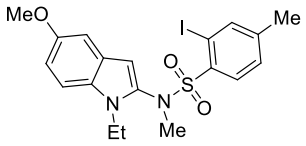
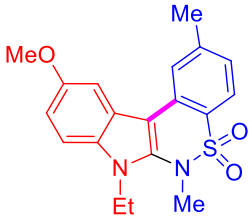
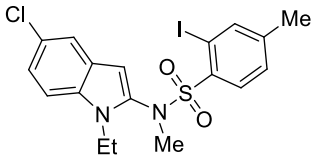
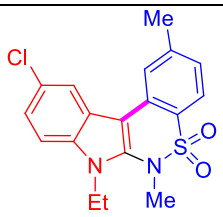
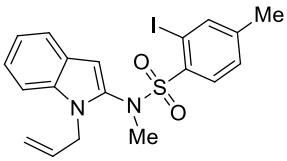
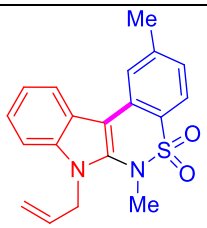
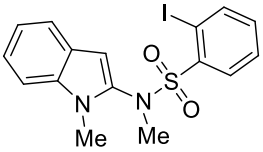
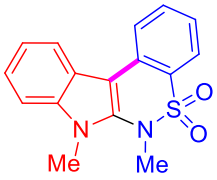
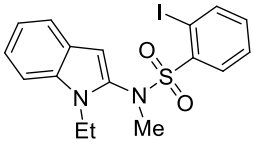
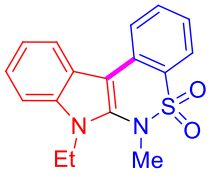
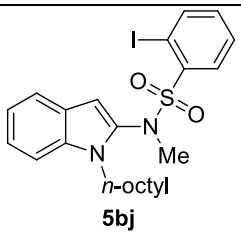
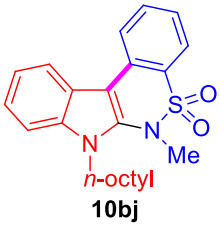
The substrate scope in cyclization is presented in Table 3. The substituents on the nitrogen atom of indole, sulfonyl attached phenyl ring, as well as fused aryl moiety, worked well

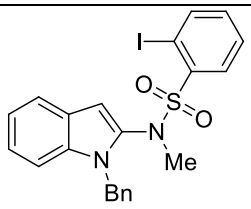
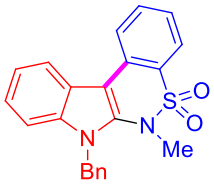
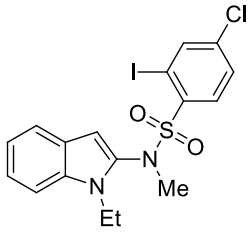
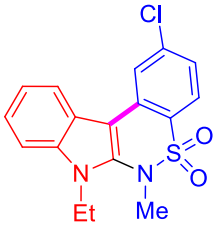
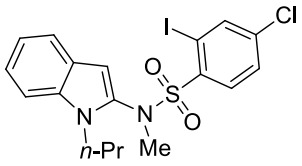
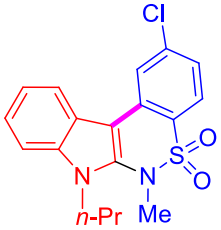
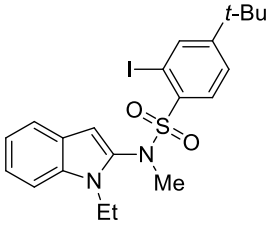
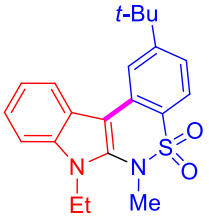
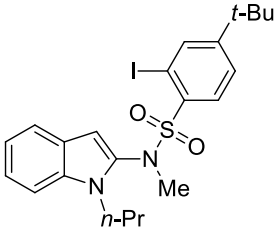
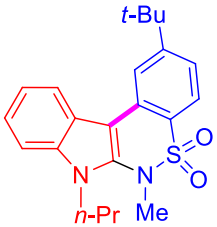
in the present strategy. Indoles possessing different alkyl substituents on nitrogen atoms furnished the desired products in moderate to good yields of 65-86%. Similarly, 4-chloro-2-iodo-*N*-methyl-*N*-(1-propyl-1*H*-pyrrolo[2,3-b]pyridin-2-yl)benzenesulfonamide also delivered the corresponding product **11** in 70% yield.

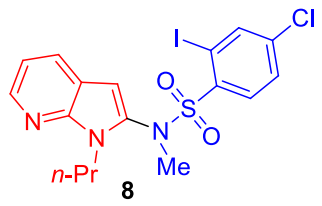
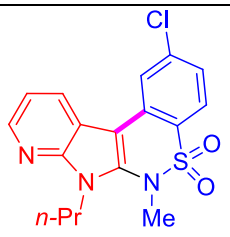
Table 3. Substrate scope for [Pd]-catalyzed synthesis of thiazino[3,4-*b*]indole 5,5-dioxides 10 and the pyrrolo-pyridine sultam 11[a,b]



Entry	2-iodo-*N*,4-dimethyl-*N*-(1-methyl-1*H*-indol-2-yl)benzenesulfonamide	Thiazino[3,4-*b*]indole 5,5-dioxides	Yield **10** and **11** (%)[b]
1	 **5aa**	 **10aa**	86
2	 **5ac**	 **10ac**	81

3	 **5ae**	 **10ae**	68
4	 **5af**	 **10af**	72
5	 **5al**	 **10al** (X-ray)	71
6	 **5ba**	 **10ba**	76
7	 **5bd**	 **10bd**	84
8	 **5bj**	 **10bj**	75

9	 **5bk**	 **10bk** (X-ray)	82
10	 **5cd**	 **10cd**	71
11	 **5cg**	 **10cg**	75
12	 **5dd**	 **10dd**	65
13	 **5dg**	 **10dg**	72

14	 8	 11	70

[a]Reaction conditions : **5aa** (0.23 mmol), Pd-catalyst (5.0 mol%), ligand (10 mol%) and Et_3N (2.5 mmol) in DMF (2.0 mL) at 130 °C (oil bath) for 3h. [b]Isolated yield of **10/11**.

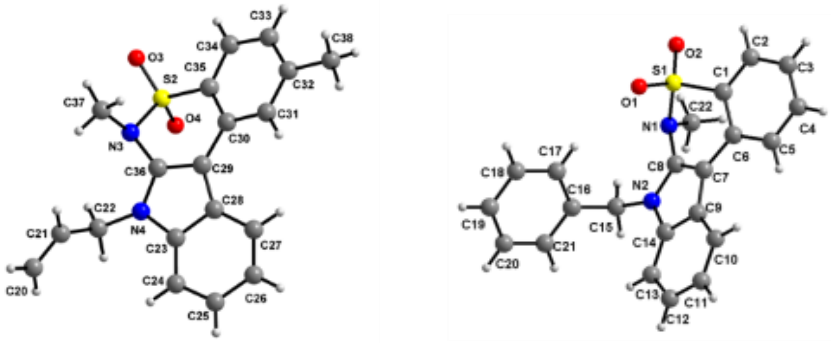
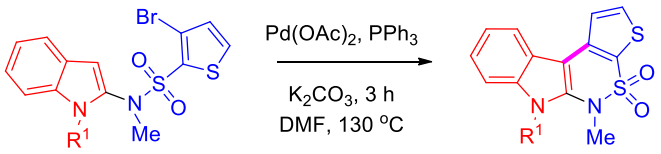


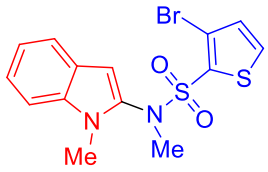
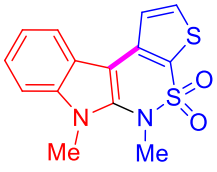
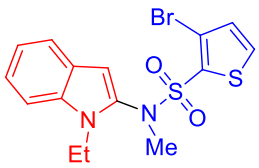
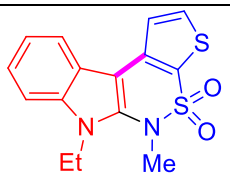
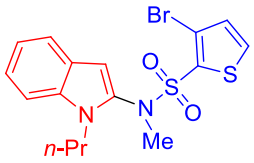
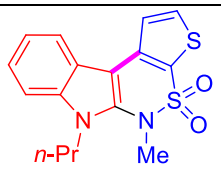
Figure 2: Molecular structures of compounds **10al** (left, CCDC No. 2202003) and **10bk** (right, CCDC No. 2202004).

In continuation of the above cyclization, we utilized sulfonyl attached heteroaromatic substrates **6aa**, **6ad**, and **6ag** under standard conditions and were successful in obtaining the corresponding cyclized products **12aa**, **12ad**, and **12ag** in 81-85% yield (Table 4).

Table 4. Synthesis of thieno[3',2':5,6][1,2]thiazino[3,4-*b*]indole-4,4-dioxides *via* intramolecular C-3 arylation of 3-bromo-*N*-alkyl-*N'*-methylthiophene sulfonamides[a,b]



Entry	Indolyl bromothiophene sulfonamides	Thiophene fused indolyl sultams	Yield **12** (%)[b]

1	 **6aa**	 **12aa**	81
2	 **6ad**	 **12ad**	83
3	 **6ag**	 **12ag**	85

[a]Reaction conditions: **6** (0.23 mmol), catalyst (5.0 mol%), ligand (10 mol%) and K_2CO_3 (2.5 mmol) in DMF (2.0 mL) at 130 °C (oil bath) for 3h. [b]Isolated yield of **12**.

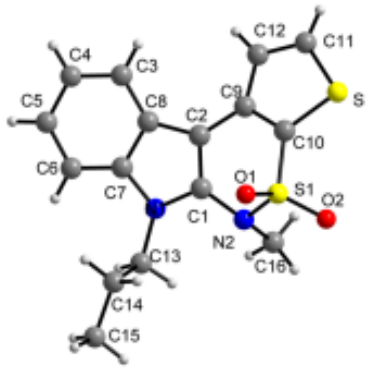
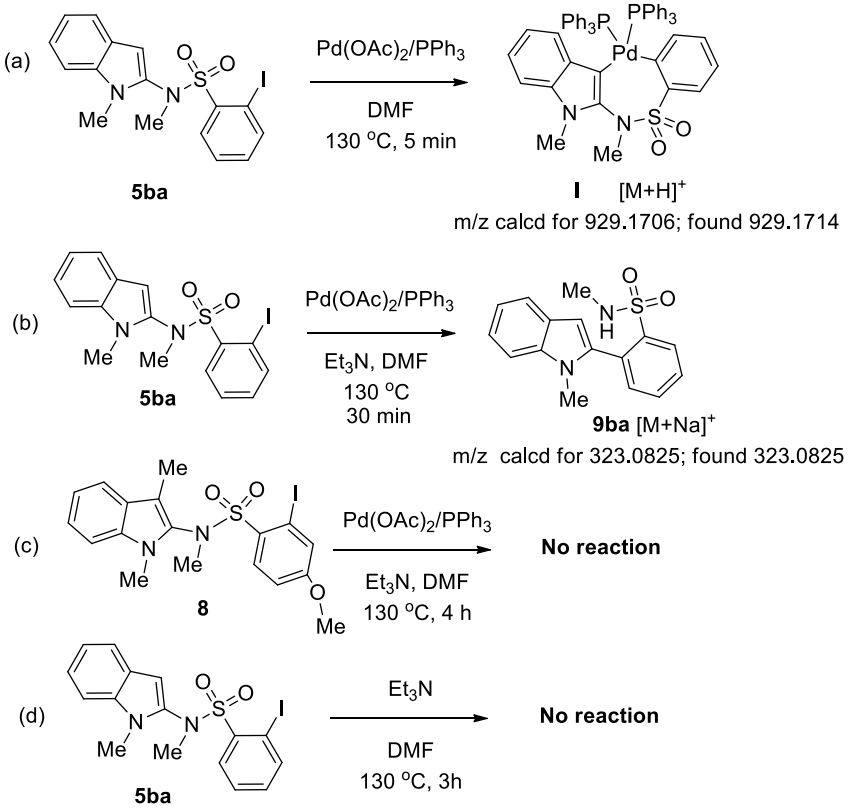


Figure 3: Molecular structure of compounds **12ag** (CCDC No. 2202005).

5.2.2 *Control experiments*

In order to get some insight into the mechanistic pathway, we checked the reaction mixture by treating **5ba** with $Pd(OAc)_2/PPh_3$ in the absence of K_2CO_3/Et_3N. We observed a

fairly intense peak that may be ascribed to species **I** {*m/z* calcd for $[M+H]^+$ 929.1706; found 929.1714}. After 30 min, in the presence of Et_3N, the expected product **9ba** could be detected. In the absence of [Pd]-catalyst, the reaction did not take place (HRMS). The indole-3-substituted precursor **8** did not undergo C(2)-arylation which suggested that indole-3-position should be free for the formation of products analogous to **9ba**. These experiments are depicted in Scheme 2.

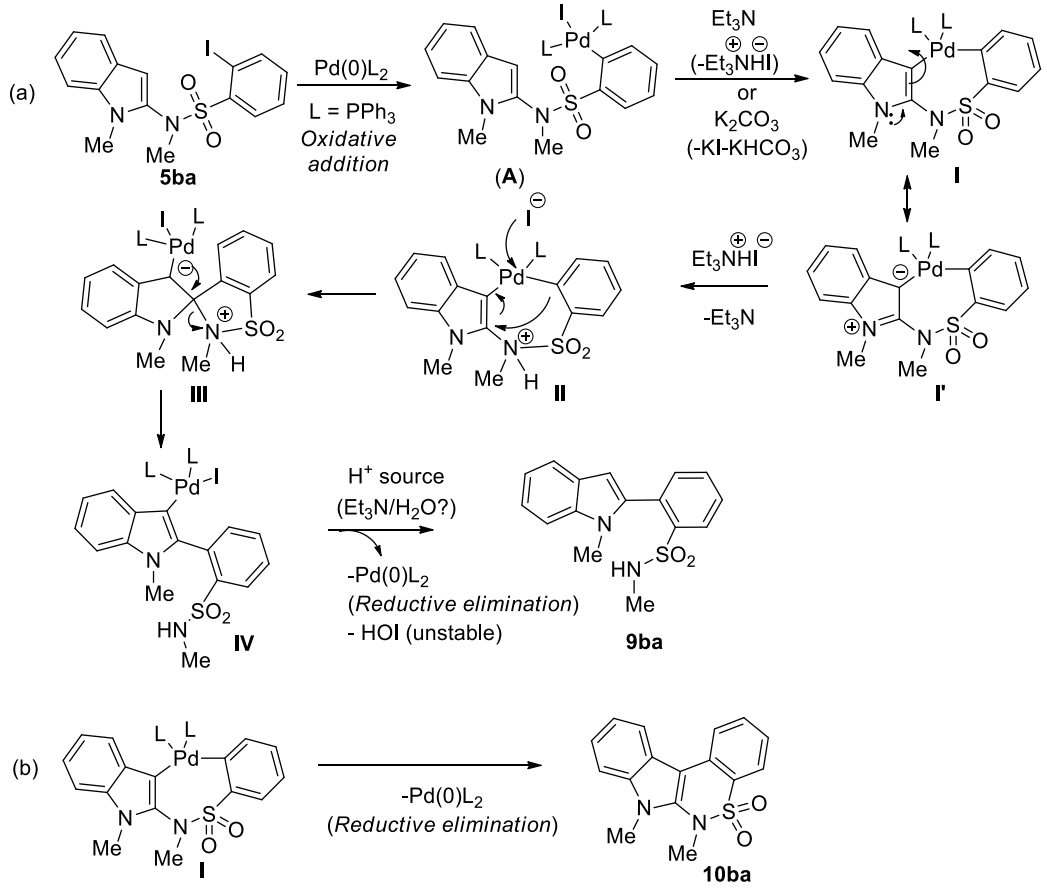


Scheme 2: Control experiments

5.2.3 *Plausible pathway for the formation of products 9ba/10ba*

On the basis of the above experiments and literature reports,[21] a plausible pathway for the formation of **9ba/10ba** is illustrated in Scheme 3. Initially, a Pd(0) species is expected to be generated. Subsequently, oxidative addition of compound **5ba** by Pd(0) furnishes Pd(II) species **A**, which is further converted to a seven-membered palladacycle intermediate **I** by cyclization utilizing with indole C3 carbon; this species is in resonance with the ionic forms **I'**. Next**,** the Pd(II) species **I**/ **I'** undergoes protonation to afford intermediate **II**. Then attack of I^- on Pd and

subsequent intramolecular attack on indole C2 position of **II** facilitated a C-N bond cleavage providing spirocyclic intermediate **III**. This intermediate **III** upon indole C2-N bond cleavage leads to species **IV** which subsequently undergoes protonation and reductive elimination in the presence of adventitious moisture to afford the product **9ba** and regenerates the active palladium(0) species. The last step is speculative at the moment, but we believe that intermediacy of the spirocyclic intermediate is required for the formation of **9ba**. In the absence of Et_3N, the product was not formed (tlc). To check whether water is involved in the reaction or not, we performed the reaction in the presence of D_2O. There was no clear-cut indication of deuterium insertion at the indole C3 position by $^1H/^{13}C\{1H\}$ NMR. The formation of sultam **10ba** follows the general [Pd]-catalyzed reactions and may directly result from intermediate **I**.

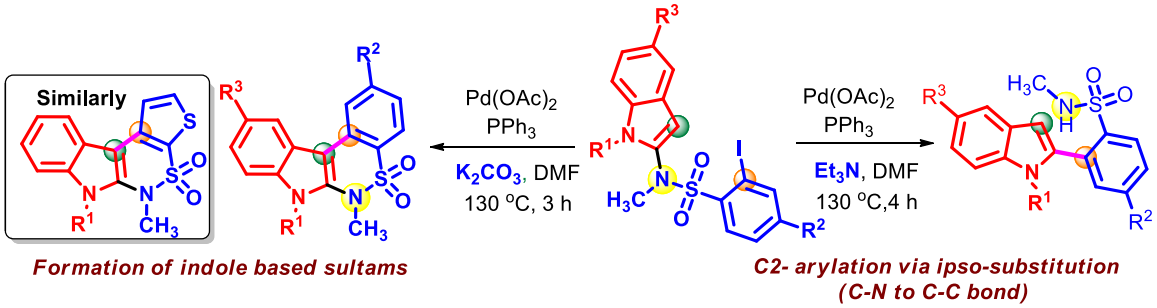


Scheme 3: Plausible pathway for the formation of **9ba** and **10ba**

Summary of PART-B

(1) [Pd]-catalyzed reaction of indolyl substituted iodo-sulfonamides using $Pd(OAc)_2/PPh_3/Et_3N$ combination involves the transformation of indole C(2)-N bond to the C(2)-aryl bond that gives 2-aryl(sulfonamido) indoles.

(2) [Pd]-catalyzed reaction of indolyl substituted iodo-aryl sulfonamides using $Pd(OAc)_2/PPh_3/K_2CO_3$ combination affords the cyclized indole-fused sultams.



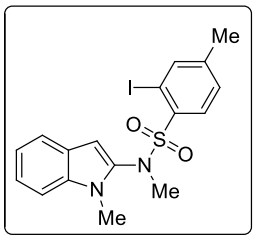
EXPERIMENTAL SECTION

General information about the chemicals, solvents, equipment used etc. is already given in Chapter 3.

6.1 General procedure for the preparation of 1, 2a, 3, and 4: 2-Iodo substituted sulfonamides **1**[43] and 3-bromo-*N*-methylthiophene-2-sulfonamide **2a**[44] were prepared by using literature procedures. Indole precursors **3-4** were prepared *via* alkylation, benzylation and allylation of the corresponding indoles according to a known procedure.[45]

6.2 General procedure for the preparation of iodo-substituted indolylbenzene/thiophene sulfonamides 5aa-5ag, 6aa-6ag, 7 and **8:** An oven-dried 25 mL round-bottomed flask was charged with sulfonamide **1** (0.32 mmol), Cs_2CO_3 (0.48 mmol) and I_2 (0.32 mmol) in acetonitrile (2.5 mL). Indole **3** (0.38 mmol) was added to it. Then the mixture was stirred at rt (25 ^oC) under nitrogen for 5-8 h. After completion of the reaction (TLC), a saturated solution of $Na_2S_2O_3$ (10 mL) was added and the mixture was treated with ethyl acetate (20 mL). After separation, the resulting organic portion was washed with water and the aqueous part was extracted with ethyl acetate (2 x 20 mL). The combined organic layer was washed with saturated brine solution (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford the desired compound. Compounds **5aa-5dg, 6aa-6ag, 7** and **8** were prepared from the appropriate sulfonamides **1a-d, 2a** and indoles **3** and **4** by using the same procedure and the same molar quantities.

Compound 5aa



Yield: 0.108 g (77%).

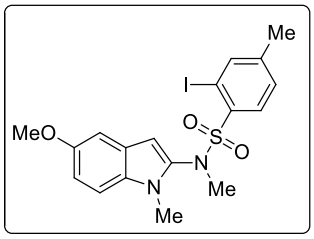
IR (neat): ν_{max} 2921, 2360, 2339, 1569, 1540, 1448, 1395, 1347, 1275, 1165, 752 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.51-7.49 (m, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.29-7.26 (m, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.13-7.10 (m, 1H), 6.02 (s, 1H), 3.76 (s, 3H), 3.50 (s, 3H), 2.39 (s, 3H) ppm.

^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 144.9, 143.6, 137.4, 135.4, 135.3, 132.5, 129.0, 126.0, 122.6, 121.0, 119.9, 109.8, 99.1, 92.3, 41.6, 29.5, 20.8 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{18}IN_2O_2S$ $[M + H]^+$ *m/z* 441.0128, found 441.0130.

Compound 5ab



Yield: 0.101 g (67%).

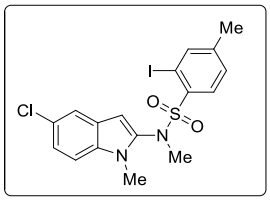
IR (neat): ν_{max} 2934, 2831, 1620, 1480, 1340, 1221, 1167, 783 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.99 (s, 1H) 7.76 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 6.95-6.92 (m, 2H), 5.94 (s, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.48 (s, 3H), 2.39 (s, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 154.3, 144.8, 143.6, 137.5, 135.5, 132.4, 130.6, 128.9, 126.2, 113.0, 110.6, 102.6, 98.7, 92.3, 55.9, 41.4, 29.6, 20.8 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{20}IN_2O_3S$ $[M + H]^+$*m/z* 471.0234, found 471.0237.

Compound 5ac



Yield: 0.107 g (70%).

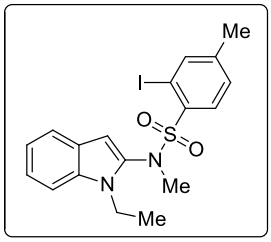
IR (neat): ν_{max} 2924, 1586, 1471, 1263, 1159, 733 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, *J* = 1.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.46 (s, 1H), 7.30-7.21 (m, 3H), 5.95 (s, 1H), 3.75 (s, 3H), 3.47 (s, 3H), 2.40 (s, 3H) ppm.

^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 145.0, 143.7, 137.1, 136.6, 133.6, 132.4, 128.9, 126.8, 125.6, 122.9, 120.3, 110.9, 98.6, 92.3, 41.4, 29.7, 20.8 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{17}ClIN_2O_2S$ $[M + H]^+$ *m/z* 474.9738, found 474.9740.

Compound 5ad



Yield: 0.104g (72%).

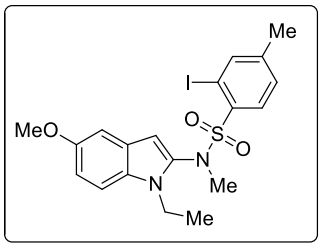
IR (neat): ν_{max} 2926, 1586, 1459, 1373, 1345, 1264, 1162, 732 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.28-7.21 (m, 1H), 7.20 (d, *J* = 1.0 Hz, 1H), 7.10 (t, *J* = 7.0 Hz, 1H), 5.99 (s, 1H), 4.29 (d, *J* = 7.0 Hz, 2H), 3.50 (s, 3H), 2.39 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 144.9, 143.6, 137.5, 134.9, 134.1, 132.6, 128.9, 126.3, 122.5, 121.1, 119.8, 110.2, 99.3, 92.4, 42.0, 37.6, 20.7, 15.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{20}IN_2O_2S$ $[M + H]^+$*m/z* 455.0285, found 455.0291.

Compound 5ae



Yield: 0.109 g (70%).

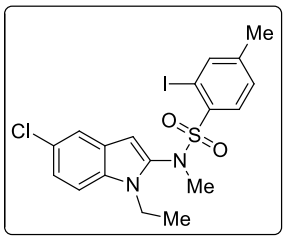
IR (neat): ν_{max} 2934, 2831, 1620, 1583, 1480, 1340, 1221, 1027, 783 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.78 (d, *J* = 8.0 Hz,, 1H), 7.26-7.20 (m, 2H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 9.0, 2.5 Hz, 1H), 5.93 (s, 1H), 4.25 (d, *J* = 6.5 Hz, 2H), 3.83 (s, 3H), 3.48 (s, 3H), 2.39 (s, 3H), 1.38 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.2, 144.8, 143.6, 137.6, 135.0, 132.5, 129.4, 128.9, 126.6, 113.0, 111.0, 102.8, 98.9, 92.4, 55.8, 41.9, 37.7, 20.7, 15.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{22}IN_2O_3S$ $[M + H]^+$*m/z* 485.0390, found 485.0392.

Compound 5af



Yield: 0.105 g (67%).

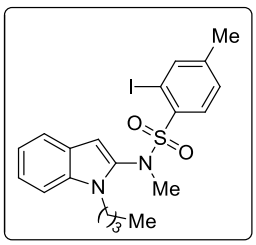
IR (neat): ν_{max} 2925, 1586, 1471, 1331, 1158, 733 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.25 (s, 1H), 7.23-7.19 (m, 2H), 5.91 (s, 1H), 4.30-4.28 (m, 2H), 3.47 (s, 3H), 2.40 (s, 3H), 1.38 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 145.0, 143.7, 137.1, 136.0, 132.5, 129.8, 128.9, 127.1, 125.5, 122.9, 120.4, 111.3, 98.9, 92.4, 41.8, 37.8, 20.8, 14.9 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{19}ClIN_2O_2S$ $[M + H]^+$*m/z* 488.9895, found 488.9905.

Compound 5ah



Yield: 0.126 g (82%).

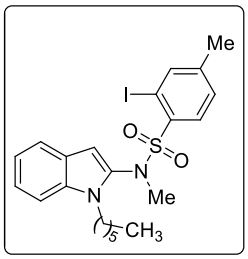
IR (neat): ν_{max} 2956, 2928, 1585, 1543, 1459, 1344, 1162, 703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.36-7.34 (m, 1H), 7.27-7.23 (m, 1H), 7.22-7.20 (m, 1H), 7.12-7.09 (m, 1H), 6.00 (s, 1H), 4.22 (bs, 2H), 3.48 (s, 3H), 2.39 (s, 3H) 1.79-7.72 (m, 2H), 1.46-1.39 (m, 2H), 1.00 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.9, 143.7, 137.2, 135.3, 134.4, 132.6, 128.9, 126.2, 122.4, 121.1, 119.8, 110.4, 99.1, 92.5, 42.8, 42.0, 31.8, 20.8, 20.4, 13.9 ppm.

HRMS (ESI-TOF): Calcd for $C_{20}H_{24}IN_2O_2S$ $[M + H]^+$ *m/z* 483.0598, found 483.0603.

Compound 5ai



Yield: 0.133 g (81%).

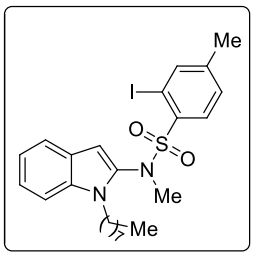
IR (neat): ν_{max} 2918, 2850, 1612, 1460, 1337, 1179, 737 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.35-7.33 (m, 1H), 7.26-7.23 (m, 1H), 7.21-7.19 (m, 1H), 7.11-7.08 (m, 1H), 6.00 (s, 1H), 4.20 (bs, 2H), 3.47 (s, 3H), 2.39 (s, 3H), 1.78-1.72 (m, 2H), 1.44-1.31 (m, 6H), 0.93 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.8, 143.6, 137.3, 135.2, 134.4, 132.6, 128.9, 126.2, 122.4, 121.0, 119.7, 110.3, 99.1, 92.4, 43.1, 42.0, 31.5, 29.7, 26.9, 22.6, 20.7, 14.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{28}IN_2O_2S$ $[M + H]^+$ *m/z* 511.0911, found 511.0917.

Compound 5aj



Yield: 0.132 g (77%).

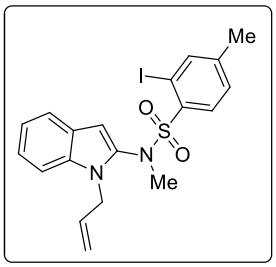
IR (neat): ν_{max} 2922, 2852, 1586, 1461, 1264, 1164, 737 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.35-7.25 (m, 1H), 7.23-7.21 (m, 1H), 7.20-7.11 (m, 1H), 7.09 (t, *J* = 7.0 Hz, 1H), 6.01 (s, 1H), 4.20 (bs, 2H), 3.48 (s, 3H), 2.39 (s, 3H), 1.78-1.72 (m, 2H), 1.40-1.29 (m, 10H), 0.92 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.8, 143.6, 137.3, 135.2, 134.4, 132.6, 128.9, 126.2, 122.4, 121.0, 119.7, 110.3, 99.1, 92.4, 43.1, 42.0, 31.8, 29.7, 29.3, 29.2, 27.2, 22.6, 20.8, 14.1 ppm.

HRMS (ESI-TOF): calcd for $C_{24}H_{32}IN_2O_2S$ $[M + H]^+$ *m/z* 539.1224, found 539.1229.

Compound 5al



Yield: 0.093g (62%).

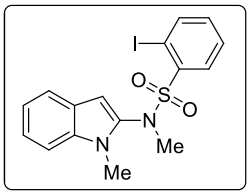
IR (neat): ν_{max} 2926, 1671, 1585, 1544, 1459, 1343, 1159, 735 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.31-7.30 (m, 1H), 7.25-7.19 (m, 2H), 7.12-7.09 (m, 1H), 6.06 (s, 1H), 5.98-5.91 (m, 1H), 5.16 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.99 (dd, *J* =17.0, 1.0 Hz, 1H), 4.87(s, 2H), 3.48 (s, 3H), 2.39 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.9, 143.6, 137.5, 135.0, 134.8, 133.7, 132.6, 129.0, 126.2, 122.7, 121.1, 120.0, 116.6, 110.7, 99.8, 92.4, 45.3, 41.9, 20.8 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{20}IN_2O_2S$ $[M + H]^+$ *m/z* 467.0285, found: 467.0293.

Compound 5ba



Yield: 0.113 g (83%).

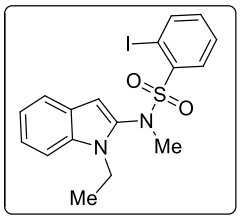
IR (neat): ν_{max} 2919, 2850, 1603, 1489, 1331, 1164, 713 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.0 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.29-7.26 (m, 1H), 7.23 (t, *J* =7.5 Hz, 1H), 7.11 (t, *J* = 7.0 Hz, 1H), 6.00 (s, 1H), 3.76 (s, 3H), 3.53 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 143.1, 140.5, 135.3, 135.1, 133.7, 132.6, 128.2, 126.0, 122.7, 121.0, 120.0, 109.8, 99.2, 92.1, 41.6, 29.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{16}H_{16}IN_2O_2S$ $[M + H]^+$ *m/z* 426.9972, found: 426.9974.

Compound 5bd



Yield: 0.100 g (71%).

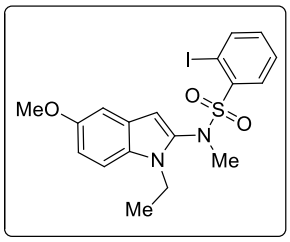
IR (neat): ν_{max} 2920, 1586, 1453, 1352, 1166, 1043, 741 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.44-7.41 (m, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.26-7.21 (m, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 5.97 (s, 1H), 4.29 (bs, 2H), 3.53 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 143.2, 140.1, 134.6, 134.1, 133.7, 132.7, 128.2, 126.2, 122.6, 121.1, 119.8, 110.2, 99.4, 92.3, 42.1, 37.6, 14.9 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{18}IN_2O_2S$ $[M + H]^+$ *m/z* 441.0128, found: 441.0129.

Compound 5be



Yield: 0.116 g (77%).

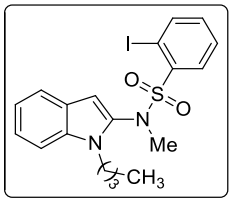
IR (neat): ν_{max} 2981, 1620, 1564, 1399, 1351, 1200, 1163, 807 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.44-7.41 (m, 1H), 7.24-7.21 (m, 2H), 6.95-6.91 (m, 2H), 5.90 (s, 1H), 4.25 (d, *J* = 7.0 Hz, 2H), 3.83 (s, 3H), 3.51(s, 3H), 1.37 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.2, 143.1, 140.5, 134.8, 133.7, 132.7,129.4, 128.2, 126.5, 113.1, 111.0, 102.7, 99.0, 92.3, 55.8, 42.1, 37.7, 15.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{20}IN_2O_3S$ $[M + H]^+$ *m/z* 471.0234, found: 471.0237.

Compound 5bh



Yield: 0.125 g (83%).

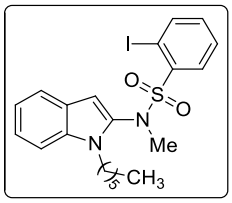
IR (neat): ν_{max} 2956, 2870, 1568, 1541, 1460, 1345, 1163, 754 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 7.5 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.27-7.21 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.00 (s, 1H), 4.23 (br q, 2H), 3.52 (s, 3H), 1.80-1.74 (m, 2H), 1.48-1.40 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 143.2, 140.3, 135.0, 134.5, 133.7, 132.7, 128.2, 126.2, 122.5, 121.1, 119.8, 110.4, 99.3, 92.4, 42.8, 42.1, 31.8, 20.4, 13.8 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{22}IN_2O_2S$ $[M + H]^+$ *m/z* 469.0441, found: 469.0447.

Compound 5bi



Yield: 0.125 g (79%).

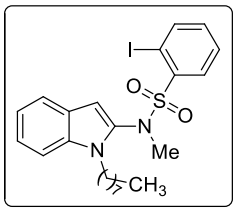
IR (neat): ν_{max} 2956, 2870, 1568, 1541, 1460, 1345, 1163, 754 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.17 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.44-7.41 (m, 1H), 7.35-7.33 (m, 1H), 7.27-7.21 (m, 2H), 7.11-7.08 (m, 1H), 5.97 (s, 1H), 4.19 (br q, 2H), 3.51(s, 3H), 1.79-1.73 (m, 2H), 1.39-1.33 (m, 6H), 0.94-.0.91(m, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 143.2, 140.2, 135.0, 134.4, 133.7, 132.7, 128.2, 126.1, 122.5, 121.1, 119.8, 110.3, 99.2, 92.3, 43.1, 42.1, 31.5, 29.7, 26.9, 22.6, 14.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{22}IN_2O_2S$ $[M + H]^+$ *m/z* 469.0441, found: 469.0447.

Compound 5bj



Yield: 0.127 g (76%).

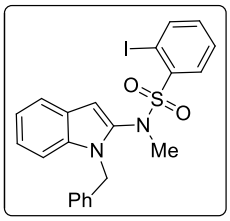
IR (neat): ν_{max} 2924, 2852, 1612, 1541, 1463, 1347, 1162, 1264, 732 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.18-8.16 (m, 1H), 7.89 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.44-7.41 (m, 1H), 7.34 (d, *J* = 7.0 Hz, 1H), 7.25-7.21 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 5.98 (s, 1H), 4.20 (br q, 2H), 3.51 (s, 3H), 1.79-1.73 (m, 2H), 1.37-1.30 (m, 10H), 0.92 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$):) δ 143.2, 140.3, 135.0, 134.4, 133.7, 132.7, 128.2, 126.2, 122.5, 121.1, 119.8, 110.3, 99.3, 92.4, 43.1, 42.1, 31.8, 29.7, 29.3, 29.2, 27.2, 22.7, 14.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{30}IN_2O_2S$ $[M + H]^+$ *m/z* 525.1067, found: 525.1074.

Compound 5bk



Yield: 0.112 g (70%).

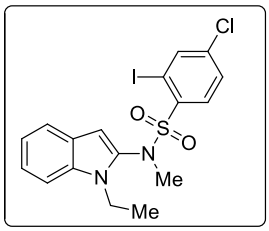
IR (neat): ν_{max} 2964, 2360, 1542, 1483, 1460, 1356, 1264, 1213, 1160, 731 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, *J* = 7.5 Hz, 1H), 7.93-7.91 (m, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.27-7.19 (m, 6H), 7.13-7.10 (m, 1H), 7.02 (t, *J* = 7.0 Hz, 2H), 6.10 (s, 1H), 5.50 (s, 2H), 3.27 (s, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$):) δ 143.2, 140.4, 137.6, 135.2, 135.1, 133.8, 132.7, 128.7, 128.2, 127.3, 126.4, 126.2, 123.0, 121.1, 120.2, 110.7, 100.3, 92.3, 46.3, 41.7 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{20}IN_2O_2S$ $[M + H]^+$ *m/z* 503.0285, found: 503.0293.

Compound 5cd



Yield: 0.109 g (72%).

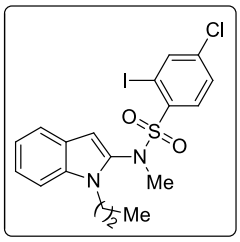
IR (neat): ν_{max} 2991, 1545, 1466, 1397, 1159, 781 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 2.0 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.40-7.36 (m, 2H), 7.29-7.26 (m, 1H), 7.13-7.10 (m, 1H), 5.96 (s, 1H), 4.30 (d, *J* = 7.0 Hz, 2H), 3.52 (s, 3H), 1.42 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$):) δ 142.4, 139.4, 139.0, 134.3, 134.2, 133.4, 128.4, 126.1, 122.7, 121.2, 119.9, 110.3, 99.4, 92.8, 42.2, 37.6, 15.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{17}ClIN_2O_2S$ $[M + H]^+$ *m/z* 474.9738, found: 474.9743.

Compound 5cg



Yield: 0.105 g (67%).

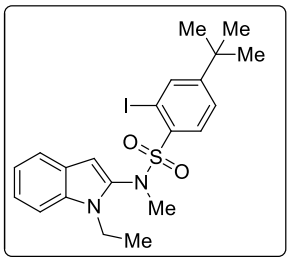
IR (neat): ν_{max} 2948, 1558, 1460, 1403, 1363, 1231, 1204, 1168, 813 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 2.0 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 7.0 Hz, 1H), 7.12-7.01 (m, 1H), 5.96 (s, 1H), 4.18 (bs, 2H), 3.49 (s, 3H), 1.83 (q, *J* = 7.5 Hz, 2H); 1.00 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$):) δ 142.4, 139.4, 138.7, 134.7, 134.5, 133.4, 128.3, 126.0, 122.7, 121.1, 119.9, 110.4, 99.2, 92.8, 44.6, 42.2, 23.0, 11.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{19}ClIN_2O_2S$ $[M + H]^+$ *m/z* 488.9895, found: 488.9901.

Compound 5dd



Yield: 0.076 (48%).

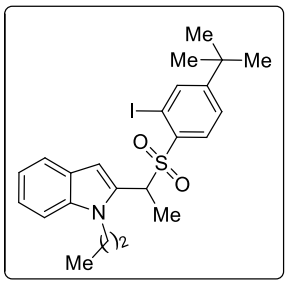
IR (neat): ν_{max} 2964, 1739, 1580, 1540, 1459, 1344, 1209, 732 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 2.0 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.41 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.27-7.24 (m, 1H), 7.12-7.09 (m, 1H), 6.04 (s, 1H), 4.29 (d, *J* = 6.5 Hz, 2H), 3.51 (s, 3H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.35 (s, 9H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$):) δ 157.9, 140.4, 137.6, 134.9, 134.1, 132.5, 126.3, 125.4, 122.5, 121.1, 119.8, 110.2, 99.4, 92.6, 42.0, 37.6, 34.9, 30.9, 14.9 ppm.

HRMS (ESI-TOF): Calcd for $C_{21}H_{26}IN_2O_2S$ $[M + H]^+$*m/z* 497.0754, found: 497.0760.

Compound 5dg



Yield: 0.098 g (60%).

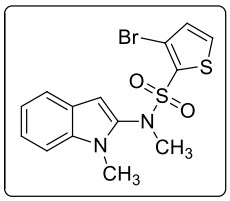
IR (neat): ν_{max} 2962, 2873, 1579, 1539, 1460, 1344, 1172, 733 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 8.0, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.28-7.23 (m, 1H), 7.11-7.08 (m, 1H), 6.05 (s, 1H), 4.16 (brm, 2H), 3.49 (s, 3H), 1.75 (d, *J* = 4.5, 2H), 1.35(s, 9H), 0.98 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$):) δ 157.9, 140.4, 137.4, 135.3, 134.4, 132.4, 126.2, 125.3, 122.4, 121.1, 119.7, 110.4, 99.3, 92.6, 44.6, 42.1, 34.9, 30.9, 22.9, 11.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{28}IN_2O_2S$ $[M + H]^+$*m/z* 511.0911, found: 511.0916.

Compound 6aa



Yield: 0.101 (82%).

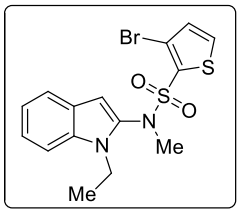
IR (neat): ν_{max} 2915, 2847, 1538, 1478, 1413, 1359, 1160, 1050, 737 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, *J* = 5.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.31-7.28 (m, 1H), 7.18 (d, *J* = 5.5 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 6.06 (s, 1H), 3.79 (s, 3H), 3.48 (s, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$):) δ 135.3$_3$, 135.3$_9$, 133.5, 133.1, 132.3, 126.0, 122.8, 121.1, 120.1, 115.1, 110.0, 98.2, 41.4, 29.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{14}H_{14}BrN_2O_2S_2$ $[M + H]^+$ *m/z* 384.9675, found 384.9681.

Compound 6ad



Yield: 0.93 g (73%).

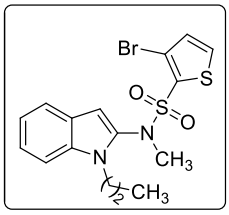
IR (neat): ν_{max} 2978, 2934, 1690, 1491, 1391, 1143, 791 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 5.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 5.0 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 5.92 (s, 1H), 4.22 (d, *J* = 4.0 Hz, 2H), 3.39 (s, 3H), 1.35 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$):) δ 134.7, 134.1, 133.6, 133.1, 132.1, 126.2, 122.7, 121.2, 119.9, 115.1, 110.3, 98.4, 41.8, 37.5, 15.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{15}H_{16}{}^{79}BrN_2O_2S_2$ $[M + H]^+$ *m/z* 398.9831, found 398.9839.

Compound 6ag



Yield: 0.106 g (80%).

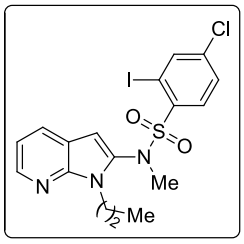
IR (neat): ν_{max} 2963, 2874, 1541, 1483, 1460, 1420, 1385, 1234, 1159, 729 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, *J* = 4.5 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 6.5 Hz, 1H), 7.18 (d, *J* = 5.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.03 (s, 1H), 4.24 (br m, 2H), 3.48 (s, 3H), 1.89 (q, *J* = 7.0 Hz, 2H), 1.00 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$):) δ 135.3, 134.6, 133.3, 133.2, 132.4, 126.2, 122.7, 121.1, 120.0, 115.3, 110.6, 98.3, 44.6, 41.9, 23.2, 11.8 ppm.

HRMS (ESI-TOF): Calcd for $C_{16}H_{18}BrN_2O_2S_2$ $[M + H]^+$ *m/z* 412.9988, found 412.9995.

Compound 7



Yield: 0.107 g (68%).

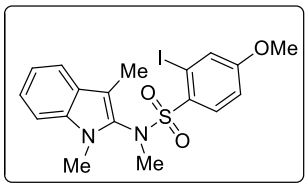
IR (neat): ν_{max} 2950, 1594, 1481, 1361, 1202, 1159, 1057, 735 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 7.74-7.70 (m, 2H), 7.32 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.98 (dd, *J* = 8.0, 5.0 Hz, 1H), 5.89 (s, 1H), 4.21 (t, *J* = 8.0 Hz, 2H), 3.41 (s, 3H), 1.78 (q, *J* = 7.5 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$):) δ 145.9, 144.2, 142.5, 139.5, 138.7, 135.5, 133.2, 128.9, 128.4, 118.9, 116.4, 97.7, 93.0, 43.7, 42.0, 23.1, 11.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{18}ClIN_3O_2S$ $[M + H]^+$ *m/z* 489.9847, found 489.9851.

Compound 8



Yield: 0.106g (70%).

IR (neat): ν_{max} 2970, 2933, 1738, 1579, 1544, 1463, 1340, 1226, 736 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.29_3-7.28_5 (m, 2H), 7.13-7.11 (m, 1H), 6.85 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 3.60 (s, 3H), 1.70 (s, 3H) ppm.

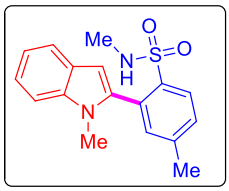
^{13}C {^1H} NMR (125 MHz, $CDCl_3$):) δ 162.2, 135.1, 134.3, 133.6, 131.2, 128.6, 126.5, 122.8, 119.3, 119.1, 113.3, 109.6, 108.3, 93.1, 55.9, 41.1, 29.5, 8.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{19}IN_2O_3S$ $[M + H]^+$ *m/z* 471.0234, found 471.0237.

6.3 General procedure for the synthesis of compounds 9aa-9dg.

To an oven dried Schlenk tube with a magnetic stirrer bar was added indolylbenzenesulfonamide **5aa** (0.23 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N (0.57 mmol) and DMF (2 mL). The contents were sealed and heated at 130 °C (oil bath) for 4h. After completion of the reaction as monitored by TLC, the crude reaction mixture was cooled to rt (25 ^oC), diluted with ethyl acetate (20 mL) and passed through a short celite column. The resulting solution was washed with water and the aqueous part was extracted with ethyl acetate (2 x 20 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) mixture as the eluent to afford the desired compounds. Thus compounds **9aa-9dg** were prepared from the appropriate indolylbenzenesulfonamides **5** by using the same procedure using same molar quantities. These compounds (**9**) had lower R_f values than the corresponding sultams (**10**).

Compound 9aa



Yield: 0.061 g (84%), white solid.

Mp: 152-154 °C.

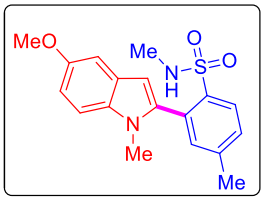
IR (neat): ν_{max} 3307, 2924, 1601, 1463, 1396, 1327, 1157, 797 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.51 (s, 1H), 4.00 (q, *J* = 5.5 Hz, 1H), 3.56 (s, 3H), 2.52 (d, *J* = 5.5 Hz, 3H), 2.50 (s, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 143.1, 137.6, 136.8, 136.0, 134.1, 131.0, 130.1, 130.0, 127.3, 122.3, 120.6, 120.2, 110.0, 100.9, 31.4, 29.1, 21.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{19}N_2O_2S$ $[M + H]^+$ *m/z* 315.1162, found: 315.1170.

Compound 9ab



Yield: 0.060 g (75%), white solid.

Mp: 145-147 °C.

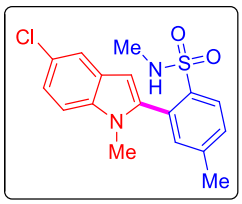
IR (neat): ν_{max} 3327, 3268, 2919, 2850, 1618, 1460, 1398, 1322, 1210, 826, 794 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.36-7.34 (m, 1H), 7.20 (d, *J* = 9.0 Hz, 1H), 7.16 (s, 1H), 7.00 (s, 1H), 6.88 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.34 (s, 1H), 3.92 (q, *J* = 5.5 Hz, 1H), 3.80 (s, 3H), 3.43 (s, 3H), 2.42 (d, *J* = 5.5 Hz, 3H), 2.40 (s, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 154.6, 143.0, 137.1, 136.0, 134.0, 133.0, 131.1, 129.9, 129.7, 127.3, 112.7, 110.7, 102.3, 100.7, 56.0, 31.2, 29.1, 21.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{21}N_2O_3S$ $[M + H]^+$ *m/z* 345.1267, found: 345.1273.

Compound 9ac



Yield: 0.055 g (69%), white solid.

Mp: 165-167 °C.

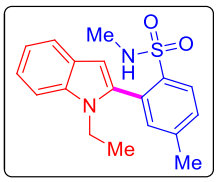
IR (neat): ν_{max} 3331, 2976, 2922, 1448, 1396, 1327, 1161, 1064, 766 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 1.5 Hz, 1H), 7.38-7.36 (m, 1H), 7.23-7.20 (m, 1H), 7.17-7.15 (m, 2H), 6.33 (s, 1H), 3.87 (q, *J* = 5.5 Hz, 1H), 3.43 (s, 3H), 2.44 (d, *J* = 5.5 Hz, 3H), 2.40 (s, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 140.7, 135.8, 133.5, 131.5, 128.1, 127.8, 127.7, 125.7, 123.4, 120.1, 117.4, 108.6, 97.8, 28.9, 26.6, 18.8 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{18}ClN_2O_2S$ $[M + H]^+$ *m/z* 349.0772, found: 349.0779.

Compound 9ad



Yield: 0.064 g (85%), white solid.

Mp: 158-160 ºC.

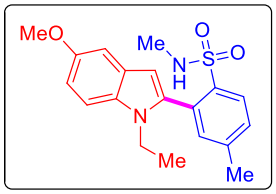
IR (neat): ν_{max} 3329, 2921, 2852, 1459, 1382, 1157, 1012, 796 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.43-7.40 (m, 2H), 7.28-7.25 (m, 2H), 7.25-7.14 (m, 1H), 6.44 (s, 1H), 4.15-4.09 (m, 1H), 3.94 (q, *J* = 5.5 Hz, 1H), 3.90-3.86 (m, 1H), 2.50-2.47 (m, 6H), 1.25 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 142.9, 136.4, 136.2, 135.8, 134.2, 131.1, 130.2, 130.0, 127.6, 122.2, 120.7, 120.1, 110.4, 101.0, 39.5, 29.1, 21.3, 15.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{21}N_2O_2S$ $[M + H]^+$ *m/z* 329.1318, found 329.1314.

Compound 9ae



Yield: 0.062 g (75%), white solid.

Mp: 185-187 ºC.

IR (neat): ν_{max} 3327, 3267, 2919, 2850, 1460, 1343, 1179, 1055, 794 cm^{-1}.

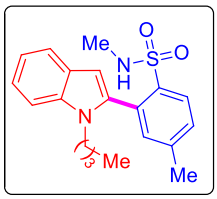
^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.28 (s, 1H), 7.10 (s, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.40 (s, 1H), 4.12-

4.07 (m, 1H), 3.96 (q, *J* = 5.0 Hz, 1H), 3.89 (m, 4H), 2.51 (d, *J* = 5.0 Hz, 3H), 2.50 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.5, 142.9, 136.6, 135.7, 134.1, 131.7, 131.1, 130.1, 130.0, 128.0, 112.6, 111.1, 102.3, 100.7, 55.9, 39.7, 29.2, 21.3, 15.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{23}N_2O_3S$ $[M + H]^+$ *m/z* 359.1424, found: 359.1449.

Compound 9ah



Yield: 0.060 g (73%), white solid.

Mp: 128-130 °C.

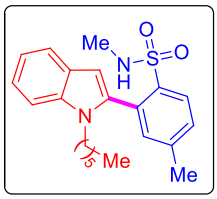
IR (neat): ν_{max} 3311, 2949, 2853, 1452, 1333, 1158, 1079, 780 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.46-7.42 (m, 2H), 7.30-7.29 (m, 2H), 7.28-7.19 (m, 1H), 6.46 (s, 1H), 4.12-4.07 (m, 1H), 3.90 (q, *J* = 5.5 Hz, 1H), 3.85-3.80 (m, 1H), 2.51-2.49 (m, 6H), 1.74-1.72 (m, 1H), 1.61-1.57 (m, 1H),1.25-1.20 (m, 2H), 0.83 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 142.9, 136.7, 136.5, 135.7, 134.4, 131.1, 130.2, 130.0, 127.5, 122.1, 120.6, 120.0, 110.6, 100.9, 44.7, 32.0, 29.1, 21.3, 20.1, 13.7 ppm.

HRMS (ESI-TOF): Calcd for $C_{20}H_{25}N_2O_2S$ $[M + H]^+$ *m/z* 357.1631, found: 357.1630.

Compound 9ai



Yield: 0.059 g (67%), white solid.

Mp: 137-139 °C.

IR (neat): ν_{max} 3334, 2923, 2853, 1459, 1331, 1159, 735 cm^{-1}.

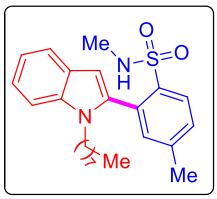
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.46-7.41 (m, 2H), 7.30-7.28 (m, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.46 (s, 1H), 4.12-4.07 (m,

1H), 3.91 (q, *J* = 5.5 Hz, 1H), 3.82-3.77 (m, 1H), 2.50-2.49 (m, 6H), 1.75-1.74 (m, 2H), 1.22-1.78 (m, 6H), 0.84 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 142.8, 136.7, 136.5, 135.7, 134.5, 131.1, 130.2, 130.0, 127.5, 122.1, 120.6, 120.0, 111.0, 100.8, 45.0, 31.2, 29.7, 29.1, 26.6, 22.4, 21.3, 13.9 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{29}N_2O_2S$ $[M + H]^+$ *m/z* 385.1944, found: 385.1950.

Compound 9aj



Yield: 0.066 g (70%), white solid.

Mp: 147-149 °C.

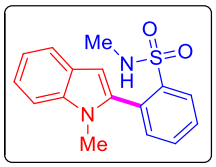
IR (neat): ν_{max} 3334, 2921, 2852, 1459, 1331, 1159, 781 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.46-7.42 (m, 2H), 7.30-7.28 (m, 2H), 7.28 (d, *J* = 4.0 Hz, 1H), 6.46 (s, 1H), 4.13-4.07 (m, 1H), 3.90 (q, *J* = 5.5 Hz, 1H), 3.84-3.78 (m, 1H), 2.50-2.49 (m, 6H), 1.75-1.74 (m, 1H), 1.62-1.58 (m, 1H), 1.28-1.18 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 142.7, 136.8, 136.5, 135.9, 134.4, 131.1, 130.1, 129.9, 127.5, 122.1, 120.6, 120.0, 110.5, 100.9, 45.0, 31.7, 29.8, 29.1, 29.0, 26.9, 22.6, 21.3, 14.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{24}H_{33}N_2O_2S$ $[M + H]^+$ *m/z* 413.2257, found: 413.2263.

Compound 9ba



Yield: 0.058 g (84%), white solid.

Mp: 155-157 °C.

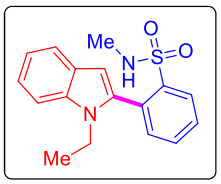
IR (neat): ν_{max} 3384, 2926, 1633, 1595, 1565, 1491, 1471, 1375, 1344, 1171, 1143, 767 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.70-7.65 (m, 3H), 7.45 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.55 (s, 1H), 4.06 (q, *J* = 5.0 Hz, 1H), 3.55 (s, 3H), 2.54 (d, *J* = 5.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 139.0, 137.6, 136.6, 133.5, 132.2, 131.2, 130.0, 129.5, 127.3, 122.4, 120.7, 120.2, 110.0, 101.3, 31.1, 29.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{16}H_{16}N_2NaO_2S$ $[M + Na]^+$ *m/z* 323.0825, found: 323.0825.

Compound 9bd



Yield: 0.056 g (77%), white solid.

Mp: 152-154 ºC.

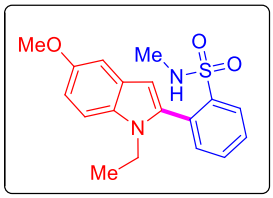
IR (neat): ν_{max} 3309, 2920, 2852, 1595, 1457, 1309, 1154, 1093, 789 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25-8.22 (m, 1H), 7.69-7.65 (m, 3H), 7.51-7.49 (m, 1H), 7.46-7.44 (m, 1H), 7.31-7.28 (m, 1H), 7.21-7.19 (m, 1H), 6.50 (s, 1H), 4.20-4.13 (m, 1H), 4.01 (q, *J* = 5.5 Hz, 1H), 3.95-3.87 (m, 1H), 2.54(d, *J* = 5.5 Hz, 3H), 1.27 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 138.7, 136.4, 136.0, 133.6, 132.2, 131.2, 130.1, 129.5, 127.6, 122.3, 120.8, 120.1, 110.4, 101.2, 39.6, 29.2, 15.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{19}N_2O_2S$ $[M + H]^+$ *m/z* 315.1162, found: 315.1166.

Compound 9be



Yield: 0.059 g (74%), white solid.

Mp: 147-149 ºC.

IR (neat): ν_{max} 3332, 2975, 1618, 1450, 1324, 1161, 1059, 784 cm^{-1}.

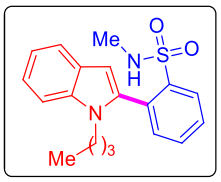
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23-8.21 (m, 1H), 7.70-7.64 (m, 2H), 7.49-7.48 (m, 1H), 7.33 (d, *J* =8.5 Hz, 1H), 7.11 (d, *J* =2.5 Hz, 1H), 6.97 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.43

(s, 1H), 4.13-4.07 (m, 1H), 4.02 (q, *J* = 5.0 Hz, 1H), 3.88 (s, 3H), 3.86-3.83 (m, 1H), 2.53 (d, *J* = 5.5 Hz, 3H), 1.25 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.5, 138.8, 136.4, 133.5, 132.1, 131.8, 131.2, 130.0, 129.4, 128.0, 112.7, 111.1, 102.4, 100.9, 55.9, 39.6, 29.1, 15.2 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{20}N_2NaO_3S$ $[M+Na]^+$ *m/z* 367.1087, found: 367.1091.

Compound 9bh



Yield: 0.064 g (81%), white solid.

Mp: 124-126 ºC.

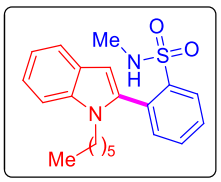
IR (neat): ν_{max} 3300, 2951, 1450, 1329, 1162, 783 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24-8.22 (m, 1H), 7.69-7.64 (m, 3H), 7.51-7.49 (m, 1H), 7.43 (dd, *J* = 8.5 Hz, 0.5 Hz, 1H), 7.31-7.29 (m, 1H), 7.29-7.17 (m, 1H), 6.48 (s, 1H), 4.14-4.08 (m, 1H), 3.94 (q, *J* = 5.5 Hz, 1H), 3.83-3.79 (m, 1H), 2.51 (d, *J* = 5.5 Hz, 3H), 1.72-1.71 (m, 1H), 1.61-1.53 (m, 1H), 1.23-1.19 (m, 2H), 0.82 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 138.9, 136.8, 136.3, 133.8, 132.0, 131.3, 130.0, 129.4, 127.5, 122.2, 120.7, 120.1, 110.6, 101.1, 44.8, 32.0, 29.1, 20.1, 13.6 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{22}N_2NaO_2S$ $[M+Na]^+$ *m/z* 365.1294, found: 365.1308.

Compound 9bi



Yield: 0.061 g (72%), white solid.

Mp: 133-135 ºC.

IR (neat): ν_{max} 3309, 2958, 2920, 1456, 1369, 1157, 788 cm^{-1}.

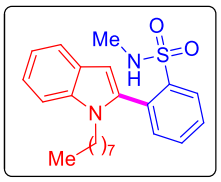
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24-8.23 (m, 1H), 7.70-7.65 (m, 3H), 7.51-7.49 (m, 1H), 7.44 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.31-7.30 (m, 1H), 7.20-7.17 (m, 1H), 6.49 (s, 1H), 4.13-4.07 (m, 1H), 3.95 (q, *J* = 5.5 Hz, 1H), 3.82-3.77 (m, 1H), 2.52 (d, *J* = 5.5

Hz, 3H), 1.78-1.72 (m, 1H), 1.61-1.55 (m, 1H), 1.28-1.16 (m, 6H), 0.84 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 138.8, 136.8, 136.3, 133.8, 132.0, 131.3, 130.0, 129.5, 127.5, 122.2, 120.7, 120.1, 110.6, 101.0, 45.0, 31.2, 29.8, 29.1, 26.6, 22.4, 13.9 ppm.

HRMS (ESI-TOF): Calcd for $C_{21}H_{27}N_2O_2S$ $[M + H]^+$ *m/z* 371.1788, found: 371.1799.

Compound 9bj



Yield: 0.065 g (71%), white solid.

Mp: 141-141 °C.

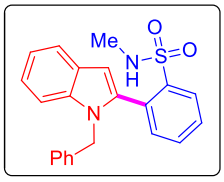
IR (neat): ν_{max} 3334, 2924, 2854, 1418, 1332, 1165, 735 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24-8.23 (m, 1H), 7.69-7.65 (m, 3H), 7.52-7.50 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.32-7.28 (m, 1H), 7.21 (t, *J* = 7.0 Hz, 1H), 6.50 (s, 1H), 4.14-4.08 (m, 1H), 3.98 (q, *J* = 5.5 Hz, 1H), 3.83-3.77 (m, 1H), 2.52 (d, *J* = 5.5 Hz, 3H), 1.76-1.74 (m, 1H), 1.29-1.25 (m, 3H), 1.19 (bs, 8H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 138.9, 136.8, 136.3, 133.8, 132.0, 131.3, 130.0, 129.5, 127.5, 122.2, 120.7, 120.1, 110.6, 101.1, 45.0, 31.7, 29.8, 29.7, 29.1, 29.0, 26.9, 22.6, 14.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{31}N_2O_2S$ $[M + H]^+$ *m/z* 399.2101, found: 399.2105.

Compound 9bk



Yield: 0.065 g (75%), white solid.

Mp: 141-143 °C.

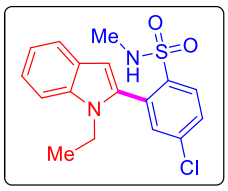
IR (neat): ν_{max} 3319, 1494, 1401, 1345, 1160, 1078, 721 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22-8.20 (m, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.61-7.58 (m, 1H), 7.51-7.47 (m, 1H), 7.25-7.18 (m, 7H), 6.89-6.88 (m, 2H), 6.60 (s, 1H), 5.36 (d, *J* = 17.5 Hz, 1H), 5.06 (d, *J* = 17.5 Hz, 1H), 4.02 (t, *J* = 5.5 Hz, 1H), 2.52 (d, *J* = 5.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 138.8, 137.9, 137.3, 136.7, 133.8, 132.0, 130.8, 129.9, 129.6, 128.5, 127.5, 127.2, 126.3, 122.7, 120.7, 120.4, 111.0, 101.9, 48.4, 29.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{21}N_2O_2S$ $[M + H]^+$ *m/z* 377.1318, found: 377.1327.

Compound 9cd



Yield: 0.058 g (72%), white solid.

Mp: 172-174 °C.

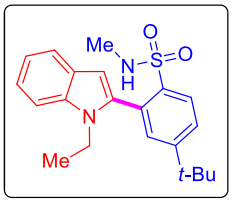
IR (neat): ν_{max} 3332, 2977, 2922, 1595, 1448, 1396, 1161, 1064, 766 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15-8.13 (m, 1H), 7.62-7.57 (m, 2H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.41-7.39 (m, 1H), 7.26 (d, *J* = 9.0 Hz, 1H), 7.26 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.53 (s, 1H), 4.06-3.99 (m, 1H), 3.87 (q, *J* = 5.5 Hz, 1H), 3.83-3.75 (m, 1H), 2.46 (d, *J* = 5.5 Hz, 3H), 1.16 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 139.0, 137.5, 134.8, 133.4, 132.1, 130.8, 130.1, 129.6, 128.5, 125.9, 122.6, 120.0, 111.3, 100.7, 39.7, 29.1, 15.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{18}ClN_2O_2S$ $[M + H]^+$ *m/z* 349.0772, found: 349.0767.

Compound 9dd



Yield: 0.060 g (70%), white solid.

Mp: 132-134 °C.

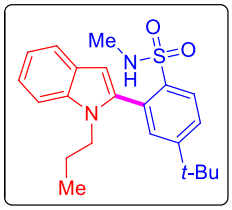
IR (neat): ν_{max} 3300, 2959, 2921, 1457, 1349, 1173, 1066, 733 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* =7.6 Hz, 2H), 7.49-7.44 (m, 2H), 7.33-7.29 (m, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.52 (s, 1H), 4.18-4.11 (m, 1H), 4.02 (q, *J* = 5.2 Hz, 1H), 3.95-3.86 (m, 1H), 2.56 (d, *J* =5.6 Hz, 3H), 1.39 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.8, 136.6, 136.3, 135.7, 131.0, 130.8, 129.9, 127.6, 126.3, 122.2, 120.7, 120.1, 110.3, 101.0, 39.4, 35.1, 31.1, 29.2, 15.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{21}H_{27}N_2O_2S$ $[M + H]^+$ *m/z* 371.1788, found: 371.1793.

Compound 9dg



Yield: 0.068 g (77%), white solid.

Mp: 176-178 ºC.

IR (neat): ν_{max} 3328, 2962, 2872, 1596, 1459, 1327, 1151, 1070, 734 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* =8.5 Hz, 1H), 7.66-7.63 (m, 2H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* =8.5 Hz, 1H), 7.31-7.27 (m, 1H), 7.20-7.17 (m, 1H), 6.51 (s, 1H), 4.11-4.05 (m, 1H), 3.95 (q, *J* = 5.5 Hz, 1H), 3.77-3.71(m, 1H), 2.53 (d, *J* =5.6 Hz, 3H), 1.80-1.70 (m, 1H), 1.69-1.65 (m, 1H), 1.38 (s, 9H), 0.81 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.7, 137.0, 136.8, 135.8, 131.2, 130.8, 129.9, 127.5, 126.2, 122.2, 120.7, 120.1, 110.6, 101.0, 46.6, 35.1, 31.0, 29.2, 23.2, 11.5 ppm.

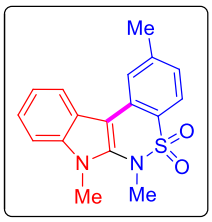
HRMS (ESI-TOF): Calcd for $C_{22}H_{29}N_2O_2S$ $[M + H]^+$ *m/z* 385.1944, found: 385.1951.

6.4 General procedure for the synthesis of compounds 10aa-10dg, 11 and 12aa-12ag.

To an oven dried Schlenk tube with a magnetic stirrer bar was added indolylbenzenesulfonamide **5** (0.23 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (0.57 mmol) and DMF (2 mL). The contents were sealed and heated at 130 °C (oil bath) for 3h. After completion of the reaction (TLC), the crude reaction mixture was cooled to rt (25 ºC), diluted with ethyl acetate (20 mL) and passed through a short celite column. The resulting solution was washed with water and the aqueous part was extracted with ethyl acetate (2 x 20 mL). The

combined organic layer was washed with brine solution (3 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) mixture as the eluent to afford the pure compounds **10, 11** and **12**. Compounds **10aa-10dg, 11** and **12aa-12ag** were prepared from the appropriate indolylbenzenesulfonamides **5** by using the same procedure using the same molar quantities.

Compound 10aa



Yield: 0.062 g (86%), white solid.

Mp: 152-154 ^{o}C.

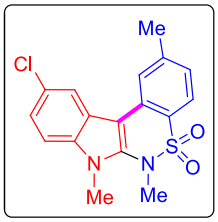
IR (neat): ν_{max} 2921, 2360, 2340, 1599, 1540, 1492, 1343, 1173, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.5 Hz, 1H), 7.91(s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.40-7.37 (m, 1H), 7.35-7.32 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.15 (s, 3H), 2.56 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 143.9, 139.5, 135.4, 132.0, 126.4$_2$, 126.4$_7$, 125.2, 124.7, 123.1, 122.9, 121.6, 120.0, 110.0, 101.3, 39.1, 29.4, 22.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{17}N_2O_2S$ $[M + H]^+$ *m/z* 313.1005, found: 313.1015.

Compound 10ac



Yield: 0.065 g (81%), white solid.

Mp: 161-163 ^{o}C.

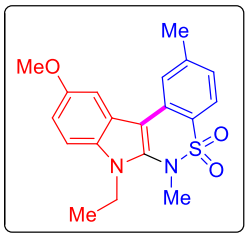
IR (neat): ν_{max} 2919, 2850, 1603, 1488, 1376, 1164, 1094, 712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.81 (s, 1H), 7.33 (bs, 2H), 7.28-7.26 (m, 1H), 3.83 (s, 3H), 3.14 (s, 3H), 2.57 (s, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.1, 140.4, 133.8, 131.3, 127.3, 126.8, 126.5, 125.3, 124.5, 123.8, 123.3, 119.5, 111.0, 101.1, 39.1, 29.5, 22.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{16}ClN_2O_2S$ $[M + H]^+$ *m/z* 347.0616, found: 347.0624.

Compound 10ae



Yield: 0.056 g (68%), white solid.

Mp: 205-207 ºC.

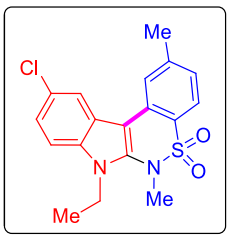
IR (neat): ν_{max} 2918, 2849, 1534, 1448, 1376, 1159, 1059, 802 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85-7.81 (m, 2H), 7.54 (s, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* =7.5 Hz, 1H), 7.01(d, *J* =8.0 Hz, 1H), 4.26 (d, *J* = 7.0 Hz, 2H), 3.95 (s, 3H), 3.13 (s, 3H), 2.55 (s, 3H), 1.50 (t, *J* =7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 155.4, 143.8, 139.5, 132.1, 129.6, 126.4, 126.2, 125.4, 124.4, 123.9, 111.9, 111.0, 103.6, 101.3, 56.2, 39.5, 38.4, 22.1, 15.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{21}N_2O_3S$ $[M + H]^+$ *m/z* 357.1267, found: 357.1270.

Compound 10af



Yield: 0.060 g (72%), white solid.

Mp: 143-145 ºC.

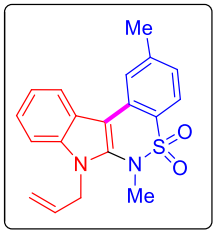
IR (neat): ν_{max} 2963, 2873, 1579, 1460, 1335, 1173, 1094, 7149 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 7.37-7.31 (m, 2H), 7.26 (d, *J* =8.0 Hz, 1H), 4.30 (q, *J* =7.0 Hz, 2H), 3.14 (s, 3H), 2.57 (s, 3H), 1.52 (t, *J* =7.0 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.1, 140.3, 132.8, 131.4, 127.2, 126.8, 126.6, 125.4, 124.6, 124.3, 123.3, 119.6, 111.3, 101.4, 39.5, 38.5, 22.0, 15.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{18}ClN_2O_2S$ $[M + H]^+$ *m/z* 361.0772, found: 361.0774.

Compound 10al



Yield: 0.055 g (71%), white solid.

Mp: 171-173 ºC.

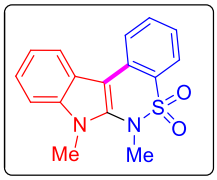
IR (neat): ν_{max} 2921, 2852, 1599, 1492, 1342, 1201, 1169, 801 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.02-8.00 (m, 1H), 7.82 (s, 1H), 7.77 (d, *J* =8.0 Hz, 1H), 7.30-7.22 (m, 3H), 7.17-7.15 (m, 1H), 6.04-6.00 (m, 1H), 5.21-5.19 (m, 1H), 5.03-4.99 (m, 1H), 4.80-4.79 (m, 2H), 3.03 (s, 3H), 2.47 (s, 3H) ppm.

^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 143.9, 139.2, 135.0, 132.3, 132.0, 126.6, 126.5, 125.3, 124.9, 123.2, 123.1, 121.7, 120.0, 117.4, 110.8, 101.7, 45.4, 39.5, 22.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{19}H_{19}N_2O_2S$ $[M + H]^+$ *m/z* 339.1162, found: 339.1164.

Compound 10ba



Yield: 0.052 g (76%), white solid.

Mp: 158-160 ºC.

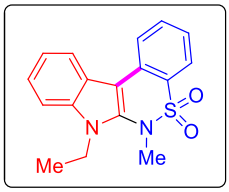
IR (neat): ν_{max} 2920, 2850, 1593, 1490, 1399, 1169, 1089, 1071, 768 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 1H), δ 8.08 (d, *J* = 7.5 Hz, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.74-7.71 (m, 1H), 7.45-7.28 (m, 4H), 3.85 (s, 3H), 3.16 (s, 3H) ppm.

^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 139.3, 135.5, 133.2, 132.0, 129.1 125.5, 125.2, 124.3, 123.1, 122.9, 121.7, 119.9, 110.1, 101.3, 39.1, 29.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{16}H_{14}N_2O_2S$ $[M + H]^+$ *m/z* 299.0849, found: 299.0847.

Compound 10bd



Yield: 0.060 g (84%), white solid.

Mp: 131-133 ºC.

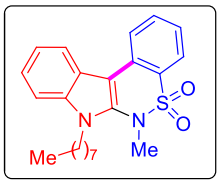
IR (neat): ν_{max} 2915, 2359, 2339, 1587, 1468, 1441, 1392, 1260, 1028 800 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.11-8.07 (m, 2H), 7.97 (d, *J* =8.0 Hz, 1H), 7.74-7.71 (m, 1H), 7.47-7.39 (m, 2H), 7.38 (t, *J* =7.0 Hz, 1H), 7.33 (d, *J* =7.0 Hz, 1H), 4.32 (q, *J* = 7.5 Hz, 2H), 3.17 (s, 3H), 1.54 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 138.9, 134.5, 133.1, 132.1, 129.2, 125.6, 125.4, 124.4, 123.3, 123.1, 121.6, 120.0, 110.4, 101.6, 39.5, 38.4, 15.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{17}N_2O_2S$ $[M + H]^+$ *m/z* 313.1005, found: 313.1012.

Compound 10bj



Yield: 0.068 g (75%), white solid.

Mp: 180-182 ºC.

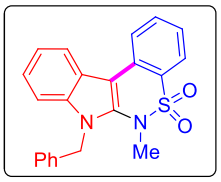
IR (neat): ν_{max} 2925, 2854, 1595, 1534, 1467, 1348, 1179, 1097, 767 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.11-8.07 (m, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.45-7.42 (m, 2H), 7.38-7.32 (m, 2H), 4.22 (t, *J* =7.5 Hz, 2H), 3.15 (s, 3H), 1.95-1.89 (m, 2H), 1.45-1.30 (m, 10H), 0.91 (t, *J* = 6.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 139.1, 134.7, 133.1, 132.1, 129.1, 125.6, 125.4, 124.3, 123.2, 123.0, 121.5, 120.0, 110.6, 101.5, 43.7, 39.5, 31.8, 29.7, 29.2, 29.1, 27.0, 22.6, 14.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{23}H_{29}N_2O_2S$ $[M + H]^+$ *m/z* 397.1944, found: 397.1953.

Compound 10bk



Yield: 0.071 g (82%), white solid.

Mp: 168-170 ºC.

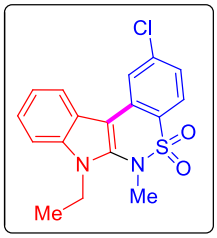
IR (neat): ν_{max} 2929, 1594, 1464, 1342, 1175, 1075, 730 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H),7.76 (d, *J* = 7.0 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.36-7.30(m, 6H), 7.21(d, *J* =7.5 Hz, 2H), 5.50 (s, 2H), 2.99 (s, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 139.3, 136.1, 135.2, 133.2, 131.9, 129.3, 129.0, 127.8, 126.3, 125.8, 125.4, 124.5, 123.4, 123.2, 121.9, 120.0, 111.0, 101.9, 46.7, 39.5 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{19}N_2O_2S$ $[M + H]^+$ *m/z* 375.1162, found: 375.1165.

Compound 10cd



Yield: 0.057 g (71%), white solid.

Mp: 166-169 ºC.

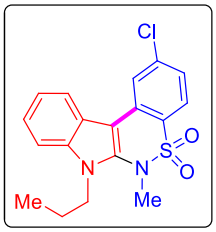
IR (neat): ν_{max} 2919, 2850, 1462, 1340, 1165, 1071, 742 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* =8.0 Hz, 2H), 7.89 (d, *J* =8.5 Hz, 1H), 7.47 (d, *J* =8.0 Hz, 1H), 7.39-7.34 (m, 3H), 4.32 (q, *J* =7.5 Hz, 2H), 3.15 (s, 3H), 1.54 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 139.6, 139.5, 134.5, 133.7, 127.3, 126.9, 125.6, 124.1, 123.4, 123.0, 122.0, 119.8, 110.5, 100.8, 39.6, 38.5, 15.0 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{16}ClN_2O_2S$ $[M+ Na]^+$ *m/z* 347.0616, found: 347.0625.

Compound 10cg



Yield: 0.062 g (75%), white solid.

Mp: 153-155 ºC.

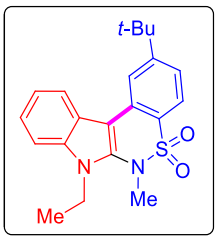
IR (neat): ν_{max} 2919, 2850, 1527, 1332, 1217, 1164, 1133, 790 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.05-8.04 (m, 2H), 7.89 (d, *J* =8.0 Hz, 1H), 7.45 (d, *J* =7.5 Hz, 1H), 7.40-7.33 (m, 3H), 4.20 (q, *J* =7.5 Hz, 2H), 3.15 (s, 3H), 1.95 (q, *J* =7.5 Hz, 2H), 1.04 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 139.8, 139.5, 134.7, 133.7, 127.3, 126.9, 125.6, 124.1, 123.3, 122.9, 121.9, 119.8, 110.7, 100.7, 45.4, 39.5, 23.0, 11.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{18}H_{18}ClN_2O_2S$ $[M + H]^+$ *m/z* 361.0772, found: 361.0774.

Compound 10dd



Yield: 0.055 g (65%), white solid.

Mp: 128-130 ºC.

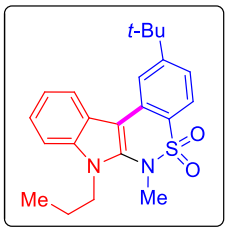
IR (neat): ν_{max} 2965, 2871, 1597, 1454, 1337, 1157, 1066, 785 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 1.5 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.41-7.33 (m, 2H), 4.32 (q, *J* = 7.0 Hz, 2H), 3.17 (s, 3H), 1.54 (t, *J* = 7.0 Hz, 3H), 1.47 (s, 9H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 156.8, 139.0, 134.5, 131.8, 126.4, 125.1, 123.3, 123.0_0, 122.9_9, 121.5, 121.3, 120.0, 110.4, 101.9, 39.6, 38.3, 35.4, 31.2, 15.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{21}H_{25}N_2O_2S$ $[M + H]^+$ *m/z* 369.1631, found: 369.1637.

Compound 10dg



Yield: 0.063 g (72%), white solid.

Mp: 190-192 ºC.

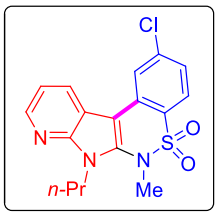
IR (neat): ν_{max} 2923, 2853, 1594, 1457, 1345, 1177, 1075, 767 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* =1.6 Hz, 1H), 8.08-8.06 (m, 1H), 7.89 (d, *J* =8.4 Hz, 1H), 7.48-7.44 (m, 2H), 7.39-7.33 (m, 2H), 4.21 (t, *J* =7.2 Hz, 2H), 3.15 (s, 3H), 2.07-1.19 (m, 2H), 1.47 (s, 9H), 1.05 (t, *J* =7.2 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 156.8, 139.3, 134.8, 131.8, 126.5, 125.1, 123.2, 123.0, 121.5, 121.3, 119.9, 110.6, 101.9, 45.2, 39.5, 35.4, 31.2, 23.0, 11.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{22}H_{27}N_2O_2S$ $[M + H]^+$ *m/z* 383.1788, found: 383.1797.

Compound 11



Yield: 0.058 g (70%), white solid.

Mp: 216-218 ºC.

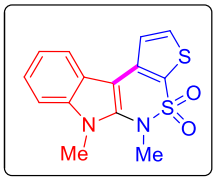
IR (neat): ν_{max} 2923, 2851, 1585, 1489, 1384, 1213, 1167, 1086, 768 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.0 Hz, 1H), 8.30 (d, *J* = 7.5 Hz, 1H), 7.93-7.90 (m, 2H), 7.42 (d, *J* =8.0 Hz, 1H), 7.30-7.28 (m, 1H), 4.35 (t, *J* =7.0 Hz, 2H), 3.22 (s, 3H), 2.03-1.99 (m, 2H), 1.03 (t, *J* =7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 146.4, 144.2, 140.3, 139.6, 133.0, 127.8, 127.6, 126.7, 126.0, 124.0, 117.8, 115.8, 99.2, 44.5, 39.2, 22.9, 11.3 ppm.

HRMS (ESI-TOF): Calcd for $C_{17}H_{17}ClN_3O_2S$ $[M + H]^+$ *m/z* 362.0725, found: 362.0727.

Compound 12aa



Yield: 0.057 g (81%), white solid.

Mp: 208-210 ºC.

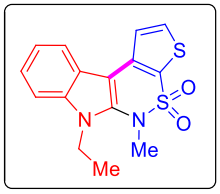
IR (neat): ν_{max} 2932, 1536, 1401, 1341, 1167, 1067, 743 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 5.0 Hz, 1H), 7.64 (d, *J* = 5.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.39-7.36 (m, 1H), 7.34-7.31 (m, 1H), 3.87 (s, 3H), 3.18 (s, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 139.8, 139.2, 135.0, 131.1, 123.4, 123.2, 122.7, 122.2, 121.6, 119.3, 110.0, 100.9, 39.3, 29.8 ppm.

HRMS (ESI-TOF): Calcd for $C_{14}H_{13}N_2O_2S_2$ $[M + H]^+$ *m/z* 305.0413, found: 305.0424.

Compound 12ad



Yield: 0.061 g (83%), white solid.

Mp: 211-213 ºC.

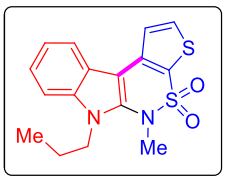
IR (neat): ν_{max} 2920, 2850, 1539, 1460, 1349, 1164, 1055, 752 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 5.0 Hz, 1H), 7.63 (d, *J* = 5.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 4.33 (q, *J* = 7.0 Hz, 2H), 3.19 (s, 3H), 1.54 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 139.5, 139.2, 134.1, 131.0, 123.4, 123.1, 122.6, 121.5, 119.5, 110.4, 101.2, 39.8, 38.8, 15.1 ppm.

HRMS (ESI-TOF): Calcd for $C_{15}H_{15}N_2O_2S_2$ $[M + H]^+$ *m/z* 319.0569, found: 319.0581.

Compound 12ag



Yield: 0.065 g (85%), white solid.

Mp: 235-237 ºC.

IR (neat): ν_{max} 2934, 1528, 1401, 1341, 1167, 1067, 744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* =7.5 Hz, 1H), 7.74 (d, *J* =5.0 Hz, 1H), 7.64 (d, *J* =5.0 Hz, 1H), 7.44 (d, *J* =8.0 Hz, 1H), 7.36 (t, *J* =7.0 Hz, 1H), 7.31 (d, *J* =7.5 Hz, 1H), 4.22 (t, *J* =7.5 Hz, 2H), 3.17 (s, 3H), 1.96 (q, *J* =7.5 Hz, 2H), 1.03 (t, *J* = 7.5 Hz, 3H) ppm.

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 139.8, 139.2, 134.4, 131.0, 123.4, 123.1, 122.5, 121.4, 119.5, 110.6, 101.1, 45.7, 39.7, 23.0, 11.4 ppm.

HRMS (ESI-TOF): Calcd for $C_{16}H_{17}N_2O_2S_2$ $[M + H]^+$ *m/z* 333.0726, found: 333.0731.

6.5 X-ray crystallography

A suitable crystal was mounted on a glass fiber (for **5aa**, **9ba**, **9bh**, **10al**, **10bk, 12ag**) and X-ray data were collected at 298 K on a Bruker AXS-SMART or on an OXFORD diffractometer [Mo-K_α (λ = 0.71073 Å) or Cu- K_α (λ = 1.54184 Å)]. Structures were solved and refined using standard methods.[46] Crystal data are summarized in Tables 5-6.

Table 5: Crystal data for compounds **5aa**, **9ba**, and **9bh**

Compound	**5aa**	**9ba**	**9bh**
Emp. formula	$C_{17}H_{17}IN_2O_2S$	$C_{16}H_{16}N_2O_2S$	$C_{19}H_{22}N_2O_2S$
Formula weight	440.29	300.37	342.44
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/c$	$P2_1/n$	P-1
a /Å	6.2737(4)	11.6333(5)	8.4303(4)
b /Å	18.0774(6)	11.3408(5)	10.1352(5)
c /Å	16.6031(8)	11.7715(5)	11.2583(4)
α/deg	90	90	80.979(4)
β/deg	112.875(8)	101.2610(19)	71.424(4)
γ/deg	90	90	89.642(4)
V /Å^3	1734.91(15)	1523.13(11)	899.57(7)
Z	4	4	2
Dcalc /g cm^{-3}]	1.686	1.310	1.264
μ /mm^{-1}	1.976	0.218	0.193
F(000)	872.0	632.0	364.0

Data/ restraints/ parameters	2513/0/212	2683/0/193	3131/0/224
S	1.074	1.053	1.083
R1 [I>2σ(I)]	0.0405	0.0464	0.0532
wR2 [all data]	0.1204	0.1128	0.1620
Max./min. residual electron dens. [eÅ^{-3}]	0.883/-0.705	0.396/-0.324	0.691/-0.273

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 6: Crystal data for compounds **10al**, **10bk** and **12ag**

Compound	**10al**	**10bk**	**12ag**
Emp. formula	$C_{22}H_{18}N_2O_2S$	$C_{19}H_{18}N_2O_2S$	$C_{16}H_{16}N_2O_2S_2$
Formula weight	374.44	338.41	332.43
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	*P*121/n1	*P*na2(1)	*P*121/n1
a /Å	9.2441(3)	37.1188(12)	10.3674(4)
b /Å	9.3416(3)	7.4217(2)	7.8969(3)
c /Å	21.8748(6)	11.9822(5)	19.6001(8)
α/deg	90	90	90
β/deg	93.805(3)	90	102.228(4)
γ/deg	90	90	90
V /Å^3	1884.83(10)	3300.9(2))	1568.26(11)

Z	4	8	4
*D*calc /g cm^{-3}]	1.320	1.362	1.408
μ /mm^{-1}	0.191	0.210	0.347
F(000)	784.0	1424.0	696.0
Data/ restraints/ parameters	3312/0/246	5529/1/438	2772/0/202
S	1.036	0.974	1.123
R1 [I>2σ(I)]	0.0535	0.0578	0.0492
wR2 [all data]	0.1430	0.1464	0.1387
Max./min. residual electron dens. [eÅ^{-3}]	0.228/-0.288	0.239/-0.304	0.493/-0.837

^{a}R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

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Copies of $^{1}H/^{13}C\{^{1}H\}$ NMR spectra for representative compounds
Part A: 11ae, 12aa, 13ea, 15aa, 15da, 15ea, 15fn, 15gd, 15hd, 16aa, 17da, 18ib, 20ag, 21ap, 22aa, and **23ad**
Part B: 5aa, 9aa, 10aa, and 12aa

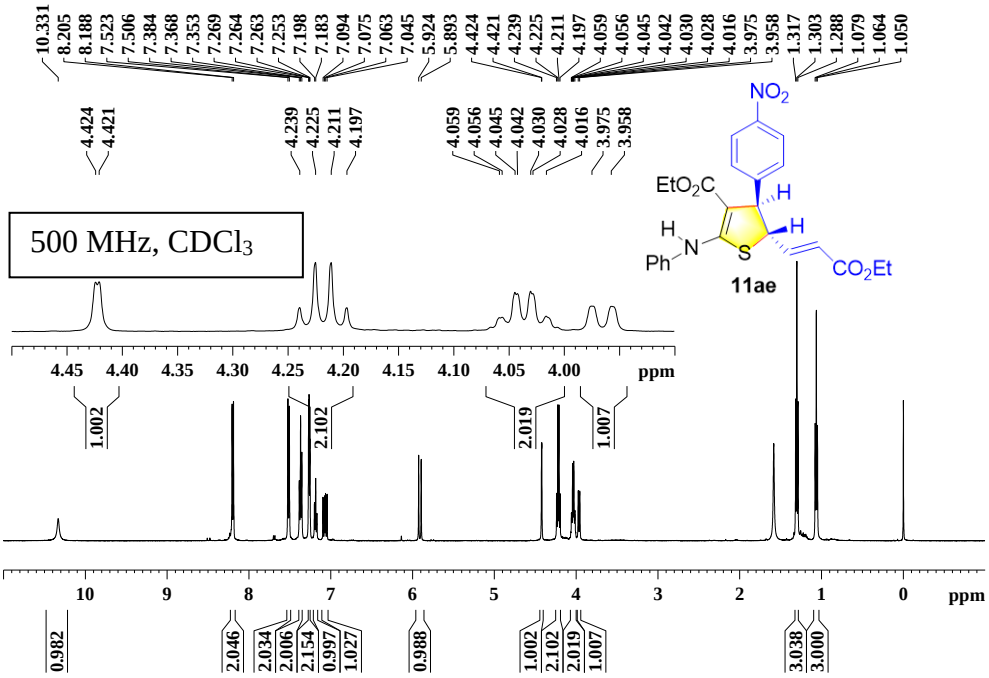

Figure A1: ^{1}H NMR spectrum of compound **11ae**

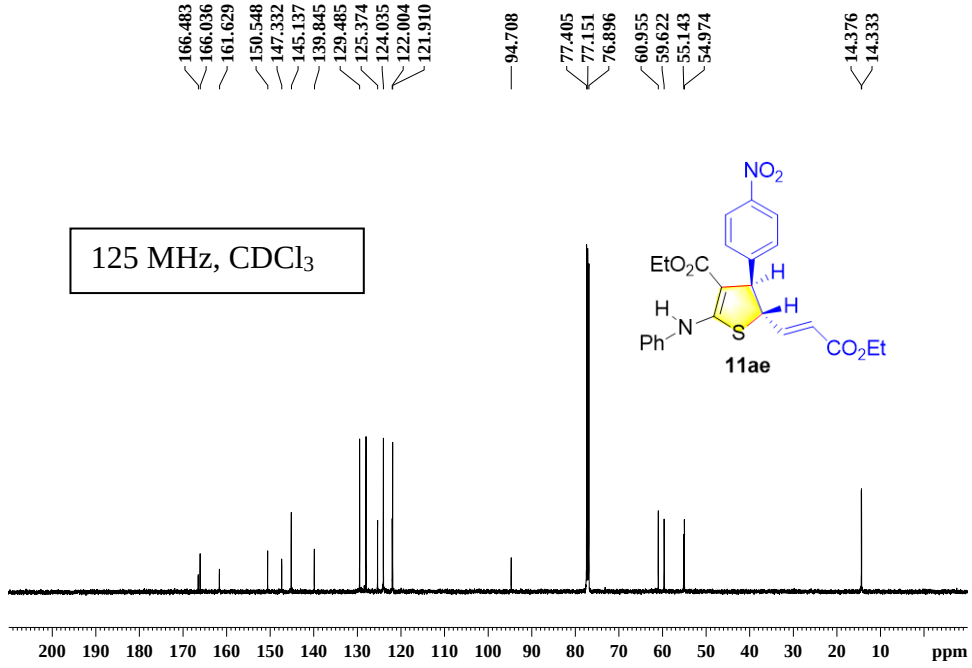

Figure A2. $^{13}C\{^{1}H\}$ NMR spectrum of compound **11ae**

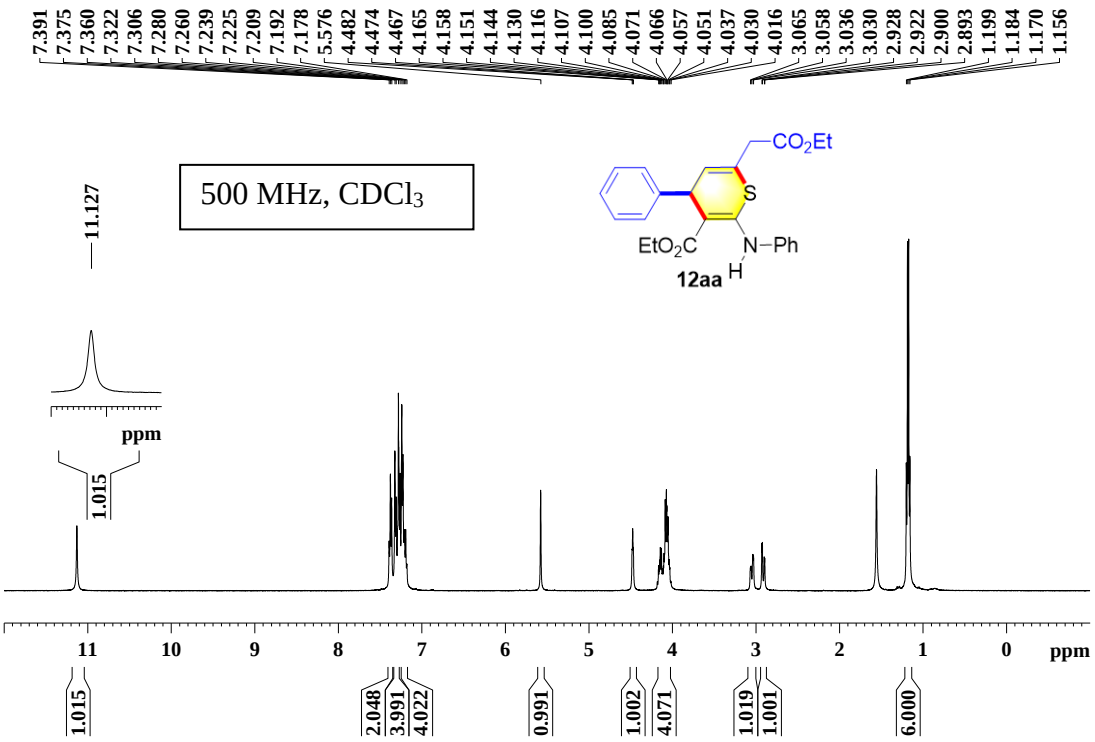

Figure A3: ^{1}H NMR spectrum of compound **12aa**

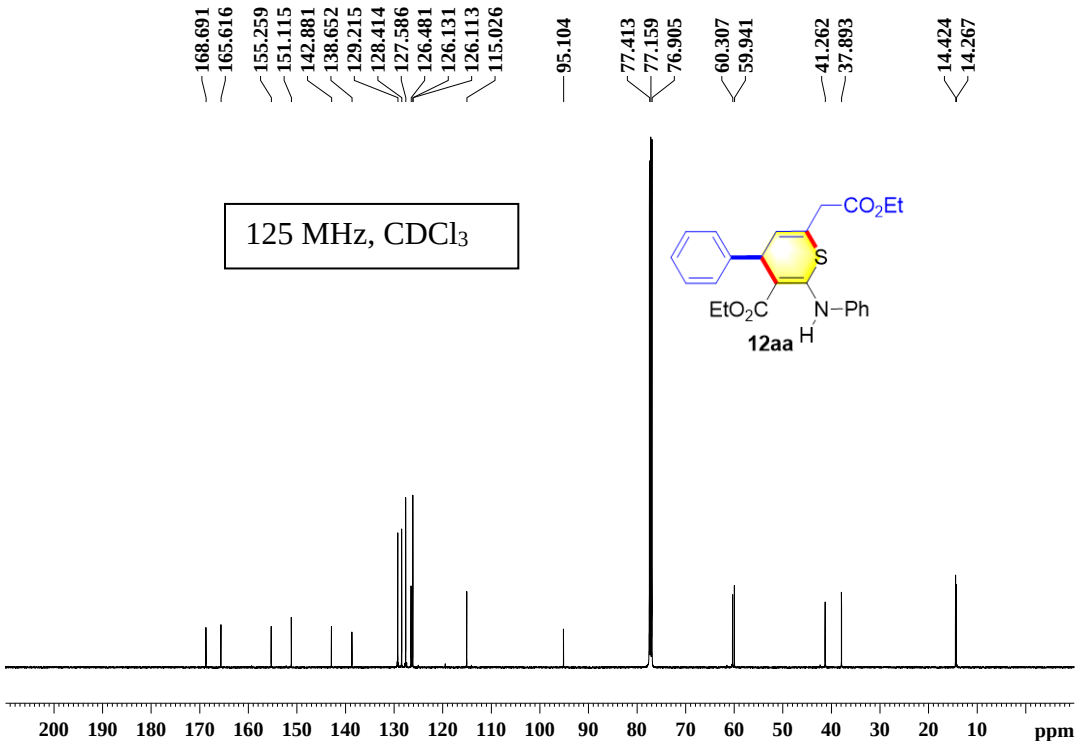

Figure A4. ^{13}C{^{1}H} NMR spectrum of compound **12aa**

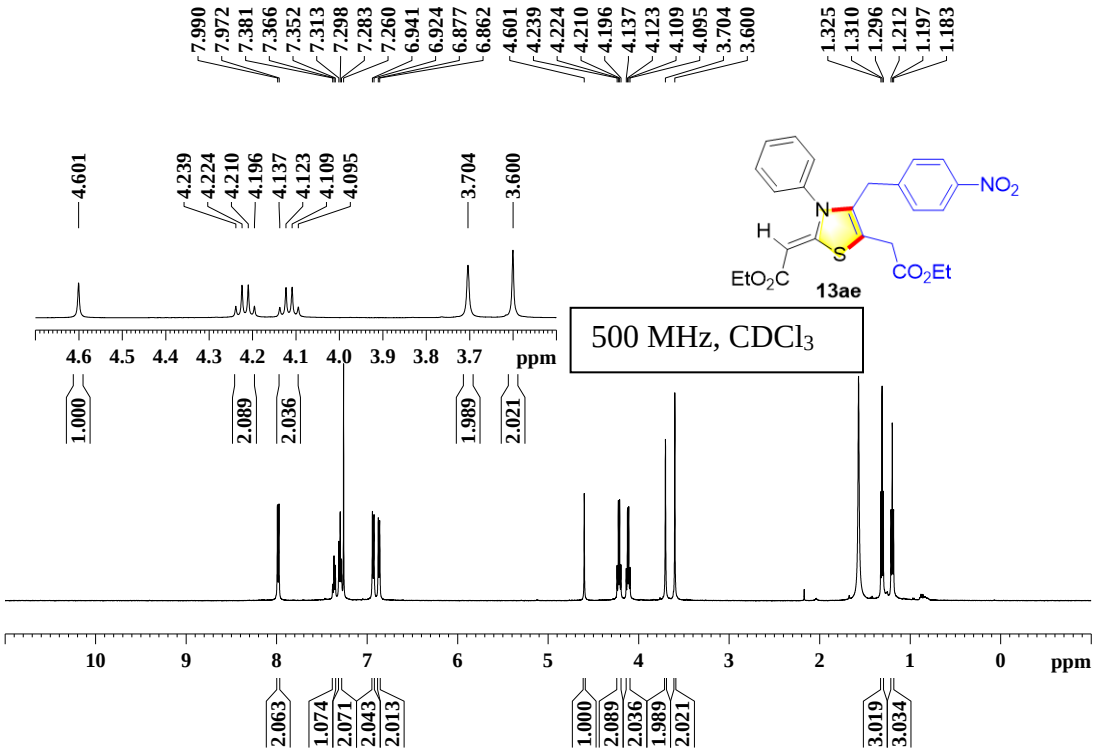

Figure A5: ^{1}H NMR spectrum of compound **13ae**

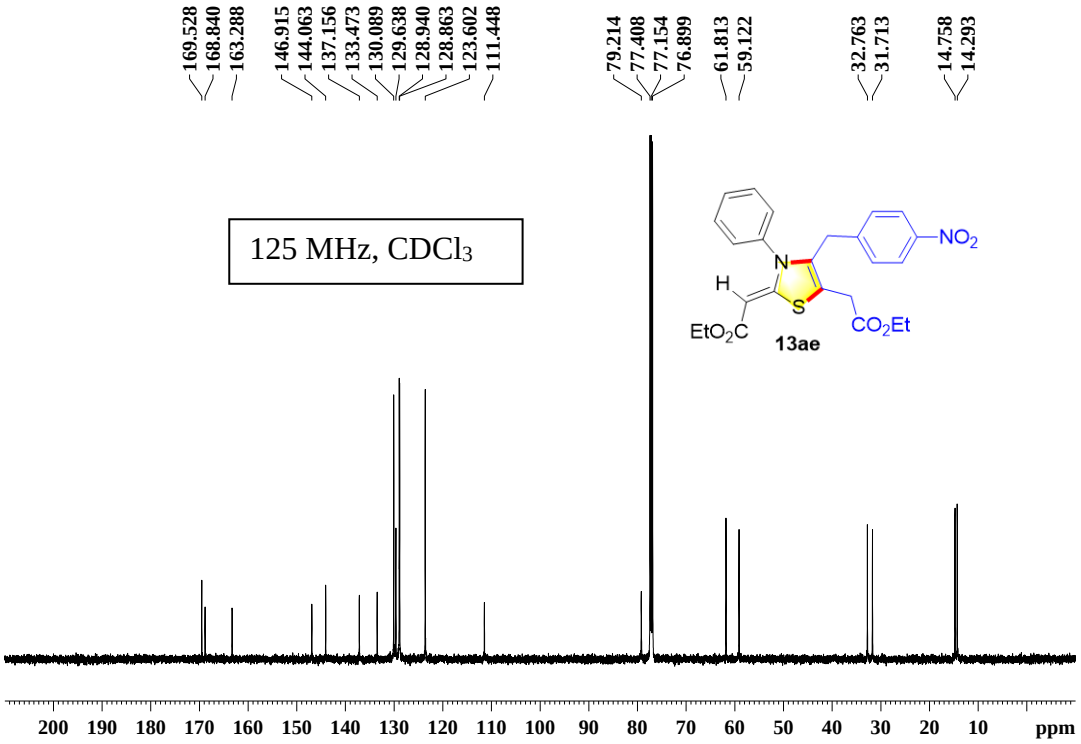

Figure A6: ^{13}C{^{1}H} NMR spectrum of compound **13ae**

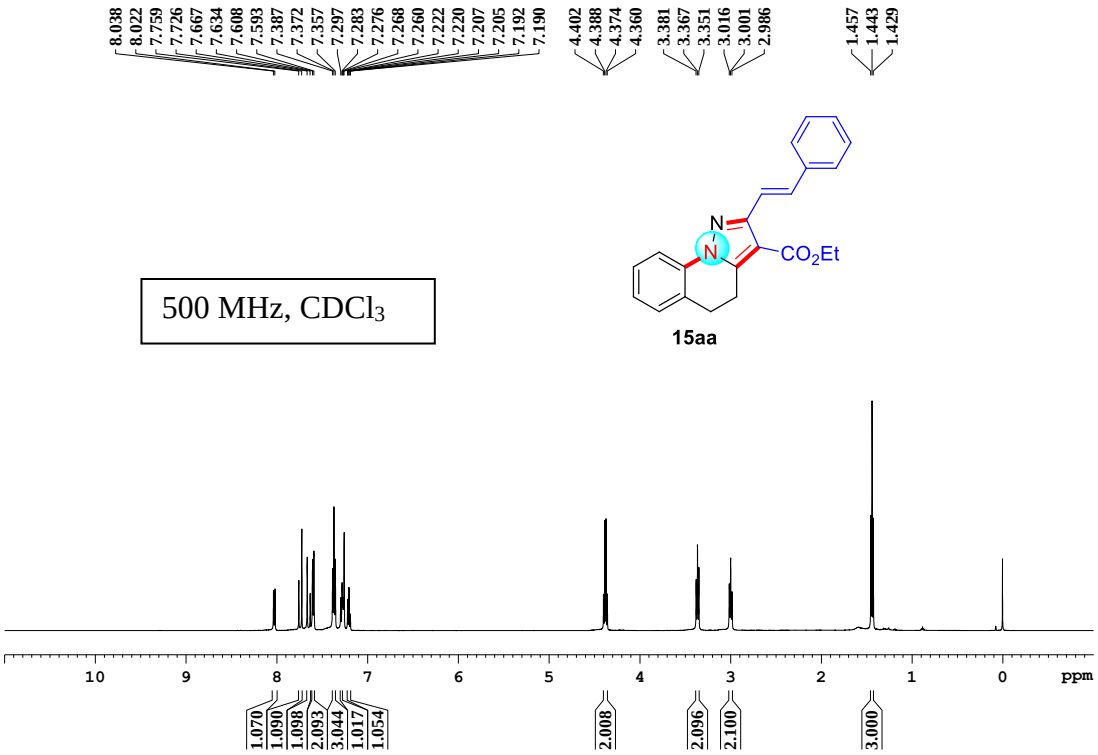

Figure A7: ^{1}H NMR spectrum of compound **15aa**

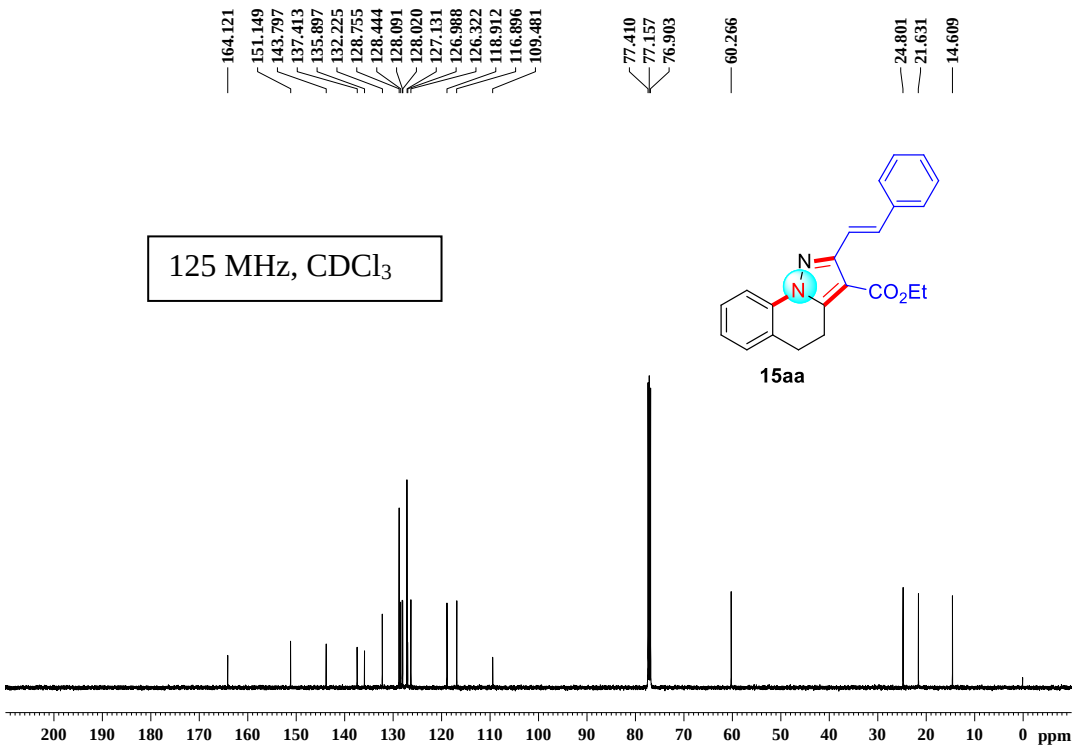

Figure A8: ^{13}C{^{1}H} NMR spectrum of compound **15aa**

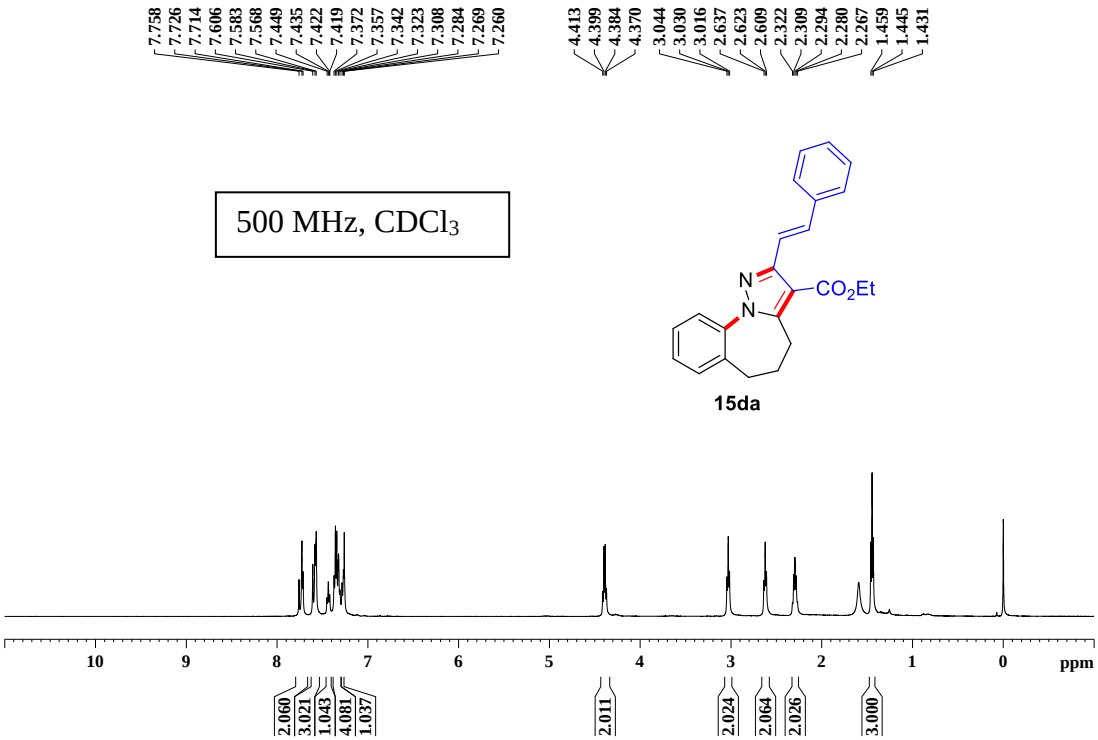

Figure A9: ^{1}H NMR spectrum of compound **15da**

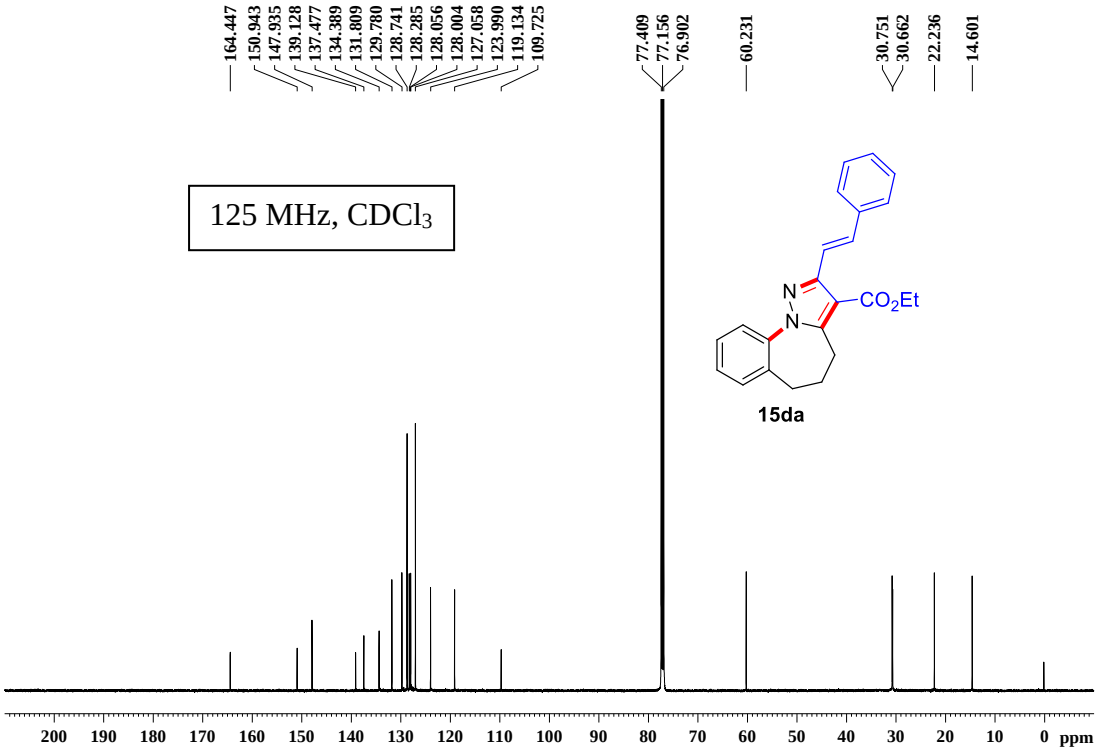

Figure A10: ^{13}C{^{1}H} NMR spectrum of compound **15da**

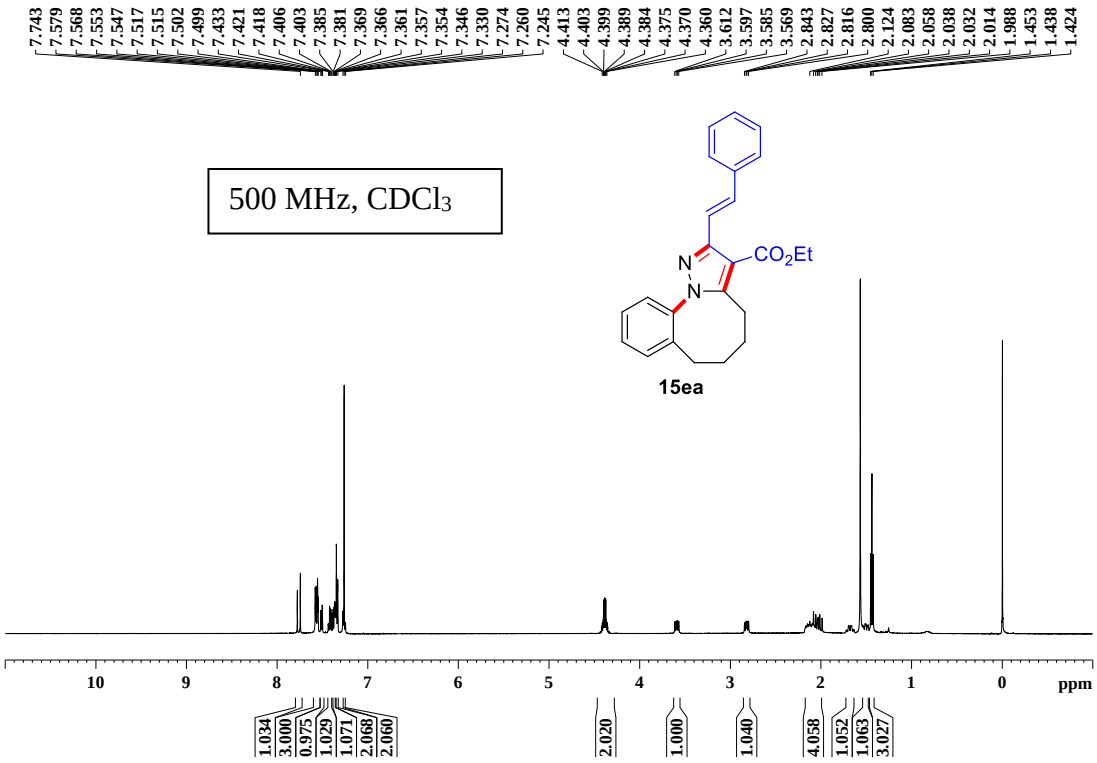

Figure A11: ^{1}H NMR spectrum of compound **15ea**

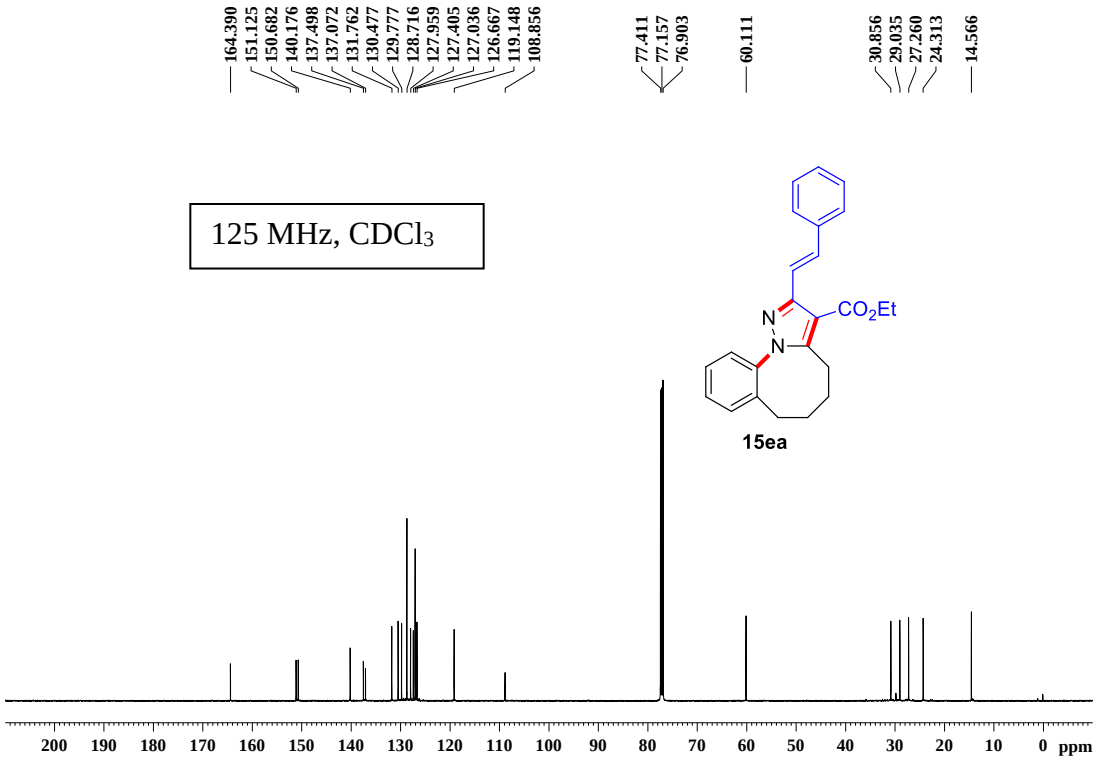

Figure A12: ^{13}C{^{1}H} NMR spectrum of compound **15ea**

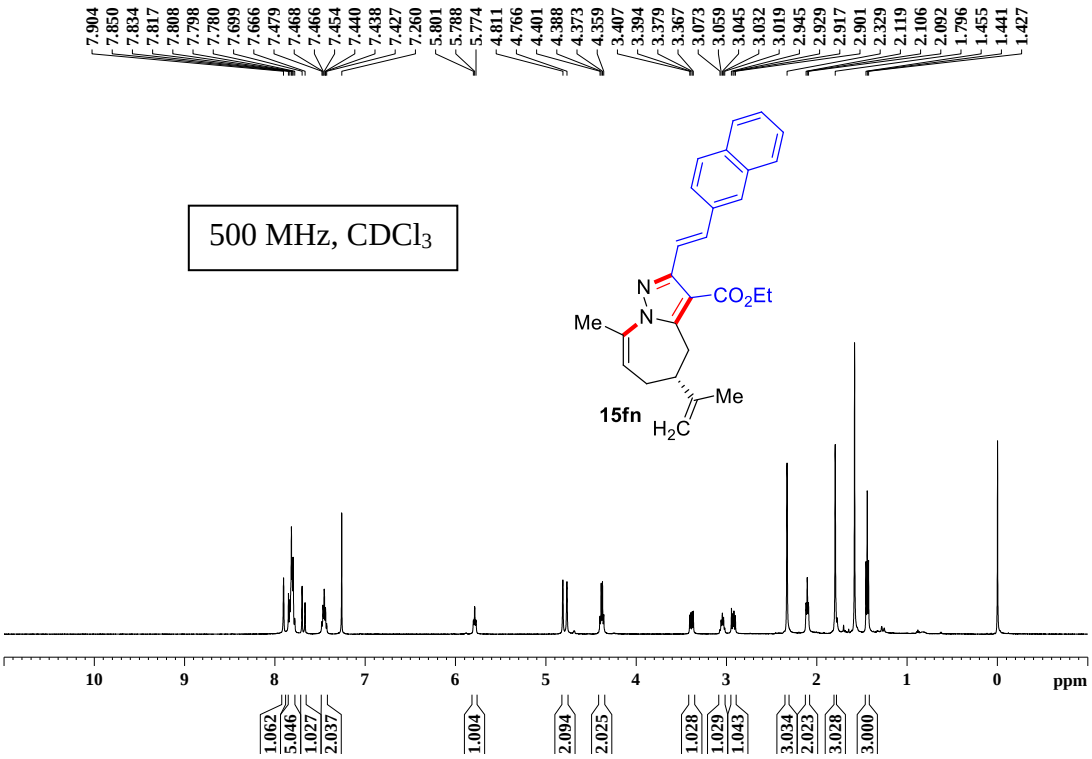

Figure A13: ^{1}H NMR spectrum of compound **15fn**

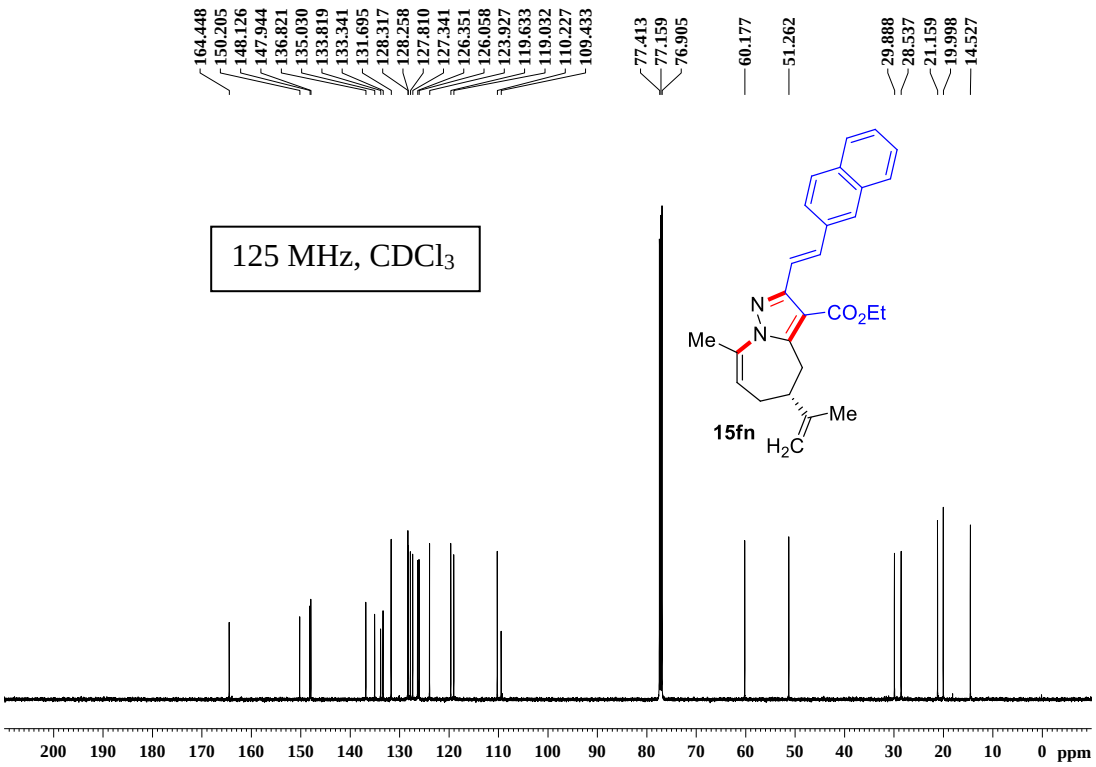

Figure A14: ^{13}C{^{1}H} NMR spectrum of compound **15fn**

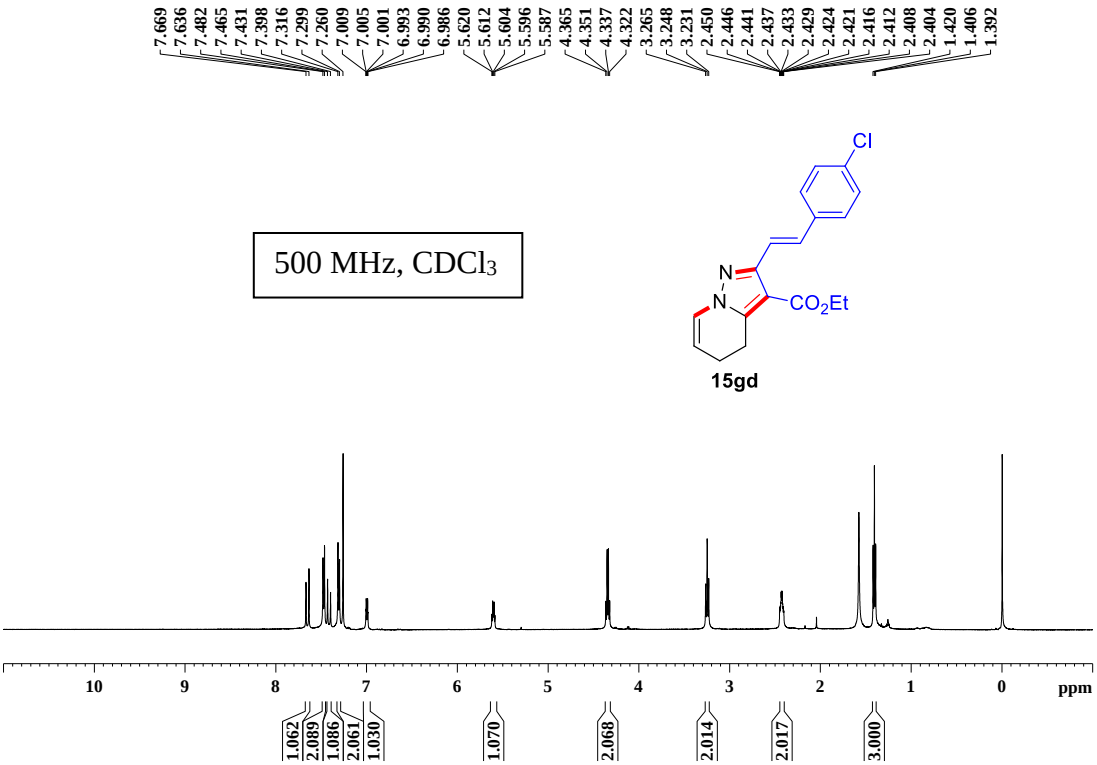

Figure A15: ^{1}H NMR spectrum of compound **15gd**

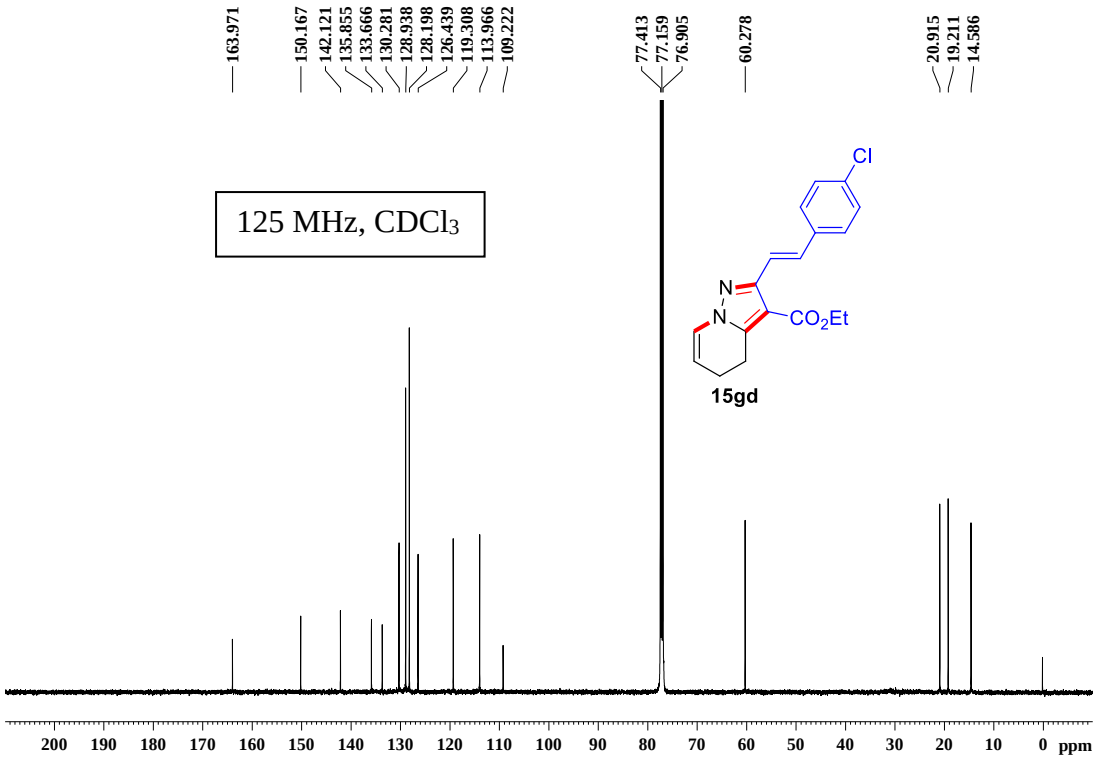

Figure A16: ^{13}C{^{1}H} NMR spectrum of compound **15gd**

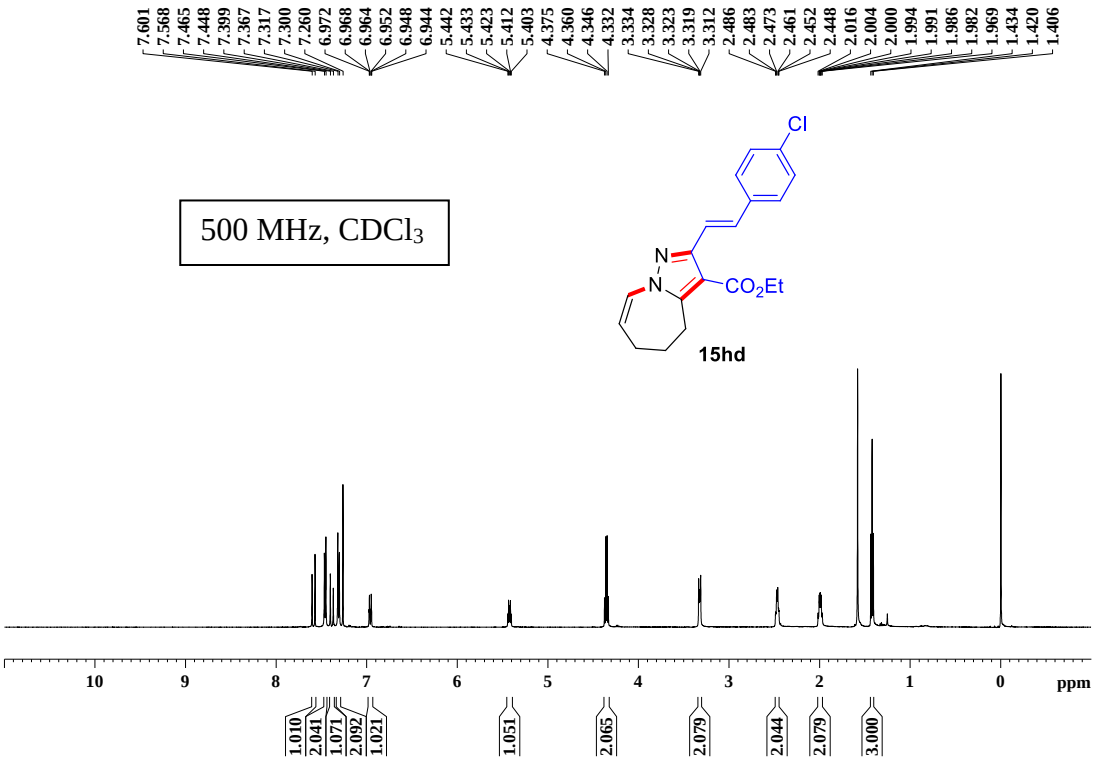

Figure A17: ^{1}H NMR spectrum of compound **15hd**

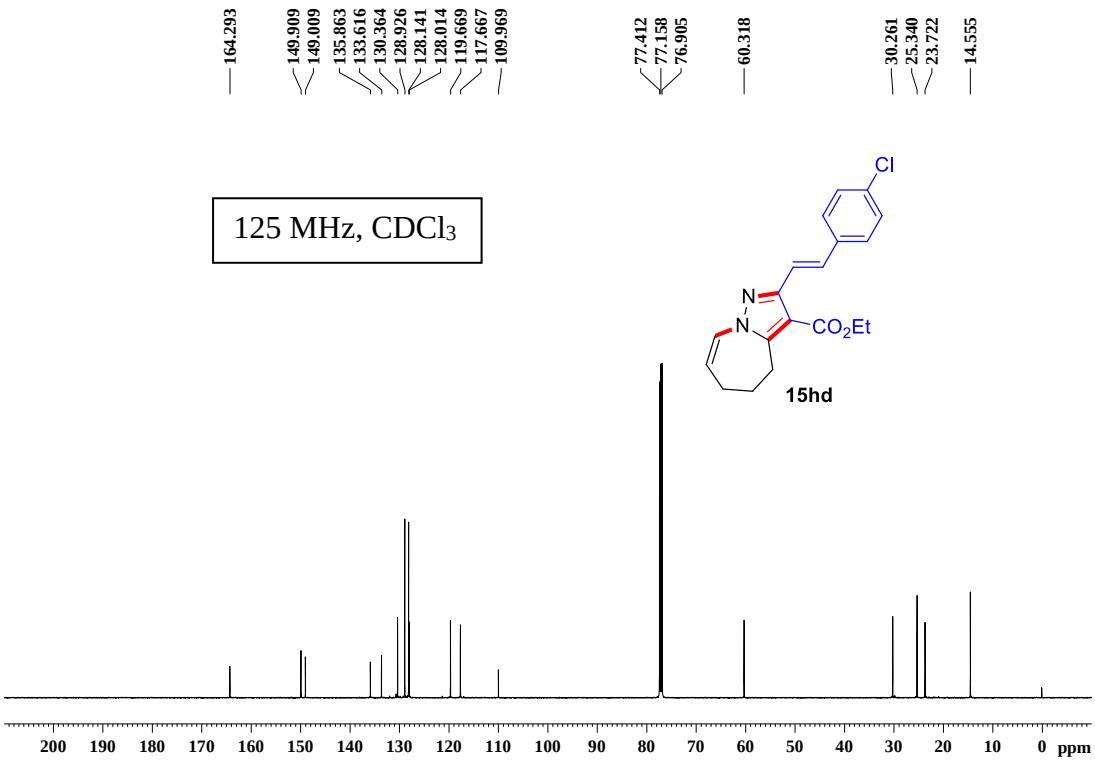

Figure A18: ^{13}C{^{1}H} NMR spectrum of compound **15hd**

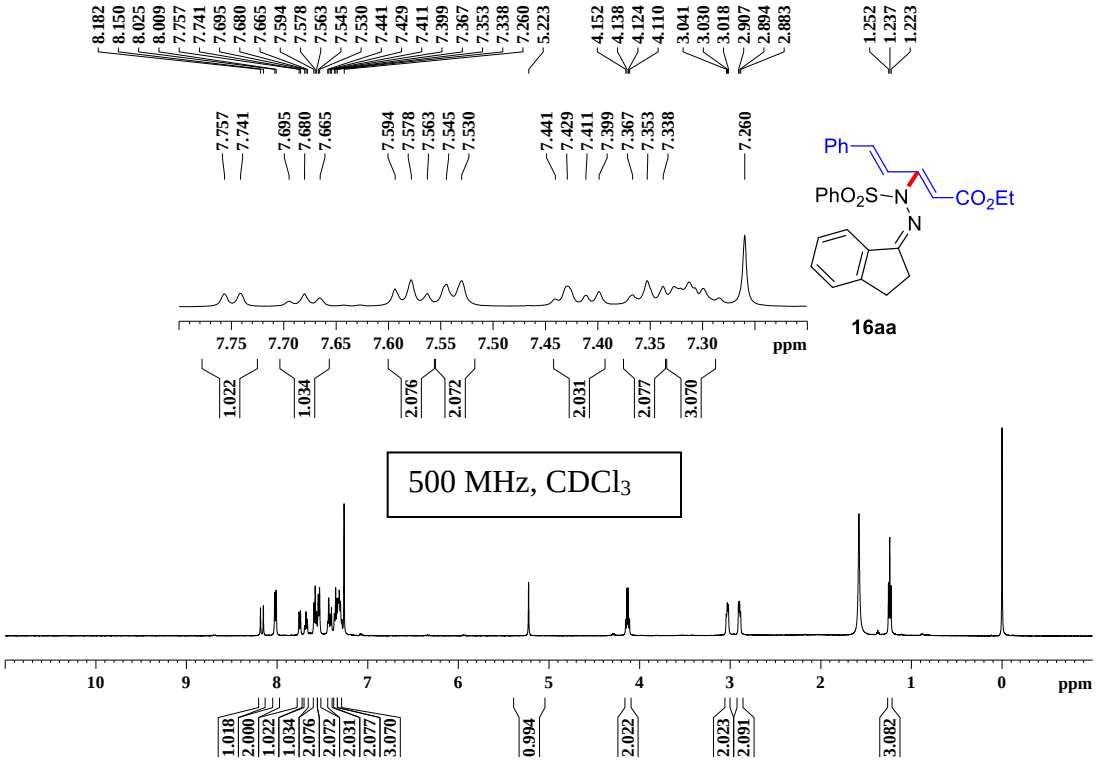

Figure A19: ^{1}H NMR spectrum of compound **16aa**

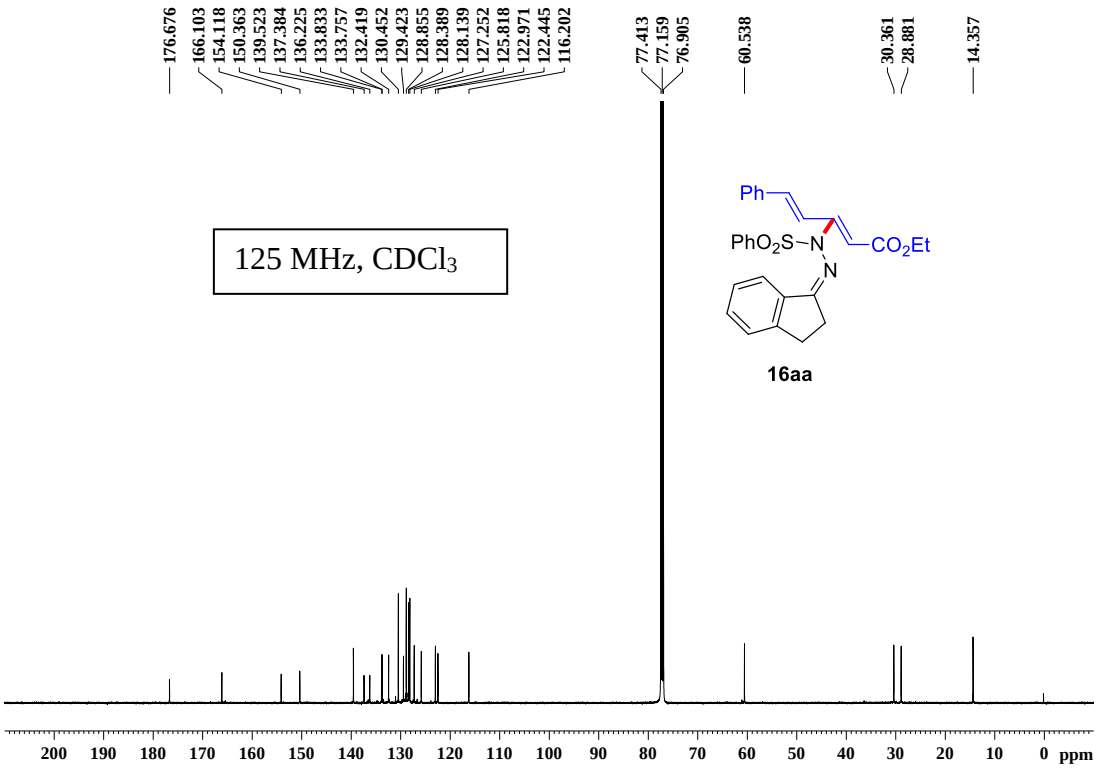

Figure A20: ^{13}C{^{1}H} NMR spectrum of compound **16aa**

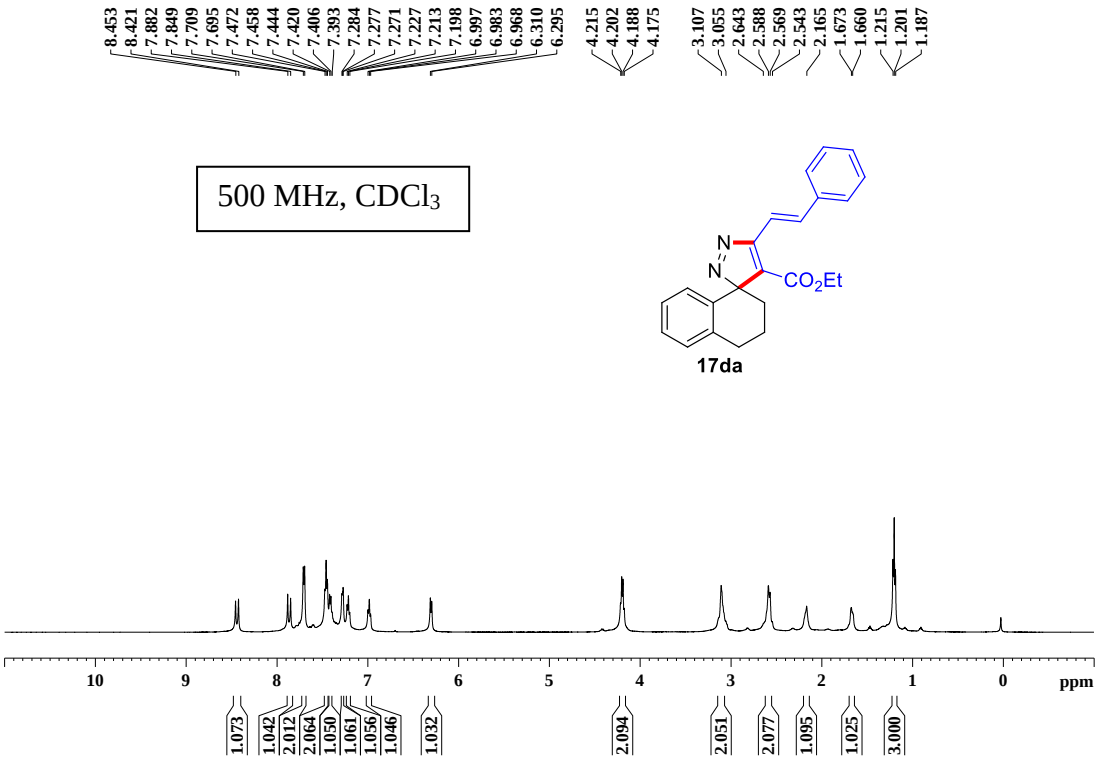

Figure A21: ^{1}H NMR spectrum of compound **17da**

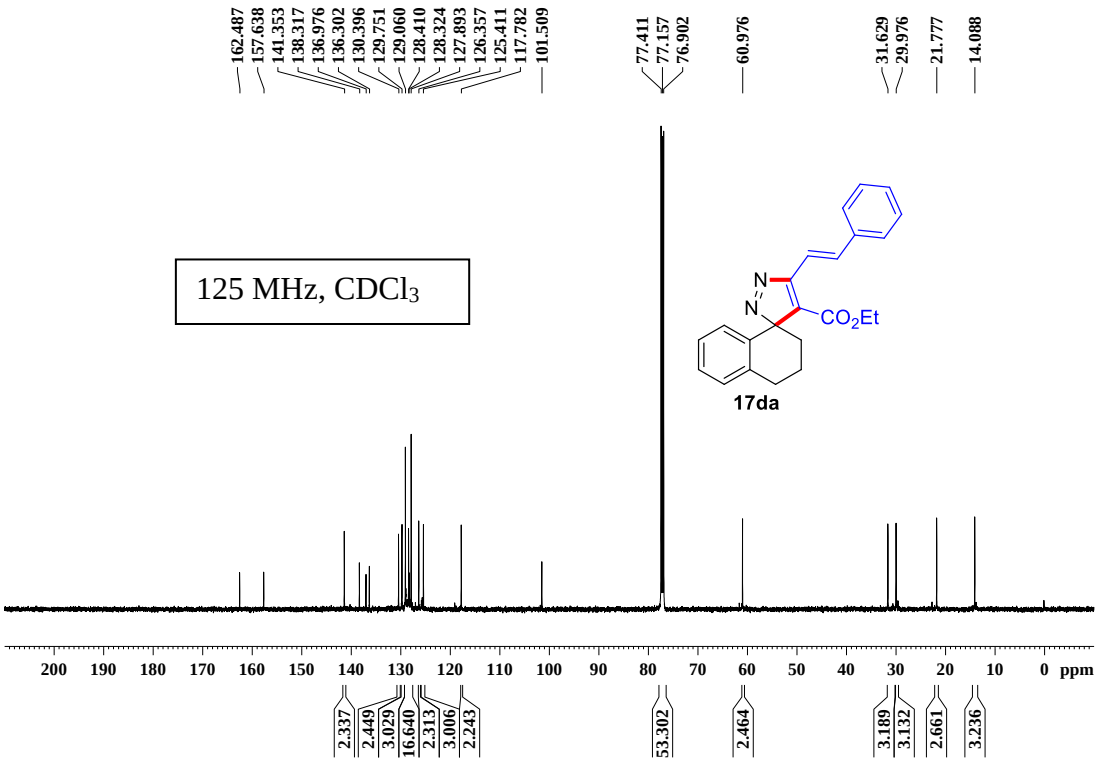

Figure A22: ^{13}C{^{1}H} NMR spectrum of compound **17da**

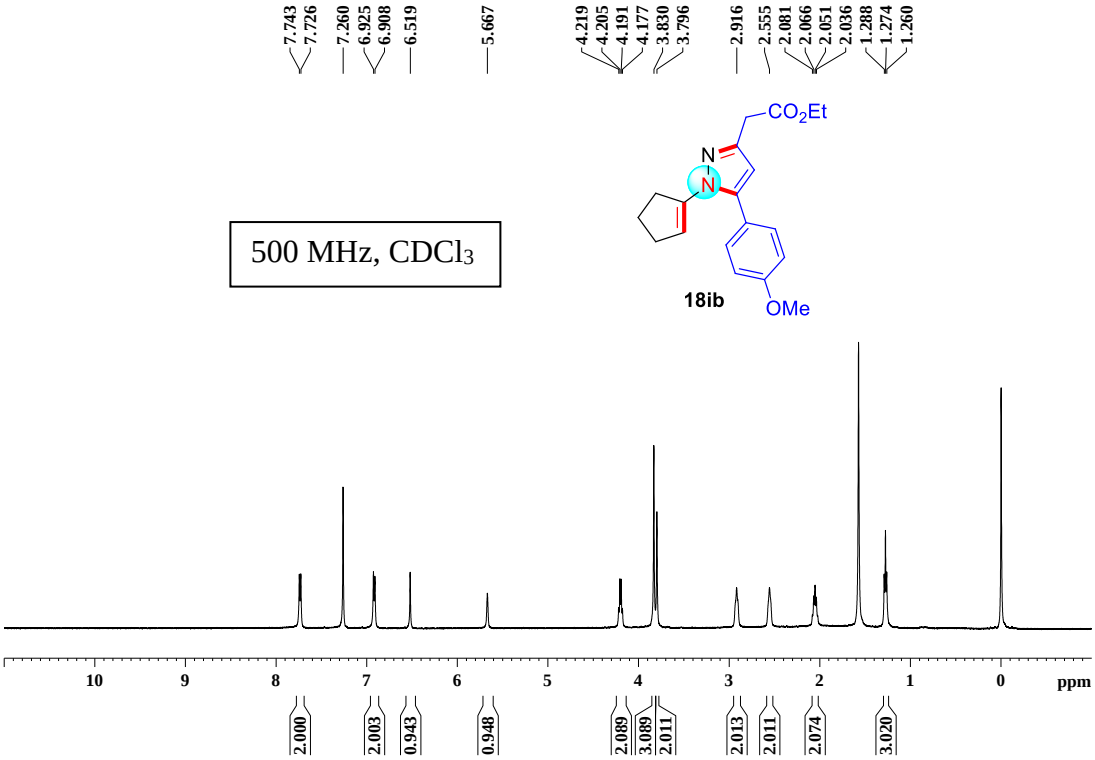

Figure A23: ^{1}H NMR spectrum of compound **18ib**

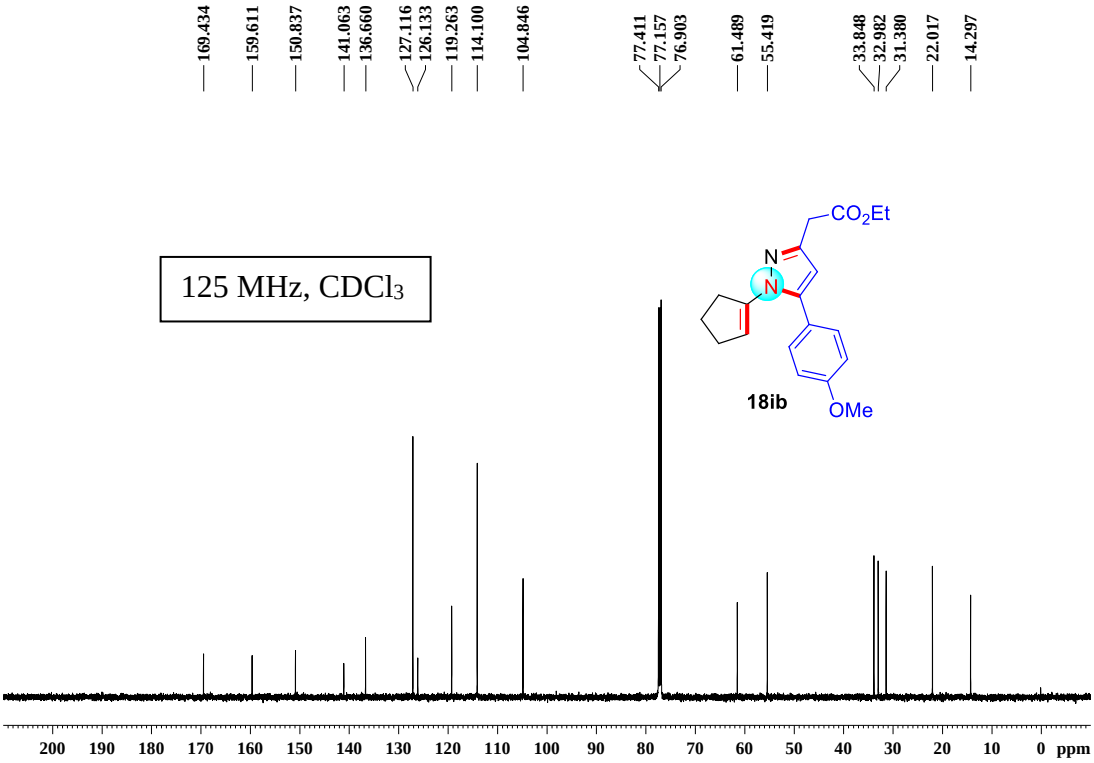

Figure A24: $^{13}C\{^{1}H\}$ NMR spectrum of compound **18ib**

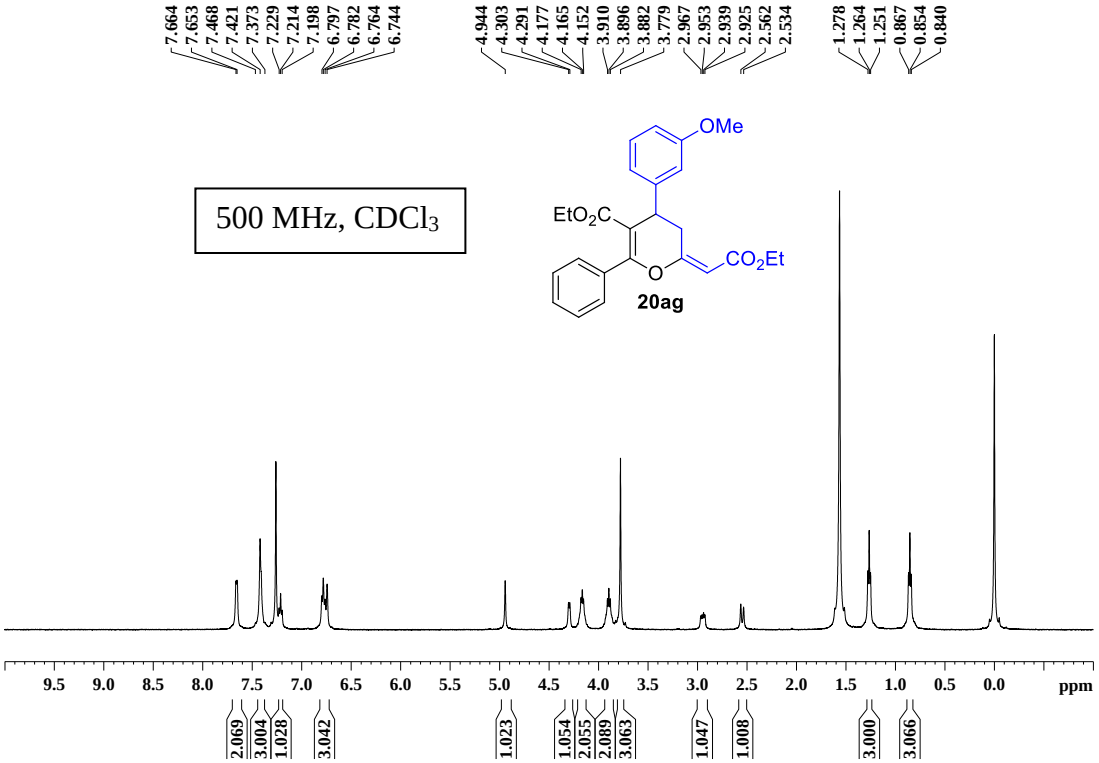

Figure A25: ^{1}H NMR spectrum of compound **20ag**

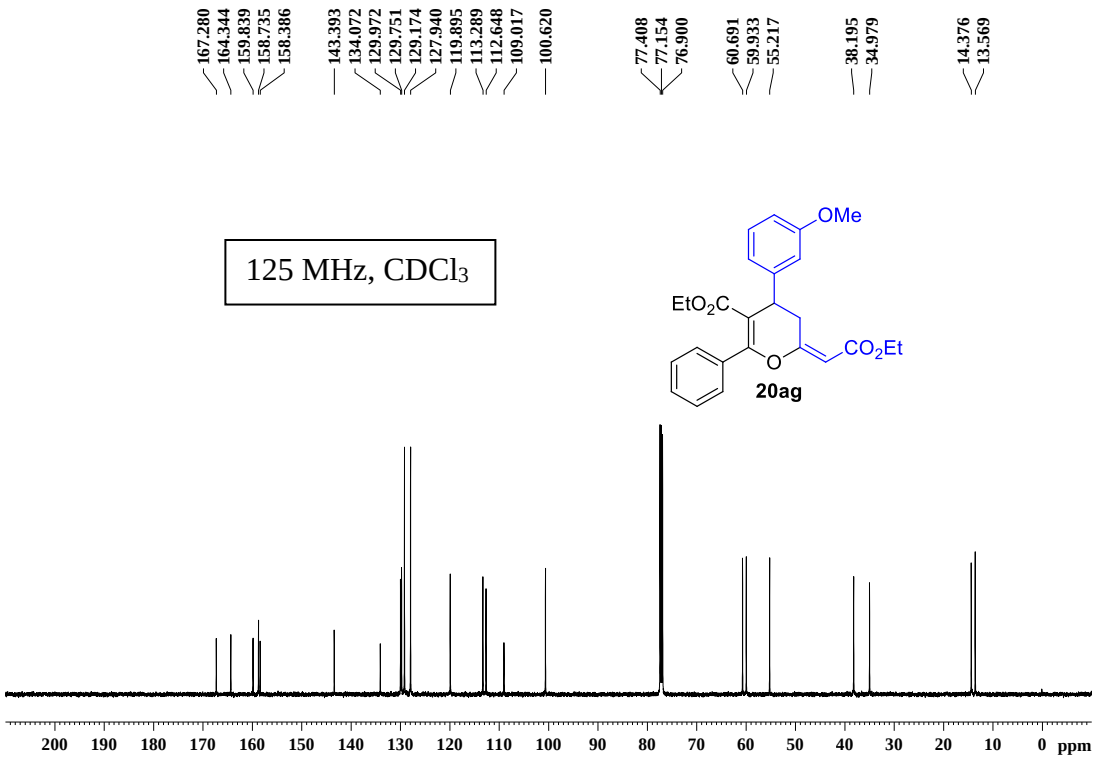

Figure A26: $^{13}C\{^{1}H\}$ NMR spectrum of compound **20ag**

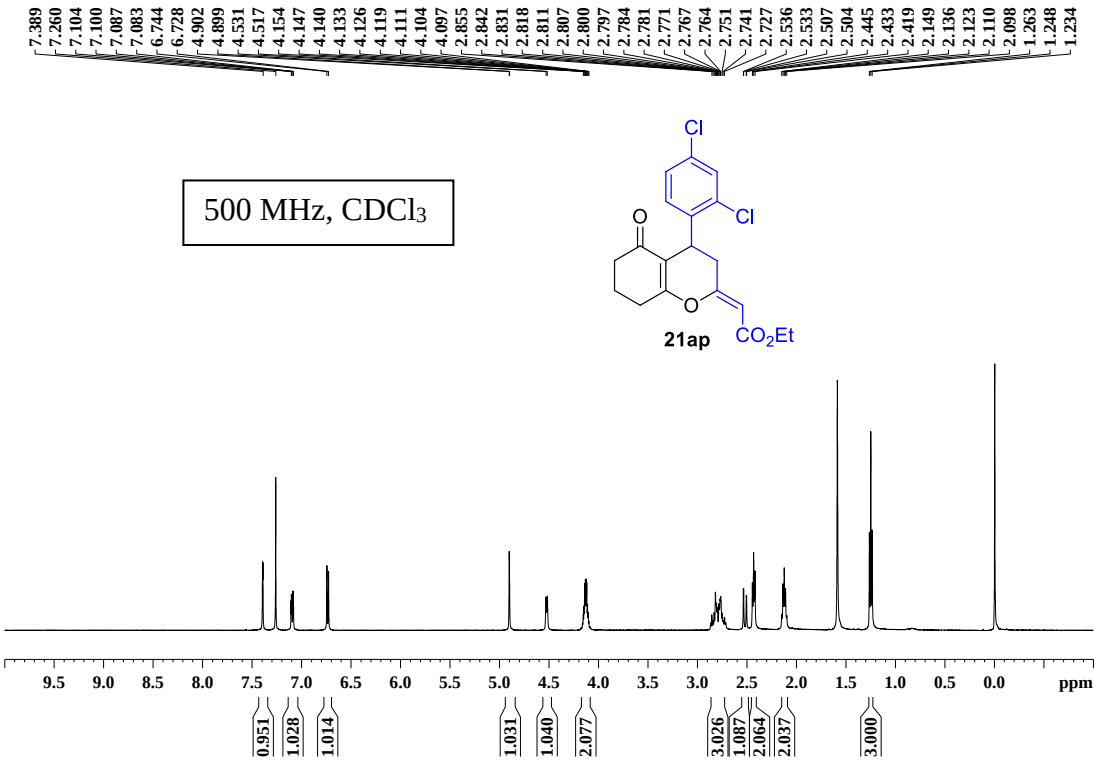

Figure A27: ^{1}H NMR spectrum of compound **21ap**

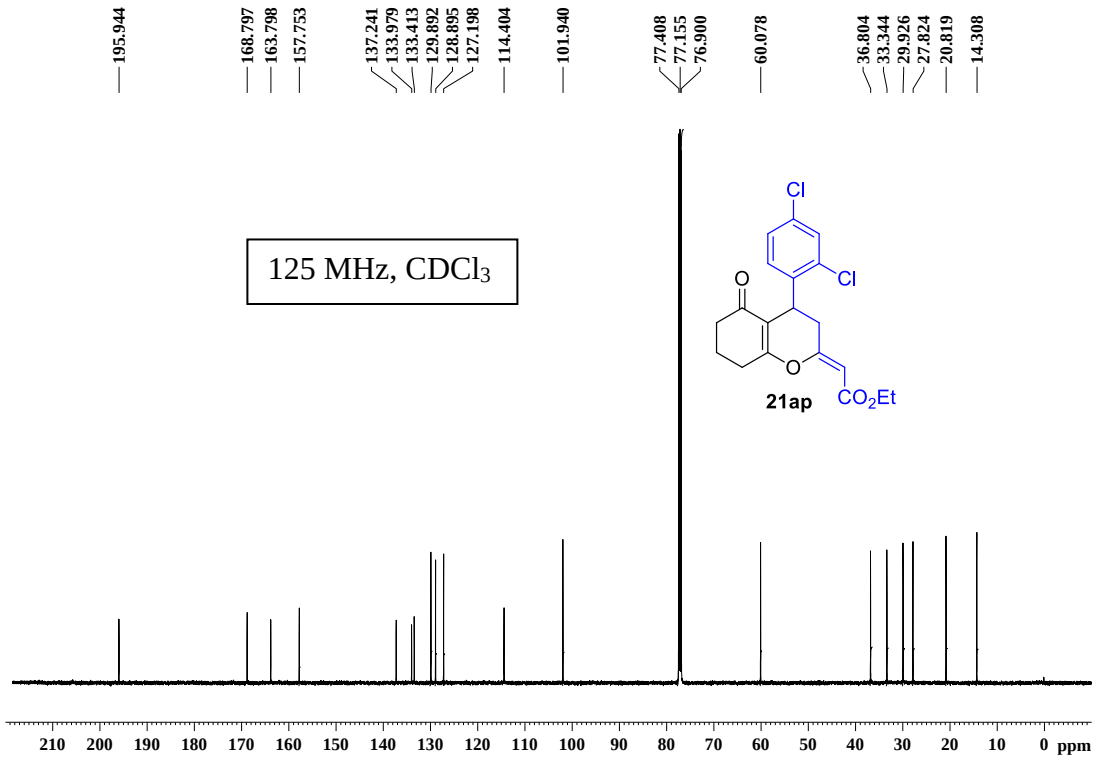

Figure A28: ^{13}C{^{1}H} NMR spectrum of compound **21ap**

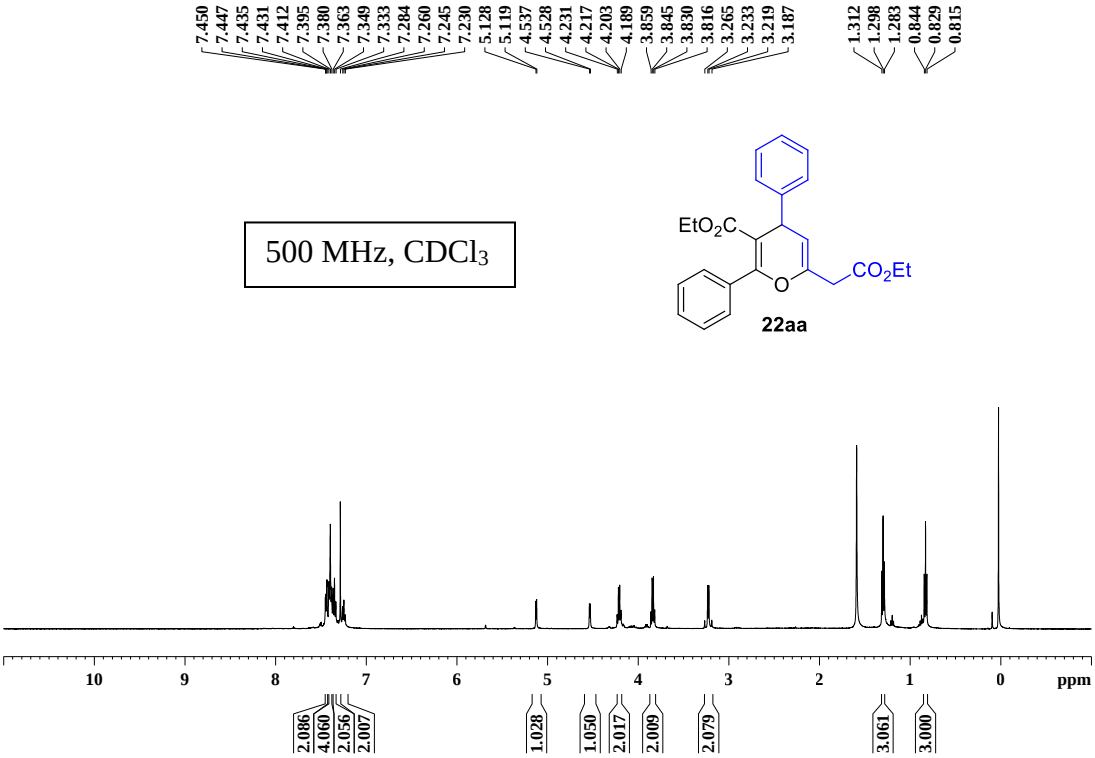

Figure A29: ^{1}H NMR spectrum of compound **22aa**

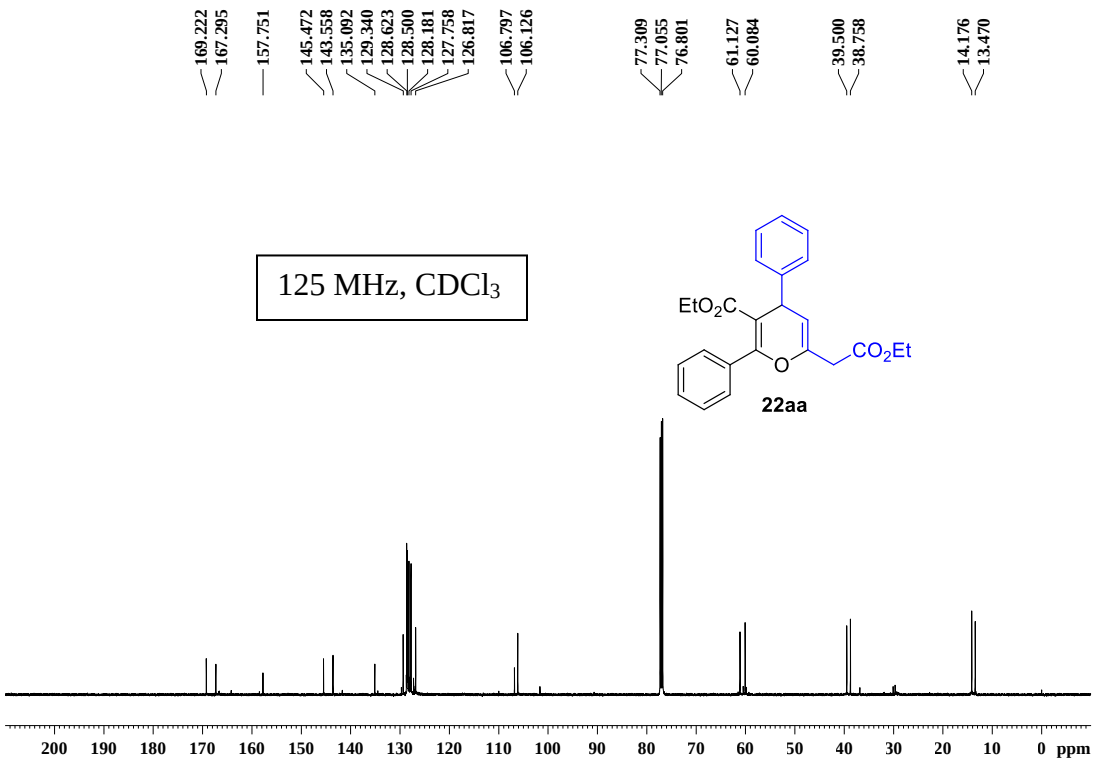

Figure A30: ^{13}C{^{1}H} NMR spectrum of compound **22aa**

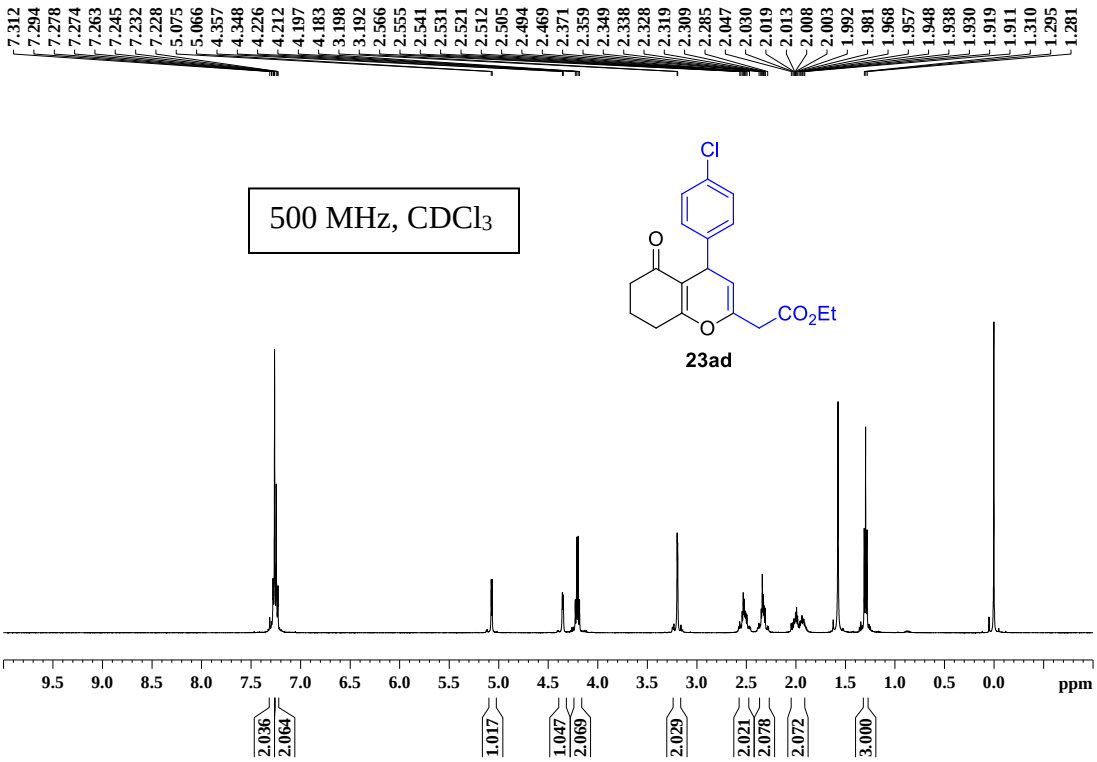

Figure A31: ^{1}H NMR spectrum of compound **23ad**

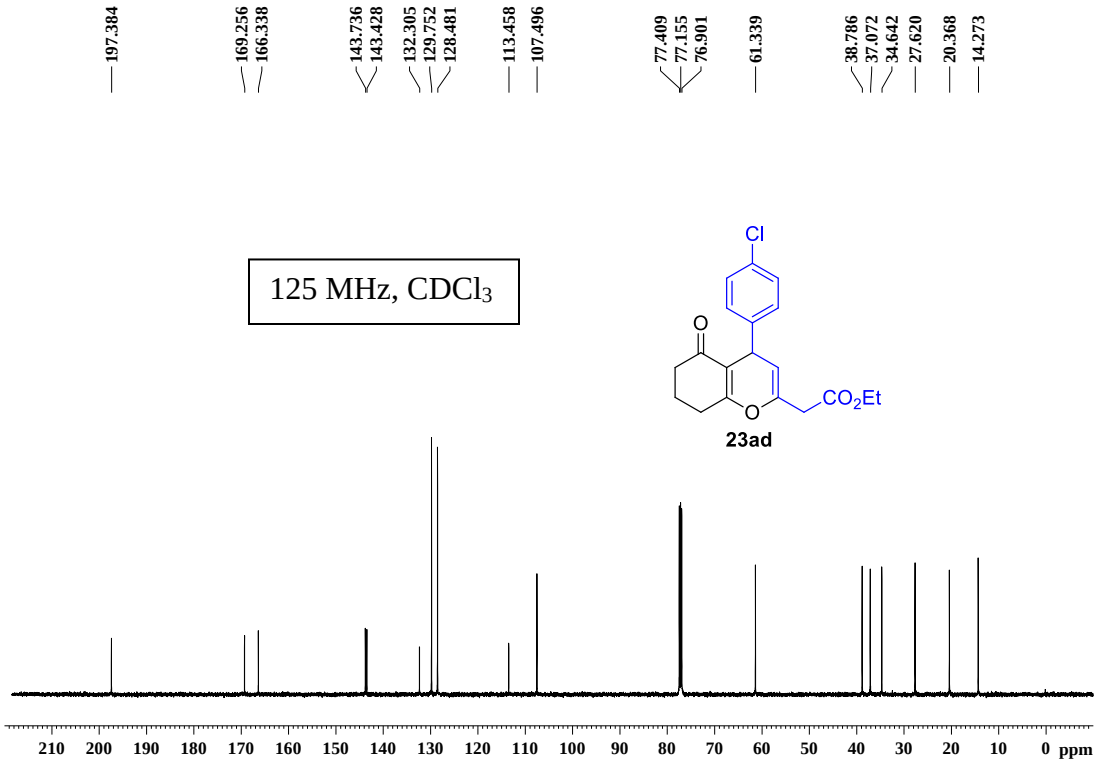

Figure A32: ^{13}C{^{1}H} NMR spectrum of compound **23ad**

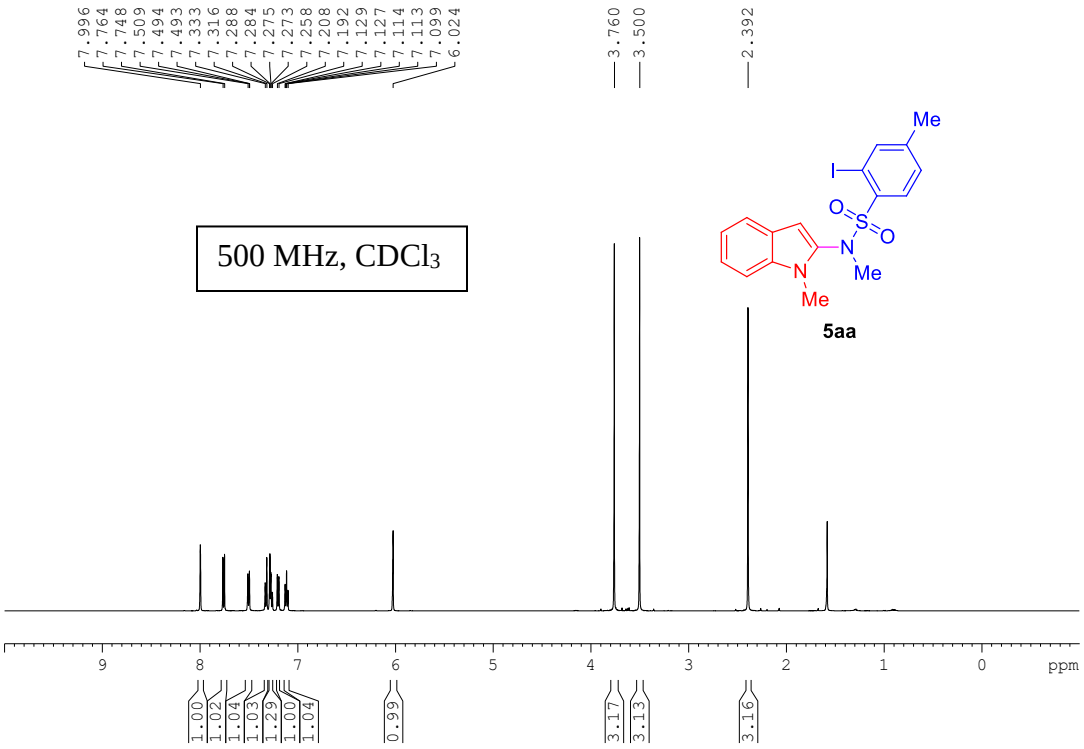

Figure A33: ^{1}H NMR spectrum of compound **5aa**

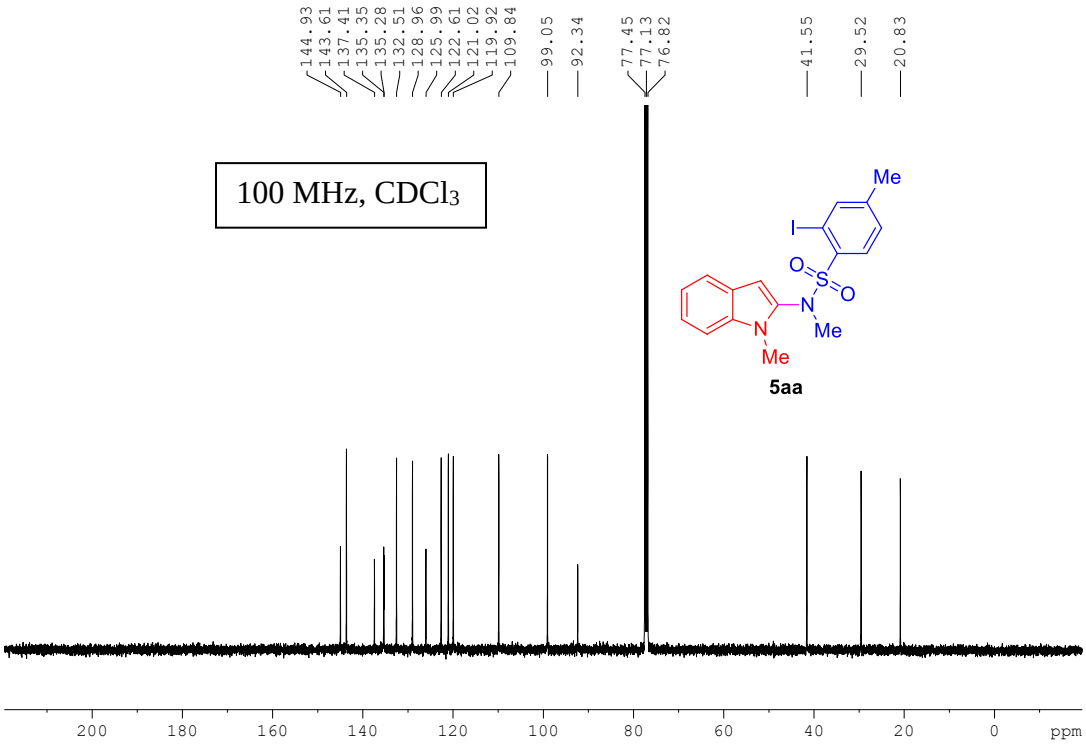

Figure A34: ^{13}C{^{1}H} NMR spectrum of compound **5aa**

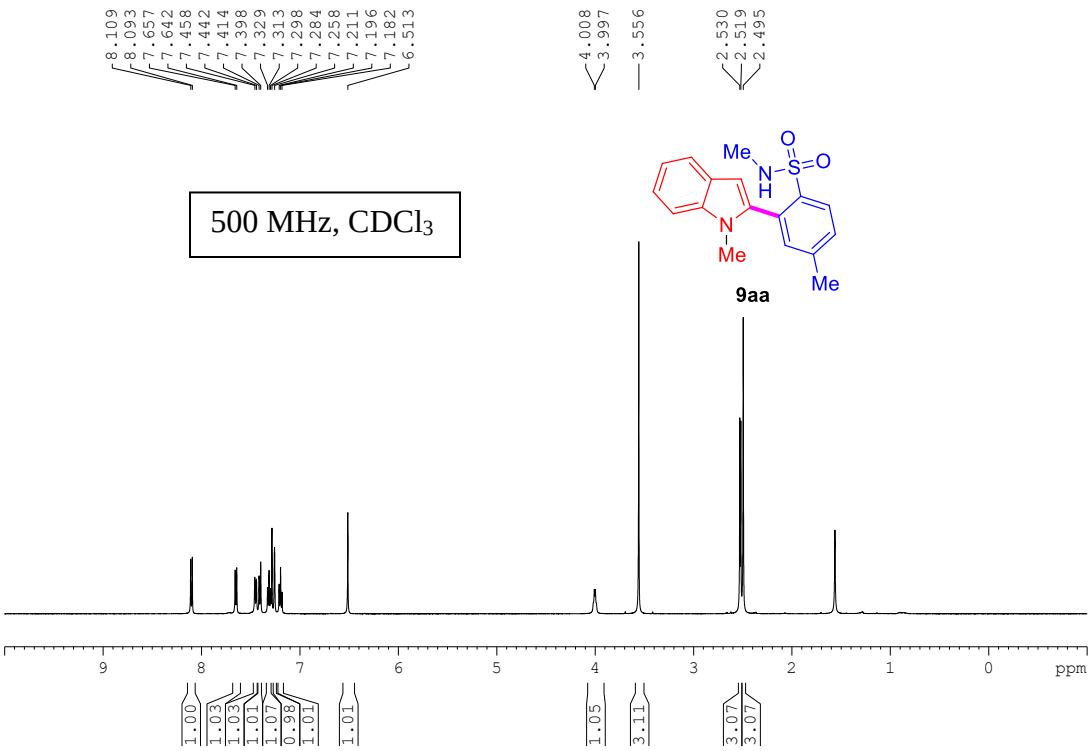

Figure A35: ^{1}H NMR spectrum of compound **9aa**

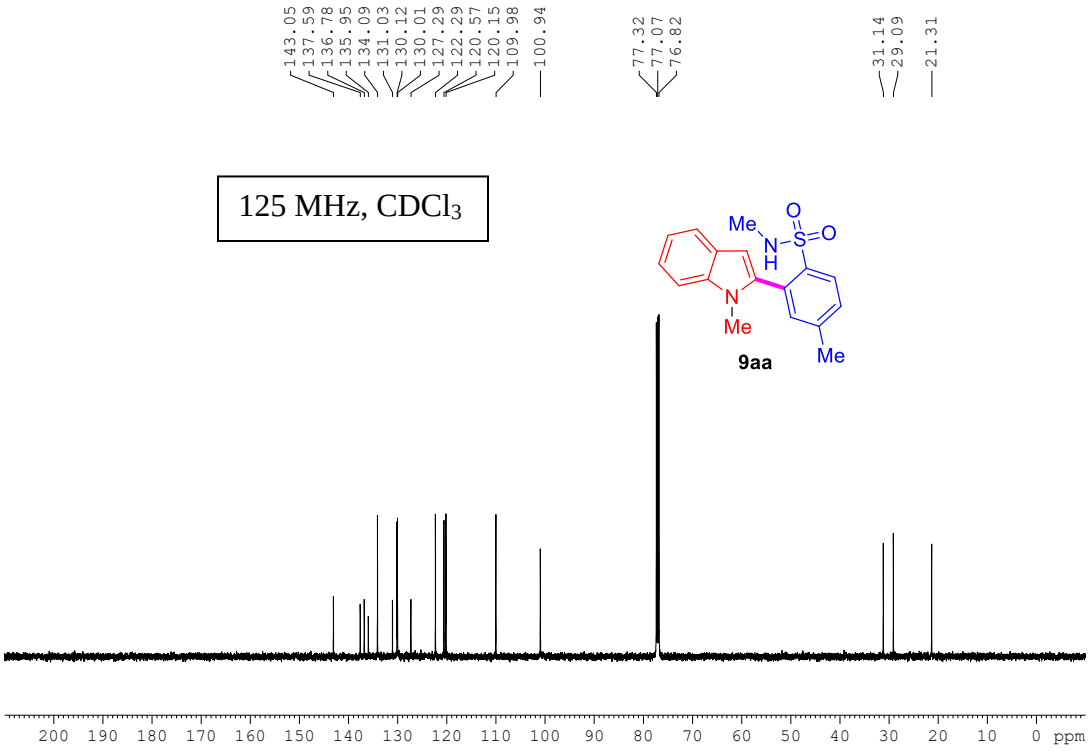

Figure A36: ^{13}C{^{1}H} NMR spectrum of compound **9aa**

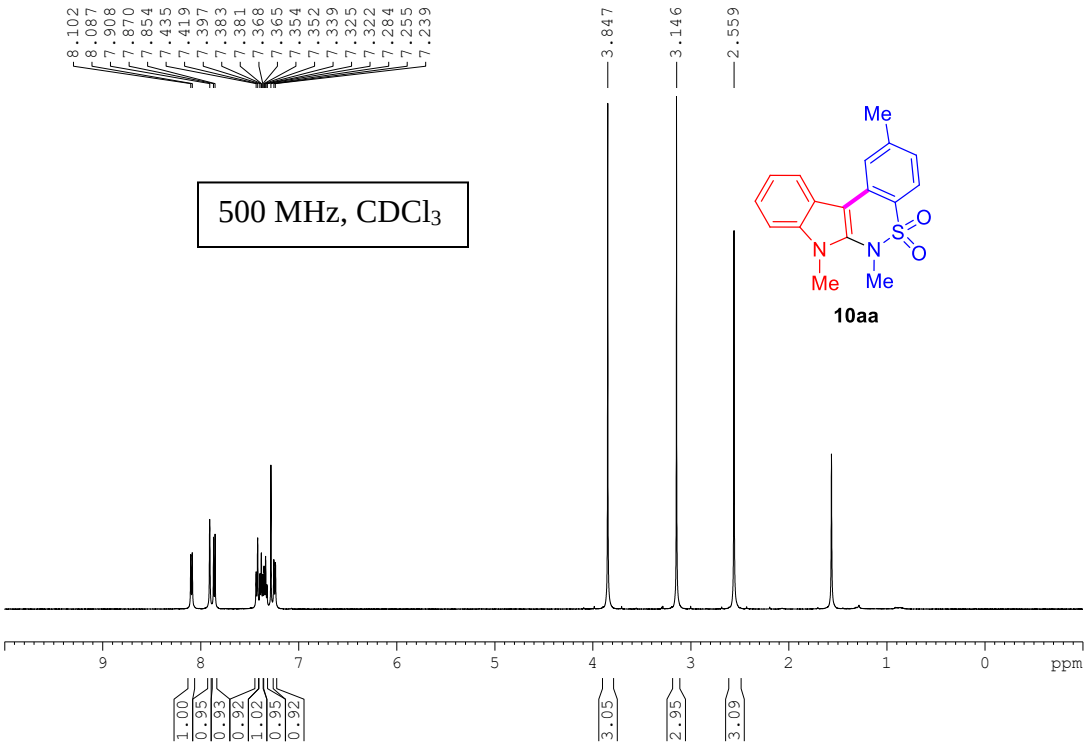

Figure A37: ^{1}H NMR spectrum of compound **10aa**

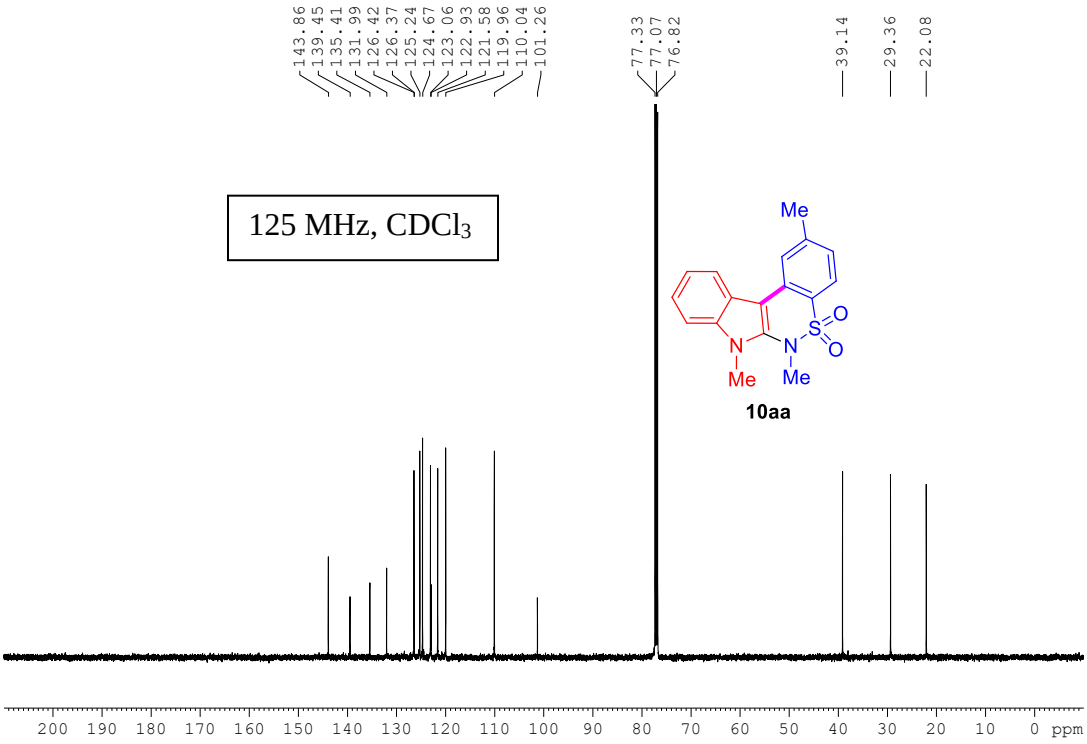

Figure A38: ^{13}C{^{1}H} NMR spectrum of compound **10aa**

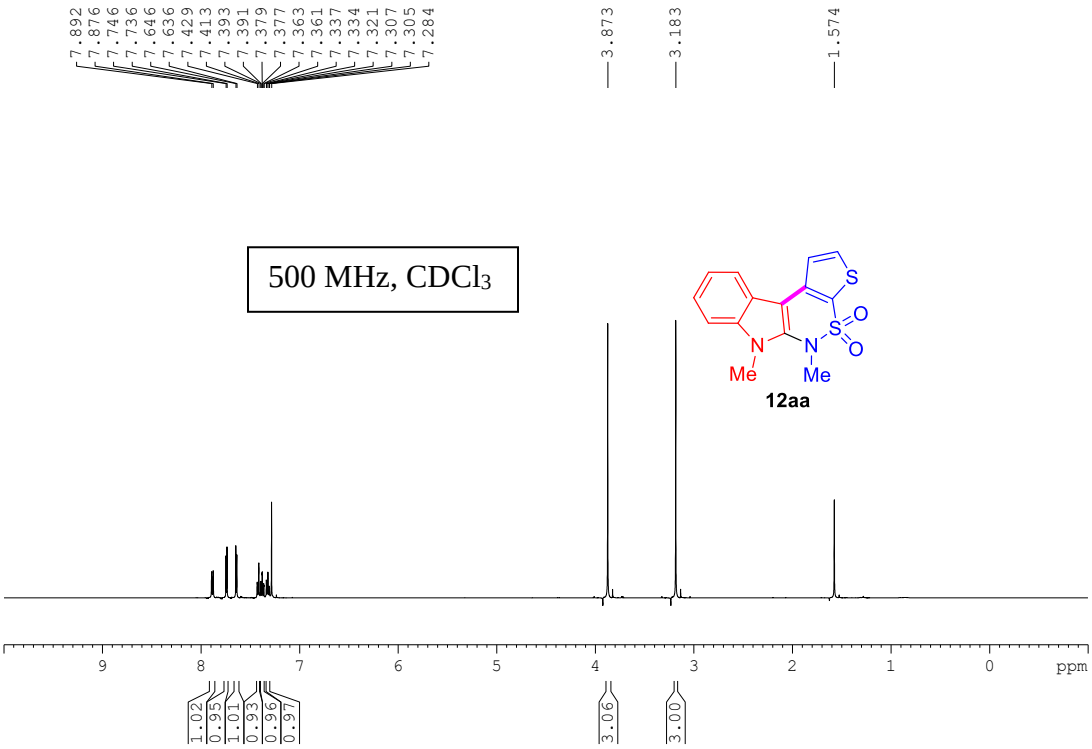

Figure A39: ^{1}H NMR spectrum of compound **12aa**

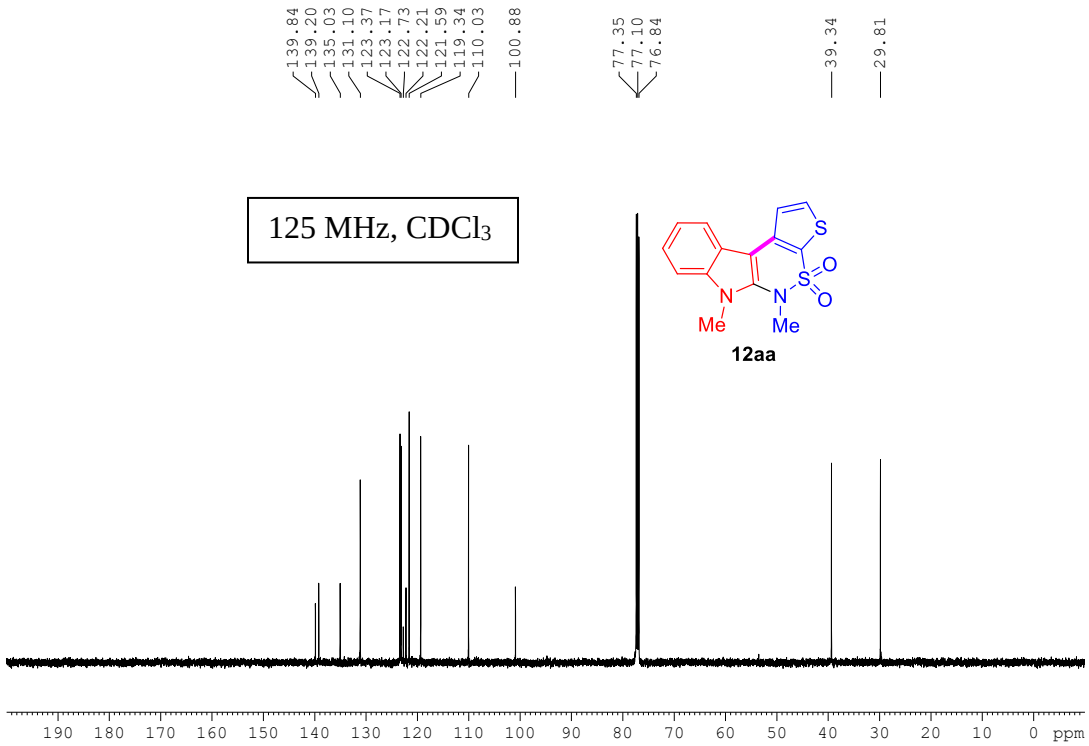

Figure A40: ^{13}C{^{1}H} NMR spectrum of compound **12aa**

(B) CCDC numbers and atomic coordinates for X-ray structures reported in this thesis

CCDC numbers for the published compounds: 11da, **11ea**, **12an**, **12db**, **13ae**, **13de**, **15aa**, **15ad**, **15db**, **15ea**, **15fn**, **15hb**, **16aa**, **17db**, **18ib**, **18ie**, **5aa**, **9ba**, **9bh**, **10al**, **10bk** and **12ag** are **2110597**, **2110598**, **2110599**, **2110600**, **2110601**, **2110602**, **2236876**, **2236877**, **2236878**, **2236879**, **2236880**, **2236881**, **2236882**, **2236883**, **2236884**, **2236885**, **2236886**, **2202000**, **2202001, 2202002, 2202003, 2202004** and **2202005**, respectively.

Unpublished compounds: 20ah, **21ad**, **and 23ad (part A)**

<u>Compound 20ah</u>

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) kck220

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: kck220

Bond precision: C-C = 0.0043 A Wavelength=0.71073

Cell: a=8.4988(2) b=12.3560(4) c=12.5322(4)
alpha=63.027(3) beta=80.888(2) gamma=89.088(2)
Temperature: 298 K

	Calculated	Reported
Volume	1155.72(7)	1155.72(7)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C24 H23 N O7	C24 H23 N O7
Sum formula	C24 H23 N O7	C24 H23 N O7
Mr	437.43	437.43
Dx,g cm-3	1.257	1.257
Z	2	2
Mu (mm-1)	0.093	0.093
F000	460.0	460.0
F000'	460.26	
h,k,lmax	10,15,16	10,15,15

Nref	5127	4960
Tmin,Tmax	0.982,0.988	0.296,1.000
Tmin'	0.982	

Correction method= # Reported T Limits: Tmin=0.296 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.967 Theta(max)= 27.179

R(reflections)= 0.0617(2325) wR2(reflections)= 0.1999(4960)

S = 1.017 Npar= 291

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

PLAT026_ALERT_3_C Ratio Observed / Unique Reflections (too) Low ..	47%	Check
PLAT340_ALERT_3_C Low Bond Precision on C-C Bonds	0.0043	Ang.
PLAT905_ALERT_3_C Negative K value in the Analysis of Variance ...	-10.336	Report
PLAT905_ALERT_3_C Negative K value in the Analysis of Variance ...	-0.016	Report

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Alert level G

PLAT793_ALERT_4_G Model has Chirality at C3 (Centro SPGR)	R	Verify
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min).	2	Note
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L= 0.600	160	Note
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.	0	Info

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0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
4 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
4 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
1 ALERT type 2 Indicator that the structure model may be wrong or deficient
5 ALERT type 3 Indicator that the structure quality may be low
2 ALERT type 4 Improvement, methodology, query or suggestion
0 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

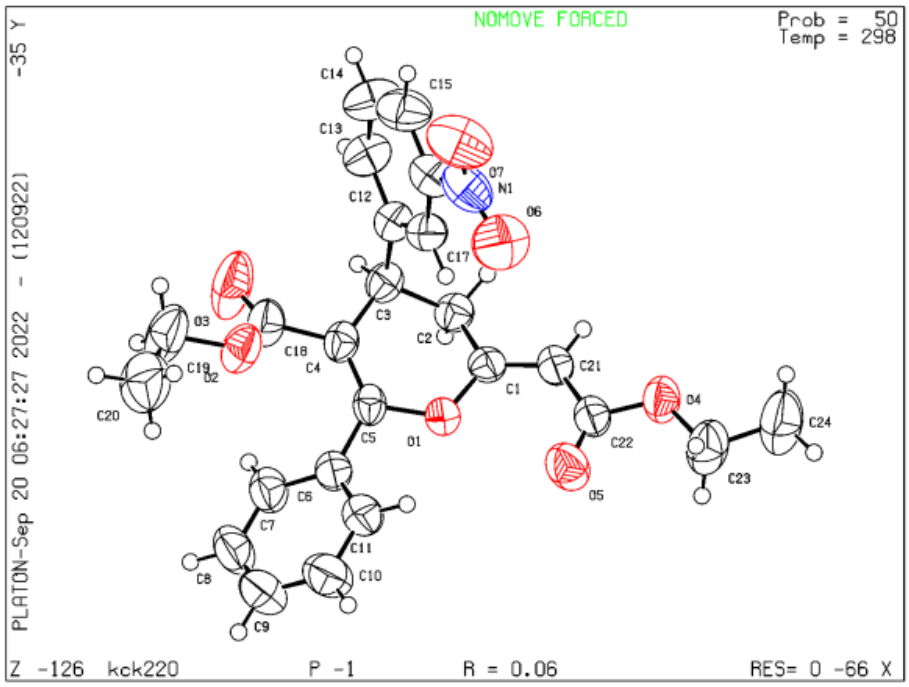
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 12/09/2022; check.def file version of 09/08/2022

Datablock kck220 - ellipsoid plot



Compound 21ad

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) kck227

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No syntax errors found. CIF dictionary Interpreting this report

Datablock: kck227

```
Bond precision:   C-C = 0.0067 A          Wavelength=0.71073

Cell:           a=12.7297(3)      b=12.8261(4)      c=12.9349(3)
                alpha=79.005(2)   beta=68.430(2)    gamma=65.172(3)
Temperature:    298 K
```

	Calculated	Reported
Volume	1780.83(9)	1780.83(9)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C19 H19 Cl O4	C19 H19 Cl O4
Sum formula	C19 H19 Cl O4	C19 H19 Cl O4
Mr	346.79	346.79
Dx,g cm-3	1.293	1.293
Z	4	4
Mu (mm-1)	0.233	0.233
F000	728.0	728.0
F000'	728.94	
h,k,lmax	16,16,16	16,16,16
Nref	7777	7434
Tmin,Tmax	0.954,0.970	0.220,1.000

```
Tmin'           0.954

Correction method= # Reported T Limits: Tmin=0.220 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.956          Theta(max)= 26.998

R(reflections)= 0.0838( 3789)                    wR2(reflections)
                                                 0.2756( 7434)
S = 1.203                 Npar= 429
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

PLAT084_ALERT_3_C	High wR2 Value (i.e. > 0.25)	0.28 Report
PLAT220_ALERT_2_C	NonSolvent Resd 1 C Ueq(max)/Ueq(min) Range	3.2 Ratio
PLAT230_ALERT_2_C	Hirshfeld Test Diff for C18 --C19 .	5.1 s.u.
PLAT241_ALERT_2_C	High 'MainMol' Ueq as Compared to Neighbors of	C7 Check
PLAT241_ALERT_2_C	High 'MainMol' Ueq as Compared to Neighbors of	C18 Check
PLAT241_ALERT_2_C	High 'MainMol' Ueq as Compared to Neighbors of	C27 Check
PLAT242_ALERT_2_C	Low 'MainMol' Ueq as Compared to Neighbors of	C13 Check
PLAT242_ALERT_2_C	Low 'MainMol' Ueq as Compared to Neighbors of	C17 Check
PLAT242_ALERT_2_C	Low 'MainMol' Ueq as Compared to Neighbors of	C32 Check
PLAT334_ALERT_2_C	Small <C-C> Benzene Dist. C10 -C15 .	1.37 Ang.
PLAT340_ALERT_3_C	Low Bond Precision on C-C Bonds	0.00666 Ang.
PLAT360_ALERT_2_C	Short C(sp3)-C(sp3) Bond C18 - C19 .	1.36 Ang.
PLAT360_ALERT_2_C	Short C(sp3)-C(sp3) Bond C25 - C26 .	1.41 Ang.
PLAT905_ALERT_3_C	Negative K value in the Analysis of Variance ...	-10.638 Report
PLAT905_ALERT_3_C	Negative K value in the Analysis of Variance ...	-0.143 Report
PLAT911_ALERT_3_C	Missing FCF Refl Between Thmin & STh/L= 0.600	7 Report

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Alert level G

PLAT072_ALERT_2_G	SHELXL First Parameter in WGHT Unusually Large	0.11 Report
PLAT171_ALERT_4_G	The CIF-Embedded .res File Contains EADP Records	1 Report
PLAT793_ALERT_4_G	Model has Chirality at C3 (Centro SPGR)	S Verify
PLAT793_ALERT_4_G	Model has Chirality at C22 (Centro SPGR)	S Verify
PLAT910_ALERT_3_G	Missing # of FCF Reflection(s) Below Theta(Min).	2 Note
PLAT912_ALERT_4_G	Missing # of FCF Reflections Above STh/L= 0.600	334 Note
PLAT978_ALERT_2_G	Number C-C Bonds with Positive Residual Density.	0 Info

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0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
16 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
7 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
13 ALERT type 2 Indicator that the structure model may be wrong or deficient
6 ALERT type 3 Indicator that the structure quality may be low

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

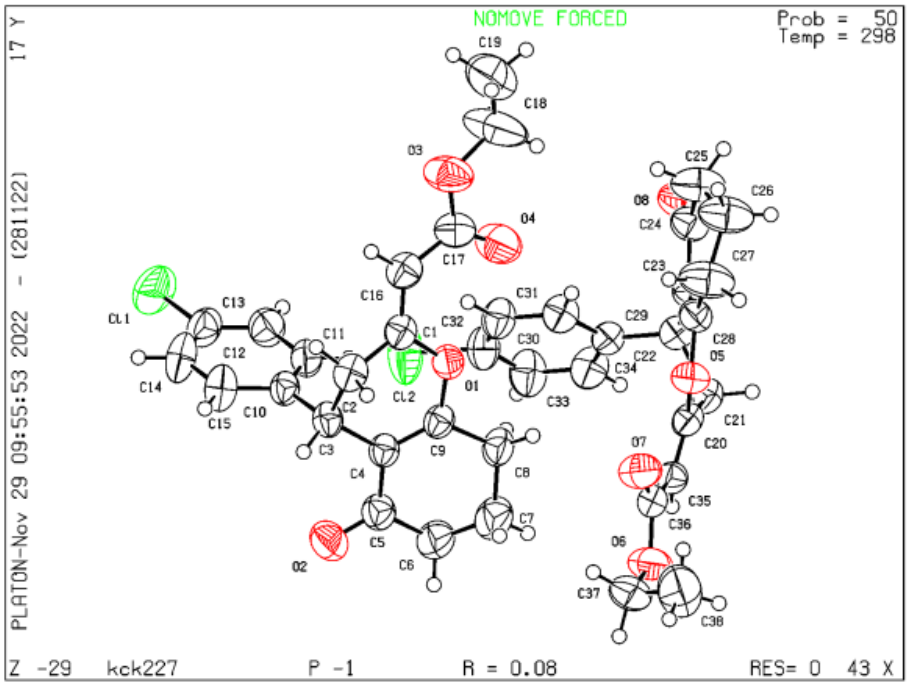
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 28/11/2022; check.def file version of 28/11/2022

Datablock kck227 - ellipsoid plot



Compound 23ad

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) kck241

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No syntax errors found. CIF dictionary Interpreting this report

Datablock: kck241

```
Bond precision:   C-C = 0.0117 A          Wavelength=0.71073

Cell:             a=8.3051(6)     b=23.4826(16)        c=9.4132(9)
                  alpha=90        beta=109.650(9)      gamma=90
Temperature:      294 K

                 Calculated                Reported
Volume           1728.9(3)                 1728.9(3)
Space group      C c                       C 1 c 1
Hall group       C -2yc                    C -2yc
Moiety formula   C19 H19 Cl O4             C19 H19 Cl O4
Sum formula      C19 H19 Cl O4             C19 H19 Cl O4
Mr               346.79                    346.79
Dx,g cm-3        1.332                     1.332
Z                4                         4
Mu (mm-1)        0.240                     0.240
F000             728.0                     728.0
F000'            728.94
h,k,lmax         10,29,11                  10,29,11
Nref             3730[ 1872]               2967
Tmin,Tmax        0.942,0.972               0.271,1.000

 Tmin'            0.942

 Correction method= # Reported T Limits: Tmin=0.271 Tmax=1.000
 AbsCorr = MULTI-SCAN

 Data completeness= 1.58/0.80        Theta(max)= 26.927

 R(reflections)= 0.0612( 1417)                wR2(reflections)=
                                              0.1667( 2967)
 S = 0.918                  Npar= 218
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

PLAT340_ALERT_3_B Low Bond Precision on C-C Bonds ..... 0.01168 Ang.
PLAT360_ALERT_2_B Short C(sp3)-C(sp3) Bond C18 - C19 . 1.33 Ang.

Alert level C

PLAT026_ALERT_3_C Ratio Observed / Unique Reflections (too) Low .. 48% Check
PLAT220_ALERT_2_C NonSolvent Resd 1 C Ueq(max)/Ueq(min) Range 3.1 Ratio
PLAT241_ALERT_2_C High 'MainMol' Ueq as Compared to Neighbors of C13 Check
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C3 Check
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C12 Check
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C17 Check
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C18 Check
PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ..... 2.025 Check

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Alert level G

PLAT792_ALERT_1_G Model has Chirality at C7 (Polar SPGR) R Verify
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min). 1 Note
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L= 0.600 46 Note
PLAT915_ALERT_3_G No Flack x Check Done: Low Friedel Pair Coverage 61 %
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density. 0 Info

---

0 **ALERT level A** = Most likely a serious problem - resolve or explain
2 **ALERT level B** = A potentially serious problem, consider carefully
8 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
5 **ALERT level G** = General information/check it is not something unexpected

1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
8 ALERT type 2 Indicator that the structure model may be wrong or deficient
5 ALERT type 3 Indicator that the structure quality may be low
1 ALERT type 4 Improvement, methodology, query or suggestion
0 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

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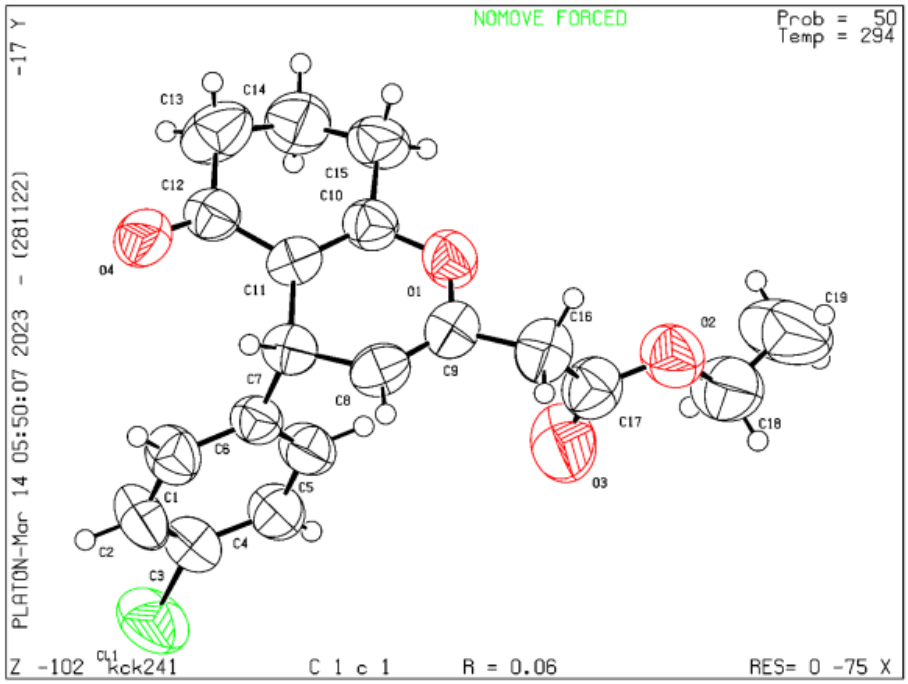
PLATON version of 28/11/2022; check.def file version of 28/11/2022

Datablock kck241 - ellipsoid plot



Investigations on the Reactions of Acetoxy Allenoates and Indolyl-iodoarylsulfonamides in Cyclization or C-C Bond Formation

by Shabbir Ahmed Khan

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2	Rajnikanth Sunke, Shabbir Ahmed Khan, K. C. Kumara Swamy. " Pd-catalysed intramolecular transformations of indolylbenzenesulfonamides: -sulfonamido-bi(hetero)aryls C2-arylation and polycyclic sultams C3 arylation ", Organic & Biomolecular Chemistry, 2022 Publication	13%
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Hyderabad- 500 046, INDIA

δ-Acetoxy Allenoates and -Sulfonyl Hydrazides ", Organic Letters, 2023
Publication

4	Submitted to University of Hyderabad, Hyderabad Student Paper	1 %
5	Deevi Basavaiah, Bhavanam Sekhara Reddy, Satpal Singh Badsara. "Recent Contributions from the Baylis–Hillman Reaction to Organic Chemistry", Chemical Reviews, 2010 Publication	1 %
6	Joydev K. Laha, Neetu Dayal, Krupal P. Jethava, Dilip V. Prajapati. "Access to Biaryl Sulfonamides by Palladium-Catalyzed Intramolecular Oxidative Coupling and Subsequent Nucleophilic Ring Opening of Heterobiaryl Sultams with Amines", Organic Letters, 2015 Publication	<1 %
7	A. Sanjeeva Kumar, Sachin Chauhan, K. C. Kumara Swamy. " Contrasting Carboannulation Involving δ-Acetoxy Allenoate as a Four-Carbon Synthon Using DABCO and DMAP: Access to Spiro-carbocyclic and -Teraryl Scaffolds ", Organic Letters, 2021 Publication	<1 %

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10	Asif Ali Qureshi, Arpula Sanjeeva Kumar, Sachin Chauhan, K. C. Kumara Swamy. "Stereo- and Regioselective [3+2] Cycloaddition of Acetoxy Allenoates with Azides: Metal-Free Synthesis of Multisubstituted Triazoles", Synthesis, 2021 Publication	<1 %
11	"Organic Reaction Mechanisms · 2016", Wiley, 2020 Publication	<1 %
12	Shubham Debnath, A. Sanjeeva Kumar, Sachin Chauhan, K. C. Kumara Swamy. "Divergent Reactivity of δ- and β'-Acetoxy Allenoates with 2-Sulfonamidoindoles via Phosphine Catalysis: Entry to Dihydro-α-carboline, α-Carboline, and Spiro-cyclopentene Motifs", The Journal of Organic Chemistry, 2021	<1 %

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13	Min Shi, Yin Wei, Mei-Xin Zhao, Jun Zhang. "Organocatalytic Cycloadditions for Synthesis of Carbo - and Heterocycles", Wiley, 2018 Publication	<1 %
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16	Alberico, Dino, Mark E. Scott, and Mark Lautens. "Aryl–Aryl Bond Formation by Transition-Metal-Catalyzed Direct Arylation", Chemical Reviews, 2007. Publication	<1 %
17	Ana L. Cardoso, Maria I.L. Soares. "1,3-Dipolar Cycloadditions Involving Allenes: Synthesis of Five-Membered Rings", Current Organic Chemistry, 2020 Publication	<1 %

18	Li, Yin-Long, Jian Li, Ai-Lun Ma, Ya-Nan Huang, and JUN DENG. "Metal-Free Synthesis of Indole via NIS Mediated Cascade C-N Bond Formation/Aromatization", The Journal of Organic Chemistry Publication	<1 %
19	Sanjeeva K. Arupula, Asif Ali Qureshi, K. C. Kumara Swamy. " Lewis Base-Switched [3 + 3] and [4 + 2] Annulation Reactions of δ-Acetoxy Allenoates with Cyclic -Sulfonyl Imines: Divergent Synthesis of Functionalized α-Pyridyl Acetates and Teraryl Scaffolds ", The Journal of Organic Chemistry, 2020 Publication	<1 %
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Publication

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