TRANSITION METAL CATALYZED C-C BOND FORMATION VIA CHELATION ASSISTED C-H ACTIVATION
AND
SYNTHESIS AND STRUCTURAL ASPECTS OF NOVEL ACYCLIC NUCLEOSIDE PHOSPHONATES

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

By

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HYDERABAD - 500 046

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JULY 2015

Dedicated to

My Family

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PART A

TRANSITION METAL CATALYZED C-C BOND FORMATION VIA CHELATION ASSISTED C-H ACTIVATION

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations 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 findings of other investigators.

Hyderabad
July 2015

Srinivasa Rao Allu

DECLARATION

I, **SRINIVASA RAO ALLU** hereby declare that this thesis entitled "***Transition Metal Catalyzed C-C Bond Formation via Chelation Assisted C-H Activation and Synthesis and Structural Aspects of Novel Acyclic Nucleoside Phosphonates*"** 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.

A report on plagiarism statistics from the University Librarian is enclosed.

Date:

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Signature of the Student:

Regd. No.:

Signature of the Supervisor:

CERTIFICATE

This is to certify that the work described in this thesis entitled "***Transition Metal Catalyzed C-C Bond Formation via Chelation Assisted C-H Activation and Synthesis and Structural Aspects of Novel Acyclic Nucleoside Phosphonates***" has been carried out by Mr. Srinivasa Rao Allu, under my supervision and the same has not been submitted elsewhere for any degree.

Hyderabad

July 2015

Prof. K. C. Kumara Swamy

(Thesis supervisor)

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I am deeply indebted to all my teachers right from my school to University for the support and training I received throughout my academic career.

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Srinivasa Rao Allu

LIST OF PUBLICATIONS

1 Alkynyl and phosphonyl substituted nucleobases: A case of thermally induced conformational polymorphism.
K. C. Kumara Swamy,* **Srinivasarao Allu**, Venu Srinivas, E. Balaraman and K. V. P. Pavan Kumar
Cryst. Growth Des. **2011**, *11*, 2302.

2 Ruthenium-catalyzed synthesis of isoquinolones with 8-aminoquinoline as a bidentate directing group in C-H functionalization.
Srinivasarao Allu and K. C. Kumara Swamy*
J. Org. Chem. **2014**, *79*, 3963.

3 Ruthenium-catalyzed oxidative annulation of 6-anilinopurines with alkynes via C-H activation: Synthesis of indole substituted purines/ purine nucleosides.
Srinivasarao Allu and K. C. Kumara Swamy*
Adv. Synth. Catal. **2015** (DOI 10.1002/adsc.201500314).

4 Palladium-catalyzed C(sp^2)-H bond acylation of 6-anilinopurines via C-H activation
Srinivasarao Allu and K. C. Kumara Swamy* (*to be communicated*)

5 Rh(III)-catalyzed carbenoid functionalization of aniline derivatives by α-diazo esters
Srinivasarao Allu, Manjula Ravi and K. C. Kumara Swamy* (*to be communicated*)

6 Synthesis and structural aspects of novel acyclic nucleoside phosphonates
Srinivasarao Allu and K. C. Kumara Swamy* (*to be communicated*)

Posters presented in symposia

1. Synthesis of Novel Acyclic Purine and Pyrimidine Nucleoside Phosphonates and Phosphonic Acids
   Srinivasarao Allu and K. C. Kumara Swamy*
   Chemfest-2013 (Annual in-house symposium), School of Chemistry, University of Hyderabad, Feb-2013

2 Ruthenium-Catalyzed Synthesis of Isoquinolones Using 8-Aminoquinoline as an Auxiliary Bidentate Directing Group in C-H Functionalization
   Srinivasarao Allu and K. C. Kumara Swamy*
   16th National Symposium in Chemistry, IIT Bombay, INDIA, Feb-2014

3 Ruthenium-Catalyzed Synthesis of Isoquinolones with 8-Aminoquinoline as an Auxiliary Bidentate Directing Group in C-H Functionalization-What is the Catalytic Intermediate?
   Srinivasarao Allu and K. C. Kumara Swamy*
   Chemfest-2014 (Annual in-house symposium), School of Chemistry, University of Hyderabad, Feb-2014 (**Poster & Oral Presentation**)

4 Ruthenium-Catalyzed Synthesis of Isoquinolones and Indole Derivatives via Chelation Assisted C-H Functionalization
   Srinivasarao Allu and K. C. Kumara Swamy*
   RTCS-2014 (International symposium), School of Chemistry, University of Hyderabad, Nov-2014 (**Poster & Oral Presentation**)

5 Ruthenium-Catalyzed C-H Functionalization- Synthesis of Isoquinolones using 8-Aminoquinoline as a Directing Group
   Srinivasarao Allu and K. C. Kumara Swamy*
   CATALYST 2015, Dr. Reddy's Laboratories, INDIA, July 2015

Synopsis

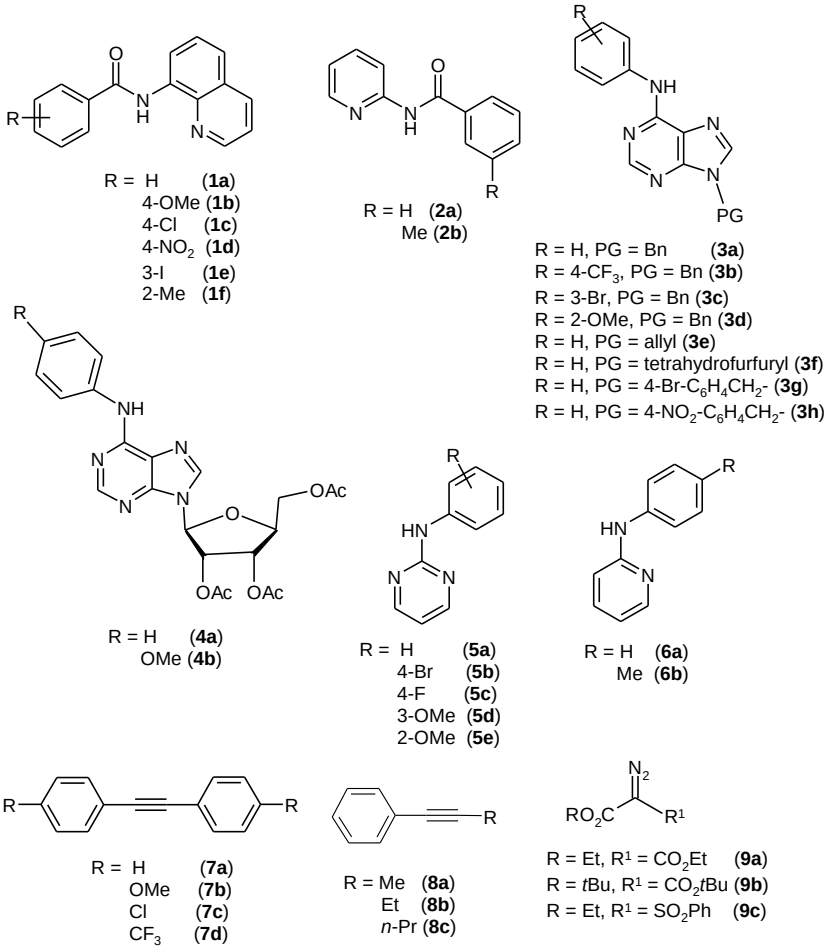
This thesis is divided into two parts: **Part-A** and **Part-B**. **Part-A** deals with (i) synthesis of isoquinolones via C-H activation by treating *N*-quinolin-8-yl-benzamides with alkynes using 8-aminoquinoline as a bidentate directing group in the presence of ruthenium-catalyst, (ii) synthesis of indole appended purine derivatives by [Ru]-catalyzed oxidative annulation of 6-anilinopurines with alkynes in open air, (iii) [Pd]-catalyzed C(sp^2)-H *ortho*-acylation of 6-anilinopurines with aldehydes/ α-oxocarboxylic acids as acylating sources and (iv) carbenoid functionalization of aromatic C-H bonds by α-diazo esters in the presence of Rh(III)-catalyst using anilinopyrimidinies/ pyridines/purines as substrates. **Part-B** delves on synthesis of alkynyl and phosphonyl substituted nucleobases with a discussion on nucleobase pairing in the presence of a strong hydrogen bond acceptor, the P=O bond.

Each part is subdivided into three chapters: (a) Introduction (literature survey), (b) Results and Discussion and (c) Experimental Section. The compounds synthesized in the present study are, in general, characterized by mp, IR and NMR (^{1}H, ^{13}C & ^{31}P as applicable) techniques followed by HRMS or elemental analyses in conjunction with LC-MS. X-ray structure determination is undertaken wherever required. Summary as well as references are given at the end of each part.

PART-A

Chapter 1 deals with a review of literature on aspects relevant to this part. In Chapter 2, the results obtained on these aspects are discussed; while in Chapter 3, the experimental details are presented. Prominent results of this part are outlined here. The precursors used in the present study are shown in Chart 1 [*Note*: The numbering of compounds given here is different from that in the main part of the thesis]. Many more precursors which are not listed here are discussed in the thesis in detail. They are prepared by methodologies available (with modifications where necessary) in the literature.

Chart 1

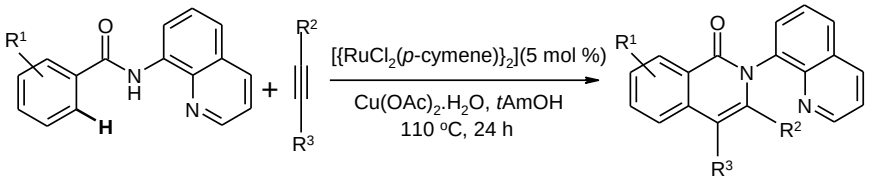


Representative precursors only are shown

(i) [Ru]-catalyzed synthesis of isoquinolones via C-H activation using 8-aminoquinoline as a bidentate directing group

8-Aminoquinoline moiety as the directing group has an advantage that after C-H functionalization, it can be removed by using ceric ammonium nitrate (CAN). Hence in the first type of reaction, we have utilized this group. Thus, the reaction of *N*-quinolin-8-yl-benzamides with alkynes in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) and $Cu(OAc)_2 \cdot H_2O$ as an oxidant afforded isoquinolone derivatives in excellent yields (Scheme 1). The reaction proceeded in open air also. High functional group tolerance was achieved with respect to both benzamides and alkynes. The annulation reaction with unsymmetrical alkynes proceeded in a highly regioselective manner and only one regioisomer was formed. The regioselectivity in the product was further confirmed by using X-ray crystallography. Reaction with heteroaryl amides was also successful in this catalytic process.

Scheme 1



R^1 = H, R^2 = R^3 = Ph	**10a** (74%, X-ray)
R^1 = H, R^2 = R^3 = 4-Cl-C_6H_4	**10b** (79%)
R^1 = H, R^2 = R^3 = 4-CF_3-C_6H_4	**10c** (66%)
R^1 = H, R^2 = R^3 = Et	**10d** (63%, X-ray)
R^1 = H, R^2 = Ph, R^3 = Me	**10e** (62%, X-ray)
R^1 = 4-Cl, R^2 = R^3 = Ph	**10f** (78%)
R^1 = 3-I, R^2 = R^3 = Ph	**10g** (61%)
R^1 = 2-Me, R^2 = R^3 = Ph	**10h** (73%)

(More examples)

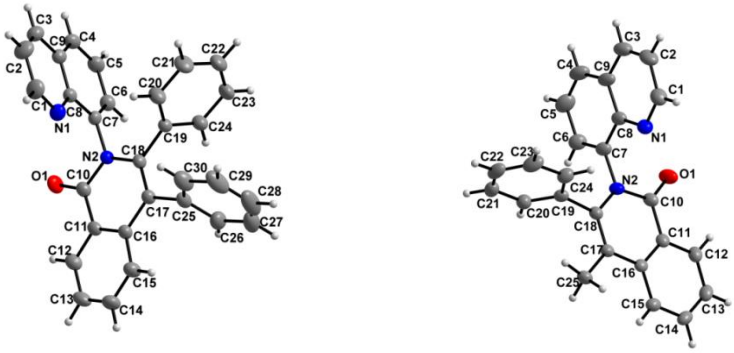
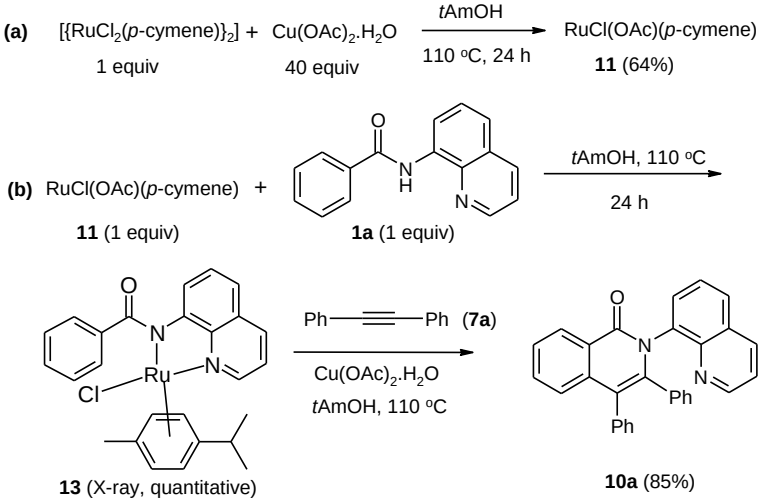
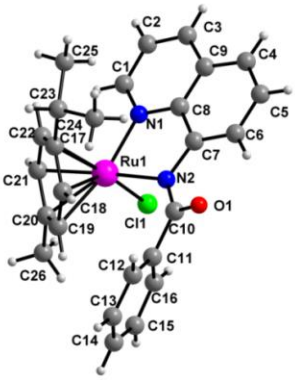


Figure 1. Molecular structures of compounds **10a** (left) and**10e** (right)

In order to gain information on the reaction pathway, we have conducted some step by step reactions (Scheme 2). Thus the reaction of [{$RuCl_2$(*p*-cymene)}$_2$] (1.0 equiv) with $Cu(OAc)_2{\cdot}H_2O$ (40.0 equiv) under reflux conditions in *t*AmOH afforded only the monoacetate complex [RuCl(OAc)(*p*-cymene)] (**11**) and not the bis(acetate) [$Ru(OAc)_2$(*p*-cymene)] (**12**) as being alluded to in some of the literature reports. In a further step, the reaction between the monoacetate **11** with an equimolar quantity of amide **1a** in stoichiometric amounts in *t*AmOH under reflux conditions afforded the ruthenium complex **13** in quantitative yield. In this complex **13**, ruthenium is coordinated to the *N*-quinolin-8-yl-benzamidyl moiety in an *N*,*N*-fashion. Treatment of chloro-ruthenium complex **13** with $Cu(OAc)_2{\cdot}H_2O$ in *t*AmOH, resulted in some unidentified products, but in the presence of stoichiometric amount of alkyne **7a**, it directly afforded the isoquinolone derivative **10a** in 85% yield. These studies were useful in deciphering some key steps in the above reaction.

Scheme 2



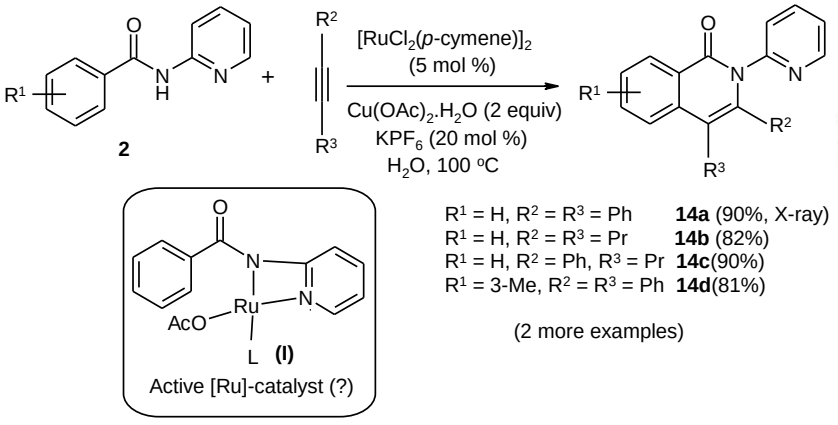


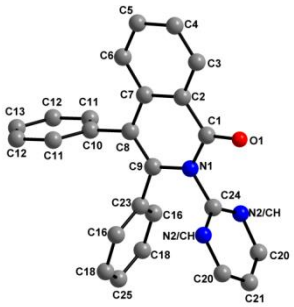
Compound **13**

Synthesis of *N*-(2-pyridinyl)isoquinolones on water via C-H activation

Similar to quinoline substituted isoquinolones, we have synthesized *N*-(2-pyridinyl)isoquinolones by treating *N*-(2-pyridinyl)benzamides with internal alkynes in the presence of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and $Cu(OAc)_2{\cdot}H_2O$ as the oxidant on water using KPF_6 as an additive (Scheme 3). The main difference between this system and the previous one is that instead of the 5-membered chelate ring, there may be a 4-membered chelate ring in the active form of the catalyst (**I**). The annulation reaction with unsymmetrical alkynes proceeded in a highly regioselective manner and gave the isoquinolone derivative **14c** as a single regioisomer.

Scheme 3





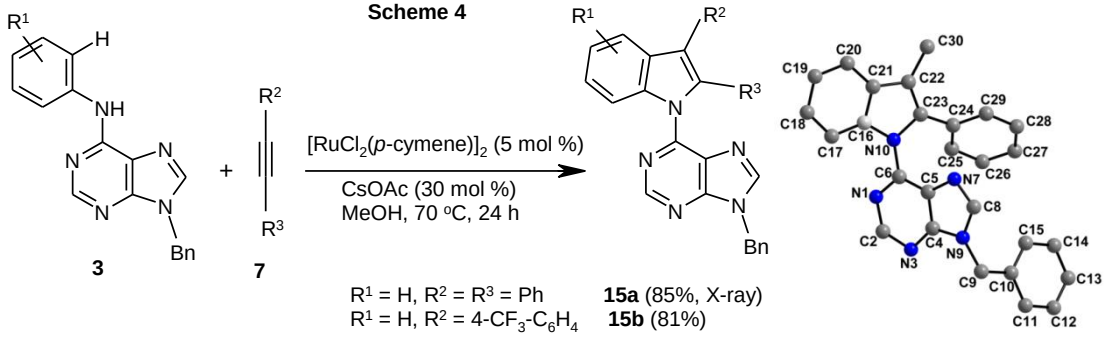
Compound **14a**

(ii) [Ru]-Catalyzed synthesis of indole substituted purines/purine nucleosides via C-H activation

Using the intrinsic directing group nature of the purine moiety, we have synthesized indole appended purine derivatives by treating 6-anilinopurines **3** with

alkynes in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) with CsOAc (30 mol %) as an additive in open air. This oxidative annulation reaction has broad substrate scope. The reaction proceeded in a highly regioselective manner when we employed unsymmetrical aryl(alkyl)alkynes as coupling partners. The regioselectivity was further confirmed by using X-ray crystallography.

Scheme 4



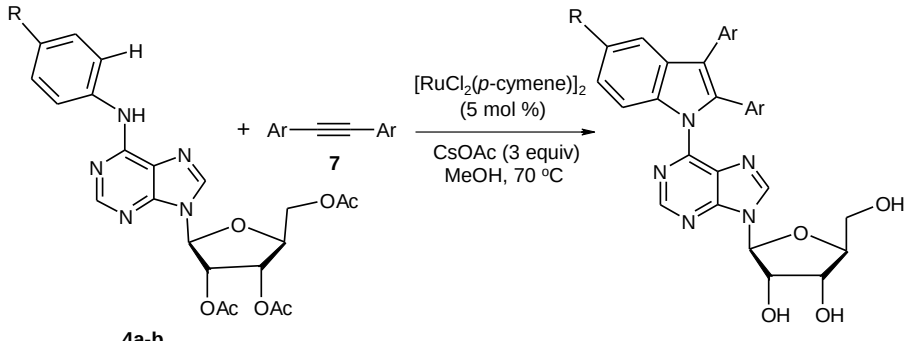
R^1 = H, R^2 = R^3 = Ph **15a** (85%, X-ray)
R^1 = H, R^2 = 4-CF_3-C_6H_4 **15b** (81%)
R^1 = H, R^2 = Me, R^3 = Ph **15c** (81%, X-Ray)
R^1 = 4-Br, R^2 = R^3 = Ph **15d** (92%)
R^1 = 3-OMe, R^2 = R^3 = Ph **15e** (89%)
R^1 = 2-OMe, R^2 = R^3 = Ph **15f** (92%)

(more examples)

Compound **15c**

In an effort to explore the utility of the above catalytic conditions, we examined the reaction of nucleosides **4a** and **4b** with alkynes (Scheme 5). We have isolated the indole appended nucleoside with the partial hydrolysis of the ester groups. With increase in the amount of CsOAc to 3 equiv, we observed the formation of indole nucleoside derivative with free hydroxyl groups, thus reducing the burden of further deprotection of the saccharide.

Scheme 5

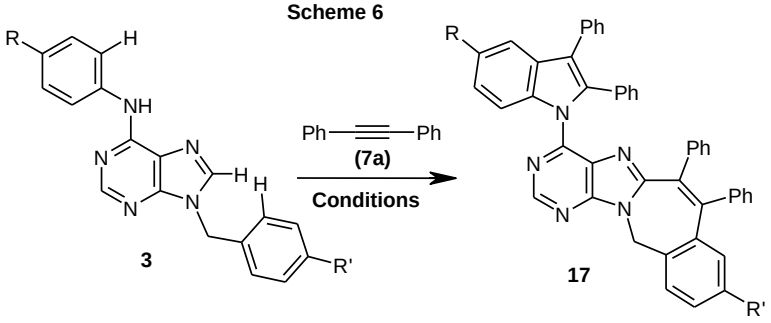


R = H, Ar = Ph **16a** (76%)
R = H, Ar = 3,5-Me-C_6H_3 **16b** (71%)
R = OMe, Ar = Ph **16c** (82%)

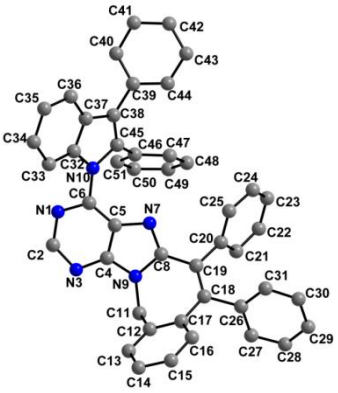
A serendipitous ***two-fold C-H activation*** product **17a** (X-ray) was observed along with indole derivative **15a**, when we treated 9-benzyl-6-anilinopurine **3a** with alkyne **7a** in the presence of $[RuCl_2(p\text{-cymene})]_2$/CsOAc and $Cu(OAc)_2.H_2O$.

Compounds **17b-17e** were prepared similarly. The corresponding mono-activated products were also present, but the double-annulated products **17a-17e** could be readily isolated. In the case of other substrates, the yield of the bis-product was low/ negligible.

Scheme 6



R = H, R' = H **17a** (44%, X-ray)
R = Me, R' = H **17b** (41%)
R = F, R' = H **17c** (34%)
R = H, R' = Br **17d** (45%)
R = H, R' = NO_2 **17e** (50%)

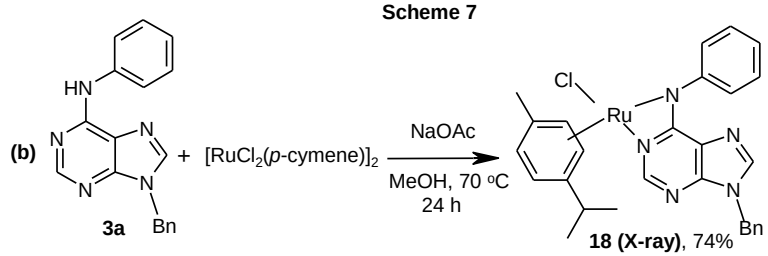


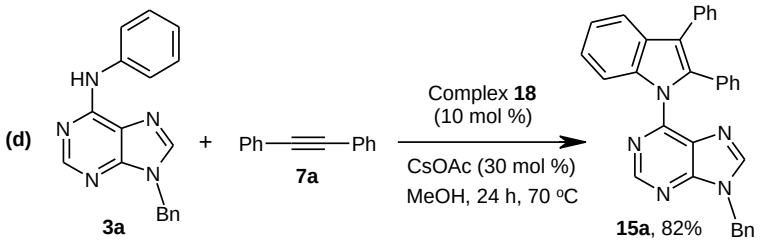
Compound **17a**

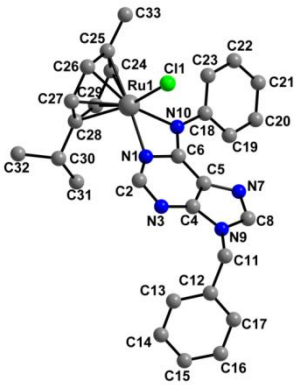
Conditions:**3** (0.5 mmol), **7a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), CsOAc (30 mol %), $Cu(OAc)_2.H_2O$ (2 equiv), MeOH (3 mL), 70 °C (oil bath), 36 h, air.

To investigate the mechanistic pathway, H/D exchange of 9-benzyl-*N*-phenyl-9-H-purin-6-amine (**3a**) was conducted in CD_3OD. Notably, 83% deuterium incorporation was observed at the *ortho*-positions of **3a**, indicating that *ortho* C-H bond activation took place. We have isolated the ruthenacycle intermediate **18** by treating **3a** with $[RuCl_2(p\text{-cymene})]_2$ in the presence of NaOAc in MeOH (Scheme 7). The N1 atom of purine is coordinated to ruthenium and forms a four membered ruthenacycle. The catalytic activity of the complex **18** suggests that this species is involved in the catalytic process.

Scheme 7





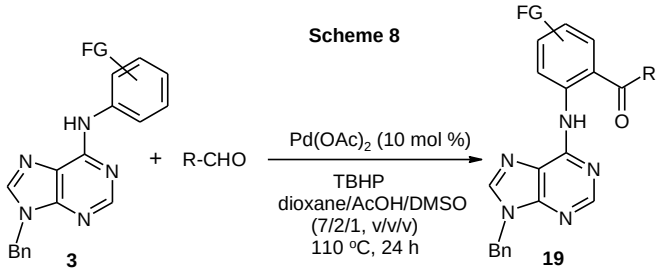


Compound **18**

(iii) [Pd]-Catalyzed *ortho*-acylation of 6-anilinopurine derivatives

After successful synthesis of indole derivatives using the purine directing group, we envisaged *ortho*-acylation of 6-anilinopurines with aldehydes/*α*-oxocarboxylic acids *via* palladium-catalyzed C-H activation. It should be noted that in cases such as these, Friedel-Crafts acylation is not feasible/desirable. Thus, the reaction of 6-anlinopurines (**3**) with aldehydes in the presence of $Pd(OAc)_2$ and TBHP as the oxidant afforded the *ortho*-acylated derivatives **19a-e** in good yields (Scheme 8). A large number of functional groups were tolerated under the catalytic conditions. The reaction was successfully applied to synthesize *ortho*-acyl nucleoside derivatives also.

Scheme 8

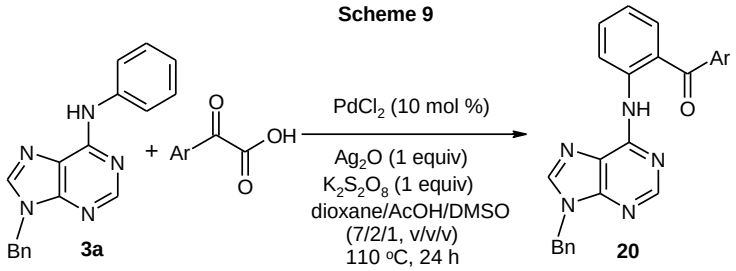


FG = 4-OMe, R = $-(CH_2)_5CH_3$ **19a** (72%)
FG = 4-Br, R = $-(CH_2)_5CH_3$ **19b** (66%)
FG = 3-Br, R = $-(CH_2)_5CH_3$ **19c** (63%)
FG = H, R = $-(CH_2)_4CH_3$ **19d** (71%, X-ray)
FG = H, R = -cyclohexyl **19e** (60%)

(more examples)

Under the above catalytic conditions, aryl aldehydes were oxidized to the corresponding carboxylic acids, and no coupled product was observed. This drawback was overcome by choosing aryl glyoxylic acid as the acylating source. Thus, the reaction of 6-anilinopurine with aryl glyoxylic acids in the presence of $PdCl_2$, with Ag_2O and $K_2S_2O_8$ as oxidant and co-oxidant respectively, afforded the *ortho*-acylated derivatives **20a-b** in good yields (Scheme 9). The Friedel-Crafts reaction is not selective in such cases.

Scheme 9

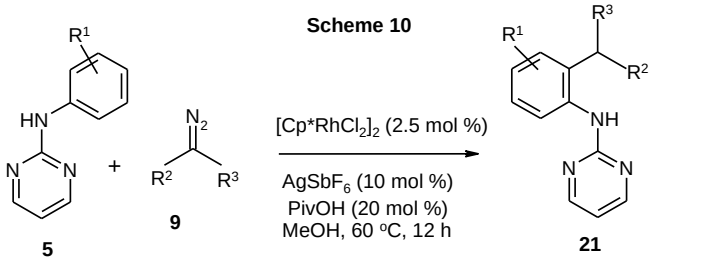


Ar = C_6H_5 **20a** (64%)
Ar = 2,4,6-Me-C_6H_2 **20b** (60%)

(iv) Rh(III)-Catalyzed carbenoid functionalization of aniline derivatives with *α*-diazo esters

Keeping abreast of the recent developments in the metal-carbene migratory insertion reactions in the presence of Rh(III)- catalyst, we have developed a protocol for the *ortho*-alkylation of aniline derivatives by using *α*-diazo esters. Thus, the reaction of 2-anilinopyrimidine **5a** with *α*-diazo malonate **9a** in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %), CsOAc (10 mol %) and PivOH (20 mol %) afforded the *ortho*-alkylated product **21a** in excellent yield. Precursors **9b-e** also led to the corresponding C(sp^2)-H functionalized products **21b-e** in good yields. This metal-carbene migratory insertion reaction was successfully extended to 6-anilinopurine (**3a** and **3d**) precursors also.

Scheme 10

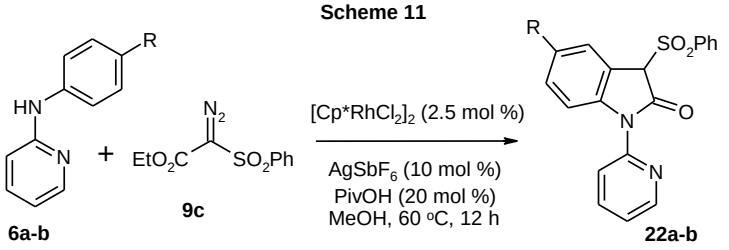


R^1 = H, R^2 = R^3 = CO_2Et **21a** (76%)
R^1 = 4-Br, R^2 = R^3 = CO_2Et **21b** (70%)
R^1 = 3-OMe, R^2 = R^3 = CO_2Et **21c** (64%)
R^1 = 2-OMe, R^2 = R^3 = CO_2Et **21d** (72%)
R^1 = H, R^2 = CO_2Et, R^3 = SO_2Ph **21e** (66%)

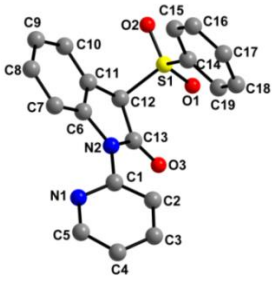
(More examples)

Under similar catalytic conditions, when the reaction was performed with 2-anilinopyridines **6a-b** with *α*-diazo esters **9c**, oxindole derivatives **22a-b** are formed in good yields (Scheme 11). Thus, we have observed the reactivity difference between the 2-anilinopyrimdines and 2-anilinopyridines in the reaction with *α*-diazo esters **9c**.

Scheme 11



R = H **22a** (68%, X-ray)
R = Me **22b** (62%)

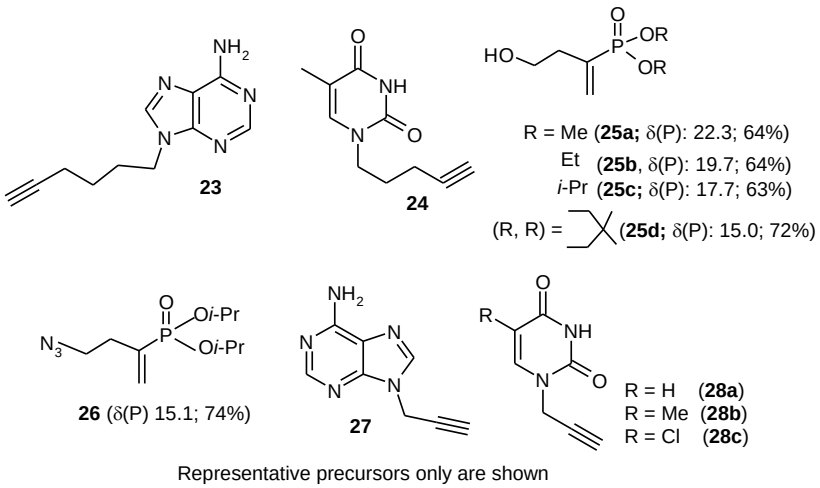


Compound **22a**

PART-B

Chapter 4 deals with a review of literature on various routes to synthesize acyclic nucleoside phosphonates. Chapter 5 describes the results obtained in the present study on these aspects. Chapter 6 is the experimental section for this part. The main precursors utilized in the present study are shown in Chart 2. Important results of this part are outlined below.

Chart 2



Representative precursors only are shown

(v)Alkynyl appended adenine 23: A case of thermally induced polymorphism

Alkynyl derivative of adenine **23** was synthesized using the Mitsunobu reaction. The objective was to utilize this as the precursor to phosphonate synthesis using the alkyne functionality. Crystals of moderate quality of this compound were obtained from methanol-toluene mixture. The space group for the structure that was solved initially showed that it belonged to $P2_1/c$. However, since there was disorder at one of the chain-carbon atoms, we decided to collect data at a low temperature (200 K) using another crystal from the same batch. Rather surprisingly, the suggested space group for this crystal (labeled as **23'**) was $P\bar{1}$ with two molecules in the asymmetric unit; the difference between the two molecules lies in the conformation of the alkyl chain as shown in Figure 2. Interestingly though, even this crystal (**23'**) at room temperature (298K) displayed $P2_1/c$ space group (of course with the same structure as the first crystal)! Since the temperature difference resulted in the same crystal to show two different forms, we believe that this is a case of ***thermally induced polymorphism***. To our knowledge such transformations in nucleobase chemistry are rather rare.

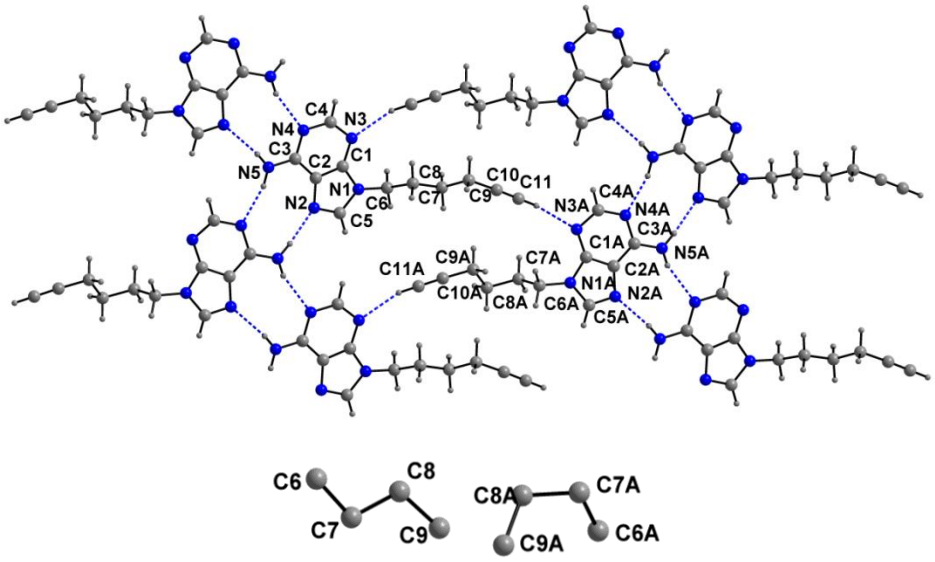
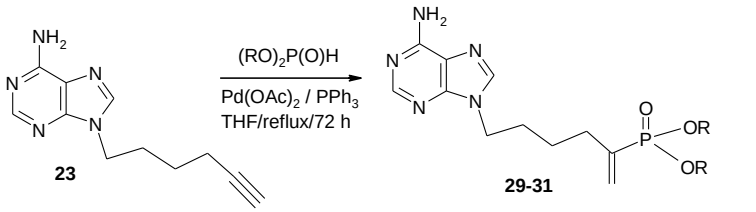


Figure 2. Molecular structure of compound **23'** (top; taken at 200 K). At the bottom is shown the conformations adapted by the two molecules in the asymmetric unit.

(vi) ***Phosphonyl substituted nucleobases 29-31: Any role for the strong hydrogen bond acceptor, the P=O bond?***

Phosphonylation of the adeninyl alkyne **23** in the presence of $Pd(OAc)_2$ afforded the phosphonyl substituted nucleobases **29-31** in good yields (Scheme 12).

Scheme 12



R = Et [**29**; δ(P): 19.2; 78%, X-ray]
= *i*-Pr [**30**; δ(P): 17.1; 74%]
= Ph [**31**; δ(P): 12.0; 41%, X-ray]

With regard to the nucleobase pairing, phosphoryl oxygen (P=O), which is a strong H-bond acceptor does not disturb the normal homo-base pairing present in the adeninyl compounds **29** and **31**. It had to be satisfied only with marginally weak C–H···O hydrogen bonds in the structure (Figure 3). Overall, the hydrogen bonding interactions appear to be extending in all the three dimensions without loss of the homo-base pairing.

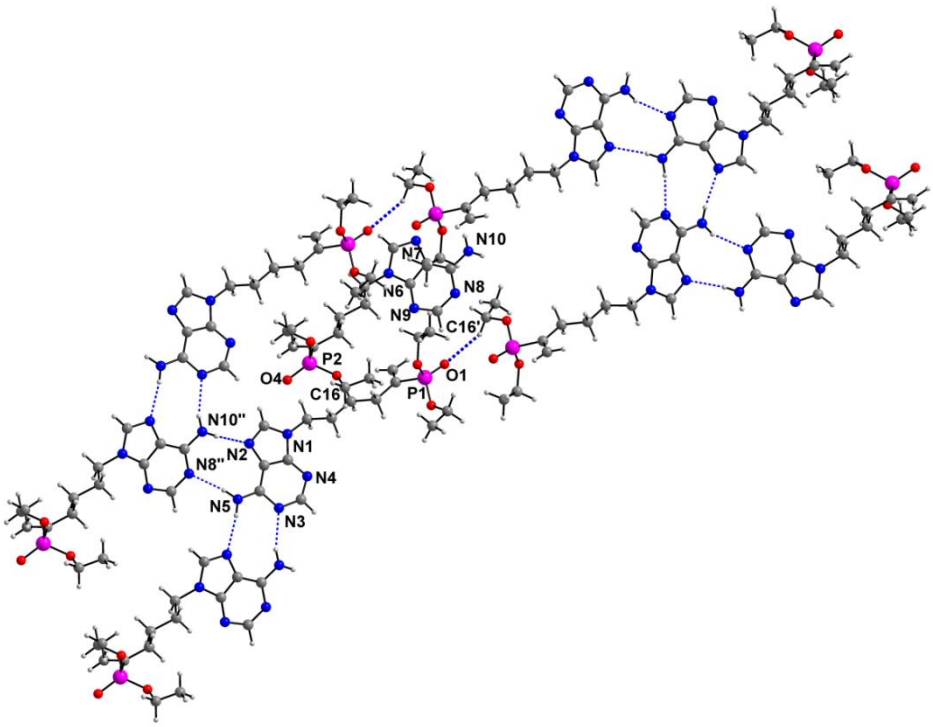
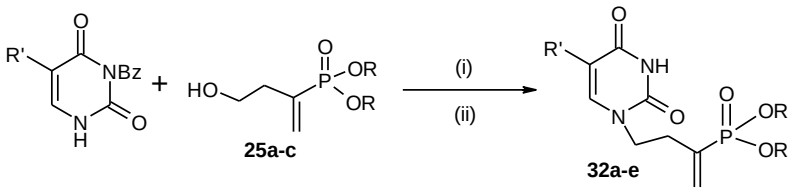


Figure 3: Diagrams showing supramolecular interactions in compound **29**.

(vii) Synthesis of alkenyl and triazole appended uracil phosphonates

In continuation of the above work on adeninyl phosphonates, we have also synthesized uracil phosphonates **32a-e** using the alcohols **25a-c** *via* the Mitsunobu reaction (Scheme 13). In contrast to adeninyl phosphonate **29**, in the thyminyl phosphonate **32d**, the phosphoryl oxygen (P=O) has disturbed the normal homo-base pairing present in the thymine residue. This phosphoryl oxygen (P=*O*) atom is involved in N-H···O bonding to the NH of the thymine moiety (Figure 4).

Scheme 13



R'= H, R = *i*Pr **32a** (δ(p):15.8; 75%)
R'= Me, R = Me **32b** (δ(p):20.6; 61%)
R'= Me, R = Et **32c** (δ(p):18.0; 56%)
R'= Me, R = *i*Pr **32d** (δ(p):15.9; 78%, X-ray)
R'= I, R = *i*Pr **32e** (δ(p):17.6; 55%)

conditions: (i) PPh_3+DEAD, toluene:DCM (10:1), rt, 1 h; (ii) NaOMe, MeOH, rt, 5h

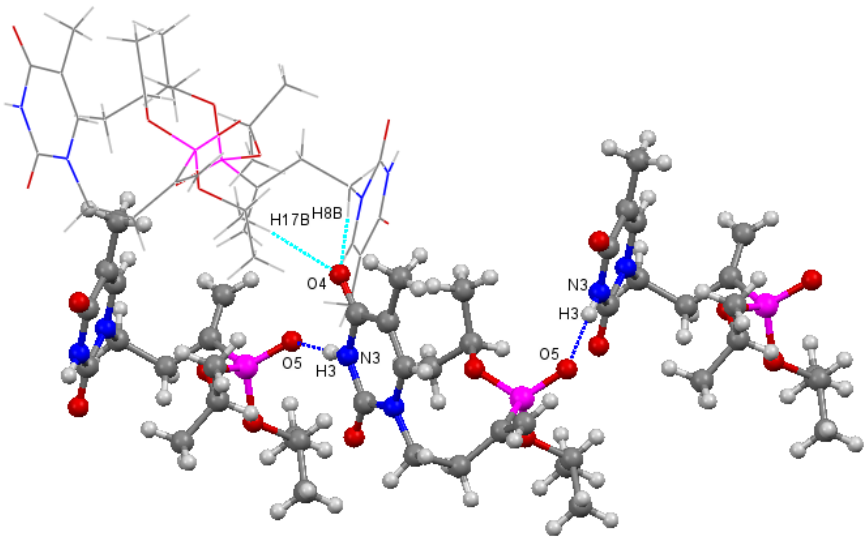
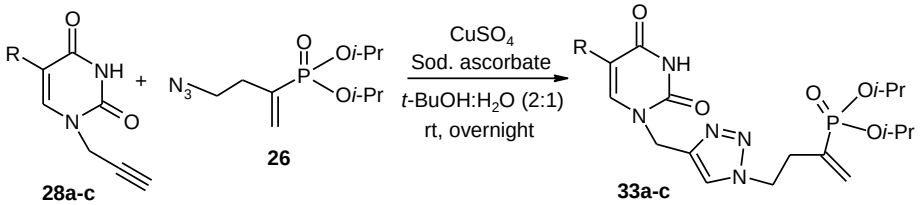


Figure 4: Diagram showing supramolecular interactions in compound **32d**.

We have also synthesized triazole appended uracil derivatives **33a-c** by treating *N*-propargyl uracil derivatives **28a-c** with the azide **26** via Cu-catalyzed azide-alkyne 1,3-dipolar cycloaddition (Scheme 14). The corresponding phosphonic acids could be obtained by de-esterification in the presence of TMSBr. Although many of these compounds could be interesting pharmaceutically, we are yet to investigate this part.

Scheme 14



R = H, **33a** (δ(P): 15.6; 86%)
R = CH_3, **33b** (δ(P): 15.6; 91%)
R = Cl, **33c** (δ(P): 15.4; 79%)

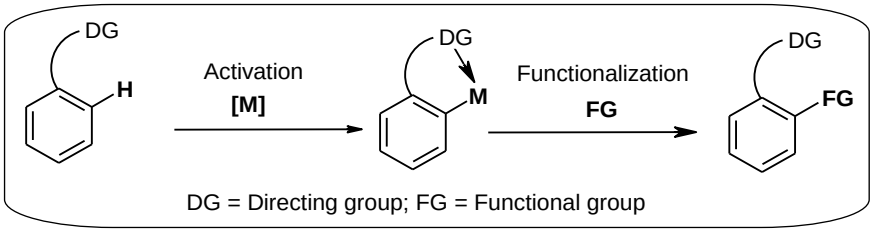
PART-A

TRANSITION METAL CATALYZED C-C BOND FORMATION VIA CHELATION ASSISTED C-H ACTIVATION

INTRODUCTION

1.1 General introduction: C-H activation/functionalization

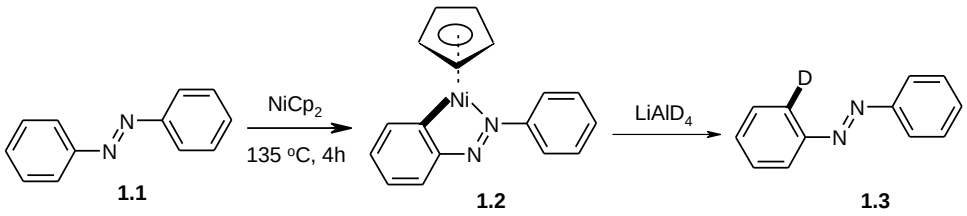
C-H bonds are ubiquitous in organic chemistry but the C-H bond dissociation energy is quite large (~440 $kJmol^{-1}$ for methane and ~460 $kJmol^{-1}$ for benzene) and hence replacing C-H bond with C-X bond (X= C or heteroatom) is a challenge. More importantly, activation of a C-H bond also requires considerable energy, since suitable pathway has to be accessible. Hence the direct activation/functionalization of C-H bonds to lead to useful products with a C-X bond (X is usually C, O or N) is a highly rewarding research topic.[1,2] Direct C-H functionalization is limited by two fundamental challenges: (i) inertness of C-H bonds in most cases, and (ii) the control of site selectivity in molecules that contain diverse C-H bonds. The first challenge is often addressed by transition metals that react with C-H bonds forming C-M bonds, which is known as "C-H activation".[3] Thus formed C-M species are far more reactive than the corresponding C-H counterparts and in many cases can be converted to new functional groups under very mild conditions. The second major challenge is to achieve good yields of a single product. For this, functionalization must occur in a highly site selective manner. This can be achieved by employing substrates that contain suitable coordinating ligands. These ligands bind to the metal center (cyclometalation) and direct the catalyst to a proximal C-H bond in a selective manner. These ligands are often called as directing groups (DGs).



1.2 Chelation assisted C-H bond functionalization

The first example of this type of ligand controlled selective C-H functionalization was reported by Kleiman and Dubeck in 1963 by treating azobenzene **1.1** with dicyclopentadienylnickel (Scheme 1.1), resulting in the azobenzene nickel complex **1.2**.[4] Here, the azo group chelates with the metal and brings the metal in close proximity to the *ortho* C-H bond that is activated in a highly selective manner. The metal ion in the complex **1.2** is replaced by deuterium when treated with lithium aluminium deuteride to give product **1.3**. This early report signifies the reactivity of transition metal complexes in activating C-H bonds with the aid of metal-coordinating directing groups and thus has opened the door for C(sp^2)-H functionalization. Subsequent developments as relevant to the present work are described in the following subsections.

Scheme 1.1



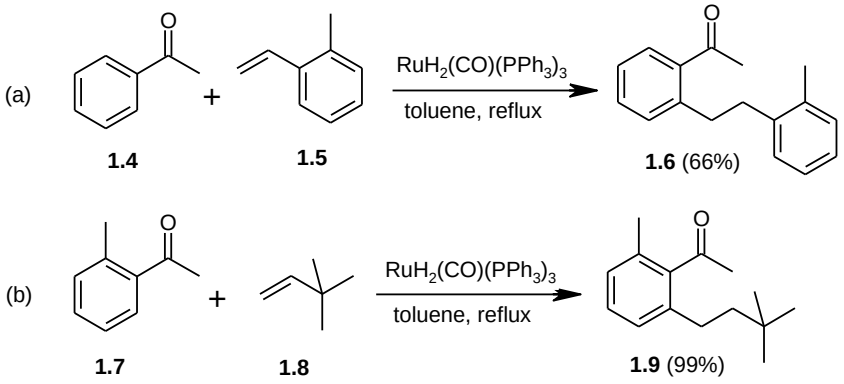
1.2.1 C-C Bond formation *via* C(sp^2)-H bond cleavage

C-C Bond formation is one of the most fundamental reactions in organic synthesis. If we use C-H bonds directly to construct C-C bonds, instead of using preactivated starting materials with a C-X bond, the methodology becomes more straightforward and atom economical. In subsequent paragraphs, we shall discuss the C-C bond formation using chelation assisted transition metal catalyzed C-H activation.

In the year 1993, in a pioneering work, Murai *et al* reported the catalytic *ortho*-C-H functionalization of aromatic ketones with olefins in the presence of a ruthenium-catalyst (Scheme 1.2). In this reaction, the carbonyl group acts as a directing group.[5a] Ever since this work, a large volume of directing group assisted catalytic C-H functionalizations have appeared. Later, this carbonyl group directed methodology was utilized by Woodgate *et al* in C(sp^2)-H functionalization of natural products like diterpenoids.[5b-d] Grigg *et al* also reported the alkylation of 3- or 4-acetyl pyridines and

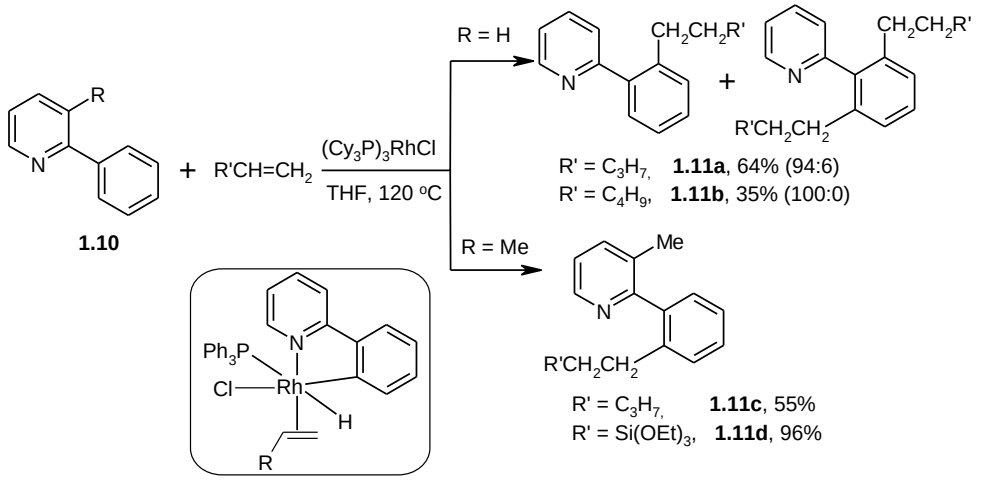
3-acetyl indoles when treated with alkenes in the presence of ruthenium complex $RuH_2(CO)(PPh_3)_3$.[5e]

Scheme 1.2



Kim *et al* discovered the rhodium-catalyzed regioselective alkylation of phenyl ring of 2-phenylpyridines **1.10** with olefins (Scheme 1.3).[6] The reaction proceeds *via* the chelation of nitrogen atom in the pyridine moiety with the rhodium complex and facilitates the *ortho*-C-H activation.

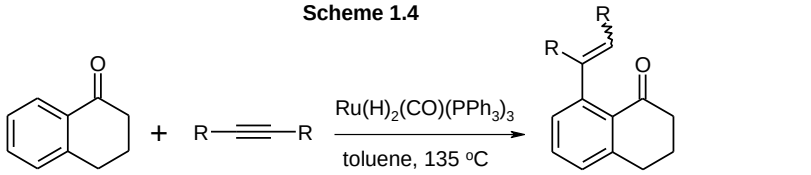
Scheme 1.3



In a subsequent report, Murai's group found that internal alkynes can couple with aromatic C-H bonds in the presence of ruthenium catalyst (Scheme 1.4).[7] For this purpose, they treated the reactive α-tetralone (**1.12**) with various internal alkynes in the presence of $RuH_2(CO)(PPh_3)_3$. Symmetrically substituted alkynes gave 1:1 coupled products as a mixture of *E*/*Z* isomers and the addition was highly *cis* selective (Scheme

1.4, cf. disposition of two R groups). The reaction was highly regio- and stereo-specific in the case of MeC≡C($SiMe_3$) with only *E*-isomer as the product.

Scheme 1.4

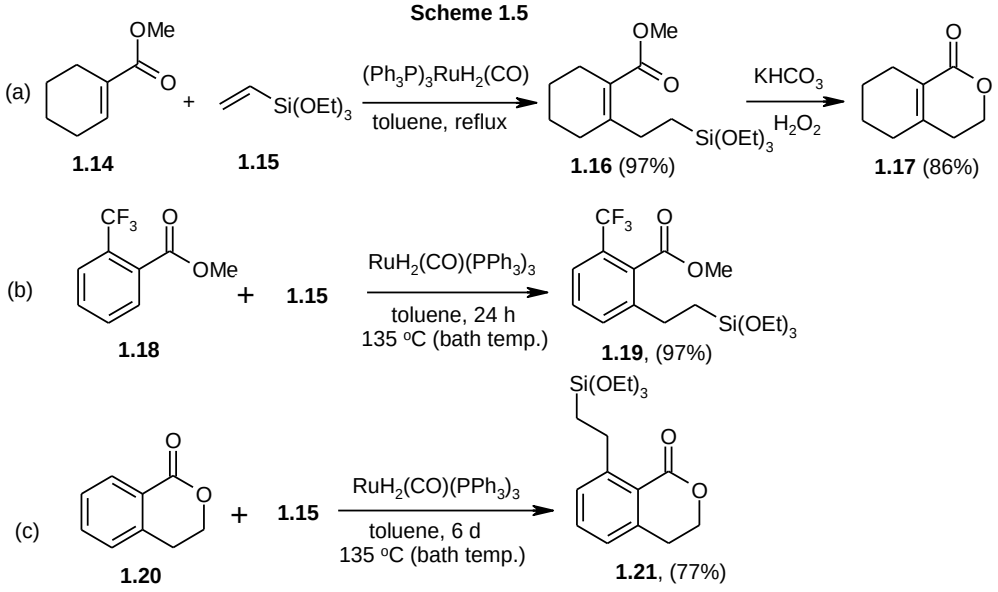


1.12

R = Pr **1.13a**, 72% (*E*/*Z* = 16/1)
R = Ph **1.13b**, 85% (*E*/*Z* = 9/1)

Trost *et al* observed the directing group nature of the esters when they treated vinylic esters with olefins in the presence of ruthenium catalyst (Scheme 1.5a).[8] Thus reaction of methyl-1-cyclopentenecarboxylate **1.14** with 1.2 equiv of alkene **1.15** afforded the alkylation product of the ester. Under basic peroxide conditions ($KHCO_3$, H_2O_2, THF, CH_3OH, room temperature), compound **1.16** was easily converted to the lactone **1.17** in 86% isolated yield. Murai's group also reported the chelating group nature of the esters for C-H/olefin coupling (Scheme 1.5b).[9] While alkyl benzoates containing strong electron withdrawing substituents like -CF_3, -F facilitated *ortho* C-H coupling, unsubstituted alkyl benzoates did not react. This method was successfully applied for the benzo-δ-lactone **1.20** also (Scheme 1.5c).

Scheme 1.5



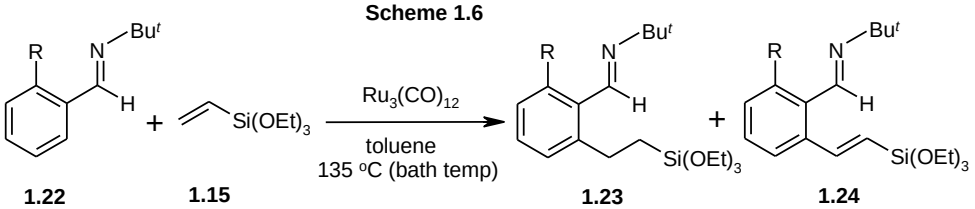
1.14 **1.15** **1.16** (97%) **1.17** (86%)

1.18 **1.19**, (97%)

1.20 **1.21**, (77%)

Aldimines and ketimines can also coordinate to transition metals and direct the metal to a proximal C-H bond *via* chelation. Using this idea, Murai's group reported a ruthenium catalyzed C(sp^2)-H/olefin coupling between aromatic imines and olefins (Scheme 1.6).[10] For this reaction, $Ru_3(CO)_{12}$ catalyst showed better activity compared to other ruthenium complexes. Both aldimines and ketimines reacted well with olefins and gave the 1:1 adducts (e.g., **1.23**) in good to excellent yields, but in some cases a dehydrogenative coupling product (e.g., **1.24**) was also obtained as a minor by-product. The same group has also found that catalytic C-H/olefin coupling is possible with aromatic imidates.[11]

Scheme 1.6

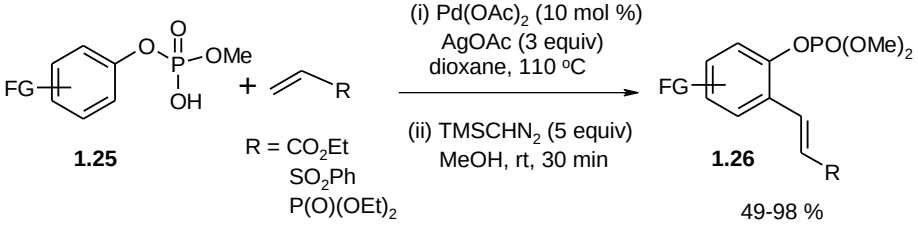


1.22 **1.15** **1.23** **1.24**

R = Me, **1.23a**, (81%); **1.24a**, (10%)
R = CF_3, **1.23b**, (75%)
R = F, **1.23c**, (79%); **1.24c**, (8%)

Recently, Kim, Lee and co-workers reported a mono-phosphoric acid-directing group *ortho*-alkenylation of organophosphates *via* C(sp^2)-H bond cleavage in the presence of a [Pd]-catalyst (Scheme 1.7).[12] Under these catalytic conditions, a variety of olefins are tolerated.

Scheme 1.7



1.25

R = CO_2Et
SO_2Ph
P(O)(OEt)$_2$

1.26

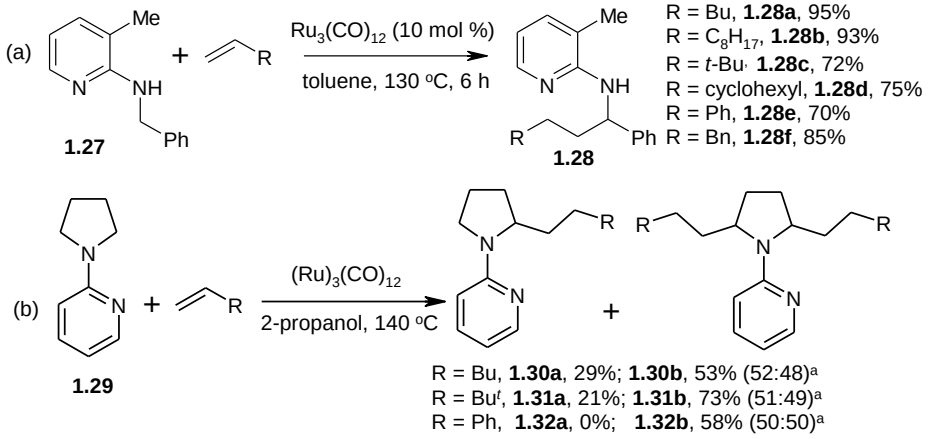
49-98 %

Many other directing groups that include amide, carbamate, sulfoximine, amine, sulfonamide and phosphite are also utilized for C-C bond formation *via* C(sp^2)-H bond cleavage.[13] Since these are not directly related to the present work, they are not elaborated further.

1.2.2 C-C bond formation *via* C(sp^3)-H bond cleavage

Reactions involving catalytic C(sp^3)-H bond functionalization are explored by several groups. Jun *et al* reported the alkylation of pyridyl substituted benzylamines in the presence of a ruthenium catalyst.[14] They treated *N*-benzyl-*N*-(3-methyl-2-pyridyl)amine (**1.27)** with monosubstituted alkenes in toluene in the presence of 10 mol % $Ru_3(CO)_{12}$ and obtained the corresponding alkylated products **1.28a-f** in 70-95% yield (Scheme 1.8a). In this report, substrates were restricted to *N*-pyridylbenzylamines, in which only benzylic C(sp^3)-H bonds added to the alkenes. Later, Murai *et al* reported alkylation of *N*-2-pyridyldialkylamines **1.29** with olefins (Scheme 1.8b).[15] In almost all the cases, di-alkylated product was the major product. The reaction also worked well with acyclic amines, but benzylic C-H bonds were more reactive than alkyl C-H bonds.

Scheme 1.8



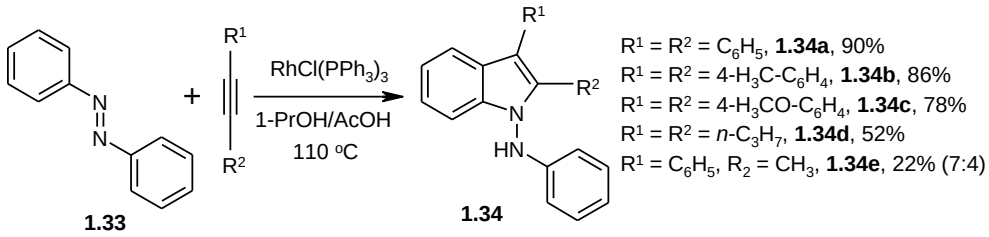
[a] The numbers in parentheses are the stereoisomeric ratios.

1.2.3 Transition metal catalyzed annulation reactions *via* C-H activation

Directing group assisted transition metal catalyzed annulation reactions that lead to the formation of heterocycles such as indoles, quinolones, isoquinolones etc discovered by various groups, will be discussed in this section. In the year 1995, Kisch *et al* reported that reaction of 1,2-diaryldiazenes (**1.33**) with disubstituted alkynes in the presence of $RhCl(PPh_3)_3$ afforded *N*-(ary1amino)indole derivatives **1.34** (Scheme 1.9).[16] They also studied the effect of electronic properties on the turnover number. The electron-withdrawing substituents on the alkyne induce a decrease of the catalytic turnover rate and electronic properties of the diazene moiety have only a little influence.

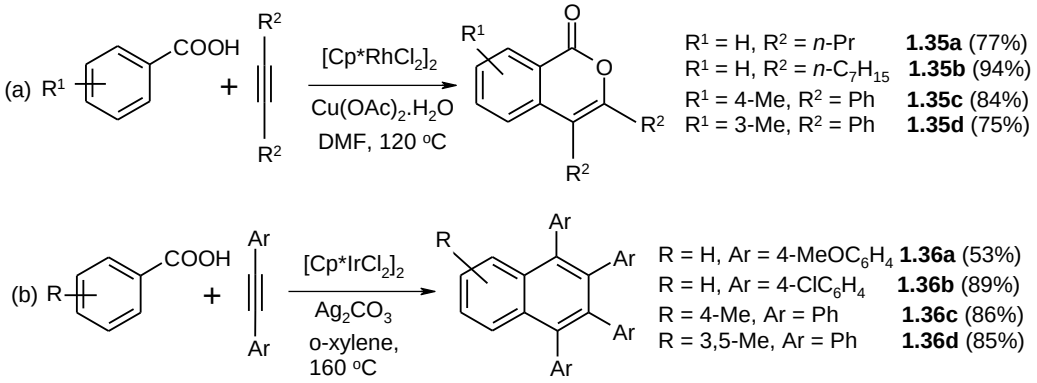
In the case of unsymmetrical alkynes, formation of a mixture of regioisomers was observed.

Scheme 1.9



Coming to recent reports on annulation reactions with the aid of directing group, Miura and co-workers reported the oxidative annulation of benzoic acids with alkynes in the presence of $[Cp^*RhCl_2]_2$ as a catalyst and $Cu(OAc)_2 \cdot H_2O$ as an oxidant that led to the formation of isocoumarin derivatives **1.35a-d** in excellent yields (Scheme 1.10a).[17] The reaction proceeds smoothly with both aliphatic and aromatic alkynes. Interestingly the reaction performed with $[Cp^*IrCl_2]_2$ as a catalyst and Ag_2CO_3 as an oxidant led to the formation of 1:2 coupled products **1.36a-d** that were accompanied by decarboxylation (Scheme 1.10b).

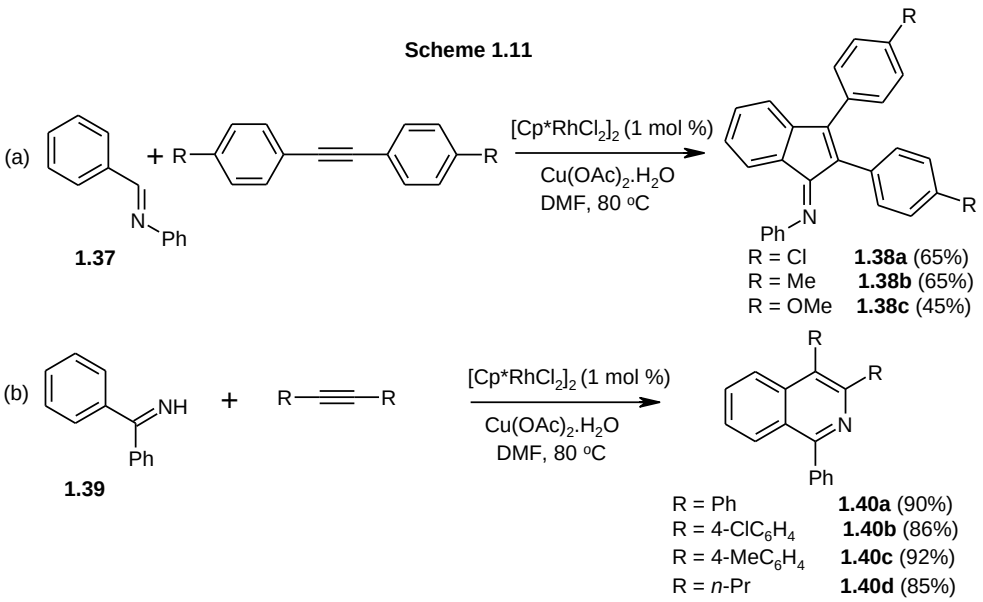
Scheme 1.10



Later, the same group of Miura reported that imines could also participate in such annulation reactions with alkynes. Thus the reaction of aromatic imines benzylideneaniline **1.37** and benzophenone imine **1.39** with internal alkynes in the presence of $[Cp^*RhCl_2]_2$ as a catalyst and $Cu(OAc)_2 \cdot H_2O$ as an oxidant led to the formation of indenone imine (**1.38**) and isoquinoline (**1.40**) derivatives, respectively (Scheme 1.11).[18] But the reaction with terminal alkyne (1-phenyl acetylene) led to the

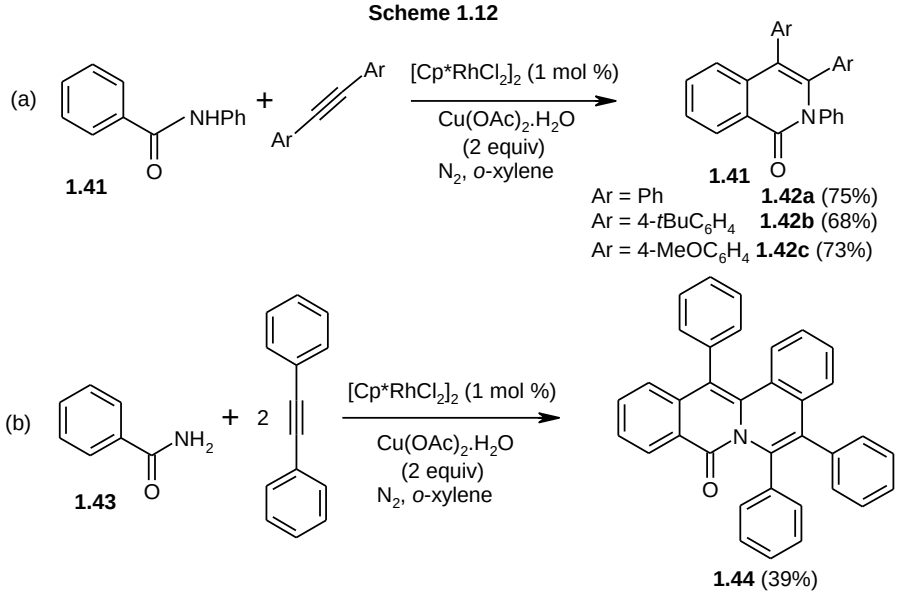
formation of only the alkyne dimer, diphenylbutadiyne; in this case, a coupled product similar to **1.37** was not observed.

Scheme 1.11



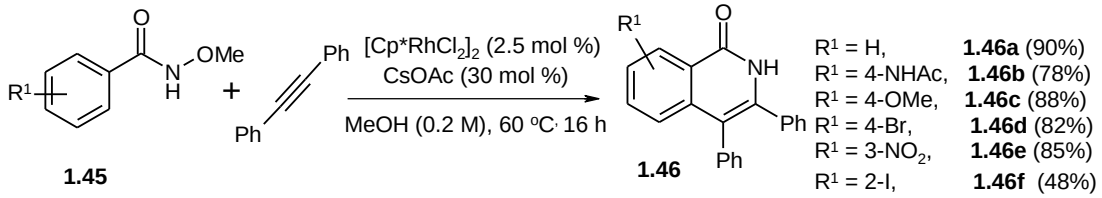
Benzamides also undergo oxidative coupling with alkynes and form isoquinolone derivatives (Scheme 1.12).[19] Thus the reaction of *N*-monosubstituted benzamides with diarylacetylenes in the presence of rhodium-catalyst lead to the formation of 1:1 coupled products, isoquinolone derivatives, in good yields (Scheme 1.12a). Under similar conditions, *N*-unsubstituted benzamides undergo 1:2 coupling with alkynes and afford tetracyclic dibenzoquinolizinone compounds (Scheme 1.12b).

Scheme 1.12



Guimond and Fagnou *et al* disclosed an intermolecular and mechanistically distinct approach for the synthesis of the isoquinolone motif **1.46** *via* Rh(III)-catalyzed annulation of benzhydroxamic acids **1.45** with alkynes (Scheme 1.13).[20] This reaction proceeds in the absence of any external oxidant and the N-O bond in the hydroxamic acid is utilized for the C-N bond formation. In the case of *meta*-substituted benzhydroxamic acids, annulation occurs regioselectively at the less hindered site. Both symmetrical and unsymmetrical alkynes successfully coupled with benzhydroxamic acids.

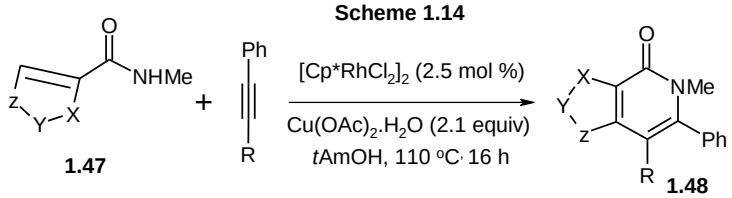
Scheme 1.13



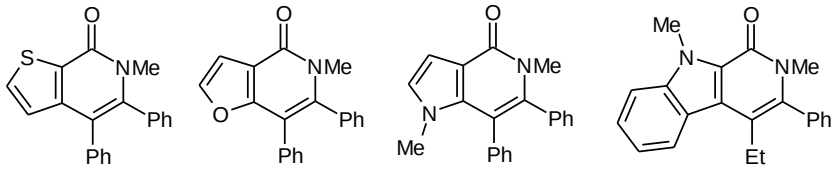
1.45 **1.46**

The synthesis of isoquinolones from benzamides and alkynes in the presence of rhodium complex was reported by Rovis *et al* (Scheme 1.14) also.[21] In this reaction, $Cu(OAc)_2.H_2O$ was used as the oxidant. The reaction has good functional group compatibility. Heteroaryl substituted carboxamides also successfully coupled with alkynes.

Scheme 1.14



1.47 **1.48**

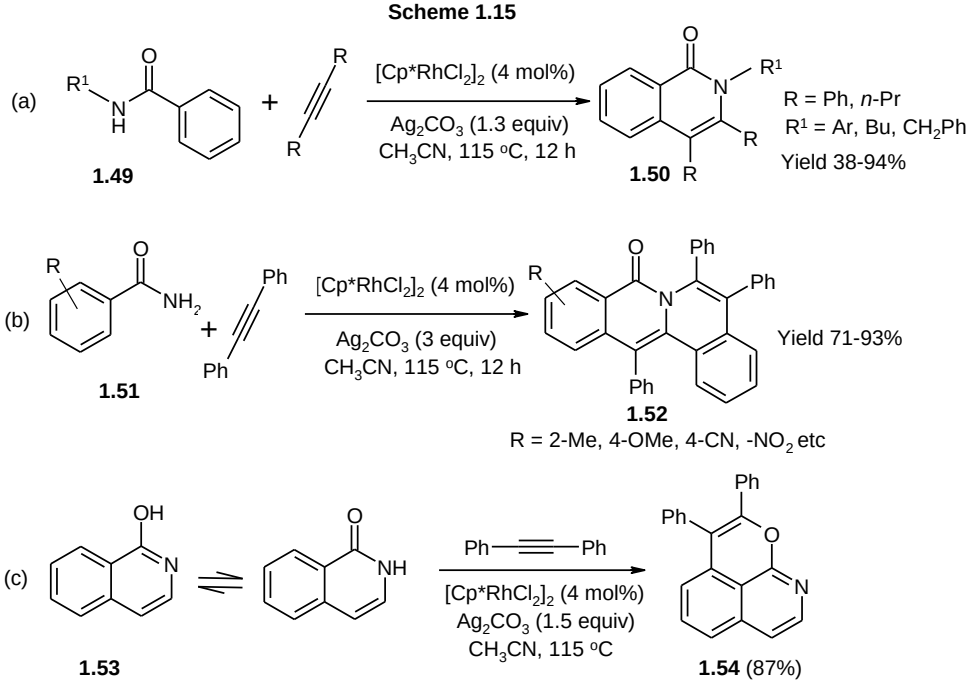


1.48a (86%) **1.48b** (82%) **1.48c** (62%) **1.48d** (93%)

Li *et al* reported the facile synthesis of isoquinolones from the reaction between benzamides and alkynes in the presence of rhodium-catalyst (Scheme 1.15).[22] Ag_2CO_3 proved to be a suitable oxidant for this reaction. Both *N*-alkyl and *N*-aryl benzamides

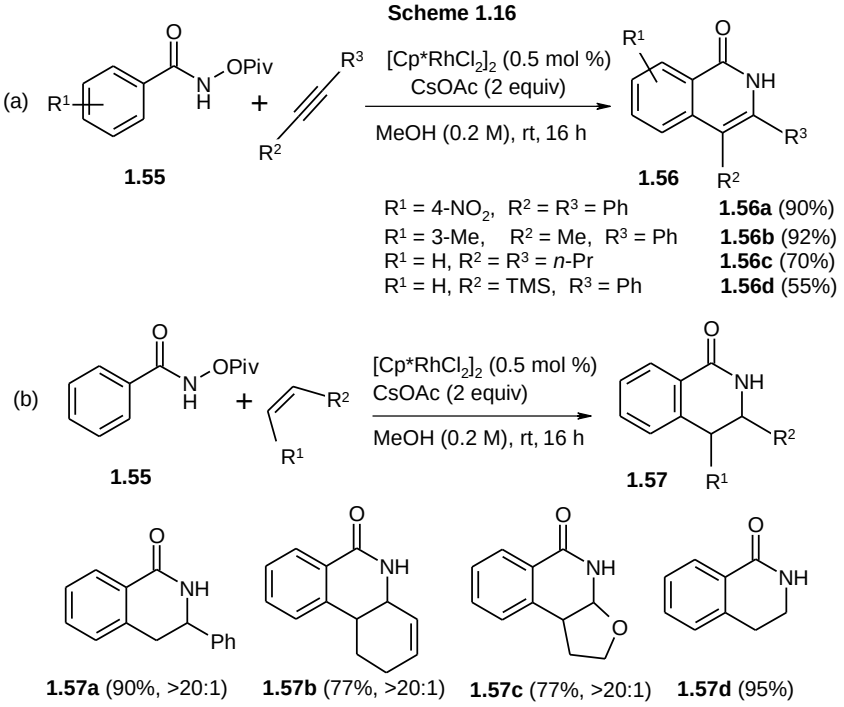
successfully coupled with alkynes and in the case of *N*-aryl substituted benzamides, C-H activation occurred selectively at *C*-aryl ring (Scheme 1.15a). Primary benzamides underwent double oxidative annulation with two equivalents of alkynes and afforded tetracyclic amides (Scheme 1.15b). The scope of this reaction was further examined by the reaction of 2-hydroxyisoquinoline which is structurally related to isoquinolone (Scheme 1.15c). In this case, oxidative annulation into O-H bond was observed.

Scheme 1.15



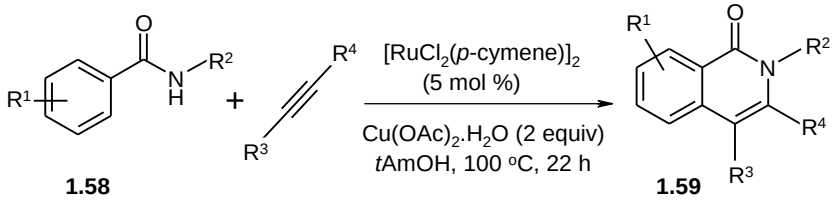
In continuation of isoquinolone synthesis, using a redox-neutral approach, Guimond and Fagnou's group developed a very reactive internal oxidant/directing group that could promote the reaction under low catalyst loadings (0.5 mol %) at room temperature (Scheme 1.16).[23] This reaction is not limited to internal alkynes. Terminal alkynes also coupled to form mono-substituted heterocycles in moderate to good yields. If the reaction is performed with alkenes instead of alkynes, 3,4-dihydroisoquinolones are formed (Scheme 1.16c). It is also proven in this study that concerted metalation-deprotonation (CMD) is the catalyst turnover limiting step.

Scheme 1.16



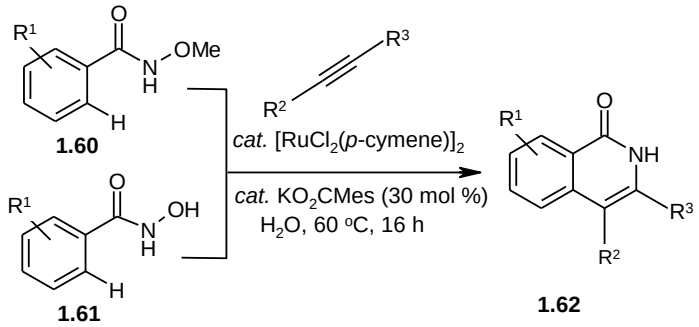
So far, we have discussed isoquinolone synthesis using rhodium complexes. Pioneering work by Ackermann *et al* disclosed that less expensive ruthenium complex can also catalyze the isoquinolone synthesis from benzamides with alkynes.[24] Thus, the reaction of *N*-substituted benzamides with internal alkynes in the presence of $[RuCl_2(p\text{-cymene})]_2$ with $Cu(OAc)_2 \cdot H_2O$ as an oxidant afforded isoquinolones with good substrate scope (Scheme 1.17). The reaction worked well with both symmetrical and unsymmetrical alkynes, and in the case of unsymmetrical alkynes, high regioselectivity was achieved. Following this report, the same group discovered a green protocol for the synthesis of isoquinolones from *N*-methoxybenzamides in water (Scheme 1.18).[25] In this reaction, carboxylate salts were used as additives along with the ruthenium complex. The green protocol was viable with free hydroxamic acids also. Li et al also reported the synthesis of isoquinolone motif using *N*-methoxybenzamides **1.60** under mild reaction conditions in the presence of ruthenium catalyst without using any external oxidant.[26] Here C-H bond functionalization occurs at room temperature.

Scheme 1.17



1.58 **1.59**

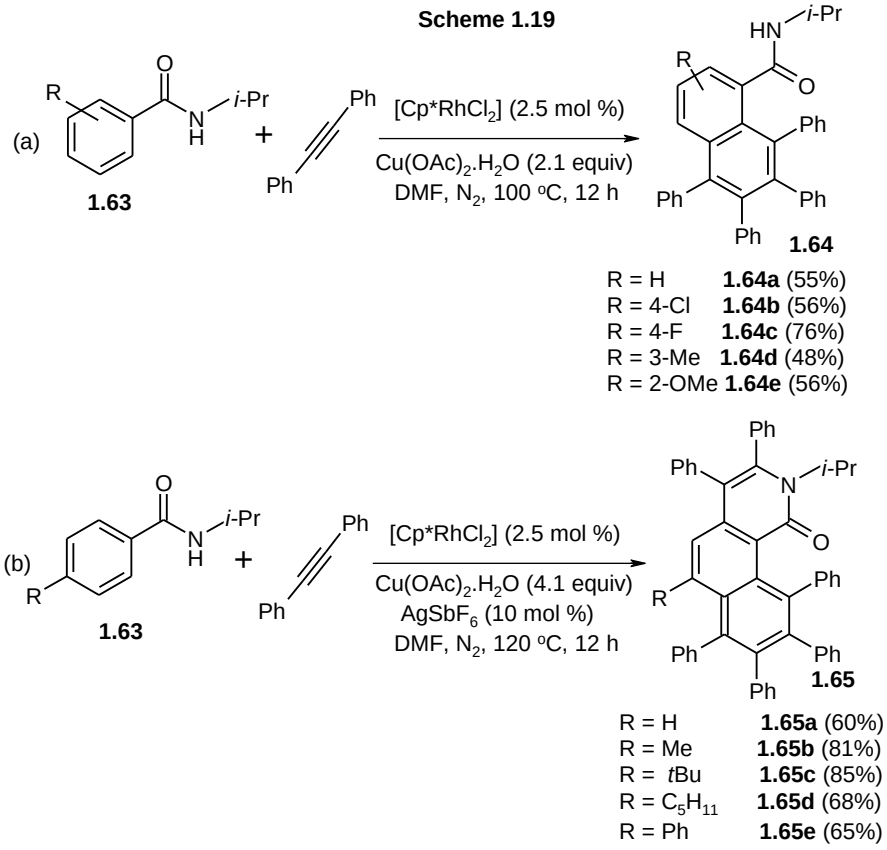
Scheme 1.18



1.60 **1.61** **1.62**

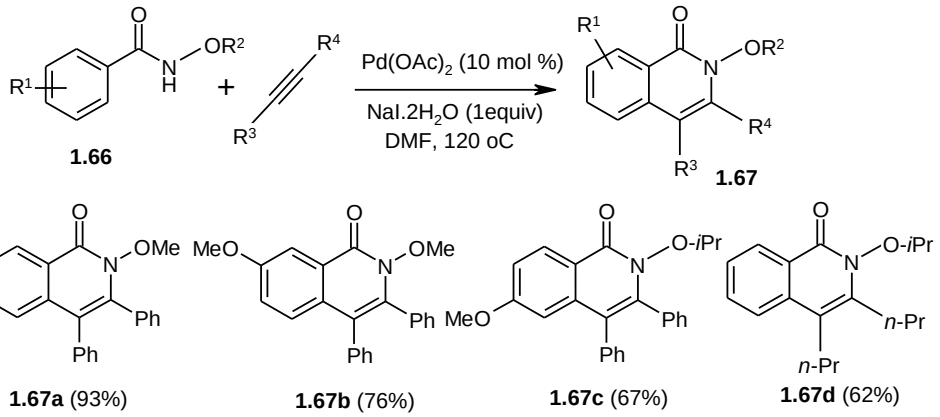
Very interestingly, Jiao *et al* discovered a different process of annulation of benzamides with alkynes that led to the formation of naphthylamide and/or isoquinolone motifs in a chemoselective manner (Scheme 1.19).[27] Thus, the reaction of *N*-isopropyl-benzamides with alkynes in the presence of Rh(III) complex with $Cu(OAc)_2 \cdot H_2O$ as an oxidant afforded naphthylamides in moderate to good yields (Scheme 1.19a) (minor or negligible amount of isoquinolone was also formed). When $AgSbF_6$ (10 mol %) was used as an additive along with the oxidant, further reaction leading to isoquinolones occurred (Scheme 1.19b).

Scheme 1.19



Huang *et al* developed the first [Pd]-catalyzed process for isoquinolones from *N*-methoxybenzamides with alkynes (Scheme 1.20).[28] The reaction is simply operable in open air. High regioselectivity was achieved in the case of unsymmetrical alkynes. A one-pot synthesis of *N*-H isoquinolones was also achieved by NaH dealkoxylation. Very recently, Li and Wang developed a protocol for the synthesis of isoquinolones from benzamides and alkynes under ligand-free conditions using Pd/C as a heterogeneous catalytic system.[29] Without a significant decrease in the catalytic activity, this Pd/C catalyst could be recovered three times.

Scheme 1.20

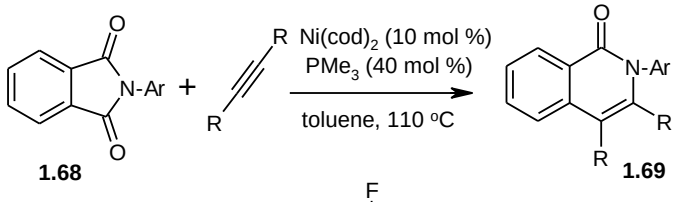


1.66 **1.67**

1.67a (93%) **1.67b** (76%) **1.67c** (67%) **1.67d** (62%)

Isoquinolones are also synthesized by using a Ni(0) catalyst. Thus, Matsubara and Kurahashi developed a nickel(0) catalyzed synthesis of isoquinolones from *N*-arylphthalimides **1.68** and alkynes (Scheme 1.21).[30] The reaction proceeds through the nucleophilic attack of Ni(0) complex on the amide C-N bond followed by alkyne insertion *via* decarbonylation. Electron-deficient *N*-arylphthalimides gave good yields compared to electron-rich substrates. A new approach was also developed for the isoquinolone synthesis *via* a nickel(0) catalyzed denitrogenative alkyne insertion into 1,2,3-benzotriazin-4(3*H*)-ones (Scheme 1.22).[31] A variety of symmetrical and unsymmetrical alkynes successfully coupled with triazinone moiety and in the case of unsymmetrical alkynes, good regioselectivity was achieved. Terminal alkynes could also be used.

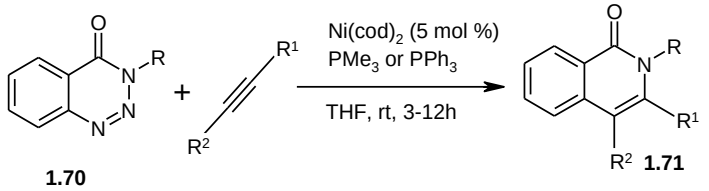
Scheme 1.21



1.68 **1.69**

1.69a (13%) **1.69b** (84%) **1.69c** (90%) **1.69d** (56%)

Scheme 1.22

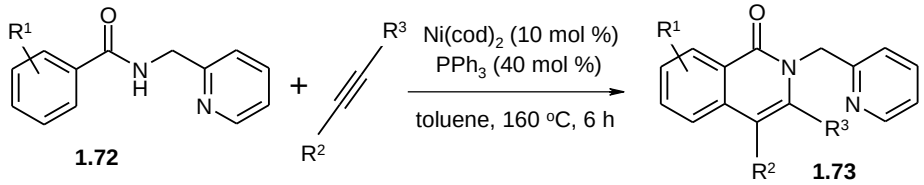


1.70 **1.71**

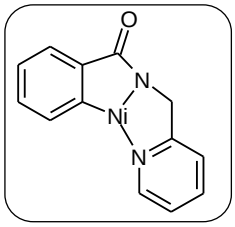
R = Ph, $R^1 = R^2 = CH_2OBn$ **1.71a** (94%)
R = 4-MeC_6H_4, R^1 = Ph, R^2 = Me **1.71b** (99%, 86:14)
R = 4-MeC_6H_4, $R^1 = R^2$ = *n*-Bu **1.71c** (98%)
R = 4-$CF_3C_6H_4$, $R^1 = R^2$ = n-Bu **1.71d** (99%)

So far, we have discussed the mono-dentate directing group chelation assisted C-H activation for the synthesis of isoquinolones and their analogues. Some bidentate directing groups are also used for this purpose. Thus, Chatani *et al* discovered a nickel catalyzed synthesis of isoquinolones from aromatic amides containing 2-pyridylmethylamine moiety **1.72** by oxidative cycloaddition with alkynes (Scheme 1.23).[32] The reaction proceeds *via* coordination of amide **1.72** to the nickel center in an N,N-fashion and leads to a cyclometalated complex. Insertion of alkyne into this *ortho*-metalated complex, followed by reductive elimination afforded the isoquinolone.

Scheme 1.23



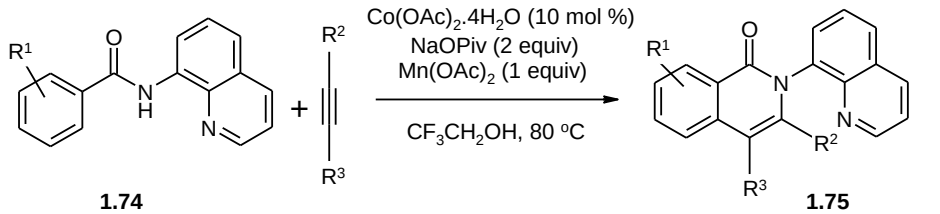
1.72 **1.73**



R^1 = 4-Me, $R^2 = R^3$ = *n*-Pr **1.73a** (84%)
R^1 = 4-Ph, $R^2 = R^3$ = *n*-Pr **1.73b** (87%)
R^1 = 3-Me, $R^2 = R^3$ = *n*-Pr **1.73c** (90%)
R^1 = H, $R^2 = R^3$ = Ph **1.73d** (92%)
R^1 = H, R^2 = Et, R^3 = Ph **1.73e** (75%, 16:1)

Recently Daugulis *et al* reported a cobalt-catalyzed 8-aminoquinoline directed oxidative annulation of aryl amides with alkynes that led to the formation of isoquinolones (Scheme 1.24).[33] They employed $Co(OAc)_2 \cdot 4H_2O$ as the catalyst, $Mn(OAc)_2$ as co-catalyst, and oxygen (from air) as the oxidant. The method allowed the use of both internal and terminal alkynes.

Scheme 1.24



1.74 **1.75**

R^1 = 4-CF_3, R^2 = R^3 = Ph	**1.75a** (70%)
R^1 = 2-Me, R^2 = R^3 = Ph	**1.75b** (86%)
R^1 = 3-I, R^2 = R^3 = Ph	**1.75c** (84%)
R^1 = H, R^2 = R^3 = CH_2OH	**1.75d** (95%)
R^1 = H, R^2 = Ph, R^3 = H	**1.75e** (95%)
R^1 = H, R^2 = TIPS, R^3 = H	**1.75f** (64%)

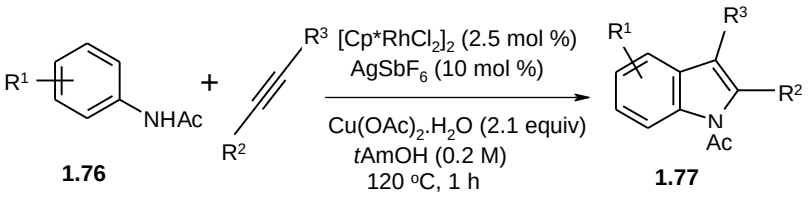
1.2.4 Indole synthesis *via* directing group assisted C-H functionalization

Indoles are important building blocks present in bioactive molecules and natural products. Their importance in pharmaceutical and heterocyclic chemistry has resulted in a strong demand for elaboration of new synthetic approaches.[34] Most of the methods involve annulation of *ortho*-halo-substituted aniline derivatives in the presence of transition metal catalyst,[35] thus reducing the ready availability of the starting materials and atom economy. To alleviate these difficulties, many groups have recently explored direct C-H functionalization with the aid of a directing group that led to indole formation. These methods are straightforward, atom economical and avoid use of preactivated starting materials.

Fagnou *et al* discovered a rhodium-catalyzed oxidative coupling of *N*-acetyl anilines **1.76** with alkynes that led to *N*-acetyl indole derivatives **1.77** in good yields (Scheme 1.25).[36] The reaction worked well with both symmetrical and unsymmetrical alkynes. In the case of *meta*-substituted anilines, high regioselectivity was achieved. Cyclization took place at the sterically less hindered side. It was also shown that free N-H indoles could be obtained from simple deprotection of acetyl moiety in the presence of KOH or K_2CO_3 in MeOH /DCM solvent at room temperature. Later, the same group reported the synthesis of indole motifs under mid conditions using $[Cp^*Rh(MeCN)_3][SbF_6]_2$ as the catalyst and molecular oxygen as the terminal oxidant.[36b] This methodology was extended to the synthesis of pyrrole moieties by activating the vinylic C-H bond. Using the same acetamido directing group, Lu's group

reported a palladium catalyzed oxidative coupling of *N*-aryl amides with alkynes that led to indoles.[37]

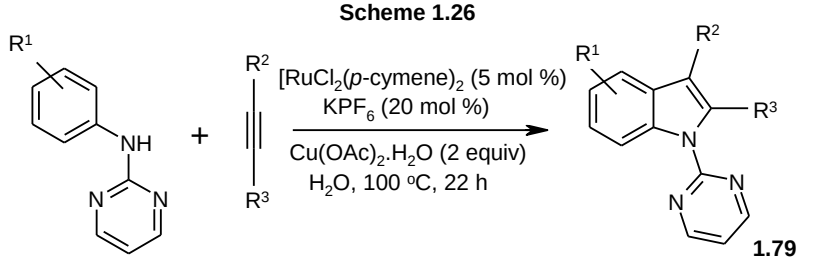
Scheme 1.25



R^1 = 4-OMe, R^2 = Ph, R^3 = Me **1.77a** (82%)
R^1 = 2-Me, R^2 = Ph, R^3 = Me **1.77b** (66%)
R^1 = 3-OMe, R^2 = Ph, R^3 = Me **1.77c** (73%)
R^1 = H, R^2 = R^3 = Ph **1.77d** (81%)
R^1 = H, R^2 = R^3 = Pr **1.77e** (68%)

Li and co-workers developed a pyridine directed oxidative coupling of *N*-aryl-2-aminopyridines with alkynes in the presence of a rhodium-catalyst that led to indole derivatives.[38a] The reaction was successful with acrylates also and afforded *N*-(2-pyridyl)quinolones. But the catalytic conditions were limited to symmetrical alkynes; unsymmetrical alkynes failed to give indole derivatives. Later, the same group reported a palladium-catalyzed oxidative coupling using *N*-aryl-2-aminopyridines and alkynes.[38b] Molecular oxygen was used as the terminal oxidant. Under these conditions, unsymmetrical alkynes also coupled well and afforded indole derivatives with high regioselectivity. Ackermann and co-workers developed a ruthenium catalyzed oxidative C-H bond functionalization with *N*-aryl-2-aminopyrimidines **1.78** that gave indole derivatives **1.79** (Scheme 1.26).[39a] The reaction worked well in water and had good functional group compatibility in arene and alkyne moieties. Later they proved that inexpensive nickel complex under neat conditions could also be used as a catalyst for this annulation process.[39b] It did not require any metal oxidant. The pyrimidyl directing group present in the final indole derivatives could be easily removed under base hydrolysis to get NH-free indoles. Wu *et al* developed an interesting protocol for the synthesis of indole derivatives by annulation of *N*-aryl-2-aminopyridines with alkynes using the heterogeneous catalytic system, Pd/CeO_2.[40] Only catalytic amount of Cu(II) salt and air as the co-oxidant were required for this reaction.

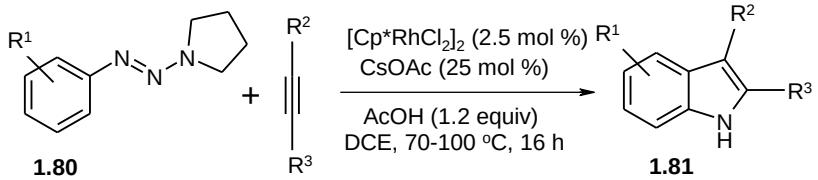
Scheme 1.26



R^1 = 2-Me, R^2 = R^3 = Ph **1.79a** (94%)
R^1 = 2-Me, R^2 = R^3 = Et **1.79b** (66%)
R^1 = 2-Me, R^2 = Me, R^3 = Ph **1.79c** (78%)
R^1 = 2-CF_3, R^2 = R^3 = Ph **1.79d** (92%)

Huang *et al* reported a triazene directed C-H annulation reaction with alkynes that led to the formation of NH-free indoles in the presence of a rhodium catalyst (Scheme 1.27).[41] A broad substrate scope was found with respect to both arenes and alkynes. Unsymmetrical alkynes also coupled well by delivering indole derivatives with high regioselectivity.

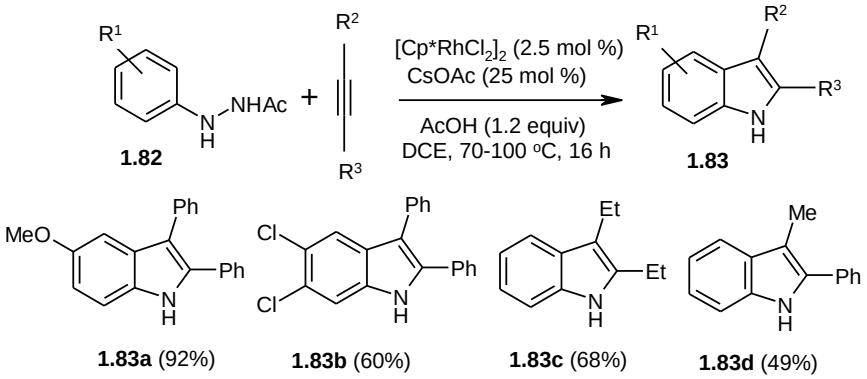
Scheme 1.27



R^1 = 4-F, R^2 = R^3 = Ph **1.81a** (70%)
R^1 = 2-I, R^2 = R^3 = Ph **1.81b** (42%)
R^1 = 3-Br, R^2 = R^3 = *n*-Pr **1.81c** (78%)
R^1 = 3-Cl, R^2 = Ph, R^3 = Me **1.81d** (73%)

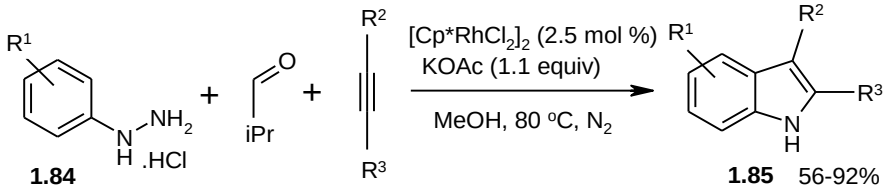
Glorius and co-workers reported a hydrazine directed Rh(III)-catalyzed C-H activation route to obtain indoles through a mechanism different from that of Fischer indole synthesis.[42a] Arylhydrazines **1.82** were used as substrates for the annulation with alkynes and indoles **1.83** were formed by N-N bond cleavage (Scheme 1.28). There was no need of any external oxidant for this reaction. Liu *et al* also employed hydrazines as coupling partners for annulation reaction with alkynes in the presence of Rh(III)-catalyst to afford 1- aminoindoles.[42b] In this reaction, 1,3-dinitrobenzene was used as an oxidant.

Scheme 1.28



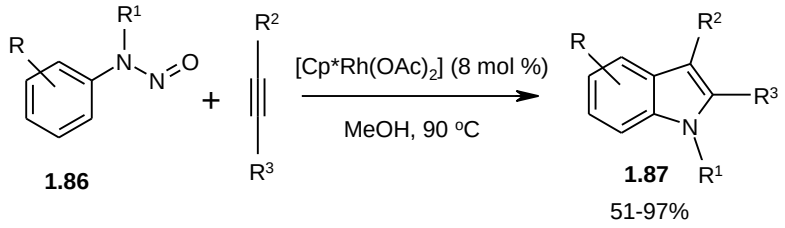
The research groups of Hua[43] and Cheng[44] individually reported three component coupling reaction of an aryl hydrazine, a C=O compound and an alkyne for the synthesis of *N*-unprotected indole derivatives in the presence of a rhodium-catalyst (Scheme 1.29). Here, aryl hydrazones are formed by the *in situ* condensation of hydrazines and the carbonyl source, while the N-N bond serves as directing group for C-H activation and oxidizing group for the catalyst turnover. The reaction is quite compatible with a variety of functional hydrazines and alkynes.

Scheme 1.29



N-Nitrosoanilines can also be used as traceless directing groups for the synthesis of *N*-alkylindoles in the presence of rhodium-catalyst by annulation reaction with alkynes (Scheme 1.30).[45] The reaction requires no external oxidant; N-N bond present in nitrosoaniline serves as an oxidant for the catalyst turnover. Good to excellent regioselectivity is achieved when unsymmetrical substituted alkynes are employed as coupling partners.

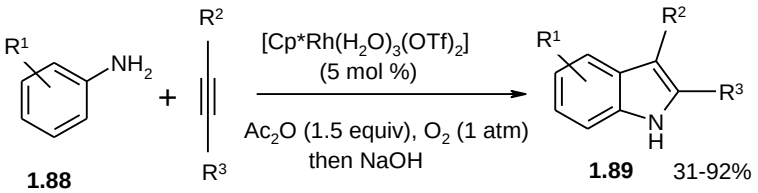
Scheme 1.30



1.86 **1.87** 51-97%

Simple anilines can actually be used as precursors for the synthesis of indoles *via* C-H activation.[46] Thus aerobic oxidative coupling of anilines with alkynes in the presence of $[Cp^*Rh(H_2O)_3(OTf)_2]$ (5 mol %)/Ac_2O (1.5 equiv) afforded indoles in good yields (Scheme 1.31). Here, molecular oxygen was used as an oxidant; under N_2 atmosphere, only trace amount of product formation was observed. The obtained *N*-acetyl indole derivatives were *in situ* hydrolyzed by simple base hydrolysis (NaOH) to the NH-free indoles.

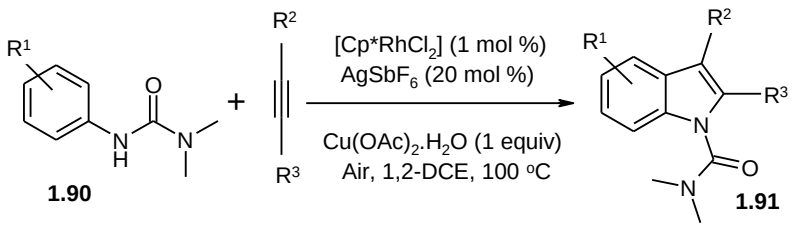
Scheme 1.31



1.88 **1.89** 31-92%

Recently, Nicholls and co-workers reported a facile synthesis of *N*-carbamoyl indole derivatives from *N*-arylureas and alkynes in the presence of Rh(III)-catalyst under aerobic conditions (Scheme 1.32).[47] Here, $Cu(OAc)_2{\cdot}H_2O$ was used as the terminal oxidant for the catalyst regeneration. The carbamoyl group was removed easily by hydrolysis in the presence of ethanol and aqueous KOH (3:1).

Scheme 1.32

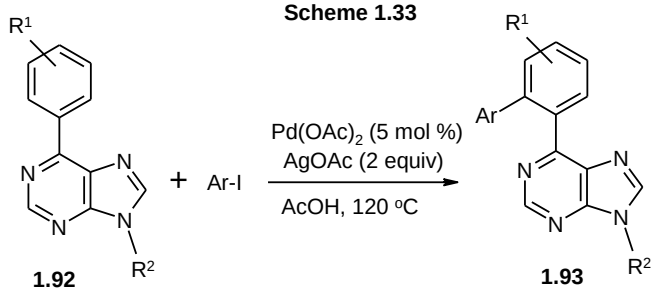


1.90 **1.91**

1.3 Purine directed C-H functionalization

Purine can be considered as a pyrimidine fused imidazole moiety, so it can also act as a directing group for C-H activation. In addition, direct functionalization on purine moiety delivers products that may have great medicinal importance.[48] But purine is a more challenging directing group compared to simple pyridine, because it possesses additional three nitrogen atoms, which can poison the metal's catalytic nature. Guo *et al* reported [Pd]-catalyzed mono-arylation of 6-arylpurines **1.92** using the intrinsic directing group nature of purine (Scheme 1.33).[49] This reaction was also successful with nucleosides which contain additional sugar moiety. Arylation was possible only with aryl iodides (30 equiv); aryl bromides/chlorides did not give any desired product under these conditions. Later Lakshman *et al* reported a similar ruthenium catalyzed arylation of 6-aryl purines.[50]Under these conditions also, nucleosides survived well. But in all the cases, a mixture of mono and di-arylated products was formed.

Scheme 1.33



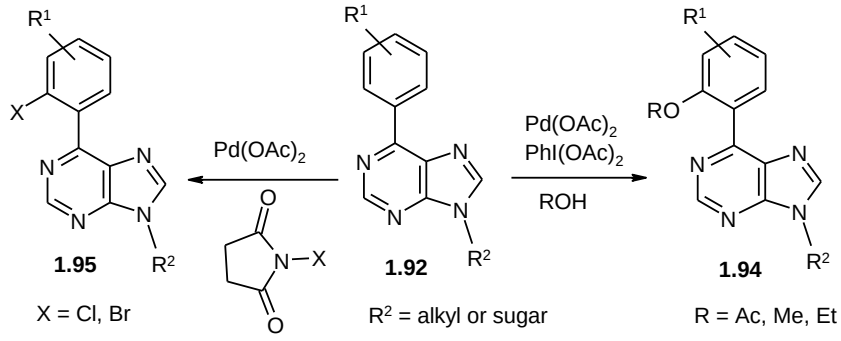
1.92 **1.93**

R^1 = 4-Me, R^2 = *n*-Bu, Ar = Ph **1.93a** (85%)
R^1 = 4-NO_2, R^2 = *n*-Bu, Ar = Ph **1.93b** (83%)
R^1 = H, R^2 = *n*-Bu, Ar = 4-BrC_6H_4 **1.93c** (69%)

Using the above concept, acetoxylation/halogenation of C-H bond *via* C-H activation was reported by Guo and co-workers.[51] Acetoxylation of N9-substituted C6-arylpurines was achieved in the presence of a [Pd]-catalyst using $PhI(OAc)_2$ as an oxidant. In the case of nucleosides, mono- and di-acetoxylated products were obtained. When an alcohol was used as a solvent, the corresponding alkyl-aryl ethers were obtained in good yields. Instead of $PhI(OAc)_2$, when *N*-bromosuccinimide or *N*-chlorosuccinimide was used as an oxidant, selective bromination or chlorination took place. Later, Lakshman *et al* developed a more widely applicable method for the acetoxylation of C6-arylpurines as well as C6-arylpurine nucleosides using

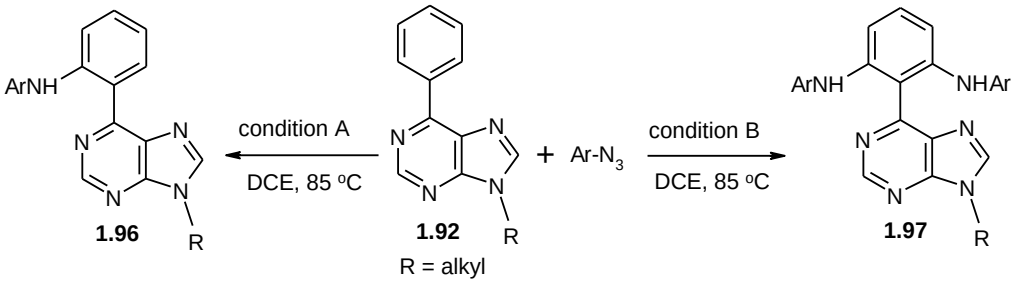
$Pd(OAc)_2/PhI(OAc)_2$ in acetonitrile.[52] They have isolated and crystallographically characterized a Pd-containing C6-naphthylpurine complex.

Scheme 1.34



Recently, Chang *et al* described C-H amination of aryl pendant in C6-arylpurines using a rhodium-catalyst.[53] Mono or bis-aminated products were obtained depending on the stoichiometry of the aryl azide used (Scheme 1.35). The first C-H amination proceeded *via* the formation of purine N1-chelation assisted rhodacycle. This complex was structurally characterized by X-ray crystallography. Intramolecular hydrogen bonding between the first introduced amino NH moiety with the purine N1 or N7 made the subsequent C-H functionalization favorable. Based on this unique chelation property, symmetrical or unsymmetrical double C-H functionalizations have been reported. From the same group, cobalt catalyzed C-H cyanation of C6-arylpurines was also reported very recently using *N*-cyanosuccinimide as a cyanating agent.[54]

Scheme 1.35



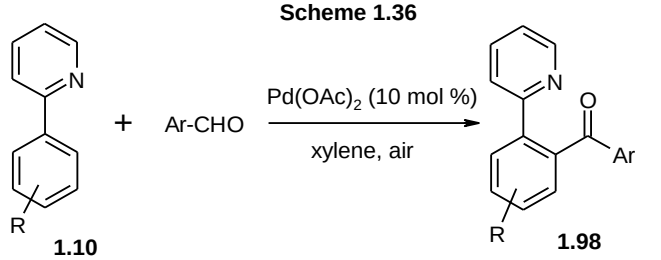
Condition A: **1.92** (2 equiv), azide (1 equiv), $[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), 12 h
Condition B: **1.92** (1 equiv), azide (3 equiv), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), 12 h

1.4 [Pd]-catalyzed *ortho*-acylation of arene C(sp^2)-H bonds

Friedel-Crafts acylation is one of the traditional methods for the acylation of arene C-H bonds.[55] But it suffers from the use of stoichiometric or more of Lewis/ Brønsted acid and poor regioselectivity. Recently, directing group assisted C-H acylation was developed by many groups using [Pd]-catalysts. Cheng and co-workers discovered a palladium catalyzed acylation of arene moiety present in 2-phenylpyridine directed by pyridine N-atom (Scheme 1.36).[56] Here, commercially available and inexpensive aldehydes were used as acylating reagents. But the reaction was limited to aromatic aldehydes only. 2-Phenoxy pyridines were acylated by using aldehydes as coupling partners, but with moderate success. Using TBHP as an oxidant, Li and co-workers reported acylation of 2-phenyl pyridines with aldehydes in the presence of $Pd(OAc)_2$ under neat conditions.[57] The reaction delivers a variety of aliphatic, aromatic and optically active ketones in good to excellent yields. Later, Ge *et al* reported *ortho*-acylation of 2-phenyl pyridines *via* decarboxylative coupling of arenes with *α*-oxocarboxylic acids.[58] The reaction proceeds smoothly with both aliphatic and aromatic *α*-oxocarboxylic acids and has good functional group tolerance. This $PdCl_2$ catalyzed acylation of 2-arylpyridines was also achieved by using alcohol as the acylating reagent and TBHP as an oxidant.[59] Fu and co-workers developed a method for the synthesis of aromatic ketones *via* C(sp^2)-H acylation of 2-phenylpyridines using carboxylic acid as the acylating agent.[60] This reaction uses $Pd(OAc)_2$ as the catalyst and trifluoroacetic anhydride (TFAA) as the activating agent to generate acyl species. Patel's[61] and Sun's[62] groups discovered an alternative by using simple toluene derivatives. Thus *ortho*-acylation of 2-phenylpyridines could be achieved by treating non-prefunctionalized toluene derivatives in the presence of [Pd]-catalyst and TBHP oxidant. Here toluene derivatives act as aldehyde surrogates *via in situ* oxidation by TBHP. In the presence of radical scavengers like TEMPO/ ascorbic acid, only traces of acylated product was observed, which confirms that the reaction proceeded *via* free radical mechanism. Arylmethyl amines and arylmethyl chlorides were also used as acylating sources for the acylation of 2-arylpyridines as reported by Wu and co-workers.[63] *α*-Diketones could also serve as acylating reagents for the synthesis of aryl ketones. Thus, a selective carbo-acylation of 2-arylpyridines/benzo[*h*]quinolone was achieved with α-diketones in

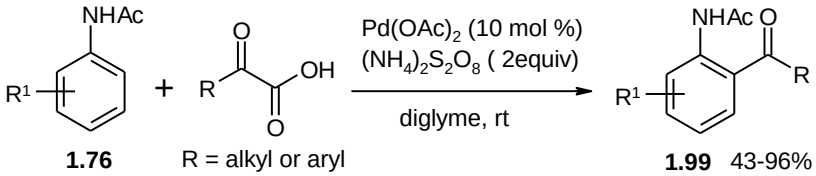
the presence of $Pd(OAc)_2$ with TBHP as the oxidant.[64] Both symmetrical and unsymmetrical diketones coupled successfully and high selectivity was observed in the case of unsymmetrical ones. The carbo-acylation reaction did not proceed in the presence of radical scavengers.

Scheme 1.36



Ge and co-workers developed a room temperature Pd-catalyzed *ortho*-acylation of acetanilides using *α*-oxocarboxylic acids (Scheme 1.37).[65] A variety of glyoxylic acids were compatible under these catalytic conditions. Later, using aldehyde as acylation source, Yu[66] and Kwong[67] groups individually reported *ortho*-C-H acylation of anilides in the presence of Pd(II)-catalyst and TBHP as oxidant. These acetanilides also could be acylated using benzyl alcohol as acylating source as reported by Yuan and co-workers.[68] Recently, a greener protocol was developed for the acylation of acetanilides *via* palladium catalyzed cross dehydrogenative coupling between anilides and aromatic aldehydes using TBHP as the oxidant in aqueous medium.[69] The groups of Sun, Kwong and Zhang individually reported acylation of acetanilides by using non-prefunctionalized toluene derivatives as aldehyde surrogates.[70]

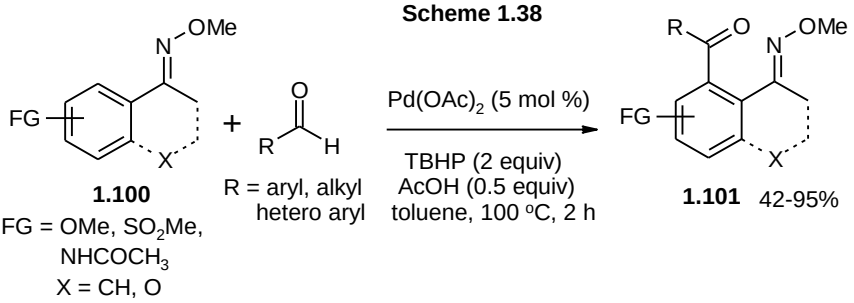
Scheme 1.37



Yu *et al* reported palladium-catalyzed acylation of aryl ketone oximes **1.100** with aldehydes using TBHP as the oxidant (Scheme 1.38).[71] This reaction has large functional group tolerance and both aliphatic and aromatic aldehydes can be used as

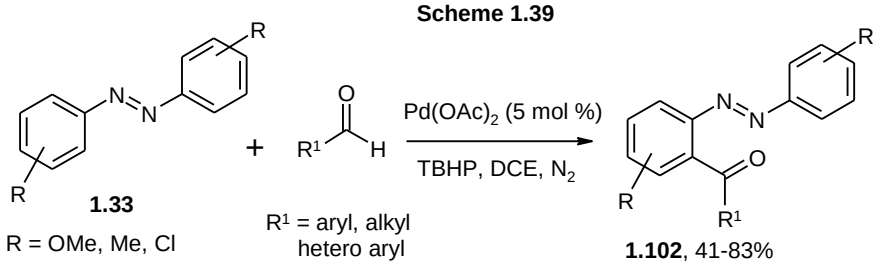
acylating reagents. The directing oxime group could be easily hydrolyzed (in HCl/dioxane) to give 1,2-diacylbenzene derivatives which were further derivatized to phthalazines by condensation with hydrazine (N_2H_4). Kim and co-workers used dibenzyl ethers as new acylating reagents for acylation of aryl ketone oximes.[72]

Scheme 1.38



Azo-substituted aryl ketones are important building blocks present in photochemical materials and food additives. Wang *et al* described a protocol for the synthesis of *ortho*-acyl azobenzenes **1.102** in the presence of [Pd]-catalyst and using aldehydes as acylating reagents (Scheme 1.39).[73] This azo-directed *ortho*-acylation was successful with aliphatic, aromatic and hetero aromatic aldehydes. These acylated azobenzenes were further transformed to indazole derivatives *via* a $Zn/NH_4Cl/MeOH$ reducing system at room temperature within 5 min. Later, the same group reported a decarboxylative *o*-acylation of azobenzenes using α-oxocarboxylic acids in the presence of $Pd(OAc)_2$.[74] The reaction proceeded readily at room temperature. Similarly, *ortho*-acyl azoarenes could be synthesized from azoarenes using toluene deivatives[75] or alcohols[76] as acylating reagents.

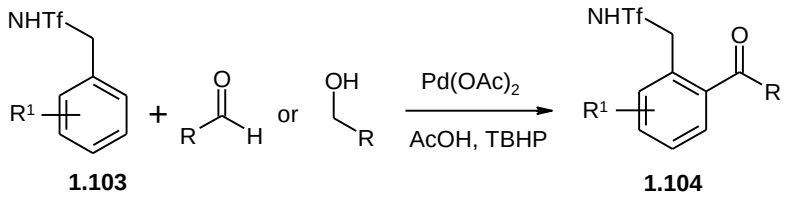
Scheme 1.39



Kim and co-workers developed an efficient protocol for the [Pd]-catalyzed *ortho*-acylation of *N*-benzyltriflamides **1.103** with aldehydes using TBHP as the oxidant.[77] Thus, benzylamines were successfully coupled with alkyl and aryl aldehydes to give the

corresponding acylated derivatives *via* C-H activation (Scheme 1.40). The same group later reported the acylation of *N*-benzyltriflamides using alcohols as acylating reagents and demonstrated a large substrate scope.

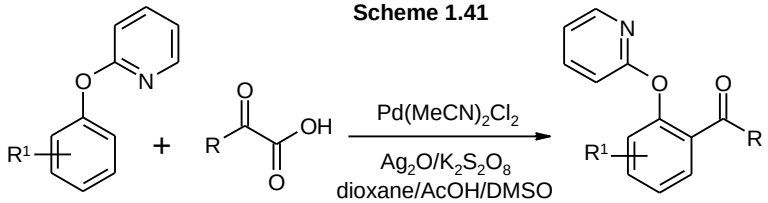
Scheme 1.40



1.103 **1.104**

Zhang *et al* reported a new protocol for the synthesis of 2-hydroxy aromatic ketones.[78] Thus treatment of 2-aryloxypyridines **1.105** with α-oxocarboxylic acids in the presence of [Pd]-catalyst afforded *ortho*-acylated products **1.106** *via* decarboxylative coupling (Scheme 1.41). The pyridine directing group could be removed by treating with MeOTf followed by reflux in Na/MeOH, which gave 2-hydroxy aromatic ketones. *Ortho*-acylation of 2-aryloxypyridines is also possible with alcohols, subsequent to oxidation by TBHP.[79]

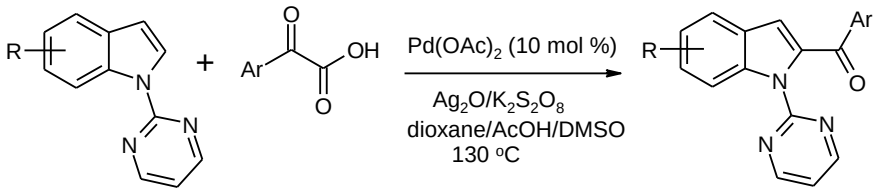
Scheme 1.41



1.105 **1.106**

Zhu and co-workers reported a [Pd]-catalyzed C2-acyaltion of indoles using α-oxocarboxylic acid as the acylating source.[80] The acylation reaction involves a two-step protocol: one is decarboxylation of the α-oxocarboxylic acid and the other one is direct C-H functionalization (Scheme 1.42). Selective C2-functionilization in indoles could be achieved by installing a suitable pyrimidine directing group. The scope, however, was limited to aromatic α-oxocarboxylic acids. Free NH-acylated indoles could be obtained easily by deprotection of the pyrimidine directing group by treatment with NaOEt in DMSO at 100 ^{o}C. Later, Liu *et al* reported C2-acylation of indoles using aldehydes as acylating reagent *via* [Pd]-catalyzed C-H activation.[81]

Scheme 1.42

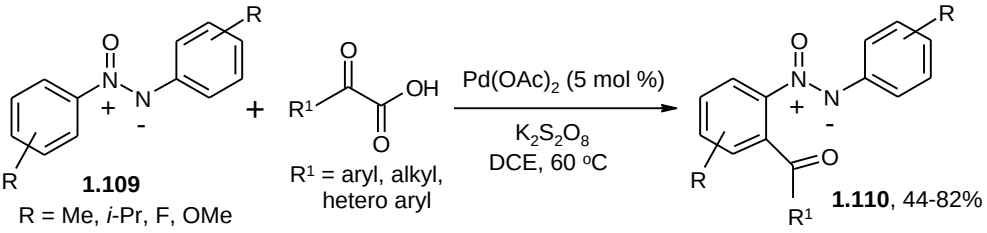


1.107 R = Me, Br, Cl, F, COOMe

1.108, 58-84%

Wang *et al* disclosed [Pd]-catalyzed synthesis of *ortho*-acylated azoxybenzenes from α-oxocarboxylic acids (Scheme 1.43).[82] Even though two coordinating sites (oxygen or nitrogen) are present in azoxybenzenes **1.109**, only one acylated derivative is selectively formed. The reaction works well with aryl, alkyl and heteroaryl α-oxocarboxylic acids and provides the corresponding *ortho*-acylated azoxybenzenes in good to excellent yields. These *ortho*-acylated azoxybenzenes can also be prepared by using aldehydes or alcohols as acylating reagents in the presence of [Pd]-catalyst and TBHP as the oxidant.[83]

Scheme 1.43



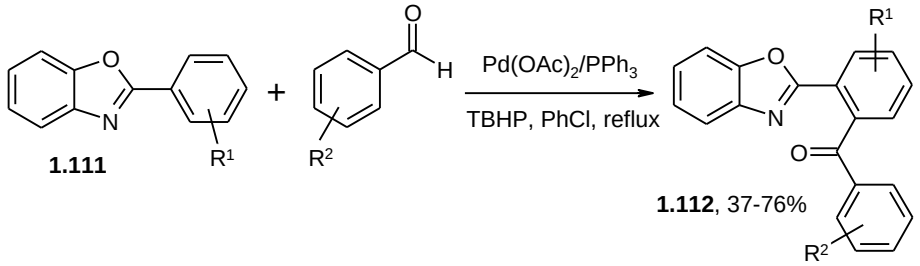
1.109
R = Me, *i*-Pr, F, OMe

R^1 = aryl, alkyl, hetero aryl

1.110, 44-82%

Wu and coworkers developed an excellent protocol for the syntheses of *ortho*-acylated 2-arylbenzoxazoles from arylbenzoxazoles and aldehydes (Scheme 1.44).[84] The reaction has a broad substrate scope and high regioselectivity with *meta*-substituted derivatives. Similar methodology was also extended for the acylation of 2-arylbenzothiazoles, 2,3-diarylquinoxalines and 3,5-diarylisoxazoles by other groups using aldehydes/alcohols/toluene derivatives as acylating agents.[85]

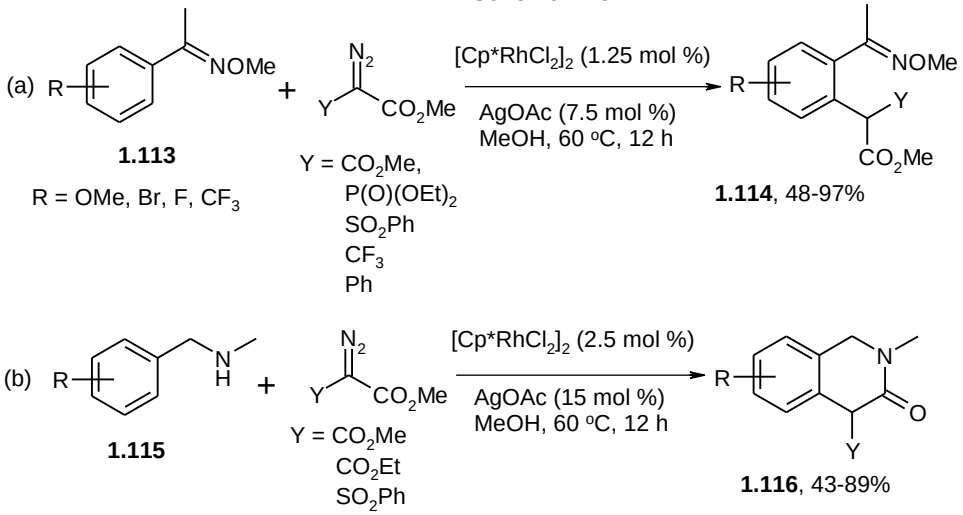
Scheme 1.44



1.5 [Rh]-Catalyzed C-H functionalization with diazo compounds

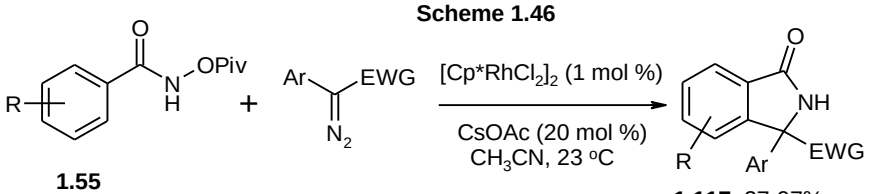
Cross coupling reactions involving metal-carbene complexes are being developed as a new type of C-C bond forming reactions. Recently, rhodium-catalyzed directing group assisted C-H bond activation involving metal carbene migratory insertion in which unreacted C(sp^2)-H bond gets functionalization with diazo compounds has been developed by Yu and co-workers (Scheme 1.45).[86] Using this methodology, acetophenone oximes, unprotected benzylamines, benzoic acids and pyridine containing substrates could be functionalized by diazo compounds. In the case of *meta*-substituted arenes, a mixture of regioisomeric products was observed. Treatment of *N*-benzylmethylamine with diazo esters under catalytic conditions afforded isoquinolones in good to excellent yields. Subsequently, Wan and Li extended this methodology by exploiting pyrazole and pyrimidine as the directing groups.[87]

Scheme 1.45



Rovis *et al* reported a Rh(III)- catalyzed coupling of *O*-pivaloyl benzhydroxamic acids with donor/acceptor diazo compounds, that gave isoindolones in high yields (Scheme 1.46).[88] A variety of benzhydroxamic acids and diazo compounds are tolerated. N-O bond present in the hydroxamic acids acts as an internal oxidant for catalytic turnover. Later, Cramer's group developed a chiral version of this methodology to synthesize chiral isoindolones in excellent regioselectivities and good yields.[89]

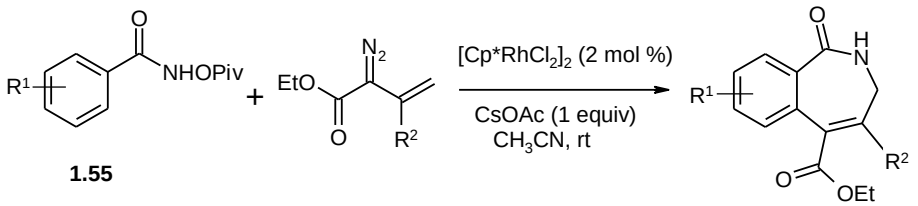
Scheme 1.46



1.55 **1.117**, 27-97%

Following the seminal work of Rovi *et al*,[88] Cui and co-workers developed a protocol for the synthesis of azepinone derivatives via Rh(III)-catalyzed C-H activation of benzamides with vinyl carbenoids (Scheme 1.47).[90] Here, vinyl carbenoids serve as three-carbon coupling partners. Recently, the same group extended this C-H activation methodology to indole and pyrrole systems using the same directing group.[91]

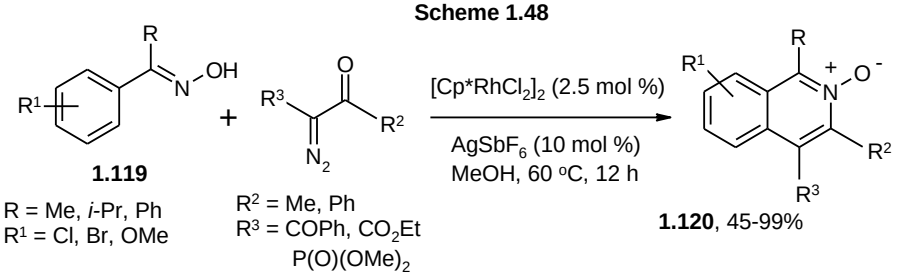
Scheme 1.47



1.55 **1.118**, 50-91%

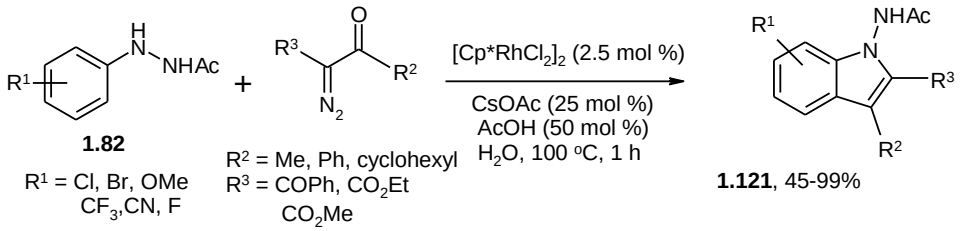
Glorius and co-workers reported the synthesis of polysubstituted isoquinoline *N*-oxides **1.120** from aromatic oximes **1.119** and diazo compounds *via* Rh(III)-catalyzed C-H activation (Scheme 1.48).[92] This reaction proceeded with $AgSbF_6$ as an additive. This methodology could be extended to *α,β*-unsaturated oximes to provide pyridine N-oxides by activating the vinylic C-H bond. This is the first report on vinylic C-H activation using diazo compounds.

Scheme 1.48



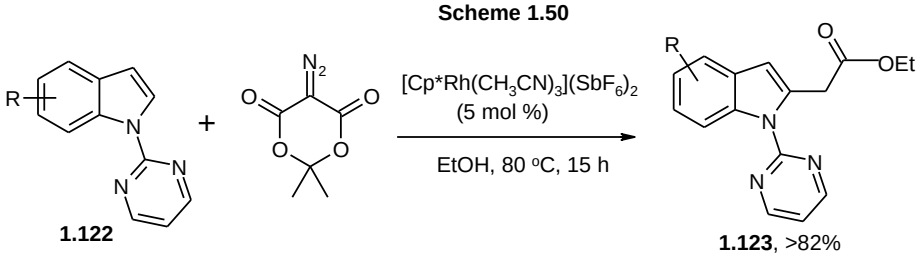
Another Rh(III)-catalyzed C-H activation reaction using diazo compounds has been reported by Wang's group.[93] Treatment of 2-acetyl-1-arylhydrazines with diazo compounds in water resulted in the formation of *N*-acetylindoles (Scheme 1.49). Various substituted arylhydrazines and diazo compounds were tolerated under these catalytic conditions. Hydrolysis of *N*-acetylindoles under acidic conditions (4N HCl/MeOH) resulted in 1-aminoindole derivatives readily.

Scheme 1.49



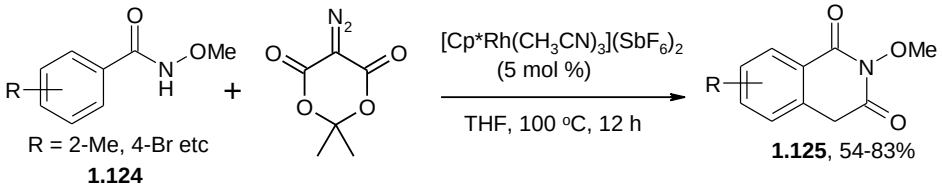
Xu, Yi and co-workers disclosed a Rh(III)-catalyzed selective C2-H functionalization of indoles using *α*-diazotized Meldrum's acid as a carbene source (Scheme 1.50).[94] This reaction proceeded *via* carbene migratory insertion into C2-position followed by decarboxylation. Alcohol played a crucial role in this reaction; depending on the alcohol source, corresponding 2-acetate substituted indoles were obtained in good to excellent yields. The reaction had a good substrate scope by tolerating substituents at all the positions (C3, C4, C5, C6, and C7) of the indole. Furthermore, the C7-alkenylation was also achieved using Rh(III)/Cu(II)-catalytic system with the C2-acetate substituted indoles as substrates. Later Yang, Zhou and co-workers have reported analogous C7-alkylation of indolines with diazo compounds in the presence of Rh(III) or Ir(III) catalyst at room temperature.[95]

Scheme 1.50



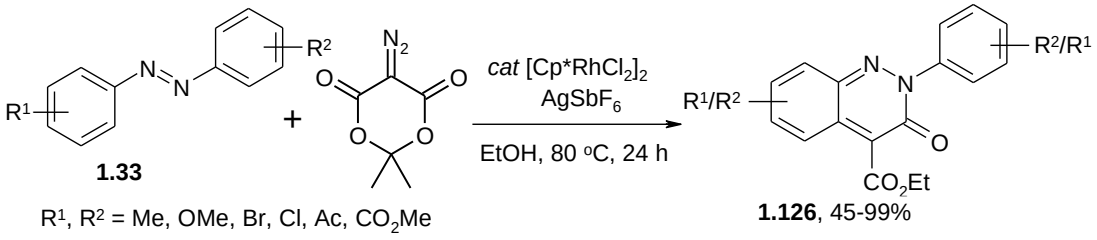
Xu, Yi and co-workers have developed a protocol for the one pot synthesis of *N*-methoxyisoquinolinediones **1.125** by using *N*-methoxybenzamides and α-diazotized Meldrum's acid *via* Rh(III)-catalysis (Scheme 1.51).[96] This reaction has a good substrate scope that includes heterocyclic moieties. This methodology could be applied to the marketed drug Edaravone and its analogs.

Scheme 1.51



Very recently, the research groups of Lee and Kim individually developed a protocol for the synthesis of cinnoline-3(2*H*)-ones **1.126** using azobenzenes and α-diazotized Meldrum's acid *via* Rh(III)-catalyzed C-H alkylation followed by cyclization (Scheme 1.52).[97] The reaction worked well with both symmetrical and unsymmetrical azoarenes. When unsymmetrical azoarenes were employed, in most cases a mixture of regioisomeric cinnoline-3(2*H*)-ones were formed. Except for the α-diazotized Meldrum's acid, remaining diazo compounds afforded only alkylated products, and no cyclization took place.

Scheme 1.52



Thus the afore-described literature clearly reveals the enormous potential in C-H functionalization using transition metal catalysts.

OBJECTIVES OF THE PRESENT WORK - PART A

The main objective of this part of the present work was to explore the new C-C bond forming reactions *via* chelation-assisted C-H bond activation using transition metal catalysts. Specifically, it was envisioned to explore the following:

(i) To utilize the bidentate directing group nature of 8-aminoquinoline for the synthesis of isoquinolone scaffolds in ruthenium-catalyzed reaction and to delineate the mechanistic features of the reaction,

(ii) To synthesize indole derivatives using the intrinsic directing group nature of purine moiety in the presence of a [Ru]-catalyst,

(iii) To investigate [Pd]-catalyzed *ortho*-acylation of 6-anilinopurines using aldehydes/ α-oxocarboxylic acids as acylating sources, and

(iv) *Ortho*-alkylation of aniline derivatives with α-diazo esters in the presence of a Rh(III)-catalyst *via* metal carbene migratory insertion.

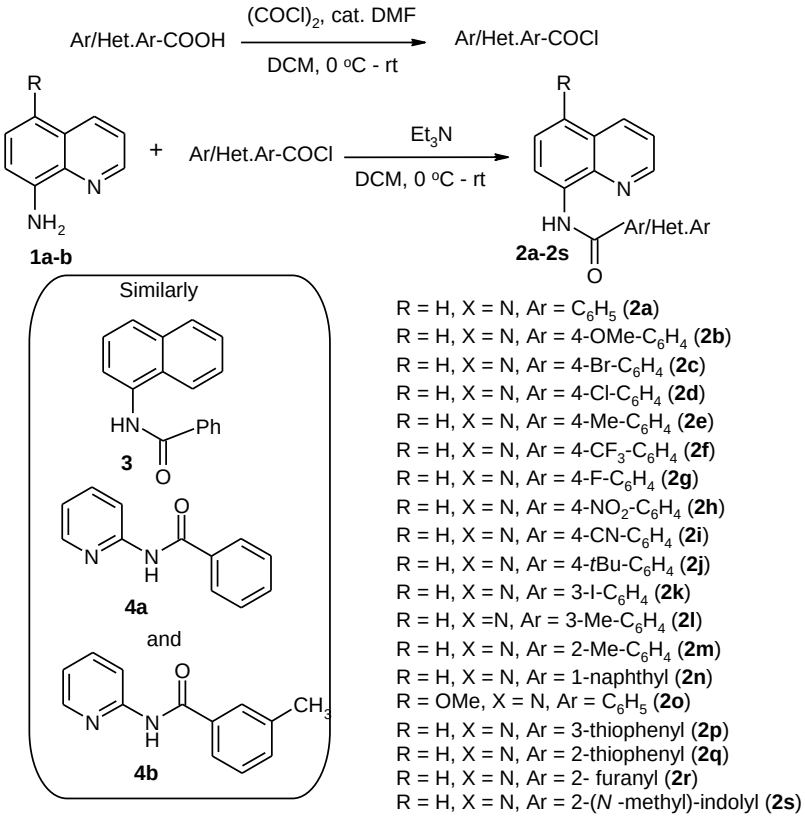
RESULTS AND DISCUSSION

The theme of this part of the work is C-H functionalization. The first few sections (2.1-2.4) deal with the preparation of the precursors required for this study. After this, synthesis of isoquinolones using 8-aminoquinoline as a bidentate directing group is discussed, followed by that on indole-substituted purine derivatives. Both of these reactions involve a ruthenium catalyst. In a later section, C(sp^2)-H bond acylation with aldehydes/oxocarboxylic acids using a palladium catalyst is described. In the last part of this work, rhodium(III)-catalyzed C(sp^2)-H functionalization of aniline derivatives with α-diazo esters is presented. Characterization of the products is generally done by using mp (for solids), IR, NMR, LCMS, and HRMS/CHN with single crystal X-ray structure determination for representative compounds.

2.1 Synthesis of *N*-quinolin-8-yl-benzamides (2a-2s), naphthyl substituted benzamide (3) and *N*-(2-pyridinyl)benzamides (4a—4b)

Quinolines used in the present study are 8-aminoquinoline (**1a**) and 5-methoxy-8-aminoquinoline (**1b**). Precursor **1a** is commercially available and precursor **1b** has been prepared in the current study by following a literature procedure.[98] All the amides bearing 8-aminoquinoline or naphthalene or pyridine moiety have been prepared by the reaction of corresponding acid chlorides with an amine according to standard procedures (Scheme 1).[99] The acid chlorides themselves were prepared by treating the carboxylic acid with oxalyl chloride using catalytic amount of DMF in dichloromethane (DCM). Among the synthesized amides, **2o** and **2r** are new, but the remaining amides are known.[99]

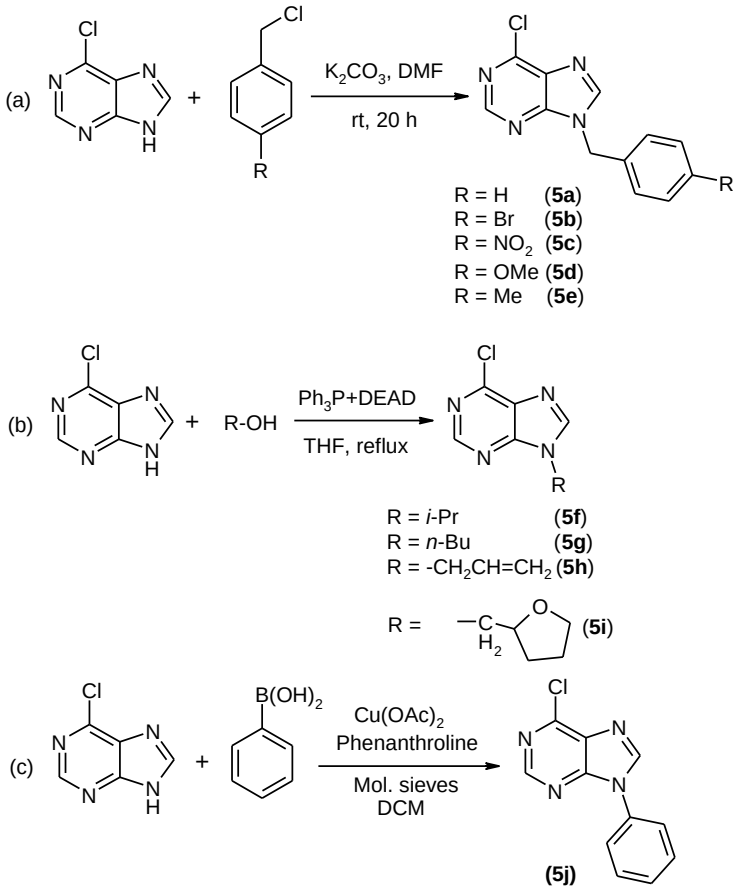
Scheme 1



2.2 Synthesis of 6–anilinopurine precursors and 2-anilinopyrimidine/pyridine substrates

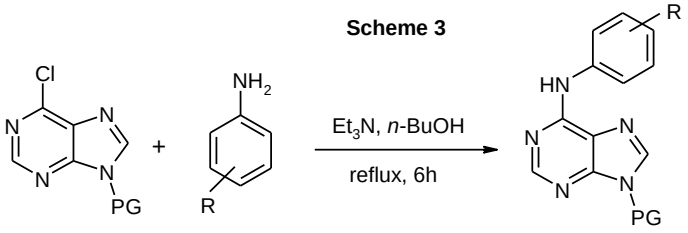
9-Substituted 6-chloropurines **5a-i** have been synthesized from 6-chloropurine either by alkylation of purine in the presence of a base using alkyl halide (Scheme 2a)[100a] or by using Mitsunobu reaction by treating with the corresponding alcohol (Scheme 2b).[100b] 6-Chloro-9-phenylpurine **5j** has been synthesized from the reaction of 6-chloropurine and phenylboronic acid in the presence of copper(II) acetate (Scheme 2c).[100c]

Scheme 2



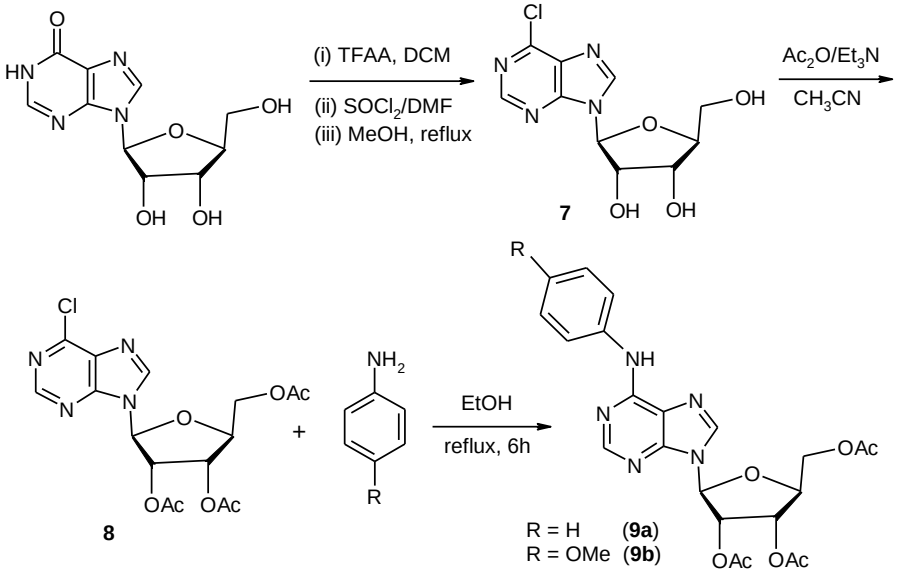
9-Alkyl/aryl substituted 6-anilinopurine derivatives were prepared from the corresponding anilines and 9-alkyl/aryl-6-chloropurine in the presence of Et_3N (Scheme 3).[100a] Among the synthesized anilinopurines, **6b**, **6d-6m**, **6q**, **6r**, **6t** and **6u** are new. These compounds show a broad band at ~ 3300 cm^{-1} [υ(N-H)] in the IR spectra; the NMR spectra are consistent with the structures as shown. We have also synthesized 6-anilinopurine nucleosides **9a** and **9b** starting from inosine according to a literature procedure (Scheme 4).[101]

Scheme 3



PG = Bn, R = H (**6a**)
PG = Bn, R = 4-Me (**6b**)
PG = Bn, R = 4-OMe (**6c**)
PG = Bn, R = 4-Br (**6d**)
PG = Bn, R = 4-Cl (**6e**)
PG = Bn, R = 4-F (**6f**)
PG = Bn, R = 4-CF_3 (**6g**)
PG = Bn, R = 3-Br (**6h**)
PG = Bn, R = 3-OMe (**6i**)
PG = Bn, R = 2-OMe (**6j**)
PG = Bn, R = 2-Me (**6k**)
PG = Bn, R = 2-Br (**6l**)
PG = *i*-Pr, R = H (**6m**)
PG = *n*-Bu, R = H (**6n**)
PG = Ph, R = H (**6o**)
PG = -$CH_2CH{=}CH_2$, R = H (**6p**)
PG = tetrahydrofurfuryl, R = H (**6q**)
PG = 4-Br-$C_6H_4CH_2$, R = H (**6r**)
PG = 4-NO_2-$C_6H_4CH_2$, R = H (**6s**)
PG = 4-OMe-$C_6H_4CH_2$, R = H (**6t**)
PG = 4-Me-$C_6H_4CH_2$, R = H (**6u**)

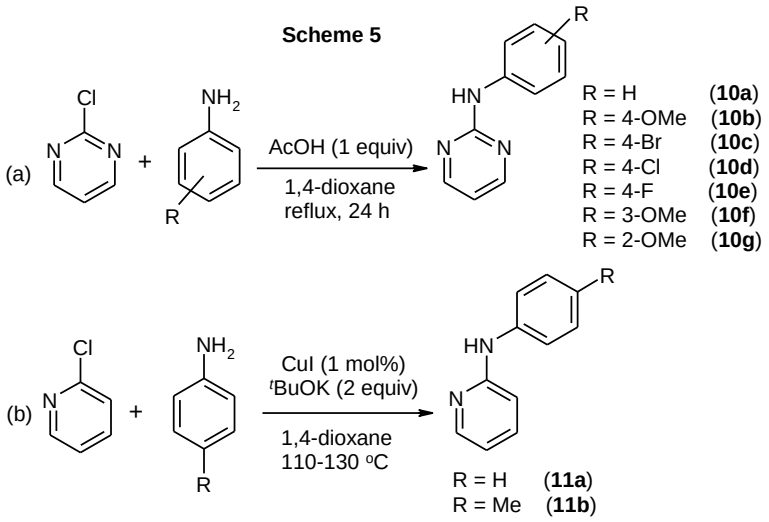
Scheme 4



R = H (**9a**)
R = OMe (**9b**)

An alternative procedure has been utilized to synthesize pyrimidine/pyridine substituted aniline derivatives (Scheme 5).[102] These substrates have been useful for comparing the difference in reactivity with the purine substituted amines of type **6**.

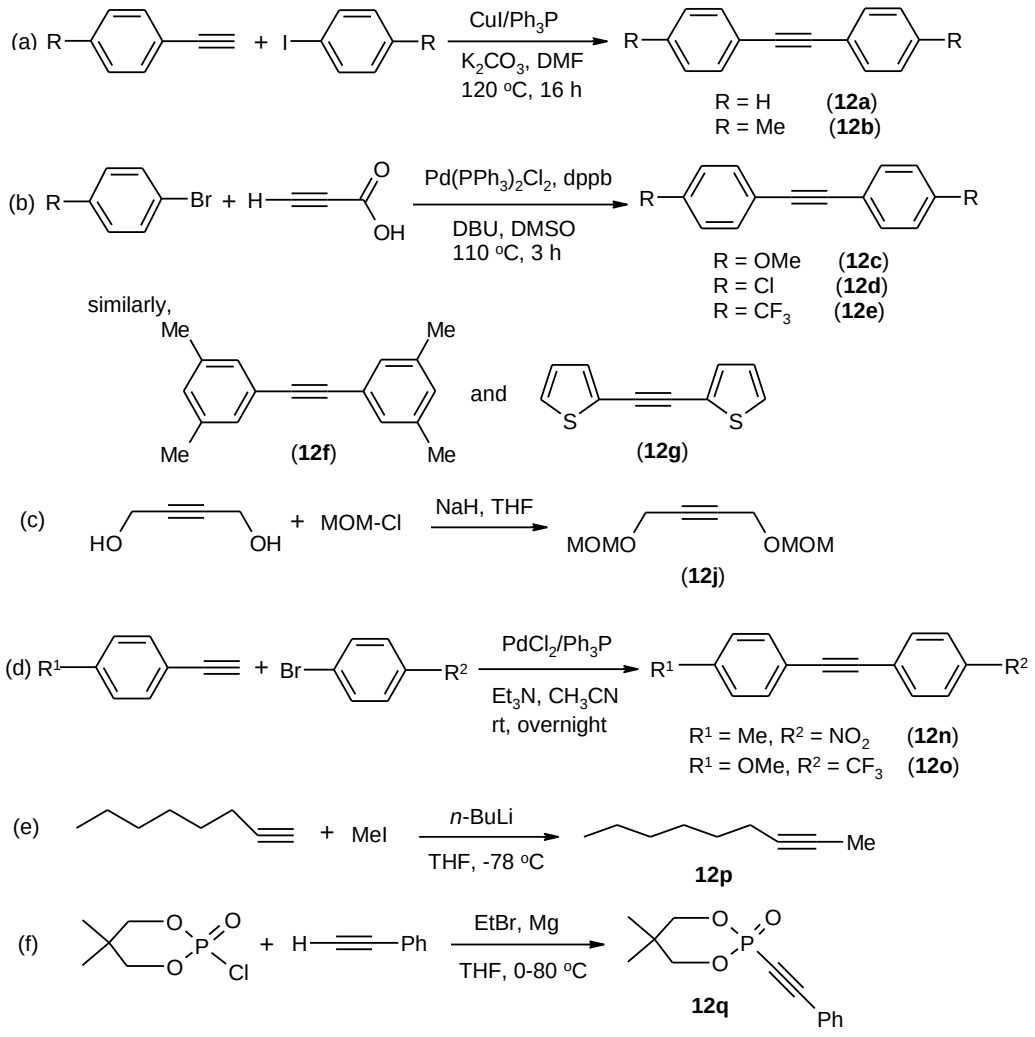
Scheme 5



2.3 Synthesis of disubstituted alkynes 12a-q

All these alkynes were synthesized following the literature methods with minor modifications where appropriate.[103] Thus alkynes **12a** and **12b** were prepared from terminal acetylenes coupling with the corresponding iodoarene in the presence of CuI/PPh_3 catalytic system with K_2CO_3 as a base (Scheme 6a).[103a] Alkynes **12c-g** were obtained from propiolic acid and aryl halide (iodo/bromo) *via* palladium-catalyzed decarboxylative coupling (Scheme 6b).[103b] 4-Octyne (**12h**), 3-Hexyne (**12i**), 1-phenyl-1-pentyne (**12k**), 1-phenyl-1-butyne (**12l**) and 1-phenyl-1-propyne (**12m**) are commercially available. 1,4-Bis(methoxymethoxy)-2-butyne **12j** was prepared by MOM protection of the corresponding 1,4-butynediol using NaH (Scheme 6c).[103c] Sonogashira coupling between acetylene derivative and bromoarenes afforded unsymmetrical alkynes **12n** and **12o** (Scheme 6d).[103d] Alkyl alkyne **12p** was prepared by methylation of 1-octyne with MeI in the presence of *n*-BuLi (Scheme 6e).[103e] The phosphonate substituted alkyne **12q** was prepared by the reaction of $(OCH_2CMe_2CH_2O)P(O)Cl$ with alkynyl magnesium bromide according to a literature procedure (Scheme 6f).[103f] All the alkynes **12a-q** used in the present study are known.[103]

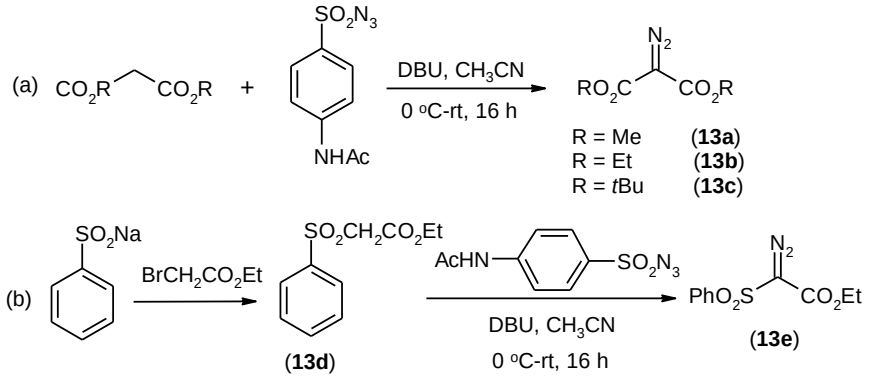
Scheme 6



2.4 Synthesis of diazoesters 13a-c and 13e

Diazo compounds **13a-c** and **13e** used in the present study have been synthesized using known literature procedures.[104] Thus treatment of the activated esters with *p*-acetamidobenzenesulfonyl azide in the presence of the base DBU afforded the corresponding diazo compounds in good yields (Scheme 7).

Scheme 7



2.5 Ruthenium-catalyzed annulation via C-H functionalization

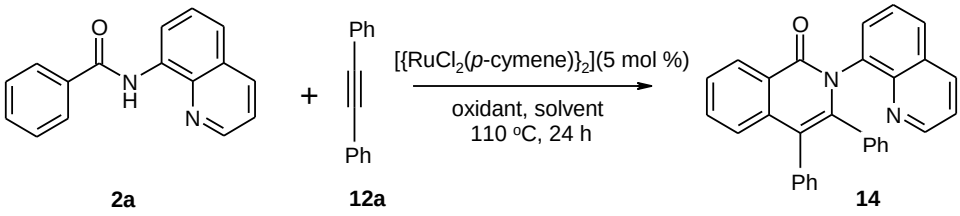
From the literature presented in Chapter 1, it is well understood that chelation assisted C-H functionalization is actively pursued by several groups to synthesize various heterocycles by activating C(sp^2)-H bond using transition metal complexes. In the present study, we have used 8-aminoquinoline and purine moieties as directing groups for the synthesis of isoquinolone and indole derivatives by annulation with alkynes in the presence of inexpensive ruthenium-catalyst. It is important to note that isoquinolone skeleton is widely found in many natural products and pharmaceutically important building blocks.[19]

2.5.1 Synthesis of isoquinolones using 8-aminoquinoline as a bidentate directing group

We began our study by investigating the Ru-catalyzed oxidative annulation of *N*-quinolin-8-yl-benzamide **2a** with diphenylacetylene **12a**. To this end, we have screened several oxidants and solvents. The reaction of amide **2a** (0.4 mmol) with alkyne **12a** (0.6 mmol) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %)/ $Cu(OAc)_2.H_2O$ (0.8 mmol) in *t*AmOH solvent at 110 ^oC afforded the product **14** in 57% yield (Table 1, entry 1). Formation of **14** was readily inferred from IR (absence of amide -N-H) and ^1H NMR spectra (integrated intensities, absence of -N-*H*). The structure of this compound was further confirmed by using X-ray crystallography (Figure 1). By increasing the amount of alkyne to 0.8 mmol (i.e. 2 equiv), complete conversion of the amide occurred, and the product was isolated in excellent yield (74%)

(entry 2).The reaction mixture showed complete consumption of the amide. Use of other solvents like H_2O, DMF, toluene, xylene, DCE or BuOH did not improve the yield (entries 3-7, 10, 11). Product formation was not observed when Ag(I) salts were used instead of $Cu(OAc)_2.H_2O$ as the oxidant (entries 8-9). Lower yield of the product was observed when the catalyst loading was decreased to 2.5 mol % (entry 12). A control experiment showed that $Cu(OAc)_2.H_2O$ is essential for the reaction (entry 13). It is noteworthy that under the same catalytic conditions in *open air* also, the reaction afforded the same amount of the product (74%) (entry 14). Rather surprisingly, when we used atmospheric oxygen as an oxidant along with $Cu(OAc)_2.H_2O$ (0.5 equiv), only 22% of the product was observed (entry 15). We have screened other ruthenium complexes like $Ru_3(CO)_{12}$ or $CpRuCl(PPh_3)_2$, we did not get good yield (entries 16-17). When KOAc used as additive along with $Cu(OAc)_2.H_2O$, lower yield of the product was observed (entry 18).

Scheme 8



2a **12a** **14**

Table 1: Optimization study for the [Ru]-catalyzed oxidative annulation[a]

Entry	Oxidant	Solvent	Yield (%)[b]
1	$Cu(OAc)_2 \cdot H_2O$	*t*AmOH	57[c]
2	**$Cu(OAc)_2 \cdot H_2O$**	***t*AmOH**	**74**
3	$Cu(OAc)_2 \cdot H_2O$	H_2O	22
4	$Cu(OAc)_2 \cdot H_2O$	DMF	45
5	$Cu(OAc)_2 \cdot H_2O$	toluene	56

6	$Cu(OAc)_2 \cdot H_2O$	*p*-xylene	56
7	$Cu(OAc)_2 \cdot H_2O$	DCE	trace
8	AgOAc	*t*AmOH	trace
9	Ag_2CO_3	*t*AmOH	trace
10	$Cu(OAc)_2 \cdot H_2O$	*n*BuOH	57
11	$Cu(OAc)_2 \cdot H_2O$	*t*BuOH	68
12	$Cu(OAc)_2 \cdot H_2O$	*t*AmOH	54[d]
13	-	*t*AmOH	trace
14	$Cu(OAc)_2 \cdot H_2O$	*t*AmOH	74[e]
15	$Cu(OAc)_2 \cdot H_2O$	*t*AmOH	22[f]
16	$Cu(OAc)_2 \cdot H_2O$ (Catalyst: 5.0 mol % cpRuCl$(PPh_3)_2$)	*t*AmOH	16
17	$Cu(OAc)_2 \cdot H_2O$ (Catalyst: 5.0 mol % $Ru_3(CO)_{12}$)	*t*AmOH	trace
18	$Cu(OAc)_2 \cdot H_2O$ (30 mol % KOAc used as additive)	*t*AmOH	27

[a]Reaction conditions: amide (0.4 mmol), alkyne (0.8 mmol), oxidant (0.8 mmol), solvent (2 mL), 110 ^oC (oil bath temperature). [b]Isolated yields. [c]1.5 equiv of alkyne used. [d]2.5 mol % catalyst used. [e]In open air. [f]0.5 equiv of $Cu(OAc)_2 \cdot H_2O$ used.

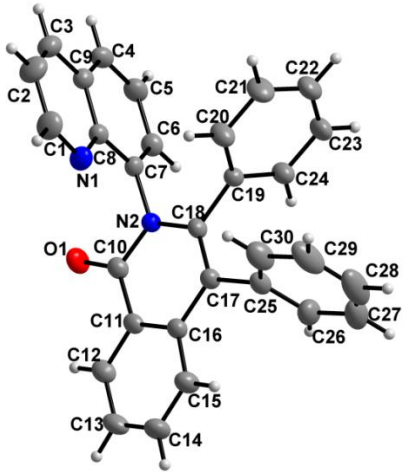
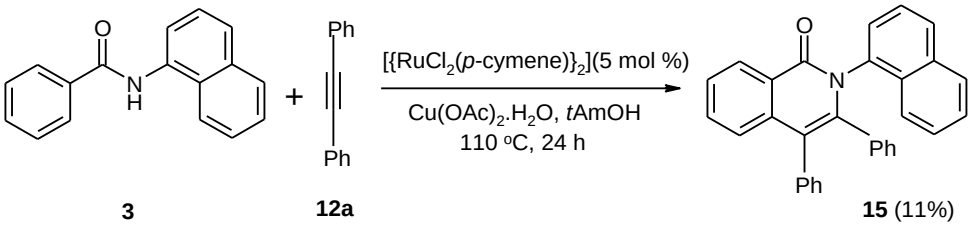


Figure 1. Molecular structure of compound **14**. Selected bond lengths [Å] with esd's in parentheses: N(2)-C(18) 1.393(3), C(17)-C(18) 1.337(3), C(17)-C(16) 1.429(4), C(11)-C(10) 1.450(4), O(1)-C(10) 1.218(3), N(2)-C(10) 1.369(3).

Under the above catalytic conditions, the structurally similar, but monodentate directing group naphthyl substituted benzamide (**3**) gave the isoquinolone derivative **15** in very poor yield (11%) (Scheme 9). This result suggests that 8-aminoquinoline (bidentate chelation) is necessary for completion of the reaction.

Scheme 9



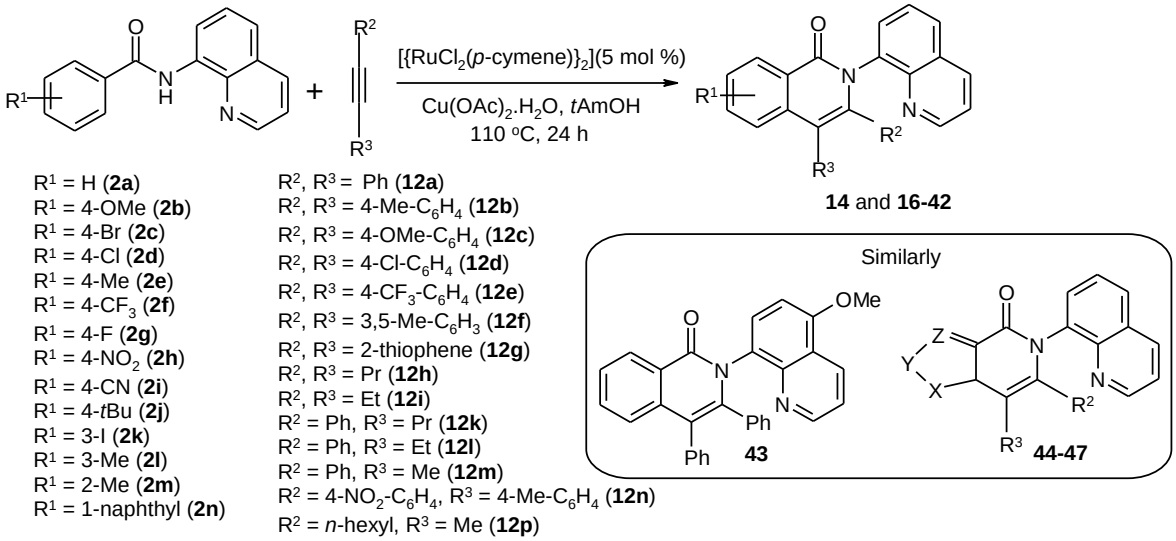
3 **12a** **15** (11%)

With the optimized conditions in hand, we investigated the substrate scope with *N*-quinolin-8-yl-benzamides (**2a-s**) and a variety of internal alkynes (**12a-i, 12k-n** and **12p**). Gratifyingly, in all the cases, good to excellent yields of the isoquinolone products were obtained (Scheme 10, Table 2, compounds **14** and **16-47**). The reaction worked well with both electron-rich (4-Me, 4-OMe, 3,5-Me) and electron-deficient (4-Cl, 4-CF_3) symmetrical arylalkynes, affording the isoquinolone derivatives (**16-20**) in 66-79%

yields. Heteroaryl alkyne **12g** was tolerated under the catalytic conditions, and the corresponding isoquinolone **21** was formed in good yield (63%). It was also found that dialkylacetylenes (**12h** and **12i**) reacted smoothly with amide **2a**. When the reaction was performed with 4-octyne or 3-hexyne, the corresponding oxidative cycloaddition products [**22**, **23** (X-ray)] were obtained in good yields (60%, 63%). When unsymmetrical phenyl(alkyl) alkynes were used, interestingly, only one isomer was obtained in a highly *regioselective* manner. Thus, the reaction of amide **2a** with alkynes 1-phenyl-1-pentyne (**12k**), 1-phenyl-1-butyne (**12l**) or 1-phenyl-1-propyne (**12m**) afforded the products **24-26**, which contain the C-aryl carbon adjacent to amide nitrogen, in good yields (62-72%). The regioselectivity of the product was further confirmed by X-ray crystallography for compound **26**. These results suggest that there might be pi-pi stacking, directing the observed regioselectivity in the products. However, the selectivity was less significant when 1-(4-nitrophenyl)-2-(4-tolyl)acetylene (**12n**) was used; the major isomer (**27**; X-ray), though, was the one with the C-nitrophenyl group adjacent to amide nitrogen. In the case of unsymmetrical dialkylacetylene (*n*-hexyl)C≡CMe (**12p**), isomeric products (**29**) in the ratio 7:3 were observed, thus showing less selectivity. We also attempted reactions using the terminal alkyne, 1-phenylacetylene. However, in this case, only dialkyne product was obtained by self-coupling. Substituted benzamides (**2b-o**) with diphenylacetylene (**12a**) behaved similarly to afford the isoquinolones **30-43** in good yields (61-78%). This oxidative annulation process took place in a highly regioselective manner when we used *meta*-substituted amides. Thus, the reactions of *meta*-iodo or methyl substituted amides (**2k**, **2l**) reacted smoothly with diphenylacetylene and gave the isoquinolones **39-40** as single regioisomers, in which the less hindered C-H bond was functionalized. The reaction also worked well with *ortho*-substituted amide **2m** or naphthylamide **2n** affording the products **41** (73%) or **42** (64%) in excellent yield. Substitution at the 5-OMe substituted *N*-quinolin-8-yl-benzamide **2o** also gave good yield of the corresponding isoquinolone **43**. Extension of this oxidative annulation process to heteroarylamides (**2p-s**) was successful. Thus, 3-thiopheneamide reacted smoothly with alkyne **12a** and furnished the cyclized product **44** in a regioselective manner. Here, the C-H functionalization occurred at the more active 2-position of the thiophene. The 2-substituted heteroamides

(thiophenyl, furanyl and indolyl) also reacted well with alkyne and gave the isoquinolone derivatives **45-47** in decent yields (51-61%).

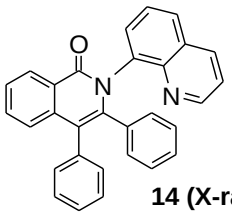
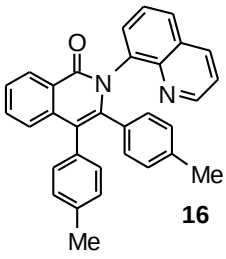
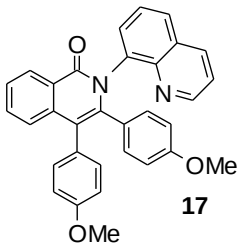
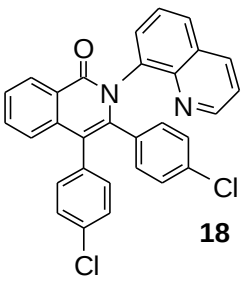
Scheme 10

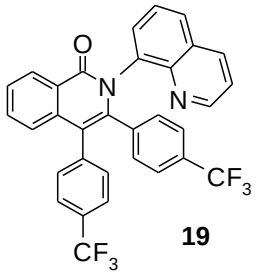
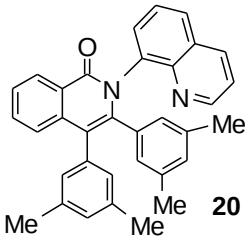
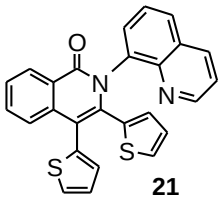
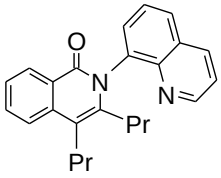
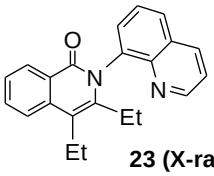
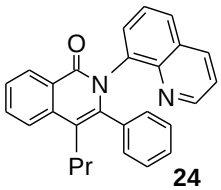
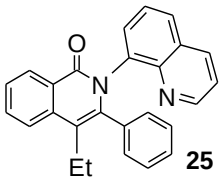
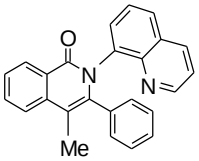
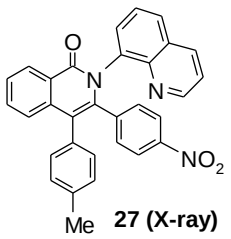
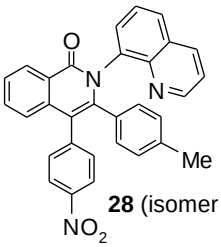
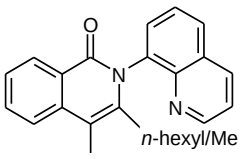


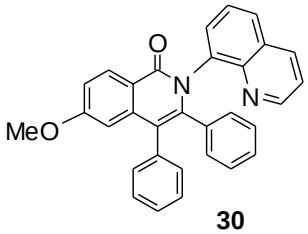
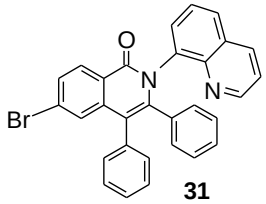
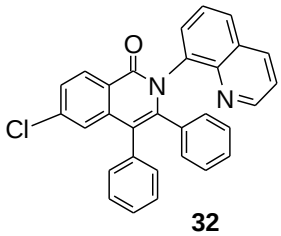
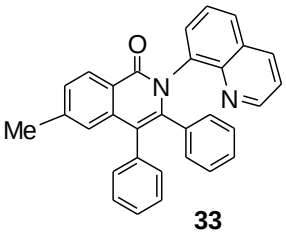
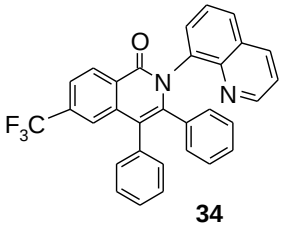
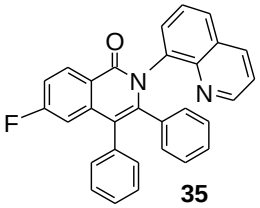
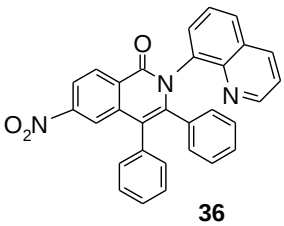
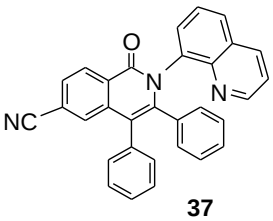
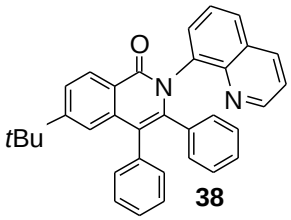
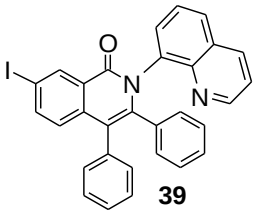
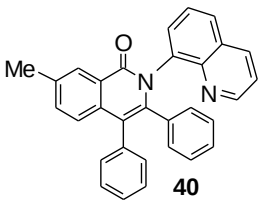
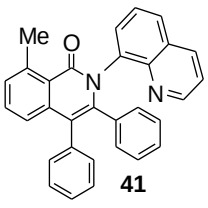
R^1 = H (**2a**)
R^1 = 4-OMe (**2b**)
R^1 = 4-Br (**2c**)
R^1 = 4-Cl (**2d**)
R^1 = 4-Me (**2e**)
R^1 = 4-CF_3 (**2f**)
R^1 = 4-F (**2g**)
R^1 = 4-NO_2 (**2h**)
R^1 = 4-CN (**2i**)
R^1 = 4-*t*Bu (**2j**)
R^1 = 3-I (**2k**)
R^1 = 3-Me (**2l**)
R^1 = 2-Me (**2m**)
R^1 = 1-naphthyl (**2n**)

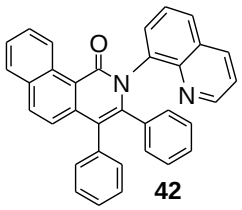
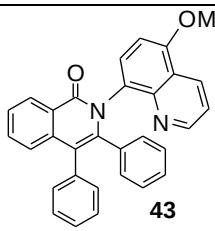
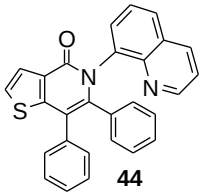
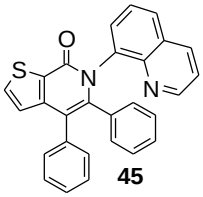
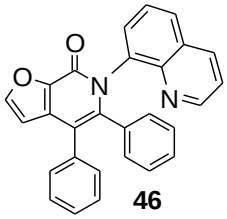
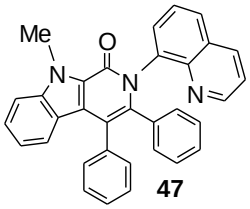
R^2, R^3 = Ph (**12a**)
R^2, R^3 = 4-Me-C_6H_4 (**12b**)
R^2, R^3 = 4-OMe-C_6H_4 (**12c**)
R^2, R^3 = 4-Cl-C_6H_4 (**12d**)
R^2, R^3 = 4-CF_3-C_6H_4 (**12e**)
R^2, R^3 = 3,5-Me-C_6H_3 (**12f**)
R^2, R^3 = 2-thiophene (**12g**)
R^2, R^3 = Pr (**12h**)
R^2, R^3 = Et (**12i**)
R^2 = Ph, R^3 = Pr (**12k**)
R^2 = Ph, R^3 = Et (**12l**)
R^2 = Ph, R^3 = Me (**12m**)
R^2 = 4-NO_2-C_6H_4, R^3 = 4-Me-C_6H_4 (**12n**)
R^2 = *n*-hexyl, R^3 = Me (**12p**)

Table 2. Substituted isoquinolones synthesized in this study by C-H functionalization[a]

Product	Yield (%)[b]		Product	Yield (%)[b]
 **14 (X-ray)**	74		 **16**	70
 **17**	71		 **18**	79

 **19**	66		 **20**	72
 **21**	63		 **22**	60
 **23 (X-ray)**	63		 **24**	72
 **25**	62		 **26 (X-ray)**	62
 **27 (X-ray)**	34[c] [64% including **28**]		 **28** (isomer of **26**)	28[c] [64% including **27**]
 Me/*n*-hexyl **29** (isomer ratio ~ 7:3)	61			

 **30**	71		 **31**	68
 **32**	78		 **33**	74
 **34**	65		 **35**	71
 **36**	72		 **37**	72
 **38**	74		 **39**	61
 **40**	67		 **41**	73

 **42**	64		 **43**	64
 **44**	62		 **45**	51
 **46**	56		 **47**	61

[a]Reaction conditions: amide (0.4 mmol), alkyne (0.8 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %)/ $Cu(OAc)_2 \cdot H_2O$ (0.8 mmol), *t*AmOH (2 mL), 110 ^oC (oil bath temperature), in open air, 24 h. [b]Isolated yield. [c]Combined yield (**26**+ **27**).

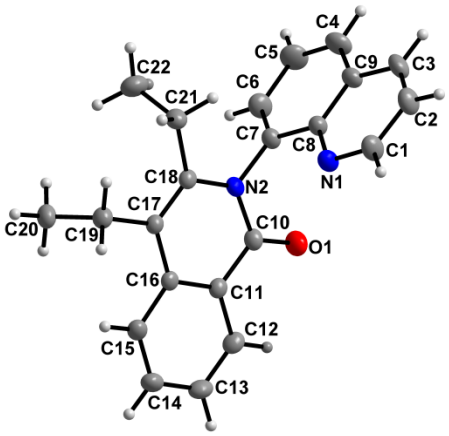


Figure 2. Molecular structure of compound **23**. Selected bond lengths [Å] with esd's in parentheses: N(2)-C(10) 1.375(2), O(1)-C(10) 1.216(2), C(11)-C(10) 1.447(2), C(17)-C(16) 1.439(2), C(17)-C(18) 1.344(2), N(2)-C(18) 1.398(2).

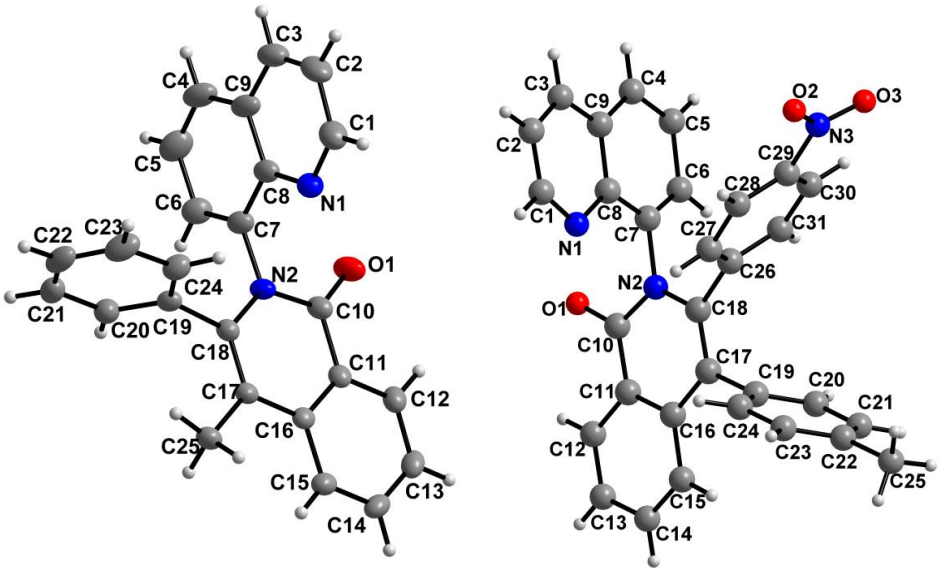


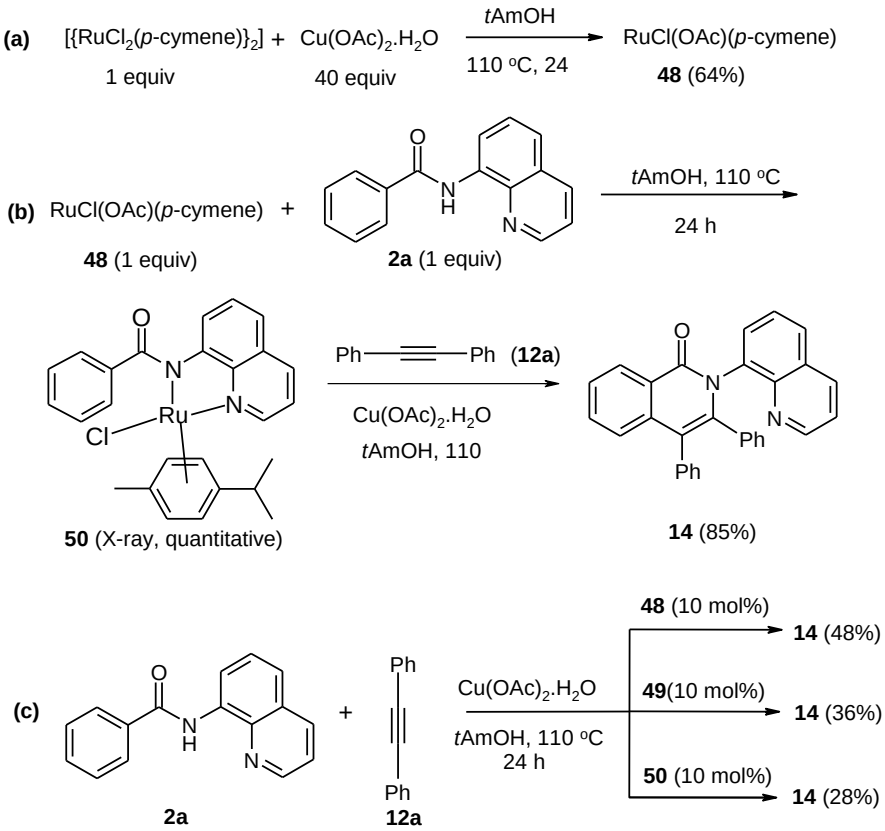
Figure 3. Left: Molecular structure of compound **26**. Selected bond lengths [Å] with esd's in parentheses: N(2)-C(10) 1.3837(19), O(1)-C(10) 1.2214(18), C(11)-C(10) 1.465(2), C(17)-C(16) 1.444(2), C(17)-C(18) 1.353(2), N(2)-C(18) 1.4006(18). **Right:** Molecular structure of compound **27**. Selected bond lengths [Å] with esd's in parentheses: N(2)-C(18) 1.398(5), C(17)-C(18) 1.346(5), C(17)-C(16) 1.444(5), C(11)-C(10) 1.450(5), O(1)-C(10) 1.225(4), N(2)-C(10) 1.380(4).

2.5.2 What are the intermediates?

For more information on the reaction pathway, we have conducted some step by step reactions (Scheme 11). The reaction of [{$RuCl_2$(*p*-cymene)}$_2$] (1.0 equiv) with $Cu(OAc)_2.H_2O$ (40.0 equiv) under reflux conditions in *t*AmOH afforded the monoacetate complex [RuCl(OAc)(*p*-cymene)] (**48**) and not the bis(acetate) complex [$Ru(OAc)_2$(*p*-cymene)] (**49**) (Scheme 11a). Previously, Požgana and Dixneuf had prepared the latter complex by reacting [{$RuCl_2$(*p*-cymene)}$_2$] with 4 mol equiv of KOAc in NMP.[105] Thus, there appears to be difference in the reactivity of [{$RuCl_2$(*p*-cymene)}$_2$] under these two conditions. In a further step, the reaction between the monoacetate complex **48** with an equimolar quantity of amide **2a** in stoichiometric amounts in *t*AmOH under reflux conditions yielded the ruthenium complex **50** in quantitative yield (Scheme 11b). The same complex **50** was also obtained by treating the *N*-quinolin-8-yl-benzamide **2a** with {$RuCl_2$(*p*-cymene)}$_2$ albeit in 52% yield; the

yield was better in the presence of NaOAc. In this complex **50**, ruthenium is coordinated to the *N*-quinolin-8-yl-benzamidyl moiety in a *N*,*N*-fashion. There was no indication to suggest the replacement of second chlorine by acetate under these conditions or even after 36 h. Treatment of chloro ligated ruthenium complex **50** with $Cu(OAc)_2.H_2O$ in *t*AmOH resulted in some unidentified products, but in the presence of stoichiometric amount of alkyne **12a**, it directly afforded the isoquinolone derivative **14** in 85% yield. In the absence of $Cu(OAc)_2.H_2O$ this annulation reaction did not proceed. However, we found that use of **50** (10 mol %) as a catalyst did not perform that well and only ca 28% yield of the product was obtained. It should be noted here that in both cases, the amount of ruthenium metal was the same. We have also checked the catalytic activity of the mono and bis-acetate ruthenium complexes. Both of these complexes showed very poor activity and resulted in low yields of **14** (Scheme 11c). Similar reactions using 2-pyridinylmethylamine in the presence of $Ni(cod)_2$ as the catalyst has been reported before.[32] The latter catalyst is air-sensitive, while $\{RuCl_2(p\text{-cymene})\}_2$ is air-stable. Thus, the reaction using $Ni(cod)_2$ had to be conducted in a glove box while our ruthenium catalyzed reaction could be conducted in open air.

Scheme 11



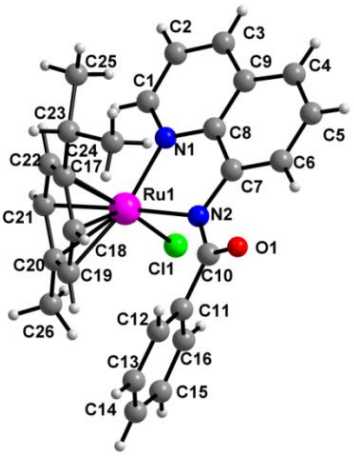
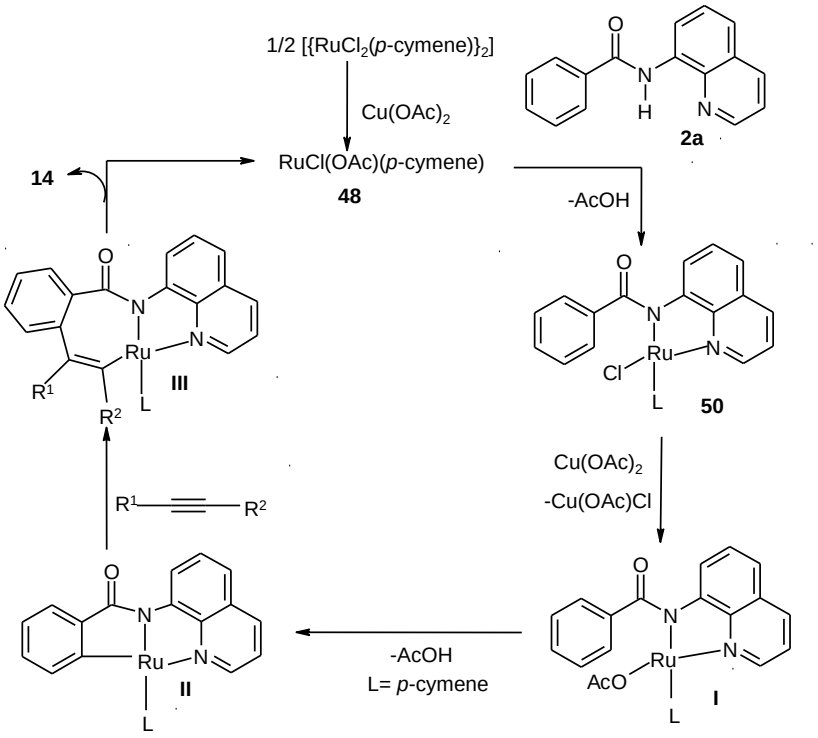


Figure 4. Molecular structure of compound **50.** Selected bond lengths [Å] with esd's in parentheses: Ru(1)-N(1) 2.064(4), Ru(1)-N(2) 2.134(4), N(2)-C(10) 1.362(7), N(2)-C(7) 1.405(6), O(1)-C(10) 1.227(7), Ru(1)-Cl(1) 2.4203(13).

2.5.3 Mechanistic pathway for the formation of isoquinolone derivatives

On the basis of the above experiments and previous mechanistic insight,[24a, 106] we propose a plausible reaction pathway shown in Scheme 12. First, [$RuCl_2$(*p*-cymene)]$_2$ undergoes ligand exchange with $Cu(OAc)_2$ to give the mono-acetate species RuCl(OAc)(*p*-cymene) (**48**), which undergoes coordination of nitrogen atom of the quinoline moiety and substitution of acetate with the amine NH giving the metal complex **50**. Then, in the presence of $Cu(OAc)_2$ and alkyne, complex **50** undergoes ligand exchange with the acetate ion to lead to (**I**). This is followed by C-H activation through the elimination of AcOH, forming the five membered metallacycle intermediate **II**. The oxidative addition of alkyne to **II** generates the intermediate **III**. Then reductive elimination gives compound **14** and the active catalyst is regenerated. The only disconcerting point here is that on its own, **50** is not very active as a catalytic intermediate.

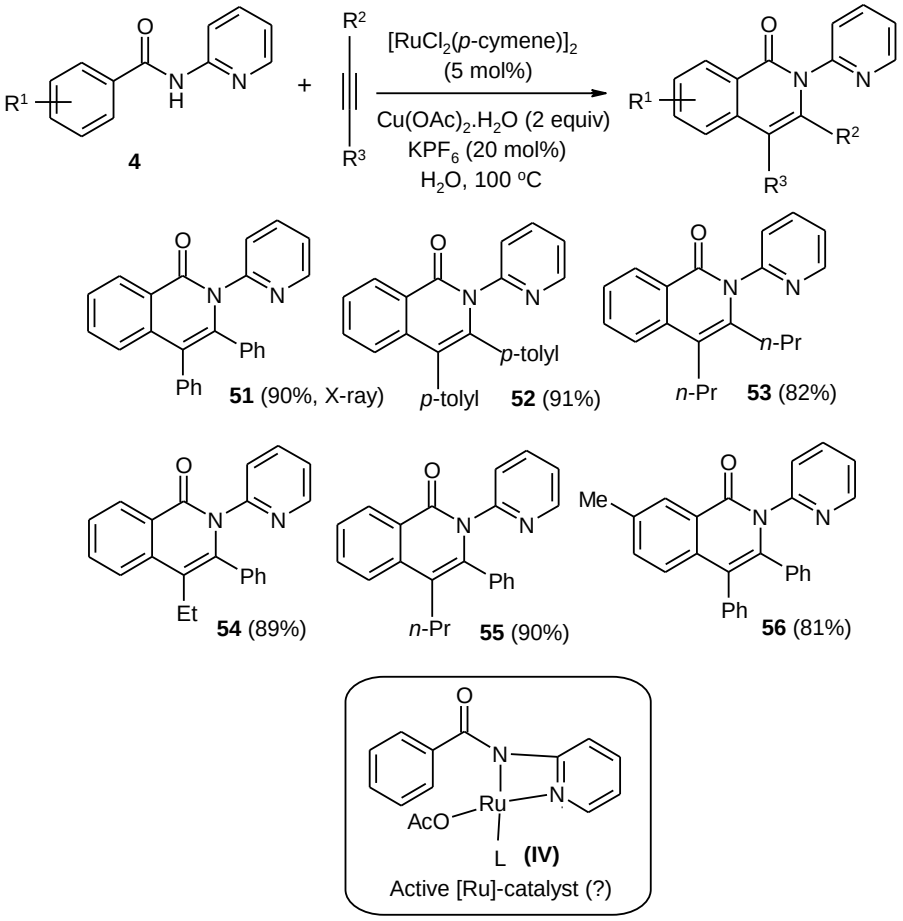
Scheme 12



2.5.4 Synthesis of N-(2-pyridinyl)isoquinolones on water

Similar to quinoline substituted isoquinolones, it should be possible to synthesize *N*-(2-pyridinyl)isoquinolones by treating *N*-(2-pyridinyl)benzamides with internal alkynes in the presence of $[RuCl_2(p\text{-cymene})]_2$ as a catalyst and $Cu(OAc)_2.H_2O$ as an oxidant. The main difference between this system and the previous one is that instead of the 5-membered chelate ring, there may be a 4-membered chelate ring in the active form of the catalyst (cf. structure **IV**). We have isolated the pyridyl substituted isoquinolone derivative **51** in 72% yield. This compound was characterized by IR, NMR and HRMS data; its structure was further confirmed by X-ray crystallography (Figure 5). We then proceeded to optimize the catalytic conditions to get the maximum yield of the product. After survey of several conditions by varying the oxidant and solvent, we obtained the maximum yield of the product on water, by using KPF_6 an additive along with $[RuCl_2(p\text{-cymene})]_2/Cu(OAc)_2.H_2O$ system. Using this protocol, we could isolate the isoquinolone derivative **51** in 90 % yield. With the optimized conditions in our hand, we further examined the substrate scope by varying the benzamide derivatives and alkyne substituents (Scheme 13). In all the cases, excellent yields of the isoquinolone derivatives were obtained. The reaction worked well with dialkyl alkyne **12h** also. The annulation reaction with unsymmetrical alkynes proceeded in a highly regioselective manner and gave the isoquinolone derivatives **54** and **55** as a single regioisomer. The scope of the cyclization reaction was also examined with *meta*-substituted benzamide **4b**. The reaction of **4b** with diphenyl acetylene afforded the isoquinolone **56** with excellent yield and high regioselectivity. In this case, C-H functionalization occurs at the sterically more accessible position.

Scheme 13



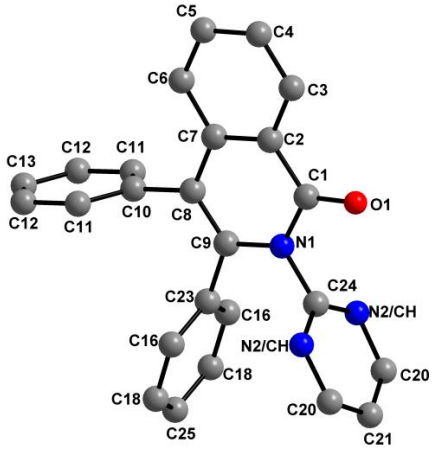


Figure 5. Molecular structure of compound **51.** Selected bond lengths [Å] with esd's in parentheses: C(7)-C(8) 1.437(4), C(8)-C(9) 1.351(4), N(1)-C(9) 1.397(3), O(1)-C(1) 1.221(4), N(1)-C(1) 1.384(4). Hydrogen atoms are omitted for clarity.

2.5.5 Synthesis of indole substituted purines/ purine nucleosides

After the synthesis of isoquinolone derivatives using 8-aminoquinoline as the directing group, we aimed for the synthesis of indole derivatives by using intrinsic directing group nature of purine. For this, we have synthesized 6-anilinopurines **6a-u** and 6-anilinopurine nucleosides **9a-b** (cf. Schemes 3-4 above). To achieve indole synthesis, we initiated our studies with the oxidative annulation of 9-benzyl-*N*-phenyl-9-H-purin-6-amine (**6a**) with diphenylacetylene (**12a**). We screened various additives and solvents with $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and the results are summarized in Table 3 and Scheme 14. To our delight, in the reaction of **6a** with **12a** in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), and NaOAc (30 mol %) as an additive in MeOH at 70 ^oC, the expected indole substituted purine **57** was obtained in 62% yield (entry 1). Encouraged by this, we screened other additives KOAc, CsOAc, $Cu(OAc)_2.H_2O$ and AcOH. Among these, CsOAc was the most effective for the annulation (entries 2-5). In this case, we isolated compound **57** in 85% yield. The structure of the compound **57** was confirmed by X-ray crystallography (Figure 6). Other solvents like DCE, CH_3CN, H_2O, or *t*AmOH (entries 6-9) were ineffective. Notably, the oxidative annulation reaction proceeded smoothly under ambient air also (entry 10). Increasing the additive loading from 30 mol % to 2 equiv did not improve the yield of **57** (entry 11). It is significant to note that in the absence of additive also the annulation reaction proceeded and product **57** was isolated in 68% yield (entry 12). Reducing the amount of catalyst or alkyne led to lower conversion to **57** (entries 13 and 14). Among other ruthenium complexes like $Ru(OAc)_2(p\text{-cymene})$ and $CpRuCl(PPh_3)_2$, only $Ru(OAc)_2(p\text{-cymene})$ was effective and compound **57** was obtained in 81% yield (entries 15 and 16). Overall, the optimal reaction conditions for the oxidative annulation were: $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) as the catalyst, CsOAc (30 mol %) as an additive in MeOH (2 mL) at 70 ^oC for 24 h under ambient air.

Scheme 14

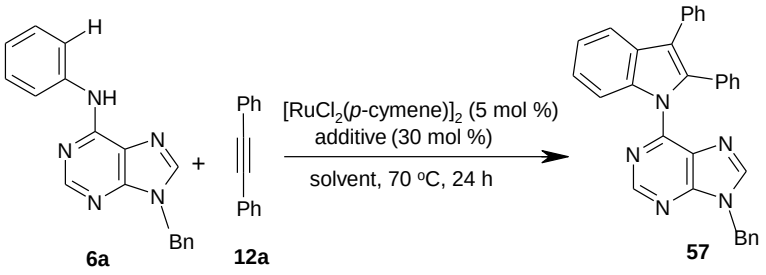


Table 3. Optimization study for the ruthenium-catalyzed oxidative annulation[a]

Entry	Additive	Solvent	Yield (%)[b]
1	NaOAc	MeOH	62
2	KOAc	MeOH	41
3	**CsOAc**	**MeOH**	**85**
4	$Cu(OAc)_2.H_2O$	MeOH	78
5	AcOH	MeOH	44
6	CsOAc	DCE	trace
7	CsOAc	CH_3CN	trace
8	CsOAc	H_2O	ND
9	CsOAc	*t*AmOH	ND
10	CsOAc	MeOH	84[c]
11	CsOAc	MeOH	83[d]
12	-	MeOH	68
13	CsOAc	MeOH	68[e]
14	CsOAc	MeOH	71[f]
15	CsOAc [Catalyst: 10 mol % $Ru(OAc)_2$(*p*-cymene)]	MeOH	81
16	CsOAc (Catalyst: 10 mol % $CpRuCl(PPh_3)_2$)	MeOH	ND

[a]Reaction conditions: **6a** (0.5 mmol), **12a** (1.0 mmol), $[RuCl_2$(*p*-cymene)$]_2$ (5 mol %), additive (30 mol %, to ensure complete consumption of the amine), solvent (2 mL), 70 °C (oil bath), 24 h. [b]Yield of the isolated product; ND = not detected. [c]in open air. [d]2 equiv CsOAc used. [e]2.5 mol % catalyst used. [f]1.5 equiv alkyne used.

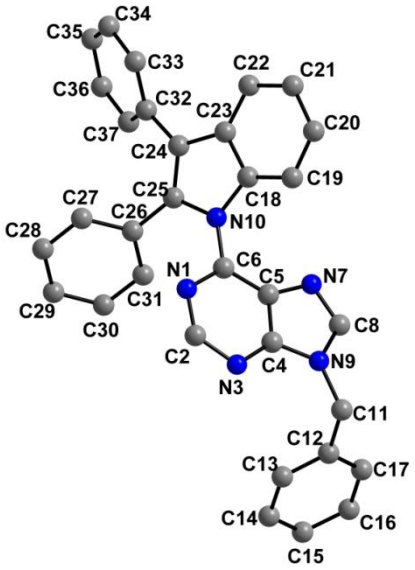


Figure 5. Molecular structure of compound **57**. Selected bond lengths [Å] with esd's in parentheses: N(10)-C(25) 1.408(2), N(10)-C(18) 1.399(2), C(24)-C(23) 1.444(3), C(24)-C(25) 1.375(3), N(10)-C(6) 1.413(2), C(18)-C(23) 1.398(3). Hydrogen atoms are omitted for clarity.

With the optimized reaction conditions in hand, we investigated the scope of this ruthenium-catalyzed oxidative annulation protocol with respect to the 6-anilinopurines **6** and alkynes **12** (Scheme 15). Both electron-rich and electron-deficient alkynes (**12a-f**) successfully coupled with **6a** to give excellent yields (80-85%) of the indole derivatives **57-62**. Alkyl or hetero-aryl substituted alkyne also gave the corresponding indole derivative (**63-66**) in good yield. We were pleased to find that the annulation reaction of **6a** with unsymmetrical aryl-alkyl alkynes **12k-12m** afforded the indole derivatives **67-69** in good yields (79-81%) with excellent regioselectivity. As expected, the regioselectivity was poor when the reaction was performed with unsymmetrical aryl-aryl (**12n, 12o**) and alky-alkyl (**12p**) alkynes, but the overall yields were good. Amines bearing electron donating or electron withdrawing substituents at *para*, *meta* or *ortho* positions reacted smoothly with diphenylacetylene **12a** and furnished the purine derivatives (**73-81**) in good to excellent yields. The bromo and chloro substituted indole derivatives **75** and **76** thus prepared are synthetically useful for

further elaboration. Introduction of strong withdrawing -CF_3 group at the *para*-position of the phenyl ring also led smoothly to the product **78** in excellent yield of 90%. In the case of cyclized products **79** and **80**, the reaction preferentially occurred at the less hindered site of the aminopurine precursor. Introduction of substituent at *ortho*-position of the aniline **6j**, also gave the coupled product (**81**) in an excellent yield of 92%. Substrates with protecting groups (PG) *n*-Bu, *i*-Pr, Ph, allyl, and tetrahydrofurfuryl afforded the oxidative cyclized products **82-86** in good yields. It is satisfying to note that the tolerance of the double bond in the formation of cyclized product (**85**) enhances the utility of this protocol.

Scheme 15

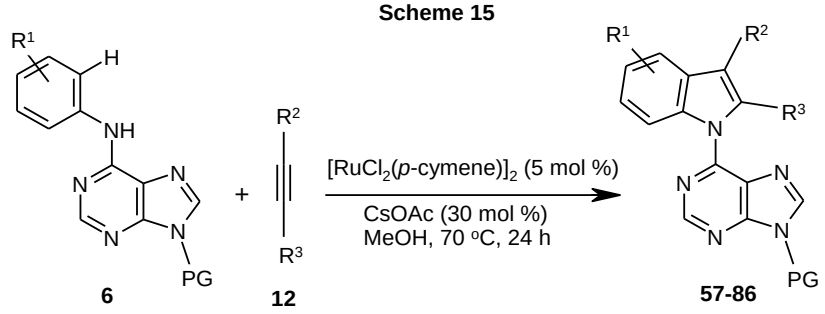
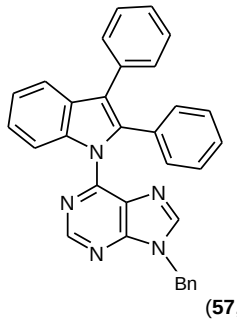
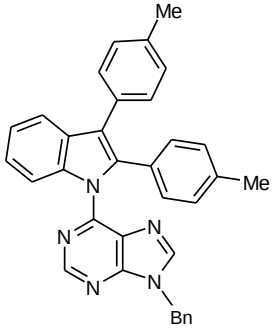
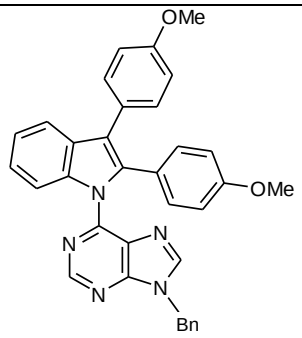
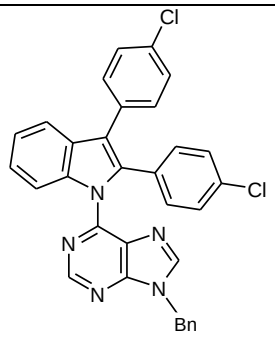
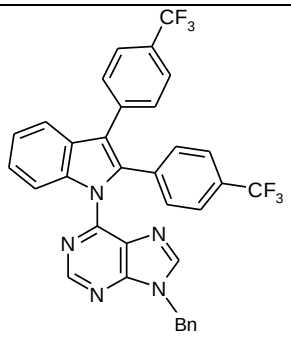
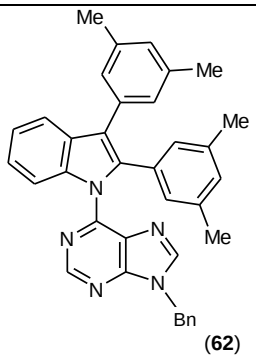
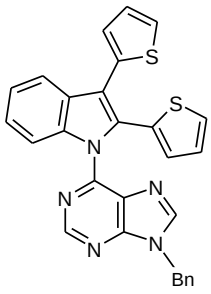
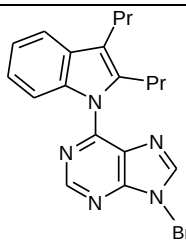
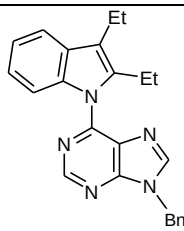
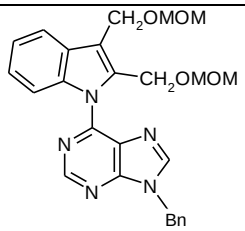
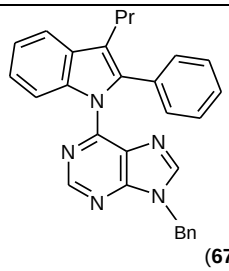
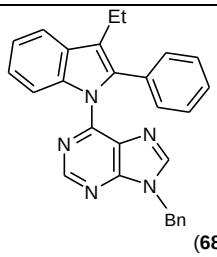
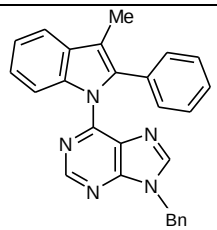
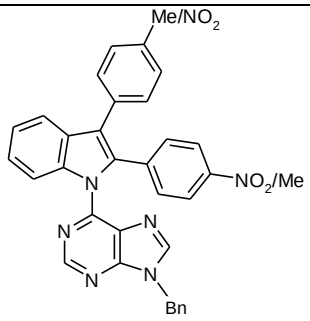
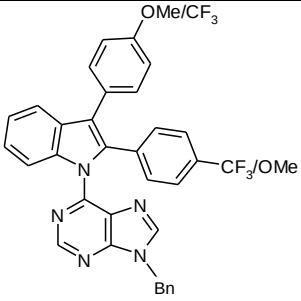
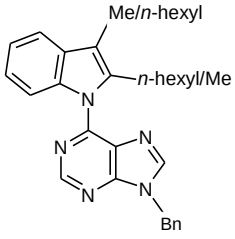
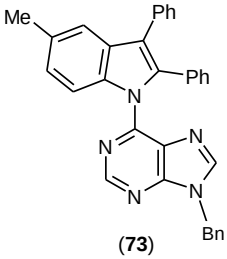
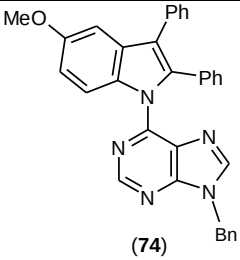
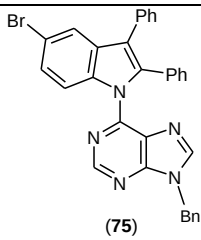
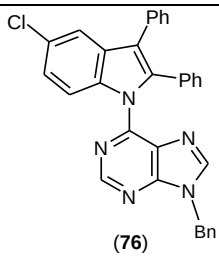
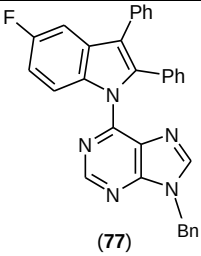
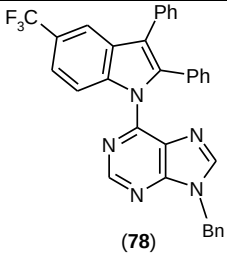
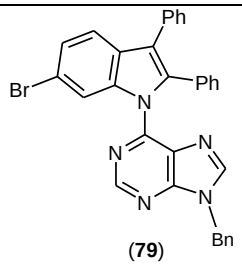
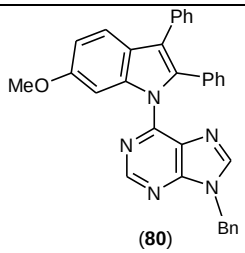
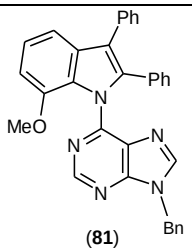
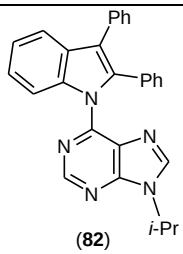
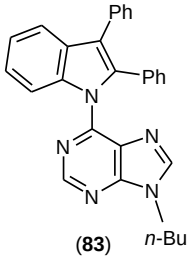
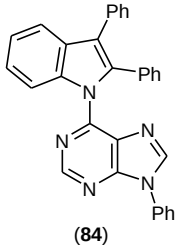
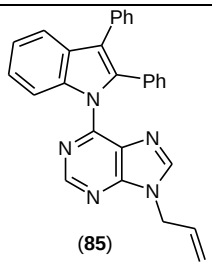
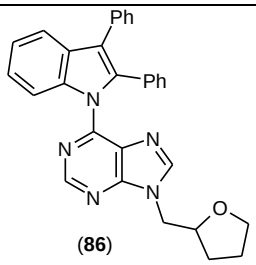


Table 4. [Ru]-Catalyzed reactions of 6-anilinopurines with internal alkynes- Synthesis of indole derivatives **57-86**[a]

Product	Yield (%)[b]		Product	Yield (%)[b]
 (**57**, **X-ray**)	85		 (**58**)	82

 (**59**)	84		 (**60**)	80
 (**61**)	81		 (**62**)	82
 (**63**)	61		 (**64**)	79
 (**65**)	73		 (**66**)	54
 (**67**)	79 (10:0.08)[c,d]		 (**68**)	79 (10:0.08)[c,d]

 (**69, X-ray**)	81 (10:1)[c,d]		 (**70**)	67 (10:9)[c]
 (**71**)	76 (2:1)[c]		 (**72**)	64 (10:8)[c]
 (**73**)	87		 (**74**)	84
 (**75**)	92		 (**76**)	80
 (**77**)	89		 (**78**)	90

 (**79**)	80		 (**80**)	89
 (**81**)	92		 (**82**)	78
 (**83**)	86		 (**84**)	73
 (**85**)	74		 (**86**)	84

[a]Reaction conditions: amine (0.5 mmol), alkyne (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %)/ CsOAc (30 mol %), MeOH (2 mL), 70 ^oC (oil bath temperature), in open air, 24 h. [b]Isolated yield, [c]isomer ratio, [d]structure shown was the major isomer.

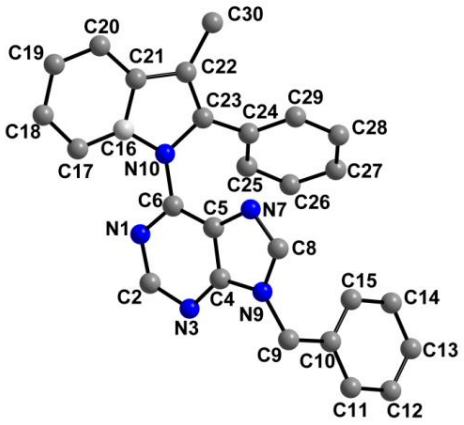
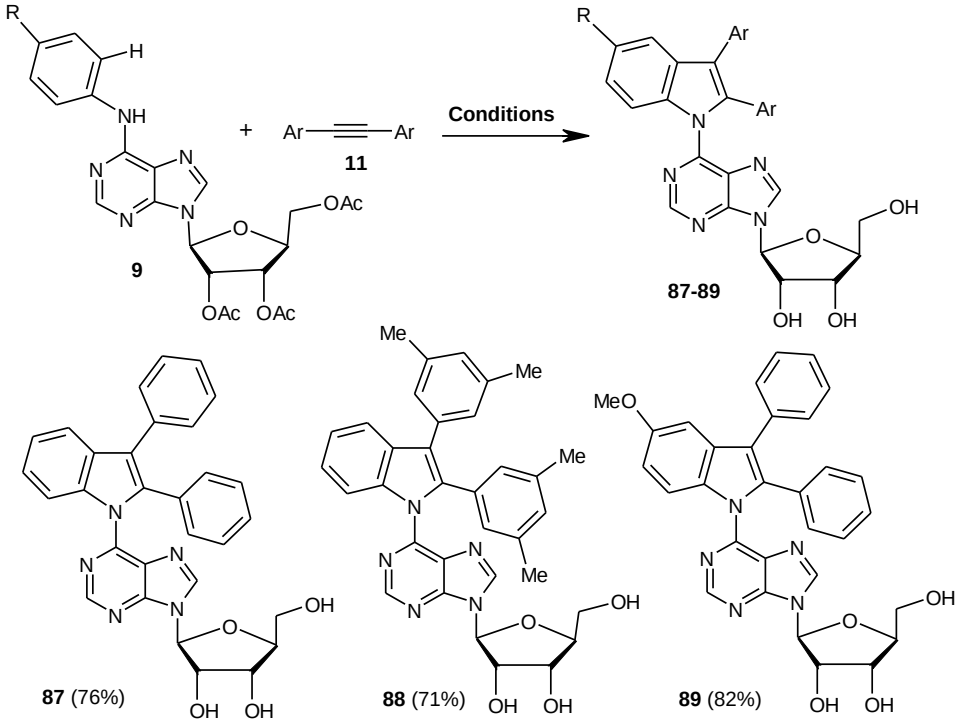


Figure 7. Molecular structure of **69**. Selected bond lengths [Å] with esd's in parentheses: N10)-C(16) 1.392(2), N(10)-C(23) 1.410(2), C(22)-C(23) 1.361(3), C(22)-C(21) 1.431(3), C(16)-C(21) 1.401(3), N(10)-C(6) 1.406(2). Hydrogen atoms are omitted for clarity.

2.5.6 Oxidative cyclization with 6-anilinopurine nucleosides

Next, we examined the general utility of these C-H bond activation conditions on nucleosides **9a** and **9b** (Scheme 16). First we treated nucleoside **9a** with alkyne **12a** under the same catalytic conditions (5 mol % catalyst, 30 mol % CsOAc, 24 h). We observed partial hydrolysis of the ester group in the corresponding indole derivative. Then we increased the CsOAc loading to 3 equiv, and isolated the indole substituted purine nucleoside **87** with the free hydroxyl groups in the sugar moiety in good yield. This reduces the burden of further deprotection of the saccharide. We have also synthesized two more indole nucleosides **88** and **89** in good yields using the same catalytic conditions. Thus, our protocol is valuable in the case of nucleosides also.

Scheme 16



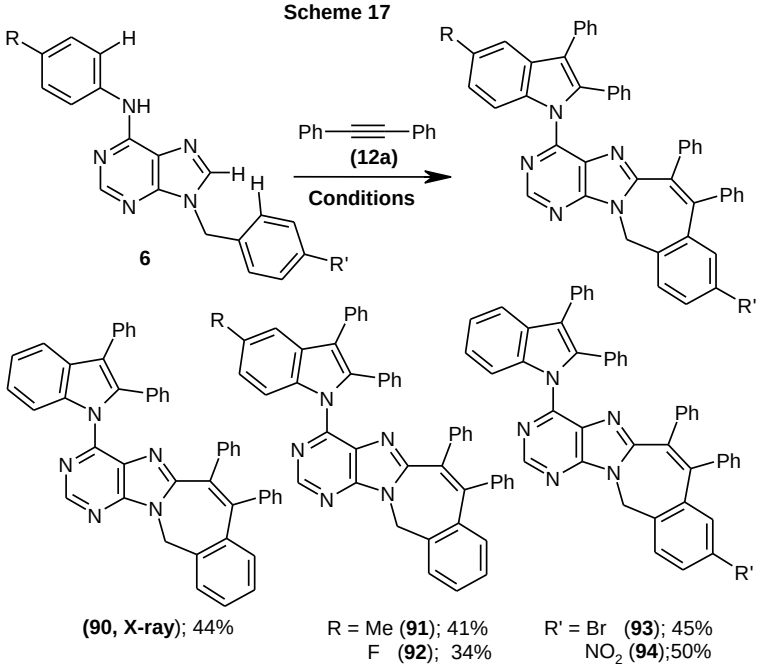
Conditions: **9** (0.3 mmol), **12** (0.6 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), CsOAc (3 equiv), MeOH (2 mL), 70 °C (oil bath), 36 h, ambient air.

2.5.7 Annulation reactions of 9-benzyl-6-anilinopurines in the presence of $Cu(OAc)_2.H_2O$ involving two-fold C-H activation

We accidentally found a ***two-fold C-H activation*** product **90** (X-ray) along with the indole derivative **57**, when we treated 9-benzyl-6-anilinopurine **6a** with alkyne **12a** in the presence of $Cu(OAc)_2 \cdot H_2O$/ CsOAc (Scheme 17). Compounds **91-94** were prepared similarly. The corresponding mono-activated products were also present, but the double-annulated products **90-94** could be isolated. In the case of other substrates, the yield of the bis-product was low/ negligible. N9-phenyl and N9-allyl-6-anilinopurines under the same catalytic conditions gave only mono-annulated products (**84** and **85**), no double annulated product was observed even by using a large excess (5 fold) of the alkyne. This observation suggests that flexibility of the benzyl group as well as the reactivity of the $C(sp^2)$-H may also be important. In the case of N9-benzyl substituents bearing electron-donating groups like -OMe or -Me, we ended up in only mono-annulated product with no two-fold C-H activation product (Scheme 18). We have also tried this double annulation reaction with an excess of di-*p*-tolylacetylene

(**12b**) as well as dialkyl acetylenes **12h** and **12i**, but in all these cases we isolated only mono-annulated products. This feature suggests that the overall length of the alkyne moiety and the low reactivity of dialkyl-substituted alkynes may not favor the second annulation. Thus, benzyl substituents bearing electron-withdrawing groups (Br/NO_2) appear to favor the second annulation reaction. So far the yields are only moderate even at somewhat higher temperatures (100 ^oC) or by using an excess of the alkyne (5 equiv). Although these products are obtained alongside the single C-H activation products, the fact that they are formed despite the absence of a suitable coordinating atom close to the phenyl moiety raises interesting possibilities for C-H activation. To the best of our knowledge, there are no such annulation reports in the ruthenium–catalyzed synthesis of higher-order nitrogen-containing C8 fused purine heterocycles, although C8-arylation as well as intramolecular cyclization utilizing C(8)-H and the *ortho*-aryl C-H of the N9-benzyl group catalyzed by other metal complexes are known.[107] In the absence of $[RuCl_2(p\text{-cymene})]_2$ or $Cu(OAc)_2.H_2O$ there was no C8-annulation. It is likely that the ruthenium complex is involved in metalation and $Cu(OAc)_2.H_2O$ acts as the oxidant in this reaction. Increase of alkyne amount from 3 equiv to 5 equiv or/and temperature from 70 ^oC to 100 ^oC did not improve the yield of the bis-annulated product. The yield could not be increased either when monoannulated derivative **57** instead of purine **6a** was used. Other polar solvents like hexafluoroisopropanol (HFIP) or trifluoroethanol (TFE) led to only traces of the product. An additional point of interest is that they are fluorescence active (Figure 9).

Scheme 17



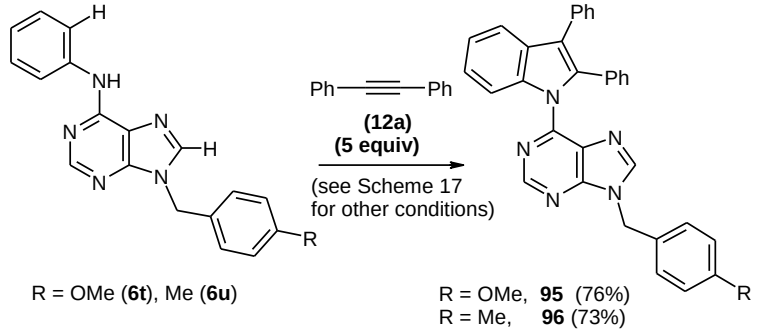
(90, X-ray); 44%

R = Me (**91**); 41%
F (**92**); 34%

R' = Br (**93**); 45%
NO_2 (**94**);50%

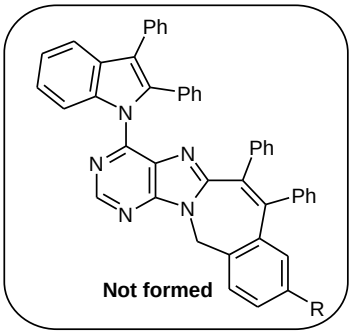
Conditions: **6** (0.5 mmol), **12a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), CsOAc (30 mol %), $Cu(OAc)_2.H_2O$ (2 equiv), MeOH (3 mL), 70 °C (oil bath), 36 h, air.

Scheme 18



R = OMe (**6t**), Me (**6u**)

R = OMe, **95** (76%)
R = Me, **96** (73%)



Not formed

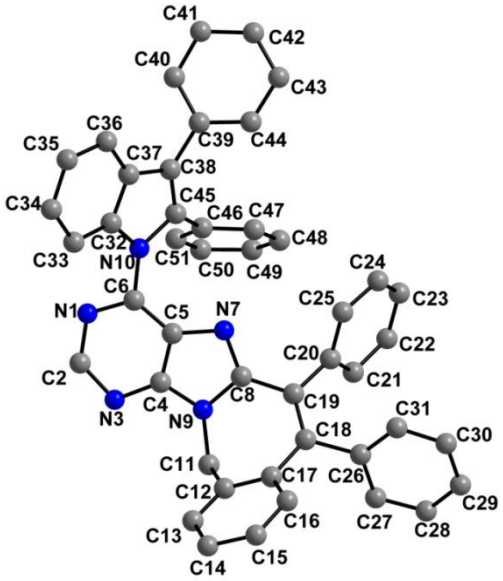


Figure 8. Molecular structure of compound **90**. Selected bond lengths [Å] with esd's in parentheses: N(10)-C(45) 1.419(13), C(38)-C(45) 1.326(14), C(38)-C(37) 1.450(15), N(10)-C(6) 1.416(12), C(8)-C(19) 1.463(13), C(19)-C(18) 1.349(14), C(17)-C(18) 1.474(15). Hydrogen atoms are omitted for clarity.

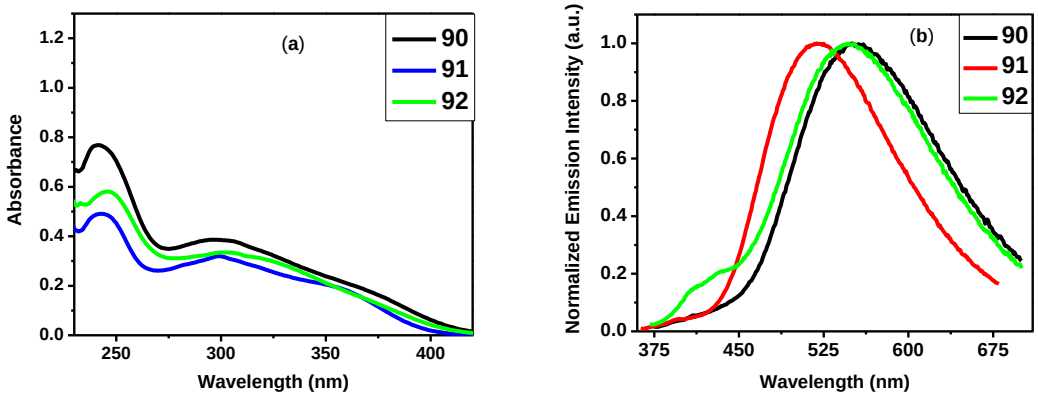


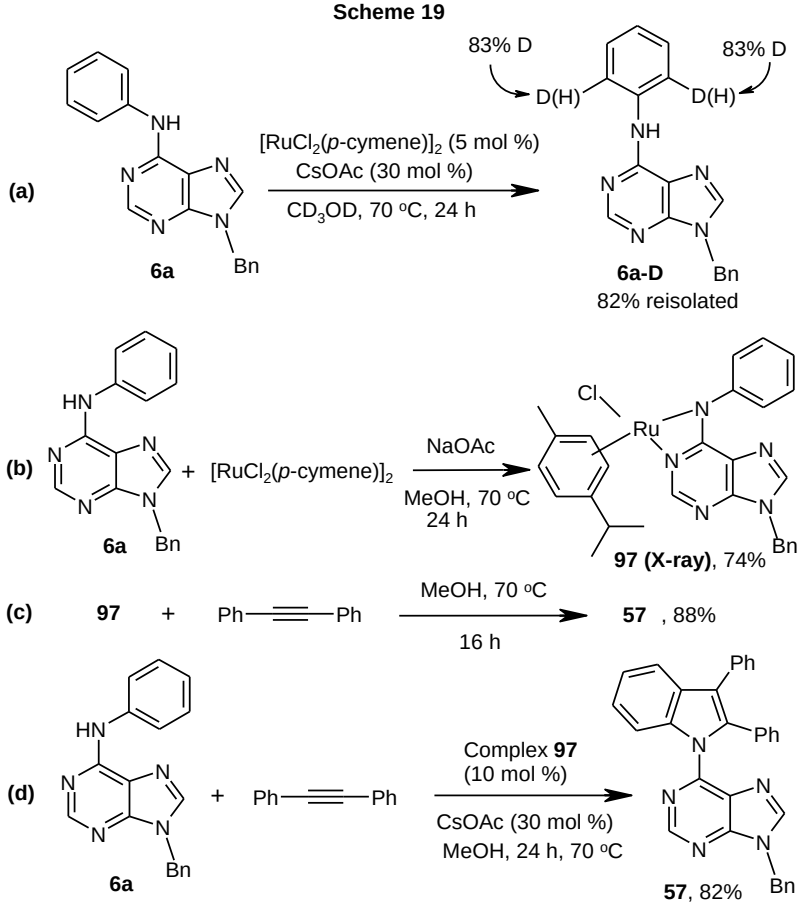
Figure 9. The absorption (a) and fluorescence emission spectra (b) of compounds **90-92** with c = 1.0 x 10^{-5} mol/L in $CHCl_3$, upon excitation at 359, 363 and 353 nm respectively.

2.5.8 Mechanistic studies on CsOAc promoted [Ru]-catalyzed oxidative annulation including H/D exchange

To investigate the mechanistic pathway, the H/D exchange of 9-benzyl-*N*-phenyl-9-H-purin-6-amine (**6a**) was conducted in CD_3OD (Scheme 19a). Notably, 83% deuterium incorporation was observed at the *ortho*-positions of **6a**. This result indicates that *ortho* C-H bond activation is involved and hence H/D exchange from the solvent takes place.

To know more about the reaction pathway, we treated **6a** with $[RuCl_2(p\text{-cymene})]_2$ in the presence of NaOAc in MeOH to obtain the ruthenacycle intermediate **97** (Scheme 19b, Figure 10).[108] The N1 atom of purine is coordinated with the ruthenium metal and forms a four membered ruthenacycle. Treatment of complex **97** with alkyne **12a** in MeOH at 70 ^oC afforded indole appended purine derivative **57** (Scheme 19c) in 88% yield, thus showing that this species is involved in the catalytic process. We then examined the catalytic activity of ruthenacycle **97** by treating **6a** with alkyne **12a** in the presence of CsOAc (30 mol %)/ MeOH. Satisfyingly, we obtained the indole derivative **57** (Scheme 19d) in 82% yield.

Scheme 19



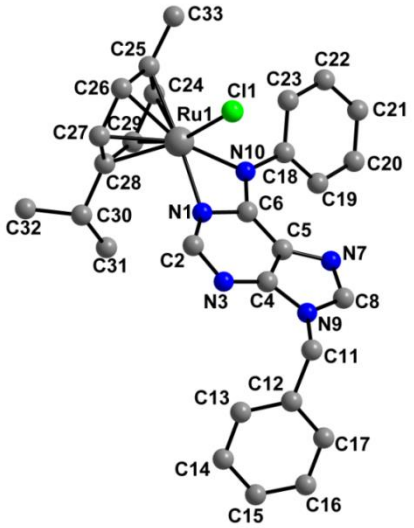
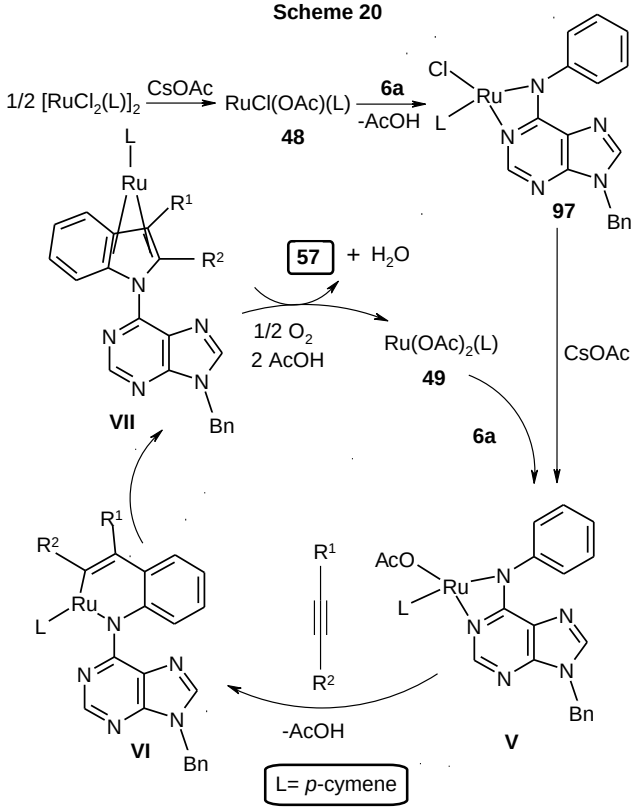


Figure 10. Molecular structure of compound **97.**CH_3CN. Selected bond lengths [Å] with esd's in parentheses: Ru(1)-N(1) 2.094(3), Ru(1)-N(10) 2.108(3), N(10)-C(6) 1.329(4), N(10)-C(18) 1.410(4), Ru(1)-Cl(1) 2.4113(9). Solvent moiety and hydrogen atoms are omitted for clarity.

2.5.9 Plausible mechanistic pathway for the formation of indole derivatives 57-89

On the basis of the above experiments and previous reports on metal catalyzed C-H bond activation,[39a,109] we propose that initially, CsOAc reacts with $[RuCl_2(p\text{-cymene})]_2$ forming RuCl(OAc)(*p*-cymene).[109a] In the present work, this compound is isolated from the reaction of $[RuCl_2(p\text{-cymene})]_2$ with 2 equivalents of CsOAc. Complex RuCl(OAc)(*p*-cymene) (**48)** undergoes coordination with the purine N1 atom and substitution of acetate with the amine NH giving the ruthenacycle **97** (X-ray, Figure 10). This species upon ligand exchange with CsOAc forms the acetate complex **V**. It promotes C-H activation through elimination of AcOH followed by alkyne insertion yielding the 6-membered ruthenacycle **VI** (Scheme 20). Intermediate **VI** undergoes reductive elimination to afford a ruthenium(0) sandwich complex **VII**. This proposition is based on the [Ru]/NaOAc catalyzed annulation reaction of benzoic acids with alkynes reported recently by Ackermann and coworkers.[110] This ruthenium(0) species is reoxidized by molecular oxygen from open air forming the active ruthenium complex **49** by the initially formed AcOH, liberating the indole derivative **57**. The bis-acetate-complex **49** reacts with amine **6a** forming the acetate complex **V**, thus continuing the catalytic cycle.

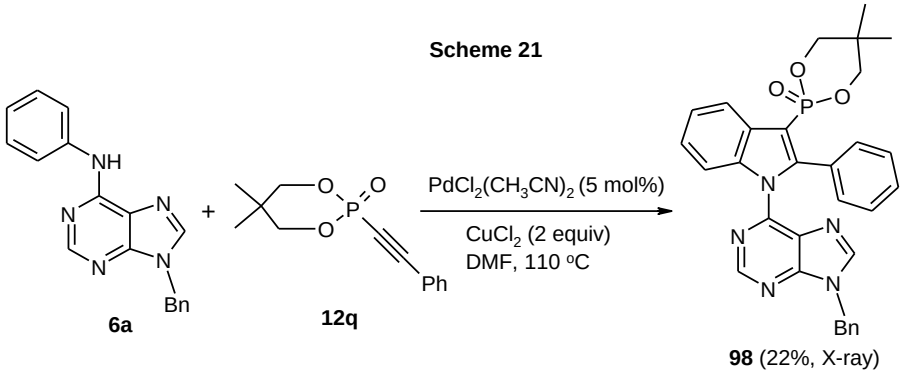
Scheme 20



2.5.10 [Pd]-Catalyzed oxidative annulation of 6-anilinopurine 6a with alkyne 12q

Similar to alkynes **12a-p**, we have tried the reaction of phosphonate substituted alkyne **12q** with 6-anilinopurine **6a** under the above optimized conditions. Disappointingly, under the $[RuCl_2(p\text{-cymene})]_2/Cu(OAc)_2.H_2O$ catalytic system, no reaction was observed and the starting material **6a** remained as such. Because of the importance of nucleobase phosphonates in medicinal chemistry, we attempted further optimization using [Pd]-catalysts. Thus, we have isolated the cyclized product **98** in 22% yield by using $PdCl_2(CH_3CN)_2$ as a catalyst and $CuCl_2$ as an oxidant in DMF (Scheme 21). This compound was characterized by IR, NMR and HRMS data. In the ^{31}P NMR, compound **98** shows a single peak at δ 10.8 which confirms the formation of a single regioisomer. The regiospecificity was further confirmed by using X-ray crystallography (Figure 11). We tried several other conditions by varying the palladium sources, different oxidants including copper and silver salts and solvents, but were not successful in increasing the yield of the product **98**. Hence, we did not proceed further.

Scheme 21



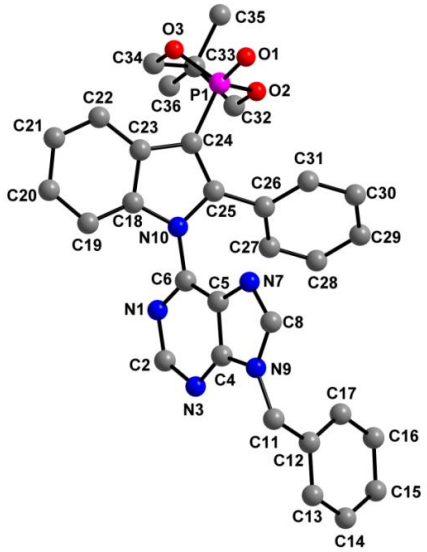


Figure 11. Molecular structure of compound **98**. Selected bond lengths [Å] with esd's in parentheses: C(24)-C(23) 1.436(5), C(24)-C(25) 1.383(4), N(10)-C(25) 1.386(4), P(1)-C(24) 1.778(3), P(1)-O(1) 1.459(3). Hydrogen atoms are omitted for clarity.

2.6 Palladium-catalyzed *ortho*-acylation of 6-anilinopurines

After successful synthesis of indole derivatives using the purine directing group, we envisaged *ortho*-acylation of 6-anilinopurines with aldehydes/*α*-oxocarboxylic acids *via* palladium-catalyzed C-H activation. The results are discussed below. It should be noted that in the normal Friedel-Crafts reaction, amines cannot be used directly and most often a stoichiometric amount of the Lewis acid is required to effect the reaction.

2.6.1 Palladium-catalyzed C(sp^2)-H bond acylation with aldehydes

To achieve *ortho*-acylation, we have used the substrates 6-anilinopurines **6** that were described above. In our first attempt, we performed the reaction of **6a** with 1-heptanal in the presence of $Pd(OAc)_2$ (5 mol %) and TBHP (3 equiv) as an oxidant under neat conditions at 110 ^oC for 24 h. We were happy to find that *ortho*-acylated purine derivative **99** was obtained in 38% isolated yield (Table 5, entry 1). Formation of **99** was suggested by spectroscopic data. In the ^1H NMR spectrum, it shows the N-*H* peak at δ 12.5 (for **6a** it is at δ ~ 8.0), probably because of hydrogen bonding with the C=O group. The ^{13}C NMR spectrum showed presence of carbonyl group at δ ~204.0. With this result, we proceeded to maximize the yield of the product **99** by varying the reaction parameters as depicted in Table 5. Among the solvents DMF, NMP, CH_3CN, DCE, dioxane, toluene, xylene and AcOH, only dioxane gave moderate yield (44%). In the remaining cases, product yield was poor or negligible (Table 5, entries 2-9). Among the palladium catalysts, only palladium acetate gave better conversion to the acylated product **99** (Table 5, entries 10-12). Proper oxidant is also crucial for this reaction. Compared to TBHP, benzoyl peroxide or H_2O_2 or benzoquinone gave lower yields of the product **99** (Table 5, entries 13-15). Further optimization revealed that reaction proceeds better in dioxane/AcOH/DMSO (7/2/1, v/v/v) solvent mixture to afford the *ortho*-acylated product in good yield of 62%. Increasing the amount of catalyst from 5 mol % to 10 mol % improved the yield of the product to 74% after isolation (Table 5, entry 17). Thus, the optimized reaction conditions for the present reaction were: $Pd(OAc)_2$ (10 mol %), TBHP (3 equiv) and dioxane/AcOH/DMSO (7/2/1, v/v/v, 3 mL) at 110 ^oC (oil bath temperature) for 24 h.

Scheme 22

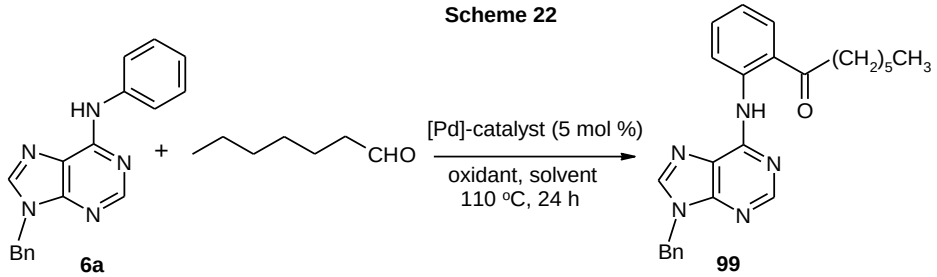


Table 5. Optimization study for the [Pd]-catalyzed *ortho*-acylation with aldehydes[a]

Entry	Catalyst (5 mol %)	Oxidant	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	TBHP	-	38
2	$Pd(OAc)_2$	TBHP	DMF	trace
3	$Pd(OAc)_2$	TBHP	NMP	21
4	$Pd(OAc)_2$	TBHP	CH_3CN (90 ^oC)	trace
5	$Pd(OAc)_2$	TBHP	DCE (90 ^oC)	23
6	$Pd(OAc)_2$	TBHP	dioxane	44
7	$Pd(OAc)_2$	TBHP	toluene	10
8	$Pd(OAc)_2$	TBHP	xylene	32
9	$Pd(OAc)_2$	TBHP	AcOH	trace
10	$PdCl_2$	TBHP	dioxane	18
11	$PdCl_2(CH_3CN)_2$	TBHP	dioxane	24
12	$PdCl_2(PPh_3)_2$	TBHP	dioxane	trace
13	$Pd(OAc)_2$	benzoyl peroxide	dioxane	ND
14	$Pd(OAc)_2$	H_2O_2	dioxane	31
15	$Pd(OAc)_2$	benzoquinone	dioxane	16
16	$Pd(OAc)_2$	TBHP	dioxane/AcOH/DMSO (7/2/1, v/v/v)	62
17	**$Pd(OAc)_2$ (10 mol %)**	**TBHP**	**dioxane/AcOH/DMSO (7/2/1, v/v/v)**	**74**

[a]Reaction conditions: **6a** (0.3 mmol), 1-heptanal (0.6 mmol), oxidant (3 equiv), solvent (3 mL), 110 ^oC (oil bath temperature). [b]Isolated yields. ND = not detected

With the optimized reaction conditions in hand, we examined the substrate scope by varying the 6-anilinopurine derivatives and aldehydes (Scheme 23, Table 6). Anilines bearing electron-donating or withdrawing substituents underwent cross-

dehydrogenative coupling (CDC) with heptanal smoothly and produced the corresponding acylated derivatives **99-106** in good to excellent yields (61-74%). Bromo and chloro functional groups were well tolerated and afforded *ortho*-acyl derivatives **102** and **103**. These products can pave way for further manipulation *via* cross-coupling reactions utilizing the –Br/-Cl functionalities. The reaction is highly regioselective when performed with *meta*-substituted amines. In these cases, only one regioisomer was observed and the sterically less hindered C-H position was acylated. We have also examined the effect of purine N9-substituent on the course of the reaction. Thus, the reaction of (9-isopropyl-9H-purin-6-yl)-phenyl-amine **6m** with heptanal afforded the *ortho*-acylated derivative **107** in good yield (70%).

We then investigated the effect of a wide range of alkyl aldehydes. The reaction worked well with isovaleraldehyde (a branched aldehyde) and produced acylated derivative **109** in good yield (68%). Cyclohexane carboxaldehyde also participated in this coupling and gave the corresponding ketone in 60% yield. It is noteworthy that citronellal, a monoterpenoid could also provide the acylated derivative **111** in moderate yield (54%). Unfortunately, aryl aldehydes underwent oxidation to the corresponding acids under these conditions. The reaction worked well in the case of simple 2-anilinopyrimidine, though. The generality of the methodology was extended to 6-anilinopurine nucleoside **9a** with 1-heptanal and 1-hexanal; in both the cases we have isolated the corresponding *ortho*-acylated nucleosides in decent yields (54-56%). The structure of one of the products (**108)** was further confirmed by using X-ray crystallography (Figure 11).

Scheme 23

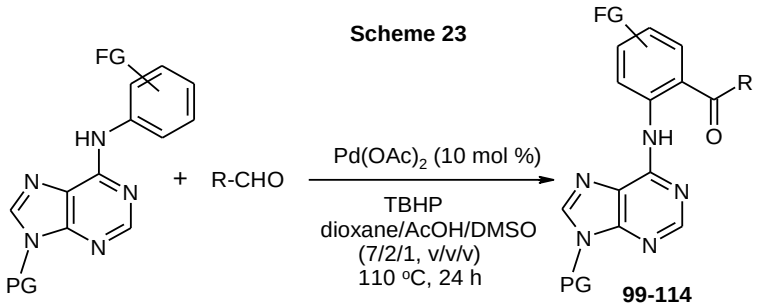
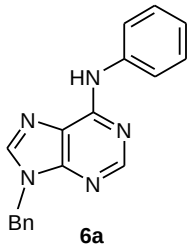
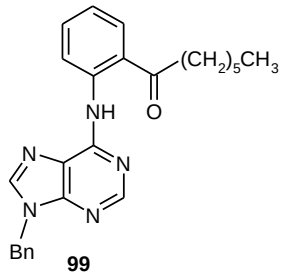
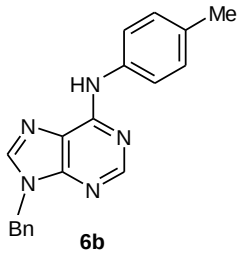
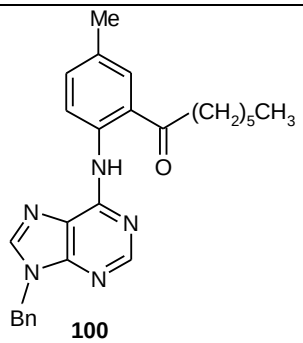
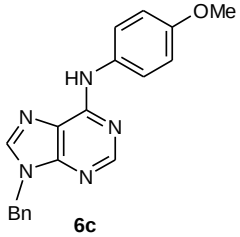
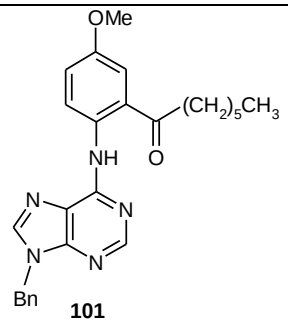
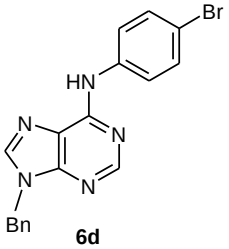
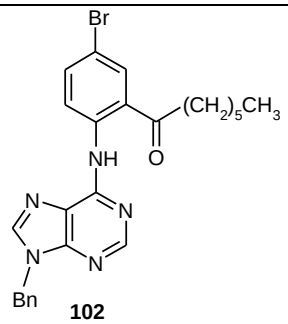
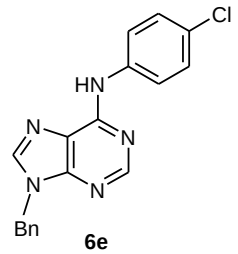
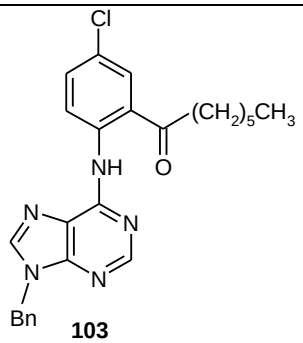
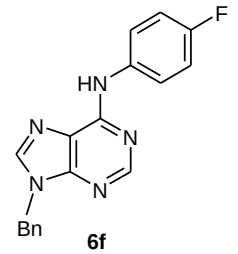
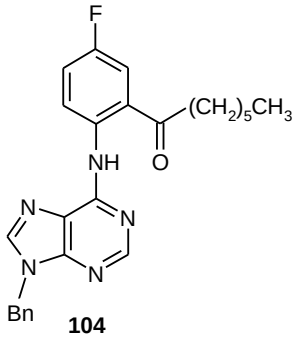
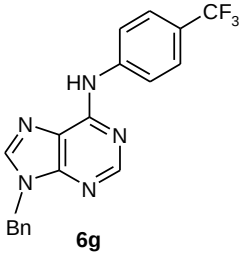
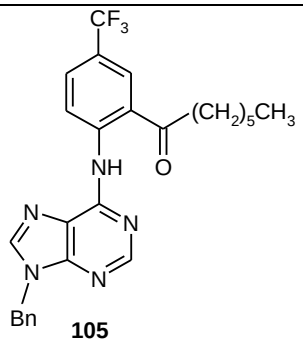
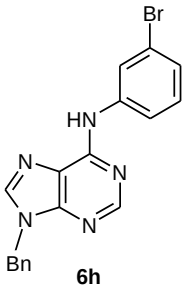
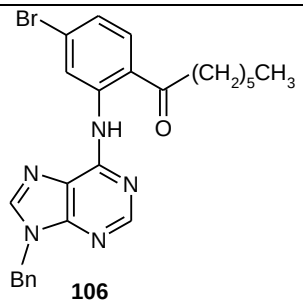
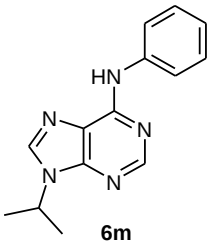
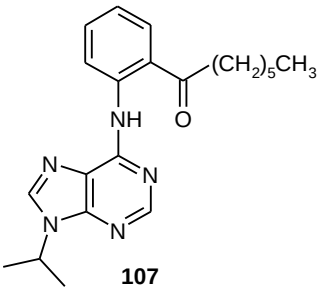
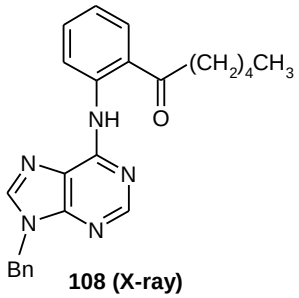
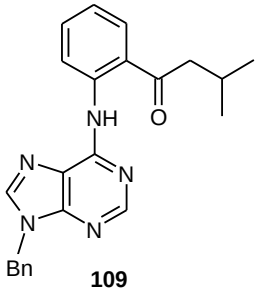
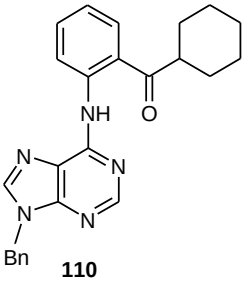
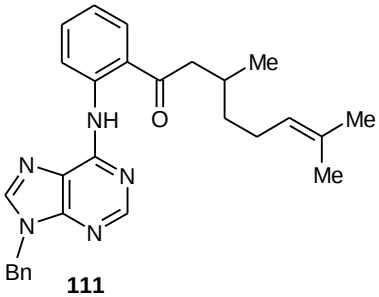
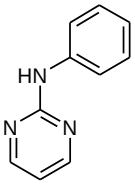
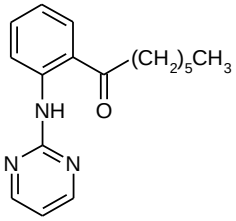
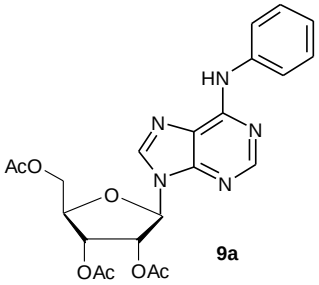
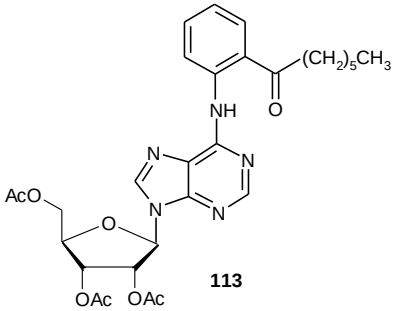
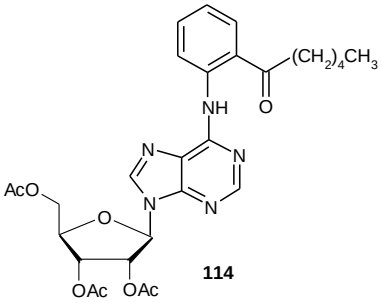


Table 6. Scope of the *ortho*-acylation reaction with 6-anilinopurines and aldehydes[a]

Entry	Substrate	Acylated derivative	Yield (%)[b]
1	 **6a**	 **99**	74
2	 **6b**	 **100**	71
3	 **6c**	 **101**	72
4	 **6d**	 **102**	66

5	 **6e**	 **103**	62
6	 **6f**	 **104**	68
7	 **6g**	 **105**	61
8	 **6h**	 **106**	63
9	 **6m**	 **107**	70

10	**6a**	 **108 (X-ray)**	71
11	**6a**	 **109**	68
12	**6a**	 **110**	60
13	**6a**	 **111**	54
14	 **10a**	 **112**	68

15	 **9a**	 **113**	56
16	**9a**	 **114**	54

[a]amine **6** (0.3 mmol), aldehyde (0.6 mmol), $Pd(OAc)_2$ (10 mol %), TBHP (3 equiv) and dioxane/AcOH/DMSO (7/2/1, v/v/v, 3 mL) at 110 ^{o}C (oil bath temperature) for 24 h.[b]Isolated yield.

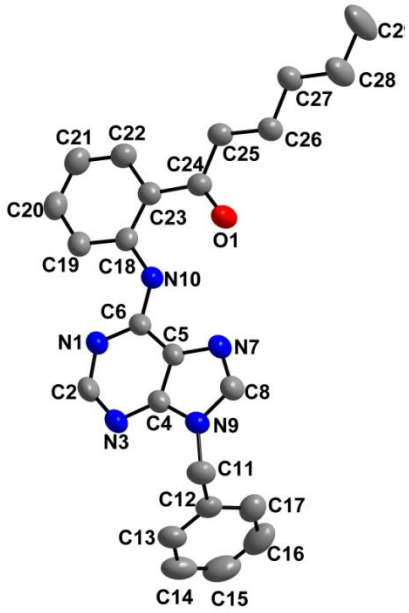
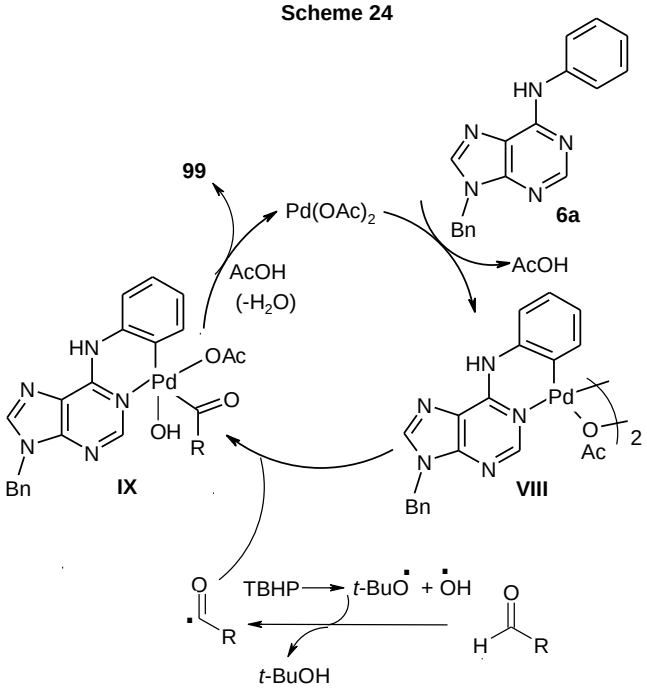


Figure 12. Molecular structure of compound **108**. Selected bond lengths [Å] with esd's in parentheses: C(24)-O(1) 1.2263(17), C(24)-C(23) 1.490(2), N(10)-C(18) 1.3964(19), N(10)-C(6) 1.3621(18), N(9)-C(11) 1.4604(18). Hydrogen atoms are omitted for clarity.

2.6.2 Plausible mechanistic pathway for the ortho-acylation using aldehydes

Based on previous reports,[56,73,77] a plausible pathway is outlined for Pd-catalyzed *ortho*-acylation in Scheme 24. Initially, through the chelate-directed C-H activation of purine N1 atom, the six-membered cyclopalladated intermediate **VIII** is formed. The reaction of aldehyde with TBHP generates reactive acyl and OH radicals which react with intermediate **VIII** to produce the Pd(IV) intermediate **IX**.[111] Finally, species **IX** undergoes reductive elimination leading to the formation of acylated derivative **99** (or **100**-**114**). The active Pd(II) is regenerated for next catalytic cycle.

Scheme 24

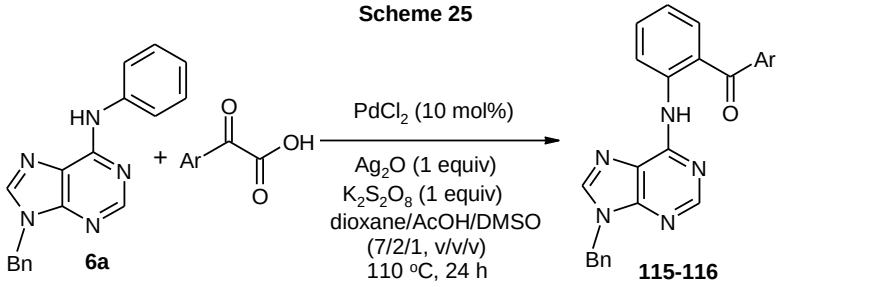


2.6.3 Palladium-catalyzed C(sp^2)-H bond acylation with α-oxocarboxylic acids

The above acylation reaction discussed in section 2.6.1 was applicable to alkyl aldehydes only; aryl aldehydes under those catalytic conditions were oxidized to corresponding acids. We overcame this drawback by choosing acylating source as *α*-oxocarboxylic acids. Ag_2O and $K_2S_2O_8$ were used as oxidant and co-oxidant respectively (Scheme 25). Since this is a decarboxylative coupling, TBHP did not work. Thus the reaction of 6-anilinopurine **6a** with phenylglyoxylic acid in the presence of $PdCl_2$ (10 mol %) afforded the corresponding acylated derivative **115** in good yield

(64%). Although $Pd(OAc)_2$ also worked, the yield was lower (50%). Under these catalytic conditions, we have also synthesized the mesityl derivative **116** in good yield (60%).

Scheme 25



Ar = C_6H_5 **115** (64%)
Ar = 2,4,6-Me-C_6H_2 **116** (60%)

2.7 Rhodium(III)-catalyzed C(sp^2)-H functionalization of aniline derivatives with *α*-diazo esters

In the previous sections, we discussed annulation reactions with alkynes and acylation reactions on C(sp^2)-H bonds. This section is devoted to carbenoid functionalization of aromatic C-H bonds by *α*-diazo esters in the presence of Rh(III)-catalyst. For this purpose, we have chosen aniline derivatives (e.g., **10a**) as substrates.

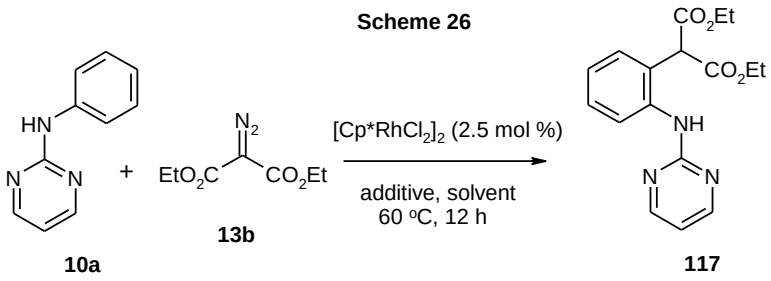
2.7.1 Alkylation of 2-anilinopyrimidines with α-diazo esters

The initial experiment was performed on 2-anilinopyrimidine **10a** with *α*-diazo malonate **13b** in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %) and CsOAc (10 mol %) as the catalytic system in MeOH solvent at 60 ^oC for 12 h. We isolated the desired alkylated product **117** in 46% yield. The identity of this compound was confirmed by IR, NMR and HRMS data. A strong band at ~ 1750 cm^{-1} in the IR spectrum indicates the presence of carbonyl group. In the ^1H NMR spectrum, it exhibits characteristic peaks at δ ~4.2 and ~1.2 due to the ester ethyl group and a peak at δ ~4.7 due to C*H*$(CO_2Et)_2$ proton. HRMS data matched with that expected for the structure shown in Scheme 26.

To maximize the yield of the product **117**, we have checked several parameters and the results are shown in Table 7. Both the additives NaOAc and AgOAc afforded

only moderate yield of the desired product (entries 2-3). A dramatic increase in yield to 68% was noticed when we used $AgSbF_6$ as the additive (entry 4). Reactions performed using the solvents DCE, CH_3CN, toluene and *t*AmOH lowered the yield (entries 5-8); other unidentified products were also formed. We were pleased to find that reaction efficacy was significantly improved by the addition of pivalic acid (PivOH) with the yield being 76% (entry 9). Compared to methanol, ethanol led to lower conversion (entry 10). There was no improvement in the yield upon increasing the amount of diazo ester from 1.2 equiv to 2 equiv (entry 11). At room temperature (25 ^oC), the yield was only 54% (entry 12). Thus the optimal reaction conditions by starting with 0.3 mmol of aniline derivative **10a** were: α- diazo ester (0.36 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %) and PivOH (20 mol %) in MeOH (3 mL) at 60 ^oC for 12 h.

Scheme 26



10a **117**

Table 7. Optimization study for the [Rh]-catalyzed alkylation with diazo compounds[a]

Entry	Additive	Solvent	Yield (%)[b]
1	CsOAc	MeOH	46
2	NaOAc	MeOH	51
3	AgOAc	MeOH	35
4	$AgSbF_6$	MeOH	68
5	$AgSbF_6$	DCE	42
6	$AgSbF_6$	CH_3CN	26
7	$AgSbF_6$	toluene	30
8	$AgSbF_6$	*t*AmOH	47

9	**$AgSbF_6$/PivOH (20 mol %)**	**MeOH**	**76**
10	$AgSbF_6$/PivOH (20 mol %)	EtOH	64
11	$AgSbF_6$/PivOH (20 mol %)	MeOH	76[c]
12	$AgSbF_6$/PivOH (20 mol %)	MeOH	54[d]

[a]Reaction conditions: **10a** (0.3 mmol), *α*-diazo ester **13b** (0.36 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), additive (10 mol %), solvent (3 mL), 60 ^oC (oil bath temperature).[b]Isolated yield, [c]*α*-diazo ester (2 equiv), [d]at room temperature.

With the optimized reaction conditions in hand, we explored the scope of this Rh(III)-catalyzed alkylation with respect to aniline derivatives and *α*-diazo esters (Scheme 27). Anilines bearing different electron-donating, -withdrawing and halogen substituents were well tolerated and produced the corresponding alkylated derivatives **117-123** in good to excellent yields (64-76%). It is noteworthy that the compatibility of the halogen containing substrates **10c** and **10d** under the reaction conditions enhances the utility of this protocol for further synthetic manipulations using derivatives **119** and **120**. For the *meta*-substituted aniline **10f**, the C-H functionalization regioselectively occurred at sterically less hindered position and only one product **122** was isolated. Importantly, *ortho*-substituted aniline derivative **10g** was smoothly derivatized to the corresponding alkylated derivative **123**, proving no detrimental steric effect of this *ortho*-substitution. In the case of diazo esters **13c** and **13e** also, reaction proceeded smoothly and afforded the products **124** and **125** in good yields.

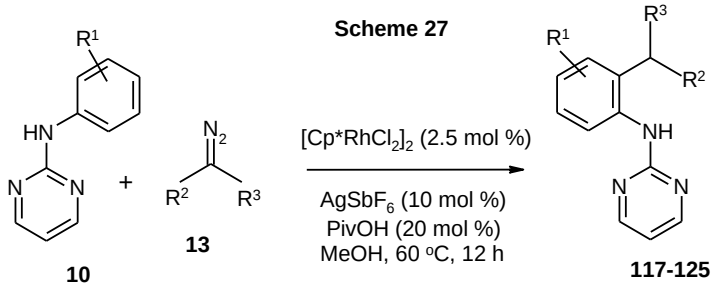
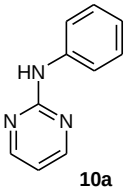
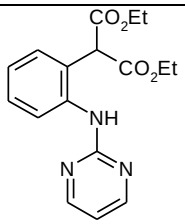
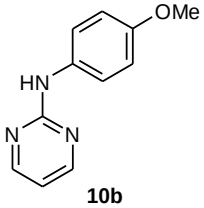
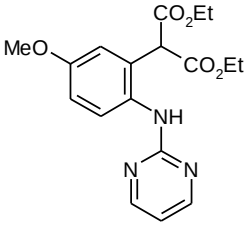
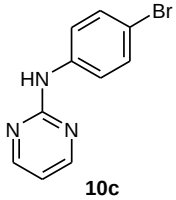
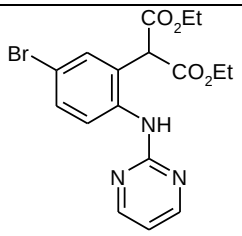
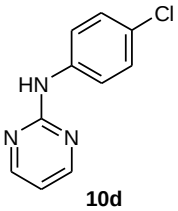
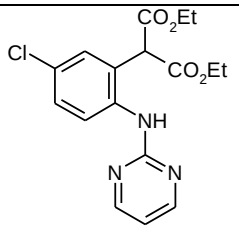
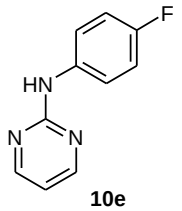
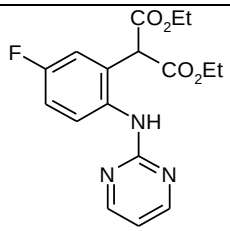
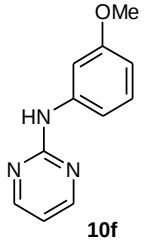
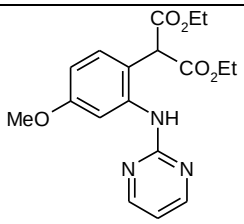
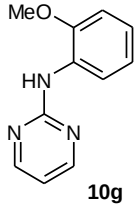
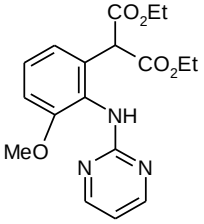
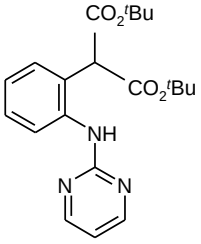
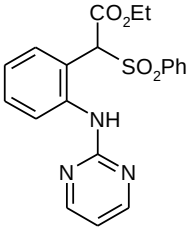


Table 8: Scope of the Rh(III)-catalyzed alkylation of 2-anilinopyrimidine derivatives with α- diazo esters[a]

Entry	Substrate	Alkylated derivative	Yield (%)[b]
1	 **10a**	 **117**	76
2	 **10b**	 **118**	75
3	 **10c**	 **119**	70
4	 **10d**	 **120**	71

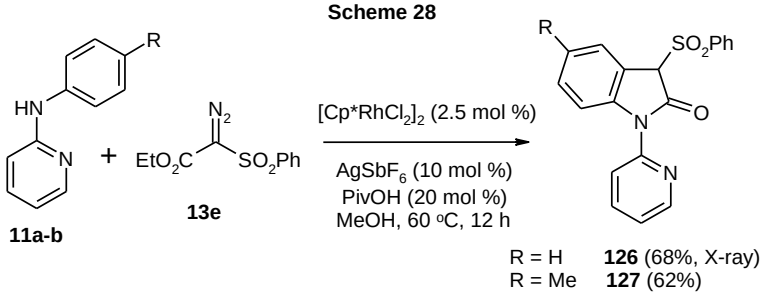
5	 **10e**	 **121**	73
6	 **10f**	 **122**	64
7	 **10g**	 **123**	72
8	**10a**	 **124**	68
9	**10a**	 **125**	66

[a]Reaction conditions: amine **10** (0.3 mmol), α-diazo ester **13** (0.36 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), PivOH (20 mol %), MeOH (3 mL), 60 ^oC (oil bath temperature). [b]Isolated yield.

2.7.2 Rh(III)-catalyzed coupling of 2-anilinopyridines 11 with α-diazo ester 13e: Synthesis of oxindole derivatives

Subsequent to the above, we investigated the scope of the reaction with 2-anilinopyridine derivatives **11a-b**. Surprisingly, the reaction of 2-anilinopyridine **11a** with *α*-diazo ester **13e** under the above catalytic conditions led to the formation of oxindole derivative **126** (Scheme 28) as shown by IR, NMR and HRMS data. The structure was further confirmed by using X-ray crystallography (Figure 11). Interestingly, under the similar catalytic conditions, 2-anilinopyrimidine **10a** gave only alkylated derivative **117** whereas the 2-anilinopyridine **11a** underwent alkylation followed by cyclization, affording oxindole **126**. We have also synthesized one more oxindole derivative **127** using **11b** as the precursor in good yield (62%).

Scheme 28



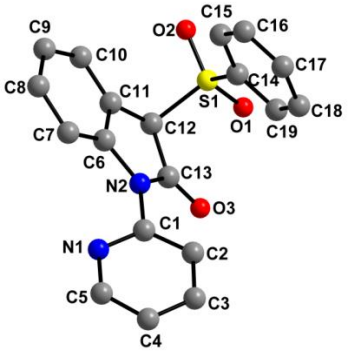


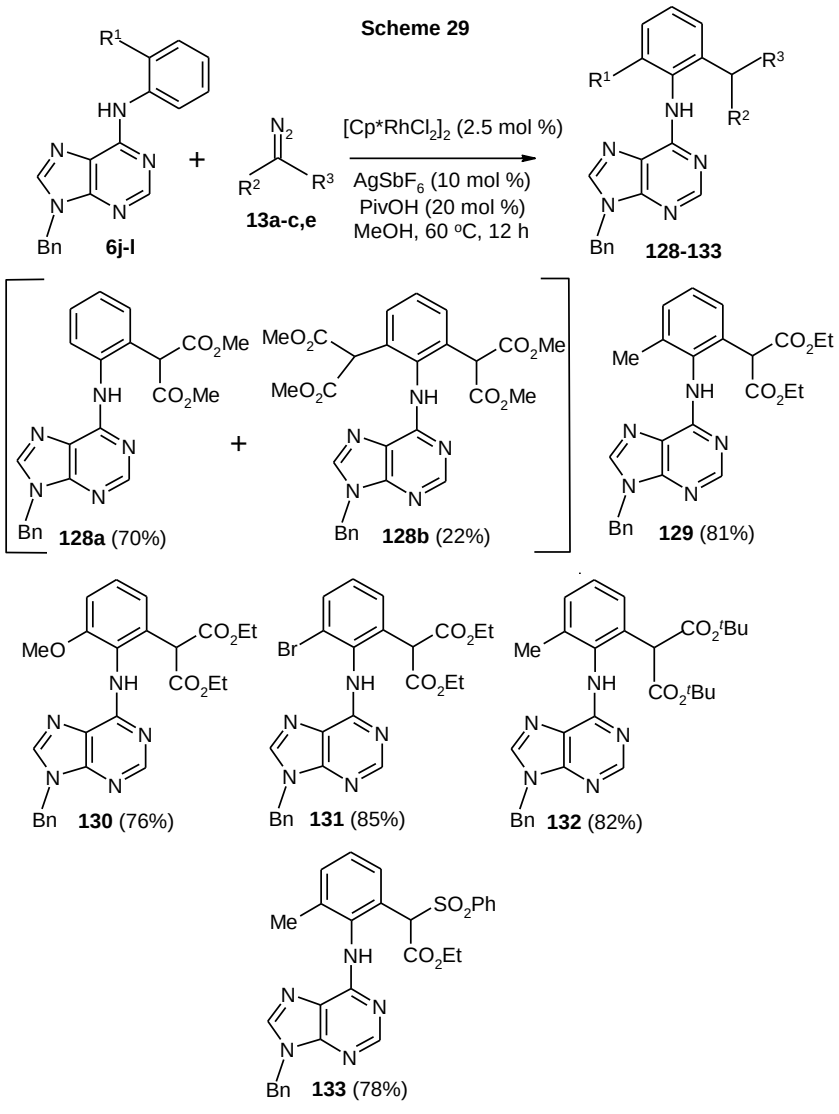
Figure 13. Molecular structure of compound **126**. Selected bond lengths [Å] with esd's in parentheses: N(2)-C(13) 1.384(2), C(11)-C(12) 1.492(3), S(1)-C(12) 1.7953(19), C(13)-C(12) 1.525(2), C(13)-O(3) 1.202(2). Hydrogen atoms are omitted for clarity.

2.7.3 Ortho-alkylation of 6-anilinopurine derivatives with α- diazo esters

After successful exploration of the *ortho*-alkylation of 2-anilinopyrimidine/pyridine substrates, we turned our attention to alkylation of 6-

anilinopurine substrates with α-diazo compounds (Scheme 29). In this connection, we first tried the reaction of anilinopurine **6a** with diazo ester **13a** under the above catalytic conditions. To our delight, the corresponding mono- and bis-functionalized products were obtained in ~3:1 ratio. We could isolate both the products through the column chromatography. The selectivity mono- over bis-functionalized product was not improved by varying the reaction parameters (solvent, additive, concentration of diazo compound and temperature). We then explored the scope of this reaction with respect to anlinopurines (**6j-l**) and α-diazo compounds (**13a-c** and **13e**); in all the cases we isolated the excellent yields of the *ortho*-alkylated derivatives **128-133**. Compatibility of the bromo functional group proves the utility of the product **131** for further cross coupling reactions.

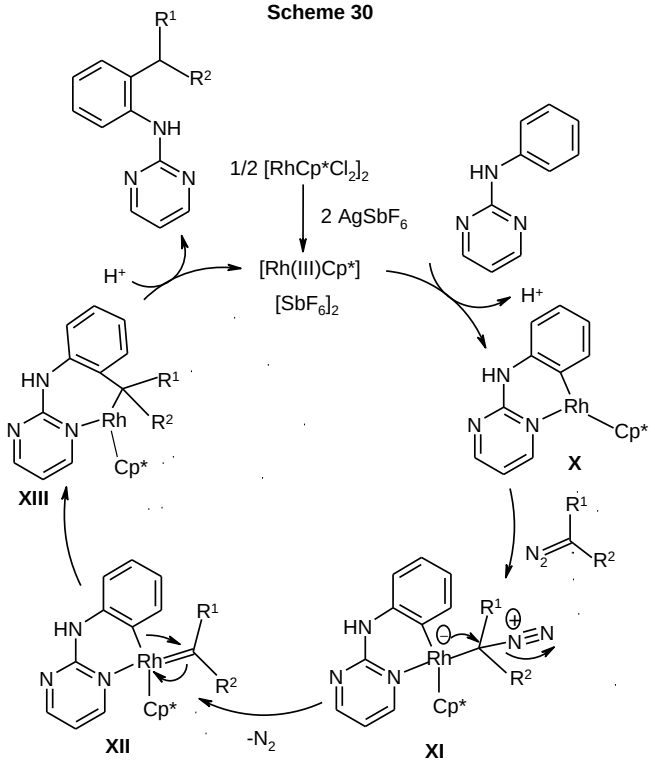
Scheme 29



2.7.4 Plausible reaction pathway for the formation of ortho-alkylated derivatives with α-diazo compounds

On the basis of the literature reports on C-H functionalization of aromatic compounds using *α*-diazo compounds,[92-97, 112] a plausible pathway is depicted in Scheme 30. Initially coordination of pyrimidine nitrogen to the cationic Rh(III) catalyst and subsequent *ortho* C-H cleavage generates a six-membered rhodacycle intermediate **X**. Then coordination of diazo compound to intermediate **X** followed by N_2 elimination results in the metal-carbenoid intermediate **XII** *via* the intermediate **XI**. Subsequently, migratory insertion of the carbene into the Rh-C bond affords intermediate **XIII**, which upon protonation delivers the alkylated product along with the active Rh(III) catalyst.

Scheme 30



SUMMARY – PART A

1) An efficient method for the synthesis of isoquinolones via the oxidative annulation of *N*-quinolin-8-yl-benzamides with alkynes with the aid of 8-aminoquinoline as bidentate directing group in the presence of Ru-catalyst in open air has been developed. The reaction features high regioselectivity, good substrate scope, and large functional group tolerance. This method was successfully extended to heterocyclic amides. A ruthenium *N*-quinolin-8-yl-benzamide complex has been isolated and characterized, showing the key role played by the quinoline moiety.
2) A new protocol of ruthenium-catalyzed oxidative annulation of 6-anilinopurine nucleobases with alkynes via C-H activation for the synthesis of a wide range of indole substituted purines has been discovered. The reaction is sustainable with purine nucleosides that contain a saccharide moiety. Novel purine C8 fused polycyclics formed via ***double C-H activation*** are also obtained in the presence of $Cu(OAc)_2 \cdot H_2O$ in selected cases involving N(9)-benzyl purine substrates. These products are endowed with fluorescence properties. A ruthenacycle intermediate has been isolated and catalytic activity of this complex suggests that purinyl N1 chelates with the metal and directs the reaction. Deuterium exchange studies also confirm the C-H activation.
3) A palladium-catalyzed *ortho*-acylation of 6-anilinopurines was achieved via $C(sp^2)$-H bond activation directed by purinyl N1 using aldehydes/α-oxocarboxylic acids as acylating sources. This protocol has high functional group tolerance in terms of aniline substrates.
4) A mild and efficient Rh(III)-catalyzed route for the *ortho*-alkylation of aniline derivatives with α-diazo esters has been developed using pyrimidine as the directing group. This carbenoid coupling reaction was successfully extended to 6-anilinopurine derivatives, where the *ortho*-alkylated 6-anilinopurine derivatives have been obtained in good yields. Interestingly, a similar reaction of 2-anilinopyridines with α-diazo ester **13e** afforded oxindole derivatives.

EXPERIMENTAL SECTION

General: Chemicals and solvents were procured from Aldrich/Fluka or local manufacturers. Further purification was done according to standard procedures wherever required.[113] All operations, unless otherwise specified, were carried out under dry nitrogen atmosphere using standard vacuum and Schlenk line techniques.[114]

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: ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded using 5 mm tubes on a Bruker 400 MHz NMR spectrometer (unless specified otherwise) [field strengths: 400, 100 and 162 MHz respectively] in $CDCl_3$ solution (unless specified otherwise) with shifts referenced to $SiMe_4$ (^{1}H, ^{13}C: $\delta = 0$) and ext. 85% H_3PO_4 (^{31}P: $\delta = 0$) 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 analyzer) equipment.

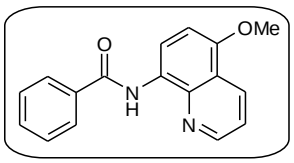
Absorbance and Fluorescence Spectroscopy: Steady state absorption and fluorescence spectra were recorded on UV-Vis-NIR scanning spectrophotometer (Shimadzu, model no. UV-3101PC) and SPEX FLUOROMAX-3 spectrofluorometer respectively.

6-Anilinopurine nucleosides **9a** and **9b** were synthesized starting from inosine according to a literature procedure.[101] 2-Anilino pyrimidine/pyridine substrates (**10a-10g** and **11a-11b**) were synthesized by following a literature procedure, all these compounds are known.[102] The known disubstituted alkynes (**12a-12q**) and diazoesters **13a-c** and **13e** used in the present study were synthesized by using known literature methods.[103, 104]

3.1 Synthesis of precursor amides 2a-2s, 3 and 4a-4b

Compound **1a** is commercially available and precursor **1b** has been prepared in the current study by following a literature procedure.[98] All the amide precursors bearing 8-aminoquinoline moiety were prepared by the reaction of corresponding acid chlorides with 8-aminoquinoline according to the literature procedures.[99] Compounds **2a-2n, 2p-2q, 2s, 3** and **4a-4b** are known.[99] Compounds **2o** and **2r** are new.

Compound 2o



Yield: 1.126 g (81%, yellow solid)

Mp: 120-124 ^{o}C.

IR (KBr): 3375, 2981, 1677, 1551, 1496, 1397, 1282, 1151, 1085, 827, 784, 679 cm^{-1}.

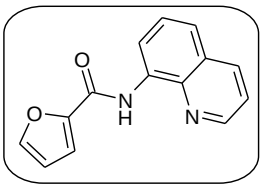
^{1}H NMR: δ 10.51 (br, 1H), 8.88 (s, 2H), 8.86 (s, 1H), 8.61 (dd, *J* = 8.4 Hz and 1.6 Hz, 1H), 8.09-8.07 (m, 1H), 7.58-7.55 (m, 3H), 7.47 (dd, *J* = 8.4 Hz and 1.6 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 4.02 (s, 3H).

^{13}C NMR: δ 165.2, 150.5, 148.8, 139.6, 135.5, 131.7, 131.4, 128.8, 128.1, 127.3, 120.9, 120.6, 116.8, 104.5, 55.9.

LC-MS: *m/z* 279 $[M+1]^{+}$.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.51; H, 5.16; N, 10.15.

Compound 2r



Yield: 0.940 g (79%, yellow solid).

Mp: 138-142 ^{o}C.

IR (KBr): 3326, 1682, 1595, 1545, 1332, 1156, 1008, 871, 750 cm^{-1}.

^{1}H NMR: δ 10.77 (br, 1H), 8.89-8.87 (m, 2H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.63 (s, 1H), 7.58-7.53 (m, 2H), 7.47 (dd, *J* ~ 8.2 Hz and 4.2 Hz, 1H), 7.31 (d, *J* = 3.2 Hz, 1H), 6.59-6.58 (m, 1H).

^{13}C NMR: δ 156.5, 148.5, 144.6, 138.7, 136.4, 134.3, 128.1, 127.5, 121.9, 121.8, 116.7, 115.2, 112.5.

LC-MS: *m/z* 239 $[M+1]^{+}$.

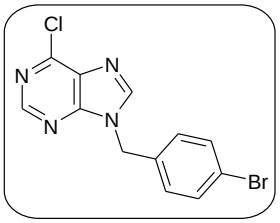
Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.46; H, 4.27; N, 11.65.

3.2 Synthesis of precursor amines 6a-6u

3.2.1 Synthesis of 9-Substituted 6-chloro-purines 5a-j

N9-Benzyl-6-chloro-purines **5a-5e** have been synthesized from 6-chloropurine by alkylation of purine in the presence of a base using alkyl halide following the literature procedure.[100a] Compounds **5a**, **5c-5e** are known,[100a] but compound **5b** is new. Compounds **5f-5i** were synthesized by using Mitsunobu reaction by treating with the corresponding alcohol.[100b] Compounds **5f-5h** are known,[100b] but compound **5i** is new. 6-Chloro-9-phenylpurine **5j** has been synthesized from 6-chloropurine and phenylboronic acid in the presence of copper(II) acetate following a known method [100c]

Compound 5b



This compound was prepared by the reaction of 4-bromobenzyl bromide with 6-chloropurine according to the literature procedure.[100a]

Yield: 0.68 g (65%); white solid.

Mp: 136-140 ^{o}C.

IR (KBr): 3066, 2920, 1589, 1557, 1329, 1172, 1067, 1011, 923, 859, 754 cm^{-1}.

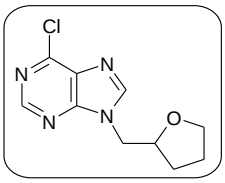
^{1}H NMR: δ 8.81 (s, 1H), 8.13 (s, 1H), 7.54-7.52 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 5.44 (s, 2H).

^{13}C NMR: δ 152.3, 151.8, 151.3, 144.8, 133.6, 132.5, 131.6, 129.6, 123.1, 47.3.

LC-MS: *m/z* 323 $[M+1]^{+}$.

Anal. Calcd. for $C_{12}H_8BrClN_4$: C, 44.54; H, 2.49; N, 17.31. Found: C, 44.62; H, 2.53; N, 17.21.

Compound 5i



This compound was prepared by the reaction of (tetrahydrofuran-2-yl) methanol with 6-chloropurine according to the literature procedure.[100b]

Yield: 0.32 g (44%); white solid.

Mp: 98-100 ^{o}C.

IR (KBr): 3288, 3063, 2981, 1726, 1556, 1496, 1342, 1233, 1058, 942, 860, 761 cm^{-1}.

^{1}H NMR: δ 8.73 (s, 1H), 8.29 (s, 1H), 4.50-4.46 (m, 1H), 4.31-4.22 (m, 2H), 3.88-3.73 (m, 2H), 2.12-2.04 (m, 1H), 1.93-1.85 (m, 1H), 1.77-1.69 (m, 1H), 1.56-1.49 (m, 1H).

^{13}C NMR: δ 152.1, 151.9, 150.9, 146.5, 131.2, 76.8, 68.6, 47.5, 28.6, 25.8.

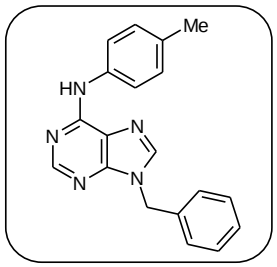
LC-MS: *m/z* 238 $[M]^{+}$.

Anal. Calcd. for $C_{10}H_{11}ClN_4O$: C, 50.32; H, 4.65; N, 23.47. Found: C, 50.41; H, 4.61; N, 23.56.

3.2.2 Synthesis of 6-anilino-9-arkyl/aryl substituted-purines 6a-u

The aniline precursors were prepared by the reaction of corresponding aniline with 6-chloropurine according to the literature procedures.[100a] Compounds **6b**, **6d-6m**, **6q**, **6r**, **6t** and **6u** are new and remaining 6-anilinopurine derivatives are known.

Compound 6b



Yield: 1.14 g (88%); white solid.

Mp: 186-188 ^{o}C.

IR (KBr): 3282, 3194, 3052, 1622, 1578, 1507, 1474, 1381, 1299, 1227, 1036, 729 cm^{-1}.

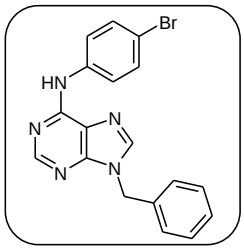
^{1}H NMR: δ 8.56 (s, 1H), 7.80 (s, 1H), 7.67-7.64 (m, 3H), 7.39-7.36 (m, 3H), 7.34-7.30 (m, 2H), 7.20 (d, *J*= 8.4 Hz, 2H), 5.41 (s, 2H), 2.36 (s, 3H).

^{13}C NMR: δ 153.2, 152.5, 149.7, 140.3, 135.9, 135.5, 133.4, 129.6, 129.1, 128.5, 127.8, 120.9, 120.1, 47.3, 20.9.

LC-MS: *m/z* 316 $[M+1]^{+}$.

Anal. Calcd. for $C_{19}H_{17}N_5$: C, 72.36; H, 5.43; N, 22.21. Found: C, 72.45; H, 5.36; N, 22.36.

Compound 6d



Yield: 0.601 g (86%); white solid.

Mp: 196-198 ^{o}C.

IR (KBr): 3271, 3200, 1611, 1573, 1479, 1392, 1288, 1145, 1068, 833, 636 cm^{-1}.

^{1}H NMR: δ 8.58 (s, 1H), 7.91 (s, 1H), 7.81 (s, 1H), 7.72 (d, *J*= 8.8 Hz, 2H), 7.48-

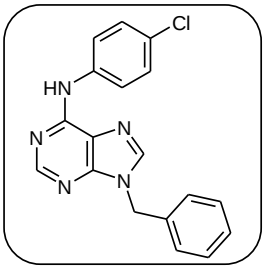
7.46 (m, 2H), 7.40-7.30 (m, 5H), 5.41 (s, 2H).

^{13}C NMR: δ 153.0, 152.0, 149.9, 140.8, 137.9, 135.4, 132.0, 129.2, 128.6, 127.9, 122.0, 120.3, 116.0, 47.4.

LC-MS: *m/z* 380 $[M]^+$ and 382 $[M+2]^+$.

Anal. Calcd. for $C_{18}H_{14}BrN_5$: C, 56.86; H, 3.71; N, 18.42. Found: C, 56.72; H, 3.65; N, 18.56.

Compound 6e



Yield: 0.46 g (83%); white solid.

Mp: 187-189 ^{o}C.

IR (KBr): 3282, 3206, 3036, 1616, 1584, 1485, 1227, 1156, 1090, 844, 794, 729, 647 cm^{-1}.

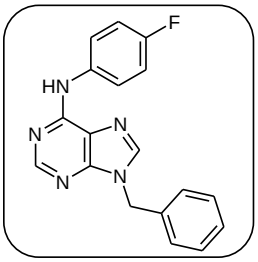
^{1}H NMR: δ 8.58 (s, 1H), 7.85 (br, 1H), 7.82-7.77 (m, 3H), 7.40-7.30 (m, 7H), 5.41 (s, 2H).

^{13}C NMR: δ 153.0, 152.1, 149.9, 140.7, 137.4, 135.4, 129.2, 129.1, 128.6, 127.9, 121.7, 120.3, 47.4.

LC-MS: *m/z* 335 $[M]^+$ and 337 $[M+2]^+$.

Anal. Calcd. for $C_{18}H_{14}ClN_5$: C, 64.38; H, 4.20; N, 20.86. Found: C, 64.21; H, 4.28; N, 20.76.

Compound 6f



Yield: 0.482 g (82%); white solid.

Mp: 182-184 ^{o}C.

IR (KBr): 3255, 3184, 3074, 1627, 1589, 1474, 1342, 1304, 1216, 1140, 1019, 833, 740 cm^{-1}.

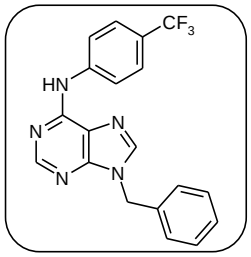
^{1}H NMR: δ 8.55 (s, 1H), 8.11 (br, 1H), 7.81 (s, 1H), 7.74-7.70 (m, 2H), 7.37-7.30 (m, 5H), 7.06 (t, *J*= 8.4 Hz, 2H), 5.40 (s, 2H).

^{13}C NMR: δ 159.3 (d, *J* = 241.5 Hz), 153.0, 152.2, 149.9, 140.5, 135.4, 134.5, 129.2, 128.6, 127.9, 122.7 (d, *J* = 7.6 Hz), 115.9, 115.6, 47.5.

LC-MS: *m/z* 320 $[M+1]^{+}$.

Anal. Calcd. for $C_{18}H_{14}FN_5$: C, 67.70; H, 4.42; N, 21.93. Found: C, 67.52; H, 4.51; N, 21.85.

Compound 6g



Yield: 0.554 g (92%); white solid.

Mp: 274-278 ^{o}C.

IR (KBr): 3310, 3074, 3003, 1660, 1611, 1485, 1419, 1337, 1162, 1074, 838, 784, 608 cm^{-1}.

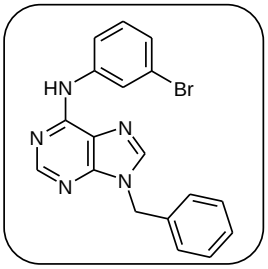
^{1}H NMR (DMSO-d_6): δ 10.71 (br, 1H), 8.83 (s, 1H), 8.55 (d, *J*= 2.0 Hz, 1H), 8.17 (d, *J*= 8.0 Hz, 2H), 7.70 (d, *J*= 11.6 Hz, 2H), 7.38-7.27 (m, 5H), 5.51 (s, 2H).

^{13}C NMR: δ 152.5, 151.2, 149.9, 143.4, 142.7, 136.7, 129.2, 128.5, 128.2, 126.3, 123.6, 123.5, 123.2, 120.9, 118.6, 47.4.

LC-MS: *m/z* 368 $[M-1]^{+}$.

Anal. Calcd. for $C_{19}H_{14}F_3N_5$: C, 61.79; H, 3.82; N, 18.96. Found: C, 61.85; H, 3.87; N, 18.79.

Compound 6h



Yield: 0.55 g (88%); white solid.

Mp: 162-164 ^{o}C.

IR (KBr): 3403, 3107, 2942, 1622, 1573, 1490, 1419, 1321, 1025, 882, 773, 723, 679 cm^{-1}.

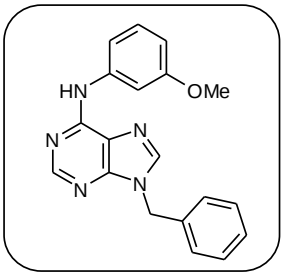
^{1}H NMR: δ 8.61 (s, 1H), 8.20 (s, 1H), 7.83-7.79 (m, 2H), 7.68-7.66 (m, 1H), 7.40-7.36 (m, 2H), 7.35- 7.31 (m, 2H), 7.27-7.23 (m, 3H), 5.42 (s, 2H).

^{13}C NMR: δ 153.0, 152.0, 150.0, 140.8, 140.2, 135.4, 130.3, 129.2, 127.9, 128.6, 126.3, 123.0, 122.7, 120.4, 118.6, 47.4.

LC-MS: *m/z* 380 [M]$^{+}$.

Anal. Calcd. for $C_{18}H_{14}BrN_5$: C, 56.86; H, 3.71; N, 18.42. Found: C, 56.72; H, 3.78; N, 18.51.

Compound 6i



Yield: 0.52 g (96%); white solid.

Mp: 122-123^{o}C.

IR (KBr): 3282, 3195, 3058, 1622, 1584, 1474, 1288, 1162, 1052, 860, 734 cm^{-1}.

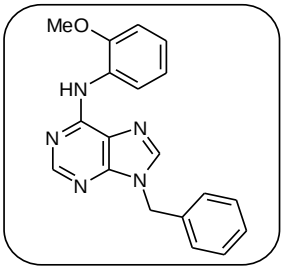
^{1}H NMR: δ 8.59 (s, 1H), 7.81 (s, 1H), 7.73 (br, 1H), 7.61, (s, 1H), 7.39-7.28 (m, 7H), 6.69-6.66 (m, 1H), 5.41 (s, 2H), 3.85 (s, 3H).

^{13}C NMR: δ 160.2, 153.1, 152.3, 149.8, 140.6, 140.0, 135.5, 129.7, 129.1, 128.5, 127.8, 120.3, 112.7, 109.0, 106.5, 55.3, 47.3.

LC-MS: *m/z* 332 [M+1]$^{+}$.

Anal. Calcd. for $C_{19}H_{17}N_5O$: C, 68.87; H, 5.17; N, 21.13. Found: C, 68.72; H, 5.23; N, 21.07.

Compound 6j



Yield: 0.55 g (81%); white solid.

Mp: 140-142 ^{o}C.

IR (KBr): 3403, 3096, 2970, 1616, 1534, 1496, 1458, 1386, 1249, 1107, 1036, 800, 745, 729 cm^{-1}.

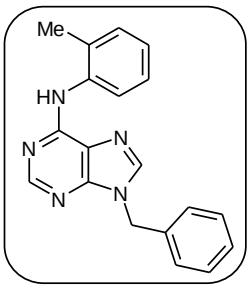
^{1}H NMR: δ 8.80-8.78 (m, 1H), 8.61 (s, 1H), 8.25 (br, 1H), 7.82 (s, 1H), 7.36-7.29 (m, 5H), 7.07-7.04 (m, 2H), 6.95-6.93 (m, 1H), 5.41 (s, 2H), 3.94 (s, 3H).

^{13}C NMR: δ 153.1, 152.2, 149.7, 148.5, 140.5, 135.6, 129.1, 128.5, 127.8, 122.9, 121.0, 120.8, 119.9, 110.1, 55.8, 47.3.

LC-MS: *m/z* 332 $[M+1]^{+}$.

Anal. Calcd. for $C_{19}H_{17}N_5O$: C, 68.87; H, 5.17; N, 21.13. Found: C, 68.76; H, 5.12; N, 21.19.

Compound 6k



Yield: 0.53 g (83%); white solid.

Mp: 124-128 ^{o}C.

IR (KBr): 3425, 3083, 1621, 1587, 1489, 1407, 1242, 1109, 941, 754 cm^{-1}.

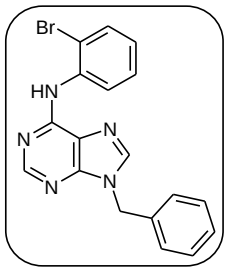
^{1}H NMR: δ 8.55 (s, 1H), 8.03 (d, *J*= 7.6 Hz, 1H), 7.81 (s, 1H), 7.50 (br, 1H), 7.40-

7.29 (m, 7H), 7.17-7.16 (m, 1H), 5.43 (s, 2H), 2.40 (s, 3H).

^{13}C NMR: δ 153.4, 153.1, 149.9, 140.4, 136.4, 135.6, 130.8, 130.7, 129.2, 128.5, 127.9, 126.8, 125.2, 123.9, 120.3, 47.3, 18.1.

HRMS (ESI): Calcd. for $C_{19}H_{18}N_5$ [M^++H]: *m/z* 316.1563. Found: 316.1564.

Compound 6l



Yield: 0.57 g (73%); white solid.

Mp: 162-166 ^{o}C.

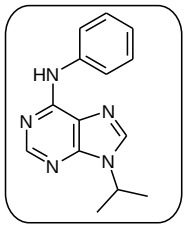
IR (KBr): 3372, 3060, 1617, 1569, 1485, 1430, 1383, 1303, 1246, 1023, 750, 727 cm^{-1}.

^{1}H NMR: δ 8.80-8.78 (m, 1H), 8.63 (s, 1H), 8.13 (br, 1H), 7.89 (s, 1H), 7.64-7.62 (m, 1H), 7.44-7.32 (m, 6H), 7.03-6.98 (m, 1H), 5.45 (s, 2H).

^{13}C NMR: δ 152.9, 152.0, 150.1, 141.1, 136.6, 135.5, 132.6, 129.2, 128.6, 128.3, 127.9, 124.3, 122.0, 121.0, 114.2, 47.4.

HRMS (ESI): Calcd. for $C_{18}H_{15}BrN_5$ [M^++H]: *m/z* 380.0512. Found: 380.0512 and 382.0492.

Compound 6m



Yield: 0.493 g (85%); white solid.

Mp: 74-76 ^{o}C.

IR (KBr): 3375, 2975, 1633, 1578, 1501, 1479, 1425, 1375, 1233, 1014, 899, 789, 751, 696 cm^{-1}.

^{1}H NMR: δ 8.53 (s, 1H), 8.12 (br, 1H), 7.87 (s, 1H), 7.78 (d, *J*= 7.2 Hz, 2H), 7.38-

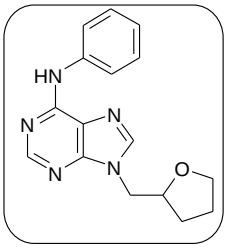
7.36 (m, 2H), 7.10 (d, *J*= 7.2 Hz, 1H), 4.86 (m, *J* ~ 5.6 Hz, 1H), 1.60 (d, *J* ~ 5.6 Hz, 6H).

^{13}C NMR: δ 152.6, 152.4, 149.3, 138.8, 138.2, 129.0, 123.5, 120.7, 120.5, 47.2, 22.7.

LC-MS: *m/z* 252 $[M-1]^+$.

Anal. Calcd. for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65. Found: C, 66.27; H, 5.91; N, 27.48.

Compound 6q



This was prepared by starting with 6-chloro-9-(tetrahydrofuran-2-ylmethyl)-9H-purine by using the same procedure as that for **1a-1m**.

Yield: 0.43 g (74%); white solid.

Mp: 114-116 ^{o}C.

IR (KBr): 3315, 3041, 2970, 2866, 1622, 1573, 1507, 1321, 1222, 1074, 745, 647 cm^{-1}.

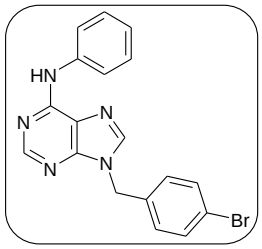
^{1}H NMR: δ 8.54 (s, 1H), 8.00 (s, 1H), 7.85-7.79 (m, 3H), 7.38 (t, *J* ~ 7.8 Hz, 2H), 7.11 (t, *J*~ 7.2 Hz, 1H*)*, 4.43-4.40 (m, 1H), 4.30-4.21 (m, 2H), 3.88-3.83 (m, 1H), 3.79-3.74 (m, 1H), 2.11-2.03 (m, 1H), 1.90-1.84 (m, 1H), 1.75-1.69 (m, 1H), 1.61-1.54 (m, 1H).

^{13}C NMR: δ 152.7, 152.2, 149.7, 141.8, 138.7, 128.9, 123.4, 120.5, 119.8, 68.4, 46.9, 28.5, 25.7.

LC-MS: *m/z* 296 $[M+1]^+$.

Anal. Calcd. for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 65.21; H, 5.87; N, 23.65.

Compound 6r



This was prepared by starting with 9-(4-bromo-benzyl)-6-chloro-9H-purine by using the same procedure as that for **1a-1o**.

Yield: 0.48 g (82%); white solid.

Mp: 186-190 ^{o}C.

IR (KBr): 3287, 3216, 3052, 1625, 1576, 1479, 1407, 1384, 1363, 1296, 1234, 1038, 757 cm^{-1}.

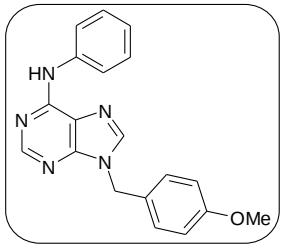
^{1}H NMR: δ 8.59 (s, 1H), 7.84-7.82 (m, 3H), 7.74 (br, 1H), 7.53-751 (m, 2H), 7.44-7.40 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.17-7.13 (m, 1H), 5.38 (s, 2H).

^{13}C NMR: δ 153.3, 152.4, 149.7, 140.3, 138.6, 134.6, 132.3, 129.5, 129.2, 123.8, 122.7, 120.5, 120.3, 46.7.

LC-MS: *m/z* 380 $[M+1]^{+}$.

Anal. Calcd. for $C_{18}H_{14}BrN_5$: C, 56.86; H, 3.71; N, 18.42. Found: C, 56.78; H, 3.65; N, 18.49.

Compound 6t



This was prepared by starting with 6-chloro-9-(4-methoxy-benzyl)-9H-purine by using the same procedure as that for **6a-6s.**

Yield: 0.66 g (85%); white solid.

Mp: 252-256 ^{o}C.

IR (KBr): 3309, 3020, 1653, 1616, 1515, 1503, 1481, 1357, 1255, 1194, 1036, 857 cm^{-1}.

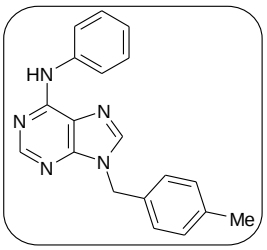
^{1}H NMR (DMSO-d_6): δ 10.60 (br, 1H), 8.78 (s, 1H), 8.49 (s, 1H), 7.86 (d, *J* = 8.4 Hz,

2H), 7.39 (t, *J* ~ 8.0 Hz, 4H), 7.17-7.12 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.44 (s, 2H), 3.73 (s, 3H).

^{13}C NMR (DMSO-d_6):δ 159.5, 151.5, 150.9, 149.2, 142.3, 138.8, 129.9, 129.3, 128.6, 124.4, 122.1, 118.2, 114.6, 55.6, 46.9.

HRMS (ESI): Calcd. for $C_{19}H_{18}N_5O$ [M^++H]: *m/z* 332.1512. Found: 332.1512.

Compound 6u



This was prepared by starting with 6-chloro-9-(4-methyl-benzyl)-9H-purine by using the same procedure as that for **6a-6s.**

Yield: 0.54 g (88%); white solid.

Mp: 266-270 ^{o}C.

IR (KBr): 3286, 2940, 1628, 1577, 1479, 1408, 1322, 1298, 1234, 1037, 754 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ 10.36 (br, 1H), 8.61 (s, 1H), 8.45 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 5.44 (s, 2H), 2.27 (s, 3H).

^{13}C NMR (DMSO-d_6):δ 151.5, 151.4, 149.6, 142.5, 139.1, 137.7, 134.0, 129.7, 129.2, 128.2, 124.1, 122.0, 119.2, 46.9, 21.1.

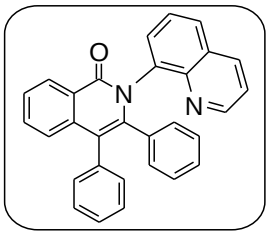
HRMS (ESI): Calcd. for $C_{19}H_{18}N_5$ [M^++H]: *m/z* 316.1563. Found: 316.1565.

3.3 General procedure for the ruthenium-catalyzed coupling of *N*-quinolin-8-yl-benzamides (2a-2s) or naphthyl benzamide (3) with alkynes: Synthesis of isoquinolone derivatives 14-47

A mixture of *N*-quinolin-8-yl-benzamide or naphthyl benzamide (0.4 mmol), diphenylacetylene (0.8 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), and $Cu(OAc)_2.H_2O$ (0.8 mmol) was taken in a Schlenk tube [under ambient conditions; no inert atmosphere needed]. To this, *t*AmOH (2 mL) was added and the mixture stirred at 110 ^{o}C (oil bath temperature) for 24 h. After cooling to rt, saturated NH_4Cl solution (50 mL) was added

and the contents extracted with EtOAc (3x30 mL). The combined organic phase was washed with brine solution (30 mL), dried over anh. Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (1:1) mixture as the eluent.

Compound 14



Yield: 0.127 g (74%, white solid).

Mp: 246-248 ^{o}C.

IR (KBr): 3052, 2926, 1655, 1595, 1490, 1332, 1178, 1030, 816, 784, 707 cm^{-1}.

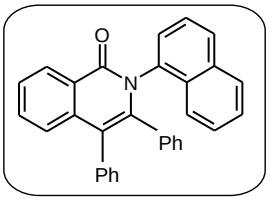
^{1}H NMR: δ 8.94 (d, *J* = 4.0 Hz, 1H), 8.59 (d, *J* = 7.6 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.61(t, *J* ~ 7.6 Hz, 1H), 7.55-7.49 (m, 2H), 7.40-7.36 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.27-7.25 (m, 2H), 7.18-7.16 (m, 3H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.76-6.71 (m, 2H), 6.50 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR: δ 162.8, 150.8, 144.7, 141.9, 138.2, 137.7, 136.6, 136.1, 134.9, 132.5, 131.9, 131.7, 130.9, 130.8, 129.8, 128.8, 128.6, 128.5, 128.1, 127.8, 127.3, 126.8, 126.7, 126.5, 125.8, 125.7, 121.5, 118.6.

HRMS (ESI): Calcd. for $C_{30}H_{21}N_2O$ [M^++H]: *m/z* 425.1655. Found: 425.1656.

X-ray structure was determined for this compound.

Compound 15



Yield: 0.018 g (11%, white solid).

Mp: 200-204 ^{o}C.

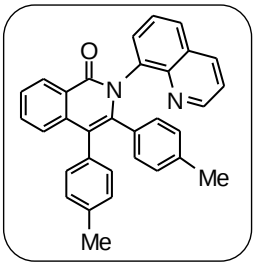
IR (KBr): 3057, 2926, 1649, 1610, 1484, 1440, 1397, 1254, 1029, 914, 777 cm^{-1}.

^{1}H NMR: δ 8.61 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* ~ 8.2 Hz, 1H), 7.69-7.63 (m, 2H), 7.59-7.56 (m, 1H), 7.52-7.43 (m, 2H), 7.35-7.28 (m, 2H), 7.26-7.24 (m, 3H), 7.19-7.14 (m, 3H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.86 (t, *J* ~ 7.4 Hz, 1H), 6.75 (t, *J* ~ 7.4 Hz, 1H), 6.61 (d, *J* = 7.6 Hz, 1H), 6.54-6.52 (m, 1H).

^{13}C NMR: δ 162.7, 142.0, 138.0, 136.4, 134.5, 134.0, 132.8, 131.8, 131.7, 131.1, 131.0, 129.5, 128.6_4, 128.5_6, 128.4, 128.1, 128.0, 127.9, 127.4, 127.1, 127.0, 126.8, 126.7, 126.2, 125.8, 125.6, 125.0, 123.0, 119.2.

HRMS (ESI): Calcd. for $C_{31}H_{22}NO$ [M^++H]: *m/z* 424.1702. Found: 424.1701.

Compound 16



Yield: 0.128 g (70%, white solid).

Mp: 278-282 ^{o}C.

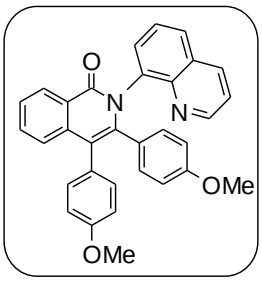
IR (KBr): 3014, 2909, 1660, 1507, 1337, 1178, 1025, 899, 734 cm^{-1}.

^{1}H NMR: δ 8.94 (d, *J* = 2.8 Hz, 1H), 8.57 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* ~ 7.6 Hz, 1H), 7.53-7.46 (m, 2H), 7.39-7.36 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.63 (t, *J* ~ 7.8 Hz, 2H), 6.29 (d, *J* = 7.6 Hz, 1H), 2.28 (s, 3H), 1.95 (s, 3H).

^{13}C NMR: δ 162.9, 150.7, 144.8, 142.0, 138.5, 137.9, 136.7, 136.1, 133.7, 132.4, 132.1, 131.7, 131.5, 130.9, 130.7, 129.6, 128.8, 128.5_3, 128.4_7, 128.4, 127.4, 127.2, 126.5, 125.8, 125.7, 125.6, 121.5, 118.6, 21.3, 21.1.

HRMS (ESI): Calcd. for $C_{32}H_{25}N_2O$ [M^++H]: *m/z* 453.1968. Found: 453.1968.

Compound 17



Yield: 0.138 g (71%, white solid).

Mp: 236-240 ^{o}C.

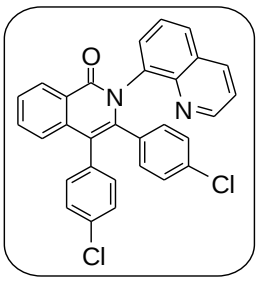
IR (KBr): 3052, 2986, 1660, 1611, 1507, 1474, 1326, 1244, 1184, 1025, 893, 816 cm^{-1}.

^{1}H NMR: δ 8.93 (d, *J* = 2.8 Hz, 1H), 8.57 (d, *J* = 7.6 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.53-7.47 (m, 2H), 7.41-7.36 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.15 (dd, *J* = 8.4 Hz and 1.6 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.88-6.86 (m, 1H), 6.80 (dd, *J* = 8.4 Hz and 2.4 Hz, 1H), 6.73 (dd, *J* = 8.4 Hz and *J* = 2.4 Hz, 1H), 6.67-6.65 (m, 1H), 6.38 (dd, *J* = 8.8 Hz and *J* = 2.4 Hz, 1H), 6.03 (dd, *J* = 8.4 Hz and *J* ~ 2.2 Hz, 1H), 3.76 (s, 3H), 3.50 (s, 3H).

^{13}C NMR: δ 162.8, 158.2, 150.7, 144.8, 141.9, 138.6, 137.9, 136.1, 132.9, 132.7, 132.4, 132.0, 131.0, 130.9, 129.0, 128.8, 128.5, 128.4, 127.6, 126.5, 125.9, 125.7, 121.5, 118.4, 113.5, 113.4, 112.1, 112.0, 55.1, 54.8.

HRMS (ESI): Calcd. for $C_{32}H_{25}N_2O_3$ [M^++H]: *m/z* 485.1866. Found: 485.1864.

Compound 18



Yield: 0.156 g (79%, white solid).

Mp: 282-286 ^{o}C.

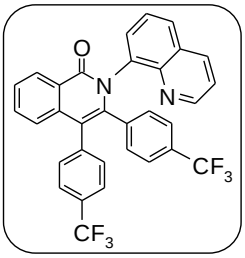
IR (KBr): 2921, 1649, 1595, 1490, 1403, 1326, 1145, 1096, 1014, 893, 822, 784, 603 cm^{-1}.

^{1}H NMR: δ 8.91 (d, *J* = 2.4 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.11-8.08 (m, 1H), 7.73-7.71 (m, 1H), 7.63-7.61 (m, 1H), 7.57-7.50 (m, 2H), 7.44-7.38 (m, 2H), 7.25-7.20 (m, 3H), 7.14 (t, *J* ~ 7.0 Hz, 2H), 6.91-6.84 (m, 2H), 6.71 (dd, *J* = 8.4 Hz and 1.2 Hz, 1H), 6.52-6.50 (m, 1H).

^{13}C NMR: δ 162.7, 150.9, 144.6, 140.9, 137.7, 137.3, 136.2, 134.9, 133.5, 133.2, 133.1_4, 133.0_8, 132.9, 132.7, 132.0, 131.1, 130.9, 129.0, 128.9, 128.6, 128.4, 127.2, 127.1, 127.0, 125.9, 125.7, 125.4, 121.7, 117.6.

HRMS (ESI): Calcd. for $C_{30}H_{19}Cl_2N_2O$ [M^++H] 493.0875. Found: *m/z* 493.0873, 495.0841 and 497.0816.

Compound 19



Yield: 0.149 g (66%, white solid).

Mp: 262-266 ^{o}C.

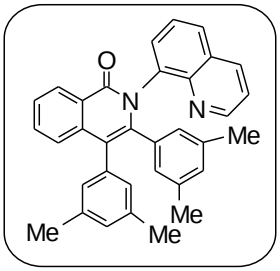
IR (KBr): 3057, 1660, 1611, 1485, 1321, 1173, 1107, 1063, 827, 679 cm^{-1}.

^{1}H NMR: δ 8.93 (d, *J* = 4.0 Hz, 1H), 8.60 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.67-7.57 (m, 2H), 7.54-7.52 (m, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.43-7.39 (m, 2H), 7.34 (t, *J* ~ 8.2 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR: δ 162.6, 151.0, 144.5, 140.7, 140.1, 138.1, 137.3, 137.0, 136.3, 132.9, 132.2, 132.0, 131.1, 131.0, 130.3, 129.8, 129.6, 129.5, 129.2, 129.0, 128.7, 127.4, 125.9, 125.4, 125.1, 124.8, 123.9, 123.6, 122.1, 121.8, 117.5.

HRMS (ESI): Calcd. for $C_{32}H_{19}F_6N_2O$ [M^++H]: *m/z* 561.1402. Found: 561.1401.

Compound 20



Yield: 0.139 g (72%, white solid).

Mp: 268-272 ^{o}C.

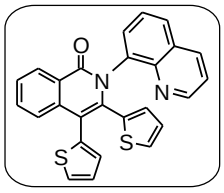
IR (KBr): 2920, 1649, 1589, 1556, 1474, 1326, 1222, 1025, 833, 795, 701 cm^{-1}.

^{1}H NMR: δ 8.96 (d, *J* = 2.4 Hz, 1H), 8.57 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* ~ 7.4 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 1H), 7.38-7.31 (m, 3H), 6.91 (br s, 1H), 6.78 (br s, 2H), 6.57 (br s, 1H), 6.33 (d, *J* = 8.4 Hz, 2H), 2.25 (s, 3H), 2.15 (s, 3H), 1.97 (s, 3H), 1.58 (s, 3H).

^{13}C NMR: δ 162.8, 150.6, 145.0, 142.0, 138.4, 138.0, 137.2, 136.8, 136.4, 135.9, 135.6, 135.5, 134.7, 132.3, 130.8, 129.7, 129.5, 128.7, 128.6, 128.4, 128.3_2, 128.2_5, 127.8, 126.4, 125.8, 125.7, 125.5, 121.3, 118.5, 21.3, 21.2, 20.9, 20.5.

HRMS (ESI): Calcd. for $C_{34}H_{29}N_2O$ [M^++H]: *m/z* 481.2281. Found: 481.2279.

Compound 21



Yield: 0.110 g (63%, white solid).

Mp: 248-252 ^{o}C.

IR (KBr): 3063, 1660, 1600, 1479, 1321, 1249, 1145, 833, 805, 696 cm^{-1}.

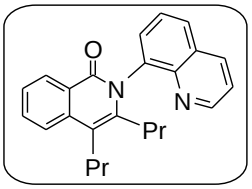
^{1}H NMR: δ 8.96 (d, *J* = 2.8 Hz, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.69-7.65 (m, 1H), 7.58-7.52 (m, 3H), 7.47-7.40 (m, 2H), 7.27 (br s, 1H), 6.97-6.94 (m, 2H), 6.85 (d, *J* = 4.8 Hz, 1H), 6.48 (d, *J* = 2.8 Hz, 1H), 6.35 (dd, *J* = 3.6, 4.0 Hz, 1H).

^{13}C NMR: δ 162.8, 151.0, 144.8, 138.1, 137.4, 137.2, 137.0, 136.3, 134.9, 132.8,

130.6, 130.0, 128.9, 128.4, 127.5, 127.2, 126.6, 126.0, 125.9, 125.8, 125.3, 121.7, 114.0.

HRMS (ESI): Calcd. for $C_{26}H_{17}N_2OS_2$ [M^++H]: *m/z* 437.0783. Found: 437.0784.

Compound 22



Yield: 0.086 g (60%, white solid).

Mp: 122-126 ^oC.

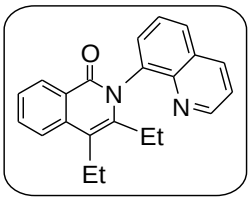
IR (KBr): 3063, 2959, 1655, 1551, 1496, 1370, 1326, 882, 833, 795, 696 cm^{-1}.

^1H NMR: δ 8.86 (d, *J* = 4.0 Hz, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.76-7.66 (m, 4H), 7.46-7.41 (m, 2H), 2.80-2.75 (m, 2H), 2.51-2.45 (m, 1H), 1.98-1.90 (m, 1H), 1.77-1.70 (m, 2H), 1.39-1.29 (m, 2H), 1.12 (t, *J* ~ 7.4 Hz, 3H), 0.54 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 163.2, 151.3, 144.9, 141.0, 137.7, 137.6, 136.3, 132.4, 130.4, 129.3, 129.1, 128.7, 126.2, 125.7, 125.6, 123.0, 121.8, 113.6, 32.8, 30.0, 23.7, 23.1, 14.6, 14.2.

HRMS (ESI): Calcd. for $C_{24}H_{25}N_2O$ [M^++H]: *m/z* 357.1968. Found: 357.1967.

Compound 23



Yield: 0.083 g (63%, white solid).

Mp: 190-194 ^oC.

IR (KBr): 3074, 2975, 1654, 1588, 1495, 1331, 1216, 1057, 832, 783, 701 cm^{-1}.

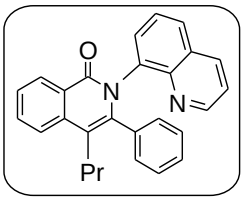
^1H NMR: δ 8.88-8.87 (m, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.74-7.67 (m, 3H), 7.47-7.42 (m, 2H), 2.91-2.85 (m, 2H), 2.61-2.55 (m, 1H), 2.12-2.06 (m, 1H), 1.34 (t, *J* ~ 7.4 Hz, 3H), 0.89 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR: δ 163.3, 151.4, 144.9, 141.8, 137.5, 136.4, 132.5, 130.7, 130.4, 129.4, 129.2, 128.8, 126.3, 125.7, 125.6, 122.9, 121.9, 114.8, 23.7, 20.7, 15.0, 14.1.

HRMS (ESI): Calcd. for $C_{22}H_{21}N_2O$ [M^++H]: *m/z* 329.1655. Found: 329.1654.

X-ray structure was determined for this compound.

Compound 24



Yield: 0.113 g (72%, white solid).

Mp: 144-148 ^{o}C.

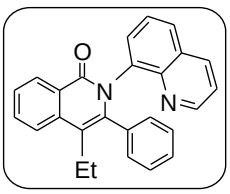
IR (KBr): 3052, 2921, 2866, 1655, 1611, 1562, 1490, 1332, 1030, 822, 795, 701 cm^{-1}.

^{1}H NMR: δ 8.90-8.89 (m, 1H), 8.58 (d, *J* = 7.6 Hz, 1H), 8.04 (dd, *J* ~ 7.8 Hz and ~ 1.4 Hz, 1H), 7.83-7.75 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* ~ 7.6 Hz, 1H), 7.46-7.44 (m, 1H), 7.38-7.34 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* ~ 7.4 Hz, 1H), 6.97 (t, *J* ~ 7.4 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.72 (t, *J* ~ 7.4 Hz, 1H), 2.49-2.43 (m, 2H), 1.63-1.59 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 162.6, 150.7, 144.7, 141.1, 137.9, 137.4, 136.0, 135.2, 132.5, 131.0, 130.3, 129.2, 128.9, 128.7, 128.4, 127.8, 127.2, 127.0, 126.4, 126.3, 125.7, 123.6, 121.4, 115.1, 30.7, 23.7, 14.4.

HRMS (ESI): Calcd. for $C_{27}H_{23}N_2O$ [M^++H]: *m/z* 391.1811. Found: 391.1809.

Compound 25



Yield: 0.094 g (62%, white solid).

Mp: 178-182 ^{o}C.

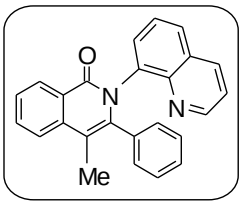
IR (KBr): 2959, 1649, 1611, 1490, 1332, 1151, 1074, 816, 784, 701 cm^{-1}.

^1H NMR: δ 8.90 (d, *J* = 2.8 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.78 (t, *J* ~ 7.4 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 6.4 Hz, 1H), 7.38-7.34 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.98 (t, *J* ~ 7.4 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.73 (t, *J* ~ 7.4 Hz, 1H), 2.59-2.50 (m, 2H), 1.15 (t, *J* ~ 7.4 Hz, 3H).

^{13}C NMR: δ 162.6, 150.8, 144.7, 140.9, 137.9, 137.1, 136.0, 135.3, 132.5, 131.0, 130.2, 129.1, 129.0, 128.8, 128.5, 127.8, 127.4, 127.1, 126.5, 125.8, 123.6, 121.5, 116.3, 21.7, 14.9.

HRMS (ESI): Calcd. for $C_{26}H_{21}N_2O$ $[M^+ + H]$: *m/z* 377.1655. Found: 377.1656.

Compound 26



Yield: 0.091 g (62%, white solid).

Mp: 186-190 ^oC.

IR (KBr): 2921, 1655, 1616, 1485, 1332, 1145, 899, 789, 756, 707 cm^{-1}.

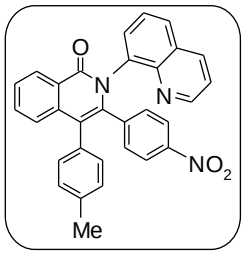
^1H NMR: δ 8.91 (d, *J* = 2.8 Hz, 1H), 8.57 (d, *J* = 8.0 Hz, 1H), 8.05 (dd, *J* = 8.4 Hz and 1.2 Hz, 1H), 7.83-7.76 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* ~ 7.4 Hz, 1H), 7.44 (d, *J* = 6.8 Hz, 1H), 7.38-7.34 (m, 2H), 7.19-7.12 (m, 2H), 6.98 (t, *J* ~ 7.4 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.74 (t, *J* ~ 7.4 Hz, 1H), 2.13 (s, 3H).

^{13}C NMR: δ 162.7, 150.9, 144.8, 140.9, 138.2, 138.0, 136.0, 135.5, 132.7, 131.0, 130.4, 129.3, 128.7, 128.5, 127.8, 127.4, 127.2, 126.6, 126.0, 125.8, 123.6, 121.5, 110.3, 14.9.

HRMS (ESI): Calcd. for $C_{25}H_{19}N_2O$ $[M^+ + H]$: m/z 363.1498. Found: 363.1498.

X-ray structure was determined for this compound.

Compound 27



Yield: 0.067g (34%, combined yield along with **18** was 62%, yellow solid).

Mp: >300 ^{o}C.

IR (KBr): 3052, 1655, 1589, 1523, 1479, 1348, 1107, 822, 789, 707 cm^{-1}.

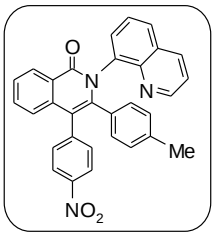
^{1}H NMR: δ 8.93 (dd, *J* = 4.0 Hz and 1.6 Hz, 1H), 8.60-8.58 (m, 1H), 8.09 (dd, *J* ~ 8.2 Hz and 1.4 Hz, 1H), 7.73-7.70 (m, 2H), 7.66-7.62 (m, 1H), 7.59-7.55 (m, 2H), 7.44-7.37 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 8.4 Hz and 1.6 Hz, 1H), 7.08-7.06 (m, 3H), 7.03-6.99 (m, 2H), 2.28 (s, 3H).

^{13}C NMR: δ 162.5, 151.0, 146.4, 144.4, 141.8, 139.4, 137.9, 137.1, 136.3, 132.7, 132.5, 131.7, 131.5, 131.3, 131.1, 130.9, 129.2, 129.1, 129.0, 128.9, 128.5, 127.3, 125.9, 125.8, 121.9, 121.8, 121.7, 118.9, 21.2.

HRMS (ESI): Calcd. for $C_{31}H_{22}N_3O_3$ [M^++H] 484.1662. Found: 484.1665.

X-ray structure was determined for this compound.

Compound 28



Yield: 0.055 g (28%, combined yield along with **17** was 62%, yellow solid).

Mp: 292-296 ^{o}C.

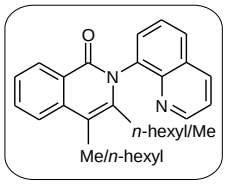
IR (KBr): 3063, 1655, 1589, 1507, 1342, 1189, 1151, 1019, 805, 712 cm^{-1}.

^{1}H NMR: δ 8.92 (d, *J* = 2.8 Hz, 1H), 8.60 (d, *J* = 7.6 Hz, 1H), 8.13-8.04 (m, 3H), 7.70 (d, *J* = 8.0, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* ~ 7.4 Hz, 1H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.44-7.36 (m, 4H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.32 (d, *J* = 7.6 Hz, 1H), 1.97 (s, 3H).

^{13}C NMR: δ 162.7, 150.8, 146.6, 144.7, 144.4, 142.7, 137.6, 137.4, 137.1, 136.1, 132.9, 132.8, 132.7, 131.2, 130.8, 130.4, 129.5, 128.8, 127.8, 127.6, 127.1, 125.8, 125.6, 124.8, 123.4, 123.1, 121.6, 116.5, 21.1.

HRMS (ESI): Calcd. for $C_{31}H_{22}N_3O_3$ [M^++H] 484.1662. Found: 484.1657.

Compound 29



Yield: 0.091 g (61%, gummy liquid, isomer ratio 7:3).

IR (neat): 2921, 1660, 1611, 1496, 1332, 1227, 800, 762 cm^{-1}.

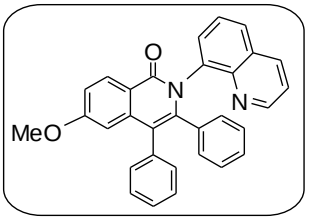
^{1}H NMR: for major isomer δ 8.90-8.89 (m, 1H), 8.49-8.45 (m, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.98-7.96 (m, 1H), 7.77-7.68 (m, 5H), 7.48-7.43 (m, 3H), 2.55-2.48 (m, 1H), 2.39 (s, 3H), 2.03-1.97 (m, 1H), 1.67-1.61 (m, 1H), 1.48 (br s, 1H), 1.36-1.35 (m, 4H), 1.05-1.00 (m, 2H), 0.72 (t, *J* ~ 7.0 Hz, 3H).

^{13}C NMR: for major isomer δ 163.3, 151.4, 144.9, 140.9, 138.4, 138.0, 137.6, 136.4, 132.5, 130.3, 130.1, 129.8, 129.5, 129.4, 129.1, 128.8, 128.5, 128.0, 126.5, 126.3, 125.8, 125.6, 125.5, 125.2, 122.8, 121.9, 113.9, 108.7, 31.0, 30.9, 29.0, 28.8, 22.3, 13.9, 13.7.

HRMS (ESI): Calcd. for $C_{25}H_{27}N_2O$ [M^++H]: *m/z* 371.2124. Found: 371.2124.

Many peaks for the minor isomer in the ^{1}H and ^{13}C NMR spectra were buried in those due to the major isomer.

Compound 30



Yield: 0.128 g (71%, white solid).

Mp: 280-284 ^{o}C.

IR (KBr): 2926, 1649, 1611, 1485, 1381, 1332, 1227, 1030, 937, 849, 784, 723 cm$^-$

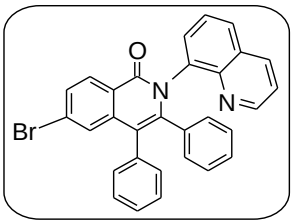
[1].

^{1}H NMR: δ 8.95 (dd, *J* = 8.4 Hz and 1.6 Hz, 1H), 8.51 (d, *J* = 8.8 Hz, 1H), 8.06 (dd, *J* = 8.4 Hz and 1.6 Hz, 1H), 7.67-7.65 (m, 1H), 7.51-7.49 (m, 1H), 7.39-7.35 (m, 2H), 7.24-7.21 (m, 2H), 7.18-7.10 (m, 4H), 6.97 (d, *J* =7.6 Hz, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 6.76-6.70 (m, 2H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.49 (t, *J* = 7.6 Hz, 1H), 3.75 (s, 3H).

^{13}C NMR: δ 163.1, 162.5, 150.8, 144.9, 142.6, 140.3, 137.8, 136.7, 136.1, 135.1, 131.9, 131.7, 131.1, 130.8, 130.7, 129.8, 128.8, 128.6, 128.1, 127.9, 127.2, 126.8, 126.7, 126.5, 125.8, 121.5, 119.6, 118.3, 115.4, 107.7, 55.4.

HRMS (ESI): Calcd. for $C_{31}H_{23}N_2O_2$ [M^++H]: *m/z* 455.1760. Found: 455.1757.

Compound 31



Yield: 0.137 g (68%, white solid).

Mp: 294-298 ^{o}C.

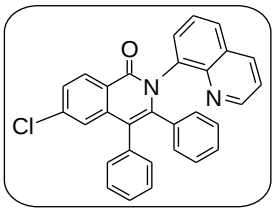
IR (KBr): 3058, 2921, 1655, 1589, 1468, 1315, 1151, 1074, 1019, 904, 816, 784, 701 cm^{-1}.

^{1}H NMR: δ 8.94 (d, *J* = 4.0 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.50-7.45 (m, 2H), 7.40-7.36 (m, 2H), 7.24-7.17 (m, 5H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.84 (t, *J* ~ 7.4 Hz, 1H), 6.73 (t, *J* ~ 8.0 Hz, 2H), 6.50 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR: δ 162.3, 150.9, 144.6, 143.4, 139.8, 137.4, 136.1, 135.8, 134.6, 131.8, 131.6, 130.8, 130.6, 130.3, 130.0, 129.7, 128.8, 128.3, 128.1_3, 128.0_8, 128.0, 127.4, 127.1, 126.8, 126.5, 125.8, 124.3, 121.6, 117.6.

HRMS (ESI): Calcd. for $C_{30}H_{20}BrN_2O$ [M^++H]: *m/z* 503.0760 and 503.0740. Found: 503.0761 and 505.0744.

Compound 32



Yield: 0.137 g (78%, white solid).

Mp: 284-288 ^{o}C.

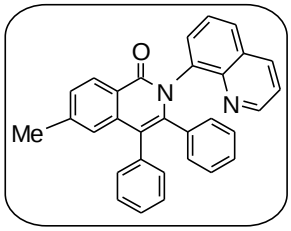
IR (KBr): 2921, 1649, 1595, 1496, 1463, 1321, 1085, 1030, 910, 827, 784, 707 cm^{-1}.

^{1}H NMR: δ 8.94 (d, *J* = 2.8 Hz, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* ~ 7.2 Hz, 2H), 7.40-7.36 (m, 2H), 7.23-7.17 (m, 6H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.84 (t, *J* ~ 7.4 Hz, 1H), 6.73 (t, *J* = 7.6 Hz, 2H), 6.50 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR: δ 162.2, 150.9, 144.6, 143.4, 139.6, 139.2, 137.4, 136.1, 135.9, 134.6, 131.8, 131.6, 130.8, 130.6, 130.3, 129.7, 128.8, 128.3, 128.1, 127.4, 127.2, 127.1, 126.8, 126.5, 125.8, 125.0, 124.0, 121.6, 117.8.

HRMS (ESI): Calcd. for $C_{30}H_{20}ClN_2O$ [M^++H]: *m/z* 459.1265 and 461.1232. Found: 459.1262 and 461.1237.

Compound 33



Yield: 0.132 g (74%, white solid).

Mp: 270-274 ^{o}C.

IR (KBr): 2921, 1649, 1616, 1490, 1447, 1331, 1178, 1025, 816, 789, 723, 701 cm^{-1}.

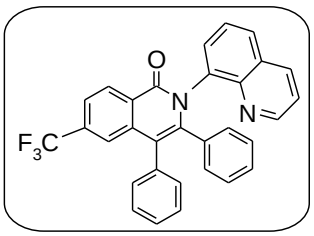
^{1}H NMR: δ 8.93 (d, *J* = 4.0 Hz, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.39-7.35 (m, 3H), 7.24 (br s, 2H), 7.18 (br s, 3H), 7.08 (br s, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.83 (t, *J* ~ 7.4 Hz, 1H), 6.75-6.70 (m, 2H), 6.48 (t, *J* ~ 7.6 Hz, 1H),

2.40 (s, 3H).

^{13}C NMR: δ 162.7, 150.8, 144.8, 143.0, 142.0, 138.3, 137.8, 136.7, 136.0, 135.1, 131.9, 131.7, 130.9, 130.8, 129.8, 128.7, 128.5_1, 128.4_7, 128.3, 128.0, 127.8, 127.2, 126.7, 126.6, 126.4, 125.8, 125.3, 123.5, 121.5, 118.4, 22.1.

HRMS (ESI): Calcd. for $C_{31}H_{23}N_2O$ [M^++H]: *m/z* 439.1811. Found: 439.1812.

Compound 34



Yield: 0.127 g (65%, white solid).

Mp: 220-224 ^{o}C.

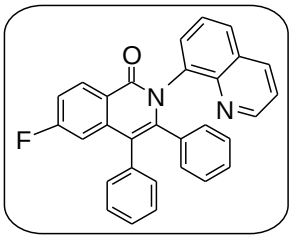
IR (KBr): 3074, 1660, 1595, 1562, 1496, 1430, 1315, 1173, 1074, 915, 784, 707 cm^{-1}.

^{1}H NMR: δ 8.93 (dd, *J* = 8.0 Hz and 1.6 Hz, 1H), 8.70 (d, *J* = 8.4, 1H), 8.08 (dd, *J* = 8.4 Hz and 1.6 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.59 (br s, 1H), 7.50 (dd, *J* = 7.2 Hz and 1.2 Hz, 1H), 7.41-7.37 (m, 2H), 7.27-7.19 (m, 5H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.77-6.72 (m, 2H), 6.51 (t, *J* ~ 7.4 Hz, 1H).

^{13}C NMR: δ 162.0, 150.9, 144.5, 143.6, 138.3, 137.3, 136.1, 135.6, 134.5, 131.7, 131.5, 130.7, 130.6, 129.6_1, 129.5_8, 128.9, 128.8, 128.4, 128.2, 127.7, 127.6, 127.3, 126.8, 126.6, 125.8, 122.9, 122.7, 121.7, 118.3.

HRMS (ESI): Calcd. for $C_{31}H_{20}F_3N_2O$ [M^++H]: *m/z* 493.1528. Found: 493.1527.

Compound 35



Yield: 0.126 g (71%, white solid).

Mp: 278-282 ^{o}C.

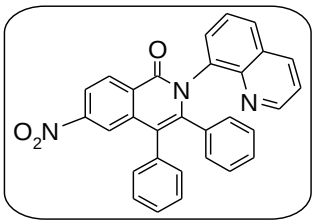
IR (KBr): 3074, 1660, 1611, 1474, 1370, 1326, 1189, 1112, 948, 866, 822, 789, 729, 696 cm^{-1}.

^{1}H NMR: δ 8.94 (dd, *J* ~ 4.2 Hz and ~ 1.4 Hz, 1H), 8.59 (dd, *J* = 8.8 Hz and 2.0 Hz, 1H), 8.08-8.06 (m, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.40-7.36 (m, 2H), 7.28-7.17 (m, 6H), 6.98-6.93 (m, 2H), 6.84 (t, *J* ~ 7.8 Hz, 1H), 6.75-6.72 (m, 2H), 6.50 (t, *J* ~ 7.4 Hz, 1H).

^{13}C NMR: δ 165.6 (d, *J* = 250.4 Hz),162.1, 150.9, 144.7, 143.3, 140.8, 140.7, 137.5, 136.0, 134.7, 131.7, 131.5, 130.8, 130.6, 129.6, 128.7, 128.2, 128.0, 127.4, 127.1, 126.7, 126.5, 125.8, 122.2, 121.6, 118.1, 115.3, 115.1, 111.0, 110.7.

HRMS (ESI): Calcd. for $C_{30}H_{20}FN_2O$ [M^++H]: *m/z* 443.1560. Found: 443.1557.

Compound 36



Yield: 0.134 g (72%, white solid).

Mp: 264-268 ^{o}C.

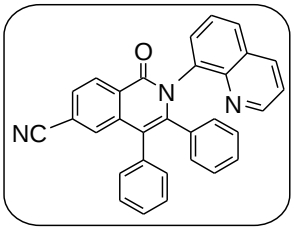
IR (KBr): 3052, 1666, 1589, 1529, 1463, 1348, 1173, 1129, 1019, 915, 816, 784, 701 cm^{-1}.

^{1}H NMR: δ 8.94 (dd, *J* = 4.0 Hz and 1.6 Hz, 1H), 8.74 (d, *J* = 8.8 Hz, 1H), 8.27 (dd, *J* ~ 8.6 Hz and ~ 2.2 Hz, 1H), 8.18 (d, *J* = 1.6 Hz, 1H), 8.09 (dd, *J* ~ 8.2 Hz, and *J* ~ 1.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.51-7.50 (m, 1H), 7.42-7.38 (m, 2H), 7.29-7.19 (m, 5H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.87 (t, *J* ~ 7.4 Hz, 1H), 6.78-6.72 (m, 2H), 6.52 (t, *J* ~ 7.4 Hz, 1H).

^{13}C NMR: δ 161.6, 151.0, 150.6, 144.5, 144.4, 139.0, 137.0, 136.2, 135.1, 134.2, 131.7, 131.4, 130.6, 130.5, 129.5, 129.2, 129.1, 128.8, 128.6, 128.4, 127.7, 127.6, 126.9, 126.7, 125.8, 121.8, 121.3, 120.3, 118.4.

HRMS (ESI): Calcd. for $C_{30}H_{20}N_3O_3$ [M^++H]: m/z 470.1505. Found: 470.1504.

Compound 37



Yield: 0.129 g (72%, white solid).

Mp: 256-260 ^{o}C.

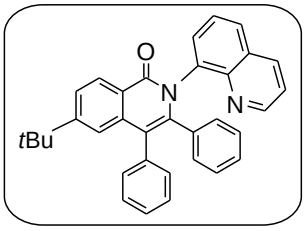
IR (KBr): 3063, 2921, 2225, 1660, 1616, 1551, 1496, 1474, 1332, 1173, 1019, 893, 789, 718 cm^{-1}.

^{1}H NMR: δ 8.93-8.92 (m, 1H), 8.66 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.72-7.68 (m, 2H), 7.65 (s, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.41-7.37 (m, 2H), 7.29-7.27 (m, 1H), 7.22-7.16 (m, 4H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.86 (t, *J* ~ 7.4 Hz, 1H), 6.77-6.72 (m, 2H), 6.51 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR: δ 161.7, 150.9, 144.4, 144.2, 138.5, 137.1, 136.2, 135.2, 134.2, 131.7, 131.4, 130.7, 130.6, 130.5, 129.6, 129.5, 129.0, 128.8, 128.5, 128.3, 128.0, 127.7, 127.5, 126.9, 126.6, 125.8, 121.7, 118.6, 117.7, 116.0.

HRMS (ESI): Calcd. for $C_{31}H_{20}N_3O$ [M^++H]: m/z 450.1607. Found: 450.1606.

Compound 38



Yield: 0.142 g (74%, white solid).

Mp: 262-266 ^{o}C.

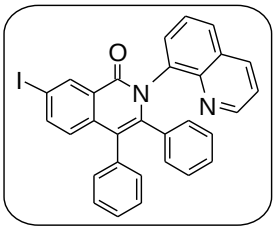
IR (KBr): 2948, 1655, 1616, 1479, 1392, 1321, 1184, 1019, 932, 827, 795, 701 cm^{-1}.

^{1}H NMR: δ 8.92 (dd, *J* ~ 4.6 Hz and ~ 1.8 Hz, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.66-7.60 (m, 2H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.39-7.32 (m, 3H), 7.26-7.16 (m, 5H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.85-6.82 (m, 1H), 6.76-6.70 (m, 2H), 6.51-6.47 (m, 1H), 1.28 (s, 9H).

^{13}C NMR: δ 162.7, 155.9, 150.8, 144.8, 141.8, 138.0, 137.9, 136.7, 136.0, 135.1, 131.9, 131.7, 131.0, 130.9, 129.9, 128.8, 128.5, 128.2, 128.0, 127.7, 127.2, 126.7, 126.6, 125.8, 124.8, 123.4, 121.8, 121.5, 118.9, 35.3, 31.1.

HRMS (ESI): Calcd. for $C_{34}H_{29}N_2O$ [M^++H]: *m/z* 481.2281. Found: 481.2280.

Compound 39



Yield: 0.135 g (61%, white solid).

Mp: 222-226 ^{o}C.

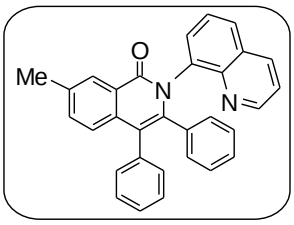
IR (KBr): 3063, 1654, 1594, 1495, 1473, 1320, 1134, 1073, 1024, 827, 788, 701 cm^{-1}.

^{1}H NMR: δ 8.95 (d, *J* = 2.8 Hz, 1H), 8.91 (br s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* ~ 8.6 Hz, and ~ 1.8 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.41-7.36 (m, 2H), 7.24-7.20 (m, 2H), 7.16-7.14 (m, 3H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.84 (t, *J* ~ 7.6 Hz, 1H), 6.75-6.71 (m, 2H), 6.50 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR: δ 161.6, 150.7, 144.2, 142.5, 141.4, 141.2, 137.3, 137.1, 136.8, 135.9, 134.5, 131.7, 131.5, 131.2, 130.7, 129.6, 128.9, 128.2, 127.9, 127.6, 127.5, 127.3, 127.0, 126.8, 126.6, 126.0, 121.7, 118.5, 91.8.

HRMS (ESI): Calcd. for $C_{30}H_{20}IN_2O$ [M^++H]: *m/z* 551.0621. Found: 551.0621.

Compound 40



Yield: 0.118 g (67%, white solid).

Mp: 274-278 ^{o}C.

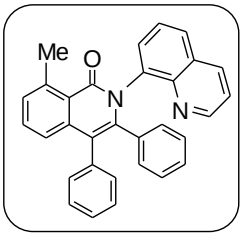
IR (KBr): 3052, 2910, 1655, 1595, 1501, 1332, 1200, 1025, 805, 789, 707 cm^{-1}.

^{1}H NMR: δ 8.94-8.93 (m, 1H), 8.40 (br s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.39-7.35 (m, 2H), 7.25-7.15 (m, 6H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.75-6.70 (m, 2H), 6.49 (t, *J* = 7.6 Hz, 1H), 2.52 (s, 3H).

^{13}C NMR: δ 162.7, 150.8, 144.8, 140.9, 137.9, 136.8, 136.0, 135.9, 135.0, 133.9, 131.9, 131.7, 130.9, 129.9, 128.8, 128.5, 128.0, 127.8, 127.2, 126.7_0, 126.6_5, 126.4, 125.8, 125.7, 125.5, 121.5, 118.5, 21.5.

HRMS (ESI): Calcd. for $C_{31}H_{23}N_2O$ [M^++H]: m/z 439.1811. Found: 439.1808.

Compound 41



Yield: 0.128 g (73%, white solid).

Mp: 276-280 ^{o}C.

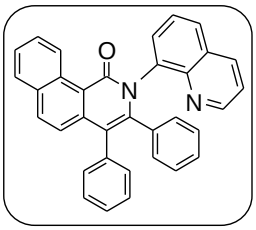
IR (KBr): 3052, 2920, 1654, 1610, 1490, 1440, 1320, 1029, 821, 783, 690 cm^{-1}.

^{1}H NMR: δ 8.94-8.93 (m, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.06-8.04 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.50-7.48 (m, 1H), 7.39-7.35 (m, 3H), 7.24 (br s, 2H), 7.18-7.16 (m, 3H), 7.08 (s, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.83 (t, *J* ~ 7.4 Hz, 1H), 6.75-6.70 (m, 2H), 6.49 (t, *J* = 7.6 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR: δ 162.7, 150.8, 144.8, 143.1, 142.0, 138.3, 137.9, 136.8, 136.0, 135.1, 131.9, 131.8, 130.9, 130.8, 129.9, 128.8, 128.5, 128.3, 128.0, 127.8, 127.2, 126.7, 126.6, 126.4, 125.8, 125.4, 123.5, 121.5, 118.4, 22.1.

HRMS (ESI): Calcd. for $C_{31}H_{23}N_2O$ [M^++H] 439.1811. Found: 439.1810.

Compound 42



Yield: 0.121 g (64%, white solid).

Mp: 234-238 ^{o}C.

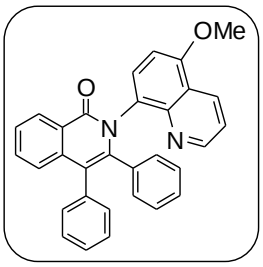
IR (KBr): 3052, 2926, 1649, 1578, 1534, 1490, 1321, 1156, 1123, 833, 805, 740, 696 cm^{-1}.

^{1}H NMR: δ 10.28 (d, *J* = 8.0 Hz, 1H), 8.93 (dd, *J* = 4.4 Hz and 1.6 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.71-7.66 (m, 2H), 7.62-7.59 (m, 2H), 7.45-7.36 (m, 3H), 7.28-7.20 (m, 5H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.86 (t, *J* ~ 7.4 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.75 (t, *J* ~ 7.6 Hz, 1H), 6.52 (t, *J* ~ 7.6 Hz, 1H).

^{13}C NMR: δ 163.2, 150.9, 144.8, 143.6, 139.7, 138.4, 137.2, 136.1, 135.0, 133.8, 132.4, 132.3, 132.1, 132.0, 130.9, 130.7, 129.6, 128.9, 128.6, 128.4, 128.1_4, 128.1_0, 128.0, 127.3, 126.9, 126.7, 126.5, 126.4, 125.9, 123.8, 121.6, 119.0.

HRMS (ESI): Calcd. for $C_{34}H_{23}N_2O$ [M^++H]: *m/z* 475.1811. Found: 475.1810.

Compound 43



Yield: 0.173 g (64%, white solid).

Mp: 278-282 ^{o}C.

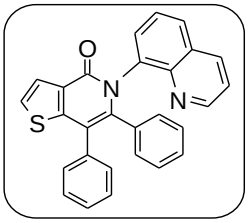
IR (KBr): 3057, 2942, 1649, 1594, 1479, 1408, 1331, 1260, 1090, 783, 701 cm^{-1}.

^{1}H NMR: δ 8.92 (d, *J* = 2.8 Hz, 1H), 8.59 (d, *J* = 7.6 Hz, 1H), 8.47-8.45 (m, 1H), 7.60 (t, *J* ~ 7.2 Hz, 1H), 7.52 (t, *J* ~ 7.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 8.4 Hz and 4.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.24 (br s, 2H), 7.17 (br s, 3H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.85 (t, *J* ~ 7.4 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.75 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.53 (t, *J* = 7.6 Hz, 1H), 3.92 (s, 3H).

^{13}C NMR: δ 163.0, 155.1, 151.0, 145.2, 142.4, 138.2, 136.8, 135.2, 132.4, 131.9, 131.7, 130.8_4, 130.7_7, 130.3, 129.9, 128.5, 128.0, 127.8, 127.2, 126.7, 126.6_3, 126.5_8, 126.5, 125.6, 121.1, 120.5, 118.4, 103.4, 55.8.

HRMS (ESI): Calcd. for $C_{31}H_{23}N_2O_2$ [M^++H] 455.1760. Found: 455.1757.

Compound 44



Yield: 0.089 g (51%, white solid).

Mp: 212-216 ^oC.

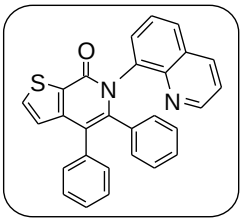
IR (KBr): 3052, 1644, 1556, 1523, 1496, 1326, 1271, 1030, 915, 811, 778, 712 cm^{-1}.

^1H NMR: δ 8.95-8.94 (m, 1H), 8.08-8.06 (m, 1H), 7.71-7.67 (m, 2H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.40-7.37 (m, 2H), 7.24-7.16 (m, 5H), 7.05 (d, *J* = 5.2 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.79-6.75 (m, 2H), 6.53 (t, *J* ~ 7.4 Hz, 1H).

^{13}C NMR: δ 158.7, 150.9, 146.8, 144.8, 143.1, 137.3, 137.0, 136.1, 134.5, 133.3, 131.0_4, 130.9_9, 130.1, 129.4, 128.8, 127.9, 127.5, 126.8, 126.6, 125.8, 125.2, 121.6, 117.5.

HRMS (ESI): Calcd. for $C_{28}H_{19}N_2OS$ [M^++H] 431.1219. Found: 431.1217.

Compound 45



Yield: 0.106 g (62%, white solid).

Mp: 258-262 ^oC.

IR (KBr): 3063, 1655, 1562, 1490, 1441, 1326, 1238, 1085, 1025, 860, 822, 712 cm^{-1}.

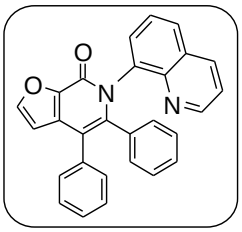
^1H NMR: δ 8.95 (dd, *J* = 4.0 Hz and 1.6 Hz), 8.07 (dd, *J* = 4.4 Hz and 1.6 Hz, 1H), 7.80 (d, *J* = 5.2 Hz, 1H), 7.69-7.67 (m, 1H), 7.50-7.48 (m, 1H), 7.40-7.36 (m, 2H), 7.32-7.28 (m, 3H), 7.23-7.12 (m, 3H), 6.98 (d, *J* = 8.0 Hz,

1H), 6.86 (t, *J* ~ 7.4 Hz, 1H), 6.80-6.77 (m, 2H), 6.54 (t, *J* ~ 7.6 Hz, 1H).

^{13}C NMR: δ 159.3, 151.4, 150.9, 144.8, 141.9, 137.5, 137.0, 136.1, 134.3, 130.9, 130.4, 130.0, 129.7, 128.8, 128.2, 127.6, 127.4, 126.9, 126.7, 126.2, 125.8, 124.9, 121.6, 116.5.

HRMS (ESI): Calcd. for $C_{28}H_{19}N_2OS$ [M^++H] 431.1219. Found: 431.1218.

Compound 46



Yield: 0.092 g (56%, white solid).

Mp: 252-256 ^{o}C.

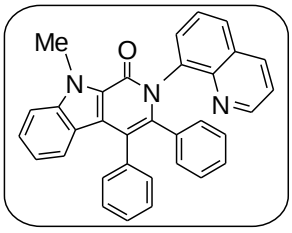
IR (KBr): 3057, 2986, 1676, 1588, 1539, 1490, 1364, 1282, 1073, 788, 755 cm^{-1}.

^{1}H NMR: δ 8.94-8.93 (m, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.40-7.36 (m, 2H), 7.17 (br s, 5H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.86 (t, *J* ~ 7.4 Hz, 1H), 6.81-6.74 (m, 2H), 6.62 (d, *J* = 1.6 Hz, 1H), 6.54 (t, *J* ~ 7.4 Hz, 1H).

^{13}C NMR: δ 153.6, 150.9, 148.4, 144.8, 142.6, 142.4, 137.1, 136.3, 136.1, 134.7, 134.5, 131.2, 130.5, 130.3, 128.9, 128.8, 128.0, 127.6, 126.9, 126.8, 126.6, 125.8, 121.6, 114.7, 107.9.

HRMS (ESI): Calcd. for $C_{28}H_{19}N_2O_2$ [M^++H] 415.1447. Found: 415.1445.

Compound 47



Yield: 0.116 g (61%, white solid).

Mp: 264-268 ^{o}C.

IR (KBr(for crystals)): 3036, 1655, 1468, 1321, 1068, 1030, 822, 751, 707 cm^{-1}.

^{1}H NMR: δ 8.97 (dd, *J* ~ 4.2 Hz and ~1.4 Hz, 1H), 8.07 (dd, *J* ~ 4.2 Hz and ~1.4

Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.58-7.56 (m, 1H), 7.49-7.37 (m, 5H), 7.32-7.28 (m, 2H), 7.25-7.22 (m, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.95 (t, *J* ~ 7.4 Hz, 1H), 6.85 (t, *J* ~ 7.4 Hz, 1H), 6.82-6.78 (m, 2H), 6.74 (t, *J* ~ 7.4 Hz, 1H), 6.51 (t, *J* = 7.6 Hz, 1H), 4.40 (s, 3H).

^{13}C NMR: δ 156.9, 151.0, 145.0, 141.5, 138.2, 137.9, 137.3, 136.1, 134.8, 131.5, 131.2_2, 131.1_7, 131.1, 130.4, 128.8, 128.6, 128.2, 128.0, 127.1, 126.6, 126.5, 126.4, 126.2, 125.8, 124.9, 123.1, 122.1, 121.6, 119.8, 117.2, 109.9, 31.5.

HRMS (ESI): Calcd. for $C_{33}H_{24}N_3O$ [M^++H] 478.1920. Found: 478.1919.

The compound crystallized as CH_3CN solvate (IR, ^{1}H NMR).

3.4 Synthesis of RuCl(OAc)(*p*-cymene) (48)

To a solution of [{$RuCl_2$(*p*-cymene)}$_2$] (0.200g, 0.33 mmol) in *t*AmOH (35 mL), $Cu(OAc)_2.H_2O$ (2.64g, 13.2 mmol) was added. The mixture was heated under reflux for 24 h. The resulting suspension was filtered through celite to give a clear orange solution from which solvent was removed to get RuCl(OAc)(*p*-cymene) as an orange solid in 64% yield (0.137g). The spectroscopic data and melting point matched with the literature data.[115]

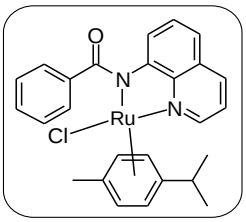
3.5 Preparation of complex 50

This compound could be prepared by two slightly different methods.

(i) A mixture of the amide **2a** (0.020g, 0.08 mmol) and **48** (0.026g, 0.08 mmol) was heated under reflux in *t*AmOH (5 mL) for 24 h. The resulting suspension was passed through a celite pad, washed with DCM (10 mL) and concentrated *in vacuo* to give the complex **50** in quantitative yield.

(ii) A mixture of [{$RuCl_2$(*p*-cymene)}$_2$] (0.122g, 0.2 mmol), *N*-quinolin-8-yl-benzamide **2a** (0.050g, 0.2 mmol) and NaOAc (0.033g, 0.4 mmol) was taken in MeOH (8 mL) and heated under reflux for 2 h at 70 ^{o}C. The reaction mixture was concentrated *in vacuo* and the product purified by column chromatography on silica gel using EtOAc as eluent to afford the ruthenium complex **50**. It was crystallized from dichloromethane-hexane (1:1) mixture.

Compound 50



Yield: 0.084 g (81%, orange crystals).

Mp: 226-230 ^{o}C.

IR (KBr): 3074, 2964, 1594, 1561, 1506, 1380, 1238, 1139, 1073, 925, 832, 723 cm^{-1}.

^{1}H NMR: δ 9.08 (d, *J* = 4.0 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 8.15-8.13 (m, 3H), 7.42-7.40 (m, 5H), 7.16 (d, *J* = 7.6 Hz, 1H), 5.56 (d, *J* = 5.6 Hz, 1H), 5.23 (d, *J* = 6.8 Hz, 1H), 5.11 (d, *J* = 5.6 Hz, 1H), 3.96 (d, *J* = 4.8 Hz, 1H), 2.32 (t, *J* = 7.4 Hz, 1H), 2.13 (s, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR: δ 180.5, 151.0, 150.9, 145.3, 142.5, 137.8, 129.8, 129.5, 129.3, 127.7, 122.9, 121.6, 117.1, 105.2, 97.9, 86.2, 85.9, 82.2, 80.6, 30.8, 22.5, 21.9, 19.1.

HRMS (ESI): Calcd. for $C_{26}H_{25}ClN_2ORuNa$ [M^{+}+Na] 541.0597. Found: 541.0602.

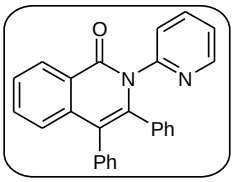
3.6 Synthesis of isoquinolone 14 using ruthenium complex 50

A mixture of **50** (40 mg, 0.08 mmol), diphenylacetylene (27 mg, 0.15 mmol), $Cu(OAc)_2 \cdot H_2O$ (30 mg, 0.15 mmol), and *t*AmOH (1 mL) was taken in a Schlenk tube. The resulting solution was heated on an oil bath at 110 ^{o}C for 24 h. The reaction mixture was filtered through a plug of celite using EtOAc (30 mL) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane:EtOAc (1:1) to afford the isoquinolone **14** (28 mg, 85%).

3.7 General procedure for the ruthenium-catalyzed coupling of *N*-(2-pyridinyl)-benzamides (4a-4b) with alkynes: Synthesis of isoquinolone derivatives 51-56

A mixture of *N*-(2-pyridinyl)-benzamide (0.5 mmol), diphenylacetylene (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $Cu(OAc)_2.H_2O$ (2 equiv) and KPF_6 was taken in a Schlenk tube [under ambient conditions; no inert atmosphere needed]. To this, H_2O (2 mL) was added and the mixture stirred at 100 ^oC (oil bath temperature) for 16 h. After cooling to rt, saturated NH_4Cl solution (50 mL) was added and the contents extracted with EtOAc (3x30 mL). The combined organic phase was washed with brine solution (40 mL), dried over anh. Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (3:1) mixture as the eluent.

Compound 51



Yield: 0.171 g (90%, white solid).

Mp: 244-248 ^oC.

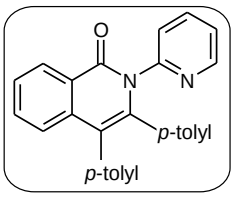
IR (KBr): 3057, 1660, 1589, 1468, 1326, 1162, 1036, 991, 762, 712 cm^{-1}.

^1H NMR: δ 8.57 (d, *J* = 8.0 Hz, 1H), 8.41-8.39 (m, 1H), 7.63-7.52 (m, 3H), 7.28-7.08 (m, 8H), 6.98-6.90 (m, 5H).

^{13}C NMR: δ 162.7, 152.8, 149.1, 140.1, 137.8, 137.6, 136.1, 134.3, 132.7, 131.6, 128.2, 128.0, 127.3, 127.1, 126.9, 125.7, 125.6, 125.0, 122.9, 119.0.

HRMS (ESI): Calcd. for $C_{26}H_{19}N_2O$ $[M^+ + H]$ 375.1498. Found: 375.1500.

Compound 52



Yield: 0.183 g (91%, white solid).

Mp: 242-246 ^{o}C.

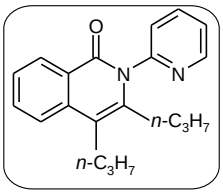
IR (KBr): 3025, 2915, 1660, 1584, 1512, 1463, 1441, 1326, 1140, 1019, 784, 756 cm^{-1}.

^{1}H NMR: δ 8.55 (d, *J* = 8.0 Hz, 1H), 8.40 (d, *J* ~ 4.2 Hz, 1H), 7.61-7.55 (m, 2H), 7.50 (t, *J* ~ 7.6 Hz, 1H), 7.26 (d, *J* ~ 8.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.10-7.07 (m, 1H), 7.03 (s, 4H), 6.86 (br, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 2.28 (s, 3H), 2.08 (s, 3H).

^{13}C NMR: δ 162.8, 152.9, 149.1, 140.1, 138.1, 137.6, 136.9, 136.4, 133.2, 132.6, 131.5, 128.8, 128.1, 127.8, 126.8, 125.7, 125.5, 125.0, 122.8, 118.9, 21.2_4, 21.1_5.

HRMS (ESI): Calcd. for $C_{28}H_{23}N_2O$ [M^++H] 403.1811. Found: 403.1809.

Compound 53



Yield: 0.126 g (82%, white solid).

Mp: 148-152 ^{o}C.

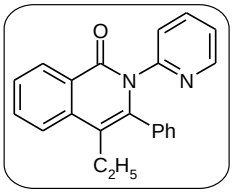
IR (KBr): 2970, 2866, 1655, 1589, 1463, 1370, 1321, 1216, 1134, 1096, 992, 784, 707 cm^{-1}.

^{1}H NMR: δ 8.69 (dd, *J* = 4.8 Hz and 1.2 Hz, 1H), 8.45-8.40 (m, 1H), 7.96-7.84 (m, 1H), 7.75-7.64 (m, 2H), 7.47-7.36 (m, 3H), 2.74-2.68 (m, 2H), 2.37-2.27 (m, 2H), 1.73-1.41 (m, 4H), 1.10 (t, *J* = 7.2 Hz , 3H), 0.70 (t, *J* = 7.2 Hz , 3H).

^{13}C NMR: δ 163.1, 153.1, 149.7, 139.3, 138.2, 137.4, 132.6, 128.4, 125.9, 125.4, 124.7, 123.7, 123.0, 114.0, 32.0, 29.6, 23.6, 22.7, 14.6, 14.3.

HRMS (ESI): Calcd. for $C_{20}H_{23}N_2O$ [M^++H] 307.1811. Found: 307.1810.

Compound 54



Yield: 0.146 g (89%, white solid).

Mp: 190-194 ^{o}C.

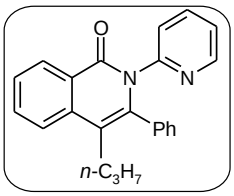
IR (KBr): 3052, 2964, 2866, 1655, 1589, 1485, 1436, 1332, 1145, 997, 789, 756, 701 cm^{-1}.

^{1}H NMR: δ 8.55 (d, *J* = 8.0 Hz, 1H), 8.37 (dd, *J* = 4.8 Hz and 1.2 Hz, 1H), 7.82-7.75 (m, 2H), 7.60-7.53 (m, 2H), 7.17-7.05 (m, 7H), 2.53 (qrt, *J* ~ 7.4 Hz, 2H), 1.13 (t, *J* ~ 7.4 Hz, 3H).

^{13}C NMR: δ 162.4, 152.9, 149.1, 139.2, 137.5, 136.8, 134.6, 132.8, 130.4, 128.7, 128.0, 127.7, 126.7, 126.3, 125.0, 123.5, 122.8, 116.8, 21.4, 14.9.

HRMS (ESI): Calcd. for $C_{22}H_{19}N_2O$ [M^++H] 327.1498. Found: 327.1488.

Compound 55



Yield: 0.154 g (90%, white solid).

Mp: 136-140 ^{o}C.

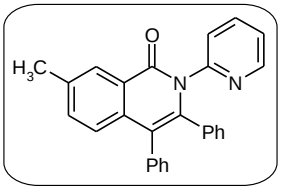
IR (KBr): 3063, 2926, 1654, 1588, 1462, 1435, 1325, 1145, 997, 766, 706 cm^{-1}.

^{1}H NMR: δ 8.55 (d, *J* = 8.0 Hz, 1H), 8.37 (dd, *J* = 4.8 Hz and 1.2 Hz, 1H), 7.79-7.75 (m, 2H), 7.59-7.52 (m, 2H), 7.16-7.04 (m, 7H), 2.48-2.44 (m, 2H), 1.57 (qrt, *J* ~ 7.6 Hz, 2H), 0.84 (t, *J* ~ 7.6 Hz , 3H).

^{13}C NMR: δ 162.5, 153.0, 149.1, 139.4, 137.5, 137.1, 134.6, 132.8, 130.8, 128.7, 128.0, 127.7, 126.7, 126.3, 125.0, 123.7, 122.8, 115.6, 30.4, 23.7, 14.4.

HRMS (ESI): Calcd. for $C_{23}H_{21}N_2O$ [M^++H] 341.1655. Found: 341.1655.

Compound 56



Yield: 0.157 g (81%, white solid).

Mp: 188-192 ^{o}C.

IR (KBr): 3052, 2932, 1666, 1605, 1463, 1326, 1244, 1036, 811, 784 cm^{-1}.

^{1}H NMR: δ 8.41 (s, 1H), 8.35 (s, 1H), 7.65-7.62 (m, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.27-7.13 (m, 8H), 6.97-6.90 (m, 5H), 2.51 (s, 3H).

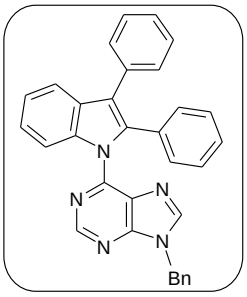
^{13}C NMR: δ 162.7, 152.7, 148.8, 139.0, 137.9, 137.2, 136.3, 135.6, 134.4, 134.3, 131.6, 128.0, 127.8, 127.3, 127.1, 126.9, 125.8, 125.5, 123.1, 119.1, 21.5.

HRMS (ESI): Calcd. for $C_{27}H_{21}N_2O$ [M^++H] 389.1655. Found: 389.1659.

3.8 General procedure for the synthesis of indole appended purine derivatives 57-86

Into a Schlenk tube, 6-anilinopurine (**6**) (0.5 mmol), alkyne (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), CsOAc (0.15 mmol), and MeOH (2 mL) were added and the contents were heated at 70 ^{o}C (oil bath temperature) for 24 h. The resulting mixture was cooled to room temperature (25 ^{o}C) and diluted with EtOAc (10 mL). This solution was treated with water (25 mL) and EtOAc (3x20 mL), the organic layer washed with brine solution, dried over anh. Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (8:2) mixture as the eluent.

Compound 57



Yield: 0.203 g (85%, white solid).

Mp: 168-170 ^{o}C.

IR (KBr): 3057, 2917, 1589, 1570, 1454, 1412, 1327, 1182, 1024, 781, 693 cm^{-1}.

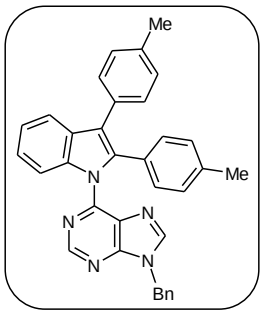
^{1}H NMR: δ 8.86 (s, 1H), 7.89 (s, 1H), 7.72-7.70 (m, 1H), 7.67-7.65 (m, 1H), 7.40-7.33 (m, 8H), 7.30-7.23 (m, 4H), 7.13-7.04 (m, 5H), 5.44 (s, 2H).

^{13}C NMR: δ 153.7, 152.5, 149.9, 144.3, 137.5, 136.6, 134.9, 134.4, 132.1, 130.5, 129.5, 129.3, 128.8, 128.3, 128.1, 127.9, 127.7, 127.1, 126.5, 123.7, 122.2, 120.3, 119.9, 112.0, 47.6.

HRMS (ESI): Calcd. for $C_{32}H_{24}N_5$ [M^++H] 478.2032. Found: 478.2024.

X-ray structure was determined for this compound.

Compound 58



Yield: 0.206 g (82%, white solid).

Mp: 114-118 ^{o}C.

IR (KBr): 3032, 2919, 1572, 1454, 1329, 1100, 1019, 820, 725 cm^{-1}.

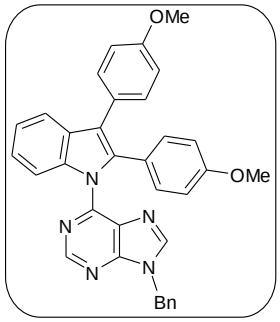
^{1}H NMR: δ 8.86 (s, 1H), 7.91 (s, 1H), 7.70 (d, *J* = 6.8 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.40-7.38 (m, 3H), 7.30-7.21 (m, 6H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 7.6 Hz, 2H), 5.44 (s, 2H), 2.39 (s, 3H), 2.23 (s, 3H).

^{13}C NMR: δ 153.7, 152.5, 150.0, 144.2, 137.4, 136.7, 136.5, 135.9, 134.9, 131.4,

130.2, 129.6, 129.2, 129.0, 128.7, 128.4, 128.2, 127.8, 123.4, 122.0, 119.9, 111.8, 47.5, 21.3.

HRMS (ESI): Calcd. for $C_{34}H_{28}N_5$ [M^++H] 506.2345. Found: 506.2340.

Compound 59



Yield: 0.224 g (84%, white solid).

Mp: 96-100 ^oC.

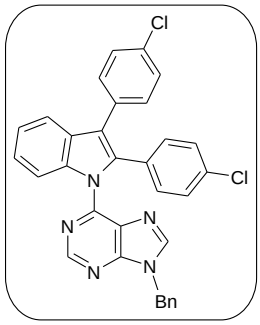
IR (KBr): 3059, 2926, 2836, 1589, 1572, 1454, 1329, 1246, 1177, 1028, 831, 727 cm^{-1}.

^1H NMR: δ 8.88 (s, 1H), 7.90 (s, 1H), 7.68 (dd, *J* ~ 6.2 Hz and *J* ~ 3.0 Hz, 1H), 7.63 (dd, *J* ~ 6.2 Hz and *J* ~ 3.0 Hz, 1H), 7.41- 7.36 (m, 3H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.27-7.22 (m, 4H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 5.43 (s, 2H), 3.84 (s, 3H), 3.71 (s, 3H).

^{13}C NMR: δ 158.6, 158.2, 153.7, 152.5, 150.0, 144.2, 137.3, 136.2, 134.9, 131.6, 131.4, 129.7, 129.2, 128.7, 128.1, 127.8, 126.8, 124.6, 123.3, 122.0, 119.7, 119.2, 113.8, 113.2, 111.8, 55.2, 55.1, 47.5.

HRMS (ESI): Calcd. for $C_{34}H_{28}N_5O_2$ [M^++H] 538.2244. Found: 538.2222.

Compound 60



Yield: 0.217 g (80%, white solid).

Mp: 140-144 ^{o}C.

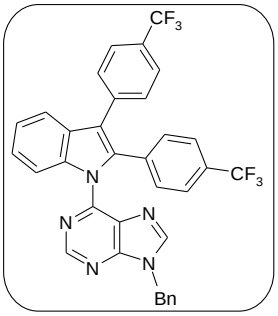
IR (KBr): 3057, 2924, 1593, 1572, 1453, 1329, 1088, 1013, 829, 723 cm^{-1}.

^{1}H NMR: δ 8.89 (s, 1H), 7.90 (s, 1H), 7.69-7.65 (m, 2H), 7.43-7.25 (m, 11H), 7.07-7.02 (m, 4H), 5.45 (s, 2H).

^{13}C NMR: δ 153.8, 152.6, 149.4, 144.6, 137.4, 135.5, 134.8, 133.3, 132.6, 131.6$_4$, 131.6$_0$, 130.4, 129.3, 129.0, 128.8$_2$, 128.7$_6$, 128.2, 127.9, 127.8, 124.1, 122.5, 119.7, 119.4, 112.1, 47.6.

HRMS (ESI): Calcd. for $C_{32}H_{22}Cl_2N_5$ [M^{+}+H] 546.1253. Found: 546.1224.

Compound 61



Yield: 0.247 g (81%, white solid).

Mp: 108-110 ^{o}C.

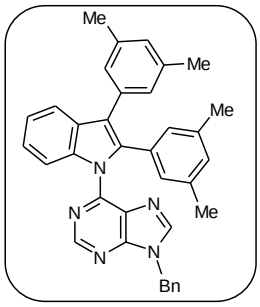
IR (KBr): 3074, 2926, 1627, 1599, 1567, 1457, 1419, 1331, 1221, 1123, 1068, 1019, 843, 750, 723 cm^{-1}.

^{1}H NMR: δ 8.90 (s, 1H), 7.89 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.40-7.29 (m, 7H), 7.25-7.21 (m, 4H), 5.45 (s, 2H).

^{13}C NMR: δ 153.9, 152.6, 149.2, 144.7, 137.8, 137.6, 135.5, 135.4, 134.7, 130.6$_4$, 130.5$_7$, 129.5, 129.3, 129.1$_4$, 129.0$_6$, 128.9, 128.8, 128.4, 127.8, 125.5, 124.9, 124.6, 123.0, 122.8, 119.9, 119.8, 112.4, 47.7.

HRMS (ESI): Calcd. for $C_{34}H_{22}F_6N_5$ [M^{+}+H] 614.1780. Found: 614.1776.

Compound 62



Yield: 0.218 g (82%, white solid).

Mp: 102-106 ^{o}C.

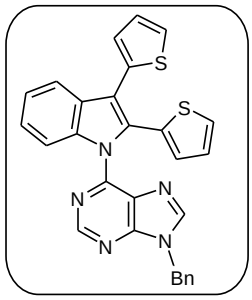
IR (KBr): 2915, 1595, 1567, 1458, 1332, 1222, 1019, 849, 723 cm^{-1}.

^{1}H NMR: δ 8.87 (s, 1H), 7.93 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.39-7.37 (m, 3H), 7.27-7.23 (m, 4H), 7.03 (s, 2H), 6.93 (s, 1H), 6.75 (s, 2H), 6.72 (s, 1H), 5.45 (s, 2H), 2.29 (s, 6H), 2.04 (s, 6H).

^{13}C NMR: δ 153.6, 152.5, 150.2, 144.3, 137.4, 136.7, 135.1, 134.2, 131.8, 129.7, 129.2, 128.7, 128.2, 128.1, 127.7, 123.4, 121.9, 120.3, 120.1, 111.8, 47.5, 21.4, 21.2.

HRMS (ESI): Calcd. for $C_{36}H_{32}N_5$ [M^++H] 534.2658. Found: 534.2657.

Compound 63



Yield: 0.148 g (61%, white solid).

Mp: mp 192-194 ^{o}C.

IR (KBr): 2964, 1595, 1573, 1496, 1458, 1332, 1266, 1025, 800, 707 cm^{-1}.

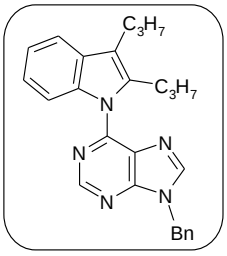
^{1}H NMR: δ 8.92 (s, 1H), 7.98 (s, 1H), 7.86-7.84 (m, 1H), 7.53-7.50 (m, 1H), 7.44-7.37 (m, 3H), 7.35-7.27 (m, 5H), 7.23-7.19 (m, 2H), 7.12-7.10 (m, 1H), 6.96 (d, *J* = 3.6 Hz, 1H), 6.85-6.82 (m, 1H), 5.45 (s, 2H).

^{13}C NMR: δ 153.8, 152.5, 149.1, 144.6, 137.3, 135.1, 134.8, 132.2, 130.6, 130.2, 129.3, 129.0, 128.8, 128.6, 128.0, 127.4, 127.3, 127.0, 126.5, 125.4,

124.3, 122.4, 120.3, 115.1, 111.9, 47.7.

HRMS (ESI): Calcd. for $C_{28}H_{20}N_5S_2$ [M^++H] 490.1161. Found: 490.1158.

Compound 64



Yield: 0.161 g (79%, gummy liquid).

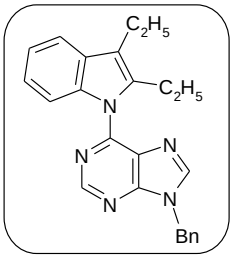
IR (neat): 3101, 2964, 2866, 1573, 1458, 1326, 1211, 1068, 1019, 751, 723 cm^{-1}.

^{1}H NMR: δ 8.99 (s, 1H), 8.07 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.43-7.41 (m, 6H), 7.18-7.10 (m, 2H), 5.51 (s, 2H), 3.07 (t, *J* ~ 7.6 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 1.76-1.70 (m, 2H), 1.30-1.25 (m, 2H), 1.04 (t, *J* = 7.2 Hz, 3H), 0.74 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 153.7, 152.6, 150.1, 143.9, 137.2, 136.8, 134.9, 130.0, 129.3, 128.8, 128.1, 127.1, 122.0, 121.0, 118.5, 117.9, 111.8, 47.7, 27.2, 26.7, 23.9, 23.3, 14.5, 14.0.

HRMS (ESI): Calcd. for $C_{26}H_{28}N_5$ [M^++H] 410.2345. Found: 410.2344.

Compound 65



Yield: 0.139 g (73%, gummy liquid).

IR (neat): 3052, 2959, 1573, 1463, 1332, 1222, 1063, 1019, 729, 696 cm^{-1}.

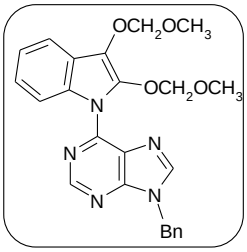
^{1}H NMR: δ 9.01 (s, 1H), 8.07 (s, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.47-7.40 (m, 6H), 7.20-7.13 (m, 2H), 5.47 (s, 2H), 3.10 (qrt, *J* ~ 6.9 Hz, 2H), 2.84 (qrt, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H), 0 98 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 153.7, 152.6, 149.9, 143.9, 138.3, 136.9, 134.9, 129.7, 129.3, 128.8, 128.1, 127.1, 122.0, 121.1, 118.9, 118.4, 111.9, 47.6, 18.6, 17.7, 15.4,

14.9.

HRMS (ESI): Calcd. for $C_{24}H_{24}N_5$ [M^++H] 382.2032. Found: 382.2032.

Compound 66



Yield: 0.127 g (54%, gummy liquid).

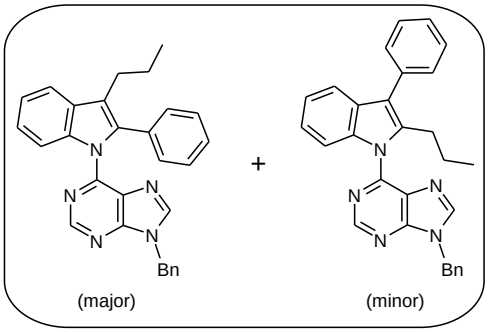
IR (neat): 2948, 2871, 1567, 1458, 1332, 1211, 1145, 1052, 849, 734, 614 cm^{-1}.

^{1}H NMR: δ 9.01 (s, 1H), 8.08 (s, 1H), 7.78 (dd, *J* ~ 5.8 Hz and ~3.0 Hz, 1H), 7.55 (dd, *J* = 6.0 Hz and 2.8 Hz, 1H), 7.40-7.38 (m, 5H), 7.27-7.23 (m, 2H), 5.49 (s, 2H), 5.19 (s, 2H), 4.94 (s, 2H), 4.74 (s, 2H), 4.34 (s, 2H), 3.47 (s, 3H), 3.07 (s, 3H).

^{13}C NMR: δ 153.9, 152.5, 149.5, 144.2, 137.2, 134.9, 129.3, 128.8, 128.7, 128.1, 127.1, 123.8, 121.9, 119.5, 116.7, 112.4, 94.9_4, 94.8_7, 59.0, 58.8, 55.4, 55.1, 47.7.

HRMS (ESI): Calcd. for $C_{26}H_{28}N_5O_4$ [M^++H] 474.2142. Found: 474.2140.

Compound 67 (isomer ratio 10:1)



Yield: 0.178 g (81%, white solid).

Mp: 68-70 ^{o}C.

IR (KBr): 3058, 3030, 2953, 2926, 1600, 1567, 1458, 1332, 1222, 745, 729, 701, 647 cm^{-1}.

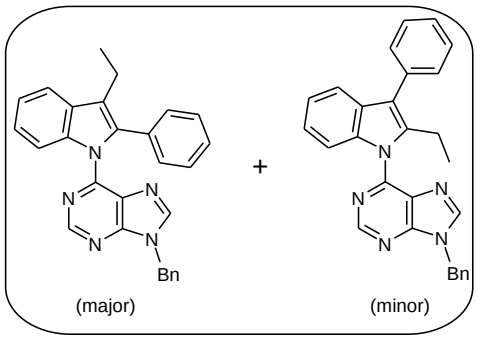
^{1}H NMR: for major isomer δ 8.80 (s, 1H), 7.87 (s, 1H), 7.72-7.69 (m, 2H), 7.42-7.35 (m, 4H), 7.29-7.18 (m, 8H), 5.40 (s, 2H), 2.86 (t, *J* = 7.6 Hz, 2H),

1.83-1.74 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); for minor isomer δ 9.05 (s), 8.12 (s), 7.60-7.58 (m), 7.53-7.48 (m), 5.52 (s), 3.19 (t, *J* = 7.6 Hz), 1.24-1.18 (m), 0.63 (t, *J* = 7.2 Hz), remaining peaks were merged with major isomer peaks.

^{13}C NMR: for major isomer δ 153.5, 152.4, 150.0, 143.8, 137.4, 136.5, 135.0, 132.9, 130.1, 129.8, 129.2, 128.6, 127.8, 126.9, 123.3, 121.5, 119.9, 119.5, 112.1, 47.4, 26.8, 24.0, 14.4; for minor isomer δ 153.9, 152.7, 149.8, 144.2, 137.8, 130.2, 129.3, 128.8, 128.5, 128.1, 127.5, 126.6, 122.6, 121.7, 119.2, 111.8, 47.7, 27.4, 23.0, 13.8, remaining peaks were merged with major isomer peaks.

HRMS (ESI): Calcd. for $C_{29}H_{26}N_5$ [M^++H] 444.2189. Found: 444.2186.

Compound 68 (isomer ratio 10:0.8)



Yield: 0.169 g (79%, white solid).

Mp: 60-62 ^{o}C.

IR (KBr): 2964, 2926, 1595, 1567, 1452, 1326, 1222, 1074, 1019, 723, 696 cm^{-1}.

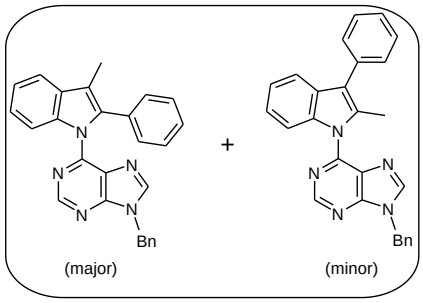
^{1}H NMR: for major isomer δ 8.79 (s, 1H), 7.87 (s, 1H), 7.71-7.68 (m, 2H), 7.39-7.36 (m, 3H), 7.26-7.16 (m, 9H), 5.42 (s, 2H), 2.89 (qrt, *J* ~ 7.5 Hz, 2H), 1.35 (t, *J* ~ 7.4 Hz, 3H); for minor isomer δ 9.05 (s), 8.11 (s), 7.60-7.57 (m), 7.52-7.43 (m), 5.54 (s), 3.20 (qrt, *J* = 7.6 Hz), 0.86-0.82 (m), remaining peaks were merged with major isomer peaks.

^{13}C NMR: for major isomer δ 153.5, 152.4, 150.0, 143.9, 137.4, 136.0, 135.0, 132.8, 129.8, 129.2, 128.6, 127.8, 126.9, 123.3, 121.5, 121.3, 119.4, 112.2, 47.4, 18.0, 15.4; for minor isomer δ 152.7, 144.3, 130.1, 129.3, 128.8, 128.5, 128.2, 127.5, 126.6, 122.6, 121.7, 119.2, 47.7, 18.9, 14.5,

remaining peaks were merged with major isomer peaks.

HRMS (ESI): Calcd. for $C_{28}H_{24}N_5$ [M^++H] 430.2032. Found: 430.2032.

Compound 69 (isomer ratio 10:0.8)



Yield: 0.163 g (79%, white solid).

Mp: 64-66 ^oC.

IR (KBr): 3058, 2910, 1589, 1567, 1452, 1332, 1249, 1216, 1079, 1019, 740, 718, 696, 641 cm^{-1}.

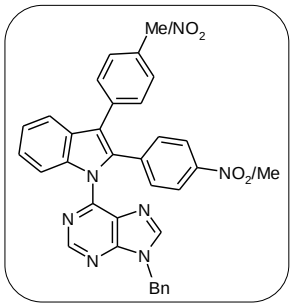
^1H NMR: for major isomer δ 8.84 (s, 1H), 7.86 (s, 1H), 7.74 (dd, *J* ~ 5.4 Hz and *J* ~ 3.0 Hz, 1H), 7.66 (dd, *J* ~ 5.8 Hz and *J* ~ 2.6 Hz, 1H), 7.36 (br, 4H), 7.29-7.16 (m, 8H), 5.39 (s, 2H), 2.47 (s, 3H); for minor isomer δ 9.05 (s), 8.12 (s), 7.57-7.49 (m), 5.50 (s), 2.59 (s), remaining peaks were merged with major isomer peaks.

^{13}C NMR: for major isomer δ 153.5, 152.4, 150.2, 143.9, 137.4, 136.4, 135.0, 132.8, 130.8, 129.8, 129.2, 128.7, 127.8_1, 127.7_6, 126.8, 123.6, 121.7, 119.2, 115.1, 112.0, 47.4, 9.8; for minor isomer δ 144.2, 130.0, 128.8, 128.5, 128.2, 127.3, 126.5, 122.6, 121.9, 47.7, 13.1, remaining peaks were merged with major isomer peaks.

HRMS (ESI): Calcd. for $C_{27}H_{22}N_5$ [M^++H] 416.1876. Found: 416.1870.

X-ray structure was determined for this compound (major isomer).

Compound 70



In this case, the isomer ratio was ~1:1 but both the isomers were isolated (overall yield after isolation 67%).

1st isomer, higher R_f

Yield: 0.094 g (35%, yellow solid).

Mp: 140-144 ^{o}C.

IR (KBr): 2915, 1595, 1578, 1450, 1332, 1213, 1159, 1108, 1014, 897, 863, 738 cm^{-1}.

^{1}H NMR: δ 8.88 (s, 1H), 7.92-7.88 (m, 3H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.42-7.37 (m, 4H), 7.35-7.27 (m, 4H), 7.25-7.19 (m, 5H), 5.44 (s, 2H), 2.41 (s, 3H).

^{13}C NMR: δ 153.9, 152.6, 149.4, 146.3, 144.5, 139.4, 137.9, 137.0, 134.7, 133.8, 130.9, 130.2, 129.5, 129.4, 128.9, 127.9, 127.5, 124.9, 123.0, 122.7, 120.5, 112.4, 47.7, 21.4.

LC-MS: *m/z* 537 $[M+1]^{+}$.

Anal. Calcd. for $C_{33}H_{24}N_6O_2$: C, 73.87; H, 4.51; N, 15.66. Found: C, 73.95; H, 4.58; N, 15.56.

2nd isomer, lower R_f:

Yield: 0.085 g (32%, yellow solid).

Mp: 104-108 ^{o}C.

IR (KBr): 2926, 1600, 1578, 1512, 1463, 1342, 1238, 1096, 855, 723 cm^{-1}.

^{1}H NMR: δ 8.89 (s, 1H), 8.20 (d, *J* = 8.8 Hz, 2H), 7.93 (s, 1H), 7.73-7.72 (m, 1H), 7.61-7.59 (m, 1H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.40-7.38 (m, 3H), 7.30-7.27 (m, 4H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 7.6 Hz, 2H), 5.45 (s, 2H), 2.25 (s, 3H).

^{13}C NMR: δ 153.9, 152.6, 149.4, 146.1, 144.7, 142.3, 138.2, 137.8, 137.5, 134.8,

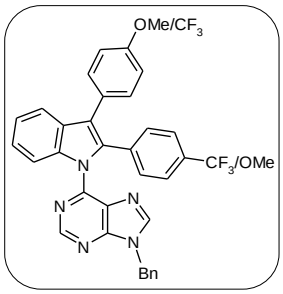
130.8, 130.4, 129.3, 128.9, 128.4, 128.3, 128.1, 127.9, 124.0, 123.7, 122.7, 119.2, 117.4, 112.2, 47.6, 21.3.

LC-MS: *m/z* 537 $[M+1]^+$.

Anal. Calcd. for $C_{33}H_{24}N_6O_2$: C, 73.87; H, 4.51; N, 15.66. Found: C, 73.97; H, 4.56; N, 15.52.

Compound 71

In this case, the isomer ratio was ~2:1 but both the isomers were isolated (overall yield after isolation 76%).



1st isomer, higher R_f

Yield: 0.147 g (51%, white solid).

Mp: 168-172 ^oC.

IR (KBr): 3051, 1573, 1520, 1323, 1265, 1166, 1066, 1031, 1018, 867, 731 cm^{-1}.

^1H NMR: δ 8.90 (s, 1H), 7.90 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.42-7.40 (m, 3H), 7.34-7.23 (m, 10H), 6.95 (d, *J* = 8.4 Hz, 2H), 5.46 (s, 2H), 3.88 (s, 3H).

^{13}C NMR: δ 158.6, 153.8, 152.6, 149.6, 144.4, 137.6, 136.1, 134.8, 134.6, 131.5, 130.5, 129.7, 129.3, 128.8, 128.5, 127.8, 127.7, 125.9, 124.6_4, 124.6_0, 124.3, 122.4, 121.4, 120.2, 114.1, 112.2, 55.3, 47.6.

HRMS (ESI): Calcd. for $C_{34}H_{25}F_3N_5O$ $[M^+ + H]$ 576.2012. Found: 576.2006.

2nd isomer, lower R_f

Yield: 0.072 g (25%, white solid).

Mp: 144-148 ^oC.

IR (KBr): 3050, 1596, 1573, 1454, 1323, 1264, 1249, 1121, 1066, 1030, 835, 733 cm^{-1}.

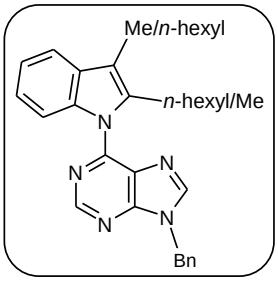
^1H NMR: δ 8.92 (s, 1H), 7.93 (s, 1H), 7.72 (d, *J* = 6.0 Hz, 1H), 7.63 (d, *J* = 7.6 Hz,

3H), 7.53-7.51 (m, 2H), 7.42-7.41 (m, 3H), 7.30-7.29 (m, 4H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 2H), 5.47 (s, 2H), 3.75 (s, 3H).

^{13}C NMR: δ 159.0, 153.8, 152.6, 149.7, 144.6, 138.7, 137.4, 137.3, 134.9, 131.8, 130.5, 129.3, 128.8, 128.3, 127.9, 125.3, 123.8, 123.7, 122.4, 119.3, 118.0, 113.5, 112.0, 55.2, 47.6.

HRMS (ESI): Calcd. for $C_{34}H_{25}F_3N_5O$ [M^++H] 576.2012. Found: 576.2004.

Compound 72 (Isomer ratio 10:8)



Yield: 0.135 g (64%, gummy liquid).

IR (neat): 3052, 2959, 2849, 1573, 1458, 1326, 1244, 729, 641 cm^{-1}.

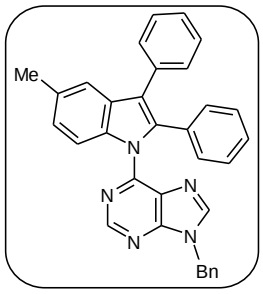
^{1}H NMR: δ 9.01 (d, *J* = 2.8 Hz), 8.06 (s), 7.58-7.54 (m), 7.50 (d, *J* = 8.0 Hz), 7.40-7.38 (m), 7.22-7.14 (m), 5.45 (d, *J* = 4.8 Hz), 3.10 (t, *J* ~ 7.4 Hz), 2.80 (t, *J* ~ 7.4 Hz), 2.52 (s), 2.36 (s), 1.74-1.67 (m), 1.46-1.31 (m), 1.16-1.11 (m), 0.94-0.88 (m), 0.78 (t, *J* ~ 6.8 Hz).

^{13}C NMR: δ 153.7, 152.5$_4$, 152.4$_6$, 150.0, 149.7, 143.9, 143.8, 137.4, 136.7, 136.5, 135.0, 132.7, 130.5, 130.1, 129.2, 128.7, 128.0$_3$, 127.9$_9$, 127.1, 122.1, 121.9, 121.1, 118.2, 118.1, 117.9, 112.8, 111.9, 111.7, 47.5, 31.9, 31.3, 30.3, 29.5, 29.4, 28.8, 25.1, 24.5, 22.7, 22.4, 14.2, 14.0, 12.1, 9.1.

LC-MS: 424 [M+1]$^+$.

Anal. Calcd. for $C_{27}H_{29}N_5$: C, 76.56; H, 6.90; N, 16.53. Found: C, 76.45; H, 6.83; N, 16.65.

Compound 73



Yield: 0.214 g (87%, white solid).

Mp: 100-104 ^{o}C.

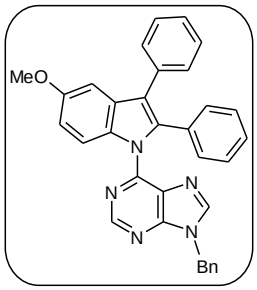
IR (KBr): 3025, 2915, 1595, 1573, 1452, 1414, 1326, 1107, 1025, 904, 800, 718 cm^{-1}.

^{1}H NMR: δ 8.84 (s, 1H), 7.89 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.48 (s, 1H), 7.41-7.34 (m, 7H), 7.31-7.26 (m, 3H), 7.12-7.03 (m, 6H), 5.44 (s, 2H), 2.45 (s, 3H).

^{13}C NMR: δ 153.7, 152.5, 150.0, 144.2, 136.6, 135.8, 135.0, 134.6, 132.2, 131.6, 130.5, 130.4, 129.7, 129.3, 128.8, 128.3, 127.9, 127.7, 127.0, 126.5, 125.2, 120.2, 119.6, 111.7, 47.6, 21.6.

HRMS (ESI): Calcd. for $C_{33}H_{26}N_5$ [M^{+}+H] 492.2189. Found: 492.2188.

Compound 74



Yield: 0.212 g (84%, white solid).

Mp: 210-212 ^{o}C.

IR (KBr): 3058, 2833, 1567, 1447, 1332, 1222, 1173, 1112, 1036, 833, 729 cm^{-1}.

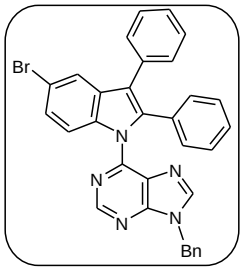
^{1}H NMR: δ 8.84 (s, 1H), 7.89 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.40-7.34 (m, 7H), 7.31-7.25 (m, 3H), 7.16-7.05 (m, 6H), 6.92 (dd, *J* = 9.2 Hz and 2.4 Hz, 1H), 5.42 (s, 2H), 3.84 (s, 3H).

^{13}C NMR: δ 155.9, 153.7, 152.5, 149.9, 144.2, 137.2, 134.9, 134.5, 132.5, 132.1,

130.4, 130.1, 129.2, 128.7, 128.4, 127.8, 127.7, 127.0, 126.5, 120.3, 113.3, 112.9, 101.8, 55.9, 47.5.

HRMS (ESI): Calcd. for $C_{33}H_{26}N_5O$ [M^++H] 508.2138. Found: 508.2137.

Compound 75



Yield: 0.256 g (92%, white solid).

Mp: 156-158 ^oC.

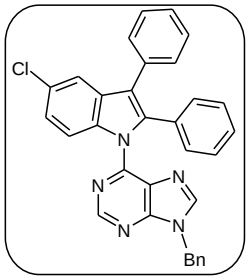
IR (KBr): 3047, 2921, 1595, 1567, 1447, 1359, 1332, 1211, 915, 866, 805, 707 cm^{-1}.

^1H NMR: δ 8.86 (s, 1H), 7.91 (s, 1H), 7.82 (d, *J* = 1.6 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.40- 7.28 (m, 11H), 7.11-7.06 (m, 5H), 5.45 (s, 2H).

^{13}C NMR: δ 153.9, 152.6, 149.4, 144.6, 137.7, 136.1, 134.8, 133.7, 131.6, 131.2, 130.4_4, 130.3_5, 129.3, 128.9, 128.5, 127.9, 127.8, 127.4, 126.8, 126.4, 122.5, 119.6, 115.5, 113.6, 47.7.

HRMS (ESI): Calcd. for $C_{32}H_{23}BrN_5$ [M^++H] 556.1137. Found: 556.1136.

Compound 76



Yield: 0.205 g (80%, white solid).

Mp: 140-142 ^oC.

IR (KBr): 3058, 2921, 1595, 1578, 1452, 1326, 1233, 1211, 1074, 926, 718, 636 cm^{-1}.

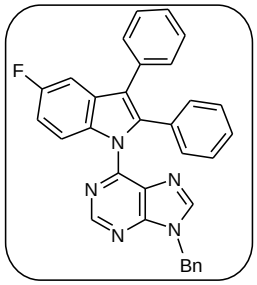
^1H NMR: δ 8.86 (s, 1H), 7.91 (s, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz,

1H), 7.40-7.33 (m, 7H), 7.32-7.28 (m, 3H), 7.22 (dd, *J* ~ 8.6 Hz and ~1.8 Hz, 1H), 7.13-7.04 (m, 5H), 5.45 (s, 2H).

^{13}C NMR: δ 153.8, 152.5, 144.5, 137.8, 135.7, 134.8, 133.7, 131.6, 130.6, 130.4, 130.3, 129.3, 128.9, 128.5, 128.0, 127.9, 127.8, 127.4, 126.8, 123.8, 119.7, 119.4, 113.2, 47.7.

HRMS (ESI): Calcd. for $C_{32}H_{23}N_5Cl$ [M^++H] 512.1643. Found: 512.1644.

Compound 77



Yield: 0.221 g (89%, white solid).

Mp: 78-80 ^{o}C.

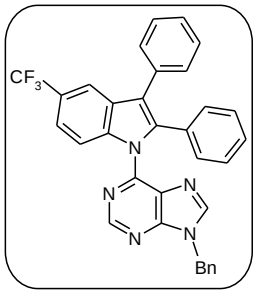
IR (KBr): 3057, 1594, 1567, 1457, 1331, 1232, 1101, 925, 799, 734, 701 cm^{-1}.

^{1}H NMR: δ 8.86 (s, 1H), 7.90 (s, 1H), 7.60 (dd, *J* ~ 9.0 Hz and ~4.2 Hz, 1H), 7.42-7.34 (m, 9H), 7.31-7.26 (m, 2H), 7.12-6.98 (m, 6H), 5.44 (s, 2H).

^{13}C NMR: δ 159.3 (d, $^{1}J_{(C\text{-}F)}$ = 235.7 Hz), 153.7, 152.4, 149.5, 144.5, 138.1, 134.8, 133.8, 133.7, 131.6, 130.3, 130.2, 129.2, 128.7, 128.4, 127.9, 127.8, 127.3, 126.7, 120.0, 113.0 (d, $^{4}J_{(CF)}$= 9.1 Hz), 111.6 (d, $^{3}J_{(CF)}$ = 25.7 Hz), 105.0 (d, $^{3}J_{(CF)}$ = 24.0 Hz), 47.5.

HRMS (ESI): Calcd. for $C_{32}H_{23}N_5F$ [M^++H] 496.1938. Found: 496.1937.

Compound 78



Yield: 0.246 g (90%, white solid).

Mp: 168-170 ^{o}C.

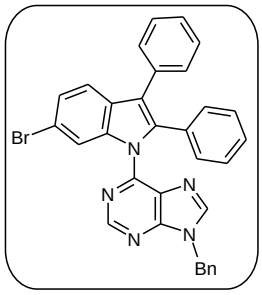
IR (KBr): 3058, 2926, 1595, 1578, 1452, 1321, 1156, 1112, 1058, 759, 701 cm^{-1}.

^{1}H NMR: δ 8.88 (s, 1H), 7.98 (s, 1H), 7.94 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.39-7.30 (m, 10H), 7.11-7.05 (m, 5H), 5.46 (s, 2H).

^{13}C NMR: δ 153.9, 152.6, 149.2, 144.8. 138.6, 138.3, 134.7, 133.5, 131.4, 130.5, 130.4, 129.3, 128.9, 128.6, 128.2, 128.0, 127.9, 127.6, 127.0, 124.7, 123.8, 120.4, 117.6, 112.3, 47.7.

HRMS (ESI): Calcd. for $C_{33}H_{23}F_3N_5$ $[M^+ + H]$ 546.1906. Found: 546.1905.

Compound 79



Yield: 0.222 g (80%, white solid).

Mp: 176-178 ^{o}C.

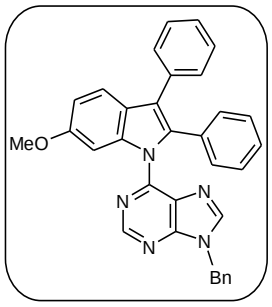
IR (KBr): 3063, 1605, 1572, 1451, 1402, 1369, 1232, 1177, 953, 805, 728, 695 cm^{-1}.

^{1}H NMR: δ 8.90 (s, 1H), 7.90 (s, 1H), 7.85 (d, *J* = 1.6 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.42-7.35 (m, 8H), 7.33-7.28 (m, 1H), 7.27-7.25 (m, 2H), 7.13-7.04 (m, 5H), 5.43 (s, 2H).

^{13}C NMR: δ 153.8, 152.5, 149.3, 144.7, 138.0, 137.2, 134.7, 133.8, 131.5, 130.3_4, 130.3_0, 129.3, 128.8, 128.4, 128.0, 127.9, 127.8, 127.3, 126.7, 125.3, 121.1, 119.9, 117.1, 115.0, 47.6.

HRMS (ESI): Calcd. for $C_{32}H_{23}BrN_5$ $[M^+ + H]$ 556.1138. Found: 556.1136.

Compound 80



Yield: 0.225 g (89%, white solid).

Mp: 142-144 ^{o}C.

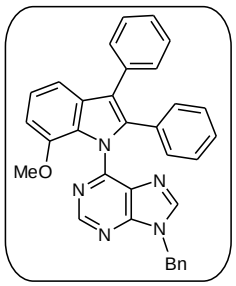
IR (KBr): 3057, 2833, 1572, 1451, 1325, 1205, 1029, 827, 772, 717, 695 cm^{-1}.

^{1}H NMR: δ 8.88 (s, 1H), 7.86 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.37-7.32 (m, 7H), 7.29-7.23 (m, 4H), 7.10-7.03 (m, 5H), 6.90 (dd, *J* = 8.8 Hz and 2.0 Hz, 1H), 5.43 (s, 2H), 3.82 (s, 3H).

^{13}C NMR: δ 157.6, 153.7, 152.5, 150.1, 144.2, 138.3, 135.5, 134.9, 134.5, 132.3, 130.4, 130.3, 129.3, 128.8, 128.3, 128.0, 127.8, 127.7, 126.8, 126.5, 123.9, 120.6, 120.2, 111.2, 96.4, 55.9, 47.6.

HRMS (ESI): Calcd. for $C_{33}H_{26}N_5O$ [M^++H] 508.2138. Found: 508.2139.

Compound 81



Yield: 0.238 g (92%, white solid).

Mp: 110-112 ^{o}C.

IR (KBr): 3058, 2926, 1600, 1573, 1490, 1463, 1337, 1233, 1074, 981, 734, 696 cm^{-1}.

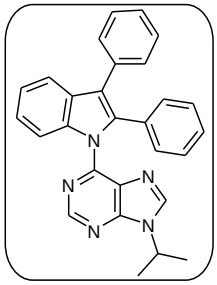
^{1}H NMR: δ 8.84 (s, 1H), 7.95 (s, 1H), 7.41-7.28 (m, 8H), 7.24-7.11 (m, 6H), 7.08-7.00 (m, 3H), 6.70 (d, *J* = 7.6 Hz, 1H), 5.46 (d, *J* = 11.2 Hz, 2H), 3.45 (s, 3H).

^{13}C NMR: δ 153.1, 151.8, 151.7, 147.1, 144.9, 137.8, 135.2, 134.7, 131.5, 131.3,

131.0, 130.7, 130.4, 129.2, 128.7, 128.2, 127.6, 127.5, 127.4, 126.2, 121.9, 118.9, 113.0, 105.3, 55.8, 47.5.

HRMS (ESI): Calcd. for $C_{33}H_{26}N_5O$ [M^++H] 508.2138. Found: 508.2138.

Compound 82



Yield: 0.167 g (78%, white solid).

Mp: 132-136 ^oC.

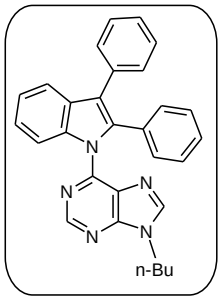
IR (KBr): 3123, 3052, 2959, 1600, 1573, 1463, 1359, 1205, 1151, 1025, 932, 789, 734, 707 cm^{-1}.

^1H NMR: δ 8.80 (s, 1H), 8.04 (s, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.41-7.34 (m, 4H), 7.30-7.23 (m, 3H), 7.16-7.06 (m, 5H), 4.98-4.93 (m, 1H), 1.67 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR: δ 153.4, 151.9, 149.8, 142.3, 137.6, 136.6, 134.5, 132.1, 131.2, 130.5, 129.5, 128.7, 128.3, 127.8, 127.1, 126.5, 123.6, 122.1, 120.3, 119.9, 112.0, 47.8, 22.6.

HRMS (ESI): Calcd. for $C_{28}H_{24}N_5$ [M^++H] 430.2032. Found: 430.2023.

Compound 83



Yield: 0.191 g (86%, white solid).

Mp: 150-152 ^oC.

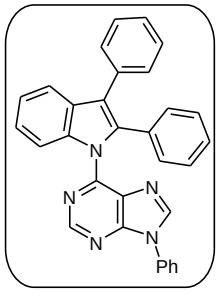
IR (KBr): 3112, 2959, 2932, 1595, 1573, 1458, 1332, 1238, 1189, 1025, 921, 784, 734 cm^{-1}.

^{1}H NMR: δ 8.83 (s, 1H), 7.93 (s, 1H), 7.73 (dd, *J* ~ 6.8 Hz and ~1.6 Hz, 1H), 7.66 (dd, *J* ~ 7.0 Hz and ~1.4 Hz, 1H), 7.42-7.34 (m, 4H), 7.31-7.23 (m, 3H), 7.16-7.13 (m, 2H), 7.12-7.05 (m, 3H), 4.27 (t, *J* = 7.2. Hz, 2H), 1.95-1.87 (m, 2H), 1.40-1.32 (m, 2H), 0.98 (t, *J* ~ 7.4 Hz, 3H).

^{13}C NMR: δ 153.7, 152.1, 149.7, 144.5, 137.4, 136.5, 134.4, 132.0, 130.4, 129.4, 128.3, 127.7, 127.0, 126.4, 123.6, 122.1, 120.1, 119.9, 111.9, 44.0, 31.8, 19.9, 13.5.

HRMS (ESI): Calcd. for $C_{29}H_{26}N_5$ [M^++H] 444.2189. Found: 444.2189.

Compound 84



Yield: 0.170 g (73%, white solid).

Mp: 142-146 ^{o}C.

IR (KBr): 3052, 2953, 1589, 1562, 1507, 1458, 1364, 1244, 1025, 921, 734, 707 cm^{-1}.

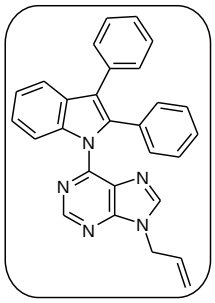
^{1}H NMR: δ 8.91 (s, 1H), 8.25 (s, 1H), 7.77-7.76 (m, 3H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.64 (t, *J* ~ 7.8 Hz, 2H), 7.53 (t, *J* ~ 7.4 Hz, 1H), 7.44-7.37 (m, 5H), 7.35-7.31 (m, 2H), 7.21-7.19 (m, 2H), 7.15-7.10 (m, 3H).

^{13}C NMR: δ 153.3, 153.0, 150.4, 143.3, 137.5, 136.6, 134.3, 134.2, 132.0, 130.5, 130.4, 130.0, 129.5, 128.7, 128.3, 127.8, 127.2, 126.5, 123.7, 123.5, 122.3, 120.5, 120.0, 112.0.

LC-MS: 464 $[M+1]^+$.

Anal. Calcd. for $C_{31}H_{21}N_5$: C, 80.32; H, 4.57; N, 15.11. Found: C, 80.45; H, 4.51; N, 15.21.

Compound 85



Yield: 0.158 g (74%, white solid).

Mp: 196-198 ^{o}C.

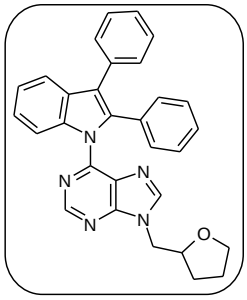
IR (KBr): 3112, 1595, 1567, 1463, 1403, 1332, 1233, 1195, 921, 778, 734, 707 cm^{-1}.

^{1}H NMR: δ 8.85 (s, 1H), 7.93 (s, 1H), 7.72 (dd, *J* ~ 6.8 Hz and ~1.6 Hz, 1H), 7.66 (dd, *J* = 7.2 Hz and 1.2 Hz, 1H), 7.41-7.33 (m, 4H), 7.31-7.23 (m, 3H), 7.14-7.04 (m, 5H), 6.12-6.02 (m, 1H), 5.36 (d, *J* = 10.0 Hz, 1H), 5.18 (d, *J* = 17.2 Hz, 1H), 4.89 (d, *J* = 5.6 Hz, 2H).

^{13}C NMR: δ 153.6, 152.4, 149.9, 144.3, 137.5, 136.6, 134.4, 132.1, 131.3, 130.5, 129.5, 128.3, 128.2, 127.7, 127.1, 126.5, 123.7, 122.2, 120.3, 120.0, 119.6, 111.9, 46.1.

HRMS (ESI): Calcd. for $C_{28}H_{22}N_5$ [M^++H] 428.1876. Found: 428.1874.

Compound 86



Yield: 0.198 g (84%, white solid).

Mp: 162-166 ^{o}C.

IR (KBr): 3052, 2970, 1589, 1573, 1452, 1321, 1211, 1074, 915, 833, 734 cm^{-1}.

^{1}H NMR: δ 8.83 (s, 1H), 8.10 (s, 1H), 7.73 (dd, *J* ~ 6.8 Hz and ~ 1.2 Hz, 1H), 7.67 (dd, *J* ~ 7.0 Hz and ~ 1.0 Hz, 1H), 7.41-7.33 (m, 4H), 7.30-7.23 (m, 3H), 7.15-7.04 (m, 5H), 4.43-4.39 (m, 1H), 4.32-4.28 (m, 2H), 3.77-3.74 (m,

2H), 2.08-2.02 (m, 1H), 1.88-1.80 (m, 1H), 1.62-1.47 (m, 2H).

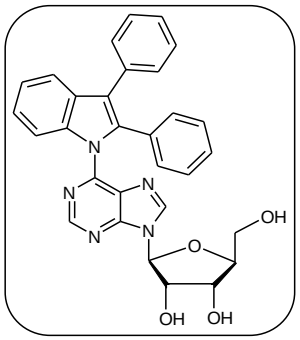
^{13}C NMR: δ 153.9, 152.1, 149.6, 145.8, 137.4, 136.6, 134.4, 132.0, 130.4, 129.4, 128.3, 127.8, 127.7, 127.0, 126.4, 123.6, 122.1, 120.1, 119.8, 111.9, 76.8, 68.5, 47.1, 28.5, 25.8.

HRMS (ESI): Calcd. for $C_{30}H_{26}N_5O$ [M^++H] 472.2138. Found: 472.2139.

3.9 General procedure for the synthesis of indole appended purine nucleoside derivatives 87-89

Into a Schlenk tube, 6-anilinopurine nucleoside **9a** or **9b** (0.3 mmol), alkyne (0.6 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol), CsOAc (0.9 mmol) and MeOH (2 mL) were added and the contents were heated at 70 ^{o}C (oil bath temperature) for 36 h. The resulting mixture was cooled to room temperature (25 ^{o}C) and diluted with EtOAc (10 mL). This solution was treated with water (25 mL) and EtOAc (3x20 mL), the organic layer washed with brine solution, dried over anh. Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (4:6) mixture as the eluent.

Compound 87



Yield: 0.119 g (76%, white solid).

Mp: 116-120 ^{o}C.

IR (KBr): 3331 (br), 2926, 1599, 1578, 1451, 1364, 1336, 1227, 1079, 914, 728, 701 cm^{-1}.

^{1}H NMR: δ 8.63 (s, 1H), 8.04 (s, 1H), 7.71 (s, 1H), 7.56 (s, 1H), 7.37-7.25 (m, 7H), 7.07 (d, *J* = 8.0 Hz, 5H), 5.79 (s, 1H), 5.53 (br, 1H), 4.69 (s, 1H), 4.51 (br, 1H), 4.26 (s, 1H), 4.15 (s, 1H), 3.98 (br, 1H), 3.81 (br, 1H), 3.60 (br,

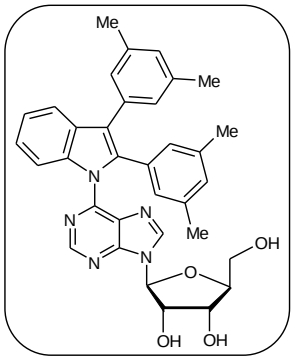
1H).

^{13}C NMR: δ 152.0, 151.7, 150.5, 144.5, 137.3, 136.4, 133.9, 131.6, 130.3, 129.5, 129.2, 128.4, 127.9, 127.4, 126.8, 123.9, 122.6, 121.0, 120.1, 111.9, 91.1, 87.2, 73.9, 71.7, 62.6.

LC-MS: 519 $[M]^+$.

Anal. Calcd. for $C_{30}H_{25}N_5O_4$: C, 69.35; H, 4.85; N, 13.48. Found: C, 69.25; H, 4.91; N, 13.36.

Compound 88



Yield: 0.123 g (71%, white solid).

Mp: 146-150 ^{o}C.

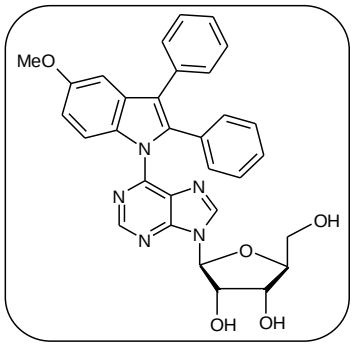
IR (KBr): 3342 (br), 2926, 1595, 1573, 1458, 1332, 1216, 1079, 849, 745 cm^{-1}.

^{1}H NMR: δ 8.66 (s, 1H), 7.96 (s, 1H), 7.72 (s, 1H), 7.60 (d, *J* = 2.4 Hz, 1H), 7.27 (s, 2H), 7.02 (s, 2H), 6.93 (s, 1H), 6.75-6.72 (m, 3H), 5.80 (d, *J* = 4.4 Hz, 1H), 5.44 (br, 1H), 4.79 (s, 1H), 4.37 (s, 1H), 4.26 (s, 2H), 3.91 (br, *J* = 12.0 Hz, 1H), 3.69 (d, *J* = 12.0 Hz, 1H), 3.40 (br, 1H), 2.29 (s, 6H), 2.05 (s, 6H).

^{13}C NMR: δ 152.0, 151.7, 151.0, 144.2, 137.5, 137.4, 136.9, 136.7, 133.8, 131.5, 129.8, 129.3, 129.1, 128.4, 128.2, 128.1, 123.7, 122.4, 121.2, 120.3, 111.9, 91.5, 87.6, 73.9, 72.1, 62.9, 21.4, 21.2.

HRMS (ESI): Calcd. for $C_{34}H_{34}N_5O_4$ $[M^+ + H]$ 576.2612. Found: 576.2615.

Compound 89



Yield: 0.134 g (82%, white solid).

Mp: 144-148 ^{o}C.

IR (KBr): 3348 (br), 2926, 1600, 1573, 1452, 1370, 1326, 1222, 1030, 904, 729, 696 cm^{-1}.

^{1}H NMR: δ 8.64 (s, 1H), 8.02 (s, 1H), 7.56 (d, *J* = 9.2 Hz, 1H), 7.38-7.30 (m, 5H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.13-7.05 (m, 5H), 6.93 (dd, *J* = 9.2 Hz and 2.4 Hz, 1H), 5.83 (d, *J* = 7.2 Hz, 1H), 5.51 (br, 1H), 4.87 (t, *J* = 5.6 Hz, 1H), 4.39 (d, *J* = 4.8 Hz, 1H), 4.29 (s, 1H), 3.99-3.91 (m, 2H), 3.85 (s, 3H), 3.71 (br, 1H), 3.41 (br, 1H).

^{13}C NMR: δ 156.1, 152.0, 151.6, 150.6, 144.3, 137.1, 134.1, 132.3, 131.7, 130.3$_4$, 130.2$_9$, 129.1, 128.5, 127.9, 127.3, 126.8, 121.1, 113.4, 113.0, 102.1, 91.3, 87.5, 73.9, 72.0, 62.8, 56.0.

LC-MS: 550 $[M+1]^{+}$.

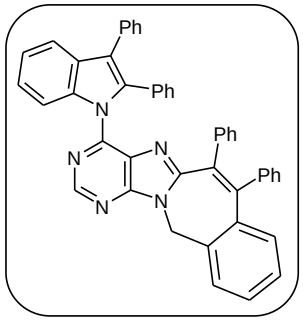
Anal. Calcd. for $C_{31}H_{27}N_5O_5$: C, 67.75; H, 4.95; N, 12.74. Found: C, 67.85; H, 4.91; N, 12.65.

3.10 General Procedure for the Synthesis of Purine fused Polycyclics 90-94 and mono-annulated derivatives 95-96 (along with 57, 73 and 77)

A mixture of 9-benzyl-6-anilinopurine **6** (0.5 mmol), alkyne **12** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$, $Cu(OAc)_2.H_2O$ (1.0 mmol), and CsOAc (0.15 mmol) was taken in a Schlenk tube. To this, MeOH (3 mL) was added and the contents heated at 70 ^{o}C for 36 h. After cooling to rt, saturated NH_4Cl solution (50 mL) was added and the contents extracted with EtOAc (3x30 mL). The combined organic phase was washed with brine solution (30 mL), dried over anh. Na_2SO_4 and concentrated in vacuo. The crude product

was purified by column chromatography on silica gel using *n*-hexane-EtOAc (4:1) mixture as the eluent.

Compound 90



Yield: 0.143 g (44%, white solid).

Mp: 278-282 ^{o}C.

IR (KBr): 3052, 2926, 1595, 1573, 1452, 1375, 1326, 1227, 1074, 921, 745 cm^{-1}.

^{1}H NMR: δ 8.79 (s, 1H), 7.75-7.69 (m, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.49-7.47 (m, 2H), 7.42-7.36 (m, 5H), 7.32-7.19 (m, 10H), 7.08-6.93 (m, 6H), 6.88-6.84 (m, 2H), 5.55 (s, 2H).

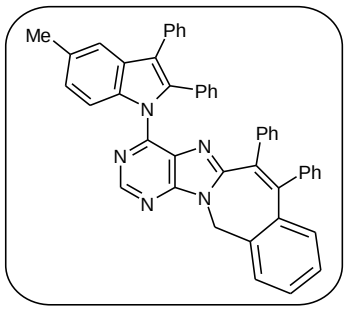
^{13}C NMR: δ 152.8, 152.6, 151.4, 149.2, 147.3, 141.8, 139.4, 138.2, 137.5, 137.0, 135.8, 134.5, 132.2, 132.1, 131.5, 131.1, 130.9, 130.5, 130.4, 129.5, 129.4, 128.4, 128.3, 127.9, 127.7, 127.5_5, 127.4_7, 127.4, 127.1, 126.8, 126.4, 123.4, 122.0, 120.2, 119.6, 112.8, 45.6.

LC-MS: 653 $[M]^{+}$.

Anal. Calcd. for $C_{46}H_{31}N_5$: C, 84.51; H, 4.78; N, 10.71. Found: C, 84.41; H, 4.86; N, 10.62.

Compound **57** (see above for data) was also obtained in 42% yield. X-ray structure was determined for the crystals of **90**.

Compound 91



Yield: 0.137 g (41%, white solid).

Mp: 294-298 ^{o}C.

IR (KBr): 3052, 3014, 1595, 1567, 1447, 1364, 1326, 1266, 1107, 1074, 932, 751, 690 cm^{-1}.

^{1}H NMR: δ 8.76 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.49-7.46 (m, 3H), 7.40-7.35 (m, 5H), 7.32-7.29 (m, 1H), 7.26-7.18 (m, 7H), 7.07-7.05 (m, 4H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.95-6.91 (m, 1H), 6.87-6.83 (m, 2H), 5.54 (s, 2H), 2.47 (s, 3H).

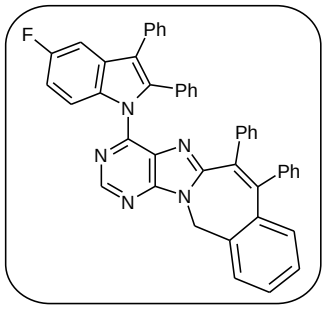
^{13}C NMR: δ 152.6, 152.5, 151.4, 149.4, 147.2, 141.8, 139.5, 138.2, 137.1, 136.0, 135.9, 134.7, 132.2_5, 132.1_9, 131.7, 131.6, 131.4, 131.1, 130.9, 130.4_8, 130.4_6, 129.7, 129.4, 128.4, 128.2, 127.9, 127.7, 127.5, 127.4, 127.1, 126.7, 126.3, 124.9, 120.1, 119.2, 112.6, 45.6, 21.6.

LC-MS: 668 $[M+1]^{+}$.

Anal. Calcd. for $C_{47}H_{33}N_5$: C, 84.53; H, 4.98; N, 10.49. Found: C, 84.45; H, 4.89; N, 10.41.

Compound **73** (see above for data) was also obtained in 38% yield.

Compound 92



Yield: 0.114 g (34%, white solid).

Mp: >300 ^{o}C.

IR (KBr): 3058, 2926, 1600, 1573, 1458, 1370, 1337, 1266, 1156, 1107, 932, 696 cm^{-1}.

^{1}H NMR: δ 8.76 (s, 1H), 7.62-7.56 (m, 2H), 7.47-7.30 (m, 9H), 7.27-7.18 (m, 7H), 7.06-6.95 (m, 6H), 6.92-6.85 (m, 3H), 5.55 (s, 2H).

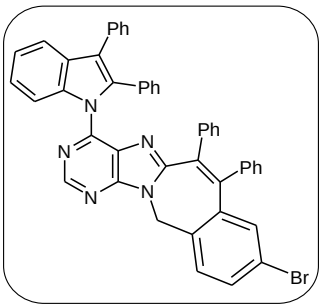
^{13}C NMR: δ 159.4 (d, $J_{(C-F)}$ = 235.6 Hz), 153.0, 152.7, 151.4, 148.9, 147.5, 141.7, 139.4, 138.5, 138.2, 135.8, 134.1, 133.9, 132.2, 131.8, 131.7, 131.5,

131.1, 130.9, 130.4, 130.2_3, 130.1_6, 129.4, 128.4, 128.3, 128.2, 127.9, 127.7, 127.5_9, 127.5_6, 127.5, 127.2, 127.1, 126.6, 120.2, 120.1, 114.0, 113.9, 111.5, 111.2, 104.9, 104.6, 45.7.

HRMS (ESI): Calcd. for $C_{46}H_{31}FN_5$ $[M^+ + H]$ 672.2564. Found: 672.2561.

Compound **77** (see above for data) was also obtained in 41% yield.

Compound 93



Yield: 0.165 g (45%, white solid).

Mp: 188-192 ^oC.

IR (KBr): 3058, 1593, 1572, 1452, 1330, 1171, 1074, 921, 885, 720 cm^{-1}.

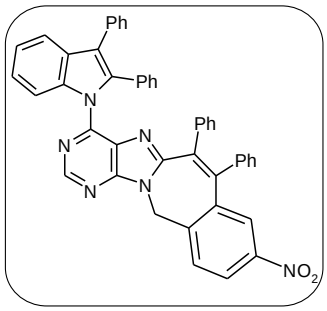
^1H NMR: δ 8.77 (s, 1H), 7.74-7.67 (m, 2H), 7.53-7.35 (m, 8H), 7.34-7.27 (m, 1H), 7.25-7.17 (m, 8H), 7.11 (br, 1H), 7.07-7.00 (m, 4H), 6.97-6.93 (m, 1H), 6.88-6.84 (m, 2H), 5.50 (s, 2H).

^{13}C NMR: δ 152.4, 152.3, 151.6, 149.3, 145.9, 141.4, 140.9, 137.8, 137.5, 136.9, 134.7, 134.5, 132.7, 132.4, 132.1, 131.0, 130.7, 130.5, 130.4, 129.5, 129.2, 128.4, 128.3, 128.1, 127.8, 127.6, 127.5, 127.3, 126.8, 126.4, 123.5, 122.5, 122.1, 120.3, 119.6, 112.8, 45.0.

LC-MS: 732 $[M+1]^+$.

Anal. Calcd. for $C_{46}H_{30}BrN_5$: C, 75.41; H, 4.13; N, 9.56. Found: C, 75.31; H, 4.18; N, 9.45.

Compound 94



Yield: 0.175 g (50%, yellow solid).

Mp: 208-212 ^{o}C.

IR (KBr): 3057, 1595, 1574, 1453, 1345, 1331, 1235, 1074, 883, 752 cm^{-1}.

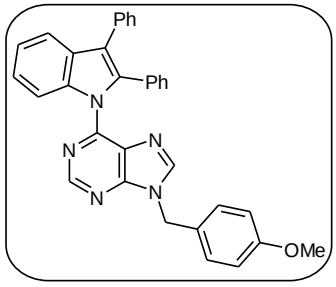
^{1}H NMR: δ 8.82 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.86 (s, 1H), 7.80-7.71 (m, 3H), 7.46-7.36 (m, 6H), 7.33-7.19 (m, 9H), 7.07-7.06 (m, 4H), 6.96-6.92 (m, 1H), 6.86-6.83 (m, 2H), 5.62 (s, 2H).

^{13}C NMR: δ 152.4, 151.8, 149.6, 148.0, 145.2, 141.4, 141.1, 140.4, 137.5, 137.4, 136.9, 134.4, 133.7, 132.0, 130.9, 130.6, 130.5, 130.4, 129.5, 128.9, 128.4, 128.3, 128.2, 127.7, 127.5$_4$, 127.4$_5$, 126.9, 126.8, 126.5, 123.9, 123.6, 122.2, 120.4, 119.7, 112.7, 44.9.

LC-MS: 698 [M]$^{+}$.

Anal. Calcd. for $C_{46}H_{30}N_6O_2$: C, 79.07; H, 4.33; N, 12.03. Found: C, 79.15; H, 4.26; N, 12.18.

Compound 95



Yield: 0.193 g (76%, white solid).

Mp: 148-152 ^{o}C.

IR (KBr): 3048, 1595, 1512, 1456, 1369, 1234, 1178, 1032, 851, 734 cm^{-1}.

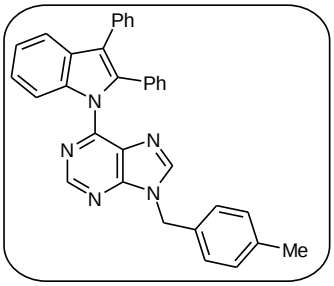
^{1}H NMR: δ 8.87 (s, 1H), 7.91 (s, 1H), 7.74-7.72 (m, 1H), 7.66-7.64 (m, 1H), 7.42-7.35 (m, 4H), 7.32-7.26 (m, 5H), 7.16-7.07 (m, 5H), 6.93 (d, *J* = 8.8 Hz,

2H), 5.39 (s, 2H), 3.83 (s, 3H).

^{13}C NMR: δ 159.9, 153.7, 152.4, 149.9, 144.3, 137.5, 136.6, 134.4, 132.1, 130.5, 129.5_3, 129.4_8, 128.3, 128.2, 127.7, 127.1, 126.8, 126.5, 123.7, 122.1, 120.3, 119.9, 114.6, 112.0, 55.4, 47.2.

HRMS (ESI): Calcd. for $C_{33}H_{26}N_5O$ [M^++H] 508.2138. Found: 508.2138.

Compound 96



Yield: 0.180 g (73%, white solid).

Mp: 180-184 ^{o}C.

IR (KBr): 3053, 1573, 1456, 1407, 1341, 1233, 1152, 1100, 1026, 864, 775, 704 cm^{-1}.

^{1}H NMR: δ 8.88 (s, 1H), 7.91 (s, 1H), 7.75-7.73 (m, 1H), 7.67 (d, *J* = 6.8 Hz, 1H), 7.43-7.36 (m, 4H), 7.32-7.27 (m, 3H), 7.25-7.07 (m, 9H), 5.41 (s, 2H), 2.39 (s, 3H).

^{13}C NMR: δ 153.7, 152.5, 149.9, 144.4, 138.7, 137.5, 136.6, 134.4, 132.1, 131.8, 130.5, 129.9, 129.5, 128.3, 128.2, 127.9, 127.7, 127.1, 126.5, 123.7, 122.1, 120.3, 119.9, 112.0, 47.4, 21.2.

HRMS (ESI): Calcd. for $C_{33}H_{26}N_5$ [M^++H] 492.2189. Found: 492.2189.

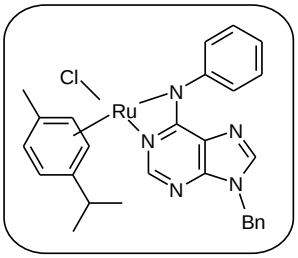
3.11 Ruthenium-catalyzed H/D exchange in 6a with isotopically labeled solvent

A mixture of 6-anilinopurine (**6a**) (75 mg, 0.025 mmol), [$RuCl_2$(*p*-cymene)$_2$] (8 mg, 5 mol %) and CsOAc (14 mg, 30 mol %) in CD_3OD (1 mL) was stirred at 70 ^{o}C for 24 h. The reaction mixture was cooled to room temperature and CD_3OD was concentrated *in vacuo*. Purification was done by column chromatography on silica gel using hexane:EtOAc (6:4) to afford the **6a-D** (62 mg, 82%) with approximately 83% H incorporation at the *ortho*-position as estimated by ^{1}H-NMR spectroscopy.

3.12 Synthesis of ruthenium-complex 97

A mixture of [{$RuCl_2$(*p*-cymene)}$_2$] (0.405g, 0.66 mmol), 6-anilinopurine **6a** (0.200g, 0.66 mmol) and NaOAc (0.109g, 1.33 mmol) was taken in MeOH (30 mL) and heated under reflux for 12 h at 70 ^oC. The reaction mixture was cooled to rt and the precipitate formed was filtered. Most of the complex was obtained in the precipitate only and the resulting decant was concentrated *in vacuo* and the residue was crystallized from MeOH-hexane (1:1) mixture to afford compound **97**.

Compound 97



Yield: 0.280 g (74%, orange solid).

Mp: 174-178 ^oC.

IR (KBr): 3047, 2959, 1605, 1589, 1501, 1463, 1337, 1315, 1233, 1047, 866, 773, 734 cm^{-1}.

^1H NMR: δ 8.18 (s, 1H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.50 (s, 1H), 7.29-7.22 (m, 7H), 7.05 (t, *J* = 6.8 Hz, 1H), 5.55 (d, *J* = 5.2 Hz, 1H), 5.49 (d, *J* = 5.4 Hz, 1H), 5.30 (d, *J* = 5.4 Hz, 1H), 5.25-5.18 (m, 3H), 2.75 (m, *J* = 6.0 Hz, 1H), 2.22 (s, 3H), 1.20 (d, *J* = 6.0 Hz, 6H).

^{13}C NMR: δ 160.1, 151.4, 149.0, 145.9, 138.1, 135.7, 128.9, 128.3, 128.1, 127.7, 123.2, 123.1, 118.9, 100.7, 98.2, 81.7, 81.0, 79.7, 79.4, 46.8, 31.3, 22.6, 22.2, 19.0.

LC-MS: 571 $[M]^+$.

Anal. Calcd. for $C_{28}H_{28}ClN_5Ru$: C, 58.89; H, 4.94; N, 12.26. Found: C, 58.76; H, 4.85; N, 12.15.

This was crystallized from acetonitrile for X-ray crystallographic studies.

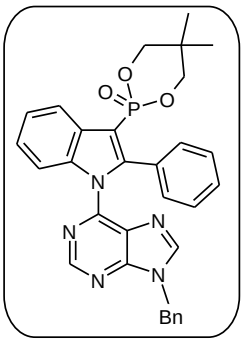
3.13 Synthesis of indole substituted purine derivative 57 using ruthenium complex 97

A mixture of **97** (57 mg, 0.1 mmol), diphenylacetylene (36 mg, 0.2 mmol) and MeOH (1 mL) was taken in a Schlenk tube. The resulting solution was heated on an oil bath at 70 ^{o}C for 24 h. The reaction mixture was filtered through a plug of celite using EtOAc (20 mL) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane:EtOAc (8:2) to afford the indole derivative **57** (42 mg, 88%). Characterization data are given above.

3.14 Synthetic procedure for the [Pd]-catalyzed oxidative annulation of 6-anilinopurine 6a with alkyne 12q

Into a Schlenk tube, 6-anilinopurine derivative **6a** (0.5 mmol), alkyne **12q** (1.0 mmol), $PdCl_2(CH_3CN)_2$ (5 mol %), $CuCl_2$ (2 equiv), and DMF (2 mL) were added and the contents were heated at 110 ^{o}C (oil bath temperature) for 24 h. The resulting mixture was cooled to room temperature (25 ^{o}C) and diluted with DCM (10 mL). This solution was treated with water (25 mL) and DCM (3x20 mL), the organic layer washed with brine solution, dried over anh. Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (6:4) mixture as the eluent.

Compound 98



Yield: 0.06 g (22%, white solid).

Mp: 202-206 ^{o}C.

IR (KBr): 3074, 2962, 1610, 1578, 1460, 1335, 1264, 1057, 1009, 990, 793, 739 cm^{-1}.

^{1}H NMR: δ 8.87 (s, 1H), 8.02 (d, *J* = 6.4 Hz, 1H), 7.92 (s, 1H), 7.47-7.18 (m, 13H), 5.44 (s, 2H), 3.66-3.58 (m, 4H), 1.23 (s, 3H), 0.62 (s, 3H).

^{13}C NMR: δ 154.1, 152.5, 148.6, 147.0 (d, *J* = 23.3 Hz), 145.1, 137.7 (d, *J* = 13.1 Hz), 134.7, 130.7, 130.6, 129.3, 129.2, 128.9 (d, *J* = 7.0 Hz), 128.5, 127.9, 127.6, 124.4, 122.3 (d, *J* = 203.6 Hz), 112.0, 100.9, 76.2 (d, *J* = 5.5 Hz), 47.7, 32.2 (d, *J* = 6.3 Hz), 22.2, 20.5.

^{31}P NMR: δ 10.84.

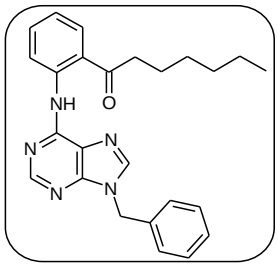
HRMS (ESI): Calcd. for $C_{31}H_{29}N_5O_3P$ [M^++H] 550.2009. Found: 550.2006.

This compound was crystallized from acetonitrile for X-ray crystallographic studies.

3.15 General procedure for the *ortho*-acylation of 6-anilinopurine derivatives with aldehydes: Synthesis of compounds 99-114

A mixture of 6-anilinopurine (0.3 mmol) and $Pd(OAc)_2$ (10 mol %) was taken in a Schlenk tube under N_2. To this, dioxane/AcOH/DMSO (7/2/1, v/v/v, 3 mL) solvent mixture was added and stirring was continued at rt for 10 min. To this mixture, aldehyde (0.6 mmol) and TBHP (0.9 mmol) were added. The contents were heated with stirring at 110 ^{o}C (oil bath temperature) for 24 h. After cooling to rt, the reaction mixture was extracted with EtOAc (3x30 mL) and water. The combined organic phase was washed with brine solution (30 mL), dried over anh. Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (4:1) mixture as the eluent.

Compound 99



Yield: 0.092 g; white solid.

Mp: 164-168 ^{o}C.

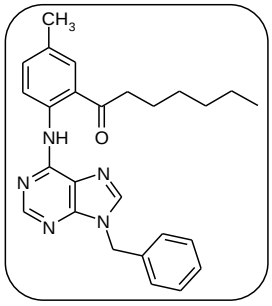
IR (KBr): 3284, 3059, 1615, 1576, 1480, 1449, 1256, 1151, 1024, 891, 725, 700 cm^{-1}.

^{1}H NMR: δ 12.66 (s, 1H), 9.27 (d, *J* = 8.4 Hz, 1H), 8.63 (s, 1H), 7.99-7.97 (m, 1H), 7.93 (s, 1H), 7.63-7.58 (m, 1H), 7.37-7.29 (m, 5H), 7.07 (t, *J* ~ 7.4 Hz, 1H), 5.42 (s, 2H), 3.06 (t, *J* ~ 7.4 Hz, 2H), 1.81-1.76 (m, 2H), 1.40-1.26 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR: δ 204.8, 152.7, 152.2, 150.1, 142.4, 141.5, 135.7, 134.5, 131.2, 129.1, 128.4, 127.7, 121.8, 121.6, 120.9, 120.8, 47.3, 40.0, 31.7, 29.1, 24.8, 22.6, 14.1.

HRMS (ESI): Calcd. for $C_{25}H_{28}N_5O$ [M^++H] 414.2295 Found: 414.2302.

Compound 100



Yield: 0.091g (71%); white solid.

Mp: 154-158 ^{o}C.

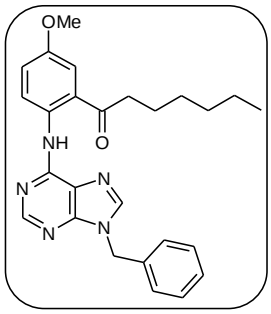
IR (KBr): 3079, 2915, 1611, 1567, 1534, 1463, 1299, 1178, 784, 723 cm^{-1}.

^{1}H NMR: δ 12.49 (s, 1H), 9.12 (d, *J* = 8.8 Hz, 1H), 8.61 (s, 1H), 7.90 (s, 1H), 7.77 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.37-7.27 (m, 5H), 5.42 (s, 2H), 3.05 (t, *J* ~ 7.4 Hz, 2H), 2.40 (s, 3H), 1.81-1.78 (m, 2H), 1.43-1.31 (m, 6H), 0.91-0.88 (m, 3H).

^{13}C NMR: δ 204.7, 152.7, 152.2, 149.9, 141.2, 139.9, 135.7, 135.2, 131.2, 130.3, 129.1, 128.4, 127.6, 121.8, 121.6, 120.8, 47.2, 39.9, 31.7, 29.1, 24.7, 22.6, 20.9, 14.1.

HRMS (ESI): Calcd. for $C_{26}H_{30}N_5O$ [M^++H] 428.2451 Found: 428.2450.

Compound 101



Yield: 0.096 g (72%); white solid.

Mp: 132-136 ^{o}C.

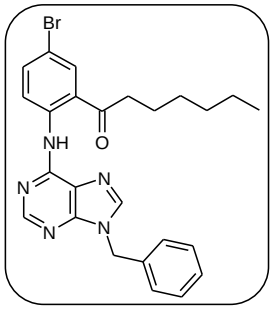
IR (KBr): 3441, 3083, 2952, 1608, 1586, 1478, 1350, 1248, 1175, 1047, 979, 840, 726 cm^{-1}.

^{1}H NMR: δ 12.20 (s, 1H), 9.15 (d, *J* = 9.6 Hz, 1H), 8.59 (s, 1H), 7.89 (s, 1H), 7.47 (d, *J* = 3.2 Hz, 1H), 7.35-7.29 (m, 5H), 7.21 (dd, *J* ~ 9.4 Hz, ~ 3.0 Hz, 1H), 5.42 (s, 2H), 3.87 (s, 3H), 3.03 (t, *J* = 7.6 Hz, 2H), 1.81-1.77 (m, 2H), 1.40-1.30 (m, 6H), 0.89 (t, *J* ~ 7.0 Hz, 3H).

^{13}C NMR: δ 204.4, 153.6, 152.8, 152.2, 149.9, 141.1, 135.9, 135.8, 129.1, 128.4, 127.7, 123.0, 122.5, 121.5, 120.1, 116.0, 55.9, 47.3, 40.1, 31.7, 29.1, 24.7, 22.6, 14.1.

HRMS (ESI): Calcd. for $C_{26}H_{30}N_5O_2$ [M^++H] 444.2400 Found: 444.2399.

Compound 102



Yield: 0.098 g (66%); white solid.

Mp: 170-174 ^{o}C.

IR (KBr): 3429, 3079, 2952, 1612, 1581, 1525, 1486, 1381, 1300, 1184, 1023, 837, 731 cm^{-1}.

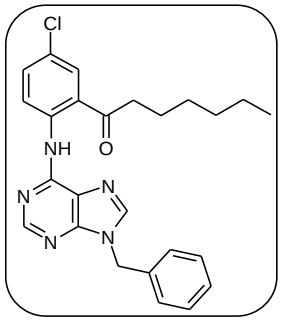
^{1}H NMR: δ 12.53 (s, 1H), 9.25 (d, *J* = 9.2 Hz, 1H), 8.63 (s, 1H), 8.06 (br, 1H), 7.93 (s, 1H), 7.67 (dd, *J* ~ 9.0 Hz, ~ 2.2 Hz, 1H), 7.38-7.28 (m, 5H), 5.43

(s, 2H), 3.03 (t, *J* ~ 7.4 Hz, 2H), 1.83-1.76 (m, 2H), 1.42-1.26 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR: δ 203.7, 152.6, 151.9, 150.3, 141.7, 141.4, 137.1, 135.6, 133.5, 129.2, 128.5, 127.7, 123.1, 122.7, 121.9, 113.0, 47.4, 40.0, 31.7, 29.0, 24.5, 22.6, 14.1.

HRMS (ESI): Calcd. for $C_{25}H_{27}BrN_5O$ [M^++H] 492.1400 Found: 492.1399.

Compound 103



Yield: 0.083 g (62%); white solid.

Mp: 184-188 ^{o}C.

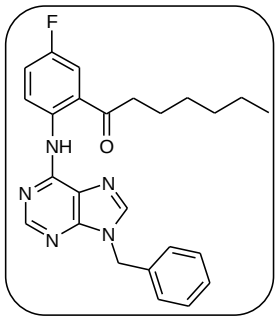
IR (KBr): 3449, 3106, 2928, 1614, 1583, 1525, 1466, 1405, 1351, 1327, 1298, 1139, 1018, 837, 725 cm^{-1}.

^{1}H NMR: δ 12.53 (s, 1H), 9.30 (d, *J* = 9.2 Hz, 1H), 8.62 (s, 1H), 7.93 (s, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.54 (dd, *J* = 9.2 Hz, = 2.4 Hz, 1H), 7.37-7.29 (m, 5H), 5.43 (s, 2H), 3.03 (t, *J* ~ 7.4 Hz, 2H), 1.83-1.75 (m, 2H), 1.42-1.32 (m, 6H), 0.91-0.89 (m, 3H).

^{13}C NMR: δ 203.7, 152.6, 151.9, 150.2, 141.7, 141.0, 135.6, 134.3, 130.6, 129.1, 128.5, 127.7, 125.7, 122.6, 122.3, 121.8, 47.3, 40.0, 31.7, 29.0, 24.5, 22.6, 14.1.

HRMS (ESI): Calcd. for $C_{25}H_{27}ClN_5O$ [M^++H] 448.1905 Found: 448.1903.

Compound 104



Yield: 0.088 g (68%); white solid.

Mp: 132-136 ^{o}C.

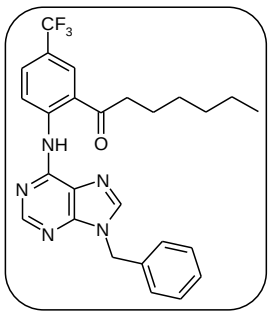
IR (KBr): 3453, 3100, 2930, 1620, 1588, 1472, 1328, 1259, 1175, 1023, 833, 726 cm^{-1}.

^{1}H NMR: δ 12.40 (s, 1H), 9.29 (dd, *J* = 9.2 Hz, 5.2 Hz, 1H), 8.61 (s, 1H), 7.92 (s, 1H), 7.64 (dd, *J* ~ 9.4 Hz, ~ 3.0 Hz, 1H), 7.37-7.28 (m, 6H), 5.43 (s, 2H), 3.02 (t, *J* = 7.6 Hz, 2H), 1.81-1.75 (m, 2H), 1.42-1.26 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR: δ 203.7, 156.5 (d, $J_{(C-F)}$ = 240.5 Hz), 152.6, 152.0, 150.1, 141.5, 138.7, 135.7, 129.2, 128.5, 127.7, 122.8, 122.7, 122.5, 121.7, 121.6, 121.5, 116.9, 116.6, 47.3, 40.1, 31.7, 29.1, 24.6, 22.6, 14.1.

HRMS (ESI): Calcd. for $C_{25}H_{27}FN_5O$ [M^++H] 432.2200 Found: 432.2200.

Compound 105



Yield: 0.088 g (61%); white solid.

Mp: 160-164 ^{o}C.

IR (KBr): 3463, 2931, 2849, 1731, 1616, 1589, 1468, 1233, 1123, 1025, 729 cm^{-1}.

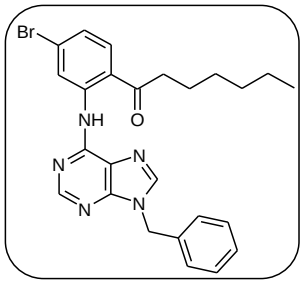
^{1}H NMR: δ 12.81 (s, 1H), 9.49 (d, *J* = 8.8 Hz, 1H), 8.67 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.38-7.29 (m, 5H), 5.44 (s, 2H), 3.10 (t, *J* ~ 7.4 Hz, 2H), 1.85-1.78 (m, 2H), 1.44-1.33 (m, 6H), 0.92-0.90 (m,

3H).

^{13}C NMR: δ 204.0, 152.5, 151.7, 150.5, 145.2, 142.0, 135.5, 130.9, 129.2, 128.6, 128.2, 127.8, 122.1, 121.0, 120.8, 47.4, 40.0, 31.7, 29.0, 24.5, 22.6, 14.1.

HRMS (ESI): Calcd. for $C_{26}H_{27}F_3N_5O$ [M^++H] 482.2168 Found: 482.2167.

Compound 106



Yield: 0.093 g (63%); white solid.

Mp: 152-156 ^{o}C.

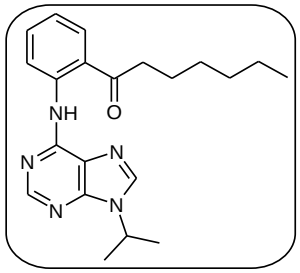
IR (KBr): 2937, 2849, 1644, 1605, 1567, 1463, 1408, 1025, 882 cm^{-1}.

^{1}H NMR: δ 12.72 (s, 1H), 9.63 (s, 1H), 8.67 (s, 1H), 7.93 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.38-7.27 (m, 5H), 7.19 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 5.43 (s, 2H), 3.02 (t, *J* ~ 7.4 Hz, 2H), 1.82-1.75 (m, 2H), 1.41-1.31 (m, 6H), 0.89 (t, *J* ~ 6.4 Hz, 3H).

^{13}C NMR: δ 204.2, 152.7, 151.8, 150.3, 143.4, 141.8, 135.6, 132.2, 129.4, 129.2, 128.5, 127.7, 123.9, 123.5, 121.9, 120.0, 47.3, 40.1, 31.7, 29.1, 24.7, 22.6, 14.1.

HRMS (ESI): Calcd. for $C_{25}H_{27}BrN_5O$ [M^++H] 492.1400 Found: 492.1399.

Compound 107



Yield: 0.077 g (70%); white solid.

Mp: 88-92 ^{o}C.

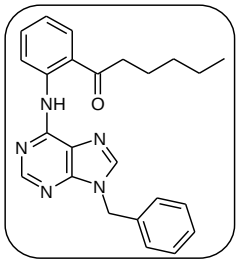
IR (KBr): 3096, 2948, 1616, 1584, 1534, 1447, 1238, 975 cm^{-1}.

^{1}H NMR: δ 12.62 (s, 1H), 9.26 (d, *J* = 8.8 Hz, 1H), 8.60 (s, 1H), 8.00 (s, 1H), 7.98 (s, 1H), 7.63-7.59 (m, 1H), 7.09-7.05 (m, 1H), 4.94-4.84 (m, 1H), 3.06 (t, *J* = 7.6 Hz, 2H), 1.88-1.78 (m, 2H), 1.64 (d, *J* = 6.8 Hz, 6H), 1.42-1.31 (m, 6H), 0.89 (t, *J* ~ 7.0 Hz, 3H).

^{13}C NMR: δ 204.8, 152.2, 152.1, 149.6, 142.5, 139.1, 134.5, 131.2, 122.3, 121.7, 120.9, 120.8, 47.2, 40.1, 31.8, 29.2, 24.8, 22.8, 22.6, 14.1.

HRMS (ESI): Calcd. for $C_{21}H_{28}N_5O$ [M^++H] 366.2295 Found: 366.2293.

Compound 108



Yield: 0.085 g (71%); white solid.

Mp: 132-136 ^{o}C.

IR (KBr): 3447, 3083, 2952, 1603, 1583, 1531, 1448, 1349, 1303, 1250, 1192, 1022, 972, 727 cm^{-1}.

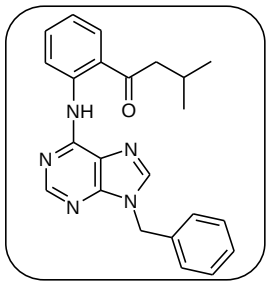
^{1}H NMR: δ 12.68 (s, 1H), 9.29 (d, *J* = 8.4 Hz, 1H), 8.65 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.94 (s, 1H), 7.62 (t, *J* ~ 7.8 Hz, 1H), 7.38-7.30 (m, 5H), 7.08 (t, *J* = 7.6 Hz, 1H), 5.44 (s, 2H), 3.07 (t, *J* ~ 7.4 Hz, 2H), 1.84-1.80 (m, 2H), 1.41-1.38 (m, 4H), 0.92 (t, *J* ~ 7.0 Hz, 3H).

^{13}C NMR: δ 204.8, 152.6, 152.1, 150.0, 142.4, 141.4, 135.7, 134.5, 131.1, 129.1, 128.4, 127.6, 121.8, 121.6, 120.9, 120.7, 47.2, 39.9, 31.6, 24.5, 22.6, 14.0.

HRMS (ESI): Calcd. for $C_{24}H_{26}N_5O$ [M^++H] 400.2138 Found: 400.2130.

X-ray structure was determined for this compound.

Compound 109



Yield: 0.079 g (68%); white solid.

Mp: 134-138 ^{o}C.

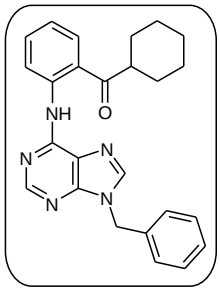
IR (KBr): 3079, 2959, 1611, 1584, 1523, 1457, 1304, 1200, 1025 cm^{-1}.

^{1}H NMR: δ 12.68 (s, 1H), 9.30-9.28 (m, 1H), 8.65 (s, 1H), 8.00-7.97 (m, 1H), 7.95 (s, 1H), 7.64-7.60 (m, 1H), 7.38-7.30 (m, 5H), 7.11-7.06 (m, 1H), 5.44 (s, 2H), 2.94 (d, *J* = 6.8 Hz, 2H), 2.46-2.36 (m, 1H), 1.03 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR: δ 204.5, 152.6, 152.1, 150.0, 142.4, 141.4, 135.6, 134.5, 131.3, 129.1, 128.9, 128.4, 127.6, 121.9, 121.8, 120.9, 120.7, 48.8, 47.2, 25.5, 22.9.

HRMS (ESI): Calcd. for $C_{23}H_{24}N_5O$ [M^++H] 386.1982 Found: 386.1978.

Compound 110



Yield: 0.074 g (60%); white solid.

Mp: 268-272 ^{o}C.

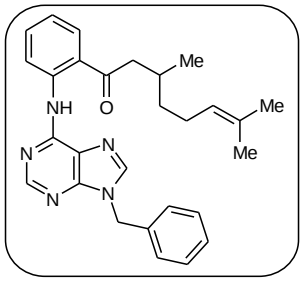
IR (KBr): 3085, 2932, 2860, 1605, 1584, 1452, 1310, 1162, 981, 723 cm^{-1}.

^{1}H NMR: δ 12.75 (s, 1H), 9.29 (d, *J* = 7.6 Hz, 1H), 8.65 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 7.65-7.61 (m, 1H), 7.39-7.29 (m, 5H), 7.11 (t, *J* = 7.6 Hz, 1H), 5.45 (s, 2H), 3.44-3.39 (m, 1H), 1.99-1.86 (m, 4H), 1.69-1.60 (m, 2H), 1.47-1.25 (m, 4H).

^{13}C NMR: δ 208.0, 152.6, 152.1, 150.0, 142.8, 141.4, 135.6, 134.4, 130.9, 129.0, 128.3, 127.6, 121.7, 120.9, 120.5, 47.2, 46.6, 29.8, 25.9.

HRMS (ESI): Calcd. for $C_{25}H_{26}N_5O$ [M^++H] 412.2138 Found: 412.2141.

Compound 111



Yield: 0.073 g (54%); white solid.

Mp: 82-86 ^oC.

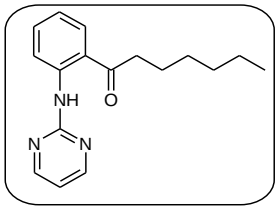
IR (KBr): 2964, 2926, 1720, 1605, 1529, 1447, 1304, 1238, 1025 cm^{-1}.

^1H NMR: δ 12.68 (s, 1H), 9.29 (d, *J* = 8.4 Hz, 1H), 8.67 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H), 7.65-7.62 (m, 1H), 7.39-7.27 (m, 5H), 7.12-7.08 (m, 1H), 5.45 (s, 2H), 5.13-5.10 (m, 1H), 3.08 (dd, *J* = 15.4 Hz and *J* = 5.2 Hz, 1H), 2.85 (dd, *J* = 15.4 Hz and *J* = 8.4 Hz, 1H), 2.35-2.27 (m, 1H), 2.10-2.00 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.49-1.42 (m, 1H), 1.38-1.29 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR: δ 204.7, 152.7, 152.2, 150.1, 142.4, 141.5, 135.7, 134.6, 131.6, 131.3, 129.2, 128.5, 127.7, 124.5, 122.1, 121.9, 121.0, 120.8, 47.3, 37.4, 30.0, 25.8, 25.6, 20.2, 17.8.

HRMS (ESI): Calcd. for $C_{28}H_{32}N_5O$ [M^++H] 454.2608 Found: 454.2610.

Compound 112



Yield: 0.058 g (68%); white solid.

Mp: 80-84 ^oC.

IR (KBr): 3216, 2931, 2849, 1655, 1573, 1562, 1523, 1441, 1304, 1162, 975, 800, 745 cm^{-1}.

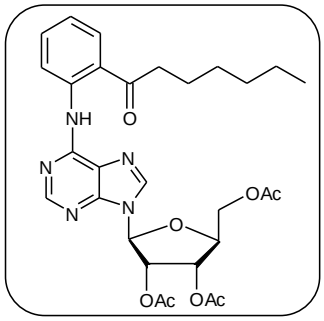
^1H NMR: δ 11.89 (s, 1H), 8.90 (d, *J* = 8.4 Hz, 1H), 8.60 (s, 1H), 8.52-8.50 (m,

1H), 7.95 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.58-7.54 (m, 1H), 7.04-7.00 (m, 1H), 6.81-6.78 (m, 1H), 3.05 (t, *J* ~ 7.4 Hz, 2H), 1.80-1.73 (m, 2H), 1.45-1.32 (m, 6H), 0.93-0.90 (m, 3H).

^{13}C NMR: δ 204.3, 160.2, 157.9, 142.7, 134.3, 131.1, 121.3, 120.1, 119.5, 113.4, 40.0, 31.8, 29.1, 24.8, 22.6, 14.1.

HRMS (ESI): Calcd. for $C_{17}H_{22}N_3O$ [M^++H] 284.1764 Found: 284.1763.

Compound 113



Yield: 0.065 g (56%); gummy liquid.

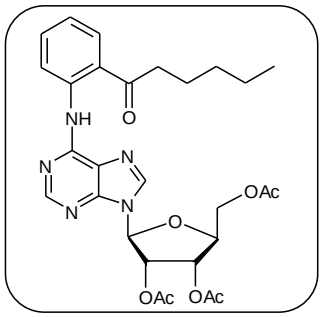
IR (neat): 2948, 2860, 1753, 1560, 1447, 1353, 1227, 1096 cm^{-1}.

^{1}H NMR: δ 12.69 (s, 1H), 9.26 (d, *J* = 8.4 Hz, 1H), 8.62 (s, 1H), 8.11 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* ~ 7.6 Hz, 1H), 7.12 (t, *J* ~ 7.6 Hz, 1H), 6.25 (d, *J* = 5.2 Hz, 1H), 6.02 (t, *J* = 5.6 Hz, 1H), 5.73-5.71 (m, 1H), 4.50-4.39 (m, 3H), 3.09 (t, *J* ~ 7.4 Hz, 2H), 2.18-2.17 (m, 6H), 2.10 (s, 3H), 1.86-1.79 (m, 2H), 1.43-1.29 (m, 6H), 0.93-0.91 (m, 3H).

^{13}C NMR: δ 204.9, 170.5, 169.7, 169.4, 152.9, 152.3, 149.6, 142.2, 139.9, 134.6, 131.2, 122.5, 121.8, 121.2, 120.9, 86.3, 80.5, 73.1, 70.9, 63.2, 40.1, 31.7, 29.1, 24.8, 22.6, 20.9, 20.6, 20.5, 14.1.

HRMS (ESI): Calcd. for $C_{29}H_{36}N_5O_8$ [M^++H] 582.2565 Found: 582.2568.

Compound 114



Yield: 0.061 g (54%); gummy liquid.

IR (neat): 2953, 2931, 1753, 1605, 1447, 1227, 1096, 1047, 756 cm^{-1}.

^1H NMR: δ 12.67 (s, 1H), 9.24 (d, *J* = 8.4 Hz, 1H), 8.60 (s, 1H), 8.11 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* ~ 7.8 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.24 (d, *J* = 5.6 Hz, 1H), 6.01 (t, *J* = 5.6 Hz, 1H), 5.71 (t, *J* ~ 4.8 Hz, 1H), 4.50-4.38 (m, 3H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.16 (s, 3H), 2.15 (s, 3H), 2.08 (s, 3H), 1.83-1.80 (m, 2H), 1.41-1.37 (m, 4H), 0.94-0.90 (m, 3H).

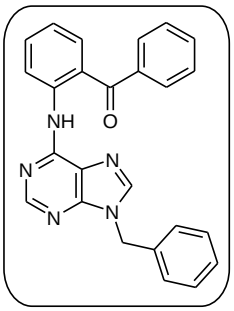
^{13}C NMR: δ 204.9, 170.4, 169.6, 169.4, 152.8, 152.3, 149.6, 142.1, 139.9, 134.5, 131.1, 122.4, 121.7, 121.1, 120.8, 86.2, 80.4, 73.1, 70.8, 63.2, 40.0, 31.6, 24.5, 22.6, 20.8, 20.6, 20.4, 14.0.

HRMS (ESI): Calcd. for $C_{28}H_{34}N_5O_8$ $[M^+ + H]$ 568.2408 Found: 568.2404.

3.16 General procedure for the *ortho*-acylation of 6-anilinopurine derivatives with α–oxocarboxylic acid: Synthesis of compounds 115 and 116

A mixture of 6-anilinopurine (0.3 mmol), $PdCl_2$ (10 mol %), Ag_2O (0.3 mmol), $K_2S_2O_8$ (0.3 mmol) and *α*–oxocarboxylic acid (0.6 mmol) was taken in a Schlenk tube under N_2 atmosphere. To this, dioxane/AcOH/DMSO (7/2/1, v/v/v, 3 mL) mixture was added and the contents stirred at 110 ^oC (oil bath temperature) for 24 h. After cooling to rt, the reaction mixture was extracted with EtOAc (3x30 mL) and washed with water (30 mL). The combined organic phase was washed with brine solution (30 mL), dried over anh. Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (3:2) mixture as the eluent.

Compound 115



Yield: 0.077 g (64%); white solid.

Mp: 190-194 ^{o}C.

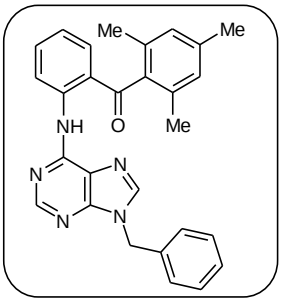
IR (KBr): 3299, 3058, 1622, 1573, 1474, 1321, 1249, 1156, 1025, 756 cm^{-1}.

^{1}H NMR: δ 11.76 (s, 1H), 9.14 (d, *J* = 8.8 Hz, 1H), 8.66 (br, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.93 (br, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 7 69-7.65 (m, 2H), 7.61-7.58 (m, 1H), 7.51-7.48 (m, 2H), 7.40-7.29 (m, 4H), 7.09 (t, *J* = 7.6 Hz, 1H), 5.45 (s, 2H).

^{13}C NMR: δ 199.4, 152.7, 152.0, 150.1, 141.8, 141.3, 138.9, 135.6, 134.1, 134.0, 132.2, 130.1, 129.1, 128.4, 128.1, 127.7, 123.1, 121.5, 121.2, 120.9, 47.2.

HRMS (ESI): Calcd. for $C_{25}H_{20}N_5O$ [M^++H] 406.1669 Found: 406.1667.

Compound 116



Yield: 0.08 g (60%); white solid.

Mp: 220-224 ^{o}C.

IR (KBr): 2926, 1748, 1605, 1584, 1452, 1249, 1151, 1019, 915 cm^{-1}.

^{1}H NMR: δ 12.82 (s, 1H), 9.37 (d, *J* = 8.4 Hz, 1H), 8.71 (s, 1H), 8.00 (s, 1H), 7.67-7.63 (m, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7 37-7.29 (m, 5H), 6.98-6.92 (m, 2H), 5.47 (s, 2H), 2.36 (s, 3H), 2.15 (s, 6H).

^{13}C NMR: δ 204.8, 152.6, 152.2, 150.2, 143.0, 141.6, 138.5, 137.3, 135.6, 135.4,

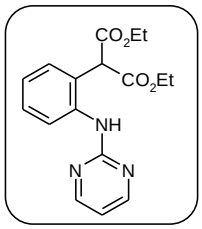
134.1$_3$, 134.0$_9$, 129.1, 128.4, 128.3, 127.7, 122.1, 121.9, 121.2, 120.4, 47.3, 21.2, 19.5.

HRMS (ESI): Calcd. for $C_{28}H_{26}N_5O$ [M^++H] 448.2138 Found: 448.2134.

3.17 General procedure for the [Rh]-catalyzed reaction of aniline derivatives with diazo compounds

A mixture of anilinopyrimidine/pyridine/purine (0.3 mmol), diazo compound (0.36 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %)and PivOH (20 mol %)) was taken in a Schlenk tube [under ambient conditions; no inert atmosphere needed]. To this, MeOH (3 mL) was added and the contents stirred at 60 ^oC (oil bath temperature) for 12 h. After cooling to rt, the reaction mixture was extracted with DCM (3x20 mL). The combined organic phase was washed with brine solution (20 mL), dried over anh. Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (4:1) mixture as the eluent.

Compound 117



Yield: 0.075 g (76%, white solid).

Mp: 116-120 ^oC.

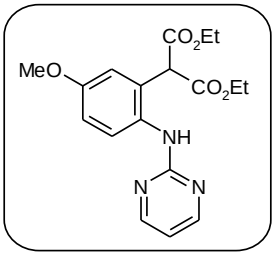
IR (KBr): 3194, 2998, 1752, 1578, 1517, 1443, 1323, 1218, 1142, 1031, 807, 762 cm^{-1}.

^1H NMR: δ 8.39-8.38 (m, 2H), 8.14 (br, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.43-7.38 (m, 2H), 7.20 (t, *J* ~ 7.2 Hz, 1H), 6.71-6.68 (m, 1H), 4.77 (s, 1H), 4.22-4.10 (m, 4H), 1.22 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR: δ 168.9, 160.8, 158.2, 137.9, 131.2, 129.1, 127.5, 126.0, 125.1, 62.2, 56.2, 14.0.

HRMS (ESI): Calcd. for $C_{17}H_{19}N_3O_4Na$ [M^++Na]: *m/z* 352.1274. Found: 352.1278.

Compound 118



Yield: 0.081 g (75%, white solid).

Mp: 98-102 ^{o}C.

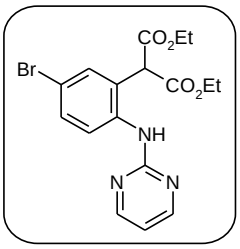
IR (KBr): 3204, 2981, 1755, 1732, 1584, 1518, 1444, 1415, 1232, 1144, 1036, 871, 803 cm^{-1}.

^{1}H NMR: δ 8.33 (d, *J* = 4.4 Hz, 2H), 7.63 (br, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 6.99-6.93 (m, 2H), 6.64 (t, *J* ~ 4.6 Hz, 1H), 4.75 (s, 1H), 4.23-4.05 (m, 4H), 3.83 (s, 3H), 1.22 (t, *J* ~ 7.0 Hz, 6H).

^{13}C NMR: δ 168.5, 161.4, 158.2, 157.2, 130.5, 130.1, 128.3, 116.1, 114.5, 112.1, 62.0, 55.6, 14.0.

HRMS (ESI): Calcd. for $C_{18}H_{21}N_3O_5Na$ [M^++Na]: *m/z* 382.1379. Found: 382.1377.

Compound 119



Yield: 0.085 g (70%, white solid).

Mp: 82-86 ^{o}C.

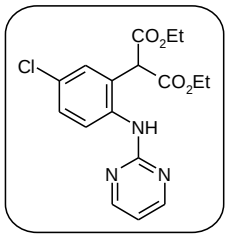
IR (KBr): 3235, 3172, 2987, 1746, 1720, 1610, 1582, 1487, 1445, 1247, 1193, 1109, 1035, 963, 828, 783 cm^{-1}.

^{1}H NMR: δ 8.39-8.38 (m, 2H), 8.15 (br, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.53-7.50 (m, 2H), 6.72 (s, 1H), 4.69 (s, 1H), 4.20-4.13 (m, 4H), 1.22 (t, *J* ~ 7.0 Hz, 6H).

^{13}C NMR: δ 168.4, 160.5, 158.2, 137.2, 133.9, 132.0, 129.1, 127.4, 117.5, 112.9, 62.4, 55.9, 14.0.

HRMS (ESI): Calcd. for $C_{17}H_{18}BrN_3O_4Na$ [M^++Na]: *m/z* 430.0379. Found: 430.0379.

Compound 120



Yield: 0.078 g (71%, white solid).

Mp: 80-84 ^{o}C.

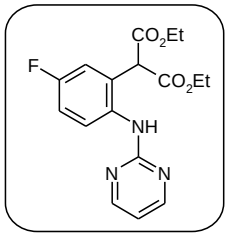
IR (KBr): 3236, 2988, 1747, 1722, 1583, 1519, 1490, 1446, 1418, 1248, 1193, 1036, 834 cm^{-1}.

^{1}H NMR: δ 8.39-8.38 (m, 2H), 8.11 (br, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.39-7.36 (m, 2H), 6.71 (t, *J* ~ 4.6 Hz, 1H), 4.71 (s, 1H), 4.23-4.11 (m, 4H), 1.22 (t, *J* ~ 7.0 Hz, 6H).

^{13}C NMR: δ 168.4, 160.6, 158.2, 136.6, 131.0, 130.0, 129.1, 128.9, 127.2, 112.9, 62.4, 55.8, 14.0.

HRMS (ESI): Calcd. for $C_{17}H_{18}ClN_3O_4Na$ [M^++Na]: *m/z* 386.0884. Found: 386.0884.

Compound 121



Yield: 0.075 g (73%, white solid).

Mp: 96-100 ^{o}C.

IR (KBr): 3205, 2920, 2851, 1753, 1585, 1500, 1444, 1320, 1226, 1142, 1031, 804 cm^{-1}.

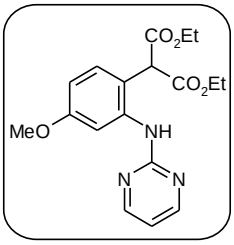
^{1}H NMR: δ 8.36 (d, *J* = 4.4 Hz, 2H), 7.82 (br, 1H), 7.66-7.63 (m, 1H), 7.20-7.09 (m, 2H), 6.71-6.70 (m, 1H), 4.77 (s, 1H), 4.23-4.13 (m, 4H), 1.23 (t, *J* = 6.8 Hz, 6H).

^{13}C NMR: δ 168.2, 161.0, 158.6, 158.2, 133.8, 130.1 (d, $J_{(C-F)}$ = 8.1 Hz), 128.2 (d, $J_{(C-F)}$ = 8.2 Hz), 117.6 (d, $J_{(C-F)}$ = 23.7 Hz), 115.9 (d, $J_{(C-F)}$ = 22.1 Hz),

112.6, 62.3, 55.3, 14.0.

HRMS (ESI): Calcd. for $C_{17}H_{19}FN_3O_4$ [M^++H]: *m/z* 348.1360. Found: 348.1357.

Compound 122



Yield: 0.069 g (64%, white solid).

Mp: 82-86 ^oC.

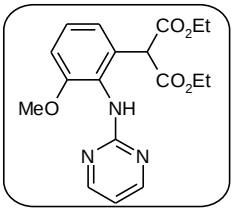
IR (KBr): 3378, 2983, 1735, 1719, 1620, 1578, 1520, 1432, 1399, 1309, 1148, 1030, 863, 803 cm^{-1}.

^1H NMR: δ 8.38 (d, *J* = 5.2 Hz, 2H), 8.21 (br, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.74-6.68 (m, 2H), 4.70 (s, 1H), 4.21-4.10 (m, 4H), 3.79 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR: δ 169.1, 160.7, 160.0, 158.2, 138.9, 131.9, 119.3, 112.6, 111.1, 110.5, 62.1, 55.5, 55.4, 14.0.

HRMS (ESI): Calcd. for $C_{18}H_{22}N_3O_5$ [M^++H]: *m/z* 360.1560. Found: 360.1558.

Compound 123



Yield: 0.078 g (72%, white solid).

Mp: 122-126 ^oC.

IR (KBr): 3211, 2985, 1755, 1728, 1585, 1525, 1446, 1409, 1286, 1141, 1037, 809, 756 cm^{-1}.

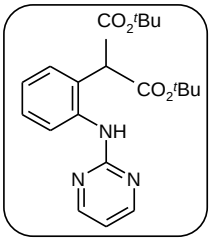
^1H NMR: δ 8.31 (d, *J* = 3.6 Hz, 2H), 7.28 (t, *J* ~ 8.2 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.02-6.95 (m, 2H), 6.66 (t, *J* ~ 4.2 Hz, 1H), 4.91 (s, 1H), 4.23-4.09 (m, 4H), 3.80 (s, 3H), 1.23 (t, *J* ~ 7.0 Hz, 6H).

^{13}C NMR: δ 168.5, 161.8, 158.0, 154.7, 132.2, 127.0, 126.8, 122.0, 112.4, 111.1,

61.7, 55.8, 54.3, 14.0.

HRMS (ESI): Calcd. for $C_{18}H_{21}N_3O_5Na$ [M^++Na]: *m/z* 382.1379. Found: 382.1378.

Compound 124



Yield: 0.079 g (68%, white solid).

Mp: 120-124 ^oC.

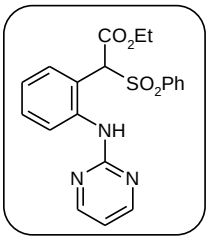
IR (KBr): 3229, 2983, 1750, 1724, 1581, 1527, 1448, 1411, 1368, 1127, 802, 763 cm^{-1}.

^1H NMR: δ 8.47 (br, 1H), 8.38 (d, *J* = 4.4 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.39-7.35 (m, 2H), 7.16-7.12 (m, 1H), 6.68-6.65 (m, 1H), 4.61 (s, 1H), 1.42 (s, 18H).

^{13}C NMR: δ 168.1, 160.8, 158.1, 138.0, 131.3, 128.7, 127.4, 125.0, 124.5, 112.3, 82.7, 58.4, 27.8.

HRMS (ESI): Calcd. for $C_{21}H_{28}N_3O_4$ [M^++H]: *m/z* 386.2081. Found: 386.2081.

Compound 125



Yield: 0.083 g (66%, white solid).

Mp: 138-142 ^oC.

IR (KBr): 3236, 2998, 1734, 1575, 1526, 1493, 1447, 1411, 1331, 1257, 1157, 1084, 1027, 805, 718 cm^{-1}.

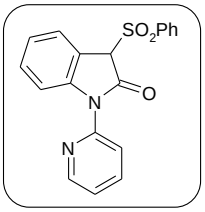
^1H NMR: δ 8.42 (d, *J* = 5.2 Hz, 2H), 7.95 (br, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.50-7.41 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 4.8 Hz, 1H), 5.70

(s, 1H), 4.21-4.09 (m, 2H), 1.17 (t, *J* ~ 7.0 Hz, 3H).

^{13}C NMR: δ 164.9, 160.9, 158.3, 138.9, 136.0, 134.4, 133.4, 130.3, 130.2, 128.6, 125.9, 125.1, 121.7, 113.0, 70.3, 62.5, 13.9.

HRMS (ESI): Calcd. for $C_{20}H_{20}N_3O_4S$ [M^++H]: *m/z* 398.1175. Found: 398.1178.

Compound 126



Yield: 0.072 g (68%, white solid).

Mp: 174-148 ^{o}C.

IR (KBr): 3083, 2858, 1737, 1607, 1586, 1463, 1444, 1323, 1142, 1085, 835, 745, 726 cm^{-1}.

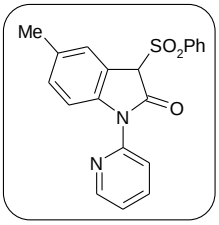
^{1}H NMR: δ 8.53 (dd, *J* = 4.8 and 1.2 Hz, 1H), 7.86-7.80 (m, 2H), 7.77-7.75 (m, 2H), 7.61 (t, *J* ~ 7.4 Hz, 1H) 7.48-7.43 (m, 4H), 7.39 (t, *J* ~ 7.8 Hz, 1H), 7.28-7.24 (m, 2H), 5.11 (s, 1H).

^{13}C NMR: δ 166.3, 148.6, 148.3, 143.3, 138.4, 136.1, 134.6, 130.6, 129.6, 128.9, 127.2, 124.2, 122.6, 119.8, 118.0, 112.8, 68.9.

HRMS (ESI): Calcd. for $C_{19}H_{15}N_2O_3S$ [M^++H]: *m/z* 351.0804. Found: 351.0804.

X-ray structure was determined for this compound.

Compound 127



Yield: 0.069 g (62%, white solid).

Mp: 218-222 ^{o}C.

IR (KBr): 3065, 2896, 1734, 1487, 1438, 1322, 1186, 1138, 1083, 840, 785, 718 cm^{-1}.

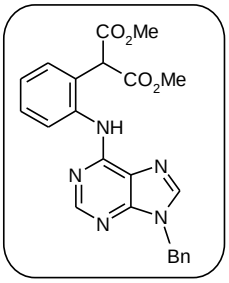
^{1}H NMR: δ 8.51 (dd, *J* = 4.8 and 1.2 Hz, 1H), 7.83-7.75 (m, 3H), 7.63-7.59 (m,

2H), 7.49-7.44 (m, 3H), 7.38 (d, *J* = 8.0 Hz, 1H) 7.26-7.23 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 5.07 (s, 1H), 2.43 (s, 3H).

^{13}C NMR: δ 166.3, 148.5, 140.9, 138.3, 136.2, 134.5, 133.9, 131.1, 129.6, 128.9, 127.7, 122.4, 119.6, 117.8, 112.7, 69.0, 21.2.

HRMS (ESI): Calcd. for $C_{20}H_{17}N_2O_3S$ [M^++H]: *m/z* 365.0961. Found: 365.0965.

Compound 128a



Yield: 0.091 g (70%, combined yield along with **128b** was 92%, white solid).

Mp: 162-166 ^{o}C.

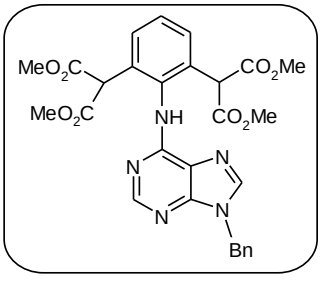
IR (KBr): 3179, 2956, 1748, 1609, 1598, 1472, 1437, 1325, 1292, 1221, 1150, 1024, 729 cm^{-1}.

^{1}H NMR: δ 8.88 (br, 1H), 8.45 (s, 1H), 7.84-7.82 (m, 2H), 7.45-7.27 (m, 8H), 5.41 (s, 2H), 4.85 (s, 1H), 3.65 (s, 6H).

^{13}C NMR: δ 169.2, 153.1, 153.0, 150.2, 141.0, 137.0, 135.6, 131.2, 129.3, 129.1, 128.5, 128.0, 127.8, 126.9, 126.0, 120.4, 55.6, 53.1, 47.3.

HRMS (ESI): Calcd. for $C_{23}H_{22}N_5O_4$ [M^++H]: *m/z* 432.1673. Found: 432.1670.

Compound 128b



Yield: 0.028 g (22%, combined yield along with **128a** was 92%, white solid).

Mp: 176-180 ^{o}C.

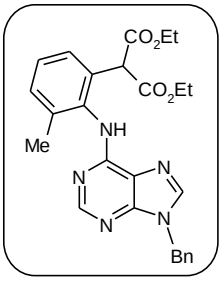
IR (KBr): 3172, 3030, 2954, 1736, 1614, 1470, 1435, 1325, 1246, 1149, 1028, 730 cm^{-1}.

^{1}H NMR: δ 9.63 (br, 1H), 8.31 (s, 1H), 7.69 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* ~ 7.6 Hz, 1H), 7.35-7.30 (m, 5H), 5.36 (s, 2H), 4.97 (s, 2H), 3.73 (s, 6H), 3.28 (s, 6H).

^{13}C NMR: δ 168.7, 153.2, 153.0, 150.0, 141.4, 135.5, 135.3, 132.2, 130.8, 129.0, 128.4, 127.9, 127.7, 119.5, 54.0, 52.9, 52.5, 47.3.

HRMS (ESI): Calcd. for $C_{28}H_{27}N_5O_8Na$ [M^++Na]: *m/z* 584.1758. Found: 584.1757.

Compound 129



Yield: 0.115 g (81%, gummy liquid).

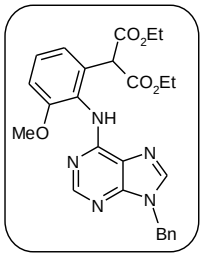
IR (neat): 2981, 1758, 1732, 1619, 1475, 1299, 1233, 1137, 1033, 730 cm^{-1}.

^{1}H NMR: δ 8.42 (s, 1H), 8.38 (br, 1H), 7.82 (s, 1H), 7.39-7.30 (m, 8H), 5.40 (s, 2H), 4.81 (s, 1H), 4.05-4.00 (m, 4H), 2.29 (s, 3H), 1.14 (br, 6H).

^{13}C NMR: δ 168.7, 153.3, 140.6, 135.6, 135.2, 131.6, 131.2, 129.0, 128.4, 127.8, 127.4, 119.8, 61.9, 55.5, 47.2, 19.0, 13.9.

HRMS (ESI): Calcd. for $C_{26}H_{28}N_5O_4$ [M^++H]: *m/z* 474.2142. Found: 474.2144.

Compound 130



Yield: 0.111 g (76%, gummy liquid).

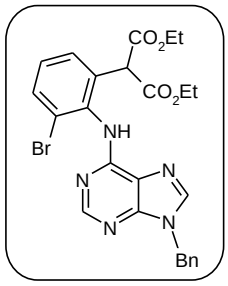
IR (neat): 3194, 2964, 1748, 1726, 1605, 1457, 1090, 1030, 970, 855 cm^{-1}.

^{1}H NMR: δ 8.37 (s, 1H), 7.82 (s, 1H), 7.69 (br, 1H), 7.39-7.35 (m, 6H), 7.23 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 5.40 (s, 2H), 4.90 (s, 1H), 4.20-4.11 (m, 4H), 3.78 (s, 3H), 1.20 (t, *J* ~ 7.0 Hz, 6H).

^{13}C NMR: δ 168.5, 154.8, 154.0, 153.1, 150.1, 140.6, 135.7, 132.3, 129.1, 128.5, 127.9, 127.6, 125.7, 122.2, 120.4, 111.3, 61.8, 55.8, 54.5, 47.3, 14.0.

HRMS (ESI): Calcd. for $C_{26}H_{28}N_5O_5$ [M^++H]: *m/z* 490.2091. Found: 490.2092.

Compound 131



Yield: 0.137 g (85%, gummy liquid).

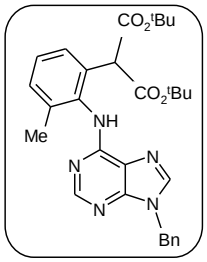
IR (neat): 3046, 1753, 1726, 1578, 1036, 970, 860 cm^{-1}.

^{1}H NMR: δ 8.78 (br, 1H), 8.38 (s, 1H), 7.72 (s, 1H), 7.63 (t, *J* ~ 8.2 Hz, 2H), 7.37-7.25 (m, 6H), 5.37 (s, 2H), 4.99 (s, 1H), 4.18-4.00 (m, 4H), 1.15 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR: δ 168.1, 153.3, 153.1, 150.2, 141.0, 135.6, 135.5, 134.4, 133.1, 129.6, 129.1, 128.7, 128.4, 127.9, 123.8, 119.9, 62.0, 54.4, 47.3, 13.9.

HRMS (ESI): Calcd. for $C_{25}H_{25}BrN_5O_4$ [M^++H]: *m/z* 538.1091. Found: 538.1089 and 540.1073.

Compound 132



Yield: 0.131 g (82%, white solid).

Mp: 170-174 ^{o}C.

IR (KBr): 3182, 2974, 1724, 1620, 1591, 1471, 1367, 1315, 1141, 1024, 727 cm^{-1}.

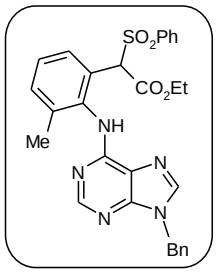
^{1}H NMR: δ 8.43 (s, 1H), 8.32 (br, 1H), 7.78 (s, 1H), 7.39-7.30 (m, 8H), 5.39 (s, 2H), 4.73 (s, 1H), 2.26 (s, 3H), 1.34 (s, 18H).

^{13}C NMR: δ 167.8, 153.6, 140.4, 135.8, 132.1, 130.9, 129.1, 128.4, 128.3, 127.9,

127.4, 119.9, 82.3, 57.0, 47.3, 27.8, 19.2.

HRMS (ESI): Calcd. for $C_{30}H_{36}N_5O_4$ [M^++H]: *m/z* 530.2768. Found: 530.2767.

Compound 133



Yield: 0.132 g (78%, white solid).

Mp: 96-100 ^oC.

IR (KBr): 3439, 2928, 1740, 1613, 1469, 1325, 1142, 1082, 1028, 720 cm^{-1}.

^1H NMR: δ 8.40 (s, 1H), 8.13 (br, 1H), 7.87 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.63 (t, *J* ~ 7.4 Hz, 1H), 7.47-7.36 (m, 9H), 7.21 (t, *J* ~ 7.8 Hz, 1H), 5.63 (s, 1H), 5.42 (s, 2H), 4.14-4.01 (m, 2H), 2.25 (s, 3H), 1.10 (t, *J* ~ 7.0 Hz, 3H).

^{13}C NMR: δ 164.8, 153.3, 140.8, 137.8, 136.7, 136.3, 135.6, 134.2, 132.6, 130.1, 129.2, 128.6, 128.5, 128.2, 128.0, 127.5, 126.1, 119.9, 70.2, 62.4, 47.4, 19.2, 13.8.

HRMS (ESI): Calcd. for $C_{29}H_{28}N_5O_4S$ [M^++H]: *m/z* 542.1863. Found: 542.1864.

3.18 X-ray crystallography

A suitable crystal was mounted on a glass fiber (for **14**, **23**, **26**, **27**, **50**, **51**, **57**, **69**, **90**, **97**.CH_3CN, **98**, **108** and **126**) and X-ray data were collected at 298 K on a Bruker AXS-SMART or on an OXFORD diffractometer using Mo-K_α radiation (for **14**, **23**, **26**, **27**, **50**, **51**, **57**, **69**, , **98**, **108** and **126**, λ = 0.71073 Å) or Cu-K_α (for **90**, **97**.CH_3CN, λ = 1.54178 Å). Structures were solved and refined using standard methods.[116] Absorption corrections were done using SADABS program, where applicable. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were fixed by geometry or located by a Difference Fourier and refined isotropically. Crystal data are summarized in Tables 9-12. In the case of compound **51**, the positions of N and CH groups adjacent to N1 are equally occupied. Hence, the refinement was done by keeping both positions as nitrogen

and giving it half occupancy that corresponds to an electron count for both N and CH is same.[117] This procedure gives slightly different values of M_r and μ, density etc.; Figure 5 also illustrates this. The quality of data in the case of **90** was only moderate and hence the R (int) and R values were a bit high. However the structure was clearly as shown.

Table 9: Crystal data for compounds **14**, **23**, **26** and **27**[a]

Compound	**14**	**23**	**26**	**27**
CCDC no.	984683	984684	984685	984686
Emp. formula	$C_{30}H_{20}N_2O$	$C_{22}H_{20}N_2O$	$C_{25}H_{18}N_2O$	$C_{31}H_{21}N_3O_3$
Formula weight	424.48	328.40	362.41	483.51
Crystal system	Triclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P2_1/n$
a /Å	10.4838(12)	13.1006(16)	7.4501(15)	9.5537(15)
b /Å	14.518(2)	14.6841(17)	8.7551(18)	16.927(3)
c /Å	15.9147(18)	8.7923(8)	14.931(3)	15.612(3)
α/deg	79.164(11)	90	95.20(3)	90
β/deg	73.907(10)	100.348(9)	98.89(3)	105.520(3)
γ/deg	71.712(11)	90	103.19(3)	90
V /Å^3	2196.2(5)	1663.9(3)	928.8(3)	2432.6(7)
Z	4	4	2	4
Dcalc /g cm^{-3}]	1.284	1.311	1.296	1.320
μ /mm^{-1}	0.078	0.081	0.080	0.086
F(000)	888	696	380	1008
Data/ restraints/ parameters	7726/2/595	2941/0/228	3613/0/254	4266/0/335
S	0.963	1.013	1.035	1.027
R1 [I>2σ(I)]	0.0596	0.0464	0.0494	0.0736
wR2 [all data]	0.1313	0.1201	0.1434	0.2303
Max./min. residual electron dens. [eÅ^{-3}]	0.152/-0.165	0.124/-0.189	0.173/-0.169	0.402/-0.231

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 10: Crystal data for compounds **50**, **51**, **57** and **69**[a]

Compound	**50**[b]	**51**	**57**	**69**
CCDC No.	984687	-	1041940	1041941
Emp. formula	$C_{26}H_{25}ClN_2ORu$	$C_{26}H_{18}N_2O$	$C_{32}H_{23}N_5$	$C_{27}H_{21}N_5$
Formula weight	518.00	374.42	477.55	415.49
Crystal system	Orthorhombic	Orthorhombic	Triclinic	Monoclinic
Space group	$P2_12_12_1$	*Pnma*	$P\bar{1}$	$P2_1/n$
a /Å	7.8508(2)	15.790(3)	10.0219(9)	7.9551(17)
b /Å	15.8682(4)	9.4300(19)	10.5021(9)	8.3463(18)
c /Å	18.2984(4)	13.210(3)	12.5853(8)	32.418(7)
α/deg	90	90	84.600(6)	90
β/deg	90	90	89.145(6)	95.876(4)
γ/deg	90	90	70.104(8)	90
V /Å^3	2279.57(10)	1967.0(7)	1239.82(17)	2141.1(8)
Z	4	4	2	4
*D*calc /g cm^{-3}]	1.509	1.268	1.279	1.289
μ /mm^{-1}	6.798	0.079	0.077	0.079
F(000)	1056	784	500	872
Data/ restraints/ parameters	3629/0/283	1836/0/160	4348/0/334	3780/0/290
S	1.039	1.088	0.987	0.994
R1 [I>2σ(I)]	0.0340	0.0552	0.0502	0.0464
wR2 [all data]	0.0915	0.1576	0.1235	0.1118
Max./min. residual electron dens. [eÅ^{-3}]	0.451/-0.511	0.241/-0.185	0.431/-0.166	0.176/-0.133

[a]$R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $wR2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$
[b]Flack parameter: 0.49(1) (racemic twin).

Table 11: Crystal data for compounds **90**, **97**.CH_3CN, **98** and **108**[a]

Compound	**90**	**97**.CH_3CN	**98**[b]	**108**
CCDC No.	1041942	1041943	-	-
Emp. formula	$C_{46}H_{31}N_5$	$C_{30}H_{31}ClN_6Ru$	$C_{31}H_{28}N_5O_3P$	$C_{24}H_{25}N_5O$
Formula weight	653.51	612.13	549.55	399.49
Crystal system	Monoclinic	Triclinic	Monoclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1$	$P\bar{1}$
a /Å	10.6333(12)	10.1801(4)	10.9466(16)	8.249(3)
b /Å	19.504(3)	10.6393(6)	9.1552(11)	9.685(3)
c /Å	19.502(3)	14.1179(6)	14.697(2)	14.060(5)
α/deg	90	83.944(4)	90	94.073(6)
β/deg	121.479(10)	74.689(4)	108.089(17)	91.653(6)
γ/deg	90	74.212(4)	90	107.489(6)
V /Å^3	3449.3(8)	1418.25(11)	1400.1(4)	1067.2(6)
Z	4	2	2	2
Dcalc /g cm^{-3}]	1.259	1.433	1.304	1.243
μ /mm^{-1}	0.582	5.570	0.140	0.079
F(000)	1368	628	576	424
Data/ restraints/ parameters	5859/0/460	5407/1/350	4667/1/ 363	3797/0/ 276
S	0.863	1.028	1.044	1.044
R1 [I>2σ(I)]	0.1133	0.0396	0.0539	0.0443
wR2 [all data]	0.3363	0.1091	0.1330	0.1258
Max./min. residual electron dens. [eÅ^{-3}]	0.196/-0.246	1.021/-0.631	0.270/-0.193	0.162/-0.225

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$
[b]Flack parameter: 0.03(1).

Table 12: Crystal data for compound **126**[a]

Compound	**126**
CCDC No.	-
Emp. formula	$C_{19}H_{14}N_2O_3S$
Formula weight	350.38
Crystal system	Monoclinic
Space group	*C*2/*c*
a /Å	20.858(3)
b /Å	8.6131(10)
c /Å	18.633(2)
α/deg	90
β/deg	98.084(3)
γ/deg	90
V /Å^3	3314.2(7)
Z	8
*D*calc /g cm^{-3}]	1.405
μ /mm^{-1}	0.216
F(000)	1456
Data/ restraints/ parameters	3387/0/230
S	0.944
R1 [I>2σ(I)]	0.0433
wR2 [all data]	0.1246
Max./min. residual electron dens. [eÅ^{-3}]	0.331/-0.179

[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

SYNTHESIS AND STRUCTURAL ASPECTS OF NOVEL ACYCLIC NUCLEOSIDE PHOSPHONATES

INTRODUCTION

4.1 General introduction: Acyclic nucleoside phosphonates (ANPs)

Acyclic nucleotides and their derivatives are widely used as potential antiviral and anticancer agents.[1] The only structural difference between these compounds and the natural nucleotides is that pentafuranosyl sugar ring present in the natural nucleotides is replaced with an acyclic moiety. During the past few decades, a large number of acyclic nucleotides have been synthesized and examined for their antiviral and/or cytostatic properties.[1] Examples of this class of compounds, including some currently used drugs (hepatitis-B/ HIV/ CMV), are shown in Chart 1. Thus it is well-recognized that the phosphonate analogues of nucleoside phosphates are pharmaceutically important since the phosphorus-carbon bond in phosphonates is not susceptible to enzymatic degradation by phosphatases, thereby enhancing physiological stability. Added to this, phosphonate esters are less polar and hence can have better cell permeability. Thus there is significant interest in developing new routes to acyclic nucleotides.[1-2]

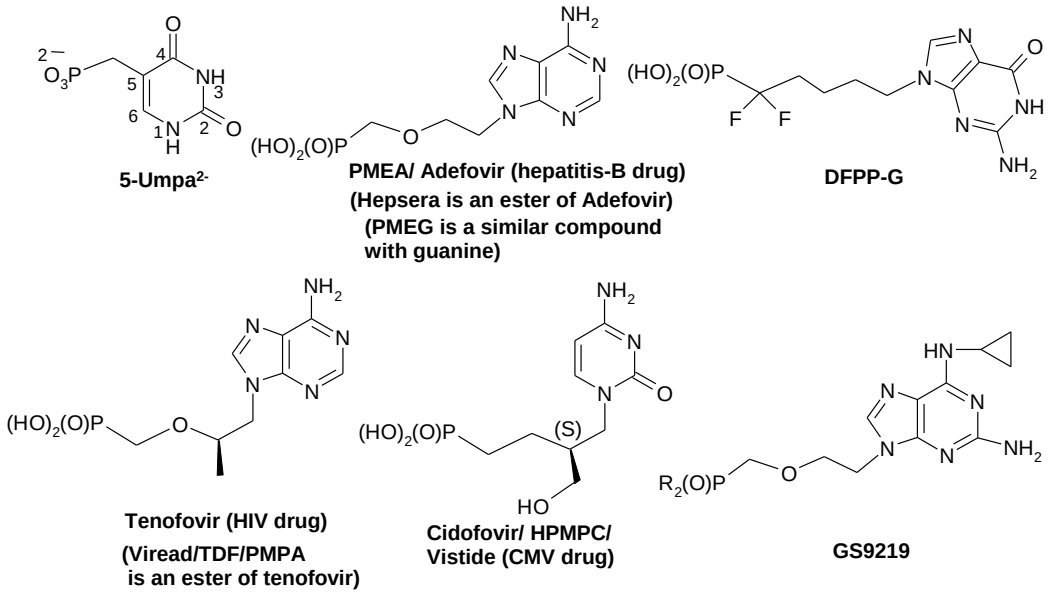


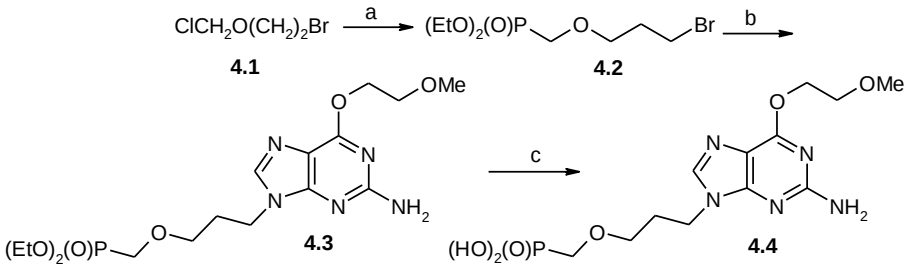
Chart 1. Examples of clinically active nucleobase appended phosphonates

4.2 Syntheses of acyclic nucleoside phosphonates

The activity of acyclic nucleotides may vary depending upon the heterocyclic base and acyclic chain length and substituents. In the subsequent paragraphs, we shall discuss the different synthetic routes developed for the synthesis of these acyclic nucleotides.

Kim and co-workers synthesized a series of 9-(phosphonoalkyl)purines, which are analogues of PMEA and PMEG (shown in Chart 1) by the coupling of bromophosphonate derivatives with the corresponding purine derivatives in the presence of sodium hydride (Scheme 4.1).[3] The phosphonic acids were obtained by treating the phosphate esters with bromotrimethylsilane (TMSBr) in DMF. These compounds were tested against antiviral activity. It was found that optimal activity was attained when two carbons are located between the purine base and the phosphonomethoxy group.

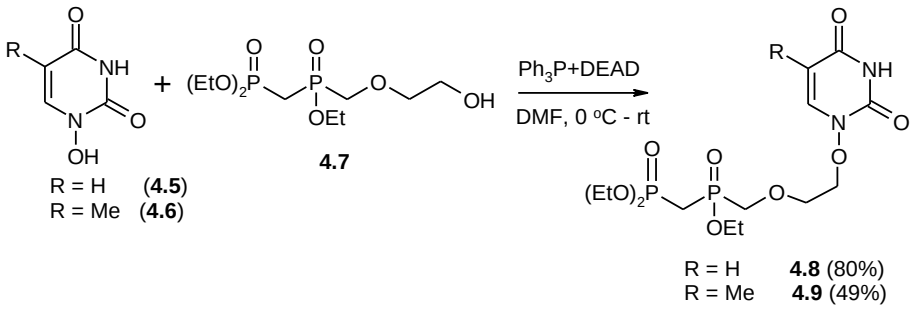
Scheme 4.1



(a) $(EtO)_2P(O)Na$; (b) 2-amino 6-(methoxyethoxy)purine/NaH; (c) TMSBr, DMF

Diphosphonate derivatives of pyrimidine and purine nucleobases were synthesized by Parkin's group.[4] The diphosphonate unit was introduced *via* Mitsunobu coupling with 1-hydroxypyrimidines or 9-hydroxypurines (Scheme 4.2). Conventional deprotection with TMSBr afforded the corresponding phosphonic acids in good yields. The antiviral activity of these diphosphonates has also been examined.

Scheme 4.2

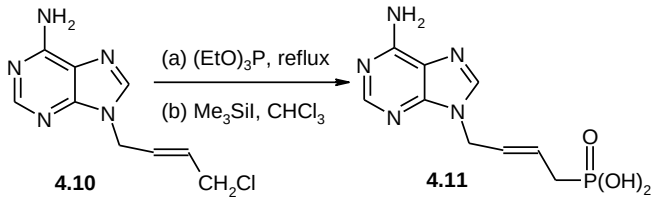


R = H (**4.5**)
R = Me (**4.6**)

R = H **4.8** (80%)
R = Me **4.9** (49%)

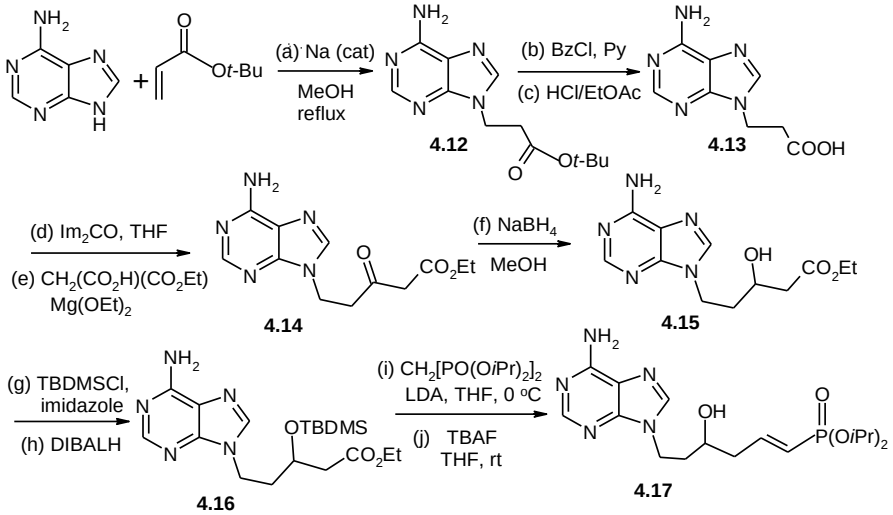
Unsaturated acyclic nucleotides were synthesized by Zemlicka and co-workers using Michaelis-Arbuzov reaction of chloro derivatives **4.10** with triethyl phosphite (Scheme 4.3).[5] Dealkylation of so obtained phosphonates afforded phosphonic acids **4.11**. Later, Parrat's group prepared a series of alkenylphosphonic acid derivatives of purine and pyrimidine bases by either Mitsunobu coupling of alcohols with 9-hydroxypurines/l-hydroxypyrimidine or alkylation of the purine/pyrimidine bases.[6] Lazrek *et al* also reported (*Z*) and (*E*) alkenyl phosphonic acid derivatives of purines and pyrimidines by Michael addition of purine/pyrimidine base with alkynylphosphonate using base catalysis.[7]

Scheme 4.3



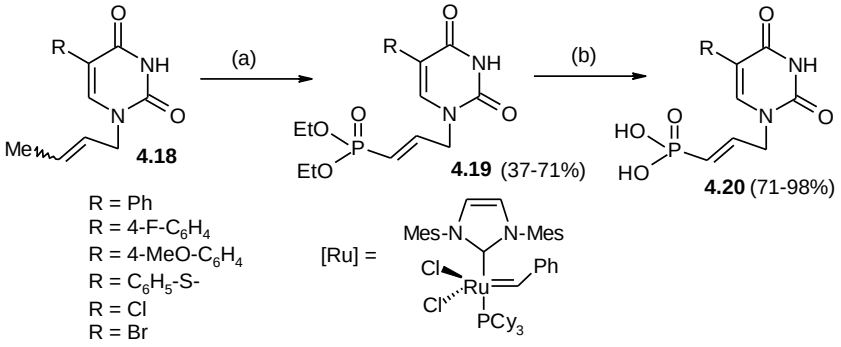
Acyclic carba-nucleoside phosphonates have been synthesized by Taddei's group from the Michael reaction of pyridine/pyrimidine nucleobases with *tert*-butyl acrylate (Scheme 4.4).[8] These Michael adducts were transformed to β-oxo esters and then to the β-hydroxy esters by selective reduction. These were converted to β-hydroxy aldehydes, which underwent Wittig-Horner-Emmons reaction with the phosphonate to give the corresponding pyridine/pyrimidine carba-phosphonates.

Scheme 4.4



Based on cross-metathesis, Agrofoglio and co-workers synthesized acyclic uracil phosphonate derivatives.[9] Thus, the reaction of N1-crotylated uracil derivatives with diethyl vinyl phosphonate in the presence of [Ru]-catalyst afforded the corresponding cross-metathesis products in moderate to good yields (Scheme 4.5). In all the cases, exclusive formation of (*E*)-isomer was observed. The reaction worked well with N3-protected and unprotected uracil derivatives.

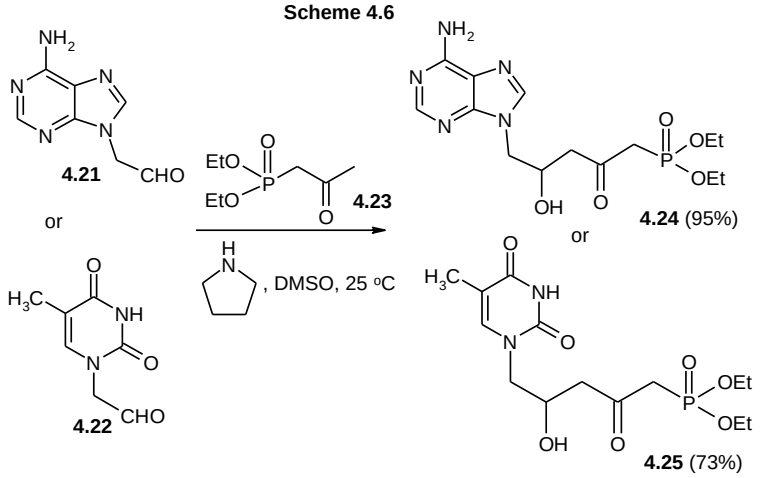
Scheme 4.5



(a) Diethyl vinyl phosphonate, [Ru]-catalyst (5 mol %), DCM
(b) TMSBr, DCM

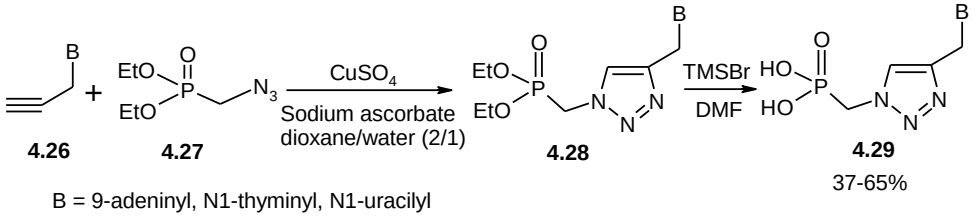
Lewkowicz *et al* developed an organocatalytic approach for the synthesis of novel purine and pyrimidine acyclic nucleosides.[10] Thus, nucleobases containing aldehydes were treated with phosphonate-substituted ketones in the presence of an amine base (pyrrolidine or silica-immobilized piperazine) to afford the acyclic phosphonate-containing nucleosides in good yields (Scheme 4.6). The products were separated from the reaction mixture by simple aqueous work up.

Scheme 4.6



Smietana and co-workers reported a series of triazoloacyclonucleoside phosphonates.[11] The reaction involves a copper(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition between azidoalkylphosphonates (**4.26**) and propargylated nucleobases (**4.27**) (Scheme 4.7). These triazole derivatives were found to be potential HCV inhibitors.

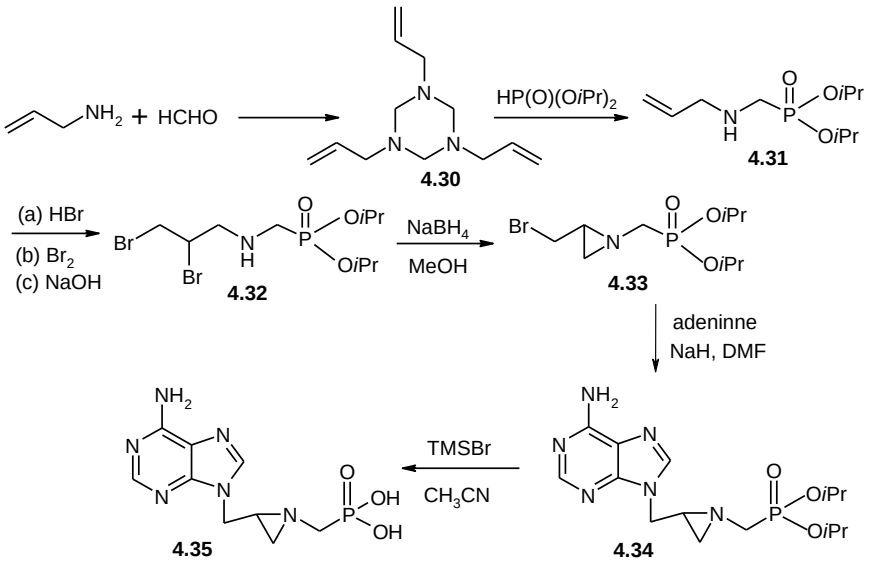
Scheme 4.7



B = 9-adeninyl, N1-thyminyl, N1-uracilyl

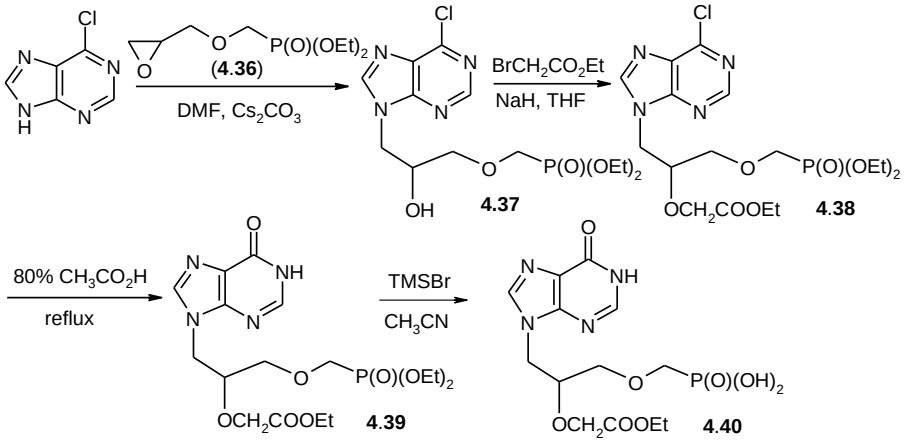
Sheikha *et al* described a new series of acyclic nucleoside phosphonates containing aziridine phosphonate moiety in the side chain.[12] The aziridine phosphonate (**4.33**) was synthesized from allylamine and formaldehyde in a 4 step procedure as described in Scheme 4.8. The base catalyzed reaction of nucleobases with bromo phosphonate (**4.33**) afforded the aziridine containing ANPs in moderate yields. The corresponding phosphonic acids were found to be active against a variety of viruses, fungi and bacteria.

Scheme 4.8



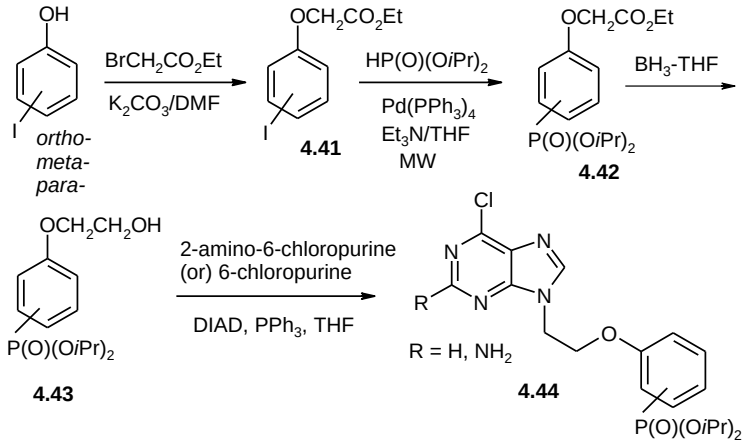
6-Oxopurine acyclic nucleoside derivatives have been synthesized by nucleophilic ring opening of the epoxide (**4.36**) with the purine derivatives (Scheme 4.9).[13] Using ethyl bromoacetate, a two-carbon chain was attached to 2'-hydoxyl position. These compounds were further converted to oxopurine derivatives (**4.39**) by treatment with acetic acid. The corresponding phosphonic acids (**4.40**) were obtained by hydrolysis in the presence of TMSBr.

Scheme 4.9



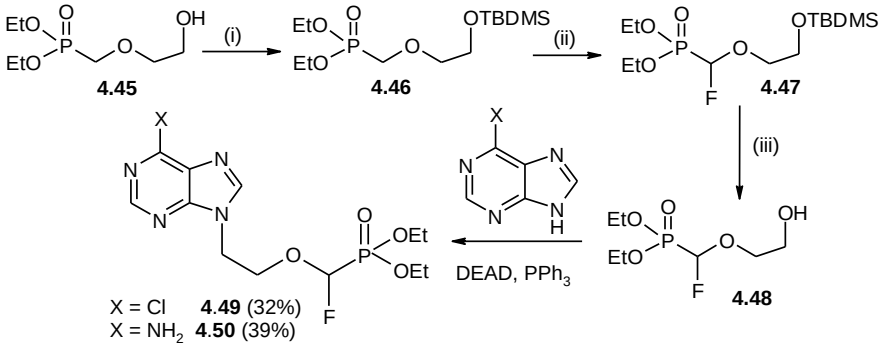
Hocková and co-workers reported a series of novel acyclic nucleoside phosphonates containing an arylphosphonate group.[14] The key step involved in this reaction was microwave-assisted cross-coupling of iodo derivatives with phosphonate in the presence of palladium-catalyst (Scheme 4.10). Reduction of ester functional group in the presence of BH_3-THF afforded the corresponding alcohol derivative **4.43**. Alkylation of 6-chloropurine or 2-amino-6-chloroopurine was done under Mitsunobu reaction conditions using alcohol containing arylphosphonate moiety in **4.43**. By applying this methodology, *ortho*-, *meta*- and *para*-substituted arylphosphonate derivatives were synthesized in moderate to good yields.

Scheme 4.10



Xu and co-workers synthesized fluorinated acyclic nucleoside phosphonates (Scheme 4.11).[15] Thus, *α*-fluorophosphonomethyl ether **4.47** was prepared by electrophilic fluorination of the corresponding phosphonomethyl ether **4.46**. Coupling of the synthesized fluorinated alcohol **4.48** with purine derivative under Mitsunobu conditions afforded the fluorinated acyclic nucleoside phosphonates (**4.49** and **4.50**) in moderate yields. The monoethyl ester of **4.50** was found to be active against HCMV and Epstein-Barr virus.

Scheme 4.11

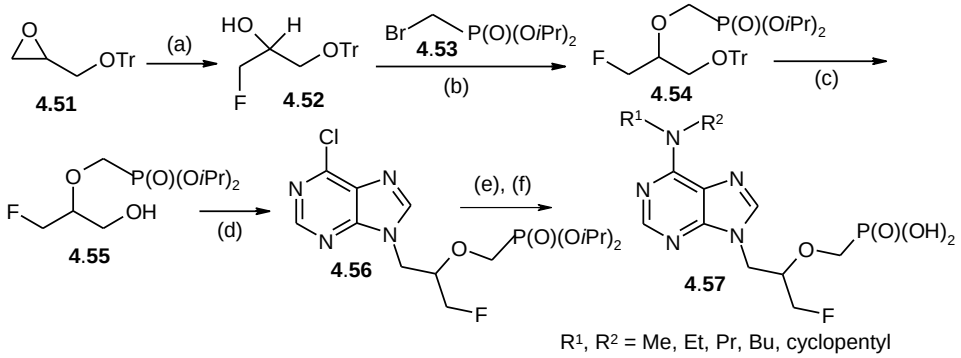


(i) TBDMS-Cl, DMAP/Et_3N; (ii) a. *sec*-BuLi, b. $(PhSO_2)_2NF$; (iii) Dowex (H^+), EtOH

Recently, Janeba *et al* reported a series of fluorinated derivatives starting from *O*-tritylated glycidols (Scheme 4.12).[16] Glycidols were converted to fluorohydrines by the epoxide ring opening with potassium hydrogen difluoride in the presence of catalytic amount of tetrabutylammonium dihydrogen trifluoride. Alkylation of fluorohydrine **4.52** was done using NaH and bromomethylphosphonate **4.53**. Detritylation, followed by Mitsunobu coupling with

6-chloropurine afforded the phosphonate **4.56** in moderate yields. Heating the 6-chloropurine derivatives with amines and hydrolysis of the phosphonate with TMSBr afforded the corresponding phosphonic acids.

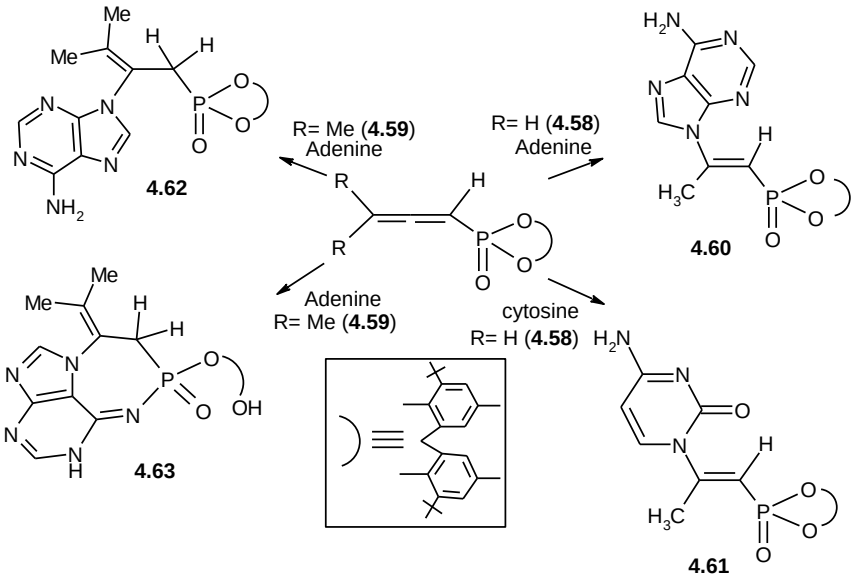
Scheme 4.12



(a) KHF_2, cat. $Bu_4NH_2F_3$; (b) NaH, DMF; (c) 80% AcOH, 90 °C; (d) 6-chloropurine, DIAD, PPh_3, THF (e)amine, CH_3CN; (f) TMSBr, CH_3CN.

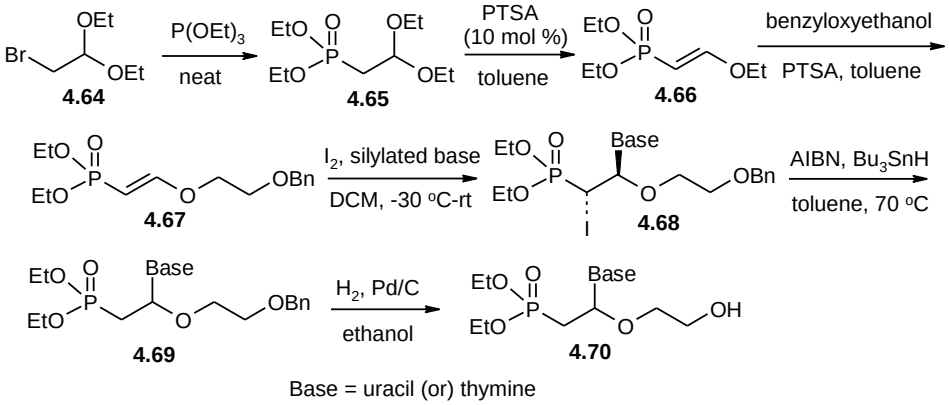
From our laboratory, nucleobase-appended phosphonates have been prepared by the reaction of allenylphosphonates with nucleobases in the presence of a base (Scheme 4.13).[17] The reaction of allene **4.58** with nucleobases (adenine, cytosine, thymine and guanine) furnished only (*E*)-vinyl phosphonates **4.60-4.61**. In contrast to this, the reaction of allene **4.46** with adenine gave allylphosphonate **4.62** and a novel cyclized product **4.63**, respectively, resulting from the N(9) and N(7) addition products with allene.

Scheme 4.13



Virieux and co-workers reported a new family of acyclic nucleoside phosphonates which are transition state analogues of thymidine phosphorylase (TPases).[18] Thus, vinylic phosphonate **4.66** was synthesized in two steps by using triethylphosphite and catalytic amount of PTSA. This was further converted to the benzyl derivative **4.67** using benzyloxyethanol. The key step for the synthesis of these ANPs was the addition of nucleobase to vinylic phosphonate **4.67**; this was achieved in the presence of iodine and *O*-silyl pyrimidine derivatives. These addition products **4.68** were racemic mixtures with the nucleobase and iodine introduced in the *trans* position (Scheme 4.14). Final deiodination by tributyltin hydride and debenzylation using Pd/C afforded pyrimidine phosphonates **4.70**, which possess on one side a phosphonate group and on the other side a hydroxy function, in moderate overall yields.

Scheme 4.14



The above brief account illustrates the utility of organophosphonates bearing nucleoside residue. We believe that, in view of the potent pharmaceutical interest this is a fertile synthetic area to be explored in detail.

OBJECTIVES OF THE PRESENT WORK - PART B

The main objective of this part of the present work was to study of the supramolecular interactions present in the phosphonyl substituted nucleobases. It was intended to study their pharmaceutical activity at a later stage. Specifically, it was intended to explore

(i) To synthesize alkynyl appended nucleobases using Mitsunobu reaction and then to hydrophosphonylate the alkyne residue in the presence of [Pd]-catalyst,

(ii) To study the nucleobase paring in the presence of strong hydrogen bond acceptor P=O bond,

(iii) To synthesize alkenyl and triazole appended nucleobase phosphonates and to study structural aspects of these compounds with regard to base pairing.

RESULTS AND DISCUSSION

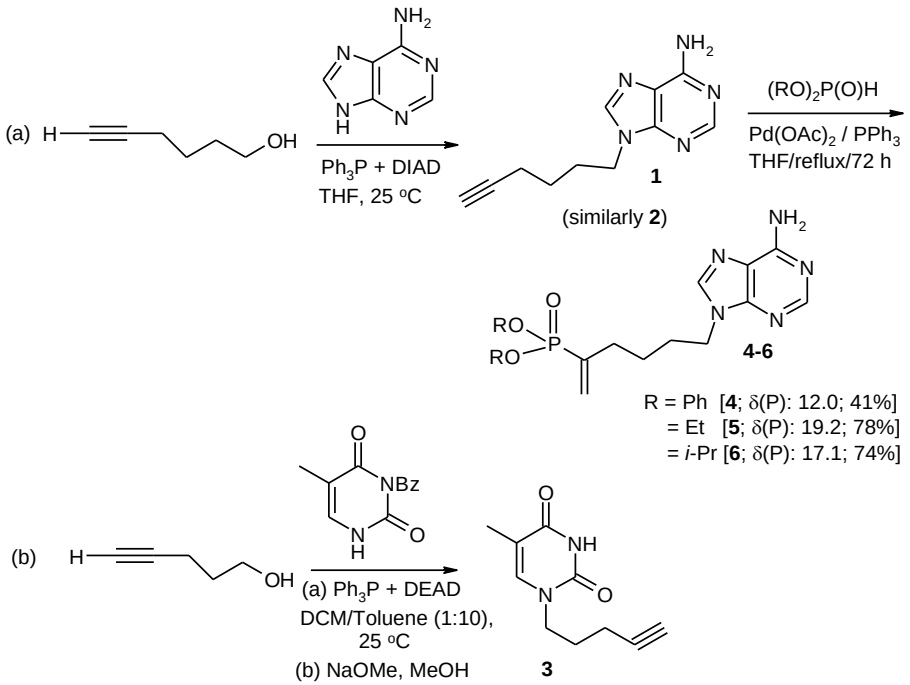
The theme of this part of the work is synthesis of acyclic nucleoside phosphonates (ANPs) and a study of the supramolecular interactions in these ANPs. Although the biological activity is not studied in this work, this aspect is the final target. Our interest in organophosphonate chemistry[19] prompted us to look into this chemistry to some measure, and in an earlier publication our group shown that several such derivatives can be prepared by addition of nucleobases to allenylphosphonates.[17] Since nucleobase pairing via hydrogen bonding is an important topic by itself,[20] we surmised that such a study in the presence of the phosphoryl bond is also worth-investigating. This is because the P=O bond is considered to be a strong hydrogen bond acceptor,[21] but several investigations suggest that in most cases this bond does not intercept nucleobase-pairing.[22] This is an aspect that we wanted to probe further. To this end, our synthetic methodology involved coupling of an alkynyl-substituted long chain alcohol to the nucleobase via Mitsunobu reaction[23] and subsequent phosphonylation of the alkyne moiety.[24] So far, we have succeeded in obtaining the X-ray structures of the adeninyl-substituted compound **1** with an alkyne moiety as the end-group (Scheme 1). For the sake of comparison, we have also included the X–ray structure of long-chain appended adenine compound **2**.[25] A structural investigation on analogous alkynyl-substituted thymine derivative **3** that exhibits an interesting case of supramolecular C-H···O interactions is also described herein.[26] Two phosphonylated products **4** and **5** obtained via a palladium-catalyzed reaction on **1**, that relate to the basic theme of the present investigations, are then discussed. ***This is a new route to phosphonylated nucleobases.*** We have also synthesized the phosphonate **6** but crystals could not be obtained. Structural aspects of these compounds are discussed.

5.1 Synthesis of alkynyl and phosphonylated nucleobases 1-6

Synthesis of the alkyne-appended nucleobases **1** and **3** as well as the long chain appended adenine derivatives **2** was accomplished by the well-known Mitsunobu reaction (Scheme 1).[23] Compound **3** was prepared by starting with

benzoylated thymine as reported in the literature.[27] A palladium-catalyzed phosphonylation was done on **1** to obtain the compounds **4-6**; the recently discovered dinuclear Pd-catalyst $(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$[19f] also worked well for the synthesis of **5** (Yield: 65%). This route represents a new approach to obtain phosphono-nucleobases and appears to have a lot more potential once we have reactive alkyne as the end group. Spectroscopic data of these compounds were as expected with no unusual behavior; the phosphonate compounds showed a single peak in the ^{31}P NMR spectrum.

Scheme 1



5.2 Alkynyl appended nucleobases 1and 3: Thermally induced polymorphism and comparison to structure of 2

Crystals of moderate quality for the adeninyl compound **1** were obtained from methanol-toluene mixture. The space group for the structure that was solved initially showed that it belonged to $P2_1/c$ (data at 298K; see Figure 1). However, since there was disorder at one of the chain-carbon atoms (penultimate carbon in the chain, C9A/C9B; C8 also had high thermals), we decided to collect data at a low temperature (200 K) using another crystal from the same batch. Rather surprisingly, the suggested space group for this crystal (labeled as **1'**) was $P\bar{1}$ with two molecules in the asymmetric unit; the difference between the two molecules lies in the

conformation of the alkyl chain as shown in Figure 2. While the C6···C9 distance is 3.85(1) Å, the C6A···C9A distance is 3.09(2) Å. The N-H···N hydrogen bond pattern in the residual base pair is similar to the large number of monosubstituted adenines.[28] However, an additional feature in our compound is the presence of a C-H···N interaction [C···N 3.425(6) Å] between alkynyl C-H and the free ring nitrogen of adeninyl moiety. We are not aware of a previous report on such an interaction. Interestingly though, even this crystal (**1'**) at room temperature (298K) displayed $P2_1/c$ space group (of course with the same structure as the first crystal)! Since the temperature difference resulted in the same crystal to show two different forms, we believe that this is a case of ***thermally induced polymorphism***.[29] That this is so is also corroborated by recording the DSC in the temperature range 173-523 K. There is a small but clearly discernible endotherm at 285 K suggesting that there is a phase transition (Figure 3). We have subsequently measured the unit cell data at 100 K (triclinic), 200 K (triclinic), and 298 K (monoclinic) that are in line with the discussion given above (Table 1). Although powder XRD at 200 and 298 K showed only a minor variation (Figure 4),[30] solid-state ^{13}C NMR spectra recorded at 298 and 263 K[31] showed clear changes in the aliphatic region [δ 15-18 and 28-29] (Figure 5). These data are also consistent with the notion that **1** and **1'** differ mainly because of the conformational variation in the long chain.

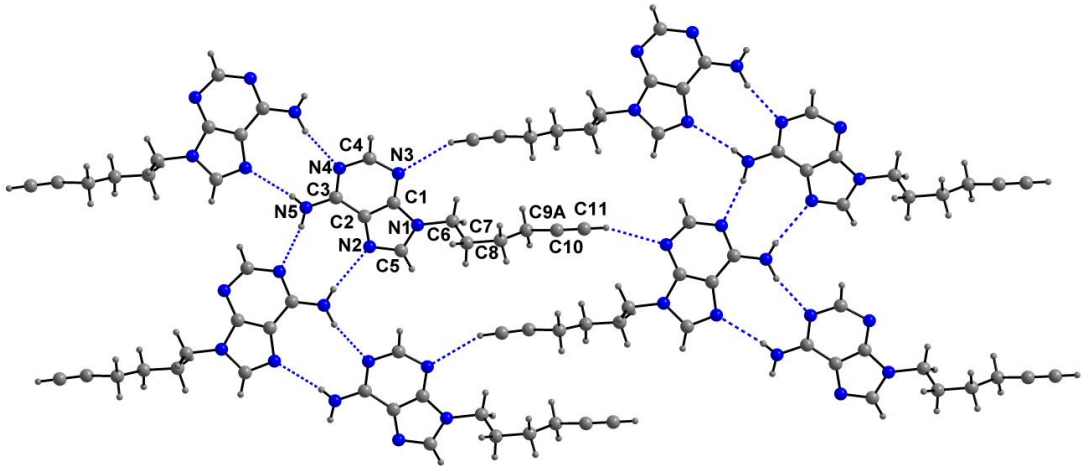


Figure 1. Molecular structure of compound **1** (taken at 298 K). There is disorder at C9 and only one of the disordered carbon atoms (C9A) is shown. Hydrogen bond parameters (Å, °): N5-H5A···N4 0.904(11), 2.10(2), 2.965(4), 160(4); symmetry code: -x, -0.5+y, 2.5-z, N5-H5B···N2 0.76(5), 2.31(5), 3.063(4), 169(5); symmetry code: -x, 0.5+y, 2.5-z, C11-H11···N3 0.93, 2.55, 3.425(6), 156.3; symmetry code: 1-x, -0.5+y, 1.5-z.

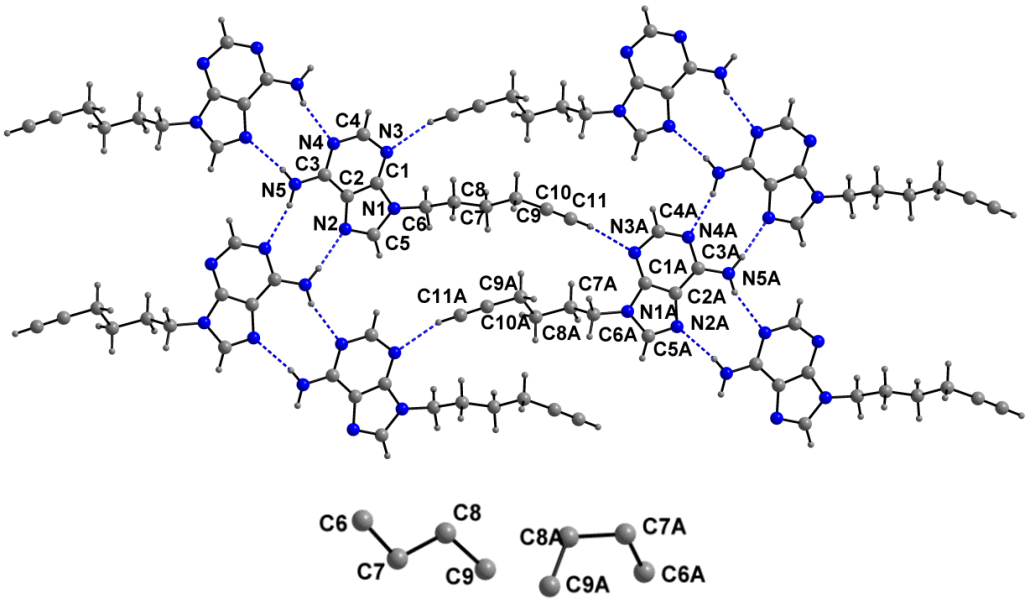


Figure 2. Molecular structure of compound **1'** (top; taken at 200 K). At the bottom is shown the conformations adapted by the two molecules in the asymmetric unit. Hydrogen bond parameters (Å, ^{o}): N5-H5A···N2A 0.81, 2.22, 3.015(7), 168.1; symmetry code: 1+x, -1+y, 1+z, N5-H5B···N4A 0.89, 2.09, 2.937(7), 158.5; symmetry code: x, -1+y, 1+z, N5A-H5C···N4 0.83, 2.16, 2.962(7), 161.2; symmetry code: -1+x, 1+y, -1+z, N5A-H5D···N2 0.93, 2.11, 3.035(7), 174.7; symmetry code: x, 1+y, -1+z, C11A-H11A···N3 0.95, 2.44, 3.338(10), 156.9; symmetry code: -1+x, y, z, C11-H11···N3A 0.95, 2.48, 3.416(9), 170.2.

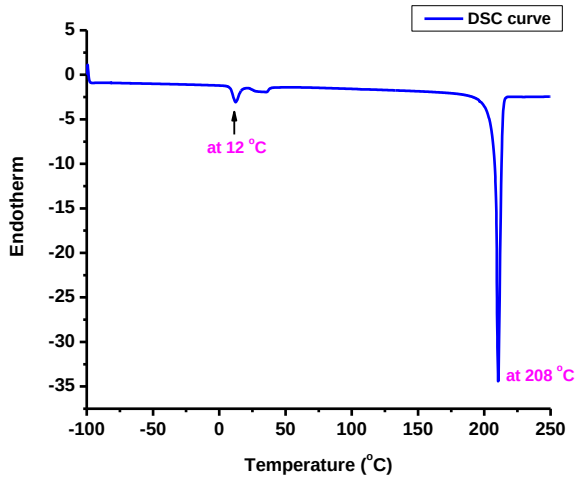


Figure 3: DSC of compound **1** from -100–250 ^{o}C (173-523 K). A small endotherm is observed at 12 ^{o}C (285K) is ascribed to the phase transition. The sharp endotherm at 208 ^{o}C (481 K) is due to the melting point.

Table 1. Cell dimensions measured for **1**/**1'** for a new crystal measured at 100 K, 200 K and 298 K

T (K)	**100**	**200**	**298**
Crystal system	triclinic	triclinic	monoclinic
a /Å	8.259(2)	8.262(1)	11.232(3)
b /Å	11.492(2)	11.501(2)	8.263(2)
c /Å	12.019(2)	12.024(4)	12.514(3)
α/deg	101.837(6)	101.426(4)	90
β/deg	96.429(7)	96.483(2)	102.662(4)
γ/deg	100.842(5)	100.526(5)	90
V /Å^3	1083.0(4)	1088.4(2)	1133(5)

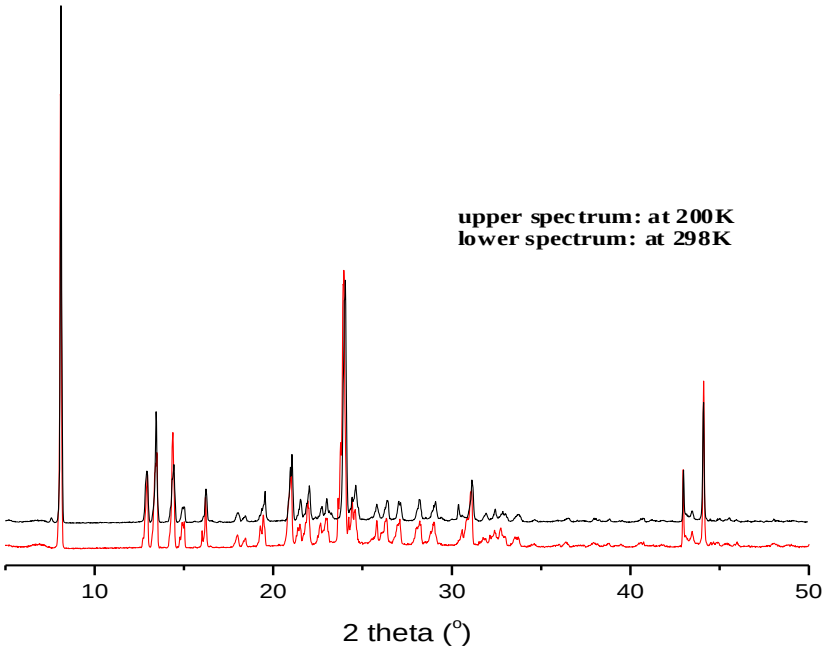


Figure 4. PXRD profile of compound **1'** at 200 K (bottom) and compound **1** at 298 K (top).

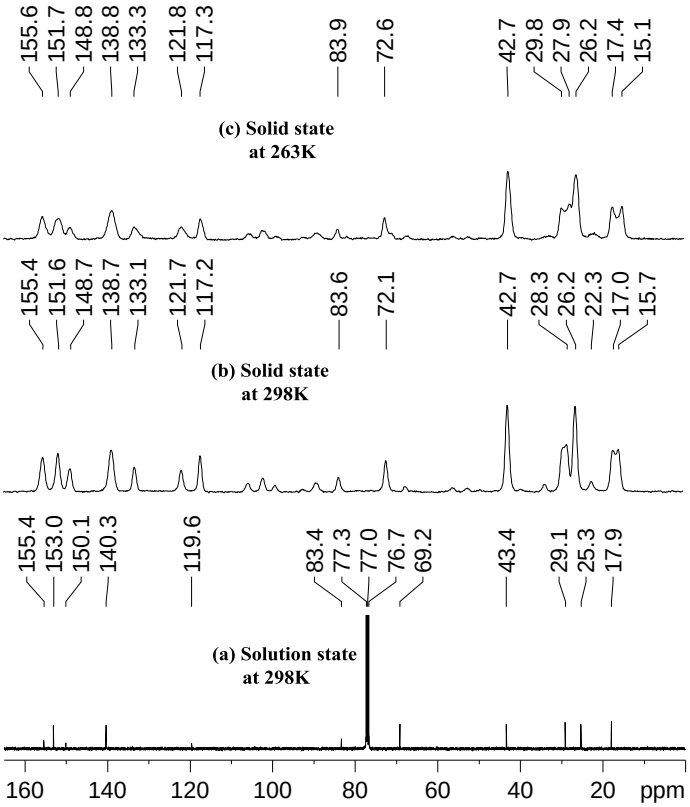


Figure 5. A diagram showing solid and solution state ^{13}C NMR spectrum of compound **1** (a) solution state at 298K, (b) solid state at 298K and (c) solid state at 263K. In (b) the splitting of the signal at ca 16 ppm is 1.3 ppm (298 K) while in (c), it is 2.3 ppm (263 K). A similar thing happens in the region 28-29 ppm. The extra peaks in solid state are due to the spinning side bands.

Alkenyl adenine derivative **2** shows the normal hydrogen bonding pattern in the nucleobase-pair (Figure 6). These N-H···N interactions are mainly responsible for the formation of two-dimensional zigzag tapes. Compound **2** showed a conformational disorder at the terminal carbon atom of the chain as shown in Figure 6. Since we were not successful in phosphonylating this compound, we did not study it further.

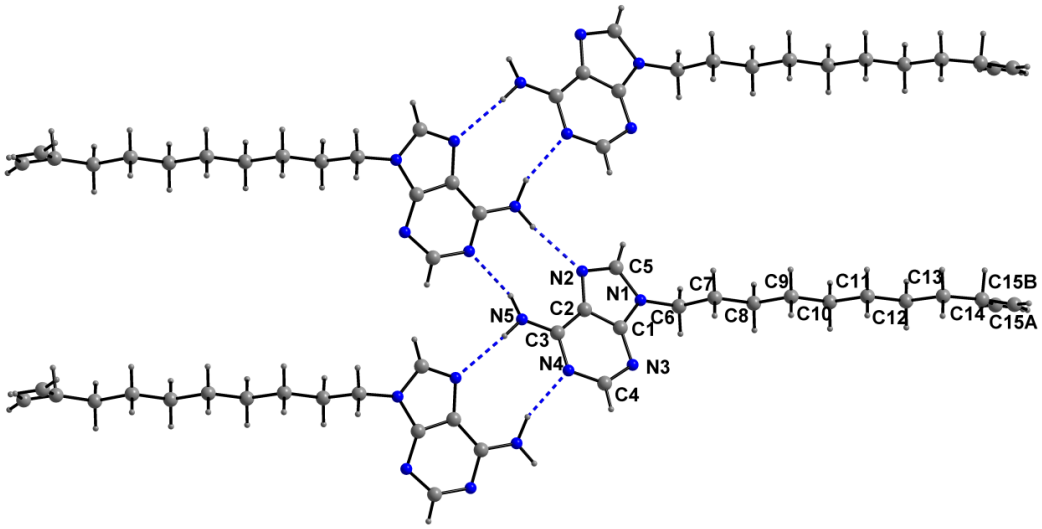


Figure 6: Molecular structure of compound **2**. Only non-hydrogen atoms are labeled. Note the disorder at the terminal alkenic carbon atom (C15A/C15B). Hydrogen bond parameters (Å, °): N5-H5B···N2 0.90(2), 2.23(3), 3.112(2), 168(2); symmetry code: -x, -0.5+x, 1.5-z, N5-H5A···N4 0.95(2), 2.08(2), 2.997(2), 160.0(17); symmetry code: -x, 0.5+y, 1.5-z.

The alkyne appended thymine derivative **3** displayed an additional feature of interest. The alkyl chain, instead of taking the normal zig-zag pattern, is bent to accommodate C-H···O interaction involving C≡CH and a carbonyl oxygen atom of the thymine residue (Figure 7). Also, there appears to be an additional interaction from the same carbonyl oxygen to one of the alkyl CH_2 hydrogen atoms. However, these features do not affect the base-pairing that involves N-H···O(=C) hydrogen bonds as observed in many other cases.[32]

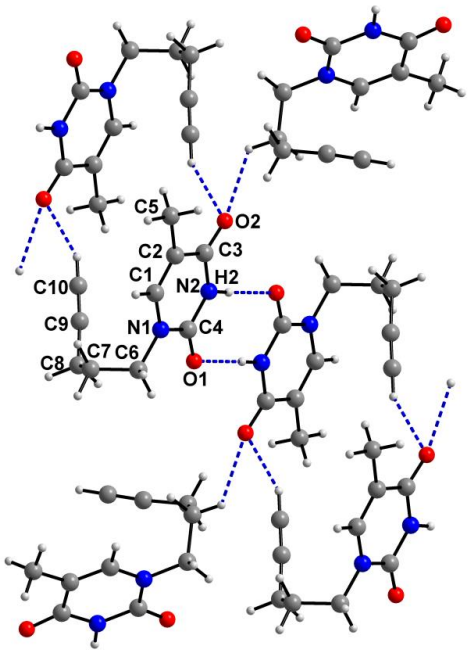


Figure 7. Molecular structure of compound **3** (at 100 K). Only non-hydrogen atoms are labeled. Hydrogen bond parameters (Å, °): N2-H2···O1 0.88, 1.98, 2.855(3), 175.6; symmetry code: 1-x, -y, 2-z, C7-H7B···O2 0.99, 2.57, 3.294(3), 130.4; symmetry code: 2-x, 0.5+y, 1.5-z, C10-H10···O2 0.95, 2.33, 3.214(3), 154.4; symmetry code: 1-x, -y, 1-z.

5.3 Phosphonyl substituted nucleobases 4 and 5: Any role for the strong hydrogen bond acceptor, the P=O bond?

We now turn our attention to the phosphonylated products **4** and **5** in which we were originally interested. In compound **4**, the asymmetric unit contains two molecules. The phosphoryl oxygen (P=O), which is a strong H-bond acceptor,[21] is unable to disturb the normal base pairing (Figure 8, top). It has to be satisfied only with marginally weak C–H···O hydrogen bonds in the structure (Figure 8, middle and bottom). These interactions involve the hydrogen atoms of the alkenic $=CH_2$ as well as those of the phenyl ring. Overall, the hydrogen bonding interactions appear to be extending in all the three dimensions without loss of the homo-base pairing. Similar is the case of compound **5**. Here again the phosphoryl bond is involved only in C-H···O interactions with OCH_2 hydrogen atoms (Figure 9). In this structure also, there are two molecules in the asymmetric unit, but phosphoryl oxygen atom (O1) of only the first molecule is involved in significant hydrogen bonding interaction with H16A.

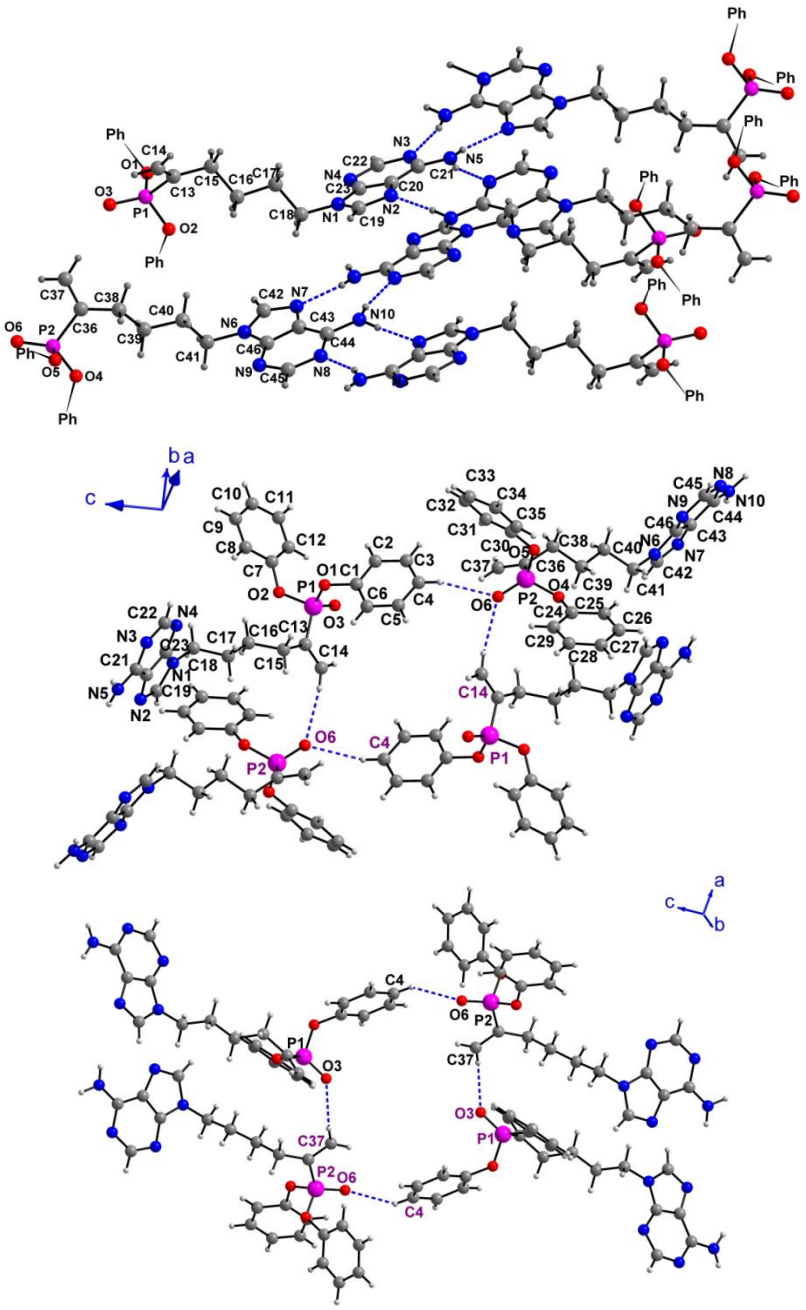


Figure 8: Diagrams showing supramolecular interactions in compound **4.** The symbol 'Ph' represents a phenyl group. Top: base pairing via N-H···N interactions. Middle and bottom: C-H···O(=P) interactions. Hydrogen bond parameters (Å, ^{o}): N5-H5A···N7 0.81(4), 2.31(4), 3.101(5), 167(4); symmetry code: x, -1+y, 1+z, N5-H5B···N8 0.86(4), 2.13(4), 2.935(5), 156(4); symmetry code: -1+x, -1+y, 1+z, N10-H10A···N2 0.96(4), 2.11(4), 3.078(5), 177(4); symmetry code: 1+x, 1+y, -1+z, N10-H10B···N3 0.85(4), 2.12(4), 2.949(5), 165(4); symmetry code: x, 1+y, -1+z, C4-H4···O6 0.93, 2.60, 3.419(7), 146.9, C14-H14A···O6 0.93, 2.56, 3.481(6), 169.5; symmetry code: -x, -y, 1-z, C37-H37A···O3 0.93, 2.50, 3.395(6), 160.6; symmetry code: -x, 1-y, 1-z.

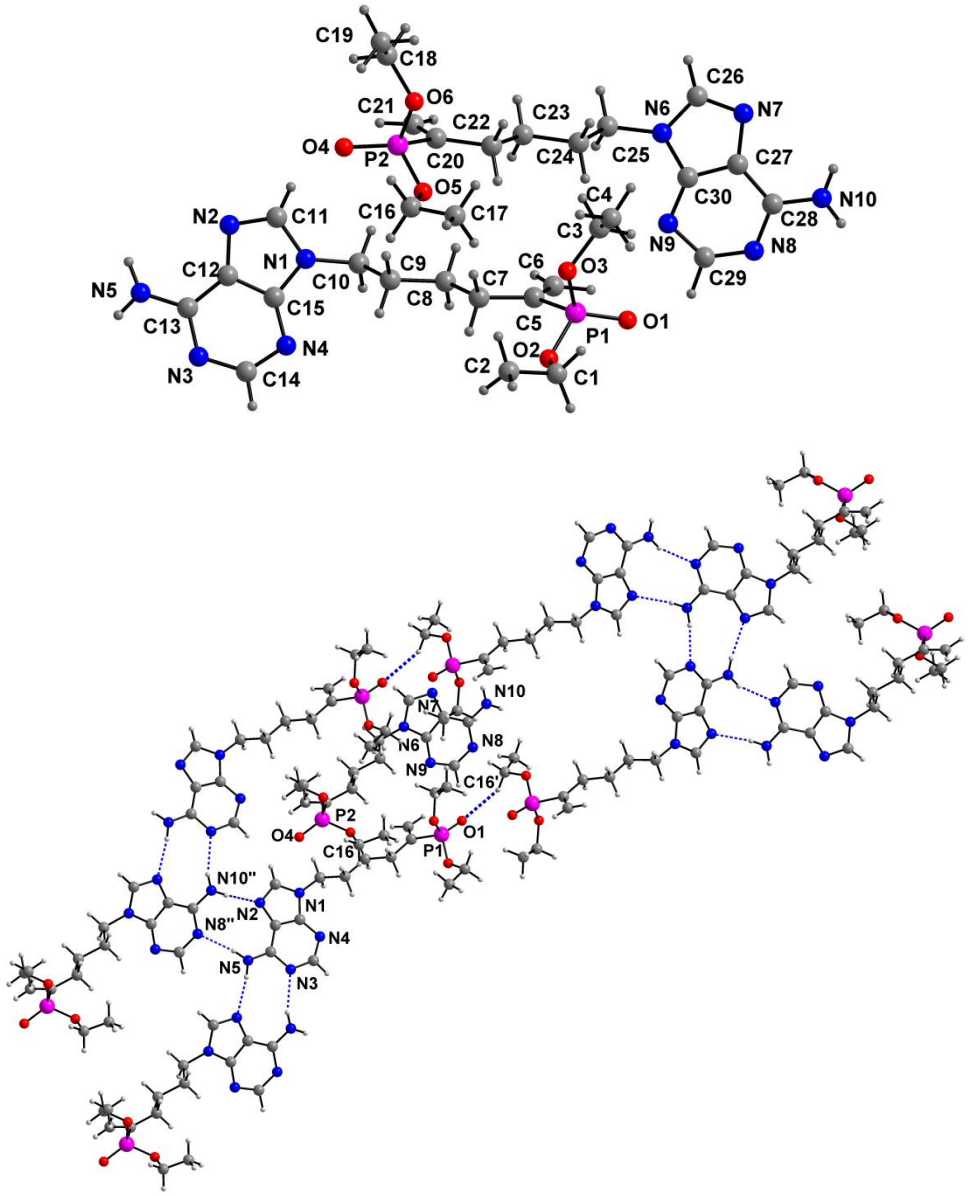
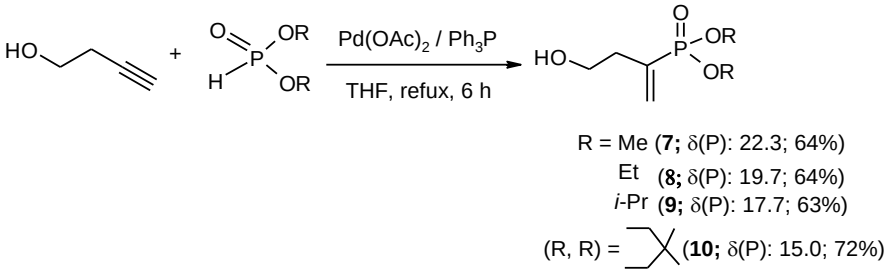


Figure 9: Diagrams showing molecular structure (top) and supramolecular interactions (bottom) in compound **5**. Hydrogen bonding parameters (Å, ^{o}): N5-H5A···N8'' 0.89(5), 2.09(5), 2.975(6), 171(5); symmetry code: x, 1+y, z, N5-H5B···N7 0.86(6), 2.14(6), 2.999(6), 171(5); symmetry code: 1+x, 1+y, z, N10-H40A···N3 0.84(5), 2.18(5), 2.986(6), 160(5); symmetry code: -1+x, -1+y, z, N10-H40B···N2 0.85(5), 2.15(5), 3.000(6), 171(5); symmetry code: x, -1+y, z, C16-H16A···O1 0.99, 2.48, 3.383(7), 151.6; symmetry code: 1-x, 0.5+y, 1.5-z.

5.4 Synthesis of Precursors: Vinyl phosphonate (7-10) with terminal –OH group, azido phosphonate 11 and N-propargyl nucleobases (12-15)

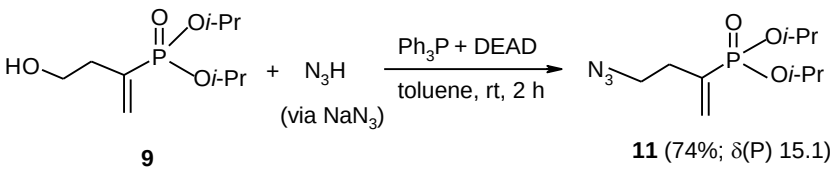
In continuation of our work on nucleoside phosphonates, we have synthesized vinyl phosphonates **7-10** that contain a terminal –OH group by Pd-catalyzed hydrophosphonylation of 3-butyn-1-ol (Scheme 2). The reaction involves the phosphonylation of alkyne in the presence of $Pd(OAc)_2/PPh_3$. Using this methodology, vinylic phosphonates **7-10** were obtained in good yields. The ^{31}P NMR spectra of vinylic phosphonates **7-10** show a peak in the range δ 15-22, whereas dialkyl phosphites show a peak in the range δ 3-8. In the ^{13}C NMR spectra, the *α*-carbon (to phosphorus) appears as a doublet at δ 134-137 [^1J(P-C) ~ 170.0 Hz] for the vinylic phosphonates **7-10**. The PC=*C* signal for all these compounds appears as a doublet in the region δ 130-132 [^2J(P-C) ~ 8.7-9.0 Hz]. The presence of alcoholic group was readily inferred from IR [3359-3381 cm^{-1}].

Scheme 2



Phosphonate **9** was converted to azidophosphonate **11** using Mitsunobu reaction with NaN_3. Thus, the reaction of alcohol **9** in the presence of PPh_3/DEAD using N_3H solution as azide source in toluene solvent afforded the azidophosphonate **11** in excellent yield (Scheme 3). The presence of azide functional group was confirmed by IR spectrum (band at 2098 cm^{-1}). In the ^{13}C NMR spectrum, the *α*-carbon (to phosphorus) and PC=*C* are appear as doublets and δ value is also in the same region as that for vinylphosphonate **9**.

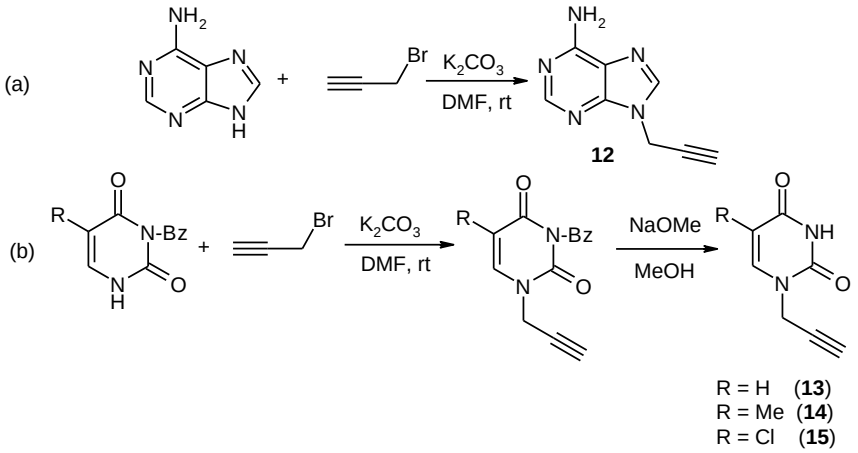
Scheme 3



9 **11** (74%; δ(P) 15.1)

Propargylated nucleobases **12-15** were synthesized following the literature procedure[27] using propargyl bromide (80 wt% in toluene) in the presence of K_2CO_3 (Scheme 4). Thus, the reaction of adenine with propargyl bromide gave the N9-propargyl adenine derivative **12** (Scheme 4a). *N3*-Benzoyl uracil derivatives were treated with propargyl bromide to give the *N1*-propargyl 3-benzoyl-uracil derivatives. The benzoyl group was deprotected in the presence of NaOMe to afford the *N1*-propargyl uracil derivatives **13-15** (Scheme 4b). All the propargylated derivatives **12-15** are known.[27,33]

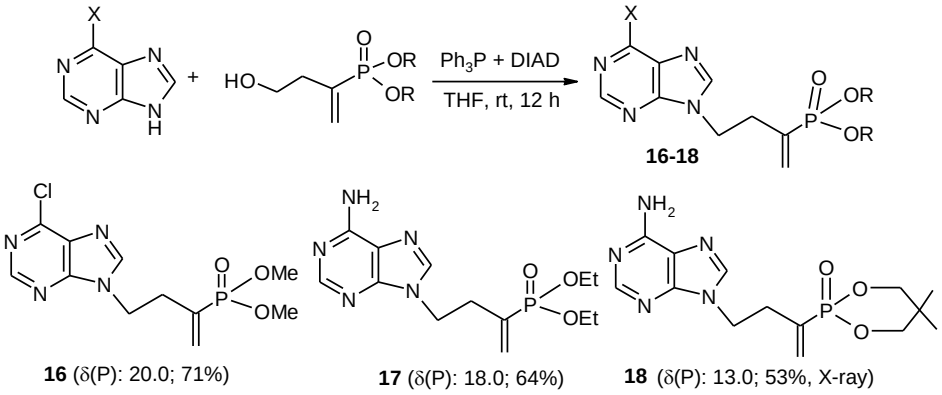
Scheme 4



5.5 Synthesis of acyclic nucleobase appended phosphonates via Mitsunobu reaction

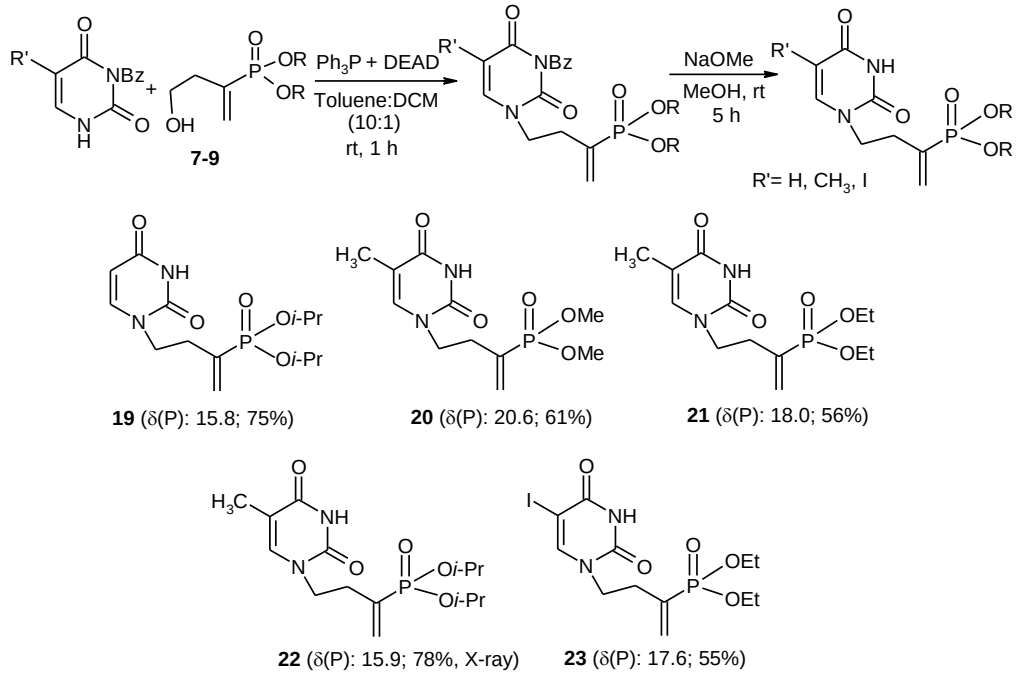
Synthesis of acyclic nucleoside phosphonates (ANPs) was achieved using the Mitsunobu reaction. Thus, the reaction of purine nucleobase with vinyl phosphonates **7-8** and **10** afforded purine appended phosphonates **16-18** in good yields (53-71%) (Scheme 5). The identity of these compounds was confirmed by IR, NMR (^{1}H, ^{13}C and ^{31}P) and HRMS data. The ^{31}P NMR spectra of ANPs **16-18** show a peak in the range δ 13-20. In the ^{13}C NMR spectra, the *α*-carbon (to phosphorus) appears as a doublet at δ 133-135 [^1J(P-C) ~ 170.0 Hz] and PC=*C* signal for these compounds appears as a doublet in the region δ 132-133 [^2J(P-C) ~ 8.4-8.8 Hz]. The structure of the compound **18** was further confirmed by using X-ray crystallography (Figure 10, section 5.7).

Scheme 5



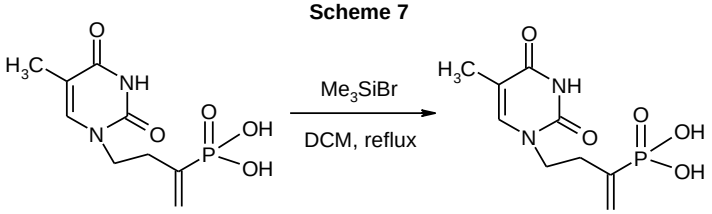
Uracil phosphonate derivatives are also synthesized using the Mitsunobu reaction. Thus, the reaction of *N3*-benzoyl uracil derivatives with vinyl phosphonates **7-9** in the presence of PPh_3/DEAD afforded *N3*-benzoyl uracil phosphonates. Deprotection of the benzoyl group in the presence of NaOMe afforded the uracil phosphonates **19-23** in good to excellent yields (Scheme 6). These compounds are characterized by IR, NMR and HRMS/LC-MS. The structure of the one of the uracil phosphonates (**22**) was confirmed by X-ray crystallography (vide infra).

Scheme 6



Thymine phosphonate derivative **22** was further converted to the corresponding phosphonic acid **24** in the presence of bromotrimethylsilane (TMSBr) (Scheme 7). Formation of the phosphonic acid (presence of OH) is readily inferred by a broad band in the IR at ~ 3430 cm^{-1}. This compound is also characterized by NMR (^{1}H, ^{13}C and ^{31}P) and HRMS data.

Scheme 7

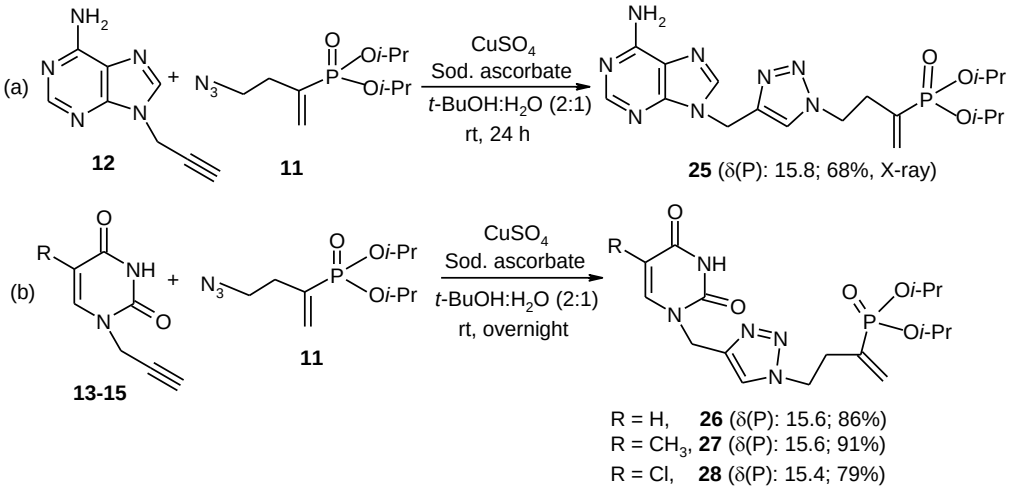


22 **24** (δ(P): 16.6; 66%)

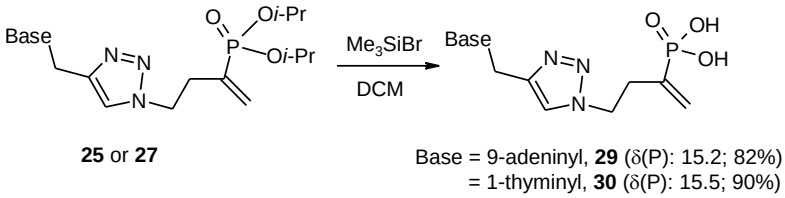
5.6 Synthesis of triazolo nucleoside phosphonates 25-28 using click reaction

Using the azido phosphonate **11**, a novel class of triazolo-nucleoside phosphonates were synthesized *via* copper-catalyzed azide-alkyne 1,3-dipolar cycloaddition. The reaction was conducted with propargyl adenine **12** and azide **11** in the presence of copper sulfate and sodium ascorbate in *t*-BuOH/H_2O solvent mixture at room temperature (Scheme 8a). This procedure furnished the triazole derivative **25** in good yield (68%). Similarly, triazole-appended uracil derivatives (**27-29**) were synthesized using *N*-propargyl uracil derivatives (**13-15**) in excellent yields (Scheme 8b). All the triazole derivatives are well characterized by IR, NMR (^{1}H, ^{13}C and ^{31}P) and HRMS. The structure of the adeninyl-triazole phosphonate **25** was further confirmed by using X-ray crystallography (Figure 12, section 5.7). The triazole phosphonates **25** and **27** were later treated with bromotrimethylsilane to give the free phosphonic acid derivatives **29** and **30**, respectively (Scheme 9).

Scheme 8



Scheme 9



5.7 Brief comments on the structural aspects of phosphonyl substituted nucleobases 18, 22 and 25: Any role for the strong hydrogen bond acceptor, the P=O bond?

As we have discussed in the above section 5.3 with regard to the phosphonyl appended nucleobases **4** and **5** it is observed that the powerful hydrogen bond acceptor property of the phosphoryl oxygen (P=O) is still not strong enough to perturb the homo-base pairing in most cases, unless assisted by other hydrogen bonding partners. In the present section, we shall discuss this aspect in the case of the nucleobase appended phosphonates **18**, **22** and **25**. In the phosphonate **18**, phosphoryl oxygen has only weak C-H···O hydrogen bonding interactions. These supramolecular interactions involve the hydrogen atoms in the phosphorinane ring OCH_2 as well as that of the methyl group. Without loss of the homo-base pairing these hydrogen bonding interactions are extended in all the three dimensions (Figure 10).

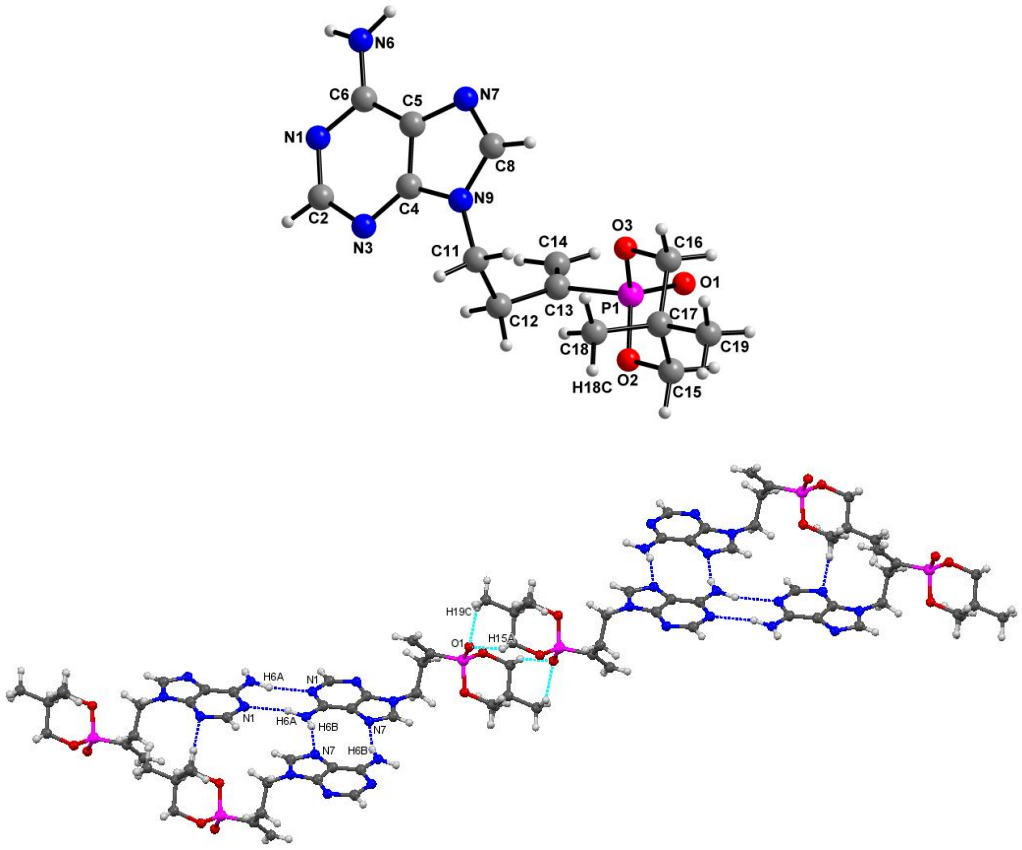


Figure 10: Diagrams showing molecular structure (top) and supramolecular interactions (bottom) in compound **18**. Hydrogen bonding parameters (Å, °): N6-H6A···N1' 0.94(5), 2.17(6), 3.084(5), 166(4); symmetry code: -x, 2-y, 1-z, N6-H6B···N7' 0.90(5), 2.17(5), 3.047(5), 165(4); symmetry code: -x, 1-y, 1-z, C15-H15A···O1' 0.97, 2.48, 3.397(5), 157.7; symmetry code: 1-x, -y, 2-z, C19-H19C···O1' 0.96, 2.61, 3.488(5), 152.5; symmetry code: 1-x, -y, 2-z.

In the case of thyminyl phosphonate **22**, the hydrogen bonding interactions are different from that observed in **3** discussed above [cf. Figure 7]. In compound **3**, the oxygen atom of $(CH_3)C\text{-}C(O)$ is involved only in C-H···O bonding to the C*H* of the alkyne and a CH_2 hydrogen atom of the alkyl chain; also base pairing took place by utilizing the other carbonyl oxygen. In compound **22**, the oxygen atom of $(CH_3)C\text{-}C(O)$ is involved in C-H···O bonding to the CH_3 of the isopropyl group and a CH_2 of the alkyl chain. Here, it is noteworthy that base pairing was disturbed. The phosphoryl oxygen atom (P=*O*) is involved in N-H···O bonding to the NH of the thymine moiety (Figure 11).

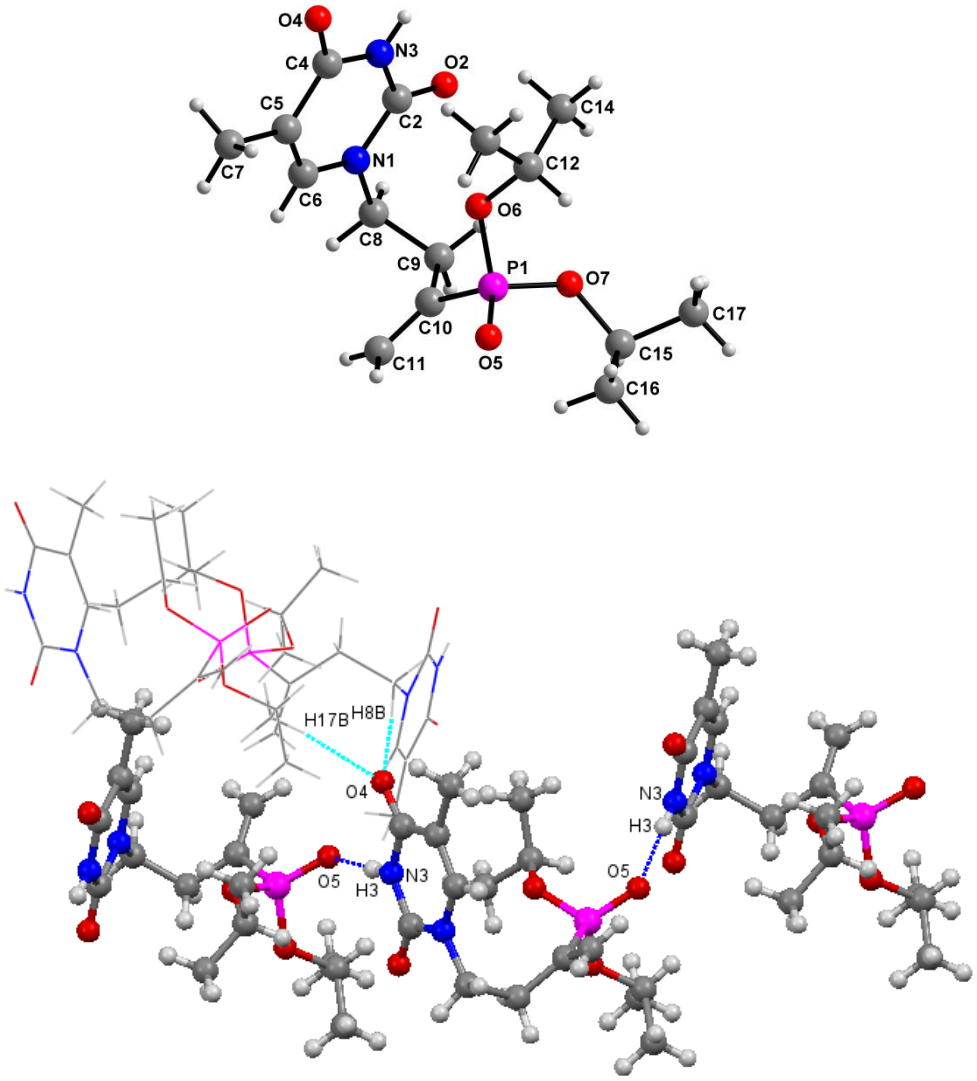


Figure 11: Diagrams showing molecular structure (top) and supramolecular interactions (bottom) in compound **22**. Hydrogen bonding parameters (Å, °): N3-H3···O5' 0.82(2), 2.05(2), 2.871(2), 177(2); symmetry code: x, 1.5-y, -0.5+z, C8-H8B···O4' 0.97, 2.26, 3.211(2), 165.2; symmetry code: -x, -0.5+y, 0.5-z, C17-H17B···O4' 0.96, 2.47, 3.423(2), 172.2; symmetry code: 1+x, y, 1+z.

In the case of adeninyl triazole phosphonate **25**, the phosphoryl oxygen (P=O) is involved only in weak C-H···O interactions with the alkyl CH_2 group and does not disturb the homo-base paring in the adeninyl moiety (Figure 12). Here also, without loss of the homo-base pairing, these hydrogen bonding interactions are extended in three dimensions as observed in the above adeninyl phosphonate **18**.

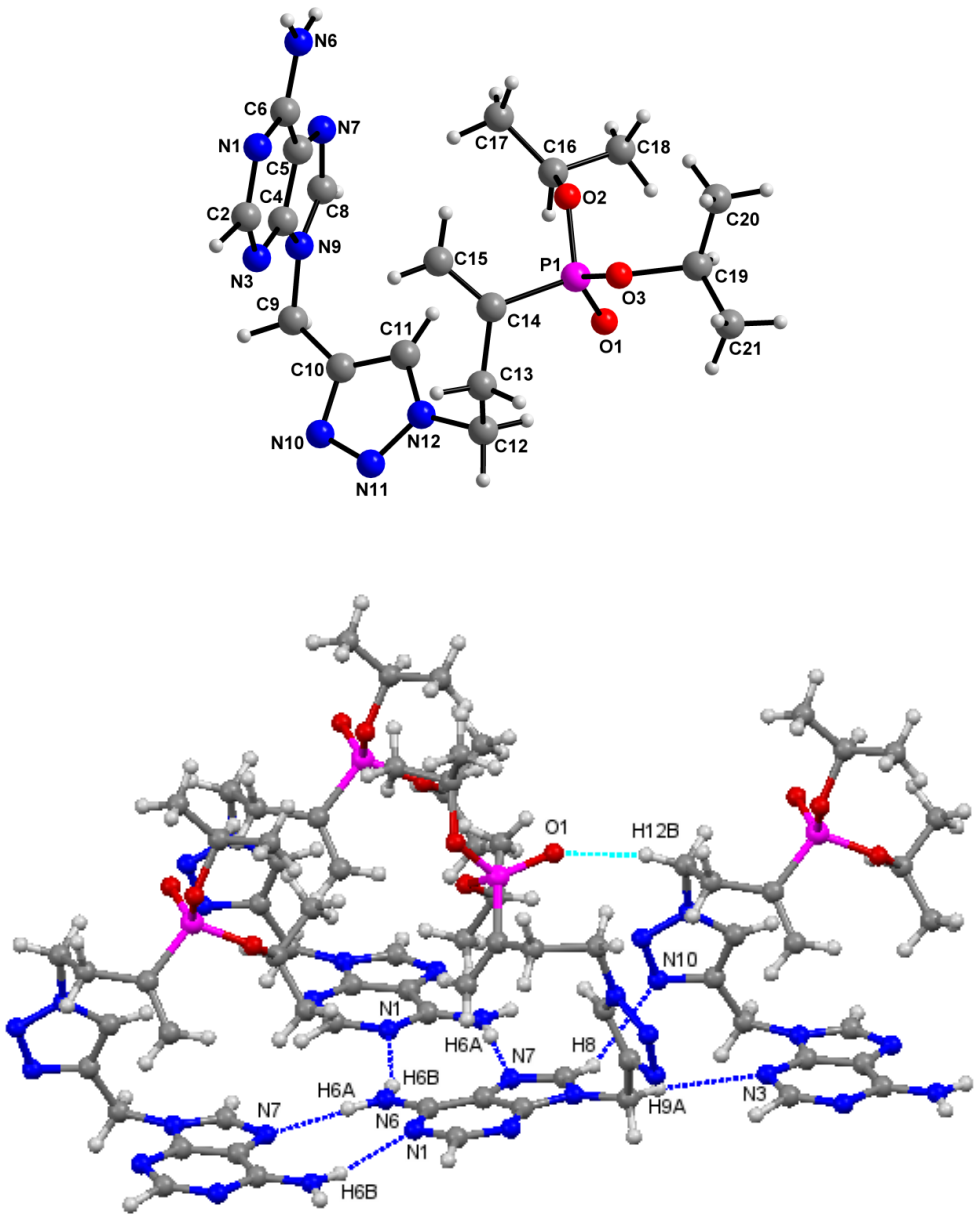


Figure 12: Diagrams showing molecular structure (top) and supramolecular interactions (bottom) in compound **25**. Hydrogen bonding parameters (Å, ^{o}): C12-H12B···O1' 0.97, 2.52, 3.423(10), 154.5; symmetry code: x, 1.5-y, -0.5+z, N6-H6B···N1' 0.94(2), 2.19(3), 3.086(7), 158(6); symmetry code: x, 0.5-y, 0.5+z, N6-H6A···N7' 0.96(2), 2.12(2), 3.081(7), 175(6); symmetry code: x, 0.5-y, -0.5+z.

SUMMARY

(1) While investigating synthetic routes to phosphonyl substituted nucleobases (sometimes called as ANPs), a novel case of thermally induced conformational polymorphism is uncovered in the case of an alkynyl substituted adenine. An uncommon homo-base pairing with an unusual bending of alkyl chain, likely due to C-H···O interactions is observed in the case of a substituted thymine with a terminal alkyne. With regard to the phosphonyl appended nucleobases, it is observed that the powerful hydrogen bond acceptor property of the phosphoryl oxygen (P=O) is still not strong enough to perturb the homo-base pairing in most cases (as in **4** and **5**), unless assisted by other hydrogen bonding partners.

(2) A novel series of alkenyl nucleobase phosphonates has been synthesized using Mitsunobu reaction. Triazole appended phosphonates are obtained via copper-catalyzed alkyne-azide cycloaddition. With regard to the homo-base pairing; in the case of adeninyl phosphonates (**18** and **25**), phosphoryl oxygen (P=O) does not disturb the normal homo-base pairing but in the case of thyminyl phosphonate **22**, the normal homo-base pairing is disturbed, as revealed by X-ray crystallography.

EXPERIMENTAL SECTION

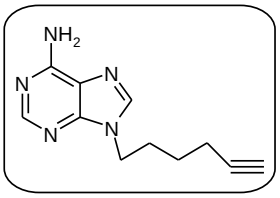
Details of instruments, standards etc. are already given in Chapter 3.

The cyclic phosphite ($OCH_2CMe_2CH_2O$)P(O)(H) [δ(P): 2.3] was prepared by following a method previously reported from our laboratory.[34] 9-(Dec-9-en-1-yl)-9*H*-purin-6-amine (**2**) and 5-Methyl-1-(pent-4-yn-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (**3**) were prepared by literature methods.[25,27] Propargyl nucleobases **12-15** were prepared by following literature procedures.[27,33]

6.1 Alkylation of adenine under Mitsunobu reaction conditions: Synthesis of compound 1

To a solution of 5-hexyne-1-ol (0.36 g, 3.1 mmol), adenine (0.50 g, 3.7 mmol) and PPh_3 (1.16 g, 4.4 mmol) in THF (30 mL) was added DIAD (0.89 g, 4.4 mmol) drop-wise at room temperature over a period of 45 min. After the addition, the reaction mixture was stirred at the same temperature for 12 h. Progress of the reaction was monitored by TLC analysis. When there was no starting material, solvent was removed *in vacuo* and the crude product obtained was purified by column chromatography [silica gel, ethyl acetate-hexane (4:1)] as a colorless solid (**1**).

Compound 1



Yield: 0.45 g (58%); white solid.

Mp: 204-208 ^{o}C.

IR (KBr): 3279, 3221, 3108, 2932, 2312, 1674, 1605, 1574, 1306, 1061 cm^{-1}.

^{1}H NMR: δ 8.37 and 7.82 (2 s, 2H, Ar-*H*), 5.65 (br, 2H, NH_2), 4.24 (t, 2H, ^{3}J(H-H) = 7.0 Hz, NCH_2), 2.29-2.25 (m, 2H, CH_2), 2.09-2.01 (m, 2H, CH_2), 1.98-1.97 (m, 1H, ≡C*H*), 1.61-1.56 (m, 2H, CH_2).

^{13}C NMR: δ 155.4, 153.0, 150.1, 140.4, 119.6, 83.4, 69.2, 43.4, 29.1, 25.3, 17.9.

LC-MS: *m/z* 216 $[M+1]^+$.

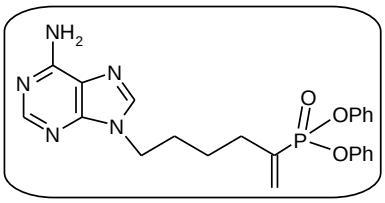
Anal. Calcd. for $C_{11}H_{13}N_5$: C, 61.38; H, 6.09; N, 32.54. Found: C, 61.48; H, 5.91; N, 32.36.

This compound (40 mg) was crystallized from methanol/toluene (4:1, 2 mL).

6.2 Synthesis of compounds 4-6: General procedure for Pd-catalyzed hydrophosphonylation of compound 1 leading to 4

A mixture of compound **1** (0.30 g, 1.4 mmol), $(PhO)_2P(O)H$ (0.39 g, 1.4 mmol), $Pd(OAc)_2$ (0.031 g, 0.14 mmol) and PPh_3 (0.15 g, 0.55 mmol) in THF (10 mL) was heated under reflux for 72 h under nitrogen atmosphere. Removal of the solvent afforded a yellow colored solid material that was chromatographed to afford the pure product **4** as colorless solid [silica gel, ethyl acetate/hexane (4:1) mixture].

Compound 4



Yield: 0.25 g (41%); white solid.

Mp: 120-124 ^{o}C.

IR (KBr): 3279, 3108, 2924, 1674, 1599, 1489, 1255, 1205 cm^{-1}.

^{1}H NMR: δ 8.36 and 7.76 (2 s, 2H, Ar-*H*), 7.33-7.30 (m, 4H, Ar-*H*), 7.17-7.16 (m, 6H, Ar-*H*), 6.31 (d, 1H, ^3J(P-H) = 24.3 Hz, PCC*H*(cis)), 5.92 (d, 1H, ^3J(P-H)= 52.3 Hz, PCC*H*(trans)), 5.65 (br, 2H, NH_2), 4.21 (t, 2H, ^3J(H-H) =7.0 Hz, NCH_2), 2.53-2.46 (m, 2H, CH_2), 1.99-1.92 (m, 2H, CH_2), 1.71-1.66 (m, 2H, CH_2).

^{13}C NMR: δ 155.7, 152.8, 150.1 (d, *J* = 7.8 Hz), 149.9, 140.1, 137.5 (d, *J* = 172.9 Hz, P*C*), 132.3 (d, *J* = 9.6 Hz, PC*C*), 129.6, 125.0, 120.2 (d, *J* = 4.1 Hz), 43.4, 31.6 (d, *J* = 11.0 Hz, PC*C*H_2), 29.4, 25.0.

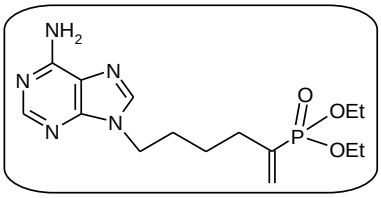
^{31}P NMR: δ 12.0.

LC-MS: *m/z* 450 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{24}N_5O_3P$: C, 61.46; H, 5.38; N, 15.58. Found: C, 61.26; H, 5.26; N, 15.61.

This compound (0.1 g) was crystallized from dichloromethane/acetonitrile (4:1, 3 mL) at 25 ^{o}C.

Compound 5



This compound was prepared in a manner similar to that for **4**. It was eluted by using ethyl acetate/methanol mixture (9:1).

Yield: 0.63 g [78%; using 2.3 mmol each of **1** and $(EtO)_2P(O)H$]; white solid.

Mp: 94-98 ^{o}C.

IR (KBr): 3447, 2986, 2932, 1651, 1476, 1418, 1227, 1024 cm^{-1}.

^{1}H NMR: δ 8.37 and 7.81 (2 s, 2H, Ar-*H*), 6.02 (d, 1H, *J* = 22.8 Hz, $=CH_AH(cis)_B$), 5.78-5.66 (m, 3H, $=CH_AH_B$ + NH_2), 4.23 (t, 2H, *J* = 7.0 Hz, NCH_2), 4.11-4.04 (m, 4H, OCH_2CH_3), 2.35-2.27 (m, 2H, CH_2), 1.96-1.92 (m, 2H, CH_2), 1.61-1.58 (m, 2H, CH_2), 1.31 (t, 6H, *J* =.6.9 Hz, $POCH_2CH_3$).

^{13}C NMR: δ 155.3, 152.8, 150.1, 140.5, 138.6 (d, *J* =171.4 Hz, P*C*), 129.5 (d, *J* = 9.0 Hz, $PC=CH_2$), 119.6, 61.9 (d, *J* =5.9 Hz), 43.7, 31.8 (d, *J* =11.0 Hz), 29.5, 25.2 (d, *J* = 5.0 Hz), 16.4 (d, *J* = 6.1 Hz, OCH_2CH_3).

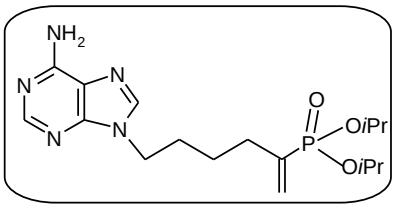
^{31}P NMR: δ 19.2.

LC-MS: *m/z* 354 $[M+1]^+$.

Anal. Calcd. for $C_{15}H_{24}N_5O_3P$: C, 50.99; H, 6.85; N, 19.82. Found: C, 51.15; H, 6.85; N, 19.68.

This compound (0.1 g) was crystallized from ethyl acetate/diethyl ether (1:10, 10 mL) [diffusion method] at 25 ^{o}C. {Yield was 0.53 g (65%) using Pd-catalyst $[(OCH_2CMe_2CH_2O)P\text{-}S\text{-}Pd(PPh_3)]_2$}.

Compound 6



This compound was prepared in a manner similar to that for **4**. It was eluted using ethyl acetate/methanol mixture (9:1).

Yield: 0.39 g [74%; using 1.4 mmol of **1** and (*i*-PrO)$_2$P(O)H]; thick oil.

IR (neat): 3326, 3179, 2928, 1903, 1645, 1597, 1469, 1385, 1105 cm^{-1}.

^{1}H NMR: δ 8.37 and 7.81 (2 s, 2H, Ar-*H*), 6.02 (d, 1H, *J* = 22.8 Hz, =CH$_A$*H*(cis)$_B$), 5.73-5.61 (m, 3H, =C*H*$_A$H$_B$ + N*H*$_2$), 4.69-4.64 (m, 2H, P(OC*H*(CH$_3$)$_2$)$_2$), 4.23 (t, 2H, *J* = 6.8 Hz, NC*H*$_2$), 2.32-2.27 (m, 2H, C*H*$_2$), 1.96-1.92 (m, 2H, C*H*$_2$), 1.62-1.58 (m, 2H, C*H*$_2$), 1.33-1.26 [m, 12H, P(OCH(C*H*$_3$)$_2$)$_2$].

^{13}C NMR: δ 155.6, 153.0, 150.1, 140.4, 140.0 (d, *J* =173.1 Hz, P*C*), 128.6 (d, *J* = 9.3 Hz, PC=*C*H$_2$), 119.7, 70.5 (d, *J* =5.7 Hz, O*C*H), 43.7, 31.7 (d, *J* = 10.8 Hz), 29.7 (d, *J* =10.6 Hz), 25.2, 24.1, 23.9 (d, *J* = 4.2 Hz).

^{31}P NMR: δ 17.1.

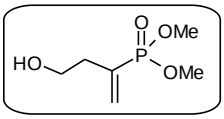
LC-MS: *m/z* 382 [M+1]$^+$.

Anal. Calcd. for C$_{17}$H$_{28}$N$_5$O$_3$P: C, 53.53; H, 7.40; N, 18.36. Found: C, 53.65; H, 7.51; N, 18.2.

6.3 General procedure for Pd-catalyzed hydrophosphonylation of 3-butyn-1-ol: Synthesis of vinyl phosphonates 7-10

A mixture of 3-butyn-1-ol (0.84 g, 12 mmol), phosphite (10 mmol), Pd(OAc)$_2$ (0.11 g, 0.5 mmol) and PPh$_3$ (0.26 g, 1 mmol) in THF (10 mL) was heated under reflux for 6 h under nitrogen atmosphere. Removal of the solvent afforded a yellow colored material that was chromatographed on silica gel using ethyl acetate/hexane mixture (6:4) as the eluent to afford the vinyl phosphonate as yellow oil.

Compound 7



Yield: 1.41 g (64%, yellow oil).

IR (neat): 3359, 2948, 2849, 1633, 1452, 1211, 1025 cm^{-1}.

^{1}H NMR: δ 6.05 (d, *J* = 22.4 Hz, 1H), 5.89 (d, *J* = 48.4 Hz, 1H), 3.78-3.72 (m, 8H), 2.54-2.49 (m, 2H), 2.02 (s, 1H).

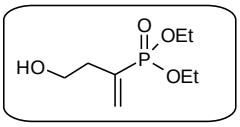
^{13}C NMR: δ 135.2 (d, *J* = 172.2 Hz), 132.2 (d, *J* = 8.7 Hz), 61.2, 52.8 (d, *J* = 5.8 Hz), 36.3 (d, *J* = 11.6 Hz).

^{31}P NMR: δ 22.3.

LC-MS: *m/z* 181 $[M+1]^{+}$.

Anal. Calcd. for $C_6H_{13}O_4P$: C, 40.00; H, 7.27. Found: C, 40.12; H, 7.21.

Compound 8



Yield: 1.15 g (64%, yellow oil).

IR (neat): 3381, 2986, 1742, 1649, 1386, 1211, 1025, 970, 800 cm^{-1}.

^{1}H NMR: δ 6.06 (d, *J* = 22.4 Hz, 1H), 5.86 (d, *J* = 47.6 Hz, 1H), 4.16-4.09 (m, 4H), 3.80 (t, *J* = 5.6 Hz, 2H), 2.93 (br, 1H), 2.59-2.52 (m, 2H), 1.35 (t, *J* ~ 7.0 Hz, 6H).

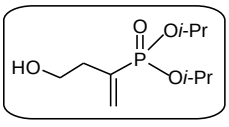
^{13}C NMR: δ 136.6 (d, *J* = 172.0 Hz), 131.3 (d, *J* = 8.7 Hz), 62.3 (d, *J* = 6.0 Hz), 61.5 (d, *J* = 3.5 Hz), 36.6 (d, *J* = 11.7 Hz), 16.4 (d, *J* = 6.4 Hz).

^{31}P NMR: δ 19.7.

LC-MS: *m/z* 209 $[M+1]^{+}$.

Anal. Calcd. for $C_8H_{17}O_4P$: C, 46.15; H, 8.23. Found: C, 46.25; H, 8.28.

Compound 9



Yield: 1.49 g (63%, yellow oil).

IR (neat): 3386, 2975, 1726, 1381, 1222, 1107, 986, 893, 767 cm^{-1}.

^{1}H NMR: δ 6.04 (d, *J* = 22.4 Hz, 1H), 5.79 (d, *J* = 47.6 Hz, 1H), 4.75-4.67 (m, 2H), 3.79 (t, *J* = 6.0 Hz, 2H), 2.58-2.51 (m, 2H), 1.34 (d, *J* = 6.0 Hz, 6H), 1.32 (d, *J* = 6.0 Hz, 6H).

^{13}C NMR: δ 137.3 (d, *J* = 173.8 Hz), 130.2 (d, *J* = 9.0 Hz), 70.7 (d, *J* = 6.1 Hz),

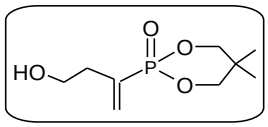
60.8 (d, *J* = 4.3 Hz), 35.7 (d, *J* = 11.1 Hz), 23.8 (d, *J* = 3.4 Hz), 23.6 (d, *J* = 4.6 Hz).

^{31}P NMR: δ 17.7.

LC-MS: *m/z* 237 $[M+1]^+$.

Anal. Calcd. for $C_{10}H_{21}O_4P$: C, 50.84; H, 8.96. Found: C, 50.96; H, 8.91.

Compound 10



Yield: 1.58 g (72%, yellow oil).

IR (neat): 3381, 2970, 1907, 1808, 1644, 1479, 1233, 986 cm^{-1}.

^{1}H NMR: δ 6.02 (d, *J* = 7.6 Hz, 1H), 5.99 (d, *J* = 79.2 Hz, 1H), 4.13 (t, *J* ~ 7.8 Hz, 2H), 3.90-3.80 (m, 4H), 3.30 (br, 1H), 2.58-2.52 (m, 2H), 1.12 (s, 3H), 1.03 (s, 3H).

^{13}C NMR: δ 134.7 (d, *J* = 167.8 Hz), 132.2 (d, *J* = 8.7 Hz), 76.0 (d, *J* = 6.1 Hz), 61.0 (d, *J* = 4.3 Hz), 36.2 (d, *J* = 13.1 Hz), 32.6 (d, *J* = 6.2 Hz), 21.6, 21.3.

^{31}P NMR: δ 15.0.

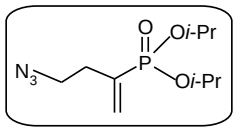
LC-MS: *m/z* 221 $[M+1]^+$.

Anal. Calcd. for $C_9H_{17}O_4P$: C, 49.09; H, 7.78. Found: C, 49.15; H, 7.71.

6.4 Synthesis of azidophosphonate 11 using Mitsunobu reaction

To a solution of alcohol **9** (0.94 g, 4 mmol) dissolved in toluene (20 mL), was added DEAD (1.39 g, 8 mmol) and PPh_3 (2.1 g, 8 mmol). To this, N_3H solution (6.7 mL, 8 mmol, 1.2 M in toluene) was added carefully. The resulting mixture was stirred at rt overnight and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane-ethyl acetate (6:4) as the eluent.

Compound 11



Yield: 0.77 g (74%, colorless oil).

IR (neat): 2980, 2360, 2098, 1732, 1386, 1221, 1105, 974 cm^{-1}.

^{1}H NMR : δ 6.13 (d, *J* = 22.4 Hz, 1H), 5.82 (d, *J* = 48.8 Hz, 1H), 4.72-4.67 (m, 2H), 3.50-3.46 (m, 2H), 2.58-2.50 (m, 2H), 1.35 (d, *J* = 6.0 Hz, 6H), 1.31 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR : δ 137.1 (d, *J* = 175.7 Hz), 131.0 (d, *J* = 9.0 Hz), 70.9 (d, *J* = 5.9 Hz), 49.7 (d, *J* = 4.1 Hz), 32.3 (d, *J* = 11.2 Hz), 24.2 (d, *J* = 3.4 Hz), 24.0 (d, *J* = 4.4 Hz).

^{31}P NMR: δ 15.1.

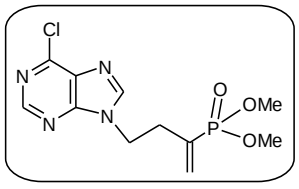
LC-MS: *m/z* 262 $[M+1]^{+}$.

Anal. Calcd. for $C_{10}H_{20}N_3O_3P$: C, 45.97; H, 7.72; N, 16.08. Found: C, 45.86; H, 7.65; N, 16.21.

6.5 Alkylation of purine nucleobases under Mitsunobu reaction conditions using alcohols 7, 8 and 10: Representative procedure for the synthesis of compound 16

To a solution of alcohol **7** (0.98 g, 6 mmol), 6-chloropurine (0.77 g, 5 mmol) and PPh_3 (2.63 g, 10 mmol) in THF (30 mL) was added DIAD (2.02 g, 10 mmol) slowly at room temperature, after that continued stirring at same temperature for 12 h. After the complete consumption of the starting material (TLC), solvent was removed *in vacuo* and the crude product was purified by column chromatography [silica gel, ethyl acetate-hexane (6:4)].

Compound 16



Yield: 1.12 g (71%, viscous oil).

IR (neat): 3052, 2800, 1715, 1682, 1441, 1216, 1030, 964 cm^{-1}.

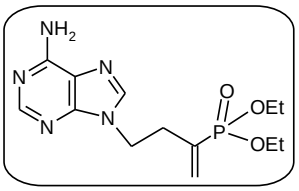
^{1}H NMR: δ 8.72 (s, 1H), 8.15 (s, 1H), 5.89 (d, *J* = 22.0 Hz, 1H), 5.48 (d, *J* = 47.2 Hz, 1H), 4.54 (t, *J* ~ 6.4 Hz, 2H), 3.74 (d, *J* = 10.8 Hz, 6H), 2.92-2.85 (m, 2H).

^{13}C NMR: δ 151.5, 150.3, 145.9, 133.5 (d, *J* = 174.6 Hz), 133.1 (d, *J* = 8.4 Hz), 131.3, 52.7 (d, *J* = 5.7 Hz), 43.0, 32.7 (d, *J* = 11.6 Hz).

^{31}P NMR: δ 20.0.

HRMS (ESI): Calcd. for $C_{11}H_{15}ClN_4O_3P$ [M^++H]: *m/z* 317.0571. Found: 317.0571.

Compound 17



This compound was prepared in a manner similar to that for **16** using adenine (1.6 mmol) and 1.9 mmol of alcohol **8.**

Yield: 0.33 g (64%, white solid).

Mp: 132-136 ^oC.

IR (KBr): 3299, 2975, 1737, 1671, 1595, 1485, 1321, 1036, 942, 805 cm^{-1}.

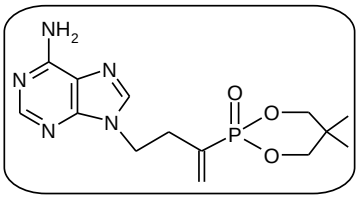
^1H NMR : δ 8.37 (s, 1H), 7.82 (s, 1H), 5.94 (d, *J* = 22.0 Hz, 1H), 5.65 (br, 2H), 5.49 (d, *J* = 47.2 Hz, 1H), 4.47 (t, *J* = 6.8 Hz, 2H), 4.17-4.12 (m, 4H), 2.92-2.86 (m, 2H), 1.36 (t, *J* ~ 7.0 Hz, 6H).

^{13}C NMR : δ 155.6, 153.0, 150.0, 141.2, 135.1 (d, *J* = 174.5 Hz), 132.5 (d, *J* = 8.8 Hz), 119.8, 62.3 (d, *J* = 6.0 Hz), 42.7, 33.3 (d, *J* = 11.7 Hz), 16.5 (d, *J* = 6.2 Hz).

^{31}P NMR: δ 18.0.

HRMS (ESI): Calcd. for $C_{13}H_{21}N_5O_3P$ [M^++H]: *m/z* 326.1383. Found: 326.1382.

Compound 18



This compound was prepared in a manner similar to that for **16,** using adenine (0.14 g, 1 mmol) and alcohol **10** (0.28 g, 1.2 mmol).

Yield: 0.19 g (53%, white solid).

Mp: 220-224 ^oC.

IR (KBr): 3310, 3140, 1666, 1600, 1573, 1490, 1414, 1326, 1238, 1052, 992, 871, 795 cm^{-1}.

^1H NMR (DMSO-d_6): δ 8.15 (s, 1H), 8.09 (s, 1H), 7.21 (br, 2H), 5.91-5.73 (m, 2H), 4.36 (t, *J* = 6.8 Hz, 2H), 4.04-3.97 (m, 2H), 3.90-3.85 (m, 2H), 2.82-2.75 (m, 2H), 1.08 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (DMSO-d_6): δ 156.4, 152.9, 149.9, 141.4, 134.5 (d, *J* = 166.8 Hz), 132.1 (d, *J* = 8.4 Hz), 119.2, 76.4 (d, *J* = 6.3 Hz), 42.1 (d, *J* = 5.0 Hz), 32.5 (d, *J* = 6.6 Hz), 32.3 (d, *J* = 12.1 Hz), 21.5, 20.6.

^{31}P NMR (DMSO-d_6): δ 13.0.

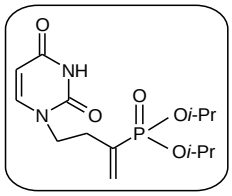
HRMS (ESI): Calcd. for $C_{14}H_{21}N_5O_3P$ [M^++H]: *m/z* 338.1383. Found: 338.1385.

This compound was crystallized from methanol/DCM (1:2, 5mL).

6.6 Alkylation of pyrimidine nucleobases under Mitsunobu reaction conditions using alcohols 7-9: Representative procedure for the synthesis of compound 19

To a solution of 3-benzoyluracil (1 mmol) in a solvent mixture of toluene and DCM (20 mL, 9:1, v/v) was added PPh_3 (2 mmol) and alcohol **9** (1.2 mmol). To this solution, DEAD (2 mmol) was added slowly at 0 ^{o}C. The stirring was continued at rt for 1 h and the mixture concentrated *in vacuo*. To this crude reaction mixture, MeOH (20 mL) and NaOMe (5 mmol) were added and the contents stirred at rt for 5 h. Water (30 mL) was added and the mixture was concentrated *in vacuo*. The crude product obtained was purified by column chromatography [silica gel, ethyl acetate-hexane (8:2)] to give the alkylated product **19** as a colorless solid.

Compound 19



Yield: 0.25 g (75%, white solid).

Mp: 110-114 ^{o}C.

IR (KBr): 3157, 3048, 2983, 1678, 1462, 1389, 1221, 1206, 1178, 1006, 988, 809, 780 cm^{-1}.

^{1}H NMR : δ 8.50 (br, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 6.03 (d, *J* = 22.0 Hz, 1H), 5.77-5.61 (m, 2H), 4.77-4.68 (m, 2H), 3.99 (t, *J* ~ 6.6 Hz, 2H), 2.72-2.65 (m, 2H), 1.36 (d, *J* = 6.4 Hz, 6H), 1.33 (d, *J* = 6.0 Hz, 6H).

^{13}C NMR : δ 164.4, 151.1, 145.7, 136.3 (d, *J* = 175.7 Hz), 132.2 (d, *J* = 9.0 Hz), 101.5, 71.2 (d, *J* = 6.1 Hz), 48.0, 32.2 (d, *J* = 11.5 Hz), 24.1 (d, *J* = 3.4 Hz), 24.0 (d, *J* = 4.4 Hz).

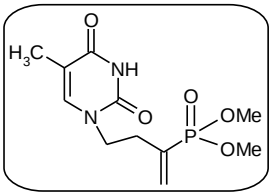
^{31}P NMR: δ 15.8.

LC-MS: *m/z* 331 $[M+1]^+$.

Anal. Calcd. for $C_{14}H_{23}N_2O_5P$: C, 50.91; H, 7.02; N, 8.48. Found: C, 50.85; H, 7.09; N, 8.41.

Compound 20

This compound was prepared in a manner similar to that for **19**, using 3-benzoylthymine (2 mmol) and alcohol **7** (2.4 mmol).



Yield: 0.35 g (61%, viscous oil).

IR (neat): 3452, 2948, 1688, 1474, 1359, 1233, 1036 cm^{-1}.

^{1}H NMR : δ 9.36 (br, 1H), 7.10 (s, 1H), 6.04 (d, *J* = 22.0 Hz, 1H), 5.82 (d, *J* = 47.6 Hz, 1H), 3.92 (t, *J* ~ 7.0 Hz, 2H), 3.77 (d, *J* = 10.8 Hz, 6H), 2.70-2.63 (m, 2H), 1.89 (s, 3H).

^{13}C NMR : δ 164.6, 151.0, 141.4, 134.0 (d, *J* = 174.3 Hz), 133.4 (d, *J* = 8.6 Hz), 110.2, 52.9 (d, *J* = 5.9 Hz), 47.8, 32.2 (d, *J* = 12.0 Hz), 12.3.

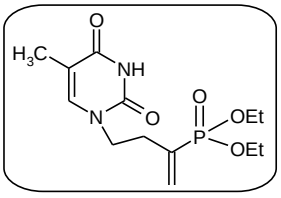
^{31}P NMR: δ 20.6.

LC-MS: *m/z* 289 $[M+1]^+$.

Anal. Calcd. for $C_{11}H_{17}N_2O_5P$: C, 45.84; H, 5.94; N, 9.72. Found: C, 45.78; H, 5.89; N, 9.65.

Compound 21

This compound was prepared in a manner similar to that for **20**, using 1.2 mmol of alcohol **8**.



Yield: 0.18 g (56%, white solid).

Mp: 122-124 ^oC.

IR (KBr): 3167, 3052, 2948, 1693, 1474, 1238, 1036, 953, 849 cm^{-1}.

^{1}H NMR : δ 9.81 (br, 1H), 7.12 (s, 1H), 6.01 (d, *J* = 22.0 Hz, 1H), 5.76 (d, *J* =

47.2 Hz, 1H), 4.15-4.07 (m, 4H), 3.92 (t, *J* ~ 7.0 Hz, 2H), 2.70-2.64 (m, 2H), 1.86 (s, 3H), 1.33 (t, *J* ~ 7.0 Hz, 6H).

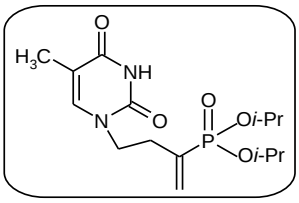
^{13}C NMR : δ 164.8, 151.0, 141.5, 135.0 (d, *J* = 174.0 Hz), 132.7 (d, *J* = 8.6 Hz), 130.0, 128.3, 110.0, 62.4 (d, *J* = 5.9 Hz), 47.7, 32.2 (d, *J* = 11.9 Hz), 16.4 (d, *J* = 5.9 Hz), 12.2.

^{31}P NMR: δ 18.0.

HRMS (ESI): Calcd. for $C_{13}H_{22}N_2O_5P$ [M^++H]: *m/z* 317.1267. Found: 317.1267.

Compound 22

This compound was prepared in a manner similar to that for **20**, using 2.4 mmol of alcohol **9**.



Yield: 0.54 g (78%, white solid).

Mp: 124-128 ^{o}C.

IR (KBr): 3162, 3047, 2981, 1710, 1671, 1463, 1392, 1364, 1222, 1101, 1014, 986, 893, 767 cm^{-1}.

^{1}H NMR : δ 9.86 (br, 1H), 7.14 (s, 1H), 6.01 (d, *J* = 22.0 Hz, 1H), 5.71 (d, *J* = 47.2 Hz, 1H), 4.76-4.67 (m, 2H), 3.95 (t, *J* = 6.8 Hz, 2H), 2.71-2.63 (m, 2H), 1.87 (s, 3H), 1.35 (d, *J* = 6.0 Hz, 6H), 1.32 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR : δ 164.7, 151.0, 141.6, 136.4 (d, *J* = 175.3 Hz), 132.0 (d, *J* = 8.9 Hz), 109.9, 71.1 (d, *J* = 6.3 Hz), 47.8, 32.3 (d, *J* = 11.7 Hz), 24.1 (d, *J* = 4.0 Hz), 23.9 (d, *J* = 4.7 Hz), 12.2.

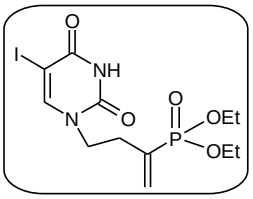
^{31}P NMR: δ 15.9.

HRMS (ESI): Calcd. for $C_{15}H_{26}N_2O_5P$ [M^++H]: *m/z* 345.1580. Found: 345.1580.

This compound was crystallized from methanol/DCM.

Compound 23

This compound was prepared in a manner similar to that for **19**, using 5-iodo-3-benzoyluracil (1 mmol) and alcohol **8** (1.2 mmol).



Yield: 0.24 g (55%, white solid).

Mp: 130-134 ^{o}C.

IR (KBr): 3151, 3052, 2800, 1715, 1682, 1441, 1419, 1216, 1030, 964 cm^{-1}.

^{1}H NMR : δ 9.84 (br, 1H), 7.83 (s, 1H), 6.01 (d, *J* = 21.6 Hz, 1H), 5.75 (d, *J* = 46.8 Hz, 1H), 4.18-4.10 (m, 4H), 4.02 (t, *J* ~ 6.6 Hz, 2H), 2.73-2.66 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR : δ 160.9, 150.6, 150.2, 134.7 (d, *J* = 174.1 Hz), 133.0 (d, *J* = 8.6 Hz), 130.1, 128.3, 67.0, 62.6 (d, *J* = 6.0 Hz), 48.2, 32.5 (d, *J* = 11.9 Hz), 16.4 (d, *J* = 6.0 Hz).

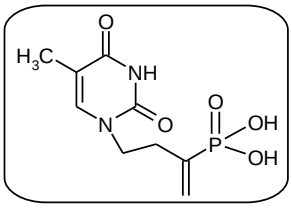
^{31}P NMR: δ 17.6.

HRMS (ESI): Calcd. for $C_{12}H_{19}IN_2O_5P$ [M^++H]: *m/z* 429.0077. Found: 429.0076.

6.7 Synthesis of thymine phosphonic acid 24 using bromotrimethylsilane

To a solution of thymine phosphonate **22** (0.17 g, 0.5 mmol) in DCM (10 mL) was added TMSBr (1.53 g, 10 mmol). The resulting mixture was heated under reflux for 20 h and then concentrated *in vacuo*. The crude product was partitioned between DCM (10 mL) and water (3x10 mL). The aqueous layer was dried *in vacuo* to give the phosphonic acid **24** as a white solid.

Compound 24



Yield: 0.086 g (66%, white solid).

Mp: 130-134 ^{o}C.

IR (KBr): 3430, 3014, 2827, 1699, 1649, 1490, 1419, 1353, 1244, 1167, 1112, 948, 762 cm^{-1}.

^{1}H NMR (D_2O): δ 7.35 (s, 1H), 5.90 (d, *J* = 22.0 Hz, 1H), 5.69 (d, *J* = 46.8 Hz, 1H), 3.86 (t, *J* ~ 6.6 Hz, 2H), 2.61-2.54 (m, 2H), 1.76 (s, 3H).

^{13}C NMR (D_2O): δ 167.0, 152.2, 143.5, 137.2 (d, *J* = 170.5 Hz), 130.6 (d, *J* = 11.7 Hz), 110.4, 48.1, 30.7 (d, *J* = 12.4 Hz), 11.2.

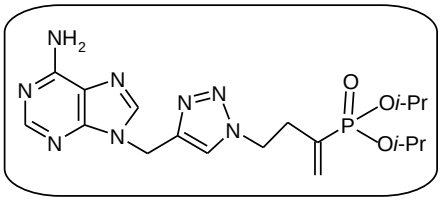
^{31}P NMR: δ 16.6.

HRMS (ESI): Calcd. for $C_9H_{14}N_2O_5P$ [M^++H]: *m/z* 261.0641. Found: 261.0640.

6.8 Synthesis of triazolo nucleoside phosphonates 25-28 using copper-catalyzed azide-alkyne cycloaddition: Representative procedure for the synthesis of compound 25

Into a 50 mL round bottom flask, propargylated nucleobase **12** (0.17 g, 1 mmol), copper sulfate (0.016 g, 10 mol %) and sodium ascorbate (0.04 g, 20 mol %) were added. To this, *t*BuOH:H_2O (20 mL, 2:1, v/v) mixture was added and contents stirred at rt for 10 min. To this mixture, azidophosphonate **11** (0.31 g, 1.2 mmol) was added and stirring continued at rt overnight. The resulting mixture was portioned between DCM (3x30 mL) and water (30 mL). The organic layer was washed with brine solution (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography [silica gel, ethyl acetate-methanol (10:1)] as a colorless solid.

Compound 25



Yield: 0.29 g (68%, white solid).

Mp: 110-114 ^{o}C.

IR (KBr): 3441, 2980, 1662, 1604, 1474, 1223, 992 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ 8.17 (s, 1H), 8.13 (s, 1H), 8.07 (s, 1H), 7.22 (br, 2H), 5.84 (d, *J* = 22.8 Hz, 1H), 5.70 (d, *J* = 47.2 Hz, 1H), 5.41 (s, 2H), 4.53-4.46 (m, 4H), 2.73-2.66 (m, 2H), 1.23 (d, *J* = 6.0 Hz, 6H), 1.16 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (DMSO-d_6): δ 156.4, 153.0, 149.7, 142.9, 141.0, 136.8 (d, *J* = 174.0 Hz), 131.0 (d, *J* = 8.1 Hz), 124.2, 119.0, 70.6 (d, *J* = 5.4 Hz), 48.3 (d, *J* = 3.7 Hz), 32.8 (d, *J* = 11.4 Hz), 24.2 (d, *J* = 3.0 Hz), 23.9 (d, *J* = 4.1 Hz).

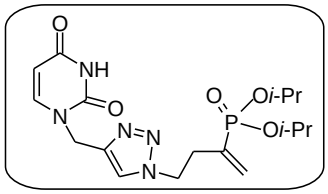
^{31}P NMR: δ 15.8.

HRMS (ESI): Calcd. for $C_{18}H_{28}N_8O_3P$ [M^++H]: *m/z* 435.2023. Found: 435.2020.

This compound was crystallized from methanol/diethyl ether (diffusion method).

Compound 26

This compound was prepared in a manner similar to that for **25** using 1.8 mmol of *N1*-propargyl uracil **13**.



Yield: 0.35 g (86%, viscous oil).

IR (neat): 3440, 2981, 1681, 1463, 1385, 1106, 983, 889, 788 cm^{-1}.

^{1}H NMR : δ 8.90 (br, 1H), 7.72 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 6.01 (d, *J* = 22.0 Hz, 1H), 5.70 (dd, *J* = 8.0 Hz, and *J* = 2.0 Hz, 1H), 5.58 (d, *J* = 47.2 Hz, 1H), 4.97 (s, 2H), 4.79-4.67 (m, 2H), 4.58 (t, *J* = 7.2 Hz, 2H), 2.91-2.84 (m, 2H), 1.36 (d, *J* = 6.0 Hz, 6H), 1.32 (d, *J* = 6.0 Hz, 6H).

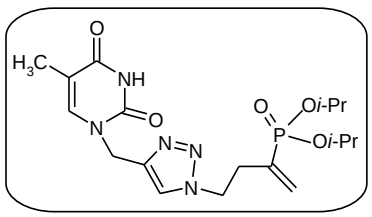
^{13}C NMR : δ 164.2, 151.1, 144.4, 141.5, 135.9 (d, *J* = 177.2 Hz), 131.8 (d, *J* = 9.0 Hz), 124.5, 102.6, 71.3 (d, *J* = 6.2 Hz), 49.0, 43.0, 33.8 (d, *J* = 11.6 Hz), 24.0 (d, *J* = 3.5 Hz), 23.9 (d, *J* = 4.4 Hz).

^{31}P NMR: δ 15.6.

HRMS (ESI): Calcd. for $C_{17}H_{26}N_5O_5PNa$ [M^++Na]: *m/z* 434.1570. Found: 434.1571.

Compound 27

This compound was prepared in a manner similar to that for **25** using 1.8 mmol of *N1*-propargyl thymine **14**.



Yield: 0.51 g (91%, viscous oil).

IR (neat): 3463, 3162, 2986, 2816, 1688, 1463, 1364, 1227, 1112, 992, 773 cm^{-1}.

^{1}H NMR : δ 9.60 (br, 1H), 7.76 (d, *J* = 3.2 Hz, 1H), 7.32 (d, *J* = 18.8 Hz, 1H),

6.03 (d, *J* = 22.4 Hz, 1H), 5.61 (d, *J* = 46.8 Hz, 1H), 4.96 (s, 2H), 4.77-4.69 (m, 2H), 4.58 (t, *J* = 7.2 Hz, 2H), 2.92-2.84 (m, 2H), 1.90 (s, 3H), 1.36 (d, *J* = 6.4 Hz, 6H), 1.32 (d, *J* = 6.0 Hz, 6H).

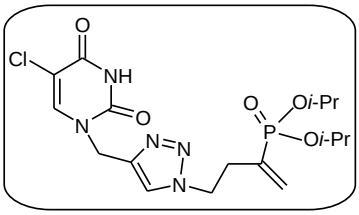
^{13}C NMR : δ 164.4, 151.0, 141.8, 140.2, 136.2 (d, *J* = 176.8 Hz), 131.7 (d, *J* = 9.2 Hz), 124.2, 111.2, 71.2 (d, *J* = 6.2 Hz), 49.1 (d, *J* = 3.3 Hz), 42.8, 33.9 (d, *J* = 10.6 Hz), 24.1 (d, *J* = 3.9 Hz), 24.0 (d, *J* = 4.6 Hz), 12.3.

^{31}P NMR: δ 15.6.

HRMS (ESI): Calcd. for $C_{18}H_{28}N_5O_5PNa$ [M^++Na]: *m/z* 448.1726. Found: 448.1726.

Compound 28

This compound was prepared in a manner similar to that for **25** using 0.8 mmol of 5-chloro-*N1*-propargyl uracil **15**.



Yield: 0.28 g (79%, viscous oil).

IR (neat): 3479, 3162, 2811, 1693, 1458, 1337, 1227, 986, 888 cm^{-1}.

^{1}H NMR : δ 9.97 (br, 1H), 7.83 (s, 1H), 7.76 (s, 1H), 5.99 (d, *J* = 22.0 Hz, 1H), 5.60 (d, *J* = 46.8 Hz, 1H), 4.99 (s, 2H), 4.79-4.69 (m, 2H), 4.60 (t, *J* = 7.2 Hz, 2H), 2.92-2.85 (m, 2H), 1.35 (d, *J* = 6.0 Hz, 6H), 1.31 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR : δ 159.4, 150.0, 140.9 (d, *J* = 7.6 Hz), 135.9 (d, *J* = 177.5 Hz), 131.8 (d, *J* = 8.5 Hz), 124.6, 109.2, 71.4 (d, *J* = 6.3 Hz), 49.1, 43.2, 34.1 (d, *J* = 12.0 Hz), 24.1 (d, *J* = 3.6 Hz), 23.9 (d, *J* = 4.4 Hz).

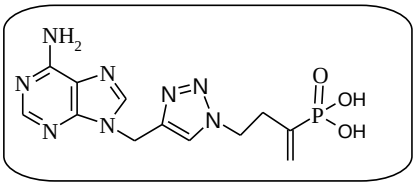
^{31}P NMR: δ 15.4.

HRMS (ESI): Calcd. for $C_{17}H_{25}ClN_5O_5PNa$ [M^++Na]: *m/z* 468.1180. Found: 468.1182.

6.9 Synthesis of nucleobase appended triazolo phosphonic acids 29 and 30 using bromotrimethylsilane

Compound 29

This compound was prepared in a manner similar to that for **24** using triazolo nucleoside phosphonate **25** (0.087 g, 0.2 mmol).



Yield: 0.057 g (82%, white solid).

Mp: 254-258 ^{o}C.

IR (KBr): 3500-3047 (br), 1693, 1616, 1512, 1408, 1233, 1189, 975, 904 cm^{-1}.

^{1}H NMR (D_2O): δ 8.37 (s, 1H), 8.32 (s, 1H), 8.02 (s, 1H), 5.67 (d, *J* = 21.6 Hz, 1H), 5.57 (s, 2H), 5.28 (dd, *J* ~ 45.0 and *J* ~ 9.4 Hz, 1H), 4.59-4.55 (m, 2H), 2.81-2.74 (m, 2H).

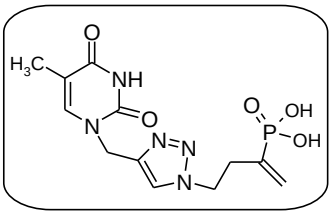
^{13}C NMR (D_2O):δ 149.9, 148.5, 144.6, 144.5, 141.4, 138.2 (d, *J* = 168.8 Hz), 128.8 (d, *J* = 7.5 Hz), 125.3, 118.3, 49.4, 39.2, 33.1 (d, *J* = 12.5 Hz).

^{31}P NMR: δ 15.2.

HRMS (ESI): Calcd. for $C_{12}H_{15}N_8O_3PNa$ [M^++Na]: *m/z* 373.0903. Found: 373.0901.

Compound 30

This compound was prepared in a manner similar to that for **24** using triazolo nucleoside phosphonate **27** (0.21 g, 0.5 mmol).



Yield: 0.15 g (90%, viscous oil).

IR (neat): 3420, 3139, 1713, 1477, 1415, 1385, 1315, 1077, 1012, 959, 842 cm^{-1}.

^{1}H NMR (D_2O): δ 7.90 (s, 1H), 7.45 (s, 1H), 5.72 (d, *J* = 21.6 Hz, 1H), 5.33 (d, *J* = 46.0 Hz, 1H), 4.92 (s, 2H), 4.54 (t, *J* = 6.8 Hz, 2H), 2.80-2.73 (m, 2H), 1.76 (s, 3H).

^{13}C NMR (D_2O): δ 167.0, 152.0, 142.4, 142.1, 137.0 (d, *J* = 171.4 Hz), 130.1 (d, *J* = 8.3 Hz), 125.2, 111.3, 48.9, 42.9, 32.8 (d, *J* = 12.5 Hz), 11.3.

^{31}P NMR: δ 15.5.

HRMS (ESI): Calcd. for $C_{12}H_{16}N_5O_5PNa$ [M^++Na]: *m/z* 364.0787. Found: 364.0793.

6.10 X-ray crystallography

The methodology was similar to that given in Chapter 3.[35] Compound **1** has disorder at C9 and only one of the disordered carbon atoms (C9A) is shown. Compound **2** has disorder at the terminal alkenic carbon atom (C15A/C15B). Crystal data for all the compounds studied by X-ray crystallography are summarized in Tables 2-4.

Table 2: Crystal data for compounds **1**, **1'**, **2** and **3**[a]

Compound	**1**	**1'**	**2**	**3**
CCDC no.	805941	805942	805944	805945
Emp. formula	$C_{11}H_{13}N_5$	$C_{11}H_{13}N_5$	$C_{15}H_{23}N_5$	$C_{10}H_{12}N_2O_2$
Formula weight	215.26	215.26	273.38	192.22
Crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$	$P2_1/c$
a /Å	11.211(3)	8.271(1)	17.181(3)	5.444(2)
b /Å	8.249(2)	11.522(1)	8.113(1)	18.033(8)
c /Å	12.563(3)	12.058(2)	11.691(2)	9.563(4)
α/deg	90	101.27(1)	90	90
β/deg	102.41(3)	96.38(1)	107.45(2)	99.228(8)
γ/deg	90	100.33(1)	90	90
V /Å^3	1134.7(5)	1095.9(2)	1554.6(5)	926.7(7)
Z	4	4	4	4
Dcalc /g cm^{-3}]	1.260	1.305	1.168	1.378
μ /mm^{-1}	0.082	0.085	0.073	0.098
F(000)	456	456	592	408
Data/ restraints/ parameters	2001/3/161	3155/0/290	2724/0/199	1633/0/128
S	1.143	1.122	1.111	1.128
R1 [I>2σ(I)]	0.0864	0.0862	0.0530	0.0596
wR2 [all data]	0.2981	0.2915	0.1647	0.1264
Max./min. residual electron dens. [eÅ^{-3}]	0.544 /-0.517	0.388 /-0.343	0.331/-0.302	0.214 /-0.190

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 3: Crystal data for compounds **4**, **5**, **18** and **22**[a]

Compound	**4**	**5**	**18**	**22**
CCDC no.	805946	805947	-	-
Emp. formula	$C_{23}H_{24}N_5O_3P$	$C_{15}H_{24}N_5O_3P$	$C_{14}H_{20}N_5O_3P$	$C_{15}H_{24}N_2O_5P$
Formula weight	449.44	353.36	337.32	343.33
Crystal system	Triclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P2_1/c$
a /Å	8.320(1)	8.209(1)	6.594(5)	10.8159(11)
b /Å	11.292(1)	17.912(2)	8.670(6)	13.6334(14)
c /Å	24.911(2)	25.091(3)	14.095(10)	14.3089(11)
α/deg	102.669(6)	90	88.989(12)	90
β/deg	91.003(5)	103.615(4)	80.325(12)	122.780(5)
γ/deg	91.806(6)	90	88.765(12)	90
V /Å^3	2281.7(3)	3585.7(7)	794.1(10)	1774.0(3)
Z	4	8	2	4
Dcalc /g cm^{-3}]	1.308	1.309	1.411	1.289
μ /mm^{-1}	0.155	0.177	0.196	0.180
F(000)	944	1504	356	732
Data/ restraints/ parameters	8020/3/589	5137/0/473	2639/0/213	3126/0/225
S	0.993.	1.031	1.111	1.029
R1 [I>2σ(I)]	0.0745	0.0746	0.0627	0.0360
wR2 [all data]	0.1745	0.1750	0.1946	0.0945
Max./min. residual electron dens. [eÅ^{-3}]	0.393/-0.290	0.600/-0.306	0.553/-0.421	0.414/-0.332

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 4: Crystal data for compound **25**[a]

Compound	**25**
CCDC no.	-
Emp. formula	$C_{18}H_{27}N_8O_3P$
Formula weight	434.45
Crystal system	Monoclinic
Space group	$P2_1/c$
a /Å	20.625(3)
b /Å	12.3096(17)
c /Å	8.6953(13)
α/deg	90
β/deg	94.749(16)
γ/deg	90
V /Å^3	2200.0(6)
Z	4
*D*calc /g cm^{-3}]	1.312
μ /mm^{-1}	0.161
F(000)	920
Data/ restraints/ parameters	3875/3/291
S	1.064.
R1 [I>2σ(I)]	0.1153
wR2 [all data]	0.3377
Max./min. residual electron dens. [eÅ^{-3}]	0.447/-0.305

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

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A) Copies of $^{1}H/^{13}C$ NMR spectra for representative compounds

PART A: Compounds 14, 26, 50, 74, 89, 91, 97, 100, 115, 118 and 126

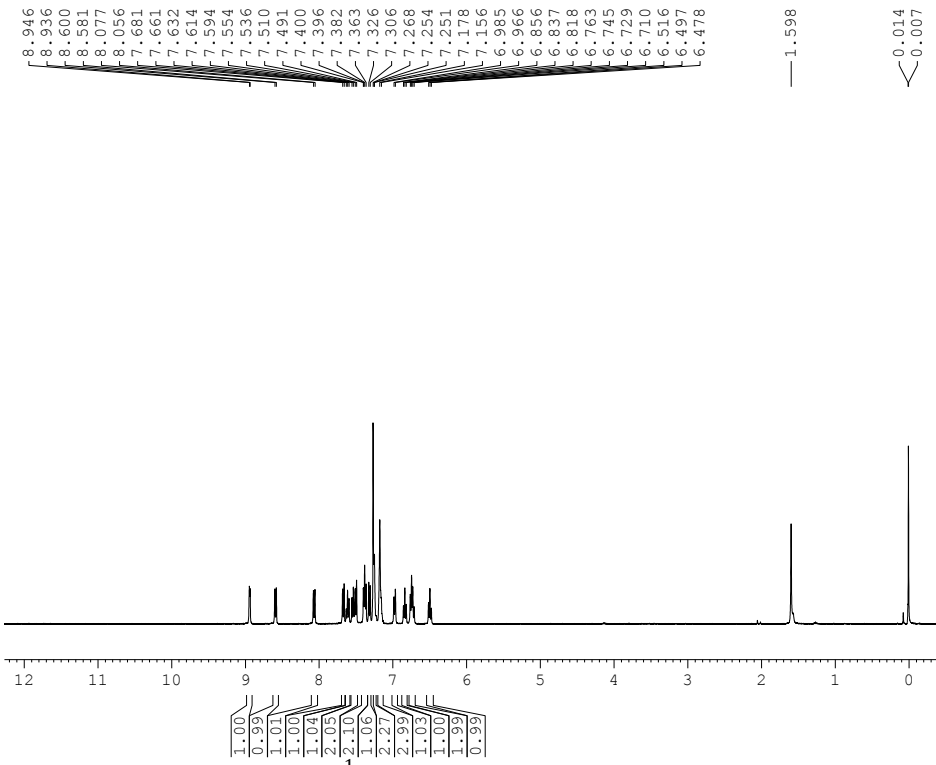

Figure A1. ^{1}H NMR spectrum of compound **14**

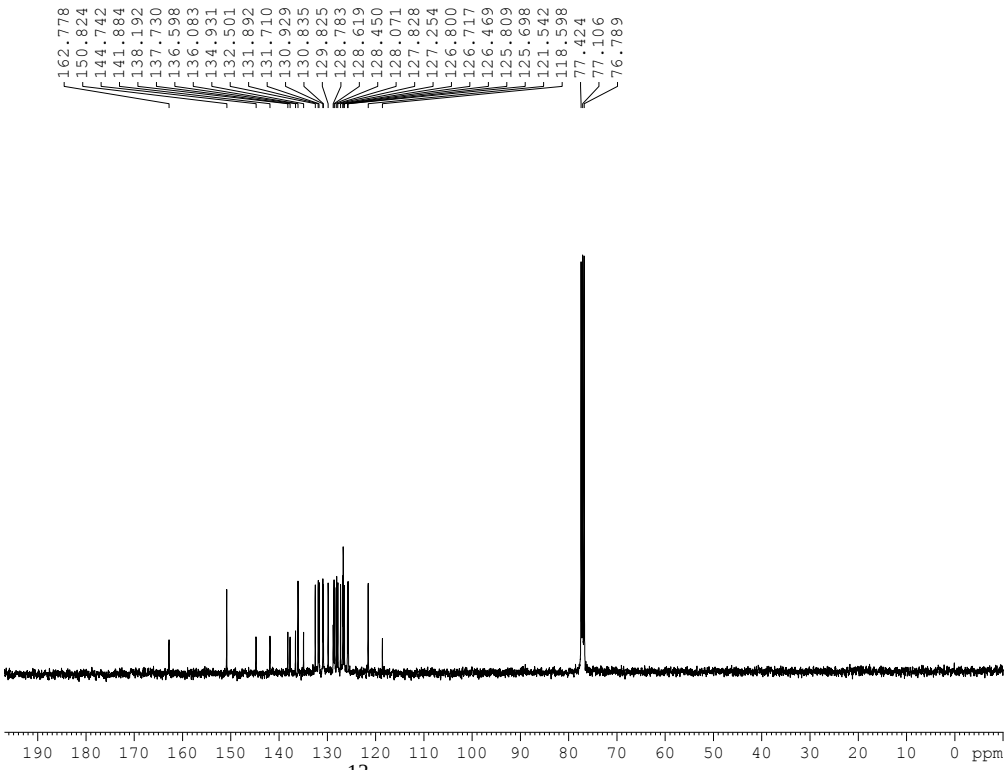

Figure A2. ^{13}C NMR spectrum of compound **14**

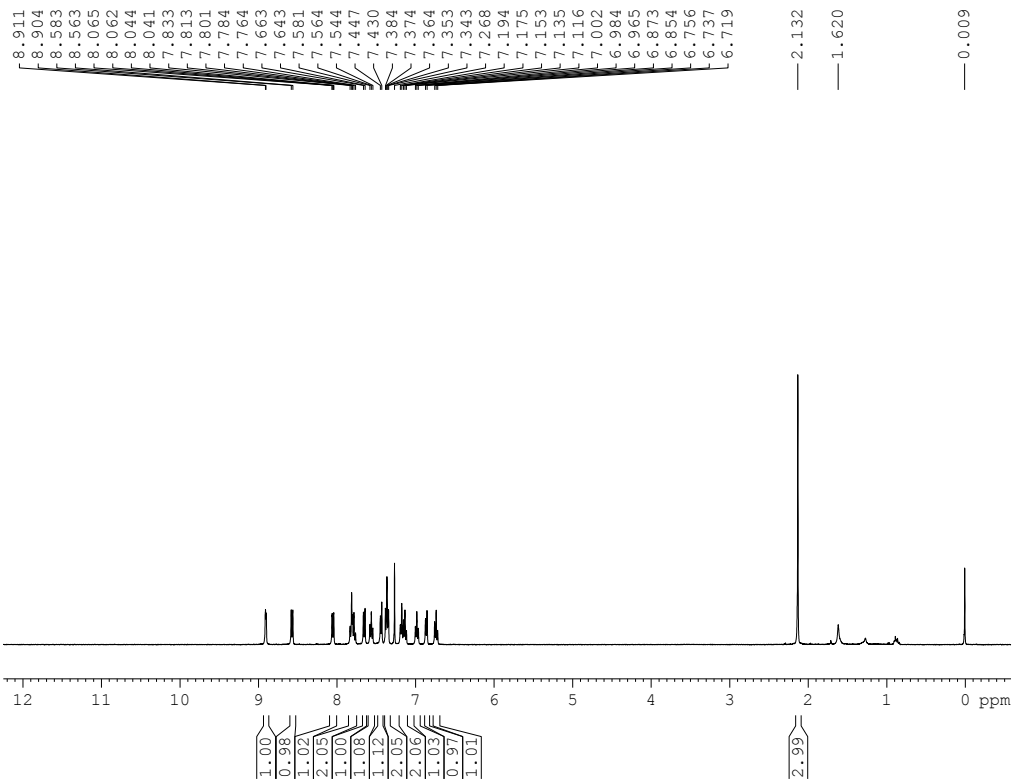

Figure A3. ^{1}H NMR spectrum of compound **26**

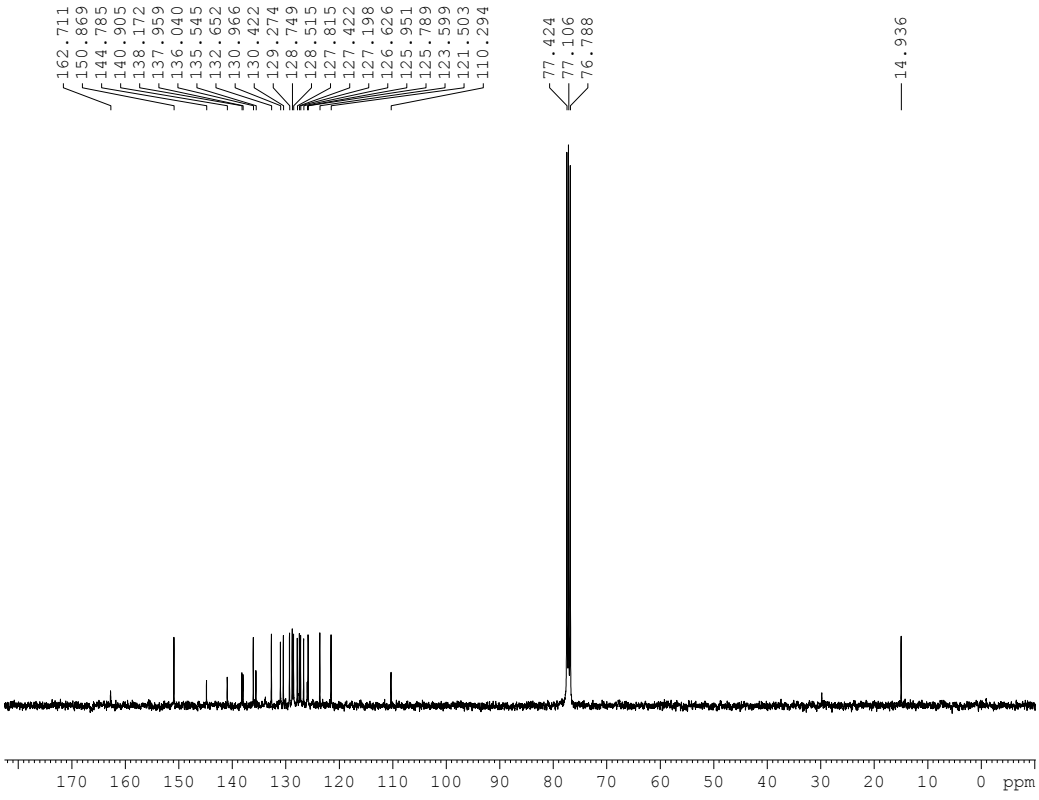

Figure A4. ^{13}C NMR spectrum of compound **26**

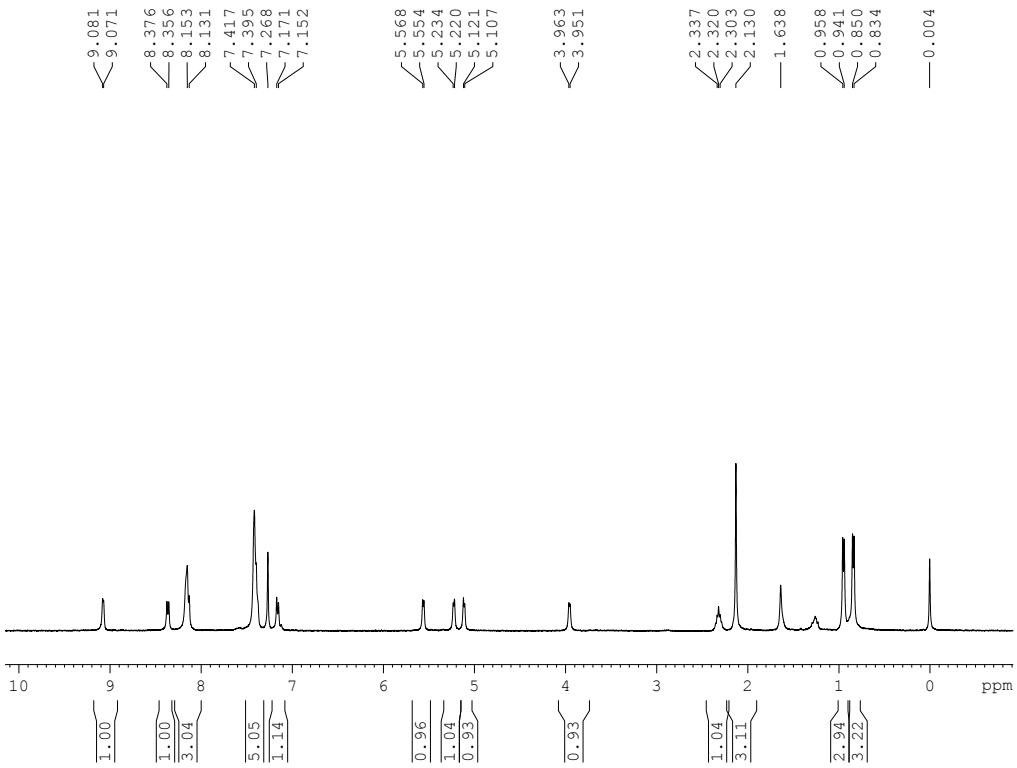

Figure A5. ^{1}H NMR spectrum of compound **50**

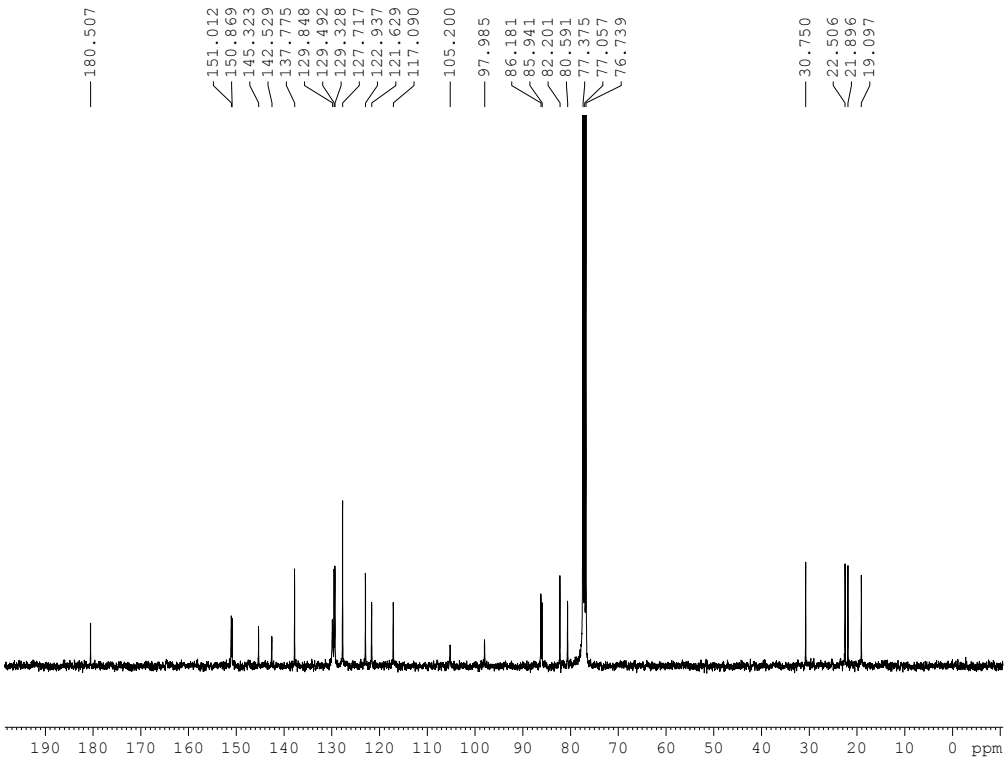

Figure A6. ^{13}C NMR spectrum of compound **50**

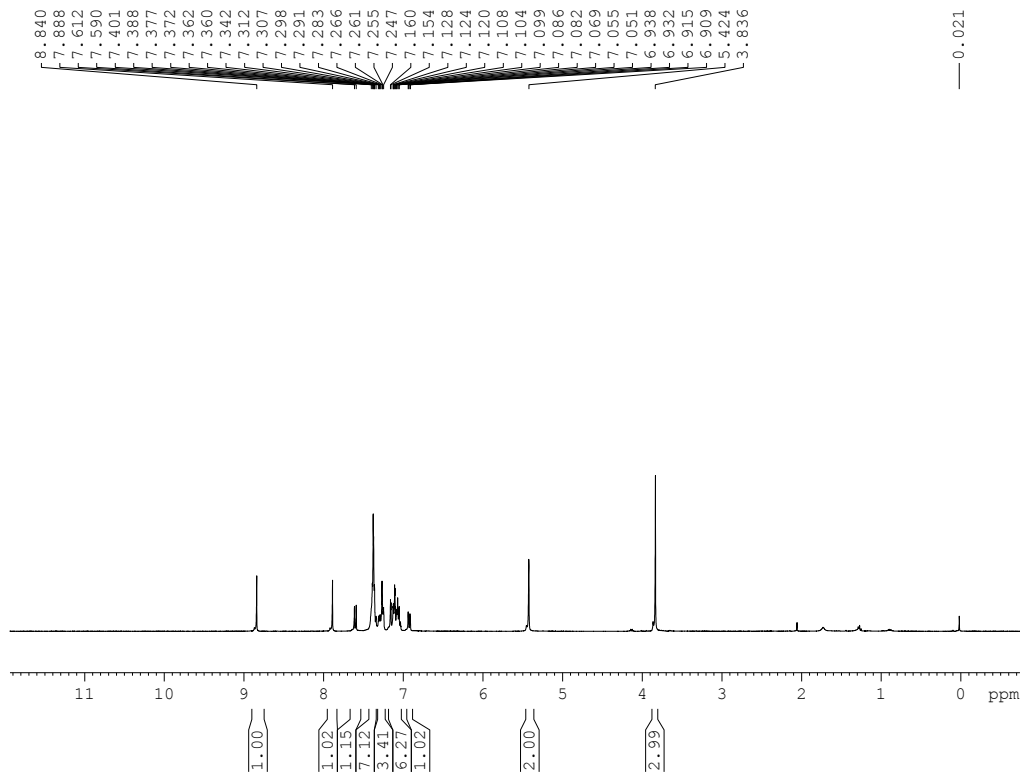

Figure A7. ^{1}H NMR spectrum of compound **74**

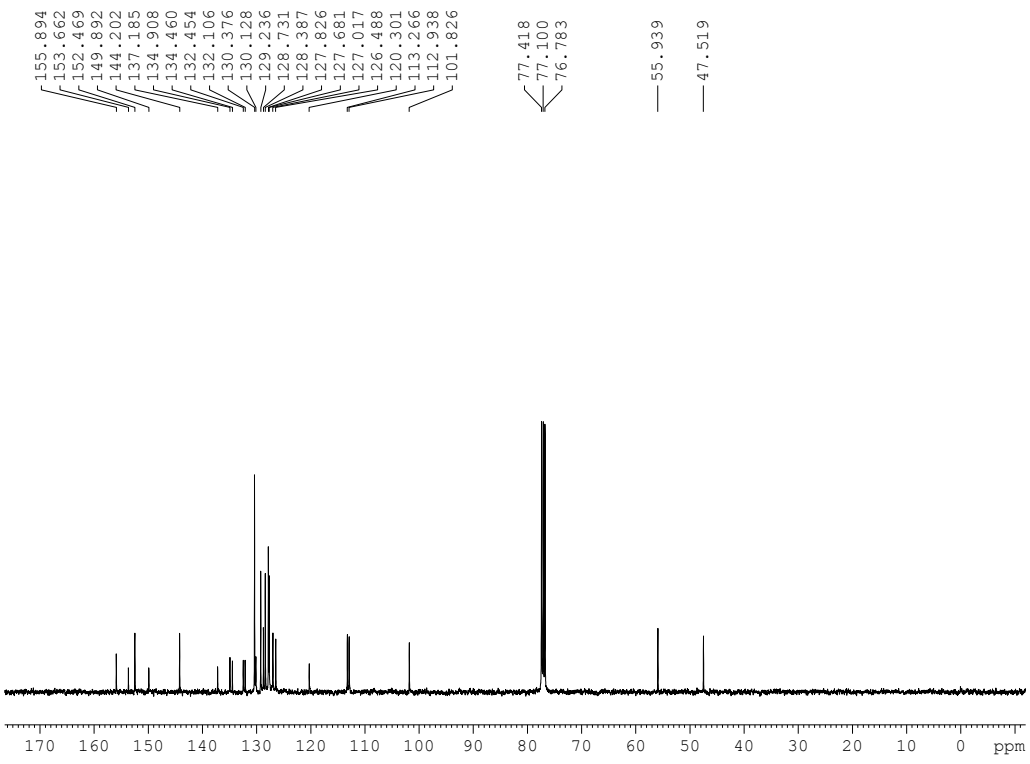

Figure A8. ^{13}C NMR spectrum of compound **74**

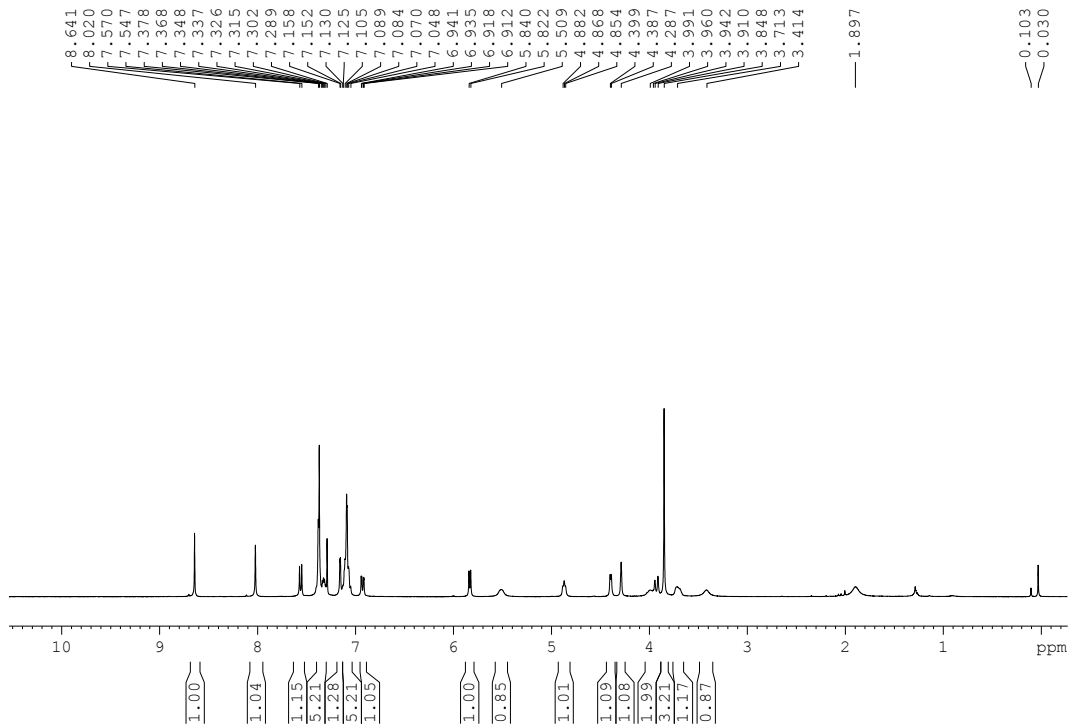

Figure A9. ^{1}H NMR spectrum of compound **89**

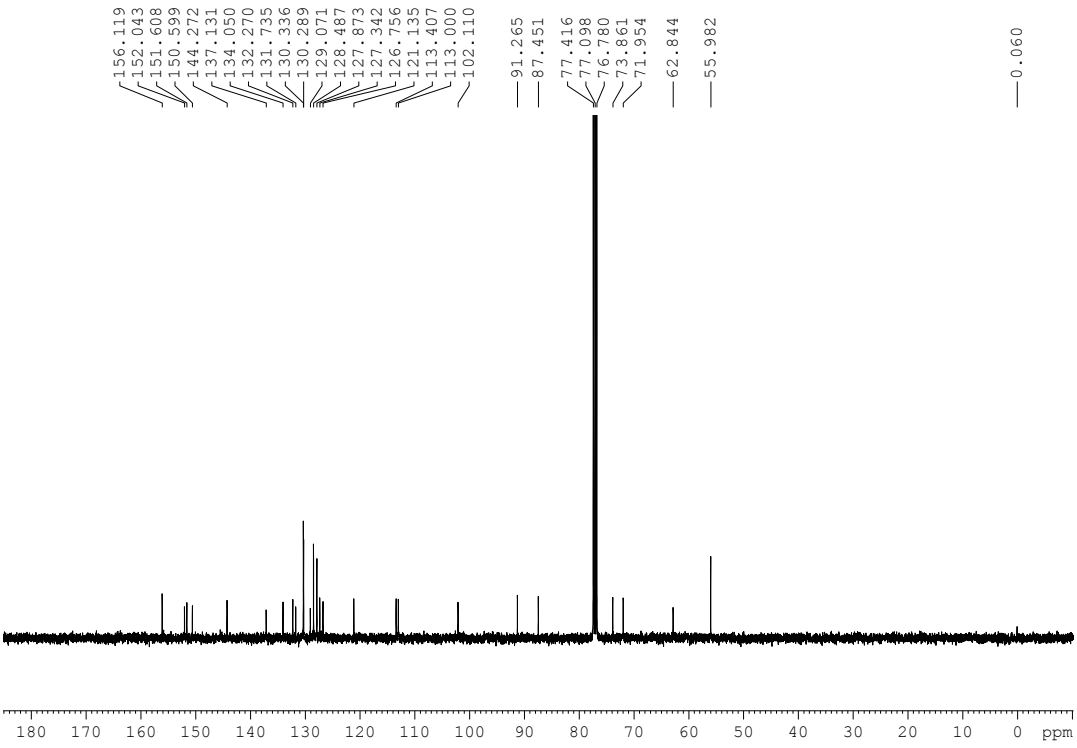

Figure A10. ^{13}C NMR spectrum of compound **89**

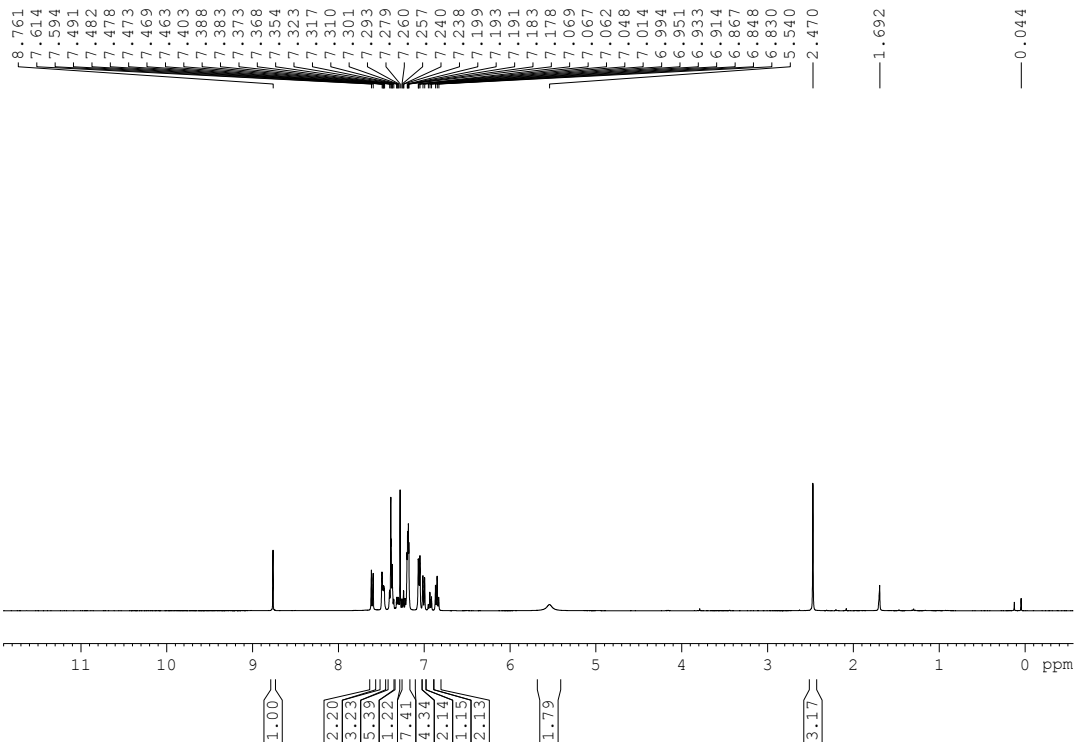

Figure A11. ^{1}H NMR spectrum of compound **91**

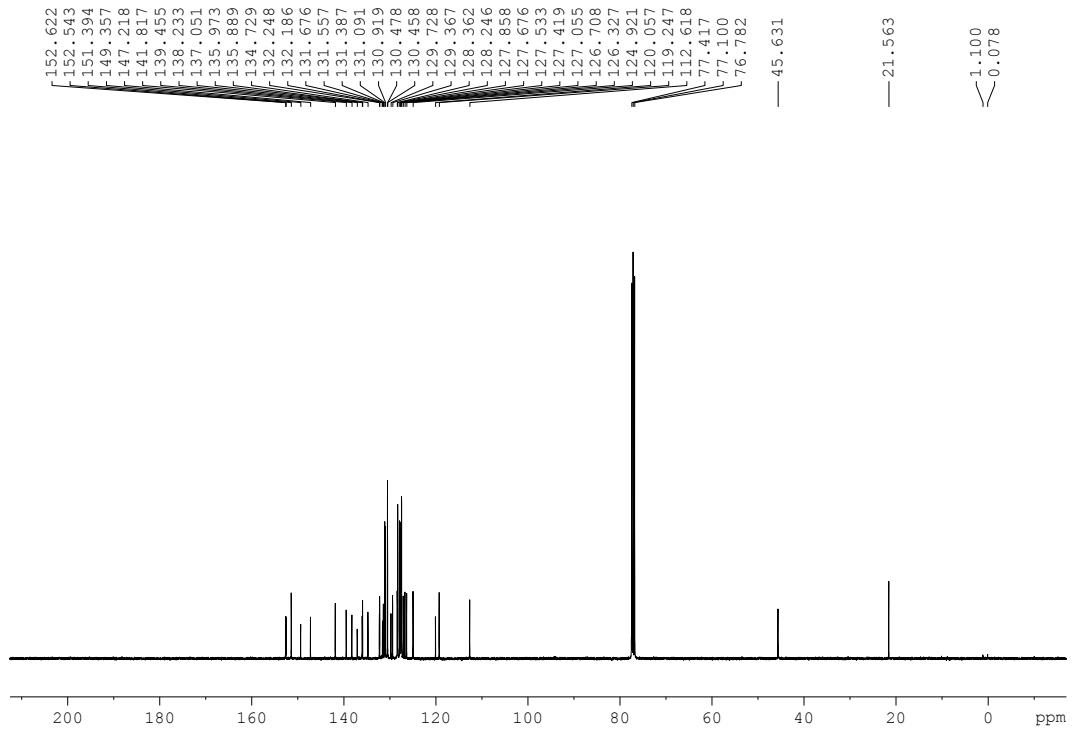

Figure A12. ^{13}C NMR spectrum of compound **91**

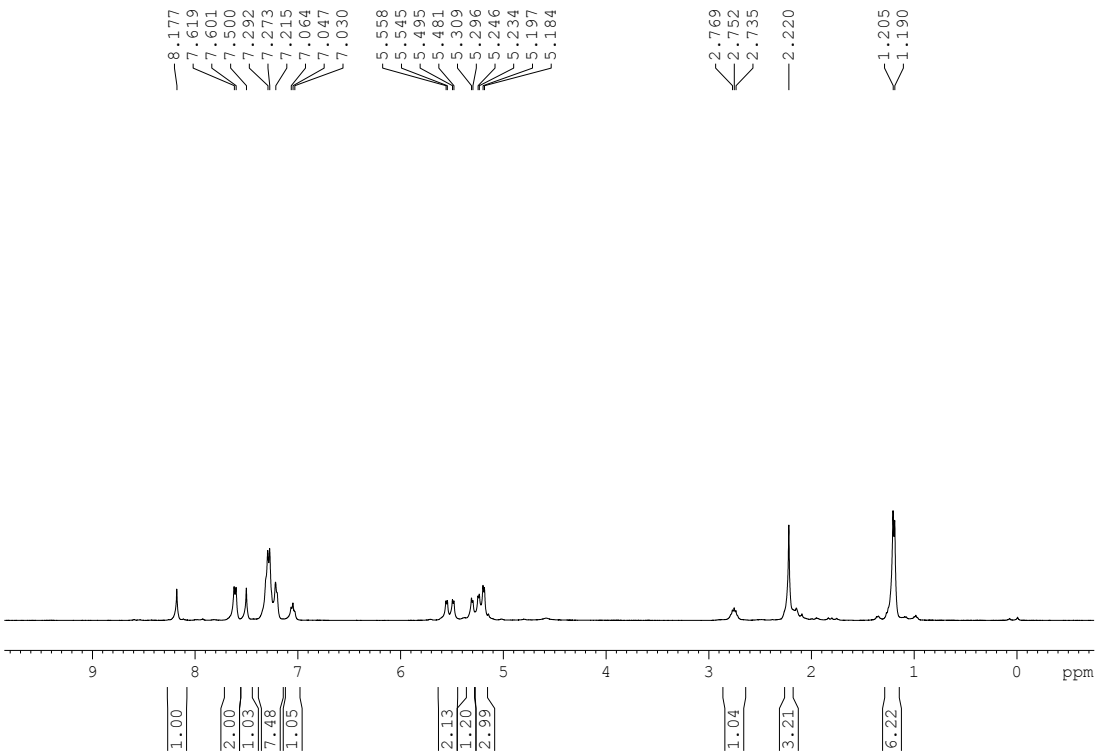

Figure A13. ^{1}H NMR spectrum of compound **97**

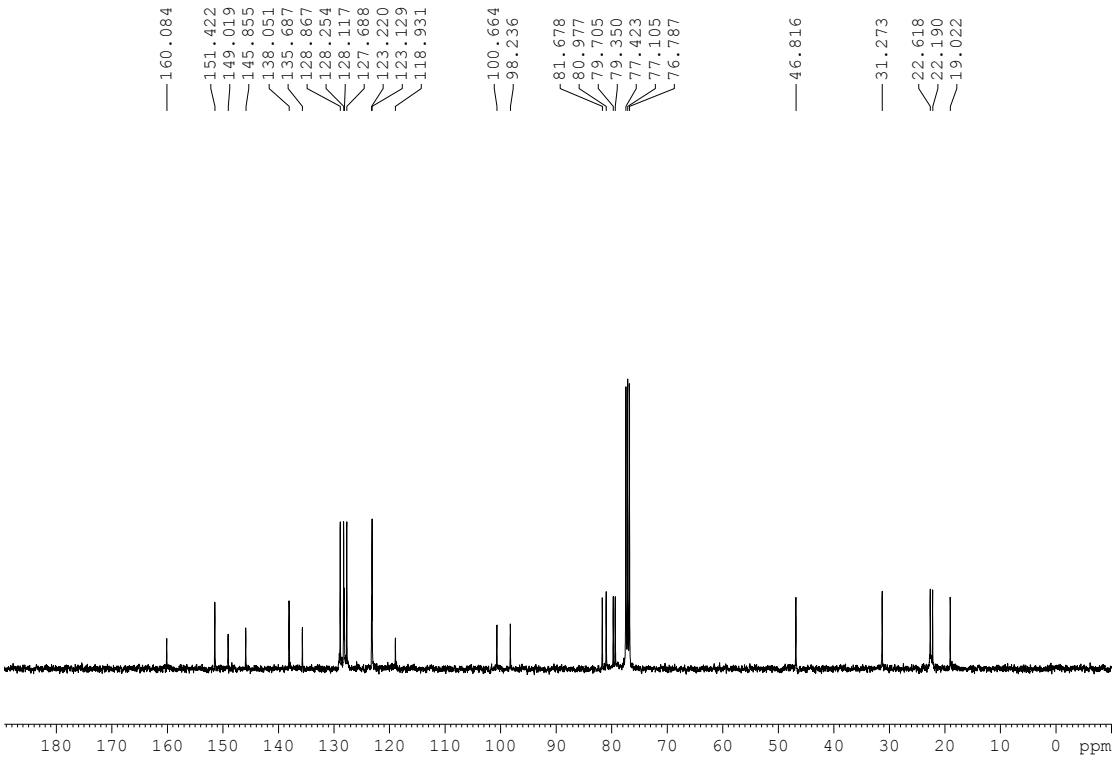

Figure A14. ^{13}C NMR spectrum of compound **97**

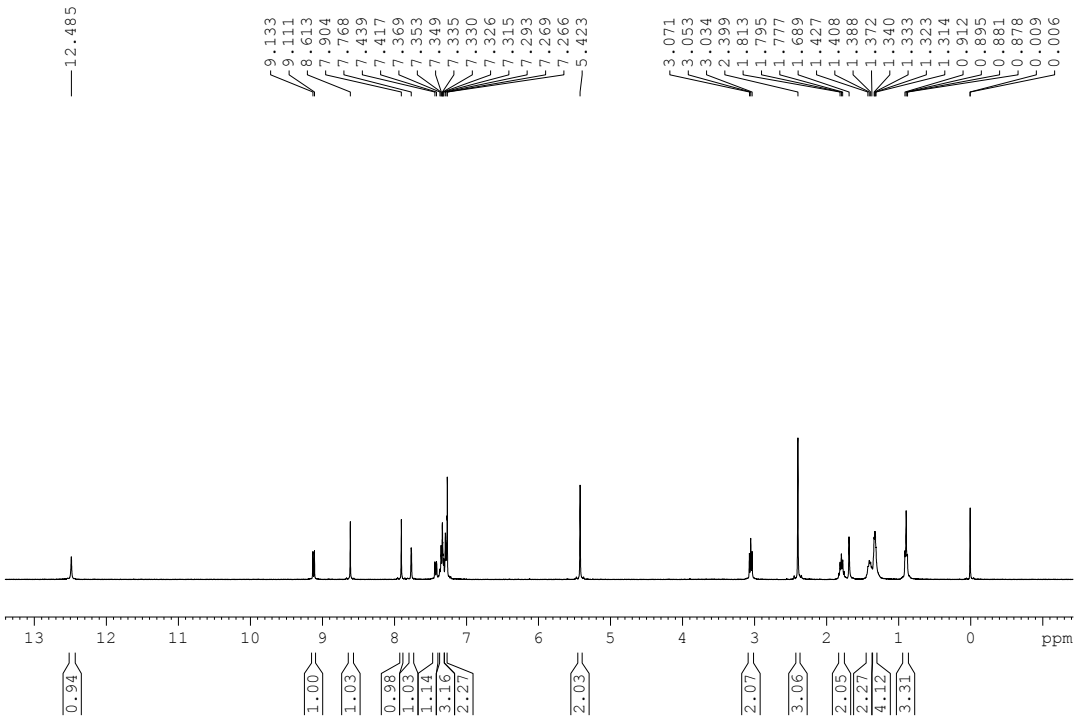

Figure A15. ^{1}H NMR spectrum of compound **100**

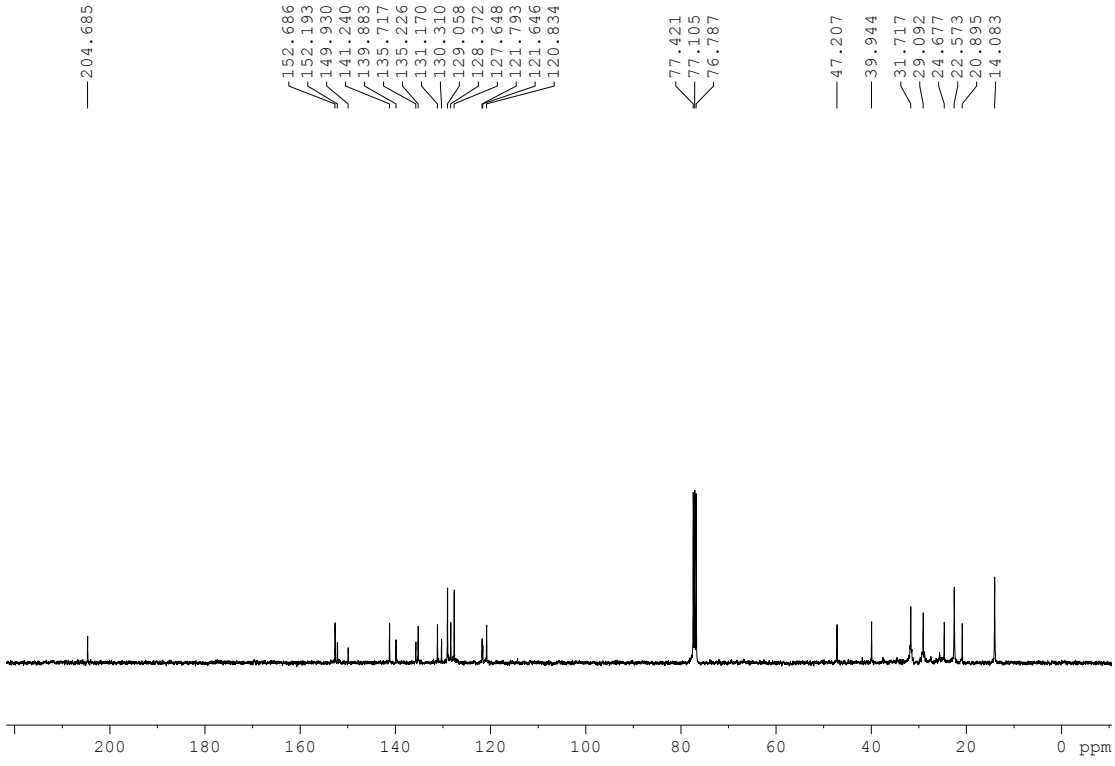

Figure A16. ^{13}C NMR spectrum of compound **100**

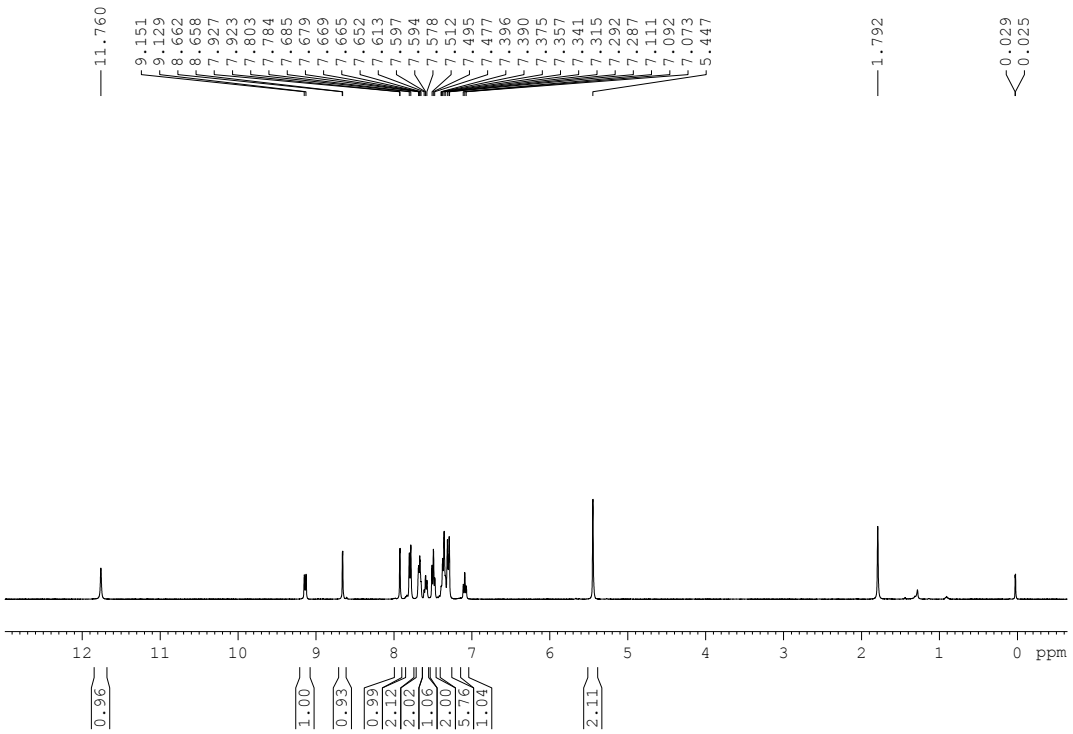

Figure A17. ^{1}H NMR spectrum of compound **115**

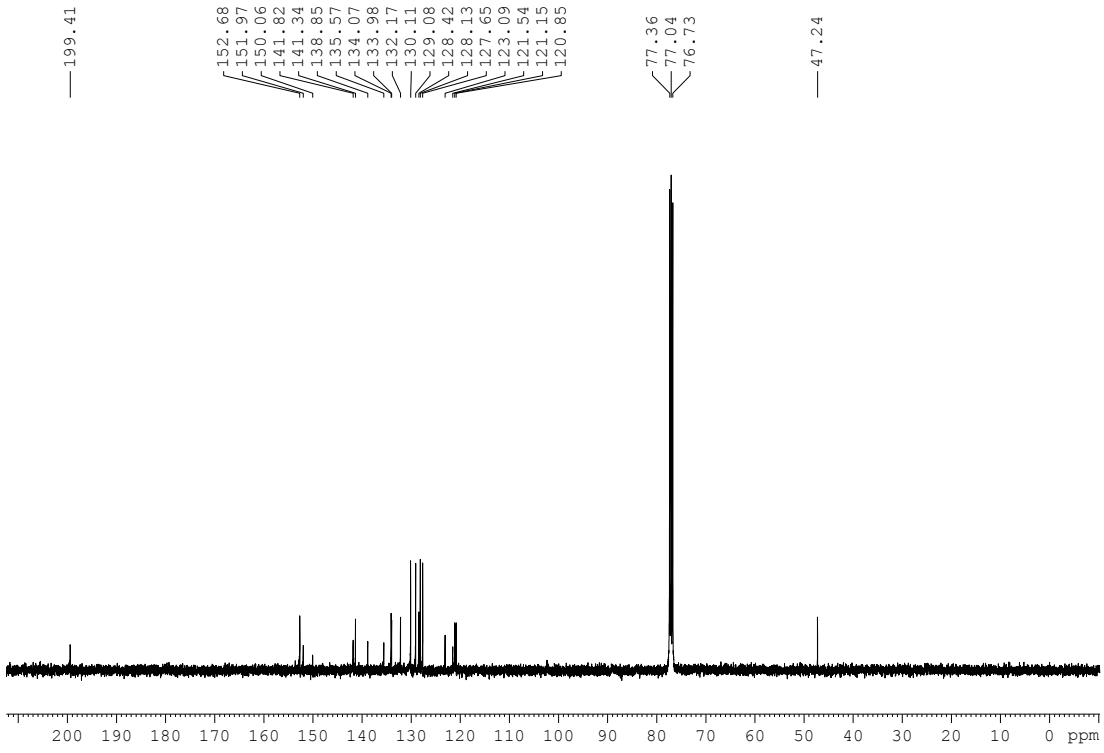

Figure A18. ^{13}C NMR spectrum of compound **115**

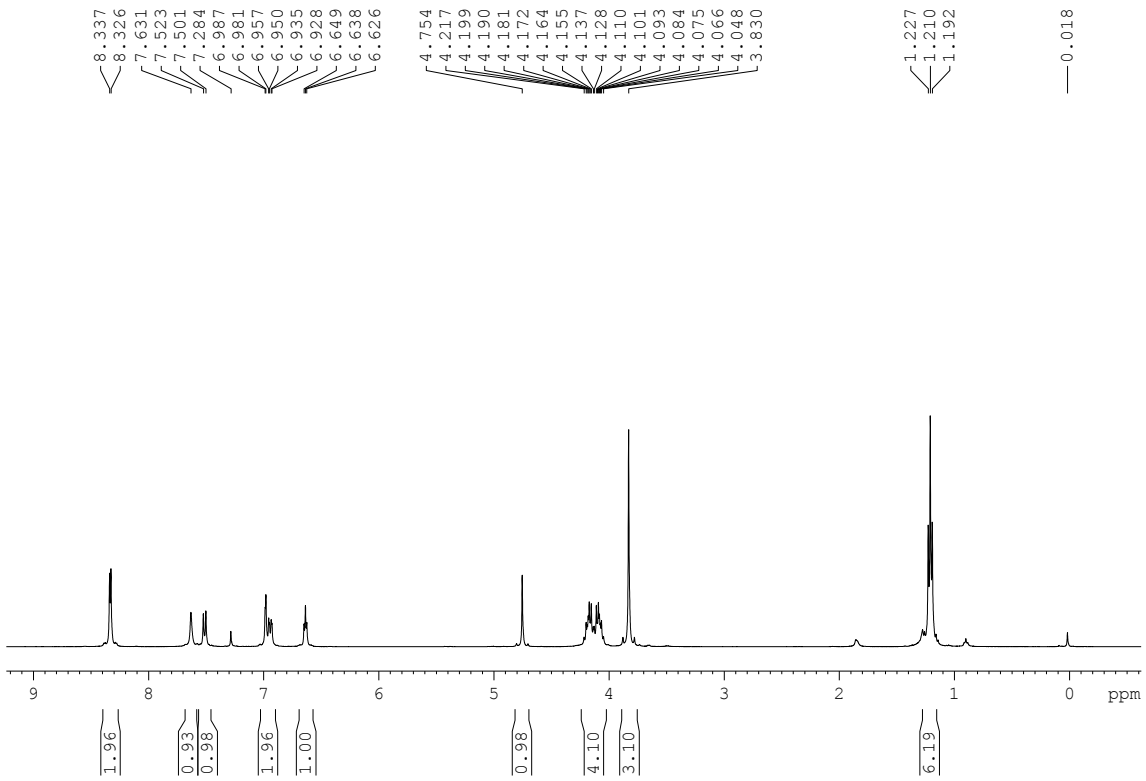

Figure A19. ^{1}H NMR spectrum of compound **118**

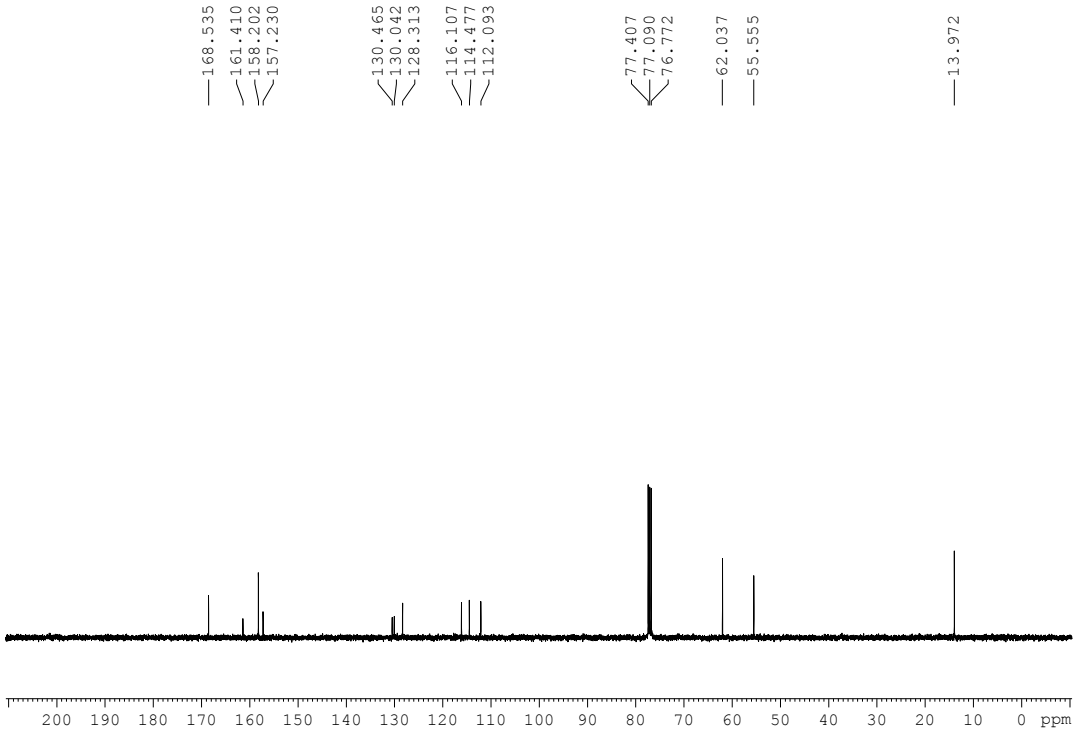

Figure A20. ^{13}C NMR spectrum of compound **118**

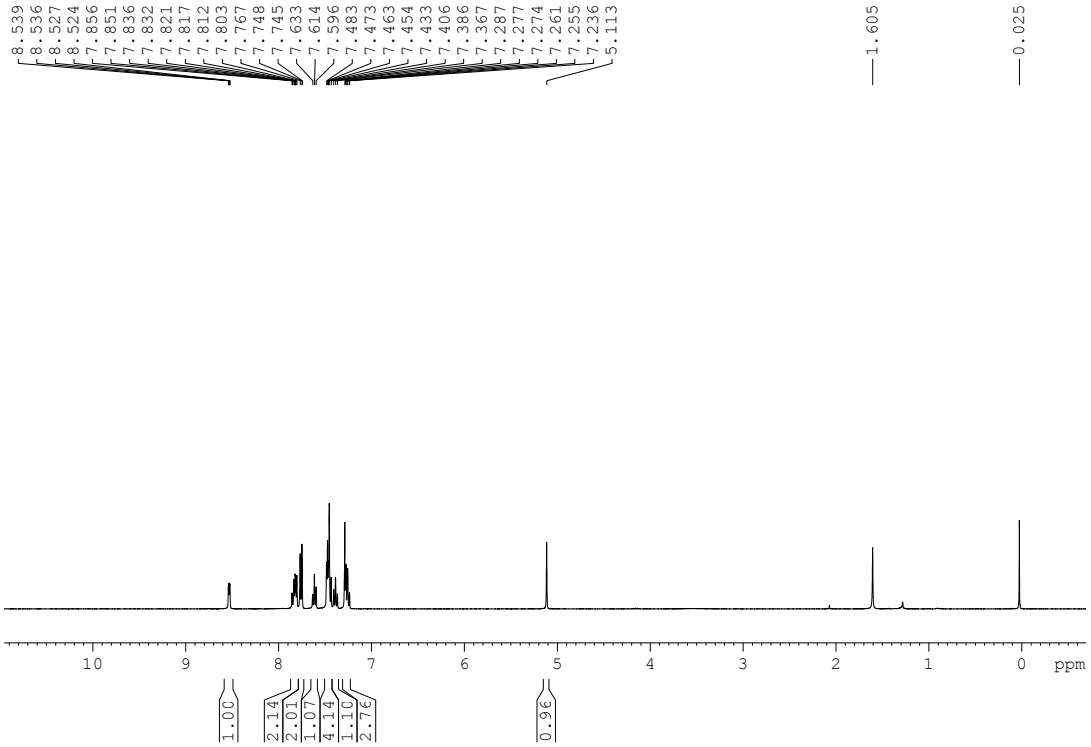

Figure A21. ^{1}H NMR spectrum of compound **126**

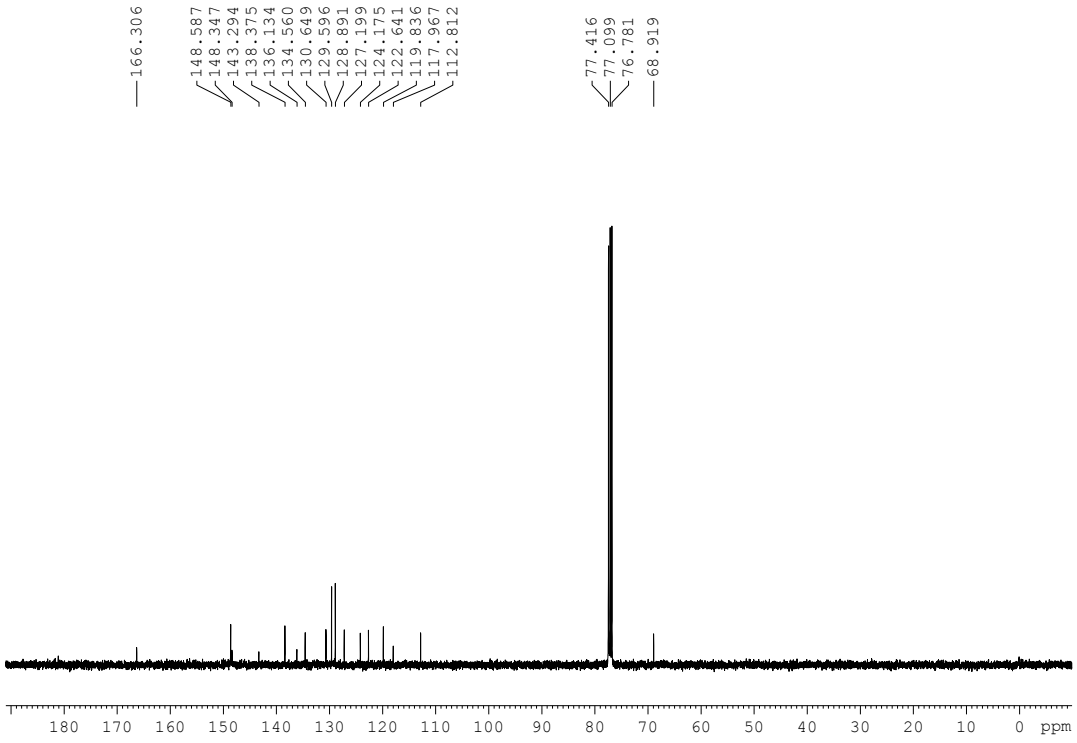

Figure A22. ^{13}C NMR spectrum of compound **126**

PART B: Compounds 17, 22, 24 and 25

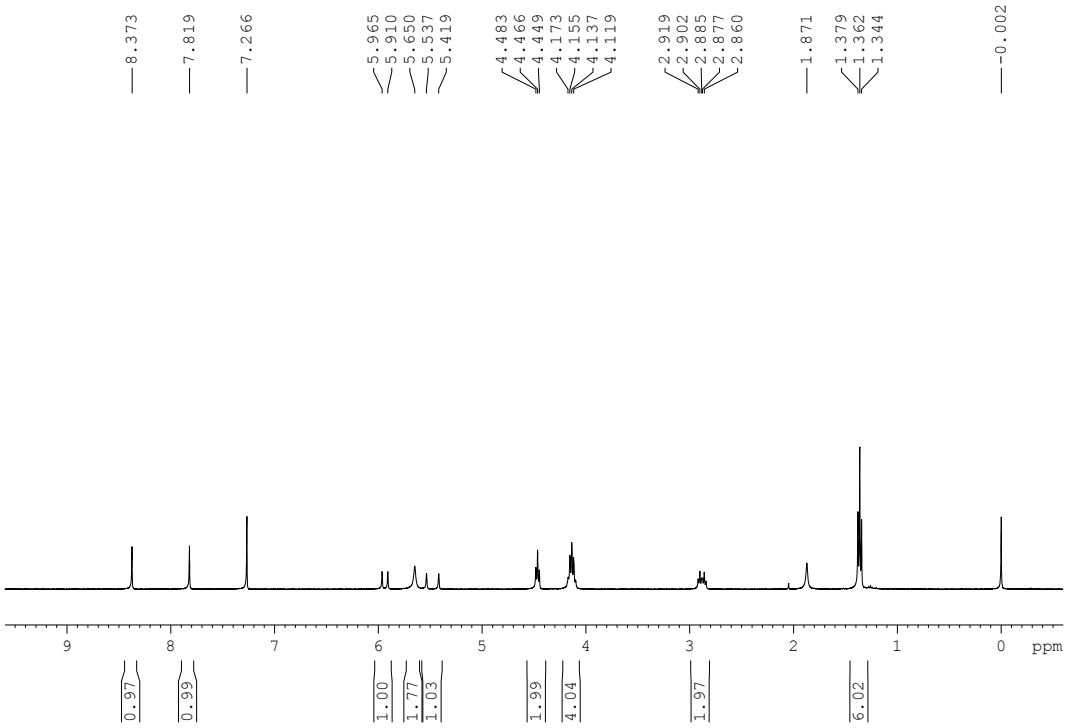

Figure A23. ^{1}H NMR spectrum of compound **17**

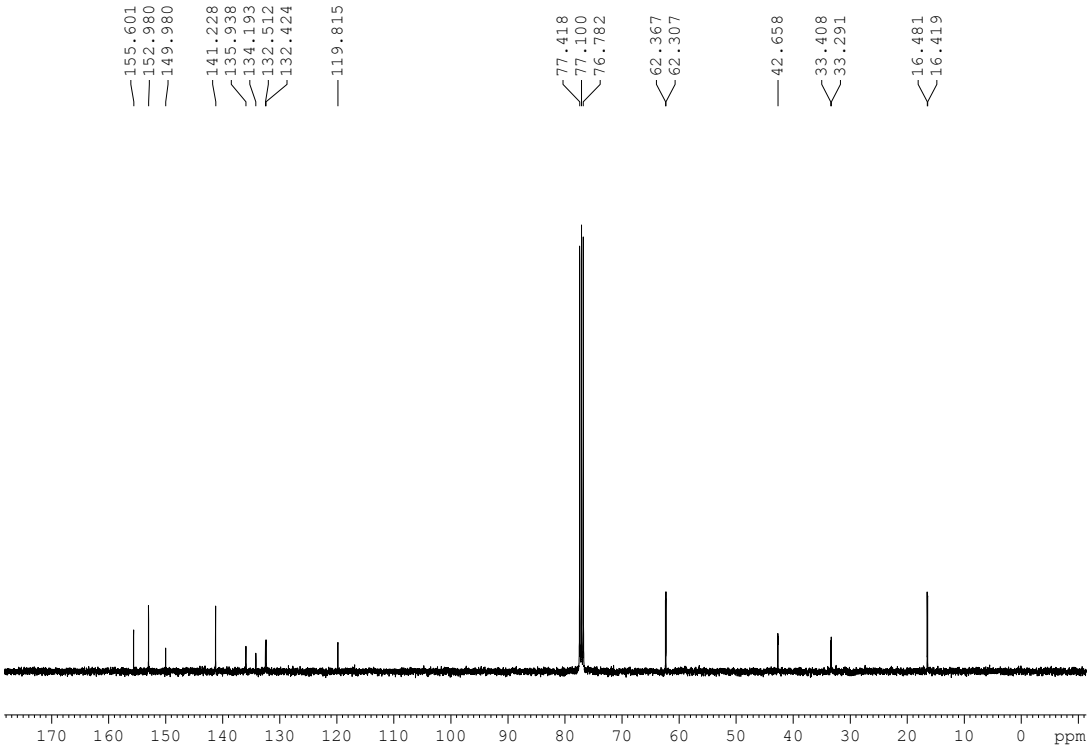

Figure A24. ^{13}C NMR spectrum of compound **17**

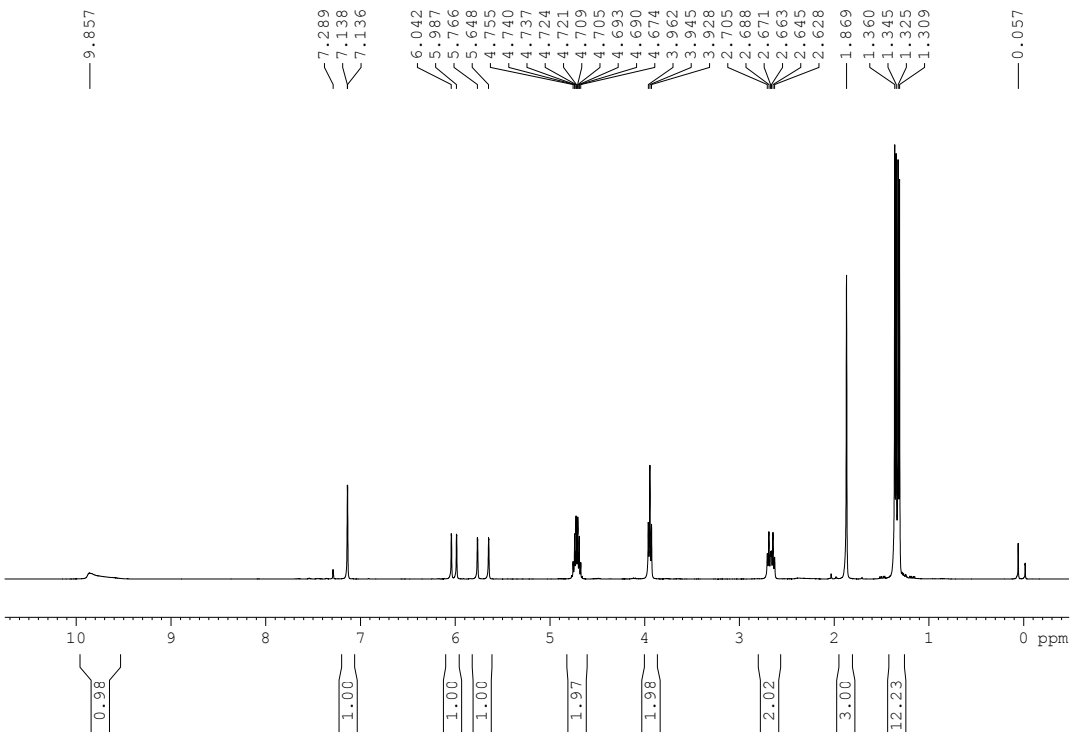

Figure A25. ^{1}H NMR spectrum of compound **22**

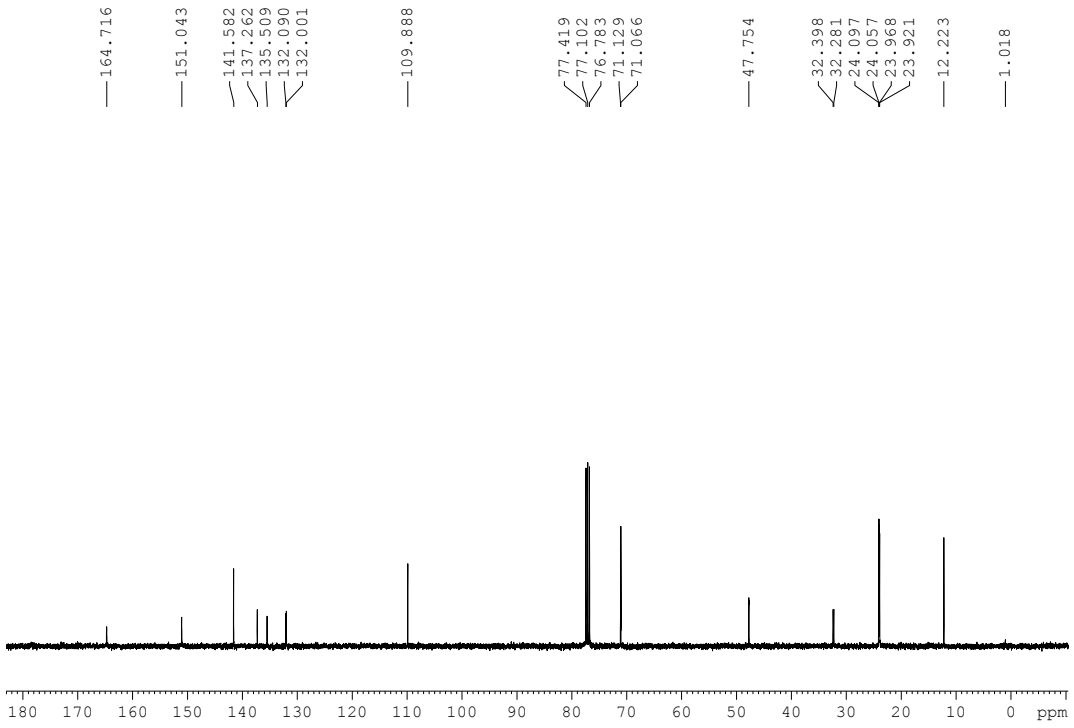

Figure A26. ^{13}C NMR spectrum of compound **22**

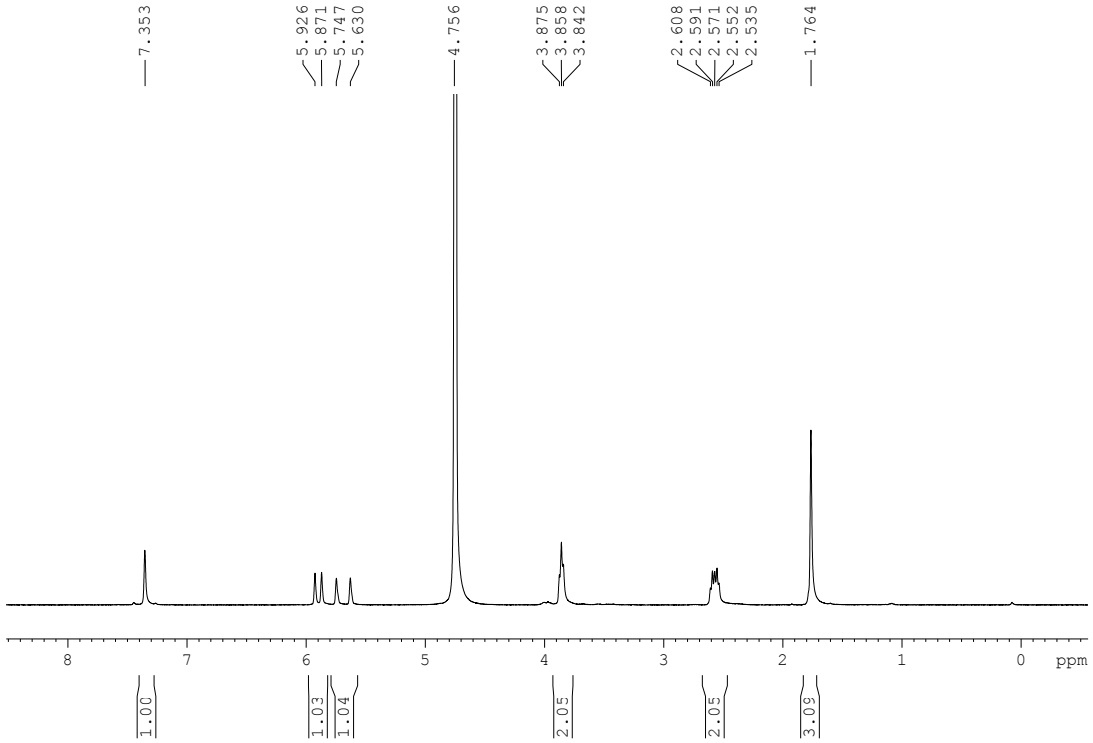

Figure A27. ^{1}H NMR spectrum of compound **24**

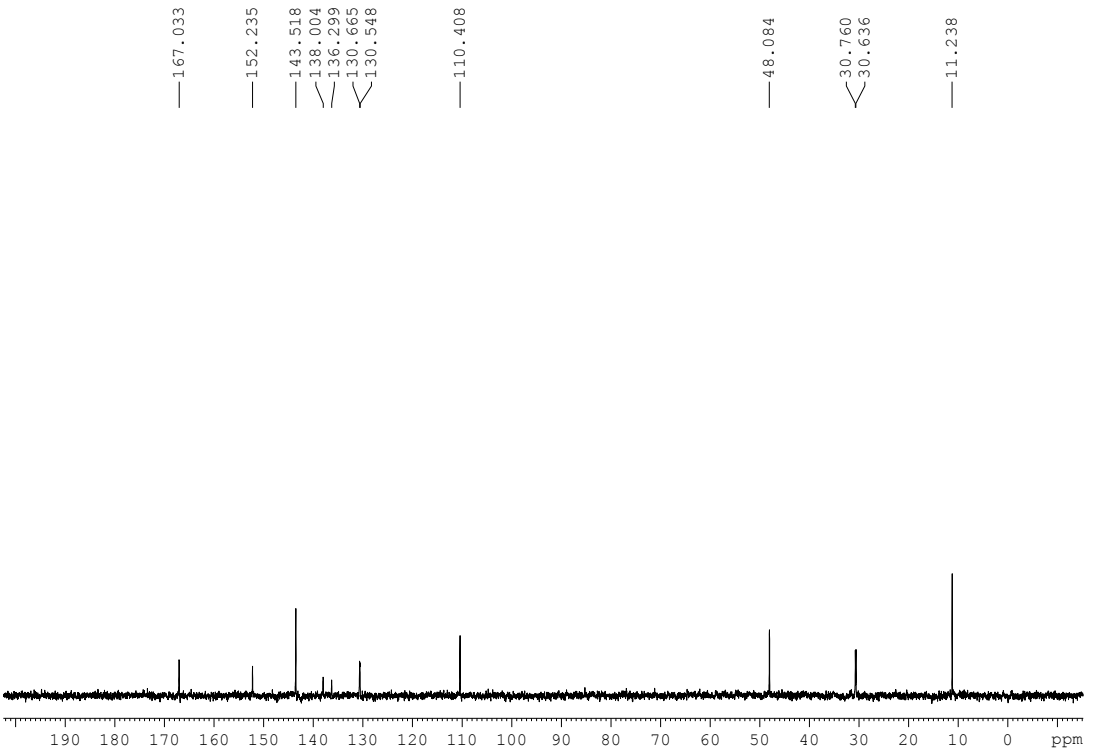

Figure A28. ^{13}C NMR spectrum of compound **24**

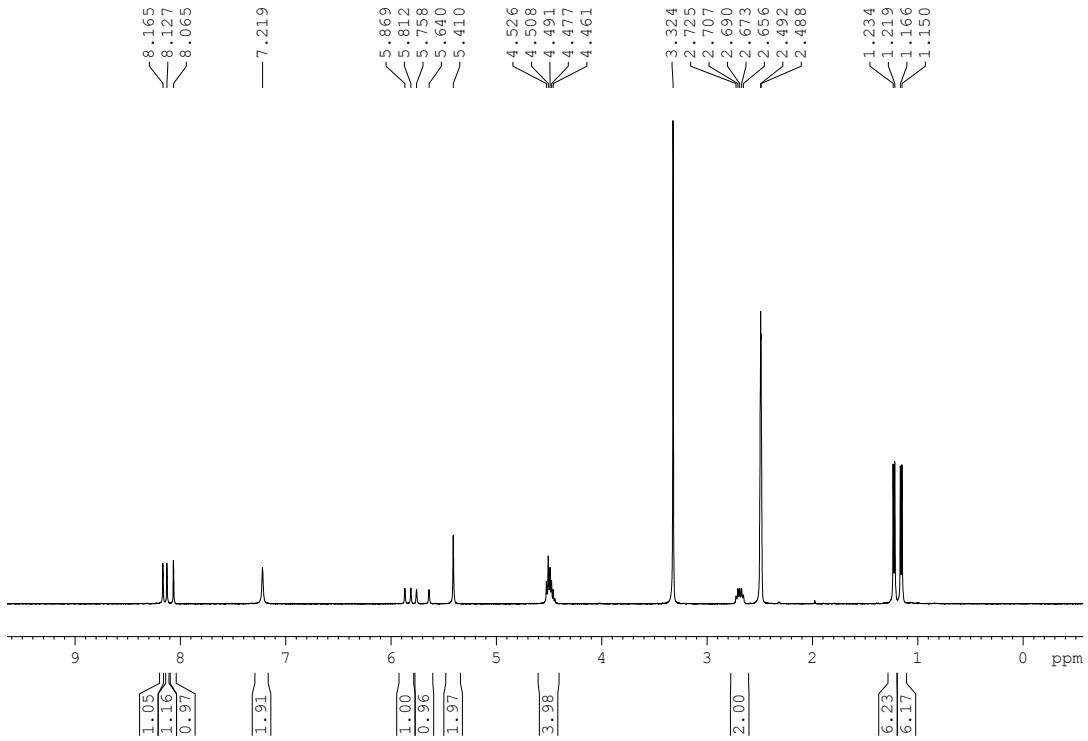

Figure A29. ^{1}H NMR spectrum of compound **25**

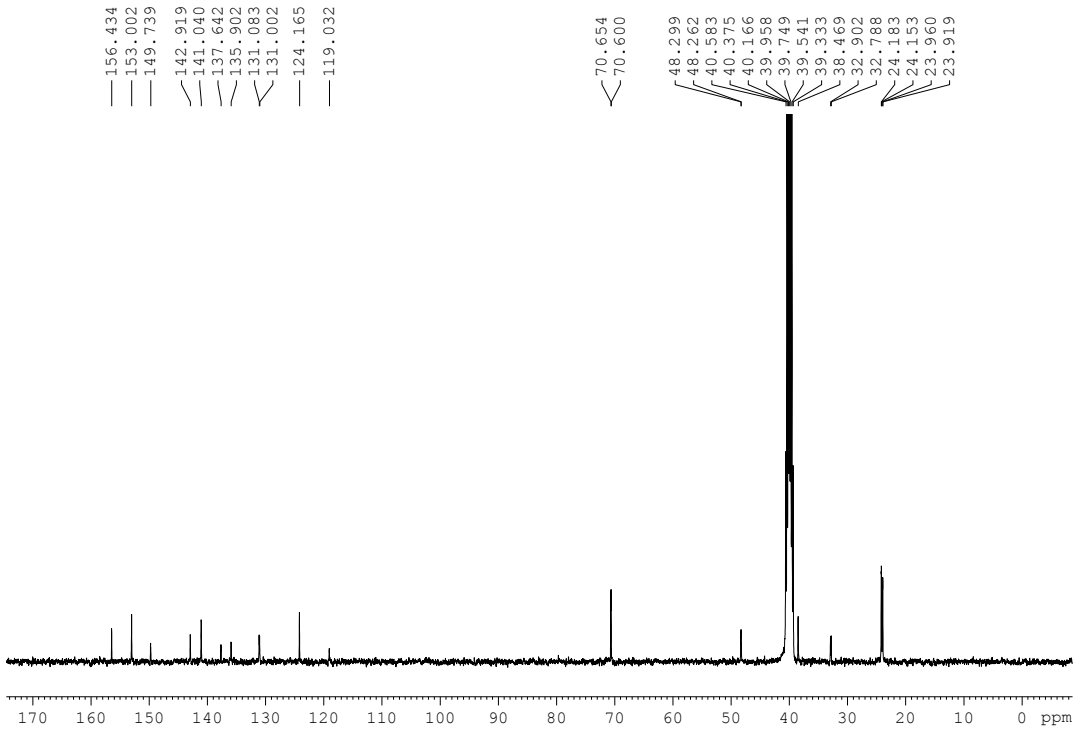

Figure A30. ^{13}C NMR spectrum of compound **25**

B) Publication numbers and atomic coordinates for X-ray structures reported in this thesis

I. Publication numbers for the published compounds

PART A: Compounds 14, 23, 26, 27 and 50: Publication no. 2
Compounds 57, 69, 90 and 97.CH_3CN: Publication no. 3
(Contents, p. xiii)

PART B: Compounds 1, 1', 2, 3, 4 and 5: Publication no. 1
(Contents, p. xiii)

II. Selected atomic coordinates for compounds 51, 98, 108 and 126 from PART A and for compounds 18, 22 and 25 from PART B.

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 4. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

PART A

Compound 51

Atom	x	y	z	U(eq)
O(1)	5760(2)	2500	3463(2)	84(1)
N(1)	4789(1)	2500	4719(2)	56(1)
N(2)	5731(1)	1243(2)	5793(2)	86(1)
C(1)	5014(2)	2500	3707(2)	63(1)
C(2)	4308(2)	2500	2997(2)	62(1)
C(3)	4479(3)	2500	1963(3)	85(1)
C(4)	3835(3)	2500	1279(3)	106(2)
C(5)	2998(3)	2500	1601(3)	96(1)
C(6)	2816(2)	2500	2611(2)	72(1)
C(7)	3465(2)	2500	3339(2)	58(1)
C(8)	3298(2)	2500	4408(2)	55(1)
C(9)	3953(2)	2500	5066(2)	52(1)
C(10)	2408(2)	2500	4793(2)	59(1)
C(11)	1988(2)	1258(3)	4978(2)	87(1)
C(12)	1169(2)	1270(4)	5337(2)	111(1)
C(13)	766(3)	2500	5513(3)	107(2)
C(16)	3796(2)	3764(4)	6701(2)	89(1)
C(18)	3710(2)	3744(11)	7743(5)	146(4)
C(20)	6305(2)	1275(3)	6574(2)	85(1)
C(21)	6585(2)	2500	6971(3)	74(1)
C(23)	3840(2)	2500	6183(2)	61(1)
C(24)	5462(2)	2500	5461(2)	54(1)
C(25)	3666(4)	2500	8255(6)	173(7)

Compound 98

Atom	x	y	z	U(eq)
P(1)	4584(1)	2587(1)	2369(1)	47(1)
N(10)	7974(3)	1025(3)	3933(2)	47(1)
C(26)	6623(3)	2481(4)	4683(2)	44(1)
C(5)	8796(3)	-187(4)	5484(2)	46(1)
C(6)	8974(3)	722(4)	4800(2)	45(1)
C(31)	5442(3)	2393(4)	4839(2)	52(1)
C(24)	6114(3)	1766(4)	2894(2)	41(1)
O(3)	4596(2)	3124(3)	1346(2)	55(1)
N(9)	9492(3)	-1277(3)	6887(2)	50(1)
C(25)	6844(3)	1774(4)	3849(2)	41(1)
N(3)	11027(3)	224(4)	6439(2)	56(1)
C(4)	9880(3)	-372(4)	6307(2)	43(1)
N(1)	10118(3)	1335(4)	4888(2)	56(1)
O(1)	3472(2)	1667(3)	2305(2)	73(1)
C(18)	7978(3)	534(4)	3045(3)	48(1)
C(23)	6824(3)	984(4)	2375(2)	44(1)
O(2)	4526(2)	4008(3)	2934(2)	58(1)
C(8)	8230(4)	-1599(5)	6408(3)	59(1)
N(7)	7780(3)	-982(4)	5575(2)	61(1)
C(2)	11056(4)	1052(5)	5703(3)	62(1)
C(27)	7579(4)	3295(4)	5326(3)	57(1)
C(22)	6615(4)	622(4)	1410(3)	58(1)
C(34)	5416(4)	4331(4)	1305(3)	64(1)
C(12)	10487(4)	-664(4)	8603(3)	55(1)
C(19)	8886(4)	-291(5)	2800(3)	63(1)
C(28)	7352(5)	3980(5)	6086(3)	74(1)
C(30)	5223(4)	3107(5)	5601(3)	59(1)
C(29)	6175(5)	3889(5)	6236(3)	69(1)
C(17)	9659(5)	467(5)	8570(3)	80(1)
C(21)	7530(5)	-167(5)	1170(3)	69(1)
C(20)	8641(5)	-641(5)	1857(4)	74(1)
C(11)	10255(4)	-1791(4)	7836(3)	61(1)
C(32)	5377(4)	5191(5)	2877(3)	73(1)
C(13)	11561(4)	-811(6)	9403(3)	75(1)
C(16)	9913(7)	1475(7)	9312(5)	103(2)
C(35)	3810(4)	6239(5)	1403(3)	83(1)
C(15)	10993(7)	1312(8)	10098(5)	106(2)
C(14)	11789(6)	182(8)	10127(4)	101(2)
C(36)	6163(6)	6806(6)	1820(5)	130(3)

Compound 108

Atom	x	y	z	U(eq)
N(10)	1117(2)	6942(1)	1210(1)	52(1)
N(9)	5352(2)	5120(1)	2151(1)	49(1)
N(1)	1596(2)	6783(1)	2864(1)	57(1)
N(3)	3850(2)	5886(1)	3452(1)	58(1)
N(7)	3903(2)	5611(1)	910(1)	53(1)
C(24)	-104(2)	7472(2)	-639(1)	51(1)
C(23)	-797(2)	7848(2)	277(1)	47(1)
C(26)	56(2)	7464(2)	-2437(1)	52(1)
C(18)	-184(2)	7589(1)	1181(1)	46(1)
C(25)	-802(2)	7827(2)	-1558(1)	49(1)
C(19)	-891(2)	7999(2)	2004(1)	54(1)
C(12)	5733(2)	3121(2)	3028(1)	51(1)
C(22)	-2103(2)	8489(2)	261(1)	57(1)
C(20)	-2173(2)	8622(2)	1944(1)	60(1)
C(13)	5474(2)	2985(2)	3984(1)	61(1)
C(27)	-719(2)	7806(2)	-3346(1)	57(1)
C(17)	5189(2)	1893(2)	2394(1)	65(1)
C(11)	6565(2)	4578(2)	2669(1)	57(1)
C(21)	-2790(2)	8870(2)	1075(1)	64(1)
C(14)	4693(2)	1653(2)	4311(2)	77(1)
C(28)	101(2)	7455(3)	-4239(1)	84(1)
C(15)	4147(2)	454(2)	3687(2)	85(1)
C(29)	-804(3)	7665(4)	-5141(1)	127(1)

O(1)	1028(2)	6891(1)	-663(1)	74(1)
C(6)	1963(2)	6579(2)	1951(1)	46(1)
C(5)	3266(2)	5975(1)	1757(1)	45(1)
C(4)	4140(2)	5671(1)	2529(1)	46(1)
C(2)	2558(2)	6424(2)	3535(1)	63(1)
C(8)	5128(2)	5110(2)	1188(1)	54(1)

Compound 126

Atom	x	y	z	U(eq)
C(17)	4255(2)	3176(3)	1795(2)	89(1)
C(18)	4108(2)	1995(3)	2232(2)	98(1)
C(19)	4121(1)	480(3)	2000(1)	74(1)
S(1)	4281(1)	-1757(1)	1018(1)	53(1)
O(2)	4700(1)	-1884(2)	476(1)	71(1)
N(2)	2547(1)	-636(2)	722(1)	45(1)
C(13)	2966(1)	-1744(2)	1060(1)	47(1)
C(1)	1996(1)	-103(2)	1020(1)	43(1)
O(1)	4375(1)	-2772(2)	1631(1)	67(1)
N(1)	1458(1)	36(2)	554(1)	54(1)
C(11)	3275(1)	-1034(2)	-76(1)	49(1)
C(6)	2719(1)	-235(2)	34(1)	45(1)
C(2)	2038(1)	233(2)	1747(1)	52(1)
C(7)	2414(1)	780(2)	-477(1)	55(1)
C(14)	4285(1)	173(2)	1324(1)	51(1)
C(4)	925(1)	879(2)	1538(1)	62(1)
C(3)	1489(1)	722(2)	2007(1)	58(1)
C(10)	3539(1)	-822(3)	-705(1)	64(1)
C(15)	4431(1)	1362(3)	881(1)	64(1)
C(5)	935(1)	537(3)	824(1)	65(1)
C(8)	2688(1)	974(3)	-1106(1)	66(1)
C(9)	3239(1)	199(3)	-1219(1)	74(1)
C(16)	4416(1)	2875(3)	1127(1)	80(1)
O(3)	2929(1)	-2335(2)	1638(1)	64(1)
C(12)	3473(1)	-2057(2)	563(1)	49(1)

PART B

Compound 18

Atom	x	y	z	U(eq)
P(1)	5085(1)	2686(1)	8938(1)	42(1)
O(2)	7216(3)	2765(3)	9281(2)	43(1)
O(3)	5612(4)	1834(3)	7945(2)	46(1)
C(4)	4148(5)	6842(4)	6222(2)	36(1)
N(7)	2236(4)	4984(3)	5733(2)	44(1)
N(1)	2168(4)	9243(3)	5599(2)	41(1)
N(3)	4885(4)	8229(3)	6387(2)	44(1)
C(5)	2520(5)	6558(4)	5769(2)	35(1)
N(9)	4908(4)	5441(3)	6473(2)	40(1)
C(15)	8429(5)	1324(4)	9277(2)	42(1)
O(1)	3453(4)	1986(3)	9620(2)	69(1)
C(6)	1482(5)	7830(4)	5441(2)	35(1)
C(17)	8847(5)	670(4)	8277(2)	39(1)
C(2)	3788(5)	9341(4)	6046(3)	45(1)
C(19)	9949(6)	-897(4)	8320(3)	55(1)
C(18)	10180(6)	1761(5)	7586(3)	50(1)
C(13)	4561(6)	4610(4)	8590(2)	46(1)
C(11)	6676(5)	5165(5)	6939(3)	54(1)
C(12)	6221(6)	5549(5)	8004(3)	57(1)
C(16)	6813(6)	397(4)	7953(3)	51(1)
C(8)	3690(6)	4390(4)	6162(3)	47(1)
C(14)	2681(7)	5154(5)	8873(3)	69(1)
N(6)	-113(5)	7741(4)	4990(2)	47(1)

Compound 22

Atom	x	y	z	U(eq)
P(1)	2486(1)	6278(1)	5996(1)	17(1)
O(6)	1862(1)	6940(1)	4935(1)	21(1)
O(7)	4144(1)	6604(1)	6718(1)	22(1)
O(5)	1717(1)	6353(1)	6583(1)	20(1)
O(2)	3174(1)	6312(1)	3032(1)	27(1)
O(4)	-1508(1)	7450(1)	1153(1)	27(1)
N(1)	1418(2)	5365(1)	3018(1)	18(1)
N(3)	812(2)	6856(1)	2098(1)	21(1)
C(6)	-29(2)	5256(1)	2674(1)	19(1)
C(5)	-1080(2)	5911(1)	2045(1)	20(1)
C(4)	-662(2)	6793(1)	1722(1)	20(1)
C(2)	1900(2)	6187(1)	2743(1)	20(1)
C(8)	2524(2)	4641(1)	3756(1)	20(1)
C(9)	3386(2)	4963(1)	4966(1)	20(1)
C(10)	2449(2)	5098(1)	5448(1)	17(1)
C(11)	1638(2)	4396(1)	5489(1)	18(1)
C(12)	1949(2)	8014(1)	5044(2)	27(1)
C(13)	404(3)	8398(2)	4357(2)	44(1)
C(14)	2941(3)	8362(2)	4679(2)	41(1)
C(15)	5036(2)	6543(1)	7935(1)	23(1)
C(16)	5814(2)	5573(1)	8272(2)	34(1)
C(17)	6056(2)	7403(2)	8333(2)	36(1)
C(7)	-2657(2)	5793(1)	1681(2)	25(1)

Compound 25

Atom	x	y	z	U(eq)
P(1)	3586(1)	4924(2)	2689(3)	64(1)
N(1)	794(3)	3728(4)	-880(6)	35(1)
N(9)	753(3)	5961(4)	2458(6)	36(1)
C(5)	714(3)	4262(5)	1678(7)	32(2)
C(6)	724(3)	3442(5)	601(7)	34(2)
N(3)	867(3)	5621(4)	-261(6)	39(1)
C(9)	816(3)	7161(5)	2493(8)	40(2)
N(10)	1543(3)	8408(5)	1244(7)	49(2)
C(4)	787(3)	5314(5)	1185(7)	31(2)
C(2)	864(4)	4781(5)	-1189(8)	44(2)
N(11)	2164(3)	8503(5)	986(9)	62(2)
C(10)	1473(3)	7505(5)	2083(8)	39(2)
N(12)	2470(3)	7633(5)	1612(8)	55(2)
O(1)	3742(3)	5769(5)	3816(7)	74(2)
C(11)	2054(4)	7009(6)	2346(10)	58(2)
O(2)	3236(3)	3904(5)	3306(8)	81(2)
O(3)	4177(3)	4428(5)	1913(7)	80(2)
C(17)	2227(6)	3307(16)	4150(20)	187(9)
C(19)	4769(5)	4112(12)	2892(15)	101(4)
C(16)	2801(7)	3975(9)	4571(18)	103(4)
C(18)	3170(9)	3645(17)	6002(19)	194(9)
C(21)	5312(7)	4668(14)	2330(20)	179(8)
C(20)	4856(8)	2944(13)	2820(30)	269(15)
N(7)	620(3)	4258(4)	3238(6)	38(1)
C(14)	3101(4)	5408(7)	1038(11)	66(2)
C(12)	3166(4)	7467(7)	1426(11)	67(2)
C(15)	2593(5)	4828(10)	429(13)	100(4)
C(13)	3272(4)	6485(8)	381(11)	73(3)
N(6)	671(3)	2379(4)	925(6)	42(2)