Introduction

A brief introduction on steroidal based heterocyclic compounds with special reference to novel methodologies

Steroids - As biological regulators

Steroids belong to a family of lipid molecules having a particular tetracyclic ring structure called perhydrocyclopentano[*a*]phenanthrene system. The system includes three cyclohexane and one cyclopentane rings and cnventionally named as A, B, C and D (Figure 1). The range of steroids is diverse, hundreds of distinct steroids are found in plants, animals and fungi. All steroids are made in cells either from the sterols lanosterol (animals and fungi) including vitamin D, and bile acids or from cycloartenol (plants).[1,2] Steroids are found predominantly in eukaryotic cells, with cholesterol being the most abundant steroid molecule. Cholesterol is the precursor of all the steroid hormones, which can be subdivided into five major classes. These include glucocorticoids, mineralocorticoids, male sex hormone androgen and female sex hormones estrogen and progestogen. Glucocorticoids such as cortisone, cortisol and mineralocorticoids such as aldosterone are steroidal adrenal cortex hormones. Steroid hormones, like all hormones, are chemical messengers as they can enter cell membranes and bind to nuclear and membrane receptors.[3]

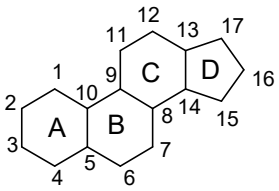


Figure 1 Numbering of steroid skeleton

Besides normal physiological role as hormones, the majority of naturally occurring steroids and their synthetic derivatives (Figure 2) have important therapeutic applications. For example, cholesterol, stigmasterol, lanosterol and their derivatives are used in cancer treatment; estrogens and their carbamates in breast cancer; cortisone in rheumatoid arthritis;

testosterone and testosterone propionate in lymphocytic leukemia; corticoids as anti-inflammatory agents.[4]

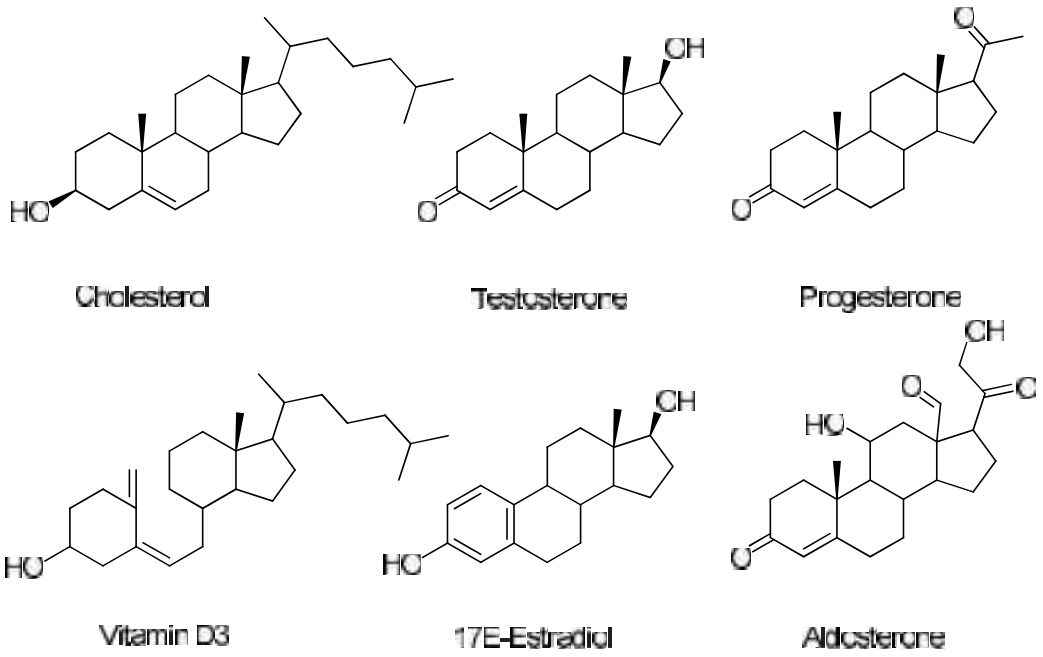


Figure 2 Examples of naturally occurring steroids

Many steroidal compounds extracted from marine organisms have exhibited excellent cytotoxic activities.[5] Further, steroidal molecules are adopted as clinical drugs and sometimes they are used as drug templates or enzyme templates because of their ease of permeability to cells, high lipophilicity and conformational rigidity.[6]

Heterocyclic compounds – Countless variety and broad spectrum activity

The majority of the biologically active compounds are comprised of heterocycles, many of which are employed in regular clinical practices. Some of these are natural products (Figure 3), for example, antibiotics, such as penicillin and cephalosporin; alkaloids such as vinblastine, ellipticine, morphine and reserpine. Heterocyclic compounds play a vital role in the metabolism of all living cells. The pyrimidine and purine bases of the genetic material

DNA; the essential amino acids, proline, histidine and tryptophan; the vitamins and co-enzyme precursors – thiamine, riboflavin, pyridoxine, folic acid and biotin; the vitamin B_{12} and E families of vitamin; oxygen transporting pigment haemoglobin, hormones and sugars are vivid examples of heterocycles that play key role in biological processes.

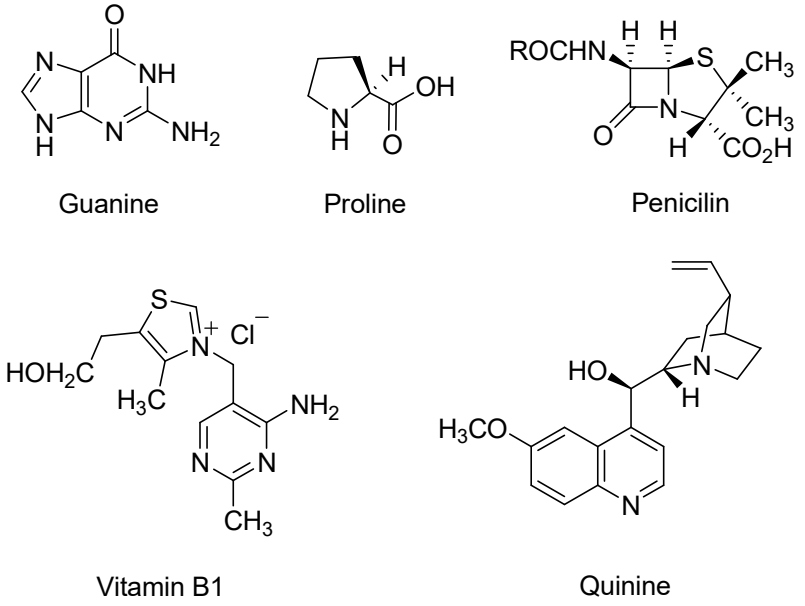
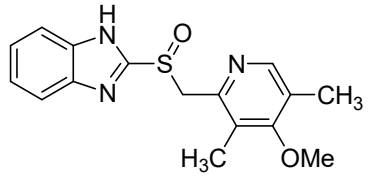
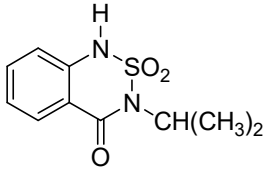


Figure 3 Naturally occurring heterocycles

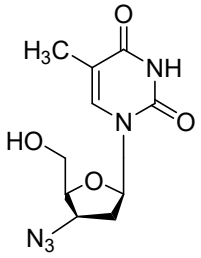
There are also a large number of synthetic heterocyclic compounds (Figure 4) with other important practical applications as anticancer, hypnotics, vasopresso modifiers, pharmaceuticals (analgesics, anti-inflammatory, analeptics), veterinary products (antimicrobial, antifungal, antibacterial), agrochemicals (pesticides, insecticides).[7] Usually the stereochemical orientation of heterocyclic molecule together with weak Van der Walls interaction, stacking effect, liophilicity and bonding between the heteroatom of the drug and active site are responsible for bioactivity of a drug molecule.



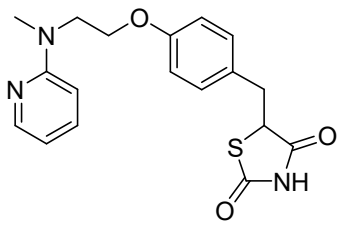
Omeprazole (anti-ulcerative)



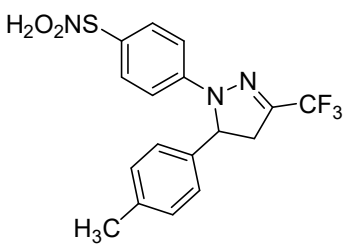
Bentazon (herbicide)



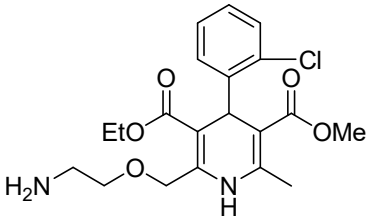
Zidvudine (anti-HIV)



Rosiglitazone (anti-diabetic)



Celecoxib (anti-arthritic)



Amlodipine (calcium channel blocker)

Figure 4 Examples of synthetic heterocyclic drugs

Steroidal heterocycle or heterosteroid – Unique combination and demanding biological activity

Steroidal systems containing atoms other than carbon at various positions in the cyclopentanophenanthrene skeleton are classified as heterocyclic steroids. The modification of steroid with a heterocyclic ring is a subject of much importance[8,9] as it leads to useful alternations of biological activity.[10] Among the heterosteroids, the potential of azasteroids, in particular, as novel drugs and the challenge of their synthesis impelled several research groups to undertake studies in this field.[11-13] Many steroids are enzyme inhibitors, such as aromatase and sulfatase inhibitors for breast cancer, 5α-reductase inhibitors for the treatment of benign prostatic hyperplasia, PI-PLC inhibitors and CYP-17 inhibitors for advanced

prostate cancer therapy.[14,15] The A-ring annelated azasteroids such as danazole is a well known drug against breast cancer and bone marrow cancer. The B-ring modified 6-azasteroid and its pregnane analogues have shown significant growth inhibition effect on HT-29 colon cancer cells and MCF-7 breast cancer cells.[16] Similarly, D-ring annelated heterosteroids like 17-imidazolyl steroid is reported to exhibit excellent biological activities against prostate cancer, which is one of the leading cause of cancer related mortalities in elderly men.[17] Cortisone is another steroid used clinically to treat arthritis for its anti-inflammatory properties. During recent years, extensive attention in the rational modifications of perhydrocyclopentanophenanthrene nucleus of steroids has yielded several important anticancer lead molecules. There also have been an increasing number of investigations in which a known non-steroidal pharmacophore has been attached to the steroid framework so that the latter might provide lipid solubility, receptor selectivity or membrane-binding properties. Exemestane and 2-methoxyestradiol are two successful leads emerged on steroidal pharmacophores.[18]

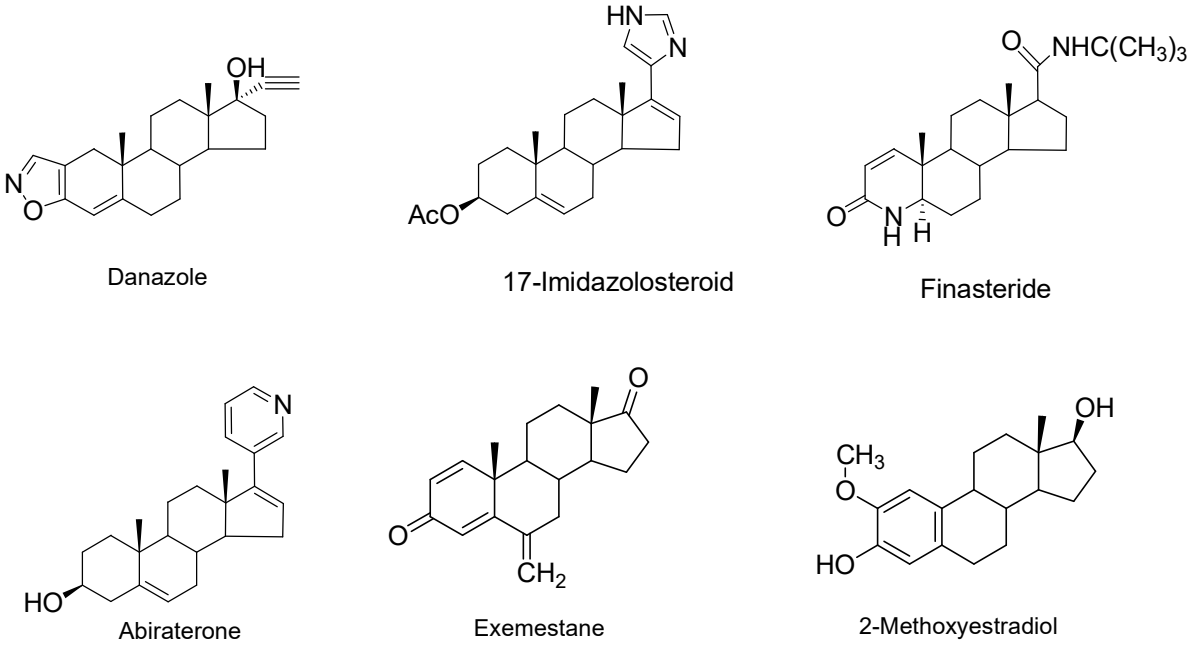
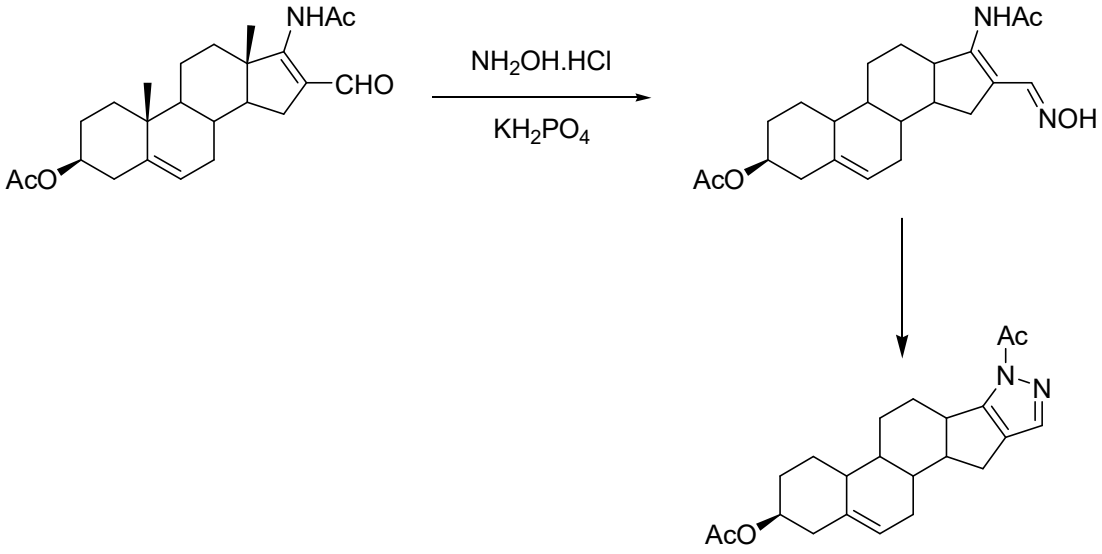


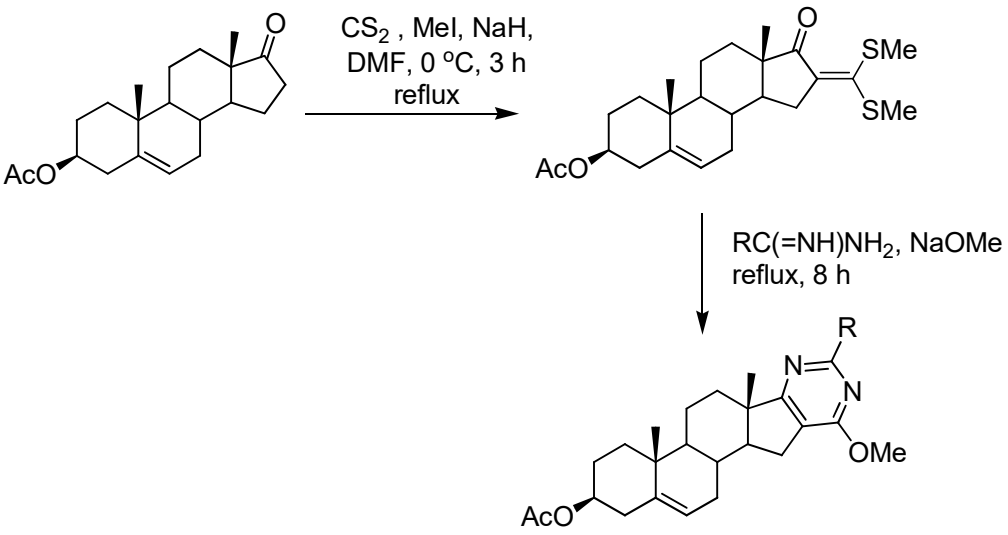
Figure 5: Some medicinally important steroidal heterocyclic molecules

Introduction of heteroatom into the steroidal framework has been proved to be an exciting challenge for the organic chemist, often demanding the development of new and generally useful reactions. Several methods for the synthesis of heterocyclic steroids have been reported in the literature.

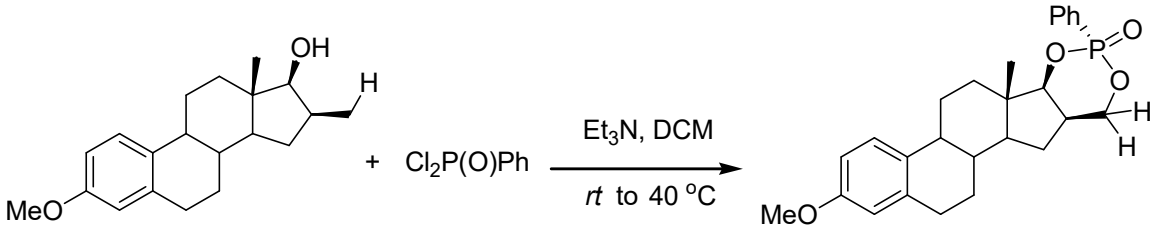
Boruah and co-workers developed a method for the synthesis of steroidal pyrazoles by the reaction of β-formyl enamides with hydroxylamine hydrochloride catalysed by potassium dihydrogenphosphate in acid medium.[19]



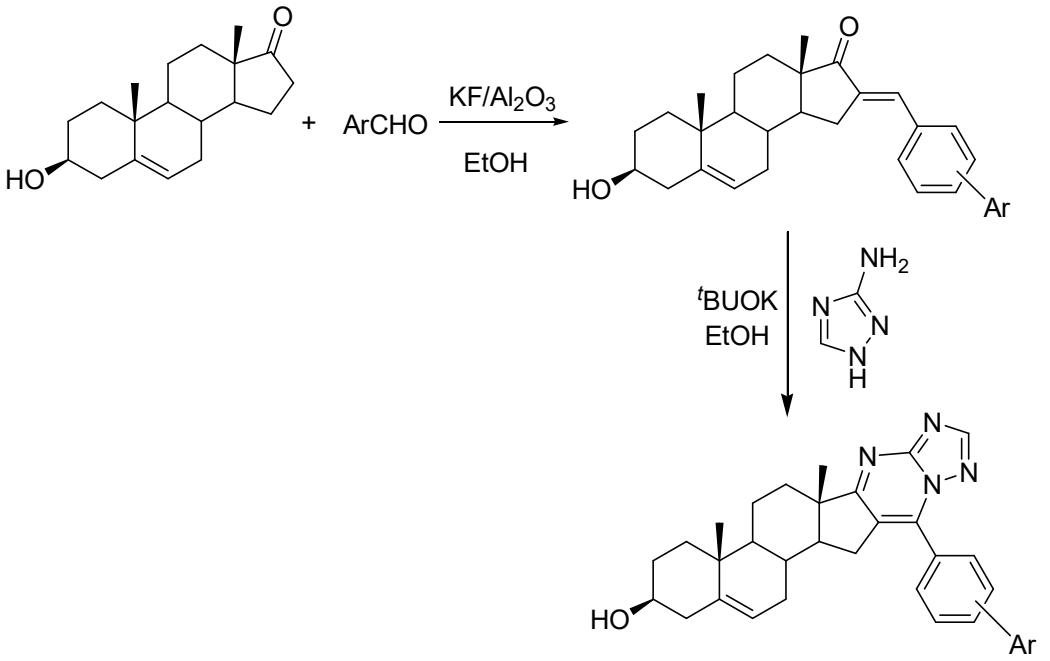
Androsterone acetate reacted with carbon disulfide, iodomethane and sodium hydride to furnish the intermediate 3β-acetoxy-16-[bis(methylthio)methylene]-androst-5-en-17-one. Treatment of the intermediate with amidinium, guanidinium, and isothiuronium salts in the presence of sodium methoxide yielded 6′-methoxy-pyrimido[5′,4′:16,17]androst-5-en-3β-ol.[20]



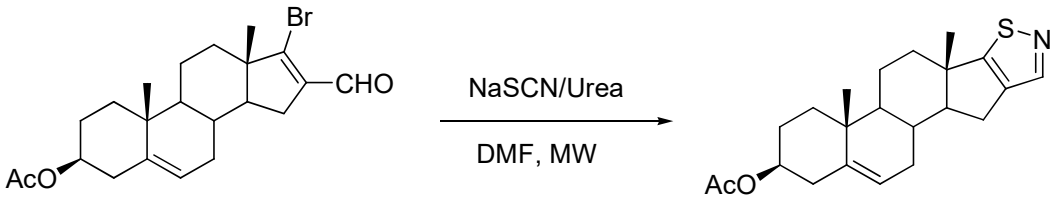
Frank and co-workers synthesized D-ring-fused dioxaphosphorinanes in the estrone series by phosphorylation reactions using phenyl dichlorophosphate. Subsequently, the influence of the substituents on the conformation of the hetero ring was also investigated.[21]



Preparation of D-ring fused 7-aryl-androstano[17,16-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines by the reaction of 3β-hydroxy-5-en-16-arylidene-17-ketosteroids and 3-amino-1,2,4-triazole in presence of ^{t}BuOK is reported by Huang and co-workers. The intermediate 3β-hydroxy-5-en-16-arylidene-17-ketosteroids was first prepared by the aldol reaction of steroidal ketone and aromatic aldehyde using catalytic amount of KF/Al_2O_3.[22]



An efficient microwave promoted one-pot synthesis of steroidal isothiazole derivatives from corresponding β-bromo-α,β-unsaturated aldehydes using a sodium thiocyanate-urea system has been described by Boruah and co-workers.[23]

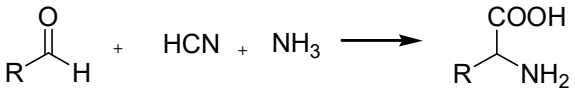


Multi-component reaction (MCR)

Multi-component Reactions (MCRs) are one-pot reactions that involve three or more starting materials to form a product, where basically all or most of the atoms contribute to the newly formed product.[24,25] This process is simple, efficient and environment friendly with high level of atom economy and minimum synthetic steps avoiding the time-consuming process of isolation and purification of synthetic intermediates.[26,27] Recently multi-

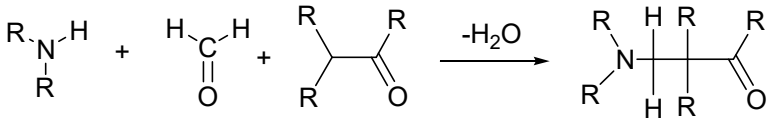
component reactions are gaining more attentions for the rapid construction of new chemically complex entities as well as for the facile synthesis of arrays of compounds in a combinatorial chemistry fashions.[28,29] Also, multi-component reactions have been extensively applied for the generation of large libraries of molecular diversity and complexity.[30]

The first multi-component reaction accepted traditionally is Strecker synthesis of α-amino acid using aldehyde, ammonia, and hydrocyanic acid as starting materials.[31]

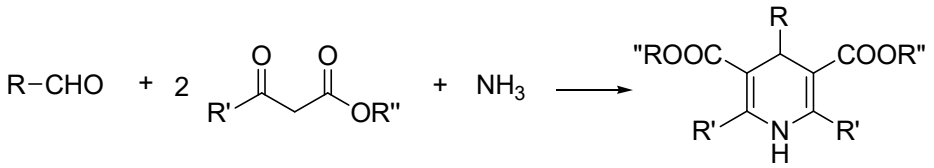


Strecker synthesis of α-amino acid

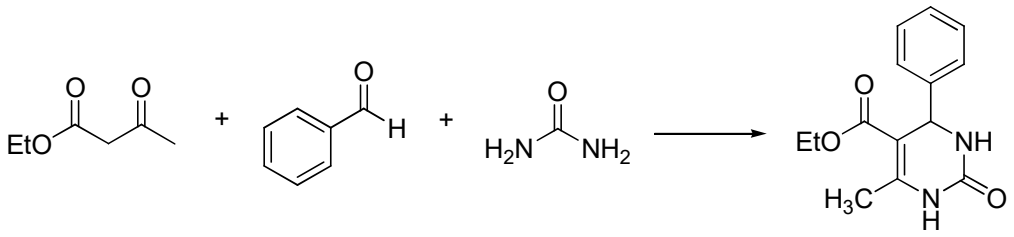
Some other important MCRs are Mannich reaction, Hantzsch pyridine synthesis, Biginelli reaction, Passerini reaction and Ugi reaction (Figure 6).



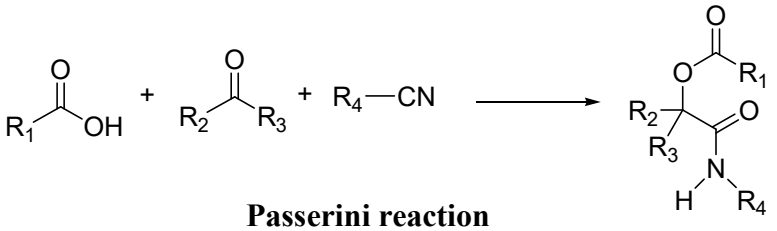
Mannich reaction



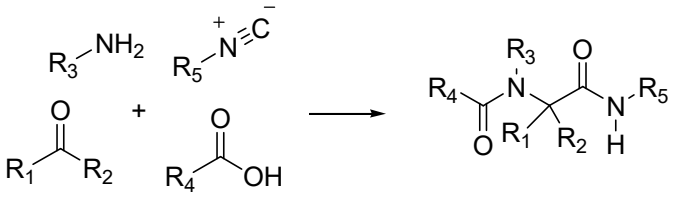
Hantzsch pyridine synthesis



Biginelli reaction



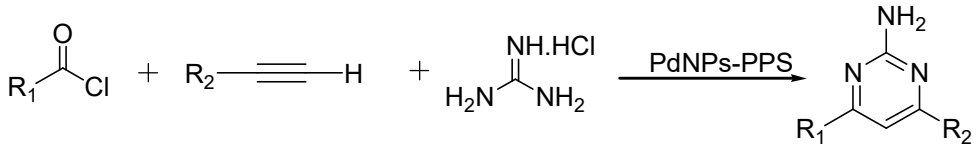
Passerini reaction



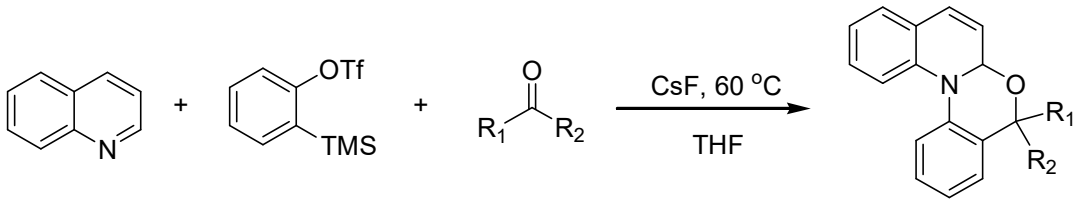
Ugi reaction

Figure 6 Examples of multi-component reaction

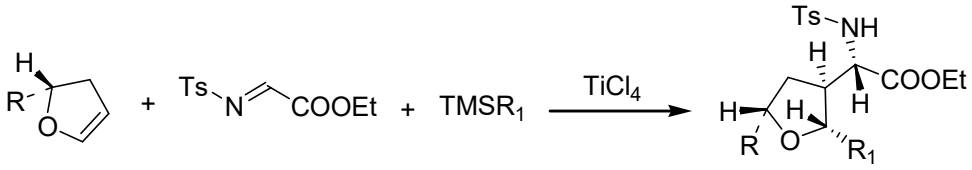
Multi-component reaction of copper-free acyl Sonogashira reaction between acyl chloride and terminal alkynes using palladium nanoparticles (PdNPs-PPS) as catalyst gives 2,4-disubstituted pyrimidines in high yield.[32]



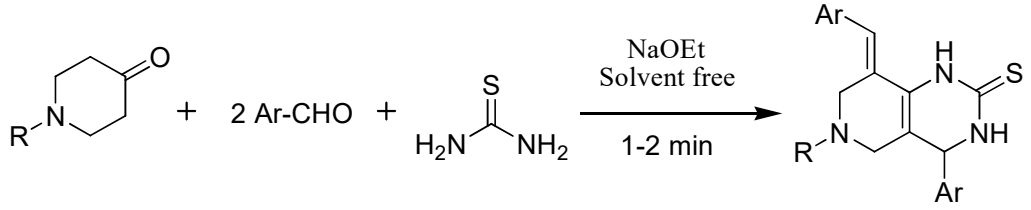
Benzo-annulated 1,3-oxazine derivatives can be obtained in good yield by a multi-component reaction of arynes with *N*-heteroaromatics and aldehydes/ketones.[33]



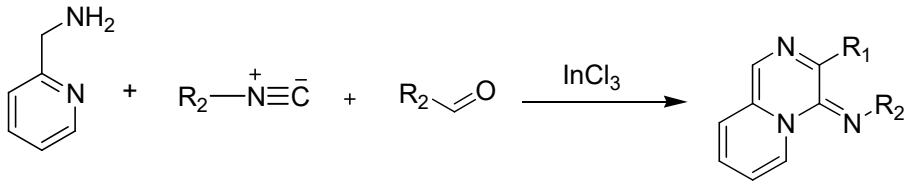
Ghosh and co-workers reported the functionalization of α-amino acids with multiple stereogenic centers in a multi-component reaction of *N*-tosyl imino ester, cyclic ether, and silane reagents using catalytic amount of $TiCl_4$.[34]



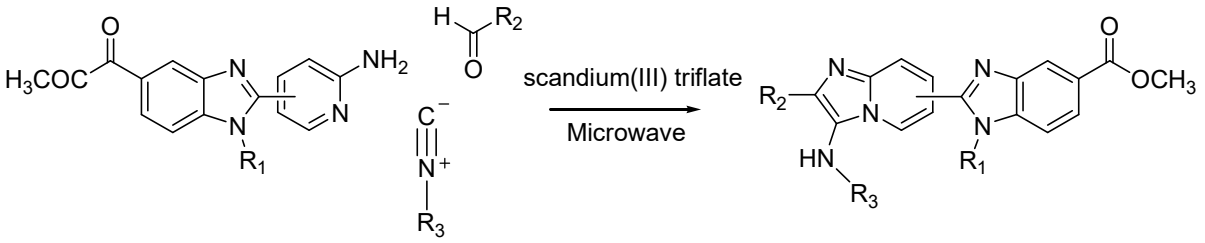
Pyridopyrimidine-2-thiones can be synthesised in good yield by a pseudo four-component domino reaction of *N*-substituted-4-piperidones, substituted aromatic aldehydes and thiourea using sodium ethoxide as base under solvent-free condition, by simply grinding for 1–2 min at ambient temperature.[35]



Carballares and co-workers developed a new reaction for the synthesis of 1*H*-imidazol-4-yl-pyridines via a one-pot, three component reaction of *o*-picolinamines, isocyanide and aldehydes.[36]



Benzimidazole-imidazo[1,2-*a*] pyridines was synthesized by Maiti and co-workers[37] by a one pot multi-componenet reaction of amino pyridines, aldehydes, and isonitriles catalyzed by scandium(III) triflate under solvent-free microwave irradiation.



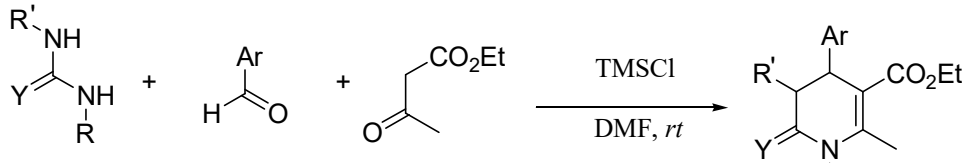
Microwave (MW) assisted organic synthesis -A route to Green Chemistry

Clean, fast and high yielding reactions avoiding waste are efficient for green and sustainable chemistry. Microwave heating particularly has proven advantageous in that regard.[38] Microwave activation as a non-conventional energy source has become a very popular and useful technology in organic synthesis. The effect of microwave in organic reaction depends upon various factors like reaction medium, reaction mechanism, selectivities.[39] Microwave radiation occurs in an area of transition between 30 GHz and 300 MHz corresponding to wavelengths of 1 cm to 1m in the electromagnetic spectrum. Although this energy is not sufficient to break chemical bonds but it facilitates chemical reactions tremendously through dielectric heating produced by the interaction of microwave energy and matter (reactant and solvent molecules in case of chemical reactions).[40] The acceleration of chemical reactions by microwave exposure results from material-wave interactions leading to the thermal and specific (non-thermal) effects. The effective application of microwave energy to perform chemical reaction was first established independently by the groups of Gedye[41] and Giguere[42] in 1986.

Being an effective tool for rapid organic synthesis, microwave energy has found vast application in different areas like organometallic chemistry, metal catalysis, coupling reactions, photochemistry, radical reactions, protection-deprotection reactions, cycloaddition reactions, heterocyclic chemistry, carbohydrate and peptide chemistry and many more. MW assisted heterocyclic chemistry is itself a broad area and since the major part of this thesis

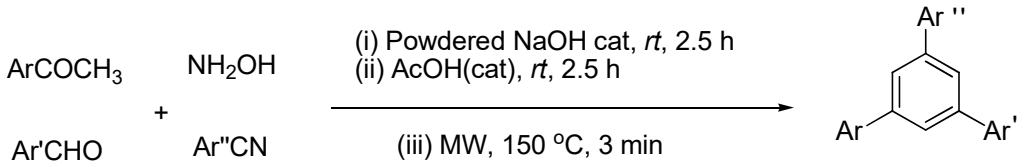
work deals with heterocyclic chemistry along with some microwave application, some examples of recent literature in MW organic synthesis were enlisted as follows:

The classical Biginelli reaction has been extended by the use of *N*-substituted ureas and thioureas. Accordingly, N^1-alkyl-, N^1-aryl-, and N^1,N^3-dialkyl-3,4-dihydropyrimidin-2(1*H*)-(thi)ones were readily prepared in excellent yields using chlorotrimethylsilane in *N,N*-dimethylformamide as promoter and water scavenger.[43]

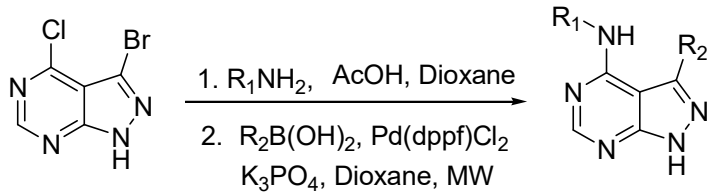


Y = O, S; R = alkyl, aryl, benzyl; R' = H, Me

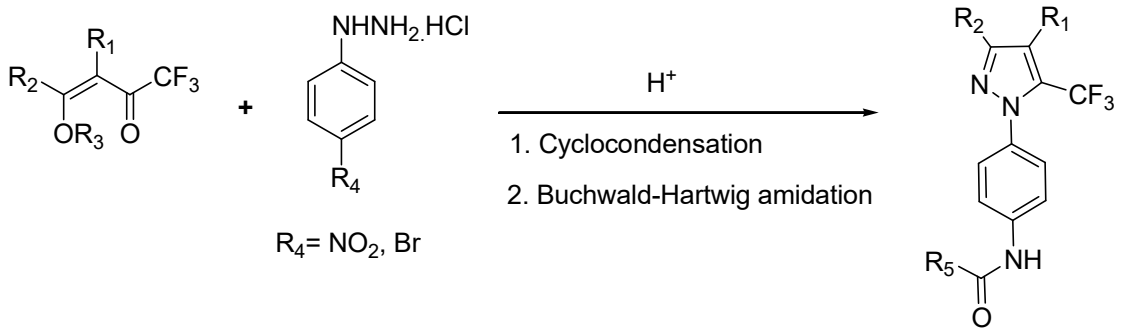
2,4,6–Triarylpyrimidines were obtained in a microwave assisted one pot four-component reaction of aryl ketone, aryl aldehyde, aryl nitrile and hydroxyl amine under solvent free conditions.[44]



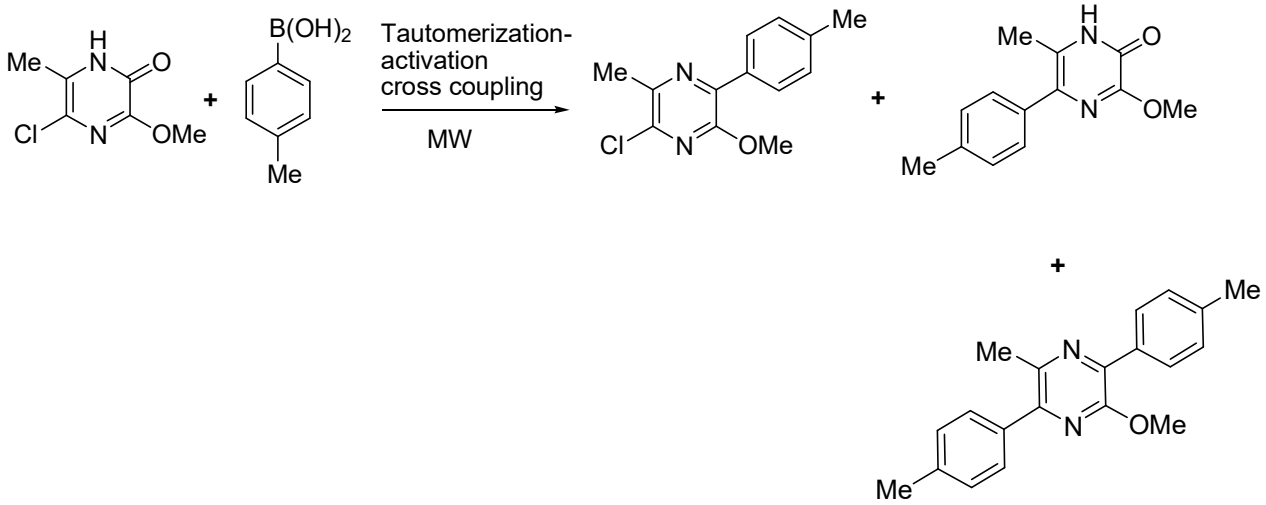
4,5-disubstituted pyrazolopyrimidines were synthesised by Wu and co-workers[45] in good yields by the reaction of C-4 chloro substituent with various anilines and amines, followed by a Suzuki coupling reaction with different boronic acids under microwave irradiation.



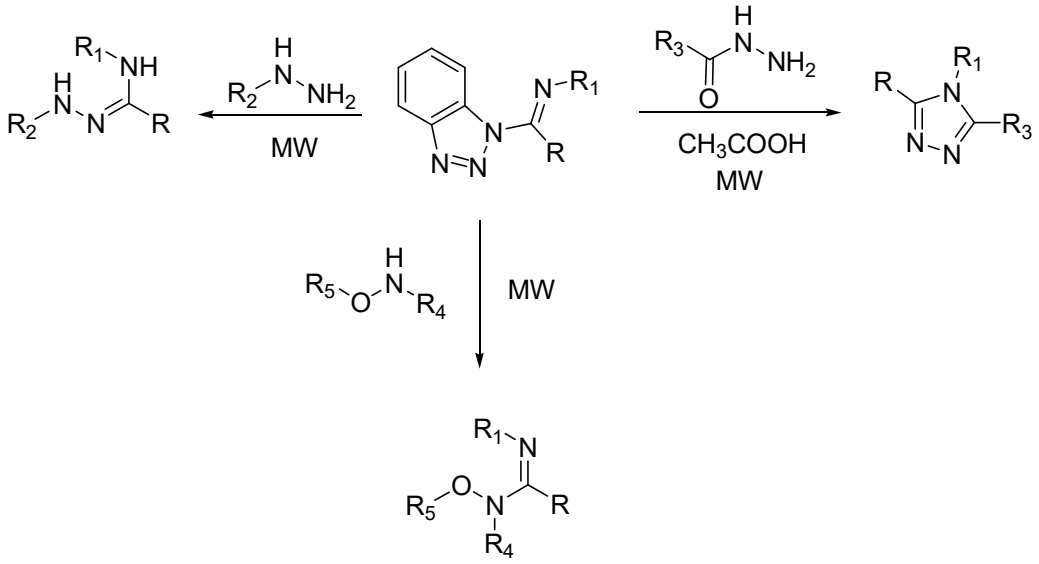
Obermayer and co-workers[46] reported a synthesis of 4-(pyrazol-1-yl)carboxanilides by condensation of 4-nitrophenylhydrazine with appropriate 1,3-dicarbonyl building blocks, followed by Pd-catalyzed Buchwald-Hartwig amidation with carboxylic acid amides.



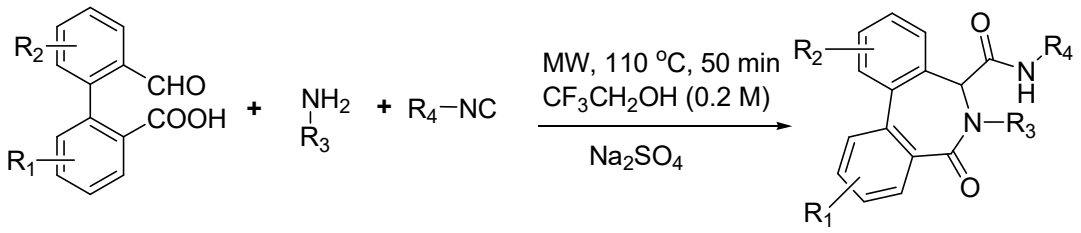
Mehta and co-workers[47] reported a palladium-catalyzed efficient C-C cross-coupling reaction of 2(1*H*)-pyrazinones under microwave irradiation.



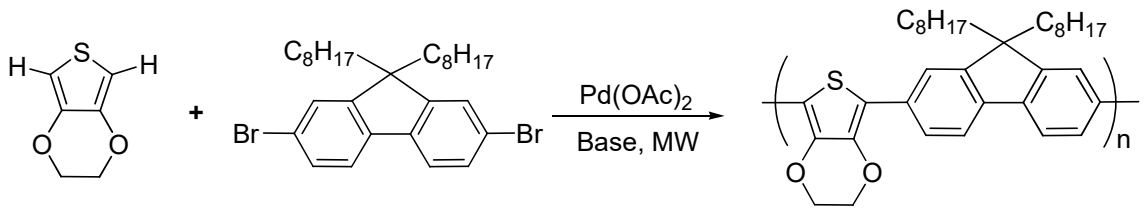
Starting from imidoylbenzotriazoles, a series of amidrazones and amidoximes were prepared treating with variety of hydrazine and amine under microwave irradiation.[48]



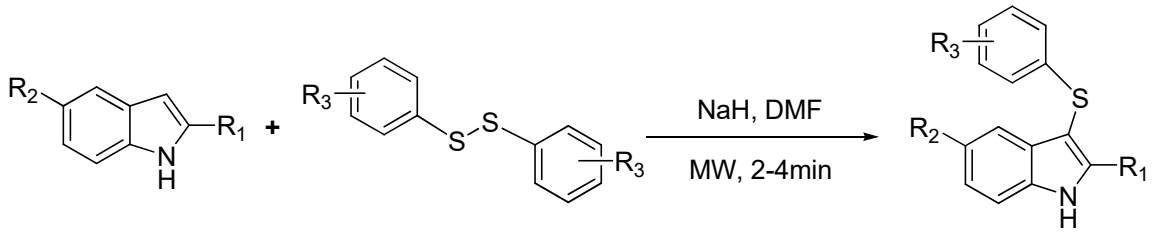
Dibenzo[c,e]azepinone can be synthesized diastereroselectively by the muticomponent reaction of 2'-formylbiphenyl-2-carboxylic acid derivatives, benzylamine, and isocyanide under microwave irradiation.[49]



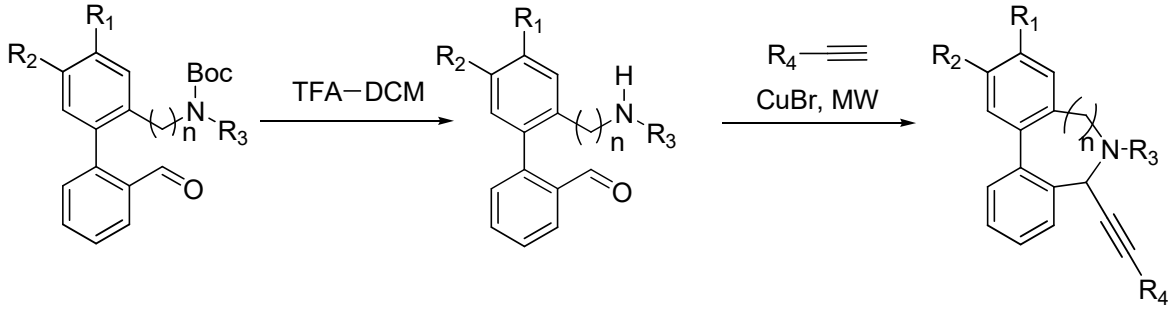
For the synthesis of π-conjugated polymers, Choi and co-workers[50] applied direct arylation of C−H bonds, by reacting 3,4-ethylenedioxythiophene with dibromofluorene using microwave as energy source. The reaction was efficiently catalyzed by $Pd(OAc)_2$ yielding corresponding polymer with an extremely high molecular weight up to 147000.



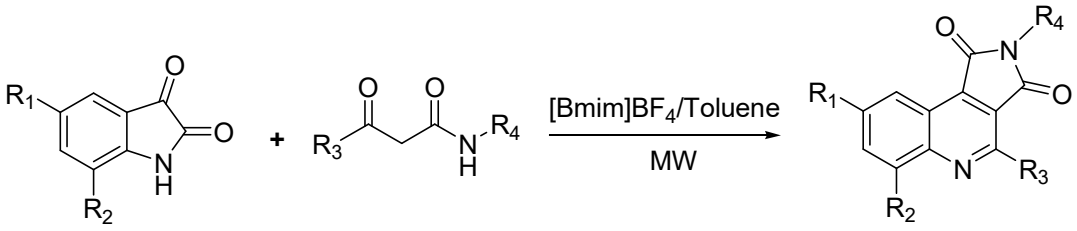
Arylthioindoles have been synthesized in excellent yield by Regina and co-workers[51] under venting-while-heating condition by reacting indoles with disulfides in the presence of sodium hydride in anhydrous *N*,*N*-dimethylformamide under microwave irradiation.



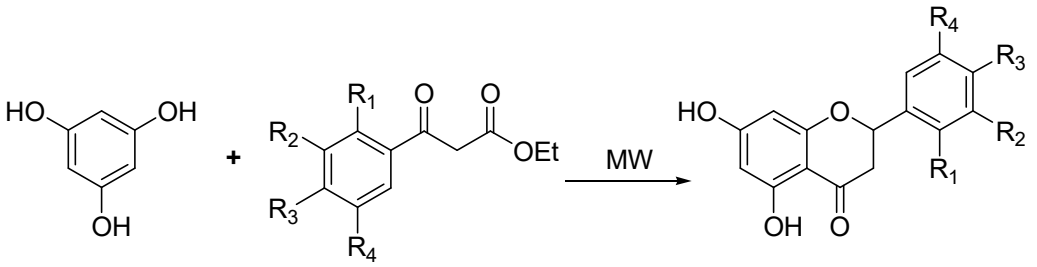
Bariwal and co-workers[52] developed a method for the synthesis of dibenzoazocines and dibenzoazepines via microwave-assisted copper-catalyzed intramolecular A^3-coupling reaction.



Synthesis of pyrrolo[3,4-*c*]quinoline-1,3-diones by a two-phase microwave-assisted cascade reaction of isatins and *β*-ketoamides in [Bmim]BF_4/toluene was reported by Xia and co-workers.[53]



Seijas[54] reported a reaction where phloroglucinol was treated with β-ketoesters under microwave irradiation. The reaction proceeds through cycloaddition of an α-oxo ketene intermediate followed by an uncatalyzed thermal Fries rearrangement to yield Flavones in good yield.



R_1, R_2, R_3, R_4 = H, OH, OMe, Cl, NO_2

Motivation and objectives of the present study

It is evident from the forgoing discussion that heterocyclic compounds, steroids and heterosteroids are the main constituents of many natural products and play a vital role in pharmaceutical chemistry. Among the heterocyclic compounds, nitrogen containing heterocycles such as pyridine, pyrimidine, pyrazole, imidazole oxazole are most common and have great importance because of their inherent biological activities. The potential of heterosteroids, in particular, as novel drugs and the challenge of their synthesis impelled several research groups to undertake studies in this field.

Accordingly, the overall goal of this research work can be described with the specific ***objectives*** as listed below:

- To explore some of the general mechanism to create and modify steroidal nucleus and related systems such as pyrazolopyrimidine, pyrimidine and pyridine derivatives using novel synthetic strategies. The work also includes hetercyclic substitution in the steroidal core and their pharmacology studies.
- Characterizations of the synthesized products using single crystal X-ray diffraction, Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry techniques.

Organization of the thesis

The contents of the thesis have been compiled into four chapters.

Chapter 1 Part-A describes the preparation of steroidal pyrazolo[1,5-*a*]pyrimidine derivatives by a one-pot reaction of steroidal ketones, aromatic aldehydes and 3-amino-1*H*-pyrazoles in the presence of potassium *tert*-butoxide under reflux condition in ethanol.

In ***Chapter 1 Part-B*** efficient method for the synthesis of steroidal and non-steroidal 7-substituted pyrazolo[1,5- *a*]pyrimidines from 1,5 dicarbonyl compound has been described.

Chapter 2 is related to the synthesis of some aryl disubstituted pyrimidine derivatives fused with steroidal and non-steroidal moiety via a three-component reaction of ketone, aldehydes and amidine derivatives under thermal conditions.

Chapter 3 Part-A deals with a new solvent free green strategy for the steroidal/nonsteroidal epoxide ring opening reaction by imidazoles and benzimidazole for the synthesis of hydroxy-(1*H*-imidazol-yl)/hydroxy-(1*H*-benzimidazol-yl) steroids and 2-(1*H*-imidazol-1-yl)/2-(1*H*-benzimidazol-1-yl)cyclohexanols under microwave irradiation.

Chapter 3 Part-B describes the evolution of *in vitro* cytotoxic activities of some Michael adducts of D-ring steroids against cervical HeLa cancer cell line, prostate DU 205 cancer cell line and breast cancer MCF-7 cell line in comparison to the drug doxorubicin.

Chapter 4 Part-A reports the synthesis of D-ring annelated pyridosteroids from steroidal 1,5-dicarbonyl compounds using ammonium acetate as an efficient and eco-friendly source of ammonia.

Chapter 4 Part-B is related to a simple and facile synthesis of a series of steroidal and non-steroidal pyrido[2,3-*d*]pyrimidine derivatives by the reaction of 6-amino-*N*,*N*-dimethyluracil and *β*-halo-*α*,*β*-unsaturated aldehydes using palladium acetate as catalyst under microwave irradiation.

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Chapter 1

Part-A

A facile synthesis of steroidal A- and D-ring fused pyrazolo[1,5-a]pyrimidines by a base induced three-component reaction

1A.1 Introduction

Pyrazolo-pyrimidine derivatives are well known as an important class of heterocyclic compounds because of their promising biological activities. The nitrogen rich aza heterocyclic system is found as purine analogues and has useful properties as antimetabolites in purine biochemical reactions.[1] Several compounds of pyrazolo[1,5-*a*]pyrimidine ring system show antitrypanosomal and antischistosomal activities,[2] many of them are used as COX-2 selective inhibitors, CRF1 antagonists, HMG-CoA reductase inhibitors, histamine-3 receptor ligands and antianxiety agents.[3] Some derivatives display potential activity against respiratory diseases[4] and some can be used as scaffolds in the dyestuff industry.[5]

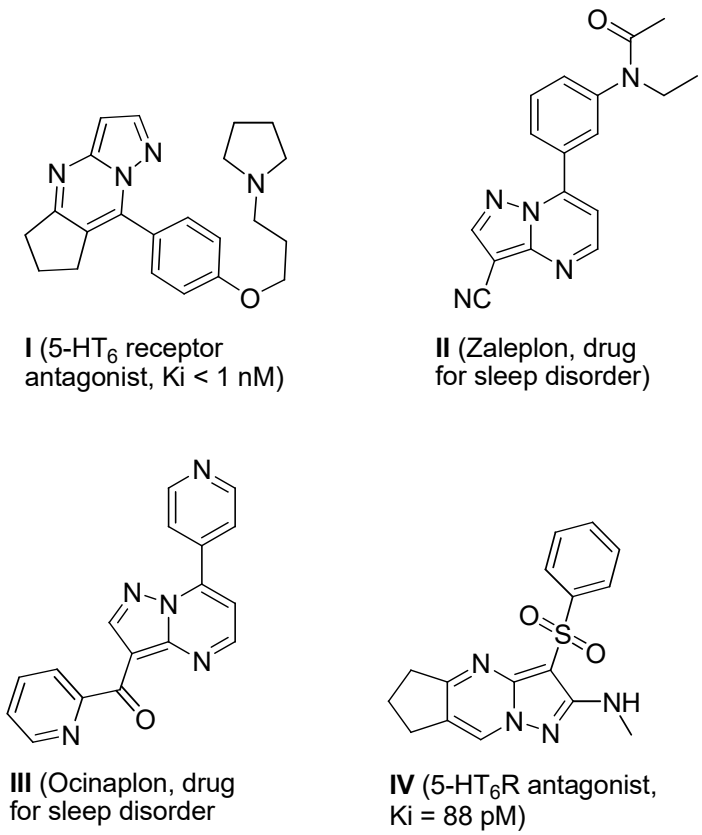
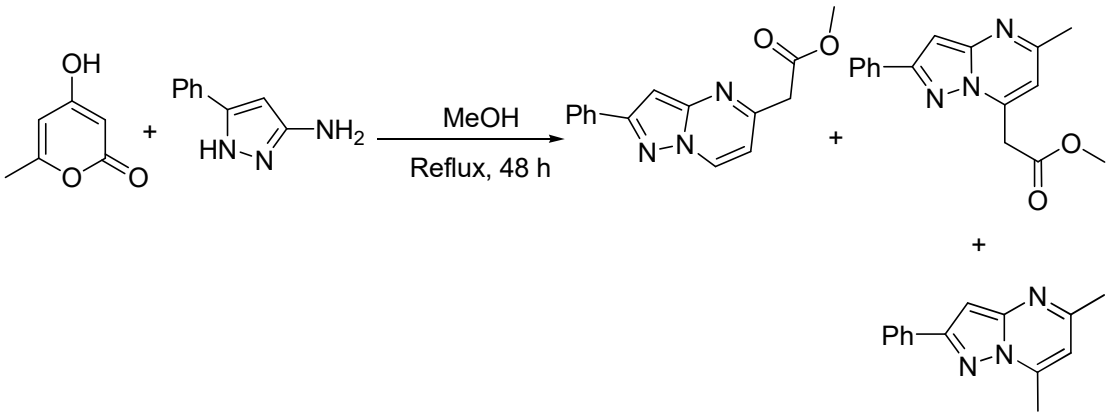


Figure 1.1 Examples of bioactive pyrazolo[1,5-*a*]pyrimidines

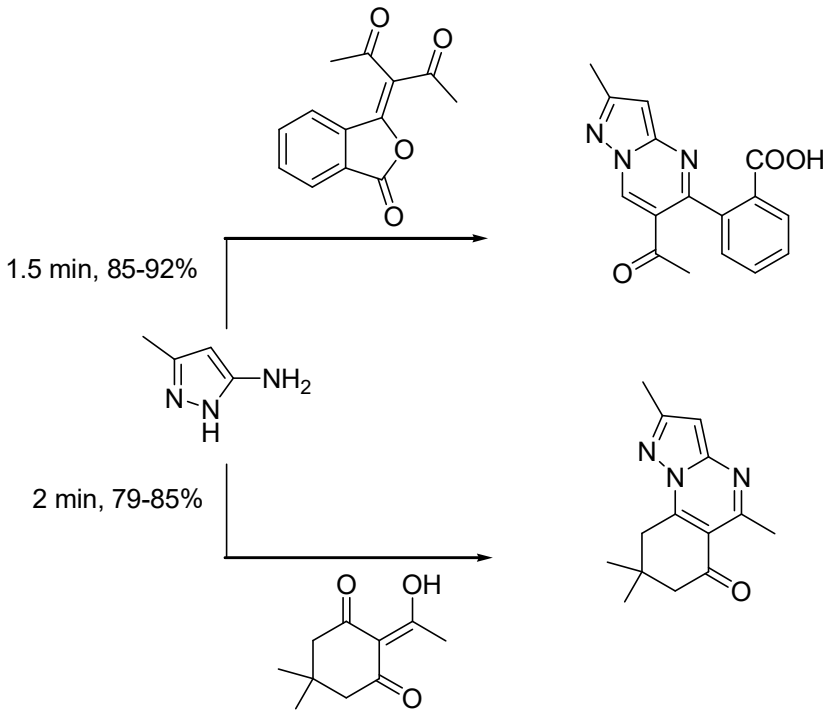
Okun and colleagues have reported the synthesis of sulfonylsubstituted cyclopentapyrazolo[1,5-*a*]pyrimidines **I** (Figure 1.1) and their evaluation as 5-HT_6 receptor antagonists. They found that these compounds are highly selective antagonists with sub-nanomolar affinities (Ki < 1 nM).[6] Among the pyrazolo[1,5-*a*]pyrimidine derivatives, recently, 7-substituted pyrazolo[1,5-*a*]pyrimidines have turned out to be very promising molecules due to their interesting biological activities. For example, 7-substituted pyrazolo[1,5-*a*]pyrimidine derivatives **II** and **III** are known drugs for the treatment of sleep disorder[7] and cyclopentane ring fused pyrazolo[1,5-*a*]pyrimidine derivative **IV** has the highest affinity (Ki = 88 pM) to the 5-HT_6 receptor[8].

Thus, synthesis of pyrazolo-pyrimidine nucleus acquired a unique position in the present scenario of drug discovery and several reports of pyrazolopyrimidine library syntheses have also appeared.

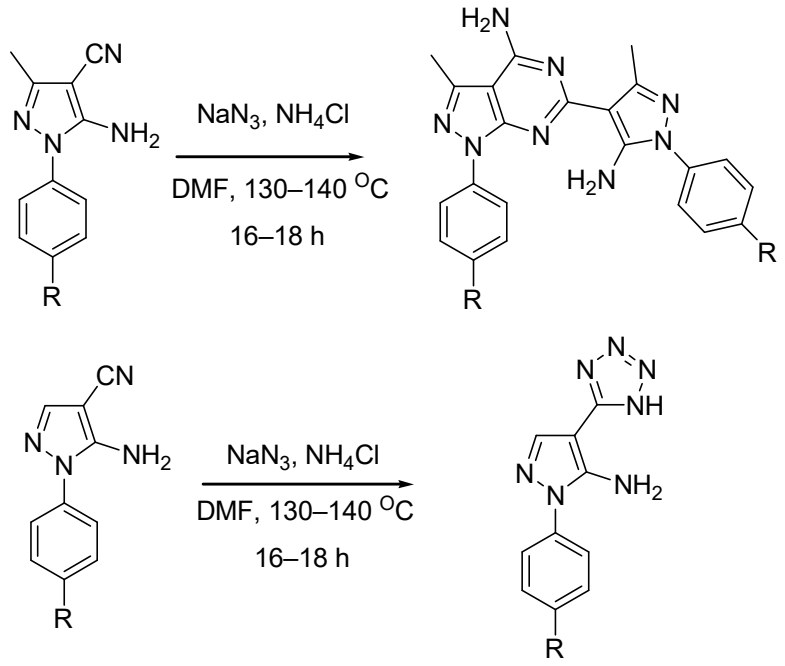
Bassoude and co-workers described the formation of pyrazolo-pyrimidine derivatives namely 5,7-dimethyl-2-arylpyrazolo[1,5-*a*]pyrimidines, 5-alkoxycarbonylmethyl-7-methyl-2-arylpyrazolo[1,5-*a*]pyrimidines and their isomeric 7-alkoxycarbonylmethyl-5-methyl-2-arylpyrazolo[1,5-*a*]pyrimidines by condensation of 5(3)-amino-3(5)-arylpyrazoles with 4-hydroxy-6-methylpyran-2-one in good to excellent yield.[9]



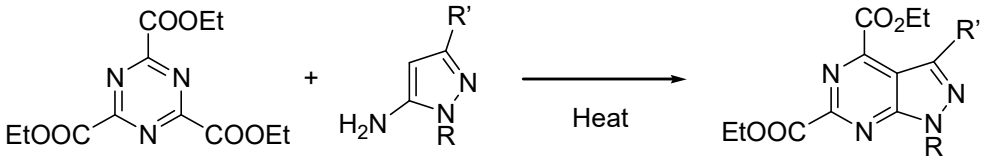
Portilla and co-workers reported the regioselective formation of a series pyrazolo[1,5-*a*]pyrimidines using alkoxymethylene-β-dicarbonyl compounds and β-triketones as starting materials. They observed that the nature of the β-dicarbonyl compounds is crucial in controlling the regiochemistry, in order to permit the formation of the product.[10]



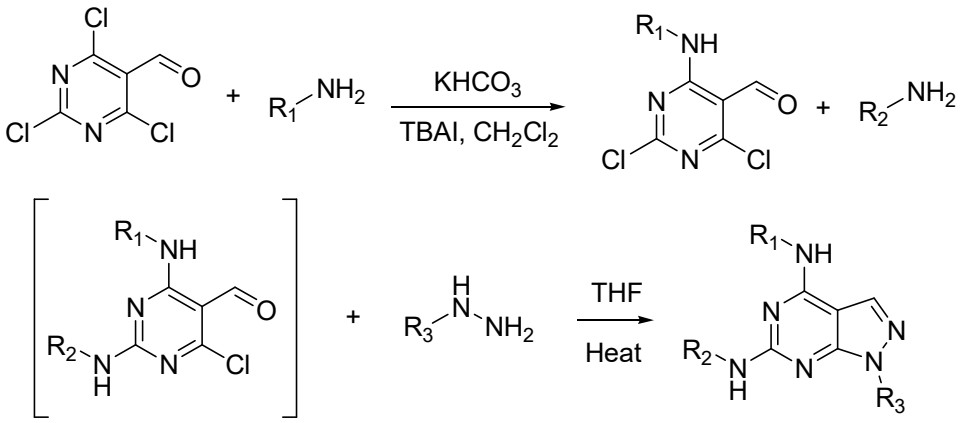
A method was developed by Faria and co-workers where pyrazolo[1,5-*a*]pyrimidines were formed unexpectedly while attempting to obtain 5-substituted tetrazoles from carbonitriles. Reaction of 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles with sodium azide in DMF yields 5-substituted tetrazole. Treatment of 5-amino-1-aryl-3-methyl-1*H*-pyrazole-4-carbonitriles under same reaction condition gives pyrazole derivative leading to the conclusion that the presence of the methyl group at C-3 position in the pyrazole ring affects the reaction.[11]



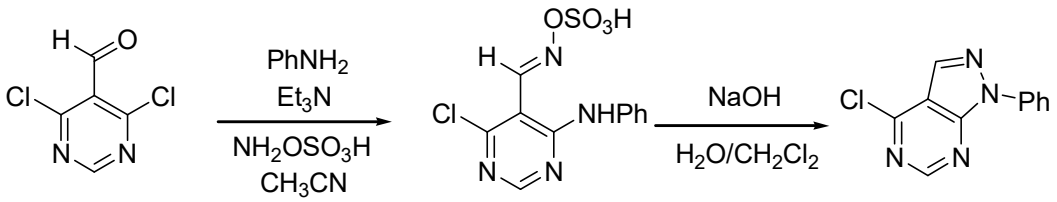
Pyrazolopyrimidines were synthesized in one step by [4 + 2] cycloaddition reaction of triazine with various 5-aminopyrazoles.[12] It was proved that 5-aminopyrazoles, as cyclic amidines, are sufficiently reactive dienophiles which could participate in efficient [4 + 2] cycloaddition reactions with triazine under mild thermal conditions.



Slavish and co-workers[13] described a rapid and productive process for the synthesis of pyrazolo[3,4-*d*]pyrimidines from carbaldehydes wherein they reported the formation of the product by amino displacement of 2,4,6-trichloropyrimidin-5-carbaldehyde followed by reaction with hydrazine.



In a recent report, the cyclization reaction of the dichloropyrimidine oxime derived from hydroxylamine-O-sulfonic acid forming N-N bond resulted the formation of *N*-aryl[3,4-*d*]pyrazolopyrimidines in good yields under mild reaction conditions.[14]

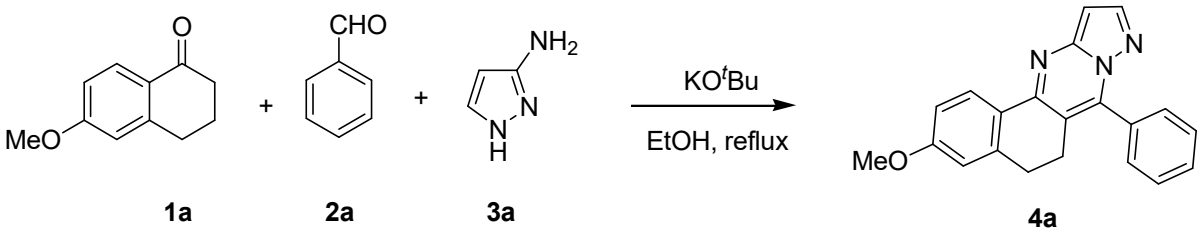


It is noteworthy that pyrazolopyrimidines constitute an interesting aza-heterocyclic class of compounds and improved methodologies for pyrazolopyrimidine ring formation are always important as they provide improved procedures to replace existing syntheses. The present study describes the synthesis of a new one-pot three component approach for the synthesis of steroid and nonsteroid fused 7-aryl substituted pyrazolo[1,5-*a*]pyrimidine derivatives under thermal conditions. For this purpose, steroidal and non steroidal ketones have been employed as readily available substrates.

1A.2 Results and discussions

Preparation of non-steroidal pyrazolo[1,5-*a*]pyrimidine

The synthetic strategy was directed towards development of a suitable method for the synthesis of pyrazolo[1,5-*a*]pyrimidine. Initially, ketone **1a**, benzaldehyde (**2a**) and 3-amino-1*H*-pyrazole (**3a**) were selected as the model substrates for the multi-component synthesis of compound **4a** (Scheme 1A.1).



1a **2a** **3a** **4a**

Scheme 1A.1

Initially, refluxing a mixture of ketone **1a** and benzaldehyde (**2a**) in anhydrous DMF in the presence of base NaOMe (two equivalent) for one hour followed by addition of 3-amino-1*H*-pyrazole (**3a**) and refluxing the reaction mixture for another two hours furnished pyrazolo[1,5-*a*]pyrimidine **4a** in 26% yield (entry 1, Table 1A.1). It was observed that increasing duration of the reaction did not increase the yield of product **4a** (entry 2, Table 1A.1). After having the product **4a,** it was identified from ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR of compound **4a** exhibited two characteristic aromatic doublet signals at δ 6.68 (J = 2.2 Hz, 1H) and at δ 8.01 (J = 2.2 Hz, 1H) for the pyrazole ring protons. The ^{1}H NMR also showed multiplet signal at δ 7.52-7.63 (5H) for the protons of phenyl ring substituted in pyrazolo[1,5-*a*]pyrimidine moiety. The phenyl part of the tetralone moiety showed two doublets at δ 6.76 (J = 2.2 Hz, 1H), δ 8.39 (J = 8.7 Hz, 1H) and a double doublet at δ 6.96 (J = 8.7 Hz & 2.4 Hz, 1H). The ^{13}C NMR spectrum of **4a** showed signals for eighteen aromatic carbons at δ 96.1, 112.8, 113.3, 114.9, 126.4, 128.1, 128.8 (2C), 129.6

(2C), 130.0, 130.4, 141.4, 143.0, 144.3, 148.4, 153.1, 161.6. The EI mass spectra of compound **4a** exhibited molecular ion peak at m/z = 327.

Apart from the usual spectral analysis, the structures of compounds **4a** was confirmed by single crystal X-ray diffraction study (Figure 1A.1).

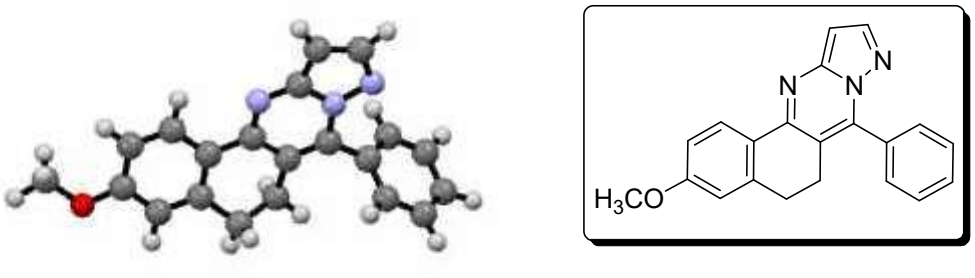
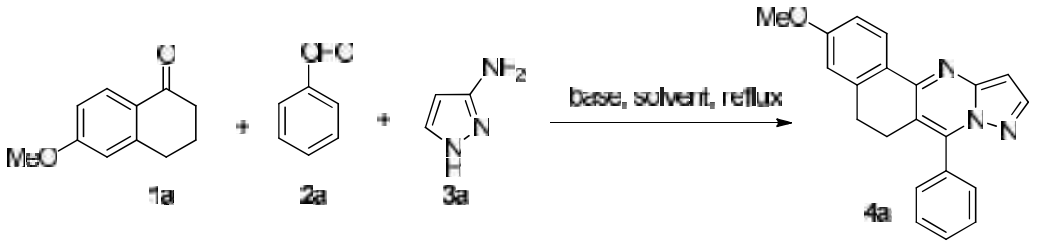


Figure 1A.1 X-ray crystallographic Ortep diagram of compound **4a**.

The model reaction was investigated with some other bases and solvents to determine the ideal base and solvent for this multi-component reaction (Table 1A.1). Bases such as KOMe, KOH and NaH were tried for the above reaction which also could not increase the yield of the compound **4a** to substantial amounts (Entry 3-5, Table 1A.1). When NaO^{t}Bu and KO^{t}Bu were used in the above reaction, it was noticed that yield of desired product **4a** increased to 57% and 59%, respectively in DMF (Entry 6-7, Table 1A.1). Further investigation on the solvent, it was found that ethanol was the most effective among the tested solvents and the yield of **4a** increased to 79% (Entry 9, Table 1A.1), while there was sharp decrease in yield of **4a** to 50% (Entry 8, Table 1A.1) when dimethylsulfoxide was used. Increase the duration of the above highest yielding reaction could not provide more yield of product **4a** (Entry 10, Table 1A.1).

Table 1A.1 Optimization of reaction conditions for the synthesis of pyrazolo[1,5-*a*]pyrimidine **4a**

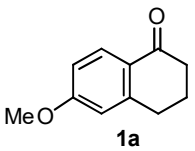
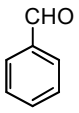
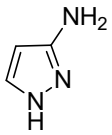
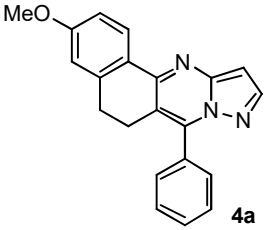
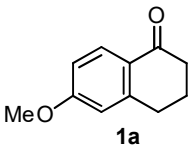
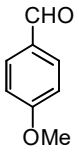
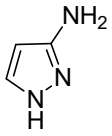
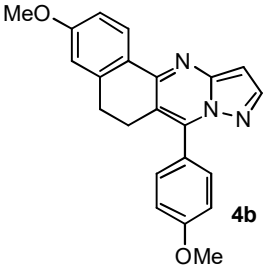
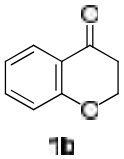
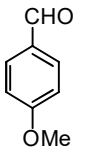
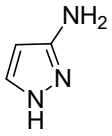
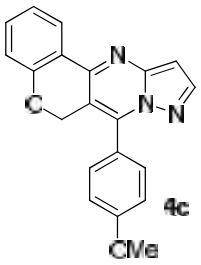
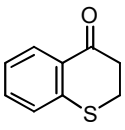
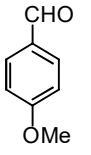
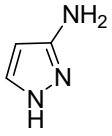
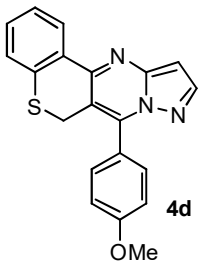


Entry	Base[a]	Solvent	Time (h)	Yield (%)[b]
1	NaOMe	DMF	3	26
2	NaOMe	DMF	12	27
3	KOMe	DMF	3	29
4	KOH	DMF	3	19
5	NaH	DMF	3	32
6	NaO^{t}Bu	DMF	3	57
7	KO^{t}Bu	DMF	3	59
8	KO^{t}Bu	DMSO	3	50
9	KO^{t}Bu	EtOH	3	79

[a] Two equivalents of the base were used. [b] Yield of the isolated product.

The utility of the reaction was studied with various non-steroidal ketone under the optimized reaction condition. The results are summarized in Table 1A.2.

Table 1A.2 Synthesis of nonsteroidal pyrazolo[1,5-*a*]pyrimidines

Entry	Ketone	Alde-hyde	Pyrazole	Product	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	 **4a**	79
2	 **1a**	 **2b**	 **3a**	 **4b**	74
3	 **1b**	 **2b**	 **3a**	 **4c**	67
4	 **1c**	 **2b**	 **3a**	 **4d**	65

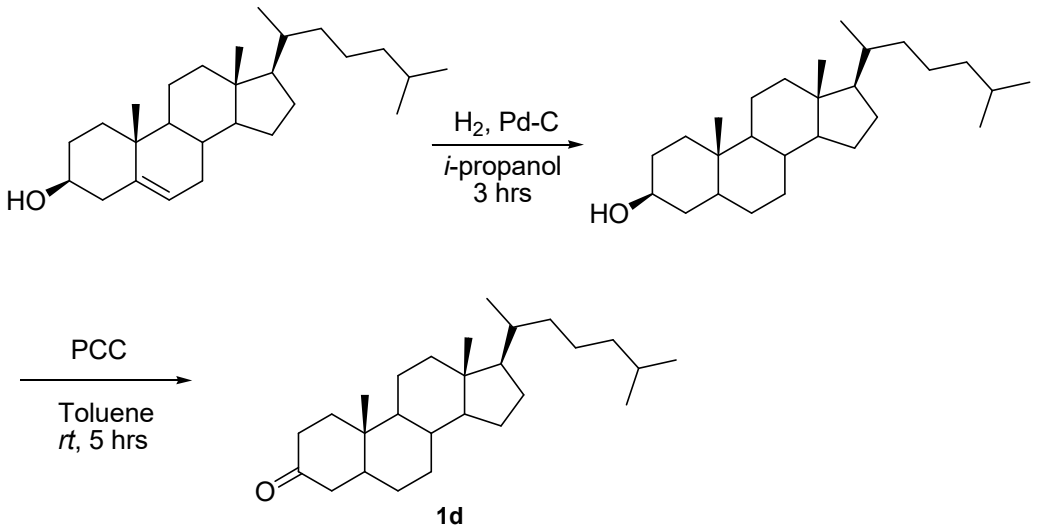
[a]Yield of the isolated product.

Reaction of ketone **1a** with aromatic aldehyde **2b** and 3-amino-1*H*-pyrazole (**3a**) afforded pyrazolo[1,5-*a*]pyrimidine **4b** in 74% yield (entry 2, Table 1A.2). Similarly, the reaction of ketone **1b** and **1c** with aromatic aldehyde **2b** and 3-amino-1*H*-pyrazoles (**3a)** under the above reaction condition afforded nonsteroidal pyrazolo[1,5-*a*]pyrimidines **4c-d** in 65-67% yield.

Preparation of steroidal pyrazolo[1,5-*a*]pyrimidine from steroidal A- and D- ring ketones:

The one pot reaction was performed with steroidal A- and D-ring ketones to have steroidal pyrazolo[1,5-*a*]pyrimidines. For this purpose, A- and D-ring ketones were tretated with variety of aromatic aldehydes and 3-amino-1*H*-pyrazoles under thermal conditions.

To begin with, readily available cholesterol was reduced to 5,6-dihydrocholesterol by hydrogenation (H_2, Pd-C) at 50 psi using *iso*-propanol as solvent. The 5,6-dihydrocholesterol was then stirred with PCC in toluene for 5 hours to have Cholestan-3-one (**1d**) (Scheme 1A.2).



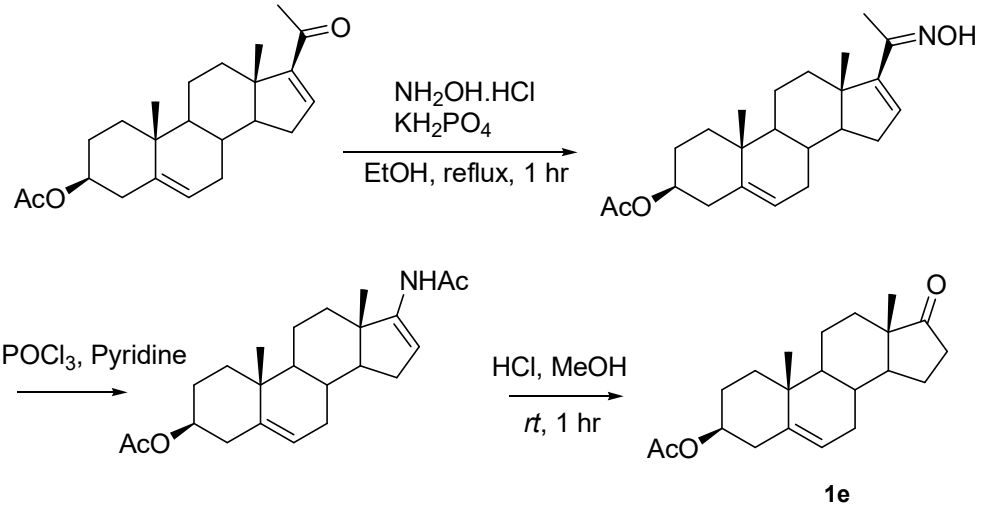
Scheme 1A.2

Under the optimized reaction condition, the reaction of **1d** was performed with tolualdehyde **2b** and 3-amino-1*H*-pyrazoles (**3a**). The product **4e** was obtained as yellow solid and was identified from ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR of compound **4e** exhibited a characteristic aromatic doublet signals at δ 6.54 (d, J = 1.2 Hz, 1H) and a singlet signal at 7.97 (s, 1H) for the pyrazole ring protons. The singlet signal at δ 3.89

(s, 3H) is because of the methyl protons. The ^{13}C NMR spectrum of **4e** showed signals for twelve aromatic carbons at δ 94.7, 114.4 (2C), 115.3, 122.4, 130.8 (2C), 144.2, 144.5, 144.7, 159.1, 160.5. The ESI mass spectra of compound **4e** exhibited $[M+1]^+$ peak at m/z = 568.

Again the reaction of **1d** was extended to different aromatic aldehydes **2b-c** and 3-amino-1*H*-pyrazoles **3a**-**f** (Table 1A.3). In all the cases steroidal A-ring fused pyrazolo[1,5-*a*]pyrimidines **4e-k** were obtained in good yields (72-76%).

In addition, the reaction was performed with steroidal D-ring ketone (**1e**) also. 3-*β*-acetoxy-androst-5-en-17-one (**1e**) was prepared from commercially available 16-dehydropregnenolone-3*β*-acetate (16-DPA) as shown in Scheme 1A.3. Oximation of 16-DPA followed by Beckmann rearrangement resulted 3*β*-acetoxy-17-acetamido-androst-5,16-diene. Acid hydrolysis of this 3*β*-acetoxy-17-acetamido-androst-5,16-diene with hydrochloric acid and methanol yielded 3-*β*-acetoxy-androst-5-en-17-one (**1e**) as white solid.

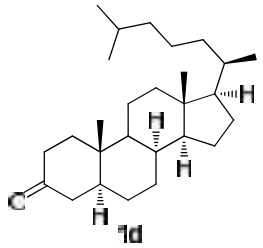
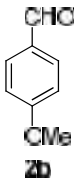
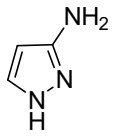
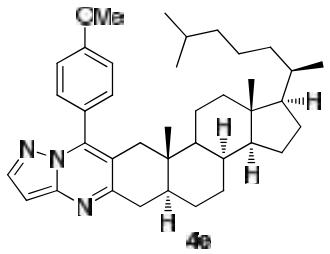
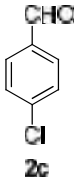
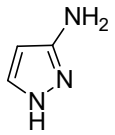
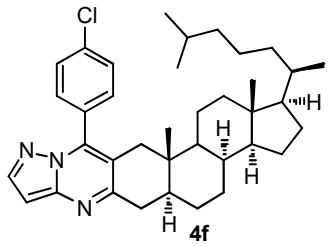
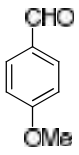
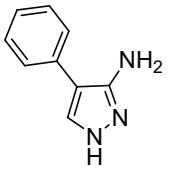
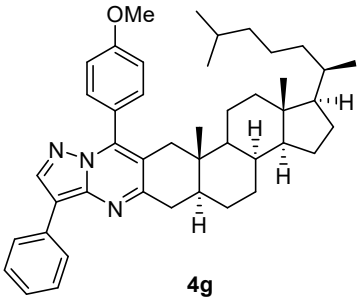
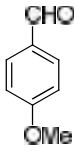
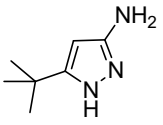
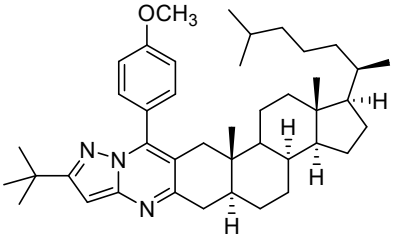
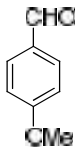
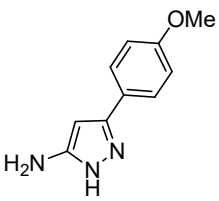
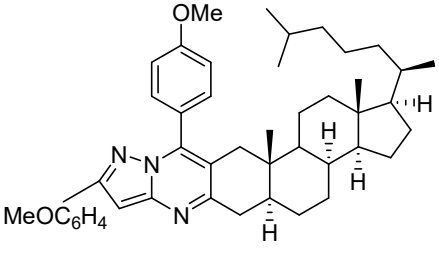


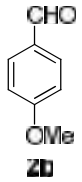
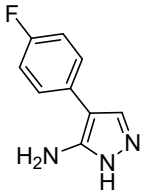
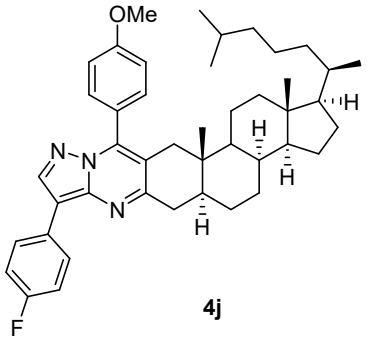
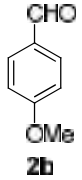
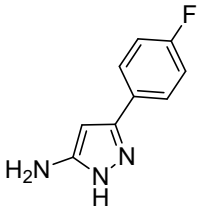
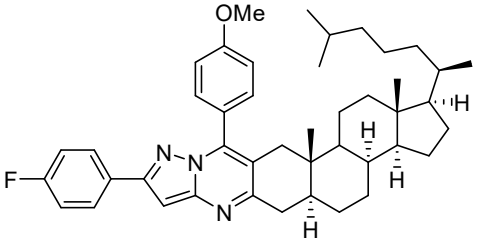
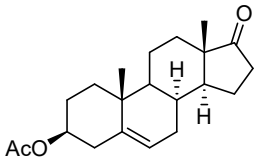
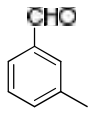
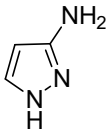
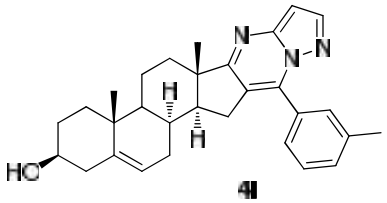
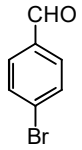
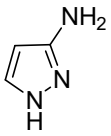
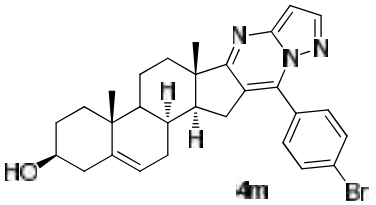
Scheme 1A.3

The base induced reaction of steroidal ketone **1e** was performed with aldehydes **2d-e** and 3-amino-1*H*-pyrazole (**3a**). Accordingly, D-ring fused steroidal pyrazolo[1,5-

a]pyrimidines **4l-m** were obtained in good yield (70-75%). The results are summarized in Table 1A.3.

Table 1A.3 Synthesis of steroidal pyrazolo[1,5-*a*]pyrimidines

Entry	Ketone	Alde-hyde	Pyrazole	Product	Yield (%)[a]
1	 **1d**	 **2b**	 **3a**	 **4e**	76
2	**1d**	 **2c**	 **3a**	 **4f**	75
3	**1d**	 **2b**	 **3b**	 **4g**	75
4	**1d**	 **2b**	 **3c**	 **4h**	72
5	**1d**	 **2b**	 **3d**	 **4i**	74

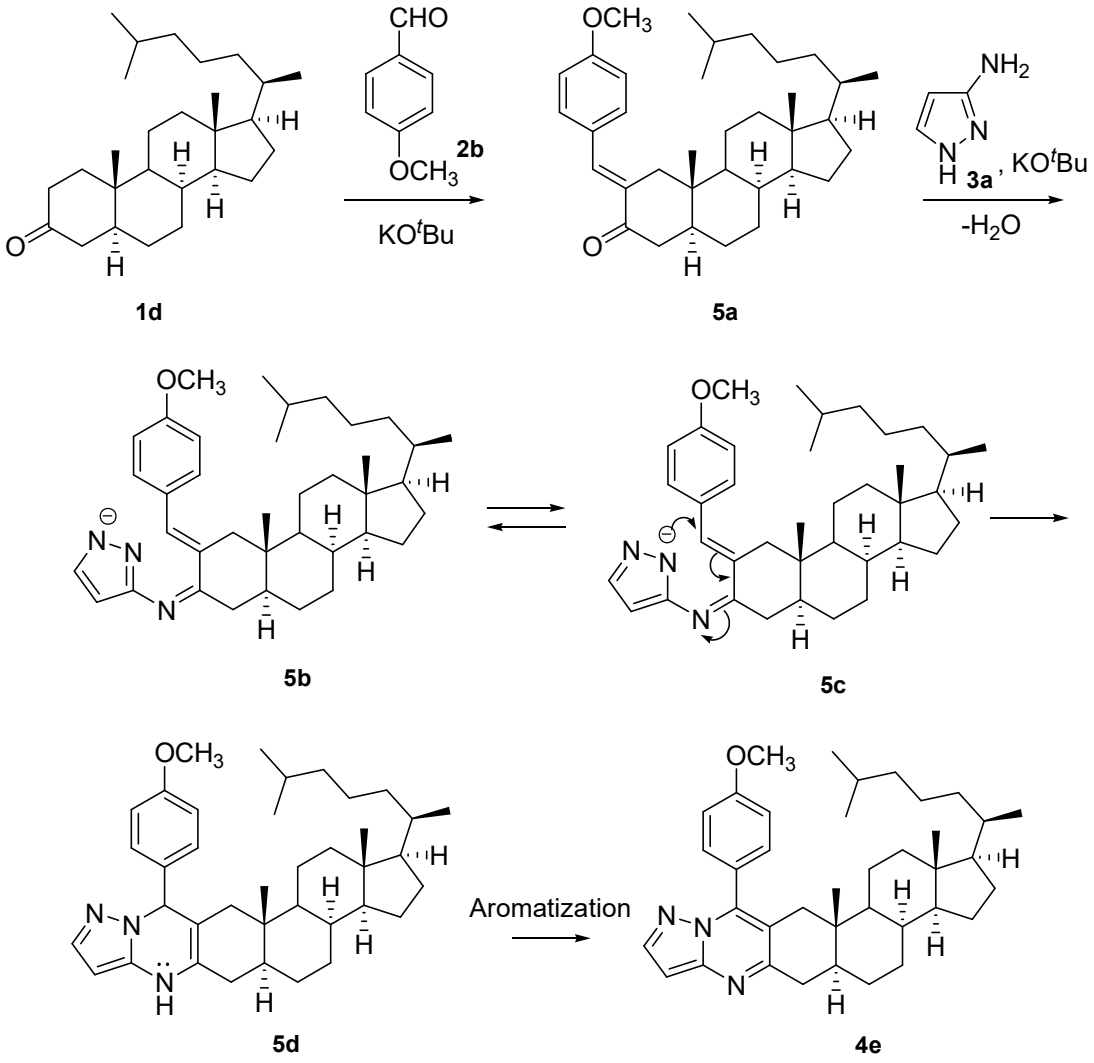
6	**1d**	 **2b**	 **3e**	 **4j**	72
7	**1d**	 **2b**	 **3f**	 **4k**	73
8	 **1e**	 **2d**	 **3a**	 **4l**	70
9	**1e**	 **2e**	 **3a**	 **4m**	75

[a]Yield of the isolated product.

It was observed that both electron-releasing group and electron-withdrawing group in the aromatic aldehydes as well as substituents in the 3-amino-1*H*-pyrazole and 5-amino-1*H*-pyrazole rings have no effect on the yield of pyrazolo[1,5-*a*]pyrimidines in this one pot reaction.

A probable mechanism for the formation of compound **4e** is shown in Scheme 1A.4. First, condensation of ketone **1d** with aldehyde **2b** in presence of base affords 2-benzylidene ketone **5a**. Then **5a** reacts with 3-amino-1*H*-pyrazole (**3a)** to afford its corresponding imine which on deprotonation in presence of base potassium *tert*-butoxide generates the pyrazolide

anion **5b**. Intramolecular aza-Michael addition of pyrazolide anion **5c** (tautomer of **5b**) followed by aromatization furnishes compound **4e**.



Scheme 1A.4 Proposed mechanism for the formation of steroidal pyrazolo[1,5-*a*]pyrimidine **4e**

1A.3 Conclusion

In summary, a new one pot reaction for the synthesis of biologically important steroidal A-, D- ring fused pyrazolo[1,5-*a*]pyrimidines and nonsteroidal pyrazolo[1,5-*a*]pyrimidines is studied in part-A of this chapter. A wide variety of steroidal/nonsteroidal

cyclic ketones, aromatic aldehydes and 3-amino-1*H*-pyrazoles/5-amino-1*H*-pyrazoles undergo this highly regioselective reaction to give good yields of pyrazolo[1,5-*a*]pyrimidines derivatives.

1A.4 Experimental

General experimental Procedure

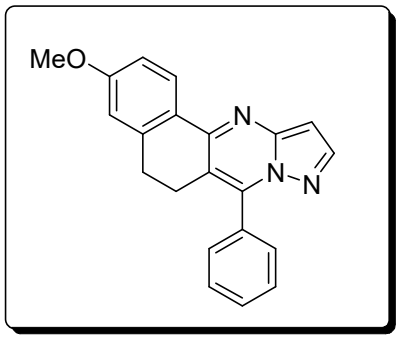
Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on Elmer FT-IR-2000 spectrometer on a thin film using chloroform. NMR spectra were recorded on Avance DPX 300 MHz FT-NMR spectrometer or Bruker Avance III 500 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Trace DSQ GCMS instrument or Bruker ESQUIRE 3000 LCMS instrument. Single Crystal XRD analysis was done on a Bruker Nonius SMART CCD diffractometer equipped with a graphite monochromator. All the commercially available reagents were used as received. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Merck). Column chromatography was performed on silica gel (100-200 mesh, Merck Chemicals).

General procedure for the synthesis of pyrazolo[1,5-*a*]pyrimidine 4

A stirring solution of ketone (**1**, 1.0 mmol), aldehyde (**2**, 1.0 mmol) and KO^{t}Bu (2.1 mmol) in anhydrous ethanol (5 mL) was refluxed for an hour. Then aminopyrazole (**3**, 1.0 mmol) was added to the reaction mixture and the reaction mixture was refluxed for another two hours. The residue obtained after removal of the solvent was extracted with ethyl acetate, washed with water, brine and dried over anhydrous sodium sulphate. The crude product obtained after removal of the solvent was purified by silica gel column chromatography using ethyl acetate/hexane as the eluent to obtain pure product **4**.

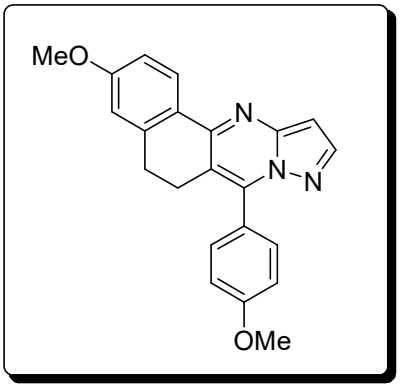
Characterization data for pyrazolo[1,5-*a*]pyrimidine

3-Methoxy-6-phenyl-5,6-dihydrobenzo[*h*]pyrazolo[5,1-*b*]quinazoline (4a)



Yellow solid, Yield 79%; m.p. 93-95 °C; IR ($CHCl_3$, cm^{-1}): 2938, 2836, 1594, 1540, 1489, 1377, 1272, 1244, 1165, 696; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.78-2.90 (m, 4H), 3.88 (s, 3H), 6.68 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 2.2 Hz, 1H), 6.96 (dd, *J* = 8.7 Hz & 2.4 Hz, 1H), 7.52-7.63 (m, 5H), 8.00 (d, *J* = 2.2 Hz, 1H), 8.39 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 24.9, 28.7, 55.4, 96.1, 112.8, 113.3, 114.9, 126.4, 128.1, 128.8, 129.6, 130.0, 141.4, 144.3, 148.4, 153.1, 161.6; MS (EI, m/z) = 327 $[M]^+$. Anal. calcd. for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.36; H, 5.44; N, 12.98.

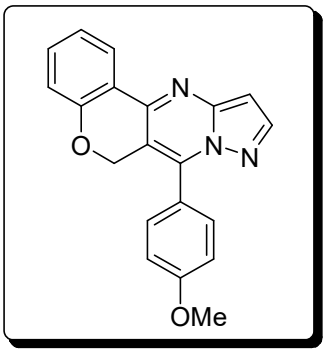
3-Methoxy-7-(4-methoxyphenyl)-5,6-dihydrobenzo[[5,1-*b*]quinazoline (4b)



Yellow solid, Yield 74%; m.p. 142-145 °C; IR ($CHCl_3$, cm^{-1}): 2932, 1591, 1542, 1270, 1168; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.83-2.94 (m, 4H), 3.89 (s, 3H), 3.91 (s, 3H), 6.77-6.83 (m, 2H), 6.99 (d, *J* = 9.0 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 8.03 (d, *J* =

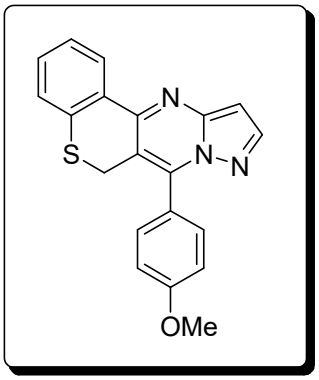
3.0 Hz, 1H), 8.54 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 25.0, 28.7, 55.4, 55.5, 96.1, 112.8, 113.2, 114.2, 114.9, 122.3, 126.4, 128.1, 131.2, 141.4, 142.9, 144.2, 148.4, 153.1, 160.7, 161.6; MS (EI, m/z) = 357.1 $[M]^+$. Anal. calcd. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.76; H, 5.12; N, 11.37.

6-(4-Methoxyphenyl)-6*H*-chromeno[4,3-*d*]pyrazolo[1,5-*a*]pyrimidine (4c)



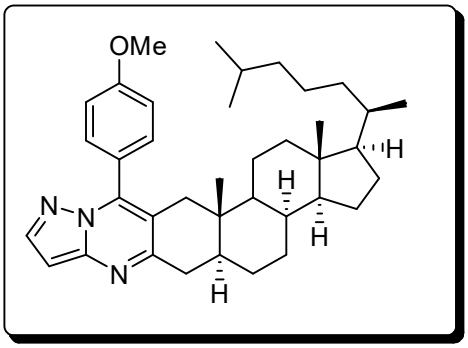
Yellow solid, Yield 67%; m.p. 99-101 °C; IR ($CHCl_3$, cm^{-1}): 2929, 1609, 1509, 1495, 1452, 1249, 1033, 754; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.81 (s, 3H), 3.91 (s, 2H), 6.71-6.80 (m, 1H), 6.85-7.59 (m, 8H), 8.11-8.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 29.7, 55.3, 95.8, 114.5, 118.1, 119.1, 119.3, 121.0, 129.8, 130.1, 131.8, 136.9, 144.9, 145.4, 156.8, 157.9, 158.6; MS (EI, m/z) = 329 $[M]^+$. Anal. calcd. for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.77; H, 4.32; N, 12.55.

7-(4-Methoxyphenyl)-6*H*-pyrazolo[1,5-*a*]thiochromeno[4,3-*d*]pyrimidine (4d)



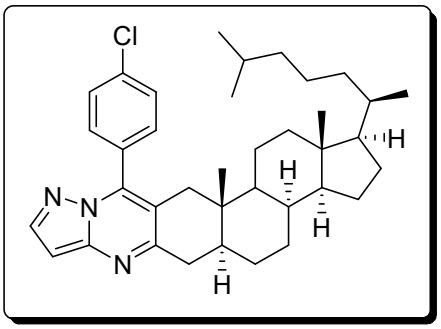
Gum, Yield 65%; IR ($CHCl_3$, cm^{-1}): 2930, 1614, 1499, 758; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.89 (s, 3H), 4.11 (s, 2H), 6.65 (s, 1H), 6.73 (d, *J* = 3.0 Hz, 1H), 6.85 (d, *J* = 6.0 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 7.29 (s, 1H), 7.49 (d, *J* = 9.0 Hz, 2H), 8.01 (d, *J* = 3.0 Hz, 1H); MS (EI, m/z) = 345 $[M]^+$. Anal. calcd. for $C_{20}H_{15}N_3OS$: C, 69.54; H, 4.38; N, 12.17. Found: C, 69.23; H, 4.14; N, 12.02.

7′-(*p*-Methoxyphenyl)-5*α*-cholest[2,3-*d*]pyrazolo[1,5-*a*]pyrimidine (4e)



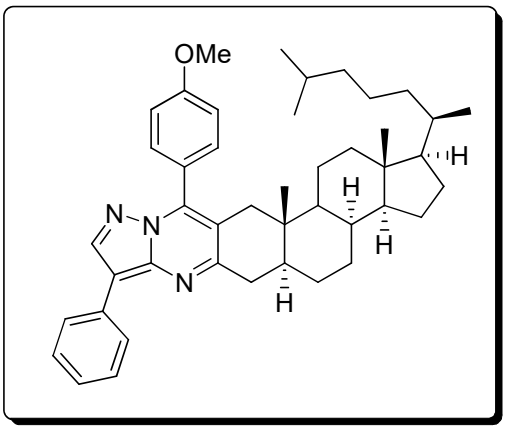
Yellow solid, Yield 76%; m.p. 125-127 °C; IR ($CHCl_3$, cm^{-1}): 2930, 2867, 1610, 1496, 1444, 1251, 754; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.74 (s, 3H), 0.81 (s, 3H), 0.70-3.02 (m, 38H), 3.89 (s, 3H), 6.54 (d, *J* = 1.2 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 11.6, 12.0, 18.7, 21.2. 22.6, 22.8, 23.8, 24.2, 28.0, 28.2, 35.2, 35.5, 35.8, 36.1, 37.2, 39.5, 41.6, 42.4, 53.5, 55.3, 56.3, 56.4, 94.7, 114.4 (2C), 115.3, 122.4, 130.8 (2C), 144.2, 144.5, 144.7, 159.1, 160.5; MS (ESI, m/z) = 568 $[M+1]^+$. Anal. calcd. for $C_{38}H_{53}N_3O$: C, 80.37; H, 9.41; N, 7.40. Found: C, 80.12; H, 9.28; N, 7.18.

7′-(*p*-Chlorophenyl)-5*α*-cholest[2,3-*d*]pyrazolo[1,5-*a*]pyrimidine (4f)



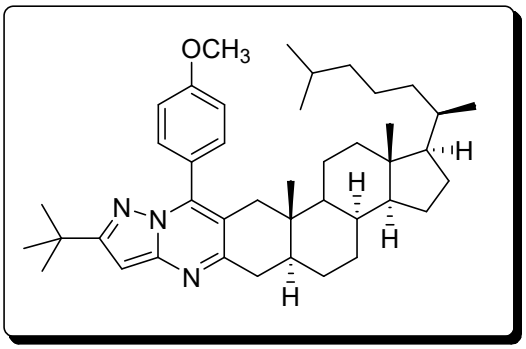
Yellow solid, Yield 75%; m.p. 126-129 °C; IR ($CHCl_3$, cm^{-1}): 2931, 2867, 1610, 1486, 1377, 1092, 1016, 771; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.64 (s, 3H), 0.75 (s, 3H), 0.71-3.04 (m, 38H), 6.63 (d, *J* = 2.1 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 8.00 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 11.6, 12.0, 18.6, 22.6, 22.8, 23.8, 24.2, 28.0, 28.2, 35.1, 35.5, 35.8, 36.1, 39.5, 39.8, 40.0, 41.5, 42.4, 44.9, 53.4, 56.3, 56.5, 95.0, 115.3, 128.7, 129.4, 130.2, 130.4, 130.7, 136.1, 143.4, 144.4, 159.2; MS (ESI, m/z) = 572 $[M+1]^+$. Anal. calcd. for $C_{37}H_{50}ClN_3$: C, 77.66; H, 8.81; N, 7.34. Found: C, 77.82; H, 8.93; N, 7.58.

3′-(Phenyl)-7′-(*p*-methoxyphenyl)-5*α*-cholest[2,3-*d*]pyrazolo[1,5-*a*]pyrimidine (4g)



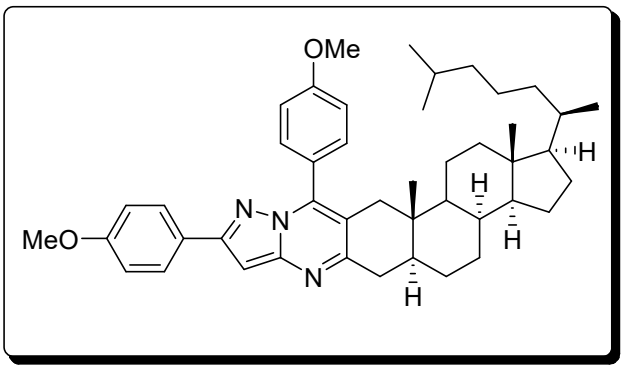
Yellow solid, Yield 75%; m.p. 103-106 °C; IR ($CHCl_3$, cm^{-1}): 2925, 1603, 1463, 1252, 1030; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.64 (s, 3H), 0.79 (s, 3H), 0.70-3.06 (m, 38H), 3.90 (s, 3H), 7.10 (d, *J* = 8.3 Hz, 2H), 7.15-7.47 (m, 5H), 8.06 (d, *J* = 7.6 Hz, 2H), 8.3 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 11.6, 12.0, 18.7, 22.6, 22.8, 23.8, 24.2, 28.0, 28.2, 28.8, 29.7, 30.9, 31.5, 31.9, 35.2, 35.6, 35.8, 36.2, 37.2, 39.5, 40.3, 40.8, 41.5, 42.4, 53.4, 55.3, 56.4, 108.6, 114.4, 115.7, 122.3, 125.7, 126.0, 128.7, 130.8, 142.1, 143.8, 144.5, 159.5, 160.6; MS (ESI, m/z) = 644 $[M+1]^+$. Anal. calcd. for $C_{44}H_{57}N_3O$: C, 82.07; H, 8.92; N, 6.53. Found: C, 82.32; H, 8.76; N, 6.22.

3′-(*tert*-Butyl)-7′-(*p*-methoxyphenyl)-5*α*-cholest[2,3-*d*]pyrazolo[1,5-*a*]pyrimidine (4h)



Yellow solid, Yield 72%; m.p. 115-117 °C; IR ($CHCl_3$, cm^{-1}): 2867, 1600, 1497, 1252, 1034; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.63 (s, 3H), 0.69 (s, 3H), 0.70-2.96 (m, 47H), 3.91 (s, 3H), 6.36 (s, 1H), 6.84-6.92 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 11.5, 12.0, 18.7, 22.6, 22.8, 23.8, 24.2, 28.0, 28.2, 29.7, 30.4, 35.2, 35.6, 35.8, 36.2, 39.5, 40.0, 42.4, 53.5, 55.2, 55.6, 56.3, 90.4, 113.5, 113.9, 114.3, 122.5, 131.6, 132.0, 144.1, 148.0, 158.0, 160.3, 166.8; MS (ESI, m/z) = 624 $[M+1]^+$. Anal. calcd. for $C_{42}H_{61}N_3O$: C, 80.85; H, 9.85; N, 6.73. Found: C, 80.71; H, 9.65; N, 6.59.

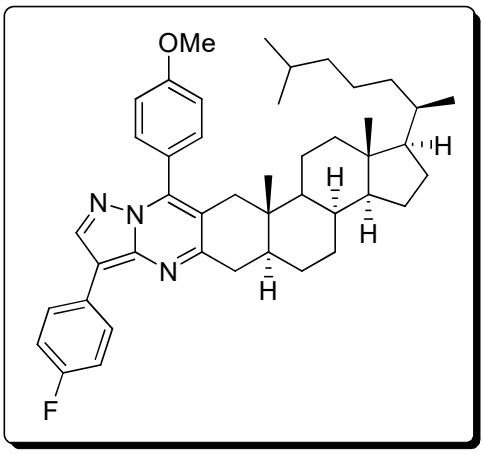
2′-(*p*-Methoxyphenyl)-7′-(*p*-methoxyphenyl)-5*α*-cholest[2,3-*d*]pyrazolo[1,5-*a*]pyrimidine (4i)



Yellow solid, Yield 74%; m.p. 106-109 °C; IR ($CHCl_3$, cm^{-1}): 2926, 2852, 1611, 1495, 1459, 1249, 1174, 1034; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.63 (s, 3H), 0.72 (s, 3H), 0.73-2.95 (m, 38H), 3.76 (s, 3H), 3.92 (s, 3H), 6.74 (s, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.5 Hz,

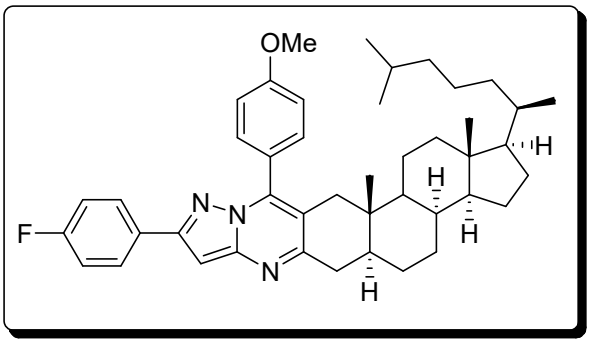
2H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.94 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 11.5, 12.0, 18.7, 22.6, 22.8, 23.9, 24.2, 28.0, 28.2, 29.7, 30.9, 35.1, 35.5, 35.8, 36.2, 39.5, 41.5, 42.4, 53.4, 55.2, 55.3, 56.3, 90.7, 113.8, 114.0, 114.1, 114.7, 122.3, 126.2, 127.8, 131.4, 139.2, 144.1, 149.0, 155.0, 158.8, 160.0, 160.4; MS (ESI, m/z) = 674 $[M+1]^+$. Anal. calcd. for $C_{45}H_{59}N_3O_2$: C, 80.19; H, 8.82; N, 6.23. Found: C, 80.33; H, 8.56; N, 6.43.

3′-(*p*-Fluorophenyl)-7′-(*p*-methoxyphenyl)-5*α*-cholest[2,3-*d*]pyrazolo[1,5-*a*]pyrimidine (4j)



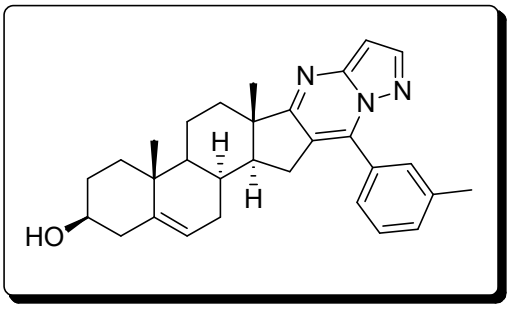
Yellow solid, Yield 72%; m.p. 134-136 °C; IR ($CHCl_3$, cm^{-1}): 2930, 1602, 1498, 1252, 771; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.64 (s, 3H), 0.76 (s, 3H), 0.74-3.06 (m, 38H), 3.90 (s, 3H), 6.82-6.92 (m, 4H), 7.43 (d, *J* = 8.3 Hz, 2H), 8.02 (d, *J* = 5.6 Hz, 1H), 8.05 (d, *J* = 5.4 Hz, 1H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 11.6, 12.0, 18.6, 22.6, 22.8, 23.8, 24.2, 28.0, 28.6, 30.9, 31.5, 35.2, 35.6, 35.8, 36.1, 39.5, 40.1, 42.4, 53.4, 55.3, 56.3, 107.2, 114.4, 115.3, 115.6, 127.5, 127.6, 130.8, 140.5, 141.7, 158.2, 160.6; MS (ESI, m/z) = 662 $[M+1]^+$. Anal. calcd. for $C_{44}H_{56}FN_3O$: C, 79.84; H, 8.53; N, 6.35. Found: C, 79.66; H, 8.45; N, 6.55.

2′-(*p*-Fluorophenyl)-7′-(*p*-methoxyphenyl)-5*α*-cholest[2,3-*d*]pyrazolo[1,5-*a*]pyrimidine (4k)



Yellow solid, Yield 73%; m.p. 132-134 °C; IR ($CHCl_3$, cm^{-1}): 2927, 1599, 1495, 1465, 1251, 1035, 772; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.64 (s, 3H), 0.67 (s, 3H), 0.71-2.95 (m, 38H), 3.91 (s, 3H), 6.70 (s, 1H), 6.83-6.90 (m, 1H), 6.99-7.15 (m, 4H), 7.44-7.52 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 11.5, 12.0, 18.7, 22.6, 22.8, 23.9, 24.2, 28.2, 29.7, 31.0, 35.2, 35.5, 35.8, 36.1, 39.5, 39.9, 42.4, 44.9, 53.5, 55.3, 56.3, 91.3, 113.5, 113.8, 115.1, 122.0, 125.2, 125.7, 127.5, 130.0, 131.4, 136.8, 144.4, 148.8, 150.4, 159.2, 160.5; MS (ESI, m/z) = 662 $[M+1]^+$. Anal. calcd. for $C_{44}H_{56}FN_3O$: C, 79.84; H, 8.53; N, 6.35. Found: C, 79.66; H, 8.41; N, 6.57.

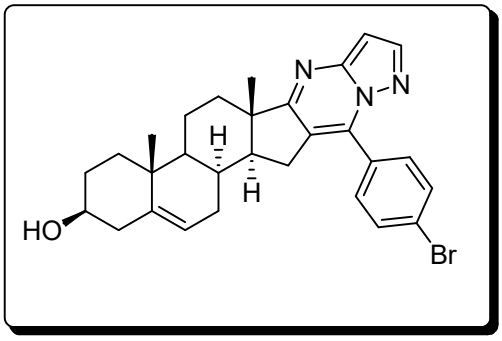
3*β*-Hydroxy-7′-(*m*-methylphenyl)-androst[16,17-*d*]pyrazolo[1,5-*a*]pyrimidine (4l)



Yellow solid, Yield 70%; m.p. 105-107 °C; IR ($CHCl_3$, cm^{-1}): 3382, 2932, 1627, 1537, 1445, 1377, 1222; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.09 (s, 3H), 1.16 (s, 3H), 2.09 (s, 3H), 0.76-2.66 (m, 17H), 3.52-3.56 (m, 1H), 4.52 (bs, 1H), 5.29-5.37 (m, 1H), 6.67 (d, J = 2.1 Hz, 1H), 7.44

(t, *J* = 8.0 Hz, 1H), 7.65-7.70 (m, 2H), 7.89 (s, 1H), 8.01 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 17.2, 19.5, 20.6, 20.8, 28.7, 31.0, 31.2, 31.4, 33.0, 36.7, 37.1, 42.0, 45.8, 50.3, 55.8, 71.6, 96.3, 120.8, 122.6, 128.2, 130.1, 132.1, 132.4, 133.4, 140.3, 141.2, 143.7, 148.9, 174.7; MS (ESI, m/z) = 454 $[M+1]^+$. Anal. calcd. for $C_{30}H_{35}N_3O$: C, 79.43; H, 7.78; N, 9.26; O, 3.53. Found: C, 79.42; H, 7.65; N, 9.46.

3*β*-Hydroxy-7′-(*p*-bromophenyl)-androst[16,17-*d*]pyrazolo[1,5-*a*]pyrimidine (4m)



Yellow solid, Yield 75%; m.p. 120-122 °C; IR ($CHCl_3$, cm^{-1}): 3374, 2930, 1622, 1054; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.10 (s, 3H), 1.16 (s, 3H), 0.76-2.69 (m, 17H), 3.52-3.63 (m, 1H), 4.63 (bs, 1H), 5.29-5.37 (m, 1H), 6.64 (d, *J* = 2.1 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 2H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.6, 21.8, 23.2, 28.7, 30.8, 31.0, 34.2, 34.8, 36.1, 37.9, 42.0, 45.9, 50.4, 55.8, 71.6, 96.2, 120.9, 121.9, 128.3, 130.2, 132.2, 132.4, 133.6, 134.3, 164.4, 172.7; MS (ESI, m/z) = 518 $[M+1]^+$. Anal. calcd. for $C_{29}H_{32}BrN_3O$: C, 67.18; H, 6.22; N, 8.10. Found: C, 67.32; H, 6.43; N, 8.28.

References

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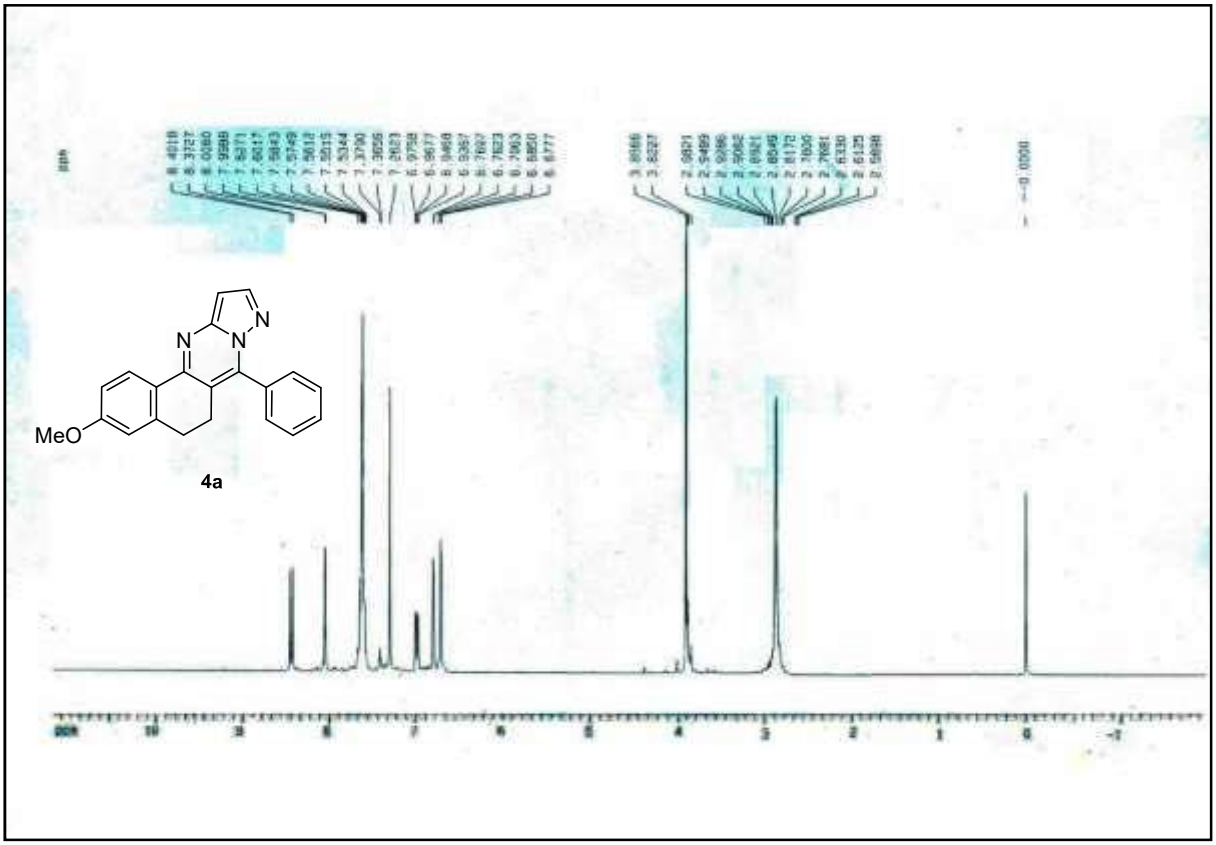
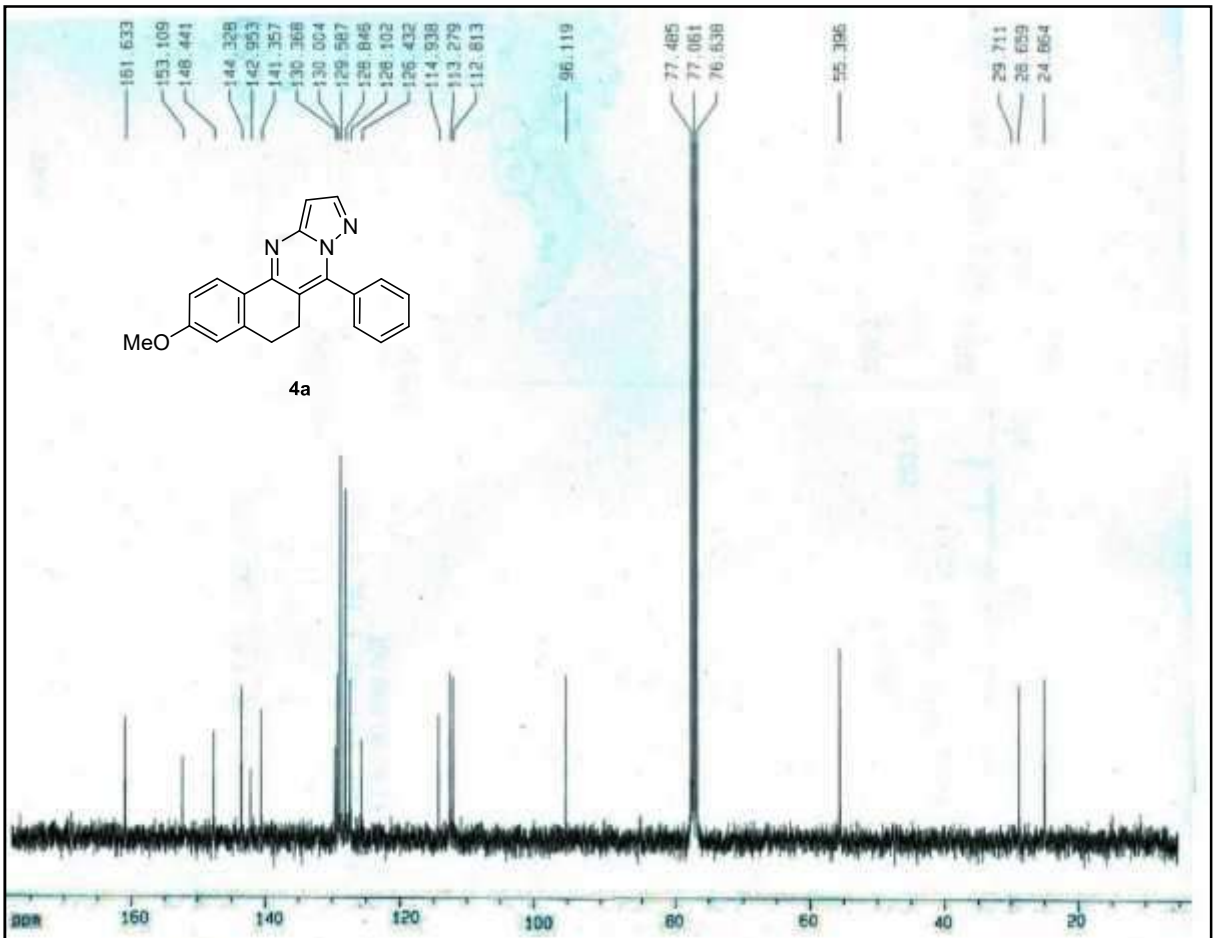
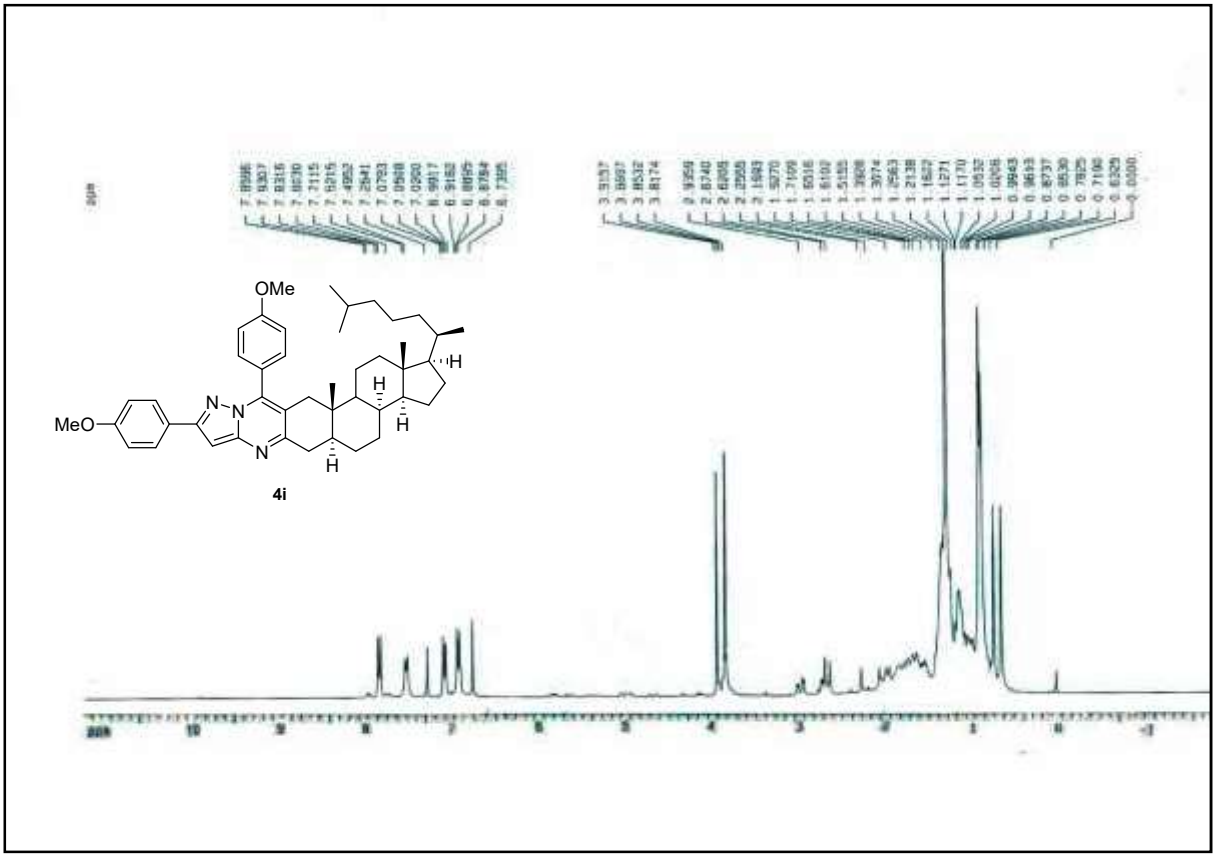
^{1}H NMR and ^{13}C NMR of some selected pyrazolo[1,5-*a*]pyrimidine compounds



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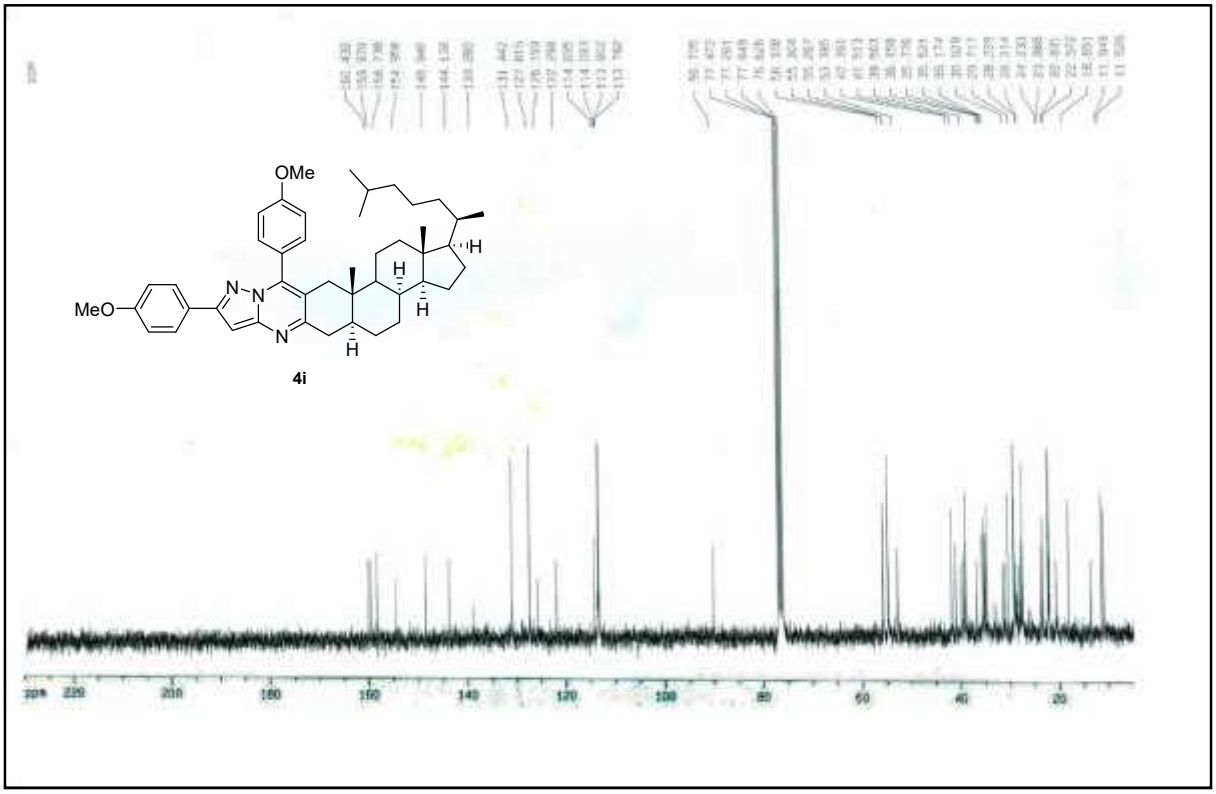
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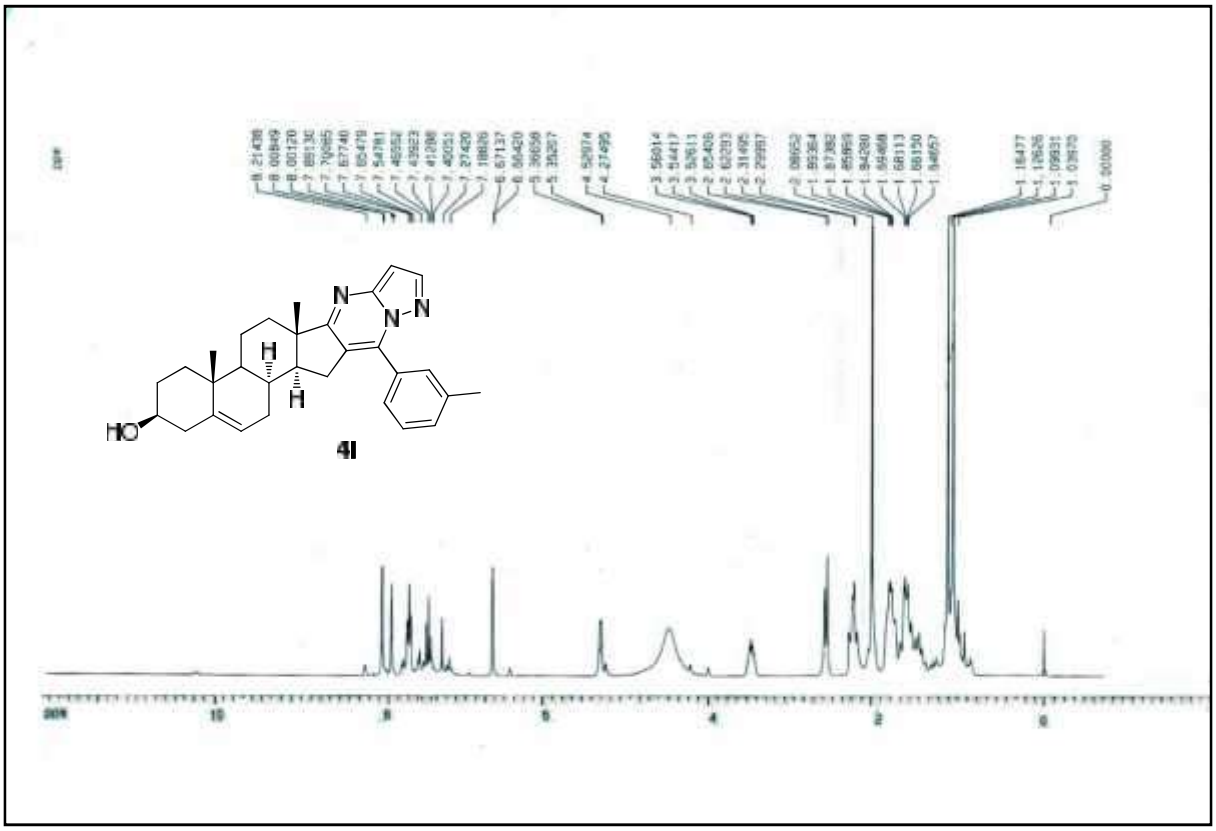

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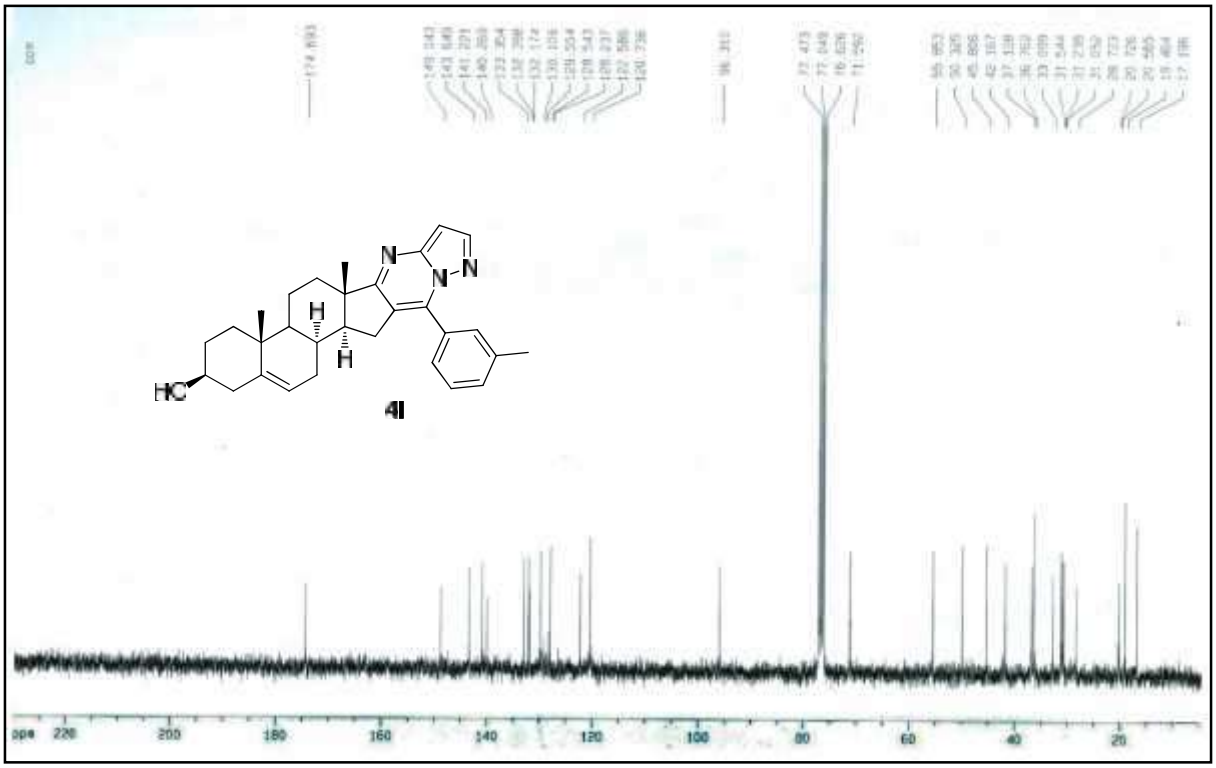


4l

Chapter 1

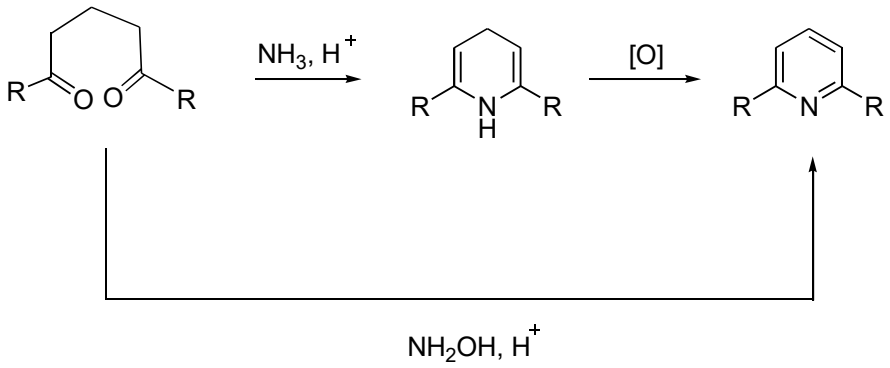
Part-B

A novel methodology for the synthesis of pyrazolo[1,5-a] pyrimidines from 1,5-dicarbonyl compounds

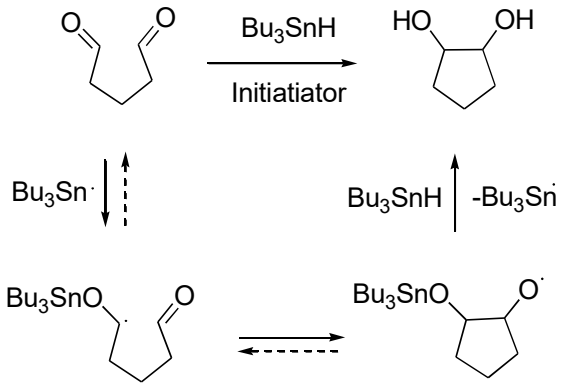
1B.1 Introduction

In the synthesis of natural and non-natural products, the chemical intermediates always attract interests of organic chemist. In particular, 1,5-dicarbonyl compounds are versatile building blocks and functional materials in various bioactive molecules.[1] This moiety serve as intermediates in the synthesis of number of bioactive molecules as it is remarkably stable in metabolic transformations. 1,5-dicarbonyl compounds are regarded as valuable synthons for the synthesis of various novel heterocycles[2,3] and a great deal of studies on this versatile moiety is reviewed in the literature.

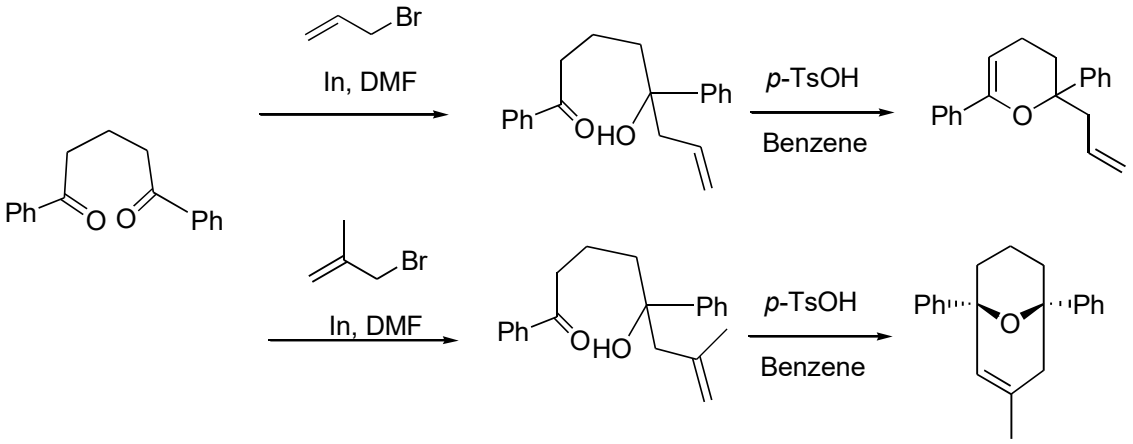
Pyridine was synthesized from 1,5-Dicarbonyl compound adapting the method of Paal Knorr pyrrole synthesis using NH_3 as nitrogen source. In a modified procedure when NH_2OH is used instead of NH_3, the oxidation of dihydropyridine occured *in situ* resulting the formation of pyridine derivatives.[4]



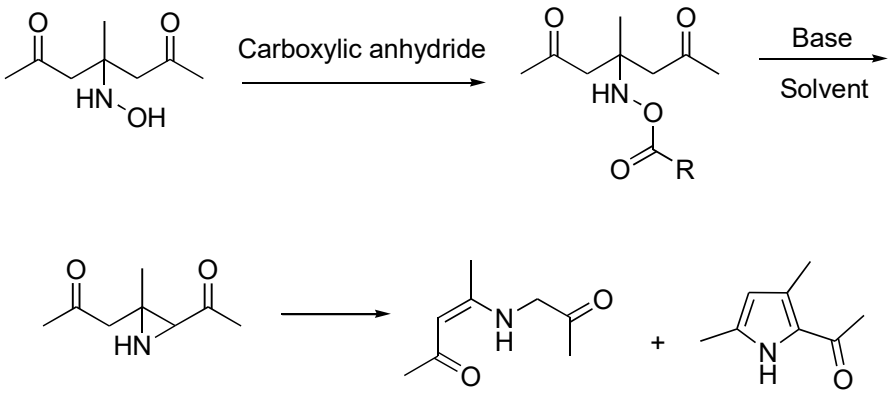
Hays and co-workers[5] described an intramolecular pinacol coupling reaction of 1,5-dicarbonyl compounds, employing Bu_3SnH as the stoichiometric reductant. The key steps in this cyclization was the addition of a tin ketyl to a carbonyl group and subsequent intramolecular SH_2 reaction.



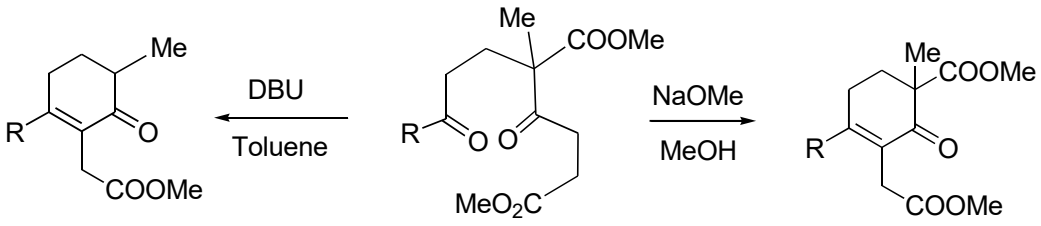
2,3-Dihydro-4*H*-pyran-4-ones and 3,4-dihydro-2*H*-[1,4]oxazines were synthesized by Kim and co-workers[6] by an indium-mediated Barbier type mono-allylation of 1,5-dicarbonyl compounds followed by acid catalyzed dehydrative cyclization reaction.



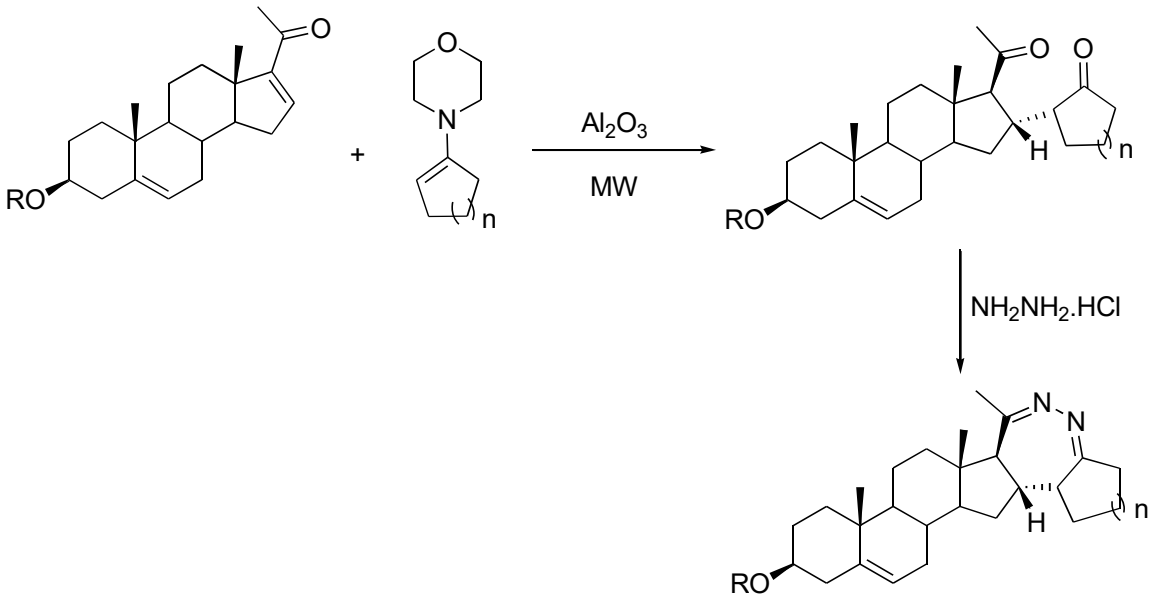
A mechanistic study of the rearrangement of 3-acyloxyamino-1,5-diketone was done by Uncuta and co-workers[7] by reacting 3-acyloxyamino-1,5-diketone with base. Enamine and pyrrole were obtained as products as a result of this rearrangement reaction.



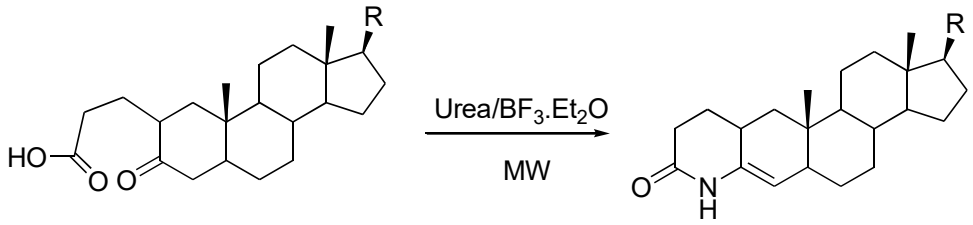
Regioselective annulation reaction of 1,5-diketones was studied by Gassama and co-workers.[8] The annulation reaction in presence of base resulted functionalized Hagemann's esters.



Boruah and co-workers[9] successfully synthesized a novel class of 1′,2′-diazepino(17,16-*d*′) steroids from steroidal 1,5-diketo compounds. These diketo compounds were intitially prepared by Michael addition of enamines with conjugated enones using alumina under MW irradiation.



In an another report[10] steroidal 1,5-diketo compounds were effectively used for the synthesis of azasteroids. The reaction of A-nor-3,5-secosteroid-3-oic acid with urea in presence of $BF_3 \cdot Et_2O$ using MW as energy source yielded 3-oxo-4-azasteroid in satisfactory yield.

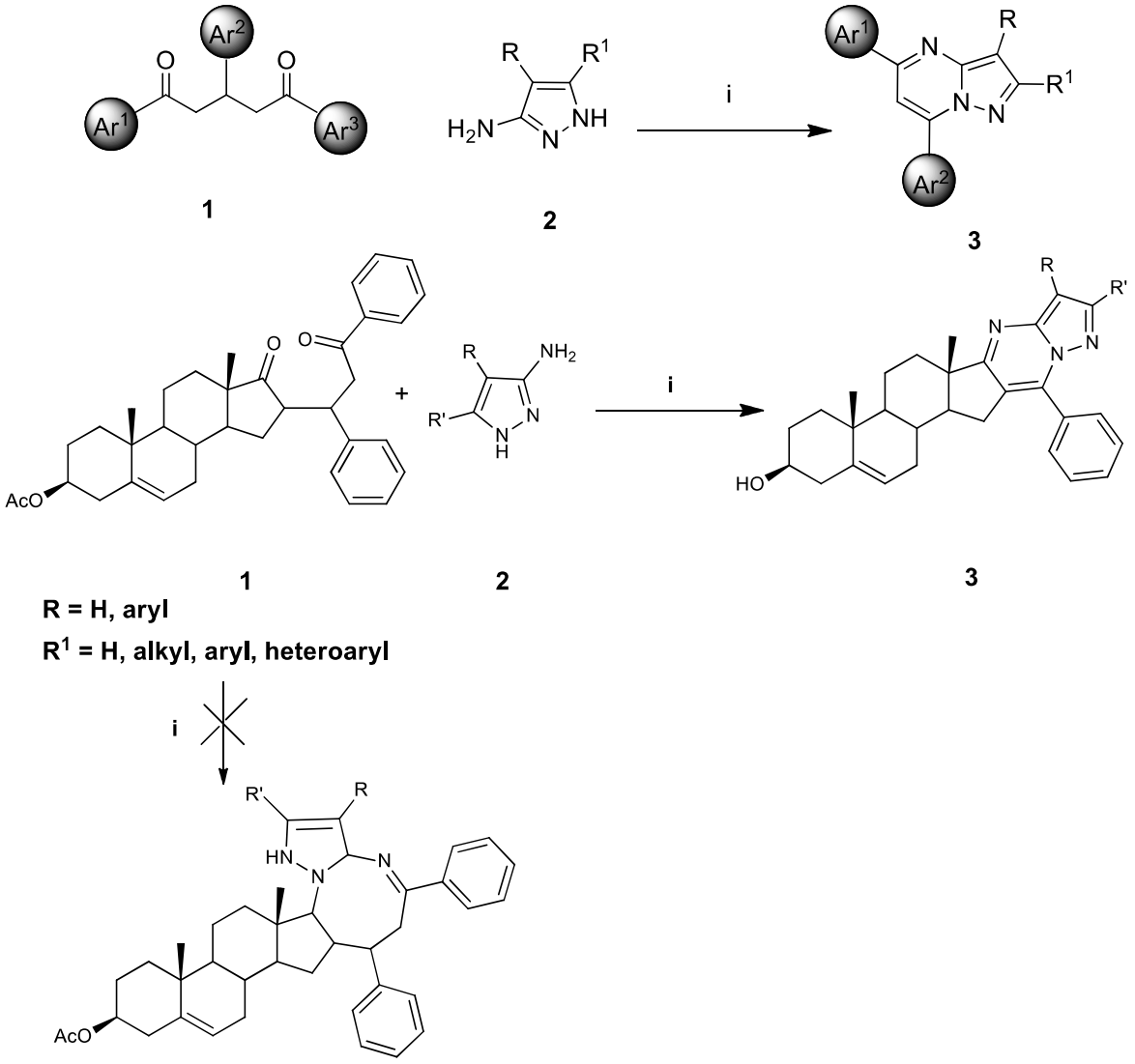


Thus, 1,5-dicarbonyl compound has been recognized an important synthetic intermediate for the preparation of variety of heterocycles and carbocycles. Consequently, further endeavour for the development of novel methodologies for the synthesis of heterocyclic compounds utilizing 1,5-dicarbonyl compounds is still seems to be exciting and demanding. In continuation of our efforts toward the development of novel heterocyclic

molecules, the present study describes the synthesis of aryl substituted pyrazolo[1,5-*a*]pyrimidine starting from 1,5-dicarbonyl compounds.

1B.2 Results and discussions

To begin with, an effort was made by treating 1,5-dicarbonyl compound with 3-amino-1*H*-pyrazole in presence of base to synthesize 8-membered 1,3-diazocine derivative. Interestingly, the desired product was not formed, instead pyrazolo[1,5-*a*]pyrimidine derivatives were obtained as products (Scheme 1B.1).



Reagents and conditions: (i) Base, Solvent, reflux

Scheme 1B.1

The synthesis was attempted with the initial effort by using 1,5-diketone **1a** and 3-amino-1*H*-pyrazole (**2a**) as starting substrates. Refluxing a mixture of **1a** and **2a** in anhydrous ethanol in the presence of two equivalents of NaOMe for eight hours furnished pyrazolo[1,5-*a*]pyrimidine **3a** in 57% yield (Entry 1, Table 1B.1). The product **3a** was identified from ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR of compound **3a** exhibited two characteristic singlet signals at δ 6.79 (s, 1H) and 7.33 (s, 1H) for the pyrazole and pyrimidine ring protons. Also a characteristic singlet signal was appeared at δ 2.47 (S, 3H) for methyl protons. The ^{13}C NMR spectrum of **3a** showed signals for eighteen aromatic carbons at δ 97.1, 104.9, 127.3 (2C), 128.6, 128.9 (2C), 129.2 (2C), 129.4 (2C), 130.3, 137.6, 141.4, 145.1, 146.9, 156.2, 161.3. The EI mass spectra of compound **3a** exhibited molecular ion peak at m/z = 285. Finally the structure of **3a** was confirmed by single X-ray diffraction study. The single X-ray crystal structure of compound **3a** is shown in Figure 1B.1.

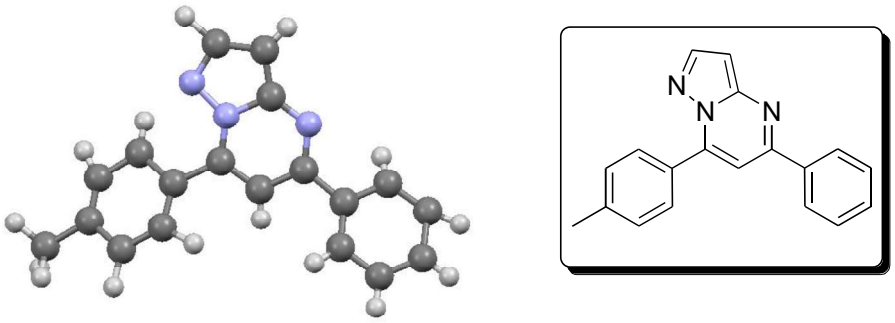


Figure 1B.1 X-ray crystallographic ORTEP drawing of compound **3a**

The reaction was studied with some other bases and solvents to determine the ideal base and solvent for the reaction as shown in Table 1B.1. Using ethanol as solvent the bases such as KOMe, NaH and KOH led to lower yield of **3a** (Entry 2, 6, 8), while bases NaO^{t}Bu and KO^{t}Bu resulted 78% and 83% yields of **3a** respectively (Entry 3, 4). Further studies on

the solvents could not improve the yield of product **3a** (Entry 5, 7). Moreover in absence of the base also the reaction could not afford the product **3a** (Entry 9).

Table 1B.1 Optimization of reaction conditions for the synthesis of **3a**

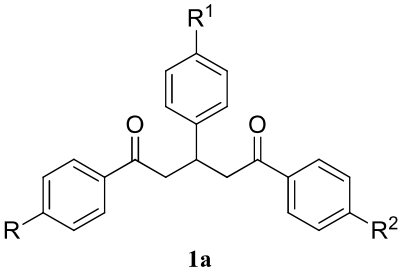
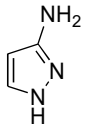
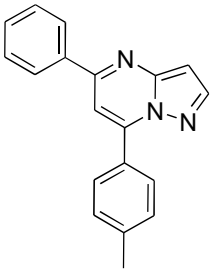
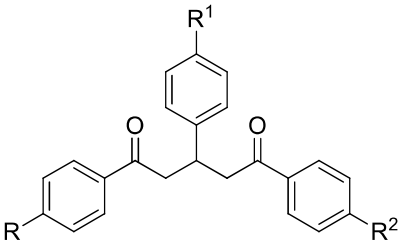
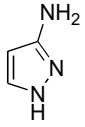
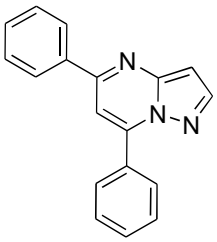
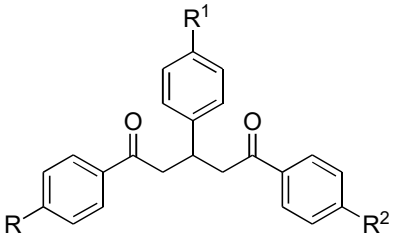
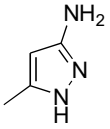
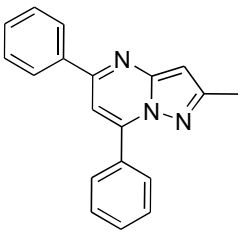
Entry	Base[a]	Solvent	Yield (%)[b]
1	NaOMe	ethanol	57
2	KOMe	ethanol	62
3	NaO^{t}Bu	ethanol	78
4	KO^{t}Bu	ethanol	83
5	KO^{t}Bu	DMF	71
6	NaH	ethanol	60
7	KO^{t}Bu	toluene	33
8	KOH	ethanol	24
9	-	ethanol	0

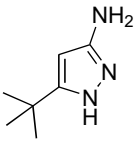
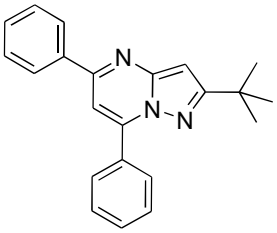
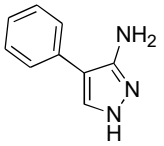
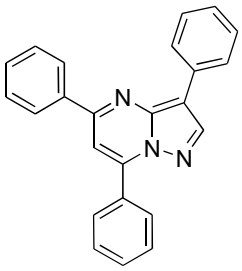
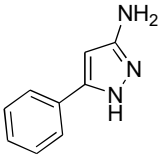
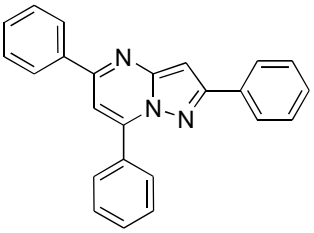
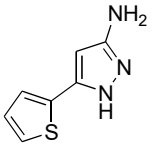
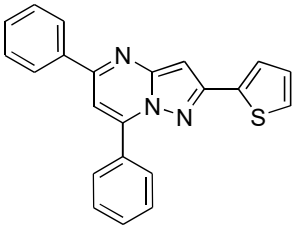
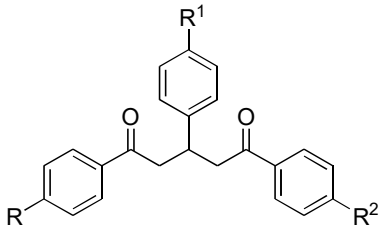
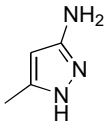
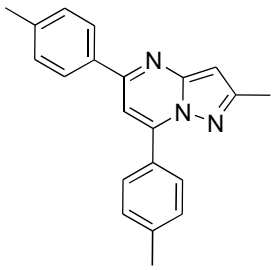
[a] Two equivalents of the base were used. [b]Yield of the isolated product.

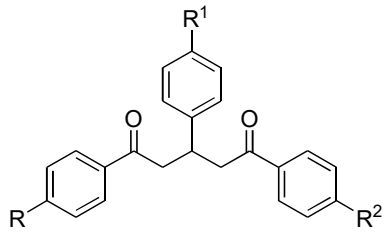
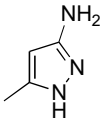
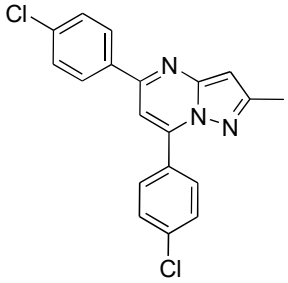
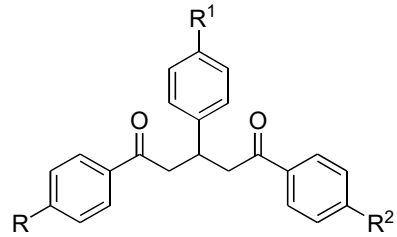
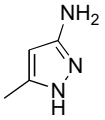
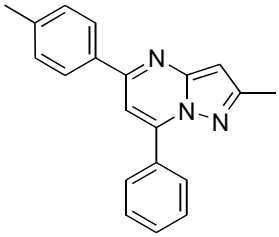
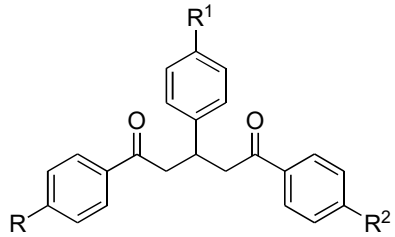
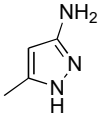
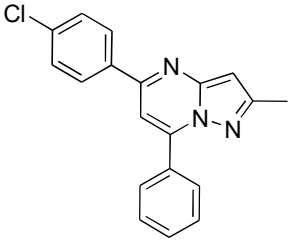
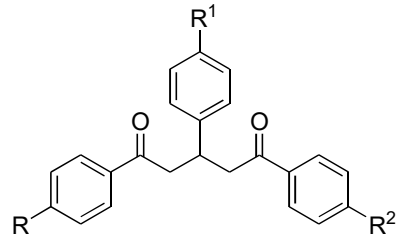
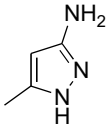
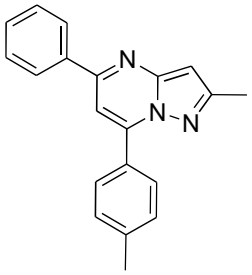
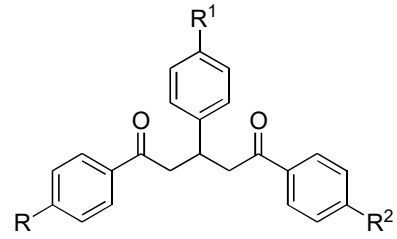
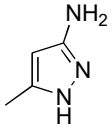
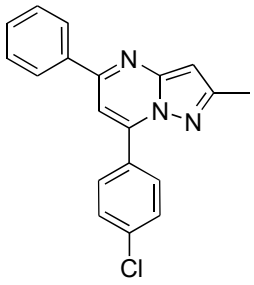
With the optimized reaction conditions (Table 1B.1, Entry 4), the scope of the substrate in the reaction of 1,5-dicarbonyls and 3-amino-1*H*-pyrazoles was explored (Table 1B.2). The base induced cyclization reaction of 1,5-dicarbonyl compounds with different 3-amino-1*H*-pyrazoles substituted with methyl, *t*-butyl and phenyl groups reacted smoothly to afford pyrazolo[1,5-*a*]pyrimidines **3c**-**f** in 78-83% yield under the optimized reaction conditions. Similarly, the reaction of compound **1c** and heterocycle substituted 3-amino-1*H*-pyrazole (**2f**) afforded pyrazolo[1,5-*a*]pyrimidine **3g** in 84% yield. Again, the reactions of 1,5-dicarbonyls with electron donating and electron-withdrawing groups such as methyl and chloro present in the aromatic rings were studied with 3-amino-5-methyl-1*H*-pyrazole, which resulted pyrazolo[1,5-*a*]pyrimidines **3h** and **3i** in 80 and 75% yield. The condensation reactions of some more symmetrical and unsymmetrical 1,5-dicarbonyls with 3-amino-5-methyl-1*H*-pyrazole (**2b**) were also performed. The reactions of 3-phenyl-1,5-di-*p*-

tolylpentane-1,5-dione (**1f**) and 3-phenyl-1,5-di-*p*-chlorophenylpentane-1,5-dione (**1g**) with **2b** proceeded very easily under the optimized condition to afford pyrazolo[1,5-*a*]pyrimidines **3j** and **3k** in 78% and 80% yields, respectively. Similarly, the cyclization reaction of 1,5-diphenyl-3-(*p*-tolyl)pentane-1,5-dione (**1h**) and 3-(4-chlorophenyl)-1,5-diphenylpentane-1,5-dione (**1i**) with **2b** gave the corresponding pyrazolo[1,5-*a*]pyrimidines **3l** and **3m** in 81% and 85% yields, respectively.

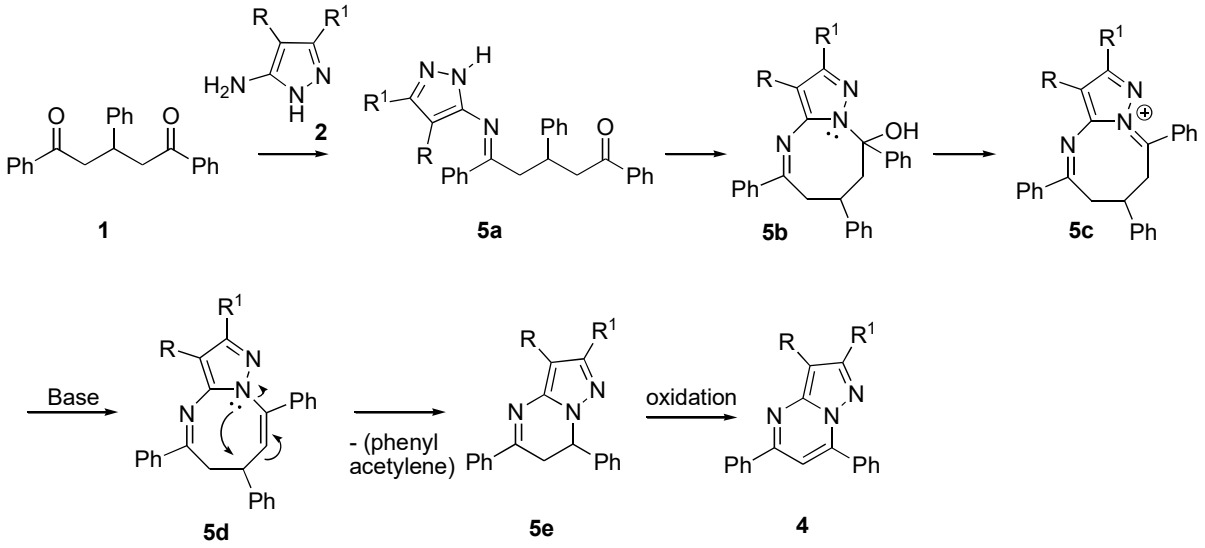
Table 1B.2 Generalization of pyrazolopyrimidine **3a-m**

Entry	Diketone	Pyrazole	pyrazolopyrimidine	Isolated Yield (%)
1	 **1a** **R, R_2 = H, R_1 = CH_3**	 **2a**	 **3a**	87
2	 **1b** **R, R_1, R_2 = H**	 **2a**	 **3b**	85
3	 **1c** **R, R_1, R_2 = H**	 **2b**	 **3c**	82

4	**1c**	 **2c**	 **3d**	78
5	**1c**	 **2d**	 **3e**	81
6	**1c**	 **2e**	 **3f**	83
7	**1c**	 **2f**	 **3g**	84
8	 **1d** **R, R_1, R_2 = CH_3**	 **2b**	 **3h**	80

9	 **1e** **R, R_1, R_2 = Cl**	 **2b**	 **3i**	75
10	 **1f** **R, R_2 = CH_3,** **R_1 = H**	 **2b**	 **3j**	78
11	 **1g** **R, R_2 = Cl,** **R_1 = H**	 **2b**	 **3k**	80
12	 **1h** **R, R_2 = H,** **R_1 = CH_3**	 **2b**	 **3l**	81
13	 **1i** **R, R_2 = H,** **R_1 = Cl**	 **2b**	 **3m**	85

The proposed mechanism for the formation pyrazolopyridine is shown in Scheme 1B.3. It is assumed that the reaction proceeds through the formation of immine intermediate **5a**. The migration of a lone pair of the immine followed by cleavage of C-C bond and C-N bond in presence of base results the desired pyrazolopyrimidine.



Scheme 3B.3 Proposed mechanism for the formation of pyrazolopyrimidine

1B.3 Conclusion

In conclusion, a novel methodology for the synthesis of substituted pyrazolo[1,5-*a*]pyrimidine derivatives by reacting 1,5-dicarbonyl compounds with substituted pyrazoles have been developed. It is assumed that the reaction proceeded through the cleavage of C-C/C-N bond cleavage. A variety of 1,5-dicarbonyl compounds and 3-amino-1*H*-pyrazoles were studied and moderate to good yields were obtained. This methodology offers a new approach for the synthesis of pyrazolo[1,5-*a*]pyrimidine from simple starting materials 1,5-dicarbonyl compounds.

1B.4 Experimental

General experimental Procedure

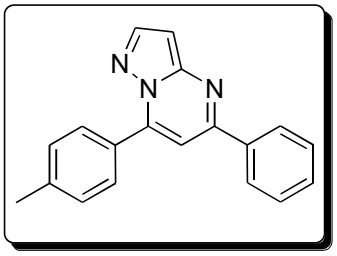
Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on Elmer FT-IR-2000 spectrometer on a thin film using chloroform. NMR spectra were recorded on Avance DPX 300 MHz FT-NMR spectrometer or Bruker Avance III 500 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Trace DSQ GCMS instrument or Bruker ESQUIRE 3000 LCMS instrument. Single Crystal XRD analysis was done on a Bruker Nonius SMART CCD diffractometer equipped with a graphite monochromator. All the commercially available reagents were used as received. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Merck). Column chromatography was performed on silica gel (100-200 mesh, Merck Chemicals).

General procedure for the synthesis of pyrazolo[1,5-*a*]pyrimidine 3

A stirring solution of 1,5-diketone (**1**, 1.0 mmol) and aminopyrazole (**2**, 1.0 mmol) in anhydrous ethanol, 2 mmol of KO^{t}Bu was added and the reaction mixture was refluxed for eight hours. When the reaction was completed (*vide* TLC), the solvent was removed and the residue was extracted with ethyl acetate, washed with water, brine and dried over anhydrous sodium sulphate. The crude product obtained after removal of the solvent was purified by silica gel column chromatography using ethyl acetate/hexane as the eluent to obtain pure product **3**.

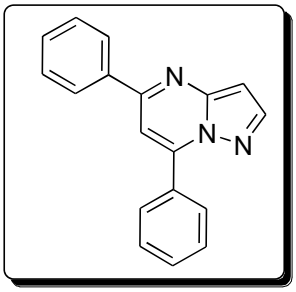
Chracterization of pyrazolo[1,5-*a*]pyrimidine 3

5-Phenyl-7-p-tolylpyrazolo[1,5-*a*]pyrimidine (3a)



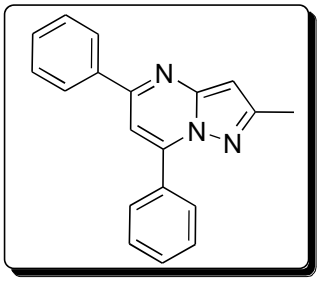
White solid, Yield 87%; mp: 110-112 ºC; IR ($CHCl_3$, cm^{-1}): 2924, 1610, 1550, 1369, 1220, 1028, 761; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.47 (S, 3H), 6.79 (s, 1H), 7.33 (s, 1H), 7.35-7.55 (m, 4H), 7.96 (d, *J* = 3.4Hz, 2H), 8.11-8.16 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 97.1, 104.9, 127.3, 128.6, 128.9, 129.2, 129.4, 130.3, 137.6, 141.4, 145.1, 146.9, 156.2, 161.3; MS (EI, *m/z*): 285.3 $[M]^+$. Anal. calcd. for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73 Found: C, 79.65; H, 4.91 N, 14.55.

5,7-Diphenylpyrazolo[1,5-*a*]pyrimidine (3b)



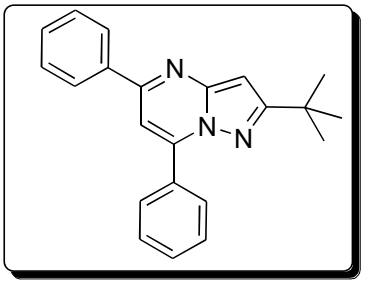
Yellow gum, Yield 85%; IR ($CHCl_3$, cm^{-1}): 2924, 1607, 1549, 1491, 1377, 1222, 1028, 760; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.81 (s, 1H), 7.34 (s, 1H), 7.51 (d, *J* = 6.5 Hz, 2H), 7.56-7.59 (m, 3H), 8.06 (d, *J* = 3.4Hz, 2H), 8.11-8.17 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 97.2, 105.2, 127.3, 128.4, 128.7, 128.9, 129.3, 130.3, 130.9, 131.6, 137.5, 145.2, 146.9, 156.2; MS (EI, *m/z*): 271.3 $[M]^+$. Anal. calcd. for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49 Found: C, 79.55; H, 4.99 N, 15.68.

2-Methyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (3c)



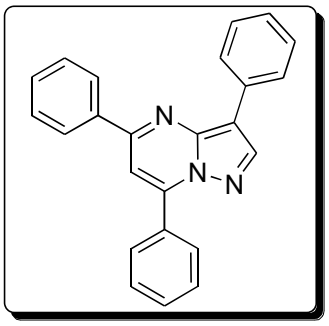
Yellow solid, Yield 82%; mp: 115-117 ºC; IR ($CHCl_3$, cm^{-1}): 2924, 1608, 1554, 1490, 1373, 1218, 1017, 771; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.53(s, 3H), 6.57 (s, 1H), 7.48-7.50 (m, 6H), 7.55 (d, *J* = 4.2 Hz, 2H), 8.06-8.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.8, 96.4, 104.3, 127.1, 128.6, 128.8, 129.2, 130.0, 130.8, 131.6, 137.6, 146.1, 150.6, 155.4, 155.7; MS (EI, *m/z*): 285.3 $[M]^+$. Anal. calcd. for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73 Found: C, 79.81; H, 5.59; N, 14.89.

2-tert-Butyl-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (3d)



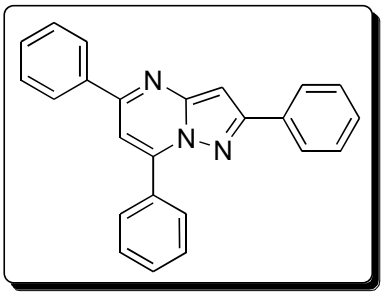
White gum, Yield 78%; IR ($CHCl_3$, cm^{-1}): 2960, 1606, 1551, 1490, 1239, 1017, 762; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43 (s, 9H), 6.65 (s, 1 H), 7.45-7.48 (m, 4H), 7.50-7.54 (m, 3H), 8.09 (d, *J* = 4.8 Hz, 2H), 8.20 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.4, 32.9, 93.0, 104.0, 127.1, 128.3, 128.8, 129.4, 129.9, 130.7, 131.6, 137.8, 145.9, 150.4, 155.4, 168.0; MS (EI, *m/z*): 327.4 $[M]^+$. Anal. calcd. for $C_{22}H_{21}N_3$: C, 80.70; H, 6.46; N, 12.83. Found: C, 80.96; H, 6.61; N, 12.55.

3,5,7-Triphenylpyrazolo[1,5-*a*]pyrimidine (3e)



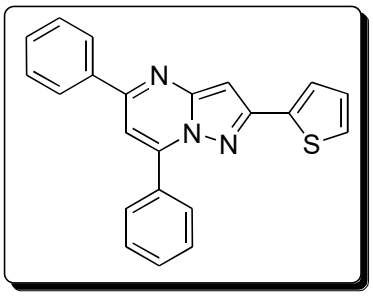
Yellow solid, Yield 81%; mp: 175-177 ºC; IR ($CHCl_3$, cm^{-1}): 2923, 1607, 1562, 1491, 1377, 1189, 1028, 761, 691; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40 (s, 1H), 7.50-7.56 (m, 7H), 7.60 (d, *J* = 6.6 Hz, 2H), 8.07 (d, *J* = 5.9 Hz, 2H), 8.21-8.25 (m, 4H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 105.1, 110.6, 126.0, 126.3, 127.3, 128.6, 128.8, 129.2, 130.3, 130.9, 132.3, 137.3, 142.9, 145.9, 146.9, 155.8; MS (EI, *m/z*): 347.4 $[M]^+$. Anal. calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10. Found: C, 82.68; H, 4.75; N, 12.39.

2,5,7-Triphenylpyrazolo[1,5-*a*]pyrimidine (3f)



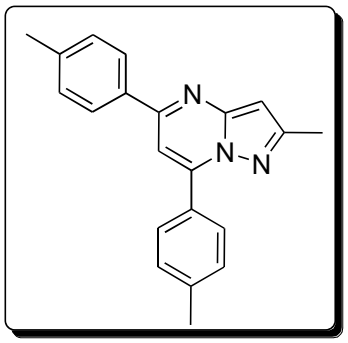
Gum, Yield 83%; IR ($CHCl_3$, cm^{-1}): 2926, 1607, 1552, 1490, 1233, 1027, 845, 759; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.10 (s, 1H), 7.36 (s, 1H), 7.45-7.61 (m, 8H), 8.02 (d, *J* = 3.1 Hz, 1H) 8.14-8.22 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 93.7, 104.9, 126.5, 127.2, 128.2, 128.5, 128.6, 128.8, 129.4, 130.2, 130.9, 131.4, 137.5, 146.3, 150.9, 156.0, 156.2; MS (EI, *m/z*): 347.4 $[M]^+$. Anal. calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10. Found: C, 82.78; H, 4.81; N, 12.34.

5,7-Diphenyl-2-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (3g)



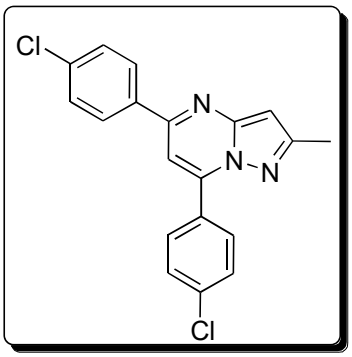
Yellow solid, Yield 84%; mp: 182-184 ºC; IR ($CHCl_3$, cm^{-1}): 2923, 1606, 1565, 1490, 1218, 1017, 762; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.96 (s, 1H), 7.09-7.58 (m, 10H), 8.12 (d, *J* = 5.4 Hz, 2H), 8.18 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 93.5, 105.0, 125.7, 126.2, 127.2, 127.6, 128.5, 128.8, 129.4, 130.2, 130.9, 137.4, 146.2, 150.9, 151.5, 156.2; MS (EI, *m/z*): 353.4 $[M]^+$. Anal. calcd. for $C_{22}H_{15}N_3S$: C, 74.76; H, 4.28; N, 11.89. Found: C, 74.59; H, 4.55; N, 11.67.

2-Methyl-5,7-dip-tolylpyrazolo[1,5-*a*]pyrimidine (3h)



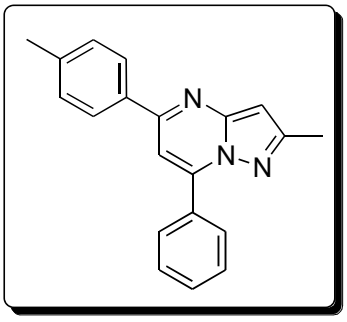
White gum, Yield 80%; IR ($CHCl_3$, cm^{-1}): 2937, 1610, 1478, 1176, 826, 762; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.42 (s, 3H), 2.46 (s, 3H), 2.52 (s, 3H), 6.54 (s, 1H), 7.21 (s, 1H), 7.31 (d, *J* = 4.8 Hz, 4H), 7.37 (d, *J* = 4.5 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.8, 21.5, 96.1, 103.8, 127.0, 129.3, 129.5, 134.6, 140.3, 141.2, 155.2, 155.7; MS (EI, *m/z*): 313.4 $[M]^+$. Anal. calcd. for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.16; H, 6.32; N, 13.66.

5,7-bis(4-Chlorophenyl)-2-methylpyrazolo[1,5-*a*]pyrimidine (3i)



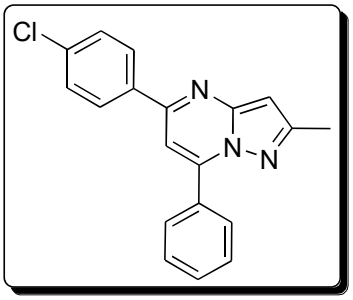
Yellow solid, Yield 75%; 172-175 ^{o}C; IR ($CHCl_3$, cm^{-1}): 2924, 1607, 1593, 1486, 1090, 1013, 817, 774; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.54 (s, 3H), 6.59 (s, 1H), 7.19 (s, 1H), 7.49 (d, *J* = 4.8 Hz, 2H), 7.56 (d, *J* = 5.1 Hz, 2H), 8.06 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.6, 96.7, 103.7, 128.4, 129.0, 129.8, 135.8, 136.4, 137.1, 145.0, 150.4, 154.3, 155.7; MS (EI, *m/z*): 354.2 $[M]^{+}$. Anal. calcd. for $C_{19}H_{13}Cl_2N_3$: C, 64.42; H, 3.70; N, 11.86 . Found: C, 64.79; H, 3.84; N, 11.62.

2-Methyl-7-phenyl-5-p-tolylpyrazolo[1,5-*a*]pyrimidine (3j)



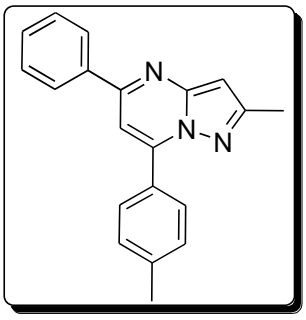
Brown Gum, Yield 78%; IR ($CHCl_3$, cm^{-1}): 2924, 1606, 1492, 1180, 817, 765; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.43 (s, 3H), 2.53 (s, 3H), 6.55 (s, 1H), 7.22 (s, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.55-7.58 (m, 2H), 8.01 (d, *J* = 4.2 Hz, 2H), 8.06-8.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.8, 21.3, 96.2, 104.2, 127.0, 128.6, 129.2, 129.5, 130.8, 131.6, 134.7, 140.4, 146.1, 150.5, 155.3, 155.7; MS (EI, *m/z*): 299.3 $[M]^{+}$. Anal. calcd. for $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.02; H, 5.84; N, 13.98.

5-(4-Chlorophenyl)-2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine (3k)



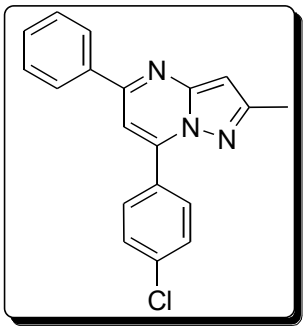
Brown solid, Yield 80%; mp: 132-134 ºC; IR ($CHCl_3$, cm^{-1}): 2924, 1594, 1556, 1488, 1013, 827, 764; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.54 (s, 3H), 6.57 (s, 1H), 7.20 (s, 1H), 7.49 (s, 1H), 7.56-7.58 (m, 3H), 8.05-8.08 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.9, 96.6, 104.0, 128.5, 128.7, 129.1, 129.3, 131.0, 131.5, 136.4, 146.4, 154.5, 155.7; MS (EI, *m/z*): 319.7 $[M]^+$. Anal. calcd. for $C_{19}H_{14}ClN_3$: C, 71.36; H, 4.41; N, 13.14. Found: C, 71.09; H, 4.65; N, 13.01.

2-Methyl-5-phenyl-7-p-tolylpyrazolo[1,5-*a*]pyrimidine (3l)



Brown solid, Yield 81%; mp: 109-111 ºC; IR ($CHCl_3$, cm^{-1}): 2922, 1661, 1596, 1463, 1019, 772; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.46 (s, 3H), 2.53 (s, 3H), 6.58 (s, 1H), 7.21 (s, 1H), 7.24 (s, 2H), 7.49-7.52 (m, 3H), 7.99-8.11 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.9, 21.6, 96.2, 96.4, 103.9, 104.1, 127.3, 128.9, 129.2, 129.4, 129.6, 130.1, 141.3, 146.4, 155.3, 155.8; MS (EI, *m/z*): 299.4 $[M]^+$. Anal. calcd. for $C_{20}H_{17}N_3$: C, 80.24; H, 5.72; N, 14.04. Found: C, 80.46; H, 5.44; N, 14.27.

7-(4-Chlorophenyl)-2-methyl-5-phenylpyrazolo[1,5-*a*]pyrimidine (3m)



Gum, Yield 85%; IR ($CHCl_3$, cm^{-1}): 2923, 1607, 1554, 1490, 1373, 1217, 1028, 763; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.54 (s, 3H), 6.58 (s, 1H), 7.51 (s, 2H), 7.56-7.59 (m, 3H), 8.08-8.12 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.9, 96.5, 104.5, 127.3, 128.7, 128.9, 129.3, 130.1, 130.9, 139.0, 143.9, 154.8, 155.0; MS (EI, *m/z*): 319.0 $[M]^+$. Anal. calcd. for $C_{19}H_{14}ClN_3$: C, 71.36; H, 4.41; N, 13.14. Found: C, 71.12; H, 4.69; N, 13.35.

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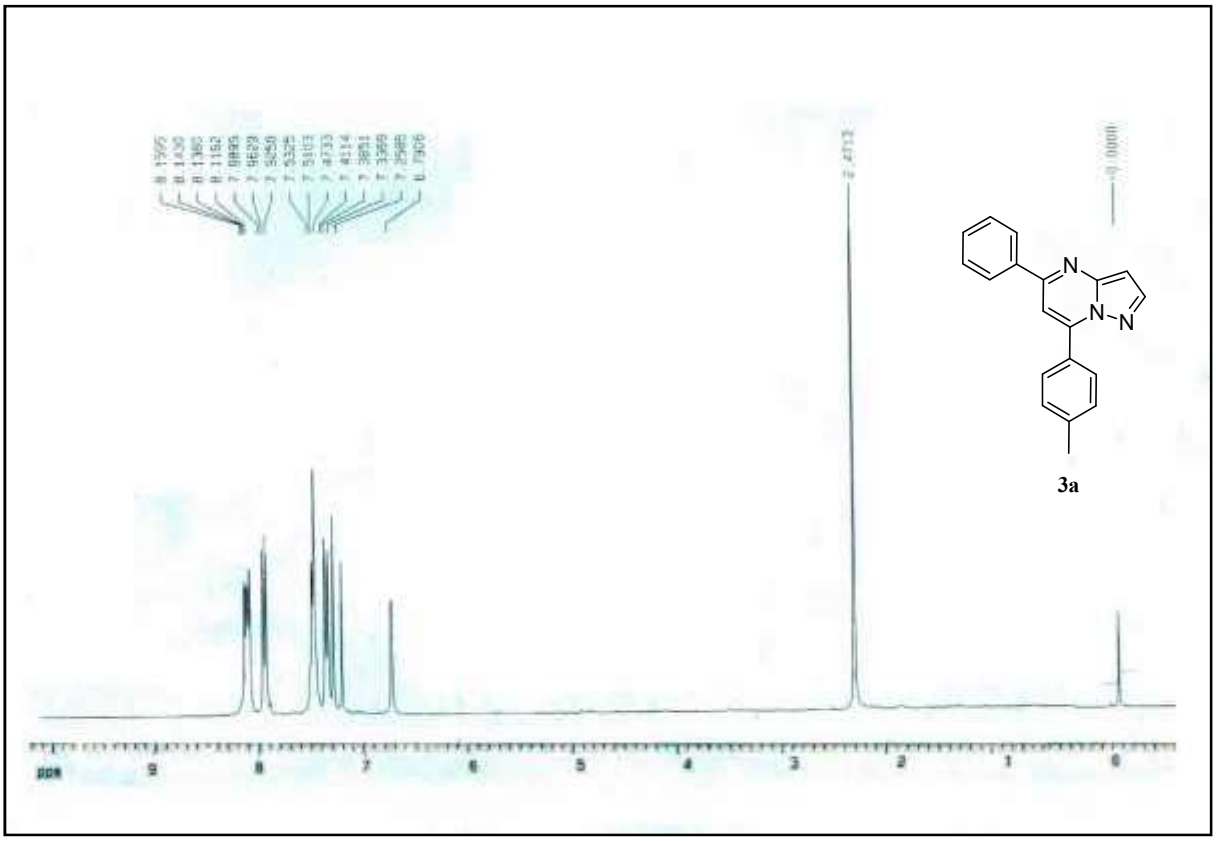
^{1}H NMR and ^{13}C NMR of some selected pyrazolo[1,5-*a*]pyrimidine compounds



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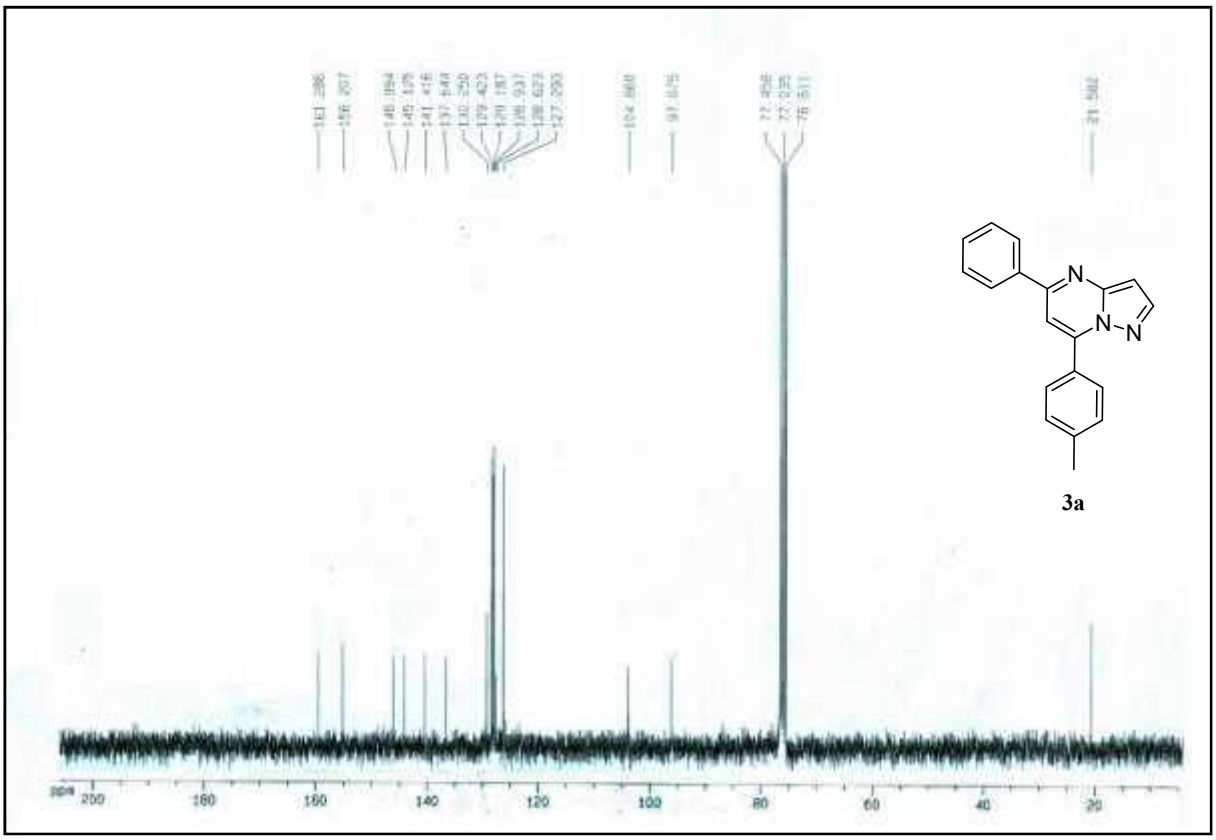

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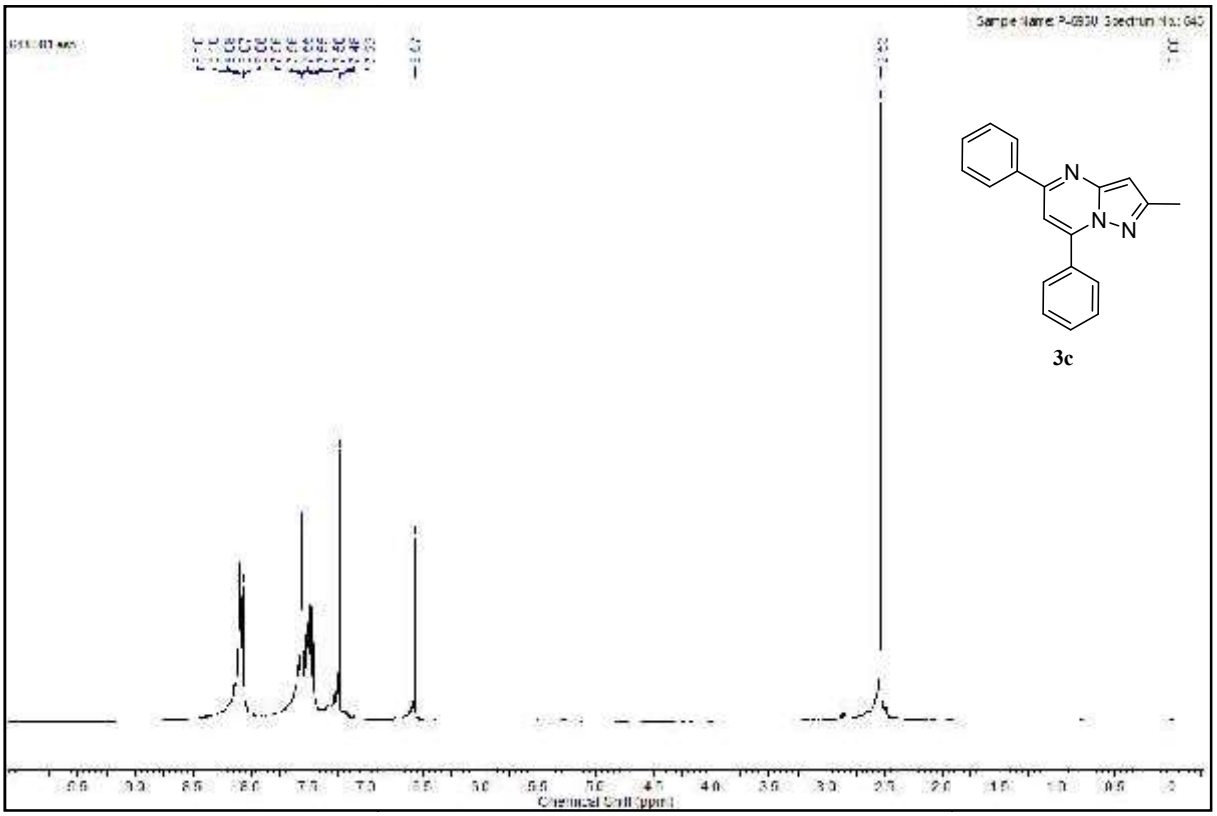

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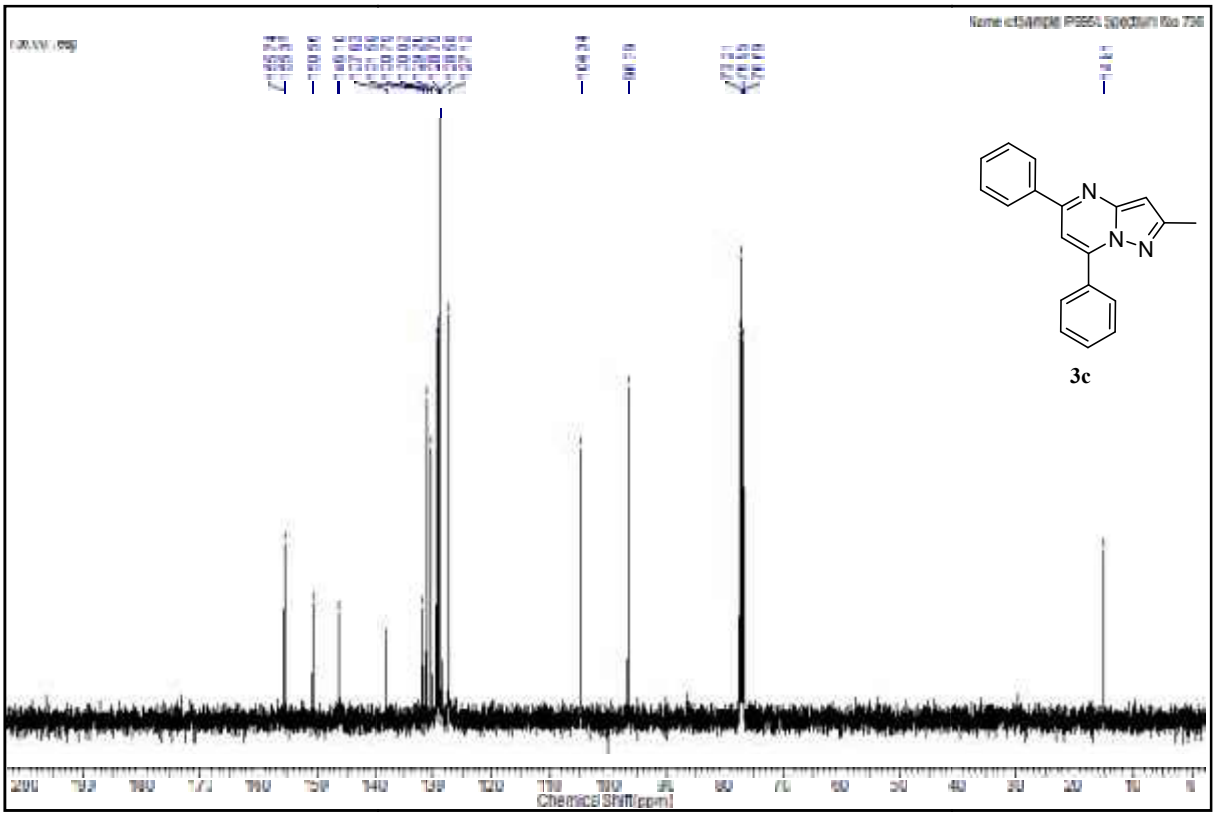

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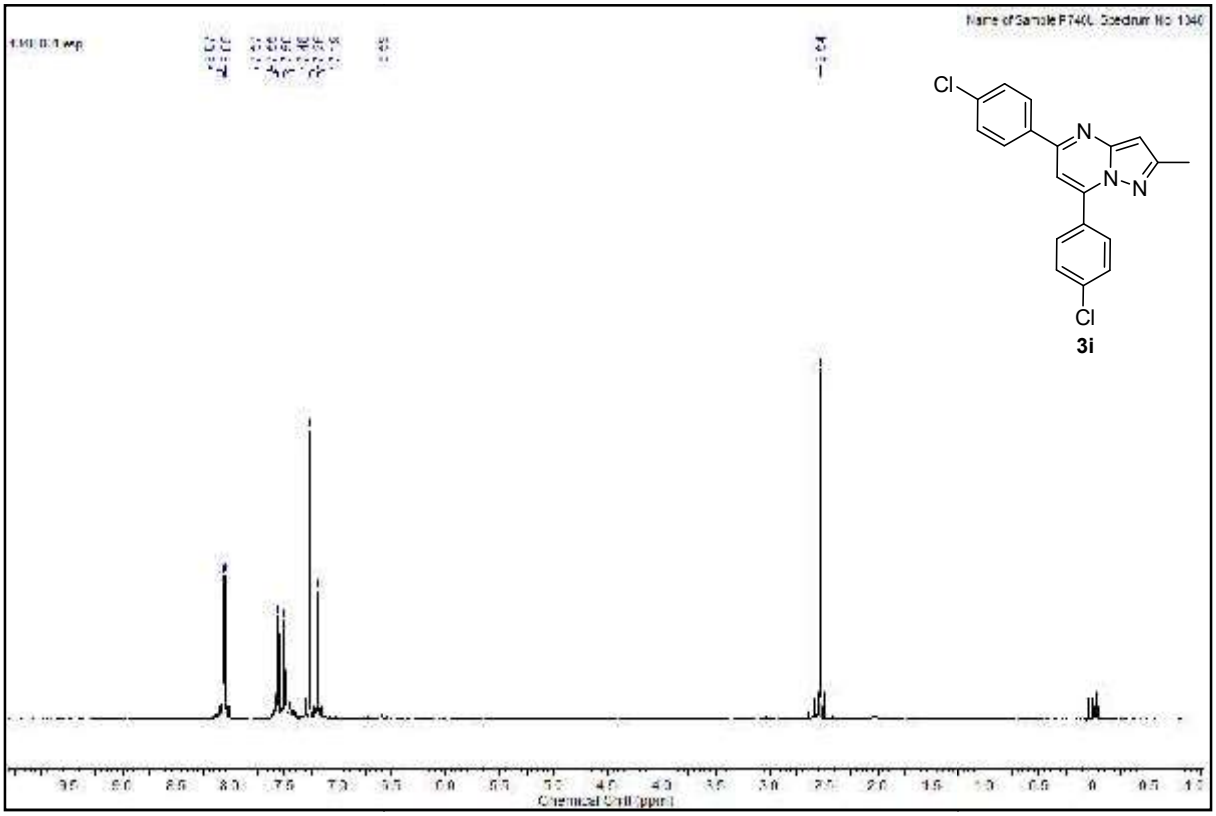
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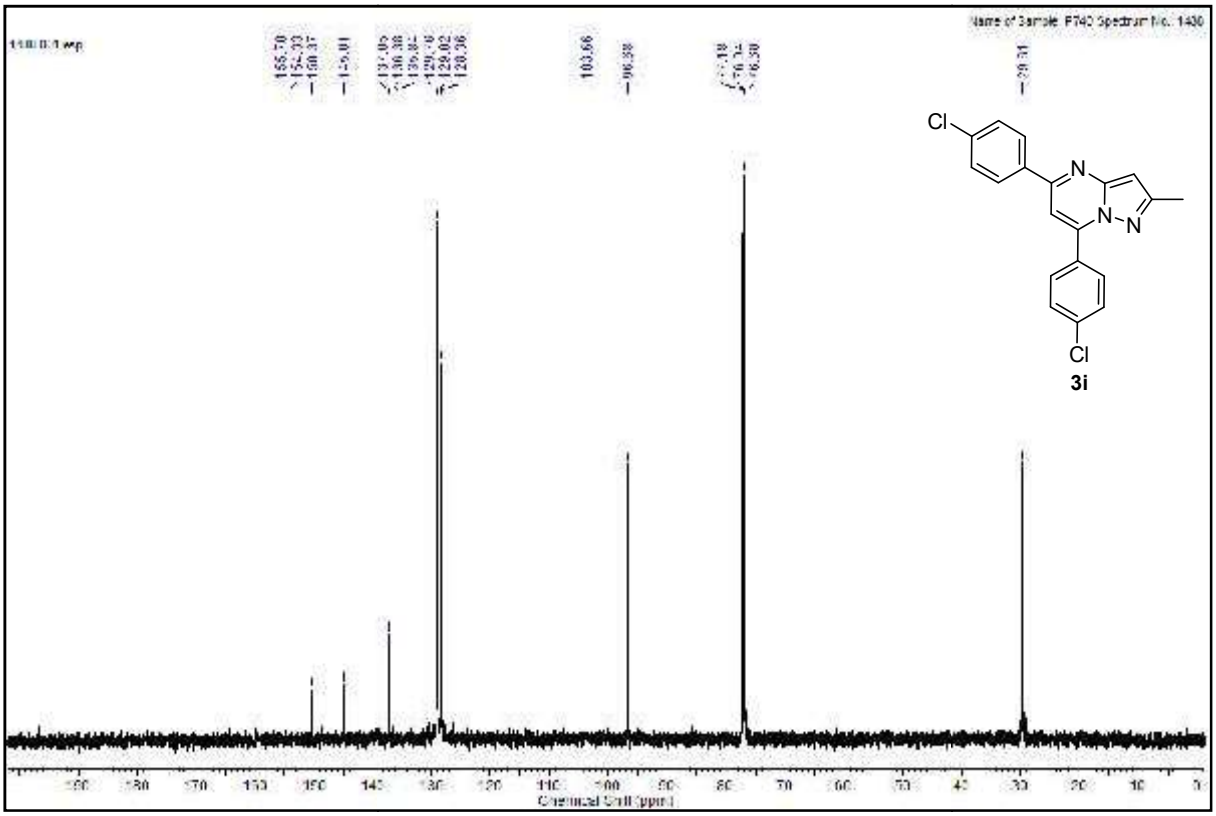
N
N
N
Cl
3i
Chemical Shift (ppm)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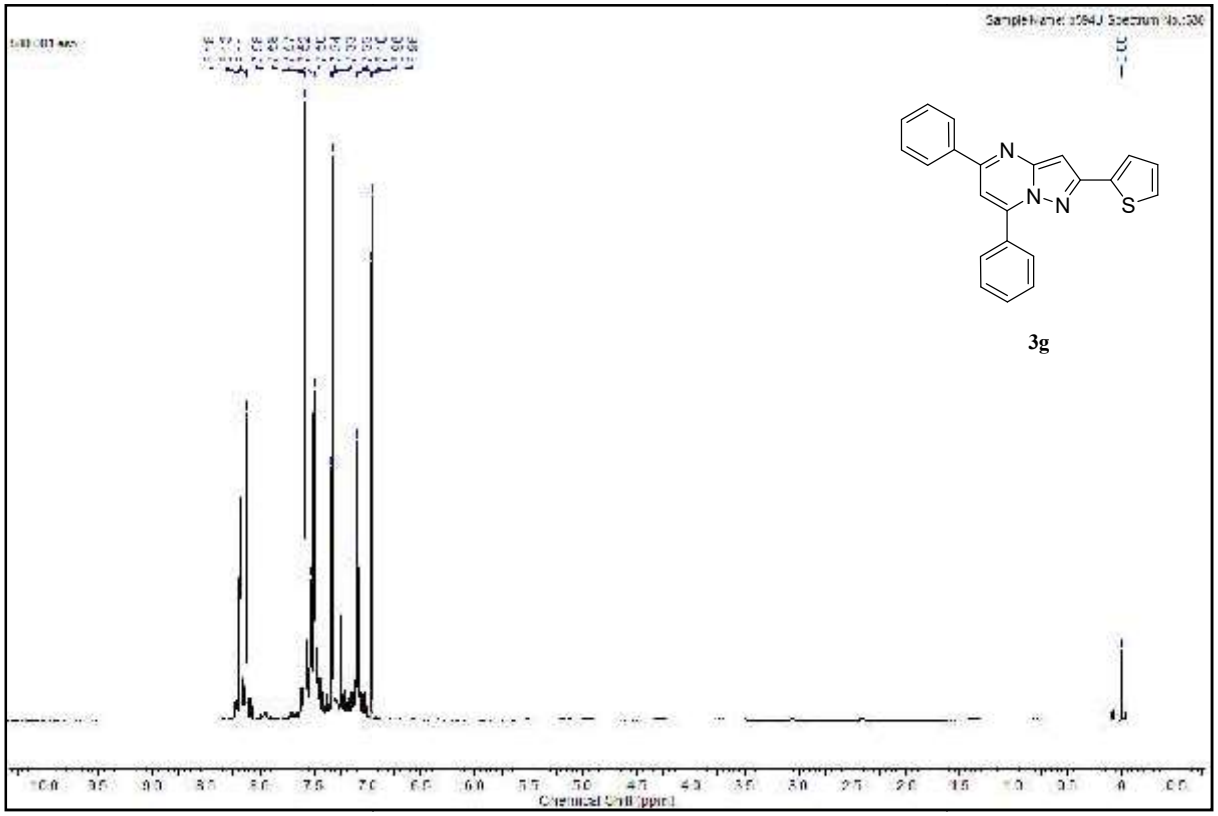
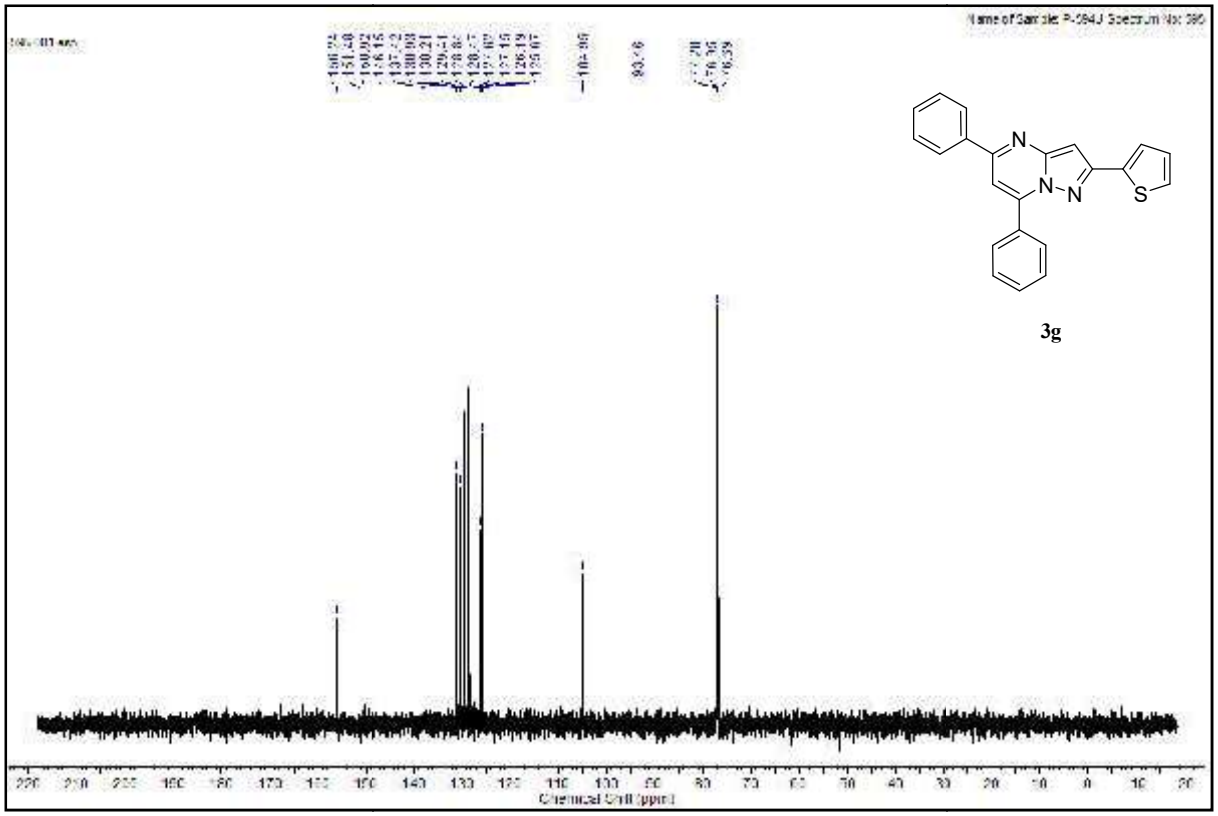
N
N
Cl
3i
Chemical Shift (ppm)



3g



3g