SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF HETEROCYCLIC ANALOGS

A THESIS SUBMITTED TO THE

SAURASHTRA UNIVERSITY

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FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

By

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UNDER THE GUIDANCE OF

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RAJKOT – 5 (GUJARAT, INDIA)

JUNE – 2009

Statement under O.Ph.D.7 of Saurashtra University

The work included in the thesis is done by me under the supervision of Dr. Yogesh T. Naliapara and the contribution made thereof is my own work.

Date:

Place: Rajkot ***Akshay M. Pansuriya***

Certificate

This is to certify that the present work submitted for the Ph. D. degree of Saurashtra University, Rajkot, Gujarat (India) by Mr. Akshay M. Pansuriya has been the result of work carried out under my supervision and is a significant contribution in the field of synthetic organic medicinal chemistry.

Date:
Place: Rajkot

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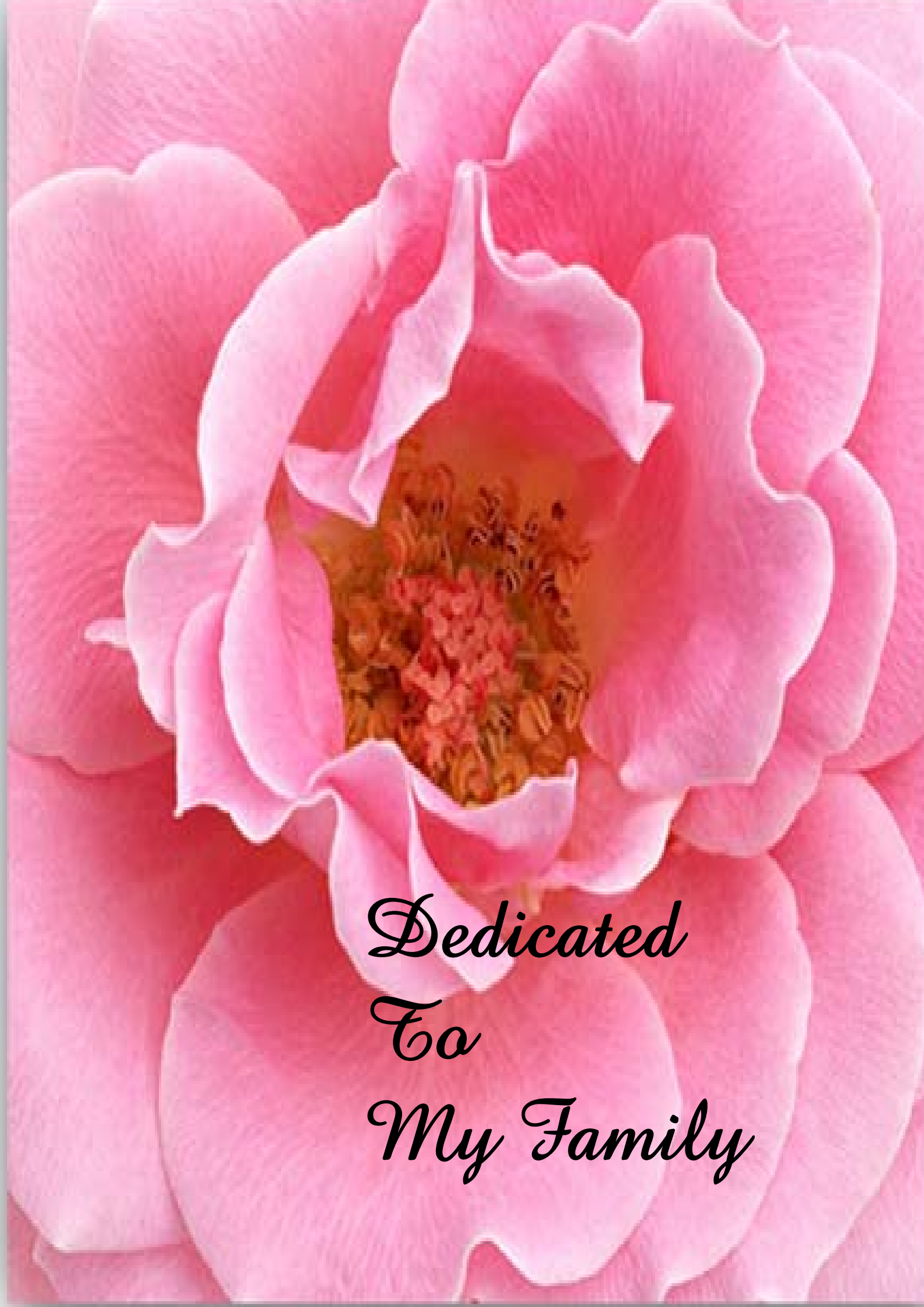
Dedicated
To
My Family

Acknowledgement

Firstly, I bow my head humbly before the Almighty God for making me capable of completing my Ph.D. Thesis; with his blessings only I have accomplished this huge task.

I express deep sense of gratitude and thankfulness to my guide **Dr. Yogesh T. Naliapara** who has helped me at each and every point of my research work with patience and enthusiasm. I am much indebted to him for his inspiring guidance, affection, generosity and everlasting enthusiasm throughout the tenure of my research work, without that the Thesis would not have appeared in the present form.

I also thank to Dr. P. H. Parsania, Professor and Head, Department of Chemistry, Saurashtra University, Rajkot for his encouragement and providing adequate research facilities.

At this juncture I thank my whole family for encouraging me and providing every help to fulfill my task especially my parents and my brother Sanjay for their invaluable support and constant motivation during tenure of my work.

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I am truly thankful to teaching and non teaching staff of my Department for their kind support. I am profoundly indebted to Department of Chemistry, Saurashtra University for providing me the excellent laboratory facility for accomplishing this work. I express my grateful acknowledgement to Gujarat State Government for Junior research Fellowship which shorted out my financial worries to some extent.

I would like to thank Regional Sophisticated Instrumentation Centre, Chandigarh for ^{1}H NMR analysis and Department of Chemistry for GC-MS and IR facility.

Akshay M. Pansuriya

Content

General Protocol

1. ^{1}H NMR spectra were recorded on Bruker avance II 400 MHz NMR spectrometer using TMS as an internal reference.

2. Mass spectra were recorded on GC-MS QP-2010 spectrometer.

3. IR spectra were recorded on Schimadzu FR-IR-8400 spectrometer.

4. Elemental analysis was carried out on Vario EL III Carlo Erba 1108.

5. Thin layer chromatography was performed on Silica Gel (Merck 60 F_{254}).

6. The chemicals used for the synthesis of compounds were purchased from Spectrochem, Merck, Thomas-baker and SD fine chemical.

7. MPs were taken in open capillary and are uncorrected.

8. Microwave assisted reaction were carried out in QPro-M microwave synthesizer.

Chapter 1

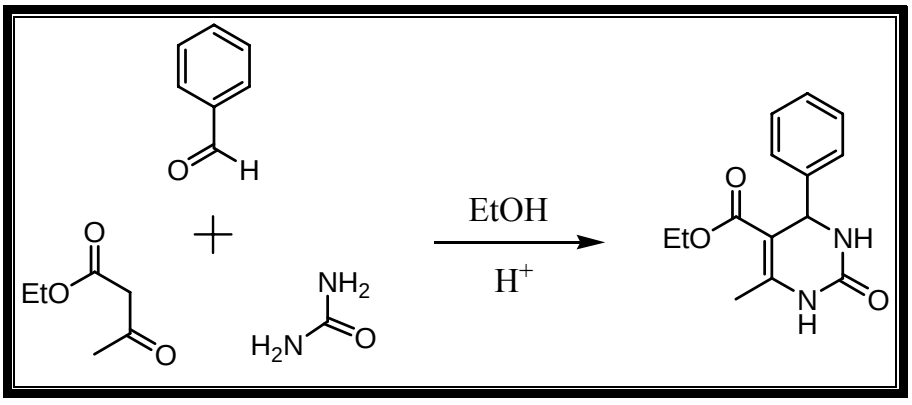
Synthesis and Characterization of Novel n-Butyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate Derivatives using conventional method and microwave synthetic approach under solid support

Chapter 1

Synthesis and characterization of novel n-butyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives using conventional method and microwave synthetic approach under solid support

1.1 Biginelli Reaction

P. Biginelli reported the synthesis of functionalized 3,4-dihydropyrimidin-(1*H*)-ones (DHPMs) via three component condensation reactions of an aromatic aldehyde, urea, and ethyl acetoacetate. In the past decade, this multicomponent reaction has experienced a remarkable revival, mainly due to the interesting pharmacological properties associated with this dihydropyrimidine scaffold.[1]



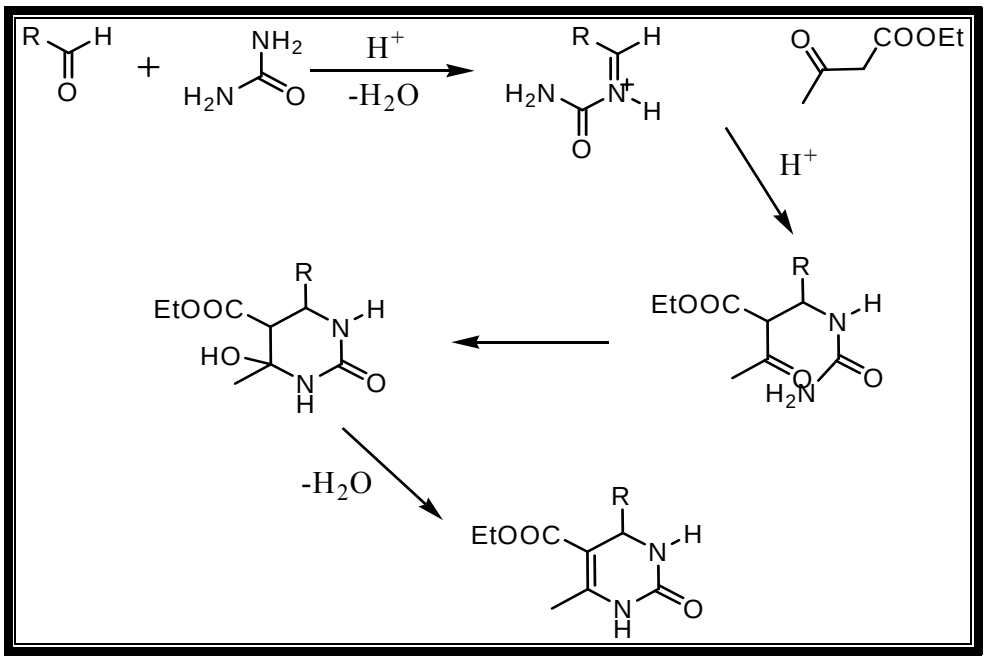
Biginelli Dihydropyrimidine Synthesis

The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one. Apart from a series of publications by the late Karl Folkers in the mid 1930s, the "Biginelli reaction" or "Biginelli

condensation" as it was henceforth called was largely ignored in the early part of the 20th century. The synthetic potential of this new heterocycle synthesis therefore remained unexplored for quite some time. In the 1970s and 1980s, interest slowly increased, and the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of multifunctionalized dihydropyrimidines.[2-4]

1.2 Mechanistic Studies of Biginelli Reaction [5-9]

The mechanism of the Biginelli reaction has been the subject of some debate over the past decades. Early work by Folkers and Johnson suggested that bisureide, i.e. the primary bimolecular condensation product of benzaldehyde and urea, is the first



intermediate in this reaction. In 1973, Sweet and Fissekis proposed a different pathway and suggested that carbenium ion, produced by an acid-catalyzed aldol reaction of benzaldehyde with ethyl acetoacetate, is formed in the first and limiting step of the Biginelli condensation. Kappe et al reinvestigated the mechanism in 1997 using $^{1}H/^{13}C$ NMR spectroscopy and trapping experiments and have established that the key step in this sequence involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate from the aldehyde and urea precursors. Interception of the iminium ion by ethyl acetoacetate, presumably through its enol tautomer, produces an open-chain ureide which subsequently cyclizes to

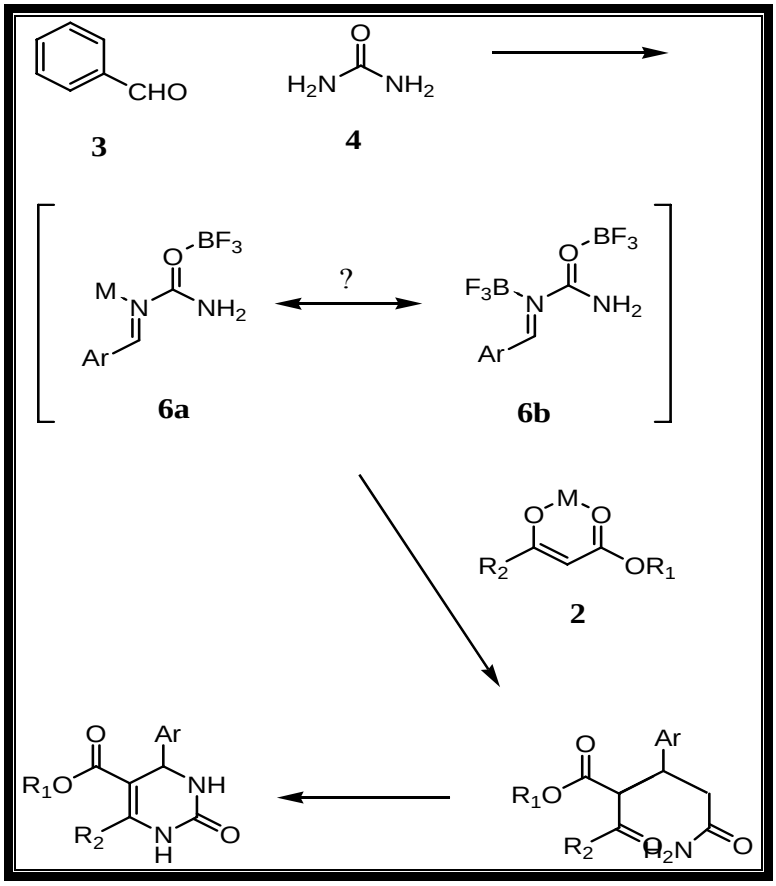
hexahydropyrimidine. Acid-catalyzed elimination of water ultimately leads to the final DHPM product. The reaction mechanism can therefore be classified as an R-amidoalkylation, or more specifically as an R-ureidoalkylation. The alternative "carbenium ion mechanism" does not constitute a major pathway; however, small amounts of enone are sometimes observed as byproduct. Although the highly reactive *N*-acyliminium ion species could not be isolated or directly observed, further evidence for the proposed mechanism was obtained by isolation of intermediates, employing sterically bulky or electron-deficient acetoacetates respectively. The relative stereochemistry in hexahydropyrimidine was established by an X-ray analysis. In fact, a number of hexahydropyrimidines could be synthesized by using perfluorinated 1,3-dicarbonyl compounds or α-keto esters as building blocks in the Biginelli condensation.

1.3 Alternative synthetic routes for better yield, shorter reaction time and to synthesize new analogs

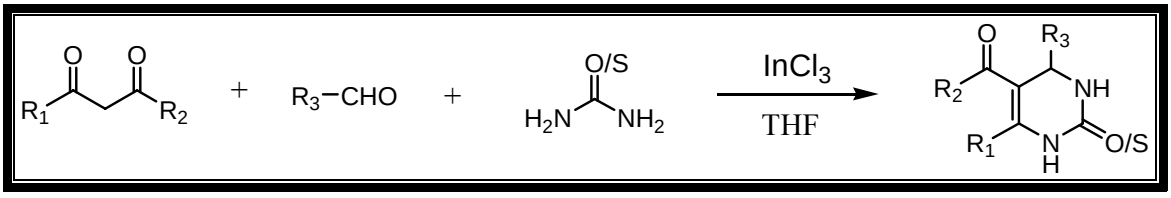
Various modifications have been applied to Biginelli reaction to get better yield and to synthesize biologically active analogs. Different catalysts have been reported to increase the yield of the reaction. Microwave synthesis strategies have also applied to shorten the reaction time. Solid phase synthesis and combinatorial chemistry has made possible to generate library of DHPM analogs.

1.3.1 Catalysts

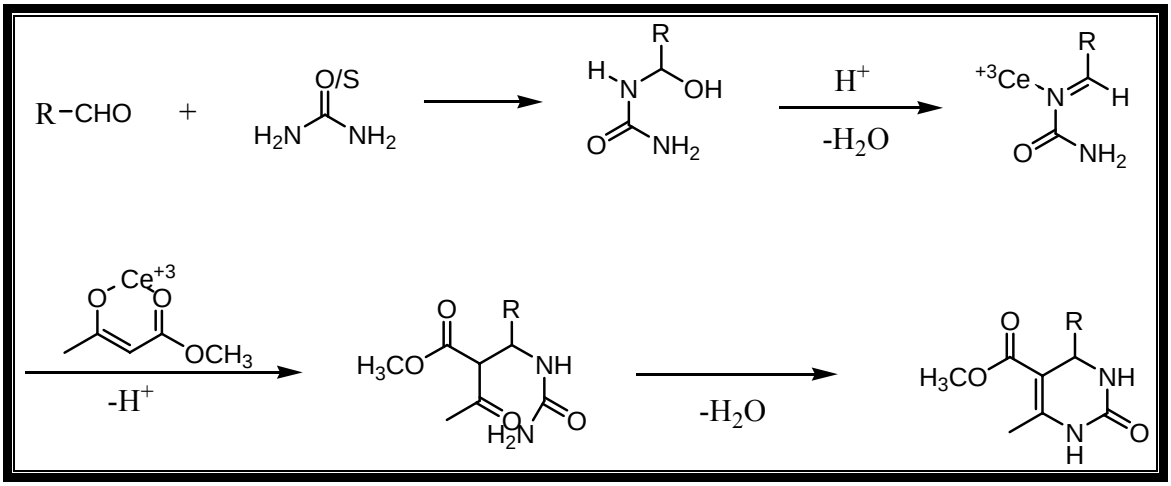
Essa H. Hu et al reported Biginelli reaction catalyzed with BF_3OEt_2, transition metal salt, and proton source to yield 80-90% Biginelli product. We propose a mechanism similar to that of Folkers and Johnson and to that of Kappe for the Biginelli reaction wherein formation of acyl imine intermediate formed by reaction of the aldehyde with urea and stabilized by either BF3 or the transition metal, is the key, rate limiting step. Subsequent addition of the α-keto ester enolate, followed by cyclization and dehydration, would afford the dihydropyrimidinone.[10]



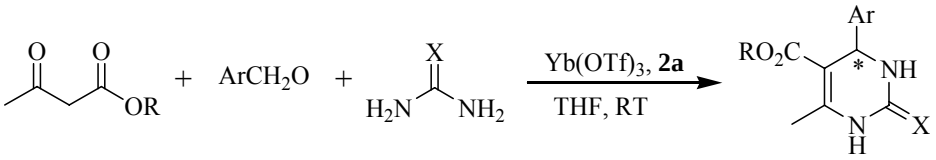
Brindaban C. Ranu et al reported Indium (III) Chloride as an efficient catalyst for Biginelli reaction. A wide range of structurally varied α-dicarbonyl compound, aldehyde and urea were coupled together by this procedure to produce the corresponding dihydropyrimidinones. A variety of substituted aromatic, aliphatic, and heterocyclic aldehydes have been subjected to this condensation very efficiently. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1H)-thiones.[11]

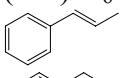


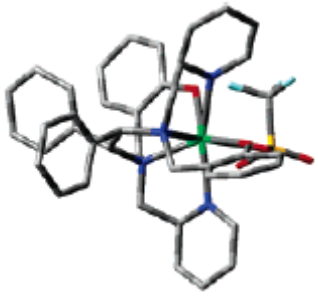
Bose et al used $CeCl_3$ as a catalyst and reported solvent free synthesis of Biginelli compounds using this new catalyst. This procedure provides higher yield, shorter reaction time and simple work up methods. Solvent free reactions using this catalyst gave about 70% yield and reaction time was about 10 hrs. If ethanol is used as solvent, 90% yield was obtained with this catalyst. 25 mol % amount of $CeCl_3.7H_2O$ was found to be sufficient to push the reaction forward. The increased amount did not build further advantage.[12]

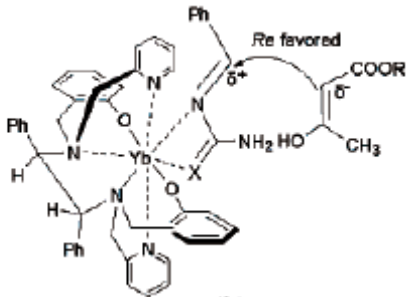


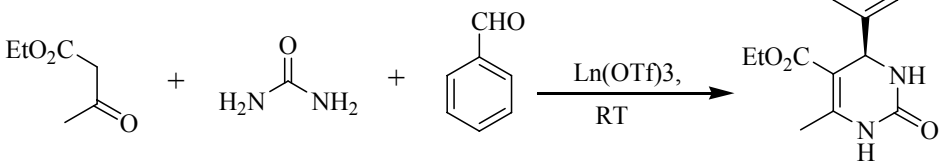
Enantioselective one pot synthesis of Biginelli reaction is reported with use of lanthanide triflates ytterbium triflates. These catalyst leads to highly enantioselectivity and up to 99% enantioselective Biginelli reaction can be carried out.[13]



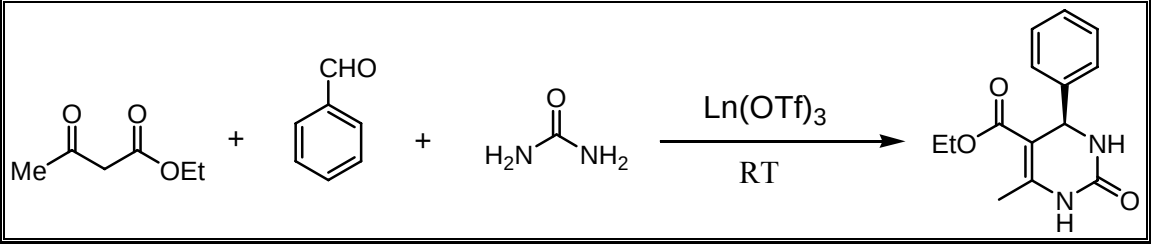
Entry	Ar	R	X	Yield, %	ee, %	Config.
1	C_6H_5	Et	O	87	90	R
2	C_6H_5	Et	S	81	99	R
3	3-(NO_2)-C_6H_4	^{i}Pr	O	90	>99	R
4	3-(NO_2)-C_6H_4	^{i}Pr	S	88	87	R
5	3-(F)-C_6H_4	Et	O	80	97	R
6	2-(Cl)-C_6H_4	Et	S	73	98	R
7	2-(Cl)-C_6H_4	Et	O	78	89	R
8	2-(Br)-C_6H_4	Et	O	82	95	R
9	3-(OH)-C_6H_4	Et	O	81	91	R
10	3-(OH)-C_6H_4	Et	S	80	99	R
11	2-(OH)-C_6H_4	Et	O	86	98	R
12		Et	O	81	80	R
13		Et	O	82	82	R
14		Et	O	87	93	R



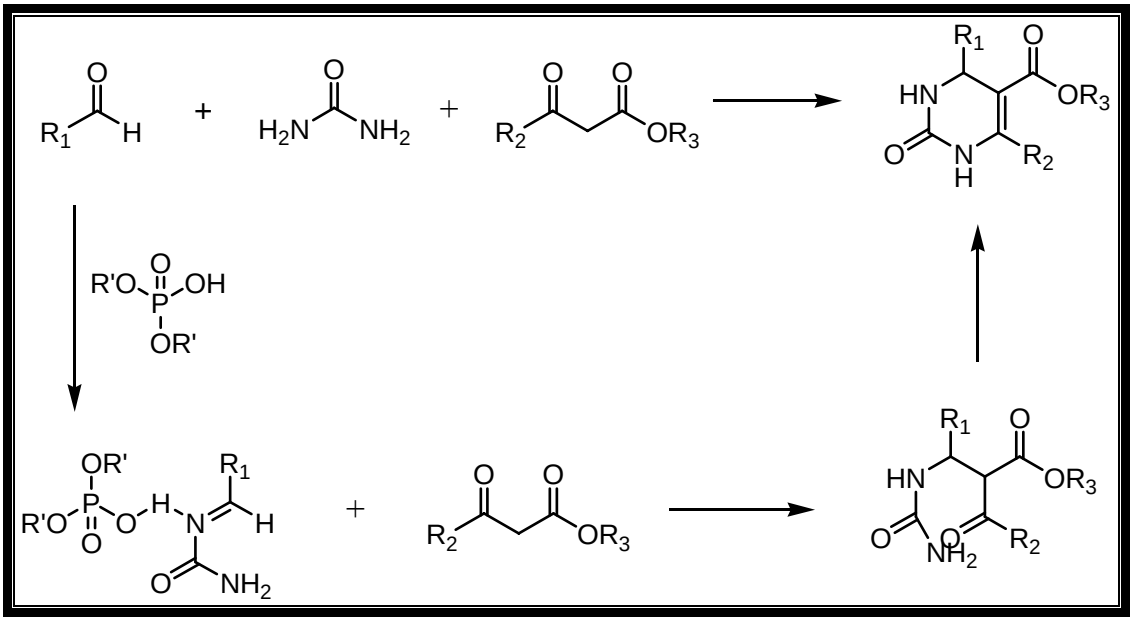




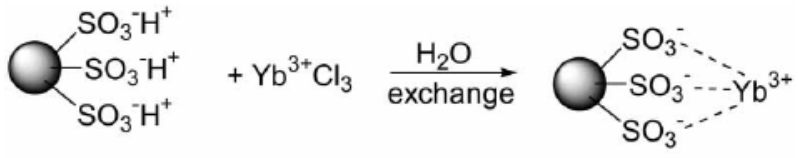
entry	Lewis acid	solvent	yield, %	ee, %	config.
1	$La(OTf)_3$	THF	83	81	R
2	$Sm(OTf)_3$	THF	81	85	R
3	$Yb(OTf)_3$	THF	87	90	R
4	$Yb(OTf)_3$	CH_2Cl_2	80	83	R
5	$Yb(OTf)_3$	CH_3CN	86	82	R
6	$Yb(OTf)_3$	CH_3OH	88	80	R
7	$Yb(OTf)_3$	THF	84	85	R

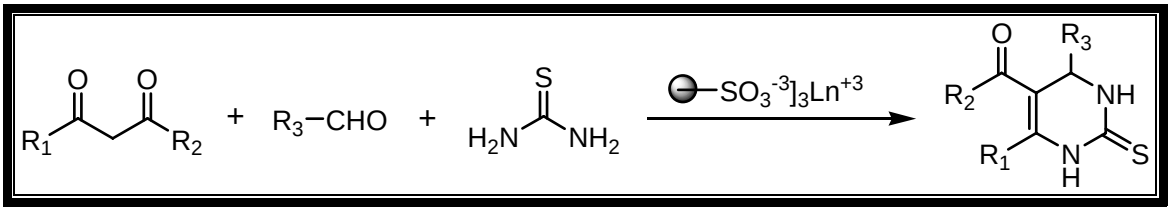


Very recently, chiral phosphoric acid is reported as highly enantioselective catalyst for Biginelli reaction. Reaction is reported in presence of 10 mol % of chiral phosphoric acid to produce desired enantioselective product. This is the first organocatalytic asymmetric Biginelli reaction. The optimal chiral phosphoric acid afforded the reaction in high yields with excellent enantioselectivities of up to 97% ee. A wide variety of substrates, including aldehydes and α-keto esters, could be tolerated. This reaction has an advantage of avoiding the contamination of transition metals in the manufacture of the medicinally relevant chiral 3,4-dihydropyrimidin-2-(1*H*)-ones.[14]



Recently Jiang and Chen reported Yb(III)-Resin catalyzed Biginelli reaction Under Solvent-free Conditions.[15]





Heravi et. al. recently reported synthesis of dihydropyrimidones using 12-molybdophosphoric acid in refluxing acetic acid to catalyze this three-component condensation reaction to afford the corresponding pyrimidinones in good yields.[16]

An improved approach has been found to carry out the Biginelli reaction for the synthesis of 3,4- dihydropyrimidine- 2(1H)-one derivatives. This synthesis was performed in the presence of hydrochloric acid and β-cyclodextrin in ethanol solution. Compared with the classical Biginelli reaction conditions, this new approach has the advantage of excellent yields and short reaction time.[17]

An efficient synthesis of 3,4-dihydropyrimidinones from the aldehyde, β-keto ester and urea in ethanol, using ferric chloride hexahydrate or nickel chloride hexahydrate as the catalyst, is described. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yields (53-97%) and short reaction time (4-5 hours).[18]

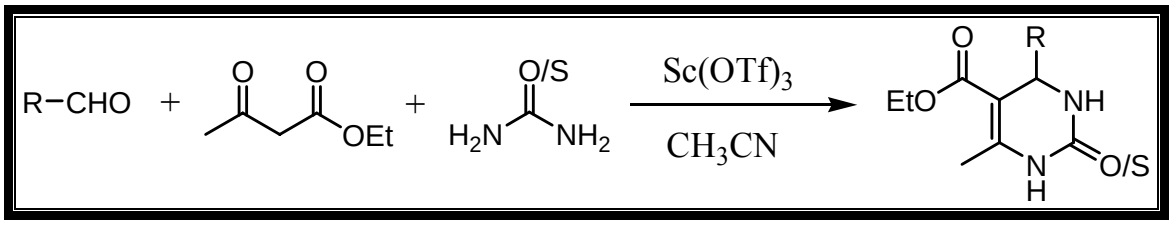
5-Alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2-ones are synthesized by the one-pot reactions of aldehydes, β-ketoesters and urea using a catalytic amount of phosphotungstic acid (PTA) in ethanol. The modified Biginelli cyclocondensation not only shortens the reaction period and simplifies the operation, but also improves the yields.[19]

Ruthenium (III) chloride efficiently catalyzes the three-component Biginelli reaction of an aldehyde, a β-keto ester, and urea or thiourea under solvent-free conditions to afford the corresponding 3,4-dihydropyrimidine-2-(1*H*)-ones in excellent yields.[20]

The Biginelli reaction, a one-pot condensation of aldehydes, urea or thiourea, and β-dicarbonyl compounds, is efficiently catalyzed by samarium diiodide. The biologically active dihydropyrimidinones are easily synthesized in moderate to excellent yields under solvent-free conditions.[21]

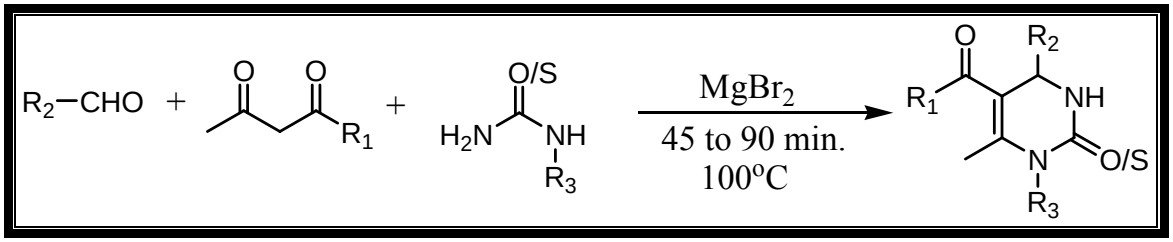
Hydroxyapatite doped with $ZnCl_2$, $CuCl_2$, $NiCl_2$ and $CoCl_2$ efficiently catalyses the three components Biginelli reaction between an aldehyde, ethyl acetoacetate and urea in refluxing toluene to afford the corresponding dihydropyrimidinones in high yields.[22]

Sc(III)triflate efficiently catalyzes the three-component condensation reaction of an aldehyde, a β-ketoester, and urea in refluxing acetonitrile to afford the corresponding 3,4-dihydropyrimidin-2(1H)-ones in excellent yields. The catalyst can be recovered and reused, making this method friendly and environmentally acceptable.[23]

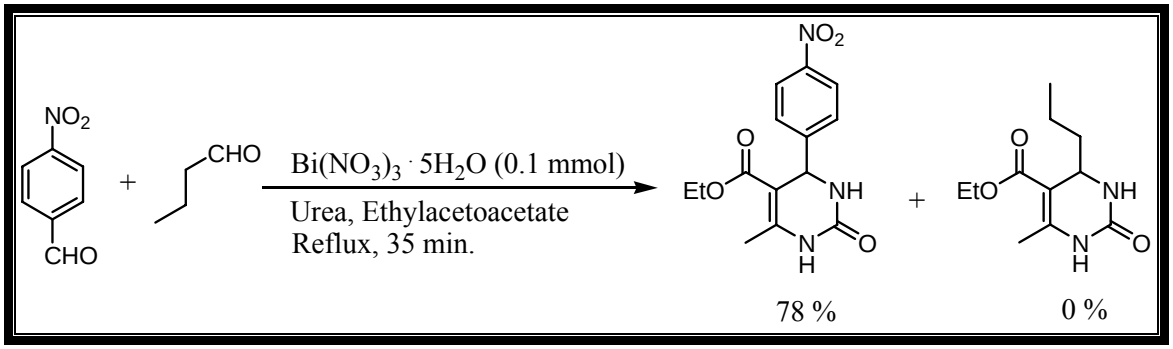


Shailaja et al have demonstrated experimentally a simple and straightforward protocol (combination system of SnCl2–LiCl) which provides dihydropyrimidin-2-one system in high yield and high purity while retaining the simplicity of the Biginelli concept.[24]

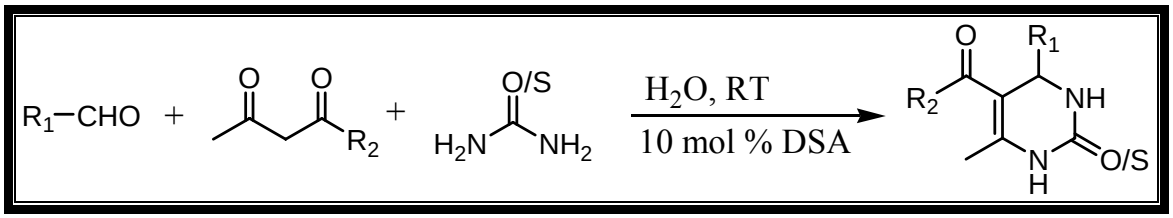
Magnesium bromide efficiently catalyzes the three-component condensation reaction of aldehyde, β-diketone and urea/thiourea under solvent free conditions to afford the corresponding dihydropyrimidinones in high yields and short reaction time.[25]



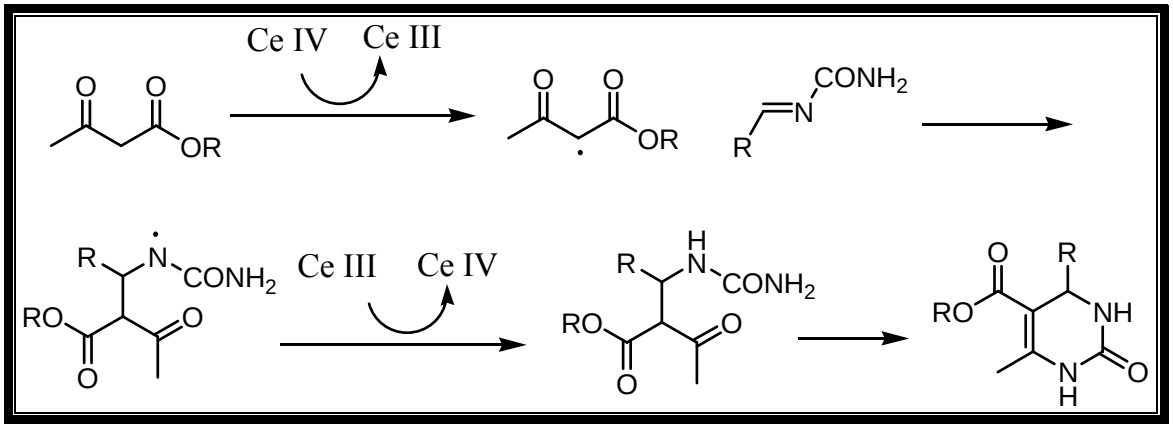
Bismuth nitrate pentahydrate catalyzes the three component condensation reaction of an aromatic aldehyde, urea and a β-ketoester or a β-diketone under solvent-free conditions to afford the corresponding dihydropyrimidinones (DHPMs) in high yields. The present method is also effective for the selective condensation of aryl aldehydes in the presence of aliphatic aldehydes.[26]



Sharma et al reported a simple, efficient, mild and green method has been developed for the synthesis of 3,4-dihydropyrimidin-2-ones employing dodecyl sulfonic acid as an excellent surfactant-type Bronsted acid catalyst in aqueous media at room temperature.[27]



Yadav et al reported that Ceric ammonium nitrate efficiently catalyzes the three component Biginelli reaction in methanol to afford the corresponding dihydropyrimidinones in excellent yields under sonication.[28a]

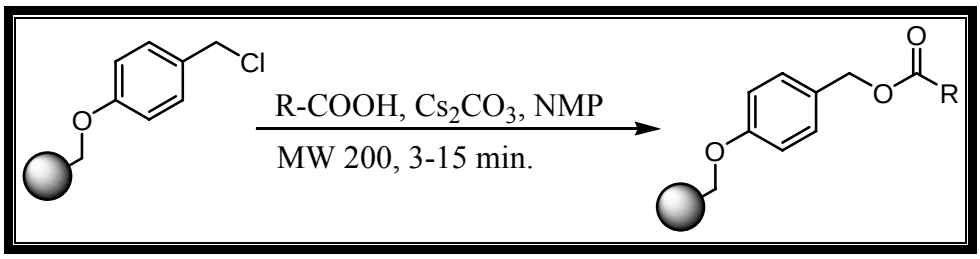


More recently, copper (II) sulfamate,[28b] ferric perchlorate,[28c] alumina-supported trifluoromethane sulfonic acid,[28d] $Al_2O_3/MeSO_3H$,[28e] cellulose sulfuric acid[28f] and CsF-Celite[28g] were reported as an efficient catalyst for one-pot Biginelli reaction.

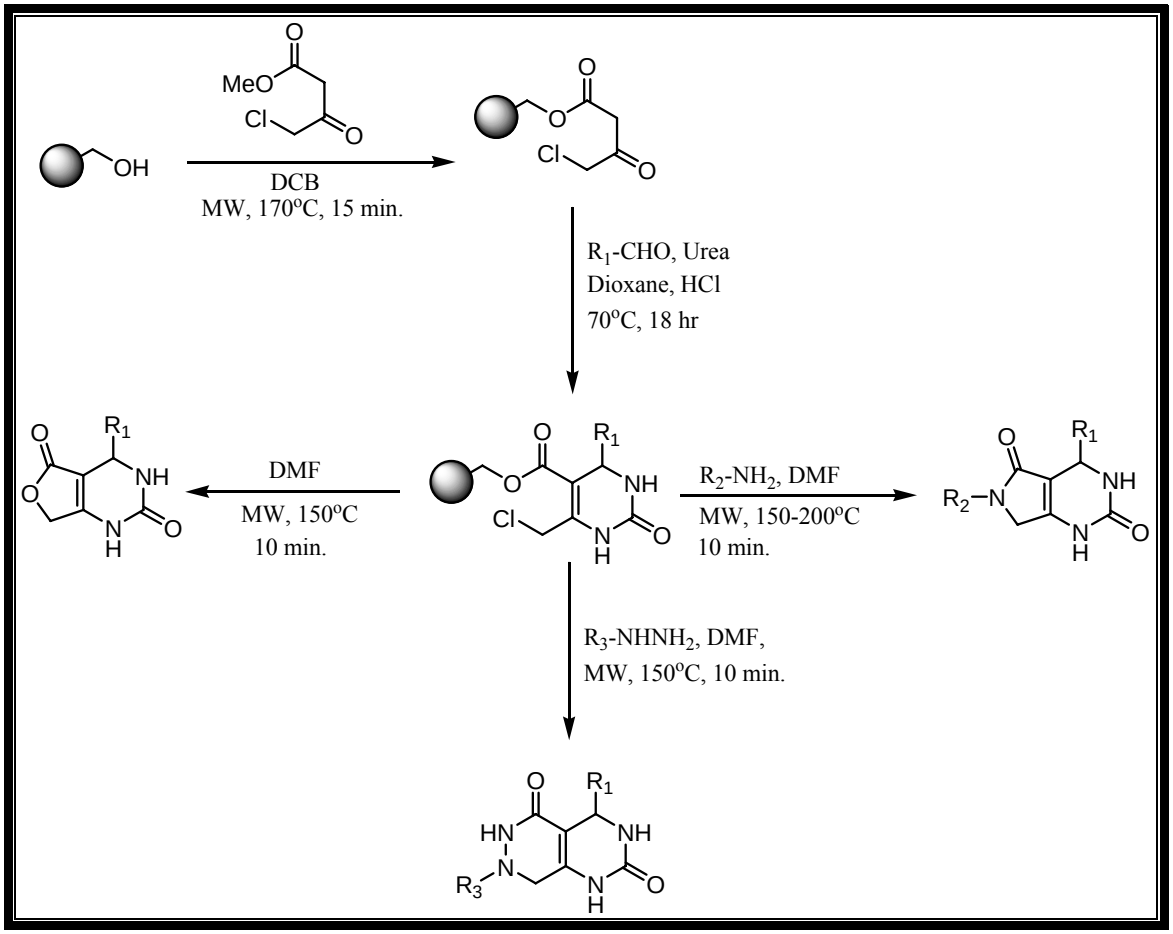
1.3.2 Solid Phase Synthesis

Solid-phase organic synthesis (SPOS) exhibits several advantages compared with classical protocols in solution. Reactions can be accelerated and driven to completion by using a large excess of reagents, as these can easily be removed by filtration and subsequent washing of the solid support. In addition, SPOS can easily be automated by using appropriate robotics and applied to "split-and-mix" strategies, useful for the synthesis of large combinatorial libraries[29-30]

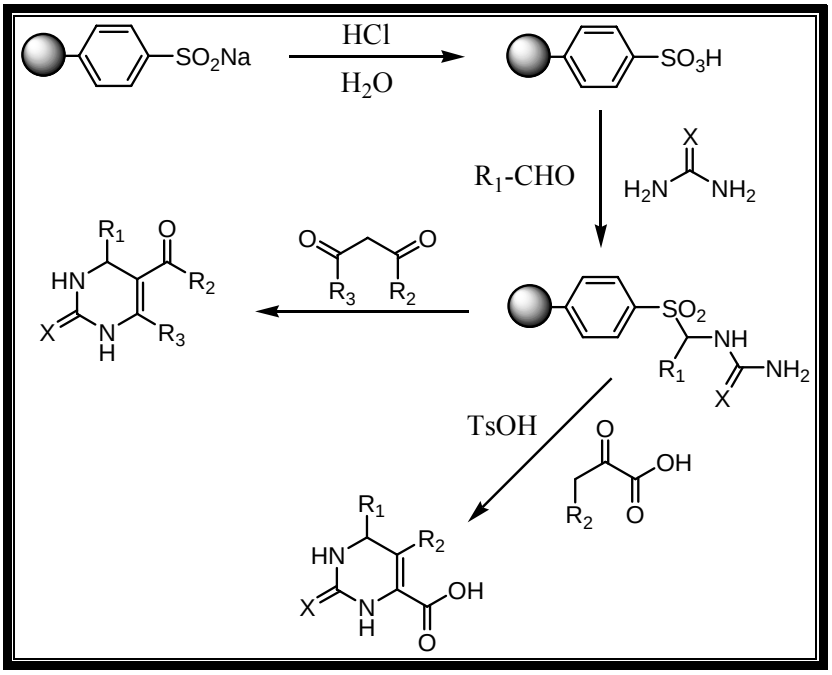
A study published in 2001 demonstrated that high temperature microwave heating (200 8C) can be effectively employed to attach aromatic carboxylic acids to chloromethylated polystyrene resins (Merrifield and Wang) by the cesium carbonate method. Significant rate accelerations and higher loadings were observed when the microwave-assisted protocol was compared to the conventional thermal method. Reaction times were reduced from 12–48 hours with conventional heating at 80 ºC to 3–15 minutes with microwave heating at 200 ºC in NMP in open glass vessels[31-32].



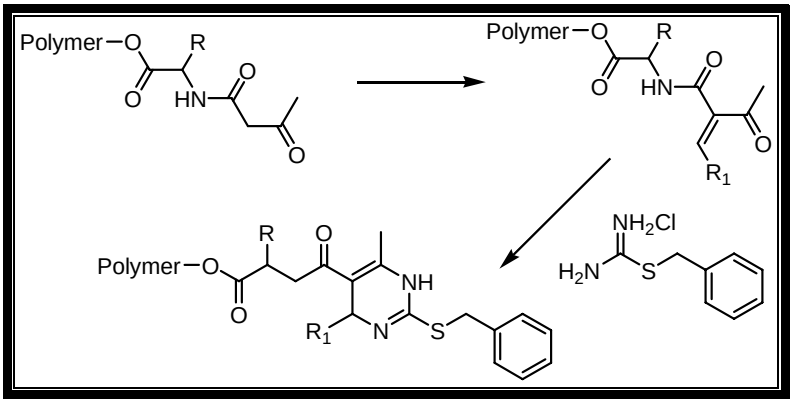
Kappe et al[33] have reported microwave assisted synthesis of bicyclic systems derived from Biginelli DHPM derivatives.



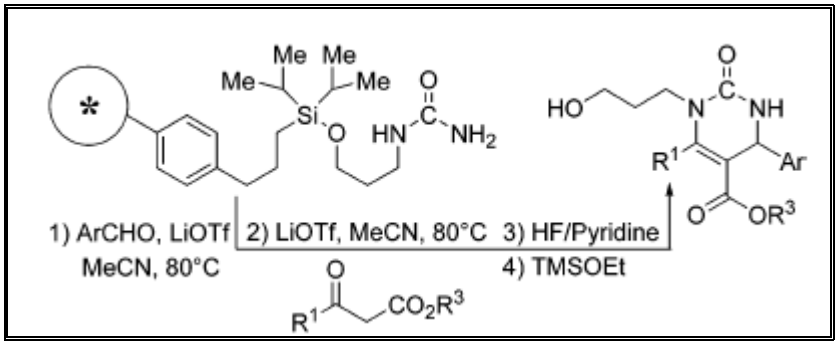
In recent years, various methods have been examined for the synthesis of DHPM on solid phase. Li and Lam describe a convenient traceless solid-phase approach to synthesize3,4-dihydropyrimidine-2-ones. Key steps in the synthesis are (i) sulfinate acidification, (ii) condensation of urea or thiourea with aldehydes and sulfinic acid, and (iii) traceless product release by a one-pot cyclization-dehydration process. Since a variety of reagents can be used in steps (ii) and (iii), the overall strategy appears to be applicable to library generation.[34]



Very recently, Gross et al developed a protocol for based on immobilized α-ketoamides to increase the diversity of DHPM. The resulting synthetic protocol proved to be suitable for the preparation of a small library using different building blocks. They found that the expected DHPM derivatives were formed in high purity and yield if aromatic aldehyde- and α-ketoamide building blocks were used. The usage of an aliphatic aldehyde leads to an isomeric DHPM mixture. Purities and yields were not affected if thiourea was used instead of urea.[35]



Lusch et al reported a direct, Lewis acid-catalyzed Biginelli synthesis of 3,4-dihydropyrimidinones on high-capacity polystyrene macrobeads with a polymer *O*-silyl-attached *N*-(3-hydroxypropyl)urea. Resin-urea was first reacted separately with either 4-bromo- or 4-chlorobenzaldehyde or LiOTf in MeCN at 80 °C. After washing, the beads were pooled and reacted with ethyl acetoacetate and LiOTf in MeCN at 80 °C. Formation of only *one* kind of Biginelli product per bead demonstrated the feasibility of a solid-phase non-Atwal two-step split-and-pool synthesis of 3,4-dihydropyrimidinones.[36]



1.3.3 Microwave assisted synthesis

The major limitations of Biginelli reaction are lower yield and longer reaction time. When thiourea is used for synthesis, yield obtained is very low and reaction completion takes longer time. Similar disadvantages are observed when different 1,3-diketone and aldehyde other than aromatic are used for the synthesis of designed molecules. Moreover, product separation and work up also cause problem and needed special techniques. Thus, three main disadvantages are lower yield, longer reaction time and work up in Biginelli reaction when different building blocks are used to synthesize library of compound.

The use of microwave as energy source in organic synthesis for better yield and shorter reaction time has been extensively investigated.[37-42] Most of the early pioneering experiments in MAOS were performed in domestic, sometimes modified, kitchen microwave ovens; the current trend is to use dedicated instruments which have only become available in the last few years for chemical synthesis. The number of publications related to MAOS has therefore increased dramatically since the late 1990s to a point where it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields, and improve reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a forefront technology for rapid optimization of reactions, for the efficient synthesis of new chemical entities, and for discovering and probing new chemical reactivity. A large numbers of review articles provide extensive coverage of the subject.[43-48] Microwave-enhanced chemistry is based on the efficient heating of materials by “microwave dielectric heating” effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat. The electric component of an electromagnetic field causes heating by two main mechanisms: dipolar

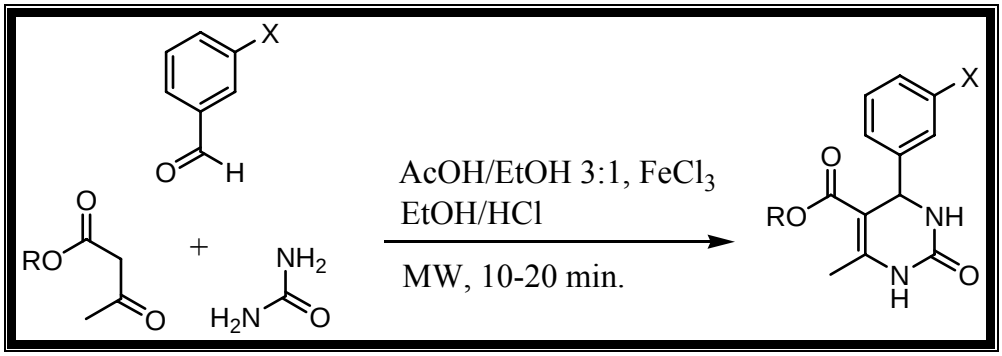
polarization and ionic conduction. Irradiation of the sample at microwave frequencies results in the dipoles or ions aligning in the applied electric field. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The amount of heat generated by this process is directly related to the ability of the matrix to align itself with the frequency of the applied field. If the dipole does not have enough time to realign, or reorients too quickly with the applied field, no heating occurs. The allocated frequency of 2.45 GHz used in all commercial systems lies between these two extremes and gives the molecular dipole time to align in the field, but not to follow the alternating field precisely.[49-50]

The heating characteristics of a particular material (for example, a solvent) under microwave irradiation conditions are dependent on its dielectric properties. The ability of a specific substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by the so-called loss factor tanδ. This loss factor is expressed as the quotient tanδ=e''/e', where e'' is the dielectric loss, which is indicative of the efficiency with which electromagnetic radiation is converted into heat, and e' is the dielectric constant describing the ability of molecules to be polarized by the electric field. A reaction medium with a high tanδ value is required for efficient absorption and, consequently, for rapid heating.[51]

Solvent	tanδ	Solvent	tanδ
ethylene glycol	1.350	DMF	0.161
ethanol	0.941	1,2-dichloroethane	0.127
DMSO	0.825	water	0.123
2-propanol	0.799	chlorobenzene	0.101
formic acid	0.722	chloroform	0.091
methanol	0.659	acetonitrile	0.062
nitrobenzene	0.589	ethyl acetate	0.059
1-butanol	0.571	acetone	0.054
2-butanol	0.447	tetrahydrofuran	0.047
1,2-dichlorobenzene	0.280	dichloromethane	0.042
NMP	0.275	toluene	0.040
acetic acid	0.174	hexane	0.020

In general, the standard procedure for the Biginelli condensation involves one-pot condensation of the three building blocks in a solvent such as ethanol using a strongly acidic catalyst, that is, hydrochloric acid. One major drawback of this procedure, apart from the long reaction times involving reflux temperatures, are the moderate yields frequently observed when using more complex building blocks. Kappe et al recently described a high yielding and

rapid microwave-assisted protocol that allows the synthesis of gram quantities of DHPMs utilizing controlled single-mode microwave irradiation. As the first model reaction for our scale-up experiments, they selected the standard Biginelli cyclocondensation, where in a one-pot process equimolar amounts of benzaldehyde, ethyl acetoacetate, and urea react under Lewis acid (FeCl3) catalysis to the corresponding dihydropyrimidine. Utilizing single-mode microwave irradiation, the reaction can be carried out on a 4.0 mmol scale in AcOH/EtOH 3:1 at 120 °C within 10 min, compared to 3-4 h using conventional thermal heating, providing DHPM in 88% isolated yield and high purity (>98%).[52]



Dihydropyrimidines were synthesised in high yields by one-pot cyclocondensation reaction of aldehydes, acetoacetates and urea using various acid catalysts like Amberlyst-15, Nafion-H, KSF clay and dry acetic acid under microwave irradiation.[53]

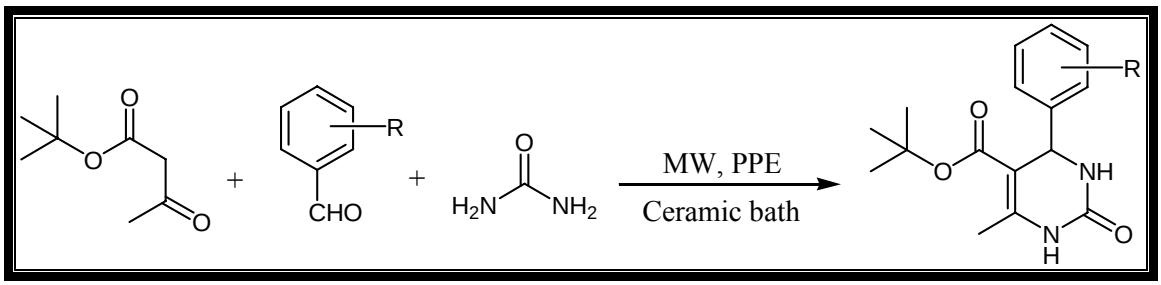
The antimony (III) chloride impregnated on alumina efficiently catalyses a one-pot, three-component condensation reaction among an aldehyde, a β-ketoester, and urea or thiourea to afford the corresponding dihydropyrimidinones in good to excellent yields. The reactions are probed in microwave (MW), ultrasonic, and thermal conditions and the best results are found using MW under solvent-free conditions.[54]

Cupric chloride dihydrate catalyzes the three-component Biginelli condensation between an aldehyde, a β-ketoester and urea or thiourea under microwave irradiation in the absence of solvent to yield various substituted 3,4-dihydropyrimidin-2(1*H*)-ones. The reaction is also effective when performed at room temperature in acetonitrile or at 100 °C in a solvent free approach, without any side reactions as observed by Biginelli and others.[55]

The publications by Gupta[56] and Dandia[57] describe 26 examples of microwave-enhanced solution-phase Biginelli reactions employing ethyl acetoacetate, (thio)ureas (X = O, S), and a wide variety of aromatic aldehydes as building blocks. Upon irradiation of the individual reaction mixtures (ethanol, catalytic HCl) in an open glass beaker inside the cavity of a domestic microwave oven the reaction times were reduced from 2–24 hours of conventional heating (80 ºC, reflux) to 3–11 minutes under microwave activation (*ca.* 200–300 W). At the same time the yields of DHPMs obtained by the authors were markedly improved compared to those reported earlier using conventional conditions.

Kappe reinvestigated above reactions using a purpose-built commercial microwave reactor with on-line temperature, pressure, and microwave power control. Transformations carried out under microwave heating at atmospheric pressure in ethanol solution show no rate or yield increase when the temperature is identical to conventional thermal heating. In the case of superheating by microwave irradiation at atmospheric pressure the observed yield and rate increases are rationalized as a consequence of a thermal (kinetic) effect. Under sealed vessel conditions (20 bar, 180 ºC) the yield of products is decreased and formation of various byproducts observed. The only significant rate and yield enhancements are found when the reaction is performed under "open system" conditions where the solvent is allowed to rapidly evaporate during microwave irradiation. However, the observed rate and yield enhancements in these experiments are a consequence of the solvent-free conditions rather than caused specifically by microwave irradiation. This was confirmed by control experiments of the solvent less Biginelli reaction under microwave and thermal heating.[58a]

N. Foroughifar et al had reported some tert-Butyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydro Pyrimidine-5-carboxylate derivatives by microwave irradiation using polyphosphate ester (PPE) as a reaction moderator in ceramic bath.[58b]



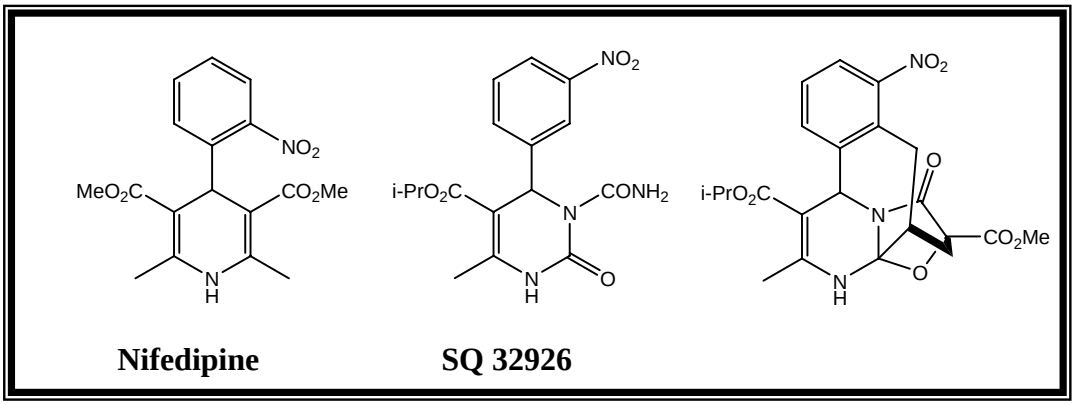
1.3.4 Ionic liquid

Wang et al reported the *Biginelli* reaction between an aromatic aldehyde, ethyl acetoacetate, and urea - catalyzed by polymer-supported, re-usable, room-temperature ionic liquids (RTIL) was shown to efficiently proceed in glacial AcOH at 100°C to afford the corresponding pyrimidine-5-carboxylates in yields up to 99% within 2 h. The catalyst(s) could be reused at least five times, basically without loss of activity, which makes this transformation not only straight-forward, but also considerably less expensive compared to methods involving classical RTIL catalysts.[59]

1.4 Reported dihydropyrimidones bearing versatile biological activities

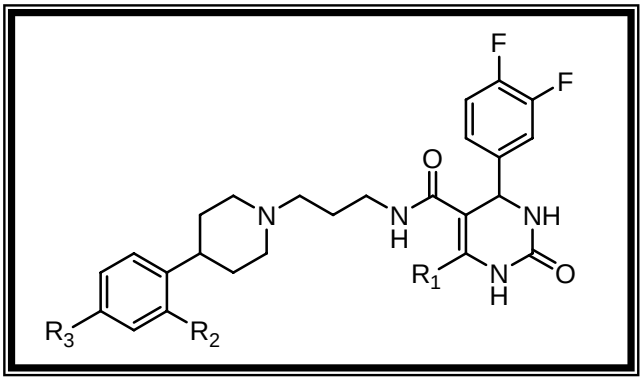
4-Aryl-1,4-dihydropyridines (DHPs, e.g. nifedipine,) are the most studied class of organic calcium channel modulators. More than 30 years after the introduction of nifedipine many DHP analogs have now been synthesized and numerous second-generation commercial products have appeared on the market.[60, 61]

In recent years interest has also focused on aza-analogs such as dihydropyrimidines (DHPMs) which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators.[62-69] Over the past few years several lead-compounds were developed (*i.e.* SQ 32,926) that are superior in potency and duration of antihypertensive activity to classical DHP drugs, and compare favorable with second-generation analogs such as amlodipine and nicardipine.[70]



Nifedipine **SQ 32926**

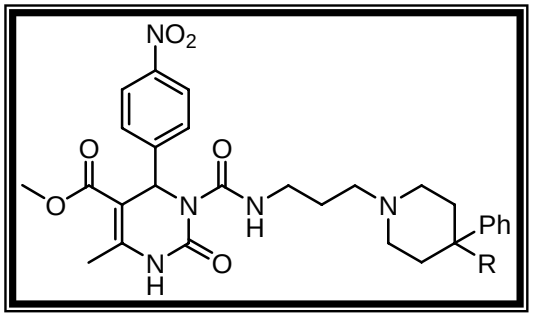
Barrow et al reported *in vitro* and *in vivo* Evaluation of Dihydropyrimidinone C-5 Amides as Potent and Selective r1A Receptor Antagonists for the Treatment of Benign Prostatic Hyperplasia. R1 Adrenergic receptors mediate both vascular and lower urinary tract tone, and R1 receptor antagonists such as terazosin are used to treat both hypertension and benign prostatic hyperplasia (BPH). Recently, three different subtypes of this receptor have been identified, with the R1A receptor being most prevalent in lower urinary tract tissue. Barrow et al reported 4-aryldihydropyrimidinones attached to an aminopropyl-4-arylpiperidine via a C-5 amide as selective R1A receptor subtype antagonists. In receptor binding assays, these types of compounds generally display *K*i values for the R1a receptor subtype <1 nM while being greater than 100-fold selective versus the R1b and R1d receptor subtypes. Many of these compounds were also evaluated in vivo and found to be more potent than terazosin in both a rat model of prostate tone and a dog model of intra-urethral pressure without significantly affecting blood pressure. While many of the compounds tested displayed poor pharmacokinetics, one compound was found to have adequate bioavailability (>20%) and half-life (>6 h) in both rats and dogs. Due to its selectivity for the R1a over the R1b and R1d receptors as well as its favorable pharmacokinetic profile, it has the potential to relieve the symptoms of BPH without eliciting effects on the cardiovascular system.[71-75]



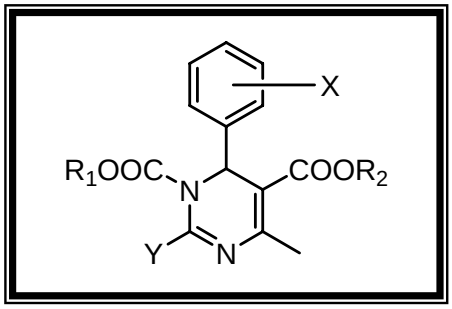
The 4-aryldihydropyrimidinone heterocycle attached to an aminopropyl-4-arylpiperidine via a C-5 amide has proved to be an excellent template for selective R1A receptor subtype antagonists. These types of compounds are exceptionally potent in both cloned receptor binding studies as well as in in vivo pharmacodynamic models of prostatic tone.

Compounds exhibited high binding affinity and subtype selectivity for the cloned human R1a receptor. Systematic modifications led to identification of highly potent and subtype-selective compounds with high binding affinity (*K*i) 0.2 nM) for R1a receptor and greater than 1500-

fold selectivity over R1b and R1d adrenoceptors. The compounds were found to be functional antagonists in human, rat, and dog prostate tissues. They exhibited excellent selectively to inhibit intraurethral pressure (IUP) as compared to lowering diastolic blood pressure (DBP) in mongrel dogs (*K*b(DBP)/*K*b(IUP))suggesting uroselectivity for R1a-selective compounds.[76]

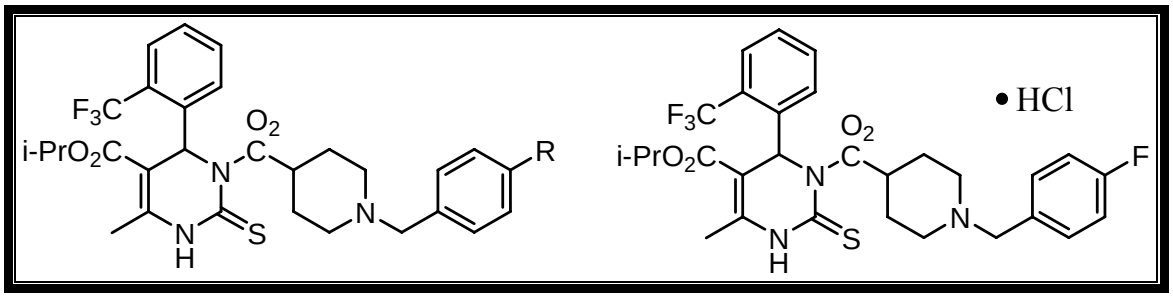


Cho et. al. reported 3-N-substituted-3,4-dihydropyrimidine and 3-N-substituted-dihydropyrimidin-2(1H)-ones as calcium channel antagonist. Compounds [especially [R_1=$(CH_2)_2$N(benzyl)(2-naphthylmethyl) R_2= i-Pr, X=o-N0_2] and [R'= $(CH_2)_2$N(benzyl)(3,4-dichlorobenzyl) R_2= i-Pr, X=o-NO_2]] exhibited not only more potent and longer lasting vasodilative action but also a hypertensive activity with slow onset as compared with dihydropyridines. Moreover, some dihydropyrimidines [R' =$(CH_2)_2$N(benzyl)(3-phenylpropyl), R_2 = CH_2(cyclopropyl), X = o-NO_2] were weaker in blocking atrioventricular conduction in anesthetized open-chest dogs and less toxic than the dihydropyridines.[77]

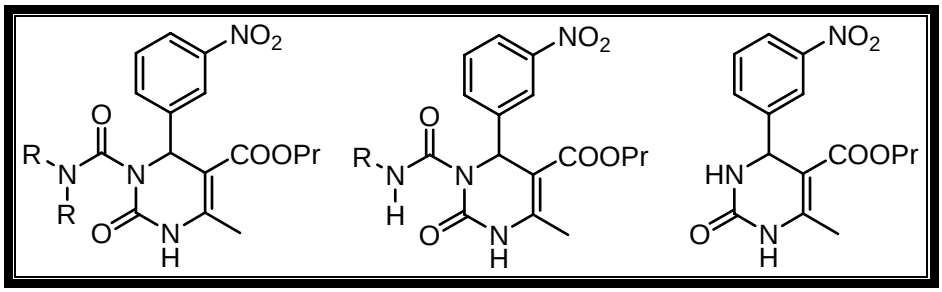


Atwal et al examined a series of novel dihydropyrimidine calcium channel blockers that contain a basic group attached to either C5 or N3 of the heterocyclic ring. Structure-activity studies show that l-(phenylmethyl)-4-piperidinyl carbamate moiety at N_3 and sulfur at C_2 are optimal for vmrelaxant activity in vitro and impart potent and long-acting antihypertensive activity in vivo. One of theae compounds was identified as a lead, and the individual enantiomers were synthesized. Two key steps of the synthesis were (1) the efficient separation of the diastereomeric ureido derivatives and (2) the high-yield transformation of 2-methoxy intermediate to the (p-methoxybenzy1)thio intermediates. Chirality was

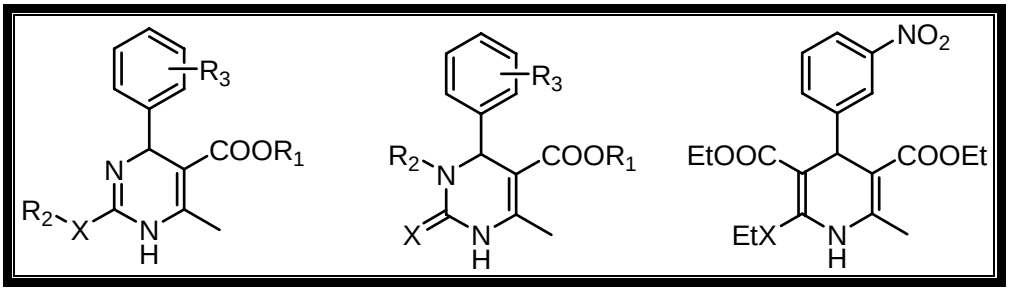
demonstrated to be a significant determinant of biological activity, with the dihydropyridine receptor recognizing the enamino ester moiety but not the carbamate moiety. Dihydropyrimidine is equipotent to nifidepine and amlodipine in vitro. In the spontaneously hypertensive rat, dihydropyrimidine is both more potent and longer acting than nifidepine and compares most favorably with the long-acting dihydropyridine derivative amlodipine. Dihydropyrimidine has the potential advantage of being a single enantiomer.[78]



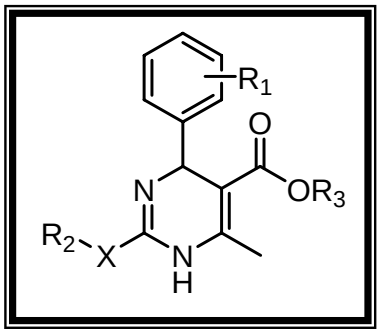
In order to explain the potent antihypertensive activity of the modestly active (ICw = 3.2 pM) dihydropyrimidine calcium channel blocker**,** Atwal et al carried out drug metabolism studies in the rat and found it is metabolized. Two of the metabolites (ICw = 16 nM) and (ICw = 12 nM), were found to be responsible for the antihypertensive activity of compound**.** Potential metabolism in vivo precluded interest in pursuing compounds related to it. Structure-activity studies aimed at identifying additional aryl-substituted analogues led to comparable potential in vivo, though these compounds were less potent in vitro. To investigate the effects of absolute stereochemistry on potency, authors resolved via diastereomeric ureas, prepared by treatment with (R)-α-methylbenzylamine. The results demonstrate that the active R-(-)-enantiomer is both more potent and longer acting than nifedipine as an antihypertensive agent in the SHR. The in vivo potency and duration is comparable to the long-acting dihydropyridine amlodipine. The superior oral antihypertensive activity compared to that of previously described carbamates (R2 = COOEt) could be explained by its improved oral bioavailability, possibly resulting from increased stability of the urea functionality.[79]



Authors modified the structure of previously described dihydropyrimidine i.e. 3-substituted 1,4-dihydropyrimidines**.** Structure- activity studies using potassium-depolarized rabbit aorta show that ortho,meta-disubstituted aryl derivatives are more potent than either ortho- or meta-monosubstituted compounds. While vasorelaxant activity was critically dependent on the size of the **C5** ester group, isopropyl ester being the best, a variety of substituents (carbamate, acyl, sulfonyl, alkyl) were tolerated at N_3. The results show dihydropyrimidines are significantly more potent than corresponding 2- heteroalkyl-l,4-dihydropyrimidines and only slightly less potent than similarly substituted 2-heteroalkyl-1-4-dihydropyridines**.** Where as dihydropyridine enantiomen usually show 10-15-fold difference in activity, the enantiomers of dihydropyrimidine show more than a 1000-fold difference in activity. These results strengthen the requirement of an enamino ester for binding to the dihydropyridine receptor and indicate a nonspecific role for the N_3-substituent.



2-Heterosubstituted-4-aryl-l,4-dihydro-6-methyl-5-pyrimidinecarboxylic esters, which lack the potential symmetry of dihydropyridine calcium channel blockers, were prepared and evaluated for biological activity. Biological assays using potassium-depolarized rabbit aorta and radio ligand binding techniques showed that some of these compounds are potent mimics of dihydropyridine calcium channel blockers.[80]



1.5 Nanoparticles

Nanoparticles are of great scientific interest as they are effectively a bridge between bulk materials and atomic or molecular structures. The properties of materials change as their size approaches the nanoscale and as the percentage of atoms at the surface of a material becomes significant. Nanoparticles exhibit a number of special properties relative to bulk material.

Nanoparticle characterization is necessary to establish understanding and control of nanoparticle synthesis and applications. Characterization is done by using a variety of different techniques, mainly drawn from materials science. Common techniques are electron microscopy [TEM,SEM], atomic force microscopy [AFM], dynamic light scattering [DLS], x-ray photoelectron spectroscopy [XPS], powder x-ray diffractometry [XRD], Fourier transform infrared spectroscopy [FTIR], Matrix-Assisted Laser-Desorption Time-of-flight mass spectrometry [MALDI-TOF], and Ultraviolet-visible spectroscopy. Whilst the theory has been known for over a century (see Robert Brown), the technology for Nanoparticle tracking analysis (NTA) allows direct tracking of the Brownian motion and this method therefore allows the sizing of individual nanoparticles in solution.

Nanoparticles of organic compounds may have interesting applications from pharmaceutical application point of view. Nanoparticles are used, nowadays, in some formulations for their capacity for drug vacterization, to reduce the amount of drug delivered and hence to reduce its secondary effects.

Out of synthesized dihydropyrimidine derivatives in this chapter, the nanoparticles of *n*-butyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate was prepared using Microemulsion Technique and their characterization was carried out using Transition Electron Microscopy (TEM), powder XRD, TGA and FTIR spectroscopy by Mr. Poorvesh M. Vyas (Research Fellow, Department of Physics, Saurashtra University, Rajkot).

1.6 Current work

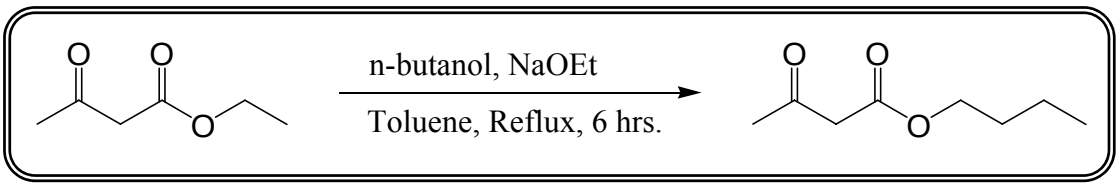
Our group is involved in the synthesis of modified 1,4-DHP and DHPM skeleton derivatives for last few years. Introduction of *n*-butyl carboxylic ester moiety at C-5 position in DHPM skeleton may show diverse activity profile. Very promising results may obtain with these modifications to DHPM skeleton. This concept prompted us to introduce *n*-butyl carboxylic ester at C-5 position in DHPM skeleton. For this modification *n*-butyl acetoacetate was required as a precursor which was obtained by transesterification of ethyl or methyl acetoacetate. A few methods for transesterification of β-keto ester are reported in literature.[81-83]

In extension of work, the same molecules when synthesized through green chemistry approach by utilizing Fuller's earth as solid support through microwave irradiation technique, resulted in formation of all newly synthesized compounds with higher yields and also reaction hours are reduced to a great extent in comparison with conventional synthetic methods as mentioned in literature. Fuller's earth is prior coated with $ZnCl_2$, acidic in nature which fulfills the requirement of the Biginelli condensation. As a result we found increased yield about 10-15% more than conventional method. All newly synthesized compounds were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. Reaction schemes are illustrated in section 1.7. Scheme 1 and 2 displays the synthesis of *n*-butyl acetoacetate by transesterification of ethyl acetoacetate and *n*-Butyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives. Physical data of all synthesized compounds is reported in section 1.10 and spectral data is discussed in section 1.11. The anti viral screening of the compounds synthesized with this modification to DHPM skeleton is under investigation.

1.7 Reaction Scheme

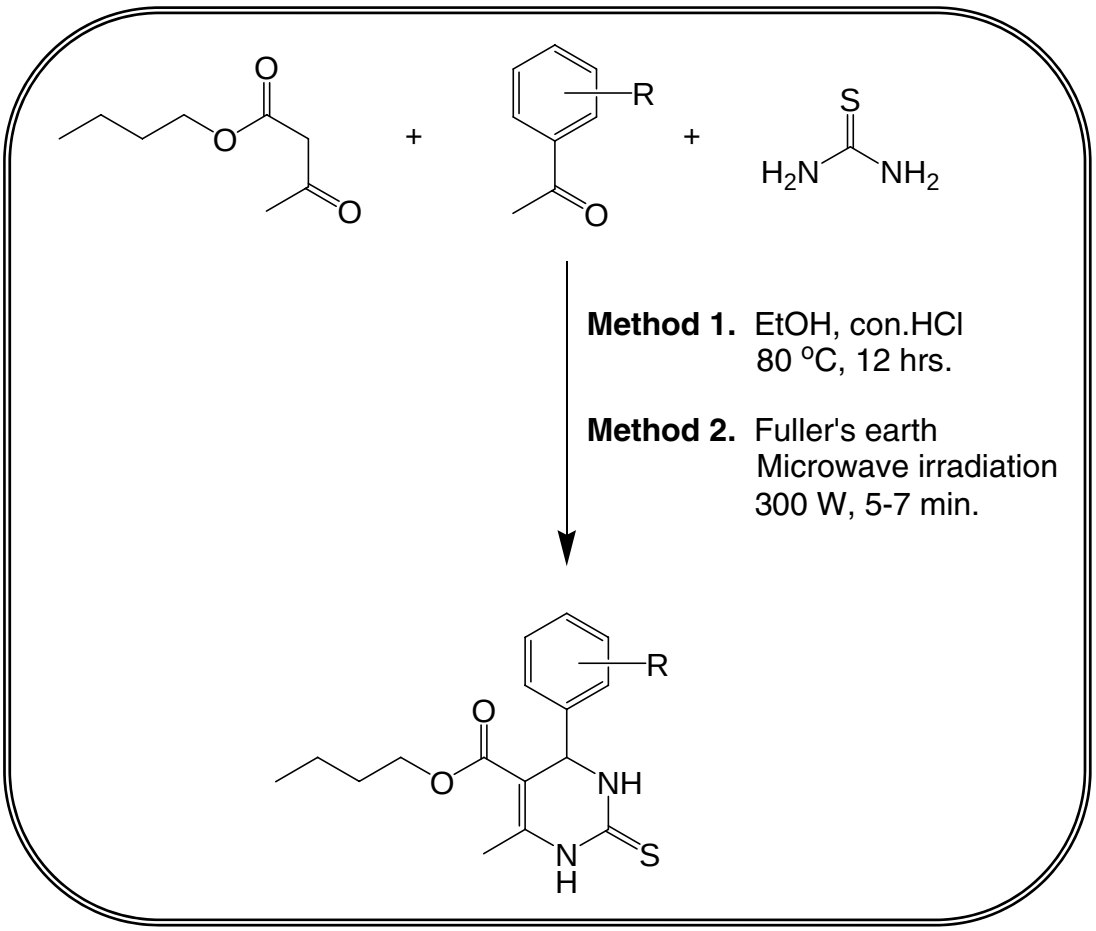
1.7.1 Scheme 1.

Transesterification of ethyl acetoacetate

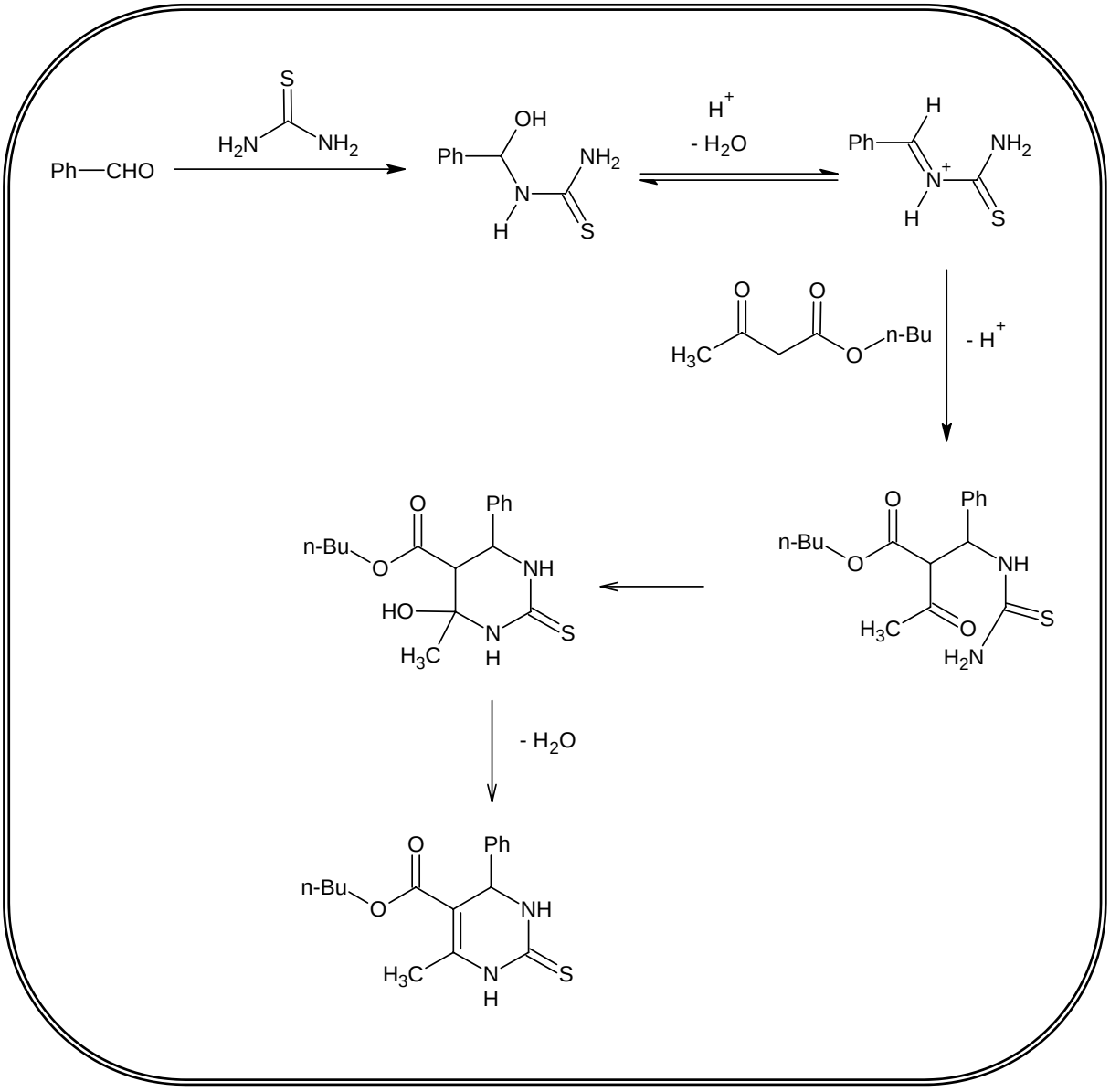


1.7.2 Scheme 2.

Synthetic approaches towards dihydropyrimidine



1.8 Reaction Mechanism:



1.9 Experimental

1.9.1 n-Butyl acetoacetate:

A mixture of ethyl acetoacetate (0.1 M) and n-butyl alcohol (0.11 M) in toluene (50 ml) was taken in a round bottom flask provided with a distillation condenser to remove methanol or ethanol. Sodium ethoxide (1 mmol) was added to the mixture as a catalyst. The mixture was heated at 100-110 °C for 5-6 hrs. After completion of reaction (TLC), the catalyst was filtered and the filterate was concentrated to get crude product. n-Butyl acetoacetate was distilled off at 92-98 ° C/20 mm Hg. Yellowish viscous oil.

1.9.2 n-Butyl 6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:

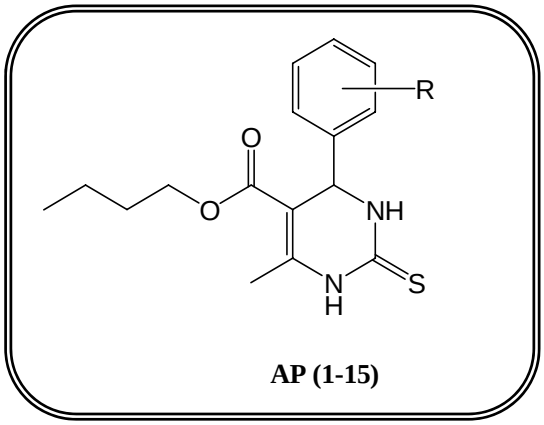
Method-1

A mixture of n-butyl acetoacetate (10 mmol), appropriate aldehyde (10 mmol) and thiourea (15 mmol) was dissolved in absolute EtOH (20 mL) and refluxed until clear solution is obtained. Few drops of con. HCl were added to reaction mixture as a catalyst and was refluxed for 8-12 hrs. The reaction was monitored with thin layer chromatography and after completion of the reaction, the mixture was allowed to cool at room temperature. The solid separated was filtered, washed with hot methanol and recrystallized from ethanol. (Yield – 45-60%).

Method-2

In 50 ml microwave flask containing 2.5 equivalent of Fuller's earth, a mixture of n-butyl acetoacetate (10 mmol), appropriate aldehyde (10 mmol) and thiourea (15 mmol) was added and stirred for 5 minutes to make a homogeneous mixture. It was subjected to microwave irradiation (300 W) for 5 - 7 minutes. After cooling at room temperature 50 mL water was added to it and extracted with 25 mL $CHCl_3$. The organic phase was separated and washed successively with H_2O, saturated $NaHSO_3$ solution and H_2O until free from unreacted aldehyde. After drying over anhydrous Na_2SO_4, the solvent was removed by vaccuo under reduced pressure. The obtained solid was crystallized from EtOH to give a pure compound as pale yellow crystals.

1.10 Physical data



AP (1-15)

Comp.	R	M.F.	M.W.	Yield %		R_f
				Method-1	Method-2	
AP-1	H	$C_{16}H_{20}N_2O_2S$	304.40	60	85	0.48
AP-2	4-OCH_3	$C_{17}H_{22}N_2O_3S$	334.43	60	84	0.45
AP-3	3,4-$(OCH_3)_2$	$C_{18}H_{24}N_2O_4S$	364.45	62	89	0.41
AP-4	2,5-$(OCH_3)_2$	$C_{18}H_{24}N_2O_4S$	364.45	62	85	0.42
AP-5	2-Cl	$C_{16}H_{19}ClN_2O_2S$	338.85	52	75	0.54
AP-6	3-Cl	$C_{16}H_{19}ClN_2O_2S$	338.85	56	79	0.56
AP-7	4-Cl	$C_{16}H_{19}ClN_2O_2S$	338.85	55	79	0.61
AP-8	3-NO_2	$C_{16}H_{19}N_3O_4S$	349.40	61	81	0.54
AP-9	4-NO_2	$C_{16}H_{19}N_3O_4S$	349.40	59	83	0.48
AP-10	2-OH	$C_{16}H_{20}N_2O_3S$	320.40	57	80	0.49
AP-11	4-OH	$C_{16}H_{20}N_2O_3S$	320.40	55	78	0.55
AP-12	4-F	$C_{16}H_{19}FN_2O_2S$	322.39	50	68	0.50
AP-13	4-CH_3	$C_{17}H_{22}N_2O_2S$	318.43	53	70	0.45
AP-14	4-dimethylamino	$C_{18}H_{25}N_3O_2S$	347.47	61	78	0.51
AP-15	[2,3] Benzo	$C_{20}H_{22}N_2O_2S$	354.46	58	80	0.62

TLC Solvent system: Ethyl acetate : Hexane – 3:7

1.11 Spectral discussion

1.11.1 Mass spectral study

Instrument : SHIMADZU GCMS-QP-2010

Sample technique : EI technique

M/z range : 40-500

Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. Systematic fragmentation pattern was observed in mass spectral analysis. Peaks for specific fragments were identified in each mass spectrum. Molecular ion peak was observed in agreement with molecular weight of respective compound. Mass fragmentation for compound AP-1 is discussed below.

Molecular ion peak M^+ was observed at 304 and M^++1 peak was also observed with very low intensity. Then four peaks were observed due to cleavage of alkyl chain at 289, 276, 261 and 247 as M^+-CH_3, M^+-C_2H_5, M^+-C_3H_7 and M^+-C_4H_9 respectively as per shown in figure 1. Another very intense peak observed at 203 due to cleavage of carboxylic ester group at C-5 position. After this cleavage another two cleavages occurs at C-4 position with removal of methyl group and at C-2 position with removal of sulfur atom which shows the peak at 188 and 171 respectively.

1.11.2 IR spectral study

Instrument : Shimadzu FT-IR-8400

Sample technique : KBr pellet

Frequency range : 400-4000cm^{-1}

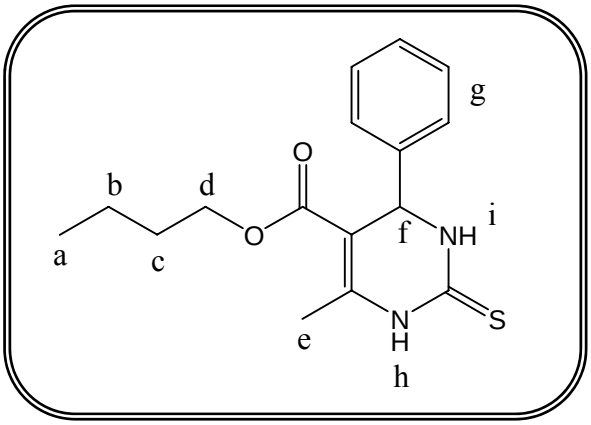
As per IR spectral study of newly synthesized dihydropyrimidine derivatives, the stretching vibration of secondary amine (>NH) appears around 3100-3200 cm^{-1}. The carbonyl (>C=O) stretching vibration of ester group is observed around 1700 cm^{-1}. The symmetric and asymmetric C-H stretching vibration of methyl and methylene group of alkyl chain was observed between 2850-2990 cm^{-1}. Methyl and methylene gives C-H bending vibration around 1380 and 1450 cm^{-1} respectively. The ring skeleton vibration is observed between 1500-1600 cm^{-1} due to the presence of phenyl ring system.

1.11.3 ^{1}H NMR spectral study

Instrument : BRUKER AC 400 MHz FT-NMR

Internal reference : TMS

Solvent : $CDCl_3$



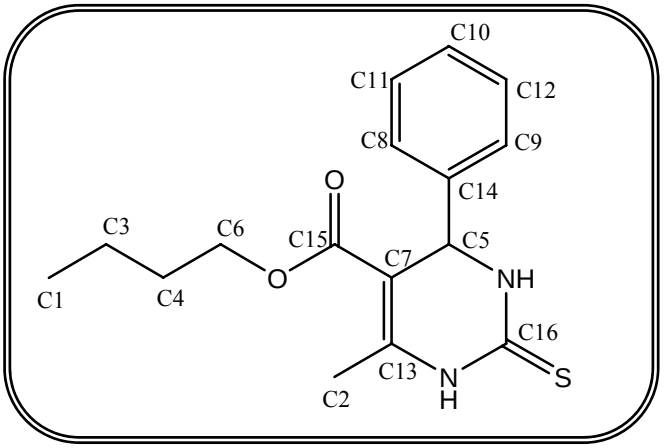
Number of protons and their chemical shifts were found to support the structure of the synthesized compounds. Protons of n-butyl chain ‘a’, ‘b’ and ‘c’ were observed at 0.82-0.86 δ ppm, 1.15-1.25 δ ppm and 1.45-1.55 δ ppm respectively. Protons ‘d’ were observed at 3.96-4.08 δ ppm due to neighboring attachment of hetero atom. Protons ‘e’ of methyl group attached at C-4 position were observed at 2.34-2.35 δ ppm as singlet and very intense peak. Asymmetric carbon proton ‘f’ was observed at 5.0-5.9 δ ppm as singlet. Protons ‘h’ and ‘i’ of >NH gave singlet peak at 8.0-9.8 δ ppm. The aromatic ring protons ‘g’ were observed at 6.50-7.80 δ ppm and J value were found according to substitution on phenyl ring.

1.11.4 ^{13}C NMR spectral study

Instrument : BRUKER AC 400 MHz FT-NMR

Internal reference : TMS

Solvent : $CDCl_3$



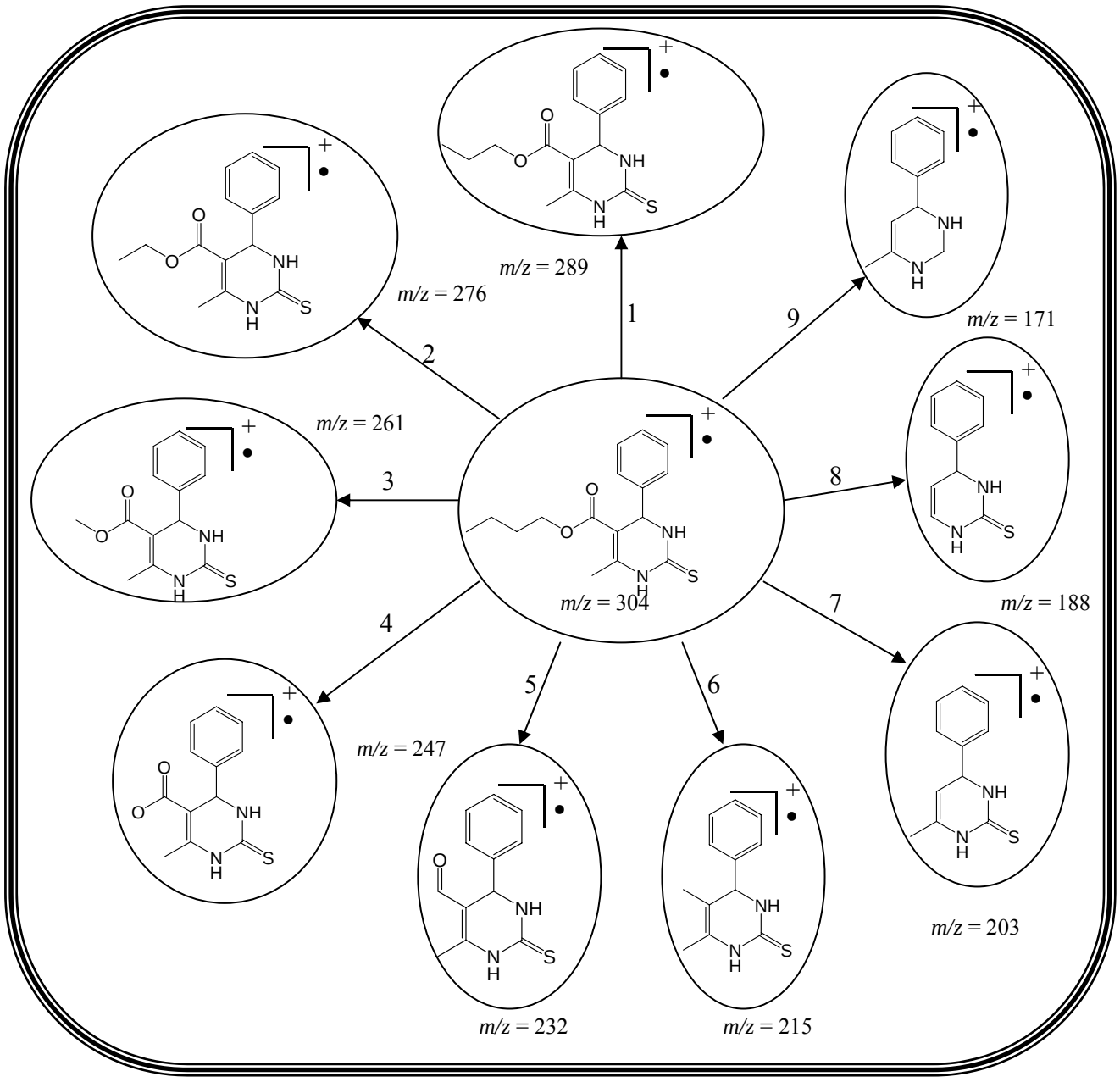
^{13}C NMR spectrum data for compound AP-1 is given below. δ ppm values are listed along with corresponding carbon atom number given in bracket and displayed in the structure.

^{13}C NMR δ ppm: 13.66 (C1), 18.29 (C2), 19.12 (C3), 30.54 (C4), 56.12 (C5), 64.34 (C6), 102.81 (C7), 126.78 (C8), 126.78 (C9), 128.37 (C10), 128.91 (C11), 128.91 (C12), 142.31 (C13), 143.03 (C14), 165.38 (C15), 174.29 (C16).

1.11.5 Elemental Analysis

Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Figure 1. Mass fragmentation of Mass spectrum of n-Butyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-1).



Spectral data of synthesized compounds (AP 1-15)

n-Butyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-1)

Pale-yellow solid; mp 206-208 ˚C; **IR (KBr):** 1180, 1427, 1456, 1707, 2868, 2976, 3215 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ ppm = 0.84 (t, 3 H, CH_3), 1.20 (m, 2 H, CH_2), 1.47 (m, 2 H, CH_2), 2.34 (s, 3 H CH_3), 4.02 (m, 2 H, CH_2), 5.35 (s, 1 H, CH), 7.29 (m, 5 H, Ph), 8.17 (s, 1 H, NH), 8.76 (s, 1 H, NH).; ^{13}C NMR (400 MHz, $CDCl_3$): 13.66, 18.29, 19.12, 30.54, 56.12, 64.34, 102.81, 126.78, 126.78, 128.37, 128.91, 128.91, 142.31, 143.03, 165.38, 174.29; **MS: m/z** = 304 (53, [M^+]), 247 (95), 227 (100).; **Anal. Calcd** for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.04; H, 6.59; N, 9.15.

n-Butyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-2)

Pale-yellow solid; mp 186-188 ˚C; **IR (KBr):** 1462, 1560, 1599, 2877, 2955, 3319 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ ppm = 0.85 (t, 3 H, CH_3), 1.21 (m, 2 H, CH_2), 1.50 (m, 2 H, CH_2), 2.35 (s, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 4.01 (m, 2 H, CH_2), 5.28 (s, 1 H, CH), 6.83 (d, 2 H, Ph), 7.20 (d, 2 H, Ph), 8.91 (s, 1 H, NH), 9.54 (s, 1 H, NH); **MS: m/z** = 334 (44, [M^+]), 277 (100); **Anal. Calcd** for $C_{17}H_{22}N_2O_3S$: C, 61.05; H, 6.63; N, 8.38. Found: C, 61.17; H, 6.51; N, 8.32.

n-Butyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-3)

Pale-yellow solid; mp 202-204 ˚C; **IR (KBr):** 1454, 1562, 1602, 2958, 2999, 3282 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ ppm = 0.85 (t, 3 H, CH_3), 1.21 (m, 2 H, CH_2), 1.50 (m, 2 H, CH_2), 2.35 (s, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.01 (m, 2 H, CH_2), 5.28 (s, 1 H, CH), 6.74-6.88 (m, 3 H, Ph), 8.91 (s, 1 H, NH), 9.54 (s, 1 H, NH); **MS: m/z** = 364 (81, [M^+]), 307 (100); **Anal. Calcd** for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 59.38; H, 6.59; N, 7.62.

n-Butyl 4-(2,5-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-4)

Pale-yellow solid; mp 198-200 ˚C; **IR (KBr):** 1451, 1538, 1668, 2855, 2957, 3224 cm^{-1}; **MS: m/z** = 364 (M^+); **Anal. Calcd** for $C_{18}H_{24}N_2O_4S$: C, 59.32; H, 6.64; N, 7.69. Found: C, 59.30; H, 6.57; N, 7.79.

n-Butyl 4-(2-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-5)

Pale-yellow solid; mp 190-192 ˚C; **IR (KBr):** 1447, 1588, 1689, 2847, 2976, 3258 cm^{-1}; **MS: m/z** = 338 (M^+); **Anal. Calcd** for $C_{16}H_{19}ClN_2O_2S$: C, 56.71; H, 5.65; N, 8.27. Found: C, 56.60; H, 5.55; N, 8.19.

n-Butyl 4-(3-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-6)

Pale-yellow solid; mp 204-206 ˚C; **IR (KBr):** 1450, 1489, 1694, 2847, 2976, 3285 cm^{-1}; **MS: m/z** = 338 (M^+); **Anal. Calcd** for $C_{16}H_{19}ClN_2O_2S$: C, 56.71; H, 5.65; N, 8.27. Found: C, 56.64; H, 5.58; N, 8.21.

n-Butyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-7)

Pale-yellow solid; mp 214-216 ˚C; **IR (KBr):** 1478, 1551, 1703, 2865, 2956, 3214 cm^{-1}; **MS: m/z** = 338 (M^+); **Anal. Calcd** for $C_{16}H_{19}ClN_2O_2S$: C, 56.71; H, 5.65; N, 8.27. Found: C, 56.67; H, 5.61; N, 8.20.

n-Butyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-8)

Yellow solid; mp 190-192 ˚C; **IR (KBr):** 1416, 1648, 2829, 2960, 3252 cm^{-1}; **MS: m/z** = 349 (M^+); **Anal. Calcd** for $C_{16}H_{19}N_3O_4S$: C, 55.00; H, 5.48; N, 12.03. Found: C, 54.89; H, 5.39; N, 12.08.

n-Butyl 6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-9)

Yellow solid; mp 202-204 ˚C; **IR (KBr):** 1528, 1598, 1671, 2812, 2934, 3319 cm^{-1}; **MS: m/z** = 349 (M^+); **Anal. Calcd** for $C_{16}H_{19}N_3O_4S$: C, 55.00; H, 5.48; N, 12.03. Found: C, 54.94; H, 5.43; N, 12.11.

n-Butyl 4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-10)

Pale-yellow solid; mp 208-210 ˚C; **IR (KBr):** 1494, 1507, 1680, 2845, 2981, 3200 cm^{-1}; **MS: m/z** = 320 (M^+); **Anal. Calcd** for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 59.91; H, 6.33; N, 8.72.

n-Butyl 4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-11)

Pale-yellow solid; mp 216-218 ˚C; **IR (KBr):** 1539, 1708, 2921, 2989, 3216 cm^{-1}; **MS: m/z** = 320 (M^+); **Anal. Calcd** for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 60.08; H, 6.39; N, 8.67.

n-Butyl 4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-12)

Pale-yellow solid; mp 195-197 ˚C; **IR (KBr):** 1459, 1528, 1572, 1660, 2801, 2937, 3222 cm^{-1}; **MS: m/z** = 322 (M^+); **Anal. Calcd** for $C_{16}H_{19}FN_2O_2S$: C, 59.61; H, 5.94; N, 8.69. Found: C, 59.58; H, 5.87; N, 8.65.

n-Butyl 6-methyl-4-(4-methylphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-13)

Pale-yellow solid; mp 187-189 ˚C; **IR (KBr):** 1555, 1669, 2850, 2971, 3201 cm^{-1}; **MS: m/z** = 318 (M^+); **Anal. Calcd** for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96; N, 8.80. Found: C, 64.03; H, 70.11; N, 8.65.

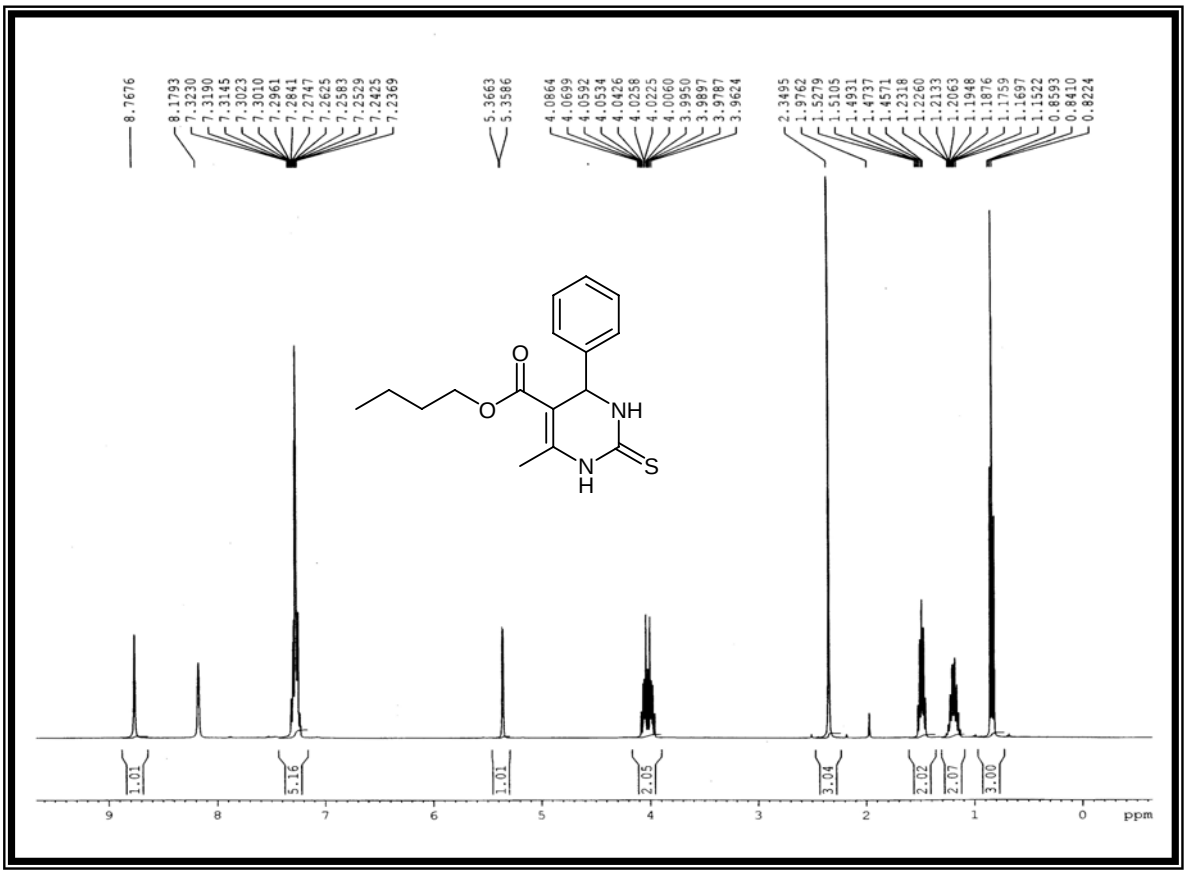
n-Butyl 4-[4-(dimethylamino)phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-14)

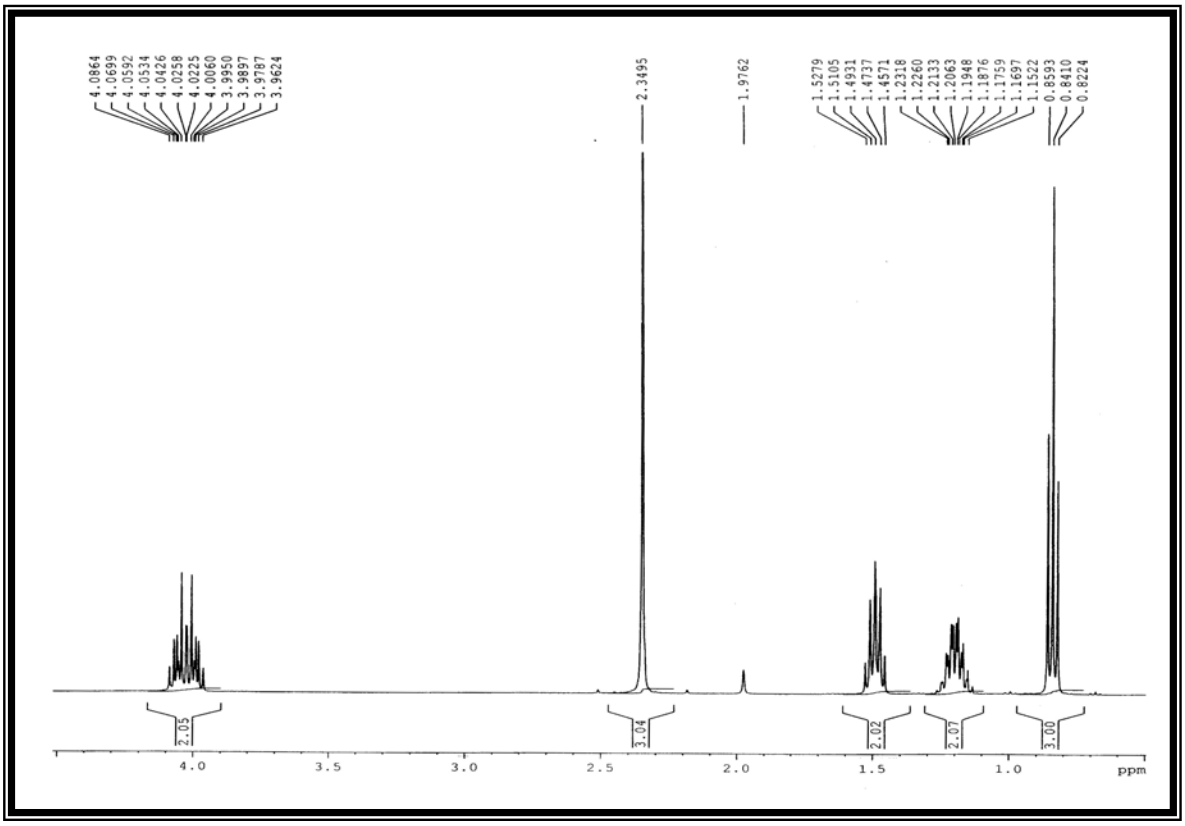
Yellow solid; mp 234-236 ˚C; **IR (KBr):** 1459, 1488, 1659, 2861, 2968, 3281 cm^{-1}; **MS: m/z** = 347 (M^+); **Anal. Calcd** for $C_{18}H_{25}N_3O_2S$: C, 62.22; H, 7.25; N, 12.09. Found: C, 62.17; H, 7.29; N, 12.04.

n-Butyl 6-methyl-4-(1-naphthyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (AP-15)

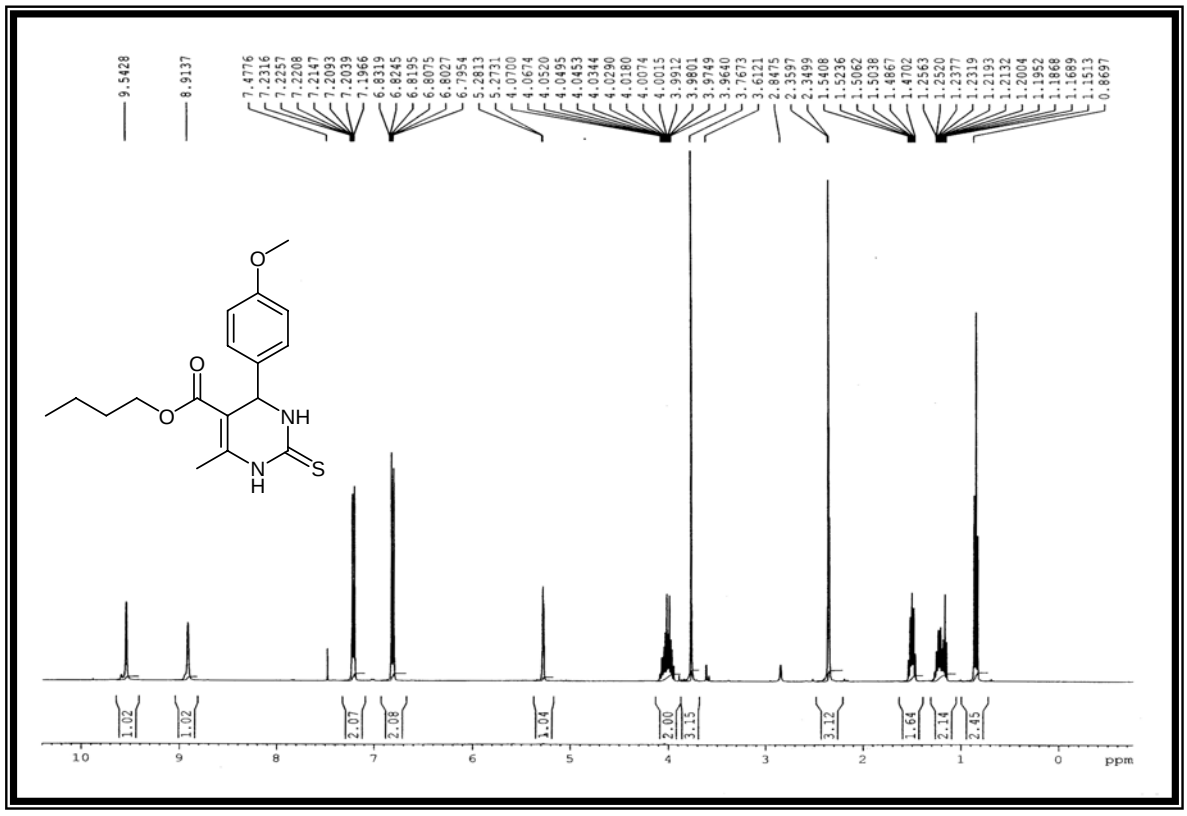
Yellow solid; mp 239-241 ˚C; **IR (KBr):** 1509, 1550, 1667, 2889, 2970, 3217 cm^{-1}; **MS: m/z** = 354 (M^+); **Anal. Calcd** for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.18; N, 7.76.

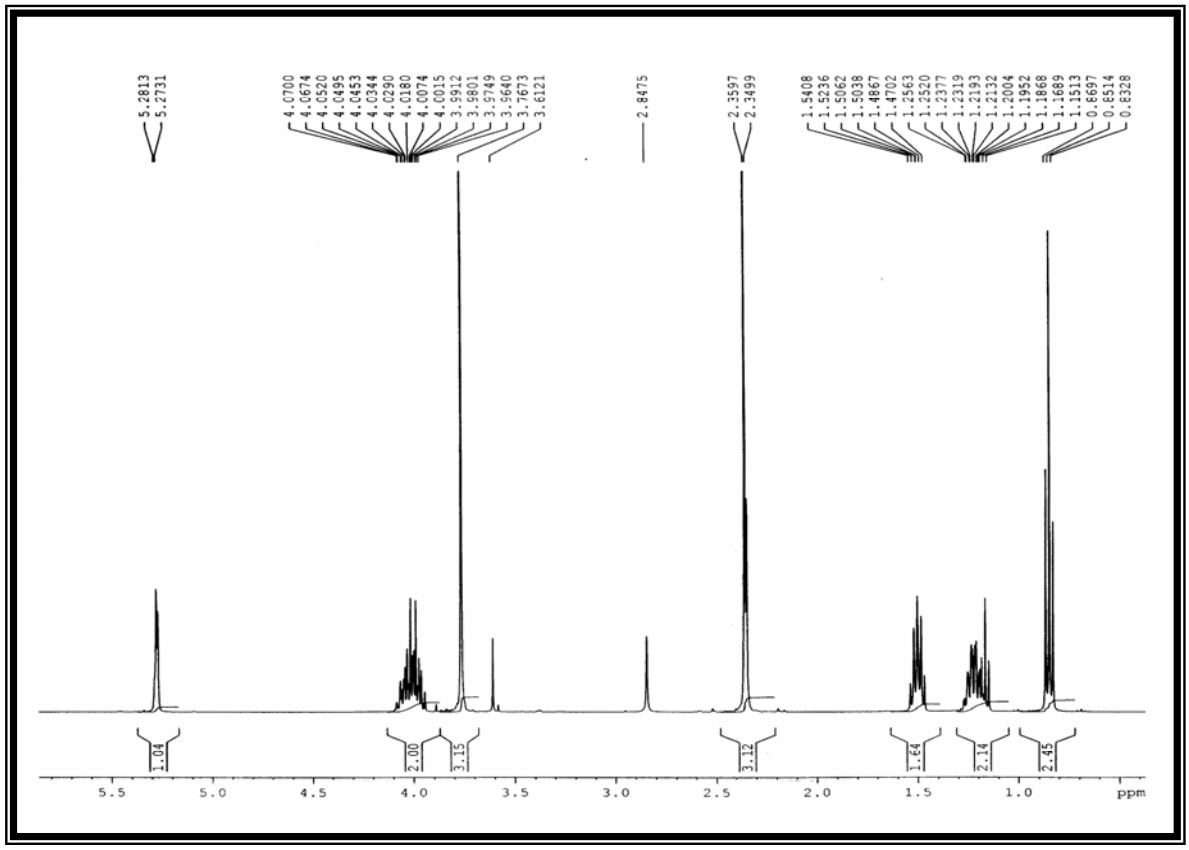
^{1}H NMR spectrum of AP-1



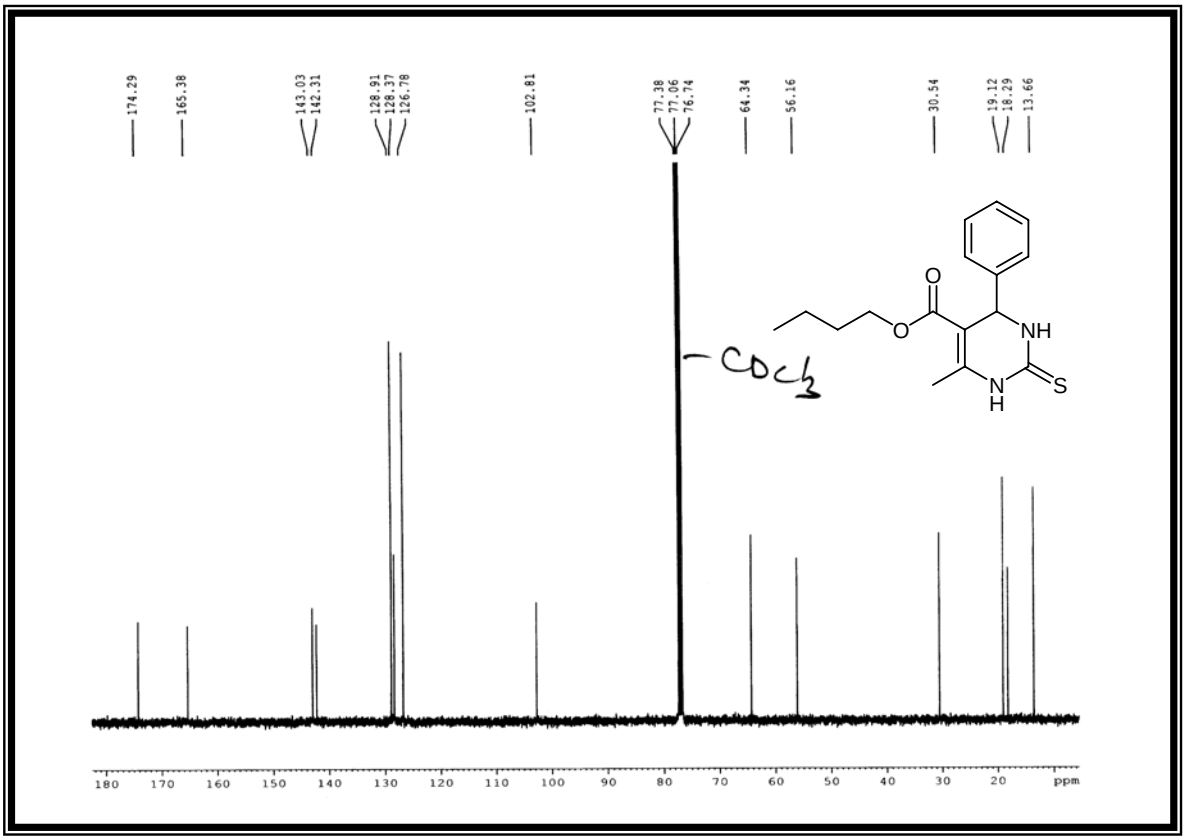


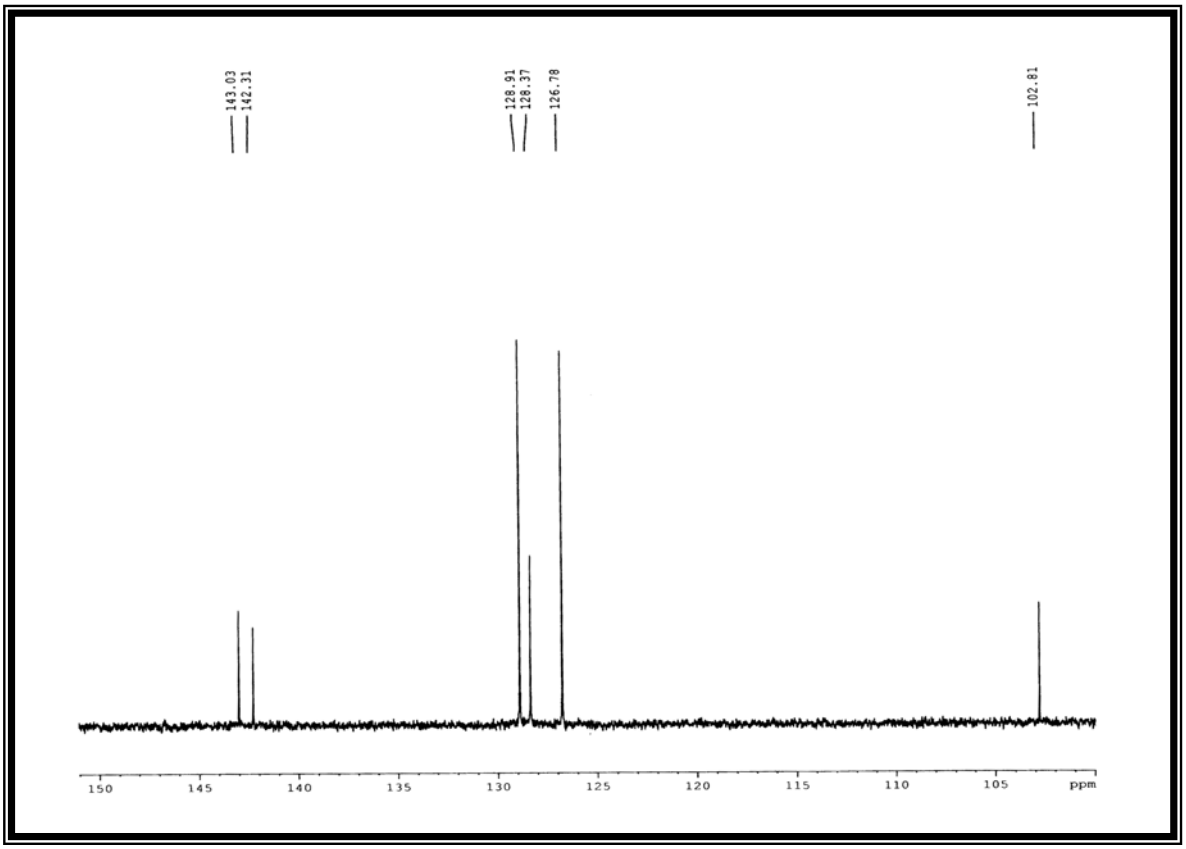
^{1}H NMR spectrum of AP-2



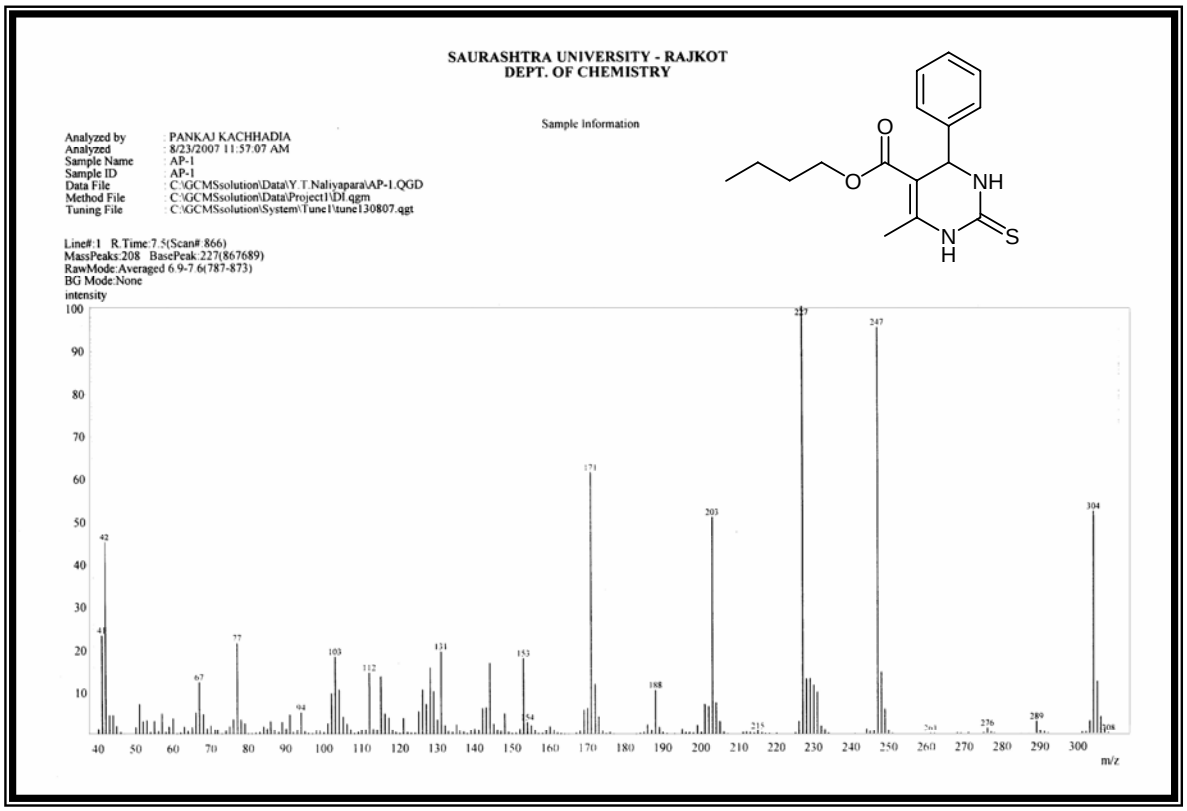


^{13}C NMR spectrum of AP-1

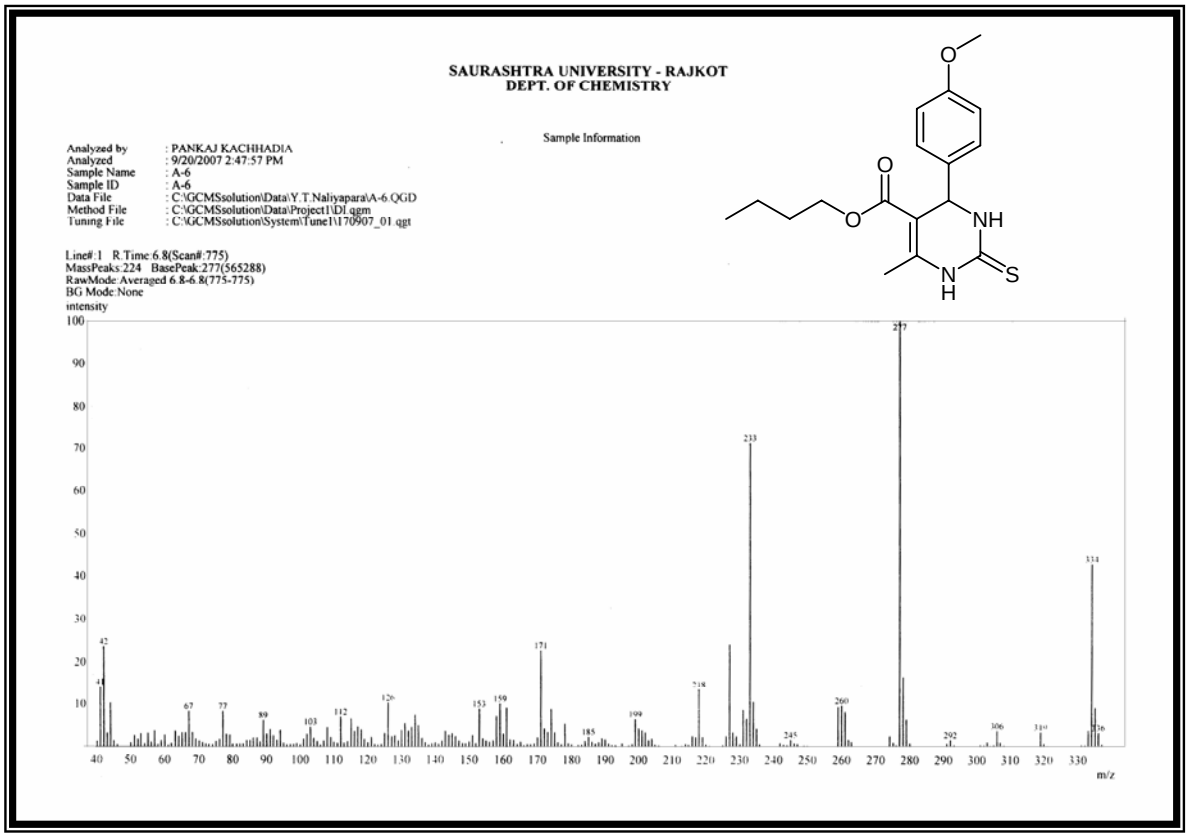




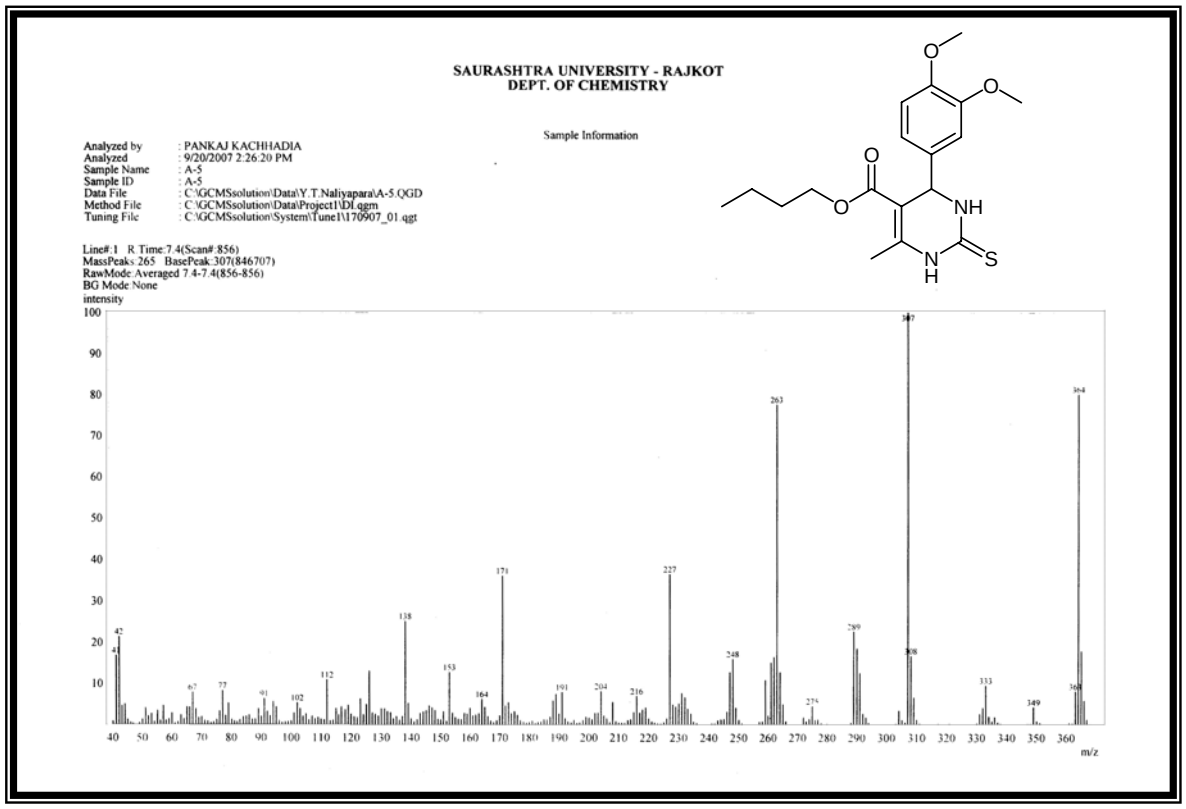
Mass Spectrum of AP-1



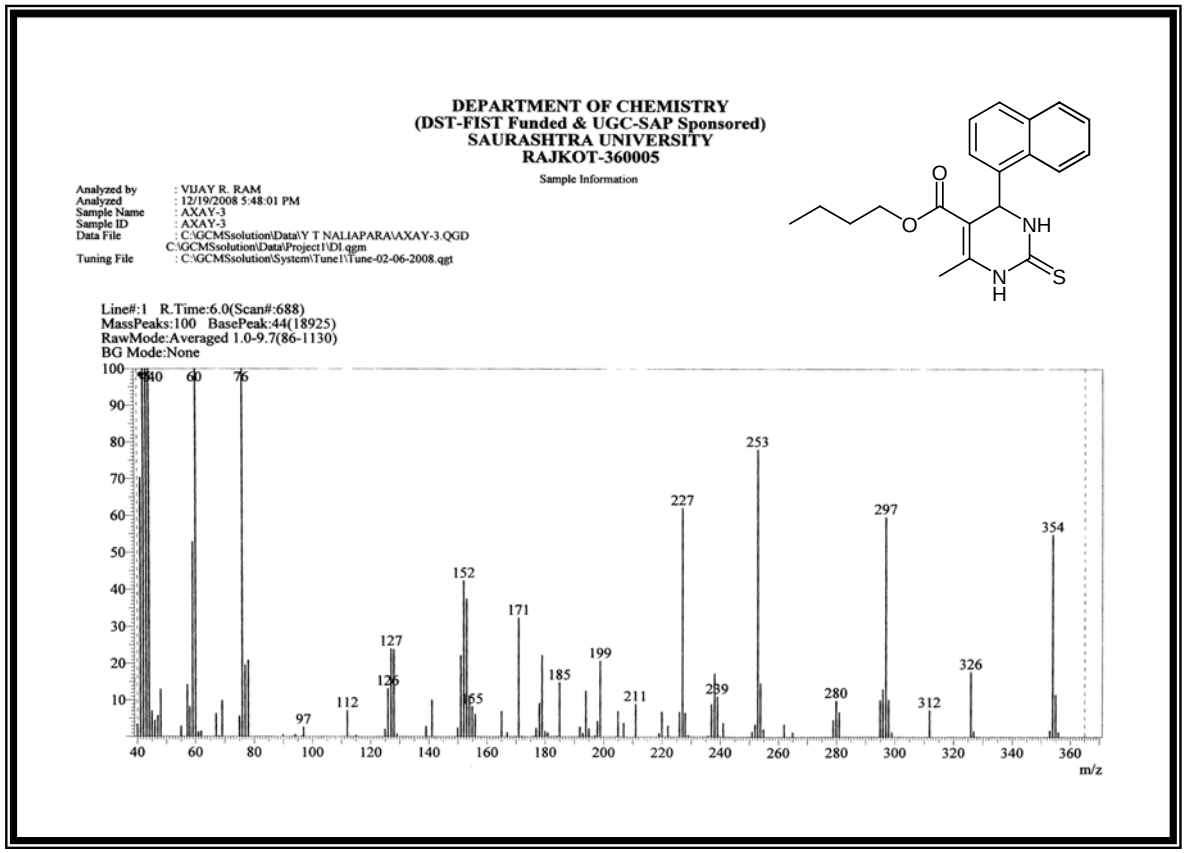
Mass Spectrum of AP-2



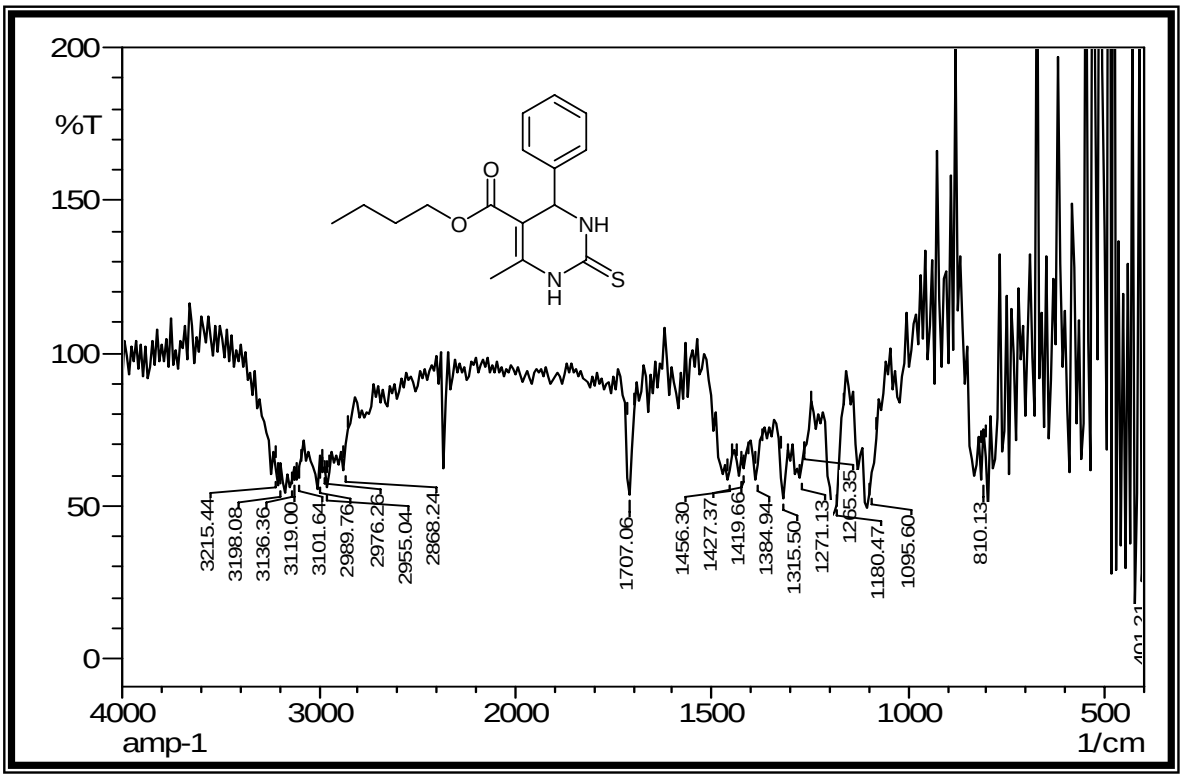
Mass Spectrum of AP-3



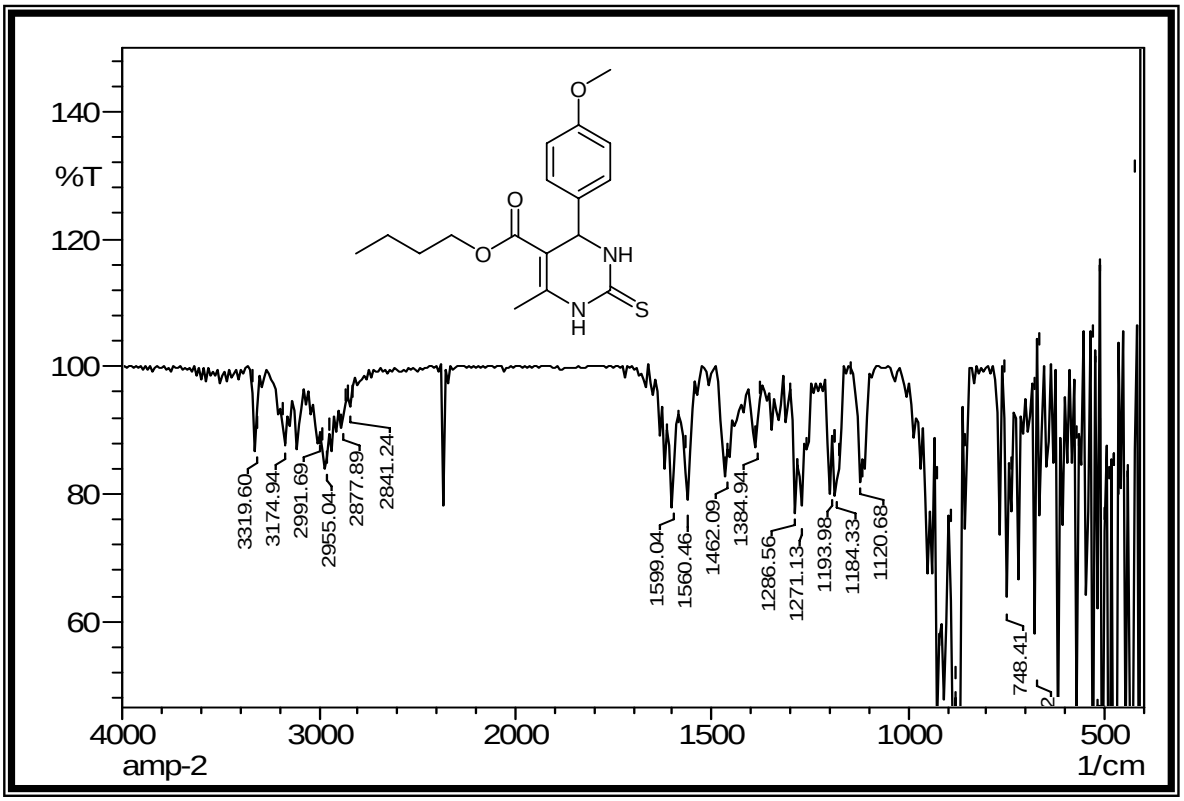
Mass Spectrum of AP-15



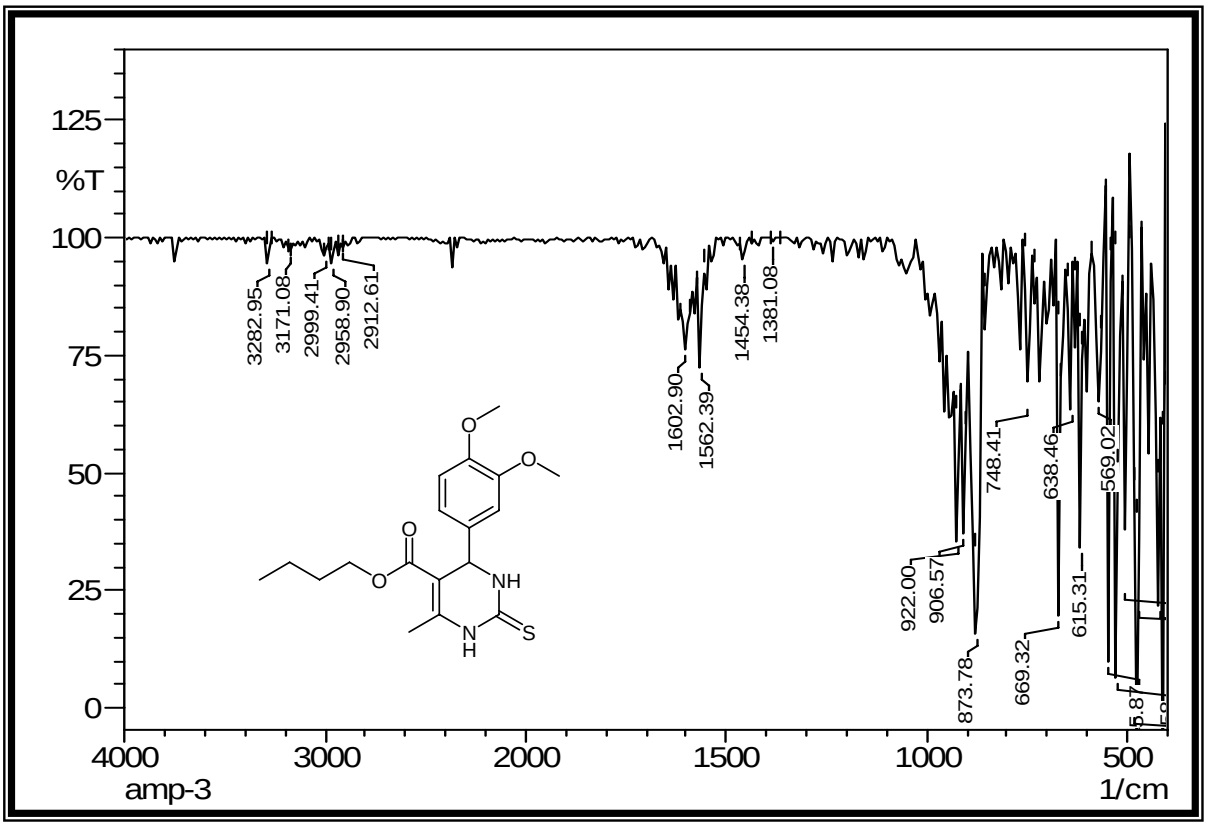
IR spectrum of AP-1



IR spectrum of AP-2



IR spectrum of AP-3



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Chapter 2

Synthesis & characterization of n-Butyl 3,7-dimethyl-5-phenyl-5*H*-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives

Chapter 2

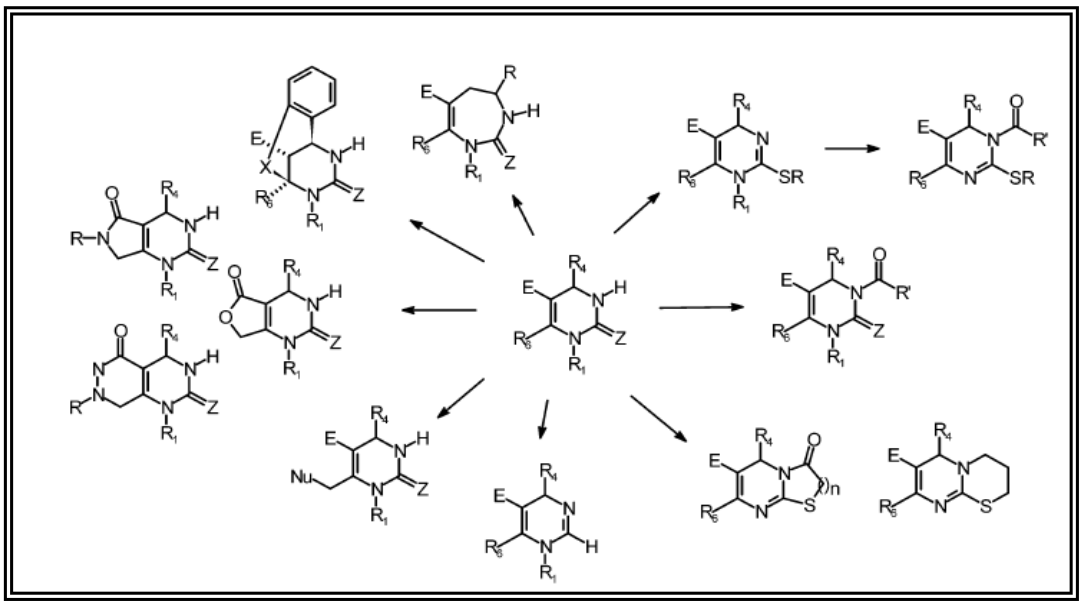
Synthesis & characterization of n-butyl 3,7-dimethyl-5-phenyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate derivatives

2.1 Scaffold decoration of DHPM ring, methods of synthesis and their biological profile

In chapter one, importance of DHPM moiety and various modifications applied to Biginelli reaction for better yield, shorter reaction time and to synthesize various analogs is surveyed in detail. The biological profile of this heterocyclic moiety is also briefly reported in chapter one.

Biginelli reaction is not only important to synthesize analogs of DHPM ring using different building block as potent bioactive heterocycles, but also various scaffolds can be synthesized from this heterocyclic scaffold.

2.1.1 Various scaffolds derived from DHPMs

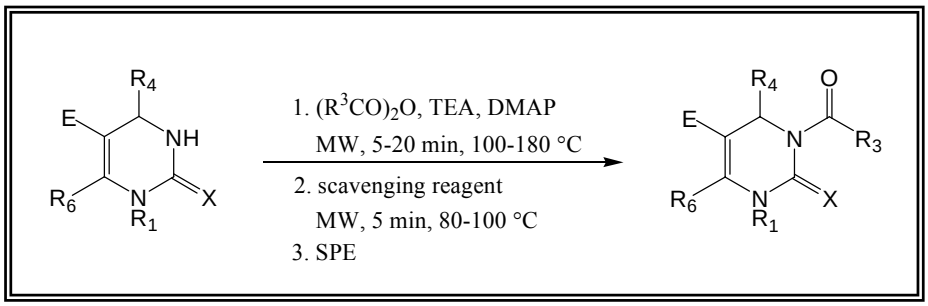


As displayed in above figure, it cab be understood that a number of scaffolds can be developed from DHPM ring.

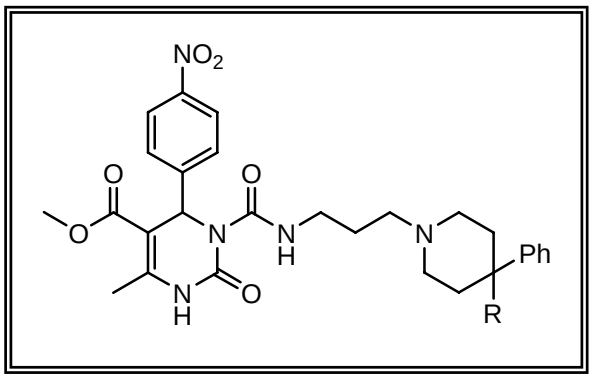
2.1.2 N3-Acylated and C5-substituted DHPMs and their biological importance

Kappe et al reported that *N*3-acylated DHPMs can be rapidly synthesized in a highthroughput fashion by combining microwave-assisted acylations with microwave-assisted scavenging techniques. Scavenging experiments can be carried out employing either supported nucleophilic amine sequestration reagents or water[2].

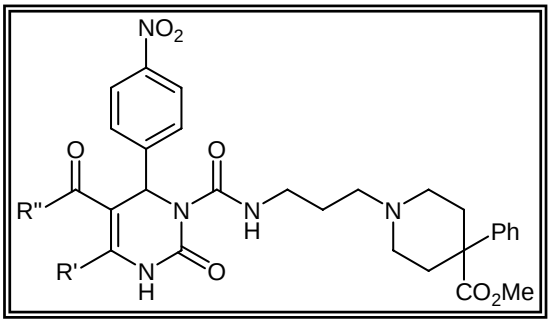
N-acylated DHPMs are pharmacologically very important scaffolds as most of bioactive DHPMs are N-acylated. N-acylation of DHPM can be performed as shown below.

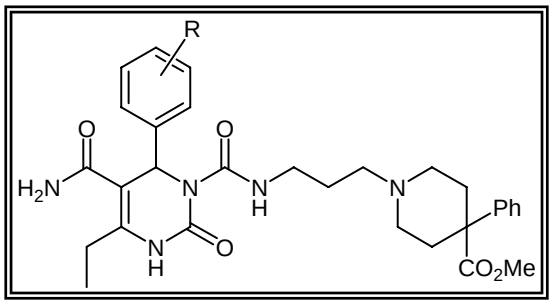


N3-substituted DHPMs have been identified to possess potent pharmacological profiles. Following compound exhibited high binding affinity and subtype selectivity for the cloned human R1a receptor[3].

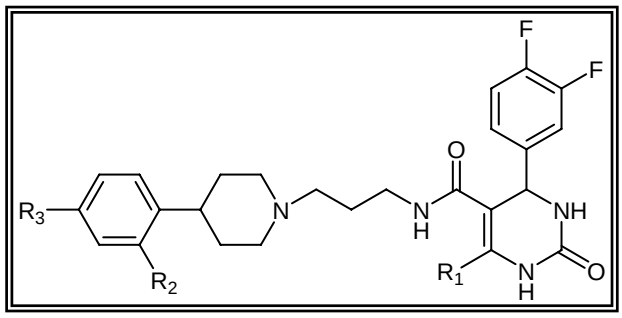


Systematic modifications of above compounds led to identification of highly potent and subtype-selective compounds with high binding affinity (*K*i) 0.2 nM) for R1a receptor and greater than 1500-fold selectivity over R1b and R1d adrenoceptors. The compounds were found to be functional antagonists in human, rat, and dog prostate tissues.



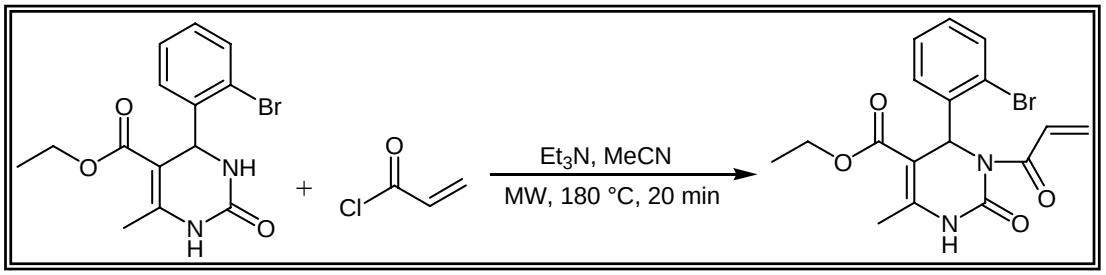


Modifications to the C5 position also play important role in potency of DHPM ring. 4-aryldihydropyrimidinones attached to an aminopropyl-4-arylpiperidine via a C-5 amide as selective R1A receptor subtype antagonists. In receptor binding assays, these types of compounds generally display *K*i values for the R1a receptor subtype <1 nM while being greater than 100-fold selective versus the R1b and R1d receptor subtypes. Many of these compounds were also evaluated in vivo and found to be more potent than terazosin in both a rat model of prostate tone and a dog model of intra-urethral pressure without significantly affecting blood pressure[4].

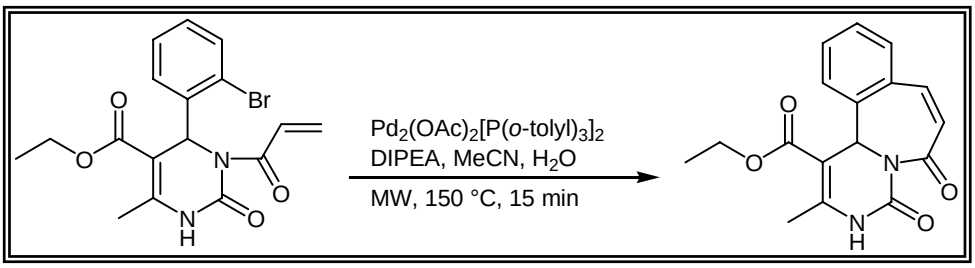


2.1.3 Intramolecular Heck cyclization of DHPMs

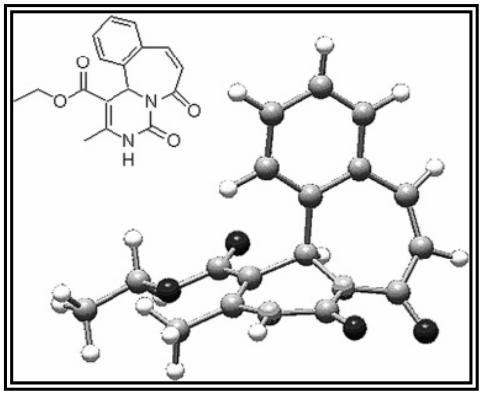
The intramolecular Heck reaction can be observed in DHPM skeleton. The starting material for the intramolecular Heck reaction, DHPM was prepared by selective N3-acylation of 4-(*o*-bromophenyl)-dihydropyrimidone with acryloyl chloride[5]



Applying intramolecular Heck reaction, tricyclic ring system can be obtained as shown below.[6]



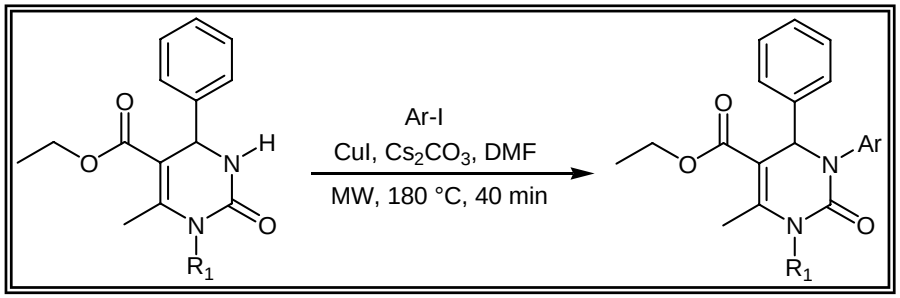
The computational experiments reveal that the formation of a tricyclic ring system did not flatten out the overall geometry. On the contrary, the aryl ring was still locked in a pseudoaxial position, resembling other nonfused 4-aryl-dihydropyrimidines.[7,8] In fact, here, the intramolecular Heck strategy allows locking of the aryl ring in the proposed bioactive, that is, the pseudoaxial, orientation.[9]



2.1.4 N3-Arylation of DHPMs

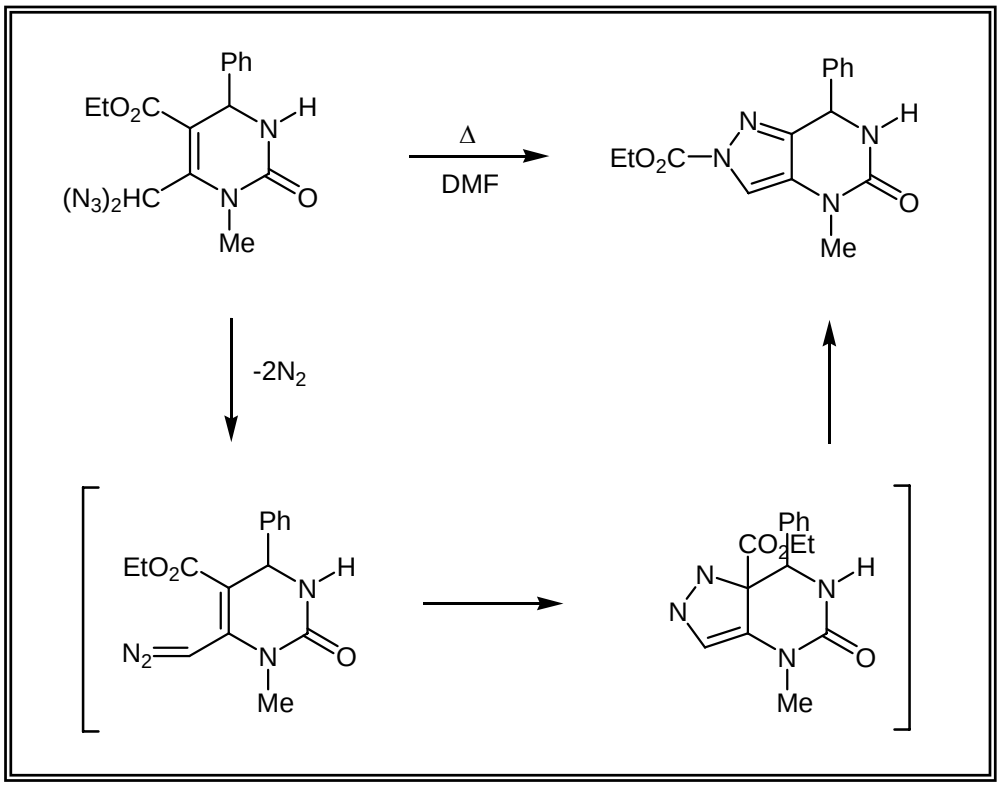
N3-arylated DHPM analogues cannot be obtained by classical Biginelli condensation strategies involving *N*-arylureas. Here, the corresponding N1-substituted derivates will be formed exclusively[10,11].

Wannberg et al reported protocol using concentrated mixture of 20 mol % of CuI as catalyst, 1.5 equiv of Cs2CO3 as base, and 5 mol equiv of DMF as solvent. The reactions were conducted at 180 °C for 40 min with a set of eight differently substituted aryl iodides.

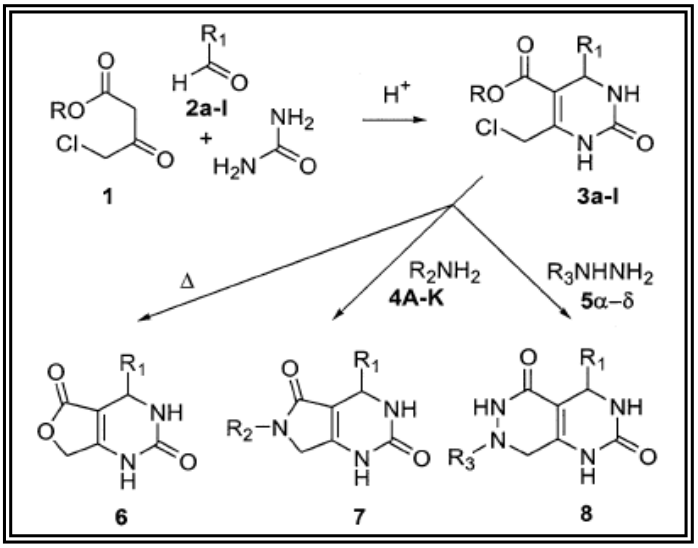


2.1.5 Bicyclic systems derived from DHPMs

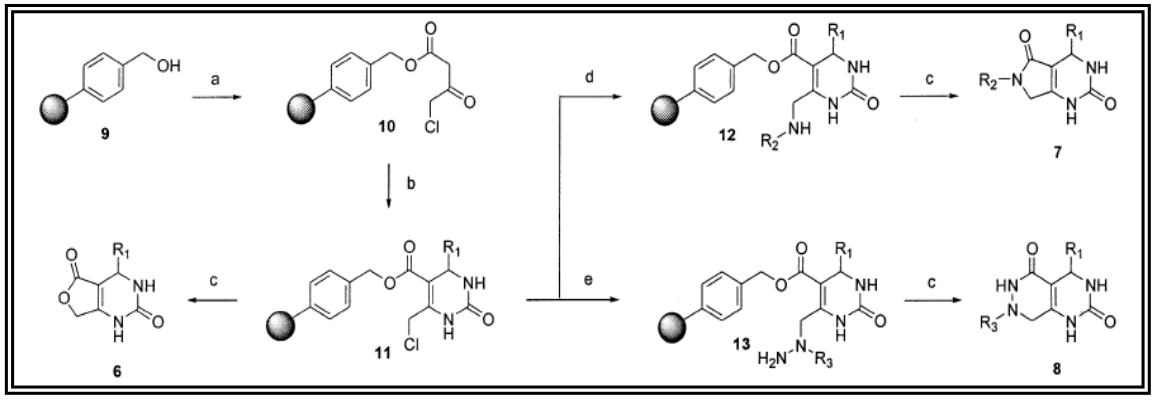
Many bicyclic systems can be synthesized from DHPM scaffold. Pyrazolo[4,3-d]pyrimidine derivatives synthesized by reacting sodium azide with N-Me, 6-Br-Me DHPM. The possible mechanism of this transformation is shown in below and involves decomposition of the diazide to vinyl diazo derivative, which undergoes spontaneous 1,5-electrocyclization to 3H-pyrazole. Subsequent migration of the ester substituent from the tetrahedral carbon to N2 (thermal van Alphen-Hüttel rearrangement) yields pyrazolo[4,3-d]pyrimidine. The structure confirming the position of the ester group at N2 was established by an X-ray analysis[a].



Use of the 4-chloroacetoacetate building block **1** in a Biginelli-type condensation is very useful to get variety of bicyclic systems. The resulting functionalized DHPM appeared to be an ideal common chemical template for the generation of a variety of interesting bicyclic scaffolds such as furo[3,4-*d*]- pyrimidines, pyrrolo[3,4-*d*]pyrimidines, and pyrimido[4,5-*d*]pyridazines .



Solid-phase and solution-phase protocols for the synthesis of furo[3,4-*d*]pyrimidines, pyrrolo[3,4-*d*]-pyrimidines, and pyrimido[4,5-*d*]pyridazines are reported. The multistep solid-phase sequence involves the initial high-speed, microwave-promoted acetoacetylation of hydroxymethylpolystyrene resin with methyl 4-chloroacetoacetate. The immobilized 4-chloroacetoacetate precursor was subsequently subjected to threecomponent Biginelli-type condensations employing urea and a variety of aromatic aldehydes. The resulting 6-chloromethyl-functionalized resin-bound dihydropyrimidones served as common chemical platforms for the generation of the desired heterobicyclic scaffolds using three different traceless cyclative cleavage strategies. The corresponding furo[3,4-*d*]pyrimidines were obtained by microwave flash heating in a rapid, thermally triggered, cyclative release. Treatment of the chloromethyl dihydropyrimidone intermediates with a variety of primary amines followed by high-temperature microwave heating furnished the anticipated pyrrolo[3,4-*d*]pyrimidine scaffolds via nucleophilic cyclative cleavage. In a similar way, reaction with monosubstituted hydrazines resulted in the formation of pyrimido[4,5-*d*]pyridazines. All compounds were obtained in moderate to good overall yields and purities[b].

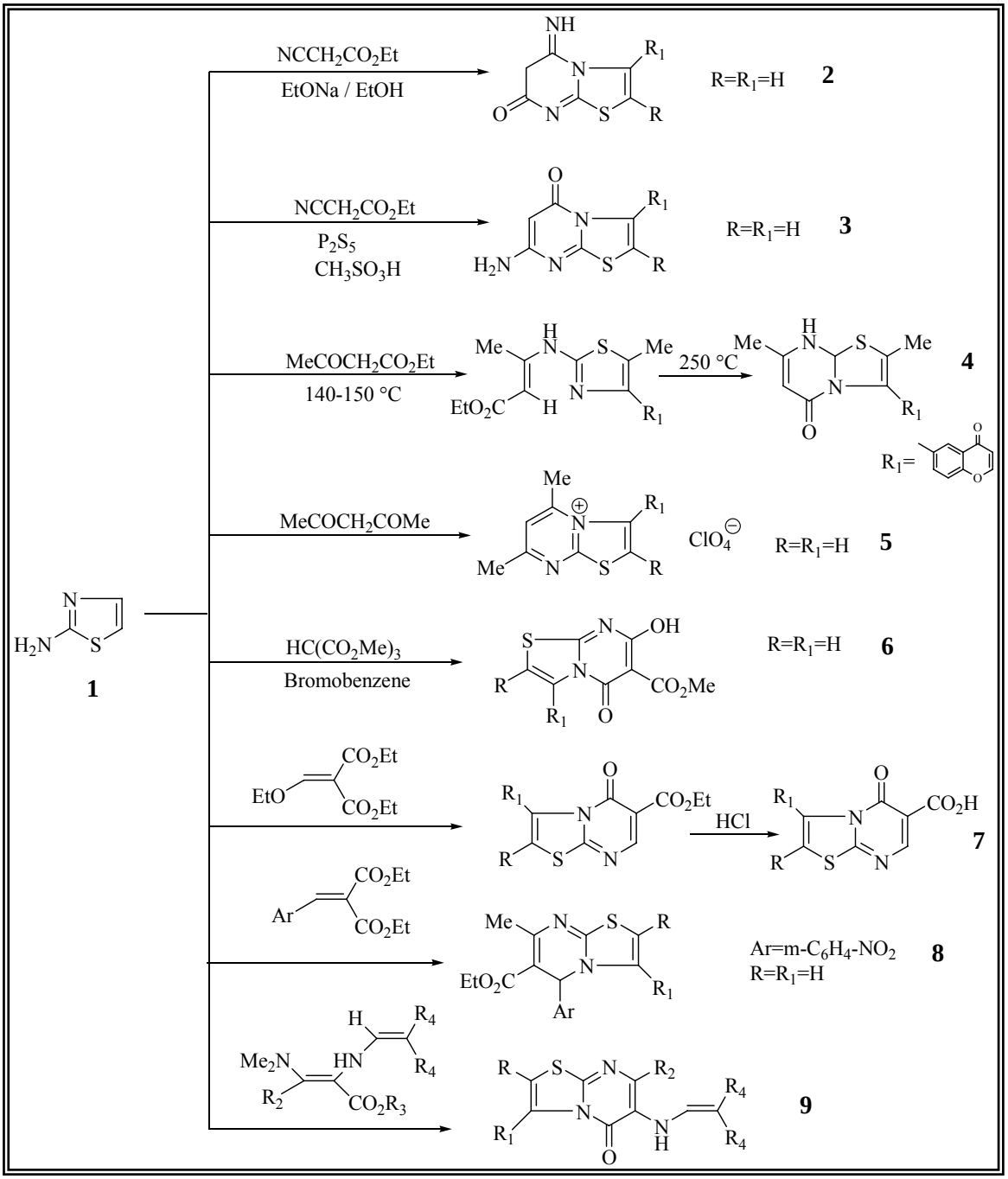


2.1.6 Chemistry and biological importance of thaizolo[3,2-a]pyrimidine and pyrimido[2,1-b][1,3]thiazines scaffolds

Preparation of thiazolo[3,2-a]pyrimidine derivatives is very well reported in literature. Two approaches is generally employed for synthesis.

1. **Azole approach:** various methods for synthesis of thiazolo[3,2-a]pyrimidine derivatives using thiazole as starting material.

Chart 1



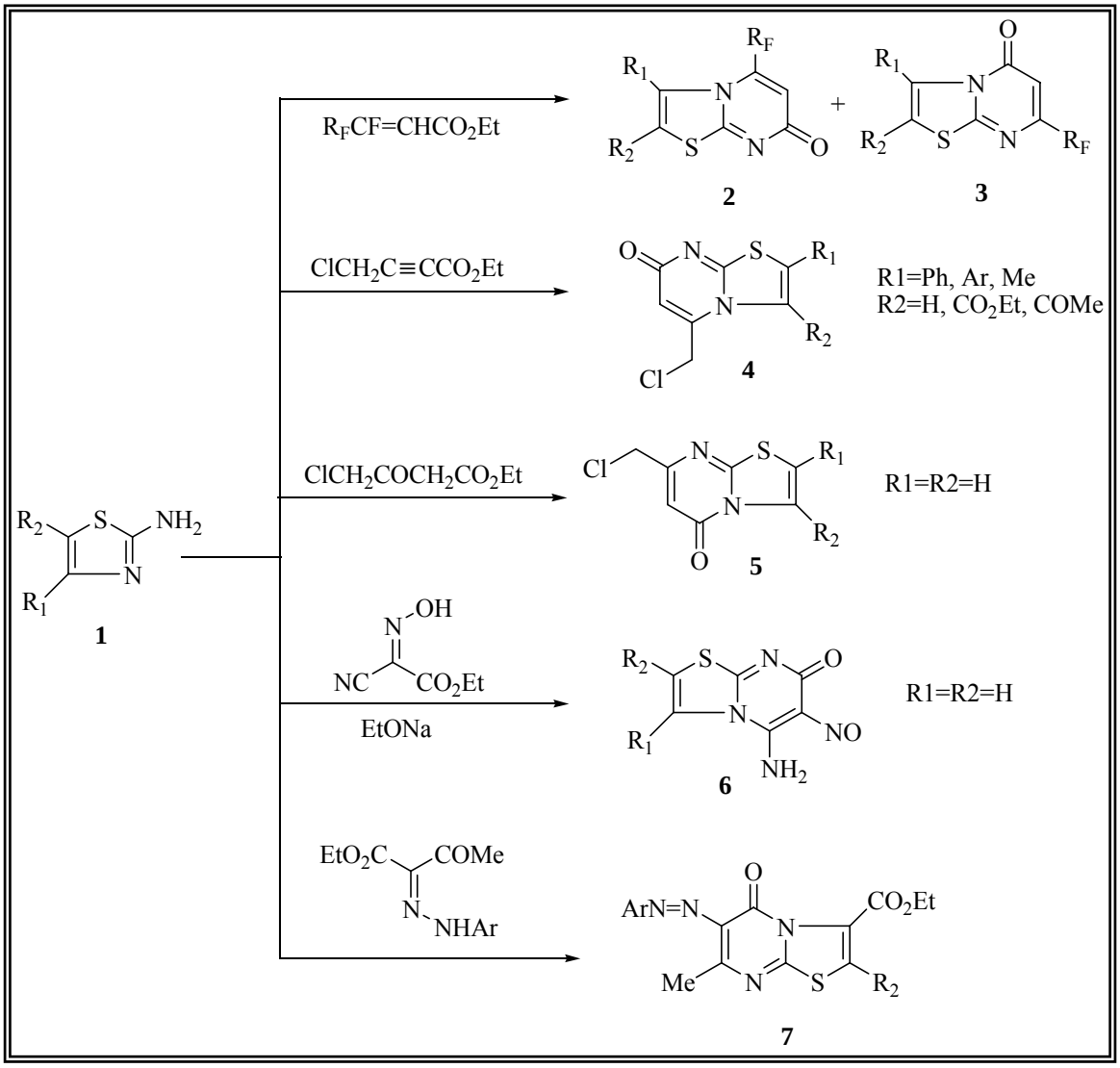
Literature survey on synthetic methodology for thiazolo[3,2-a]pyrimidine derivatives can be summarized in chart 1 & 2 where various methods are illustrated for synthesis of this class of compounds.

Chart 1: Thiazolo[3,2-a]pyrimidine **2** was prepared in 30% yield by the reaction of 2-aminothiazole **1** with ethyl cyanoacetate in a sodium ethoxide/ethanol mixture or using polyphosphoric acid or acetic acid. However, oxothiazolopyrimidine **3** was obtained upon treatment with phosphorous pentoxide and methanesulfonic acid.

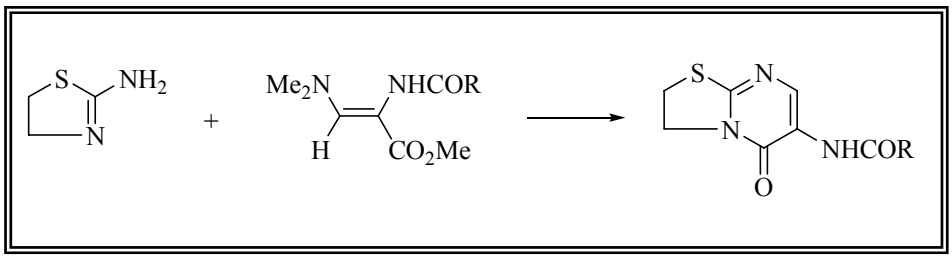
The reaction of **1** with ethyl acetoactate at 140-150°C resulted in the formation of compound that was then converted to the Z-isomer upon heating at 250°C and cyclized to give **4**. 2-Aminothiazole **5** cyclized with acetylacetone at lOO"C, in the presence of methanesulfonic acid-phosphorus pentoxide or formic acid-phosphorus pentoxide, followed by treatment with 70% perchloric acid, to give the thiazolopyrimidin-4-ium salt **5**. The ester **6** was obtained from 2-aminothiazole **1** with an excess of methyl methanetricarboxylate in 61 % yield. Cyclocondensation of **1** with diethyl ethoxymethylene malonate in acetic acid followed by hydrolysis of the ester gave **7.** Similarly, 2-aminothiazole **1** reacted with benzylidine in ethanol to give **8**. Stanovink ***et al.,*** [13-171 reported the synthesis of a series of thiazolopyrimidine derivatives upon reacting 2-aminothiazole with a variety of different reagents. Thus, dimethylaminobut- 2-enoate (or pentenoate), **reacted** with **1** to give thiazolopyrimidines **23. (Ref. 12-25)**

Chart 2: The reaction of 2-aminothiazole **1** with 2-hydropolyfluoroalk-2-enoate in basic medium gave two isomers, 7-oxo **2** and its isomeric 5-0x0 **3.** The structure of both **2** and **3** was established through **'H** NMR, **^{19}F NMR** and mass spectra[26]**.** 2-Aminothiazole derivatives**,** (R' = **H,** C02Et; R2 = Ph, aryl, Me), reacted with the acetylenic derivative and ester derivative in ethanol and polyphosphoric acid, respectively, to give the isomeric oxothiazolopyrimidine derivatives **4** and **5,** in 5-32% and 8-97 % yield, respectively[27]. Condensation of 2-aminothiazole **1** in absolute ethanol with the sodium salt of ethyl oximinocyanoacetate gave after acidification (pH 6) with diluted hydrochloric acid, the nitroso derivative **6** in 92% yield[28]. Treatment of the 2-aminothiazaole derivatives **5** with the hydrazone derivatives gave the oxothiazolo [3,2-a] pyrimidine derivatives **7.**[29]

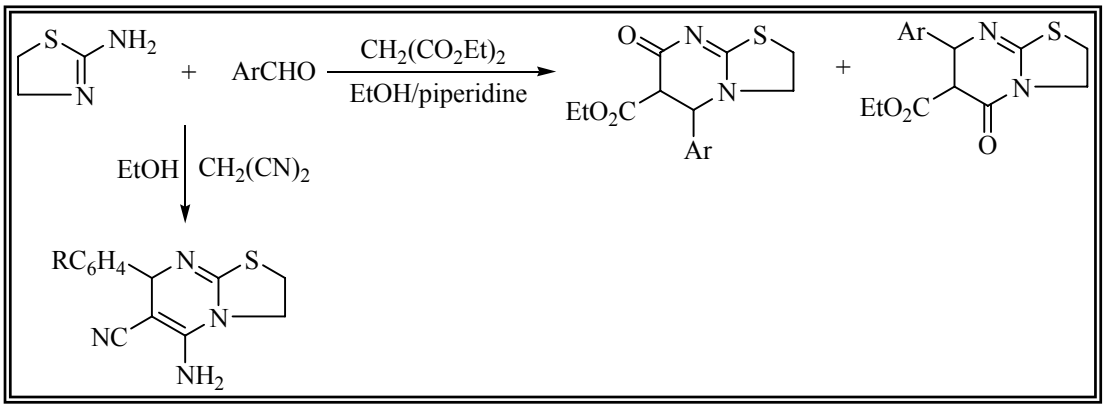
Chart 2



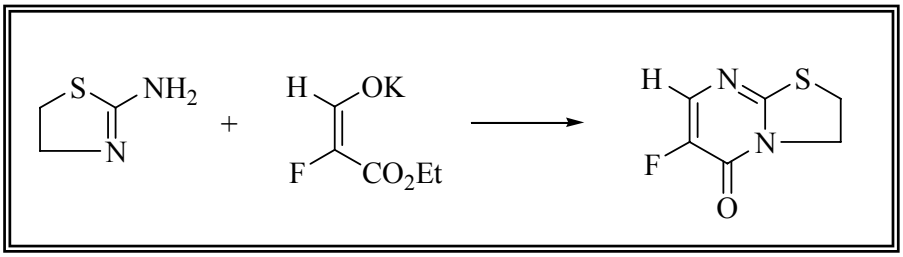
2-Amino-2-thiazoline reacted with 2-acylamino-3-dimethylamino-propenoates in acetic acid to yield 6-acylamino-5-oxo-2,3-dihydro-5~-thiazolo[3,2-a]pyrimidines in 73 and 12% yields, respectively[30].



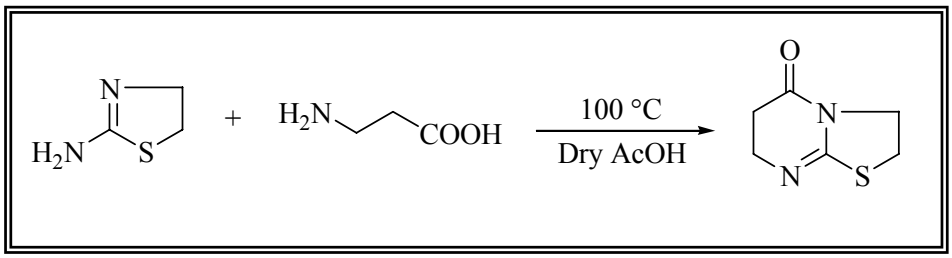
Moreover, 2-amino-2-thiazoline reacted with an aromatic aldehyde and diethyl malonate, to give a mixture of thiazolidino[3,2-a]pyrimidines. Furthermore, malononitrile reacted to give following product.[31-32]



2-Amino-Zthiazoline reacted with potassium 2-ethoxycarbonyl-2-fluorovinyl alcoholate in a sodium methoxide/methanol mixture to give 6-fluoro-2,3-dihydro-5-oxothiazolo[3,2-a]pyrimidine[33].

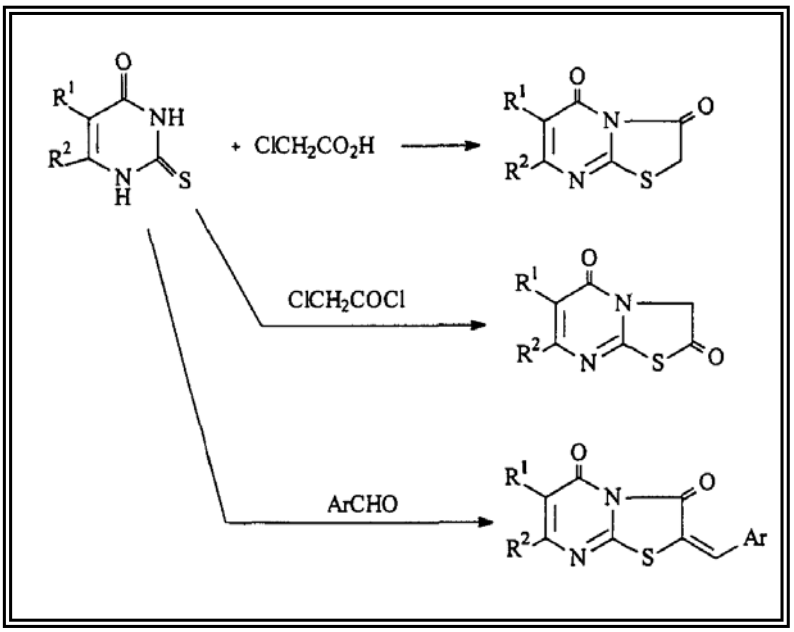


2-(Methylthio)-24hiazoline reacted with /3-alanine to give a 5-oxothiazolo[3,2-a]-pyrimidine derivative in 23% yield[34].

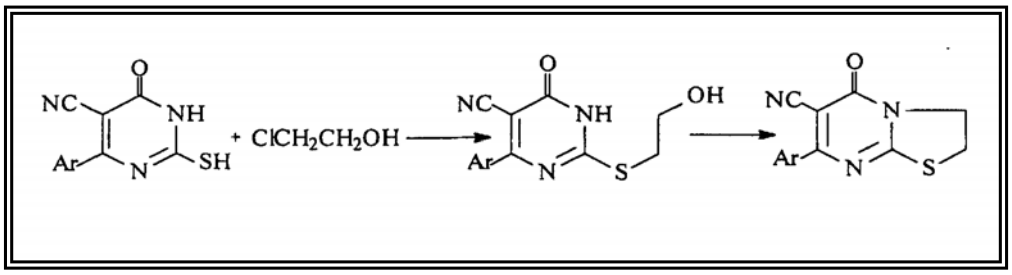


2. Azine approache

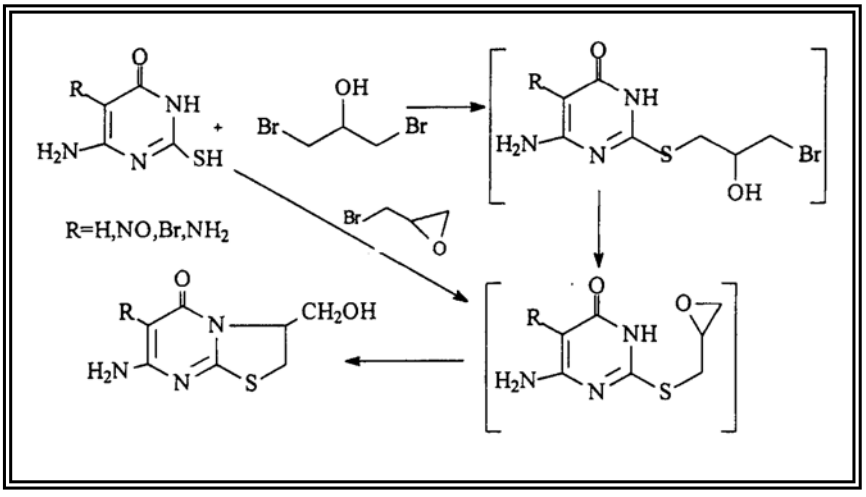
Pyrmidinethione derivatives were alkylated with monochloroacetic acid or chloroacetyl chloride and then cyclized to give thiazolopyrimidine derivatives.[35-48] Thus, pyrimidinethione reacted in DMF[35] or in an acetic anhydride/pyridine mixture[37] to give thiazolo-pyrimidines**.** Alkylation in the presence of an aromatic aldehyde gave the ylidene. Similarly, pyrimidinethione derivatives reacted with monochloroacetic acid in acetic acid/acetic anhydride/sodium acetate mixture or with chloroacetyl chloride in dry dioxane to give the corresponding thiazolopyrimidines[39,40].



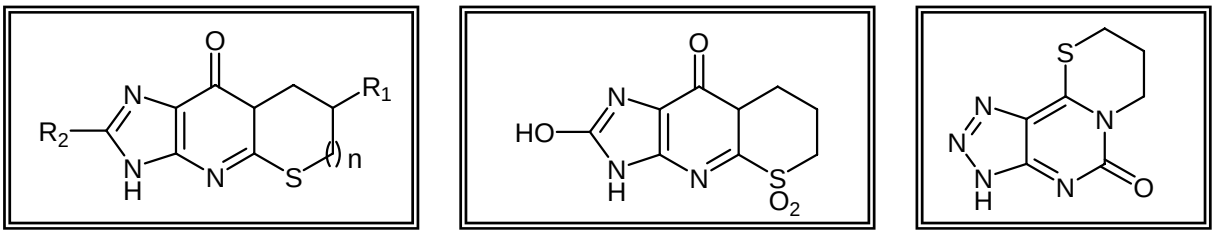
Treatment of mercaptopyrimidine derivative with 2-chloroethanol in DMF gave the asymmetrical thioether which underwent cyclization on refluxing with a mixture of acetic anhydride-pyridine, to give the oxothiazolopyrimidine[49].



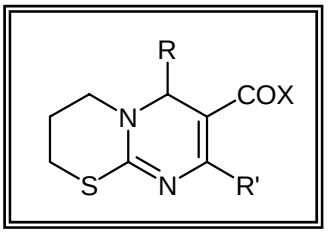
1,3-Dibromopropan-2-ol reacted with mercaptopyrimidine derivative to give product through the non isolated intermediates**.** The same reaction product was obtained by reacting with I-bromomethyloxirane.[50]



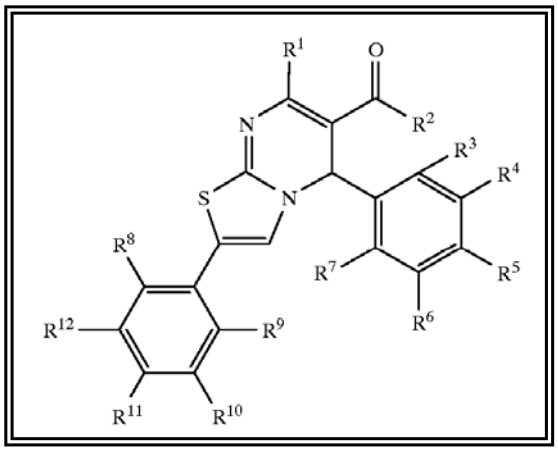
Several derivatives of 4,5-disubstituted imidazole, 2,4,5-trisubstituted pyrimidine, 2-substituted purine, thiazolo[3,2-*a*]purine, [1,3]thiazino[3,2-*a*]purine, thiazolo[2,3-*i*]purine, [1,3]thiazino-[2,3-*i*]purine, and 6-substituted pyrazolo[3,4-*d*]pyrimidine were synthesized and tested as inhibitors of the xanthine oxidase enzyme[51].



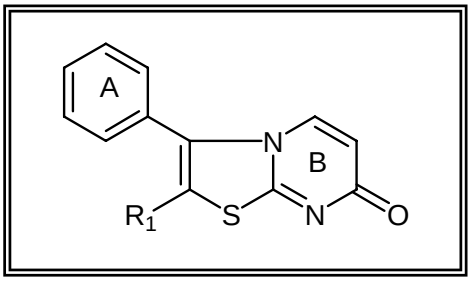
Dihydropyrimidines are well-known calcium channel blockers. According to the literature analogous derivatives are anti-inflammatories. Thus Bo´szing and co-workers decided to synthesize the pyrimidothiazines and assay these compounds for the same profile. Acute anti-inflammatory activity was tested by inhibition of the carrageenan-induced paw edema in rats[52].



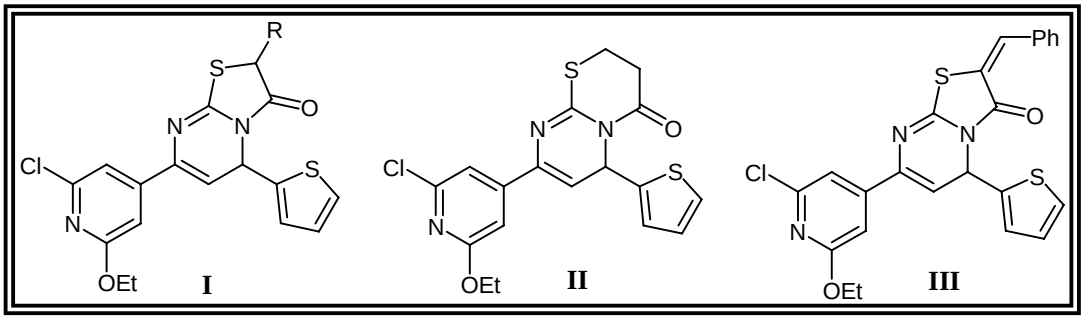
Adam et al filed US patent for phenyl substituted thiazolo pyrimidine derivatives synthesized from DHPM. These compounds and their slats are novel and are distinguished by valuable therapeutic properties. Specifically it has been found that the compounds of general formula given below are metabotropic glutamate receptor antagonists. These compounds are capable of high affinity binding to group II mGluR receptors[53].



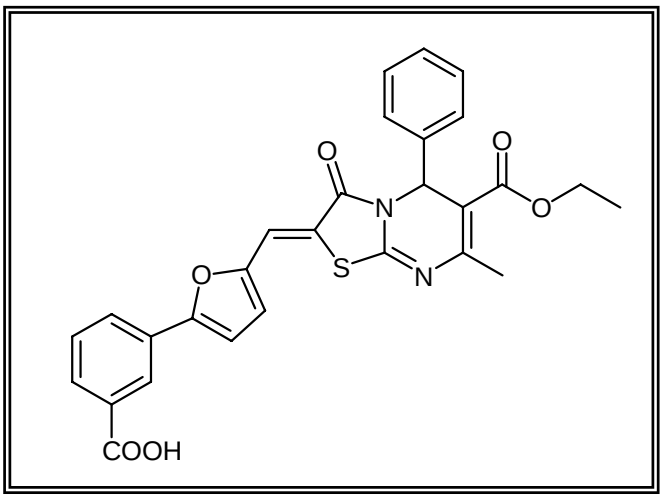
Compounds displayed by general formulae given below exhibit excellent adenosine A_3 receptor antagonism where A is an optionally substituted benzene ring. B may be substituted and R_1 is optionally substituted cyclic group[54].



Amr, A. E. G. E. and Maigali, S. S. described the analgesic and antiparkinsonian activity of some thiazolopyrimidine derivatives as shown below. Out of them compound of type III are potent antiparkinsonian agents.[55]



CDC25 phosphatases play critical roles in cell cycle regulation and are attractive targets for anticancer therapies. Several small non-peptide molecules are known to inhibit CDC25, but many of them appear to form a covalent bond with the enzyme or act through oxidation of the thiolate group of the catalytic cysteine. Matthieu Montes et al reported thiazolopyrimidine structure based compound as CDC25 phosphatases inhibitor.[56]



2.2 Current work

Importance of DPHM ring to develop variety of bicyclic systems is briefly surveyed in section 2.1. N3-substitution in DHPM ring is reported to enhance activity profile.[3,4] Similarly, substitutions at C5 position may plays key role in activity profile. In our work, n-butyl carboxylic ester side chain is introduced at C5 position of DHPM ring. Further, thiazolo pyrimidine derivatives with n-butyl carboxylic ester moiety at C5 position are synthesized and characterized.

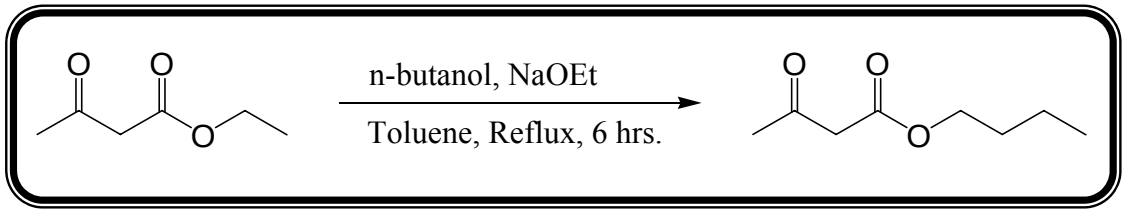
Thiazolo pyrimidine and pyrimido thiazine are very important bicyclic system in medicinal chemistry.[51-56] Various synthetic routes have been reported in literature to synthesize these bicyclic systems. Utility of DHPM ring to synthesize different bicyclic system is discussed. Derivatives of these bicyclic systems with n-butyl carboxylic ester as side chain on pyrimidine ring of bicyclic system can be synthesized using this methodology.

DHPM ring, substituted with n-butyl carboxylic ester side chain at C5 position, was synthesized as described in Chapter 1. This DHPM ring was reacted with α-halo ketone to get bicyclic systems. In synthesis of thiazolo pyrimidine system, mono chloroacetone was used as α-halo ketone. Various solvents were utilized as reaction media to get better results. Among them glacial acetic acid with sodium acetate as catalytic amount was succeeded to give better yield with shorten reaction time and easy in isolation of product. All newly synthesized compounds were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. Reaction schemes are illustrated in section 2.3. Physical data of synthesized compounds is reported in section 2.6 and spectral data is discussed in section 2.7. The antiviral screening of compounds is under investigation.

2.3 Reaction Scheme

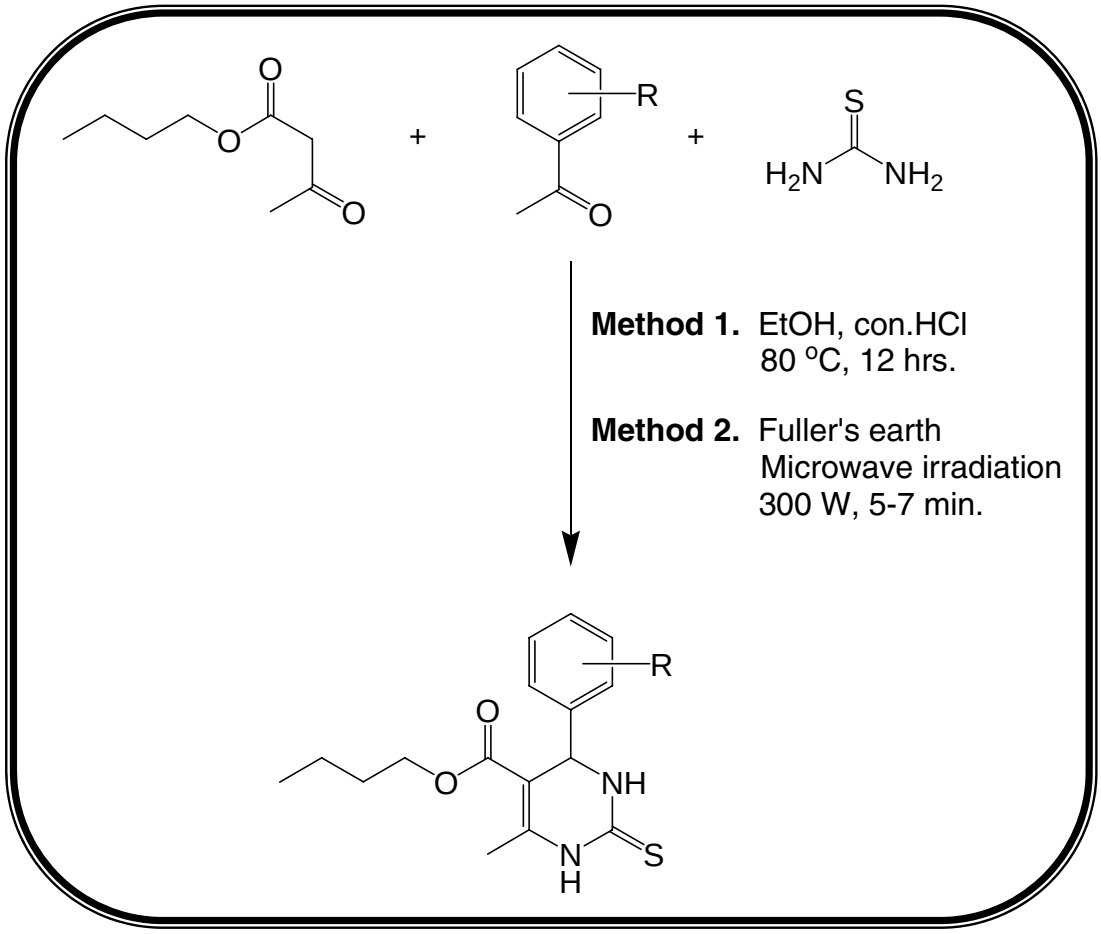
2.3.1 Scheme 1

Transesterification of ethyl acetoacetate



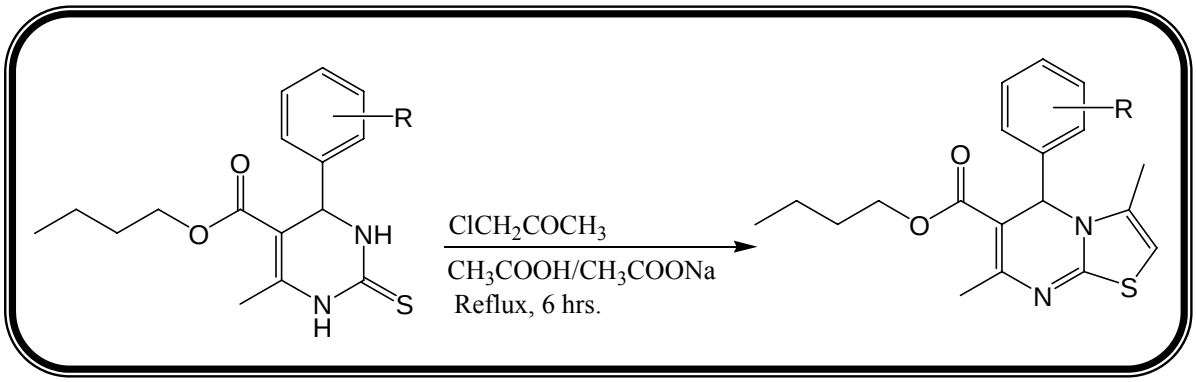
2.3.2 Scheme 2

Synthetic approaches towards dihydropyrimidine

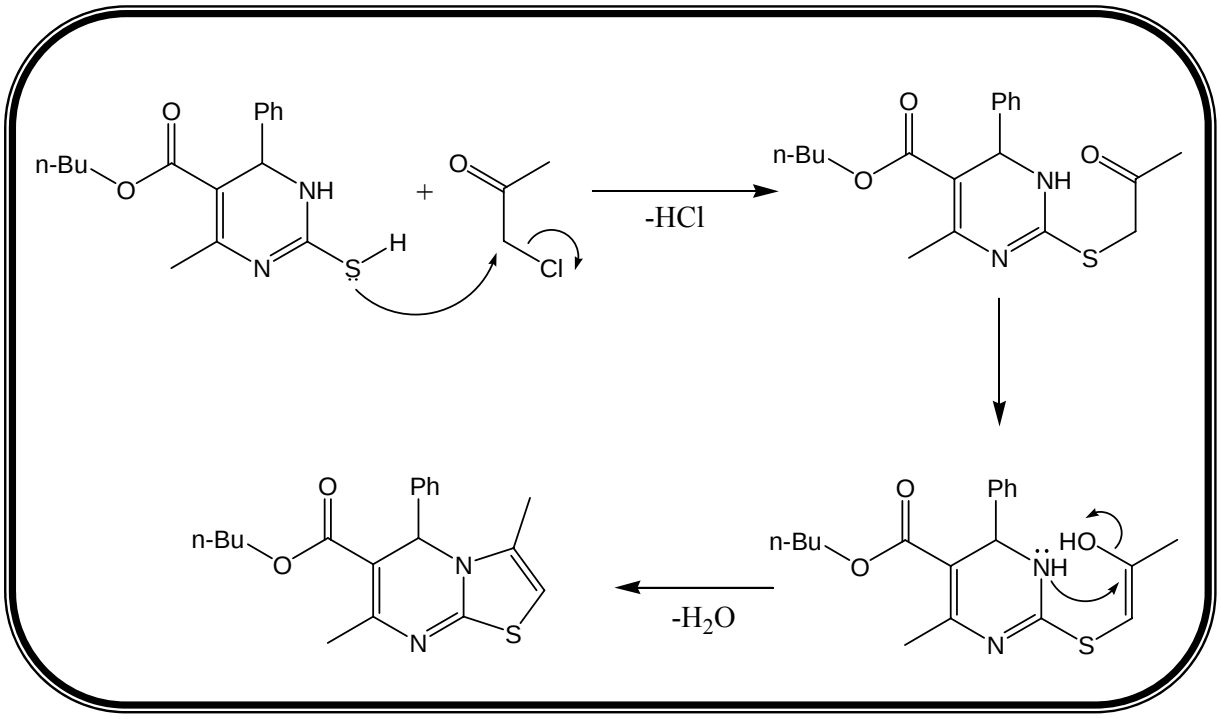


2.3.3 Scheme 3

Synthetic approach towards thiazolopyrimidine



2.4 Reaction Mechanism



2.5 Experimental

2.5.1 n-Butyl acetoacetate:

A mixture of ethyl acetoacetate (0.1 M) and n-butyl alcohol (0.11 M) in toluene (50 ml) was taken in a round bottom flask provided with a distillation condenser to remove methanol or ethanol. Sodium ethoxide (1 mmol) was added to the mixture as a catalyst. The mixture was heated at 100-110 °C for 5-6 hrs. After completion of reaction (TLC), the catalyst was filtered and the filterate was concentrated to get crude product. n-Butyl acetoacetate was distilled off at 92-98 ° C/20 mm Hg. Yellowish viscous oil.

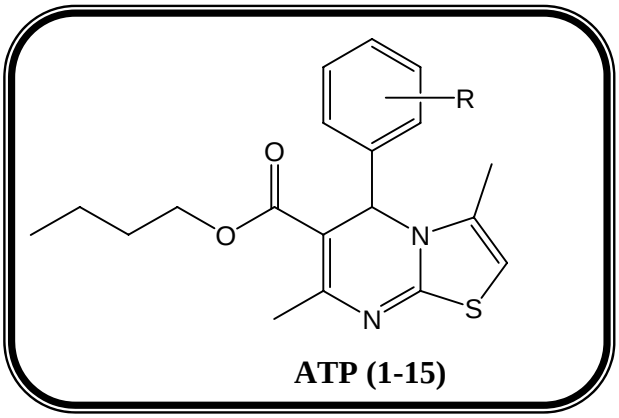
2.5.2 n-Butyl 6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate:

A mixture of n-butyl acetoacetate (10 mmol), appropriate aldehyde (10 mmol) and thiourea (15 mmol) was dissolved in absolute EtOH (20 mL) and refluxed until clear solution is obtained. Few drops of con. HCl were added to reaction mixture as a catalyst and was refluxed for 8-12 hrs. The reaction was monitored with thin layer chromatography and after completion of the reaction, the mixture was allowed to cool at room temperature. The solid separated was filtered, washed with hot methanol and recrystallized from ethanol. **(AP 1-15)** (Yield – 45-60%).

2.5.3 n-Butyl 3,7-dimethyl-5-phenyl-5*H*-[1,3]thiazolo[3,2-a]pyrimidine-6-carboxylate:

Compound AP(1-15) (10 mmol) and mono chloroacetone (10 mmol) were dissolved in glacial acetic acid with sodium acetate and refluxed for 6 hrs. The reaction was monitored with thin layer chromatography and after completion of the reaction, the reaction mixture was poured on crushed ice and was extracted with chloroform. The chloroform was removed in vacuum. The residue was dried and recrystallized from ethanol. **(ATP 1-15)** (Yield: 55-65%).

2.6 Physical data



ATP (1-15)

Comp.	R	M.F.	M.W.	Mp °C	Yield %	R_f
ATP-1	H	$C_{19}H_{22}N_2O_2S$	342.45	240-242	75	0.48
ATP-2	4-OCH_3	$C_{20}H_{24}N_2O_3S$	372.48	225-227	74	0.62
ATP-3	3,4-$(OCH_3)_2$	$C_{21}H_{26}N_2O_4S$	402.50	235-237	79	0.41
ATP-4	2,5-$(OCH_3)_2$	$C_{21}H_{26}N_2O_4S$	402.50	238-240	75	0.42
ATP-5	2-Cl	$C_{19}H_{21}ClN_2O_2S$	376.90	242-244	65	0.56
ATP-6	3-Cl	$C_{19}H_{21}ClN_2O_2S$	376.90	235-236	69	0.56
ATP-7	4-Cl	$C_{19}H_{21}ClN_2O_2S$	376.90	238-240	69	0.61
ATP-8	3-NO_2	$C_{19}H_{21}N_3O_4S$	387.45	239-240	71	0.54
ATP-9	4-NO_2	$C_{19}H_{21}N_3O_4S$	387.45	243-244	73	0.58
ATP-10	2-OH	$C_{19}H_{22}N_2O_3S$	358.45	240-242	70	0.49
ATP-11	4-OH	$C_{19}H_{22}N_2O_3S$	358.45	228-230	68	0.56
ATP-12	4-F	$C_{19}H_{21}FN_2O_2S$	360.44	244-245	58	0.54
ATP-13	4-CH_3	$C_{20}H_{24}N_2O_2S$	356.48	251-253	60	0.47
ATP-14	4-dimethylamino	$C_{21}H_{27}N_3O_2S$	385.52	244-246	68	0.59*
ATP-15	[2,3] Benzo	$C_{23}H_{24}N_2O_2S$	392.51	241-243	70	0.60*

TLC Solvent system: Ethyl acetate : Hexane – 4:6, *$CHCl_3$: MeOH – 9:1

MPs were taken in open capillary and are not corrected.

2.7 Spectral discussion

2.7.1 Mass spectral study

Instrument : SHIMADZU GCMS-QP-2010

Sample technique : EI technique

M/z range : 40-500

Systematic fragmentation pattern was observed in mass spectral analysis. Peaks for specific fragments were identified in each mass spectrum. Molecular ion peak was observed in agreement with molecular weight of respective compound. Mass fragmentation for compound ATP-1 is discussed below.

Molecular ion peak M^+ was observed at 342 and M^++1 peak was also observed with very low intensity. The three peaks were observed due to cleavage of alkyl chain at 327, 314, and 285 as M^+-CH_3, M^+-C_2H_5, and M^+-C_4H_9 as per shown in figure 1. One low intense peak was observed at 269 due to cleavage of n-butoxy group from carboxylic ester group at C-6 position as M^+-OC_4H_9. This fragment was further undergone to cleavage from both methyl groups at C3 and C7 position of thiazolo pyrimidine moiety and gave very intense peak at 241. A base peak was observed at 265 due to cleavage of phenyl ring from thiazolo pyrimidine moiety as M^+-C_6H_5. This fragment was further undergone to cleavage of ethyl and butyl group from alkyl chain of carboxylic ester at C6 of thiazolo pyrimidine moiety and gave two intense peaks at 237 and 209 respectively.

2.7.2 IR spectral study

Instrument : Shimadzu FT-IR-8400

Sample technique : KBr pellet

Frequency range : 400-4000cm^{-1}

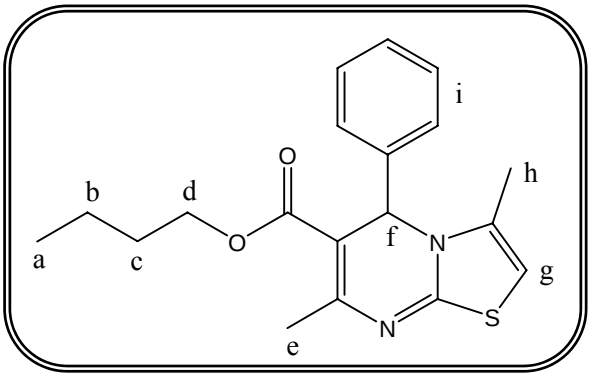
As per IR spectral study of synthesized thiazolopyrimidine derivatives, there was not observed NH stretching vibration around 3200-3500 cm^{-1}, which revealed the complete transformation of dihydropyrimidine to thiazolopyrimidine. Alkyl chain of carboxylic acid ester showed C-H stretching vibration between 2800-2900 cm^{-1} while C-H bending vibration was observed at near 1450 and 1375 cm^{-1}. Ring skeleton vibration was shown between 1500 to 1600 cm^{-1}.

2.7.3 ^{1}H NMR spectral study

Instrument : BRUKER AC 400 MHz FT-NMR

Internal reference : TMS

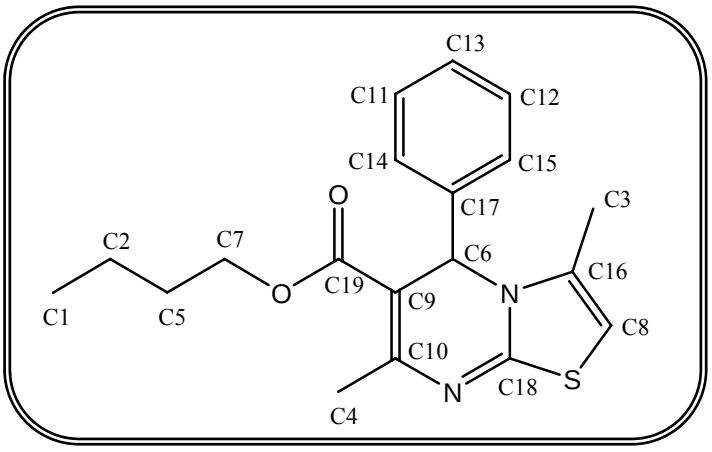
Solvent : $CDCl_3$



Number of protons and their chemical shifts were found to support the structure of the synthesized compounds. Protons of n-butyl chain 'a', 'b' and 'c' were observed at 0.90-0.95 δ ppm, 1.32-1.42 δ ppm and 1.58-1.67 δ ppm respectively. Protons 'd' were observed at 4.06-4.18 δ ppm due to neighboring attachment of hetero atom. Protons 'e' and 'h' of methyl group attached at C-7 and C-3 position respectively were observed at 2.36-2.40 δ ppm and 2.06-2.08 δ ppm as singlet and very intense peak. Asymmetric carbon proton 'f' was observed at 5.0-5.9 δ ppm as singlet. Proton of thiazole ring 'g' was observed at 6.1-6.2 δ ppm. The aromatic ring protons 'i' were observed at 6.50-7.80 δ ppm.

2.7.4 ^{13}C NMR spectral study

^{13}C NMR spectrum data for compound ATP-1 is given below. δ ppm values are listed along with corresponding carbon atom number given in bracket and displayed in the structure.

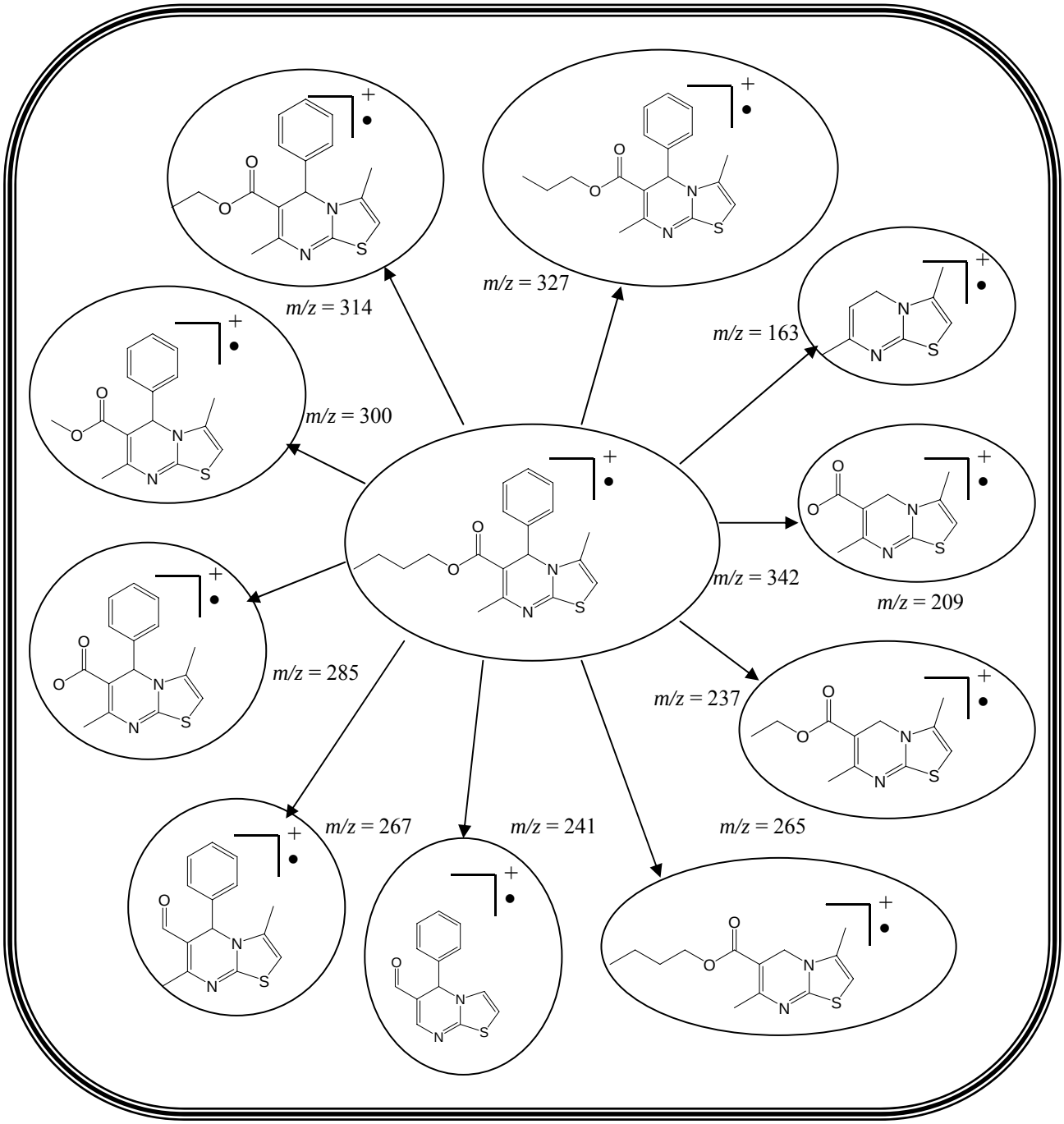


^{13}C NMR δ ppm: 13.78 (C1), 14.02 (C2), 19.38 (C3), 23.51 (C4), 30.87 (C5), 57.87 (C6), 63.98 (C7), 100.35 (C8), 126.52 (C9), 126.52 (C10), 128.36 (C11), 128.36 (C12), 128.80 (C13), 128.80 (C14), 128.80 (C15), 135.52 (C16), 142.76 (C17), 166.29 (C18), 166.86 (C19).

2.7.5 Elemental Analysis

Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Figure 1. Mass fragmentation of Mass spectrum of n-butyl 3,7-dimethyl-5-phenyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-1).



Spectral data of synthesized compounds (ATP 1-15)

n-butyl 3,7-dimethyl-5-phenyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-1)

Yellow solid; mp 240-242 ˚C;

IR (KBr): 3032, 2947, 2875, 2775, 1681, 1521, 1492, 1442, 1342 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ ppm = 0.92 (t, 3H, CH_3), 1.37 (m, 2H, CH_2), 1.63 (m, 2H CH_2), 2.07 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.11 (m, 2H, CH_2), 6.02 (s, 1H, CH), 6.17 (s, 1H, CH), 7.24–7.33 (m, 5H, Ph); **^{13}C NMR (400 MHz, $CDCl_3$):** δ ppm = 13.78, 14.02, 19.38, 23.51, 30.87, 57.87, 63.98, 100.35, 126.52, 126.52, 128.36, 128.36, 128.80, 128.80, 128.80, 135.52, 142.76, 166.29, 166.86; **MS: m/z** = 342 (M^+); **Anal. Calcd** for $C_{19}H_{22}N_2O_2S$: C, 66.64; H, 6.48; N, 8.18. Found: C, 66.56; H, 6.39; N, 8.01.

n-butyl 5-(4-methoxyphenyl)-3,7-dimethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-2)

Yellow solid; mp 225-227 ˚C;

IR (KBr): 3006, 2924, 2875, 1674, 1556, 1521, 1468, 1338 cm^{-1}; **MS: m/z** = 372 (M^+); **Anal. Calcd** for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N, 7.52. Found: C, 64.58; H, 6.31; N, 7.43.

n-butyl 5-(3,4-dimethoxyphenyl)-3,7-dimethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-3)

Yellow solid; mp 235-237 ˚C;

IR (KBr): 2958, 2914, 2859, 1690, 1445, 1371 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ ppm = 0.93 (t, 3H, CH_3), 1.39 (m, 2H, CH_2), 1.63 (m, 2H CH_2), 2.08 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.83 (s, 6H, OCH_3), 4.11 (m, 2H, CH_2), 5.96 (s, 1H, CH), 6.11 (s, 1H, CH), 6.74–6.88 (m, 3H, Ph); **MS: m/z** = 402 (M^+); **Anal. Calcd** for $C_{21}H_{26}N_2O_4S$: C, 62.66; H, 6.51; N, 6.96. Found: C, 62.71; H, 6.45; N, 7.23.

n-butyl 5-(2,5-dimethoxyphenyl)-3,7-dimethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-4)

Yellow solid; mp 238-240 ˚C;

IR (KBr): 2944, 2898, 2832, 1672, 1416, 1345 cm^{-1}; **MS: m/z** = 402 (M^+); **Anal. Calcd** for $C_{21}H_{26}N_2O_4S$: C, 62.66; H, 6.51; N, 6.96. Found: C, 62.46; H, 6.37; N, 7.01.

n-butyl 5-(2-chlorophenyl)-3,7-dimethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-5)

Yellow solid; mp 242-244 ˚C;

IR (KBr): 2875, 2821, 1645, 1596, 1446 cm^{-1}; **MS: m/z** = 376 (M^+); **Anal. Calcd** for $C_{19}H_{21}ClN_2O_2S$: C, 60.55; H, 5.62; N, 7.43. Found: C, 60.38; H, 5.56; N, 7.33.

n-butyl 5-(3-chlorophenyl)-3,7-dimethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-6)

Yellow solid; mp 235-236 ˚C;

IR (KBr): 2970, 2845, 1689, 1450, 1381 cm^{-1}; **MS: m/z** = 376 (M^+); **Anal. Calcd** for $C_{19}H_{21}ClN_2O_2S$: C, 60.55; H, 5.62; N, 7.43. Found: C, 60.69; H, 5.34; N, 7.19.

n-butyl 5-(4-chlorophenyl)-3,7-dimethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-7)

Yellow solid; mp 238-240 ˚C;

IR (KBr): 2865, 1696, 1556, 1460, 1551, cm^{-1}; **MS: m/z** = 376 (M^+); **Anal. Calcd** for $C_{19}H_{21}ClN_2O_2S$: C, 60.55; H, 5.62; N, 7.43. Found: C, 60.44; H, 5.75; N, 7.32.

n-butyl 3,7-dimethyl-5-(3-nitrophenyl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-8)

Yellow solid; mp 239-240 ˚C;

IR (KBr): 2968, 2875, 1682, 1416, 1346 cm^{-1}; **MS: m/z** = 387 (M^+); **Anal. Calcd** for $C_{19}H_{21}N_3O_4S$: C, 58.90; H, 5.46; N, 10.85. Found: C, 58.76; H, 5.36; N, 10.71.

n-butyl 3,7-dimethyl-5-(4-nitrophenyl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-9)

Yellow solid; mp 243-244 ˚C;

IR (KBr): 2925, 2881, 1674, 1535, 1378 cm^{-1}; **MS: m/z** = 387 (M^+); **Anal. Calcd** for $C_{19}H_{21}N_3O_4S$: C, 58.90; H, 5.46; N, 10.85. Found: C, 58.86; H, 5.38; N, 10.81.

n-butyl 5-(2-hydroxyphenyl)-3,7-dimethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-10)

Yellow solid; mp 240-242 ˚C;

IR (KBr): 3405, 2974, 2945, 1681, 1507, 1464, 1328 cm^{-1}; **MS: m/z** = 358 (M^+); **Anal. Calcd** for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.73; H, 6.32; N, 8.05.

n-butyl 5-(4-hydroxyphenyl)-3,7-dimethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-11)

Yellow solid; mp 228-230 ˚C;

IR (KBr): 3488, 2934, 2889, 1708, 1545, 1447, 1361 cm^{-1}; **MS: m/z** = 358 (M^+); **Anal. Calcd** for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.47; H, 6.11; N, 7.68.

n-butyl 5-(4-fluorophenyl)-3,7-dimethyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-12)

Yellow solid; mp 244-245 ˚C;

IR (KBr): 2901, 2827, 1674, 1459, 1328 cm^{-1}; **MS: m/z** = 360 (M^+); **Anal. Calcd** for $C_{19}H_{21}FN_2O_2S$: C, 63.31; H, 5.87; N, 7.77. Found: C, 63.17; H, 5.73; N, 7.80.

n-butyl 3,7-dimethyl-5-(4-methylphenyl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-13)

Yellow solid; mp 251-253 ˚C;

IR (KBr): 2850, 2971, 1669, 1453, 1357 cm^{-1}; **MS: m/z** = 356 (M^+); **Anal. Calcd** for $C_{20}H_{24}N_2O_2S$: C, 67.38; H, 6.79; N, 7.86. Found: C, 67.32; H, 6.70; N, 7.95.

n-butyl 3,7-dimethyl-5-[4-(dimethylamino)phenyl]-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-14)

Yellow solid; mp 244-246 ˚C;

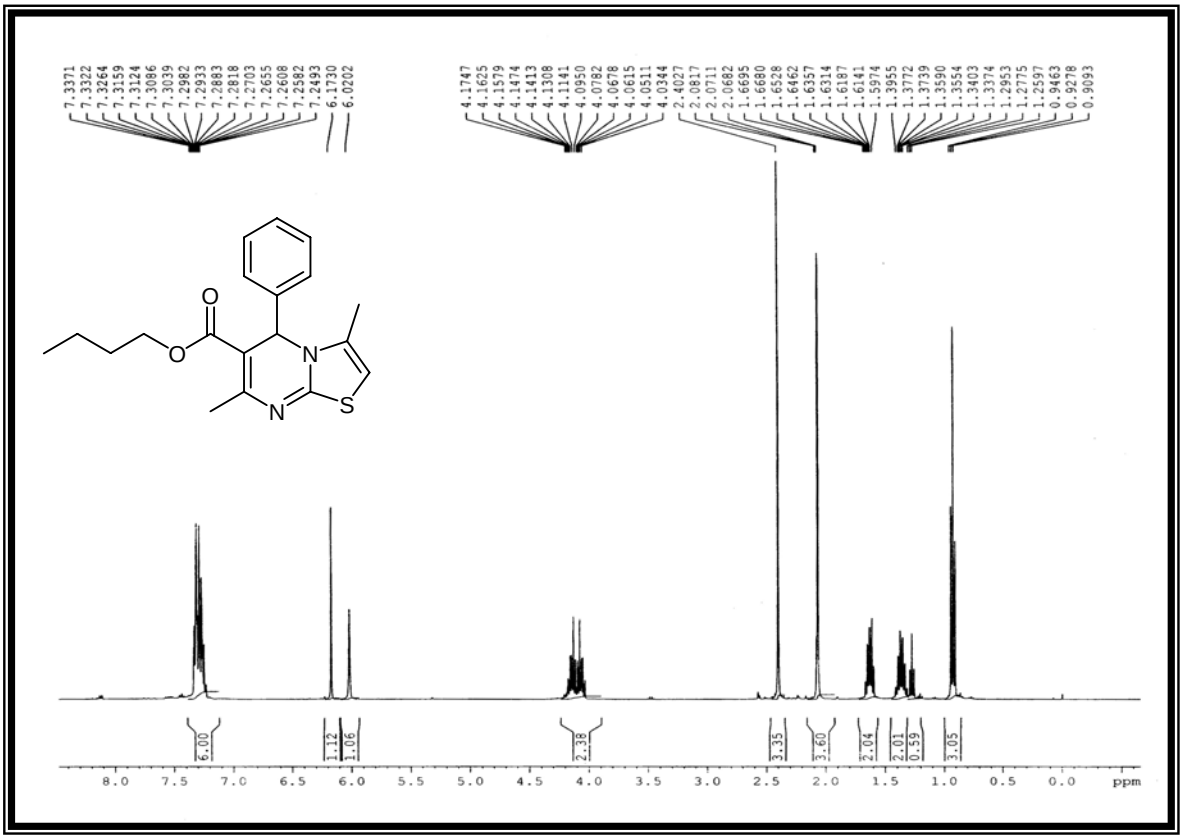
IR (KBr): 2962, 2908, 1683, 1478, 1364 cm^{-1}; **MS: m/z** = 385 (M^+); **Anal. Calcd** for $C_{21}H_{27}N_3O_2S$: C, 65.42; H, 7.06; N, 10.90. Found: C, 65.50; H, 6.89; N, 11.17.

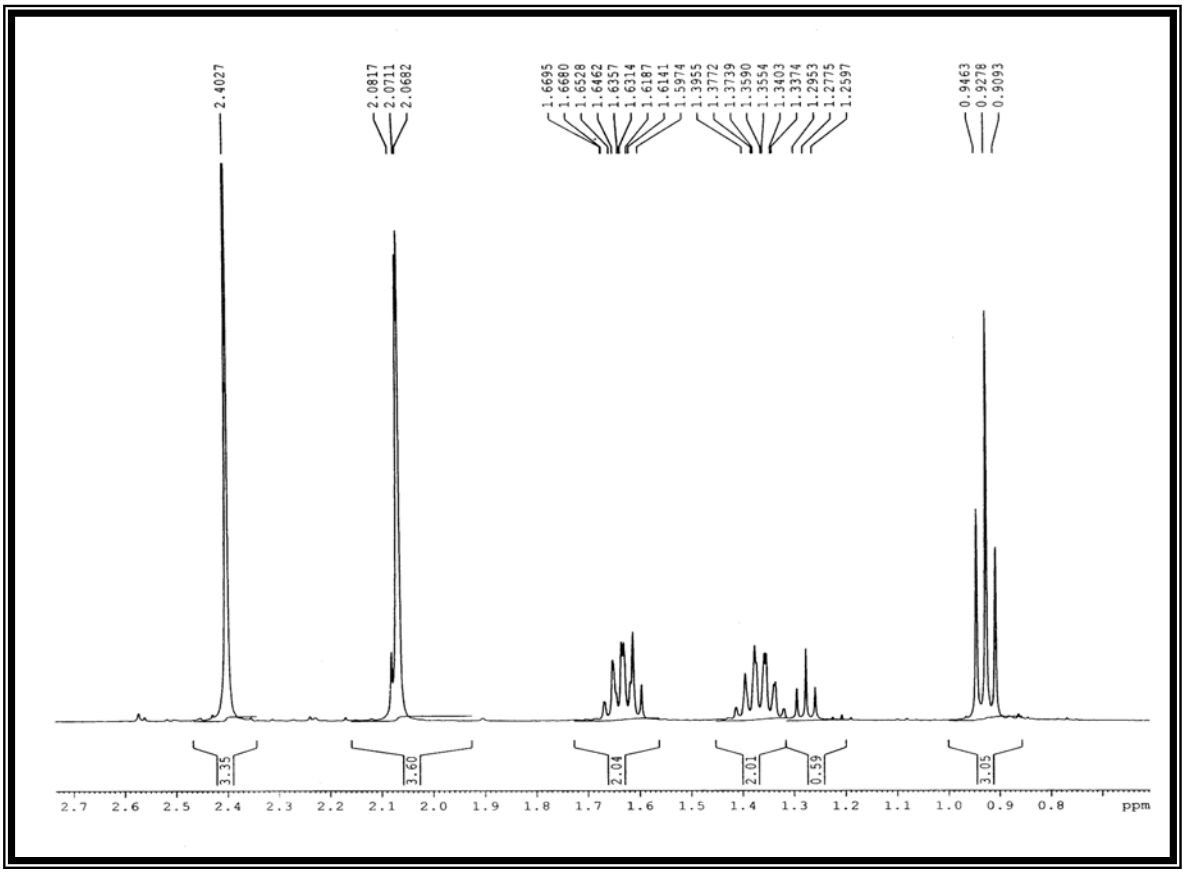
n-butyl 3,7-dimethyl-5-(1-napthyl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (ATP-15)

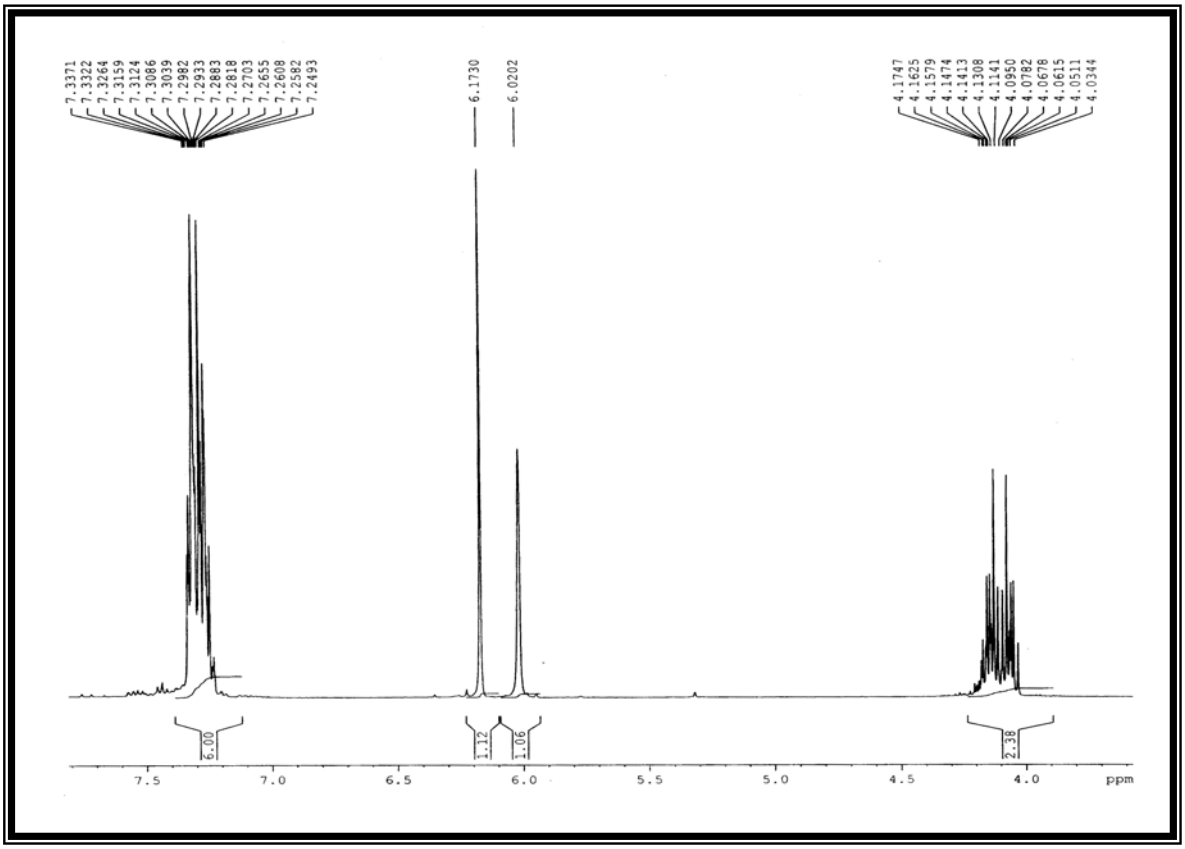
Yellow solid; mp 241-243 ˚C;

IR (KBr): 2969, 2944, 2889, 1691, 1554, 1518, 1461, 1373 cm^{-1}; **MS: m/z** = 392 (M^+); **Anal. Calcd** for $C_{23}H_{24}N_2O_2S$: C, 70.38; H, 6.16; N, 7.14. Found: C, 70.73; H, 6.25; N, 7.02.

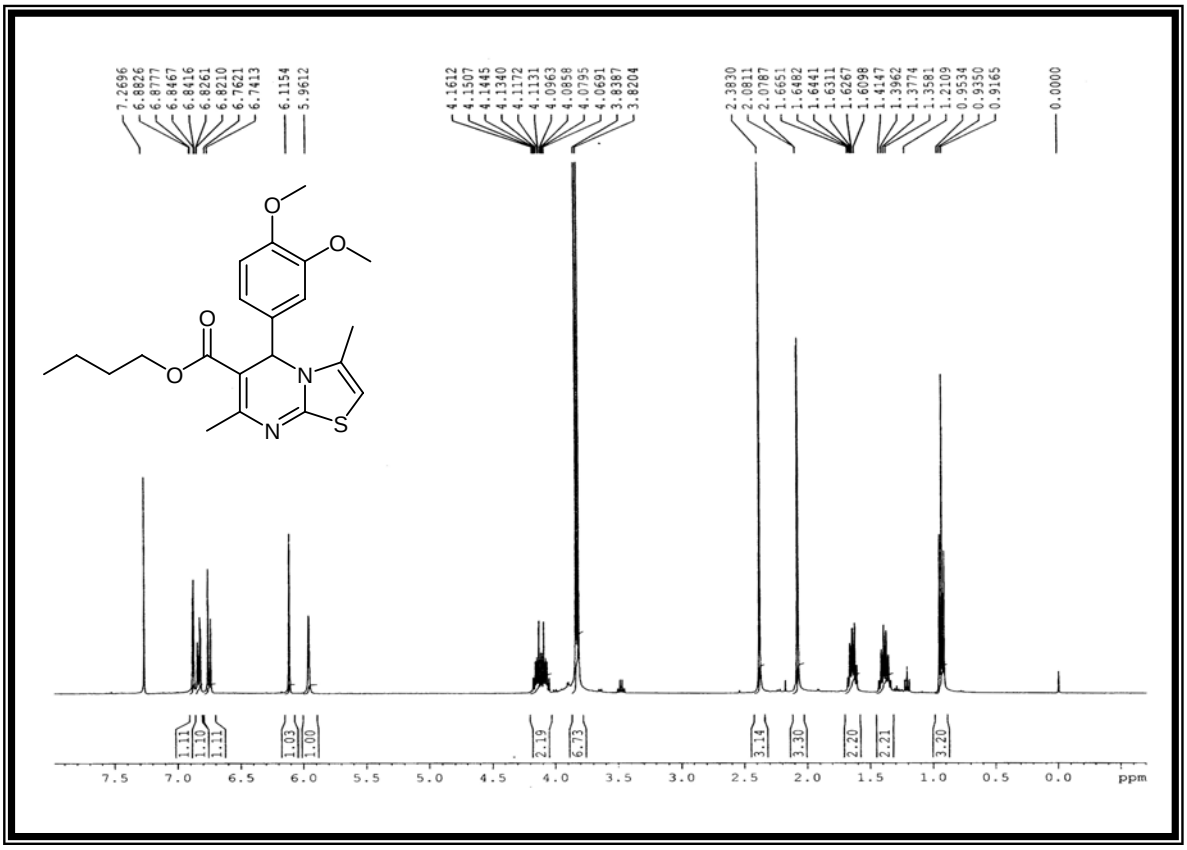
^{1}H NMR spectrum of ATP-1

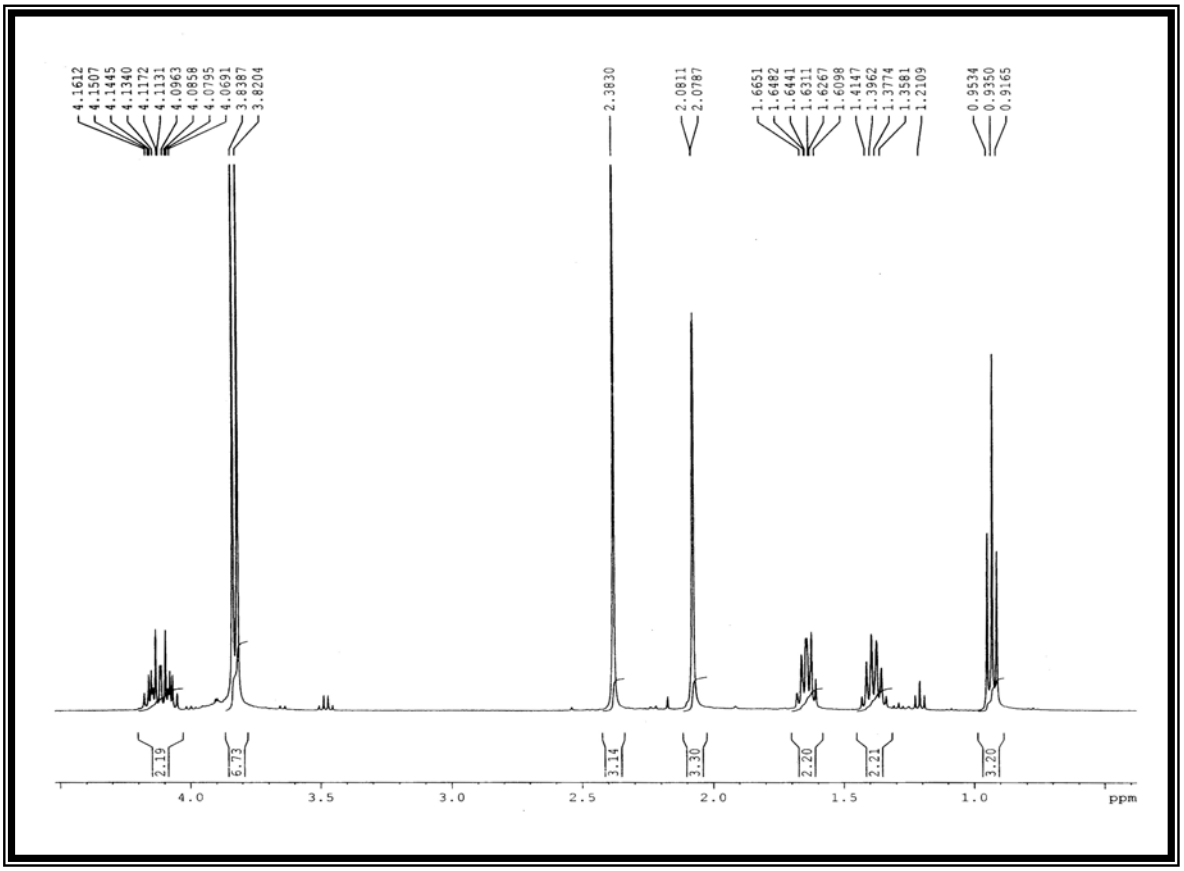






^{1}H NMR spectrum of ATP-3

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4.0963
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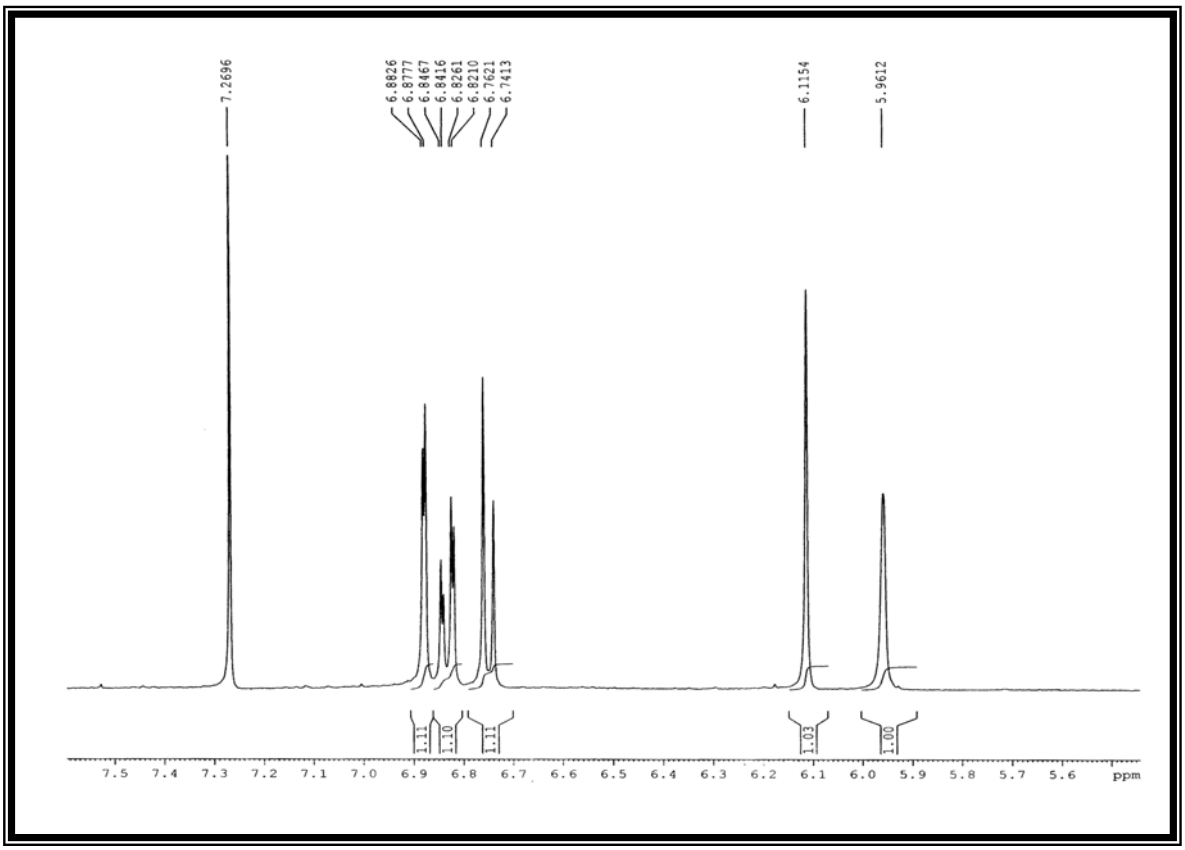
4.0691
3.8387
3.8204
2.3830
2.0811
2.0787
1.6651
1.6482
1.6441
1.6311
1.6267
1.6098
1.4147
1.3962
1.3774
1.3581
1.2109
0.9534
0.9350
0.9165
2.19
6.73
3.14
3.30
2.20
2.21
3.20
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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1.11
1.10
1.11
1.03
1.00
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
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5.9
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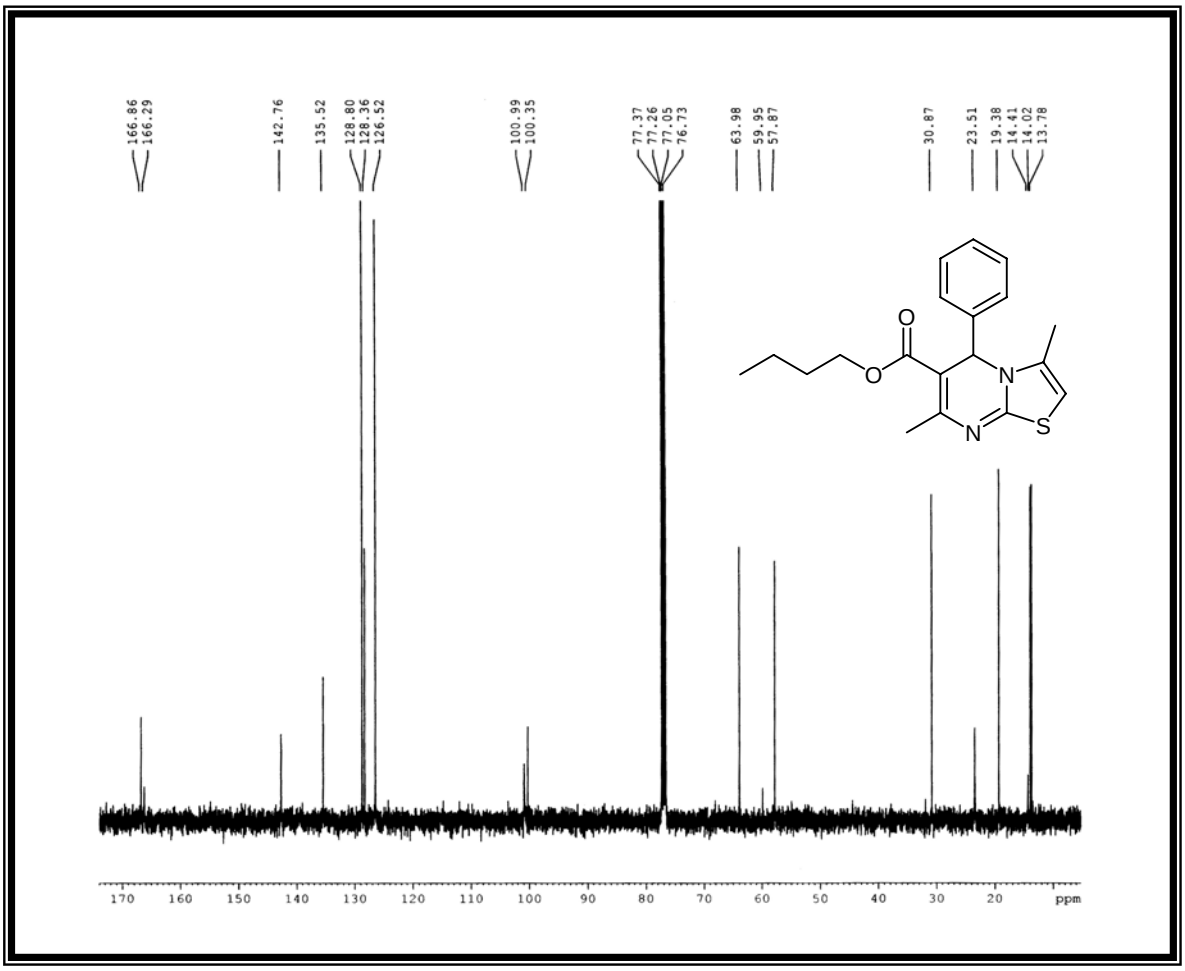
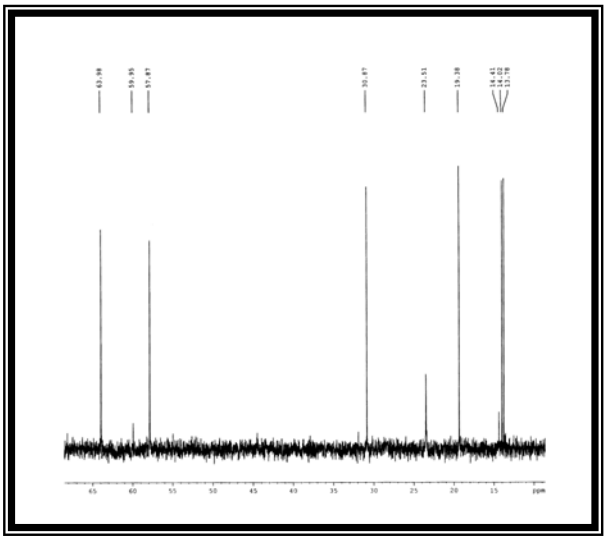
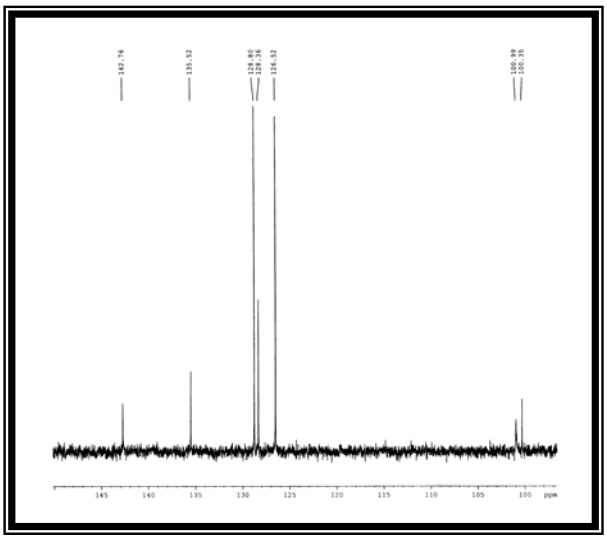
5.7
5.6
ppm

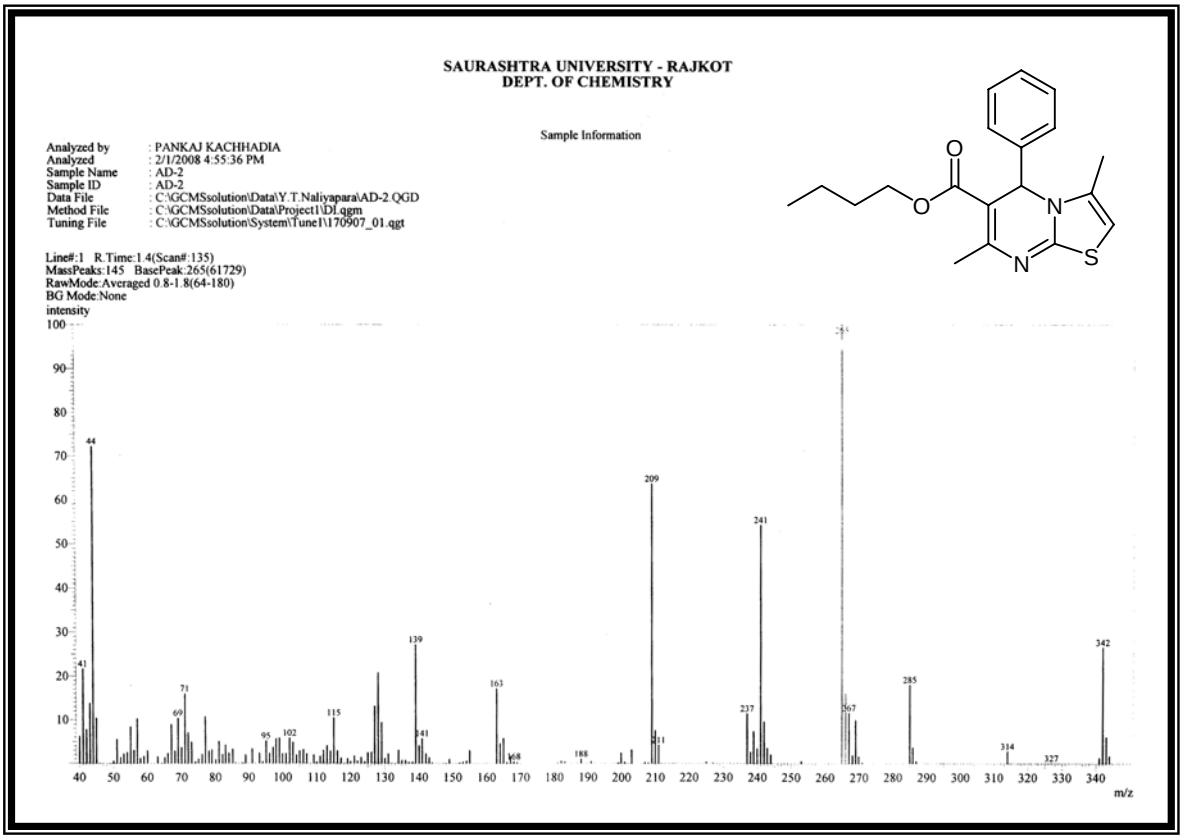
^{13}C NMR spectrum of ATP-1



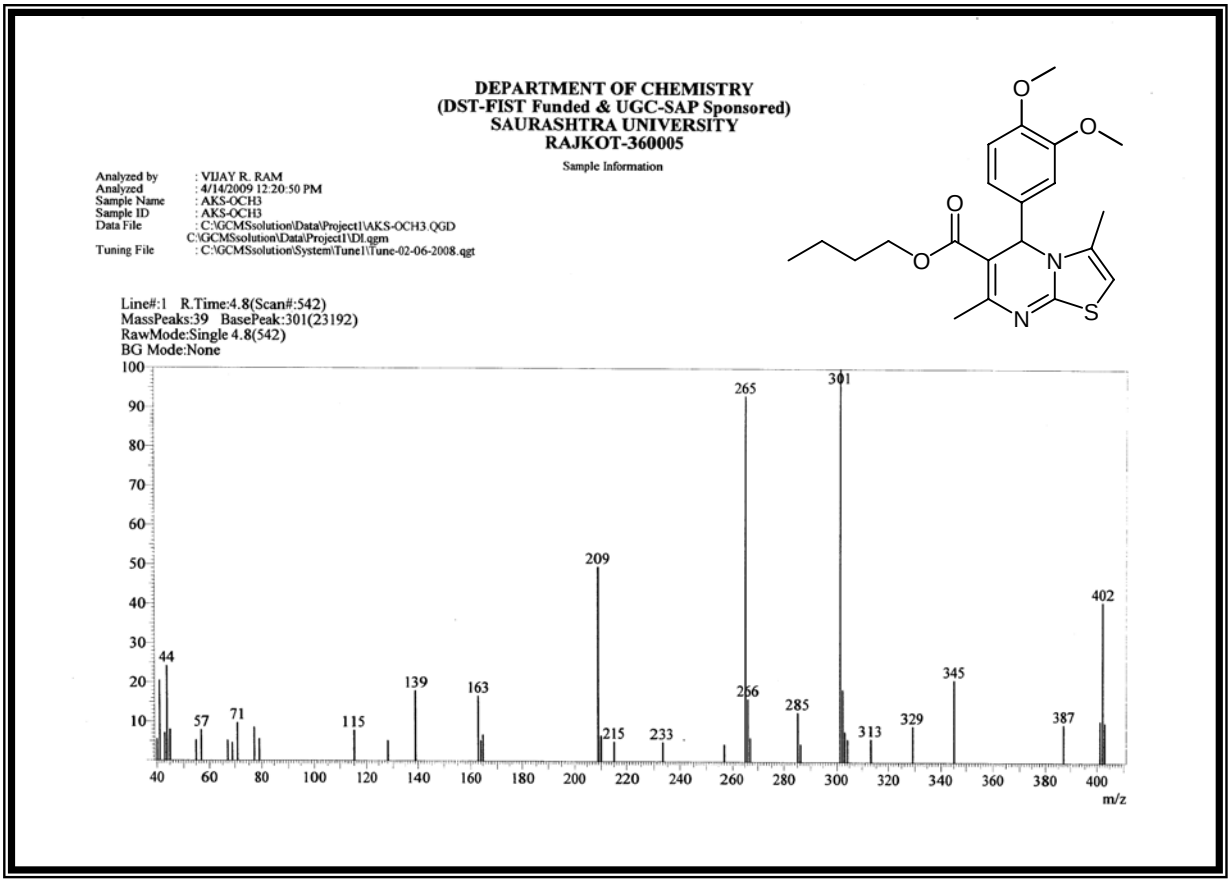




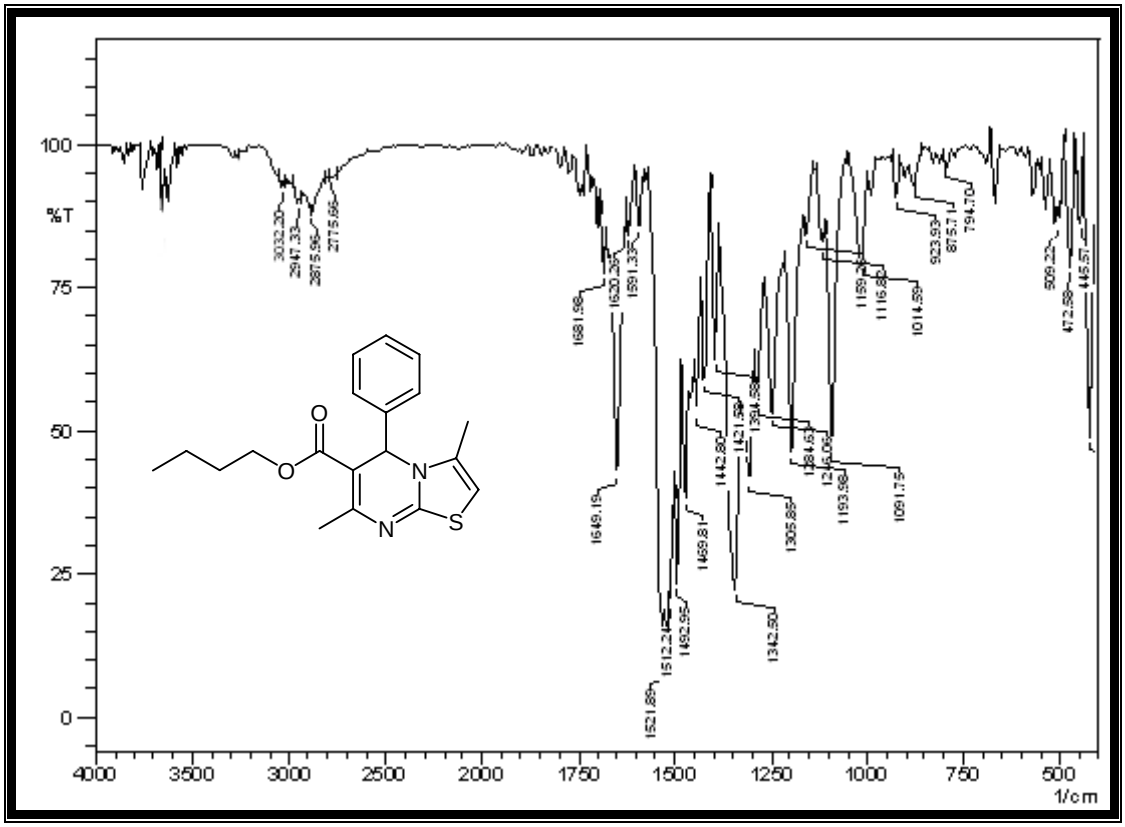
Mass spectrum of ATP-1



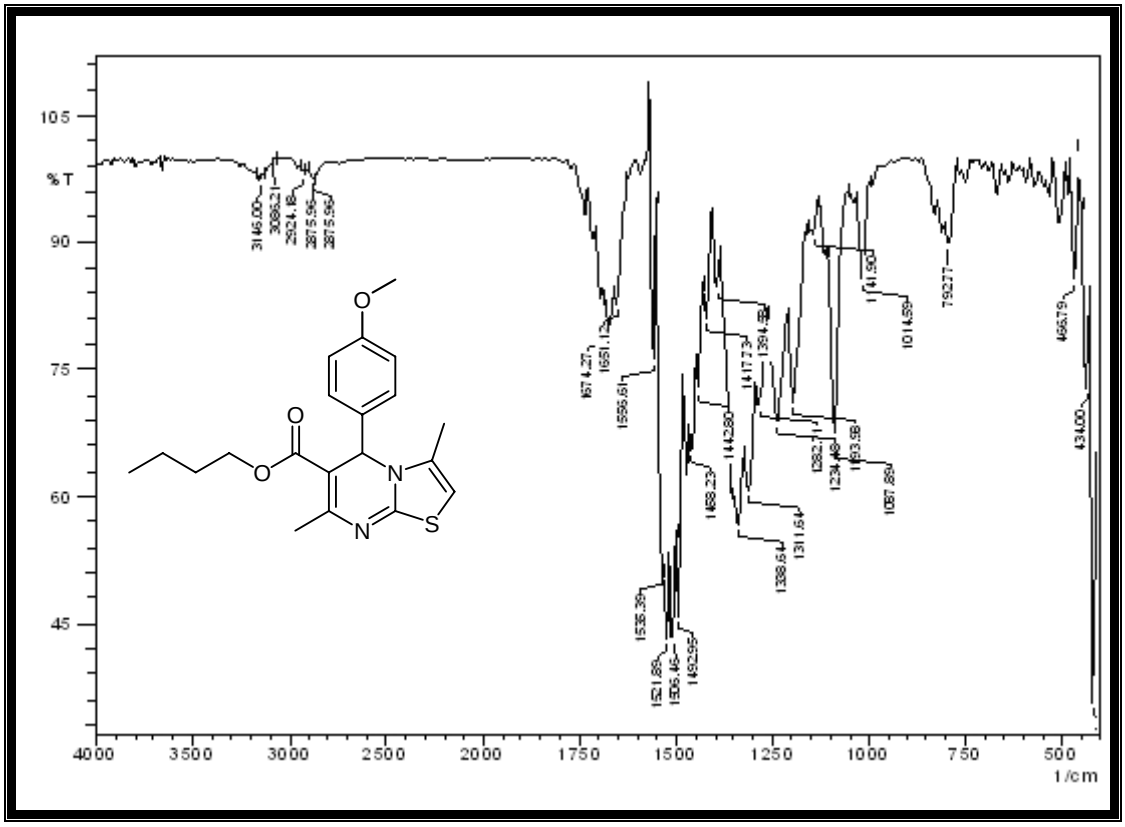
Mass spectrum of ATP-3



IR spectrum of ATP-1



IR spectrum of ATP-2



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Chapter 3

Synthesis and characterization of spiro 2-amino-3-cyano pyrano[3,2-*c*]chromene derivatives

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Synthesis and characterization of spiro 2-amino-3-cyano pyrano[3,2-*c*]chromene derivatives

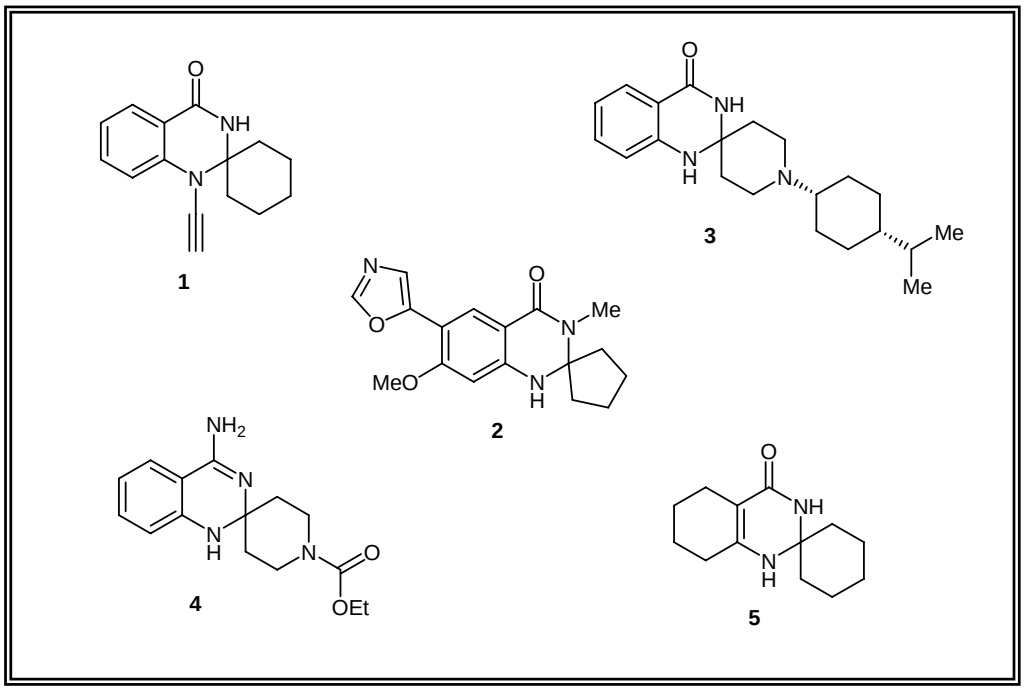
3.1 Introduction

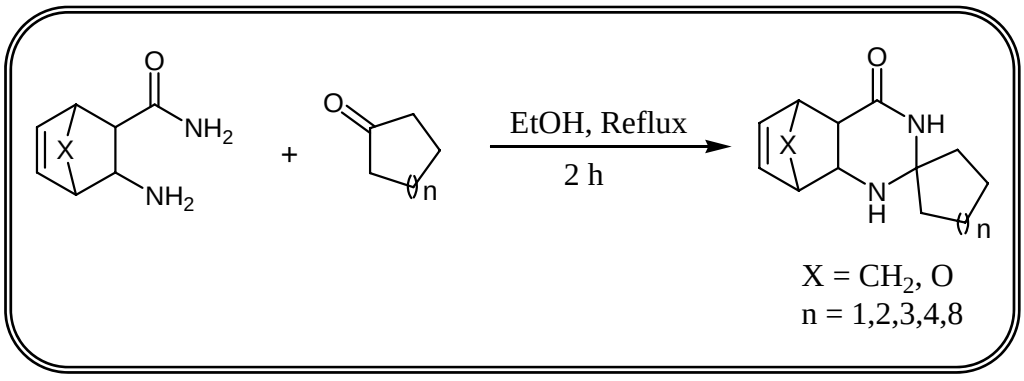
Spiro compounds can be defined as cyclic molecules containing at least two rings joined together by a single carbon atom. This unique structural feature has been observed in natural products and has also been the target of methodological studies and synthesis.

A number of 2-spiroquinazolinones have been reported to possess biological and pharmaceutical activities. Tranquilizing activity has been observed in 1'*N*-substituted spiro [cyclohexane-1,2'(1*H*)-quinazolin]-4'(3'*H*)-one[1] **1**. Compound **2** was found to be a potent inhibitor of inosine 5'-monophosphate dehydrogenase type II.[2] As a ligand of the nociceptin receptor, *cis*-spiropiperidine **3** exhibited a 20-fold higher affinity than that of its *trans* stereoisomer.[3] Spiro-cyclic carbamate **4** has been tested as a novel, highly selective[4] nitric oxide synthase inhibitor. Some spiro[heterocycloalkyl-2'(1'*H*)quinazolin]-4'(3'*H*)-ones demonstrate antiamebic activity *in vitro*[5] and had been investigated as central nervous system depressants. The plant-growth regulator agent octahydroquinazoline-2-spirocyclohexane **5**[6] increases the height and green mass of barley and wheat.[7] 2-Spiroquinazolinones are also key intermediates for the synthesis of cycloalkanone-2-carboxamides,[8] acridin-9-ones[9] and *cis*-3-azacepham analogs.[10]

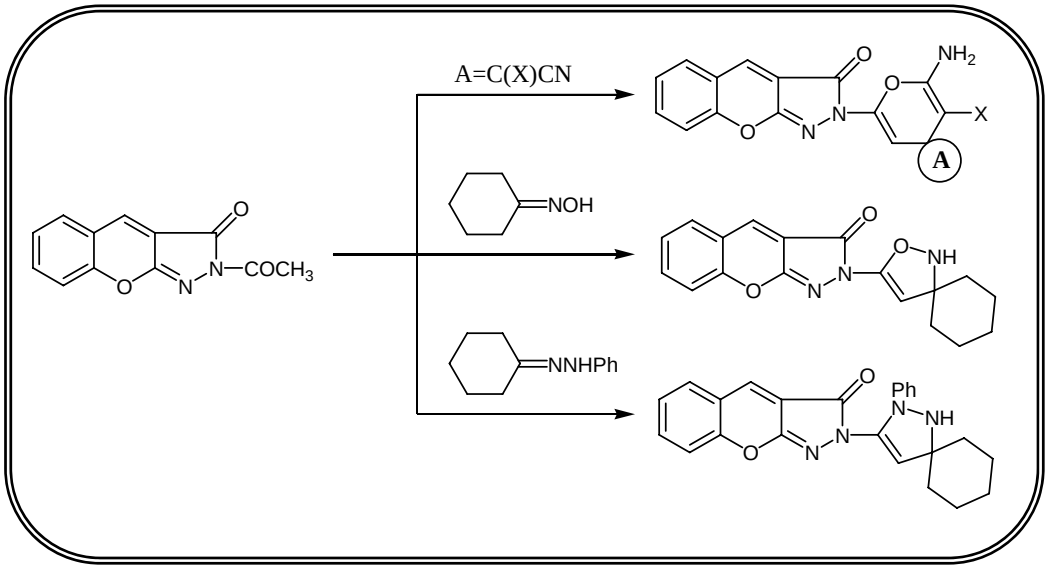
Böhme et. al. reported[11] that the room-temperature treatment of anthranilamide with cyclohexanone or cyclopentanone in ethanol saturated with hydrogen chloride provided a facile synthesis of spiro [cycloalkane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-ones. Heating of monosubstituted anthranilamides with cyclic ketones without solvents[12] was an effective method for the preparation of spiroquinazolinones. The cyclization of anthranilamide with

ketones in absolute ethanol,[13] in refluxing trifluoroethanol[14] or under microwave irradiation[15] is also known. Other methodologies too have been employed, for example with isatoic anhydride[16,17] or anthranylhydrazide[18] as starting compound. For the preparation of spiro-1,2-dihydroquinazolin-4(3*H*)ones, a new method, the reductive cyclization of 2-nitrobenzamides with carbonyl compounds, was introduced by *Shi et al.*[19,20] Ferenc Miklós[21] reported the synthesis of methylene- and epoxy-bridged spiroquinazolinones.

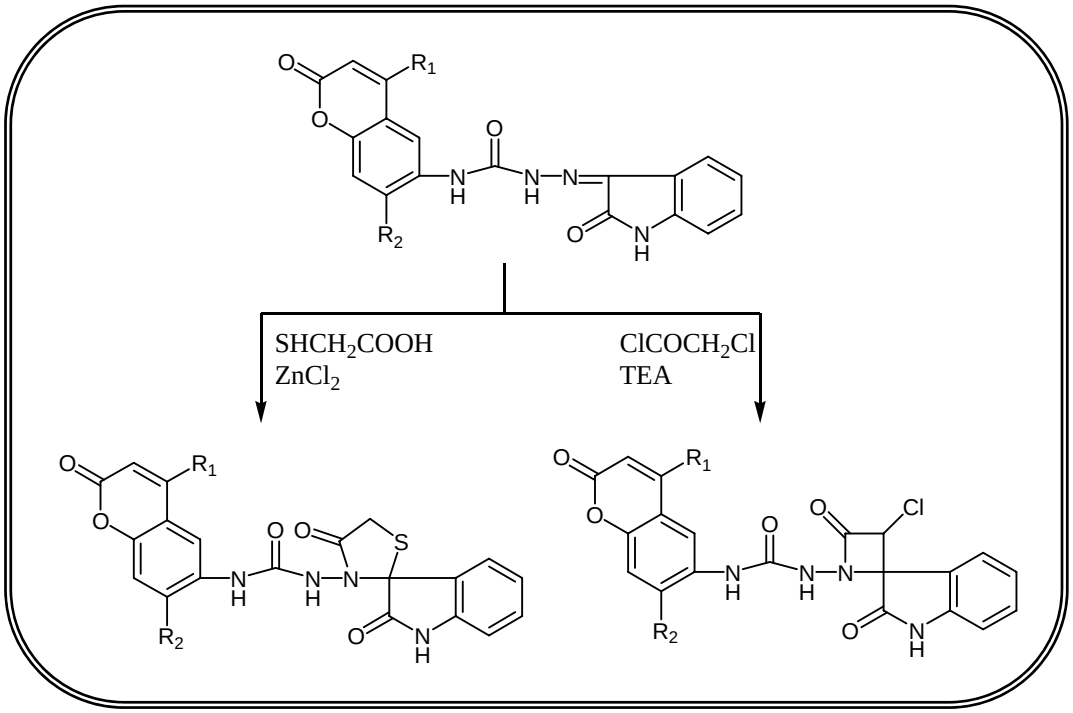




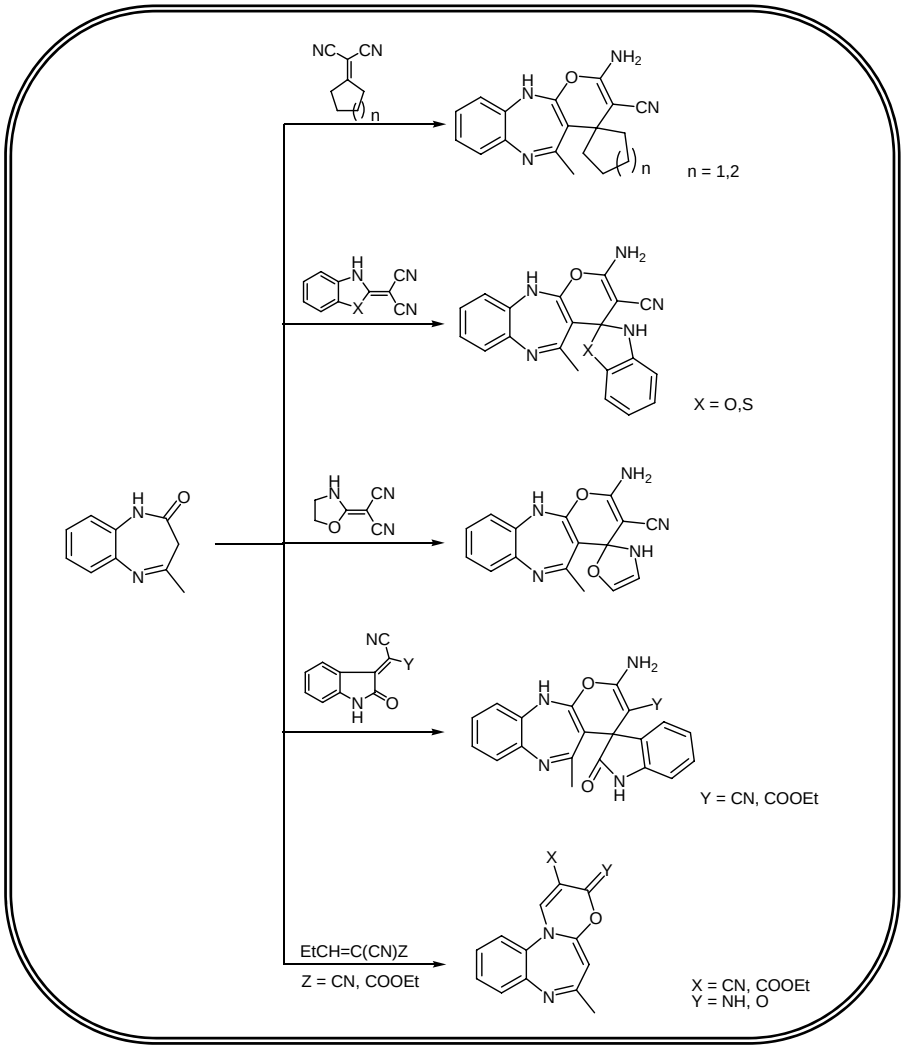
It has been found that coumarin is one of the most interesting molecules since it shows a wide spectrum of chemical reactivity. The reported antibacterial and the antibiotic novobiocin of many heterocyclic compounds containing coumarin moiety encourages to use a benzopyrano[2,3-c]pyrazol-3-one as a building block for the synthesis of poly fused heterocycles containing pyran, oxazine, pyrazole, thienyl, thiophene and substituted benzene derivatives. A. Khodairy[22] reported synthesis of such type of spiro compounds having coumarin core.



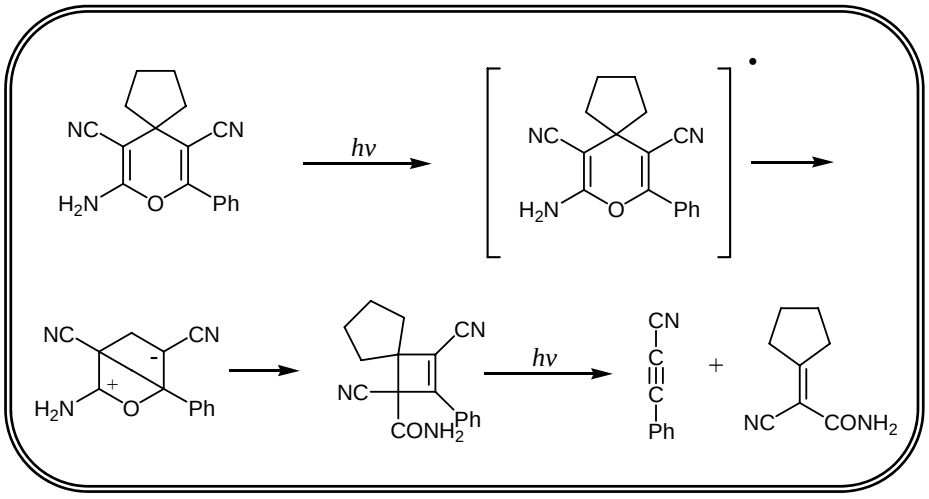
V. V. Mulwad and Abid Ali Mir[23] had reported the synthesis of N-[coumarin-6-yl] spiro-indoloazetidin-2-ones/thiazolidin-4-one derivatives and evaluated in *vitro* antimicrobial activity.



A. M. El-Snyed[24] synthesized some novel pyrano, oxazino, triazolo, oxazolo, furano, and 3-substituted (1,5) benzodiazepines from thereaction of lH(alkyl)-2,3-dihydro-4-methyl1, 5-benzodiazepin-2-ones with the proper reagents.

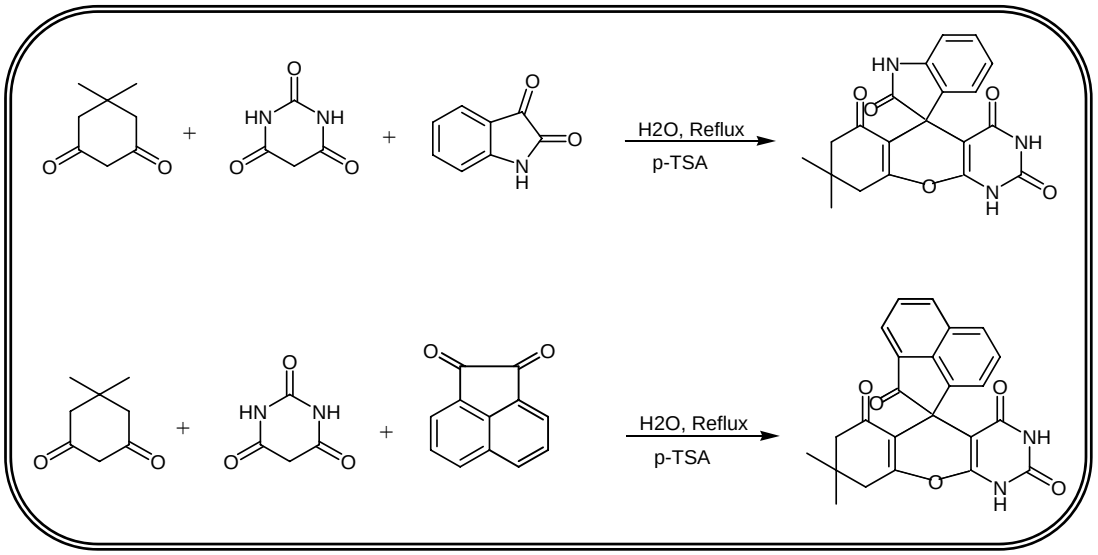


Diego Armesto[25] synthesized cyclobutenes by the photochemical ring contraction of 4-substituted 2-amino-3,5-dicyano-6-phenyl-4H-pyrans.

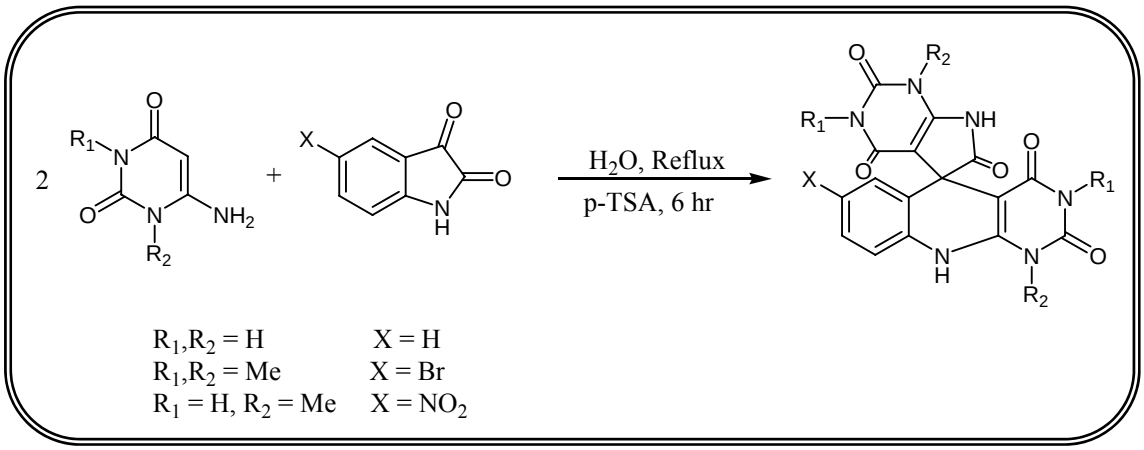


An efficient one-pot synthesis of novel 8,9-dihydrospiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]-2,2′,4,6(1*H*,3*H*,7*H*)-tetraone derivatives by a three-component condensation

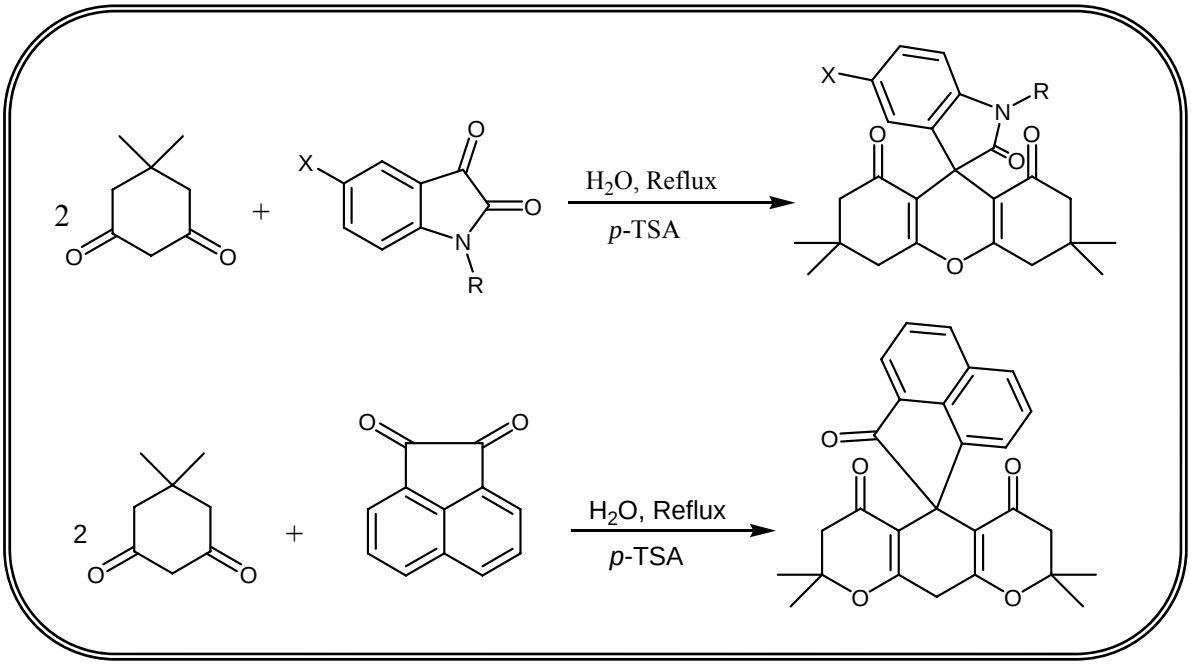
reaction of barbituric acids, isatins and cyclohexane-1,3-diones in refluxing water in the presence of *p*-TSA for 10 h is reported.[26] Reaction of 5,5-dimethyl-cyclohexane-1,3-dione and acenaphthylene-1,2-dione with barbituric acids resulted in the formation of spiro[acenaphthylene-1,5′-chromeno[2,3-*d*]pyrimidine] derivatives.



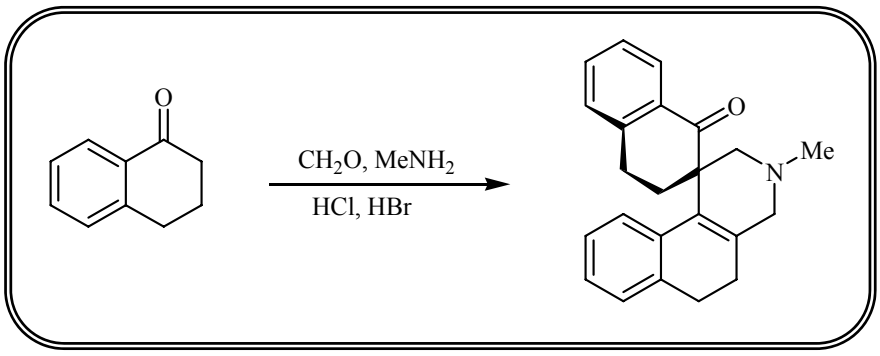
Ramin Ghahremanzadeh et al[27] described a simple, clean and efficient method for the synthesis of spiro[pyrimido[4,5-*b*]quinoline-5,5'-pyrrolo[2,3-*d*]pyrimidine]-pentaone derivatives by condensation reaction of 6-amino-uracils and isatins in aqueous media. These products were evaluated *in vitro* for their antibacterial activities.



A simple, clean and efficient method for the synthesis of spiro[indoline-3,9'-xanthene]trione derivatives and spiro[acenaphthene-1,9'-xanthene]-1',2,8'(2'*H*,5'*H*)-trione by condensation reaction of dimedone and isatins or acenaphthene in aqueous media using *p*-TSA is reported by Somayeh Ahadi.[28]

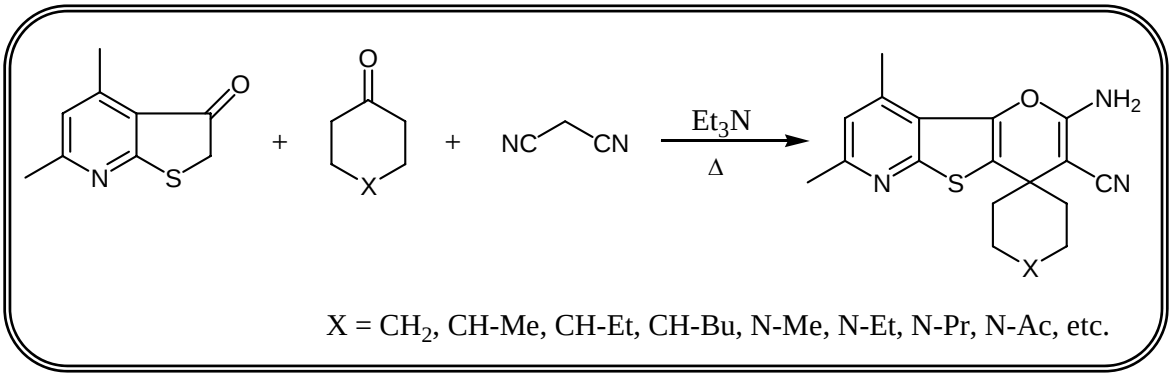


A. T. Soldatenkov[29] reported one-pot synthesis of spiro-N-methylhexahydrobenzo[f]isoquinoline-1,2'-(tetrahydro-1'-napthalenone) by the condensation of α-tetralone with formaldehyde and methylamine.

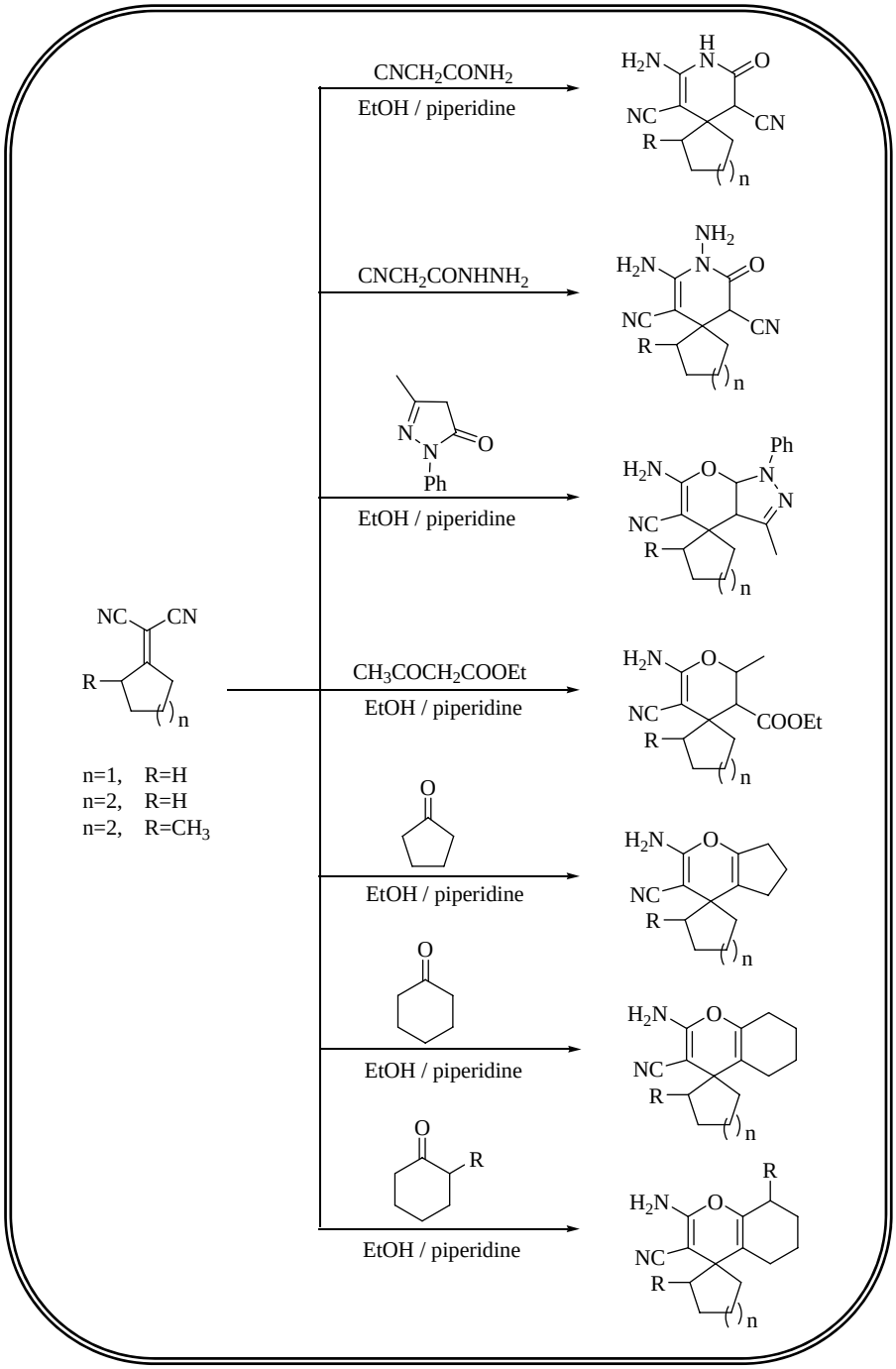


Regio- and stereoselective methods for the synthesis of substituted 2-amino-4-aryl-3-cyano-4*H*-pyrans are under extensive development because of biological activities of these compounds.[30-38] 2-Amino-4-aryl-3-cyano-4*H*-pyrans fused with fragments of coumarin[39] and substituted benzenes,[40] quinolines,[41] naphthalenes,[42] and pyrazolones,[43,44] which exhibit anticoagulating, antisclerotic, anticancer, and other practically important properties, are of the greatest interest as biologically active compounds.

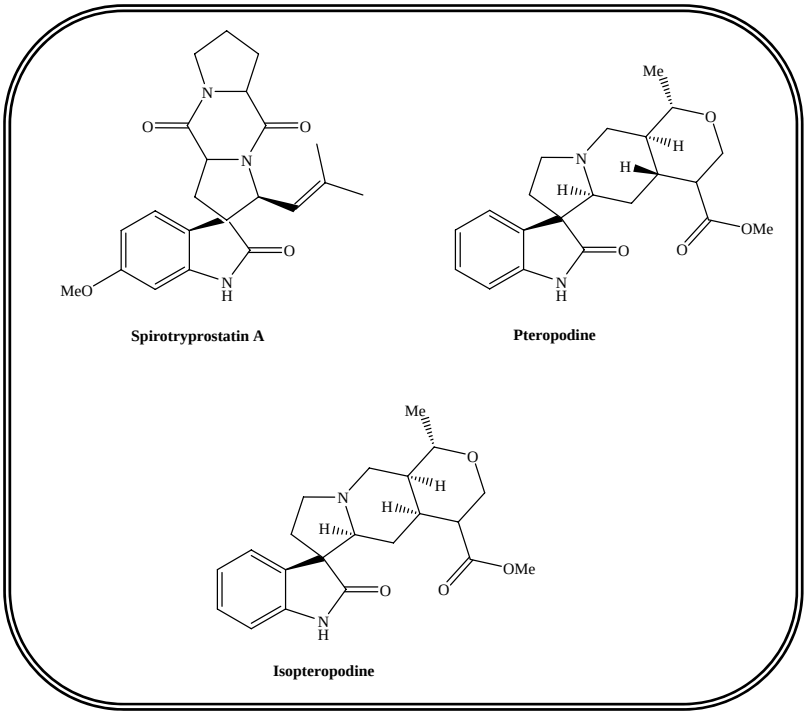
A. M. Shestopalov et al[45] synthesized spiro pyrano[2′,3′:4,5]thieno[2,3-*b*]pyridines by the reaction of 4,6-dimethyl-2*H*-thieno[2,3-*b*]pyridine-3-one with cyclic ketone and malanonitrile.



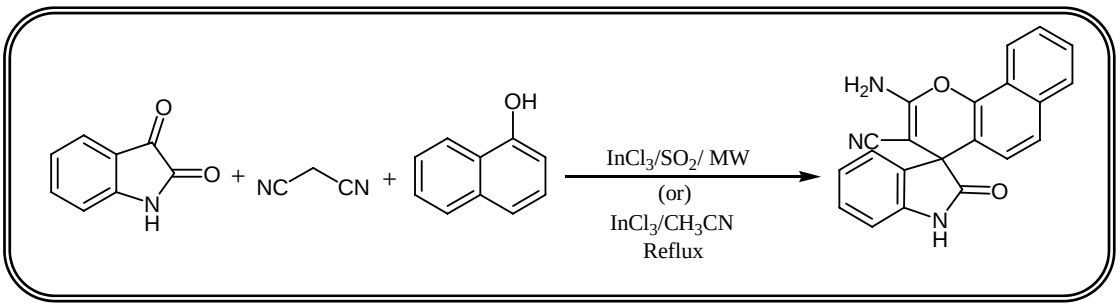
A.K. El-Shafei[46] reported the the reaction of cycloalkylidenemalononitriles with some active methylene reagents as well as cycloalkanones in boiling ethanol containing piperidine catalyst affords a series of new spiro heterocyclic systems.



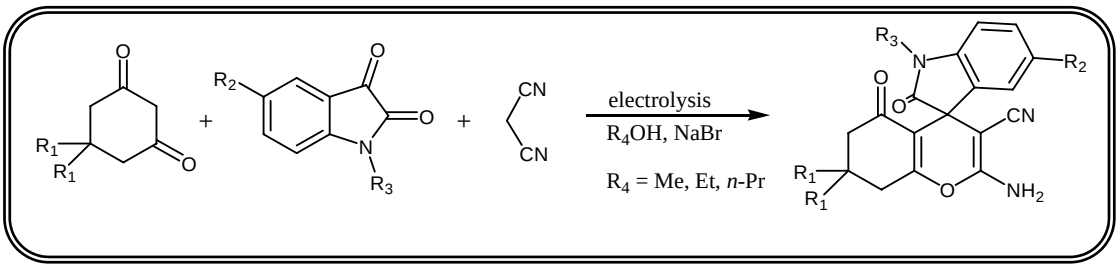
The indole moiety is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents.[47] Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[48–51] For example, spirotryprostatin A, a natural alkaloid isolated from the fermentation broth of Aspergillus fumigatus, has been identified as a novel inhibitor of microtubule assembly,[51] and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors.[48]



Fused chromenes have been found to have a wide spectrum of activities such as antimicrobial,[52] antiviral,[53] mutagenicity,[54] antiproliferative,[55] sex pheromone,[56] antitumor,[57] and central nervous system activities.[58] Many research group had investigated spirooxindoles. Gnanamani Shanthi et al[59] reported new $InCl_3$-catalyzed, facile and efficient method for the synthesis of spirooxindoles under conventional and solvent-free microwave conditions.

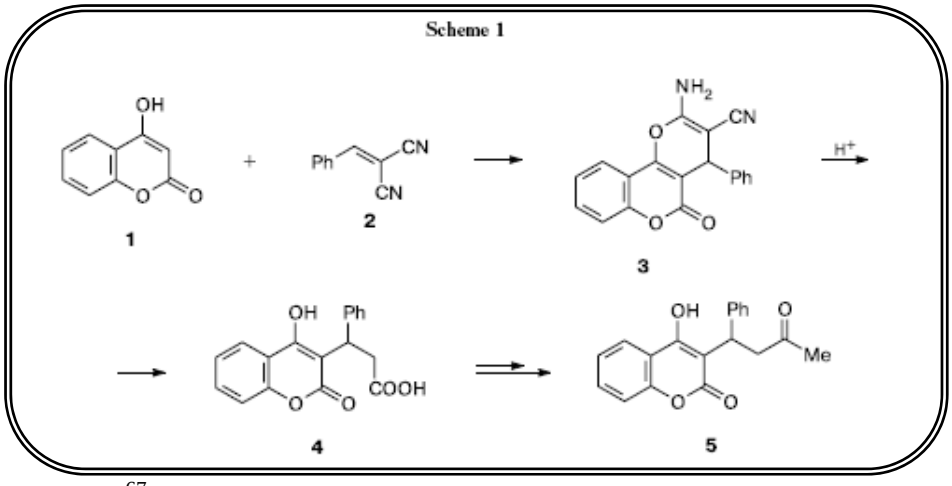


Michail N. Elinson[60] described facile and convenient way to functionalized spirocyclic (5,6,7,8-tetrahydro-4*H*-chromene)-4,3'-oxindole system by electrocatalytic multicomponent transformation of cyclic 1,3-diketones, isatins, and malononitrile.

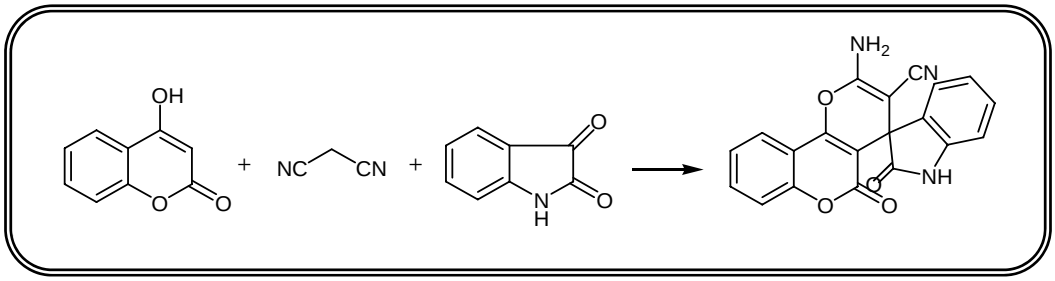


A key compound in the synthesis (Scheme 1) of warfarin (rodenticide, a blood anticoagulant) is 2-amino-3-cyano-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene **3** prepared by heating of 4-hydroxycoumarin **1** with benzylidenemalononitrile **2** in pyridine[61] or water.[62] Acid hydrolysis of substituted pyrano[3,2-*c*]chromene **3** gives compound **4**, which is used to synthesize warfarin **5**.[61–65] 2-Amino-4-aryl-3-(thiocarbamoyl, alkoxycarbonyl, or cyano)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes were also obtained[63,66] by morpholine catalyzed reactions of 4-hydroxycoumarin with arylidenecyanothioacetamide, alkyl arylidenecyanoacetates, or arylidenemalononitrile in hot benzene or ethanol.

Scheme 1



A. A. Shestopalov[67] described the three component reactions of 4-hydroxycoumarin, carbonyl compounds, and malononitrile or alkyl cyanoacetates in ethanol in the presence of Et_3N as a catalyst give substituted 2-amino-5-oxo-4,5-dihydropyrano[3,2-*c*]chromenes.



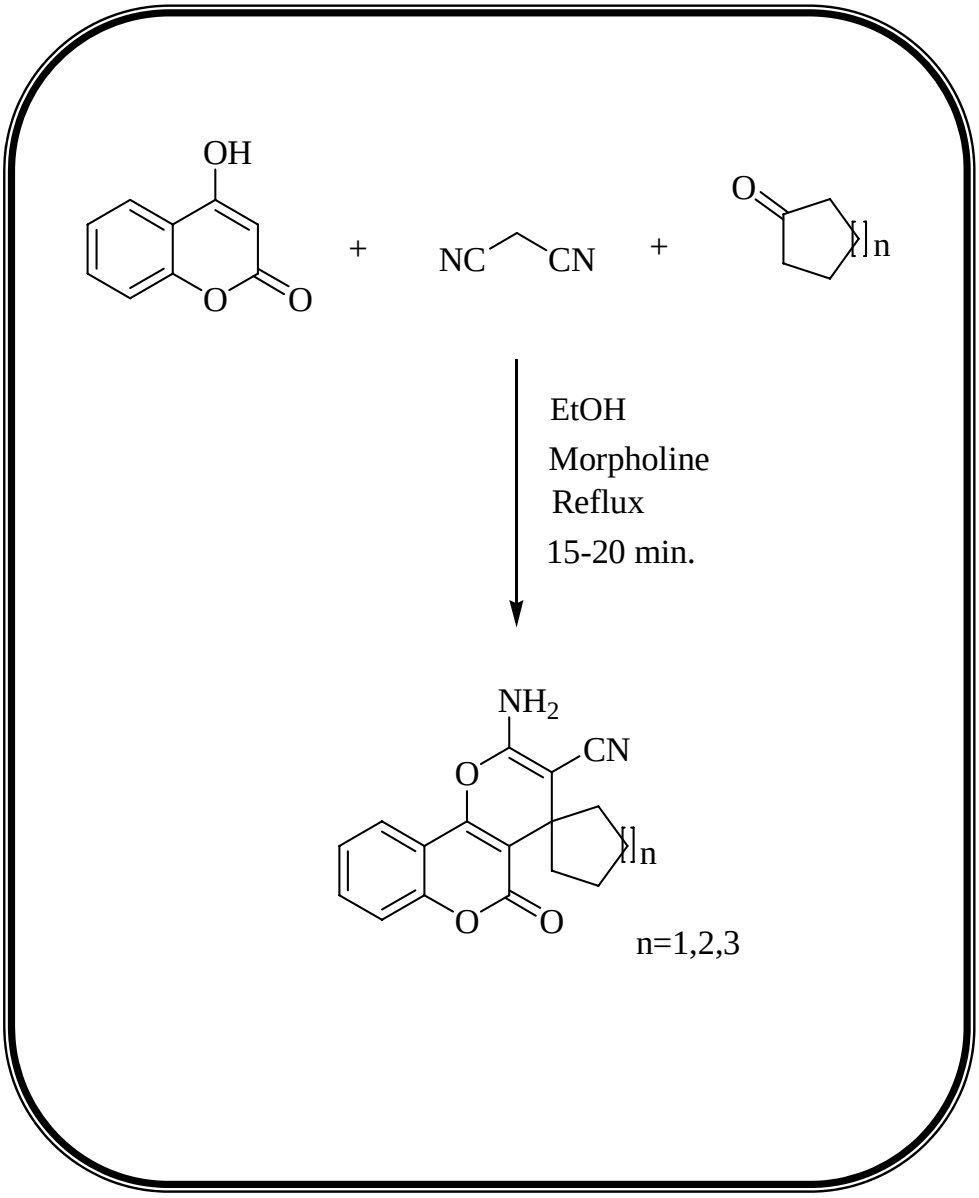
3.2 Current work

In view of marked importance of spiro heterocyclic compounds in the field of organic chemistry as well as medicinal chemistry, we sought to develop some diversified spiro heterocycles. As per mentioned above, 2-amino-3-cyano-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene has attained great importance in the field of medicinal chemistry. Despite some achievements attained in recent years in the synthesis of 2-amino-3-cyano-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene type compounds with other substituents in position 4, preparation and isolation of unsaturated nitriles, which are analogs of toxic agents CS,[68] substantially complicated the synthesis of pyrano[3,2-*c*]chromene. In some cases, the condensation does not yield the target unsaturated nitrile at all: in the reaction of pyridine-4-carbaldehyde with malononitrile, 1-amino-2,4,4,6,6-pentacyano-3,5-di(4-pyridyl)cyclohex-1-ene was obtained instead.[69] In further investigations of cross reactions of malononitrile with carbonyl compounds with the aim of developing one-step syntheses of functionalized spiro-heterocycles, we studied three-component reactions of 4-hydroxycoumarin, malononitrile and carbonyl compounds.

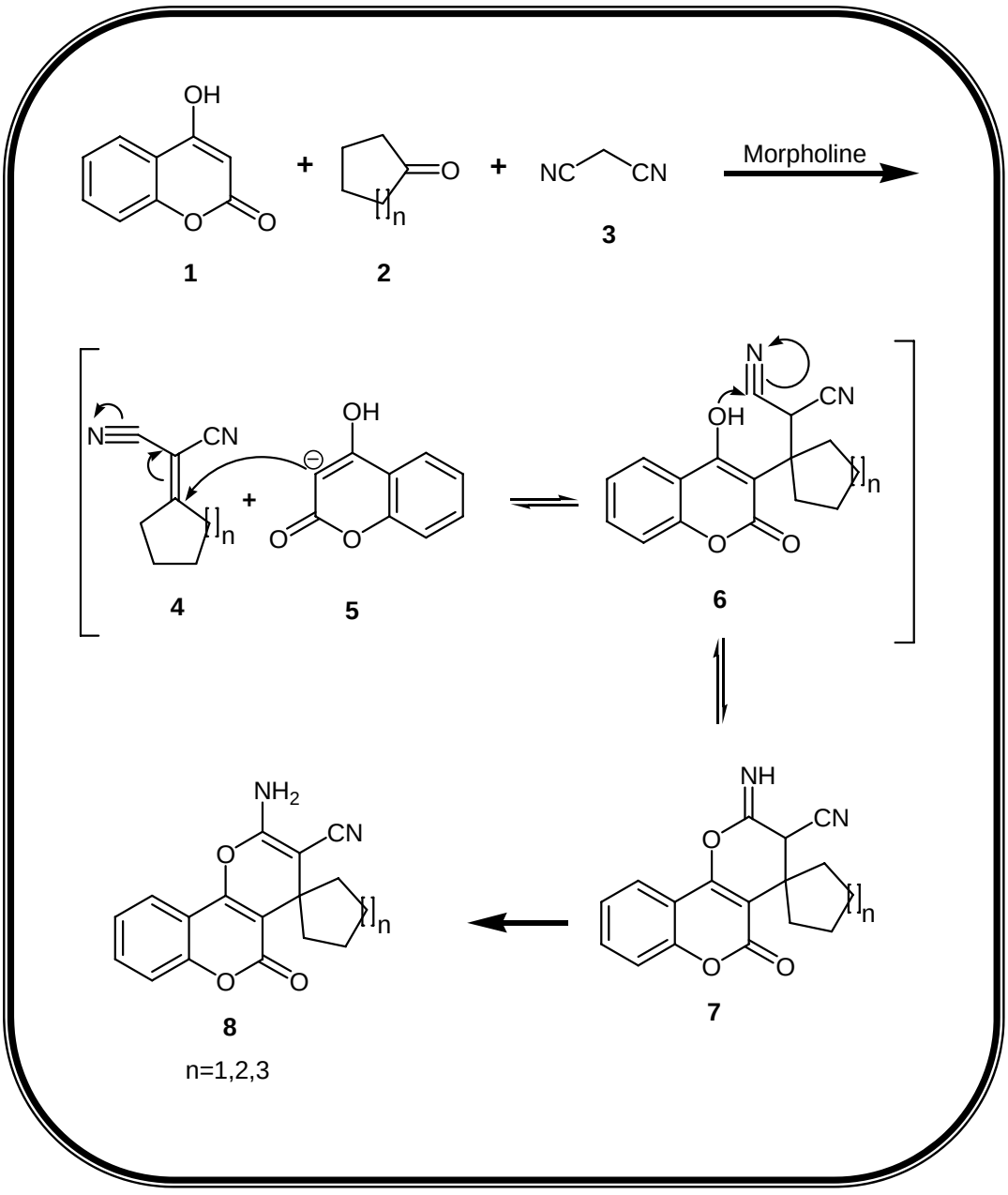
The brief heating of 4-hydroxy coumarin with cyclic aliphatic ketone (cyclopentanone, cyclohexanone, and cycloheptanone) and malononitrile in boiling ethanol in the presence of morpholine as a catalyst gave 2-amino-3-cyano pyrano[3,2-*c*]chromene derivatives in high yields. The three component reaction between 4-hydroxy coumarin, malononitrile and various substituted acetphenone as the carbonyl compound under analogous condition didn't follow the same pathway. Substituted acetophenone reacts with malononitrile to give unsaturated nitrile, which does not undergo Michael addition reaction with coumarin anion. Thus coumarin remains out of the process.

All newly synthesized compounds were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. Reaction scheme is illustrated in section 3.3. The plausible reaction mechanism is demonstrated followed by reaction scheme. Spectral data is discussed in section 3.6 which is consistent with proposed structure. The anti viral screening of the synthesized compounds is under investigation.

3.3 Reaction Scheme



3.4 Reaction Mechanism



Apparently, the initial Knoevenagel condensation of cyclic ketone **2** with malononitrile **3** gives unsaturated nitrile **4**, which, when at the "reaction intersection", enters into the Michael reaction with coumarin anion **5**. The resulting Michael adduct **6** undergoes intramolecular cyclization into annelated iminopyran **7**. Subsequent tautomeric [1,3]sigmatropic shift gives compound **8** .

3.5 Experimental

3.5.1 Preparation of spiro pyrano[3,2-*c*]chromene derivatives: General Procedure

A stirred mixture of 4-hydroxy coumarin (10 mmol), carbonyl compound (cyclopentanone, cyclohexanone, and cycloheptanone) (10 mmol), malononitrile (10 mmol), and morpholine (0.5 mmol) in anhydrous EtOH (50 mL) was refluxed for 15 to 20 min and allowed to crystallize at 4 °C for 12 h. The precipitate that formed was filtered off, washed with ethanol and hexane, and recrystallized from 1,4-dioxane to give desired compound as a white solid powder in good to excellent yield.

3.6 Spectral discussion

3.6.1 Mass spectral study

Instrument : SHIMADZU GCMS-QP-2010

Sample technique : EI technique

M/z range : 40-500

Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. Systematic fragmentation pattern was observed in mass spectral analysis. Molecular ion peak was observed in agreement with molecular weight of respective compound.

3.6.2 IR spectral study

Instrument : Shimadzu FT-IR-8400

Sample technique : KBr pellet

Frequency range : 400-4000cm^{-1}

As per IR spectral study of newly synthesized spiro pyrano[3,2-c]chromene derivatives, the stretching vibration of primary amine (-NH_2) appeared around 3200-3300 cm^{-1}. Methylene groups of cycloalkane ring showed C–H stretching vibration between 2850 to 2990 cm^{-1}. The carbonyl (>C=O) stretching vibration of lactone ring was observed around 1720 cm^{-1}. Nitrile

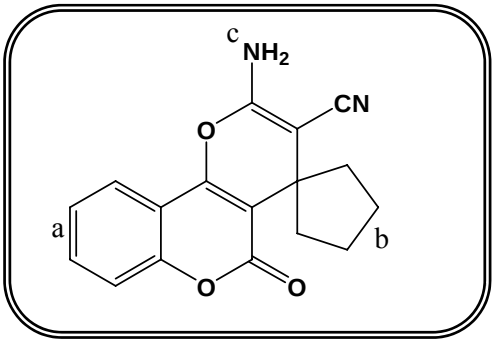
group attached to pyran ring showed C≡N stretching vibration around 2180–2280 cm^{-1}. Methylene group also gave C-H bending vibration around 1450 cm^{-1}. The benzenoid part showed C=C ring skeleton vibration around 1500-1600 cm^{-1}.

3.6.3 *^{1}H NMR spectral study*

Instrument : BRUKER AC 400 MHz FT-NMR

Internal reference : TMS

Solvent : $CDCl_3$



Number of protons and their chemical shifts were found to support the structure of the synthesized compounds. Benzenoid protons of coumarin ring 'a' were found between 7 to 8 δ ppm with its characteristic pattern. Methylene protons of cycloalkane ring 'b' were observed between 2 to 2.5 δ ppm. Proton 'c' of primary amine attached to pyran ring was observed at 5.5-6.0 δ ppm as a singlet and very intense sharp peak.

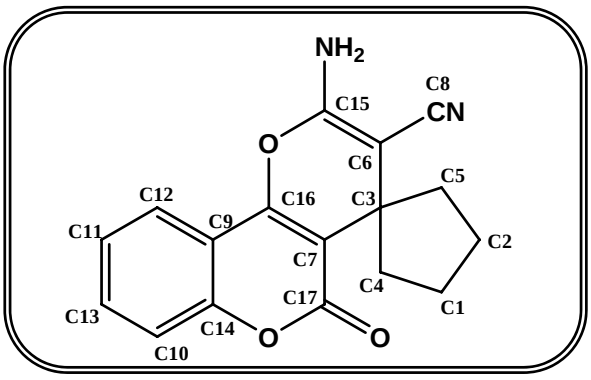
3.6.4 *^{13}C NMR spectral study*

Instrument : BRUKER AC 400 MHz FT-NMR

Internal reference : TMS

Solvent : $CDCl_3$

^{13}C NMR spectrum data for compound AS-1 is given below. δ ppm values are listed along with corresponding carbon atom number given in bracket and displayed in the structure.



^{13}C NMR δ ppm: 27.6 (C1, C2), 41.0 (C3), 43.1 (C4, C5), 70.9 (C6), 109.3 (C7), 113.0 (C8), 116.5 (C9), 119.2 (C10), 122.3 (C11), 124.3 (C12), 132.3 (C13), 152.2 (C14), 152.4 (C15), 154.6 (C16), 159.7 (C17).

3.6.5 Elemental Analysis

Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Spectral data of synthesized compounds (AS 1-3)

Spiro(2–amino–3–cyano pyrano[3,2–*c*]chromene–4,1'–cyclopentane) (AS–1)

White solid; mp 230–232 ˚C;

IR (KBr): 3308 (NH_2), 2962, 2947, 2872 (CH_2), 2187 (C≡N), 1730 (C=O), 1602, 1492 (ArC=C), 1450 (CH_2), 1030 (C–O) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ ppm = 1.84–1.90 (m, 2H, CH_2), 1.93–2.06 (m, 4H, CH_2), 2.33–2.39 (m, 2H, CH_2), 5.78 (s, 2H, NH_2), 7.30–7.34 (m, 2H, ArH), 7.55–7.60 (m, 1H, ArH), 7.82–7.84 (m, 1H, ArH); **^{13}C NMR (400 MHz, $CDCl_3$):** δ ppm = 27.6, 41.0, 43.1, 70.9, 109.3, 113.0, 116.5, 119.2, 122.3, 124.3, 132.3, 152.2, 152.4, 154.6, 159.7; **MS: m/z** = 294 (M^+); **Anal. Calcd** for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.22; H, 4.65; N, 9.41.

Spiro(2–amino–3–cyano pyrano[3,2–*c*]chromene–4,1'–cyclohexane) (AS–2)

White solid; mp 230–232 ˚C;

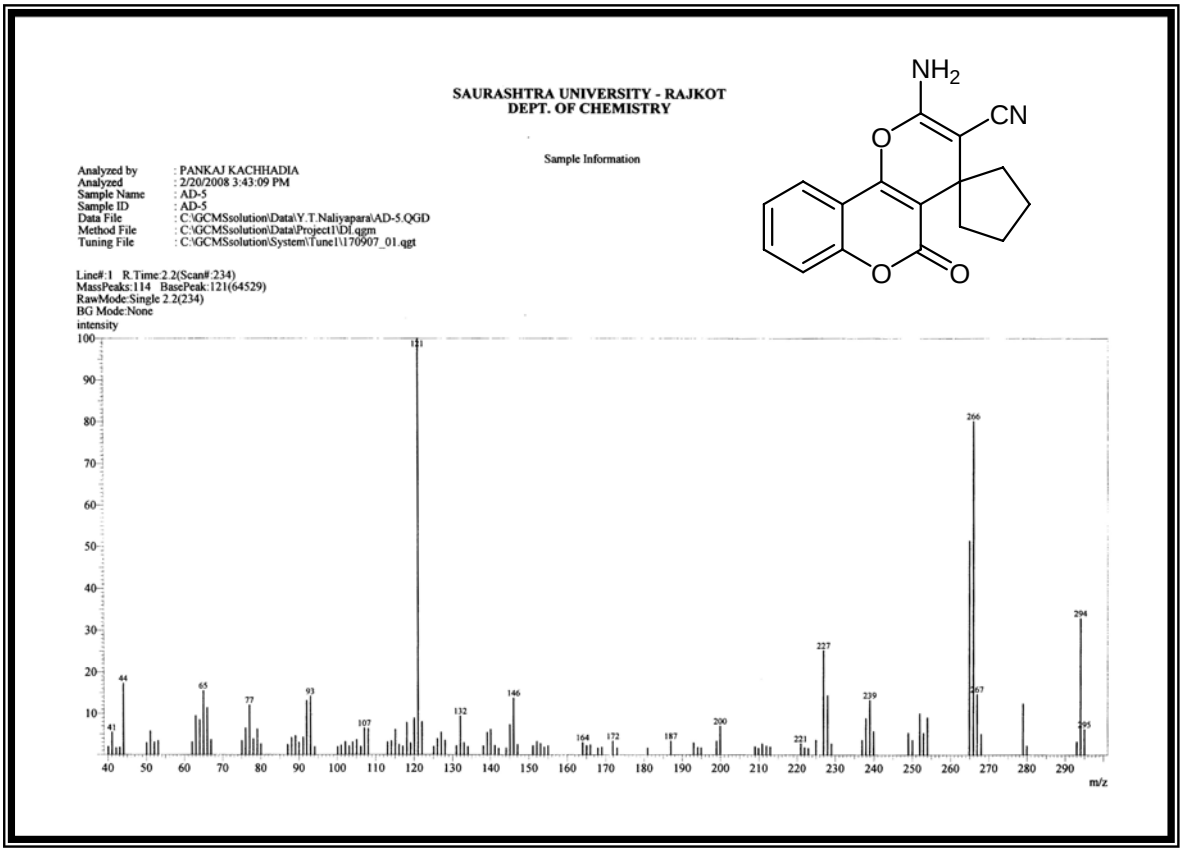
IR (KBr): 3400 (NH_2), 2887 (CH_2), 2279 (C≡N), 1714 (C=O), 1614, 1556, 1523 (ArC=C), 1415 (CH_2), 1031 (C–O) cm^{-1}; **MS: m/z** = 308 (M^+); **Anal. Calcd** for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.99; H, 5.10; N, 9.02.

Spiro(2–amino–3–cyano pyrano[3,2–*c*]chromene–4,1'–cycloheptane) (AS–3)

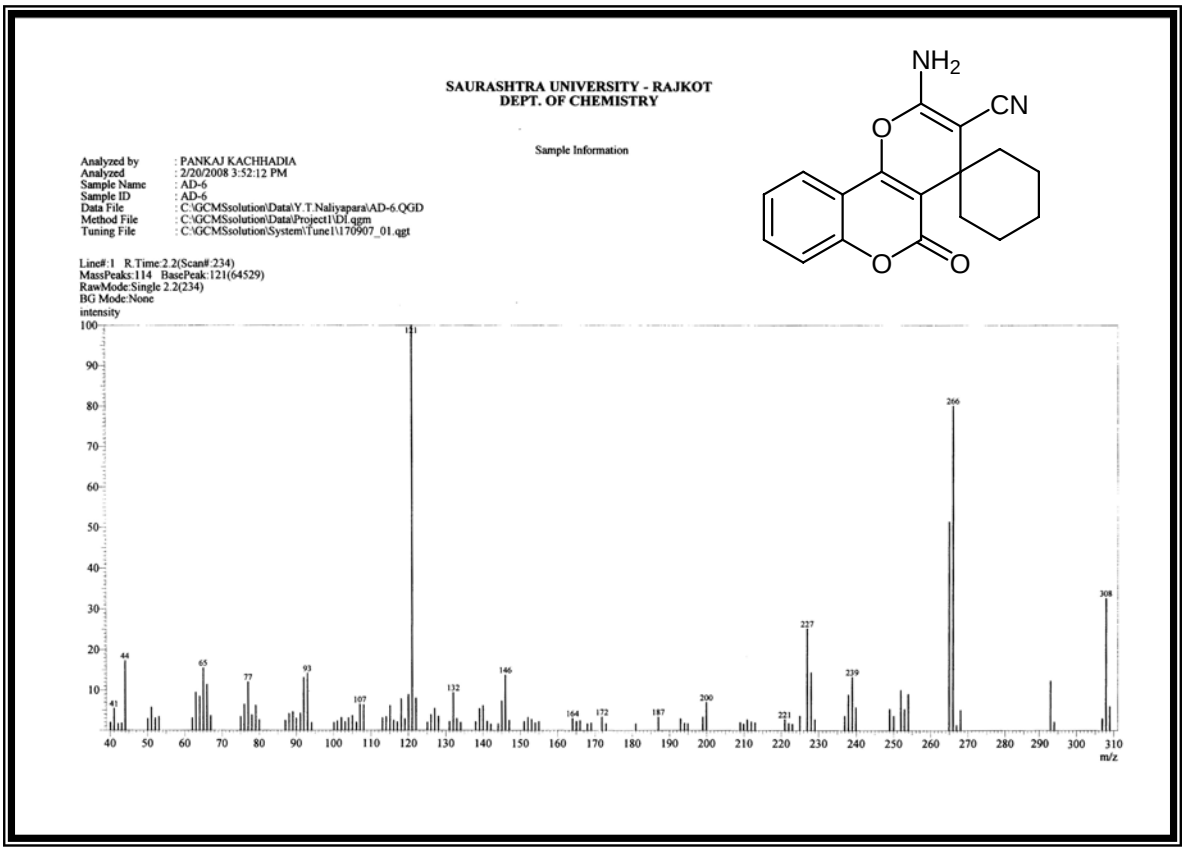
White solid; mp 225–226 ˚C;

IR (KBr): 3314 (NH_2), 2956, 2872 (CH_2), 2196 (C≡N), 1718 (C=O), 1545 (ArC=C), 1442 (CH_2) cm^{-1}; **MS: m/z** = 322 (M^+); **Anal. Calcd** for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.64; H, 5.51; N, 8.54.

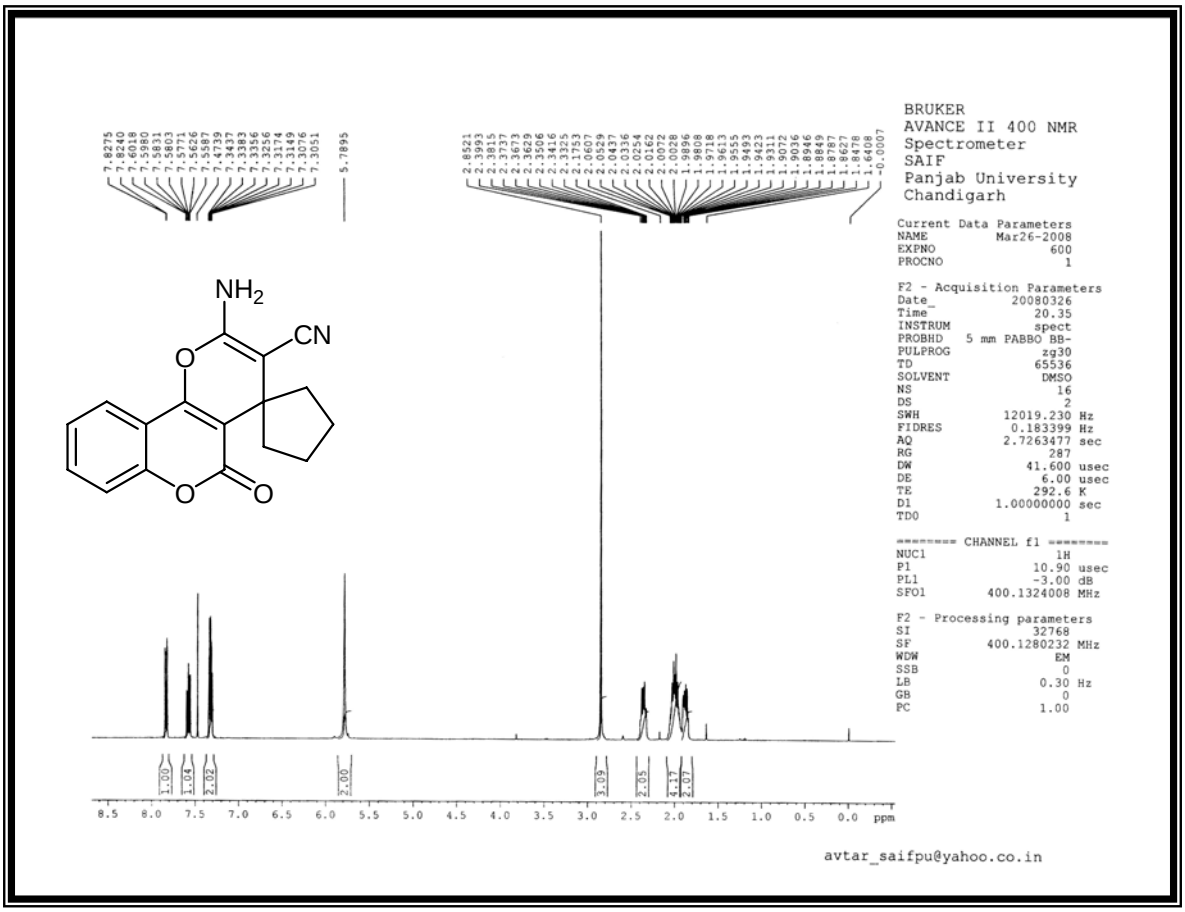
Mass spectrum of AS-1

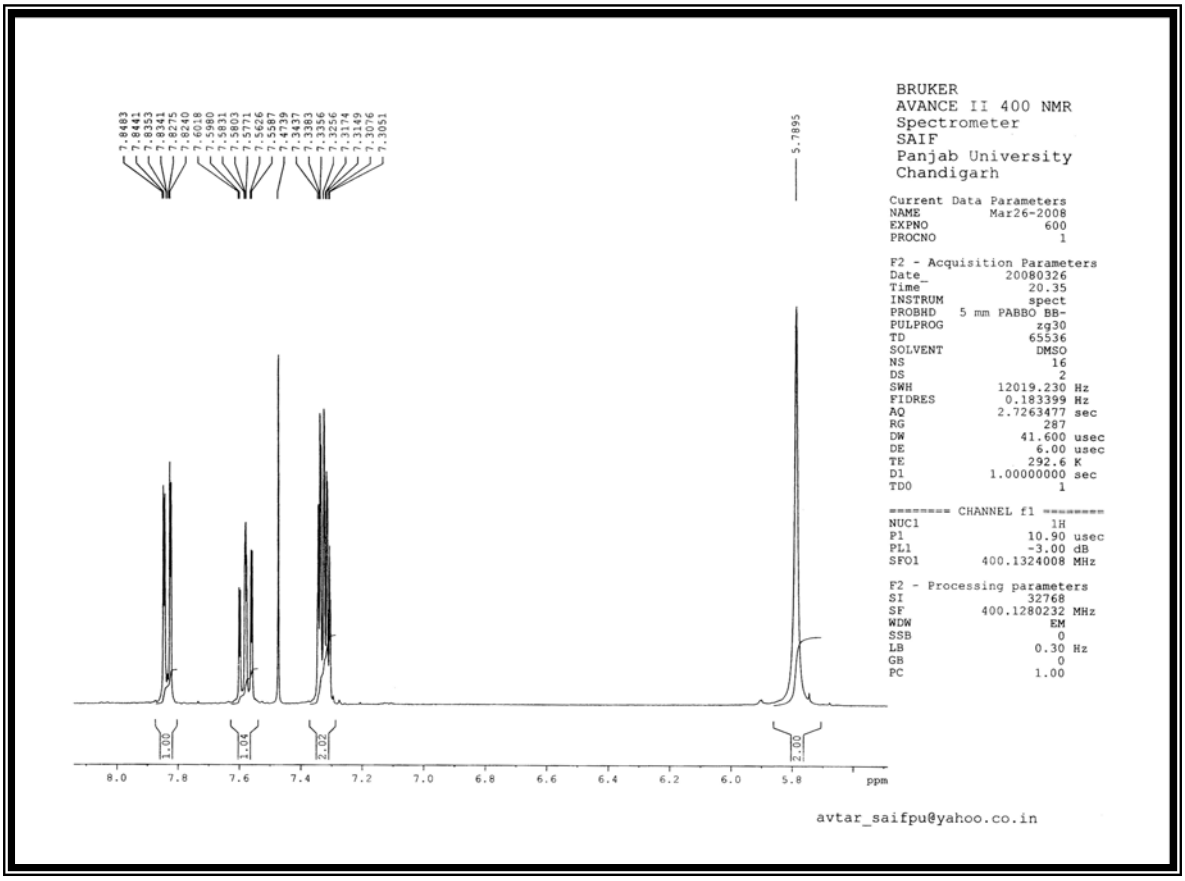


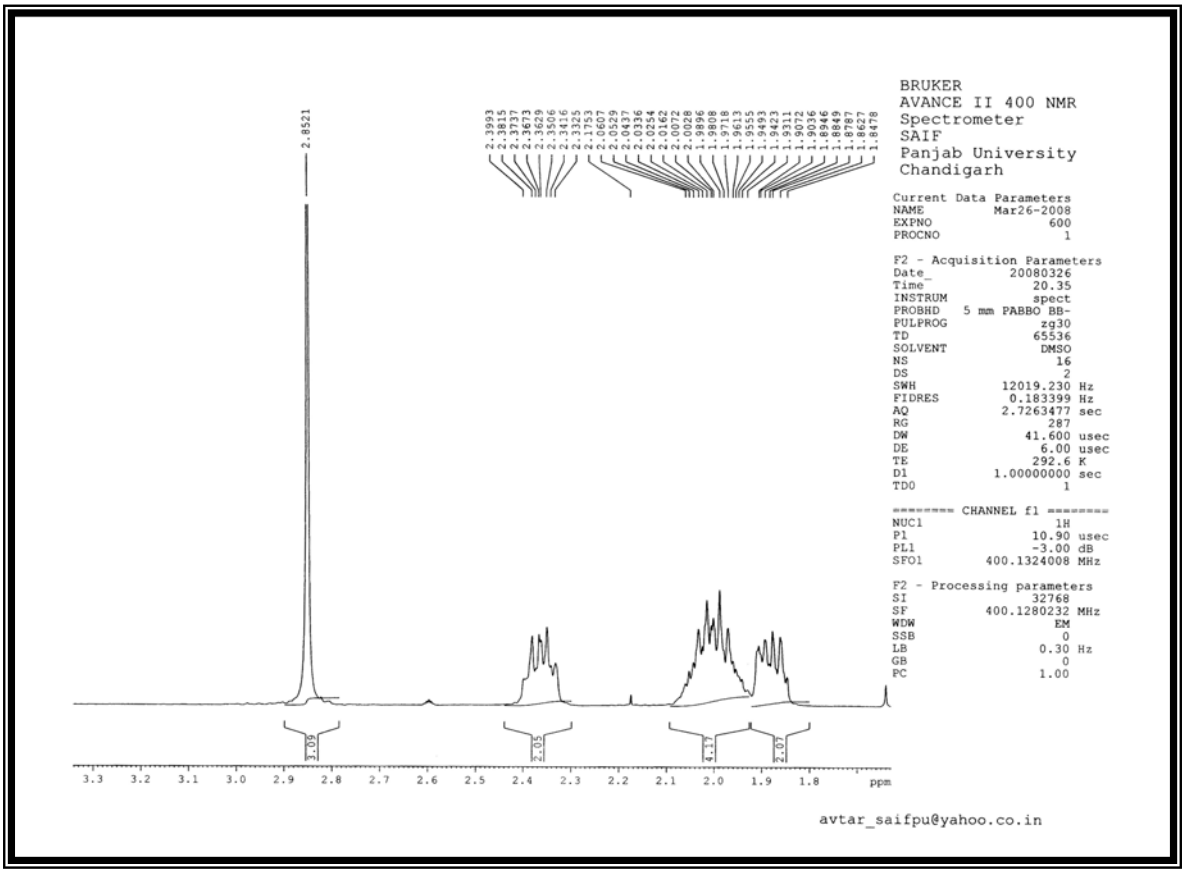
Mass spectrum of AS-2



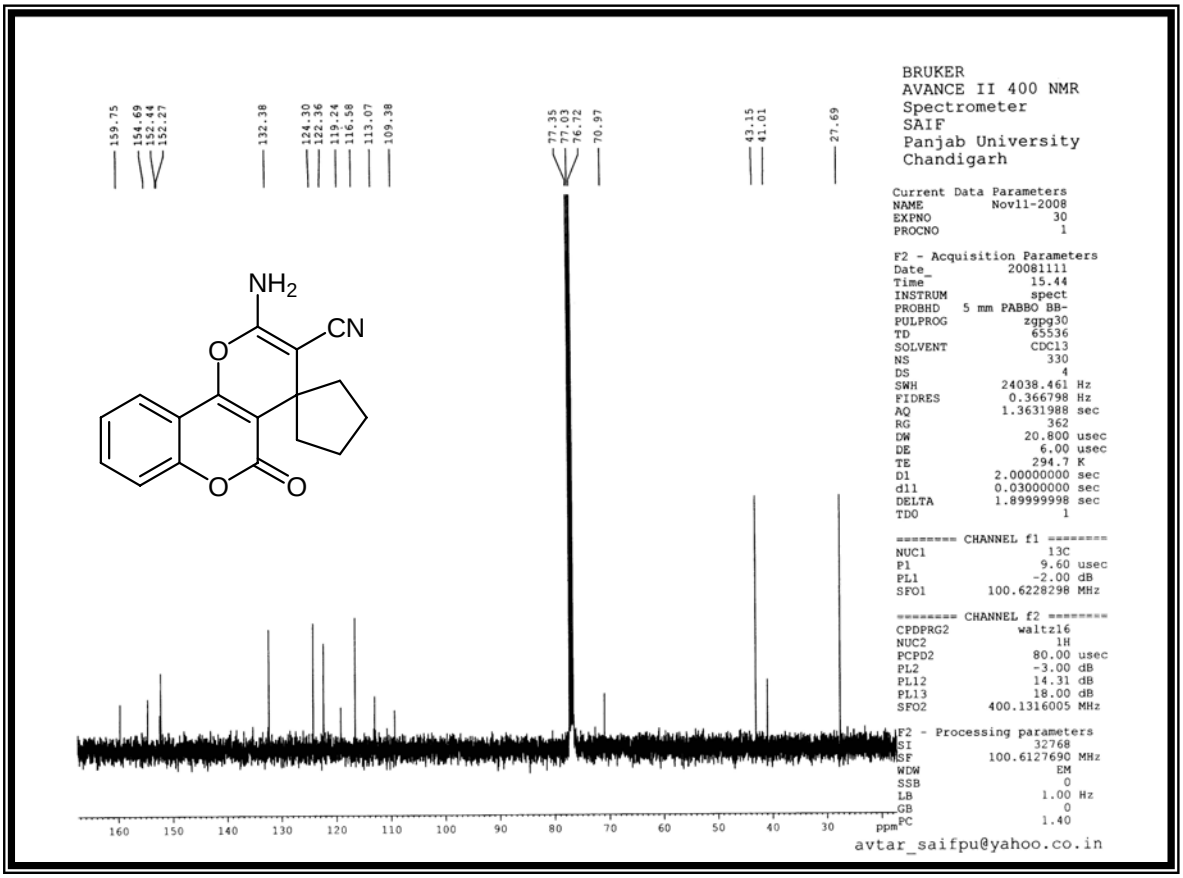
^{1}H NMR spectrum of AS-1



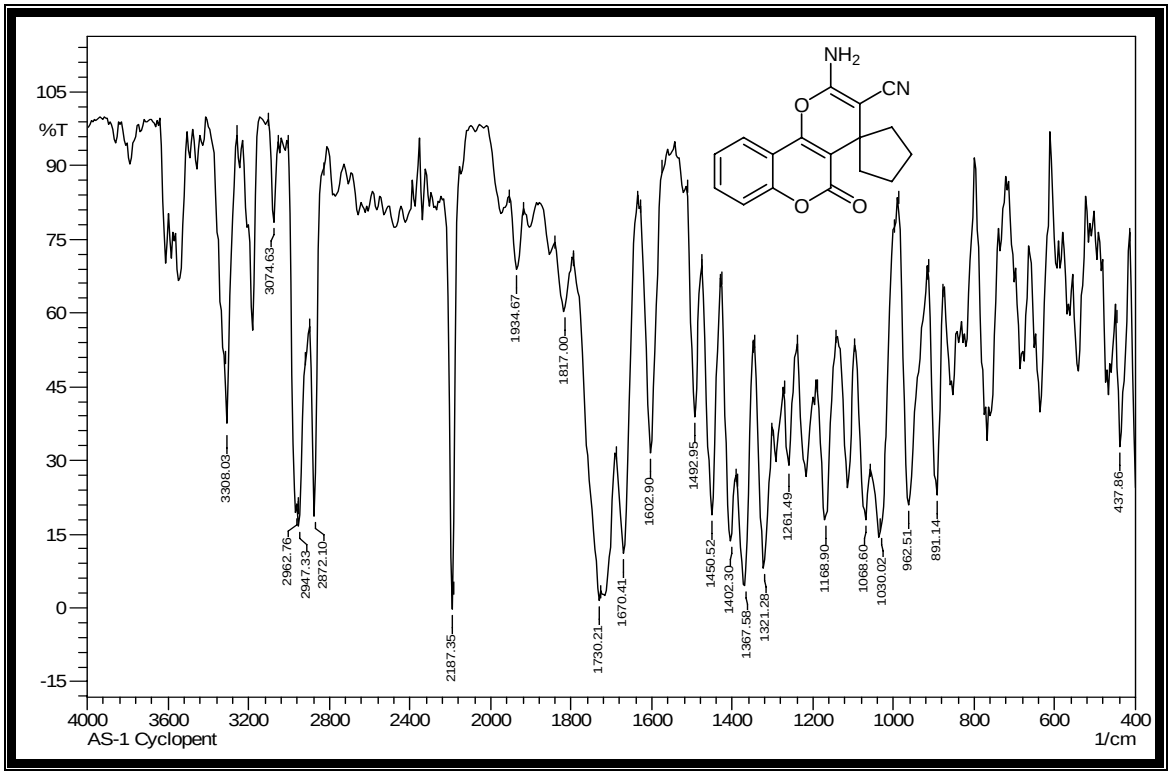




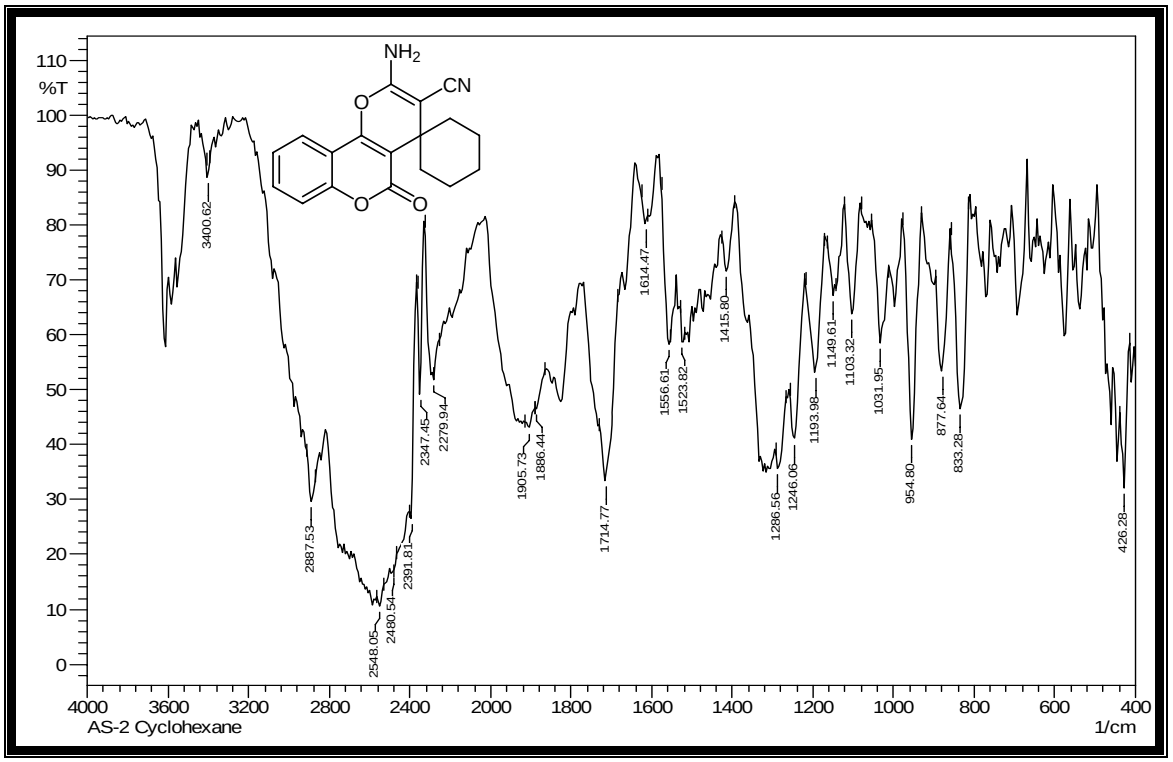
^{13}C NMR spectrum of AP-1



IR spectrum of AS-1



IR spectrum of AS-2



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Chapter 4

Synthesis and Characterization of Novel 4-hydroxy-3-(4-phenyl-3,4-dihydro-1,2-diazet-3-yl)-2H-chromen-2-one Derivatives

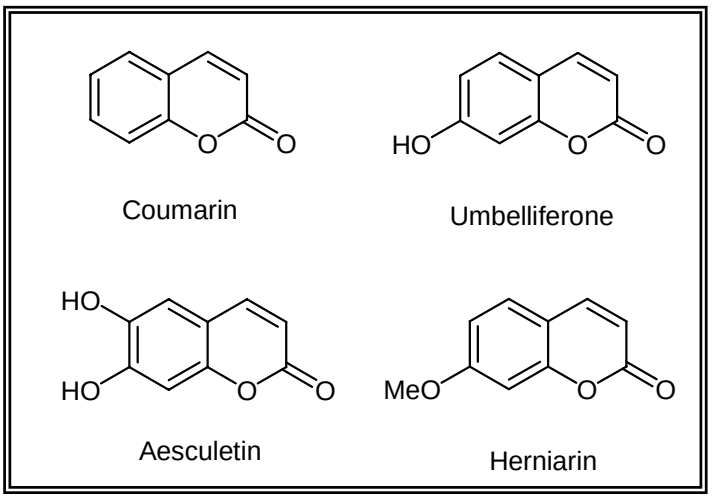
Chapter 4

Synthesis and characterization of novel 4-hydroxy-3-(4-phenyl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one derivatives

4.1 Introduction to Coumarin

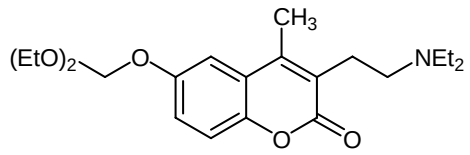
Heterocycles containing Oxygen and Nitrogen possess many biological and pharmacological properties. Besides, these they are also known to exhibit properties and applications such as anti-oxidants, heat stabilizers, photo sensitizers, indicators, lubricants and many more.

Six membered oxygen heterocycles constitute a group of compounds, which occur widely throughout the plant kingdom. Coumarin (2*H*-1-benzopyran-2-one) is one of the naturally occurring heterocycles in many natural products. It is widely distributed in plant world either in free state or in combined state. It was first isolated from tonka beans (*Dipteryx odorata*). It also occurs in sweet clover (*Melilotus Officinalis and Melilotus Alba*) and woodruff (*Aperula odorata*). It is the parent substance of a very large group of derivatives and fused compounds, many of which occur naturally and are of economic importance for example, Umbelliferone, Aesculetin and Herniarin etc.

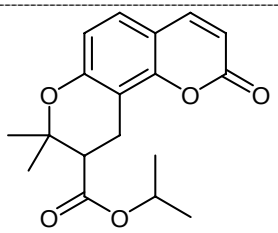


Coumarin chemistry has become important because of the discovery of varied biochemical properties, industrial uses and analytical applications. Coumarins have been found to be physiologically active for animals as well as humans. It acts as narcotics for rabbits, frogs and many other animals. 3-Chlorocoumarin have been proved to be sedative as well as hypnotic for mice and humans. However, it is toxic to dogs and humans.[1] Werder synthesized over hundred derivatives of coumarin-3-carboxilic acids – they were found to be sedative in small doses and hypnotic in large doses.[2] Coumarin also shows various other biological activities such as antifungal,[3] anticoagulants,[4] anti-psoriasis,[5] anti-carcinogen,[6] antibacterial[7] and insecticidal.[8]

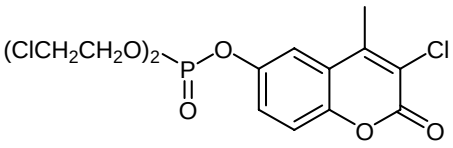
Some of the commercial drugs having an application as vasodialators such as Chromonar and Visnadin, Antithelmintics like Haloxon, diuretics like mercumallylic acid, and systemic insecticide like Hymercromone. Antibiotic novobiocin produced by *Streptomyces Spheroids* and *Sreptomyces Niveus* has been marketed as antibacterial or antimicrobial preparations.



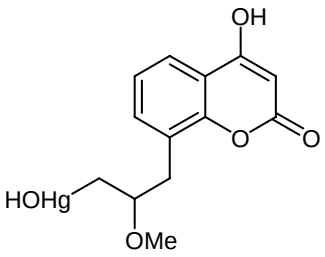
Chromonar



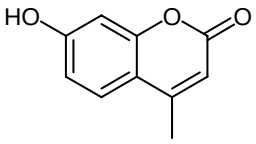
Visnadin



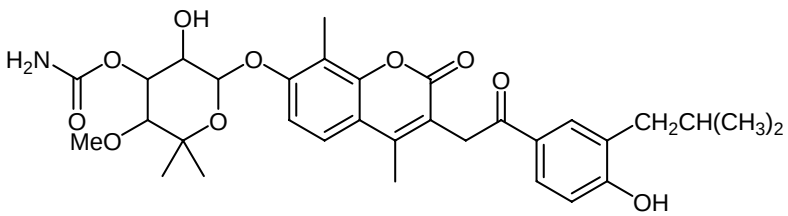
Haloxan



Mercumallylic Acid



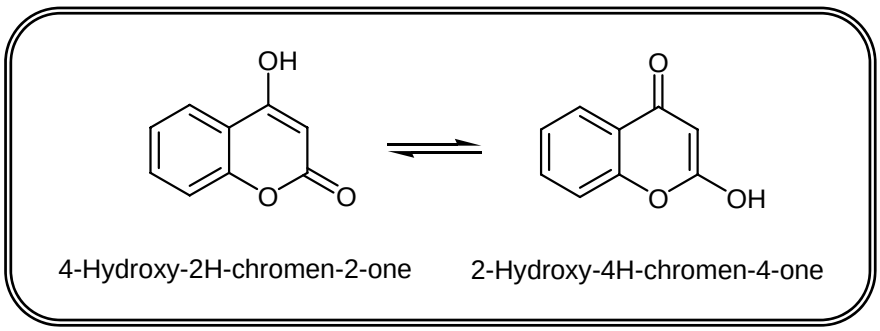
Hymercromone



Novobiocin

Coumarin is also used as synthetic intermediates for preparation of many heterocyclic compounds of biological and pharmacological importance.[9-12] Some biological activities such anti-HIV[13] and antitumor agents[14] are also reported.

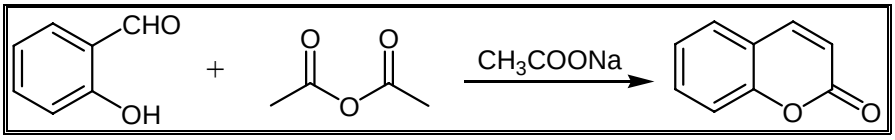
4-Hydroxy coumarin is a metabolite of coumarin oxygen heterocycles, which are studied for their tautomeric structures.[12] It can exist in 2 forms as shown below. Chemically, it is acidic in nature and therefore reacts easily at 3rd position.



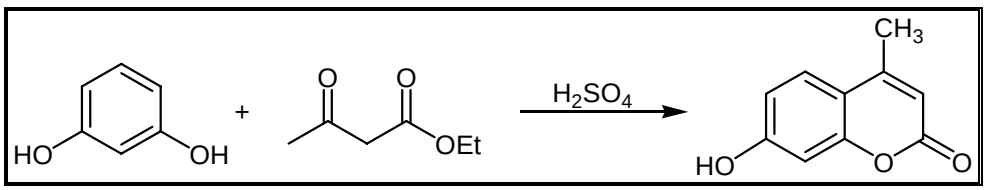
4.1.1 Preparation of coumarin

There are many synthetic approaches for the preparation of coumarin skeleton.

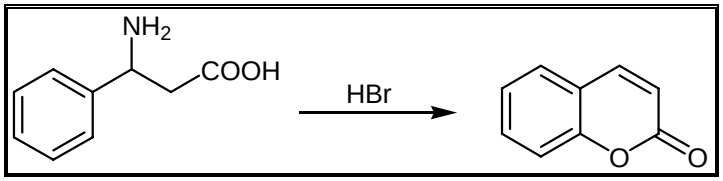
1. The biosynthesis of coumarin in plants is *via* hydroxylation, glycoysis and cyclization of cinnamic acid. Coumarin can be prepared in laboratory with the help of Perkin reaction between salicylaldehyde and acetic anhydride.[15]



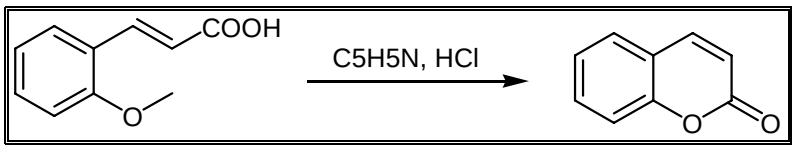
2. One of the most reliable method for preparation of coumarin and its derivatives is Pechmann condensation. It was discovered by the German chemist Hans von Pechmann.[16] It is a condensation starting from phenol and a carboxylic acid or ester containing a β-carbonyl group under acidic conditions.



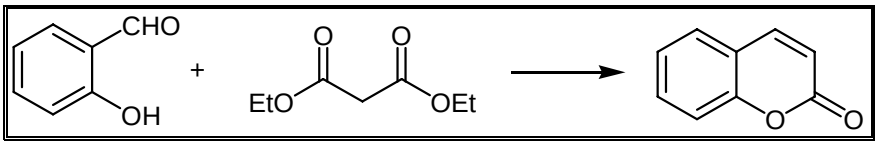
3. Cyclization of 3-amino-3-phenyl propanoic acid in presence of HBr results in 58% yield of coumarin.[17]



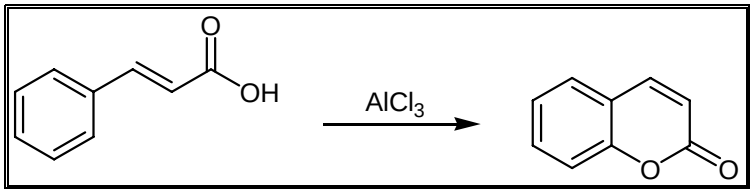
4. O-demethylation and lactonisation of *E*-cinnamic acid in presence of pyridine and HCl gives 55% yield of coumarin.[18]



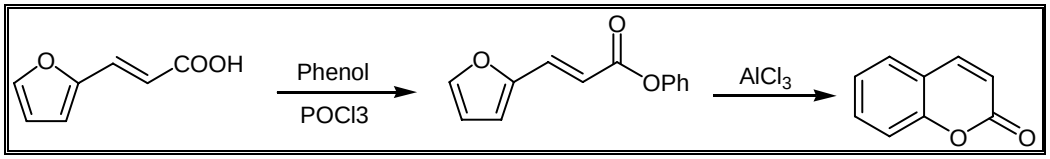
5. Malonic acid diethyl ester condenses with salicylaldehyde to give coumarin.[19]



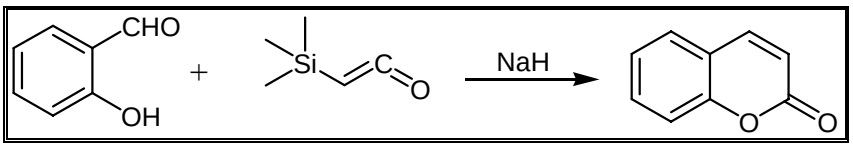
6. Manimaran *et al* synthesized coumarins, thiocoumarins and carbostyrils in the presence of $AlCl_3$.[20]



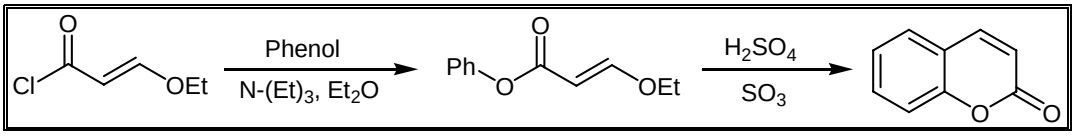
7. Substituted coumarins and benzocoumarins were prepared by esterification of 2-furan acrylic acid with substituted phenols in presence of $POCl_3$ and pyridine. Further, cyclization of furan acrylates were effected in presence of $AlCl_3$ to yield 73% of coumarin.[21]



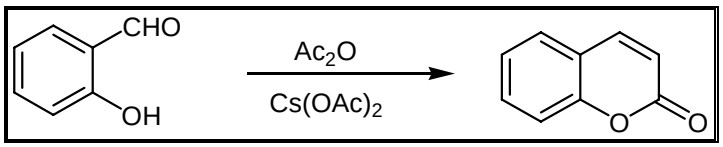
8. Coumarin was also prepared via cyclization-elimination followed by cyclo condensation reaction between 2-hydroxybenzaldehyde and trimethylsilylketene in presence of NaH.[22]



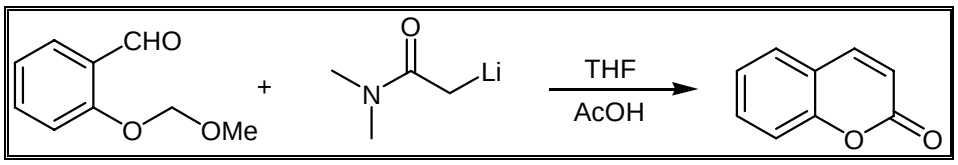
9. 3-Ethoxy acrolyl chloride with phenol in presence of triethyl amine and diethyl ether yielded phenyl ester, which on treatment with H_2SO_4 and SO_3 cyclised to give coumarins in good yields (69%).[23]



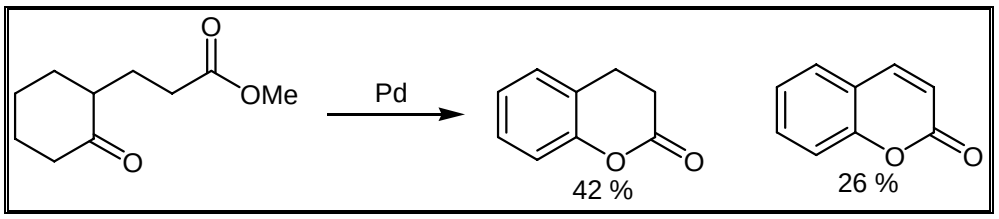
10. Koepp Erich *et al* used $Cs(OAc)_2$ instead of NaOAc in Perkin synthesis of cinnamic acid to yield coumarin 79%.[24]



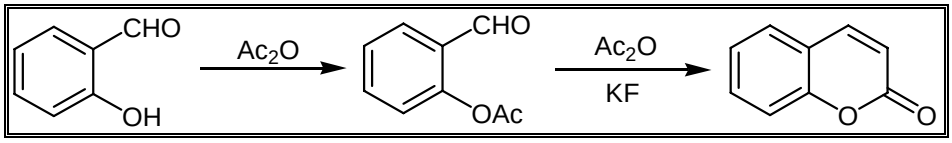
The same group discussed a new approach of using aroamatic metallation reaction of aldehydes such as 2-(methoxymethoxy)benzaldehyde with $LiCH_2$-CO-NMe_2 and deblocking and cyclization of the adducts with AcOH.[25]



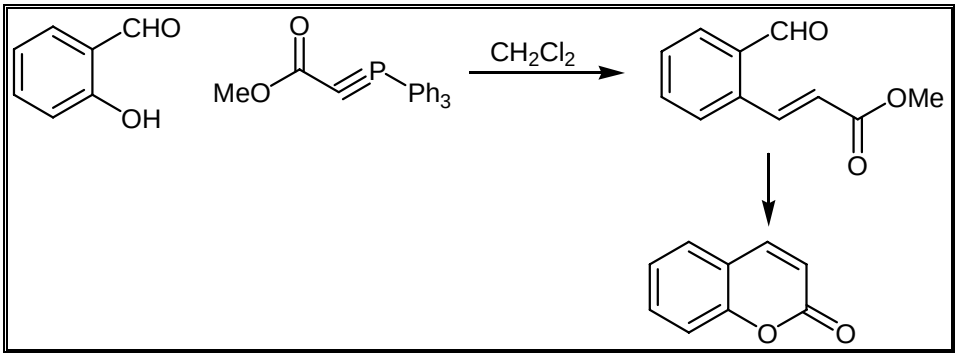
11. An European patent disclosed preparation of coumarin by cayalytivally dehydrogenation followed by cyclization of the cyclohexanoyl propionic acid esters at 100-300 °C in presence of catalyst comprising of a carrier having Pd supported either on CrO_3 or $Cr(OH)_3$.[26]



12. Zhou, Chengdong *et al* described an improved synthesis of coumarin by using salicylaldehyde. Salicylaldehyde was heated with Ac_2O and PEG at 185 °C for 1 hour to give 2-acetoxy benzaldehyde. It was further heated with Ac_2O and KF at 180-190 °C for 4-5 hours to give 76% of coumarin.[27]

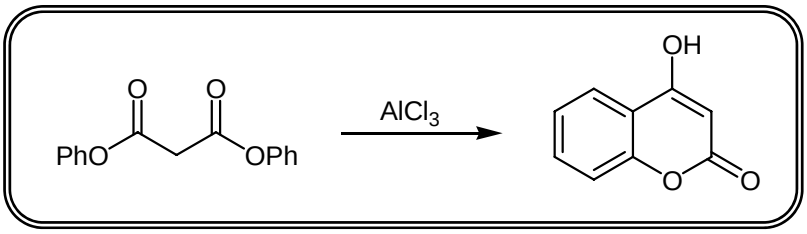


13. Flash Vacuum Pyrolysis of salicylaldehyde and triphenyl phosphine adduct in presence of methylendichloride gave coumarin in 87% yield.[28]

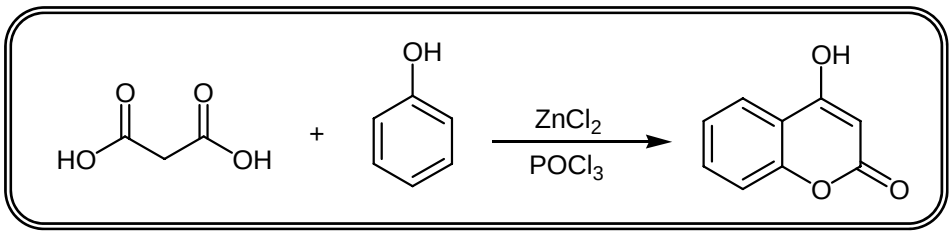


4.1.2 Preparation of 4-Hydroxy coumarin

1. Zeigler and coworkers cyclised malonic acid diphenyl ester in presence of $AlCl_3$ using Friedal Craft's alkylation to give 4-hydroxy coumarin in 85% yield.[29]

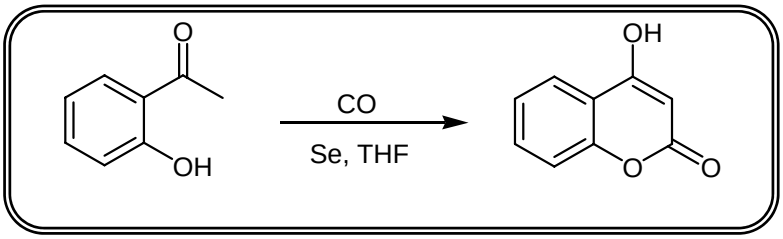


2. Shah *et al* synthesized 4-hydroxy coumarin by fusion of Equimolar amount of malonic acid and phenol with 2-3 moles of $POCl_3$ and $ZnCl_2$ admixture which gave 64% yield.[30]

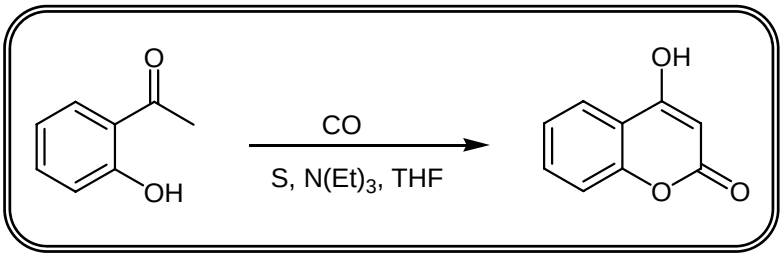


3. Sheikh *et al* synthesized trimethoxy and tetramethoxy substituted 4-hydroxy coumarins by Friedal Craft's acylation.[31]

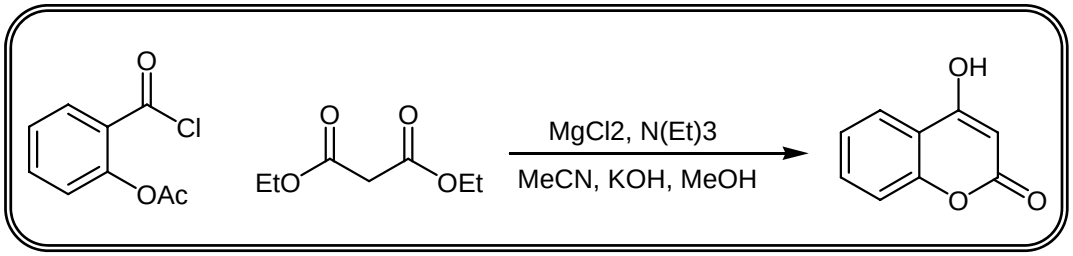
4. Selenium catalyzed carbonylation of 2-hydroxy acetophenone in THF containing nitrotoluene under carbon monoxide atmosphere at 90 °C for 30 hours giving 68% yield.[32]



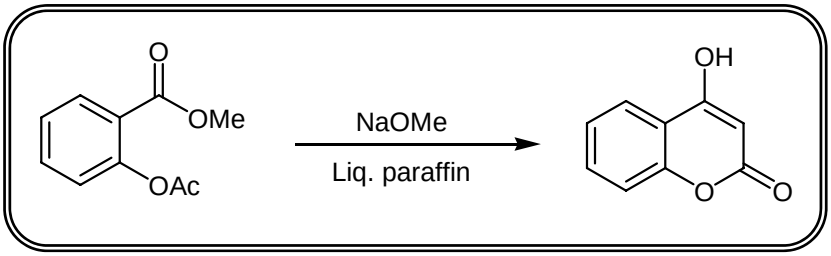
5. A facile synthesis of 4-hydroxy coumarin in presence of sulfur from 2-hydroxy acetophenone with carbon monoxide in presence of triethylamine and THF yielded 96% of 4-hydroxy coumarin.[33]



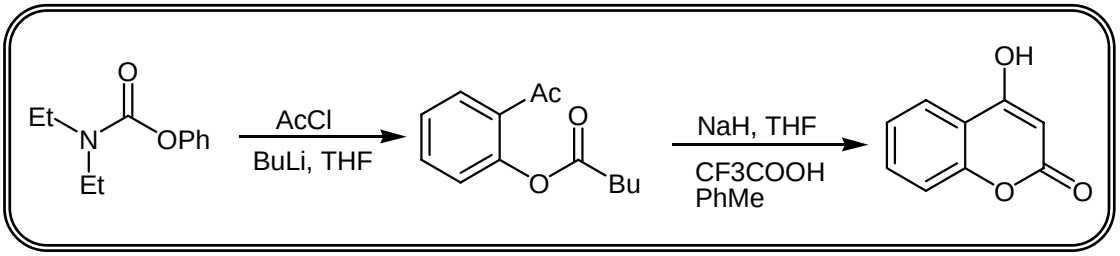
6. Coumarins were also prepared by treating malonic acid diesters with $MgCl_2$ and acetylsalicylic chloride and further cyclasation of resulting dialkyl 2-(2-acetoxybenzoyl)malonate by alkali. Diethylmalonate, $MgCl_2$ and acetylsalicylic chloride were treated with acetonitrile and triethylamine mixture at 0 °C for one hour. The product obtained was heated with KOH in methanol at 50 °C for 3 hours to give 77% target compound.[34]



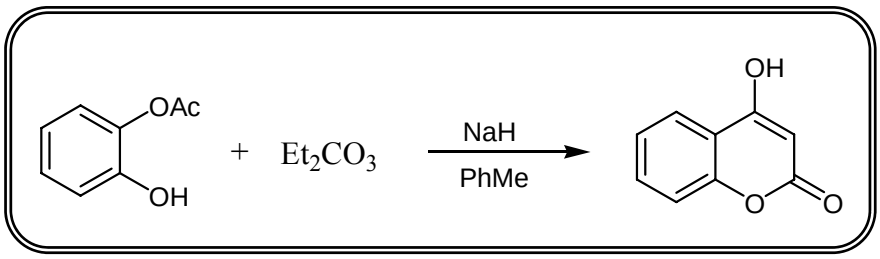
7. Intraolecular Claisen condensation of methylacetylsalicylate with NaOMe in liquid paraffin at 160-260 °C for 5 hours gave 20% of 4-hydroxy coumarin.[35]



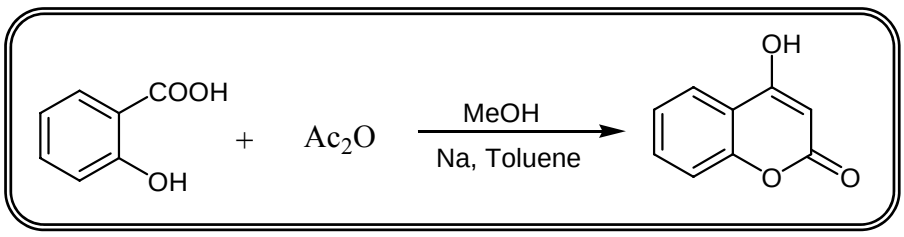
8. Substituted 4-hydroxy coumarin was synthesized via new Bakew-Venkatraman rearrangement.[36]



9. One-pot synthesis of coumarin and 4-hydroxucoumarin by acylation followed by internal ring closure.[37]

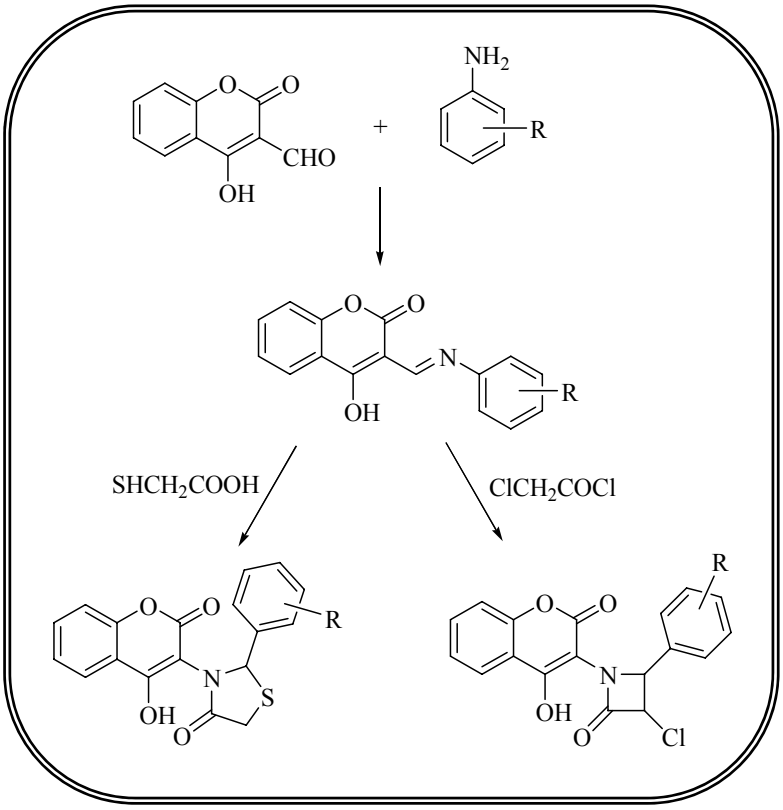


10. Salicylic acid was esterified and acetylated. It was further cyclized with metallic sodium in dry toluene.[38a]

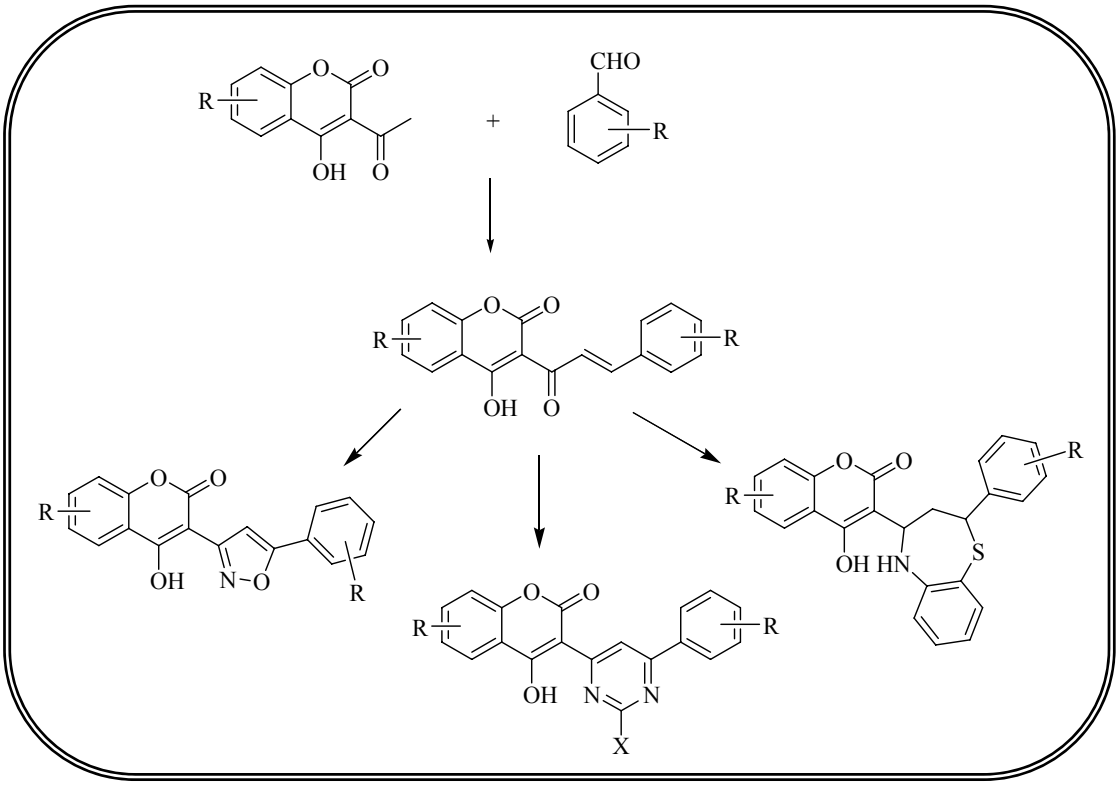


4.1.3 3-Substituted 4-Hydroxy coumarin

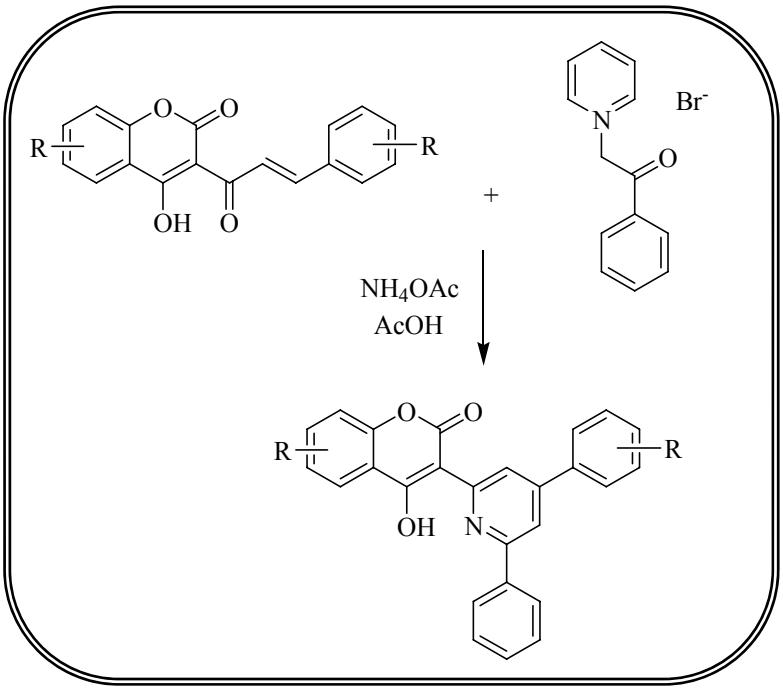
V. V. Mulwad et. al. had synthesized 4-hydroxy coumarin-3-carbaldehyde and used to construct thiazolidinone and azetidinone ring system at 3 position of 4-hydroxy coumarin. All the compounds were screened for antimicrobial activity and shown good activity against *S. typhi* and *S. aureus*.[38b]



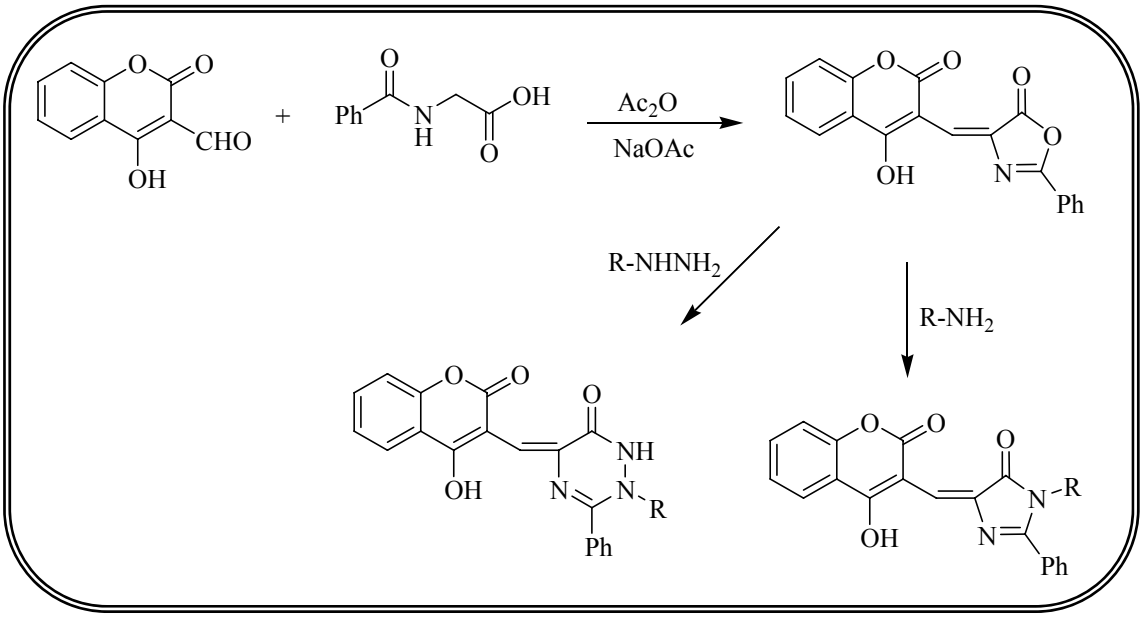
V. V. Mulwad et. al. synthesized some 4-hydroxy coumarin substituted at 3-position with oxazole, pyrimidine and thiazepine derivatives by condensation of 4-hydroxy-3-coumarinyl chalcon with ammonium hydroxide, urea and 2-aminothiophenol respectively and reported as good antibacterial agents.[38c]



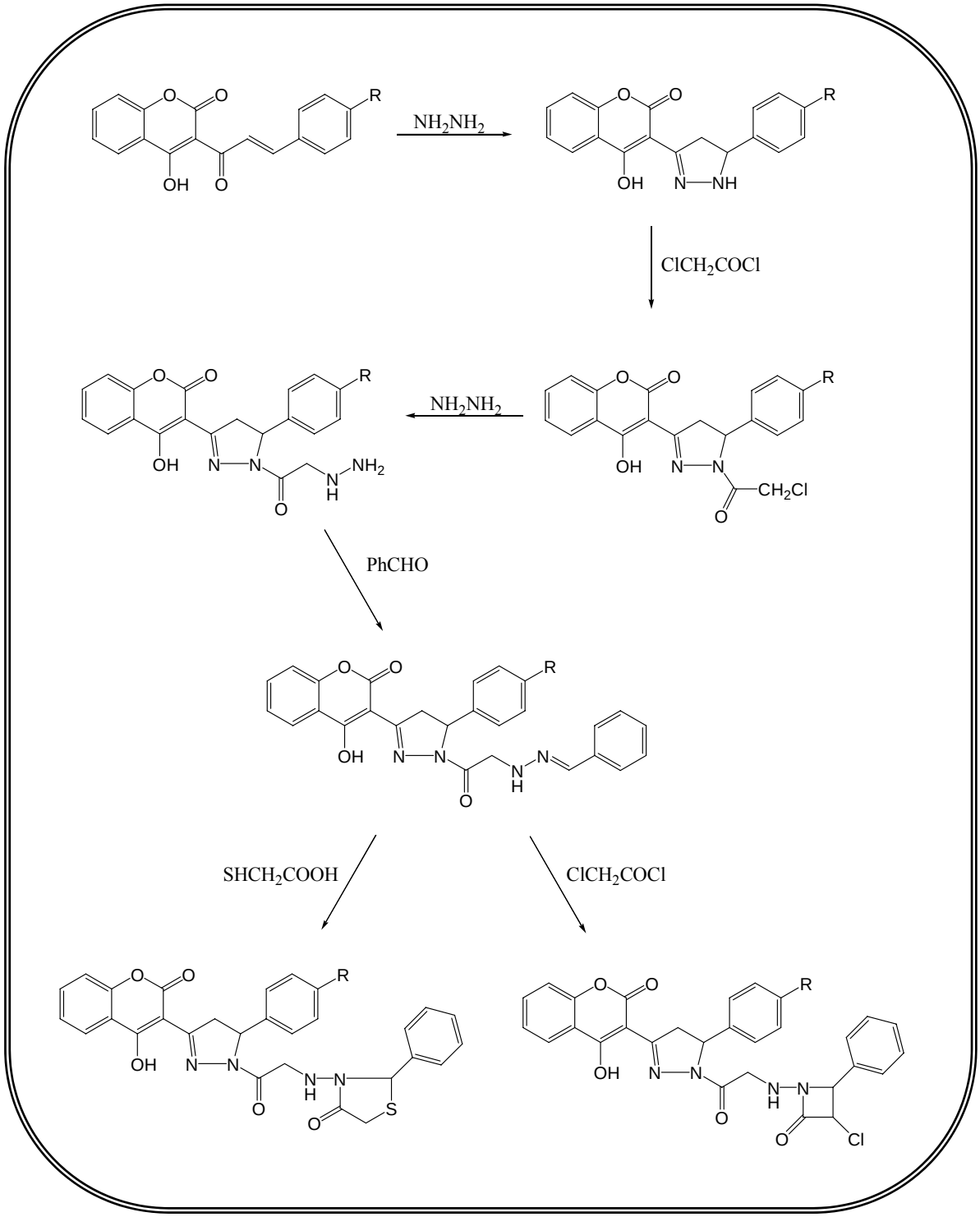
In further investigation 4-hydroxy-3-coumarinyl chalcon was condensed with pyridinium salt of phenacyl bromide and ammonium acetate in acetic acid to afford 4-hydroxy-3-pyridyl coumarin derivatives. All the compounds were screened for their antimicrobial activity and shown good activity.[38d]



D. S. Satwe et. al. synthesized 4-hydroxy-3-coumarinylidene oxazolone by the reaction of 4-hydroxy coumarin-3-carbaldehyde and 2-benzamidoacetic acid in acetic anhydride. It was further reacted with various hydrazine and various aromatic amines to give corresponding trazine and imidazol derivatives.[38e,f]



4-hydroxy-3-pyrazoline coumarin reacted with chloroacetylchloride to give corresponding N-chloracetylpyrazoline which resulted into hydrazine derivative with hydrazine hydrate. This hydrazine derivative was utilized to prepare a number of thiazolidinine and azetidinone derivatives.[38g]



4.2 Introduction to Diazete

Summary of the general chemistry of four-membered heterocycles:

- The stability and reactivity of the compounds are determined by the ring strain and the nature of the heteroatom or heteroatoms. While azete, as an antiaromatic system, is extremely reactive, the aromatic systems 1,2-dithiete and l,2-dihydro-l,2-diazete are hardly any more stable and are very reactive.
- Ring-opening by nucleophiles proceeds more slowly than with three-membered heterocycles and is catalyzed by acids.
- Special ring-openings are [2+2] cycloreversions (oxetan-2-ones, 1,2-dioxetanes, l,2-dioxetan-3-ones, 1,2-diazetidines, l,2-diazetidin-3-ones) and valence isomerizations (1,2-dithiete, 1,2-dihydro-1,2-diazete).
- Oxetan-2-ones, azetidin-2-ones and l,2-diazetidin-3-ones are more reactive than five- and six membered homologues. They are attacked by nucleophiles on the C-atom of the carbonyl group. Ring-opening occurs to give γ-substituted carboxylic acids or carboxylic acid derivatives.
- An important synthetic principle is the intramolecular nucleophilic substitution of a γ-substituted leaving group

  — by an O-atom (oxetanes, oxetan-2-ones, 1,2-dioxetanes, 1,2-dioxetan-2-ones)

  — by an S-atom (thietanes)

  — by an N-atom (azetidines, azetidin-2-ones)

  The rate of reaction is greater than that of the three-membered heterocycles because of the smaller ring strain of the products. At the same time, however, the entropy gain is smaller, because two degrees of freedom of inner rotation are lost en route to the activated complex.
- [2+2] Cycloadditions are of great importance for synthetic purposes

  — carbonyl compounds + alkenes -> oxetanes

  — aldehyde + ketenes -> oxetan-2-ones

  — imine + ketenes —> azetidin-2-ones

  — isocyanates + alkenes —> azetidin-2-ones

  — singlet oxygen + alkenes —> 1,2-dioxetanes

  — alkenes + azo compounds —» 1,2-diazetidines

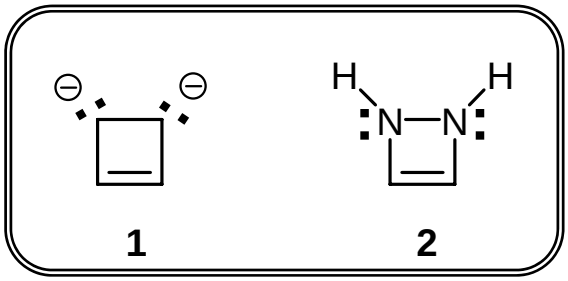
— ketene + azo compounds —» l,2-diazetidin-3-ones

- The importance of four-membered heterocycles for organic synthesis is limited. Examples are the alkene synthesis involving oxetan-2-ones and the /?-aminocarboxylic acid synthesis involving azetidin-2-ones.

1,2-Diazetines are a class of strained four membered ring azo compounds.[39,40] Their properties remain largely unexplored presumably as a result of the difficulty of their synthesis. Even though the first member of this family of compounds was described in 1962, fewer than a dozen diazetines are currently known.[41] Despite the propensity for decomposition of diazetines to ultimately afford nitrogen and the corresponding alkene, diazetines are quite thermally robust.[39,42] This has prompted questions concerning the mechanism of decomposition of these compounds with advocacy of concerted (both [2s + 2s] and [2s + 2a] retrocycloadditions being suggested) and nonconcerted (i.e., via diradical intermediates) processes.[39,43] Detailed studies on the decomposition process have been hampered by the inaccessibility of diazetine substrates.[39a,44]

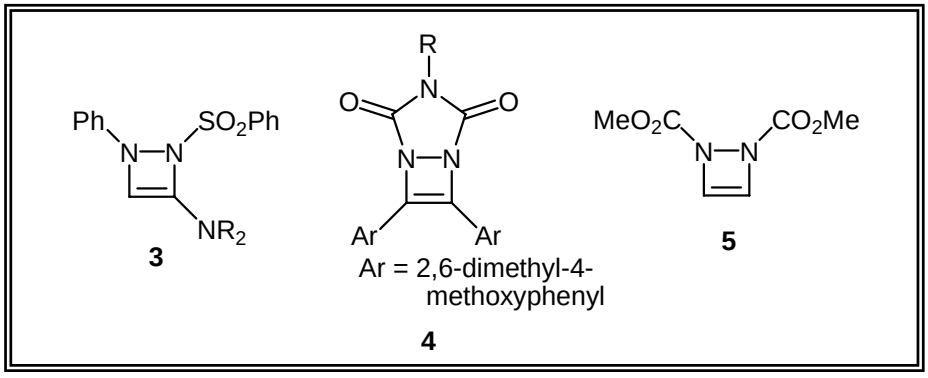
4.2.1 Aromaticity

Aromaticity continues to be an actively investigated area of chemistry.[45] The simplest criteria for aromatic compounds are that they possess cyclic conjugated π-systems
containing the proper number of π-electrons (i.e., the Huckel rule). While these criteria are robust enough to predict the aromaticity of a host of neutral and charged ring systems, it is not always a clear indicator of aromaticity for more complex systems. For instance,
applying these criteria to the cyclobutadienyl dianion (**1**) one would predict an aromatic compound since it contains six π-electrons akin to that of benzene and the cyclopentadienyl anion.

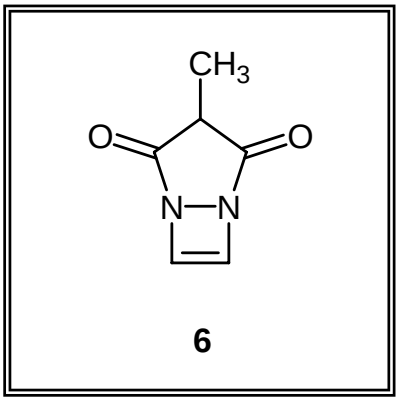


Early computational studies suggested that **1** adopted a folded structure and was therefore not aromatic.[46] More recent studies, however, suggested that the dianion is planar but adopts a structure with C_{2h} symmetry rather than the D_{4h} symmetry that would be expected for a fully delocalized aromatic structure.[47] The failure to adopt a D_{4h} structure was attributed to repulsive interaction of the negative charges within the ring. Indeed, only when two Li^+ cations were added to the model system to stabilize the charges did the ring adopt the expected D_{4h} symmetry.[47] Recently, the synthesis and characterization of a cyclobutadienyl dianion substituted at each of the four carbons of the ring with anion-stabilizing trimethylsilyl groups was reported.[48] The resulting compound was planar and almost square (as determined by X-ray crystallography), suggesting that it may be aromatic.

The charge repulsion problem in the cyclobutadienyl dianion could be minimized by substituting the two adjacent negatively charged carbons of the ring by nitrogen atoms to afford a 1,2-dihydrodiazete (**2**). The 1,2-dihydrodiazetes are isoelectronic with the cyclobutadienyl dianion, but should experience considerably less charge/ charge repulsion and might, therefore, exhibit aromaticity without the need for additional stabilization. Only a few 1,2-dihydrodiazetes have been reported in the literature. The first to be reported were rather highly substituted derivatives (**3**) and their characterization did not include spectroscopic data.[49] Greene reported the syntheses of **4** (R = Me, Ph) as stable crystalline compounds.[50] Neither of these investigators discussed the possibility of aromaticity of the ring system. Warrener synthesized compound **5**, which is substituted at the nitrogen by carbomethoxy groups.[51] This compound proved to be of limited thermal stability and underwent spontaneous electrocyclic ring-opening at room temperature ($t_{1/2}$[20 °C] = 6.9 h). Warrener considered the possibility of the ring's aromaticity but ultimately rejected it based on its low thermal stability, 1H NMR spectroscopic data, and theoretical arguments.[51b]



Gary W. Breton* et al reported the synthesis of compound **6**, an analogue of Greene's compound **4**.[52] Compound **6** is a stable crystalline compound that lent itself to thorough structural and chemical analyses. Gary W. Breton presently reported our experimental work with **6** along with additional computational studies on **6** and 1,2-dihydrodiazetes in general to determine whether the 1,2-dihydrodiazete ring system exhibits any characteristics that may be attributed to aromaticity.[53]



6

4.2.2 Biological Importance

3,4-Dihydrodiazete 1,2-dioxides (diazetine dioxides, DD) were described for the first time about 20 years ago;[54] however, their biological activity was studied only recently.[55] These compounds were found to exert strong vasorelaxant and antiaggregant effects.[55] Spontaneous decomposition of DD was considered to be a source of nitric oxide (NO),[54b,55] and the rate constants of this reaction were measured for a series of DD in aqueous solutions.[55b] However, the rate constants were in the range of 10^{-7} s^{-1}, too low to account for the strong vasorelaxation induced by DD.[55a,d] Typical concentrations of diazetine dioxides causing significant vasodilation were determined to be in the range of 10^{-6} M.[2] It has been shown that the activity of various NO liberating compounds is considerably influenced by thiols.[56] Diazetine dioxides are known to react with various nucleophilic and reducing agents. These reactions can proceed via diazetine ring opening and may be accompanied by a loss of one of the nitrogen atoms of the heterocycle.[57]

4.3 Current work

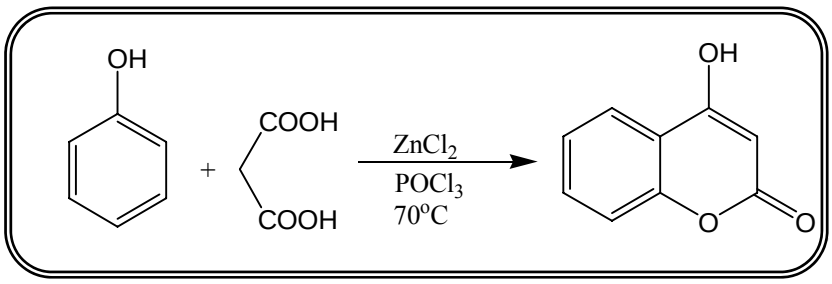
In view of marked importance of coumarin core attached at 3 position with four membered nitrogen heterocycles in the field of vast area of organic and medicinal chemistry,[38b-g] Our interest was to develop a moieties containing coumarin core attached with nitrogen heterocycles. The precursor 4-hydroxy coumarin was synthesized as per mentioned in literature methods. Further microwave technique was utilized wherein, a mixture of 4-hydroxy coumarin and triethyl orthoformate with catalytic amount of *p*-toluene sulfonic acid (PTSA) was subjected to microwave irradiation to prepare 3-ethoxymethylene-3*H*-2,4-dione. Further, the hydrolysis of 3-ethoxymethylene-3*H*-2,4-dione with K_2CO_3 resulted into 4-hydroxy coumarin-3-carbaldehyde.[58] Subsequently treatment of the 3-ethoxymethylene-3*H*-2,4-dione with excess 50% solution of hydrazine hydrate at ambient temperature afforded 4-hydroxy-2-oxo-2*H*-cromene-3-carbaldehyde hydrazone (scheme 2) in excellent yield. It was also found that the reaction does not require any solvent or external heating. The formation of hydrazone was further confirmed by mass and ^{1}H NMR spectral study. The resulted hydrazone was reacted with various aldehydes in DMSO to afford 4-hydroxy-2-oxo-2*H* chromene-3-carbaldehyde(arylmethylene)hydrazone. Finally afforded derivative arylmethylene hydrazone undergoes 4π electron cyclization to construct a four membered 1,2-diazete ring system and resulted into 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one derivatives **AA(1-18)** (scheme 2). The formation of 1,2-diazete ring system was confirmed by IR, Mass, and ^{1}H NMR spectral study. Physical properties of all newly synthesized compounds **AA(1-18)** are discussed in section 4.7.

The plausible mechanism of 4π electron cyclization is presented in section 4.5. Arylmethylene hydrazone is a hetero analog of conjugated 1,3-butadiene system containing 4π electron system which undergoes conrotatory or disrotatory 4π electron cyclization as per pericyclic reaction to construct a four membered 3,4-dihydro-1,2-diazete ring system at 3 position of coumarin core. The anti viral screening of the synthesized compounds is under investigation.

4.4 Reaction Scheme

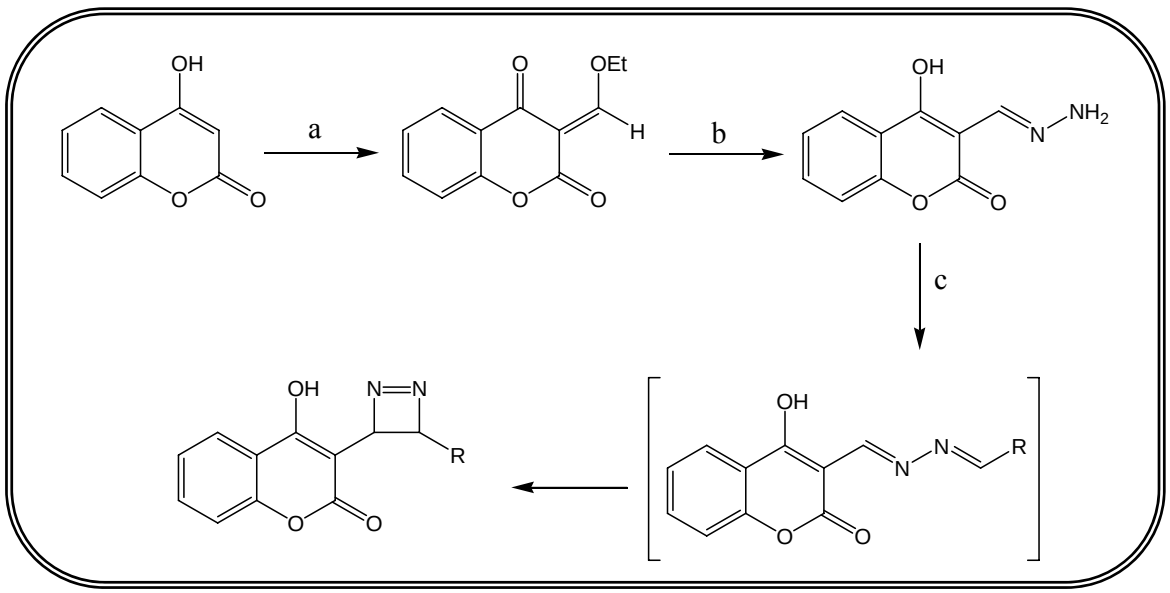
4.4.1 Scheme 1.

Synthesis of 4-hydroxy coumarin



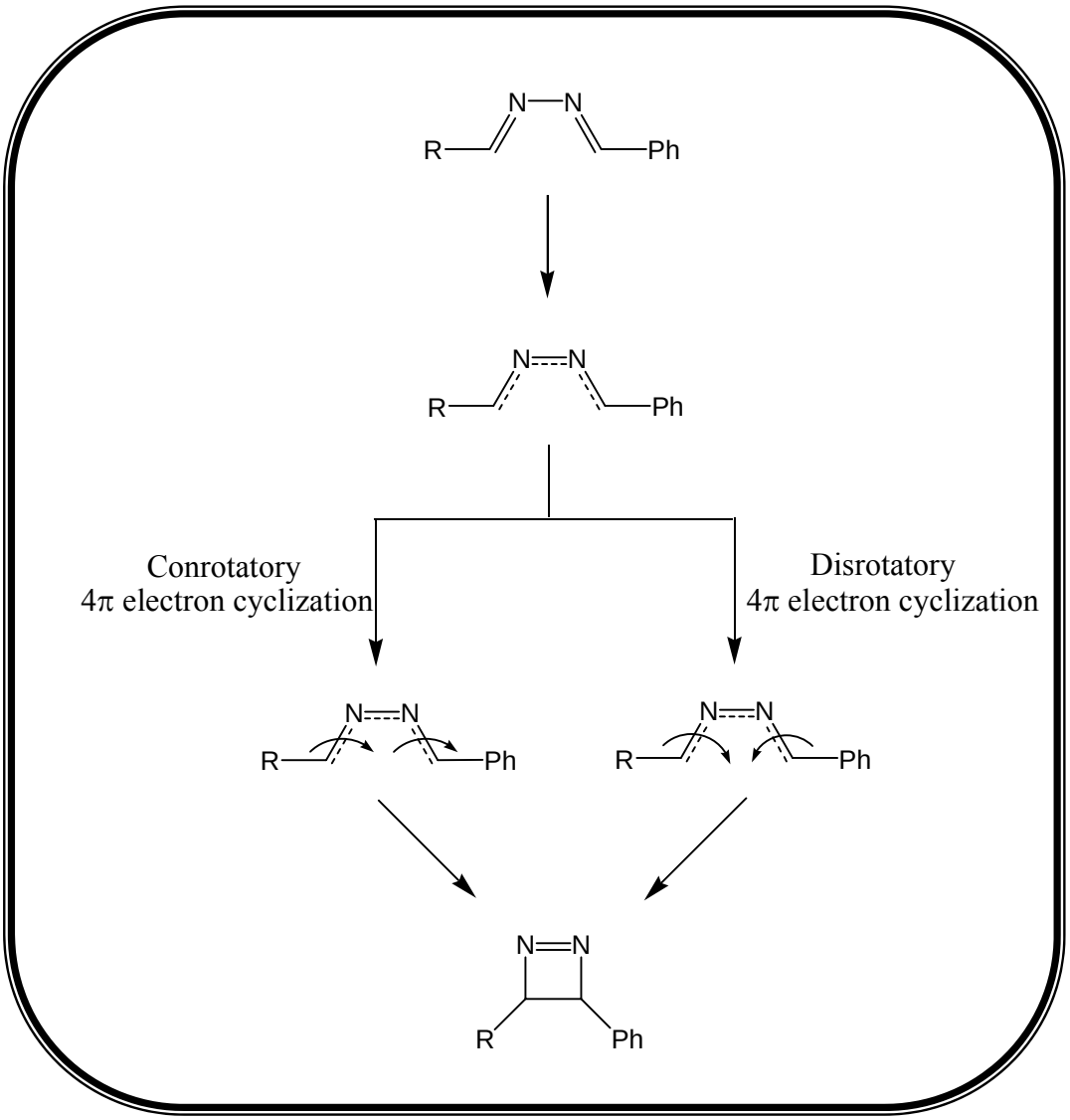
4.4.2 Scheme 2.

Synthetic approach towards 4-hydroxy-3-(4-phenyl-3,4-dihydro-1,2-diazet-3-yl)-2H-chromen-2-one derivatives



Reagents and conditions: **(a)** Triethyl orthoformate, p-Toluenesulfonic acid, MW 240 W, 2 min.; **(b)** $NH_2NH_2 \bullet H_2O$, r.t., Stirring; **(c)** R–CHO, DMSO, con. HCl, 100ºC, 30 min.

4.5 Reaction Mechanism



4.6 Experimental

4.6.1 4-hydroxy coumarin:

Phenol (9.41g, 0.1M) and malonic acid (10.4g, 0.1M) were added to a mixture of phosphorus oxychloride (40 ml) and anhydrous zinc chloride (30 g) which was preheated to 60 ºC. The reaction mixture was heated on a water bath at 70 ºC for 10 hours. It was cooled and decomposed with ice and water which forms a yellow solid. It was filtered and washed with water. It was further triturated with 10 % sodium carbonate and filtered. The filtrate was slowly acidified with dilute hydrochloric acid. At the neutral point, some solid product was separated, which was filtered, washed with water, dried and recrystallized from ethanol. White solid; m.p. 210 ºC; Yield: 55%.

4.6.2 3-(ethoxymethylene)-2*H*-chromene-2,4(3*H*)-dione:

A mixture of 6.2 mmol of 4-hydroxy coumarin, 7 ml of triethyl orthoformate, and 0.02 g of *p*-toluenesulfonic acid monohydrate was placed in a 50 ml beaker. The beaker was covered with a stemless funnel and irradiated in a microwave oven for 1 minute at 240 W and then 1 minute at 180 W. The resultant residue was cooled to room temperature, the solvent was decanted, and the residue was crystallized in a chloroform to obtain target compound as a yellow solid. m.p. 140 ºC; Yield: 65%.

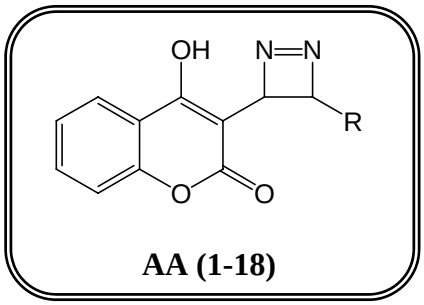
4.6.3 4-hydroxy-2-oxo-2*H*-cromene-3-carbaldehyde hydrazone:

3-(ethoxymethylene)-2*H*-chromene-2,4(3*H*)-dione (20.41g, 0.1M) was added to a 50% hydrazine hydrate solution (50 ml). Now the reaction mixture was stirred at room temperature for 10-15 minutes. The solid was filtered off, washed with water until free from hydrazine hydrate, dried and crystallized in chloroform to give pure 4-hydroxy-2-oxo-2*H*-chromene-3-carbaldehyde hydrazone as yellow solid. m.p. 138 ºC; Yield: 85%.

4.6.4 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2H-chromen-2-one:

4-hydroxy-2-oxo-2*H*-chromene-3-carbaldehyde hydrazone (0.01M) and appropriate aryl aldehyde (0.01M) were dissolved in 10 ml of DMSO and 2-3 drops of con. HCl was added as a catalyst. The reaction mixture was heated at 100 °C for 30 min. The separated solid was filtered off, washed with cold methanol and dried. The obtained crude product was recrystallized in chloroform to give 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one as yellow crystals.

4.7 Physical data



AA (1-18)

Comp.	R	M.F.	M.W.	Mp ºC	Yield %	R_f
AA-1	Ph	$C_{17}H_{12}N_2O_3$	292.28	230-232	75	0.35
AA-2	4-CH_3-C_6H_4	$C_{18}H_{14}N_2O_3$	306.31	214-216	71	0.41
AA-3	4-OCH_3-C_6H_4	$C_{18}H_{14}N_2O_4$	322.31	206-208	76	0.36
AA-4	3,4-di-OCH_3-C_6H_4	$C_{19}H_{16}N_2O_5$	352.34	218-220	86	0.34
AA-5	2,5-di-OCH_3-C_6H_4	$C_{19}H_{16}N_2O_5$	352.34	210-212	79	0.39
AA-6	2-Cl-C_6H_4	$C_{17}H_{11}ClN_2O_3$	326.73	212-214	65	0.46
AA-7	3-Cl-C_6H_4	$C_{17}H_{11}ClN_2O_3$	326.73	217-219	71	0.45
AA-8	4-Cl-C_6H_4	$C_{17}H_{11}ClN_2O_3$	326.73	224-226	75	0.32
AA-9	4-F-C_6H_4	$C_{17}H_{11}FN_2O_3$	310.27	206-208	65	0.48
AA-10	2-OH-C_6H_4	$C_{17}H_{12}N_2O_4$	308.28	210-212	70	0.49
AA-11	3-NO_2-C_6H_4	$C_{17}H_{11}N_3O_5$	337.28	223-225	80	0.30
AA-12	4- NO_2-C_6H_4	$C_{17}H_{11}N_3O_5$	337.28	214-216	80	0.33
AA-13	2- NO_2-C_6H_4	$C_{17}H_{11}N_3O_5$	337.28	224-226	76	0.29
AA-14	3-Br-C_6H_4	$C_{17}H_{11}BrN_2O_3$	371.18	216-218	70	0.41
AA-15	4-N,N-di-CH_3-C_6H_4	$C_{19}H_{17}N_3O_3$	335.35	204-206	60	0.47
AA-16	3-Pyridyl	$C_{16}H_{11}N_3O_3$	293.27	228-230	62	0.50
AA-17	2-Furyl	$C_{15}H_{10}N_2O_4$	282.25	214-216	58	0.48
AA-18	1-napthyl	$C_{21}H_{14}N_2O_3$	342.34	227-229	72	0.32

TLC Solvent system: Ethyl acetate : Hexane – 3.5:6.5

4.8 Spectral discussion

4.8.1 Mass spectral study

Instrument : SHIMADZU GCMS-QP-2010

Sample technique : EI technique

M/z range : 40-500

Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. Systematic fragmentation pattern was observed in mass spectral analysis. Peaks for specific fragments were identified in each mass spectrum. Molecular ion peak was observed in agreement with molecular weight of respective compound. M^++1 peak was also observed with very low intensity. Another characteristic peak M^+-N_2 was observed. Extrusion of N2 from compound in the mass spectra reveals the existence of the cyclic product, which is in accordance with the assigned structure. After this fragmentation another cleavage was observed with removal of hydroxy group.

4.8.2 IR spectral study

Instrument : Shimadzu FT-IR-8400

Sample technique : KBr pellet

Frequency range : 400-4000cm^{-1}

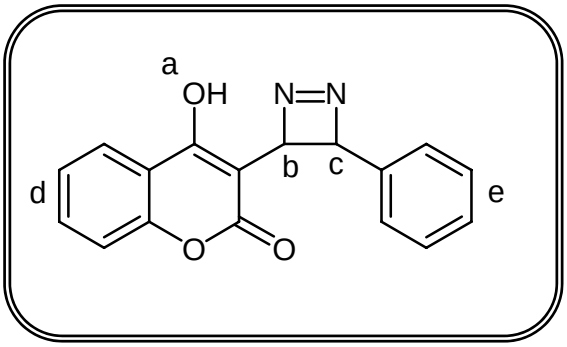
As per IR spectral study of newly synthesized 4-hydroxy-3-(4-aryl-3,4-dihydro-1,2-diazet-3-yl)-2H-chromen-2-one derivatives, the O–H stretching vibration of hydroxy group attached at 4 position of coumarin ring was appeared around 3100-3400 cm^{-1}. The carbonyl (>C=O) stretching vibration of coumarin lactone ring was observed around 1690–1715 cm^{-1}. The N=N stretching vibration was observed between 1575 to 1600 cm^{-1}. The ring skeleton vibration was observed between 1500 to 1600 cm^{-1} due to the presence of phenyl ring system.

4.8.3 ^{1}H NMR spectral study

Instrument : BRUKER AC 400 MHz FT-NMR

Internal reference : TMS

Solvent : $CDCl_3$



Number of protons and their chemical shifts were found to support the structure of the synthesized compounds. Proton of hydroxy group attached with coumarin ring at 4 position 'a' was observed at 14.02-14.15 δ ppm. Two methine protons of diazete ring 'b' and 'c' were observed as a doublet at around 8.8 and 8.6 δ ppm. The coupling constants for the splitting were calculated which were observed between 12 to 15 Hz. Methine protons of 1,2-diazete ring have been observed variable in ^{1}H NMR spectrum depending upon the substitutions at 3 and 4 position of 1,2-diazete ring. G. W. Breton et al.[59]observed methine proton of 1,2-diazete ring between 4 to 5 δ ppm. Yutaka Ishida et al.[60] observed methine proton of 1,3-diazete ring at 8.69 δ ppm. In the proposed structure, methine proton of diazete ring were observed with very downfield chemical shift in ^{1}H NMR spectrum due to attachment of coumarin and phenyl ring at 3 and 4 positions of diazete ring. Benzenoid protons of coumarin 'd' were observed between 7.60 to8.10 δ ppm in its characteristic pattern doublet-triplet-doublet. Protons 'e' of phenyl ring attached with diazete ring were observed at 6.90-7.45 δ ppm as a multiplate. All ^{1}H NMR data are consistent with proposed structure.

4.8.5 Elemental Analysis

Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Spectral data of synthesized compounds (AA 1-18)

4-hydroxy-3-(4-phenyl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one (AA-1)

Yellow solid; mp 230-232 ˚C;

IR (KBr): 3200, 1690 cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 14.04 (s, 1H, OH), 8.80 (d, 1H, CH), 8.67 (d, 1H, CH), 7.96 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.57 (t, 1H, Ar), 7.45-7.39 (m, 3H, Ar), 7.26-7.17 (m, 2H, Ar); **MS: m/z** = 292 (78, [M^+]), 264 (4, [M^+-N_2]), 188 (60), 121 (100); **Anal. Calcd** for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.84; H, 4.10; N, 9.55.

4-hydroxy-3-[4-(4-methylphenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (AA-2)

Yellow solid; mp 214-216 ˚C;

IR (KBr): 3190, 1690 cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 14.14 (s, 1H, OH), 8.95 (d, 1H, CH), 8.60 (d, 1H, CH), 8.05 (t, 1H, Ar), 7.69 (d, 2H, Ar), 7.67 (t, 1H, Ar), 7.64-7.60 (m, 4H, Ar), 2.42 (s, 3H, CH_3); **MS: m/z** = 306 (87, [M^+]), 278 (4, [M^+-N_2]), 188 (56), 121 (100); **Anal. Calcd** for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, C, 70.53; H, 4.69; N, 9.16.

4-hydroxy-3-[4-(4-methoxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (AA-3)

Yellow solid; mp 206-208 ˚C;

IR (KBr): 3140, 1716 cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 14.07 (s, 1H, OH), 8.86 (d, 1H, CH), 8.70 (d, 1H, CH), 8.02 (t, 1H, Ar), 7.73 (d, 2H, Ar), 7.62 (t, 1H, Ar), 7.31-7.23 (m, 2H, Ar), 7.00-6.98 (m, 2H, Ar), 3.86 (s, 3H, OCH_3); **MS: m/z** = 322 (96, [M^+]), 294 (3, [M^+-N_2]), 188 (35), 134 (100); **Anal. Calcd** for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.01; H, 4.34; N, 8.74.

3-[4-(3,4-dimethoxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (AA-4)

Yellow solid; mp 218-220 ˚C;

IR (KBr): 3210, 1699 cm^{-1}; **MS: m/z** = 352 (M^+); **Anal. Calcd** for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.76; H, 4.54; N, 7.96.

3-[4-(2,5-dimethoxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (AA-5)

Yellow solid; mp 210-212 ˚C;

IR (KBr): 3200, 1690, 1654, cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 14.07 (s, 1H, OH), 8.96 (d, 1H, CH), 8.90 (d, 1H, CH), 8.03 (t, 1H, Ar), 7.91 (d, 2H, Ar), 7.62 (t, 1H, Ar), 7.44 (t, 1H, Ar), 7.30 (t, 1H, Ar); 7.26 (t, 1H, Ar), 3.88 (s, 6H, OCH_3); **MS: m/z** = 352 (M^+); **Anal. Calcd** for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.78; H, 4.52; N, 7.93.

3-[4-(2-chlorophenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (AA-6)

Yellow solid; mp 212-214 ˚C;

IR (KBr): 3221, 1702 cm^{-1}; **MS: m/z** = 326 (M^+); **Anal. Calcd** for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.47; H, 3.33; N, 8.54.

3-[4-(3-chlorophenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (AA-7)

Yellow solid; mp 217-219 ˚C;

IR (KBr): 3180, 1715 cm^{-1}; **MS: m/z** = 326 (M^+); **Anal. Calcd** for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.53; H, 3.35; N, 8.60.

3-[4-(4-chlorophenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (AA-8)

Yellow solid; mp 224-226 ˚C;

IR (KBr): 3240, 1717 cm^{-1}; **MS: m/z** = 326 (M^+); **Anal. Calcd** for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.46; H, 3.37; N, 8.54.

3-[4-(4-fluorophenyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (AA-9)

Yellow solid; mp 206-208 ˚C;

IR (KBr): 3088, 1716 cm^{-1}; **MS: m/z** = 310 (M^+); **Anal. Calcd** for $C_{17}H_{11}FN_2O_3$: C, 65.81; H, 3.57; N, 9.03. Found: C, 65.84; H, 3.56; N, 9.01.

4-hydroxy-3-[4-(2-hydroxyphenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (AA-10)

Yellow solid; mp 210-212 ˚C;

IR (KBr): 3400, 3259, 1696 cm^{-1}; **MS: m/z** = 308 (M^+); **Anal. Calcd** for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.23; H, 3.91; N, 9.06.

4-hydroxy-3-[4-(3-nitrophenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (AA-11)

Yellow solid; mp 223-225 ˚C;

IR (KBr): 3565, 1693 cm^{-1}; **MS: m/z** = 337 (M^+); **Anal. Calcd** for $C_{17}H_{11}N_3O_5$: C, 60.54; H, 3.29; N, 12.46. Found: C, 60.55; H, 3.29; N, 12.43.

4-hydroxy-3-[4-(4-nitrophenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (AA-12)
Yellow solid; mp 214-216 ˚C;
IR (KBr): 3490, 1697 cm^{-1}; **MS: m/z** = 337 (M^+); **Anal. Calcd** for $C_{17}H_{11}N_3O_5$: C, 60.54; H, 3.29; N, 12.46. Found: C, 60.50; H, 3.25; N, 12.44.

4-hydroxy-3-[4-(2-nitrophenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (AA-13)
Yellow solid; mp 224-226 ˚C;
IR (KBr): 3423, 1702 cm^{-1}; **MS: m/z** = 337 (M^+); **Anal. Calcd** for $C_{17}H_{11}N_3O_5$: C, 60.54; H, 3.29; N, 12.46. Found: C, 60.50; H, 3.29; N, 12.47.

4-hydroxy-3-[4-(3-bromophenyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (AA-14)
Yellow solid; mp 216-218 ˚C;
IR (KBr): 3211, 1686 cm^{-1}; **MS: m/z** = 371 (M^+); **Anal. Calcd** for $C_{17}H_{11}BrN_2O_3$: C, 55.01; H, 2.99; N, 7.55. Found: C, 55.05; H, 2.97; N, 7.53.

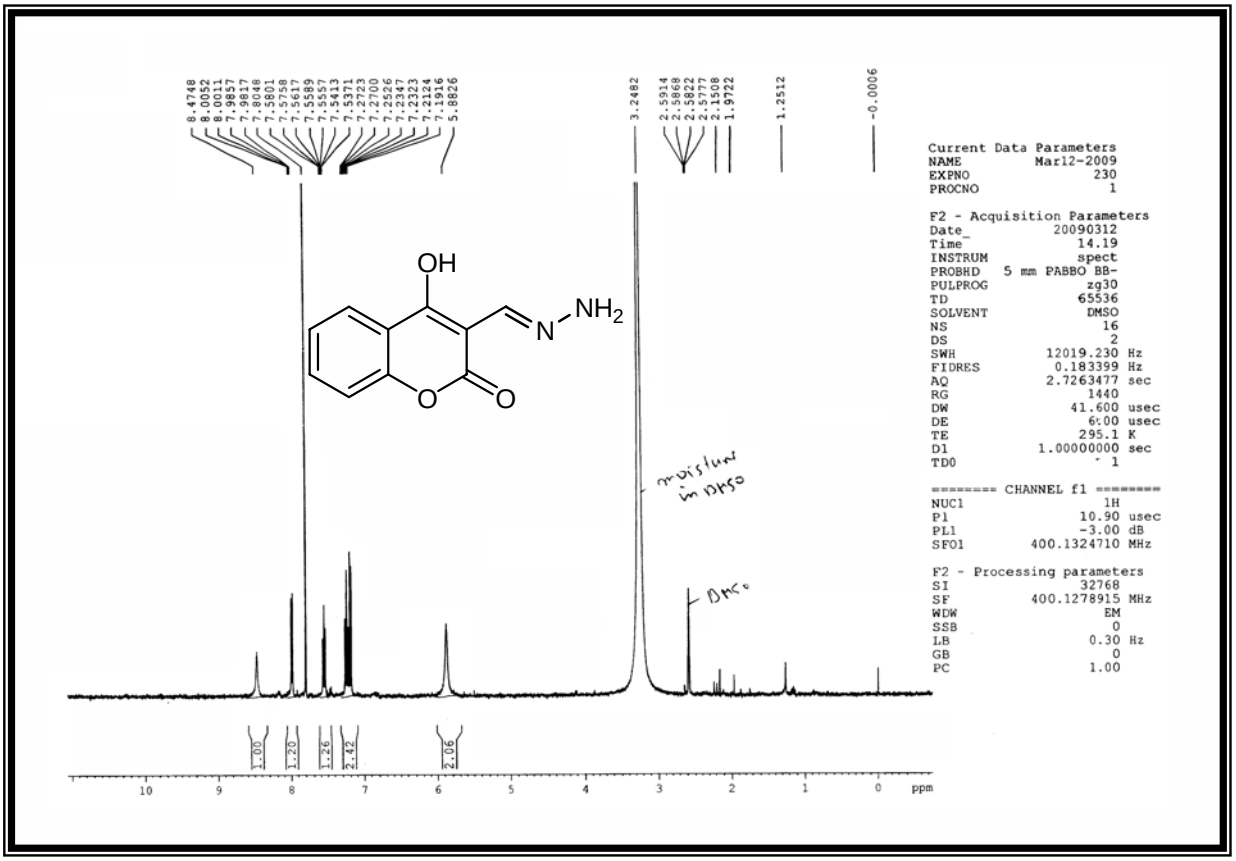
3-{4-[4-(dimethylamino)phenyl]-3,4-dihydro-1,2-diazet-3-yl}-4-hydroxy-2*H*-chromen-2-one (AA-15)
Yellowish red solid; mp 204-206 ˚C;
IR (KBr): 3209, 1719 cm^{-1}; **MS: m/z** = 335 (M^+); **Anal. Calcd** for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.02; H, 5.14; N, 12.50.

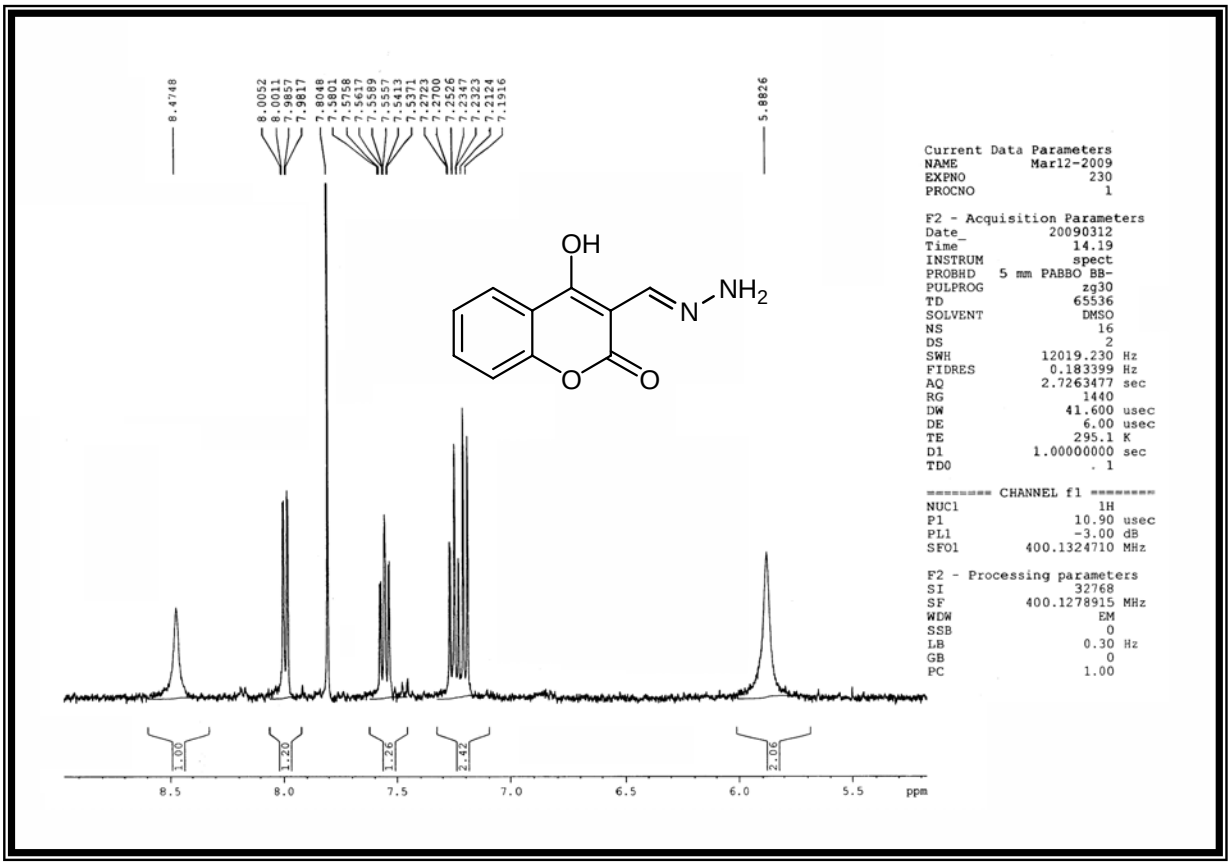
4-hydroxy-3-(4-pyridin-3-yl-3,4-dihydro-1,2-diazet-3-yl)-2*H*-chromen-2-one (AA-16)
Yellow solid; mp 228-230 ˚C;**IR (KBr):** 3235, 1699 cm^{-1}; **MS: m/z** = 293 (M^+); **Anal. Calcd** for $C_{16}H_{11}N_3O_3$: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.51; H, 3.72; N, 14.36.

3-[4-(2-furyl)-3,4-dihydro-1,2-diazet-3-yl]-4-hydroxy-2*H*-chromen-2-one (AA-17)
Yellow solid; mp 214-216 ˚C;**IR (KBr):** 3266, 1689 cm^{-1}; **MS: m/z** = 282 (M^+); **Anal. Calcd** for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.92. Found: C, 63.90; H, 3.53; N, 9.89.

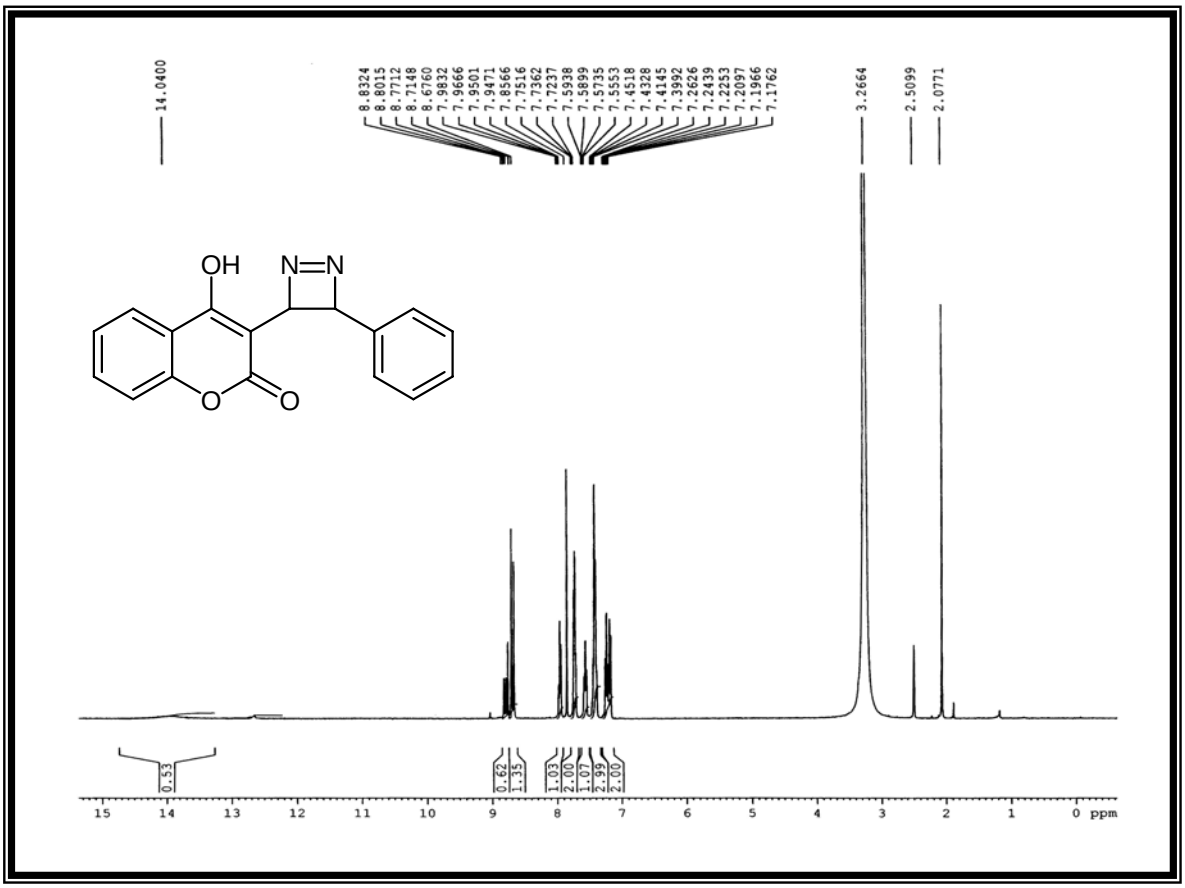
4-hydroxy-3-[4-(1-naphthyl)-3,4-dihydro-1,2-diazet-3-yl]-2*H*-chromen-2-one (AA-18)
Yellow solid; mp 227-229 ˚C;**IR (KBr):** 3253, 1717 cm^{-1}; **MS: m/z** = 342 (M^+); **Anal. Calcd** for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.12; N, 8.18. Found: C, 73.35; H, 4.19; N, 8.03.

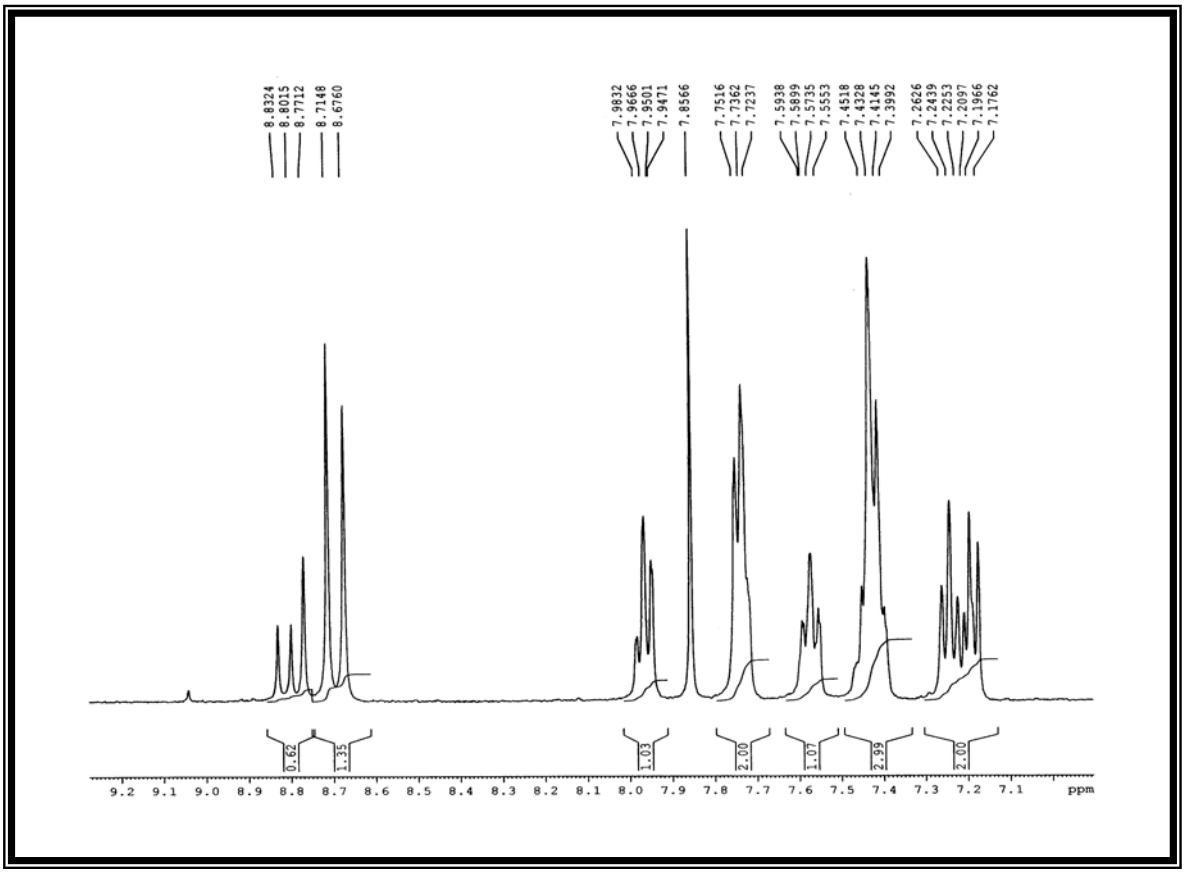
^{1}H NMR spectrum of Hydrazone



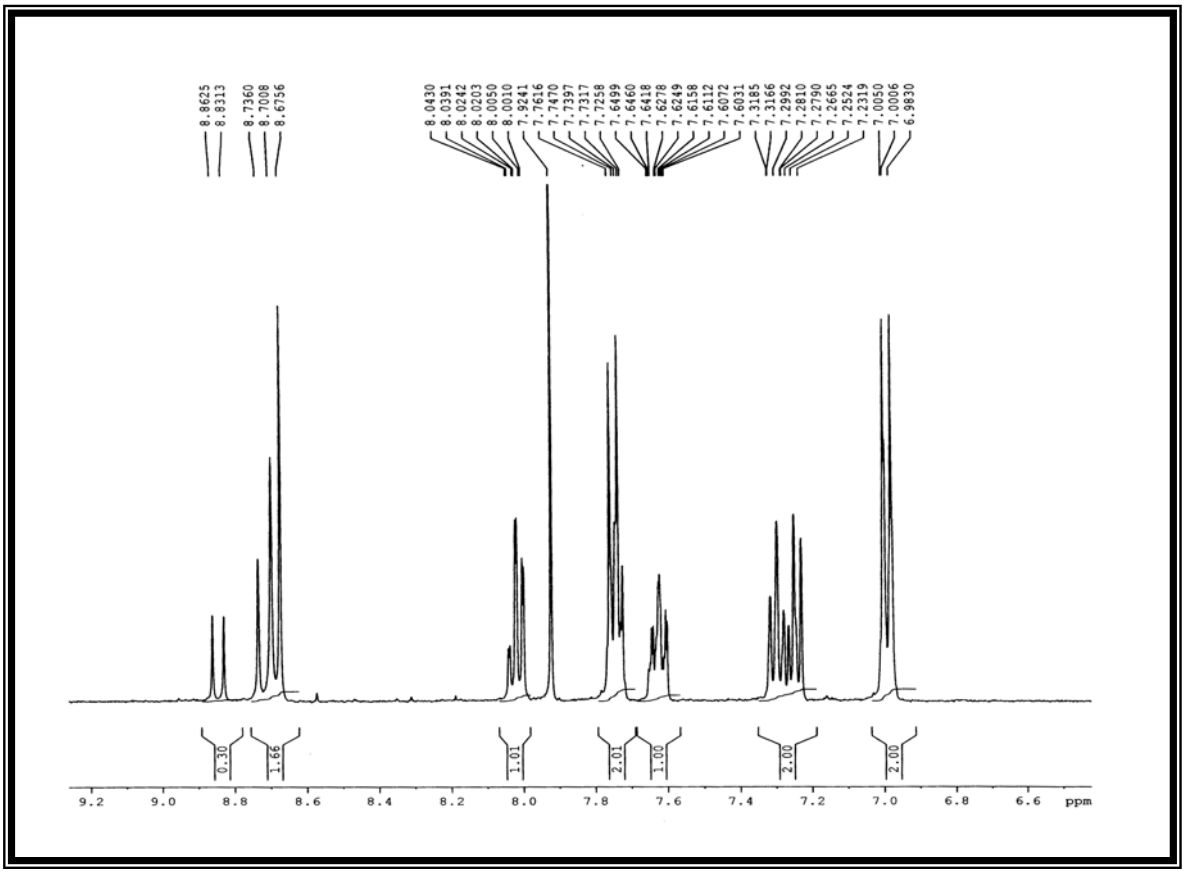


^{1}H NMR spectrum of AA-1

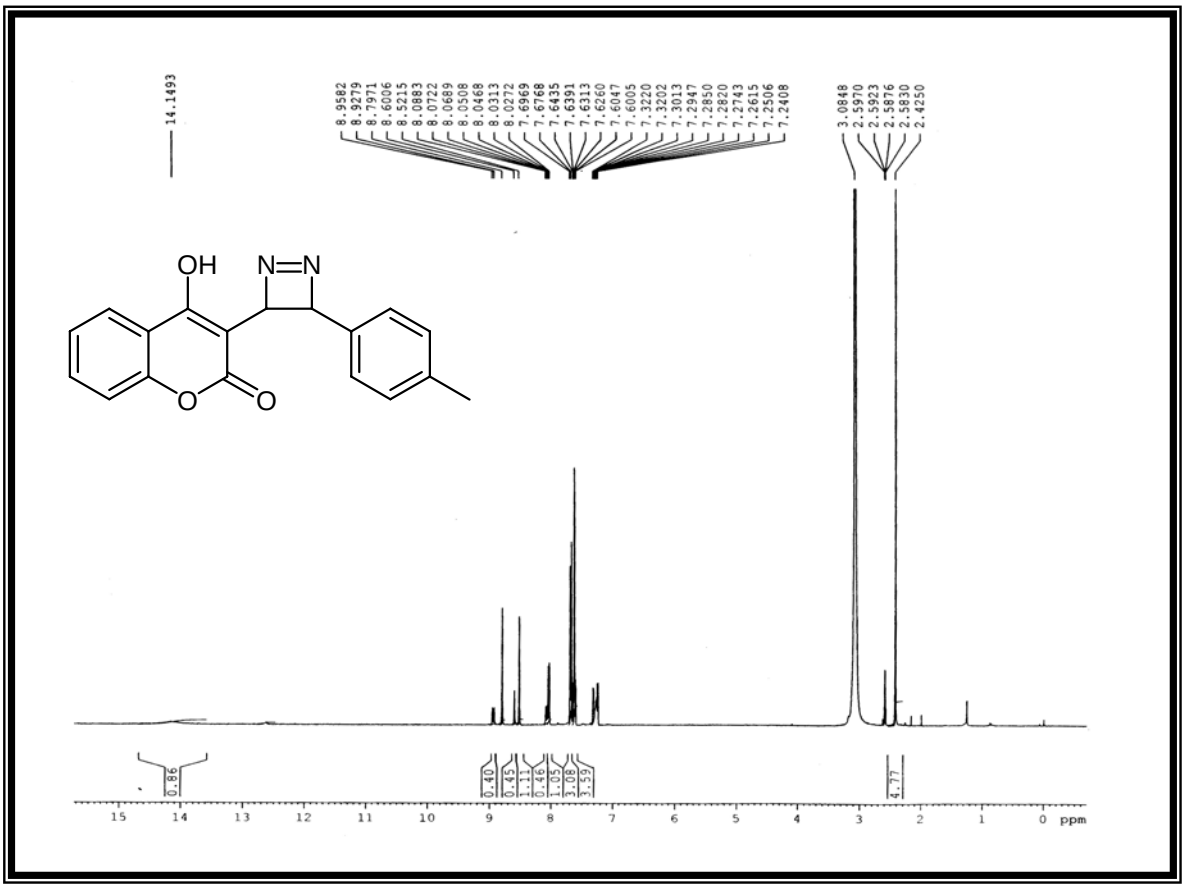


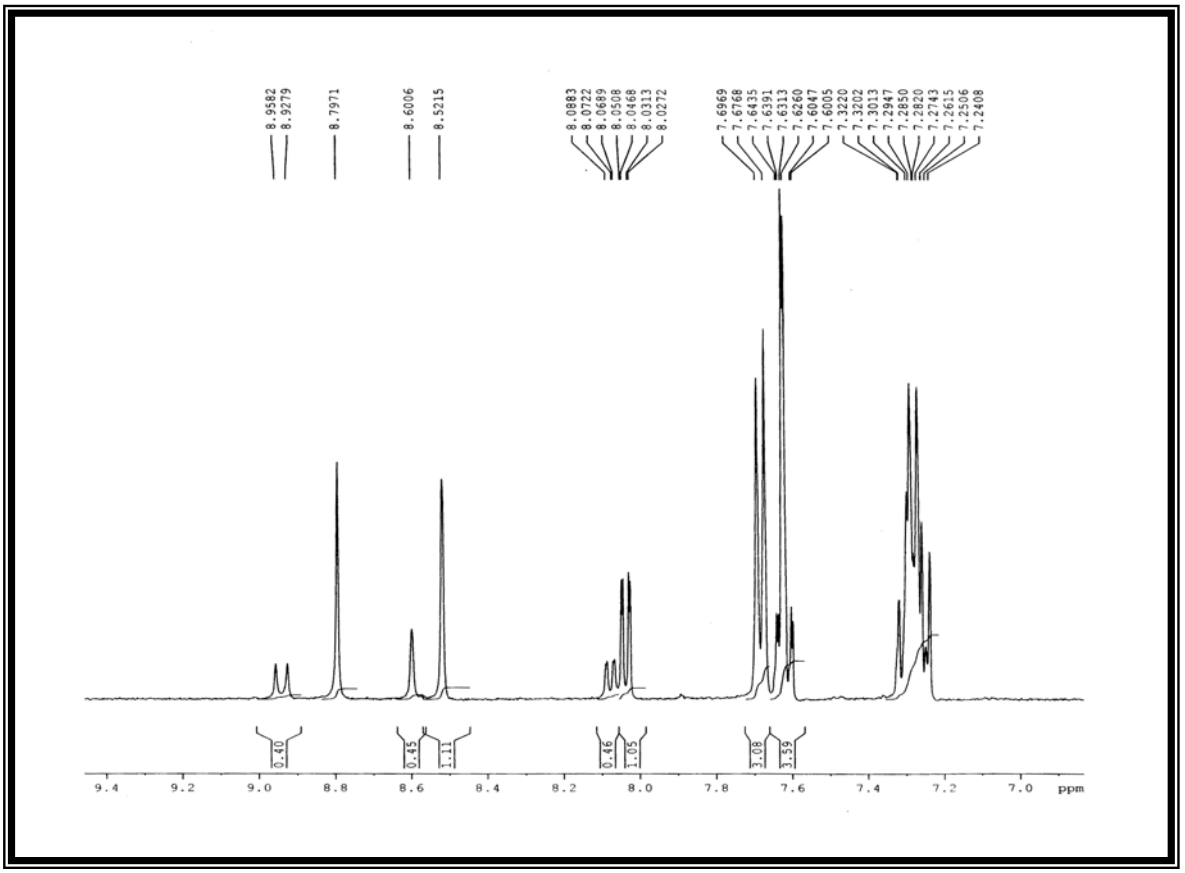


^{1}H NMR spectrum of AA-3

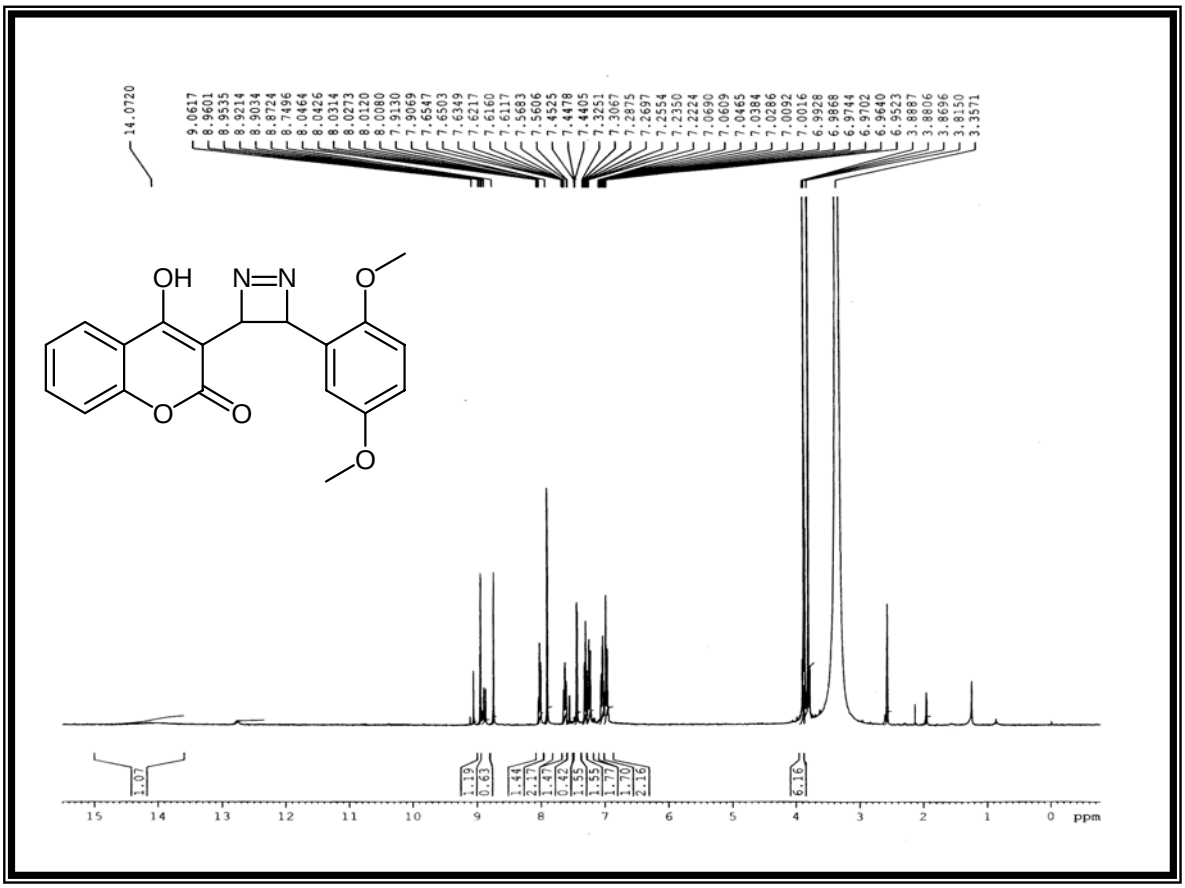


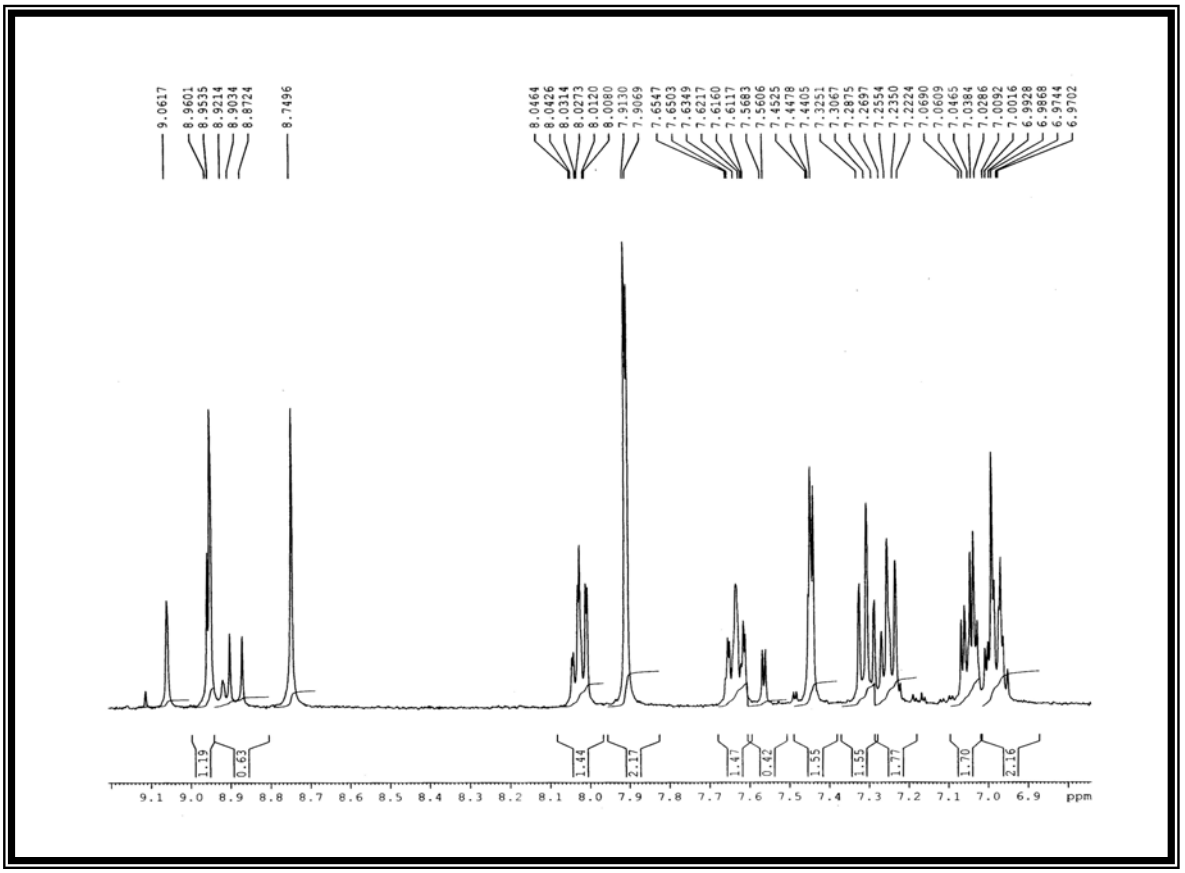
^{1}H NMR spectrum of AA-2



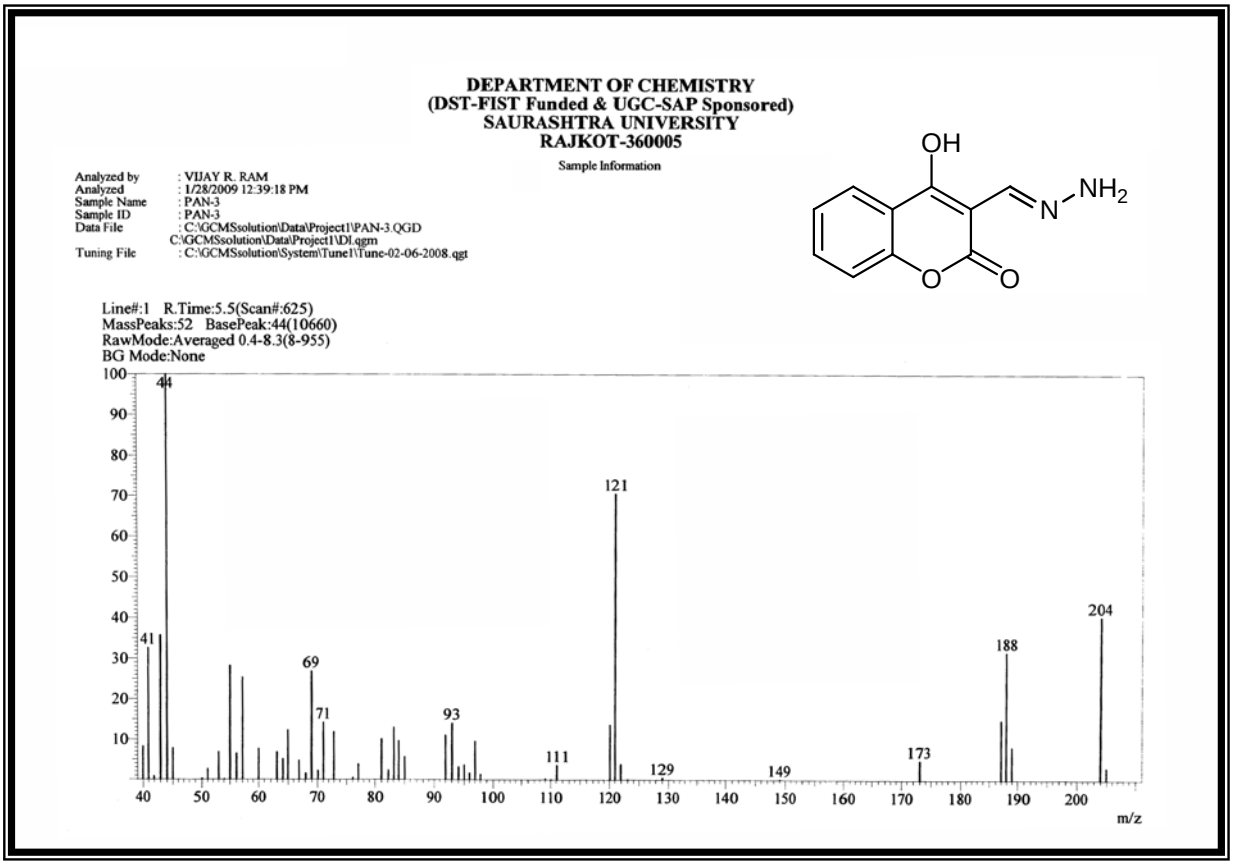


^{1}H NMR spectrum of AA-5

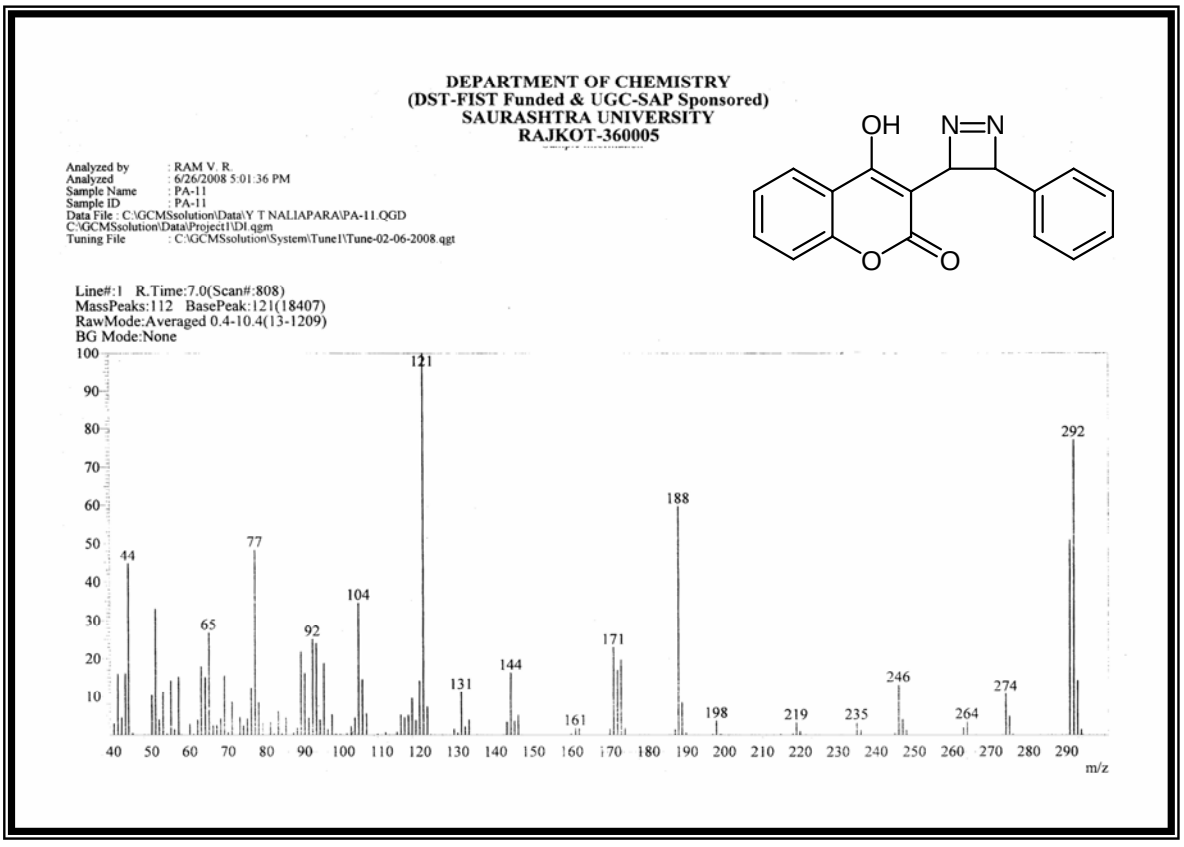




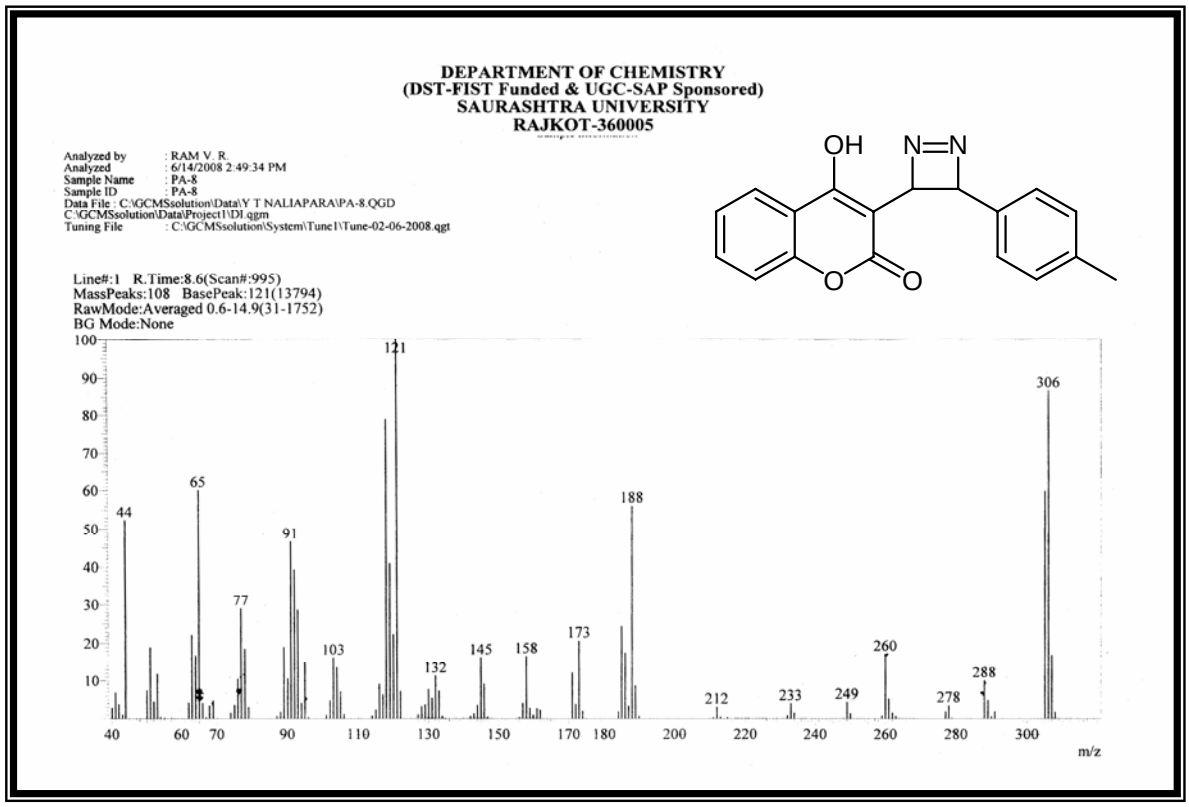
Mass Spectrum of Hydrazone



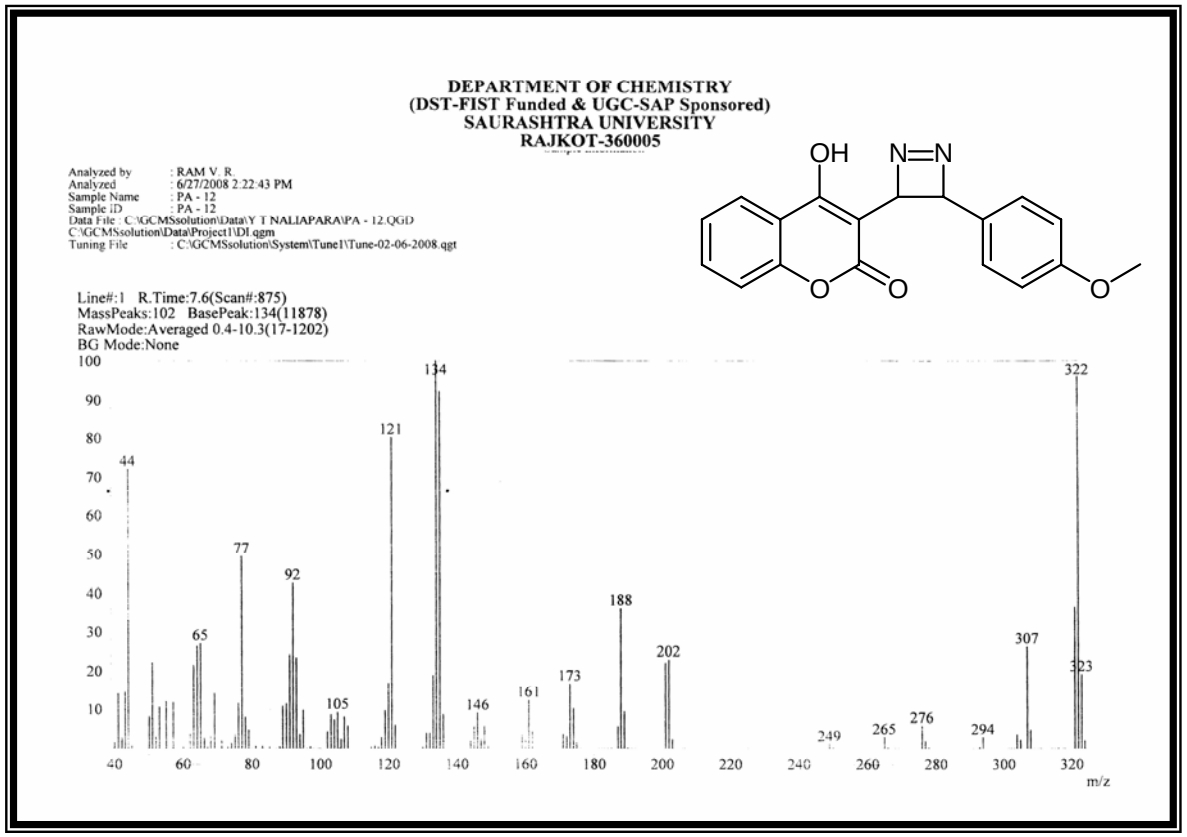
Mass Spectrum of AA-1



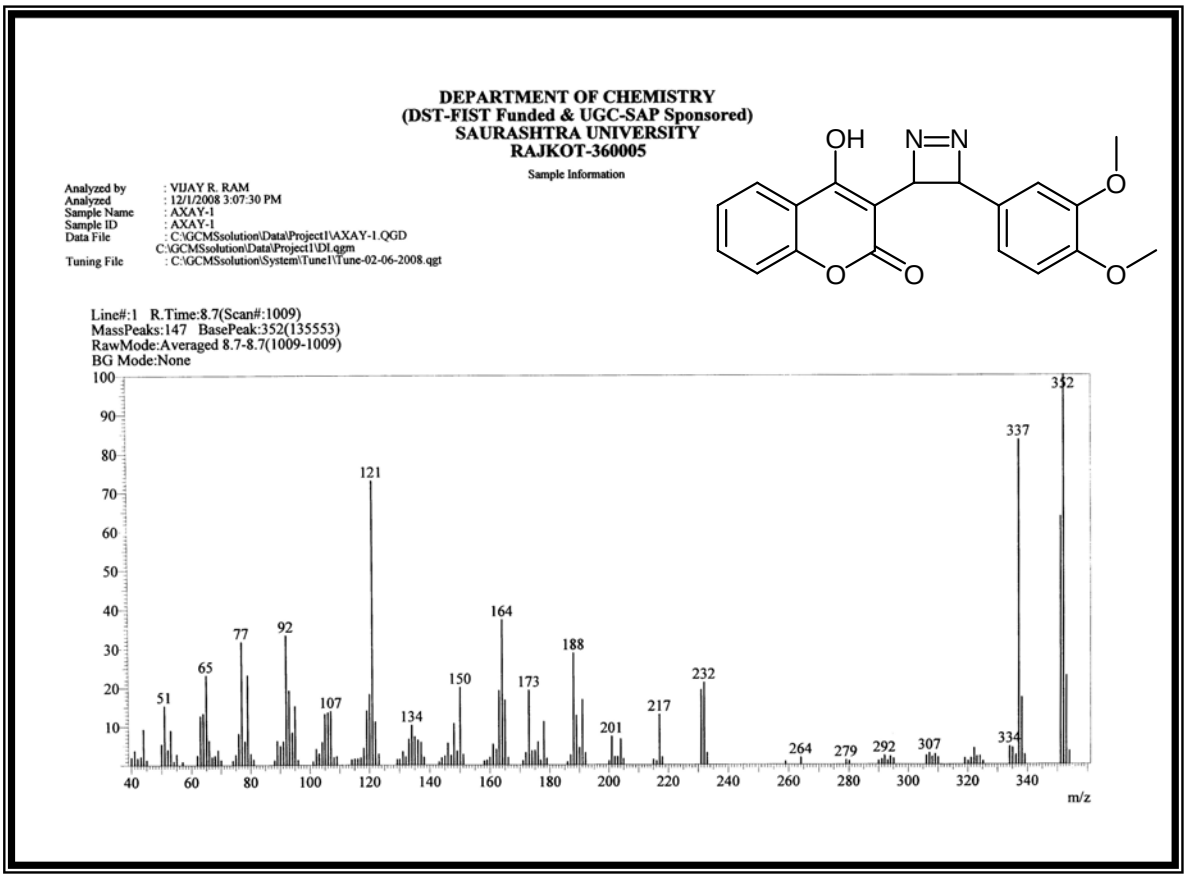
Mass Spectrum of AA-2



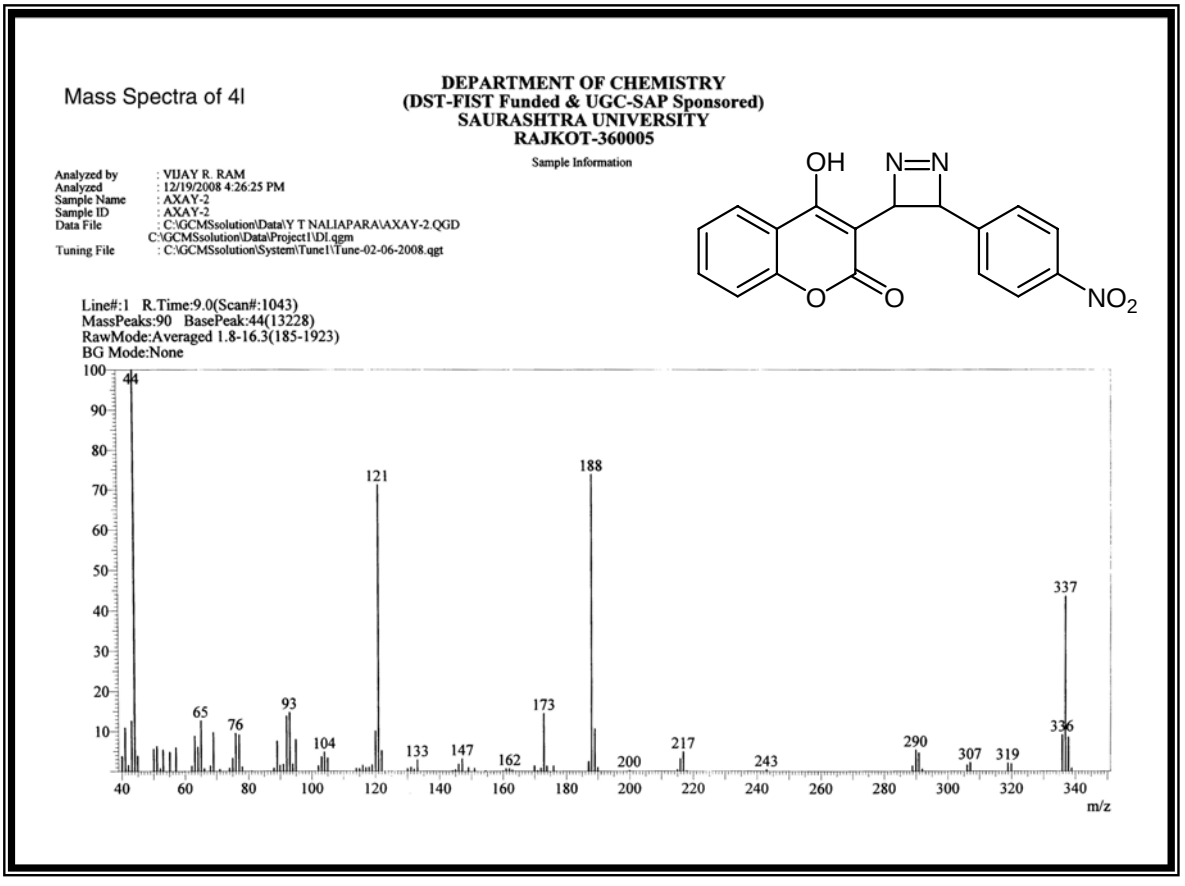
Mass Spectrum of AA-3



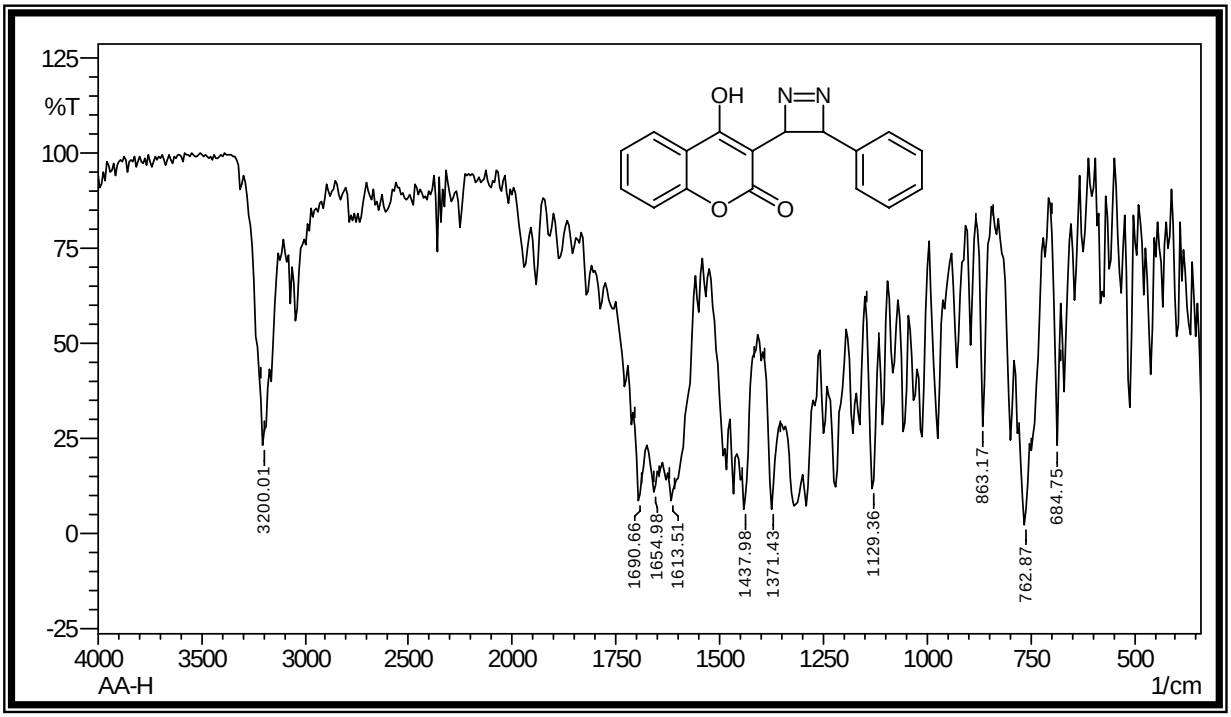
Mass Spectrum of AA-4



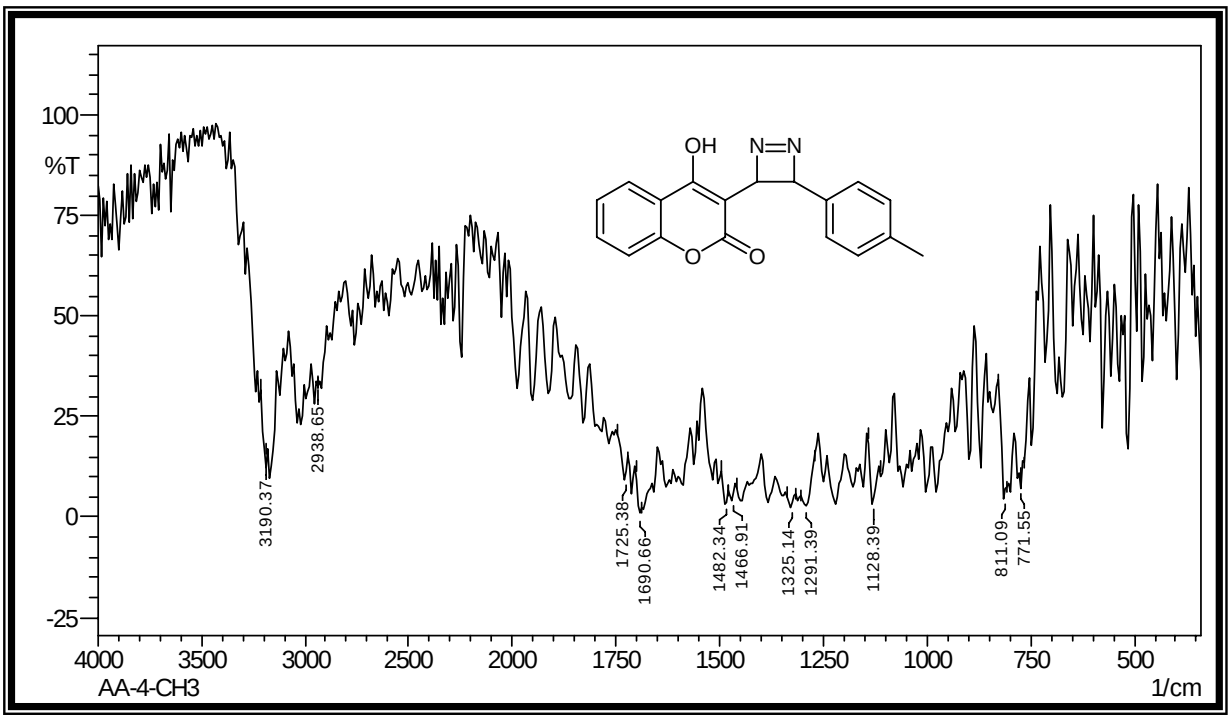
Mass Spectrum of AA-12



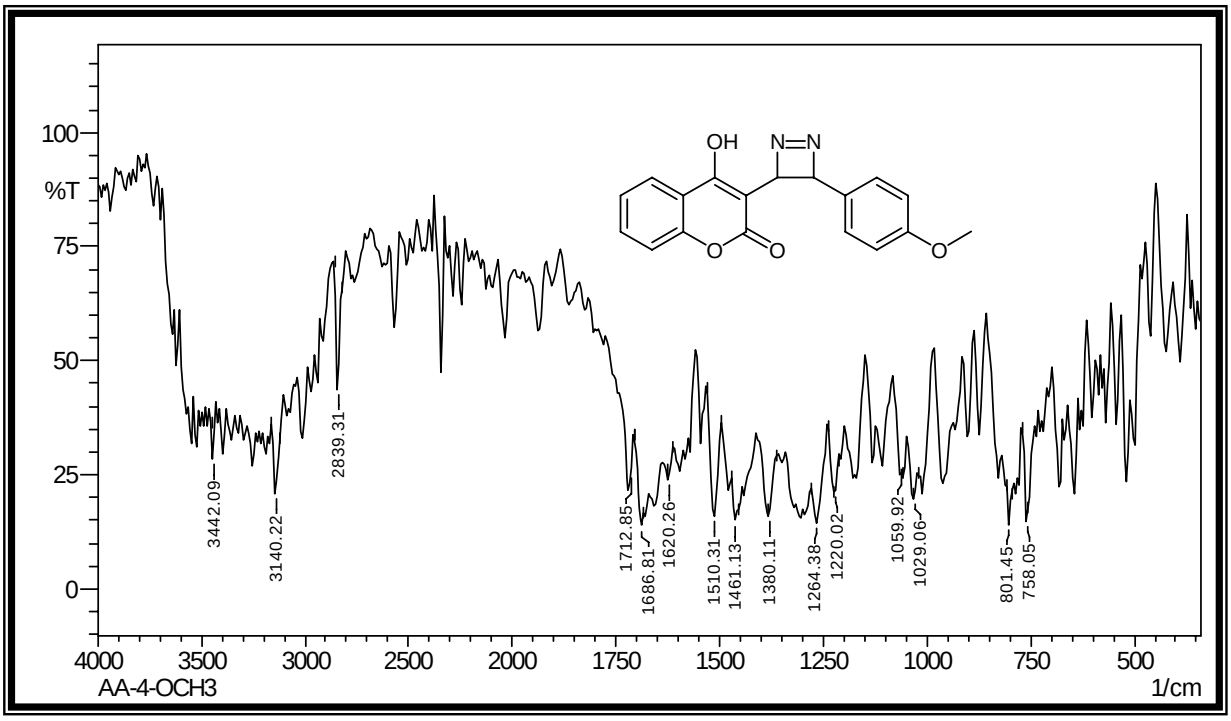
IR spectrum of AA-1



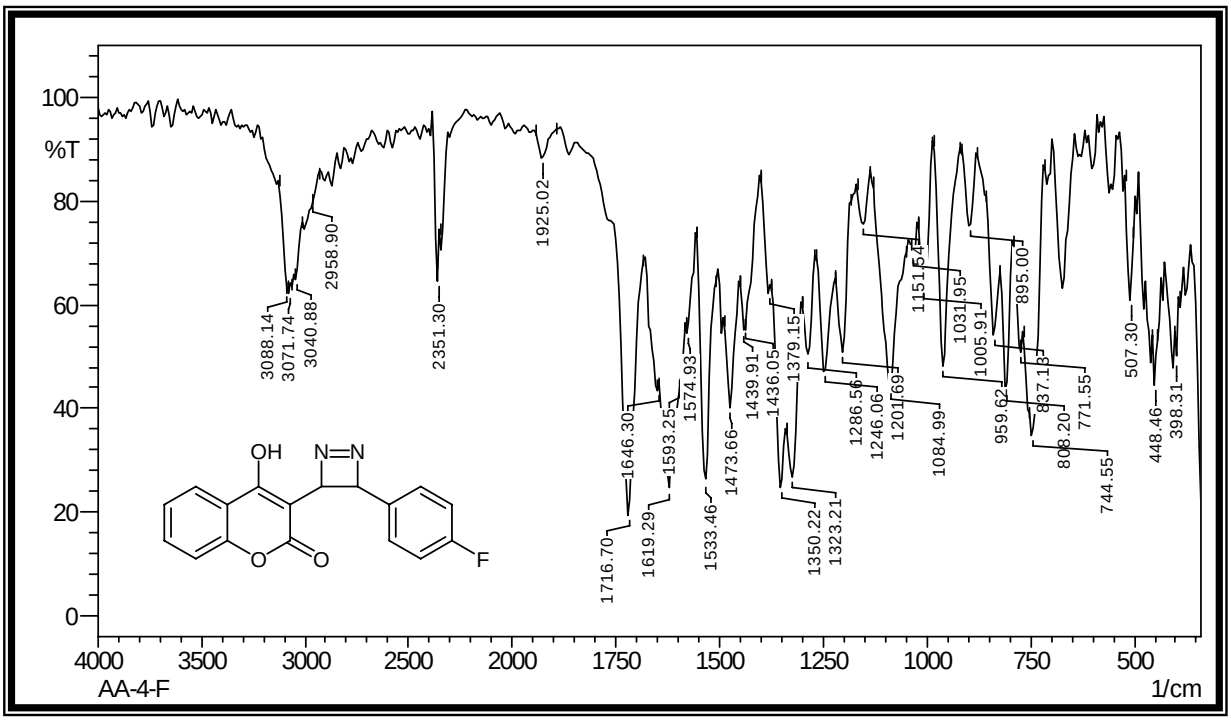
IR spectrum of AA-2



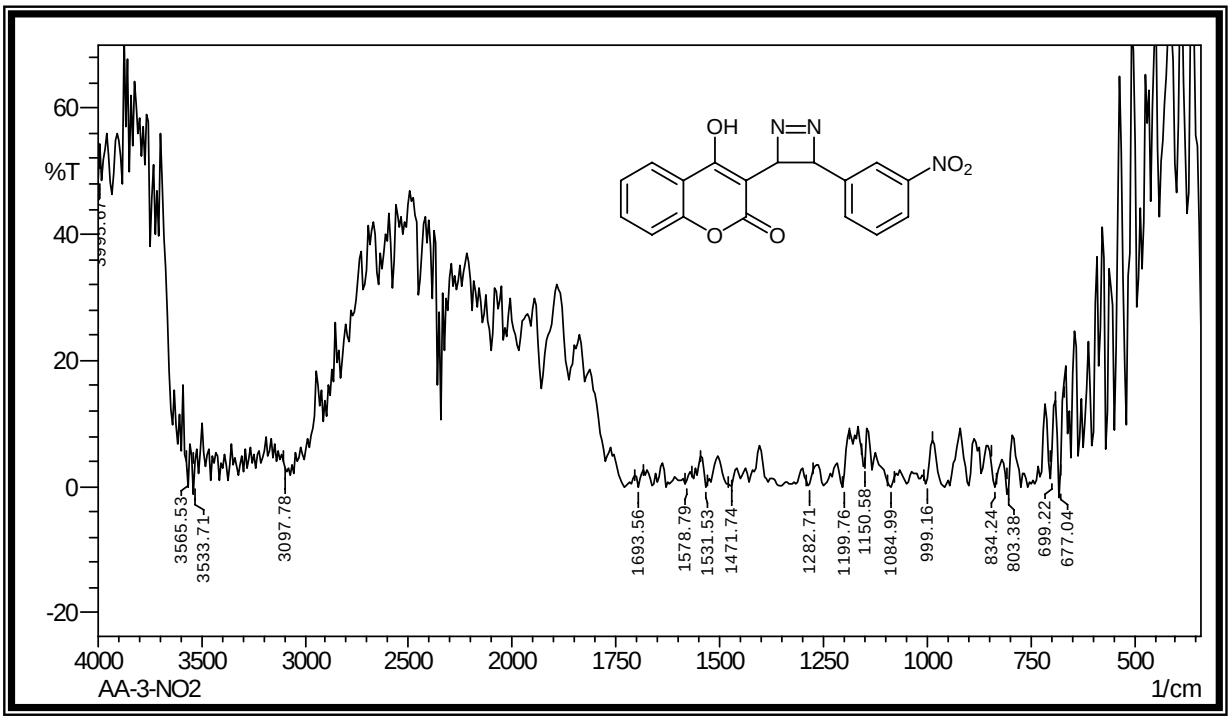
IR spectrum of AA-3



IR spectrum of AA-9



IR spectrum of AA-11



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Chapter 5

Synthesis and Characterization of Novel 3-(1-phenyl-4-thioxo-1,3 diazetidin-2-yl)-2*H*-chromene-2,4(3*H*)-dione Derivatives

Chapter 5

Synthesis and characterization of novel 3-(1-phenyl-4-thioxo-1,3-diazetidin-2-yl)-2*H*-chromene-2,4(3*H*)-dione derivatives

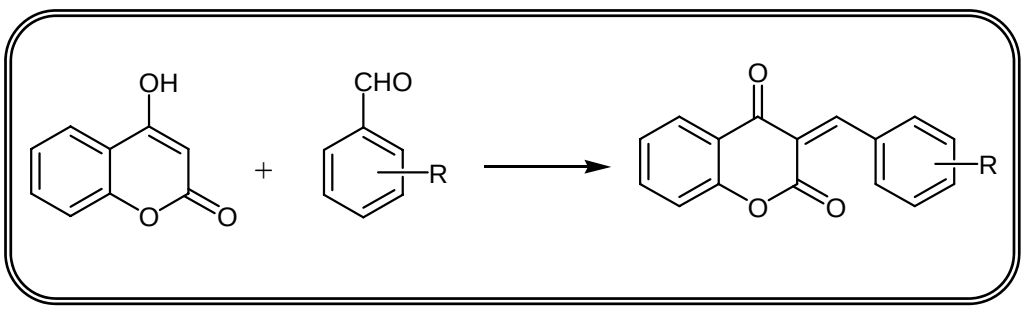
5.1 Introduction to chromene-2,4-dione

In earlier chapter, it was observed that coumarins from a part of many heterocyclic compounds with important pharmacological activity and are being evaluated for potential biological activities. Since coumarins are active at C-3 position, these moieties easily undergo C-3 substitution reactions.

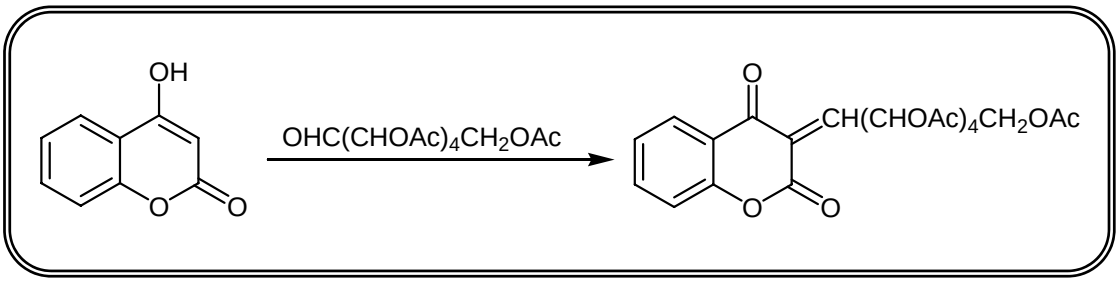
Biological systems easily accept the chromene nucleus of coumarin as against its tautomeric chromane and hence were studied extensively as antimicrobial.[1-3]

Antimicrobial and anti-tubercular activity of 2,4-chromane dione were studied and established by Chavda and Shah et al.[4] They observed that the introduction of electron with-drawing group like nitro and fluoro at the benzenoid part of chromane may help in increasing the potency at much lower concentration.

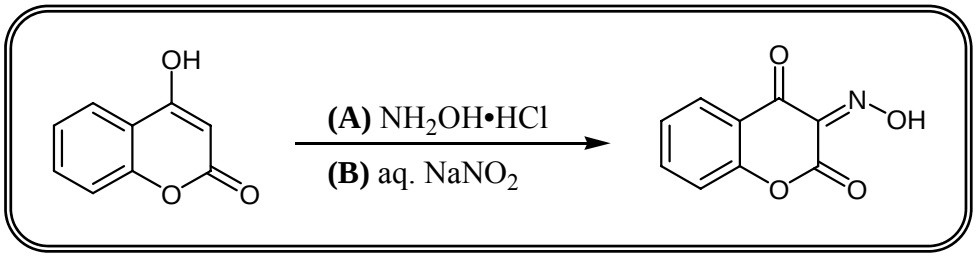
4-hydroxy coumarins frequently react with aromatic aldehydes to give 3-benzylidene-2,4-chromandiones.[5-8]



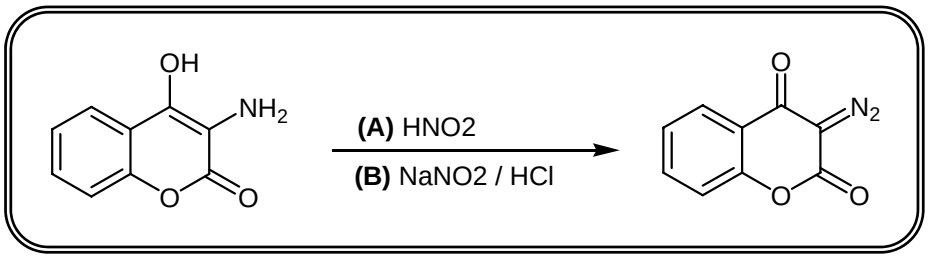
Similarly, reaction of 4-hydroxycoumarin with acetylated aldehydohexoses in ethanol for 24 hours gave 2,4-chromanedione as given below.[9]



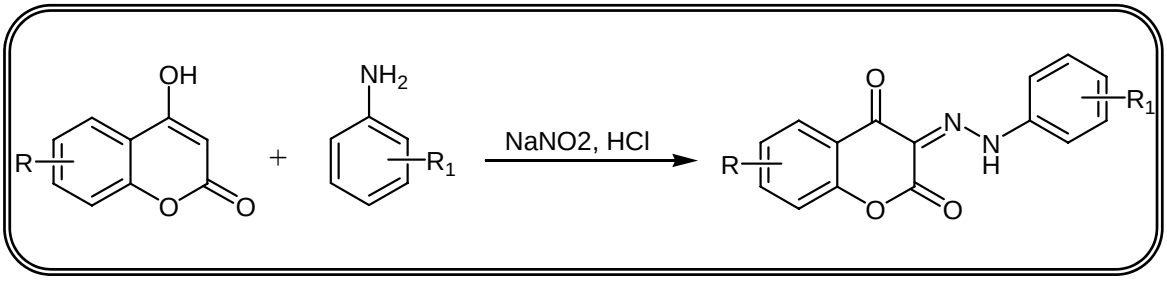
Reaction between 4-hydroxycoumarin and hydroxylamine hydrochloride gave corresponding 2,4-chromandione-3-oxime.[10] However, reaction of 4-hydroxycoumarin with sodium nitrite afforded 2,3,4-chromantrione-3-oxime which forms a silver salt.[11]



When 3-amino-4-hydroxycoumarin was reacted with nitrous acid gave 3-diazo-2,4-chromandione. The same product was also obtained in 72% yield when sodium nitrite in dilute hydrochloric acid was added to 3-amino-4-hydroxycoumarin.[12]

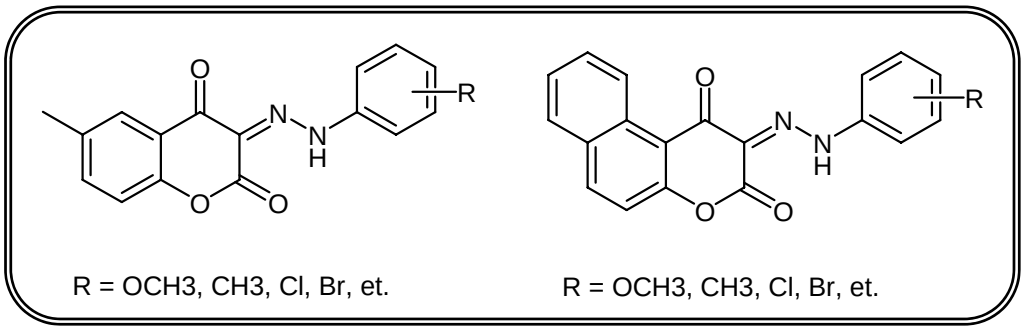


Treatment of substituted 4-hydroxycoumarin with diazotized anilines at temperature below 0°C gave 3-phenylhydrazone-2,3,4-chromantrione.[13]

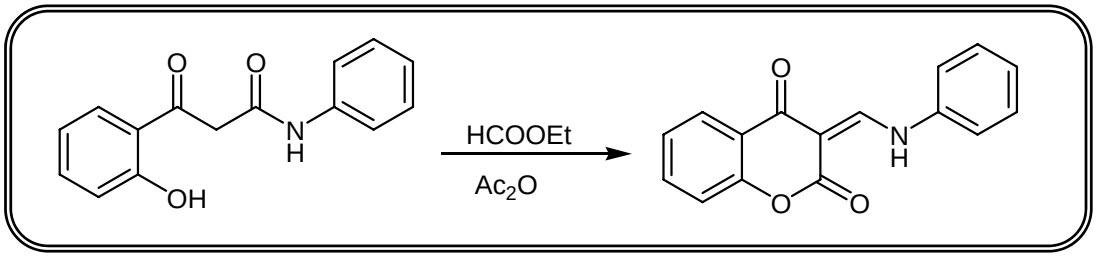


Sureja D.[14] synthesized 2,3,4-chromantrione phenylhydrazones by diazo coupling of 4-hydroxy-6-methyl coumarin with various arylamines. The compounds were tested for

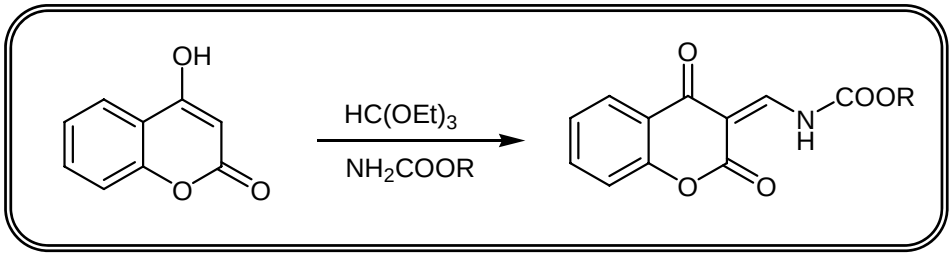
antitubercular activitiy and the results were very promising. In few cases, MIC was observed <12.5 μg/mg bearing 90% inhibition against $H_{37}Rv$ strain, when compared to Rifampicin (0.125 μg/mg).



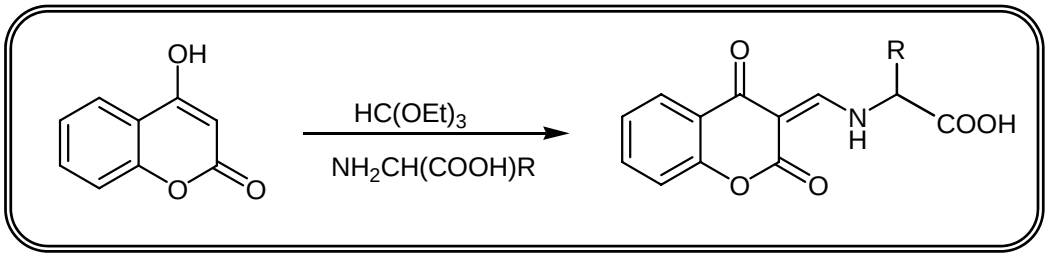
When a mixture of (2-hydroxy benzoyl) acetanilide, ethyl orthoformate and acetic anhydride was heated at 100–110 °C for 7 minutes, 3-anilinomethylene-2,4-chromandione was isolated in 44% yield.[15]



Hamdi and coworkers synthesized many new compounds N-(methylene-4-oxo-coumarinyl) caebamates by condensation of carbamates with 4-hydroxy coumarin in the presence of triethylorthoformate with good yields.[16]



Further, when 4-hydroxy coumarin reacted with an amino acid in the presence of excess triethyl orthoformate gave the compounds outlined as below with good yield. The amino acids like glycine, alanine, leucine, phenyl alanine, tyrosine, tryptophan, L-DOPA, serine, cysteine and glutamine were used.[17]



5.2 Introduction to 1,3-diazetidine

In four-membered heterocycles, the ring strain is less than in the corresponding three-membered compounds and is approximately equal to that found in cyclobutane. Nevertheless, ring-opening reactions forming acyclic products predominate. At the same time, analogy with the reactivity of the corresponding aliphatic compounds (ethers, thioethers, secondary and tertiary amines, imines) becomes more evident.

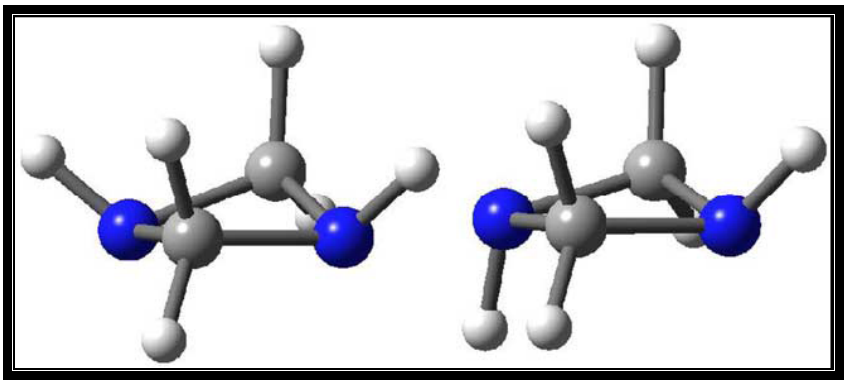
1,3-Diazetidines are a class of strained four membered ring azo compounds. Their properties remain largely unexplored presumably as a result of the difficulty of their synthesis. Even though a dozen diazetines are currently known. Despite the propensity for decomposition of diazetines to ultimately afford nitrogen and the corresponding alkene, diazetines are quite thermally robust.

According to the Huckel $(4n + 2)/4n$ rule, four-membered-ring compounds should be aromatic with 2 or 6π-electrons and antiaromatic with 4π-electrons.[18] Despite these predictions, few four-membered-ring 6π-systems are known. The instability of the 6π cyclobutadiene dianion has been attributed to the large negative charge per carbon atom[19] and more recently also to the strong 1,3-repulsive interactions in the π-system.[20,21] The isoelectronic neutral dioxetenes $(CHO)_2$ and diazetines $(CHNH)_2$ suffer less from electrostatic repulsions and might be expected to be more favorable. The structures of 1,3-diazetine, 1,2-diazetine, and diazabicyclobutane have already been studied at the MIND0/3 level by Minyaev and Minkin.[22]

Peter H. M. Budzelaar et al[23] reported that the lack of aromaticity of four-membered-ring 6π-heterocycles can be attributed to two main factors, viz., the strongly 1,2- and/or 1,3-

antibonding character of the higher occupied π-orbitals and the electronegativity difference between C and 0 or C and N. Both factors favor localization of π-electrons and ring-opening reactions. Presumably, 6π-aromaticity requires at least a five membered-ring system, where the nonbonded repulsions are much less severe.

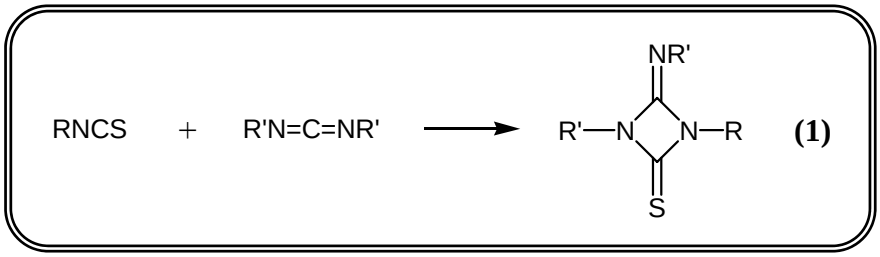
Kevin J. Gessner et al[24] had calculated some fundamental properties like geometries, vibrations, enthalpies and other energies of 1,3-diazitidine using Gaussian-X and two complete basis set of methods. Most of the bonding parameters are, again, unremarkable. However, for the trans isomer, the minimum-energy geometry is predicted to have a planar backbone, giving the molecule a nominal C_{2v} symmetry instead of the C_s symmetry of the puckered geometry. Because of this, the calculated dihedral angles that the hydrogen atoms make with the ring backbone are very different for these methods. The cis-1,3-diazetidine molecule has C_{2v} symmetry even when puckered. For the 1,3-diazetidine isomers the predicted enthalpies of formation are lower by 60–80 kJ/mol. The diazetidines produce less energy per mole of oxidant, but at about 530 kJ/mol O_2 they still produce more energy than methane on that basis. For 1,3-diazetidine, the NH groups are on opposite corners of the ring, so the effects on the proton affinity due to cis/trans isomerism should be minimized. Although the calculated proton affinity of the cis isomer is consistently higher that that of the trans isomer, it is only by 1–2 kJ/mol. Proton affinity calculations suggest that diazetidines will react strongly as bases.



The normal mode frequencies and corresponding vibrational assignments of 1,3-dichloro-1,3-diazetidine-2,4-dione were examined theoretically using the Gaussian 98 set of quantum chemistry codes by James O. Jensen[25] Crystal structures of 1,3-dichloro-1,3-diazetidine-2,4-dione have been determined by X-ray crystallography, and new infrared and Raman data of

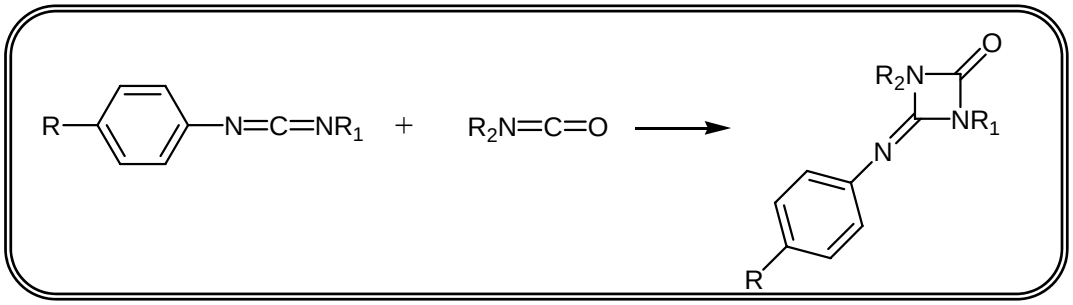
that have been recorded in the solid state, leading to revised and complete fundamental frequency assignments by Ferdinand Belaj[26] 1,3-Diazetidine show a planar ring with a trans-configuration of the chlorine substituent. The angles between the C-N-C plane and the exocyclic N-Cl bond are 32.5°.

H. Ulrich et al[27] found that 2-imino-4-thioxo-1,3-diazetidines (1) are formed in quantitative yields when *iso*thiocyanates activated by an electron-withdrawing substituents (such as p-nitrophenyl or alkyl- and arylsulfonyl) and carbodiimides are mixed at room temperature in a molar ratio of 1 : 1 with *or* without solvent. The reaction can be followed by infrared spectroscopy by the disappearance of the absorptions in the cumulative double bond region (4.7-4.9 μ**)** and by the appearance of a new C=N absorption at 6.05 μ in the case of (**1a**) and (**1b**), at 6.19 μ in the case of (**1c**) and at 6.25 μ in the case of (**1d**).

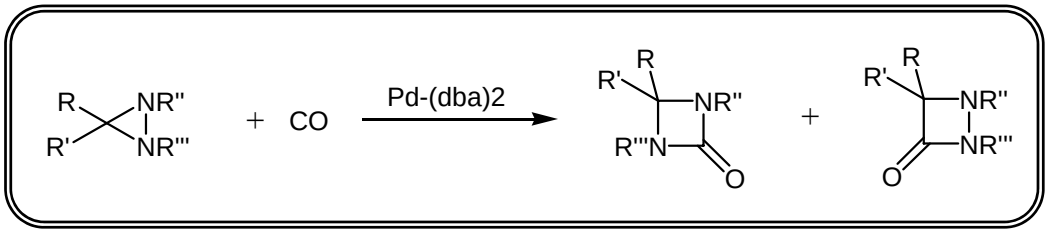


(**1a**)	R = p-Nitrophenyl,	R' = Isopropyl,	m.p. 51-52°C
(**1b**)	R = p-Nrtrophenyl,	R' = Cyclohexyl,	m.p. 73-75°C
(**1c**)	R = Methylsulfonyl,	R' = Phenyl,	m.p. 173-174°C
(**1d**)	R = p-Tolylsulfonyl,	R' = Tolyl,	m.p. 128-129°C

Henri Ulrich et al[28] reprted that *N*-alkyl-*N*-arylcarbodiimides add alkyl and aryl isocyanates to the *N*-alkyl substituted CN double bond to yield 4-arylimino1,3-diazetidine-2-ones.

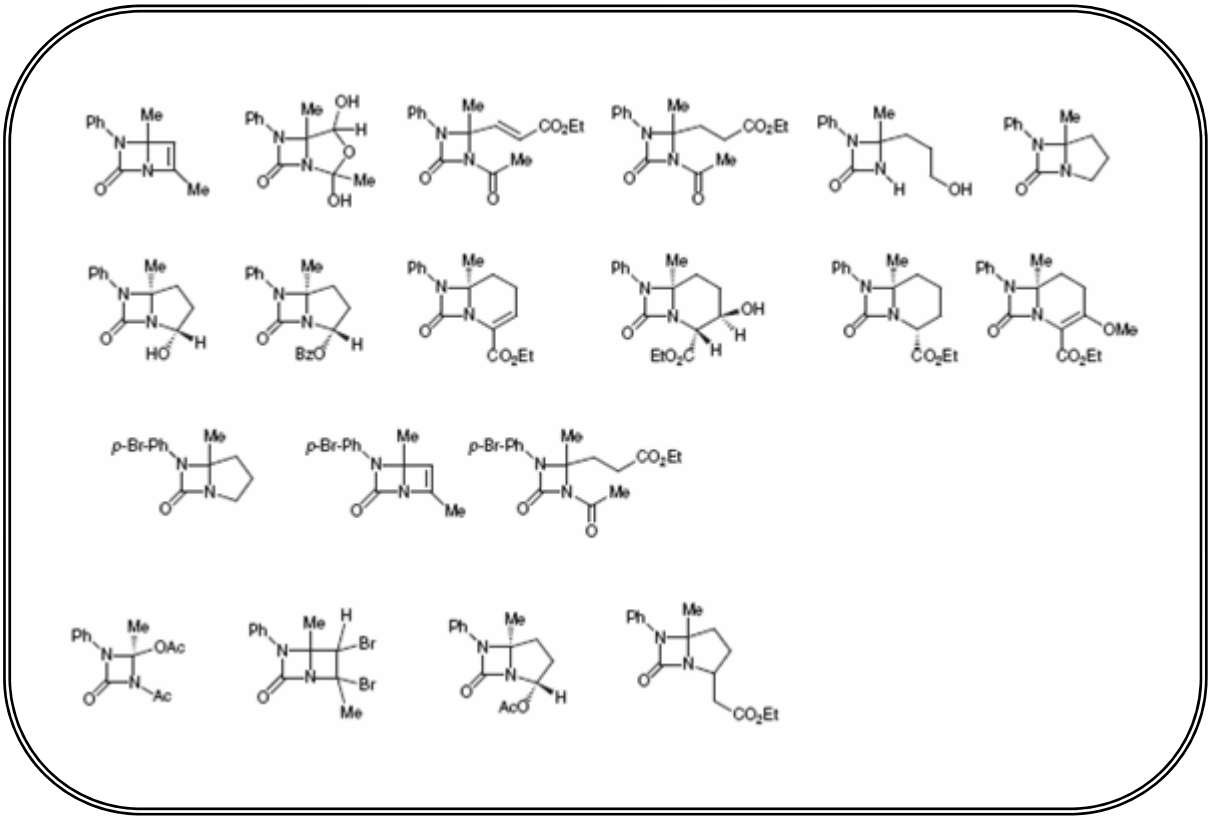


Howard Alper et al[29] reported the preparation of 1,3-diazetidinones by bis(dibenzylideneacetone)palladium(0)-catalyzed carbonylation of diaziridines having one substituent attached to the ring carbon atom. This regiospecific insertion into the nitrogen-nitrogen bond also occurs for 3,3-disubstituted diaziridines, provided one uses stoichiometric quantities of cobalt carbonyl.

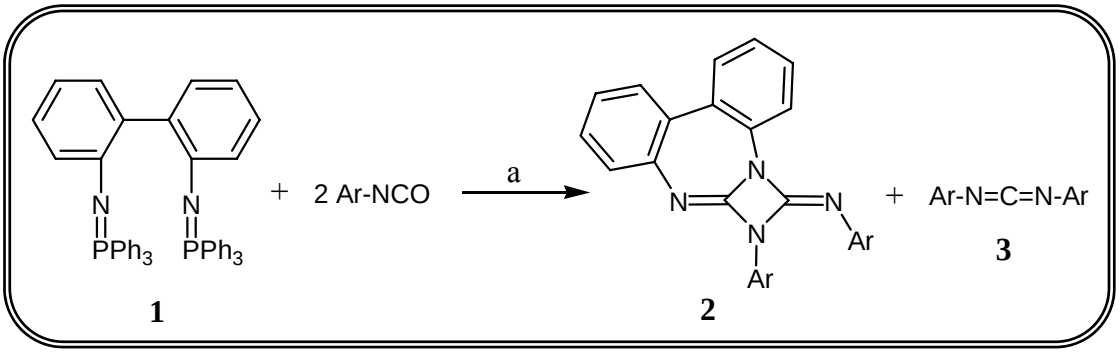


Yasunori Aoyama et al[30] demonstrated that the 1,3-diazetidine-2,4-dione nucleus is effective as a scaffold for the inhibition of serine proteases.

P. S. Chandrakala et al[31] synthesized some mono- and bi-cyclic 1,3-diazetidin-2-ones (aza-β-lactams), and evaluated as non-natural analogues of β-lactams.



Mateo Alajarın et al[32] reported that Aza-Wittig reactions of bis(iminophosphorane) **1** derived from 2,2'-diazidobiphenyl with aromatic isocyanates provides dibenzo[*d*,*f*]-1,3-diazetidino[1,2-*a*]diazepine derivatives **2** in moderate yields.



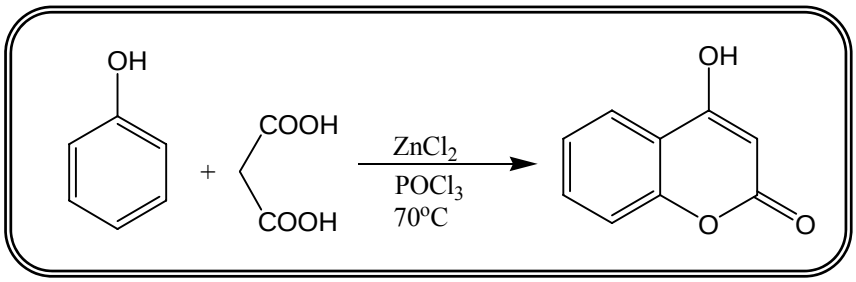
5.3 Current work

In view of marked importance of chromene core and four membered nitrogen heterocycles in the field of vast area of organic and medicinal chemistry, four membered ring 1,3-diaztedine-2-thione is constructed at 3 position of chromene 2,4-dione moiety. The precursor 4-hydroxy coumarin was synthesized as per mentioned in literature methods. A mixture of 4-hydroxy coumarin and triethyl orthoformate with catalytic amount of *p*-toluene sulfonic acid (PTSA) was subjected to microwave irradiation to prepare 3-ethoxymethylene-3*H*-2,4-dione. The hydrolysis of 3-ethoxymethylene-3*H*-2,4-dione with K_2CO_3 results into 4-hydroxy coumarin-3-carbaldehyde.[33] Subsequently 3-ethoxymethylene-3*H*-2,4-dione was reacted with various *N*-aryl thiourea in chloroform at reflux temperature for 30 minutes which results into 3-(1-aryl-4-thioxo-1,3-diazetidin-2-yl)-2*H*-chromene-2,4(3*H*)-dione via intramolecular cyclization. The plausible mechanism for the cyclization is shown in section 5.5. All the synthesized compounds were characterized by IR, Mass, and ^{1}H NMR discussed in section 5.8. The anti viral screening of the synthesized compounds is under investigation.

5.4 Reaction Scheme

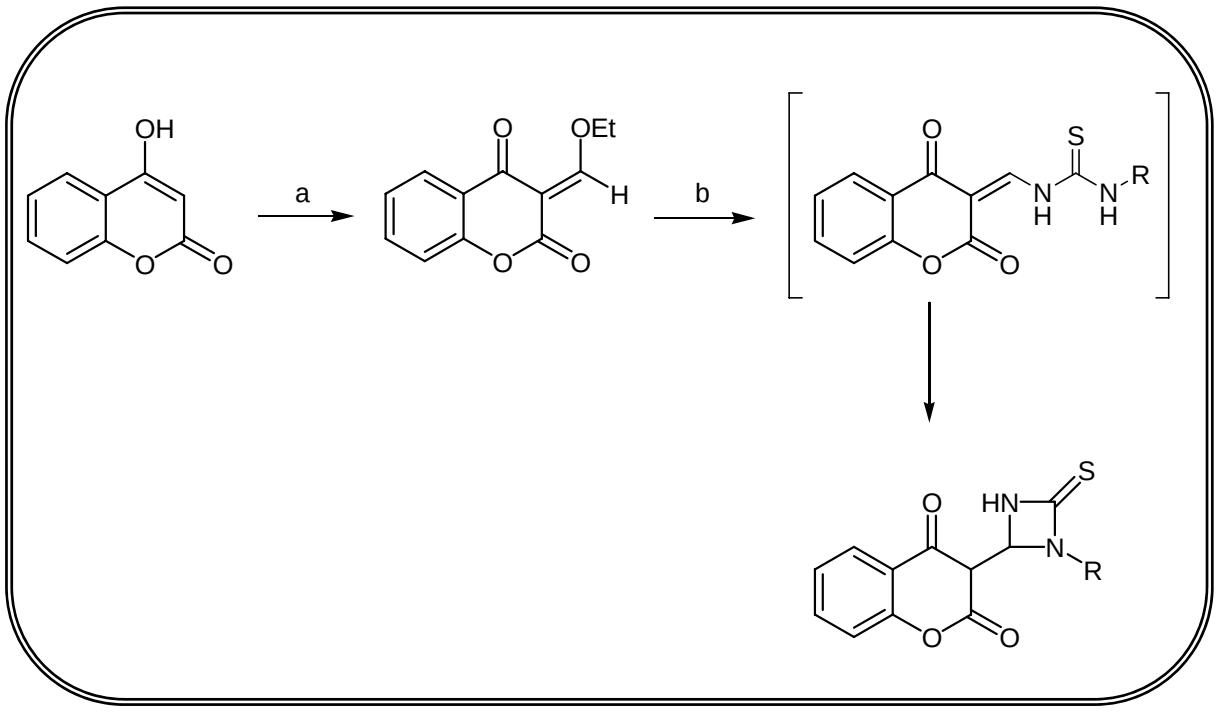
5.4.1 Scheme 1.

Synthesis of 4-hydroxy coumarin



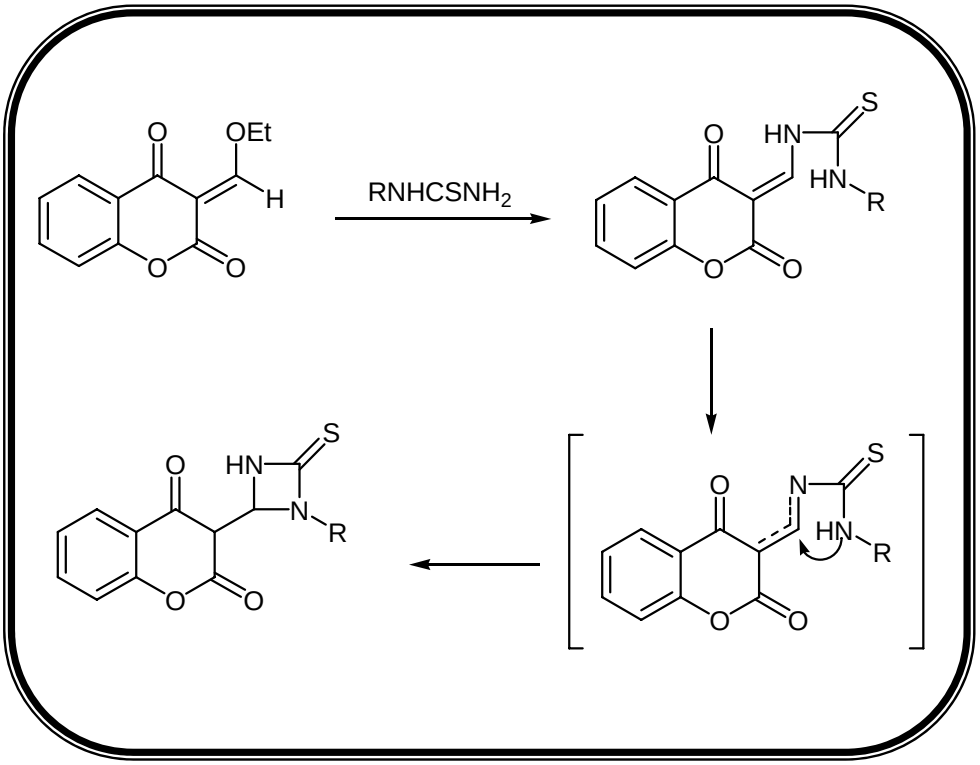
5.4.2 Scheme 2.

Synthetic approach towards 3-(1-phenyl-4-thioxo-1,3-diazetidin-2-yl)-2*H*-chromene-2,4(3*H*)-dione derivatives



Reagents and conditions: (a) Triethyl orthoformate, p-Toluenesulfonic acid, MW 240 W, 2 min.; **(b)** $RNHCSNH_2$, $CHCl_3$, Reflux, 30 min.

5.5 Reaction Mechanism:



5.6 Experimental

5.6.1 4-hydroxy coumarin:

Phenol (9.41g, 0.1M) and malonic acid (10.4g, 0.1M) were added to a mixture of phosphorus oxychloride (40 ml) and anhydrous zinc chloride (30 g) which was preheated to 60 ºC. The reaction mixture was heated on a water bath at 70 ºC for 10 hours. It was cooled and decomposed with ice and water which forms a yellow solid. It was filtered and washed with water. It was further triturated with 10 % sodium carbonate and filtered. The filtrate was slowly acidified with dilute hydrochloric acid. At the neutral point, some solid product was separated, which was filtered, washed with water, dried and recrystallized from ethanol. White solid; m.p. 210 ºC; Yield: 55%.

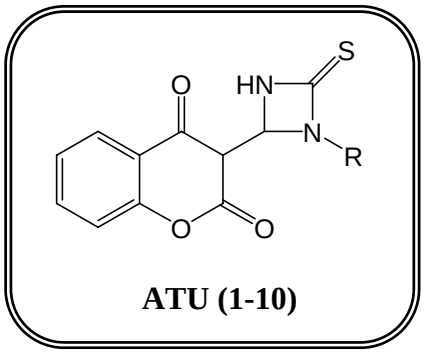
5.6.2 3-(ethoxymethylene)-2*H*-chromene-2,4(3*H*)-dione:

A mixture of 6.2 mmol of 4-hydroxy coumarin, 7 ml of triethyl orthoformate, and 0.02 g of *p*-toluenesulfonic acid monohydrate was placed in a 50 ml beaker. The beaker was covered with a stemless funnel and irradiated in a microwave oven for 1 minute at 240 W and then 1 minute at 180 W. The resultant residue was cooled to room temperature, the solvent was decanted, and the residue was crystallized in a chloroform to obtain target compound as a yellow solid. m.p. 140 ºC; Yield: 65%.

5.6.3 3-(1-aryl-4-thioxo-1,3-diazetidin-2-yl)-2*H*-chromene-2,4(3*H*)-dione:

In a round bottom flask, 3-propylidene-2*H*-chromene-2,4-dione **2** (0.01 mol), appropriate substituted phenyl thiourea (0.015 mol) and $CHCl_3$ (25 mL) were placed and refluxed for 30 minutes with stirring. Then reaction mixture was allowed to cool at ambient temperature and solvent was evaporated in vaccuo. The crude mixture was added 50 mL water and extracted with ethyl acetate (3 × 15 mL). Organic phase was dried over $MgSO_4$ and then concentrated under reduced pressure to afford crude material which was crystallized in chloroform to give pure target compound in 75-80 % yield.

5.7 Physical data



ATU (1-10)

Comp.	R	M.F.	M.W.	Mp ºC	Yield %	R_f
ATU-1	Ph	$C_{17}H_{12}N_2O_3S$	324.35	230-232	75	0.48
ATU-2	4-OCH_3-C_6H_4	$C_{18}H_{14}N_2O_4S$	354.37	206-208	76	0.45
ATU-3	2,4-di-CH_3-C_6H_4	$C_{19}H_{16}N_2O_3S$	352.40	218-220	81	0.41
ATU-4	2,5-di-CH_3-C_6H_4	$C_{19}H_{16}N_2O_3S$	352.40	210-212	79	0.42
ATU-5	3-Cl-C_6H_4	$C_{17}H_{11}ClN_2O_3S$	358.79	217-219	71	0.54
ATU-6	4-Cl-C_6H_4	$C_{17}H_{11}ClN_2O_3S$	358.79	224-226	75	0.56
ATU-7	3-NO_2-C_6H_4	$C_{17}H_{11}N_3O_5S$	369.35	223-225	80	0.61
ATU-8	4- CH_3-C_6H_4	$C_{17}H_{12}N_2O_3S$	326.73	214-216	76	0.54
ATU-9	3-Br-C_6H_4	$C_{17}H_{11}BrN_2O_3S$	403.24	216-218	70	0.48
ATU-10	2-OH-C_6H_4	$C_{17}H_{12}N_2O_4S$	340.35	210-212	72	0.49

TLC Solvent system: Ethyl acetate : Hexane – 3.5:6.5

5.8 Spectral discussion

5.8.1 Mass spectral study

Instrument : SHIMADZU GCMS-QP-2010

Sample technique : EI technique

M/z range : 40-500

Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. No specific fragmentation pattern was observed in mass spectral analysis but molecular ion peak was observed in agreement with molecular weight of respective compound. In mass spectra a peak of 2,4-chromane dione was observed at 163.

5.8.2 IR spectral study

Instrument : Shimadzu FT-IR-8400

Sample technique : KBr pellet

Frequency range : 400-4000cm^{-1}

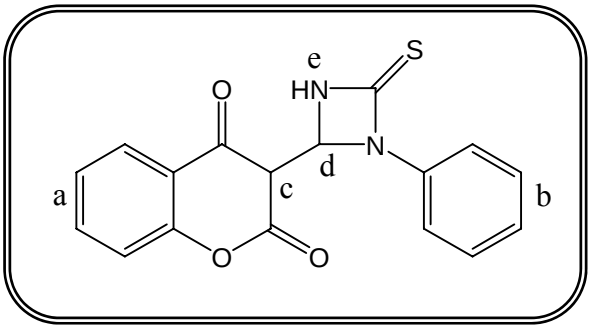
As per IR spectral study of newly synthesized compounds **(ATU 1-10)**, the stretching vibration of secondary amine (>NH) was appeared around 3500-3600 cm^{-1}. The C=O stretching vibration of carbonyl group of chromene ring was observed around 1680-1690 cm^{-1}. The C=S stretching vibration was also observed at near about 1720 cm^{-1}. The aromatic ring skeleton vibration was observed between 1500 to 1600 cm^{-1}.

5.8.3 ^{1}H NMR spectral study

Instrument : BRUKER AC 400 MHz FT-NMR

Internal reference : TMS

Solvent : $CDCl_3$



Number of protons and their chemical shifts were found to support the structure of the synthesized compounds. Protons of benzenoid part of chromene ring 'a' were observed between 7.6 to 8.1 δ ppm. Protons of phenyl ring 'b' were observed at 7.00-7.40 δ ppm. Two methine protons 'c' and 'd' were observed as a double doublet in very downfield between 9 to 10 δ ppm with higher value of coupling constant. Proton of secondary amine 'e' was observed at 13.4 δ ppm.

5.8.4 Elemental Analysis

Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Spectral data of synthesized compounds (ATU 1-10)

3-(1-phenyl-4-thioxo-1,3-diazetidin-2-yl)-2*H*-chromene-2,4(3*H*)-dione (ATU-1)

Yellow solid; mp 230-232 ˚C;

IR (KBr): 3614, 3581, 1724, 1681, 1662, 1510, 1444, 1390, 1220, 1107, 721 cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 7.24-7.43 (m, 5H, Ar), 7.61-8.09 (m, 4H, $Ar_{(Coum)}$), 9.68-9.86 (dd, *J* = 12.8, 12.1 Hz, 1H, CH), 11.99-12.23 (dd, *J* = 12.6, 28.0 Hz, 1H, CH), 13.42 (s, 1H, NH); **MS: m/z** = 324 (M^+); **Anal. Calcd** for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64. Found: C, 62.83; H, 3.69; N, 8.55.

3-[1-(4-methoxyphenyl)-4-thioxo-1,3-diazetidin-2-yl]-2*H*-chromene-2,4(3*H*)-dione (ATU-2)

Yellow solid; mp 206-208 ˚C;

IR (KBr): 3536, 2988, 1719, 1690, 1545, 1378, 1109, 714 cm^{-1}; **MS: m/z** = 354 (M^+); **Anal. Calcd** for $C_{18}H_{14}N_2O_4S$: C, 61.01; H, 3.98; N, 7.90. Found: C, 60.89; H, 3.91; N, 7.96.

3-[1-(2,4-dimethylphenyl)-4-thioxo-1,3-diazetidin-2-yl]-2*H*-chromene-2,4(3*H*)-dione (ATU-3)

Yellow solid; mp 218-220 ˚C;

IR (KBr): 3535, 2916, 1718, 1687, 1452, 1384, 1219, 1107, 518 cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 2.22 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.05-7.35 (m, 3H, Ar), 7.65-8.07 (m,

4H, $Ar_{(Coum)}$), 9.65-9.83 (dd, *J* = 12.9, 12.2 Hz, 1H, CH), 11.57-12.26 (dd, *J* = 13.0, 35.8 Hz, 1H, CH), 13.45 (s, 1H, NH); **MS: m/z** = 352 (M^+); **Anal. Calcd** for $C_{19}H_{16}N_2O_3S$: C, 64.76; H, 4.58; N, 7.95. Found: C, 64.61; H, 4.45; N, 7.78.

3-[1-(2,5-dimethylphenyl)-4-thioxo-1,3-diazetidin-2-yl]-2*H*-chromene-2,4(3*H*)-dione (ATU-4)

Yellow solid; mp 210-212 ˚C;

IR (KBr): 3581, 3018, 2984, 1706, 1681, 1654, 1527, 1460, 1384, 1217, 817 cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 2.23 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.14-7.35 (m, 3H, Ar), 7.67-8.06 (m, 4H, $Ar_{(Coum)}$), 9.62-9.81 (dd, *J* = 12.8, 12.2 Hz, 1H, CH), 11.64-11.73 (dd, *J* = 12.8, 37.1 Hz, 1H, CH), 13.43 (s, 1H, NH); **MS: m/z** = 352 (M^+); **Anal. Calcd** for $C_{19}H_{16}N_2O_3S$: C, 64.76; H, 4.58; N, 7.95. Found: C, 64.63; H, 4.49; N, 7.88.

3-[1-(3-chlorophenyl)-4-thioxo-1,3-diazetidin-2-yl]-2*H*-chromene-2,4(3*H*)-dione (ATU-5)

Yellow solid; mp 217-219 ˚C;

IR (KBr): 3511, 1724, 1684, 1618, 1507, 1110, 687 cm^{-1}; **MS: m/z** = 358 (M^+); **Anal. Calcd** for $C_{17}H_{11}ClN_2O_3S$: C, 56.91; H, 3.09; N, 7.81. Found: C, 56.76; H, 3.01; N, 7.84.

3-[1-(4-chlorophenyl)-4-thioxo-1,3-diazetidin-2-yl]-2*H*-chromene-2,4(3*H*)-dione (ATU-6)

Yellow solid; mp 224-226 ˚C;

IR (KBr): 3504, 1718, 1678, 1554, 1221, 821 cm^{-1}; **MS: m/z** = 358 (M^+); **Anal. Calcd** for $C_{17}H_{11}ClN_2O_3S$: C, 56.91; H, 3.09; N, 7.81. Found: C, 56.68; H, 2.87; N, 7.72.

3-[1-(3-nitrophenyl)-4-thioxo-1,3-diazetidin-2-yl]-2*H*-chromene-2,4(3*H*)-dione (ATU-7)

Yellow solid; mp 223-225 ˚C;

IR (KBr): 3548, 3011, 1715, 1688, 1569, 1107, 796 cm^{-1}; **MS: m/z** = 369 (M^+); **Anal. Calcd** for $C_{17}H_{11}N_3O_5S$: C, 55.28; H, 3.00; N, 11.38. Found: C, 55.18; H, 2.87; N, 11.25.

3-[1-(4-methylphenyl)-4-thioxo-1,3-diazetidin-2-yl]-2*H*-chromene-2,4(3*H*)-dione (ATU-8)

Yellow solid; mp 214-216 ˚C;

IR (KBr): 3528, 2967, 1701, 1678, 1377, 1221, 814 cm^{-1}; **MS: m/z** = 338 (M^+); **Anal. Calcd** for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.17; N, 8.28. Found: C, 63.74; H, 4.01; N, 8.14.

3-[1-(3-bromophenyl)-4-thioxo-1,3-diazetidin-2-yl]-2*H*-chromene-2,4(3*H*)-dione (ATU-9)

Yellow solid; mp 216-218 ˚C;

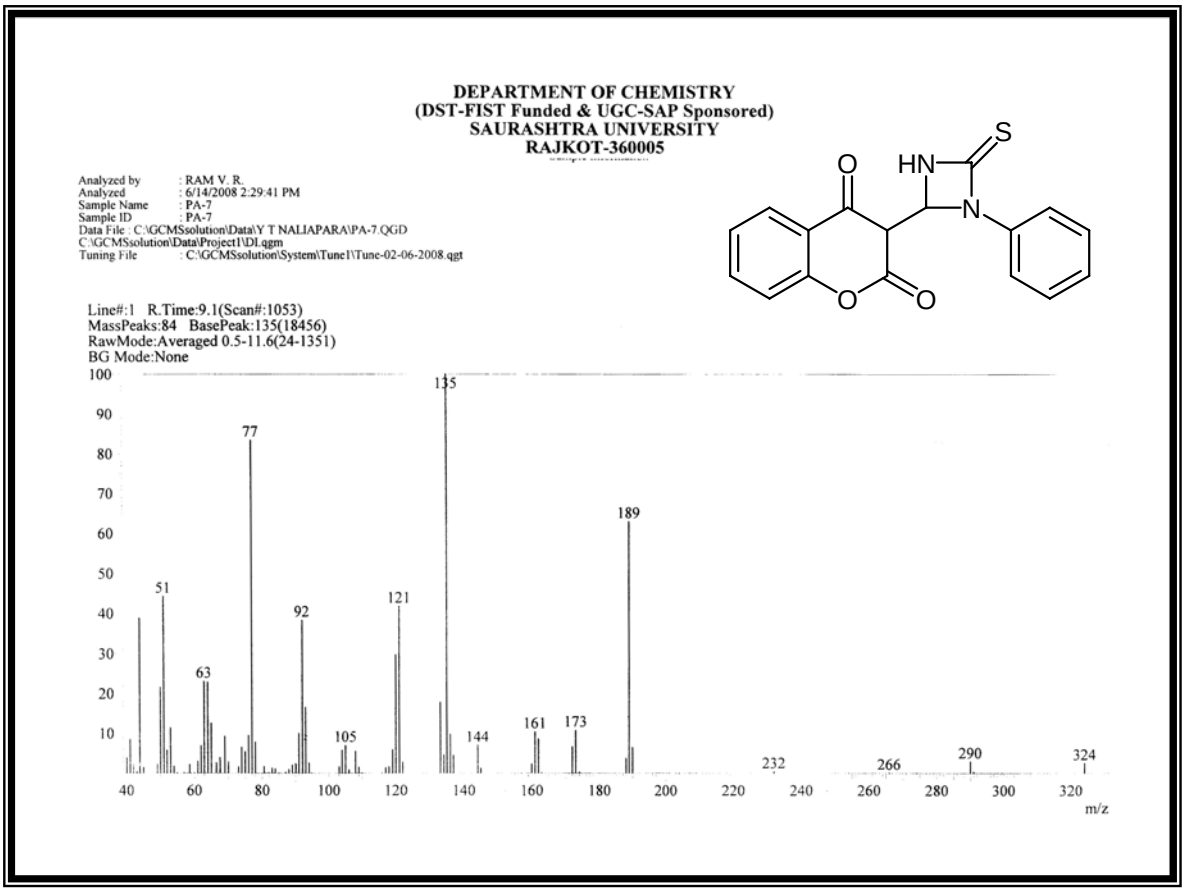
IR (KBr): 3514, 1729, 1690, 1648, 1534, 1121, 678 cm^{-1}; **MS: m/z** = 403 (M^+); **Anal. Calcd** for $C_{17}H_{11}BrN_2O_3S$: C, 50.63; H, 2.75; N, 6.95. Found: C, 50.47; H, 2.58; N, 6.74.

3-[1-(2-hydroxyphenyl)-4-thioxo-1,3-diazetidin-2-yl]-2*H*-chromene-2,4(3*H*)-dione (ATU-10)

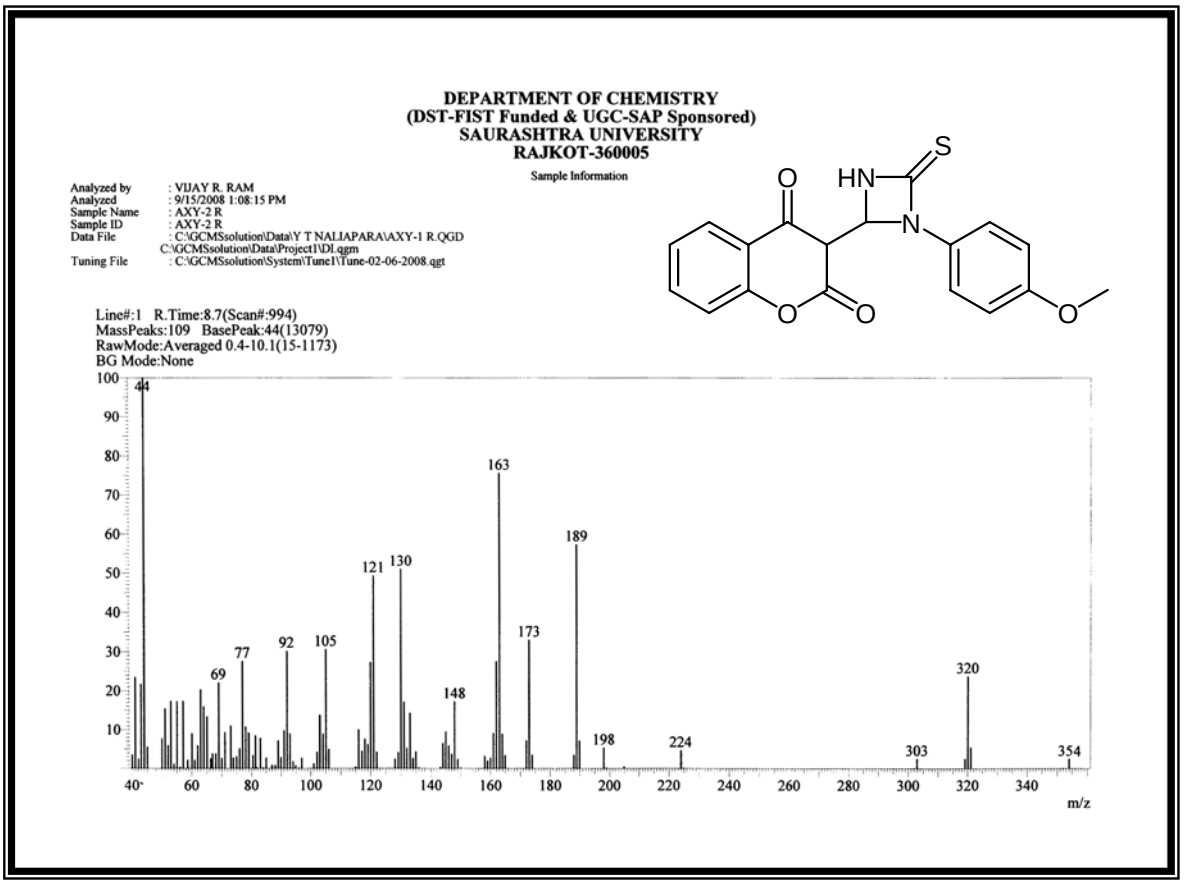
Yellow solid; mp 210-212 ˚C;

IR (KBr): 3598, 3536, 1721, 1691, 1545, 1302, 1108 cm^{-1}; **MS: m/z** = 340 (M^+); **Anal. Calcd** for $C_{17}H_{12}N_2O_4S$: C, 59.99; H, 3.55; N, 8.23. Found: C C, 59.81; H, 3.34; N, 8.10.

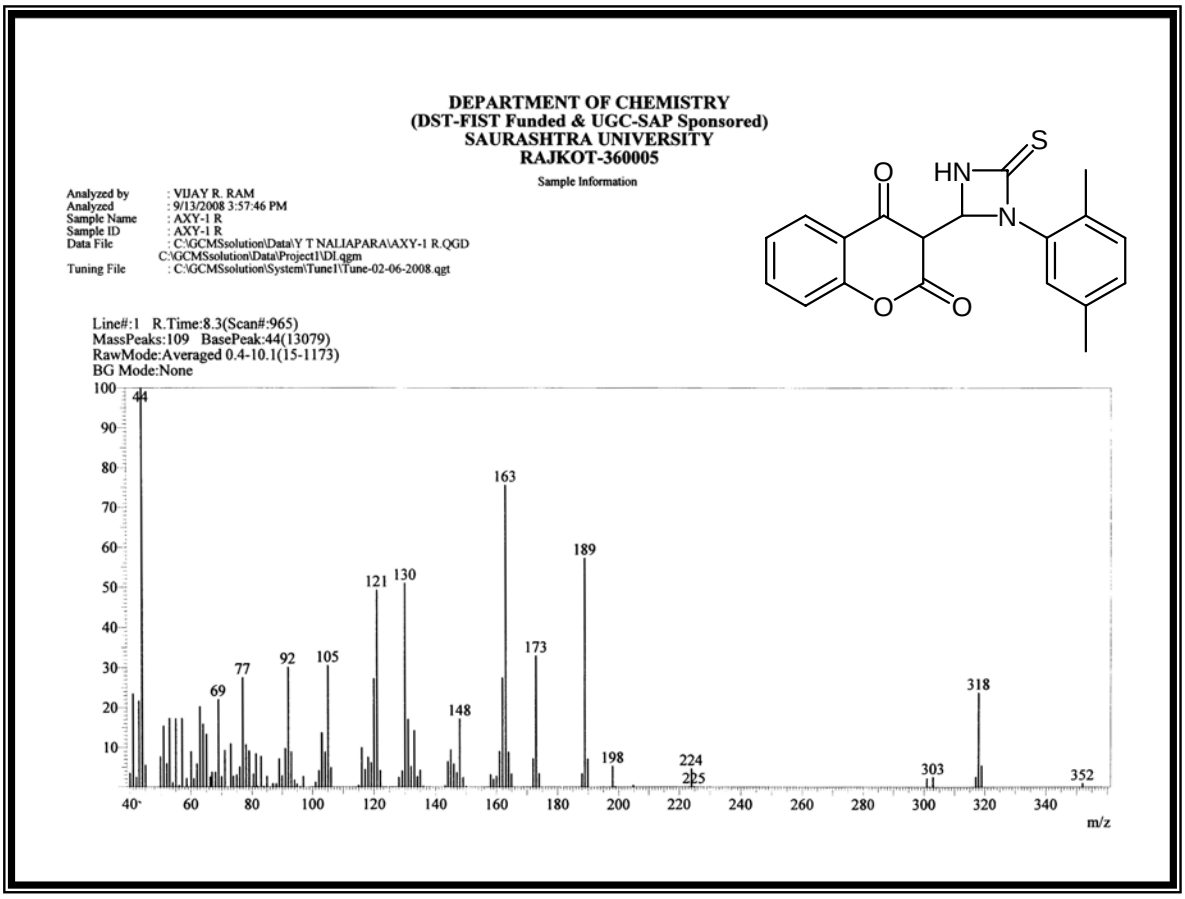
Mass Spectrum of ATU-1



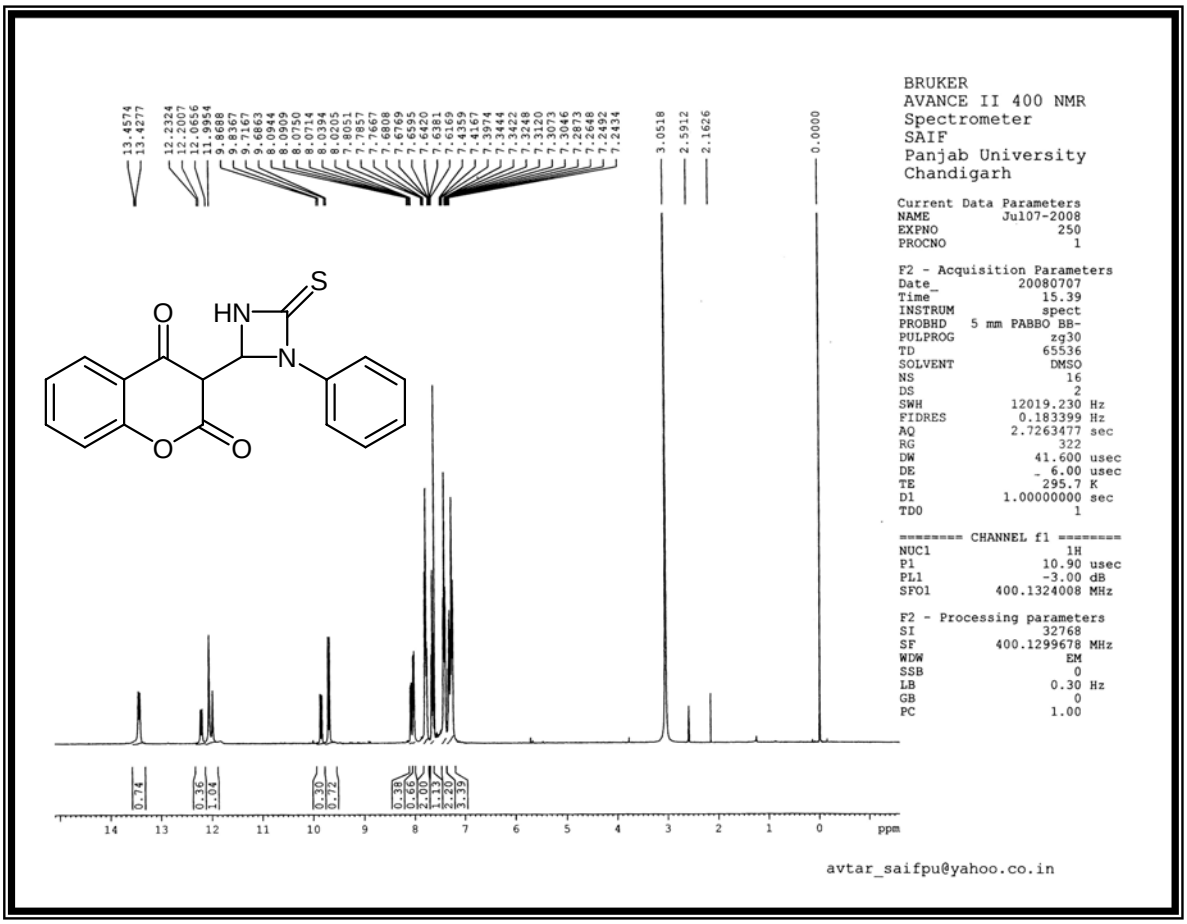
Mass Spectrum of ATU-2

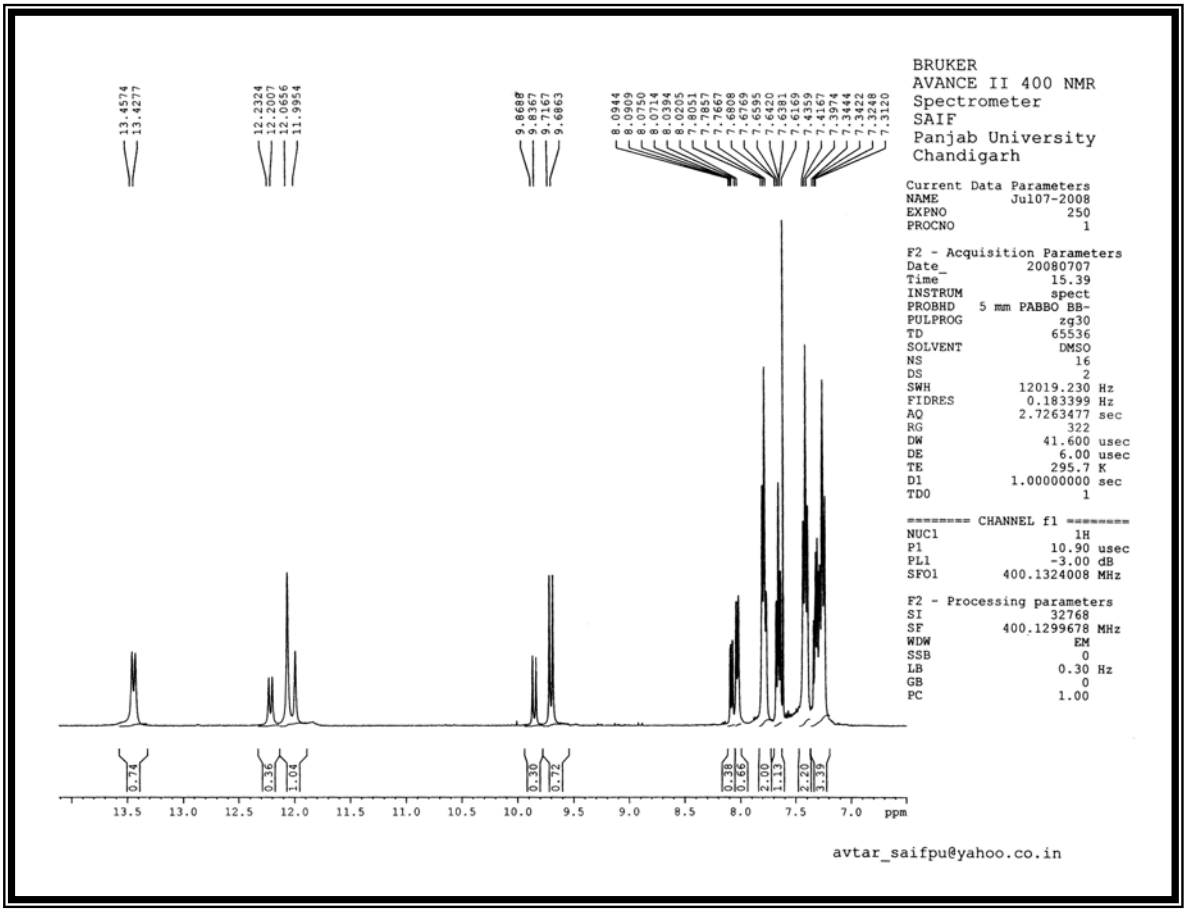


Mass Spectrum of ATU-4

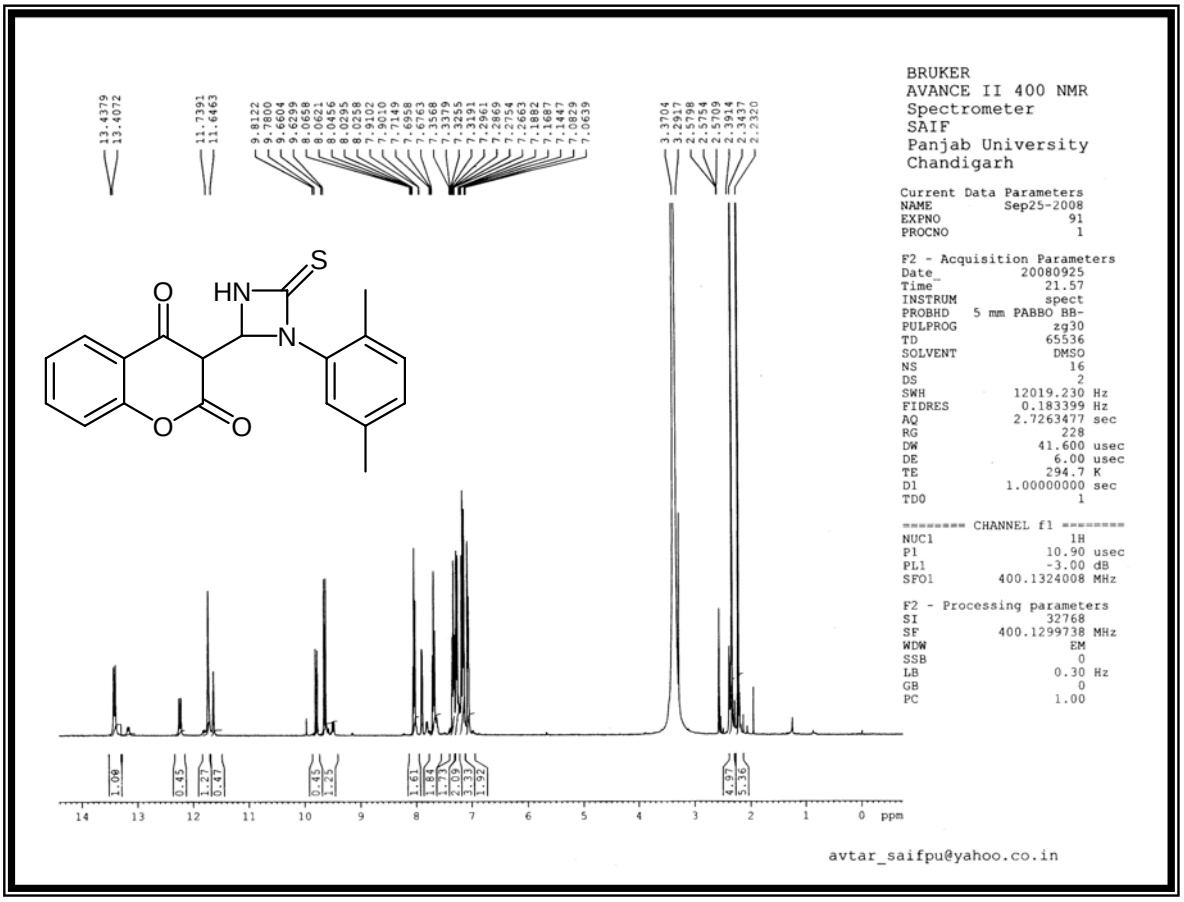


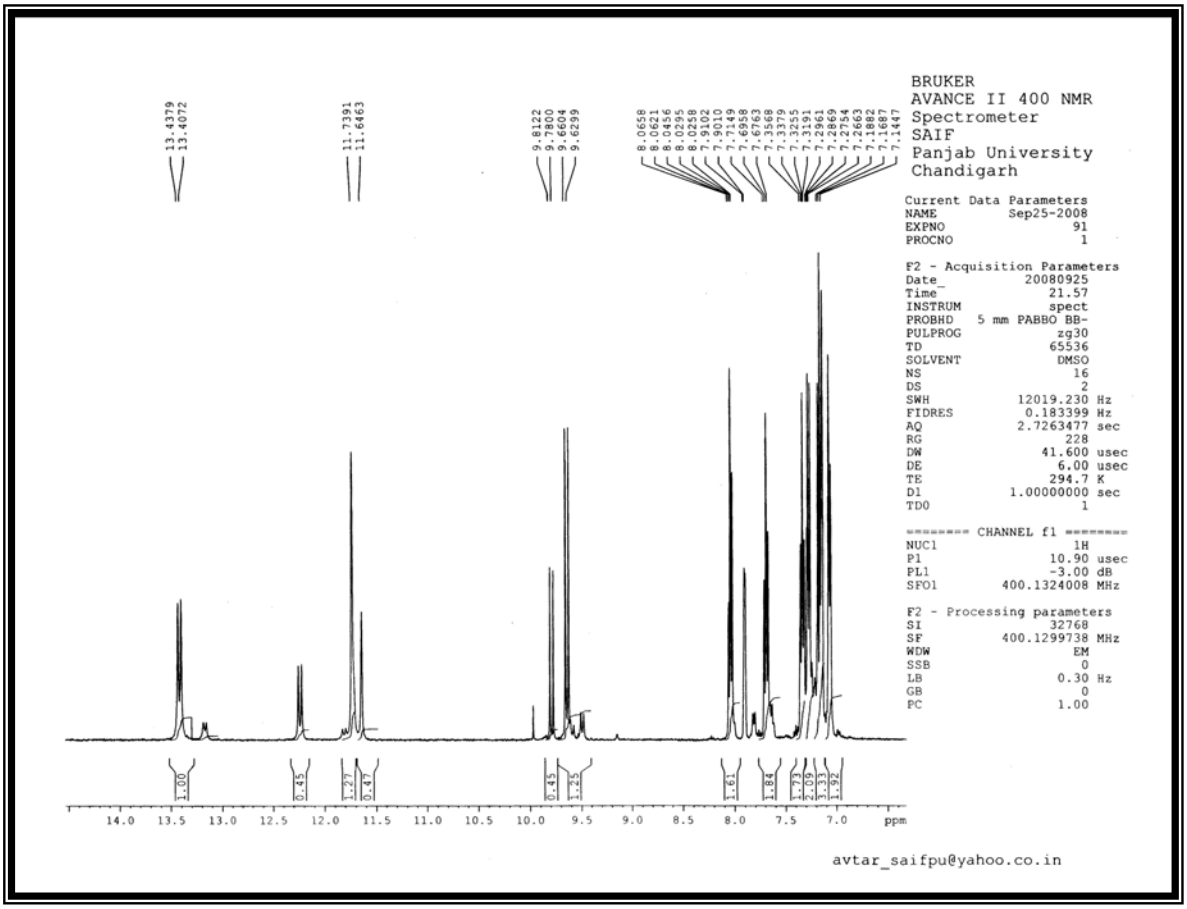
^{1}H NMR Spectrum of ATU-1



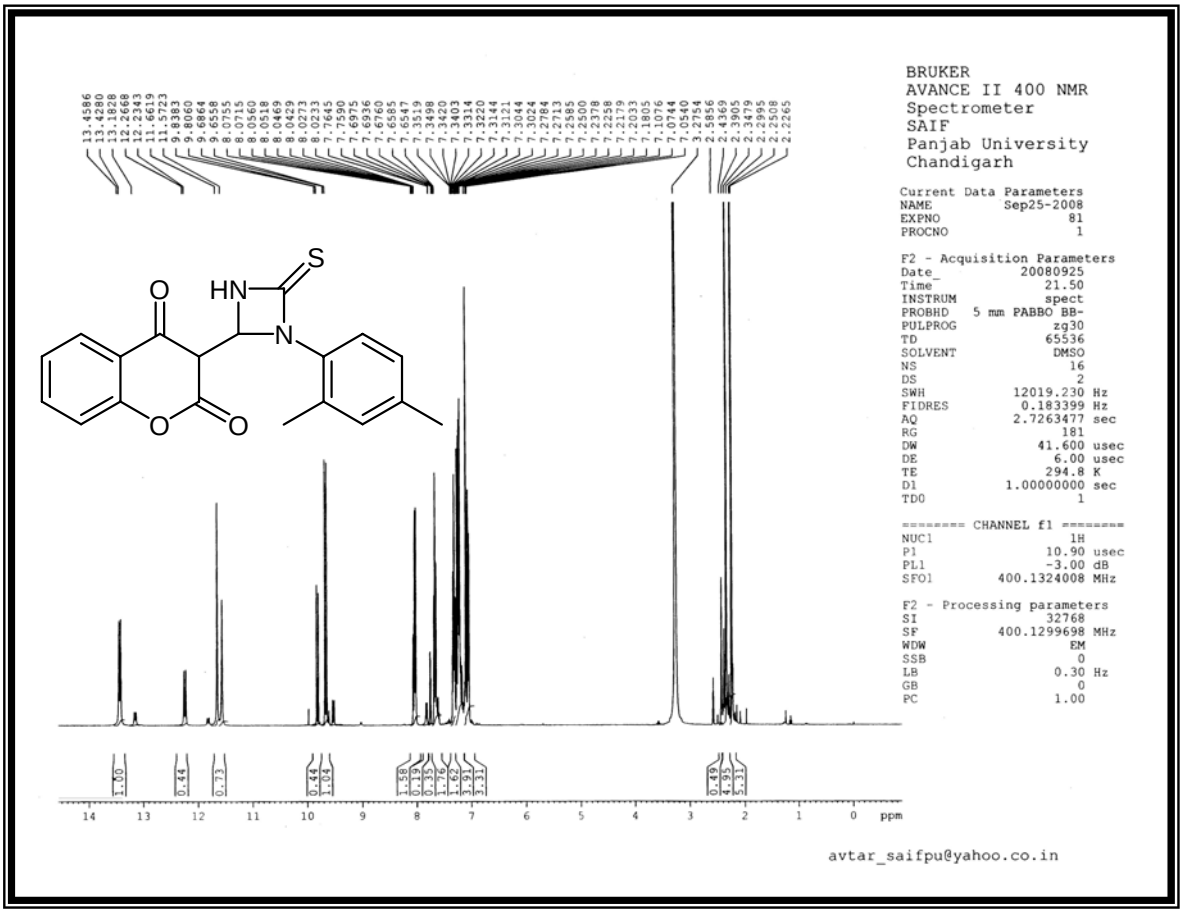


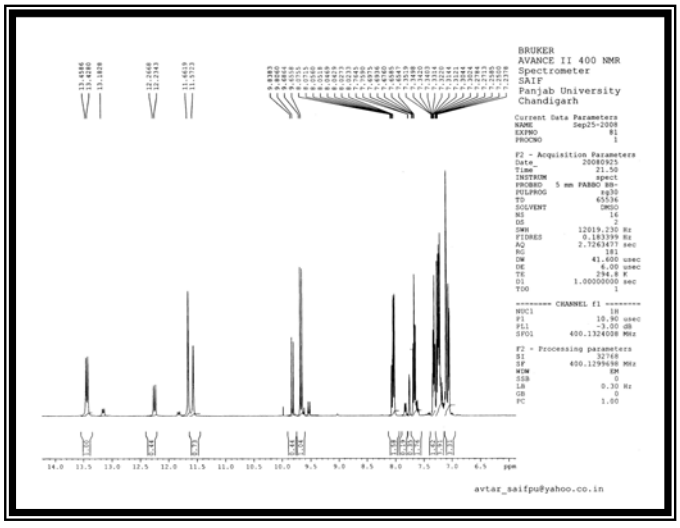
^{1}H NMR Spectrum of ATU-4

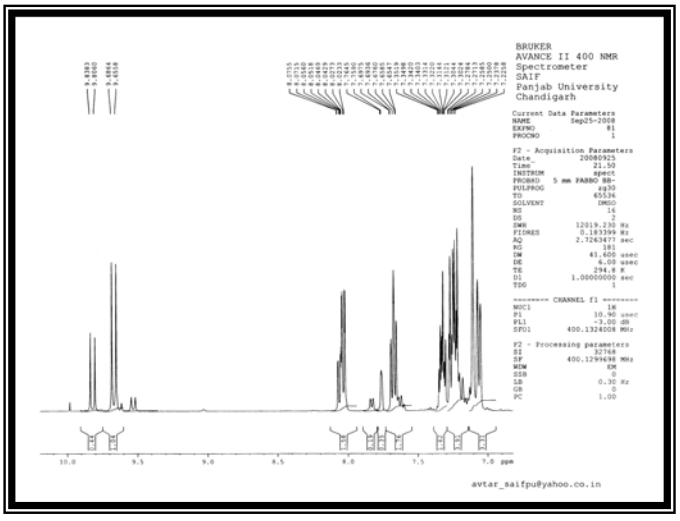




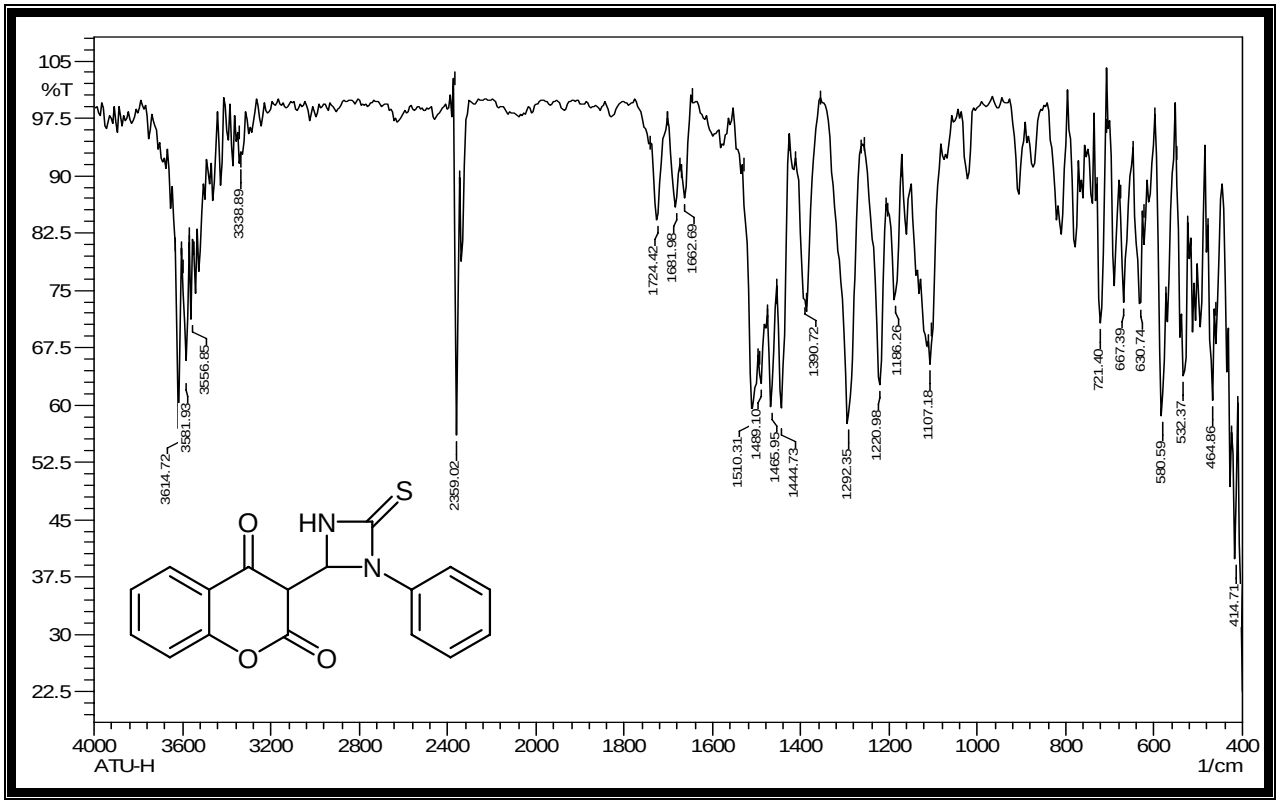
^{1}H NMR Spectrum of ATU-3



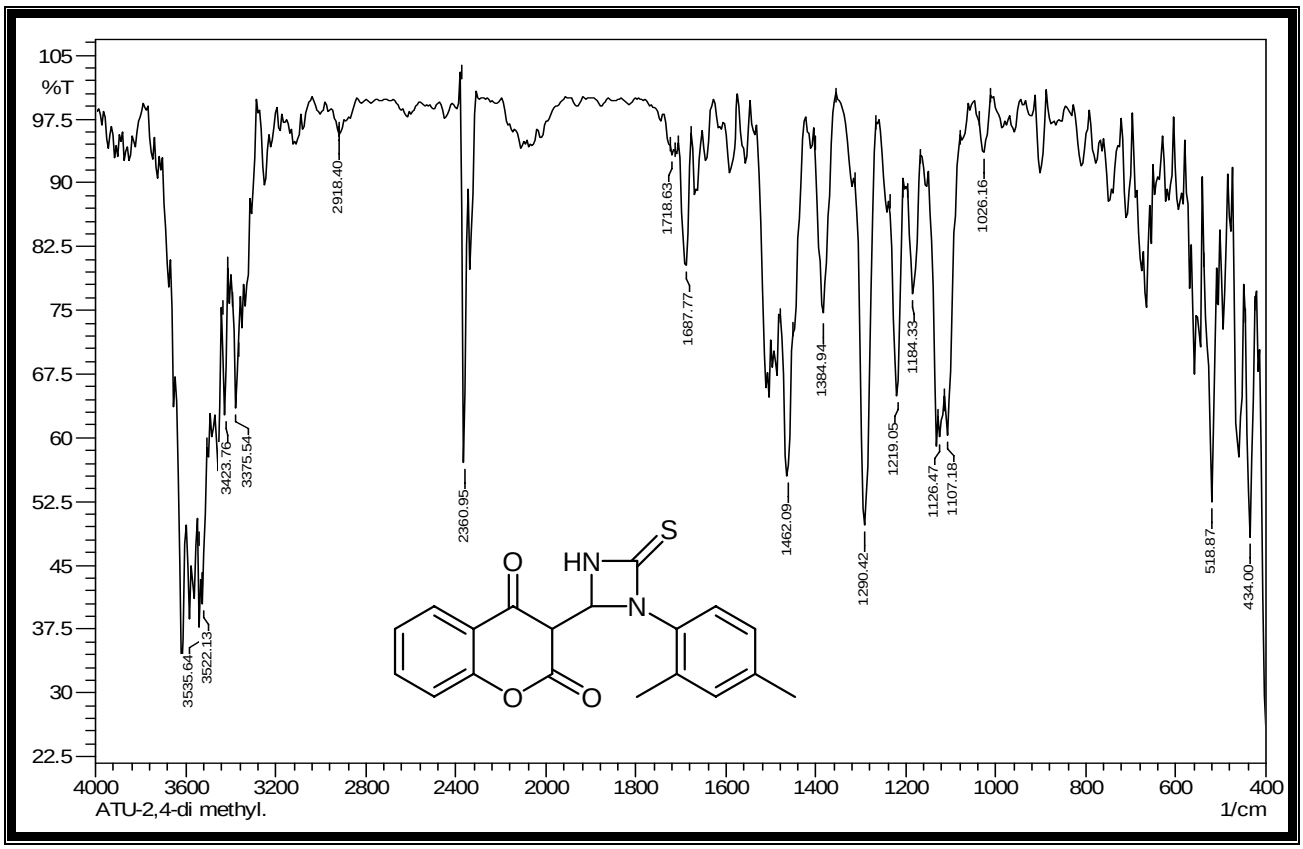




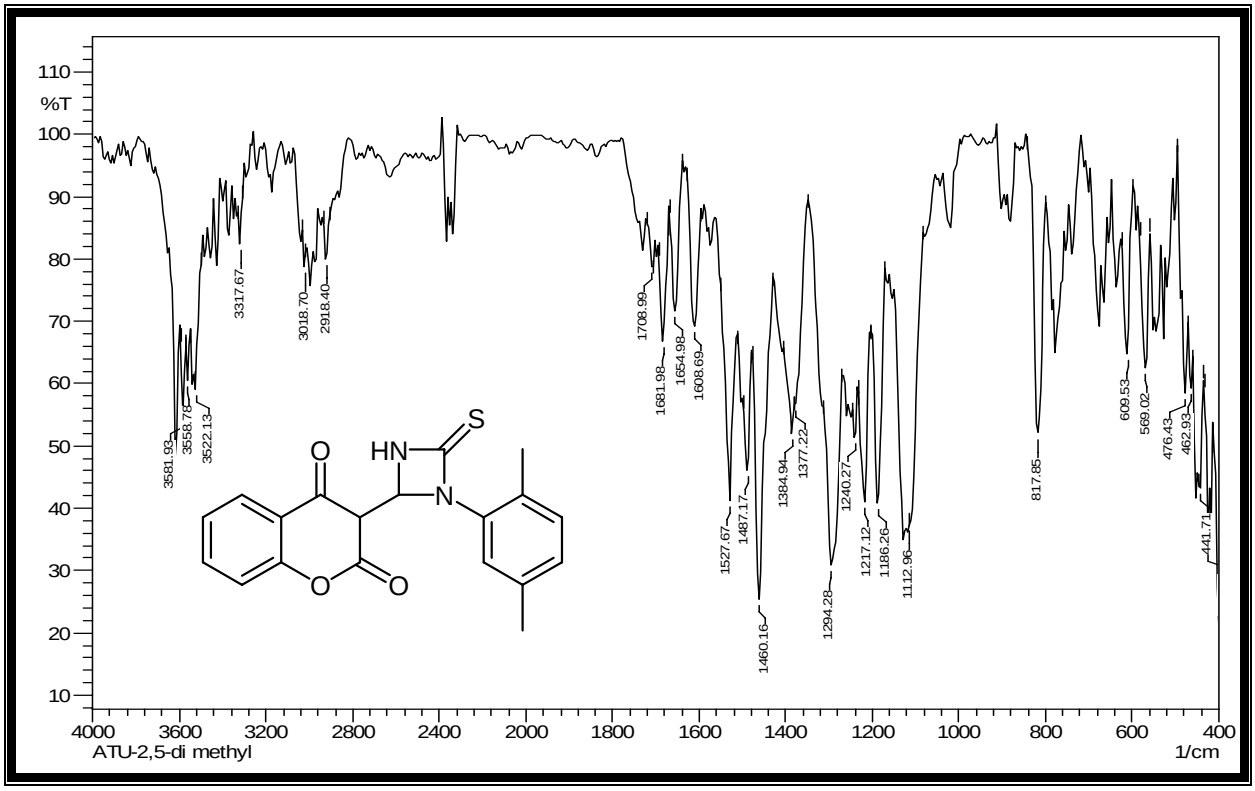
IR Spectrum of ATU-1



IR Spectrum of ATU-3



IR Spectrum of ATU-4



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Chapter 6

Synthesis and characterization of *N'*-arylmethylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide derivatives

Chapter 6

Synthesis and characterization of *N'*-arylmethylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide derivatives

6.1 Introduction

The systematic IUPAC name benzo[*c*]pyrazole is not used in the *Ring Index* or in *Chemical Abstract* and the heterocycle is normally referred to by its trivial name indazole or more correctly 1*H*-indazole (CAS registry number 271-244-3). Alternative names for indazole such as 1,2-benzodiazole, are not used. Benzo-fused derivatives are known as benzoindazoles. The first indazoles were synthesized in 1880,[1] and a systematic investigation of the heterocycle was performed by V. Auwers in 1924.[2] Indeed, general synthetic pathways to indazoles were developed in the early years of the 20th century and many recent publications describe improvements of known methods. Methods for the synthesis of indazoles are described in *Houben-Weyl*,[3] and well-tested procedures for the synthesis of 1*H*-indazole,[4-7] 2-phenyl-2*H*-indazole[8] and 5-nitro-1*H*-indazole,[9] can be found in *Organic Synthesis*.

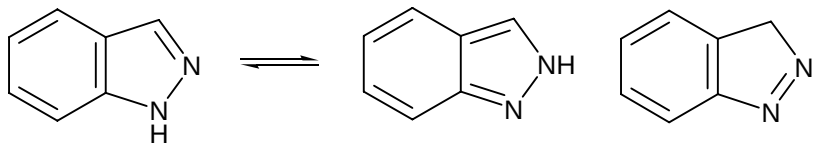
Natural products bearing an indazole structure are rare[10] and at present only two examples are known: nigellicine[11] and nigellidine.[12] However, many synthetic indazoles are known, and a number are important because of their pharmaceutical activity; some act as dopamine antagonists, anti-inflammatory, analgesic, or antipyretic agents.[13-41] Others also exhibit CNS activity,[42-45] and 6- and 7-nitroindazoles are used to study the behavior of nitric oxide in vivo.[46-50] 1-Benzyl-1*H*-indazole-3-carboxilic acids have antispermatogenetic and anticancer activity,[51-56] the latter effect being shared by other indazole derivatives.[57-61] 1-Benzoyl-1*H*-indazoles behave as antiarthritic drugs,[62] and 4-nitro- and 4-amino-2-ribofuranosyl-2*H*-indazole 3',5'-cyclic monophosphates act as potent mimics of adenosine-3',5'-cyclic

monophosphates.[63] Cortivazol[64] is an indazole-based drug possessing glucocorticoid properties. Many indazoles act as enzyme inhibitors,[65-70] and some also show specific virucide,[71] bronchodilatory,[72-74] vasodilatory,[75] or neuroprotectant[76] activities; others are used in the treatment of diabetes.[77-79] 3-Trifluoromethyl-1*H*-indazoles possess trichomonacide properties,[80] and fused indazoles with an azasteroid ring system show antimicrobial activity.[81,82] Some 1*H*-indazole-4,7-quinones possess anthelmintic[83] and diuretic activity.[84] A series of indazole derivatives exhibit herbicide activity, behave as growth inhibitors,[85-89] or are used as bactericides and fungicides in polymer based paints.[90,91] Guanidino-1*H*-indazoles are used as sweeteners.[92,93]

Certain indazoles form violet to blue azo dyes,[94-96] and arylazoindazoles are used as reagents for the determination of vanadium.[97] Indazoles act as dyes in erasable drawing inks,[98] and others form pigments.[99] In addition, some are used in photographic materials,[100] as fog inhibitors,[101] in photographic layers,[102,103] in photographic developers,[104-107] in instant photographic processes,[108-110] and for preparing recording sheets with migration imaging.[111,112] Indazoles are also used with polyisocyanates in one-component adhesives.[113] They find application in complexones,[114] in polyimide films,[115] and as corrosion inhibitors.[116] Patents disclose the value of preparations containing indazole for sealing gold plated metals as electric connectors, see ref.[117,118]

In older reviews[119-121] the structural assignment of 1*H*- and 2*H*-isomers is described in great detail and more recent surveys[122,123] contain much spectroscopic and physical data. Although 1*H*-indazole (**1**) has two other potential tautomers 2*H*-indazole (**2**) and 3*H*-indazole (**3**) (Scheme 1), these only exist as substituted derivatives. Both in the solid phase and in solution, N-unsubstituted indazoles exist predominantly as the 1*H*-tautomers. The electronic spectra of 1*H*-indazole and 1-methyl-1*H*-indazole are nearly identical,[124-126] but differ widely from the spectrum of 2-methyl-2*H*-indazole. The favored tautomers can also be ascertained with care (see below)from ^{1}H NMR spectra,[127-131] but these conclusions should be refined by using combined NMR data, such as those from the ^{13}C and ^{15}N NMR spectra of fixed 1-alkyl-1*H*- and 2-alkyl-2*H*-derivatives.[132-134] X-ray crystallographic studies of indazoles confirm the general preference for 1*H*-tautomers in the solid state,[23,24,135-143] as do CNDO calculations.[145] The dominance of the tautomeric 1*H* form can also be shown from the K_T-value of indazole itself (K_T=40).[144] Microwave spectra support these conclusions.[146]

Scheme 1 Tautomeric forms of indazole



1*H*-indazole **1** 2*H*-indazole **2** 3*H*-indazole **3**

Tautomeric equilibria between 1*H*- and 2*H*-indazoles has been investigated by photophysical and thermochemical techniques, as well as by calculations,[147-149] the results indicate, for example, that 1-methyl-1*H*-indazole is 3.2-3.6 kcal more stable than 2-methyl-2*H*-indazole. 1-Unsubstituted indazole shows a high degree of association as a dimer, whereas 1-substituted derivatives are unassociated.[150] 2*H*-Indazoles with substituents at position 2 are obtained in many substitution reactions; however, 3*H*-indazoles are not obtained in this way and only a few examples are known,[151] they lack heteroaromatic character and are not described further in this contribution.

Indazoles are weak bases that form, for example, sodium and silver salts. Their p*K* values have been determined by electron and photoelectron spectroscopy (p*K* 1.01 and 1.31 for 1*H*-indazole, 0.42 for 1-methyl-1 *H*-indazole). 2-Methyl-2*H*-indazole is a much stronger base (p*K* values for this compound range between 1.72 and 2.02).[144,152-156] 1*H*-Indazole also has weakly acidic properties (p*K* 13.8).[157] A theoretical study of its acidity by INDO and AM1 calculations has been undertaken.[158] Indazoles undergo electrophilic substitution reactions mainly at C3; further reactive positions are C5 and C7. The N1 atom resembles that of pyrrole, but N2 has a pyridine-like lone pair of electrons, these are available for protonation and thus N2 is more basic than N1. The rate of N-alkylation is lower than that of pyrazole, but the quaternization of 2-methyl-2*H*-indazole is three times faster than that of 1-methyl-1*H*-indazole.[159] Alkylation either at N1 or at N2 is very sensitive towards steric effects caused by substituents at C3 and C7.[152,160] The ratio of 1- to 2-alkylation in unsubstituted indazole is 1:1, in 3-phenyl-1*H*-indazole 74:26, and in 7-nitro-1*H*-indazole 29:70.[160] A number of methods have been applied for the calculation of ionization potential and electron affinity, charge distribution, basicity and total π-energy.[145,161-163] Heat capacities, entropies, and thermodynamic parameters for phase transitions have all been summarized.[164]

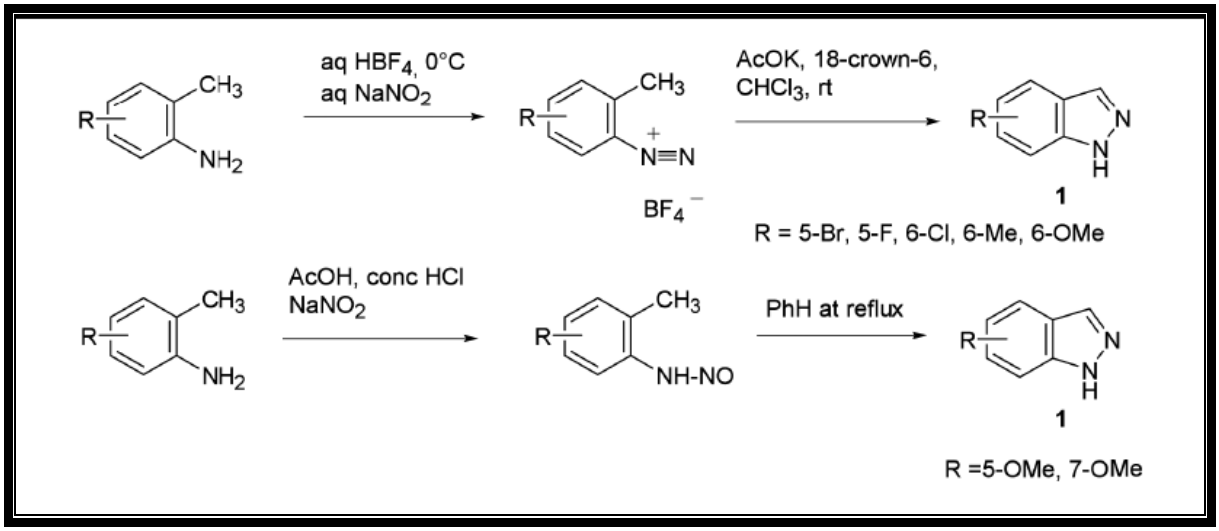
Although many derivatives of indazole show biological activity, no special toxicity has been reported and no special handling precautions have been recommended. The biodegradability of indazole is included in an ecological survey of heterocyclic compounds.[165]

6.2 Synthetic aspect

A. Methods for the preparation of substituted 1*H*-indazole compounds

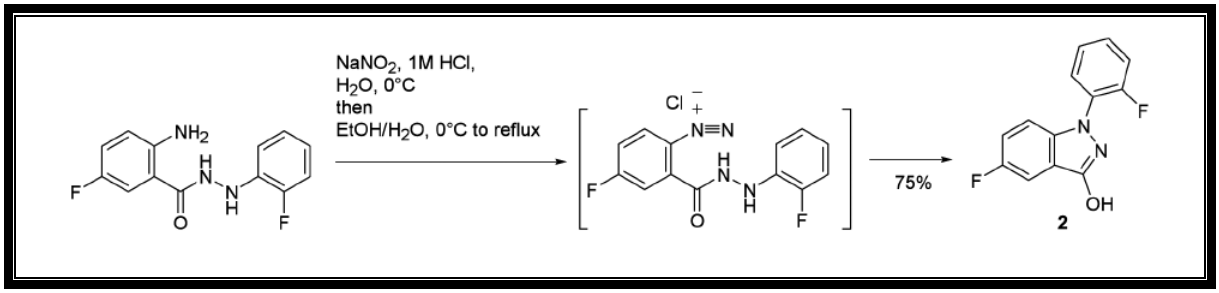
1. Creation of a C-N bond

Diazotation of an *o*-toluidine followed by capture of the generated diazonium salt is an old yet common way of accessing 1*H*-indazoles. This can be realized following two routes : the first and most common proceeds by a phase transfer-catalyzed reaction from *o*-methyl-benzendiazonium tetrafluoroborates (method of Bartsch and Yang);[166] the second takes place via *N*-nitroso derivatives (method of Kovach and Barnes).[167] These two procedures are well illustrated in the following example[168a] (Scheme 1). Several other examples are provided in refs.[168b-i]



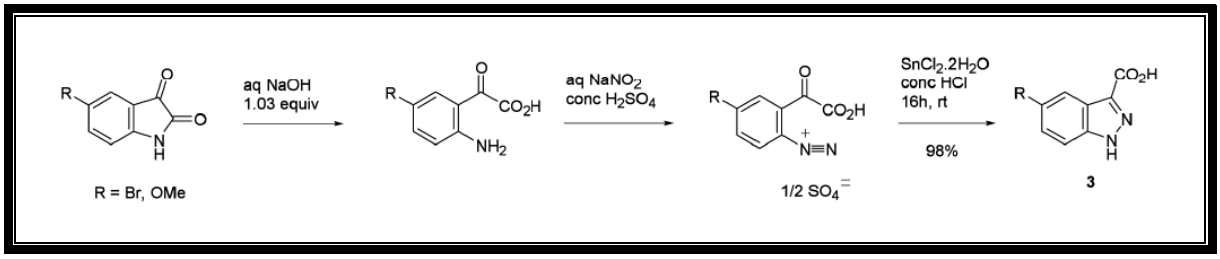
Scheme 1

A different protocol proceeding *via* the intermediacy of a diazonium ion has also been reported. Thus, in the course of the preparation of an 1*H*-indazolone compound acting as norepiephedrine/serotonin reuptake inhibitor for the treatment of fibromyalgia, the construction of the 1*H*-indazolone core structure of precursor **2** has been accomplished via the decomposition of a diazonium ion and capture of the resulting aryl cation by an *ortho*-disposed hydrazide (Scheme 2).[169]



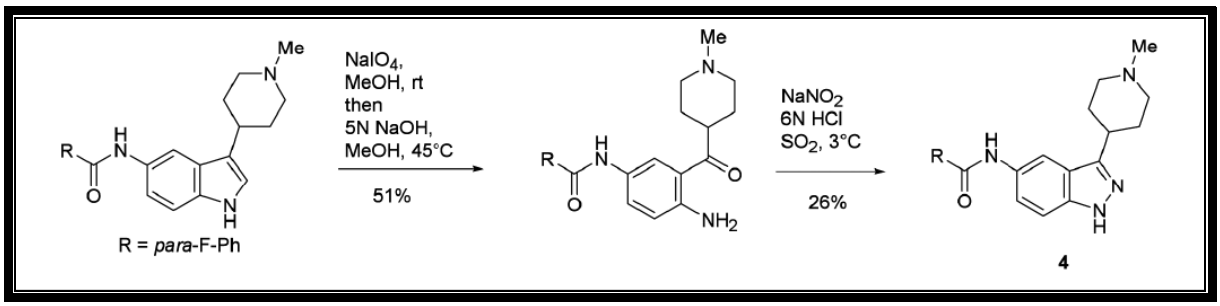
Scheme 2

Reduction of a diazonium ion, or of a *N*-nitroso species, to the corresponding hydrazine and intramolecular reaction of the latter with an *ortho*-disposed carbonyl functionality is another way to reach 3-substituted-1*H*indazoles. Following this protocol, 5-bromo and 5-methoxy-3-carboxy-1*H*-indazoles **3** have been prepared from properly substituted isatines (Scheme 3).[170a]



Scheme 3

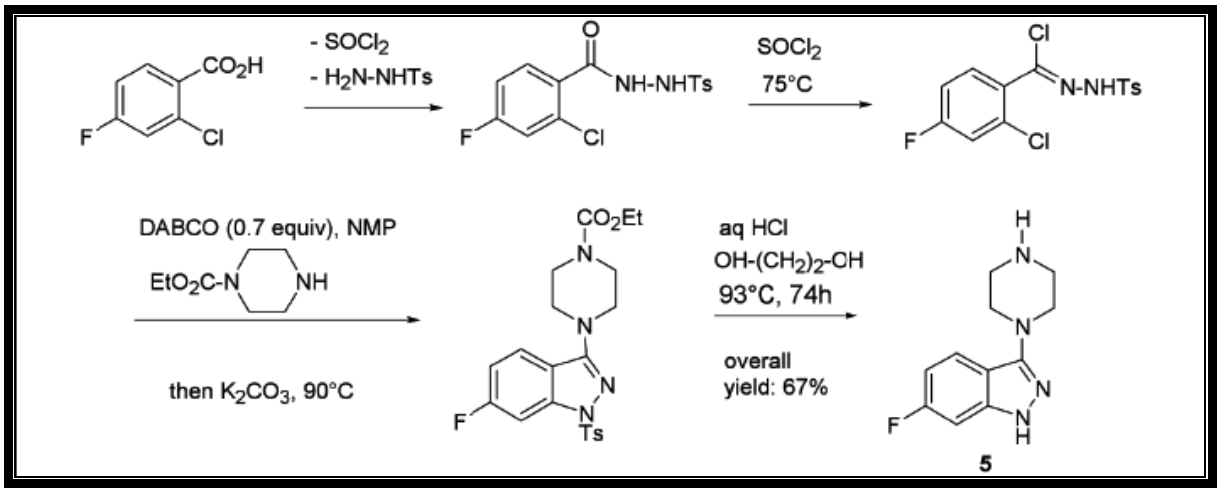
Another example can be found in the work of Zhang et al.[170b] which, in the course of a study aimed at preparing bicyclic benzamides as novel 5-HT1F receptor agonists, have reported the preparation of 1*H*-indazole **4** (Scheme 4). It is worth noting that this example features an indole to indazole conversion[171] and reduction of the diazo intermediate with SO2. References[170c-e] give additional examples.



Scheme 4

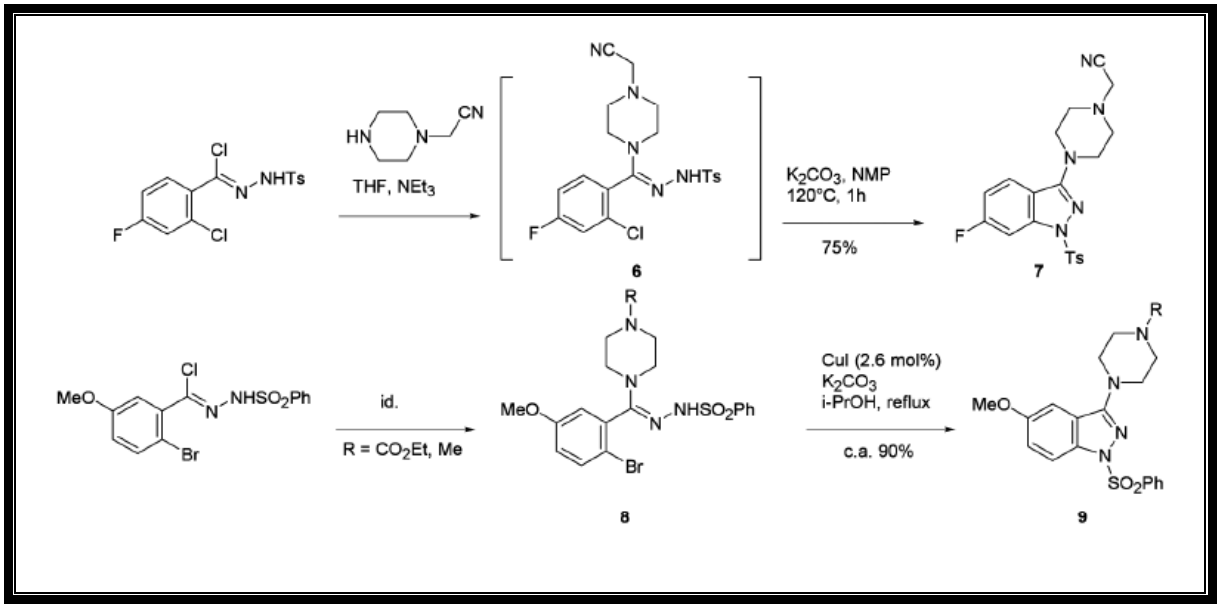
One common synthetic route to 1*H*-indazoles is the condensation of an arylketone, substituted in *ortho* by a leaving group (halogen, OMs), with hydrazine, followed by cyclization of the resulting hydrazone by simple heating or in the presence of a base. For example[172], a short and convenient synthesis of the 3-(1-piperazinyl)-1*H*-indazole derivative

5 has been successfully achieved. Compound **5** was obtained in 67% overall yield without the need for chromatographic purification (Scheme 5).



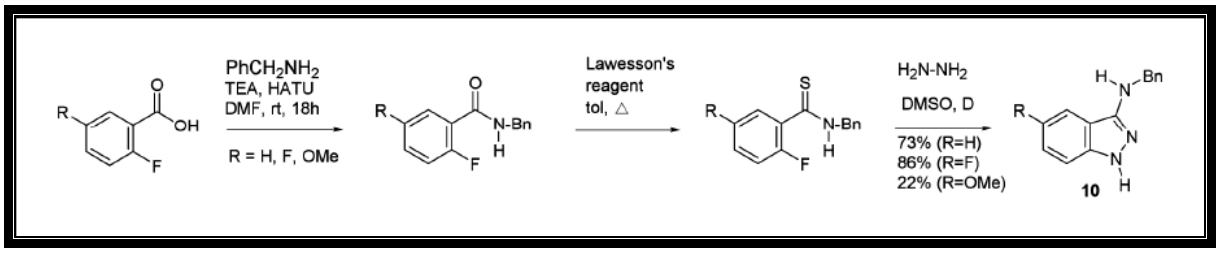
Scheme 5

Success in such an approach is greatly dependent on the phenyl ring electron density. This was clearly demonstrated in the following examples.[173a] Thus, if the cyclization of tosylhydrazone intermediate **6**, to give the corresponding 3-(1-piperazinyl)-1*H*-indazole **7**, could be easily accomplished by heating in NMP at 120°C in the presence of K2CO3 (see also Scheme 5), the much more electron-rich hydrazone intermediate **8** failed to cyclize, even at higher temperature (up to 160°C). However, the use of a catalytic amount of CuI promotes cyclization at reflux of isopropanol and in excellent yield (Scheme 6). Another example of CuI promoted cyclization of an arylhydrazone under microwave irradiation to give 1-aryl-1*H*-indazoles can be found in reference.[173b]



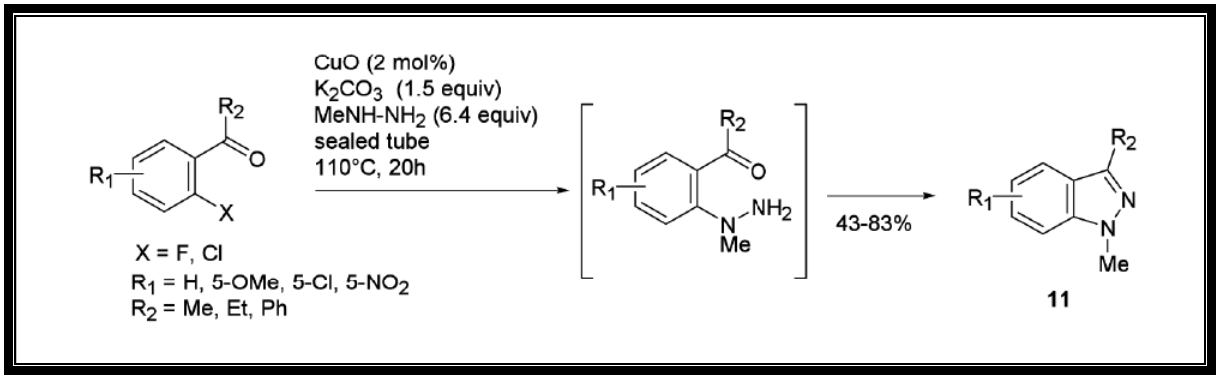
Scheme 6

Based on the same strategy, the following example[174] depicts a slightly different route to 3-amino-1*H*indazoles (Scheme 7). Three other examples of preparation of 3-amino-1*H*-indazoles can be found in references[175]; references[176] give additional examples of preparation of differently substituted 1*H*-indazoles.



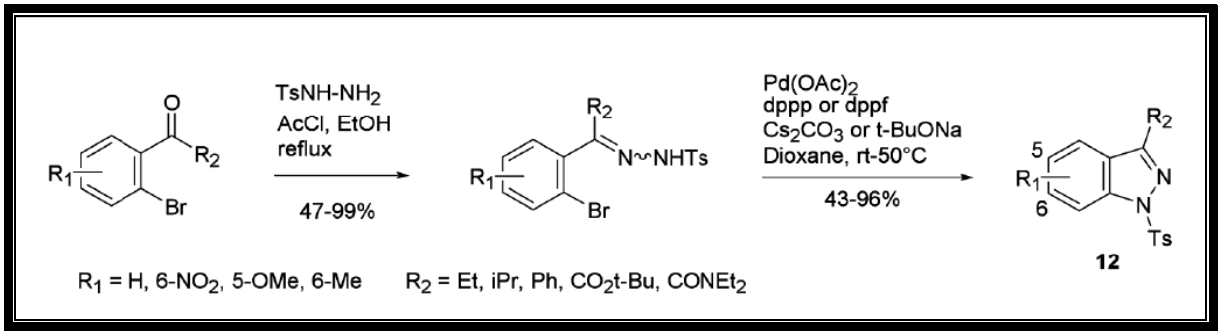
Scheme 7

A regioselective one-step procedure to reach 1-alkyl and 1-phenyl-1*H*-indazoles has been recently reported based on the CuO-catalyzed reaction of *N*-methylhydrazine with 2-haloalkyl- or 2-halophenylketones.[177] Reactions were conducted in a sealed tube at 110°C and were interpreted as an Ullmann-type amination followed by cyclization. The same protocol could also be applied to 2-haloarylcarboxylic acids to give 1-methyl-3-hydroxy-1*H*-indazoles, although in quite lower yields. The reaction was also carried out with 2-fluorophenylmethylketone and differently substituted 1-hydrazines (R3NH-NH2, R3 = *t*-Bu, Ph, CH2-CH2OH) to give differently 1-substituted-3-methyl-1*H*-indazoles in low to fair yields (Scheme 8).



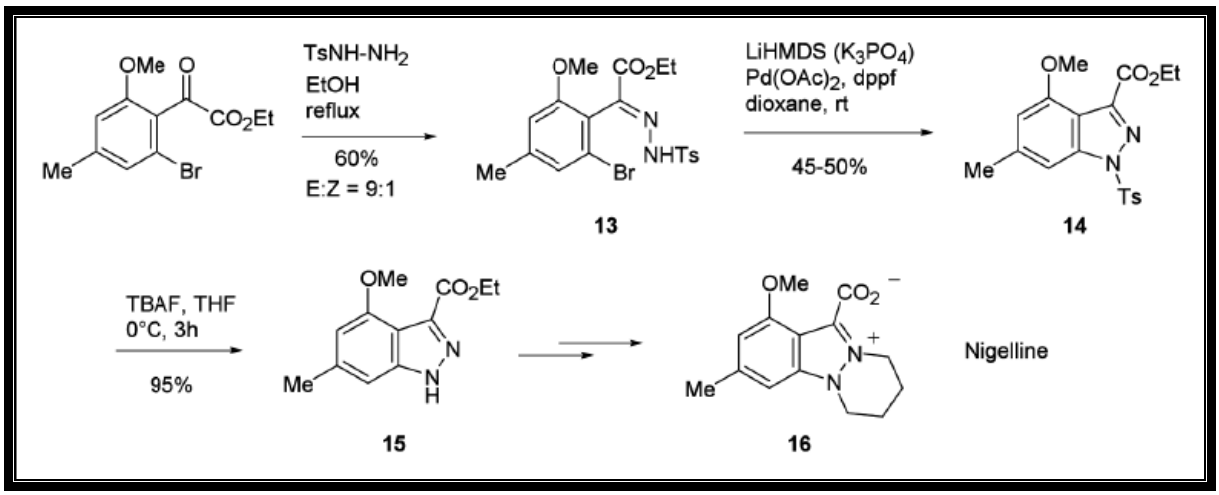
Scheme 8

Several examples of preparation of 1-aryl-1*H*-indazoles *via* an intramolecular Pd-catalyzed amination reaction of tosylhydrazones have been reported. A recent example due to Inamoto et al.[178] is depicted in scheme 9.



Scheme 9

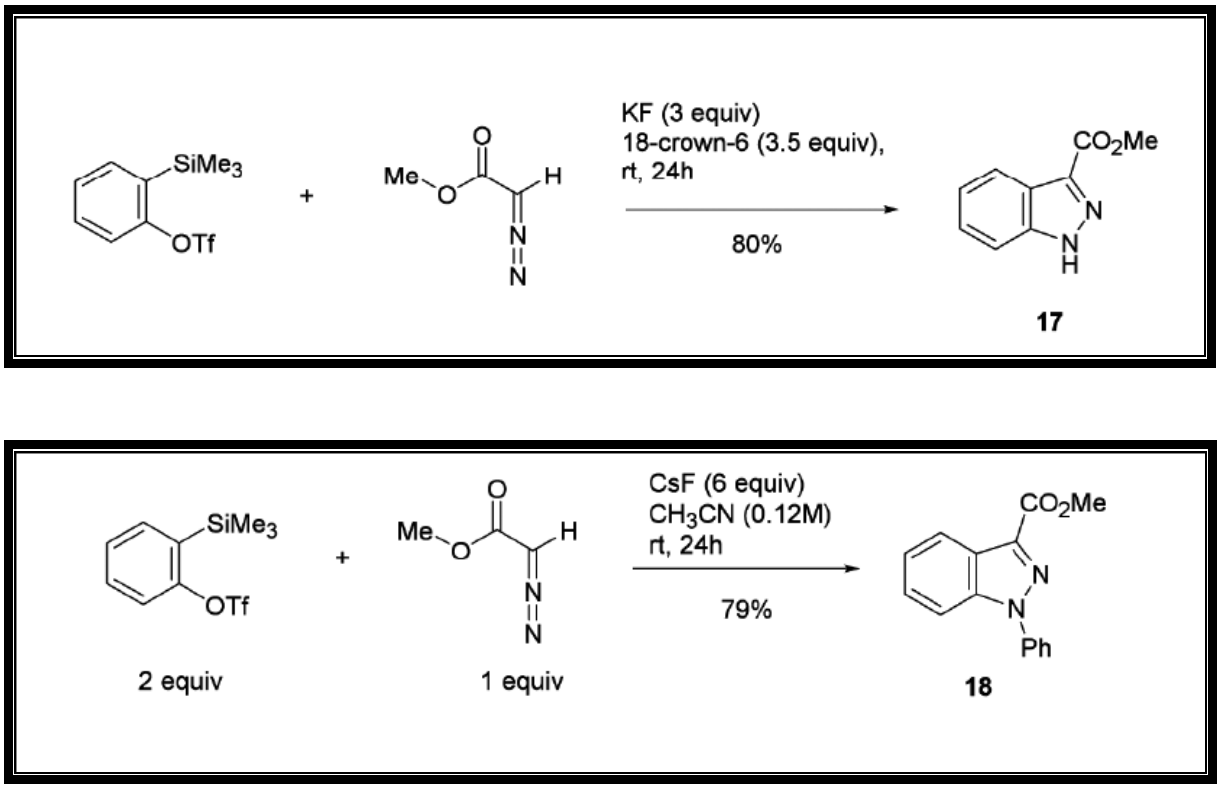
In the case of tosylhydrazone **13**, the catalyst system that gave good results in the precedent example induced the formation of 1*H*-indazole **14** in only poor yield. Instead, extensive degradation of tosylhydrazone **13** was observed, even at room temperature. After having tested several other conditions, it was finally discovered that the use of LiHMDS or K_3PO_4 as a base allowed the cyclization to proceed at room temperature in fair yield (45-50%). Indazole **14** was then *N*-deprotected to give **15**, the transformation of which to the natural alkaloid nigelline **16** could be achieved in two steps (Scheme 10). Other examples of palladium-induced formation of 1-aryl-1*H*-indazoles are listed in references.[179]



Scheme 10

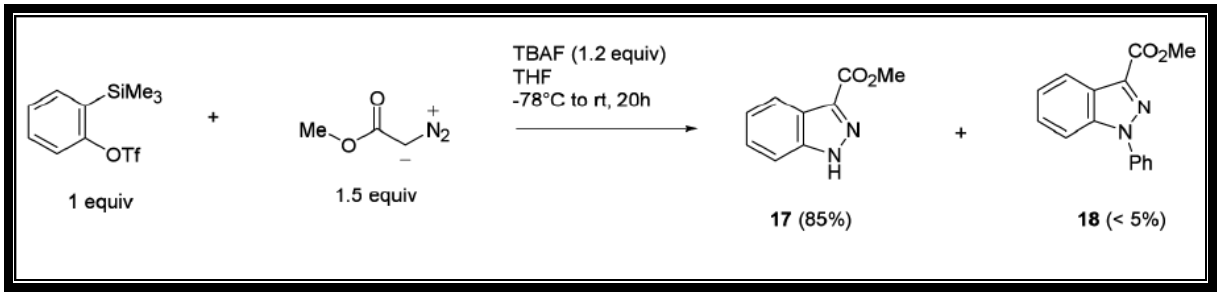
Recently, Yamamoto et al.[180] reported efficient procedure for synthesizing *N*-unsubstituted and 1-arylated-1*H*-indazoles via a [3+2] dipolar cycloaddition between arynes and diazomethane derivatives. Thus, treatment of *o*-TMS-phenyltriflate, as a benzyne precursor, and ethyldiazoacetate in THF at rt, in the presence of KF and a crown ether, afforded 3-ethoxycarbonyl-1*H*-indazole **17** in 80% yield. Substitution of the phenyl ring and use of several other diazo compounds (R-CH_2N_2 with R = t-BuO_2C, TMS, Ph) proved compatible with the reaction. In contrast, when *o*-TMS-phenyltriflate (2 equiv) was treated with ethyldiazoacetate in acetonitrile at rt in the presence of CsF in excess, 1-phenyl-3-

ethoxycarbonyl-1*H*-indazole **18** was isolated in 79% yield (Scheme 11). Of course, compound **18** arised from arylation of intermediate **17** by the excess of *o*-TMS-phenyltriflate (→benzyne) in the medium. Variations in the structure of both cycloaddition reaction partners are possible.



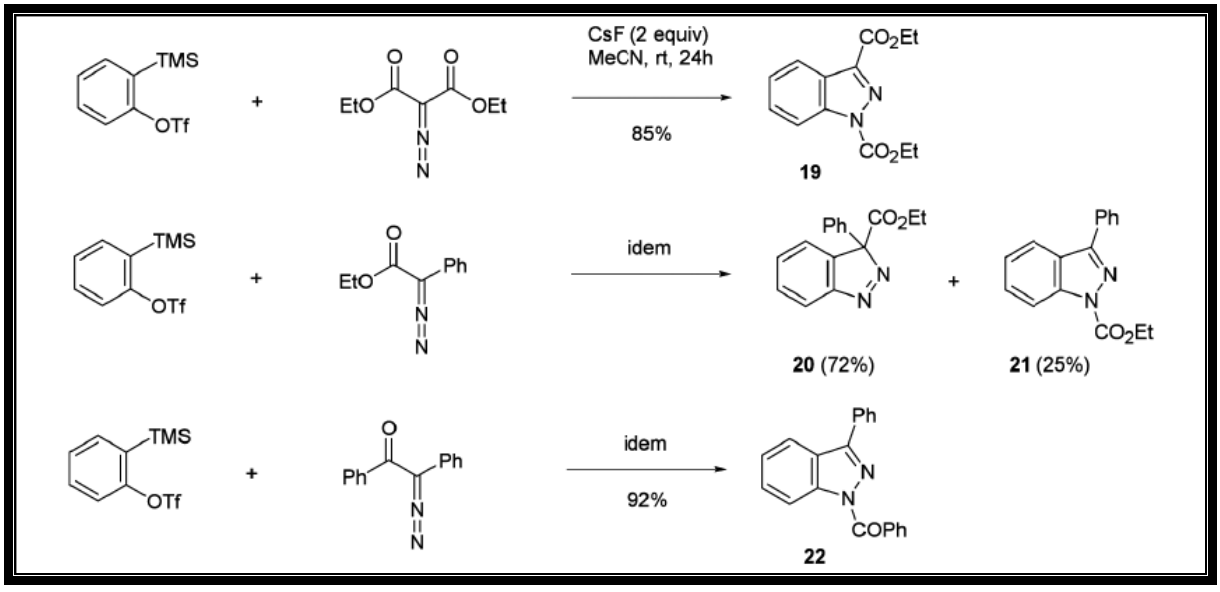
Scheme 11

Almost at the same time, Larock and coll.[181] reported a more exhaustive study on similar work. The [3+2] dipolar cycloaddition between ethyldiazoacetate (1.5 equiv) and *o*-TMS-phenyl triflate (1 equiv) was accomplished in the presence of TBAF (1.2 equiv) as a fluoride source in THF at low temperature. In these conditions, 3-ethoxycarbonyl-1*H*-indazole **17** was formed in up to 85% yield along with small quantities (less than 5%) of 1-phenyl-3-ethoxycarbonyl-1*H*-indazole **18** (Scheme 12). Subsequent exploration of the scope and limitations of the reaction demonstrated that, by applying the same experimental conditions as above, a variety of benzyne precursors and monosubstituted diazomethane derivatives allowed the preparation of substituted 1*H*indazoles in fair to good yields. Using an excess of benzyne precursor (2.4 equiv) led to 1-aryl substituted 1*H*indazole compounds by capture of the excess aryne at nitrogen N1.



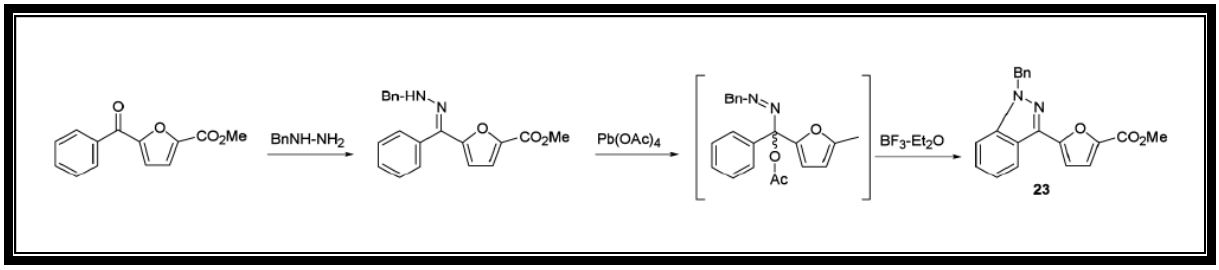
Scheme 12

In a second part of their work, and following the pioneering work of Shechter and coll.[182], Larock and coll. Focused on the reaction of arynes with diazo substrates that do not have hydrogen on the diazo carbon. Thus, reaction of benzyne (from *o*-TMS-phenyl triflate) with diazo compounds having two carbonyl groups attached to the diazo carbon led quite generally to the product arising from [3+2] cycloaddition and 1,3-migration (carbon C3 to nitrogen N1) in good yield. When only one ester group was branched at the diazo carbon, the reaction led mainly, if not exclusively, to the product of cycloaddition. In contrast, when a ketone rather than an ester was attached at the diazo carbon, the product of cycloaddition-acyl migration was solely formed. Examples are shown in Scheme 13.



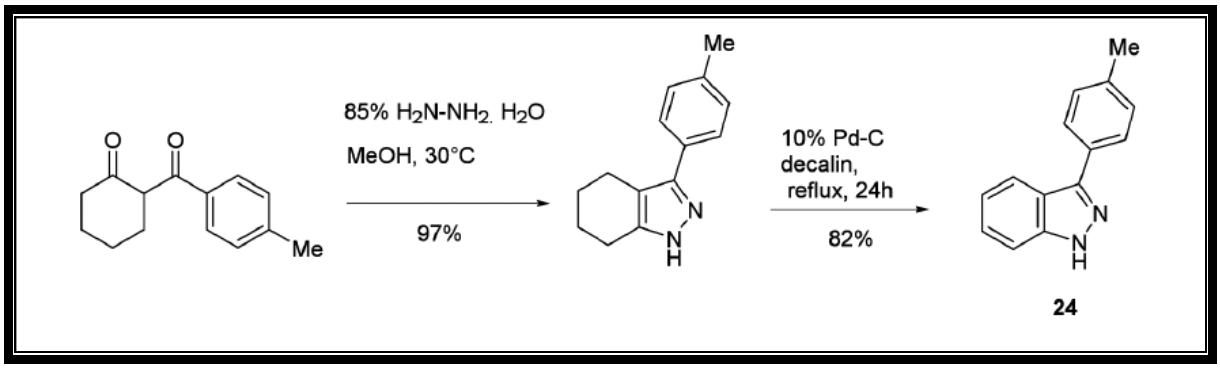
Scheme 13

In the course of a work aimed at discovering novel antiplatelet agents derived from 1-benzyl-3-(5'-hydroxymethyl-2'-furyl) indazole, Lee et al.[183] reported an unusual synthesis of the 1*H*-indazole derivative **23** from a diaryketone. This ketone was first treated with benzylhydrazine to give the corresponding hydrazones (E+Z mixture). The latter mixture was then, under the action of lead tetraacetate, transformed to an azo compound intermediate which was subsequently cyclized to the desired 1*H*-indazole under Lewis acid activation (Scheme 14).



Scheme 14

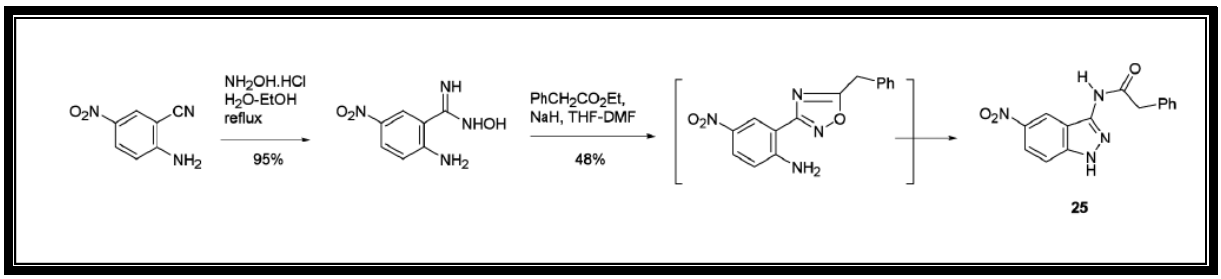
In all above examples the 1*H*-indazoles were prepared from a substituted phenyl precursor. In relation with the search for novel compounds with anti-angiogenic activity, a recent paper[184] reported the preparation of 3-aryl-1*H*-indazoles by aromatization of 4,5,6,7-tetrahydro-1*H*-indazoles (Scheme 15).



Scheme 15

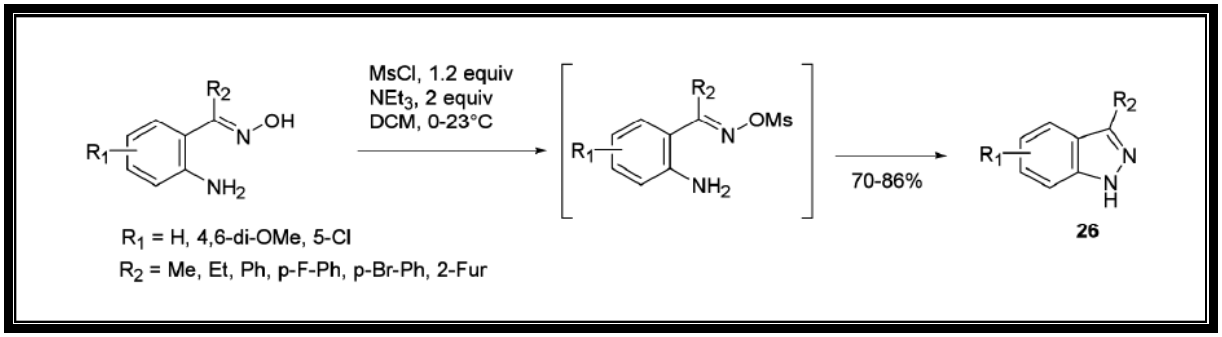
2. Creation of the N1-N2 bond

Not surprisingly, the methods of preparation of substituted 1*H*-indazoles via the formation of the N1-N2 bond are scarce in comparison to the methods that create a C-N bond. Few examples have been recently reported. In order to evaluate a series of 3,5-diamino-1*H*-indazoles as cyclin-dependent kinases (CDKs) inhibitors, Lee et al.[185] prepared the key intermediate 1*H*-indazole **25** from 2-amino-5-nitro-benzonitrile. Their approach features the transformation of the starting benzonitrile into a *N*-hydroxylamidine followed by its transformation to the target 1*H*-indazole via the formation of a 1,2,4-oxadiazole intermediate (Scheme 16).

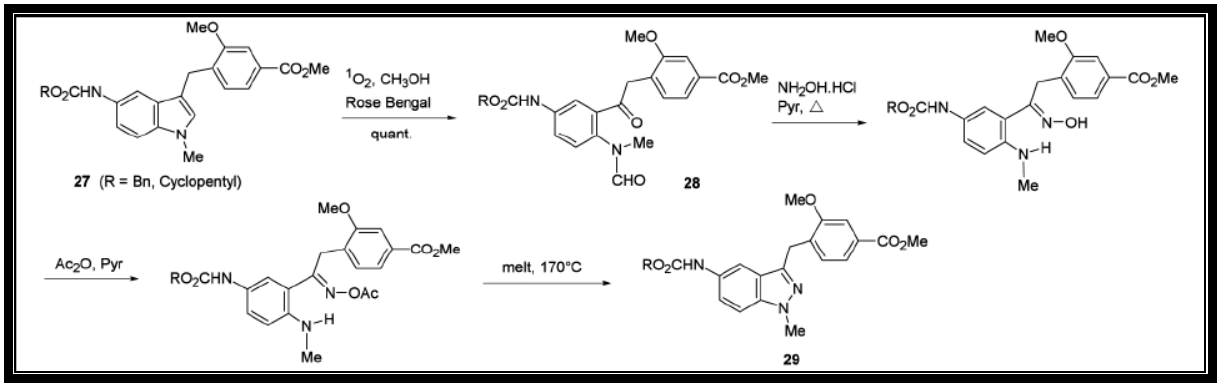


Scheme 16

A protocol for the synthesis of 1*H*-indazoles from *o*-aminobenzoximes with creation of the N-N bond has been reported by Canceller et al.[186] It features the selective activation of the oxime group by reaction with a slight excess of methanesulfonyl chloride followed by cyclization to the 1*H*-indazoles by exposure to triethylamine at rt (Scheme 17). A similar strategy to reach 1*H*-indazoles had been reported previously by Matassa et al.[187] in a study directed at discovering potent and selective peptidoleukotriene antagonists, However, in the Matassa's report (Scheme 18) the synthesis of 1*H*-indazole **29** was achieved following an indole to indazole conversion. In practice, indole **27**, prepared in four steps from nitro-5-indole, was first submitted to the action of singlet oxygen to give the C2-C3 double bond oxidation product **28**. *(E)*-Oxime formation with concomitant removal of the formyl group, acetylation to give the corresponding oxime acetate then cyclization completed the synthesis of 1*H*-indazole **29**.

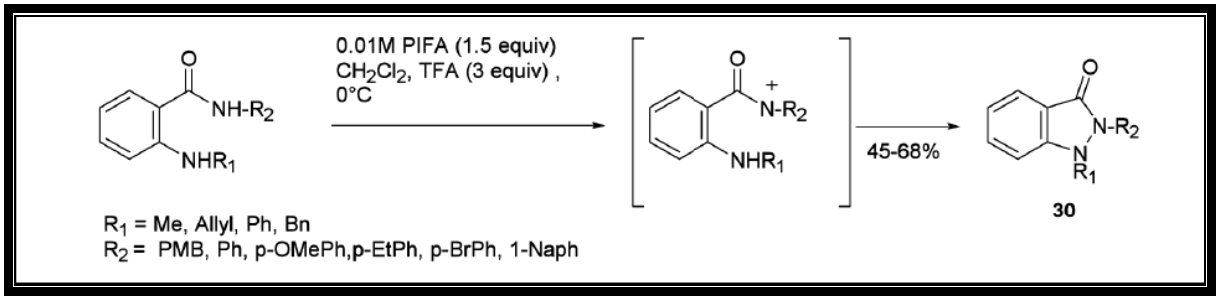


Scheme 17



Scheme 18

The synthesis of a series of 1*H*-indazol-3-ones with creation of the N-N bond has been achieved via the intramolecular trapping of an *N*-acylnitrenium intermediate by an *ortho*-disposed amino group[188]. Starting from an *o*-aminobenzamide the *N*-acylnitrenium cation was best generated by action of the hypervalent iodine reagent PIFA in DCM at 0°C (Scheme 19).



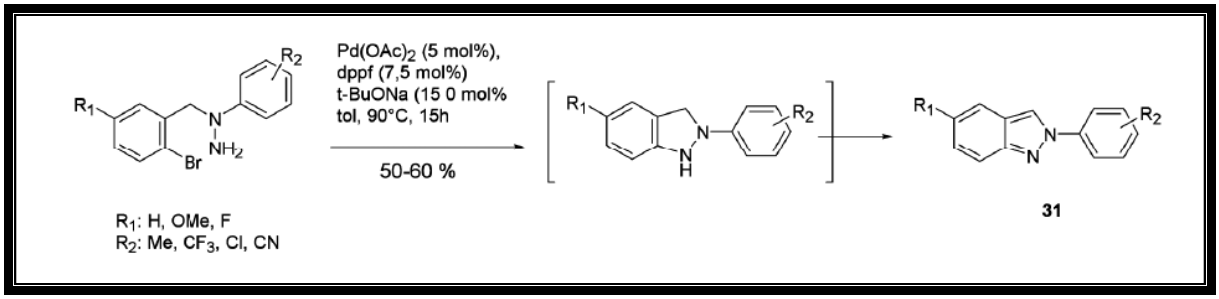
Scheme 19

B. Methods for the preparation of *N*-2 substituted 2*H*-indazole compounds

1. Creation of a C-N bond

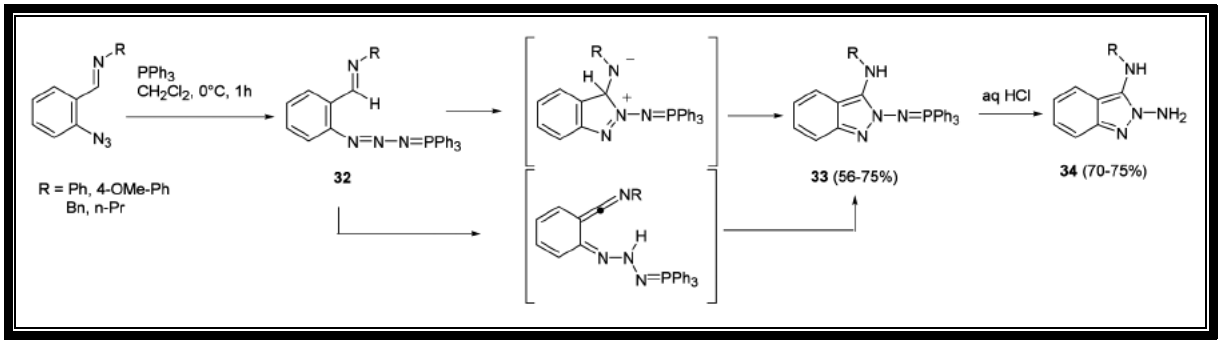
The chemistry of 2*H*-indazoles has not been explored as well as the chemistry of 1*H*-indazoles. However, the discovery that *N*-2 substituted 2*H*-indazole compounds may exhibit biological activities has generated recent interest in their simple and efficient preparation.

A synthesis of 2-aryl-2*H*-indazoles *via* a palladium-mediated intramolecular amination reaction of *N*-aryl-*N*-(*o*bromobenzyl)-hydrazines has been reported by Song and Yee.[189] The best conditions to effect the transformation are heating in toluene at 90°C for 15h in the presence of $Pd(OAc)_2$ (5 mol%), dppf (7.5 mol%), and t-BuONa (15 0 mol%). Yields were comprised in the 50 to 60% range. The catalytic system is equally effective for electron-rich and electron-deficient substituents on both phenyl rings. In a mechanistic point of view the formation of the sp_2 C-N bond is followed by the spontaneous oxidation of the dihydroindazole intermediates to give the 2-aryl-2*H*-indazole products (Scheme 20).



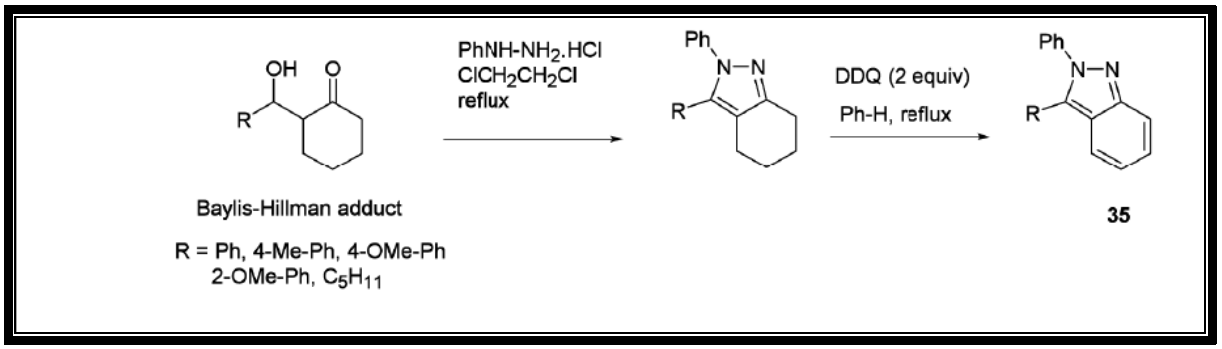
Scheme 20

Molina et al.[190] reported the preparation of 2,3-diamino-2*H*-indazoles by treatment of *o*-azidobenzaldimines with tertiary phosphines followed by acidic hydrolysis. The reaction led first to the formation of 2*H*-indazole derivatives **33** whose subsequent hydrolysis furnished the 2,3-diamino-2*H*-indazoles **34**. The transformation may be accounted for by an initial Staudinger reaction to give a reactive phosphazide intermediate **32** followed by a cyclization reaction or by the formation of a ketenimine through a 1,5 sigmatropic shift and subsequent ring closure (Scheme 21).



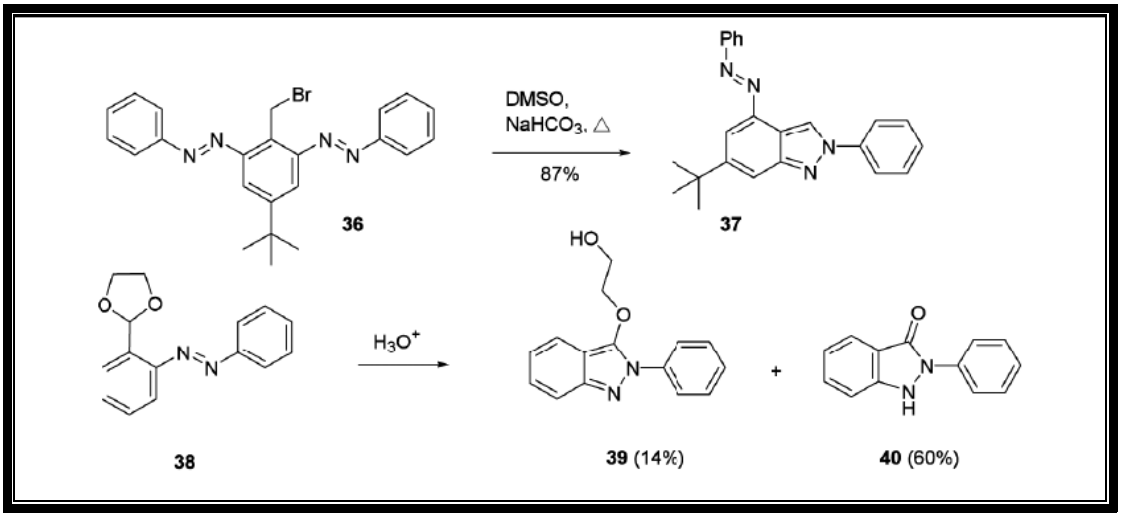
Scheme 21

Starting from Baylis-Hillman adducts of cyclohexenone, a two-step procedure for the formation of *N*-Ph-2*H*-indazoles featuring DDQ oxidation of pyrazoles intermediates has been reported[191] (Scheme 22). Moderate overall yields were obtained (c.a 35%).



Scheme 22

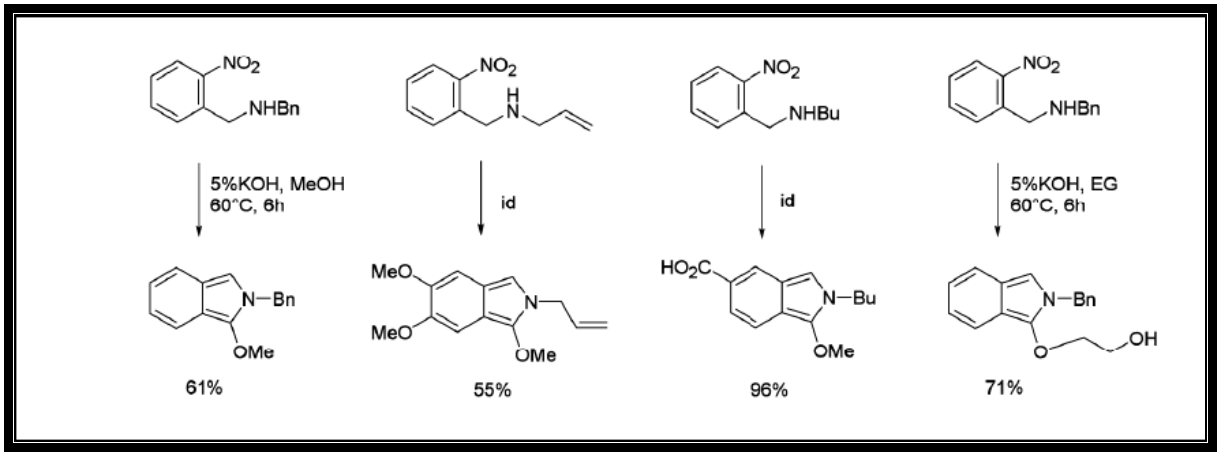
German scientists[192] observed that several oxidation procedures, such as the Kornblum oxidation, applied to benzyl bromide **36**, instead of giving the expected aldehyde, led in fact to the 2-phenyl-2*H*-indazole compound **37**. In an other example, acidic hydrolysis of acetal **38** failed to give the corresponding aldehyde but led instead to a mixture of 2-phenyl-2*H*-indazole compound **39** and 2-phenyl-1*H*-indazol-3-one compound **40** (Scheme 23).



Scheme 23

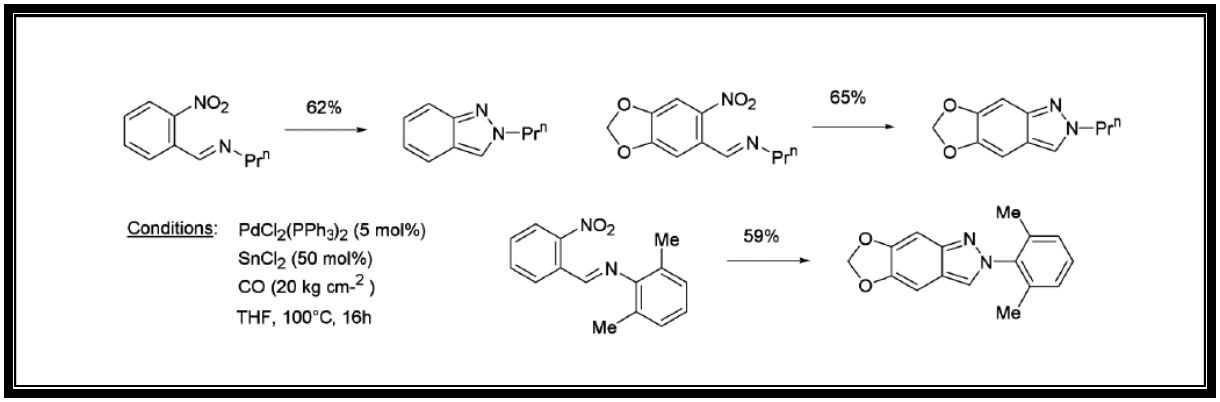
2. Creation of the N1-N2 bond

A one-step synthesis of 3-alkoxy-2*H*-indazoles by heating *o*-nitrobenzylamines in a solution of 5% KOH in an alcoholic solvent has been reported by Kurth and coll.[193a] The starting amines were prepared from either *o*-nitrobenzylbromides or *o*-nitrobenzaldehydes in excellent yields. As shown in Scheme 24, an electron-withdrawing group in the starting o-nitrobenzylamine has a beneficial influence on the reaction productivity. Several other alcohols may be employed instead of methanol. A mechanism has been proposed to account for these transformations.[193b] This synthetic strategy was subsequently applied to generate a library of 2-alkyl-3-alkoxy-2*H*-indazole-6-carboxamides (200 compounds).[193c]



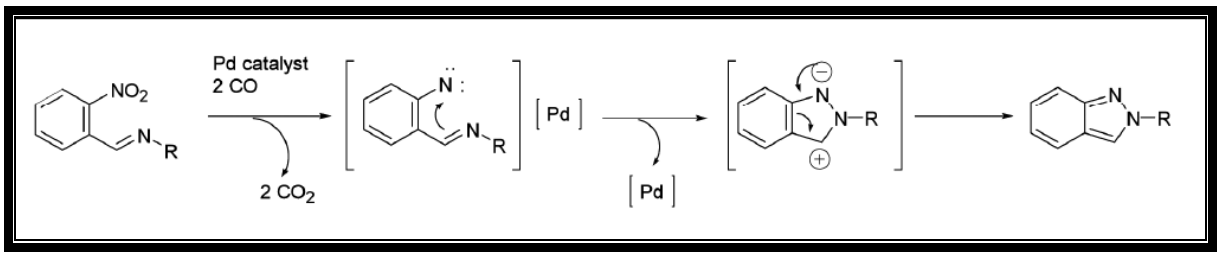
Scheme 24

Akazome et al.[194] reported the palladium-catalyzed intramolecular reductive *N*-heterocyclization of (2-nitrobenzylidene) amines to give the corresponding 2*H*-indazole products in 48-75% isolated yields. Reactions were conducted in a stainless reactor at 100°C for 16h under 20 kg cm^{-2} of initial CO pressure and in the presence of a $PdCl_2(PPh_3)_2$ (5 mol%)-SnCl2 (50 mol%) system. Some examples are shown in Scheme 25.



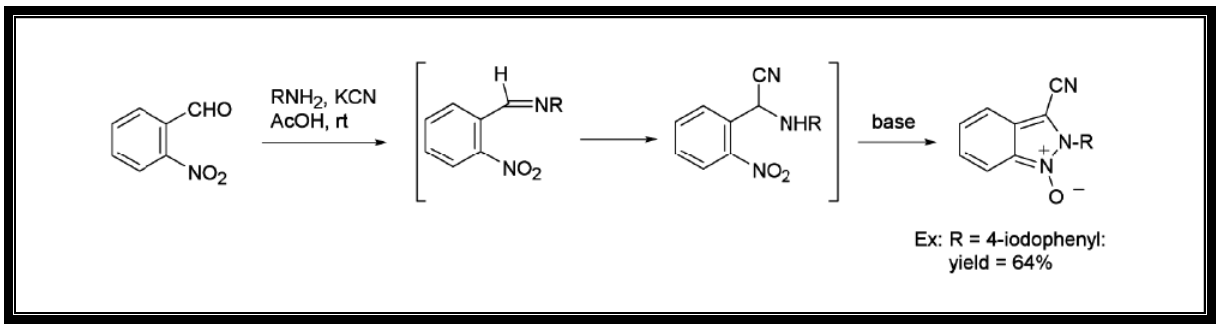
Scheme 25

On the basis of experimental observations and deuterium labelling experiments, a mechanism involving the formation of a nitrene, intermediate, strongly coordinated to the metal, was postulated (Scheme 26).



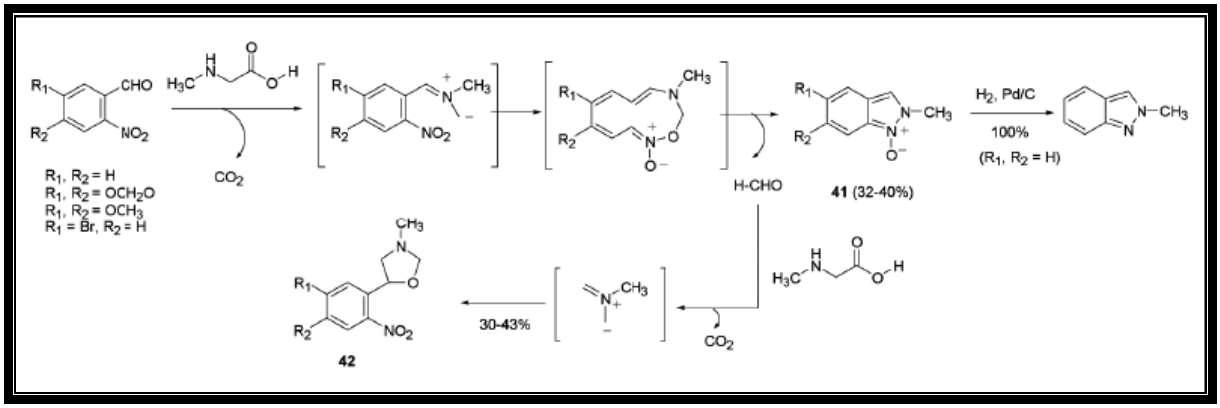
Scheme 26

A series of 3-cyano-2*H*-indazole N^1-oxides has been synthesized in order to evaluate the trypanocidal and leishmanocidal activities of each derivative[195]. Following the route shown in Scheme 27, *o*-nitrobenzaldehyde was first transformed, *via* a Schiff base, to an α-aminonitrile derivative which was next cyclized to a 3-cyano-2*H*-indazole N^1-oxide by treatment with a base (Et_3N or $NaHCO_3$).



Scheme 27

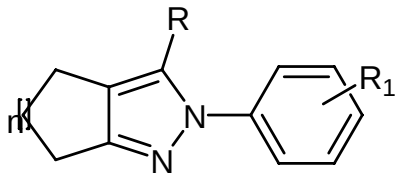
Nyerges et al.[196] reported the synthesis of 2*H*-indazole-N^1-oxides *via* a 1,7-electrocyclization reaction of azomethine ylides onto a nitro group. Thus, *o*-nitrobenzaldehyde reacted with sarcosine to generate, following a decarboxylative condensation process, an unstabilized azomethine ylide. The latter reacted with the nitro group to give, by way of a 1,7-electrocyclization, an oxadiazepine intermediate, which then undergoes a ring contraction to ultimately give the 2*H*-indazole-N^1-oxides **41** in modest yield. The formaldehyde formed during the contraction step is trapped by the excess of sarcosine to give an azomethine ylide, which, by reaction with the starting *o*-nitrobenzaldehyde, led to an oxazolidine by-product **42**. Reduction of 2*H*-indazole-N^1-oxide **41** (R1,R2 = H) led to the corresponding 2*H*-indazole (Scheme 28).



Scheme 28

6.3 Biological Profile

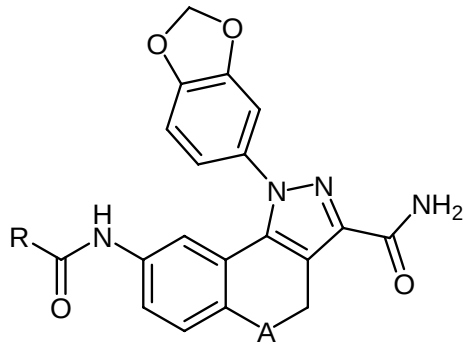
Wolf A. D. et. al.[197] reported the compounds of formula **(1)** as useful for the selective preemergence control of undesired vegetation e.g., barnyard grass, in crops such as rice, in particular paddy rice, wheat, and peanuts. These compounds also have utility for the post emergence control of weeds in certain crops, for example, rice. Furthermore, compounds of this invention can be used as directed treatments for the pre- or post-emergence control of weeds in various crops including soybeans, peanuts, cotton, garden beans and row planted rice.



(1)

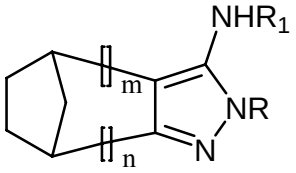
n = 1,2,3
R = fluorine, chlorine, bromine or iodine
R1= fluorine, chlorine, bromine, iodine, cyano, methoxy or nitro

Metz, S. et. al.[198] described fused pyrazolo compounds **(2)** for the treatment of inflammation, while Bauer, V. J. et. al.[199] described new fused bicyclic aminopyrazoles **(3)** and their physiologically acceptable salts possessing anti-inflammatory and analgesis properties.



A = O, NH, NCOCH3, NSO2CH3
R = o-Cl-Pyridine, o-Cl-Ph

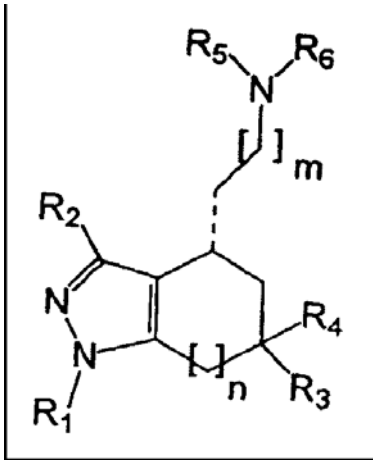
(2)



Where
R = H, alkyl of 1-4 carbon atoms, phenyl or halophenyl;
R_1= alkyl of 1-4 carbon atoms, cycloalkyl of 3-7 carbon atoms, phenyl or halophenyl;
m and n are 0 or 1.

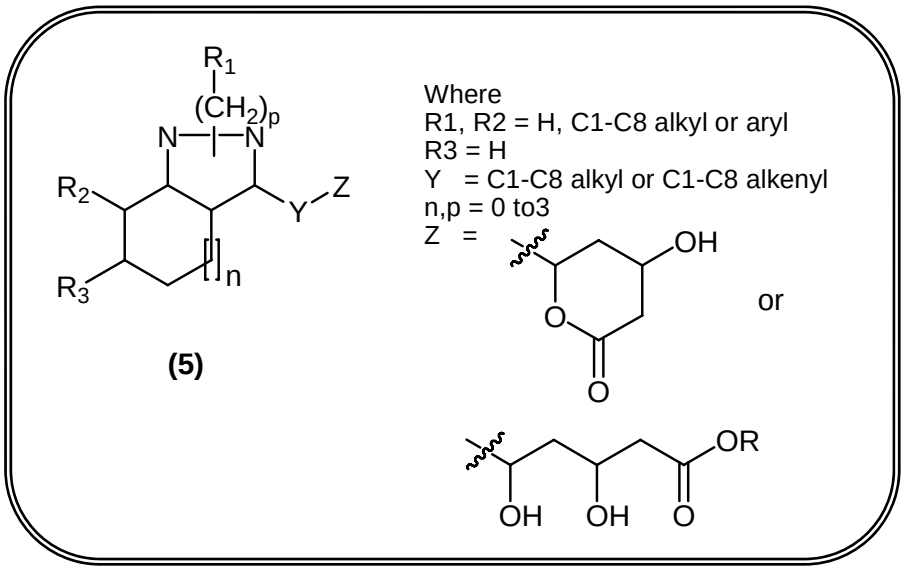
(3)

Corbera A. and Esteve, S.A. et. al.[200] had reported some tetrahydroindazole and fused pyrazole derivatives **(4)** having pharmacological activity towards the sigma receptor, and their use in particular for the treatment of psychosis or pain.

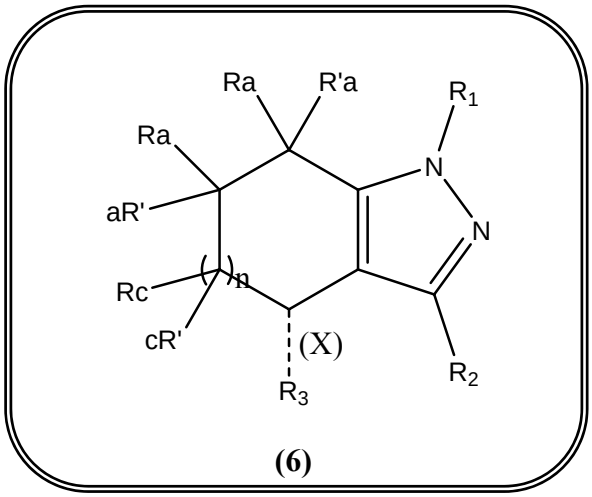


(4)

Peter J. Connolly et al[201] demonstrated the synthesis of some tetrahydroindazole, tetrahydrocyclopentapyrazole, and hexahydrocycloheptapyrazole compounds **(5)** and their use as HMG-COA reductase inhibitors.



Paolo Pevarello, and Menuela Villa, et. al.[202] reported 4,5,6,7-tetrahydroindazole derivatives **(6)** as antitumor agents.



Where doted line (X) is single or double bond

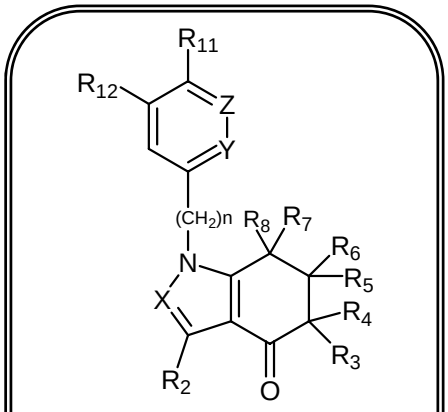
n = 0 or 1

R1, R2 = H, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, nitro, cyano or hydroxyl

R3 = O, S or NH

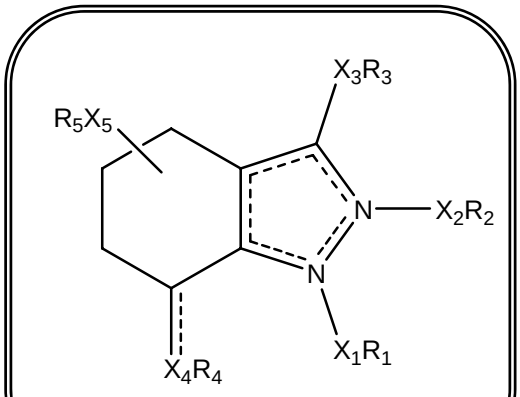
Ra, R'a, Rb, R'b, Rc, R'c = each independently H or branched C_1-C_6 alkyl chain

Zhang, T. et al[203] described the synthesis of tetrahydroindole and tetrahydroindazole **(7)** and characterized their activities of inhibiting the growth of tumor cells and malignant cells, such as breast carcinoma, pulmonary carcinoma, cervical carcinoma, rectal carcinoma, prostatic carcinoma, hepatic carcinoma and leucocythaemia and the like cancer cells.



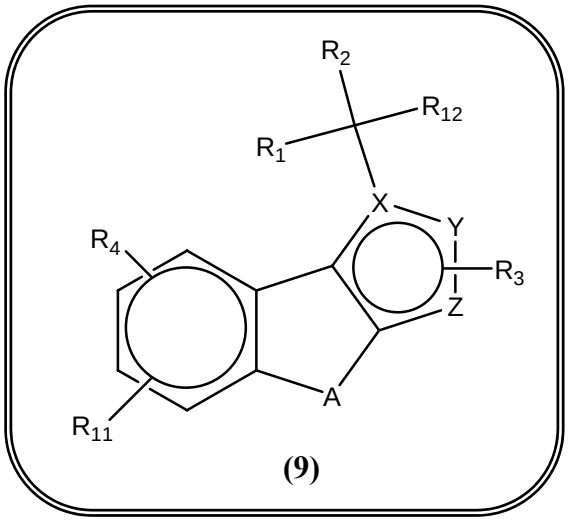
(7)

Lagu, Bharat et. al.[204] reported some tetrahydroindazole derivatives **(8)** as cannabinoid modulator, and a method for use in treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease.



(8)

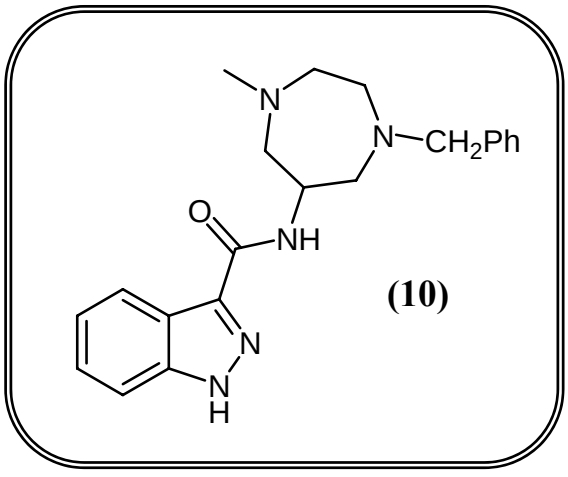
Metz, S. et. al.[205] had described fused pyrazolo systems **(9)** and methods for treating cancer, inflammation and inflammation-associated disorders, such as arthritis.



(9)

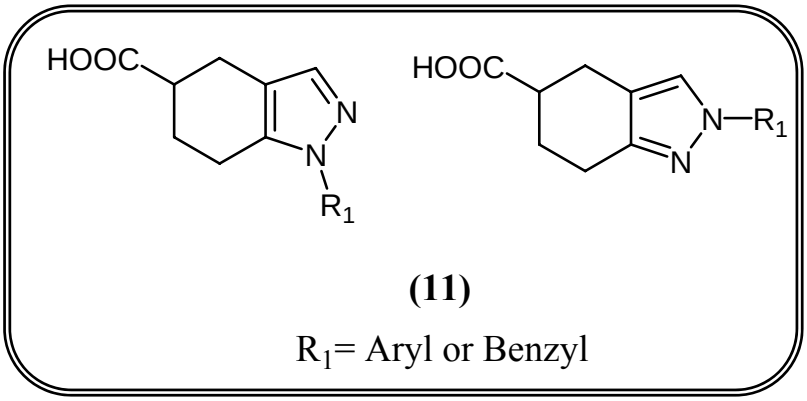
Where A is $(CH_2)_m$-Q-$(CH_2)_n$, wherein each CH_2 may be independently substituted with one or more substitution selected from the group consisting of: hydroxyl, halo, alkoxy, lower alkyl, amino, amino alkyl, alkenyl and alkynyl; B is a 5 or 6 membered heteroaryl, or aryl, optionally saturated, or optionally substituted with R_1, R_2, or R_{12}; X is selected from the group consisting of: N, C, CH, CR_3, S and O.

Harada, H. et. al.[206] had studied on structurally novel N-(1-benzyl-4-methylhexahydro-1H-indazole-3-ca.rboxamide **(10)** as potent and selective **5-HT3** receptor antagonists.



(10)

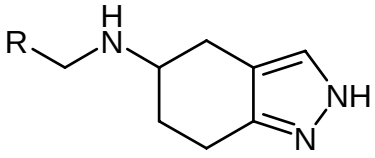
Masahiko Nagakura et.al.[207] synthesized series of 1-aryl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acids and 2-aryl-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylic acids **(11)** and the anti-inflammatory activity was determined. In the carrageenan edema test, 1-aryl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acids exhibited fairly high anti-inflammatory activity. However, the 2-aryl isomer were far less active than the former.



(11)

R_1= Aryl or Benzyl

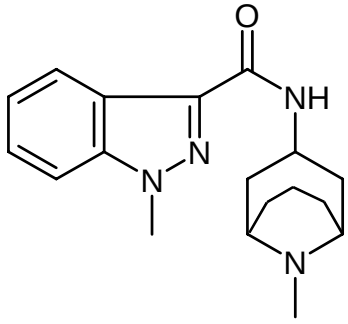
Loretta A. McQuaid et. al.[208] investigated that substituted 5-Amino-4,5,6,7-tetrahydroindazole **(12)** as s partial ergoline structures possessed dopaminergic activity.



(12)

Where R = CH_3, CH_2CH_3, $CH_2CH_2CH_3$,
CH_2Ph, CH_2-2-Thienyl, CH_2CH_2SMe

Granisetron is an antiemetic agent to prevent the nausea and vomiting in conjunction with cancer chemotherapy or with radiation therapy, by blocking 5-HT_3 receptors without effect on other receptors such as dopamine D_2 receptor and 5-HT_4 receptor. Chemical designation is endo-*N*-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1*H*-indazole-3-carboxamide **(13)**.



(13)

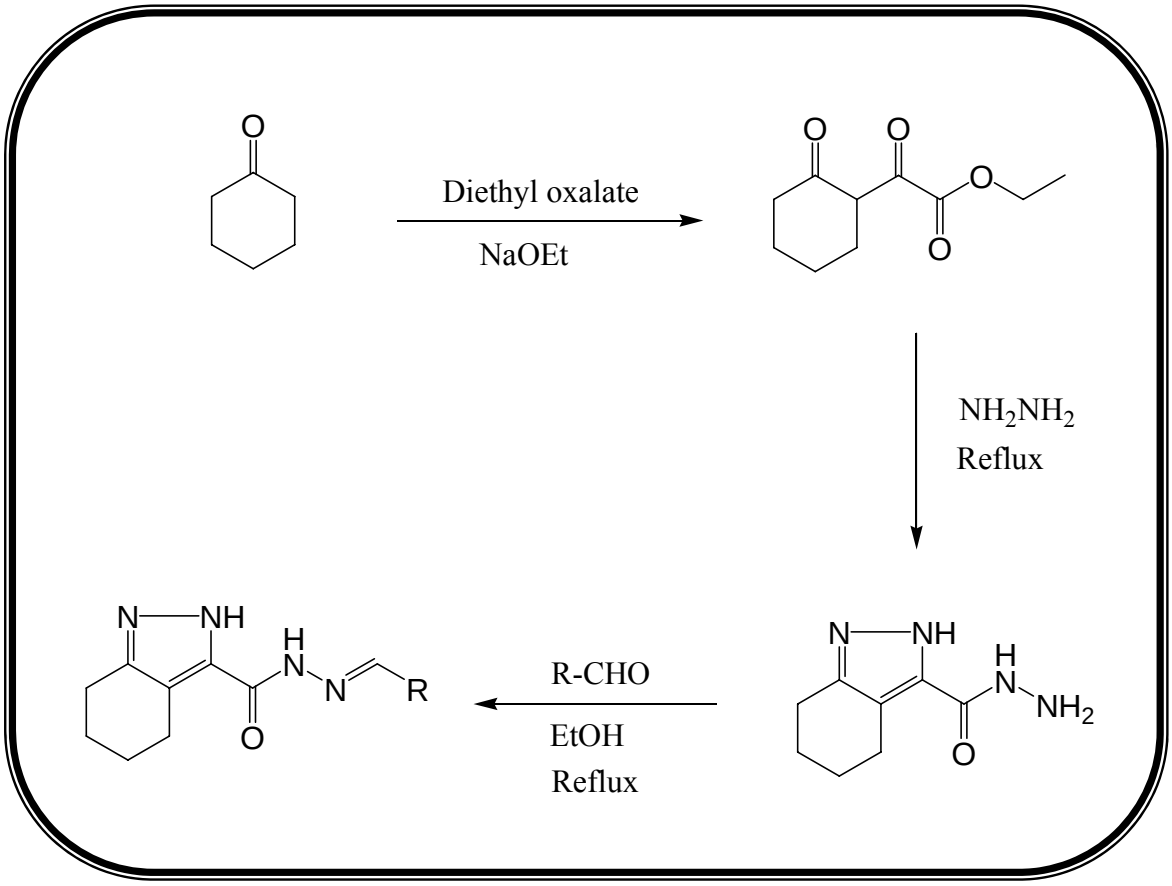
6.4 Current work

Our group is involved in design, synthesis and biological screening of heterocyclic compounds. On conducting literature survey, it was found that tetrahydroindazole is not more explored though it has great importance in the field of medicinal chemistry. On the observation of medicinal importance of tetrahydroindazole, its derivatization is necessary.

The 3-carboxamide derivatives of 1*H*- and 2*H*-indazole possess good medicinal values. We sought to develop some 3-carbohydrazide 4,5,6,7-tetrahydro-2*H*-indazole derivatives. As per mentioned in literature[209], ethyl-2-oxo-2-(2-oxocyclohexyl)acetate was prepared by reacting cyclohexanone and diethyl oxalate with the help of sodium ethoxide in ethanol at 0-5 °C. Subsequent treatment of ethyl-2-oxo-2-(2-oxocyclohexyl)acetate with hydrazine hydrate in ethanol resulted into ethyl 4,5,6,7-tetrahydro-2H-indazole-3-carboxylate, while without solvent in excess hydrazine hydrate on reflux resulted into 4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide as per shown in reaction scheme. The obtained hydrazide was condensed with various aldehydes to generate series of aryl methylene hydrazone derivatives.

All newly synthesized compounds were characterized by IR, Mass, ^{1}H NMR spectroscopy and elemental analysis. Reaction scheme is illustrated in section 6.5. The brief experimental methods are outlined in section 6.6. Physical data of all synthesized compounds is reported in section 6.7 and spectral data is discussed in section 6.8. The compounds synthesized with this modification at 3 position of 4,5,6,7-tetrahydro-2*H*-indazole skeleton are under investigation for their anti HIV activity. The anti viral screening of the synthesized compounds is under investigation.

6.5 Reaction Scheme



6.6 Experimental

6.6.1 Ethyl 2-oxo-2-(2-oxocyclohexyl) acetate:

To the stirred solution of sodium ethoxide (0.2 gram atom), a mixture of cyclohexanone (0.2 mol) and diethyl oxalate (0.2 mol) was added drop wise below 5-10 ºC. Vigorous stirring is required to prevent complete solidification of the reaction mixture. When the addition is complete, the ice bath is retained for an hour, and then the mixture is stirred at room temperature for about six hours. The reaction mixture is then decomposed by the careful addition of cold dilute sulfuric acid solution. The ethyl 2-ketocyclohexylglyoxalate separates as heavy oil and is separated. It is sufficient pure for further reaction. Yield-60%.

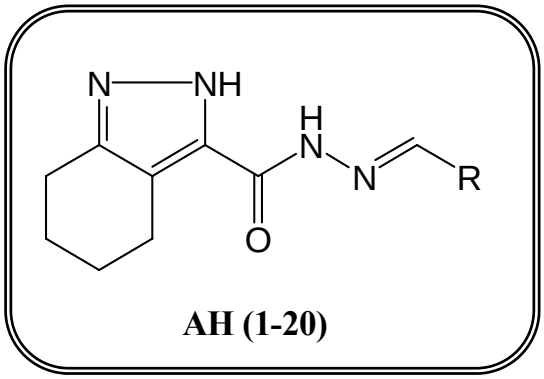
6.6.2 4,5,6,7-Tetrahydro-2H-indazole-3-carbohydrazide:

Ethyl 2-oxo-2-(2-oxocyclohexyl) acetate is added into access 80% hydrazine hydrate and refluxed for 5 to 6 hours. The reaction mixture was allowed to cool at room temperature and the precipitate obtained was filtered, dried and recrystallized from ethanol. White crystals. Yield-65%.

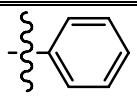
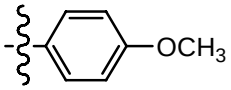
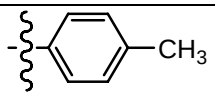
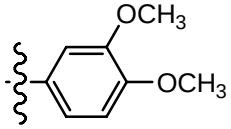
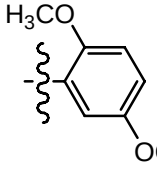
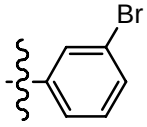
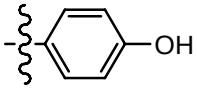
6.6.3 N'-arylmethylene-4,5,6,7-tetrahydro-2H-indazole-3-carbohydrazide:

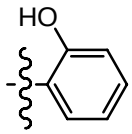
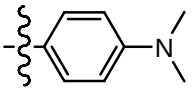
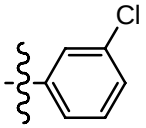
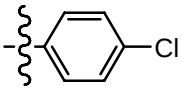
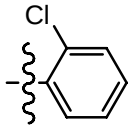
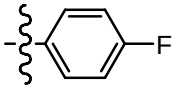
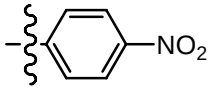
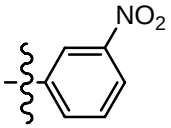
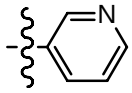
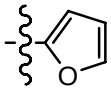
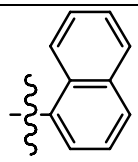
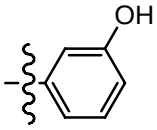
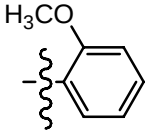
Equimolar amount of 4,5,6,7-tetrahydro-2H-indazole-3-carbohydrazide and appropriate aldehyde were taken in absolute alcohol and added 2 drops of con. HCl as a catalyst. The reaction mixture was refluxed for 1 hour and allowed to cool at room temperature. The solid was filtered, dried and recrystallized from ethanol to give pure white to yellow crystals in 85-90% yield.

6.7 Physical data



AH (1-20)

Comp.	R	M.F.	M.W.	Yield %
AH-1		$C_{15}H_{16}N_4O$	268.31	95
AH-2		$C_{16}H_{18}N_4O_2$	298.33	91
AH-3		$C_{16}H_{18}N_4O$	282.34	86
AH-4		$C_{17}H_{20}N_4O_3$	328.36	85
AH-5		$C_{17}H_{20}N_4O_3$	328.36	89
AH-6		$C_{15}H_{15}N_4OBr$	347.20	95
AH-7		$C_{15}H_{16}N_4O_2$	284.31	91

AH-8		$C_{15}H_{16}N_4O_2$	284.31	85
AH-9		$C_{17}H_{21}N_5O$	311.38	85
AH-10		$C_{15}H_{15}N_4OCl$	302.75	90
AH-11		$C_{15}H_{15}N_4OCl$	302.75	90
AH-12		$C_{15}H_{15}N_4OCl$	302.75	90
AH-13		$C_{15}H_{15}N_4OF$	286.30	86
AH-14		$C_{15}H_{15}N_5O_3$	313.31	80
AH-15		$C_{15}H_{15}N_5O_3$	313.31	80
AH-16		$C_{14}H_{15}N_5O$	269.30	92
AH-17		$C_{13}H_{14}N_4O_2$	258.27	88
AH-18		$C_{19}H_{18}N_4O$	318.37	92
AH-19		$C_{15}H_{16}N_4O_2$	284.31	93
AH-20		$C_{16}H_{18}N_4O_2$	298.33	87

6.8 Spectral discussion

6.8.1 *Mass spectral study*

Instrument : SHIMADZU GCMS-QP-2010

Sample technique : EI technique

M/z range : 40-500

Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. Systematic fragmentation pattern was observed in mass spectral analysis. Peaks for specific fragments were identified in each mass spectrum. Molecular ion peak was observed in agreement with molecular weight of respective compound. Three characteristic peak was observed in all mass spectrum due to specific fragmentation. First a much intense peak was observed at 165 due to the cleavage of N-NH single bond. Another very intense peak at 149 was shown due to the cleavage of single bond between C=O and NH group atom. A very low intense peak at 191 was also observed due to the removal of aryl ring.

6.8.2 *IR spectral study*

Instrument : Shimadzu FT-IR-8400

Sample technique : KBr pellet

Frequency range : 400-4000cm^{-1}

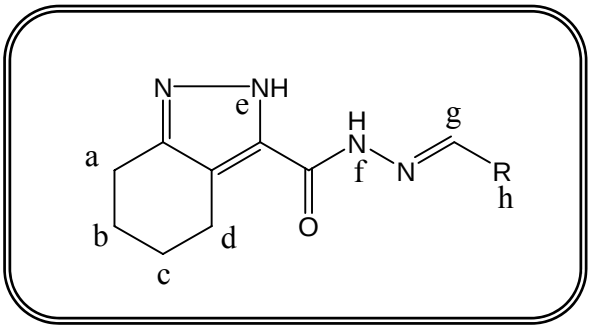
As per IR spectral study of newly synthesized 4,5,6,7-tetrahydro-2*H*-indazole derivatives, the stretching vibration of secondary amine (>NH) was appeared at around 3500-3600 cm^{-1}. The carbonyl (>C=O) stretching vibration of amide group was observed around 1680 cm^{-1}. The symmetric and asymmetric C-H stretching vibration of methylene group of cyclohexane rind system was observed between 2850-2990 cm^{-1} while C-H bending vibration of methylene group was appeared around 1450 cm^{-1}. The ring skeleton vibration was observed between 1500-1600 cm^{-1} due to the presence of phenyl ring system.

6.8.3 *^{1}H NMR spectral study*

Instrument : BRUKER AC 400 MHz FT-NMR

Internal reference : TMS

Solvent : $CDCl_3$



Number of protons and their chemical shifts were found to support the proposed structure of the synthesized compounds. Methylene protons of cyclohexane ring ‘a’, ‘b’, ‘c’ and ‘d’ were observed between 1.7 to 2.9 δ ppm. Amide proton ‘f’ was observed at 10.7-11.00 δ ppm as a singlet, while cyclic NH protons ‘e’ was observed at very down field with 12.34-2.85 δ ppm value as singlet. The ethylenic proton ‘g’ was observed around the 8.3 to 8.8 δ ppm as singlet. The aromatic ring protons ‘h’ were observed between 6.8 to 7.80 δ ppm with splitting according to substitution on phenyl ring.

6.8.4 Elemental Analysis

Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

Spectral data of synthesized compounds (AH 1-20)

***N*'-phenylmethylene-4,5,6,7-tetrahydro-2H-indazole-3-carbohydrazide (AH-1)**

White solid; mp 230-232 ˚C;

IR (KBr): 3626, 3593, 2889, 2947, 2852, 1666, 1554, 1492, 1448, 1261, 709, 630 cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 12.36 (S, 1H, NH), 10.78 (S, 1H, NH), 8.34 (s, 1H, =CH), 7.76-7.67 (m, 2H, Ar), 7.40-7.37 (m, 3H, Ar), 3.15-2.78 (m, 4H, CH_2), 1.81-1.75 (m, 4H, CH_2); **MS: m/z** = 268 (M^+); **Anal. Calcd** for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.10; H, 6.12; N, 20.84.

***N*'-(4-methoxyphenyl)methylene-4,5,6,7-tetrahydro-2H-indazole-3-carbohydrazide (AH-2)**

White solid; mp 216-218 ˚C;

IR (KBr): 3628, 2989, 2966, 2943, 2033, 1905, 1680, 1627, 1605, 1508, 1460, 1251, 835 cm^{-1}; **MS: m/z** = 298 (M^+); **Anal. Calcd** for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.58; H, 5.93; N, 18.56.

***N*'-(4-methylphenyl)methylene-4,5,6,7-tetrahydro-2H-indazole-3-carbohydrazide (AH-3)**

White solid; mp 208-210 ˚C;

IR (KBr): 3628, 2941, 2864, 1681, 1529, 1498, 1452, 1246, 854 cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 12.57 (S, 1H, NH), 10.85 (S, 1H, NH), 8.31 (s, 1H, =CH), 7.75-7.62 (m, 2H, Ar), 7.20-7.18 (m, 2H, Ar), 2.97-2.77 (m, 2H, CH_2), 2.66-2.58 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 1.80-1.74 (m, 4H, CH_2); **MS: m/z** = 282 (M^+); **Anal. Calcd** for : C, 68.06; H, 6.43; N, 19.84. Found: C, 68.18; H, 6.50; N, 19.77.

***N*'-(3,4-dimethoxyphenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-4)**

Yellow solid; mp 220-222 ˚C;

IR (KBr): 3628, 2905, 2847, 1681, 1554, 1428, 1221, 836 cm^{-1}; **MS: m/z** = 328 (M^+); **Anal. Calcd** for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06. Found: C, 62.38; H, 6.29; N, 17.01.

***N*'-(2,5-dimethoxyphenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-5)**

Pale-yellow solid; mp 212-214 ˚C;

IR (KBr): 3650, 3128, 2991, 2883, 1664, 1545, 1508, 1492, 1427, 1255, 889 cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 12.50 (S, 1H, NH), 10.60 (S, 1H, NH), 8.61 (s, 1H, =CH), 7.57 (t, 1H, Ar), 6.90 (t, 2H, Ar), 3.83 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.80 (d, 2H, CH_2), 2.65 (t, 2H, CH_2), 1.81-1.74 (m, 4H, CH_2); **MS: m/z** = 328 (M^+); **Anal. Calcd** for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06. Found: C, 62.31; H, 6.25; N, 17.02.

***N*'-(3-bromophenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-6)**

White solid; mp 214-216 ˚C;

IR (KBr): 3648, 2998, 2915, 1678, 1614, 1595, 1539, 1445 cm^{-1}; **MS: m/z** = 346 (M^+); **Anal. Calcd** for $C_{15}H_{15}BrN_4O$: C, 51.89; H, 4.35; N, 16.14. Found: C, 51.92; H, 4.17; N, 16.53.

***N*'-(4-hydroxyphenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-7)**

White solid; mp 219-220 ˚C;

MS: m/z = 284 (M^+); **Anal. Calcd** for Calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.64; H, 5.45; N, 19.69.

***N*'-(2-hydroxyphenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-8)**

White solid; mp 226-228 ˚C;

IR (KBr): 3614, 2978, 2949, 2853, 1678, 1660, 1549, 1428 cm^{-1}; **MS: m/z** = 284 (M^+); **Anal. Calcd** for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.58; H, 5.51; N, 19.80.

***N*'-[4-(dimethylamino)phenyl]methylene}-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-9)**

Yellowish-orange solid; mp 208-210 ˚C;

IR (KBr): 3614, 2998, 2989, 2850, 2828, 1680, 1441 cm^{-1}; **MS: m/z** = 311 (M^+); **Anal. Calcd** for $C_{17}H_{21}N_5O$: C, 65.57; H, 6.80; N, 22.49. Found: C, 65.68; H, 6.69; N, 22.67.

***N*'-(3-chlorophenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-10)**

Pale-yellow solid; mp 212-214 ˚C;

MS: m/z = 302 (M^+); **Anal. Calcd** for $C_{15}H_{15}ClN_4O$: C, 59.51; H, 4.99; N, 18.51. Found: C, 59.35; H, 5.17; N, 18.19.

***N*'-(4-chlorophenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide(AH-11)**

White solid; mp 225-226 ˚C;

MS: m/z = 302 (M^+); **Anal. Calcd** for $C_{15}H_{15}ClN_4O$: C, 59.51; H, 4.99; N, 18.51. Found: C, 59.39; H, 5.06; N, 18.27.

***N*'-(2-chlorophenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide(AH-12)**

Pale-yellow solid; mp 216-218 ˚C;

IR (KBr): 3656, 3545, 3014, 2978, 2914, 2856, 1678, 1505, 1428 cm^{-1}; **MS: m/z** = 302 (M^+); **Anal. Calcd** for $C_{15}H_{15}ClN_4O$: C, 59.51; H, 4.99; N, 18.51. Found: C, 59.42; H, 4.91; N, 18.40.

***N*'-(4-fluorophenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide(AH-13)**

White solid; mp 226-228 ˚C;

IR (KBr): 3626, 2947, 1629, 1506, 1413, 1228, 829 cm^{-1}; **MS: m/z** = 286 (M^+); **Anal. Calcd** for $C_{15}H_{15}FN_4O$: C, 62.93; H, 5.28; N, 19.57. Found: C, 62.78; H, 5.39; N, 19.55.

***N*'-(4-nitrophenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide(AH-14)**

Yellow solid; mp 217-218 ˚C;

MS: m/z = 313 (M^+); **Anal. Calcd** for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.83; N, 22.35. Found: 57.29; H, 4.74; N, 22.46.

***N*'-(3-nitrophenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-15)**

Yellow solid; mp 204-206 ˚C;

IR (KBr): 3619, 2914, 2855, 1645, 1515, 1496, 1447, 1221 cm^{-1}; **MS: m/z** = 313 (M^+); **Anal. Calcd** for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.83; N, 22.35. Found: C, 57.40; H, 4.99; N, 22.21.

***N*'-pyridin-3-ylmethylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-16)**

White solid; mp 228-230 ˚C;

IR (KBr): 3641, 2927, 2894, 1675, 1589, 1528, 1456, 1205 cm^{-1}; **^{1}H NMR (400 MHz, DMSO):** δ ppm = 12.61 (S, 1H, NH), 11.24 (S, 1H, NH), 8.45 (s, 1H, =CH), 8.84 (d, 1H, Ar), 8.57-8.55 (m, 1H, Ar), 8.17 (d, 1H, Ar), 8.38-8.35 (m, 1H, Ar), 2.97-2.77 (m, 2H, CH_2),

2.67-2.57 (m, 2H, CH_2), 1.82-1.75 (m, 4H, CH_2); **MS: m/z** = 269 (M^+); **Anal. Calcd** for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.54; H, 5.38; N, 25.88.

***N*'-2-furylmethylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-17)**

White solid; mp 214-216 ˚C;

IR (KBr): 3629, 2974, 2889, 1692, 1606, 1519, 1468, 1427, 1221 cm^{-1}; **MS: m/z** = 258 (M^+); **Anal. Calcd** for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.36; H, 5.36; N, 21.61.

***N*'-1-naphthylmethylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-18)**

White solid; mp 227-228 ˚C;

IR (KBr): 3626, 3593, 3028, 2978, 2912, 2852, 1668, 1554, 1492, 1448, 1282 cm^{-1}; **MS: m/z** = 318 (M^+); **Anal. Calcd** for $C_{19}H_{18}N_4O$: C, 71.68; H, 5.70; N, 17.60. Found: C, 71.78; H, 5.46; N, 17.51.

***N*'-(3-hydroxyphenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-19)**

White solid; mp 215-216 ˚C;

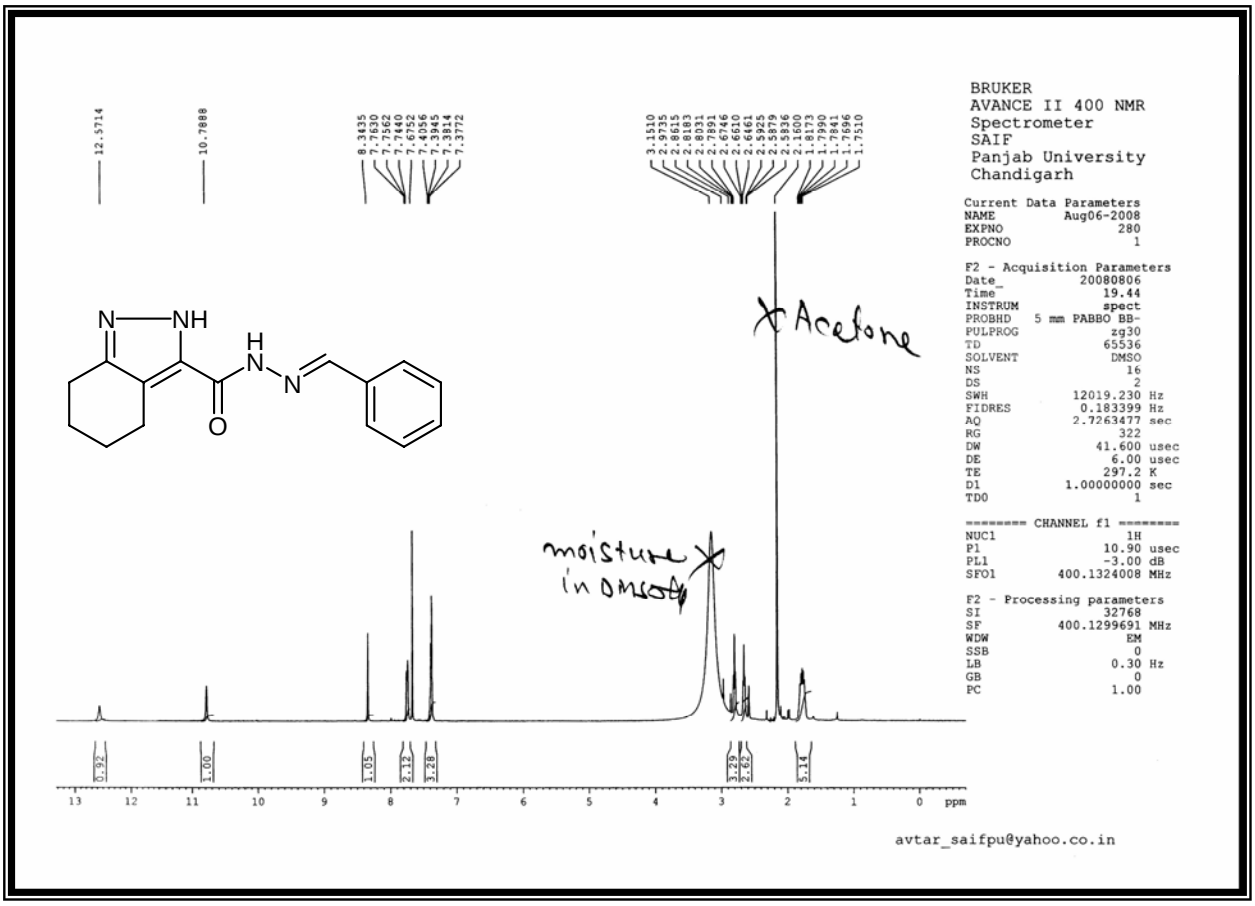
MS: m/z = 284 (M^+); **Anal. Calcd** for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.22; H, 5.56; N, 19.61.

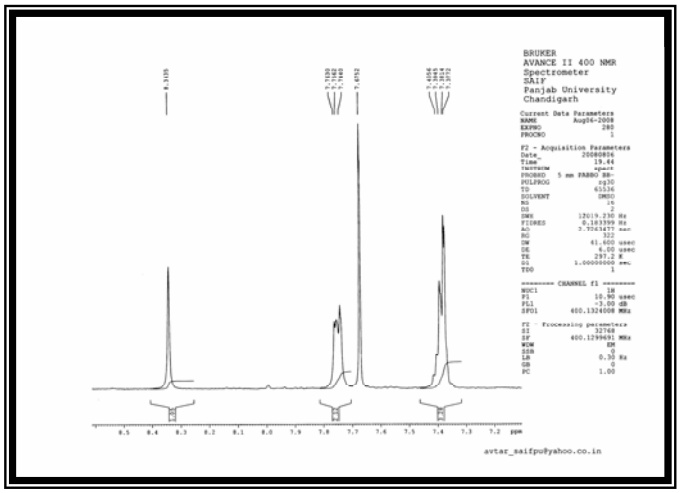
***N*'-(2-methoxyphenyl)methylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide (AH-20)**

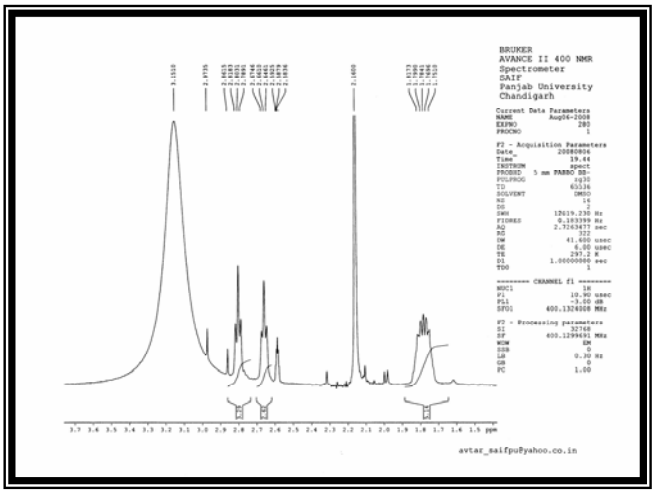
White solid; mp 223-224 ˚C;

MS: m/z = 298 (M^+); **Anal. Calcd** for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.32; H, 5.91; N, 18.66.

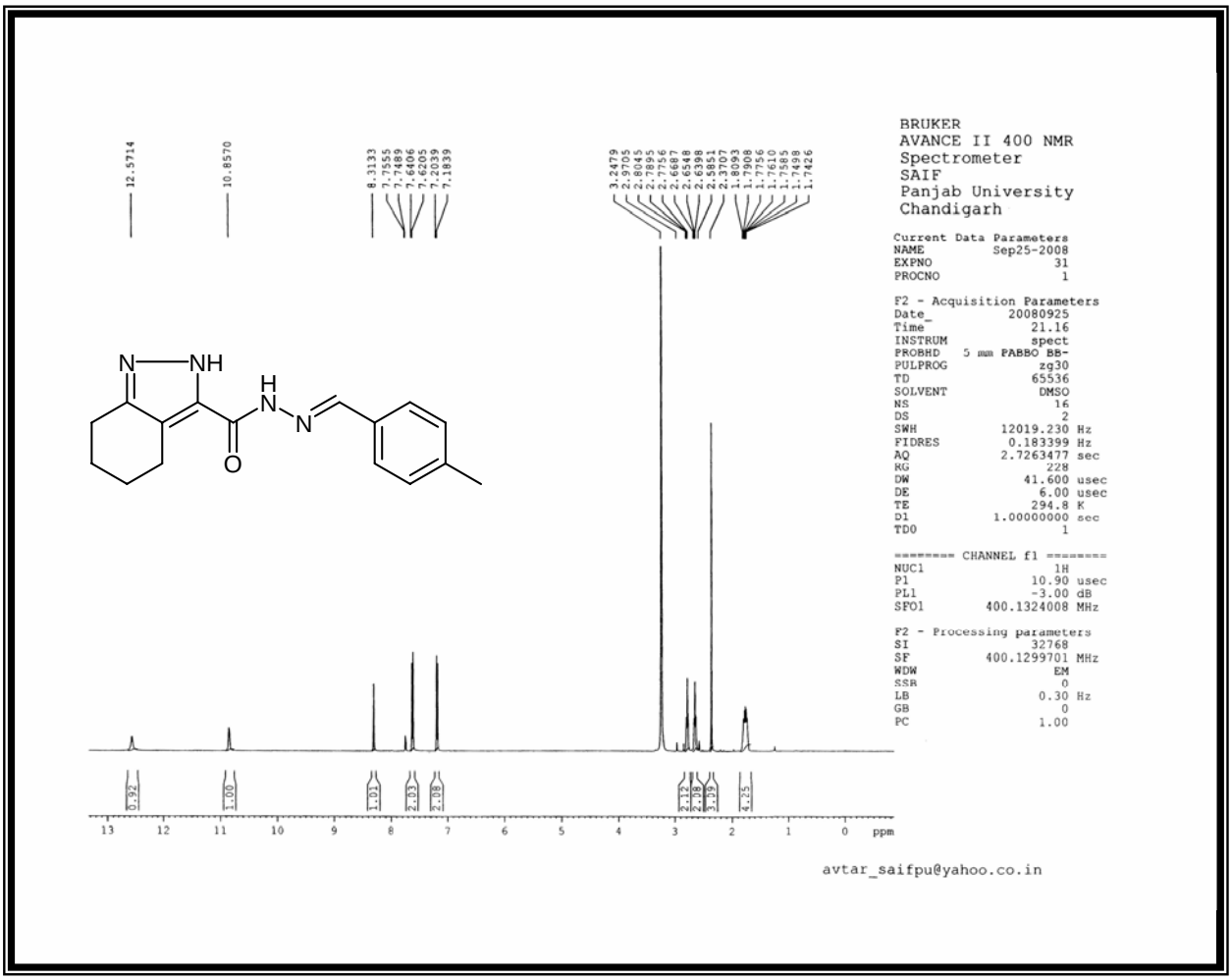
^{1}H NMR spectrum of AH-1:

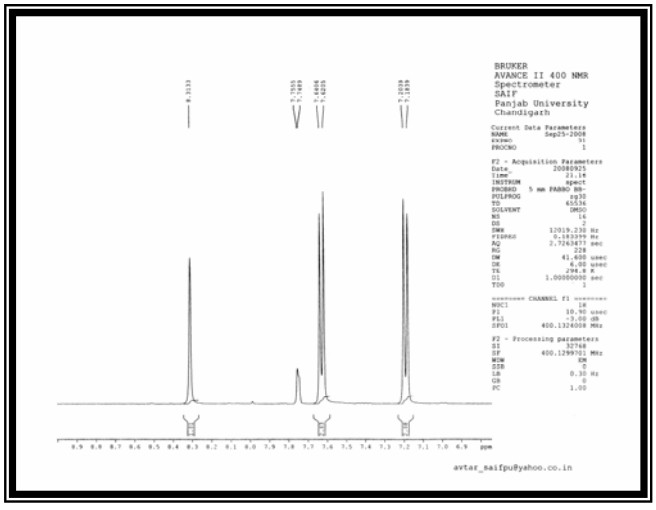


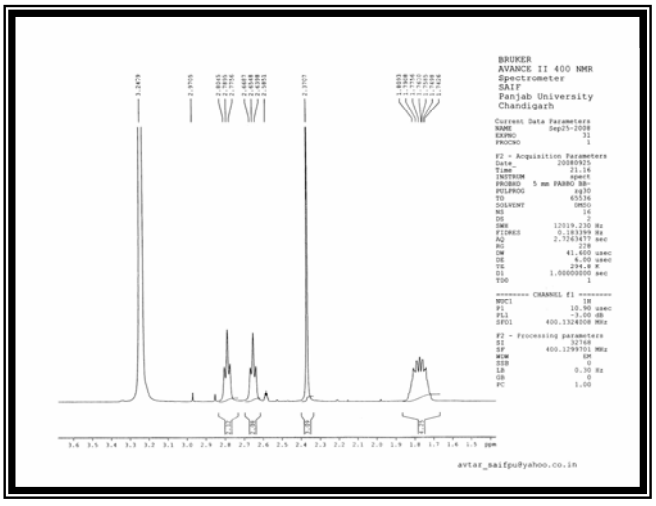




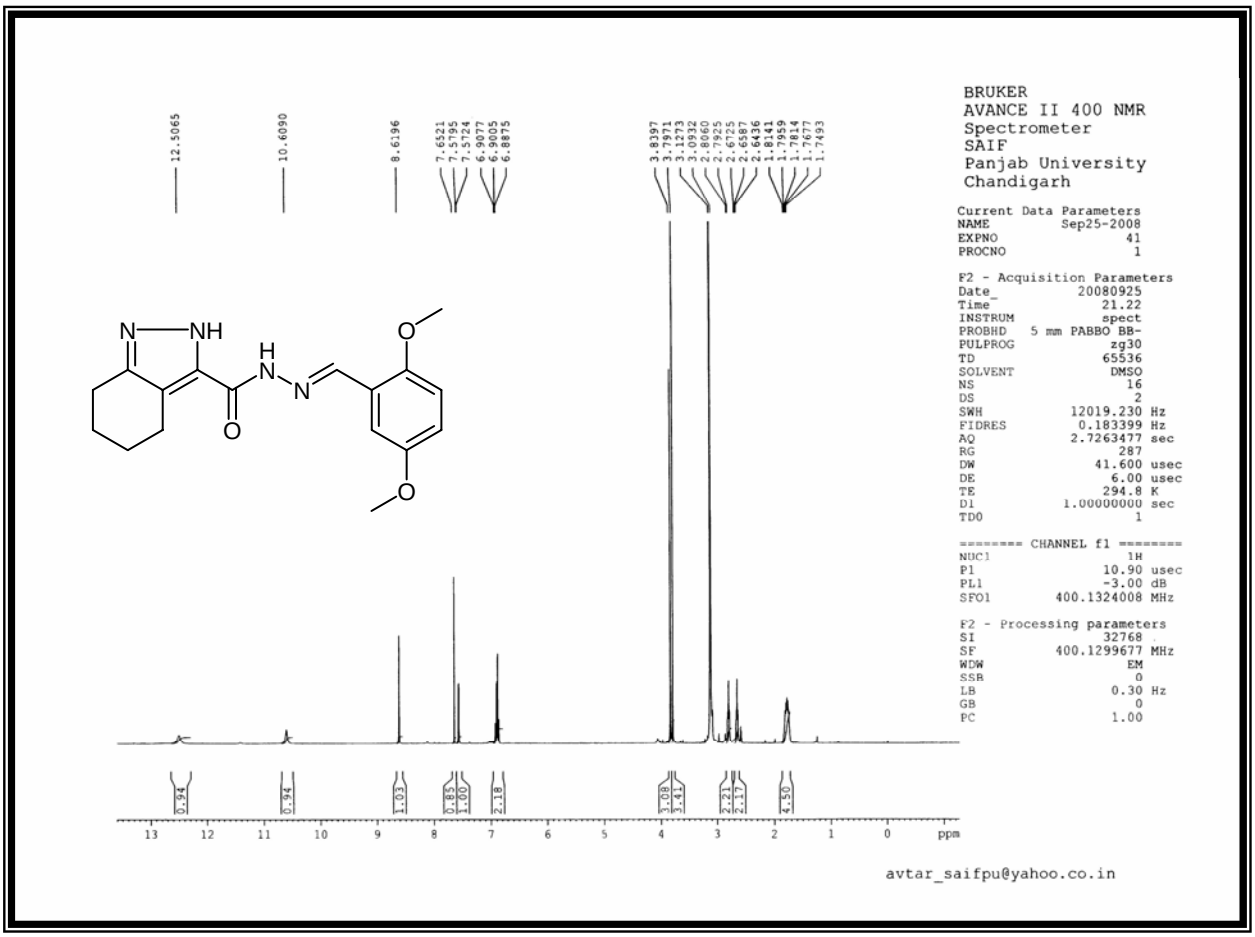
^{1}H NMR spectrum of AH-3:

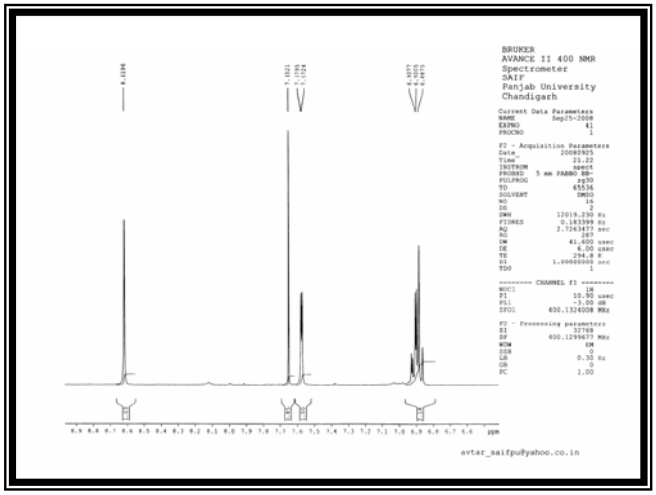


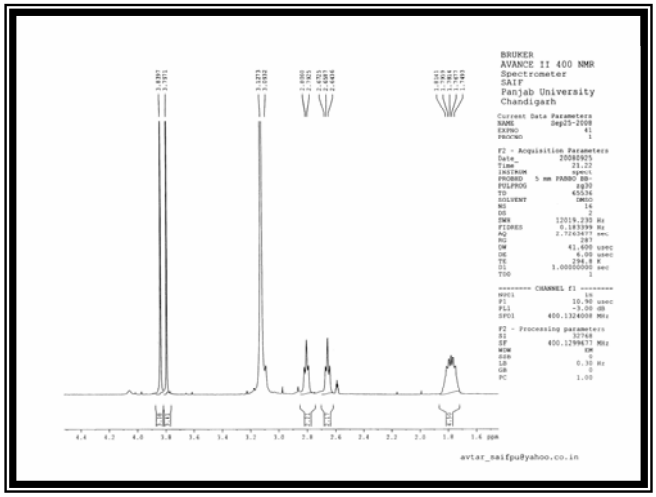




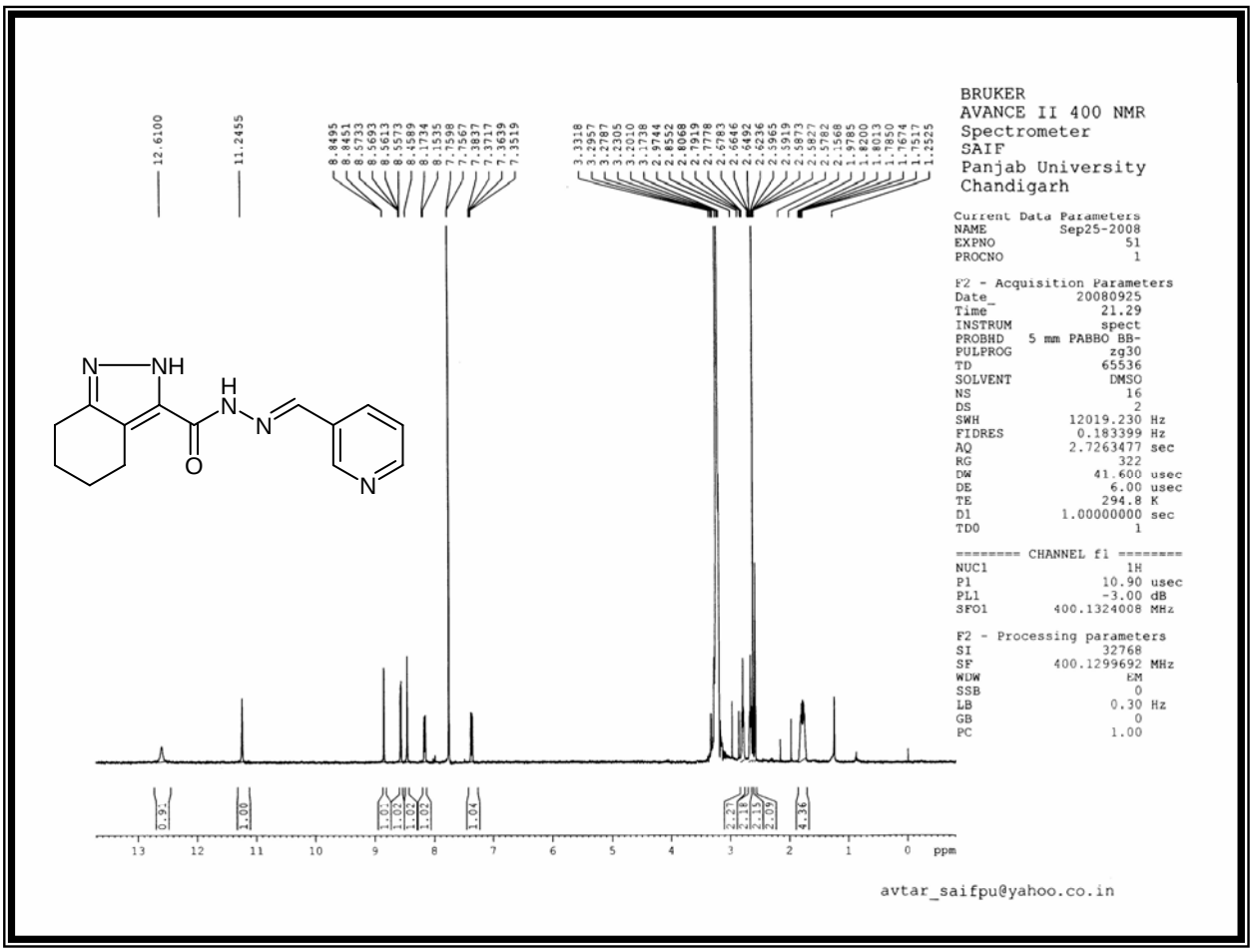
^{1}H NMR spectrum of AH-5:

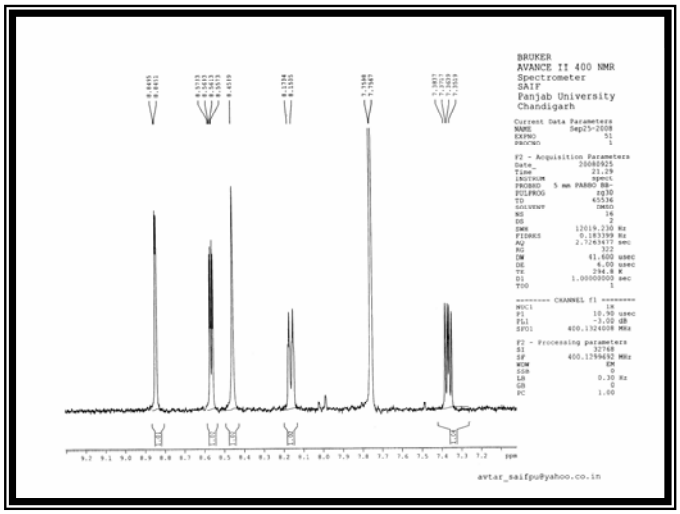


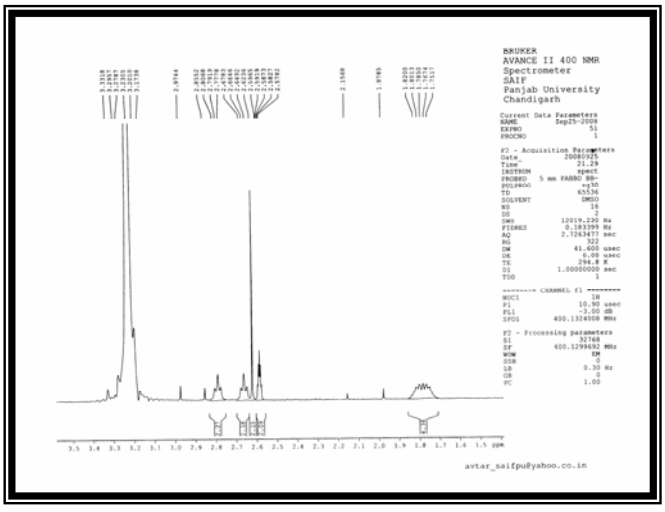




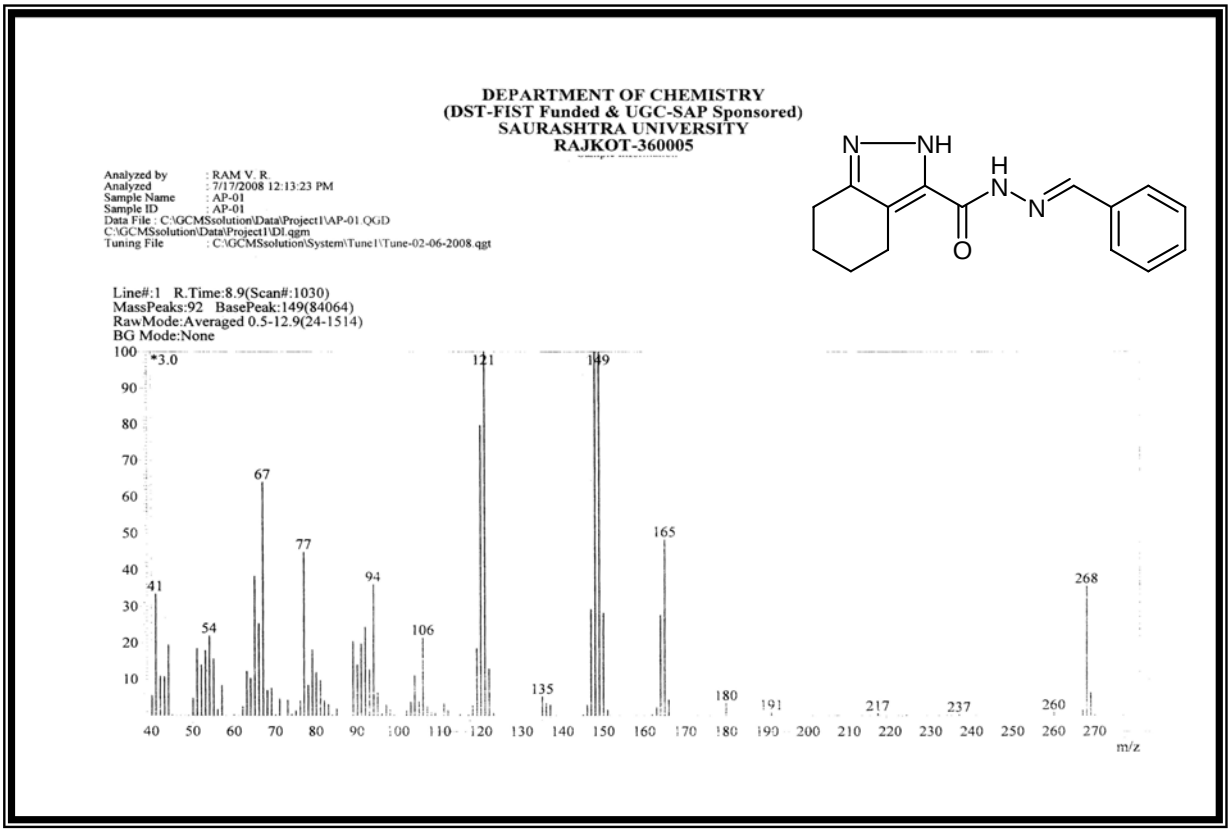
^{1}H NMR spectrum of AH-16:



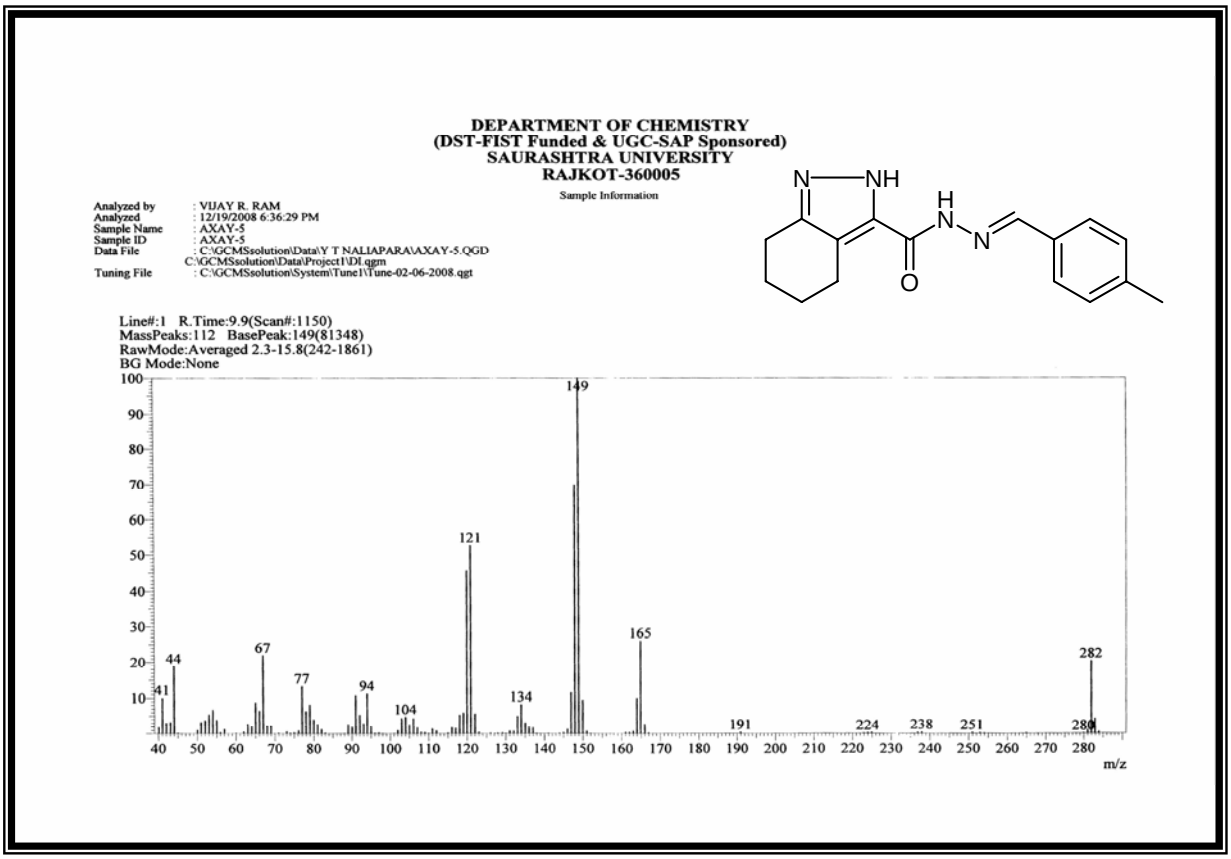




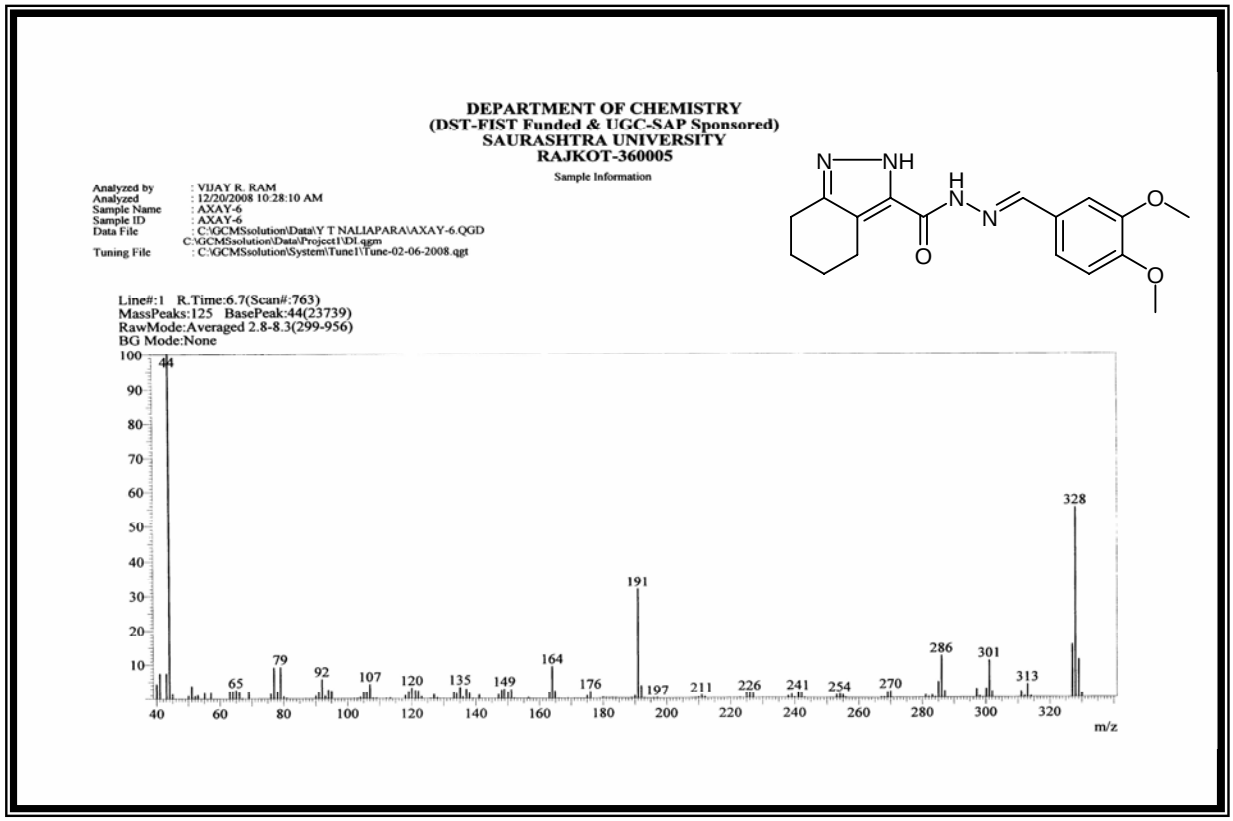
Mass spectrum of AH-1:



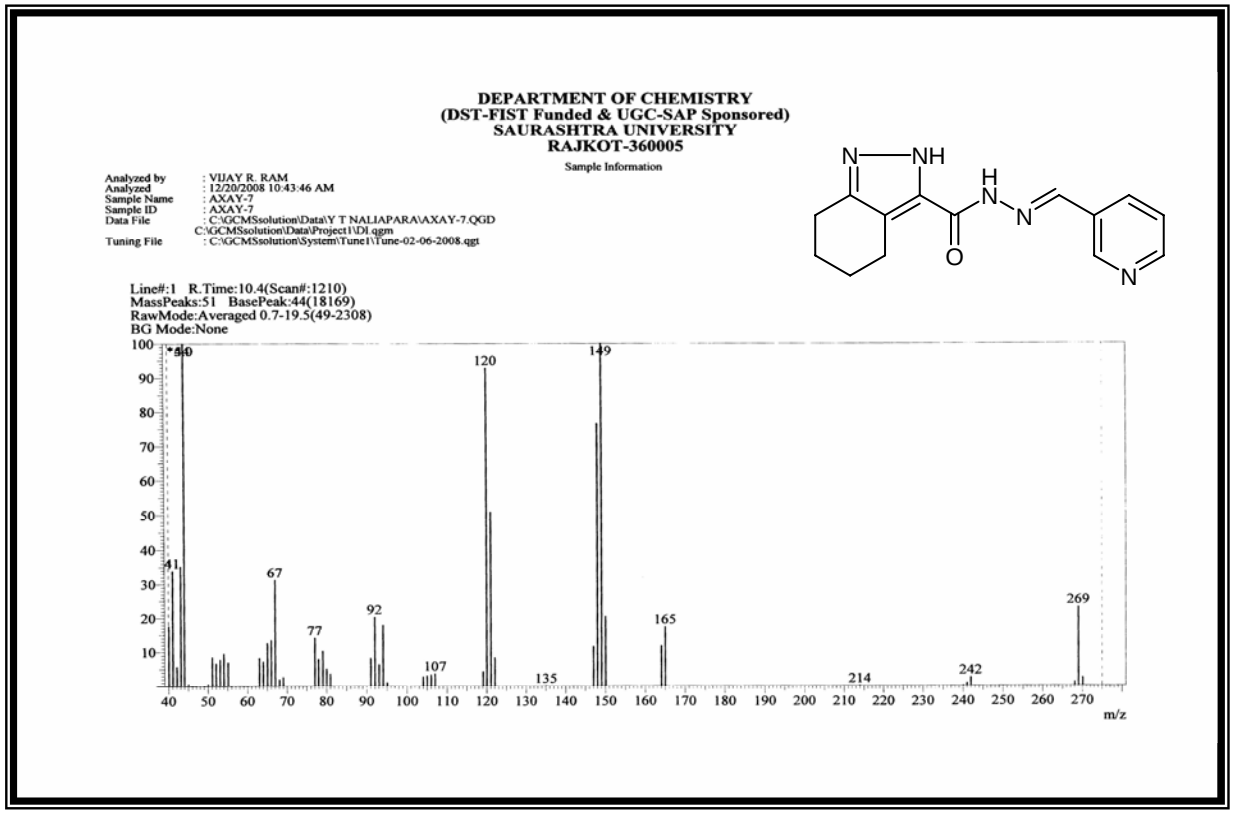
Mass spectrum of AH-3:



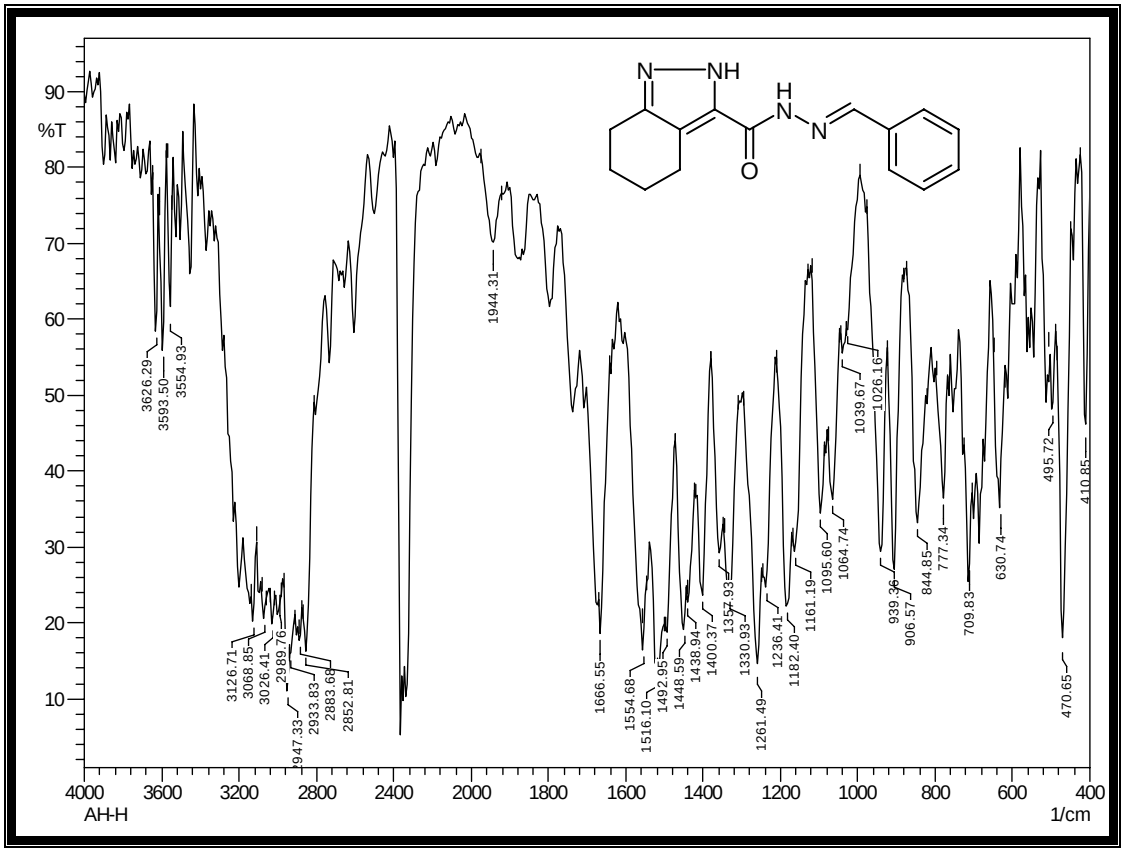
Mass spectrum of AH-4:



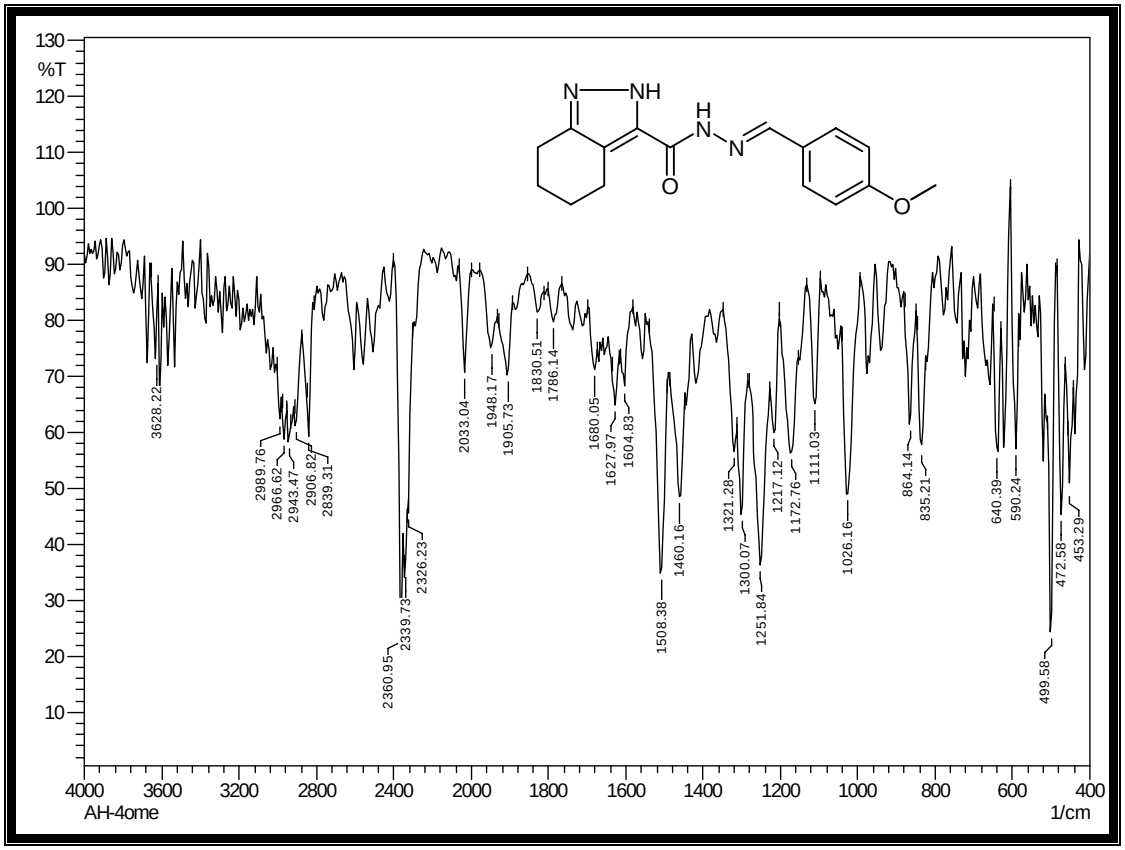
Mass spectrum of AH-16:



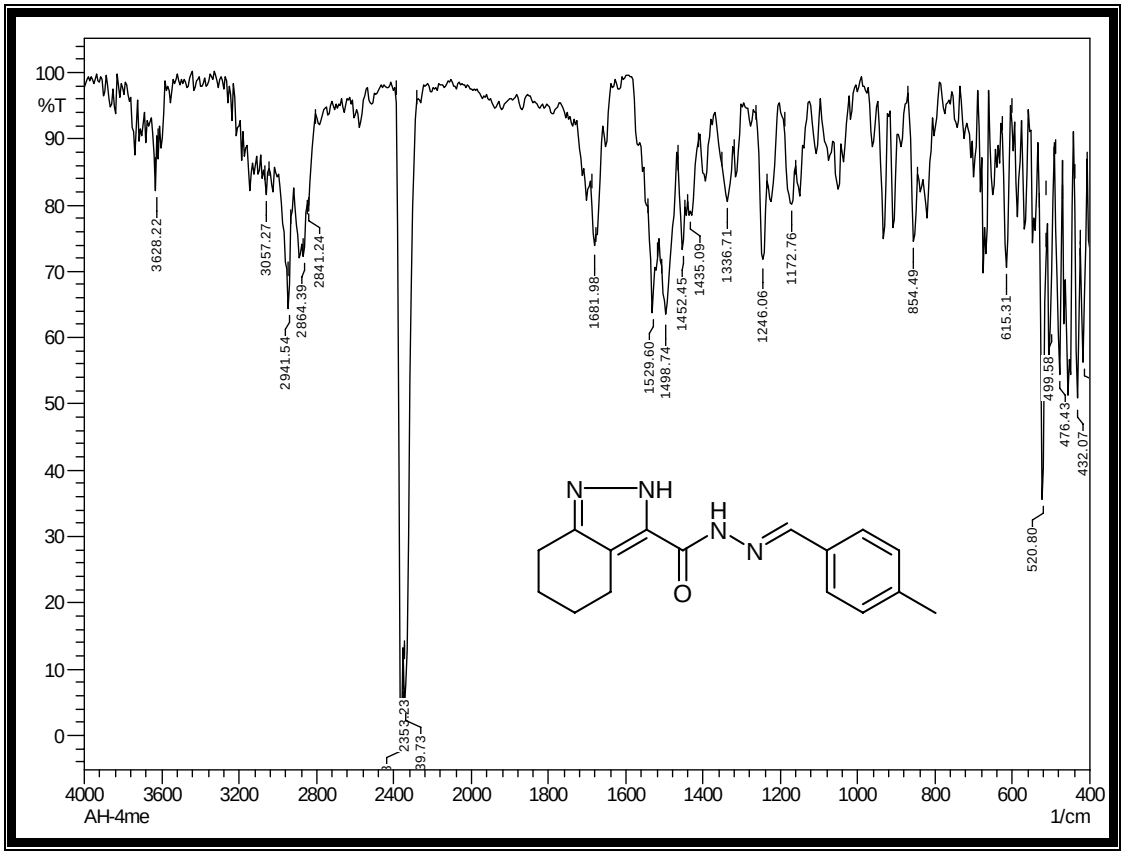
IR spectrum of AP-1



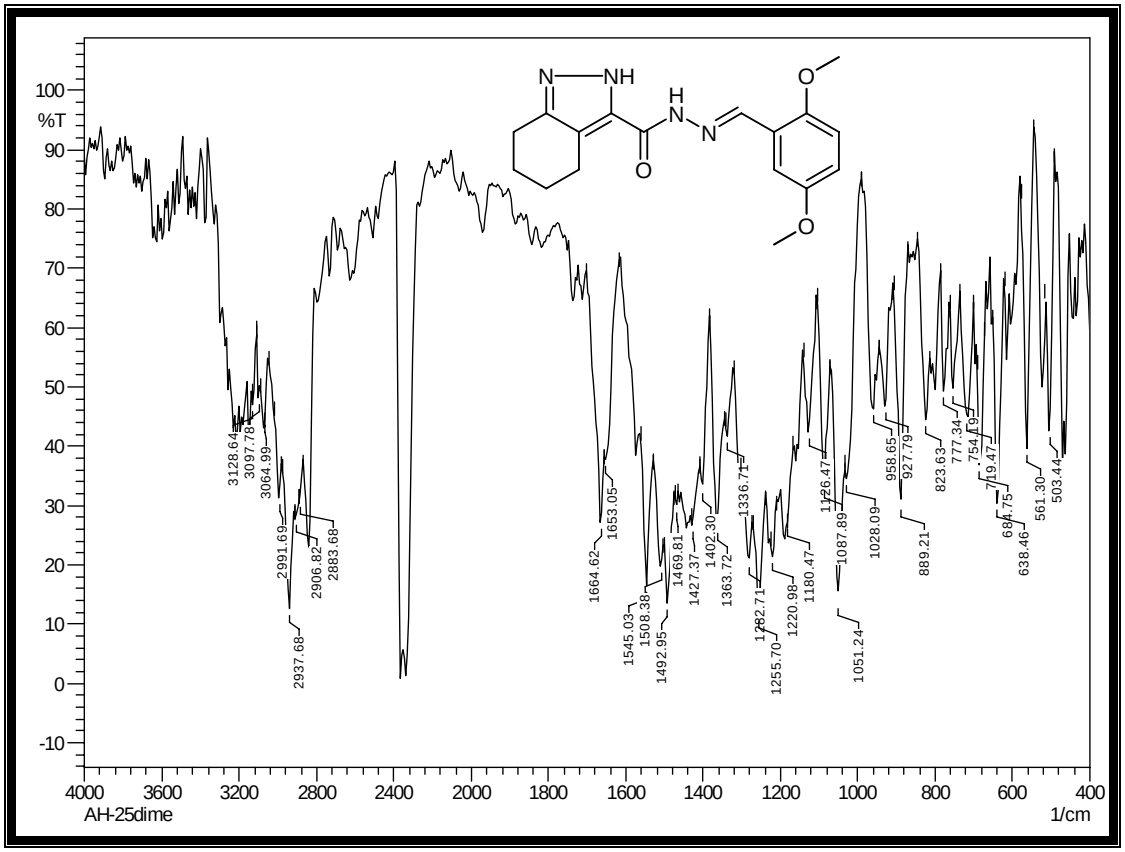
IR spectrum of AP-2



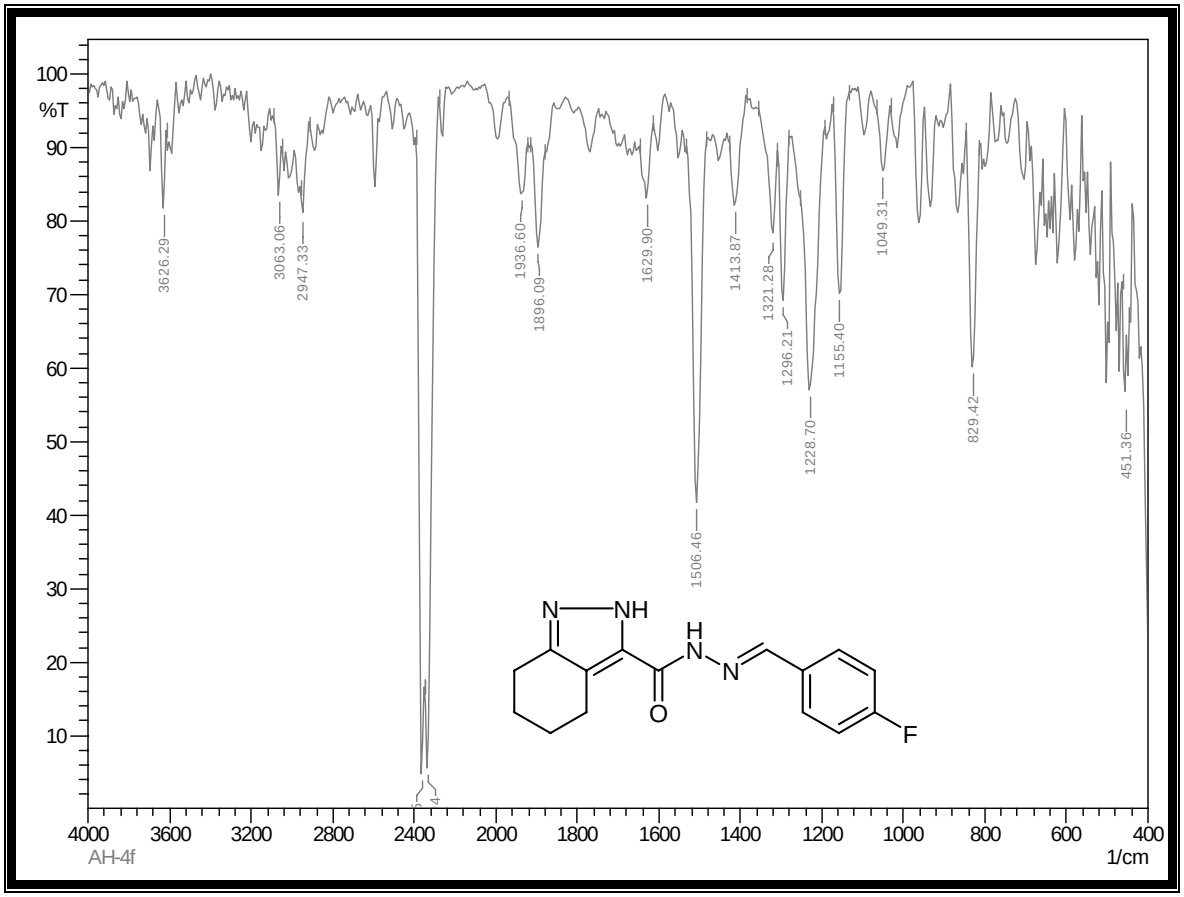
IR spectrum of AH-3



IR spectrum of AH-5



IR spectrum of AH-13



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Summary

The work presented in the Thesis entitled “Synthesis and pharmacological properties of heterocyclic analogs” can be summarized as below.

Chapter 1 covers the synthesis of novel dihydropyrimidine derivatives via three component Biginelli reaction between n-butyl acetoacetate, aromatic aldehydes and thiourea. Synthesized molecules have n-butyl carboxylic ester moiety at 5^{th} position of DHPM skeleton. n-butyl acetoacetate was prepared from ethyl acetoacetate by transesterification with the help of n-butanol and sodium methoxide as a catalyst in toluene as a solvent. Components of the reaction, thus prepared, were reacted in ethanol using catalytic con. HCl to afford corresponding DHPMs. The same molecules were prepared using solvent free microwave irradiation technique under Fuller’s earth as a solid support. As a result of this green chemistry approach, the improvement in the reaction time, yield and work up procedure was achived. The spectral data is presented to support the structure of synthesized molecules.

In chapter 2, bicyclic systems are synthesized from Biginelli dihydropyrimidine derivatives. DHPM skeleton is very important scaffold to synthesize variety of bicyclic systems. n-Butyl acetoacetate, synthesized as mentioned in chapter 1, was reacted with thiourea and various aromatic aldehydes. The DHPMs, thus synthesized, were reacted with mono chloroacetone to obtain fused bicyclic thiazolo-pyrimidine system. The thiazolo-pyrimidine derivatives thus synthesized were studied by IR, Mass, ^{1}H NMR and ^{13}C NMR spectroscopy.

Chapter 3 includes application of cyclic aliphatic ketones in the formation of spiro pyrano[3,2-*c*]chromene derivatives. Cyclopentanone, cyclohexanone and cycloheptanone were utilized as a cyclic ketone in one-pot three component reaction with 4-hydroxy coumarin and malononitrile in ethanol with morpholine as a catalyst to afford spiro 2-amino-3-cyano pyrano[3,2-*c*]chromene derivatives. The synthesized compounds were characterized by IR, Mass, ^{1}H NMR and ^{13}C NMR spectroscopy.

In chapter 4 & 5, construction of 1,2-diazete and 1,3-diazetidine ring system at 3 position of 4-hydroxy coumarin is demonstrated. 3-(ethoxymethylene)-2*H*-chromene-2,4(3*H*)-dione was prepared as per literature method which on subsequent treatment with hydrazine hydrate gives 4-hydroxy-2-oxo-2*H*-cromene-3-carbaldehyde. The prepared hydrazone was confirmed by mass and ^{1}H NMR spectroscopy. Thus prepared hydrazone was condensed with various aromatic aldehydes to afford arylmethylenehydrazone. Afforded arylmethylene hydrazone underwent elctrocyclic reaction and constructed 1,2-diazete ring system. When 3-(ethoxymethylene)-2*H*-chromene-2,4(3*H*)-dione was reacted with substituted phenyl thiourea, 1,3-diazetidine-2-thione ring was constructed at 3 position of 4-hydroxy coumarin. The structural elucidation of all the synthesized compounds was carried out by IR, Mass and NMR spectral study. Spectral data are consistent with the proposed structures.

Chapter 6 covers a brief literature survey on indazole system, their synthesis and biological profile. This chapter deals with the synthesis of *N'*-arylmethylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide derivatives. 4,5,6,7-Tetrahydro-2H-indazole-3-carbohydrazide was synthesized in two step, starting from cyclohexanone and diethyl oxalate, subsequent treatment with hydrazine hydrate. A library of *N'*-arylmethylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide was generated by condensation of hydrazide and various aromatic aldehydes. The spectral characterizations of synthesized compounds are reported.

All the synthesized compounds are sent for their antiviral screening and results are awaited.

Publications

1. One-pot synthesis of 5-carboxanilide-dihydropyrimidinones using etidronic acid. **Akshay M. Pansuriya**, Mahesh M. Savant, Chirag V. Bhuva, Jyoti Singh, Yogesh T. Naliapara. ***ARKIVOC***, 2009, vii, 79-85.

2. Synthesis and evaluation of antimicrobial activity of some new 5-imidazolinone derivatives. Mahesh M. Savant, **Akshay M. Pansuriya**, Chirag V. Bhuva, Yogesh T. Naliapara. ***Organic chemistry: An Indian Journal***, Accepted (In Press).

3. Use of cyclic aliphatic ketones for spiro 2-amino-3-cyano pyrano[3,2-*c*]chromene formation. **Akshay M. Pansuriya**, Mahesh M. Savant, Chirag V. Bhuva, Jyoti Singh, Yogesh T. Naliapara. ***ARKIVOC***, Submitted.

4. Synthesis of Dihydropyrimidine and Thiazolo[3,2-*a*]pyrimidine Library. **Akshay M. Pansuriya**, Mahesh M. Savant, Chirag V. Bhuva, Jyoti Singh, Yogesh T. Naliapara. ***Journal of Combinatorial Chemistry***, Submitted.

5. Water mediated synthesis of *N*'-arylmethylene-4,5,6,7-tetrahydro-2*H*-indazole-3-carbohydrazide library. **Akshay M. Pansuriya**, Mahesh M. Savant, Chirag V. Bhuva, Naval Kapuriya, Jyoti Singh, Yogesh T. Naliapara, ***Tetrahedron***, Submitted.

Conference/Seminar participated

- International Conference on "Bioactive Heterocycles and Drug Discovery Paradigm" Jointly organized by Department of Chemistry, Saurashtra University and ISCB at Rajkot, India (January 8-10, 2005)

- INDO-US Conference on "New bioactive molecules in pharmaceutical research-Contribution of Natural Products" Jointly organized by National Centre for Natural Products Research, University of Mississippi, USA and Indian Institute of Chemical Technology IICT, Hyderabad, India (November 13-14, 2006)

- "2nd International Conference on Heterocyclic Chemistry" Organized by Department of Chemistry, University of Rajasthan, Jaipur (December 16-19, 2006)

- "11th CRSI National Symposium in Chemistry" Jointly Organized by National Chemical Laboratory, Pune, Indian Institute of Science Education & Research, Pune and University of Pune (February 6-8, 2009)

- "Two Days National Workshop on Updates in Process & Medicinal Chemistry" Jointly Organized by Department of Chemistry, Saurashtra University, Rajkot and National Facility for Drug Discovery Through NCE's Development & Instrumentation Support to Small Manufacturing Pharma Enterprises and Think Pharma USA (March 3-4, 2009)

- "National Conference on Spectroscopy & Stereochemistry" Organized by Department of Chemistry, Saurashtra University, Rajkot Sponsored by UGC, New Delhi and GUJCOST, Gandhinagar (March 18-20, 2009)