SYNTHESIS, CHARACTERIZATION AND SCREENING OF PHARMACOLOGICALLY ACTIVE CHEMICAL ENTITIES

A THESIS SUBMITTED TO THE

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

The work included in the thesis is done by me under the supervision of Prof. Anamik Shah and the contribution made thereof is my own work.

Date:

Place: **Rupesh C. Khunt**

Certificate

This is to certify that the present work submitted for the Ph.D. degree of Saurashtra University by Mr. Rupesh C. Khunt has been the result of work carried out under my supervision and is a good contribution in the field of Synthetic Organic Chemistry.

Date:

Place: **Prof. Anamik Shah**

Dedicated to My

Family,

With Love

Content

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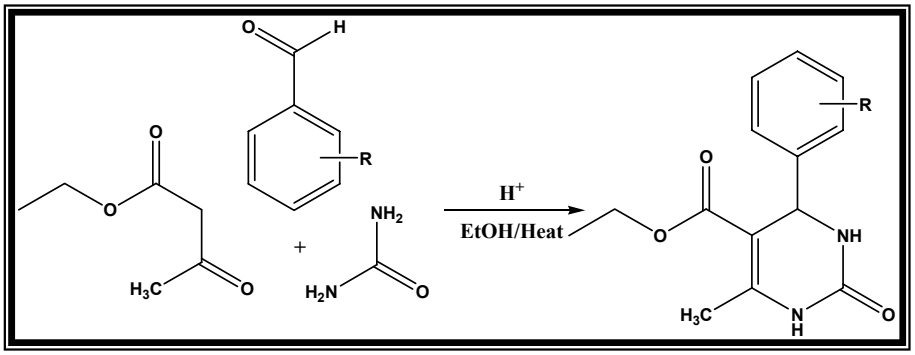
Introduction

P. Biginelli reported the synthesis of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) via three-component condensation reaction 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.



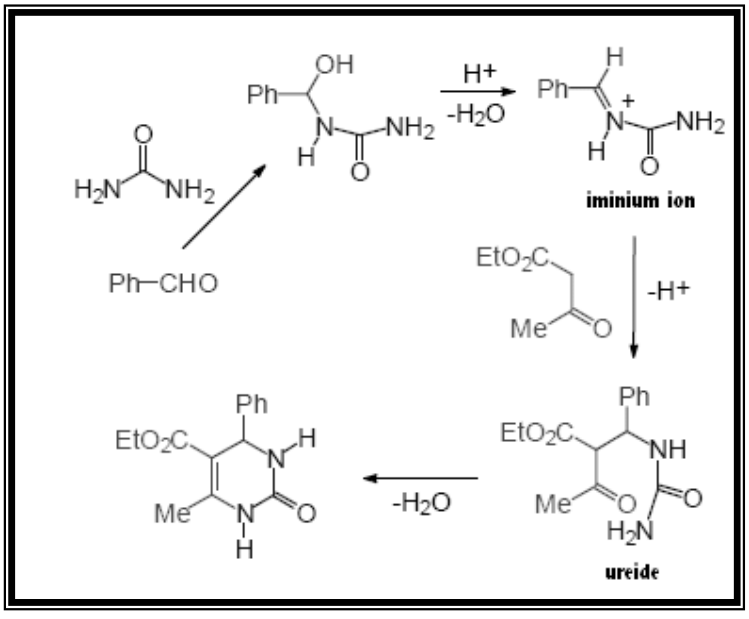
The classical three-component Biginelli condensation is usually carried out in alcoholic solution containing a few drops of concentrated hydrochloric or sulfuric acid as catalyst, although other systems such as THF/HCl, dioxane/HCl, or acetic acid/HCl have also been employed. Multicomponent reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy, applications in combinatorial chemistry, and diversity-oriented synthesis.[1] The classical Biginelli reaction, one pot cyclocondensation of aldehyde, 1,3-ketoester, and urea or thiourea, is inarguably one of the most useful MCRs.[2] Polyfunctionalized dihydropyrimidines (DHPMs) represent a heterocyclic system of remarkable pharmacological activity.

4-Aryl-1,4-dihydropyridines of the nifedipine type are the most studied class of organic calcium channel modulators and, since their introduction into clinical medicine in 1975 have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrythamias, or angina. In recent years research interest has also focused on aza-analogs such as Dihydropyrimidines which shows similar pharmacological profile to this type of classical dihydropyridines calcium channel modulators. [3]

Mechanistic Studies

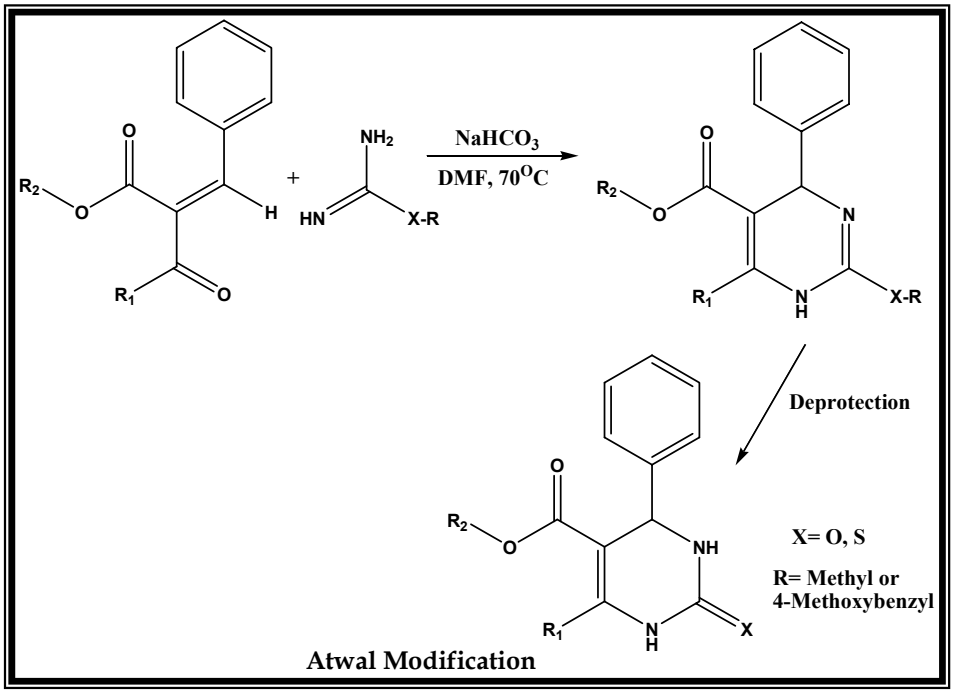
The mechanism of the Biginelli reaction has been the subject of some debate over the past decades. Early work by Folkers and Johnson suggested that bisureide i.e., the primary bimolecular condensation product of benzaldehyde and urea is the first intermediate in this reaction.[4] In 1973, Sweet and Fissekis proposed that a carbenium ion, produced by an acid-catalyzed aldol reaction of benzaldehyde with ethyl acetoacetate, is the key intermediate and is formed in the first and limiting step of the Biginelli reaction [5].

Oliver Kappe et al reinvestigated the mechanism in 1997 using ^{1}H and ^{13}C NMR spectroscopy (CD_3OH/HCl) and have established that the first step in this reaction involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate from the aldehyde and urea component. Interception of the iminium ion by ethyl acetoacetate, possibly through its enol tautomer, produces an open-chain ureide which subsequently cyclize to dihydropyrimidine. 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[6] or electron-deficient acetoacetates,[7] respectively. The relative stereochemistry in hexahydropyrimidine was established by an X-ray analysis.

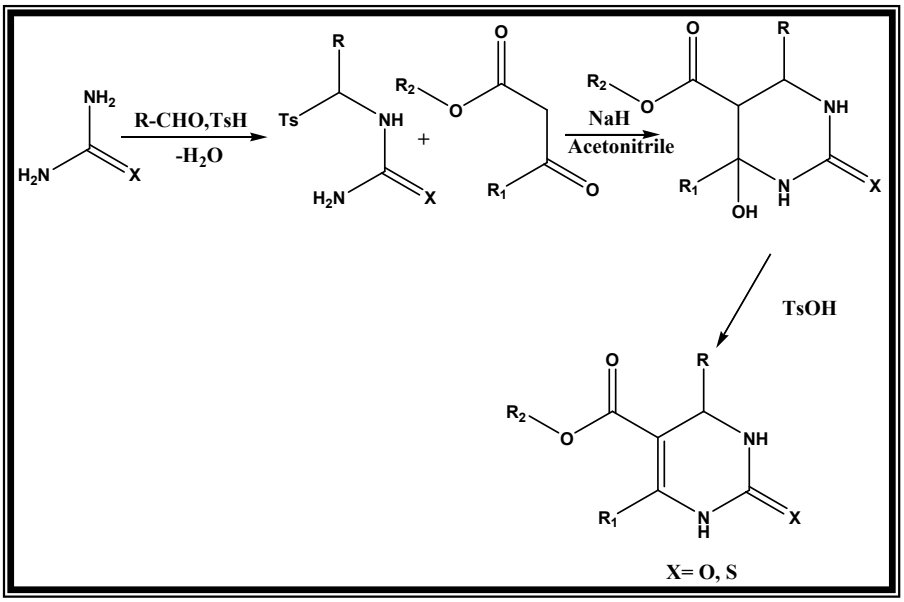


Atwal alternative synthetic route

Apart from the traditional Biginelli condensation, there are only few other synthetic methods available that lead to DHPMs. Since most of these protocols lack the experimental and conceptual simplicity of the Biginelli one-pot, one-step procedure, none of these have any significance today or can compete with the original Biginelli MCR approach. One noticeable exception is the so-called "Atwal modification" of the Biginelli reaction. [8] Here, arylidene is first condensed with a suitable protected urea or thiourea derivative under almost neutral conditions. Deprotection of the resulting 1,4-dihydropyrimidine with HCl or TFA/EtSH leads to the desired DHPMs. Although this method requires prior synthesis of enones (Arylidenes), its reliability and broad applicability make it an attractive alternative to the traditional one step Biginelli condensation.



Another novel approach to DHPMs has been described by Shutalev et al. and is outlined below. [9] This synthesis is based on the condensation of readily available R-tosyl-substituted (thio)ureas with the (in situ prepared) enolates of acetoacetates or 1,3-dicarbonyl compounds. The resulting hexahydropyrimidines need not to be isolated and can be converted directly into DHPMs. This method works particularly well for aliphatic aldehydes and thioureas and produces high overall yields of the desired target compounds.

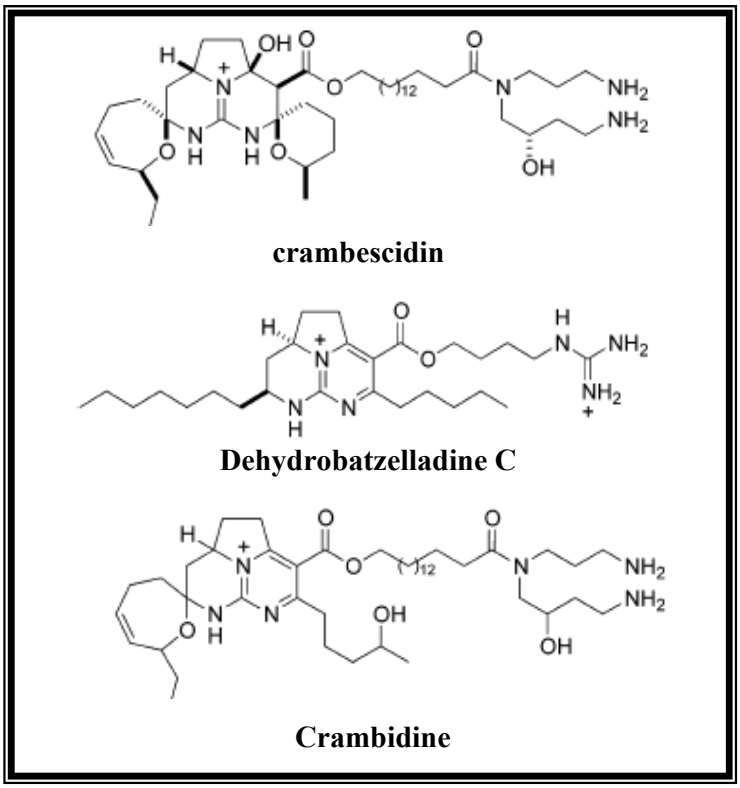


Pharmacological Profile

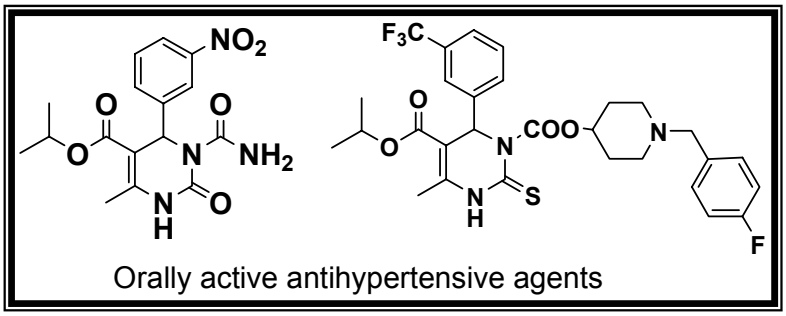
The interest in synthesis of dihydropyrimidines - Biginelli compounds stems from their close structural relationship [10] to clinically important 1,4-dihydropyridine calcium channel modulators of the type nifedipine *etc.* and also because of interesting biological properties of several marine alkaloids [11-13] based upon dihydropyrimidine *viz.* crambine, batzelladine (potent HIV gp-120-CD4 inhibitor) and ptilomycelin A. Derivatization of the dihydropyrimidines especially [14] at C-4 has led to the recoginition of several lead compounds that show a very similar pharmacological profile[15-17] to 1,4-dihydropyridine based drugs.

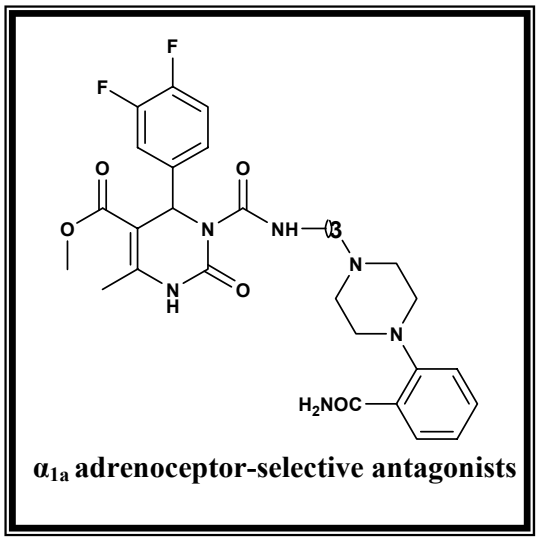
C. crambe is a bright red marine sponge, that is the most wide spread in the northwestern meditettanean [18]. Extract of *C. crambe* have been known to be ichthyotoxic and shown various pharmacological activies. A variety of structurally intricate guanidine alkaloids are present in marine sources. [19] Diverse biological activities are associated with many of these alkaloids, likely reflecting the multiples ways that a guanidinium cation can participate in noncovalent interactions. Among the most notable marine alkaloids of these are the crambescidin [20] and batzelladine [21] alkaloids, which have been isolated primarily from sponges belonging to the orders Poecilosclerida and Axinellida. Diverse biological activities have been reported for these secondary metabolites, including cytotoxicity toward several cancer cell lines, antifungal and antiviral activities, and inhibition of HIV-1 fusion. The novel structures of these marine alkaloids have inspired

the development of many strategies for assembling polycyclic guanidines that contain the octahydro-5,6,6a-triazaacenaphthalene and hexahydro-5,6,6a-triazaacenaphthalene moieties common to the crambescidin and batzelladine alkaloids.[22, 23]



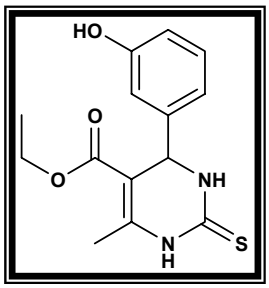
More recently, appropriately functionalized DHPMs have emerged as, e.g., orally active antihypertensive agents [24-26] or α_{1a} adrenoceptor-selective antagonists [27]





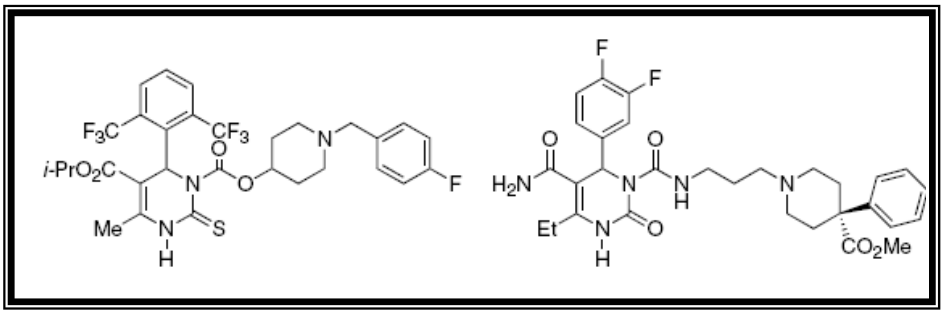
α_{1a} adrenoceptor-selective antagonists

Simple DHPM monastrol as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest.[28]



Kappe et al reported N-substituted 3,4-dihydropyrimidinones entities shows very good activity as a calcium channel blockers[29]

DHPM calcium channel blockers and biological active DHPM lead compounds

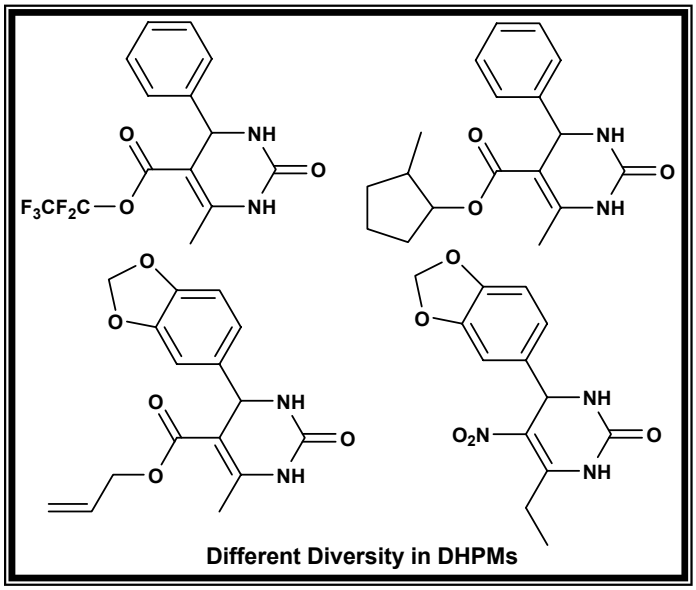


Keith Demarest et al reported that calcitonin, a 32 amino acid polypeptide hormone secreted by the thyroid and thymus glands, plays an important role in inhibiting bone resorption through the mediation of osteoclasts. By inhibiting bone resorption and promoting renal calcium excretion, calcitonin has therapeutic applications in a variety of

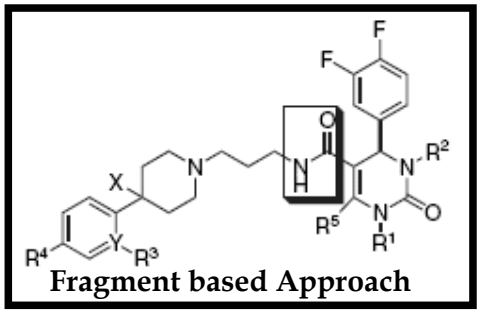
clinical disorders, including hypercalcemia associated with Paget's disease [30] and osteoporosis.[31-32]

A multiplex mimetic cell based assay was designed for high-throughput screening. In an effort to differentiate activity amongst similar G-protein coupled receptors, 6 cell lines-calcitonin receptor-2 (CTR-2; clone #33), glucogen-like peptide 1 (GLP1-7; clone #7), gastric inhibitory polypeptide (GIP-1; clone #1), parathyroid hormone receptor 1 (EPTH-1-1; clone #1) and calcitonin gene related peptide-1 (CGRP1-7; cone 7) were cloned onto the human embryonic kidney (HEK 293) cell line and plated together in one assay well.

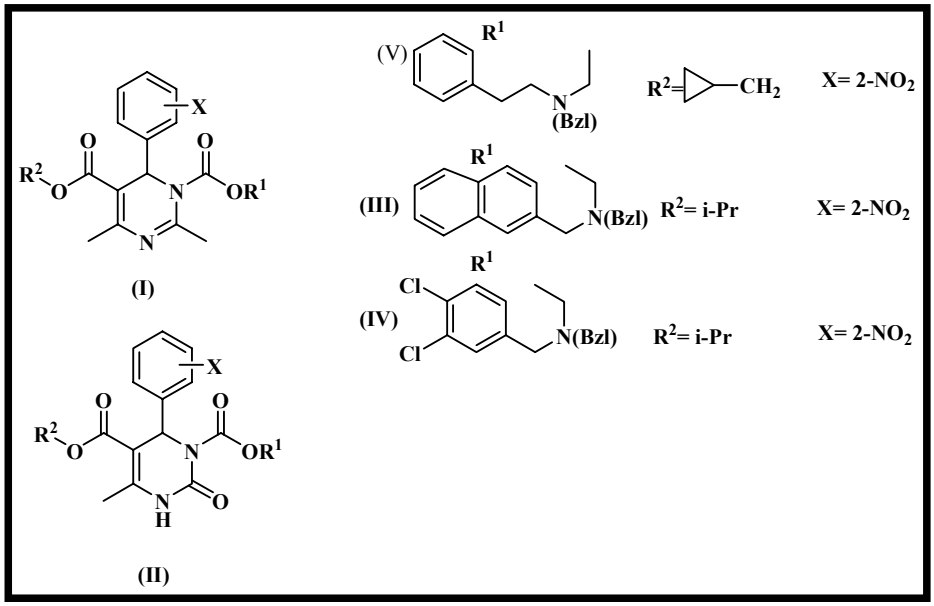
The following compounds are examples of an active series of 1,4-dihydropyrimidines that stimulated cAMP accumulation in HEK 293 cells expressing the CTR-2 ligand.[33]



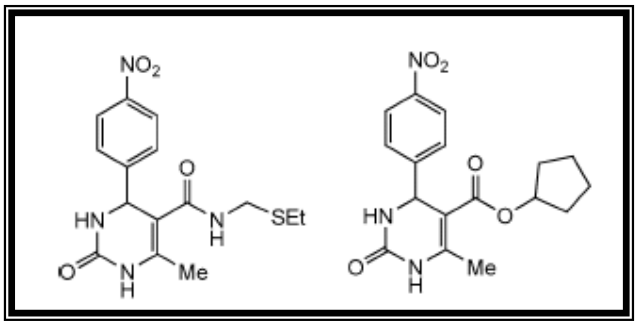
Research interest in multifunctionalized DHPMs of privileged heterocyclic core associated with several pharmacological properties. Small molecules targeting the mitotic machinery.[34] Notably, 4-aryldihydropyrimidinone heterocycles attached to an aminopropyl-4-piperidine moiety via a C_5 amide linkage have proven to be excellent templates for selective α_{1a} receptor subtype antagonists to warrant further consideration for the treatment of Benign Prostatic Hyperplasia (BPH). [35] In the synthesis of these DHPM-5-carboxamides, amide bond formation between the requisite amines and the corresponding DHPM acids was performed using standard solution phase amide coupling chemistry involving carbodiimide coupling reagents [35-36]



Some dihydropyrimidines (**V**), (**III),** and **(IV)** were weaker in blocking atrioventricular conduction in anesthetized open-chest dogs and less toxic than the dihydropyridines.[37]

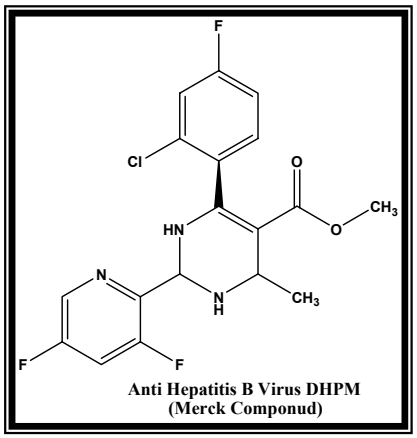


Christopher Blackburn et al synthesized 3,4-dihydropyrimidinone analogues as a fatty acid transporter FATP4. Among these some of the compounds hit by high through put screening and optimized FATP4 inhibitors. Blocking the absorption of fats (triglycerides) by administration of an anti-absorptive agent is of interest for the treatment of obesity.[38]



Ingested dietary triglycerides are hydrolyzed by gastric and pancreatic lipases, and the resulting fatty acids are taken up by enterocytes lining the small intestine where they are re-esterified to triglycerides and then transported into the blood. The lipase inhibitor orlistat (XenicalTM) blocks fat absorption by inhibiting the hydrolysis of dietary fat to fatty acids [39] with administration leading to a concomitant decrease in body weight and improvement of blood lipid profiles. A family of proteins, termed fatty acid transport proteins (FATPs), that mediate the uptake of fatty acids into cells has been described.[40, 41] earlier studies[42-45] provided evidence that fatty acid transport protein 4 (FATP4) mediates the transport of fatty acids from the gut into enterocytes both *in vitro* and *in vivo*. We therefore reasoned that inhibitors of FATP4 might be expected to have benefits similar to orlistat. Since FATP4 inhibition would result in the accumulation of free fatty acids rather than triglycerides, we would also expect a different, possibly improved, side-effect profile compared to orlistat. The FATP family of proteins is most closely related in sequence to the ATP-utilizing acyl-CoA synthetase enzymes. [46-49]

Moreover, Merck and Co. developed a compounds which is very active as non-nucleoside inhibitors of human hepatitis B virus (IC 50=53 nM) for reduction of HBV DNA in human hepatoma HepG2.2.15 cells) with low cytotoxicity in uninfected cells (CC50 = 7 mcM). This compound inhibited both viral DNA and viral cores in Hep G2.2.15 cells and HBV- transfected cell lines, whereas it did not affect the activity of endopolymerase and had no effect on other DNA and RNA viruses. *In vivo*, in a transgenic mouse model, oral doses of 3-100 mg/kg b.i.d or t.i.d for 28 days dose.[50]

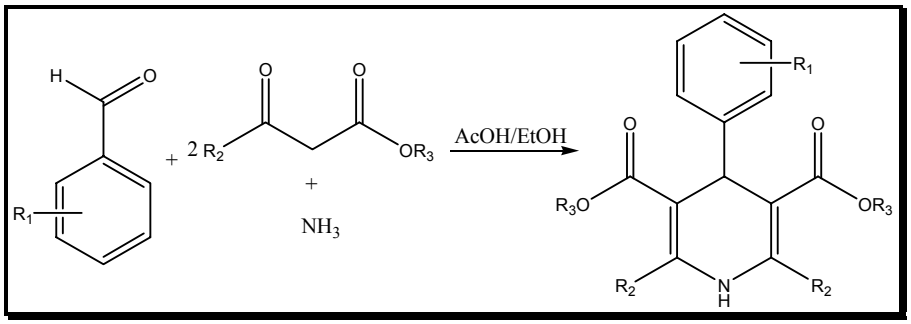


Anti Hepatitis B Virus DHPM (Merck Componud)

Synthetic Approaches

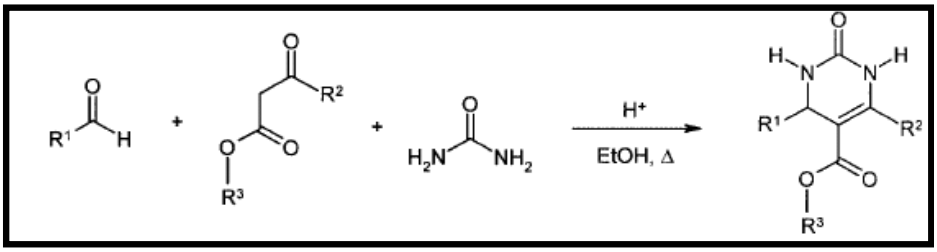
Utilization of 1,3-Dicarbonyl Derivatives in Multicomponent Reactions

[a] Hantzsch's Heterocyclic Syntheses



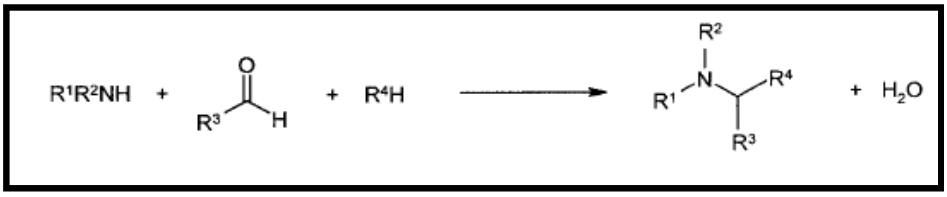
A. Hantzsch, *Justus Liebigs Ann. Chem.* **1882,** *215,* 1.

[b] Biginelli Dihydropyrimidine Syntheses



P. Biginelli, *Gazz. Chim. Ital.* **1893**, *23*, 360-413.

[c] The Mannich Reaction

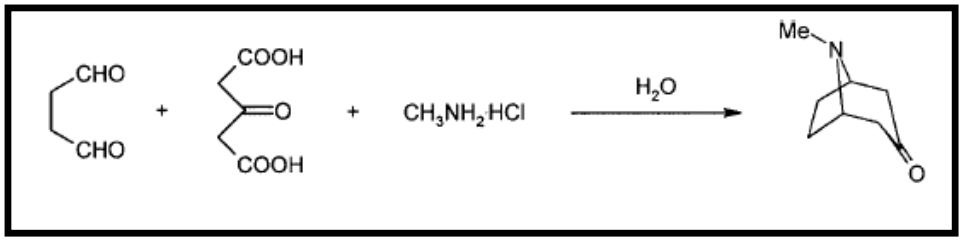


C. Mannich, *Arch. Pharm. Berl.* **1934**, *272*, 323_359.

[d] The Knoevenagel Reaction

L. F. Tietze, U. Beifuss, in Comprehensive *Organic Synthesis* (Ed.: B. M. Trost), Pergamon Press, Oxford, 1991, vol. 2, 341-394

[e] The Robinson Schöpf Reaction

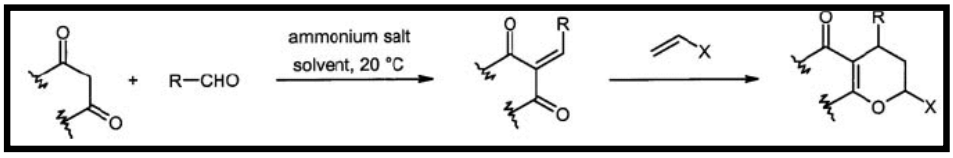


R. Robinson, *J. Chem. Soc.* **1917**, *111*, 762.

C. Schöpf, *Angew. Chem.* **1937**, *50*, 779.

C. Schöpf, *Angew. Chem.* **1937**, *50*, 797.

[f] The Domino-Knoevenagel Hetero-Diels_Alder Reaction

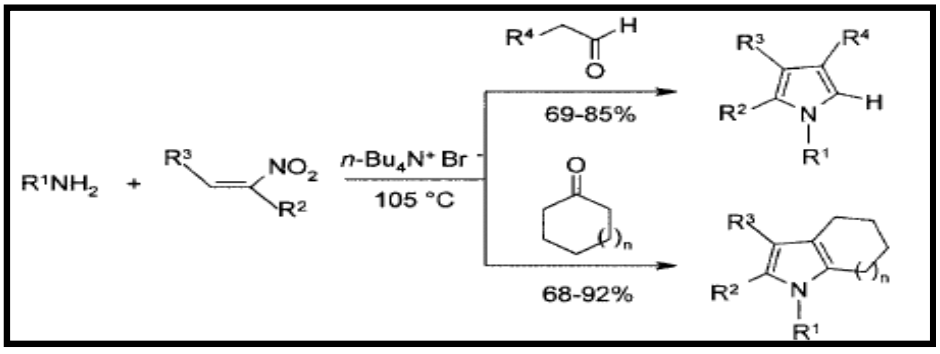


L. F. Tietze, *J. Het. Chem.* **1990**, *27*, 47.

L. F. Tietze, U. Beifuss, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131-163.

L. F. Tietze, A. Modi, *Med. Res. Rev.* **2000**, *20*, 304-322.

[g] Knorr-Pyrrole synthesis



V. F. Ferreira, M. C. B. V. De Souza, A. C. Cunha, L. O. R. Pereira, M. L. G. Ferreira, *Org. Prep. Proc. Int.* **2001**, *33*, 411-454

Catalysts

Previous reported protocols normally required prolonged reaction times and high temperature with moderate yields, so there has been considerable interest to explore mild, rapid, and higher yielding protocol. The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in huge amounts for organic reactions have posed a serious threat to the environment. Thus, so many improved protocols have been designed for preparing these types of entities have been developed to improve and modify this reaction by several catalysts. Catalytic reaction has received tremendous attention in recent times in the area of green synthesis. However, it has been observed that the solvent and Lewis acids employed are not always ecofriendly, and because of this severe environmental pollution often results during the process of waste disposal. This prompted us to initiate a systematic investigation to look into the feasibility of a reaction under modified experimental conditions towards development of real green methodology for useful molecules.

Different catalysts have been employed for these types of reaction are listed below.

$FeCl_3$/ tetracthyl orthosilicate[51]

Triflates [52,53]

Metal bromide[54, 55]

Polyoxometalate [56]

Strontium(II) nitrate[57]

Cerium(III)chloride [58]

Li (OTf) [59], $Ln(OTf)_3$ [60]

Heteropolyacids [61-65]

Ion exchange resins, Polymer based solid acid [66, 67]

L-Proline [68, 69]

Chiral phosphoric acid [70]

TMSCl [71]

$ZrCl_4$ [72]

Dowex [73]

BF_3. Etharate [74]

BF_3. Etharate/ CuCl [74]

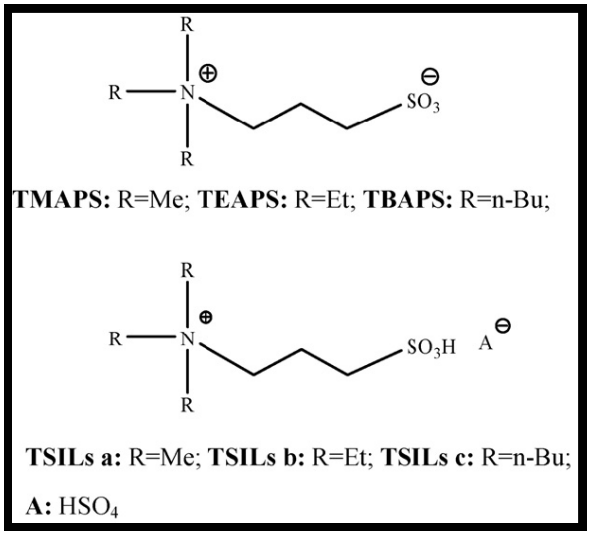
VCl_3[75]

$LiClO_4$[76]

Numerous modifications on Lewis acid adsorbed on mineral inorganic solid supports, silica, different clays are also reported and discloses a simple modification of the Biginelli DHPM synthesis. Excellent yields enhanced reaction rates, compatibility with various functional groups, environmentally friendly procedure, timesaving process, low cost and easy availability of the catalyst are some of the salient features of this reaction. This procedure will offer an easy access to substituted dihydropyrimidin-2(1*H*)-ones and thiones with different substitution patterns in high to excellent yields.

Ionic Liquids

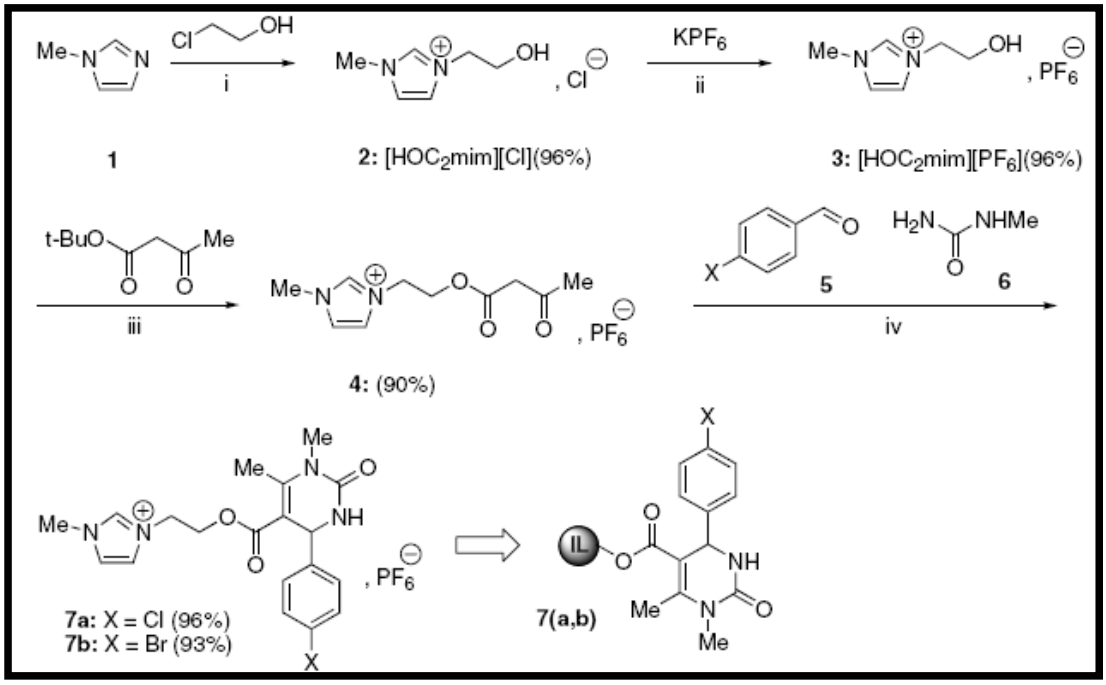
Liu Zuliang and coworkers used cheap and reusable task-specific ionic liquids that bear an alkanesulfonic acid group in an acyclic trialkylammonium cation were found to be effective catalysts for synthesizing 3,4-dihydropyrimidine-2-(1*H*)-ones via the one-pot three-component Biginelli reaction. The satisfactory results were obtained with good yields, short reaction time and simplicity in the experimental procedure. The catalysts could be recycled and reused six times without noticeably decrease in the catalytic activity. [77]



Jean Pierre Bazureau and coworkers reported new N-3 functionalized 3,4-dihydropyrimidine-2(1*H*)-ones with 1,2,4-oxadiazole group as amide isostere were synthesized in six steps by ionic liquid-phase organic synthesis (IoLiPOS) methodology

from ILP bound acetoacetate. The 3,4-dihydropyrimidine- 2(1H)-one (3,4-DHPM) core was prepared in the first step by one-pot three-component Biginelli condensation followed by N-alkylation with chloroacetonitrile. Then the nitrile group appended on the 3,4-DHPM heterocycle was quantitatively transformed into amidoxime. Addition of aliphatic carboxylic anhydride or aromatic carboxylic acid to the amidoxime produced the expected 1,2,4-oxadiazole via the O-acylamidoxime intermediate grafted on the ILP bound 3,4-DHPM using two convergent methods. After cleavage by transesterification under mild conditions, the target compounds were obtained in good overall yields. The structures and the purities of the reaction intermediates in each step were verified easily by routine spectroscopic analysis. [78]

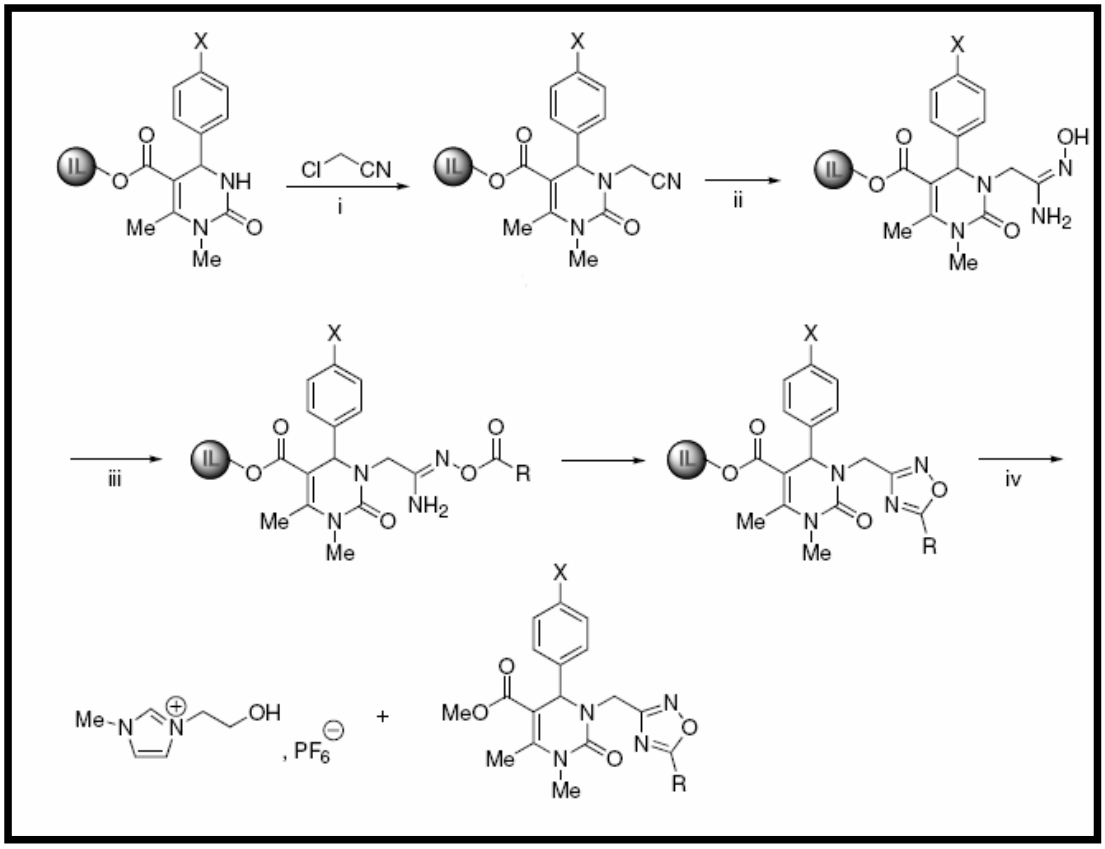
Preparation of ionic liquid-phases bound 3,4-dihydropyrimidine-2(1H)-ones. Reagents and reaction conditions: (i) chloroethanol (1 equiv), mw, 180 ^{0}C, 60 W, 10 min; (ii) KPF6 (1 equiv), MeCN, 25 ^{0}C, 18 h; (iii) *tert*-butyl acetoacetate (2.6 equiv), μω, 170 ^{0}C, 150 W, 10 min; (iv) 100 ^{0}C, HCl cat., 60 min



Preparation of N-3 functionalized 3,4-dihydropyrimidine-2(1H)-ones

Reagents and reaction conditions: (i) NaH (2 equiv), 0^{o}C, MeCN, 18 h; (ii) KOH (1.7 equiv), NH2OH, HCl (1.6 equiv), EtOH, 0^{o}C, 1 h then reflux, 18 h; (iii) Method A: a. $(RCO)_2O$ (20 equiv), 25^{o}C , 18 h; b. H2O, reflux, 18 h.; Method B: a. RCO_2H (1.09

equiv), DCC (1.02 equiv), DMAP 5%, MeCN, 25°C , 48 h; b. H_2O, reflux, 36 h; (iv) MeONa (1 equiv), MeOH, reflux, 18 h.



Zlotin, S.G. et al reported the synthesis of dihydropyrimidinones by condensation of aromatic (heteroaromatic) aldehydes with 1,3-dicarbonyl compounds under the 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4]) ionic liquid-piperidinium acetate catalytic system (0.2 equiv. of each component) in the absence of a solvent affords, depending on the structures of the reagents, 2-arylidene derivatives of methyl acetoacetate and acetylacetone, diethyl 2,4-bis(trifluoroacetyl)-3-phenylpentanedioate, or dimethyl 2-aryl-4-hydroxy-6-oxocyclohexane-1,3-dicarboxylates. The reactions of the resulting 2-arylidene derivatives with O-methylisourea in the [Bmim][BF_4] ionic liquid produced methyl 2-methoxy-4-methyl-6-aryldihydropyrimidine-5-carboxylates and 1-(2-methoxy-4-methyl-6-phenyldihydropyrimidin-5-yl)ethanone (mixtures of 3,6- and 1,6-dihydro isomers), which were transformed into the corresponding 3,4-dihydropyrimidin-2(1H)-one derivatives. [79]

Jingxing Du et al used novel ionic liquid, 3-carboxymethyl-1-methylimidazolium bisulfate ($CMImHSO_4$) as a recyclable catalyst for the Biginelli reaction under solvent-free conditions. [80] Jean Pierre Bazureau et al reported ionic liquid phase bound acetoacetate for the synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones [81] These compounds can also be synthesised in high yields in the presence of catalytic amounts of room temperature ionic liquids such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (BMImBF4) orhexafluorophosphate (BMImPF6) [82] It has been also reported that not only trialkylammonium halides [83] but also very inexpensive and easily available ammonium chloride [84] Gholap et al reported the synthesis of DHPMs by using *N*-Butylimidazolium tetrafluoroborate ($[Hbim]BF_4$) [85]. Jain et al used $[bmim]BF_4$ immobilized Cu (II) as a catalyst in synthesis of DHPMs [86] Hua-Zheng and cowerkers reported non-toxic room temperature ionic liquid l-n-butyl-3-methylimidazolium saccharinate (BMImSac). [87]

Recent years, task-specific room-temperature ionic liquids (TSILs) have emerged as a powerful alternative to conventional molecular organic solvents or catalysts due to their particular properties, such as undetectable vapour pressure, wide liquid range, as well as the ease of recovery and reuse The TSILs have also been used as catalysts for Biginelli reaction. [88-97]

However, TSILs with imidazole as the cation are relatively expensive, which hinders their industrial applications. Furthermore, typical ionic liquids consist of halogen containing anions (such as $[PF_6]^-$, $[BF_4]^-$, $[CF_3SO_3]^-$ and $[(CF_3SO_2)_2N]^-$) which in some regard limit their “greenness” [98-100]. Therefore, it is necessary to synthesize less expensive and halogen-free TSILs.

Shaabani and Rahmati [101] used room-temperature ionic liquid 1,1,3,3-tetramethylguanidinium trifluoroacetate as catalyst.

Building Blocks and Diversity

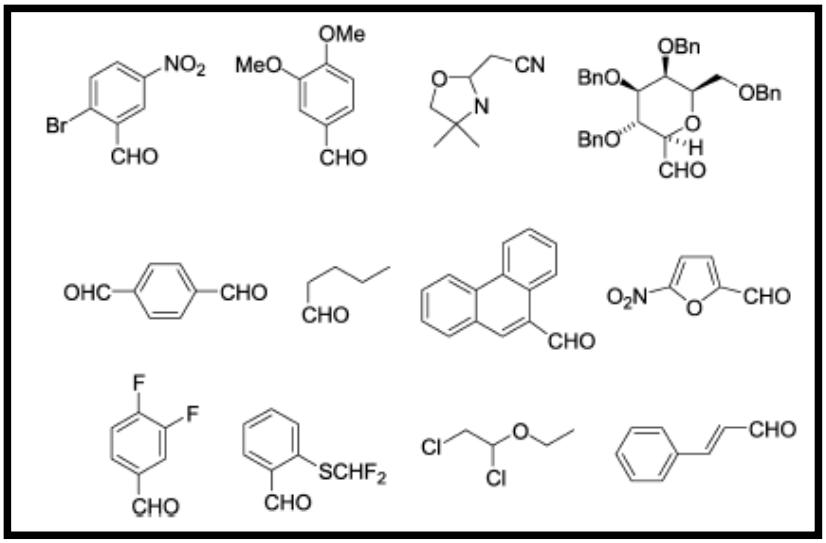
Out of the three building blocks in the Biginelli reaction it is the aldehyde component, which can be varied to the largest extent. In general, the reaction works best with aromatic aldehydes. These can be substituted in the o-, m- or –p- position with either electron-withdrawing or –donating groups. Good yields are usually obtained with m- or p-substituted aromatic aldehydes carrying electron-withdrawing substituents. For o-

substituted benzaldehydes having bulky substituents, yields can be significantly lower. Heterocyclic aldehydes derived from furan, thiophene, and pyridine rings also generally furnish acceptable yields of DHPM products [102].Aliphatic aldehydes typically provide only moderate yields in the Biginelli reaction unless special reaction conditions are employed, i.e. Lewis acid catalysts/solvent free methods, or using the aldehydes in protected form [103]. The C_4 unsubstituted DHPM can be prepared in a similar manner employing suitable formaldehyde synthons [103]. Of particular interest are reactions where the aldehyde component is derived from a carbohydrate. In such transformations, DHPMs having a sugar-like moiety in position 4 (C-nucleoside analogs) are obtained [104]. In a few cases, bisaldehydes have been used as synthons in Biginelli reactions [105]. Traditionally, simple alkyl acetoacetates are employed as CH-acidic carbonyl building blocks, but other types of 3- oxoalkanoic esters or thioesters can also be used successfully. With methyl 4-chloroacetoacetate, for example, the corresponding 6-chloromethyl-substituted DHPMs which can serve as valuable templates for further synthetic transformations are obtained [106]. Benzoylacetic esters react analogously, but yields are usually significantly lower and the overall condensation process is more sluggish [102]. Primary, secondary, and tertiary acetoacetamides can be used in place of esters to produce pyrimidine-5-carboxamide [102]. In addition, β-diketones serve as viable substrates in Biginelli reactions. Condensations can also be achieved employing cyclic β-diketones such as cyclohexane-1,3-dione [107], and other cyclic β-dicarbonyl compounds [108].

If a C_6-unsubstituted DHPM derivative needs to be synthesized, the corresponding 3-oxopropanoic ester derivative in which the aldehyde function is masked as an acetal can be employed [109]. Apart from ester-derived CH-acidic carbonyl compounds, nitroacetone also serves as a good building block, leading to 5-nitro-substituted DHPM derivatives in generally high yields [110]. The urea is the component in the Biginelli reaction that faces the most restrictions in terms of allowed structural diversity [111]. Therefore, most of the published examples involve urea itself as building block. However, simple monosubstituted alkyl ureas generally react equally well, in a regiospecific manner, to provide good yields of N_1- substituted DHPMs. Thiourea and substituted thioureas follow the same general rules as ureas, although longer reaction times are required to achieve good conversions. Yields are typically lower when compared to the corresponding urea derivatives. In some instances, it is also possible to

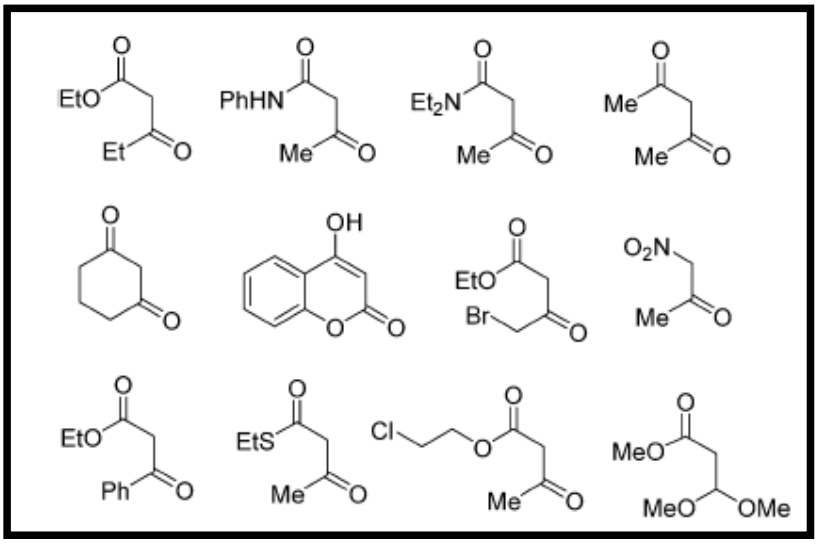
react protected urea or thioureas (isoureas), or guandidines under weak basic conditions with the aldehyde and CH-acidic carbonyl component (or with a precondensed Knoevenageltype enone) to yield the corresponding protected DHPMs [112, 113].

Aldehyde and protected aldehyde building blocks used in the Biginelli reaction



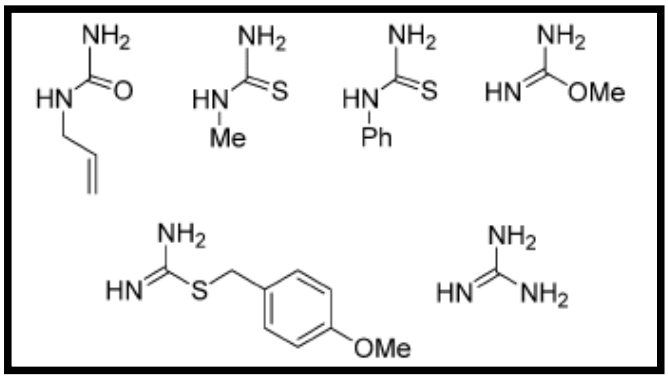
This latter method, using precondensed enones of type 5 has been frequently referred to as the "Atwal modification" of the Biginelli reaction [102, 103, 113]. Given the diversity in building block selection that is tolerated in the Biginelli reaction it is evident that a large number of DHPM derivatives of the general structure can be synthesized by combination of a relatively small number of (commercially available or proprietary) individual building blocks.

CH-Acidic carbonyl building blocks used in the Biginelli reaction

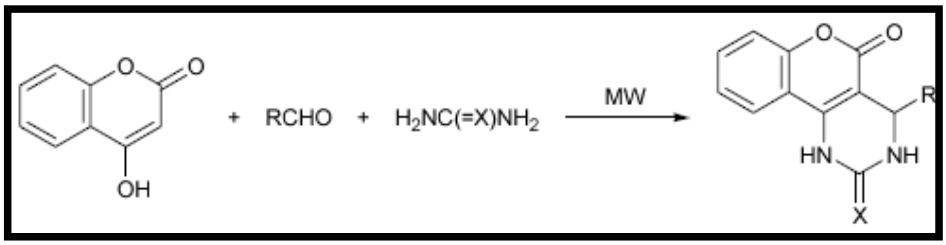


Employing different aldehydes (point of diversity at C4 position), different CH-acidic carbonyl derivatives (points of diversity at 5 and 6 position) and thiourea analogs (points of diversity at 2 position) in a Biginelli- or Atwal type condensation would lead to a library of 1.000 DHPM compounds, with a total of five diversity points around the dihydropyrimidine core [114]. It is therefore not surprising that a literature search for the general DHPM structure in the Chemical Abstracts Registry database led to well over 10.000 hits [114]. It is interesting to note however, that only a small fraction of these compounds has been published in the chemical literature (<1.000) [114]. On the other hand, more than half the 10,000 structures of type are commercially available, typically from companies specializing in chemical library generation.

Urea-type building blocks used in the Biginelli reaction



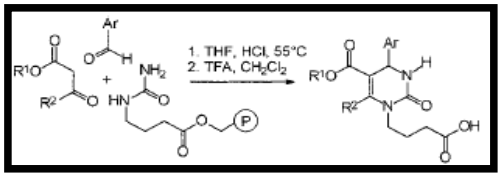
M. Kidwai and co-workers have proposed an ecologically benign method for the synthesis of benzopyranopyrimidines by reactions of 4-hydroxycoumarin (instead of 1,3 diketones or β-ketoesters) with aldehydes and urea and thiourea in the absence of solvent under microwave irradiation.[115]



Solid Phase Synthesis

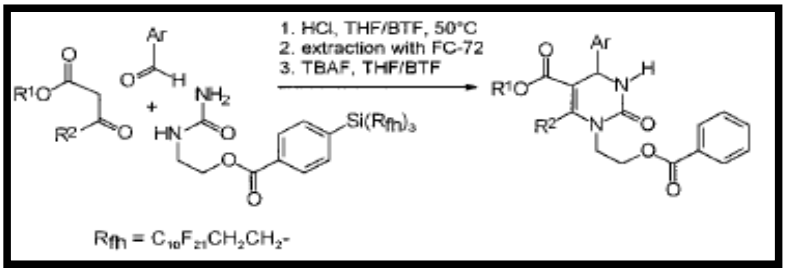
The generation of combinatorial libraries of heterocyclic compounds by solid phase synthesis is of great interest for accelerating lead discovery and lead optimization in pharmaceutical research. Multicomponent reactions (MCRs) leading to heterocycles are particularly useful for the creation of diverse chemical libraries, since the combination of n ≥3 small molecular weight building blocks in a single operation leads to high combinatorial efficacy. Therefore, solid phase modifications of MCRs are rapidly becoming the cornerstone of combinatorial synthesis of small-molecule libraries.One such MCR that has attracted considerable attention in recent years is the Biginelli reaction, which involves the one-pot cyclocondensation of a β-ketoester with an aryl aldehyde and an urea derivative.The resulting 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones. O.Kappe and coworkers reported the 4-aryl-3,4-dihydropyrimidines using Resin-Bound Isothiourea Building Blocks and Multidirectional Resin Cleavages. Solid phase organic synthesis remains one of the cornerstones of combinatorial chemistry, since this technique allows the chemist to take full advantage of the powerful principles (i.e. split-and-mix synthesis) offered by combinatorial technologies. For a multicomponent reaction such as the Biginelli condensation, various solid-phase strategies can be envisaged and in fact a number of different approaches have been disclosed in recent years, utilizing different resin-bound building blocks and linker combinations. Given the regioselectivity encountered in using N-substituted urea building blocks in the Biginelli condensation, a solid phase modification where the urea component is linked to the solid support via the amide nitrogen is an obvious choice.

The first actual solid-phase modification of the Biginelli condensation was reported by Wipf and Cunningham in1995. [116] In this sequence, *γ*-aminobutyric acid-derived urea was attached to Wang resin using standard procedures. The resulting polymer-bound urea was condensed with excess β-ketoesters and aromatic aldehydes in THF at 55°C in the presence of a catalytic amount of HCl to afford the corresponding immobilized DHPMs.

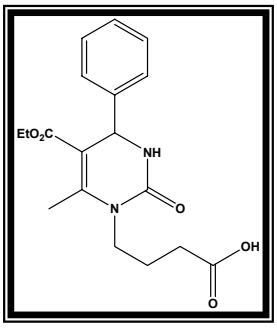


In an interesting variation of this protocol, the Biginelli reaction was also adapted to fluorous-phase conditions by the Wipf and Curran groups.[116, 117] In fluorous

synthesis, an organic molecule is rendered soluble in fluorocarbon solvents by attachment of a suitable fluorocarbon group ("fluorous tag"). Fluorocarbon solvents are usually immiscible with organic solutions, and fluorous molecules partition out of an organic phase and into a fluorous phase by standard liquid-liquid extraction. At the desired stage of the synthesis, the fluorous label is cleaved and the product is rendered "organic" again.[118] In the fluorous Biginelli reaction, the fluorous urea derivative was prepared by attachment of a suitable fluorous tag to hydroxyethylurea. The fluorous urea was then condensed with 10 equiv each of the corresponding acetoacetates and aldehydes in THF-benzotrifluoride (BTF) containing HCl. After extraction of the fluorous DHPMs with fluorous solvent (perfluorohexanes, FC-72), desilylation with tetrabutylammonium fluoride (TBAF) followed by extractive purification provided the "organic" Biginelli products DHPMs in good overall yields. Considering the simple experimental techniques used in this fluorous chemistry, automation should be feasible, thus allowing the preparation of DHPM libraries.[118]

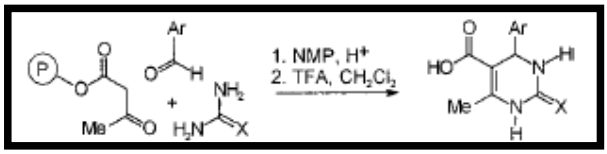


O. Kappe and co-workers reported the procedure in which urea component is linked to the solid (or fluorous) support via the amide nitrogen, which invariably leads to the formation of N1-functionalized, so far pharmacologically active, DHPMs.

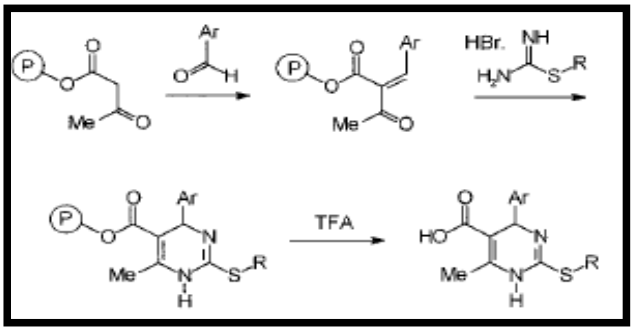


O. Kappe and co-workers have developed an alternative protocol, where the acetoacetate building block is linked to the solid support. Thus, Biginelli condensation of Wang-bound acetoacetate with excess aldehydes and ureas/thioureas in NMP(N-methyl

pyrollidine/HCl provided the desired DHPMs on solid support. Subsequent cleavage with 50% TFA (Trifluoro Acetic acid) furnished the free carboxylic acids **in** high overall yield.



In addition to solid-phase adaptions of the traditional three-component Biginelli condensation, solid-phase variations of the "Atwal modification" of the Biginelli reaction (see above) have also been reported. Robinett et al have disclosed the synthesis of a 648-member combinatorial library of 1,4-dihydropyrimidines. Toward this end, polymer-bound acetoacetate was subjected to Knoevenagel condensation with aromatic aldehydes, followed by condensation with isothioureas. The resulting polymer-bound 1,4-dihydropyrimidines were cleaved from the resin with 50% TFA to produce carboxylic acid.[119]

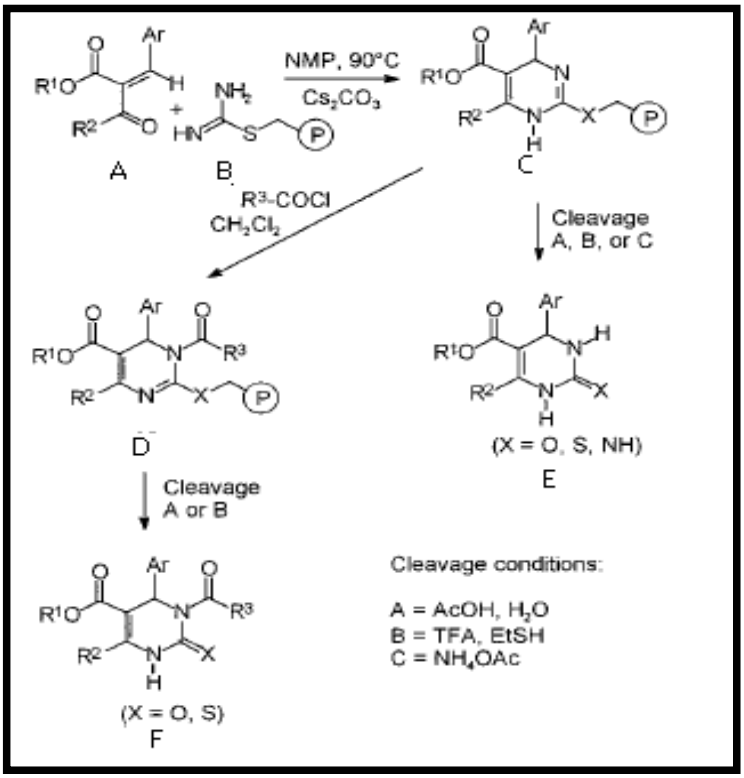


In an effort to increase the molecular diversity in solid phase syntheses of DHPM scaffolds, a novel and versatile solid-phase approach was adopted where an isourea building block is attached to the solid support.[120]

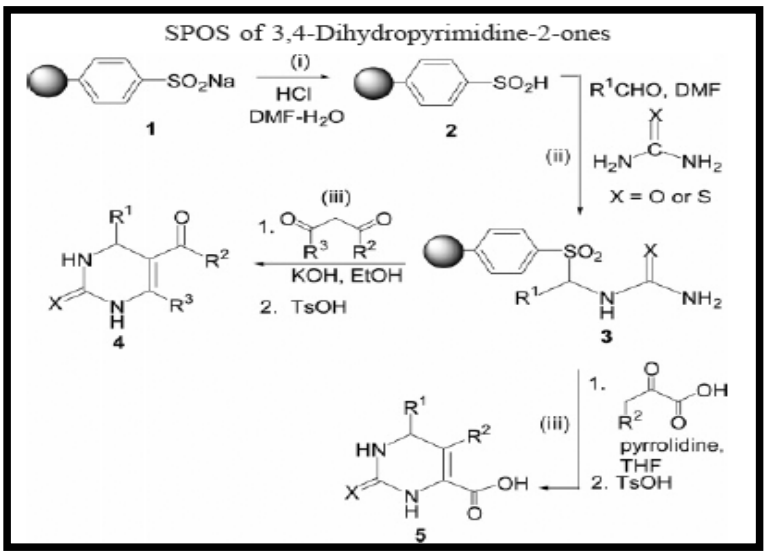
In the key step, polymer-bound (Wang) isothiourea **B** is condensed with enones in *N*-methylpyrrolidone (NMP) in the presence of base. Thepolymer-bound dihydropyrimidine can then be directly cleaved from the resin (**C→E**) by employing different cleavage strategies. Therefore, three types of DHPMs **E** (X =O, S, and NH) can be obtained by applying the appropriate cleaving conditions A, B, or C. On the other hand, an additional element of diversity can be introduced onto the pyrimidine nucleus by regioselective N_3-acylation of the polymer-bound intermediate **C** with suitable electrophiles (e.g., acyl chlorides, R^3COCl). By applying different cleaving strategies to **D**, the corresponding N_3-functionalized DHPMs **F** were obtained in moderate to high overall yields. This solid-

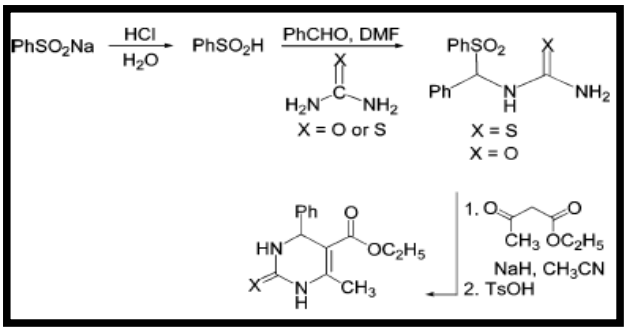
phase approach is therefore particularly attractive for the preparation of pharmacologically active N_3-acylated analogues such as DHPMs and should be useful for the generation of targeted libraries of this heterocyclic scaffold.

Diversity in solid phase DHPM synthesis



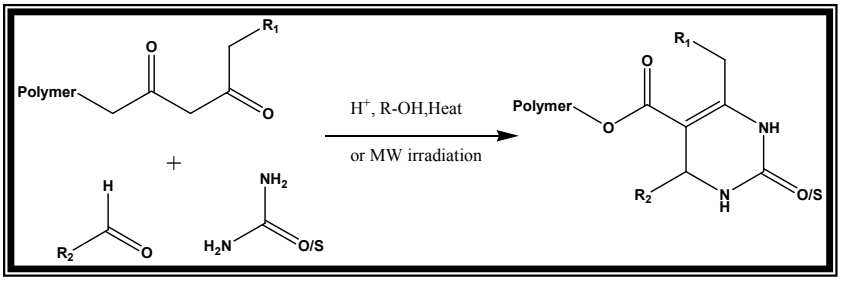
Weiwei Li and Yulin Lam had developed Solid-Phase Synthesis of DHMPs Using Sodium Benzenesulfinate as a Traceless Linker. [121]



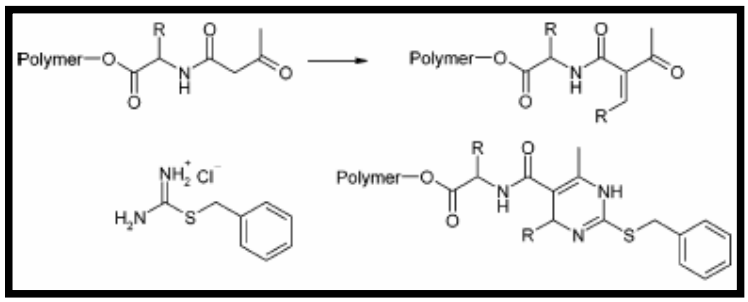


Andreas Schober developed synthetic protocol based on Immobilized β-Ketoamides to increase the diversity of DHPM derivatives by varying the substituents in position 4 in a simple manner. Depending on the building blocks for the three-component reaction, the immobilization strategies were chosen. At least three different strategies for the preparation of DHPM derivatives on solid support were described in recent literature. The first one makes use of immobilized urea or thiourea moieties . The second uses an immobilized β-ketoester, and the third one uses an S-linked isothiouronium salt, Biginelli protocols depending on immobilized aldehydes were not found. [122]

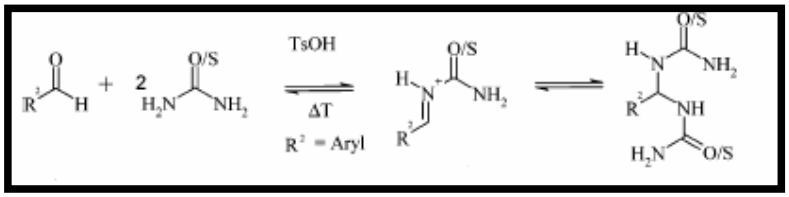
DHPM Synthesis with Immobilized -Ketoesters



DHPM Synthesis with Immobilized β- Ketoamides Using Atwal's Route



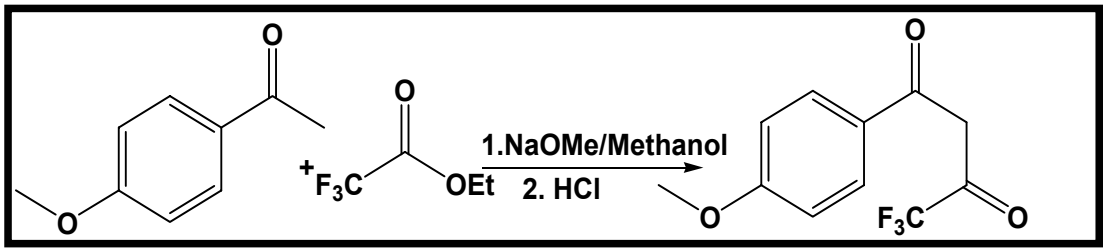
***N*-Acyliminium Ion, the Essential Reaction Intermediate**



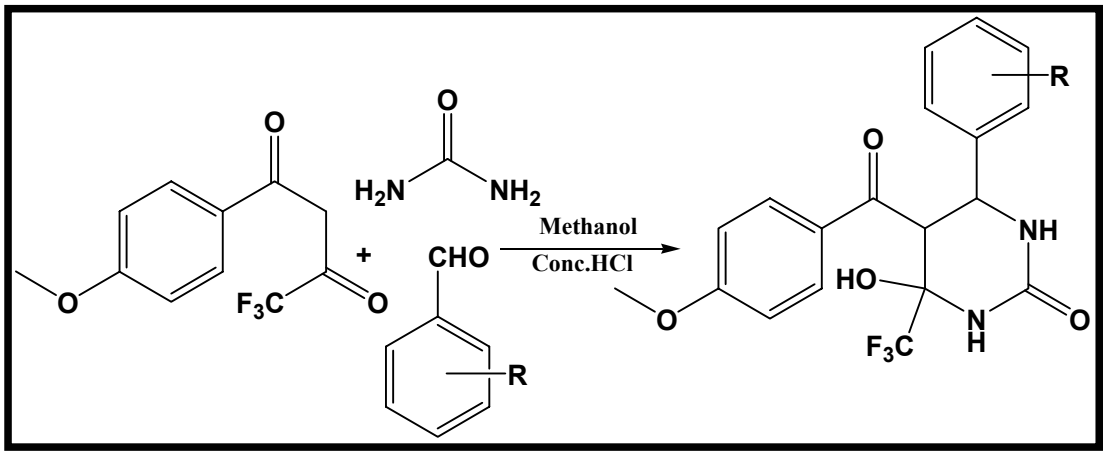
Thus by employing any of the solid-phase synthesis methods described above, libraries of DHPMs can be generated in a relatively straightforward fashion. Biginelli products are therefore contained in many commercially available small molecule libraries or compound collections and have undoubtely been subjected to many high-throughput screening (HTS) processes. However, all of these products would still be racemic, and therefore screening will not address possible enantioselective effects on molecular activity.

Reaction Scheme

Step-I

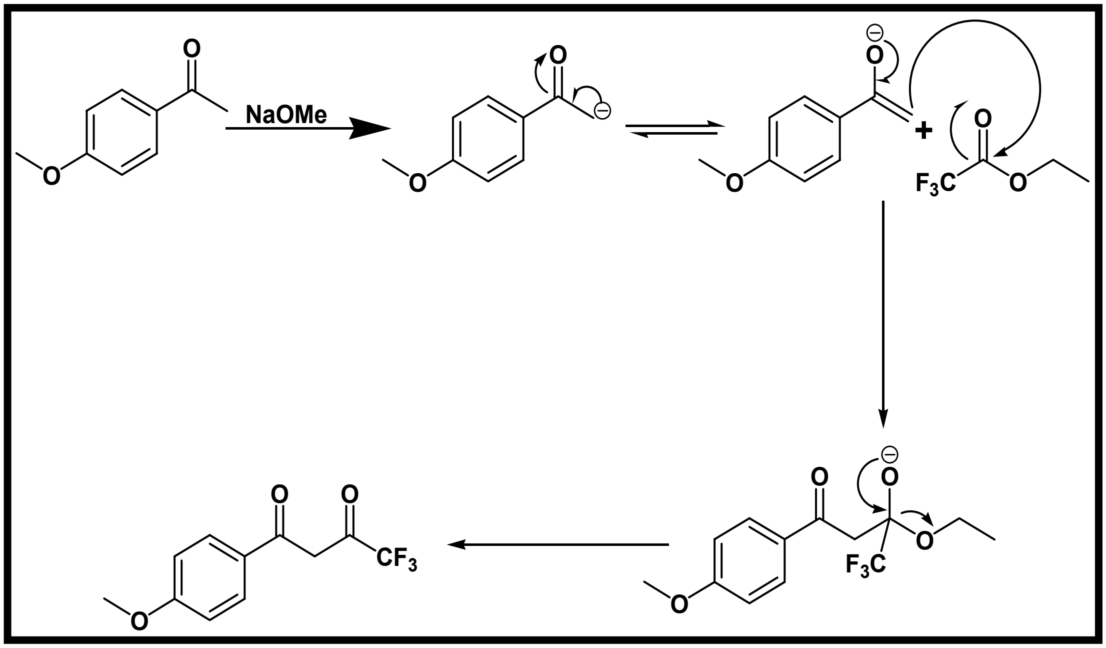


Step-II



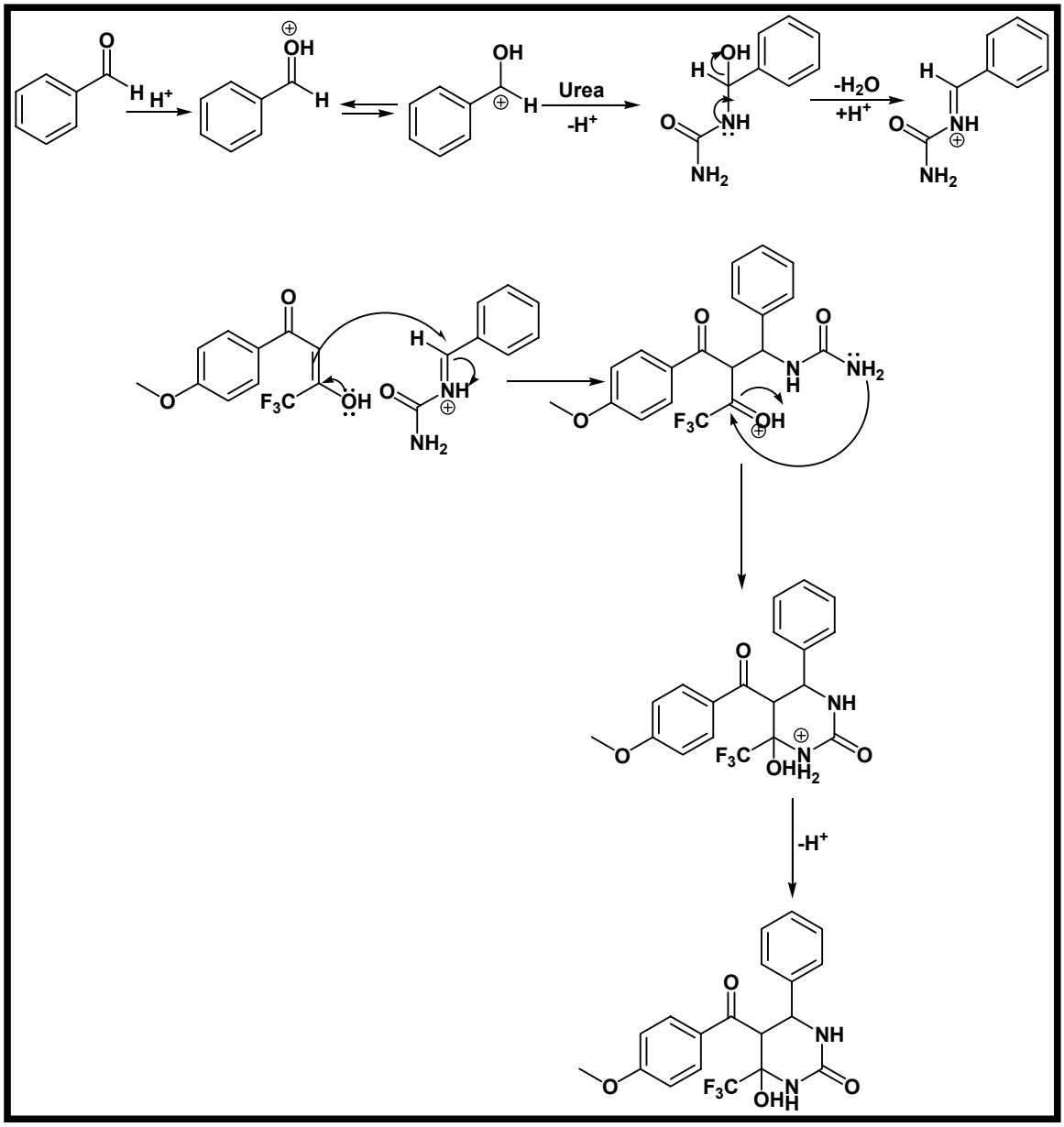
Reaction Mechanism

Step 1

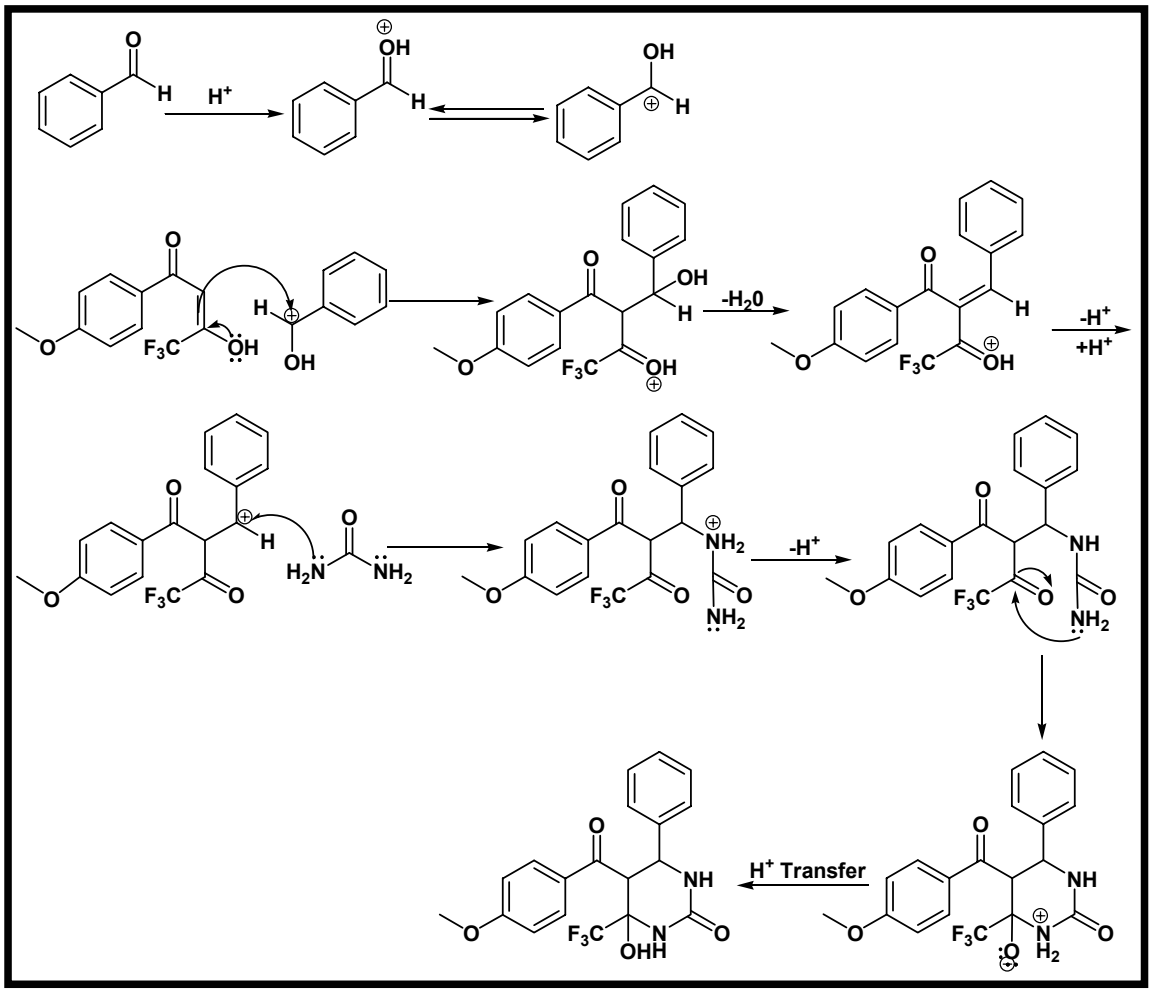


Step-II

Route-1



Route-II



Experimental

Step-1

Preparation of 4,4,4-Trifluoro-1-(4-methoxyphenyl) Butane-1,3 -dione

In freshly prepared Sodium Methoxide (1.7equivalent) in methanol, 4-methoxy acetophenone was added into it at 15-20 ^{0}C. It was stirred for 30 minutes at 20 ^{0}C. 1.2 equivalent of trifluoroethyl acetate was added into it by dropping funnel within 30 minutes at 20 ^{0}C,stirred for 12 hrs at 60 ^{0}C. TLC was checked for completion of reaction. Reaction mixture was poured in to 10%HCl solution & stirred for 15 minutes. Product was precipitated; it was filtered and washed twice successively with 100 ml water. Product was recrystallized in methanol: water (80:20)

Note: - The entire reaction was carried out under nitrogen atmosphere

It was dried in vacuum at 30-40 ^{0}C

Yield: 78% MP: - 68 ^{0}C

TLC System: (Hexane: Ethyl acetate)

9 : 1

Step-2

Preparation of 4-Hydroxy-5-(4-methoxybenzoyl)-6-substituted-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-ones (General Method)

1.5 equivalent of Urea was dissolved in to 15 ml methanol until clear solution was observed. 1.0 equivalent of each of 1,3 diketone and Substituted benzaldehyde was added into stirred well, clear solution was observed. 2-3 drops of Conc.HCl was added into it, stirred for 5-6 hours according to the reactivity of the substituted benzaldehyde. Reaction mixture was cooled at room temperature. TLC was checked for completion of reaction. Reaction mixture was poured in crushed ice & extracted with ethyl acetate. Ethyl acetate

layer was collected, washed with twice 15 ml of water and 20 ml brine. It was dried over anh. Na_2SO_4. Solvent was evaporated by using vacuum rotavapor at 40 ^{0}C. Solid product was observed. It was purified by methanol

Yield: 65-70%

TLC System: (Chloroform: Methanol)

7 : 3

The physical data are given as separate table No. 1

Physical data of 4-hydroxy-5-(4-methoxybenzoyl)-6-substituted-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-ones

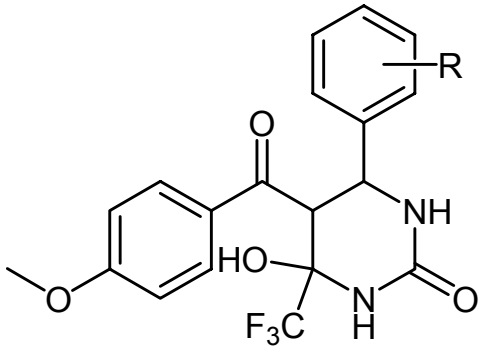


Table No: - 1

Sr. No	Code.No	Substitution R	M.F	M.W	M.P	C, H , N Analysis		
						C	H	N
1	**RK-1001**	2-Cl	$C_{19}H_{16}ClF_3N_2O_4$	428.79	218-219	53.22 (53.19)	3.76 (3.74)	6.53 (6.48)
2	**RK-1002**	3-NO_2	$C_{19}H_{16}F_3N_3O_6$	439.34	187-189	51.94 (51.90)	3.67 (3.66)	9.56 (9.58)
3	**RK-1003**	4-OCH_3	$C_{20}H_{19}F_3N_2O_5$	424.37	185-187	56.60 (56.57)	4.51 (4.48)	6.60 (6.57)
4	**RK-1004**	2-OH	$C_{19}H_{17}F_3N_2O_5$	410.34	212-213	55.61 (55.56)	4.18 (4.22)	6.83 (6.85)
5	**RK-1005**	4-F	$C_{19}H_{16}F_4N_2O_4$	412.33	216-217	55.34 (55.32)	3.91 (3.89)	6.79 (6.82)
6	**RK-1006**	2-OCH_3	$C_{20}H_{19}F_3N_2O_5$	424.37	195-197	56.60 (56.67)	4.51 (4.48)	6.60 (6.56)

Table No: - 1

Sr. No	Code.No	Substitution R	M.F	M.W	M.P	C, H , N Analysis		
						C	H	N
7	**RK-1007**	4-Cl	$C_{19}H_{16}ClF_3N_2O_4$	428.79	220-222	53.22 (53.18)	3.76 (3.78)	6.53 (6.48)
8	**RK-1008**	3-OH	$C_{19}H_{17}F_3N_2O_5$	410.34	234-236	55.61 (55.56)	4.18 (4.22)	6.83 (6.85)
9	**RK-1009**	3,4-di OCH_3	$C_{21}H_{21}F_3N_2O_6$	454.4	220-221	55.51 (55.47)	4.66 (4.68)	6.16 (6.19)
10	**RK-1010**	4-SCH_3	$C_{20}H_{19}F_3N_2O_4S$	440.44	198-200	54.54 (54.50)	4.35 (4.38)	6.36 (6.32)
11	**RK-1011**	H	$C_{19}H_{17}F_3N_2O_4$	394.34	187-189	57.87 (55.76)	4.35 (4.39)	7.10 (7.05)
12	**RK-1012**	3-OCH_3	$C_{20}H_{19}F_3N_2O_5$	424.37	192-194	56.60 (56.62)	4.51 (4.54)	6.60 (6.62)
13	**RK-1013**	4-NO_2	$C_{19}H_{16}F_3N_3O_6$	439.34	178-179	51.94 (51.87)	3.67 (3.70)	9.56 (9.60)
14	**RK-1014**	2-NO_2	$C_{19}H_{16}F_3N_3O_6$	439.34	182-183	51.94 (51.89)	3.67 (3.63)	9.56 (9.62)
15	**RK-1015**	3-Cl	$C_{19}H_{16}ClF_3N_2O_4$	428.79	195-197	53.22 (53.19)	3.76 (3.69)	6.53 (6.52)
16	**RK-1016**	3-Br	$C_{19}H_{16}BrF_3N_2O_4$	473.24	213-215	48.22 (48.20)	3.41 (3.43)	5.92 (5.89)
17	**RK-1017**	3-OPh	$C_{25}H_{21}F_3N_2O_5$	486.44	201-203	61.73 (61.70)	4.35 (4.38)	5.76 (5.70)
18	**RK-1018**	3,4,5-tri OCH_3	$C_{22}H_{23}F_3N_2O_7$	484.42	207-209	54.55 (54.52)	4.79 (4.80)	5.78 (5.75)

Spectral Discussion

PMR spectral study

^{1}HNMR of the synthesized 4-Hydroxy-5-(4-methoxybenzoyl)-6-substituted-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-ones were recorded on DPX-300MHz FT-NMR spectrophotometer (Bruker) instrument using TMS (Tetramethyl silane) as an internal reference standard in DMSO-D_6 solvent. The singlet observed for methoxy (-OCH3) of 4-methoxy phenyl in the range of δ 3.7-3.9. Methine (-CH) attached with –NH and substituted phenyl ring gives typical doublet at δ 4.2-4.6 with J Value 11.4 *Hz* and methine (-CH) group attached with carbonyl shows clear doublet at δ 4.7-5.0 with J Value 11.3 *Hz*. Hydroxyl group (-OH) attached to quaternary carbon and two different -NH protons of the cyclic ring appears at δ 7.0 -8.5. Proton of the aromatic ring attached to the carbonyl group appeared at δ 6.6-7.5. The pattern of the ^{1}HNMR spectra between δ 6.8-8.0 clearly indicated that the benzene ring attached to the unsymmetrical carbon atom is meta or para substituted.

Individual ^{1}HNMR data of synthesized compounds are mentioned in Spectral data details.

^{13}C NMR Spectral study

4-Hydroxy-5-(4-methoxybenzoyl)-6-substituted-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-ones

^{13}C NMR spectra were recorded on Bruker 400MHz instruments using DMSO and $CHCl_3$ as the solvents with tetramethylsilane (TMS) as the respective internal standard. . In the spectrum, a doublet or quartet for the carbon atom connected with the trifluoromethyl substituent is located at 79-81 ppm (^{3}J(C-F) =31-33 Hz) which is typical for a quaternary carbon rather than a carbonyl carbon atom. Methoxy group attached to phenyl ring is located at 54-56 ppm. The –CH (asymmetric) group attached with different substituent is appeared at 46-47 ppm and –CH (asymmetric) group attached with carbonyl is located at 54-56 ppm. The carbonyl carbon attached with phenyl ring and –CH group is located at 191-196 ppm and carbonyl carbon attached with –NH group is 160-165 ppm. The pattern of phenyl ring depends up on the substitution it is appeared between 110-160 ppm.

IR spectral study

The infrared spectra of all compounds of this chapter were recorded on Shimadzu 8400 FT-IR spectrophotometer by KBr pellet method.

The different frequencies of infrared spectrum of 4-hydroxy-5-(4-methoxybenzoyl)-6-substituted-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-ones are discussed here. The Hydroxy group (-OH) appeared in the range of (3350-3400cm^{-1}), typical carbonyl frequencies appeared for this cyclic urea in the range of (1620-1660cm^{-1}). The carbonyl group attached with 4-methoxyphenyl appeared at (1670-1699cm^{-1}). The secondary –NH frequencies appeared in all the compounds in the range of 3160-35400cm^{-1}.The –OCH_3 functional group frequencies are also observed like 1205-1215cm^{-1} for Ar-O-C stretching. The trifluoromethyl group stretching vibrations observed at 1000-1380cm^{-1}

Mass spectral Study

The mass spectrums of the 4-hydroxy-5-(4-methoxybenzoyl)-6-substituted-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-ones were recorded by GCMS-QP2010 spectrometer (EI method). The molecular ion peak (M^+) values are in superior match with molecular formula for synthesized compounds. In some cases, molecular ion peak (M^+) peak does not appear due to the loss of H_2O from the synthesized compounds, so it exhibit M-18 peak. Probable mass fragmentation of 4-hydroxy-5-(4-methoxybenzoyl)-6-substituted-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-ones is given in spectral data of each compounds separately.

Elemental Analysis

Elemental analysis of the compounds was carried out on Elementar Vario EL III Carlo Erba 1108 model at CDRI, Lucknow and the results are in agreement with the structures assigned.

Spectral Data

4-Hydroxy-5-(4-methoxybenzoyl)-6-(2-chlorophenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1001)

IR (KBr Pellet): 3435cm^{-1}(-OH), 3320cm^{-1}(-NH), 2976.26(C-H), 1670 cm^{-1}(-C=O) 1659 cm^{-1}(-CO-NH), 1599 cm^{-1} (-NH Bend), 1223-1275 cm^{-1} (C-O-C), 1170 cm^{-1} (C-F), 750 cm^{-1} (C-Cl)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3-nitrophenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one(RK-1002)

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ 3.74 (s, 3H), 4.53 (d, 1H, *J*=11.09 Hz), 5.10 (d, 1H, *J*=11.06 Hz), 6.81 (d, 2H, *J*=8.77 Hz), 7.16 (s, 1H), 7.44 (t, 2H, *J*=8.21Hz) 7.74 (d, 2H, *J*=8.80Hz), 7.83 (d, 2H, *J*=8.52 Hz), 7.97 (d, 1H, *J*=8.08 Hz), 8.28 (s, 1H)

^{13}C NMR (CDCl$_3$): *δ* 195.53, 163.76, 154.22, 147.39, 139.69, 133.73, 130.13, 129.10, 129.04, 122.81, 122.23, 113.38, 81.30, 55.02, 54.69, 46.59

IR (KBr Pellet): 3470cm^{-1}(-OH), 3340cm^{-1}(-NH), 2954(C-H), 1690 cm^{-1}(-C=O) 1659 cm^{-1}(-CO-NH), 1576 cm^{-1} (-NH Bend), 1570 cm^{-1} (-C-NO$_2$), 1243 cm^{-1} (C-O-C), 1140 cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-methoxyphenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1003)

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ 3.60 (s, 3H), 3.76 (s, 3H), 4.32 (d, 1H, *J*=11.13 Hz), 4.87 (d, 1H, *J*=11.06 Hz), 6.70 (d, 2H, *J*=8.52 Hz), 6.84 (d, 2H, *J*=8.75 Hz), 7.01 (s, 1H), 7.75 (s, 1H), 7.28 (d, 2H, *J*=8.51 Hz) 7.68 (t, 2H, 8.78 Hz)

^{13}C NMR (CDCl$_3$): *δ* 196.34, 163.47, 158.90, 154.14, 130.12, 129.31, 129.13, 128.38, 113.30, 113.24, 81.22, 55.00, 54.58, 46.84

IR (KBr Pellet): 3466cm^{-1} (-OH), 3321cm^{-1} (-NH), 2920-2959cm^{-1}(C-H), 1690 cm^{-1} (-C=O) 1662.69 cm^{-1}(-CO-NH), 1576 cm^{-1} (-NH Bend), 1271 cm^{-1} (C-O-C), 1190 cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(2-hydroxyphenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1004)

IR (KBr Pellet): 3520cm^{-1}(-OH)**,** 3440cm^{-1}(-OH), 3399.29cm^{-1}(-NH), 2910-2949cm^{-1}(C-H), 1700.12 cm^{-1}(-C=O) 1645.54 cm^{-1}(-CO-NH), 1578 cm^{-1} (-NH Bend), 1229.54 cm^{-1} (C-O-C), 1140-1170 cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-fluorophenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1005)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.76 (s, 3H), 4.36 (d, 1H, *J*=11.09 Hz), 4.93 (d, 1H, *J*=11.06 Hz), 6.84 (d, 2H, *J*=8.73 Hz), 6.97 (t, 2H, *J*=8.58 Hz), 7.06 (s, 1H), 7.22 (s, 1H), 7.41 (m, 2H, *J*=5.64 Hz), 7.70 (d, 3H, *J*=8.30 Hz)

^{13}C NMR ($CDCl_3$): *δ* 195.77, 163.49, 162.85, 160.40, 154.02, 133.48, 130.07, 129.27, 129.19, 114.81, 114.60, 113.28, 81.21, 55.01, 54.44, 46.87

IR (KBr Pellet): 3471.47cm^{-1}(-OH), 3345cm^{-1}(-NH), 2954cm^{-1} (C-H), 1699.98 cm^{-1} (-C=O) 1659 cm^{-1}(-CO-NH), 1498-1529 cm^{-1} (-NH Bend), 1243 cm^{-1} (C-O-C), 1140-1210 cm^{-1} (CF_3 & C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(2-methoxyphenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1006)

^{13}C NMR ($CDCl_3$): *δ* 195.67, 177.03, 163.68, 156.67, 129.96, 129.77, 129.11, 128.90, 123.06, 120.15, 113.18, 110.65, 80.38, 54.96, 42.14

IR (KBr Pellet): 3520cm^{-1}(-OH), 3374cm^{-1}(-NH), 2910-2949cm^{-1}(C-H), 1668.84cm^{-1} (-C=O) 1599 cm^{-1} (-CO-NH), 1498-1529 cm^{-1} (-NH Bend), 1219-1244 cm^{-1} (C-O-C),1140-1210 cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-chlorophenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1007)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.76 (s, 3H), 4.37 (d, 1H, *J*=11.10 Hz), 4.93 (d, 1H, *J*=11.06 Hz), 6.85 (d, 2H, *J*=8.70 Hz), 7.10 (s, 1H), 7.23 (t, 3H, *J*=7.53 Hz), 7.40 (d, 2H, *J*=8.32 Hz), 7.71 (d, 3H, *J*=8.00 Hz)

IR (KBr Pellet): 3462.31cm^{-1}(-OH), 3345cm^{-1}(-NH), 2902-2947cm^{-1}(C-H), 1698cm^{-1} (-C=O) 1662 cm^{-1} (-CO-NH), 1491-1511cm^{-1} (-NH Bend), 1211-1249 cm^{-1} (C-O-C),1018-1104cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3-hydroxyphenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1008)

IR (KBr Pellet): 3466.32cm^{-1}(-OH), 3356cm^{-1}(-NH), 2921-2950cm^{-1}(C-H), 1690cm^{-1} (-C=O), 1662.6 cm^{-1} (-CO-NH), 1491-1502cm^{-1} (-NH Bend), 1206-1271 cm^{-1} (C-O-C),1111-1271cm^{-1} (C-F)

^{13}C NMR ($CDCl_3$): δ 196.61, 163.53, 159.92, 157.03, 154.23, 138.60, 130.12, 129.33, 129.03, 117.65, 115.19, 114.16, 113.22, 81.30, 55.19, 55.01, 46.68

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3,4-dimethoxyphenyl)-4-(trifluoromethyl) tetrahydropyrimidin-2(1*H*)-one (RK-1009)

^{1}H-NMR (300 MHz, DMSO-d_6):δ 3.58 (s, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 4.48 (d, 1H, *J*=11.02 Hz), 4.83 (d, 1H, *J*=11.60 Hz), 6.72 (m, 2H, *J*=8.12 Hz), 6.85 (d, 2H, *J*=8.67 Hz), 6.96 (s, 1H), 7.10 (d, 2H, *J*=7.12 Hz), 7.68 (s, 1H), 7.78 (d, 2H, *J*=8.73 Hz)

IR (KBr Pellet): 3478cm^{-1}(-OH), 3321cm^{-1}(-NH), 2910-2950cm^{-1}(C-H), 1699.98 cm^{-1} (-C=O), 1674.12 cm^{-1} (-CO-NH), 1498-1522cm^{-1} (-NH Bend), 1211-1249 cm^{-1} (C-O-C), 1107-1171cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-methylthiophenyl)-4-(trifluoromethyl) tetrahydropyrimidin-2(1*H*)-one (RK-1010)

IR (KBr Pellet): 3450cm^{-1}(-OH), 3340cm^{-1}(-NH), 2912-2950cm^{-1}(C-H), 1685 cm^{-1} (-C=O), 1674.12 cm^{-1} (-CO-NH), 1490-1510cm^{-1} (-NH Bend), 1206-1248 cm^{-1} (C-O-C), 1170-1204cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one (RK-1011)

IR (KBr Pellet): 3440cm^{-1}(-OH), 3329cm^{-1}(-NH), 2930-2956cm^{-1}(C-H), 1701 cm^{-1} (-C=O), 1674.33cm^{-1} (-CO-NH), 1493-1530cm^{-1} (-NH Bend), 1190-1226 cm^{-1} (C-O-C), 1090-1204cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3-methoxyphenyl)-4-(trifluoromethyl) tetrahydropyrimidin-2(1*H*)-one (RK-1012)

IR (KBr Pellet): 3470cm^{-1}(-OH), 3350.11cm^{-1}(-NH), 2921-2956cm^{-1}(C-H), 1704 cm^{-1} (-C=O), 1665.2cm^{-1} (-CO-NH), 1493-1522cm^{-1} (-NH Bend), 1185-1240 cm^{-1} (C-O-C), 1089-1172cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(4-nitrophenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1013)

IR (KBr Pellet): 3452cm^{-1}(-OH), 3349cm^{-1}(-NH), 2911-2946cm^{-1}(C-H), 1697.63 cm^{-1} (-C=O), 1656.23 cm^{-1} (-CO-NH), 1580.12 cm^{-1} (-C-NO_2), 1498-1520cm^{-1} (-NH Bend), 1107-1199 cm^{-1} (C-O-C), 1107-1182cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(2-nitrophenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1014)

IR (KBr Pellet): 3478cm^{-1}(-OH), 3350cm^{-1}(-NH), 2903-2922cm^{-1}(C-H), 1710 cm^{-1} (-C=O), 1662.35 cm^{-1} (-CO-NH), 1578 cm^{-1} (-C-NO_2), 1510-1523cm^{-1} (-NH Bend), 1201-1230cm^{-1} (C-F)1112-1175 cm^{-1} (C-O-C)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3-chlorophenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1015)

IR (KBr Pellet): 3456cm^{-1}(-OH), 3321cm^{-1}(-NH), 2911-2976(C-H), 1678 cm^{-1}(-C=O) 1658 cm^{-1}(-CO-NH), 1599 cm^{-1} (-NH Bend), 1170-1209 cm^{-1} (C-O-C), 1170-1181cm^{-1} (C-F), 750-760 cm^{-1} (C-Cl)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3-bromophenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1016)

IR (KBr Pellet): 3441cm^{-1}(-OH), 3309cm^{-1}(-NH), 2905-2923(C-H), 1699.9 cm^{-1}(-C=O) 1674 cm^{-1}(-CO-NH), 1599-1607 cm^{-1} (-NH Bend), 1170-1178 cm^{-1} (C-O-C), 1170-1181cm^{-1} (C-F), 550-556 cm^{-1} (C-Br)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3-phenoxyphenyl)-4-(trifluoromethyl)tetra hydropyrimidin-2(1*H*)-one (RK-1017)

IR (KBr Pellet): 3445cm^{-1}(-OH), 3326.65cm^{-1}(-NH), 2910-2956cm^{-1}(C-H), 1697 cm^{-1} (-C=O), 1668.82cm^{-1} (-CO-NH), 1493-1520cm^{-1} (-NH Bend), 1190-1226 cm^{-1} (C-O-C), 1050-1170cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-(3,4,5-trimethoxyphenyl)-4-(trifluoromethyl) tetrahydropyrimidin-2(1*H*)-one (RK-1018)

IR (KBr Pellet): 3482cm^{-1}(-OH), 3311cm^{-1}(-NH), 2908-2978(C-H), 1689 cm^{-1}(-C=O) 1668 cm^{-1}(-CO-NH), 1499-1523 cm^{-1} (-NH Bend), 1161-1209 cm^{-1} (C-O-C), 1170-1181cm^{-1} (C-F)

4-Hydroxy-5-(4-methoxybenzoyl)-6-napthyl-4-(trifluoromethyl)tetrahydro pyrimidin-2(1*H*)-one (RK-1019)

^{13}C NMR ($CDCl_3$): δ 191.04, 162.25, 155.41, 132.78, 130.78, 130.15, 129.49, 128.75, 128.63, 127.86, 126.50, 125..18, 124.56, 120.80, 112.49, 84.31, 54.72, 50.85, 48.87, 43.15

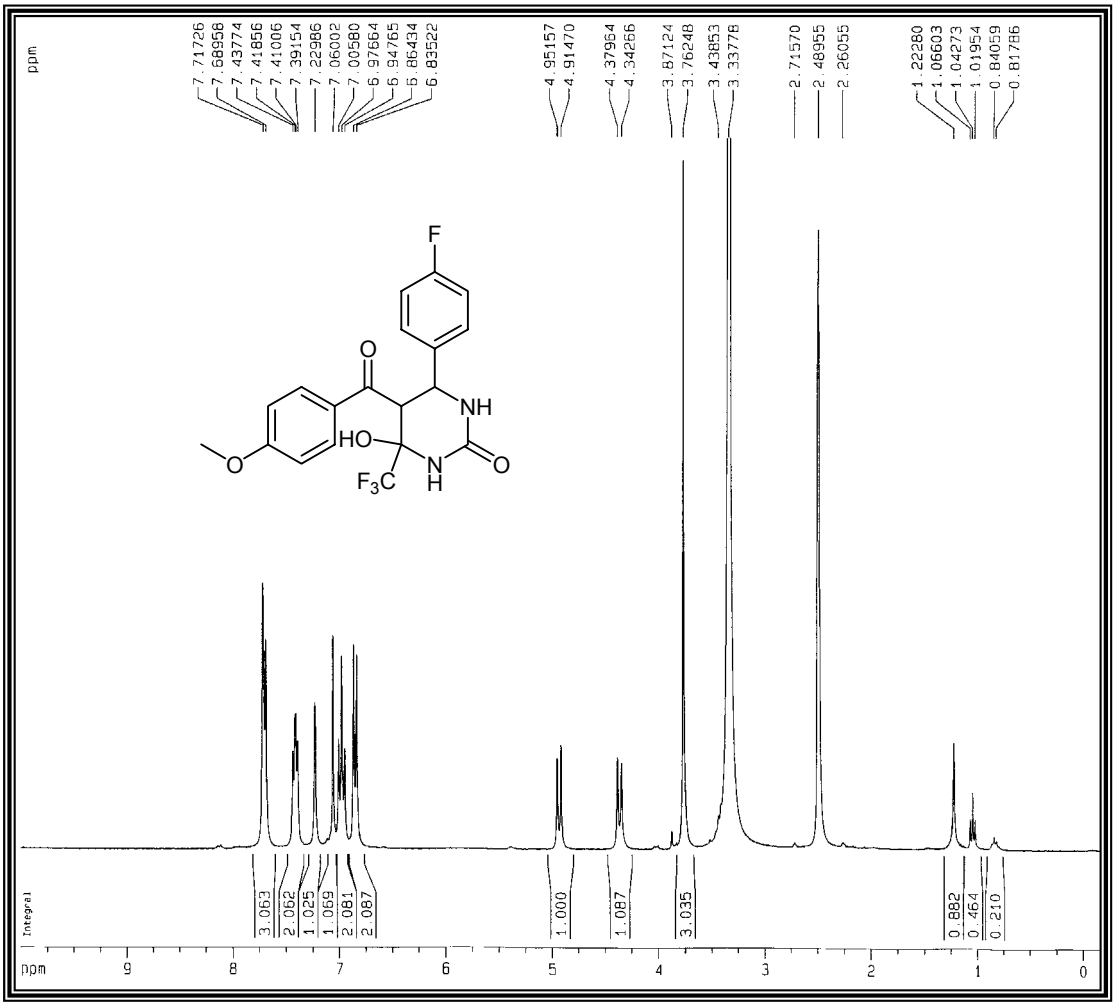
IR (KBr Pellet): 3462.34cm^{-1}(-OH), 3219cm^{-1}(-NH), 2902-2947cm^{-1}(C-H), 1691 cm^{-1} (-C=O), 1559 cm^{-1} (-CO-NH), 1506-1523cm^{-1} (-NH Bend), 1219-1244cm^{-1} (C-F),1022-1109 cm^{-1} (C-O-C)

Mass value of 4-hydroxy-5-(4-methoxybenzoyl)-6-substituted-phenyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-ones

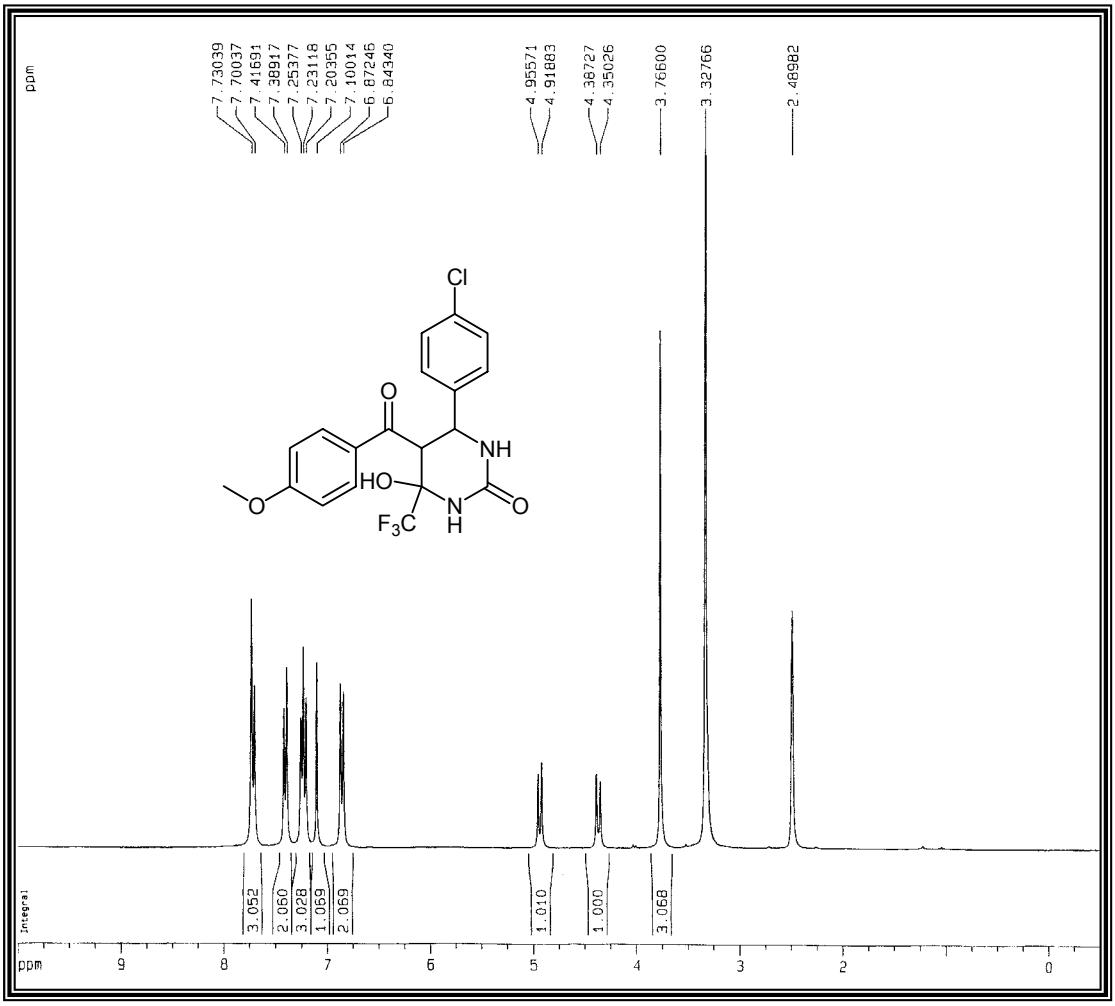
Compound Code.No	(m/z) Relative intensity
RK-1001	428 (09%)
RK-1002	439-18 (12%)
RK-1003	424 (15%)
RK-1004	410 (25%)
RK-1005	412 (18%)
RK-1006	424 (10%)
RK-1007	428 (11%)
RK-1008	410 (15%)
RK-1009	454 (17%)
RK-1010	440 (05%)
RK-1011	394 (10%)
RK-1012	424-18 (14%)
RK-1013	439(15%)
RK-1014	439 (20%)
RK-1015	428 (12%)
RK-1016	473-18 (14%)
RK-1017	486 (18%)
RK-1018	484-18 (20%)
RK-1019	444.4(17%)

Spectra of the Representative compounds

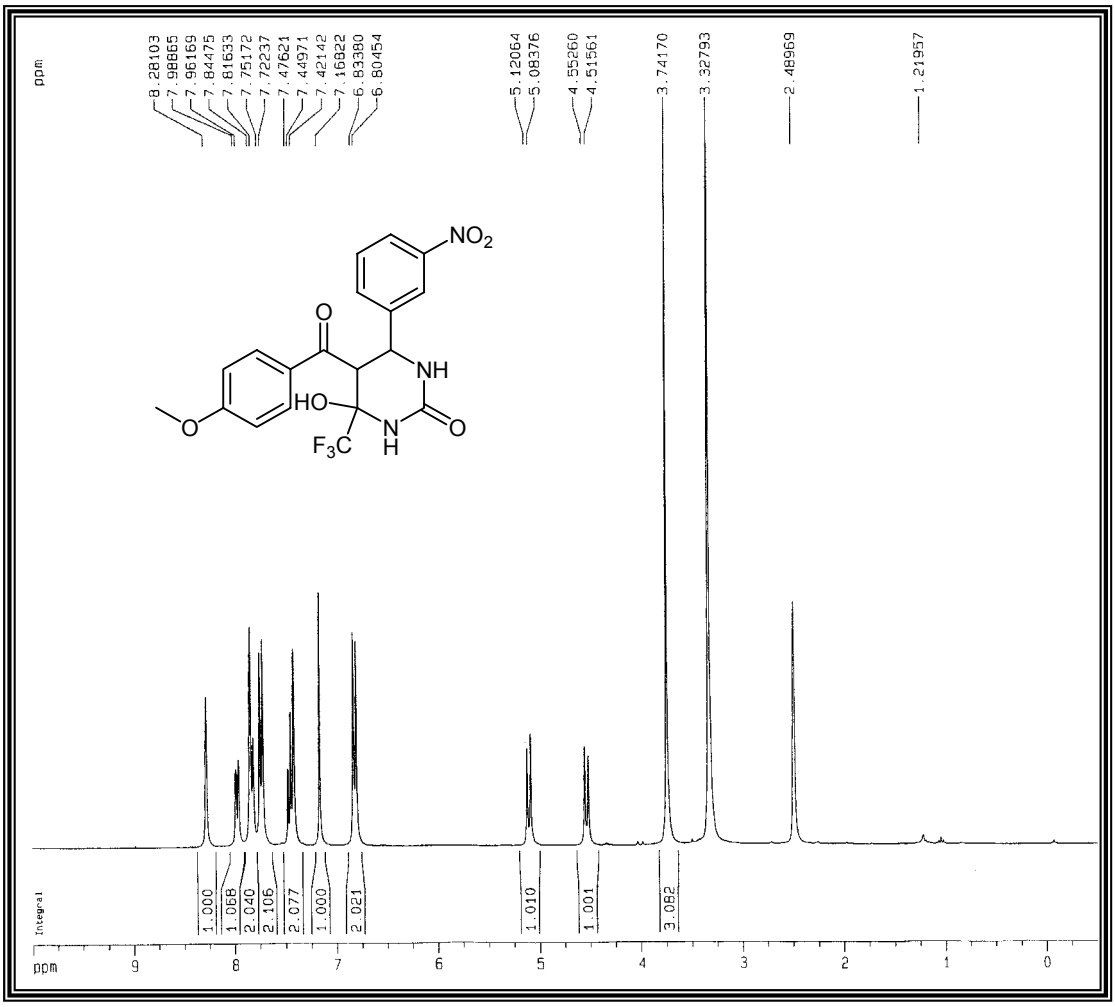
[a] ^{1}H NMR Spectra of RK-1005



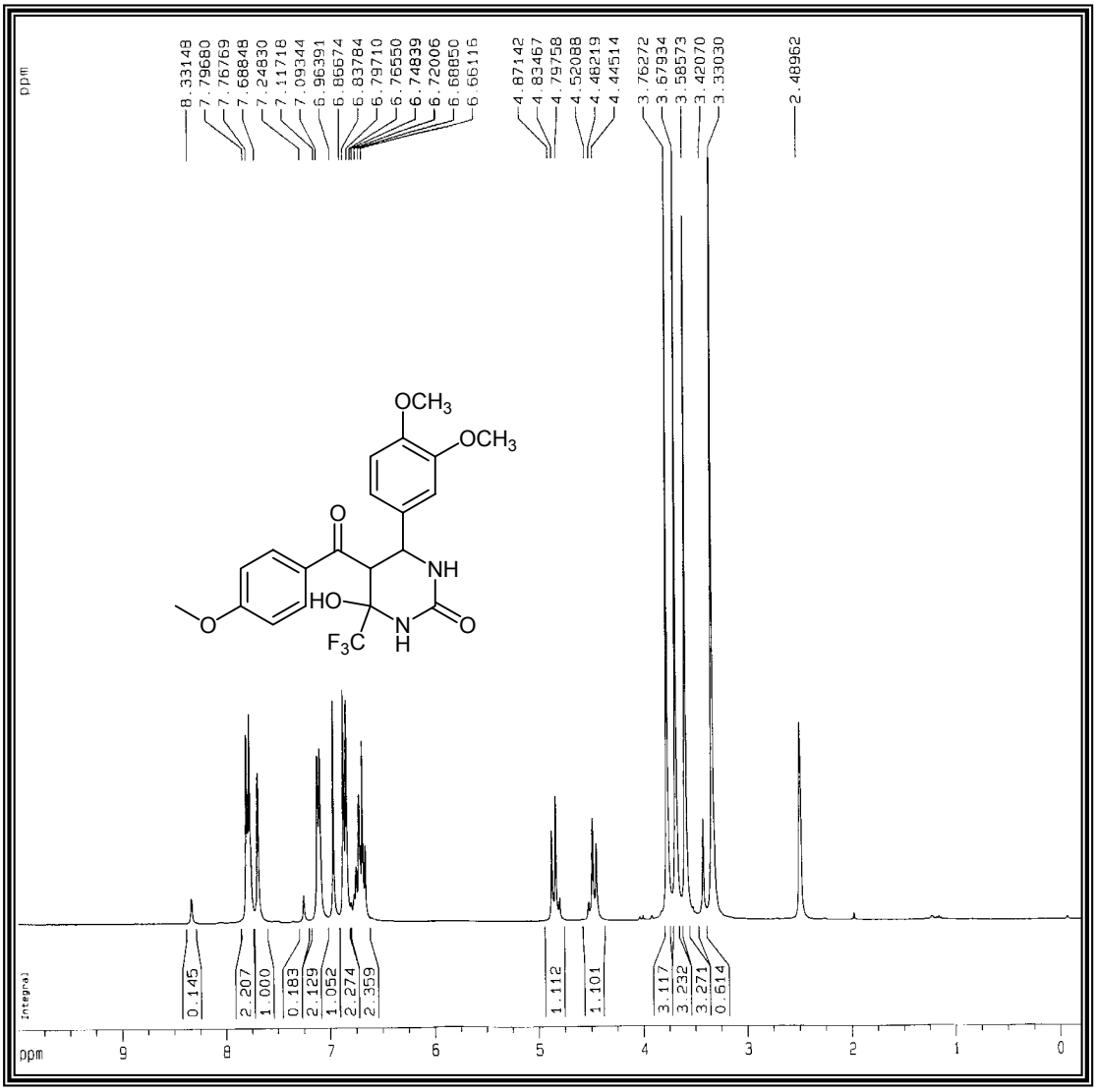
[b] ^{1}H NMR Spectra of RK-1007



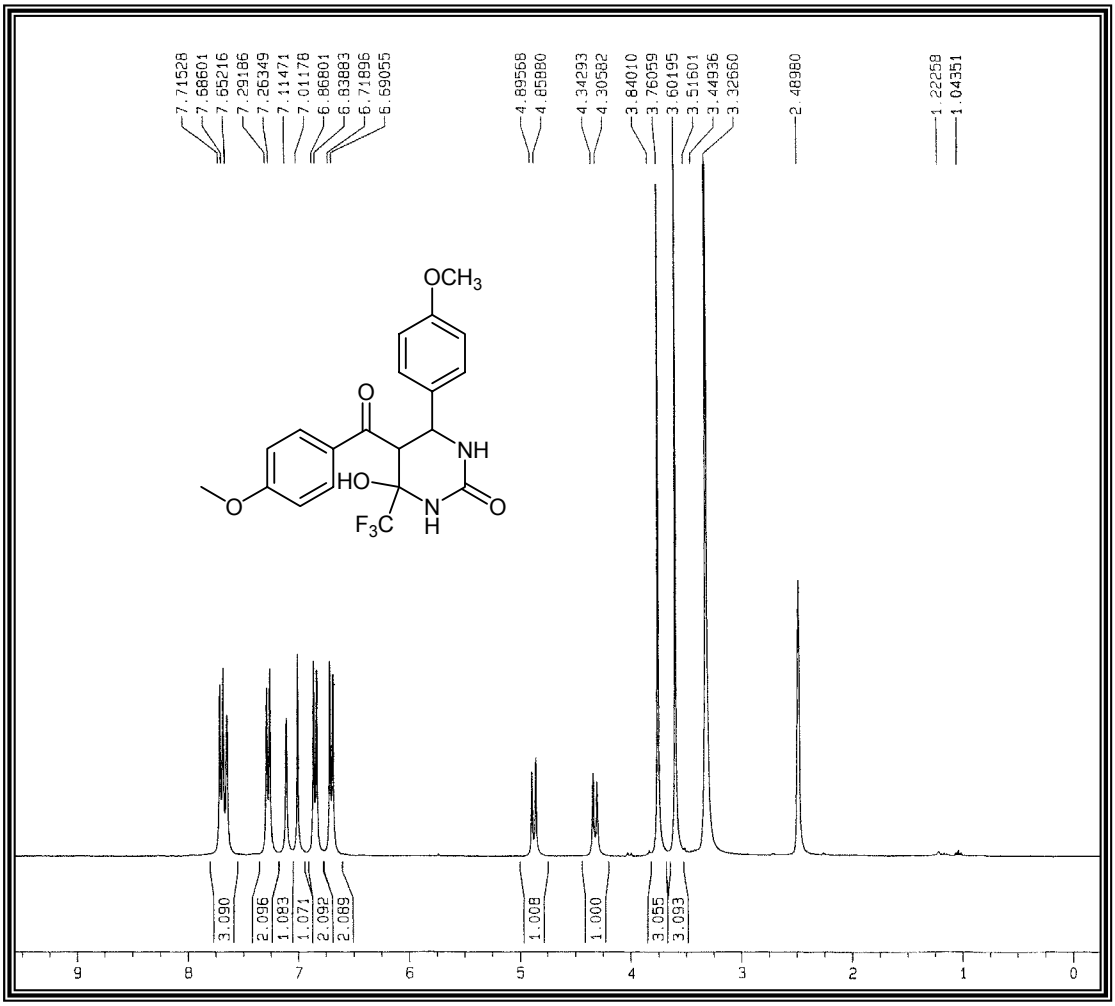
[c] ^{1}H NMR Spectra of RK-1002



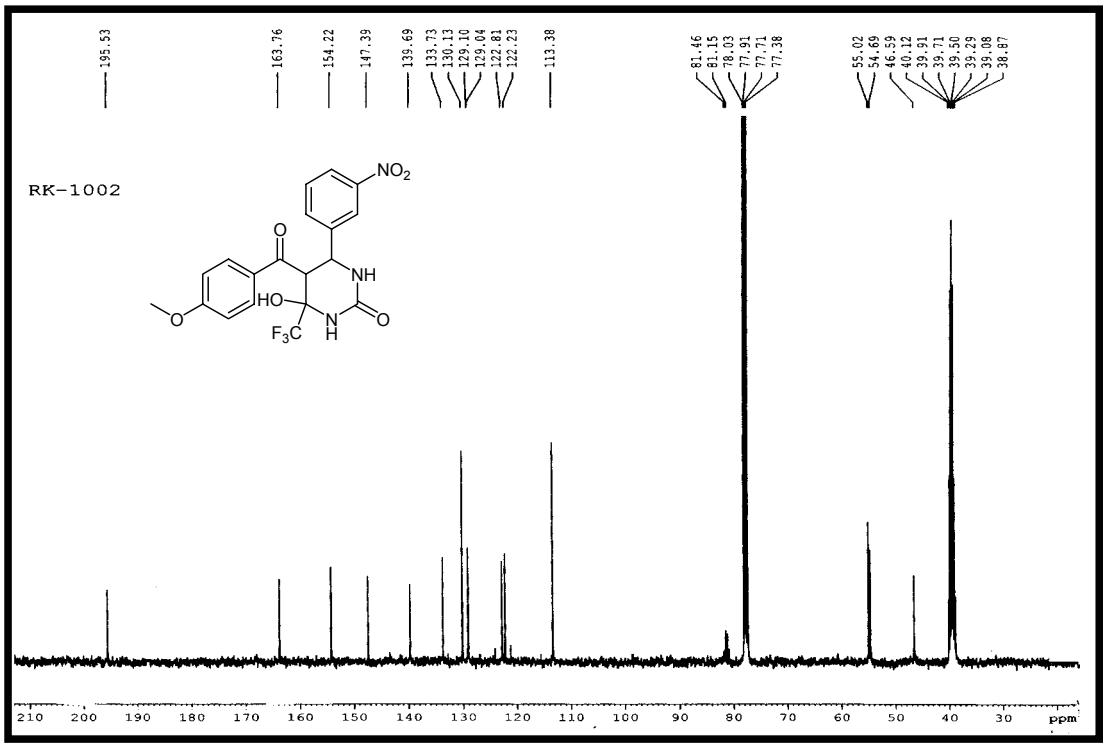
[d] ^{1}H NMR Spectra of RK-1009

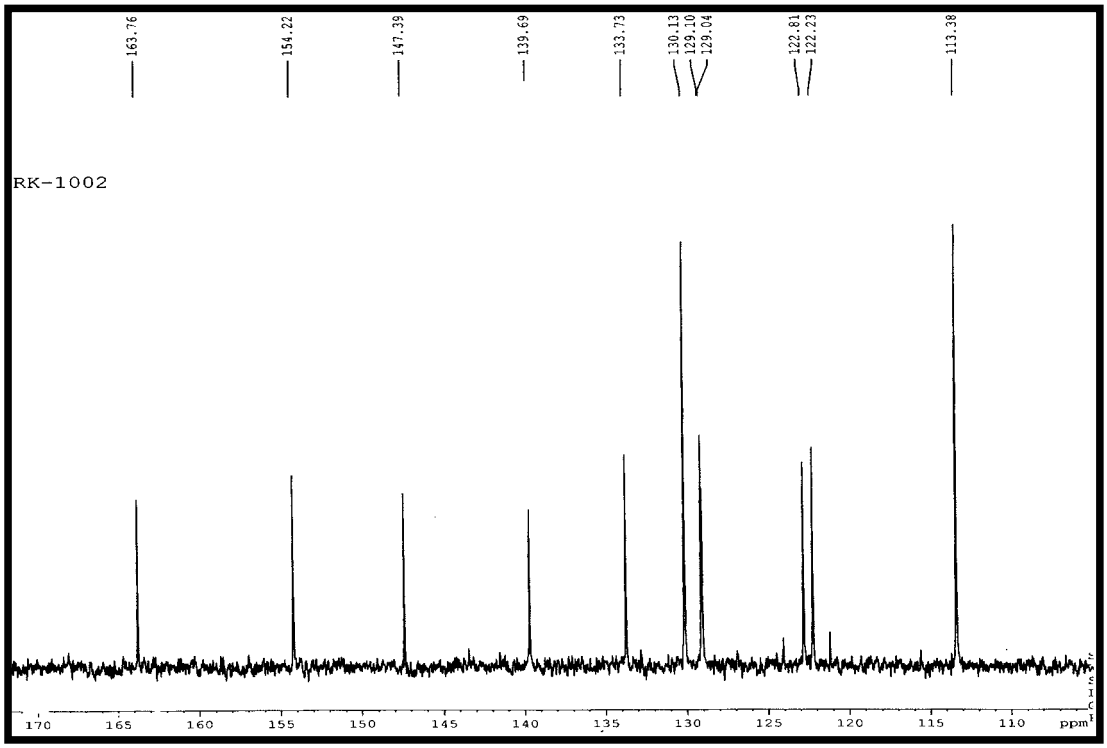


[e] ^{1}H NMR Spectra of RK-1003

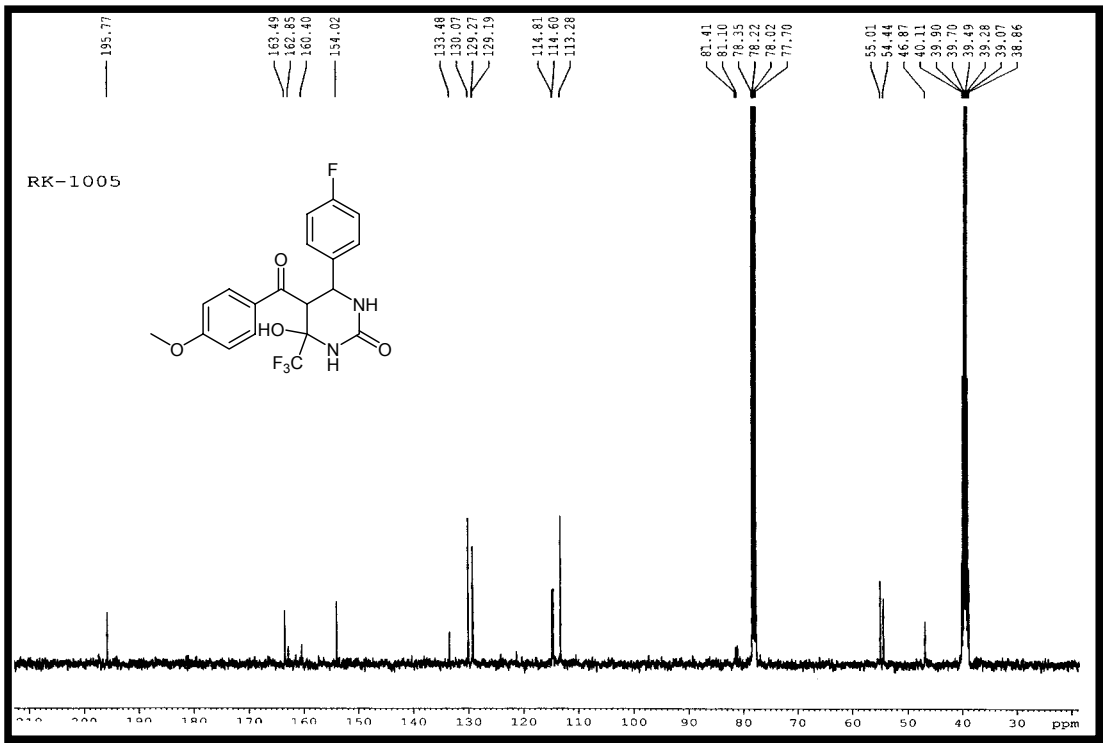


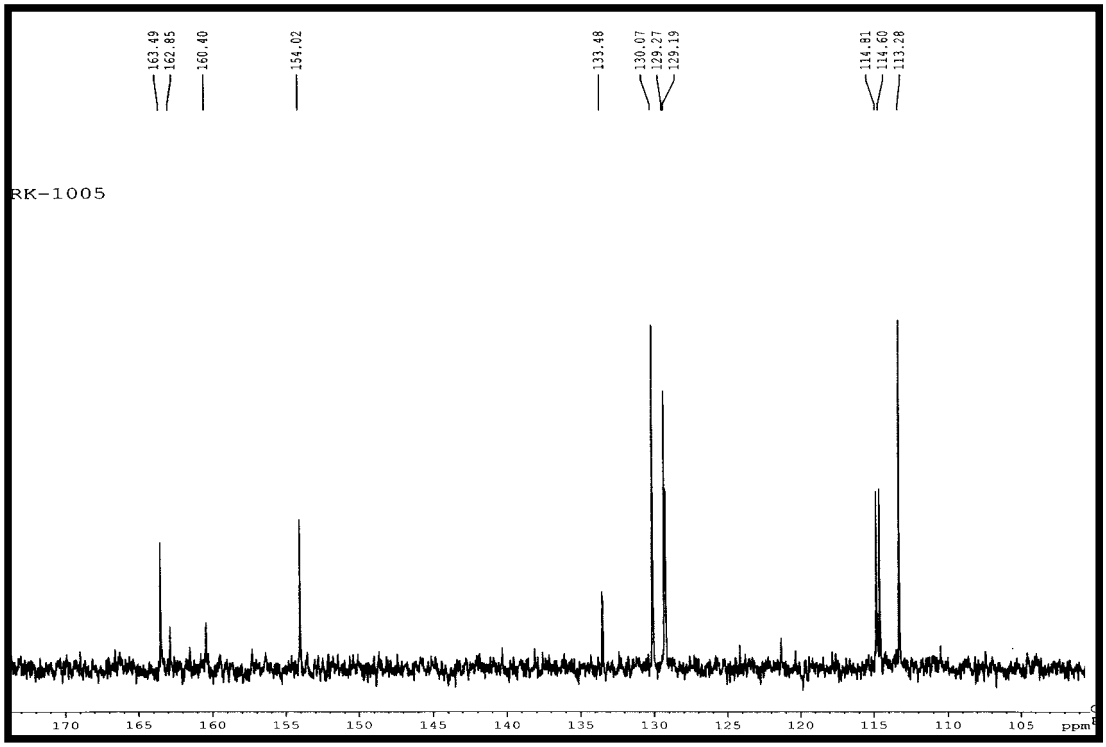
[f] ^{13}C NMR of RK-1002



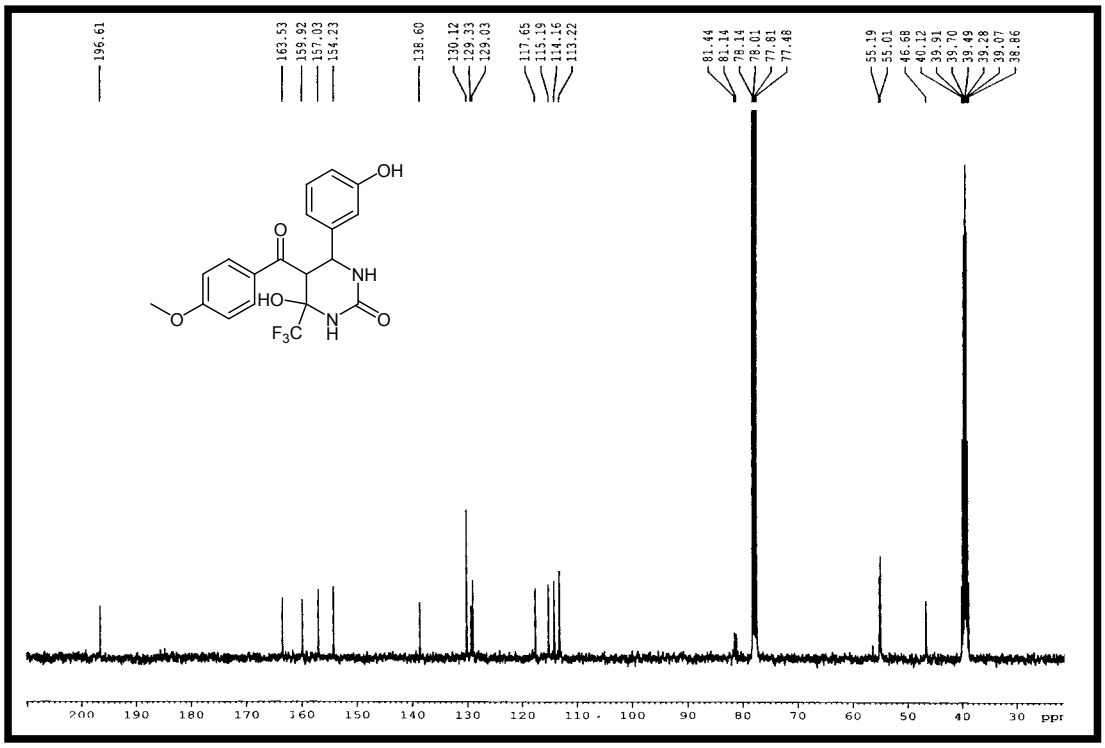


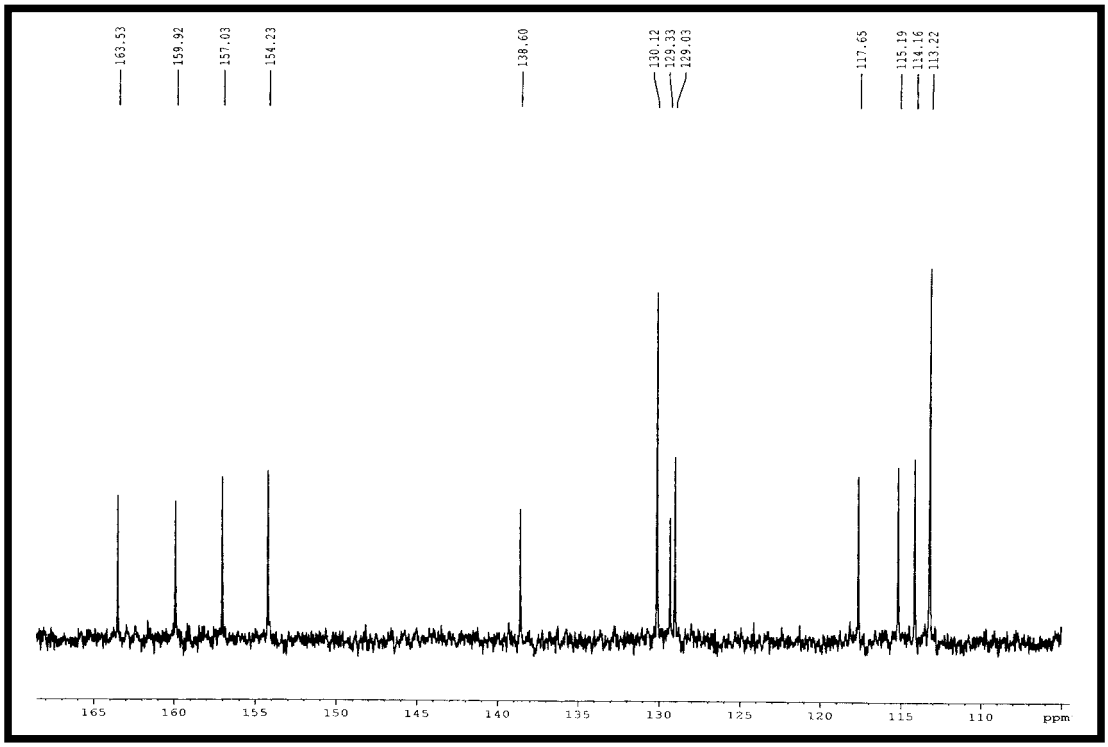
[g] ^{13}C NMR of RK-1005



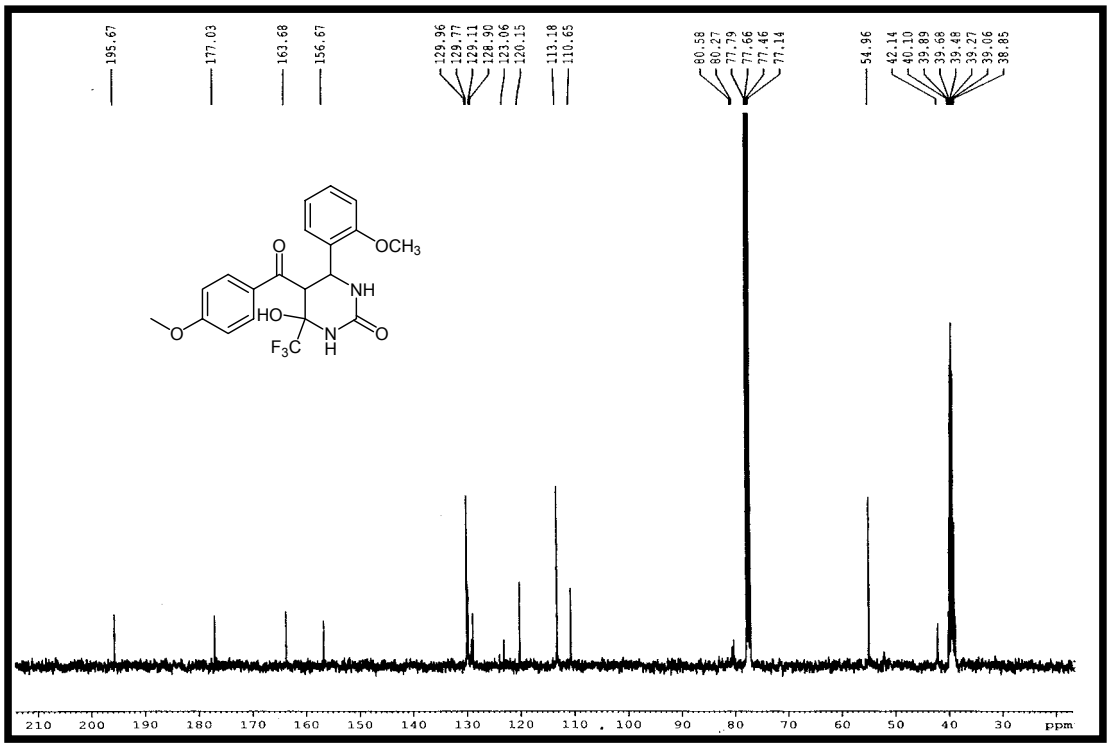


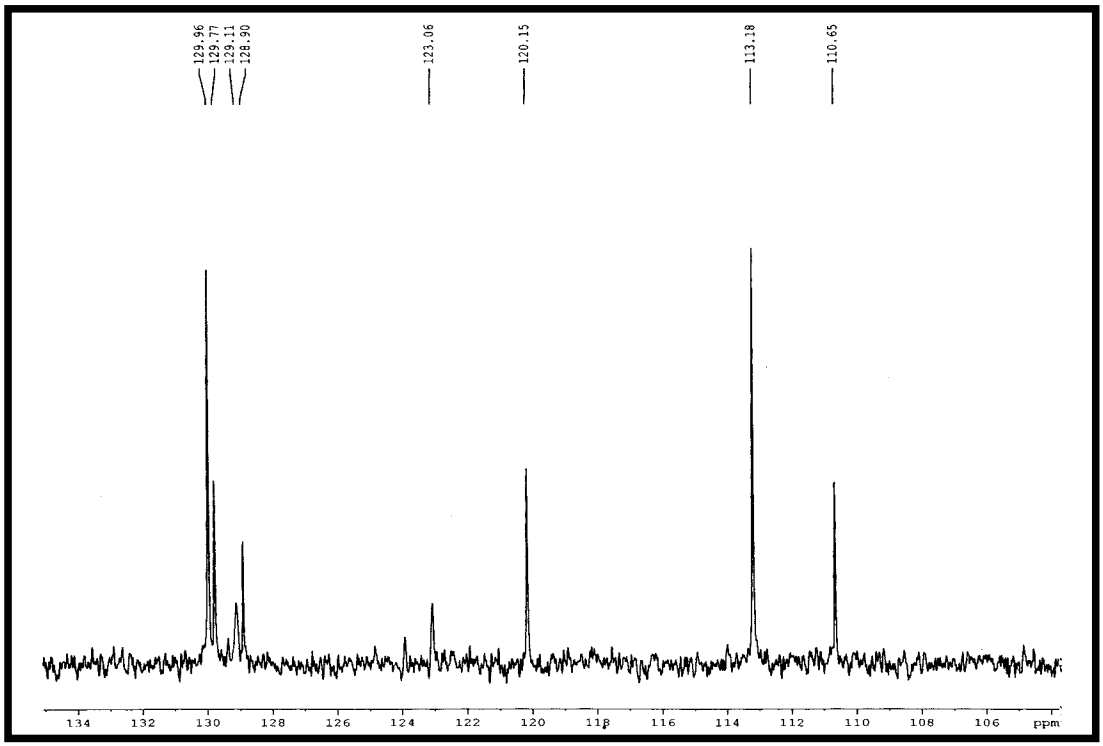
[h] ^{13}C NMR of RK-1008



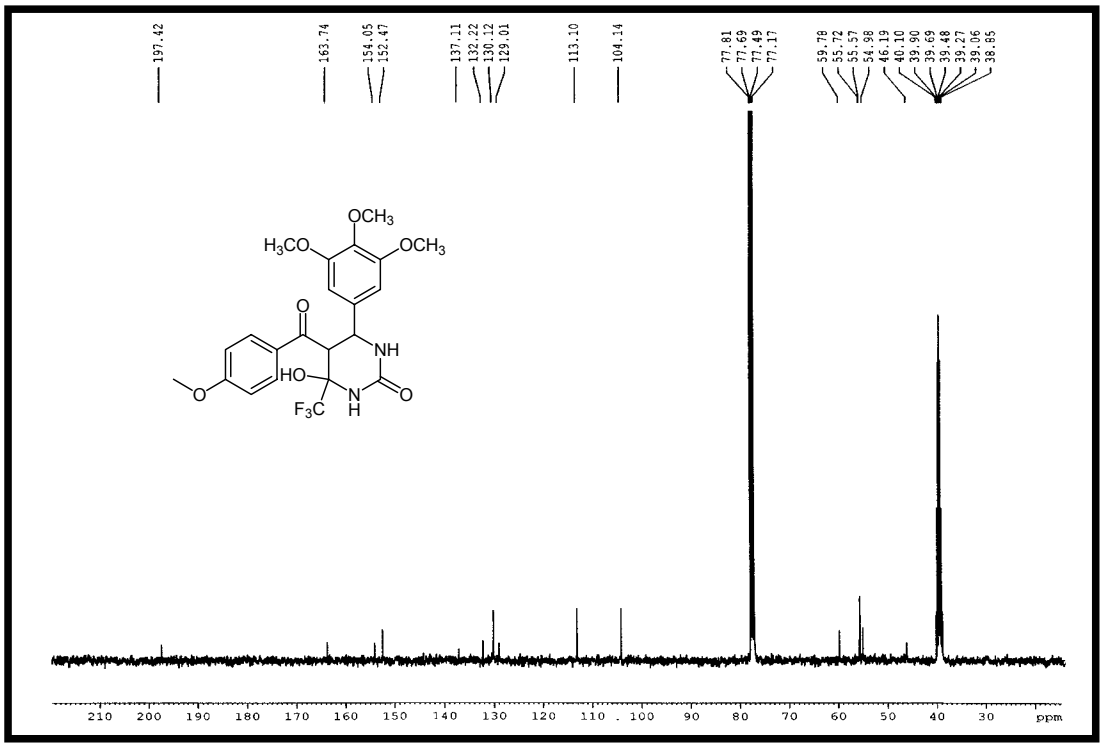


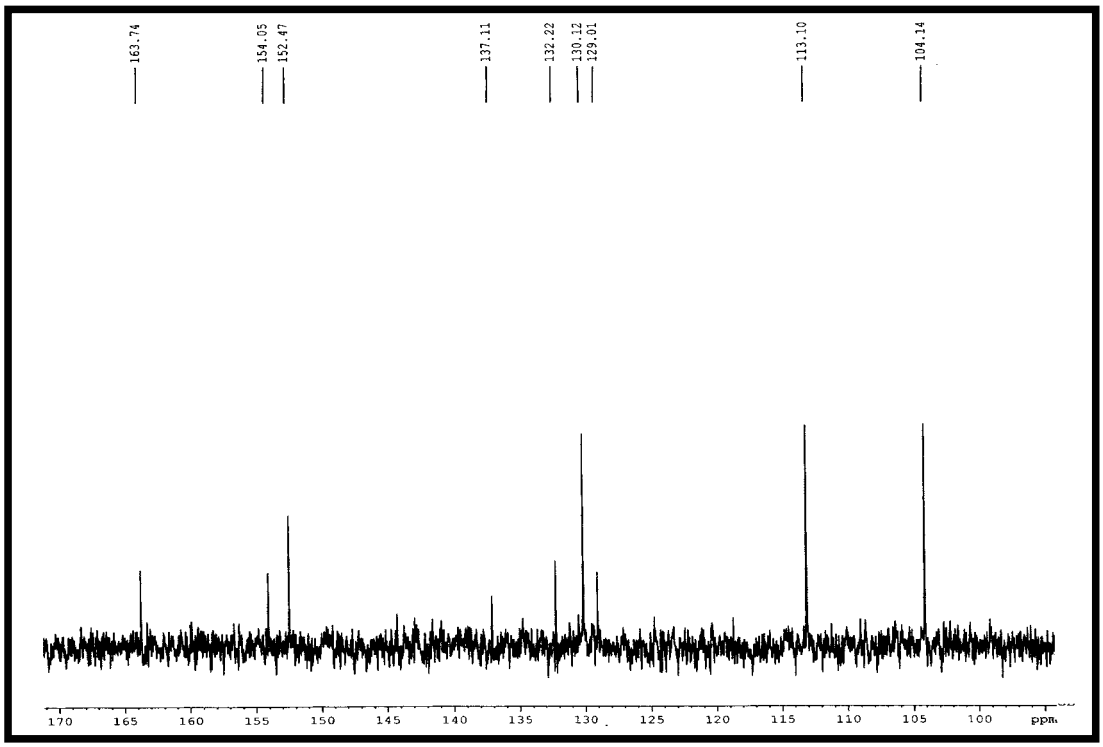
[i] ^{13}C NMR of RK-1006



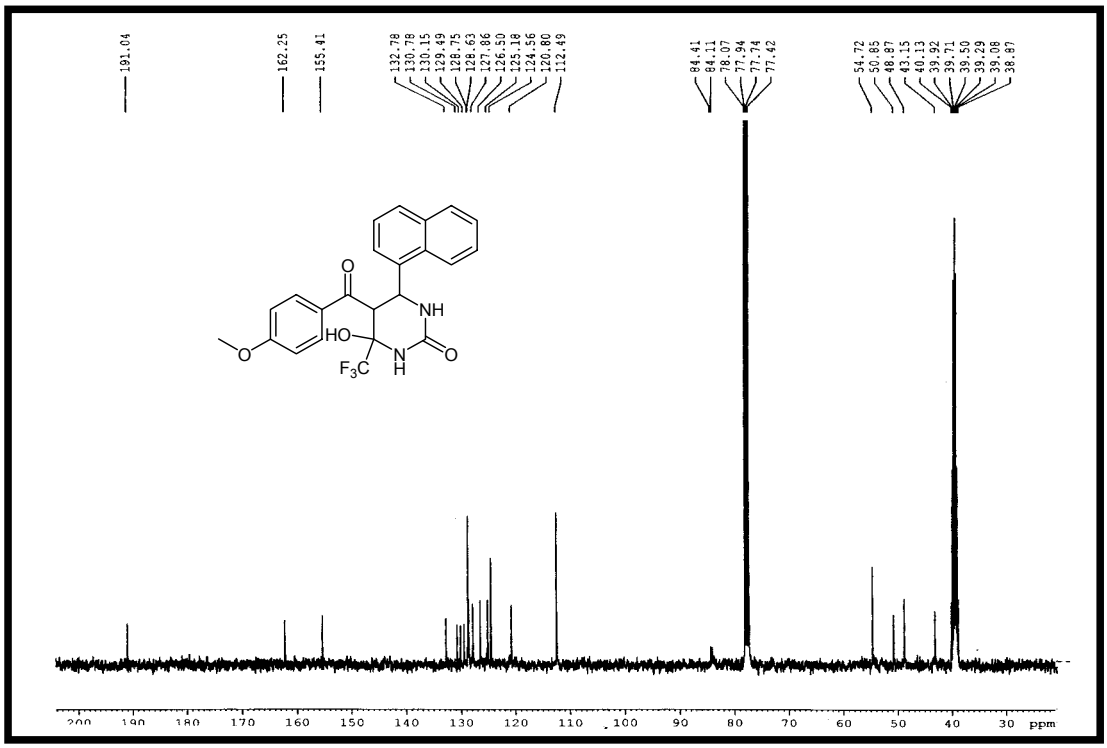


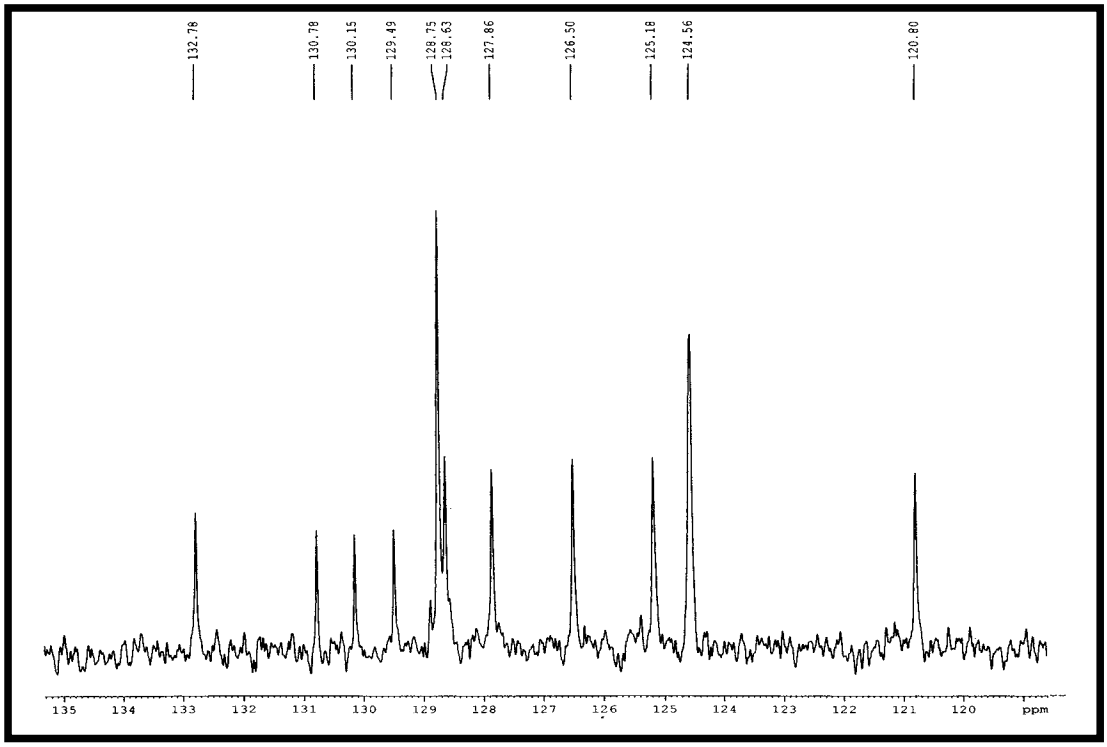
[j] ^{13}C NMR of RK-1018



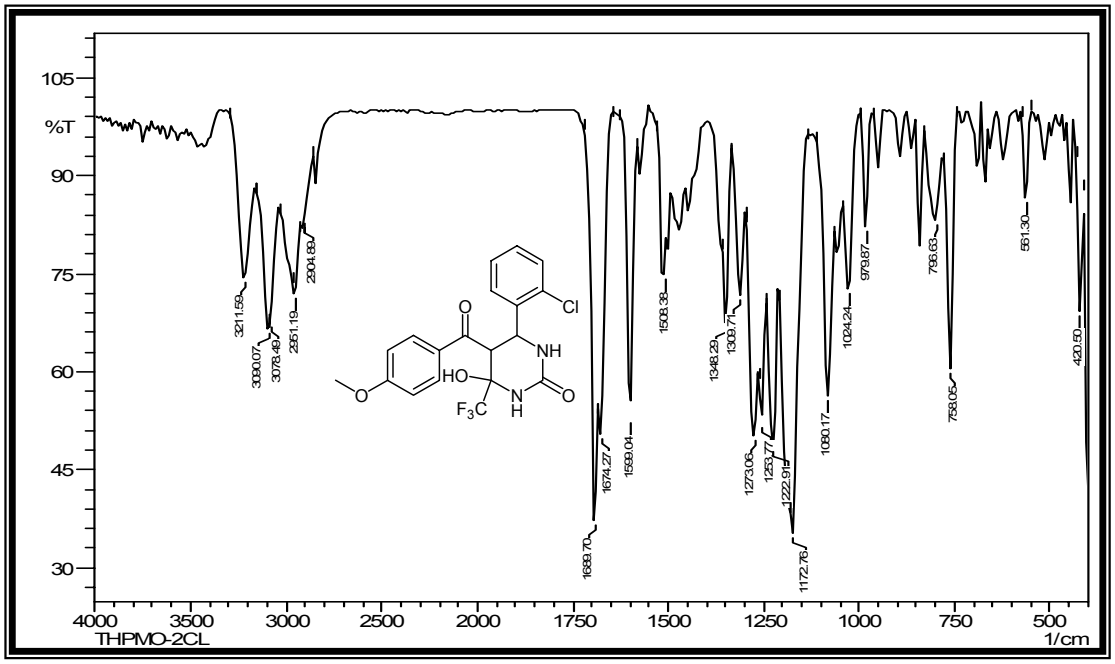


[k] ^{13}C NMR of RK-1019

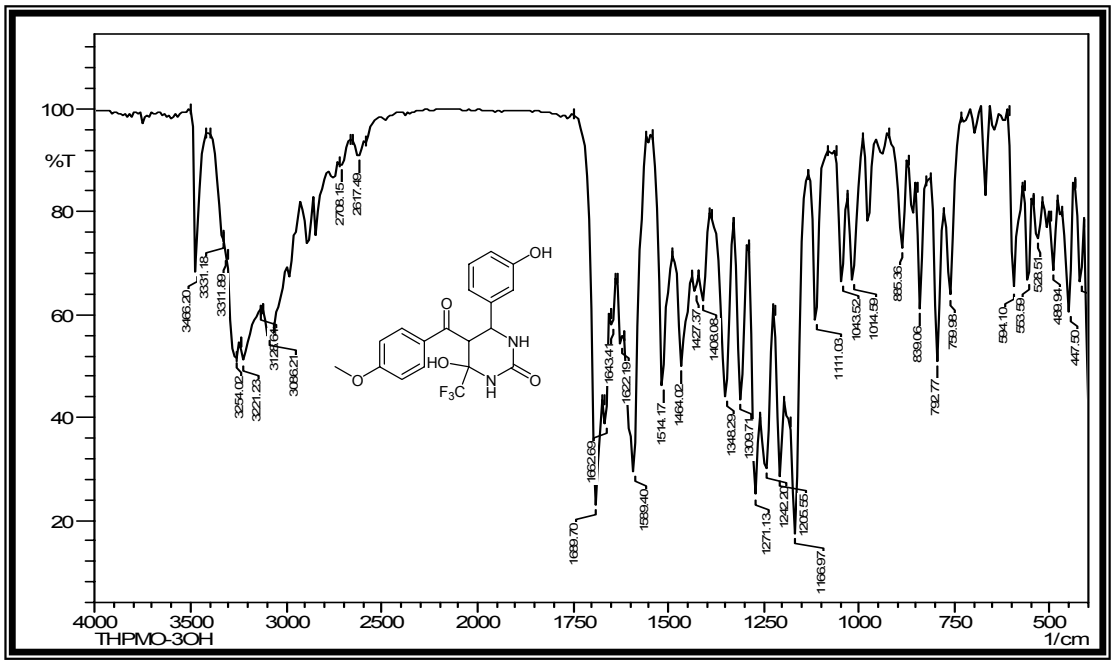




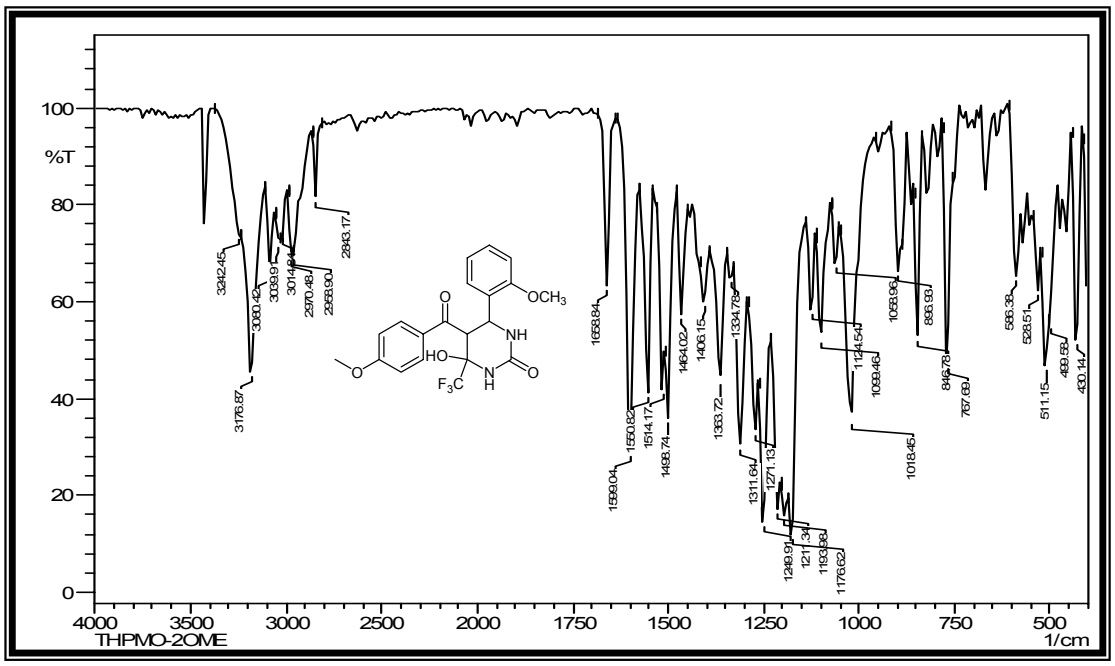
[l] IR Spectra of RK-1001



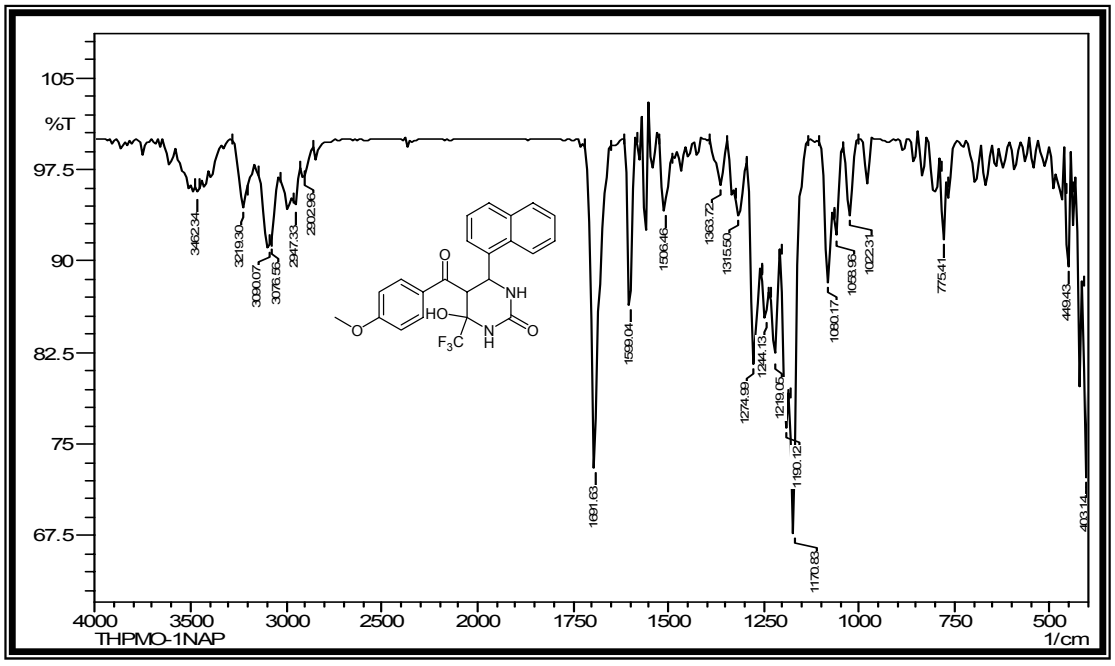
[m] IR Spectra of RK-1008



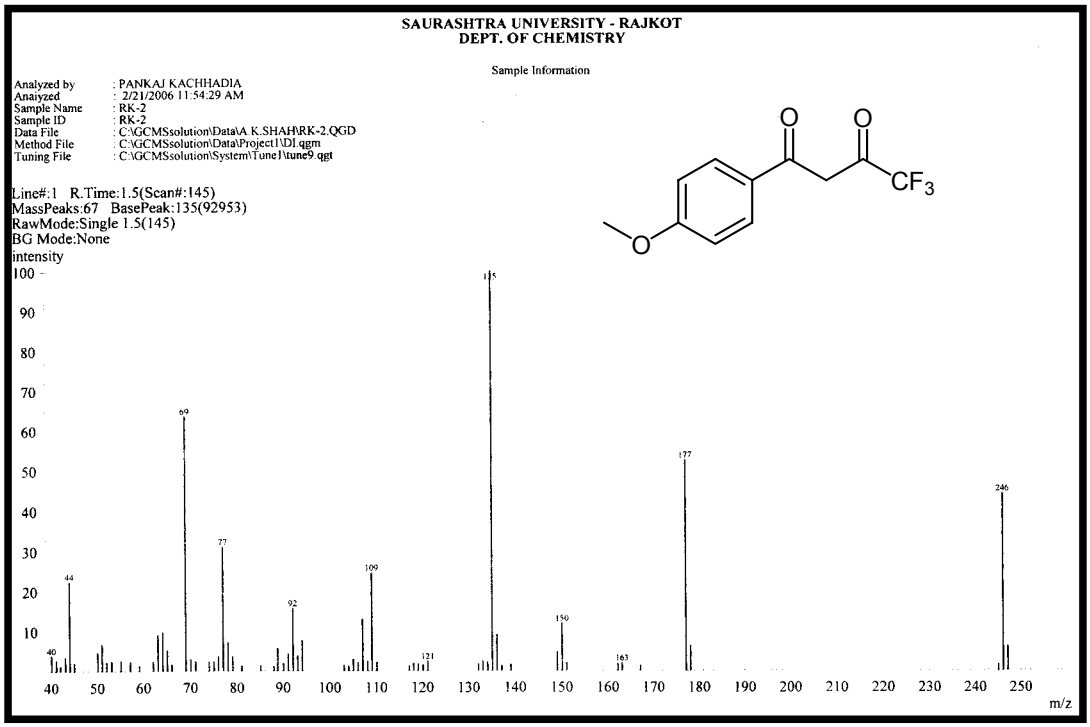
[n] IR Spectra of RK-1006



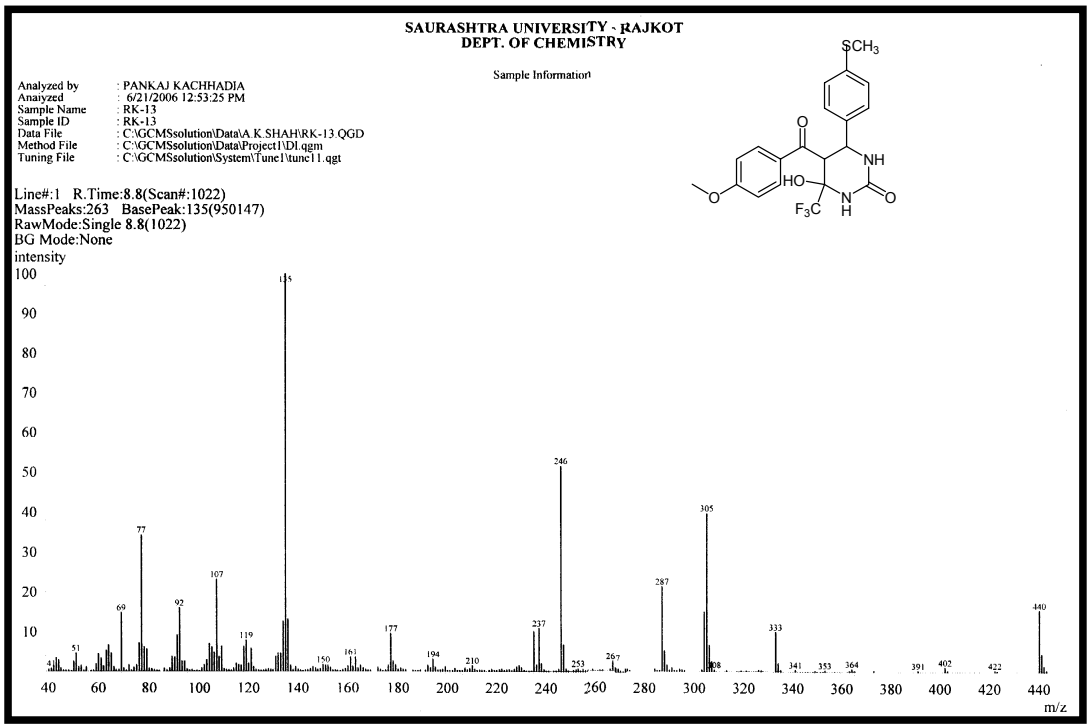
[o] IR Spectra of RK-1019



[p] EI-MS of 1,3 DIKETONE

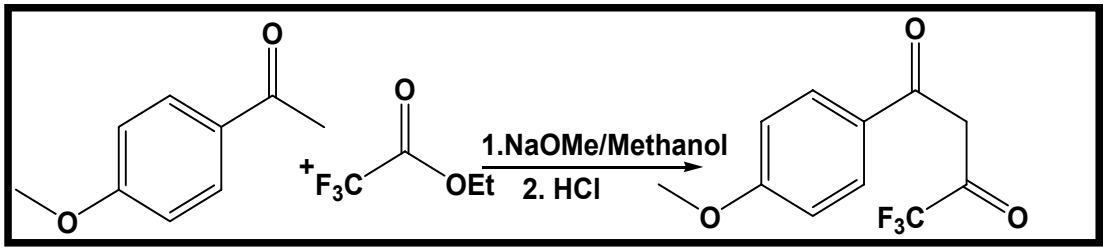


[q] EI-MS of RK-1010

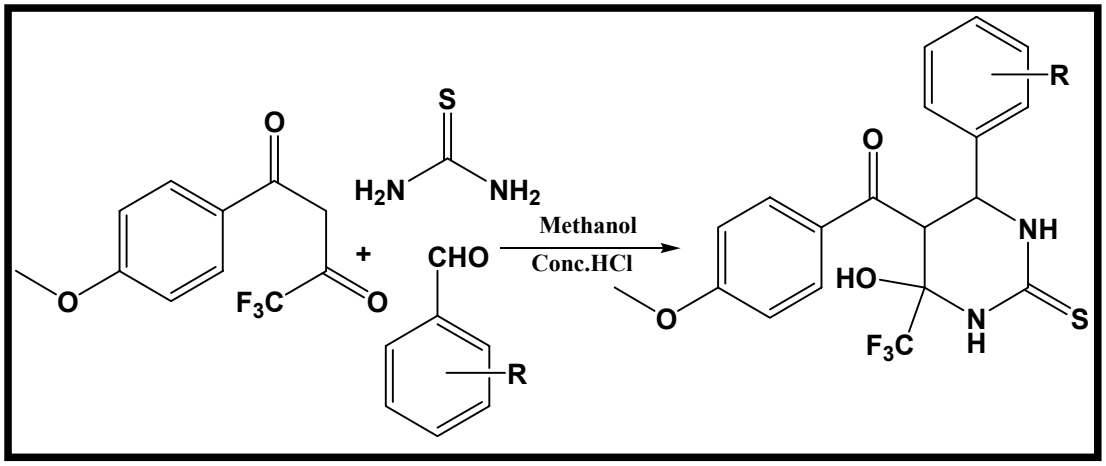


Reaction Scheme

Step-I



Step-II



Experimental

Step-1

Preparation of 4,4,4-Trifluoro-1-(4-methoxyphenyl)Butane-1,3-dione

In freshly prepared Sodium methoxide (1.7equivalent) in methanol, 4-methoxy acetophenone was added into it at 15-20 ^{0}C. It was stirred for 30 minutes at 20 ^{0}C. 1.2 equivalent of trifluoroethyl acetate was added into it by dropping funnel within 30 minutes at 20 ^{0}C, stirred for 12 hrs at 60^{O}C. TLC was checked for completion of reaction. Reaction mixture was poured in to 10%HCl solution & stirred for 15 minutes. Product was precipitated; it was filtered & washed with twice by 100 ml water. Product was recrystallized in methanol: water (80:20). It was dried in vacuum at 30-40 ^{0}C

Note: - The entire reaction was carried out under nitrogen atmosphere

Yield: 78%

TLC System: (Hexane: Ethyl acetate)

9 : 1

Step-2

Preparation of [4-Hydroxy-6 substituted-phenyl-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl) Methanones (General Method)

1.5 equivalent thiourea was dissolved in to 15 ml methanol until clear solution was observed.1.0 equivalent of 1,3 diketone & 1.0 equivalent of Substituted Benzaldehyde was added in to stirred well, clear solution was observed. 2-3 drops of Conc.HCl was added in to it, stirred for 5-6 hours according to the reactivity of the substituted benzaldehyde. Reaction mixture was cooled at room temperature. TLC was checked for completion of reaction. Reaction mixture was cooled to room temperature , kept in a fridge until solid product was observed.15 ml Methanol was added in to it, heated to reflux temperature. Product was filtered through suction and washed twice by 20 ml of methanol.

Product was dried in oven at 60 ^{0}C

Yield: 65-70%

TLC System: (Chloroform: Methanol)

7 : 3

The physical data are given in table No. 2

Physical data of [4-hydroxy-6 substituted-phenyl-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanones

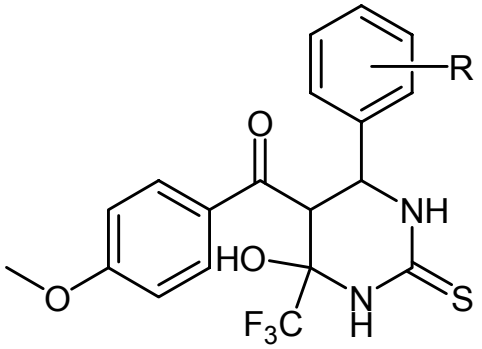


Table No: - 2

Sr. No	Code.No	Substitution R	M.F	M.W	M.P^{O}C	C, H , N Analysis		
						C	H	N
1	**RK-2001**	3,4-di OCH_3	$C_{21}H_{21}F_3N_2O_5S$	470.46	187-190	53.61 (53.59)	4.50 (4.53)	5.95 (5.92)
2	**RK-2002**	4-F	$C_{19}H_{16}F_4N_2O_3S$	428.40	175-178	53.27 (53.24)	3.76 (3.78)	6.54 (6.55)
3	**RK-2003**	3-Br	$C_{19}H_{16}BrF_3N_2O_3S$	489.31	156-158	46.64 (46.62)	3.30 (3.28)	5.73 (5.69)
4	**RK-2004**	3-NO_2	$C_{19}H_{16}F_3N_3O_5S$	455.41	145-147	50.11 (50.08)	3.54 (3.54)	9.23 (9.22)
5	**RK-2005**	2-OCH_3	$C_{20}H_{19}F_3N_2O_4S$	440.44	152-155	54.54 (54.51)	4.35 (4.31)	6.36 (6.30)
6	**RK-2006**	3-OH	$C_{19}H_{17}F_3N_2O_4S$	426.41	191-192	53.52 (53.50)	4.02 (3.99)	6.57 (6.59)

Table No: - 2

Sr. No	Code.No	Substitution R	M.F	M.W	M.P	C, H , N Analysis		
						C	H	N
7	**RK-2007**	4-OCH_3	$C_{20}H_{19}F_3N_2O_4S$	440.44	156-157	54.54 (54.52)	4.35 (4.33)	6.36 (6.35)
8	**RK-2008**	3-OCH_3	$C_{20}H_{19}F_3N_2O_4S$	440.44	165-168	54.54 (54.50)	4.35 (4.36)	6.36 (6.37)
9	**RK-2009**	4-Cl	$C_{19}H_{16}ClF_3N_2O_3S$	444.86	159-160	51.30 (51.28)	3.63 (3.61)	6.30 (6.28)
10	**RK-2010**	H	$C_{19}H_{17}F_3N_2O_3S$	410.41	148-150	55.60 (55.58)	4.18 (4.15)	6.83 (6.85)
11	**RK-2011**	4-SCH_3	$C_{20}H_{19}F_3N_2O_3S_2$	456.5	178-180	52.62 (52.59)	4.20 (4.21)	6.14 (6.15)
12	**RK-2012**	3-Cl	$C_{19}H_{16}ClF_3N_2O_3S$	444.86	185-187	51.30 (51.28)	3.63 (3.61)	6.30 (6.28)
13	**RK-2013**	2-Cl	$C_{19}H_{16}ClF_3N_2O_3S$	444.86	150-152	51.30 (51.27)	3.63 (3.66)	6.30 (6.31)
14	**RK-2014**	4-NO_2	$C_{19}H_{16}F_3N_3O_5S$	455.41	163-164	50.11 (50.10)	3.54 (3.51)	9.23 (9.26)
15	**RK-2015**	2-NO_2	$C_{19}H_{16}F_3N_3O_5S$	455.41	168-170	50.11 (50.07)	3.54 (3.51)	9.23 (9.26)
16	**RK-2016**	3-OPh	$C_{25}H_{21}F_3N_2O_4S$	502.51	175-178	59.75 (59.73)	4.21 (4.18)	5.57 (5.58)

Spectral discussion

^{13}C NMR spectral study

^{13}C NMR spectral discussion of [4-Hydroxy-6 substituted-phenyl-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone

^{13}C NMR spectra of [4-hydroxy-6 substituted-phenyl-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone were recorded on Bruker 400MHz instruments using DMSO and $CHCl_3$ as the solvents with tetramethylsilane (TMS) as the respective internal standard. . In the spectrum, a quartet for the carbon atom connected with the trifluoromethyl substituent is located at 80-81 ppm (^{3}J(C-F) =32-34 Hz) which is typical for a quarternary carbon rather than a carbonyl carbon atom. Methoxy group attached to phenyl ring is located at 54-56 ppm. The –CH (asymmetric) group attached with different substituent is appeared at 46-47 ppm and –CH (asymmetric) group attached with carbonyl is located at 54-56 ppm. The carbonyl carbon attached with phenyl ring and –CH group is located at 191-196 ppm and (C=S)carbon attached with –NH group is 165-175 ppm. The pattern of phenyl ring depends up on the substitution; it is appeared between 110-160 ppm.

PMR spectral study

PMR spectral discussion of [4-Hydroxy-6 substituted-phenyl-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone

^{1}HNMR of the synthesized compounds were recorded on DPX-300MHz FT-NMR spectrophotometer (Bruker) instrument using TMS as an internal reference standard in DMSO-D6 solvent. ^{1}HNMR spectra show the number of proton & chemical environment of each proton in each compound. The singlet observed for methoxy proton of 4-methoxy phenyl in the range of δ 3.7-3.9. Methine (-CH) attached with –NH and substituted phenyl ring gives typical doublet at δ 4.2-4.6 with J Value 11.4 *Hz* and methine (-CH) group attached with carbonyl shows clear doublet at δ 4.7-5.0 with J Value 11.3 *Hz*. Hydroxyl group (OH) attached to quaternary carbon represents singlet at δ 7.4-7.6. The proton of the aromatic ring attached to the carbonyl group appeared at δ 6.6-7.5. The two protons of the different –NH shows peak at δ 8.7-9.0. In some case, it shows different singlet peak for each of –NH proton. The pattern of the ^{1}HNMR spectra between

δ 6.8-8.0 clearly indicated that the benzene ring attached to the unsymmetrical carbon atom is meta or para substituted.

Individual ^{1}HNMR data of synthesized compounds is mentioned in spectral data.

IR spectral study

The infrared spectra of all compounds of this chapter were recorded on Shimadzu 8400 FT-IR spectrophotometer by KBr pellet method.

The different frequencies of infrared spectrum of [4-hydroxy-6 substituted-phenyl-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone are discussed here. The Hydroxy group (-OH) appeared in the range of (3350-3400cm^{-1}), typical thiocarbonyl frequencies appeared for this cyclic thiourea in the range of (1050-1200cm^{-1}). The carbonyl group of 4-methoxyphenyl appeared at (1670-1699cm^{-1}). The secondary –NH frequencies appeared in all the compounds in the range of 3160-3540cm^{-1}. The –OCH_3 functional group frequencies are also observed like 1205-1215cm^{-1} for C-O-Ar stretching. The CF_3 group stretching vibrations observed at 1000-1380cm^{-1}

Detail of each synthesized compounds IR spectra is depicted in spectral data.

Mass spectral study

The mass spectrums of the all compounds of this series were recorded by GCMS-QP2010 spectrometer (EI method). The molecular ion peak (M^+) values are in good match with molecular formula for synthesized compounds. In some cases, molecular ion peak (M^+) peak does not appear due to the loss of H_2O from the synthesized compounds, so it exhibit M-18 peak. Probable mass fragmentation of [4-hydroxy-6 substituted-phenyl-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanones is written in spectral data for individual compounds separately.

Elemental Analysis

Elemental analysis of the compounds was carried out on Elementar Vario EL III Carlo Erba 1108 model at CDRI, Lucknow and the results are in agreement with the structures assigned.

SPECTRAL DATA

[4-Hydroxy-6(3,4-dimethoxyphenyl)-2-thioxo-4-(trifluoromethyl)hexahydro pyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2001)

^{1}H-NMR (300 MHz, DMSO-d_6):δ 3.60 (s, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 4.62 (d, 1H, *J*=11.44 Hz), 4.88 (d, 1H, *J*=11.41 Hz), 6.73 (m, 2H, *J*=8.23 Hz), 6.85 (d, 2H, *J*=8.63 Hz), 7.11 (s, 1H), 7.47 (s, 1H), 7.83 (d, 2H, *J*=8.67 Hz), 8.92 (d, 2H, *J*=8.62 Hz)

^{13}C NMR ($CDCl_3$): *δ* 195.65, 177.56, 163.77, 148.65, 148.37, 130.17, 128.96, 127.63, 120.04, 113.25, 110.50, 110.15, 80.12, 56.06, 55.46, 55.20, 54.96, 44.90

IR (KBr Pellet): 3478cm^{-1}(-OH), 3321cm^{-1}(-NH), 2910-2950cm^{-1}(C-H), 1699.98 cm^{-1} (-C=O), 1674.12 cm^{-1} (-CO-NH), 1498-1522cm^{-1} (-NH Bend), 1211-1249 cm^{-1} (C-O-C), 1107-1171cm^{-1} (C-F)

[4-Hydroxy-6(4-fluorophenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2002)

^{13}C NMR ($CDCl_3$): *δ* 194.18, 177.33, 163.47, 163.01, 160.56, 132.25, 130.04, 129.59, 129.51, 129.33, 80.20, 55.26, 55.00, 45.61

IR (KBr Pellet): 3471.47cm^{-1}(-OH), 3345cm^{-1}(-NH), 2954cm^{-1} (C-H), 1699.98 cm^{-1} (-C=O) 1659 cm^{-1}(-CO-NH), 1498-1529 cm^{-1} (-NH Bend), 1243 cm^{-1} (C-O-C), 1140-1210 cm^{-1} (CF_3 & C-F)

[4-Hydroxy-6(3-bromophenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2003)

IR (KBr Pellet): 3441cm^{-1}(-OH), 3309cm^{-1}(-NH), 2905-2923(C-H), 1699.9 cm^{-1}(-C=O) 1674 cm^{-1}(-CO-NH), 1599-1607 cm^{-1} (-NH Bend), 1170-1178 cm^{-1} (C-O-C), 1170-1181cm^{-1} (C-F), 550-556 cm^{-1} (C-Br)

[4-Hydroxy-6(3-nitrophenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2004)

^{1}H-NMR (300 MHz, DMSO-d_6):δ 3.74 (s, 3H), 4.70 (d, 1H, *J*=11.40 Hz), 5.13 (d, 1H, *J*=11.39 Hz), 6.82 (d, 2H, *J*=8.70 Hz), 7.46 (t, 1H, *J*=7.94 Hz), 7.66 (s, 1H), 7.81 (m, 3H), 7.99 (d, 1H, *J*=8.04 Hz), 8.83 (s, 1H), 9.15 (s, 1H), 9.26 (s, 1H)

IR (KBr Pellet): 3470cm^{-1}(-OH), 3340cm^{-1}(-NH), 2954(C-H), 1690 cm^{-1}(-C=O) 1659 cm^{-1}(-CO-NH), 1576 cm^{-1} (-NH Bend), 1570 cm^{-1} (-C-NO_2), 1243 cm^{-1} (C-O-C), 1140 cm^{-1} (C-F)

[4-Hydroxy-6(2-methoxyphenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2005)

IR (KBr Pellet): 3520cm^{-1}(-OH), 3374cm^{-1}(-NH), 2910-2949cm^{-1}(C-H), 1668.84cm^{-1} (-C=O) 1599 cm^{-1} (-CO-NH), 1498-1529 cm^{-1} (-NH Bend), 1219-1244 cm^{-1} (C-O-C),1140-1210 cm^{-1} (C-F)

[4-Hydroxy-6(3-hydroxyphenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2006)

IR (KBr Pellet): 3466.32cm^{-1}(-OH), 3356cm^{-1}(-NH), 2921-2950cm^{-1}(C-H), 1690cm^{-1} (-C=O), 1662.6 cm^{-1} (-CO-NH), 1480-1520cm^{-1} (-NH Bend), 1206-1271 cm^{-1} (C-O-C),1111-1271cm^{-1} (C-F)

[4-Hydroxy-6(4-methoxyphenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2007)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.61 (s, 3H), 3.76 (s, 3H), 4.45 (d, 1H, *J*=11.46 Hz), 4.90 (d, 1H, *J*=11.44 Hz), 6.72 (d, 2H, *J*=8.44 Hz), 6.85 (d, 2H, *J*=8.70 Hz), 7.29 (d, 2H, 8.44 Hz), 7.52 (s, 1H), 7.75 (d, 2H, *J*=8.71 Hz), 8.94 (d, 2H, *J*=8.62 Hz)

IR (KBr Pellet): 3466cm^{-1} (-OH), 3321cm^{-1} (-NH), 2920-2959cm^{-1} (C-H), 1690 cm^{-1} (-C=O) 1662.69 cm^{-1}(-CO-NH), 1576 cm^{-1} (-NH Bend), 1271 cm^{-1} (C-O-C), 1190 cm^{-1} (C-F)

[4-Hydroxy-6(3-methoxyphenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2008)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.52 (s, 3H), 3.65 (s, 3H), 4.53 (d, 1H, *J*=11.40 Hz), 4.92 (d, 1H, *J*=11.39 Hz), 6.68 (d, 1H, *J*=8.04 Hz), 6.86 (t, 3H, *J*=8.29 Hz), 6.98 (s, 1H), 7.06 (t, 1H, *J*=7.80 Hz), 7.53 (s, 1H), 7.78 (d, 2H, *J*=8.68 Hz), 8.96 (s, 1H), 9.03 (s, 1H)

^{13}C NMR ($CDCl_3$): *δ* 194.45, 177.29, 163.42, 158.94, 137.65, 130.06, 129.40, 129.03, 119.76, 113.89, 113.22, 112.99, 80.19, 55.96, 54.99, 54.73, 45.34

IR (KBr Pellet): 3470cm^{-1}(-OH), 3350.11cm^{-1}(-NH), 2921-2956cm^{-1}(C-H), 1704 cm^{-1} (-C=O), 1665.2cm^{-1} (-CO-NH), 1493-1522cm^{-1} (-NH Bend), 1185-1240 cm^{-1} (C-O-C), 1089-1172cm^{-1} (C-F)

[4-Hydroxy-6(4-chlorophenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2009)

^{1}H-NMR (300 MHz, $CDCl_3$):δ 3.83 (s, 3H), 4.15 (d, 1H, *J*=11.32 Hz), 4.98 (d, 1H, *J*=11.29 Hz), 6.31 (s, 1H), 6.78 (d, 3H, *J*=8.94 Hz), 7.07 (s, 1H), 7.17-7.26 (m, 5H), 7.53 (s, 1H), 7.56 (s, 1H)

IR (KBr Pellet): 3462.3 cm^{-1}(-OH), 3345cm^{-1}(-NH), 2902-2947cm^{-1}(C-H), 1698cm^{-1} (-C=O) 1662 cm^{-1} (-CO-NH), 1491-1511cm^{-1} (-NH Bend), 1211-1249 cm^{-1} (C-O-C),1018-1104cm^{-1} (C-F)

[4-Hydroxy-6-phenyl-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2010)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H), 4.17 (d, 1H, *J*=11.28 Hz), 4.99 (d, 1H, *J*=11.28 Hz), 6.42 (s, 1H), 6.73 (d, 2H, *J*=8.97 Hz), 6.79 (s, 1H), 7.05 (s, 1H), 7.22 (m, 4H), 7.50 (d, 2H, *J*=8.68 Hz)

^{13}C NMR ($CDCl_3$): *δ* 194.03, 177.36, 163.54, 135.03, 133.46, 130.06, 129.30, 129.20, 128.03, 113.36, 80.34, 55.33, 55.01, 45.50

IR (KBr Pellet): 3440cm^{-1}(-OH), 3329cm^{-1}(-NH), 2930-2956cm^{-1}(C-H), 1701 cm^{-1} (-C=O), 1674.33cm^{-1} (-CO-NH), 1493-1530cm^{-1} (-NH Bend), 1190-1226 cm^{-1} (C-O-C), 1090-1204cm^{-1} (C-F)

[4-Hydroxy-6(4-thiomethylphenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2011)

^{13}C NMR ($CDCl_3$): *δ* 196.21, 163.56, 154.07, 138.41, 133.82, 130.13, 129.22, 127.65, 125.59, 113.25, 81.43, 55.00, 54.78, 46.67, 14.74

IR (KBr Pellet): 3450cm^{-1}(-OH), 3340cm^{-1}(-NH), 2912-2950cm^{-1}(C-H), 1685 cm^{-1} (-C=O), 1674.12 cm^{-1} (-CO-NH), 1490-1510cm^{-1} (-NH Bend), 1206-1248 cm^{-1} (C-O-C), 1170-1204cm^{-1} (C-F)

[4-Hydroxy-6(3-chlorophenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2012)

IR (KBr Pellet): 3456cm^{-1}(-OH), 3321cm^{-1}(-NH), 2911-2976(C-H), 1678 cm^{-1}(-C=O) 1658 cm^{-1}(-CO-NH), 1599 cm^{-1} (-NH Bend), 1170-1209 cm^{-1} (C-O-C), 1170-1181cm^{-1} (C-F), 750-760 cm^{-1} (C-Cl)

[4-Hydroxy-6(2-chlorophenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2013)

IR (KBr Pellet): 3435cm^{-1}(-OH), 3320cm^{-1}(-NH), 2976.26(C-H), 1670 cm^{-1}(-C=O) 1659 cm^{-1}(-CO-NH), 1599 cm^{-1} (-NH Bend), 1223-1275 cm^{-1} (C-O-C), 1170 cm^{-1} (C-F), 750 cm^{-1} (C-Cl)

[4-Hydroxy-6(4-nitrophenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2014)

^{13}C NMR ($CDCl_3$): δ 182.32, 169.64, 165.85, 162.60, 146.52, 146.03, 145.30, 129.29, 127.56, 125.72, 122.88, 113.97, 113.56, 107.12, 59.98, 54.93, 54.71

IR (KBr Pellet): 3452cm^{-1}(-OH), 3349cm^{-1}(-NH), 2911-2946cm^{-1}(C-H), 1697.63 cm^{-1} (-C=O), 1656.23 cm^{-1} (-CO-NH), 1580.12 cm^{-1} (-C-NO_2), 1498-1520cm^{-1} (-NH Bend), 1107-1199 cm^{-1} (C-O-C), 1107-1182cm^{-1} (C-F)

[4-Hydroxy-6(2-nitrophenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2015)

IR (KBr Pellet): 3478cm^{-1}(-OH), 3350cm^{-1}(-NH), 2903-2922cm^{-1}(C-H), 1710 cm^{-1} (-C=O), 1662.35 cm^{-1} (-CO-NH), 1578 cm^{-1} (-C-NO_2), 1510-1523cm^{-1} (-NH Bend), 1201-1230cm^{-1} (C-F)1112-1175 cm^{-1} (C-O-C)

[4-Hydroxy-6(3-phenoxyphenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl)methanone (RK-2016)

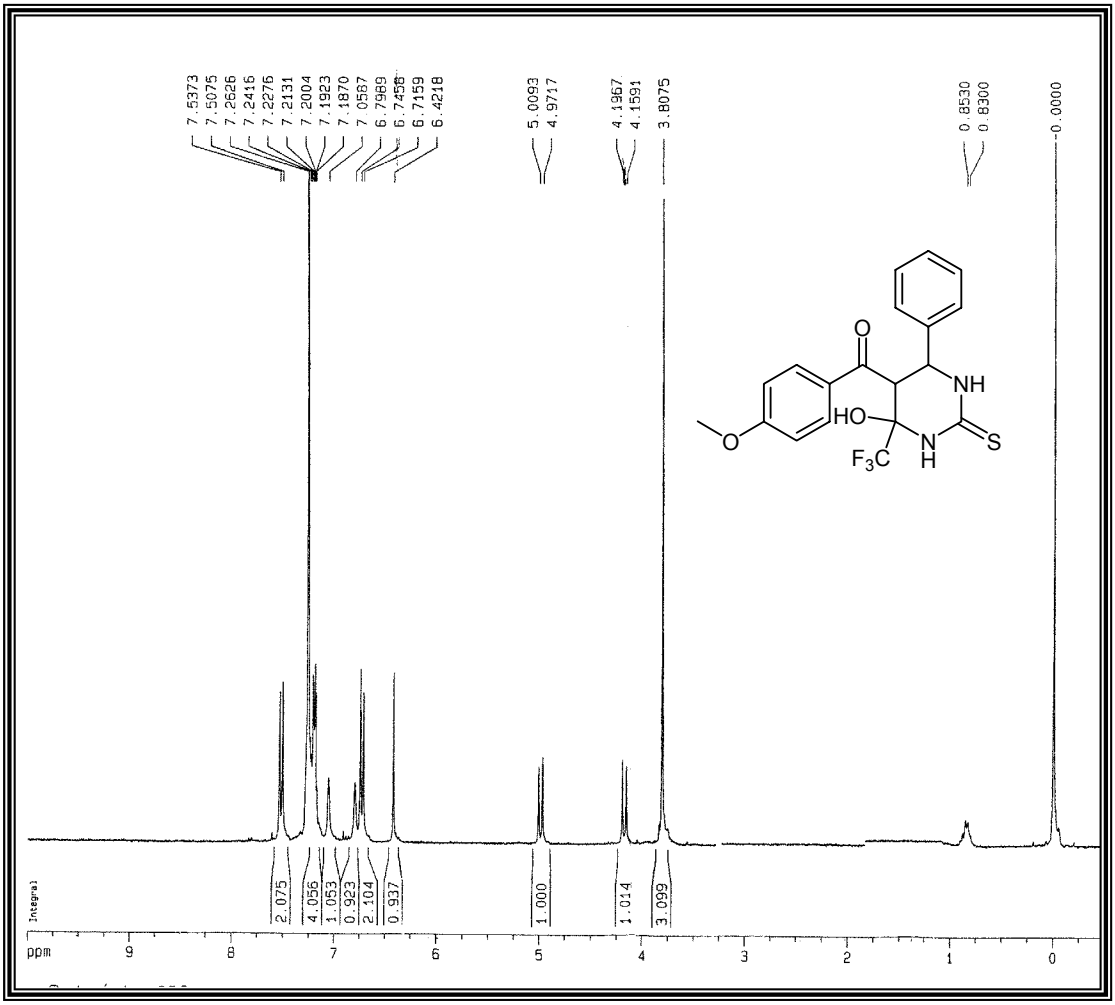
IR (KBr Pellet): 3445cm^{-1}(-OH), 3326.65cm^{-1}(-NH), 2910-2956cm^{-1}(C-H), 1697 cm^{-1} (-C=O), 1668.82cm^{-1} (-CO-NH), 1493-1520cm^{-1} (-NH Bend), 1190-1226 cm^{-1} (C-O-C), 1050-1170cm^{-1} (C-F)

Mass value of [4-Hydroxy-6 substituted-phenyl-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl](4-methoxyphenyl) methanones

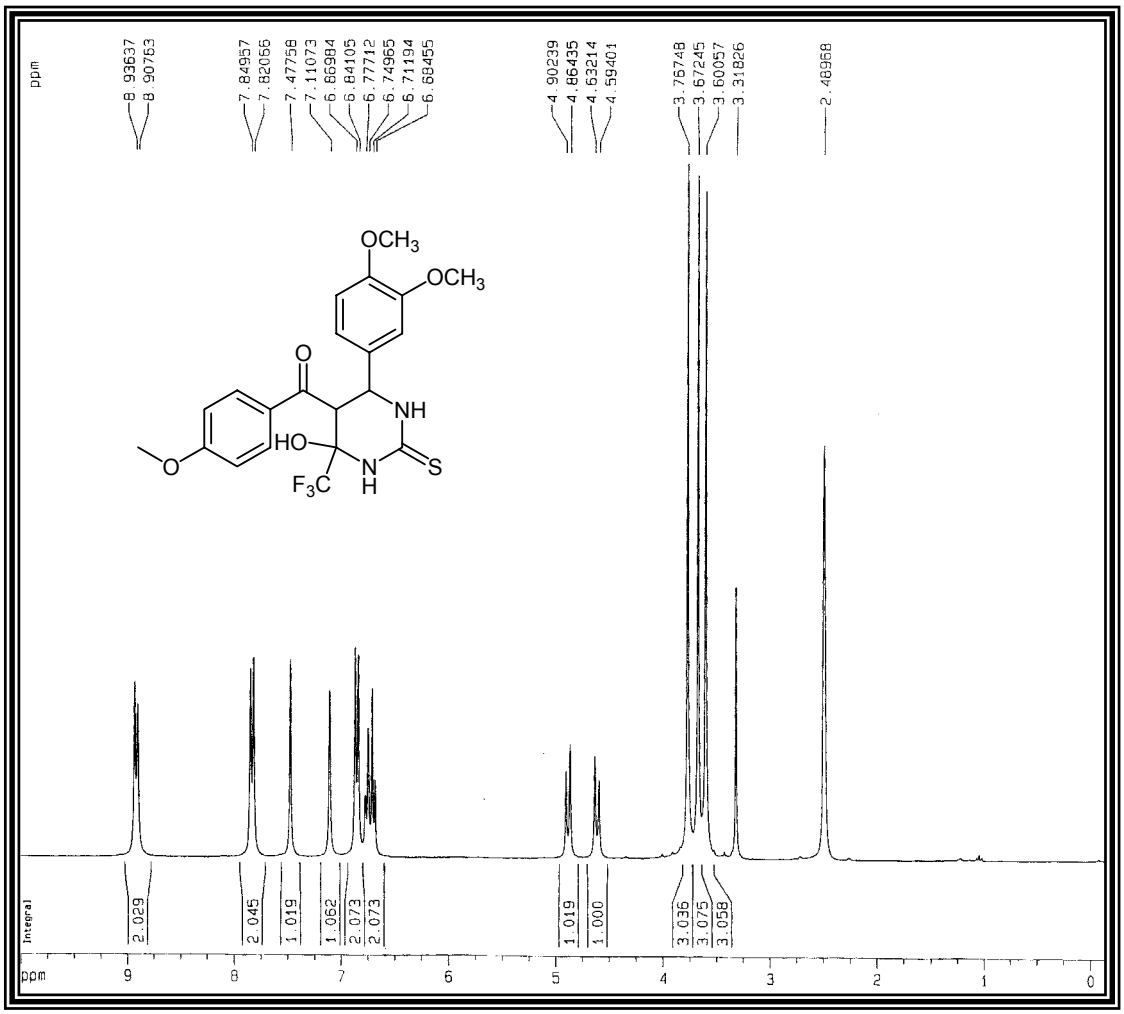
Compound Code.No	(m/z) Relative intensity
RK-2001	470 (8 %)
RK-2002	428-18 (9 %)
RK-2003	489 (6 %)
RK-2004	455 (11 %)
RK-2005	440 (7 %)
RK-2006	426 (8 %)
RK-2007	440 (4 %)
RK-2008	440 (5 %)
RK-2009	444-18 (5 %)
RK-2010	410 (7 %)
RK-2011	456 (7 %)
RK-2012	444 (5 %)
RK-2013	444 (4 %)
RK-2014	455 (10 %)
RK-2015	455 (7 %)
RK-2016	502 (8 %)

Spectra of the Representative compounds

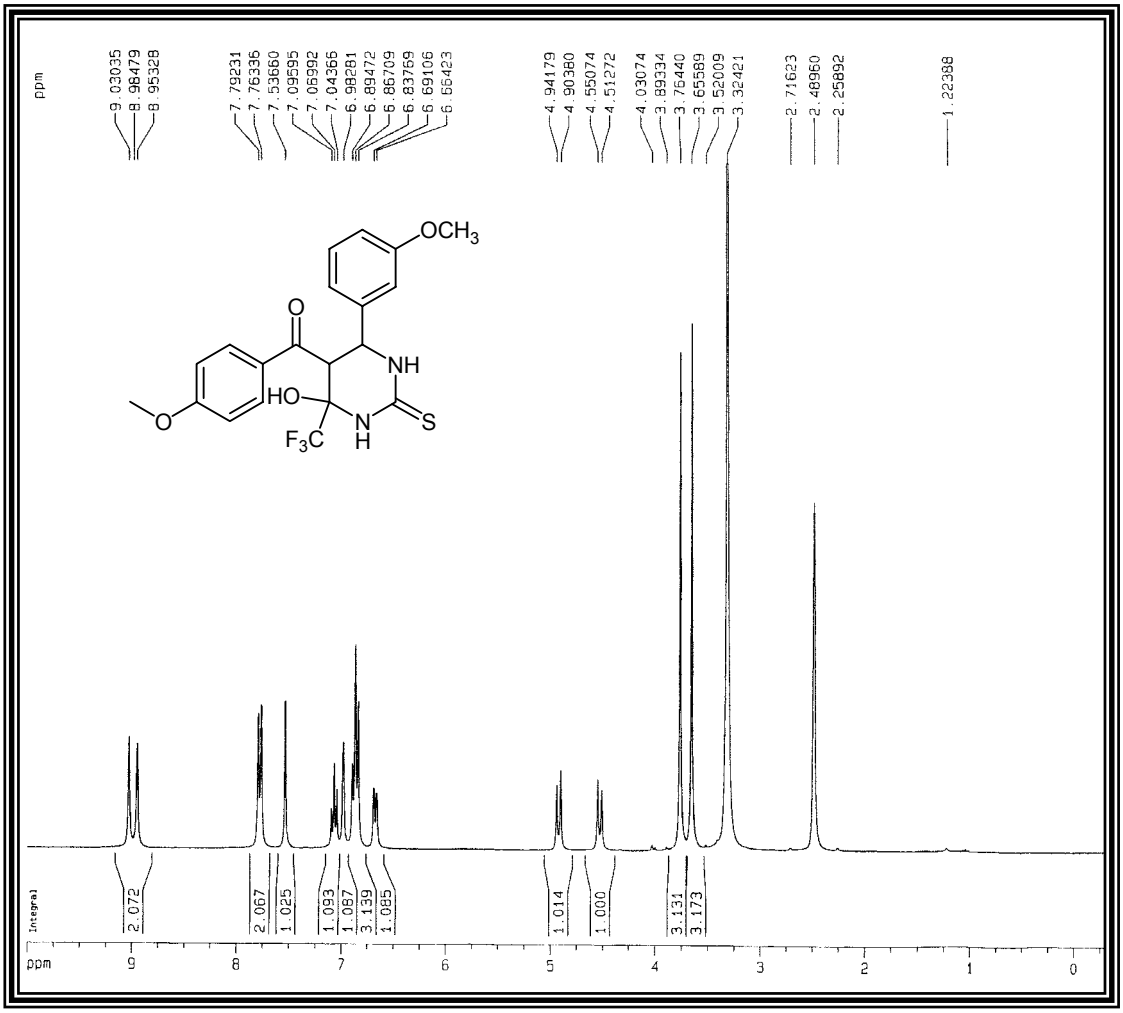
[a] ^{1}H NMR Spectra of RK-2010



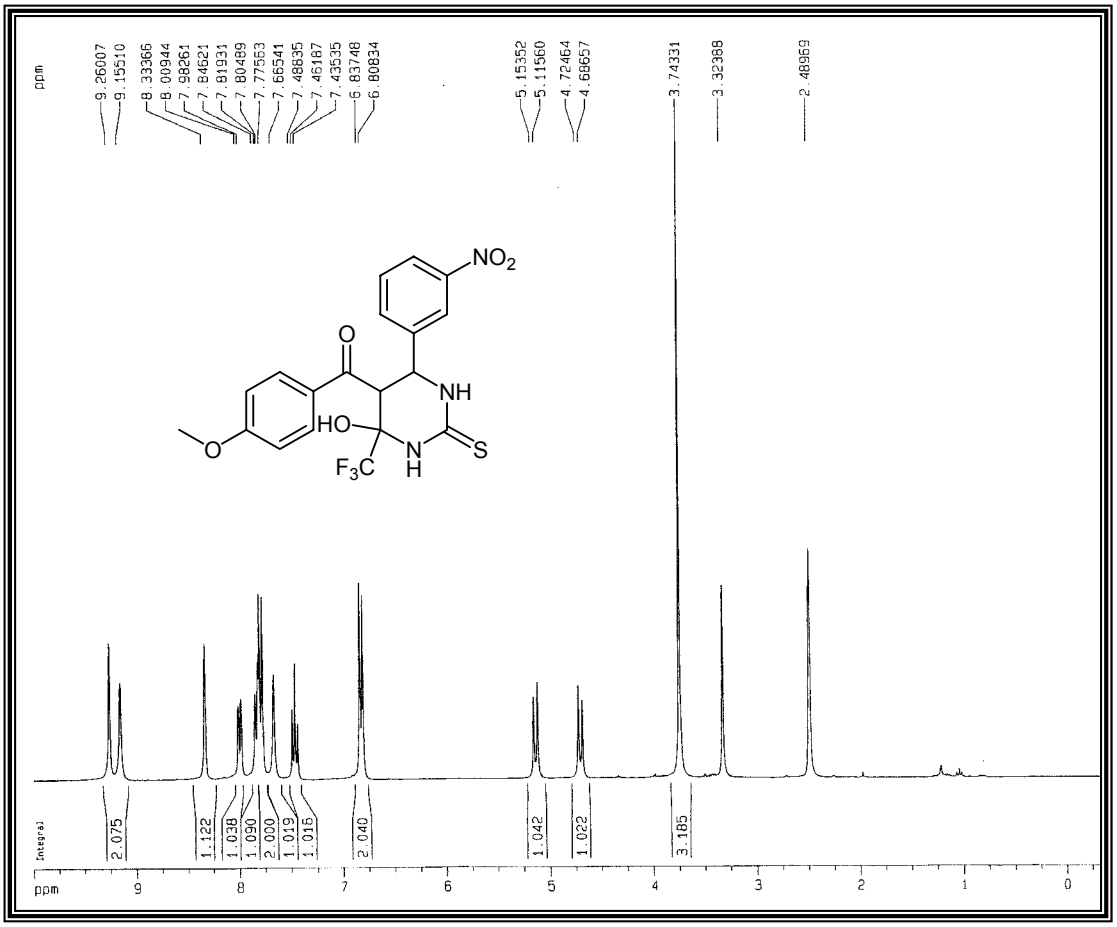
[b] ^{1}H NMR Spectra of RK-2001



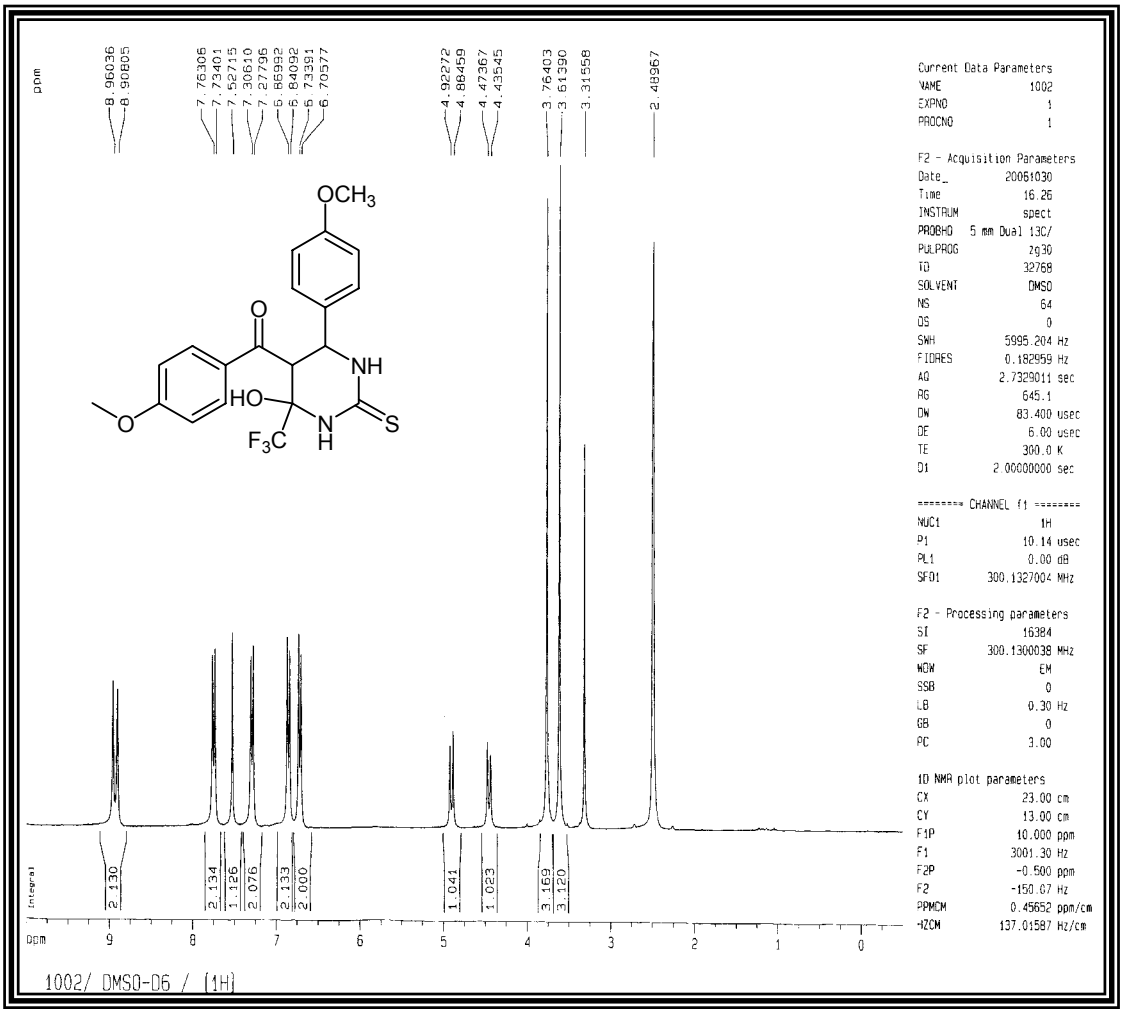
[c] ^{1}H NMR Spectra of RK-2008



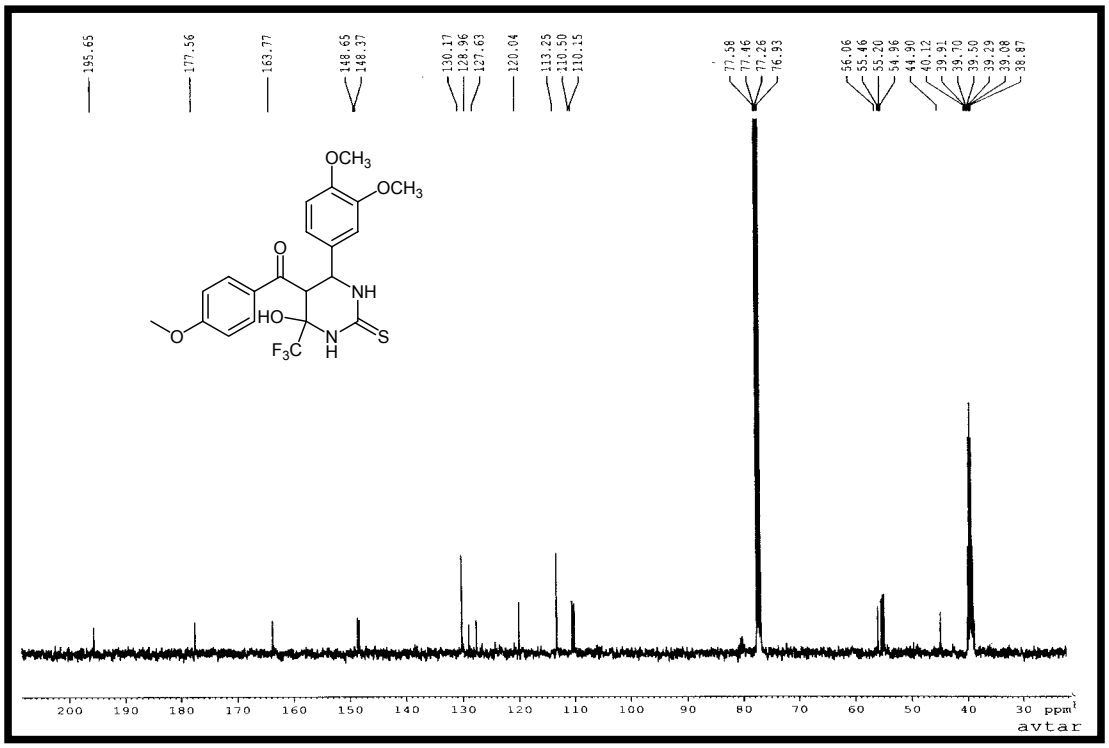
[d] ^{1}H NMR Spectra of RK-2004

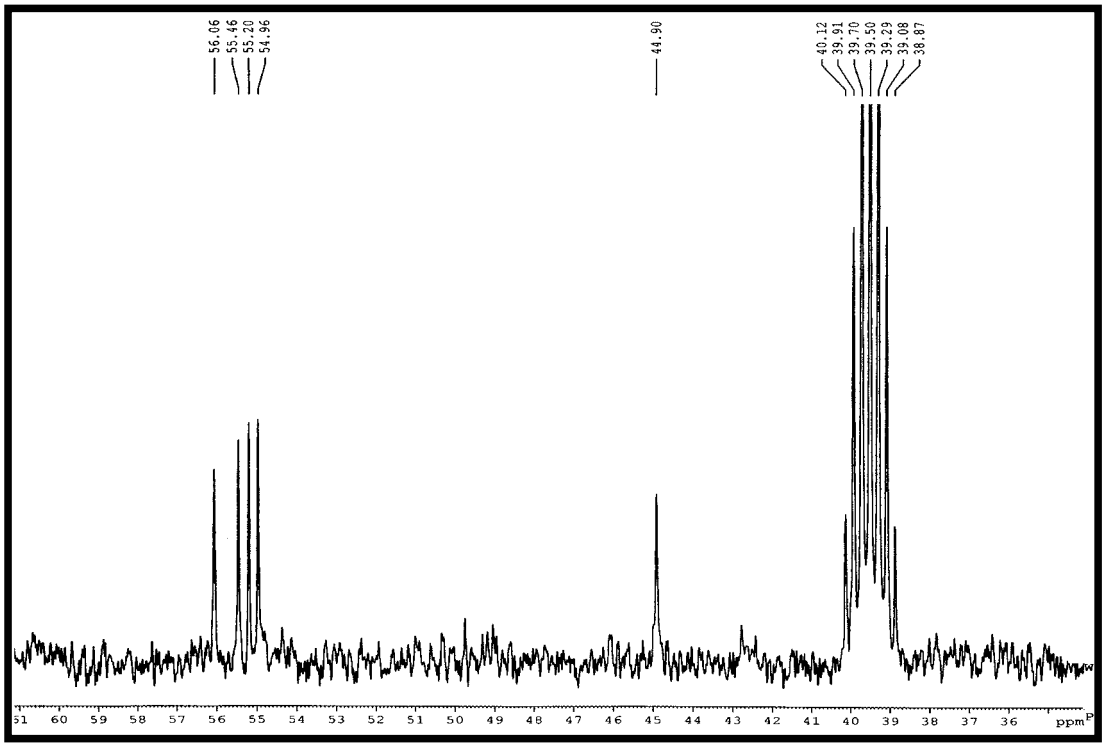


[e] ^{1}H NMR Spectra of RK-2007

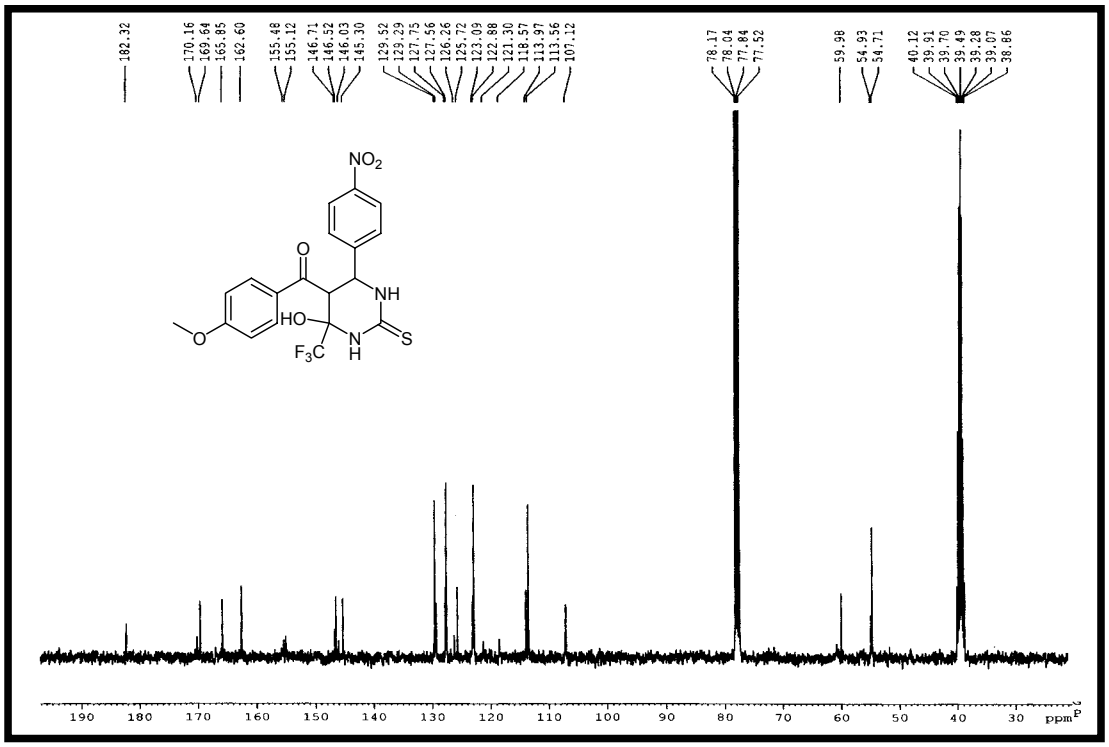


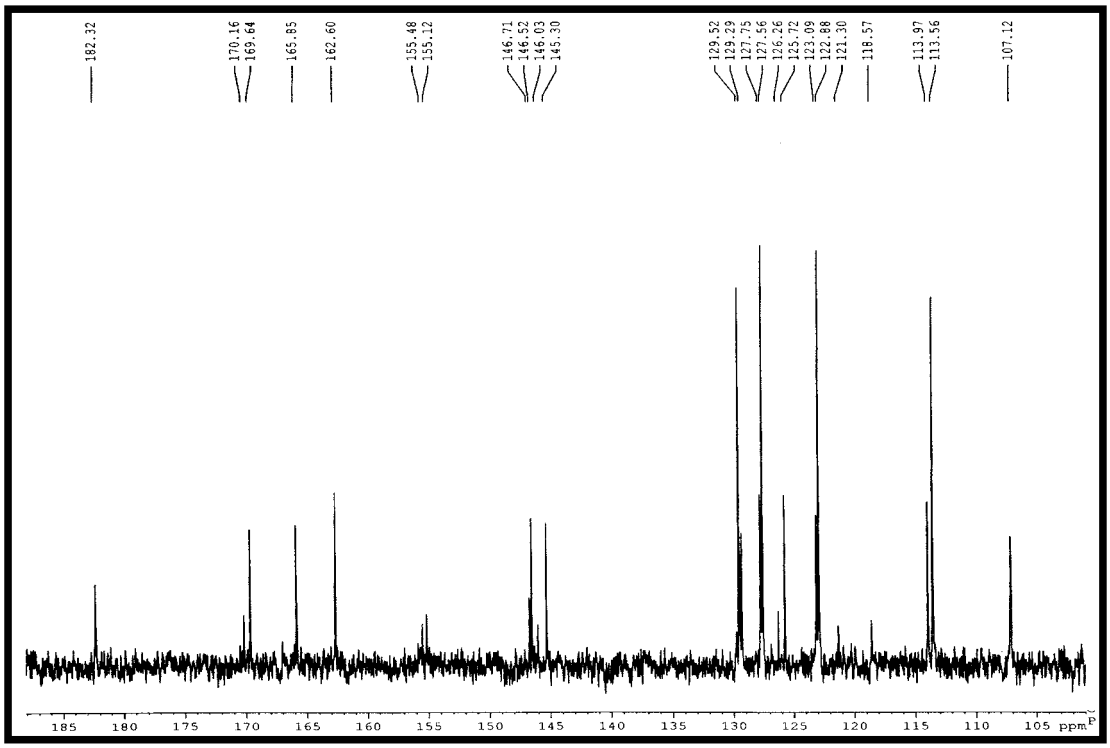
[f] ^{13}C NMR of RK-2001



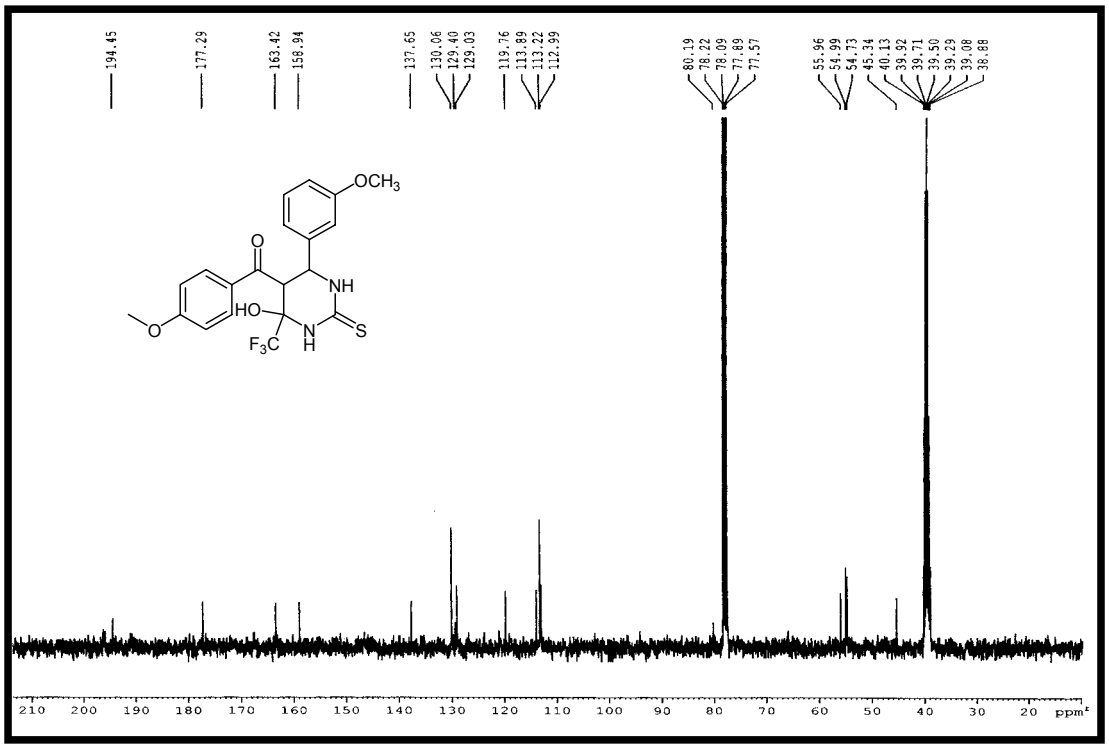


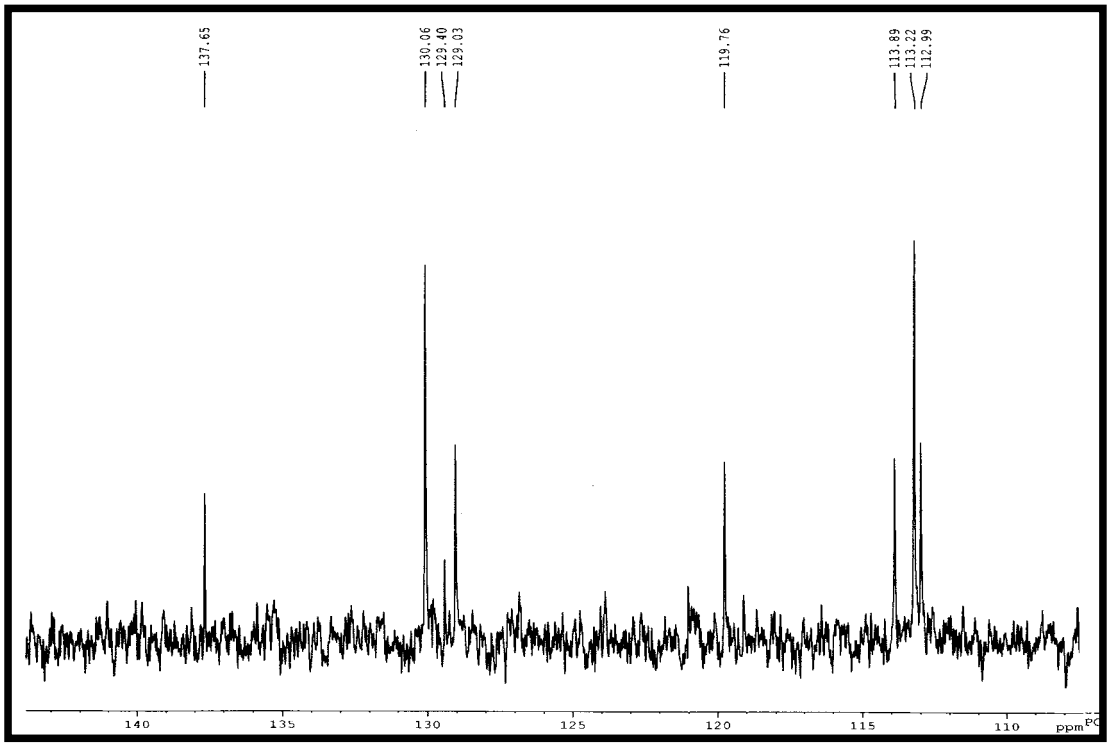
[g] ^{13}C NMR of RK-2014



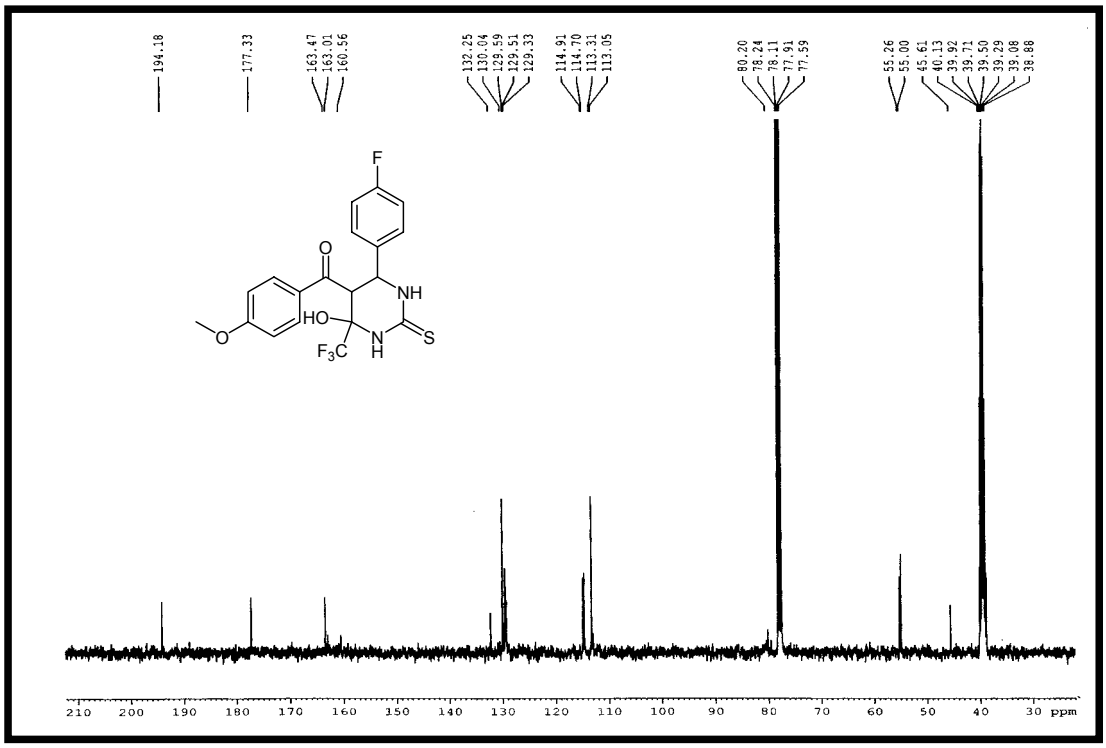


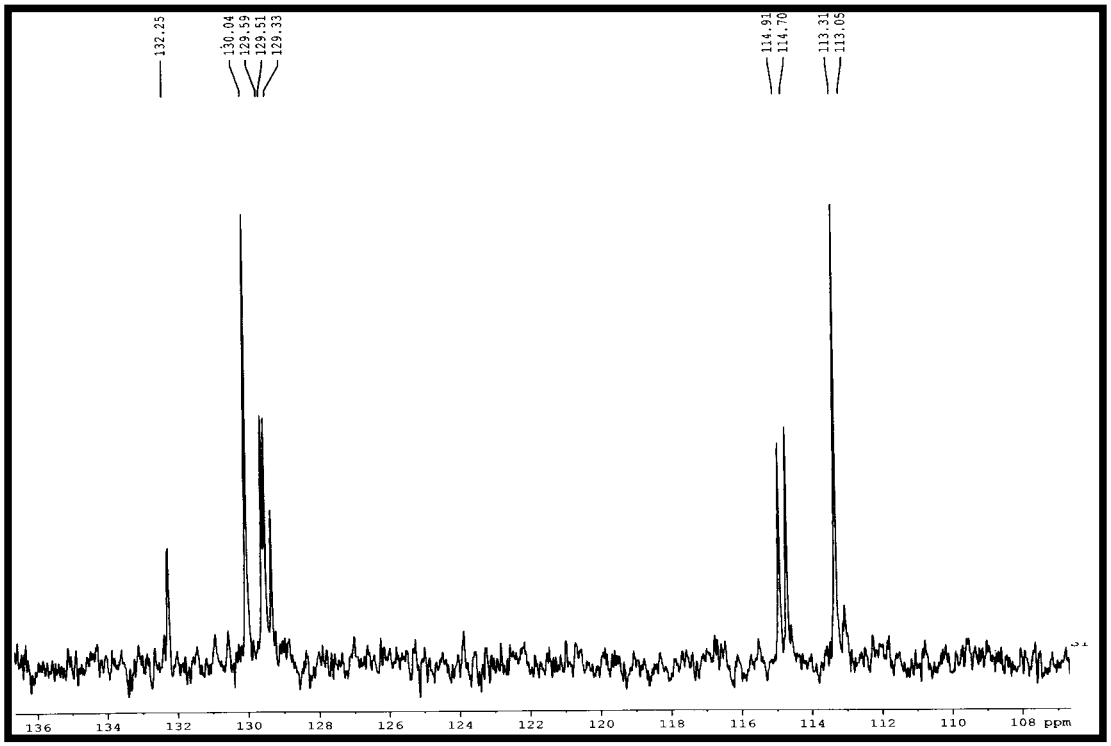
[h] ^{13}C NMR of RK-2008



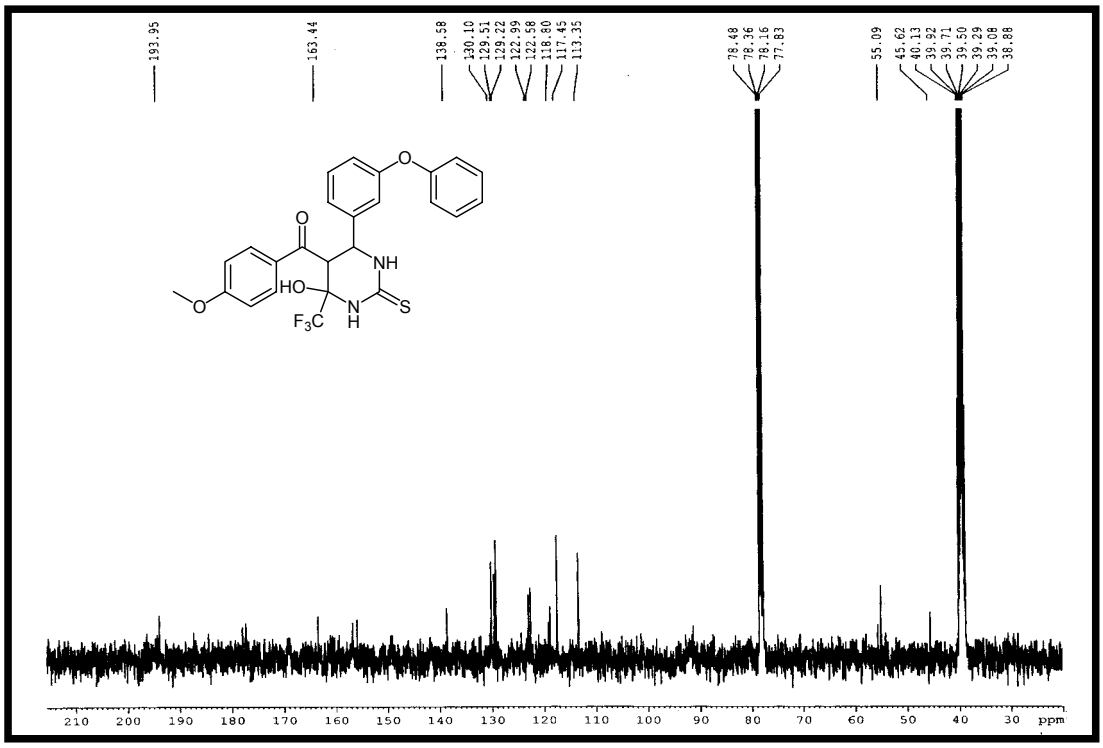


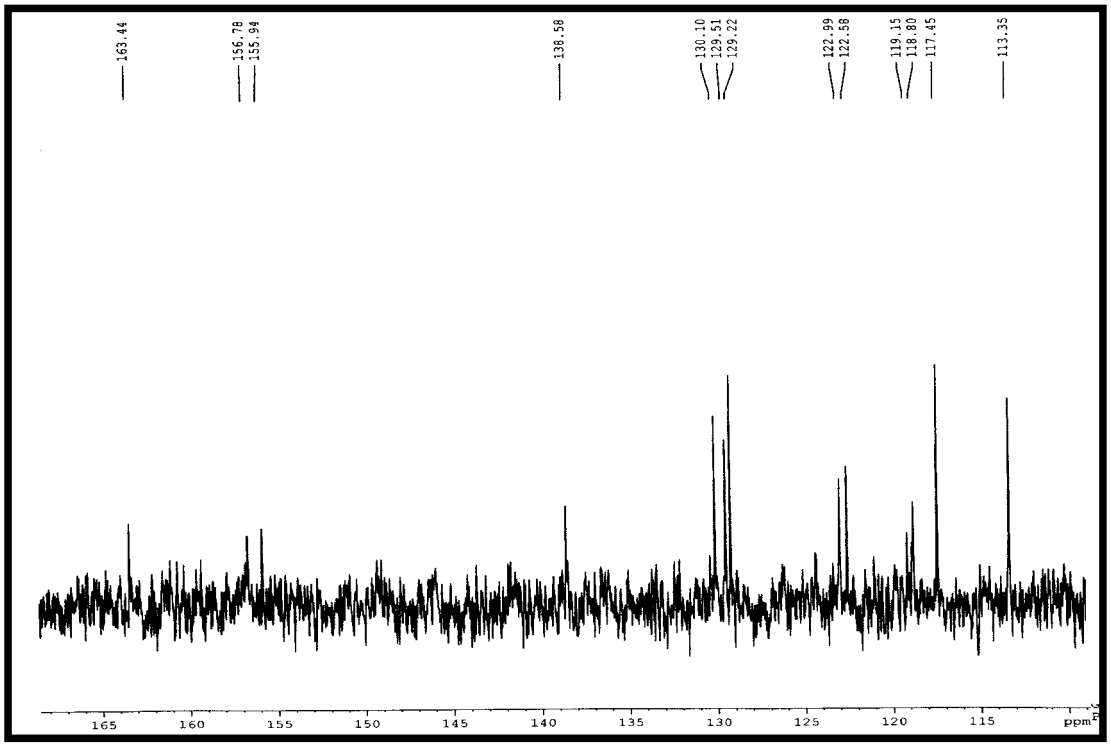
[i] ^{13}C NMR of RK-2002



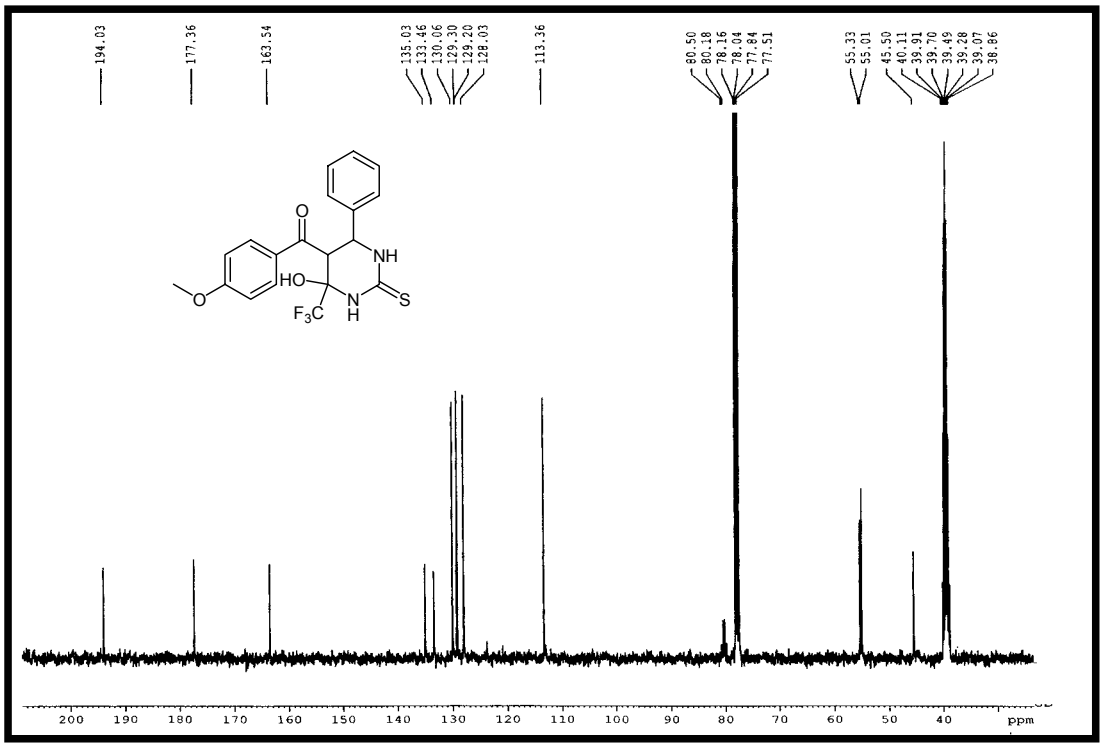


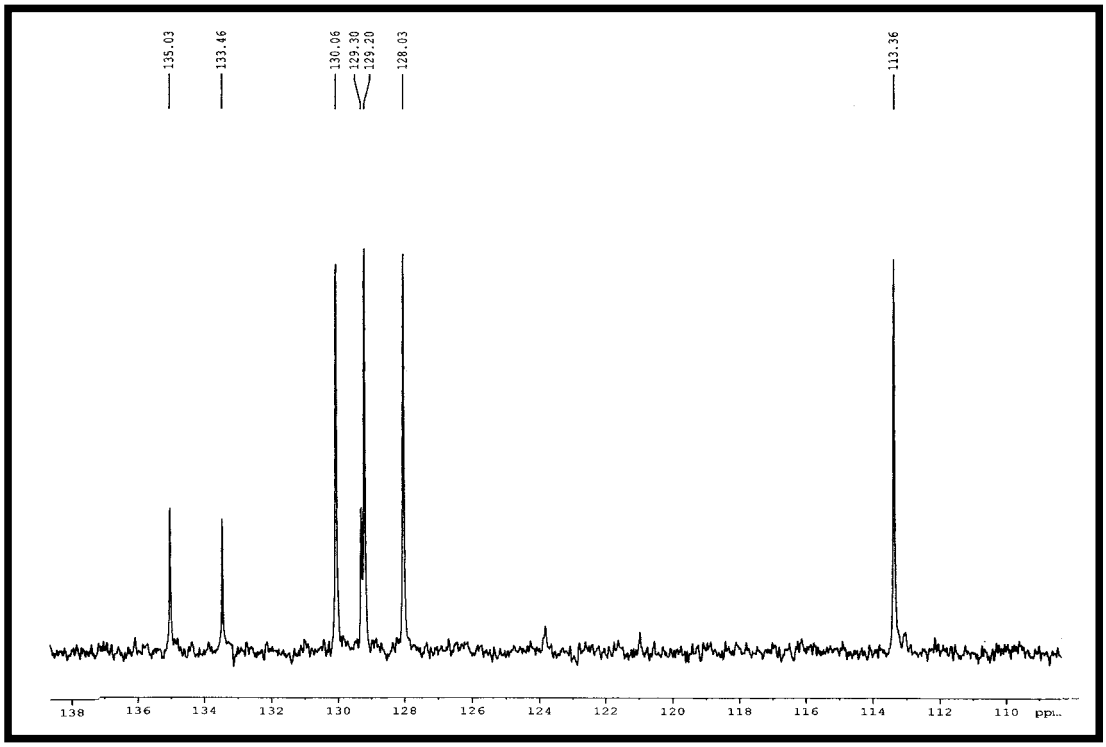
[j] ^{13}C NMR of RK-2016



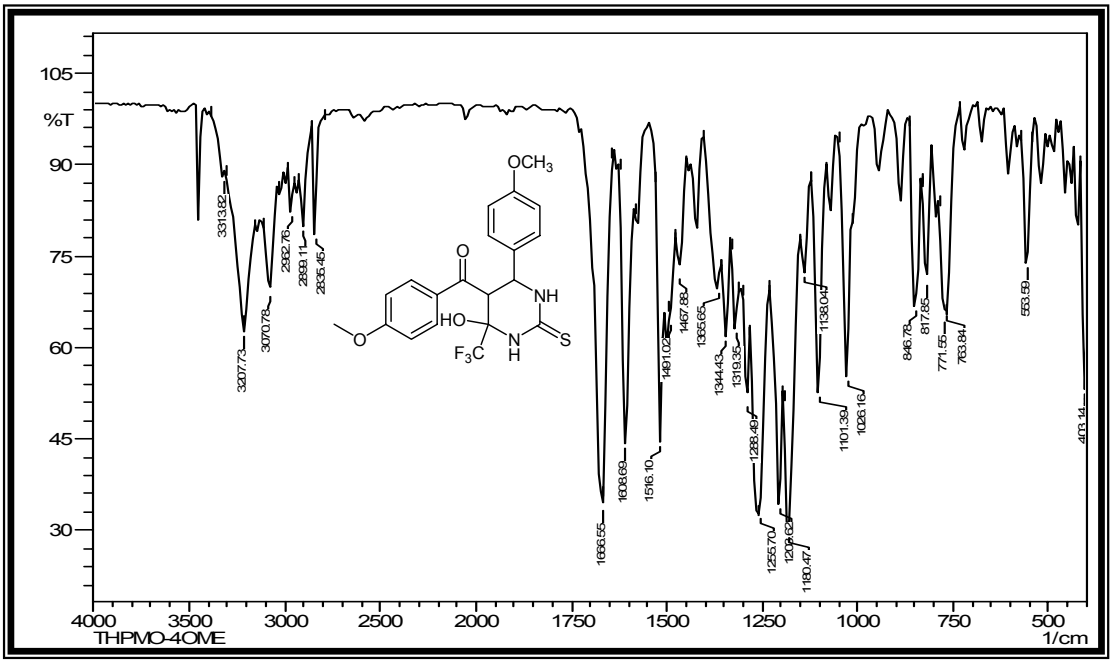


[k] ^{13}C NMR of RK-2011

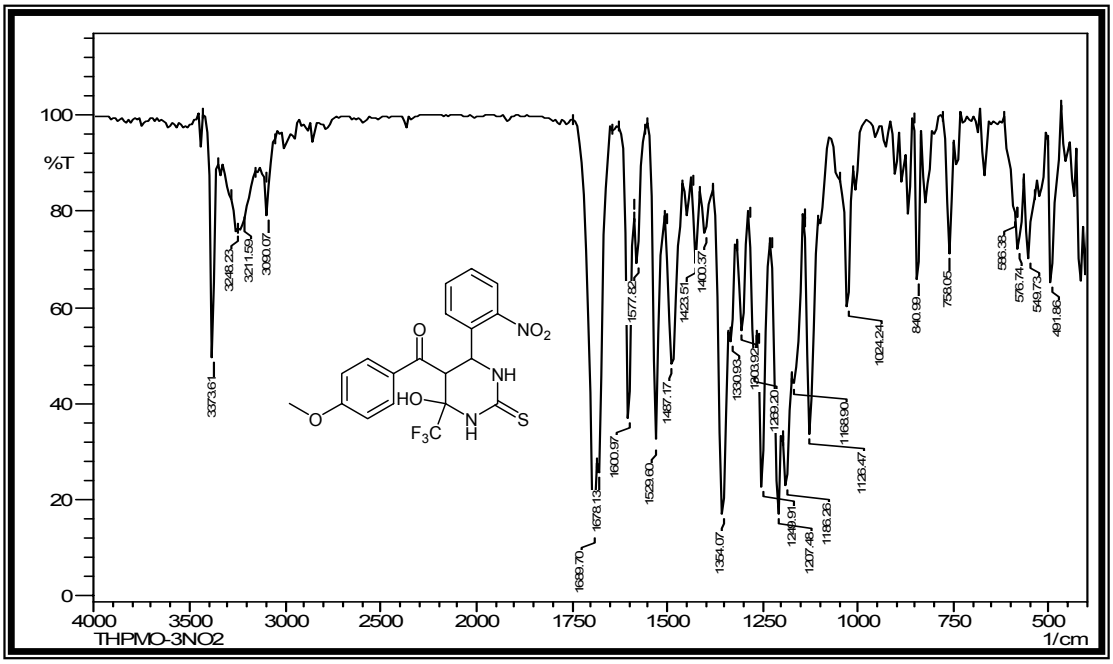




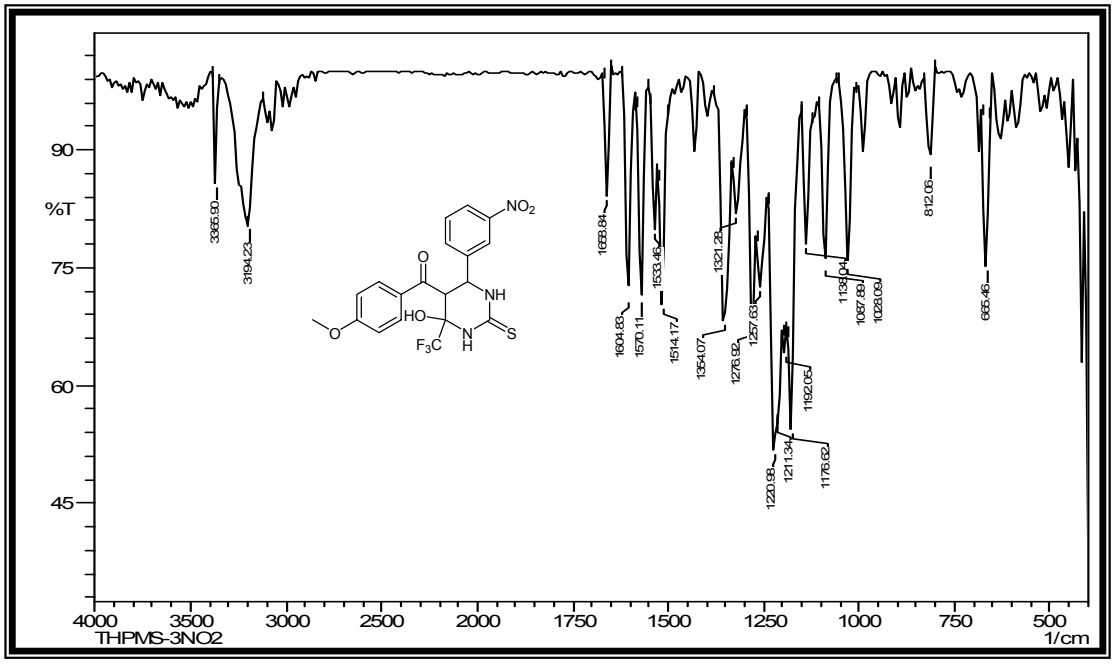
[l] IR Spectra of RK-2007



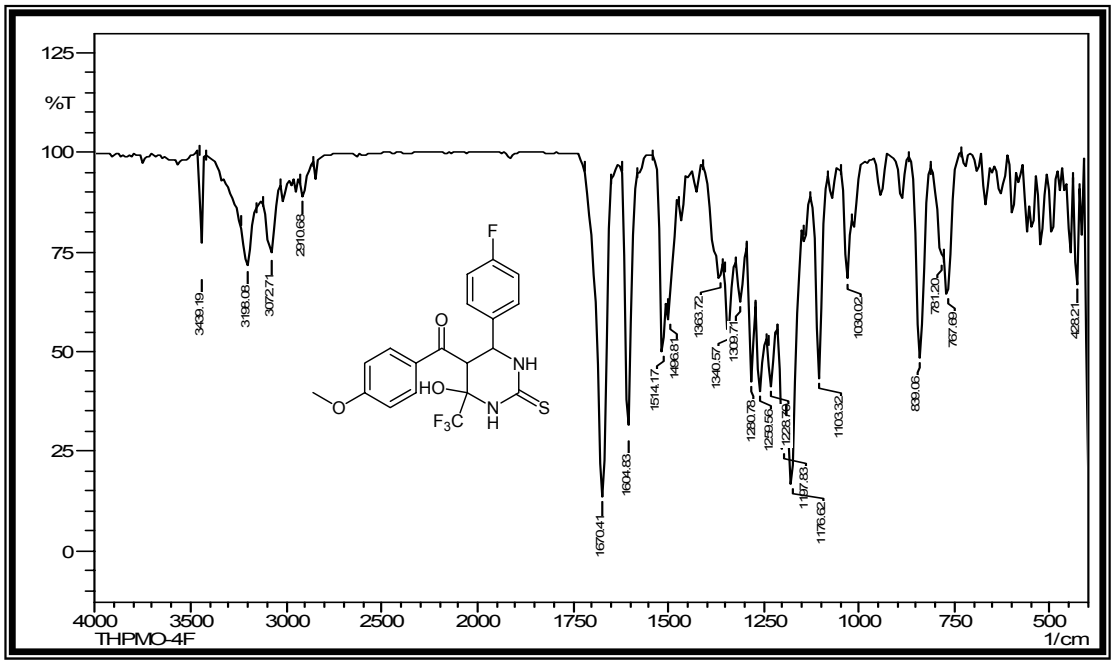
[m] IR Spectra of RK-2015



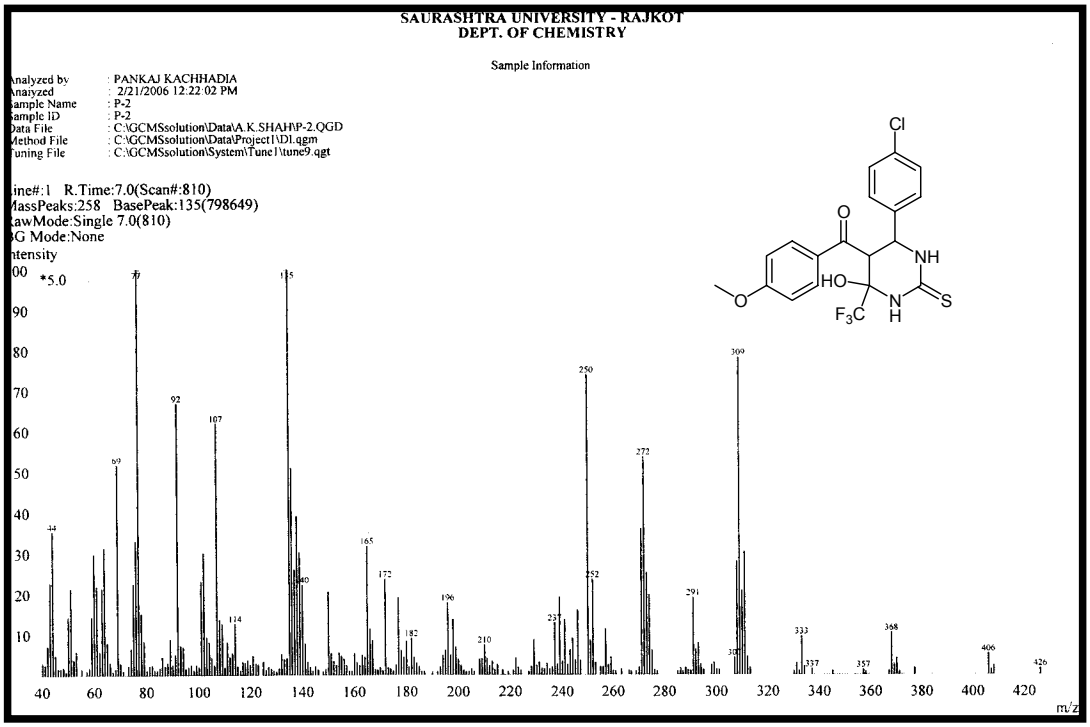
[n] IR Spectra of RK-2004



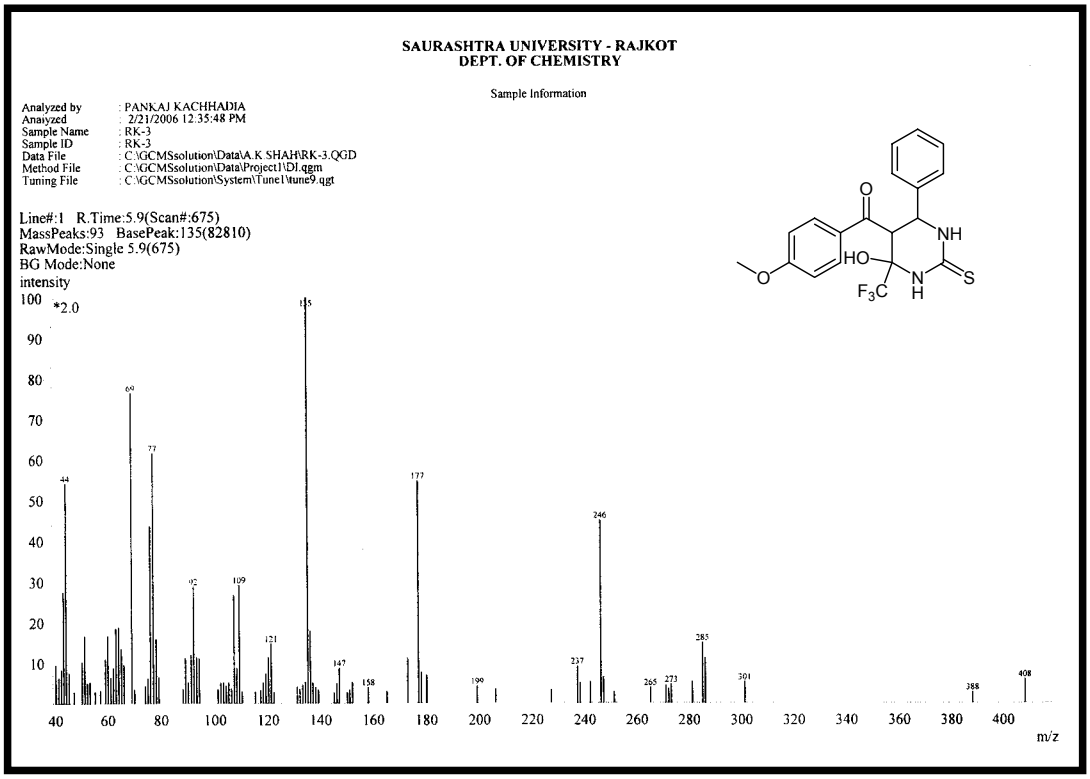
[o] IR Spectra of RK-2002



[p] EI-MS of RK-2009



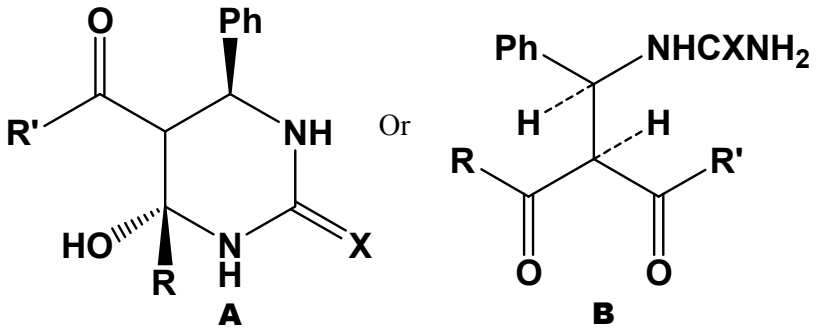
[q] EI-MS of RK-2010



Conclusion

In the present work, the Biginelli type cyclocondensation of a fluorine containing 1, 3 diketone have been studied. In analogy to the reaction of 1,3-diketone with different substituted benzaldehyde and urea, we find hexahydropyrimidine. These reactions were conventionally carried out in methanol in the presence of the catalytical amount of Conc. HCl for 5-6 hours providing hexahydropyrimidine products in moderate to good yields. In principle, one has to consider two isomeric structures for these condensation products, namely hexahydropyrimidine structure of type **A** or the isomeric acyclic ureidopropionate structure of keto and enol tautomers.

It has to be mentioned that an earlier report on the condensation of 1,3-diketone with urea and benzaldehyde postulated the formation of the corresponding ureidopropionate **B** (R= CF_3, R= 4-methoxyphehyl , X=O, S) under essentially similar reaction conditions. Based on comparison of melting points and spectral data, we assume that the identical material has been isolated. However, we assign the structure **B** of the corresponding hexahydropyrimidine of type **A** to this product based on the detailed spectroscopic characterization that we have carried out.



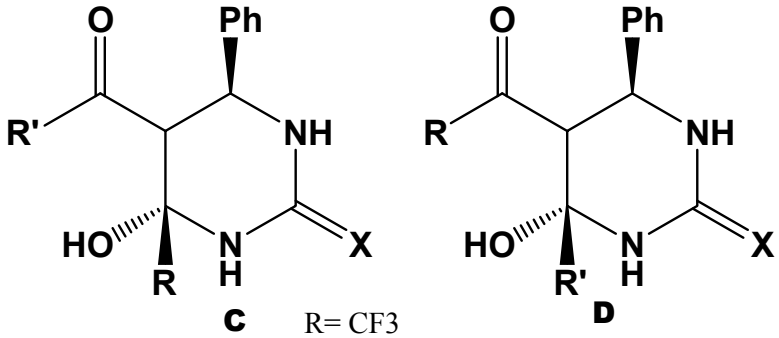
The IR spectra of products are characterized by the absence of two narrow absorption bands corresponding to the asymmetric and symmetric vibration of the amino groups in structures **B**. However, sharp and intense signals for the hydroxy functionality in structure **A** are present in all cases.

In the ^{1}H NMR spectra of compounds, the most characteristic signals are two doublets corresponding to the two *trans-axial* methine protons in **A**. The observed coupling constants (J=11.0-11.8 Hz) agree very well with the values previously found for our reference compound A. (R= CF_3, R= 4-methoxyphehyl, X=O, S). It is therefore

reasonable to assume that the same relative stereochemistry as shown in **A** and ring orientation is observed in all cases

In addition, the cyclic nature of compound was confirmed by ^{13}C NMR spectroscopy. In the spectrum, a quartet for the carbon atom connected with the trifluoromethyl substituent is located at 79-81 ppm ($^{3}J(C\text{-}F)$ =31.1 Hz) which is typical for a quarternary carbon rather than a carbonyl carbon atom. Therefore, all the spectroscopic data clearly confirm the cyclic structure of type A for the products obtained.

Non-symmetrical 1,3-diketones are employed in the above Biginelli-type cyclocondensation process two isomeric products may possibly be formed. Cyclization of the pyrimidine nucleus may occur on the carbonyl group at the fluorinated substituent or the carbonyl group connected with the non-fluorinated substituent to form the corresponding heterocycles **C** or **D**, respectively, or a mixture of both isomers. Literature data indicate that condensation of amines with non-symmetrical 1,3-diketones having one fluorinated substituent preferably occurs at the carbonyl group attached to the non-fluorinated radical.



R= CF3
R'=4-methoxy phenyl
X= O, S

In the NMR spectra of compounds, signals for only one isomer are observable. The distinction between structures C and D was easily made on the basis of ^{13}C NMR spectroscopic data, as the quartet signal of the carbon atom attached to the trifluoromethyl group ($^{3}JC\text{-}F$=30-34 Hz) is located at 80.69 ppm, which is typical for a quarternary carbon atom (structure C,O-C-N) rather than carbonyl carbon in structure D. Thus, the above cyclocondensation occurs regioselectively on the carbonyl group at the fluorinated substituent.

In conclusion, we have synthesized a family of novel fluoroalkyl substituted hexahydropyrimidines by Biginelli-type three-component cyclocondensation reaction of fluorinated 1,3-dicarbonyl compounds with benzaldehyde and (thio)urea.

The antimicrobial activities of these compounds are investigated against eight different bacterial strains. The results are shown in tabular form. Some of the shown in Tabular form. Some of the compounds show moderate activity but not comparable to Linezolid, a standard drug

The other biological properties of these substances are currently under investigation.

Antimicrobial Activity

Background for antibacterial screening

Antibiotic resistance is a serious concern worldwide as it would result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either gram-positive or gram-negative pathogens. Antibiotics compounds with effective activity against both gram-positive and gram-negative pathogens are generally regarded as having a broad spectrum of activity. The synthesized compounds were preliminary screened against gram-positive and gram-negative pathogens.

Gram-positive pathogens, for example *Staphylococci, Entprococci, Streptococci* and *Micobacteria* bacteria, are particularly because of the development of resistant strain which are difficult to eradicate from the hospital environment once established. Example of such strains are methicillin resistance *staphylococcus* (MRSA), methicillin resistance coagulase negative *staphylococci* (MRCNS), penicilline resistance *streptococcus pnumoniae* and multiplied resistance *enterococcus faecium*, community acquired pathogens (CAP), and so on.

Quinolones as a class of antibacterial agents are well known and are being used extensively throughout the world. They are potent inhibitor of gram-positive and gram-negative pathogens and may be administered orally or intravenously. A wide range of quinoline antibacterial has been introduced in the last decades which includes

norfloxacin, ciprofloxacin, ofloxacin and recently launched gutifloxacin and moxifloxacin.

However, some of quinoline antibacterials have been associated with significant side effects. (J. Antimicrob. Chemother. 1994, 33, 685) and some of them have been discontinoued at different stage of development. (eg. Trovafloxacin)

However, due to increase in antibacterial resistance and also otherwise there is a continue need for other compounds which are more effective against resistance bacteria, have improved intestinal absorption, metabolic stability and exhibit less toxicology.

Protocol for antibacterial activity

The minimum inhibitory concentrations (MIC) of the compounds for the microorganisms were determined by preparing working solution for each compound of concentration of 128 μg/ml after dissolving it in DMSO. Two fold serial dilution of above solution was prepared in duplicate using Muller Hinton Borth, in well Tissue culture plate with cover flat bottom wells to give a final volume of 150 and concentration of compound ranging from 64 μg/ml -0.12 μg/ml. 30 μg/ml of Standard suspension of each organism which was prepared with turbidity equivalent to the 1:10 diluted 0.5 McFarland standard with density 10^7 CFU/ml. These 96-well tissue culture plate containing the test samples and positive and negative controls, were incubated at 37^oC for 16-18 hours. The wells were visually inspected for growth and were also read at 630 nm by Automated Micropalte Reader [(EL800) Trinity Biotech] and the MICs were recorded as the lowest concentration of drug which inhibits the growth of bacteria. The compounds inhibited the growth of these bacteria with MICs in a range of about 0.25 to about 64

Abbreviations

Bp : *Bacillus pumilus* MTCC 1607

S.e. : *Staphylococcus epidermidis* MTCC 155

S.p. : *Staphylococcus pyogenes* MTCC 442

S.a.1. : *Staphylococcus aureus* MTCC 96

S.a.2. : *Staphylococcus aureus* ATCC 14154

S.a.3. : *Staphylococcus aureus* ATCC 25923

S.a.4. : *Staphylococcus aureus* ATCC 29213

E.f.1 : *Enterococcus faecalis* MTCC 439

E.f.2 : *Enterococcus faecalis* ATCC 14506

Table **MIC [minimum inhibitory concentration in vitro activity µg/ml] values of synthesized compounds in various Gram positive and Gram negative bacteria.**

Code	Bp	Se	Sp	Sa1	Sa2	Sa3	Sa4	Ef1	Ef2
RK-1001	0.5	1	4	8	8	16	>8	64	2
RK-1002	2	0.5	2	16	16	8	16	32	4
RK-1003	4	4	1	32	16	32	>64	>32	2
RK-1004	2	0.5	>16	>16	ND	16	32	16	8
RK-1005	2	2	8	4	32	4	2	>8	>16
RK-1006	4	1	2	ND	ND	ND	ND	4	32
RK-1007	2	4	1	>8	>32	>32	4	32	16
RK-1008	2	0.5	4	>32	4	8	16	>8	8
RK-1009	1	2	16	16	2	16	>16	4	4
RK-1010	2	8	32	8	0.5	ND	ND	ND	ND
RK-1011	4	8	>32	ND	ND	8	8	8	4
RK-1012	2	4	64	>64	16	>8	16	8	8
Linezolid	1	2	0.5	4	4	4	4	2	4

Code	Bp	Se	Sp	Sa1	Sa2	Sa3	Sa4	Ef1	Ef2
RK-2001	2	4	1	8	4	16	64	4	16
RK-2002	1	8	4	8	8	32	16	8	8
RK-2003	0.5	>16	2	16	16	64	>8	16	8
RK-2004	4	8	8	ND	ND	16	ND	ND	8
RK-2005	8	8	4	>32	16	4	>16	8	>32
RK-2006	2	2	2	64	8	ND	32	8	64
RK-2007	2	ND	2	ND	ND	8	8	4	4
RK-2008	4	4	2	8	64	16	16	16	16
RK-2009	>8	2	4	4	32	ND	ND	>32	>64
RK-2010	16	>16	8	8	16	32	8	8	32
Linezolid	1	2	0.5	4	4	4	4	2	4

Note:- ND = not done

References

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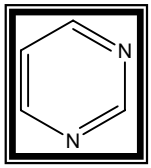
Introduction

Pyrimidine is a six membered heterocyclic compound consisting of two nitrogen atoms at 1 and 3 positions of heterocyclic ring.

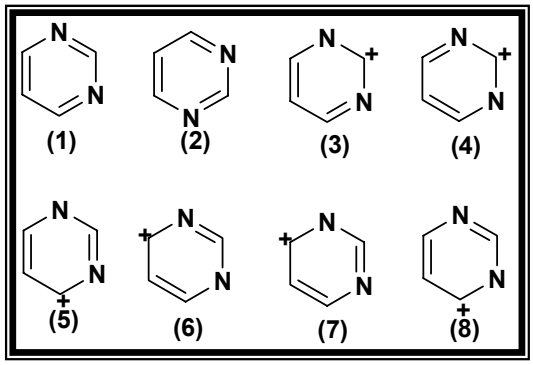


Pyrimidines have been isolated from the nucleic acid hydrolysates. Pyrimidine ring carrying various substituents may be built up from two or three aliphatic fragments by the principle synthesis or by a variety of other syntheses, which are complimentary rather than alternative to it. An alternative method of synthesis is the isomerisation or break down of another heterocycles such as hydration of purine, but such methods are rarely used. Pyrimidine is best considered as a resonance hybrid to which the uncharged equivalent Kekule. In present chapter, pyrimidine derivatives such as 2-hydroxy-substituted-pyrimidines are studied.

Pyrimidines are among those molecules that make life possible, have been present in some of the building blocks of DNA and RNA.

Several analogues of pyrimidines have been used as compounds that interfere with the synthesis and functioning of nucleic acids e.g. fluorouracil, which has been used in cancer treatment. Also there are some thiouracil derivatives, which produce adverse reduction in susceptible patients and found more potent and less likely to produce side effects and is being widely used [1]. There are several other important groups of pyrimidines with medicinal uses.

Structures **1**, **2** and charged structures **3** and **8** contributes. The self consistent (pπ), electron densities required for the ground state of pyrimidine are 0.776, 0.825 and 1.103 for positions **2, 4** and **5** respectively[2]. Despite considerable localization of (pπ) electrons at nitrogen atoms of pyrimidines, the ring system is still sufficiently aromatic to possess substantial stability. This has a great advantage in the primary synthesis of pyrimidines.



The first primary synthesis from aliphatic fragments was carried out by Frankland et al. in 1848. Since then many distinct primary synthetic methods have been devised [3-12]. It is also possible to prepare pyrimidines from other heterocyclic compounds such as pyrrole[13], imidazole[14], isoxazole and oxazole[15,16], pyridine[17], pyrazine[18], 1,3,5-triazine[19], oxazine[20], thiazine[21] by different processes.

Synthetic Methods for Pyrimidines

Various methods for synthesis of pyrimidines which are reported in the literature are as follows.

(a) By the condensation of urea and malonic acid led to formation of pyrimidine [22].

(b) By the condensation of malonic ester and urea led to formation of pyrimidine [23].

(c) By the condensation of formamide with phenylazomalononitrile led to formation of 4,5,6-triamino pyrimidine [24].

(d) By the condensation of aromatic aldehydes, ß-ketoester or substituted ß-ketoester with urea or thiourea led to formation of pyrimidines [25].

(e) By the condensation of thiourea and substituted ß-ketoester in presence of sodium ethoxide led to formation of 2-mercapto pyrimidines [26]

(f) By the condensation of chalcones with dicyandiamide in presence of piperidine led to formation of pyrimidines [27].

(g) By thermal or microwave irradiation of thiourea and substituted β-ketoester in presence of dimethylformamide led to formation of substituted tetra hydro pyrimidines. [28]

(h) One pot synthesis of substituted dihydropyrimidin-2-ones catalyzed by $CuCl_2$. [29]

(i) Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones under microwave irradiation.[30]

(j) One pot efficient and novel synthesis of dihydropyrimidin-2-(1*H*)-ones catalyzed by Tin (II) chloride ($SnCl_2$). [31]

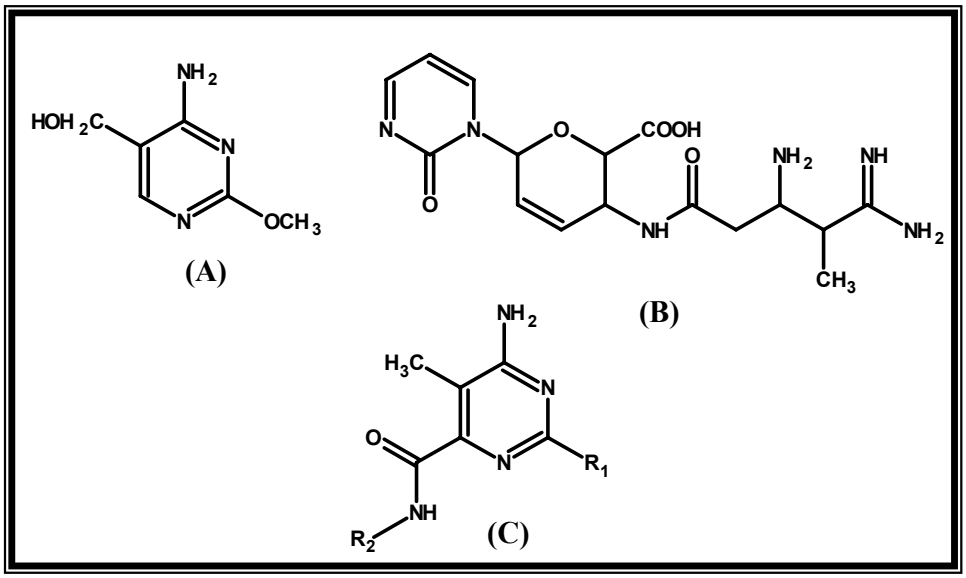
(k) By microwave induced eco-friendly solvent free Biginelli reaction catalysed by calcium chloride. [32]

Pyrimidines have found their applications as herbicidal [33] and pesticidal [34,35] agents. Yoshida et al., [36] have synthesized 4-amino-5-formyl-2-mercapto pyrimidines as agrochemical intermediates. Srivastava C. et al., [37] have synthesized new substituted

pyrimidines (3) as potential insecticides. N. Yasushi et al.,[38] synthesized 6-(1-fluoro ethyl)-5-iodo-4-alkylamino pyrimidines (4) as pesticides for agriculture and horticulture. Besides such a great biological importance of pyrimidines, they also contribute to an important class of dye viz. trichloro pyrimidine [39] dye which is a reactive dye. Pyrimidines also have applications in liquid crystal composition.[40] Many synthetic members of pyrimidines are important as vulcanizing accelerator agents and photography stabilizer.[41]

Pharmacological Importance of Pyrimidines

Numerous pyrimidines are well known drugs for variety of diseases. They may be placed in four categories viz. barbiturates, sulfonamides, antimicrobials and antitumor agents. Uracil, thymine, alloxan, vicine and divicine, cytosine, chroticacid, willardiline, tetradotoxine, becimethrian (A), blasticidine (B), cougerotin, amicetin, bamicetin and plicacetin, phleomicine, blemycin and related families (C).



Pyrimidine derivatives have wide varieties of usages. Pyrimidine ring system is also present in Vitamin B_2 and folic acid. Pyrimidine ring system having a mercapto group occupy a unique position in medicinal chemistry.[42] These types of derivatives play a vital role in biological processes[43-45] as well as synthetic drugs.[46]

Some of the therapeutic activities of pyrimidine derivatives can be summarized as follows.

Antithyroid [47,48]

Antihypertensive[52-54]

Diuretic [58]

Antispasmodic [62]

Antineoplastic[64,65]

Antimicrobial [67-92]

Antiviral [96-99]

Antihistamine[102,103]

Antitubercular[106]

Antitumor [49-51]

Antiinflammatory [55-57]

Antimalarial [59-61]

Anticonvulsant [63]

Anthelmintic [66]

Cardiovascular [93-95]

Platelet aggregation inhibitor [100-01]

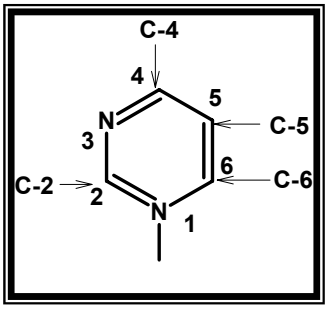
Anti-HIV[104,105]

The basis of any rational drug discovery programme is fundamently, the Medicinal Chemistry. Although the synthesis of modified nucleic acids has been a subject of interest for some time, the intense focus on the medicinal chemistry of oligonucleotides dates perhaps to not more than five years. As a result of this, the scope of medicinal chemistry has recently been expanded enormously, but the biological data of supporting the conclusions about synthetic strategies have just begun to emerge.

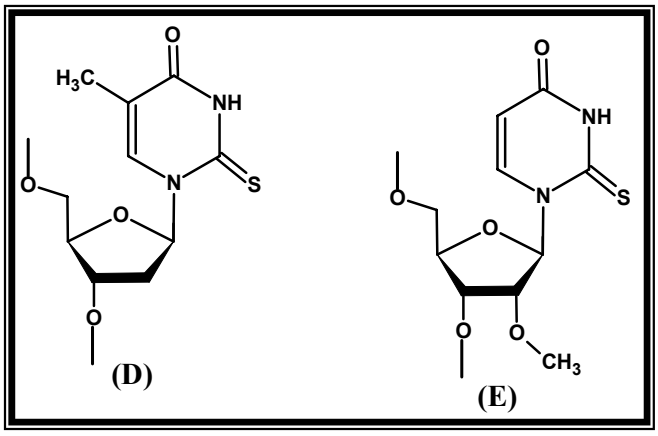
Modifications in the base, sugar and phosphate moeities of oligonucleotides and oligonucleotide conjugates have been reported. The subjects of medicinal chemistry programmes include approaches to create enhanced affinity and more selective affinity for RNA or duplex structures, the ability to cleave nucleic acid targets, enhanced nuclease stability, cellular uptake and distribution, *in vivo* tissue distribution, metabolism and clearance. Although substantial progress in the medicinal chemistry of oligonucleotides has been made in the past three years, it is not yet possible to reach the conclusion about the therapeutic ability of the novel modifications. Preliminary data on effects on nuclease stability and hybridization properties for a few modifications and activity *in vitro* suggest that the next generation of oligonucleotides may display substantially improved potencies and selectivity.

Pyrimidine Modifications (Nucleotide)

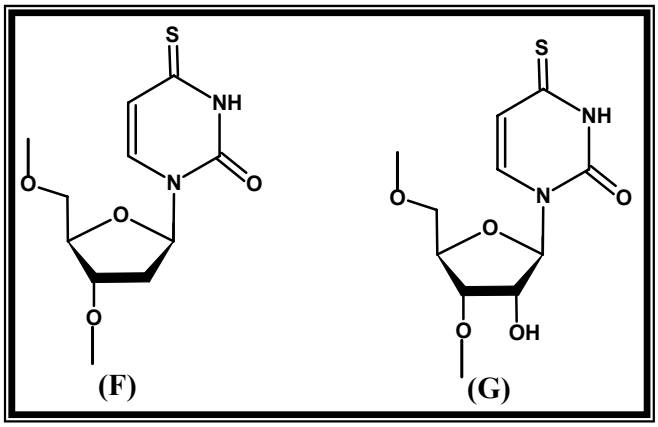
A relatively large number of modified pyrimidines have been synthesized and now incorporated into oligonucleotides and evaluated. The principle sites of modification are C_2, C_4, C_5 and C_6. These and other nucleoside analogues have recently been thoroughly reviewed. [107]



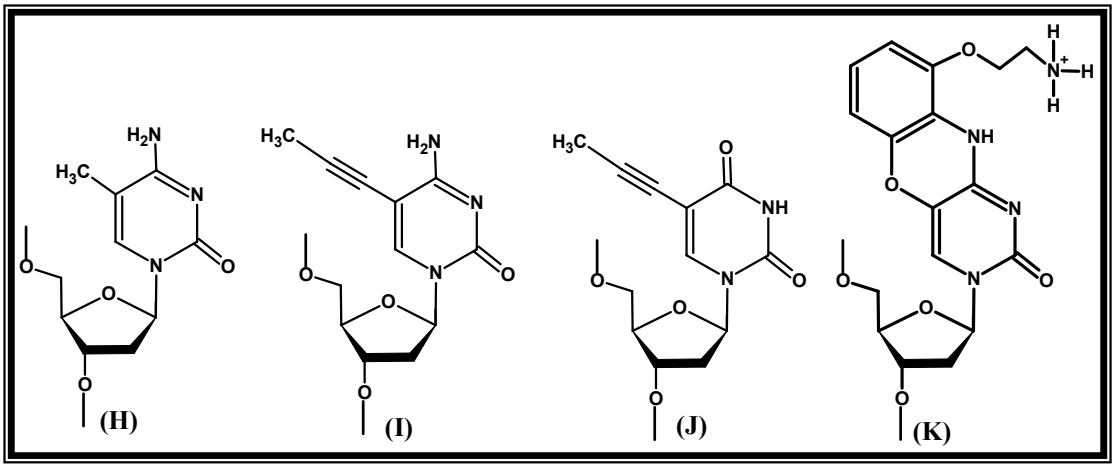
In as much as the C_2 position is involved in Watson-Crick hybridization, oligonucleotides containing C_2 alkyl modified pyrimidines have shown unattractive hybridization characters. However, an oligonucleotide containing 2-thio thymidine(D) was found to hybridize well to DNA and, in fact even better to RNA with a thermal melting temperature (DTm) value of 1.5°C/modification. In a different study, oligoribonucleotides with 2'-O-methyl-2-thiouridine(E) exhibited a thermal melting temperature (DTm) value of +5.5°C/modification when hybridized against RNA resulting from a highly preorganized RNA-like C3'-endo conformation (attributed to the combination of 2-thio modification and 2'-O-Me substituent). Oligonucleotides with this modification also exhibit better hybridization discrimination for the uracil-guanosine (U-G) base pair formation compared to the normal uracil-adenine (U-A) base pair. This selectivity is a result of weaker hydrogen bonding and increased steric bulk of 2-thiocarbonyl group. [108]



In contrast, the pyrimidine modifications in 4-position with interesting properties have been reported. 4-Thiopyrimidines(F,G) have been incorporated into oligonucleotides with no significant negative effect on hybridization. However, recent studies have shown destabilization in the normal uracil-adenine (U-A) base pair formation and stabilization of the wobble uracil-guanosine (U-G) base pair for 4-thiouridine. A bicyclic and an 4-methoxy analog of cytosine were shown to hybridize with both purine bases in DNA with thermal melting temperature (Tm) values approximately equal to that of natural base pairs. Additionally, a fluorescent base has been incorporated into oligonucleotides and shown to enhance DNA-DNA duplex stability. [109]



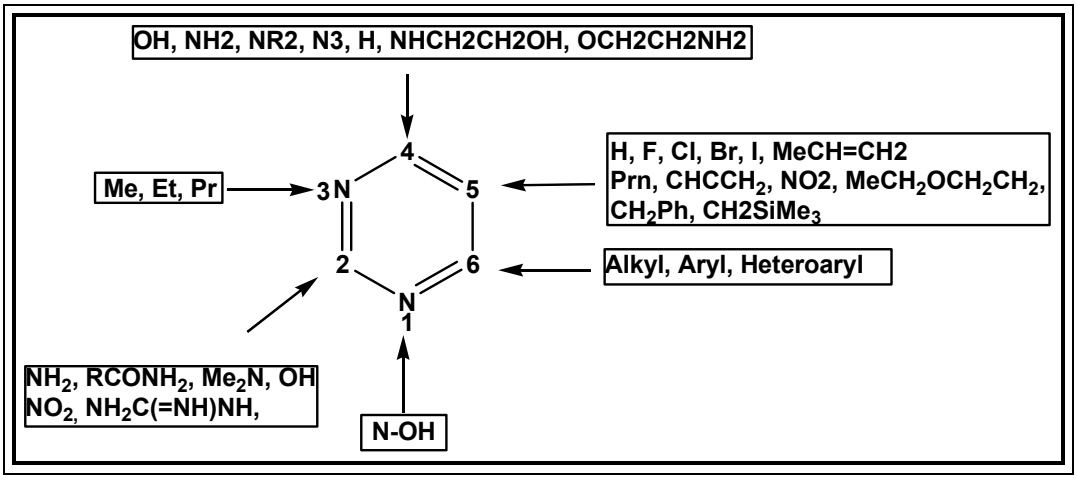
The pyrimidine modifications at C_5 position including halogenated nucleosides have been reported. Although the stability of duplexes may be enhanced by incorporation 5-halogenated uracil containing nucleosides, the occasional mispairing with guanidine and the potential that the oligonucleotide might degrade and release toxic nucleosides analogs cause concern. Oligonucleotides containing 5-propynylpyrimidine (I, J) modification have been shown to enhance the duplex stability thermal melting temperature (DTm = 1.6°C/modification), and support RNase H activity. The 5-heteroaryl-pyrimidines were also shown to increase the stability of duplexes . A more dramatic influence was reported for the tricyclic 2'-deoxycytidine analoges, termed phenoxazine, exhibiting an enhancement of 2-5°C/modification, depending on the positioning of the modified bases. [110]



As expected, modifications in the C_6 position of pyrimidines are highly destabilizing. Oligonucleotides containing 6-azapyrimidines(K) have been shown not only to reduce the thermal melting temperature (Tm) value by 1-2°C per modification, but also to enhance the nuclease stability of oligonucleotides and to support E. coli RNase H-induced degradation of RNA targets.[111]

The increasing interest in the early 1970s in properties and use of interferon (IFN) together with the difficulty in producing useful amounts of interferon (IFN) led to the search for agents that would induce IFN in the host. Precedenced at that time for interferon (IFN) inducers included viruses and bacterial wall constituents and entities of large molecular weight such as the polynucleotides. There were also several examples of low molecular weight substances such as certain antibiotics and the antiviral agent, tilorone.[112-113] In 1976, it was reported that 6-methyl pyrimidinone (2-amino-5-bromo-6-methyl-4-(3H)pyrimidinone, ABMP) induced circulating levels of interferon (IFN) in several animal specis upon oral or intraperitoneal administration.[114] Subsequent structure-activity studies yielded a more potent and less toxic 6-phenyl ananlog called ABPP or bropirimine (2-amino-5-bromo-6-phenyl-4-(3H)pyrimidinone) (figure 1 and Table 1).[115,116] Bropirimine and related 6-aryl analogs were examined extensively for efficacy in virus and tumor models, along with their immunomodulatory properties and overall pharmacological effects.[117]

Preliminary SAR of antiviral activity of pyrimidinones

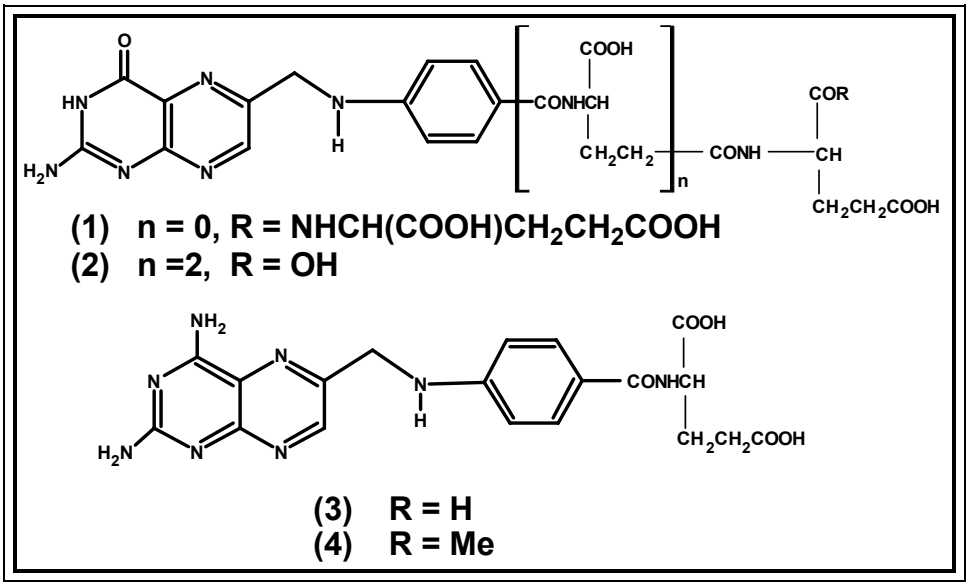


Anti viral activity spectrum of pyrimidines			
	Monosubstituted	**Disubstituted**	**Heterocyclic**
Active	2-F,OMe, Me, 3-F,OMe, 2-Cl, NO_2, Me, CF_3, $MeCH_2CH_2O$, Br, I, 4-F, 4-Cl	3,5-OMe, 2,5-Cl_2, 3,5-OMe, 3,4-Cl_2, 3,5-Cl_2	1-Naphthyl, 2-Furyl, 2,3-pyridyl, 2-Pyrazyl
Inactive	4-Me, CN, Butyl, OH,OCH_2ph, OMe	2,3-OMe	2-Napthyl, 1-Furyl, 4-Pyridyl, 2-Quinoline

As with the polynucleotides, the pyrimidinones exhibited significant activity against interferon (IFN) sensitive viruses such as Semliki Forest virus *in vivo*. However, in addition, they exhibited prophylactic and therapeutic activity upon either local or systemic administration to rodents infected with a variety of DNA viruses, such as the herpes viruses (HSV-1, HSV-2 , CMV and pseudorabies), and when administered intranasally for upper respiratory infections, such as infectious bovine rhinortacheites, influenza A and para-influenza-3. Particularly interesting activity was noted with bropirimine on intravaginal administration in protection against HSV-2 intravaginal infection in guinea pigs, an important model for genital herpes in humans. [118] Bropirimine also exhibited activity when given either intraperitoneally or orally to mice infected with Listera monocytogenes. The efficacy in this model was not abrogated by the addition of anti-interferon (IFN) antibody. [119]

Pyrimidines as Antifolates

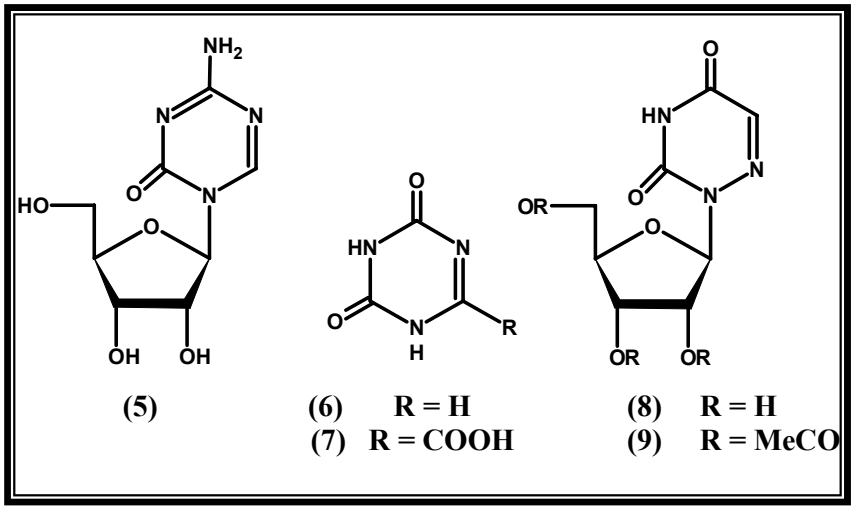
During a preliminary clinical trial designed to establish safety and suitability for use in the treatment of cancer, Farber found the folic acid derivatives pteroyldiglutamic acid (1) and pteroyltriglutamic acid (2) were accelerating the growth of malignant cells in the bone marrow of patients with acute leukemia. He obtained the newly synthesized antifolate pteroylaspartic acid from a natural product, from which encouraging results were obtained in children with acute leukemia. Better responses were observed with the aminopterin (3) and methotrexate(4). Injections of methotrexate induced temporary remissions in 30% of children, but Farber and his colleagues later combined it with drugs such as cortisone and mercaptopurine to achieve results which paved the way towards the currentposition where most children can be cured of the disease if given the appropriate treatment. The precise model of action of the antifolates became apparent in 1952. This was the inhibition of dihydrofolate reductase, the enzymes that catalyzed the transformation of folic acid so that it could be utilized for the synthesis of thymine for incorporation into DNA. Surprisingly, no other antifolate has emerged to rival methotrexate in the treatment of either acute leukemia or cancers.



5-Azacytidine (Azacitidine; 5) the most active of the azapyrimidines, shows substantial activity in the treatment of murine and human leukemia, but little useful activity against solid tumours.[120] It is phosphorylated *in vivo* to the mono-,di- and tri- phosphate levels, and inhibits nucleic acid synthesis and function. In calf thymus nuclei, the synthesis of mRNA is inhibited, while the incorporation of 5-azacytidine into tRNA decreases amino

acid acceptor activity for most of the amino acids, further suppressing protein synthesis. [121]

5-Azauracil (6) and 5-azaorotic acid (7) are competitive inhibitors of orotate phosphoribosyltransferase [122] and show activity against adenocarcinoma 755, but not against LI210 leukemia.



(5) **(6) R = H** **(7) R = COOH** **(8) R = H** **(9) R = MeCO**

6-Azauridine (8) was formerly used to treat chronic myelogenous and acute leukemia [123], as well as psoriasis and mycosal infection. For the latter conditions, it was applied as its prodrug 2',3',5'-tri-O-acetyl-6-azauridine (Azaribine; 9) which has been withdrawn from the market. 6-Azauridine is phosphorylated *in vivo* to it's 5'-monophosphate, which inhibits orotidylic acid metabolism, is primarily responsible for it's cytotoxic effects.

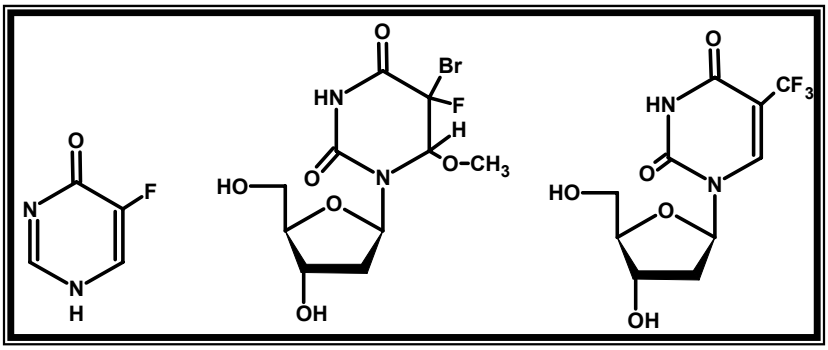
Halogenated Pyrimidines & Their Reactivity

Of the various halogenated pyrimidines which have been prepared, only the fluorinated pyrimidines and nucleosides have useful antitumor activity, and of these, the most significant are 5-fluorouracil (FU) and it's 2'-deoxyribo- nucleside (FUdR; Floxuridine). Both of these drugs have found wide uses in patients suffering from metastatic cancer, and have been administered both singly and in combination therapy.

The presence of fluorine, which cannot be abstracted by base, halts the process. In contrast, the 5'-monophosphate of 5- chloro-, 5- bromo- and 5-iodo-2'-deoxyuridine, in which the halogen atom is bulkier and less electronegative, have little or no useful inhibitory activity for the enzyme. The drugs of fluorouracil (FU) showing good antitumour activity includes it's 1-t-butylcarbamoyl[124],1-hexylcarbamoyl [125] and 1-methoxycarbonylmethylcarbamoyl[126]derivatives, 5'-deoxy-5-fluorouridine[127] and

methyl-1-(5-fluoro-(1*H*)-2-oxopyrimidin -4-yl)-B-D-glucopyranuronate (26).[128] All of these contain in essence the fluorouracil (FU) moiety, ready via oxidative or hydrolytic means. 5-Fluoropyrimidin-4(1*H*)-one, with activity against tumors in experimental animals, is a different type of prodrug, being oxidized to 5-fluorouracil (FU) by xanthine oxidase.[129]

A number of prodrugs of (FUdR; Floxuridine) have also been prepared a notably potent member being 5-bromo-6-methoxydihydro-5-fluro-2'-deoxyuridine (10).[130] finally, a different species of fluoro-pyrimidine derivative, which as its 5'-monophosphate inhibits thymixylate synthetase is 5-trifluoromethyl-2'-deoxyuridine (Trifluridine ; 11,12) it possesses a higher therapeutic index against adenocarcinoma 755 in mice than 2'-deoxyribo-nucleoside (FUdR; Floxuridine).[131]



(10) (11) (12)

Pyrimidines as Antitumor Agents

A number of other pyrimidine antagonists displaying antitumor activity, in which the base is conjugated to a modified sugar ring have been reported. Although D-Arabinofuranosyl uridine (ara-uridine) shows no useful acitivity, and 5-bromo-and 5-iodo-D-arabinofuranosyl uridine inhibit the growth of sarcoma 180 and L1210 cells in culture.[132] Other thymidine analogues with similar activity include 5-azidomethyl-,5-aminomethyl and 5-hydroxymethyl-2'-deoxyuridine[133].3'-Amino-3'-deoxy thymidine[134] and 3'-amino-2',3'-dideoxycytidine[135] also posses strong activity against L1210 leukaemia 2'-Deoxy-2'-fluoro-5-methyl-1-B-D-arabinofuranosyluracil (FMAU; 29) is highly active against arabinofuranosyl cytidine (ara-C) resistant L1210 and P815 cell lines both *in vitro* and *in vivo*.[136] 2-B-D-Ribofuranosylthiazole-4-carboxamide (Tiazofurin; 30) has aroused much interest recently for its activity against solid tumor such as lung carcinoma. It is metabolized to an analogue of NAD in which

the thiazole-4-carboxamide moiety replaces the nicotinamide ring. However, it also depresses the synthesis of DNA and RNA, and thus merits inclusion as an antagonist of normal purine and pyrimidine metabolism. [137]

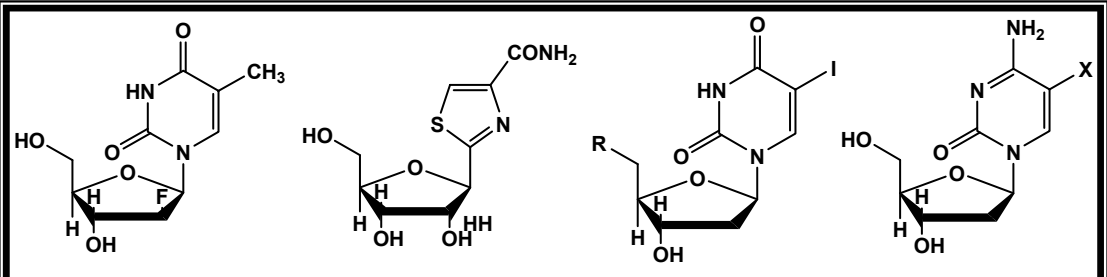
Target for Antiviral Chemotherapy

Viral chemotherapy presents a quite different problem from tumor chemotherapy. A virus [138] consists of a core of nuclear material, DNA or RNA, containing specific viral genes, which may be associated with 'core proteins', and which is surrounded by a protective protein coat. The coat may have functional protein appendages, and there may be present an 'envelope', rich in lipoprotein and glycoprotein. The virus possesses no energy-producing or protein-synthesizing machinery of its own. In order to reproduce, it must therefore become adsorbed to a host cell, be transported across the cell membrane, and uncoat in order that its viral genes may be expressed. The genome may require to be transported to the cytoplasm or the nucleus. The nuclear material must then be replicated, and the viral genes also transcribed into RNA (assuming that we are dealing with a DNA virus) and translated into virally specified protein. In addition to the coat protein, viral enzymes will be produced in this process, and these are vital for suborning the host cell's internal biochemistry to serve the requirements of the virus. Before the viral proteins can be made, a process of maturation of the viral mRNA molecules, involving guanylylation and methylation to produce a 'cap' structure containing 7-methylguanosine 5'-phosphate in a 5'- 5'-pyrophosphate structure at the 5'- end of the mRNA, must occur. Once the synthesis of the components needed to make fresh viral particles has been completed, maturation occurs, in which the nucleic acid and protein components are assembled to from the complete viral particle or virion, and finally this is released from the cell as a new , infective virus. RNA viruses require that their nucleic acid be replicated also, in order that new viral particles can form. Some RNA viruses code for an enzyme 'transcriptase' or 'replicase' (RNA-directed RNA polymerase), which replicates RNA strands directly without involving DNA[139] while others encode an enzyme 'reverse transcriptase' (RNA -directed DNA polymerase), which transcribes the RNA sequence into DNA-the reverse of the usual sequence which can subsequently become integrated into the host cell chromosome and is transcribed to from copies of the viral RNA.[140] Purine and pyrimidine antimetabolites which are active against viruses are thus most likely to be effective by inhibiting specifically the viral enzymes which are required to

replicate the viral nucleic acids, or inhibiting the viral enzymes responsible for transcription and capping of mRNA, without inhibiting the corresponding enzymes of the host cell.

Alternatively, incorporation of an antimetabolite into a viral nucleic acid causing the cessation of strand synthesis, or otherwise disturbing the normal function of the nucleic acid in replication or in directing protein synthesis, offers another way of preventing the replication of functional virus.[141] Again, it is important that the integrity of the nuclear material of the host cell should not be compromised. One therefore seeks to exploit the differences between the viral enzymes to the discomfiture of the virus.

5'- Amino-5-iodo-2',5'-dideoxyuridine(Aminoidoxuridine; 16) displays good antiherpes activity and is less cytotoxic than (15).[142,143] The phosphorylation of Aminoidoxuridine(16) is catalyzed specifically by virus-induced thymidine kinase, and thus Aminoidoxuridine(16) is only potentiated in virus-infected cells. It inhibits the synthesis of DNA in infected cells. The 5-bromo-, 5-chloro- and 5-trifluoro-methyl derivatives of 5'-amino-2',5'-dideoxyuridine also exhibit antiviral activity[144]. 5-Iodo-2'-deoxcytidine (17) and 5-bromo-2'-deoxycytidine (18) also show useful activity against herpes viruses and vaccinia with less cytotoxicity than the uridine compounds and more selective inhibition of virus replication.



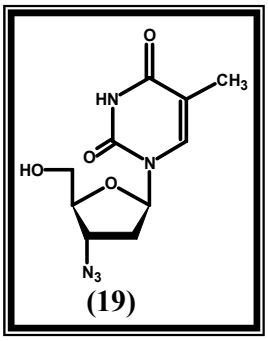
(13) **(14)** **(15) R= OH** **(16) R= NH2** **(17) X= I** **(18) X= Br**

Pyrimidines as Anti-HIV Agents

The strategy of designing nucleoside analogs that are selective for viral DNA polymerases is the most well-studied and successful approach to viral chemotherapy, and has led to the discovery of several clinically useful antiviral drugs. This strategy, however, has inherent limitations. Human DNA polymerases also required dNTP's and the chemical mechanisms of polymerization by the viral and human enzymes are similar. Nucleoside analogs often have significant host toxicity that is probably related to

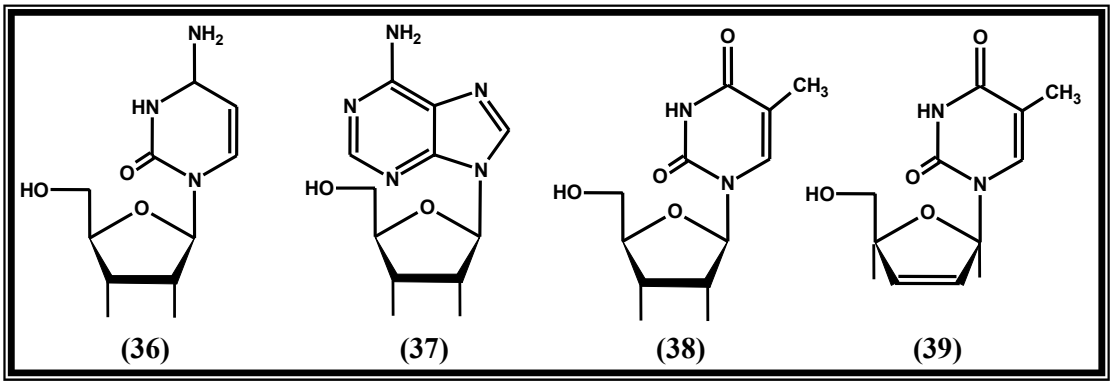
inhibition of host cell DNA synthesis. These compounds constitute the major class of antiviral drugs, and this approach is likely to yield additional active compounds in the near future. For the long term, however, other strategies may ultimately lead more selective agent within lower toxicity.

Obviously, the key to design analogue with a lower affinity for the host enzyme than the viral enzyme, which requires that there be structural differences between the enzyme active sites. For reverse transcriptase, the most well studied inhibitor is 3'-azido-3'-deoxythymidine (AZT; 19), which is currently used clinically to treat AIDS. [145,146]



(19)

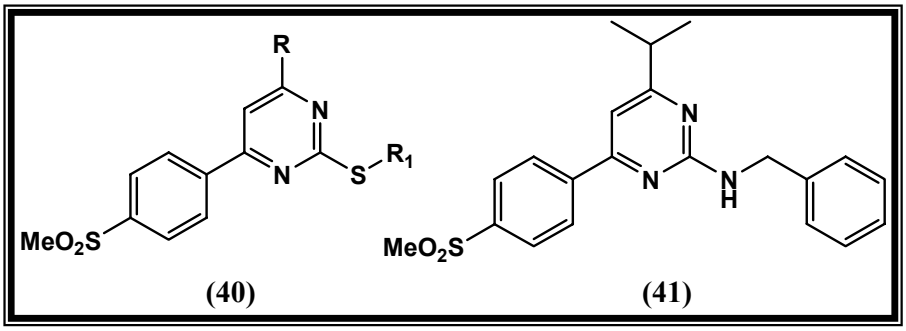
3'-azido-3'-deoxythymidine (AZT) inhibits HIV reverse transcriptase with an IC50 of 40nM[147], but is 100-300 times less active against mammalian DNA polymerase a and DNA polymerase g. The reason for this selectivity is not clear since 3'-azido-3'-deoxythymidine (AZT) is a chain terminator for mammalian DNA polymerases and inhibits normal cellular DNA synthesis.[148] Several other dideoxynucleoside analogs have been shown to be potent inhibitors of HIV replication *in vitro*.[149,150] In general, these compounds have the same mechanism of action as 3'-azido-3'-deoxythymidine (AZT), that is, intracellular conversion to the triphosphate derivative and subsequent inhibition of HIV reverse transcriptase. Some of these compounds are simply analogs of the natural 2'-deoxy- nucleoside in which the 3'-OH group has been replaced with a hydrogen, such as 2',3'-dideoxycytidine(20), 2',3'-dideoxyadenosine(21) and 2',3'-dideoxy thymidine(22). Other analogs contain a 2'-3' double bond, such as 2'3'-didehydro-2',3'-dideoxythymidine (23). Several related analogs with other modifications to the ribose ring or the heterocyclic base moiety have also been reported to have activity against HIV or HIV reverse transcriptase.[151,152]



(36) **(37)** **(38)** **(39)**

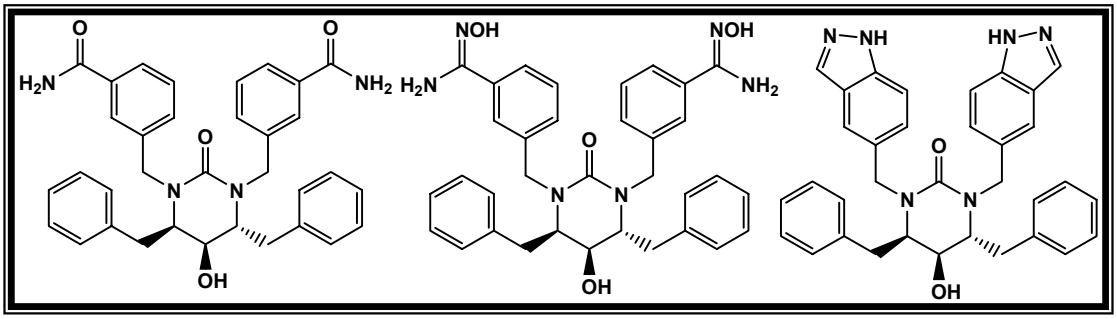
Recently, P. Khalili et al.[153] have carried out biochemical and pharmacokinetic evaluation of a novel nitric oxide donor pyrimidine nucleoside hybrid drug as a potential anticancer / antiviral agent. Rostom et al.[154] have synthesized and screened certain 2-(benzoxazol-2-yl-amino)-3*H*-4-oxopyrimidines for *in vitro* anti-HIV activity.

A family of trisubstituted pyrimidines has been described as selective COX-2 inhibitors. To explore the usefulness of pyrimidine derivatives as potential NSAIDs. Aurelio Orjales et al [155] have synthesized novel pyrimidine derivatives 40 and 41. *In vitro* biological evaluation of these compounds has provided information to determine the structural features necessary for COX-2 inhibitory activity.



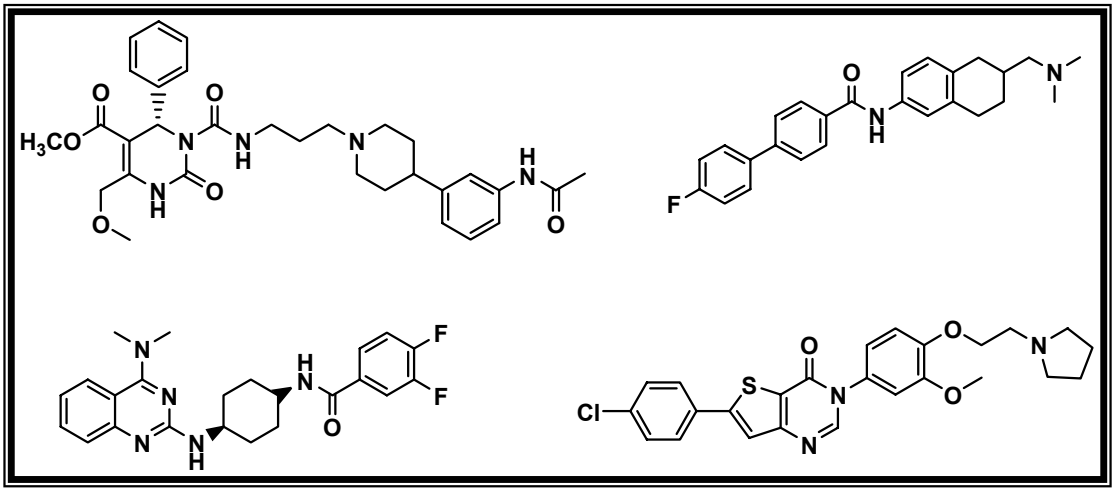
(40) **(41)**

George L. Trainor et al synthesized & reported cyclic urea derivatives as a HIV protease inhibitors. They describe the potency, efficacy, bioavailability, structure activity relationship of cyclic urea derivatives. Some of the cylic urea compounds depicted below, active against HIV protease inhibitors [156]



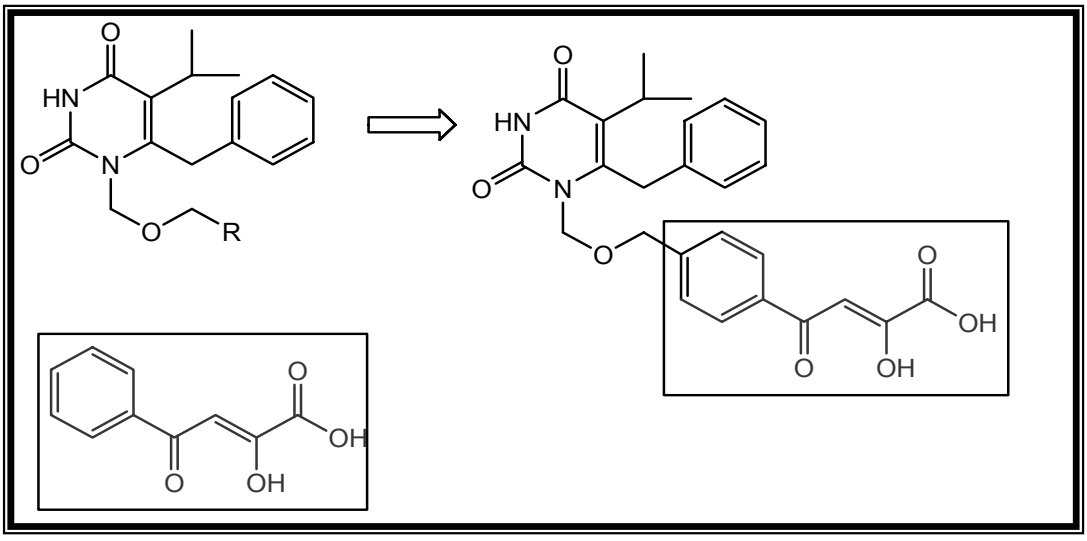
Pyrimidines as a Melanin-Concentrating Hormone 1 Receptor

Mohammad R. Marzabadi et al synthesized and carry out SAR Investigations for Novel Melanin-Concentrating Hormone 1 Receptor (MCH1) Antagonists. Melanin-concentrating hormone (MCH) is a cyclic peptide originally isolated from salmonid pituitaries, where it was named for its ability to cause aggregation of melanin within skin melanophores, resulting in skin lightening.[157] Mammals, MCH is a cyclic 19-amino acid neuropeptide that is produced predominantly by neurons in the lateral hypothalamus and zonaincerta, which project broadly throughout the brain.[158]Mammalian MCH is highly conserved between rat, mouse, and human species, exhibiting 100% amino acid identity.2 The biological function of MCH is mediated by two receptors, MCH1 receptor and MCH2 receptor, which have been identified in several species, including human, rhesus monkey, ferret, and dog; [159] however, functional MCH2 receptor has not been found in rat, mouse, hamster, guinea pig, or rabbit.[160] Recent reports have suggested that the MCH peptide plays a major role in regulation of food intake and stress in rodents.[161] For example, the central administration of MCH stimulates food intake, while fasting results in an increase in MCH expression.[162] Furthermore, mice lacking the gene encoding MCH are lean, hypophagic and maintain elevated metabolic rates.[163] In contrast, mice over expressing the MCH gene are susceptible to obesity and insulin resistance.[164] In addition, MCH seems to be an activator of the HPA stress axis.[165] These findings suggest that small-molecule antagonists of the MCH1 receptor can potentially be used in the treatment of obesity and mood disorders.[161] The high-throughput screening of Lund beck GPCR-directed compound collection identified dihydropyrimidines as a high affinity and selective MCH1 receptor antagonist. The *in vitro* and *in vivo* properties of dihydropyrimidines were described recently.[166] However, experience with dihydropyrimidines as a highly metabolized and hydrolyzed analog resulting in low bioavailability, as well as experience with previously described dihydropyrimidinone substituted compounds,[167] prompted a search for alternative templates to circumvent hydrolysis and metabolism issues.

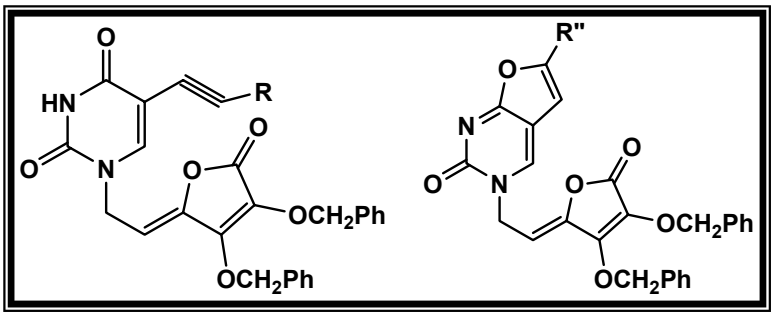


Pyrimidine as a HIV Reverse Transcriptase and Integrase

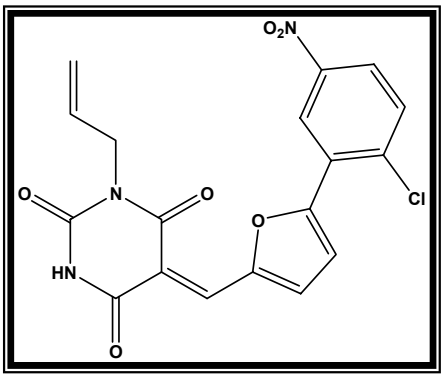
Robert Vince et al synthesized Dual Inhibitors of HIV Reverse Transcriptase and Integrase. Inhibitors of HIV RT and protease (PR) constitute the core of chemotherapy for AIDS treatment.[168] The therapeutic effect of nucleoside RT inhibitors (NRTIs) is greatly hampered by their intrinsic toxicity,[169, 170] whereas the less toxic protease inhibitors (PIs) and non-nucleoside RT inhibitors (NNRTIs) are severely compromised by the quick emergence of resistant viral strains.[171, 172] In general, disease resistant to a single-target therapy can be mitigated by developing multitarget therapies. In the case of AIDS, highly active antiretroviral therapy (HAART)[173] combines NRTIs with NNRTIs or PIs and successfully suppresses HIV viral load to an undetectable level, dramatically improving the life quality of AIDS patients.[174]



Silvana Raic´-Malic et al synthesized 5-Substituted Pyrimidine Furo[2,3-*d*]pyrimidine 4,5-Didehydro-L-ascorbic acid derivatives and carried out antiviral and cytostatic evaluations.[175]

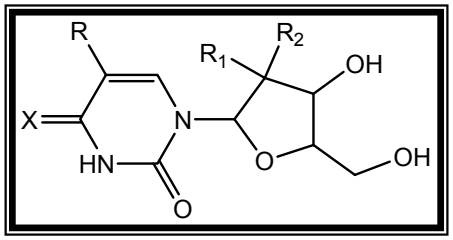


C. Erec Stebbins et al carried out Multiple Conformational Virtual Screening for the Discovery of *Yersinia* Protein Kinase A Inhibitors. *Yersinia* spp. is currently an antibiotic resistance concern and a re-emerging disease. The essential virulence factor *Yersinia* protein kinase A (YpkA) contains a Ser/Thr kinase domain whose activity modulates pathogenicity.[176]

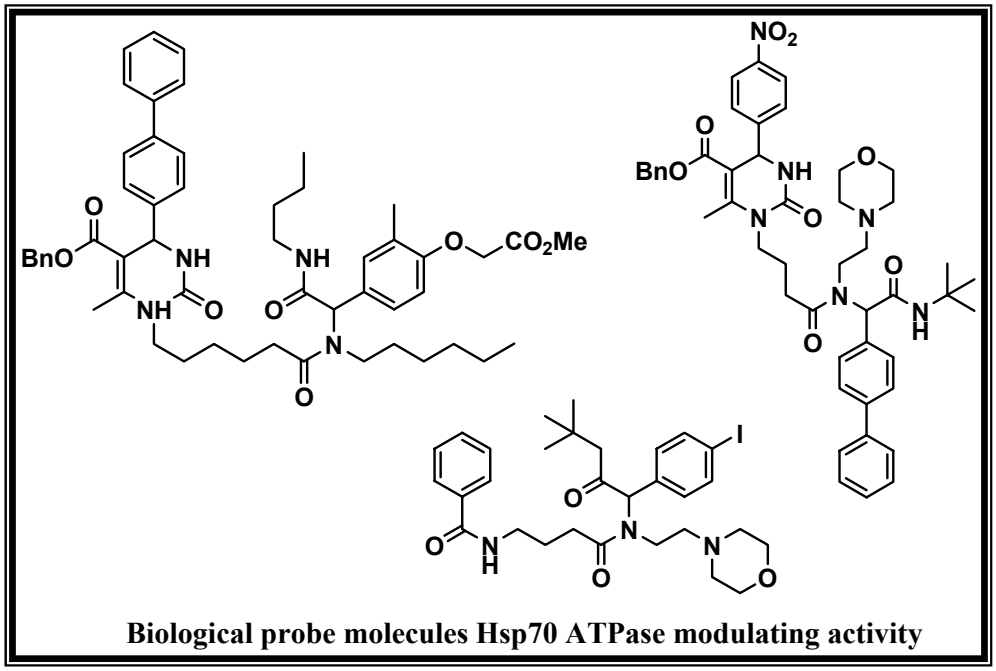


Mycobacterium tuberculosis (*M. tuberculosisa*), *Mycobacterium avium* (*M. avium*), and *Mycobacterium bovis* (*M. bovis*) are clinically significant species of the genus *Mycobacterium* that are causative agents of tuberculosis (TB), killing over 2-3 million people annually worldwide.[177] TB bacilli are highly contagious, airborne, slow-growing, gram-positive, aerobic, acidfast mycobacteria. The World Health Organization (WHO) estimates that between 1 and 2 billion people are latently infected with TB bacilli.[178-180] Approximately 8 million people develop active disease each year.[181] TB is the world's second most common cause of death from infectious disease, after acquired immuno deficiency syndrome (AIDS).[182] TB and human immunodeficiency virus (HIV) have formed a new and deadly combination. There is resurgence in the

incidence of TB in developed and developing countries with high rates of HIV-TB coinfection. The increase in TB incidence is strongly associated with the prevalence of HIV infection.[183] *M. tuberculosis* and *M. avium* pose a significant challenge to the clinical management of tuberculosis in HIV-infected patients and are often responsible for their death.[184] For both TB and HIV, misdiagnosis and noncompliance with treatment regimens further compound the problem and facilitate the development of drug resistance.[183, 185] A number of pyrimidine nucleoside derivatives in which the 2**'**-hydroxyl group has the opposite configuration (1-β-D-2**'**- arabinofuranosyl) to that of a ribonucleoside, exhibit potent antiviral, and anticancer properties.[186, 187]

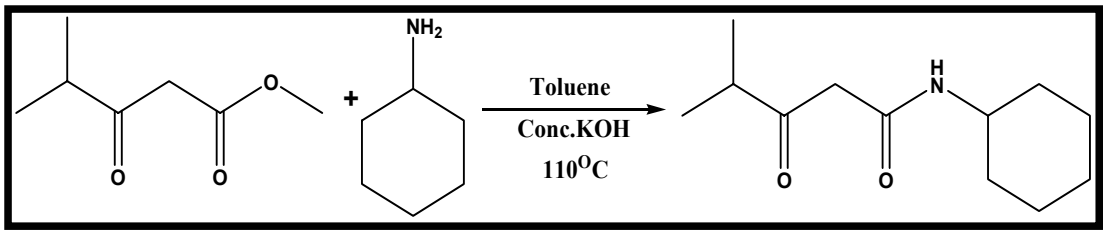


Peter Wipf et al generated focused library of 30 tetrahydropyrimidinone amides was prepared. The design was based on the structure of an Hsp70 modulator. This small library demonstrates the utility of tandem multi-component reactions in structure–activity relationship studies of biological lead molecules. The tandem Biginelli–Ugi multi component reaction facilitated the effective variation of four different substituents and allowed the synthesis of the library members in a sequence of only two one-pot reactions.[188]

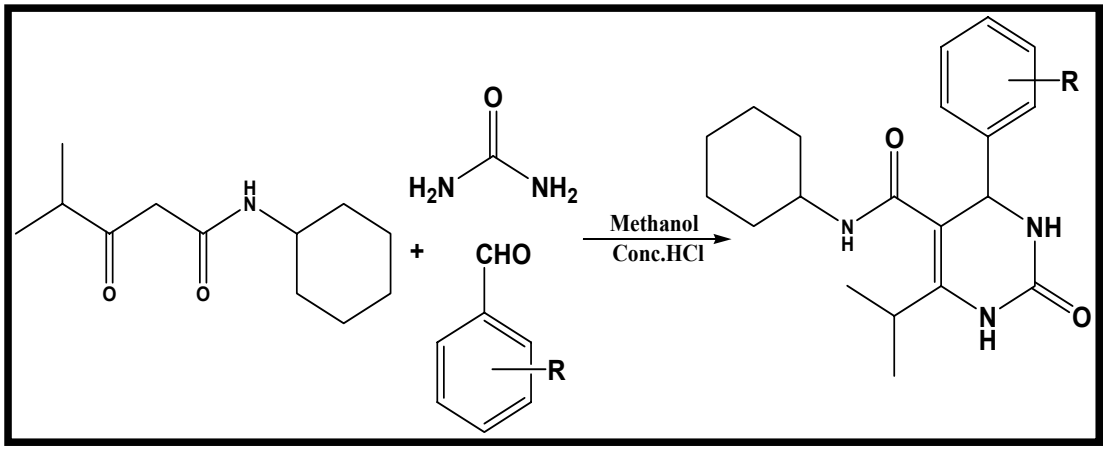


Reaction Scheme

Step-I



Step-II



Experimental procedure

Step-I

Preparation of N-Cyclohexyl-4-methyl-3-oxopentanamide

3.0 ml concentrated KOH solution in water was added into 23.6 ml (0.206mol) cyclohexylamine and stirred well until the clear solution was observed. 25 ml (0.175mol) methyl-4-methyl-3-oxo pentanoate was added into it, stirred for five minutes, exothermicity was observed. 150 ml toluene was added into it and refluxed for 6-7 hours, TLC was checked for the completion of the reaction, slight starting materials remain unreacted. Reaction mixture was cooled to room temperature, it was added into 250 ml 5% HCl solution, it was transferred into separating funnel, and toluene layer was collected. Toluene layer was again washed with 100 ml 5% HCl solution and twice with 100 ml of water and 50 ml Brine solution. Organic layer was collected, dried over anhydrous sodium sulphate. Solvent was distilled out by using rotavapor at 40^{o}C, Oily residue was observed. 50 ml Pet. Ether was added into it and kept in refrigerator, stirred well for 30 minutes at 20^{o}C. Pet. Ether was decanted. Again 50 ml Pet. Ether was added and scratched out at 20^{o}C. Solid product was separated; it was dried in an oven.

TLC System: (Hexane: Ethyl acetate)

8 : 2

Yield: 65% MP:-130-132^{O}C

Step-II

Preparation of N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxo-4-(Substituted) phenyl pyrimidine-5-carboxamide (General Method)

In 100 ml RBF 1.5 equivalent Urea and 15 ml of methanol was added and heated until clear solution was observed. It was cooled to room temperature. 1.0 equivalent of N-cyclohexyl-4-methyl-3-oxopentanamide and an aldehyde and 1-2 drops of Con. HCl was added into above solution and stirred for 6-7 hours at reflux temperature. In some cases solid products were obtained. It was filtered and washed twice with 20 ml of methanol. It was again purified by methanol at reflux temperature if needed. If solid product is not obtained, then reaction mixture was kept in a refrigerator for 5-6 hours. Solid product was separated 10 ml methanol was added into it and heated for 5 minutes. It was filtered and

washed twice with 10 ml of methanol. It was again purified by methanol at reflux temperature, if needed.

TLC System: (Chloroform: Methanol)

7 : 3

Yield: 57-72%

The physical data are given in table No. 3

Physical constants of N-cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxo-4-substitued phenylpyrimidine-5-carboxamides

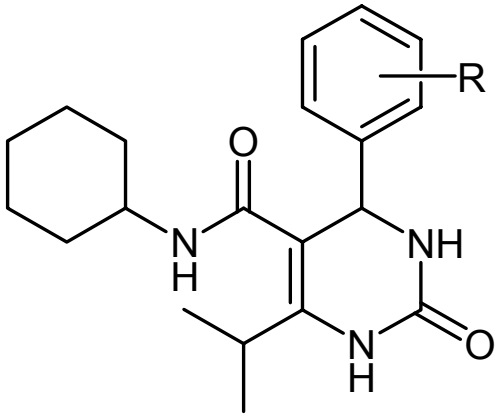


Table No. 3

Sr. No	Code.No	Substitution R	M.F	M.W	M.P	C, H , N Analysis		
						C	H	N
1	RK-4001	H	$C_{20}H_{27}N_3O_2$	341.45	141-143	65.61 (65.64)	6.29 (6.21)	21.86 (21.80)
2	RK-4002	4-SCH3	$C_{21}H_{29}N_3O_2S$	387.53	145	59.58 (59.50)	6.00 (5.92)	18.53 (18.42)
3	RK-4003	4-OCH_3	$C_{21}H_{29}N_3O_3$	371.47	137-139	62.92 (62.81)	6.34 (6.30)	19.57 (19.51)
4	RK-4004	2-Cl	$C_{20}H_{26}ClN_3O_2$	375.89	151-152	57.83 (57.71)	5.20 (5.40)	19.27 (19.11)
5	RK-4005	3-Br	$C_{20}H_{26}BrN_3O_2$	420.34	158-159	50.16 (50.11)	4.51 (4.56)	16.71 (16.69)
6	RK-4006	2-NO_2	$C_{20}H_{26}N_4O_4$	386.44	143-145	55.81 (55.78)	5.02 (4.99)	23.24 (23.19)

Table No. 3

Sr. No	Code.No	Substitution R	M.F	M.W	M.P	C, H , N Analysis		
						C	H	N
7	RK-4007	4-NO_2	$C_{20}H_{26}N_4O_4$	386.44	158-160	55.81 (55.78)	5.02 (5.05)	23.24 (23.18)
8	RK-4008	3-Cl	$C_{20}H_{26}ClN_3O_2$	375.89	131-133	57.83 (57.80)	5.20 (5.18)	19.27 (19.25)
9	RK-4009	3-NO_2	$C_{20}H_{26}N_4O_4$	386.44	166-068	55.81 (55.78)	5.02 (5.07)	23.24 (23.19)
10	RK-4010	2-OCH_3	$C_{21}H_{29}N_3O_3$	371.47	135-137	62.92 (62.90)	6.34 (6.31)	19.57 (19.52)
11	RK-4011	4-Cl	$C_{20}H_{26}ClN_3O_2$	375.89	143-145	57.83 (57.80)	5.20 (5.24)	19.27 (19.25)
12	RK-4012	3-OCH_3	$C_{21}H_{29}N_3O_3$	371.47	139-141	62.92 (62.94)	6.34 (6.31)	19.57 (19.59)
13	RK-4013	3,4-di OCH_3	$C_{16}H_{20}N_4O_3$	316.35	157-159	60.75 (60.71)	6.37 (6.41)	17.71 (17.72)
14	RK-4014	3,4,5-tri OCH_3	$C_{17}H_{22}N_4O_4$	346.38	165-166	58.95 (58.92)	6.40 (6.42)	16.17 (16.20)
15	RK-4015	3-OPh	$C_{20}H_{20}N_4O_2$	348.4	178-179	68.95 (68.93)	5.79 (5.83)	16.08 (16.11)
16	RK-4016	2-OH	$C_{14}H_{16}N_4O_2$	272.3	150-152	61.75 (61.72)	5.92 (5.90)	20.58 (20.61)
17	RK-4017	3,4 di OH	$C_{14}H_{16}N_4O_3$	288.3	169-171	58.32 (58.30)	5.59 (5.57)	19.43 (19.48)

Spectral discussion

^{1}H NMR spectral study

^{1}HNMR of the synthesized N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxo-4-substitued phenylpyrimidine-5-carboxamides were recorded on DPX-300MHz FT-NMR spectrophotometer (Bruker) instrument using TMS (Tetramethyl silane) as an internal reference standard in DMSO-D_6 solvent. Numbers of proton identified from NMR spectrum and their chemical shift (δ ppm) were in agreement of structure of molecule. Isopropyl methine (-CH) proton gave a multiplet at 2.9-3.4 δ ppm. Both methyl groups of isopropyl chain protons gave a multiplet at 0.8-1.6 δ ppm and merge with cyclohexyl's methelyne protons as cyclohexyl proton gave a multiplet in the range of 0.8-1.6 δ ppm. The proton on C_4 carbon atom gave a singlet in range of 5.12-5.80 δ ppm. Aromatic protons were observed between 6.7-7.8 δ ppm. J values were calculated to identify ortho and meta coupling. In some typical cases, aromatic protons were obtained as multiplet. Singlet observed for the (–NH) proton attached to cyclohexyl ring & both cyclic (–NH) were gave a in the aromatic ring at 6.8-7.8 δ ppm. (For further details see individual compound Spectral data and ^{1}H NMR Spectrum)

^{13}C NMR Spectral study

^{13}C NMR spectra of synthesized N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxo-4-substitued phenylpyrimidine-5-carboxamides were recorded on Bruker 400MHz instrument using DMSO-d_6 as the solvent with tetramethylsilane (TMS) as the respective internal standard. The chemical shifts were recorded in ppm. Numbers of carbon present in the parent molecules investigate are comparable with the experimental and ^{13}C spectral evidences. The carbon C_4(Asymmetric) of pyrimidine ring appear around 45-50 and carbon of the cyclohexyl ring which attached to the –NH is appears around 43-70 δ ppm. The both methyl group of isopropyl chain show around 18-23 δ ppm. In such cases, two the methyl group show single peak, instead of two different peaks. Quaternary carbon atom of the pyrimidine nucleolus appears between 100-105 δ ppm. The aromatic carbon atoms of the phenyl ring appear around 124-145 δ ppm. The carbonyl carbon of the cyclic ketone appears at 148-153 δ ppm and ketone of the amide linkage is 159-165 δ ppm.

DEPT 135

The presence of all five methylene groups, two methyl groups and methine are also confirmed by DEPT-135 experiment of the selected compounds.

Mass spectral study

Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe Technique. The molecular ion peak was found in agreement with molecular weight of the respective compound. DHPMs having chlorine atom showed characteristic M^{+2} peak. Characteristic M^{+2} ion peaks with one-third intensity of molecular ion peak were observed in case of compounds having chlorine atom. In some cases M-14, M-28, M-42 peaks were observed due to the cleavage of the cyclohexyl ring present in parent DHPMs. Fragmentation pattern and mass values are for each compound summarized below.

1. Cleave of C-N bond (adjacent bond to C=O bond at carbamoyl side chain at C-5 position) gave intense peak in each spectrum.
2. Cleavage of methyl group at C-6 position from above fragment gave characteristic peak at m/e value less than 15.
3. Cleavage at chiral carbon of DHPMs, which gives substituted phenyl derivatives peak.
4. In some cases bond breaking between C=O and C-5 position of the DHPMs gave peak at M-112.

IR spectral study

Different functional groups present in the molecule were identified by distinguishing frequency obtained by their functional groups. Presence of two carbonyl groups is confirmed by IR spectra as two different carbonyl stretching frequencies were observed. Cyclic C=O group peak was observed between 1680-1710 cm^{-1} while another C=O group due to amide linkage (NH-CO-) was observed between 1650-1680 cm^{-1}. Two N-H groups gave peaks between 3210-3380 cm^{-1}. Cyclohexyl $–CH_2$ appeared as per their characteristics between 2860-2945 cm^{-1}. Substitution at the phenyl ring i.e. nitro, hydroxyl, chloro, methoxy, fluoro etc. gave bands characteristic as per their characteristic. (**For further details see individual Spectral data**)

Elemental analysis

Elemental analysis of the synthesized compounds was carried out Elementar Vario EL III Carlo Erba 1108 model at CDRI, Lucknow and result calculated for percentage values of carbon, hydrogen and nitrogen in support of structure of synthesized compounds. The spectral and elemental analysis data are given in Physical data table of individual compounds.

Spectral Data

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxo-4-phenylpyrimidine-5- carboxamide (RK-4001)

IR (KBr Disc): 3355.25cm^{-1}(-NH), 3271cm^{-1}(-NH), 2936-2966(C-H, alkyl), 1450-1550cm^{-1}(-C=C) 1708.99 cm^{-1}(-CO-NH, cyclic), 1647cm^{-1} ((-CO-NH)

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-4-(4-(methylthio)phenyl)-2-oxopyrimidine-5-carboxamide (RK-4002)

^{13}C NMR (400 MHz, $CDCl_3$): δ 165.16, 155.01, 137.14, 136.56, 135.08, 129.94, 127.93, 125.67, 124.72, 71.33, 57.73, 51.51, 47.45, 46.21, 31.16, 24.92, 24.08, 19.58, 16.48, 15.54, 14.81

IR (KBr Disc): 3344.68cm^{-1}(-NH), 2854-2931(C-H), 1710.92 cm^{-1}(-C=O) 1675cm^{-1} (-CO-NH), 1599 cm^{-1} (-NH Bend), 1450-1550 cm^{-1} (C=C)1170-1211 cm^{-1} (C-S-C),

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-4-(4-methoxyphenyl)-2-oxopyrimidine-5 –carboxamide (RK-4003)

IR (KBr Disc): 3350.46cm^{-1}(-NH), 2854-2933(C-H), 1708 cm^{-1}(-C=O, cylic) 1643.41 cm^{-1}(-CO-NH), 1450-1550 cm^{-1} (C=C), 1247cm^{-1} (C-O-C)

4-(2-Chlorophenyl)-N-cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxopyrimidine--5-carboxamide (RK-4004)

^{1}H-NMR (300 MHz, DMSO-d_6):δ 0.9-1.3 (m, 11H, *J*=10.84 Hz{Average}), 1.4-1.56 (m, 6H), 2.9-3.09 (m, 1H), 5.59 (s, 1H), 7.00 (s, 1H), 7.14-7.65 (m, 5H), 8.14 (s, 1H)

IR (KBr Disc): 3421.83cm^{-1}(-NH), 2862-2935(C-H), 1691.63 cm^{-1}(-C=O, cylic) 1668 cm^{-1}(-CO-NH), 1450-1550 cm^{-1} (C=C), 758.05 cm^{-1} (C-Cl)

4-(3-Bromophenyl)-N-cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxopyrimidine-5-carboxamide (RK-4005)

^{13}C NMR (400 MHz, $CDCl_3$): δ 165.43, 153.04, 145.53, 143.14, 130.00, 129.73, 129.15, 124.84, 121.82, 103.84, 55.59, 47.47, 32.05, 31.94, 27.87, 24.81, 24.23, 19.28, 19.09

^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.87-1.10 (m, 11H), 1.2-1.4 (m, 3H), 1.49-1.59 (m, 3H), 3.45 (Broad Peak, 1H), 5.18 (s, 1H), 7.2-7.3 (m, 2H), 7.37-7.41 (m, 4H), 8.18 (s, 1H)

IR (KBr Disc): 3284.88cm^{-1}(-NH), 2864-2933(C-H), 1693.56 cm^{-1}(-C=O) 1666 cm^{-1} (-CO-NH), 1558-1600 cm^{-1} (-NH Bend), 550-556 cm^{-1} (C-Br)

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-4-(2-nitrophenyl)-2-oxopyrimidine-5-carboxamide (RK-4006)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.98-1.15 (m{Broad Peak}, 11H), 1.45-1.60 (m, 6H), 3.02 (m, 1H), 5.78 (s, 1H), 7.07 (s, 1H), 7.19 (d, 1H, *J*=13.91 Hz), 7.49 (t, 1H) 7.60 (d, 1H, *J*=6.47 Hz) 7.70 (t, 1H), 7.85 (d, 1H, *J*=7.30 Hz), 8.27 (s, 1H)

IR (KBr Disc): 3279.10cm^{-1}(-NH), 1693.56cm^{-1}(-C=O) 1647.27 cm^{-1}(-CO-NH), 1599 cm^{-1} (-NH Bend), 1448-1480 cm^{-1}(C=C), 1150 cm^{-1}(C-NO_2), 650 cm^{-1}(-NO_2 bend)

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-4-(4-nitrophenyl)-2-oxopyrimidine-5-carboxamide (RK-4007)

IR (KBr Disc): 3261.74cm^{-1}(-NH), 2856-2933 cm^{-1}(C-H), 1708.94 cm^{-1}(-C=O) 1646cm^{-1}(-CO-NH), 1545 cm^{-1} (-NH Bend), 1150 cm^{-1}(C-NO_2), 650 cm^{-1}(-NO_2 bend)

4-(3-Chlorophenyl)-N-cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxopyrimidine-5-carboxamide (RK-4008)

^{13}C NMR (400 MHz, $CDCl_3$): δ 165.46, 153.08, 145.19, 143.12, 133.57, 129.44, 127.15, 126.26, 124.39, 103.97, 55.08, 47.48, 32.05, 31.96, 27.90, 24.81, 24.22, 19.29, 19.12

IR (KBr Disc): 3281.02cm^{-1}(-NH), 2854-2946(C-H), 1693 cm^{-1}(-C=O) 1666.51 cm^{-1}(-CO-NH), 750 cm^{-1} (C-Cl)

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-4-(3-nitrophenyl)-2-oxopyrimidine-5-carboxamide (RK-4009)

^{13}C NMR (400 MHz, $CDCl_3$): δ 166.84, 165.38, 153.19, 147.67, 145.31, 144.27, 143.95, 132.65, 131.71, 129.02, 121.88, 121.72, 121.26, 120.03, 112.28, 103.56

IR (KBr Disc): 3399.83cm^{-1}(-NH), 2856-2933 cm^{-1}(C-H), 1718 cm^{-1}(-C=O, cyclic) 1672cm^{-1}(-CO-NH), 1545 cm^{-1} (-NH Bend), 1136 cm^{-1}(C-NO_2), 590 cm^{-1}(-NO_2 bend)

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-4-(2-methoxyphenyl)-2-oxopyrimidine-5-carboxamide (RK-4010)

IR (KBr Disc): 3270cm^{-1}(-NH), 2862-2937(C-H), 1697.77 cm^{-1}(-C=O, cylic) 1688.48 cm^{-1}(-CO-NH), 1450-1550 cm^{-1} (C=C), 1125cm^{-1} (C-O-C)

4-(4-Chlorophenyl)-N-cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxopyrimidine -5-carboxamide (RK-4011)

IR (KBr Disc): 3271cm^{-1}(-NH), 2884-2933(C-H), 1708.99 cm^{-1}(-C=O) 1647 cm^{-1}(-CO-NH), 1545 cm^{-1} (-NH Bend), 705 cm^{-1} (C-Cl)

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-4-(3-methoxyphenyl)-2-oxopyrimidine-5-carboxamide (RK-4012)

IR (KBr Disc): 3450.48cm^{-1}(-NH), 2823-2945(C-H), 1711 cm^{-1}(-C=O, cylic) 1676.52 cm^{-1}(-CO-NH), 1450-1550 cm^{-1} (C=C), 1186.21cm^{-1} (C-O-C)

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-4-(3,4-dimethoxyphenyl)-2-oxopyrimidine-5-carboxamide (RK-4013)

IR (KBr Disc): 3350.24cm^{-1}(-NH), 2870-2978(C-H), 1705.23 cm^{-1}(-C=O,cylic) 1674.52 cm^{-1}(-CO-NH), 1440-1580 cm^{-1} (C=C), 1158-1185cm^{-1} (C-O-C)

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-4-(3,4,5-trimethoxyphenyl)-2-oxopy rimidine-5-carboxamide (RK-4014)

IR (KBr Disc): 3325cm^{-1}(-NH), 2823-2945(C-H), 1699.98 cm^{-1}(-C=O, cylic) 1666.3 cm^{-1}(-CO-NH), 1450-1550 cm^{-1} (C=C), 1140-1186.21cm^{-1} (C-O-C)

N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxo-4-(3-phenoxyphenyl)pyrimidine-5-carboxamide (RK-4015)

IR (KBr Disc): 3339.48cm^{-1}(-NH), 2810-2943(C-H), 1701.08 cm^{-1}(-C=O, cylic) 1676.52 cm^{-1}(-CO-NH), 1443-1552 cm^{-1} (C=C), 1086-1120cm^{-1} (C-O-C)

N-Cyclohexyl-1,2,3,4-tetrahydro-4-(2-hydroxyphenyl)-6-isopropyl-2-oxopyrimidine-5-carboxamide (RK-4016)

IR (KBr Disc): 3438cm^{-1}(-OH), 3340cm^{-1}(-NH), 2825-2945(C-H), 1698 cm^{-1}(-C=O) 1663.36 cm^{-1}(-CO-NH), 1540-1559 cm^{-1} (-NH Bend)

N-Cyclohexyl-1,2,3,4-tetrahydro-4-(3,4-dihydroxyphenyl)-6-isopropyl-2-oxopyri -midine-5-carboxamide (RK-4017)

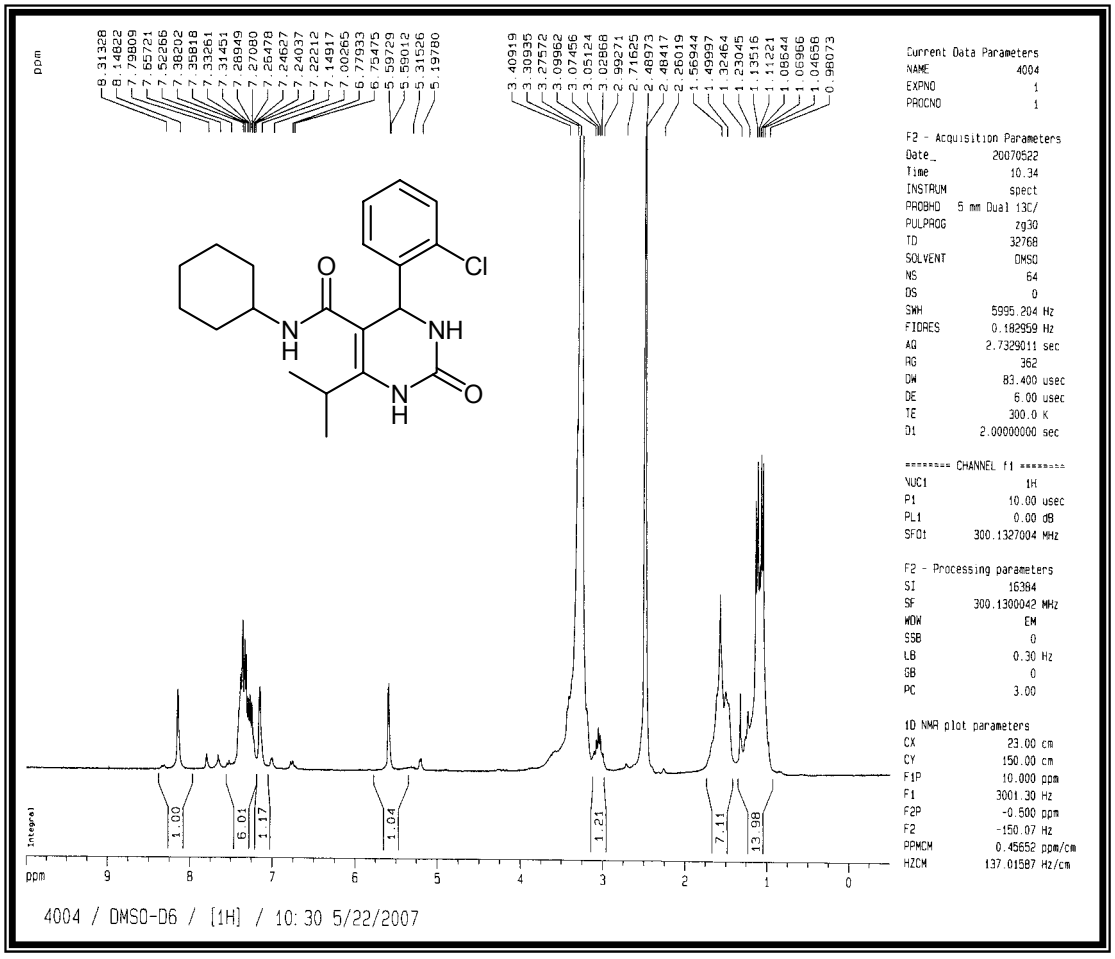
IR (KBr Disc): 3522cm^{-1}(-OH), 3339cm^{-1}(-NH), 2830-2977(C-H), 1687 cm^{-1}(-C=O) 1678 cm^{-1}(-CO-NH), 1529 cm^{-1} (-NH Bend)

m/z Mass values of N-Cyclohexyl-1,2,3,4-tetrahydro-6-isopropyl-2-oxo-4-substitued phenylpyrimidine-5-carboxamides

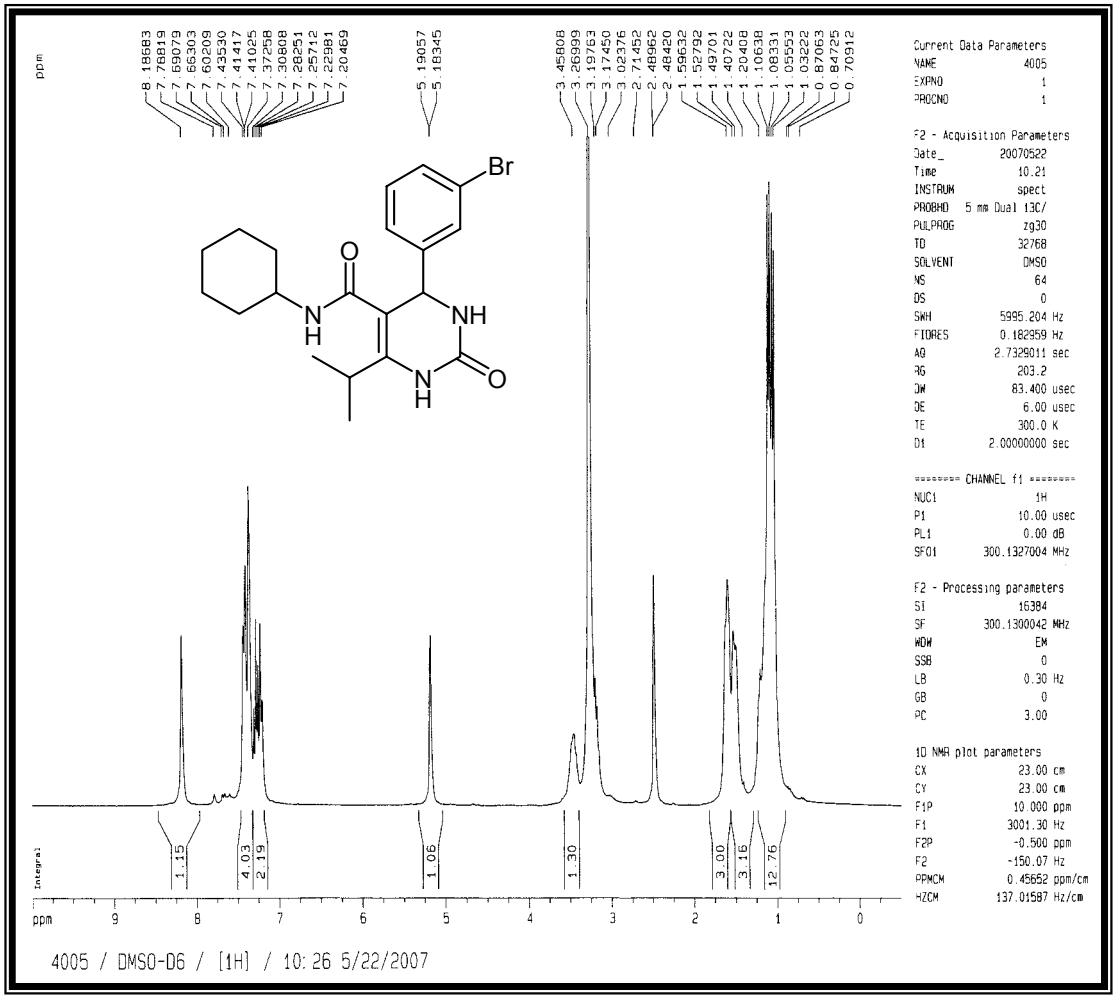
Compound Code. No	(m/z) Relative intensity
RK-4001	341 (15%)
RK-4002	387 (08%)
RK-4003	371-28 (10%)
RK-4004	375 (09%)
RK-4005	420-42 (05%)
RK-4006	386 (06%)
RK-4007	386 (13%)
RK-4008	375 (12%)
RK-4009	386 (11%)
RK-4010	371 (07%)
RK-4011	375 (10%)
RK-4012	371 (13%)
RK-4013	316-14 (28%)
RK-4014	346 (12%)
RK-4015	348 (11%)
RK-4016	272 (09%)
RK-4017	288 (08%)

Spectra of the Representative compounds

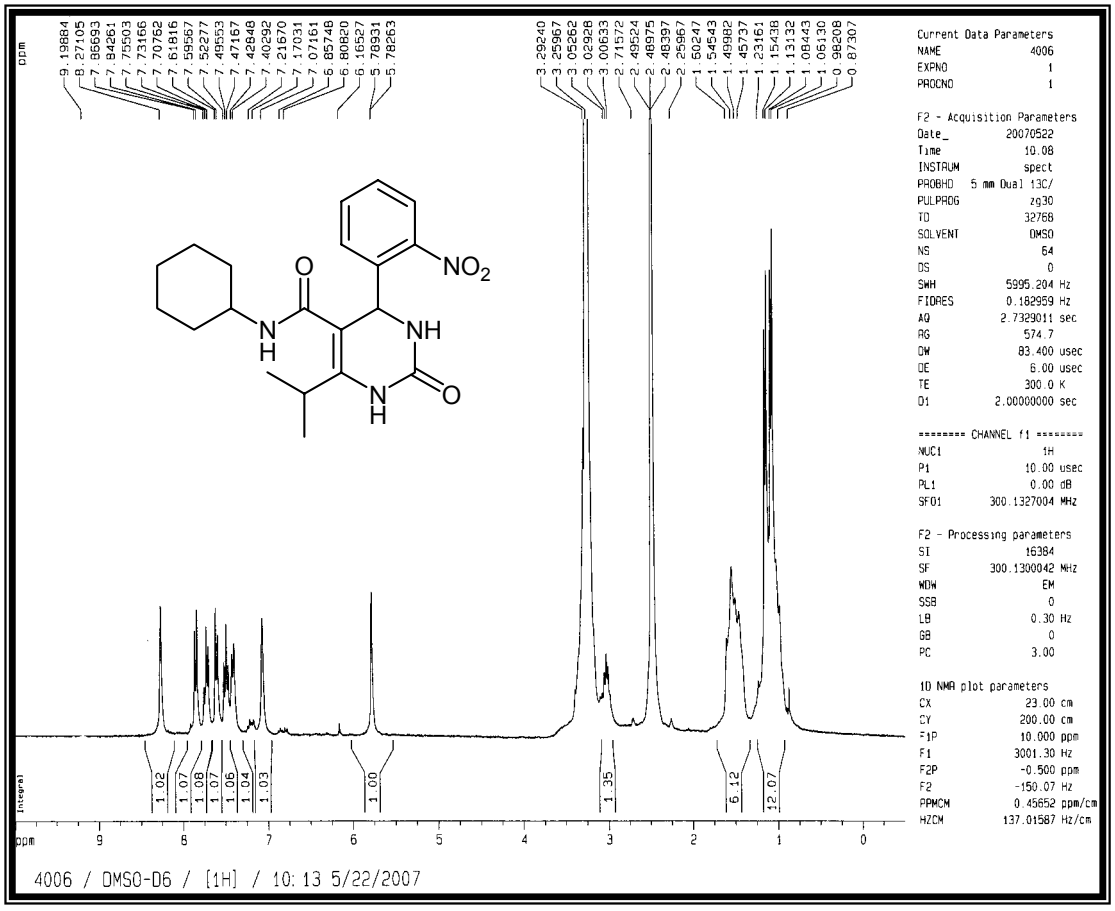
[a] ^{1}H NMR Spectra of RK-4004



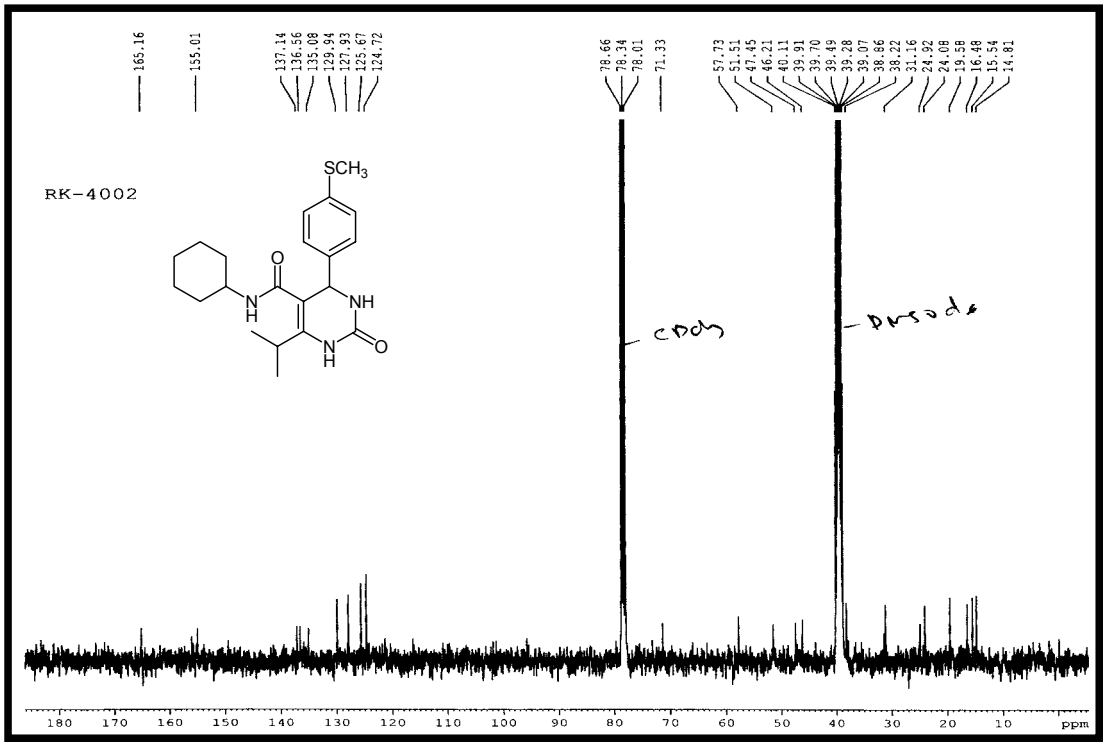
[b] ^{1}H NMR Spectra of RK-4005

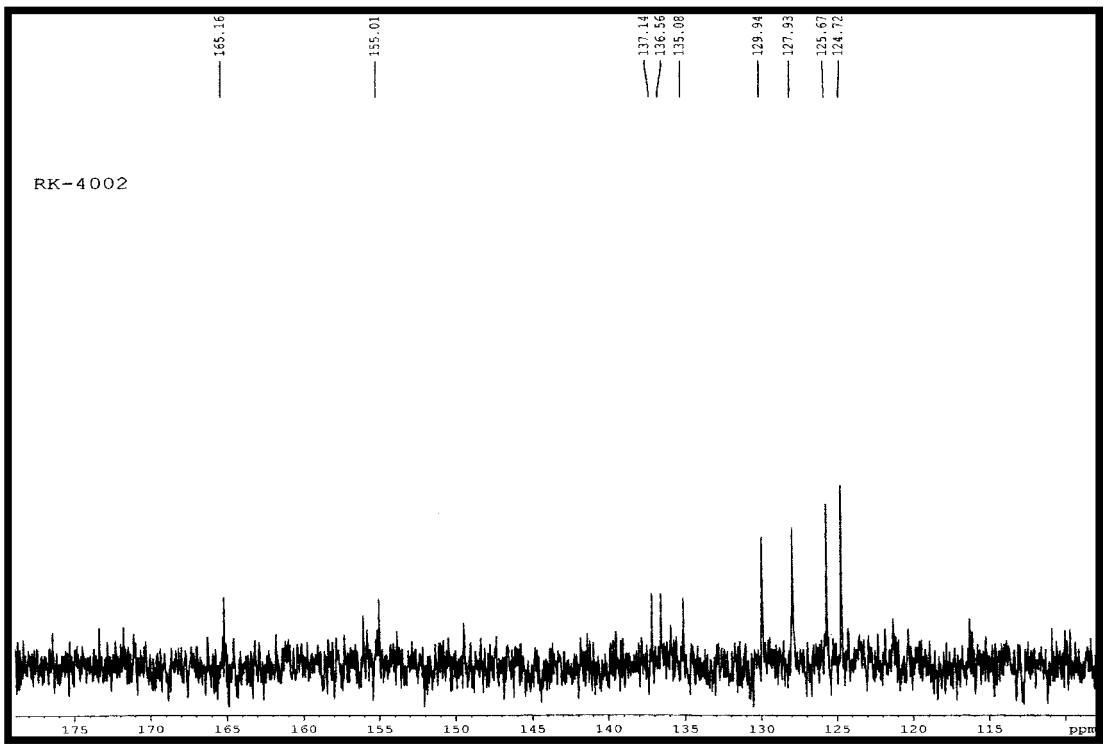


[c] ^{1}H NMR Spectra of RK-4006

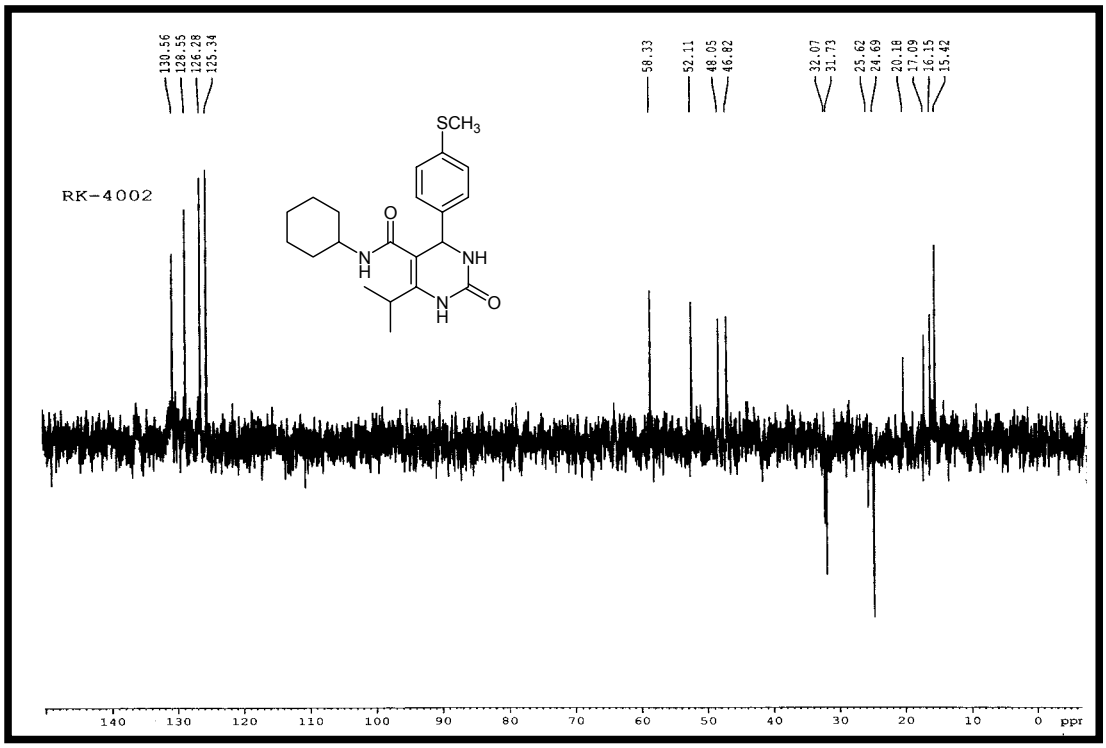


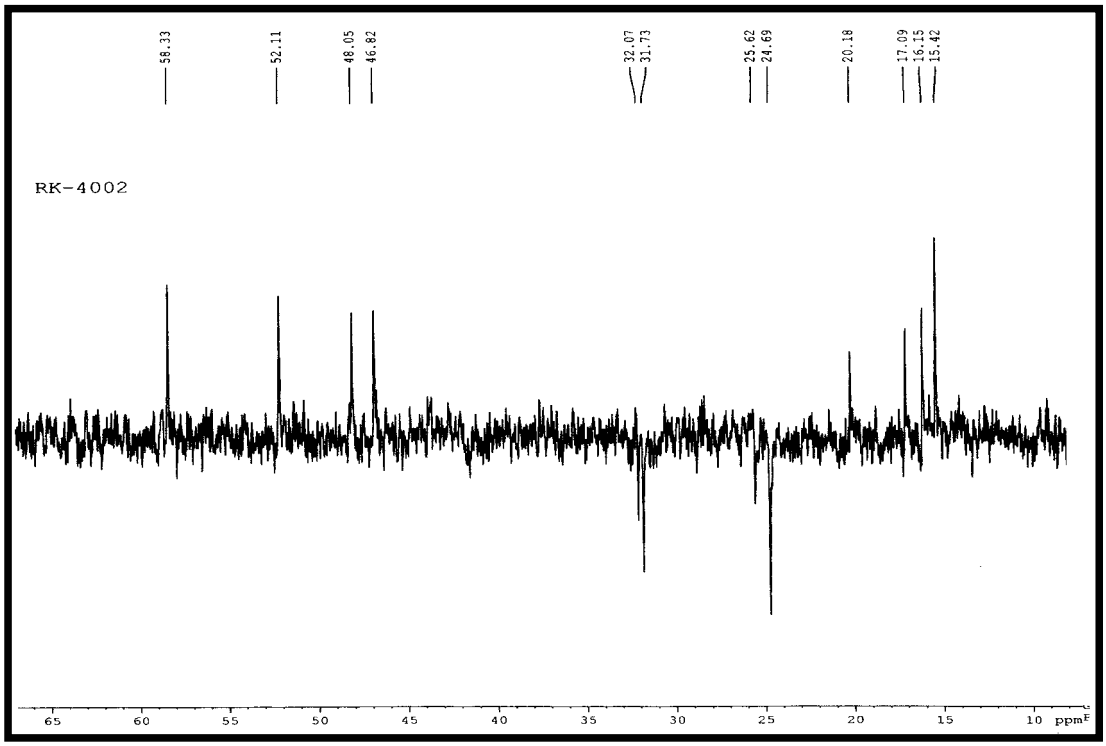
[d] ^{13}C NMR of RK-4002



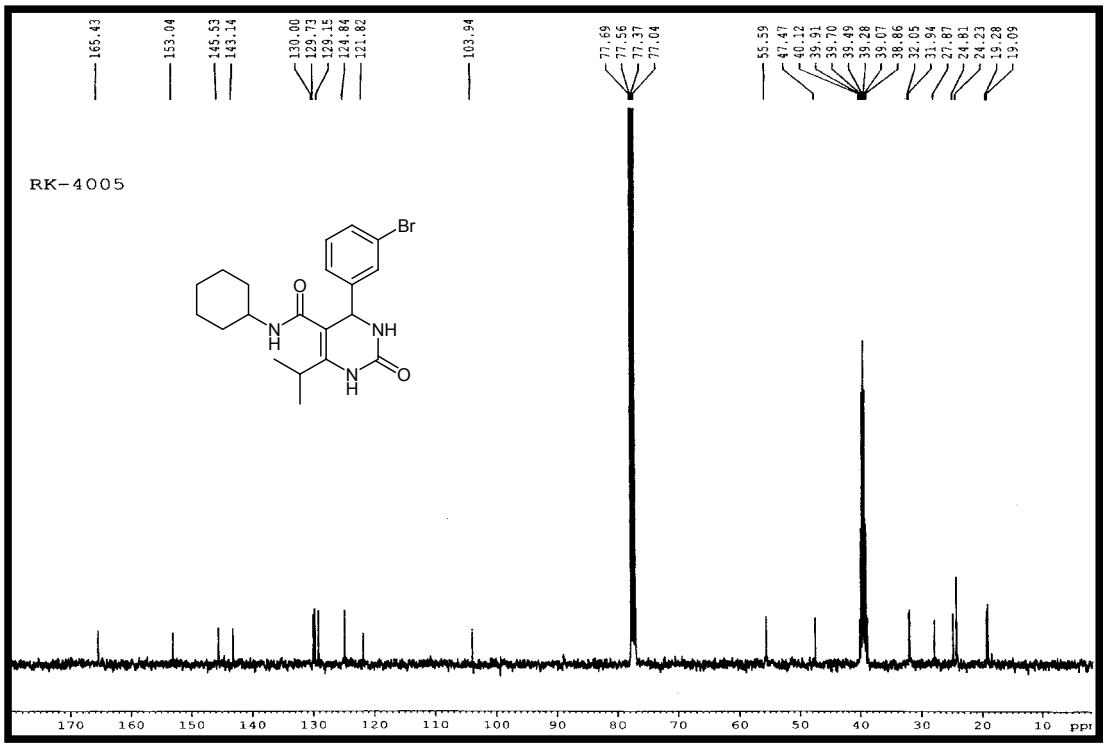


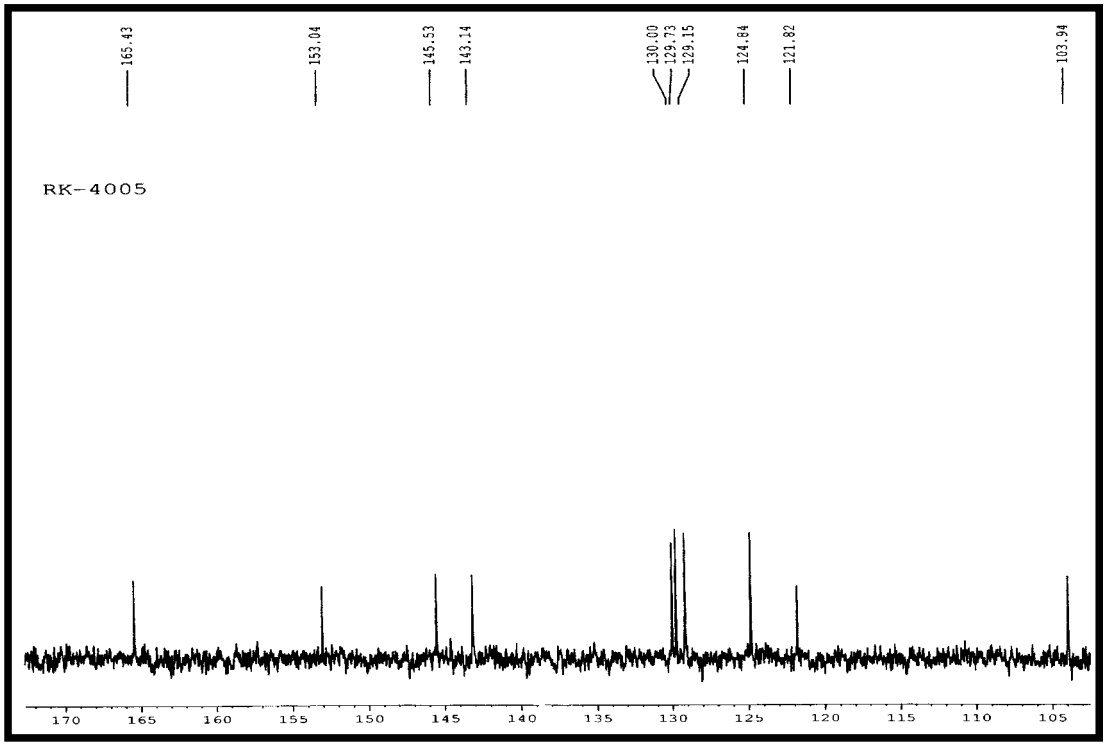
[e] ^{13}C DEPT at 135 of RK-4002 for identification of methylene proton



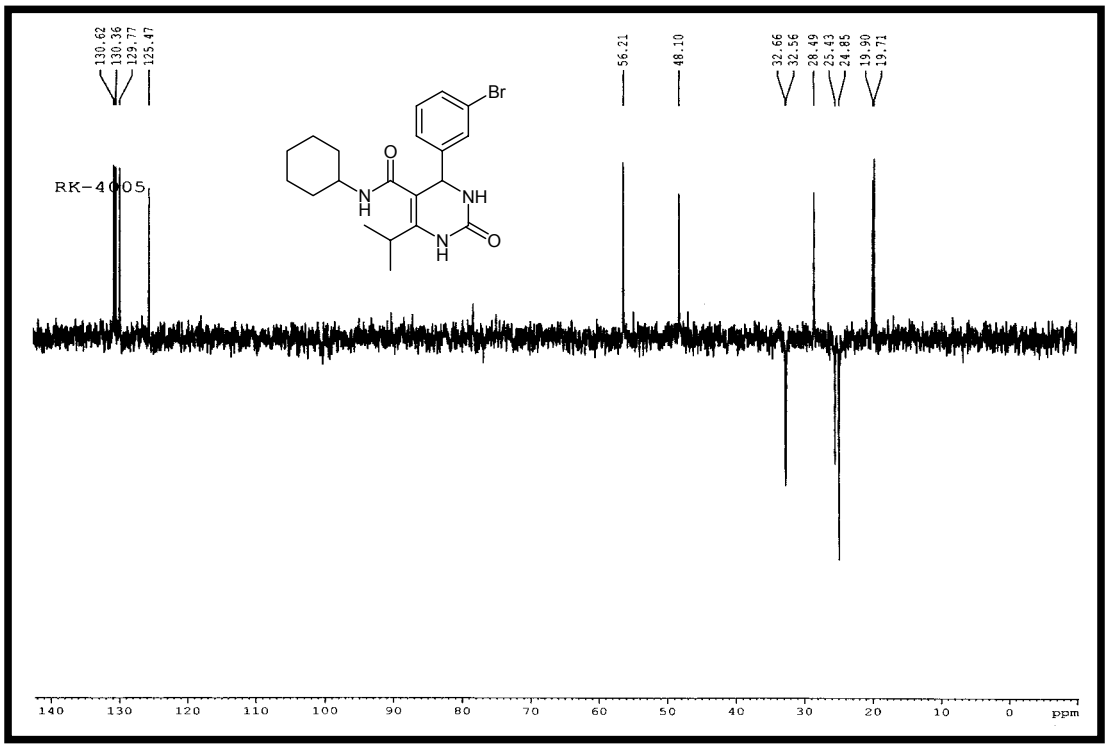


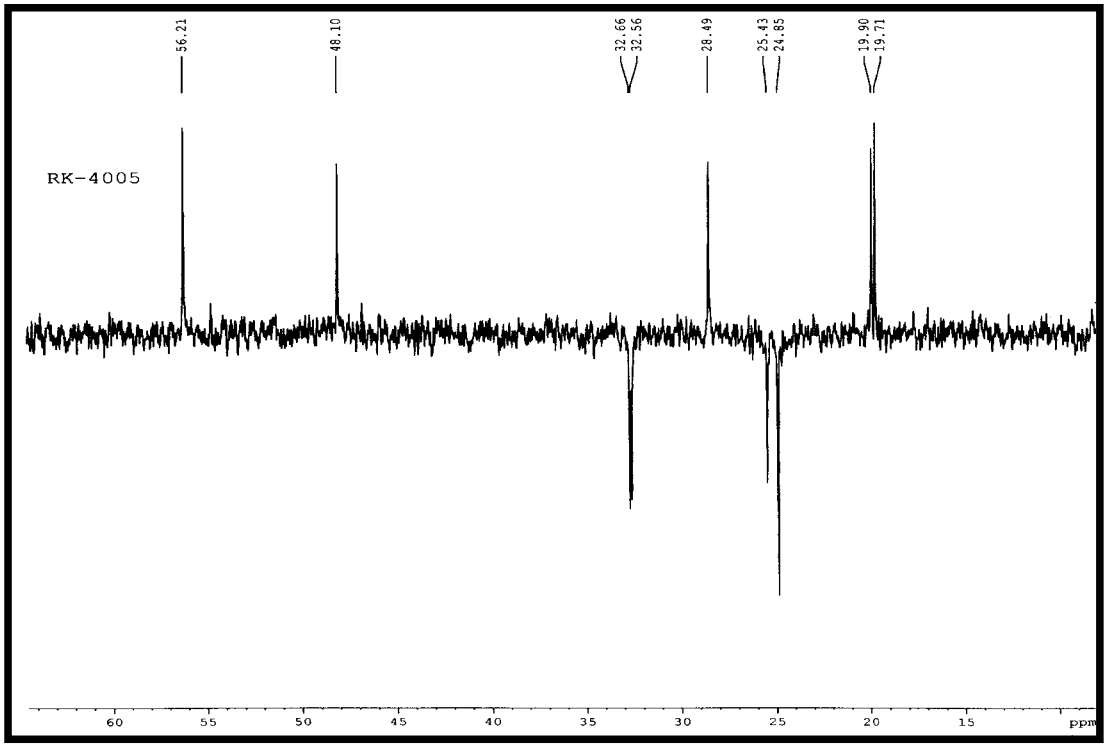
[f] ^{13}C NMR of RK-4005



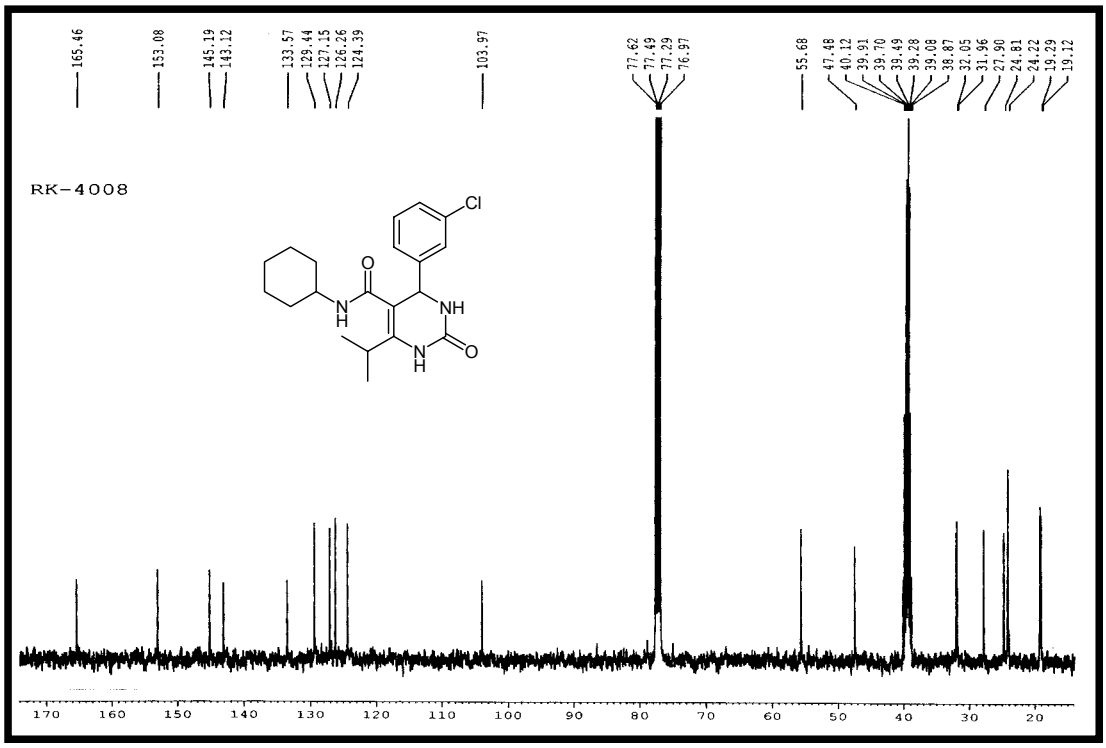


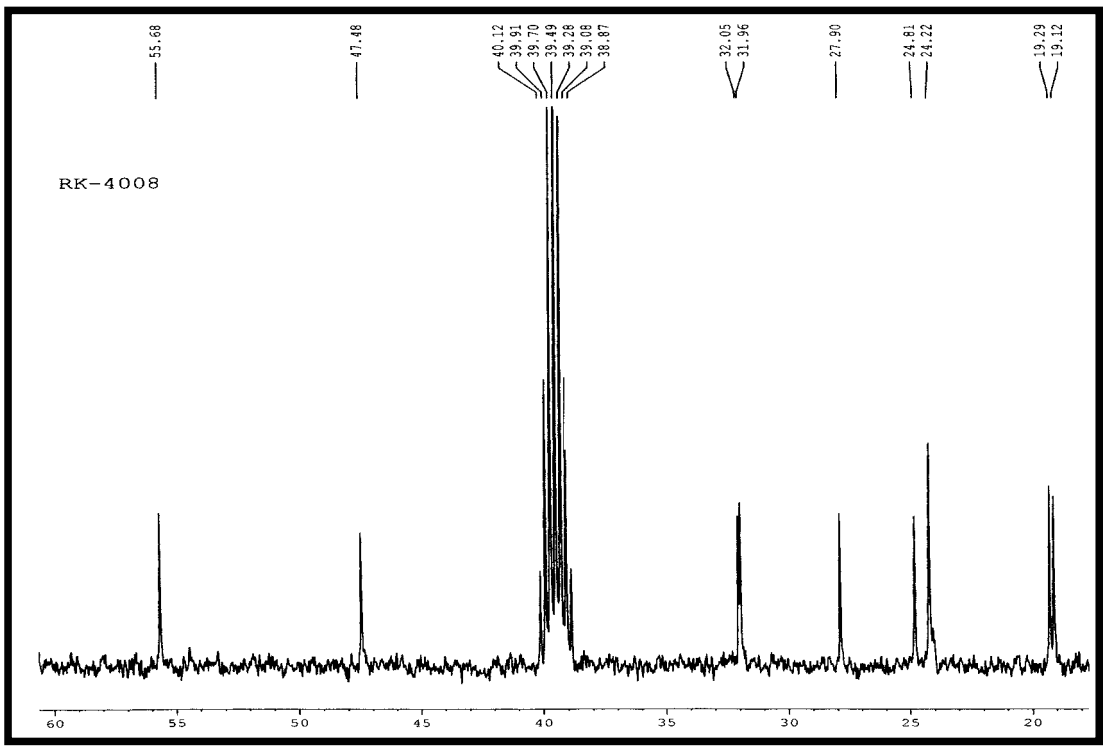
[g] ^{13}C DEPT at 135 of RK-4005 for identification of methylene proton



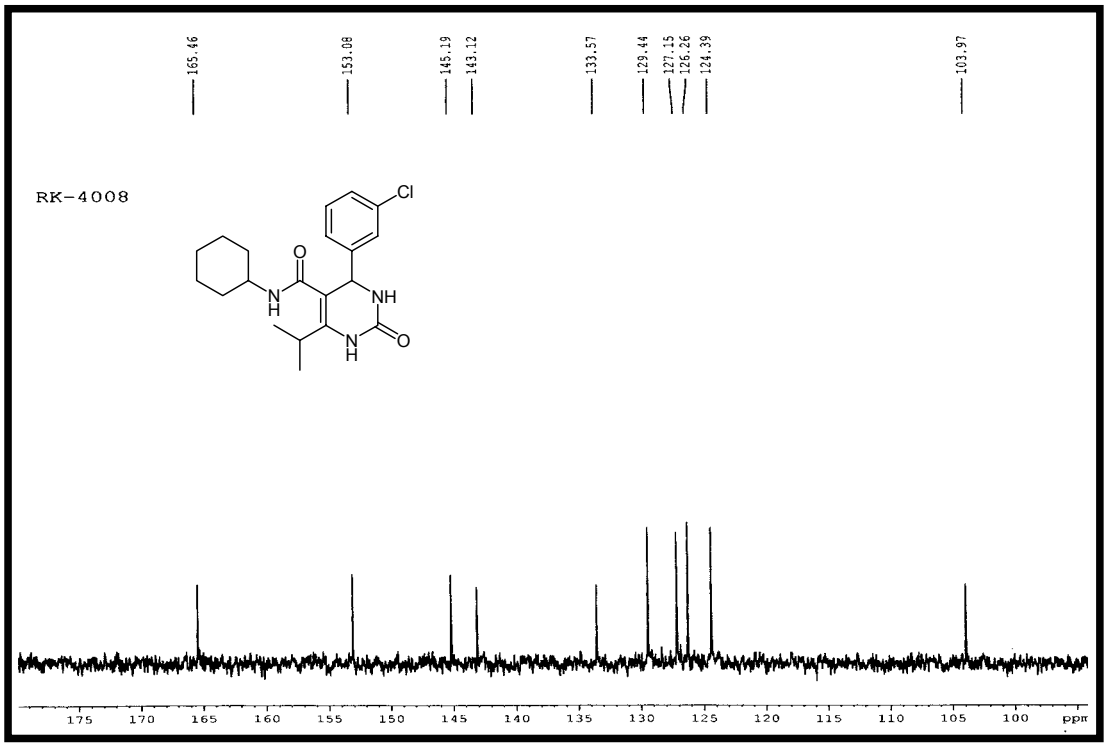


[h] ^{13}C NMR of RK-4008

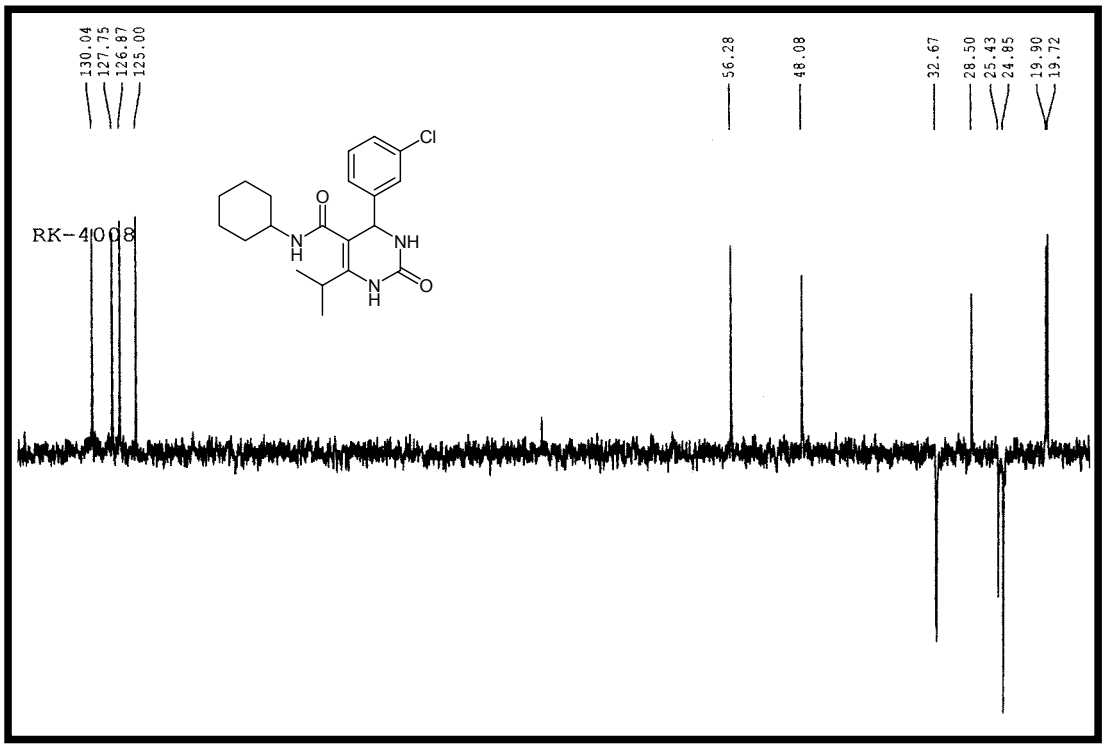




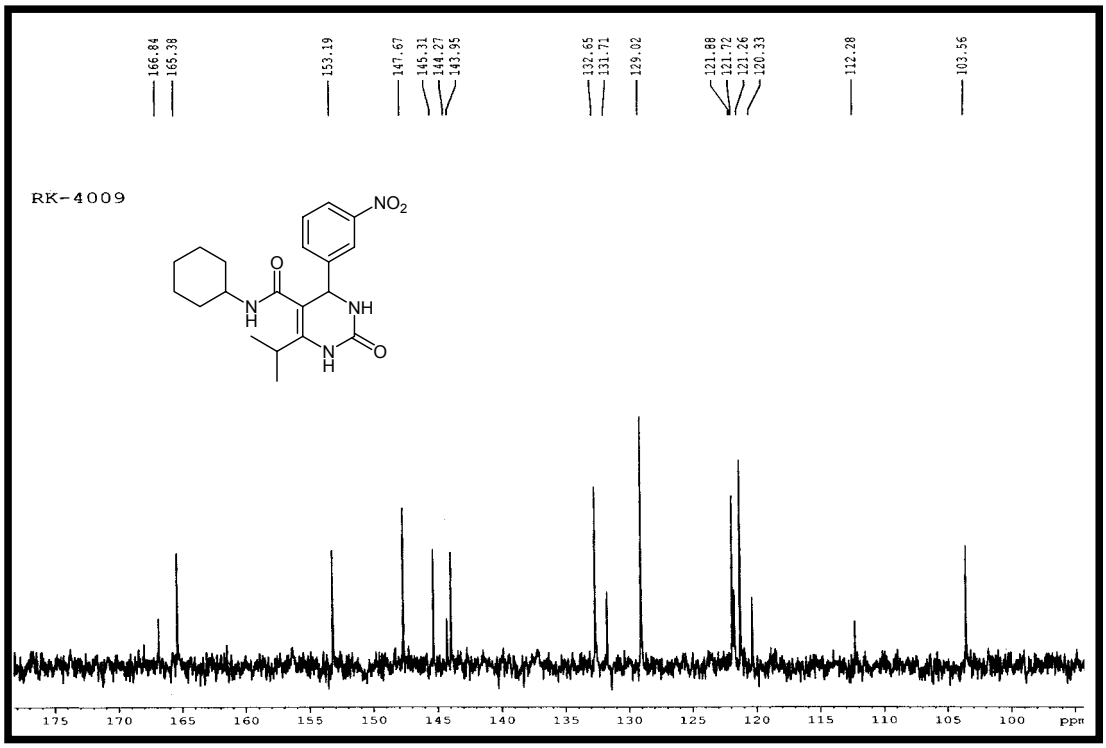
[i] ^{13}C NMR of RK-4008



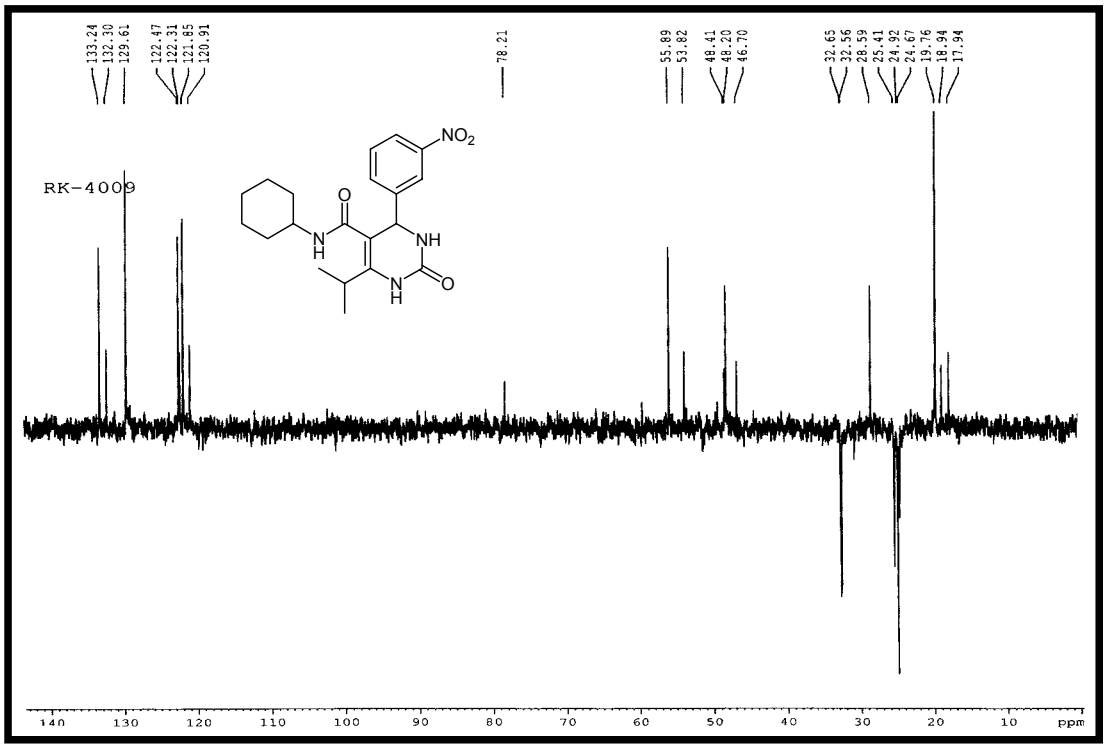
[j] ^{13}C DEPT at 135 of RK-4008 for identification of methylene proton



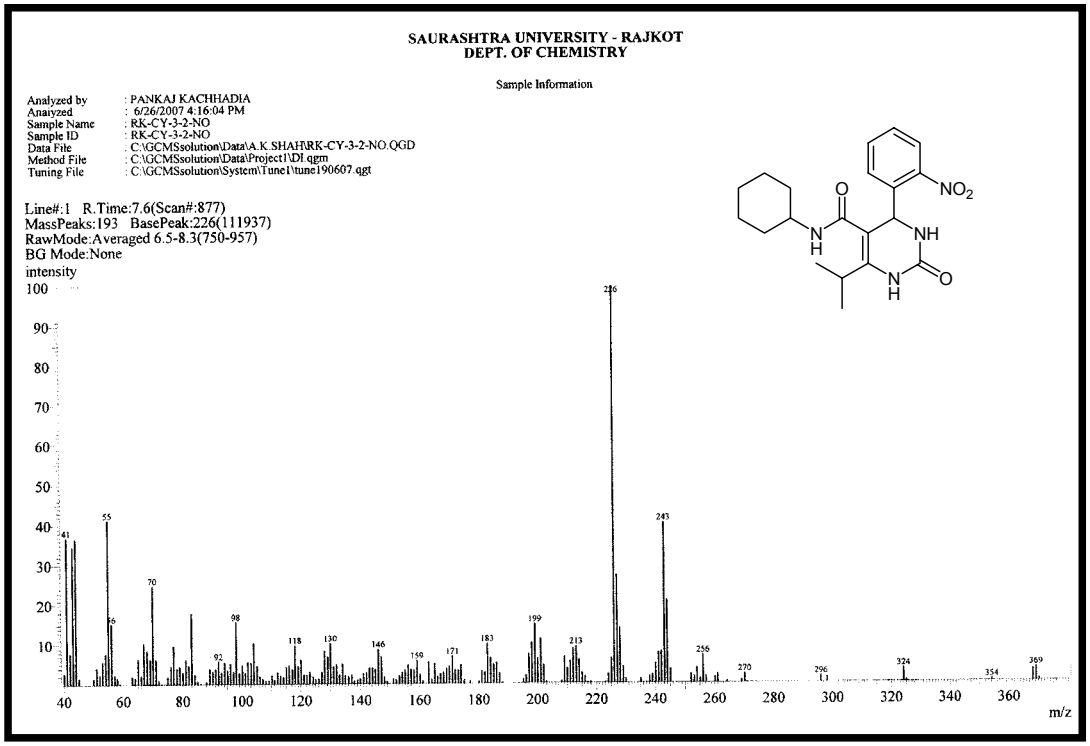
[k] ^{13}C NMR of RK-4009



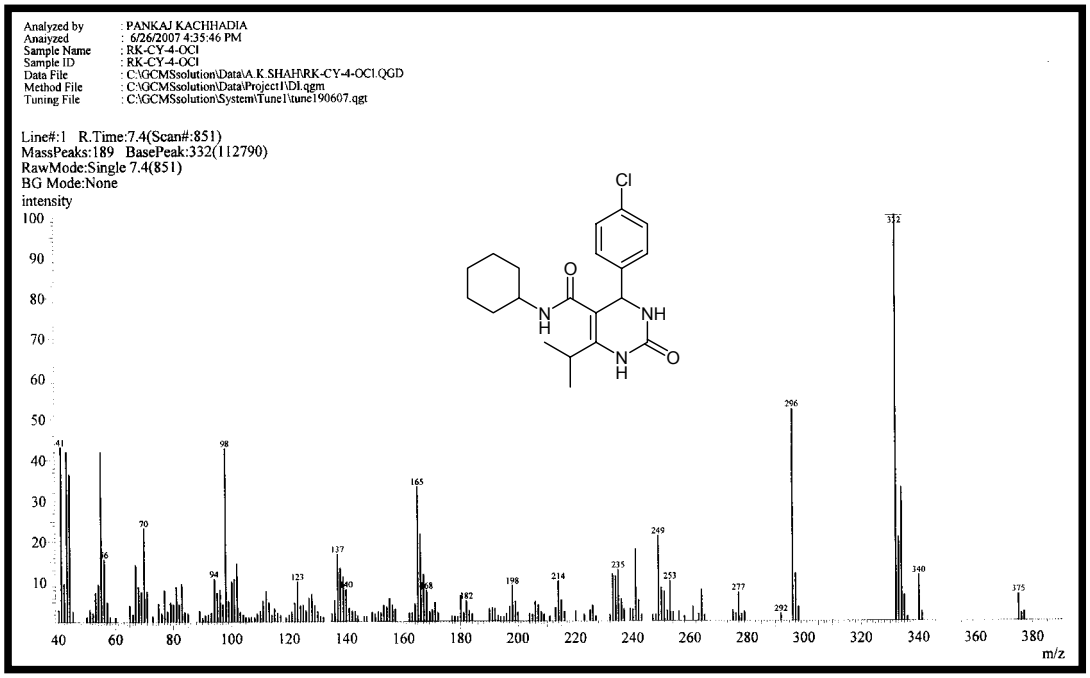
[l] ^{13}C DEPT at 135 of RK-4009 for identification of methylene proton



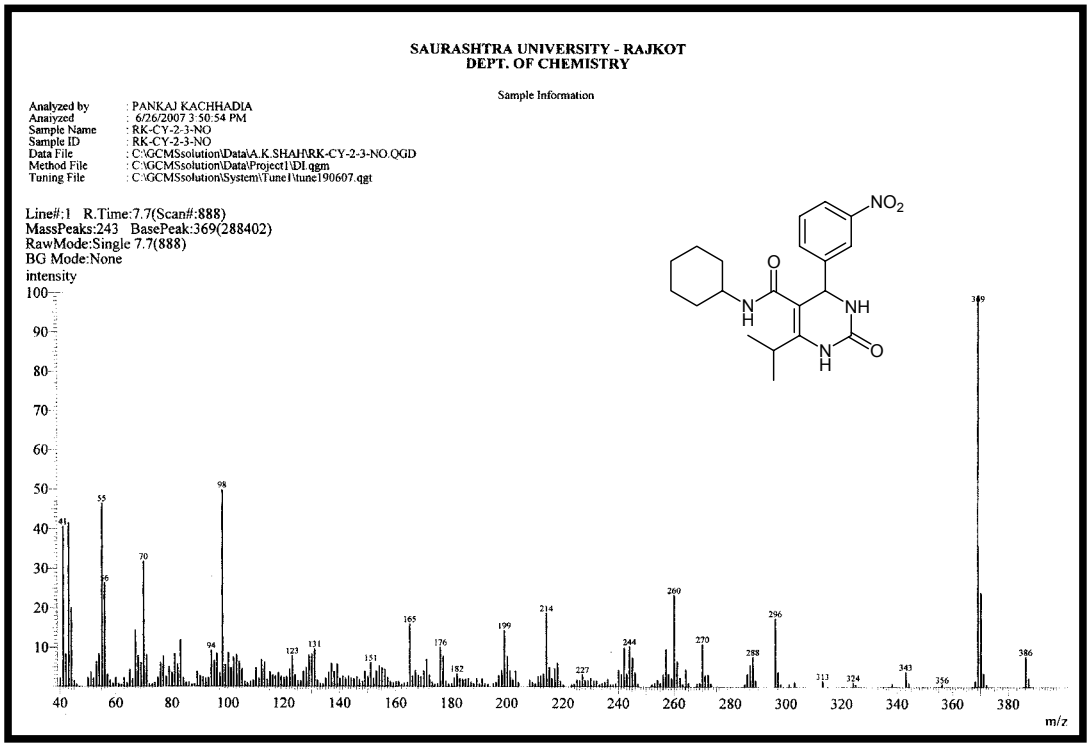
[m] EI-MS Spectra of RK-4006



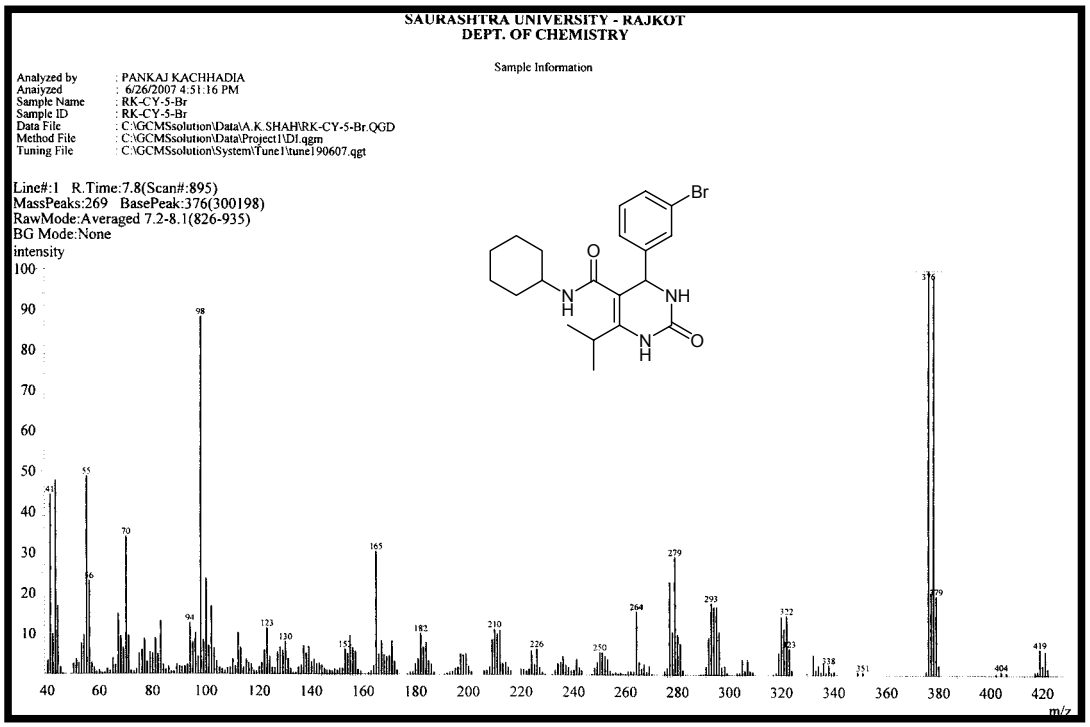
[n] EI-MS Spectra of RK-4011



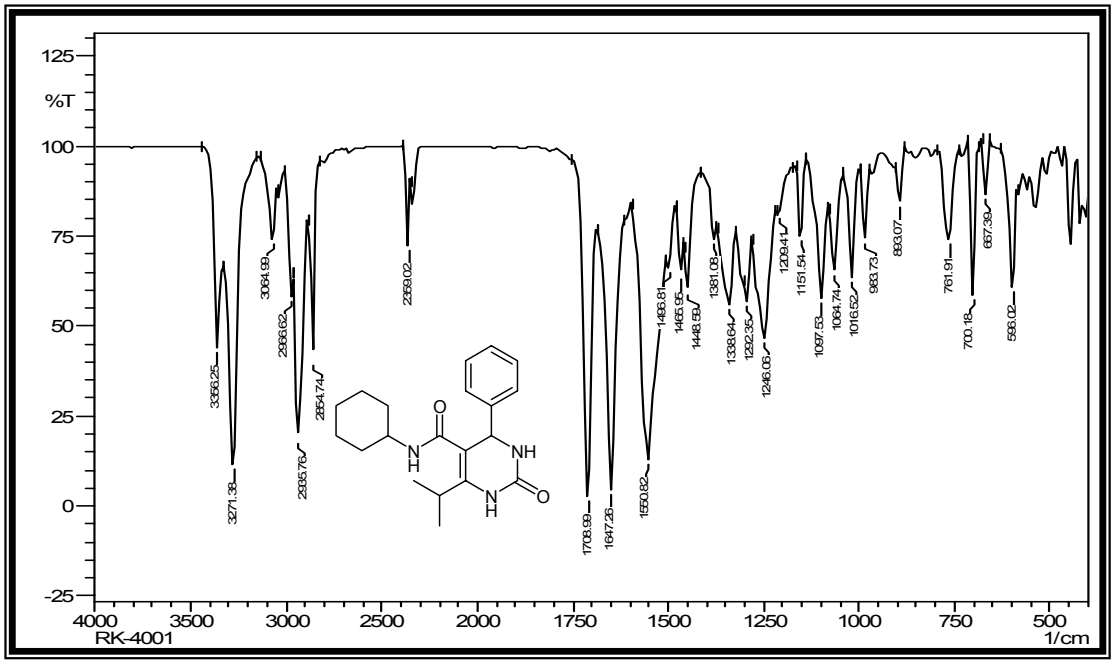
[o] EI-MS Spectra of RK-4009



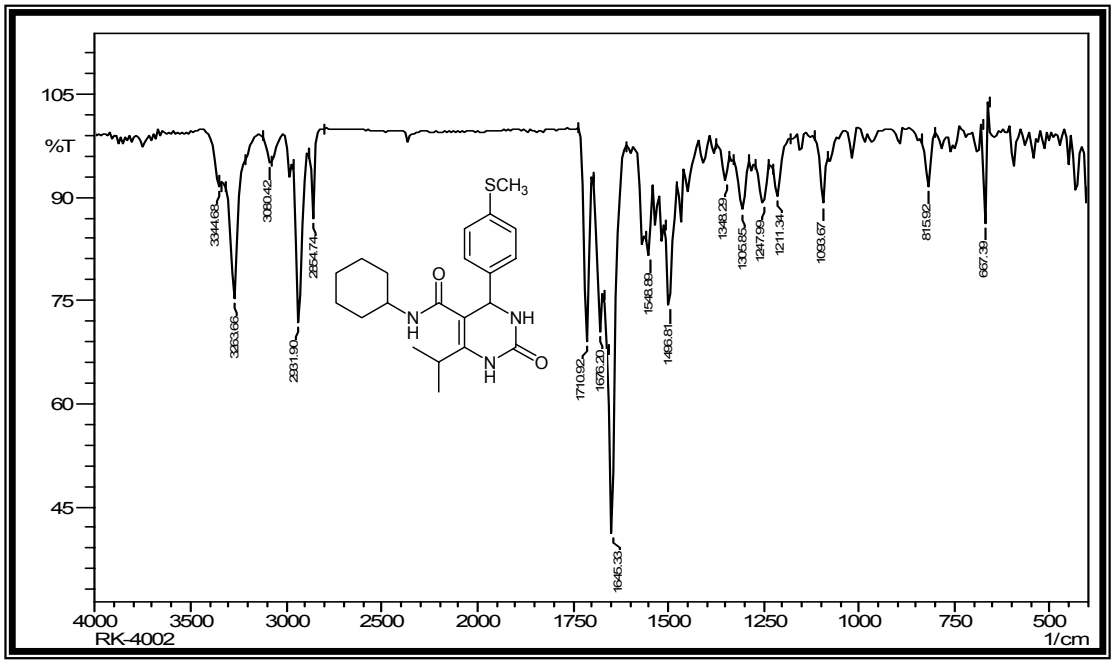
[p] EI-MS Spectra of RK-4005



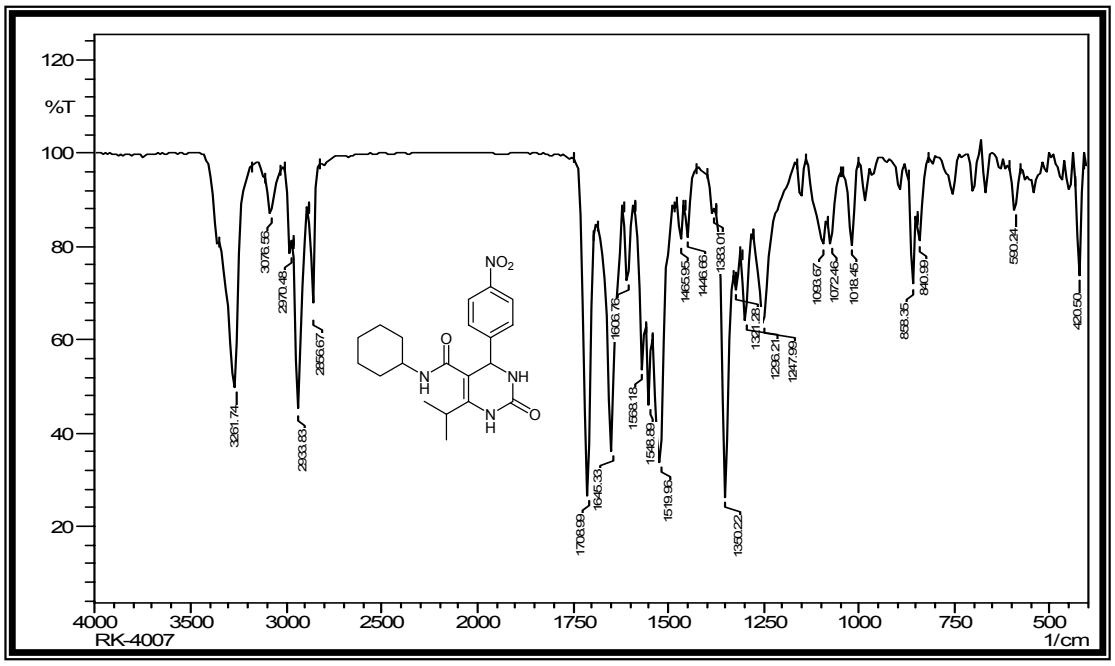
[q] IR Spectra of RK-4001



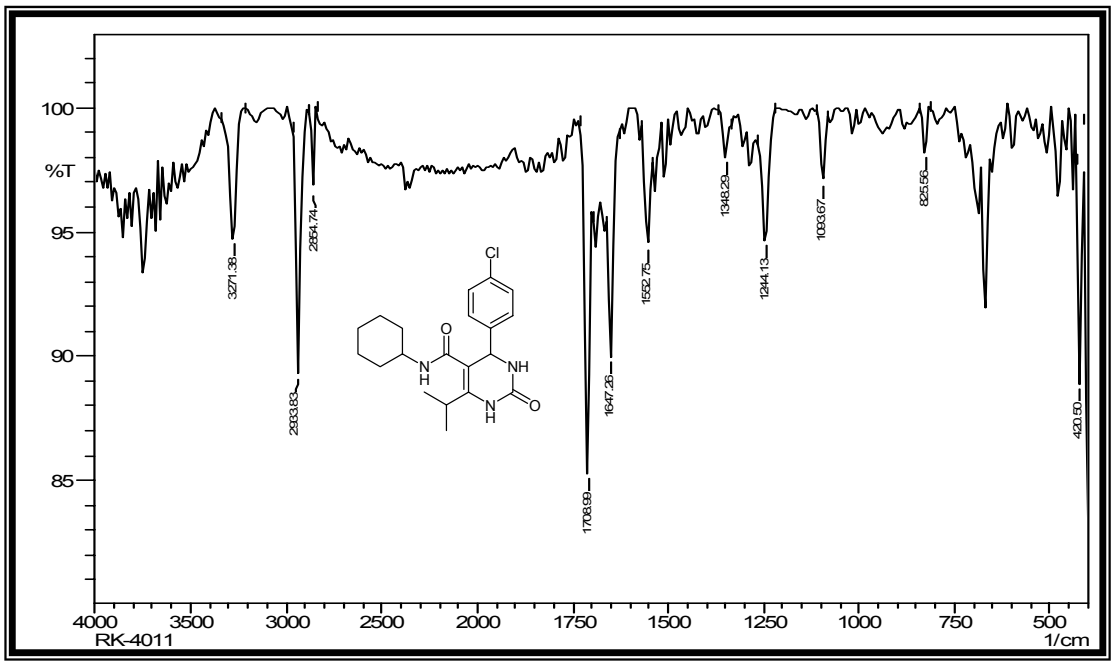
[r] IR Spectra of RK-4002



[s] IR Spectra of RK-4007



[t] IR Spectra of RK-4011



Conclusion

Our interest in dihydropyrimidinones stems from numerous pharmacologically activity and their presence as marine natural products.

In the present work, the Biginelli type cyclocondensation(MCRs) of acetoacetanilide bearing a cyclohexyl ring have been studied. In correlation to the reaction of acetoacetanilide bearing a cyclohexyl ring with different substituted benzaldehyde and urea, we obtained a Dihydropyrimines posture at C_5 position with cyclohexyl carbamoyl functional group. These reactions were conventionally carried out in methanol in the presence of the catalytical amount of Conc. HCl for 5-6 hours providing Dihydropyriminones in moderate to good yields.

In continuation of this work, a replacement of phenyl ring by cyclohexyl group and methyl group by isopropyl group by Biginelli-type three-component cyclocondensation reaction with slight modification in acetoacetanilide. It shows that slight change in the building blocks can create a new diversity and ultimately a small library of novel dihydropyrimidinones is obtained.

All the novel compounds are well characterized by spectral investigation as reported in earlier pages.

In the IR spectra of compounds, the most characteristic sharp absorption bands of the secondary –NH group were obtained.

In the ^{1}H NMR spectra of compounds, the characteristic signals for the cyclohexyl protons are observed at 0.8-1.5 δppm. Isopropryl group protons agree very well with the standard values. All ^{13}C NMR shows each of carbon atom. ^{13}CNMR experiment-DEPT for the identification of the methylene carbon for cyclohexyl ring & methine carbon was carried out and its values agree with standard values.

The biological properties of these substances are currently under investigation.

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Introduction

Dihydropyridines (DHP) are the important class of organic compounds in view of its ample of application in the pharmaceuticals.[1,3] Arthur Hantzsch in 1882 [2] first reported the classical synthesis of 1,4-dihydropyridines(1,4-DHPs) which involves one pot three-component coupling reaction of 1 equivalent of alkyl or aryl aldehyde, 2 equivalents of β-ketoester and 1 equivalent of ammonia at reflux temperature using either acetic acid or ethanol as a solvent. However, the yield of 1,4-DHPs are generally low. Hence numerous methodologies with improved reaction conditions have been documented.[3] Many of these still suffer some serious drawbacks such as unsatisfactory yields, tedious work-up procedure, occurrence of side reactions including aromatization, economically non-viable, long reaction rate, high reaction temperature etc.

To overcome these problems, numerous modifications attempted including new Lewis acid catalyst, Zn[L-proline] [4] under microwave condition. The catalyst is also recycled up to five runs but it appreciably loss the catalytic activity for the next successive runs and ultimately yield loss were observed. 1,4-DHPs were also synthesized by using water-ethanol solvent[5] system using MWI, but this process fails at high microwave power, because reaction mixture is rapidly heated at high microwave power leading to solvent evaporation and hence precipitation of the reaction mixture were observed. The synthesis of 1,4-DHPs is also reported in room temperature ionic liquids[6] but the rate of reaction is sluggish than the microwave counterparts. Of all these methodologies, the ionic liquid medium is the sole protocol which allows the recycling of the solvent. There is despite the fact that, unlike several of 'neoteric solvent' like ionic liquids(ILs) where toxicity and environmental burden data are for the most part unknown while complete toxicity profiles are available for a range of polyethylene glycol(PEG) molecular weights and indeed, many are already approved for internal consumption by US-FDA.[7] Moreover, the vapor density for low molecular weight PEG is greater than 1 and this is consistent with the industry standard for selection of alternative solvents to Volatile Organic Chemicals (VOCs).[8]

Biological profile of 1,4-dihydropyridine

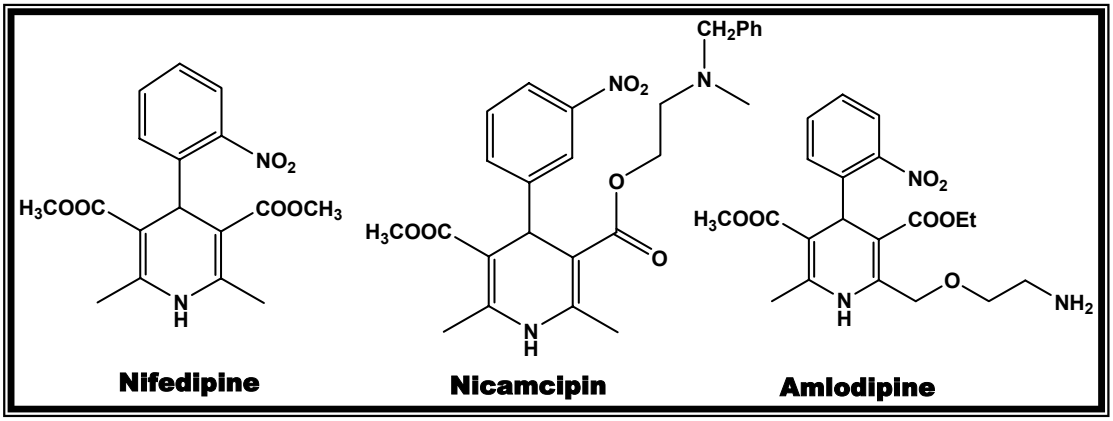
The DHP skeleton is common to numerous bioactive compounds which include various vasodilator, geroprotective, antihypertensive, bronchodilator, antiatherosclerotic, hepatoprotective, antitumor, antimutagenic and antidiabetic agents [9-14].

DHPs nucleolus has number of pharmacologically commercial utility as calcium channel blockers, as exemplified by therapeutic agents such as Nifedipine [15] Nitrendipine[16] and Nimodipine[17]. Second-generation calcium antagonists include DHP derivatives with improved bioavailability, tissue selectivity, and/or stability, such as the antihypertensive/antianginal drugs like Elgodipine[18], Furnidipine[19,20], Darodipine[21], Pranidipine[22], Lemildipine[23], Dexniguldipine[24], Lacidipine[25], and Benidipine[26]. Number of DHP calcium agonists has been introduced as potential drug candidates for treatment of congestive heart failure [27, 28].

The key characteristic of calcium channel blockers is their inhibition of entry of calcium ions via a subset of channels, thereby leading to impairment of contraction. There are three main groups of calcium channel blockers, i.e. dihydropyridines, phenylalkylamines and benzothiazepines, classic examples of which are nifedipine, verapamil and diltiazem, respectively [29-32]. Each has a specific receptor on the calcium channel and a different profile of pharmacological activity. Dihydropyridines have a less negative inotropic effect than phenylalkylamines and benzothiazepines but can sometimes cause reflex tachycardia. Dihydropyridines are able to reduce peripheral resistance, generally without clinically significant cardiodepression.

Among DHPs with other types of bioactivity, Cerebrocrast[33] has been recently introduced as a neuroprotectant and cognition enhancer lacking neuronal-specific calcium antagonist properties. In addition, a number of DHPs with platelet antiaggregatory activity have also been discovered [34]. These recent examples highlight the level of ongoing interest toward new DHP derivatives and have prompted us to explore this pharmacophoric scaffold to develop a fertile source of bioactive molecules.

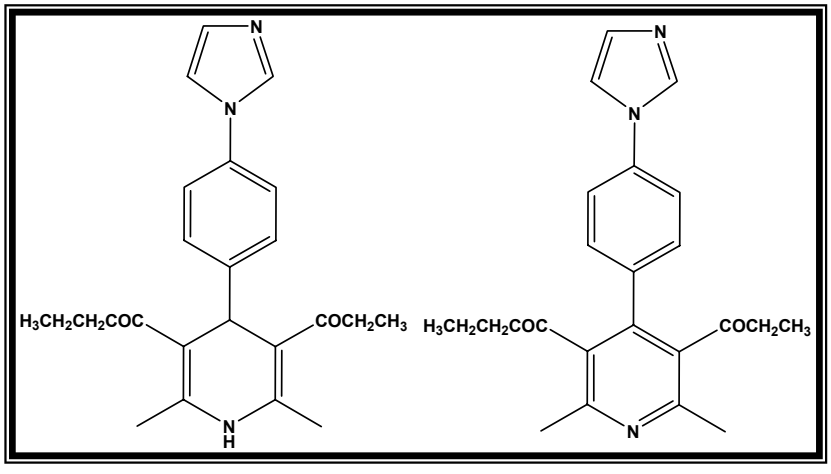
Some representative Ca^{2+} antagonists of Dihydropyridine class are as shown below:



In particular, DHP-CA (calcium channel antagonist DHP) are extensively used for the treatment of hypertension,[35] subarachnoid hemorrhage,[36, 37] myocardial infarction[38-41]and stable[42, 43] and unstable angina[44,45] even though recently their therapeutic efficacy in myocardial infarction and angina has been questioned[46]. This class of compounds is also under clinical evaluation for the treatment of heart failure [47], ischemic brain damage [48] nephropathies, and atherosclerosis [49].

1,4- DHPs having different pharmacological activities such as antitumor[50], vasodilator[51], coronary vasodilator and cardiopathic[52], antimayocardiac ischemic, antiulcer[53], antiallergic[54], antiinflammatory[55] and antiarrhythmic[56], PAF antagonist[57], Adenosine A3 receptor antagonist[58] and MDR reversal activity[59,60].

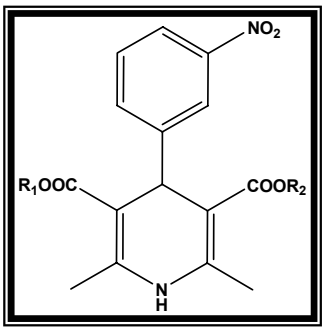
It is found recently that when the imidazolyl moiety is linked to the phenyl ring by means of a C-N bridge, the activity tends to decrease. Finally, the replacement of DHP itself by a pyridine ring gives an inactive compound [61].



Cozzi et al[56] have synthesized a series of 4-phenyl-1,4-dihydropyridines bearing imidazol-1-yl or pyridine-3-yl moieties on the phenyl ring, with the aim of combining

Ca^{2+} antagonism and thermboxane $A_2(TxA_2)$ synthase inhibition in the same molecules. Some of the compounds showed significant combined activity *in vitro*, while other showed single activity. As far as Ca^{2+} antagonism is concerned, two points deserve comment. First, the SAR, in most cases, does not differ substantially from that reported for classic DHP-CA, even though the potency is lower than that found with the most potent drugs of this class as, for example, reference compound nifedipine. In fact, Ca^{2+} antagonism is dramatically reduced by (a) replacement of DHP by a pyridine ring, (b) substitution of DHP nitrogen N-1 by a methyl group, (c) para substitution on the phenyl ring, and (d) replacement of one ester function by a ketone or carboxy group. All these variations are also detrimental in classic DHP-CA.[62]

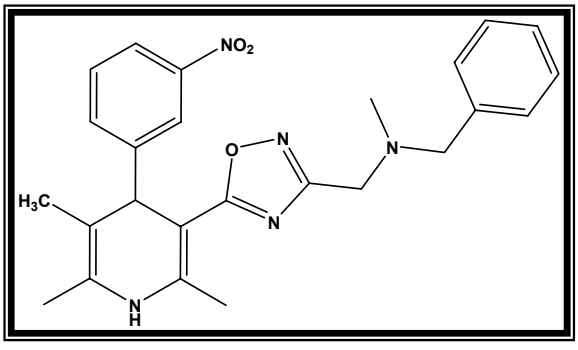
Hernandez-Gallegos et al [63] have synthesized new 1,4-dihydropyridines and evaluated their relaxant ability (rat aorta), antihypertensive activity in spontaneously hypertensive rats and their microsomal oxidation rate (MOR) was determined.



R = 3-NO2, 4-F, 3,5-di-F, 3-Br-4-F.

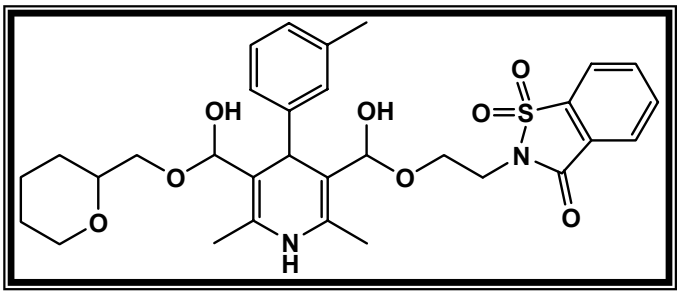
$R_1 = R_2$= Me, Et, $-CH_2-CF_3$, $-CH_2CH_2-OPh$, $-(CH_2)_2-N(CH_3)-CH_3-Ph$

Christiaans and Timmerman [64] studied new molecules like CV-159 for possible variation at 3-position.



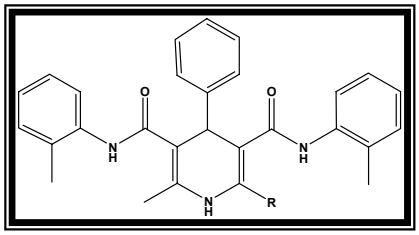
Carlos et al [65] reported 1,4-DHPs derivatives with a 1,2-benzothiazol-3-one-1-sulphoxide group, linked through an alkylene bridge to the C_3 carboxylate of the DHP

ring, with both vasoconstricting and vasorelaxant properties were obtained. In blocking Ca^{2+} evoked contractions of K^+ depolarized rabbit aortic strips. Many compounds were 10 times more potent than nifedipine. Their vascular versus cardiac selectivity was very pronounced.

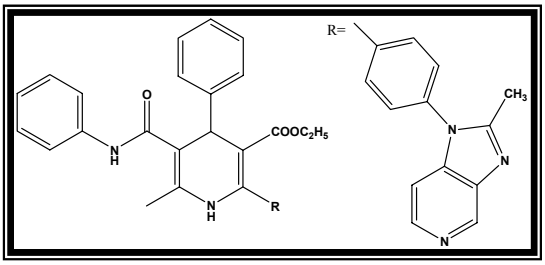


Schramm and coworker [66] have proved that phenyl carbamoyl moiety in dihydorpyridine affords for cardiovascular selective activity.

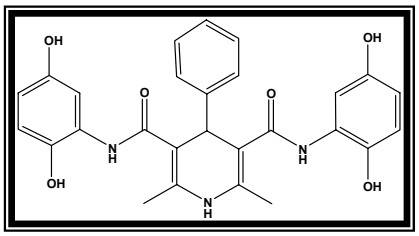
Reddy and coworkers[67] synthesized 4-aryl hetroaryl-2,6-dimethyl-3,5-bis-N-(2-methyl / 2-chloro phenyl)carbamoyl-1,4-dihydropyridines through one-pot synthesis using appropriate aromatic aldehydes and liquid ammonia. Pharmacological screening of the new 1,4-dihyropyridines were also carried out for CNS depresant (anticonvulsant and analgesic) and cardiovascular (inotropic and blood pressure) activities by standard methods.



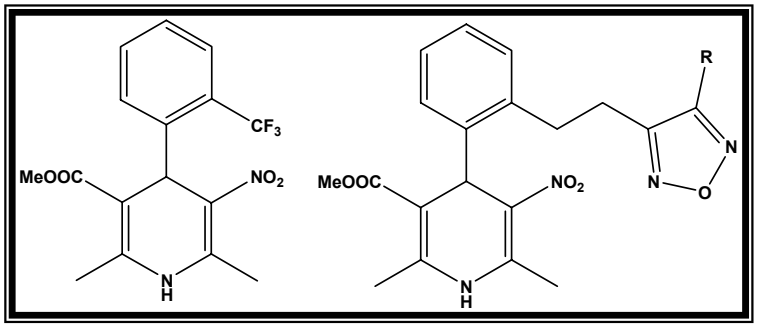
Similarly Kelvin Cooper (Pfitzer , USA) et al[68] found that DHP can be highly selective as platlet activating factor (PAF) antagonist. They found potent compounds and prove that platlet aggregating activity (PAF) exhibits a wide spectrum of biological activities elicited either directly or via the release of other powerful mediator such as Thromboxane A_2 or the Leukotrienes. *In vitro* PAF stimulates the movement and aggregation and the release there from of tissue damaging enzymes and oxygen radicals. Accordingly compounds like UK-74505, antagonize the action of PAF and consequently also prevent mediator release by PAF, will have clinical utilities in the treatment of the variety of the allergic, inflammatory and hypersecretory conditions such as asthama, arthritis, rhinitis, bronchitis and utricaria in future. [69]



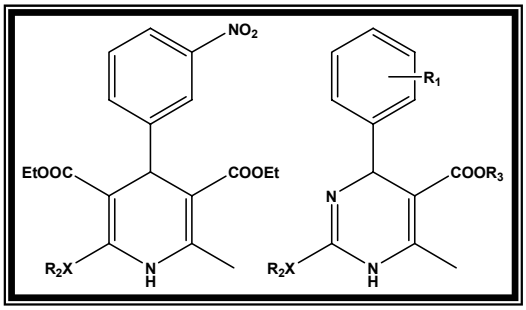
Neamati and coworkers [70] reported that a 1,4-dihydorpyridine NCS-372643 came out with its anti-HIV activity, which has opened up the synthetic as well as pharmacological importance in antiviral area also.



Sonja [71] and group have synthesized a new series of calcium channel agonists structurally related to Bay K8644, containing NO donor furoxans and the related furazans unable to release NO. The racemic mixtures were studied for their action on L-type Ca^{2+} channels expressed in cultured rat insulinoma RINm5F cells. All the products proved to be potent calcium channel agonists



2-Heterosubstituted-4-aryl-l,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters, which lack the potential C_3 symmetry of dihydropyridine calcium channel blockers, were evaluated for biological activity. Biological assays using potassium-depolarized rabbit aorta and radioligand binding techniques showed that some of these compounds are potent mimics of dihydropyridine calcium channel blockers. The combination of a branched ester (e.g. isopropyl, sec-butyl) and an alkylthio group (e.g. SMe) was found to be optimal for biological activity[72].



Labedipinedilol-A, a novel dihydropyridine-type calcium antagonist, has been shown to induce hypotension and vasorelaxation. Liouand co-workers have studied to investigate the effect of labedipinedilol-A on vascular function of rat aortic rings and cultured human umbilical vein endothelial cells (HUVECs). [73]

Recent reports show that efonidipine, a dihydropyridine Ca^{2+} antagonist, has blocking action on T-type Ca channels, which may produce favorable actions on cardiovascular systems. However, the effects of other dihydropyridine Ca antagonists on T-type Ca channels have not been investigated yet. Therefore, Furukawa and group [74] have examined the effects of dihydropyridine compounds clinically used for treatment of hypertension on a T-type Ca channel subtype, alpha1G, expressed in Xenopus oocytes. Twelve DHPs (**amlodipine, barnidipine, benidipine, clinidipine, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nitrendipine**) mibefradil were tested. Cilnidipine, felodinpine, nifedipine, nilvadipine, minodipine and nitrendipine had little effect on the T-type channel. The blocks by drugs at 10 muM were less than 10% at a holding potential of -100 mV. The remaining 6 drugs had blocking action on the T-type channel comparable to that on the L-type channel. These results show that many dihydropyridine Ca^{2+} antagonists have blocking action on the T-type channel comparable to that on the L-type channel. These results show that many dihydropyridine Ca^{+2} antagonists have blocking action on the alpha1G channel subtype. Joanna Rzeszowska-Wolny et al reported that compounds of the 1,4-dihydropyridine (1,4-DHP) series have been shown to reduce spontaneous, alkylation- and radiation induced mutation rates in animal test systems. Studies using AV-153, the 1,4-DHP derivative that showed the highestantimutagenic activity in those tests, to examine if it modulates DNA repair in human peripheral blood lymphocytes and in two human lymphoblastoid cell lines.[75]

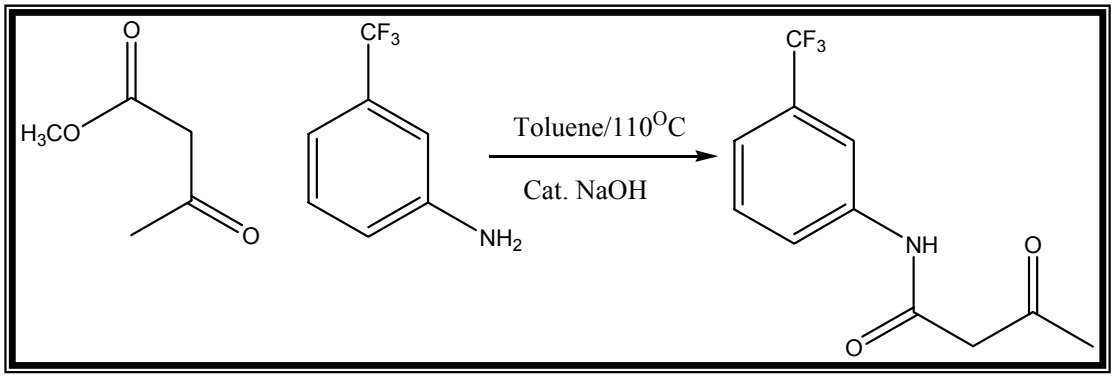
1,4-Dihydropyridines are now established as heterocycles having numerous applications and having widened scope for its pronounced drug activity like calcium channel antagonism and antihypertensive action. Many other activities are associated with such compounds and they can be presented in the structure as 2,6-dimethyl-3,5-diacetyl or dicarboxylate or dicarbamoyl or many other homoaryl or heteroaryl carbon chain having C_2 to C_8 1,4-dihydropyridines substituted at 4-position.[76-81]

In continuation of earlier work on DHPs, an improved synthetic protocol is used to prepare several structurally diverse 1,4-dihydropyridines.

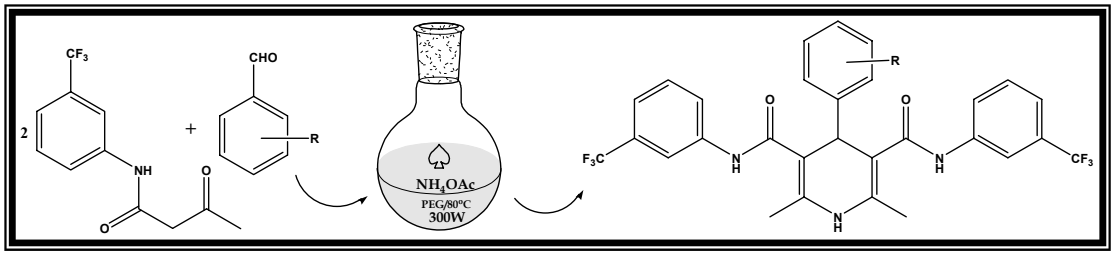
In short, in viewing the benignity and superiority of PEG as a solvent over ionic liquids and other reported protocols for the synthesis of 1,4-DHPs as mentioned earlier, herein we disclose our findings by using PEG-400 as a solvent for the rapid microwave assisted multi component reaction (MCR)

Reaction Scheme

Step-I



Step-II



Experimental Protocol

Step-I **Preparation of N-(3-(Trifluoromethyl)phenyl)-3-oxobutanamide**

3-trifluoromethyl aniline (0.3 mol) and 3 ml concentrated KOH solution in water was stirred well until the clear solution was observed. methyl acetoacetate (0.27 mol) was added into it, stirred for five minutes. 100 ml toluene was added into it and refluxed for 6-7 hours, TLC was checked for the completion of the reaction, slight starting materials remain unreacted. Reaction mixture was cooled to room temperature and added 100 ml toluene. It was added into 250 ml 5% HCl solution and transferred into separating funnel, and toluene layer was collected. Toluene layer was again washed with 100 ml 5% HCl solution, twice with 100 ml of water and 50 ml Brine solution. Organic layer was collected, dried over anhydrous sodium sulphate. Solvent was distilled out by using rotavapor at 40^{o}C, Oily residue was observed. 50 ml Pet. Ether was added into it and kept in refrigerator, stirred well for 30 minutes at 20^{o}C. Pet. Ether was decanted. Again 50 ml Pet. Ether was added and scratched out at 20^{o}C. Solid product was separated; it was dried in an oven.

TLC System: (Hexane: Ethyl acetate)

8 : 2

Yield: 65%

Step-II **Preparation of N^3,N^5-Bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl-4-(Substituted phenyl)pyridine-3,5-dicarboxamide (General Method)**

In 150 ml microwave flask, 2.5 equivalent of ammonium acetate and 15 ml PEG was added and stirred until the clear solution was observed. 1.0 equivalent of acetoacetanilide and 1.0 equivalent of different substituted banzaldehyde was added. It was subjected to microwave irradiation (300 W) at 80^{o}C temperature for 5-8 minutes. Remove microwave flask from microwave instrument, it was stand to room temperature until solid product was observed. It was filtered and recrystallized in methanol.

In some cases, solid product was observed. It was filtered and recrystallized in Methanol.

Reaction time and yield are depicted in physical data table No. 4

TLC System: (Chloroform: Ethyl Acetate)

7 : 3

Physical data of N^3,N^5-bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl-4-(Substituted phenyl)pyridine-3,5-dicarboxamide

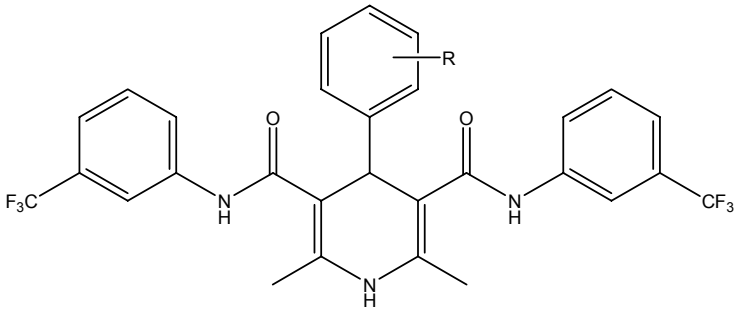


Table. No: 4

Code.No	Substitution R	M.F	M.W	M.P ^{O}C	Time (Min)	Yield (%)	C, H , N Analysis		
							C	H	N
RKDHP-1	H	$C_{29}H_{23}F_6N_3O_2$	559.5	239-240	5	78	62.25 (62.20)	4.14 (4.17)	7.51 (7.48)
RKDHP-2	-2-Cl	$C_{29}H_{22}ClF_6N_3O_2$	593.95	220-222	7	82	58.64 (58.61)	3.73 (3.78)	7.07 (7.10)
RKDHP-3	-4-SCH_3	$C_{30}H_{25}F_6N_3O_2S$	605.59	258-260	6	85	59.50 (59.55)	4.16 (4.13)	6.94 (6.98)
RKDHP-4	-4-OCH_3	$C_{30}H_{25}F_6N_3O_3$	589.53	225-226	5	74	61.12 (61.08)	4.27 (4.22)	7.13 (7.18)
RKDHP-5	-2-OCH_3	$C_{30}H_{25}F_6N_3O_3$	589.53	250-251	5	82	61.12 (61.17)	4.27 (4.23)	7.13 (7.18)
RKDHP-6	-3,4-diOCH_3	$C_{31}H_{27}F_6N_3O_4$	619.55	222-223	8	71	60.10 (60.07)	4.39 (4.36)	6.78 (6.80)
RKDHP-7	-3-NO_2	$C_{29}H_{22}F_6N_4O_4$	604.5	242-244	7	76	57.62 (57.58)	3.67 (3.72)	9.27 (9.31)

Table. No: 4

Code.No	Substitution R	M.F	M.W	M.P ^{o}C	Time (Min)	Yield (%)	C, H , N Analysis		
							C	H	N
RKDHP-8	-4-Cl	$C_{29}H_{22}ClF_6N_3O_2$	593.95	220-222	6	83	58.64 (58.61)	3.73 (3.78)	7.07 (7.10)
RKDHP-9	3-Br	$C_{29}H_{22}BrF_6N_3O_2$	638.4	178-180	6	79	54.56 (54.51)	3.47 (3.41)	6.58 (6.54)
RKDHP-10	-4-NO_2	$C_{29}H_{22}F_6N_4O_4$	604.5	240-242	5	84	57.62 (57.57)	3.67 (3.65)	9.27 (9.22)

Spectral Discussion

^{1}H NMR spectral study

^{1}HNMR of the N^3,N^5-bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl-4-(Substitutedphenyl)pyridine-3,5-dicarboxamide compounds were recorded on DPX-300MHz FT-NMR spectrophotometer (Bruker) instrument using TMS as an internal reference standard in DMSO-D6 solvent. ^{1}HNMR spectra show the number of proton & chemical environment of each proton in each compound. The singlet observed for both methyl ($-CH_3$) of two and six position of dihydropyridine in the range of δ 1.8-2.2. Asymmetric Methine proton gives singlet in the range of δ 5.0-5.4. The pattern of the ^{1}-HNMR spectra between δ 6.8-8.0 clearly indicated that the benzene ring attached to the unsymmetrical carbon atom is meta or para substituted. Both carbamoyl (-CO-NH) protons gives singlet in the range of δ 9.0-9.2. dihydropyrimidine (-NH) gives singlet in the range of δ 8.0-8.3. Both (-CH) attached between –NH and (C-CF3) gives singlet δ 7.4-7.8.

FT-IR spectral study

IR spectra were recorded on Shimadzu FTIR-8400 using KBr Disc and DRS techniques. The percentage transmission is given in cm-1. The different frequencies of infrared spectrum of N^3,N^5-bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl-4-(Substituted phenyl)pyridine-3,5-dicarboxamide are studied. The carbonyl frequencies appeared for amide in the range of (1650-1690cm^{-1}). The presence of secondary amine was confirmed at 3000-3400 cm-1. The CF_3 group stretching vibrations observed at 1000-1380cm^{-1}.

Mass spectral study

The mass spectrums of the all compounds of this series were recorded by GCMS-QP2010 spectrometer. (EI method) The molecular ion peak (M^+) values are in good match with molecular formula for synthesized compound. Probable mass fragmentation of N^3,N^5-bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl-4-(Substituted phenyl)pyridine-

3,5-dicarboxamide is represented in subsequent pages. Different fragmentation pattern is also observed in all synthesized compounds.

Elemental Analysis

Elemental analysis of the synthesized compounds was carried out Elementar Vario EL III Carlo Erba 1108 model at CDRI, Lucknow and the results are in agreement with the structures assigned.

Spectral Data

N^3,N^5-Bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxamide (RKDHP-1)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.10 (s, 6H), 5.12 (s, 1H), 7.08 (m, 1H), 7.22 (t, 4H, *J*=3.048 Hz), 7.31 (d, 2H, *J*=7.386 Hz) 7.47 (m, 2H, *J*=7.85 Hz), 7.78 (d, 2H, *J*=7.965 Hz), 8.06 (s, 2H), 8.21 (s, 2H), 9.65 (s, 2H)

IR (KBr Disc): 3298-3408cm^{-1}(-NH), 2850-2976cm^{-1} (C-H), 1672cm^{-1}(-CO-NH), 1599 cm^{-1} (-NH Bend), 1150-1170cm^{-1} (C-F)

4-(2-Chlorophenyl)-N^3,N^5-bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl pyridine-3,5-dicarboxamide (RKDHP-2)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.09 (s, 6H), 5.44 (s, 1H), 7.15 (m, 2H), 7.30 (m, 3H, *J*=8.074 Hz), 7.45 (m, 3H, *J*=7.85 Hz) 7.74 (d, 2H, *J*=8.007 Hz), 8.06 (s, 2H), 8.31 (s, 1H), 9.76 (s, 2H)

IR (KBr Disc):): 3294-3421cm^{-1}(-NH), 2850-2976cm^{-1} (C-H), 1660 cm^{-1}(-CO-NH), 1602 cm^{-1} (-NH Bend), 1124-1165cm^{-1} (C-F), 750 cm^{-1} (C-Cl)

N^3,N^5-Bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl-4-(4-(methylthio) phenyl)pyridine-3,5-dicarboxamide (RKDHP-3)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.10 (s, 6H), 2.26 (s, 3H), 5.08 (s, 1H), 7.13 (m, 4H, *J*=8.30 Hz), 7.31 (d, 2H, *J*=7.869 Hz), 7.47 (t, 2H, *J*=7.90 Hz) 7.79 (d, 2H, *J*=7.971 Hz), 8.07 (s, 2H), 8.22 (s, 1H), 9.65 (s, 2H)

IR (KBr Disc):): 3199-3430cm^{-1}(-NH), 2860-2985cm^{-1} (C-H), 1680cm^{-1}(-CO-NH), 1605 cm^{-1} (-NH Bend), 1135-1156cm^{-1} (C-F)

N^3,N^5-Bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxamide (RKDHP-4)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.09 (s, 6H), 3.64 (s, 3H), 5.07 (s, 1H), 6.76 (d, 2H, *J*=8.58 Hz), 7.14 (d, 2H, *J*=8.56 Hz), 7.30 (d, 2H, *J*=7.485 Hz), 7.47 (t, 2H, *J*=7.914 Hz), 7.78 (d, 2H, *J*=8.076 Hz), 8.07 (s, 2H), 8.17 (s, 1H), 9.60 (s, 2H)

IR (KBr Disc): 3288-3352cm^{-1}(-NH), 2870-2960cm^{-1} (C-H), 1666.55cm^{-1}(-CO-NH), 1599 cm^{-1} (-NH Bend), 1228 cm^{-1} (C-O-C), 1118-1166cm^{-1} (C-F)

N^3,N^5-Bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-4-(2-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxamide (RKDHP-5)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.16 (s, 6H), 3.59 (s, 3H), 5.37 (s, 1H), 6.85 (m, 2H), 7.07(t, 1H, *J*=4.365 Hz), 7.20 (d, 1H, *J*=6.06 Hz), 7.32 (d, 2H, *J*=7.41 Hz), 7.50 (t, 2H, *J*=7.89 Hz), 7.78 (d, 2H, *J*=7.95 Hz), 8.10 (s, 2H), 8.34 (s, 1H), 9.54 (s, 2H)

IR (KBr Disc): 3308-3399cm^{-1}(-NH), 2829-2952cm^{-1} (C-H), 1678.13cm^{-1}(-CO-NH), 1597.11 cm^{-1} (-NH Bend), 1238 cm^{-1} (C-O-C), 1124-1163cm^{-1} (C-F)

N^3,N^5-Bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-4-(3,4-dimethoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxamide (RKDHP-6)

IR (KBr Disc): 3360-3459cm^{-1}(-NH), 2854-2976cm^{-1} (C-H), 1697.32cm^{-1}(-CO-NH), 1596.65 cm^{-1} (-NH Bend), 1238-1245 cm^{-1} (C-O-C), 1111-1176cm^{-1} (C-F)

N^3,N^5-Bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxamide (RKDHP-7)

IR (KBr Disc): 3312-3345cm^{-1}(-NH), 2829-2952cm^{-1} (C-H), 1678.13cm^{-1}(-CO-NH), 1597.11 cm^{-1} (-NH Bend), 1238 cm^{-1} (C-O-C), 1124-1163cm^{-1} (C-F)

4-(4-Chlorophenyl)-N^3,N^5-bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxamide (RKDHP-8)

IR (KBr Disc): 3258-3480cm^{-1}(-NH), 2847-2951cm^{-1} (C-H), 1680.85cm^{-1}(-CO-NH), 1576.32 cm^{-1} (-NH Bend), 1235 cm^{-1} (C-O-C), 1124-1163cm^{-1} (C-F), 750 cm^{-1} (C-Cl)

4-(3-Bromophenyl)-N^3,N^5-bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxamide (RKDHP-9)

IR (KBr Disc): 3329-3431cm^{-1}(-NH), 2827-2943cm^{-1} (C-H), 1678.13cm^{-1}(-CO-NH), 1578 cm^{-1} (-NH Bend), 1215-1236 cm^{-1} (C-O-C), 1144-1153cm^{-1} (C-F),

N^3,N^5-Bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxamide (RKDHP-10)

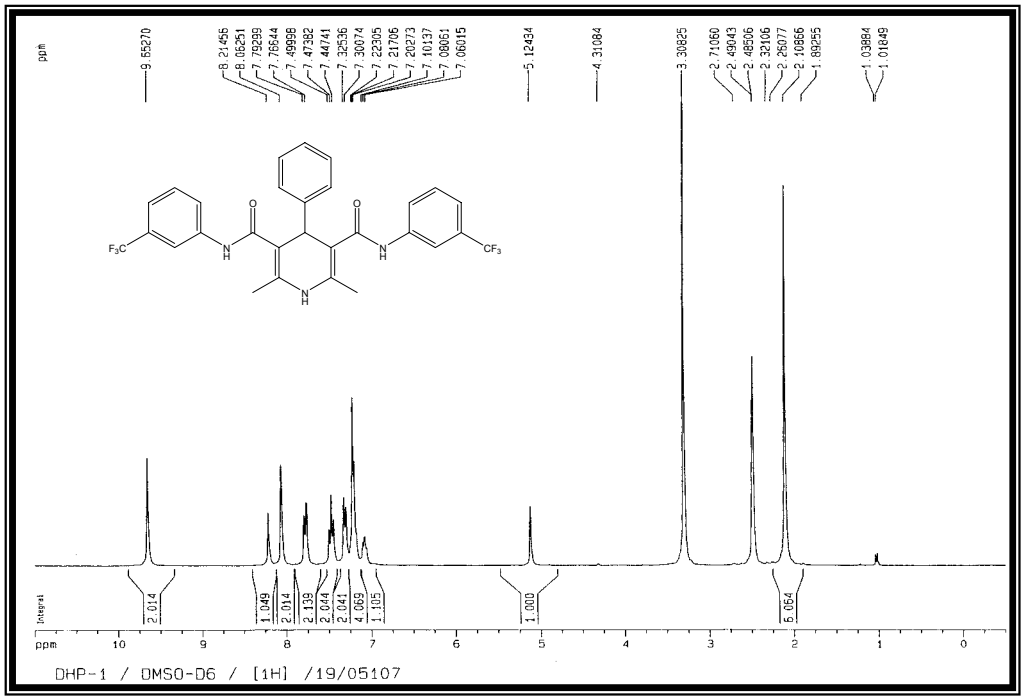
IR (KBr Disc): 3340-3480cm^{-1}(-NH), 2870-2957cm^{-1} (C-H), 1690.52cm^{-1}(-CO-NH), 1576 cm^{-1} (-NH Bend), 1224-1234 cm^{-1} (C-O-C), 1120-1135cm^{-1} (C-F)

Mass value of N^3,N^5-bis(3-(trifluoromethyl)phenyl)-1,4-dihydro-2,6-dimethyl-4-(Substitutedphenyl)pyridine-3,5-dicarboxamide

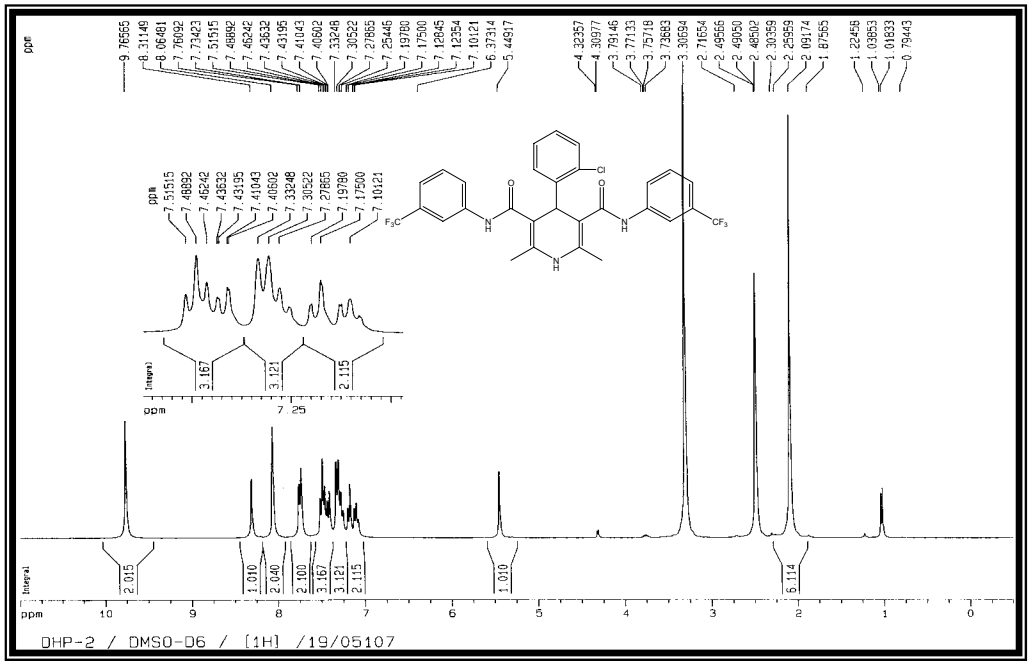
Compound Code.No	(m/z) Relative intensity
RKDHP-1	559.5 (35%)
RKDHP-2	593.95 (40%)
RKDHP-3	605.59 (42%)
RKDHP-4	589.53 (45%)
RKDHP-5	589.53 (37%)
RKDHP-6	619.55 (32%)
RKDHP-7	604.5 (30%)
RKDHP-8	593.95 (30%)
RKDHP-9	638.4 (30%)
RKDHP-10	604.5 (30%)

Spectra of the representative compounds

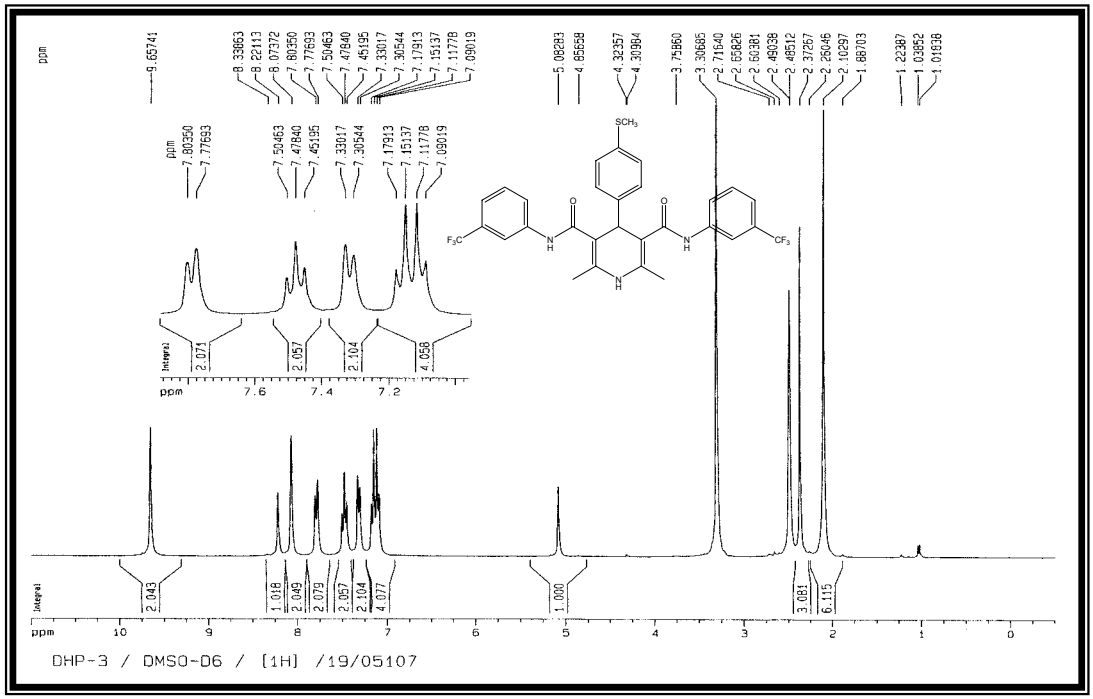
[a] ^{1}H NMR Spectrum of RKDHP-1



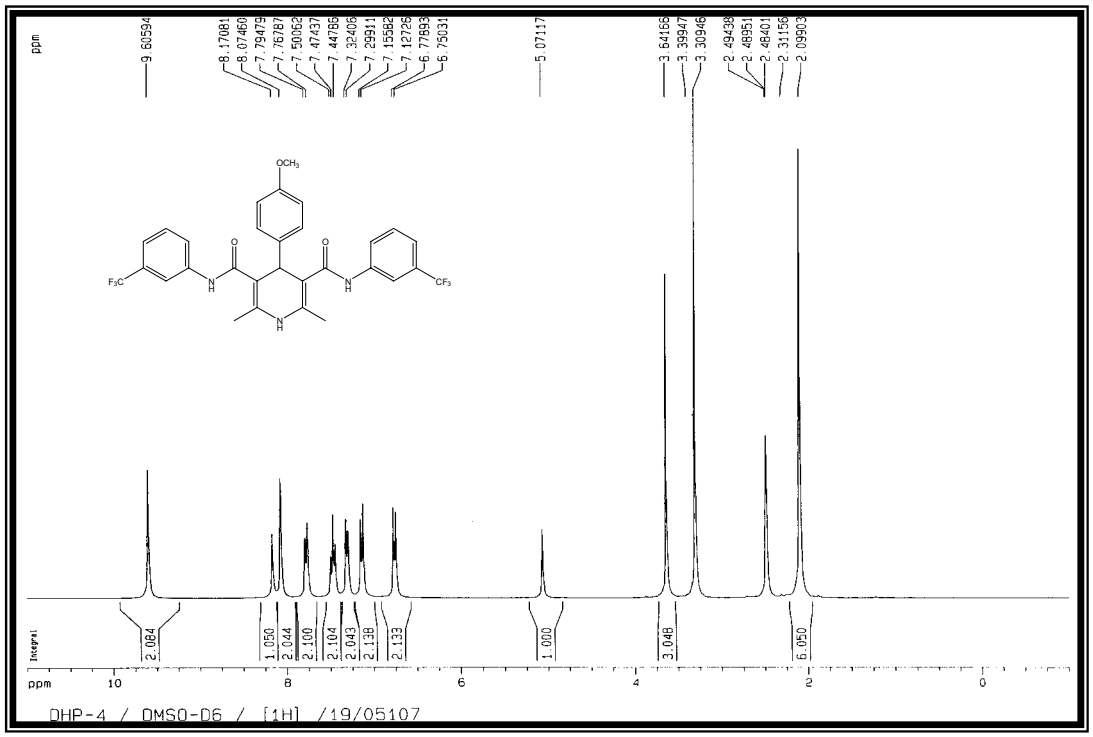
[b] ^{1}H NMR Spectrum of RKDHP-2



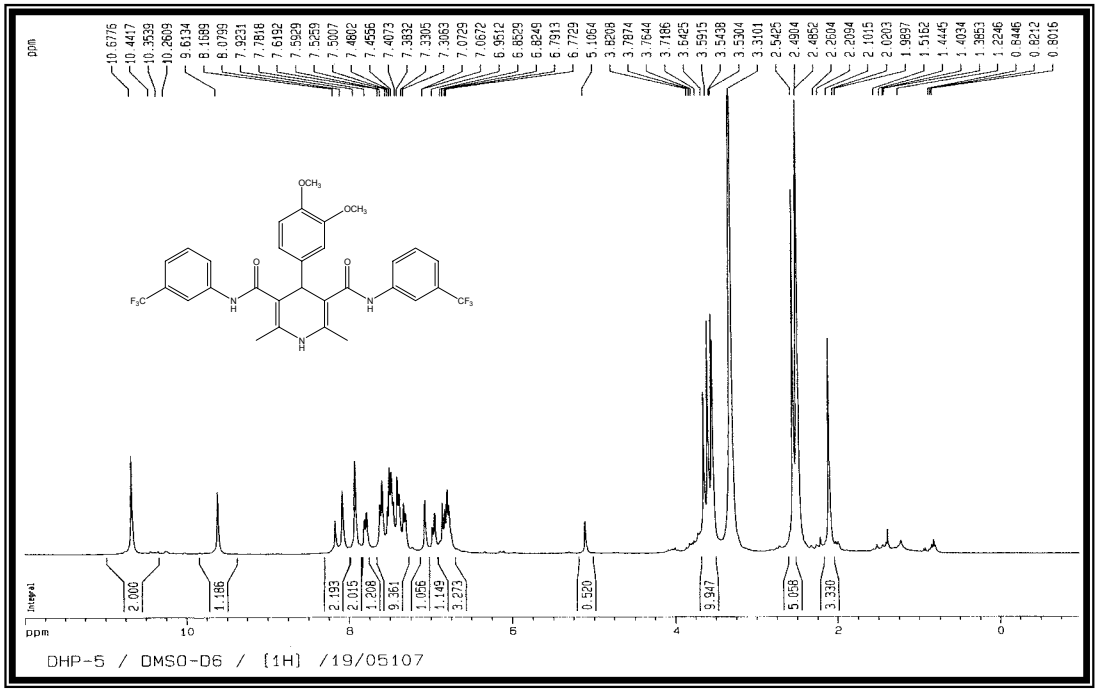
[c] ^{1}H NMR Spectrum of RKDHP-3



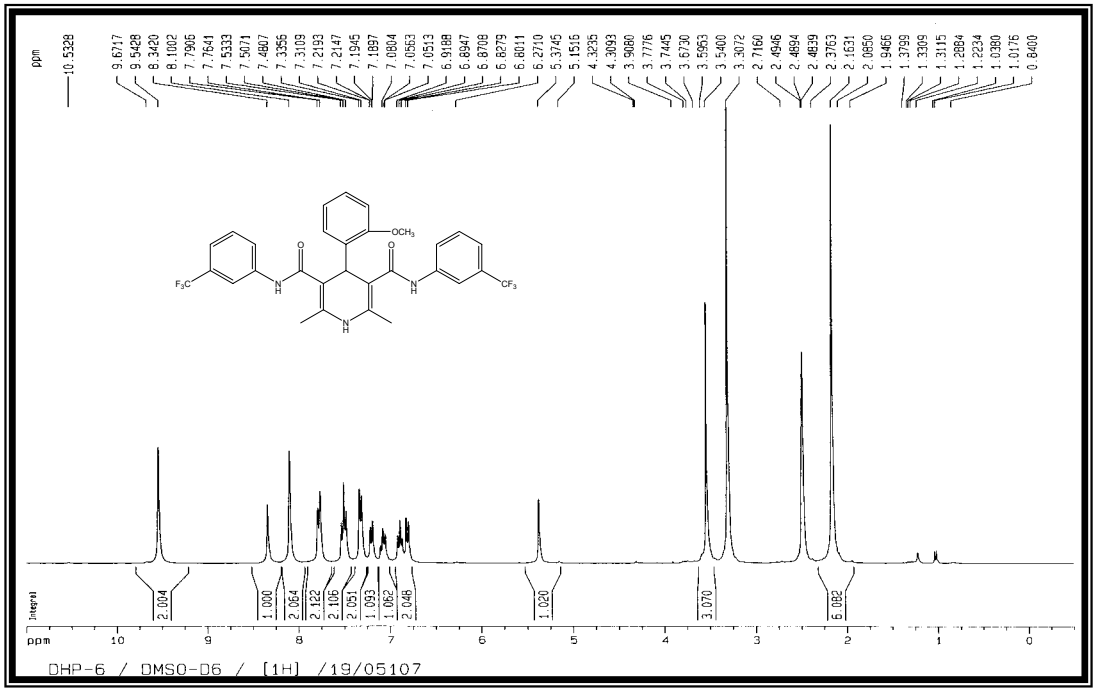
[d] ^{1}H NMR Spectrum of RKDHP-4



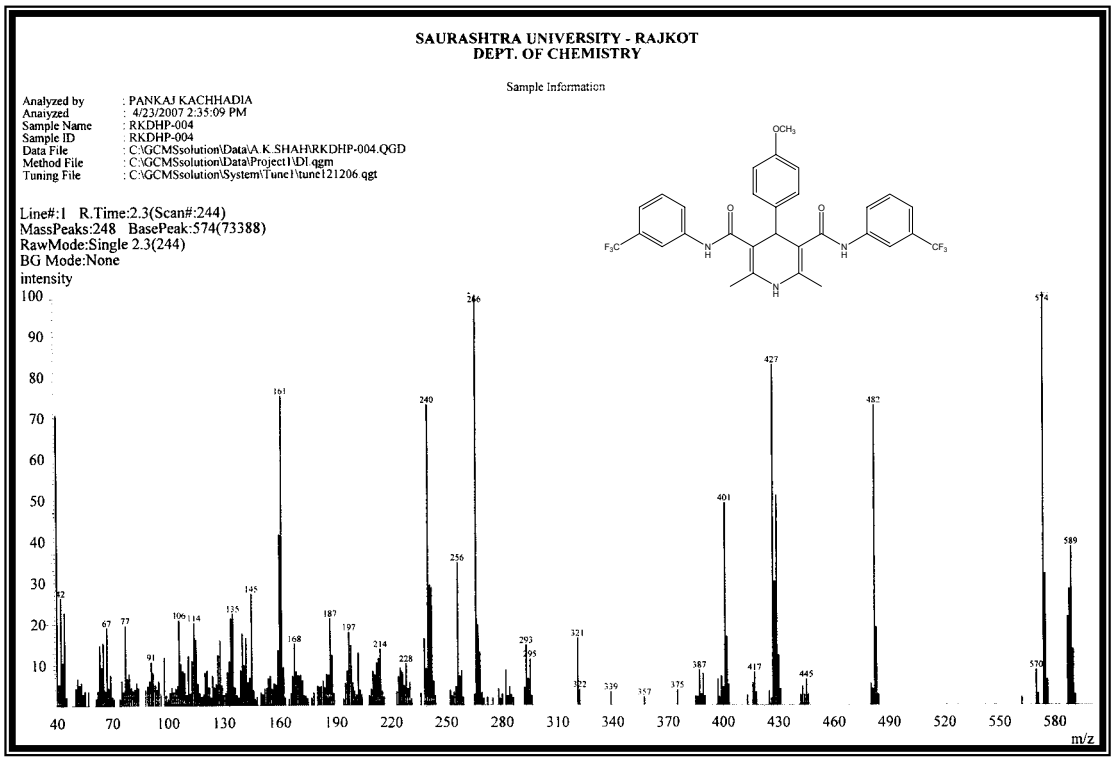
[e] ^{1}H NMR Spectrum of RKDHP-5



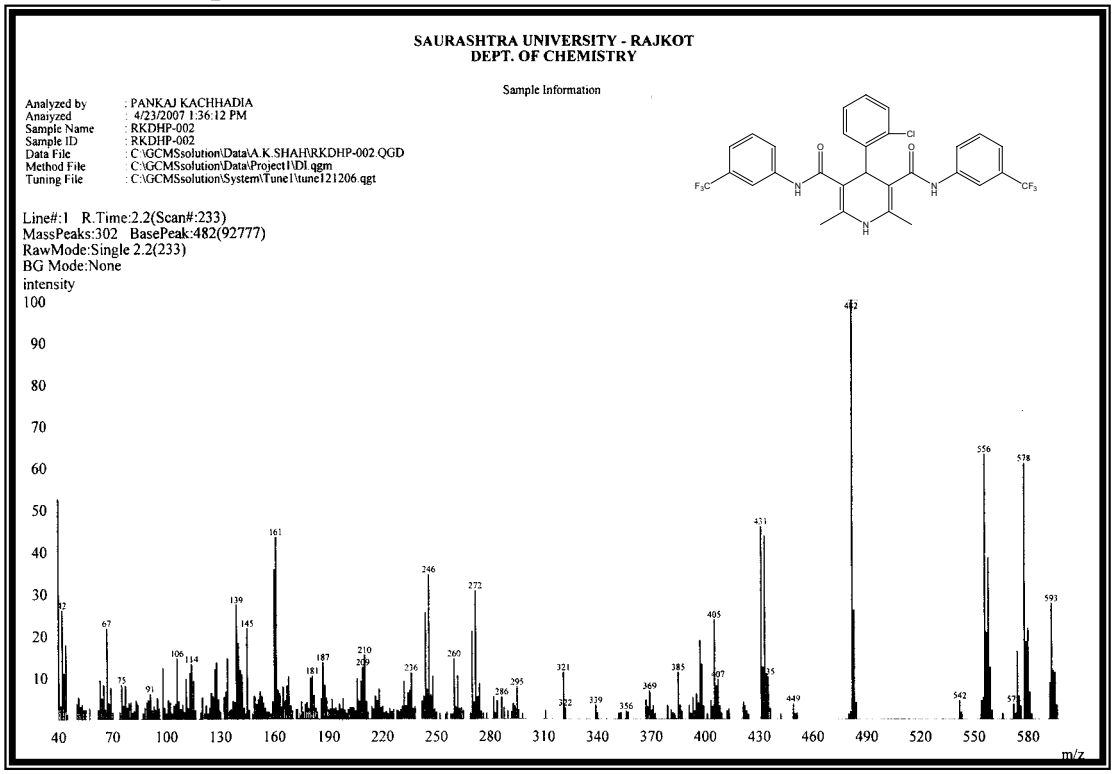
[f] ^{1}H NMR Spectrum of RKDHP-6



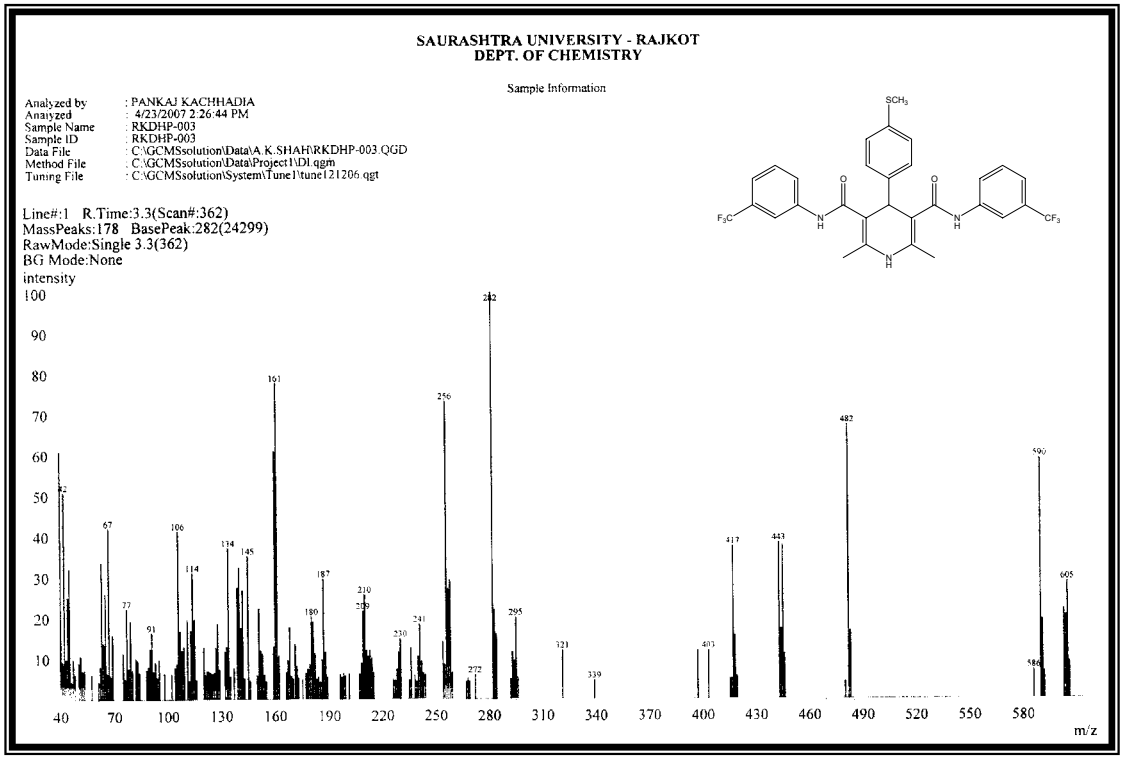
[g] Mass Spectrum of RKDHP-4



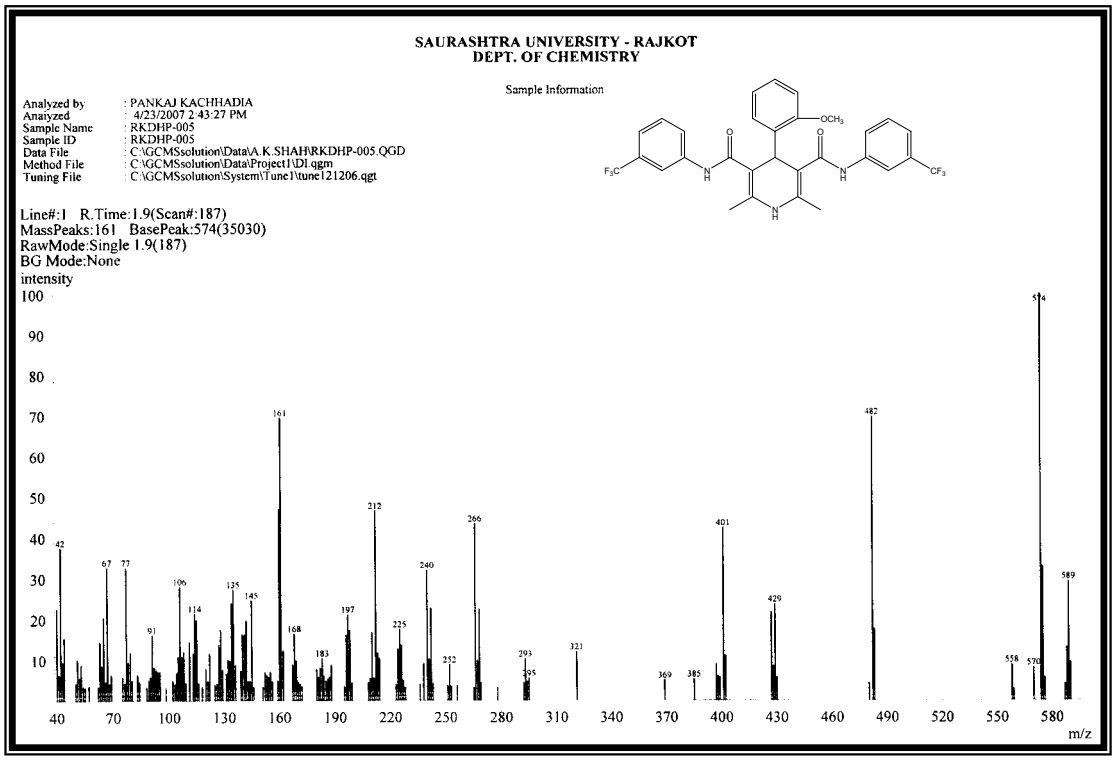
[h] Mass Spectrum of RKDHP-2



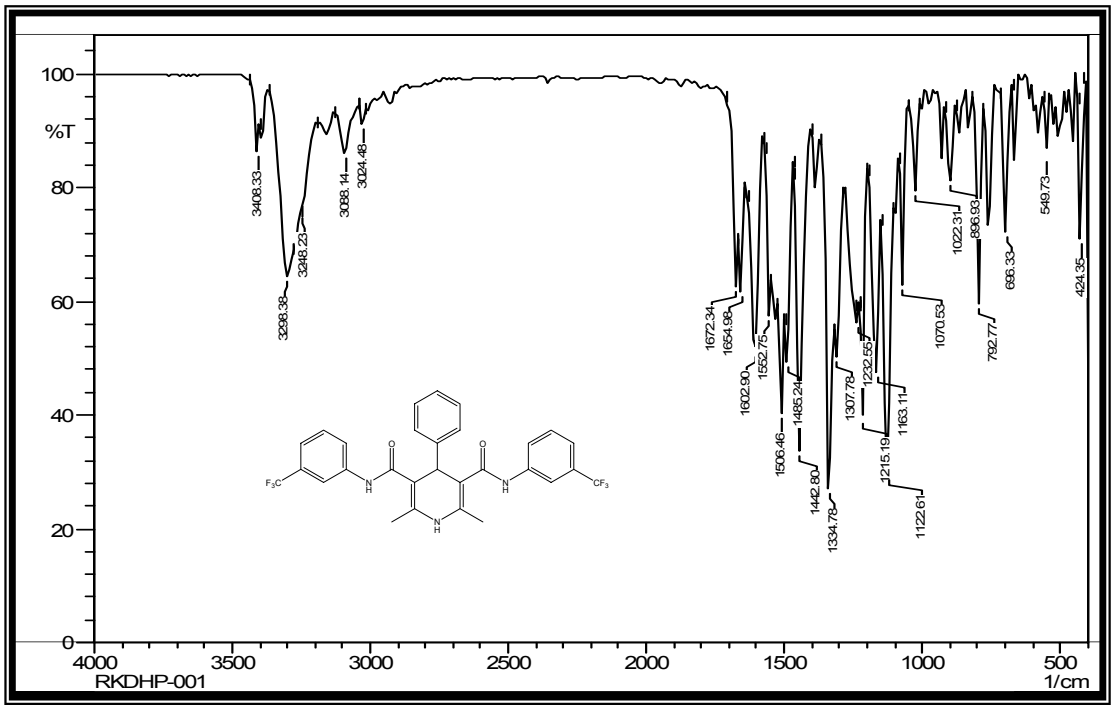
[i] Mass Spectrum of RKDHP-3



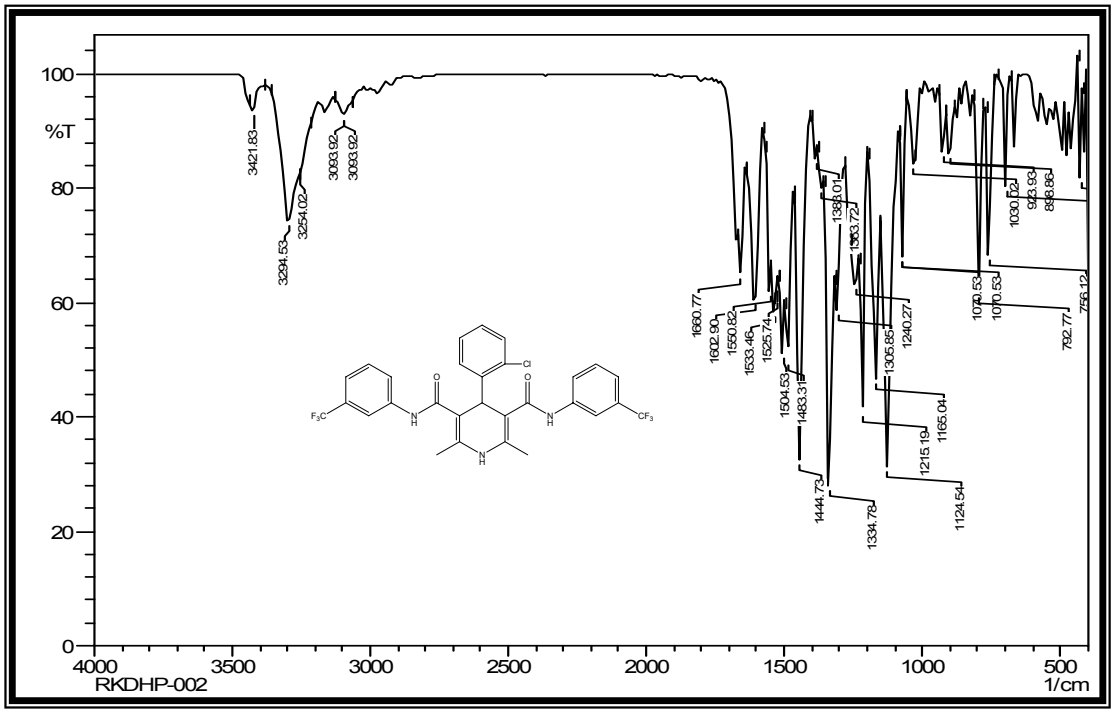
[j] Mass Spectrum of RKDHP-5



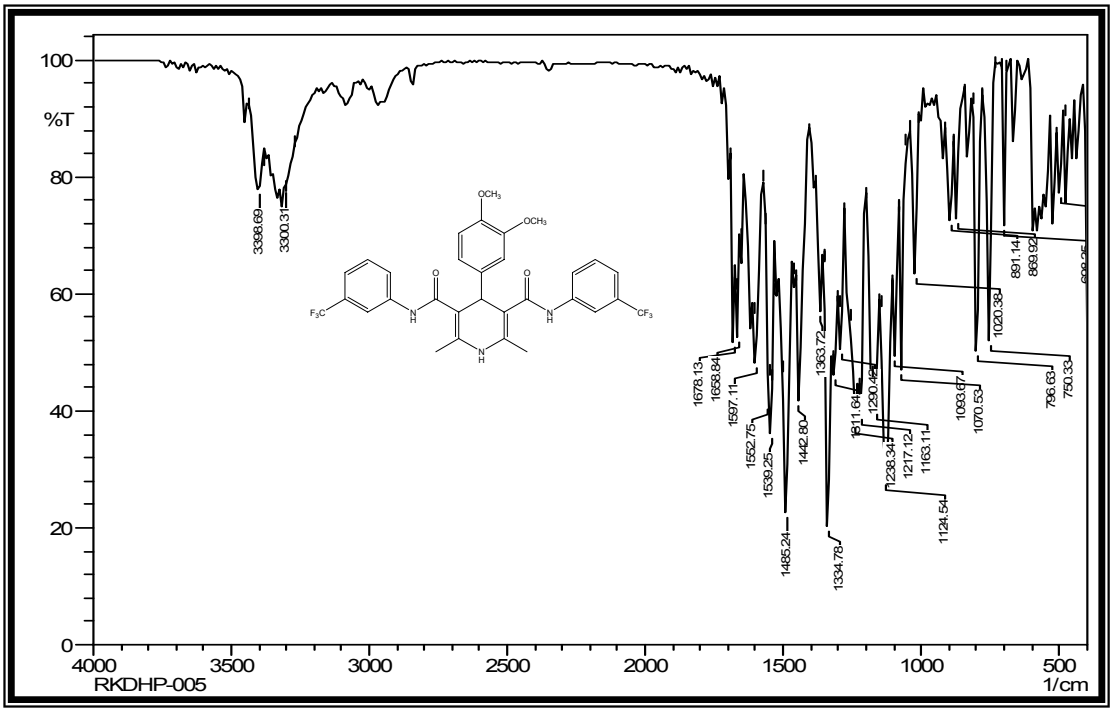
[k] Spectrum of RKDHP-1



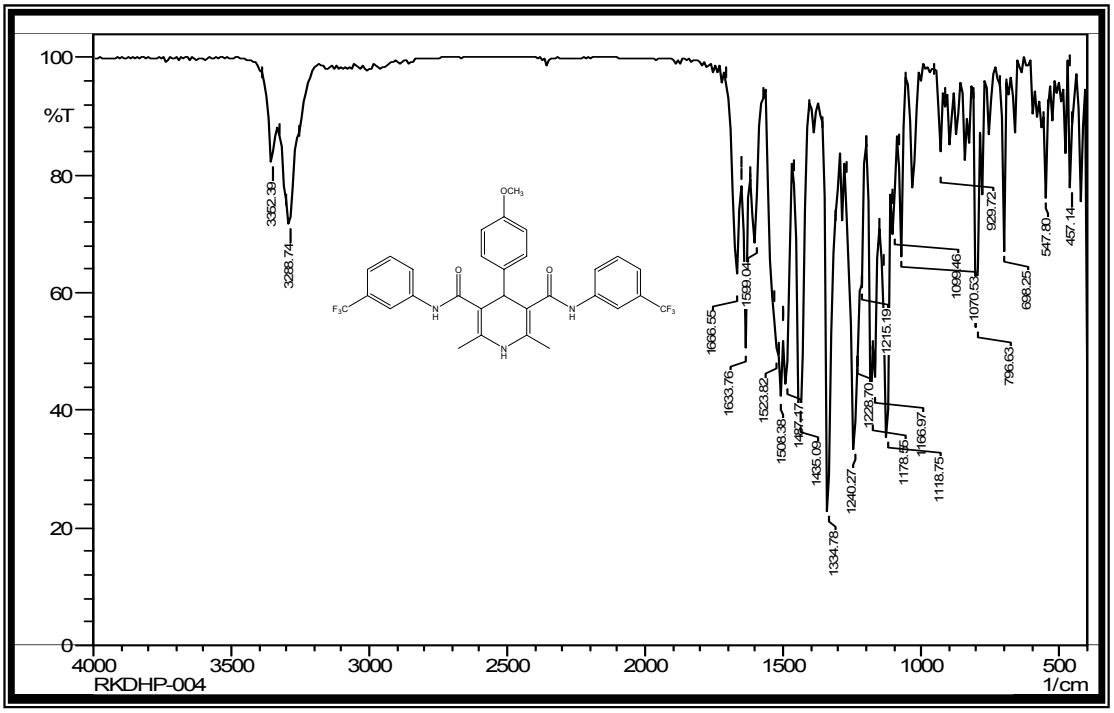
[l] Spectrum of RKDHP-2



[m] Spectrum of RKDHP-5



[n] IR Spectrum of RKDHP-4



Conclusion

In the present work, the Hantzch-pyridine type cyclocondensation(MCRs) of acetoacetanilide bearing a 3-Trifluoromethyl group have been studied. In order to reduce the reaction time, increase the yield and clean process, reaction of acetoacetanilide with different substituted benzaldehyde and ammonium acetate in PEG-400 at $80^{o}C$ temperature under influence of microwave (300W) was afforded, Dihydropyridines at carbon C_3 and C_5 with 3-Trifluoromethyl Phenyl carbamoyl functional group were prepared.

In current work replacement of ester group with (3-triflouromethyl) phenyl ring by Hantzch-pyridine three-component cyclocondensation reaction with slight modification in acetoacetanilide was successfully employed with dual support of PEG mediated and microwave supported synthetic method. It shows that slight change in the building blocks can create a new diversity and ultimately several novel dihydropyridines are obtained. The biological properties of these substances are currently under investigation.

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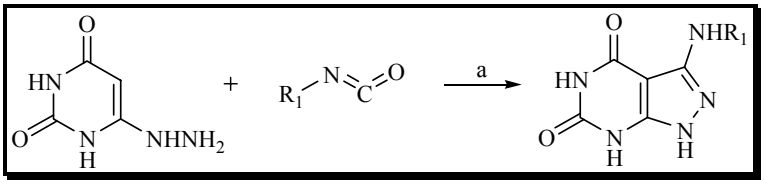
Introduction

SYNTHETIC APPROACH

Several methods have been reported for the different isomer of the Pyrazolo pyrimidines. Several synthetic outlines from the literature survey are depicted below.

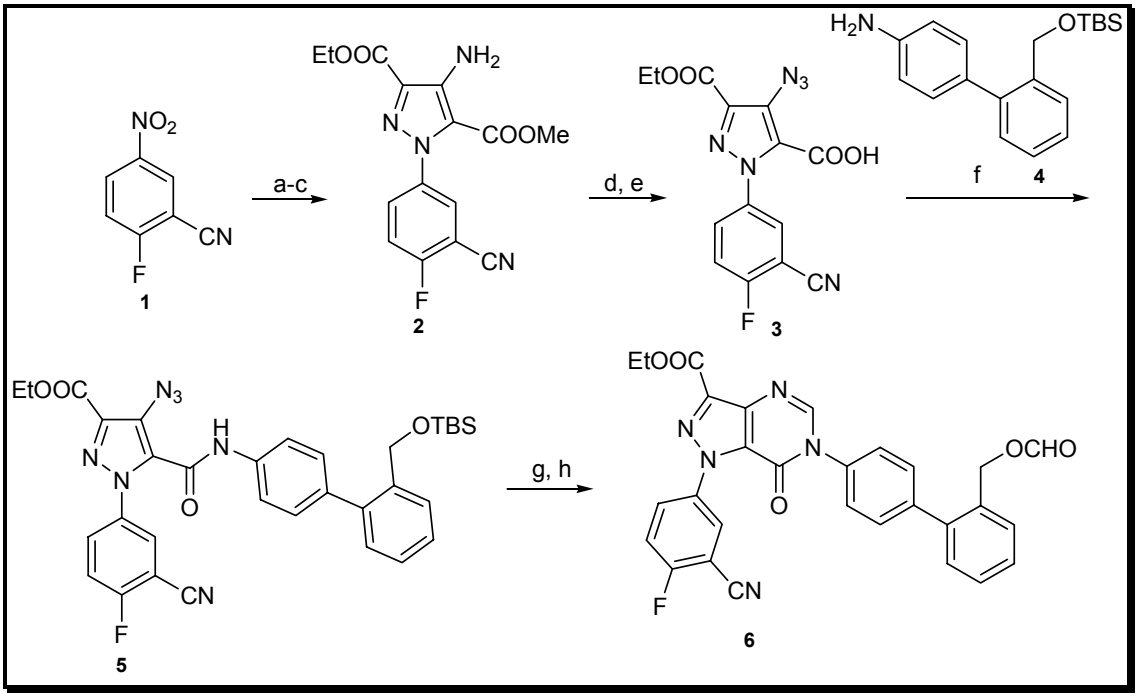
SCHEME 1 [1]



Reagents and condition

Acetic acid, reflux (30min)

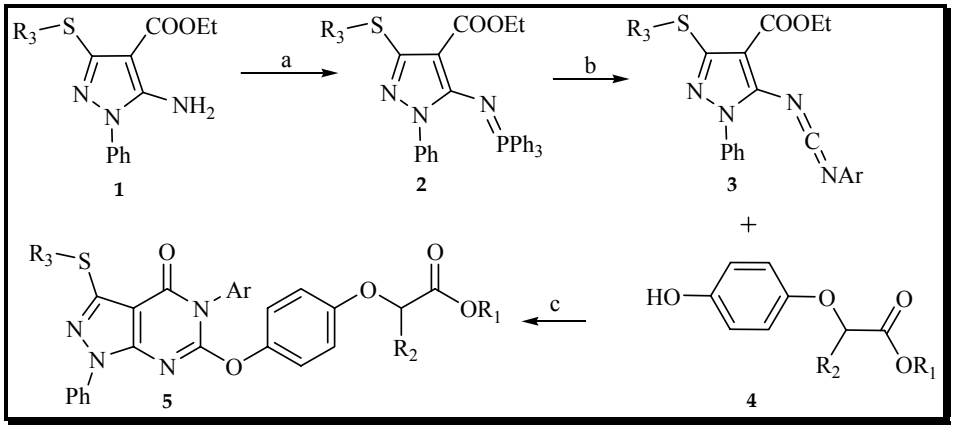
SCHEME 2 [2]



Reagents and condition

(a) H_2 (1 atm), 10% Pd/C, EtOH (95%); (b) $NaNO_2$, HCl/H_2O, 0^oC; then ethyl cyanoacetate, NaOAc, $MeOH/H_2O$, 0^oC (55%); (c) $BrCH_2CO_2Me$, K_2CO_3, DMF, 90^oC (10– 20%); (d) $NaNO_2$, TFA, 0^oC; then NaN_3 (80%); (e) LiOH, THF/H_2O (90%); (f) $(COCl)_2$, CH_2Cl_2; then 4, DMAP, CH_2Cl_2 (70%); (g) $SnCl_2ÆH_2O$, MeOH, 65^oC; (h) 95% HCO_2H, reflux (70% for two steps); (i) AcNHOH, K_2CO_3, DMF; (j) K_2CO_3, EtOH, 65^oC (45% for two steps); (k) PBr_3, CH_2Cl_2; (l) pyrrolidine, CH_3CN, (50% for two steps).

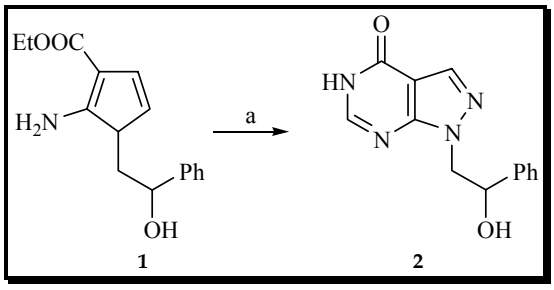
SCHEME 3 [3]



Reagents and condition

(a) PPh_3/Br_2 (b) ArNCO (c) K_2CO_3

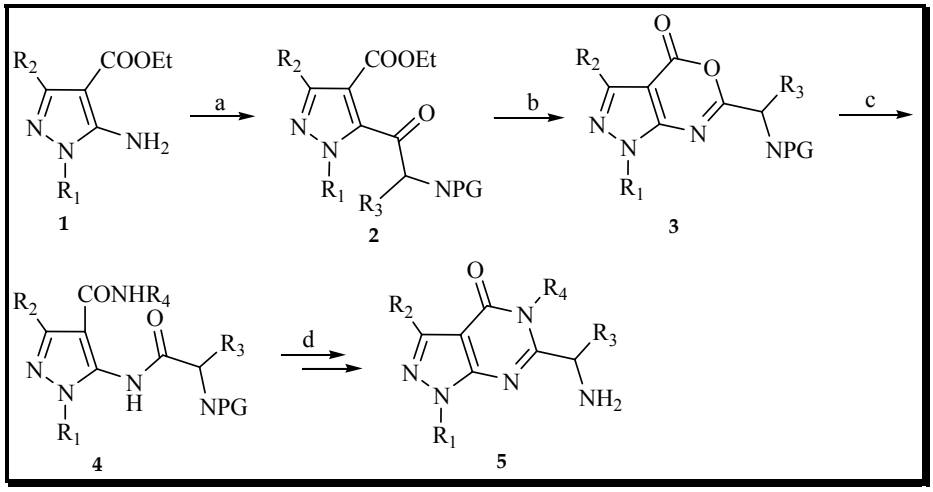
SCHEME 4 [4]



Reagents and condition

(a) $HCONH_2$/ 190^oC

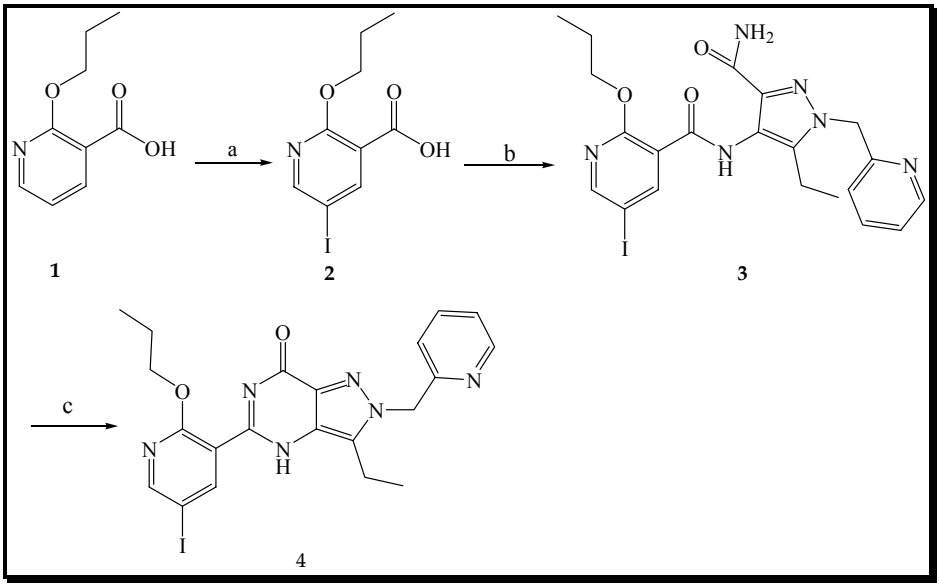
SCHEME 5 [5]



Reagents and condition

(a) i-Pr_2NEt, Toluene, 1h, reflux (b) Cl_3CCl_3, PPh_3, EDC, i-Pr_2NEt, (c) R-NH_2, $CHCl_3$, reflux

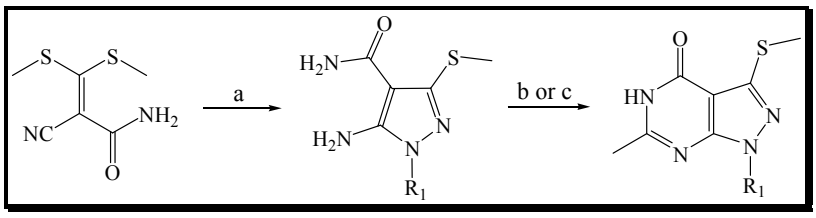
SCHEME 6 [6]



Reagents and condition

(a) NIS (N-Iodo succinimide), TFA (Trifluoro acetic acid) , TFAA (Trifluoro acetic anhydride, reflux (b) $(COCl)_2$, MDC, DMF, 0^oC to RT, then 4-amino-5-ethyl-1-(2-pyridinylmethyl)-1*H*-pyrazole-3-carboxamide, Pyridine, MDC, rt (c) KHDMS, n-propanol, reflux

SCHEME 7 [7]



Reagents and condition

(a) R_1 $NHNH_2$, MeOH, reflux (b) CH_3CONH_2, Heat (c) CH_3CO_2Et, NaOEt, EtOH

Biological Activity Displayed by Pyrazolo pyrimidines

The biological activity of pyrazolo pyrimidines is enlisted as below.

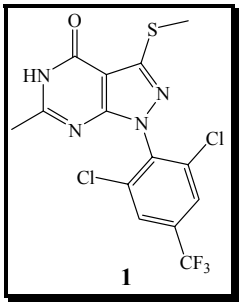
1. CDK-inhibitors
2. Phosphodiesterase 5 inhibitors (PDE5 inhibitors)
3. Activity against Thromboembolic disease
4. Herbicidal activity
5. Antiproliferative activity
6. p38 Kinase inhibitors

1. CDK-inhibitors

Controlling the cell cycle by inhibition of the proteins that regulate its progression is an attractive strategy for addressing cancer and other diseases associated with abnormal cellular proliferation. [8] One family of such proteins, the cyclin-dependent kinases (CDKs), is made up of at least nine highly homologous enzymes that in association with specific regulatory subunits (cyclins) control progression of the cell cycle. [9] CDK/cyclin activity oscillates with cyclin expression/degradation and is further regulated by the action of several families of protein kinases and phosphatases. [10, 11] A series of checkpoints serves to ensure the viability of progeny cells by preventing progression of cells with damaged DNA, an inappropriate chromosome count, or for which necessary structural features or conditions of nourishment do not exist. Passage through an initial G1 restriction point occurs upon release by the retinoblastoma protein (pRb) of the transcription factor E2F. [12] This is triggered by phosphorylation of several S/T residues on pRb, the primary substrate of CDK4/cyclin D. The fate of cells that enter G1 but which do not progress through the G1 or subsequent checkpoints is to undergo apoptosis. [13]

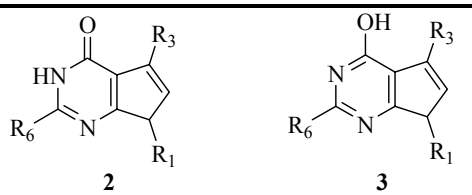
Since tumour cells have misregulated cell cycles, it has been postulated that they may be especially sensitive to agents that restore checkpoint control. The importance of these kinase pathways is highlighted by the fact that the genes encoding CDKs, their cyclin partners, or their endogenous peptide inhibitors (CKIs) are mutated in a large proportion of human tumours. [14] One family of CKIs, the CIP/KIP class, is relatively promiscuous, having affinity for CDK2, CDK3, CDK4, and CDK6. [15] CKIs in the INK4 class, however, are highly selective for the closely related CDKs 4 and 6,

suggesting the possibility of selective inhibition by small molecule mimics. For these reasons, we sought to discover small-molecule protein kinase inhibitors that were selective for CDK/cyclin complexes, specifically CDK4/cyclin D1. Applicability of this approach to cancer chemotherapy is still an unresolved question. While a number of small-molecule CDK inhibitors have been disclosed, clinical experience is limited to the ATP-competitive agent flavopiridol. [16] Flavopiridol is relatively nonselective in its inhibition of the various CDKs; it also appears to inhibit other protein kinases. More recently, great strides have been made in the search for CDK-selective kinase inhibitors, including the discovery of a highly selective CDK4/cyclin D inhibitor by optimization of a nonselective lead. [17] Markwalder, J. A. et al [18] identified a lead compound 4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-one **(1)** by high-throughput screening of a subset of ~160000 compounds. The compound is active against CDK4/cyclin D1 was performed with a readout of percentage inhibition of pRb phosphorylation at 20μM. Discrete IC_{50} values were obtained for compounds that were active upon retest and appeared chemically attractive. This screening strategy identified several series of inhibitors with modest potency (IC_{50}‹ 50μM)



1

Recently Markwalder et al [19] have patented the following core structure **2** or it isomeric structure **3** as a potent CDK inhibitors.



2 **3**

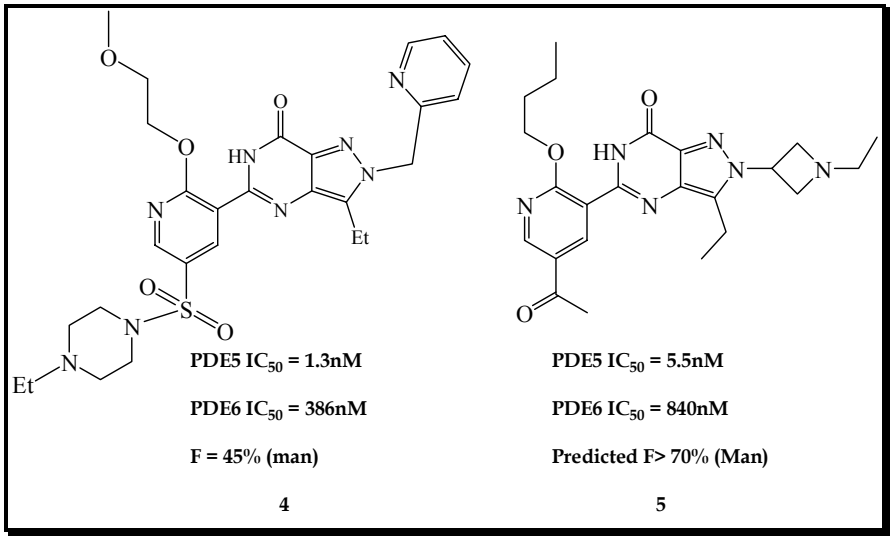
Where R_1= Hydrogen, alkyl, cycloalkyl, aralkyl, etc.

R_3=Hydrogen or lower alkyl

R_6= Substituted or unsubstituted aralkyl or heteroaralkyl

2. PDE5 inhibitors

Phosphodiesterases (PDEs) are a superfamily of enzymes that degrade the intracellular second messengers cyclic AMP and cyclic GMP [20-22]. As essential regulators of cyclic nucleotide signaling with diverse physiological functions, PDEs are drug targets for the treatment of various diseases, including heart failure, depression, asthma, inflammation and erectile dysfunction [23-26]. Of the 12 PDE gene families, cGMP-specific PDE5 carries out the principal cGMP-hydrolysing activity in human corpus cavernosum tissue. It is well known as the target of sildenafil citrate (Viagra) and other similar drugs for the treatment of erectile dysfunction. Despite the pressing need to develop selective PDE inhibitors as therapeutic drugs, only the cAMP-specific PDE4 structures are currently available [27-28].



The launch of sildenafil as the first oral treatment for male erectile dysfunction revolutionized the treatment of this disease. [29]

Following the development of sildenafil, the PDE5 inhibitors with greater selectivity over phosphodiesterase type 6 (PDE6), since this enzyme is believed to be responsible for the low incidence of adverse visual events, such as abnormalities in color vision, associated with high doses of sildenafil. SAR describing how this selectivity was achieved through the discovery of the pyridyl methyl analogue **4** has already been published. [30] Compound **4** is a potent PDE5 inhibitor displaying approximately 300-fold selectivity over canine cone PDE6. [30] In clinical trials, compound **4** showed dose-dependent increases in *C*max and AUC over the dose range 1-800 mg and increases in these

parameters when coadministered with ketoconazole (a potent inhibitor of P-glycoprotein and CYP3A4).15 Further studies showed that compound **4** is a substrate for human P-glycoprotein and CYP3A4, which explains the variations in pharmacokinetic data that arose when these species were either saturated or inhibited. As a consequence of these clinical data, we desired a PDE5 inhibitor with high and dose-independent oral bioavailability, since this would minimize the impact of any interactions with coadministered drugs in the clinic. [31]

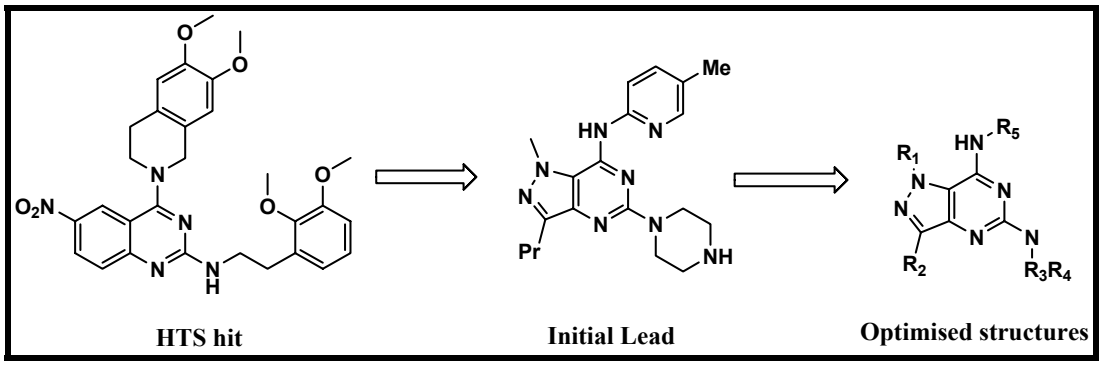
In order to identify a potent and selective PDE5 inhibitor with high and dose-independent oral bioavailability, to minimize the impact on *C*max of any interactions with coadministered drugs. In general, good solubility, high absorption across the intestinal wall, and low first-pass clearance are required for high oral bioavailability. [32] Focused was on reducing the first-pass clearance of soluble, rule-of-five compliant [33] PDE5 inhibitors to achieve this objective. The piperazine sulfonamide group is the primary site of metabolism in the sildenafil series. [34] Consequently, finding of a more metabolically stable replacement for this functionality. This led to a novel series of potent and selective PDE5 inhibitors, with a methyl ketone at the 5'-position of the 5-(2-alkoxy-3-pyridinyl)-2, 6-dihydro-7*H*-pyrazolo [4,3-*d*]pyrimidin-7-one **5** template. These compounds are relatively small (MW<500) with moderate lipophilicity, and this results in good oral absorption. In addition, they have low clearance (the predominant metabolite in human hepatocytes being the secondary alcohol) and a basic group attached at the N_2 position, which provides good aqueous solubility *via* salt formation. The combination of these factors leads to high oral bioavailability *in vivo*.

Pfizer Global Research and Development, United Kingdom team has carried out SAR of pyrazolo-pyrimidines for getting optimized structure of the PDE5 inhibitors. The clinical knowledge gained from the pioneering PDE5 inhibitor sildenafil and subsequent agents, has highlighted the potential of PDE5 inhibition for treatment of additional indications beyond male erectile dysfunction. Such indications would be best treated by highly selective agents suitable for chronic once daily oral dosing. This talk details the discovery and progression of a pyrazolopyrimidine PDE5 inhibitor series designed to display inherently good physicochemistry, and targeting a chronic once daily treatment goal. Key features can be summarized.

1. Rationalisation of SAR in the pyrazolopyrimidine series with emphasis on the C_3 substituent. Rationalisation includes the use of co-crystal structure information to guide design for potency and selectivity.

2. An assessment of physical properties in the series with emphasis on optimising permeability and clearance to drive long half-life oral pharmacokinetics.

3. In depth assessment of a PDE5 selective and physicochemically optimised lead with the potential for once daily dosing in man.[35]

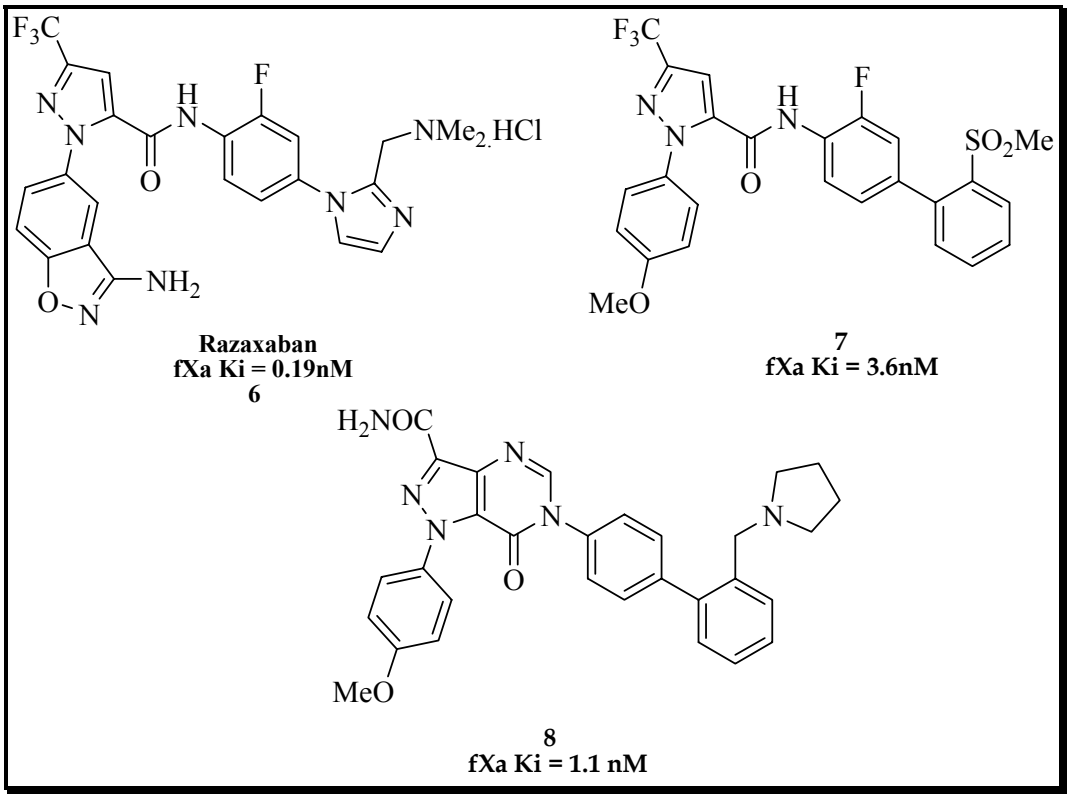


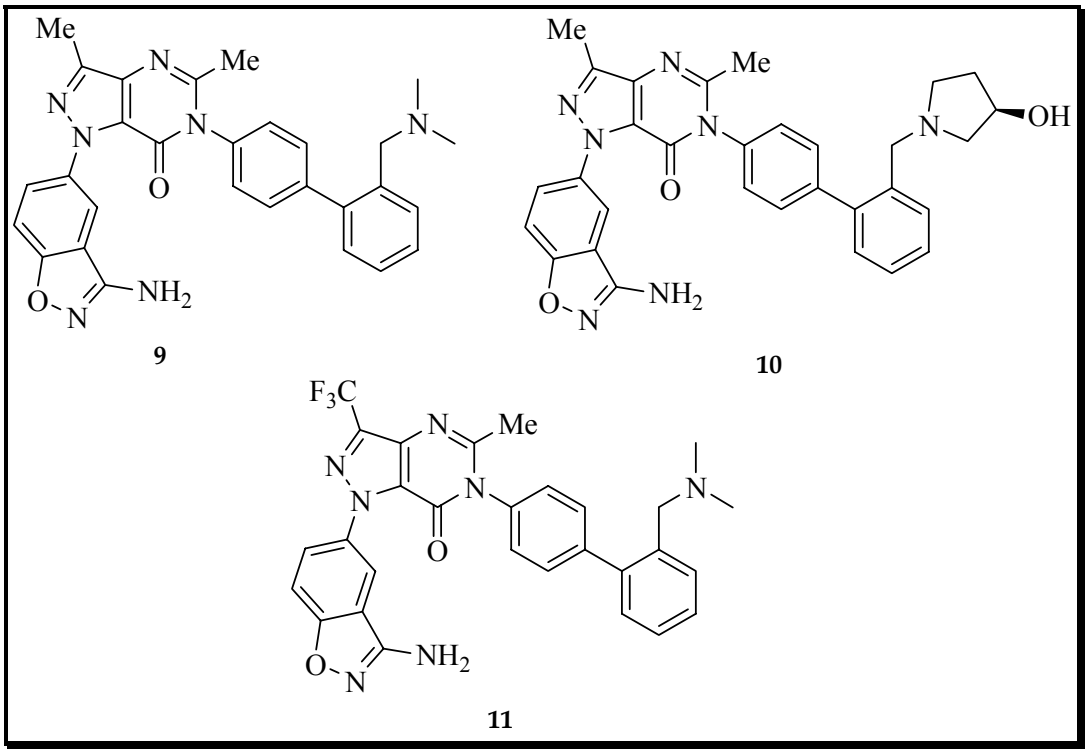
3. Coagulation factor Xa

Thromboembolic diseases remain the leading cause of death and disability in developed countries. This reality, combined with the limitations of current therapies, has led to extensive efforts to develop novel antithrombotic agents. [36] Factor Xa has become a major focus of pharmaceutical intervention in the past decade because of its central role in the blood coagulation cascade. [37] Extensive preclinical and clinical evidence has demonstrated that inhibition of factor Xa is efficacious in both venous and arterial thrombosis. [38, 39] Previously, it was demonstrated that a series of non-benzamidine N-arylpyrazole carboxamides, represented by the 3-aminobenzisoxazole P1 analog razaxaban [40] were highly potent, selective, and orally bioavailable small molecule fXa inhibitors (Fig. 1). Razaxaban has been shown to be efficacious in phase II deep vein thrombosis (DVT) clinical trials. [41] Furthermore, it was demonstrated that the 4-methoxyphenyl residue could be an effective P1 group when combined with an optimized pyrazole-P4 subunit, as in compound **7.** [42] Recently, bicyclic core variants of 2, represented by the 1H-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one **8**, [43] have been shown to retain potent binding affinity for fXa. These bicyclic variants were also expected to be less susceptible to *in vivo* amide hydrolysis, which in the case of N-arylpyrazole

carboxamides such as **(6)** and **(7)** would liberate a biarylaniline fragment. However, compound **(8)** was found to have only modest efficacy in a rabbit rteriovenous (A-V) shunt thrombosis model [44] relative to razaxaban. This was rationalized on the basis of 3 being 5-fold less potent than razaxaban. [43]

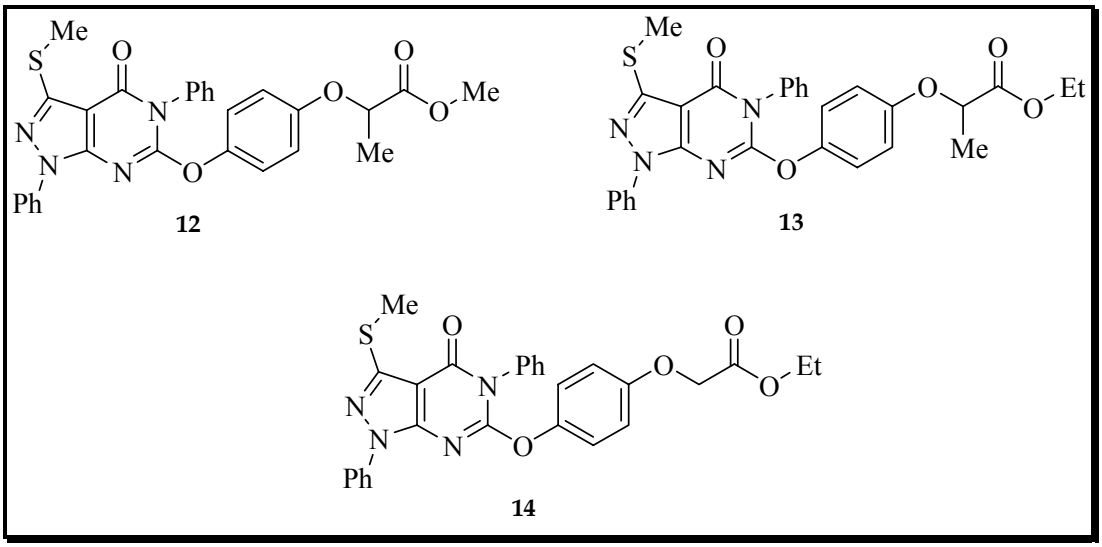
Li, Y. L. et al [45] have synthesized and screened a small library and screened for their coagulation factor Xa. Among the designed series compounds **9, 10** and **11** are not only potent fXa inhibitors, but they are also highly selective versus relevant serine protease. Compound has a favourable pharmacokinetic profile in dogs, with lower clearance and longer hald-life relative to Razaxaban. Furthermore, **9, 10** and **11** are highly efficacious in the rabbit A-V shunt thrombosis model, with activity comparable to the clinical candidate, razaxaban.

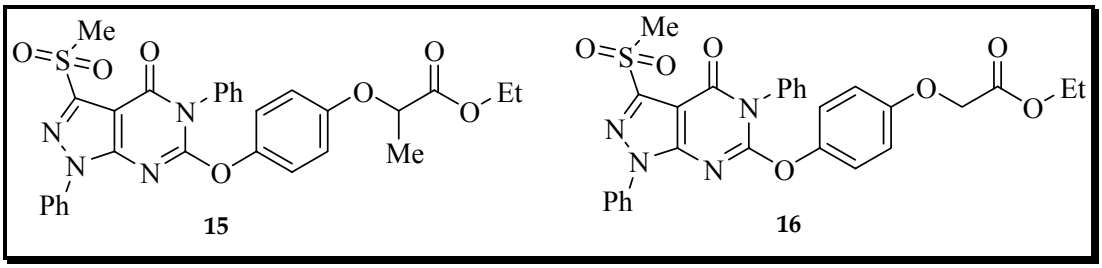




4. Herbicidal activity

Liu, Z. et al [46] have synthesized the small library of 6-(4-alkoxycarbonylalkoxy)phenoxy-3-alkylthio(alkylsulphonyl)-1-phenyl-5-(substituted phenyl)pyrazole[3,4-*d*]pyrimidin-4-ones and screened for the herbicidal activity. The herbicidal activity of all the compounds were taken against *brassica napus* (rape) and *echinochloa crus-galli* (barnyard grass) has been investigated at the dosage of 100 and 10mg/L using the reported procedure, compared with the distilled water and 2,4-dichlorophenoxyl acetic acid (2,4-D), a commercially available herbicide in the market. The results of preliminary bioassay showed that some of them exhibit good herbicidal activities. Out of the designed series compounds **12, 13, 14, 15** and **16** showed more than 90% inhibitory rate to root of rape and barnyard grass at 100mg/L. it is also interesting to note that ethyl ester showed higher herbicidal activity than the corresponding methyl ester and n-propyl ester in general. The reason may be the hydrolysis of the products.

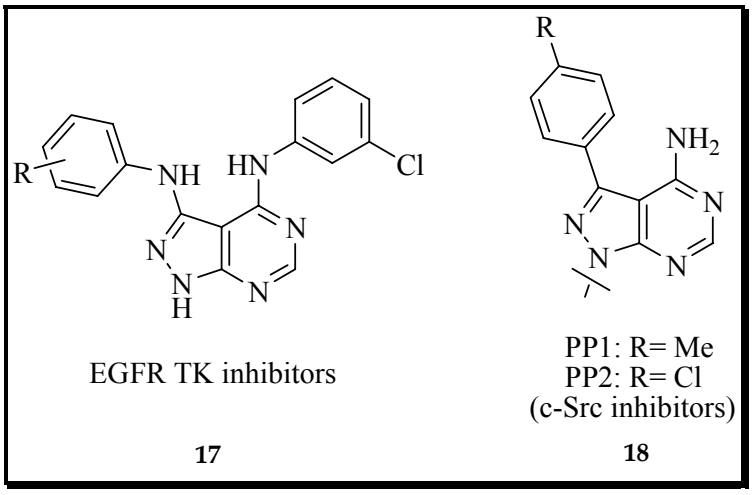




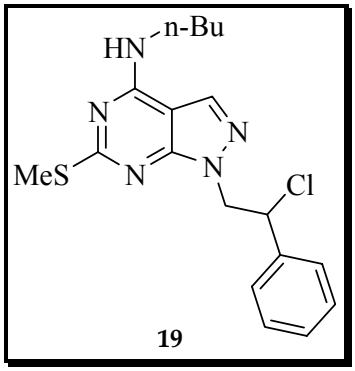
5. Antiproliferative activity

The understanding of the fundamental biology of cancer increased dramatically in recent years [47] and has strongly impacted on both experimental and gradually also on clinical tumour therapy. We now believe that the future of tumour therapy is in the development of molecularly targeted agents that specifically block key mechanisms involved in development and progression of specific types of cancer. [48] Due to their critical role in tumour development and progression, molecules capable of inhibiting protein kinases are of central interest in targeted cancer therapy. In particular, tyrosine kinases (TKs) are enzymes that catalyze the specific phosphorylation of tyrosine residues on proteins. Protein tyrosine kinases (PTKs) participate in a wide variety of cellular activities including proliferation, secretion, adhesion, and responses to mitogens and stress. [49, 50] The TK Src is the prototype member of the nonreceptor Src family of PTKs that include c-Yes, Fyn, c-Fgr, Lyn, Lck, Hck, Clk, Yrk, and c-Src. [51] In particular, the nonreceptor pp60c-Src PTK transduces signals that control the above cellular processes. [52-54] Src is activated following engagement of many different classes of cellular receptors and

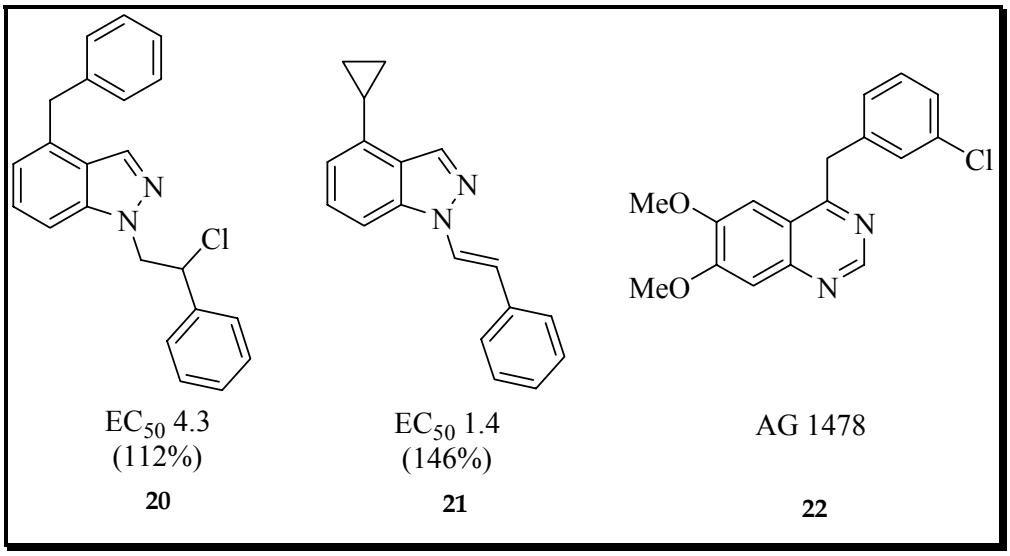
participates as a convergence point in different signaling pathways. [49, 50, 55] In this regard, Src is a critical component of the signaling cascades initiated by tyrosine kinase-linked receptors, such as the epidermal growth factor receptor (EGFR), and Gprotein coupled receptors and is directly associated with, and may regulate signaling via, the EGFR and HER-2/ neu receptor PTKs, [56, 57] both of which are involved in cancer. Finally, Src overexpression and activation has been correlated with a large number of growth-regulatory processes in which Src participates. In particular, the Src protein is overexpressed in many tumours such as colon, breast, gastric, and prostatic tumours and plays a key role in controlling their proliferation and invasiveness. [58, 59] On the basis of these considerations, inhibitors of Src phosphorylation process may stop uncontrolled tumour cell growth and play an important role as new therapeutic agents for the treatment of cancer. During the past decade, examples of pyrazolo[3,4-*d*]-pyrimidines active as TKs inhibitors have been reported in the literature by different authors. Many of these compounds were highly active, and some of them have been largely used as standard or reference compounds and as a tool to set up *in vitro* assays and to prove their functionality. However, only a few demonstrated *in vivo* activity. As an example, approaches aimed at identifying ATP-competitive small molecules led to the characterization of derivatives 1 as potent inhibitors of EGFR TK, **(17)** [60] while PP1 and PP2 **(10)** were described as very strong and selective inhibitors of the c-Src family of kinases. [61] Unfortunately, attempts to improve the biological profile of the latter compounds have so far met little success. Following these studies, some other inhibitors, possessing different chemical structures and interesting c-Src inhibitory activity, have been recently reported. In particular, pyrrolo[2,3-*d*]pyrimidines have been described as selective and potent inhibitors of c-Src with inhibition potency of about 10nM and 20-fold selectivity toward a panel of other TKs. [62] Other efforts directed to c-Src kinase inhibitors included substituted 5,10-dihydropyrimido[4,5-*b*]quinolines, showing an *in vitro* c-Src inhibition activity in the nanomolar range. [63]



Schenone et al [64] synthesized and screened 4-aminopyrazolo[3,4-*d*]pyrimidines bearing various substituents at position 1 and 6. The synthesized compounds were screened for their anti porliferative activity agintst A431 cell line. The compound **19** shows the better inhibitors of the Src phosphorylation than the reference compound PP2 **(18).**



Schenone et al [65] have also synthesized a series of 4-aryl-4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidine and tested against tumour cell lines A 431. Among the designed series the most potent having EC_{50} values 4.3 **(20)** and 1.4 **(21).** The values in the parenthesis denote the % inhibition of relative to the reference compound (AG1478) **(22).**



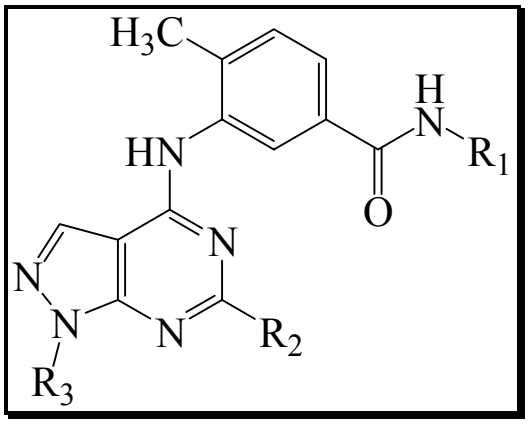
EC_{50} 4.3 (112%) **20**

EC_{50} 1.4 (146%) **21**

AG 1478 **22**

6. p38 Kinase inhibitors

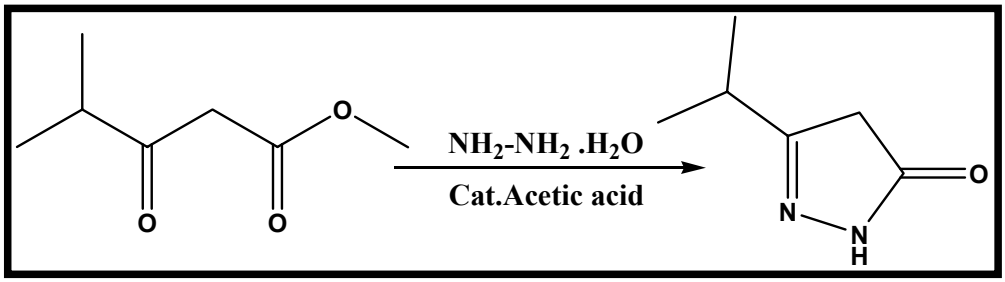
Bristol-Myers Squibb Pharmaceutical Research institute reported that Pyrazolo-pyrimidines as selective and potent p38 inhibitors. P38 kinase is a key enzyme involved in regulating the production and action of pro inflammatory cytokines such as tumour necrosis factor (TNF). Inhibitors of p38 kinase therefore may have utility in the treatment of multiple inflammatory diseases such as rheumatoid arthritis (RA). BMS team has recently discovered a novel series of pyrazolo-pyrimidines as highly potent and selective p38 inhibitors. The lead compound from this series possesses activity in an *in vivo* preclinical model of acute inflammation. Synthesis, SAR studies and an X-ray co-crystal structure of a prototypical analog bound to the enzyme will be presented. [66]



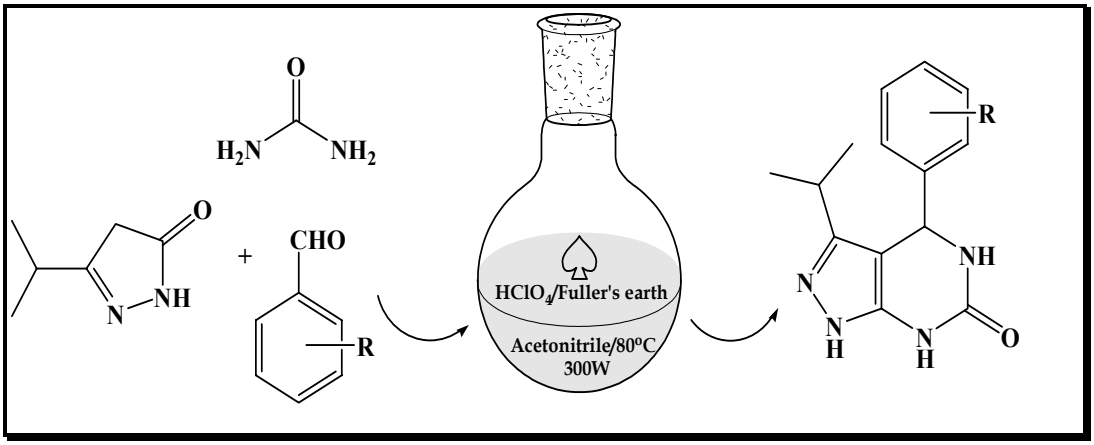
In current chapter, synthetic work carried out leading to the formation of pyrazolo[3,4-*d*]-pyrimidinones by multicomponent single step reaction. The synthesis was initiated with the reaction of β-ketoester with hydrazine hydrate in catalytic amount of acetic acid to obtain pyrazolones, which further reacted with urea and substituted banzaldehyde in presence of $HClO_4$-fuller's earth and under the influence of the microwave irradiation to get the title compounds.

Reaction Scheme

Step-I

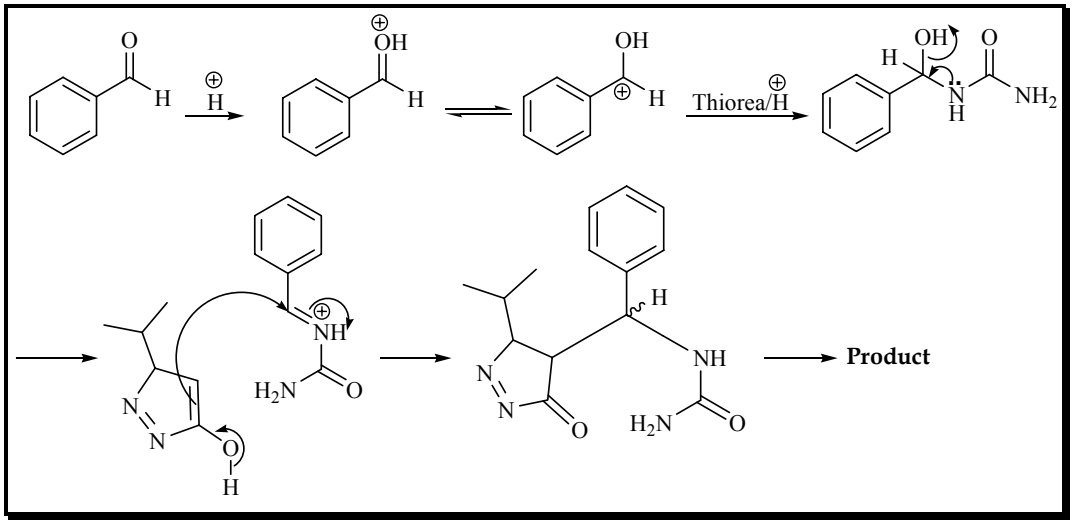


Step-II

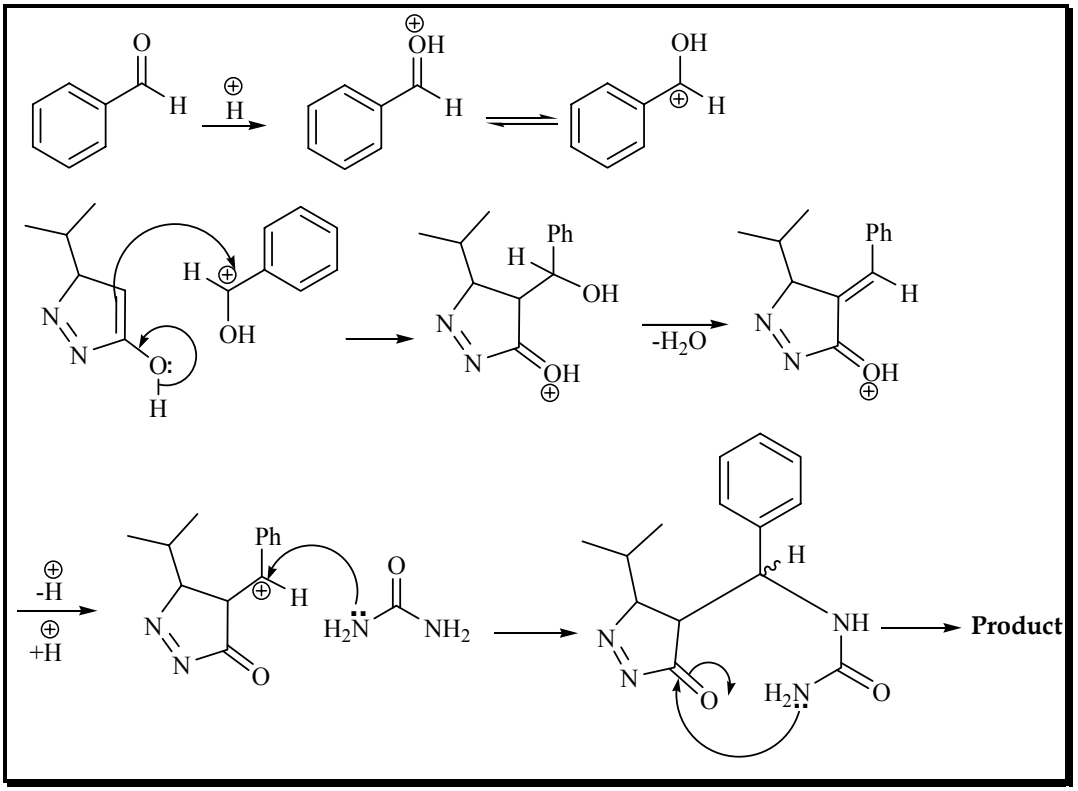


Plausible mechanisms

Path A



Path B



Experimental protocol

Preparation of Catalyst

A 70% aqueous perchloric acid (1.8 g, 12.5 mmol) was added to a suspension of Fuller's earth 23.7 g) in ether (50 ml). The mixture was concentrated and the residue was heated at 100°C for 48 h under vacuum to give Fuller's earth-$HClO_4$ (0.5 mmol/g) as free flowing powder (50 mg = 0.025 mmol of $HClO_4$).

Step-I Synthesis of 3-Isopropyl-1*H*-pyrazol-5(4*H*)-one

1.0 equivalent of β-ketoester (methyl 4-methyl-3-oxopentanoate) and 2-3 drops of acetic acid was stirred at 20°C. 1.1 equivalent of hydrazine hydrate was added into it. It was stirred for 5-10 minutes at 15-20°C maintained temperature range. Solid product was precipitated, filtered by suction and washed twice with 20 ml of water. Then it was washed with methanol: water (50:50). It was dried at 40°C under vacuum for 2 hours.
The structure of the product was confirmed by ^{1}H NMR and ^{13}C NMR.

TLC System: (Hexane: Ethyl acetate)
8 : 2
Yield: 75%, MP: - 185°C.

Step-II Synthesis of 4,5-Dihydro-3-isopropyl-4-(substituted phenyl)-1*H*-pyrazolo[3,4-*d*]-pyrimidine-6(7*H*)-ones by influence of microwave (General Method)

1.5 equivalents of urea and 15 ml acetonitrile were taken in microwave flask, stirred until clear solution was observed. 1.0 equivalent of substituted benzaldehyde, pyrazolone and 25mol% heterogeneous catalyst $HClO_4$/Fuller's earth was added into it. The reaction mixture was subjected to microwave irradiation at 300W power and 80°C for an appropriate time. Reaction was monitored by TLC, after completion of reaction as indicated by TLC, it was filtered at 60-65°C by suction and kept it in fridge for 2-3 hours. Solid product was obtained, filtered, and washed twice with 10 ml acetonitrile. It was dried at 50°C for 2 hours. The reaction time and percentage yields are depicted in the Physical Data Table.

TLC System: (Chloroform: Methanol) +1-2 drops of acetic acid
7 : 3

Step-II Synthesis of 4,5-Dihydro-3-isopropyl-4-(substituted phenyl)-1*H*-pyrazolo[3,4-*d*]-pyrimidine-6(7*H*)-ones by conventional method (General Method)

The intimate mixture of banzaldehyde (1.0 equivalent), pyrazolone (1.0 equivalent) and urea (1.5 equivalents) was stirred in acetonitrile (20ml) until clear solution was observed. Conc. HCl (3-4 drops) was added as the catalyst. The reaction mixture was allowed to reflux for an appropriate time. After the completion of reaction, the reaction mixture was cooled. In some reaction, the solid product was found during the reflux. The product was filtered and washed with acetonitrile and dried in oven.

The reaction time and percentage yields of the respective products are shown in the Physical Data Table No. 5

Physical data of 4,5-dihydro-3-isopropyl-4-substitued phenyl-1H-pyrazolo [3,4-d]pyrimidine-6(7*H*)-ones

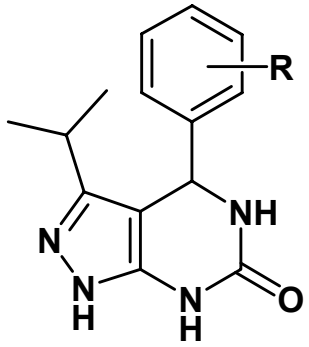


Table. No: 5

Code.No	Substitution R	M.F	"Conventional heating		Microwave irradiation		M.W	M.P ^{O}C	C, H , N Analysis		
			Yields (%)	Time (h)	Yields (%)	Time (min)			C	H	N
RK-5001	H	$C_{14}H_{16}N_4O$	70	5:30	92	3	256.3	≥ 250	65.61 (65.34)	6.24 (6.11)	21.86 (21.70)
RK-5002	-2-NO_2	$C_{14}H_{15}N_5O_3$	78	6:00	90	4	301.3	≥ 250	55.81 (55.75)	5.02 (4.89)	23.24 (23.50)
RK-5003	-3-NO_2	$C_{14}H_{15}N_5O_3$	69	6:00	92	3	301.3	≥ 250	55.81 (55.75)	5.02 (4.89)	23.24 (23.50)
RK-5004	-4-NO_2	$C_{14}H_{15}N_5O_3$	78	5:30	88	5	301.3	≥ 250	55.81 (55.75)	5.02 (4.89)	23.24 (23.50)
RK-5005	-3-OC_6H_5	$C_{20}H_{20}N_4O_2$	75	8:00	93	2	348.4	≥ 250	68.95 (68.50)	5.79 (5.63)	16.08 (16.21)
RK-5006	3-Br	$C_{14}H_{15}BrN_4O$	72	7:00	85	3	335.2	≥ 250	50.16 (50.11)	4.51 (4.53)	23.84 (23.70)

Table. No: 5

RK-5007	3,4- di-OCH_3	$C_{16}H_{20}N_4O_3$	73	6:30	90	4	316.35	≥ 250	60.75 (60.60)	6.37 (6.40)	17.71 (17.52)
RK-5008	3,4,5-tri-OCH_3	$C_{17}H_{22}N_4O_4$	76	7:30	87	5	346.38	≥ 250	58.95 (58.64)	6.40 (6.55)	16.17 (16.22)
RK-5009	3- OCH_3	$C_{15}H_{18}N_4O_2$	69	5:30	90	5	286.33	≥ 250	62.92 (62.81)	6.34 (6.25)	19.57 (19.63)
RK-5010	2- OCH_3	$C_{15}H_{18}N_4O_2$	78	6:45	86	2	286.33	≥ 250	62.92 (62.83)	6.34 (6.35)	19.57 (19.62)
RK-5011	4- OCH_3	$C_{15}H_{18}N_4O_2$	76	6:30	91	3	286.33	≥ 250	62.92 (62.87)	6.34 (6.38)	19.57 (19.63)
RK-5012	3-Cl	$C_{14}H_{15}ClN_4O$	65	6:00	90	3	290.75	≥ 250	57.83 (57.63)	5.20 (5.15)	19.27 (19.21)
RK-5013	4-Cl	$C_{14}H_{15}ClN_4O$	72	6:00	87	4	290.75	≥ 250	57.83 (57.80)	5.20 (5.16)	19.27 (19.34)
RK-5014	2-Cl	$C_{14}H_{15}ClN_4O$	71	7:15	95	2	290.75	≥ 250	57.83 (57.56)	5.20 (5.31)	19.27 (19.36)
RK-5015	2-OH	$C_{14}H_{16}N_4O_2$	68	5:00	89	3	272.3	≥ 250	61.75 (61.62)	5.92 (6.00)	20.58 (20.62)
RK-5016	4-SCH_3	$C_{15}H_{18}N_4OS$	73	6:30	85	5	302.39	≥ 250	59.58 (59.42)	6.00 (5.91)	18.53 (18.64)
RK-5017	3,4 di-OH	$C_{14}H_{16}N_4O_3$	82	5:30	92	2	288.3	≥ 250	58.32 (58.37)	5.59 (5.50)	19.43 (19.39)
RK-5018	4-F	$C_{14}H_{15}FN_4O$	75	6:30	87	3	274.29	≥ 250	61.30 (61.27)	5.51 (5.48)	20.43 (20.38)

Spectral discussion

FT-IR Spectra

IR spectra were recorded on Shimadzu FTIR-8400 using KBr disc and DRS techniques. The percentage transmittance is given in cm^{-1}. The presence of isopropyl group shows at ~1395 and 1365 wave numbers as doublet. It strongly indicates the presence of isopropyl group. The presence of amine shows at ~3450 wave numbers. The absence of peak at ~1680 wave number indicates the presence hydroxyl group instead of carbonyl functionality. The hydroxyl functional group gives a broad peak ~3350. The SP^2 =C-H will show at ~3100 wave numbers, while C=C at ~1649 wave numbers. Rests of the informations are given in the spectra of the compounds.

^{1}H NMR Spectra

Proton NMR spectra of synthesized 4,5-dihydro-3-isopropyl-4-(substituted phenyl)-1*H*-pyrazolo[3,4-*d*]-pyrimidine-6(7*H*)-ones were recorded on Bruker 300 and 400MHz(Avance-II) instruments using DMSO and TFA as the solvents with tetramethylsilane (TMS) as the respective internal standard. Chemical shifts were recorded in *(δ)* and coupling constants were recorded in Hertz *(J)*. Number of protons found in NMR is concomitant with the theoretical value. The compounds are hardly soluble in the solvent like DMSO or TFA even on heating. The solution becomes hazy on dissolution.

EI-MS Spectra

EI-MS spectra were recorded on Shimadzu GC-MS QP-2010 by Electron Impact method. In all the compounds, the molecular weights were found to be 43 *m/z* less than the molecular ion peak. No particular fragmentation pattern is observed from the spectra.

Elemental Analysis

Elemental analysis of the all synthesized compounds was carried out Elementar Vario EL III Carlo Erba 1108 model at CDRI, Lucknow and the results are in agreement with the structures assigned.

Spectral data

4,5-Dihydro-3-isopropyl-4- phenyl-1H-pyrazolo[3,4-d]pyrimidine-6(7H)-one (RK-5001)

IR (KBr Disc): 3722.34 cm^{-1}(-OH enol form), 3362-3441 cm^{-1}(-NH), 2920-2964 cm^{-1}(C-H), 1531-1589 cm^{-1} (-NH Bend)

4,5-Dihydro-3-isopropyl-4-(2-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5002)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.82-0.92 (Broad, 13H), 1.21-1.25 (Broad, 29H), 5.21 (m, 1H), 6.71 (m, 1H), 7.57 (m, 2H), 7.73 (m, 2H), 7.78 (m, 2H), 8.1 (d, 1H)

IR (KBr Disc): 3477.77 cm^{-1}(-OH enol form), 3362-3441 cm^{-1}(-NH), 2920-2966 cm^{-1}(C-H), 1521-1589 cm^{-1} (-NH Bend), 1589.4 cm^{-1} (-C-NO_2)

4,5-Dihydro-3-isopropyl-4-(3-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5003)

IR (KBr Disc): 3439.19 cm^{-1}(-OH enol form), 3385 cm^{-1}(-NH), 2872-2966 cm^{-1}(C-H), 1550-1577 cm^{-1} (-NH Bend), 1529 cm^{-1} (-C-NO_2)

4,5-Dihydro-3-isopropyl-4-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5004)

IR (KBr Disc): 3527 cm^{-1}(-OH enol form), 2968 cm^{-1}(-NH), 2870-2928 cm^{-1}(C-H), 1518-1589 cm^{-1} (-NH Bend), 1518-1527cm^{-1} (-C-NO_2)

4,5-Dihydro-3-isopropyl-4-(3-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5005)

IR (KBr Disc): 3543cm^{-1}(-OH enol form), 3462.34cm^{-1}(-NH), 2870-2968cm^{-1}(C-H), 1543-1583 cm^{-1} (-NH Bend)

4,5-Dihydro-3-isopropyl-4-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5006)

IR (KBr Disc): 3319 cm^{-1}(-OH enol form), 3240 cm^{-1}(-NH), 2920-2966cm^{-1}(C-H), 1550-1579 cm^{-1} (-NH Bend), 550-578 cm^{-1} (C-Br)

4,5-Dihydro-3-isopropyl-4-(3,4-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5007)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.83 (m, Broad, 6H), 1.3 (m, 1H), 3.7-3.8 (d, 6H), 5.23 (s Broad, 1H), 7.00 (d, 1H), 7.06 (m, 4H), 7.39 (s, 1H), 7.51 (m, 1H), 9.89 (s, 1H)

IR (KBr Disc): 3441cm^{-1}(-OH enol form)**,** 3338.89cm^{-1}(-NH), 2920-2966cm^{-1}(C-H), 1510-1589 cm^{-1} (-NH Bend), 1109-1166cm^{-1} (C-O-C)

4,5-Dihydro-3-isopropyl-4-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one(RK-5008)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.19-1.23 (Broad, 6H), 1.29 (Broad, 1H), 3.09 (m, 3H), 3.50 (m, 3H), 3.6-3.7 (m, 3H), 3.75-3.8 (d, 1H), 5.23 (m, 1H), 6.45 (m, 5H)

IR (KBr Disc): 3441cm^{-1}(-OH enol form)**,** 3338.89cm^{-1}(-NH), 2920-2966cm^{-1}(C-H), 1510-1589 cm^{-1} (-NH Bend), 1109-1166cm^{-1} (C-O-C)

4,5-Dihydro-3-isopropyl-4-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5009)

IR (KBr Disc): 3527cm^{-1}(-OH enol form)**,** 3338.89cm^{-1}(-NH), 2914-2956cm^{-1}(C-H), 1510-1589 cm^{-1} (-NH Bend), 1109-1166cm^{-1} (C-O-C)

4,5-Dihydro-3-isopropyl-4-(2-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5010)

IR (KBr Disc): 3520cm^{-1}(-OH enol form)**,** 3000cm^{-1}(-NH), 2920-2966cm^{-1}(C-H), 1536-1578 cm^{-1} (-NH Bend), 1186-1290cm^{-1} (C-O-C)

4,5-Dihydro-3-isopropyl-4-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5011)

IR (KBr Disc): 3441cm^{-1}(-OH enol form)**,** 3387.11cm^{-1}(-NH), 2934-2966cm^{-1}(C-H), 1510-1525 cm^{-1} (-NH Bend), 1109-1174cm^{-1} (C-O-C)

4,5-Dihydro-3-isopropyl-4-(3-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5012)

IR (KBr Disc): 3527cm^{-1}(-OH enol form)**,** 3466.20cm^{-1}(-NH), 2926-2986cm^{-1}(C-H), 1527-1583 cm^{-1} (-NH Bend), 709-783 cm^{-1} (C-Cl)

4,5-Dihydro-3-isopropyl-4-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5013)

IR (KBr Disc): 3527.927cm^{-1}(-OH enol form)**,** 3460cm^{-1}(-NH), 2889-2964cm^{-1}(C-H), 1517-1558 cm^{-1} (-NH Bend), 740-785 cm^{-1} (C-Cl)

4,5-Dihydro-3-isopropyl-4-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5014)

IR (KBr Disc): 3537cm^{-1}(-OH enol form)**,** 3462 cm^{-1}(-NH), 2868-2966cm^{-1}(C-H), 1527-1583 cm^{-1} (-NH Bend), 720-748 cm^{-1} (C-Cl)

4,5-Dihydro-3-isopropyl-4-(2-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5015)

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ 1.1-1.3 (m, Broad, 6H), 5.2-5.3 (Broad, 1H), 6.75 (m, 3H), 6.85 (d, 1H), 6.99 (m, 1H), 7.31 (m, 1H), 7.37 (m, 1H), 9.11 (dd, 1H), 9.30 (s, 1H)

IR (KBr Disc): 3319 cm^{-1}(-OH enol form)**,** 3240cm^{-1}(-NH), 2926-2968cm^{-1}(C-H), 1529-1575 cm^{-1} (-NH Bend)

4,5-Dihydro-3-isopropyl-4-(4-(methylthio)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5016)

IR (KBr Disc): 3539cm^{-1}(-OH enol form)**,** 3462.20cm^{-1}(-NH), 2950-2964cm^{-1}(C-H), 1533-1577 cm^{-1} (-NH Bend)

4,5-Dihydro-3-isopropyl-4-(3,4-dihydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5017)

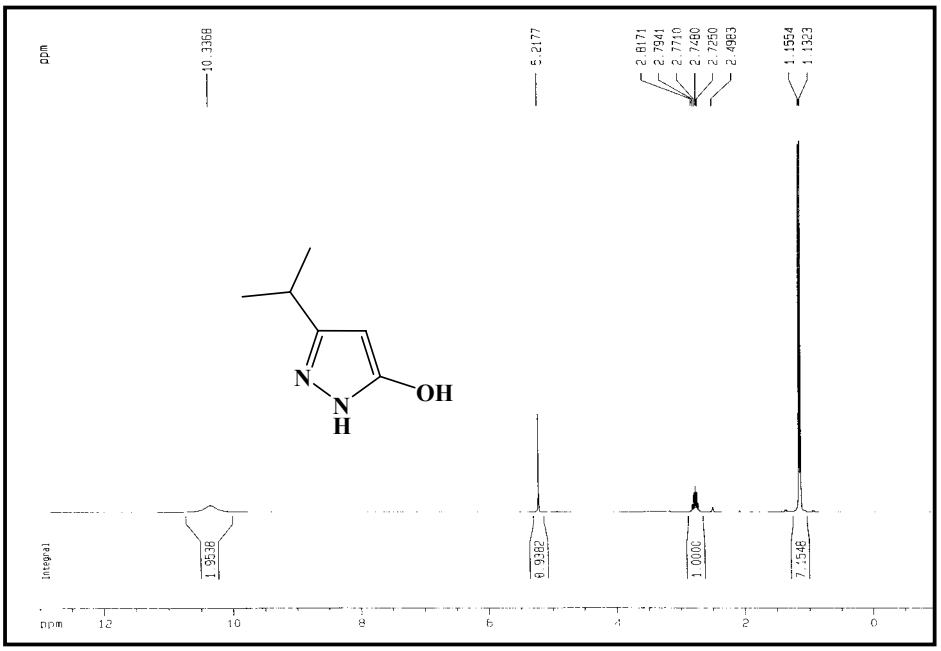
IR (KBr Disc): 3583 cm^{-1}(-OH) **,** 3334-3360 cm^{-1}(-NH), 2930-2966 cm^{-1}(C-H), 1521-1556 cm^{-1} (-NH Bend)

4,5-Dihydro-3-isopropyl-4-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one (RK-5018)

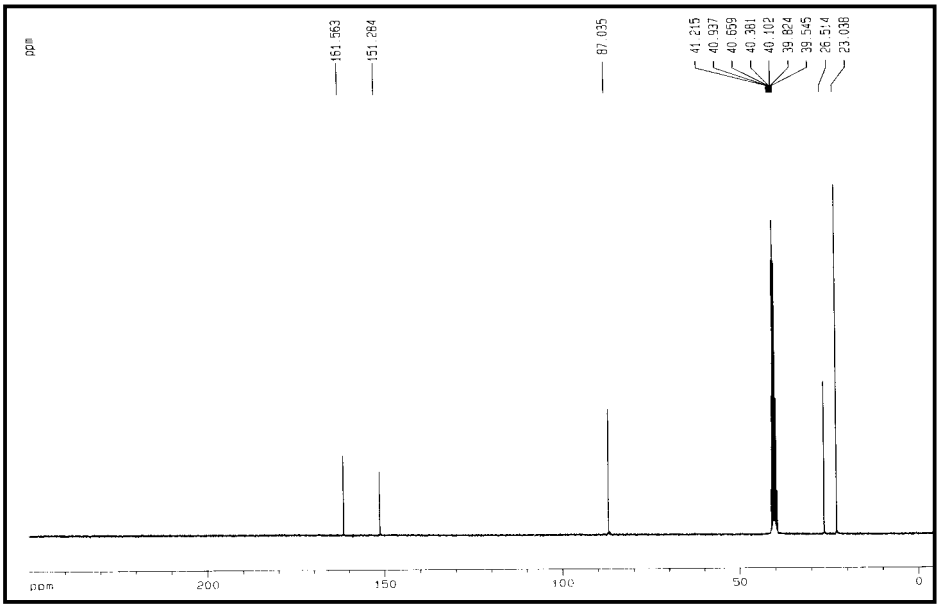
IR (KBr Disc): 3527.927cm^{-1}(-OH enol form)**,** 3460cm^{-1}(-NH), 2889-2964cm^{-1}(C-H), 1520-1568 cm^{-1} (-NH Bend)

Spectra of the representative compounds

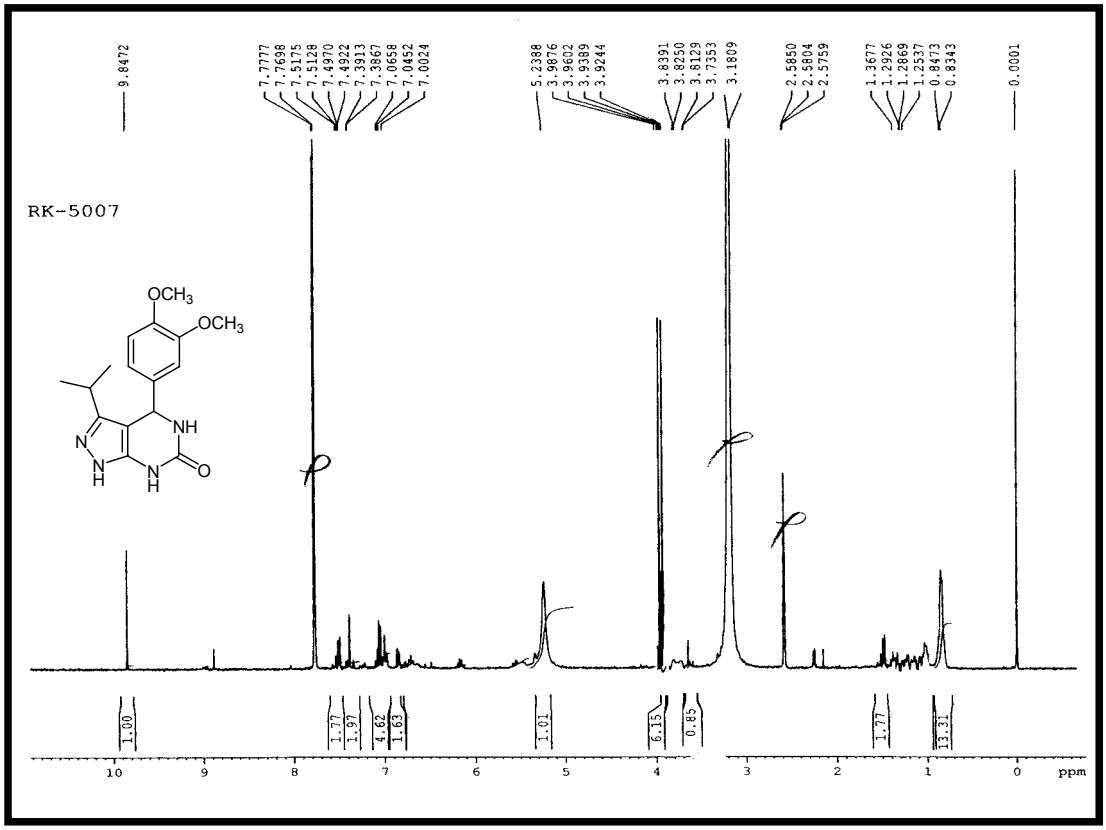
^{1}H NMR Spectrum of 3-isopropyl-1*H*-pyrazol-5(4*H*)-one

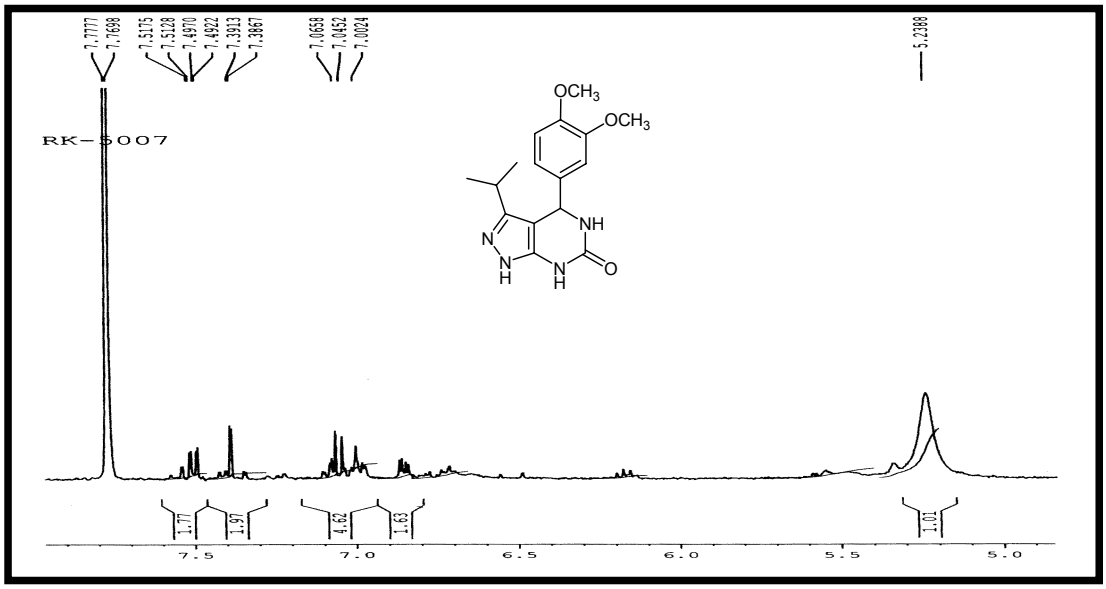


^{13}C NMR Spectrum of 3-isopropyl-1*H*-pyrazol-5(4*H*)-one

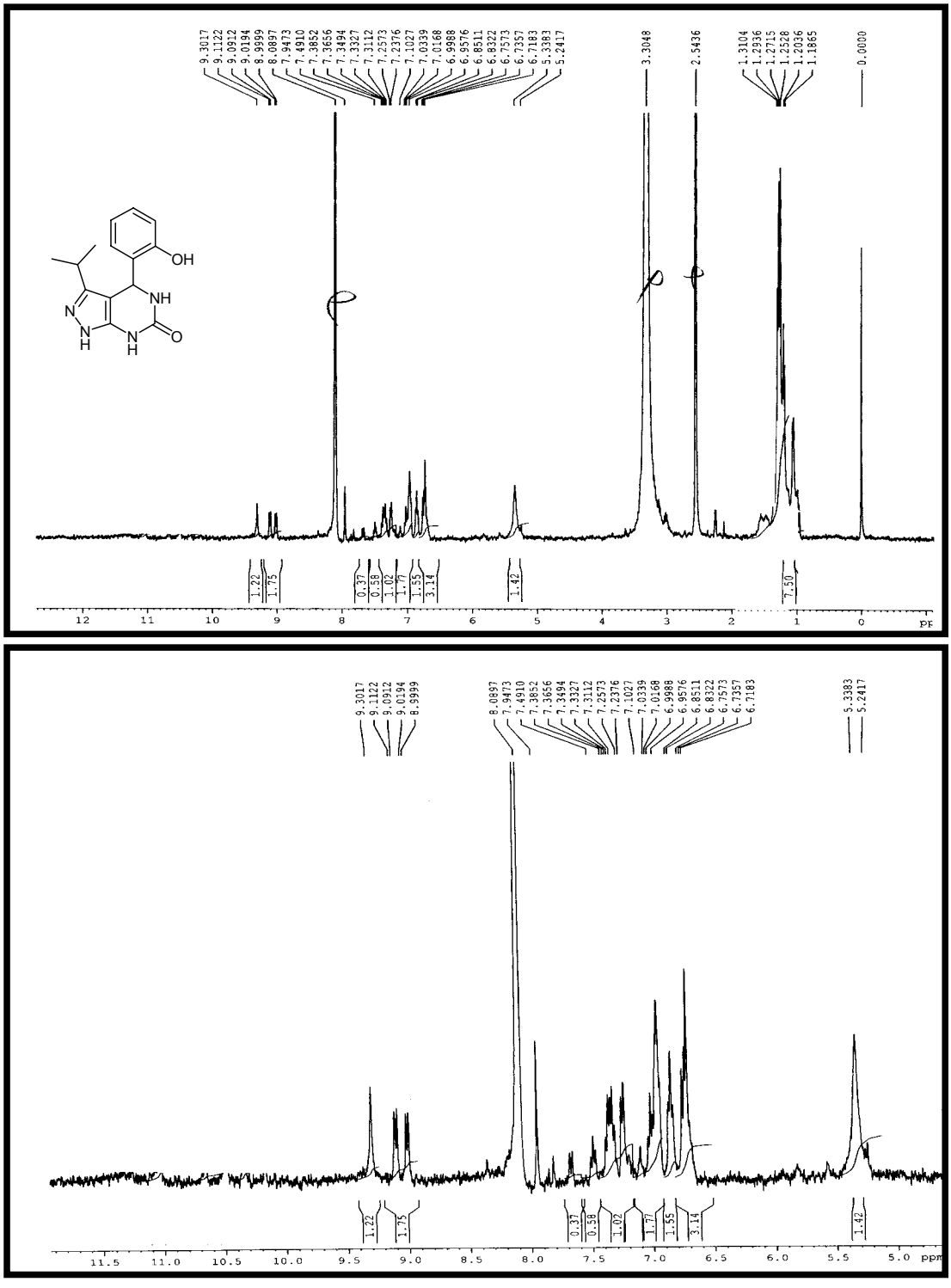


^{1}H NMR Spectrum of RK-5007

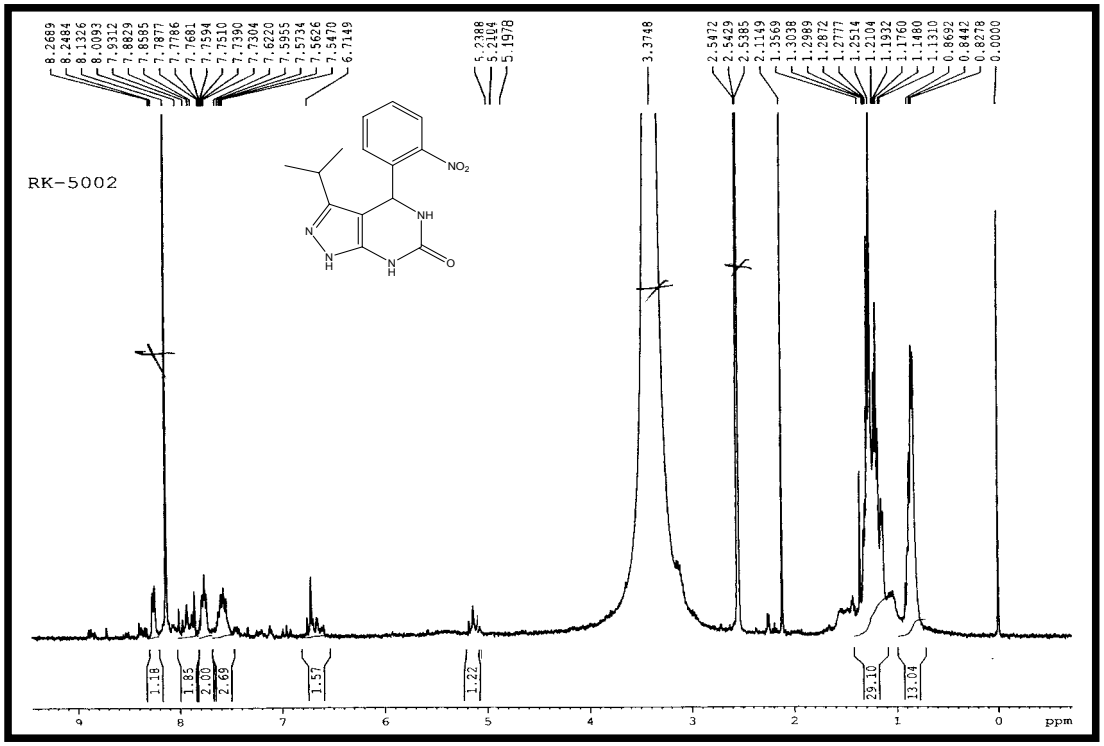


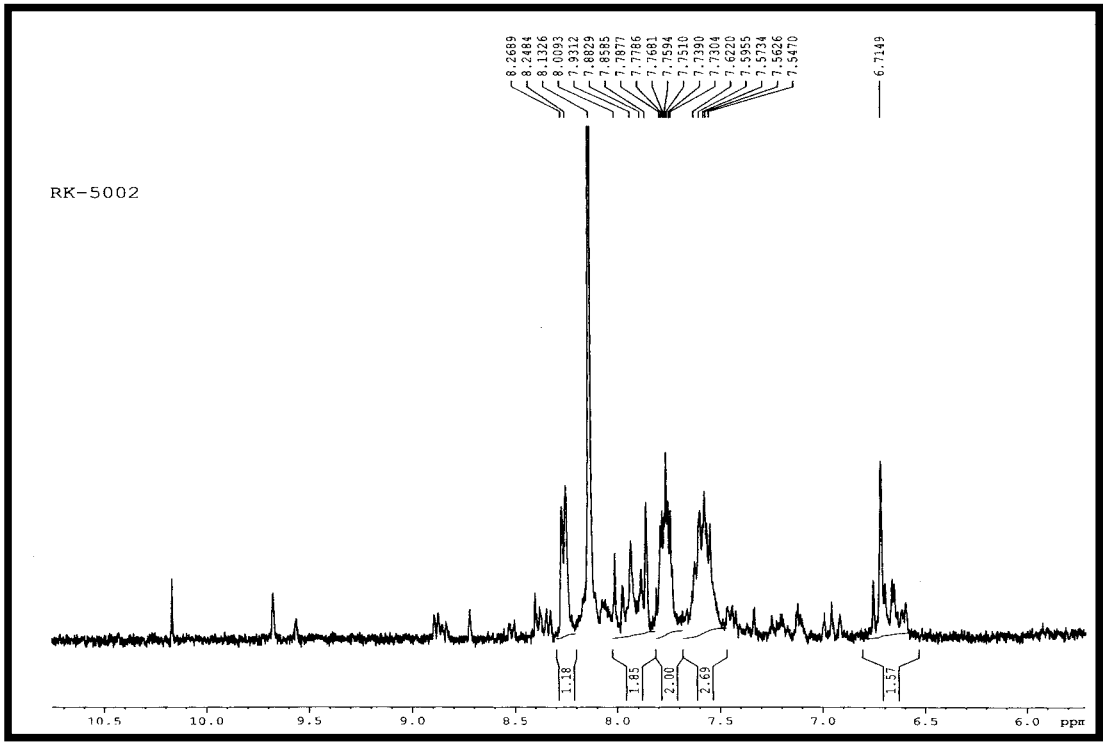


^{1}H NMR Spectrum of RK-5015

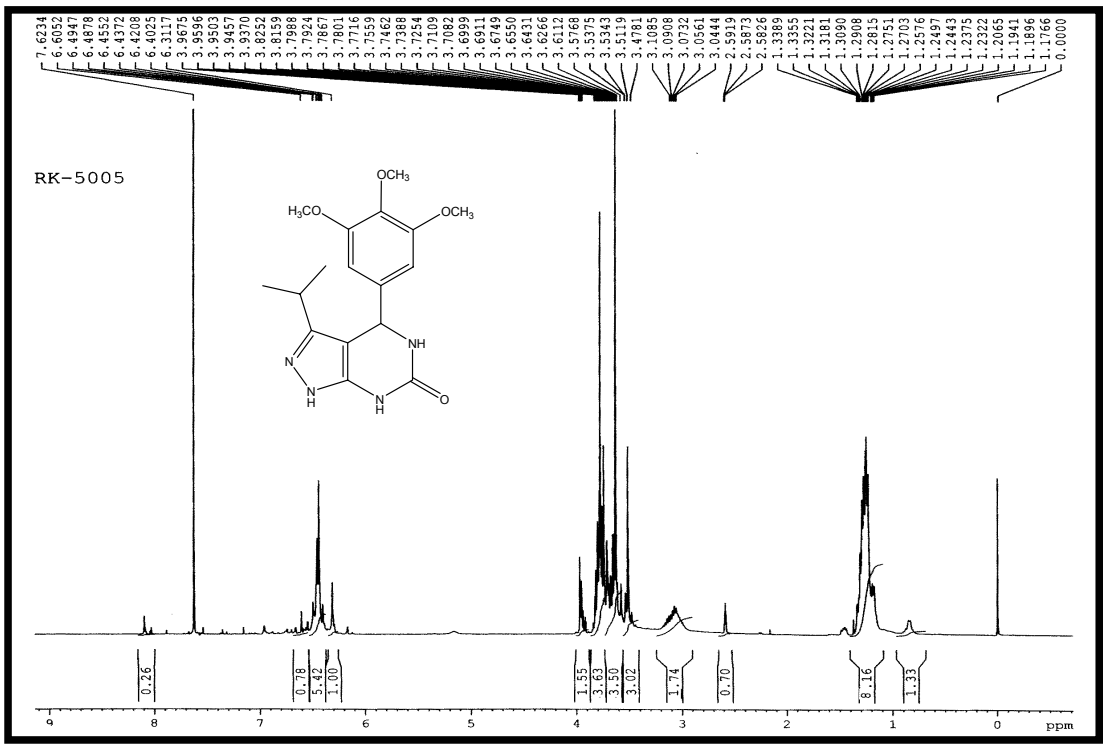


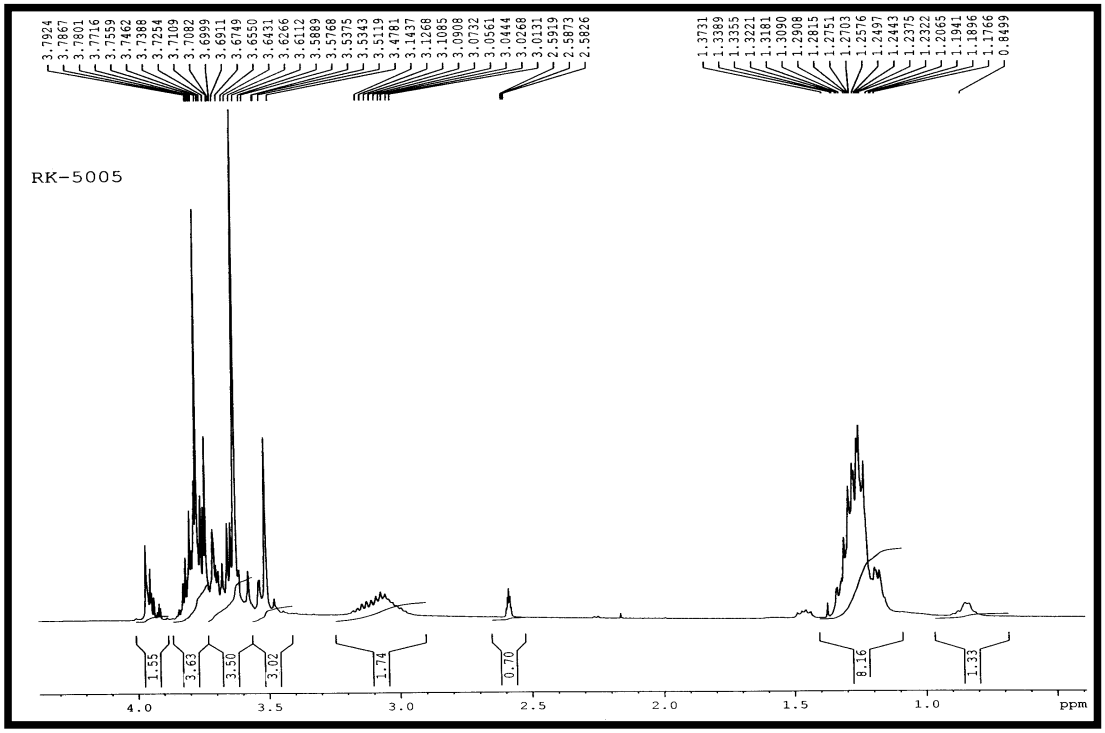
^{1}H NMR Spectrum of RK-5002



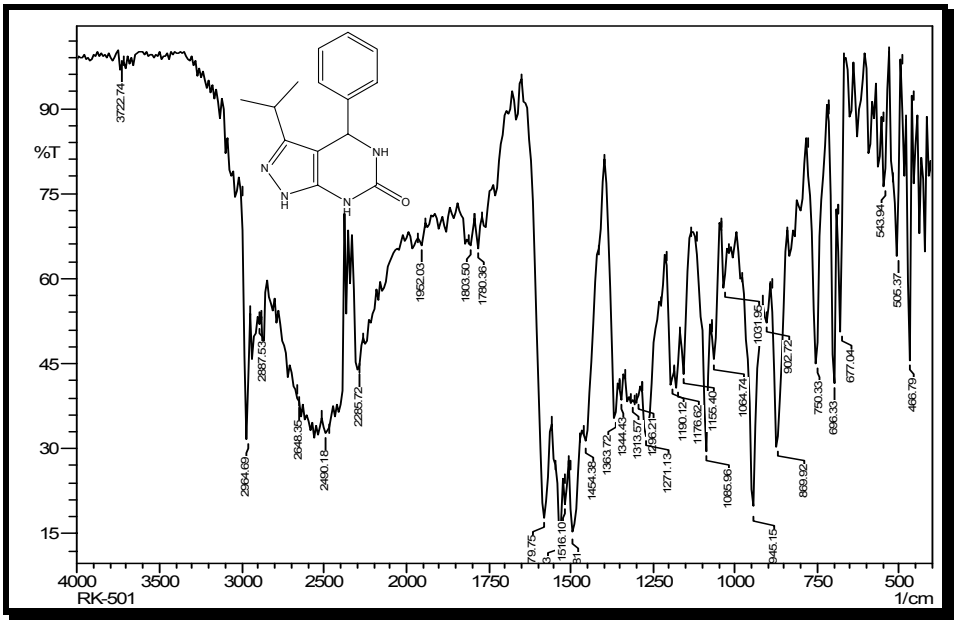


^{1}H NMR Spectrum of RK-5008

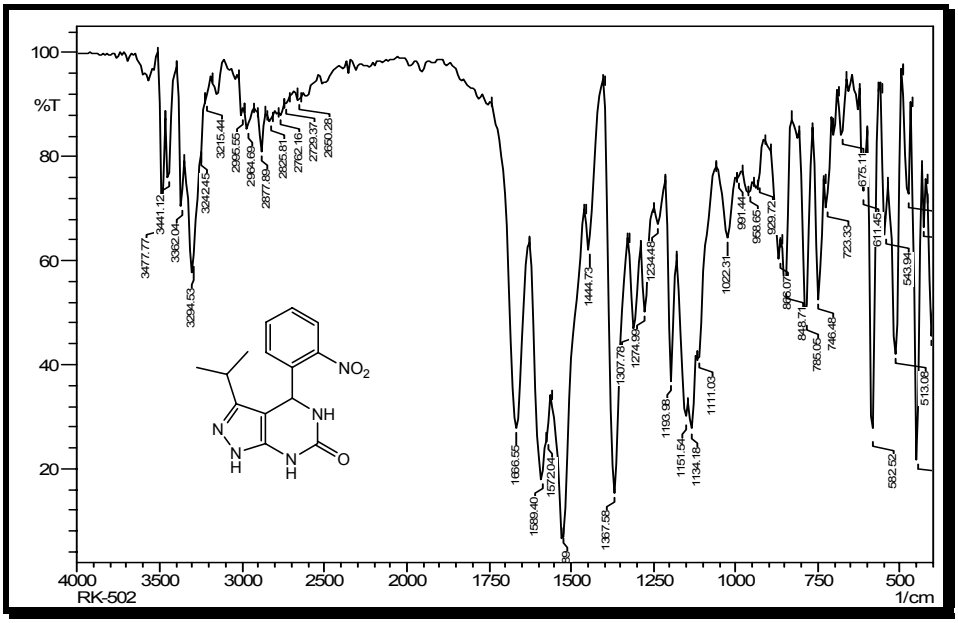




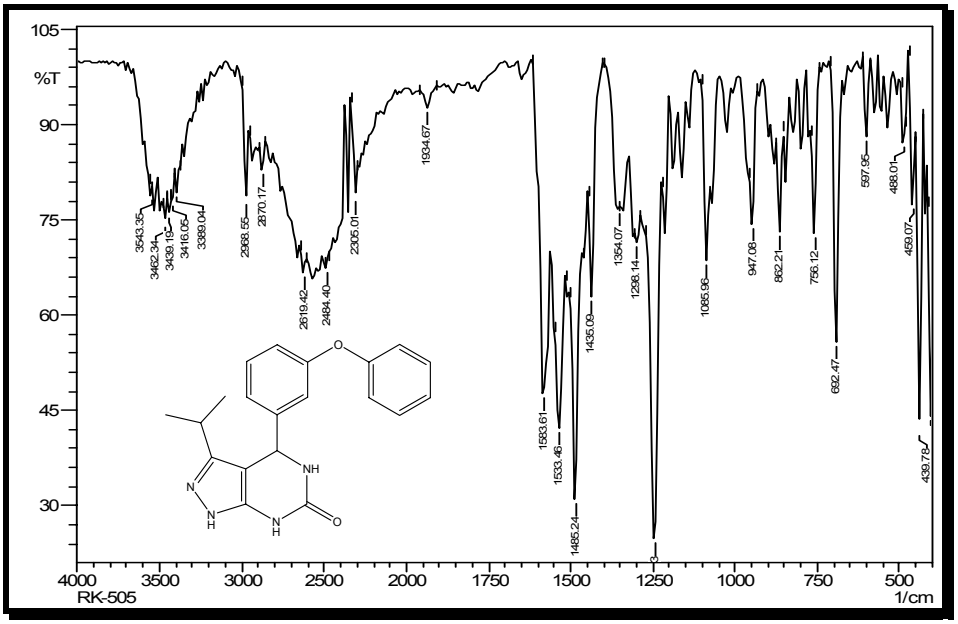
IR Spectrum of RK-5001



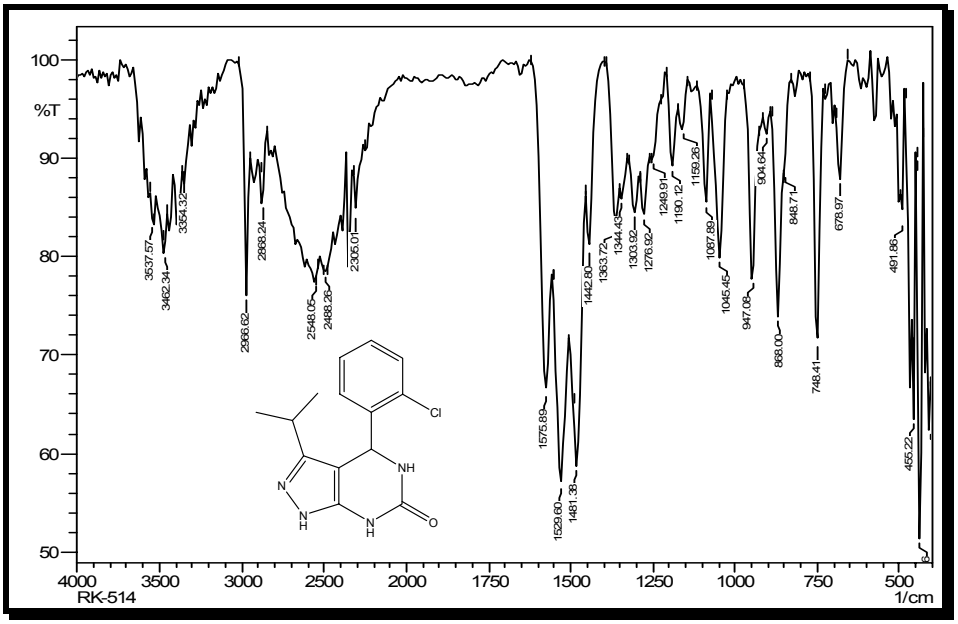
IR Spectrum of RK-5002



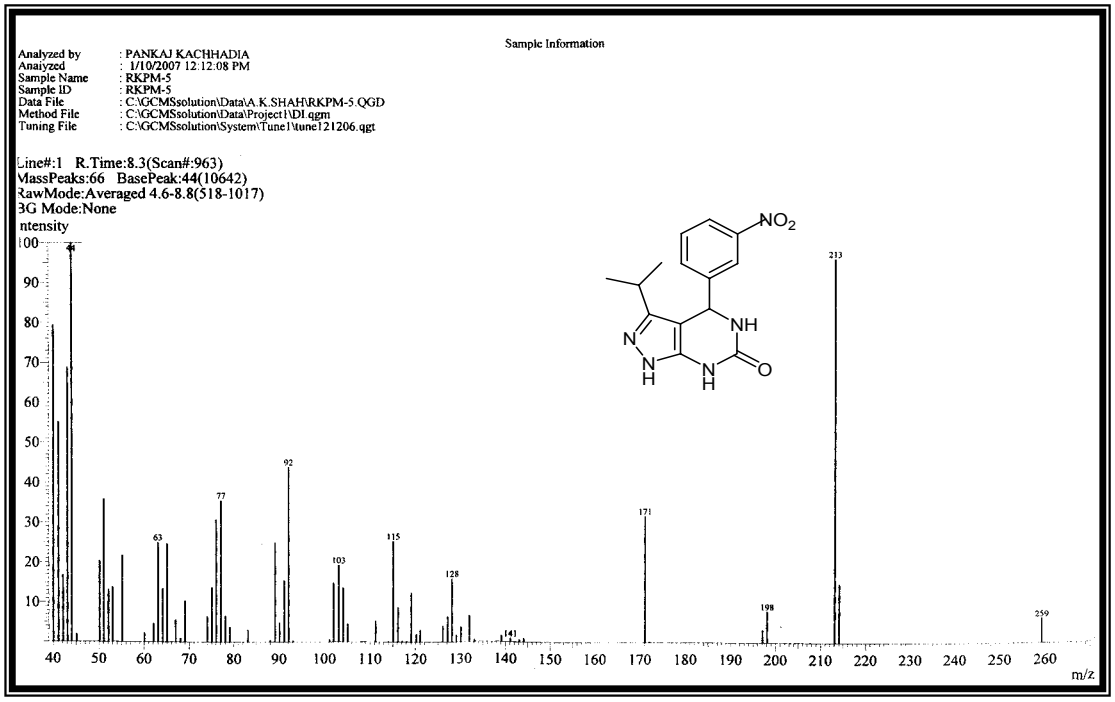
IR Spectrum of RK-5005



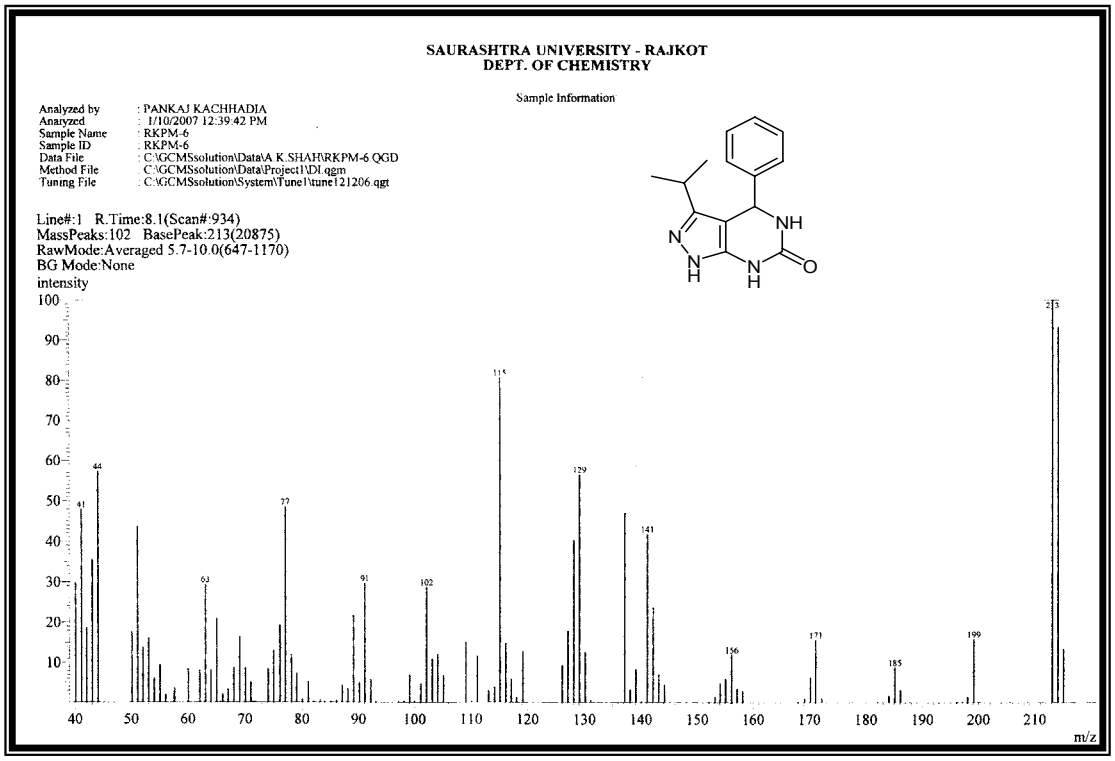
IR Spectrum of RK-5014



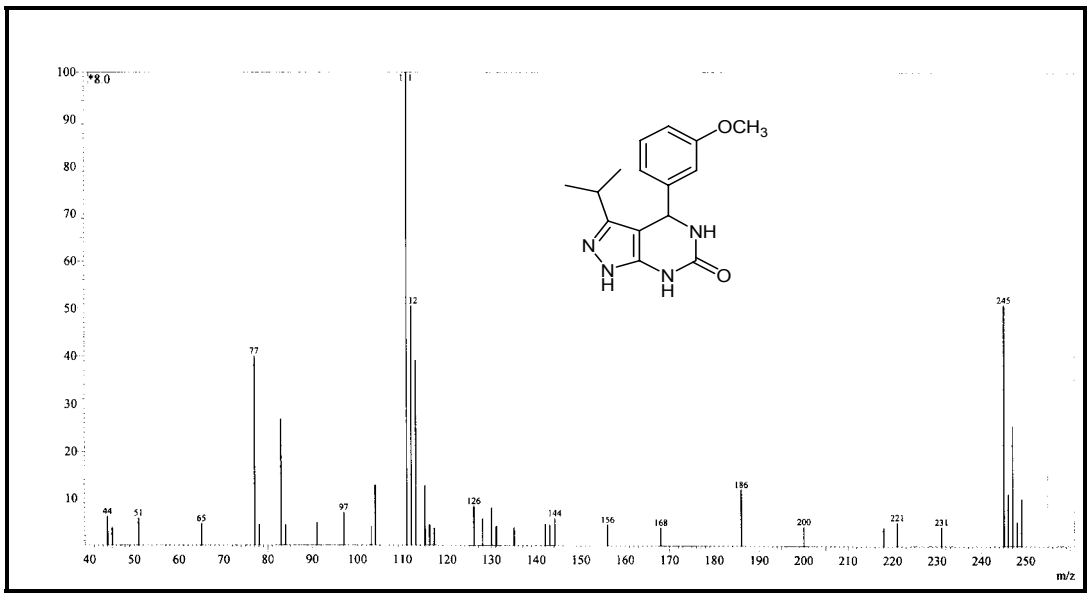
EI-MS Spectrum of RK-5004



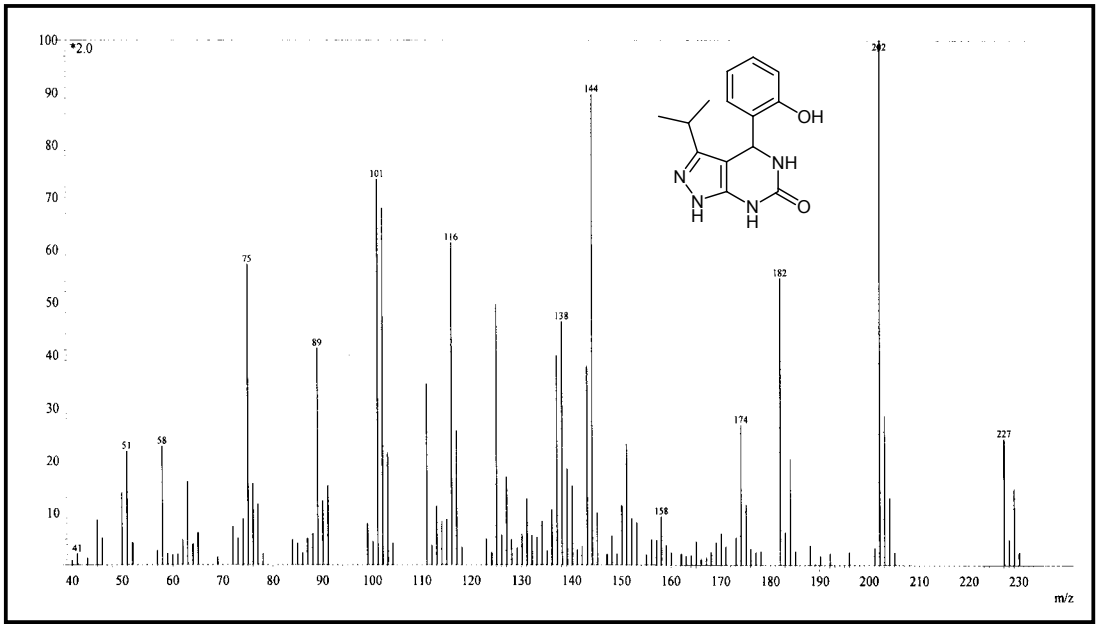
EI-MS Spectrum of RK-5001



EI-MS Spectrum of RK-5009



IR Spectrum of RK-5015



Conclusion

Here we reported catalytic green method for the synthesis of pyrazolone pyrimidine using $HClO_4$-fuller's earth as an efficient ecofriendly heterogeneous inorganic catalyst and carried out comparison of yield obtained by classical heating using Conc. HCl as the acid catalyst with this green and eco friendly approach.

From the ^{13}C NMR and ^{1}H NMR spectrum of the starting material (Pyrazolone), we concluded that the starting material is stable in the enol form.

This data of pyrazolone spared us to work out on it. So we used this heterocyclic ketone as a building block in Biginelli-type multi component reaction, ultimately we got a new and Diversed Heterocyclic Synthon in single step.

Earlier literature survey shows that most of work carried out by using different symmetrical, unsymmetrical and cyclic 1,3-diketones and different β-keto esters. No one used the heterocyclic ketone that is stable in enol form.

Various methodologies for the synthesis of pyrazolo pyrimidines were reported by different authors, represented in the synthetic approaches in the introduction part and also not single step process. Several step has been carried out for formation of this type of core structure Here we introduced a phenyl ring at C_4 position of the pyrazolo pyrimidine by Conventional as well as Microwave assisted Organic synthesis (MAOS) through modification in building block of the Biginelli type Multi component reaction and eventually, we got a diversity in core structure of the pyrazolo pyrimidines

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General Protocol

1. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 300 and 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 using KBr pellet or DRS method.

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, Loba, Merck, Rankem, Thomas-baker and SD fine chemicals, India.

7. Melting Points were taken in open capillary and are uncorrected.

8. Microwave synthesizer (Questron Technologies Corporation, Canada) QPro-M model monomode open-vessel was used in the MAOS.

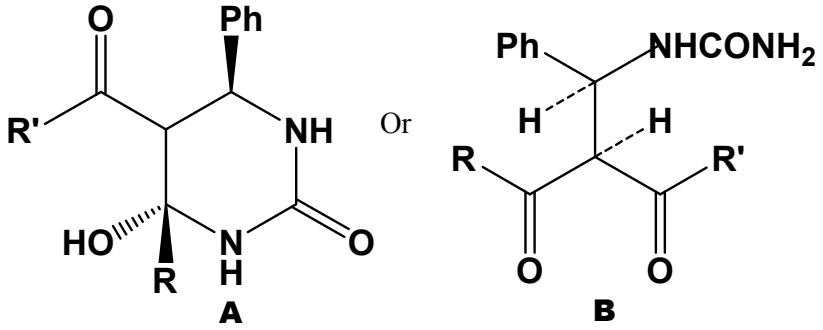
Summary

The work represented in the Thesis entitled "Synthesis, Characterization and Screening of Pharmacologically Active Chemical Entities" can be summarized as below.

Chapter 1.1 covers literature survey on mechanistic studies, various alternative synthetic methodologies in Multi component Biginelli reaction. Various natural products containing DHPMs *viz.* crambine, batzelladine display activity as potent HIV gp-120-CD4 inhibitor. Several Synthetic DHPMs shows pharmacologically activity like orally active antihypertensive agents, α_{1a} adrenoceptor-selective antagonists, calcium channel blockers, gastric inhibitory and fatty acid transporter FATP4 Inhibitors are recapitulated in this chapter. Fragment based approach for the core structure of Dihydropyrimidines also described. Different synthetic approaches for the 1,3 Diketones used in Multi component reaction are discussed. Various Catalysts for the rapid, mild and higher yielding protocols, several ionic liquids for the clean synthesis and modern chemistry are descried in detail. Various building blocks and diversity created by this advance and solid phase synthesis also described in introductory part of this chapter.

In Chapter 1.2 contains design for the synthesis of starting material which has been used for Target Molecules (TMs), plausible mechanism of the hexahydropyrimidinones. The Biginelli type cyclocondensation of a fluorine containing 1, 3 diketone have been studied in this chapter. In analogy to the reaction of 1,3-diketone with different substituted benzaldehyde and urea. These reactions were conventionally carried out in methanol in the presence of the catalytical amount of Conc. HCl for 5-6 hours. Here, we consider that two isomeric structures for these condensation products, namely the hexahydropyrimidine

structure of type **A** or the isomeric acyclic ureidopropionate structure of keto and enol tautomers.



By the help of the IR spectra, ^{1}H NMR, ^{13}C NMR and Mass spectra of products, prove the correct structure is represented in this part. In all, total 19 compounds are synthesized in this chapter.

Chapter 1.3 contains the synthetic details for the Trifluoromethyl bearing hexahydro thiopyrimidinones. The entire synthesized compounds are well characterized by ^{1}H NMR, ^{13}C NMR, IR spectra. From the literature and studies of the spectral analysis, the cyclic nature of this compounds are illustrated in detail. In all, total 17 compounds are synthesized in this chapter.

The antimicrobial profile of representative chapters where studied and are given at the end of the chapter.

Chapter 2 covers the various synthetic routes for the formation of the pyrimidines nucleolus. Some of the therapeutic activities of pyrimidine derivatives like antithyroid, antitumor, antihypertensive, diuretic, antiviral, antiinflammatory, platelet aggregation inhibitor, anticonvulsant, antitubercular, melanin-concentrating Hormone 1 Receptor,

HIV Reverse Transcriptase and Integrase and Preliminary SAR of antiviral activity of pyrimidinones are represented in detail. Synthetic approach for the targeted molecules (Dihydropyrimines at C_5 position with cyclohexyl carbamoyl functional group) is discussed . All the synthesized compounds were well characterized by the ^{1}H NMR, ^{13}C NMR, IR spectra and Mass spectral investigations are represented on this chapter.

Chapter 3 contains microwave assisted multi component synthesis for Trifluoromethyl containing dihydropyridines by using PEG-400 as a solvent. In the introductory part, the detail of the some serious drawbacks of the previously reported procedure such as unsatisfactory yields, tedious work-up procedure, occurrence of side reactions including aromatization, economically non-viable, long reaction rate, high reaction temperature etc and biological profile of the 1,4-Dihydropyridines are mentioned. This chapter covers experimental details, spectra of the new synthesized compounds. All compounds were well characterized by modern techniques like ^{1}H NMR, IR and Mass. In all, total 10 compounds are synthesized in this chapter.

Chapter 4 involves the conventional and non-conventional method for the synthesis of various Pyrazolo [4,3-*d*]Pyrimidines. Both the methods consist of the solution phase synthesis. The classical heating was carried out in acetonitrile and by using conc. HCl as the acid catalyst whilst the microwave assisted reaction was also carried out in acetonitrile but novel heterogeneous catalyst $HClO_4$-Fuller's earth was utilized for the reactions. The compounds are characterized by ^{1}H NMR, IR and Mass spectral techniques. Fifteen compounds were synthesized in this series. The biological study of newly synthesized compounds for anti-HIV screening is underway.

Publications

1. Microwave-assisted and Zn[L-proline]$_2$ Catalyzed Tandem Cyclization under Solvent Free Condition: Rapid Synthesis of chromeno[4,3-*c*]pyrazol-4-ones
   Atul Manvar, Pravin Bochiya, Vijay Virsodia, Rupesh Khunt and *Anamik Shah (*Journal of Molecular Catalysis A: Chemical* ***2007,*** 275, 148-152)

2. PEG-400 Promoted and Microwave assisted one pot three-component coupling reactions: Expedient and Rapid synthesis of Hantzsch 1,4-dihydropyridines
   Atul Manvar, Vijay Virsodiya, Rupesh Khunt, Nikhil Vekariya and *Anamik Shah (Communicated to *Bioorganic & Medicinal Chemistry Letters)*

3. An Improved protocol for the synthesis of alkyl or acyl azides by using [Bmim]BF_4 or [Bmim] PF_6 at ambient temperature under solvent free and neutral condition
   Atul Manvar, Dinesh Manvar, Nikhil Vekariya, Rupesh Khunt and *Anamik Shah (Communicated to *Organic Chemistry: An Indian Journal*)

Conferences/Seminar/Symposium/Workshop participated

- **International Conference on "Advances in Drug Discovery Research" Organized by ISCB at Aurangabad, India (24-26 Feb, 2007)**

- **The Ramanbhai Foundation 3rd International Symposium "Current Trends in Pharmaceutical Sciences: Advances in diabetes therapy - basic science and clinical aspects". Organized by Zydus Research Centre, Ahmedabad, India (February 1-3, 2007)**

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

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

- **Conference on "Advance in Organic Chemistry and Chemical Biology [AOCCB 2006]" jointly organized by American Chemical Society (ACS) and Indian Institute of Chemical Technology IICT, Hyderabad, India. (January 11-12, 2006)**

- **International conference on "Building Bridges and forging bonds for 21st Century Organic Chemistry and Chemical Biology" jointly organized by American Chemical Society (ACS) and National Chemical Laboratory (NCL) at NCL Pune, India (January 7-9, 2006)**

- **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)**

- **Ramanbhai Foundation 2nd International Symposium 'Current Trends in Pharmaceutical Sciences' with an emphasis on the role of genomics & proteomics research in drug discovery and development process. Organized by Zydus Research Centre, Ahmedabad, India (January 23-25, 2005)**

- **International Symposium on " Current trends in Pharmaceutical Science" Organized by Zydus Research Center, Ahmedabad, India (January 23-25, 2003)**