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Chemistry of biologically active dihydropyrimidones of Biginelli type compounds

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ABSTRACT

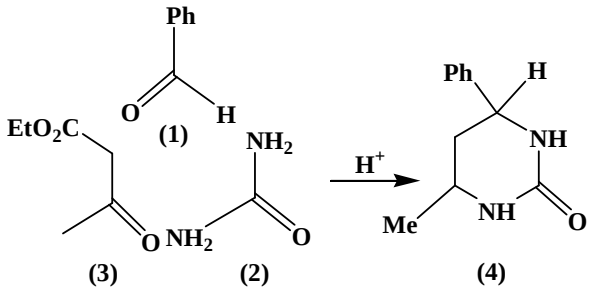
One pot cyclocondensation of β-keto ester, urea and aromatic or aliphatic aldehyde in ethanolic solution in presence of acid catalyst leads to the synthesis of 4-aryl-3, 4- dihydropyrimidines- 2(H)-ones. The reaction is called as Biginelli reaction. The classical reaction was modified by several researchers by using different catalysts and several structural variants to synthesize large number of Biginelli type compounds possessing a wide range of pharmacological activity namely anti-inflammatory, antimicrobial, anticancer, α adrenergic antagonistic, anti HIV-CD_4 cell inhibitor, and cardiovascular etc. The present review is a complete compilation of literature available related to large number of Biginelli type compounds possessing different biological activities, with a focus on various advance synthetic methods, mechanistic approach, stereochemical aspects, and conformational studies.

INTRODUCTION

Dihydropyrimidones are considerably important group of compounds which have wide range of pharmacological activity profile like anti-inflammatory, antimicrobial, anticancer, cardiovascular and anti HIV gp-120-CD_4 inhibitor and α-1a adrenergic receptor antagonistic activity, neuropeptide Y(NYP) antagonist.

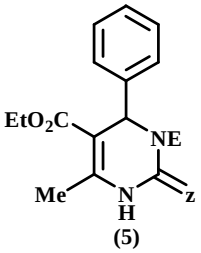
Faced with increasing demand of novel drug target, considerable current interest has been focused to accelerate the technologies associated with high through out put synthesis of Biginelli type compounds[1].

In 1983 Pietro Biginelli, for the first time reported one pot synthesis of 4-aryl-3,4 dihydropyrimidine-2(H)-ones compound**(4)** by using acid catalyzed reaction of aromatic aldehyde **(1)**, urea **(2)** and ethylacetoacetate **(3)** in ethanolic solution[2].



Initially this efficient method was ignored, and thus synthetic potential of reduced pyrimidines remained unexplored for several years. Furthermore, several marine alkaloids with interesting biological activities containing dihydropyrimidine-5-carboxylate core have been isolated or synthesized in past few years[3]. Hence in

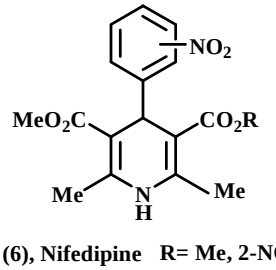
recent years, interest in these compounds has increased rapidly, and thus different newer derivatives of dihydropyrimidines have been synthesized by variations of all three components. The major reason of popularity of these dihydropyrimidines is mainly due to their close structural resemblance with 4-aryl dihydropy rimidines **(5)** (Nifedipine type), which are already established drugs for cardiovascular problems[4](potent calcium channel modulator) in clinical medicine since 1975.



(5)

Z= O, S

E= Ester, acyl, amide



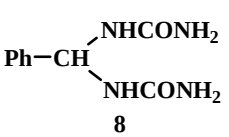
(6), Nifedipine R= Me, 2-NO_2

(7), Nitredipine R= Et, 3-NO_2

Due to increasing importance of Biginelli type compounds several improved and highly efficient methods are going to develop for easy synthesis of dihydropy rimidines. In this article we have summarized the work done in the area of dihydropyrimidine chemistry and present literature survey on recent development in this field up to 2006, and a specialized attention has been given on mechanistic, structural and various advance methods in classical Biginelli reaction to improve the yield and stereochemical aspect with reference to the design of new cardiovascular drugs of the DHPM type.

Mechanistic approach of Biginelli cycloconden sation classical Biginelli reaction

Mechanism of Biginelli reaction has been investigated by several research groups based on the dependence of acid catalysis[5,6,7], but accepted proposed mechanism for the first time was given by Folkers & Coworkers[6] in 1933. In their work they suggested that there is possible bimolecular product **(8,9,10)** intermediate formed by three component acid catalyzed (urea, ethyl acetate, aromatic aldehyde) reaction.



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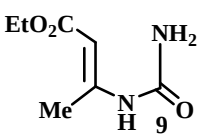

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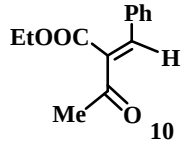

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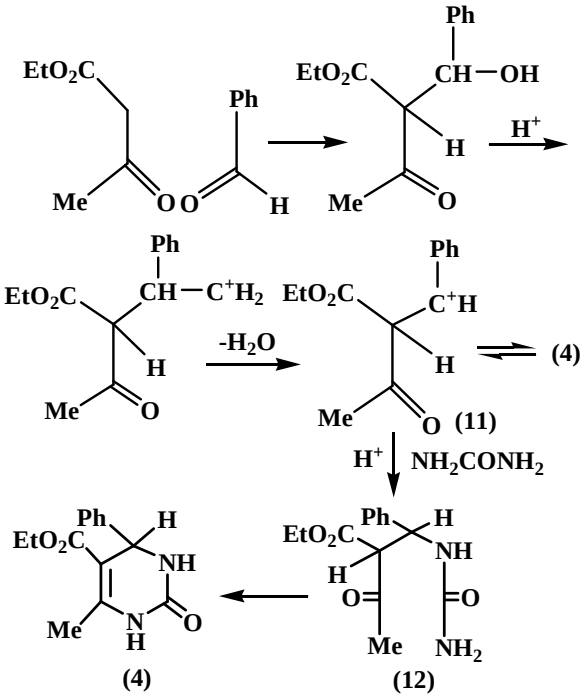
Experimentally they had only proved that **(8,9)** converted in to pyrimidine **(4)** after further reaction with ethyl acetoacetate and benzaldehyde, compound **(10)** did not react or gave a very low yield of compound **(4)** on reacting with urea. Since they suggested that N, N benzylidene bis-urea (i.e. the primary bimolecular condensation product of benzalehyde and urea as the key intermediate step-in Biginelli reaction[6]. Infact**(8)** is useful reagent for the synthesis of a variety of related dihydro pyrimidines as also supported by Mannaev and co- workers[8]. Later, in 1973 Sweet and Fissekis[9] proposed that carbonium ion**(11)** produced by an acid catalyzed aldol reaction of benzaldehyde with ethyl acetoacetate, is the key intermediate which is formed first and is the rate limiting step of the Biginelli reaction. Intermediate**(11)** gave intermediate**(12)** after reacting with urea **(12)** cyclized readily to give dihydropyrimidine under strong acid catalyzed condition. It has also been noted that sometimes dihydropyridines of the Hantzch type are isolated as the side product in the standard Biginelli reaction[10].

The Atwal modification



The alternative method of preparation of Biginelli type compounds(DHPMs) was given by Atwal and coworkers in 1987[11-13]. This method was found more reliable approach as compared to classical Biginelli

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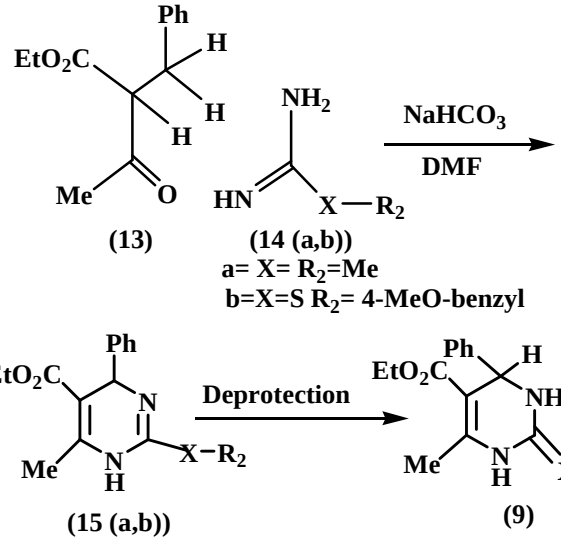
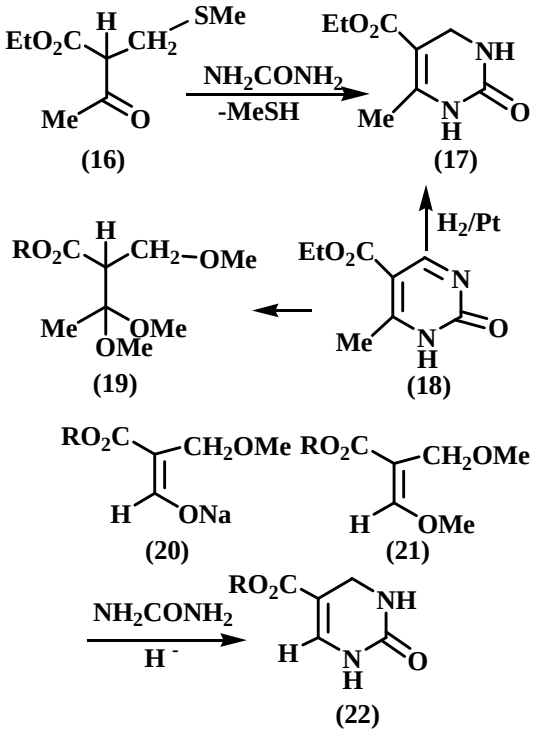
method, in which low yield was encountered particularly when aliphatic or ortho-substituted aromatic aldehyde are employed. Here, an enone of type **(13)** is first condensed with a suitable protected urea or thiourea **(14)**(a,b) in presence of sodium bicarbonate. The reaction probably proceeds through Michael adduct product and forms 1,4-dihydropyrimidines **(15)**(a,b) [11,13], which after deprotaction with HCl or trifluroacetic acid/ethanethiol leads to desired Biginelli compound **(4)**.

Similar result were obtained when **(13)** was condensed with guanidine or N,N,dimethyl guanidine to give 2, amino-substituted pyrimidine **(15)**(XR_2=NH_2, Me_2) [14,15].



Other procedures

Despite of procedure mentioned above there are other alternative methods to prepare Biginelli type compounds but most of them, have limited application for synthetic purpose, thus, substituted acetoacetate **(16)** can react with urea with elimination of MeSH to furnish **(17)**[16]. The same compound can also be, obtained by selective dehydrogenation of pyrimidine **(18)** with H_2/Pt[17]. Dihydropyrimidine **(22)** containing hydrogen at 6th position is the acid catalyzed condensation product of urea with precursors such as **(19)**[9,18], **(20)**[9,19], or **(21)** [9,18]. Here mechanism is supported by involvement of carbenium ion of type **(11)**[9]. Another method also has been reported to synthesize Biginelli compound with a hydrogen atom in position **(6)** is the condensation of ethyl propionate with N- methyl urea and benzaldehyde[20].



C.O kappe[21] in 1997 reinvestigated the mechanism of Biginelli reaction using ^1H and ^{13}C NMR spectroscopy and established that first step in this reaction is the acid catalyzed aldol type condensation, which takes place by reaction of aromatic aldehyde and urea and form N, aclyliminium intermediate **(23)** a key product which is intercepted by enolic form of beta ketoester and form cyclised Biginelli product (DHPMs)[21] **(4)** via open chain uride **(24)** intermediate.

The classical three component Biginelli reaction is usually carried out in either ethnolic or methanolic solution containing few drops of conc. HCl or H_2SO_4 as catalyst. Although other systems such as THF/HCl or dioxane/HCl have also been applied[22], but the major drawback associated with acid catalyzed reaction is low yield[22](26 to 60%) particularly for substituted aromatic and aliphatic aldehyde and longer reaction time (24-36 hours). Increasing demand of Biginelli type compound **(4)** and its derivatives due to multi directional pharmacological profile led to the development of other multistep synthetic strategies like Lewis acid catalyzed cyclocondensation (transitional metal salt)-e.g. $BF_3.Et_2O$[23], $InCl_3$, $In(OTf)_3$, [38]$BiCl_3$, [39]$NiCl_2$[40], [24]$Mn(OAc)_3.2H_20$, [25]$La(OTf)_3$, [26]$LaCl_3.7H_2O$[27], $CeCl_3.7H_2O$[28], $LiClO_4$[29], $Yb(OTf)_3$ clays[30], $COCl_2$.

$6H_2O$[31], $MnCl_2.4H_2O$[31], $SnCl_2$[31], $Zn(OAC)_2.2H_2O$, [32]$InBr_3$, $LnCl_3$[33], $LnCl_5$[34], $Cu(OTf)_3$[35], $KHSO_4$, Phosphotungstic acid/ EtOH[36], $CaCl_2$/microwave[37], $FeCl_3.6H_2O$[41], $CdCl_2$[42], $ZnCl_2$[43], $BiOClO_4.xH_2O$/ CH_3CN[44], ZnI_2[45], LiBr[46], $ZrCl_4$[47], IBr_3[48] have been implied to improve yield and high purity grade.

In last two decades, automated solid phase, solvent free organic synthesis[49], polymer- associated solution phase (PASP)[50], phase-tags organic synthesis[51] via parallel combinatorial approach has been efficient tools for rapid generation of Biginelli type compound. Polymer supported resin bonded isothiourea[52], poly(4-vinylpyridine-Co-divinyl benzene-Cu(II) complex[53], Ceria/vinyl-pyramidine polymer nanocomposite[54], Strontium (II) triflate[55], L-proline methyl ester L-prolinols, pyrolidine, aminoquinuclidine[56], $KAl(SO_4).12H_2O$ supported on silica gel[57], Polyaniline-fluuroboric acid-dodecylhydrogensulphate(DANI-HBF_4-DMS)[58] N-butyl- N,N-dimethyl- α phenyl ethyl ammonium bromide[59], ammonium chloride[60], Yb(III)–resin[61] have been implied to synthesize Biginelli type **(4)** compound, where yield of compounds goes to 90% and reaction time becomes shorter.

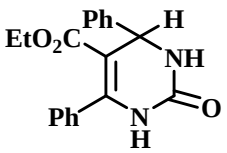
Several other improved protocols for the synthesis of DHPMs e.g. I_2 catalyzed[62], grinding process in presence of (magnesium sulphate)[63], natural HEU type zeolite[64], fluroapetite doped with metal halide[65], silica sulphuric acid[66], KSF montmorilonite[67], water based biphasic media with simple stirring[68], ionic liquid phase organic synthesis(LOGIPOS) methodology (PEG-ILPs)[69], silica aerogel-iron oxide nanocompo site technology[70] also has been recently used to synthesis Bigineli type compound **(4)**.

Structural variation of reactants

In Biginelli cycloadition reaction possibilities of structural variation have been extended widely in all three components. Various aromatic[2,5,7,71-82], aliphatic[5,7,78,83,83-85], heterocyclic aldehyde[5,78,83,86-89] as well as aldehyde component derived form carbohydrate has been taken previously in Biginelli reaction **(25,26,27, 28)**.

In spite of simple alkyl acetoacetates several other acetoacetic acid esters such as benzyl acetoacetate[90], (-) menthyl acetoacetate[90], β-chloro ethyl acetate[91], 2- furanylmethyl acetoacetate[92] and ethylthio-acetoacetate[92] have been successfully used in the Biginelli reaction, similarly benzoylic acid esters, can react analogously to form **(29)**[92], **(30)**[71]

In place of β-ketoester primary, secondary, tertiary acetoacetamide have been used successfully in Biginelli reaction to produce pyrimidine-5 carboxamides [73,82,94-97] **(31)** while substituted urea and thiourea form exclusively N-1 substituted dihydropy rimidines of type **(32)**[97-100], N,N disubstiuted urea don't react at all under there conditions.



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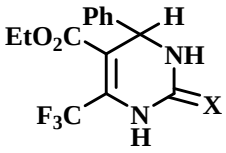

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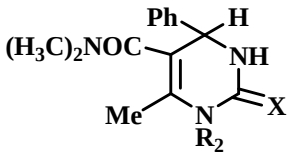
Steriochemical aspects



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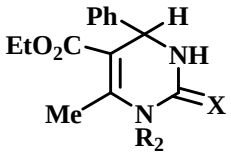

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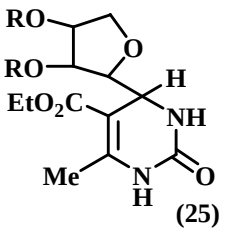
Conformational studies

Rovnyak & co workers[101] in 1995 have studied detailed structure activity profile for a series of DHPM/ DHP analogues as calcium channel modulators **(33)**.

On the basis of pharmacological studies it has been



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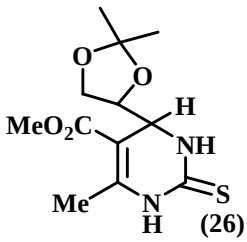

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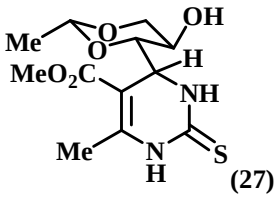

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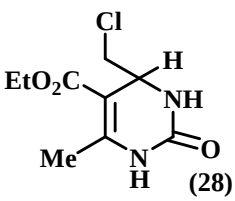

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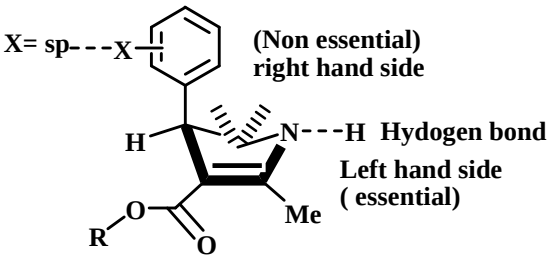

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Proposed receptor- bound conformation of DHP/DHPM calcium channel modulators

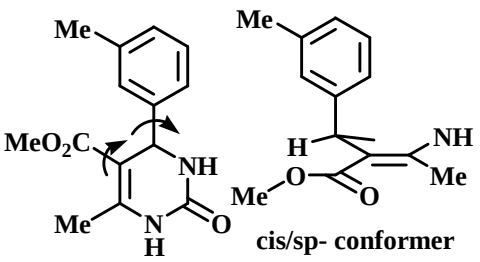
proved that calcium channel modulator(antagonist verses agonist) activity of DHPMs dependent on the absolute configuration of aryl group at C-4 enantiomers having a pseudo axially up- oriented aryl group(normal boat will elicit calcium antagonist activity, whereas enantiomers having a pseudo axially down-oriented aryl group will elicit calcium channel agonist activity. Furthermore, in the receptor bonded conformation the substituted aryl ring should be positioned axially, perpendicular to, and bisecting the boat like, dihydropyridine, pyrimidine, ring or with 4-aryl subsistent(X) preferring the synperiplanar (relative to C4-H) orientation[101].

Calcium channel modulators require alkylester with cis-carbonyl orientation to the left of a plane perpendicular to and bisecting the DHP ring. Importantly, only the "left hand side' of the DHP/DHPM molecule has been proposed to be essential for activity[101].

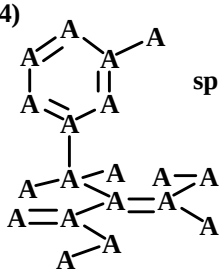
Recently conformational features of DHPs have been studied extensively by computational(semipirical and ab initio) X- ray diffraction and NMR studies.

In compound **(34)**, simple model studies have been carried out which have shown conformational flexibilities. The aryl group and the ester group can rotate and possibility of change at three sites[101-106]. Model compound **(34)** has found four distinct, local minima (AMI, Hf/3-21G) for geometries, whereas the ester group is in coplanar arrangement with the double bond of the dihydropyrimidine ring(carbonyl group cis or trans with respect to the C-5(6) double bond), and(b) where the methyl substituted on the aryl ring adopts either a syn(sp) or antiperiplanar (sp) orientation with respect to(C4- H)[102].

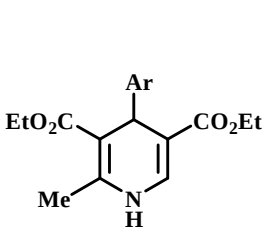
In all four conformation, the aryl ring is positioned axially, perpendicular to and(nearly) bisecting the half boat like structure of dihydropyrimidine ring(no minima were found for equatorially arranged C-4 aryl rings). The lowest energy conformer generally is the cis/sp conformer, however the other rotamers are usually only a few Kcal/mole higher in energy coupled with the relatively low calculated rotational barriers[102]. It can be concluded that in a biological cycle all four distinct minima geometrics are accessible, with no clear preference for one particular conformer. This general trend has been confirmed for a verity of DHPM structure[102-105]. It should be noted that the overall conformational



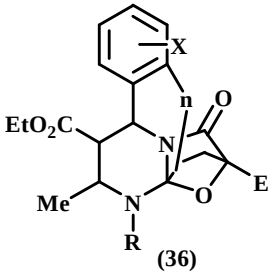
(34) cis/sp- conformer



trans/sp- conformer



(35) (DHP)



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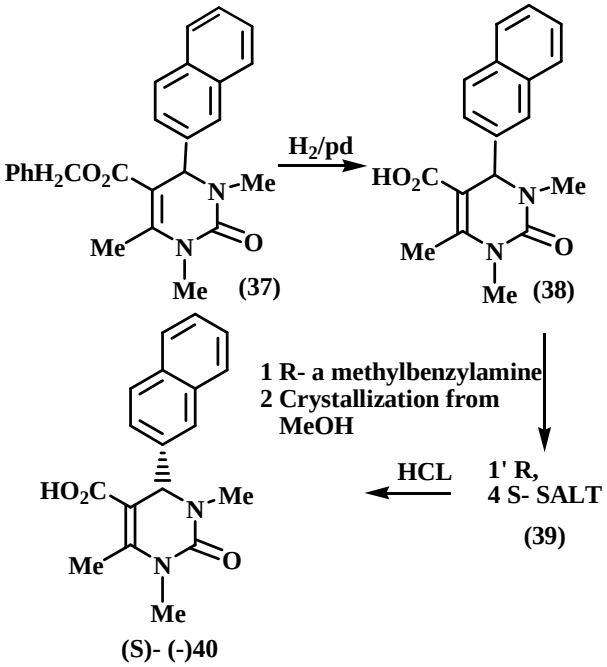
and structural preferences observed for DHPM**(4)** are quite similar to those found for dihydropyrimidines of type **(35)**. In recent years C.O.Kappe and coworkers[106] have developed synthetic methodologies leading towards novel type of conformationaly restricted dihydyhdropyrimidine**(36)** that closely mimics the recently proposed receptor bounded conformation of DHPM/DHP calcium channel modulators shown in the figure, the aryl group in **(36)** is "tide" into axial position perpendicular to and(nearly) bisecting the boat-like dihydropyrimidine ring. Any substitution on aromatic ring

(i.e. X in **36**) would be forced into the synperiplanar orientation relative to C4-H.

Enantiomerically pure dihydropyrimidines

DHPMs are inherently asymmetric and therefore, usually obtained as recmic mixture but enantiomereric purity was neglected for several years since individual enantiomers of DHPMs have opposite pharmacological profile leading to the development of enantiomerically pure form of DHPMs. Few years ago enantiomerically pure form of DHPMs have been developed by resolution of corresponding recemic 5-carboxylic acid **(38)** via fractional benzyl- ammonium salt **(39)**[108]. Absolute configuration of DHPM **(39)** was proven by single-crystal X ray analysis of a suitable diasterio salt. Other related methods[109-111] has been carried out to get enantio merically pure DHPMs **(40)** a,b,c.

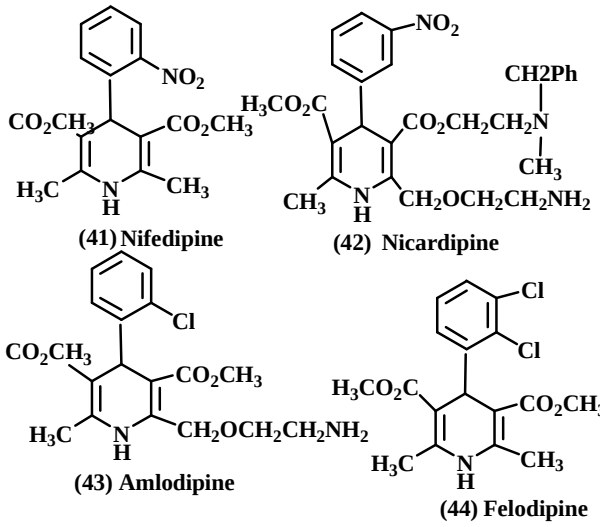
Biological activity of dihydropyrimidine



4-aryl- 1,4- dyhydropyridines of Nifedipine **(41)** type are most important class of organic compounds as calcium channel blockers in clinical medicine since 1975 for treatment of cardiovascular problems such as hypertension, cardiac arrhythmia or angina[112]. Dihydro pyrimidines have found widespread use in cardiovascular medicine and have served key role in study of calcium channel structure and function[113].

After the introduction of Nifedipine **(41)**, several other DHP analogs have now been synthesized and numerous second generation more potent commercial products have approached the market e.g.(Nicardipine **(42)**, amlodipoine **(43)** and felodipine **(44)**[114].

Cardiovascular activity of DHPMs namely, eta



amino ethyl esters**(45)** were for the first time reported by Khanine and coworkers[115] in 1978. Since 1986 a number of compounds have been synthesized**(46-48)** [116,113,74,79], on the basis of simple modification in aromatic ring showing moderate cardiovascular activity and calcium channel blocking activity, but they don't show any significant antihypertensive activity *in vivo*[109]. Other bicyclic derivatives of dihydropy rimidines **(49,50)**[117], have been synthesized, but they were devoid of antihypertensive activity. Further structural modification led to the development of DHPMs of type **(51-54)**[118,119,109], bearing an ester group at N-3, which closely resembles to DHPs. Nifedipine**(41)** and compound**(51)** posses not only more potent vasodilator action, but also a hypotensive activity compared with DHPs**(50)**. The most active compound is DHPM bearing ester derivative **(54)**[119]. Further modification led to the development of orally active long acting anti hypertensive derivative, SQ 32926**(55)**[120], SQ 32547 (**56**)[121] having improved oral bioavailability. Compound **(54,56)** have been shown to posses anti ischemic properties in animal model[122]. Not only monocyclic derivatives, but various other bicyclic compounds have been synthesized which are fused analogue**(57-60)**[123-125], and posses calcium channel blocking activity.

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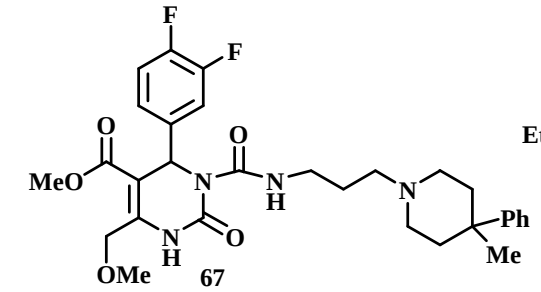
Rovanyak et al. proposed structure activity relationship and pharmacological studies for N-3 functionalized DHPM calcium channel blockers of type **(52-56)**[121] C-5 alkyl group was found essential for optimal activity *in vitro*. Additionally, an order of potency for the heteroatom at position 2-was found to be[121](S>O>N). Other DHPMs derivatives have also been synthesized which have minor or weaker calcium channel blocking activity.

DHPMs in cancer chemotherapy



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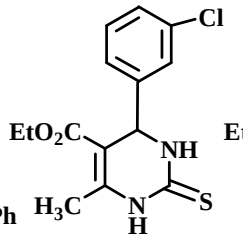

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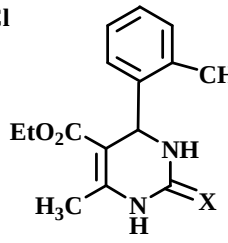

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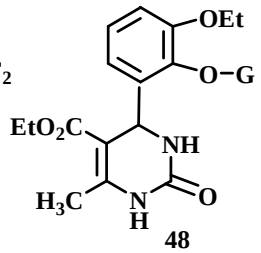

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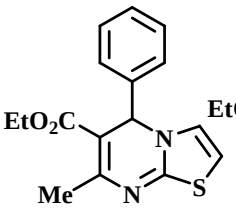
G=2,3,4,6-tetra-6 acetyl-beta-D- lucopyronosyl



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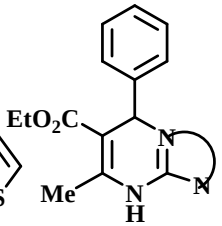

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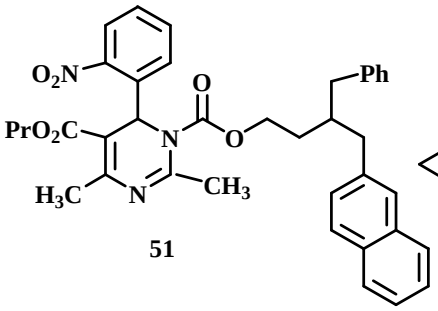

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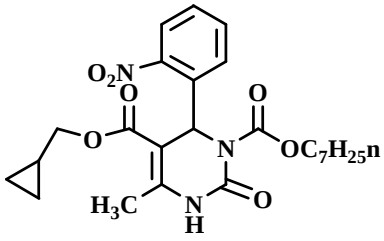

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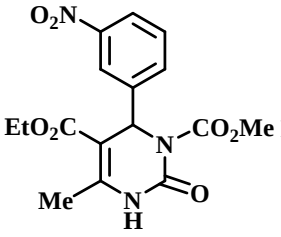

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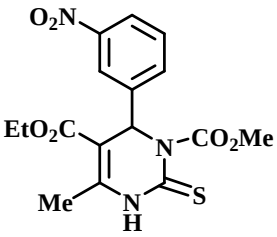

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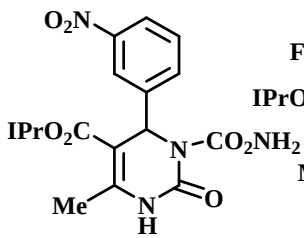
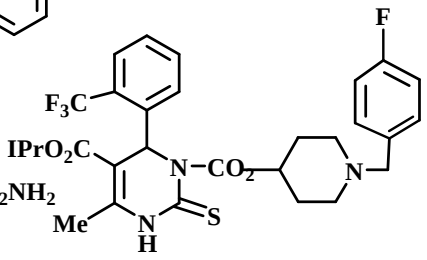


55 (SQ32926)



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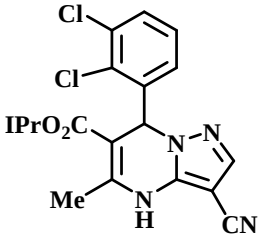

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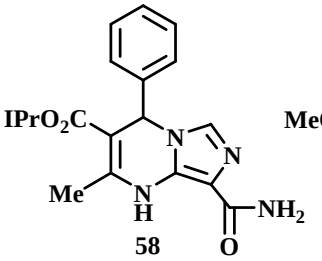

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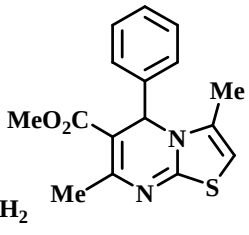

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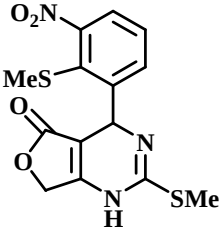

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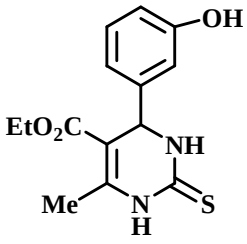
In cancer chemotherapy a common fundamental is applied to develop new drugs that interferes cell cycle during the mitosis stage. Compounds interact with microtubules and cause either lengthening(polymerization) or depolymerisation(shorting) and finely cause arrest of the cell cycle in mitosis. There are a number of drugs prepared currently which binds tubulin and have been used in cancer therapy e.g. paclitaxel, docetaxel[126]. Out of 16320 members of the library of diverse small compounds**(61)**, was found a novel cell permeable molecule which blocks normal bipolar mitotic spindle assembly in mammalian cells and cause cell cycle ar-

rest[127]. Compound termed as monastrol, which blocks mitosis by inhibiting kinase Eg_5, a motor protein required for spindle bipolarity and considered as lead compound for development of newer anticancerus drugs. DHPMs structure**(62)** was also found to have colchicine like tubulin inhibitor activity[128].



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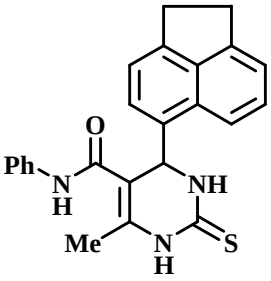
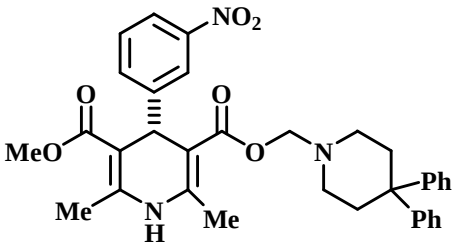


(62)

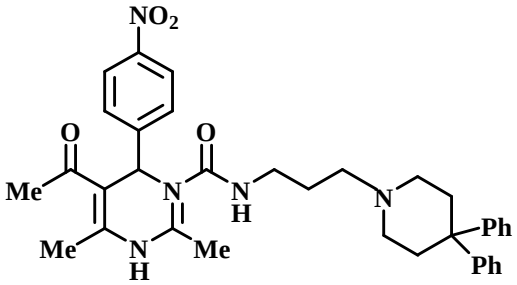
α-1a Adrenergic receptor antagonists

A number of DHPM derivatives has been screened for α-1a antagonistic activity and found to be useful in benign prostate hyperplasia. BPH has been characterized as a progressive disorder associated with enlargement of the prostate resulting in a number of obstructive and irritable symptoms[129]. Non selective α-1blockers are commonly used for therapy of BPH[130]. Niguldipine**(63)** was seen to be potent antagonist of the α-1a receptor subtype. Furthermore, structural modification led to the development of SNAP 5089 **(64)**[131], **(65)**[132] SNAP, which maintained potency and selectivity verses other α- receptor subtype.

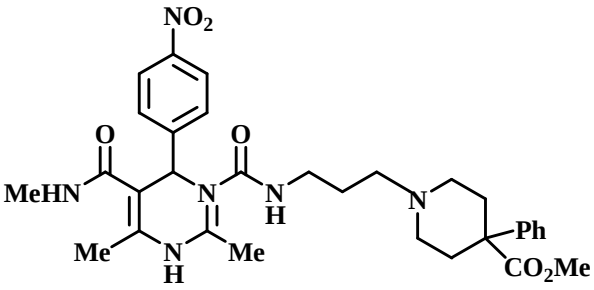
Other structural modification in DHPMs led to development of **(66)** SNAP 6201, which showed good binding affinity(<1nm) and excellent subtype selectivity (>300 fold) for the α-1a receptor, cardiovascular activity and a good pharmacodynmic profile[133]. Modification of compound**(66)** led to development of**(67)** which had better binding capacity and more selectivity. The corresponding DHPM**(68)** maintained a binding and functional profile comparable to that of SNAP 6201[134]. Compounds**(66-68)** were also replaced by a 2- methyl-dihydopyrimidine core leading to derivatives such as compound**(69)** which however, displaced suboptimal pharmacokinetic profile[135]. In another related study it was demonstrated that furo(3, 4-d) pyrimidines of type**(70)** are metabolite of DHPM**(68)** that also show selective α-1a[136] antagonistic activity. Apart from attachment at N-3 of the dihydropyrimidine ring, as exemplified by DHPM, **(66-70)**, the piperidine/ piperazine side chain can also be linked via an amide bond to the C-5 carboxy functionality e.g. in compound**(71)**. *In vivo* testing of these compounds in both rat and dog models confirmed the result from receptor studies and suggested that DHPMs of this type have significant activity to relieve the symptoms of BPH with out eliciting effect on the cardiovascular system.



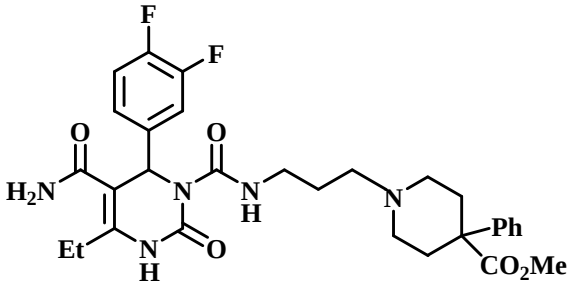
63 (S)-niguldipine



64 SNAP 5089



65 SNAP 5540



66 SNAP 6201

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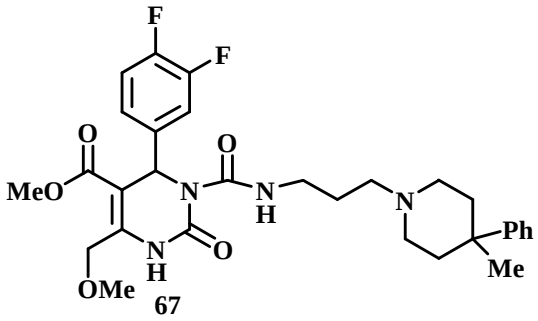
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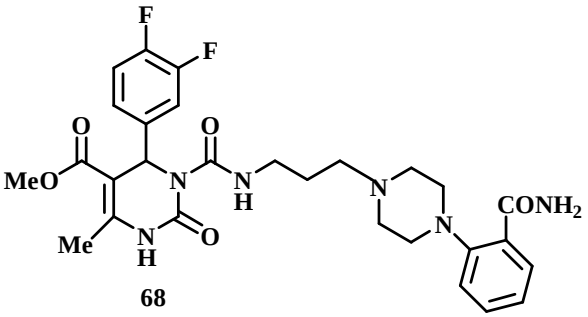
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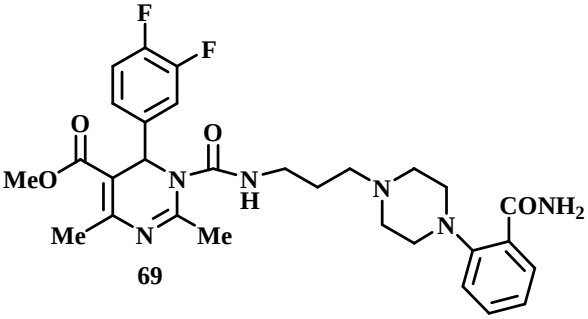
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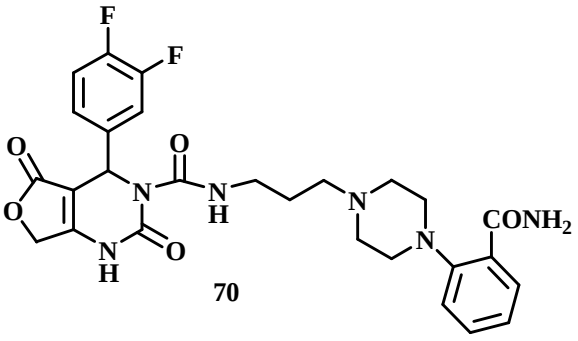
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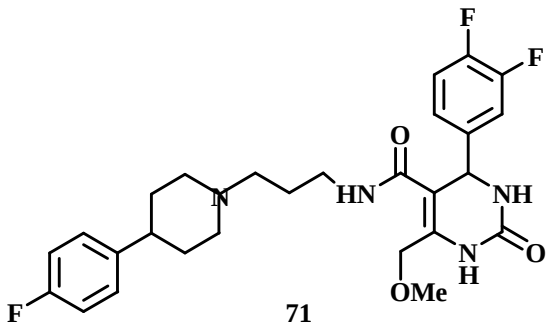
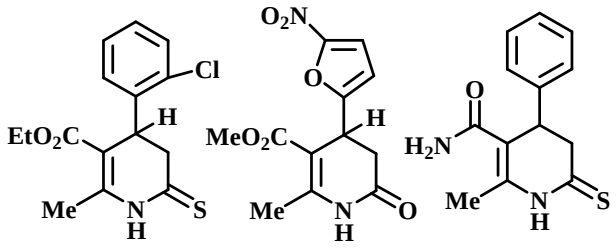

71

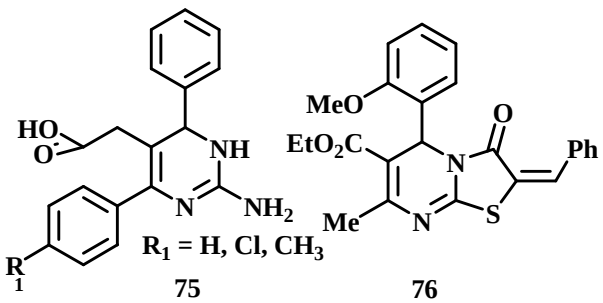
Other biological activity of DHPMs

Biginelli type compounds not only showed CVS activity but also immerged in various other biological activities. In early 1930 compound**(46)** was patented as agent for the protection of wool against moths[137]. As early as 1940s DHPM nitrofuryl- substituted analogue nitracin**(73)** has been shown active against viruses of trachoma group[138] have been also screened for antibacterial activity[139].

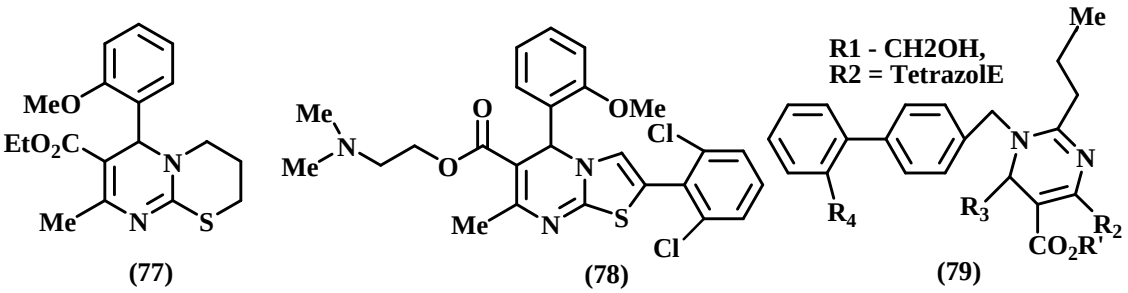
Some other structural analogue of DHPMs have been screened for antitumour activity and found to be active against Walker carcinoma in rats and mice[140]. Compound**(74)** has been found to have anticarcinogenic activity while other derivatives were screened for blood platelet aggregation inhibitory activity[141] and were also shown to inhibit the uptake of adenosine by thrombocytes[142]. 4- Phenyl substituted DHPMs having acetic acid group at 5th position the compound**(75)** has been reported for analgesic activity[143]. Fused thiazol (3,2-a)-pyrimidine**(76)** and pyrimido(2,1-b)(1,3) thiazine **(77)** were reported to have anti-inflammatory activity[144]. Recently, thiazolo(3, 2a) pyrimidine**(78)** has been found to be micromolar group-2 metabotropic glutamate receptor antagonist[145].

Some simple 2- thixo DHPMs have been found to be active fungicides[146] towards *Aspergillus niger* A.*achraceus*. A recent patent disclosed structure of DHPMs with neuropeptide Y (NPY) antagonist activity. In 1992 Atwal and coworkers had reported


72 73 74


R_1 = H, Cl, CH_3

75 76



DHPMs compounds **(79)** as AT_1 antagonistic and compared antihypertensive activity with Losartan[147].

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