Genesis of Dihydropyrimidinone$^{\Psi}$ Calcium Channel Blockers: Recent Progress in Structure-Activity Relationships and Other Effects

K. Singh*, D. Arora, K. Singh and S. Singh

Organic Synthesis Laboratory, Department of Applied Chemical Sciences & Technology, Guru Nanak Dev University, Amritsar – 143 005, India

Abstract: In the armamentarium of calcium channel blockers appropriately functionalized 3,4-dihydropyrimidin-2(*1H*)-ones have received considerable attention in recent past owing to their structural similarity with 1,4-dihydropyridine based drugs. In this review, we highlight detailed investigations in the calcium channel blocking and other activities of this category of compounds as well as trace their genesis from 1,4-dihydropyridine based drugs.

Key Words: Dihydropyridines, dihydropyrimidines, dihydropyrimidinones, calcium channel blockers, mitotic kinesin inhibitors, α-adrenergic receptor antagonists, structure- activity relationships.

$^{\Psi}$Dedicated to (Late) Dr. K. S. Atwal for his Invaluable Contribution to Dihydropyrimidinone Chemistry & Biology.

INTRODUCTION

Drug discovery in the late 20th century has increasingly focused on the definition and characterization of the molecular scaffolds that serve as targets for drug design. Genomics and molecular biology [1] revolution has permitted the definition of new drug targets in addition to the understanding of the genetic basis of disease states, which is complemented with rigorous research input from the chemist community. The introduction of powerful new techniques such as high throughput screening (HTS) [2] has greatly accelerated the pace of new drug discovery and meets the challenge posed by genomics by enhancing the potential drug targets. A salient feature of all these activities has been the advancement in the area of modification of the existing drug leads through systematic alterations at the key molecular centers, a concept that compares well with the design of altogether new molecular frameworks.

In the area of calcium channel blockers (CCBs) (calcium antagonists, calcium channel modulators) structurally diverse groups of organic compounds have been recognized as calcium channel antagonists [3]. They are known to regulate the activity of voltage gated L-type calcium channels through binding to specific sites on the channel proteins [4]. CCBs bind to L-type calcium channels located on the vascular smooth muscle, cardiac myocytes, and cardiac nodal tissue (sinoatrial and atrioventricular nodes). These channels are responsible for regulating the influx of calcium into muscle cells, which in turn stimulates smooth muscle contraction and cardiac myocyte contraction. Therefore, by blocking calcium entry into the cell, CCBs cause vascular smooth muscle relaxation (vasodilation), decreased myocardial force generation (negative inotropy), decreased heart rate (negative chronotropy), and decreased conduction velocity within the heart (negative dromotropy), particularly at the atrioventricular node.

There are three classes of CCBs e.g., 1,4-dihydropyridines (1,4-DHPs), phenylalkylamines and benzothiazepines. They differ not only in their basic chemical structure, but also in their relative selectivity toward cardiac versus vascular L-type calcium channels. The most smooth muscle selective class of CCBs is the 1,4-DHPs. Because of their high vascular selectivity, these drugs are primarily used to reduce systemic vascular resistance and arterial pressure, and therefore are primarily used to treat hypertension. They are not, however, generally used to treat angina because their powerful systemic vasodilator and pressure lowering effects can lead to reflex cardiac stimulation (tachycardia and increased inotropy), which can dramatically increase myocardial oxygen demand. Receptor sites of 1,4-dihydropyridines have been most extensively studied to define drug action at the cellular level and to rationalize the process of design of drugs active at these voltage-gated ion channels. As a result of this, a number of 1,4-dihydropyridines have been inducted into clinical use. These compounds exert a profound negative inotropic effect on heart muscle and a marked relaxation of the smooth muscle [4].

Structurally closely related pyrimidines [5] were also explored as potential calcium channel blockers but did not show promise. However, the resuscitation of 2-oxo-3,4-dihydro analogues of pyrimidines which were known since 1893 [6] witnessed an unprecedented activity both in the synthesis and biological evaluations. A literature survey [7] on these molecules was presented almost eight years ago. Since then a renaissance in the structural elaboration of 3,4-dihydropyrimidinone scaffolds has taken place [8], in search of molecules with improved therapeutic efficacy and with the hope to find superior CCBs. In the process, in addition to the calcium channel antagonistic properties, many additional interesting biological effects have been recognized. This

*Address correspondence to this author at the Organic Synthesis Laboratory, Department of Applied Chemical Sciences & Technology, Guru Nanak Dev University, Amritsar – 143 005, India;
E-mail: kamaljit19in@yahoo.co.in

1389-5575/09 $55.00+.00

mini review complements the existing literature survey [7] and additionally a sequential genesis from the first generation CCBs is presented under the following sub-headings:

1. 1,4-DHP and dihydropyrimidine CCBs

2. Structure-activity relationships in 3,4-dihydropyrimidinones

3. Other biological effects of 3,4-dihydropyrimidinones

However, this review is not intended to be a comprehensive treatment on the general synthetic aspects, which are excluded in view of earlier published reviews [8, 9].

1. 1,4-DHP and DIHYDROPYRIMIDINE CCBs

1,4-DHPs (Hantzsch esters) [10] have since 1975 been established as the first generation cardiovascular agents such as nifedipine (**1**) (Adalat®), or the second-generation calcium antagonists such as nicardipine (**2**) (Cardene®), nitrendipine (**3**) (Nidrel®), amlodipine (**4**) (Norvasc®) and felodipine (**5**) (Plendil®) etc. and are in clinical use for the treatment of cardiovascular disorders such as hypertension, cardiac arrhythmias or angina [11].

The proficiency of the pharmacological effects of 1,4-DHPs has been adequately reviewed in some excellent treatises [12]. Several structure-activity relationships (SAR) have been established for these molecules [13]. In the receptor-bound conformation, the substituted aryl ring is positioned axially, perpendicular to and bisecting the flattened boat like conformation of the DHP ring as shown in Fig. (**1**). The C-4 aryl substituent prefers a synperiplanar (relative to C-4H) orientation. The ester group (carbonyl) shows preference for *cis*-orientation w.r.t C-5, C-6 double bond. Interestingly, it has been recognized that the absolute configuration at the C-4 position of the 1,4-DHP nucleus is indispensable for the activity modulation. When the substituents at C-2/C-6 and the esters at C-3 and C-5 are equivalent, the molecule possesses C_s symmetry and is nonchiral. Unsymmetrical substitution at these positions generates a chiral centre at C-4. Indeed, enantiomers of an unsymmetrical 1,4-DHP usually differ in their biological properties and sometime they could depict exactly opposite action profile [calcium antagonists (blockers) *vs* calcium agonists (activators)] [14]. Distinction between the opposing activities has been determined by the "port-side" substituent: esters for antagonists *e.g.,* **1** and nitro (or fused lactone or simply hydrogen) for activators, *e.g., (S)*-Bay K 8644 (**6**) [13].

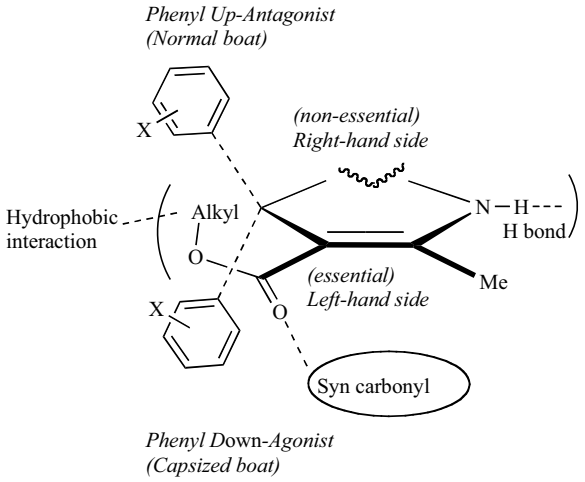
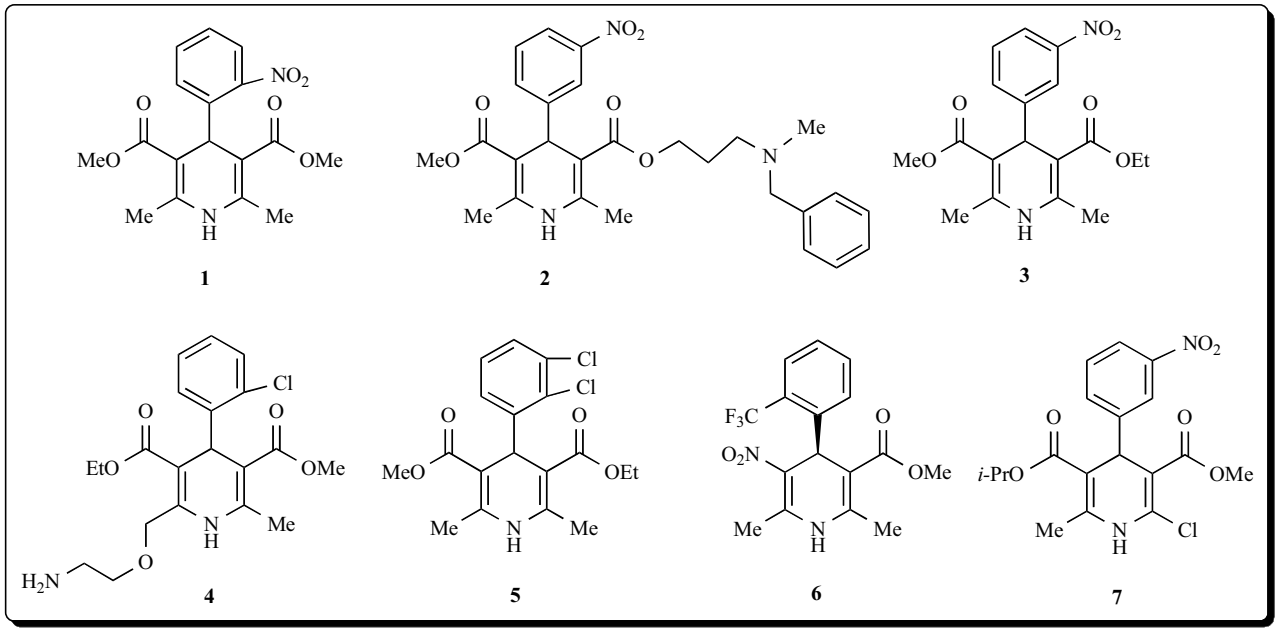


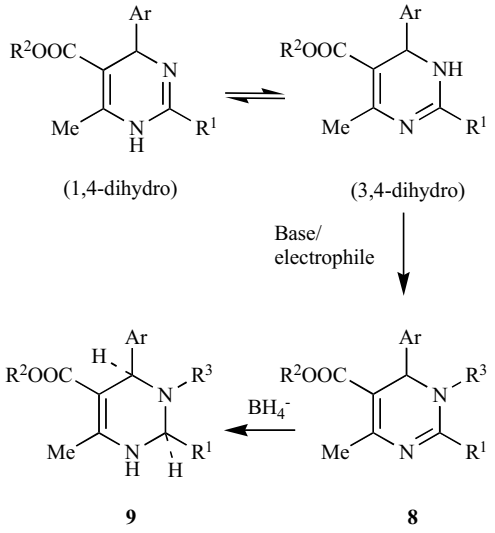
Fig. (**1**). Proposed receptor bound conformation of 1,4-DHPs.

Although highly successful, traditional 1,4-DHP based drugs such as **1**, face limitation of relatively short plasma half-lives [15] attributable to metabolic oxidation to pyridines [16], as a consequence of which these need to be administered repeatedly to achieve enough clinical efficacy and the requirement of multiple dosages lowers compliance. 2-Chloro-1,4-dihydropyridine (**7**) derivatives [17] exhibited rather prolonged calcium antagonistic activity in comparison to 1,4-DHPs having methyl substituents at C-2 and C-6 position (*e.g.* **3**). The activity of *e.g.,* **7** upon oral administration



in spontaneously hypertensive rats (SHR) was found to be similar to **3**, however the onset of hypotensive action in the case of **7** was slower than the traditional 1,4-DHPs.

The genesis of partially reduced pyrimidines can be traced from pyrimidine nucleus itself, which in addition to being essential component of naturally occurring nucleic acids, is integral part of such biologically important compounds as antiviral [18], antitumor [19] and cardiovascular agents [20]. Contrary to the initial opinion regarding their instability, lack of information on stabilization-destabilization parameters, ambiguous structural tautomerism (1,4 dihydro ↔ 3,4-dihydro, Scheme **1**) and isomerisation, creditable work on the chemistry and biology of pyrimidines has been reported [21]. Because of the structural similarity between DHPs and dihydropyrimidines, the cardiovascular activity of N-3 substituted (alkoxycarbonylated, acylated and alkylated)-3,4-dihydropyrimidine (**8**) has been thoroughly investigated. It has been further argued that unlike 1,4-DHPs such as **1**, which are light sensitive [16] and aromatize, the dihydropyrimidines **8** are stable owing to structural characteristics (presence of N-3 substituent).



Scheme 1.

N-3 substitution of pyrimidine derivatives to obtain **8** is very facile. The N-3 site being sterically less hindered owing to the perpendicular disposition of the C-4 aryl ring with respect to the ring, generates a stronger nucleophilic centre upon treatment with a suitable base and rendering the substitution reaction highly regioselective. However, an ortho substituent on the C-4 aryl ring often directs the reaction at N-1. Reduction of dihydro derivative **8** (Scheme **1**) with borohydride furnishes tetrahydropyrimidines (**9**). Although dihydropyrimidines **8** lack N-1 hydrogen, a prerequisite for good affinity for the 1,4-DHP receptor, it was found that some derivatives of **8** competitively displaced [^{3}H] nitrendipine from its binding site on the cell membrane prepared from the rat cerebral cortex [5].

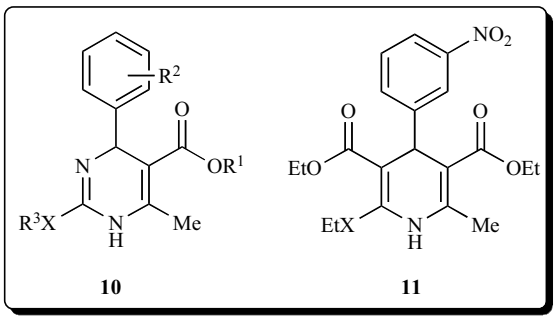
N-3 Unsubstituted-1,4/3,4-dihydropyrimidines when tested for the potency (ED_{30}) and the duration ($t_{1/2}$) of the vasodilative action on the vertebral artery and were found to be ineffective [5]. However, N-3 substituted **8** exhibited very potent vasodilative activity (ED_{30} = 1.0 to 3.0 μg/kg) comparable to **2**, but the duration of action was short as **1** [5]. Further, vasodilative activity was found to be dependant on the substituent on the aryl ring which followed the order *o*-NO_2 (ED_{30} = 3.0 μg/kg) >*o*-Cl/*o*-Br (ED_{30} = 5.0 μg/kg) >*m*-NO_2 (ED_{30} = 10.0 μg/kg). Further, evaluating the modifications such as lengthening the alkyl chain of the alkyl ester, compounds with short chains were found to be potent vasodilators, but exhibited shorter duration of action and the trend getting reversed in case of derivatives possessing longer alkyl ester chains. Compounds with longer chains at N-3, rather than C-5 were more potent. In these compounds, the duration of action was observed to increase by increase in hydrophobicity of the alkyl chains. Unlike, 1,4-DHPs, the replacement of C-6 methyl with Cl did not enhance pharmacological activity of the pyrimidine. Further, tetrahydropyrimidines **9** were found to be less potent than their dihydro analogues.

Out of a number of dihydropyrimidines studied, significant vasodilative activity was depicted by derivatives **8** {Ar = 2-NO_2Ph, R^1 = Me, R^2 = *i*-Pr, R^3 = $COOR^4$ [R^4 = -$(CH_2)_2$N-benzyl-(2-naphthylmethyl) (**8a**) (ED_{30} = 1.8 μg/kg)/-$(CH_2)_2$N-benzyl-(3,4-dichlorobenzyl) (**8b**) (ED_{30} = 2.1 μg/kg)]}. Oral administration of **8a** and **8b** (10 mg/kg) caused a decrease in mean blood pressure and an increase in heart rate similar to those caused by **2** and **3**, however, the hypotensive activity was found to be maximum after 2h of administration of **8a** and **8b**, unlike **2** and **3**, in which it started almost immediately. Further, the hypotensive response of **8a** and **8b** for duration more than 2 h was superior to **2** and **3** [5].

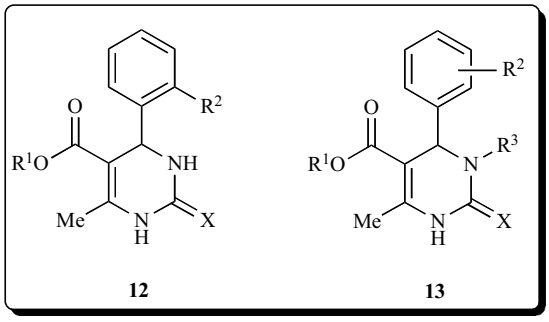
2-Heterosubstituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters (**10**), which lack C_s symmetry of 1,4-DHP CCBs have also been evaluated for biological activity [22]. This study on inherently unsymmetrical molecules further substantiated information about the structural requirements as well as the effect of absolute stereochemistry on CCB activity. Assays using potassium-depolarized rabbit arota and radioligand binding techniques showed that some of these compounds having combinations of a branched ester (*i*-Pr, *s*-butyl) and an alkylthio group (*e.g.,* **10** R^3X = SMe) at 2-position are potent mimics of traditional 1,4-DHP CCBs [22]. When compared directly with similarly substituted 2-hetero-1,4-DHPs, these compounds were found to be 30 fold less active. Evidence of similarity of conformation of 2-heterosubstituted dihydropyrimidine using X-ray crystallographic analysis further established that these compounds exhibit conformational preference similar to 1,4-DHPs although these lack C_s symmetry of 1,4-DHPs. These molecules demonstrated lower affinity for the DHP receptor than similarly substituted 2-heteroalkyl 1,4-DHPs. However, regardless of their potency *in vitro*, for the reasons unknown, none of the 2-heterosubstituted dihydropyrimidines **10** or DHPs **11** (X = O, S) showed antihypertensive activity when administered to SHR at 135 μmol/kg po [22].

2. STRUCTURE-ACTIVITY RELATIONSHIPS IN 3, 4–DIHYDROPYRIMIDINONES

The synthesis of derivatives of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-one (DHPM) (**12**) (X = O) was reported in



1978. These compounds depicted moderate antihypertensive and coronary vasodilation activity [20, 23]. Direct functionalization of derivatives of **12** (X = O, NH or S) was either unsuccessful or found to be slow and depicted total lack of regioselectivity to furnish mixture of products. However, using 2-heterosubstituted 1,4-dihydropyrimidines **10** (X = S, O) which encompass difference in reactivity of the two nitrogens in the pyrimidine ring, selectivity in their reaction with an electrophile was achieved. Thus, using appropriate **10**, N-3 acylated DHPM derivatives **13** (X = S, O) have been obtained [24].



N-3 Substituted 1,4-dihydropyrimidines **13** constitute an inherently asymmetric system capable of tolerating a variety of substituents such as carbamate, sulfonyl, acyl and alkyl at N-3 [25]. Structure-activity studies using potassium depolarized rabbit arota, depicted **13** (R^1 = *i*-Pr, R^2 = *m*-NO_2, R^3 = COOEt, X = S) to be at least 10 fold more potent (IC_{50} = 1.7 nM) than the corresponding ethyl ester (R^1 = Et) (IC_{50} = 17 nM) and at least 60 fold more potent than the methyl ester (R^1 = Me) (IC_{50} = 100 nM), Fig. (**2**) [25]. Likewise, evaluating the effect of substituents at N-3 in **13** (R^1 = Et, R^2 = *m*-NO_2, R^3 = ester, X = S), changing COOMe to COOEt and COO*i*-Pr, in that order as depicted in Fig. (**2**) [25] saw a 4.7 and 3.8 fold, respective decrease in potency: both pyrimidinone and thione **13** (R^1 = Et, R^2 = *m*-NO_2, X = S and O) lacking a N-3 substituent (R^3 = H), were found to be devoid of potency. A variation at the aryl substituents (R^2) revealed *o*-, *m*-disubstituted aryl derivatives to be more potent than *o*- and *m*-monosubstituted analogues, in that sequence. In the series of 3-substituted dihydropyrimidinones, it has further been found that among individual substituents at the *o*- or *m*-position, the nitro derivatives were more potent than the chloro and trifluoromethyl derivatives. Among individual enantiomers of **13** (R^1 = *i*-Pr, R^2 = *m*-NO_2, R^3 = COOEt, X = S), (*R*)-enantiomer was found to be at least 1000 fold more potent than the corresponding (*S*)-enantiomer (Fig. (**2**)) [25].

Thus upon comparison with other CCBs, the order of potency among different types of derivatives is 2-heteroalkyl-1,4-DHPs (3-5 fold)≥ 3-substituted 1,4-dihydropyrimidines (5-7 fold)> 2-heteroalkyl-1,4-dihydropyrimidines. A comparison of the 2-oxo-, 2-thiono and 2-imino DHPM derivative revealed the thiono derivative to be nearly one order of magnitude more potent.

From these studies the requirement of an enaminoester moiety for the calcium channel binding activity of DHPM related systems was ascertained [25]. A direct comparison of activity difference between enantiomers of 1,4-DHPs and DHPMs reveal that whereas individual enantiomers of the former category showed a 10-15 fold difference in activity and (*S*)-enantiomer was more potent than the (*R*)-enantiomer, in DHPM derivatives, the trend is reversed and the difference between the two enantiomers is of the order of 1000 as depicted in Fig. (**2**).

However, the N-3 ester substituted DHPM derivatives **13** were ineffective in lowering blood pressure in SHR following oral administration probably due to metabolic instability of some of these derivatives; they generally possessed the desired vasorelaxant potency *in vitro*. Further, upon oral administration of these ethyl carbamate derivatives to rats (*in vivo*) or employing rat liver homogenates (*in vitro*), the identification of the metabolized carbamate hydrolyzed product **13** (R^3 = H), explained the lack of antihypertensive activity of these compounds in the SHR. In order to overcome this limitation, interest was shifted on the N-3 carbamoyl derivatives as potential CCBs [26].

Initial screening of N-3 carbamoyl derivatives revealed the metabolic conversion of **13a** (R^1 = *i*-Pr, R^2 = *m*-NO_2, R^3

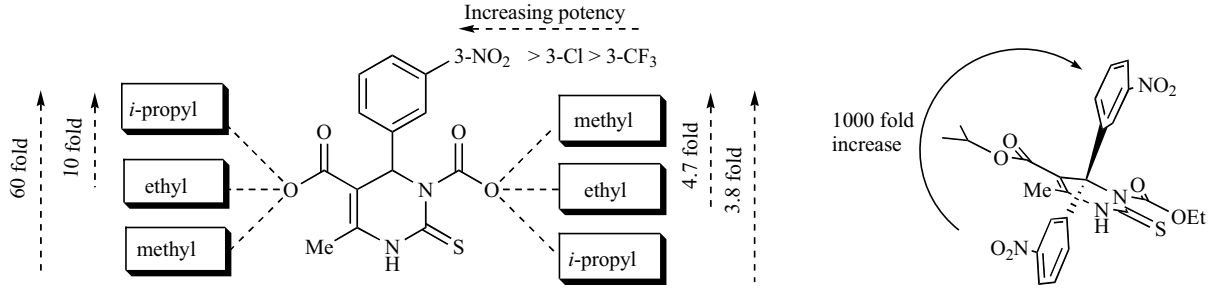


Fig. (2). Structure-activity relationship of dihydropyrimidinethione calcium channel blockers.

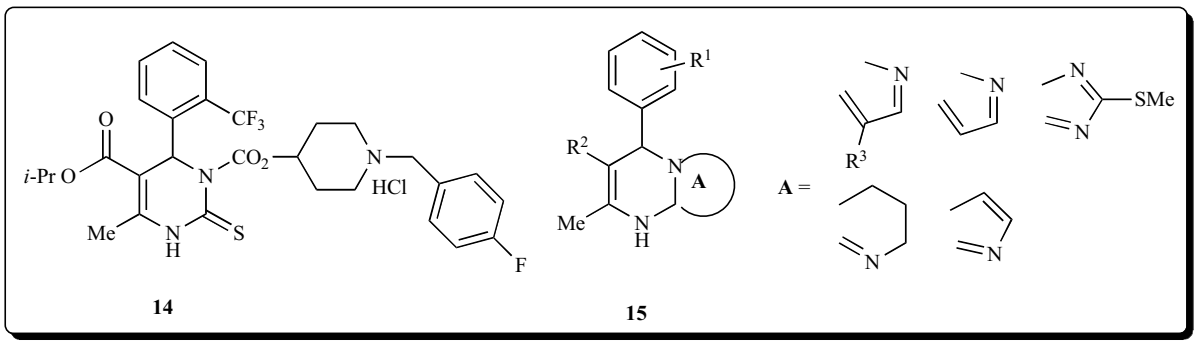
= $CONMe_2$, X = O), into the monodesmethylated derivative **13b** (R^3 = CONHMe) and demethylated derivative **13c** (R^3 = $CONH_2$). The DHPM **13c** (SQ-32926) was found to be the most potent (IC_{50} = 12 nM) than **13b** (IC_{50} = 3200 nM) as well as **13a** (IC_{50} = 16 nM). The activity of **13a** was attributed to its metabolism into **13c**. The effect of size of C-5 ester on derivatives of **13c** was also evaluated. DHPM **13c** substituted with an isopropyl group at C-5 ester is almost 3 fold more potent (IC_{50} = 12 nM) than the corresponding ethyl derivative (IC_{50} = 39 nM), which in turn was found to be nearly 22.5 fold more potent than the methyl substituted dihydropyrimidine (IC_{50} = 880 nM) derivative [26]. However, for the carbamoyl substituent, the decreasing trend in the *in vitro* potency was **13** (R^1 = *i*-Pr, R^2 = *m*-NO_2) R^3 = $CONHCH_2Ph$ (IC_{50} = 3 nM) > R^3 = H (IC_{50} = 1580 nM). Likewise, **13** (R^1 = *i*-Pr, R^2 = *m*-NO_2) R^3 = CONHMe ≅ CONHEt (IC_{50} = 16 and 13 nM, respectively) is more potent than R^3 = CONH*i*-Pr (IC_{50} = 60 nM) derivative. Thus the lower potency of **13** substituted with *i*-Pr groups, at ester as well as carbamoyl functionality, is indicative of deleterious effect of branching on potency. Comparing the effect of the aryl substituent on potency, four dihydropyrimidine derivatives **13** R^1 = *i*-Pr, R^2 = *o*-NO_2, *m*-NO_2, *m*-Cl and 2,3-oxadiazoyl, R^3 = $CONH_2$ were recognized with good antihypertensive activity. These derivatives depicted maximum reduction in blood pressure in the range 28-34 after 6 h of administration in SHR at 45 μmol/kg po [26]. Upon resolution of **13c**, the biological activity was found to reside in the *R*-(-)-enantiomer (IC_{50} = 8 nM) which is both more potent (more than 400 fold) than the *in vivo* inactive, *S*-(+)-enantiomer (IC_{50} = 3790 nM) and longer lasting than **1** as an antihypertensive agent in SHR. The *in vivo* potency and duration of *R*-(-)-**13c** is comparable to the long-lasting **4**, although it is 3-fold less potent *in vitro* than both **1** and **4** (IC_{50} = 2.5 nM). Upon comparison with **1** and **4** for its effect on decreasing blood pressure (associated with increase in heart rate) in SHR at an oral dose of 15 mmol/kg, *R*-(-)-**13c** was found to be more potent than **1** and similar to **4**, this effect lasts for longer duration than **1**. Thus *R*-(-)-**13c** qualified to be a long-acting antihypertensive agent and offered potential for single daily dosing regimen for the treatment of hypertension. Further, it is expected to demonstrate an improved side-effect profile because of its superior pharmacokinetic properties than 1,4-DHPs.

Further structural manipulations at various positions in line with the structural features of **4** which carry a basic amino group in the 1,4-DHP skeleton, a basic amine group was introduced into the N-3 carbamate or the C-5 ester moiety of the dihydropyrimidines [27], and a modest improvement of the *in vivo* antihypertensive activity was observed. Out of these basic amine functions, 1-benzyl-4-piperidinyl carbamate (N-3) derivative (**14**) (SQ-32547, Table **1**) emerged as a lead compound and exhibited a remarkable enhancement of antihypertensive activity in SHR. In contrast to **1**, dihydropyrimidine **14** is both more potent and longer acting in SHR. Out of the individual isomers of **14**, the (*R*)-enantiomer compared most favorably with the long-acting derivative **4** [27].

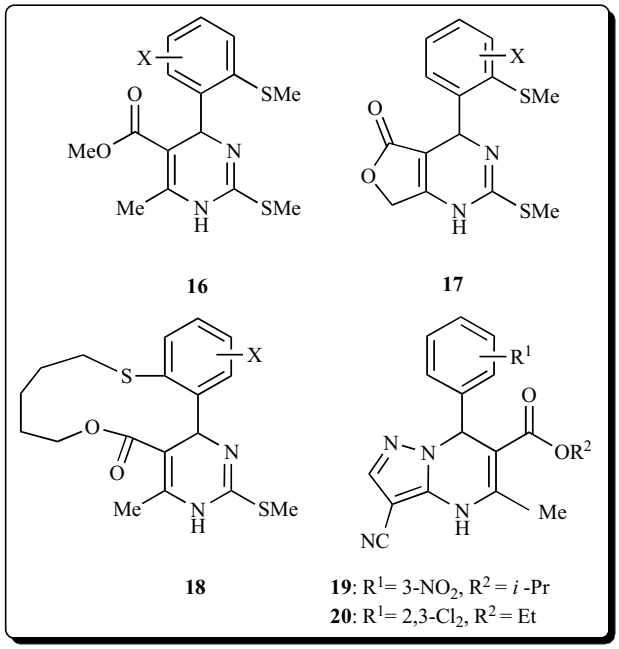
In addition to the monocyclic derivatives, bicyclic dihydropyrimidines **15** imitating the *in vitro* potency of dihydropyridine CCBs have also been described [28]. Structure-activity studies have shown that a pyrazole ring can act as an effective surrogate and effectively mimic the combined effect of N-3 substituent and a C-2 heteroatom of the monocyclic dihydropyrimidines. The vasorelaxant potency of several analogues is similar to that of the potent **1**. These investigations further affirmed the requirement of the enaminoester moiety of 1,4-DHPs for CCB activity and a non-specific role of both the N-3 substituent as well as C-2 heteroatom [28].

A series of dihydropyrimidines **16**, **17** and **18** (X = H, NO_2) have been designed to unambiguously establish structural and conformational requirements of pyrimidine derivatives for modulation of calcium channel functions [13]. These results firmly established a preference for *syn*- orientation of an unsymmetrically substituted aryl moiety at the dihydropyrimidine receptor. Similar to 1,4-DHPs, dihydropyrimidines have been proposed to adopt boat conformation (normal *vs* capsized) for activity modulation. Other features for maximal dihydropyrimidine receptor affinity include *cis* orientation of the ester carbonyl and Up and Down orientation of the C-4 pseudoaxial aryl group to evoke calcium antagonistic and agonistic activities, respectively. Further, *(S)*-enantiomers of **18** (X = H) exhibit antagonistic activity, whereas the *(R)*-enantiomers are agonistic. This model also explained the observation of chiral inversion and potency diminution upon replacement of ester by hydrogen as in **6** [13].

A comparison of the most potent of the DHPM derivatives with clinically used 1,4-DHP based CCBs is summarized in Table **1**. The vasorelaxation potency of some of these derivatives such as **19** (R^1 = 3-NO_2, R^2 = *i*-Pr) and **20**



(R^1 = 2,3-Cl_2, R^2 = Et) compare favorably well with **1**, **3** and **4**, although the antihypertensive effect is not revealed.



Likewise, antihypertensive effect of some of these derivatives such as *(RS)*-**13c** is comparable to *e.g.,* **1** and that of *(R)*-**14** is even better than **1** particularly in terms of duration of action. However, none of these potent dihydropyrimidinone derivatives are in clinical use.

Thus in general accord with the structure-activity relationships of 1,4-DHP based CCBs, N-3 substituted-2-hetero-1,4-dihydropyrimidines emerged as potent mimics of 1,4-DHP CCBs. It has been found that in addition to 2-hetero substituent (S>O>N), *ortho* and/or *meta* aromatic substitution (Cl, NO_2, CF_3) and ester alkyl group (isopropyl> ethyl>methyl) was essential for optimal *in vitro* activity. Additionally, a substituent (alkyl, acyl, carbamate, sulfonyl, uriedo) on N-3 was required for activity Fig. (**3**). Finally, DHPM CCBs that contain a basic group such as 1-(phenylmethyl)-4-piperidinyl carbamate attached at N-3 **14** are found to be equipotent to **1** and **4** in the rabbit arota smooth muscle vasorelaxant assay *in vitro*. Further, analogues bearing sulphur at the 2-position show greater antihypertensive activity in the SHR than the corresponding 2-oxo derivatives.

Some scattered reports on the calcium channel blocking activity of DHPM derivative of the type **21** (5-acetyl) [29] and bicyclic **22** (X = O) [30] have appeared in literature with-out much discussion on the structure-activity relationships. The DHPMs **22** (X = O) showed activity comparable to **2** when tested on rat ileum. Compounds of the type **23** and **24** exhibited antispasmodic and/or vasodilation activity on $BaCl_2$- stimulated rat ileum [31, 32].

To further expand the existing understanding of structure-activity relationships in DHPMs, structural variants through elaboration of diversity oriented sites (C-6, C-4, N-3, N-1, N-1/N-3 and N1-C6 linked) using rational designs of synthetic methodologies have been obtained [33]. Thus a variety of substituents could be incorporated at all these positions to obtain DHPM derivatives **25** and **26**. Some of these newly synthesized compounds were screened for their CCB activity based on their ability to relax a membrane depolarization induced contraction of vascular smooth muscle and

Table 1. Comparison of Calcium Channel Effects of Key 1,4-dihydropyridine and Dihydropyrimidinone Derivatives

Sr. No.	Calcium Channel Blocker	Vasorelaxation IC_{50} (nM) 95% CI	Antihypertensive Effect % Decrease (± 5%) in Blood Pressure in SHR[a]	
			(0-6h)	(6-18h)
1	Nifedipine 1	2 (1-3)	33	22
2	Nitrendipine 3	1 (0.2-3.0)	-	-
3	Amlodipine 4	3 (2-4)	46	37
4	*(RS)*- 13c	12 (8-17)	32	30
5	*(R)*-13c	8.5 (7-11)	-	-
6	*(S)*-13c	3790 (2140-6730)	5	4
7	*(RS)*-14	7(4-11)	51	32
8	*(R)*-14	15 (18-27)	60	46
9	*(S)*-14	>1000	-	-
10	19	1.5 (1.4-1.9)	-	-
11	20	7 (6.3-7.8)	-	-

[a]dose level: 45μmol/kg po.

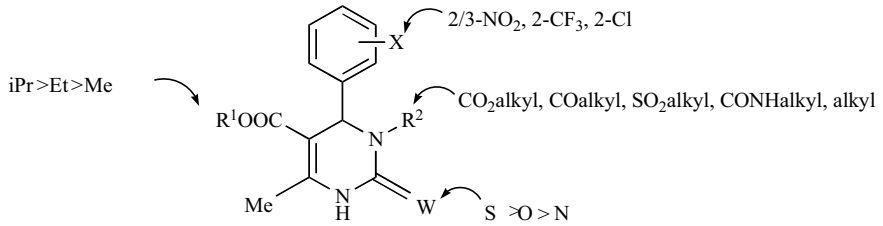


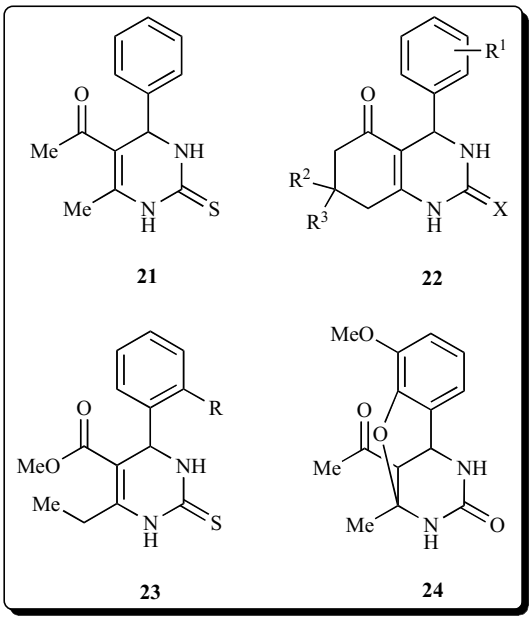
Fig. (3). General structure-activity relationship of dihydropyrimidine CCBs.

results compared against nifedipine. Whereas nifedipine completely relaxed the KCl-induced contraction with an IC_{50} in the 10 μM range, the tested DHPMs **25** relaxed the KCl-induced contractions by only 40% with IC_{50}s ranging from 100 - 300 μM [34].

3. OTHER BIOLOGICAL EFFECTS OF 3,4-DIHYDROPYRIMIDINONES

3.1. Mitotic Kinesin Inhibitors

Cancer is considered second only to heart disease as a cause of mortality and is linked to uncontrolled proliferation of tumor cells which leads to organ failure and eventual death through disruption the normal functioning of tissues [35]. Drugs used in chemotherapy interrupt the cell cycle through intervention in mitosis, during which, chromosomes are segregated by the microtubule based spindle. Some cancer drugs such as paclitaxel, docetaxel, vinblastine, vincristine are known to perturb microtubule lengthening (polymerization) or shortening (depolymerisation) arrest cell cycle through inhibition of formation of spindle [36]. As microtubules are also involved in many other cellular processes, interference with their formation or depolymerisation often leads to dose-limiting side effects.



One of the DHPM derivatives: 4-(3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (monastrol, **27**). *(RS)*-**27** was found [37] to cause cell cycle arrest by disrupting yet another target, a kinesin-related motor protein Eg5 that is necessary for formation of a bipolar spindle. Even human Eg5 has been recently identified as one of the potential targets of (*RS)*-**27**. *(S)*-**27**, the biologically active enantiomer is 15 fold more potent than *(R)*-**27**, and is a more potent inhibitor of Eg5 ATPase activity [38].

Surprisingly, closely related 4-OMe/OHAr DHPM derivatives of **27** did not effect mitotic kinesin Eg5 or arrest cells in mitosis [39]. DHPM **28** also show colchicin like property of destabilizing microtubules, in addition to mitotic kinesin inhibitor [40]. DHPM analogue **29** has been identified as a more potent cytotoxic agent than **27** against various cancer cell lines [39]. Likewise, it has been reported that DHPM **30** is nearly five fold (IC_{50} = 9.2 μM), more potent than monastrol (IC_{50} = 51.3 μM) on comparing inhibition of Eg5 activity using two *in vitro* steady-state ATPase assays (basal and microtubule simulated) as well as a cell based assay [41].

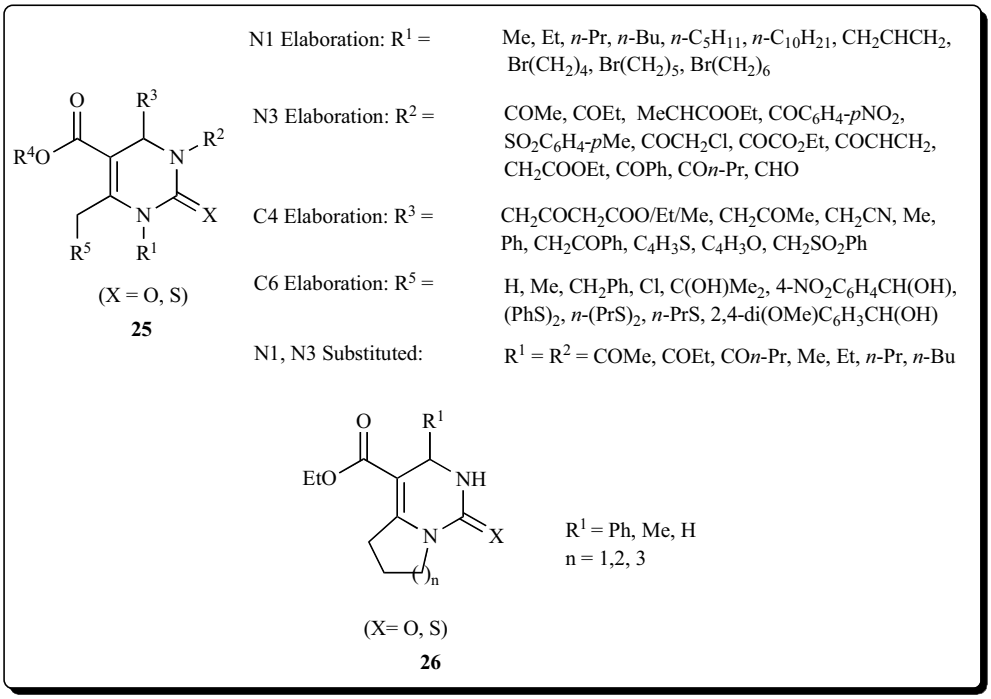
Recently, derivatives of DHPM **22** (R^1 = 3-OH, R^2 = R^3 = H and Me, X = S) have been reported to be 10 and 100 fold, respectively, more potent than **27** (R = *m*-OH) in inhibiting Eg5 [42].

3.2. α_{1a}-Adrenergic Receptor Antagonists

Benign prostatic hyperplasia (BPH) is a urological disorder in the aging male population which leads to an obstructive urination from a combination of mechanical constriction of the urethra due to increased prostatic mass and a dynamic component attributable to increased nonadrenergic tone in the hyperplasic prostate [43].

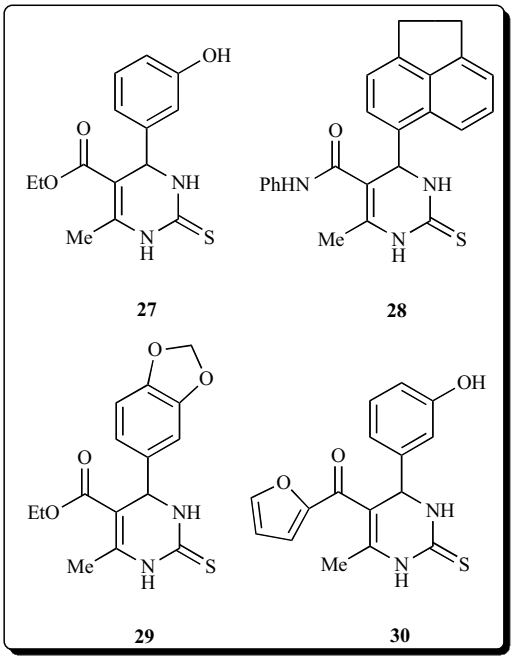
Of the selective and non-selective α_{1a} antagonists, the selective antagonists are able to effectively block the contraction of prostatic smooth muscle without significant effects on blood pressure; the non-selective antagonists show significant effects on lowering blood pressure at the required dose level. Certain 1,4-DHP based antagonists such as SNAP 5089 and SNAP 5540, selectively bind to the α_{1a} subtype [44] and have structural resemblance with a known calcium channel antagonist niguldipine, but show negligible affinity for L-type calcium channel blockers. However, DHPM derivatives **31** (**a**, R^1 = OMe, R^2 = Me and **b**, R^1 = NH_2, R^2 = Et) depicted better pharmacokinetic profile [44] owing to their structural stability.

Dihydropyrimidinone (+)-**31a** displayed better binding affinity and improved selectivity than a corresponding 1,4-DHP analogue. DHPM (+)-**31b** showed more than 1000 fold



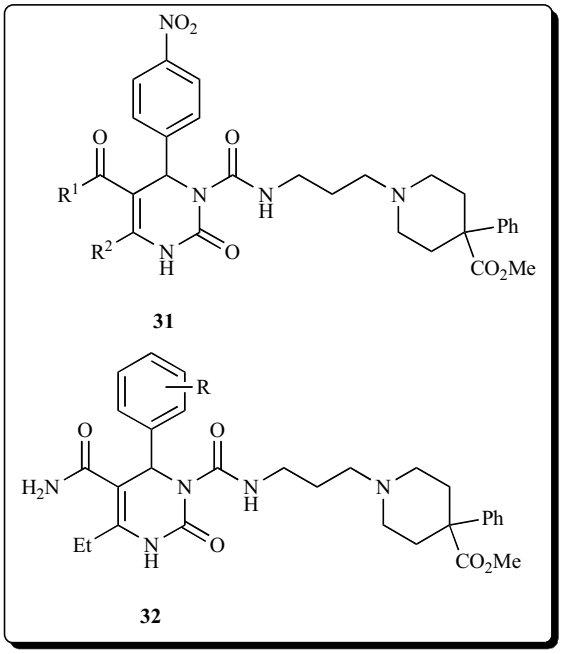
selectivity for the α_{1a}-receptor over a number of recombinant human G–protein coupled receptors such as α_{2a}, α_{2b}, and α_{2c}-adrenoceptors, histamine H_2 and 5HT (1A, 1B, 1D and 2A) and for the rat L-type calcium channel. Difluoro analogue **32a** (R = 3,4-F_2, SNAP 6201) showed high affinity and selectivity for the α_{1a}-adrenoceptor subtype and no cardiovascular side effects, **32b** (R = 2,4-F_2) was devoid of α_{1a}-antagonist activity.

To further improve the therapeutic potential, modifications on the linker as well as piperidine moieties led to the synthesis of DHPM derivatives **33** and **34** [44], and the latter showed binding affinities similar to **32**.

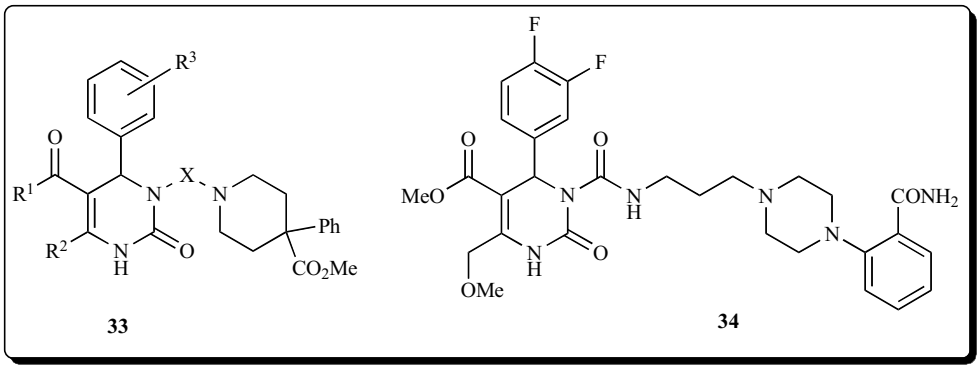


3.3. Miscellaneous Biological Effects

Some DHPM derivatives of the type (**35**-**38**) show antibacterial [45] and antifungal activity [46] against appropriate strains. Several potent, cell permeable 4-aryl dihydropyrimidinones of type **39**, as inhibitors of fatty acid transporter [(*S*)-enantiomer approximately 100 times more potent than (*R*)-enantiomer] have been reported [47].



Structure features such as a lipophilic ester substituent at the 5- position and presence of preferably a *p*-NO_2 and CF_3 at 4-aryl group led to active compounds. Boronic acid substi-



33 **34**

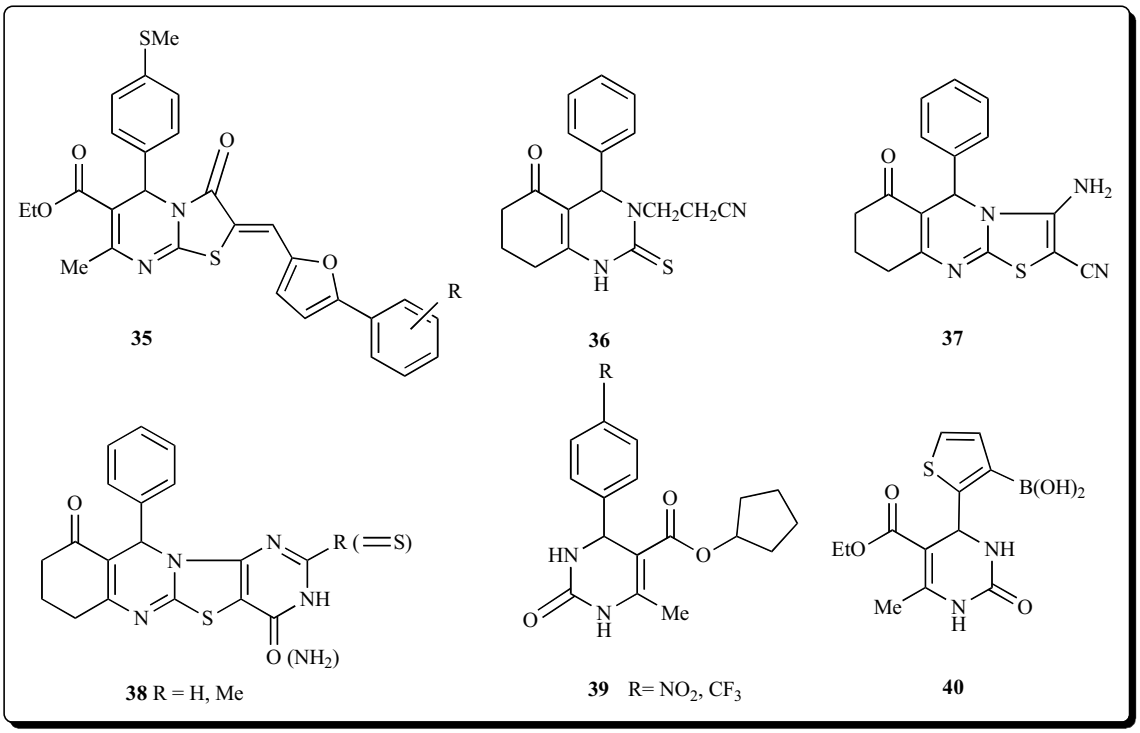
tuted DHPM derivatives, especially **40** has been found to be active against breast cancer cell lines (MCF7) [48]. Appropriately ester modified DHPMs of type **41** and **42** display antioxidant ability against lipid peroxidation induced by Fe + EDTA, when studied on male adult albino Wistar rats [49].

DHPM derivatives of the type **43** were identified as calcitonin mimetic (EC_{50} = 6μ M), active *in vivo* in the Weanling rat model when administered subcutaneously [50]. Compound of the type **44** plays a role in the activation of molecular chaperones that are responsible for a variety of protective, anti- apoptotic functions [51, 52]. The activation of molecular chaperones blocks Aβ aggregation and thus might have a favorable effect on neurodegenerative diseases like the Alzheimer disease. DHPM **45** (R^1 = Et, R^2 = 4-OH) have been found to display cardiovascular effects when studied on isolated perfused frog heart and found to be more active than a well known drug digoxin [53]. Compounds of the type **45** (R^1 = Me, R^2 = 2-Cl) and **45** (R^1 = Et, R^2 = 2-Cl) showed β-adrenergic receptor antagonistic activity [53].

DHPM derivatives of type **46** are high affinity ligands for peroxisomes proliferations activated receptor γ and show antidiabetic activity [54] and compounds of type **47** exhibited moderate activity against *Aspergillus fumigatus* [55].

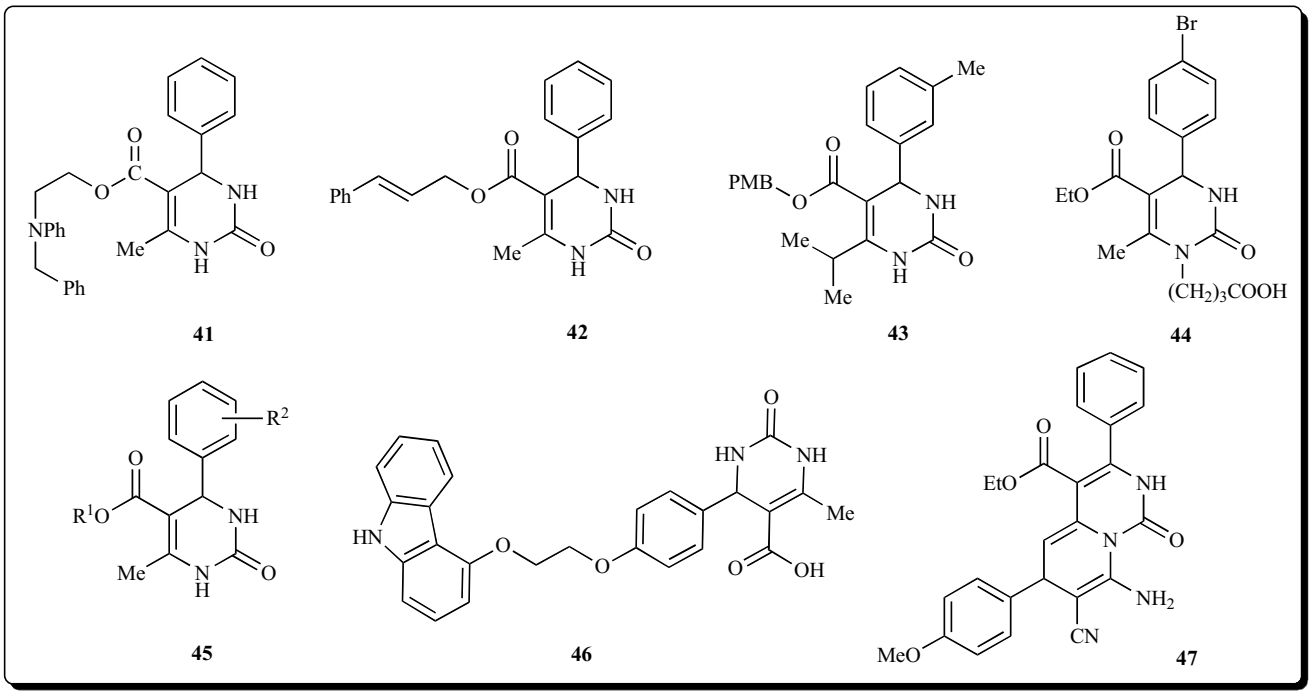
4. CONCLUDING REMARKS

Ever since the discovery of DHPMs in 1893 by P. Biginelli and resurgence of interest of the medicinal as well as organic chemist community, the research in the structure diversification of this heterocyclic species has witnessed an unprecedented activity. In this review, the genesis of this class of compounds from traditional 1,4-dihydropyridines has been traced. Overcoming the limitation such as short plasma half lives of 1,4-DHPs, DHPMs have convincingly established their superior therapeutic potential not only as calcium channel blockers, but also for other biological effects. It is hoped that with the emergence of advanced techniques such as combinatorial chemistry and high throughput synthesis (HTS), many more interesting biological effects of this important heterocycle shall be discovered.



35 **36** **37**

38 R = H, Me **39** R= NO_2, CF_3 **40**



ACKNOWLEDGEMENTS

Our work in the area of dihydropyrimidinone chemistry is generously supported by CSIR (01(1960)/04/EMR-II) and UGC (F. No. 31-53/2005 /SR), New Delhi.

ABBREVIATIONS

CCB = Calcium channel blocker

BPH = Benign prostatic hyperplasia

DHP = 1,4-Dihydropyridine

DHPM = 3,4-Dihydropyrimidinone

HTS = High throughput screening

PMB = p-Methoxybenzyl

SAR = Structure-activity relationship

SHR = Spontaneously hypertensive rats

REFERENCES

[1] Primrose, S. B.; Twyman, R. *Principles of Gene Manipulation and Genomics*, Wiley- Blackwell: **2006**.

[2] Fox, S.; Farr-Jones, S. Yund, M. A. High throughput screening for drug discovery: Continually transitioning into new technology. *J. Biomol. Screen.*, **1999**, *4*, 183-6.

[3] Eisenberg, M. J.; Brox, A.; Bestawros, A. N. Calcium channel blockers: An update. *Am. J. Med.*, **2004**, *116*, 35-43.

[4] Mason, R. P.; Marche, P.; Hintze, T. H. Novel vascular biology of third- generation L-type calcium channel antagonists ancillary actions of Amlodipine. *Arterioscler. Thromb. Vasc. Biol.*, **2003**, *23*, 2155-63.

[5] Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Satoh, F.; Morita, M.; Noguchi, T. Dihydropyrimidines: Novel calcium antagonists with potent and long-lasting vasodilative and antihypertensive activity. *J. Med. Chem.*, **1989**, *32*, 2399-406.

[6] Biginelli, P. Aldureides of ethylic acetoacetate and ethylic oxalacetate. *Gazz. Chim. Ital.*, **1893**, *23*, 360-416.

[7] Kappe, C. O. Biologically active dihydropyrimidones of the Biginelli-type-a literature survey. *Eur. J. Med. Chem.*, **2000**, *35*, 1043-52.

[8] Dallinger, D.; Kappe, C.O. Creating chemical diversity space by scaffold decoration of dihydropyrimidines. *Pure Appl. Chem.*, **2005**, *77*, 155-61.

[9] Kappe, C. O. 100 years of the Biginelli dihydropyrimidine synthesis. *Tetrahedron*, **1993**, *49*, 6937-63.

[10] (a) Hantzsch, A. Condensationprodukte aus aldehydammoniak und ketoniartigen verbindungen. *Chem. Ber.*, **1881**, *14*, 1637-8. (b) Hantzch, A. Ueber die Synthese pyridinartiger Verbindungen aus Acetessigäther und Aldehydammoniak. *Just. Leib. Ann. Chem.*, **1882**, *215*, 1-82.

[11] Triggle, D. J.; Janis, R. A. Calcium channel ligands. *Ann. Rev. Pharmacol. Toxicol.*, **1987**, *27*, 347-69.

[12] (a) Goldmann, S.; Stoltefuss, J. 1,4-Dihydropyridines: Effects of chirality and conformation on the calcium antagonist and calcium agonist activities. *Angew. Chem., Int. Ed. Eng.*, **1991**, *30*, 1559-78. (b) Stout, D. M.; Meyers, A. I. Recent advances in the chemistry of dihydropyridines. *Chem. Revs.*, **1982**, *82*, 223-43. (c) Triggle, D. J. 1,4-Dihydropyridines as calcium channel ligands and privileged structures. *Cell. Mol. Neurobiol.*, **2003**, *23*, 293-303.(d) Lavilla, R. Recent developments in the chemistry of dihydropyridines. *J. Chem. Soc., Perkin Trans. 1*, **2002**, *9*, 1141-56. (e) Achiwa, K.; Kato, T. Asymmetric synthesis of optically active 1,4-dihydropyridines as calcium antagonist. *Curr. Org. Chem.*, **1999** *3*, 77-106.

[13] Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; Di-Marco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. Calcium entry blockers and activators: Conformational and structural determinants of dihydropyrimidine calcium channel modulators. *J. Med. Chem.*, **1995**, *38*, 119-29.

[14] Gjorstrup, P.; Harding, H.; Isaksson, R.; Westerlund, C. The enantiomers of the dihydropyridine derivative H 160/51 show opposite effects of stimulation and inhibition. *Eur. J. Pharmacol*., **1986**, *122*, 357-61 and references cited therein.

[15] Buhler, F. R.; Hukthen, U. L.; Kiowski, W.; Muller, F. B.; Bolli, P. The place of the calcium antagonist verapamil in antihypertensive therapy. *J. Cardiovasc. Pharmacol.*, **1982**, *4*, 350-7.

[16] Morad, N.; Goldman, Y. E.; Trentham, D. R. Rapid photochemical inactivation of Ca^{2+}-antagonists shows that Ca^{2+} entry directly activates contraction in frog heart. *Nature (London)*, **1983**, *304*, 635-8.

[17] Cho, H.; Ueda, M.; Mizuno, A.; Ishihara, T.; Aisaka, K.; Noguchi, T. Synthesis of novel 2-chloro-1,4-dihydropyridines by chlorina-

tion of 2-hydroxy-1,4-dihydropyridines with phosphorous oxychloride. *Chem. Pharm. Bull.*, **1989**, *37*, 2117-21.

[18] McKinstry, D.W.; Reading, E. H. Synthesis of ethyl esters of some 2-oxo-and 2-thio-1,2,3,4-tetrahydro-5- pyrimidinecarboxylic acids. *J. Franklin Inst*., **1944**, *237*, 203-5.

[19] Hurst, E. W.; Hull, R. Two new synthetic substances active against viruses of the psittacosis- lymphogranulomatrachoma group. *J. Med. Pharm. Chem.*, **1961**, *3*, 215-29.

[20] Khanina, E. L.; Siliniece, G.; Ozols, J.; Duburs, G.; Kimenis, A. Synthesis and pharmacological studies of some 1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives. *Khim-Farm. Zh*., **1978**, *12*, 72-4.

[21] (a) Cho, H.; Shima, K.; Hayashimatsu, M.; Ohnaka, Y.; Mizuno, A.; Takeuchi, Y. Synthesis of novel dihydropyrimidines and tetrahydropyrimidines. *J. Org. Chem*., **1985**, *50*, 4227-30. (b) Cho, H.; Takeuchi, Y.; Ueda, M.; Mizuno. A. Regioselective synthesis of *N*-substituted dihydropyrimidin-2(1*H*) or (3*H*)-one. *Tetrahedron Lett.*, **1988**, *29*, 5405-8.

[22] Atwal, K. S.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. M. Dihydropyrimidine calcium channel blockers: 2-heterosubstituted 4-aryl-1,4-dihydro-6-methyl-5-pyrimidine carboxylic acid esters as potent mimics of dihydropyridines. *J. Med. Chem.*, **1990**, *33*, 1510-5.

[23] (a) Kastron, V. V.; Vitolin, R. A.; Khanina, E. L.; Duburs, G.; Kimenis, A. Fluorine- containing derivatives of 1,2,3,4-tetrahydropyrimidines: synthesis and pharmacological activity. *Khim.-Farm. Zh.*, 1987, 21, 948-52. (b) Vitolina, R.; Kimenis, A. Effects of tetrahydropyrimidine derivatives on the cardiovascular system. *Khim.-Farm. Zh.*, **1989**, *23*, 285-7.

[24] (a) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. Substituted 1,4-dihydropyrimidines. 3. Synthesis of selectively functionalized 2- hetero-1,4-dihydropyrimidines. *J. Org. Chem.*, **1989**, *54*, 5898-907. (b) O'Reilly, B. C.; Atwal, K. S. Synthesis of substituted 1,2,3,4-tetrahydro-6-methyl-2-oxo-5-pyrimidinecarboxylic acid esters: The Biginelli condensation revisited. *Heterocycles*, **1987**, *26*, 1185-8. (c) Atwal, K. S.; O'Reilly, B. C.; Gougoutas, J. Z.; Malley, M. F. Synthesis of substituted 1,2,3,4-tetrahydro-6-methyl-2-thioxo-5-pyrimidinecarboxylic acid esters. *Heterocycles*, **1987**, *26*, 1189-92.

[25] Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. Dihydropyrimidine calcium channel blockers. 2. 3-Substituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters as potent mimics of dihydropyridines. *J. Med. Chem.*, **1990**, *33*, 2629-35.

[26] Atwal, K. S; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. Dihydropyrimidine calcium channel blockers. 3. 3-carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents. *J. Med. Chem.*, **1991**, *34*, 806-11.

[27] Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. Dihydropyrimidine calcium channel blockers. 4. Basic 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents. *J. Med. Chem.*, **1992**, *35*, 3254-63.

[28] Atwal, K. S.; Moreland, S. Dihydropyrimidine calcium channel blockers. 5: Bicyclic dihydropyrimidines as potent mimics of dihydropyridines. *Bioorg. Med. Chem. Lett.*, **1991**, *1*, 291-4.

[29] Yarim, M.; Sarac, S.; Ertan, M.; Batu, O.; Erol, K. Synthesis, structural elucidation and pharmacological properties of some 5-acetyl-3,4-dihydro-6-methyl-4-(substituted phenyl)-2(1*H*)- pyrimidinones. *IL Farmaco*, **1999**, *54*, 359-63.

[30] Yarim, M.; Sarac, S.; Kilic, F. S., Erol, K. Synthesis and *in vitro* calcium antagonist activity of 4-aryl-7,7-dimethyl/1,7,7-trimethyl-1,2,3,4,5,6,7,8 octahydroquinazoline-2,5-dione derivatives. *IL Farmaco*, **2003**, *58*, 17-24.

[31] Zorkun, I. S.; Sarac, S.; Celebi, S.; Erol, K. Synthesis of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-thione derivatives as potential calcium channel blockers. *Bioorg. Med. Chem.*, **2006**, *14*, 8582-9.

[32] El-Hamouly, W. S.; El-Khamry, A.-M. A.; Abbas, E. M. H. Synthesis of new 4-aryl-isoxazolo[5,4-*d*]pyrimidin-6-one(thione) and 4-aryl-pyrazolo[3,4-*d*]-pyrimidin-6-one derivatives of potential antihypertensive activity. *Indian J. Chem. B*, **2006**, *45B*, 2091-8.

[33] (a) Singh, K.; Singh, J.; Deb, P. K.: Singh, H. An expedient protocol of the Biginelli dihydropyrimidine synthesis using carbonyl equivalents. *Tetrahedron*, **1999**, *55*, 12873-80. (b) Singh, K.; Singh, S.; Mahajan, A. Metalation of Biginelli compounds. A general unprecedented route to C-6 functionalized 4-aryl-3,4-dihydropyrimidinones. *J. Org. Chem.*, **2005**, *70*, 6114-7. (c) Singh, K.; Singh, S.; Kaur, P. Efficacious preparation of Biginelli compounds. A comparative study of different reaction techniques. *Lett. Org. Chem.*, **2006**, *3*, 201-3. (d) Singh, K.; Arora, D.; Singh, S. Dowex promoted general synthesis of N,N'-disubstituted-4- aryl-3,4-dihydropyrimidinones using a solvent-free Biginelli condensation protocol. *Tetrahedron Lett.*, **2006**, *47*, 4205-7. (e) Singh, K.; Singh, S. A mild and practical method for the regioselective synthesis of N-acylated 3,4-dihydropyrimidin-2-ones. New acyl transfer reagents. *Tetrahedron Lett.*, **2006**, *47*, 8143-6. (f) Singh, K.; Arora, D.; Singh, S. A highly regio- and chemoselective addition of carbon nucleophiles to pyrimidinones. A new route to C4 elaborated Biginelli compounds. *Tetrahedron Lett.*, **2007**, *48*, 1349-1352. (g) Singh, K.; Singh, S. Unprecedented single-pot protocol for the synthesis of N1, C6-linked bicyclic 3,4-dihydropyrimidinones *via* lithiation of Biginelli compounds. *Tetrahedron*, **2008** (doi: 10.1016/j.tet.2008.10.001). (h) Singh, K.; Singh, K. An efficacious protocol for the oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones using pyridinium chlorochromate as catalyst. *Aust. J. Chem.*, **2008** (10.1071/CH07432).

[34] Singh, K.; Arora, D.; Poremsky, E.; Lowery, J.; Moreland, R. S. N1-alkylated 3,4-dihydropyrimidine-2(1H)-ones: Convenient one-pot selective synthesis and evaluation of their calcium channel blocking activity. *Eur. J. Med. Chem*. **2008**, (doi: 10.1016/j.ejmech. 2008.10.002).

[35] Compton, D. A. New tools for the antimitotic toolbox. *Science*, **1999**, *286*, 913-5.

[36] (a) Hamel, E. Antimitotic natural products and their interactions with tubulin. *Med. Res. Rev*., **1996**, *16*, 207-31. (b) Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. Tubulin as a target for anticancer drugs: agents which interact with the mitotic spindle. *Med. Res. Rev.*, **1998**, *18*, 259-96.

[37] Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. *Science*, **1999**, *286*, 971-4.

[38] Cavazzini, A.; Massi, A.; Bergamaschi, G.; Braga, S.; Dondi, F.; Dondoni, A. Combining synthetic and analytical strategies for preparative HPLC enantioseparation of monastrol racemic mixture. *Biotechnol. Prog.*, **2004**, *20*, 603-12 and references cited therein.

[39] Russowsky, D.; Canto, R. F. S.; Sanches, S. A. A.; D'Oca, M. G. M.; Fatima, A.; Pilli, R. A.; Kohn, L. K.; Antonio, M. A.; de Carvalho, J. E. Synthesis and differential antiproliferative activity of Biginelli compounds against cancer cell lines: Monastrol, oxo-Monastrol and oxygenated analogues. *Bioorg. Chem.*, **2006**, *34*, 173-82.

[40] Haggarty, S. J.; Mayer, T. U.; Miyamoto, D.T.; Fathi, R.; King, R. W.; Mitchison, T. J.; Schreiber, S. L. Dissecting cellular processes using small molecules: identification of colchicine-like, taxol-like and other small molecules that perturb mitosis. *Chem. Biol.*, **2000**, *7*, 275-86.

[41] Klein, E.; DeBonis, S.; Thiede, B.; Skoufias, D. A.; Kozielski, F.; Lebeau, L. New chemical tools for investigating human mitotic kinesin Eg5. *Bioorg. Med. Chem.*, **2007**, *15*, 6474-88.

[42] Dallinger, D.; Kappe, C. O. Rapid preparation of mitotic kinesin Eg5 inhibitor monastrol using controlled microwave-assisted synthesis. *Nat. Protoc.*, **2007**, *2*, 317-21.

[43] Kirby, R. S.; Christmas, T. J. J. *Benign Prostatic Hyperplasia*, Gower Medical Publishing: London, England, **1993**.

[44] (a) Lagu, B.; Tian, D.; Chiu, G.; Nagarathnam, D.; Fang, J.; Shen, Q.; Forray, C.; Ransom, R. W.; Chang, R. S. L.; Vyas, K. P.; Zhang, K.; Gluchowski, C. Synthesis and evaluation of furo[3,4-*d*]pyrimidinones as selective α_{1a}-adrenergic receptor antagonists. *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 175-8. (b) Dhar, T. G. M.; Nagarathnam, D.; Marzabadi, M. R.; Lagu, B.; Wong, W. C.; Chiu, G.; Tyagarajan, S.; Miao, S. W.; Zhang, F.; Sun, W.; Tian, D.; Shen, Q.; Zhang, J.; Wetzel, J. M.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Schorn, T. W.; Chen, T. B., O' Malley, S.; Ransom, R.; Schneck, K.; Bendesky, R.; Harrel, C. M.; Vyas, K. P.; Zhang, K.; Gilbert, J.; Pettibone, D. J.; Patane, M. A.; Bock, M. G.; Freidinger, R. M.; Gluchowski, C. Design and synthesis of novel α_{1a} adrenoceptor-selective antagonists. 2. Approaches to eliminate

opioid agonist metabolites *via* modification of linker and 4-methoxycarbonyl-4-phenylpiperidine moiety. *J. Med. Chem.*, **1999**, *42*, 4778-93. (c) Lagu, B.; Tian, D.; Nagarathnam, D.; Marzabadi, M. R.; Wong, W. C.; Miao, S. W.; Zhang, F.; Sun, W.; Chiu, G.; Fang, J.; Forray, C.; Chang, R. S. L.; Ransom, R. W.; Chen, T. B., O' Malley, S.; Zhang, K.; Vyas, K. P.; Gluchowski, C. Design and synthesis of novel α_{1a} adrenoceptor-selective antagonists. 3. Approaches to eliminate opioid agonist metabolites by using substituted phenylpiperazine side chains. *J. Med. Chem.*, **1999**, *42*, 4794-803.

[45] Ashok, M.; Holla, B. S.; Kumari, N. S. Convenient one pot synthesis of some novel derivatives of thiazolo[2,3-*b*]dihydropyrimidinone possessing 4-methylthiophenyl moiety and evaluation of their antibacterial and antifungal activities. *Eur. J. Med. Chem*., **2007**, *42*, 380-5.

[46] Ghorab, M. M.; Abdel-Gawad, S. M.; El-Gaby, M. S. A. Synthesis and evaluation of some new fluorinated hydroquinazoline derivatives as antifungal agents. *IL Farmaco*, **2000**, *55*, 249-55.

[47] Blackburn, C.; Guan, B.; Brown, J.; Cullis, C.; Condon, S. M.; Jenkins, T. J.; Peluso, S.; Ye, Y.; Gimeno, R. E.; Punreddy, S.; Sun, Y.; Wu, H.; Hubbard, B.; Kaushik, V.; Tummino, P.; Sanchetti, P.; Sun, D.Y.; Daniels, T.; Tozzo, E.; Balani, S. K.; Raman, P. Identification and characterization of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones as inhibitors of fatty acid transporter FATP4. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 3504-9.

[48] Blacquiere, J. M.; Sicora, O.; Vogels, C. M.; Cuperlovic-Culf, M.; Decken, A.; Ouellette, R. J.; Westcott, S. A. Dihydropyrimidinones containing boronic acids. *Can. J. Chem.*, **2005**, *83*, 2052-9.

[49] Stefani, H. A.; Oliveira, C. B.; Almeida, R. B.; Pereira, C. M. P.; Braga, R. C.; Cella, R.; Borges, V. C.; Savegnago, L.; Nogueira, C. W. Dihydropyrimidin-(2*H*)-ones obtained by ultrasound irradiation: a new class of potential antioxidant agents. *Eur. J. Med. Chem.*, **2006**, *41*, 513-8.

[50] Matthews, J. M.; Liotta, F.; Hageman, W.; Rivero, R. A.; Westover, L.; Yang, M.; Xu, J.; Demarest, K. Discovery of a dihydropyrimidine series of molecules that selectively mimic the biological actions of calcitonin. *Bioorg. Med. Chem. Lett*., **2004**, *14*, 1155-9.

[51] Wisen, S.; Androsavich, J.; Evans, C. G.; Chang, L.; Gestwicki, J. E. Chemical modulators of heat shock proteins 70 (Hsp70) by sequential, microwave-accelerated reactions on solid phase. *Bioorg. Med. Chem. Lett*., **2008**, *18*, 60-5.

[52] Wright, C. M.; Chovatiya, R. J., Jameson, N. E.; Turner, D. M.; Zhu, G.; Werner, S.; Huryn, D. M.; Pipas, J. M.; Day, B. W.; Wipf, P.; Brodsky, J. L. Pyrimidinone-peptoid hybrid molecules with distinct effects on molecular chaperone function and cell proliferation. *Bioorg. Med. Chem.*, **2008**, *16*, 3291-301.

[53] Sujatha, K.; Shanmugam, P.; Perumal, P. T.; Muralidharan, D.; Rajendran, M. Synthesis and cardiac effects of 3,4-dihydropyrimidin-2-(1*H*)-one-5 carboxylates. *Bioorg. Med. Chem. Lett*., **2006**, *16*, 4893-7.

[54] Kumar, R.; Mittal, A.; Ramachandran, U. Design and synthesis of 6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives as PPARγ activators. *Bioorg. Med. Chem. Lett*., **2007**, *17*, 4613-8.

[55] Kheder, N., A.; Mabkhot, Y. N.; Farag, A. M. Synthesis and antimicrobial evaluation of some new pyrimidine derivatives. *Heterocycles*, **2008**, *75*, 887-97.

Received: 26 July, 2008 **Revised: 26 September, 2008** **Accepted: 26 September, 2008**