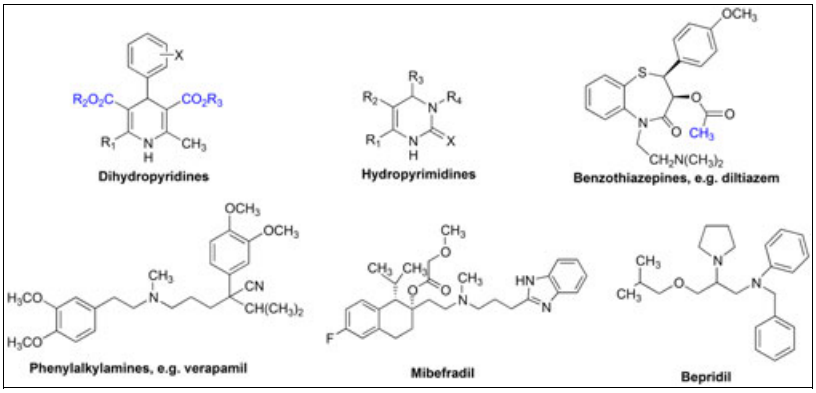
Cardiovascular Calcium Channel Blockers: Historical Overview, Development and New Approaches in Design

Iryna Drapak,[a] Lina Perekhoda,[b] Tetiana Tsapko,[b]* Natalia Berezniakova,[b] and Yevgen Tsapko[c]

[a]Department of General, Bioinorganic, Physical and Colloidal Chemistry, Lvivsʹkyj nacionalʹnyj medychnyj universytet imeni Danyla Halycʹkoho, Lviv 58666, Ukraine
[b]Department of Medicinal Chemistry, Nacionalʹnyj farmacevtychnyj universytet, Kharkiv 199318, Ukraine
[c]Department of Inorganic Chemistry, Nacionalʹnyj farmacevtychnyj universytet, Kharkiv 199318, Ukraine
*E-mail: tsapko.tatyana@gmail.com; medchem@nuph.edu.ua

Received July 8, 2016
DOI 10.1002/jhet.2837
Published online 00 Month 2017 in Wiley Online Library (wileyonlinelibrary.com).



The data on historical development and modern design approaches for calcium channels blockers (mainly L-type) are summarized in this review. Chemical groups such as dihydropyridine and hydropyrimidine derivatives, as well as phenylalkylamines and benzothiazepines are discussed.

J. Heterocyclic Chem., **00,** 00 (2017).

INTRODUCTION

Role of calcium and calcium channels in vascular smooth muscle contraction. Calcium is a key component of the excitation–contraction coupling process, which occurs within the cardiovascular system. It acts as a cellular messenger to link internal or external excitation with cellular response. Increased cytosolic concentrations of Ca^{2+} result in the binding of Ca^{2+} to a regulatory protein, either troponin C in cardiac and skeletal muscle or calmodulin in vascular smooth muscle. This initial binding of Ca^{2+} uncovers myosin binding on the actin molecule, and subsequent interaction between actin and myosin result in muscle contraction. All these events are reversed once the cytosolic concentration of Ca^{2+} decreases. In this situation, Ca^{2+} binding troponin C or calmodulin is diminished or removed, binding sites are concealed, actin and myosin no longer interact and muscle contraction ceases [1,2].

Mechanisms of calcium movement and storage. The regulation of cytosolic calcium levels occurs via specific influx, efflux, and sequestering mechanism (Fig. 1) [3].

Intracellular calcium increases via the voltage-gated channels, receptor-mediated channels, $Na^{2+}/Ca^{2+}$and Na^{2+}/H^{+}-exchangers store-operated channels. Influx via either receptor-operated or voltage-dependent channels has been proposed to be the major entry pathway for Ca^{2+}. Receptor-operated channels have been defined as those associated with cellular membrane receptors and activated by specific agonist-receptor interactions. In contrast, potential-dependent channels, also known as voltage-dependent or voltage-gated calcium channels, have been defined as those activated by membrane depolarization. The Na^{+}/Ca^{2+} exchange process can promote either influx or efflux because the direction of Ca^{2+} movement depends upon the relative intracellular and extracellular ratio of Na^{+} and Ca^{2+}. The «leak» pathways, which include unstimulated Ca^{2+} entry as well as entry during the fast inward Na^{+} phase of an action potential, play only a minor role in calcium influx.

Ca^{2+} decreases via the sarco/endoplasmic reticulum calcium ATPase (SERCA) pump, plasma membrane calcium ATPase pump, permeability transition pore, and Na^{2+}/Ca^{2+} exchangers. In addition to these influx and efflux mechanisms, the sarcoplasmic reticulum and the mitochondria function as internal storage/release sites. These storage sites work in concert with the influx and efflux processes to assure that cytosolic calcium level are appropriate for cellular needs. While influx and release processes are essential for excitation–contraction coupling, efflux and sequestering processes are equally important for terminating the contractile process and for protecting the cell from the deleterious effects of Ca^{2+} overload [4–6].

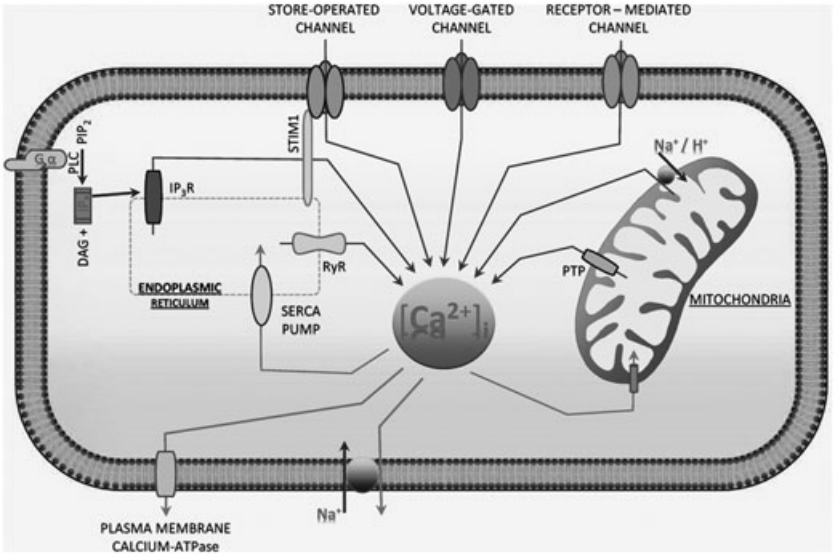


Figure 1. Cellular homeostasis by calcium influx and efflux.

Types of calcium channels. The pharmacologic class of agents known as calcium channel blockers (CCBs) produces their effects through interaction with potential-dependent channels. To date, six functional subclasses, or types, of potential-dependent Ca^{2+} channels are been identified: T, L, N, P, Q, and R. Voltage-gated calcium channels regulate numerous physiological functions, across a wide range of organ systems including heart, muscle, and brain. Different calcium channel subtypes have evolved to mediate specific cellular functions in these tissues.

Nowadays, calcium channels blockers widely discussed as anticancer agents (T-type CCBs) [7], as drugs targeting in central nervous system (CNS) disorders (for example, epilepsy) (L-type CCBs) [8], agents for the treatment of certain types of pain (N-type CCBs) [9,10], and so on; their tocolytic effect also is widely applicable in obstetrics [11]. In addition, calcium channels are emerging as targets for novel therapeutic indications [12].

Of these six types of Ca^{2+} channels, the L (long-lasting, l) channels, also known as the dihydropyridine channels, is the site of action of currently available CCBs and has therefore been extensively studied. It is located in skeletal, cardiac, and smooth muscles and is thus highly involved in organ and vessel contraction within the cardiovascular system. Thus, in this review, the only CCBs for the management of cardiovascular diseases will be discussed.

Cardiovascular disorders associated with potential-dependent calcium channels. As described previously, the movement of calcium underlies the basic excitation–contraction coupling process. Thus, vascular tone and contraction are primarily determined by the availability of calcium from extracellular or intracellular sources. Potential-dependent Ca^{2+} channels are important in regulating the influx of Ca^{2+}; therefore, inhibition of Ca^{2+} flow through these channels results in both vasodilation and decreased cellular response to contractile stimuli. Arterial smooth muscle is more sensitive to this action than venous smooth muscle. Additionally, coronary and cerebral arterial vessels are more sensitive than other arterial beds [4,13]. As a result of these actions, CCBs are useful in the treatment of hypertension, congestive heart failure, and ischemic heart disease that encompasses a variety of syndromes such as angina pectoris, silent myocardial ischemia, acute coronary insufficiency, and myocardial infarction.

Calcium antagonists superior in preventing stroke and all-cause death, but inferior in preventing heart failure comparing with other classes of blood pressure-lowering drugs (diuretics, beta-blockers, ACE inhibitors, and renin-angiotensin system blockers) [14].

CHANNEL BLOCKERS AS CARDIOVASCULAR AGENTS: DESIGN AND DEVELOPMENT

Historical overview. The discovery of L-type CCBs and their utility in coronary disease occurred by chance in 1963, when it was reported that new compounds such as the phenylalkyamine (later named verapamil) mimicked the cardiac effect of simple calcium withdrawal, diminishing calcium-dependent high energy phosphate utilization, contractile force and oxygen requirement. In 1969, the term “calcium antagonist” was given a novel drug designation. In an extensive search for other calcium antagonists, a considerable number of substances that also met these criteria were identified; in

1975, the first dihydropyridines (e.g., nifedipine) were discovered followed by many other members of this class in the following decades, including longer-acting compounds such as amlodipine. Also in 1975, a third class of L-type CCBs was discovered, the benzothiazepine class, for example, diltiazem [15]. CCBs are also known as slow channel blockers, calcium entry blockers, and calcium antagonists [11].

Chemical classifications. There are currently around 24 CCBs according to the anatomical therapeutic chemical (ATC) classification (subgroup C08) [16]. These compounds have different chemical structures and can be grouped into one of four chemical classifications (Fig. 2), each of which produces a distinct pharmacologic profile: 1,4-dihydropyridines (e.g., nifedipine), phenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem), and diaminopropanol ethers (e.g., bepridil). The majority of CCBs are 1,4-dihydropyridines (1,4-DHPs), and a detailed description of the structure activity relationship (SAR) for this chemical class is provided later. In contrast, verapamil, diltiazem, and bepridil are the lone resentatives of their respective chemical classes and are thus discussed as individual agents.

1,4-Dihydropyridines. ***History and nomenclature.*** The chemistry of dihydropyridines can be traced back to an 1882 paper in which Hantzsch described their utility as intermediates for the synthesis of substituted pyridines. Fifty years later, interest in this chemical class of compounds increased when it was discovered that a 1,4-dihydropyridine ring was responsible for the "hydrogen-transfer" properties of the coenzyme NADH. Numerous biochemical studies followed this discovery; however, it was not until the early 1970s that the pharmacologic properties of 1,4-DHPs were fully investigated. Loev and coworkers at Smith Klein&French laboratories investigated the activities of «Hantzsch-type» compounds [17,18]. As shown at Figure 3 the Hantzsch reaction produced a symmetrical compound in which both the esters (i.e., CO_2R_2) and the C_2 and C_6 substituents (i.e., CH_3) are identical with each other. Structural requirements necessary for activity were identified by sequentially modifying the C_4 substituent (i.e., the R_1 group), the C_3-ester and C_5-ester (i.e., the CO_2R_2 groups), the C_2-alkyl and C_6-alkyl groups, and the N_1–H substituent [19].

Since then, efficient, uncatalysed, and green methods for the synthesis of 1,4-DHP derivatives in an aqueous media through one-pot condensation process has been developed [20–23]. This procedures offer several advantages including high yields, environmentally benign solvent, and simple work-up process. Nomenclature and structures of the dihydropyridine medicines are represented in Table 1.

Structure-activity relationships. Structure-activity relationships for 1,4-DHP derivatives (see Table 1) indicate that the following structural features are important for activity:

1. A substituted phenyl ring at the C_4 position optimizes activity (heteroaromatic rings, such as pyridine, produce similar therapeutic effect, but are not used because of observed animal toxicity). Substitution with a small nonplanar alkyl or cycloalkyl group decreases activity. The first aromatic ring used was *ortho*-nitrophenyl as shown by the prototype nifedipine. Other heteroaromatic rings were used such as imidazole, 2,1,3-benzoxadiazole, 2,3-methylenebisoxybenzene, 5-phenylisoxazole, chloroindole, chlorobenzene, and 2,3-dichlorobenzene [24].
2. Phenyl ring substitution (X) is important for size and position rather than for electronic nature. Compounds with *ortho*-substituent or *meta*-substituent possess optimal activity, while those that are unsubstituted or contain a *para*-substituent show a significant decrease in activity. Electron-withdrawing *ortho*-substituent or *meta*-substituent or electron donating demonstrated good activity. The importance of the *ortho*-substituent and *meta*-substituent is to provide sufficient bulk to «lock» conformation of the 1,4-DHP such as that the C_4 aromatic ring is perpendicular to the 1,4-DHP ring (Fig. 4). This perpendicular conformation has proposed to be essential for the activity of the 1,4-DHPs.
3. The 1,4-dihydropyridine ring is essential for activity. Substitution at the N_1 position or the use of oxidized (piperidine) or reduced (pyridine) ring systems greatly decreases or abolishes activity. Oxidation of the ring,

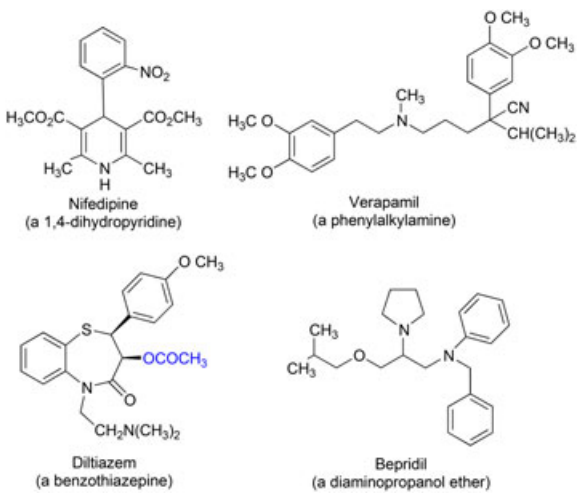


Figure 2. Main representatives of chemical classes of calcium channel blockers. [Color figure can be viewed at wileyonlinelibrary.com]

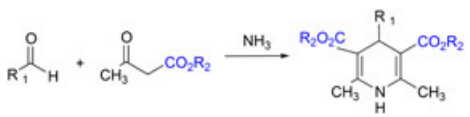
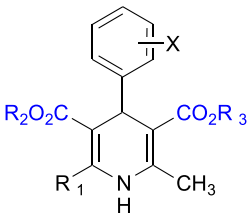
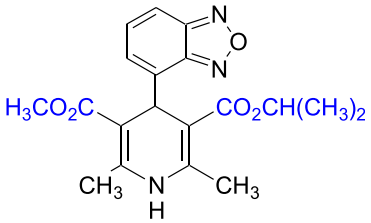
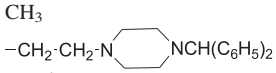
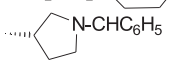
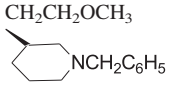


Figure 3. Synthesis of 1,4-DHPs by Hantzsch reaction. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1

Dihydropyridine calcium channel blockers (ATC code: 1.1C08CA dihydropyridine derivatives).



Compound	R_1	R_2	R_3	X
Isradipine				
Amlodipine	$CH_2OCH_2CH_2NH_2$	CH_2CH_3	CH_3	2-Cl
Clevidipine	CH_3	$CH_2OC(=O)nC_3H_7$	CH_3	2,3-diCl
Felodipine	CH_3	CH_2CH_3	CH_3	2,3-diCl
Nicardipine	CH_3	$CH_2CH_2N(CH_3)CH_2C_6H_5$	CH_3	3-NO_2
Nifedipine	CH_3	CH_3	CH_3	2-NO_2
Nimodipine	CH_3	$CH_2CH_2OCH_3$	$CH(CH_3)_2$	3-NO_2
Nisoldipine	CH_3	$CH_2CH(CH_3)_2$	CH_3	2-NO_2
Nitrendipine	CH_3	CH_2CH_3	CH_3	3-NO_2
Lacidipine	CH_3	CH_2CH_3	CH_2CH_3	2-CH = $CHCO_2C(CH_3)_3$
Nilvadipine	CN	CH_3	$CH(CH_3)_2$	3-NO_2
Manidipine	CH_3		CH_3	3-NO_2
Barnidipine	CH_3		CH_3	3-NO_2
Lercanidipine	CH_3	$C(CH_3)_2CH_2N(CH_3)$-$CH_2CH_2C(C_6H_5)_2$	CH_3	3-NO_2
Cilnidipine	CH_3	$CH_2CH_2OCH_3$	$CH_2CH = CHC_6H_5$	3-NO_2
Benidipine	CH_3		CH_3	3-NO_2

protonation of N_1, or substitution at this position changes boat conformation (Fig. 4) and the position of hydrogen bonding. So this hydrogen atom is involved in a direct interaction with the receptor. N–H at position-1 is a hydrogen bond donor [24].

4. Ester groups at the C_3 and C_5 positions optimize activity. Other electron-withdrawing groups show decreased antagonist activity and may even show agonist activity. For example, the replacement of the C_3 ester of isradipine with an NO_2 group produces a calcium channel activator, or agonist (Fig. 5). Replacement of C_3 ester with ketone or nitrile group greatly reduces activity because of replacement of bidentate chelating ester group with monodentate chelating ketone group and nonchelating nitrile group.

Thus, the term, «calcium channel modulators», is a more appropriate classification for the 1,4-DHPs.

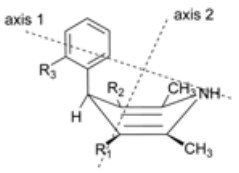


Figure 4. 1,4-DHPs general structure showing the orientation of affinity axis (axis 1) and chirality-activity axis (axis 2) on the boat conformation.

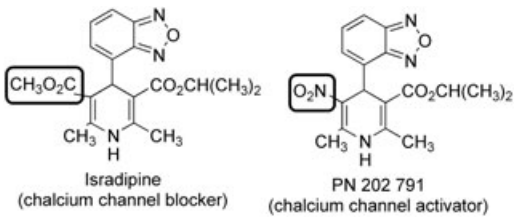


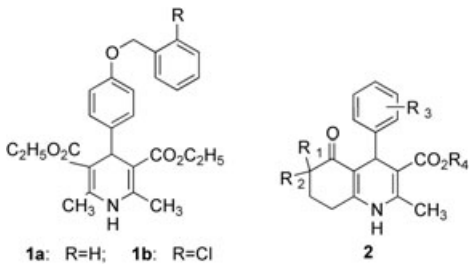
Figure 5. Structures of isradipine and its analogous 3-nitro derivative.

5. When the esters at C_3 and C_5 are nonidentical, the C_4 carbon becomes chiral and stereoselectivity between the enantiomers is observed. Additionally, there is evidence that the C_3 and C_5 positions of the dihydropyridine ring are not equivalent positions. Crystal structures of nifedipine, a symmetrical 1,4-DHP, have shown that the C_3 carbonyl is synplanar to the C_2-C_3 bond but that the C_5 carbonyl is antiperiplanar to the C_5-C_6 bond (Fig. 6). Asymmetrical compounds have shown enhanced selectivity for specific blood vessels and are preferentially being developed. Nifedipine, the first 1,4-DHP to be marketed, is the only symmetrical compound in this chemical class.
6. With the exception of amlodipine, all 1,4-DHPs have C_2 and C_6 methyl groups. The enhanced potency of amlodipine (vs. nifedipine) suggests that the 1,4-DHP receptor can tolerate one bulky group like phenyl group at C_6 position that increases activity and selectivity because of its interaction with high lipophilic pocket in the receptor and also improves penetration into organs. On the other hand, the activity data indicate a decrease in activity when the methyl group at C_2 position is replaced by a phenyl substituent [25]. This observation of decreasing activity is in contrast to the effect of increasing lipophilicity. This is due to the increase in steric hindrance by phenyl group. So there is a challenge to make a suitable balance between lipophilicity and steric hindrance for the calcium channel antagonist activity of DHPs.

One amino group is tolerated and can increase activity because of hydrogen bonding with the receptor and plasma protein, which leads to slow dissociation from the receptor and from blood, respectively. The amino group at C_2, such as amlodipine, imparts aqueous solubility and ionization at physiological pH.

From the aforementioned discussions, the 1,4-DHPs structure has two axes: affinity axis and chirality-activity axis (Fig. 4). Affinity axis is in charge of binding to the receptor and consists of N–H group and C-4 position aromatic substitution. Chirality-activity axis is composed of the two ester functional groups of substituents at C-3 and C-5 positions of the DHP ring. It is responsible for distinguishing the activity, agonist and antagonist, and also enantiomeric selectivity; that is, some enantiomers are more active than the others. The two axes are cross not parallel [24].

Recent development among DHPs. Datar et al. synthesized a series of novel 1,4-dihydropyridine CCBs of general formula **1** bearing in C-4 position of the ring bulky substituted phenyl and tested them for hypotensive activity, including electrocardiographic and effect on heart rate. All synthesized compounds lowered rat blood pressure significantly in comparison with nifedipine. Diethyl 4-(4-benzyloxy phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**1a**) and diethyl 4-(2-(2-chlorobenzyloxy) phenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (**1b**) were the most potent in this series. Results have shown that the QSAR, based on which the molecules have been designed, has proven to be promising at least in these preliminary *in vivo* pharmacological screening models [18].



The primary target of DHPs in the cardiovascular system is the $Cav_{1.2}$ L-type calcium channel isoform; however, a number of DHPs also block low-voltage-activated T-type calcium channels. The synthesis of a series of novel fused dihydropyridines (hexahydroquinoline) **2** (R_1 = R_2 = H, Me; R_3 = 2,3-F_2, 2-Cl-3-F_3C, 2-OH-5-NO_2, 2-$PhCO_2$–5-NO_2; R_4 = Me, Et, i-Bu, t-Bu, $PhCH_2$, 3-pyridylmethyl) and their abilities to block both L- and T-type calcium channels are described. Within this series of compounds, modification of a key ester moiety not only regulates the blocking affinity for both L-type and T-type channels but also allows for the development of DHPs with 30-fold selectivity for T-type channels over the L-type. The data suggest that a condensed dihydropyridine-based scaffold may serve as a pharmacophore for a new class of T-type selective inhibitors [26].

Structure modification of DHPs also includes replacement of 4-aryl substituent by some heterocycles. Thus, synthesis of novel chiral 1,4-dihydropyridinyl Schiff-base ligands with thiophene cycle in C-4 position have been carried out by Valigura et al. [27]. All these derivatives in their chiral and racemic forms, including

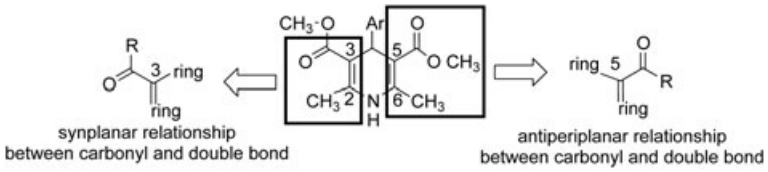
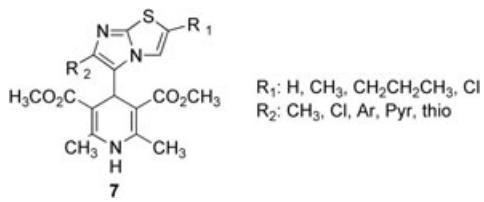


Figure 6. Conformation of the C3 and C5 esters of nifedipine (Ar = 2-nitrophenyl).

starting reagents 2-formyl-1,4-DHPs **3**, and final products, that is, imidazolo-DHPs **4**, pyrimidino-DHPs **5**, and 2-thiazolo-DHPs **6** (Fig. 7), were tested as potential CCBs on human blood cells. Herein, basal and vanadate-induced $^{45}Ca^{2+}$ influx were measured, and the tested compounds have shown no effects up to interesting ones depending on the chirality of their stereogenic centers.

Also the synthesis, characterization, and functional *in vitro* assay in cardiac and smooth muscle (vascular and nonvascular) of a series of 4-imidazo[2,1-b]thiazole-1,4-dihydropyridines **7** are reported by group of Italian scientists [28]. It was shown that the substituents at imidazo[2,1-b]thiazole ring can modulate the activity of compounds on different heart function influenced by cardiac L-type calcium channels isoforms $Cav_{1.2}$ and $Cav_{1.3}$. In particular, the choice of an appropriate substituent in position 6 in the heterocyclic nucleus of the imidazo[2,1-b]thiazole allows obtaining of some 1,4-DHPs with a particular activity probably because of their binding with $Cav_{1.2}$ or $Cav_{1.3}$ with potential therapeutic effects. An appropriately substituted phenyl ring with one or two methoxy group (**7**, R_2 = Ar) enhances the negative inotropic activity. Bioisosteric replacement of phenyl ring, as for the pyridine ring (**7**, R_2 = Pyr), leads to a derivative with higher negative chronotropic potency.



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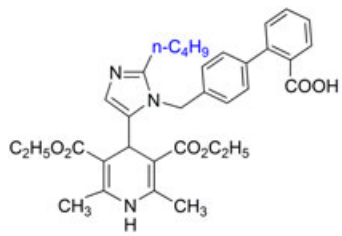
New DHPs with dual activity. The beneficial properties of new nonpeptide angiotensin II receptor (type AT_1) antagonists, such as losartan, have stimulated the design of many different congeners. All the new nonpeptide angiotensin II antagonists that have been designed contain a biphenyl fragment bearing an acidic moiety (i.e., a tetrazole, carboxylic-, or sulphonamidocarboxyl group), linked to a heteroaromatic or acyclic system by a methylene group. Almost all chemical manipulations of the fundamental skeleton of sartans have focused on the substitution of the imidazole ring of losartan with different heteroaromatic groups or acyclic structures [29].

It is thought that merging the key structural elements present in an AT_1 receptor antagonists such as [2 -(acidic moiety)biphenyl-4-yl]imidazole pharmacophores with key structural elements in 1,4-dihydropyridine CCBs would yield compounds with potential dual activity for both receptors. Advantages of combination therapy of angiotensin receptor blockers and CCBs, which include low dose, low side effect, cardioprotection, renoprotection, and anti-atherosclerosis, are reported in literatures [30–32].

Hadizadeh *et al.* have synthesized a novel analog of losartan in which a biphenyl fragment was retained, and the imidazole nucleus was connected to a dihydropyridine moiety (compound **8**) and showed its dual calcium channel blocking (comparable with nifedipine) and AT_1 antagonist activity. Moreover, the effects of derivatives of compound **8** on AT_1 receptors are 1000 and 100 000 times more than losartan [33].



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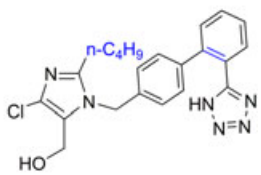
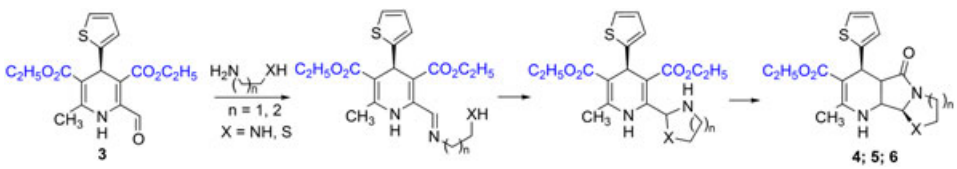


Losartan

In the next study, the effects of compound **8** on the blood pressure and the heart rate of normotensive rats were investigated and compared with losartan. It was concluded that compound **8** has greater hypotensive potency than losartan [34].

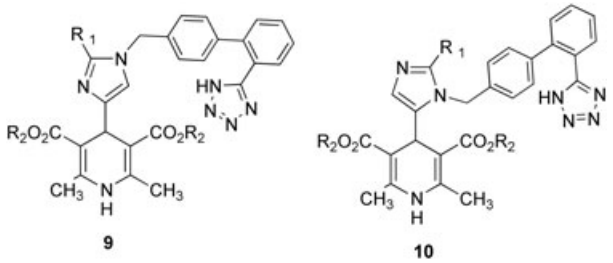
Encouraged by results of research Hadizadeh *et al.* discussed previously, group of Shahbazi Mojarrad *J. et al.* performed the synthesis of 3,5-pyridinedicarboxylates **9** (R_1 = n-Pr, n-Bu; R_2 = Me, Et) and their corresponding 4-imidazolyl analogs **10**, via N-alkylation of 2-alkylimidazolecarboxaldehydes with tritylated [4′-(bromomethyl)biphenyl-2-yl]tetrazole and Hantzsch cyclocondensations with $MeC(O)CH_2CO_2R_2$ was reported. The second method was more efficient than the first method because the deprotection and



3 **4; 5; 6**

Figure 7. Synthesis of novel chiral 1,4-dihydropyridinyl Schiff-base and their further cyclization. [Color figure can be viewed at wileyonlinelibrary.com]

ring closure reaction occurs simultaneously in one pot [35,36].

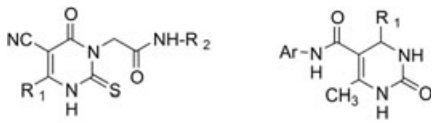


9 **10**

Non-dihydropyridine calcium channel blockers. ***Modifications of dihydropyridine ring: other heterocycles perspective.*** The currently available DHPs are effective for the treatment, but still many of these drugs have disadvantages such as light sensitivity, pharmacokinetic, and ADMET problems such as very short plasma half-life, and clinical administration of drugs with negative inotropic activity that is not desirable because of their cardiosuppresive effects, especially in patients with a tendency toward heart failure [37]. Thus, there is a need for development of promising novel drug candidates free from these detrimental effects. That is why numerous attempts to create a medicine with structural analogs of dihydropyridine ring have been performed. Recent results of this work are enlisted later.

Dihydropyrimidine derivatives are widely used for the variety of pharmacological actions and are screened for diverse range of biological activities, in particular, as CCBs. It is not surprising that dihydropyrimidines are often reported as CCBs because dihydropyrimidines are aza-analogs of dihydropyridines, which are well established as cardiovascular agents [38]. In fact, they have been found to be bioisosteres of DHPs [39].

Choudhari *et al*. have designed and developed novel CCBs based on the pyrimidine scaffold and identified some structure requirement of these molecules in the form of 3D descriptors and pharmacophoric features for optimization of these ligands. The studied compounds included 4-aryl-5-cyano-3,6-dihydro-6-oxo-2-thioxo-1(2H)-pyrimidineacetic acid hydrazides (**11**, R_2 = NH_2), phenylhydrazides (**11**, R_2 = NH-Ph), hydrazones (**11**, R_2 = NH-CH-Ar), and 1,2,3,4-tetrahydro-4-aryl-6-methyl-2-oxo-5-pyrimidinecarboxamides (**12**). All of them were tested *in vitro* for their pulmonary vein relaxant activity. The computational studies showed hydrogen bond donor, hydrogen bond acceptor, and hydrophobic group are important features for calcium channel blocking activity. These studies showed that pyrimidine scaffold can be utilized for designing of novel calcium channels blockers for cardiovascular system (CVS) disorders [40].



11 **12**

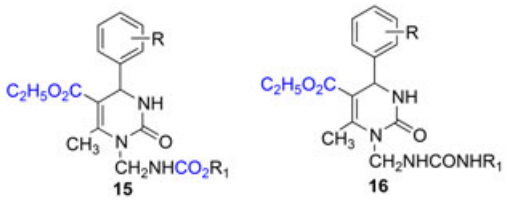
R_1= C_6H_5, 4-CH_3O-C_6H_4

Other dihydropyrimidine derivatives **13** and **14** were synthesized and evaluated for their CCB activity. Synthesis involves the modification of dihydropyrimidine pharmacophore with thiosemicarbazide, semicarbazide, and hydrazide functions. Among all the synthesized compounds, derivatives with semicarbazide residue have shown the most significant activity; and its representative – compound **13** (X = O, R_1 = 4-Cl, R_2 = CH_3) – was found to show the most potent CCB activity (EC_{50} = $1.78*10^{-7}$ M) [41].

13 **14**

X = S, O; R_1= H, 3-Cl, 4-Cl; R_2= CH_3, $NHNH_2$

Most of the clinically used CCBs like nifedipine and amlodipine have 1,4-DHP ring system containing methylcarboxylate side chain at third position. Kshirsagar *et al.* have studied CCB effect of 1,2,3,4-tetrahydropyrimidine derivatives containing carbamate and carbamide moiety (compounds **15** and **16**). Synthesized compounds shows calcium channel blocking activity on rat aorta. Some of the developed compounds showed maximal response comparable with nifedipine [42].



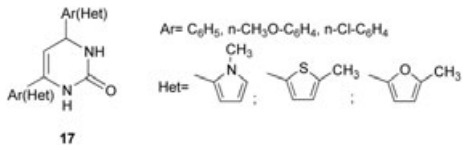
15 **16**

R=Cl, OH, NH_2, OCH_3

R_1= C_2H_5, C_6H_5, n-CH_3-C_6H_4, n-Cl-C_6H_4, n-NO_2-C_6H_4,

Microwave assisted simple, efficient procedure for one-pot Biginelli condensation reaction of aldehydes, β-ketoesters, and urea or thiourea in solvent-free condition employing solid silica-based sulfonic acid as a novel, heterogeneous reusable catalyst is described by Jetti *et al*. Compared with the classical Biginelli reaction conditions, the present method has the advantages of good yields, short reaction times, and experimental simplicity. The newly synthesized 3,4-hydropyrimidin-2-(1H)-one derivatives **17** have been screened to *in vitro* antihypertensive and calcium

channel blocking activity performed by IC_{50} measurement method with nifedipine as standard [43].



17

A pre-synthetic QSAR was run and on its basis a series of 23 pyrimidobenzothiazole-3-carboxylate derivatives (Fig. 8, compounds **19**) was synthesized as selective L-type CCBs and studied by noninvasive and invasive blood pressure methods, which showed better percentage inhibition compared with nifedipine. The lead compound, namely, ethyl 2-methyl-4-(3-nitrophenyl)-4H–pyrimido[2,1-b] [1,3]benzothiazole-3-carboxylate (**19**: R = 3-NO_2, R_1 = C_2H_5), presented a triclinic structure with polymeric chain packing in lattice. Compounds with significant efficacy were studied for their single crystal X-ray diffraction, molecular docking, molecular dynamics, and post-synthetic QSAR. Post-synthetic QSAR of newly synthesized molecules indicates toward improvement with respect to steric descriptor, which contributed negatively in former series [44].

Hydropyrimidine derivatives are popular scaffold for non-DHP CCBs, but not the only one. For example, a series of novel 2-(diarylalkyl)aminobenzothiazoles (Fig. 9;, compounds **20**) with dual activities were designed based on SAR analysis of commercial synthetic CCBs and ACE inhibitors.

These hybrid molecules contain two aryl groups and one 2-aminobenzothiazole group that are attached to the same carbon with the properties based on CCB property and with at least one hydroxyl group on aryl groups based on natural products, which are ACE inhibitors (**20**). It is known that all the CCBs are having phenyl group as aromatic group, and they do not carry any hydroxyl group, whereas most of the natural products such as xanthones and flavones, which are ACE inhibitors, carry multiple hydroxyl groups on aromatic rings. Based upon earlier report, decrease in free hydroxyl groups on them decreases ACE inhibition [45]. So it has been aimed to substitute 2-(diarylalkyl)aminobenzothiazole derivatives with at least one hydroxyl group on aryl groups.

Completely green protocol was developed for their synthesis (Fig. 10). Out of 42 compounds, two lead molecules were identified as ACE inhibitors (Fig. 9, compounds **20a,b**), which were further screened for CCB. As expected, both were identified as CCBs with different selectivity over ACE inhibition. Their selectivity over ACE and CCB can be used to treat resistant hypertension [20].

Korean scientists patented series of 3-R-thio-1,2,4-triazoles derivatives as new representatives of CCBs. For example, one of these compounds – substance **21** – showed 55.9% inhibition (at 10 μM) of calcium movement in T-type calcium channel [46].

18 19

Figure 8. Development of pyrimidobenzothiazole-3-carboxylate derivatives. [Color figure can be viewed at wileyonlinelibrary.com]

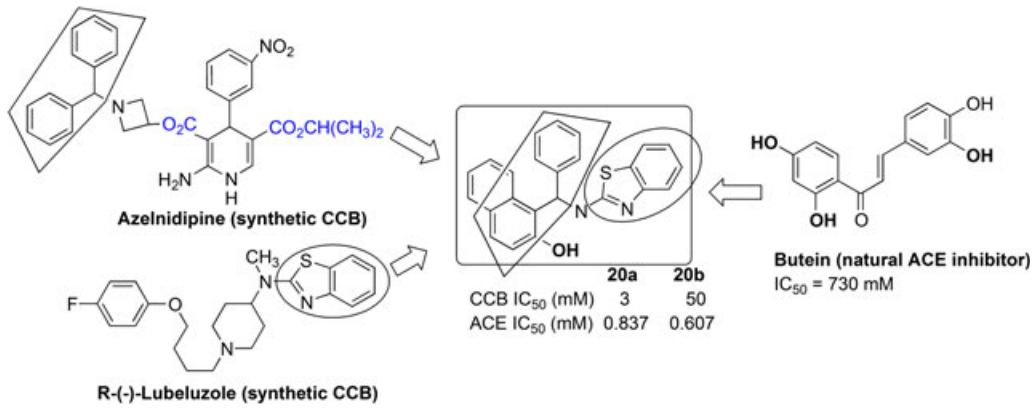


Figure 9. Design strategy for 2-(diarylalkyl)aminobenzothiazoles synthesis. [Color figure can be viewed at wileyonlinelibrary.com]

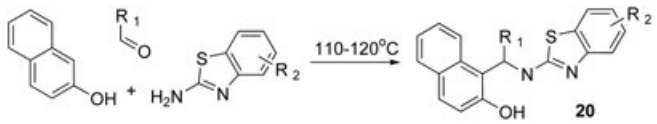
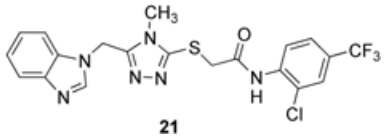


Figure 10. Synthesis of 2-(diarylalkyl)aminobenzothiazoles.



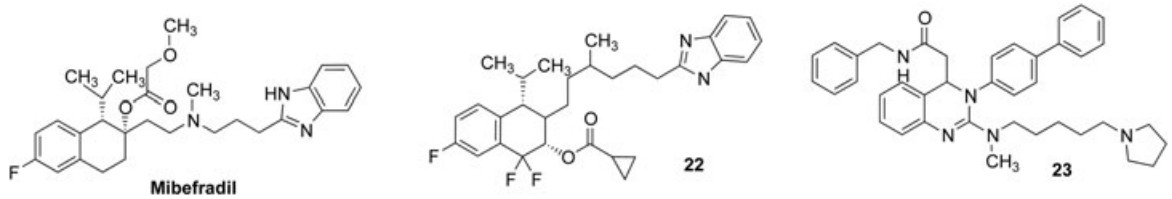
Abbott Laboratories (USA) has patented preparation of novel substituted octahydrocyclopenta[c]pyrrol-4-amines as novel CCBs [47].

Mibefradil (Posicor, Roche®; ATC code: 1.2C08CX Other selective CCBs with mainly vascular effects), the first selective T-type CCB, was approved by the FDA in 1997 for the treatment of hypertension and chronic angina pectoris. Because of its high oral bioavailability and long half-life, it was initially administered to patients as a suitable and convenient once-a-day medication [48]. However, despite the excellent pharmacokinetic features, on June 8, 1998, Roche announced the voluntary withdrawal of the drug from the market because of unfavorable cardiovascular side effects, which were derived from a drug–drug interaction likely resulting from an L-type calcium channel blockade [49].

pharmaceutically acceptable salts was patented for treating diseases and conditions that are beneficially treated by administering a selective T-type CCB [50].

3,4-Dihydroquinazoline analogs substituted by *N*-methyl-*N*-(5-pyrrolidinopentyl)amine at the 2-position were synthesized, and their blocking effects were evaluated for T-type and N-type calcium channels. One of them, compound **23**, compared with mibefradil (IC_{50} = 1.34 ± 0.49 μM), was about fivefold potent (IC_{50} = 0.26 ± 0.01 μM) for T-type calcium channel (α_{1G}) blocking and its selectivity of T/N-type was also improved (7.5 versus 1.4 of mibefradil) [51].

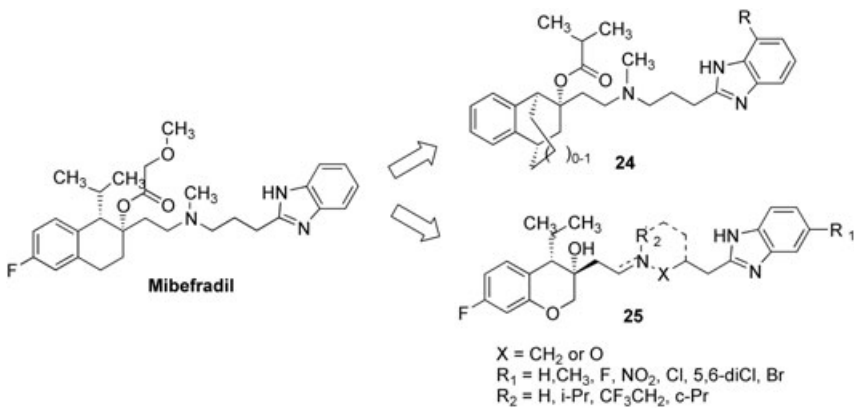
Lately, Hubler *et al.* have performed the chemical evolution of mibefradil that resulted in the identification of novel bridged tetrahydronaphthalene derivatives **24** as potent T/L-type CCBs useful in the treatment or prevention of chronic stable angina, hypertension, ischemia (renal and cardiac), cardiac arrhythmias including atrial fibrillation, cardiac



There clearly is a demand for novel compounds, which act as T/L-type CCBs but have an improved safety profile with respect to mibefradil.

In 2013, a series of novel tetrahydronaphthalene derivatives (for example, compound **22**) and

hypertrophy, or congestive heart failure. An SAR study, *in vitro* and *in vivo* drug metabolism and pharmacokinetic properties as well as the *in vivo* antihypertensive effect in rats are presented in this study [52,53].



Lee *et al*. have designed new stable *in vivo* mibefradil analogs **25**. To prevent metabolic degradation of the drug, further changes have been performed: 1) addition of oxygen to the site of hydroxylation for improvement of the stability; 2) alteration of the tertiary amine moiety to other preventive linkers such as bulkier tertiary amines or oximes to avoid the metabolic dealkylation process; and 3) introduction of R1 substituents at the C5 position of benzimidazole to inhibit the phenolic oxidation on the benzimidazole unit. Thus, it was suggested that these structural changes could diminish the formation of metabolic cytochrome P_{450} inhibitors.

As a result of further work, a total of 22 mibefradil derivatives **25** were synthesized and evaluated for *in vitro* activities. Most compounds **25** were confirmed to be potent T-type CCBs comparable with mibefradil. Moreover, *in vitro* stabilities of the selected compounds **25** in the cytochrome P_{450} enzymes and the human hepatic microsomes were also significantly improved. These findings highlight the importance of this structural modification of mibefradil for reducing cytochrome P_{450} inhibition and metabolic degradation [54].

Mibefradil was reported to protect the heart from atrial remodeling, a key process involved in the development of atrial fibrillation and arrhythmias. It was found that mibefradil is not a selective T-type calcium channel inhibitor and also affects the function of different ion channels. Thus, the aim of the next work was to develop a selective T-type calcium channel inhibitor to validate the importance of T-type–related pharmacology in atrial fibrillation. Structural optimization of a previously disclosed hit series focused on minimizing exposure to the central nervous system and improving pharmacokinetic properties, while maintaining adequate potency and selectivity. This resulted in the design of *N*-[[1-[2-(*tert*-butylcarbamoylamino)ethyl]-4-(hydroxymethyl)-4-piperidyl]methyl]-3,5-dichlorobenzamide (Fig. 11, compound **27**), a novel, selective, peripherally restricted chemical probe to verify the role of T-type calcium channel inhibition on atrial fibrillation protection [55].

Phenylalkylamine and benzothiazepine derivatives. Belong to the CCBs with direct cardiac effects (ATC code: 2C08D). Verapamil and gallopamil (phenylalkylamine derivatives) are L-type CCBs that are used in the treatment of cardiac arrhythmias, hypertension, and angina pectoris. Fendiline, lidoflazine, and perhexiline are mentioned among other similar medicine (Fig. 12). Fendiline is also one of phenylalkylamines and L-type CCB, which is well-known for its coronary vasodilator effects. Lidoflazine is a piperazine derivative. It is a coronary vasodilator with some antiarrhythmic action that was discovered at Janssen Pharmaceutica in 1964. Perhexiline (Pexsig), a piperidine derivative, is a prophylactic antianginal agent used primarily in Australia and New Zealand [56].

Benzothiazepines such as diltiazem (**28**, R = H) and its first analogs substituted in aromatic ring of the heterocycle developed in the early 1970s became popular in the 1980s and were pharmacologically characterized for a long time. It is in the 1990s that several research groups carried out structural variations identifying novel scaffolds for diltiazem-related

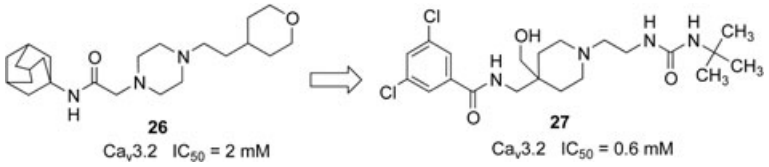


Figure 11. Design of novel T-type calcium channel inhibitors.

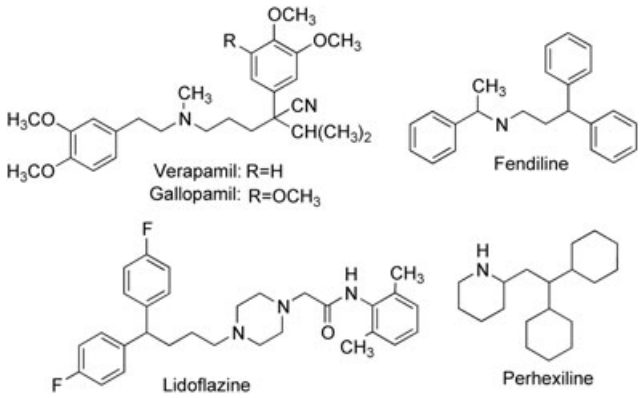


Figure 12. Phenylalkylamine calcium channel blockers.

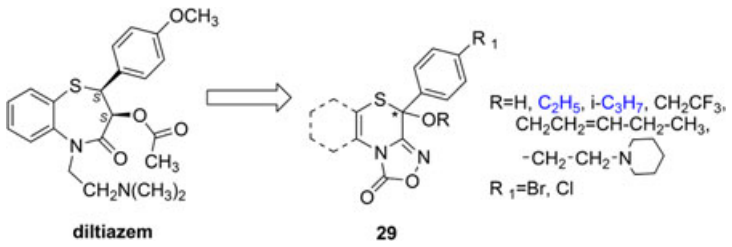
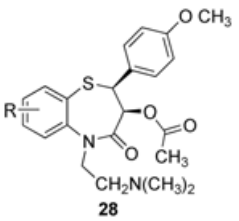


Figure 13. Discovery of new dual acting oxadiazolothiazinone derivatives. [Color figure can be viewed at wileyonlinelibrary.com]

compounds, with significant calcium antagonist behavior [57,58].



In 2010, Milestone Pharmaceuticals Inc. patented diltiazem analogs with substituted benzene ring of benzothiazepine cycle (**28**, R = COOAlk) as short-acting CCB compounds and their use to treat ischemic heart conditions, cardiac arrhythmias, hypertensive crisis in an emergency room setting, and hypertension in general [59].

Group of Italian scientists (Budriesi *et al.*) developed oxadiazolothiazinone molecular scaffold for compounds active as L-type CCBs and P-glycoprotein inhibitors (Fig. 13). They presented the synthesis and *in vitro* data for a series of new derivatives (**29**), and used their scaffold to develop a QSAR model with recent *in silico* techniques and a template for ligand-based virtual screening [60–62].

Bepridil (trade name Vascor, Fig. 2) is an amine nonselective CCB once used to treat angina. It has been discussed as a possible option in the treatment of atrial fibrillation. In June 2015, a research paper was published revealing bepridil resulted in a 100% survival rate for mice exposed to Ebola during an experiment searching for potential pharmaceutical Ebola treatments, indicating its potential use in future Ebola research and therapy [63].

CONCLUSIONS

This review has attempted to summarize historical development and modern design approaches for calcium channels blockers (mainly L-type). The most important representatives of this group are dihydropyridine derivatives that form cornerstone in cardiovascular diseases management nowadays. Also variety of non-dihydropyridine molecules, mostly heterocycles, has been developed based upon SAR analysis and chemical modification that lead to new active substances. Provided review could be helpful for researchers who deal with design and development of new drugs for cardiovascular diseases.

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