Fused 1,4-Dihydropyridines as Potential Calcium Modulatory Compounds

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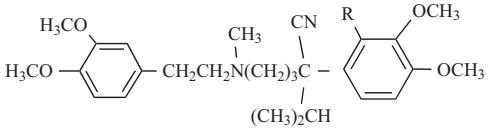
Abstract: 1,4-Dihydropyridine (1,4-DHP) derivatives nifedipine of which the prototype, are the most popular drugs having calcium antagonistic activity. Fused 1,4-dihydropyridines (DHPs) have also exhibit calcium modulatory activities. In this article, we emphasize calcium channels and fused 1,4-DHP derivatives affecting calcium channels. In addition, the basic considerations of synthesis, metabolism, structure-activity relationships and the latest developments on fused 1,4-DHP derivatives will be reviewed. This review also has extended examples of fused 1,4-DHP derivatives having cited activities synthesized by our group.

Key Words: 1,4-Dihydropyridine, hexahydroquinoline, calcium modulatory activity, synthesis, biotransformation, structure-activity relationships.

INTRODUCTION

The first observation of the importance of Ca^{2+} ion for the maintenance of cellular activity was reported by Ringer in 1883 [1, 2]. At the end of 1960, Fleckenstein and Godfraind initiated experimental studies to alter calcium function in excitation-contraction coupling by pharmacological ligands in their laboratory. Haas and Hartfelder described verapamil in 1962 as a coronary vasodilator [3]. In 1967, Fleckenstein and Grun presented evidence that the vasodilating properties of verapamil were related to calcium antagonism. Gallopamil (D600), which is a verapamil derivative, blocks Ca^{2+} influx through the calcium channel shown by Kohlhardt *et al*. in 1972.



R: H Verapamil
R: OCH_3 Gallopamil

Fig. (1). Structure of verapamil and gallopamil.

Later, dihydropyridines, diltiazem and flunarizine were also shown to be calcium antagonists [4, 5]. In 1972, Fleckenstein and co-workers found that 1,4-DHP derivatives act by blocking the entry Ca^{2+} ions into the cardiac and vascular muscle through voltage dependent calcium channels [6]. Nifedipine, as the most promising drugs for the treatment of cardiovascular diseases, was introduced to medical practice in 1975 as Adalat [7].

A compound or a drug which alters the cellular function of calcium by inhibiting its entry and (or) its release and(or) by interfering with one of its intracellular actions which compete with Ca^{2+} for a binding site known as a calcium antagonist. Calcium channel blockers (CCBs) specifically inhibit Ca^{2+} entry into cells due to tissue excitation by various stimuli [8].

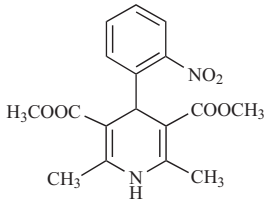


Fig. (2). Structure of nifedipine.

DHPs have many biological features included vasodilator, antihypertensive, bronchodilator, antiatherosclerotic, anticonvulsant, hepatoprotective, antitumor, antimutagenic, geroprotective, antidiabetic, antioxidant, antiradical and controlling cellular proliferation [9-24]. Although DHP's have been developed as cardiovascular agents some of them have been used for other medical applications. For example, nimodipine is used an antiischemic agent in the treatment of Alzheimer's disease and other dementias, migraine and posthemorrhagic vasospasm. Nifedipine is also used in the treatment of migraine, hypertrophic cardiomyopathy and Raynaud's phenomenon, it could also be used in the treatment of diabetic neuropathy. Platelet anti-aggregatory DHP series included trombodipine, have protective effects against *Listeria monocytogenes*. Dexniguldipine is a chemosensitizer with low hypotensive properties. It is clear that the new generation DHP derivatives are a potential source of valuable drug candidates with remarkable potential and ongoing interest [25]. 1,4-DHP derivatives have great significance as CCBs. Today there are many efforts to prepare additional cardioselective compounds and many drugs are under clinical investigation [26].

CALCIUM CHANNELS

Ion channels permit passage of specific ions and play important roles in the generation of cellular responses and are classified according to ion selectivity and ligand sensitivity. Calcium channels can be classified according to their

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activation mechanism as receptor operated (ROC) and voltage-operated channels (VOC). The former is activated by membrane depolarization and leads to change in voltage across the membrane. This causes calcium channels to open. Ligand gated calcium channels are regulated by binding of norepinephrine to receptors. This situation gives the regulation of calcium release from intracellular stores [27]. Calcium channels are in excitable membranes permitting the movement of Ca^{2+} across plasma membrane. This movement exhibited many cellular functions such as muscle contraction, enzyme regulation and the secretion of some transmitters and hormones [28]. CCBs have a common target of the voltage-gated Ca^{2+} channels. These appear across the myocardial and vascular smooth muscle cell [29-35]. Calcium ions have an important role in the contraction of heart and smooth muscle cells. VOC are formed by subunits $\alpha 1$, β and $\alpha 2$-δ whereas skeletal muscle have DHP receptor containing five protein subunit named $\alpha 1$, $\alpha 2$, β, γ, and δ [36, 37]. VOCs formed by L, T, N, P, Q and R subtypes. N, P, Q and R are found in central nerveous system. Calcium antagonists bind to the $\alpha 1$ subunits of L-type channel with high affinity. The pores are formed by $\alpha 1$ subunits which consists of four homolog helices, each of which is composed of six transmembrane segments. The identical structural elements lead to primary function of the Ca^{2+} channel pore. This function is the regulation of Ca^{2+} current which included promotion or interruption of Ca^{2+} ions [36, 38]. Cardiac and smooth muscle cells are the major binding site being Ca^{2+} channel for 1,4-DHP. Triggle and co-workers demonstrated that calcium antagonists such as nifedipine and verapamil have an effect on voltage dependent calcium channels [39]. Radioligand binding studies showed that dihydropyridine agonist and antagonist bind to same receptor site [40].

CALCIUM CHANNEL MODULATORY COMPOUNDS

Many compounds with different structures receptor-binding characteristics, and features are mentioned as calcium antagonists. Although calcium channel antagonists are a heterogeneous group, they can be divided to three major groups: phenylalkylamine (verapamil), benzothiazepine (diltiazem) and 1,4-DHP (nifedipine) in therapy [41]. There are some examples of hybridization to take dual effects in 1,4-DHP derivatives. Liang and co-workers proposed that some hybride molecules having 1,4-DHPs with α-/β-adreno-receptor blocker are in the same molecule [42]. It was also showed that the hybride molecules carrying 1,4-DHP and diazen function in same molecule gave positive results in patients with congestive heart failure [43].

Active derivatives can be obtained by introducing the 1,4-DHP structure into the condensed ring systems [44-54]. Some examples are given in Fig. (**3**).

Racemic hexahydroquinolines, furoquinolines and indeno-pyridines exhibited calcium antagonistic effects on smooth muscle and positive inotropic activity on electrically stimulated atria of guinea pigs [55, 56].

Although, it has been proposed that the 2-methyl group in 1,4-DHPs and its condensed analogs are required for activity, replacement of methyl group with various alkyl groups also affords activity. However, the activity of these derivatives decreases in comparison with the methyl analogs. It has been thought that the ethyl group could affect receptor binding of the molecule due to its steric effect [48].

The first synthesis of 1,4-DHPs were accomplished by the reaction of acetoacetic ester, aldehyde and ammonia by

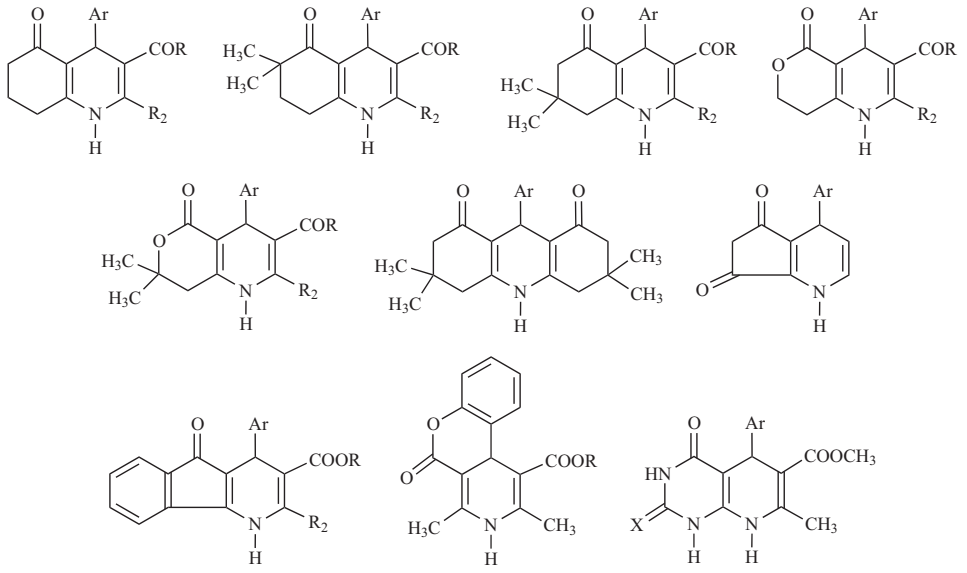

Fig. (3). Structures of some fused 1,4-DHPs.

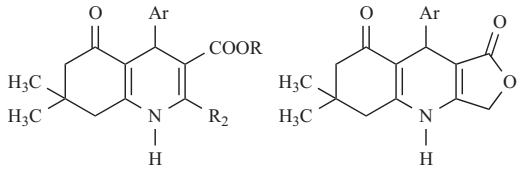

Fig. (4). Structure of hexahydroquinoline and furoquinoline.

Hantzsch in 1882 [57]. This reaction is still widely used for 1,4-DHP synthesis [58].

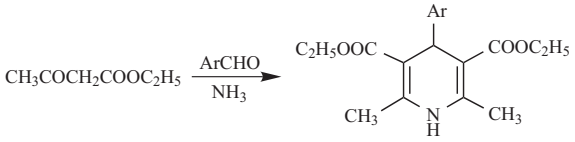

Fig. (5). Hantzsch synthesis.

Bossert and Vater starting with condensed pyrane derivative and proceeding *via* quinoline [59].

There are many reactions which lead to the synthesis of condensed 1,4-DHP derivatives. Enamine derivatives can be used in this reaction instead of acetoacetic acid ester-ammonia. In addition, any synthetic routes such as reduction, rearrangement and cycloaddition reaction could have been applied in the synthesis of 1,4-DHP derivatives [60]. The reaction of some oxazinane derivatives with ethyl β-aminocrotonate and dimedone provides unsymmetrically condensed 1,4-DHP compounds [61].

The Hantzsch-like three component reactions is the most useful and easiest method in order to obtain hexahydroquinoline derivatives. 1,3-cyclohexanedione, benzaldehyde derivatives, and alkyl β-aminocrotonate are useful components as described above. It is possible to obtain different esters by using different β-aminocrotonate or acetoacetate/ammonia with different alkyl substitution.

Combinatorial chemistry has recently come up with a powerful tool for drug discovery. Synthesis of compounds on solid supports is the most important feature of combinatorial chemistry. Accordingly, it is the prerequisite challenge to develop solid-phase synthesis on solid supports for biologically active molecules. Afterwards, it is also a

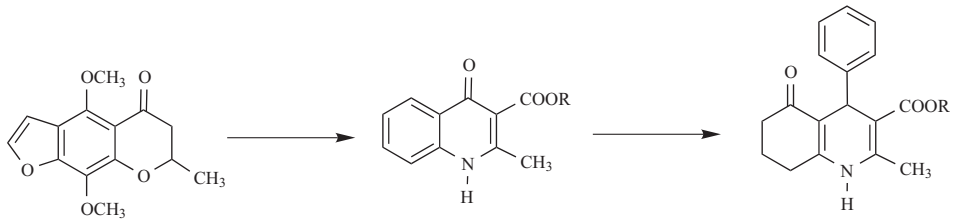

Fig. (6). Synthesis of hexahydroquinoline.

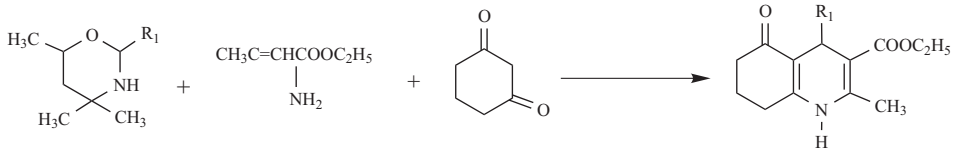

Fig. (7). Synthesis of hexahydroquinolines from oxazine derivatives.

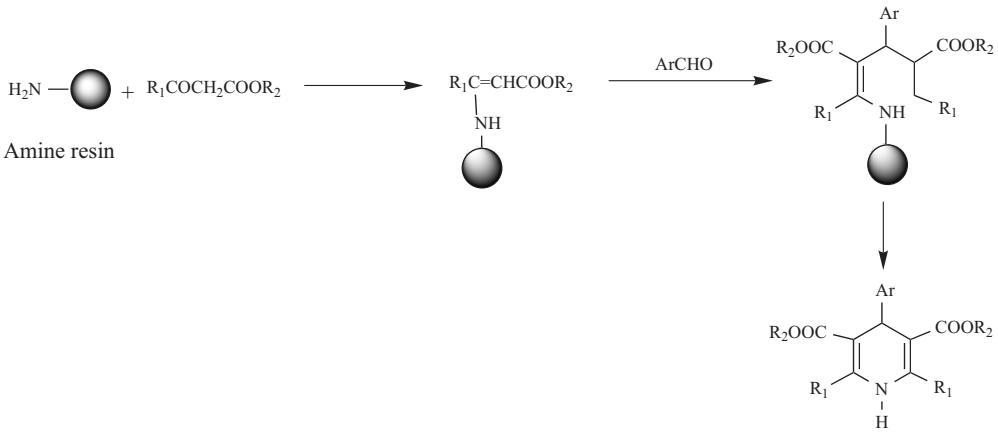

Fig. (8). Schematic representation of solid phase synthesis of 1,4-DHPs.

prerequisite challenge to explore the utility of such synthetic methodologies for forming of combinatorial libraries. The synthesis of nifedipine, nitrendipine and nimodipine has been achieved by solid-phase synthesis. Gordeev and co-workers reported the preparation of a 300-member dihydropyridine library and screened their calcium channel binding activity. The same authors also reported the synthesis of 1,4-DHPs on solid supports which was based on a two or three component cyclocondensation [18, 25, 62, 63].

STRUCTURE-ACTIVITY RELATIONSHIPS

Active derivatives can be obtained by replacing ester groups with other electron drawing substituents such as acyl, amide, nitrile, nitro, and sulfonyl [45, 46, 49, 53, 64-67]. Many studies defined the structure-activity relationships of 1,4-DHPs. These properties summarized by Triggle are given in the below figure [68].

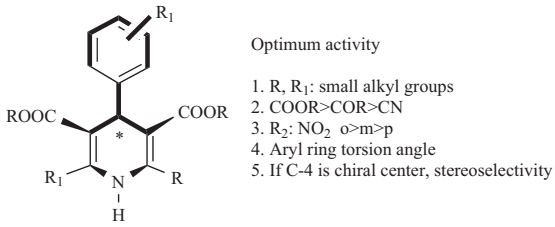

Fig. (9). Outline of structure-activity relationships of 1,4-DHPs.

The 4-position of 1,4-DHP is critical. If this position is chiral, one enantiomer may serve as an agonist and the other one as an antagonist. Traditional antagonistic 1,4-DHPs have ester groups in both the 3 and 5 positions. However, 1,4-DHPs with different ester groups at C-3 and C-5 have an asymmetric center at C-4. This case causes activity differences depending on the isomers [47, 69-71]. Bay K 8644 and 202-791 are illustrative examples for this case.

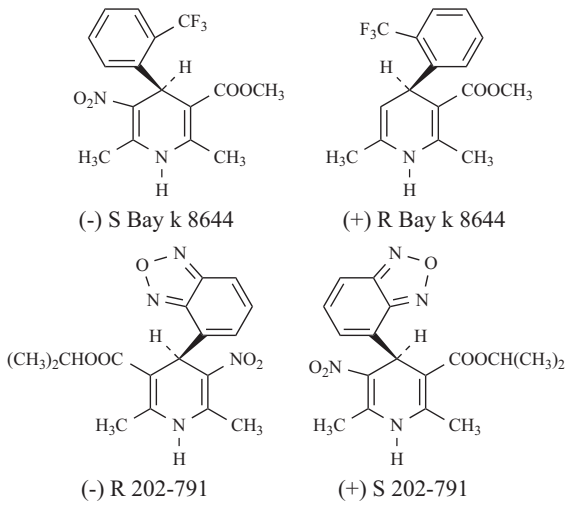

Fig. (10). Isomers of Bay-K and 202-791.

For example, (-) S Bay K 8644 has calcium agonistic properties, whereas (+) R Bay K 8644 shows calcium antagonistic activity. Schramm and coworkers explained that nifedipine and Bay K 8644 bind a specific dihydropyridine receptor, but Bay K 8644 affects diametrically opposite to those of nifedipine. This mechanism leads to the development of agonistic dihydropyridines [70, 72, 73].

Calcium agonist and antagonists bind to the same receptor and replace each other competetively. [74].

Similar findings were obtained in lactone derivatives. While the R enantiomer was found to be an agonist, the S-enantiomer was found to be antagonist, S-enantiomer is 50-fold more active than R-enantiomer in respect to receptor binding [59].

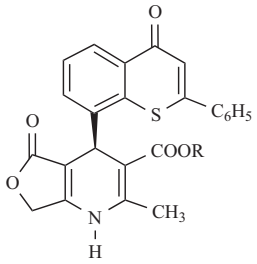

Fig. (11). Lactone derivative of 1.4-DHP.

H 160/51 is an analog of calcium antagonist felodipine. In contrast to felodipine, its racemic form showed stimulatory properties and was classified as a calcium agonist. Gjorstrup *et al*. showed that the enantiomers of H160/51, is a 1,4-DHP derivative, opposing actions in the cat papillary muscle and rat portal vein [75]. In addition, racemic PY 202-791 has stimulation and inhibition properties on calcium channels. It was separated into enantiomers, which behaved as pure agonist and antagonist.

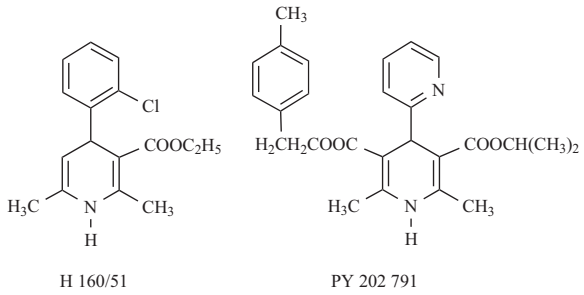

Fig. (12). H160/51 and PY 202-791.

The axial position of 4-aryl group is required for the pharmacological activity of the compounds. If compound has a substituent in the ortho or meta position, this substituent may be at the same side (synperiplanar-sp) with H-4 or lie above the DHP ring (antiperiplanar-ap) [59].

In order to fix the ester group in an antiperiplanar orientation, the ester group was converted to a lactone ring. The lactone derivatives show agonist-antagonist properties [44-50, 56, 69, 76].

In vinylogous hexahydroquinoline derivatives, linkage of a dihydropyridine ring through a vinyl group resulted in a

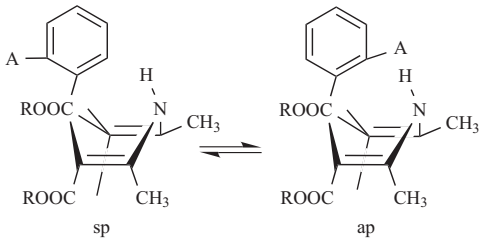

Fig. (13). Synperiplanar and antiperiplanar conformation of 4-aryl-1.4-DHP derivative.

decrease in positive inotropic activity as compared to the directly linked annelated or nonannelated dihydropyridines. This activity was attributed to release of catecholamines from intracellular stores. It was observed that the antagonistic activity of dihydropyridines with symmetrical ester functions reduces with increasing steric effects of these groups [77, 78].

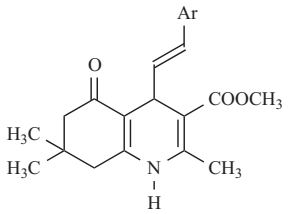

Fig. (14). 4-Vinylogous hexahydroquinoline derivative.

Various 4-arylhexahydroquinoline derivatives showed positive inotropic effects in stimulated left guinea pig atrium, whereas barium chloride induced contractions are suppressed in a dose dependently manner in guinea pig ileum [67]. Similar results were obtained in 5-oxo-1,4-indenopyridine (I) and furoquinoline (II) derivatives [66, 79].

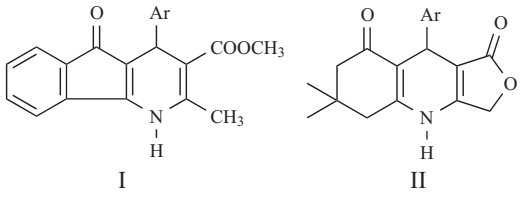

Fig. (15). Indenopyridine (I) and furoquinoline (II) derivatives.

The 4-arylhexahydroquinoline derivatives having an electron withdrawing substituent on the phenyl ring showed high calcium antagonist activity. In addition, using naphthalene and heteroaromatic rings instead of the phenyl ring increases activity [46]. It has also been reported that some dihydropyridines having any substituents at the 2 and 6 positions showed calcium agonist activity [80].

Optimal biological activity for 1,4-DHP derivatives:

1. Nitrogen atom should be unsubstituted in the 1,4-DHP ring.
2. The substituents in 2. and 6. position should be lower alkyl groups.
3. The compounds having ester groups in the 3. and 5. positions are the most effective compounds. Ester groups can be replaced by other electron-withdrawing groups such as acetyl, nitro and nitrile.
4. The aryl group in the 4 position of 1,4-DHP ring is the basic requirement for optimal activity. In addition, substituent position on the benzene ring is of great importance. Ortho and meta substitution is prefered to para substitution.

The 1,4-DHP ring has a boat form with the 4-aryl substituent being at the axial position and orthogonal to the plane of the dihydropyridine nucleus. The substituent on the aryl ring is positioned on the same side of the hydrogen atom of C(4)-aryl bond. The synperiplanar rotamer is favorable. The ester groups are at the equatorial positions. In this case, carbonyls of the ester groups are in a cis position relative located to the 2 and/or 6 substituents of the DHP ring. This situation ensures the optimal activity. The position of the 4-aryl substituent has importance on the activity. Ortho substituent exists as synperiplanar orthogonal arrangement of the aryl substituent, as well as cis/cis conformation of ester groups at the 3- and 5 positions [81]. The Hansch analysis was applied to DHP derivatives to elucidate structural requirements for the binding to their receptor and to develop the new analogs [74].

PHOTOSTABILITY

The photooxidation of 1,4-DHPs results in the conversion of a 1,4-DHP structure to pyridine ring [82, 83]. The photochemical stability of 2,6,6-trimethyl-3-carbmethoxy-4-aryl-5-oxo-1,4,5,6,7,8-hexahydroquinoline derivatives have been examined. The photodegradation rate was found to depend on the type and position of the substituent in the aryl ring. The compounds with alkyl and trifluoromethyl substituent showed the greatest photochemical stability [83, 84]. In addition, the compounds having substituents in the ortho position were found much less photostable than the meta isomers.

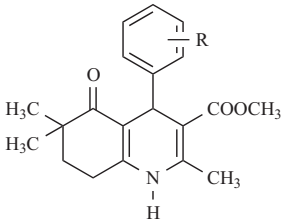

Fig. (16). Hexahydroquinoline derivative.

The photodegradation of some complexes forming 1,4-DHP compounds and β-cyclodextrin were studied in the liquid phase and their photodegradation rates were compared. The results showed that photochemical stability can be reduced by replacing nitro group in the compounds with halogeno and cyano group [74].

BIOTRANSFORMATION

In biotransformation studies of 1,4-DHPs, the main products are pyridine analogs, monoacid, and lactone [85-

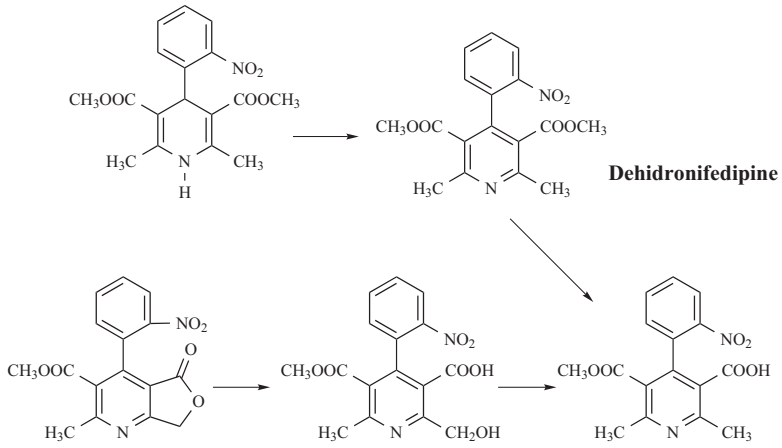

Fig. (17). Main pathways in the biotransformation of nifedipine.

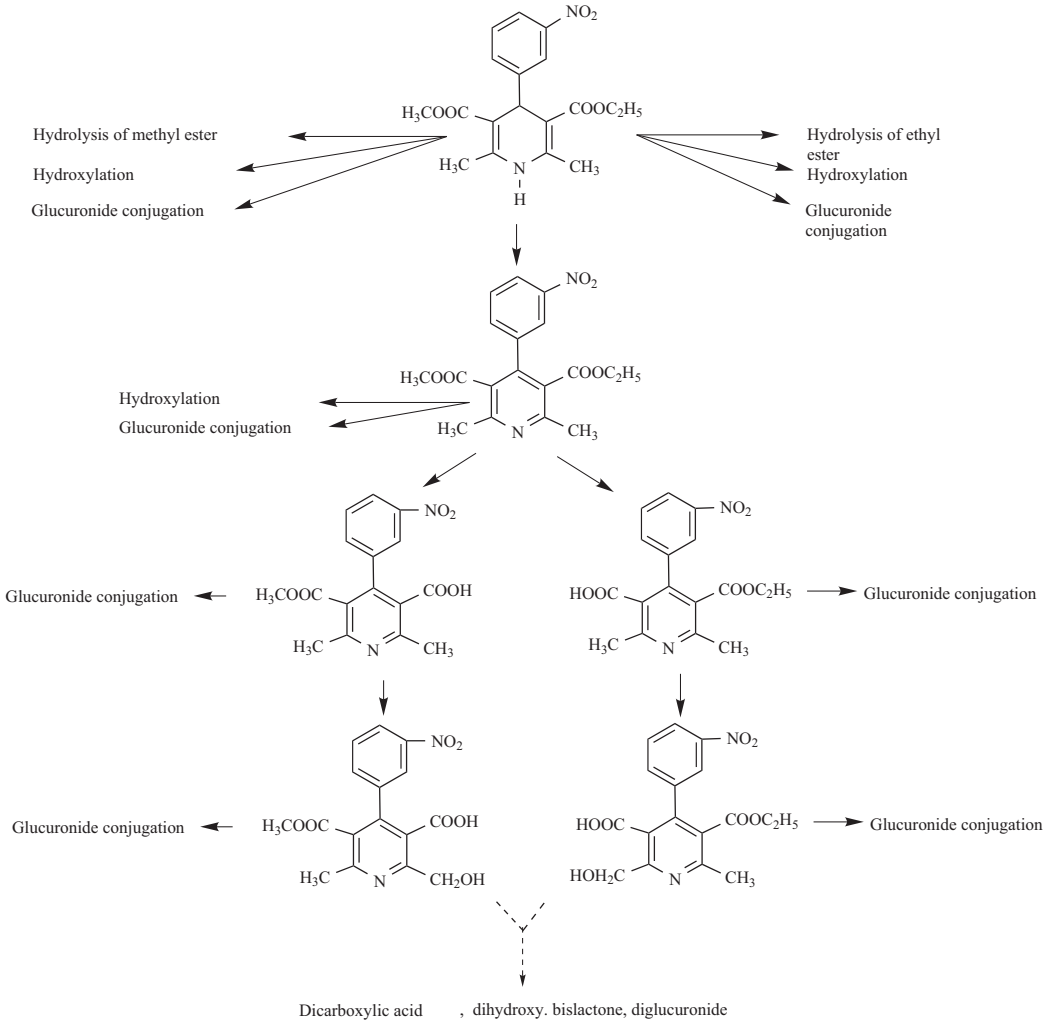

Fig. (18). Biotransformation of nitrendipine.

88]. In phase I reactions, dehydrogenation of 1,4-DHP system, oxidative o-demethylation, ester cleavage, hydroxylation of the methyl groups at 2 and 6-position occur. Conversion of the 1,4-DHP ring to pyridine gives inactive analogs. Biotransformation was catalyzed by cytochrome P-450 mixed function oxidase system and these studies have been shown in man as well as animals. This dehydrogenation, that occurs *via* stepwise electron transfer is catalyzed by cytochrome P-450. This step is followed by ester cleavage and lactone formation. P-450 oxidation is also involved in the ester cleavage and hydroxylation of the methyl groups. Another pathway is relatively independent of the substitution on the aryl ring at the 4-position. P-450$_{NF}$ is the form of P-450 that oxidizes nifedipine. In the nifedipine biotransformation, the first step of metabolism is the formal 2-electron oxidation of the nifedipine dihydropyridine ring. In principle, such an oxidation could be catalyzed by a number of oxidoreductases, but some oxidation was formed by P-450s. The primary metabolite is further followed by ester saponification and ring methyls' hydroxylation [89]. Characterization of rat and human liver microsomal cytochrome P-450 forms involved in nifedipine oxidation is a prototype for genetic polymorphism in oxidative drug metabolism [88-97].

Nitrendipine, which is a 1,4-DHP derivative with antihypertensive activity has been subjected to bioequivalance and biotransformation studies on healthy volunteers by Kann *et al*. The authors explained the metabolic pathways of nitrendipine as shown in Fig. (**18**) [98].

Nimodipine, which is another 1,4-DHP derivative has also potent inhibitor effect on vascular and other smooth muscles contractions. The (-)-isomer of nimodipine is more active than the (+) isomer. The known metabolites of nimodipine are less potent than the parent compound [99].

Biotransformation of benidipine, also gives metabolic products similar to nimodipine and these are detected by HPLC, LC and GC in human plasma [100, 101].

The biotransformation of fused 1,4-DHPs gives similar metabolites. *In vitro* hepatic microsomal biotransformation of 2,6,6-trimethyl-4-(2-bromophenyl)l-5-oxo-1,4,5,6,7,8-hexahydroquinoline produced 1,3,4,5,6,7,8,9,-octahydro-7,7-dimethyl-9-(2-bromophenyl)furo[3,4-b]quinoline-1,8-dione, and this biotransformation was proved by HPLC [50, 76].

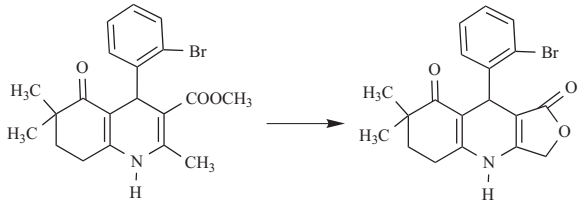

Fig. (19). Metabolic conversion of hexahydoquinolines to furoquinolines.

Glucuronidation is a main phase II reaction. Metabolites were identified in comparison with the reference substances using instrumental techniques such as HPLC, MS, GC-MS and ^{1}H-NMR spectroscopy [76, 102, 103].

CONCLUSION

Hypertension is an important health problem and is one of major cause of morbidity and mortality in the world. Although there are many efficacious antihypertensive drugs, but they have different side effects. Furthermore, there is a need to design new drugs with less side effects and long-term safety.

Clinical trials pointed out that calcium antagonistic drugs are effective in the prevention of cardiovascular events. Calcium channel antagonists are also used for the treatment of angina and arrhythmia. These drugs were introduced as fast-acting vasodilators exhibiting powerful antihypertensive activities. They are also preferred due to their smooth onset and long duration of action.

Developing molecular biology techniques has increased our knowledge of calcium channel types and their functions. This has led to the developed of CCBs which are specific for these channels. Thus, it could be possible to treat diseases that resulted from raised calcium channel function. In addition, binding studies, biotransformation experiments and the elucidation of metabolites will be guided for the development of new and effective drugs [104-110].

ABBREVIATIONS

CCBs = Calcium channel blockers

DHP = Dihydropyridine

DHPs = Dihydropyridines

VOC = Voltage operated channel

ROC = Receptor operated channel

REFERENCES

[1] Janis, R. A.; Triggle, D. J. *J. Med. Chem.,* **1983**, *26*, 775.
[2] Janis, R. A.; Triggle, D. J. *Drug Dev. Res.,* **1984**, *4*, 257.
[3] Haas, H.; Hartfelder, G. *Arzneim. Forsch. Drug Res*., **1962**, *12*, 549.
[4] Fleckenstein, A.; Tritthart, H.; Doring, H. J.; Byon, Y. K. *Arzneim. Forsch. Drug Res*., **1972**, *22,* 22.
[5] Nayler, W.G. *Calcium Antagonists*, Academic Pres: London, **1988**.
[6] Fleckenstein, A.; Grun, G. *Vascular Smooth Muscle*, Springer-Verlag: Berlin, **1972**.
[7] Goldmann S.; Stoltefuss, J. *Angew. Chem.,* **1991**, 1559.
[8] Godfraind, T.; Miller, R.; Wibo, M. *Pharmacol. Rev.*, **1986**, *38*(4), 321.
[9] Morön, M. A.; Stevens, C. W.; Yaksh, T.L. *J. Pharmacol. Exp. Ther*., **1990**, *252*(3), 1150.
[10] Russo, E.; Constanti, A.; Ferreri, G.; Citraro, R.; De Sarro, G. *Neuropharmacology*, **2004**,*46*(6), 865.
[11] Yiu, S.; Knaus, E. E. *Arch. Pharm. (Weinheim)*, **1997**, *330,* 35.
[12] Palmer, G. C.; Stagnitto, M. L.; Wynn, H.; Wolowyk, M.; Triggle, C. R.; Ray, R. K.; Knowles, M. A.; Harvey, R.; Garske, G. E. *Epilepsia*, **1993**, *34*(2), 372.
[13] Navidpour, L.; Shafaroodi, H.; Miri, R.; Dehpour, A.R.; Shafiee, A. *Il Farmaco*, **2004**, *59,* 261.
[14] Anana, R. D. Ng, H.; Hwlett, S. E.; Knaus, E. E. *Arch. Pharm. (Weinheim)*, **1997**, *330*, 53.
[15] Ohsumi, K.; Ohishi, K.; Morinaga, Y.; Nakagawa, R.; Suga, Y.; Sekiyama, T.; Akiyama, Y.; Tsuji, T.; Tsuruo, T. *Chem. Pharm. Bull*., **1995**, *43*(5), 818.
[16] Zidermane, A.A.; Dauvarte, A.; Kozhukhov, A.N.; Merena, D.V.; Nemane, D.U. *Eksperimental Naia Onkologiia*, **1987**, *9*(2), 50.
[17] Im, C.; Knaus, E.E.; Thuynsma, R.P.; Allen, T.M. *Drug Des. Deliv.,* **1990**, *5*(3), 239.

[18] Shah, A.; Gaveriya, H.; Motohashi, N.; Kawase, M.; Saito, S.; Sakagami, H.; Satoh, K. Tada, Y.; Solymosi, A.; Walfard, K.; Molnar, J. *Anticancer Res*., **2000**, *20*(1A), 373.
[19] Kiue, A.; Sano, T.; Naito, A.; Inada, H.; Suziki, K.; Okumura, M.; Kikuchi, J.; Sato, S.; Takano, H.; Kohno, K. *Jpn. J. Cancer Res*., **1990,** *81,* 1057.
[20] McCalmont, W.F.; Patterson, J.R.; Lindenmuth, M.A.; Heady, T.N.; Haverstick, D.M.; Gray, L.S., Macdonald, T.L. *Biorg. Med. Chem*., **2005**, *13,* 3821.
[21] Wang, L.; Zhang, H.; Konga, L.; Shi, J. *Helv. Chim. Acta,* **2004**, *87*(6), 1515.
[22] Tirzite, D.; Krauze, A.; Zubareva, A.; Tirzitis, G.; Duburs, G. *Chem. Heterocycl. Compd.,* **2002**, *38*(7), 795.
[23] Lopez-Alarcon, C.; Navarrete, P.; Camargo, C.; Squella, J.A.; Nunez-Vergara, L.J. *Chem. Res. Toxicol.,* **2003**, *16*(2), 208.
[24] McCalmont, W.F.; Heady, T.N.; Patterson, J.R.; Lindenmuth, M.A.; Haverstick, D.M.; Gray, L.S.; Macdonald, T.L. *Biorg. Med. Chem.,* **2004**, *14*, 3691.
[25] Gordeev, M.F.; Patel, D.V.; England, B.P.; Jonnalagadda, S.; Combs, J.D.; Gordon, E.M. *Bioorg. Med. Chem*., **1998**, *6*, 883.
[26] Yagupolskii, L. M.; Maletina, I.I.; Petko, K. I.; Fedyuk, D. V. *J. Fluor. Chem.,* **1996,** *80*, 3.
[27] Weiner, D.A. *Cardiovasc. Pharmacother.,* **1988**, *72*, 83.
[28] Reuter, H. *Nature*, **1983,** *301*(17)*,* 569.
[29] Triggle, D.J. *Eur. J. Pharmacol*., **1999**, *375*, 311.
[30] Towart, R.; Schramm, M. *Trends Pharmacol. Sci.,* **1984**, 111.
[31] Bean, P.B. *Proc. Natl. Acad. Sci. USA*, **1984**, *81*, 6388.
[32] Höltje, H. D. *Quant. Struct. Act. Relat.,* **1992**, *11*, 224.
[33] Sanguinetti, M. C.; Kass, R. S. *Circ. Res*., **1884**, *55*, 336.
[34] Triggle, D.J. *Cell Mol. Neurobiol*., **2003**, *23*(3), 293.
[35] Triggle, D.J. *Mini Rev. Med. Chem*., **2003**, *3*(3), 215.
[36] Hering, S.; Berjukow, S.; Aczel, S.; Timin, E.N. *Curr. Awar.*, **1998**, *19*, 439.
[37] Perez-Reyes, E.; Kim, H.S.; Lacerda, A.E.; Horne, W.; Wei, X.; Rampe, D.; Campell, K.P.; Brown, A.M.; Birnbaumer, L. *Nature*, **1989**, *340*, 233.
[38] Budriesi, R.; Bisi, A.; Ioan, P.; Rampa, A.N.; Gobbi, S.; Belluti, F.; Piazzi, L.; Valenti, P.; Chiarini, A. *Biorg. Med. Chem.,* **2005**, *13*, 3423.
[39] Triggle, D.J. *Chest*, **1980**, *78*, 174.
[40] Janis, R.A.; Rampe, D.; Sarmiento, J.L.; Triggle, D.J. *Biochem. Biophys. Res. Comm.* **1984**, *121*, 317.
[41] Horowitz, J.D.; Powel, A.C. *Med. J. Austr*., **1989**, *150,* 591.
[42] Liang, J.; Yeh, J.; Wang, C.; Liou, S.; Tsai, C.; Chen, I. *Bioorg. Med. Chem.,* **2002**,*10,* 719.
[43] Velazquez, C.; Knaus, E.E. *Bioorg Med Chem*. **2004**, *12*(14), 3831.
[44] Şafak, C.; Erdemli, İ.; Sunal, R. *Arzneim. Forsch. Drug Res*., **1993**, *43,* 1052.
[45] Şafak, C.; Özkanlı, F.; Erol, K.; Aktan, Y. *Arzneim. Forsch. Drug Res*., **1995**, *45,* 1154.
[46] Altaş, Y.; Şafak, C.; Batu, Ö.S.; Erol, K. *Arzneim. Forsch. Drug Res.*, **1999**, *49*(II), 824.
[47] Şimşek, R.; İsmailoğlu, U. B.; Şafak, C.; Sahin-Erdemli, İ. *Il Farmaco,* **2000**, *55,* 665.
[48] Şimşek, R.; Şafak, C.; Erol, K.; Sırmagül, B. *Arzneim. Forsc. Drug Res*., **2001**, *51*(II) 959.
[49] Kısmetli, E.; Şafak, C.; Erol, K.; Sırmagül, B.; Linden, A. *Arzneim. Forsch. Drug Res.,* **2004**, *54*(7), 371.
[50] Aydın, F.; Şafak, C.; Şimşek, R.; Erol, K.; Ülgen, M.; Linden, T. *Pharmazie,* **2006**, (in press).
[51] Sausins, A.; Duburs, G. *Heterocycles*, **1988**, *27*(1), 269.
[52] Sausins, A.: Duburs, G. *Heterocycles*, **1988**, *27*(1), 291.
[53] Şafak, C.; Şimşek, R.; Altaş,Y.; Boydağ, S.; Erol, K. *Boll. Chim. Farmaceutico,* **1997**, *136*(11), 665.
[54] Pastor, A.; Alajarin, R.; Vaquero, J.J.; Alvarez-Builla, J.; Casa-Juana, M.F.; Sunkel, C.; Priego, J.G.; Fonseca, I.; Sanz-Aparicio, J. *Tetrahedron,* **1994**, *50,* 8085.
[55] Rose, U.; Dräger, M. *J. Med. Chem*., **1992**, *35,* 2238.
[56] Rose, U. *Arzneim. Forsch. Drug Res*., **1991**, *41*(3), 199.
[57] Hantzsch, A. *Justus Liebigs Ann. Chim*., **1882**, *215*, 1.
[58] Sridhar, R.; Perumal, P.T. *Tetrahedron*, **2005**, *61,* 2465.
[59] Bossert, F.; Vater, W. *Naturwissenschaften*, **1971**, *58*, 578.
[60] Stout, D. M.; Meyers, A. I. *Chem. Rev*., **1982**, *82,* 223
[61] Singh, H. *J. Chem. Res*., **1993**, 120.
[62] Gordeev, M.F.; Patel, D.V.; England, B.P.; Jonnalagadda, S.; Combs, J.D.; Gordon, E.M. *Bioorg. Med. Chem.,* **1998**, *6,* 883.
[63] Gordeev, M.F.; Patel, D.V.; Gordon, E.M. *J. Org. Chem.,* **1996**, *61,* 924.
[64] Şafak, C.; Şahin, İ.; Sunal, R. *Arzneim Forsch. Drug Res*., **1990**, *40,* 119.
[65] Ivanami, M.; Shibanauma, T.; Fujimato, M.; Kawai, R.; Tamazawa, K.; Takenaka, K.; Takahashi, K.; Murakami, M. *Chem. Pharm. Bull*, **1979**, *27,* 1426.
[66] Rose, U. *Arzneim. Forsch. Drug Res*., **1989**, *39*(2), 1393.
[67] Rose, U. *Arch. Pharm*., **1990**, *323*, 281.
[68] Triggle, D.J. In *Drug Discovery Technologies* (Colin R. Clark and Walter H. Moos, Eds.) John Wiley & Sons, Chicester, **1990**.
[69] Şimşek, R.; Şafak, C.; Erol, K.; Sırmagül, B. *Pharmazie*, **2001**, *56,* 665.
[70] Franckowiak, G.; Bechem, M., Schramm, M.; Thomas, G. *Eur. J. Pharmacol*., **1985**, *114*, 223.
[71] Görlitzer, K.; Schmidt, E. *Arch. Pharm*., **1991**, *324,* 879.
[72] Schramm, M.; Thomas, G.; Towart, R.; Franckowiak, G. *Nature*, **1983**, *303,* 535.
[73] Hof, R.P. *J. Cardivas. Pharmacol*., **1985**, *7,* 689.
[74] Mahmoudian, M., Richards, G. *J. Chem. Soc. Chem. Comm.,* **1986**, 739.
[75] Gjorstrup P.; Harding, H.; Isaksson, R.; Westerlund, C. *Eur. J. Pharmacol*., **1986**, 357.
[76] Şimşek, R.; Şafak, C.; Erol, K.; Ataman, Ş.; Ülgen, M.; Linden, A. *Arzneim. Forsch. Drug Res*., **2003**, *53*(3), 159.
[77] Rose, U. Pharm. *Acta Helv*., **1990**, *65*(7), 178.
[78] Rose, U. Pharm. *Acta Helv*., **1991**, *66*(3), 68.
[79] Rose, U. *J. Heterocycl. Chem*., **1990**, *27,* 237.
[80] Thomas, G.; Gross, R.; Schramm, M. *J. Card. Pharm.,* **1984**, *6,* 1170.
[81] Yagupolskii, L. M.; Maletina, I. I.; Petko, K. I.; Fedyuk, D. V. *J. Fluor. Chem.*, **1996,** *80*, 3.
[82] Ragno, G. *J. Pharm. Biomed. Anal.,* **2002**, *27,* 19.
[83] Mielcarek, J.; Şafak, C.; Şimşek, R.; Matloka, A. *Arch. Pharm. Pharm. Med. Chem.*, **2002**, *2,* 77.
[84] Mielcarek, J.; Matloka, A. *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci*., **2005**, *819,* 17.
[85] Guengerich, F. P. *J. Biol. Chem*., **1988**, *263*(17), 8168.
[86] Guengerich, F. P.; Brian, W. R.; Iwasaki, M.; Sari, M.; Bäärnhielm, C.; Berntsson, P. *J. Med. Chem*., **1991**, *34,* 1838.
[87] Kann, J. *J. Cardiovasc. Pharmacol.,* **1984**, *6,* 968.
[88] Funaki, T.; Soons, P. A.; Guengerich, F. P.; Breimer, D. D. *Biochem. Pharmacol*., **1989**, *38*(23), 4213.
[89] Guengerich, F. P.; Peterson, L. A.; Böcker, R. H. *J. Biol. Chem*., **1988**, *263*(17), 8176.
[90] Guengerich, F. P.; Martin, M. V.; Beaune, P. H.; Kremers, P.; Wolff, T.; Waxman, D. J. *J.Biol. Chem.,* **1980**, *261*(11), 5051.
[91] Mcallister, R.G. *Am. J. Cardiol*., **1985**, *25,* 30B.
[92] Hamann, S.R.; McAllister, R.G. *Clin. Chem.,* **1983**, *29*, 158.
[93] Kleinbloesem, C. H.; van Brummelen, P.; Faber, H.; Danhof, M.; Vermeulen, N.P.E.; Breimer, D.D. *Biochem. Pharmacol.,* **1984**, *33,* 3721.
[94] Love, S.J.; Yeh, K.; Kann, J.; Levitt, M.J.; Reitberg, D.P. *Clin. Pharmacol. Ther*., **1985**, *37,* 209.
[95] Raemsch, K.D.; Sommer, J. *Hypertension,* **1983**, *5,* II.
[96] Kleinbloesem, C. H.; van Harten, J.; Leedde, L.G.J.; van Brummelen, P.; Breimer, D. D. *Clin. Pharmacol. Ther*., **1984**, *36,* 396.
[97] Foster, T.S.; Hamann, S.R.; Richards, V.R., Bryant, P.J.; Graves, D.A.; McAllister, R.G. *J.Clin. Pharm*. **1983,** *23,* 161.
[98] Kann, J.;Krol, G. J.; Raemsch, K. D.; Burkholder, D. E.; Levitt, M. J. *J. Cardiovas. Pharmacol.,* **1984**, *6* (7), 968.
[99] Towart, R. *Arzneim. Forsch. Drug Res*., **1982**, *32*(I), 338.
[100] Meyer H.; Wehinger E.; Bossert F.; Scherling, D. *Arzneim. Forsch. Drug Res.,* **1983**, *33*(1), 106.
[101] Nagasawa, M.; Sasabe, H.; Shimtz, T.; Mori, H. *J. Chromatogr*., **1982**, *577,* 275.
[102] Scherling D.; Bühner K.; Krause H. P.; Karl W.; Wünsche C. *Arzneim. Forsch. Drug Res*., **1991**, *41*(I), 392.
[103] Scherling, D.; Karl, W., Radtke, M., Ahr, H. J., Siefert, H. M. *Arzneim. Forsch. Drug Res.,* **1992**, *42*(II), 1292.
[104] Nayler, W.G. *Calcium Antagonists*, Academic Pres: London, **1988**.

[105] Shah, M. K.; Hugghins, S. Y.; Champion, H. C.; Bivalacqua, T. J. *J. La State Med. Soc.,* **2000**, *152*(7), 334.
[106] Elmslie, K. S. *J. Neurosci. Res*., **2004,** *75,* 733.
[107] Messerli, F. H. *Clin. Cardiol*., **2003**, *26*(2), 12.
[108] Opie, L. H.; Yusuf, S., Kubler. W. *Prog Cardiovasc Dis*., **2000**, *43*(2), 171.
[109] Rosenthal, T. *Kidney Int. Suppl*., **2002**, *82,* 32.
[110] Kim-Mitsuyama, S. *Clin. Calcium*, ***2005***, *15*(1), 81.

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