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Dihydropyridines: evaluation of their current and future pharmacological applications

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The 1,4-dihydropyridines (DHPs), a class of drugs, possess a wide variety of biological and pharmacological actions, have represented one of the most important groups of calcium-channel-modulating agents and have experienced widespread use in the treatment of cardiovascular disease. Moreover, it has been demonstrated that DHPs could prove to be highly important as multidrug-resistance-reversing agents in cancer chemotherapy. Recent reports suggest that this class also has other notable activities, particularly as antimycobacterial and anticonvulsant agents. Finally, it might be possible for the DHP motif to serve as a scaffold for other pharmacological applications.

Introduction

Dihydropyridines (DHPs) represent a group of small organic compounds based on a pyridine core. Theoretically, five isomeric DHPs can exist; but actually, most of the recognized DHPs have either the 1,2-dihydro or the 1,4-dihydro structure [1]. DHPs have a broad range of pharmacological actions as agents in vasodilation, bronchodilation, hepatoprotection and geroprotection and as antiatherosclerosis, antidiabetes, antitumor, antimutagenic, antioxidant, anticonvulsant and antiradical agents [2].

Although DHPs were primarily developed as cardiovascular agents, several have been used for other medical applications. For example, nimodipine is used as an anti-ischemic agent in the treatment of Alzheimer's disease and other dementias, migraine and posthemorrhagic vasospasm [3]. Nifedipine is also used in the treatment of migraine, hypertrophic cardiomyopathy and Raynaud's phenomenon [4]; it could also be used in the treatment of diabetic neuropathy. The platelet antiaggregatory DHP series, including trombodipine, have protective effects against *Listeria monocytogenes*. Dexniguldipine is a chemosensitizer with low hypotensive properties. It is clear that the new generation of DHP derivatives are a potential source of valuable drug candidates with remarkable potential and ongoing interest [5].

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Calcium channels and calcium-channel blockers

Calcium is a ubiquitous second messenger that plays key parts in numerous physiological functions. Calcium entry into the cytosol is mediated by multiple types of calcium channel, each with a distinct physiological role [6]. At least five different types of voltage-dependent Ca^{2+} channel (VDCC) exist in electrically excitable mammalian cells. These channels have major roles in both normal functioning and in pathologies affecting neuronal, neurosecretory and muscle cells [7]. It has become apparent that in several tissues – including certain cardiac muscle cells and, subsequently, neurons and other excitable cells – there are two types of calcium current. One is activated by small depolarizations and shows rapid voltage-dependent inactivation; this is termed 'low-voltage activated', or 'T' (for transient). The second is activated by large depolarization and is termed 'high-voltage activated' (HVA). HVA channels have been classified into N, L, P, Q and R types [8,9]. L-type channels are highly sensitive to DHPs and are typically confined to cell bodies, where they probably regulate calcium-dependent enzyme, gene expression and, in muscle cells, contractility [6].

It has been demonstrated that a special feature of L-type calcium channels (LCCs) is their unique response to therapeutically useful calcium entry blockers, such as DHPs (e.g. nifedipine), phenylalkylamines (e.g. verapamil), and benzothiazepines (e.g. diltiazem), and the exceptional DHP channel activators (Bay K 8644, RS30026, CGP 28392 or Bay K 5959) [10]. The binding domains of these

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drugs have been probed extensively by radiolabeled ligands in particulate and purified Ca^{2+} channel preparations [11]. Because the three-dimensional structure of the human LCC is not available, theoretical models of this channel and docking calculations of ligands have been developed to identify new, potent and selective LCC ligands [12–14].

DHPs as Ca^{2+} channel blockers

Very soon after the development of the type **1a** (Fig. 1) DHPs, which were characterized by their vasodilator activity [15], Fleckenstein *et al.* found that such compounds act by blocking the entry of Ca^{2+} ions into cardiac and vascular muscle cells via VDCCs [16].

The 2-nitrophenyl derivative **1b** (Fig. 1) was successfully introduced in Germany at the beginning of 1975 for the treatment of coronary disease as nifedipine **1b** (Adalat®) [2].

DHPs are a known class of calcium antagonists, which are among the most frequently used drugs for the treatment of cardiovascular diseases [17]. Resembling the other calcium-channel blockers, the predominant pharmacological effects of DHPs are coronary, peripheral and cerebral vasodilation; negative inotropic effect; and inhibition of excitation of sinoatrial and atrioventricular nodes [18]. These effects explain their remarkable therapeutic value in angina pectoris, hypertension, posthemorrhagic cerebral vasospasm and supraventricular tachycardia [18]. Although the DHPs are still the most potent group of calcium-channel blockers, there are many efforts to prepare additional cardioselective compounds, and many drugs are currently under clinical investigation [5].

Dihydropyridine partial agonists

Glossmann *et al.* [19] reported that derivatives of DHP containing 3,5-dicarboxylic acid esters might exhibit a spectrum of activity toward the calcium channel somewhere between the extremes of antagonism and agonism. Soon after, Matowe *et al.* [20] described the pharmacological properties of AK-2–38 **1c** (Fig. 1), a C-4 2-pyridinyl DHP analog that exhibited twice the potency of nifedipine on smooth muscle. In the dosage range that inhibited smooth muscle, AK-2–38 exhibited partial agonism on cardiac muscle. This high differential activity could be therapeutically beneficial as an antihypertensive agent, especially in the treatment of congestive heart failure [20]. Compounds with the above properties are also known as 'dual cardioselective calcium-channel agonist–smooth muscle selective calcium-channel antagonists' (alternatively, as 'dual-acting agents', or 'third-generation DHPs') [21].

Structure–activity relationship (SAR) studies of these compounds have revealed that although C-4 2-pyridinyl isomer acts as a dual-acting agent, the 3-pyridinyl and 4-pyridinyl isomers were calcium-channel agonists on both heart and smooth muscle [22]. Therefore, the position of the pyridinyl nitrogen-free electron pair and/or charge distribution on the pyridinyl might be important determinants of calcium-channel agonist–antagonist modulatory effects [23]. Accordingly, it was determined that DHPs possessing a C-4-appropriate thienyl isomeric substituent also exhibited desirable calcium-modulating effects [10].

Other studies indicate that dual-acting derivatives can be obtained by introducing the DHP structure into condensed ring systems [2]. Some examples are given in Fig. 2. Racemic hexahydroquinolines, fluroquinolines and indenopyridines exhibited calcium-antagonistic effects on smooth muscle and positive inotropic activity on electrically stimulated guinea pigs' atria [24]. The lactone derivatives also show agonist–antagonist properties [2].

Combination of DHPs with organic nitrates

It has been demonstrated that organic nitrate compounds activate guanylate cyclase to increase cGMP (cyclic guanosine monophosphate) in various smooth muscle tissues and promote relaxation

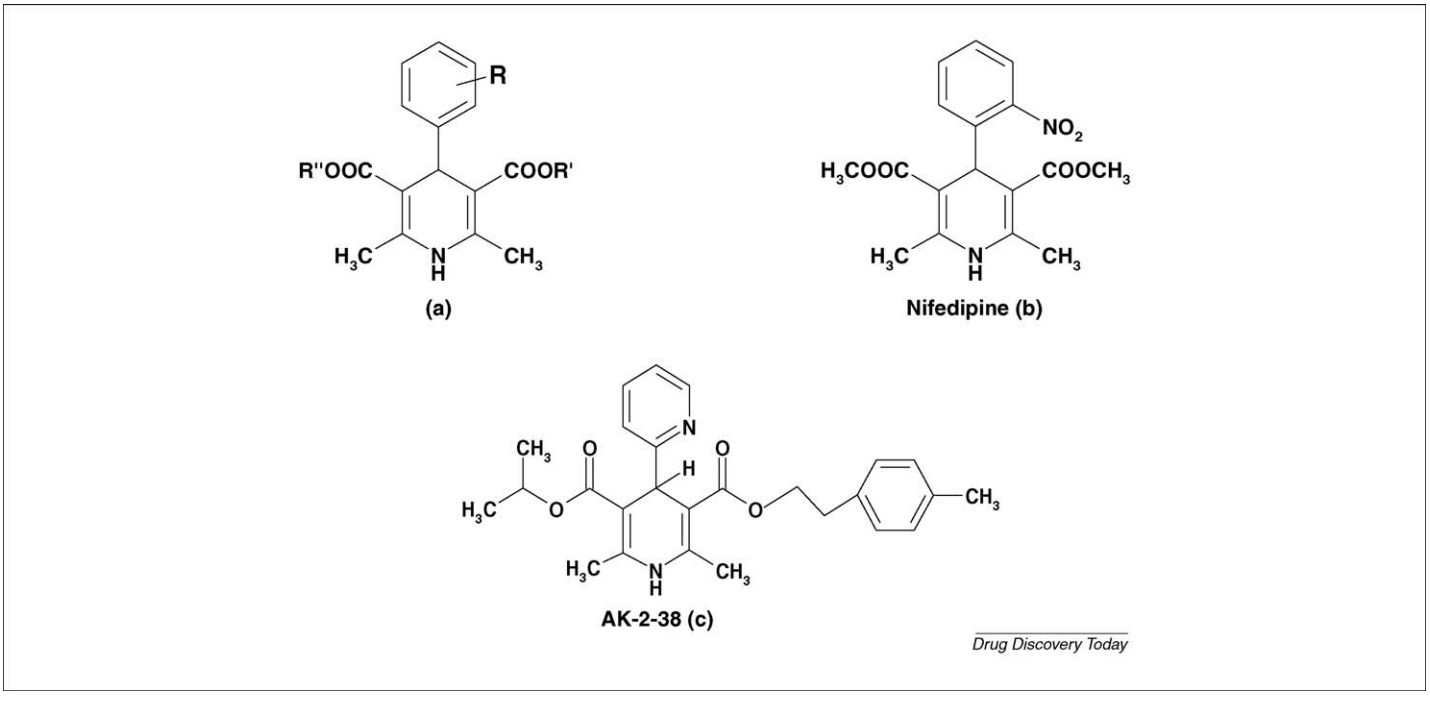

FIGURE 1

Structure of some 1,4-dihydropyridines.

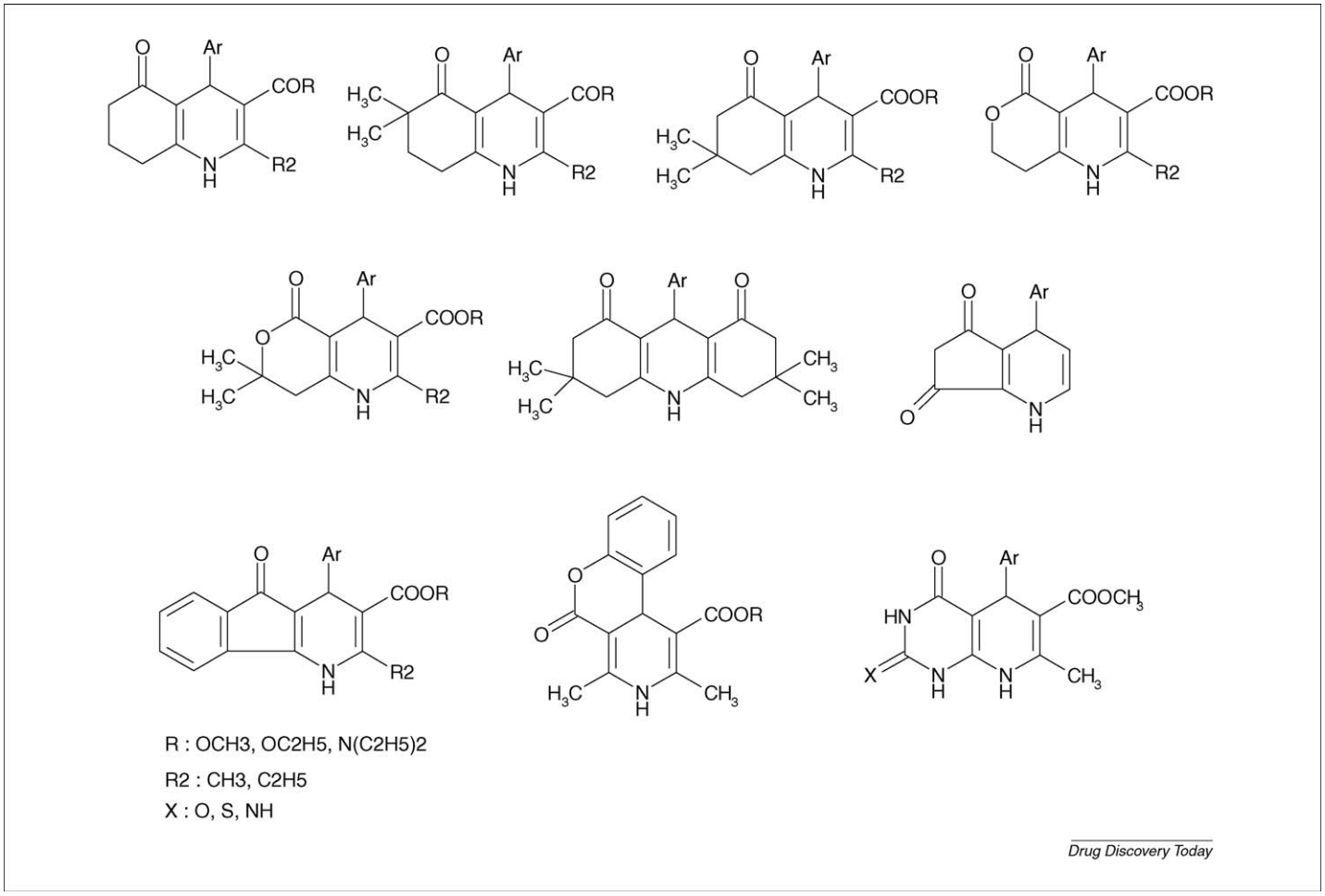

FIGURE 2

Structures of some fused DHPs [2].

[25]. Therefore, various studies have indicated that the concomitant use of calcium antagonists and nitrate compounds could enhance antihypertensive action with few side-effects [26]. Ogawa *et al.* [27] reported that combination of nitrate-like and calcium-blocking agents in a single molecule would be expected to have a potential vasodilating activity superior to that of known DHPs. Different studies designed DHP compounds with nitrooxy substitution at the C-3 and C-5 ester positions of the DHP ring that showed more *in vitro* activity than similar compounds lacking nitrooxy substitution. This is probably because those compounds possessing a nitrooxy moiety could also serve as nitric oxide donors, thus inducing vascular muscle relaxation [26,27].

SAR of 1,4-dihydropyridine as calcium-channel-blocking agents

Since the introduction of DHPs into clinical medicine, they have become almost indispensable in the treatment of cardiovascular disease. More than 30 years after the introduction of nifedipine, many DHP analogs have been synthesized and numerous second-generation commercial products have appeared on the market with superior bioavailability and a slower onset and longer duration of action. Such compounds include nimodipine, nisoldipine, nitrendipine, amlodipine, felodipine, isradipine, manidipine, nicardipine and nilvadipine [28] (Fig. 3). For example, amlodipine is a DHP with slow absorption and prolonged effect. There is less reflex tachycardia with amlodipine, possibly because the long half-life reduces the plasma concentration peaks and troughs. Felodipine seems to have even greater vascular specificity than either nifedipine or amlodipine. At concentrations producing vasodilation, there is no negative inotropic effect. Nisoldipine is more than 1000 times as potent in preventing contraction of human cardiac muscle *in vitro*, suggesting a very high degree of vascular selectivity. Nimodipine, because of its high lipid solubility, was developed as an agent to relax the cerebral vasculature [29].

DHP calcium-channel antagonists of the nifedipine type are flexible molecules, in which the C-4-aryl moiety and the C-3 and C-5 ester substituents can rotate and the conformation of the 1,4-DHP ring can change [15]. Despite many studies on the SARs of DHPs with respect to calcium-channel antagonist–agonist modulation, there still remains debate on the exact stereochemical and/or conformational requirements for activity [30].

SAR studies of DHP derivatives show that the following structural features are important for their Ca^{2+}-channel-blocking activity:

(i) The nature and position of C-4-aryl ring substituents optimizes activity. Phenyl is preferred, owing to animal toxicity observed with heteroaromatic rings. The pseudoaxial conformation of C-4 aryl ring is also important [31–33].

(ii) The 1,4-DHP ring is essential for activity because it is necessary for hydrogen bonding. Substitution at the N-1

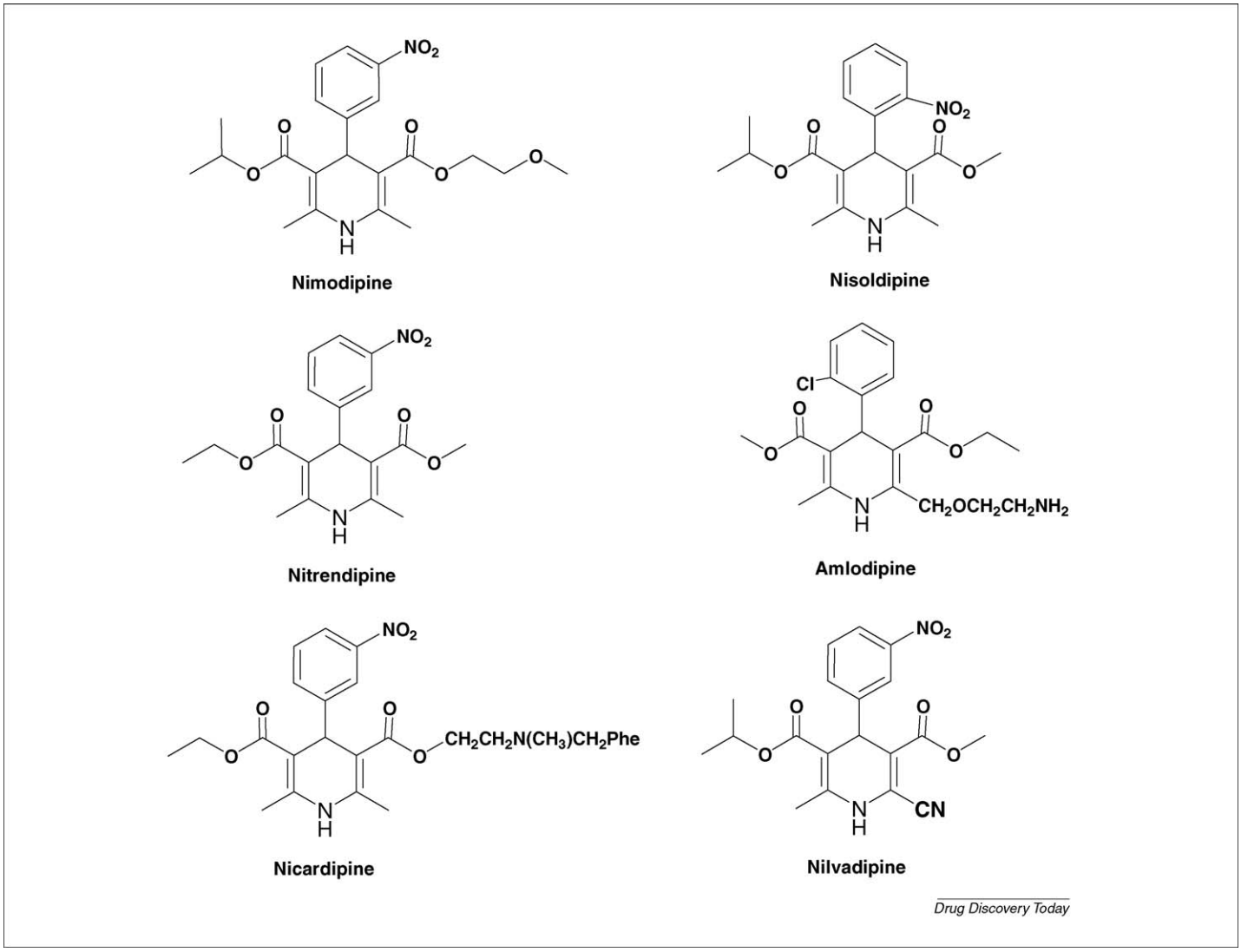

FIGURE 3

Structures of some of the commercially available DHPs.

position or the use of oxidized (piperidine) or reduced (pyridine) ring systems greatly decrease or abolish activity [31]. Dagnino *et al.* [34] have shown that nifedipine and related analogs exist in a boat conformation. Conformational analysis of DHPs by AM1 and MM+ calculations, however, has indicated that protonation of the DHP ring nitrogen results in a slight deviation of the boat-like conformer of the protonated DHPs from the planarity and produces a twist-like conformation [35].

(iii) C-3 and C-5 substituents modulate activity and tissue selectivity [22,33]. It has been shown that asymmetrical substituents in C-3 and C-5 alter the activity [36]. In fact, it has been observed that the electronic features of the oxygen of the carboxyl ester group influenced biological activity. Carbonyl oxygen participates in hydrogen bonding with the receptor [37]. Molecular orbital conformational calculations suggest that in DHPs, both carboxy groups are preferentially oriented in a plane that intersects the plane of the DHP ring with an angle of between 30° and 60° [37]. In addition, it has been proposed that based on the orientation of the individual carbonyl groups of the C-3 and C-5 ester substituents with respect to the DHP ring double bond, three different conformations are, in principle, possible for the ester groups: *trans*/*trans*, in which the carbonyl groups of the both esters are *trans* to the double bond of DHP (Fig. 4a); *cis*/*cis*, with a *cis* arrangement of both carbonyl groups (Fig. 4c); and enantiomeric *cis*/*trans* and *trans*/*cis* arrangements (Fig. 4b) [15,35]. X-ray structural investigations, theoretical calculations and *in vitro* analyses of fused 1,4-DHPs (compounds with an immobilized ester group) indicate that at least one ester must be in the *cis* arrangement, which is necessary for hydrogen bonding to the receptor [15].

In addition, it has been suggested that synperiplanar carbonyl groups might be a common feature of DHP calcium-channel antagonists and that an antiperiplanar carbonyl group, such as the lactone group in the rigid compounds, might be a requirement for calcium-channel agonist activity [33] (Fig. 5).

(iv) When the esters at C-3 and C-5 are nonidentical, C-4 carbon becomes chiral and stereoselectivity between enantiomers is observed [38].

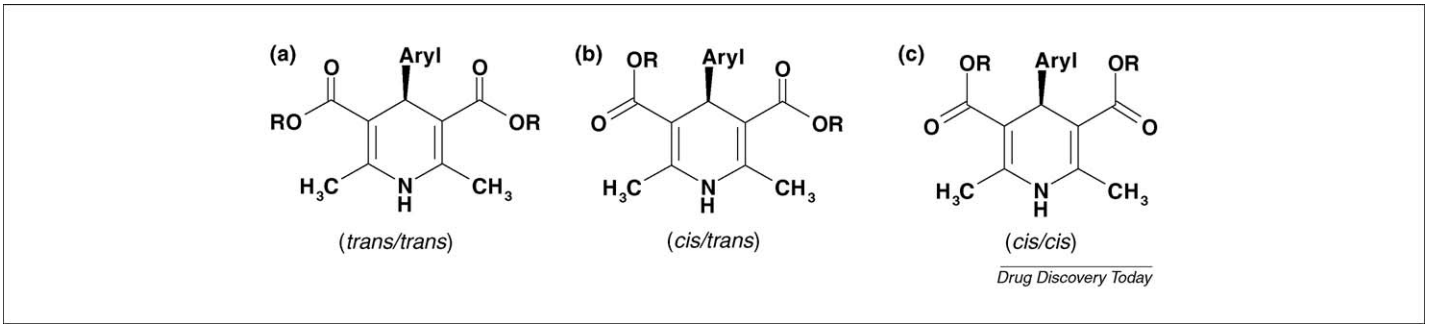

FIGURE 4

Representation of different conformations of the ester groups as determined by X-ray structural analysis [15].

(v) DHP receptor can tolerate different changes at C-2 and C-6 substituents, and modified activity can be obtained by altering these groups [33,36].

As mentioned above, in unsymmetrical DHPs, C-4 is a chiral center. It was proposed that calcium-channel modulation (antagonist versus agonist activity) is dependent on the absolute configuration at C-4, whereby the orientation of the 4-aryl group (*R*-versus *S*-enantiomer) acts as a 'molecular switch' between antagonist and agonist activity [30,39]. In addition, if larger lipophilic ester groups are replaced by smaller groups having a negative potential (e.g. nitro group), the C-4 will be the point of chirality and the resulting individual enantiomers of DHP racemates have exactly the opposite pharmacological effect [15]. Instead of blocking the entry of calcium into cardiac and vascular muscle, these derivatives enhance it. Therefore, these derivatives are known as 'calcium agonists', or 'calcium-channel activators' [15]. Bay K 8644 and PN 202–791 are the most well-known examples of calcium-channel activators [2,15]. These results indicate that racemic Bay K 8644 acts as a calcium-channel agonist on both smooth and cardiac muscle; the (−)-(*S*)-enantiomer is approximately tenfold more potent as an agonist than the (+)-(*R*)-enantiomer that acts as an antagonist [40].

QSARs of DHPs

The DHP-class of compounds has been the aim of many quantitative structure–activity relationship (QSAR) studies to find the most important quantitative parameter for optimal activity of these compounds. Coburn *et al.* [10] have applied the Hansch analysis method to a series of 4-phenyl-substituted DHPs. They concluded that the biological activity of DHPs is dependent on the lipophilic, as well as the electronic and steric properties, of the substituents on 4-phenyl DHP analogs of nifedipine [10]. Mahmoudian and Richard have conducted a Hansch analysis on a small number of the same DHPs and found that bulky and lipophilic groups at the *ortho*-position and bulky groups with high Hammet electronic constant (σ) at the *meta*-position of the 4-phenyl ring increase the DHPs' activity. They also concluded that the potency of DHPs decreases with the increase in minimum width (B1) or length of substituents at the *para*-position, and optimal values were found to be those for hydrogen [41,42]. Gaudio *et al.* [43] have reported a QSAR study on a large number of 4-phenyl-substituted nifedipine analogs by the combination of substituent constants and molecular descriptors. They found that the activity of *meta*-substituted compounds is affected by both steric and electronic parameters, whereas the hydrophobic and electronic parameters of the *para*-substituted DHPs affect the drug's activity. Hemmateenejad *et al.* [44] also used Hansch analysis for those nifedipine analogs containing nitroimidazolyl, phenylimidazolyl and methylsulphonylimidazolyl groups at the C-4 position and different ester substituents at C-3 and C-5 positions of DHP ring and showed that Hammett's electronic and hydrophobic properties are highly correlated with the biological activity. Different linear and nonlinear methods have been used in QSAR studies (Non-3D, also known as classical QSAR) of DHP analogs to obtain additional and more precise parameters that are important for the biological activity of these compounds. Partial least squares [45] and principal component artificial neural network [46] were employed, using theoretically derived descriptors for different DHP analogs. In addition, the quantum chemical QSAR study of these compounds indicated the importance of electronic features of the DHP derivatives for receptor binding [47].

Compared with classical QSAR investigations, 3D QSAR approaches yield better results for the correlation of the internal dataset and prediction of test set DHP derivatives. Different 3D QSAR approaches have been conducted to simplify the design of optimized DHP derivatives with increased calcium antagonist activity. 3D QSAR study (comparative molecular field analysis and comparative molecular similarity studies) of 4-phenyl-substituted DHPs indicates unfavorable steric interactions for bulky moieties in the *para*-position of the phenyl ring and that bulky substituents are favorable in *ortho*- and *meta*-positions. The best combination is obtained when the bulky substituents at *ortho* or *meta* produce negatively charged electrostatic potential. In addition, this study indicated that repulsive electronic interaction with binding-site residue or to the potential of electron-deficient 4-aryl

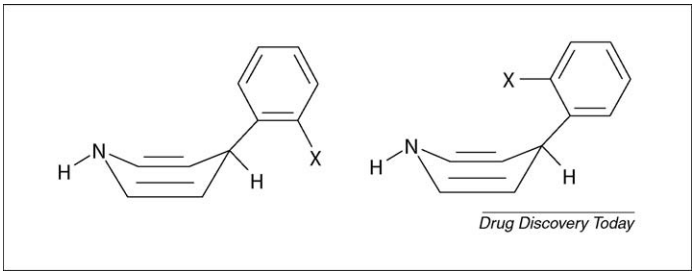

FIGURE 5

Definitions of synpreplanar (*sp*) and antiperiplanar (*ap*) rotamers. Substituents on the DHP ring omitted for clarity.

moieties behave as electron acceptors in charge transfer mechanism [48].

DHPs and MDR

Multidrug-resistance (MDR) is defined as resistance of a tumor cell to the cytostatic or cytotoxic action of different drugs with no structural resemblance to those commonly used in chemotherapy. Such resistance is considered to be one of the key reasons for the breakdown of chemotherapy for the majority of cancer patients. In the early 1980s, it was found that calcium-channel blockers can be MDR-reversing agents [49]. Tsuruo *et al.* [50] showed that DHPs have inhibitory effects on MDR in cancer cell lines. As a result, Philip *et al.* performed clinical trials with nifedipine in the 1990s. The clinical trial failed, however, owing to very poor outcome (6% response, 1 patient out of 15); moreover, the cardiotoxicity of nifedipine was dose-limiting [51]. These constraints resulted in the development of a new generation of DHPs that are labeled second-generation MDR reversers. In their development, two aims were paramount: to increase the MDR-reversing effect and notably reduce the Ca^{2+}-channel-blocking activity, which in this case is seen as an adverse effect. Some of these modifications are shown in Table 1 [52–57]. In this way, some lead compounds were introduced, which were effective in classical MDR (ATP-binding cassette, or ABC, transporter-mediated MDR) that are currently in preclinical studies. For example, Kuwano and his group prepared many derivatives of DHP as P-glycoprotein-mediated MDR-reversing agents. Most of the reported compounds have pyridyl group on 3,5 positions [57]. In addition, Zhou *et al.* synthesized some derivatives based on structure optimization of dexniguldipine, which were effective on P-gp, MRP (Multiple Drug Resistance Protein) and BCRP (Breast Cancer resistance Protein)-associated MDR [58–60]. A central point in most studies is that they have included general considerations recommended by Ford. Ford *et al.* showed that some drug categories exposed structural features effective in the reversal of MDR. They demonstrated that compounds with tertiary amines were better anti-MDR agents than those with secondary or primary amines. In addition, cyclic amines resulted in greater activity. Therefore, they concluded the importance of tertiary and cyclic amino groups in the reversal of MDR [61].

However, very recently, we published two reports that showed the effect of DHPs on atypical MDR, in which some newly synthesized derivatives had good effects on MDR reversal in HL60/MX1 cell line. It was shown that this cell line exhibits MDR in the absence of P-glycoprotein. Its MDR mechanism is postulated to be mediated by altered topoisomerase II activity or level. Some compounds could reduce the IC_{50} of mitoxantrone more than tenfold, which indicates their high potency against atypical kinds of MDR [62,63]. These findings showed that DHPs might have the ability to reverse atypical MDR, in addition to their capability in modulating ABC transport-mediated MDR (classical MDR). Therefore, a general SAR that considered all aspects of MDR activity simultaneously gave a comprehensive pharmacophore that might be effective on several MDR targets [64].

Other therapeutic applications

Although the DHP nucleus has been particularly well explored as L-type calcium channel modulator, DHP is a privileged structure or scaffold that can, when appropriately decorated, interact at diverse receptors and ion channels, including potassium and sodium channels and receptors of the G-protein class [65]. Nifedipine blocks the Ca^{2+}-activated K^+ transport in human erythrocytes and (+)-niguldipine activates Ca^{2+}-dependent, large-conductance potassium (BK_{Ca}) channels in human mesenteric vascular smooth muscle. Various DHP-like structures were detected that activate KATP channels in bladder, and these structures are candidates for urinary incontinence [66].

Recent studies have demonstrated that several widely used DHP-class calcium-channel blockers are able to inhibit

TABLE 1

Different structure–activity relationships (SARs) of DHP and their relevance to various types of MDR and also their effect on Ca^{2+} channel-blocking activity[a]

Modifications	Effects				Refs
	P-gp-mediated MDR	Other transporter-mediated MDR[b]	Atypical MDR	Decrease in Ca-channel-blocking activity	
1 Position					
Addition of acyloxy group to N_{DHP}	+	ND	ND	+	[57]
2,6 Positions					
Deletion of methyl's from C-2,6	++	ND	ND	++	[56]
3,5 Positions					
Presence of pyridyl group on C-3,5 positions	+++	ND	++	++	[57,63]
Presence of 4,4-diphenyl piperidine group on C-3,5 positions	+++	+++	ND	++	[58–60]
Conversion ester group on C-3,5 positions into acetyl group	++	ND	ND	++	[53,55]
4 Position					
Presence of dithiene group on C-4 positions	++	ND	ND	+	[57]
Presence of dioxene group on C-4 positions	++	ND	ND	–	[57]
Presence of nitroimidazolyl group on C-4 positions	++	ND	ND	+	[62,63]
Alkyl chain at 4-position	ND	ND	++	++	[57]
Others					
Cage-dimeric DHP	+	ND	ND	+	[54]

[a] Updated from Ref. [64]. Abbreviation: ND, not determined.
[b] Other ABC transporters, such as MRP and BCRP.

aldosterone-induced activation of mineralocorticoid receptor in high doses. These DHPs varied in the extent of their effects on mineralocorticoid receptor; nimodipine and felodipine were the most potent and amlodipine the least. This finding might prove useful for the design of novel antihypertensive drugs with good potency at both calcium channel and mineralocorticoid receptor [67].

Some observations have shown that Ca^{2+} channel agonists could induce seizure in a dose-dependent manner, pointing to the potential value of Ca^{2+} channel antagonists as a novel class of anticonvulsant agents. In addition, some experiments have shown synergistic effects of DHPs with some anticonvulsant drugs, such as carbamazepine [68,69].

Certain derivatives of DHPs can bind to the A_1, A_{2A} and A_3 subtypes of adenosine receptors. Some newer derivatives, however, are selective for the A_3 subtype; for example, the *S*-enantiomer of niguldipine is totally inactive at the A_1 and A_{2A} receptors, yet it can bind to human A_3 receptors with a k_i of 28 μm [70,71].

Recent studies have demonstrated that 4-aryl-1,4-DHPs containing lipophilic dicarbamoyl groups on the C-3 and C-5 position of the DHP ring have considerable antitubercular activity against *Mycobacterium tuberculosis* H37Rv [72]. Other studies developed the new DHP derivatives containing diethyl carbamoyl and ester substituents on C-3 and C-5 and a nitroimidazolyl group on the C-4 position of the DHP ring (nitroimidazolyl derivatives have been demonstrated to be potential antitubercular agents, especially against resistant strains). Aryl ester analogs of these derivatives (especially the 3-phenylpropyl ester analog) exhibited comparable antitubercular activity against *M. tuberculosis* H37Rv with the reference drug isoniazid and minimal calcium-channel-blocking activity [73].

Some highly lipophilic derivatives of DHP were developed by Bodor in an attempt to increase the selective delivery of drugs to the brain [74]. In addition, Yiu and Knaus [69] coupled some derivatives of DHP to valproic and valeric acid for delivery to the brain. El-Sherbeny *et al.* [75] used this method for delivery of cytotoxic drugs into the brain based on a 1,4-dihydropyridine ⇌ pyridinium salt-type redox system.

DHPs reduced hyperglycemia considerably, improved glucose metabolism and increased insulin sensitivity in diabetic rats. In addition, administration of nisoldipine in streptozocin-induced diabetes lowers the blood glucose level by peripheral vasodilation and increased glucose turn over. Moreover, it was reported that nifidepine has an inhibitory effect on TNF-α-induced neovascularization in streptozocin-induced diabetic rats [76,77].

Several DHP derivatives have been found to have bronchodilatory, vasculoprotective, hepatoprotective, antiplatelet and antifungal properties [78]. They have also shown analgesic properties, as well as antioxidant activity and inhibition of GABA receptors [79].

Concluding remarks

DHP is an important scaffold with a wide range of biological features. 4-Aryl-DHPs of the nifedipine type with special structural and conformational requirements – including the flat boat conformation of the DHP ring, the nature and pseudoaxial orientation of the C-4-aryl group and so on – are considered to be one of the most important classes of calcium-channel-modulating agents with widespread use in the treatment of cardiovascular disease. Other studies have demonstrated that DHPs could prove to be important as MDR-reversing agents in chemotherapy. Therefore, numerous efforts have been made to describe optimal structural requirements to increase the latter effect and decrease calcium-blocking activity.

Although we have concentrated on the importance of the scaffold in cardiovascular disease and MDR, many other effects (such as their anticonvulsant properties and actions as antimycobacterial agents) have been reported. In addition, the oxidizable and lipophilic property of the DHP ring enabled it to be modified to allow delivery to the brain. It is speculated that the DHP ring could represent a potential starting point for the development of drugs with varied pharmacological applications.

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