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QSAR Studies on Calcium Channel Blockers

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Abstract Calcium channel blockers (CCBs) have potential therapeutic uses against several cardiovascular and non-cardiovascular diseases. For vasospastic angina, CCBs have been found to be the most effective drugs. These drugs selectively inhibit Ca^{2+} influx into heart muscles by blocking slow inward channels for Ca^{2+} or inhibit Ca^{2+} influx into vascular smooth muscles. The result is negative inotropism of smooth muscle relaxation, which is translated into hypotension. The three principal structural classes have been found to act as potent calcium channel blockers and they are phenylalkylamines, 1,4-dihydropyridines (DHPs), and benzothiazepines. Recently, a few more classes of CCBs have been studied. This article presents a comprehensive review on quantitative structure-activity relationship (QSAR) studies on all kinds of CCBs. These QSAR studies highlight the essential structural features and physicochemical properties that the compounds should possess to act as potential CCBs and vividly describe the mechanism of interaction of CCBs with the calcium channel.

Keywords Calcium channel blockers ·
Quantitative structure-activity relationship · Phenylalkylamines · 1,4-Dihydropyridines · Benzothiazepines · Verapamil · Nifedipine · Diltiazem · Dihydropyrimidines · Phenylsulfonylindolizines

Abbreviations

CCBs	calcium channel blockers
CoMFA	comparative molecular field analysis
DHPs	1,4-dihydropyridines
QSAR	quantitative structure-activity relationship
SAR	structure-activity relationship

1 Introduction

Calcium is well known to play critical roles in cellular communication and regulation. The critical role of cellular Ca^{2+} was recognized early by Ringer [1], who noted its essential role in cardiac excitation-contraction coupling. Equally, the significance of the pharmacological regulation of cellular Ca^{2+} was recognized by Fleckenstein [2]. Calcium in excess is a lethal cation, however, and uncontrolled involvement of Ca^{2+} subsequent to cellular insult or injury can lead to irreversible cell destruction and death [3]. It is anticipated that the cellular movements and storage of Ca^{2+} will be subject to a variety of regulatory processes, though all of which may not assume equal importance in every cell type or during every stimulus.

The calcium channel may be viewed as a pharmacological receptor with several specific sites with which a variety of drugs may interact. However, Fleckenstein and coworkers drew attention to a chemically heterogeneous group of agents that served as electrochemical uncouplers in the heart and whose effects were mimicked by extracellular Ca^{2+} withdrawal. These fundamental properties, extended in understanding through more detailed biochemical and electrophysiological studies [4], have served to define a group of drugs with particular chemical utility in the cardiovascular diseases. Such studies led to definition of the site of action of these agents as the L class of voltage-gated Ca^{2+} channels and to localize their site of action as the α_1-transmembrane protein [5, 6]. There exists several other classes also of voltage-gated Ca^{2+} channel, such as T, P, N, etc., distinguishable from each other by biochemical, electrophysiological, and pharmacological characteristics [7].

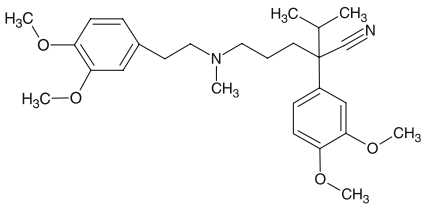
Calcium channels are expected to possess the following general properties [6]: (1) specific binding sites for both activator and antagonist ligands, and the possible existence of an endogenous species; (2) coupling of the binding sites to the permeation and gating machinery of the channel; (3) association with regulatory guanine nucleotide binding proteins; (4) regulation by homologous influences; and (5) alteration of expression and function in disease states. Except for the discovery of an endogenous species [8], all other properties have been largely found to be associated with the L class of voltage-gated channels [9, 10].

2 Calcium Channel Blockers

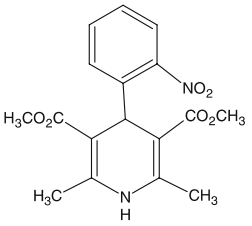
The three principal structural classes of compounds have been found to bind with the L subclass calcium channel, and they are phenylalkylamines, 1,4-dihydropyridines, and the benzothiazepines, of which the protypical rep-

resentatives are verapamil (**1**), nifedipine (**2**), and diltiazem (**3**), respectively. For the treatment of vasospastic angina, the calcium channel blockers (CCBs; also called calcium channel antagonists) have been found to be the most effective. These drugs selectively inhibit Ca^{2+} influx into the heart muscles by blocking the slow inward channels for Ca^{2+} or inhibit Ca^{2+} influx in the vascular smooth muscle. The result is negative inotropism of smooth muscle relaxation, which is translated into hypotension. Calcium channel blockers are economically and therapeutically important for the treatment of several cardiovascular diseases, such as angina, hypertension, arrhythmias, etc. (Table 1). Besides, they are also useful for the treatment of several non-cardiovascular diseases, such as asthma, dysmenorrhea, premature labor, and several miscellaneous ailments such as cancer, epilepsy, glaucoma, etc. (Table 1) [5].

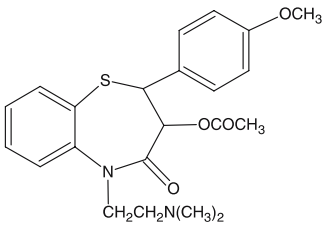
Thus, the calcium channel blockers are a major therapeutic group of agents that interact preferentially with the L class of voltage-gated channel. Their varying therapeutic actions are due to mainly the existence of several sites at



1(verapamil)



2 (nifedipine)



3 (diltiazem)

Table 1 Potential therapeutic uses of calcium channel blockers [6]

Cardiovascular	Non-cardiovascular	Other
Angina	Achalasia	Aldosteronism
Atherosclerosis	Asthma	Cancer chemotherapy
Cardioplegia	Dysmenorrhea	Epilepsy
Cerebral ischemia	Eclampsia	Glaucoma
Hypertension	Esophageal spasm	Tinnitus
Congestive heart failure	Intestinal hyperacidity	Manic syndrome
Migraine	Premature labor	Vertigo
Peripheral vascular diseases	Urinary incontinence	Motion sickness
Pulmonary hypertension	Obstructive lung disease	Tourette's syndrome
Subarachnoid hemorrhage		Spinal cord injury
Tachyarrhythmias		Antimalarial drug resistance

the L channel and the ability of these drugs to have state-dependent interaction according to the membrane potential and stimulus frequency. Analysis of the structural requirements that determine affinity and voltage dependence is important for the design of potent drugs of desired selectivity.

3 Selectivity of Calcium Channel Blockers

The calcium channel blockers are a group of drugs that exhibit a major selectivity of action both between and within structural classes. This selectivity arises from a variety of factors, such as pharmacokinetics (absorption, distribution, and metabolism), mode of Ca^{2+} mobilization (voltage-gated channel, intracellular stores, or other sources), class and subclass of voltage-gated Ca^{2+} channels modulated, state-dependent interactions (frequency and voltage dependence), and pathological state (homologous and heterologous influence on channel expression and function [5]). Of these, the state-dependent interaction of drug actions at ion channels and its significance have been explained in the terms of the modulated receptor hypothesis [4, 6, 11]. The concept of state-dependent interaction is critical to the interpretation of structure-activity relationships (SARs), because it indicates that (a) drugs may bind selectively to different channel states and many have preferential access pathways to these states and (b) drugs may exhibit qualitatively different SARs according to the channel state with which they preferentially interact.

The state-dependent interactions are critically related to the molecular features of the drugs and thus the determination of the molecular features of the compounds that would favor the state dependence of the interactions can fa-

cilitate the design of the drugs with selectivity enhanced, or reduced, to their voltage-dependent interactions.

4 Molecular Features Essential for Ca^{2+} Channel Blocking Action

Among the three principal classes of compounds acting on the calcium channel, the 1,4-dihydropyridines (DHPs) have attracted particular attention since they act both as calcium channel blockers and activators. Several SAR studies are available for 1,4-dihydropyridine antagonists, but such studies on activators are limited [12, 13]. It has been proposed that the active conformation of 1,4-dihydropyridine includes a 1,4-dihydropyridine ring in a flattened boat confirmation with the 4-phenyl group orientated in a pseudoaxial confirmation [14]. An early study of Loev et al. [15] on in vivo hypotensive activity of a series of 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyiridines led to the definition of some basic structural requirements for the antagonist activity of DHPs:

1. Activity increases with 4-substitution in the sequence H < Me < cycloalkyl < heterocyclic < phenyl and substituted phenyl.
2. Substituents in the 4-phenyl ring enhance activity in the order ortho > meta ≫ para. Electron withdrawing substituents in the ortho position are optimum but any substituent in the para position reduces the activity.
3. The 1,4-dihydropyridine ring is essential. Oxidation to pyridine abolishes the activity.
4. The presence of N1–H is essential.
5. Ester groups at the C3 and C5 are optimum. Replacement by other electron withdrawing groups including – CN and – COMe leads to reduction in the activity.

The most important determinants of antagonist activity were, however, indicated to be the 4-phenyl and C3 and C5 ester substituents. These studies of Loev et al. were largely confirmed in a variety of subsequent investigations based on in vitro pharmacological and radioligand bind approaches [4].

The high activity of 4-phenyl-DHPs was in fact attributed to their conformational properties, in which the aryl ring was supposed to have perpendicular orientation relative to the 1,4-dihydropyridine ring [15]. The 1,4-dihydropyridine ring exists as a non-planar boat-shaped structure with the N1 and C4 atoms defining the stern and bowsprit positions (Fig. 1) [16]. The phenyl ring is bound to it at a pseudo axial position and approximately bisects the pyridine ring. The rotational freedom of the phenyl ring about the C4-C1′ bond is sterically restricted and the plane of the phenyl ring is forced to lie close to the N1–C4 vertical symmetry plane of the 1,4-dihydropyridine ring. This conformation of 4-phenyl-1,4-dihydropyridines is in accordance to the

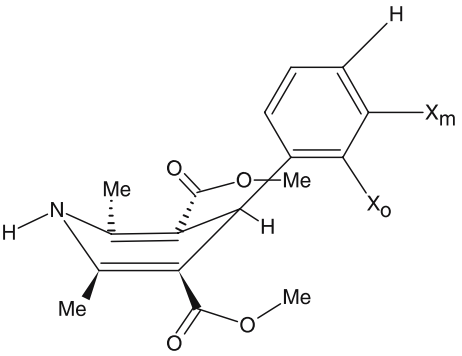
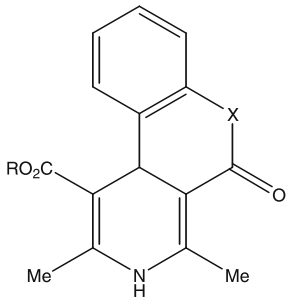


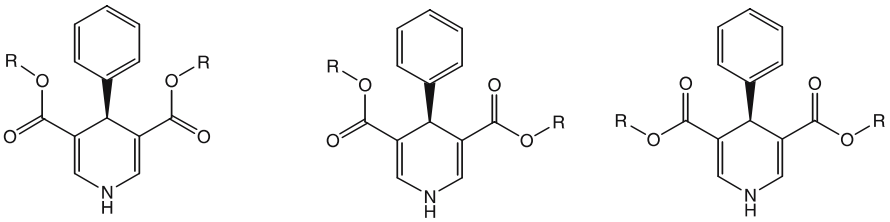
Fig. 1 The molecular geometry of DHP analogues. This geometry was adopted by Gaudio et al. to calculate some quantum mechanical parameters, which they used in their QSAR study [16]. The 1,4-dihydropyridine ring is shown to have a boat-like conformation and the phenyl ring to be bound to it at a pseudoaxial position and approximately bisecting the pyridine ring. From [16]. © 1994 John Wiley & Sons, Inc., reprinted by permission



4; X = O, O–$(CH_2)_{1\text{-}2}$, O–$(CH_2)_{2\text{-}5}$–O

findings of solid-state structural studies [17, 18], which were well supported by the synthesis and activity of rigid analogues [19, 20] and by additional conformational studies [14, 21–23]. In a series of analogues, having a bridge of lactone ring between the phenyl and 1,4-dihydropyridine rings (**4**), the activity was found to increase as the rings approached the perpendicular orientation [19, 20].

The conformations of ester groups have also been found to be crucial for the activity of 1,4-dihydropyridines. Their conformations are defined with respect to the orientation of the carbonyl groups relative to the neighboring C = C bond of the 1,4-dihydropyridine ring. Both the ester groups are always found to be nearly coplanar with adjacent edges of the 1,4-dihydropyridine ring and the carbonyl group can be oriented either cis (*sp*) or trans (*ap*) to the neighboring C = C bond of the ring. Thus, the two ester groups can adopt one of the three conformations (Fig. 2): *cis–cis* (*sp*,*sp*), *cis–trans* (*sp*,*ap*) or *trans–trans* (*ap*,*ap*). It has been observed that ortho-substituted compounds have a



a **b** **c**

Fig. 2 Conformations of ester groups in 1,4-dihydropyridines with respect to orientation of carbonyl group relative to the neighboring C = C bond of the ring; **a** *cis-cis* (*sp,sp*), **b** *cis-trans* (*sp,ap*), **c** *trans-trans* (*ap,ap*)

preference for the *sp,sp* conformation and non-ortho-substituted compounds have generally a preference for the *sp,ap* conformation. Although the relationship between these conformational preferences and the biological activity has not been well established as yet, they support the idea that there are non-equivalent binding sites adjacent to the 1,4-dihydropyridine ring, differential occupancy of which is critical to the determination of the quantitative and qualitative levels of agonist and antagonist activity.

5 QSAR Studies

QSAR (quantitative structure-activity relationship) studies provide the guidelines for making structural changes in the compounds so that drugs of higher potency can be obtained. It tries to explain the variance in biological activities of a given series of compounds in terms of physicochemical and structural properties of the molecules and thus provides a deeper insight into the mechanism of drug receptor-interactions which help tailor the drug to have the optimal interaction with the receptor.

Primarily, the QSAR studies on calcium channel blockers were related to only the 1,4-dihydropyridine class to which belongs nifedipine (**2**). A series of nifedipine analogues (**5**) as listed in Table 2 were studied by Bolger et al. [24] for their calcium channel blocking activity in terms of the molar concentration of drug (IC_{50}) leading to the 50% inhibition of the binding of [^{3}H]nitrindipine to guinea pig ileal preparation.

For this series of compounds, Mahmoudian and Richards [25] showed that the activity of ortho-substituted analogues (including the parent compound 1) had a significant correlation with Verloop's B1 parameter [26], defining the minimum width of the substituent (Eq. 1), and that the activity of meta-substituted analogues (including the parent compound 1) had a significant

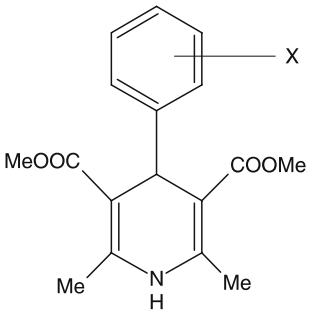


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Table 2 Bolger's data on the binding of nifedipine analogues (**5**) with the receptor and the physicochemical parameters [25]

Compd	X	$\log(1/IC_{50}^{a})$	π	σ	B1	L
1	H	7.85	0.00	0.00	1.00	2.06
2	2-CN	9.18	– 0.33	–	1.60	4.23
3	2-NO_2	9.08	– 0.23	1.24	1.70	3.44
4	2-Me	8.71	0.86	– 0.13	1.52	3.00
5	2-Cl	9.78	0.76	0.68	1.80	3.52
6	2-OMe	7.87	– 0.33	0.00	1.35	3.98
7	2-F	8.44	0.00	0.54	1.35	2.06
8	3-NO_2	9.97	0.11	0.71	1.70	3.44
9	3-N_3	8.67	0.46	0.27	1.50	4.62
10	3-OMe	7.27	0.12	0.12	1.35	3.98
11	3-CN	8.68	– 0.31	0.56	1.60	4.23
12	3-Cl	9.30	0.77	0.37	1.80	3.52
13	3-F	8.49	0.22	0.34	1.35	2.06
14	3-Me	7.28	0.52	– 0.07	1.52	3.00
15	4-Cl	6.22	0.73	0.23	1.80	3.52
16	4-Me	7.18	0.63	– 0.17	1.52	3.00
17	4-F	7.46	0.15	0.06	1.35	2.06
18	4-NO_2	6.52	0.22	1.24	1.70	3.44

[a] The molar concentration of the drug leading to 50% inhibition of the binding of [^{3}H]nitrendipine to guinea pig ileal preparation.

correlation with the electronic parameter σ (Hammelt constant) (Eq. 2). In Eqs. 1 and 2, n is the number of data points, r is the correlation coefficient, s is the standard deviation, and F is the F-ratio between the variances of calculated and observed activities. These equations exhibited that ortho-

substituents can affect the activity by their width and the meta-substituents can do so by their electron-withdrawing capabilities.

$$\log(1/IC_{50}) = 5.152 + 2.407B1_0$$
$$n = 7,\ r = 0.91,\ s = 0.32,\ F_{1,5} = 23.81 \quad (1)$$
$$\log(1/IC_{50}) = 7.543 + 3.116\sigma_m$$
$$n = 8,\ r = 0.882,\ s = 0.48,\ F_{1,6} = 21.01\ . \quad (2)$$

For the five para-substituted compounds (including the parent one), the activity was, however, found to be correlated with Verloop's length parameter L of the substituents [25] (Eq. 3), which indicated that lengthy substituents at the para position will not be advantageous to the activity.

$$\log(1/IC_{50}) = 9.152 - 0.876L_p$$
$$n = 5,\ r = 0.94,\ s = 0.27,\ F_{1,3} = 22.27\ . \quad (3)$$

For the whole series of Table 2, the correlation obtained was as follows:

$$\log(1/IC_{50}) = 7.430 + 2.376B1_{o,m} - 0.472L_m - 0.674L_p + 1.928\sigma_m$$
$$n = 18,\ r = 0.93,\ s = 0.43,\ F_{4,13} = 23.10\ . \quad (4)$$

This equation suggested that the length of not only the para substituent but also of the meta substituents will be detrimental to the activity of the compounds and that the width of not only the ortho substituents but also of the meta substituents will be beneficial to the activity. However, the electronic character (electron-withdrawing) of only the meta substituents was shown to affect the activity. The hydrophobic property of substituents was found to have little effect, but when a detailed QSAR study was made by Coburn et al. [27] on a fairly large series of nifedipine analogues (Table 3) that also included the compounds of Table 2, a significant role of hydrophobic constant π of all the substituents had surfaced (Eq. 5). The IC_{50} in Eq. 5 was, however, related to the effect of compounds on tonic contractile response of longitudinal muscle strips of guinea pig ileum [27].

$$\log(1/IC_{50}) = 0.62(\pm0.09)\pi + 1.96(\pm0.29)\sigma_m - 0.44(\pm0.09)L_m -$$
$$- 1.51(\pm0.26)L_{m'} - 3.26(\pm0.33)B1_p + 14.23(\pm0.78)$$
$$n = 46,\ r = 0.90,\ s = 0.67,\ F_{5,40} = 33.93\ . \quad (5)$$

In this equation π and σ_m have been entered for all substituents without regard to their position in the phenyl ring, but m and m' in L refer to meta positions, separately, exhibiting a marked difference in the steric effects from two meta positions. The figures with $\pm$ sign within parentheses refer to 95% confidence intervals.

For a slightly extended series of compounds than that used in deriving Eq. 4, Coburn et al. [27] found that Bolger's binding data could also depend

Table 3 Activities of nifedipine analogues (**5**) against muscle contraction and physicochemical parameters [28]

Compd	X	$\log(1/IC_{50}^{a})$	π	σ_m	B1	L
1	3-Br	8.89	0.86	0.39	1.95	3.83
2	2-CF_2	8.82	0.88	0.43	1.98	3.30
3	2-Cl	8.66	0.71	0.37	1.80	3.52
4	3-NO_2	8.40	− 0.28	0.71	1.70	3.44
5	2-CH = CH_2	8.35	0.82	0.05	1.60	4.29
6	2-NO_2	8.29	− 0.28	0.71	1.70	3.44
7	2-Me	8.22	0.56	− 0.07	1.52	3.00
8	2-Et	8.19	1.02	− 0.07	1.52	4.11
9	2-Br	8.12	0.86	0.39	1.95	3.83
10	2-CN	7.80	− 0.57	0.56	1.60	4.23
11	3-Cl	7.80	0.71	0.37	1.80	3.52
12	3-F	7.68	0.14	0.34	1.35	2.65
13	H	7.55	0.00	0.00	1.00	2.06
14	3-CN	7.46	− 0.57	0.56	1.60	4.23
15	3-I	7.38	1.12	0.35	2.15	4.23
16	2-F	7.37	0.14	0.34	1.35	2.65
17	2-I	7.33	1.12	0.35	2.15	4.23
18	2-OMe	7.24	− 0.02	0.12	1.35	3.98
19	3-CF_3	7.13	0.88	0.43	1.98	3.30
20	3-Me	6.96	0.56	− 0.07	1.52	3.00
21	3-OEt	7.96	0.38	0.10	1.35	4.92
22	3-OMe	6.72	− 0.02	0.12	1.35	3.98
23	3-NMe_2	6.05	0.18	− 0.15	1.50	3.53
24	3-OH	6.00	− 0.67	0.12	1.35	2.74
25	3-NH_2	5.70	− 1.23	− 0.16	1.50	2.93
26	3-OAc	5.22	− 0.64	0.39	1.35	4.87
27	3-OCOPh	5.20	1.46	0.21	1.70	8.15
28	2-NH_2	4.40	− 1.23	− 0.16	1.50	2.93
29	3-N^+Me_3	4.30	− 5.96	0.88	2.56	4.02
30	4-F	6.89	0.14	0.34	1.35	2.65
31	4-Br	5.40	0.86	0.39	1.95	3.83
32	4-I	4.64	1.12	0.35	2.15	4.23
33	4-NO_2	5.50	− 0.28	0.71	1.70	3.44
34	4-NMe_2	4.00	0.18	− 0.15	1.50	3.53
35	4-CN	5.46	− 0.57	0.56	2.06	4.23
36	4-Cl	5.09	0.71	0.37	1.80	3.52
37	2,6-Cl_2	8.72	1.42	0.74		
38	F5	8.36	0.70	1.70		
39	2-F,6-Cl	8.12	0.85	0.71		
40	2,3-Cl_2	7.72	1.42	0.74		
41	2-Cl,5-NO_2	7.52	0.43	1.08		

Table 3 continued

Compd	X	$\log(1/IC_{50}^{a})$	π	σ_m	B1	L
42	3,5-Cl_2	7.03	1.42	0.74		
43	2-OH,5-NO_2	7.00	– 0.95	0.83		
44	2,5-Me_2	7.00	1.12	– 0.14		
45	2,4-Cl_2	6.40	1.42	0.74		
46	2,4,5-Me_3	3.00	– 0.06	0.36		

[a] The molar concentration of the drug necessary for 50% inhibition of the contraction of guinea pig ileum induced by methylfurmethide.

upon the hydrophobicity, since they were able to derive the correlation as:

$$\log(1/IC_{50}) = 0.81(\pm 0.11)\pi + 2.36(\pm 0.51)\sigma_m + 0.99(\pm 0.35)B1_o - \\ - 3.18(\pm 0.49)B1_m + 9.83(\pm 0.80)$$
$$n = 21,\ r = 0.95,\ s = 0.49,\ F_{4,16} = 38.91\ . \qquad (6)$$

Some quantum mechanical parameters were also found to be useful in accounting for the variance in calcium channel blocking activity of nifedipine analogues. For the same set of compounds as treated by Coburn et al. (Table 3), Gaudio et al. [16] had correlated the contractile response inhibition data as

$$\log(1/IC_{50}) = 0.44(\pm 0.26)\pi + 1.47(\pm 0.93)\sigma_m - 0.032(\pm 0.011)V_w - \\ - 1.65((\pm 0.53)B1_p - 6.5(\pm 1.9)F_5^{(e)} + 0.217(\pm 0.071)\in_{rot} + \\ + 17.4(\pm 3.2)$$
$$n = 45,\ r = 0.95,\ s = 0.49,\ F_{6,38} = 54.69\ . \qquad (7)$$

In this equation, $F_5^{(e)}$ refers to the frontier electron density at the 5-position of the phenyl ring, V_w refers to the van der Walls volume of the whole molecule, and $\in_{rot}$ refers to the energy barrier of the rotation of the phenyl ring. Equation 7, therefore, suggests, in addition to what one would conclude from Eq. 5, that high electron density at the 5-position and the bulk of the molecule will not be advantageous, rather a high energy barrier of the rotation of the phenyl ring will be beneficial. A high-energy barrier will mean the conformational rigidity of the phenyl ring with respect to the pyridine ring. All the quantum mechanical parameters used in Eq. 7 by Gaudio et al. were calculated using the AM1 method [28] and fully optimized geometries of the compounds.

Both Eqs. 5 and 7 show that a dominant steric effect can be produced from the para position. In fact, Gaudio et al. [16] found that the parameter V_w was relevant for only para-substituted analogues. For all mono-substituted para

analogues, the correlation obtained by these authors was:

$$\log(1/\mathrm{IC}_{50}) = 26.4(\pm 8.4) - 0.073(\pm 0.029)V_{\mathrm{w}}$$
$$n = 8,\ r = 0.93,\ s = 0.46,\ F_{1,3} = 37.08\,. \tag{8}$$

That the bulky substituents at the para position will be detrimental to the activity was also shown by Bernstein and Wold [29] in a study on the binding affinity of a small set of compounds. However, these authors had also observed that electron-withdrawing substituents on the ring will enhance the activity.

Analogues of verapamil (**1**) were also studied for their calcium channel antagonist activity, and their potency for isotonic contractile response of cat capillary muscle preparation was reported [30], which was found to be correlated with the electronic constant and the molecular volume of the B-ring substituents as:

$$\log(1/\mathrm{IC}_{50}) = 0.96\sigma + 0.63\mathrm{MV}$$
$$n = 7,\ r = 0.994,\ s = 0.064\,, \tag{9}$$

which suggested that along with the electronic property, the size of the substituents will also be important for the activity of the compounds.

Calcium channel blockers bind specifically to receptor sites associated with the voltage-dependent calcium channels [31, 32]. These blockers inhibit calcium uptake [33, 34] and block smooth muscle contraction [35, 36]. All these three activities of calcium channel blockers have been found to be mutually correlated. For ten known calcium channel blockers (Table 4), Papaionnou et al. [37] derived the correlations:

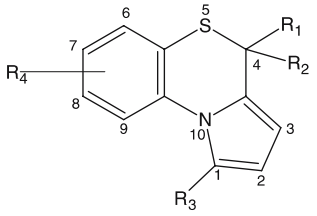
$$\log \mathrm{IC}_{50}(\text{Ca uptake}) = 0.863(\pm 0.12)\log \mathrm{IC}_{50}(\text{binding}) - 0.538(\pm 0.87)$$
$$n = 10,\ r = 0.93,\ p < 0.0001 \tag{10}$$
$$\log \mathrm{IC}_{50}(\text{contraction}) = 0.815(\pm 0.12)\log \mathrm{IC}_{50}(\text{Ca uptake}) - 1.212(\pm 0.81)$$
$$n = 10,\ r = 0.925,\ p < 0.0001\,. \tag{11}$$

For a series of diltiazem-like calcium channel blockers **(6)**, a comparative molecular field analysis (CoMFA) made by Corelli et al. [38] suggested that these calcium channel blockers can interact with the receptor at its negative charge site, two hydrogen-bonding sites, and three hydrophobic regions (Figs. 3 and 4). As shown in Fig. 3 (top view), the hydrophobic region 1 of the receptor surrounds the polycyclic core quite closely so that it does not accept substituents at carbons 6–8. The hydrophobic region 2 surrounds less tightly the side chain, allowing the presence of, at most, one bulky substituent. This hydrophobic region is closely adjacent to the negative charge site and a hydrogen bonding site, which interact with the protonated basic nitrogen and the lactam carbonyl oxygen, respectively, depending upon the molecules. The second hydrogen-bonding site is located in the pocket which accommodates the 4β-phenyl ring and interacts with the oxygen of the *p*-methoxy group.

Table 4 Some known calcium channel blockers and their different biological activities [37]

Compd	C_{50} (M) (calcium uptake) [a]	C_{50} or ED_{50} (M) (binding) [b]	IC_{50} (M) (concentration) [c]
Nifedipine	2.0×10^{-9}	9.5×10^{-10}	7.9×10^{-9}
(±)-Nimodipine	3.0×10^{-9}	1.7×10^{-9}	3.0×10^{-9}
(–)-202-791	4.0×10^{-9}	1.3×10^{-9}	3.2×10^{-8}
(±)-Verapmil	2.0×10^{-7}	(4.0×10^{-7}) [d]	1.4×10^{-7}
(±)-D-600	4.0×10^{-7}	(2.9×10^{-8}) [d]	4.4×10^{-8}
(±)-Bepridil	4.0×10^{-6}	1.3×10^{-5}	1.0×10^{-5}
(+)-Diltiazem	7.0×10^{-7}	(1.2×10^{-7}) [d]	3.8×10^{-7}
Cinnarizine	2.0×10^{-6}	2.5×10^{-6}	1.4×10^{-6}
Flunarizine	1.7×10^{-6}	1.2×10^{-6}	1.7×10^{-6}
(±)-Prenylamine	6.0×10^{-6}	3.9×10^{-7}	4.3×10^{-6}

[a] Inhibition of K^+-induced Ca^{2+}-uptake in rabbit aortic smooth muscle cells
[b] Inhibition of [^{3}H]nitrendipine binding to rat ventricular membrane preparations
[c] Inhibition of K^+-induced contraction of vascular smooth muscle
[d] ED_{50} value



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This last interaction is supposed to be of particular importance for the affinity of CCBs.

Figure 4 presents an edge view of the compounds in the putative binding site, showing that the 4α-substituents lie almost perpendicular to the plane of the tricyclic system and occupy the hydrophobic region 3 that in turn can accept substituents as long as there is a phenyl group, but it is shaped to prevent para-substituted analogues from fitting.

For the activity of a series of **6**, however, the substituted phenyl ring at C4 and the basic side chain at C1 on the pyrrole ring were found to constitute two important pharmacophores [39] and Campiani et al. [39] also suggested that substitution on the fused phenyl ring (R_4-substituents) and the double substitution at C4 were beneficial to the activity. The substitution of the

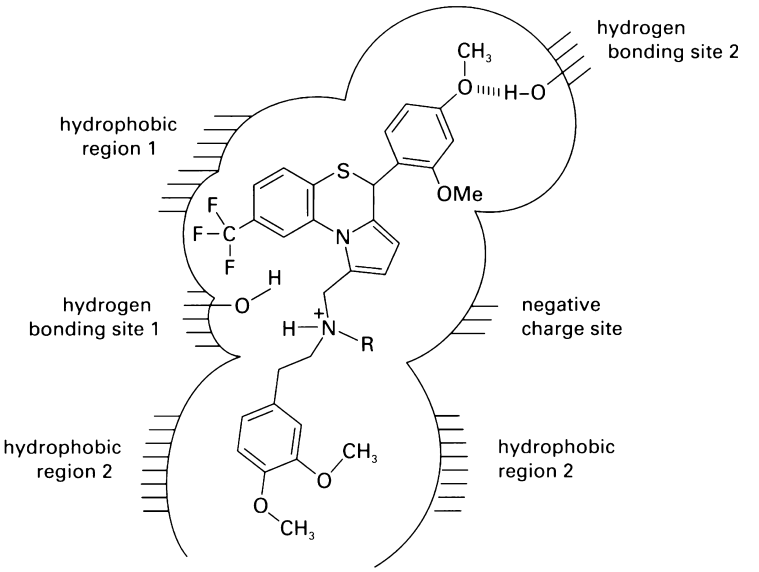


Fig. 3 A model proposed by Corelli et al. for the binding of diltiazem-like CCBs with the receptor [38]. A hypothetical compound is shown to interact with a negative charge site, two hydrogen binding sites, and two hydrophobic sites of the receptor (*top view*). Reprinted with permission from [38]. © 1997 American Chemical Society

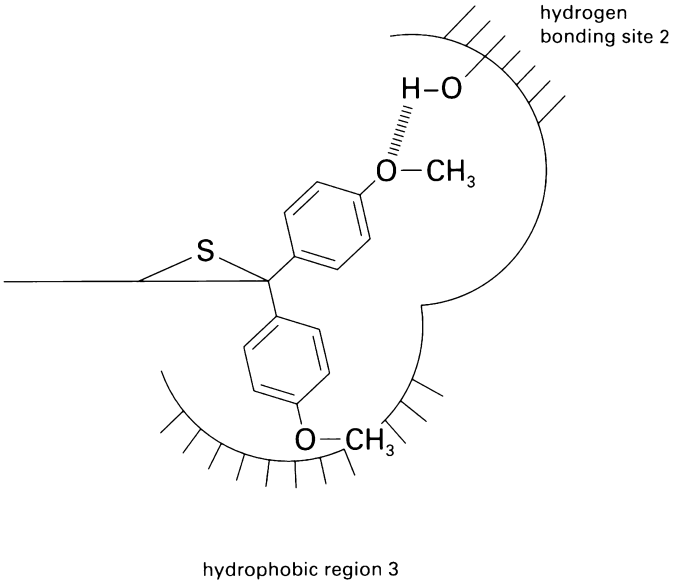
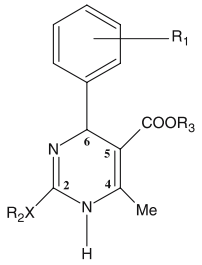


Fig. 4 An edge view of Corelli et al.'s model of the binding of diltiazem-like CCBs with the receptor [38], wherein a compound is shown to interact with hydrogen-bonding site 2 and a third hydrophobic site of the receptor. Reprinted with permission from [38]. © 1997 American Chemical Society

electron-withdrawing group in the fused phenyl ring was found to enhance the activity.

For a series of benzazepinone and benzothiazepine CCBs, Kimball et al. [40] had also identified two pharmacophores: the basic nitrogen and the phenyl methyl ethers, and proposed that the polycyclic core of these compounds could serve as a scaffold and function essentially to position the two pharmacophores in an optimal spatial situation. Accordingly, CCBs would bind to the calcium channel protein in an "inboard" binding conformation in which the side chain amine is placed over the mean plane of the molecule and in proximity to the phenyl methyl ether pharmacophore.

To explore further the mechanism of calcium channel blocking, a few series of 1,4-dihydropyrimidines (**7**–**9**) that mimic DHPs were studied for their



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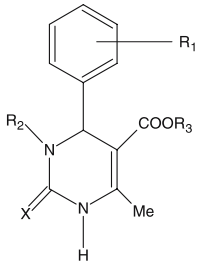

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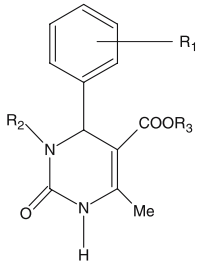


9

calcium channel blocking activity [41–44]. A QSAR study was made on three different series of these dihydropyrimidines, as listed in Tables 5–7, by Gupta et al. [45] to derive the following correlations.

$$\log(1/IC_{50}) = 0.733(\pm 0.287)\log P + 1.207(\pm 0.453)I_{R2} + 3.928(\pm 1.0)$$
$$n = 16,\ r = 0.894,\ s = 0.41,\ r^2_{cv} = 0.72,\ F_{2,13} = 25.86 \quad (12)$$

$$\log(1/IC_{50}) = 0.463(\pm 0.234)MR - 0.918(\pm 0.585)\pi_m(R_1) - $$
$$- 1.558(\pm 0.637)\sigma_m(R_1) + 1.315(\pm 0.581)I_{R3}$$
$$n = 17,\ r = 0.921,\ s = 0.34,\ r^2_{cv} = 0.64,\ F_{4,12} = 16.76 \quad (13)$$

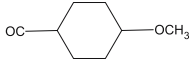
$$\log(1/IC_{50}) = 0.695(\pm 0.230)\ {}^1\chi^v_{R2} + 1.330(\pm 0.734)\ {}^1\chi^v_{R3} +$$
$$+ 0.947(\pm 0.527)D_{R2} + 3.60(\pm 1.467)$$
$$n = 17,\ r = 0.902,\ s = 0.35,\ r^2_{cv} = 0.45,\ F_{3,13} = 18.83\,. \quad (14)$$

Table 5 Analogues of 7 and their calcium entry blocking activity and physicochemical parameters

Compd	X	R_1	R_2	R_3	log *P*	I_{R_2}	log(1/IC$_{50}$) Obsd[a]	Calcd Eq. 12
1	S	3-NO_2	Me	Et	2.42	1	6.89	6.91
2	S	2-NO_2	Me	Et	2.34	1	6.52	6.85
3	S	2-CF_3	Me	Et	3.44	1	7.44	7.66
4	S	2,3-Cl_2	Me	Et	3.88	1	7.80	7.98
5	S	3-NO_2	$CH_2CH=CH_2$	Et	2.94	0	6.52	6.08
6	S	3-NO_2	$CH_2(CH_2)3CH_3$	Et	4.39	0	6.74	7.14
7	S	3-NO_2	$CH_2C_6H_5$	Et	3.50	0	6.72	6.49
8	S	3-NO_2	$CH_2CH_2N(Me)Bn$	Et	3.70	0	6.77	6.64
9	S	3-NO_2	$CH_2CH_2N(Me)_2$	*i*Pr	3.23	0	5.92	6.30
10	S	3-NO_2	Me	Me	2.00	1	6.55	6.60
11	S	3-NO_2	Me	*i*Pr	2.82	1	8.15	7.20
12	S	3-NO_2	Me	*s*Bu	3.33	1	8.05	7.57
13	S	2,3-Cl_2	Me	*i*Pr	4.23	1	8.22	8.23
14	S	3-NO_2	Me	$CH_2CH_2N(Me)Bn$	3.33	1	7.52	7.57
15	S	2-NO_2	Me	$CH_2CH_2N(Me)Bn$	3.24	1	5.72[b]	7.51
16	S	2-CF_3	Me	$CH_2CH_2N(Me)Bn$	4.39	1	4.00[b]	8.35
17	O	3-NO_2	Me	Et	2.15	1	6.15	6.71
18	N	3-NO_2	Me	Et	1.77	0	5.21	5.22

[a] Taken from [41]
[b] Not used in the derivation of Eq. 12

Table 6 Analogues of **8** and their calcium entry blocking activity and physicochemical parameters

Compd	X	R_1	R_2	R_3	$\pi_{m(R_1)}$	$\sigma_{m(R_1)}$	MR	I_{R_3}	I_X	log(1/IC_{50}) Obsd[a]	log(1/IC_{50}) Calcd Eq. 13
1	S	3-NO_2	COOEt	Et	− 0.28	0.71	10.28	0	1	7.77	7.35
2	S	2-NO_2	COOEt	Et	0.00	0.00	10.28	0	1	8.51	8.19
3	S	3-Cl	COOEt	Et	0.71	0.37	10.16	0	1	7.06	6.91
4	S	2-Cl	COOEt	Et	0.00	0.00	10.16	0	1	7.77	8.14
5	S	3-CF_3	COOEt	Et	0.88	0.43	10.18	0	1	6.55	6.67
6	S	2-CF_3	COOEt	Et	0.00	0.00	10.18	0	1	7.86	8.15
7	S	2,3-Cl_2	COOEt	Et	0.00	0.00	10.65	0	1	8.82	8.37
8	S	2-Cl,3-NO_2	COOEt	Et	0.00	0.00	10.77	0	1	8.57	8.42
9	S	3-NO_2	COOEt	Me	− 0.28	0.71	9.82	0	1	7.00	7.13
10	S	3-NO_2	COOEt	*i*Pr	− 0.28	0.71	10.75	1	1	8.77	8.88
11	S	3-NO_2	COOMe	Et	− 0.28	0.71	12.45	0	1	8.44 [b]	7.14
12	S	3-NO_2	COO*i*Pr	Et	− 0.28	0.71	10.50	0	1	7.85	7.56
13	S	3-NO_2		Et	− 0.28	0.71	12.45	0	1	7.96	8.35
14	S	3-NO_2	$CONMe_2$	Et	− 0.28	0.71	10.50	0	1	6.57 [b]	7.45
15	S	3-NO_2	SO_2Ph	Et	− 0.28	0.71	12.09	0	1	8.28	8.18
16	S	3-NO_2	$CH_2CH_2CH_3$	Et	− 0.28	0.71	10.09	0	1	7.30	7.26
17	O	3-NO_2	COOEt	Et	− 0.28	0.71	9.43	0	0	6.85	6.95
18	O	3-NO_2	COOEt	iPr	− 0.28	0.71	9.89	1	0	8.59	8.48
19	NH	3-NO_2	COOEt	Et	− 0.28	0.71	9.58	0	0	6.80	7.02

[a] Taken from [42]
[b] Not used in the derivation of Eq. 13

To derive these equations, log *P* (hydrophobic parameter), MR (molar refractivity index), and MV (molar volume) were calculated using software freely available on the internet (www.logP.com, www.daylight.com). The first-order valence molecular connectivity index $^1\chi^v$ of substituents was calculated as suggested by Kier and Hall [46, 47]. In these equations, r^2_{cv} is cross-validated r^2 obtained by the leave-one-out jackknife procedure. Its value higher than 0.6 defines the good predictive ability of the equation. The different indicator variables in these equations were defined as follows.

I_{R2} = 1 for R_2 in Table 5 being a methyl group, otherwise its value is zero.

I_{R3} = 1 for R_3 being, in any table, an isopropyl group, otherwise its value is zero.

I_X = 1 or 0 for $X = S$ or 0 in any Table.

D_{R2} = 1 for R_2 in Table 7 being $CONH_2$ group, otherwise its value is zero.

Table 7 Analogues of **9** and their calcium entry blocking activity and physicochemical parameters

Compd	R_1	R_2	R_3	$^1\chi^v_{R_2}$	$^1\chi^v_{R_3}$	D_{R_2}	log(1/IC$_{50}$) Obsd[a]	Calcd Eq. 14
1	3-NO_2	$CONMe_2$	*i*Pr	1.55	1.80	0	5.50 [b]	7.16
2	3-NO_2	CONHMe	*i*Pr	1.18	1.80	0	7.80 [b]	6.90
3	3-NO_2	$CONH_2$	*i*Pr	0.72	1.80	1	7.92	7.53
4	3-NO_2	H	*i*Pr	0.00	1.80	0	5.80	6.08
5	3-NO_2	$CONH_2$	Et	0.72	1.40	1	7.41	7.00
6	3-NO_2	$CONH_2$	Me	0.72	0.81	1	6.05	6.21
7	3-NO_2	CONHEt	*i*Pr	1.74	1.80	0	7.88	7.29
8	3-NO_2	CONH*i*Pr	*i*Pr	1.86	1.80	0	7.22	7.38
9	3-NO_2	$CONHCH_2Ph$	*i*Pr	3.30	1.80	0	8.52	8.38
10	3-NO_2	$CH_2CH_2N(Me)Bn$	*i*Pr	4.16	1.80	0	8.69	8.98
11	2-NO_2	$CONH_2$	*i*Pr	0.72	1.80	1	7.69	7.53
12	3-CF_3	$CONH_2$	*i*Pr	0.72	1.80	1	5.77 [b]	7.53
13	2-CF_3	$CONH_2$	*i*Pr	0.72	1.80	1	7.35	7.53
14	3-Cl	$CONH_2$	*i*Pr	0.72	1.80	1	7.39	7.53
15	2-Cl	$CONH_2$	*i*Pr	0.72	1.80	1	7.47	7.53
16	3-Br	$CONH_2$	*i*Pr	0.72	1.80	1	7.26	7.53
17	2-Br	$CONH_2$	*i*Pr	0.72	1.80	1	7.51	7.53
18	2,6-Cl_2	$CONH_2$	*i*Pr	0.72	1.80	1	7.08	7.53
19	2,3-Cl_2	$CONH_2$	*i*Pr	0.76	1.80	1	7.37	7.56
20	3-NO_2	$CONH_2$	*i*Pr	0.72	1.80	1	8.07	7.53

[a] Taken from [43]

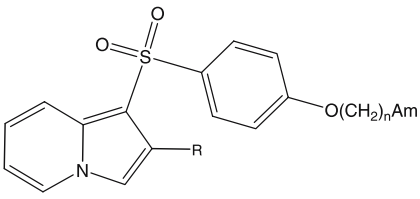
[b] Not used in the derivation of Eq. 14

In all the equations, IC_{50} stands for vasorelaxant activity of the compounds and refers to the molar concentration of the compound required to inhibit the potassium contracted rabbit aorta strips by 50%.

A very critical analysis of these equations led Gupta et al. to suggest that the most important factors that can commonly affect the activity of all the three series (Tables 5–7) are the esters group present at N1 and C6 of the pyrimidine ring. At N1, the smallest ester group (COOMe) is found to be the best and if it is replaced by an amide group, the amide group should be totally unsubstituted ($CONH_2$). Both esters and amide groups can be expected to form hydrogen bonds with the receptors, which can be sterically hindered by the presence of any bulky group in them.

At the C6 atom, the isopropyl containing ester group was suggested to be optimum. Here the ester group seems to have a steric interaction which is optimal with the isopropyl group.

In the last decade, several new classes of calcium entry blockers were studied in which phenyl sulfonylindolzine analogues had drawn more attention. Consequently, Gubin et al. [48, 49] reported two different series of these indolizine analogues: **10**, in which the variations were made in the R-substituent at the 2-position of the indolizine ring and in the amine moiety (Am) of the 4-substituent of the phenyl ring; and **11**, in which the indolizine ring was replaced by a variety of heterocyclic rings along with the variation in the Am moiety. These two series are listed in Tables 8 and 9, respectively. The two different assays were reported for both these series: $(IC_{50})_A$, referring to the molar concentration of the compound required to reduce [^{3}H]nitrendipine binding by 50%, and $(IC_{50})_B$, referring to the molar concentration of the compound required to block Ca^{2+} induced concentration of K^+ depolarized rat aorta by 50%. For both these activities of **10** and **11** a QSAR analysis was made by Gupta et al. [50] and the following correlations were obtained.



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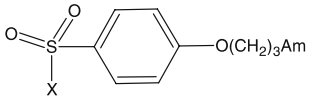

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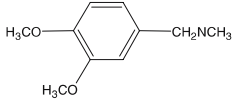
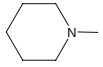
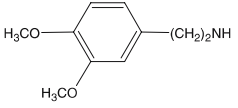
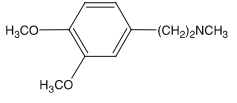
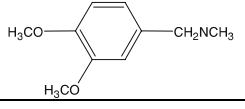
Table 8 Analogues of **10** with calcium entry blocking activities and the correlates

Compd	R	Am	n	π_R	σ_R	$^1\chi^v_{Am}$	I_1	I_2	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 15	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 16
1	CH_3	$(C_2H_5)_2N$	3	0.56	− 0.17	2.05	0	0	5.28	5.66	5.47	5.71
2	CH_3	$(n\text{-}C_3H_7)_2N$	3	0.56	− 0.17	3.05	0	0	6.19	6.19	6.02	6.13
3	$i\text{-}C_3H_7$	$(CH_3)_2N$	3	1.53	− 0.15	0.89	0	0	6.70	6.63	6.41	6.08
4	$n\text{-}C_4H_9$	$(n\text{-}C_3H_7)_2N$	3	2.13	− 0.16	3.05	0	0	6.89	7.23	6.24	6.36
5	$n\text{-}C_4H_9$	$(n\text{-}C_4H_9)_2N$	3	2.13	− 0.16	4.05	0	0	7.66	7.60	6.55	6.46
6	$i\text{-}C_3H_7$	$(C_2H_5)_2N$	3	1.53	− 0.15	2.05	0	0	7.29	7.45	6.64	6.96
7	$i\text{-}C_3H_7$	$(n\text{-}C_3H_7)_2N$	3	1.53	− 0.15	3.05	0	0	7.39	7.99	6.99	7.39
8	$i\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	3	1.53	− 0.15	4.05	0	0	8.68	8.36	7.67	7.49
9	$t\text{-}C_4H_9$	$(n\text{-}C_4H_9)_2N$	3	1.98	− 0.20	4.05	0	0	8.02	8.30	7.28	7.18
10	$c\text{-}C_3H_5$		3	1.14	− 0.21	4.05	1	0	8.72	9.03	8.33	8.50
11	C_6H_{11}	$(n\text{-}C_4H_9)_2N$	3	2.51	− 0.22	4.05	0	0	6.95	6.77	5.39	5.44
12	C_6H_5	$(n\text{-}C_4H_9)_2N$	3	1.96	− 0.01	4.05	0	0	6.81	6.73	5.79	5.77
13	CH_3	$(n\text{-}C_4H_9)_2N$	3	0.56	− 0.17	4.05	0	0	7.16	6.57	6.79	6.24
14	$n\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	3	1.55	− 0.13	4.05	0	0	7.85	8.18	7.27	7.32
15	C_2H_5	$(n\text{-}C_3H_7)_2N$	3	1.02	− 0.15	3.05	0	0	6.74	7.47	6.82	7.14
16	C_2H_5	$(n\text{-}C_4H_9)_2N$	3	1.02	− 0.15	4.05	0	0	7.85	7.84	7.50	7.24
17	$c\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	3	1.14	− 0.21	4.05	0	0	8.60	8.57	7.96	7.86
18	C_2H_5	$(n\text{-}C_4H_9)_2N$	5	1.02	− 0.15	4.05	0	0	7.70	7.84	7.01	7.24

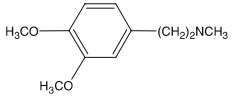
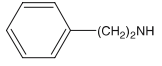
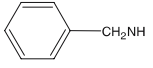
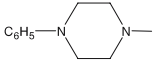
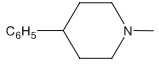
[a] Taken from [48]
[b] Not included in the derivation of Eq. 15
[c] Not included in the derivation of Eq. 16

Table 8 continued

Compd	R	Am	n	π_R	σ_R	$^1\chi^v_{Am}$	I_1	I_2	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 15	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 16
19	C_2H_5	$(n\text{-}C_5H_{11})_2N$	3	1.02	− 0.15	5.05	0	0	8.20	8.05	7.20	7.02
20	C_2H_5	$(n\text{-}C_4H_9)_2N$	2	1.02	− 0.15	4.05	0	0	7.48	7.84	7.14	7.24
21	C_2H_5	$(n\text{-}C_4H_9)_2N$	4	1.02	− 0.15	4.05	0	0	8.34	7.84	7.48	7.24
22	C_2H_5		3	1.02	− 0.15	2.65	0	0	6.56	7.28	6.45	7.01
23	C_2H_5	$t\text{-}C_4H_9NH$	3	1.02	− 0.15	1.75	0	0	6.89	6.74	6.38	6.53
24	C_2H_5		3	1.02	− 0.15	4.05	1	0	8.34	8.33	7.96	7.88
25	C_2H_5		3	1.02	− 0.15	4.58	1	0	8.64	8.42	7.87	7.81
26	$i\text{-}C_3H_7$	$t\text{-}C_4H_9NH$	3	1.53	− 0.15	1.75	0	0	7.76	7.26	7.38	6.78
27	$i\text{-}C_3H_7$		4	1.53	− 0.15	4.08	1	0	8.35	8.82	7.84	8.13

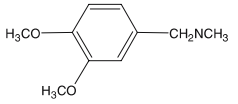
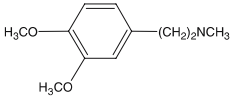
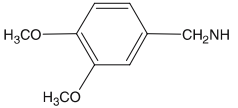
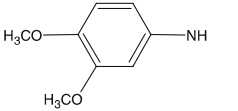
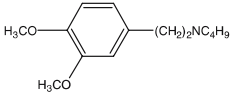
[a] Taken from [48]
[b] Not included in the derivation of Eq. 15
[c] Not included in the derivation of Eq. 16

Table 8 continued

Compd	R	Am	n	π_R	σ_R	$^1\chi^v_{Am}$	I_1	I_2	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 15	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 16
28	i-C_3H_7		3	1.53	− 0.15	4.58	1	0	9.21	8.94	8.25	8.06
29	i-C_3H_7		3	1.53	− 0.15	2.78	0	0	8.40	7.86	7.09	7.31
30	i-C_3H_7		3	1.53	− 0.15	2.62	0	0	8.35	7.78	7.64	7.24
31	i-C_3H_7		3	1.53	− 0.15	4.65	0	0	7.85	8.50	6.69	7.39
32	i-C_3H_7		3	1.53	− 0.15	4.65	0	0	8.18	8.50	7.09	7.39
33	i-C_3H_7	$(n\text{-}C_8H_{17})_2N$	3	1.53	− 0.15	8.05	0	0	8.19	8.22	4.52	4.69
34	i-C_3H_7	$(n\text{-}C_5H_{11})_2N$	3	1.53	− 0.15	5.05	0	0	9.05	8.57	7.05	7.27
35	i-C_3H_7	$(n\text{-}C_4H_9)_2N$	4	1.53	− 0.15	4.05	0	0	8.89	8.36	7.69	7.49

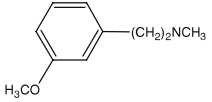
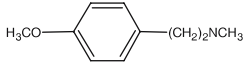
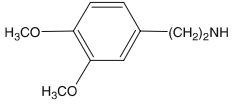
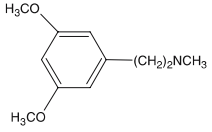
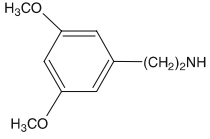
[a] Taken from [48]
[b] Not included in the derivation of Eq. 15
[c] Not included in the derivation of Eq. 16

Table 8 continued

Compd	R	Am	n	π_R	σ_R	$^1\chi^v_{Am}$	I_1	I_2	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 15	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 16
36	*i*-C_3H_7		3	1.53	− 0.15	4.08	1	0	9.21	8.82	8.50	8.13
37	*i*-C_3H_7		4	1.53	− 0.15	4.58	1	0	8.64	8.94	7.67	8.06
38	*i*-C_3H_7		3	1.53	− 0.15	3.67	1	0	8.92	8.69	7.89	8.13
39	*i*-C_3H_7		3	1.53	− 0.15	3.11	1	0	6.42 [b]	9.62	6.40 [c]	9.17
40	*i*-C_3H_7		3	1.53	− 0.15	6.16	1	0	9.08	9.06	7.73	7.30

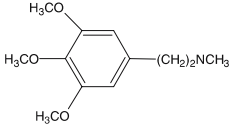
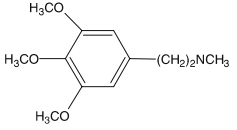
[a] Taken from [48]
[b] Not included in the derivation of Eq. 15
[c] Not included in the derivation of Eq. 16

Table 8 continued

Compd	R	Am	n	π_R	σ_R	$^1\chi^v_{Am}$	I_1	I_2	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 15	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 16
41	*i*-C_3H_7		3	1.53	− 0.15	4.05	0	0	8.59	8.36	8.10	7.49
42	*i*-C_3H_7		3	1.53	− 0.15	4.05	0	0	8.06	8.36	7.65	7.49
43	*i*-C_3H_7		3	1.53	− 0.15	4.08	1	0	8.74	8.82	8.30	8.13
44	*i*-C_3H_7		3	1.53	− 0.15	4.57	0	1	9.72	9.26	8.67	8.47
45	*i*-C_3H_7		3	1.53	− 0.15	4.16	0	1	9.28	9.16	8.63	8.53

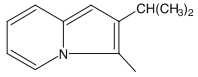
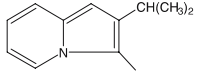
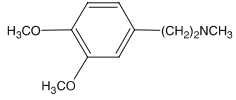
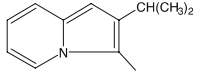
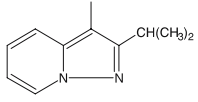
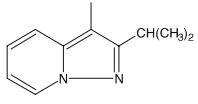
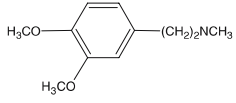
[a] Taken from [48]
[b] Not included in the derivation of Eq. 15
[c] Not included in the derivation of Eq. 16

Table 8 continued

Compd	R	Am	n	π_R	σ_R	$^1\chi^v_{Am}$	I_1	I_2	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 15	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 16
46	*i*-C_3H_7		3	1.53	– 0.15	5.11	1	1	9.21	9.80	8.65	8.95
47	*c*-C_3H_5		3	1.14	– 0.21	2.78	1	0	9.13	8.53	8.41	8.32
48	*c*-C_3H_5	*t*-C_4H_9NH	3	1.14	– 0.21	1.75	0	0	7.37	7.47	7.18	7.15
49	*t*-C_4H_9	*t*-C_4H_9NH	3	1.98	– 0.20	1.75	0	0	7.05	7.21	6.35	6.47

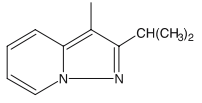
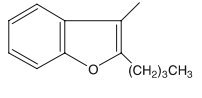
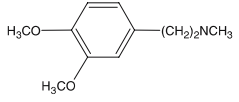
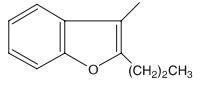
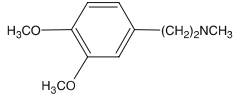
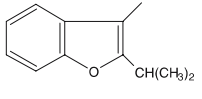
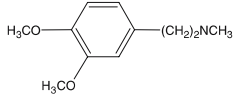
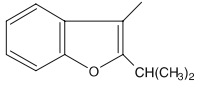
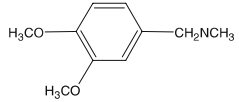
[a] Taken from [48]
[b] Not included in the derivation of Eq. 15
[c] Not included in the derivation of Eq. 16

Table 9 Analogues of **11** with calcium entry blocking activities and the correlates

Compd	R	Am	$^1\chi^v_X$	$^1\chi^v_{Am}$	I_1	I_2	D_{NI}	D_5	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 17	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 18
1		$(n\text{-}C_4H_9)_2N$	4.265	4.047	0	0	0	0	9.00 [b]	7.31	7.88 [c]	7.10
2			4.265	4.580	1	0	0	0	9.66	8.80	8.23	7.82
3		$t\text{-}C_4H_9NH$	4.265	1.750	0	0	0	0	7.92	7.30	7.48	7.11
4		$(n\text{-}C_4H_9)_2N$	4.137	4.047	0	0	0	0	7.87	7.44	7.51	7.59
5			4.137	4.580	1	0	0	0	8.59	8.94	7.73	8.30

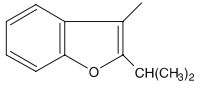
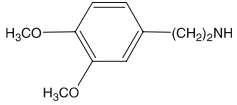
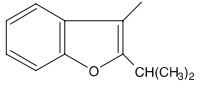
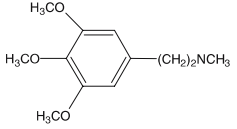
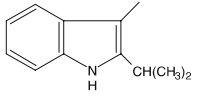
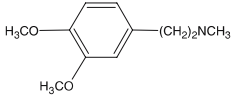
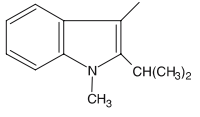
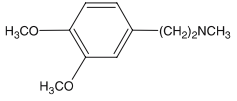
[a] Taken from [49]
[b] Not included in the derivation of Eq. 17
[c] Not included in the derivation of Eq. 18

Table 9 continued

Compd	R	Am	$^1\chi^v_X$	$^1\chi^v_{Am}$	I_1	I_2	D_{NI}	D_5	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 17	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 18
6		*t*-C_4H_9NH	4.137	1.750	0	0	0	0	6.82	7.44	6.77 [c]	7.58
7			4.796	4.580	1	0	0	0	8.10	7.90	6.64 [c]	7.67
8			4.296	4.580	1	0	0	0	8.28	8.77	7.29	7.73
9			4.244	4.580	1	0	0	0	9.19	8.83	7.69	7.89
10			4.244	4.080	1	0	0	0	8.72	8.83	7.84	7.89

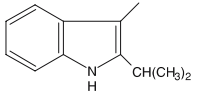
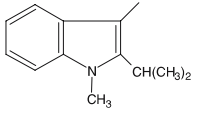
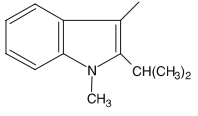
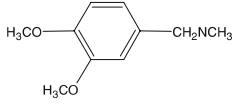
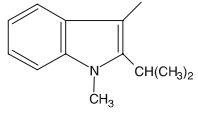
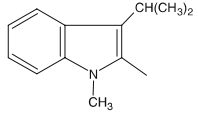
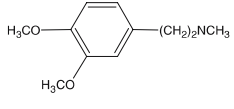
[a] Taken from [49]
[b] Not included in the derivation of Eq. 17
[c] Not included in the derivation of Eq. 18

Table 9 continued

Compd	R	Am	$^1\chi^v_X$	$^1\chi^v_{Am}$	I_1	I_2	D_{NI}	D_5	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 17	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 18
11			4.244	4.170	1	0	0	0	8.80	8.83	7.77	7.89
12			4.244	5.109	1	1	0	0	9.23	8.95	8.24	7.89
13			4.336	4.580	1	0	0	0	7.96	8.71	7.72	7.63
14			4.730	4.580	1	0	1	0	8.96	9.12	8.37	8.24

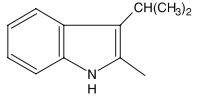
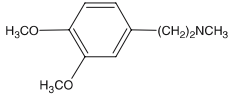
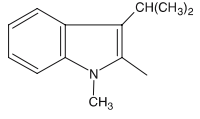
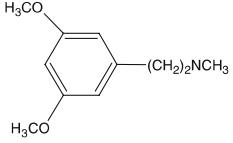
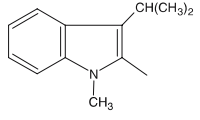
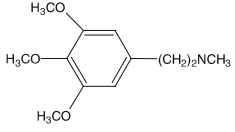
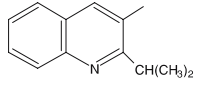
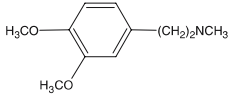
[a] Taken from [49]
[b] Not included in the derivation of Eq. 17
[c] Not included in the derivation of Eq. 18

Table 9 continued

Compd	R	Am	$^1\chi^v_X$	$^1\chi^v_{Am}$	I_1	I_2	D_{NI}	D_5	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 17	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 18
15		$(n\text{-}C_4H_9)_2N$	4.336	4.047	0	0	0	0	6.96	7.21	7.26	6.93
16		$(n\text{-}C_4H_9)_2N$	4.730	4.047	0	0	1	0	7.96	7.62	7.62	7.53
17			4.730	4.080	1	0	1	0	9.00	9.12	8.43	8.24
18		$t\text{-}C_4H_9NH$	4.730	1.750	0	0	1	0	6.94	7.62	7.00	7.53
19			4.665	4.580	1	0	1	0	10.14	9.25	8.43	8.14

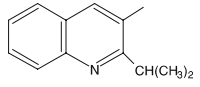
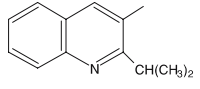
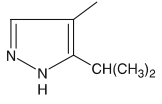
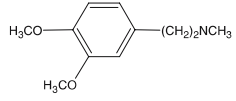
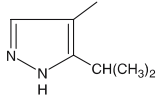
[a] Taken from [49]
[b] Not included in the derivation of Eq. 17
[c] Not included in the derivation of Eq. 18

Table 9 continued

Compd	R	Am	$^{1}\chi^{v}_{X}$	$^{1}\chi^{v}_{Am}$	I_1	I_2	D_{NI}	D_5	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 17	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 18
20			4.271	4.580	0	1	1	0	8.66	8.49	7.43	7.80
21			4.271	4.580	0	1	1	0	10.03 [b]	8.44	7.79	7.80
22			4.271	5.109	1	1	1	0	9.55	9.99	8.72	8.51
23			4.545	4.580	1	0	0	0	7.88	8.40	7.07	7.38

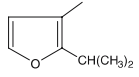
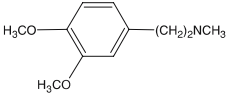
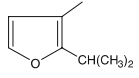
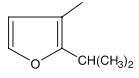
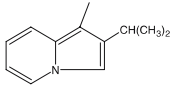
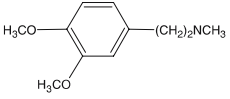
[a] Taken from [49]
[b] Not included in the derivation of Eq. 17
[c] Not included in the derivation of Eq. 18

Table 9 continued

Compd	R	Am	$^1\chi^v_X$	$^1\chi^v_{Am}$	I_1	I_2	D_{NI}	D_5	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 17	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 18
24		$(n\text{-}C_4H_9)_2N$	4.545	4.047	0	0	0	0	7.03	6.90	6.70	6.67
25		$t\text{-}C_4H_9NH$	4.545	1.750	0	0	0	0	6.74	6.90	6.43	6.67
26			2.641	4.580	1	0	0	1	–	–	5.77	5.96
27		$(n\text{-}C_4H_9)_2N$	2.641	4.047	0	0	0	1	–	–	5.30	5.25

[a] Taken from [49]
[b] Not included in the derivation of Eq. 17
[c] Not included in the derivation of Eq. 18

Table 9 continued

Compd	R	Am	$^1\chi^v_X$	$^1\chi^v_{Am}$	I_1	I_2	D_{NI}	D_5	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq. 17	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq. 18
28			2.575	4.580	1	0	0	1	8.14	8.16	7.07	7.30
29		$(n\text{-}C_4H_9)_2N$	2.575	4.047	0	0	0	1	6.73	6.66	6.92	6.59
30		$t\text{-}C_4H_9NH$	2.575	1.750	0	0	0	1	6.61	6.66	6.63	6.59
31			4.261	4.580	1	0	0	0	9.21	8.81	8.25	7.83

[a] Taken from [49]
[b] Not included in the derivation of Eq. 17
[c] Not included in the derivation of Eq. 18

Series of 10 (Table 8)

$$\log(1/IC_{50})_A = 6.577(\pm1.553)\pi_R - 2.179(\pm0.532)(\pi_R)^2 + \\ + 0.949(\pm0.354)\ {}^1\chi^v_{Am} - 0.081(\pm0.042)({}^1\chi^v_{Am})^2 - \\ - 8.496(\pm4.320)\sigma_R + 0.452(\pm0.303)I_1 + 0.768(\pm0.506)I_2 - \\ - 0.387(\pm1.700)$$

$$n = 48,\ r = 0.919,\ s = 0.41,\ F_{7,40} = 31.10,\ (\pi_R)_{opt} = 1.51, \\ ({}^1\chi^v_{Am})_{opt} = 5.86 \qquad (15)$$

$$\log(1/IC_{50})_B = 5.831(\pm1.217)\pi_R - 2.097(\pm0.417)(\pi_R)^2 + \\ + 1.238(\pm0.278)\ {}^1\chi^v_{Am} - 0.160(\pm0.033)({}^1\chi^v_{Am})^2 - \\ - 7.700(\pm3.315)\sigma_R + 0.647(\pm0.238)I_1 + 1.057(\pm0.396)I_2 - \\ - 0.067(\pm1.332)$$

$$n = 48,\ r = 0.948,\ s = 0.32,\ F_{7,40} = 50.20,\ (\pi_R)_{opt} = 1.39, \\ ({}^1\chi^v_{Am})_{opt} = 3.87 \qquad (16)$$

Series of 11 (Table 9)

$$\log(1/IC_{50})_A = 7.180(\pm4.169)\ {}^1\chi^v_X - 0.993(\pm0.584)({}^1\chi^v_X)^2 + \\ + 1.505(\pm0.398)I_1 + 1.133(\pm0.537)D_{N1} - 5.246(\pm7.116)$$

$$n = 27,\ r = 0.90,\ s = 0.48,\ F_{4,22} = 23.39,\ ({}^1\chi^v_X)_{opt} = 3.62 \qquad (17)$$

$$\log(1/IC_{50})_B = 114.705(\pm44.798) - 47.415(\pm20.218)\ {}^1\chi^v_X + \\ + 5.202(\pm2.281)({}^1\chi^v_X)^2 + 0.706(\pm0.261)I_1 + \\ + 0.706(\pm0362)D_{N1} - 20.518(\pm7.686)D_5$$

$$n = 28,\ r = 0.933,\ s = 0.32,\ F_{5,22} = 29.47,\ ({}^1\chi^v_X)_{opt} = 4.56\,. \qquad (18)$$

Equations 15 and 16 obtained for the analogues of **10** exhibited the parallel correlations for the two activities, indicating that for both the activities the hydrophobic property and electron-donating nature of the R-substituents will be crucial. The Am moiety was shown to affect both the activities through its size delineated by the molecular connectivity index ${}^1\chi^v_{Am}$. In both Eqs. 15 and 16, however, π_R and ${}^1\chi^v_{Am}$ were shown to have parabolic correlations with the activities, each with an optimum value as shown in the equations.

The two variables I_1 and I_2 used in the above equations were the indicator parameters related to the Am moiety. The I_1 stands with a value of unity for an Am that had the methoxy groups at the 3-and 4-positions of the phenyl ring and I_2 stands with a value of unity for an Am that had the methoxy group only at the 5-position of the phenyl ring. A comparison of the coefficients of I_1 and I_2 in Eqs. 15 and 16 had suggested that the presence of the methoxy group at the 5-position would be better than at the 3,4-positions.

The parallelism between Eqs. 15 and 16 indicated that there could be good mutual relations between the two assays. This was nicely verified by Gupta

et al. [50] for both the series (**10** and **11**) by deriving Eqs. 19 and 20, respectively, although such a nice parallelism was not observed to exist between Eqs. 17 and 18 obtained for the series of **11**.

$$\log(1/IC_{50})_B = 0.769(\pm 0.11)\log(1/IC_{50})_A + 1.152(\pm 0.891)$$
$$n = 48,\ r = 0.90,\ s = 0.37,\ F_{1,46} = 194.33 \quad (19)$$
$$\log(1/IC_{50})_B = 0.557(\pm 0.107)\log(1/IC_{50})_A + 3.036(\pm 0.891)$$
$$n = 27,\ r = 0.90,\ s = 0.27,\ F_{1,25} = 111.60\,. \quad (20)$$

For the series of **11** where there was a variation in the heterocyclic ring along with the variation in the Am moiety, the activities were shown to be primarily governed by the nature and size of the heterocyclic rings and little by the nature of the Am moiety. For the latter, only the parameter I_1 was found to be significant. However, the dependence of the activities on $^1\chi^v$ of X (the heterocyclic rings) for the two activities was not similar. While for activity A Eq. 17 exhibited a normal parabolic correlation with $^1\chi^v$, for activity B Eq. 18 exhibited the inverted parabolic correlation. This difference was attributed by Gupta et al. to the conformational changes in the receptors while interacting with the compounds.

However, the studies on the calcium channel blockers remained centered even today around the 1,4-dihydropyridine class. Since this class of compounds can also act as calcium channel activators, attention has always been drawn towards their structure-activity relationship studies. Attempts were made to differentiate in the mechanisms of their agonist and antagonist activities. On the basis of the force field and quantum mechanical calculations, Holtze and Marrer [51] discovered a unique area of the molecular potentials where Ca agonists and antagonists possess potential of opposite sign. These authors demonstrated that the molecular potential of a simple receptor site was reduced by interaction with calcium channel activators and, on the contrary, increased by interaction with calcium channel blockers. These opposite effects probably could be the basis for the opposite actions of DHP enantiomers at the potential-dependent calcium channel.

In order to explore deeper insight into the mechanism of actions of DHPs, several authors carried out molecular modeling studies on these compounds [52–54]. In a recent molecular modeling study on calcium channel blockers, nifedipine and black mamba toxin FS2 (a venom of the black mamba snake, which has been demonstrated to block the L-type calcium channel [55, 56], is a small peptide consisting of 58-74 amino acid residues and having 4–5 intramolecular disulfide bridges formed by cystein residues), Schleifer [54] observed the following:

a) Both compounds revealed pronounced hydrophobic regions parallel to aromatic and aliphatic ring systems.
b) Both compounds have two hydrogen bond acceptor spaces (*ap*, *sp* ester oxygens in conjugation with 2′-nitro in nifedipine).

c) At the deepest place in regard to the superposition, both molecules possess a hydrogen bond group (N1–H in nifedipine).
d) Both possess similar molecular electrostatic potentials.
e) Additional hydrophobic interactions may be postulated for bulky substituents in both the CCBs (at the *sp* ester side chain of DHPs).

Although the 3D binding site of DHPs is still not well defined, site-directed mutagenesis experiments identify hydrophobic amino acid residues in the putative trans-membrane segment IVS6 of L-type voltage-gated calcium channels as the molecular determinants for high affinity DHP binding [57].

With respect to a maximum activity possessed by DHPs, Mager et al. [52] found the following rank order of substituents parameters and positions: lipophilicity ≈ ortho-position > inductivity > minimum width > meta-position. A few neural network studies [58–60] on these DHPs were also made, but they were of only predictive value and could throw little light on the mechanism of their action.

A molecular modeling study on some rigid analogues of verapamil (**1**) suggested that the two actions of verapamil analogues—negative inotropic (decrease in force of cardiac muscle contraction) and negative chronotropic (decrease in rate of cardiac muscle contraction)—were because of the conformations of the molecules that differ in the orientation of their phenylethylamino groups [61].

Regarding diltiazem (**3**), some additional molecular features favorable for binding with the calcium channel and showing antagonistic effects were in-

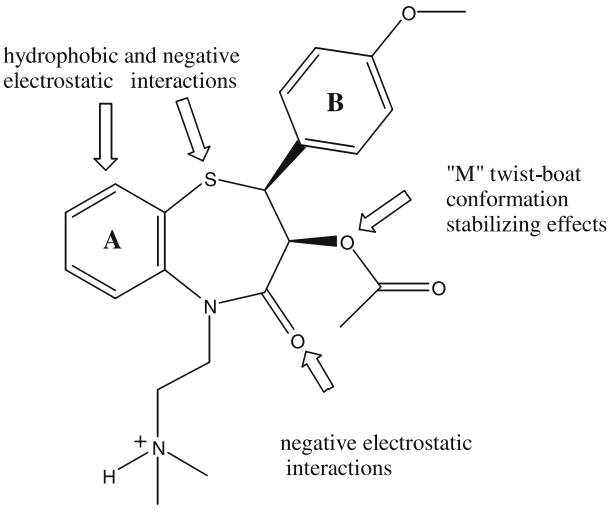


Fig. 5 Additional molecular features in diltiazem, as suggested by Schleifer and Tot [62], favorable for binding and showing antagonistic activity. From [62]. © 2000 Springer Science and Business Media. Reprinted with kind permission of Springer Science and Business Media

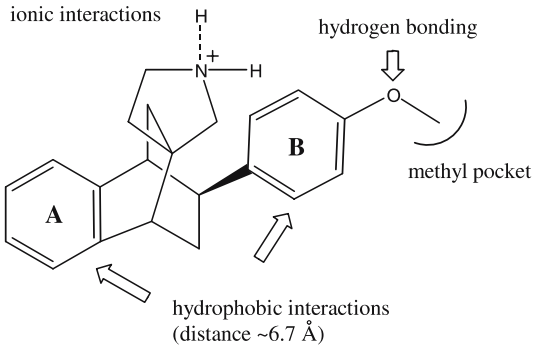


Fig. 6 The minimum requirements for binding with the diltiazem site as suggested by Schleifer and Tot [62] (shown for *spiro*-linked benzocyclo[2,2,2]octyl amine as an example). From [62]. © 2000 Springer Science and Business Media. Reprinted with kind permission of Springer Science and Business Media

dicated by Schleifer and Tot [62] as shown in Fig. 5. However, for several diltiazem mimics that did not contain sulfur, the minimum requirements for binding with the diltiazem site were suggested to be as shown in Fig. 6 for spiro-linked benzocyclo[2,2,2]octyl amine derivative, as an example.

6 Concluding Remarks

The three principal classes of compounds have been found to act as calcium channel blockers (CCBs), of which the 1,4-dihydropyridine (DHP) class has drawn the maximum attention. The various experimental and theoretical studies have delineated in detail the relationships between the structure and activity of this class of CCBs. The high activity of 4-phenyl DHPs was attributed to their conformational properties, in which the aryl ring was supposed to have perpendicular orientation relative to the DHP ring. The DHP ring exists as a non-planar boat-shaped structure with the N1 and C4 atoms defining the stern and bowsprit position. The phenyl ring is bound to it at a pseudoaxial position and approximately bisects the pyridine ring. The rotational freedom of the phenyl ring about the C4–C1′ bond is sterically restricted and the plane of the phenyl ring is forced to lie close to N1–C4 vertical symmetry plane.

The conformation of the ester groups of DHPs have also been indicated to be crucial for the activity. QSAR studies have exhibited the importance of steric factors in binding of DHPs to the calcium channel. The length and width of phenyl ring substituents are shown to govern the activity. Certain electronic properties, particularly the electron-withdrawing ability, of the meta substituents have been shown to be beneficial for the potency. A quanti-

tative correlation has been found to exist between the conformational rigidity of the phenyl ring and the CCB activity of the DHPs and in the binding of these DHPs with the receptors the hydrophobic and hydrogen bonding interactions have been shown to be of paramount importance.

Certain other classes of compounds, e.g., dihydropyridines (**7–9**) and phenylsulfonylindolizines (**10, 11**), have also been studied for CCB activity. In these also, the hydrophobicity and steric factors have been found to play the important roles. Thus, QSAR studies have provided valuable information for the design of potent calcium channel blockers of pharmaceutical importance.

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