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European Journal of Medicinal Chemistry 38 (2003) 867–873
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
www.elsevier.com/locate/ejmech

Original article

A quantitative structure–activity relationship study on a novel class of calcium-entry blockers: 1-[{4-(aminoalkoxy)phenyl}sulphonyl]indolizines

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Received 19 November 2002; received in revised form 15 July 2003; accepted 6 August 2003

Abstract

A quantitative structure–activity relationship (QSAR) study has been made on two different series of 1-[{4-(aminoalkoxy)phenyl}sulphonyl]indolizines acting as calcium entry blockers, using some physicochemical and structural parameters. Two different assays were reported for both the 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 that required to block Ca^{2+} induced concentration of K^+ depolarised rat aorta by 50%. For series 1, where the 2-position substituents of indolizine ring were varied along with the aminoalkoxy moieties of the phenyl ring, the QSAR analysis shows that the 2-position substituents can equally affect both the activities through their hydrophobic and electronic properties and the aminoalkoxy moiety through some steric effects. For series 2, where the indolizine ring has been replaced by varying heterocyclic rings, along with the changes in aminoalkoxy moiety of the phenyl ring, the QSAR exhibits that these different heterocyclic rings affect both the activities through some steric roles, altering the conformations of the receptors from system A to system B. Among the different heterocyclic rings, the N-substituted indole ring is shown to be more conducive to both the activities than any other ring. However, a 5-membered ring is indicated to be less effective than a 9- or 10-membered ring for activity B. Additionally, the amino moieties having phenyl ring with methoxy groups at 3,4,and 5-positions are shown to favour both A and B activities.

Keywords: quantitative structure–activity relationship; calcium channel blockers; indolizines

1. Introduction

Calcium channel blockers (also called calcium antagonists) have been found to be most effective for the treatment of vasospactic angina. These drugs selectively inhibit Ca^{2+} influx into heart muscles by blocking the slow inward channels for Ca^{2+} or inhibit Ca^{2+} influx into vascular smooth muscle. The result is negative inotropism of smooth muscle relaxation, which is translated into hypertension.

However, despite the great interest in the design and development of calcium channel blockers during the last two decades, the attention remained greatly focused on 1,4-dihydropyridine class of drugs, of which only one member, nifedipine (**1**), could be developed for clinical use. Two other classes of compounds, namely phenylalkylamines and benzothiazepines, were also studied for their calcium channel blocking activity, from which were approved verapamil (**2**) and diltiazem (**3**), respectively, for clinical applicability (Scheme 1) [1]. The structural parameters important to potency of dihydropyridines in vitro have been well described [2,6]. Rovnyak et al. [7–9] and others [3–5,10] examined the effect of unsymmetrically substituted 4-aryl-1,4-dihydropyridines on calcium antagonist activity, leading to the conclusion that the receptor bound conformation positions the substituted aryl ring axially, perpendicular to and bisecting the flattened boat like dihydropyridine ring, with the 4-aryl substituent preferring the synperiplanar (relative to C4-H) orientation.

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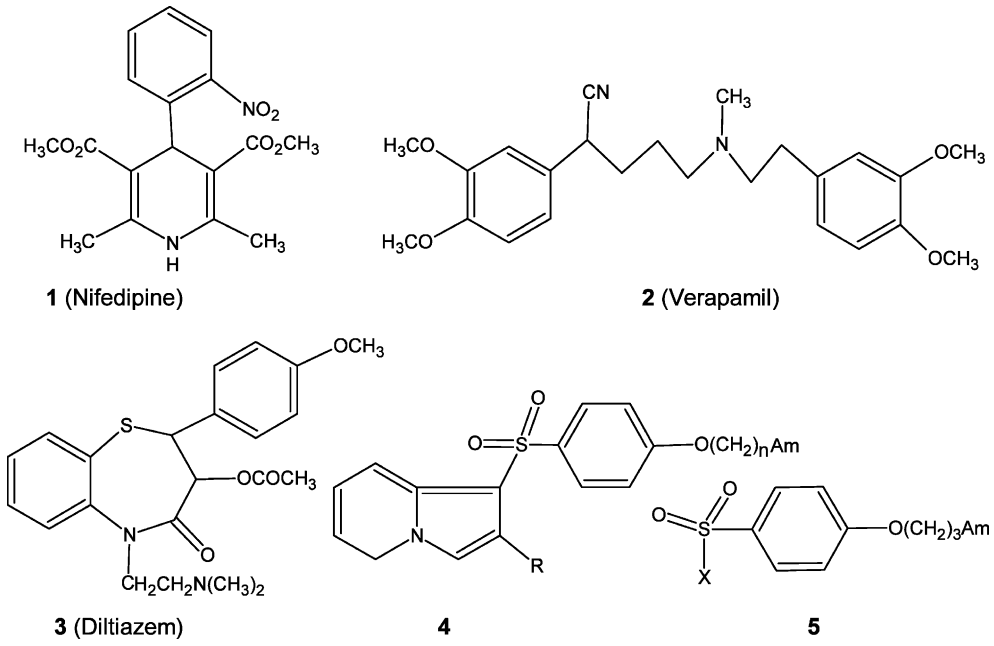
0223-5234/03/$ - see front matter
doi:10.1016/j.ejmech.2003.08.001



Scheme 1.

The binding for the phenyl alkyl amines appears to be allosterically linked to the dihydropyridine binding site [3,11–13]. Similar to phenylalkylamines, diltiazem series (benzothiazepines) bind to a site on the calcium channel that is allosterically linked to the dihydropyridine receptor [14]. However, a recent comparative molecular field analysis (CoMFA) has suggested that diltiazem compounds bind with receptors through a negative charged site, two hydrogen bonding sites, and three different hydrophobic regions [15].

In the last decade, however, several new classes of calcium entry blockers (CEBs) also emerged, in which 1-[{4-(aminoalkoxy)phenyl}sulphonyl]indolizines drew more attention. Gubin et al. [16,17] reported successively two different series of indolizines: **4**, in which were varied the R-substituents at the 2-position of the indolizine ring and the amine moiety (Am) of the 4-substituents of the phenyl ring, and **5**, in which the indolizine ring was replaced by a variety of heterocyclic rings along with the changes in the Am moiety. In both the series, certain structural features important for the activity were pointed out. However, Gubin et al.'s reports were based only on qualitative observations, which can be fortuitous also. A quantitative structure–activity relationship (QSAR) study describes a definite role in a quantitative term of a structural feature in molecule with a definite contribution to the activity of a particular physiochemical property of that structural feature. Thus, QSAR studies have predictive ability and simultaneously provide deeper insight into the mechanism of drug receptor interactions. We therefore report here a QSAR study on both the series reported by Gubin et al. [16,17].

2. Materials and method

The two series of 1-sulphonylindolizine analogues studied by Gubin et al. [16,17] are listed in Tables 1 and 2, respectively. The activity parameters are given in terms of $\log(1/IC_{50})$, where $(IC_{50})_A$ refers to the molar concentration of the compound required to reduce [^{3}H]nitrendipine binding by 50% and $(IC_{50})_B$ refers to that required to block Ca^{2+} induced concentration of K^+ depolarised rat aorta by 50%.These activity parameters have been correlated with some physiochemical parameters, such as hydrophobic constant π, electronic constant σ, or with some structural parameters such as the first-order valence molecular connectivity index ($^1\chi^v$) of the substituents. π- and σ-values have been taken from the literature [18] and $^1\chi^v$ has been calculated as suggested by Kier and Hall [19] and as described below:

$^1\chi^v$ is calculated according to the equation

$$^1\chi^v = (\sum \delta_i^v \delta_j^v)^{-1/2} \quad (1)$$

where δ_i^v and δ_j^v are the vertex connectivity indices of atoms i and j, respectively, and the summation extends to all the bonded pairs of non-hydrogenic atoms in the group or molecule. For the second and third rows of atoms, a unified definition of δ_i^v as expressed by Eq. (2) was given [20]. In this equation, Z_i^v is the number of valence electrons of the atom i, h_i is the number of hydrogen atoms attached to it, and Z_i is its atomic number.

$$\delta_i^v = (Z^{v-}h_i)/(Z - Z_i^{v-}1) \quad (2)$$

The connectivity index $^1\chi^v$ signifies the degree of branching, connectivity of atoms, and the unsaturation

Table 1
A series of 1-sulphonylindolizines (**4**) with calcium entry blocking activities and the correlates

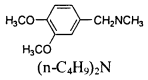
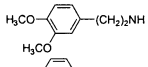
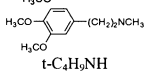
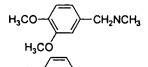
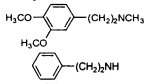
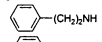
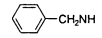
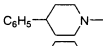
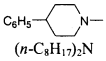
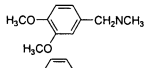
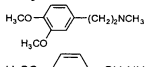
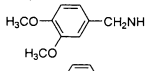
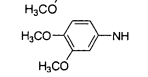
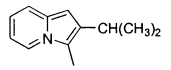
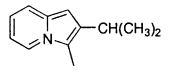
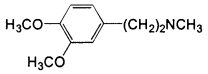
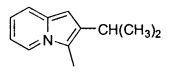
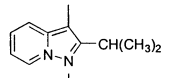
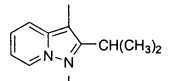
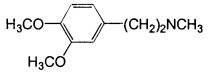
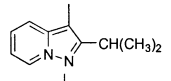
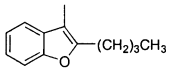
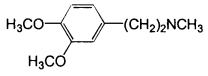
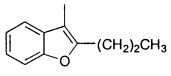
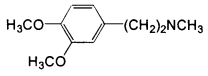
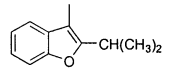
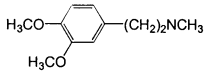
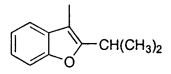
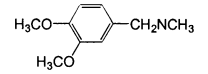
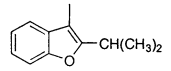
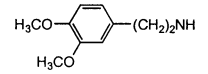
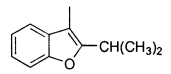
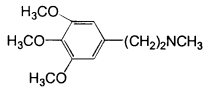
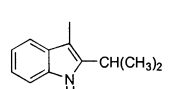
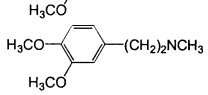
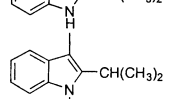
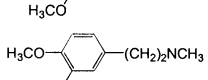
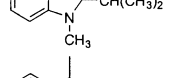
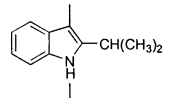
No.	R	Am	n	π_R	σ_R	$^1\chi^v_{Am}$	I_1	I_2	$\log(1/IC_{50})_A$ Obsd[a]	$\log(1/IC_{50})_A$ Calcd Eq.(3)	$\log(1/IC_{50})_B$ Obsd[a]	$\log(1/IC_{50})_B$ Calcd Eq.(4)
1	CH_3	$(C_2H_5)_2N$	3	0.56	-0.170	2.047	0	0	5.28	5.66	5.47	5.71
2	CH_3	$(n\text{-}C_3H_7)_2N$	3	0.56	-0.170	3.047	0	0	6.19	6.19	6.02	6.13
3	$i\text{-}C_3H_7$	$(CH_3)_2N$	3	1.53	-0.150	0.894	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	-0.160	3.047	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	-0.160	4.047	0	0	7.66	7.60	6.55	6.46
6	$i\text{-}C_3H_7$	$(C_2H_5)_2N$	3	1.53	-0.150	2.047	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	-0.150	3.047	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	-0.150	4.047	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	-0.200	4.047	0	0	8.02	8.30	7.28	7.18
10	$c\text{-}C_3H_5$		3	1.14	-0.210	4.048	1	0	8.72	9.03	8.33	8.50
11	C_6H_{11}	$(n\text{-}C_4H_9)_2N$	3	2.51	-0.220	4.047	0	0	6.95	6.77	5.39	5.44
12	C_6H_5	$(n\text{-}C_4H_9)_2N$	3	1.96	-0.010	4.047	0	0	6.81	6.73	5.79	5.77
13	CH_3	$(n\text{-}C_4H_9)_2N$	3	0.56	-0.170	4.047	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	-0.130	4.047	0	0	7.85	8.18	7.27	7.32
15	C_2H_5	$(n\text{-}C_3H_7)_2N$	3	1.02	-0.150	3.047	0	0	6.74	7.47	6.82	7.14
16	C_2H_5	$(n\text{-}C_4H_9)_2N$	3	1.02	-0.150	4.047	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	-0.210	4.047	0	0	8.60	8.57	7.96	7.86
18	C_2H_5	$(n\text{-}C_4H_9)_2N$	5	1.02	-0.150	4.047	0	0	7.70	7.84	7.01	7.24
19	C_2H_5	$(n\text{-}C_5H_{11})_2N$	3	1.02	-0.150	5.047	0	0	8.20	8.05	7.20	7.02
20	C_2H_5	$(n\text{-}C_4H_9)_2N$	2	1.02	-0.150	4.047	0	0	7.48	7.84	7.14	7.24
21	C_2H_5	$(n\text{-}C_4H_9)_2N$	4	1.02	-0.150	4.047	0	0	8.34	7.84	7.48	7.24
22	C_2H_5		3	1.02	-0.150	2.652	0	0	6.56	7.28	6.45	7.01
23	C_2H_5	$t\text{-}C_4H_9NH$	3	1.02	-0.150	1.750	0	0	6.89	6.74	6.38	6.53
24	C_2H_5		3	1.02	-0.150	4.047	1	0	8.34	8.33	7.96	7.88
25	C_2H_5		3	1.02	-0.150	4.580	1	0	8.64	8.42	7.87	7.81
26	$i\text{-}C_3H_7$	$t\text{-}C_4H_9NH$	3	1.53	-0.150	1.750	0	0	7.76	7.26	7.38	6.78
27	$i\text{-}C_3H_7$		4	1.53	-0.150	4.080	1	0	8.35	8.82	7.84	8.13
28	$i\text{-}C_3H_7$		3	1.53	-0.150	4.580	1	0	9.21	8.94	8.25	8.06
29	$i\text{-}C_3H_7$		3	1.53	-0.150	2.784	0	0	8.40	7.86	7.09	7.31
30	$i\text{-}C_3H_7$		3	1.53	-0.150	2.618	0	0	8.35	7.78	7.64	7.24
31	$i\text{-}C_3H_7$		3	1.53	-0.150	4.648	0	0	7.85	8.50	6.69	7.39
32	$i\text{-}C_3H_7$		3	1.53	-0.150	4.648	0	0	8.18	8.50	7.09	7.39
33	$i\text{-}C_3H_7$	$(n\text{-}C_8H_{17})_2N$	3	1.53	-0.150	8.047	0	0	8.19	8.22	4.52	4.69
34	$i\text{-}C_3H_7$	$(n\text{-}C_5H_{11})_2N$	3	1.53	-0.150	5.047	0	0	9.05	8.57	7.05	7.27
35	$i\text{-}C_3H_7$	$(n\text{-}C_4H_9)_2N$	4	1.53	-0.150	4.047	0	0	8.89	8.36	7.69	7.49
36	$i\text{-}C_3H_7$		3	1.53	-0.150	4.080	1	0	9.21	8.82	8.50	8.13
37	$i\text{-}C_3H_7$		4	1.53	-0.150	4.580	1	0	8.64	8.94	7.67	8.06
38	$i\text{-}C_3H_7$		3	1.53	-0.150	3.670	1	0	8.92	8.69	7.89	8.13
39	$i\text{-}C_3H_7$		3	1.53	-0.150	3.109	1	0	6.42[b]	9.62	6.40[c]	9.17

Table 2
A series of 1-sulphonylindolizines (**5**) with calcium entry blocking activities and the correlates

No.	X	Am	$^1\chi^v_X$	$^1\chi^v_{Am}$	I_1	I_2	D_{NI}	D_5	$\log(1/IC_{50})_A$ Obsd[a]	Calcd Eq.(7)	$\log(1/IC_{50})_B$ Obsd[a]	Calcd Eq.(8)
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
6		$t\text{-}C_4H_9NH$	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
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
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

in the molecule and is simple to calculate. It is a good structural parameter to account for the variation in the activity, particularly when no experimental data for any physicochemical properties of the molecules are available as is the case here. Both Tables 1 and 2 list the calculated $^1\chi^v$ values of pertinent substituents and also the useful π- and σ-values for some substituents. In addition to these parameters, some dummy variables (also called indicator variables) have also been used, which are defined within the text. The $^1\chi^v$ values of only substituents have been calculated since considering $^1\chi^v$ of only substituents, instead of the whole molecule, leads to describe the exclusive effect of substituents on the activity. To calculate the $^1\chi^v$ of only substituents, each substituent has been considered as a whole molecule. The bond by which the substituents are attached to the parent structure has been taken into account to calculate the δ^v value for the attached atom of the substituents, but its connectivity $[(\delta_i^v\delta_j^v)^{-1/2}]$ has not been taken into account, as it remains constant for all substituents. Its addition would not affect the regression results.

3. Results and discussion

For the data of Table 1, the best equations that could be obtained were as follows:

$$\begin{aligned}\log(1/IC_{50})_A &= 6.577(\pm1.553)\pi_R - 2.179(\pm0.532)(\pi_R)^2 \\ &+ 0.949(\pm0.354)^1\chi^v_{Am} - 0.081(\pm0.042) \\ &\times (^1\chi^v_{Am})^2 - 8.496(\pm4.230)\sigma_R + 0.452(\pm0.303)I_1 \\ &+ 0.768(\pm0.506)I_2 - 0.387(\pm1.700) \qquad (3)\end{aligned}$$

$n = 48$, $r = 0.919$, $s = 0.41$, $F_{7,40} = 31.10(3.12)$, $(\pi_R)_{opt} = 1.51$, $(^1\chi^v_{Am})_{opt} = 5.86$

$$\begin{aligned}\log(1/IC_{50})_B &= 5.831(\pm1.217)\pi_R - 2.097(\pm0.417)(\pi_R)^2 \\ &+ 1.238(\pm0.278)^1\chi^v_{Am} - 0.160(\pm0.033) \\ &\times (^1\chi^v_{Am})^2 - 7.700(\pm3.315)\sigma_R + 0.647(\pm0.238)I_1 \\ &+ 1.057(\pm0.396)I_2 - 0.067(\pm1.332) \qquad (4)\end{aligned}$$

$n = 48$, $r = 0.948$, $s = 0.32$, $F_{7,40} = 50.20(3.12)$, $(\pi_R)_{opt} = 1.39$, $(^1\chi^v_{Am})_{opt} = 3.87$

In these equations, π_R refers to hydrophobic constant of R-substituent, σ_R refers to its electronic constant (Hammett constant), and $^1\chi^v_{Am}$ refers to the connectivity of Am moiety of 4-substituent of the phenyl ring. I_1 and I_2 are two indicator variables, where I_1 stands, with a value of unity for an A_m moiety having 3,4-dimethoxy substituted phenyl ring, and I_2 stands, with a value of unity, for an A_m moiety having a 5-methoxy substituted phenyl ring. Among the statistical parameters, 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. The figures within the parentheses with $\pm$ sign are 95% confidence intervals and the figures within the parentheses following the F-values are the theoretical F-values at 99% level.

Now Eqs. (3) and (4) exhibit that both types of calcium channel binding activity of the series belonging to **4** (Table 1) are governed by the hydrophobic and electronic properties of R-substituents of the indolizine ring and the connectivity index of the Am moiety of the phenyl ring. However, both the equations exhibit the parabolic correlations of the activities with π_R and $^1\chi^v_{Am}$, indicating that both these parameters will have an optimum value in each case as given in each equation. The optimum values for π_R, $(\pi_R)_{opt}$, in both the equations are essentially same but that of $(^1\chi^v_{Am})_{opt}$ widely differing, suggesting that the structural characteristic (particularly size) of the A_m moiety will be better tolerated by the receptor for activity A than for activity B, as the value of $(^1\chi^v_{Am})_{opt}$ for the former (Eq. (3)) is higher than for the latter (Eq. (4)).However, slightly smaller coefficients of I_1 and I_2 in Eq. (3) than in Eq. (4) suggest that 3,4-dimethoxy and/or 5-methoxy groups present at the phenyl ring of Am moieties will be less beneficial for activity A than for activity B, although in both they will have positive effects. These methoxy groups can be expected to form the hydrogen bonds with the receptors or else they can have the steric effects, which can be verified by synthesising compounds with higher alkoxy groups, e.g. OEt, OPr, etc. Thus the Am moieties seem to be important because of their size and OCH_3-like functional groups. However, the length of the linker chain, i.e. $(OCH_2)_n$, was found to have little effect, as the variation in the value of n was found to be totally insignificant statistically when included in the correlations (Eqs. (5) and (6)).

$$\begin{aligned}\log(1/IC_{50})_A &= 6.560(\pm1.576)\pi_R - 2.172(\pm0.541)(\pi_R)^2 \\ &+ 0.942(\pm0.363)^1\chi^v_{Am} - 0.081(\pm0.043) \\ &\times (^1\chi^v_{Am})^2 - 8.510(\pm4.283)\sigma_R + 0.451(\pm0.307)I_1 \\ &+ 0.776(\pm0.515)I_2 \\ &+ 0.043(\pm0.292)n - 0.496(\pm1.877) \qquad (5)\end{aligned}$$

$n = 48$, $r = 0.919$, $s = 0.41$, $F_{8,39} = 26.60(3.01)$, $(\pi_R)_{opt} = 1.51$, $(^1\chi^v_{Am})_{opt} = 5.81$

$$\log(1/IC_{50})_B = 5.860(\pm1.230)\pi_R - 2.108(\pm0.422)(\pi_R)^2 + 1.251(\pm0.283)^1\chi^v_{Am} - 0.162(\pm0.033) \times (^1\chi^v_{Am})^2 - 7.677(\pm3.342)\sigma_R + 0.649(\pm0.240)I_1 + 1.044(\pm0.402)I_2 - 0.073(\pm0.228)n + 0.121(\pm1.464) \quad (6)$$

$n = 48$, $r = 0.948$, $s = 0.32$, $F_{8,39} = 43.34(3.01)$, $(\pi_R)_{opt} = 1.39$, $(^1\chi^v_{Am})_{opt} = 3.86$

In both Eqs. (3) and (4), the negative coefficient of σ_R suggests that electron-donating property of the R-substituents would be beneficial. The electron donation from these substituents may affect the electronic population at indolizine nitrogen and thus the participation of this nitrogen is indicated, which can be either through charge–charge interaction or through hydrogen bond formation with the receptor. The R-substituents otherwise may have hydrophobic interaction with some hydrophobic site of the receptor which may have limited bulk tolerance.

For Table 2, we found the following correlations:

$$\log(1/IC_{50})_A = 7.180(\pm4.169)^1\chi^v_X - 0.993(\pm0.584)(^1\chi^v_X)^2 + 1.505(\pm0.398)I_1 + 1.133(\pm0.537)D_{NI} - 5.246(\pm7.116) \quad (7)$$

$n = 27$, $r = 0.900$, $s = 0.48$, $F_{4,22} = 23.39(4.31)$, $(^1\chi^v_X)_{opt} = 3.62$

$$\log(1/IC_{50})_B = 114.705(\pm44.798) - 47.415(\pm20.218)^1\chi^v_X + 5.202(\pm2.281)(^1\chi^v_X)^2 + 0.706(\pm0.261)I_1 + 0.706(\pm0.362)D_{NI} - 20.518(\pm7.686)D_5 \quad (8)$$

$n = 28$, $r = 0.933$, $s = 0.32$, $F_{5,22} = 29.47(3.99)$, $(^1\chi^v_X)_{opt} = 4.56$

These equations do not exhibit any role of $^1\chi^v_{Am}$ in the activities of the compounds belonging to series of **5**, where the heterocyclic rings attached to the sulphur are varying. Thus, the A_m moiety does not seem to play any specific role; however, the presence of I_1 parameter with positive coefficient in both Eqs. (7) and (8) does show that the 3,4-dimethoxy groups present in their phenyl ring are as important as they are in the series of **4** (Table 1), but the absence of I_2 parameter in both the equations indicates that 5-methoxy group has to play no role in this series of compounds. It is however to be noted that the coefficient of I_1 in Eq. (7) is approximately twice that in Eq. (8), suggesting that the effect of 3,4-dimethoxy groups for activity A may be almost two times (in log term) higher than for activity B.

A major difference is, however, shown in the roles of $^1\chi^v$ of X-substituents. In both Eqs. (7) and (8), though activities are shown to have parabolic correlations with $^1\chi^v_X$, the natures of parabola are exactly opposite to each other. Thus while Eq. (7) shows that activity A will initially increase with the increase in the value of $^1\chi^v_X$ and may decrease after an optimum value of $^1\chi^v_X$ equal to 3.62, Eq. (8) exhibits that activity B will initially decrease with the increase in the value of $^1\chi^v_X$ and then may increase after an optimum value (to be better called the worst value) of $^1\chi^v_X$ equal to 4.56. This difference and the absence of any specific role of A_m moiety in either of the two activities and the presence of no role of its 5-methoxy group all can be attributed to probable conformational changes in the receptors in system A and B. Derivatives of **5** may be able to change the conformation of the receptors in systems A and B such that their A_m moiety may not have any opportunity to play any specific role with the receptors and that the hydrogen bonding site in the latter may not be properly oriented towards 5-methoxy group of A_m moiety to interact with. On the other hand, the conformation of the receptor in A may be such that the X-substituents therein may initially play a positive steric role and the same receptor in B may acquire such a conformation that the X-substituents may initially play a negative steric role as accounted for by their $^1\chi^v_X$ parameter in this case.

It is found that activities A and B for derivatives of both **4** (Table 1) and **5** (Table 2) are mutually well correlated (Eqs. (9) and (10)) with exception of one or two compounds.

Table 1

$$\log(1/IC_{50})_B = 0.769(\pm0.11)\log(1/IC_{50})_A + 1.152(\pm0.891) \quad (9)$$

$n = 48$, $r = 0.90$, $s = 0.37$, $F_{1,46} = 194.33(7.21)$, compound 33 excluded

Table 2

$$\log(1/IC_{50})_B = 0.557(\pm0.107)\log(1/IC_{50})_A + 3.036(\pm0.891) \quad (10)$$

$n = 27$, $r = 0.90$, $s = 0.27$, $F_{1,25} = 111.60(7.77)$, compounds 9 and 21 excluded

These mutual correlations of activities in system A and B suggest that if QSARs do not show the same mode of interactions of compounds in two different systems, an expected results in one system from the other can be had only when there are conformational changes in the receptors.

There is, however, an indicator parameter, D_{NI}, in both Eqs. (7) and (8) that shows a positive effect on both A and B activities of an X-substituents containing N-

substituted indole nucleus. $D_{NI} = 1$ for such X-substituents and zero for others. Further, the presence with a negative coefficient of an additional parameter D_5 in Eq. (8), that has been used with a value of unity for an X-substituent containing 5-membered ring, suggests that a 5-membered ring would be of less value than a 9-membered or 10-membered ring for activity B. This delirious effect of a 5-membered ring however could not surface in the case of activity A.

Thus, it is found that the compounds of series **4** adopt almost same mode of interactions with receptors in both A and B systems and involve steric, electronic and hydrophobic interactions, but those of series **5**, where heterocyclic rings of sulphonyl group vary, adopt quite different modes of interactions in the two systems, that may be based upon drastic conformational changes of the receptors from system A to B.

However, in deriving all the above equations, some compounds were excluded, viz, compound 39 of Table 1 in deriving Eqs. (3) and (4), compounds 1 and 21 of Table 2 in deriving Eq. (7), and compounds 1, 6 and 7 of the same Table in deriving Eq. (8). All these compounds exhibited aberrant behaviours. However, while the low observed activities of compounds 39, which has been excluded from Eqs. (3) and (4), as compared to the corresponding predicted ones from these equations can be attributed to the nature of Am moiety, where NH is directly attached to the phenyl ring reducing the flexibility of the latter, no convincing reasons can be assigned to such aberrations of compounds excluded from Eqs. (7) and (8).

Acknowledgements

The required financial assistance and facilities provided by the Institute (BITS) are gratefully acknowledged.

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