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Quantitative Structure–Activity Relationship Studies on Some Nonbenzodiazepine Series of Compounds Acting at the Benzodiazepine Receptor

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Abstract—Quantitative structure–activity relationship (QSAR) studies have been made on a few non-benzodiazepine series of compounds such as 3-substituted imidazo[1,2-b]pyridazines, 2-phenylimidazo[1,2-α]pyridines, 2-(alkoxycarbonyl)imidazo[2,1-b]benzothiazoles, and 2-arylquinolines. For the first series of compounds a Fujita–Ban approach has been followed, which revealed the highest activity contribution for 3,4-OCH_2O group of 2-phenyl moiety and for a methoxy group at 6-position. For the rest of the series, a Hansch approach has been adopted. The hydrophobic and electronic properties of the various substituents have been found to play major roles in the binding of these compounds with the receptor. Based on these studies, a hypothetical model for the drug–receptor interaction has been proposed.

Introduction

Ever since the discovery of specific binding sites for benzodiazepines in mammalian brain,[1,2] the benzodiazepine receptor (BZR) has been widely investigated. The pharmacological effects of the benzodiazepines result from their affinity for a special binding site on the GABA receptor, which is associated with a transmembrane chloride ion channel. This macromolecular complex has several major binding domains, including BZ sites.[3] In addition to the classical benzodiazepines, a large number of structurally different non-BZ molecules have been identified as endogenous ligands for BZRs.[4] A detailed structure–activity relationship (SAR) study on several of them has been recently presented.[5] Variety of these non-BZ ligands were studied for their quantitative structure–activity relationship (QSAR) to have a better understanding of the modes of their interactions with the receptor,[6–15] and the models for binding of a few of them were discussed.[16] In continuation to our investigation, we present here QSAR studies on some more series of non-BZ compounds binding to $GABA_A$/BZ receptors.

Materials and Methods

The series of compounds subjected to QSAR analysis are 6-alkoxyimidazo[1,2-b]pyridazines (I) studied by Harrison et al.,[17] 2-phenylimidazo[1-2-α]pyridines (II) studied by Trapani et al.,[18] imidazo[2,1-b]benzothiazoles (III) studied by Trapani et al.,[19] and 2-aryl-4-piperidinoquinolines studied by Andersen et al.[20] All these series of compounds are listed in Tables 1–4. In all the tables, IC_{50} refers to the concentration of the test compound causing 50% inhibition of the specific binding of [^{3}H]diazepam or [^{3}H]flunitrazepam to BZR as specified in the tables. Since in the first series (Table 1) the variation in the substituents at each substituted position is small, a Fujita–Ban approach[21] has been adopted to estimate the de novo contribution of substituents to the activity of the molecules. For the rest of

Key words: QSAR; non-benzodiazepines; 3-substituted imidazo[1,2-b]pyridazines, 2-phenylimidazo[1,2-α]pyridines, 2-(alkoxycarbonyl)imidazo[2,1-b]benzothiazoles; 2-arylquinolines; BZR.
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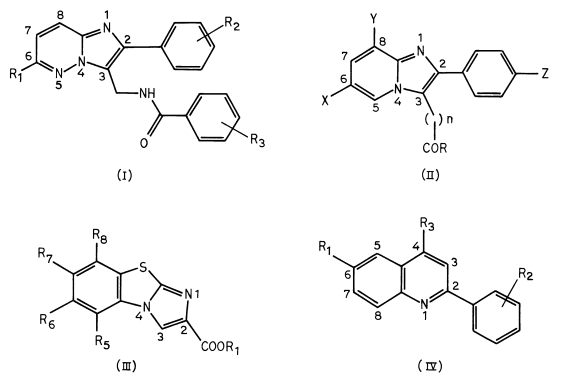
Table 1. 3-Substituted imidazo[1,2-b]pyridazines (I) and their BZR binding affinities against [^{3}H]diazepam binding.[17]

S. No.	R_1	R_2	R_3	log(1/IC_{50})	
				Obsd[a]	Calcd[b]
1	OCH_3	3,4-OCH_2O	H	8.15	7.90
2	OCH_3	4-Cl	H	7.54	7.53
3	OCH_3	H	2-F	6.86	7.09
4	OCH_3	4-CH_3	2-F	7.68	7.61
5	OCH_3	3,4-OCH_2O	2-F	7.85	7.90
6	OC_2H_5	H	H	6.73	6.77
7	OC_2H_5	4-CH_3	H	7.46	7.29
8	OC_2H_5	3,4-OCH_2O	H	7.60	7.57
9	OC_2H_5	4-Cl	H	7.19	7.20
10	OC_2H_5	H	2-F	6.68	6.77
11	OC_2H_5	4-CH_3	2-F	7.29	7.29
12	OC_2H_5	3,4-OCH_2O	2-F	7.51	7.57
13	OC_3H_7	4-CH_3	H	6.74	6.78
14	OC_3H_7	3,4-OCH_2O	H	6.94	7.06
15	OC_3H_7	H	2-F	6.62	6.26
16	OC_3H_7	4-CH_3	2-F	6.84	6.78
17	OCH_2OCH_3	4-CH_3	H	6.50	6.78
18	OCH_3	3,4-OCH_2O	3-NO_2	8.10	7.90
19	OCH_3	3,4-OCH_2O	4-NO_2	7.64	7.90

[a] Taken from ref. 17.
[b] Calculated using data of Table 5.

the series, Hansch approach has been applied to correlate the activity with some physicochemical or structural parameters, which were either taken directly from the literature or calculated.



Results and Discussion

In Fujita–Ban approach, the total biological activity (BA) of a molecule is given by

$$BA = \sum_i G_i X_i + \mu \quad (1)$$

Table 2. 2-Phenylimidazo[1-2-α]pyridine derivatives (II) and their BZR binding affinities against [^{3}H]flunitrazepam binding[18] and physicochemical parameters

S. No	X	Z	R	n	π_X	log(1/IC_{50})	
						Obsd[a]	Calcd, eq (2)
1	Cl	Cl	$N(C_2H_5)_2$	0	0.71	5.08	5.22
2	Cl	Cl	$N(C_3H_7)_2$	0	0.71	5.06	5.22
3	Cl	Cl	N-$(CH_2)_4$-	0	0.71	5.53	5.22
4	H	H	$N(C_3H_7)_2$	1	0	6.33	6.08
5	Cl	H	$N(C_3H_7)_2$	1	0.71	7.07	6.87
6	Br	H	$N(C_3H_7)_2$	1	0.86	6.94	6.87
7	I	H	$N(C_3H_7)_2$	1	1.12	6.54	6.73
8	CH_3	H	$N(C_3H_7)_2$	1	0.56	6.90	6.82
9	CH_3O	H	$N(C_3H_7)_2$	1	−0.02	5.55	6.04
10	NO_2	H	$N(C_3H_7)_2$	1	−0.28	5.56	5.40
11	Br	H	$N(C_3H_7)_2$	1	0.86	7.24	6.87
12	Cl	H	N-$(CH_2)_4$-	1	0.71	7.04	6.87
13	Cl	H	N-$(CH_2)_5$-	1	0.71	6.62	6.87
14	Cl	H	$N(C_3H_7)_2$	2	0.71	6.51	6.87
15	Cl	H	OC_2H_5	0	0.71	5.67	5.82
16	CH_3	CH_3	OC_2H_5	0	0.56	5.94	5.76
17	CH_3	H	OC_2H_5	1	0.56	5.86	5.76
18	Cl	H	OC_2H_5	1	0.71	5.93	5.82
19[b]	Cl	Cl	OC_2H_5	1	0.71	6.16	4.17
20	Cl	H	OC_2H_5	2	0.71	5.95	5.82
21	CH_3	H	OC_4H_9	1	0.56	5.50	5.76
22	Cl	H	OC_4H_9	1	0.71	5.60	5.82
23[b]	Cl	Cl	OC_4H_9	1	0.71	5.56	4.17
24	Cl	H	OC_4H_9	2	0.71	5.93	5.82

[a] Taken from ref. 18.
[b] Not included in the derivation of eq (2).

Table 3. 2-(Alkoxycarbonyl)-4*H*-imidazo[2,1-b]benzothiazoles (III) and their BZR binding affinities against [^{3}H]flunitrazepam[19] and physicochemical parameters

S. No.	R_1	R_5	R_6	R_7	π_{R7}	log(1/IC_{50})	
						Obsd[a]	Calcd, eq (3)
1	OCH_3	H	H	H	0	7.22	7.12
2	OC_2H_5	H	H	H	0	6.92	7.12
3	$OCH_2C_6H_5$	H	H	H	0	7.30	7.12
4	OC_2H_5	H	H	C_2H_5	1.02	5.40	5.37
5	OC_2H_5	H	H	F	0.14	7.29	7.52
6	OC_2H_5	H	H	Cl	0.71	6.83	7.04
7	OC_2H_5	H	H	Br	0.86	6.51	6.35
8	OC_2H_5	H	H	NO_2	−0.28	5.54	5.72
9	OC_2H_5	Cl	H	H	0	7.44	7.12
10	OC_2H_5	OCH_3	H	H	0	7.40	7.12
11	OC_2H_5	CH_3	H	H	0	7.01	7.12
12[b]	OC_2H_5	H	CH_3	CH_3	0.56	6.47	7.49
13	OC_2H_5	H	Cl	Cl	0.71	6.98	7.64
14	OCH_3	Cl	H	H	0	7.21	7.12
15	$OCH_2C_6H_5$	Cl	H	H	0	6.86	7.12

[a] Taken from ref. 19.
[b] Not included in the derivation of eq (3).

Table 4. 2-Arylquinolines (IV) and their BZR binding affinities against [^{3}H]flunitrazepam binding[20] and physicochemical parameters

S. No.	R_1	R_2	R_3	πR_2	σR_1	σR_2	$V_{w,R3}$ ($10^2 A^{\circ 3}$)	log(1/IC_{50})	
								Obsd[a]	Calcd, eq (4)
1	H	H	OH	0	0	0	0.137	5.19	6.06
2	CH_3	H	OH	0	−0.17	0	0.137	6.23	5.76
3	Cl	H	OH	0	−0.23	0	0.137	6.37	6.47
4	H	H	A	0	0	0	1.410	7.07	7.18
5	H	H	B	0	0	0	1.372	7.30	7.22
6	H	H	C	0	0	0	1.133	7.95	7.49
7	CH_3	H	C	0	−0.17	0	1.133	6.98	7.19
8	Cl	H	C	0	0.23	0	1.133	7.69	7.90
9	H	2-OCH_3	C	−0.02	0	−0.27	1.133	5.97	6.62
10	H	2-OH	C	−0.67	0	−0.37	1.133	7.71	7.49
11	F	2-OCH_3	C	−0.02	0.06	−0.27	1.133	7.29	6.73
12	F	2-OH	C	−0.67	0.06	−0.37	1.133	8.15	7.60
13	F	4-F	C	0.14	0.06	0.06	1.133	8.06	7.54
14	F	4-Cl	C	0.71	0.06	0.23	1.133	7.44	7.06
15	H	H	D	0	0	0	1.423	6.74	7.16
16	F	2-OH	D	−0.67	0.06	−0.37	1.423	6.86	7.26
17	CH_3	H	E	0	0	0	1.437	7.20	7.14
18	Cl	H	E	0	−0.17	0	1.437	6.60	6.84
19	H	H	E	0	0.23	0	1.437	7.09	7.55
20	H	2-OCH_3	E	−0.02	0	−0.27	1.437	5.76	6.27
21	H	2-OH	E	−0.067	0	−0.37	1.437	7.50	7.14
22	F	2-OCH_3	E	−0.02	0.06	−.027	1.437	6.72	6.38
23	F	2-OH	E	−0.67	0.06	−0.37	1.437	7.44	7.25
24	F	4-F	E	0.14	0.06	0.06	1.437	7.53	7.19
25	F	4-Cl	E	0.71	0.06	0.23	1.437	6.66	6.71
26	H	H	F	0	0	0	1.050	7.17	7.59
27	F	2-OH	F	−0.67	0.06	−0.37	1.050	7.30	7.69
28	H	H	G	0	0	0	1.437	7.16	7.14
29	H	H	OCH_3	0	0	0	0.304	6.33	5.87
30	CH_3	H	OCH_3	0	−0.17	0	0.304	5.35	5.57
31	H	H	$OC_6H_5CH_2$	0	0	0	1.000	5.64	5.07
32	CH_3	H	$OC_6H_5Ch_2$	0	−0.17	0	1.000	4.63	4.77
33[b]	H	H	$O(CH_2)_3COO$ E t	0	0	0	1.176	6.19	4.87
34	H	H	O-(m-$CO_2C_2H_5$)C_6H_4	0	0	0	1.532	4.55	4.46
35	H	H	O-(m-$CONHC_2H_5$)C_6H_4	0	0	0	1.561	4.17	4.43

[a] Taken from ref. 20.

[b] Not included in the derivation of eq (4).

A = N-1-ethyl-1-piperazine carboxamide.
B = methylamino-piperazinyl methanethione.
C = 4-piperidine carboxamide.
D = ethyl-4-piperidine carboxylate.
E = 3-methyl-5-(4-piperidinyl)-1,2,4-oxadiazole.
F = 4-piperidine carbonitrile.
G = 5-methyl-3-(4-piperidinyl)-1,2,4-oxadiazole.

where G_i is the activity contribution of the *i*th substituent relative to H, and X_i is a parameter which takes the value of 1 or 0 according to the presence or absence of the *i*th substituent in the molecule. The constant μ is the activity of the unsubstituted molecule. Thus eq (1) yields simultaneous equations equal in number to that of the compounds in the series. If the number of compounds in a set is sufficiently large as compared to the number of total substituents, a least-square method[22] is used to find out the values of G_i and μ.

For the first series of compounds in Table 1, the Fujita–Ban analysis gave the results as shown in Table 5. The activity contributions of only those substituents for which they were statistically significant are reported. In the table, r is the correlation coefficient, s is the standard deviation, F is the F-ratio between the variance of calculated and observed activities and data in the parentheses are 95% confidence intervals. Now from the results as listed in Table 5, we find that, of R_1 substituents, the OCH_3 group and, of R_2 substituents, the

3,4-OCH_2O group make the largest contributions. At R_1, the OCH_3 group might be having the optimum shape and size required for the interaction with the receptor and hence the less favourable effect of OC_2H_5 may be attributed to some steric role played by it. This proposition is based on the observation that of all the alkoxy substituents used, or that can be used, for R_1, the OCH_3 group is the smallest in size and has the activity contribution larger than the next smallest group, OC_2H_5. Groups bigger than OC_2H_5 have not been found to make any significant contributions. This essentially indicates the shape and size effects and points out that the receptor site may not be able to accommodate a substituent bigger than OCH_3. Just next in the alkoxy series OC_2H_5 is probably accommodated but with some strain, resulting into a statistically significant effect, but less than that of OCH_3.

The largest contribution of 3,4-OCH_2O at R_2 can be attributed to its ring structure and its planarity, producing the best possible interaction with the receptor through polar interaction or hydrogen bonding.

Using the Hansch approach, we correlated the activity of phenylimidazopyridines (Table 2) as,

$$\log(1/IC_{50}) = 2.051(\pm0.929)\pi_X - 1.320(\pm1.087)(\pi_X)^2 - 1.650(\pm0.376)I_Z + 1.054(\pm0.290)I_R + 5.028$$
$$n = 22,\ r = 0.936,\ s = 0.26,\ F_{4,17} = 29.92\ (4.67),\ (\pi_X)_0 = 0.78 \quad (2)$$

The π_X in this equation refers to the hydrophobic constant of X-substituent and I_Z and I_R are two indicator parameters used for Z- and R-substituents. I_Z takes a value of 1 for Z = Cl and zero for any other substituent. Similarly, I_R takes a value of 1 for R = an alkylamine group and zero for others. Thus eq (2) expresses that an X-substituent will have a hydrophobic effect on the activity, but since there is a parabolic correlation with π_X, the π_X will have an optimum value equal to 0.78, suggesting a limited bulk tolerance at the receptor site. The negative coefficient of I_Z points out that Z = Cl would have a detrimental effect, probably because of having a number of lone pairs of electrons that can cause a repulsive effect with a negatively charged site of the receptor. The positive coefficient of I_R, however, suggests that an amine group at the position of R will have a favourable effect, which can be attributed to the formation of highly polar amide group, [-CON-], which can participate in strong polar interaction with the receptor.

The chain length at the 3-position (the value of n) was not found to matter. However, in the derivation of eq (2), compounds **19** and **23** were not included as they exhibited aberrant behaviour. The equation predicts very low activity for them as compared to their corresponding observed activity (see Table 2). The reasons for these aberrations are not very apparent.

For the series of imidazobenzothiazoles (Table 3), the best correlation obtained was as,

$$\log(1/IC_{50}) = 3.549(\pm1.089)\pi_{R7} - 5.169(\pm1.290)(\pi_{R7})^2 + 7.123$$
$$n = 14,\ r = 0.945,\ s = 0.23,\ F_{3,11} = 46.16\ (6.22),\ (\pi_{R7})_0 = 0.34 \quad (3)$$

which suggested the hydrophobic role of R_7-substituent with an optimum value of $\pi_{R7} = 0.34$. Such a low optimum value points out that highly hydrophobic R_7-substituents will not be tolerated. In the derivation of this equation, compound **12**, whose observed activity (6.47) was found to be much lower than the predicted one (7.49), was not included. Its lower observed activity than expected can be due to the presence, at the two adjacent positions (6 and 7), of CH_3 groups in tetrahedral geometry, producing steric hindrance for each other.

In this series the variation in R group in 2-position substituent was not found to matter, which meant that R moiety had nothing to do in the interaction, if any, of COOR group with the receptor. In this group, it may be only COO moiety which can have a constant polar interaction or hydrogen bonding with the receptor. As suggested in the case of derivative of II (eq (2)), a -CON- may have better effect than -COO- group, and it may be due to the greater polarity of the former than the latter.

For the series of oxadiazoles (Table 4), we could correlate the activity of the compounds as,

$$\log(1/IC_{50}) = 2.574(\pm0.477)D - 1.850(\pm0.985)\pi_{R2} + 3.362(\pm1.914)\sigma_{R2} + 1.784(\pm1.573)\sigma_{R1} - 1.148(\pm0.469)V_{w,R3} + 6.220$$
$$n = 34,\ r = 0.923,\ s = 0.43,\ F_{5,28} = 32.32\ (3.76) \quad (4)$$

which suggested that the hydrophobic nature of R_2-substituent will not be conducive to the activity. Rather its electronic nature-electron-withdrawing property as reflected by σ (Hammett's electronic constant)-will be highly favourable to the activity. Similarly, the electron-withdrawing property of R_1-substituent is also exhibited to be highly effective. However, the negative coefficient of $V_{w,R3}$, the van der Waals volume of R_3-substituent, indicates that the large size of R_3-substituent will not be

Table 5. Activity contributions of substituents in Table 1 obtained by Fujita–Ban approach

R_1	R_2	μ
$OCH_3 = 0.837$ (± 0.270)	3,4-$OCH_2O = 0.803(\pm 0.269)$	6.257
$OC_2H_5 = 0.513$ (± 0.225)	4-Cl = $0.433(\pm 0.366)$	
	4-$CH_3 = 0.518(\pm 0.274)$	
n = 19, r = 0.946	s = 0.197	$F_{5,13} = 22.05$ (4.86)

advantageous, but all nitrogen-containing substituents, for which the indicator variable D has been used with a value of unity, seem to be quite favourable. All these substituents may be expected to have some constant electron-withdrawing effect.

In the derivation of eq (4), however, compound **33** was found to be slightly misfit, hence excluded. The equation predicts a very low activity for this compound as compared to its observed activity (Table 4). Its high activity may be attributed to its R_3-substituent $O(CH_2)_3COOEt$, which is not a nitrogen-containing group but can produce some electron-withdrawing effect directly or indirectly.

Now if we compare derivatives of IV with those of III, we find that the R_1-substituent in the former and the R_7-substituent in the latter are at identical positions. Equation (3) suggests that a highly hydrophobic R_7-substituent ($\pi_{R7} > 0.34$) will not be beneficial. This is supplemented by eq (4) which indicates that instead of a hydrophobic substituent an electron-withdrawing substituent at that position (R_1-substituent) will be more advantageous. Thus R_7 in III or R_1 in IV can be assumed to interact with a site at the receptor which is basically nonpolar in nature, capable of interacting with small hydrophobic substituents, but can be polarized by large substituents, and thus strength of the binding will depend on the extent of the polarization of the active site which would be the function of the electronic charge over the substituents withdrawn from some electron-rich position of the molecule. Similarly, a R_3-substituent is also indicated by eq (4) to interact with a polarizable or already a polar or cationic site, affecting the binding by its electron-withdrawing ability. Similar behaviour then can be expected from N1 in I and II and S9 in III. COR group has been already discussed to be involved in polar interaction with a better effect if R is an amine moiety. Thus the electronic interactions seem to dominate the activity of the compounds. However, there can also be assumed the presence of certain hydrophobic pockets, too, in the receptor, engulfing some hydrophobic moieties present in the compounds.[5] A general model of interaction of a non-BZ ligand can be visualized as represented by Figure 1.

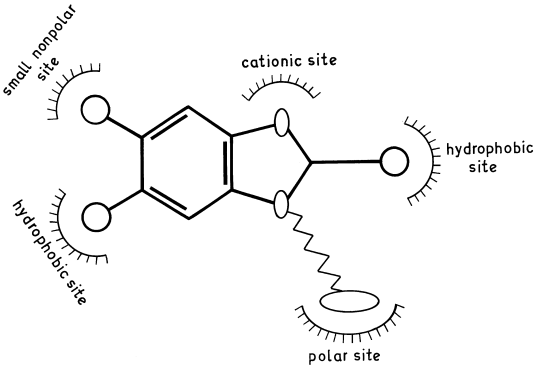


Figure 1. A hypothetical model of interaction of a non-BZ ligand with BZR.

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