Quantitative Structure–Activity Relationships of the Benzodiazepines. A Review and Reevaluation

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Received September 24, 1993 (Revised Manuscript Received April 20, 1994)

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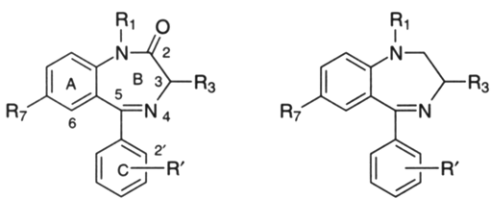
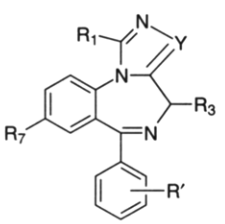
I. Introduction

The benzodiazepines (BZDs), which were discovered by chance in the mid1950s,[1–3] are the most frequently prescribed drugs for the pharmacotherapy of anxiety, of status epilepticus and convulsive, and emotional disorders. They can be divided into three major classes:



I

II



III

Y = N or CH

Structure I represents the "classical" 1,4-benzodiazepin-2-ones, II represents the 1,4-benzodiazepines, and III the 1,2-annelated imidazo- or triazolobenzodiazepines.

In this report we first review past efforts to formulate quantitative structure–activity relationships (QSAR) for the benzodiazepines and then discuss our own efforts to extend these studies. We have also derived from suitable data QSAR for a few other heterocycles which bind to the benzodiazepine receptor.

Considering the enormous therapeutic and financial success of these drugs it is surprising that so few QSAR have been reported for either in vitro or in vivo studies. It has been suggested[4] that metabolism may

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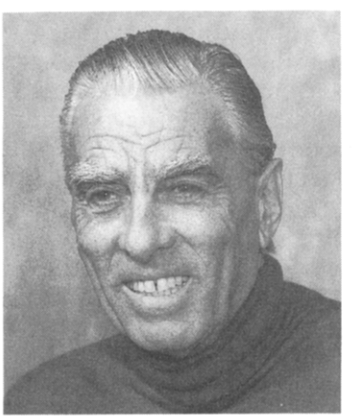

Corwin Hansch received his undergraduate education in chemistry at the University of Illinois and his Ph.D. in organic chemistry from New York University in 1944. After working with the DuPont Company, first on the Manhattan Project and then in Wilmington, DE, he joined the Pomona College faculty in 1946. He has remained at Pomona College except for two sabbaticals—one at the Federal Institute of Technology in Zurich and the other at the University of Munich. His primary interest is in the relationship between the structure of organic compounds and their biological properties.

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confound efforts to understand the structure–activity picture and this appears to have discouraged such efforts. Early qualitative inferences from animal studies (mice, rats, cats) pointed to the importance of electron-withdrawing substituents (Cl, NO_2, Br, CF_3) in the 7-position of ring A. N-Methylation at position 1 of the B ring seemed to make moderate increases in efficacy while the presence of a small electron-withdrawing group (Cl, F) in position 2′ of ring C strongly increases activity. These conclusions were often drawn from data sets which contained limited variation in the substituents so that it was difficult to guess the role of the electronic, steric, and hydrophobic components of the substituents. These conclusions now seem simplistic.

A. Benzodiazepine Receptor (BDZ-R) Binding

In 1977 experiments suggested that the BDZs are bound to specific receptors in the membranes of rat brain cells[5,6] which are closely related (allosterically) to a GABA receptor and to a chloride ionophore channel. Tallman[7] supported the idea that this binding site may be the means through which the BDZs produce their pharmacological response. The binding sites appear to be distributed unevenly through the brain and the existence of two different subtypes of BDZ-R (BDZ-R_1 and BDZ-R_2) have been proposed. However, "classical" BDZs do not appear to differentiate between these two types.[8]

The most recent studies have shown that the $GABA_A$ receptors are composed of various combinations of five (or fewer) of 15 possible subunits: six, α, four β, three σ, one δ, and one ϱ. This allows for an amazing number of possible receptors.[9-11] By taking 1–5 units at a time all possible combinations of the 15 would mean 151 887 possible $GABA_A$ receptors.[11] Other authors have suggested that there are only 13 possible subunits.[12] It is generally agreed that the actual number which occurs in the brain is far less than this. All of the subunits are similar in size and contain around 450 amino acids; also they seem to be strongly conserved across species.

The fact that there are multiple receptors of somewhat different types may help account for the less than perfect QSAR so far obtained. Eventually it should be possible to do QSAR studies on homogeneous cloned receptors.[13]

The study of the interaction of BDZs with receptors offers a means of avoiding the metabolism problem. However, as Fryer[14] has pointed out the complex nature of the receptor and its connection with the GABA receptor make QSAR difficult. The receptors bind many compounds not closely related to the BDZs so that Fryer recommends the study of very tight binding compounds in SAR work.

In a review of the SAR of BDZs, Fryer[14,15] discussed general requirements and proposed a BDZ–receptor interaction based on the proper alignment of three π-electron systems with certain separation and orientation requirements, but this cannot be used to formulate classical QSAR.

Borea[16] has made a Free–Wilson analysis of the inhibitory binding constants of 39 BDZs using 29 variables. Naturally the correlation was high (r = 0.968) but the conclusion provides little if any insight as to which properties of the structural features are important. His conclusion that the 2′-substituent on the 5-phenyl was important sterically and that this ring is important hydrophobically is, however, significant as we shall see. Borea et al. summarized his conclusions in a subsequent publication.[17]

Loew et al.[18] calculated conformational and electronic properties of 21 1,4-BDZs using empirical energy and semiempirical molecular orbital methods. Although they did not formulate a QSAR they interpreted their results to indicate the presence of cationic subsites near C_2=O, N_4, and position 7. An anionic subsite was postulated to be near 4′ on the 5-phenyl ring. Their results offered some evidence for hydrophobic interactions.[19,20] Recently Loew's group has reviewed in qualitative terms the structure–activity relationships proposed for the benzodiazepines.[21]

Ghose and Crippen[22] have applied the distance geometry approach to 29 BDZs, mostly agonists acting in vitro. Their results are based on eq 1. In

$$E_{\text{calcd}} = -WE_c + \sum_{i=1}^{n_s}\sum_{j=1}^{n_p}[C_{ij}\sum_{k=1}^{n=0}P_{jk}] \qquad (1)$$

$$n = 29,\ r = 0.980,\ s = 0.228$$

this expression E_c is the conformational energy with weighting factor W. The C values are the site pocket- and physicochemical property-dependent coefficients determined by regression analysis, n_s is the number of site pockets, n_p is the number of ligand atoms occupying the site pocket, and P_{jk} is the jth physicochemical property of the kth occupying atom of the ligand. For the 29 compounds a model containing nine site pockets was devised using 18 parameters for three types of interactions: hydrophobic, dispersive, and electrostatic. Of course with such a large number of parameters a good correlation was obtained: r = 0.980, s = 0.223. The qualitative conclusions are of more interest. These are that the N_1 substituent should be small and hydrophilic; C_7 should be dispersive and hydrophilic. Substituents in the 4′-position encounter steric repulsion. The results suggest replacing the 5-phenyl ring with a thiophene ring. It is of particular interest that they found little role for hydrophobic interactions, except for C_3, and little importance for 2′-substituents.

Recently a dual approach applying traditional QSAR and CoMFA (comparative molecular field analysis) to the structure–activity problem was made by a group at the University of Naples.[23] They selected in vitro data from the compilation of Haefely et al.[8] One set of 30 compounds contained variations only in the C_7, the 2′-position and the 1-position (in this latter position the substituent was either CH_3 or H). The second set referred to as heterogeneous included the first, plus 18 compounds with variations in the seven-membered ring as well as at the positions corresponding to C_7. They used the AM1 methodology to calculate HOMO and LUMO energies and total dipole moments. In addition they considered π, MR, and F for local hydrophobic, steric, and field/inductive effects of substituents. The sterimol parameters B_1, B_5, and L were also studied.

The "best" equations obtained are eq 2 for the homogeneous set and eq 3 for the heterogeneous set.

$$\log 1/C = 0.87I_2 + 0.59\pi_7 - 0.038\epsilon\text{LUMO} + 6.59 \quad (2)$$

$$n = 30, r = 0.932, s = 0.300$$

$$\log 1/C = 0.99I_2 + 0.41\pi_7 - 0.035\epsilon\text{HOMO} + 0.41 \quad (3)$$

$$n = 48, r = 0.867, s = 0.410$$

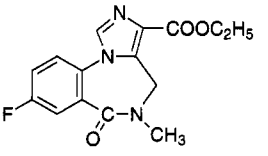
I_2 is an indicator variable which takes the value of 1 or 0 for the presence or absence of a substituent in the 5-phenyl ring at 2′. The hydrophobic parameter π_7 refers only to substituents in the 7-position. The two QSAR strongly point to a hydrophobic interaction of 7-substituents, but the indicator variable says nothing about the possible hydrophobic effect of 2′-substituents which Borea had found. Indeed, I_2 is the most important variable in each of the Naples equations accounting for almost half of the total explained variance. Their conclusion that 7-substituents interact hydrophobically differs from that of Loew et al.[18,19] and Codding et al.[24] who favor direct electrostatic interaction of these substituents with a cationic subsite of the receptor. It is also at odds with the finding of Ghose and Crippen[22] who proposed that this subsite favors hydrophilic groups. The meaning of the HOMO and LUMO terms is not clear since the authors note that there is high collinearity (r^2 = 0.758) between these two parameters. In the development of eq 2, ϵLUMO is the last term to enter the QSAR. In QSAR 3, ϵHOMO is the second term to enter the QSAR. Despite the ϵHOMO term in eq 3 they conclude that binding with an electron-rich receptor occurs. Of special interest to us is their observation that the sterimol parameter B_1 seemed to have some significance for 7-substituents, although in the final analysis this was discounted.

The results of the CoMFA analysis by the Naples group confirmed the QSAR analysis of eq 3. The electrostatic parameters were not important as would be expected if hydrophobic interactions are involved. That is, we do not believe that electrostatic parameters can really substitute for hydrophobic parameters.

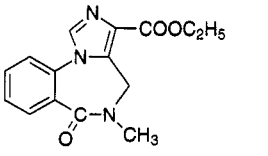
B. Other BDZ-R Ligands and New Binding Assays

Recently many new substances, sometimes rather unrelated structurally to the BDZs, have been found to show high affinity to the BDZ-R. Sometimes the biological activities of these substances differ from those of the BDZs. The term BDZ-R ligand is used for compounds that are bound competitively to the BDZ-R. Structures IV–VIII illustrate some of these fascinating new discoveries. BDZ-R antagonists have the ability to bind strongly to the BDZ-R and thereby block all of the pharmacological and biochemical effects of the classical BDZs. In 1981 a group at Hoffmann-La Roche in Basel[25] announced the discovery of IV, a quite nontoxic antagonist of BDZs, and the discovery of other such compounds followed. The β-carbolines VII stimulated considerable research

Antagonists



IV



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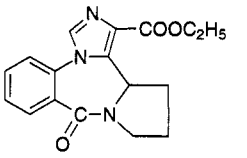

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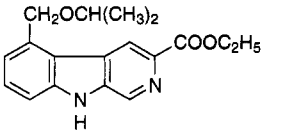
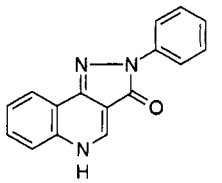


VII

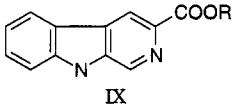


VIII

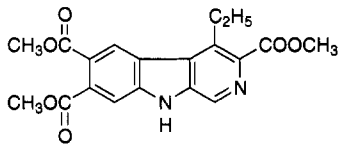
since they appeared to be endogenous modulators of the BDZ-R.[26]

By convention, agents that are bound to the BDZ-R and reduce the receptor/channel function have been termed inverse agonists (e.g. compounds IX and X).

Inverse Agonists

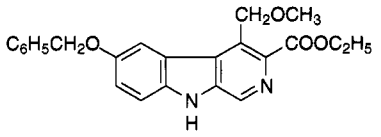


IX

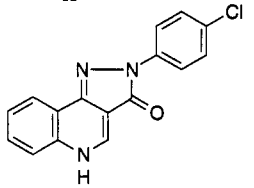


X

Partial Antagonists

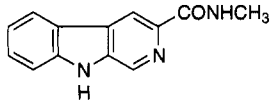


XI



XII

Partial Inverse Agonist



XIII

Partial agonists (XI and XII) have affinity for the BDZ-R and show few BDZ pharmacological activities, whereas partial inverse agonists (XIII) are bound to the BDZ-R and possess pharmacological features opposite those of agonists. Clearly the exceedingly complex types of interactions which may occur with structural variation of these heterocycles make QSAR studies difficult, to say the least, especially in animals. An enormous effort over the years has been made to develop reliable standard assays, but whether or not these are sharp enough to delineate a single type of receptor interaction for QSAR analysis remains an unanswered question.

For a series of 1-aryl-3-methylpyrazolo[4,5-*c*]quinolinones (see Table 6),[27] which caused 50% inhibition of [^{3}H]flunitrazepam's binding in vitro, QSAR 4 was formulated.[28] Equation 4 suggests that hydrophobic interactions occur with 3′- and 5′-substituents on the

$$\log 1/C = 0.48E_{s2',6'} + 0.61\pi_{3',5'} + 4.81 \quad (4)$$

$$n = 20, r = 0.870, s = 0.278$$

aryl ring and that negative steric effects occur with groups in the 2′- and 6′-positions (bear in mind that E_s values are negative). For the same data a correlation between the binding affinities and the chemical shift of $^{13}C_5$ was found (eq 5).[27]

$$\log 1/C = 0.35^{13}C_5 - 43.7 \quad (5)$$

$$n = 17, r = 0.817, s = 0.315$$

The coefficient with π in QSAR 4 is in the normal range 0.4−1.1 often found for receptor binding. Equation 5 suggests that there may be a missing electronic term in eq 4. Indeed this seems to be true (see eq 39).

The activities of many inverse agonists have been reported,[29−35] but the data sets are too small for QSAR analysis. A 3-D (CoMFA) QSAR for 37 compounds has been developed by Allen et al.[29] The conclusion from this study is that the 3-substituents of the β-carbolines bind in a hydrophobic pocket. We too find this for a different set of data via eq 35. Their work and eq 35 both point to steric effects for 3-substituents.

C. In Vivo QSAR

Blair and Webb[36] investigated 52 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones with a variety of substituents in the 7- and 2′-positions. They assumed that if the geometry of the seven-membered ring remained essentially constant, electronic effects of the substituents should be related to their relative biological activities. They analyzed the results from four types of tests: (1) inclined screen (IS), a measure of muscle relaxant activity in mice, (2) footshock (FS), a measure of taming activity in mice, (3) inhibition of pentylenetetrazole (Met), an assay of anticonvulsant activity in mice, and (4) a test of muscle relaxation in cats (Cat).

Using CNDO/2 methodology they calculated the dipole moment (μ) and the net charge on the carbonyl oxygen (qo) and derived equations 6−9. Although the

$$\text{IS:} \quad \log 1/C = -0.32(\pm 0.05)\mu + 1.62(\pm 0.15) \quad (6)$$

$$n = 45, r = 0.719, s = 0.429, F = 46.0$$

$$\text{FS:} \quad \log 1/C = -0.34(\pm 0.05)\mu + 2.21(\pm 0.15) \quad (7)$$

$$n = 39, r = 0.748, s = 0.386, F = 46.9$$

$$\text{Met:} \quad \log 1/C = -0.50(\pm 0.09)\mu + 3.26(\pm 0.29) \quad (8)$$

$$n = 52, r = 0.621, s = 0.886, F = 31.3$$

$$\text{Cat:} \quad \log 1/C = -0.48(\pm 0.07)\mu + 4.24(\pm 0.19) \quad (9)$$

$$n = 39, r = 0.761, s = 0.485, F = 51.0$$

correlations are not very high, they are significant in terms of F and the dependence on μ is consistent throughout the series. They interpret the negative coefficient with μ to indicate that the higher the dipole moment the more likely the drug would bind at some point other than the active site. It was also noted that the addition of terms in π to these QSAR did not improve the correlation. This is especially surprising since it is rare to find a QSAR from animal studies that does not contain a hydrophobic term. They conclude that μ was a more significant parameter than qo.

Borea et al.[37] applied the Free-Wilson method of analysis to the data of Blair and Webb.[36] Their results are summarized as follows:

$$\text{Met:} \quad n = 48, r = 0.986$$

$$\text{IS:} \quad n = 43, r = 0.935$$

$$\text{FS:} \quad n = 41, r = 0.937$$

While the correlations are high the results have little value because of the large number of variables employed >30. Also, the indicator variables used in the Free-Wilson method provide very little mechanistic insight.

Biagi et al.[38] studied a set of benzodiazepines in three types of activity tests. They used chromatographic R_m values as a measure of relative hydrophobicity. Using the nonspecific depressant effect on rats of an exploratory behavior test as a measure of activity they formulated eq 10. In this expression I_3

$$\log 1/C = 2.26R_m - 0.62(R_m)^2 + 1.24I_3 - 0.80 \quad (10)$$

$$n = 26, r = 0.878, s = 0.441, \text{ideal } R_m = 1.82$$

is a 1 or 0 indicator variable for 2′-substituents. In this analysis hydrophobicity is by far the most important parameter. For small data sets QSAR were derived for two other types of activity. Equations 11 and 12 correlate two types of punished (eq 11) and nonpunished (eq 12) conflict response in a skinner box in which food could be released on the pressing of a lever, but an electric shock could also be administered. QSAR 11 and 12 are essentially

$$\log 1/C = 1.60R_m + 0.80I_3 - 1.20 \quad (11)$$

$$n = 17, r = 0.876, s = 0.330$$

$$\log 1/C = 1.11R_m + 1.01I_3 - 0.78 \quad (12)$$

$$n = 17, r = 0.845, s = 0.394$$

identical, but in these smaller sets the variation in R_m was not great enough to bring out the parabolic effect as in eq 10. Of course I_3 provides no information as to whether it is the steric, hydrophobic, or electronic properties of 2′-substituents or all three properties that is important. The use of R_m implies that hydrophobic effects of all parts of the compounds are important. Biagi showed that R_m was well correlated with measured log P (eq 13). From the

$$\log P = 1.67R_m - 0.44 \quad (13)$$

$$n = 9, r = 0.987, s = 0.118$$

relationship between R_m and log P they showed for eq 10 that the ideal log P (log P_o) was 2.5.

Yoshimoto et al.[39] in an extensive study of a new type (see Table 9) of benzodiazepinooxazole derivative used nine different assays. From these results they derived QSAR 14–22.

antibemegride activity (anxiolytic-sedative activity)

$$\log 1/C = -0.29(\pm0.13)\pi_7 + 2.29(\pm0.63)F_3 + 1.70(\pm0.37)F_4 - 0.39(\pm0.26)I_1 + 0.47(\pm0.20)I_2 - 0.29(\pm0.16)I_3 + 4.31(\pm0.35) \quad (14)$$

$$n = 54, r = 0.938, s = 0.254$$

anti-pentylenetetrazole test (CNS depressant effect)

$$\log 1/C = -0.69(\pm0.25)\pi_7 + 1.53(\pm0.27)F_3 + 1.81(\pm0.30)F_4 - 0.36(\pm0.24)I_1 + 0.20(\pm0.17)I_2 - 0.27(\pm0.12)I_3 + 4.44(\pm0.38) \quad (15)$$

$$n = 30, r = 0.962, s = 0.144$$

antifighting test (taming ability)

$$\log 1/C = -0.91(\pm0.29)\pi_7 + 1.32(\pm0.85)F_3 + 1.19(\pm0.35)F_4 - 0.21(\pm0.19)I_2 - 0.23(\pm0.14)I_3 + 4.15(\pm0.44) \quad (16)$$

$$n = 30, r = 0.934, s = 0.170$$

antimaximal electroshock test (anticonvulsant activity)

$$\log 1/C = -0.96(\pm0.36)\pi_7 + 0.41(\pm0.41)F_4 - 0.40(\pm0.35)I_1 - 0.27(\pm0.18)I_3 + 4.29(\pm0.16) \quad (17)$$

$$n = 31, r = 0.827, s = 0.220$$

inclined plane test (sedative–muscle relaxant activity)

$$\log 1/C = 2.04(\pm0.85)F_3 + 0.77(\pm0.34)F_4 + 0.37(\pm0.18)I_2 + 2.69(\pm0.44) \quad (18)$$

$$n = 30, r = 0.799, s = 0.172$$

rotating rod test (ataxic and muscle-uncoordinating activity)

$$\log 1/C = 2.21(\pm0.77)F_3 + 0.71(\pm0.30)F_4 - 0.29(\pm0.16)I_2 - 0.11(\pm0.13)I_3 + 3.04(\pm0.40) \quad (19)$$

$$n = 32, r = 0.826, s = 0.155$$

traction test (muscle-relaxant effect)

$$\log 1/C = -0.58(\pm0.42)\pi_7 + 1.62(\pm1.2)F_3 + 1.04(\pm0.52)F_4 - 0.52(\pm0.40)I_1 - 0.32(\pm0.20)I_3 + 3.93(\pm0.62) \quad (20)$$

$$n = 30, r = 0.807, s = 0.249$$

balance test (lack of muscular coordination and vistibular function)

$$\log 1/C = -0.65(\pm0.49)\pi_7 + 1.38(\pm1.44)F_3 + 1.17(\pm0.61)F_4 - 0.48(\pm0.49)I_1 - 0.40(\pm0.24)I_3 + 4.09(\pm0.75) \quad (21)$$

$$n = 30, r = 0.803, s = 0.293$$

anesthesia potentiating test (sleep-inducing activity)

$$\log 1/C = -0.57(\pm0.33)\pi_7 + 1.78(\pm0.94)F_3 + 1.46(\pm0.39)F_4 - 0.32(\pm0.30)I_1 + 0.28(\pm0.21)I_2 + 3.96(\pm0.49) \quad (22)$$

$$n = 30, r = 0.898, s = 0.189$$

In the above QSAR C is the ED_{50} concentration in moles per kilogram (mol/kg), $I_1 = 1$ or 0 for the presence/absence of CH_3 at R_8, $I_2 = 1$ or 0 for the pressure/absence of CH_3 at R_9, and $I_3 = 1$ or 0 for $R_{10} = CH_3/H$. Except for eqs 18 and 19 all of the others contain a negative π_7 term. The negative coefficient with this term must be considered. It may be due to the high log P for these compounds. Calculated values for this set range from 3.20 to 6.53 which are above the log P_o we have found for benzodiazepines (see section II). The calculated values are for the neutral form of compounds so that these may be a bit high for pH 7.4.[40] The lipophilic character of this set may also make them more susceptible to P-450 oxidation. Except for eqs 18 and 19 the rest have terms in F_3 and/or F_4 showing that electron-withdrawing (field/inductive) substituents increase potency, which is in line with the early qualitative conclusions discussed above, as well as eq 2. The negative coefficients with the indicator variables bring out deleterious effects at these positions which would seem to be steric.

There have been applications of neural networks to previously studied data[41] and the use of complex parameters such as $\cos(\pi \cdot MR_7)$.[42] Since it is not possible to compare these approaches to those based on the traditional use of physicochemical parameters these will not be discussed.

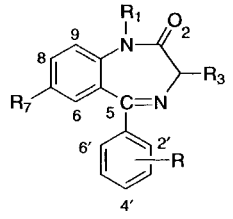
It is difficult to draw general conclusions from the above QSAR. Clearly 2′-substituents are important in increasing potency, but which properties of the substituents are important has not been delineated. There is evidence that hydrophobicity is an important property, but not all analyses agree on this point. Equations 2 and 3 and 8–10 seem convincing. The former four equations suggest that hydrophobic interactions are important at the receptor level, while the last indicate that overall hydrophobicity must be considered in the whole animal.

We now reanalyze some of the data sets discussed above and consider some unanalyzed data.

D. Parameters and Data Sets

It is well known that hydrophobicity is an important property of drugs acting in the CNS[43] and it is also an important factor in the susceptibility of drugs

Table 1. Comparison of Experimental and Calculated log *P* Values of 1,4-Benzodiazepin-2-ones and Derivatives



no.	substituent	log *P*	CLOGP	dev	no.	substituent	log *P*	CLOGP	dev
1	$R_7 = NH_2$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	1.00[a]	1.01	0.01	45	$R_7 = Cl$, $R_1 = H$, $R_{2'} = Br$, $R_3 = H$	3.17[a]	3.22	0.05
2	$R_7 = NH_2$, $R_1 = CH_3$, $R_{2'} = F$, $R_3 = H$	1.30[a]	1.09	0.21	46	$R_7 = CF_3$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	3.10[a]	3.42	0.32
3	$R_7 = NH_2$, $R_1 = CH_3$, $R_{2'} = H$, $R_3 = H$	1.46[a]	1.29	0.17	47	$R_7 = SOCH_3$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	0.80[b]	1.12	0.32
4	$R_7 = Cl$, $R_1 = CH_2CH(OH)CH_2OH$, $R_{2'} = F$, $R_3 = H$	1.51[a]	1.50	0.01	48	$R_7 = Br$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	3.11[g]	3.21	0.10
5	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = NO_2$, $R_3 = H$	1.61[a]	1.47	0.14	49	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	2.25[c]	2.38	0.13
6	$R_7 = COCH_3$, $R_1 = H$, $R_{2'} = F$, $R_3 = H$	1.75[a]	1.80	0.05	50	$R_7 = Br$, $R_1 = H$, $R_5 =$ 2-pyridyl, $R_3 = H$	1.69[h]	1.72	0.03
7	$R_7 = CN$, $R_1 = CH_3$, $R_{2'} = H$, $R_3 = H$	1.80[b]	1.80	0.00	51	$R_7 = Br$, $R_1 = H$, $R_{2'} = F$, $R_3 = H$	2.98[b]	3.00	0.02
8	$R_7 = CN$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	1.82[a]	2.12	0.30	52	$R_6 = CF_3$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	3.18[b]	3.42	0.24
9	$R_7 = NO_2$, $R_1 = CH_2OCH_3$, $R_{2'} = H$, $R_3 = H$	2.05[a]	2.03	0.02	53	$R_7 = CH_3$, $R_9 = CH_3$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	2.94[b]	3.18	0.24
10	$R_7 = NO_2$, $R_1 = CH_3$, $R_{2'} = F$, $R_3 = H$	2.06[a]	1.91	0.15	54	$R_7 = Cl$, $R_1 = H$, $R_{2'} = H$, $R_{4'} = F$, $R_3 = H$	2.90[a]	3.20	0.30
11	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = F$, $R_3 = H$	2.15[a]	2.17	0.02	55	$R_7 = NH_2$, $R_1 = CH_2OCH_3$, $R_{2'} = H$, $R_3 = OH$	0.75[a]	0.59	0.16
12	$R_7 = NO_2$, $R_1 = CH_3$, $R_{2'} = H$, $R_3 = H$	2.16[a]	2.11	0.05	56	$R_7 = NO_2$, $R_1 = CH_2CH(OH)CH_2(OH)$, $R_{2'} = H$, $R_3 = H$	0.96[a]	0.74	0.22
13	$R_7 = H$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	2.18[a]	2.18	0.00	57	$R_7 = NH_2$, $R_1 = CH_2OCH_3$, $R_{2'} = F$, $R_3 = H$	1.31[a]	1.00	0.31
14	$R_7 = Cl$, $R_1 = CH_3$, $R_{2'} = H$, $R_3 = OH$	2.19[c]	2.46	0.27	58	$R_7 = NH_2$, $R_1 = CH_2OCH_3$, $R_{2'} = H$, $R_3 = H$	1.32[a]	1.21	0.11
15	$R_7 = Cl$, $R_1 = H$, $R_{2'} = H$, $R_3 = OH$	2.24[d]	2.33	0.09	59	$R_7 = NH_2$, $R_1 = C_2H_5$, $R_{2'} = H$, $R_3 = H$	1.81[a]	1.82	0.01
16	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	2.25[c]	2.38	0.13	60	$R_7 = I$, $R_1 = CH_2CH(OH)CH_2(OH)$, $R_{2'} = F$, $R_3 = H$	1.81[a]	1.91	0.10
17	$R_7 = F$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	2.32[a]	2.48	0.16	61	$R_7 = NH_2$, $R_1 = CH_2SCH_3$, $R_{2'} = H$, $R_3 = H$	1.92[a]	1.91	0.01
18	$R_7 = F$, $R_1 = CH_3$, $R_{2'} = F$, $R_3 = H$	2.41[b]	2.31	0.10	62	$R_7 = OCH_3$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	2.24[a]	2.18	0.06
19	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = Cl$, $R_3 = H$	2.41[e]	2.44	0.03	63	$R_7 = NO_2$, $R_9 = CH_3$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	2.44[b]	2.88	0.44
20	$R_7 = N(CH_3)_2$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	2.43[a]	2.41	0.02	64	$R_7 = H$, $R_1 = H$, $R_{2'} = H$, $R_{4'} = F$, $R_3 = H$	2.38[a]	2.33	0.05
21	$R_7 = NO_2$, $R_1 = CH_3$, $R_{2'} = CF_3$, $R_3 = H$	2.45[b]	2.30	0.15	65	$R_7 = H$, $R_1 = H$, $R_{2'} = CF_3$, $R_3 = H$	2.47[a]	2.37	0.10
22	$R_7 = Cl$, $R_1 = H$, $R_{2'} = Cl$, $R_3 = OH$	2.51[c]	2.40	0.11	66	$R_7 = Cl$, $R_1 = CH_2OCH_3$, $R_{2'} = H$, $R_3 = H$	2.86[a]	3.00	0.14
23	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = CF_3$, $R_3 = H$	2.51[a]	2.56	0.05	67	$R_7 = C_2H_5$, $R_1 = H$, $R_{2'} = F$, $R_3 = H$	2.92[a]	3.00	0.08
24	$R_7 = NO_2$, $R_1 = CH_3$, $R_{2'} = Cl$, $R_3 = H$	2.56[b]	2.18	0.38	68	$R_7 = Cl$, $R_1 = CH_3$, $R_{2'} = CH_3$, $R_3 = H$	3.03[a]	3.18	0.15
25	$R_7 = CH_3$, $R_1 = H$, $R_{2'} = H$, $R_3 = H$	2.62[a]	2.68	0.06	69	$R_7 = F$, $R_1 = CH_3$, $R_{2'} = H$, $R_{4'} = Cl$, $R_3 = H$	3.10[a]	3.23	0.13
26	$R_7 = N(CH_3)_2$, $R_1 = CH_3$, $R_{2'} = H$, $R_3 = H$	2.63[a]	2.66	0.03	70	$R_7 = Cl$, $R_1 = CH_3$, $R_{2'} = H$, $R_{4'} = OCH_3$, $R_3 = H$	3.15[a]	3.08	0.07
27	$R_7 = Cl$, $R_1 = H$, $R_{2'} = OCH_3$, $R_3 = H$	2.63[a]	2.60	0.03	71	$R_7 = H$, $R_1 = H$, $R_{2'} = H$, $R_{3'} = CF_3$, $R_3 = H$	3.19[a]	3.07	0.12
28	$R_7 = Cl$, $R_1 = H$, $R_{2'} = F$, $R_{6'} = F$, $R_3 = H$	2.68[a]	2.64	0.04	72	$R_7 = Cl$, $R_1 = H$, $R_{2'} = CF_3$, $R_3 = H$	3.19[a]	3.24	0.05
29	$R_7 = Cl$, $R_1 = H$, $R_{2'} = F$, $R_3 = H$	2.70[a]	2.85	0.15	73	$R_7 = Cl$, $R_1 = C_2H_5$, $R_{2'} = H$, $R_3 = H$	3.21[a]	3.61	0.40
30	$R_7 = N(CH_3)_2$, $R_1 = CH_3$, $R_{2'} = Cl$, $R_3 = H$	2.72[b]	2.72	0.00	74	$R_7 = Cl$, $R_1 = CH_2OCH_3$, $R_{2'} = Cl$, $R_3 = H$	3.23[a]	3.06	0.17
31	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = Cl$, $R_3 = CH_3$	2.72[a]	2.96	0.24	75	$R_7 = Br$, $R_1 = H$, $R_{2'} = Br$, $R_3 = H$	3.30[g]	3.37	0.07

32	$R_7 = Cl, R_1 = CH_3, R_{2'} = F, R_3 = H$	2.75[a]	2.88	0.07	76	3.30[d]	3.27	0.03
33	$R_7 = Cl, R_1 = CH_3, R_{2'} = H, R_3 = H$	2.99[f]	3.08	0.29	77	3.32[a]	3.70	0.38
34	$R_8 = Cl, R_1 = H, R_{2'} = R_{6'} = F, R_3 = H$	2.88[a]	2.64	0.24	78	3.33[a]	3.58	0.25
35	$R_7 = SCH_3, R_1 = H, R_{2'} = H, R_3 = H$	2.92[a]	2.77	0.15	79	3.34[a]	3.07	0.27
36	$R_7 = Cl, R_1 = H, R_{2'} = H, R_3 = H$	2.93[a]	3.06	0.13	80	3.36[i]	4.16	0.80
37	$R_7 = SCH_3, R_1 = CH_3, R_{2'} = H, R_3 = H$	2.95[a]	3.02	0.07	81	3.40[a]	3.67	0.27
38	$R_7 = Cl, R_1 = CH_3, R_{2'} = Cl, R_3 = H, R_{6'} = Cl$	3.04[a]	3.21	0.17	82	3.63[g]	3.92	0.29
39	$R_7 = CF_3, R_1 = H, R_{2'} = H, R_3 = H$	3.10[a]	3.42	0.32	83	3.63[a]	3.49	0.14
40	$R_7 = Cl, R_1 = CH_3, R_{2'} = Cl, R_3 = H$	3.12[a]	3.15	0.03	84	3.78[g]	3.92	0.14
41	$R_7 = Cl, R_1 = H, R_{2'} = CH_3, R_3 = H$	3.12[a]	3.16	0.04	85	3.88[g]	4.07	0.19
42	$R_7 = I, R_1 = CH_3, R_{2'} = F, R_3 = H$	3.14[a]	3.29	0.15	86	4.03[i]	4.31	0.28
43	$R_7 = Cl, R_1 = H, R_{2'} = H, R_3 = R_{3'} = OCH_3$	3.14[a]	3.00	0.14	87	4.04[g]	4.07	0.03
44	$R_7 = Cl, R_1 = H, R_{2'} = Cl, R_3 = H$	3.15[a]	3.12	0.03	88	4.41[c]	4.38	0.03

[a] Seiler, P.; Zimmerman, I. *Arzneim.-Forsch.* **1983**, *33*, 1519. [b] Debnath, G.; Hansch, C. Unpublished results, Pomona College. [c] Craf, E.; El-Meshawy, M. *Pharm. Uns. Zeit.* **1977**, *6*, 171. [d] Smukskii, S. P.; Bogatskii, A. A. V.; Andronati, S. A.; Vikhlyaev, Y. I.; Zhilina, Z. I. *Dokl. Akad. Nauk SSSR* **1977**, *235*, 369. [e] Muller, W.; Wallert, U. N.-S. *Archiv. Pharmacol.* **1973**, *278*, 301. [f] Yogokawa, K.; Nakashima, E.; Ishizaki, J.; Maeda, H.; Nagano, T.; Ichimura, F. *Pharm. Res.* **1990**, *7*, 691. [g] Andronati, S. A.; Chepeler, V. M.; Yakuborskaya, L. N.; Val'dman, A. V.; Voronina, T. A.; Rozhanets, V. V.; Zhulin, V. V.; Korotkov, K. O. *Bioorg. Khim.* **1983**, *9*, 1357. [h] Rodriquez, L.; Chiarini, A.; Zecchi, V. *Il Farmaco* **1981**, *36*, 304. [i] Hilbert, J. M.; Gural, R. P.; Symchowicz, S.; Zampaglione, N. *J. Clin. Pharmacol.* **1984**, *24*, 457.

to attack by the P-450 enzymes.[44] Also from our review there is some evidence that this property of the benzodiazepines is important in the isolated receptor interactions as well as in the whole animal. Thus at the outset it is important to have reliable log *P* values. For only a fraction of the compounds of interest have log *P* values been reported. In Table 1 we have listed all of the log *P* values we have been able to find along with calculated values using the CLOGP program of Leo.[45,46] The agreement between experimental and calculated values is surprisingly good for such complex molecules. One might expect less satisfactory agreement knowing that the experimental values come from eight different laboratories. In the formulation of the QSAR we have used only calculated values since we believe that the relative errors in doing so may be less than using a mixture of the two.

In addition to the log *P* of compounds used in our review (numbers 1–54) we have included other results (55–88) to give the reader a better idea of our present ability to calculate log *P* for this class of drugs.

The values of substituent constants (π, σ, σ^-, E_s, MR, B_1, B_5, and L) have been taken from the literature.[47–50]

In Tables 2–11 we have collected all of the reported experimental data that we could find for sets large enough for meaningful analysis where the results were obtained for each case from a single laboratory.

II. Reevaluation of Earlier Work and New Results

A. In Vitro QSAR of Benzodiazepines

In Table 2 the results for the 50% inhibition of the binding of [^{3}H]diazepam to homogenates of rat brain cell membranes by benzodiazepines are listed along with the essential parameters used to formulate eqs 23–25. The data were selected from the review of

$$\log 1/C = 1.20(\pm 0.39)\log P - 2.74(\pm 0.84) \log(\beta \cdot 10^{\log P} + 1) + 5.50(\pm 0.82) \quad (23)$$

$$n = 74,\ r = 0.618,\ s = 0.571,\ F_{3,71} = 14.4,\ \log P_o = 2.73,\ \log \beta = -2.84$$

$$\log 1/C = 1.19(\pm 0.37)\log P - 2.75(\pm 0.70) \log(\beta \cdot 10^{\log P} + 1) + 1.06(\pm 0.40)B_{1-7} + 4.04(\pm 0.87) \quad (24)$$

$$n = 74,\ r = 0.743,\ s = 0.487,\ F_{1,70} = 33.3,\ \log P_o = 2.57,\ \log \beta = -2.69$$

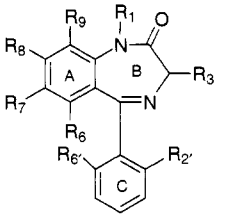
$$\log 1/C = 1.30(\pm 0.37)\log P - 2.30(\pm 0.59) \log(\beta \cdot 10^{\log P} + 1) + 1.08(\pm 0.32)B_{1-7} + 1.05(\pm 0.32)B_{1-2'} + 2.54(\pm 0.89) \quad (25)$$

$$n = 74,\ r = 0.847,\ s = 0.390,\ F_{1,69} = 42.4,\ \log P_o = 2.51(\pm 0.23),\ \log \beta = -2.41$$

correlation matrix (r)

	log *P*	B_{1-7}	$B_{1-2'}$	σ	*F*
log *P*	1	0.405	−0.214	−0.009	0.420
B_{1-7}		1	−0.108	0.363	0.466
$B_{1-2'}$			1	0.236	0.120
σ				1	0.543
F					1

Table 2. Parameters Used in the Derivation of Eqs 23–25



		log 1/C					
no.	substituent	obsd	calcd[b]	|Δlog 1/C|	log P	B_{1-7}	$B_{1-2'}$
1	$R_7 = NH_2$, $R_1 = CH_3$, $R_{2'} = H$	6.34	6.65	0.31	1.29	1.35	1.00
2	$R_7 = NH_2$, $R_1 = H$, $R_{2'} = H$	6.41	6.32	0.09	1.01	1.35	1.00
3[a]	$R_7 = CN$, $R_1 = CH_3$, $R_{2'} = H$	6.42	7.43	1.01	1.80	1.60	1.00
4	$R_7 = H$, $R_1 = H$, $R_{2'} = H$	6.45	7.03	0.58	2.18	1.00	1.00
5	$R_7 = NHOH$, $R_1 = CH_3$, $R_{2'} = F$	7.02	6.66	0.36	0.99	1.35	1.35
6	$R_7 = NH_2$, $R_1 = H$, $R_{2'} = Cl$	7.12	7.24	0.12	1.07	1.35	1.80
7	$R_7 = CHO$, $R_1 = H$, $R_{2'} = H$	7.37	7.58	0.21	1.99	1.60	1.00
8	$R_7 = F$, $R_1 = H$, $R_{2'} = H$	7.40	7.48	0.08	2.45	1.35	1.00
9	$R_7 = C_2H_5$, $R_1 = H$, $R_{2'} = H$	7.44	7.39	0.05	3.21	1.52	1.00
10	$R_7 = CN$, $R_1 = CH_3$, $R_{2'} = F$	7.52	7.61	0.09	1.60	1.60	1.35
11	$R_7 = CH=CH_2$, $R_1 = H$, $R_{2'} = H$	7.62	7.66	0.04	2.91	1.60	1.00
12	$R_7 = H$, $R_1 = H$, $R_{2'} = F$	7.68	7.28	0.40	1.98	1.00	1.35
13	$R_7 = COCH_3$, $R_1 = H$, $R_{2'} = F$	7.74	7.80	0.06	1.80	1.60	1.35
14	$R_7 = CF_3$, $R_1 = H$, $R_{2'} = H$	7.89	7.74	0.15	3.42	1.99	1.00
15	$R_7 = Cl$, $R_1 = CH_3$, $R_{2'} = H$	8.09	7.78	0.31	3.08	1.80	1.00
16	$R_7 = Cl$, $R_1 = CH_3$, $R_{2'} = Cl$, $R_{6'} = Cl$	8.26	8.54	0.28	3.21	1.80	1.80
17	$R_7 = N_3$, $R_1 = H$, $R_{2'} = F$	8.27	8.01	0.27	2.42	1.50	1.35
18	$R_7 = NO_2$, $R_1 = CH_3$, $R_{2'} = F$	8.42	7.99	0.43	1.91	1.70	1.35
19	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = CF_3$	8.45	8.90	0.45	2.56	1.70	1.99
20	$R_7 = I$, $R_1 = CH_3$, $R_{2'} = F$	8.54	8.39	0.15	3.29	2.15	1.35
21	$R_7 = Br$, $R_1 = CH_3$, $R_{2'} = F$, $R_{6'} = F$	8.62	8.44	0.18	2.82	1.95	1.35
22	$R_7 = Cl$, $R_1 = H$, $R_{2'} = F$	8.70	8.27	0.43	2.85	1.80	1.35
23	$R_7 = Cl$, $R_1 = H$, $R_{2'} = Cl$	8.74	8.60	0.14	3.12	1.80	1.80
24	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = Cl$	8.74	8.70	0.04	2.44	1.70	1.80
25	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = F$	8.82	8.15	0.67	2.17	1.70	1.35
26	$R_7 = F$, $R_1 = CH_3$, $R_{2'} = F$	8.29	7.82	0.47	2.31	1.35	1.35
27	$R_7 = F$, $R_1 = CH_3$, $R_{2'} = H$	7.77	7.48	0.29	2.51	1.35	1.00
28	$R_7 = F$, $R_1 = H$, $R_{2'} = F$	8.13	7.81	0.32	2.28	1.35	1.35
29	$R_7 = Cl$, $R_1 = H$, $R_{2'} = H$	8.03	7.80	0.24	3.06	1.80	1.00
30	$R_7 = Cl$, $R_1 = H$, $R_{2'} = F$, $R_{6'} = F$	8.79	8.33	0.47	2.64	1.80	1.35
31	$R_7 = Cl$, $R_1 = CH_3$, $R_{2'} = F$, $R_{6'} = F$	8.39	8.32	0.07	2.67	1.80	1.35
32	$R_7 = Cl$, $R_1 = H$, $R_{2'} = Cl$, $R_{6'} = F$	8.52	8.71	0.19	2.91	1.80	1.80
33	$R_7 = Cl$, $R_1 = H$, $R_{2'} = Cl$, $R_{6'} = Cl$	8.15	8.56	0.41	3.58	1.80	1.80
34	$R_7 = NO_2$, $R_1 = H$, $R_{2'} = H$	7.99	7.85	0.14	2.38	1.70	1.00
35	$R_7 = NO_2$, $R_1 = CH_3$, $R_{2'} = Cl$	8.66	8.63	0.04	2.18	1.70	1.80
36	$R_7 = NH_2$, $R_1 = CH_3$, $R_{2'} = F$	7.19	6.78	0.41	1.09	1.35	1.35
37	$R_7 = NHCONHCH_3$, $R_1 = CH_3$, $R_{2'} = F$	6.34	7.01	0.67	1.28	1.35	1.35
38	$R_7 = Cl$, $R_1 = CH_2CF_3$, $R_{2'} = H$	7.04	6.66	0.38	4.37	1.80	1.00
39	$R_7 = Cl$, $R_1 = CH_2C{\equiv}CH$, $R_{2'} = H$	7.03	7.72	0.68	3.68	1.80	1.00
40	$R_7 = Cl$, $R_1 = CH_2C_3H_5$, $R_{2'} = H$	6.96	6.97	0.01	4.06	1.80	1.00
41[a]	$R_7 = NO_2$, $R_1 = CH_2OCH_3$, $R_{2'} = H$	6.37	7.71	1.34	2.03	1.70	1.00
42	$R_7 = Cl$, $R_1 = C(CH_3)_3$, $R_{2'} = H$	6.21	6.71	0.50	4.32	1.80	1.00
43	$R_7 = Cl$, $R_1 = CH_2CH_2OH$, $R_{2'} = F$	7.61	8.31	0.70	2.33	1.80	1.35
44	$R_7 = Cl$, $R_1 = (CH_2)_2OCH_2CONH_2$, $R_{2'} = F$	7.37	7.97	0.60	1.75	1.80	1.35
45[a]	$R_7 = Cl$, $R_1 = CH_2CHOHCH_2OH$, $R_{2'} = F$	6.85	7.74	0.89	1.50	1.80	1.35
46[a]	$R_7 = NO_2$, $R_1 = C(CH_3)_3$, $R_{2'} = Cl$	6.52	8.27	1.75	3.41	1.70	1.80
47	$R_7 = Cl$, $R_1 = H$, $R_3 = (s)CH_3$, $R_{2'} = F$	8.46	7.95	0.51	3.37	1.80	1.35
48	$R_7 = NO_2$, $R_1 = H$, $R_3 = (s)CH_3$, $R_{2'} = Cl$	8.92	8.58	0.34	2.94	1.70	1.80
49	$R_7 = NO_2$, $R_1 = CH_3$, $R_3 = (s)CH_3$, $R_{2'} = F$	8.15	8.22	0.07	2.43	1.70	1.35
50	$R_7 = Cl$, $R_1 = CH_3$, $R_3 = (rac.)CH_3$, $R_{2'} = H$	7.31	7.39	0.08	3.60	1.80	1.00
51	$R_7 = Cl$, $R_1 = H$, $R_3 = (rac.)OH$, $R_{2'} = H$	7.74	7.95	0.21	2.33	1.80	1.00
52	$R_7 = Cl$, $R_1 = CH_3$, $R_3 = (rac.)OH$, $R_{2'} = H$	7.79	7.97	0.18	2.46	1.80	1.00
53	$R_7 = Cl$, $R_1 = H$, $R_3 = (rac.)OH$, $R_{2'} = H$	8.46	7.95	0.51	2.40	1.80	1.00
54[a]	$R_7 = Cl$, $R_1 = CH_3$, $R_3 = (rac.)OCON(CH_3)_2$, $R_{2'} = H$	6.05	7.42	1.37	3.56	1.80	1.00
55	$R_7 = Cl$, $R_1 = CH_3$, $R_3 = (rac.)Cl$, $R_{2'} = F$	8.27	7.83	0.44	4.51	1.80	1.35
56	$R_7 = Cl$, $R_1 = H$, $R_5 =$ cyclohexenyl,[d] $R_{2'} = H$	7.47	7.34	0.14	3.66	1.80	1.00
57	$R_7 = Cl$, $R_1 = CH_3$, $R_5 =$ cyclohexenyl,[d] $R_{2'} = H$	7.47	7.31	0.16	3.68	1.80	1.00
58	$R_7 = Br$, $R_1 = H$, $R_5 =$ 2-pyridyl,[e] $R_{2'} = H$	7.74	7.74	0.00	1.72	1.95	1.00
59	$R_7 = Cl$, $R_1 = H$, $R_5 =$ cyclohexyl,[f] $R_{2'} = H$	7.06	7.21	0.15	3.80	1.80	1.00
60	$R_7 = Cl$, $R_1 = H$, $R_5 =$ naphthyl,[g] $R_{2'} = H$	6.54	6.80	0.26	4.23	1.80	1.00
61	$R_7 = Cl$,[c] $R_1 = H$, $R_{2'} = Cl$	8.03	8.76	0.73	2.81	1.80	1.80

Table 2 (Continued)

no.	substituent	log 1/C obsd	log 1/C calcd[b]	|Δlog 1/C|	log P	B_{1-7}	$B_{1-2'}$
62	$R_7 = CH_3$, $R_1 = H$, $R_{2'} = H$, $R_6 = CH_3$	6.77	7.45	0.68	3.13	1.52	1.00
63	$R_7 = H$, $R_1 = H$, $R_{2'} = F$, $R_{6'} = F$	7.72	7.12	0.60	1.71	1.00	1.35
64	$R_7 = H$, $R_1 = CH_3$, $R_{2'} = F$	7.85	7.40	0.46	2.16	1.00	1.35
65	$R_7 = H$, $R_1 = CH_3$, $R_{2'} = Cl$	8.42	7.94	0.48	2.43	1.00	1.80
66	$R_7 = H$, $R_1 = H$, $R_{2'} = H$, $R_6 = Cl$	6.49	6.93	0.44	3.06	1.00	1.00
67	$R_7 = H$, $R_1 = CH_3$, $R_{2'} = F$, $R_6 = Cl$	6.82	7.39	0.57	2.88	1.00	1.35
68	$R_7 = H$, $R_1 = H$, $R_{2'} = F$, $R_{6'} = F$, $R_8 = Cl$	7.55	7.46	0.09	2.64	1.00	1.35
69	$R_7 = H$, $R_1 = H$, $R_{2'} = F$, $R_8 = CH_3$	7.72	7.47	0.25	2.48	1.00	1.35
70	$R_7 = H$, $R_1 = CH_3$, $R_{2'} = F$, $R_9 = Cl$	7.14	7.39	0.25	2.88	1.00	1.35
71	$R_7 = H$, $R_1 = CH_3$, $R_{2'} = F$, $R_6 = Cl$, $R_8 = Cl$	6.52	6.90	0.38	3.59	1.00	1.35
72	$R_7 = Cl$, $R_1 = CH_3$, $R_{2'} = H$, $R_8 = Cl$	7.40	7.32	0.08	3.68	1.80	1.00
73	$R_7 = Cl$, $R_1 = H$, $R_{2'} = F$, $R_8 = Cl$	8.44	7.85	0.59	3.47	1.80	1.35
74	$R_7 = CH_3$, $R_1 = H$, $R_{2'} = F$, $R_8 = Cl$	7.85	7.66	0.19	3.38	1.52	1.35
75	$R_7 = Cl$, $R_1 = H$, $R_{2'} = H$, $R_9 = Cl$	7.43	7.19	0.24	3.82	1.80	1.00
76	$R_7 = Cl$, $R_1 = H$, $R_{2'} = H$, $R_9 = CH_3$	7.28	7.43	0.15	3.56	1.80	1.00
77	$R_7 = H$,[c] $R_1 = H$, $R_{2'} = Cl$	7.43	7.76	0.33	1.99	1.00	1.80
78	$R_7 = Cl$,[c] $R_1 = H$, $R_{2'} = Cl$	8.41	8.76	0.35	2.81	1.80	1.80
79	$R_7 = Cl$,[c] $R_1 = H$, $R_{2'} = H$	7.15	7.93	0.78	2.74	1.80	1.00

[a] Data points omitted from the derivation of eq 25. [b] Calculated using eq 25. [c] The A-ring is a thienyl group instead of the phenyl. [d-g] In these groups $R_{2'} = H$.

Haefely et al.[8] and are based on the testing procedure of Möhler and Okada.[5] Part of this data was used to derive eqs 2 and 3.

The most important parameter in the development of eq 25 is log P as shown in eq 23. Following log P, B_1 for 7-substituents and B_1 for 2′-substituents enter the QSAR. The six outliers not included in this analysis are marked in Table 2. We had expected that an electronic term would be needed for 7-substituents from the qualitative analyses as well as from eqs 2 and 3. However, the conflicting messages from the HOMO and LUMO terms in these equations leaves one in some doubt. We could find no role for σ or F in eq 25. The highly significant B_{1-7} term points to a steric effect of the first atom of groups in the 7-position. The positive coefficient with B_{1-7} means that the larger the atom attached to the ring the more effective the binding. This could imply that atoms at this position produce a conformational change in the receptor. This importance of B_{1-7} recalls the observation of the Naples group in deriving eqs 2 and 3 that B_{1-7} seemed to show some correlation. The bilinear model used in eqs 23−25 was developed by Kubinyi.[51]

The initial slope for log P is reasonable in terms of past experience, but log P_o of 2.51 is surprisingly low for in vitro results. For studies of this type we have generally found log P_o to be higher, often in the range of 4 to 5. This low value suggests that the homogenate contains lipophilic material which sequesters drugs strongly enough so that compounds having log P of 2.51 and higher do not attain the same equilibrium binding as do their more hydrophilic counterparts. Another view would be that the receptor is rather hydrophilic; however, there is nothing in our QSAR to support this view. The role of log P in eq 25 is similar to the finding of Biagi et al. with eq 10, although their studies were with animals.

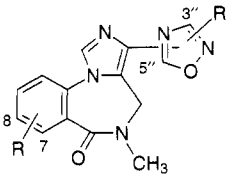
The $B_{1-2'}$ term appears to confirm a positive steric effect for 2′-substituents on the 5-phenyl ring, but this point needs further study since the range of substituents covered is not great. The fact that log P has been used to model hydrophobicity, implies that 2′-substituents also have a hydrophobic effect. One compound in Table 2 (no. 58) allows deeper insight. This substance with a 5-pyridine moiety replacing the usual 5-phenyl ring is very well fit despite the fact that it is much more hydrophilic than phenyl (1.3 log units). The presence of the very strong electron-attracting N in the 2-position would be expected to confer high activity if it is the electronic effect of 2′-substituents which is important. Thus its modest activity discounts the importance of the field/inductive effect of the ring nitrogen. Of course not much weight can be placed on a single data point. However, other examples of pyridine moieties in the 5-position are well correlated by QSAR 64.

The positive steric effect of 2′-substituents must be associated, in part, with twisting the 5-phenyl ring out of the plane of the seven-membered ring. Of course, hydrophobicity is also involved as the importance of log P shows. Thus two important steric factors which may act cooperatively are the size of the first atom of the 7-substituent and the angle the 5-phenyl group makes with the larger ring system.

If we use the indicator I_2 as used in eq 2 in place of $B_{1-2'}$ in eq 25, a very similar equation is obtained with $r = 0.875$ and $s = 0.353$ which shows that the two terms are almost equivalent. A better selection of 2′-substituents is needed to clearly resolve this problem.

Very recently[52] the Naples group joined Kim of Abbott laboratories to reevaluate the earlier CoMFA study[23] (eq 3). In the new approach the GRID H_2O probe gave the best correlation followed by the CH_3 and H^+ probes. The correlation between the latent variables Z_{H_2O}'s and Z_{CH_3}'s is high, suggesting collinearity between the hydrophobic and steric parameters. The best correlation with the H_2O probe contained three latent variables with $r = 0.885$. The best correlation obtained from both the H_2O and H^+

Table 3. Compounds and Physicochemical Parameters Used for Derivation of Eqs 26–28



no.	substituent	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	$\pi_{7,8}$	$B_{1-3''}$	$\sigma_{7,8}$
1	$R_{7,8}$ = H, $R_{3''}$ = CH_3	7.17	7.12	0.05	0.00	1.52	0.00
2	$R_{7,8}$ = H, $R_{3''}$ = C_2H_5	7.29	7.12	0.17	0.00	1.52	0.00
3[a]	$R_{7,8}$ = H, $R_{3''}$ = C_3H_7	6.92	7.12	0.20	0.00	1.52	0.00
4	$R_{7,8}$ = H, $R_{3''}$ = $CH(CH_3)_2$	6.98	6.89	0.09	0.00	1.90	0.00
5	$R_{7,8}$ = H, $R_{5''}$ = CH_3	7.57	7.44	0.13	0.00	1.00	0.00
6	$R_{7,8}$ = H, $R_{5''}$ = C_2H_5	7.66	7.44	0.22	0.00	1.00	0.00
7	$R_{7,8}$ = H, $R_{5''}$ = C_3H_7	7.47	7.44	0.03	0.00	1.00	0.00
8	$R_{7,8}$ = H, $R_{5''}$ = $CH(CH_3)_2$	7.27	7.44	0.17	0.00	1.00	0.00
9[a]	R_8 = Cl, $R_{3''}$ = C_2H_5	6.22	7.96	1.74	0.71	1.52	0.23
10	R_7 = Cl, $R_{3''}$ = CH_3	8.09	8.07	0.02	0.71	1.52	0.37
11	R_7 = Cl, $R_{3''}$ = C_2H_5	8.01	8.07	0.06	0.71	1.52	0.37
12	R_7 = Cl, $R_{3''}$ = C_3H_7	8.22	8.07	0.15	0.71	1.52	0.37
13	R_7 = Cl, $R_{3''}$ = $CH(CH_3)_2$	7.86	7.84	0.02	0.71	1.90	0.37
14	R_7 = Cl, $R_{5''}$ = CH_3	8.47	8.38	0.09	0.71	1.00	0.37
15	R_7 = Cl, $R_{5''}$ = C_2H_5	8.19	8.38	0.19	0.71	1.00	0.37
16	R_7 = Cl, $R_{5''}$ = C_3H_7	8.42	8.38	0.04	0.71	1.00	0.37
17	R_7 = Cl, $R_{5''}$ = $CH(CH_3)_2$	8.44	8.38	0.06	0.71	1.00	0.37
18	R_7 = F, $R_{3''}$ = CH_3	7.66	7.52	0.14	0.14	1.52	0.34
19	R_7 = F, $R_{3''}$ = C_2H_5	7.38	7.52	0.14	0.14	1.52	0.34
20	R_7 = F, $R_{3''}$ = C_3H_7	7.62	7.52	0.10	0.14	1.52	0.34
21	R_7 = F, $R_{3''}$ = $CH(CH_3)_2$	7.17	7.29	0.12	0.14	1.90	0.34
22	R_7 = F, $R_{5''}$ = CH_3	7.96	7.84	0.12	0.14	1.00	0.34
23	R_7 = F, $R_{5''}$ = C_2H_5	7.83	7.84	0.01	0.14	1.00	0.34
24	R_7 = F, $R_{5''}$ = C_3H_7	7.85	7.84	0.01	0.14	1.00	0.34
25	R_7 = F, $R_{5''}$ = $CH(CH_3)_2$	7.72	7.84	0.12	0.14	1.00	0.34
26	R_8 = F, $R_{3''}$ = CH_3	7.30	7.30	0.00	0.14	1.52	0.06
27	R_8 = F, $R_{3''}$ = C_2H_5	6.98	7.30	0.32	0.14	1.52	0.06
28	R_8 = F, $R_{3''}$ = C_3H_7	7.38	7.30	0.08	0.14	1.52	0.06
29	R_8 = F, $R_{3''}$ = $CH(CH_3)_2$	6.99	7.07	0.08	0.14	1.90	0.06
30	R_8 = F, $R_{5''}$ = CH_3	7.68	7.61	0.07	0.14	1.00	0.06
31	R_8 = F, $R_{5''}$ = C_2H_5	7.56	7.61	0.05	0.14	1.00	0.06
32	R_8 = F, $R_{5''}$ = C_3H_7	7.56	7.61	0.05	0.14	1.00	0.06
33	R_8 = F, $R_{5''}$ = $CH(CH_3)_2$	7.37	7.61	0.24	0.14	1.00	0.06

[a] Omitted points from derivation of eq 28. [b] Calculated with eq 28.

probes contained seven latent variables with r = 0.977. These results are based on the analysis of the 48 compounds used to derive eq 3 rather than the 74 points used to derive eq 25.

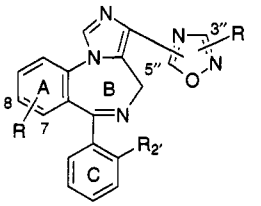
The contour map shows that 7-substituents and 2′-substituents make positive hydrophobic interactions which agrees with the log P terms of eq 25. The CoMFA results indicate that there may be a positive electrostatic effect from 2′-substituents which eq 25 has no term for. Our analysis suggests only steric and hydrophobic interactions; however, the data are not well suited to make a decision on this point. The Abbott–Naples group conclude, in agreement with us, that hydrophobic effects alone explain the majority of the variance in the data. There is nothing in the two CoMFA studies which corresponds to B_{1-7} terms in eq 25 or in the other QSAR.[53]

The CoMFA results would indicate that about 18% of the variance in the data for the 48 compounds is due to electrostatic effects, but since there is considerable collinearity between hydrogen bonding effects accounted for by the H_2O probe and electrostatic effects accounted for by the H^+ probe it is not possible to clearly delineate the roles of these two properties of the benzodiazepines. As mentioned before, we believe that the nonhomogeneity of the receptors may, in part, be the cause of the less than perfect QSAR.

In the analysis of eq 28 we note that 8-substituents appear (compound no. 9, Table 3) to display a negative steric effect. The CoMFA contour map confirms this.[53] The contour map also agrees with the negative $B_{1-3''}$ term in eq 28.[53] In addition, CoMFA contours agree with the negative L_1 term in eq 58.[53] Thus, overall there is rather good agreement on the essential features of the SAR of the benzodiazepines from the two quite different QSAR approaches. The points of difference in the two methodologies are steric effects of the 7- and 2′-positions brought out by the traditional QSAR, not by CoMFA, and the importance of the electrostatic effect brought out by CoMFA, but not by our QSAR.

In Tables 3 and 4 are listed two sets of oxadiazolylimidazobenzodiazepines. It was hoped that the

Table 4. Compounds and Physicochemical Parameters Used for Derivation of Eqs 29–32

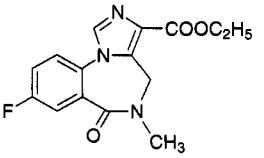


no	substituent	log 1/C obsd	log 1/C calcd[b]	|Δ log 1/C|	B_{1-7}	$B_{1-3''}$	$B_{1-2'}$	I_8
1	$R_{7,8}$ = H, $R_{2'}$ = H, $R_{3''}$ = CH_3	7.62	7.44	0.18	1.00	1.52	1.00	0.00
2	$R_{7,8}$ = H, $R_{2'}$ = H, $R_{3''}$ = C_2H_5	7.72	7.44	0.28	1.00	1.52	1.00	0.00
3	$R_{7,8}$ = H, $R_{2'}$ = H, $R_{3''}$ = iC_3H_7	7.28	7.44	0.16	1.00	1.90	1.00	0.00
4	$R_{7,8}$ = H, $R_{2'}$ = H, $R_{3''}$ = nC_3H_7	7.36	7.22	0.14	1.00	1.52	1.00	0.00
5[a]	$R_{7,8}$ = H, $R_{2'}$ = H, $R_{5''}$ = CH_3	8.15	7.74	0.41	1.00	1.00	1.00	0.00
6	$R_{7,8}$ = H, $R_{2'}$ = H, $R_{5''}$ = C_2H_5	7.79	7.74	0.05	1.00	1.00	1.00	0.00
7	$R_{7,8}$ = H, $R_{2'}$ = H, $R_{5''}$ = iC_3H_7	7.74	7.74	0.00	1.00	1.00	1.00	0.00
8	R_8 = Cl, $R_{2'}$ = H, $R_{3''}$ = CH_3	6.74	7.07	0.33	1.00	1.52	1.00	1.00
9	R_8 = Cl, $R_{2'}$ = H, $R_{3''}$ = C_2H_5	6.79	7.07	0.28	1.00	1.52	1.00	1.00
10	R_8 = Cl, $R_{2'}$ = H, $R_{3''}$ = nC_3H_7	6.92	7.07	0.15	1.00	1.52	1.00	1.00
11	R_8 = Cl, $R_{2'}$ = H, $R_{3''}$ = iC_3H_7	6.92	6.85	0.07	1.00	1.90	1.00	1.00
12	R_8 = Cl, $R_{2'}$ = H, $R_{5''}$ = CH_3	7.15	7.37	0.22	1.00	1.00	1.00	1.00
13	R_8 = Cl, $R_{2'}$ = H, $R_{5''}$ = C_2H_5	7.36	7.37	0.01	1.00	1.00	1.00	1.00
14	R_8 = Cl, $R_{2'}$ = H, $R_{5''}$ = nC_3H_7	7.35	7.37	0.02	1.00	1.00	1.00	1.00
15	R_8 = Cl, $R_{2'}$ = H, $R_{5''}$ = iC_3H_7	7.27	7.37	0.10	1.00	1.00	1.00	1.00
16	R_8 = Cl, $R_{2'}$ = Cl, $R_{5''}$ = nC_3H_7	8.07	7.74	0.32	1.00	1.00	1.80	1.00
17	R_8 = Cl, $R_{2'}$ = Cl, $R_{5''}$ = iC_3H_7	7.92	7.74	0.18	1.00	1.00	1.80	1.00
18	R_7 = Cl, $R_{2'}$ = H, $R_{3''}$ = CH_3	8.47	8.41	0.06	1.80	1.52	1.00	0.00
19	R_7 = Cl, $R_{2'}$ = H, $R_{3''}$ = C_2H_5	8.38	8.41	0.03	1.80	1.52	1.00	0.00
20	R_7 = Cl, $R_{2'}$ = H, $R_{3''}$ = nC_3H_7	8.28	8.41	0.13	1.80	1.52	1.00	0.00
21	R_7 = Cl, $R_{2'}$ = H, $R_{3''}$ = iC_3H_7	8.14	8.19	0.05	1.80	1.90	1.00	0.00
22	R_7 = Cl, $R_{2'}$ = H, $R_{5''}$ = CH_3	8.88	8.70	0.18	1.80	1.00	1.00	0.00
23	R_7 = Cl, $R_{2'}$ = H, $R_{5''}$ = C_2H_5	8.55	8.70	0.15	1.80	1.00	1.00	0.00
24	R_7 = Cl, $R_{2'}$ = H, $R_{5''}$ = nC_3H_7	8.41	8.70	0.29	1.80	1.00	1.00	0.00
25[a]	R_8 = Cl, $R_{2'}$ = Cl, $R_{3''}$ = CH_3	6.96	7.45	0.49	1.00	1.52	1.80	1.00
26	R_8 = Cl, $R_{2'}$ = Cl, $R_{3''}$ = C_2H_5	7.60	7.45	0.15	1.00	1.52	1.80	1.00
27	R_8 = Cl, $R_{2'}$ = Cl, $R_{3''}$ = nC_3H_7	7.47	7.45	0.02	1.00	1.52	1.80	1.00
28	R_8 = Cl, $R_{2'}$ = Cl, $R_{3''}$ = iC_3H_7	7.35	7.23	0.12	1.00	1.90	1.80	1.00
29	R_8 = Cl, $R_{2'}$ = Cl, $R_{5''}$ = CH_3	7.69	7.74	0.05	1.00	1.00	1.80	1.00
30	R_8 = Cl, $R_{2'}$ = Cl, $R_{5''}$ = C_2H_5	8.03	7.74	0.29	1.00	1.00	1.80	1.00
31[a]	R_7 = Cl, $R_{2'}$ = H, $R_{5''}$ = iC_3H_7	8.16	8.70	0.54	1.80	1.00	1.00	0.00
32	$R_{7,8}$ = H, $R_{2'}$ = Cl, $R_{3''}$ = CH_3	7.51	7.82	0.31	1.00	1.52	1.80	0.00
33	$R_{7,8}$ = H, $R_{2'}$ = Cl, $R_{3''}$ = iC_3H_7	7.51	7.60	0.09	1.00	1.90	1.80	0.00
34	$R_{7,8}$ = H, $R_{2'}$ = Cl, $R_{5''}$ = CH_3	8.17	8.11	0.06	1.00	1.00	1.80	0.00
35	$R_{7,8}$ = H, $R_{2'}$ = Cl, R_5 = C_2H_5	7.88	8.11	0.23	1.00	1.00	1.80	0.00
36	$R_{7,8}$ = H, $R_{2'}$ = Cl, $R_{5''}$ = nC_3H_7	7.92	8.11	0.19	1.00	1.00	1.80	0.00
37	$R_{7,8}$ = H, $R_{2'}$ = Cl, $R_{5''}$ = iC_3H_7	7.85	8.11	0.26	1.00	1.00	1.80	0.00
38	R_7 = F, $R_{2'}$ = H, $R_{3''}$ = CH_3	8.08	7.86	0.22	1.35	1.52	1.00	0.00
39	R_7 = F, $R_{2'}$ = H, $R_{3''}$ = C_2H_5	8.01	7.86	0.15	1.35	1.52	1.00	0.00
40[a]	R_7 = F, $R_{2'}$ = H, $R_{3''}$ = iC_3H_7	8.85	7.65	1.20	1.35	1.90	1.00	0.00
41	R_7 = F, $R_{2'}$ = H, $R_{5''}$ = CH_3	8.62	8.16	0.46	1.35	1.00	1.00	0.00
42	R_7 = F, $R_{2'}$ = H, $R_{5''}$ = C_2H_5	8.12	8.16	0.04	1.35	1.00	1.00	0.00
43	R_7 = F, $R_{2'}$ = H, $R_{5''}$ = nC_3H_7	8.27	8.16	0.11	1.35	1.00	1.00	0.00
44	R_7 = F, $R_{2'}$ = H, $R_{5''}$ = iC_3H_7	8.21	8.16	0.05	1.35	1.00	1.00	0.00

[a] These points excluded from the derivation of eq 32. [b] Calculated according to eq 32.

isosteric replacement of the ester linkage with the oxadiazole ring in the 6-oxo- and 6-arylimidazobenzodiazepines would provide novel partial agonists with a favorable separation between anxiolytic and sedative properties. This replacement was found to give compounds with higher intrinsic activity[54] compared to the ethyl esters.

The log 1/C values in Tables 3 and 4 refer to the molar concentrations which cause 50% inhibition of the in vitro binding of [^{3}H]R_o 15-1788 to rat cortical membrane homogenate.



R_o 15-1788

From this data we have derived eqs 26–28.

$$\log 1/C = 1.28(\pm0.35)\pi_{7,8} + 7.31(\pm0.13) \quad (26)$$

$$n = 32,\ r = 0.808,\ s = 0.267,\ F_{1,30} = 54.7$$

$$\log 1/C = 1.28(\pm0.22)\pi_{7,8} - 0.62(\pm0.18)B_{1-3''} + 8.12(\pm0.26) \quad (27)$$

$$n = 32,\ r = 0.929,\ s = 0.169,\ F_{1,29} = 45.8$$

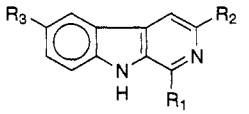
$$\log 1/C = 0.92(\pm0.26)\pi_{7,8} - 0.62(\pm0.15)B_{1-3''} + 0.84(\pm0.43)\sigma_{7,8} + 8.04(\pm0.22) \quad (28)$$

$$n = 32,\ r = 0.955,\ s = 0.137,\ F_{1,28} = 16.2$$

correlation matrix (r)

	$\pi_{7,8}$	$B_{1-3''}$	$\sigma_{7,8}$
$\pi_{7,8}$	1	0.00	0.71
$B_{1-3''}$		1	0.00
$\sigma_{7,8}$			1

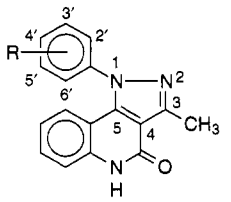
Table 5. Compounds and Physicochemical Parameters Used for the Derivation of Eqs 33–35



no.	substituent	log $1/K_i$ obsd	log $1/K_i$ calcd[b]	$\lvert\Delta \log 1/K_i\rvert$	π_2	E_{s_1}	I_2
1	$R_1 = C_2H_5$, $R_2 = CO_2CH_3$, $R_3 = OH$	5.24	5.35	0.11	−0.01	−1.31	1.00
2	$R_1 = C_2H_5$, $R_2 = CO_2CH_3$, $R_3 = H$	5.12	5.35	0.23	−0.01	−1.31	1.00
3	$R_1 = C_6H_5$, $R_2 = CO_2CH_3$, $R_3 = H$	5.41	5.98	0.57	−0.01	−1.01	1.00
4	$R_1 = CH=CH_2$, $R_2 = H$, $R_3 = H$	3.60	3.76	0.16	0.00	−1.31	0.00
5	$R_1 = CH_3$, $R_2 = H$, $R_3 = H$	4.91	3.91	1.00	0.00	−1.24	0.00
6	$R_1 = H$, $R_2 = CO_2CH_3$, $R_3 = H$	8.98	8.10	0.88	−0.01	0.00	1.00
7[a]	$R_1 = H$, $R_2 = COOH$, $R_3 = H$	4.62				0.00	1.00
8	$R_1 = H$, $R_2 = COCH_3$, $R_3 = H$	7.24	7.53	0.29	−0.55	0.00	1.00
9	$R_1 = H$, $R_2 = CHO$, $R_3 = H$	7.21	7.42	0.21	−0.65	0.00	1.00
10	$R_1 = H$, $R_2 = CO_2CH_3$, $R_3 = OH$	8.58	8.10	0.48	−0.01	0.00	1.00
11	$R_1 = H$, $R_2 = CO_2C_2H_5$, $R_3 = H$	8.96	8.65	0.30	0.51	0.00	1.00
12	$R_1 = H$, $R_2 = CO_2C_3H_7$, $R_3 = H$	9.00	9.25	0.25	1.07	0.00	1.00
13	$R_1 = H$, $R_2 = CH_2OH$, $R_3 = H$	5.83	5.42	0.41	−1.03	0.00	0.00
14	$R_1 = H$, $R_2 = CHOHCH_3$, $R_3 = H$	5.50	6.02	0.52	−0.47[c]	0.00	0.00
15	$R_1 = H$, $R_2 = H$, $R_3 = H$	5.79	6.52	0.73	0.00	0.00	0.00

[a] Omitted point from derivation of eq 35. [b] According to eq 35. [c] Estimated by adding a π of 0.56 to the π of $-CH_2OH$.

Table 6. Compounds and Physicochemical Parameters for Derivation of Eqs 36–38



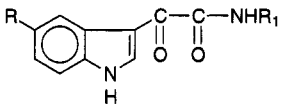
no.[a]	substituent	log $1/C$ obsd	log $1/C$ calcd[b]	$\lvert\Delta \log 1/C\rvert$	$\Sigma\pi$	$\Sigma\sigma$	$E_{s_{2,6}}$
1	$R_{2',3',4',5',6'} = H$	4.64	4.75	0.11	0.00	0.00	0.00
2	$R_{2'} = Cl$	4.40	4.65	0.25	0.71	0.23	−0.97
3	$R_{3'} = Cl$	5.36	5.39	0.04	0.71	0.37	0.00
4[a]	$R_{4'} = Cl$	4.66	5.31	0.85	0.71	0.23	0.00
5	$R_{2'} = CH_3$	4.44	4.13	0.31	0.56	−0.17	−1.24
6	$R_{3'} = CH_3$	5.05	5.03	0.02	0.56	−0.07	0.00
7	$R_{4'} = CH_3$	4.68	4.97	0.29	0.56	−0.17	0.00
8	$R_{2'} = OCH_3$	4.25	4.20	0.05	−0.02	−0.27	−0.55
9	$R_{3'} = OCH_3$	5.12	4.81	0.32	−0.02	0.12	0.00
10	$R_{4'} = OCH_3$	4.40	4.57	0.17	−0.02	−0.27	0.00
11	$R_{2'} = Br$	4.70	4.61	0.09	0.86	0.23	−1.16
12	$R_{3'} = Br$	5.60	5.49	0.11	0.86	0.39	0.00
13	$R_{3'} = F$	4.85	5.04	0.19	0.14	0.34	0.00
14	$R_{4'} = F$	4.99	4.87	0.13	0.14	0.06	0.00
15	$R_{3',5'} = CH_3$	5.52	5.32	0.21	1.12	−0.14	0.00
16	$R_{2',4'} = CH_3$	4.35	4.36	0.01	1.12	−0.34	−1.24
17	$R_{2',3'} = CH_3$	4.03	4.42	0.39	1.12	−0.24	−1.24
18	$R_{3',4'} = CH_3$	5.43	5.25	0.18	1.12	−0.24	0.00
19	$R_{2',6'} = CH_3$	3.66	3.52	0.14	1.12	−0.34	−2.48
20	$R_{2',5'} = CH_3$	4.33	4.42	0.09	1.12	−0.24	−1.24

[a] Omitted point from the derivation of eq 38. [b] Calculated according to eq 38.

The most important term is $\pi_{7,8}$ which substantiates our other correlations as to the importance of the hydrophobic effect and shows that substituents in both of these positions contact hydrophobic space. It is noteworthy that π correlates both 7- and 8-substituents for this set of compounds which lack the normal 5-phenyl substituents. In eq 32, which contains the phenyl group, 8-substituents require a negative indicator variable. It seems that the positioning of the phenyl ring is quite sensitive to steric effects of both the 2′- and 8-substituents.

The σ term in eq 28 would seem to imply a significant role for electron-attracting groups in the 7- and 8-positions. However, σ and π are rather collinear as is apparent from the correlation matrix and σ is the last term to enter eq 28. Moreover, we have used π from the benzene system, and it is well known that electron-attracting substituents conjugated with an amino nitrogen increase π beyond simple additivity.[55] Hence, the σ term in eq 28 cannot be taken very seriously. It is probably a correction on π.[55]

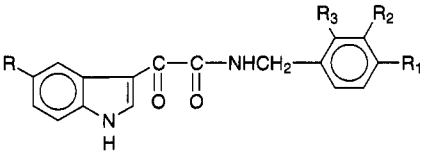
Table 7. Compounds and Physicochemical Parameters for the Derivation of Eqs 39–41



no.	substituent	log 1/K_i obsd	log 1/K_i calcd[b]	$\|\Delta \log 1/K_i\|$	σ_p	I_1	I_2
1	R = H, R_1 = amino-ethyl-indole	5.82	6.15	0.33	0.00	0.00	0.00
2[a]	R = NO_2, R_1 = amino-ethyl-indole	6.45	6.92	0.47	0.78	0.00	0.00
3	R = H, R_1 = 4-hydroxyphenethyl	5.61	5.53	0.08	0.00	1.00	0.00
4	R = Cl, R_1 = 4-hydroxyphenethyl	5.66	5.76	0.10	0.23	1.00	0.00
5	R = Br, R_1 = 4-hydroxyphenethyl	5.64	5.76	0.12	0.23	1.00	0.00
6	R = NO_2, R_1 = 4-hydroxyphenethyl	6.45	6.31	0.14	0.78	1.00	0.00
7	R = H, R_1 = 3,4-dihydroxyphenethyl	5.37	5.65	0.28	0.00	0.00	1.00
8	R = Cl, R_1 = 3,4-dihydroxyphenethyl	6.00	5.88	0.12	0.23	0.00	1.00
9	R = Br, R_1 = 3,4-dihydroxyphenethyl	5.92	5.88	0.04	0.23	0.00	1.00
10	R = NO_2, R_1 = 3,4-dihydroxyphenethyl	6.55	6.43	0.12	0.78	0.00	1.00
11	R = H, R_1 = phenethyl	6.42	6.15	0.27	0.00	0.00	0.00
12[a]	R = H, R_1 = 4-methoxyphenethyl	7.04	6.15	0.89	0.00	0.00	0.00
13[a]	R = H, R_1 = 3-methoxyphenethyl	7.07	6.15	0.92	0.00	0.00	0.00
14	R = H, R_1 = 3,4-dimethoxyphenethyl	6.29	6.15	0.14	0.00	0.00	0.00
15	R = Cl, R_1 = 3,4-dimethoxyphenethyl	6.15	6.38	0.23	0.23	0.00	0.00
16	R = NO_2, R_1 = 3,4-dimethoxyphenethyl	6.74	6.92	0.18	0.78	0.00	0.00
17	R = H, R_1 = 4-chlorophenethyl	6.46	6.15	0.31	0.00	0.00	0.00

[a] Points omitted from eq 41. [b] Calculated according to eq 41.

Table 8. Compounds and Physicochemical Parameters for Derivation of Eqs 42–44



no.	substituent	log 1/K_i obsd	log 1/K_i calcd[b]	$\|\Delta \log 1/K_i\|$	σ	I_2	I_3
1	R = H, R_1 = H, R_2 = H, R_3 = H	6.93	6.56	0.37	0.00	0.00	0.00
2[a]	R = Cl, R_1 = H, R_2 = H, R_3 = H	6.21	6.80	0.59	0.23	0.00	0.00
3	R = NO_2, R_1 = H, R_2 = H, R_3 = H	6.93	7.35	0.42	0.78	0.00	0.00
4	R = H, R_1 = OCH_3, R_2 = H, R_3 = H	6.78	6.56	0.22	0.00	0.00	0.00
5	R = Cl, R_1 = OCH_3, R_2 = H, R_3 = H	6.68	6.80	0.12	0.23	0.00	0.00
6	R = NO_2, R_1 = OCH_3, R_2 = H, R_3 = H	7.27	7.57	0.30	0.78	0.00	0.00
7	R = H, R_1 = H, R_2 = OCH_3, R_3 = H	6.54	6.56	0.02	0.00	0.00	0.00
8	R = Cl, R_1 = H, R_2 = OCH_3, R_3 = H	6.79	6.80	0.01	0.23	0.00	0.00
9	R = NO_2, R_1 = H, R_2 = OCH_3, R_3 = H	7.42	7.35	0.07	0.78	0.00	0.00
10	R = H, R_1 = OCH_3, R_2 = OCH_3, R_3 = H	7.03	7.16	0.13	0.00	1.00	0.00
11	R = Cl, R_1 = OCH_3, R_2 = OCH_3, R_3 = H	7.52	7.40	0.12	0.23	1.00	0.00
12	R = NO_2, R_1 = OCH_3, R_2 = OCH_3, R_3 = H	7.96	7.95	0.02	0.78	1.00	0.00
13[a]	R = H, R_1 = Cl, R_2 = H, R_3 = H	7.17	6.56	0.61	0.00	0.00	0.00
14[a]	R = H, R_1 = H, R_2 = H, R_3 = Cl	5.59	6.56	0.97	0.00	0.00	0.00
15	R = H, R_1 = OH, R_2 = H, R_3 = H	6.37	6.56	0.19	0.00	0.00	0.00
16	R = Cl, R_1 = OH, R_2 = H, R_3 = H	6.82	6.80	0.02	0.23	0.00	0.00
17	R = NO_2, R_1 = OH, R_2 = H, R_3 = H	7.92	7.35	0.57	0.78	0.00	0.00
18	R = H, R_1 = H, R_2 = OH, R_3 = H	6.09	6.17	0.08	0.00	0.00	1.00
19	R = Cl, R_1 = H, R_2 = OH, R_3 = H	6.24	6.40	0.16	0.23	0.00	1.00
20	R = NO_2, R_1 = H, R_2 = OH, R_3 = H	7.19	6.95	0.24	0.78	0.00	1.00
21	R = H, R_1 = OH, R_2 = OH, R_3 = H	6.46	6.56	0.10	0.00	0.00	0.00
22	R = Cl, R_1 = OH, R_2 = OH, R_3 = H	6.75	6.80	0.05	0.23	0.00	0.00
23	R = NO_2, R_1 = OH, R_2 = OH, R_3 = H	7.32	7.35	0.03	0.78	0.00	0.00

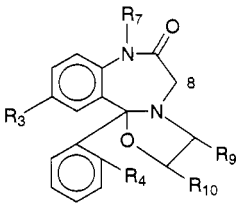
[a] Dropped points. [b] Calculated according to eq 44.

Most interesting is the parameterization of the oxadiazole ring. The substituents on this ring are small alkyl groups (CH_3, C_2H_5, C_3H_7, i-C_3H_7) in the 3″- or 5″-positions. Thus there is considerable variation in the hydrophobicity of this ring, yet we were unable to parameterize it. This strongly suggests that this ring and its substituents do not contact hydrophobic space on the receptor. This raises a question as to what the negative role of $B_{1-3''}$ might be. Substituents in the 5″-position receive no parameterization and yet they are well fit by eq 28. It is likely that 3″-substituents do contact the receptor, but that 5″ do not. In any case we could discern no hydrophobic effect for these substituents.

One data point, 9, in Table 3 was not used in the formulation of eqs 26–28.

Table 9. Compounds and Physicochemical Parameters for Derivation of and Biological Data Correlated in Eqs 45–57

Compounds and Physicochemical Parameters



		log 1/C								
no.	substituent	obsd	calcd[a]	|Δ log 1/C|	log P	MR_7	I_2	I_3	B_{1-3}	B_{1-4}
1	$R_4 = Cl, R_{10} = CH_3$	3.96	4.50	0.54	4.14	0.10	0.00	1.00	1.00	1.80
2	$R_{10} = CH_3$	4.32	3.83	0.49	3.43	0.10	0.00	1.00	1.00	1.00
3	$R_3 = Cl, R_7 = CH_2C_6H_4$-2′Cl	4.33	4.39	0.06	6.53	3.51	0.00	0.00	1.80	1.00
4	$R_3 = Cl, R_7 = C_4H_9, R_{10} = CH_3$	4.35	4.21	0.14	6.22	1.96	0.00	1.00	1.80	1.00
5	$R_3 = Cl, R_4 = CH_3, R_{10} = CH_3$	4.63	5.40	0.77	4.85	0.10	0.00	1.00	1.80	1.52
6	$R_3 = Cl, R_8 = CH_3$	4.71	4.96	0.25	4.40	0.10	0.00	0.00	1.80	1.00
7	R_3= Cl, $R_7 = CH_2$-CH=$CH_2, R_{10} = CH_3$	4.77	4.75	0.02	5.21	1.44	0.00	1.00	1.80	1.00
8	$R_3 = Cl, R_7 = CH_2C_6H_5, R_{10} = CH_3$	4.77	4.39	0.38	6.34	3.00	0.00	1.00	1.80	1.00
9	$R_3 = Cl, R_7 = CH_3, R_{10} = CH_3$	4.80	4.92	0.12	4.63	0.56	0.00	1.00	1.80	1.00
10	$R_3 = Br, R_8 = CH_3$	4.80	5.20	0.40	4.55	0.10	0.00	0.00	1.95	1.00
11	$R_3 = Cl, R_7 = CH_3$	4.86	5.27	0.41	4.12	0.56	0.00	0.00	1.80	1.00
12	$R_3 = Cl, R_7 = CH_2CH_2Cl$	4.90	5.10	0.20	4.71	1.50	0.00	0.00	1.80	1.00
13	$R_3 = Br, R_7 = CH_3, R_{10} = CH_3$	4.92	5.16	0.24	4.78	0.56	0.00	1.00	1.95	1.00
14	$R_3 = Cl, R_7 = C_2H_5, R_{10} = CH_3$	4.93	4.68	0.25	5.16	1.03	0.00	1.00	1.80	1.00
15	$R_3 = Cl, R_7 = C_2H_5$	4.96	5.03	0.07	4.64	1.03	0.00	0.00	1.80	1.00
16	$R_3 = Br, R_7 = CH_3$	5.09	5.50	0.41	4.27	0.56	0.00	0.00	1.95	1.00
17	$R_3 = Cl, R_4 = Cl, R_7 = CH_3, R_{10} = CH_3$	5.11	5.58	0.47	5.35	0.56	0.00	1.00	1.80	1.80
18	$R_3 = Cl, R_4 = Cl, R_8 = CH_3, R_{10} = CH_3$	5.13	5.28	0.15	5.63	0.10	0.00	1.00	1.80	1.80
19	$R_3 = Cl, R_{10} = CH_3$	5.16	4.96	0.20	4.40	0.10	0.00	1.00	1.80	1.00
20	$R_3 = NO_2, R_7 = CH_3, R_{10} = CH_3$	5.17	5.22	0.05	3.86	0.56	0.00	1.00	1.70	1.00
21	$R_3 = Cl$	5.20	5.31	0.11	3.88	0.10	0.00	0.00	1.80	1.00
22	$R_3 = NO_2, R_7 = C_2H_5$	5.21	5.33	0.12	3.87	1.03	0.00	0.00	1.70	1.00
23	$R_3 = Br, R_7 = C_2H_5$	5.25	5.27	0.02	4.79	1.03	0.00	0.00	1.95	1.00
24	$R_3 = Br, R_{10} = CH_3$	5.34	5.20	0.14	4.55	0.10	0.00	1.00	1.95	1.00
25	$R_3 = Br$	5.35	5.55	0.20	4.03	0.10	0.00	0.00	1.95	1.00
26	$R_3 = NO_2, R_{10} = CH_3$	5.49	5.20	0.29	3.72	0.10	0.00	1.00	1.70	1.00
27	$R_3 = NO_2, R_7 = CH_3$	5.53	5.57	0.04	3.34	0.56	0.00	0.00	1.70	1.00
28	$R_3 = Br, R_4 = Cl, R_7 = CH_3, R_{10} = CH_3$	5.55	5.82	0.27	5.50	0.56	0.00	1.00	1.95	1.80
29	$R_3 = Cl, R_7 = CH_3, R_9 = CH_3$	5.60	5.74	0.14	4.63	0.56	1.00	0.00	1.80	1.00
30	$R_3 = NO_2$	5.62	5.55	0.07	3.20	0.10	0.00	0.00	1.70	1.00
31	$R_3 = Cl, R_4 = F, R_{10} = CH_3$	5.70	5.37	0.33	4.54	0.10	0.00	1.00	1.80	1.35
32	$R_3 = Cl, R_4 = F, R_7 = CH_3$	5.81	5.67	0.14	4.26	0.56	0.00	0.00	1.80	1.35
33	$R_3 = Cl, R_4 = Cl, R_7 = CH_3$	5.84	5.93	0.09	4.83	0.56	0.00	0.00	1.80	1.80
34	$R_3 = Cl, R_4 = Cl, R_7 = C_2H_5$	5.84	5.69	0.15	5.36	1.03	0.00	0.00	1.80	1.80
35	$R_3 = Cl, R_9 = CH_3$	5.87	5.78	0.09	4.40	0.10	1.00	0.00	1.80	1.00
36	$R_3 = Cl, R_4 = Cl, R_8 = CH_3$	5.91	5.63	0.28	5.11	0.10	0.00	0.00	1.80	1.80
37	$R_3 = Br, R_4 = Cl, R_7 = C_2H_5$	5.93	5.93	0.00	5.51	1.03	0.00	0.00	1.95	1.80
38	$R_3 = Br, R_9 = CH_3$	5.96	6.02	0.06	4.55	0.10	1.00	0.00	1.95	1.00
39	$R_3 = Cl, R_4 = F$	5.98	5.72	0.26	4.02	0.10	0.00	0.00	1.80	1.35
40	$R_3 = Cl, R_4 = Cl, R_{10} = CH_3$	6.00	5.63	0.37	5.11	0.10	0.00	1.00	1.80	1.80
41	$R_3 = Br, R_4 = Cl, R_8 = CH_3$	6.01	5.86	0.15	5.26	0.10	0.00	0.00	1.95	1.80
42	$R_3 = Br, R_4 = Cl, R_7 = CH_3$	6.11	6.17	0.06	4.98	0.56	0.00	0.00	1.95	1.80
43	$R_3 = Cl, R_4 = Cl$	6.18	6.02	0.16	4.53	0.10	0.00	0.00	1.80	1.80
44	$R_3 = NO_2, R_9 = CH_3$	6.23	6.24	0.01	3.72	1.00	1.00	0.00	1.70	1.00
45	$R_3 = Cl, R_4 = Cl, R_7 = CH_3, R_9 = CH_3$	6.23	6.40	0.17	5.35	0.56	1.00	0.00	1.80	1.80
46	$R_3 = Br, R_4 = Br$	6.26	6.33	0.07	4.89	0.10	0.00	0.00	1.95	1.95
47	$R_3 = Br, R_4 = Cl, R_{10} = CH_3$	6.43	5.86	0.57	5.26	0.10	0.00	1.00	1.95	1.80
48	$R_3 = Br, R_4 = F$	6.45	5.95	0.50	4.17	0.10	0.00	0.00	1.95	1.35
49	$R_3 = Br, R_4 = Cl$	6.45	6.21	0.24	4.74	0.10	0.00	0.00	1.95	1.80
50	$R_3 = Br, R_4 = Br, R_9 = CH_3$	6.48	6.80	0.32	5.41	0.10	1.00	0.00	1.95	1.95
51	$R_3 = Cl, R_4 = F, R_9 = CH_3$	6.50	6.19	0.31	4.54	0.10	1.00	0.00	1.80	1.35
52	$R_3 = Cl, R_4 = Cl, R_9 = CH_3$	6.52	6.45	0.07	5.11	0.10	1.00	0.00	1.80	1.80
53	$R_3 = Br, R_4 = Cl, R_9 = CH_3$	6.61	6.68	0.07	5.26	0.10	1.00	0.00	1.95	1.80
54	$R_3 = Br, R_4 = F, R_9 = CH_3$	6.73	6.42	0.31	4.69	0.10	1.00	0.00	1.95	1.35

Biological Data for Eqs 50–57

	log 1/C		log 1/C		log 1/C		log 1/C		log 1/C		log 1/C		log 1/C		log 1/C	
no.	obsd	calcd[c]	obsd	calcd[d]	obsd	calcd[e]	obsd	calcd[f]	obsd	calcd[g]	obsd	calcd[h]	obsd	calcd[i]	obsd	calcd[j]
9	4.66	4.42	4.06	3.93	3.30	3.36	3.60	3.58	3.65	3.72	3.86	3.99	3.84	3.79	4.46	4.30
11	4.72	4.77	4.12	4.23			3.56	3.72	3.79	3.94	4.19	4.16	4.12	4.28	4.07	4.43
13	4.59	4.51	4.11	4.09	3.53	3.60	3.81	3.81	3.91	3.90	4.00	4.21	4.03	4.12	4.38	4.50

Table 9 (Continued)

Biological Data of Eqs 50–57

	log 1/C		log 1/C		log 1/C		log 1/C		log 1/C		log 1/C		log 1/C		log 1/C	
no.	obsd	calcd[c]	obsd	calcd[d]	obsd	calcd[e]	obsd	calcd[f]	obsd	calcd[g]	obsd	calcd[h]	obsd	calcd[i]	obsd	calcd[j]
16	4.82	4.86	4.17	4.38	3.87	3.91	4.02	3.96	4.14	4.11	4.34	4.38	4.57	4.61	4.57	4.64
17	4.88	5.09	4.35	4.44	3.38	3.55	3.88	3.89	3.90	4.00	4.53	4.50	4.32	4.25	4.79	4.92
19	4.79	4.83	4.17	4.45	3.94	3.85	3.61	3.79	3.66	3.82	4.44	4.27	4.40	4.01	4.44	4.54
20	4.75	4.82	4.21	4.21	3.81	3.61	4.10	4.05	4.34[b]	3.88	4.76	4.67	4.76[b]	4.22	4.99	4.87
21	4.81	5.19	4.50	4.75	4.08	4.16	3.86	3.95	3.91	4.04	4.73	4.46	4.73	4.51	4.90	4.69
24	4.86	4.92	4.74	4.61	4.14	4.08	4.11	4.03	4.25	4.00	4.40	4.50	4.37	4.34	4.75	4.75
25	5.06	5.28	4.99	4.91	4.30	4.40	4.16	4.18	4.19	4.21	4.75	4.68	4.76	4.84	5.06	4.90
26	5.12	5.17	4.88	4.69	4.05	4.04	4.30	4.18	4.38[b]	3.94	4.30[b]	4.84	4.25	4.35	4.93	5.02
27	5.33	5.17	4.53	4.51	4.08	3.93	4.42	4.20	4.53[b]	4.10	4.63	4.85	4.49	4.72	4.89	5.02
28	5.03	5.18	4.55	4.59	3.60	3.79	4.12	4.13	4.26	4.18	4.30[b]	4.72	4.30	4.58	4.88	5.13
30	5.37	5.52	5.01	4.99	4.01	4.36	4.37	4.34	4.43	4.16	5.02	5.03	4.89	4.85	5.10	5.17
31	5.69	5.24	4.75	4.78	4.26	4.04	3.97	4.10	3.98	4.01	4.16[b]	4.71	4.08	4.38	5.20	5.00
32					4.06	3.86			4.94[b]	4.13						
33	5.41	5.45	4.78	4.74	3.76	3.87	4.04	4.04	4.20	4.22	4.56	4.68	4.71	4.75	5.22	5.07
35	5.24	5.35	5.01	4.88	4.29	4.23	4.19	4.10	4.24	4.21	4.61	4.49	4.61	4.44	4.92	4.93
36	5.33	5.51	5.04	4.97	4.11	4.04	4.20[b]	3.78	4.16	4.10	4.36	4.33	4.48	4.48	4.85	4.77
38	5.34	5.44	5.04	5.04	4.34	4.47	4.23	4.34	4.29	4.39	4.49	4.72	4.59	4.77	5.12	5.14
39	5.90	5.60	5.08	5.08	4.32	4.35	4.16	4.25	4.20	4.23	4.58	4.90	4.74	4.88	5.24	5.15
40	5.64	5.51	5.14	4.97	4.04	4.04	4.10	4.12	4.20	4.10	4.78	4.79	4.71	4.48	5.41	5.17
41	5.61	5.60	5.13	5.12	4.01	4.28	4.31	4.01	4.30	4.28	4.68	4.56	4.87	4.81	5.13	4.98
42	5.61	5.54	5.13	4.89	4.21	4.10	4.38	4.28	4.43	4.40	4.99	4.91	4.94	5.08	5.31	5.28
43	5.67	5.91	5.14	5.30	4.13	4.40	4.04	4.32	4.24	4.35	4.99	5.05	5.07	5.04	5.08	5.39
46					4.16[b]	4.62			4.34	4.55						
47	5.77	5.60	5.15	5.12	4.61	4.28	4.43	4.35	4.53	4.28	5.18	5.02	5.38[b]	4.81	5.36	5.38
48	5.98	5.69	5.42	5.23	4.76	4.59	4.42	4.49	4.34	4.41	5.36	5.12	5.66	5.21	5.34	5.36
49	5.92	5.95	5.25	5.42	4.75	4.60	3.88[b]	4.51	4.52	4.50	5.15	5.21	5.39	5.31	5.60	5.53
51	6.11	5.76	5.29	5.20	4.34	4.42	4.50	4.40	4.54	4.40	5.34	4.93	5.43[b]	4.81	5.67	5.39
52	5.98	6.02	5.30	5.39	4.60	4.43	4.48	4.42	4.52	4.49	4.82	5.01	4.91	4.92	5.33	5.56
53	6.01	6.11	5.43	5.55	4.64	4.66	4.53	4.66	4.57	4.67	5.13	5.24	5.27	5.25	5.74	5.77

[a] Calculated according to eq 49. [b] Points omitted from the derivation of the corresponding eqs 50–57. [c] Calculated according to eq 50. [d] Calculated according to eq 51. [e] Calculated according to eq 52. [f] Calculated according to eq 53. [g] Calculated according to eq 54. [h] Calculated according to eq 55. [i] Calculated according to eq 56. [j] Calculated according to eq 57.

Data for a more complex set of oxadiazoles is presented in Table 4 tested in the same fashion.[54] The difference in these two sets is the phenyl ring in the congeners of Table 4 which replaces the carbonyl unit in the congeners in Table 3. QSAR 29–32 have been developed from this data.

$$\log 1/C = 1.23(\pm 0.38)B_{1-7} + 6.31(\pm 0.47) \quad (29)$$

$$n = 40, r = 0.730, s = 0.361, F_{1,38} = 41.4$$

$$\log 1/C = 1.24(\pm 0.31)B_{1-7} - 0.61(\pm 0.29)B_{1-3''} + 7.09(\pm 0.54) \quad (30)$$

$$n = 40, r = 0.828, s = 0.300, F_{1,37} = 18.0$$

$$\log 1/C = 1.49(\pm 0.30)B_{1-7} + 0.46(\pm 0.25)B_{1-2'} - 0.57(\pm 0.25)B_{1-3''} + 6.17(\pm 0.67) \quad (31)$$

$$n = 40, r = 0.881, s = 0.258, F_{1,36} = 14.3$$

$$\log 1/C = 1.21(\pm 0.26)B_{1-7} + 0.47(\pm 0.19)B_{1-2'} - 0.57(\pm 0.19)B_{1-3''} - 0.37(\pm 0.15)I_8 + 6.62(\pm 0.56) \quad (32)$$

$$n = 40, r = 0.931, s = 0.201, F_{1,35} = 24.1$$

correlation matrix (r)

	B_{1-7}	$B_{1-2'}$	$B_{1-3''}$	I_8	π_7	σ_7
B_{1-7}	1	−0.38	0.05	−0.49	0.97	−0.49
$B_{1-2'}$		1	−0.08	0.23	−0.38	0.23
$B_{1-3''}$			1	−0.03	0.05	−0.003
I_8				1	−0.43	1.00
π_7					1	−0.42
σ_7						1

At first glance eq 32 seems strange because it contains no π or log P term. The reason for this is apparent from the correlation matrix where it is seen that B_{1-7} and π_7 are almost perfectly collinear. Again and again we find in QSAR analysis of data that little attention has been given to experimental design so that collinearity problems confound a clear interpretation of the data.

The indicator variable I_8 applies to 8-substituents. Actually only Cl was used at this point so $I_8 = 1$ or 0 for Cl or H. A negative steric effect appears to override the hydrophobic interaction at this point implied by QSAR 28. The coefficient with $B_{1-3''}$ is almost identical to that in eq 28.

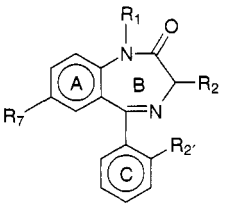
Four data points were omitted in the derivation of eq 29–32 as marked in Table 4. It is surprising that they do not contain any unusual substitution pattern.

In the case of QSAR 32 $B_{1-2'}$ and I_2 yield the same result since chlorine was the only substituent employed in the 2′-position in this data set.

B. In Vitro QSAR of Non-Benzodiazepines

Considerable excitement developed when Nielsen and co-workers isolated from urine the ethyl ester of β-carboline-3-carboxylic acid and proposed that this substance was an endogenous factor that regulates the BDZ receptor. However, subsequent studies have shown[56,57] that this compound is probably formed during the extraction and isolation procedure. Nevertheless, β-carbolines potently inhibit the binding

Table 10. Compounds and Physicochemical Parameters for Derivation of Eqs 58 and 59



		exploratory behavior test: log 1/C							punish conflict test: log 1/C	
no.	substituent	obsd	calcd[a]	|Δ log 1/C|	R_m[c]	$B_{1-2'}$	L_1	log P	obsd	calcd[e]
1	R_7 = Cl, R_1 = H, R_2 = H, $R_{2'}$ = H	1.25	1.81	0.56	1.77	1.00	2.06	3.06	1.83	1.73
2	R_7 = Cl, R_1 = H, R_2 = H, $R_{2'}$ = Cl	2.79	2.99	0.20	1.94	1.80	2.06	3.12	2.68	2.77
3	R_7 = Cl, R_1 = CH_3, R_2 = H, $R_{2'}$ = H	1.79	1.58	0.21	1.95	1.00	2.87	3.08	1.88	2.02
4	R_7 = Cl, R_1 = CH_3, R_2 = H, $R_{2'}$ = Cl	2.41	2.71	0.30	2.15	1.80	2.87	3.15	2.82	3.11
5	R_7 = Cl, R_1 = H, R_2 = H, $R_{2'}$ = F	2.05	2.33	0.28	1.73	1.35	2.06	2.85	2.28	2.00
6	R_7 = Cl, R_1 = CH_3, R_2 = H, $R_{2'}$ = F	2.60	2.12	0.48	1.90	1.35	2.87	2.88	2.72	2.28
7	R_7 = Cl, R_1 = CH_2CF_3, R_2 = H, $R_{2'}$ = H	1.10	0.72	0.38	2.54	1.00	4.70	4.37		
8	R_7 = Cl, R_1 = $CH_2C_3H_5$, R_2 = H, $R_{2'}$ = H	0.71	0.75	0.04	2.41	1.00	5.14	4.06		
9	R_7 = NO_2, R_1 = H, R_2 = H, $R_{2'}$ = H	2.33	1.72	0.61	1.47	1.00	2.06	2.38		
10	R_7 = Cl, R_1 = $(CH_2)_2Cl$, R_2 = OC_2H_5, $R_{2'}$ = H	0.19	0.72	0.53	2.32	1.00	5.57	4.02		
11	R_7 = Cl, R_1 = H, R_2 = OH, $R_{2'}$ = H	1.19	1.74	0.55	1.51	1.00	2.06	2.33	1.19	1.31
12	R_7 = Cl, R_1 = CH_3, R_2 = OH, $R_{2'}$ = H	1.63	1.56	0.07	1.58	1.00	2.87	2.46	1.88	1.43
13	R_7 = Cl, R_1 = $(CH_2)_2OH$, R_2 = OH, $R_{2'}$ = H	0.80	0.96	0.16	1.34	1.00	4.79	1.91	0.36	1.05
14	R_7 = Cl, R_1 = H, R_2 = OH, $R_{2'}$ = Cl	3.14	2.98	0.16	1.64	1.80	2.06	2.40	2.44	2.30
15	R_7 = Cl, R_1 = CH_3, R_2 = OH, $R_{2'}$ = Cl	2.59	2.80	0.21	1.82	1.80	2.87	2.52	2.66	2.57
16	R_7 = Cl, R_1 = $(CH_2)_2OH$, R_2 = OH, $R_{2'}$ = Cl	2.00	2.30	0.30	1.65	1.80	4.79	1.98	1.96	2.31
17[d]	R_7 = Cl, R_1 = H, R_2 = OH, $R_{2'}$ = F	2.50	2.24	0.26	1.48	1.35	2.06	2.13	2.36	1.60
18[d]	R_7 = Cl, R_1 = CH_3, R_2 = OH, $R_{2'}$ = F	2.81	2.10	0.71	1.62	1.35	2.87	2.25	2.58	1.83
19	R_7 = Cl, R_1 = $(CH_2)_2OH$, R_2 = OH, $R_{2'}$ = F	2.24	1.48	0.76	1.34	1.35	4.79	1.71	1.65	1.38
20	R_7 = NO_2, R_1 = $(CH_2)_2OH$, R_2 = OH, $R_{2'}$ = H	0.34	0.42	0.08	0.87	1.00	4.79	0.94		
21[b]	R_7 = Cl, R_1 = H, R_2 = $OCOC_6H_2(OCH_3)_3$, $R_{2'}$ = H	0.36	1.50	1.14	2.43	1.00	2.06	3.81		
22	R_7 = Cl, R_1 = H, R_2 = $OCO(CH_2)_2COOH$, $R_{2'}$ = H	1.38	1.63	0.25	1.33	1.00	2.06			
23	R_7 = Cl, R_1 = H, R_2 = $OCOCH(CH_2CH_2CH_3)_2$, $R_{2'}$ = H	0.50	0.65	0.15	3.01	1.00	2.06	5.82		
24	R_7 = Cl, R_1 = CH_3, R_2 = H, $R_{2'}$ = H	1.44	1.04	0.40	2.65	1.00	2.87	4.38		
25	R_7 = Cl, R_1 = $(CH_2)_2OH$, R_2 = H, N→O, $R_{2'}$ = H	0.35	0.61	0.26	1.00	1.00	4.79			
26	R_7 = Cl, R_1 = $(CH_2)_2OCO(CH_2)_2COOH$, R_2 = H, N→O, $R_{2'}$ = H	0.76			0.77	1.00				
27	R_7 = Cl, R_1 = H, C_2 = $NHCH_3$, R_2 = H, N→O, $R_{2'}$ = H	1.63	1.81	0.18	1.81	1.00	2.06		1.58	1.80
28[b]	R_7 = Cl, R_1 = $(CH_2)_2N(C_2H_5)_2$, R_2 = H, $R_{2'}$ = F	1.94	0.99	0.95	1.68	1.35	7.11		1.74	1.60

[a] Calculated according to eq 58. [b] Omitted points from the derivation of eq 58. [c] R_m values from the silicone system.[31] [d] Omitted points from the derivation of eq 59. [e] Calculated according to eq 59.

of [^{3}H]diazepam which makes these substances useful in elucidating the molecular pharmacology of the BDZ-R. They are interesting benzodiazepine inverse agonists. From the data in Table 5[33] the following QSAR have been developed:

$$\log 1/K_i = 2.11(\pm 1.24)E_s\text{-}1 + 7.46(\pm 0.92) \quad (33)$$
$$n = 14,\ r = 0.731,\ s = 1.270,\ F_{1,12} = 13.8$$

$$\log 1/K_i = 1.97(\pm 0.78)E_s\text{-}1 + 1.97(\pm 0.98)I_2 + 6.13 \quad (34)$$
$$n = 14,\ r = 0.913,\ s = 0.793,\ F_{1,11} = 19.7$$

$$\log 1/K_i = 2.10(\pm 0.61)E_s\text{-}1 + 1.60(\pm 0.80)I_2 + 1.06(\pm 0.75)\pi_2 + 6.52(\pm 0.74) \quad (35)$$
$$n = 14,\ r = 0.955,\ s = 0.605,\ F_{1,10} = 8.9$$

correlation matrix (r)

	E_s-1	I_2	π_2
E_s-1	1	0.09	−0.12
I_2		1	0.33
π_2			1

In deriving the above QSAR one data point for a carboxyl-containing congener (no. 7) was not employed. A significant difference in the QSAR of the β-carbolines and diazepines is that log P cannot be used to correlate the former. Of the three points at which substituents are varied only position 2 appears to show a hydrophobic effect. In addition two substituents containing a carbonyl group are parameterized by the indicator variable I_2. After the correction the coefficient with π_2 falls into the expected range of about 0.5 to 1.1. Compounds containing an OH group at R3 are reasonably well fit without any parameterization. Of course eq 33 shows that the negative steric effect of 1-substituents is the most important factor in the QSAR.

The number of data points/variable is low for eq 35 so that not much weight can be placed on this QSAR. However, it is of value for the design of new compounds in this class.

A second set of 1-aryl-3-methylpyrazolo[4,5-c]-quinolin-4-ones (Table 6)[27] which differs from the benzodiazepines has been found to displace [^{3}H]-flunitrazepam from binding to bovine brain mem-

branes. From the data in Table 6 eqs 36–38 have been derived.

$$\log 1/C = 0.57(\pm0.23)E_s\text{-}2',6' + 5.03(\pm0.21) \quad (36)$$

$$n = 19, r = 0.780, s = 0.342, F_{1,17} = 26.5$$

$$\log 1/C = 0.76(\pm0.21)E_s\text{-}2',6' + 0.59(\pm0.33)\Sigma\pi + 4.77(\pm0.22) \quad (37)$$

$$n = 19, r = 0.888, s = 0.259, F_{1,16} = 13.6$$

$$\log 1/C = 0.67(\pm0.19)E_s\text{-}2',6' + 0.59(\pm0.28)\Sigma\pi + 0.62(\pm0.48)\Sigma\sigma + 4.75(\pm0.18) \quad (38)$$

$$n = 19, r = 0.927, s = 0.218, F_{1,15} = 7.66$$

correlation matrix (r)

	E_s-2′,6′	$\Sigma\pi$	$\Sigma\sigma$
E_s-2′,6′	1	−0.513	0.406
$\Sigma\pi$		1	−0.228
$\Sigma\sigma$			1

All of the variation in the substituents is confined to the phenyl ring. $\Sigma\pi$ and $\Sigma\sigma$ apply to substituents on all ring positions, while E_s-2′,6′ refers only to substituents in the 2′ and 6′ positions. Actually only one example is present where substituents are present in both the 2′- and 6′-positions. It is well fit by using the sum of E_s. One data point (4′-Cl) is poorly predicted and was omitted in the development of eq 38. It is about 7 times less active than expected.

The phenyl ring does appear to fall on a hydrophobic surface and the positive coefficient with E_s-2′,6′ reveals that twisting the phenyl ring out of the plane of the rest of the molecule results in poorer binding.

Although from eq 5 it was known[27] that there was a significant correlation between potency and chemical shift, the author of eq 4[28] did not include a term for the electronic effect of the substituents in his equation.

Table 7 contains data[58] for a group of partial inverse agonists acting in vitro from which we have derived eqs 39–41:

$$\log 1/K_i = 0.77(\pm0.71)\sigma + 5.88(\pm0.28) \quad (39)$$

$$n = 14, r = 0.563, s = 0.361, F_{1,13} = 5.78$$

$$\log 1/K_i = 0.84(\pm0.59)\sigma + 0.41(\pm0.39)I_1 + 5.98(\pm0.26) \quad (40)$$

$$n = 14, r = 0.719, s = 0.317, F_{1,12} = 5.17$$

$$\log 1/K_i = 0.99(\pm0.48)\sigma - 0.61(\pm0.34)I_1 - 0.49(\pm0.34)I_2 + 6.15(\pm0.23) \quad (41)$$

$$n = 14, r = 0.873, s = 0.224, F_{1,11} = 11.1$$

correlation matrix (r)

	σ	I_1	I_2
σ	1	0.13	0.13
I_1		1	−0.40
I_2			1

In these equations σ applies to R in the 5-position of the indole ring. Attempts to parameterize R′, except in terms of I_1 and I_2, were unsuccessful and log P was not a useful parameter. I_1 takes the value of 1 for four compounds where R′ = $CH_2CH_2C_6H_4$-3,4-$(OH)_2$ and I_2 takes the value of 1 for four examples where R′ = $CH_2CH_2C_6H_4$-4-OH. The negative coefficients with these terms for the presence of the polar OH group might indicate a hydrophobic patch at the corresponding point on the receptor. Three data points were omitted in this analysis. As in the case of QSAR 38 σ is the most important term.

To achieve this rather mediocre result with the low ratio of data points/parameters it was necessary to drop three points. Again we find hydrophobic effects to be absent which emphasizes the differences in binding mode for this class of compound compared to the BDZs.

The lack of importance for hydrophobic interactions in binding of the indole compounds is also demonstrated by the data in Table 8[58] from which QSAR 42–44 have been developed. Here too competitive binding with bovine brain membranes was studied.

$$\log 1/K_i = 1.00(\pm0.50)\sigma + 6.60(\pm0.25) \quad (42)$$

$$n = 20, r = 0.706, s = 0.373, F_{1,18} = 17.90$$

$$\log 1/K_i = 1.01(\pm0.30)\sigma + 0.67(\pm0.37)I_2 + 6.49(\pm0.20) \quad (43)$$

$$n = 20, r = 0.853, s = 0.282, F_{1,17} = 14.25$$

$$\log 1/K_i = 1.01(\pm0.33)\sigma + 0.60(\pm0.33)I_2 - 0.40(\pm0.33)I_3 + 6.56(\pm0.18) \quad (44)$$

$$n = 20, r = 0.900, s = 0.246, F_{1,16} = 6.53$$

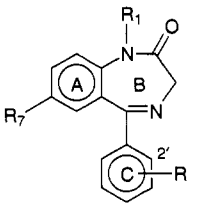
correlation matrix (r)

	σ	I_2	I_3
σ	1	−0.02	−0.02
I_2		1	−0.18
I_3			1

In the above expressions the indicator variable I_2 = 1 for three examples where R_1 and R_2 are OCH_3, while I_3 = 1 for three instances where R_2 = OH. The former structure has a positive effect while the latter has a negative effect. Three data points were omitted. One was a unique structure containing an o-Cl. As in QSAR 38 and 41 for eq 44 the most important term is σ with a coefficient near 1. It is of interest that the benzylamine moiety for the compounds in Table 8 produces more active drugs than the phenethyl moiety of the congeners in Table 7.

Although eq 35 points to a hydrophobic patch on the receptor the net conclusion from eqs 35, 38, and 41 is that a rather large hydrophobic region is not being utilized for receptor binding by these nonbenzodiazepines. If indeed they do bind at the same receptor utilized by the BDZs, it must be in quite a different manner. One wonders if their competitive binding with BDZs may be allosterically controlled.

Table 11. Compounds and Physicochemical Parameters for Derivation of Eqs 60–63



		log 1/C						
no.[a]	substituent	obsd	calcd[c]	|Δ log 1/C|	log P	B_{1-7}	q_O	$B_{1-2'}$
1	$R_1 = H, R_7 = Cl, R_{2'} = H$	1.65	1.58	0.07	3.06	1.80	−0.339	1.00
2	$R_1 = H, R_7 = CN, R_{2'} = H$	2.30	1.64	0.65	2.12	1.60	−0.340	1.00
3	$R_1 = H, R_7 = NO_2, R_{2'} = H$	2.75	2.59	0.16	2.38	1.70	−0.333	1.00
4[a]	$R_1 = H, R_7 = CF_3, R_{2'} = H$	2.48	0.92	1.56	3.42	1.99	−0.343	1.00
5	$R_1 = H, R_7 = CH_3, R_{2'} = H$	0.15	0.74	0.58	2.68	1.52	−0.345	1.00
6	$R_1 = H, R_7 = N(CH_3)_2, R_{2'} = H$	0.82	0.48	0.34	2.41	1.35	−0.346	1.00
7	$R_1 = H, R_7 = SCH_3, R_{2'} = H$	1.15	1.35	0.20	2.77	1.70	−0.341	1.00
8	$R_1 = H, R_7 = SC_2H_5, R_{2'} = H$	0.27	0.90	0.63	3.30	1.70	−0.342	1.00
9	$R_1 = H, R_7 = SOCH_3, R_{2'} = H$	1.08	1.23	0.15	1.12	1.40	−0.338	1.00
10	$R_1 = H, R_7 = SO_2CH_3, R_{2'} = H$	0.28	1.10	0.82	1.11	2.03	−0.344	1.00
11	$R_1 = CH_3, R_7 = Cl, R_{2'} = H$	2.31	1.66	0.65	3.08	1.80	−0.338	1.00
12	$R_1 = CH_3, R_7 = NO_2, R_{2'} = H$	2.69	2.42	0.27	2.11	1.70	−0.335	1.00
13	$R_1 = CH_3, R_7 = CN, R_{2'} = H$	2.44	1.68	0.76	1.80	1.60	−0.339	1.00
14	$R_1 = CH_3, R_7 = SCH_3, R_{2'} = H$	0.60	1.24	0.64	3.02	1.70	−0.341	1.00
15	$R_1 = CH_3, R_7 = N(CH_3)_2, R_{2'} = H$	1.69	0.56	1.13	2.66	1.35	−0.345	1.00
16	$R_1 = CH_3, R_7 = Cl, R_{2'} = F$	2.88	2.14	0.74	2.88	1.80	−0.338	1.35
17	$R_1 = CH_3, R_7 = Cl, R_{2'} = Cl$	2.88	2.50	0.38	3.15	1.80	−0.337	1.80
18	$R_1 = CH_3, R_7 = NO_2, R_{2'} = F$	2.42	2.73	0.31	1.91	1.70	−0.335	1.35
19	$R_1 = CH_3, R_7 = NO_2, R_{2'} = Cl$	3.44	3.30	0.14	2.18	1.70	−0.334	1.80
20	$R_1 = CH_3, R_7 = NO_2, R_{2'} = CF_3$	2.71	3.28	0.57	2.30	1.70	−0.335	1.99
21	$R_1 = CH_3, R_7 = H, R_{2'} = F$	1.53	0.77	0.76	2.16	1.00	−0.344	1.35
22	$R_1 = CH_3, R_7 = F, R_{2'} = F$	0.33	1.35	1.02	2.31	1.35	−0.342	1.35
23	$R_1 = CH_3, R_7 = N(CH_3)_2, R_{2'} = Cl$	2.82	3.26	0.44	2.72	1.35	−0.344	1.80
24	$R_1 = H, R_7 = H, R_{2'} = H, R_6 - Cl$	0.13	1.10	0.97	2.25	1.00	−0.339	1.00
25	$R_1 = H, R_7 = H, R_{2'} = H, R_8 = Cl$	−0.09	0.83	0.92	3.06	1.00	−0.338	1.00
26[a]	$R_1 = H, R_7 = NO_2, R_{2'} = H, R_9 = CH_3$	1.56	2.85	1.29	2.88	1.70	−0.335	1.00
27	$R_1 = H, R_7 = Cl, R_{2'} = H, R_9 = Cl$	1.56	1.52	0.04	3.82	1.80	−0.333	1.00
28	$R_1 = H, R_7 = CH_3, R_{2'} = H, R_8 = CH_3$	0.30	0.91	0.61	3.13	1.52	−0.345	1.00
29	$R_1 = H, R_7 = Br, R_{2'} = H$	2.20	1.94	0.25	3.21	1.95	−0.336	1.00
30	$R_1 = H, R_7 = Br, R_{2'} = H, R_8 = OCH_3$	1.66	2.04	0.38	2.96	1.95	−0.337	1.00
31	$R_1 = H, R_7 = Br, R_{2'} = F$	2.82	2.44	0.38	3.00	1.95	−0.336	1.35
32[a]	$R_1 = H, R_7 = Cl, R_{2'} = F$	3.46	2.16	1.30	2.85	1.80	−0.338	1.35
33	$R_1 = H, R_7 = Cl, R_{2'} = H, R_{3'} = F$	1.84	1.66	0.18	3.20	1.80	−0.337	1.00
34	$R_1 = H, R_7 = Cl, R_{2'} = Br$	2.76	2.65	0.11	3.22	1.80	−0.337	1.95
35	$R_1 = H, R_7 = Cl, R_{2'} = Cl$	2.88	2.53	0.35	3.12	1.80	−0.337	1.80
36	$R_1 = H, R_7 = Cl, R_{2'} = OCH_3$	1.60	2.06	0.46	2.60	1.80	−0.340	1.35
37	$R_1 = H, R_7 = Cl, R_{2'} = H, R_{3'} = OCH_3$	2.22	1.68	0.54	3.00	1.80	−0.338	1.00
38[a]	$R_1 = H, R_7 = Cl, R_{2'} = H, R_{4'} = OCH_3$	−0.42	1.55	1.97	3.00	1.80	−0.339	1.00
39	$R_1 = H, R_7 = Cl, R_{2'} = CH_3$	1.57	1.94	0.37	3.16	1.80	−0.339	1.52
40	$R_1 = H, R_7 = Cl, R_{2'} = H, R_{3'} = CH_3$	0.85	1.06	0.21	3.56	1.80	−0.339	1.00
41	$R_1 = H, R_7 = CN, R_{2'} = F$	2.63	1.93	0.70	1.91	1.60	−0.340	1.35
42	$R_1 = H, R_7 = NO_2, R_{2'} = F$	2.49	2.85	0.35	2.17	1.70	−0.334	1.35
43	$R_1 = H, R_7 = NO_2, R_{2'} = Cl$	3.29	3.37	0.08	2.44	1.70	−0.333	1.80
44	$R_1 = H, R_7 = NO_2, R_{2'} = CF_3$	2.70	3.20	0.51	2.56	1.70	−0.335	1.99
45	$R_1 = H, R_7 = NO_2, R_{2'} = NO_2$	2.97	2.74	0.23	1.47	1.70	−0.336	1.70
46[a]	$R_1 = H, R_7 = NO_2, R_{2'} = H, R_{3'} = NO_2$	0.81	3.12	2.31	2.12	1.70	−0.330	1.00
47	$R_1 = H, R_7 = CF_3, R_{2'} = CF_3$	1.97	1.70	0.26	3.60	1.99	−0.342	1.99
48	$R_1 = H, R_7 = Cl, R_{2'} = Cl, R_{4'} = Cl$	−0.37	0.73	1.00	3.83	1.80	−0.355	1.80
49[b]	$R_1 = H, R_7 = H, R_{2'} = H$	−0.23	0.16	−0.39	0.70	1.00	−0.343	1.00
50[b]	$R_1 = H, R_7 = CF_3, R_{2'} = H$	2.48	2.50	0.02	1.94	1.99	−0.336	1.00
51[b]	$R_1 = H, R_7 = Br, R_{2'} = H$	2.14	2.13	0.01	1.72	1.95	−0.338	1.00
52[b]	$R_1 = H, R_7 = Cl, R_{2'} = H$	2.71	1.89	0.81	1.57	1.80	−0.339	1.00

[a] Omitted points from the derivation of eq 63. [b] For these compounds R_5 is not a phenyl ring but a 2-pyridyl ring. [c] Calculated according to eq 63.

The lack of importance of hydrophobic interactions is reminiscent of the QSAR for inhibitors of serotonin uptake.[59]

C. In Vivo Studies

Our finding in QSAR 25 of the importance of log P and B_{1-7} encouraged us to reevaluate earlier QSAR using these parameters. We first consider the study of Yoshimoto et al.[39] which yielded eqs 14–22 based on π, F, and indicator variables. Redoing these equations produced QSAR 49–57. For one example (antibemegride test) based on 54 data points we have presented the stepwise development shown in eqs 45–49.

$$\log 1/C = 0.98(\pm 0.43)B_{1-4} + 4.21(\pm 0.59) \quad (45)$$

$$n = 54,\ r = 0.530,\ s = 0.590,\ F_{1,52} = 20.9$$

$$\log 1/C = 0.90(\pm 0.35)B_{1-4} + 0.85(\pm 0.34)I_2 + 4.16(\pm 0.49) \quad (46)$$

$$n = 54,\ r = 0.720,\ s = 0.490,\ F_{1,51} = 24.7$$

$$\log 1/C = 0.82(\pm 0.30)B_{1-4} + 0.79(\pm 0.29)I_2 + 1.43(\pm 0.64)B_{1-3} + 1.69(\pm 1.18) \quad (47)$$

$$n = 54,\ r = 0.810,\ s = 0.420,\ F_{1-50} = 19.9$$

$$\log 1/C = -0.46(\pm 0.14)\log P + 1.14(\pm 0.24)B_{1-4} + 0.76(\pm 0.22)I_2 + 2.01(\pm 0.50)B_{1-3} + 2.37(\pm 0.89) \quad (48)$$

$$n = 54,\ r = 0.905,\ s = 0.306,\ F_{1,49} = 43.4$$

$$\log 1/C = -0.67(\pm 0.21)\log P + 0.25(\pm 0.20)\text{MR-7} + 1.43(\pm 0.33)B_{1-4} + 0.82(\pm 0.21)I_2 + 2.23(\pm 0.51)B_{1-3} + 2.46(\pm 0.85) \quad (49)$$

$$n = 54,\ r = 0.916,\ s = 0.291,\ F_{1,48} = 6.3$$

correlation matrix (r)

	B_{1-4}	I_2	B_{1-3}	log P	MR-7	π_3	σ_3	F_3	F_4
B_{1-4}	1	0.088	0.116	0.404	−0.310	0.307	−0.310	−0.217	0.306
I_2		1	0.108	0.038	−0.173	0.063	0.006	0.059	0.338
B_{1-3}			1	0.366	0.009	0.629	0.007	0.506	0.056
log P				1	0.529	0.601	−0.462	−0.198	0.123
MR-7					1	−0.011	0.042	0.063	−0.152
π_3						1	−0.771	−0.344	0.183
σ_3							1	0.863	−0.186
F_3								1	−0.126
F_4									1

The most important parameter is B_{1-4} as is evident in eq 45. This corresponds to $B_{1-2'}$ for the classical BDZs. B_{1-3} enters the development at eq 47. Unfortunately the compounds included in this set contain rather little variation in position 3; except for one example containing a methoxyl group and five examples containing nitro groups all of the rest of the substituents are either Br or Cl. The physicochemical properties of the two halogens are quite similar. Be that as it may, log P and B_{1-3} are found to displace F_3, F_4, and π_7, and QSAR 49 with one less parameter is almost as sharp as QSAR 14. Only a linear log P term is found having a negative coefficient. Note that the calculated log P values for this set are unusually high, the lowest being 3.2 which is above log P_o of about 2.5. These calculated values may be somewhat high since they pertain to the unprotonated form. At pH 7.4 log P would be lower depending on the pK_a[40] of the amino group.

B_{1-4} is found to be the most important variable for this set and the sterimol parameters are found to replace the electronic parameters in eq 14.

If in QSAR 49 I-4 is used to replace B_{1-4}, we again find essentially the same result: $r = 0.912$, $s = 0.297$. Again the problem is lack of variation in the 4-substituents (position 2′ is called 4 here).

QSAR 50−57 are reformulations of the QSAR derived by Yoshimoto et al. (eqs 15−22). These eight examples based on different biological tests are based on fewer compounds and the equations differ somewhat from eq 49. How much of this difference might be due to fundamental differences in the tests and how much is due to noise in the data is not clear. For two of the eight examples (eqs 50 and 54) the correlations are not as good as those of Yoshimoto et al. The net result is that B_{1-3} and B_{1-4} correlate the data as well or better than the electronic terms.

anti-pentylenetetrazole test

$$\log 1/C = -0.68(\pm 0.27)\log P - 0.55(\pm 0.41)\text{MR}_7 + 0.51(\pm 0.24)I_2 + 1.45(\pm 0.37)B_{1-4} + 1.28(\pm 1.10)B_{1-3} + 4.13(\pm 1.67) \quad (50)$$

$$n = 30,\ r = 0.915,\ s = 0.210,\ F_{5,24} = 24.6$$

antifighting test

$$\log 1/C = -0.58(\pm 0.19)\log P - 0.85(\pm 0.29)\text{MR}_7 + 0.43(\pm 0.17)I_2 + 1.15(\pm 0.26)B_{1-4} + 1.62(\pm 0.77)B_{1-3} + 3.02(\pm 1.18) \quad (51)$$

$$n = 30,\ r = 0.951,\ s = 0.148,\ F_{5,24} = 45.0$$

antimaximal electroshock test

$$\log 1/C = -0.61(\pm 0.23)\log P - 0.75(\pm 0.34)\text{MR}_7 + 0.38(\pm 0.20)I_2 + 0.78(\pm 0.31)B_{1-4} + 2.17(\pm 0.94)B_{1-3} + 1.89(\pm 1.43) \quad (52)$$

$$n = 30,\ r = 0.898,\ s = 0.180,\ F_{5,24} = 20.1$$

(one point out)

inclined plane test

$$\log 1/C = -0.94(\pm 0.38)\log P + 0.65(\pm 0.19)I_2 + 0.34(\pm 0.18)I_3 + 1.24(\pm 0.33)B_{1-4} + 2.53(\pm 0.95)B_{1-3} + 1.82(\pm 1.23) \quad (53)$$

$$n = 28,\ r = 0.896,\ s = 0.136,\ F_{5,22} = 17.9$$

(two points out)

rotating rod test

$$\log 1/C = -0.42(\pm 0.17)\log P + 0.39(\pm 0.14)I_2 + 0.73(\pm 0.21)B_{1-4} + 1.61(\pm 0.71)B_{1-3} + 2.03(\pm 1.20) \quad (54)$$

$$n = 28,\ r = 0.880,\ s = 0.130,\ F_{4,23} = 20.3$$

(four points out)

traction

$$\log 1/C = -1.24(\pm 0.36)\log P + 0.68(\pm 0.26)I_2 + 0.46(\pm 0.26)I_3 + 1.76(\pm 0.44)B_{1-4} + 2.75(\pm 1.17)B_{1-3} + 2.56(\pm 1.65) \quad (55)$$

$$n = 27,\ r = 0.890,\ s = 0.190,\ F_{5,21} = 16.7$$

(three points out)

balance test

$$\log 1/C = -0.96(\pm0.24)\log P + 0.43(\pm0.23)I_2 + 1.44(\pm0.33)B_{1-4} + 3.16(\pm1.06)B_{1-3} + 1.11(\pm1.68) \quad (56)$$

$$n = 27, r = 0.904, s = 0.200, F_{4,22} = 24.1 \text{ (three points out)}$$

anesthesia potentiating test

$$\log 1/C = -1.07(\pm0.32)\log P + 0.79(\pm0.24)I_2 + 0.41(\pm0.22)I_3 + 1.74(\pm0.40)B_{1-4} + 2.46(\pm1.09)B_{1-3} + 2.66(\pm1.50) \quad (57)$$

$$n = 30, r = 0.910, s = 0.180, F_{5,24} = 22.3$$

Another correlation of in vivo data for the exploratory behavior of rats is that of Biagi et al.[38] shown in eq 10. We have reformulated eq 10 as follows:

$$\log 1/C = 2.89(\pm2.40)R_m - 0.80(\pm0.62)R_m^2 - 0.25(\pm0.15)L_1 + 1.50(\pm0.62)B_{1-2'} - 1.79(\pm2.25) \quad (58)$$

$$n = 25, r = 0.900, s = 0.420, \text{optimum } R_m = 1.81(1.22 - 2.05), F_{4,20} = 20.7$$

correlation matrix (r)

	$B_{1-2'}$	L_1	R_m
$B_{1-2'}$	1	−0.16	0.02
L_1		1	−0.06
R_m			1

The parameter L_1 refers to substituents on N_1 where there was considerable variation. The negative coefficient with this sterimol parameter brings out the negative effect of substituents after the hydrophobic effects are accounted for by R_m. Of course no B_{1-7} term appears in eq 58. The reason behind this is that there is almost no variation at this point. All substituents at this position were Cl except for two examples of NO_2. Although there is a large difference electronically between Cl and NO_2 (σ = 0.23 and 0.78), there is only a small difference in B_{1-7} (1.80 and 1.70). The optimum R_m for eq 58 is identical to that for eq 10.

A point of particular interest is that there is significant variation at R_2 in hydrophobicity. Compounds having substituents other than H at this point are well fit which suggests that R_2 contacts hydrophobic space on the receptor.

Since it was not possible to calculate log P for a number of substances in this set we have not attempted to derive a QSAR with log P. However, eq 13 shows that the two parameters are very closely related for this data set. Equation 58 contains one less data point than eq 10 for lack of a sterimol parameter.

In eq 59 we have used $B_{1-2'}$ in place of I_3 used in eq 11. Two data points have been omitted for lack of log P values. The result is essentially the same as eq 11.

$$\log 1/C = 1.60(\pm0.90)R_m + 0.96(\pm0.59)B_{1-2'} - 2.06(\pm1.49) \quad (59)$$

$$n = 15, r = 0.880, s = 0.340, F_{2,12} = 20.7$$

The study of Blair and Webb[36] is of particular interest since it contains wide variation in the substituents at position 7 and four examples where the 5-phenyl group has been replaced by a 2-pyridyl moiety. In attempting to formulate QSAR for data of Sternbach et al.[1] they used two calculated parameters: the dipole moment and q_O (the charge on the carbonyl oxygen). Although correlation with the dipole moment (μ) gave better results than q_O the correlations were not good (see eqs 7−9). In particular they were unable to find a role for hydrophobic effects. In reevaluating their work we were only able to obtain satisfactory results with data from the pentylenetetrazole test using q_O instead of μ.

Using the data in Table 11 we have developed eq 63 as follows:

$$\log 1/C = 169(\pm56)\,q_O + 58.9(\pm19) \quad (60)$$

$$n = 47, r = 0.669, s = 0.798, F_{1,45} = 36.5$$

$$\log 1/C = 159(\pm49)q_O + 1.13(\pm0.57)B_{1-2'} + 54.5(\pm17) \quad (61)$$

$$n = 47, r = 0.771, s = 0.692, F_{1,44} = 15.9$$

$$\log 1/C = 157(\pm44)q_O + 0.92(\pm0.54)B_{1-2'} + 0.90(\pm0.57)B_{1-7} + 52.3(\pm15.3) \quad (62)$$

$$n = 47, r = 0.818, s = 0.632, F_{1,43} = 9.84$$

$$\log 1/C = 134.4(\pm41)q_O + 0.95(\pm0.48)B_{1-2'} + 1.04(\pm0.53)B_{1-7} + 1.72(\pm1.3)\log P - 0.41(\pm0.27)(\log P)^2 + 43(\pm15) \quad (63)$$

$$n = 47, r = 0.867, s = 0.561, F_{2,41} = 6.73, \log P_o = 2.08(1.34 - 2.38)$$

correlation matrix (r)

	q_O	$B_{1-2'}$	B_{1-7}	log P
q_O	1	0.076	0.02	−0.062
$B_{1-2'}$		1	0.31	0.104
B_{1-7}			1	0.232
log P				1

It is noteworthy that even though q_O, an electronically determined parameter, is the most significant variable in QSAR 63, both $B_{1-2'}$ and B_{1-7} contribute significantly to the correlation.

In this data set we have the most variation in 2′-substituents so it constitutes the best test of the $B_{1-2'}$ parameter. If $B_{1-2'}$ in QSAR 63 is replaced with I_2, the correlation is almost the same: r = 0.859, s = 0.575. It has occurred to us that $B_{1-2'}$ might not account for an electronic effect of this class of substituent. Most investigators have used only, or very predominately, halogens. The F values for F, Cl, Br, and CF_3 are 0.45, 0.42, 0.45, and 0.38, i.e. essentially constant. Thus the collinearity between I_2 and $B_{1-2'}$

for these substituents is almost perfect. In this set we have CH_3, OCH_3, and NO_2 whose F values are not collinear with the halogens and CF_3: 0.01, 0.29, and 0.65. These substituents are well fit with deviations less than the standard deviation. However the electronic effect of 2′-substituents is taken into account in the calculation of q_O so that again we are left with the unsatisfactory feeling that there may be an electronic role for substituents which is brought out by QSAR 2 and 63 which we cannot capture by substituent constants such as F and σ. It is our belief that, if so, it is probably small.

There are four examples where the usual 5-phenyl group has been replaced with a 2-pyridyl group and three of the four are very well fit by QSAR 63. This indicates that the 2-nitrogen falls into hydrophobic space. However this cannot be taken as evidence that 2-substituents do not have an electronic effect as well as a steric effect since the electronic effect of the pyridine nitrogen would be incorporated into q_O. In the derivation of eq 63 five outliers have been omitted. Except for one with an NO_2 in the 3-position the outliers contain no special features and appear to have no common structural features.

Lien et al.[60] derived QSAR for 10 and 11 data points from Blair's sets showing that activity was parabolically related to π_7 and dependent on σ_7. However, since three terms were required to correlate 10 or 11 points and correlations were not very high (r = 0.824−0.867) the work has attracted little attention. Lien et al. limited their analysis to compounds having changes only in the 7-position.

III. Discussion

Despite the synthesis and testing of untold numbers of benzodiazepine analogs and a number of attempts to formulate QSAR, it is clear that we still do not have an ideal set of congeners to properly delineate the structure−activity relationship. Although many different biological tests have been devised to assess their activity it is not very clear whether differences in the QSAR point toward fundamental differences in structure. This said, there are a number of important conclusions which our review can point to.

Early on in the SAR and QSAR analysis of the benzodiazepines it seemed that substituents in the 7-position which are electron-withdrawing increased potency. Unfortunately, this conclusion led researchers to concentrate on such groups without making stronger efforts to look for possible separate roles for steric, electronic, and hydrophobic effects. For one reason or another those doing the synthesis often neglected to incorporate into their derivatives a satisfactory spread in physicochemical properties. While some evidence did develop that 7-substituents affect activity electronically and/or hydrophobically no evidence was advanced to support a steric effect.

The QSAR by Blair and Webb (eqs 6−9) points to electronic effects of substituents and eq 63 shows that hydrophobic and steric properties are important. Also the results of Yoshimoto et al. (eqs 14−22) suggest electronic effects. However, QSAR 49−55 discount this, but the nature of the substituents in this position tends to compromise this conclusion. Equation 2 does offer evidence for an electronic effect of substituents, but the contradictive result of eq 3 and QSAR 25 discount the role of electronic effects.

Equation 64 (a reformulation of eq 2) also discounts the importance of electronic effects suggested by QSAR 2. In eq 64 the ϵLUMO term has been displaced and with the exception of I the parameters of eq 64 are close to those of eq 25 based on the much larger set. While I provides a better correlation of the data for this small set of 30 compounds $B_{1-2'}$ does a better job for the larger set where the variation in 2′-substituents is greater. Our belief at this time is electronic effects cannot be ruled out, but that they are not of great importance.

$$\log 1/C = 0.85(\pm0.31)\log P - 3.57(\pm1.70)(\beta\cdot10^{\log P} + 1) + 0.76(\pm0.26)I_2 + 0.74(\pm0.62)B_{1-7} + 4.50(\pm0.82) \quad (64)$$

$$n = 30,\ r = 0.933,\ s = 0.309,\ F_{5,24} = 32.1,$$
$$\text{optimum } \log P_o = 2.91(\pm0.39),$$
$$\log \beta = -3.41$$

Possibly the greatest barrier to advancing our understanding of the SAR of the benzodiazepines has been the neglect of the possible role of hydrophobic interactions. It is hard to understand this considering that it has long been recognized that hydrophobicity plays an important role in getting drugs across the blood−brain barrier. Fortunately it is clear from the section on methodology that we can now calculate log P for this class of compounds with some degree of accuracy. Equation 65 shows the relationship between the calculated (log P) and the experimental values (log P_B) determined by Biagi et al.[38] via chromatography (log P_B).

$$\log P = 0.99(\pm0.11)\log P_B + 0.36(\pm0.31) \quad (65)$$

$$n = 23,\ r = 0.971,\ s = 0.265,\ F_{1,21} = 343.7$$

Despite early evidence to the contrary our review shows that in almost every case log P (or R_m) plays a significant part in the QSAR from the receptor to the whole animal level. Although the substituent variations are not nearly as good as they should be, it appears for "normal"-size substituents of typical BDZs (I and II) most of the molecule must be interacting with a hydrophobic surface of a receptor.

We formulated eq 25 for a large set of in vitro data which can be compared to eqs 2 and 3. log P is by far the most important term in eq 25. This suggests that all of the points where substituents have been entered hydrophobic contacts are being made. We were especially concerned with substituents on the 1 nitrogen atom. Subtracting π for these substituents from log P to obtain a modified log P gave a poorer correlation. There seem to be steric effects from this position, but these seem to be in addition to the hydrophobic effect.

So little has been reported on the 5-phenyl ring, except in the 2 position, that nothing definite can be said about the other portions of the ring. The fact that in 4 out of 5 instances 5-(2-pyridyl) substituents are well fit using log P shows that at this position

hydrophobic space is encountered. It would be interesting to test more of these substituents in the in vitro receptor systems to be more certain that it is the hydrophobicity of the receptor we are assaying and not just that of the whole animal. Testing 5-(3-pyridyl) and 5-(4-pyridyl) substituents would tell more about this region.

A most interesting aspect of eq 25 is that the addition of the sterimol parameter B_{1-7} displaces the need for an electronic term for 7-substituents. That is, if a term in σ or F is added to eq 25 no improvement in the correlation occurs. We believe that σ and/or F should give at least as good a correlation as LUMO and HOMO suggested by QSAR 2 and 3. In fact it is rare that molecular orbital parameters serve as well in correlation analysis as Hammett constants when the two have been compared.

A fascinating point is the dual positive steric effects brought out by B_{1-7} and $B_{1-2'}$ in eq 25. The 2'-substituents would appear to twist the phenyl ring out of the plane of the larger ring system indicating that it may bind in a hydrophobic cleft. This fit must in some way be dependent on the first atom of the 7-substituents. Up to this point no evidence has been advanced for a positive steric effect at the 7-position. Even the CoMFA study, which is particularly well designed to search for steric effects, did not suggest this possibility.

Equation 28 provides another point of view. It does not contain a B_{1-7} term despite the fact that the 7-position (called 8 by the authors) contains only H, F, and Cl substituents and in the case of eqs 29−32 there is a strong B_{1-7} term based on the same spread in substituents. The difference between these two data sets is that the one with the B_{1-7} term contains a 5-phenyl moiety. This supports our feeling, mentioned above, that there is a kind of cooperative effect between the dual steric effect of 7- and 2'-substituents. Equation 28 also suggests some role for σ, although this term is the last to enter the QSAR and is rather collinear with π. The collinearity problem is frustrating.

While QSAR 32 is strongly dependent on B_{1-7}, it is a surprise to see no π term. The reason for this is immediately apparent from the correlation matrix where it is seen that B_{1-7} and π_7 are almost perfectly collinear.

The evidence found for the twin steric effects in the in vitro studies of eq 25 is clearly supported in vivo by QSAR 49. In this equation B_{1-4} (corresponding to B_{1-7}) and B_{1-3} (corresponding to $B_{1-2'}$) replace F_4 and F_3, giving almost as good a correlation (with one *less* parameter) as eq 14. Equations 50−57, based on the same type of compounds but on fewer data points, give a mixed view with two equations favoring the electronic parameterization used by Yoshimoto et al. and five favoring the use of steric parameters. These smaller sets are more compromised in terms of substituent variation than the set used to obtain eqs 14 and 49.

Equation 63 would seem to offer the best evidence for a specific electronic interaction between the BDZs and the receptor. It would also indicate that hydrophobic effects are relatively unimportant. However the two steric parameters still play important parts in the correlation, independent of the electronic effects. The positive q_O term implies that the higher the electron density on the carbonyl oxygen the more potent the compound. This stands in opposition to all of our other QSAR where we have found that electronic effects are of doubtful importance. Moreover, the parameters which suggest an electronic effect show that electron withdrawal by 7-substituents favors activity. This would tend to decrease electron density on oxygen by decreasing electron density on nitrogen. QSAR 63 means that the next step in clarifying the mechanism of action of the BDZs must be to make a more extensive study of the BDZs using molecular orbital parameters.

It is noteworthy that the role of q_O in eq 63 is in line with the observation of Loew et al. that the carbonyl group seems to be located near a cationic site on the receptor.

Equations 35, 38, and 41 correlate in vitro binding to the BDZ receptor by chemicals rather different in structure from the BDZs and which probably possess different modes of binding. Hence it is not surprising that these QSAR bear little resemblance to those of the BDZs. Indeed the QSAR are so different that it is hard to believe that the same binding sites are involved. The most conspicuous difference is the limited or nonexistent hydrophobic interactions. As noted above this reminds us of the QSAR for the inhibitors of serotonin uptake.

In conclusion our review of the QSAR of the BDZs firmly establishes the importance of hydrophobic interactions beyond the 7-position. By the use of the global hydrophobic parameter log P three cases are found where the optimum hydrophobicity (log P_o) can be established. It is also established that steric effects are more significant than electronic effects for substituents in the 7- and 2'-positions. Our study shows that log P calculated by the CLOGP program version 3.70 are suitable for QSAR studies of the BDZs, although it would be desirable to have more experimental values. The satisfactory results in Table 1 taken with other comparisons of calculated and experimental log P support the use of calculated values in deriving QSAR.[61−63] However, we believe that before embarking on the use of calculated log P one must have some experimental values or published data to provide a firm foundation.

Acknowledgments. We are indebted to Dr. Norman Gilman of Hoffman-LaRoche for samples of benzodiazepines which we have used to measure a number of log P values in Table 1. We also have had very helpful discussions with Ki Kim and Carlo Silipo. We thank Litai Zhang for technical assistance.

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