Comparative Quantitative Structure−Activity Relationship Studies (QSAR) on Non-Benzodiazepine Compounds Binding to Benzodiazepine Receptor (BzR)

D. Hadjipavlou-Litina,*,† Rajni Garg,‡ and Corwin Hansch§

Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki, Greece, Chemistry Department, Clarkson University, Potsdam, New York 13699-5810, and Chemistry Department, Pomona College, Claremont, California 91711

Received July 23, 2003

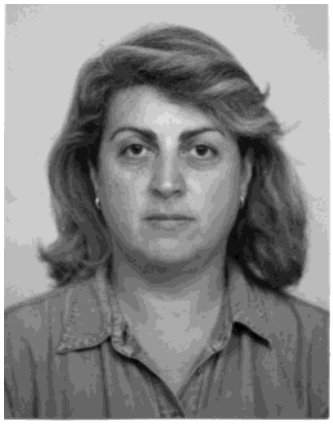
Contents

* Author to whom correspondence should be addressed (fax 30-2310-997679; e-mail hadjipav@pharm.auth.gr).
† Aristotleian University of Thessaloniki.
‡ Clarkson University.
§ Pomona College.

1. Introduction

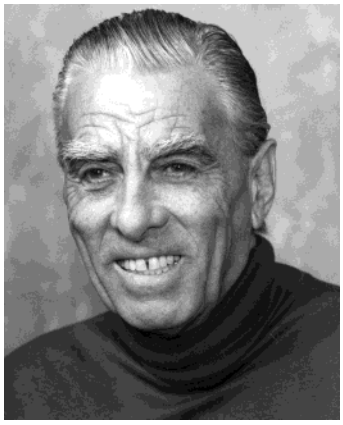
Benzodiazepines (BDZs) are the drugs of choice in the pharmacotherapy of anxiety and related emotional disorders, sleep disorders, status epilepticus, and other convulsive states; they are used as centrally acting muscles relaxants, for premedication, and as inducing agents in anesthesiology. They act via the benzodiazepine receptor site (BzR) on the γ-aminobutyric acid receptor ($GABA_A$) family and have been subjected to extensive quantitative structure−activity relationship (QSAR) studies.[1−4] GABAergic inhibition is one of the most rapidly developing topics in neuropharmacology.[5a] New therapeutic opportunities arise due to increasing insights into the molecular architecture and diversity of the components involved in signal transduction such as $GABA_A$ receptors, $GABA_B$ receptors, and GABA transporters. $GABA_A$ receptors are the major inhibitory neurotransmitter receptors in the brain, in the site of action of many clinically important drugs, and are important drug targets representing the sites of action of benzodiazepines, barbiturates, and neurosteroids. These receptors are ligand-gated chloride channels composed of five subunits that can belong to eight different subunit classes. All subunits possess an extracellulaar amino-terminal domain containing a conserved disulfide bridge, followed by four transmembrane segments. $GABA_A$ receptors belong to the superfamily of pentameric ligand-gated ion channels ("cys-loop receptors").[5b] At synapses $GABA_A$ receptors are activated by a brief nonequilibrium exposure to high concentrations of GABA. On the basis of the presence of 7 subunit families comprising at least 18 subunits in the central nervous system (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ϵ, θ, ρ_{1-3}), the $GABA_A$ receptors

10.1021/cr0304469 CCC: $48.50
Published on Web 08/10/2004



Dimitra Hadjipavlou-Litina received a B.S. in pharmacy and a Ph.D. in pharmaceutical chemistry in 1990 for a synthetic and biological study of novel anti-inflammatory hydroxyamino and diamino ketones under Professor P. N. Kourounakis's supervision. From 1992 to 1993 she spent a postdoctoral year with Professor C. Hansch in the Chemistry Department, Pomona College, California. Currently she is an associate professor of pharmaceutical chemistry at the University of Thessaloniki, School of Pharmacy, Greece. Her research interests involve studies on anti-inflammatory and antioxidant agents (synthesis, design, and biological evaluation) and the relationships between structure and activity of various drug classes as well as comparative QSAR, computer-assisted drug design (CADD), and cheminformatics.

Rajni Garg received her Ph.D. in chemistry under the supervision of Professor S. P. Gupta at the Birla Institute of Technology and Science, Pilani, India, where she was also a faculty member from 1991 to 1996. Her doctoral work was on QSAR studies on anti-HIV agents. She joined Professor Corwin Hansch in 1997 as a postdoctoral research associate. Currently, she is a research associate professor in the Chemistry Department of Clarkson University, Potsdam, NY, where she is involved in teaching biochemistry and medicinal chemistry. Her research interests include QSAR, comparative QSAR, computer-assisted drug design (CADD), and cheminformatics.



Corwin Hansch received his undergraduate education at the University of Illinois and his Ph.D. degree in organic chemistry from New York University in 1944. After working with the DuPont Co., first on the Manhattan Project and then in Wilmington, DE, he joined the Pomona College faculty in 1946. He has remained at Pomona except for two sabbaticals: one at the Federal Institute of Technology in Zurich, Switzerland, with Professor Prelog and the other at the University of Munich with Professor Huisgen. The Pomona group published the first paper on the QSAR approach relating chemical structure with biological activity in 1962. Since then, QSAR has received widespread attention. Dr. Hansch is an honorary fellow of the Royal Society of Chemistry and recently received the ACS Award for Computers in Chemical and Pharmaceutical Research for 1999.

display an extraordinary structural heterogeneity. Most $GABA_A$ receptor sybtypes in vivo are believed to be composed of α-, β-, and γ-subunits.The benzodiazepine site is thought to be located at the interface of the respective α-subunit (α_{1-3}, α_5) and the γ_2-subunit. The classical benzodiazepine site is mainly found on $GABA_A$ receptors at the interface between the α- and γ_2-subunits and can be rendered diazepam-insensitive by a point mutation in the α-subunit in which a histidine residue is placed by an arginine residue in recombinant receptors.[5c]

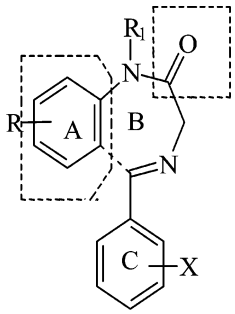
When BDZs bind to their receptors, they appear to induce a conformational change leading to an increase in the availability of $GABA_A$ receptors for $GABA_A$, leading to higher chloride influx and hyperpolarization. BDZs interact with two classes of recognition sites, "central" and "peripheral" (mitochondrial) types. Recently a novel low-affinity benzodiazepine site was identified on recombinant $GABA_A$ receptors ($\alpha_1\beta_3\gamma_2$).[5b]

Receptors containing the α_{1-5}-subunits in combination with any of the β-subunits and the γ_2-subunit are most prevalent in the brain. These receptors are sensitive to benzodiazepine modulation. The major receptor subtype is assembled from the subunits $\alpha_1\beta_2\gamma_2$ (diazepam-sensitive $GABA_A$ receptors). $GABA_A$ receptors that do not respond to clinically used ligands, such as diazepam, flunitrazepam, clonazepam, and zolpidem, are of low abundance in the brain and are largely characterized by the α_4- and α_6-subunits (diazepam-insensitive $GABA_A$ receptors). L-838,417, SL65.149, and CL 284,846 are some novel subtype-selective benzodiazepine site ligands, whereas [^{3}H]RY 80 can be used as a radioligand to examine the properties of $GABA_A$ receptors containing α_5 subunits.[5d]

The central receptors located in the neuronal tissues[6,7a,b] are functionally linked to a $GABA_A$ receptor chloride ionophore complex[7] and are apparently located on synaptic membranes.[8] Central BDZ receptors mediate classical pharmacological properties of the clinically widely used BDZs[6] (anxiolytic, anticonvulsants, sedative, and muscle relaxants). The $GABA_A$-independent[9,10] peripheral or "mitochondrial" benzodiazepine receptors (MBR) have been identified in a wide range of peripheral tissues as well as in the central nervous system,[11] and their subcellular location has been reported to be mainly "mitochondrial",[12−14] nuclear,[10,11] and in the plasma membrane.[15,16] During the past decade the MBR has been the object of several studies aimed to understand its physiological role. The peripheral benzodiazepine receptor (PBR) is a multimeric protein

complex located on the outer mitochondrial membrane of astroglial cells and is expressed in both central and peripheral tissues. The physiological role of mitochondrial BzR is still not clear. PBR-selective ligands known to date belong to structurally unrelated classes of compounds such as BDZs, isoquinolines, imidazopyridines, 2-aryl-3-indoleacetamides, benzofuracetamides, and benzothiazepines. They are involved in various cellular functions such as the inhibition of oxidative phosphorylation,[9] the inhibition of cell proliferation, and steroidogenesis.[16,17] The BzR is unique in the way it responds to three different types of ligands, which act as allosteric modulators of the $GABA_A$ receptor complex. GABA- or benzodiazepine-induced conformational changes originate in the extracellular domain and are transduced to other, allosteric binding sites and the ion channel. The initial trigger that drives an allosteric motion is thought to entail some rearrangement in the binding site itself. In fact, allosteric modulators can either enhance (agonists) or reduce (inverse agonists) the $GABA_A$-induced Cl^- ion flux. A third group of ligands, interacting with the allosteric site of $GABA_A$ receptor, does not influence $GABA_A$-induced ion flux but antagonizes (antagonists) the actions of the agonists and inverse agonists. The interrelationships of these three types of BzR ligands can be explained on the basis of changes in the conformation of the receptor from its unoccupied resting state.[18,19] An argument for the homogeneity of BzR binding sites might lie in the activities displayed after minor structural modifications of compounds with similar binding interactions. Thus, all compounds that bind to the BzR should have certain common characteristics that allow for recognition by the receptor regardless of the type of (in vivo) activity. Many types of compounds have been shown to bind at the BzR, for example, BDZs, arylpyrazolo-quinolines, β-carbolines, imidazopyridazines, and cyclo-pyrrolones. BDZs agonists are believed to bind to sites associated with the $GABA_A$ receptor, an ion channel linked receptor. $GABA_A$ acts on at least two different receptor types.[20−24] The action of BDZs seems to be restricted to synaptic effects of $GABA_A$, which are mediated by the $GABA_A$ receptors. The conformational form of the receptor complex that binds BDZs agonists (e.g., diazepam) has a little affinity for $GABA_A$ at its associated site. In equilibrium is a conformational form of the receptor complex that binds BDZ inverse agonists (e.g., β-carbolines) that have a low affinity for $GABA_A$ and thus is not associated with the opening of the associated ion channel. Antagonist drugs at the BzR will prevent the binding of either agonists or inverse agonists. Currently, only two different BzR subtypes, Bz_1R and Bz_2R, can be distinguished pharmacologically.

Comparative modeling (synonymous with the term "homology modeling") is based on the observation that in protein families, structure is more conserved than sequence. Due to the absence of several bulky side chains, the volume of the benzodiazepine pocket is larger than that of the $GABA_A$ pocket. Competitive antagonists inhibit agonist action by binding into a partially overlapping pocket. Because they are larger than agonists, the pocket geometry requires that they extend further into the membrane-near par of the cleft and thus block allosteric changes that possibly involve motions on the complementary side on the principal side.[5b] Molecular mechanics approaches combined with comparative modeling may provide additional and complementary information with respect to the conformational changes proposed from the electron crystallography study. Molecular modeling studies[25] have determined that all BDZ ligands share the presence of an aromatic or heteroaromatic A ring, believed to undergo π/π stacking with aromatic amino acid residues within the receptor, as well as a proton-accepting group that exists in the same plane of the aromatic A ring and interacts with a histidine residue on the receptor. A 5-phenyl aromatic group, C, may contribute steric or hydrophobic interactions with the receptor. For an agonist, substitution of the para-position on ring C is sterically unfavorable. The amide nitrogen, its methyl substituent, and the 4,5-(methyleneimino) group are not required for in vitro binding of ligands. Substitution of the methylene 3-position or the imine nitrogen is sterically unfavorable for agonist activity but does not affect antagonists.



In continuation of our previous quantitative structure−activity relationship studies[4] on BDZs, we present a new QSAR study on some non-BDZs binding to $GABA_A$/Bz receptors.

2. Materials and Methods

In a search for receptor-specific ligands, several groups of compounds active for the $GABA_A$/benzodiazepine receptor have been synthesized based on pharmacophore receptor models for BzR subtypes. These compounds have been evaluated pharmacologically on recombinant $GABA_A$/benzodiazepine receptor subtypes. A few new ligands were found to display selectivity at one receptor subtype. However, this evaluation provides data sets suitable for quantitative structure−activity analysis. The present paper presents and analyzes comprehensively the QSARs of only non-BDZs. In the past and recently, many QSAR studies on classical BDZ molecules have been reported.[2−4,26,27] The in vitro data usually refer to the molar concentration of compounds leading to a 50% inhibition of [^{3}H]diazepam or [^{3}H]flunitrazepam binding to the BzR from rat brain preparations and are expressed by IC_{50} values. For a valuable study, there is a need to distinguish between the

agonistic, antagonistic, and inverse agonistic activities of the ligands. Unfortunatey, the experimental conditions do not allow the investigator to make such a differentiation among the examined ligands. For drugs acting in the central nervous system (CNS), hydrophobicity[28] is an important property. It is also a significant factor in the susceptibility of drugs to be attacked by the P-450 enzymes.[29] Concerning the classical BDZs, we have found in an earlier analysis[4] that lipophilicity is important in the isolated receptor interactions, as well as in the whole animal. In the formulation of the QSAR we have used only calculated log *P* values, using the CLOG*P* program.[30] The values of substituent constants (π, σ, σ^-, E_s, MR, B_1, B_5, and L) have been taken from the literature,[31−36] and the QSAR regression analyses were executed with the C-QSAR program.[37] Multivariate linear/nonlinear regression models were used. This technique is simple and can produce equal or better models compared to partial least-squares or neural network models. The equations were derived by starting from a relatively small set of descriptors, and this research deals with relatively small sets of compounds, so that the choice of linear or nonlinear multivariate regression analysis is reasonable and most appropriate. The parameters used in this paper have been discussed in detail along with their applications. Here we provide a brief definition. CMR is the calculated molar refractivity for the whole molecule. MR is calculated as we describe: $(n^2 - 1/n^2 + 2)$ (MW/d), where n is the refractive index, MW is the molecular weight, and d is the density of a substance. MR is dependent on volume and polarizability. MR values have been scaled by 0.1. MR can be used for a substituent or for the whole molecule. MgVol is the molar volume calculated according to the methods of McGowan.

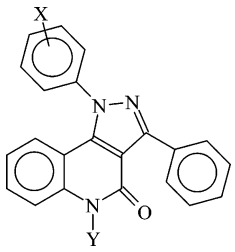
B_1, B_5, and L are Verloop's sterimol parameters for substituents. B_1 is a measure of the width of the first atom of a substituent, B_5 is an attempt to define the overall volume, and L is the substituent length. E_s is Taft's steric constant. Clog *P* is a calculated partition coefficient in octanol/water and is a measure of hydrophobicity, and π is the hydrophobic parameter for substituents usually measured for substituents attached to benzene. Clog *P* and CMR are for the neutral form of partially ionized compounds.

σ and σ^- are Hammett electronic parameters that apply to substituent effects on aromatic systems. The normal σ for substituents on aromatic systems in which strong resonance between substituent and reaction center does not occur is defined as $\sigma = \log K_X - \log K_H$, where K_H is the ionization constant for benzoic acid (normally in water or in 50% ethanol) and K_X is that for substituted benzoic acid. σ^- is employed when there is a strong resonance interaction between substituent and reaction center. It is defined using the ionization constants from phenols or anilines similar to σ: $\sigma^- = \log K_X - \log K_H$, where K refers to the ionization of anilines or phenols. Whereas σ and σ^- are defined via equilibrium constants, σ^+ is defined by the rate of solvolysis of cumene chlorides in 90% acetone/10% water. σI is a measure of the inductive effect of aliphatic substituents. Taft's σ^* electronic effects in aliphatic systems. The indicator variable I is assigned the value of 1 or 0 for special features with special effects that cannot be parametrized and has been explained wherever used. Each regression equation includes 95% confidence limits for each term in parentheses, the correlation coefficient r, between observed values of the dependent and the values calculated from the equation, the s standard deviation; q^2m the square of cross-validated correlation coefficients (a measure of the quality of model, calculated as described by Cramer et al.[38]), is often computed in order to test the stability of model and the F values for the individual term. All of the derived equations were obtained without outliers. The outliers are indicated in the corresponding tables with an asterisk. The fitted values (calculated) given in the tables were calculated by using the corresponding equations. All values given in the tables for molecules indicated as outliers were predicted from the corresponding equation.

In Tables 1−66 we have collected several experimental data from non-BDZ molecules that we could find for sets large enough for a meaningful analysis. These results were obtained for each case from a different laboratory.

3. Results and Discussion: QSAR Evaluation

3.1. 1,3-Diarylpyrazolo[4,5-*c*]quinolin-4-ones



The great structural differences among nonbenzodiazepine compounds with affinity for the BzR make it difficult to generalize the molecular requirements of the recognition site of the receptor itself. Consequently, in an effort to elucidate these requirements Palazzino et al.[39] reported the synthesis of some 1,3-diarylpyrazolo[4,5-*c*]quinolin-4-ones and their abilities to displace specific [^{3}H]flunitrazepam binding from bovine brain membranes (Table 1). The data were used to derive eq 1. The most important parameter is term π_{X-3}, which substantiates our other correlations as to the importance of the hydrophobic effect and shows that only substituents in position 3 of the phenyl ring contact hydrophobic space.

$$\log 1/IC_{50} = 1.588\ (\pm 0.365)\pi_{X-3} + 1.354\ (\pm 0.266)I_Y + 4.516\ (\pm 0.229) \quad (1)$$

$n = 12$ $r^2 = 0.962$ $q^2 = 0.933$ $s = 0.204$ $F_{2,9} = 114.456$ $\alpha = 0.01$

The indicator variable I_Y takes the value of 1 for Y = CH_3. Log *P* cannot be used to correlate the above

Table 1. IC_{50} Inhibition[39] of [^{3}H]Flunitrazepam Binding to Brain Membranes: Compounds and Physicochemical Parameters for Derivation of Equation 1

no.	X	Y	obsd log 1/IC_{50}	calcd log 1/IC_{50}	Δlog 1/IC_{50}	π_{X_3}	I_Y
1	H	H	4.678	4.516	0.162	0.000	0
2	3-Cl	H	5.523	5.643	−0.121	0.710	0
3	3-Br	H	5.824	5.882	−0.058	0.860	0
4	3-Me	H	5.523	5.405	0.118	0.560	0
5	4-Cl	H	4.523	4.516	0.007	0.000	0
6	4-Me	H	4.409	4.516	−0.107	0.000	0
7	H	Me	5.509	5.870	−0.362	0.000	1
8	3-Cl	Me	7.155	6.998	0.157	0.710	1
9	3-Br	Me	7.000	7.236	−0.236	0.860	1
10	3-Me	Me	7.046	6.759	0.286	0.560	1
11	4-Cl	Me	5.936	5.870	0.065	0.000	1
12	4-Me	Me	5.959	5.870	0.088	0.000	1

data. Compounds containing a 4-substituent (Cl, CH_3) are reasonably well fit without any parametrization.

3.2. Imidazo[1,2-*a*]pyrimidin-2-ylphenylmethanones

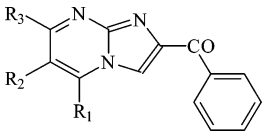


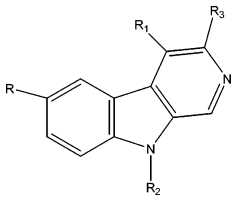
Table 2 contains data[40] for a group of imidazo[1,2-*a*]pyrimidin-2-ylphenylmethanones and related compounds that inhibit the binding of [^{3}H]flunitrazepam from rat brain preparations. From them the following QSAR has been developed.

$$\log 1/IC_{50} = 0.606\ (\pm 0.170)\pi_{R-2} + 0.953\ (\pm 0.348)I_{R_3} + 6.401\ (\pm 0.206) \quad (2)$$

$n = 19 \quad r^2 = 0.829 \quad q^2 = 0.748 \quad s = 0.257 \quad F_{2,16} = 38.95 \quad \alpha = 0.01$

One data point ($R_2 = C_2H_5$, $R_3 = OCH_3$, compound **20**) is poorly predicted and was omitted in the development of eq 2. In these equations π_{R-2} applies to R_2 in position 5 of the pyrimindine ring. I_{R_3} takes the value of 1 for five compounds in which $R_3 = SCH_3$, whereas compounds containing an $R_3 = OCH_3$ group are well fit. The lipophilic contribution of group R_2 is the most important factor in the QSAR 2.

3.3. β-Carbolines



The β-carbolines possess a broad spectrum of pharmacological actions mediated via occupation of BzR in the central nervous system. Many of these ligands displayed better selectivity for the α1 subunit containing $GABA_A$ isoform. QSAR studies of binding affinities of 44-β-carbolines for each receptor subtype have been carried out via acomparative molecular field analysis and a volume analysis. Geometries and charge distributions have been optimized using ab initio methods. The results support that β-carbolines with different intrinsic activities may follow an alternative alignment rule when they bind into the pharmacophore/receptor site of the BzR.[41]

From the data[42a,b,43] in Table 3 several β-carbolines with or lacking a carbonyl group at position 3, the following correlation has been developed.

$$\log 1/IC_{50} = 0.648\ (\pm 0.244)L_3 + 1.251\ (\pm 0.806)\Sigma\sigma_{3-4} + 4.306\ (\pm 1.102) \quad (3)$$

$n = 16 \quad r^2 = 0.850 \quad q^2 = 0.724 \quad s = 0.535 \quad F_{2,13} = 20.8 \quad \alpha = 0.01$

The length of the 3-substituents is the most important factor in QSAR 3. Log *P* could not be used to

Table 2. IC_{50} Inhibition[40] of Imidazo[1,2-α]pyrimidines against to [^{3}H]Flunitrazepam Binding to Brain Membranes: Compounds and Physicochemical Parameters for Derivation of Equation 2

no.	substituents R_1, R_2, R_3	obsd log 1/IC_{50}	calcd log 1/IC_{50}	Δlog 1/IC_{50}	π_{R_2}	I_{R_3}
1	R_1 = Me, R_2 = $CH_2CH{=}CH_2$, R_3 = SMe	8.097	8.021	0.076	1.10	1
2	R_1 = Me, R_2 = Et, R_3 = SMe	7.921	7.693	0.0227	0.56	1
3	R_1 = Me, R_2 = $CH_2C_2H_5$, R_3 = OMe	7.523	7.298	0.225	1.48	0
4	R_1 = Et, R_2 = Pr, R_3 = OMe	7.469	7.340	0.128	1.55	0
5	R_1 = Et, R_2 = But, R_3 = OMe	7.469	7.692	−0.223	2.13	0
6	R_1 = Me, R_2 = But, R_3 = OMe	7.377	7.692	−0.315	2.13	0
7	R_1 = Et, R_2 = $CH_2CH{=}CH_2$, R_3 = OMe	7.377	7.068	0.309	1.10	0
8	R_1 = Me, R_2 = $CH_2CH{=}CH_2$, R_3 = OMe	7.347	7.068	0.279	1.10	0
9	R_1 = Et, R_2 = Pr, R_3 = OMe	7.328	7.340	−0.013	1.55	0
10	R_1 = Et, R_2 = Et, R_3 = OMe	7.252	7.019	−0.270	1.02	0
11	R_1 = Me, R_2 = Pr, R_3 = OMe	7.071	7.340	−0.303	1.55	0
12	R_1 = Pr, R_2 = H, R_3 = SMe	7.051	7.354	0.000	0.00	1
13	R_1 = Et, R_2 = Et, R_3 = OMe	6.971	7.019	−0.049	1.02	0
14	R_1 = Me, R_2 = H, R_3 = SMe	6.721	6.401	0.320	0.00	0
15	R_1 = Et, R_2 = H, R_3 = OMe	6.530	6.401	0.129	0.00	0
16	R_1 = But, R_2 = H, R_3 = OMe	6.469	6.401	0.068	0.00	0
17	R_1 = Pr, R_2 = H, R_3 = OMe	6.272	6.401	−0.129	0.00	0
18	R_1 = Me, R_2 = H, R_3 = OMe	6.097	6.401	−0.304	0.00	0
19	R_1 = Me, R_2 = OMe, R_3 = OMe	6.000	6.389	−0.389	−0.02	0
20[a]	R_1 = H, R_2 = Et, R_3 = OMe	5.824	7.019	−1.195	1.02	0

[a] Data point not included in equation derivation.

Table 3. IC_{50} Inhibition[42a,b,43] of [^{3}H]Diazepam Binding to the Benzodiazepine Receptors: Compounds and Physicochemical Parameters for Derivation of Equation 3

no.	substituents R, R_1, R_2, R_3	obsd log $1/IC_{50}$	calcd log $1/IC_{50}$	Δlog $1/IC_{50}$	$\Sigma\sigma_{3,4}$	L_3
1	R = R_1 = R_2 = H, R_3 = Cl	7.350	6.873	0.477	0.23	3.52
2	R = R_1 = R_2 = H, R_3 = NO2	6.900	7.510	−0.610	0.78	3.44
3	R = R_1 = R_2 = H, R_3 = NCS	8.100	7.560	0.540	0.38	4.29
4	R = R_1 = R_2 = H, R_3 = COOMe	8.300	7.932	0.368	0.45	4.73
5	R = R_1 = R_2 = H, R_3 = H	5.790	5.640	0.150	0.00	2.06
6	R = R_1 = R_2 = H, R_3 = OMe	6.910	6.545	0.365	−0.27	3.98
7	R = R_1 = R_2 = H, R_3 = OEt	7.620	7.114	0.506	−0.24	4.80
8	R = R_1 = R_2 = H, R_3 = OC_3H_7	7.960	7.911	0.049	−0.25	6.05
9	R = R_1 = R_2 = H, R_3 = NH_2	4.600	5.280	−0.680	−0.66	2.78
10	R = R_1 = R_2 = H, R_3 = OH	5.400	5.617	−0.217	−0.37	2.74
11	R_3 = COOEt, R_1 = CH_2OMe, R = $OCH_2C_6H_5$, R_2 = H	9.000	8.823	0.177	0.53	5.95
12	R_3 = COOEt, R_1 = CH_2OMe, R = OH, R_2 = H	9.050	8.823	0.227	0.53	5.95
13[a]	R_3 = COOEt, R_1 = CH_2OMe, R = $OCH_2C_6H_5$, R_2 = Me	6.020	8.823	−2.803	0.53	5.95
14	R_3 = COOEt, R_1 = CH_2OMe, R = OMe, R_2 = H	9.300	8.823	0.477	0.53	5.95
15	R_3 = COOEt, R_1 = $-CH_2OMe$, R = R_2 = H	8.64	8.823	−0.183	0.53	5.95
16	R_3 = COOEt, R_1 = Et, R = $OCH_2C_6H_5$, R_2 = H	7.660	8.635	−0.975	0.38	5.95
17	R_3 = COOEt, R = $OCH_2C_6H_5$, R_1 = R_2 = H	8.050	8.722	−0.672	0.45	5.95

[a] Data point not included in equation derivation.

correlate the data; $\Sigma\sigma_{3-4}$ applies to R in positions 3 and 4 of the β-carboline ring.

Compounds containing 6-$OCH_2C_6H_5$, 6-OCH_3, and 6-OH as substituents are reasonably well fit without any parametrization. Whereas one data point (no. 13) containing a 9-CH_3 group was not employed in deriving eq 3. Electronic interactions occur with the 3 and 4 substituents of the β-carboline ring.

Previous studies[4] on the structure activity of β-carbolines had indicated that an ester moiety was required at position 3 in order for the compound to display high affinity for the BzR (as inverse agonist) and that a negative steric effect occurs with the group in the 1-position[4] (eq 4).

$$\log 1/K_i = 2.10\ (\pm 0.61)E_{s1} + 1.60\ (\pm 0.80)I_2 + 1.06\ (\pm 0.75)\pi_2 + 6.52\ (\pm 0.74) \quad (4)$$

(I_2 takes 1 for a 3-CO− group)

$$n = 14 \quad r = 0.955 \quad r^2 = 0.911 \quad s = 0.605$$

3.4. *N*-(Indolo-3-yl-glyoxyl) Amino Derivatives

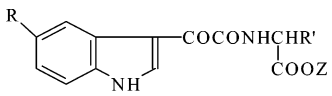


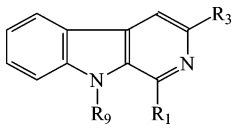
Table 4 contains data[44,45] for a group of some *N*-(indolo-3-yl-glyoxyl) amino derivatives acting as inverse agonists in vitro from which we have derived eq 5.

$$\log 1/IC_{50} = 1.260\ (\pm 0.331)I_D + 0.568\ (\pm 0.387)I_{LD} - 0.451\ (\pm 0.347)I_{R'} + 1.497\ (\pm 0.457)\sigma_R + 0.990\ (\pm 0.292)I_Z + 3.621\ (\pm 0.314) \quad (5)$$

$n = 39 \quad r^2 = 0.826 \quad q^2 = 0.761 \quad s = 0.444 \quad F_{5,31} = 31.47 \quad \alpha = 0.01$

In these equations σ_R applies to R in the 5-position of the indole ring. Attempts to parametrize R′ except in terms I_Z and $I_{R'}$ were unsuccessful. π also was not a useful parameter. I_Z takes the value of 1 for compounds in which Z = C_2H_5 and $I_{R'}$ = $CH_2C_6H_5$. I_D takes the value of 1 for the 16 D forms of the amino acid moiety of the compounds, and I_{LD} takes the value of 1 for the racemic form. Three data points were omitted in this analysis. One (no. 15) was in the racemic form, whereas the others (no. 16 and 18) were the D form of the amino acid. Again, we find hydrophobic effects to be absent, which emphasizes the differences in binding mode for this class of compound compared to the classical BDZs. It is of interest that the benzylamine moiety for the compounds in Table 4 produces drugs that are less active than does the methyl moiety of the congeners in the same table.

3.5. β-Carbolines



For another series of β-carbolines,[46−48] which has been found to displace [^{3}H]flunitrazepam (10 μM) from binding to rat cerebral cortical membranes, the following QSARs (Table 5) have been derived.

$$\log 1/IC_{50} = -0.903\ (\pm 0.378)B_{5-R_1} - 0.871\ (\pm 0.454)\text{Clog } P + 0.599\ (\pm 0.219)L_{R_3} + 8.183\ (\pm 1.345) \quad (6)$$

$n = 16 \quad r^2 = 0.914 \quad q^2 = 0.859 \quad s = 0.440 \quad F_{3,12} = 42.34 \quad \alpha = 0.01$

Stepwise regression shows that the most important terms are the two sterimole parameters B_{5-R_1} and L_{R_3}. B_{5-R_1} expresses the largest width of R_1 substituents. At this position, increasing bioactivity (compound **16**, whereas **1** ≫ **15**, **17** > **16**) while increasing the length L_{R3} of substituents R_3 increases potency. Compound **14** was omitted from the derivation of eq 6.

Table 4. IC_{50} Inhibition of [^{3}H]Flunitrazepam Binding to Benzodiazepine Receptor:[44,45] Compounds and Physicochemical Parameters for Derivation of Equation 5

no.	substituents R, R′, Z	obsd log 1/IC_{50}	calcd log 1/IC_{50}	Δlog 1/IC_{50}	I_D	I_{LD}	$I_{R'}$	σ^-_X	I_Z
1	R = H, R′ = CH_3, Z = C_2H_5 (L, D)	4.89	5.178	−0.288	0	1	0	0	1
2	R = H, R′ = CH_3, Z = C_2H_5 (D)	5.13	5.871	−0.741	1	0	0	0	1
3	R = H, R′ = CH_3, Z = C_2H_5 (L)	4.77	4.611	0.159	0	0	0	0	1
4	R = Br, R′ = CH_3, Z = C_2H_5 (L, D)	5.32	5.523	−0.203	0	1	0	0.23	1
5	R = Br, R′ = CH_3, Z = C_2H_5 (D)	6.74	6.215	0.525	1	0	0	0.23	1
6	R = Br, R′ = CH_3, Z = C_2H_5 (L)	4.29	4.955	−0.665	0	0	0	0.23	1
7	R = Cl, R′ = CH_3, Z = C_2H_5 (L, D)	6.30	5.523	0.777	0	1	0	0.23	1
8	R = Cl, R′ = CH_3, Z = C_2H_5 (D)	6.82	6.215	0.605	1	0	0	0.23	1
9	R = Cl, R′ = CH_3, Z = C_2H_5 (L)	4.60	4.955	−0.355	0	0	0	0.23	1
10	R = NO_2, R′ = CH_3, Z = C_2H_5 (L, D)	6.70	6.346	0.354	0	1	0	0.78	1
11	R = NO_2, R′ = CH_3, Z = C_2H_5 (D)	7.15	7.038	0.112	1	0	0	0.78	1
12	R = NO_2, R′ = CH_3, Z = C_2H_5 (L)	5.52	5.778	−0.258	0	0	0	0.78	1
13	R = OCH_3, R′ = CH_3, Z = C_2H_5 (D)	6.05	5.466	0.584	1	0	0	−0.27	1
14	R = OCH_3, R′ = CH_3, Z = C_2H_5 (L)	3.96	4.207	−0.247	0	0	0	−0.27	1
15[a]	R = Br, R′ = $CH_2C_6H_5$, Z = C_2H_5 (L, D)	3.74	5.071	−1.331	0	1	1	0.23	1
16[a]	R = Br, R′ = $CH_2C_6H_5$, Z = C_2H_5 (D)	4.26	5.763	−1.503	1	0	1	0.23	1
17	R = Br, R′ = $CH_2C_6H_5$, Z = C_2H_5 (L)	3.66	4.504	−0.844	0	0	1	0.23	1
18[a]	R = Cl, R′ = $CH_2C_6H_5$, Z = C_2H_5 (D)	4.42	5.763	−1.243	1	0	1	0.23	1
19	R = Cl, R′ = $CH_2C_6H_5$, Z = C_2H_5 (L)	4.35	4.504	−0.154	0	0	1	0.23	1
20	R = NO_2, R′ = $CH_2C_6H_5$, Z = C_2H_5 (D)	7.00	6.587	0.413	1	0	1	0.78	1
21	R = NO_2, R′ = $CH_2C_6H_5$, Z = C_2H_5 (L)	5.55	5.327	0.223	0	0	1	0.78	1
22	R = H, R′ = CH_3, Z = H (L, D)	3.98	4.188	−0.208	0	1	0	0	0
23	R = H, R′ = CH_3, Z = H (D)	4.32	4.881	−0.561	1	0	0	0	0
24	R = H, R′ = CH_3, Z = H (L)	3.52	3.621	−0.101	0	0	0	0	0
25	R = Br, R′ = CH_3, Z = H (L, D)	4.40	4.533	−0.133	0	1	0	0.23	0
26	R = Br, R′ = CH_3, Z = H (D)	5.16	5.225	−0.065	0	0	0	0.23	0
27	R = Br, R′ = CH_3, Z = H (L)	4.10	3.965	0.135	0	0	0	0.23	0
28	R = Cl, R′ = CH_3, Z = H (L, D)	4.66	4.533	0.127	0	1	0	0.23	0
29	R = Cl, R′ = CH_3, Z = H (D)	5.30	5.225	0.075	0	1	0	0.23	0
30	R = Cl, R′ = CH_3, Z = H (L)	4.34	3.965	0.375	0	0	0	0.23	0
31	R = NO_2, R′ = CH_3, Z = H (L, D)	5.21	5.356	−0.146	0	1	0	0.78	0
32	R = NO_2, R′ = CH_3, Z = H (D)	5.52	6.048	−0.528	1	0	0	0.78	0
33	R = NO_2, R′ = CH_3, Z = H (L)	4.72	4.788	−0.068	0	0	0	0.78	0
34	R = OCH_3, R′ = CH_3, Z = H (D)	4.66	4.477	0.183	0	1	0	−0.27	0
35	R = OCH_3, R′ = CH_3, Z = H (L)	3.77	3.217	0.553	0	0	0	−0.27	0
36	R = Br, R′ = $CH_2C_6H_5$, Z = H (L, D)	3.80	4.081	−0.281	0	1	1	0.23	0
37	R = Br, R′ = $CH_2C_6H_5$, Z = H (D)	4.22	4.774	−0.554	1	0	1	0.23	0
38	R = Br, R′ = $CH_2C_6H_5$, Z = H (L)	3.61	3.514	0.096	0	0	1	0.23	0
39	R = Cl, R′ = $CH_2C_6H_5$, Z = H (D)	4.92	4.774	0.146	1	0	1	0.23	0
40	R = Cl, R ′ = $CH_2C_6H_5$, Z = H (L)	4.32	3.514	0.806	0	0	1	0.23	0
41	R = NO_2, R′ = $CH_2C_6H_5$, Z = H (D)	5.40	5.597	−0.197	1	0	1	0.78	0
42	R = NO_2, R′ = $CH_2C_6H_5$, Z = H (L)	4.68	4.337	0.343	0	0	1	0.78	0

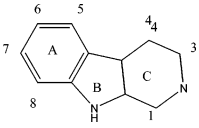
[a] Data points not included in equation derivation.

Table 5. IC_{50} Antagonistic Activity on Benzodiazepine Receptors by Carbolines:[46−48] Compounds and Physicochemical Parameters for Derivation of Equation 6

no.	substituents R_1, R_3, R_9	obsd log 1/IC_{50}	calcd log 1/IC_{50}	Δlog 1/IC_{50}	Clog *P*	B_{5-R_1}	L_{R_3}
1	R_3 = COOMe, R_1 = R_9 = H	8.300	8.141	0.159	2.266	1	4.73
2	R_3 = $COOC_2H_5$, R_1 = R_9 = H	8.300	8.411	−0.111	2.795	1	5.95
3	R_3 = OC_2H_5, R_1 = R_9 = H	7.62.	7.105	0.515	3.503	1	4.80
4	R_3 = $OCHMe_2$, R_1 = R_9 = H	6.290	6.836	−0.546	3.812	1	4.80
5	R_3 = OC_4H_9, R_1 = R_9 = H	7.010	7.418	−0.408	4.561	1	6.86
6	R_3 = OCH_3, R_1 = R_9 = H	6.910	7.075	−0.165	2.97	1	3.98
7	R_3 = OC_3H_7, R_1 = R_9 = H	7.960	7.393	0.567	4.032	1	6.05
8	R_3 = COC_3H_7, R_1 = R_9 = H	7.640	7.605	0.035	3.837	1	6.12
9	R_3 = C_4H_9, R_1 = R_9 = H	6.640	6.932	−0.292	4.645	1	6.17
10	R_3 = H, R_1 = R_9 = H	5.790	6.286	−0.496	2.559	1	2.06
11	R_3 = $COOCMe_3$, R_1 = R_9 = H	8.000	7.794	0.206	3.503	1	5.95
12	R_3 = Cl, R_1 = R_9 = H	7.350	6.517	0.833	3.298	1	3.52
13	R_3 = NO_2, R_1 = R_9 = H	6.900	7.195	−0.295	2.464	1	3.44
14[a]	R_3 = $COOCH_2CMe_3$, R_1 = R_9 = H	6.120	7.357	−1.237	4.122	1	6.12
15	R_3 = COOMe, R_1 = C_2H_5, R_9 = H	5.120	5.287	−0.167	3.294	3.17	4.73
16	R_3 = H, R_1 = C_2H_5, R_9 = H	3.600	3.432	0.168	3.587	3.17	2.06
17	R_3 = H, R_1 = CH_3, R_9 = H	4.910	4.913	−0.003	3.058	2.04	2.06

[a] Data point not included in equation derivation.

3.6. β-Carbolines



In Table 6 are presented some more substituted β-carbolines,[49] for which a QSAR study by Borea et al.[49] showed the influence of lipophilic character and hydrogen-bonding capability of substituents in position 3 as an indicator variable I_1. Indicator variable I_1 was used by Borea for the compounds characterized

Table 6. IC_{50} Binding Affinities of β-Carbolines to the Benzodiazepine Receptor Measured as Concentration Required To Displace 50% of [^{3}H]Flunitrazepam:[49] Compounds and Physicochemical Parameters for Derivation of Equation 10

no.	substituents	calcd log 1/IC_{50}	obsd log 1/IC_{50}	Δlog 1/IC_{50}	Clog *P*	I_{CH_3}
1[a]	3-COOH	−1.49	−1.03	2.52	−0.743	0
2	1-CH_3	−0.450	−1.86	1.41	1.728	1
3	1-CH_3, 7-OCH_3	−1.980	−1.81	−0.17	1.831	1
4	1-CH_3, 7-OH	−1.90	−2.20	0.30	1.061	1
5	3-CH_2OH	1.591	1.67	−0.08	0.525	0
6	3-$COOCH_3$	2.097	2.00	0.10	1.174	0
7	3-$COOC_2H_5$	2.155	2.26	−0.11	1.703	0
8	3-$COOC_3H_7$	1.921	2.53	−0.61	2.232	0
9	3-$COOCH_3$, 4-C_2H_5, 6,7-di-OCH_3	2.40	2.37	0.03	1.924	0
10	3-$COOCH_3$, 4-CH_2OCH_3, 5-$OCH_2C_6H_5$	2.959	2.71	0.24	2.606	0
11	3-$COOCH_3$, 4-CH_3, 5-$OCH(CH_3)_2$	2.960	2.96	0	3.087	0
12	3-$COONHCH_3$	1.780	1.61	0.17	0.412	0
13	1-CH_3, 7-OCH_3	−2.813	−1.81	−1.0	1.831	1
14	1-CH_3, 7-OH	−2.748	−2.20	−0.55	1.061	1
15	3-$COOC_2H_5$, 3-CH_2OCH_3, 6-$OCH_2C_6H_5$	2.959	2.71	0.24	2.606	0
16[a]	H	−1.0	2.01	−3.01	1.209	0

[a] Data points not included in equation derivation.

in position 3 by substituents able to accept a hydrogen bond The role of the lipophilic character was expressed as R_m values by the HPTLC determinations and as log K' values by the HPLC measurements. The log *P* values for harman, harmine, and norharman were determined at pH 13.0 in octanol/water. The log *P* values of the other carboline derivatives were calculated from the experimental log *P* values of norharman, by taking advantage of the additive property of the Hansch π values. The investigators[49] did not provide the q^2 values for eqs 7−9 in order to test the quality of model.

$$\log 1/IC_{50} = -4.784\ (\pm 0.376) + 1.089\ (\pm 0.120)R_m + 3.132\ (\pm 0.244)I_1 \quad (7)$$

$n = 16 \quad r = 0.981 \quad s = 0.455 \quad F = 168.62 \quad p < 0.005$

$$\log 1/IC_{50} = -4.300\ (\pm 0.444) + 1.175\ (\pm 0.177) \log K' + 2.917\ (\pm 0.328)I_1 \quad (8)$$

$n = 16 \quad r = 0.969 \quad s = 0.588 \quad F = 98.33 \quad p < 0.005$

$$\log 1/IC_{50} = -3.401\ (\pm 0.257) + 0.663\ (\pm 0.074) \log P + 3.136\ (\pm 0.247)I_1 \quad (9)$$

$n = 16 \quad r = 0.981 \quad s = 0.459 \quad F = 165.52 \quad p < 0.005$

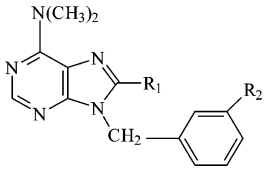
From the same data[49] we derived eq 10

$$\log 1/IC_{50} = 0.502\ (0.474)\ \text{Clog}\ P - 4.138\ (\pm 0.751)I_{CH_3} + 1.405\ (\pm 0.963) \quad (10)$$

$n = 14 \quad r^2 = 0.939 \quad q^2 = 0.904 \quad s = 0.600 F_{2,11} = 84.9 \quad \alpha = 0.01$

Two data points, compounds **1** and **16**, were rejected from the derivation of eq 10. Clog *P* values are the theoretically calculated lipophilicity values using the C-QSAR program. An indicator variable I_{CH_3} with a value of 1 was used for the compounds bearing a CH_3 in position 1. The negative coefficient associated with the indicator variable seems to indicate that a methyl group in that position decreases receptor binding affinity. The existence of a region of steric hindrance around the heterocyclic nitrogen atom in position 1 is possible. No collinearity was shown between the independent variables. The previous investigators did not find any significant improvement in their equations with the introduction of I_{CH_3}. When our approach was used, no role was found to exist for their indicator I_1 (eq 9).

3.7. 6,9-Disubstituted Purines



Compounds of diverse structure bind to the BzR.[3,4] Purines were proposed as possible endogenous ligands, and several papers describe structure−activity studies on the interaction of purines with the BzR.[26,27] Several 6,9-disubstituted purines[44,50,51] were tested for their binding activity to the BzR in rat brain tissue. The IC_{50} values represent inhibition of specific binding of 1.5 nM [^{3}H]diazepam to rat brain receptors. From these results in Table 7 eq 11 has been derived.

$$\log 1/IC_{50} = 0.446\ (\pm 0.197)B_{5-R_2} + 0.608\ (\pm 0.402)\pi_{R_1} - 0.527\ (\pm 0.358)\pi_{R_2} + 4.567\ (\pm 0.410) \quad (11)$$

$n = 28 \quad r^2 = 0.767 \quad q^2 = 0.669 \quad s = 0.467 \quad F_{3,24} = 26.33 \quad \alpha = 0.01$

The collinearity among the parameters is minimal. The three data points, compounds **20**, **21**, and **23**, not included in this analysis, are marked in Table 7. They do not contain any unusual substituents. For compound **23** parameter B_{5-R_2} has the higher value (4.130). Correlation 11 is rather poor. Again, no role for an electronic effect was found. It is likely that R_2 substituents do contact a hydrophobic space on the receptor, whereas the negative coefficient with π_{R1} shows that there is a need for a less lipophilic R_1 substituent.

Table 7. IC_{50} Inhibition of of [^{3}H]Diazepam Binding to Rat Brain Benzodiazepine Receptors:[44,50,51] Compounds and Physicochemical Parameters for Derivation of Equation 11

no.	substituents R_1, R_2	obsd log $1/IC_{50}$	calcd log $1/IC_{50}$	Δlog $1/IC_{50}$	B_{5-R_2}	π_{R_1}	π_{R_2}
1	$R_1 = R_2 = H$	4.890	5.013	−0.123	1	0	0.00
2	$R_1 = Br$, $R_2 = H$	5.520	5.536	−0.016	1	0.86	0.00
3	$R_1 = CH_3$, $R_2 = H$	5.070	5.353	−0.283	1	0.56	0.00
4	$R_1 = OCH_3$, $R_2 = H$	5.270	5.004	0.269	1	−0.02	0.00
5	$R_1 = N(CH_3)_2$, $R_2 = H$	5.240	5.122	0.118	1	0.18	0.00
6	$R_1 = NHCH_3$, $R_2 = H$	4.770	4.727	0.043	1	−0.47	0.00
7	$R_1 = H$, $R_2 = 3\text{-}NH_2$	6.050	6.094	−0.049	1.97	0.0	−1.23
8	$R_1 = Br$, $R_2 = 3\text{-}NH_2$	6.960	6.617	0.343	1.97	0.86	−1.23
9	$R_1 = Cl$, $R_2 = 3\text{-}NH_2$	6.720	6.526	0.194	1.97	0.71	−1.23
10	$R_1 = OCH_3$, $R_2 = 3\text{-}NH_2$	6.000	6.082	−0.082	1.97	−0.20	−1.23
11	$R_1 = N(CH_3)_2$, $R_2 = 3\text{-}NH_2$	6.220	6.204	0.016	1.97	0.18	−1.23
12	$R_1 = NHCH_3$, $R_2 = 3\text{-}NH_2$	5.140	5.809	−0.669	1.97	−0.47	−1.23
13	$R_1 = OH$, $R_2 = 3\text{-}NH_2$	5.740	5.687	0.053	1.97	−0.67	−0.98
14	$R_1 = H$, $R_2 = 3\text{-}NHCHO$	7.470	6.694	0.776	3.61	0.00	−0.98
15	$R_1 = Br$, $R_2 = 3\text{-}NHCHO$	7.960	7.217	0.743	3.61	0.86	−0.98
16	$R_1 = N(CH_3)_2$, $R_2 = 3\text{-}NHCHO$	6.960	6.803	0.157	3.61	0.18	−0.98
17	$R_1 = NHCH_3$, $R_2 = 3\text{-}NHCHO$	6.440	6.408	0.032	3.61	−0.47	−0.98
18	$R_1 = OH$, $R_2 = 3\text{-}NHCHO$	6.890	6.287	0.603	3.61	−0.67	−0.97
19	$R_1 = Br$, $R_2 = 3\text{-}NHCOCH_3$	6.080	7.211	−1.131	3.61	0.86	0.49
20[a]	$R_1 = Br$, $R_2 = 3\text{-}NHCOC_6H_5$	5.100	6.486	−1.386	3.71	0.86	−0.52
21[a]	$R_1 = Br$, $R_2 = 3\text{-}NHCOOCH_3$	5.280	7.144	−1.864	3.99	0.86	−1.3
22	$R_1 = Br$, $R_2 = 3\text{-}NHCONH_2$	7.600	7.385	0.215	3.61	0.86	−1.18
23[a]	$R_1 = Br$, $R_2 = 3\text{-}NHSO_2CH_3$	5.820	7.554	−1.734	4.13	0.86	
24	$R_1 = H$, $R_2 = 3\text{-}F$	5.140	5.095	0.045	1.350	0.00	0.14
25	$R_1 = H$, $R_2 = 3\text{-}CH_2OH$	5.300	6.314	−1.014	2.70	0.00	−1.03
26	$R_1 = H$, $R_2 = 3\text{-}OH$	5.920	5.781	0.139	1.93	0.00	−0.67
27	$R_1 = H$, $R_2 = 3\text{-}OCOC(CH_3)_3$	5.800	6.259	−0.459	4.030	0.00	0.2
28	$R_1 = H$, $R_2 = 3\text{-}OCOCH_3$	6.360	6.546	−0.181	3.670	0.00	−0.64
29	$R_1 = H$, $R_2 = 2\text{-}F$	5.270	4.939	0.331	1	0.00	0.14
30	$R_1 = H$, $R_2 = 2\text{-}Cl$	4.890	4.639	0.251	1	0.00	0.71
31	$R_1 = H$, $R_2 = 2\text{-}OCH_3$	4.700	5.024	−0.324	1	0.00	−0.02

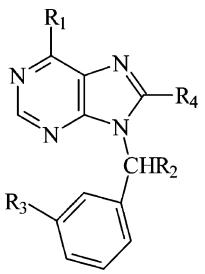
[a] Data points not included in equation derivation.

Table 8. IC_{50} Inhibition of Specific Binding of [^{3}H]Diazepam to Rat Brain of Benzodiazepine Receptors:[52] Compounds and Physicochemical Parameters for Derivation of Equation 12

no.	substituents R_1, R_2, R_3, R_4	obsd log $1/IC_{50}$	calcd log $1/IC_{50}$	Δlog $1/IC_{50}$	B_{1-R_3}	I_{8-Br}	I_S
1	$R_1 = 6\text{-}NMe_2$, $R_3 = 3\text{-}NH_2$, $R_2 = R_4 = H$	4.886	4.870	0.016	1	0	0
2	$R_1 = 6\text{-}NMe_2$, $R_2 = R_3 = R_4 = H$	6.046	6.180	−0.135	1.35	0	0
3	$R_1 = 6\text{-}NMe_2$, $R_2 = R_3 = H$, $R_4 = 8\text{-}Br$	5.523	5.940	−0.417	1	1	0
4	$R_1 = 6\text{-}NMe_2$, $R_4 = 8\text{-}Br$, $R_3 = 3\text{-}NH_2$, $R_2 = H$	6.959	7.250	−0.292	1.35	1	0
5	$R_1 = 6\text{-}NMe_2$, $R_4 = 8\text{-}Br$, $R_3 = 3\text{-}NHCHO$, $R_2 = H$	7.959	7.250	0.708	1.35	1	0
6	$R_1 = 6\text{-}NMe_2$, $R_2 = CH_3$ (S), $R_3 = R_4 = H$	5.678	5.709	−0.031	1	0	1
7	$R_1 = 6\text{-}NMe_2$, $R_2 = CH_3$ (R), $R_3 = R_4 = H$	4.000	4.031	−0.031	1	0	−1
8	$R_1 = 6\text{-}NMe_2$, $R_2 = CH_3$ (R, S), $R_3 = 3\text{-}NH_2$	6.796	6.180	0.616	1.35	0	0
9	$R_1 = 6\text{-}NMe_2$, $R_4 = 8\text{-}Br$, $R_2 = CH_3$ (R, S), $R_3 = 3\text{-}NH_2$	6.284	7.25	−0.966	1.35	1	0
10[a]	$R_1 = 6\text{-}NMe_2$, $R_3 = 3\text{-}OH$, $R_2 = R_4 = H$	5.921	6.180	−0.259	1.35	0	0
11	$R_1 = 6\text{-}NMe_2$, $R_3 = 3\text{-}OCOMe$, $R_2 = R_4 = H$	6.357	6.180	0.176	1.35	0	0
12	$R_3 = 6\text{-}OH$, $R_1 = R_2 = R_4 = H$	4.721	4.870	−0.149	1	0	0
13	$R_3 = 6\text{-}SMe$, $R_1 = R_2 = R_4 = H$	5.481	4.870	0.612	1	0	0
14	$R_1 = 6\text{-}NMe_2$, $R_2 = CH_3$ (R, S), $R_3 = 3\text{-}OH$, $R_4 = H$	6.319	6.180	0.138	1.35	0	0
15	$R_1 = 6\text{-}OH$, $R_2 = CH_3$ (R, S), $R_3 = 3\text{-}OH$, $R_4 = H$	5.658	6.180	−0.523	1.35	0	0
16	$R_1 = 6\text{-}SMe$, $R_2 = CH_3$ (R, S), $R_3 = OH$, $R_4 = H$	5.921	6.180	−0.259	1.35	0	0
17	$R_1 = 6\text{-}NMe_2$, $R_2 = CH_3$ (R, S), $R_3 = 3\text{-}OCOMe$, $R_4 = H$	6.420	6.180	0.240	1.35	0	0
18	$R_1 = 6\text{-}SMe$, $R_2 = CH_3$ (R, S), $R_3 = 3\text{-}OCOMe$, $R_4 = H$	5.770	6.180	−0.411	1.35	0	0

[a] Data point not included in equation derivation.

3.8. α-Methyl Analogues of the Benzyl-purines



From the data in Table 8, concerning α-methyl analogues of the benzyl-purines,[52] eq 12 was derived.

The IC_{50} values are the concentration at which specific binding of 1.5 nM [^{3}H]diazepam to rat brain receptors was decreased by 50%. Increased potency of the compound as an inhibitor of [^{3}H]diazepam binding was assumed to reflect increased affinity of the agent for the receptor.

$$\log 1/IC_{50} = 3.744\ (\pm 1.588) B_{1-R_3} + 1.070\ (\pm 0.697) I_{8-Br} + 0.839\ (\pm 0.634) I_s + 1.126\ (\pm 1.967) \quad (12)$$

$n = 17$ $r^2 = 0.832$ $q^2 = 0.702$ $s = 0.415$ $F_{3,13} = 21.409$ $\alpha = 0.01$

B_{1-R_3} models the minimum width of R_3 substituents.

Table 9. IC_{50} Inhibition of the 10-Substituted 7,12-Dihydropyridodiindoles against [^{3}H]Diazepam Binding to the Benzodiazepine Receptors:[53,54] Compounds and Physicochemical Parameters for Derivation of Equation 13

no.	substituents R, X	obsd log 1/IC_{50}	calcd log 1/IC_{50}	Δlog 1/IC_{50}	MR_3	F_4	R_R	π_2
1	R = H, X = H	8.400	8.052	0.348	0.103	0	0	0
2	R = H, X = 3-F	8.220	8.088	0.132	0.092	0	0	0
3	R = H, X = 3-Cl	5.670	6.398	−0.728	0.603	0	0	0
4	R = H, X = 3-Br	6.130	5.456	0.674	0.888	0	0	0
5	R = H, X = 3-CH_3	6.650	6.524	0.126	0.565	0	0	0
6	R = H, X = 3-OCH_3	6.050	5.790	0.260	0.787	0	0	0
7[a]	R = H, X = 3-$OCH_2C_6H_5$	5.800	−2.252	8.050	3.219	0	0	0
8	R = H, X = 3-OH	6.940	7.450	0.510	0.285	0	0	0
9	R = H, X = 1-F	7.920	7.876	0.064	0.103	0	0	0.14
10	R = H, X = 1-Cl	7.100	7.160	−0.060	0.103	0	0	0.71
11	R = H, X = 1-Br	7.550	6.971	0.579	0.103	0	0	0.86
12	R = H, X = 1-CH_3	7.080	7.348	−0.268	0.103	0	0	0.56
13	R = H, X = 2-F	8.160	8.052	0.108	0.103	0	0	0
14	R = H, X = 2-Cl	8.000	8.052	−0.052	0.103	0	0	0
15	R = H, X = 2-Br	7.720	8.052	0.332	0.103	0	0	0
16	R = H, X = 2-CH_3	8.090	8.052	0.038	0.103	0	0	0
17	R = H, X = 2-OCH_3	8.090	8.052	0.038	0.103	0	0	0
18	R = H, X = 2-OH	8.220	8.052	0.168	0.103	0	0	0
19[a]	R = H, X = 2-$OCOCF_3$	6.700	8.052	−1.352	0.103	0	0	0
20	R = H, X = 4-Cl	6.150	5.985	0.165	0.103	0.42	0	0
21	R = H, X = 4-OCH_3	6.600	6.625	0.025	0.103	0.29	0	0
22	R = H, X = 4-OH	6.240	6.428	−0.188	0.103	0.33	0	0
23	R = NO_2, X = H	8.400	8.197	0.203	0.103	0	0.13	0
24	R = NO_2, X = 3-Cl	5.930	6.543	−0.613	0.603	0	0.13	0
25[a]	R = NO_2, X = 2-Cl	6.900	8.197	−1.297	0.103	0	0.13	0
26	R = NH_2, X = H	7.360	7.226	0.134	0.103	0	−0.74	0
27	R = NH_2, X = 2-Cl	7.010	7.226	0.216	0.103	0	−0.74	0
28	R = Br, X = H	8.220	7.806	0.360	0.103	0	−0.22	0
29	R = Cl, X = 1-Cl	6.510	6.948	0.438	0.103	0	−0.19	0.71

[a] Data points not included in equation derivation.

The indicator variable $I_{8Br} = 1$ for R_4 = 8-Br groups (0 for other substituents), which are more potent; $I_s = 1$ for the congener in the *S* configuration, whereas it is −1 for the *R* enantiomer, which is the less active congener. No parametrization for R_1 substituents has been done. However, all fit the pattern of QSAR 12. No evidence for a hydrophobic effect of the substituents has been found for these studies. One data point was omitted in eq 12, and it was a racemic analogue.

3.9. 7,12-Dihydropyrido[3,2-*b*][5,4-*b*]diindoles

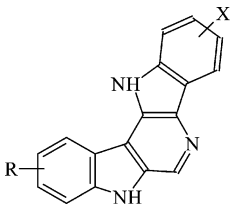


Table 9 contains data for some 7,12-dihydropyrido-[3,2-*b*][5,4-*b*]diindoles.[53,54] Their effect as IC_{50} values measured against [^{3}H]diazepam and [^{3}H]flunitrazepam at 10 μM (to define nonspecific binding) was correlated with π_2, MR_3, *F*, and *R* in QSAR 13.

$$\log 1/IC_{50} = -1.256\ (\pm 0.624)\pi_2 - 3.307\ (\pm 0.700)MR_3 - 4.921\ (\pm 1.434)F_4 + 1.116\ (\pm 0.769)R_R + 8.392\ (\pm 0.277) \quad (13)$$

$n = 26$ $r^2 = 0.850$ $q^2 = 0.745$ $s = 0.374$ $F_{4,21} = 29.96$ $\alpha = 0.01$

The parameters are reasonably orthogonal. Three data points (7, 19, and 25, Table 9) are omitted in the development of the above equations, and of these, compound **7** has the higher value for parameter MR_3. MR represents the molar refractivity of substituents [$MR = (\eta^2 - 1/\eta^2 - 2) \times MW/d$, where η is the index of refraction]. It is primarily a measure of volume with a small component of polarizability. MR_3 is the most important parameter, and its negative sign suggests steric hindrance either directly or through a conformational change in the receptor. The large coefficient clearly indicates that large groups hinder the binding of derivatives to the receptor or a different binding mode or a different receptor for these congeners compared with classical BDZs. Again, we find a negative hydrophobic effect (π_2). The Swain−Lupton factor *F* for inductive field electronic effect refers to substituents in position 4 (three compounds only) and improves the equation. R_R, the Swain−Lupton parameter for resonance electronic effect, refers to R_{10} substituents. Electron-releasing substituents at position 10, which potentiates the acidity of the indole (N-7)-H, strongly support a hydrogen-bonding interaction at the active site. Adding a term in π_1 or MR_1 does not improve the correlation, so that hydrophobic or steric effects of R in position 1 appear to be unimportant. Thus, no parametrization for these substituents was done. Although the IC_{50} values are well predicted, eq 13 strongly suggests that both steric and, to a lesser degree, electronic factors are imposed upon the rigid pyridodi-indole ligands by the receptor site.

Table 10. IC_{50} Inhibition of [^{3}H]Diazepam Binding to Benzodiazepine Receptors by 4*H*-Pyrimido[2,1-*b*]benzothiazol-4-ones:[55] Compounds and Physicochemical Parameters for Derivation of Equation 14

no.	substituents R_1, R_2	obsd log $1/IC_{50}$	calcd log $1/IC_{50}$	Δlog $1/IC_{50}$	MR_{R_2}	$\Sigma\sigma$
1	$R_1 = OMe$, $R_2 = H$	6.292	6.237	0.055	0.103	0.00
2	$R_1 = OEt$, $R_2 = H$	6.260	6.237	0.023	0.103	0.00
3	$R_1 = OCHMe_2$, $R_2 = H$	6.398	6.237	0.161	0.103	0.00
4[a]	$R_1 = OC_4H_9$, $R_2 = H$	5.939	6.237	−0.298	0.103	0.00
5	$R_1 = OEt$, $R_2 = 8$-F	5.996	6.157	−0.161	0.092	0.060
6	$R_1 = OEt$, $R_2 = 8$-Cl	5.509	5.560	0.051	0.603	0.230
7[a]	$R_1 = OEt$, $R_2 = 6$-Me	6.770	5.900	0.871	0.103	0.230
8	$R_1 = OEt$, $R_2 = 6$-OMe	6.699	6.632	0.067	0.103	−0.270
9	$R_1 = OEt$, $R_2 = 6$-Me	6.585	6.486	0.099	0.103	−0.170
10	$R_1 = OEt$, $R_2 = 7,8$-Me_2	6.222	6.274	−0.052	0.565	−0.240
11	$R_1 = OEt$, $R_2 = 6,8$-Cl	5.319	5.223	0.096	0.103	0.460
12	$R_1 = NH_2$, $R_2 = H$	6.000	6.237	0.237	0.103	0.000

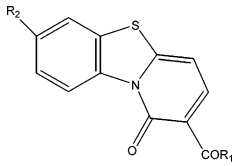
[a] Data points not included in equation derivation.

Table 11. K_i Affinity of Imidazo[1,5-*a*][1,4]benzodiazepines[56] for the DS-Type Benzodiazepine Receptor: Compounds and Physicochemical Parameters for Derivation of Equation 15

no.	substituents R_3, R_8	obsd log $1/K_I$	calcd log $1/K_i$	Δlog $1/K_i$	L_{R_3}	I_{Cl}
1	$R_3 = C_2H_5$, $R_8 = N_3$	8.276	8.809	−0.533	4.11	0
2	$R_3 = C_2H_5$, $R_8 = F$	9.097	8.809	0.288	4.11	0
3	$R_3 = CH_3$, $R_8 = F$	8.509	8.345	0.163	2.87	0
4	$R_3 = CH_3$, $R_8 = H$	8.201	8.345	−0.145	2.87	0
5	$R_3 = C_2H_5$, $R_8 = H$	8.886	8.809	0.077	4.11	0
6	$R_3 = C(CH_3)_3$, $R_8 = H$	8.959	8.809	0.150	4.11	0
7	$R_3 = CH_3$, $R_8 = Cl$	7.526	7.615	−0.089	2.87	1
8	$R_3 = C_2H_5$, $R_8 = Cl$	8.268	8.978	0.189	4.11	1
9	$R_3 = C_3H_7$, $R_8 = Cl$	7.606	7.858	−0.253	4.92	1
10	$R_3 = CH(CH_3)_2$, $R_8 = Cl$	7.979	8.078	−0.099	4.11	1
11	$R_3 = CH_2$-cyclopropane, $R_8 = Cl$	8.013	7.727	0.286	5.14	1
12	$R_3 = C(CH_3)_3$, $R_8 = Cl$	8.398	8.078	0.320	4.11	1
13	$R_3 = CH(C_2H_5)_2$, $R_8 = Cl$	7.570	7.951	−0.381	4.72	1
14[a]	$R_3 = CH_2C(CH_3)_3$, $R_8 = Cl$	6.302	7.874	−1.572	4.89	1
15	$R_3 = CH_2CH_2C(CH_3)_3$, $R_8 = Cl$	6.735	6.708	0.027	6.17	1

[a] Data point not included in equation derivation.

3.10. 4*H*-Pyrimidino[2,1-*b*]benzothiazol-4-ones



In an attempt to discover novel BzR ligands with potential anxiolytic activity, Trapani et al.[55] synthesized and tested some 4*H*-pyrimidino[2,1-*b*]benzothiazol-4-ones (Table 10). Their IC_{50} values (concentration necessary for 50% inhibition of specific [^{3}H]-diazepam binding) were correlated with $\Sigma\sigma$ and MR_{R_2} in QSAR 14.

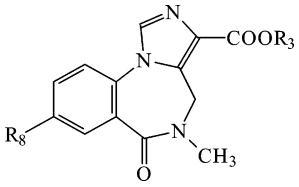
$$\log 1/IC_{50} = -0.681\ (\pm 0.539)MR_{R_2} - 1.464\ (\pm 0.585)\Sigma\sigma + 6.307\ (\pm 0.169) \quad (14)$$

$n = 10$ $r^2 = 0.919$ $q^2 = 0.829$ $s = 0.142$, $F_{2,7} = 39.825$ $\alpha = 0.01$

MR_{R_2} is the more significant parameter. Fifty-one percent of the variance in the data can be explained by the steric factor MR. The negative MR term suggests that fit to a macromolecule of limited steric capacity is important. R substituents receive no parametrization,yet they are well fit by eq 14. $\Sigma\sigma$ for R_1, R_2, R_3, and R_4 substituents on the benzo-thiazolyl ring seems to imply a significant role for electron-attracting groups and accounts for the remaining 41%. Compound **4** and the congener with the higher activity, compound *7* (Table 10), were omitted from the derivation of eq 14.

To probe the requirements for selective high-affinity binding to the diazepam-insensitive (DI) isoform of the benzodiazepine receptor, the affinities of 47 BDZs have been determined at both DI and diazepam-sensitive (DS) BzR.[56] 3D-QSAR analyses were carried out on ligand affinities at both BzR isoforms, and some CoMFA regression equations and maps have been derived. From these data (Tables 11−14) we formulated QSAR 15.

3.11. 5,6-Dihydro-5-methyl-6-oxo-4*H*-imidazo-[1,5-α][1,4]benzodiazepine-3-carboxylic Acid Derivatives



For 15 5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic acid derivatives, the K_i affinities (Table 11) for the DS benzodiazepine receptor were correlated with the sterimol parameter L_{R_3} (for the length of the substituent), in a parabolic approach. I_{Cl} is an indicator variable assigning the value 1/0 for the presence/absence of R_8 = Cl. It is

Table 12. K_i Affinity of Imidazo[1,5-*a*][1,4]benzodiazepines[57] for the DI-Type Benzodiazepine Receptor: Compounds and Physicochemical Parameters for Derivation of Equation 16

no.	substituents R_3, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_I$	Clog *P*
1[a]	$R_3 = C_2H_5$, $R_8 = N_3$	8.50	7.65	0.85	2.0
2	$R_3 = C_2H_5$, $R_8 = F$	7.24	7.17	0.06	1.29
3	$R_3 = CH_3$, $R_8 = F$	6.622	6.32	0.30	0.76
4	$R_3 = CH_3$, $R_8 = H$	5.85	5.92	−0.07	0.58
5	$R_3 = C_2H_5$, $R_8 = H$	6.67	6.92	−0.25	1.01
6	$R_3 = C(CH_3)_3$, $R_8 = H$	7.67	7.60	0.07	1.81
7	$R_3 = CH_3$, $R_8 = Cl$	6.91	7.22	−0.31	1.33
8	$R_3 = C_2H_5$, $R_8 = Cl$	7.77	7.62	0.15	1.86
9	$R_3 = C_3H_7$, $R_8 = Cl$	7.48	7.60	−0.12	2.39
10	$R_3 = CH(CH_3)_2$, $R_8 = Cl$	8.06	7.66	0.40	2.17
11	$R_3 = CH_2$-cyclopropane, $R_8 = Cl$	7.40	7.63	−0.23	2.31
12[a]	$R_3 = C(CH_3)_3$, $R_8 = Cl$	8.77	7.49	1.28	2.57
13	$R_3 = CH(C_2H_5)_2$, $R_8 = Cl$	6.12	6.69	0.22	3.23
14	$R_3 = CH_2C(CH_3)_3$, $R_8 = Cl$	6.52	6.76	−0.24	3.19

[a] Data points not included in equation derivation.

the most important term and has some lowering effect. The importance of position 7 (here R_8) recalls previous observations.[2,4] Actually, only Cl was used at this point so $I_{Cl} = 1/0$ for Cl/H. Compounds **2** and **3** have a F atom at the 8-position. For them indicator I_{Cl} takes a value of zero. However, both compounds fit well by eq 15.

$$\log 1/K_i = 2.571\ (\pm 1.420)L_{R_3} - 0.315\ (\pm 0.164)L_{R_3}^{\ 2} - 0.731\ (\pm 0.406)I_{Cl} + 3.560\ (\pm 3.021) \quad (15)$$

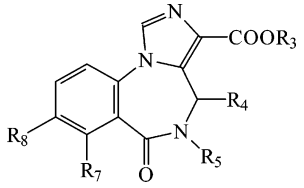
$n = 14$ $r^2 = 0.835$ $q^2 = 0.726$ $s = 0.298$ $F_{3,10} = 16.84$ $\alpha = 0.01$

L_{R3} optimum = 4.084 (± 0.294) from 3.566 to 4.456

No correlation with a hydrophobic factor was found. The L_{R_3}, I_{Cl}, and Clog *P* are significantly collinear.

Again, we find in a QSAR analysis of data that little attention has been given to experimental design, so that collinearity problems confound a clear interpretation of the data. In terms of r^2 we found it necessary to omit one data point (compound **14**, Table 11).

3.12. Imidazo[1,4-α][1,4]benzodiazepine-3-carboxylic Acid Derivatives



A QSAR analysis was carried out on ligand affinities at the DI site[57] (Table 12). Parabolic dependence

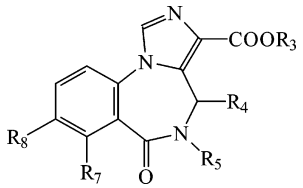
$$\log 1/K_i = 3.166\ (\pm 0.989)\ \text{Clog}\ P - 0.755\ (\pm 0.251)\ \text{Clog}\ P^2 + 4.342\ (\pm 0.866) \quad (16)$$

$n = 12$ $r^2 = 0.857$ $q^2 = 0.731$ $s = 0.263$ $F_{2,9} = 26.97$ $\alpha = 0.01$

optimum value of lipophilicity: Clog P_o = 2.096 (±0.186) from 1.959 to 2.774

of Clog P_o provides an optimum hydrophobicity of 1.467, which is close to log P_o of ∼2.5, the ideal log P_o value for CNS penetration. No role for an electronic factor was found. The two outliers—compounds **1** and **12**—not included in this analysis are marked in Table 12. Compound **1** has a N_3 group as substituent at R_8 position.

3.13. Imidazo-benzodiazepinecarboxylic Acid Derivatives



In Tables 13 and 14 are presented some more imidazo-benzodiazepine carboxylic acid derivatives.[57] Their affinity K_i values for the DS and DI benzodiazepine receptor are listed along with the essential parameters used to formulate eq 17.

$$\log 1/K_i\ (\text{DS}) = -1.020\ (\pm 0.500)\ \text{Clog}\ P + 2.328\ (\pm 0.773)B_{1-R_7} + 7.061\ (\pm 1.449) \quad (17)$$

$n = 13$ $r^2 = 0.868$ $q^2 = 0.776$ $s = 0.498$ $F_{2,10} = 32.98$ $\alpha = 0.01$

The most important term is the hydrophobicity (lipophilicity with a negative sign). No effect of the electronic factor was found. The B_{1-R_7} term (the sterimol smallest width) appears to confirm a positive steric effect for R_7 substituents. This is in accordance with previous findings,[4] as we have already mentioned. Compound **7** is excluded (with the higher Clog *P* value, 2.56).

3.14. Imidazo-benzodiazepinecarboxylic Acid Derivatives

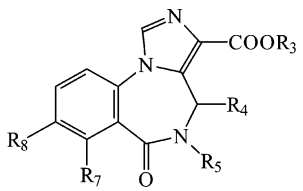


Table 13. K_i Affinity of Imidazo[1,5-*a*][1,4]benzodiazepines[57] for the DS-Type Benzodiazepine Receptor: Compounds and Physicochemical Parameters for Derivation of Equation 17

no.	substituents R_3, R_4-R_5, R_7, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	Clog *P*	B_{1-R_7}
1	$R_3 = CH_2$-cyclopropane, $R_4-R_5 = -CH_2CH_2-$, R_7 = 7-Cl, R_8 = H	10.00	9.707	0.293	1.470	1.800
2	$R_3 = C_2H_5$, $R_4-R_5 = -CH_2CH_2-$, R_7 = 7-Cl, R_8 = H	9.699	10.160	−0.461	1.026	1.800
3	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2-$, R_7 = 7-Cl, R_8 = H	8.959	9.438	−0.479	1.734	1.800
4	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2-$, R_7 = H R_8 = 8-F	8.745	8.157	0.588	1.164	1.000
5	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = 7-Br, R_8 = H	9.301	9.064	0.237	2.443	1.950
6	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = 7-OCH_3, R_8 = H	8.292	8.373	−0.080	1.751	1.350
7[a]	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = 7-C_2H_5, R_8 = H	9.000	7.936	1.064	2.567	1.520
8	$R_3 = C_2H_5$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = 7-Cl, R_8 = H	9.699	9.590	0.109	1.585	1.800
9	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = 7-Cl, R_8 = 8-F	9.000	8.709	0.291	2.448	1.800
10	$R_3 = C_2H_5$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_8 = 8-Cl, R_7 = H	7.139	7.727	−0.588	1.585	1.800
11	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_8 = 8-Cl, R_7 = H	7.186	7.005	0.180	2.293	1.000
12	R_3 = cyclo-C_6H_{11}, $R_4-R_5 = -CH_2CH_2CH_2-$, R_8 = 8-Cl, R_7 = H	6.408	6.196	0.212	3.087	1.000
13	$R_3 = CH_2$-cyclopropane, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = H, R_8 = 8-Cl	6.423	7.275	−0.852	2.029	1.000
14	$R_3 = C_2H_5$, $R_4-R_5 = -CH_2CH_2CH_2-$ (S), R_7 = H, R_8 = H	9.046	8.496	0.549	0.831	1.000

[a] Data point not included in equation derivation.

Table 14. K_i Affinity of Imidazo[1,5-*a*][1,4]benzodiazepines[57] for the DI-Type Benzodiazepine Receptor: Compounds and Physicochemical Parameters for Derivation of Equations 18 and 19

no.	substituents R_3, R_4-R_5, R_7, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	MgVol	B_{1-R_3}	B_{5-R_7}
1	$R_3 = CH_2$-cyclopropane, $R_4-R_5 = -CH_2CH_2-$, R_7 = 7-Cl, R_8 = H	7.260	7.097	0.162	2.399	1.52	1.80
2	$R_3 = C_2H_5$, $R_4-R_5 = -CH_2CH_2-$, R_7 = 7-Cl, R_8 = H	7.469	7.387	0.081	2.225	1.52	1.80
3	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2-$, R_7 = 7-Cl, R_8 = H	7.824	7.542	0.282	2.507	2.60	1.80
4	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2-$, R_8 = 8-F, R_7 = H	7.772	7.909	−0.137	2.403	2.60	1.00
5[a]	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = 7-Br, R_8 = H	8.000	7.182	0.818	2.701	2.60	1.95
6	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = 7-OCH_3, R_8 = H	6.586	6.872	−0.286	2.725	2.60	3.07
7	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = 7-C_2H_5, R_8 = H	6.786	6.711	0.075	2.808	2.60	3.17
8	$R_3 = C_2H_5$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = 7-Cl, R_8 = H	7.162	7.152	0.011	2.366	1.52	1.80
9[a]	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_7 = 7-Cl, R_8 = 8-F	7.627	7.276	0.351	2.666	2.60	1.80
10	$R_3 = C_2H_5$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_8 = 8-Cl, R_8 = H	7.269	7.343	−0.074	2.366	1.52	1.00
11	$R_3 = C(CH_3)_3$, $R_4-R_5 = -CH_2CH_2CH_2-$, R_8 = 8-Cl, R_7 = H	7.572	7.498	0.074	2.648	2.60	1.00
12	R_3 = cyclo-C_6H_{11}, $R_4-R_5 = -CH_2CH_2CH_2-$, R_8 = 8-Cl, R_7 = H	6.783	6.808	−0.025	2.821	1.91	1.00
13	$R_3 = CH_2$-cyclopropane, $R_4-R_5 = -CH_2CH_2CH_2-$, R_8 = 8-Cl, R_7 = H	7.092	7.053	0.038	2.540	1.52	1.00
14	$R_3 = C_2H_5$, $R_4-R_5 = -CH_2CH_2CH_2-$ (S), R_7 = H, R_8 = H	7.346	7.548	−0.202	2.244	1.52	1.00

[a] Data points not included in equation derivation.

In continuation, eq 18 was derived from the data[57] in Table 14.

$$\log 1/K_i = -1.764\ (\pm 0.798)\mathrm{MgVol} + 0.580\ (\pm 0.306)B_{1-R_3} - 0.24\ (\pm 0.18)B_{5-R_7} + 10.663\ (\pm 1.687) \quad (18)$$

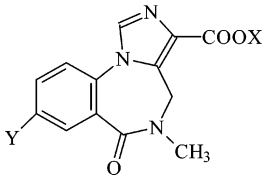
$n = 12 \quad r^2 = 0.837 \quad q^2 = 0.627 \quad s = 0.185 \quad F_{3,8} = 13.65 \quad \alpha = 0.01$

The number of data points is small (12). Compounds **5** and **9** are not included in these analyses. MgVol is the most important parameter following the sterimol parameters B_{1-R_3} and B_{5-R_7} for the corresponding R_3 and R_7 substituents. B_{1-R_3} has a positive effect on the activity, whereas B_{5-R_7} has a negative one. No correlation with a hydrophobic parameter was found. MgVol expresses the calculated molar volume according to Abraham and McGowan and has sometimes been used lately instead of MR as an alternative theoretically assessible bulk factor. Thus, the negative MgVol brings out a steric problem. The correlation matrix for MgVol versus Clog *P*, $r^2 = 0.913$, MgVol versus MR, $r^2 = 0.985$, indicates a collinearity problem. Attempts to develop a better equation using the sterimol parameter B_{5-R_8} led to correlation (QSAR 19). Two data points were omitted (12 and 14). The foregoing results support the role of MgVol as an alternative theoretically assessible bulk factor.

$$\log 1/K_i = 0.438\ (\pm 0.280)\mathrm{B}_{1-R_3} - 0.77\ (\pm 0.302)B_{5-R_7} - 1.006\ (\pm 0.607)B_{5-R_8} + 9.051\ (\pm 1.222) \quad (19)$$

$n = 12 \quad r^2 = 0.824 \quad q^2 = 0.610 \quad s = 0.208 F_{3,8} = 13.645 \quad \alpha = 0.01$

3.15. Imidazo[1,5-α][1,4]benzodiazepine Esters



For another series of imidazo [1,5-α][1,4]benzodiazepine[57] esters (Table 15) with high affinities and selectivities at DI and DS benzodiazepine receptors, the following QSARs were derived. Their binding affinities K_i at DI BzR in vitro (cerebella or cortices homogenate from adult male Sprague−Dawley rats) were correlated with Clog *P* values.

Table 15. K_i Binding Affinities of Imidazo[1,5-α][1,4]benzodiazepine Esters on the DI-Type Benzodiazepine Receptor:[57] Compounds and Physicochemical Parameters for Derivation of Equation 20

no.	X, Y	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	Clog P
1	X = C_2H_5, Y = H	6.670	6.649	0.021	0.477
2	X = C_2H_5, Y = Cl	7.772	7.625	0.147	1.231
3	X = $C(CH_3)_3$, Y = H	7.674	7.596	0.078	1.185
4[a]	X = $C(CH_3)_3$, Y = Cl	8.770	7.564	1.206	1.939
5	X = CH_3, Y = Cl	6.908	7.052	−0.114	0.702
6	X = C_3H_7, Y = Cl	7.478	7.669	−0.191	1.760
7	X = $CH(CH_3)_2$, Y = Cl	8.056	7.715	0.341	1.540
8	X = CH_2-cy-C_3H_5, Y = Cl	7.400	7.697	−0.297	1.675
9	X = $CH(C_2H_5)_2$, Y = Cl	6.912	6.655	−0.256	2.598
10	X = $CH_2C(CH_3)_3$, Y = Cl	6.523	6.734	−0.211	2.558

[a] Data point not included in equation derivation.

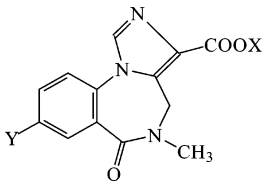
$$\log 1/K_i\ (\mathrm{DI}) = 2.909\ (\pm 1.440)\ \mathrm{Clog}\ P - 0.945\ (\pm 0.422)\ \mathrm{Clog}\ P^2 + 5.476\ (\pm 1.043) \quad (20)$$

$n = 9 \quad r^2 = 0.824 \quad q^2 = 0.592 \quad s = 0.258 \quad F_{2,6} = 14.075 \quad \alpha = 0.01$

optimum lipophilicity value: Clog P_o = 1.539 (± 0.174) from 1.339 to 1.710

Equation 20 gave a good correlation between observed and calculated K_i values, the greatest deviation being noted for the 8-Cl-substituted *tert*-butyl derivative (compound **4**, Table 15). It is the most active in the set.

3.16. Imidazo[1,5-α][1,4]benzodiazepine Esters



Adding some more derivatives in the previous set (congeners containing X = *tert*-butyl group), QSAR 21 is derived (Table 16).[57]

$$\log 1/K_i = 2.236\ (\pm 1.598)\ \mathrm{Clog}\ P - 0.723\ (\pm 0.469)\ \mathrm{Clog}\ P^2 + 1.692\ (\pm 0.591) I_{t-butyl} + 5.918\ (\pm 1.217) \quad (21)$$

$n = 14 \quad r^2 = 0.879 \quad q^2 = 0.749 \quad s = 0.358 \quad F_{3,10} = 17.33 \quad \alpha = 0.01$

optimum value of lipophilicity: Clog P_o = 1.546 (±0.301) from 1.111 to 1.818

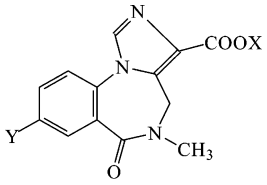
The indicator variable $I_{t-butyl}$ applies to *tert*-butyl-substituted derivatives (compounds **3**, **4**, and **11**−**16**, Table 16). The positive coefficient with $I_{t-butyl}$ means that the presence of a *tert*-butyl group is correlated with more effective displacement. In this case, four outliers were found (compounds **3**, **14**, **15**, and **17**; all had a *tert*-butyl group in the X substituent). Rejecting all of the *tert*-butyl congeners, eq 22 is derived from the rest of the compounds.

$$\log 1/K_i = 3.38\ (\pm 2.062)\ \mathrm{Clog}\ P_o - 1.114\ (\pm 0.630)\ \mathrm{Clog}\ P^2 + 5.344\ (\pm 1.508) \quad (22)$$

$n = 10 \quad r^2 = 0.726 \quad q^2 = 0.494 \quad s = 0.390 \quad F_{2,7} = 9.238 \quad \alpha = 0.01$

optimum value of lipophilicity: Clog P_o = 1.517 (±0.166) from 1.23 to 1.727

3.17. Imidazo-benzodiazepinecarboxylic Acid Derivatives



Their effect as K_i binding affinities (Table 17) at DS BzR in vitro was correlated with MgVol and sterimol factor B_{1-X} (for the alkyl group X of the ester moiety) in QSARs 23.

Table 16. K_i Binding Affinities of Imidazo[1,5-α][1,4]benzodiazepine Esters on the DS-Type Benzodiazepine Receptor:[57] Compounds and Physicochemical Parameters for Derivation of Equations 21 and 22

no.	X, Y	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	$I_{t-butyl}$	Clog P
1	X = C_2H_5, Y = H	6.670	6.821	−0.150	0	0.477
2	X = C_2H_5, Y = Cl	7.772	7.575	0.197	0	1.231
3[a]	X = $C(CH_3)_3$, Y = H	7.674	5.244	2.430	1	1.185
4	X = $C(CH_3)_3$, Y = Cl	8.770	5.227	3.543	1	1.939
5	X = CH_3, Y = Cl	6.908	7.132	−0.224	0	0.702
6	X = C_3H_7, Y = Cl	7.478	7.614	−0.136	0	1.760
7	X = $CH(CH_3)_2$, Y = Cl	8.056	7.647	0.409	0	1.540
8	X = CH_2-cy-C_3H_5, Y = Cl	7.400	7.635	0.235	0	1.675
9	X = $CH(C_2H_5)_2$, Y = Cl	6.912	6.847	0.005	0	2.598
10	X = $CH_2C(CH_3)_3$, Y = Cl	6.523	6.907	−0.384	0	2.558
11	X = $C(CH_3)_3$, Y = Cl	8.760	8.883	−0.123	1	2.340
12	X = $C(CH_3)_3$, Y = Br	8.550	8.695	−0.145	1	2.490
13	X = $C(CH_3)_3$, Y = I	8.820	8.291	0.529	1	2.750
14*	X = $C(CH_3)_3$, Y = NO_2	7.960	9.332	−1.372	1	1.450
15*	X = $C(CH_3)_3$, Y = NCS	8.568	7.397	1.171	1	3.210
16	X = $C(CH_3)_3$, Y = N_3	9.366	9.169	0.197	1	2.030
17*	X = C_2H_5, Y = N_3	8.508	7.610	0.898	0	1.320
18	X = C_2H_5, Y = F	7.936	7.476	0.476	0	1.060

[a] Data points not included in equation derivation.

Table 17. K_i Binding Affinities of Imidazo[1,5-α][1,4]benzodiazepine Esters on the DS-Type Benzodiazepine Receptor:[57] Compounds and Physicochemical Parameters for Derivation of Equation 23

no.	X, Y	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	MgVol	B_{1-X}
1	X = C_2H_5, Y = H	8.886	8.715	0.171	2.071	1.52
2	X = C_2H_5, Y = Cl	8.268	8.293	−0.026	2.193	1.52
3	X = $C(CH_3)_3$, Y = H	8.959	8.876	0.083	2.353	2.60
4	X = $C(CH_3)_3$, Y = Cl	8.398	8.454	−0.056	2.475	2.60
5[a]	X = CH_3, Y = Cl	7.526	8.779	−1.253	2.052	1.52
6	X = C_3H_7, Y = Cl	7.606	7.808	−0.203	2.334	1.52
7	X = $CH(CH_3)_2$, Y = Cl	7.979	8.206	−0.227	2.334	1.90
8	X = CH_2-cy-C_3H_5, Y = Cl	8.013	7.697	0.316	2.366	1.52
9	X = $CH(C_2H_5)_2$, Y = Cl	7.570	7.476	0.094	2.616	2.13
10	X = $CH_2C(CH_3)_3$, Y = Cl	6.302	6.837	−0.536	2.616	1.52
11[a]	X = CH_3, Y = H	8.200	9.201	−1.001	1.930	1.52
12	X = $(CH_2)_2C(CH_3)_3$, Y = Cl	6.735	6.352	0.383	2.757	1.52

[a] Data points not included in equation derivation.

Table 18. IC_{50} Inhibition Values of [^{3}H]Flunitrazepam Binding to Benzodiazepine Receptors by 5-Furyl- and 5-Thienyl-Substituted Benzodiazepines:[58] Compounds and Physicochemical Parameters for Derivation of Equation 24

no.	substituents R_1, R_2, X	obsd log $1/IC_{50}$	calcd log $1/IC_{50}$	Δlog $1/IC_{50}$	MR_{R_2}	B_{5-7}
1	R_1 = H, R_2 = 5-(2-thienyl), X = 7-Cl	7.553	7.700	−0.147	2.404	1.800
2	R_1 = H, R_2 = 5-(2-furyl), X = 7-Cl	6.573	6.535	0.039	1.788	1.800
3	R_1 = H, R_2 = 5-(2-thienyl), X = 7-F	6.886	7.010	−0.124	2.404	1.350
4[a]	R_1 = H, R_2 = 5-(3-thienyl), X = 7-Cl	6.854	7.700	−0.846	2.404	1.800
5[a]	R_1 = H, R_2 = 5-(2-thienyl), 4-Br, X = 7-Cl	6.335	9.33	−3.05	3.267	1.800
6	R_1 = CH_3, R_2 = 5-(2-thienyl), X = 7-Cl	7.745	7.700	0.045	2.404	1.800
7	R_1 = CH_3, R_2 = 5-(2-furyl), X = 7-Cl	6.570	6.535	0.036	1.788	1.800
8	R_1 = CH_3, R_2 = 5-(2-thienyl), X = 7-F	7.137	7.010	0.126	2.404	1.350
9	R_1 = CH_3, R_2 = 5-(3-thienyl), X = 7-Cl	6.959	7.700	−0.741	2.404	1.800
10	R_1 = H, R_2 = 5-C_6H_5, X = 7-Cl	8.027	7.949	0.077	2.536	1.800
11	R_1 = CH_3, R_2 = 5-C_6H_5, X = 7-Cl	8.092	7.949	0.142	2.536	1.800
12	R_1 = H, R_2 = 5-(2-ClC_6H_4), X = 7-Cl	8.745	8.895	−0.150	3.036	1.800
13	R_1 = H, R_2 = 5-(2-FC_6H_4), X = 7-Cl	8.699	8.008	0.691	2.567	1.800
14	R_1 = H, R_2 = 5-(2-pyridyl), X = 7-Br	7.745	7.738	0.006	2.303	1.950

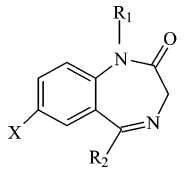
[a] Data point not included in equation derivation.

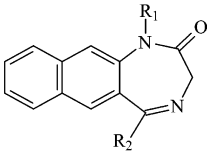
$$\log 1/K_i\ (\mathrm{DS}) = -3.445\ (\pm 1.187)\mathrm{MgVol} + 1.048\ (\pm 0.548)B_{1-X} + 14.257\ (\pm 2.928) \quad (23)$$

$n = 10$ $r^2 = 0.896$ $q^2 = 0.767$ $s = 0.311$ $F_{2,7} = 30.69$ $\alpha = 0.01$

Two points were rejected from the derivation of this correlation (compounds **5** and **11**). Both are methyl esters, and these results demonstrate that as the smallest width of the ester side chain increased DS affinities increased, too. No effect of the electronic factor was found. For this set and for the DS binding affinities the MgVol parameter is found to replace the hydrophobic effect (MgVol versus Clog P, r^2 = 0.973).

3.18. Substituted 5-Thienyl and 5-Furyl Benzodiazepines





For 14 substituted 5-thienyl and 5-furyl benzodiazepines,[58] which displace [^{3}H]flunitrazepam from BzR in vitro, the IC_{50} values (Table 18) were used to derive eq 24:

$$\log 1/K_i = 1.891\ (\pm 0.726)\mathrm{MR}_{R_2} + 1.532\ (\pm 1.303)B_{5-7} - 0.395\ (\pm 2.922) \quad (24)$$

$n = 12$ $r^2 = 0.817$ $q^2 = 0.751$ $s = 0.355$ $F_{2,9} = 20.196$ $\alpha = 0.01$

Two data points (compounds **4** and **5**) were rejected from the development of eq 24. We had expected that an electronic term would be needed for 7-substituents (X). We could find no role for σ or F in eq 24. The highly significant B_{5-7} term points to a steric effect of the first atom of groups in the 7-position. This is in accordance with previous findings.[2] The positive coefficient with B_{5-7} means that the larger the atom attached to the ring, the more effective the binding. MR_5 is the most significant term. Its positive coefficient indicates that the larger R_5 is, the better the binding. The main difficulty of eq 20 is that for the substituents on which it is based, there is a collinearity problem (MR_5 versus π_5, r^2 = 0.721) between π_5 and MR_5, lending uncertainty as to whether interaction is occurring with polar or hydrophobic space. Our previous QSARs on BDZs show that hydrophobic and steric properties are important.

Table 19. IC_{50} Inhibition Values of [^{3}H]Flunitrazepam Binding to Benzodiazepine Receptor by 1-(2-Phenyl-4-quinolinyl)-4(1,2,4-oxadiazoles):[59] Compounds and Physicochemical Parameters for Derivation of Equation 25

no.	substituents X, Y, Z	obsd log $1/IC_{50}$	calcd log $1/IC_{50}$	Δlog $1/IC_{50}$	Clog P	B_{5-Y}
1	X = H, Y = H, Z = NH_2	7.947	8.036	−0.089	3.667	1
2[a]	X = CH_3, Y = H, Z = NH_2	6.893	7.745	−0.762	4.166	1
3	X = Cl, Y = H, Z = NH_2	7.686	7.587	0.099	4.437	1
4[a]	X = H, Y = 2-OCH_3, Z = NH_2	5.974	7.393	−1.419	3.125	3.070
5	X = H, Y = 2-OH, Z = NH_2	7.712	8.040	−0.327	2.921	1.930
6	X = F, Y = 2-OCH_3, Z = NH_2	7.295	7.280	0.015	3.319	3.070
7	X = F, Y = 2-OH, Z = NH_2	8.149	7.293	0.226	3.121	1.930
8	X = F, Y = 4-F, Z = NH_2	8.060	7.833	0.227	4.015	1
9	X = F, Y = 4-Cl, Z = NH_2	7.444	7.502	−0.058	4.585	1
10	X = H, Y = H, Z = OC_2H_5	6.742	6.904	−0.162	5.612	1
11	X = F, Y = 2-OH, Z = OC_2H_5	6.860	6.791	0.069	5.066	1.930

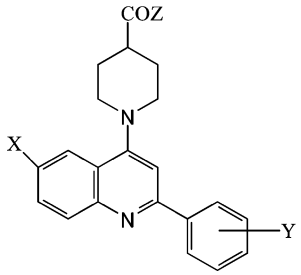
[a] Data points not included in equation derivation.

Table 20. K_i Binding Affinities to Benzodiazepine Receptors (Displacement of [^{3}H]Flunitrazepam) by X-[5,1-C][1,2,4]benzotriazines and 5-Oxide Derivatives:[60] Compounds and Physicochemical Parameters for Derivation of Equation 26

no.	substituents R_3, R_7, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	Clog P	I_{NO}	B_{1-R_3}
1	R_3 = $COOCH_3$, 5-O, R_7 = R_8 = H	6.234	6.223	0.012	0.992	1	1.640
2	R_3 = $COOC_2H_5$, 5-O, R_7 = H, R_8 = CH_3	6.975	7.020	−0.045	2.020	1	1.640
3	R_3 = Br, 5-O, R_7 = H, R_8 = CH_3	7.274	6.902	0.373	2.514	1	1.950
4	R_3 = $COOC_2H_5$, 5-O, R_7 = H, R_8 = Cl	7.456	7.186	0.270	2.234	1	1.640
5	R_3 = Br, 5-O, R_7 = H, R_8 = Cl	6.921	7.068	−0.147	2.729	1	1.950
6	R_3 = CN, 5-O, R_7 = H, R_8 = Cl	6.466	6.433	0.033	1.179	1	1.600
7	R_3 = Br, 5-O, R_7 = H, R_8 = $O(CH_2)_2OC_2H_5$	6.837	6.952	−0.115	2.579	1	1.950
8[a]	R_3 = $COOC_2H_5$, 5-O, R_7 = H, R_8 = $N(C_2H_5)_2$	6.180	7.827	−1.646	3.060	1	1.640
9	R_3 = $COOC_2H_5$, 5-O, R_7 = H, R_8 = SCH_3	7.114	7.350	−0.237	2.445	1	1.640
10	R_3 = Br, 5-O, R_7 = H, R_8 = SCH_3	7.029	7.232	−0.203	2.940	1	1.950
11	R_3 = $COOC_2H_5$, 5-O, R_7 = H, R_8 = OC_2H_5	7.087	7.264	−0.177	2.335	1	1.640
12	R_3 = Br, 5-O, R_7 = H, R_8 = OC_2H_5	7.433	7.146	0.287	2.830	1	1.950
13	R_3 = $COOC_2H_5$, 5-O, R_7 = H, R_8 = OH	6.643	6.717	−0.074	1.629	1	1.640
14	R_3 = Br, 5-O, R_7 = H, R_8 = NH_2	6.268	6.244	0.024	1.667	1	1.950
15	R_3 = $COOCH_3$, R_7 = H, R_8 = H	5.672	5.542	0.130	1.038	0	1.640
16	R_3 = $COOC_2H_5$, R_7 = H, R_8 = Cl	6.551	6.505	0.046	2.281	0	1.640
17	R_3 = Br, R_7 = H, R_8 = SCH_3	6.980	6.641	0.339	3.104	0	1.950
18	R_3 = $COOC_2H_5$, R_7 = H, R_8 = OC_2H_5	6.716	6.678	0.038	2.503	0	1.640
19	R_3 = Br, R_7 = H, R_8 = OC_2H_5	6.321	6.555	−0.234	2.993	0	1.950
20	R_3 = Br, R_7 = H, R_8 = 8-NHCOCH$_3$	5.446	5.765	−0.319	1.974	0	1.950

[a] Data point not included in equation derivation.

3.19. 1-(2-Phenyl-4-quinolyl)-4-(1,2,4-oxadiazoles)



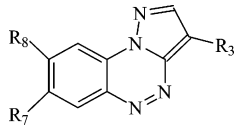
A series of 1-(2-phenyl-4-quinolyl)-4-(1,2,4-oxadiazoles)[59] was tested for their affinity to the BzR using [^{3}H]flunitrazepam as radioligand. The IC_{50} values (Table 19) were used to formulate eq 25.

$$\log 1/IC_{50} = -0.582\ (\pm 0.227)\ \text{Clog}\ P - 0.463\ (\pm 0.283)B_{5-Y_2} + 10.632\ (\pm 1.217) \quad (25)$$

$n = 9$ $r^2 = 0.870$ $q^2 = 0.732$ $s = 0.209$ $F_{2,6} = 20.198$ $\alpha = 0.01$

Two data points are omitted (compounds **2** and **4**, Table 19). They do not contain any unusual substitution moieties. Compound **4** is the least active derivative. Z substituents receive no parametrization, and yet they are well fit by eq 25. The negative coefficient with log P shows that the more hydrophobic the molecle, the higher the affinity to the BzR (the faster the [^{3}H]diazepam displacement from the BzR).

3.20. Pyrazolo-[5,1-*c*]benzotriazines



Several tricyclic heterocycles containing a pyrazole moiety were found to show affinity for the BzR complex. Pyrazolo[5,1-*c*]benzotriazines[60] and their 5-oxides (Table 20) were tested for their ability in vitro to displace [^{3}H]flunitrazepam (at 0.2 nM, K_d = 1.8 nM) from its specific binding in bovine brain membranes. K_i values were correlated with Clog P and I_{NO}, an indicator variable, and the sterimol parameter B_{1-R_3}.

$$\log 1/K_i = 0.776\ (\pm 0.215)\ \text{Clog}\ P + 0.771\ (\pm 0.238)I_{NO} - 1.619\ (\pm 0.864)B_{1-R_3} + 7.392\ (\pm 1.337) \quad (26)$$

$n = 19$ $r^2 = 0.857$ $q^2 = 0.771$ $s = 0.225$ $F_{3,15} = 31.21$ $\alpha = 0.01$

Table 21. IC_{50} Values for Displacement of [^{3}H]Diazepam Binding to Benzodiazepine Receptor by Substituted 6-Alkoxy-imidazo[1,2-*b*]pyridazines:[61] Compounds and Physicochemical Parameters for Derivation of Equation 27

no.	substituents R_1, R_2, R_3	obsd log $1/IC_{50}$	calcd log $1/IC_{50}$	Δlog $1/IC_{50}$	L_{R_1}	MR_{R_2}
1	$R_1 = OCH_3$, R_2 = 3,4-OCH_2O-, $R_3 = H$	8.155	7.911	0.244	3.980	0.900
2	$R_1 = OCH_3$, R_2 = 4-Cl, $R_3 = H$	7.538	7.580	−0.043	3.980	0.603
3	$R_1 = OCH_3$, $R_2 = H$, R_3 = 2-F	6.857	7.024	−0.167	3.980	0.103
4	$R_1 = OCH_3$, R_2 = 4-CH_3, R_3 = 2-F	7.678	7.538	0.140	3.980	0.565
5	$R_1 = OCH_3$, R_2 = 3,4-OCH_2O-, R_3 = 2-F	7.854	7.911	−0.057	3.980	0.900
6	$R_1 = OC_2H_5$, $R_2 = H$, $R_3 = H$	6.733	6.754	−0.021	4.800	0.103
7	$R_1 = OC_2H_5$, R_2 = 4-CH_3, $R_3 = H$	7.456	7.268	0.188	4.800	0.565
8	$R_1 = OC_2H_5$, R_2 = 3,4-OCH_2O-, $R_3 = H$	7.602	7.229	0.373	6.050	0.900
9	$R_1 = OC_2H_5$, R_2 = 4-Cl, $R_3 = H$	7.194	7.310	−0.116	4.800	0.603
10	$R_1 = OC_2H_5$, $R_2 = H$, R_3 = 2-F	6.682	6.754	−0.072	4.800	0.103
11	$R_1 = OC_2H_5$, R_2 = 4-CH_3, R_3 = 2-F	7.292	7.268	0.025	4.800	0.565
12	$R_1 = OC_2H_5$, R_2 = 3,4-OCH_2O-, R_3 = 2-F	7.509	7.641	−0.132	4.800	0.900
13	$R_1 = OC_3H_7$, R_2 = 4-CH_3, $R_3 = H$	6.742	6.856	−0.114	6.050	0.565
14	$R_1 = OC_3H_7$, R_2 = 3,4-OCH_2O-, $R_3 = H$	6.936	7.229	−0.293	6.050	0.900
15	$R_1 = OC_3H_7$, $R_2 = H$, R_3 = 2-F	6.623	6.342	0.282	6.050	0.103
16	$R_1 = OC_3H_7$, R_2 = 4-CH_3, R_3 = 2-F	6.845	6.856	−0.011	6.050	0.565
17	$R_1 = O(CH_2)_2OCH_3$, R_2 = 4-CH_3, R_3 = 2-F	6.498	6.639	−0.141	6.710	0.565
18	$R_1 = OCH_3$, R_2 = 3,4-OCH_2O-, R_3 = 3-NO_2	8.097	7.911	0.186	3.980	0.900
19	$R_1 = OCH_3$, R_2 = 3,4-OCH_2O-, R_3 = 4-NO_2	7.638	7.911	−0.272	3.980	0.900

Linear Clog *P* is the more significant model. I_{NO} is an indicator variable assigning the value 1/0 for the presence/absence of a N-5-O. From the positive sign of I_{NO} it is assumed that the presence of *N*-oxide is favorable for the activity. The parameter B_{1-R_3} represents the smallest width of the first atom. The smaller the substituent, the better the binding. Equation 26 gave good correlation between observed and calculated K_i values, the greatest deviation being noted for the 8-diethylamino derivative (compound **8**, Table 20). It should be noted that no parametrization has been made for congeners having a substituent in position 7/8 of the ring. However, all derivatives do fit well, indicating that they contact a hydrophobic space of the receptor.

3.21. 3-Substituted Imidazo[1,2-*b*]pyridazines

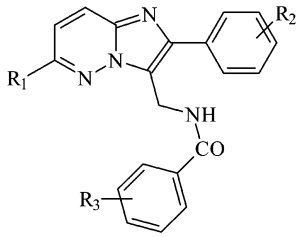


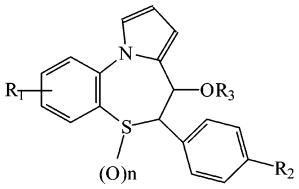
Table 21 contains the in vitro BzR affinities (displacement of [^{3}H]diazepam in rat brain membranes cortex) of some 3-substituted imidazo[1,2-*b*]pyridazines.[61] From these data eq 27 was derived.

$$\log 1/IC_{50} = -0.329\ (\pm 0.106)L_{R_1} + 1.113\ (\pm 0.333)MR_{R_2} + 8.220\ (\pm 0.588) \quad (27)$$

$n = 19$ $r^2 = 0.868$ $q^2 = 0.798$ $s = 0.199$ $F_{2,16} = 52.57$ $\alpha = 0.01$

Equation 27 seems strange because it contains no π or Clog *P* term. MR_{R_2} refers to substituents in position 4. Addition of a term in π does not improve the result. Thus, one assumes contact is occurring with polar space. The coefficient with L_{R_1} is negative, suggesting that the relatively high affinities are related with a low steric effect of R_1. No parametrization was made for R_3 (two to three substituents). However, they all do fit eq 27 well.

3.22. 6-Aryl-pyrrolo[2,1-*d*][1,5]benzothiazepines



A set of 6-aryl-pyrrolo[2,1-*d*][1,5]benzothiazepines[62−64] (Table 22) tested as selective ligands of the mitochondrial benzodiazepine MBR receptor have been investigated using the comparative field analysis (CoMFA) approach. The results from the 3D-QSAR studies rationalize the steric and electronic factors that modulate affinity to the MBR. We tried to correlate the IC_{50} values (affinity values for [^{3}H]-PK 11195 binding inhibition) and obtained eq 28.

$$\log 1/IC_{50} = -0.705\ (\pm 0.27)L_{R_1} - 2.952\ (\pm 0.504)I_{ring} + 9.005\ (\pm 0.726) \quad (28)$$

$n = 30$ $r^2 = 0.870$ $q^2 = 0.836$ $s = 0.501$ $F_{2,26} = 274.114$ $\alpha = 0.01$

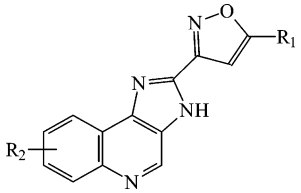
We were not able to formulate a QSAR with lipophilicity as Clog *P* or π. L_{R_1} is the sterimol parameter for the length of the first atom of substituent R_1. I_{ring} is an indicator variable assigning the value 1/0 for the presence/absence of a ring as an R_3 substituent in position C_7. From the negative sign, it is assumed that the absence of the ring is favorable for the activity. I_{ring} provides no information as to which property of the substituent is the most important for the increase in the activity. No collinearity problems were found between the parameters used in the equation (I_{ring} versus $L_{R_1} = 0.012$). We had expected that an electronic term would be needed for R_1 substituents. Unfortunately, the compounds included in this set contain rather little variation in

Table 22. IC_{50} Values of the 6-Arylpyrrolo[2,1-*d*][1,5]benzothiazepines[62−64] To Displace the Specific Binding of [^{3}H]PK 11195 by 50%: Compounds and Physicochemical Parameters for Derivation of Equation 28

no.	R_1, R_2, R_3	obsd log $1/IC_{50}$	calcd log $1/IC_{50}$	Δlog $1/IC_{50}$	L_{R_1} for position 2	I_{ring}
1	$R_1 = R_2 = H$, $R_3 = SO_2CH_3$	7.240	7.378	−0.138	2.060	0
2	$R_1 = R_2 = H$, $R_3 = COCH_3$	7.710	7.378	0.332	2.060	0
3	$R_1 = R_2 = H$, $R_3 = COC_2H_5$	7.180	7.378	−0.198	2.060	0
4	$R_1 = R_2 = H$, $R_3 = COC_3H_7$	7.670	7.378	0.292	2.060	0
5	$R_1 = R_2 = H$, $R_3 = COC_4H_9$	7.320	7.378	0.058	2.060	0
6	$R_1 = R_2 = H$, $R_3 = COC_5H_{11}$	7.630	7.378	0.252	2.060	0
7	$R_1 = R_2 = H$, $R_3 = CON(CH_3)_2$	8.040	7.378	0.662	2.060	0
8	$R_1 = H$, $R_2 = OCH_3$, $R_3 = COC_3H_7$	7.560	7.378	0.182	2.060	0
9	$R_1 = 2\text{-}CF_3$, $R_2 = OCH_3$, $R_3 = COCH_3$	5.340	6.399	−1.059	3.300	0
10	$R_1 = 2\text{-}CF_3$, $R_2 = OCH_3$, $R_3 = COC_2H_5$	5.530	6.399	−0.869	3.300	0
11	$R_1 = 2\text{-}CF_3$, $R_2 = OCH_3$, $R_3 = CON(CH_3)_2$	6.530	6.399	0.131	3.300	0
12	$R_1 = 2\text{-}CF_3$, $R_2 = OCH_3$, $R_3 = COC_6H_2$−(3,4,5-OCH_3)	4.000	3.447	0.553	3.300	1
13	$R_1 = 2\text{-}Cl$, $R_2 = H$, $R_3 = COCH_3$	6.250	6.226	0.024	3.520	0
14	$R_1 = 2\text{-}Cl$, $R_2 = H$, $R_3 = COC_2H_5$	6.090	6.226	−0.136	3.520	0
15	$R_1 = 2\text{-}Cl$, $R_2 = OCH_3$, $R_3 = COCH_3$	6.190	6.226	−0.036	3.520	0
16	$R_1 = 2\text{-}Cl$, $R_2 = OCH_3$, $R_3 = COC_2H_5$	6.310	6.226	0.084	3.520	0
17	$R_1 = 2\text{-}Cl$, $R_2 = OCH_3$, $R_3 = CON(CH_3)_2$	6.780	6.226	0.554	3.520	0
18	$R_1 = 2\text{-}Cl$, $R_2 = OCH_3$, $R_3 = COC_6H_2$-(3,4,5-OCH_3)	4.000	3.274	0.726	3.520	1
19	$R_1 = 3\text{-}Cl$, $R_2 = H$, $R_3 = COCH_3$	6.640	7.378	−0.738	2.060	0
20	$R_1 = 3\text{-}Cl$, $R_2 = OCH_3$, $R_3 = COCH_3$	6.620	7.378	−0.758	2.060	0
21	$R_1 = 4\text{-}Cl$, $R_2 = H$, $R_3 = COCH_3$	8.120	7.378	0.742	2.060	0
22	$R_1 = 4\text{-}C$, $R_2 = OCH_3$, $R_3 = COCH_3$	7.690	7.378	0.312	3.980	0
23	$R_1 = 2\text{-}OCH_3$, $R_2 = OCH_3$, $R_3 = COCH_3$	5.740	5.862	−0.122	2.060	0
24	$R_1 = H$, $R_2 = OCH_3$, $R_3 = CON(CH_3)_2$	8.040	7.378	0.662	2.060	0
25	$R_1 = H$, $R_2 = OCH_3$, $R_3 = COCH_3$	7.470	7.378	0.092	2.060	0
26	$R_1 = H$, $R_2 = OCH_3$, $R_3 = SO_2CH_3$	7.020	7.378	−0.358	2.060	0
27	$R_1 = H$, $R_2 = OCH_3$, $R_3 =$ CO-3-pyridyl	4.000	4.426	−0.426	2.060	1
28	$R_1 = H$, $R_2 = OCH_3$, $R_3 = COC_6H_2$−(3,4,5-OCH_3)	4.000	4.426	−0.426	2.060	1
29	$R_1 = H$, $R_2 = OCH_3$, $R_3 = COC_2H_5$	7.530	7.378	0.152	2.060	0
30	$R_1 = H$, $R_2 = OCH_3$, $R_3 =$ CO-4-pyridyl	4.000	4.426	−0.426	2.060	1

positions 2−4 (Cl, CF_3, OMe, H). The physicochemical properties for some of them are quite similar. Although no parametrization has been done for substituents R_2 and R_3 (except the I_{ring}), all compounds fit well eq 28.

3.23. 2-Arylimidazo[4,5-*c*]quinoline and Analogue-Fused Imidazopyridines



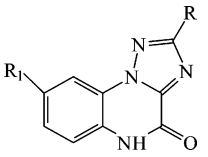
2-Arylimidazo[4,5-*c*]quinoline and analogue-fused imidazopyridines[65,66] (Table 23) were evaluated as benzodiazepine receptor ligands. From the detailed pharmacological evaluation the K_i affinity values concerning the displacement to [^{3}H]diazepam binding in rat cerebral cortex eq 29 is derived.

$$\log 1/K_i = 3.413\ (\pm 0.317)E_{s6} - 1.603\ (\pm 0.418)\ MR_7 + 1.131\ (\pm 0.317)E_{s9} - 0.285\ (\pm 0.176)I_{R_1} - 9.367\ (\pm 0.174) \quad (29)$$

$n = 26$ $r^2 = 0.962$ $q^2 = 0.934$ $s = 0.214$ $F_{4,21} = 131.25$ $\alpha = 0.01$

The indicator variable I_{R_1} for the examples in which an alkyl group is present (R_1 = Me, Et) seems to be important. The E_{s6}, E_{s9}, and MR_7 terms appear to confirm a negative steric effect for the 6-, 9-, and 7-substituents on the phenyl ring. E_s was designed for intramolecular steric effects. Bearing in mind that the more sterically hindering the substituent, the more negative its E_s value, the positive coefficient with the 6- and 9-substituents shows that substitution at positions 6 and 9 makes less effective compounds. Electronic and hydrophobic effects of substituents are negligible.

3.24. 1,2,4-Triazolo[1,2-*a*]quinoxalines



Some 1,2,4-triazolo[1,2-*a*] quinoxalines[67] (Table 24) displayed similar affinities. They were tested for their ability to displace [^{3}H]flunitrazepam (at 0.2 nM) from its specific binding in bovine brain membranes. Equation 30 shows a linear dependence on overall log *P*, which is a significant term. The MR_{R_1} term appears to confirm a negative steric effect for R_1 substituents (H, Cl, Br, Me). We had expected that an electronic term would be needed for R_1 substituents, but this point needs further study, because the range of substituents covered is not great. The fact that log *P* has been used to model hydrophobicity implies that R substituents also have a hydrophobic effect.

$$\log 1/K_i = 0.989\ (\pm 0.386)\ \text{Clog}\ P - 0.361\ (\pm 0.325)MR_{R_1} + 6.221\ (\pm 0.993) \quad (30)$$

$n = 11$ $r^2 = 0.815$ $q^2 = 0.637$ $s = 0.226$ $F_{2,8} = 17.594$ $\alpha = 0.01$

Table 23. K_i Values (Displacing Potential to [^{3}H]Diazepam Binding in Rat Cerebral Cortex) of Fused Imidazopyridines:[65,66] Compounds and Physicochemical Parameters for Derivation of Equation 29

no.	R_1, R_2	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	E_{S6}	MR_7	E_{S9}	I_{R_1}
1	$R_1 = R_2 = H$ (A)	9.220	9.202	0.018	0.00	0.103	0.00	0
2	$R_1 = CH_3$, $R_2 = H$ (A)	9.050	8.917	0.133	0.00	0.103	0.00	1
3	$R_1 = C_2H_5$, $R_2 = H$ (A)	8.960	8.917	0.043	0.00	0.103	0.00	1
4	$R_1 = H$, $R_2 = 6$-F (A)	7.400	7.325	0.075	−0.55	0.103	0.00	0
5	$R_1 = H$, $R_2 = 6$-Cl (A)	6.280	5.892	0.388	−0.97	0.103	0.00	0
6	$R_1 = H$, $R_2 = 7$-F (A)	9.050	9.220	−0.170	0.00	0.092	0.00	0
7	$R_1 = H$, $R_2 = 7$-Cl (A)	8.460	8.401	0.059	0.00	0.603	0.00	0
8	$R_1 = H$, $R_2 = 7$-OCH_3 (A)	8.140	8.106	0.034	0.00	0.787	0.00	0
9	$R_1 = H$, $R_2 = 8$-F (A)	9.100	9.202	−0.102	0.00	0.103	0.00	0
10	$R_1 = H$, $R_2 = 8$-Cl (A)	9.100	9.202	−0.102	0.00	0.103	0.00	0
11	$R_1 = H$, $R_2 = 8$-OCH_3 (A)	9.300	9.202	0.098	0.00	0.103	0.00	0
12	$R_1 = H$, $R_2 = 9$-F (A)	8.470	8.580	−0.110	0.00	0.103	−0.55	0
13	$R_1 = H$, $R_2 = 9$-Cl (A)	8.120	8.106	0.014	0.00	0.103	−0.97	0
14	$R_1 = R_2 = H$ (B)	9.000	9.202	−0.202	0.00	0.103	0.00	0
15	$R_1 = CH_3$, $R_2 = H$ (B)	9.050	8.917	0.133	0.00	0.103	0.00	1
16	$R_1 = C_2H_5$, $R_2 = H$ (B)	8.920	8.917	0.003	0.00	0.103	0.00	1
17	$R_1 = CH_3$, $R_2 = 6$-F (B)	6.520	7.040	−0.520	−0.55	0.103	0.00	1
18	$R_1 = CH_3$, $R_2 = 6$-Cl (B)	5.470	5.606	−0.136	−0.97	0.103	0.00	1
19	$R_1 = CH_3$, $R_2 = 7$-F (B)	8.850	8.935	−0.085	0.00	0.092	0.00	1
20	$R_1 = CH_3$, $R_2 = 7$-Cl (B)	7.730	8.115	−0.385	0.00	0.603	0.00	1
21	$R_1 = CH_3$, $R_2 = 7$-OCH_3 (B)	8.020	7.820	0.200	0.00	0.787	0.00	1
22	$R_1 = CH_3$, $R_2 = 8$-F (B)	8.960	8.917	0.043	0.00	0.103	0.00	1
23	$R_1 = CH_3$, $R_2 = 8$-Cl (B)	9.300	8.917	0.383	0.00	0.103	0.00	1
24	$R_1 = CH_3$, $R_2 = 8$-OCH_3 (B)	9.050	8.917	0.133	0.00	0.103	0.00	1
25	$R_1 = CH_3$, $R_2 = 9$-F (B)	8.310	8.295	0.015	0.00	0.103	−0.55	1
26	$R_1 = CH_3$, $R_2 = 9$-Cl (B)	7.860	7.820	0.040	0.00	0.103	−0.97	1

Table 24. K_i Binding Constants at Benzodiazepine Receptor for 1,2,4-Triazolo[1,5-*a*]quinoxalines and 1-Deazaimidazo[1,2-*a*]quinoxalines Analogues:[67] Compounds and Physicochemical Parameters for Derivation of Equation 30

no.	R, R_1	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	Clog *P*	MR_R
1	R = 2-furyl, $R_1 = H$	7.148	7.206	−0.059	1.649	1.788
2	R = 2-furyl, $R_1 = Cl$	7.839	7.925	−0.086	2.375	1.788
3	R = 2-furyl, $R_1 = Br$	7.879	8.073	−0.193	2.525	1.788
4	R = 3-furyl, $R_1 = Cl$	8.009	7.717	0.292	2.165	1.788
5	R = 2-thienyl, $R_1 = H$	7.662	7.477	0.185	2.147	2.404
6[a]	R = 2-thienyl, $R_1 = Cl$	7.759	8.194	−0.435	2.873	2.404
7	R = 3-thienyl, $R_1 = Cl$	7.799	7.987	−0.188	2.663	2.404
8[a]	R = C_6H_4-2-F, $R_1 = H$	8.051	7.689	0.361	2.407	2.525
9	R = C_6H_4-2-F, $R_1 = Cl$	8.538	8.407	0.130	3.133	2.525
10[a]	R = C_6H_4-3-F, $R_1 = Cl$	7.484	8.407	−0.923	3.133	2.525
11	R = C_6H_4-4-OCH_3, $R_1 = H$	7.057	7.323	−0.267	2.273	3.174
12	R = C_6H_4-4-OCH3, $R_1 = Cl$	8.268	8.042	0.226	3.000	3.174
13	R = C_6H_4-4-OH, $R_1 = H$	7.171	7.009	0.162	1.789	2.718
14	R = C_6H_4-4-OH, $R_1 = Cl$	7.526	7.727	−0.202	2.516	2.718

[a] Data points not included in equation derivation.

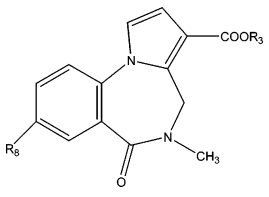
The three outliers not included in this analysis are marked in Table 24. They do not contain any unusual substitution moiety except that all are Cl derivatives.

3.25. Imidazobenzodiazepines

Cook et al.[68] carried out a QSAR study on a number of imidazobenzodiazepines exhibiting affinities at recombinant $\alpha_1\beta_3\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$, $\alpha_5\beta_3\gamma_2$, and $\alpha_6\beta_3\gamma_2$ $GABA_A$/benzodiazepine receptor subtypes (α_1, α_2, α_3, α_5, α_6), by means of CoMFA. As a result, all of the CoMFA models[68] offered good cross-validated correlation for the ligands in the test set (Tables 25−35). Using the above-mentioned affinities we evaluated eqs 31−35 (MR and σ^*_3 were the parameters used in most cases). No role for hydrophobicity was found (Clog *P* or π).

(a) $\log 1/K_i\,[\alpha 1] = -0.388\ (\pm 0.131)\mathrm{CMR} + 1.113\ (\pm 0.185)\sigma^*_3 + 8.695\ (\pm 1.140)$ (31)

$n = 35$ $r^2 = 0.824$ $q^2 = 0.787$ $s = 0.417$ $F_{2,35} = 75.27$ $\alpha = 0.01$



CMR versus σ^*_3 = 0.352; three compounds were omitted (**21**, **30**, and **31**, Table 25)

In the above equation CMR refers to the overall molar refractivity. The negative term suggests steric

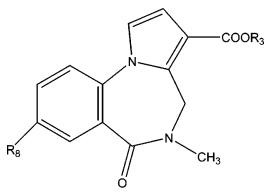
Table 25. K_i Binding Affinities of Imidazobenzodiazepines for the a_1 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 31

no.	substituents R_3, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR	σ^*_3
1	$R_3 = COOC_2H_5$, $R_8 = F$	9.097	8.490	0.607	7.705	2.260
2	$R_3 = COOC_2H_5$, $R_8 = Cl$	8.167	8.305	−0.138	8.181	2.260
3	$R_3 = COOC_2H_5$, $R_8 = Br$	7.585	8.194	−0.609	8.467	2.260
4	$R_3 = COOC_2H_5$, $R_8 = CN$	8.000	8.310	−0.310	8.167	2.260
5	$R_3 = COOC_2H_5$, $R_8 = CH{=}CH_2$	8.081	8.116	−0.035	8.668	2.260
6	$R_3 = COOC_2H_5$, $R_8 = C_2H_5$	7.690	8.136	−0.445	8.617	2.260
7	$R_3 = COOC_2H_5$, $R_8 = OC_2H_5$	7.951	8.076	−0.126	8.771	2.260
8	$R_3 = COOC_2H_5$, $R_8 = N_3$	8.481	8.204	0.277	8.441	2.260
9	$R_3 = COOC_2H_5$, $R_8 = CH{=}C{=}CH_2$	8.426	7.927	0.499	9.154	2.260
10	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}CH$	7.547	8.185	−0.638	8.491	2.260
11	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}C(CH_3)$	7.996	8.005	−0.009	8.954	2.260
12	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}C[Si(CH_3)_3]$	6.917	7.300	−0.383	10.770	2.260
13	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}CCH_2[Si(CH_3)_3]$	6.523	7.122	−0.599	11.230	2.260
14	$R_3 = COOC(CH_3)_3$, $R_8 = Cl$	7.762	7.945	−0.183	9.109	2.260
15	$R_3 = COOC(CH_3)_3$, $R_8 = Br$	7.943	7.834	0.109	9.394	2.260
16	$R_3 = COOC(CH_3)_3$, $R_8 = I$	8.013	7.629	0.385	9.924	2.260
17	$R_3 = COOC(CH_3)_3$, $R_8 = OH$	8.824	8.076	0.748	8.771	2.260
18	$R_3 = COOC(CH_3)_3$, $R_8 = OCH_3$	8.171	7.896	0.275	9.234	2.260
19	$R_3 = COOC(CH_3)_3$, $R_8 = N(CH_3)_2$	7.883	7.633	0.250	9.914	2.260
20	$R_3 = COOC(CH_3)_3$, $R_8 =$ *N*-tetrahydropyrrole	8.237	7.343	0.894	10.660	2.260
21[a]	$R_3 = COOC(CH_3)_3$, $R_8 =$ *N*-hexahydropyridine	8.191	7.161	1.030	11.130	2.260
22	$R_3 = COOC(CH_3)_3$, $R_8 = N_3$	8.140	7.844	0.296	9.369	2.260
23	$R_3 = COOC(CH_3)_3$, $R_8 = NCS$	7.767	7.535	0.232	10.169	2.260
24	$R_3 = COOC(CH_3)_3$, $R_8 = NO_2$	7.893	7.898	0.006	9.229	2.260
25	$R_3 = COOC(CH_3)_3$, $R_8 = C_2H_5$	7.830	7.776	0.054	9.545	2.260
26	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}CH$	7.570	7.825	−0.255	9.418	2.260
27	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}C[Si(CH_3)_3]$	6.706	6.939	−0.233	11.700	2.260
28	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}CCH_2[Si(CH_3)_3]$	6.561	6.761	−0.200	12.160	2.260
29	$R_3 = COOCH_2$-cy-C_3H_5, $R_8 = Cl$	7.785			8.971	
30[a]	$R_3 = COCH_3$, $R_8 = Cl$	4.756	7.865	−3.109	7.564	1.65
31[a]	$R_3 = COC_4H_9$, $R_8 = Cl$	5.801	7.325	−1.524	8.956	1.65
32	$R_3 = CH_2OH$, $R_8 = Cl$	6.523	6.787	−0.264	7.218	0.560
33	$R_3 = CH_2OCH_3$, $R_8 = Cl$	6.523	6.652	−0.039	7.682	0.520
34	$R_3 = CH_2Cl$, $R_8 = Cl$	6.523	7.156	−0.633	7.556	1.010
35	$R_3 = CH_2OC_2H_5$, $R_8 = Cl$	6.523	6.449	0.074	8.146	0.580
36	$R_3 = CH_2N(C_2H_5)_2$, $R_8 = Cl$	5.023	5.267	−0.604	9.289	0.240
37	$R_3 = CH_2N[CH(CH_3)]_2$, $R_8 = Cl$	5.377	5.267	0.110	10.126	0.240
38	$R_3 = C_2H_5$, $R_8 = Cl$	6.389	5.931	0.458	7.529	−0.100
39	$R_3 = C_5H_{11}$, $R_8 = Cl$	5.588	5.247	0.442	8.920	−0.230

[a] Data points not included in equation derivation.

hindrance. Electron-withdrawing groups seem to have a significant role. Compound **29** was not included in the derivation of the equation due to a missing σ^*_3 value.

(b)



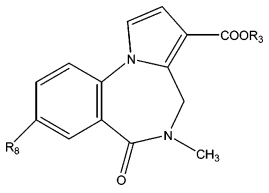
$$\log 1/K_i\ [\alpha 2] = -0.407\ (\pm 0.135)\text{CMR} + 1.105\ (\pm 0.189)\sigma^*_3 + 8.880\ (\pm 1.172) \quad (32)$$

$n = 30$ $r^2 = 0.846$ $q^2 = 0.809$ $s = 0.411$ $F_{2,27} = 252.72$ $\alpha = 0.01$

CMR versus $\sigma^*_3 =$ 0.339; two compounds were omitted (**24** and **25**, Table 26)

Again, a negative CMR seems to be the most significant variable followed by σ^*.

(c)



$$\log 1/K_i\ [\alpha 3] = -0.451\ (\pm 0.110)\text{CMR} + 1.13\ (\pm 0.161)\sigma^*_3 + 9.348\ (\pm 0.956) \quad (33)$$

$n = 35$ $r^2 = 0.868$ $q^2 = 0.843$ $s = 0.359$ $F_{2,33} = 70.539$ $\alpha = 0.01$

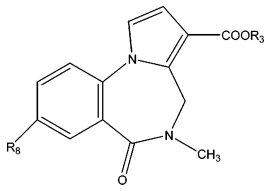
Table 27 omitted compounds **17**, **30**, and **31**. Compound **29** was not included in the derivation of equation due to a missing σ^*_3 value.

Table 26. K_I Binding Affinities of Imidazobenzodiazepines for the a_2 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 32

no.	substituents R_3, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR	σ^*_3
1	$R_3 = COOC_2H_5$, $R_8 = F$	9.046	8.243	0.803	7.705	2.260
2	$R_3 = COOC_2H_5$, $R_8 = Cl$	7.788	8.049	−0.262	8.181	2.260
3	$R_3 = COOC_2H_5$, $R_8 = Br$	7.569	7.933	−0.365	8.467	2.260
4	$R_3 = COOC_2H_5$, $R_8 = CN$	7.347	8.055	−0.708	8.167	2.260
5	$R_3 = COOC_2H_5$, $R_8 = CH{=}CH_2$	7.991	7.851	0.140	8.668	2.260
6	$R_3 = COOC_2H_5$, $R_8 = C_2H_5$	7.569	7.872	−0.303	8.617	2.260
7	$R_3 = COOC_2H_5$, $R_8 = OC_2H_5$	7.444	7.810	−0.366	8.771	2.260
8	$R_3 = COOC_2H_5$, $R_8 = N_3$	8.585	7.944	0.641	8.441	2.260
9	$R_3 = COOC_2H_5$, $R_8 = CH{=}C{=}CH_2$	8.143	7.654	0.489	9.154	2.260
10	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}CH$	7.670	7.924	−0.254	8.491	2.260
11	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}C(CH_3)$	7.654	7.735	−0.081	8.954	2.260
12	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}C[Si(CH_3)_3]$	6.848	6.996	−0.148	10.770	2.260
13	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}CCH_2[Si(CH_3)_3]$	6.523	6.809	−0.286	11.230	2.260
14	$R_3 = COOC(CH_3)_3$, $R_8 = Cl$	7.666	7.672	−0.007	9.109	2.260
15	$R_3 = COOC(CH_3)_3$, $R_8 = Br$	7.971	7.556	0.415	9.394	2.260
16	$R_3 = COOC(CH_3)_3$, $R_8 = I$	7.951	7.341	0.610	9.924	2.260
17	$R_3 = COOC(CH_3)_3$, $R_8 = NCS$	7.472	7.243	0.230	10.169	2.260
18	$R_3 = COOC(CH_3)_3$, $R_8 = NO_2$	7.303	7.623	−0.320	9.229	2.260
19	$R_3 = COOC(CH_3)_3$, $R_8 = C_2H_5$	7.252	7.495	−0.243	9.545	2.260
20	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}CH$	7.580	7.546	0.034	9.418	2.260
21	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}C[Si(CH_3)_3]$	6.845	6.618	0.227	11.700	2.260
22	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}CCH_2[Si(CH_3)_3]$	6.412	6.431	−0.019	12.160	2.260
23[a]	$R_3 = COOCH_2$-cy-C_3H_5, $R_8 = Cl$	7.317			8.971	
24[a]	$R_3 = COCH_3$, $R_8 = Cl$	4.471	7.626	−3.156	7.564	1.65
25[a]	$R_3 = COC_4H_9$, $R_8 = Cl$	5.543	7.060	−1.517	8.956	1.65
26	$R_3 = CH_2OH$, $R_8 = Cl$	6.520	6.563	−0.043	7.218	0.560
27	$R_3 = CH_2OCH_3$, $R_8 = Cl$	6.520	6.330	0.190	7.682	0.520
28	$R_3 = CH_2Cl$, $R_8 = Cl$	6.520	6.922	−0.402	7.556	1.010
29	$R_3 = CH_2OC_2H_5$, $R_8 = Cl$	6.520	6.207	0.313	8.146	0.580
30	$R_3 = CH_2N(C_2H_5)_2$, $R_8 = Cl$	4.523	5.367	−0.814	9.289	0.240
31	$R_3 = CH_2N[CH(CH_3)]_2$, $R_8 = Cl$	4.900	4.989	−0.089	10.126	0.240
32	$R_3 = C_2H_5$, $R_8 = Cl$	5.816	5.707	0.109	7.529	−0.100
33	$R_3 = C_5H_{11}$, $R_8 = Cl$	5.538	4.997	0.540	8.920	−0.230

[a] Data points not included in equation derivation.

(d)

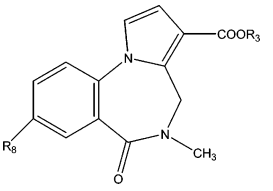


$$\log 1/K_i\ [\alpha 5] = -0.275\ (\pm 0.163)\mathrm{CMR} + 1.34\ (\pm 0.228)\sigma^*_3 + 8.457\ (\pm 1.41) \quad (34)$$

$n = 36$ $r^2 = 0.810$ $q^2 = 0.773$ $s = 0.773$ $F_{2,33} = 70.539$ $\alpha = 0.01$

CMR versus $\sigma^*_3 = 0.353$; three outliers (compounds **13**, **29**, and **30**, Table 28)

(e)



$$\log 1/K_i\ [\alpha 6] = -0.378\ (\pm 0.17)\mathrm{CMR} + 1.197\ (\pm 0.266)\sigma^*_3 + 8.455\ (\pm 1.447) \quad (35)$$

$n = 31$ $r^2 = 0.751$ $q^2 = 0.704$ $s = 0.501$ $F_{2,26} = 42.42$ $\alpha = 0.01$

CMR versus $\sigma^*_3 = 0.458$; six outliers (compounds **1**, **4**, **5**, **29**, **30**, and **38**, Table 29)

Compound **28** was not included in the derivation of equation due to a missing σ^*_3 value.

Parameter Importance: σ^*_3 > CMR. Equations 33−35 define the role that steric hindrance plays for affinities at recombinant BzR subtypes. Clog *P* cannot replace CMR. Substituting Clog *P* for CMR in eqs 33−35 gives a very poor fit, indicating interaction in nonhydrophobic space. The negative CMR term suggests a fitting to a macromolecule of limited steric capability.

The σ^* values have been estimated for $COO(CH_3)_3$, COC_4H_9, and $CH_2N(CH(CH_3)_2)_2$ groups as those of $COOC_2H_5$, $COCH_3$, and $CH_2N(C_2H_5)_2$ respectively. The QSARs of eqs 31−35 show a remarkable consistency for the σ term. Its coefficient is almost the same for all of the different $\alpha 1$, $\alpha 2$, $\alpha 3$, $\alpha 5$, and $\alpha 6$ BzR subtypes. The positive sign of σ^* for R_3 indicates that electron-withdrawing groups promote high binding affinity for all five benzodiazepine receptor isoforms.

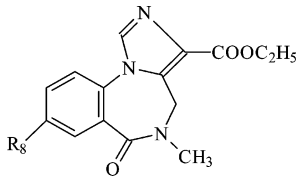
For the following 36−40 QSARs correlating in vitro affinities of framework-constrained imidazobenzodiazepines[68] (Tables 30−34) at recombinant BzR subtypes, the most significant parameters are CMR and I_s. I_s assigns 1 for 4H in the *S* configuration and 0 for 4H in the *R* configuration. Its positive coefficient demonstrates that only the *S* series of imidazobenzodiazepines bind tightly to all five recombinant receptor subtypes, which is in agreement with the earlier work of Fryer and Haefely.[69,70]

Table 27. K_I Binding Affinities of Imidazobenzodiazepines for the a_3 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 33

no.	substituents R_3, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR	σ^*_3
1	$R_3 = COOC_2H_5$, $R_8 = F$	8.979	8.424	0.555	7.705	2.260
2	$R_3 = COOC_2H_5$, $R_8 = Cl$	8.036	8.209	−0.173	8.181	2.260
3	$R_3 = COOC_2H_5$, $R_8 = Br$	7.886	8.080	−0.194	8.467	2.260
4	$R_3 = COOC_2H_5$, $R_8 = CN$	7.721	8.215	−0.494	8.167	2.260
5	$R_3 = COOC_2H_5$, $R_8 = CH{=}CH_2$	8.161	7.989	0.172	8.668	2.260
6	$R_3 = COOC_2H_5$, $R_8 = C_2H_5$	7.583	8.012	−0.428	8.617	2.260
7	$R_3 = COOC_2H_5$, $R_8 = OC_2H_5$	7.772	7.943	−0.171	8.771	2.260
8	$R_3 = COOC_2H_5$, $R_8 = N_3$	8.602	8.091	0.511	8.441	2.260
9	$R_3 = COOC_2H_5$, $R_8 = CH{=}C{=}CH_2$	8.383	7.770	0.613	9.154	2.260
10	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}CH$	7.588	8.069	−0.481	8.491	2.260
11	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}C(CH_3)$	7.783	7.860	−0.077	8.954	2.260
12	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}C[Si(CH_3)_3]$	6.702	7.040	−0.338	10.770	2.260
13	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}CCH_2[Si(CH_3)_3]$	6.523	6.832	−0.310	11.230	2.260
14	$R_3 = COOC(CH_3)_3$, $R_8 = Cl$	7.536	7.790	−0.254	9.109	2.260
15	$R_3 = COOC(CH_3)_3$, $R_8 = Br$	8.036	7.661	0.375	9.394	2.260
16	$R_3 = COOC(CH_3)_3$, $R_8 = I$	7.963	7.422	0.540	9.924	2.260
17[a]	$R_3 = COOC(CH_3)_3$, $R_8 = OH$	9.276	7.943	1.333	8.771	2.260
18	$R_3 = COOC(CH_3)_3$, $R_8 = OCH_3$	8.130	7.733	0.396	9.234	2.260
19	$R_3 = COOC(CH_3)_3$, $R_8 = N(CH_3)_2$	7.419	7.427	−0.008	9.914	2.260
20	$R_3 = COOC(CH_3)_3$, $R_8 = N$-tetrahydropyrrole	6.772	7.090	−0.318	10.660	2.260
21	$R_3 = COOC(CH_3)_3$, $R_8 = N$-hexahydropyridine	6.830	6.878	−0.048	11.130	2.260
22	$R_3 = COOC(CH_3)_3$, $R_8 = N_3$	8.247	7.673	0.574	9.369	2.260
23	$R_3 = COOC(CH_3)_3$, $R_8 = NCS$	7.301	7.314	−0.012	10.169	2.260
24	$R_3 = COOC(CH_3)_3$, $R_8 = NO_2$	7.520	7.736	−0.216	9.229	2.260
25	$R_3 = COOC(CH_3)_3$, $R_8 = C_2H_5$	7.597	7.593	0.004	9.545	2.260
26	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}CH$	7.728	7.650	0.078	9.418	2.260
27	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}C[Si(CH_3)_3]$	6.593	6.620	−0.027	11.700	2.260
28	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}CCH_2[Si(CH_3)_3]$	6.472	6.413	0.060	12.160	2.260
29	$R_3 = COOCH_2$-cy-C_3H_5, $R_8 = Cl$	7.372			8.971	
30[a]	$R_3 = COCH_3$, $R_8 = Cl$	4.655	7.798	−3.143	7.564	1.65
31[a]	$R_3 = COC_4H_9$, $R_8 = Cl$	5.562	7.170	−1.607	8.956	1.65
32	$R_3 = CH_2OH$, $R_8 = Cl$	6.523	6.722	−0.199	7.218	0.560
33	$R_3 = CH_2OCH_3$, $R_8 = Cl$	6.523	6.468	0.055	7.682	0.520
34	$R_3 = CH_2Cl$, $R_8 = Cl$	6.523	7.078	−0.555	7.556	1.010
35	$R_3 = CH_2OC_2H_5$, $R_8 = Cl$	6.523	6.326	0.197	8.146	0.580
36	$R_3 = CH_2N(C_2H_5)_2$, $R_8 = Cl$	4.812	5.426	−0.614	9.289	0.240
37	$R_3 = CH_2N[CH(CH_3)]_2$, $R_8 = Cl$	5.203	5.007	0.196	10.126	0.240
38	$R_3 = C_2H_5$, $R_8 = Cl$	5.949	5.836	0.113	7.529	−0.100
39	$R_3 = C_5H_{11}$, $R_8 = Cl$	5.537	5.061	0.476	8.920	−0.230

[a] Data points not included in equation derivation.

(f)

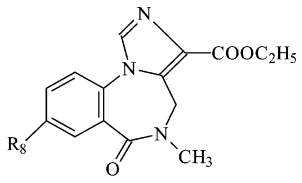


$$\log 1/K_i\ [\alpha 1] = -0.229\ (\pm 0.166)\mathrm{CMR} + 1.038\ (\pm 0.387)I_s + 8.476\ (\pm 1.688) \quad (36)$$

$n = 10$ $r^2 = 0.893$ $q^2 = 0.74$ $s = 0.235$ $F_{2,7} = 28.93$ $\alpha = 0.01$

CMR versus $I_s = -0.143$

(g)

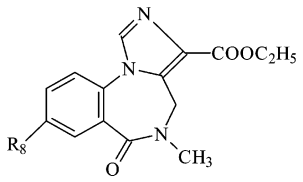


$$\log 1/K_i\ [\alpha 2] = 1.242\ (\pm 0.370)I_s - 0.230\ (\pm 0.158)\mathrm{CMR} + 8.462\ (\pm 1.611) \quad (37)$$

$n = 10$ $r^2 = 0.923$ $q^2 = 0.814$ $s = 0.224$ $F_{2,7} = 42.40$ $\alpha = 0.01$

CMR versus $I_s = -0.143$

(h)

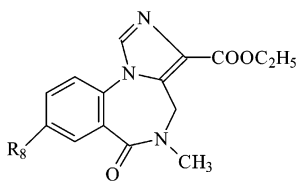


$$\log 1/K_i\ [\alpha 3] = 1.237\ (\pm 0.515)I_s - 0.270\ (\pm 0.221)\mathrm{CMR} + 9.025\ (\pm 2.245) \quad (38)$$

$n = 10$ $r^2 = 0.868$ $q = 0.685$ $s = 0.312$, $F_{2,7} = 23.08$ $\alpha = 0.01$

CMR versus $I_s = -0.143$

(i)



$$\log 1/K_i\ [\alpha 5] = 2.839\ (\pm 0.535)I_s - 0.261\ (\pm 0.200)\mathrm{CMR} + 8.71\ (\pm 2.119) \quad (39)$$

$n = 9$ $r^2 = 0.976$ $q^2 = 0.889$ $s = 0.263$ $F_{2,6} = 108.246$ $\alpha = 0.01$

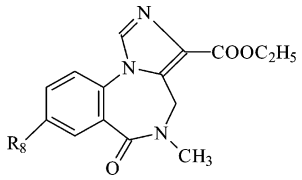
CMR versus $I_s = -0.265$, one outlier (compound 6)

Table 28. K_I Binding Affinities of Imidazobenzodiazepines for the a_5 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 34

no.	substituents R_3, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR	σ^*_3
1	$R_3 = COOC_2H_5$, $R_8 = F$	9.222	9.366	−0.144	7.705	2.260
2	$R_3 = COOC_2H_5$, $R_8 = Cl$	9.071	9.235	−0.164	8.181	2.260
3	$R_3 = COOC_2H_5$, $R_8 = Br$	9.155	9.156	−0.001	8.467	2.260
4	$R_3 = COOC_2H_5$, $R_8 = CN$	8.222	9.239	−1.017	8.167	2.260
5	$R_3 = COOC_2H_5$, $R_8 = CH{=}CH_2$	9.398	9.101	0.297	8.668	2.260
6	$R_3 = COOC_2H_5$, $R_8 = C_2H_5$	8.824	9.115	−0.291	8.617	2.260
7	$R_3 = COOC_2H_5$, $R_8 = OC_2H_5$	8.971	9.073	−0.102	8.771	2.260
8	$R_3 = COOC_2H_5$, $R_8 = N_3$	9.569	9.163	0.405	8.441	2.260
9	$R_3 = COOC_2H_5$, $R_8 = CH{=}C{=}CH_2$	8.955	8.967	−0.013	9.154	2.260
10	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}CH$	9.310	9.150	0.160	8.491	2.260
11	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}C(CH_3)$	8.775	9.022	−0.248	8.954	2.260
12	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}C[Si(CH_3)_3]$	8.301	8.523	−0.222	10.770	2.260
13[a]	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}CCH_2[Si(CH_3)_3]$	6.523	8.397	−1.874	11.230	2.260
14	$R_3 = COOC(CH_3)_3$, $R_8 = Cl$	9.187	8.980	0.207	9.109	2.260
15	$R_3 = COOC(CH_3)_3$, $R_8 = Br$	9.328	8.901	0.427	9.394	2.260
16	$R_3 = COOC(CH_3)_3$, $R_8 = I$	9.420	8.756	0.664	9.924	2.260
17	$R_3 = COOC(CH_3)_3$, $R_8 = OH$	9.854	9.073	0.781	8.771	2.260
18	$R_3 = COOC(CH_3)_3$, $R_8 = OCH_3$	9.533	8.945	0.588	9.234	2.260
19	$R_3 = COOC(CH_3)_3$, $R_8 = N(CH_3)_2$	9.108	8.758	0.349	9.914	2.260
20	$R_3 = COOC(CH_3)_3$, $R_8 =$ *N*-tetrahydropyrrole	8.034	8.553	−0.590	10.660	2.260
21	$R_3 = COOC(CH_3)_3$, $R_8 =$ *N*-hexahydropyridine	8.374	8.424	−0.050	11.130	2.260
22	$R_3 = COOC(CH_3)_3$, $R_8 = N_3$	9.523	8.908	0.615	9.369	2.260
23	$R_3 = COOC(CH_3)_3$, $R_8 = NCS$	8.602	8.690	−0.087	10.169	2.260
24	$R_3 = COOC(CH_3)_3$, $R_8 = NO_2$	8.456	8.947	−0.041	9.229	2.260
25	$R_3 = COOC(CH_3)_3$, $R_8 = C_2H_5$	8.764	8.860	−0.095	9.545	2.260
26	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}CH$	9.398	8.895	0.503	9.418	2.260
27	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}C[Si(CH_3)_3]$		8.267	0.316	11.700	2.260
28	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}CCH_2[Si(CH_3)_3]$	8.583	8.141	−0.503	12.160	2.260
29[a]	$R_3 = COOCH_2$-cy-C_3H_5, $R_8 = Cl$	8.009			8.971	
30[a]	$R_3 = COCH_3$, $R_8 = Cl$	5.583	8.587	−3.004	7.564	1.65
31	$R_3 = COC_4H_9$, $R_8 = Cl$	6.780	8.205	−1.425	8.956	1.65
32	$R_3 = CH_2OH$, $R_8 = Cl$	6.523	7.222	−0.700	7.218	0.560
33	$R_3 = CH_2OCH_3$, $R_8 = Cl$	7.411	7.041	−0.37	7.682	0.520
34	$R_3 = CH_2Cl$, $R_8 = Cl$	7.545	7.732	−0.187	7.556	1.010
35	$R_3 = CH_2OC_2H_5$, $R_8 = Cl$	7.082	6.994	0.088	8.146	0.580
36	$R_3 = CH_2N(C_2H_5)_2$, $R_8 = Cl$	5.588	6.224	−0.636	9.289	0.240
37	$R_3 = CH_2N[CH(CH_3)]_2$, $R_8 = Cl$	5.871	5.969	−0.098	10.126	0.240
38	$R_3 = C_2H_5$, $R_8 = Cl$	6.740	6.253	0.487	7.529	−0.100
39	$R_3 = C_5H_{11}$, $R_8 = Cl$	6.433	5.696	0.737	8.920	−0.230

[a] Data points not included in equation derivation.

(k)



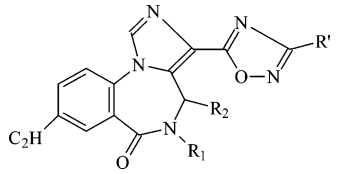
$$\log 1/K_i\ [\alpha 6] = 0.903\ (\pm 0.490) I_s - 0.221\ (\pm 0.183)\mathrm{CMR} + 8.29\ (\pm 1.941) \quad (40)$$

$n = 9$ $r^2 = 0.866$ $q^2 = 0.487$ $s = 0.241$ $F_{2,6} = 19.40$ $\alpha = 0.01$

CMR versus $I_s = -0.265$, one outlier (compound **6**); parameter importance: I_s > CMR

Equations 36−40 show a linear relationship of binding affinity with I_s and CMR. Because MR is a measure of bulk, a negative term suggests steric hindrance, either directly or through a conformational change in the receptor. In terms of CMR the binding of imidazobenzodiazepines in α1, α2, α3, α5, and α6 subtypes is identically the same.

(m) From the affinities of 3-alkyl-1,2,4-oxadiazole-4,5-substituted imidazobenzodiazepines[68] (Table 35) at α5, BzR isoform eq 41 is derived.



$$\log 1/K_i\ [\alpha 5] = -0.607\ (\pm 0.303) L_{R'} + 10.415\ (\pm 1.367) \quad (41)$$

$n = 8$ $r^2 = 0.799$ $q^2 = 0.636$ $s = 0.430$ $F_{1,6} = 23.989$ $\alpha = 0.01$

The most important single variable is $L_{R'}$, the sterimol parameter for the length of the first atom of the substituent R′. $L_{R'}$ points to a steric effect that brings out the critical fit of the ligands to the macromolecule. The omitted compound (compound **2**, Table 35) has the 4H in the *R* configuration.

3.26. Imidazobenzodiazepines

Cook et al.,[71a−c] continuing the attempts on pharmacophore/receptor models for recombinant $GABA_A$/BzR subtypes, have published a SAR ligand-mapping approach. Their study was based on the affinities of

Table 29. K_i Binding Affinities of Imidazobenzodiazepines for the α_6 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 35

no.	substituents R_3, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR	σ^*_3
1[a]	$R_3 = COOC_2H_5$, $R_8 = F$	6.830	8.251	−1.421	7.705	2.260
2	$R_3 = COOC_2H_5$, $R_8 = Cl$	7.263	8.072	−0.809	8.181	2.260
3	$R_3 = COOC_2H_5$, $R_8 = Br$	7.658	7.964	−0.306	8.467	2.260
4[a]	$R_3 = COOC_2H_5$, $R_8 = CN$	6.000	8.077	−2.077	8.167	2.260
5[a]	$R_3 = COOC_2H_5$, $R_8 = C_2H_5$	6.754	7.907	−1.152	8.617	2.260
6	$R_3 = COOC_2H_5$, $R_8 = OC_2H_5$	7.288	7.849	−0.561	8.771	2.260
7	$R_3 = COOC_2H_5$, $R_8 = N_3$	8.420	7.973	0.447	8.441	2.260
8	$R_3 = COOC_2H_5$, $R_8 = CH{=}C{=}CH_2$	7.354	7.704	−0.351	9.154	2.260
9	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}CH$	7.541	7.955	−0.414	8.491	2.260
10	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}C(CH_3)$	7.000	7.094	−0.780	8.954	2.260
11	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}C[Si(CH_3)_3]$	6.944	6.920	−0.150	10.770	2.260
12	$R_3 = COOC_2H_5$, $R_8 = C{\equiv}CCH_2Si(CH_3)_3]$	6.523	7.721	−0.398	11.230	2.260
13	$R_3 = COOC(CH_3)_3$, $R_8 = Cl$	8.398	7.613	0.677	9.109	2.260
14	$R_3 = COOC(CH_3)_3$, $R_8 = Br$	8.027	7.414	0.413	9.394	2.260
15	$R_3 = COOC(CH_3)_3$, $R_8 = I$	8.337	7.849	0.924	9.924	2.260
16	$R_3 = COOC(CH_3)_3$, $R_8 = OH$	8.162	7.674	0.313	8.771	2.260
17	$R_3 = COOC(CH_3)_3$, $R_8 = OCH_3$	8.082	7.417	0.408	9.234	2.260
18	$R_3 = COOC(CH_3)_3$, $R_8 = N(CH_3)_2$	6.928	7.136	−0.489	9.914	2.260
19	$R_3 = COOC(CH_3)_3$, $R_8 =$ *N*-tetrahydropyrrole	6.488	6.958	−0.648	10.660	2.260
20	$R_3 = COOC(CH_3)_3$, $R_8 =$ *N*-hexahydropyridine	6.607	7.623	−0.351	11.130	2.260
21	$R_3 = COOC(CH_3)_3$, $R_8 = N_3$	8.280	7.623	0.657	9.369	2.260
22	$R_3 = COOC(CH_3)_3$, $R_8 = NCS$	7.513	7.323	0.190	10.169	2.260
23	$R_3 = COOC(CH_3)_3$, $R_8 = NO_2$	7.648	7.676	−0.028	9.229	2.260
24	$R_3 = COOC(CH_3)_3$, $R_8 = C_2H_5$	7.640	7.557	0.084	9.545	2.260
25	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}CH$	8.292	7.604	0.688	9.418	2.260
26	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}C[Si(CH_3)_3]$	7.232	6.743	0.489	11.700	2.260
27	$R_3 = COOC(CH_3)_3$, $R_8 = C{\equiv}CCH_2[Si(CH_3)_3]$	6.521	6.569	−0.048	12.160	2.260
28	$R_3 = COOCH_2$-cy-C_3H_5, $R_8 = Cl$	6.775			8.971	
29[a]	$R_3 = COCH_3$, $R_8 = Cl$	4.530	7.574	−3.044	7.564	1.65
30[a]	$R_3 = COC_4H_9$, $R_8 = Cl$	5.553	7.049	−1.516	8.956	1.65
31	$R_3 = CH_2OH$, $R_8 = Cl$	6.523	6.400	0.123	7.218	0.560
32	$R_3 = CH_2OCH_3$, $R_8 = Cl$	6.523	6.177	0.346	7.682	0.520
33	$R_3 = CH_2Cl$, $R_8 = Cl$	6.523	6.811	−0.288	7.556	1.010
34	$R_3 = CH_2OC_2H_5$, $R_8 = Cl$	6.523	6.074	0.449	8.146	0.580
35	$R_3 = CH_2N(C_2H_5)_2$, $R_8 = Cl$	4.521	5.235	−0.714	9.289	0.240
36	$R_3 = CH_2N[CH(CH_3)]_2$, $R_8 = Cl$	5.066	4.885	0.181	10.126	0.240
37	$R_3 = C_2H_5$, $R_8 = Cl$	5.438	5.492	−0.054	7.529	−0.100
38[a]	$R_3 = C_5H_{11}$, $R_8 = Cl$	6.018	4.811	1.206	8.920	−0.230

[a] Data points not included in equation derivation.

Table 30. K_I Binding Affinities of Imidazobenzodiazepines for the α_1 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 36

no.	substituents R_1, R_2, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR	I_S
1	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = Br$ (S)	7.310	7.399	−0.089	9.217	1
2	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = Br$ (R)	6.000	6.361	−0.361	9.217	0
3	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = C{\equiv}C[Si(CH_3)_3]$ (S)	6.699	6.87	−0.171	11.520	1
4	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = C{\equiv}C[Si(CH_3)_3]$ (R)	6.000	5.832	0.168	11.520	0
5	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = C{\equiv}C$ (S)	7.229	7.393	−0.094	9.241	1
6	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = C{\equiv}CH$ (R)	6.548	6.355	0.179	9.241	0
7	R_1, $R_2 = 4,5\text{-}(CH_2)_2$, $R_8 = Br$ (S)	7.770	7.505	0.265	8.753	1
8	R_1, $R_2 = 4,5\text{-}(CH_2)_2$, $R_8 = C{\equiv}C[Si(CH_3)_3]$ (S)	7.081	6.978	0.103	11.050	1
9	R_1, $R_2 = 4,5\text{-}(CH_2)_2$, $R_8 = C{\equiv}CH$ (S)	7.678	7.500	0.178	8.777	1
10	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = OCH_3$ (S)	7.314	7.435	−0.121	9.057	1

Table 31. K_i Binding Affinities of Imidazobenzodiazepines for the α_2 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 37

no.	substituents R_1, R_2, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR	I_S
1	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = Br$ (S)	7.538	7.586	−0.049	9.217	1
2	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = Br$ (R)	6.000	6.334	−0.344	9.217	0
3	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = C{\equiv}C[Si(CH_3)_3]$ (S)	6.907	7.057	−0.159	11.520	1
4	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = C{\equiv}C[Si(CH_3)_3]$ (R)	6.000	5.815	0.185	11.520	0
5	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = C{\equiv}CH$ (S)	7.357	7.581	−0.224	9.241	1
6	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = C{\equiv}CH$ (R)	6.498	6.339	0.159	9.241	0
7	R_1, $R_2 = 4,5\text{-}(CH_2)_2$, $R_8 = Br$ (S)	7.886	7.693	0.193	8.753	1
8	R_1, $R_2 = 4,5\text{-}(CH_2)_2$, $R_8 = C{\equiv}C[Si(CH_3)_3]$ (S)	7.222	7.165	0.057	11.050	1
9	R_1, $R_2 = 4,5\text{-}(CH_2)_2$, $R_8 = C{\equiv}CH$ (S)	7.921	7.687	0.234	8.777	1
10	R_1, $R_2 = 4,5\text{-}(CH_2)_3$, $R_8 = OCH_3$ (S)	7.562	7.623	−0.061	9.057	1

Table 32. K_I Binding Affinities of Imidazobenzodiazepines for the α_3 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 38

no.	substituents R_1, R_2, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR	I_S
1	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = Br (S)	7.824	7.776	0.021	9.217	1
2	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = Br (R)	6.000	6.540	−0.88	9.217	0
3	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C≡C[Si$(CH_3)_3$] (S)	7.102	7.155	0.060	11.520	1
4	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C≡C[Si$(CH_3)_3$] (R)	6.000	5.919	−0.119	11.520	0
5	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C≡CH (S)	7.569	7.770	−0.227	9.241	1
6	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C≡CH (R)	6.991	6.533	0.119	9.241	0
7	R_1, R_2 = 4,5-$(CH_2)_2$, R_8 = Br (S)	8.174	7.901	0.218	8.753	1
8	R_1, R_2 = 4,5-$(CH_2)_2$, R_8 = C≡C[Si$(CH_3)_3$] (S)	7.319	7.282	0.121	11.050	1
9	R_1, R_2 = 4,5-$(CH_2)_2$, R_8 = C≡CH (S)	8.000	7.815	0.052	8.777	1
10	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = OCH_3 (S)	7.611	7.819	−0.245	9.057	1

Table 33. K_I Binding Affinities of Imidazobenzodiazepines for the α_5 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 39

no.	substituents R_1, R_2, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR	I_S
1	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = Br (S)	9.000	9.140	−0.14	9.217	1
2	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = Br (R)	6.000	6.301	−0.301	9.217	0
3	R_1 R_2 = 4,5-$(CH_2)_3$, R_8 = C≡C[Si$(CH_3)_3$] (S)	8.398	8.538	−0.14	11.520	1
4	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C≡C[Si$(CH_3)_3$] (R)	6.000	5.699	0.301	11.520	0
5	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C≡CH (S)	8.886	9.134	−0.248	9.241	1
6[a]	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C≡CH (R)	8.143	6.295	1.848	9.241	0
7	R_1, R_2 = 4,5-$(CH_2)_2$, R_8 = Br (S)	9.523	9.261	0.262	8.753	1
8	R_1, R_2 = 4,5-$(CH_2)_2$, R_8 = C≡C[Si$(CH_3)_3$] (S)	8.585	8.661	−0.076	11.050	1
9	R_1, R_2 = 4,5-$(CH_2)_2$, R_8 = C≡CH (S)	9.432	9.235	0.177	8.777	1
10	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = OCH_3 (S)	9.347	9.182	0.165	9.057	1

[a] Data point not included in equation derivation.

Table 34. K_i Binding Affinities of Imidazobenzodiazepines for the a_6 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 40

no.	substituents R_1, R_2, R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR	I_S
1	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = Br (S)	7.337	7.157	0.180	9.217	1
2	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = Br (R)	6.000	6.254	−0.254	9.217	0
3	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C═[CSi$(CH_3)_3$] (S)	6.469	6.648	−0.179	11.520	1
4	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C≡C[Si$(CH_3)_3$] (R)	6.000	5.746	0.254	11.520	0
5	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C≡CH (S)	6.900	7.152	−0.252	9.241	1
6[a]	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = C≡CH (R)	7.215	6.249	0.966	9.241	0
7	R_1, R_2 = 4,5-$(CH_2)_2$, R_8 = Br (S)	7.509	7.259	0.250	8.753	1
8	R_1, R_2 = 4,5-$(CH_2)_2$, R_8 = C≡C[Si$(CH_3)_3$] (S)	6.745	6.752	−0.007	11.050	1
9	R_1, R_2 = 4,5-$(CH_2)_2$, R_8 = C≡CH (S)	7.377	7.254	0.123	8.777	1
10	R_1, R_2 = 4,5-$(CH_2)_3$, R_8 = OCH_3 (S)	7.080	7.192	−0.112	9.057	1

[a] Data point not included in equation derivation.

Table 35. K_i Binding Affinities of 3-(3-X-1,2,4-oxadiazole)-4,5-substituted Imidazobenzodiazepines for the a_5 Benzodiazepine Receptor Isoform:[68] Compounds and Physicochemical Parameters for Derivation of Equation 41

no.	substituents R′, R_1, R_2	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	$L_{R'}$
1	R′ = 3-CH_3, R_1, R_2 = 4,5-$(CH_2)_3$ (S)	8.432	8.674	−0.243	2.870
2[a]	R′ = 3-CH_3, R_1, R_2 = 4,5-$(CH_2)_3$ (R)	6.804	8.674	−1.87	2.870
3	R′ = 3-C_2H_5, R_1, R_2 = 4,5-$(CH_2)_3$ (S)	8.620	7.922	0.698	4.110
4	R′ = 3-$CH(CH_3)_2$, R_1, R_2 = 4,5-$(CH_2)_3$ (S)	8.319	7.922	0.397	4.110
5	R′ = 3-C_6H_5, R_1, R_2 = 4,5-$(CH_2)_3$ (S)	6.342	6.606	−0.264	6.280
6	R′ = 3-CH_3, R_1, R_2 = 4,5-$(CH_2)_2$ (S)	8.143	8.674	−0.532	2.870
7	R′ = 3-C_2H_5, R_1, R_2 = 4,5-$(CH_2)_2$ (S)	7.896	7.922	0.026	4.110
8	R′ = 3-$CH(CH_3)_2$, R_1, R_2 = 4,5-$(CH_2)_2$ (S)	8.071	7.922	0.148	4.110
9	R′ = 3-C_6H_5, R_1, R_2 = 4,5-$(CH_2)_2$ (S)	6.427	6.606	−0.179	6.280

[a] Data point not included in equation derivation.

151 BzR ligands at five distinct $\alpha_{1-3,5,6}\beta_3\gamma_2$ recombinant $GABA_A$/BzR receptor subtypes from at least nine different structutral families. Examination of the included volumes of the α_1-, α_5-, and α_6-containing subtypes indicated that region L_2 for the α_5-containing subtype appeared to be larger in size than the analogous region of the other receptor subtypes. Region L_{DI}, in contrast, appeared to be larger in the α_1 subtype than in the other two subtypes. In the α_6 subtype, region L_3 is either very small or nonexistent.

The in vitro affinities for ligands in Tables 36−39, 41−43, and 45−48 employed in the study were obtained by competition for [^{3}H]Ro 151788 binding to recombinant receptor subtypes at 4 °C, whereas for ligands in Tables 40 and 44 the in vitro affinities were obtained by competition for [^{3}H]Ro 154513

Table 36. Affinities of 5,6-Dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic Acid Ethyl Esters for $\alpha_1\beta_3\gamma_2$ Benzodiazepine Isoform:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 42

no.	substituents R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	CMR
1	H	8.921	8.624	0.297	7.69
2	F	9.097	8.615	0.482	7.71
3	Cl	8.167	8.328	−0.160	8.18
4	Br	7.583	8.155	−0.570	8.47
5	CN	8.000	8.336	−0.336	8.17
6	$CH{=}CH_2$	8.081	8.034	0.047	8.67
7	C_2H_5	7.690	8.064	−0.374	8.62
8	OC_2H_5	7.955	7.972	−0.017	8.77
9	N_3	8.481	8.171	0.311	8.44
10[a]	$CH{=}C{=}CH_2$	8.426	7.740	0.686	9.15
11[a]	$C{\equiv}CH$	7.547	8.141	−0.594	8.49
12	$C{\equiv}CCH_3$	7.996	7.861	0.135	8.95
13	$C{\equiv}CSi(CH_3)_3$	6.917	6.765	0.152	10.77
14	$C{\equiv}CCH_2Si(CH_3)_3$	6.523	6.488	0.035	11.23

[a] Data points not included in equation derivation.

Table 37. Affinities of 5,6-Dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic Acid Ethyl Esters for $\alpha_2\beta_3\gamma_2$ Benzodiazepine Isoform:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 43

no.	substituents R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	B_5	MgVol
1	H	8.70	8.64	0.06	1.0	2.071
2	F	9.05	8.69	0.36	1.35	2.089
3	Cl	7.79	8.10	−0.31	1.80	2.193
4	Br	7.57	7.76	−0.20	1.95	2.246
5	CN	7.35	7.73	−0.39	1.60	2.225
6	$CH{=}CH_2$	7.99	7.88	0.11	3.09	2.310
7	C_2H_5	7.57	7.59	−0.02	3.17	2.353
8	OC_2H_5	7.44	7.22	0.22	3.36	2.411
9	N_3	8.59	8.69	−0.10	4.18	2.284
10[a]	$CH{=}C{=}CH_2$	8.14	7.14	1.00	3.78	2.451
11	$C{\equiv}CH$	7.67	7.41	0.26	1.60	2.267
12[a]	$C{\equiv}CCH_3$	7.65	6.53	1.13	2.040	2.408
13	$C{\equiv}CSi(CH_3)_3$	6.85				2.935
14	$C{\equiv}CCH_2Si(CH_3)_3$	6.52				3.076

[a] Data points not included in equation derivation.

Table 38. Affinities of 5,6-Dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic Acid Ethyl Esters for $\alpha_3\beta_3\gamma_2$ Benzodiazepine Isoform:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 44

no.	substituents R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	B_5	MgVol
1	H	8.96	8.76	0.19	1.0	2.071
2	F	8.96	8.80	0.16	1.35	2.089
3	Cl	8.04	8.26	−0.22	1.80	2.193
4	Br	7.89	7.95	−0.06	1.95	2.246
5	CN	7.72	7.93	−0.21	1.60	2.225
6	$CH{=}CH_2$	8.16	8.03	0.13	3.09	2.310
7	C_2H_5	7.58	7.75	−0.17	3.17	2.353
8	OC_2H_5	7.77	7.42	0.35	3.36	2.411
9	N_3	8.60	8.73	−0.13	4.18	2.284
10[a]	$CH{=}C{=}CH_2$	8.39	7.34	1.05	3.78	2.451
11	$C{\equiv}CH$	7.59	7.63	−0.04	1.60	2.267
12[a]	$C{\equiv}CCH_3$	7.78	6.82	0.96	2.040	2.408
13	$C{\equiv}CSi(CH_3)_3$	6.70				2.935
14	$C{\equiv}CCH_2Si(CH_3)_3$	6.52				3.076

[a] Data points not included in equation derivation.

binding to recombinant receptor subtypes at 4 °C. Using the above-mentioned affinities we evaluated eqs 42−55.

Table 39. Affinities of 5,6-Dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic Acid Ethyl Esters for $\alpha_5\beta_3\gamma_2$ Benzodiazepine Isoform:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 45

no.	substituents R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	MgVol
1	H	9.40	9.80	−0.40	2.071
2[a]	F	9.22	9.75	−0.53	2.089
3	Cl	9.07	9.43	−0.36	2.193
4	Br	9.15	9.27	−0.12	2.246
5[a]	CN	8.22	9.39	−1.11	2.225
6	$CH{=}CH_2$	9.40	9.08	0.32	2.310
7	C_2H_5	8.82	8.95	−0.13	2.353
8	OC_2H_5	8.97	8.78	0.20	2.411
9	N_3	9.52	9.16	0.36	2.284
10	$CH{=}C{=}CH_2$	8.96	8.66	0.30	2.451
11	$C{\equiv}CH$	9.31	9.21	0.10	2.267
12	$C{\equiv}CCH_3$	8.77	8.79	−0.01	2.408
13	$C{\equiv}CSi(CH_3)_3$	8.30	7.19	1.11	2.935
14	$C{\equiv}CCH_2Si(CH_3)_3$	6.52	6.77	−0.25	3.076

[a] Data points not included in equation derivation.

Table 40. Affinities of 5,6-Dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic Acid Ethyl Esters for $\alpha_6\beta_3\gamma_2$ Benzodiazepine Isoform:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 46

no.	substituents R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	B_5	σ_I
1	H	6.52	6.85	0.24	1.0	0
2[a]	F	6.83	7.39	−0.56	1.35	0.52
3	Cl	7.26	7.44	−0.18	1.80	0.47
4	Br	7.66	7.44	0.22	1.95	0.44
5	C_2H_5	6.75	6.97	−0.21	1.60	−0.01
6	OC_2H_5	7.29	7.59	−0.30	3.09	0.28
7	N_3	8.42	7.22	0.13	3.17	0.42
8	$CH{=}C{=}CH_2$	7.35	7.03	0.51	3.36	0.020
9[a]	$C{\equiv}CH$	7.54	7.20	−0.20	4.18	0.29
10	$C{\equiv}CCH_3$	7.00	7.394	−0.394	3.78	0.30
11	$C{\equiv}CSi(CH_3)_3$	6.94			1.60	
12	$C{\equiv}CCH_2Si(CH_3)_3$	6.52			2.040	

[a] Data points not included in equation derivation.

Table 41. Affinities of 5,6-Dihydro-5-methyl-6-oxo-*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic Acid *tert*-Butyl Esters for $\alpha_1\beta_3\gamma_2$ Benzodiazepine Isoform:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 47

no.	substituents R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	MgVol
1	H	7.762	8.207	−0.445	2.475
2	Br	7.943	8.105	−0.162	2.528
3	I	8.013	7.945	0.069	2.611
4	OH	8.824	8.330	0.494	2.411
5	OCH_3	8.171	8.058	0.114	2.552
6	$N(CH_3)_2$	7.883	7.706	0.176	2.734
7	N_3	8.140	8.031	0.109	2.566
8	NCS	7.767	7.829	−0.062	2.671
9	NO_2	7.893	8.107	−0.214	2.527
10	C_2H_5	7.83	7.899	−0.069	2.634
11[a]	$C{\equiv}CH$	7.57	8.065	−0.495	2.548
12	$C{\equiv}CSi(CH_3)_3$	6.706	6.775	−0.069	3.217
13	$C{\equiv}CCH_2Si(CH_3)_3$	6.561	6.503	0.058	3.358

[a] Data point not included in equation derivation.

For the QSARs correlating in vitro affinities of imidazobenzodiazepine 3-carboxylic acid ethyl esters at recombinant BzR subtypes, Tables 36−40, the

Table 42. Affinities of 5,6-Dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic Acid *tert*-Butyl Esters for $\alpha_3\beta_3\gamma_2$ Benzodiazepine Isoform:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 48

no.	substituents R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	MgVol
1[a]	H	7.536	7.967	−0.431	2.475
2	Br	8.036	7.873	0.164	2.528
3	I	7.963	7.724	0.239	2.611
4[a]	OH	9.276	8.081	1.195	2.411
5	OCH_3	8.130	7.829	0.301	2.552
6	$N(CH_3)_2$	7.419	7.503	−0.084	2.734
7	N_3	8.007	7.804	0.203	2.566
8	NCS	7.301	7.616	−0.315	2.671
9	NO_2	7.520	7.874	−0.35	2.527
10	C_2H_5	7.597	7.682	−0.085	2.634
11	C≡CH	7.728	7.835	−0.107	2.548
12	$C{\equiv}CSi(CH_3)_3$	6.593	6.639	−0.046	3.217
13	$C{\equiv}CCH_2Si(CH_3)_3$	6.472	6.387	0.085	3.358

[a] Data points not included in equation derivation.

Table 43. Affinities of 5,6-Dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic Acid *tert*-Butyl Esters for $\alpha_5\beta_3\gamma_2$ Benzodiazepine Isoform:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 49

no.	substituents R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	MgVol
1	H	9.187	9.490	−0.303	2.475
2	Br	9.328	9.376	−0.048	2.528
3	I	9.420	9.196	0.224	2.611
4	OH	9.854	9.627	0.227	2.411
5	OCH_3	9.538	9.323	0.215	2.552
6	$N(CH_3)_2$	9.108	8.930	0.178	2.734
7	N_3	9.523	9.293	0.230	2.566
8	NCS	8.602	9.067	−0.465	2.671
9[a]	NO_2	8.456	9.378	−0.922	2.527
10	C_2H_5	8.764	9.145	−0.381	2.634
11	C≡CH	9.398	9.331	0.067	2.548
12[a]	$C{\equiv}CSi(CH_3)_3$	8.583	7.886	0.697	3.217
13	$C{\equiv}CCH_2Si(CH_3)_3$	7.638	7.582	0.056	3.358

[a] Data points not included in equation derivation.

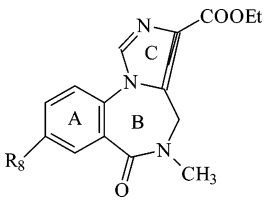
Table 44. Affinities of 5,6-Dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic Acid *tert*-Butyl Esters for $\alpha_6\beta_3\gamma_2$ Benzodiazepine Isoform:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 50

no.	substituents R_8	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	MgVol	*L*
1	H	8.40	8.20	0.20	2.475	3.520
2	Br	8.03	8.06	−0.04	2.528	3.820
3[a]	I	8.34	7.83	0.51	2.611	4.230
4	OH	8.16	8.16	0.00	2.411	2.740
5	OCH_3	8.08	8.01	0.07	2.552	3.980
6	$N(CH_3)_2$	6.93	6.86	0.06	2.734	3.530
7	N_3	8.28	8.24	0.04	2.566	4.620
8	NCS	7.51	7.54	−0.03	2.671	4.290
9	NO_2	7.65	7.89	−0.24	2.527	3.440
10	C_2H_5	7.64	7.65	−0.01	2.634	4.110
11	C≡CH	8.29	8.35	−0.05	2.548	4.660
12	$C{\equiv}CSi(CH_3)_3$	7.23			3.217	
13	$C{\equiv}CCH_2Si(CH_3)_3$	6.52			3.358	

[a] Data point not included in equation derivation.

most significant parameters are CMR, MgVol, B_5, and in one case the electronic effect, σ (eq 46).

(a)

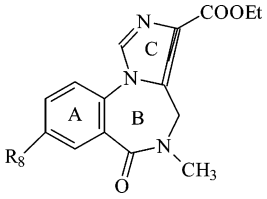


$$\log 1/K_i = -0.603\ (\pm 0.199)\text{CMR} + 13.264\ (\pm 1.767) \quad (42)$$

$n = 12$ $r^2 = 0.819$ $q^2 = 0.761$ $s = 0.326$ $F_{1,10} = 28.760$ $\alpha = 0.01$

Two points are omitted (**10** and **11**, Table 36). The negative term with CMR suggests steric hindrance.

(b)



$$\log 1/K_i = -7.969\ (\pm 3.335)\text{MgVol} + 0.551\ (\pm 0.339)B_5 + 24.586\ (\pm 6.893) \quad (43)$$

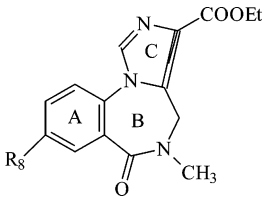
$n = 10$ $r^2 = 0.824$ $q^2 = 0.631$ $s = 0.283$ $F_{2,7} = 16.40$ $\alpha = 0.01$

parameter importance:

MgVol > B_5, MgVol versus B_5 0.611

Two points are omitted (**10** and **12**, Table 37).

(c)



$$\log 1/K_i = -7.235\ (\pm 2.630)\text{MgVol} + 0.474\ (\pm 0.268)B_5 + 23.272\ (\pm 5.437) \quad (44)$$

$n = 10$ $r^2 = 0.863$ $q^2 = 0.628$ $s = 0.223$ $F_{2,7} = 22.176$ $\alpha = 0.01$

parameter importance:

MgVol > B_5, MgVol versus $B_5 = 0.611$

Two points are omitted (**10** and **12**, Table 38).

In both the above eqs 43 and 44 the negative sign with MgVol refers to steric hindrance, whereas the variable B_5 is the sterimol parameter for the largest width of the first atom of the substituent. Both parameters bring out the critical fit of the ligands to the macromolecule.

Table 45. Affinities of 3-Alkyl-1,2,4-oxadiazole-4,5-substituted Imidazobenzodiazepines at Recombinant $\alpha_5\beta_3\gamma_2$ $GABA_A$/Benzodiazepine Receptor Subtypes:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 51

no.	substituents	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	L
1	X = CH_3, Y = $-CH_2CH_2CH_2-$ (S)	8.432	8.764	−0.243	2.87
2[a]	X = CH_3, Y = $-CH_2CH_2CH_2-$ (R)	6.804	8.764	−1.870	2.87
3	X = C_2H_5, Y = $-CH_2CH_2CH_2-$ (S)	8.620	7.922	0.698	4.11
4	X = $CH(CH_3)_2$, Y = $-CH_2CH_2CH_2-$ (S)	8.319	7.922	0.397	4.11
5	X = C_6H_5, Y = $-CH_2CH_2CH_2-$ (S)	6.342	6.606	−0.264	6.28
6	X = CH_3, Y = $-CH_2CH_2-$ (S)	8.143	8.764	−0.532	2.87
7	X = C_2H_5, Y = $-CH_2CH_2-$ (S)	7.896	7.922	−0.026	4.11
8	X = $CH(CH_3)_2$, Y = $-CH_2CH_2-$ (S)	8.071	7.922	0.148	4.11
9	X = C_6H_5, Y = $-CH_2CH_2-$ (S)	6.427	6.606	−0.179	6.28

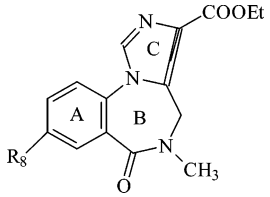
[a] Data point not included in equation derivation.

Table 46. Affinities of Substituted Pyridoindoles at $\alpha_1\beta_3\gamma_2$ Benzodiazepine Receptor:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 52

no.	substituents	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	MgVol
1	H	8.959	8.749	0.209	1.873
2[a]	10-NO_2	6.613	8.279	−1.667	2.047
3	2-Cl	8.409	8.419	−0.010	1.996
4	2-OCH_3	8.292	8.702	−0.409	1.891
5	2-F	8.469	8.211	0.258	2.073
6	2-$OCH_2C_6H_5$	6.365	6.571	−0.207	2.681
7	2-$OCOC(CH_3)_3$	6.807	6.648	0.159	2.652

[a] Data point not included in equation derivation.

(d)



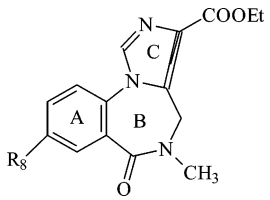
$$\log 1/K_i = -3.018\ (\pm 0.804)\text{MgVol} + 16.052\ (\pm 1.917) \quad (45)$$

$n = 11$ $r^2 = 0.889$ $q^2 = 0.517$ $s = 0.290$ $F_{1,9} = 63.047$ $\alpha = 0.01$

Three points are omitted (**2**, **5**, and **13**, Table 39).

MgVol, the most important single variable, expresses steric effect. In general, no correlation with a hydrophobic factor was found.

(e)



$$\log 1/K_i = 0.325\ (\pm 0.235)B_5 + 1.912\ (\pm 1.362)\sigma_I + 5.957\ (\pm 0.801) \quad (46)$$

$n = 8$ $r^2 = 0.815$ $q^2 = 0.416$ $s = 0.290$ $F_{2,5} = 11.676$ $\alpha = 0.05$

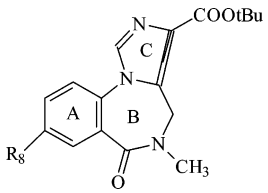
parameter importance: $\sigma_I > B_5$

Two points are omitted (Table 40).

σ_I is the most important parameter in the development of eq 46, indicating a significant role for electron-withdrawing groups. No correlation with hydrophobic effect was found.

From the affinities of 5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic acid *tert*-butyl esters for BzR isoforms,the following four correlations are developed.

(a) For $\alpha_1\beta_3\gamma_2$ BzR isoform:



$$\log 1/K_i = -1.930\ (\pm 0.577)\text{MgVol} + 12.983\ (\pm 1.506) \quad (47)$$

$n = 12$ $r^2 = 0.8555$ $q^2 = 0.801$ $s = 0.243$ $F_{1,10} = 59.61$ $\alpha = 0.01$

One point (compound **11**) is omitted (Table 41).

(b) For $\alpha_3\beta_3\gamma_2$ BzR isoform:

$$\log 1/K_i = -1.789\ (\pm 0.570)\text{MgVol} + 12.394\ (\pm 1.560) \quad (48)$$

$n = 11$ $r^2 = 0.841$ $q^2 = 0.794$ $s = 0.230$ $F_{1,9} = 50.294$ $\alpha = 0.01$

Compounds **1** and **4** are omitted (Table 42).

(c) For $\alpha_5\beta_3\gamma_2$ BzR isoform:

$$\log 1/K_i = -2.161\ (\pm 0.786)\text{MgVol} + 14.838\ (\pm 2.086) \quad (49)$$

$n = 11$ $r^2 = 0.812$ $q^2 = 0.697$ $s = 0.278$ $F_{1,9} = 38.667$ $\alpha = 0.01$

Two datapoints, **9** and **12**, are omitted (Table 43).

For the above three equations, 47−49, the molar volume is the most important single parameter, which through its negative term suggests that fit to a macromolecule of limited steric capacity is important.

(d) For $\alpha_6\beta_3\gamma_2$ BzR isoform:

$$\log 1/K_i = -5.158\ (\pm 1.195)\text{MgVol} + 0.463\ (\pm 0.191)L + 19.332\ (\pm 2.832) \quad (50)$$

$n = 10$ $r^2 = 0.939$ $q^2 = 0.885$ $s = 0.129$ $F_{2,7} = 53.31$ $\alpha = 0.01$

parameter importance: MgVol > L (Table 44)

Table 47. Affinities of Substituted 1,4-Benzodiazepines at $\alpha_1\beta_3\gamma_2$ Benzodiazepine Receptor:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 53

no.	substituents R_1, R_5, R_7	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	MgVol	L_7	B_{1-7}
1	R_1 = Me, R_5 = (2-thienyl), R_7 = Cl	7.72	7.52	0.19	1.999	3.52	1.80
2	R_1 = H, R_5 = (2-thienyl), R_7 = F	6.76	6.38	0.38	1.753	2.65	1.35
3	R_1 = Me, R_5 = (2-thienyl), R_7 = F	6.85	7.11	−0.26	1.894	2.65	1.35
4	R_1 = H, R_5 = (2-azidophenyl), R_7 = N_3	5.67	5.87	−0.20	2.237	4.62	1.50
5	R_1 = Me, R_5 = (2-NO_2-phenyl), R_7 = NO_2	9.31	8.93	0.38	2.300	3.44	1.70
6	R_1 = Me, R_5 = phenyl, R_7 = C≡CSi$(CH_3)_3$	7.03			2.816		
7[a]	R_1 = Me, R_5 = phenyl, R_7 = C≡CH	7.12	5.64	1.48	2.147	4.66	1.60
8	R_1 = Me, R_5 = phenyl, R_7 = CN	6.49	6.19	0.30	2.106	4.23	1.60
9	R_1 = R_7 = H, R_5 = phenyl	6.54	6.63	−0.09	1.811	2.06	1
10	R_1 = Me, R_5 = phenyl, R_7 = H	7.09	7.37	−0.27	1.951	2.06	1
11	R_1 = H, R_5 = (2-NO_2-phenyl), R_7 = Br	7.80	8.30	−0.51	2.160	3.82	1.95
12	R_1 = Me, R_5 = phenyl, R_7 = Br	8.03	8.13	−0.10	2.126	3.82	1.95
13	R_1 = Me, R_5 = phenyl, R_7 = Cl	7.85	7.92	−0.06	2.074	3.52	1.80
14	R_1 = Me, R_5 = (2-NO_2-phenyl), R_7 = F	8.66	8.42	0.24	2.143	2.65	1.35

[a] Data point not included in equation derivation.

Table 48. Affinities of Substituted 1,4-Benzodiazepines at $\alpha_2\beta_3\gamma_2$ Benzodiazepine Receptor:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 54

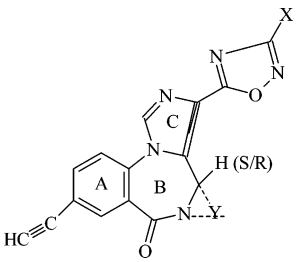
no.	substituents R_1, R_5, R_7	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	MgVol	π_7
1	R_1 = Me, R_5 = (2-thienyl), R_7 = Cl	7.88	7.53	0.35	1.999	0.71
2	R_1 = H, R_5 = (2-thienyl), R_7 = F	6.47	6.63	−0.15	1.753	0.14
3	R_1 = Me, R_5 = (2-thienyl), 7-F	6.67	6.83	−0.16	1.894	0.14
4	R_1 = Me, R_5 = phenyl, 7-C≡CSi$(CH_3)_3$	7.14			2.816	
5	R_1 = Me, R_5 = phenyl, 7-C≡CH	7.38	7.44	−0.07	2.147	0.40
6	R_1 = Me, R_5 = phenyl, 7-CN	6.51	6.45	0.06	2.106	−0.57
7	R_1 = H, R_5 = phenyl, R_7 = H	6.63	6.58	0.05	1.811	0
8	R_1 = Me, R_5 = phenyl, R_7 = H	6.86	6.78	0.08	1.951	0
9	R_1 = H, R_5 = (2-NO_2-phenyl), R_7 = Br	7.51	7.90	−0.40	2.160	0.86
10	R_1 = Me, R_5 = phenyl, R_7 = Br	8.03	7.86	0.17	2.126	0.86
11	R_1 = Me, R_5 = phenyl, R_7 = Cl	7.70	7.64	0.06	2.074	0.71
12[a]	R_1 = Me, R_5 = (2-NO_2-phenyl), R_7 = F	8.60	7.19	1.41	2.143	0.14

[a] Data point not included in equation derivation.

One point is omitted (compound **3**), whereas compounds **12** and **13** are not included, because their descriptors are not available. Once again, MgVol seems to be the most significant parameter. Both parameters point to a steric effect.

Equations 42−50 seem strange because they contain no π or Clog *P* term. From the correlation matrix it is shown that Clog *P* and MgVol are not collinear. For all cases 42−50 no parametrization has been done for the different positions; all of the points are fit well by eqs 42−50.

(e) Using the affinities of 3-alkyl-1,2,4-oxodiazole 4,5-substituted imidazobenzodiazepines for recombinant $\alpha_5\beta_3\gamma_2$ BzR, eq 51 is derived:



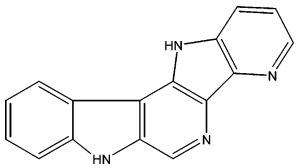
$$\log 1/K_i = -0.607\ (\pm 0.303)L + 10.415\ (\pm 1.637) \quad (51)$$

$n = 8$ $r^2 = 0.799$ $q^2 = 0.656$ $s = 0.430$ $F_{1,6} = 23.989$ $\alpha = 0.01$

One datapoint is omitted (compound **2**, Table 45).

No role for hydrophobicity is found. The reason for this is apparent from the correlation matrix, where it is seen that *L* and Clog *P* are significantly collinear (0.932). The sterimol parameter *L* (for the length of the first atom of substituent R′) has a negative sign, indicating that steric interactions at the 3-position of the 1,2,4-oxodiazolyl ring are unfavorable.

(f) For the affinities of pyrido-diindoles at the $\alpha_1\beta_3\gamma_2$ $GABA_A$/BzR receptor, correlation 52 is developed.



$$\log 1/K_i = -2.698\ (\pm 0.978)\text{MgVol} + 13.803\ (\pm 2.173) \quad (52)$$

$n = 6$ $r^2 = 0.937$ $q^2 = 0.852$ $s = 0.294$ $F_{1,4} = 58.52$ $\alpha = 0.01$

Compound **2** is omitted (Table 46).

Clog *P* and MgVol are significantly collinear (0.612). MgVol with a negative sign refers to a steric hindrance.

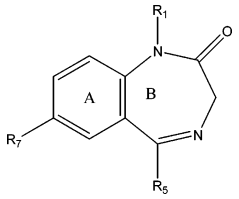
(g) In vitro affinities of substituted 1,4-benzodiazepines at recombinant α_1, α_2, α_3, and $\alpha_5\beta_3\gamma_2$ $GABA_A$/

Table 49. Affinities of Substituted 1,4-Benzodiazepines at $\alpha_3\beta_3\gamma_2$ Benzodiazepine Receptor:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 55

no.	substituents R_1, R_5, R_7	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	B_{5-7}
1	R_1 = Me, R_5 = (2-thienyl), R_7 = Cl	7.873	7.596	0.277	1.80
2	R_1 = H, R_5 = (2-thienyl), R_7 = F	6.393	6.83	−0.438	1.35
3	R_1 = Me, R_5 = (2-thienyl), R_7 = F	6.688	6.83	−0.142	1.35
4[a]	R_1 = H, R_5 = (2-azidophenyl), R_7 = N_3	5.335	11.648	−6.313	4.18
5	R_1 = Me, R_5 = (2-NO_2-phenyl), R_7 = NO_2	9.199	8.686	0.433	2.44
6	R_1 = Me, R_5 = phenyl, R_7 = C≡CSi$(CH_3)_3$	6.693			
7	R_1 = 1-Me, R_5 = phenyl, R_7 = C≡CH	7.324	7.256	0.068	1.60
8[a]	R_1 = Me, R_5 = phenyl, R_7 = CN	6.456	7.256	−0.80	1.60
9	R_1 = H, R_5 = phenyl, R_7 = H	6.456	6.234	0.222	1.0
10	R_1 = Me, R_5 = phenyl, R_7 = H	6.498	6.234	0.263	1.0
11	R_1 = H, R_5 = (2-NO_2-phenyl), R_7 = Br	7.284	7.852	−0.568	1.95
12	R_1 = Me, R_5 = phenyl, R_7 = Br	7.509	7.852	−0.343	1.95
13	R_1 = Me, R_5 = phenyl, R_7 = Cl	7.824	7.596	0.228	1.80
14[a]	R_1 = Me, R_5 = (2-NO_2-phenyl), R_7 = F	8.347	6.83	1.517	1.35

[a] Data points not included in equation derivation.

BzR were used to develop the following QSAR.



$$\log 1/K_i = 5.219\ (\pm 2.009)\mathrm{MgVol} - 1.782\ (\pm 0.503)L_7 + 3.143\ (\pm 1.113)B_{1-7} - 2.290\ (\pm 3.314) \quad (53)$$

$n = 12$ $r = 0.958$ $q^2 = 0.779$ $s = 0.343$ $F_{3,8} = 29.76$ $\alpha = 0.01$

parameter importance: MgVol > L_7 > B_{1-7}

No role for the hydrophobic effect was found, whereas MgVol and Clog *P* were significantly collinear (0.702). One data point was rejected (compound **7**, Table 47). All three of the used parameters bring out steric effects and the critical fit of the ligands to the macromolecule.

(h) $$\log 1/K_i = 1.432\ (\pm 1.376)\mathrm{MgVol} + 0.961\ (\pm 0.429)L_7 + 3.143\ (\pm 1.113)\pi_7 - 3.984\ (\pm 2.709) \quad (54)$$

$n = 10$ $r^2 = 0.881$ $q^2 = 0.759$ $s = 0.234$ $F_{2,7} = 26.18$ $\alpha = 0.01$

parameter importance: π_7 > MgVol

One data point is omitted (Table 48).

Although no parametrization has been done for the different positions R_1 and R_5, all of the points are fit well by eq 54.

$$\log 1/K_i = 1.702\ (\pm 0.623)B_{5-7} - 4.532\ (\pm 1.046) \quad (55)$$

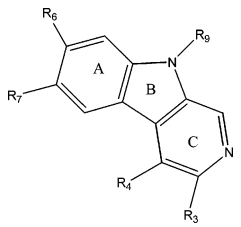
$n = 10$ $r^2 = 0.832$ $q^2 = 0.699$ $s = 0.369$ $F_{1,8} = 39.736$ $\alpha = 0.01$

Three points are rejected. One of them, compound **4**, is the least active, whereas compound **14** is the second most active (Table 49). The third analogue has a CN group at position 7, which is possible to be biotransformed to a $-CH_2NH_2$ group. The B_{1-7} parameter does not cover a hydrophobic effect.

(k) $$\log 1/K_i = -1.145\ (\pm 0.336)B_{5-7} + 1.505\ (\pm 0.479)\mathrm{CMR} - 2.362\ (\pm 3.469) \quad (56)$$

$n = 10$ $r^2 = 0.912$ $q^2 = 0.839$ $s = 0.293$ $F_{2,7} = 36.62$ $\alpha = 0.01$

Three data points were omitted, namely, compounds **8**, **10**, and **11** (Table 50). Their predicted affinities are higher than their experimental parameter importance: B_{5-7} > CMR. Again, the B_{5-7} parameter does not cover a hydrophobic effect. The negative sign with this parameter indicates steric interactions at the 7-position of the phenyl ring. Equation 56 is not very satisfactory according to the confidence limits of the constant term. There is a little correlation between the CMR and Clog *P* (0.432) and B_{5-7} and CMR (0.422).



In continuation, the affinities of β-carbolines at α_1,α_2 and $\alpha_3\beta_3\gamma_2$ receptors were studied and eqs 57−59 were developed.

(l) $$\log 1/K_i = 0.752\ (\pm 0.652)\ \mathrm{Clog}\ P - 0.158\ (\pm 0.078)\ \mathrm{Clog}\ P^2 + 2.174\ (\pm 1.128)B_{1-3} + 0.674\ (\pm 0.250)B_{5-3} + 0.956\ (\pm 2.587) \quad (57)$$

$n = 26$ $r^2 = 0.823$ $q^2 = 0.745$ $s = 0.459$ $F_{4,21} = 24.44$ $\alpha = 0.01$

optimum value of lipophilicity: Clog P_o = 2.384 (±1.382) from 0.608 to 3.607

parameter importance: Clog *P* > B_{5-3} > B_{1-3}

Three compounds are omitted, namely, **10**, **13**, and **29** (Table 51).

No parametrization has been done for different positions R_4, R_6, R_7, and R_9. All points fit well by eq

Table 50. Affinities of Substituted 1,4-Benzodiazepines at $\alpha_5\beta_3\gamma_2$ Benzodiazepine Receptor:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 56

no.	substituents R_1, R_5, R_7	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	B_{5-7}	CMR
1	R_1 = Me, R_5 = (2-thienyl), R_7 = Cl	7.94	7.51	0.43	1.80	7.926
2	R_1 = H, R_5 = (2-thienyl), R_7 = F	6.82	6.61	0.21	1.35	6.986
3	R_1 = Me, R_5 = (2-thienyl), R_7 = F	7.18	7.31	−0.12	1.35	7.450
4	R_1 = H, R_5 = (2-azidophenyl), R_7 = N_3	5.79	5.90	−0.11	4.18	8.664
5	R_1 = Me, R_5 = (2-NO_2-phenyl), R_7 = NO_2	8.11	8.16	0.05	2.44	8.848
6	R_1 = Me, R_5 = phenyl, R_7 = C≡CSi$(CH_3)_3$	7.20				10.70
7	R_1 = Me, R_5 = phenyl, R_7 = C≡CH	8.17	8.49	−0.32	1.60	8.426
8[a]	R_1 = Me, R_5 = phenyl, R_7 = CN	6.58	8.00	−1.43	1.60	8.103
9	R_1 = H, R_5 = phenyl, R_7 = H	6.85	7.27	−0.42	1.0	7.161
10[a]	R_1 = Me, R_5 = phenyl, R_7 = H	7.02	7.97	−0.95	1.0	7.625
11[a]	R_1 = H, R_5 = (2-NO_2-phenyl), R_7 = Br	6.70	8.28	−1.58	1.95	8.550
12	R_1 = Me, R_5 = phenyl, R_7 = Br	8.11	8.05	0.06	1.95	8.402
13	R_1 = Me, R_5 = phenyl, R_7 = Cl	7.96	7.80	0.16	1.80	8.117
14	R_1 = Me, R_5 = (2-NO_2-phenyl), R_7 = F	8.68	8.52	0.16	1.35	8.252

[a] Data points not included in equation derivation.

Table 51. Affinities of Substituted β-Carbolines at $\alpha_2\beta_3\gamma_2$ Benzodiazepine Receptor:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 57

no.	substituents R_3, R_4, R_6, R_7, R_9	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	Clog P	B_{1-3}	B_{5-3}
1	R_3 = COC_3H_7, R_4 = R_6 = R_7 = R_9 = H	7.796	8.314	−0.518	3.233	1.63	4.50
2	R_3 = $COOC(CH_3)_3$, R_4 = R_6 = R_7 = R_9 = H	7.824			2.836		
3	R_3 = $COOC_2H_5$, R_4 = R_6 = R_7 = R_9 = H	8.310	8.38	−0.07	2.128	1.64	4.41
4	R_3 = OC_2H_5, R_4 = R_6 = R_7 = R_9 = H	7.60	6.89	0.71	3.402	1.35	3.36
5	R_3 = NCS, R_4 = R_6 = R_7 = R_9 = H	6.92	7.61	−0.69	3.886	1.50	2.24
6	R_3 = Cl, R_4 = R_6 = R_7 = R_9 = H	6.90	6.96	−0.06	2.713	1.80	1.80
7	R_3 = OC_3H_7, R_4 = R_6 = R_7 = R_9 = H	7.28	7.39	−0.11	3.931	1.35	4.42
8	R_3 = OC_4H_9, R_4 = R_6 = R_7 = R_9 = H	6.71	6.96	−0.25	4.460	1.35	4.79
9	R_3 = $OCH_2CH(CH_3)_2$, R_4 = R_6 = R_7 = R_9 = H	6.91	7.39	−0.48	4.330	1.35	4.42
10[a]	R_3 = $OCH_2CH(CH_3)_2$, R_4 = R_6 = R_7 = R_9 = H	6.09	7.17	−1.08	4.330	1.70	4.42
11	$R_{3,6}$ = $-NO_2$, R_4 = R_7 = R_9 = H	7.08	7.08	0	1.545	1.50	4.42
12	$R_{3,6}$ = NCS, R_4 = R_7 = R_9 = H	6.37	6.42	−0.05	5.523	1.64	2.44
13[a]	R_3 = $COOC_2H_5$, R_6 = $OCH_2C_6H_5$, R_4 = R_7 = R_9 = H	6.77	7.87	−0.10	4.197	1.64	4.24
14	R_3 = $COOCH_3$, R_6 = NH-cy-C_6H_{11}, R_4 = R_7 = R_9 = H	7.76	7.30	0.46	3.939	1.64	4.41
15	R_3 = $COOCH_3$, R_6 = $NHCH_2C_6H_5$, R_4 = R_7 = R_9 = H	7.52	7.53	−0.01	3.356	1.64	3.36
16	R_3 = $COOCH_3$, R_6 = NHCH2-naphthyl, R_4 = R_7 = R_9 = H	6.69	6.95	−0.27	4.530	1.64	3.36
17	R_3 = $COOCH_3$, R_4 = CH_2OCH_3, R_6 = R_7 = R_9 = H	8.55	8.35	0.20	1.906	1.64	4.41
18	R_3 = $COOC_2H_5$, R_4 = C_2H_5, R_6 = $OCH_2C_6H_5$, R_7 = R_9 = H	7.11	7.11	−0.01	5.225	1.64	4.41
19	R_3 = $COOC_2H_5$, R_4 = C_2H_5, R_6 = OCH_2-2-naphthyl, R_7 = R_9 = H	6.54	5.84	0.69	6.399	1.64	4.41
20	R_3 = $COOC_2H_5$, R_4 = C_2H_5, R_6 = OCH_3, R_7 = R_9 = H	8.54	8.21	0.33	3.457	1.64	4.41
21	R_3 = $COOC_2H_5$, R_4 = C_2H_5, R_6 = $O(CH_2)_7CH_3$, R_7 = R_9 = H	4.53	4.79	−0.26	7.160	1.64	4.41
22	R_3 = $COOC_2H_5$, R_4 = CH_2OCH_3, R_6 = OCH_3, R_7 = R_9 = H	8.92	8.38	0.54	2.207	1.64	4.41
23	R_3 = $COOC_2H_5$, R_4 = CH_2OCH_3, R_6 = OC_3H_7, R_7 = R_9 = H	8.92	8.27	0.65	3.265	1.64	4.41
24	R_3 = OC_3H_7, R_4 = CH_2OCH_3, R_6 = OC_3H_7	6.67	6.63	0.04	5.069	1.35	4.42
25	R_3 = $CONHNH_2$, R_4 = CH_2OCH_3, R_6 = OC_3H_7, R_7 = R_9 = H	6.37	7.15	−0.78	1.867	1.50	3.09
26	R_3 = NH_2, R_4 = CH_2OCH_3, R_6 = OC_3H_7, R_7 = R_9 = H	6.27	6.06	0.21	2.965	1.35	1.97
27	R_3 = $COOC_2H_5$, R_4 = CH_2OCH_3, R_6 = $OCH_2C_6H_5$, R_7 = R_9 = H	8.38	7.99	0.39	3.975	1.64	4.41
28	R_3 = $COOCH(CH_3)_2$, R_4 = CH_2OCH_3, R_6 = $OCH_2C_6H_5$, R_7 = R_9 = H	7.81	8.25	−0.43	4.284	2.14	3.43
29[a]	R_3 = NCS, R_4 = CH_2OCH_3, R_6 = $-OCH_2C_6H_5$, R_7 = R_9 = H	7.08	6.20	0.88	5.734	1.50	4.24
30	R_3 = $COOC_2H_5$, R_4 = CH_2OCH_3, R_6 = OH, R_7 = R_9 = H	8.27	8.37	−0.10	2.034	1.64	4.41

[a] Data points not included in equation derivation.

57. No role for an electronic effect was found, whereas Clog P is the most important parameter, following the sterimol parameters B_{1-3} and B_{5-3}. Both terms have a positive effect on the affinity.

$$\textbf{(m)}\ \log 1/K_i = -0.839\ (\pm 0.183)\ \text{Clog}\ P + 3.478\ (\pm 1.109)B_{1-6} + 0.565\ (\pm 0.262)B_{5-3} + 4.638\ (\pm 1.747) \quad (58)$$

$n = 26$ $r^2 = 0.823$ $q^2 = 0.760$ $s = 0.473$ $F_{3,22} = 34.14$ $\alpha = 0.01$

parameter importance: Clog $P > B_{1-6} > B_{5-3}$

Five data points are omitted (compounds **4**, **7**, **14**, **29**, and **35,** Table 52). Hydrophobicity has a negative sign, whereas B_{1-6} and B_{5-3} are the sterimol parameters for the corresponding substituents in positions 6 and 3 of the phenyl and pyridinyl rings.

$$\textbf{(n)}\ \log 1/K_i = 0.839\ (\pm 0.674)\ \text{Clog}\ P - 0.173\ (\pm 0.081)\ \text{Clog}\ P^2 + 2.895\ (\pm 1.076)B_{1-3} + 0.641\ (\pm 0.246)B_{5-3} + 0.355\ (\pm 2.623) \quad (59)$$

$n = 25$ $r^2 = 0.848$ $q^2 = 0.749$ $s = 0.430$ $F_{4,20} = 27.91$ $\alpha = 0.01$

optimum lipophilicity value: Clog P_o = 2.424 (±1.056) from 0.876 to 3.062

parameter importance: Clog $P > B_{5-3} > B_{1-3}$

Four data points are omitted, namely, compounds **4**, **12**, **18**, and **28** (Table 53).

Although no parametrization has been done for positions R_4, R_6, R_7, and R_9, all compounds are well predicted by eq 59. Using the parabolic model we

Table 52. Affinities of Substituted β-Carbolines at $\alpha_1\beta_3\gamma_2$ Benzodiazepine Receptor:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 58

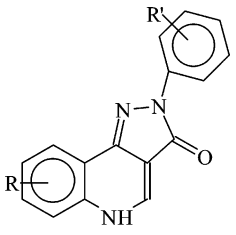
no.	substituents R_3, R_4, R_6, R_7, R_9	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	Clog P	B_{1-6}	B_{5-3}
1	$R_3 = COC_3H_7$, $R_4 = R_6 = R_7 = R_9 = H$	8.678	7.828	0.85	3.233	1.0	4.5
2	$R_3 = COOC(CH_3)_3$, $R_4 = R_6 = R_7 = R_9 = H$	9.143	8.113	1.03	2.836	1.0	
3	$R_3 = COOC_2H_5$, $R_4 = R_6 = R_7 = R_9 = H$	8.921	8.621	0.30	2.128	1.0	4.41
4[a]	$R_3 = OC_2H_5$, $R_4 = R_6 = R_7 = R_9 = H$	8.192	7.707	0.484	3.402	1.0	3.36
5	$R_3 = NCS$, $R_4 = R_6 = R_7 = R_9 = H$	7.173	7.360	−0.188	3.886	1.0	4.24
6	$R_3 = Cl$, $R_4 = R_6 = R_7 = R_9 = H$	7.219	8.201	−0.982	2.713	1.0	1.80
7[a]	$R_3 = OC_3H_7$, $R_4 = R_6 = R_7 = R_9 = H$	8.276	7.328	0.948	3.931	1.0	4.420
8	$R_3 = OC_4H_9$, $R_4 = R_6 = R_7 = R_9 = H$	7.433	6.949	0.484	4.460	1.0	4.79
9	$R_3 = OCH_2C_6H_5$, $R_4 = R_6 = R_7 = R_9 = H$	6.081	7.106	−1.025	4.241	1.0	3.50
10	$R_3 = OCH_2CH(CH_3)_2$, $R_4 = R_6 = R_7 = R_9 = H$	7.604	7.042	0.562	4.330	1.0	4.42
11	$R_3 = OCH_2CH_2CH(CH_3)_2$, $R_4 = R_6 = R_7 = R_9 = H$	6.456	6.663	−0.207	4.859	1.0	5.710
12	$R_3 = OCH(CH_3)_2$, $R_4 = R_6 = R_7 = R_9 = H$	6.548	7.486	−0.938	3.711	1.0	4.10
13	$R_3 = OCH_2CH(CH_3)_2$, $R_4 = R_6 = R_7 = R_9 = H$	6.611	7.042	−0.431	4.330	1.0	4.420
14[a]	$R_{3,6} = NO_2$, $R_4 = R_7 = R_9 = H$	7.889	10.877	−2.988	1.545	1.70	2.44
15	$R_{3,6} = NCS$, $R_4 = R_7 = R_9 = H$	7.866	7.501	0.366	5.523	1.50	4.24
16	$R_3 = COOCH_3$, $R_6 = NCS$, $R_4 = R_7 = R_9 = H$	8.467	9.126	−0.658	3.256	1.50	3.36
17	$R_3 = COOC_2H_5$, $R_6 = OCH_2C_6H_5$, $R_4 = R_7 = R_9 = H$	8.143	8.057	0.086	4.197	1.35	4.41
18	$R_3 = COOCH_3$, $R_6 = NH\text{-cy-}C_6H_{11}$, $R_4 = R_7 = R_9 = H$	8.622	8.242	0.380	3.939	1.35	3.36
19	$R_3 = COOCH_3$, $R_6 = NHCH_2C_6H_5$, $R_4 = R_7 = R_9 = H$	8.266	8.660	−0.394	3.356	1.35	3.36
20[a]	$R_3 = COOCH_3$, $R_6 = NHCH_2$-naphthyl, $R_4 = R_7 = R_9 = H$	7.513			4.530		3.36
21	$R_3 = COOC_2H_5$, $R_4 = CH_2OCH_3$, $R_6 = R_7 = R_9 = H$	9.201	8.780	0.421	1.906	1	4.41
22	$R_3 = COOC_2H_5$, $R_4 = C_2H_5$, $R_6 = OCH_2C_6H_5$, $R_7 = R_9 = H$	7.682	7.442	0.24	5.225	1.35	4.41
23[a]	$R_3 = COOC_2H_5$, $R_4 = C_2H_5$, $R_6 = OCH_2$-2-naphthyl, $R_7 = R_9 = H$	6.738			6.399		4.41
24	$R_3 = COOC_2H_5$, $R_4 = C_2H_5$, $R_6 = OCH_3$, $R_7 = R_9 = H$	8.796	8.925	−0.129	3.457	1.35	4.41
25	$R_3 = COOC_2H_5$, $R_4 = C_2H_5$, $R_6 = O(CH_2)_7CH_3$, $R_7 = R_9 = H$	5.438	5.933	−0.495	7.160	1.35	4.41
26	$R_3 = COOC_2H_5$, $R_4 = CH_2OCH_3$, $R_6 = OCH_3$, $R_7 = R_9 = H$	9.854	9.483	0.371	2.207	1.35	4.41
27	$R_3 = COOC_2H_5$, $R_4 = CH_2OCH_3$, $R_6 = OC_3H_7$, $R_7 = R_9 = H$	9.310	8.725	0.585	3.365	1.35	4.41
28	$R_3 = OC_3H_7$, $R_4 = CH_2OCH_3$, $R_6 = OC_3H_7$, $R_7 = R_9 = H$	7.609	7.432	0.177	5.069	1.35	4.42
29[a]	$R_3 = CONHNH_2$, $R_4 = CH_2OCH_3$, $R_6 = OC_3H_7$, $R_7 = R_9 = H$	7.337	9.727	−2.390	1.867	1.35	3.09
30	$R_3 = NH_2$, $R_4 = CH_2OCH_3$, $R_6 = OC_3H_7$, $R_7 = R_9 = H$	7.347	8.940	−1.593	2.965	1.35	1.97
31	$R_3 = COOC_2H_5$, $R_4 = CH_2OCH_3$, $R_6 = OCH_2C_6H_5$, $R_7 = R_9 = H$	8.387	8.216	0.171	3.975	1.35	4.41
32	$R_3 = COOCH(CH_3)_2$, $R_4 = CH_2OCH_3$, $R_6 = OCH_2C_6H_5$, $R_7 = R_9 = H$	7.907	7.994	−0.087	4.284	1.35	3.43
33	$R_3 = NCS$, $R_4 = CH_2OCH_3$, $R_6 = OCH_2C_6H_5$, $R_7 = R_9 = H$	7.602	6.955	0.647	5.734	1.35	4.24
34[a]	$R_3 = COOC_2H_5$, $R_4 = CH_2OCH_3$, $R_6 = OCH_2$-2-naphthyl, $R_7 = R_9 = H$	7.812			5.149		4.41
35[a]	$R_3 = COOC_2H_5$, $R_4 = CH_2OCH_3$, $R_6 = OH$, $R_7 = R_9 = H$	8.699	9.607	−0.908	2.034	1.35	4.41

[a] Data points not included in equation derivation.

found that the Clog P_o value is close to the usual value of the CNS agents.

3.27. 2-Aryl(heteroaryl)-2,5-dihydropyrazolo[4,3-*c*]-quinolin-3(3*H*)-ones

Savini et al.[72a] synthesized, tested, and studied in terms of QSAR a large series of 2-aryl(heteroaryl)-2,5-dihydropyrazolo[4,3-*c*]quinolin-3(3*H*)-ones (Table 54), carrying appropriate substituents at the quinolines and N-2-phenyl rings. Their results were in full agreement with previously proposed results. The electronic and hydrophobic effects of substituents were assessed by the Hammett (σ) and Hansch (π) substituent constants, whereas the molar refractivity, the van der Waals volume, and the sterimol Verloop parameters were employed to model bulkiness and polarizability effects. Therefore, for the 8-substituted-2-phenyl congeners, the 6-substituted-2-phenyl congeners, and the 8-OCF_3-2-phenyl substituted congeners the following equations were derived:[72]



$$pIC_{50} = -0.32vW + 9.63$$

$$n = 9 \quad r^2 = 0.883 \quad q^2 = 0.745 \quad s = 0.208 \quad (60)$$

$$pIC_{50} = -2.63\ vW + 9.35$$

$$n = 5 \quad r^2 = 0.912 \quad q^2 = 0.801 \quad s = 0.543 \quad (61)$$

$$pIC_{50} = -1.40\sigma - 1.55MR + 9.46$$

$$n = 15 \quad r^2 = 0.803 \quad s = 0.418 \quad (62)$$

We reanalyzed all of the congeners (Table 54), and QSAR 63 has been developed from these data.

$$\log 1/IC_{50} = -2.449\ (\pm 0.556)\sigma_{R'} - 0.442\ (\pm 0.218)MR_{R_8} - 0.415\ (\pm 0.187)L_{R'_{4'}} - 0.593\ (\pm 0.369)I - 2.025\ (\pm 0.405)B_{5R} + 12.150\ (0.765) \quad (63)$$

$n = 52 \quad r^2 = 0.823 \quad q^2 = 0.749 \quad s = 0.512 \quad F_{5,46} = 42.48 \quad \alpha = 0.01$

I is an indicator (1/0) for the 7-substituted compounds. The $\sigma_{R'}$ term would seem to imply a negative role for electron-attracting groups in the 3′- and 4′-positions. For compounds **5**, **20**, **23**, **25**, and **53** the $\sigma_{R'}$ values are missing. Thus, they are not included in the derivation of the equation. The equations point out a significant steric hindrance in the 8-, 6-, and 4′-positions. The negative signs with $\sigma_{R'}$, $L_{R'_{4'}}$, B_{5R}, and MR_{R_8} indicates that the interaction is favored by small electron-donating groups. The lipophilic character of the substituents and the overall lipophilicity do not play any role in the receptor−ligand interaction.

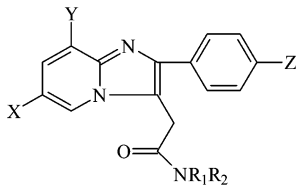
Table 53. Affinities of Substituted β-Carbolines at $\alpha_3\beta_3\gamma_2$ Benzodiazepine Receptor:[71a] Compounds and Physicochemical Parameters for Derivation of Equation 59

no.	substituents R_3, R_4, R_6, R_7, R_9	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	Clog P	B_{1-6}	B_{5-3}
1	$R_3 = COC_3H_7$, $R_4 = R_6 = R_7 = R_9 = H$	7.678	7.941	−0.264	3.233	1.63	4.50
2[a]	$R_3 = COOC(CH_3)_3$, $R_4 = R_6 = R_7 = R_9 = H$	7.724			2.836		
3	$R_3 = COOC_2H_5$, $R_4 = R_6 = R_7 = R_9 = H$	8.244	8.095	0.149	2.128	1.64	4.41
4[a]	$R_3 = OC_2H_5$, $R_4 = R_6 = R_7 = R_9 = H$	7.548	7.306	0.243	3.402	1.35	3.36
5	$R_3 = NCS$, $R_4 = R_6 = R_7 = R_9 = H$	6.851	7.527	−0.676	3.886	1.50	4.24
6	$R_3 = Cl$, $R_4 = R_6 = R_7 = R_9 = H$	6.90	6.719	0.181	2.713	1.80	1.80
7	$R_3 = OC_3H_7$, $R_4 = R_6 = R_7 = R_9 = H$	7.162	7.594	−0.431	3.931	1.35	4.42
8	$R_3 = OC_4H_9$, $R_4 = R_6 = R_7 = R_9 = H$	6.611	7.454	−0.843	4.460	1.35	4.79
9	$R_3 = OCH_2CH(CH_3)_2$, $R_4 = R_6 = R_7 = R_9 = H$	6.857	7.355	−0.498	4.330	1.35	4.42
10	$R_3 = OCH_2CH(CH_3)_2$, $R_4 = R_6 = R_7 = R_9 = H$	6.060	7.355	−1.295	4.330	1.35	4.42
11	$R_{3,6} = NO_2$, $R_4 = R_7 = R_9 = H$	7.523	7.359	0.164	3.256	1.64	3.36
12[a]	$R_{3,6} = NCS$, $R_4 = R_7 = R_9 = H$	6.547	7.434	−0.888	4.197	1.64	4.41
13	$R_3 = COOC_2H_5$, $R_6 = OCH_2C_6H_5$, $R_4 = R_7 = R_9 = H$	7.842	7.055	0.786	3.939	1.64	3.36
14	$R_3 = COOCH_3$, $R_6 = NH\text{-cy-}C_6H_{11}$, $R_4 = R_7 = R_9 = H$	7.311	7.323	−0.012	3.356	1.64	3.36
15	$R_3 = COOCH_3$, $R_6 = NHCH_2C_6H_5$, $R_4 = R_7 = R_9 = H$	6.567	6.684	−0.117	4.530	1.64	3.36
16	$R_3 = COOCH_3$, $R_6 = NHCH_2$-naphthyl, $R_4 = R_7 = R_9 = H$	8.314	8.092	0.222	1.906	1.64	4.41
17	$R_3 = COOCH_3$, $R_4 = CH_2OCH_3$, $R_6 = R_7 = R_9 = H$	7.231	6.646	0.585	5.225	1.64	4.41
18[a]	$R_3 = COOC_2H_5$, $R_4 = C_2H_5$, $R_6 = OCH_2C_6H_5$, $R_7 = R_9 = H$	6.523	5.373	1.150	6.399	1.64	4.41
19	$R_3 = COOC_2H_5$, $R_4 = C_2H_5$, $R_6 = OCH_2$-2-naphthyl, $R_7 = R_9 = H$	8.553	7.813	0.740	3.457	1.64	4.41
20	$R_3 = COOC_2H_5$, $R_4 = C_2H_5$, $R_6 = OCH_3$, $R_7 = R_9 = H$	4.456	4.334	0.121	7.160	1.64	4.41
21	$R_3 = COOC_2H_5$, $R_4 = C_2H_5$, $R_6 = O(CH_2)_7CH_3$, $R_7 = R_9 = H$	8.764	8.092	0.672	2.207	1.64	4.41
22	$R_3 = COOC_2H_5$, $R_4 = CH_2OCH_3$, $R_6 = OCH_3$, $R_7 = R_9 = H$	8.658	7.885	0.773	3.265	1.64	4.41
23	$R_3 = COOC_2H_5$, $R_4 = CH_2OCH_3$, $R_6 = OC_3H_7$, $R_7 = R_9 = H$	6.568	6.791	−0.223	5.069	1.35	4.42
24	$R_3 = OC_3H_7$, $R_4 = CH_2OCH_3$, $R_6 = OC_3H_7$, $R_7 = R_9 = H$	6.398	7.425	−1.027	1.867	1.50	3.09
25	$R_3 = CONHNH_2$, $R_4 = CH_2OCH_3$, $R_6 = OC_3H_7$, $R_7 = R_9 = H$	6.155	6.748	−0.593	2.965	1.35	1.97
26	$R_3 = NH_2$, $R_4 = CH_2OCH_3$, $R_6 = OC_3H_7$, $R_7 = R_9 = H$	8.222	7.565	0.657	3.975	1.64	4.41
27	$R_3 = COOC_2H_5$, $R_4 = CH_2OCH_3$, $R_6 = OCH_2C_6H_5$, $R_7 = R_9 = H$	8.125	6.886	1.239	4.284	2.14	3.43
28[a]	$R_3 = COOCH(CH_3)_2$, $R_4 = CH_2OCH_3$, $R_6 = OCH_2C_6H_5$, $R_7 = R_9 = H$	7.231	6.057	1.172	5.734	1.50	4.24
29	$R_3 = NCS$, $R_4 = CH_2OCH_3$, $R_6 = OCH_2C_6H_5$, $R_7 = R_9 = H$	6.533	6.715	−0.182	5.149	1.64	4.41
30	$R_3 = COOC_2H_5$, $R_4 = CH_2OCH_3$, $R_6 = OH$, $R_7 = R_9 = H$	7.900	8.226	−0.259	2.034	1.64	4.41

[a] Data points not included in equation derivation.

3.28. 2-Phenyl-imidazopyridines Analogues

In recent years, considerable effort has been focused toward the identification of new peripheral benzodiazepine receptors (PBR) ligands with increased activity and selectivity over central benzodiazepine receptors (CBR).



For some analogues of 2-phenyl-imidazopyridines,[73] the affinities for CBR and PBR were evaluated by measuring their ability to displace [^{3}H]flunitrazepam and [^{3}H]PK 11195 from binding to membrane preparations from the cerebral cortex and ovary and were subjected to structure−activity relationships studies. For the whole set of compounds, a linear regression analysis has been reported, showing a good correlation between data from ovary membranes and brain cerebral cortex cells (n = 32, r^2 = 0.959). The researchers suggest that there are no significant differences in the PBR structure in the two examined tissues.

Using the same data we developed a bilinear correlation for the PBR cortex (Table 55) and a

$$\log 1/IC_{50} = 1.015\ (\pm 0.166)\ \text{Clog}\ P_o - 2.949\ (\pm 0.634)\ \log(\beta \times 10^{\log P} + 1) + 3.271\ (\pm 0.745) \quad (64)$$

$n = 28$ $r^2 = 0.868$ $q^2 = 0.846$ $s = 0.354$ $F_{3,24} = 39.145$, $\alpha = 0.01$

optimum value of lipophilicity: Clog P_o = 6.028 (±0.377) log β = −6.308

bilinear equation for the PBR ovary, too (Table 56).

$$\log 1/IC_{50} = 0.929\ (\pm 0.177)\ \text{Clog}\ P_o - 2.680\ (\pm 0.708)\ \log(\beta \times 10^{\log P} + 1) + 3.452\ (\pm 0.796) \quad (65)$$

$n = 28$ $r^2 = 0.829$ $q^2 = 0.803$ $s = 0.381$ $F_{3,24} = 53$, $\alpha = 0.01$

optimum value of lipophilicity: Clog P_o = 6.094 (±0.328) log β = −6.369

Both equations are in agreement with the previous findings. Compounds **2**, **18**, and **31** are not included in the derivation of both QSARs, although they do

Table 54. IC_{50} Displacement of [^{3}H]Flunitrazepam from Central Benzodiazepine Receptor:[72] Compounds and Physicochemical Parameters for Derivation of Equation 63

no.	substituents R, R′	obsd log 1/IC_{50}	calcd log 1/IC_{50}	Δlog 1/IC_{50}	$\sigma_{R'}$	MR_{R8}	$L_{R'4'}$	I	B_{5R}
1	R = R′ = H	9.35	9.22	0.13	0	0.103	2.06	0	1
2	R = H, R′ = 4-Cl	9.00	8.06	0.94	0.23	0.103	3.52	0	1
3	R = H, R′ = 4-OCH_3	9.17	9.09	0.08	−0.27	0.103	3.98	0	1
4	R = 6-F, R′ = H	8.16	8.52	−0.36	0	0.103	2.06	0	1.35
5	R = 6-CH_3, R′ = H	7.18			0	0.103		0	2.61
6	R = 6-CF_3, R′ = H	5.73	5.96	−0.23	0	0.103	2.06	0	3.07
7	R = 6-OCH_3, R′ = H	5.66	5.03	0.63	0	0.103	2.06	0	1
8	R = 8-F, R′ = H	9.54	9.23	0.31	0	0.092	2.06	0	1
9[a]	R = 8-F, R′ = 3-NO_2	8.70	7.49	1.21	0.71	0.092	2.06	0	1
10	R = 8-F, R′ = 3-NH_2	9.26	9.62	−0.36	−0.16	0.092	2.06	0	1
11	R = 8-F, R′= 4-OCH_3	9.48	9.09	0.39	−0.27	0.092	3.98	0	1
12	R = 8-F, R′ = 4-OH	9.34	9.85	−0.51	−0.37	0.092	2.74	0	1
13	R = 8-Cl, R′ = H	9.37	9.00	0.37	0	0.600	2.06	0	1
14	R = 8-OCH_3, R′ = H	9.17	8.92	0.25	0	0.787	2.06	0	1
15	R = 8-OC_2H_5, R′ = H	8.85	8.72	0.13	0	1.247	2.06	0	1
16	R = 8-C_4H_9, R′ = H	9.00	8.40	0.60	0	1.959	2.06	0	1
17	R = 8-C_4H_9, R′ = 4-COOH	5.93	6.54	−0.61	0.45	1.959	3.91	0	1
18[a]	R = 8-C_4H_9, R′ = 2-pyridyl-2′-yl	9.50	7.99	1.51	0.17	1.959	2.06	0	1
19[a]	R = 8-C_4H_9, R′ = 2-pyrimidyl-2′-yl	8.77	7.11	1.66	0.53	1.959	2.06	0	1
20	R = 8-C_4H_9, R′ = 2-pyrazinyl-2′-yl	9.22				1.959	2.06	0	1
21	R = 8-cyC_6H_{11}, R′ = H	8.35	8.09	0.26	0	2.669	3.91	0	1
22	R = 8-cyC_6H_{11}, R′ = 4-COOH	5.55	6.22	−0.67	0.45	2.669	3.91	0	1
23[a]	R = 8-cyC_6H_{11}, R′ = 2-pyridyl-2′-yl	8.60				2.669		0	1
24[a]	R = 8-cyC_6H_{11}, R′ = 2-pyrimidyl-2′-yl	8.36	6.79	1.57	0.53	2.669	2.06	0	1
25	R = 8-cyC_6H_{11}, R′ = 2-pyrazinyl-2′-yl	8.16				2.669	2.06	0	1
26	R = 8-$OCH_2C_6H_5$, R′ = H	7.75	7.85	−0.10	0	3.219	2.06	0	1
27	R = 8-OCF_3, R′ = H	9.15	8.92	0.23	0	0.786	2.06	0	1
28	R = 8-OCF_3, R′ = 2-F	9.40	8.78	0.62	0.06	0.786	2.06	0	1
29	R = 8-OCF_3, R′ = 2-Cl	8.60	8.36	0.24	0.23	0.786	2.06	0	1
30	R = 8-OCF_3, R′ = 2-CH_3	8.47	9.34	−0.87	−0.17	0.786	2.06	0	1
31	R = 8-OCF_3, R′ = 3-Br	7.46	7.97	−0.51	0.39	0.786	3.82	0	1
32	R = 8-OCF_3, R′ = 3-CH_3	8.20	9.09	−0.89	−0.07	0.786	2.87	0	1
33	R = 8-OCF_3, R′ = 3-Cl	7.62	8.02	−0.40	0.37	0.786	3.52	0	1
34[a]	R = 8-OCF_3, R′ = 3-F	9.40	8.09	1.31	0.34	0.786	2.65	0	1
35	R = 8-OCF_3, R′ = 3-NO_2	7.20	7.18	0.02	0.71	0.786	3.44	0	1
36	R = 8-OCF_3, R′ = 3-NH_2	9.62	9.31	0.30	−0.16	0.786	2.78	0	1
37	R = 8-OCF_3, R′ = 4-Br	7.82	7.63	0.19	0.23	0.786	3.82	0	1
38	R = 8-OCF_3, R′ = 4-CH_3	8.79	9.00	−0.21	−0.17	0.786	2.87	0	1
39	R = 8-OCF_3, R′ = 4-Cl	7.90	7.75	0.15	0.23	0.786	3.52	0	1
40	R = 8-OCF_3, R′ = 4-F	9.00	8.53	0.47	0.06	0.786	2.65	0	1
41	R = 8-OCF_3, R′ = 4-NO_2	7.40	6.44	0.96	0.78	0.786	3.44	0	1
42[a]	R = 8-OCF_3, R′ = 4-NH_2	9.10	10.24	−1.14	−0.66	0.786	2.78	0	1
43	R = 8-OCF_3, R′ = 4-OCH_3	9.22	8.79	0.43	−0.27	0.786	3.98	0	1
44	R = 8-OCF_3, R′ = 4-OH	9.63	9.55	0.08	−0.37	0.786	2.74	0	1
45	R = 9-OH, R′ = H	9.62	9.22	0.40	0	0.103	2.06	0	1
46	R = 9-OCH_3, R′ = H	8.84	9.22	−0.38	0	0.103	2.06	0	1
47	R = 6, 8 F, R′ = H	7.87	8.52	−0.65	0	0.092	2.06	0	1.35
48	R = 6, 8-F, R′ = 3-F	8.02	7.69	0.33	0.34	0.092	2.06	0	1.35
49	R = 6, 8-F, R′ = 4-Br	6.79	7.23	−0.44	0.23	.092	3.82	0	1.35
50	R = 6, 8-F, R′ = 4-OCH_3	8.12	8.39	−0.27	−0.27	0.092	3.98	0	1.35
51	R = 6, 8-F, R′ = 2-pyridyl-2′-yl	7.82	8.10	−0.28	0.17	0.092	2.06	0	1.35
52	R = 6, 8-F, R′ = 2-pyrimidyl-2′-yl	6.47	7.22	−0.75	0.53	0.092	2.06	0	1.35
53	R = 6, 8-F, R′ = 2-pyrazin-2′-yl	6.94				0.092	2.06	0	1.35
54	R = 7, 9-Cl, R′ = H	8.43	8.63	−0.20	0	0.103	2.06	1	1
55	R = 6,7,8-F, R′ = H	7.70	7.93	−0.23	0	0.092	2.06	1	1.35
56	R = 6,7,8-F, R′ = 4-CH_3	7.15	8.01	−0.86	−0.17	0.092	2.87	1	1.35
57	R = 6,7,8-F, R′ = 4-Cl	7.13	6.76	0.37	0.23	0.092	3.52	1	1.35
58	R = 6,7,8-F, R′ = 4-F	7.68	7.54	0.14	0.06	0.092	2.65	1	1.35
59	R = 6,7,8-F, R′ = 4-OCH_3	8.14	7.79	0.35	−0.27	0.092	3.98	1	1.35
60	R = 7,8,9-OCH_3, R′ = H	8.90	8.33	0.57	0	0.787	2.06	1	1
61	R = 7,8,9-OCH_3, R′ = 4-COOH	5.52	6.46	−0.94	0.45	0.787	3.91	1	1
62	R = 7,8,9-OCH_3, R′ = 2-pyridyl-2′-yl	8.50	7.91	0.59	0.17	0.787	2.06	1	1
63	R = 7,8,9-OCH_3, R′ = 2-pyrimidyl-2-yl	7.24	7.03	0.21	0.53	0.787	2.06	1	1

[a] Data points not included in equation derivation.

not contain any unusual structural features. The above relationships showed that the ideal log P (log P_o) for affinity at PBR holds a value of ~6, as beyond this value the affinity decreases.

Table 57 contains the affinities of the same 31 congeners for CBR. The affinities were evaluated by measuring their ability to displace [^{3}H]flunitrazepam from binding to membrane preparations.

Table 55. IC_{50} Inhibition Values to Peripheral Benzodiazepine Receptor Cortex by *N,N*-Substituted Imidazo[1,2-*a*]pyridin-3-yl]acetamides:[73] Compounds and Physicochemical Parameters for Derivation of Equation 64

no.	substituents X, Y, Z, R_1, R_2	obsd log $1/IC_{50}$	calcd log $1/IC_{50}$	Δlog $1/IC_{50}$	Clog *P*
1	X = Y = Z = H, $R_1 = R_2 = C_3H_7$	7.000	7.269	−0.269	3.944
2[a]	X = NO_2, Y = Z = H, $R_1 = R_2 = C_3H_7$	8.120	−4.008	12.128	3.764
3	X = Y = Cl, Z = H, $R_1 = R_2 = C_3H_7$	8.520	8.592	−0.072	5.384
4	X = Y = Z = Cl, $R_1 = R_2 = C_3H_7$	9.000	8.845	0.155	6.097
5	X = Y = Br, Z = Cl, $R_1 = R_2 = C_3H_7$	9.100	8.738	0.362	6.397
6	X = CF_3, Y = Z = Cl, $R_1 = R_2 = C_3H_7$	8.740	8.785	−0.045	6.308
7	X = Br, Y = CH_3, Z = H, $R_1 = R_2 = C_3H_7$	8.790	8.543	0.247	5.316
8	X = $COOCH_3$, Y = Z = H, $R_1 = R_2 = C_3H_7$	7.780	7.294	0.486	3.969
9	X = $CONH_2$, Y = Z = H, $R_1 = R_2 = C_3H_7$	6.340	6.183	0.157	2.869
10	X = H, Y = CH_3, Z = H, $R_1 = R_2 = C_3H_7$	7.700	7.764	−0.064	4.443
11	X = H, Y = CH_3, Z = Cl, $R_1 = R_2 = C_3H_7$	8.850	8.420	0.430	5.159
12	X = H, Y = NO_2, Z = H, $R_1 = R_2 = C_3H_7$	7.070	7.088	−0.018	3.764
13	X = H, Y = NO_2, Z = Cl, $R_1 = R_2 = C_3H_7$	8.240	7.798	0.442	4.478
14	X = H, Y = OCH_3, Z = H, $R_1 = R_2 = C_3H_7$	7.330	7.500	−0.170	4.175
15	X = H, Y = OCH_3, Z = Cl, $R_1 = R_2 = C_3H_7$	7.780	8.186	−0.406	4.889
16	X = H, Y = Cl, Z = H, $R_1 = R_2 = C_3H_7$	7.640	7.980	−0.340	4.667
17	X = H, Y = Z = Cl, $R_1 = R_2 = C_3H_7$	8.370	8.590	−0.220	5.381
18[a]	X = H, Y = NH_2, Z = H, $R_1 = R_2 = C_3H_7$	8.370	−3.338	11.708	3.417
19	X = H, Y = NH_2, Z = Cl, $R_1 = R_2 = C_3H_7$	8.200	7.458	0.742	4.133
20	X = H, Y = $NHCH_3$, Z = Cl, $R_1 = R_2 = C_3H_7$	8.430	8.215	0.215	4.922
21	X = H, Y = $NHCOCH_3$, Z = H, $R_1 = R_2 = C_3H_7$	6.590	6.923	−0.333	3.600
22	X = H, Y = $NHCOCH_3$, Z = Cl, $R_1 = R_2 = C_3H_7$	8.000	7.639	0.361	4.316
23	X = Y = Z = H, $R_1 = R_2 = C_2H_5$	6.360	6.200	0.160	2.886
24	X = Y = H, Z = Cl, $R_1 = R_2 = C_3H_7$	8.000	7.973	0.027	4.660
25	X = Y = Z = H, $R_1 = R_2 = C_4H_9$	7.770	8.287	−0.517	5.002
26	X = Y = H, Z = Cl, $R_1 = R_2 = C_4H_9$	8.230	8.782	−0.552	5.718
27	X = Y = Z = H, $R_1 = R_2 = C_6H_{13}$	7.720	7.921	−0.201	7.118
28	X = Y = H, Z = Cl, $R_1 = R_2 = C_6H_{13}$	6.740	6.683	0.057	7.834
29	X = Y = Z = H, $R_1 = C_3H_7$, R_2 = H	5.700	5.921	−0.221	2.610
30	X = Y = H, Z = Cl, $R_1 = C_3H_7$, R_2 = H	6.230	6.646	−0.416	3.326
31[a]	X = Y = Cl, Z = H, $R_1 = C_4H_9$, R_2 = H	6.530	−5.584	12.114	4.579

[a] Data points not included in equation derivation.

We formulated eq 66.

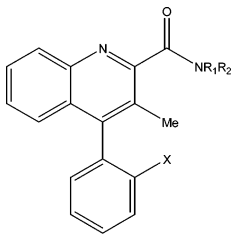
$$\log 1/IC_{50} = -1.885\ (\pm 1.057)\mathrm{MgVol} - 4.922\ (\pm 1.742)B_{1-Y} + 0.571\ (\pm 0.420)\sigma_{Y'} + 6.081\ (\pm 3.621) \quad (66)$$

$n = 27 \quad r^2 = 0.730 \quad q^2 = 0.630 \quad s = 0.771 \quad F_{3,23} = 20.80 \quad \alpha = 0.01$

In this equation B_{1-Y} applies to Y in the 8-position of the benzimidazole ring and appears to confirm a negative steric effect, but this point needs further study, because the range of substituents covered is not great. B_{1-Y} is found to be the most important variable for this set. The negative coefficient means that the larger the atom attached to the ring, the less effective the binding. Attempts to parametrize X and Z except in terms of MgVol were unsuccessful, and log *P* and CMR were not useful parameters (CMR and MgVol were found to be perfectly collinear, $r = 0.994$). The fact that MgVol has been used implies that X and Z substituents also have a negative steric effect. Three data points were omitted in this analysis. Two of them, compounds **5** and **6**, although different in structure, possess the same affinity values. The electronic term σ does not seem to imply a significant role. Although QSAR 66 is not very good, it is quite significant, and the dependence on steric effects is evidence.

3.29. Carboxamide Derivatives

Anzini et al.[74] applied several computational methodologies to an enlarged series of carboxamide derivatives to rationalize the variation in the binding affinities to the PBR.



CoMFA and CoMSIA models were developed and exhibit a satisfactory performance in the affinity prediction. These 3D-QSAR models tolerate quite well the additional steric bulk in a region for which the model is relatively trained or the information on the lipophilic amide side chain is dominant. The QSAR model obtained is

$$\mathrm{pIC_{50}} = 1.44\ (\pm 0.13)E_{\mathrm{inter}} + 4.08\ (\pm 0.37) \quad (67)$$

$$n = 34 \quad r^2 = 0.70 \quad q^2 = 0.38 \quad F = 73.93$$

E_{inter} is the energy interaction that gives a quantitative description of the ligand receptor site comple-

Table 56. IC_{50} Inhibition of [^{3}H]PK 11195 Binding of Peripheral Benzodiazepine Receptor (Ovary):[73] Compounds and Physicochemical Parameters for Derivation of Equation 65

no.	substituents X, Y, Z, R_1, R_2	obsd pIC_{50}	calcd pIC_{50}	ΔpIC_{50}	Clog *P*
1	X = Y = Z = H, $R_1 = R_2 = C_3H_7$	7.02	7.113	−0.093	3.944
2[a]	X = NO_2, Y = Z = H, $R_1 = R_2 = C_3H_7$	8.11	−3.137	11.247	3.764
3	X = Y = Cl, Z = H, $R_1 = R_2 = C_3H_7$	8.37	8.340	0.030	5.384
4	X = Y = Z = Cl, $R_1 = R_2 = C_3H_7$	8.58	8.620	−0.040	6.097
5	X = Y = Br, Z = Cl, $R_1 = R_2 = C_3H_7$	8.80	8.552	0.248	6.397
6	X = CF_3, Y = Z = Cl, $R_1 = R_2 = C_3H_7$	8.55	8.587	−0.037	6.308
7	X = Br, Y = CH_3, Z = H, $R_1 = R_2 = C_3H_7$	8.58	8.294	0.286	5.316
8	X = $COOCH_3$, Y = Z = H, $R_1 = R_2 = C_3H_7$	7.57	7.136	0.434	3.969
9	X = $CONH_2$, Y = Z = H, $R_1 = R_2 = C_3H_7$	6.52	6.118	0.402	2.869
10	X = H, Y = CH_3, Z = H, $R_1 = R_2 = C_3H_7$	7.38	7.568	−0.188	4.443
11	X = H, Y = CH_3, Z = Cl, $R_1 = R_2 = C_3H_7$	8.55	8.176	0.374	5.159
12	X = H, Y = NO_2, Z = H, $R_1 = R_2 = C_3H_7$	6.92	6.947	−0.027	3.764
13	X = H, Y = NO_2, Z = Cl, $R_1 = R_2 = C_3H_7$	8.06	7.598	0.462	4.478
14	X = H, Y = OCH_3, Z = H, $R_1 = R_2 = C_3H_7$	7.31	7.325	−0.015	4.175
15	X = H, Y = OCH_3, Z = Cl, $R_1 = R_2 = C_3H_7$	7.68	7.957	−0.277	4.889
16	X = H, Y = Cl, Z = H, $R_1 = R_2 = C_3H_7$	7.80	7.766	0.034	4.667
17	X = H, Y = Z = Cl, $R_1 = R_2 = C_3H_7$	8.13	8.339	−0.209	5.381
18[a]	X = H, Y = NH_2, Z = H, $R_1 = R_2 = C_3H_7$	8.24	−2.530	10.770	3.417
19	X = H, Y = NH_2, Z = Cl, $R_1 = R_2 = C_3H_7$	8.34	7.286	1.054	4.133
20	X = H, Y = $NHCH_3$, Z = Cl, $R_1 = R_2 = C_3H_7$	8.10	7.985	0.115	4.922
21	X = H, Y = $NHCOCH_3$, Z = H, $R_1 = R_2 = C_3H_7$	6.35	6.796	−0.446	3.600
22	X = H, Y = $NHCOCH_3$, Z = Cl, $R_1 = R_2 = C_3H_7$	7.48	7.452	0.028	4.316
23	X = Y = Z = H, $R_1 = R_2 = C_2H_5$	6.18	6.134	0.046	2.886
24	X = Y = H, Z = Cl, $R_1 = R_2 = C_3H_7$	7.48	7.760	−0.280	4.660
25	X = Y = Z = H, $R_1 = R_2 = C_4H_9$	7.64	8.052	−0.412	5.002
26	X = Y = H, Z = Cl, $R_1 = R_2 = C_4H_9$	7.98	8.531	−0.551	5.718
27	X = Y = Z = H, $R_1 = R_2 = C_6H_{13}$	7.88	7.869	0.011	7.118
28	X = Y = H, Z = Cl, $R_1 = R_2 = C_6H_{13}$	6.75	6.768	−0.018	7.834
29	X = Y = Z = H, $R_1 = C_3H_7$, R_2 = H	5.70	5.878	−0.178	2.610
30	X = Y = H, Z = Cl, $R_1 = C_3H_7$, R_2 = H	5.79	6.542	−0.752	3.326
31[a]	X = Y = Cl, Z = H, $R_1 = C_4H_9$, R_2 = H	6.41	−4.563	10.973	4.579

[a] Data points not included in equation derivation.

mentary. The more negative the value of E_{inter}, the more stable the interaction between ligands and receptor.

(a) Taking under consideration the compounds with the above structure (Table 58), eq 68 was derived:

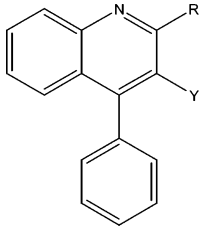
$$\log 1/IC_{50} = 3.510\ (\pm 0.833)B_{1(R_1+R_2)} + 0.266\ (\pm 0.158)B_{5(R_1+R_2)} - 4.812\ (\pm 3.211) \quad (68)$$

$n = 11$ $r^2 = 0.923$ $q^2 = 0.867$ $s = 0.352$ $F_{2,8} = 47.78$ $\alpha = 0.01$

parameter importance: $B_{1(R_1+R_2)} > B_{5(R_1+R_2)}$

The collinearity between the parameters is minimal. The IC_{50} values represent inhibition of the binding of [^{3}H]-1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinolinecarboxamide (PK11195). $B_{1(R_1+R_2)}$ and $B_{5(R_1+R_2)}$ are the two sterimol parameters. $B_{1(R_1+R_2)}$ models the smallest width of the first atom of substituents R_1/R_2, whereas $B_{5(R_1+R_2)}$ expresses the largest width of the first atom of substituents R_1/R_2. Although the correlation for the hydrophobic effect, Clog *P*, is low ($r = 0.659$), $B_{1(R_1+R_2)}$ and $B_{5(R_1+R_2)}$ seem to be collinear enough to Clog *P* (Clog *P* versus $B_1 = 0.575$, Clog P versus $B_5 = 0.583$).

Compound **2** is rejected from the derivation of the equation. No parametrization for substituent X has been done. However, all fit well by eq 68.



(b) For the carboxamides with the above structure in Table 59 QSAR 69 was obtained:

$$\log 1/IC_{50} = 0.369\ (\pm 0.236)c\pi_R - 0.439\ (\pm 0.182)c\pi_Y + 5.430\ (\pm 0.511) \quad (69)$$

$n = 10$ $r^2 = 0.872$ $q^2 = 0.792$ $s = 0.160$ $F_{2,7} = 23.93$ $\alpha = 0.01$

parameter importance: $c\pi_R > c\pi_Y$

Two data points, compounds **7** and **12**, are not included in this analysis and they do not contain any unusual substituents. Calculated π_R and π_Y values are used to model the lipophilic contribution of the substituents R and Y. Correlation shows that substituents R contact hydrophobic space, whereas substituents Y contact a more hydrophilic space. Again, no role for an electronic effect was found.

Table 57. IC_{50} Inhibition of [^{3}H]Flunitrazepam Binding of Central Benzodiazepine Receptor:[73] Compounds and Physicochemical Parameters for Derivation of Equation 66

no.	substituents X, Y, Z, R_1, R_2	obsd pIC_{50}	calcd pIC_{50}	ΔpIC_{50}	MgVol	B_{1-Y}	σ'_Y
1	X = Y = Z = H, $R_1 = R_2 = C_3H_7$	6.28	6.244	0.036	2.756	1.00	0.49
2	X = NO_2, Y = Z = H, $R_1 = R_2 = C_3H_7$	5.47	5.916	−0.446	2.930	1.00	0.49
3	X = Y = Cl, Z = H, $R_1 = R_2 = C_3H_7$	2.40	3.244	−0.844	3.001	1.80	2.940
4	X = Y = Z = Cl, $R_1 = R_2 = C_3H_7$	2.40	3.013	−0.613	3.123	1.80	2.94
5[a]	X = Y = Br, Z = Cl, $R_1 = R_2 = C_3H_7$	5.00	1.977	3.003	3.228	1.95	2.80
6[a]	X = CF_3, Y = Z = Cl, $R_1 = R_2 = C_3H_7$	5.00	2.878	2.112	3.195	1.80	2.94
7[a]	X = Br, Y = CH_3, Z = H, $R_1 = R_2 = C_3H_7$	4.27	2.890	1.461	3.072	1.52	0.00
8	X = $COOCH_3$, Y = Z = H, $R_1 = R_2 = C_3H_7$	4.92	5.572	−0.652	3.112	1.00	0.49
9	X = $CONH_2$, Y = Z = H, $R_1 = R_2 = C_3H_7$	5.58	5.761	−0.181	3.012	1.00	0.49
10[a]	X = H, Y = CH_3, Z = H, $R_1 = R_2 = C_3H_7$	4.85	3.139	1.711	2.897	1.52	0.00
11	X = H, Y = CH_3, Z = Cl, $R_1 = R_2 = C_3H_7$	2.40	2.908	−0.508	3.019	1.52	0.00
12	X = H, Y = NO_2, Z = H, $R_1 = R_2 = C_3H_7$	4.80	4.852	−0.052	2.930	1.70	4.66
13	X = H, Y = NO_2, Z = Cl, $R_1 = R_2 = C_3H_7$	5.00	4.621	0.379	3.052	1.70	4.66
14	X = H, Y = OCH_3, Z = H, $R_1 = R_2 = C_3H_7$	5.27	8.760	0.394	2.955	1.35	1.77
15	X = H, Y = OCH_3, Z = Cl, $R_1 = R_2 = C_3H_7$	4.19	6.450	−0.455	3.078	1.35	1.77
16	X = H, Y = Cl, Z = H, $R_1 = R_2 = C_3H_7$	4.59	3.475	1.115	2.878	1.80	2.94
17	X = H, Y = Z = Cl, $R_1 = R_2 = C_3H_7$	2.40	3.244	−0.844	3.001	1.80	2.94
18	X = H, Y = NH_2, Z = H, $R_1 = R_2 = C_3H_7$	5.27	4.407	0.863	2.856	1.35	0.62
19	X = H, Y = NH_2, Z = Cl, $R_1 = R_2 = C_3H_7$	5.07	4.177	0.893	2.978	1.35	0.62
20	X = H, Y = $NHCH_3$, Z = Cl, $R_1 = R_2 = C_3H_7$	4.00	4.094	−0.094	3.119	1.35	0.94
21	X = H, Y = $NHCOCH_3$, Z = H, $R_1 = R_2 = C_3H_7$	4.96	4.292	0.668	3.153	1.35	1.40
22	X = H, Y = $NHCOCH_3$, Z = Cl, $R_1 = R_2 = C_3H_7$	4.09	4.061	0.029	3.275	1.35	1.40
23	X = Y = Z = H, $R_1 = R_2 = C_2H_5$	5.68	6.775	−1.095	2.474	1.00	0.49
24	X = Y = H, Z = Cl, $R_1 = R_2 = C_3H_7$	7.19	6.013	1.177	2.878	1.00	0.49
25	X = Y = Z = H, $R_1 = R_2 = C_4H_9$	6.30	5.713	0.587	3.038	1.00	0.49
26	X = Y = H, Z = Cl, $R_1 = R_2 = C_4H_9$	7.04	5.482	1.558	3.160	1.00	0.49
27	X = Y = Z = H, $R_1 = R_2 = C_6H_{13}$	3.93	4.650	−0.720	3.601	1.00	0.49
28	X = Y = H, Z = Cl, $R_1 = R_2 = C_6H_{13}$	3.83	4.420	−0.590	3.724	1.00	0.49
29	X = Y = Z = H, $R_1 = C_3H_7$, R_2 = H	6.09	7.041	−0.951	2.333	1.00	0.49
30	X = Y = H, Z = Cl, $R_1 = C_3H_7$, R_2 = H	6.93	6.810	0.120	2.455	1.00	0.49
31	X = Y = Cl, Z = H, $R_1 = C_4H_9$, R_2 = H	4.00	3.775	0.225	2.719	1.80	2.94

[a] Data points not included in equation derivation.

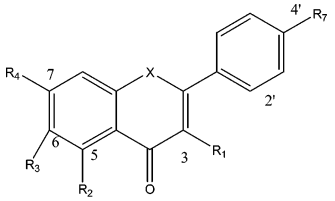
Table 58. PBR Binding Affinities of Carboxamide Derivatives:[73] Compounds and Physicochemical Parameters for Derivation of Equation 68

no.	substituents X, R_1, R_2	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	$B_{1(R_1+R_2)}$	$B_{5(R_1+R_2)}$
1	X = H, R_1 = CH(Me)CH_2CH_3, R_2 = H	6.638	6.56	0.08	2.90	4.49
2[a]	X = F, R_1 = CH(Me)CH_2CH_3, R_2 = H	7.886	6.56	1.33	2.90	7.02
3	X = H, R_1 = $CH_2C_6H_5$, R_2 = H	5.921	5.90	0.02	2.52	8.44
4	X = H, R_1 = 4-Cl$CH_2C_6H_4$, R_2 = H	5.770	6.28	−0.51	2.52	8.44
5	X = F, R_1 = 4-Cl$CH_2C_6H_4$, R_2 = H	6.569	6.28	0.29	2.52	5.53
6	X = H, R_1 = CH(Me)CH_2CH_3, R_2 = CH_3	8.678	8.66	0.02	3.42	5.53
7	X = F, R_1 = CH(Me)CH_2CH_3, R_2 = CH_3	8.538	8.66	−0.12	3.42	8.06
8	X = H, R_1 = $CH_2C_6H_5$, R_2 = CH_3	8.678	8.00	0.68	3.04	9.48
9	X = H, R_1 = 4-Cl$CH_2C_6H_5$, R_2 = CH_3	8.009	8.38	−0.37	3.04	9.48
10	X = F, R_1 = 4-Cl$CH_2C_6H_5$, R_2 = CH_3	8.469	8.38	0.09	3.04	5.15
11	X = H, R_1 = 4-ClC_6H_5, R_2 = CH_3	8.194	8.21	−0.02	3.32	5.15
12	X = H, R_1 = 4-$OCH_3C_6H_5$, R_2 = CH_3	8.056	8.21	−0.16	3.32	2.04

[a] Data point not included in equation derivation.

3.30. Flavonoids

The affinities for the benzodiazepine binding site of the GABA receptor of 21 flavonoids



have been studied using [^{3}H]flumazenil binding to rat cortical membranes in vitro. Dekermendjian et al.[75] studied the receptor-bonding properties of the flavonoids, which can successfully be rationalized in terms of a comprehensive pharmacophore model recently developed by Cook and co-workers.[76] From the analysis of the binding affinities K_i of 3′- and 4′-substituted flavones, we developed eq 70.

$$\log 1/K_i = 1.344\ (\pm 0.819) I_{3'} + 0.837\ (\pm 0.727) B_{5-5} + 1.885\ (\pm 1.239) B_{1-6} + 2.461\ (\pm 2.151) \quad (70)$$

$n = 17$ $r^2 = 0.819$ $q^2 = 0.725$ $s = 0.576$ $F_{3,13} = 19.65$ $\alpha = 0.01$

parameter importance: $I_{3'} > B_{5-5} > B_{1-6}$

No collinearity problems were found among the parameters. We were not able to formulate a QSAR with Clog P. $I_{3'}$ is an indicator variable that takes the value of 1 when there is a substituent at the 3′-position. No efffect of the electronic factor in binding affinity for the flavonoids was found. The B_{1-6} and

Table 59. PBR Binding Affinities of Carboxamide Derivatives:[73] Compounds and Physicochemical Parameters for Derivation of Equation 69

no.	substituents R, Y	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	$c\pi_Y$	$c\pi_R$
1	R = $CH_2N(C_2H_5)CH_2C_6H_5$, Y = $COOC_2H_5$	6.155	5.928	0.227	6.51	2.131
2	R = $N(C_2H_5)CH_2C_6H_5$, Y = $COOC_2H_5$	6.268	6.252	0.016	6.51	3.011
3	R = Cl, Y = $COOC_2H_5$	5.432	5.437	−0.006	6.51	0.797
4	R = CH_2THIQ, Y = $COOC_2H_5$	5.926	5.838	0.088	6.51	1.887
5	R = $CH_2N(C_2H_5)CH_2C_6H_5$, Y = $CON(CH_3)_2$	6.640	6.714	−0.074	−1.139	2.131
6	R = $CH_2N(C_2H_5)CH_2C_6H_5$, Y = $CON(C_2H_5)_2$	6.428	6.249	0.179	−0.081	2.131
7[a]	R = $CH_2N(C_2H_5)CH_2C_6H_5$, Y = $CON(C_3H_8)_2$	6.341	5.785	0.556	0.977	2.131
8	R = $CH_2N(C_2H_5)CH_2C_6H_5$, Y = $CON(CH_3)C_6H_5$	5.880	5.937	−0.057	0.630	2.131
9	R = $CH_2N(C_2H_5)CH_2C_6H_5$, Y = $CON(CH_3)$-4-ClC_6H_5	5.606	5.603	0.003	1.392	2.131
10	R = $CH_2N(C_2H_5)CH_2C_6H_5$, Y = $CONHC_3H_8$	6.059	6.187	−0.128	0.061	2.131
11	R = $CH_2N(C_2H_5)CH_2C_6H_5$, Y = $CONHCH_2C_6H_5$	5.538	5.788	−0.249	0.971	2.131
12[a]	R = $CH_2N(C_2H_5)CH_2C_6H_5$, Y = H	5.469	6.214	−0.745	0	2.131

[a] Data points not included in equation derivation.

Table 60. K_i Binding Affinities of Substituted Flavones for the Benzodiazepine Binding Site of the $GABA_A$ Receptor:[75,76] Compounds and Physicochemical Parameters for Derivation of Equation 70

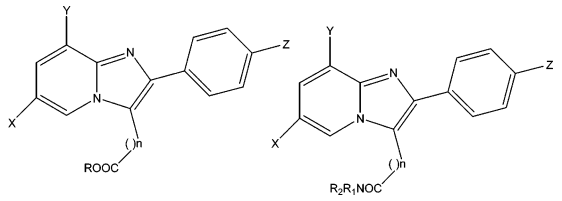
no.	substituents	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	B_{5-5}	B_{1-6}	$I_{3'}$
1	H	5.38	5.18	0.19	1	1	0
2	3-Br	4.12	5.18	−1.06	1	1	0
3	5-OH	5.72	5.96	−0.24	1.93	1	0
4	6-CH_3	6.90	6.16	0.74	1	1.52	0
5	6-OH	6.40	5.84	0.55	1	1.35	0
6	6-OCH_3	6.24	5.84	0.40	1	1.35	0
7	6-Br	7.15	6.97	0.18	1	1.95	0
8	7-OH	5.38	5.18	0.19	1	1	0
9	5,7-di-OH	6.04	5.96	0.07	1.93	1	0
10	6-CH_3, 2′-NO_2	6.00	6.16	−0.16	1	1.52	0
11	3′,6-di-CH_3	7.54	7.51	0.03	1	1.52	1
12	6-CH_3, 3′-NO_2	8.25	7.51	0.74	1	1.52	1
13	6-Br, 3′-NO_2	7.80	8.32	−0.52	1	1.95	1
14	3′,6-di-NO_2	7.59	7.86	−0.26	1	1.70	1
15	6-CH_3, 4′-NO_2	5.14	6.16	−1.03	1	1.52	0
16[a]	4′,6-di-NO2	4.77	6.50	−1.73	1	1.70	0
17	6-CH_3, 3′,5-di-NO_2	8.72	8.71	0.01	2.44	1.52	1
18	4′,5,7-tri-OH	6.11	5.96	0.15	1.93	1.0	0

[a] Data point not included in equation derivation.

B_{5-5} terms confirm a positive steric effect for 5- and 6-substituents. For this set the sterimol parameters are found to be more important without replacing the hydrophobic effect (no collinearity among B_{1-6}, B_{5-5}, and Clog *P*). One data point is omitted (compound **16**), which is a disubstituted $-NO_2$ derivative.

3.31. 2-Phenylimidazo[1,2-*a*]pyridine Derivatives

A new series of 2-phenylimidazo[1,2-*a*]pyridine derivatives[76] for both central CBR and peripheral benzodiazepine PBR receptors has been synthesized,



and their affinites for the CBR receptor have been evaluated. The ability of the compounds to interact with the CBR was investigated by a binding assay using [^{3}H]flunitrazepam as radioligand and membranes from rat brain tissues as receptor source.

From the IC_{50} values in Table 61, QSAR 71 was obtained:

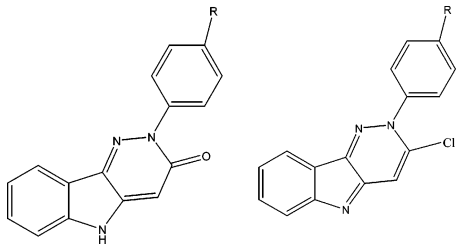
$$\log 1/IC_{50} = 2.046\ (\pm 0.923)\pi_X - 1.313\ (1.077)\pi^2_X + 1.052(\pm 0.289)I_{R_1R_2} - 1.652\ (\pm 0.374)I_Z + 5.029\ (\pm 0.328) \quad (71)$$

$n = 22$ $r^2 = 0.876$ $q^2 = 0.747$ $s = 0.258$ $F_{4,17} = 30.22$ $\alpha = 0.01$

π_X optimum = 0.779 from 0.570 to 2.597

Parabolic dependence on π_X provides an optimum lipophilicity $\pi_{Xo} = 0.779$. It is likely that X substituents do contact a lipophilic space on the receptor. The indicator variable $I_{R_1R_2}$ is for the examples where an alkylamine moiety is present, not a ring (compounds **1**−**14**). I_Z is used to indicate the presence of a Cl. No parametrization was made for the length (*n*) of the carbon chain between the heterocyclic nucleus and the amide function and for the substituent Y. Compounds included in this set contain rather little variation in substituent Y (H, Cl, Br, CH_3). Two data points (compounds **19** and **23**) are omitted in the development of the above equation. Both are esters and not amide derivatives. Again, no effect for the electronic effect was found.

3.32. 2-Aryl-2,5-dihydropyridozino[4,3-*b*]indolo-3(3*H*)-ones



Campagna et al.[77−79] had an interesting contribution in the 2D and 3D QSAR studies of a new class of BzR ligands, namely, the 2-aryl-2,5-dihydropyridozino[4,3-*b*]indolo-3(3*H*)-ones, which are structurally related to the well-known 2-aryl-2,5-dihydropyrazolo[4,3-*c*]quinoline-3(3*H*)-ones.[80] As a continuation a series of 2-aryl-3-chloro-2*H*-pyridazino[4,3-*b*]indoles, 2-aryl-3-methoxy-2*H*-pyridazino[4,3-*b*]indoles and 2-aryl-2,5-dihydroindeno[1,2-*c*]pyridazino-3(3*H*)-ones has been prepared and tested for their ability

Table 61. Inhibition Values IC_{50} of [^{3}H]Flunitrazepam Binding to the Central Benzodiazepine Receptor; Inhibition by 6X-3Y-2(4Z-Phenyl)imidazo[1,2-*a*]pyridin-3-yl:[76] Compounds and Physicochemical Parameters for Derivation of Equation 71

no.	substituents X, Y, Z	obsd log 1/IC_{50}	calcd log 1/IC_{50}	Δlog 1/IC_{50}	πX	$I_{R_1R_2}$	I_Z
1	X = Cl, $CON(C_2H_5)_2$, Z = Cl	5.08	5.22	−0.14	0.71	1	1
2	X = Cl, $CON(C_3H_7)_2$, Z = Cl	5.06	5.22	−0.16	0.71	1	1
3	X = Cl, $CON(CH_2)_4$, Z = Cl	5.53	5.22	0.31	0.71	1	1
4	X = Cl, $CH_2CON(C_3H_7)_2$, Z = Cl	6.33	6.08	0.25	0	1	0
5	X = Cl, $CH_2CON(C_3H_7)_2$, Y = H	7.07	6.87	0.19	0.71	1	0
6	X = Br, $CH_2CON(C_3H_7)_2$, Z, Y= H	6.94	6.87	0.07	0.86	1	0
7	X = l, $CH_2CON(C_3H_7)_2$, Y = H	6.54	6.73	−0.18	1.12	1	0
8	X = CH_3, $CH_2CON(C_3H_7)_2$, Y = H	6.90	6.82	0.09	0.56	1	0
9	X = OCH_3, $CH_2CON(C_3H_7)_2$, Y = H	5.55	6.04	−0.49	−0.02	1	0
10	X = NO_2, $CH_2CON(C_3H_7)_2$, Y = H	5.56	5.41	0.16	−0.28	1	0
11	X = Br, $CH_2CON(C_3H_7)_2$, Y = H	7.24	6.87	0.37	0.86	1	0
12	X = Cl, $CH_2CON(CH_2)_4$, Y = Cl	7.04	6.87	0.16	0.71	1	0
13	X = Cl, $CH_2CON(CH_2)_5$, Y = Cl	6.62	6.87	−0.25	0.71	1	0
14	X = Cl, $CH_2CH_2CON(C_3H_7)_2$, Y = H	6.51	6.87	−0.36	0.71	1	0
15	X = Cl, $COOC_2H_5$, Z = H	5.67	5.82	−0.15	0.71	0	0
16	X = CH_3, $COOC_2H_5$, Z = CH_3	5.94	5.76	0.18	0.56	0	0
17	X = CH_3, $CH_2COOC_2H_5$, Z = H	5.86	5.76	0.09	0.56	0	0
18	X = Cl, $CH_2COOC_2H_5$, Z = H	5.93	5.82	0.11	0.71	0	0
19[a]	X = Cl, $CH_2COOC_2H_5$, Z = Cl	6.16	4.17	1.99	0.71	0	1
20	X = Cl, $CH_2CH_2COOC_2H_5$, Z = H	5.95	5.82	0.13	0.71	0	0
21	X = CH_3, $CH_2COOC_4H_9$, Z = H	5.50	5.76	−0.26	0.56	0	0
22	X = Cl, $CH_2COOC_4H_9$, Z = H	5.60	5.82	−0.22	0.71	0	0
23[a]	X = Cl, $CH_2COOC_4H_9$, Z = Cl	5.56	4.17	1.39	0.71	0	1
24	X = Cl, $CH_2CH_2COOC_4H_9$, Z = H	5.93	5.82	0.11	0.71	0	0

[a] Data points not included in equation derivation.

Table 62. Inhibition Values IC_{50} of [^{3}H]Flunitrazepam Binding to the Benzodiazepine Receptor by N−X, 2-(Y-Phenyl-3,5-dihydropyridazino[4,3-*b*]indolones:[77−79] Compounds and Physicochemical Parameters for Derivation of Equation 72

no.	substituents R	obsd log 1/IC_{50}	calcd log 1/IC_{50}	Δlog 1/IC_{50}	Clog *P*
1	R = H	6.623	6.974	−0.350	−0.985
2	R = Cl	7.507	7.431	0.077	−2.558
3	R = Br	7.405	7.431	−0.026	−2.558
4	R = OCH_3	7.622	7.426	0.196	−2.541
5	R = H	5.807	5.833	−0.027	2.939
6	R = Cl	5.605	5.626	−0.022	3.652
7	R = OCH_3	6.003	5.851	0.152	2.880

Table 63. Inhibition Values IC_{50} of [^{3}H]Flunitrazepam Binding to the Benzodiazepine Receptor Inhibition by 2-(Y-Phenyl-3-X,2*H*-pyridazino[4,3-*b*]indoles:[77−79] Compounds and Physicochemical Parameters for Derivation of Equation 73

no.	substituents R	obsd log 1/IC_{50}	calcd log 1/IC_{50}	Δlog 1/IC_{50}	Clog *P*
1	R = H	5.604	5.786	−0.182	5.155
2	R = H	6.597	6.405	0.192	5.871
3	R = Br	6.550	6.538	0.011	6.024
4[a]	R = OCH_3	7.042	5.831	1.212	5.206
5	R = Cl	6.039	5.999	0.039	5.401
6	R = Br	5.928	6.129	−0.201	5.551
7	R = OCH_3	5.453	5.313	0.141	4.607

[a] Data point not included in equation derivation.

to inhibit the [^{3}H]flunitrazepam binding to the central benzodiazepine receptor (Tables 62−64).

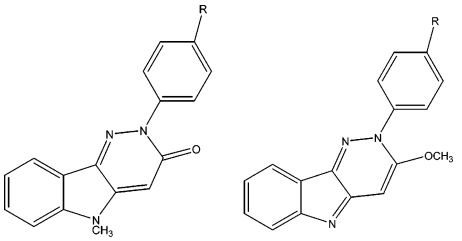


Table 64. Inhibition Values IC_{50} of [^{3}H]Flunitrazepam Binding to the Benzodiazepine Receptor Inhibition by 2-(Y-Phenyl)indeno[1,2-*c*]pyridazinone Analogues:[77−79] Compounds and Physicochemical Parameters for Derivation of Equation 74

no.	substituents R	obsd log 1/IC_{50}	calcd log 1/IC_{50}	Δlog 1/IC_{50}	L_Y
1	R = H	5.573	5.651	−0.078	2.06
2	R = Cl	6.767	6.447	0.320	3.52
3	R = Br	6.745	6.611	0.134	3.82
4	R = OCH_3	6.745	6.698	0.047	3.98
5	R = H	5.662	5.651	0.010	2.06
6	R = Cl	6.390	6.447	−0.057	3.52
7	R = Br	6.533	6.611	−0.078	3.82
8	R = OCH_3	6.400	6.698	−0.298	3.98

(a) From the results in Table 62 eq 72 has been derived:

$$\log 1/IC_{50} = -0.291\ (\pm 0.071)\ \text{Clog}\ P + 6.687\ (\pm 0.191) \quad (72)$$

$n = 7$ $r^2 = 0.956$ $q^2 = 0.930$ $s = 0.196$ $F_{1,5} = 109.056$ $\alpha = 0.01$

No role for an electronic effect was found. Activity decreases with increasing hydrophobicity as brought by −0.291 Clog *P*. The more hydrophobic the molecule, the higher the affinity to the BzR.

(b) For the data in Table 63 equation has 73 been derived:

$$\log 1/IC_{50} = 0.865\ (\pm 0.439)\ \text{Clog}\ P + 1.329\ (\pm 2.396) \quad (73)$$

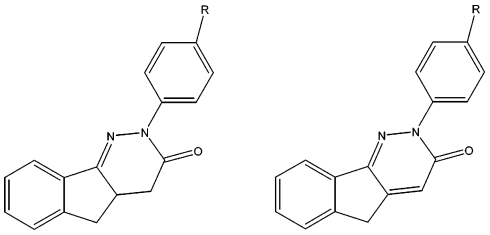
$n = 6$ $r^2 = 0.881$ $q^2 = 0.643$ $s = 0.182$ $F_{1,3} = 29.818$ $\alpha = 0.01$

One point (compound **4**, Table 63) was rejected from the derivation of this correlation. The number of data points is small. QSAR is not exceedingly significant because there is a problem with the confidence limits

Table 65. BzR Binding Affinities of Pyrazolo[1,5-*a*]pyrimidine Derivatives:[81] Compounds and Physicochemical Parameters for Derivation of Equation 75

no.	substituents Ar, R, Ar′	calcd log $1/K_i$	obsd log $1/K_i$	Δlog $1/K_i$	Clog *P*
1	Ar = C_6H_5, R = H, Ar′ = C_6H_5	6.433	6.387	0.046	3.206
2	Ar = C_6H_5, R = CH_3, Ar′ = C_6H_5	6.062	6.331	−0.269	3.235
3	Ar = C_6H_5, R = CH_2CH_3, Ar′ = C_6H_5	5.730	5.334	0.397	3.764
4	Ar = 3′-thienyl, R = H, Ar′ = C_6H_5	7.141	7.050	0.092	2.854
5	Ar = 3′-$OCH_3C_6H_4$−, R = H, Ar′ = C_6H_5	6.717	6.524	0.192	3.133
6	Ar = C_6H_5, R = H, Ar′ = 3′-thienyl	6.955	7.044	−0.090	2.857
7	Ar = 3′-$OCH_3C_6H_4$−, R = H, Ar′ = 3′-thienyl	7.375	7.184	0.191	2.783
8	Ar = 3′-$OCH_3C_6H_4$−, R = H, Ar′ = 2′-thienyl	6.440	6.788	−0.348	2.993
9	Ar = C_6H_5, R = H, Ar′ = 3′-$OCH_3C_6H_4$−	6.224	6.525	−0.301	3.133
10	Ar = 3′-thienyl, R = H, Ar′ = 3′-thienyl,	7.788	7.709	0.079	2.505
11	Ar = 3′-thienyl, R = H, Ar′ = 2′-thienyl	7.057	7.313	−0.256	2.715
12	flunitrazepam	8.664	8.397	0.267	2.140

of the constant term. All of the rings with their substituents do appear to reach a hydrophobic surface.



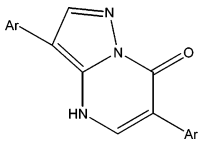
(c) Equation 74 has been derived for the 2-aryl-2,5-dihydroindeno[1,2-*c*]pyridazino-3(3*H*)-ones (Table 64)

$$\log 1/IC_{50} = 0.545\ (\pm 0.221)L_Y + 4.528\ (\pm 0.759) \quad (74)$$

$n = 8$ $r^2 = 0.859$ $q^2 = 0.785$ $s = 0.194$ $F_{1,6} = 36.290$ $\alpha = 0.01$

and gave a good correlation between observed and calculated IC_{50} values. The above correlation does not contain a Clog *P* or a π term.

3.33. 3,6-Diaryl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidin-7-ones



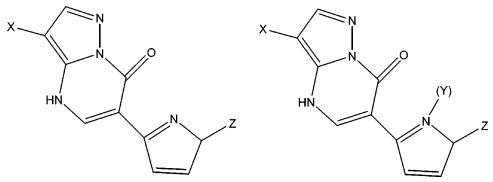
Bruni et al.[81] designed a novel class of 3,6-diaryl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-ones and determined the groups involved in the BzR recognition. 3,6-Diphenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-one was synthesized and investigated by a binding assay using [^{3}H]RO15-1788 as radioligand and bovine brain membranes from brain tissues as receptor source. They have tried to predict the in vitro efficacy of the most active compounds by determining the $GABA_A$ ratio (IC_{50} without $GABA_A$/IC_{50} with $GABA_A$). The resulting affinity and efficacy were quite comparable with those of the reference compound of the 6-pyrazolo-3′/(5′)-yl series. As an extension, the phenyl groups at the 3- and 6-positions were in turn replaced either by 3′-methoxyphenyl or by a thienyl ring to verify the maintenance of BzR recognition and possibly to identify a potential bioisosteric series. Using these data (Table 65) we developed eq 75:

$$\log 1/K_i = -1.886\ (\pm 0.428)\ \text{Clog}\ P + 12.432\ (\pm 1.270) \quad (75)$$

$n = 12$ $r^2 = 0.906$ $q^2 = 0.819$ $s = 0.260$ $F_{1,10} = 96.474$ $\alpha = 0.01$

The negative coefficient with Clog *P* shows that the more hydrophobic the molecule, the higher affinity to the BzR. All data fit well by QSAR 75.

3.34. 3-Aryl-4,7-dihydro-6(*N*-alkylpyrazol-3′- or 5′-yl)pyrazolo[1,5-*a*]pyrimidin-7-ones



In continuation by the same research group[82] the synthesis and the in vitro affinities of a series of 3-aryl-4,7-dihydro-6-(*N*-alkylpyrazol-3′- or 5′-yl)pyrazolo[1,5-*a*]pyrimidin-7-ones was investigated, to evaluate the conformational requirements of the lipophilic pockets into which the 3- and 6-substituents fit to provide better insight into the structure−affinity and −activity relationships of those compounds. According to their observations, the molecular interaction of pyrazolo[1,5-*a*]pyrimidine ligands with BzR necessitates the following: (1) a triple recognition involving a hydrogen-bonding site H_1 (donor site) of the receptor protein and C^7, O, and N_1 of the ligand; (2) a hydrogen acceptor bonding site A_2, which interacts with protonated N_4 of the ligand; and (3) two lipophilic regions L_1/L_2 and L_3, where the 3- and 6-substituents are proposed to fit.

From their data eq 76 was derived:

$$\log 1/K_i = 0.474\ (\pm 0.177)\ \text{Clog}\ P + 0.600\ (\pm 0.359)B_{1-3X} - 0.903\ (\pm 0.212)B_{5-Z} + 6.681\ (\pm 0.541) \quad (76)$$

$n = 22$ $r^2 = 0.885$ $q^2 = 0.838$ $s = 0.288$ $F_{3,18} = 46.35$ $\alpha = 0.01$

B_{1-3X} is the most important factor in the QSAR, following the overall lipophilicity Clog *P* of the molecules and the sterimol parameter B_{5-Z}. No para-

Table 66. BzR Binding Affinities of 3-(Aryl)-4,7-dihydro-6-(*N*-alkylpyrazol-3′ or 5′-yl)pyrazolo[1,5-*a*]-pyrimidin-7-ones:[82] Compounds and Physicochemical Parameters for Derivation of Equation 76

no.	substituents X, Z	obsd log $1/K_i$	calcd log $1/K_i$	Δlog $1/K_i$	Clog P	B_{1-3X}	B_{5-Y}
1	X = 2-Br, Y = Z = H	7.180	6.749	0.432	0.779	1.00	1.00
2	X = 3-Br, Y = Z = H	7.264	7.461	−0.198	1.079	1.95	1.00
3	X = 4-Br, Y = Z = H	6.499	6.891	−0.392	1.079	1.00	1.00
4	X = 2-F, Y = Z = H	6.467	6.550	−0.082	0.359	1.00	1.00
5	X = 3-F, Y = Z = H	7.149	6.760	0.389	0.359	1.35	1.00
6[a]	X = 4-F, Y = Z = H	7.166	6.550	0.616	0.359	1.00	1.00
7	X = 3-CH_3, Y = Z = H	7.056	7.031	0.025	0.715	1.52	1.00
8	X = 3-CF_3, Y = Z = H	7.712	7.495	0.217	1.099	1.99	1.00
9	X = 4-OCH_3, Y = Z = H	6.186	6.446	−0.259	0.140	1.00	1.00
10	X = 3-OH, Y = Z = H	6.238	6.382	−0.144	−0.437	1.35	1.00
11[a]	X = 4-OH, Y = Z = H	7.281	6.172	1.109	−0.437	1.00	1.00
12[a]	X = 2-Br, Y = Z = CH_3	5.899	7.376	−1.477	2.103	1.00	1.00
13	X = 3-Br, Y = Z = CH_3	7.959	8.089	−0.130	2.403	1.95	1.00
14	X = 3-F, Y = H, Z = CH_3	6.979	7.387	−0.408	1.683	1.35	1.00
15	X = 4-F, Y = H, Z = CH_3	7.523	7.177	0.346	1.683	1.00	1.00
16	X = 3-CF_3, Y = H, Z = CH_3	8.509	8.122	0.386	2.423	1.99	1.00
17	X = 3-Br, Y = Z = CH_3	6.893	7.150	−0.257	2.403	1.95	2.04
18	X = 3-F, Y = Z = CH_3	6.780	6.448	0.332	1.683	1.35	2.04
19	X = 4-F, Y = Z = CH_3,	5.971	6.238	−0.268	1.683	1.00	2.04
20	X = 3-CF_3, Y = Z = CH_3	7.264	7.184	0.080	2.423	1.99	2.04
21	X = 3-Br, Y = H, Z = C_2H_5	8.465	8.340	0.125	2.932	1.95	1.00
22	X = 3-F, Y = H, Z = C_2H_5	6.588	7.638	−1.050	2.212	1.35	1.00
23	X = 4-F, Y = H, Z = C_2H_5	7.355	7.428	−0.073	2.212	1.00	1.00
24	X = 3-CF_3, Y = H, Z = C_2H_5	8.199	8.373	−0.174	2.952	1.99	1.00
25	X = 3-Br, Y = Z = C_2H_5	6.234	6.381	−0.146	2.932	1.95	3.17
26	X = 4-F, Y = Z = C_2H_5	5.670	5.469	0.201	2.212	1.00	3.17

[a] Data points not included in equation derivation.

metrization for the 2′,4′-position on the phenyl ring has been done. The phenyl ring with these substituents does appear to reach a hydrophobic surface.

The B_{5-Z} term appears to confirm a negative steric effect for alkyl substituents on the N. B_{1-3X} has a positive effect on the inhibition. The lipophilic surface where the 3-aryl substituent fits possesses some steric requirements. Electronic factors are not found to play any definite role. The existence of linear-only correlation between the log $1/K_i$ and Clog P suggests that the log P values were not great enough to establish the upper limit of the binding inhibition. Three points (compounds **6**, **11**, and **12**, Table 66) are omitted. Compound **12** is a very weak displacer, whereas compound **6** possesses a very low Clog P value (Clog $P = 0.359$). It is important that compound **11** is one of the two less lipophilic derivatives in the series (Clog $P = -0.437$).

4. Overview

Despite the synthesis and testing of untold numbers of benzodiazepine and non-benzodiazepine analogues 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 relationships. From all of the above QSAR studies, for different kinds of BzR ligands there have surfaced certain crucial features in each kind of ligand, without which they would not be able to interact with the receptor at all. There are similarities and differences in the crucial features for binding for structurally different classes of ligands. Several models for the BzR pharmacophore have been developed and summarized by Villar et al.[83] and Gupta.[84] The fused aromatic rings and the planarity of the molecules seem to be of primary importance.

From most of the equations steric parameters, for example, B_1, B_5, L, MR, MgVol, or E_s, seem to play important and significant parts in the correlations. They would also indicate that hydrophobic effects are relatively unimportant and there is no hydrophobic barrier between the point of entry and the site of interaction. The derived equations correlate in vitro binding to the BzR 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 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. This reminds us of the QSAR for the inhibitors of serotonin uptake. The existence of linear correlations between inhibition values and log P (eqs 2, 4, 6, 10 11, 13, 17, 26, 30, 54, 58, 69, 72, 73, 75, and 76) simply suggests that log P values were not great enough to establish the upper limit for the rate of penetration. These equations may be interpreted as indicating a situation where the maximum inhibition has not been reached. The negative coefficient with Clog P lacks hydrophobic terms. The receptor cleft or pocket may not be completely homogeneous (hydrophobic) so that log P does not fit very well to a large molecule with multiple positions of substitution. In the cases when the relationship between log $1/IC_{50}$ and log P is well approximated by parabola or a billinear model, the role of the lipophilic character of non-BDZs can be at least roughly separated from their electronic and steric characteristics. Our study shows that in 25 of 76 QSAR Clog P (and π) plays a significant part in the QSAR of the non-BDZs on the receptor. The presence of steric terms suggests that

a protein receptor is involved. Thus, coefficients with steric terms may reflect the complex process of displacement of the ligand and/or the receptor wall. The negative steric terms (MR, B_1, B_5, and L) imply that the critical effects are occurring on (in) an active site on a macromolecule. In three cases MgVol (eqs 18, 23, 43−45, 47−50, 52−54, and 66) becomes of marginal importance. The parabolic dependence on L provides an optimum length of 4.084 (0.294). A fascinating point is the dual positive steric effects brought out by B_1 and B_5, for example, in eq 68.

The Hammett's constant σ and the Swain−Lumpton F have been the major electronic factors influencing binding. In eqs 3, 5, 13, 14, 27, 32−35, 46, and 63, activity was shown to have a significant dependence on σ or F (eq 13) or R (eq 13). In eqs 3, 5, 27, 32−35, and 46 there was a positive role of σ, whereas in eqs 13, 14, and 63 a negative role was found. At this time from the data sets under study and the nature of the substituents, electronic effects cannot be ruled out. Electronic parameters indicative of dipole−dipole interactions, charge-transfer phenomena, and hydrogen bond formation are not found to govern the binding to the receptor of the data sets.

For some structural features eqs 1, 5, 9, 10, 12, 15, 21, 26, 28, 29, 36−40, 63, 70, and 71, we had to use indicator variables as a device to account for the effect of a specific feature that cannot be accounted for by a more specific parameter.

Because the experimental work on which these evaluated equations are based was almost all done in different laboratories, this tends to increase differences in the results. Another confusion arises as to the role of heteroatoms which confer different degrees of specificity in terms of potency and in the quality of the biological response.

5. Acknowledgments

This research was supported by NIEHS Grant R01 ES 07595 (to C.H.).

6. References

(1) Blair, T.; Webb, G. A. *J. Med. Chem*. **1977**, *20*, 1206.
(2) Greco, G.; Novellino, E.; Silipo, C.; Vittoria, A. *Quant. Struct.−Act. Relat*. **1992**, *11*, 461.
(3) Gupta, S. P.; Paleti, A. *Quant. Struct.−Act. Relat*. **1996**, *15*, 12.
(4) Hadjipavlou-Litina, D.; C. Hansch, C. *Chem. Rev*. **1993**, 93.
(5) (a) Möhler, H.; Fritsch, J. M.; Rudolph, U. *J. Pharm. Exp. Ther*. **2002**, *300*, 2. Sieghart, W.; Sperk, G. *Curr. Top. Med. Chem*. **2002**, *2*, 795. (b) Ernst, M.; Brauchart, D.; Boresch, S.; Sieghart, W. *Neuroscience* **2003**, *119*, 933. (c) Möhler, H.; Crestani, F.; Rudolph, U. *Curr. Opin. Pharm*. **2001**, *1*, 22. (d) Skolnick, P.; Hu, R.; Cook, C.; Hurt, S.; Trometer, J.; Liu, R.; Huang, Q.; Cook, J. *J. Pharm. Exp. Ther*. **1997**, *283*, 488.
(6) Bosmann, H. B.; Penney, D. P.; Case, K. R.; Di Stefano, P.; Averill, K. *FEBS Lett*. **1978**, *87*, 199.
(7) (a) Tallmann, J. F.; Paul, S. M.; Skolnick, P.; Gallager, D. W. *Science* **1980**, *207*, 274. (b) Tallmann, J. F.; Thomas, J. W.; Gallager, D. W. *Nature (London)* **1978**, *274*, 383.
(8) Schoch, P.; Richards, J. G.; Harig, P.; Takacs, B.; Mohler, H. *Adv. Biochem. Psycopharmacol*. **1986**, *41*, 11.
(9) Marangos, P. J.; Patel, J.; Boulenger J. P.; Clark-Rosemberg, R. *Mol. Pharmacol*. **1982**, *22*, 26.
(10) Shoemaker, H.; Boles, R. G.; Horst, W. D.; Yamamura, H. I. *J. Pharmacol. Exp. Ther*. **1983**, *225*, 61.
(11) Katz, Y.; Amiri, Z.; Weizman, A.; Gavish, M. *Biochem. Pharmacol*. **1990**, *40*, 817.
(12) Basile, A. S.; Skolniick, P. *J. Neurochem*. **1986**, *46*, 305.
(13) O'Beirne, G. B.; Williams, D. C. *Eur. J. Biochem*. **1988**, *175*, 413.
(14) Mukherjee, S.; Das, S. K. *J. Biol. Chem*. **1989**, *264*, 16713.
(15) Doble, A.; Martin, I. L. *Trends Pharm. Sci*. **1992**, *13*, 76. Doble, A.; Benavides, J.; Ferris, O.; Bertrand, P.; Menager, J.; Vaucher, N.; Burgevin, M. C.; Uzan, A.; Gueremy, C.; Le Fur, G. *Eur. J. Pharmacol*. **1989**, *161*, 197.
(16) Papadopoulos, V.; Guarneri, P.; Kneger, K. E.; Guidotti, A.; Costa, E. *Proc. Natl. Acad. Sci. U.S.A*. **1992**, *89*, 511314.
(17) Anholt, R. R. H.; Pedersen, P. L.; DeSouza, F. B.; Snyder, S. H. *J. Biol. Chem*. **1986**, *261*, 576. McEnery, M. W.; Snowman, A. M.; Trifletti, R. R.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A*. **1992**, *89*, 3170. Wang, J. K. T.; Morgan, J. I.; Specto, R. S. *Proc. Natl. Acad. Sci. U.S.A*. **1984**, *81*, 3770.
(18) Pole, P.; Bonetti E.; Schaffner, R.; Haefely, W. *Arch. Pharmacol*. **1982**, *321*, 260.
(19) Fryer, R. I.; Gilman, N. W.; Madison, V.; Walser, A. In *Proceedings of the VIIIth International Symposium on Medicinal Chemistry*; Dahlbom, R., Nilsson, J. L., Eds.; Swedish Pharmaceutical Press: Stockholm, Sweden, 1985; Vol. 2, p 265.
(20) Nistri, A.; Constani, A. *Neuropharmacology* **1978**, *17*, 127.
(21) Simmonds, M. A. *Trends Neurosci*. **1983**, *6*, 279.
(22) Simmonds, M. A. In *Actions and Interactions of GABA and Benzodiazepines*; Bowery, N. G., Ed.; Raven Press: New York, 1984; p 27.
(23) Bowery, N. G.; Hill, D. R.; Hudson, A. L. *Br. J. Pharmacol*. **1983**, *78*, 191.
(24) Bowery, N. G.; Hill, D. R.; Hudson, A. L.; Price, G. W.; Turnbull, M. J.; Wilkin, G. P. In *Actions and Interactions of GABA and Benzodiazepines*; Bowery, N. G., Ed.; Raven Press: New York, 1984; p 81.
(25) Fryer, R. I. In *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: New York, 1990; Vol. 3, p 539.
(26) Gupta, S. P. *Prog. Drug Res*. **1995**, *45*, 67.
(27) Gupta, S. P.; Paleti, A. *Proc. Indian Natl. Sci. Acad*. **1997**, *63A*, 365.
(28) Hansch, C. *Acc. Chem. Rev*. **1969**, *2*, 232.
(29) Hansch, C.; Zhang, L. *Drug Metab. Rev*. **1993**, *25* (1−2), 1.
(30) Leo, A. J. *Chem. Rev*. **1993**, *93*, 1871.
(31) Hansch, C.; Leo, A. J.; Taft, W. R. *Chem. Rev*. **1991**, *91*, 165.
(32) Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem*. **1976**, *12*, 91.
(33) Hansch, C.; Leo, A. J. Exploring QSAR: *Fundamentals and Applications in Chemistry and Biology*; American Chemical Society: Washington, DC, 1995.
(34) Hansch, C.; Leo, A. J.; Hoekman, D. *Exploring QSAR: Hydrophobic, Electronic and steric Constants*; American Chemical Society: Washington, DC, 1995.
(35) Silippo, C.; Vittoria, A. *Comprehensive Medicinal Chemistry. Three-Dimensional Structure of Drugs*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: New York, 1990; Vol. 4, Chapter 18.4, p 153.
(36) Verloop, A. *The Sterimol Approach to Drug Design*; Dekker: New York, 1987.
(37) BioByte Corp. C.-QSAR database, Claremont, CA.
(38) Cramer, R. D., III.; Bruce, J. D.; Patterson, D. E.; Frank, I. E. *Quant. Struct.−Act. Relat*. **1988**, *7*, 18.
(39) Palazzino, G.; Cecchi, L.; Melani, F.; Colotta, V.; Fillachione, G.; Martini, C.; Lucacchini, A. *J. Med. Chem*. **1987**, *30*, 1737.
(40) Clements-Jewery, S.; Danswan, G.; Gardner, C. R.; Matharu, S. S.; Murdoch, R.; Tilly, W. R.; Westwood, R. *J. Med. Chem*. **1988**, *31*, 1220.
(41) Huang, Q.; Cox, E. D.; Gan, T.; Ma, C.; Bennett, D. W.; McKernan, R. M.; Cook, J. *Drug Des. Discov*. **1999**, *16*, 55.
(42) (a) Sharma, R. C.; Ojha, T. N.; Tiwari, S.; Singh, P. *Drug Des. Discov*. **1992**, *9*, 135. (b) Allen, M. S.; Hagen, T. J.; Trudell, M. L.; Codding, P. W.; Skolnick, P.; Cook, J. M. *J. Med. Chem*. **1988**, *31*, 1854.
(43) Hollinshead, S. P.; Trudel, l M. L.; Skolnick, P.; Cook, J. M. *J. Med. Chem*. **1990**, *33*, 1062.
(44) Saha, R. N.; Meera, J.; Agrawal, N.; Gupta, S. P. *Drug Des. Delivery* **1991**, *7*, 219.
(45) Primofiore, G.; Martini, A. M.; Settimo, F. D.; Martini, C.; Bardellini, A.; Gianaccini, G.; Lucacchini, A. *J. Med. Chem*. **1989**, *32*, 2514.
(46) So, S. S.; Karplus, M. *J. Med. Chem*. **1997**, *40*, 4360.
(47) Good, A. C.; Peterson, S. J. *J. Med. Chem*. **1993**, *36*, 2929.
(48) Allen, M. S.; Tan, Y. C. *J. Med. Chem*. **1990**, *33*, 2343.
(49) Borea, P. A.; Pietrogrande, M. C.; Biagi, G. L. *Biochem. Pharmacol*. **1988**, *37*, 3953.
(50) Kelley, J. K.; McLean, E. W.; Ferris, R. M.; Howard, J. L. *J. Med. Chem*. **1989**, *32*, 1020.
(51) Kelley, J. L.; McLean, E. W.; Linn, J. A.; Krochmal, M. P.; Ferris, R. M.; Howard, J. L. *J. Med. Chem*. **1990**, *33*, 196.
(52) Kelley, J. K.; McLean, E. W.; Ferris, R. M.; Howard, J. L. *J. Med. Chem*. **1990**, *33*, 1910.
(53) Sharma, R. C.; Ojha, T. N.; Tiwari, S.; Singh, P. *Drug Des. Discov*. **1992**, *9*, 134.

(54) Trudell, M. L.; Lifer, S. L.; Tan, Y. C.; Martin, M. J.; Deng, L.; Skolnick, P.; Cook, J. M. *J. Med. Chem*. **1990**, *33*, 2412.
(55) Trapani, G.; Franco, M.; Latrofa, A.; Genchi, G.; Liiso, G. *Eur. J. Med. Chem*. **1992**, *27*, 39.
(56) Wong, G.; Koehler, K. F.; Skolnick, P.; Gu, Z. Q.; Ananthan, S.; Schonholzer, P.; Hunkeler, W.; Zhang, W.; Cook, J. M. *J. Med. Chem*. **1993**, *36*, 1820.
(57) Gu, Z. Q.; Wong, G.; Dominguez, C.; De Costa, B. R.; Rice, K. G.; Skolnick, P. J. *J. Med. Chem*. **1993**, *36*, 1001.
(58) Zhang, W.; Lin, R.; Huang, Q.; Zhang, P.; Koehler, K. F.; Harris, B.; Skolnick, P.; Cook, J. M. *Eur. J. Med. Chem*. **1995**, *30*, 483.
(59) Andersen, K. E.; Lundt, B. F.; Jorgensen, A. S.; Braestrup, C. *Eur. J. Med. Chem*. **1996**, *31*, 417.
(60) Guerrini, G.; Constanzo, A.; Bruni, F.; Selleri, S.; Casilli, L.; Giusti, L.; Martini, C.; Lucacchini, A.; Aiello, P. M.; Ipponi, A. *Eur. J. Med. Chem*. **1996**, *31*, 259.
(61) Harrison, P. W.; Barlin, G. B.; Davies, L. P.; Ireland, S. J.; Matyu, S. P.; Wong, M. G. *Eur. J. Med. Chem*. **1996**, *31*, 651.
(62) Greco, G.; Novellino, E.; Fiorini, I.; Nacci, V.; Campiani, G.; Giani, S. M.; Garofalo, A.; Bernasconi, P.; Mennini, T. *J. Med. Chem*. **1994**, *37*, 4100.
(63) Garofalo, A.; Campiani, G.; Savini, L.; Novellino, E.; Greco, G.; Bernasconi, P.; Mennini, T. J. *J. Med. Chem*. **1994**, *37*, 1427.
(64) Fiorini, I.; Nacci, V.; Giani, S. M.; Garofalo, A.; Campiani, G.; Savini, L.; Novellino, E.; Greco, G.; Bornasconi, P.; Mennini, T. *J. Med Chem*. **1994**, *37*, 1427.
(65) Paleti, P.; Gupta, S. P. *Quant. Struct.−Act. Relat*. **1997**, *16*, 367.
(66) Takada, S.; SasaTani, T.; Chomei, N.; Adachi, M.; Fujishita, T.; Eigyo, M.; Murata, S.; Kawasaki, K.; Matsushita, A. *J. Med. Chem*. **1996**, *39*, 2844.
(67) Catarzi, D.; Cecchi, L.; Collota, V.; Melani, F.; Fillachioni, G.; Martini, C.; Giusti, L.; Lucacchini, A. *J. Med. Chem*. **1994**, *37*, 2846.
(68) Huang, Q.; Liu, R.; Zhang, P.; He, X.; McKernan, R.; Gan, T.; Bennett, D. W.; Cook, J. M. *J. Med. Chem*. **1998**, *41*, 4130.
(69) Fryer, R. I.; Zhang, P.; Lin, K. Y.; Upasani, R. B.; Wong, G.; Skolnick, P. *Med. Chem. Res*. **1993**, *3*, 183.
(70) Haefely, W.; Kyburz, E.; Gerecke, M.; Mohler, H. In *Advances in Drug Research*; Testa, B., Ed.; Academic Press: New York, 1985; Vol. 14, p 165.
(71) (a) Huang, Q.; He, X.; Ma, C.; Liu, R.; Yu, S.; Dayer, C. A.; Wenger, G. R.; McKernan, R.; Cook, J. M. *J. Med. Chem*. **2000**, *43*, 71. (b) He, X.; Huang, Q.; Ma, C.; Yu, S.; Mckernan, R.; Cook, J. *Drug Des. Discov*. **2000**, *17*, 131. (c) He, X.; Huang, Q.; Yu, S.; Ma, C.; Mckernan, R.; Cook, J. *Drug Des. Discov*. **1999**, *16*, 77.
(72) Savini, L.; Massarelli, P.; Nencini, C.; Pellerano, C.; Biggio, G.; Maciocco, A.; Tuligi, G.; Carrieri, A.; Cinone, N.; Carotti, A. *Bioorg. Med. Chem*. **1998**, *6*, 389.
(73) Trapani, G.; Franco, M.; Latrofa, A.; Riccardi, L.; Carrotti, A.; Serra, M.; Sanna, E.; Biggio, G.; Liso, G. *J. Med. Chem*. **1999**, *42*, 3934.
(74) Anzini, M.; Capelli, A.; Vomero, S.; Seeber, M.; Menziani, M. C.; Langer, T.; Hagen, B.; Manzoni, C.; Bourguignon, J. J. *J. Med. Chem*. **2001**, *44*, 1134.
(75) Dekermendjian, K.; Kahnberg, P.; Witt, M. R.; Sterner, O.; Nielsen, M.; Liljefos, T. *J. Med. Chem*. **1999**, *42*, 4343.
(76) Trapani, G.; Franco, M.; Riccardi, L.; Latrofa, A.; Genchi, G.; Sanna, E.; Tuveri, F.; Cagetti, E.; Biggio, G.; Liso, G. *J. Med. Chem*. **1997**, *40*, 3109.
(77) Campagna, F.; Palluoto, F.; Carotti, A.; Casini, G.; Genchi, G. *Bioorg. Med. Chem*. **1999**, *7*, 1533.
(78) Campagna, F.; Carotti, A.; Casini, G.; Palluoto, F.; Genchi, G.; De Sarro, G. B. *Biorg. Med. Chem*. **1993**, *1*, 437.
(79) Palluoto, F.; Carotti, A.; Casini, G.; Campagna, F.; Genchi, G.; Rizzo, M.; De Sarro, G. B. *Bioorg. Med. Chem*. **1996**, *4*, 2091.
(80) Savini, L.; Massarelli, P.; Nencini, C.; Pellerano, C.; Biggio, G.; Maciocco, E.; Tuligi, G. A.; Carrieri, A.; Cinone, N.; Carotti, A. *Bioorg. Med. Chem*. **1998**, *6*, 389.
(81) Selleri, S.; Bruni, F.; Costagli, C.; Constanzo, A.; Guerini, G.; Ciciani, G.; Costa, B.; Martini, C. *Bioorg. Med. Chem*. **1999**, *7*, 2705.
(82) Selleri, S.; Bruni, F.; Costagli, C.; Constanzo, A.; Guerini, G.; Ciciani, G.; Aiello, P. M.; Lamberti, C.; Costa, B.; Martini, C. *Med. Chem*. **2000**, *10*, 92.
(83) Villar, H. O.; Davies, M. F.; Loew, G. H.; Maguire, P. A. *Life Sci*. **1991**, *48*, 593.
(84) Gupta, S. P. *Indian J. Chem*. **1994**, *33B*, 105.

CR0304469