Synthesis, Pharmacology, and Structure−Activity Relationships of Novel Imidazolones and Pyrrolones as Modulators of $GABA_A$ Receptors

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New series of imidazolones and pyrrolones were synthesized. The compounds were tested regarding their anxiolytic properties due to modulation of the $GABA_A$ receptor response. Several derivatives exhibit considerable pharmacological activity while lacking the typical side effects of benzodiazepine receptor agonists. 1-(4-chlorophenyl)-4-morpholin-1-yl-1,5-dihydro-imidazol-2-one (**2**) and 1-(4-chlorophenyl)-4-piperidin-1-yl-1,5-dihydro-imidazol-2-one (**3**) were protective in the pentylenetetrazole test in rats with oral ED_{50} of 27.4 and 12.8 mg/kg and TD_{50} (rotarod) of >500 and 265 mg/kg, respectively. The minimum effective dose in the Vogel conflict test was 3 mg/kg for both compounds. Common structure−activity relationship and comparative molecular field analysis models of the various series of derivatives could be established which are in accordance with a $GABA_A$ mediated pharmacological action. The findings fit well into an established pharmacophore model. This model is refined by an additional steric restriction feature.

Introduction

Chronic anxiety and epilepsy are common and serious diseases of the central nervous system. It is assumed that 50 million people worldwide suffer from epilepsy.[1] Anxiety is even more common with a lifetime prevalence of 5% for generalized anxiety disorders.[2] About 17% of men and 21% of women over 55 experience symptoms which need some form of treatment.[3,4] Although the genesis and the appearance of these disorders differ, both can be treated by modulators of $GABA_A$ receptors.

$GABA_A$ receptors are chloride ion channels that are controlled by the inhibitory neurotransmitter γ-aminobutyric acid (GABA). They influence the chloride ion conductivity of the neuronal membrane. Binding of GABA to the receptor causes an opening of the channel and a decrease of membrane excitability by the influx of chloride ions into the cell. $GABA_A$ receptors are symmetric heteropentamers forming a central chloride ion-selective pore.[5] Until now, 21 subunits (6 α, 4 β, 4 γ, 1 δ, 1 ϵ, 1 π, 1 θ, 3 ρ) have been identified.[6,7] The α, β, and γ subunit classes are most abundant[8] and constitute pentamers that comprise two α, two β, and one γ subunit. Various mechanisms are known for the activation and modulation of $GABA_A$ receptors.[9] GABA and the competitive ligands muscimol (agonist) and bicuculline (antagonist) bind to the GABA binding site. Picrotoxin blocks the ion channel directly. Additionally, there are modulatory sites for barbiturates, steroids, and benzodiazepines.

The benzodiazepine receptor (BzR), often termed benzodiazepine binding site, is a modulatory site of the $GABA_A$ receptor. Beside benzodiazepines, a wide variety of structurally different compounds are ligands of BzR as for instance β−carbolines, pyridoindoles, triazolophthalazines, imidazoquinoxalines, flavones, and pyrazoloquinolinones. Depending on their intrinsic activity, they modulate the GABA response as full agonists, partial agonists, antagonists, partial inverse agonists, or inverse agonists. Agonists and partial agonists amplify GABA-induced currents, thus causing anticonvulsive, anxiolytic, and sedative effects. On one hand, anxiolytics acting as BzR ligands are efficient drugs of low toxicity that are relatively safe against overdosing,[8] while, on the other hand, the use of BzR agonists is limited because of side effects such as sedation, myorelaxation, ethanol interaction, ataxia and amnesia, psychical and physical dependence, tolerance, and abuse liability.[10,11] The potential for dependence and drug tolerance constitutes an impediment to the long-term use of benzodiazepines. There is a broad consensus that the development of partial or, as discussed more recently, subtype-specific BzR ligands could help in the discovery of new drugs without these disadvantages.[12−26]

Here, we present novel methods for the synthesis of imidazolones and pyrrolones aimed at the detection of pharmacologically active benzodiazepine receptor agonists without the side effects of sedation, tolerance, and abuse liability. In vitro receptor binding and in vivo pharmacological screens were exploited to characterize a wide variety of derivatives obtained in this way.

Chemistry

The synthesis of the imidazolones **1**−**19** listed in Table 1 is depicted in Scheme 1. These compounds are easily available by heating hydantoins with the appropriate amines and the corresponding amine hydrochloride. When the reagents are heated without the acid or when the reaction is performed in a solvent, the main products are amides.

The pyrrolones **20**−**27** were prepared by a three-step synthesis (Scheme 2). Methyl-4-chloro-3-methoxybutenoate was treated with one equivalent of an aniline derivative and subsequently cyclized in acetic acid to a methoxy pyrrolone. Substitution with one equivalent of an appropriate amine, with 10 mol % of the amine hydrochloride as catalyst, yielded the pyrrolone derivatives **20**−**27**. This route of synthesis is more convenient than a formerly reported procedure.[27] It allows the introduction of different substituents starting with an easily available material.

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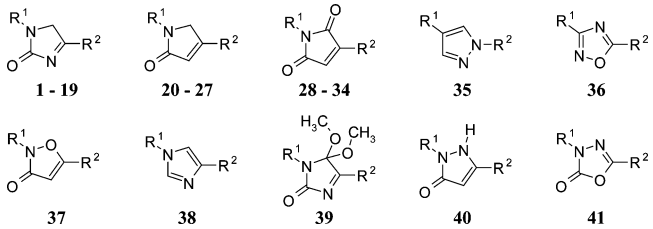
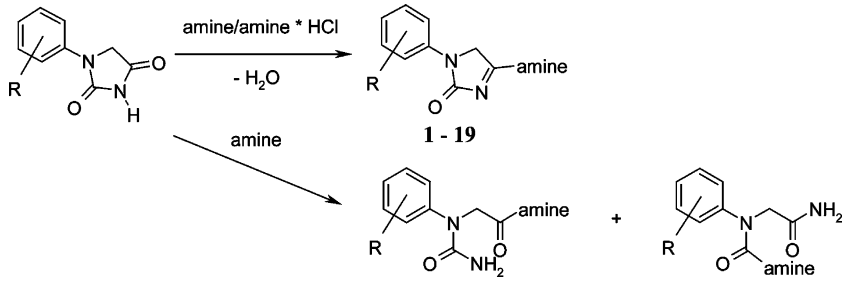
Table 1. Physical Properties of Imidazolones, Pyrrolones, and Related Substances



cpd	R^1	R^2	yield, %	mp, °C	logP[a]	formula
1	Ph	$N(CH_2CH_2)_2O$	69	246	0.6	$C_{13}H_{15}N_3O_2$
2	Ph-4-Cl	$N(CH_2CH_2)_2O$	67	264	1.5	$C_{13}H_{14}ClN_3O_2$
3	Ph-4-Cl	1-piperidinyl	65	242	2.3	$C_{14}H_{16}ClN_3O$
4	Ph-4-Cl	1-pyrrolidinyl	55	305	2.0	$C_{13}H_{14}ClN_3O$
5	benzyl	$N(CH_2CH_2)_2O$	67	158	0.5	$C_{14}H_{17}N_3O_2$
6	Ph-4-Cl	$N(CH_2CH_2)_2NCH_3$	79	245	2.2	$C_{14}H_{17}ClN_4O$
7	Ph-4-Cl	$N(CH_3)_2$	32	292	1.6	$C_{11}H_{12}ClN_3O$
8	benzyl-2-Cl	$N(CH_2CH_2)_2O$	57	172−173	1.0	$C_{14}H_{16}ClN_3O_2$
9	Ph-3,4-Cl_2	$N(CH_2CH_2)_2O$	72	271	1.9	$C_{13}H_{13}Cl_2N_3O_2$
10	$CH_2(CH_3)$-Ph	$N(CH_2CH_2)_2O$	71	180−182	0.8	$C_{15}H_{19}N_3O_2$
11	benzyl-2,6-Cl_2	$N(CH_2CH_2)_2O$	82	196−197	1.3	$C_{14}H_{15}Cl_2N_3O_2$
12	Ph-4-Br	$N(CH_2CH_2)_2O$	85	270	1.4	$C_{13}H_{14}BrN_3O_2$
13	Ph-4-I	$N(CH_2CH_2)_2O$	81	275	1.7	$C_{13}H_{14}IN_3O_2$
14	Ph-4-F	$N(CH_2CH_2)_2O$	78	268	n.d.[f]	$C_{13}H_{14}FN_3O_2$
15	Ph-3-Cl	$N(CH_2CH_2)_2O$	75	242−243	1.3	$C_{13}H_{14}ClN_3O_2$
16	Ph-4-Cl	1-azepanyl	87	217	n.d.	$C_{15}H_{18}ClN_3O$
17	Ph-4-Cl	1-azocanyl	91	202	2.7	$C_{16}H_{20}ClN_3O$
18	Ph-4-OCH_3	1-piperidinyl	64	195	1.5	$C_{15}H_{19}N_3O_2$
19	Ph-4-Cl	$N(CH_3)$-c-C_6H_{11}	57	236−238	2.7	$C_{16}H_{20}ClN_3O$
20	Ph-4-Cl	$N(CH_2CH_2)_2O$	71	232−234 dec	1.9	$C_{14}H_{15}ClN_2O_2$
21	Ph-4-Cl	1-pyrrolidinyl	67	226	2.6	$C_{14}H_{15}ClN_2O$
22	Ph-4-Cl	1-acepanyl	41	185	3.4	$C_{16}H_{19}ClN_2O$
23	Ph-4-Cl	1-piperidinyl	69	211	3.0	$C_{15}H_{17}ClN_2O$
24	Ph-4-F	$N(CH_2CH_2)_2O$	70	228	n.d.	$C_{14}H_{15}FN_2O_2$
25	Ph-3-Me	$N(CH_2CH_2)_2O$	68	121−122	1.5	$C_{15}H_{18}N_2O_2$
26	Ph-4-Me	$N(CH_2CH_2)_2O$	65	215−216	1.4	$C_{15}H_{18}N_2O_2$
27	Ph-3-Cl-4-F	$N(CH_2CH_2)_2O$	62	165−166	2.2	$C_{14}H_{14}ClFN_2O_2$
28[b]	Ph-4-Cl	Ph-4-Cl	48	214−215	3.0	$C_{16}H_9Cl_2NO_2$
29[c]	Ph-4-Cl	$N(CH_2CH_2)_2O$	62	139	2.3	$C_{14}H_{13}ClN_2O_3$
30	Ph-4-Cl	1-piperidinyl	60	95−96	3.4	$C_{15}H_{15}ClN_2O_2$
31	Ph-4-Cl	1-pyrrolidinyl	55	169	3.0	$C_{14}H_{13}ClN_2O_2$
32	Ph-4-F	$N(CH_2CH_2)_2O$	53	115	1.5	$C_{14}H_{13}FN_2O_3$
33	Ph-4-F	1-piperidinyl	50	112	2.6	$C_{15}H_{15}FN_2O_2$
34	Ph-4-F	1-pyrrolidinyl	45	102−103	2.3	$C_{14}H_{13}FN_2O_2$
35	Ph-4-Cl	2-pyridinyl	89	143	4.3	$C_{14}H_{10}ClN_3$
36	Ph-4-Cl	$N(CH_2CH_2)_2O$	34	125−126	3.1	$C_{12}H_{12}ClN_3O_2$
37	Ph-4-Cl	Ph	27	112−113	4.1	$C_{15}H_{10}ClNO_2$
38[d]	Ph-4-Cl	Ph	52	138	3.7	$C_{15}H_{11}ClN_2$
39	Ph-4-Cl	$N(CH_2CH_2)_2O$	27	230−233	1.7	$C_{15}H_{18}ClN_3O_4$
40[e]	Ph-4-Cl	Ph	55	162	2.6	$C_{15}H_{11}ClN_2O$
41	Ph-4-Cl	Ph	72	156−157	2.6	$C_{14}H_9ClN_2O_2$

[a] Experimental partition coefficient 1-octanol/water. [b] mp[29] 215.5 °C. [c] mp[30] 138−139 °C. [d] mp[34] 182 °C. [e] mp[35] 161−162 °C. [f] n.d.: not determined.

Scheme 1. Compounds **1**−**19**



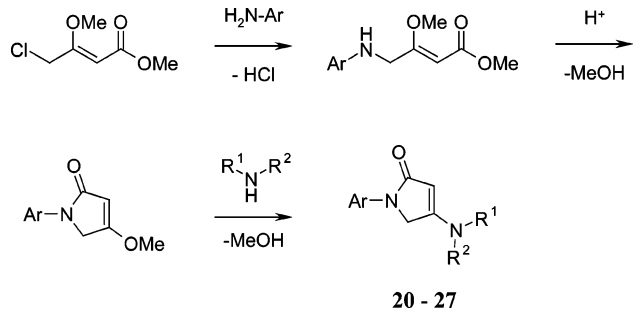
The synthesis of compound **39** was carried out by chlorination of compound **2** using thionyl chloride and treatment of the resulting product with methanol as described in Scheme 3.

The syntheses of the compounds **28**, **29**−**34**, **35**, **36**, **37**, **38**, **40**, **41**, and the reference compound **42** (CGS 9896,[28] Chart 1) were performed using literature methods.[28−36]

Biology and Pharmacology

Affinities of the Derivatives. The method employed for the determination of the affinities of the various compounds to the benzodiazepine receptor is described in detail in the Experimental Section. The affinities were determined as K_i, or percentage inhibition values, at a given concentration for 37

Scheme 2. Compounds **20**−**27**



20 - 27

Scheme 3. Compound **39**

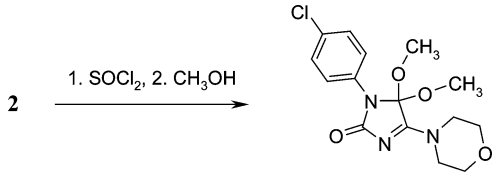


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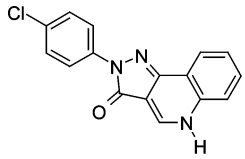
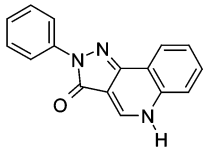
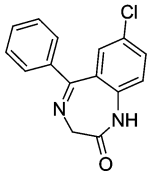
Chart 1. Reference Compounds



42



43



diazepam

out of 41 imidazolone and pyrrolone derivatives and for **42** (Table 2). For 13 of the 37 compounds and for **42**, the experimental determination of the K_i values was possible. The K_i values of another 12 compounds were calculated on the basis of the single percentage inhibition data *P*, as described in the Experimental Section (Table 2).

Pharmacological Activities. The pharmacological activities were investigated for all compounds and **42**. The rotarod test was used to record neurotoxicological effects, and the pentylenetetrazole (PTZ) test was selected for identifying pharmacologically active compounds in vivo. PTZ-induced seizures are commonly used as a simple seizure model, but PTZ is also well-known to induce anxiety both in animals and humans. A suppression of PTZ-induced seizures can thus be used as a simple screening model to predict anxiolytic activity. The PTZ model clearly has advantages over anxiety models, which are experimentally time-consuming and which often lack robustness.[37] For selected compounds, the data obtained in mice after i.p. administration were supported by data obtained in rats after oral administration using both the PTZ seizure model and the Vogel conflict test as the specific anxiety model. For both PTZ models, we selected a PTZ dose that induced seizures in 97% of control animals. Thus, only compounds with potent activity were detected. The tests were carried out at elbion and/or at the NIH (Bethesda, MD). Selected screening results and all ED_{50} or TD_{50} values determined are compiled in Tables2 and 3. (For details of the models used and for methods, see the Experimental Section.) ED_{50} values of 19 compounds which passed the initial test were determined in mice. For further evaluation in rats, compounds with an ED_{50} below 40 mg/kg in mice and a clear separation of pharmacological effects from neurotoxicity were selected. Eight compounds as well as the two reference compounds diazepam (Chart 1) and **42** were also tested in rats

Table 2. Affinities for Benzodiazepine Binding Site and in Vivo Activity and Tolerability in Mice

cpd	K_i (rat) [μM]	PTZ ED_{50} [mg/kg i.p.]	rotarod TD_{50} [mg/kg i.p.]
1	6.28	121	>300
2	4.35	17.2[a]	75.6; 175.9[a]
3	1.04	40.5[a]	92; 147[a]
4	4.29	>300	>300
5	n.e.[b]	>300	>300
6	n.e.	>300	>100
7	n.e.	>300	>300
8	n.a.[c]	>300	>300
9	n.e.	>300	>300
10	n.a.	>300	>100
11	n.a.	>300	>300
12	3.06[d]	21.8	345
13	3.32[d]	43[a]	>300[a]
14	n.e.	35[a]	>500[a]
15	n.e.	>300	>300
16	11.6[d]	>300	>300
17	n.a.	>300	>300
18	0.938	65.6	>100
19	n.a.	>300	>300
20	0.141	10.9	97.0; 60.9[a]
21	0.067	>300	>300
22	0.44	234	>100
23	0.09	58.2	ca. 30
24	0.494	337	>300
25	4.45[d]	62.3	<100
26	0.344	89.3	ca. 100
27	2.05[d]	22.3	>30; <100
28	n.e.	>300	>300
29	8.88[d]	120	>300
30	4.34[d]	360	>300
31	3.26[d]	>300	>300
32	n.e.	128	>100
33	5.41[d]	289	>100
34	n.e.	>200	>300
35	4.48[d]	>300	>300
36	26.1[d]	>300	>300
37	1.12	253	<300
38	3.29[d]	>300	>300
39	n.e.	>100	>30
40	n.e.	>300	>300
41	n.e.	>300	>300
42[e]	0.0024	1.36	302
diazepam	0.0068	0.4	2

[a] Results from NIH. [b] n.e.: not effective. Percentage inhibition $P < 20\%$ at highest available concentration (2 μM). [c] n.a.: not available. [d] K_{iEW} based on single inhibition data (see Experimental Section, Calculations). [e] The known compound **42** (mp 324−327 °C) was resynthesized, and the physical and spectral data were found to be consistent with literature values.[28]

Table 3. Activity and Tolerability of Selected Compounds in Rats after Oral Administration

cpd	PTZ ED_{50} [mg/kg]	Vogel conflict test MED[a] [mg/kg]	rotarod TD_{50} [mg/kg]	protective index (PI) TD_{50}/ED_{50} PTZ
2	27.4, 12.9[b], 16.2[b]	3	998	36.4
3	19.3, 12.8[b]	3	265	13.7
4	14.2[b]	3	>500[b]	>35.2[b]
12	27.7	100	473	17.1
13	50[b]	n.t.[c]	≫50[b]	≫1.0[b]
14	34.1[b]	n.t.	≫60[b]	≫1.8[b]
20	12.9, 10.5[b]	10	>500	>38.8
21	>200	n.e.[d]	n.t.	−
42	2.7	0.3	>500	>185.0
diazepam	6.3	1	13	2.1

[a] MED minimal effective dose. [b] Results from NIH. [c] n.t.: not tested. [d] n.e.: not effective at 3 and 10 mg/kg.

to determine the ED_{50} after oral administration in the PTZ test and to obtain initial insight into the anxiolytic activity. In addition, compound **21** without activity in mice was selected due to its high affinity to the benzodiazepine binding site, and compound **4** was also included in testing in rats due to structural similarity to **3** (see Tables 2 and 3). Among those candidates, all except **21** were found also to be active in the PTZ model in rats and, again, all compounds except **21** also showed at least some activity in the Vogel conflict model predictive of anxiolytic activity. This indicates that our screening approach using the PTZ seizure model was successful. Interestingly, the compounds identified were better tolerated than diazepam in both mice and rats as assessed employing the rotarod test in rats. Among these compounds, **2**, **3**, **4**, and **20** were most interesting due to the best separation of pharmacological activity and unwanted side effects in rats after oral administration. The protective index (PI) calculated as the ratio of effective dose in the PTZ seizure model versus the dose inducing side effects as observed in the rotarod test were more than 7-fold better than that for diazepam (see Table 3). However, the effect size for **4** observed in the Vogel conflict test was low, indicating a weak anxiolytic potential which could not be increased at higher doses. For **20**, the duration of effect was very short even at high doses as tested in the rotarod test. This may be related to low acid stability. Therefore, **2** and **3** were selected for further development because of their potent anxiolytic activity, their anticonvulsive potential, and their excellent tolerability. Compound **2** potently suppressed PTZ seizures in dogs and reduced the seizure frequency in epileptic dogs.[38] In models of anxiety, a strong effect could be shown in the elevated maze, the Vogel conflict test, and in the light and dark box.[39] Further studies in monkeys indicate that **2** has a low abuse liability.[40] Compound **3** was found to be even more potent in models of anxiety, and no development of tolerance could be seen.[41] The potent anxiolytic activity could be reversed by using the selective antagonist flumazenil, indicating that the effect was indeed mediated by the benzodiazepine binding site.[41] If the pharmacological results were compared with the effect of diazepam, it becomes obvious that the activity profile, both in models of anxiety and in models of epilepsy, is similar, while these compounds are much better tolerated. Mechanistic studies revealed that **2** acts as a partial low-affinity agonist at the benzodiazepine binding site.[42] This partial agonism as well as the low affinity may be related to the compound's excellent tolerability. Very recently, we found **3** to be a subtype-selective benzodiazepine agonist preferring $GABA_A$ receptors with the $\alpha 3$ subunit over receptors containing the $\alpha 1$ subunit.[43] Further characterization of this subtype selectivity is ongoing.

Structure−Activity Relationships

BzR Affinity. The comparison of substituent effects on the binding affinity of the imidazolones, pyrrolones, and pyrrolediones in Table 2 shows some similarities. Thus, all compounds with an at least low affinity have a phenyl group at the R^1 position. Among these, the 4-chlorophenyl derivatives exhibit a higher affinity than the 4-fluorophenyl structures. Substituents at the 3-position of the phenyl ring reduce the affinity excessively in comparison with substituents at the 4-position. The substituents R^2 seem to contact a receptor region with limited steric accessibility. Morpholin-4-yl, piperidin-1-yl, and pyrrolidin-1-yl derivatives are of comparable affinity, whereas substitution by azepane or other larger rings decreases the affinity. Regarding the central heterocycles, all derivatives of the series bear at least one hydrogen acceptor group, but they have no other common structural elements. Nevertheless, the obvious structural similarities between the various derivatives point to a similar mode of binding.

Table 4. BzR Affinity: Evaluation of CoMFA Fields with SAMPLS[a]

field type[b]	all data	training set only
s	0.572 (5)	0.689 (5)
e	0.715 (5)	0.744 (5)
l	0.526 (4)	0.532 (4)
se	0.687 (5)	0.745 (5)
sl	0.559 (4)	0.614 (6)
el	0.696 (5)	0.716 (6)
sel	0.672 (5)	0.727 (6)

[a] Cross-validated coefficients of correlation q^2 and number of components in parentheses. [b] CoMFA field types: s, steric; e, electrostatic; l, lipophilic field.

Three-dimensional quantitative structure−activity relationship (3D-QSAR) models were derived on the basis of the measured and estimated K_i values for compounds **1**−**4**, **12**, **13**, **16**, **18**, **20**−**27**, **29**, **30**, **31**, **33**, and **35**−**38** in Table 2. From these data, the compounds **3**, **13**, **21**, and **29** were used as the test set. The conformational and tautomeric structure of the various compounds was determined employing quantum chemical methods. In those cases, where a comparison with experimental data is possible, the agreement is excellent. Generally, planar structures were found for all compounds. The details of the structure calculations are given in the Supporting Information. Comparative molecular field analysis (CoMFA) studies were carried out examining all combinations of steric, electrostatic, and hydrophobic fields. The details of the alignment and CoMFA calculations are given in the Calculation part of the Experimental Section. The CoMFA results are listed in Table 4. The most reliable model was derived on the basis of the electrostatic field ($q^2 = 0.72$). Less predictive models were computed using steric ($q^2 = 0.57$) and lipophilic ($q^2 = 0.53$) fields. The combination of the various fields did not improve q^2 in comparison with the model based solely on the electrostatic field. To visualize both the steric and electrostatic properties, a PLS model without cross-validation was derived on the basis of the training set (no column filtering, 5 components, $r^2 = 0.970$, $F = 91.106$, $p = 0.000$, relative contributions: 0.363 steric, 0.637 electrostatic). The model is illustrated in Figure 1. The affinities of the test compounds could be predicted by this model (Figure 2).

PTZ Activity. Next, some relationships between structure and pharmacological activity will be discussed. It has been stated above that similar substitution across the three different structural classes yielded similar effects on affinity. This trend is also found when one compares the substituent effects on the PTZ activity for the imidazolone, pyrrolone, and pyrroledione derivatives. For instance, the replacement of a morpholin-1-yl group at R^2 position by a piperidin-1-yl residue reduces the activity by a factor of 2−5. Smaller and larger aliphatic rings lead to inactive compounds or strongly reduce the activity as in the case of **22**. Six-membered aromatic rings generally yield inactive compounds with exception of compound **37**, which is weakly active. Substituents at the 3-position of R^1 reduce the activity or even result in inactive compounds. Accordingly, **36** should be active. The measured inactivity of this compound points to the need for a carbonyl group at the 2-position of the five-membered central ring. There are some other common patterns of active compounds with respect to this ring. Thus, the atoms equivalent to N^1 of **1** and the atoms at the 4-position are always nitrogen and carbon atoms, respectively. Besides, atoms 3 and 4 are always connected by a double bond. These findings support the assumption of a similar mode of action for all derivatives.

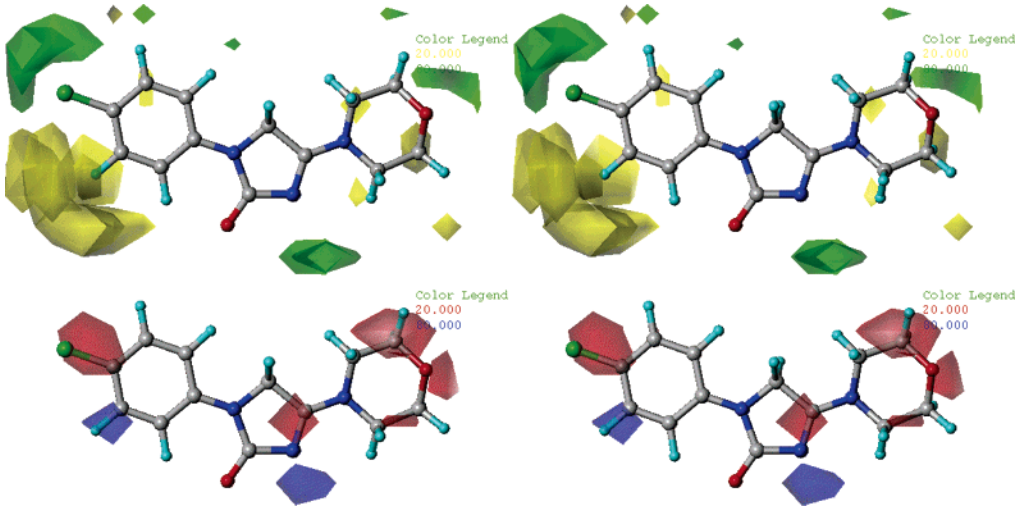


Figure 1. Stereo representation of the CoMFA model of BzR affinity. Top: steric field, bottom: electrostatic field. The color coding is as follows: green/yellow regions, more steric bulk increases/decreases the affinity; red/blue regions, more negative charge increases/decreases affinity.

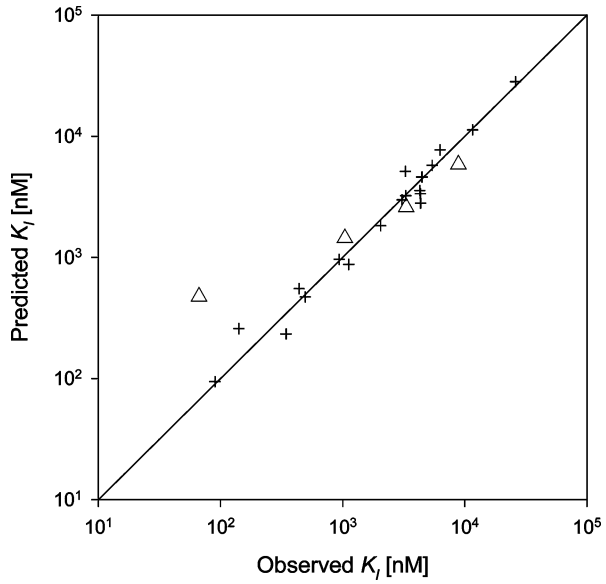


Figure 2. Observed K_i values of BzR affinity vs predicted data using the CoMFA model ("+" training set, "Δ" test set).

To establish 3D-QSAR models based on the activity data, the 19 compounds with ED_{50} data (**1**−**3**, **12**−**14**, **18**, **20**, **22**−**27**, **29**, **30**, **32**, **33**, and **37**) were used (Table 2). Because of the relatively small number of compounds, it was not possible to establish a test set. As in the case of the affinity data, all combinations of standard steric and electrostatic CoMFA fields and the hydrophobic CLIP field were studied. Using the entire training set, no predictive CoMFA model could be derived. A systematic search identified compounds **22** and **24** as outliers. Excluding **22** and **24** from the data set, models with q^2 up to 0.7 were obtained. For **24**, an ED_{50} of 337 mg/kg was found, which corresponds to a decrease in activity by a factor of 31 compared with the 4-chlorophenyl derivative **20**. In contrast to this, there are only small differences of the BzR affinities between these two compounds. Therefore, differences between **24** and the other compounds could be assumed with respect to receptor activation or pharmacokinetics. The results of the various PLS calculations are listed in Table 5. As in the case of the affinity models, the best model was derived on the basis of the electrostatic field. Consideration of the other fields decreased q^2. Therefore, a PLS model without cross-validation, taking account of all data except those for **22** and **24**, was derived (no column filtering, 4 components, $r^2 = 0.930$, $F = 40.021$, $p < 0.001$, only electrostatic field). As expected from the initial SAMPLS calculations, a good correlation between measured and predicted EC_{50} values of all compounds but **22** and **24** was obtained (Figure 3), which confirms a uniform mechanism of the action of all substances.

Table 5. PTZ Activity: Evaluation of CoMFA Fields with SAMPLS[a]

field type[b]	all data	all without **22**	all without **24**	all without **22** + **24**
s	0.215 (1)	0.288 (1)	0.347 (1)	0.506 (2)
e	0.258 (1)	0.287 (1)	0.481 (2)	0.707 (3)
l	0.231 (1)	0.293 (1)	0.337 (1)	0.446 (2)
se	0.254 (1)	0.299 (1)	0.458 (4)	0.677 (4)
sl	0.261 (1)	0.324 (1)	0.393 (1)	0.509 (1)
el	0.288 (1)	0.329 (1)	0.497 (5)	0.677 (4)
sel	0.281 (1)	0.328 (1)	0.458 (5)	0.654 (5)

[a] Cross-validated coefficients of correlation q^2 and number of components in parentheses. [b] CoMFA field types: s, steric; e, electrostatic; l, lipophilic field.

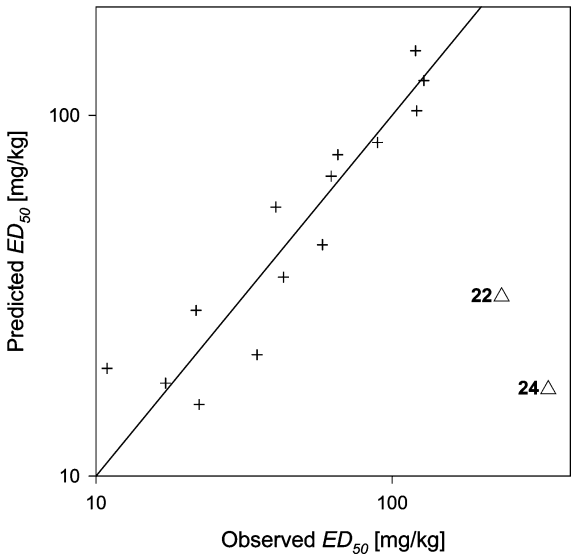


Figure 3. Observed ED_{50} values of PTZ activity vs predicted data using the CoMFA model ("+" training set, "Δ" excluded data).

Affinity vs Activity. A comparison between receptor affinity and PTZ activity could provide hints of parameters beyond pharmacodynamics that may influence activity. On the basis of

a good agreement of K_i values from experiments with rat and mice receptor preparations from preliminary studies, we tried to correlate rat K_i and mice PTZ values. Assuming BzR interaction of our compounds as the basic mechanism for PTZ activity, active compounds must be affine and common features of structure-affinity and structure−activity relationships should be found. Actually, nearly all affine compounds are also active. The two compounds **14** and **32**, which are active in the PTZ test but do not have a significant receptor affinity, have a relatively low solubility in aqueous media. As expected, similarities between the SARs can be found. Thus, derivatives with 4-chlorophenyl substitution are both affine and active. However, affine compounds need not be active due to poor pharmacokinetics/ADME properties or due to antagonistic or inverse agonistic receptor activation. Accordingly, seven compounds **4**, **16**, **21**, **31**, **35**, **36**, **38** with affinity to the BzR do not elicit effects in the PTZ test. With respect to the central rings in the derivatives, it seems to be sufficient for affinity to have one hydrogen acceptor group while active compounds show a closer correspondence in structure and have more atom and bonding patterns in common. The replacement of the morpholin-1-yl moiety by pyrrolidin-1-yl or aromatic groups does not change the affinity very much, but it leads to distinctly less active or inactive compounds. The compounds **4**, **21**, and **31**, bearing a pyrrolidin-1-yl substituent, are all affine, but are not active.

Hints on an excellent bioavailability of some of our compounds can be found by analyzing affinity/activity ratios. Thus, compound **2** has an affinity which is weaker by 3 orders of magnitude than that of **42**. In contrast to this, the PTZ activities differs by just 1 order of magnitude pointing to differences regarding pharmacokinetics. We used own data and data from literature[44,45] to compare these compounds. Owing to the heterogeneous character of these data, only qualitative or semiquantitative conclusions can be drawn. There are considerable differences between the two drugs regarding their plasma concentrations and biodegradation. Using comparable oral doses of 30 mg/kg for **2** and 5 mg/kg for **42**,[44] an approximately 1000-fold higher plasma concentration of **2** was found (39 μM for **2** and 0.027 μM for **42**). Furthermore, high concentrations of **2** in the brain were detected represented by a brain/plasma ratio (BP) of 1:1.5. In contrast to this finding, the BP of **43** (CGS 8216,[28] Chart 1, dechloro-derivative of **42**) is 1:20.[45] The BP of **42** is not known, but it may be assumed to be similar. On the basis of these values, it can be estimated that **2** reaches peak brain concentrations of about six times the K_i value at an oral application of 30 mg/kg, whereas with a comparable oral dose of **42** only very small brain concentrations could be reached. Nevertheless, these concentrations also correspond to the K_i value of this compound. Thus, similar pharmacological effects of both compounds can be expected despite their very different affinities.

Pharmacophore. The structural basis of our data can well be referred to the comprehensive pharmacophore/receptor model of Cook et al.,[46] which is widely accepted. It is based on 136 ligands from 10 different structural families and includes previous models for BzR agonists, antagonists, inverse agonists, and ligands on the diazepam-insensitive (DI) site.[47−54] The assumption of a unique binding site for all types of ligands is based on the biochemical and pharmacological competition between all ligands, the continuum of pharmacological effects ranging from agonists over antagonists to inverse agonists, and on the observation that small structural modifications cause shifts between these types. Figure 4 illustrates the most important features of the Cook model together with the structures of diazepam and **42**.[46] Being a representative example of our compounds, **2** was added to Figure 4 using the alignment with **42** mentioned above.

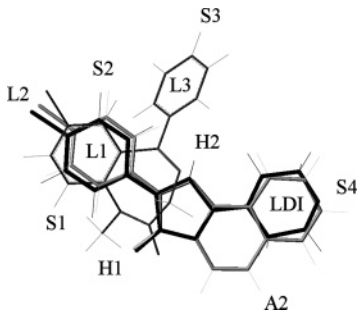


Figure 4. Alignment of diazepam (thin dark gray sticks), **42** (thick light gray sticks), and **2** (black sticks) according to the pharmacophore/receptor model of Cook et al.[46] and alignment calculations. H, A, L, and S are hydrogen-bond donor sites, hydrogen-bond acceptor sites, lipophilic receptor regions, and sterically limited regions, respectively.

The features depicted in Figure 4 are suggested attributes of the BzR receptor which the ligands have to correspond to. In detail, there are two hydrogen-bond donor sites H1 and H2, a hydrogen-bond acceptor site A2, four lipophilic regions L1, L2, L3, and LDI, and regions S of steric repulsion. L3 is located out of the plane of the other regions. Inverse agonists interact with L1, H1, and A2. Agonists additionally interact with H2 and L2 or L3. Occupation of the out-of-plane region L3 is a prerequisite of full agonism.[55] The DI binding site is smaller than the diazepam-sensitive (DS) site. Ligands with substituents capable of filling L3 do not fit into DI binding sites. The initial model has been extended to describe the differences between the pharmacophores of recombinant BzR $\alpha x\beta 3\gamma 2$ subtypes[56−59] with "*x*" ranging from 1 to 6.

The planar structure of our compounds is in agreement with the generally flat geometry of BzR ligands of different structure classes. It can be seen from the alignment results that the phenyl ring and its 4-chloro substituent occupy the hydrophobic pockets L1 and L2, respectively, of the BzR binding site. Our compounds do not have substituents that fit into the out-of-plane lipophilic pocket L3. Therefore, full agonism should not be possible according to Cook's pharmacophore model. This is consistent with the results from electrophysiological studies on **2**,[42] which show a partial agonistic behavior. Furthermore, in agreement with the pharmacophore model, our compounds with affinity to the BzR binding site possess a hydrogen-bonding acceptor structure that can interact with the H1 donor site of the model. In most cases, this acceptor is a carbonyl group. However, the imidazolones and pyrrolones do not have an acceptor structure for the H2 donor size. This could be one reason for their reduced affinity compared with **42**, but it cannot be the only one, because the oxadiazolone **41** has a nitrogen atom in the corresponding position although it is not affine. This may hint at an influence of the quinoline nitrogen of **42** on the affinity as a hydrogen bond donor. Furthermore, the existence of an H2 counterpart is considered to be a prerequisite of compounds with affinity to diazepam-insensitive (DI) receptor subtypes. In agreement with this, no affinity of **2** to DI subtypes was found up to a concentration of 20 μM, whereas **42** binds to these subtypes with $K_i = 0.77$ μM. A result of the SAR studies is that substituents in the 3-position of R1 reduce the affinity. This suggests steric restrictions within this region and corresponds to the S1 and S2 features of the Cook model, which are regions of negative steric repulsion. The reduced affinity of

the 4-fluorophenyl derivatives may be caused by unfavorable interactions of the fluoro group with the hydrophobic region L2. There are differences between fluoro groups and the other halogen substituents with respect to the hydrophobic properties indicated by a hydrophobic constant for a fluoro substituent of $\pi = -0.17$, whereas the corresponding constants of the other halogen substituents are > 0.[60] Furthermore, a fluoro substituent is a hydrogen-bond acceptor[61] and interacts with water molecules. It has already been mentioned that R2 substituents with more than six atoms reduce the affinity. This indicates the possibility of steric restrictions in this region, which is denoted by S4 in Figure 4. There is no corresponding feature in the Cook model, but similar results were also found in a study on imidazo[1,2-*b*]pyridazines[62] and in a study on flavones.[63] As mentioned above, the occupation of the lipophilic region L2 or L3 is a prerequisite for agonists according to Cook's pharmacophore model. L2 is occupied by the chloro atom of the partial agonist **2**. However, compound **1** also shows weak anticonvulsive activity in the PTZ test and, therefore, must be an at least partial agonist at the BzR binding site.

In summary, our derivatives fit well into the pharmacophore model of Cook but show some features not yet considered in this model.

Conclusions

Based on novel syntheses of imidazolones and pyrrolones, various compounds have been obtained for the first time. Among these, we found anxiolytic compounds lacking the side effects of full benzodiazepine receptor agonists. Qualitative structure−activity relationships and CoMFA models were derived on the basis of compounds from different classes. The results can be interpreted within the pharmacophore model of Cook et al. which could be refined. Compounds **2** and **3** were selected for further development because of their excellent pharmacological profiles. The partial agonistic activity, which is consistent with the pharmacophore model, is a possible reason for the excellent tolerability. Recently, we obtained hints on subtype selectivity of compound **3**. Future work will have to focus on the identification of the structural elements responsible for subtype selectivity.

Experimental Section

Chemistry. All melting points were determined on a Boetius melting-point apparatus PHMK 05 and are uncorrected. The IR spectra were registered on a Perkin-Elmer 1725x spectrometer. All absorption values are expressed in wavenumbers (cm^{-1}). Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker ARX 300 NMR spectrometer. Chemical shifts (δ) are in parts per million (ppm) relative to Si(CH$_3$)$_4$, and coupling constants (J) are in hertz. The partition coefficients were determined according to Yamagami and Takao[64] and are given as log P values for 1-octanol/water.

Key Intermediates. 1-Aryl-hydantoins and 1-Aralkyl-hydantoins. The synthesis of the used hydantoins is described by Biltz and Slotta.[65]

Methyl 4-(Arylamino)-3-methoxybut-2-enoates. A mixture of 60 mmol of a substituted aniline derivative, 60 mmol of methyl 4-chloro-3-methoxybutenoate (easily prepared from methyl 4-chloroacetoactetate[66]), 22.8 g of sodium phosphate dodecahydrate, and 0.9 g of sodium iodide in 300 mL acetonitrile was heated under reflux for 24 h. The mixture was allowed to cool to room temperature, and the remaining salts were removed by filtration. The filtrate was evaporated to yield a dark brown oil, which was used without further purification.

1-Aryl-2,4-dihydro-4-methoxy-pyrrol-2-ones. A solution of 40 g of methyl-4-aryl-3-methoxybut-2-enoate in 10 mL of acetic acid was heated under reflux. After 2 h the solution was diluted with 20 mL of ethanol and allowed to cool to room temperature. The precipitate was isolated by filtration and washed with 150 mL of cold ethanol. The 1-aryl-2,4-dihydro-4-methoxy-pyrrol-2-ones obtained by this method were used without further purification.

Synthesis of 1-Ar(alk)yl-4-amino-1,5-dihydro-imidazol-2-ones 1−19. General Procedure. A mixture of 30 mmol of 1-ar(alk)-yl-hydantoin and 60 mmol of the appropriate amine hydrochloride in 50 mL of the corresponding amine was stirred and heated at a bath temperature of 100−140 °C for 2−12 h. After the mixture had been cooled to room temperature, a solid precipitated, which was collected by filtration, washed with water, and purified by recrystallization from alcohol. Compounds **3**, **4**, and **18** were synthesized in a high-pressure reaction vessel.

1-Phenyl-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (1). IR (KBr) 2862, 1703, 1592, 1504;^{13}C NMR (DMSO-d_6) 41.4 (**C**H$_2$−N), 51.3 (**C**H$_2$−N), 66.5 (**C**H$_2$−O), 119.7, 125.1, 125.9, 129.4, 136.2 (**C**$_{Ar}$), 165.8 (**C**═O), 174.1 (N═**C**−N). Anal. C, H, N.

1-(4-Chlorophenyl)-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (2). IR (KBr) 2863, 1707, 1592, 1498; ^{1}H NMR (DMSO-d_6) 4.7 (s, C**H**$_2$−N), 7.3, 7.7 (Ar−**H**); ^{13}C NMR (DMSO-d_6) 40.3 (**C**H$_2$−N), 49.71 (**C**H$_2$−N), 65.5 (**C**H$_2$−O), 118.4, 125.5, 128.4, 138.2 (**C**$_{Ar}$), 165.4 (**C**═O), 173.3 (N═**C**−N). Anal. C, H, N.

1-(4-Chlorophenyl)-4-piperidin-1-yl-1,5-dihydro-imidazol-2-one (3). IR (KBr) 2943, 2858, 1702, 1587;^{1}H NMR (DMSO-d_6) 2.2 (s, N−C**H**$_3$), 4.7 (s, C**H**$_2$−N), 7.4, 7.7 (Ar−**H**); ^{13}C NMR (DMSO-d_6) 23.7, 21.8 (**C**H$_2$), 45.9 (N−**C**H$_2$), 48.4 (**C**H$_2$−N), 116.9, 123.8, 126.9, 136.9 (**C**$_{Ar}$), 164.2 (**C**═O), 171.1 (N═**C**−N). Anal. C, H, N.

1-(4-Chlorophenyl)-4-pyrrolidin-1-yl-1,5-dihydro-imidazol-2-one (4). IR (KBr) 2979, 2881, 1703, 1607; ^{1}H NMR (DMSO-d_6) 1.92 (mC**H**$_2$), 3.49 (m, C**H**$_2$), 4.61 (s, NC**H**$_2$), 7.41 (m, Ar−**H**), 7.76 (m, Ar−**H**); ^{13}C NMR (DMSO-d_6) 120.7, 127.6, 130.2, 140.5 (**C**$_{Ar}$), Anal. C, H, Cl.

1-Benzyl-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (5). IR (KBr) 2971, 2844, 1695, 1592;^{1}H NMR (DMSO-d_6) 3.6 (m, C**H**$_2$), 4.2 (s, C**H**$_2$−N), 4.5 (s, C**H**$_2$−N), 7.2, 7.4 (Ar−**H**); ^{13}C NMR (DMSO-d_6) 44.8 (**C**H$_2$−N), 46.1 (**C**H$_2$−N), 49.7 (**C**H$_2$−N), 65.7 (**C**H$_2$−O), 127.5, 127.9, 129.0, 138.4 (**C**$_{Ar}$), 168.7 (**C**═O), 175.1 (N═**C**−N). Anal. C, H, N.

1-(4-Chlorophenyl)-4-(4-methyl piperazin-1-yl)-1,5-dihydro-imidazol-2-one (6). IR (KBr) 2944, 2789, 1707, 1583; ^{1}H NMR (DMSO-d_6) 2.2 (s, N−C**H**$_3$), 4.7 (s, C**H**$_2$−N), 7.4, 7.7 (Ar−**H**); ^{13}C NMR (DMSO-d_6) 45.9 (N−**C**H$_3$), 54.1 (**C**H$_2$−N), 118.9, 125.9, 128.9, 138.7 (**C**$_{Ar}$), 165.4 (**C**═O), 173.1 (N═**C**−N). Anal. C, H, N.

Synthesis of 1-(4-Chlorophenyl)-4-(dimethylamino)-1,5-dihydro-imidazol-2-ones (7). Instead of dimethylamine hydrochloride, dimethylammonium dimethyl carbamate (DIMCARB) was used. The reaction time was 48 h. IR (KBr) 2992, 1707, 1620, 1498;^{13}C NMR (DMSO-d_6) 39.8 (**C**H$_2$−N), 58.6 (N−**C**H), 118.8, 119.8, 129.0, 136.0 (**C**$_{Ar}$), 166.6 (**C**═O), 174.7 (N═**C**−N). Anal. C, H, Cl, N.

1-(2-Chlorobenzyl)-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (8). IR (KBr) 2990, 2865, 1692, 1592;^{1}H NMR (DMSO-d_6) 3.7 (m, C**H**$_2$), 4.1 (s, C**H**$_2$−N), 4.5 (s, C**H**$_2$−N), 7.2, 7.4 (Ar−**H**); ^{13}C NMR (DMSO-d_6) 44.8 (**C**H$_2$−N), 46.1 (**C**H$_2$−N), 49.7 (**C**H$_2$−N), 65.7 (**C**H$_2$−O), 127.5, 128.9, 129.1, 129.4, 132.1, 135.2 (**C**$_{Ar}$), 168.3 (**C**═O), 174.7 (N═**C**−N). Anal. C, H, N.

1-(3,4-Dichlorophenyl)-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (9). IR (KBr) 3106, 2919, 1704, 1592, 1484, 1435, 1370, 805. Anal. C, H, Cl, N.

1-(1-Phenylethyl)-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (10). IR (KBr) 3423, 2913, 1685, 1587, 1449, 1290, 1108, 699. Anal. C, H, Cl, N.

1-(2,6-Dichlorobenzyl)-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (11). IR (KBr) 3068, 2966, 1698, 1581, 1451, 1289, 1114, 766. Anal. C, H, Cl, N.

1-(4-Bromophenyl)-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (12). IR (KBr) 2862, 1704, 1503; ^{1}H NMR (DMSO-d_6) 4.7 (s, C**H**$_2$−N), 7.4, 7.7 (Ar−**H**); ^{13}C NMR (DMSO-d_6) 45.7 (**C**H$_2$−N),

50.8 (**C**H_2−N), 66.5 (**C**H_2−O), 114.4, 119.8, 132.4, 139.7 (**C**$_{Ar}$), 166.4 (**C**═O), 174.3 (N═**C**−N). Anal. C, H, N.

1-(4-Iodophenyl)-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (13). IR (KBr) 2920, 1704; ^{1}H NMR (DMSO-d_6) 3.33−3.87 (m, NC**H**$_2$CH$_2$O), 4.65 (s, C**H**$_2$), 7.32 (d, Ph−**H**), 7.65 (d, Ph−**H**); ^{13}C NMR (DMSO-d_6) 45.11 (**C**H_2−N), 50.01 (**C**H_2), 65.75 (**C**H_2O), 85.34 (**C**−I), 119.57 (**C**Ph), 137.67 (**C**Ph), 139.56 (**C**N), 165.87 (N**C**N), 173.88 (**C**═O). Anal. C, H, Cl, N.

1-(4-Fluorophenyl)-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (14). ^{13}C NMR (DMSO-d_6) 45.61 (N−**C**H_2), 50.09 (**C**H_2), 66.25 (**C**H_2O), 118.27 (**C**Ph), 128.47 (**C**Ph), 138.21 (**C**N), 156.98 (d, J = 234.0 Hz, **C**−F), 164.38 (NCN), 173.48 (**C**═O). Anal. C, H, Cl, N.

1-(3-Chlorophenyl)-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (15). IR (KBr) 1723, 1598; ^{13}C NMR (DMSO-d_6) 45.12 (N**C**H_2), 50.26 (**C**H_2), 65.85 (**C**H_2O), 116.30 (**C**Ph), 121.77 (**C**Ph), 130.72 (**C**Ph), 133.78 (**C**−Cl), 141.21 (**C**N), 165.87 (N**C**N), 173.88 (**C**═O). Anal. C, H, Cl, N.

1-(4-Chlorophenyl)-4-azepan-1-yl-1,5-dihydro-imidazol-2-one (16). IR (KBr) 3063, 2932, 1699, 1582; ^{1}H NMR (DMSO-d_6) 1.6, 1.8 (m, C**H**$_2$−C**H**$_2$), 3.6 (m, N−C**H**$_2$), 4.7 (s, C**H**$_2$−N), 7.4, 7.7 (Ar−**H**); ^{13}C NMR (DMSO-d_6) 26.8, 28.0 (**C**H_2−CH_2), 48.9 (**C**H_2−N), 50.4 (**C**H_2−N), 119.0, 125.9, 128.9, 138.8 (**C**$_{Ar}$), 166.2 (**C**═O), 174.1 (N═**C**−N). Anal. C, H, N.

1-(4-Chlorophenyl)-4-azocan-1-yl-1,5-dihydro-imidazol-2-one (17). IR (KBr) 2930, 1701; ^{13}C NMR (DMSO-d_6) 24.72 (**C**H_2), 25.41 (**C**H_2), 25.71 (**C**H_2), 25.91 (**C**H_2), 26.22 (**C**H_2), 49.15 (N**C**H_2), 118.44 (**C**Ph), 127.02 (**C**−Cl), 128.74 (**C**Ph), 137.56 (**C**N), 165.89 (N**C**N), 172.33 (**C**═O). Anal. C, H, Cl, N.

1-(4-Methoxyphenyl)-4-piperidin-1-yl-1,5-dihydro-imidazol-2-one (18). ^{1}H NMR (DMSO-d_6) 1.53 (m, C**H**$_2$), 3.46 (m, NC**H**$_2$), 3.55 (s, OC**H**$_3$), 4.65 (s, C**H**$_2$), 6.88 (d, Ph−**H**), 7.59 (d, Ph−**H**); ^{13}C NMR (DMSO-d_6) 23.32 (**C**H_2), 24.13 (**C**H_2), 45.33 (N**C**H_2), 50.33 (**C**H_2), 55.12 (O**C**H_2), 113.11 (**C**Ph), 118.02 (**C**−Ph), 132.78 (**C**Ph), 138.96 (CN), 154.32 (**C**−O), 165.09 (N**C**N), 172.27 (**C**═O). Anal. C, H, Cl, N.

1-(4-Chlorophenyl)-4-(1-cyclohexyl-1-methyl)-1,5-dihydro-imidazol-2-one (19). IR (KBr) 2926, 2854, 1693, 1595;^{1}H NMR (DMSO-d_6) 1.7 (m, C**H**$_2$), 3.4 (m, C**H**$_2$−N), 4.6 (s, N−C**H**$_2$), 6.9, 7.4 (Ar−**H**); ^{13}C NMR (DMSO-d_6) 23.3 (**C**H_2), 25.5 (**C**H_2), 46.7 (**C**H_2−N), 50.0 (**C**H_2−N), 55.1 (**C**H_3−O), 113.8, 118.6, 132.8, 154.3 (**C**$_{Ar}$), 165.7 (**C**═O), 172.7 (N═**C**−N). Anal. C, H, Cl, N.

Synthesis of 4-Substituted 1-Aryl-2,4-dihydro-pyrrol-2-ones 20−27. General Procedure. A solution of 22.4 mmol of 1-aryl-2,4-dihydro-4-methoxy-pyrrole-2-one and 0.25 g of the corresponding amine hydrochloride in 22 mL of the amine was heated to reflux or, in the case of higher-boiling amines, to a temperature of 120−125 °C for 7 h. The solution was allowed to cool to room temperature, and the precipitate was separated by filtration. To obtain the pure compound, the crude product was washed with 5 mL of cold ethanol and 50 mL of water. Recrystallization from *n*-butanol afforded the analytically pure pyrrolones.

1-(4-Chlorophenyl)-4-morpholin-4-yl-2,4-dihydro-pyrrol-2-one (20). IR (KBr) 2968, 1672, 1616, 1495; ^{1}H NMR (DMSO-d_6) 3.21 (m, −C**H**$_2$−N−C**H**$_2$−), 3.72 (m, −C**H**$_2$−O−C**H**$_2$−), 4.43 (s, C5−**H**$_2$), 4.81 (s, C3−**H**), 7.28 (m, 2Ar−**H**), 7.70 (m, 2Ar−**H**); ^{13}C NMR (DMSO-d_6) 46.4 (−**C**H_2−N−**C**H_2−), 49.8 (**C**5), 65.8 (−**C**H_2−O−**C**H_2−), 89.8 (**C**3), 118.8 (Ar−**C**2, Ar−**C**2′), 125.2 (Ar−**C**4), 128.8 (Ar−**C**3, Ar−**C**3′), 139.7 (Ar−**C**1), 162.5 (**C**4), 172.9 (**C**2). Anal. C, H, N.

1-(4-Chlorophenyl)-4-pyrrolidin-1-yl-2,4-dihydro-pyrrol-2-one (21). IR (KBr) 2862, 1667, 1617; ^{1}H NMR (DMSO-d_6) 1.92 (m, −C**H**$_2$−C**H**$_2$−), 3.25 (m, C**H**$_2$−N−C**H**$_2$), 4.38 (s, C5−**H**$_2$), 4.50 (s, C3−**H**), 7.25 (m, 2Ar−**H**), 7.70 (m, 2Ar−**H**); ^{13}C NMR (DMSO-d_6) 24.2 (−**C**H_2−**C**H_2−), 47.2 (−**C**H_2−N−**C**H_2−), 49.2 (**C**5), 86.8 (**C**3), 118.0 (Ar−**C**2, Ar−**C**2′), 124.6 (Ar−**C**4), 127.7 (Ar−**C**3, Ar−**C**3′), 139.2 (Ar−**C**1), 159.1 (**C**4), 171.1 (**C**2). Anal. C, H, N.

1-(4-Chlorophenyl)-4-azepan-1-yl-2,4-dihydro-pyrrol-2-one (22). IR (KBr) 2920, 1662, 1607, 1494; ^{1}H NMR (DMSO-d_6) 1.49 (m, 2-C**H**$_2$), 1.68 (m, 2-C**H**$_2$), 3.29 (m, −C**H**$_2$−N−C**H**$_2$−), 4.45 (s, C5−**H**$_2$), 4.61 (s, C3−**H**), 7.28 (m, 2Ar−**H**), 7.75 (m, 2Ar−**H**); ^{13}C NMR (DMSO-d_6) 25.8 (**C**H_2), 26.8 (**C**H_2), 27.5 (**C**H_2), 29.0 (**C**H_2), 49.0 (−**C**H_2−N−**C**H_2−), 49.7 (**C**5), 87.1 (**C**3), 118.6 (Ar−**C**3, Ar−**C**3′), 125.1 (Ar−**C**4), 128.7 (Ar−**C**2, Ar−**C**2′), 139.9 (Ar−**C**1), 161.9 (**C**4), 172.2 (**C**2). Anal. C, H, N.

1-(4-Chlorophenyl)-4-piperidin-1-yl-2,4-dihydro-pyrrol-2-one (23). IR (KBr) 3061, 2939, 1673, 1615, 1494; ^{1}H NMR (DMSO-d_6) 1.68 (m, −C**H**$_2$−C**H**$_2$−C**H**$_2$−), 3.18 (m, −C**H**$_2$−N−C**H**$_2$−), 4.40 (s, C5−**H**$_2$), 4.79 (s, C3−**H**), 7.28 (m, 2Ar−**H**), 7.77 (m, 2Ar−**H**); ^{13}C NMR (DMSO-d_6) 23.8 (−CH$_2$−**C**H$_2$−CH$_2$−), 25.2 (−**C**H$_2$−CH$_2$−**C**H$_2$−), 47.7 (−**C**H$_2$−N−**C**H$_2$−), 50.0 (**C**5), 88.5 (**C**3), 118.6 (Ar−**C**2, Ar−**C**2′), 125.2 (Ar−**C**4), 128.7 (Ar−**C**3, Ar−**C**3′), 140.0 (Ar−**C**1), 162.0 (**C**4), 172.2 (**C**2). Anal. C, H, N.

1-(4-Fluorophenyl)-4-morpholin-4-yl-2,4-dihydro-pyrrol-2-one (24). IR (KBr) 2978, 1668, 1606, 1510; ^{1}H NMR (DMSO-d_6) 3.25 (m, −C**H**$_2$−N−C**H**$_2$−), 3.69 (m, −C**H**$_2$−O−C**H**$_2$−), 4.49 (s, C5−**H**$_2$), 4.88 (s, C3−**H**), 7.14 (m, 2Ar−**H**), 7.73 (m, 2Ar−**H**); ^{13}C NMR (DMSO-d_6) 46.0 (−**C**H$_2$−N−**C**H$_2$−), 49.3 (**C**5), 64.9 (−**C**H$_2$−O−**C**H$_2$−), 89.4 (**C**3), 114.4 (2d, J = 22 Hz, Ar−**C**3, Ar−**C**3′), 118.7(2d, J = 7.5 Hz, Ar−**C**2, Ar−**C**2′), 136.4 (d, J = 2.3 Hz, Ar−**C**1), 156.9 (d, J = 239 Hz, Ar−**C**4), 161.3 (**C**4), 170.8 (**C**2). Anal. C, H, N.

1-(3-Methylphenyl)-4-morpholin-1-yl-2,4-dihydro-pyrrol-2-one (25). IR (KBr) 2966, 1673, 1613, 1594; ^{1}H NMR (DMSO-d_6) 2,22 (Ar−C**H**$_3$), 3.25 (m, −C**H**$_2$−N−C**H**$_2$−), 3.65 (m, −C**H**$_2$−O−C**H**$_2$−), 4.47 (s, C5−**H**$_2$), 4.89 (s, C3−**H**), 6.75 (m, Ar−**H**), 7.18 (m, Ar−**H**), 7.78 (m, 2Ar−**H**); ^{13}C NMR (DMSO-d_6) 21.7 (Ar−**C**H$_3$), 46.7 (−**C**H$_2$−N−**C**H$_2$−), 49.9 (**C**5), 65.8 (−**C**H$_2$−O−**C**H$_2$−), 90.2 (**C**3), 114.7, 118.0, 122.6, 128.8 (4Ar−**C**), 138.1, 140.7 (Ar−**C**1, Ar−**C**3), 162.3 (**C**4), 171.9 (**C**2). Anal. C, H, N.

1-(4-Methylphenyl)-4-morpholin-4-yl-2,4-dihydro-pyrrol-2-one (26). IR (KBr) 2861, 1666, 1608, 1515; ^{1}H NMR (DMSO-d_6) 2,22 (Ar−C**H**$_3$), 3.23 (m, −C**H**$_2$−N−C**H**$_2$−), 3.66 (m, −C**H**$_2$−O−C**H**$_2$−), 4.42 (s, C5−**H**$_2$), 4.80 (s, C3−**H**), 7.09 (m, 2Ar−**H**), 7.57 (m, 2Ar−**H**); ^{13}C NMR (DMSO-d_6) 18.7 (Ar−**C**H$_3$), 44.8 (−**C**H$_2$−N−**C**H$_2$−), 47.9 (**C**5), 63.8 (−**C**H$_2$−O−**C**H$_2$−), 88.3 (**C**3), 115.6 (Ar−**C**3, Ar−**C**3′), 127.4, (Ar−**C**2, Ar−**C**2′), 128.8 (Ar−**C**4), 136.4 (Ar−**C**1), 160.3 (**C**4), 169.8 (**C**2). Anal. C, H, N.

1-(3-Chloro-4-fluorophenyl)-4-(morpholin-4-yl)-1,5-dihydro-pyrrole-2-one (27). IR (KBr) 2850, 1673, 1613; ^{1}H NMR (DMSO-d_6) 3.19 (m, −C**H**$_2$−N−C**H**$_2$−), 3.62 (m, −C**H**$_2$−O−C**H**$_2$−), 4.39 (s, C5−**H**$_2$), 4.79 (s, C3−**H**), 7.23 (m, Ar−H), 7.60 (m, Ar−H), 7.90 (m, Ar−H); ^{13}C NMR (DMSO-d_6) 45.94 (−**C**H$_2$−N−**C**H$_2$−), 49.10 (**C**$_5$), 64.90 (−**C**H$_2$−O−**C**H$_2$−), 88.62 (**C**4), 116.10 (d, J = 22.2 Hz, Ar), 117.62 (Ar), 118.70 (d, J = 18.0 Hz, Ar), 136.40 (d, J = 2.3 Hz, Ph), 156.92 (d, J = 239.1 Hz, Ar), 161.35 (s, **C**$_3$), 170.78 (s, **C**$_2$). Anal. C, H, N.

Synthesis of 1-Aryl-3-amino-pyrrole-2,5-diones (29−34).[30] The compound **29** is known. The physical and spectral data of the resynthesized compound are consistent with literature values. The compounds **30**−**34** were synthesized in the same manner.

1-(4-Chlorophenyl)-3-piperidin-1-yl-pyrrole-2,5-dione (30). ^{1}H NMR (DMSO-d_6) 1.61 (s, C**H**$_2$), 3.70 (s, C**H**$_2$−N), 5.31 (m, Ar−**H**), 7.28 (m, Ar−**H**), 7.51 (m, Ar−**H**); ^{13}C NMR (DMSO-d_6) 22.87 (**C**H_2), 25.75 (**C**H_2), 48.11 (**C**H_2N), 88.68 (**C**−Ph), 127.66, 128.08 (**C**−Ph); 130.32 (**C**−Ph); 131.01 (**C**−Ph), 149.40 (**C**−Ph); 164.77, 168.04 (**C**O 2,5). Anal. C, H, N.

1-(4-Chlorophenyl)-3-pyrrolidin-1-yl-pyrrole-2,5-dione (31). ^{1}H NMR (DMSO-d_6) 1.95 (m, C**H**$_2$) 3.30 and 3.82 (t, C**H**$_2$), 5.31 (m, Ar−**H**), 7.28 (m, Ar−**H**), 7.51 (m, Ar−**H**); ^{13}C NMR (DMSO-d_6) 24.00 and 26.21 (**C**H_2), 49.21 and 50.79 (**C**H_2−N); 88.68 (**C**−Ph), 127.63, 128.06 (**C**−Ph), 130.30 (**C**−Ph), 131.03 (**C**−Ph), 149.38 (**C**−Ph), 164.74, 168.02 (**C**O 2,5). Anal. C, H, N.

1-(4-Fluorophenyl)-3-morpholin-4-yl-pyrrole-2,5-dione (32). ^{1}H NMR (DMSO-d_6) 3.7 (s, C**H**$_2$), 5.30 (m, Ar−C**H**), 7.31 (m, Ar−**H**); ^{13}C NMR (DMSO-d_6) 46.69 (**C**H_2−N), 66.09 (**C**H_2−O), 88.18 (**C**−Ph), 115.92 (**C**−Ph, H−, $^2J_{CF}$ = 23.15), 128.50 (**C**−Ph, $^4J_{CF}$ = 1.69), 129.82 (**C**−Ph, $^3J_{CF}$ = 8.72), 150.51 (**C**−Ph), 161.24 (**C**−Ph, $^1J_{CF}$ = 243.18), 166.06 and 169.38 (**C**O, 2,5). Anal. C, H, N.

1-(4-Fluorophenyl)-3-piperidin-1-yl-pyrrole-2,5-dione (33). ^{1}H NMR (DMSO-d_6) 1.62 (s, C**H**$_2$,), 3.71 (s, C**H**$_2$−N), 5.30 (m, Ar−**H**), 7.31 (m, Ar−**H**); ^{13}C NMR (DMSO-d_6) 22.94 (**C**H$_2$), 25.78 (**C**H$_2$), 48.20 (**C**H$_2$N), 88.18 (**C**−Ph), 115.92 (**C**−Ph, $^2J_{CF}$ = 23.15), 128.50 (**C**−Ph, $^4J_{CF}$ = 1.69), 129.82 (**C**−Ph, $^3J_{CF}$ = 8.72), 150.51 (**C**−Ph), 161.24 (**C**−Ph, $^1J_{CF}$ = 243.18), 166.06 and 169.38 (**C**O). Anal. C, H, N.

1-(4-Fluorophenyl)-3-pyrrolidin-1-yl-pyrrole-2,5-dione (34). ^{1}H NMR (DMSO-d_6) 1.95 (m, C**H**$_2$), 3.30 and 3.82 (m, C**H**$_2$−N), 5.00 (s, Ar−**H**), 7.30 (m, Ar−**H**); ^{13}C NMR (DMSO-d_6) 24.02 and 26.25 (**C**H$_2$), 49.25 and 50.82 (**C**H$_2$), 85.69 (**C**Ph), 115.90 (**C**Ph, $^2J_{CF}$ = 23.05); 128.96 (**C**Ph, $^4J_{CF}$ = 1.64), 129.26 (**C**Ph, $^3J_{CF}$ = 8.78) 148.79 (**C**Ph), 161.16 (**C**Ph, $^1J_{CF}$ = 243.16), 165.37 and 160.79 (**C**O, 2,5). Anal. C, H, N.

4-(4-Chlorophenyl)-1-pyrid-2-yl-pyrazole (**35).** The 1-phenyl derivative is known.[31] Compound **35** was synthesized in the same manner. IR (KBr) 1596, 1459; ^{13}C NMR (DMSO-d_6) 112.34 (**C**Ph), 122.39 (**C**Ph), 123.45 (**C**Ph), 124.05 (**C**Ph), 127.56 (**C**Ph), 129.10 (**C**Ph), 130.78 (**C**Ph), 131.61 (**C**Ph), 139.75 (**C**Ph), 140.22 (**C**Ph), 148.57 (**C**Ph), 151.04 (**C**Ph), Anal. C, H, Cl, N.

3-(4-Chlorophenyl)-5-morpholin-4-yl-1,2,4-oxadiazole (36). This compound was synthesized by the route described by Weber et al.[32] Instead of *N*-(morpholinyl-thiocarbonyl) benzimide chloride the 4-chlorphenyl derivative was used. IR (KBr) 1639, 1416; ^{13}C NMR (DMSO-d_6) 45.04 (N**C**H$_2$CH$_2$O), 65.15 (NCH$_2$**C**H$_2$O), 125.93 (**C**Ph), 122.41 (**C**−Cl), 128.36 (**C**Ph), 129.24 (**C**Ph), 166.70 (NCN), 170.77 (OCN). Anal. C, H, Cl, N.

Synthesis of 2-(4-Chlorophenyl)-5-phenyl-4-isoxazolin-3-one (37). The synthesis is described for 2,5-diphenyl-4-isoxazolin-3-one.[33] The cyclization of phenyl propionic acid *N*-hydroxy-4-chloroanilide in alkaline media leads to the desired compound. ^{1}H NMR (DMSO-d_6) 6.7 (s, =C**H**−), 7.7, 7.9 (Ar−**H**); ^{13}C NMR (DMSO-d_6) 95.2 (=**C**H), 117.8, 125.3, 125.8, 129.0, 129.4, 131.9, 135.2 (**C**$_{Ar}$), 163.6 (=**C**−O), 167.6 (**C**=O). Anal. C, H, N.

1-(4-Chlorophenyl)-5,5-dimethoxy-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (39). Ten grams of 1-(4-chloro-phenyl)-4-morpholin-4-yl-1,5-dihydro-imidazol-2-one (**2**), 0.1 mL of pyridine, and 100 mL of thionyl chloride were stirred and heated under reflux for 2 h. The solution was concentrated in vacuo, and the residue was dissolved in 50 mL of methanol. After heating for 0.5 h, the methanol was evaporated off and the crude product was purified by chromatography (silica gel 60, ethyl acetate). ^{1}H NMR (DMSO-d_6) 3.15 (s, OC**H**$_3$), 3.80 (m, C**H**$_2$), 7.40 (d, Ph−**H**), 7.60 (d, Ph−**H**); ^{13}C NMR (DMSO-d_6) 45.55 (N**C**H$_2$), 51.42 (O**C**H$_3$), 65.785 (**C**H$_2$O), 110.50 (**C**Ph), 122.48 (**C**−Cl), 128.44 (**C**Ph), 128.53 (**C**Ph), 133.85 (**C**N), 161.46 (N**C**N), 168.02 (**C**=O). Anal. C, H, Cl, N.

3-(4-Chlorophenyl)-5-phenyl-3*H*-1,3,4-oxadiazol-2-one (41).[36] The synthesis of 3,5-diphenyl-3*H*-1,3,4-oxadiazol-2-one has been described.[36] The 4-chloro derivative **41** was synthesized in the same manner.

Receptor Preparation. Male Wistar rats (180 to 200 g) were killed by suffocation in a CO_2 chamber for 2 min. Whole brains without cerebellum were removed and dissected on ice, placed in closed vials, and stored at −70 °C. To isolate membrane fractions with receptors, 1 g of the brains was placed into 10 mL of 0.05 M Tris/HCl buffer, pH 7.7, at 4 °C and homogenized for 30 s at 20 000 rpm with an Ultraturrax T25 (Jahnke & Kunkel, IKA-Labortechnik, Staufen, Germany). The homogenate was centrifuged at 4 °C for 30 min at 48 000*g* (OPTIMA XL-70, Beckman, Palo Alto, CA). The resulting pellet was resuspended and homogenized in 100 mL of 0.05 M Tris/HCl buffer, pH = 7.7, 4 °C, at 20 000 rpm with an Ultraturrax and used for binding assays.

Receptor Binding Screening. During preparation of the assays, a volume of 150 μL of the membrane preparation (1.5 mg original tissue) was incubated with 0.5 nM [^{3}H]-flunitrazepam for 30 min at 4 °C. Nonspecific binding was estimated in the presence of 10 μM diazepam. Binding was terminated by filtration of the incubated membrane preparations using Filtermat A (Pharmacia, Uppsala, Sweden) and a Micro Cell Harvester (Skatron, Lier, Norway). The Filtermat A had been presoaked with 1% polyethylene imine, and after filtration it was carefully washed with 0.05 mol Tris/HCl buffer at pH = 7.7 to separate free and bound radioactivity. The filters were counted in a scintillation counter (Betaplate 1205, Berthold, Wildbad, Germany) in order to determine the specific binding of [^{3}H]-flunitrazepam. With the help of preliminary saturation experiments, the dissociation constant, K_d, of [^{3}H]-flunitrazepam of 1.5 nM, the maximum number of binding sites B_{max} of 0.38 nM, and the specific binding in the assay of 90% were determined. Generally, test compounds were screened at 6−10 increasing concentrations for the determination of IC_{50} values, and the K_i values were calculated according to the Cheng−Prusoff relationship[67] (eq 1) with [L] being the concentration of the radioactive ligand and K_d its dissociation constant. If at the highest used concentration an inhibition of less than 50% was measured, then this percentage inhibition P was used. Determinations of IC_{50} and P values, respectively, were repeated at least four times and arithmetic means were used.

$$K_i = \frac{IC_{50}}{1 + [L]/K_d} \quad (1)$$

Estimation of K_i Values. As mentioned above, in some cases percentage inhibition data P instead of K_i values were determined. To broaden the data basis of CoMFA modeling, IC_{50E} values were estimated by using these data according to eq 2. Equation 2 results from the standard sigmoidal curve assuming a Hill coefficient of 1. The K_i values were calculated according to eq 1.

$$IC_{50E} = [I] \cdot \frac{100 - P}{P} \quad (2)$$

To validate this approach, all raw data (393 percentage inhibition values) from receptor-binding studies of the 13 available compounds with regularly measured IC_{50} values were used to calculate IC_{50E} values according to eq 2. The results were related to the experimental IC_{50} values. The ratios of estimated to measured values were grouped according to the height of percentage inhibition, and the 95% confidence limits of these groups were calculated. For ratios from percentage inhibition data lower than 10%, lower and upper confidence interval limits of 0.17 and 5.94 were found. This indicates that ratios of estimated to experimental IC_{50} values of up to 6 may be found. Using percentage inhibition values between 10% and 20%, ratios of up to 4 (0.38, 3.78) can be expected. For data > 20%, ratios < 3 were found. This seems to be acceptable in view of a ratio of 2 generally found due to biological variance and other experimental effects. According to these results, IC_{50E} values were calculated on the basis of percentage inhibition values if P was greater than 20%. It should be noted that such an approach is valid only if the Hill coefficient is close to 1.

Experimental Procedure for Screening in Mice. For screening of compounds, we usually use the MES (maximal electroshock), the PTZ, and the rotarod test. Data described here only come from the PTZ and rotarod tests. At elbion, the substance to be screened or vehicle was administered to three male mice (Crl:NMRI BR, Charles River, Sulzfeld, Germany) each per dose, pre-treatment time, and per experimental model. At the NIH,[68] up to five male mice (Crl:CF-1, Charles River, Wilmington, MA) were used. The doses applied i.p. were 30, 100, and 300 mg/kg. The pre-treatment time chosen was 30 min and 4 h. Shortly before the seizure tests were carried out, possible side effects of the screening compounds were assessed in the rotarod test. For selected compounds the median effective doses (ED_{50}, TD_{50}) in the tests were determined. Furthermore, selected compounds were also tested in rats after oral administration.

PTZ Test. PTZ (pentylenetetrazole 85 mg/kg b.w. mouse) was injected s.c. (0.2 mL/20 g mouse) into the back of the neck of the mouse. In rats, a dose of 70 mg/kg of PTZ was administered s.c. (0.2 mL/100 g rat). After injection, the animals were observed for 30 min. The first generalized clonic seizure with loss of righting reflex (convulsions of fore and hind legs, lateral position) was used

as the endpoint. Animals with no seizure with a duration of at least 5 s were considered to be protected.

Rotarod Test. Motor impairment was identified in male mice and rats by the rotarod procedure. Inability of an animal to maintain its equilibrium for 1 min in at least one of three trials on the rotating rod (6 rpm and diameter 0.9 cm for mice; 8 rpm and diameter 6 cm for rats) was used as an indication of the impairment. The animals were trained before drug experiments.

Anxiety Model. To obtain more detailed insight into the possible anxiolytc activity, a modification of the method of Vogel et al.[69] was used. The method has been recently described in detail.[41] In the Vogel conflict test, thirsty rats have to decide whether to drink and take the risk of being punished with a brief electric shock or whether to stay thirsty. Anxiolytics increase the number of licks during punishment. The test required three consecutive days in which drinking sessions were performed once a day, always at the same time. On the first day, rats were allowed to drink water for 15 min without being punished, to become accustomed to the operant box. They were put back into their home cage then and left without water for 24 h. On the second day, water was replaced by 5.0% glucose solution, and the rats were allowed to drink for five minutes during the training session. Then, they were again left without water for the next 24 h in their home cage. On the last day, the rats were offered drinking water again. The whole test session lasted for 210 s. For the first 30 s, the rats were allowed to drink water without punishment. In the remaining 180 s, rats received a mild electric shock when touching the drinking tube. The number of unpunished and punished licks were counted by a computer program "Graphic state notation" (Coulbourn Instruments, Allentown, USA).

Calculation of ED_{50}, TD_{50}, and Protective Index. In the PTZ test an approximation of the time peak effect was achieved by administrating the test substance using different groups of animals ($n = 3-4$) at different pre-treatment times and determining the percentage of protection. The time at which the highest protection was measured was used for the dose−response curve and determination of the median effective dose (ED_{50}). The dose−response curve was based upon at least three different active dose groups and one vehicle-treated group ($n = 8$/group). In the rotarod test, an approximation of the time of peak effect was achieved by testing the same animals after administration of the test substance (at least three dose groups, $n = 8$/group) at different time points and determining the percentage of animals with disturbance of motor coordination. The time at which the highest neurotoxic effect was measured was used for the dose−response curve and determination of the median effective dose (TD_{50}). The ED_{50} or TD_{50} were calculated by probit analysis.[70] The protective index (PI) in rats was calculated as ratio between TD_{50} and the ED_{50} in the PTZ seizure model. Only data generated in the same lab were used.

Calculations of Molecular Structures. Initial molecular models of all compounds were built using the molecular sketcher and energy-minimizing tools within SYBYL.[71] Subsequently, geometries were fully optimized by means of various methods of ab initio and semiempirical MO theory. Details can be found in the Supporting Information.

Alignment of Structures. We used the program ASP within TSAR[72] to align our compounds with **42** as the target structure. A systematic search was carried out with an increment of 15°. The Carbó molecular similarity index was used as the optimization criterion on the basis of three equally weighted Gaussian approximations of electrostatic potential and molecular shape. Carbó indices range between 0 and 1 (steric fields) and −1 and 1 (electrostatic fields). The results were optimized by a Simplex procedure without simulated annealing using default parameters. We found an alignment of the halogen-substituted phenyl groups, the central rings, and the (mostly) aliphatic moieties, respectively. There was not only a high steric (0.91 ± 0.08), but also a good electrostatic similarity (0.74 ± 0.07). The similarities of substances with measurable affinities and pharmacological activities are still slightly higher with values of 0.94 ± 0.03 (steric) and 0.76 ± 0.05 (electrostatic). An alternative alignment would result from matching the chlorophenyl ring of **42** with the aliphatic rings of our compounds. To check this, an ASP calculation was carried out without a systematic search, but with Simplex optimization using the assumption as an initial alignment. We found a persistently high steric similarity, with a mean Carbó index of 0.85 ± 0.09, but a very low electrostatic similarity with a Carbó index of only 0.27 ± 0.13. This indicates that there is only one well-defined alignment.

CoMFA Calculations. CoMFA steric and electrostatic fields were calculated employing the SYBYL[71] defaults (Tripos standard field class, distance-dependent electrostatic energy calculation, no smoothing of field values, cutoff 30 kcal/mol, smoothed cutoff transition). A 1 Å grid spacing and an sp^3 carbon probe atom with the charge +1 was used. In addition to the steric and electrostatic fields, hydrophobic fields were calculated using the program CLIP.[73] Models were derived based on all possible combinations of these three fields. The calculations with cross-validation were performed employing SAMPLS. Only models with cross-validated r^2 (q^2) > 0.5 were considered to be predictive.

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Supporting Information Available: Results from elemental analysis, conformation analysis of **2**, tautomeric structure of **42**, and additional references. This material is available free of charge via the Internet at http://pubs.acs.org.

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