Synthesis of Some 2-Aryl-1,2,4-triazolo[1,5-c][1,3]benzoxazin-5-ones as Tools To Define the Essential Pharmacophoric Descriptors of a Benzodiazepine Receptor Ligand

Daniela Catarzi, Lucia Cecchi,* Vittoria Colotta, Guido Filacchioni, and Flavia Varano

Dipartimento di Scienze Farmaceutiche, Universita' di Firenze, Via Gino Capponi 9, 50121 Firenze, Italy

Claudia Martini, Laura Giusti, and Antonio Lucacchini

Istituto Policattedra di Discipline Biologiche, Universita' di Pisa, Via Bonanno 6, 56100 Pisa, Italy

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The synthesis and benzodiazepine receptor (BZR) affinity of some 1,2,4-triazolo[1,5-c][1,3]-benzoxazin-5-ones, **2**–**22**, are reported. Compounds **2**–**22** are devoid of the proton donor group, which according to a BZR schematic model was one of the pharmacophoric descriptors for receptor–ligand interaction. The binding data show that 2-(2-fluorophenyl)-9-chloro-1,2,4-triazolo[1,5-c][1,3]benzoxazin-5-one (**12**) and some other compounds display nanomolar BZR affinity, indicating that the hydrogen donor group is not essential for the anchoring of 6,6,5-tricyclic systems to the BZR but only affects the potency of a ligand.

Introduction

Benzodiazepines (BDZ) and related non-BDZ hypnotic or anxiolytic agents interact allosterically with the $GABA_A$ receptor–chloride ion channel complex, facilitating the inhibitory action of GABA. The allosteric site which binds BDZ was called benzodiazepine receptor (BZR). The modulatory nature of the BZR resulted from the fact that compounds which bind to them can mediate a continuum of intrisic activity ranging from full agonists (such as hypnotic, anxiolytic, and anticonvulsant BDZs) to antagonists (devoid of pharmacological effect) to inverse agonists (proconvulsant and anxiogenic agents).

Structure–activity relationships (SAR)[1-8] and a computer modeling study,[9,10] which are available for a number of structurally different BZR ligands, have led to the development of several models of the BZR pharmacophore. A common feature of these models is the attempt to explain ligand efficacy as a function of ligand–receptor interaction at the molecular level, on the basis of changes in the conformation of the receptor from its unoccupied resting state.

It follows that all BZR ligands should have certain common characteristics that allow for recognition regardless of the type of intrinsic activity. Rationalization of the common structural requirements for the binding to the BZR of some 6,6,5-tricyclic heteroaromatic systems has led us to propose a schematic representation of the BZR binding site,[11] in which the following pharmacophoric descriptors were identified (Figure 1) (i) two lipophilic areas, called L_1 and L_2; (ii) a hydrogen donor site, called d; and (iii) two proton acceptor sites, called a_1 and a_2, each divided into two subregions, indicated as a_{1a} and a_{1b} and a_{2a} and a_{2b}, respectively.

Recently we reported the synthesis and BZR affinity of 2-phenyl-1,2,4-triazolo[1,5-c][1,3]benzoxazin-5-one (**1**).[12] Compound **1** contains all the pharmacophoric descriptors of a BZR ligand except the proton donor group d. Nevertheless 1 showed some BZR affinity (K_i = 132 nM). This suggested that the proton donor d was not essential to the anchoring of a ligand to the BZR recognition site and that inactivity of similar N-methylated 6,6,5-tricyclic derivatives[11,13,14] was not due to the lack of the hydrogen donor d but to the steric hindrance of the alkyl substituent in the receptor–ligand interaction. To confirm this hypothesis, which cannot be based on the BZR affinity of a single compound, the syntheses of further triazolobenzoxazines, **2**–**22**, are reported.

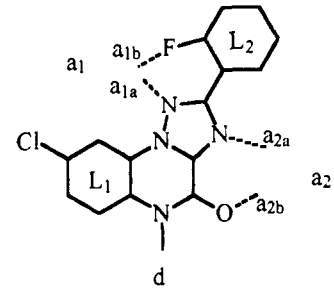
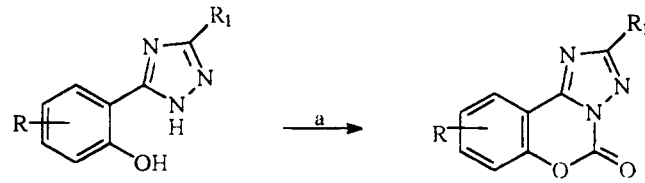


Figure 1. Two-dimensional schematic representation of BZR binding site using as template the 4,5-dihydro-2-(2-fluorophenyl)-8-chloro-1,2,4-triazolo[1,5-a]quinoxalin-4-one.[11] L_1 and L_2 designate lipophilic areas; d represents the hydrogen donor site; a_1 and a_2 are hydrogen acceptor regions. The latter sites are each subdivided into two subregions, indicated as a_{1a} and a_{1b} and a_{2a} and a_{2b}, respectively. Due to the free rotation of the substituent at position 2 around the σ bond, the a_{1b} proton acceptor subregion could fall into the a_2 area, reinforcing the hydrogen-bonding interaction in this region.

Scheme 1[a]



26-27: R_1 = COOEt

65-83: R_1 = aryl

2-22

[a] (a) $(CCl_3O)_2CO/Et_3N/THF$.

Chemistry

The synthesis of the 1,2,4-triazolo[1,5-c][1,3]benzoxazin-5-ones **2**–**22** was achieved by cyclizing the 3-substituted-5-(2-hydroxyaryl)-1,2,4-triazoles **26**, **27**, and **65**–**83** with triphosgene (Scheme 1). Two different pathways were

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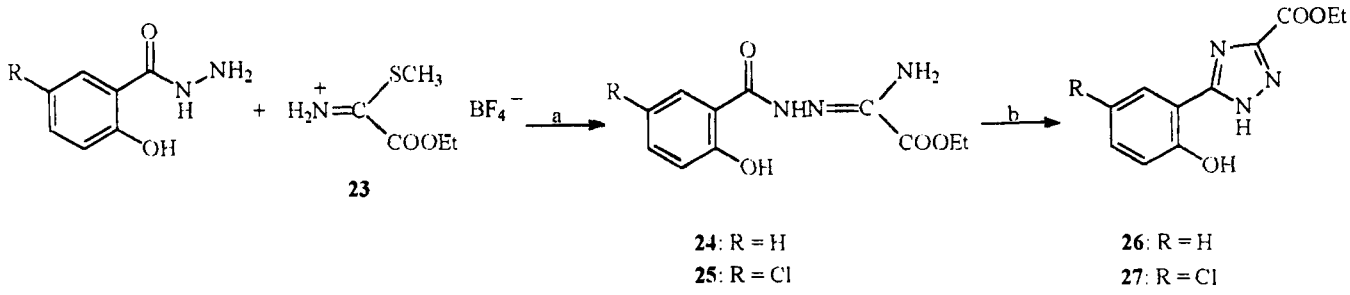
Scheme 2[a]



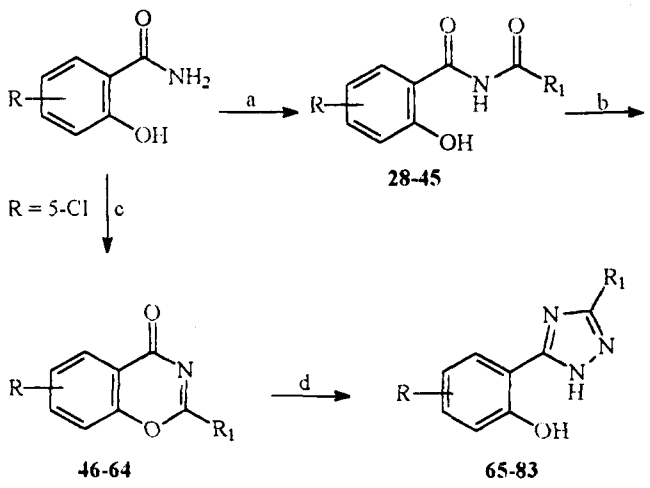
23

24: R = H
25: R = Cl

26: R = H
27: R = Cl

[a] (a) Et_3N/CH_2Cl_2; (b) heating over their melting points.

Scheme 3[a]



28-45

46-64

65-83

[a] (a) R_1COCl/pyridine; (b) heating over their melting points; (c) C_6H_5COCl/pyridine/xylene; (d) $N_2H_4 \cdot H_2O$/ethanol.

followed to obtain either the 3-carbethoxytriazoles **26** and **27** or the 3-aryltriazoles **65**–**83**.

The ethyl 5-(2-hydroxyaryl)-1,2,4-triazole-3-carboxylates **26** and **27** (Scheme 2) were obtained by reacting salicylhydrazides with carbethoxy-*s*-methylthioformimidium tetrafluoborate (**23**) through the oxamidrazonates **24** and **25**. Compound **23** was obtained by alkylation of the commercially available ethyl 2-thiooxamate with trimethyloxonium tetrafluoborate. On heating **24** and **25** at a temperature just over their melting points, the key intermediates **26** and **27** were isolated.

The synthesis of the 3-aryl-5-(2-hydroxyaryl)-1,2,4-triazoles **65**–**83** (Scheme 3) resulted from the reaction of hydrazine hydrate on 2-aryl-1,3-benzoxazin-4-ones **46**–**64**. Preparation of the latter was achieved following two reported methods.[15,16]

A Geigy patent[15] describes the synthesis of some 2-aryl-1,3-benzoxazin-4-ones by a one-stage process involving condensation of an acid halide with salicylamides in the presence of pyridine, as reaction accelerator, and boiling xylene. 2-Phenyl-6-chloro-1,3-benzoxazin-4-one (**51**) was obtained following this method. However, our attempts to prepare other 2-aryl-1,3-benzoxazin-4-ones using this method were unsuccessful.

A second method[16] provides the two-step synthesis of 2-aryl-1,3-benzoxazin-4-ones: refluxing the suitable salicylamide with aroyl chloride in pyridine followed by cyclization of the isolated aroylsalicylamides **28**–**45** in anisole and hydrogen chloride. The herein reported 2-aryl-1,3-benzoxazin-4-ones **46**–**50** and **52**–**64** were prepared following the first step of this method, while cyclization was achieved by heating the isolated intermediates just over their melting points. Unfortunately we were unable to isolate and thus to characterize **63**, which was used as a crude product in the next reaction. It must be noted that the ^1H NMR spectrum of the intermediate **28**[16] revealed that it is the more stable *N*-(4-methoxybenzoyl)salicylamide rather than its isomer *O*-aroylsalicylamide.[16] The two signals at 11.63 and 11.76 ppm are in fact attributable to two different exchangeable protons which are indicative of N-acylation rather than O-acylation. The IR spectrum of **28** shows a sole stretching band at 3250 cm^{-1}; this is characteristic of a secondary amido group. The ^1H NMR and IR spectra of all the other intermediates **29**–**45** behave in a similar way.

The structures of the final 1,2,4-triazolo[1,5-*c*][1,3]-benzoxazin-5-ones **2**–**22** were attributed by ^{13}C NMR spectroscopy. In fact, the C-2, C-10a, and C-10b displayed chemical shifts and multiplicities similar to those of 2-phenyl-1,2,4-triazolo[1,5-*c*][1,3]benzoxazin-5-one (**1**)[12] whose structure was unambiguously attributed by X-ray spectroscopy.

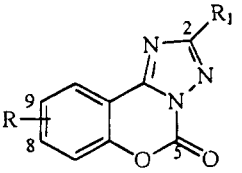
Biochemistry

Compounds **2**–**22** were tested for their ability to displace [^3H]flunitrazepam (at 0.2 nM, K_D = 1.8 nM) from its specific binding in bovine brain membranes. First, the percentage of inhibition (*I*%) was determined at 10 μM, and then the IC_{50} values of the more active ones were calculated by log-probit plots. From the latter, the K_is used to define BZR affinity were derived. To roughly determine the intrinsic activity of the reported compounds "in vitro", the GABA ratio, i.e., the ratio between the IC_{50} of a ligand in the absence of GABA and in its presence, was also calculated. According to some authors,[17–19] the GABA ratio in fact generally predicts the expected behavioral properties of a BZR ligand. The binding data for compounds **2**–**22** and the previously reported parent compound **1**,[12] included as reference, are listed in Table 1.

Results and Conclusions

The binding data in Table 1 indicate that the affinity of the lead structure **1** remains unchanged upon replacement of the 2-phenyl ring with the carbethoxy group (**2**, **9**). The position and nature of the substituent in the 2-phenyl ring are instead of paramount importance. In fact, the presence of a 4-chloro substituent dramatically affects the BZR affinity, compounds **4** and **11** being completely inactive, while the presence of a 2-fluoro (**5**, **12**) resulted in a 9- or 12-fold increased binding activity, respectively. Even the double-substituted 2,3-difluoro **17** and 2,6-difluoro **18** displayed

Table 1. Binding Constants at BZR for the Reported Compounds[a]



compd	R	R_1	K_i (nM)[b]	GR[c]
1[d]	H	C_6H_5	132 ± 11	0.98[e]
2	H	COOEt	120 ± 10	0.81[e]
3	H	4-$OMeC_6H_4$	300 ± 27	1.31
4	H	4-ClC_6H_4	0%[f]	
5	H	2-FC_6H_4	15.3 ± 1.3	0.95[e]
6	H	2-furyl	27.9 ± 2.3	0.84[e]
7	H	2-thienyl	32.1 ± 2.8	0.98[e]
8	9-Cl	C_6H_5	568 ± 47	0.78
9	9-Cl	COOEt	125 ± 12	1.20
10	9-Cl	4-$OMeC_6H_4$	72.8 ± 6.5	0.50
11	9-Cl	4-ClC_6H_4	3%[f]	
12	9-Cl	2-FC_6H_4	5.2 ± 0.3	0.90[e]
13	9-Cl	2-furyl	62.3 ± 5.1	0.90
14	9-Cl	2-thienyl	100 ± 10	0.80
15	9-Cl	3-furyl	105 ± 9.8	0.80
16	9-Cl	3-thienyl	211 ± 19	1.02
17	9-Cl	2,3-$F_2C_6H_3$	11.8 ± 1.0	1.11
18	9-Cl	2,6-$F_2C_6H_3$	42.2 ± 4.0	0.76
19	9-Me	2-FC_6H_4	44.8 ± 3.7	0.84
20	9-OMe	2-FC_6H_4	43.7 ± 3.8	1.13
21	8-Cl	2-FC_6H_4	47%[f]	
22	8-OMe	2-FC_6H_4	45%[f]	

[a] The tests were carried out using DMSO as solvent, unless otherwise stated. [b] K_i values are means ± SEM of four determinations. [c] GABA ratio = IC_{50}(compound)/IC_{50}(compound + 10 μM GABA) performed in five independent experiments. [d] See ref 12. [e] The test was carried out using ethanol as solvent. [f] Percentage of inhibition (*I*%) of [^{3}H]flunitrazepam binding at 10 μM concentration.

enhanced BZR affinity as compared to the parent compound **1**, although the monosubstitution seems to be the preferred kind. Replacement of the 2-phenyl ring with a heterocycle is advantageous in the case of the 2-furyl **6** and **13** and 2-thienyl **7**, does not affect the 9-chloro 2-thienyl **14** or 9-chloro 3-furyl **15**, and is deleterious in the case of the 9-chloro 3-thienyl **16**.

The nonadditive 9-substituent effect is in agreement with previous findings.[11,14] Only in the cases of 9-chloro 2-(2-fluorophenyl) **12** and 9-chloro 2-(4-methoxyphenyl) **10** is there a 3- and 4-fold increase in affinity with respect to their 9-H analogues **5** and **3**. In other cases, i.e., **13** versus **6** and **14** versus **7**, the 9-halo substituent decreases the BZR affinity. However comparison of the 2-(fluorophenyl)triazolobenzoxazines bearing different 9-substituents (**5**, **12**, **19**, **20**) indicates an order of potency Cl > H > OMe = Me.

Displacement of the substituent from position 9 to position 8 (**21**, **22**) resulted in a loss of binding activity. This too is in accordance with previous data[14] confirming the presence, in the recognition site of the BZR, of an accessory area able to accommodate the 9-substituent.

The SAR on the 1,2,4-triazolo[1,5-*c*][1,3]benzoxazin-5-ones **1**–**22** are very similar to those of the previously reported 1,2,4-triazolo[1,5-*a*]quinoxalin-5-ones.[11] It follows that compounds **1**–**22** bind to the BZR in a similar way and that the pharmacophoric descriptors shown in Figure 1 should be the same. However **1**–**22** are devoid of the proton donor d. Since the two analogues 2-(2-fluorophenyl)-9-chloro-1,2,4-triazolo[1,5-*c*][1,3]benzoxazin-5-one (**12**) and 2-(2-fluorophenyl)-8-chloro-1,2,4-triazolo-[1,5-*a*]quinoxalin-4-one,[11] which is the template used in Figure 1, display similar BZR affinity (5.2 and 2.9, respectively), our starting hypotheses are confirmed (i) that the proton donor d, in our 6,6,5-tricyclic heteroaromatic systems, is not essential for the anchoring to the BZR; (ii) that the proton donor d is an auxiliary binding site only affecting potency; and (iii) that the inactivity of N-alkylated ligands of similar size and shape is due to the steric hindrance by the alkyl substituent in the receptor–ligand interaction. This conclusion is supported by the inactivity of the N-alkylated 2-carbethoxy- and 2-phenyl-1,2,4-triazoloquinoxalines[11,14] and the *N*-methyl-2-phenylimidazoquinoxaline[11] compared to the BZR affinity of their corresponding NH analogues.[11,14] If the inactivity of these N-alkylated compounds was due to the lack of the proton donor group d, the hereby reported triazolobenzoxazine analogues would be inactive.

In Table 1 the GABA ratios (GR) of **1**–**22** are also shown. This "in vitro" classification method is useful for roughly estimating the functional properties of test compounds.[17-19] Thus a full agonist would have a GR greater than or equal to 2.0, an antagonist would have a GR in the vicinity of 1.0, and an inverse agonist would have a GR of less than or equal to 0.7.[20] The general trend of compounds **1**–**22** is that of antagonists/partial inverse agonists with only one full inverse agonist, i.e., compound **10**. The nonadditive 9-substituent effect is also present in the case of the GR. In fact, the antagonist efficacy trend of the 9-unsubstituted derivatives **2**, **5**, and **6** is retained in the corresponding 9-chloro analogues **9**, **12**, and **13**, respectively, while, upon 9-substitution, the antagonists **1** and **7** are converted into the partial inverse agonists **8** and **14**, respectively, and **3** becomes the full inverse agonist **10**.

In conclusion, the BZR affinity and efficacy of compounds **1**–**22** indicate that the hydrogen donor group d is not essential for the anchoring of a 6,6,5-tricyclic system to the BZR but only affects the potency.

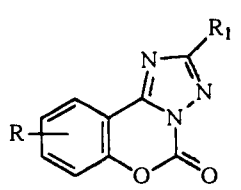
Experimental Section

Chemistry. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck; 70-230 mesh) were used for analytical and column chromatography, respectively. All melting points were determined on a Gallenkamp melting point apparatus. Microanalyses were performed with a Perkin–Elmer 260 elemental analyzer for C, H, N, and the results are within ±0.4% of the theoretical values. The IR spectra were recorded with a Perkin–Elmer 1420 spectrometer in Nujol mull and are expressed in cm^{-1}. The ^{1}H and ^{13}C NMR spectra were obtained with a Varian Gemini 200 instrument at 200 and 50 MHz, respectively. The chemical shifts are reported in ppm relative to the central peak of the solvent. The following abbreviations are used, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet, br = broad, and ar = aromatic protons. The physical data of the newly synthesized compounds are shown in Table 2.

Materials. Beside the commercially available starting materials, the following products were prepared according to reported methods: 5-chlorosalicylhydrazide,[21] 5-methylsalicylamide,[22] 4-methoxy- and 5-methoxysalicylamide,[23] 4-chlorosalicylamide,[24] 3-furoyl chloride, and 3-thiophenecarboxylic acid chloride.[25]

Carbethoxy-S-methylthioformimidium Tetrafluoborate (23). Trimethyloxonium tetrafluoborate (22 mmol, 3.2 g) was added to a cooled (−5 °C) solution of ethyl 2-thiooxamate (15 mmol, 2.0 g) in CH_2Cl_2 (80 mL). The mixture was stirred at −5 °C overnight. Evaporation of the solvent afforded

Table 2. Physical Data of the Newly Synthesized Compounds



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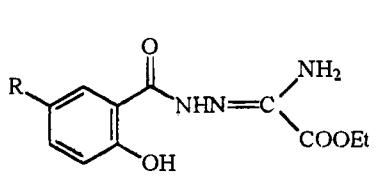

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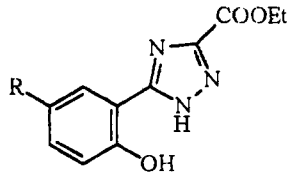

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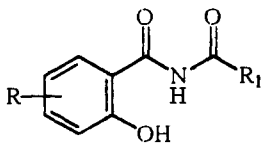

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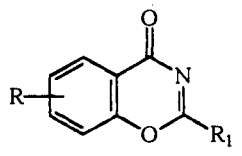

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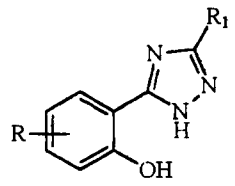

65-83

compd	R	R_1	mp (°C)	solvent[a]	yield (%)	compd	R	R_1	mp (°C)	solvent[a]	yield (%)
2	H	COOEt	224–225	A	63	**43**	5-OMe	2-FC_6H_4	188–189	B	60
3	H	4-$OMeC_6H_4$	245–246	A	91	**44**	4-Cl	2-FC_6H_4	205–209	E	54
4	H	4-ClC_6H_4	296–297	A	52	**45**	4-OMe	2-FC_6H_4	182–183	F	67
5	H	2-FC_6H_4	247–248	B	90	**46**[c]	H	4-$OMeC_6H_4$	167–168	C	55
6	H	2-furyl	239–240	C	82	**47**	H	4-ClC_6H_4	172–174	B	33
7	H	2-thienyl	248–250	A	95	**48**	H	2-FC_6H_4	117–118	K	38
8	9-Cl	C_6H_5	286–288	A	28	**49**	H	2-furyl	128–129	B	40
9	9-Cl	COOEt	206–208	B	53	**50**	H	2-thienyl	165–166	E	40
10	9-Cl	4-$OMeC_6H_4$	272–273	A	76	**51**	6-Cl	C_6H_5	216–218	B	13
11	9-Cl	4-ClC_6H_4	294–295	D	85	**52**	6-Cl	4-$OMeC_6H_4$	218–220	L	30
12	9-Cl	2-FC_6H_4	250–251	B	79	**53**	6-Cl	4-ClC_6H_4	230–232	D	21
13	9-Cl	2-furyl	262–263	A	88	**54**	6-Cl	2-FC_6H_4	193–194	E	40
14	9-Cl	2-thienyl	264–265	A	51	**55**	6-Cl	2-furyl	211–213	M	15
15	9-Cl	3-furyl	264–266	A	64	**56**	6-Cl	2-thienyl	221–223	M + F	18
16	9-Cl	3-thienyl	274–275	A	86	**57**	6-Cl	3-furyl	173–174		27
17	9-Cl	2,3-$F_2C_6H_3$	245–246	A	72	**58**	6-Cl	3-thienyl	210–212	L	47
18	9-Cl	2,6-$F_2C_6H_3$	210–211	A	58	**59**	6-Cl	2,3-$F_2C_6H_3$	191–193	E	38
19	9-Me	2-FC_6H_4	190–191	A	95	**60**	6-Cl	2,6-$F_2C_6H_3$	198–200	N + B	10
20	9-OMe	2-FC_6H_4	196–197	A	92	**61**	6-Me	2-FC_6H_4	169–172	F	44
21	8-Cl	2-FC_6H_4	263–264	A	91	**62**	6-OMe	2-FC_6H_4	133–135	F	50
22	8-OMe	2-FC_6H_4	224–226	A	27	**64**	7-OMe	2-FC_6H_4	153–155	E	52
24	H		172–173	E	60	**65**[d]	H	4-$OMeC_6H_4$	187–188	E	68
25	5-Cl		170–172	F	45	**66**	H	4-ClC_6H_4	258–260	B	85
26	H		222–223	E	40	**67**	H	2-FC_6H_4	240–241	E	60
27	5-Cl		210–211	G + H	23	**68**	H	2-furyl	218–220	K	95
28[b]	H	4-$OMeC_6H_4$	210–211	A	60	**69**	H	2-thienyl	238–240	E	83
29	H	4-ClC_6H_4	224–226	I	62	**70**	5-Cl	C_6H_5	258–259	E	62
30	H	2-FC_6H_4	174–176	E	55	**71**	5-Cl	4-$OMeC_6H_4$	263–265	B	86
31	H	2-furyl	204–206	E	75	**72**	5-Cl	4-ClC_6H_4	306–308	F	81
32	H	2-thienyl	222–223	I	95	**73**	5-Cl	2-FC_6H_4	243–245	E	78
33	5-Cl	4-$OMeC_6H_4$	220–222	J	65	**74**	5-Cl	2-furyl	285–287	E	80
34	5-Cl	4-ClC_6H_4	224–226	J	83	**75**	5-Cl	2-thienyl	279–280	F	94
35	5-Cl	2-FC_6H_4	218–219	E	73	**76**	5-Cl	3-furyl	284–286	E	77
36	5-Cl	2-furyl	225–230	E	67	**77**	5-Cl	3-thienyl	289–290	E	69
37	5-Cl	2-thienyl	241–242	E	70	**78**	5-Cl	2,3-$F_2C_6H_3$	259–261	E	80
38	5-Cl	3-furyl	246–248	J	50	**79**	5-Cl	2,6-$F_2C_6H_3$	250–253	E	53
39	5-Cl	3-thienyl	240–244	J	40	**80**	5-Me	2-FC_6H_4	234–236	E	84
40	5-Cl	2,3-$F_2C_6H_3$	213–214	A	75	**81**	5-OMe	2-FC_6H_4	202–203	E	90
41	5-Cl	2,6-$F_2C_6H_3$	199–200	A	70	**82**	4-Cl	2-FC_6H_4	259–261	O + B	32
42	5-Me	2-FC_6H_4	191–193	E	63	**83**	4-OMe	2-FC_6H_4	238–241	E	81

[a] Recrystallization solvents: A = glacial acetic acid, B = ethyl acetate, C = benzene, D = tetrahydrofuran, E = ethanol, F = acetone, G = column chromatography, eluting system cyclohexane/ethyl acetate (1:1), H = diethyl ether, I = dimethylformamide/water, J = dimethylformamide, K = ethyl acetate/cyclohexane, L = dioxane, M = column chromatography, eluting system cyclohexane/ethyl acetate (6:4), N = column chromatography, eluting system chloroform/cyclohexane (9.5:0.5), and O = column chromatography, eluting system chloroform/tetrahydrofuran (9:1). [b] Lit.[16] mp 198 °C (ethanol). [c] Lit.[16] mp 168 °C (ethanol); 68% yield. [d] Lit.[16] mp 186 °C (ethanol); 79% yield.

an orange residue which could not be either recrystallized or characterized and was then used without purification, 94% yield.

Ethyl N^1-Salicyloyl-N^2-oxamidrazonate (24). Salicylhydrazide (3.75 mmol, 0.6 g) and triethylamine (5.6 mmol, 0.78 mL) were added to a solution of **23** (3.75 mmol, 0.9 g) in CH_2Cl_2 (25 mL). The solution was refluxed for 20 min. Evaporation of the solvent yielded a residue which was worked up with CH_2Cl_2, collected, and recrystallized. ^1H NMR (DMSO-d_6): δ 1.31 (t, 3H, CH_3), 4.29 (q, 2H, CH_2), 6.88–6.96 (m, 4H, ar + NH_2), 7.41 (t, 1H, ar, J = 7.2 Hz), 7.86 (d, 1H, ar, J = 7.2 Hz), 10.29 (s, 1H, exchangeable proton), 11.83 (s, 1H, exchangeable proton). IR: 3400, 3210, 1755, 1740.

Ethyl N^1-(5-Chlorosalicyloyl)-N^2-oxamidrazonate (25). Two separate solutions of **23** (9.36 mmol, 2.2 g) in CH_2Cl_2 (20 mL) and triethylamine (11 mmol, 1.5 mL) in CH_2Cl_2 (20 mL)

were added to a suspension of 5-chlorosalicylhydrazide[21] (5.3 mmol, 1.0 g) in CH_2Cl_2 (400 mL). The mixture was refluxed for 3 h. The orange organic solution was washed three times with water (250 mL each time), dried (Na_2SO_4), and evaporated at reduced pressure to yield a red residue. On treatment with diethyl ether/ethanol (10:1), this afforded a white solid, which was recrystallized. ^{1}H NMR (DMSO-d_6): δ 1.31 (t, 3H, CH_3), 4.29 (q, 2H, CH_2), 6.83–6.99 (m, 4H, ar + NH_2), 7.42 (dd, 1H, ar, J = 8.7, 2.7 Hz), 7.91 (d, 1H, ar, J = 2.7 Hz), 10.3 (br s, 1H, exchangeable proton), 11.9 (br s, 1H, exchangeable proton). IR: 3480, 3460, 3320, 1745, 1730.

Ethyl 5-(2-Hydroxyaryl)-1,2,4-triazole-3-carboxylates 26 and 27. Compound **24** or **25** (6 mmol) was heated in an oil bath over its melting point for 20 min. The cooled fused mass was worked up with diethyl ether, collected, and purified. Compound **26** displayed the following spectral data. ^{1}H NMR (DMSO-d_6): δ 1.36 (t, 3H, CH_3), 4.38 (q, 2H, CH_2), 6.96–7.08 (m, 2H, ar), 7.39 (t, 1H, ar, J = 7.3 Hz), 7.99 (d, 1H, ar, J = 7.3 Hz), 12.4 (br s, 1H, exchangeable proton). IR: 1750, 1620, 1235.

***N*-Aroylsalicylamides 28–45.** The title compounds were prepared from aroyl chloride (1.8 mmol) and salicylamide (1.8 mmol) in pyridine (20 mL), following the method reported in ref 16. The mixture was refluxed for 2 h. Treatment of the cooled solution with ice/water (30 mL) and ethanol (5 mL) afforded a precipitate which was collected, washed with water, and recrystallized. Compound **28** displayed the following spectral data. ^{1}H NMR (DMSO-d_6): δ 3.88 (s, 3H, CH_3), 6.98–7.14 (m, 4H, ar), 7.48 (t, 1H, ar, J = 7.3 Hz), 7.88–7.95 (m, 3H, ar), 11.63 (s, 1H, exchangeable proton), 11.76 (s, 1H, exchangeable proton). IR: 3250, 1720, 1680, 1610.

2-Aryl-1,3-benzoxazin-4-ones 46–64. Method A. Compound **51** was prepared from an equimolar amount (5.8 mmol) of 5-chlorosalicylamide (1.0 g) and benzoyl chloride (0.8 g) following the one-stage process described in ref 15. ^{1}H NMR (DMSO-d_6): δ 7.63–8.01 (m, 6H, ar), 8.35 (d, 2H, ar, J = 7.3 Hz). IR: 1690, 1620.

Method B. Compounds **28–45** (8.3 mmol) were heated over their melting point for 1 h. The crude mass was worked up in three different ways to isolate the title compounds. B-1: The cooled mass containing compounds **47**, **52–53**, **57–58**, **61–62**, and **64** was worked up with diethyl ether/acetone (1:1, 10 mL), collected, washed with petroleum ether (40–60 °C), and recrystallized. Compound **17** could not be recrystallized but was pure enough to be characterized. B-2: The cooled mass containing compounds **46**, **48–50**, **54**, and **59** was dissolved in benzene (200 mL) and washed three times with an iced solution of 3% NaOH (60 mL each time) and two times with water (100 mL each time). The dried (Na_2SO_4) organic layer was evaporated at reduced pressure to afford a residue which was recrystallized. B-3: The cooled mass containing compounds **55–56**, **60**, and **63** was worked up with diethyl ether (10 mL), collected, purified by column chromatography, and recrystallized. Compound **57** could not be recrystallized but was pure enough to be characterized. Unfortunately we were unable to separate compound **63** from the starting material; thus it was not characterized and was used as a mixture in the next reaction. Compound **54** displayed the following spectral data. ^{1}H NMR (DMSO-d_6): δ 7.45–7.55 (m, 2H, ar), 7.75–7.87 (m, 2H, ar), 7.95–8.03 (m, 2H, ar), 8.19–8.27 (m, 1H, ar). IR: 3090, 1700, 1615.

3-Aryl-5-(2-hydroxyaryl)-1,2,4-triazoles 65–83. The title compounds were obtained from **46–64** (3.6 mmol) and hydrazine hydrate (4.7 mmol) following the method described in ref 16. In those instances in which the product precipitated upon cooling (**70–72**, **76–77**, **82–83**), the solid was collected, washed with petroleum ether (40–60 °C), and recrystallized. When a solid product was not present, the cooled solution was diluted with water (100 mL) and the resulting precipitate (**65–66**, **74–75**) was collected, washed with water, and recrystallized. However in some instances, the solution did not give a precipitate upon dilution (**67–69**, **73**, **78–81**); in these instances the mixture was extracted three times with chloroform (100 mL each time). The combined organic layers were washed with water (100 mL), dried (Na_2SO_4), and evaporated at reduced pressure to afford a residue which was recrystallized. In the case of compound **82**, which was yielded by the impure **63**, a purification through column chromatography (see Table 2) was necessary before recrystallization. Compound **73** displayed the following spectral data. ^{1}H NMR (DMSO-d_6): δ 7.08 (d, 1H, ar, J = 8.8 Hz), 7.37–7.48 (m, 3H, ar), 7.53–7.64 (m, 1H, ar), 8.04–8.17 (m, 2H, ar), 11.5 (br s, 1H, OH), 14.5 (br s, 1H, NH). IR: 3300, 1630.

Ethyl 5-Oxo-1,2,4-triazolo[1,5-*c*][1,3]benzoxazine-2-carboxylates 2 and 9 and 2-Aryl-1,2,4-triazolo[1,5-*c*][1,3]-benzoxazin-5-ones 3–8 and 10–22. Triphosgene (0.29 mmol) and triethylamine (1.44 mmol) were successively added to a solution of triazole **26**, **27**, or **65–83** (0.72 mmol) in anhydrous tetrahydrofuran (80 mL). The mixture was stirred at room temperature (minimum 3 h, maximum 17 days). The reaction was monitored by TLC, and subsequent amounts of triphosgene and triethylamine were added until the disappearance of the starting triazole. Elimination of the triethylamine hydrochloride and evaporation at reduced pressure of the solvent yielded a residue which was worked up with anhydrous diethyl ether, collected, and recrystallized. Compound **12** displayed the following spectral data. ^{1}H NMR (DMSO-d_6): δ 7.43–7.53 (m, 2H, ar), 7.63–7.78 (m, 2H, ar), 7.88–7.94 (m, 1H, ar), 8.20–8.27 (m, 2H, ar). IR: 1800, 1825, 1620.

Biochemistry. [^{3}H]Flunitrazepam binding assays on bovine cerebral cortex were carried out as previously described.[26]

Supplementary Material Available: ^{13}C NMR spectral data of some significant 1,2,4-triazolobenzoxazines (1 page). Ordering information is given on any current masthead page.

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