Structure–Activity Relationships of 1,2,4-Triazolo[1,5-*a*]quinoxalines and Their 1-Deaza Analogues Imidazo[1,2-*a*]quinoxalines at the Benzodiazepine Receptor

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The synthesis, BZR binding activity, and GABA ratio of some 1,2,4-triazolo[1,5–*a*]quinoxalines and imidazo[1,2-*a*]quinoxalines are reported. Both series of compounds displayed similar affinities while their efficacies were different. The structure–activity relationships have provided the opportunity to localize on the BZR accessory areas which are able to enhance the affinity and evaluate the importance of the presence or absence of a proton acceptor atom to determine different trends of efficacy.

Introduction

The benzodiazepine receptor (BZR) is unique in the way it responds to three different types of ligands, which act as allosteric modulators of the $GABA_A$ receptor complex. In fact, allosteric modulators can either enhance (agonists) or reduce (inverse agonists) the GABA-induced Cl^- ion flux. A third group of ligands, interacting with the allosteric site of $GABA_A$ receptor (BZR), does not influence GABA-induced ion flux but antagonizes (antagonists) the actions of the agonists and inverse agonists.

The interrelationships of these three types of BZR ligands can be explained on the basis of changes in the conformation of the receptor from its unoccupied resting state. An argument for the homogeneity of BZR binding sites might lie in the fact that the activities displayed after minor structural modifications of compounds with similar binding interaction, i.e. Ro 15-1788 and Ro 15-3505, β-carbolines and pyrazoloquinolines, range across the whole spectrum of efficacy.[1]

Thus all compounds that bind to the BZR should have certain common characteristics that allow for recognition by the receptor regardless of the type of "in vivo" activity. The latter could be roughly determined "in vitro" using the GABA ratio, i.e. the ratio between the receptor affinity of a ligand measured as the concentration of the displacer able to inhibit 50% of radioligand binding (IC_{50}) in the absence of GABA and in its presence.

Rationalization of the common structural requirements for the binding of 6,6,5-tricyclic heteroaromatic systems to the BZR has led us to the synthesis of nearly two hundred compounds of similar size and shape.[2–16] More recently our interest has been focused on the synthesis of some 1,2,4-triazolo[1,5-*a*]quinoxalines.[16] In this paper, in accordance with a reported model,[17] we identified a series of pharmacophoric descriptors (Figure 1): (i) two lipophilic areas, called L_1 and L_2, corresponding to the fused benzo ring and to the 2-substituent, respectively; (ii) a hydrogen donor site, called d, and corresponding to the NH of the six-membered heterocyclic ring; (iii) two proton acceptor sites, called a_1 and a_2, corresponding to the nitrogen at position-1 and to the nitrogen at position-3 and/or the carbonyl oxygen at position-4. The lone pair orientation of the nitrogen at position-3 and carbonyl oxygen at position-4 suggests the presence of a three-centered hydrogen bonding formation which strongly reinforces the receptor–ligand interaction.

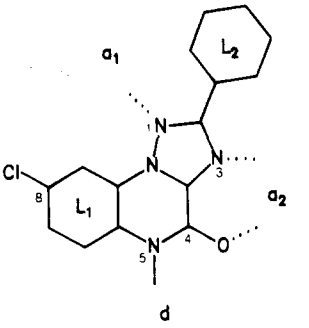

Figure 1. Two-dimensional schematic representation of BZR binding site using as template the 4,5-dihydro-2-phenyl-8-chloro-1,2,4-triazolo[1,5-*a*]quinoxalin-4-one.[16] L_1 and L_2 designate the lipophilic regions of hydrophobic interactions; a_1 and a_2 are hydrogen bond acceptor atoms. The latter, due to the lone pair orientation of the nitrogen at position-3 and carbonyl oxygen at position-4, engages a favorable three-centered hydrogen bond with a proton donor of the receptor site; d represents the hydrogen donor site.

The promising binding data on some triazoloquinoxalines led us to the synthesis of further 1,2,4-triazoloquinoxaline derivatives **1–14** and of some imidazo[1,2-*a*]quinoxalines **68–70, 74**. These 1-deaza analogues of **1–14**, although reported in a recent patent,[18] were synthesized specifically to probe the importance in the BZR affinity and efficacy of the nitrogen at position-1.

Chemistry

The synthesis of the 4,5-dihydro-2-aryl-1,2,4-triazolo-[1,5-*a*]quinoxalin-4-ones **1–14** is shown in Scheme 1. In brief, by reacting the arylhydrazines **15a–c**[19–20] with aroyl chlorides, the aroyl hydrazines **16–27**[21] were prepared. The latter were transformed into the α-chloroarylidene derivatives **28–39** which, when treated with ammonia, gave the amidrazones **40–51**.

Reaction of compounds **40, 42–44, 46, 47, 50**, and **51** with ethyl oxalyl chloride directly yielded the ethyl 1,3-diaryl-1,2,4-triazole-5-carboxylates **52, 54–56, 58, 59,**

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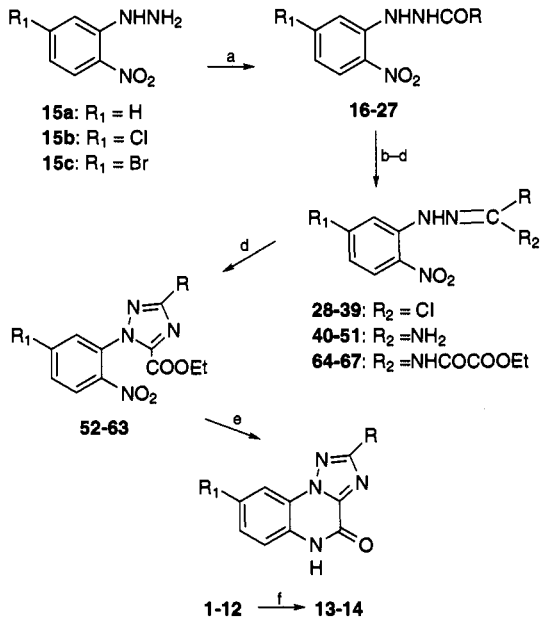
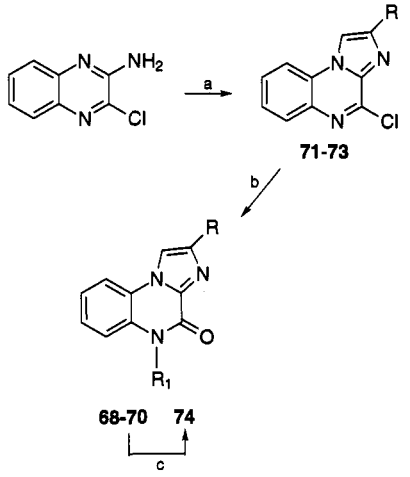
Scheme 1[a]



[a] (a) RCOCl; (b) $POCl_3$; (c) NH_3 (g); (d) ClCOCOOEt; (e) Fe/CH_3COOH; (f) HBr/CH_3COOH.

Scheme 2[a]



[a] (a) $RCOCH_2Br$; (b) 3% NaOH in dioxane; (c) NaH and MeI.

62, and **63** while compounds **41**, **45**, **48**, and **49** with the same reagent yielded a mixture of the triazoles **53**, **57**, **60**, **61** and N^3-ethoxalyl derivatives **64–67**. After separation of the mixture, the intermediates **64–67** were heated over their melting points to give a second crop of the triazoles **53**, **57**, **60**, and **61**. Reduction of **52–63** afforded the tricyclic derivatives **1–12**. Demethylation of the 2-(4-methoxyphenyl) compounds **11** and **12** produced the 2-(4-hydroxyphenyl)-substituted **13** and **14**.

Finally the synthesis of the 2-substituted imidazo[1,2-*a*]quinoxalin-4-ones **68–70** was performed (see Scheme 2). By reacting the 3-chloro-2-quinoxalinamine[22] with bromomethyl aryl ketones[23] were obtained the 4-chloroimidazoquinoxalines **71–73**. Nucleophilic replacement of the 4-chloro substituent of **71–73** with alkali yielded the cyclic amides **68–70**. N-Alkylation of **68** afforded the 5-*N*-methyl derivative **74**.

Biochemistry

The triazoloquinoxalines **1–14** and their 1-deaza analogues imidazoquinoxalines **68–70**, and **74** were tested for their ability to displace [^{3}H]flunitrazepam (at 0.2 nM, K_D = 1.8 nM) from its specific binding in bovine brain membranes. The percentage of inhibition (I%) was at first 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_i, used to define the BZR affinity, and the GABA ratio, which according to different authors[24–26] generally predicts the expected behavioral properties of a BZR ligand, were derived. The binding results are listed in Table 1.

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

compd	R	R_1	K_i (nM)[b]	GR[c]
1	2-furyl	H	71.2 ± 9.1	1.05
2	2-furyl	Cl	14.5 ± 1.6	0.67
3	2-furyl	Br	13.2 ± 1.4	0.77
4	3-furyl	Cl	9.8 ± 1.1	0.84
5	2-thienyl	H	21.8 ± 2.0	0.92
6	2-thienyl	Cl	17.4 ± 1.9	1.09
7	3-thienyl	Cl	15.9 ± 1.3	0.80
8	2-FC_6H_4	H	8.9 ± 0.9	1.04
9	2-FC_6H_4	Cl	2.9 ± 0.4	0.77
10	3-FC_6H_4	Cl	32.8 ± 1.8	0.82
11	4-$MeOC_6H_4$	H	87.8 ± 9.5	1.04
12	4-$MeOC_6H_4$	Cl	5.4 ± 0.7	1.03
13	4-HOC_6H_4	H	67.5 ± 5.2	0.90
14	4-HOC_6H_4	Cl	29.8 ± 3.1	0.88
68	C_6H_5	H	42.3 ± 5.0	1.36
69	4-$MeOC_6H_4$	H	56.4 ± 4.3	1.21
70	2-thienyl	H	15.9 ± 1.1	1.13
74	C_6H_5	Me	2 (10 μM)[d]	

[a] The tests were carried out using DMSO as solvent. [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] Percentage of inhibition (I%) of [^{3}H]flunitrazepam binding at 10 μM concentration, as shown in brackets.

Results and Conclusions

The binding results listed in Table 1 show that the triazoloquinoxalines **1–14** and their 1-deaza analogues imidazoquinoxalines **68–70** are equipotent, displaying a BZR affinity ranging from 3 to 90 nM.

As previously observed,[16] the 5-N-alkylation is detrimental to the receptor binding. In fact, the 5-*N*-methylimidazoquinoxaline **74** is devoid of BZR affinity.

The GABA ratios[24–26] indicate a different trend in the efficacies of the reported compounds. In fact the GABA ratio values of the triazoloquinoxalines **1–14** show that they may function as antagonists/partial inverse agonists (GABA ratio close to or below 1) while those of the imidazoquinoxalines **68–70** are that of partial agonists (GABA ratio above 1). Since the only difference between **1–14** and **68–70** is the presence or absence of the nitrogen at position-1, respectively, their discrepancy in efficacies may be caused by this nitrogen atom.

The only two other variables on the reported compounds **1–14** and **68–70** are the substituent at position-8 and the aryl at position-2. There is evidence in the binding data shown in Table 1 for nonadditive 8-substituent effects. In general the presence of the 8-halo substituent produces a small increase of binding potency except the 8-chloro-4-methoxyphenyl-substituted **12** which is 16-fold more potent than the corresponding 8-H analogue **11**. There are not obvious reasons to justify the increased potency of **12** versus **11**. We may only suggest that the presence of the 8-halo atom combined with that of the 4-methoxy group on the 2-phenyl moiety produces a steric effect that ameliorates

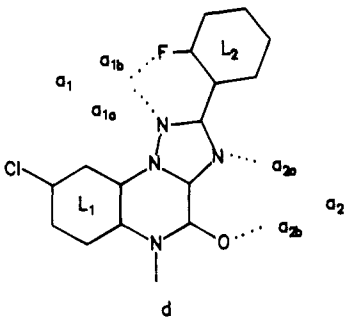


Figure 2. Modified representation of BZR binding site using compound **9** as template. The two proton-accepting regions a_1 and a_2 are each divided into two subregions, indicated by a_{1a}–a_{1b} and a_{2a}–a_{2b}, respectively.

the anchoring of **12** to the recognition site of the BZR. A previous finding[16] indicated that the 8-methyl substituent also enhanced the receptor affinity and that displacement of the halo-substituent from position-8 to position-7 resulted in a reduction in binding activity. Taking together the present and previous findings, we may suggest that an accessory area, which is able to sterically accommodate the 8-substituent, is present in the recognition site of the BZR.

The results also show that the introduction of another proton-accepting atom such as the furan oxygen, the thiophene sulfur, and, most importantly, the 2-fluoro substituent on the 2-phenyl moiety, also increases the receptor affinity, especially when combined with the presence of the 8-halo substituent. The presence of this new proton acceptor atom prompted us to propose the slightly-modified model shown in Figure 2. The model is built taking the most active compound **9** as template. In this modified model the two proton-accepting regions a_1 and a_2 are each divided into two subregions, called a_{1a}–a_{1b} and a_{2a}–a_{2b}, respectively. It has to be noted that, due to the free rotation of the substituent at position-2 around the σ bond, the a_{1b} proton acceptor could fall in the a_2 area, reinforcing the three-centered hydrogen bonding interaction in this region.

In conclusiton, the synthesis of the triazoloquinoxalines **1**–**14** and that of their 1-deaza analogues imidazoquinoxalines **68**–**70**, their binding results, and their structure–activity relationships have provided the opportunity to localize on the BZR recognition site accessory areas, which are able to enhance the affinity, and evaluate the importance of the presence or absence of proton acceptor nitrogen in the a_1 region to determine different trends of efficacy.

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 were 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 ^1H NMR spectra were obtained with a Varian Gemini 200 instrument at 200 MHz. The chemical shifts are reported in δ (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, ar = aromatic protons. The physical data of the newly synthesized compounds are shown in Table 2.

***N*¹-(2-Nitroaryl)-*N*²-aroylhydrazines 16–27. Method A.** Aroyl chloride (17.9 mmol) was slowly added to a solution of

Table 2. Physical Data of the Reported Compounds

compd	R	R_1	mp, °C (solvent)[a]	% yield
1	2-furyl	H	>300 (A)	44
2	2-furyl	Cl	>300 (A)	70
3	2-furyl	Br	>300 (A)	70
4	3-furyl	Cl	>300 (A)	85
5	2-thienyl	H	>300 (A)	62
6	2-thienyl	Cl	>300 (A)	77
7	3-thienyl	Cl	>300 (A)	67
8	2-FC_6H_4	H	>300 (A)	76
9	2-FC_6H_4	Cl	>300 (A)	90
10	3-FC_6H_4	Cl	>300 (A)	50
11	4-$MeOC_6H_4$	H	>300 (A)	66
12	4-$MeOC_6H_4$	Cl	>300 (A)	40
13	4-HOC_6H_4	H	>300 (A)	40
14	4-HOC_6H_4	Cl	>300 (A)	66
16	2-furyl	H	132–134 (B)	90
17	2-furyl	Cl	154–156 (B)	65
18	2-furyl	Br	177–179 (B)	73
19	3-furyl	Cl	140–142 (B)	74
20	2-thienyl	H	150–152 (B)	93
21	2-thienyl	Cl	140–142 (B)	80
22	3-thienyl	Cl	158–160 (B)	40
23	2-FC_6H_4	H	183–185 (C)	54
24	2-FC_6H_4	Cl	196–198 (C)	49
25	3-FC_6H_4	Cl	176–178 (C)	92
26[b]	4-$MeOC_6H_4$	H	178–180 (C)	70
27	4-$MeOC_6H_4$	Cl	227–229 (C)	62
28	2-furyl	H	126–128 (D)	40
29	2-furyl	Cl	169–171 (D)	60
30	2-furyl	Br	127–129 (E)	51
31	3-furyl	Cl	135–137 (C)	68
32	2-thienyl	H	117–119 (C)	47
33	2-thienyl	Cl	163–165 (D)	78
34	3-thienyl	Cl	150–152 (D)	72
35	2-FC_6H_4	H	108–110 (D)	76
36	2-FC_6H_4	Cl	160–162 (D)	50
37	3-FC_6H_4	Cl	165–167 (D)	35
38	4-$MeOC_6H_4$	H	129–131 (D)	49
39	4-$MeOC_6H_4$	Cl	159–161 (D)	66
40	2-furyl	H	146–148 (D)	73
41	2-furyl	Cl	163–165 (D)	79
42	2-furyl	Br	159–161 (C)	79
43	3-furyl	Cl	144–146 (D)	80
44	2-thienyl	H	145–147 (B)	85
45	2-thienyl	Cl	194–196 (D)	80
46	3-thienyl	Cl	187–189 (B)	91
47	2-FC_6H_4	H	181–183 (C)	78
48	2-FC_6H_4	Cl	158–160 (C)	76
49	3-FC_6H_4	Cl	172–174 (C)	83
50	4-$MeOC_6H_4$	H	154–156 (C)	82
51	4-$MeOC_6H_4$	Cl	157–159 (C)	93
52	2-furyl	H	174–176 (F)	53
53	2-furyl	Cl	174–176 (G)	60
54	2-furyl	Br	173–175 (D)	33
55	3-furyl	Cl	141–143 (D)	36
56	2-thienyl	H	183–185 (F)	56
57	2-thienyl	Cl	186–188 (G)	55
58	3-thienyl	Cl	159–161 (G)	70
59	2-FC_6H_4	H	156–158 (G)	61
60	2-FC_6H_4	Cl	175–177 (G)	68
61	3-FC_6H_4	Cl	171–173 (D)	70
62	4-$MeOC_6H_4$	H	170–172 (F)	60
63	4-$MeOC_6H_4$	Cl	201–203 (G)	70
64	2-furyl	Cl	168–169 (F)	40
65	2-thienyl	Cl	187–189 (F)	30
66	2-FC_6H_4	Cl	167–169 (F)	30
67	3-FC_6H_4	Cl	184–186 (F)	36
68	C_6H_5	H	>300 (C)	83
69	4-$MeOC_6H_4$	H	>300 (I)	93
70	2-thienyl	H	>300 (I)	80
71	C_6H_5		169–170 (H)	55
72	4-$MeOC_6H_4$		215–216 (H)	45
73	2-thienyl		164–165 (H)	40
74	C_6H_5	Me	>300 (J)	87

[a] Recrystallization solvents: A = acetone, B = ethanol/water, C = ethanol, D = cyclohexane/ethyl acetate, E = ethanol/diethyl ether, F = toluene, G = ethyl acetate, H = column chromatography, eluting system: chloroform/ethyl acetate, 9:1, I = water/dioxane, J = glacial acetic acid. [b] Previously described, ref 21.

the suitable hydrazine (16.3 mmol) in ethanol/pyridine (15:1, 32 mL). The mixture was heated at reflux for 1 h. Upon cooling and dilution with water (25 mL) a solid precipitated which was collected and recrystallized. By this method compounds **17**–**22** were prepared.

Method B. Aroyl chloride (17.9 mmol) was slowly added to a solution of **15a** (16.3 mmol) in pyridine (50 mL). The mixture was heated at reflux for 0.5 h. Evaporation of the solvent at reduced pressure afforded a residue which was acidified with 2 N HCl. The resulting solid was collected, washed with water, and recrystallized. By this method compounds **16** and **23** were prepared.

Method C. A solution of the suitable hydrazine (16.3 mmol) and aroyl chloride (17.9 mmol) in pyridine (50 mL) was heated at reflux for 0.5 h. Evaporation of the pyridine at reduced pressure afforded a residue which was treated as described in method B. By this method compounds **24**–**27** were prepared. Compound **21** displayed the following spectral data: IR 3380, 3330, 1665; ^{1}H NMR (DMSO-d_6) 6.93 (dd, 1H, ar, J = 9.19 Hz, J = 1.83 Hz), 7.11 (d, 1H, ar, J = 1.91 Hz), 7.22–7.27 (m, 1H, ar), 7.86–7.97 (m, 2H, ar), 8.16 (d, 1H, ar, J = 9.16 Hz), 9.65 (s, 1H, NH), 10.86 (s, 1H, NH).

***N*^{1}-(2-Nitroaryl)-*N*^{2}-(α-chloroarylidene)hydrazines 28–39.** A solution of the suitable hydrazide **16**–**27** (4 mmol) in $POCl_3$ (11 mL) was heated at reflux for 1 h. The excess of $POCl_3$ was removed at reduced pressure and the residue was treated with cyclohexane (30 mL). Evaporation of the solvent under vacuum afforded a crude product which was recrystallized.

Compound **33** displayed the following ^{1}H NMR ($CDCl_3$): 6.89 (dd, 1H, ar, J = 9.24 Hz, J = 2.32 Hz), 7.06–7.11 (m, 1H, ar), 7.44–7.58 (m, 2H, ar), 7.82–7.83 (m, 1H, ar), 8.16 (d, 1H, ar, J = 10.42 Hz), 11.29 (s, 1H, NH).

***N*^{1}-(2-Nitroaryl)-*N*^{2}-(α-aminoarylidene)hydrazines 40–51.** The title compounds were prepared from the suitable α-chloroarylidene derivatives **28**–**39** as described in ref 16.

Compound **45** displayed the following spectral data: IR 3500, 3380, 3290; ^{1}H NMR ($CDCl_3$) 4.8 (br s, 2H, NH_2), 6.73 (dd, 1H, ar, J = 9.11 Hz, J = 2.20 Hz), 7.09–7.14 (m, 1H, ar), 7.38–7.45 (m, 2H, ar), 7.75–7.76 (m, 1H, ar), 8.11 (d, 1H, ar, J = 9.16 Hz), 10.09 (s, 1H, NH).

Ethyl 1-(2-Nitroaryl)-3-aryl-1,2,4-triazole-5-carboxylates 52, 54–56, 58, 59, 62, and 63. The title compounds were obtained from the corresponding amidrazones **40**, **42**–44, **46**, **47**, **50**, and **51** and ethyl oxalyl chloride as described in ref 16.

Compound **58** displayed the following spectral data: IR 1725; ^{1}H NMR ($CDCl_3$) 1.36 (t, 3H, CH_3), 4.41 (q, 2H, CH_2), 7.39–7.43 (m, 1H, ar), 7.63–7.73 (m, 3H, ar), 8.11–8.12 (m, 1H, ar), 8.24 (d, 1H, ar, J = 8.79 Hz).

***N*^{1}-(2-Nitroaryl)-*N*^{2}-[α-(ethoxalylamino)arylidene]hydrazines 64–67 and Ethyl 1-(2-Nitroaryl)-3-aryl-1,2,4-triazole-5-carboxylates 53, 57, 60, and 61.** By reacting the amidrazones **41**, **45**, **48**, and **49** with ethyl oxalyl chloride in the same conditions as described above, a mixture of the intermediates **64**–**67** and triazoles **53**, **57**, **60**, and **61** was obtained, rather than the triazoles directly. Upon cooling the solution, the intermediates **64**–**67** precipitated. Evaporation of the solvent at reduced pressure afforded the crude triazoles **53**, **57**, **60**, and **61**. A second crop of the latter was obtained by heating the intermediates **64**–**67** over their melting points.

Compound **65** displayed the following spectral data: IR 3310, 3120, 1705; ^{1}H NMR ($CDCl_3$) 1.49 (t, 3H, CH_3), 4.50 (q, 2H, CH_2), 6.84–6.89 (m, 1H, ar), 7.07–7.11 (m, 1H, ar), 7.26–7.32 (m, 1H, ar), 7.45–7.47 (m, 1H, ar), 7.93–7.94 (m, 1H, ar), 8.12–8.22 (m, 1H, ar), 8.94 (s, 1H, NH), 10.91 (s, 1H, NH).

4,5-Dihydro-2-aryl-1,2,4-triazolo[1,5-*a*]quinoxalin-4-ones 1–12. The title compuonds were obtained by reduction of **52**–**63** (1 mmol) with iron (1 g) in glacial acetic acid (6 mL) as described in ref 27.

Compound **1** displayed the following spectral data: IR 1695; ^{1}H NMR (DMSO-d_6) 6.76–6.86 (m, 1H, ar), 7.25–7.27 (m, 1H, ar), 7.37–7.54 (m, 3H, ar), 7.98–7.99 (m, 1H, ar), 8.13 (d, 1H, ar, J = 7.69 Hz), 12.45 (s, 1H, NH).

4,5-Dihydro-2-(4-hydroxyphenyl)-8-R$_1$-1,2,4-triazolo-[1,5-*a*]quinoxalin-4-ones 13 and 14. A mixture of **11** and **12** (1 mmol), glacial acetic acid (8 mL), and HBr (48%, 9 mL) was heated at reflux for 96 h. Upon cooling a solid precipitated; this was collected, treated with a saturated solution of Na_2CO_3, and recrystallized.

Compound **13** displayed the following spectral data: IR 3460–3100, 1685; ^{1}H NMR (DMSO-d_6) 6.95 (d, 2H, ar, J = 8.71), 7.37–7.54 (m, 3H, ar), 8.05–8.33 (m, 3H, ar), 10.0 (br s, 1H, OH), 12.4 (br s, 1H, NH).

2-Aryl-4-chloroimidazo[1,2-*a*]quinoxalines 71–73. A mixture of 3-chloro-2-quinoxalinamine[22] (4.47 mmol) and the suitable bromomethyl aryl ketone[23] (2.76 mmol) was heated at 150 °C for 1 h under nitrogen flow. The resulting crude mass was purified by column chromatography.

Compund **71** displayed the following ^{1}H NMR (DMSO-d_6): 7.36–7.59 (m, 3H, ar), 7.65–7.73 (m, 1H, ar), 7.79–7.89 (m, 1H, ar), 8.01–8.11 (m, 3H, ar), 8.40 (d, 1H, ar, J = 8.34 Hz), 9.51 (s, 1H, H-1).

4,5-Dihydro-2-arylimidazo[1,2-*a*]quinoxalin-4-ones 68–70. A suspension of **71**–**73** (0.72 mmol) in a solution of NaOH (7.2 mmol in 10 mL of water) and dioxane (5 mL) was heated at reflux for 1 h. Upon cooling a colorless solid precipitated; this was collected, washed with water, and recrystallized.

Compound **68** displayed the following spectral data: IR 1710; ^{1}H NMR (DMSO-d_6) 7.13–7.20 (m, 1H, ar), 7.30–7.40 (m, 3H, ar), 7.43–7.52 (m, 2H, ar), 7.96–8.08 (m, 3H, ar), 8.95 (s, 1H, H-1).

4,5-Dihydro-2-phenyl-5-methylimidazo[1,2-*a*]quinoxalin-4-one (74). The title compound was prepared by reacting **68** (0.57 mmol) with NaH (1.15 mmol) and MeI (0.86 mmol) following the procedure described in ref 16: IR 1720; ^{1}H NMR (DMSO-d_6) 3.70 (s, 3H, CH_3), 7.36–7.70 (m, 6H, ar), 8.01–8.04 (m, 2H, ar), 8.19–8.20 (m, 1H, ar), 9.14 (s, 1H, H-1).

Biochemistry. [^{3}H]Flunitrazepam binding assays on bovine cerebral cortex were carried out as previously described.[15]

Supplementary Material Available: Copies of ^{1}H NMR and IR spectra of compounds in Table 2 (7 pages). Ordering information is given on any current masthead page.

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