Antagonist, Partial Agonist, and Full Agonist Imidazo[1,5-a]quinoxaline Amides and Carbamates Acting through the $GABA_A$/Benzodiazepine Receptor†

Ruth E. TenBrink,*‡ Wha B. Im,§ Vimala H. Sethy,§ Andrew H. Tang,§ and Don B. Carter§

Departments of Medicinal Chemistry and Central Nervous System Diseases, Upjohn Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

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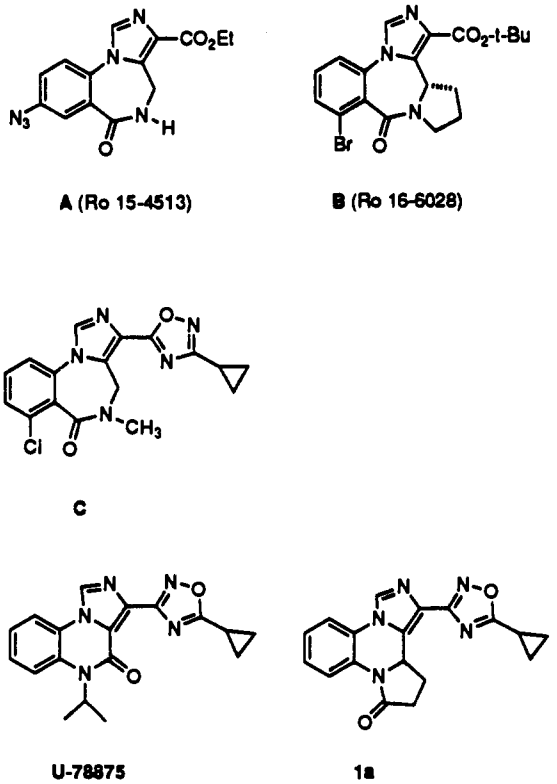
(4*RS*)-1-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-12,12a-dihydroimidazo[1,5-*a*]pyrrolo[2,1-*c*]quinoxalin-10(11*H*)-one (**1a**), 5-benzoyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydroimidazo[1,5-*a*]quinoxaline (**13b**), and *tert*-butyl (4*S*)-12,12a-dihydroimidazo[1,5-*a*]pyrrolo[2,1-*c*]quinoxaline-1-carboxylate (**1e**), as well as other imidazo[1,5-*a*]quinoxaline amides and carbamates, represent a new series of compounds which bind with high affinity to the $GABA_A$/benzodiazepine receptor. These compounds exhibit a wide range of intrinsic efficacies as measured by [^{35}S]TBPS binding ratios. The synthesis of **1a** begins with the addition of DL-glutamic acid to 1-fluoro-2-nitrobenzene, followed by reduction of the nitro group and subsequent ring closure to form 3-(carbethoxymethyl)-1,2,3,4-tetrahydroquinoxalin-2-one, followed by a second ring closure to afford (4*RS*)-1,5-dioxo-1,2,3,4,5,6-hexahydropyrrolo[1,2-*a*]quinoxaline as the key intermediate. Appendage of a substituted imidazo ring via the anion of 5-cyclopropyl-1,2,4-oxadiazol-3-yl gives **1a**. The (−)- and (+)-isomers of **1a** were prepared from 1-fluoro-2-nitrobenzene and L- and D-glutamic acid, respectively. **1a** and its enantiomers demonstrated affinity for the [^{3}H]flunitrazepam binding site with K_i's of 0.87, 0.62, and 0.65 nM, respectively.

Introduction

1,4-Benzodiazepines constitute a class of effective and widely-prescribed agents for the treatment of anxiety and sleep disorders.[1] The benzodiazepine binding site is part of the $GABA_A$/chloride channel complex and is composed of α, β, and γ subunits in various combinations.[2-4] Compounds which bind to the receptor complex may elicit inverse agonist, antagonist, or full agonist properties or may fall at some intermediate point within that spectrum.[5] Full agonists exert a maximal response at the $GABA_A$ receptor and, as such, frequently exhibit ethanol potentiation, amnesia, muscle relaxation, and physical dependency as side effects. Partial agonists are of particular interest due to their expected lower incidence of these side effects.[6] Attempts have been made to correlate the common features of various compounds in order to gain insight into the structure of the receptor and to aid in the design of new therapeutic agents.[7]

Ro 15-4513 (**A**, Chart 1) illustrates a series of benzodiazepines with an imidazo ester appended to the 1,2-position of the benzodiazepine ring system. The Roche group further modified the ring system to produce **B**, wherein a five-membered carbocyclic ring was appended to the benzodiazepine ring system to produce a partial agonist.[8] More recently, Skolnick *et al.* have prepared a series of imidazo[1,5-*a*]benzodiazepine esters with varying affinities at the benzodiazepine-sensitive and -insensitive receptor subtypes.[9] Wajten *et al.* replaced the imidazo ester with substituted oxadiazoles to give a series of oxadiazolylimidazobenzodiazepines, an example of which is **C**, with partial agonist activity.[10] Wajten further modified the system by contracting the seven-membered ring of the benzodiazepine system to imidazo[1,5-*a*]-quinoxalin-4-ones with a range of inverse, partial, and full agonist activities.[11] One of these compounds, U-78875 (Chart 1) was developed as an anxiolytic with antagonist/partial agonist properties.[12]

Chart 1. Selected Benzodiazepine/$GABA_A$ Receptor Ligands



In general, intrinsic efficacy is linked to modulation of the movement of chloride ions through the ion channel of the $GABA_A$ receptor. A ligand may alter movement of chloride ions in a manner that ranges from a positive increase (high intrinsic efficacy) to neutral to a negative effect on chloride ion flux. Diazepam is the prototypical full agonist (high efficacy ligand); it is chosen to represent

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‡ Department of Medicinal Chemistry.
§ Department of Central Nervous Systems Diseases.
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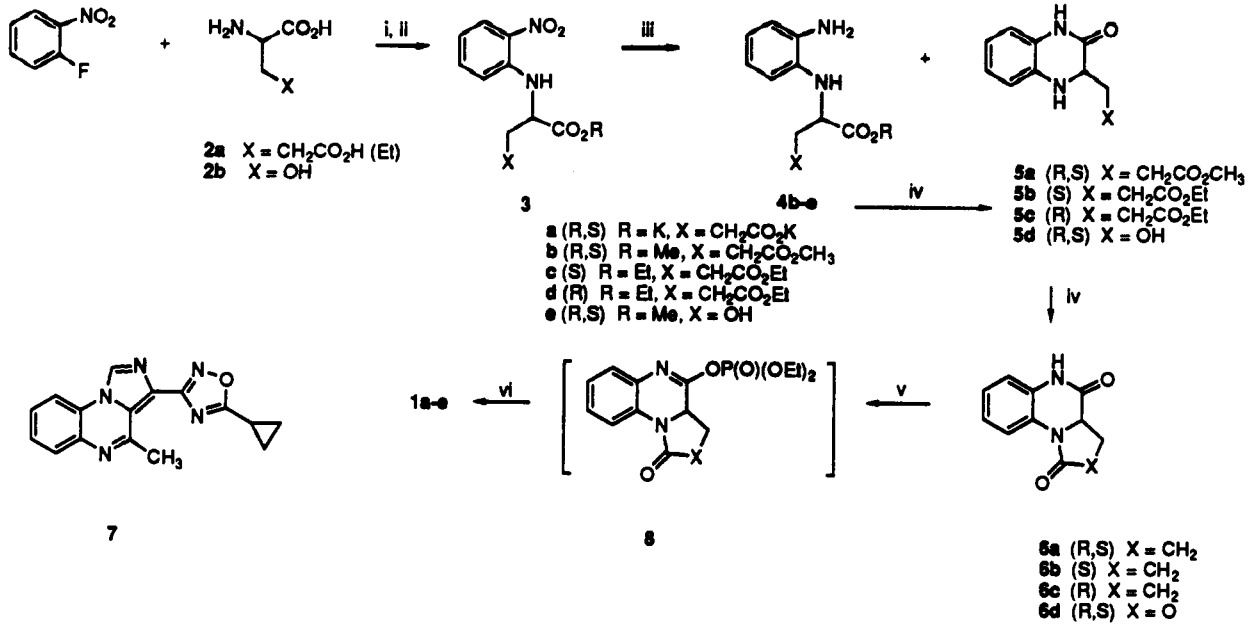
Scheme 1[a]



[a] Reagents: (i) glutamic acid, K_2CO_3, H_2O, EtOH; (ii) MeI, K_2CO_3, DMF; (iii) H_2, 10% Pd on carbon, MeOH; (iv) 60 °C or CDI, THF, 80 °C for **5d**; (v) (1) 1 M *t*-BuOK, THF, DMF, (2) diethyl chlorophosphate; (vi) 1 M *t*-BuOK, 5-cyclopropyl-3-(isocyanomethyl)-1,2,4-oxadiazole (**9**) or *tert*-butyl isocyanoacetate.

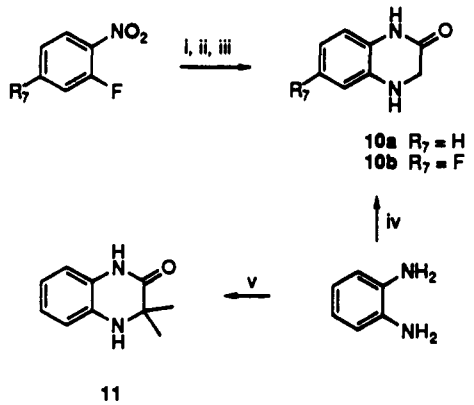
full (positive) opening of the ion channel to the movement of chloride ions. A neutral ligand will occupy the receptor, but by itself have no effect on ion flux and thus exhibit neutral efficacy; an inverse agonist (typified by certain β-carbolines) will cause a negative change in ion movement. Though diazepam is chosen to represent a full agonist, as measured by its effects on the ion channel (ascertained directly by measurements of chloride flux or indirectly by measuring changes in [^{35}S]TBPS shift), the choice is essentially arbitrary and ligands which elicit an even stronger positive modulatory response as compared to diazepam can be found (i.e., superagonists; *vide infra*).

We report herein a series imidazo[1,5-*a*]quinoxaline amides and carbamates with high affinity for the $GABA_A$/benzodiazepine receptor and with intrinsic efficacies indicating a range of inverse agonist, antagonist, and partial, full, and super agonist (i.e., greater than diazepam) properties.

Chemistry

The preparation of tricyclic compounds **1a–e** is illustrated by the synthesis of **1a** (Scheme 1). 1-Fluoro-2-nitrobenzene and DL-glutamic acid (**2a**) were refluxed in water and ethanol with potassium carbonate to give **3a**. The solvents were removed under reduced pressure and replaced with DMF, and diesterification with methyl iodide proceeded to give **3b** in 85% overall yield from 1-fluoro-2-nitrobenzene. Glutamic acid diethyl ester may be used in place of glutamic acid, but losses are suffered due to competing dimerization of the amino acid diester to the diketopiperazine. Reduction of the nitro group of **3b** with hydrogen and 10% Pd/C as catalyst gave a mixture of **4b** and **5a**. Upon standing or brief heating, **4b** cyclized to **5a**, and continued heating gave tricyclic dihydroquinoxalinone lactam **6a**. When DL-serine was used as the amino acid component, intermediate **5d** was heated with 1,1′-carbonyldiimidazole to effect ring closure to **6d**. Treatment of **6a–c** with potassium *tert*-butoxide, followed by addition of diethyl chlorophosphate, gave intermediate **8**, which after addition of 5-cyclopropyl-3-(isocyanomethyl)-1,2,4-oxadiazole (**9**) or *tert*-butyl isocyanoacetate and potassium *tert*-butoxide gave **1a–e**. A major side reaction in the preparation of **1d** was **7**, which may be envisioned as resulting from removal of the C-4 proton of **6d** under the strongly basic conditons, followed by loss of CO_2.

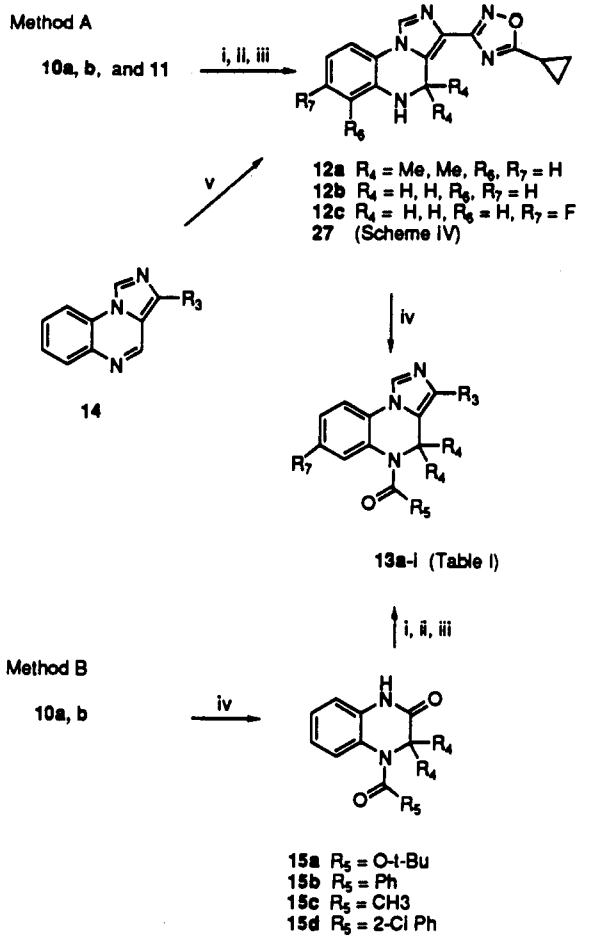
Scheme 2[a]



[a] Reagents: (i) ethylglycine, EtN*i*-Pr$_2$, CH_3CN; (ii) H_2, 10% Pd on carbon, MeOH; (iii) stirring with or without *p*-TsOH; (iv) ethyl 2-bromoacetate, EtN*i*-Pr$_2$, THF; (v) ethyl 2-bromoisobutyrate, EtN*i*-Pr$_2$, DMF, 80–100 °C.

Schemes 2 and 3 depict the routes used to prepare the tetrahydroquinoxalinone intermediates used in the preparation of the nonconstrained amide analogs **13a–l**. 1-Fluoro-2-nitrobenzene and ethylglycine afforded *N*-(2-nitrophenyl)glycine ethyl ester, which after reduction and ring closure gave **10a**. A simpler, one-step route to **10a** used *o*-phenylenediamine and ethyl bromoacetate. Interestingly, the addition of ethyl 2-bromoisobutyrate to *o*-phenylenediamine in the presence of Hunig's base and DMF at 80–100 °C led to **11** in 76% yield. Lai has prepared **11** from *o*-phenylenediamine, acetone, chloroform, and aqueous NaOH under phase-transfer conditions.[13] Aspinall, in 1940, prepared 3,3-dimethyl-2-ketopiperazine in 40% yield from ethylenediamine and ethyl 2-bromoisobutyrate, hypothesizing as the initial step a low-

Scheme 3[a]



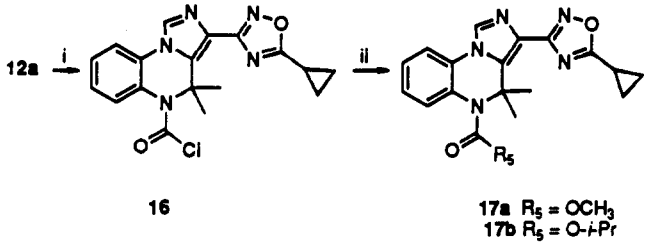
[a] Reagents: (i) *t*-BuOK, THF; (ii) diethyl chlorophosphate; (iii) **9**, *t*-BuOK, THF; (iv) R_3COCl or $(R_3CO)_2O$; (v) $NaCNBH_3$, MeOH.

temperature alkylation, followed by a high temperature (200 °C) ring closure to form 2-keto-3,3-dimethylpiperazine.[14] That mechanism seems unlikely in our case, where an anilino nitrogen replaces a primary alkylamine and lower temperatures are used. In the event, formation of the phosphate intermediates analogous to **8** from **10a**, **10b**, and **11**, followed by the addition of the anion of isocyanide **9**, led to **12a–c** (Scheme 3, method A). After being allowed to stand for several days unprotected from oxygen, **12b** was observed to be slowly converted to imine **14**. Reduction of **14** back to **12b** was accomplished in excellent yield with $NaCNBH_3$ in MeOH. Finally, acylation of **12a–c** and **27** (Scheme 6) gave **13a–c** and **13g–l**; **12a** was sluggish at best with all but the most reactive acylating agents. In method B, intermediate **10a** was first acylated to give amides **15b–d** or carbamate **15a**, followed by formation of the imidazo ring under the standard conditions to give **13d–f**.

Carbamate analogs **17a** and **17b** were prepared by treatment of **12a** with phosgene to give **16** (Scheme 4). Intermediate **16** may be isolated and stored for a time if so desired but is most conveniently treated directly with an alkoxide anion to give **17a** and **17b**. The *N,O*-oxadiazole compound **20** was prepared by the route depicted in Scheme 5. Ethyl isocyanoacetate was used to form the imidazo ester **18**.[15] Addition of cyclopropyl carboxamide oxime[11] in the presence of sodium hydride gave **19**, which after acylation gave **20**.

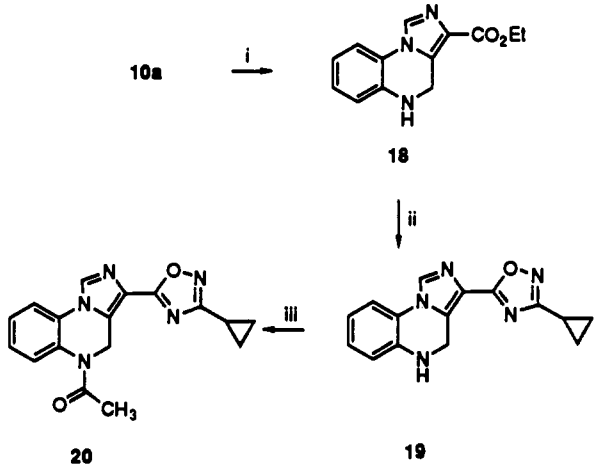
The preparation of fluoro intermediate **27** is depicted in Scheme 6. A Hoffmann-like rearrangement of **22** using

Scheme 4[a]



[a] Reagents: (i) phosgene in toluene; (ii) $R_5O^-Na^+$.

Scheme 5[a]



[a] Reagents: (i) ethyl isocyanoacetate, *t*-BuOK, THF; (ii) cyclopropyl amidoxime, NaH, THF, DMF; (iii) Ac_2O, 100 °C.

lead tetraacetate and *tert*-butanol gave **23**.[16] Reduction of the nitro group of **23**, followed by addition of 2-bromoacetyl bromide, gave **28**, but this compound could not be induced to close to **25** (or to the corresponding compound without the Boc protecting group) in acceptable yield. Instead, the key step proved to be formation of the anion of **23** with potassium *tert*-butoxide, followed by alkylation with ethyl 2-bromoacetate, to give **24**. Reduction of the nitro group, followed by stirring with *p*-toluenesulfonic acid, gave the ring-closed intermediate **25**. Imidazo ring formation under the standard conditions gave **26**, which after treatment with HCl/methanol and basic workup gave **27**.

Results and Discussion

A comparison of computer-generated models of benzodiazepine **C** and U-78875 (Figure 1) highlights the very different three-dimensional shapes of these two series.[17] Compound **C** has pronounced convex and concave faces, whereas U-78875 is very nearly a planar structure, with only the oxadiazole ring rotated out of the plane of the imidazoquinoxalin-4-one ring system. The imidazoquinoxaline amides fall somewhere intermediate in three-dimensional structure between these two classes (Figure 1). These compounds may be further subdivided into the open-chain compounds of Table 1 and the lactam-type structures of Table 2. Variation of the amide groups of the open-chain compounds shows that simple acetyl substitution gives compounds with generally high affinity as measured by the ability of the compounds to displace [^{3}H]flunitrazepam, a ligand for the benzodiazepine receptor (Table 1). However, comparison of **20** and **13c**, acetamide structures differing only in the oxadiazole ring appended at C-3, differ 4-fold in their affinity for the

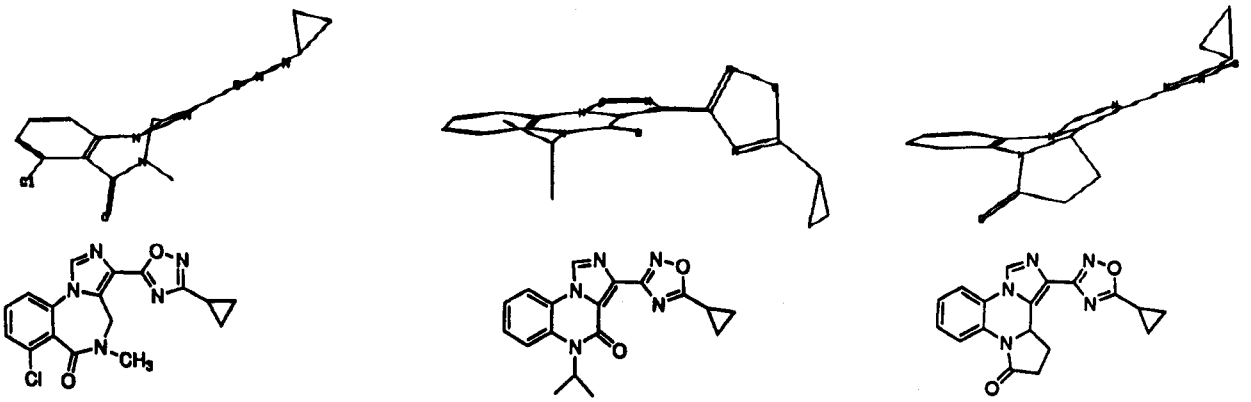
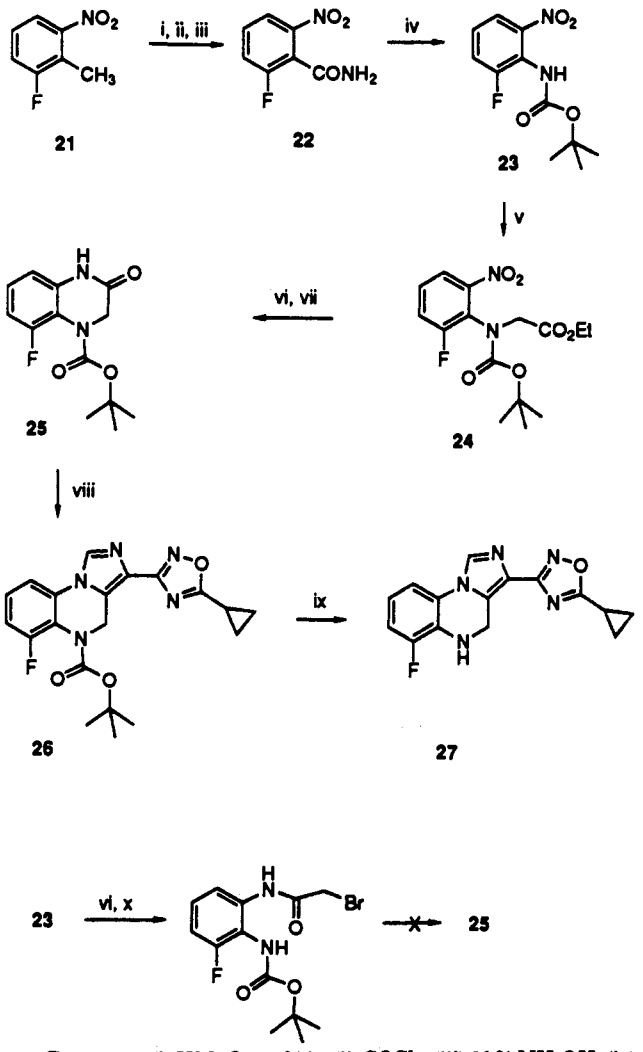


Figure 1. Energy-minimized conformations of **C**, U-78875, and **1b**.

Scheme 6[a]



[a] Reagents: (i) $KMnO_4$ (ref 21); (ii) $SOCl_2$; (iii) 30% NH_4OH; (iv) $Pb(OAc)_4$, absolute *t*-BuOH; (v) (1) 1 M *t*-BuOK, THF, (2) ethyl 2-bromoacetate; (vi) H_2, 10% Pd on carbon, MeOH; (vii) *p*-TsOH, MeOH; (viii) (1) *t*-BuOK, THF, (2) diethyl chlorophosphate, (3) **9**, *t*-BuOK; (ix) HCl/MeOH; (x) $BrCH_2COBr$.

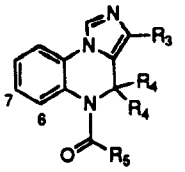
receptor. The addition of *gem*-dimethyl groups at C-4 (**13d**) also led to a slight drop in affinity, suggesting that the methyl groups change either the C-3 oxadiazole or C-5 amide group orientation, or both.

tert-Butylbicyclophosphorothionate (TBPS) binds with high affinity to a site located near the mouth of the chloride channel of the $GABA_A$ receptor complex. The binding of a ligand to the benzodiazepine site on the receptor complex allosterically affects the binding of TBPS, and this modulation in binding is expressed as the shift in TBPS binding in the presence and absence of a test compound. Benzodiazepine receptor agonists enhance the [^{35}S]TBPS binding shift (defined here for full agonists as having a value of 1.0), whereas inverse agonists reduce the [^{35}S]-TBPS shift and antagonists have no effect ([^{35}S]TBPS shift = 0). Thus, measurement of the [^{35}S]TBPS shift allows for an estimation of the intrinsic efficacy of a test compound, based on its ability to alter the [^{35}S]TBPS shift relative to known compounds. The [^{35}S]TBPS shifts for **13c**, **13d**, **13k**, **17a**, and **20** suggest intrinsic efficacies consistent with full agonists; however, the metrazole antagonism ED_{50} values[18] for these compounds are not consistent with the values for known full agonists such as diazepam and triazolam, which typically have low ED_{50} values (high potency) by this measure. Blockade of metrazole-induced clonic and tonic convulsions is a property of compounds which are full agonists at the $GABA_A$ receptor complex, and thus the degree of antagonism of an induced convulsion shown by a test compound is often used as a measure of the agonist properties of that ligand. Typically, full agonists have ED_{50} values in the 0.5–5 mg/kg range, whereas neutral antagonists will have ED_{50} values in the 25–50 mg/kg range. In the case at hand, differences in metabolism may be a factor, as the metrazole antagonism assay is an *in vivo* assay, or differential binding to subreceptors may be responsible for the differences observed [^{35}S]TBPS shift and the metrazole data.

Compound **13h**, with *tert*-butyl ester substitution at C-3 in place of the oxadiazole, is an exception to the above-mentioned *in vitro* efficacy measurement of full agonism for the acetamides. The [^{35}S]TBPS shift of **13h** is zero, consistent with an antagonist. This shift to the antagonist end of the efficacy spectrum, on going from oxadiazole to *tert*-butyl ester at C-3, was determined to be typical for the series (*vide infra*) as a whole.

Benzamide substitution (**13b**, **13j**, **13l**, **13e**, **13f**) also gives compounds with high affinity for the receptor; however, the intrinsic efficacies now begin a trend toward partial agonist or antagonist activities. The [^{35}S]TBPS shifts and chloride uptake values (GABA modulates synaptic membrane chloride conductance by activating the $GABA_A$ receptor complex; application of various test ligands in the presence of GABA will thus modulate chloride current, with full agonists giving a value of 1.0 and partial agonists values between approximately 0.3 and 0.7) for the 2-chlorobenzamides **13e** and **13f** in particular indicate antagonist or partial agonist activities, both with the oxadiazole and *tert*-butyl ester substituents at C-3.

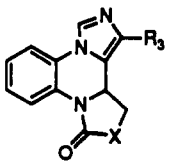
Table 1. [^{3}H]Flu Binding, TBPS Shift, $^{36}Cl^-$ Uptake, and Metrazole Antagonism Data for Imidazo[1,5-*a*]quinoxaline Amides and Carbamates



compd	R_3	R_4	R_5	K_i (nM)[a]	[^{35}S]TBPS shift[b]	$^{36}Cl^-$ uptake[c]	metrazole[d] (ED_{50}, mg/kg, ip)
20	N,O-ox[e]	H, H	CH_3	6.6	0.7	0.6	42
17a	N,N-ox[e]	H, H	CH_3 (6-F)	0.71	1.04	1.18	
13k	N,N-ox	H, H	CH_3 (7-F)	0.69	1.11		
13c	N,N-ox	H, H	CH_3	1.5	0.9		35
13d	N,N-ox	CH_3, CH_3	CH_3	4.8	0.7		30
13h	CO_2-*t*-Bu	H, H	CH_3	2.8	−0.06	0	
13b	N,N-ox	H, H	Ph	4.3	0.5		
13j	N,N-ox	H, H	Ph (7-F)	0.58	0.98	0.67[f]	
13l	N,N-ox	H, H	Ph (6-F)	0.77	0.87	0.9	25
13e	N,N-ox	H, H	2-Cl Ph	1.4	0	0.28	>50
13f	CO_2-*t*-Bu	H, H	2-Cl Ph	4	0.2	−0.15	>50
17a	N,N-ox	CH_3, CH_3	OCH_3	6.8	0.8	0.4	>50
17b	N,N-ox	CH_3, CH_3	O-*i*-Pr	6.7	1.2	0.7	3.7
13a	N,N-ox	H, H	O-*t*-Bu	1.9	2.9		0.06
13g	CO_2-*t*-Bu	H, H	O-*t*-Bu	5.1	0.45	0.14[f]	
diazepam				6	1.0 ± 0.2	1.0 ± 0.15	0.5 (0.38–1.2)
zolpidem				25			4.4 (2.6–7.7)

[a] Mean binding affinity against [^{3}H]flunitrazepam; see: Sethy, V. H.; Harris, D. W. Determination of Biological Activity of Alprazolam, Triazolam and their Metabolites. *J. Pharm. Pharmacol.* **1982**, *34*, 115–116, for methods. The standard error was less than ±10% of the mean. [b] Diazepam is defined as a full agonist which gives a value of one (1). Antagonists are defined as having a shift value of zero (0); partial agonists are intermediate. [c] See the Experimental Section. [d] Antagonism of metrazole-induced clonic convulsions in the rat after ip injection. [e] N,O-ox: 3-cyclopropyl-1,2,4-oxadiazol-5-yl; N,N-ox: 5-cyclopropyl-1,2,4-oxadiazol-3-yl. [f] Measured at $\alpha1\beta2\gamma2$ subreceptor.

Table 2. [^{3}H]Flu Binding, TBPS Shift, $^{36}Cl^-$ Uptake, and Metrazole Antagonism Data for Lactam and Oxazolidinone Imidazo[1,5-*a*]quinoxalines



compd	R_3	X	K_i (nM)[a]	[^{35}S]-TBPS	$^{36}Cl^-$	metrazole[d]
1a	N,N-ox	CH_2	0.87	1.15	0.29	
1b	N,N-ox	CH_2	0.62	1.05		1.1
1c	N,N-ox	CH_2	0.65	0.9		1.9
1d	N,N-ox	O	2.4	0.96	0.5[e]	
1e	CO_2-*t*-Bu	CH_2	0.76	0.06		>50
diazepam			6	1.0	1.0	0.67
zolpidem			25			4.5

[a] See footnote *a*, Table 1. [b] See footnote *b*, Table 1. [c] See the Experimental Section. [d] Antagonism of metrazole-induced clonic convulsions. [e] Measured at $\alpha1\beta2\gamma2$ subreceptor.

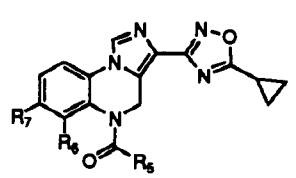
The high ED_{50} values (low potency) for metrazole antagonism are consistent with these low [^{35}S]TBPS shift values.

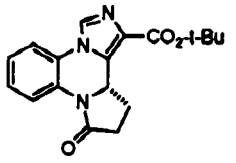
The effect of carbamate substitution at C-5 is to increase the intrinsic efficacy as the size (and overall lipophilicity) of the appended group increases, from methyl (**17a**) to isopropyl (**17b**), to the "super agonist" *tert*-butyl carbamate, **13a**. The high potency of this compound in metrazole antagonism is consistent with the super-agonist designation. Again, when the substituent at C-3 is changed from oxadiazole (**13a**) to *tert*-butyl ester (**13g**), the [^{35}S]TBPS shift drops off to the partial agonist range (note that $^{36}Cl^-$ current, measured on cells expressing the $\alpha_1\beta_2\gamma_2$ subtype, gives a value of 0.14, also consistent with a weak partial agonist).

The ability to substitute with methyl groups at C-4 without substantial loss in affinity (**13c** vs **13d**) suggests two questions: first, what is the effect on affinity and intrinsic efficacy of joining C-4 and N-5 in a ring, such that the carbonyl is constrained to point in one direction, and second, what is the effect of the chirality thus generated on affinity, [^{35}S]TBPS shift, and metrazole antagonism? Table 2 lists imidazoquinoxalines with lactam and oxazolidinone ring systems joining C-4 and N-5. The racemic lactam compound **1a** has a K_i of 0.87 nM and a [^{35}S]TBPS shift of 1.15, suggesting high affinity coupled with full agonism. The individual enantiomers of **1a**, **1b**, and **1c**, derived from L- and D-glutamic acid, respectively, have identical affinities and [^{35}S]TBPS shifts and compararble values for metrazole antagonism. When a *tert*-butyl ester group was substituted for the oxadiazole at C-3, affinity remained high but the [^{35}S]TBPS shift value dropped from 1.05 for the oxadiazole compound (**1b**) to 0.06 for the *tert*-butyl ester compound (**1e**), indicating a shift from full agonist to antagonist properties. The metrazole antagonism values are consistent with this shift in intrinsic efficacy. Racemic oxazolidinone **1d** has a somewhat lower affinity than racemic lactam **1a**, but again with a [^{35}S]-TBPS value consistent with a full agonist.

Benzodiazepines, β-CCE, DMCM, zolpidem, and CL 218872 all exhibit high affinity for the $\alpha_1\beta_2\gamma_2$ subrecptor; however, the classical benzodiazepines do not bind to the $\alpha_6\beta_2\gamma_2$ subreceptor.[19] Ro 15-4513 (Figure 1) has been identified as a high-affinity ligand for the $\alpha_6\beta_2\gamma_2$ subtype, with a K_i of 15 nM for the $\alpha_1\beta_2\gamma_2$ subreceptor and a K_i of 5 nM for $\alpha_6\beta_2\gamma_2$. Luddens *et al.* hypothesized that the $\alpha_6\beta_2\gamma_2$ subreceptor played a role in the process of ethanol potentiation,[19] though others have disputed this,[20] and the functional role of the $\alpha_6\beta_2\gamma_2$ subreceptor remains speculative. Several acetamide and benzamide compounds were prepared and examined to determine the effect of fluorine substitution at the C-6 and C-7 positions of the imidazoquinoxaline benzene ring against the $\alpha_1\beta_2\gamma_2$ and

Table 3. Binding Affinities for Selected Compounds against the $\alpha_1\beta_2\gamma_2$ and $\alpha_6\beta_2\gamma_2$ Subreceptors





				K_i (nM)[a]	
compd	R_5	R_6	R_7	$\alpha_1\beta_2\gamma_2$	$\alpha_6\beta_2\gamma_2$
13c	CH_3	H	H	2.7 ± 0.8	124 ± 20
13i	CH_3	F	H	0.8 ± 0.2	107 ± 21
13k	CH_3	H	F	0.6 ± 0.1	81 ± 1
13b	Ph	H	H	0.3 ± 0.1	1140 ± 10
13j	Ph	F	H	0.4 ± 0.1	>10,000
13l	Ph	H	F	0.3 ± 0.1	681 ± 4
1e	lactam	H	H	0.4 ± 0.1	13.2
diazepam				13	>7000
Ro 15-4513[b]				15 ± 4	5.4 ± 0.4

[a] The ability of the compounds to displace [^{3}H]flunitrazepam was measured in membranes from Sf-9 insect cells expressing the $\alpha1\beta2\gamma2$ subtype and to displace [^{3}H]Ro 15-4513 in insect cell membranes expressing the $\alpha6\beta2\gamma2$ subtype, as described in the Experimental Section. The IC_{50} value was obtained from dose–response curves consisting of six different concentrations and was converted to a K_i value using the equation: $K_i = IC_{50}/(1 + [\text{test ligand}]/K_d$ of flunitrazepam or Ro 15-4513. The data represent the mean ± standard errors from at least three separate experiments. [b] From ref 19.

$\alpha_6\beta_2\gamma_2$ subreceptors (Table 3). Fluorine would be expected to have largely electronic effects on the ring system and not affect substantially the neighboring N-5 group via steric effects. In Table 3 are listed the $\alpha_1\beta_2\gamma_2$ and $\alpha_6\beta_2\gamma_2$ subreceptor binding affinities for compounds substituted with fluorine on the aromatic ring. Binding affinities in general remained constant for the $\alpha_1\beta_2\gamma_2$ subreceptor, but varied considerably at $\alpha_6\beta_2\gamma_2$. Most striking is the total loss in $\alpha_6\beta_2\gamma_2$ affinity on going from acetamide (**13i**) to benzamide (**13j**) when fluorine is present at C-6. The lactam **1e** was also examined at the $\alpha_1\beta_2\gamma_2$ and $\alpha_6\beta_2\gamma_2$ subreceptors and found to have a relatively high affinity for the $\alpha_6\beta_2\gamma_2$ subtype (K_i = 0.40 nM at $\alpha_1\beta_2\gamma_2$ and K_i = 13.2 nM at $\alpha_6\beta_2\gamma_2$).

Conclusions

The imidazo[1,5-*a*]quinoxaline amide system provides high affinity ligands for the $GABA_A$/benzodiazepine receptor, giving compounds which range in efficacy from antagonists to super agonists. Intrinsic efficacy can be modulated by proper choice of substitution at C-3 and N-5. The amide carbonyl may be constrained by incorporation into a lactam or oxazolidinone ring system, and though the individual lactam enantiomers were not distinguishable by affinity measurements using rat cortical tissue, they did exhibit stereospecific activities in metrazole antagonism measurements. Furthermore, fluorine substitution on the benzene ring of the "open-chain" imidazoquinoxaline amides strongly influences $\alpha_1\beta_2\gamma_2$ and $\alpha_6\beta_2\gamma_2$ subtype binding affinities. Thus this series serves as a tool for exploring the effects of structural modifications on compounds which bind to the $GABA_A$/benzodiazepine receptor and its subtypes and may lead to agents useful in the treatment of anxiety and sleep disorders.

Experimental Section

Mass spectra, elemental analyses, infrared spectra, and optical rotations were performed by the Physical and Analytical Chemistry Department, Upjohn Laboratories, the Upjohn Company. Unless noted, infrared spectra were run as a mineral oil mulls. Only the first several most intense peaks are cited. ^{1}H-NMR spectra were recorded on a Bruker 300 MHz instrument. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Solvents were purchased from EM Science or Baxter (Burdick and Jackson brand). THF was freshly distilled from benzophenone/sodium, and DMF was dried over 3-Å molecular sieves. Other solvents were used as received. Ethyl isocyanoacetate, diethyl chlorophosphate, and potassium *tert*-butoxide (1 M in THF) were purchased from the Aldrich Chemical Co., Milwaukee, WI. *tert*-Butyl isocyanoacetate and phosgene in toluene (CAUTION: phosgene is highly toxic and should be used with utmost care) were purchased from Fluka Chemie AG.

***N*-(2-Nitrophenyl)-DL-glutamic Acid Dimethyl Ester (3b).** A mixture of 4.80 g (34 mmol) of 1-fluoro-2-nitrobenzene, 5.62 g (34 mmol) of DL-glutamic acid hydrate, 8.00 g (57.8 mmol) of potassium carbonate, 50 mL of ethanol, and 10 mL of water was heated at 105 °C for 24 h. The reaction mixture was then stripped of solvents and the residue stirred in DMF with 4 mL of methyl iodide. After about a week, the DMF was removed and the residue was partitioned between dichloromethane and water. Silica gel chromatography (500 mL) using EtOAc/hexane (30/70) gave 8.53 g (85%) of **3b** as an orange oil: ^{1}H NMR ($CDCl_3$) δ 2.28 (m, 2H), 2.51 (t, *J* = 6.6 Hz, 2H), 3.69 (s, 3H), 3.79 (s, 3H), 4.40 (app q, *J* = 7.1 Hz, 1H), 6.73 (dd, *J* = 7.2, 8.5 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 7.45 (t, *J* = 8.1 Hz, 1H), 8.20 (dd, *J* = 1.6, 8.5 Hz, 1H), 8.33 (br d, 1H).

***N*-(2-Nitrophenyl)-L-glutamic Acid Diethyl Ester (3c).** To 6.56 g (46.5 mmol) of 1-fluoro-2-nitrobenzene and 20.26 mL (116 mmol) of diisopropylethylamine in 50 mL of ethanol was added 11.15 g (46.5 mmol) of L-glutamic acid diethyl ester. After the reaction mixture was heated at 70 °C for 2 days, an additional 2.57 g of L-glutamic acid diethyl ester was added. The reaction was heated an additional 2 days, cooled, and concentrated in vacuo. The residue was partitioned between dichloromethane and water. The organic layers were dried over sodium sulfate and concentrated, and the residue was chromatographed on silica gel (600 mL) using a gradient of EtOAc/hexane (10/90 to 20/80) to give 3.83 g (28%) of **3c** as an orange oil: $[\alpha]_D$ = −47.5° (0.86, MeOH); IR 1737, 1618, 1513, 1270, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 2.28 (m, 2H), 2.50 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.38 (dd, *J* = 6.7, 14 Hz, 1H), 6.70 (t, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 8.5 Hz, 1H), 8.20 (dd, *J* = 1.6, 8.6 Hz, 1H), 8.36 (br d, *J* = 7.6 Hz, 1H).

***N*-(2-Nitrophenyl)-D-glutamic Acid Diethyl Ester (3d).** In the same manner as for **3b**, 1-fluoro-2-nitrobenzene (5.35 g, 37.9 mmol) and D-glutamic acid diethyl ester (11.9 g, 58.6 mmol) afforded 5.20 g (47%) of **3d** as an orange oil: $[\alpha]_D$ = +50° (0.848, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 2.27 (m, 2H), 2.49 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.38 (app q, *J* = 7.3 Hz, 1H), 6.73 (dd, *J* = 7.0, 7.1 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 7.0 Hz, 1H), 8.20 (dd, *J* = 1.6, 8.6 Hz, 1H), 8.36 (br d, 1H).

***N*-(2-Nitrophenyl)-DL-serine Methyl Ester (3e).** A mixture of 15.66 g (0.111 mol) of 1-fluoro-2-nitrobenzene, 11.66 g (0.111 mol) of DL-serine, and 16.87 g (0.122 mol) of K_2CO_3 was stirred at 90 °C overnight in 100 mL of 95% ethanol and 40 mL of water. After cooling, the solvents were removed in vacuo and the residue was azeotroped with toluene several times to remove residual water. The solid was washed sequentially with ethyl ether and toluene to remove unreacted fluoronitrobenzene, and the crude product was stirred at room temperature with 15.34 g (0.111 mol) of K_2CO_3, 24 mL (0.39 mol) of methyl iodide, and 80 mL of DMF. After the mixture was stirred overnight, DMF was removed and the residue was partitioned between water and dichloromethane–chloroform. The organic layers were filtered through sodium sulfate and concentrated. Ethyl ether and hexane were added to afford 15.88 g (60% for both steps) of **3e** as a yellow solid: mp 138–140 °C; MS (FAB) 241 (m + H); IR 1735, 1512, 744, 1619, 1243, 1217, 1160, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.15 (br m, 1H), 3.83 (s, 3H), 4.10 (br m, 2H), 4.41 (m, 1H), 6.77 (m, 2H), 7.46 (t, *J* = 8 Hz, 1H), 8.22 (d, *J* = 10 Hz, 1H), 8.61 (br d, 1H). Anal. ($C_{10}H_{12}N_2O_5$) C, H; N: calcd, 11.66; found, 12.11.

3,3a-Dihydropyrrolo[1,2-*a*]quinoxaline-1,4(2*H*,5*H*)-dione (6a). To 5.09 g (17.2 mmol) of **3b** in 150 mL of MeOH was

added 0.158 g (0.83 mmol) of *p*-toluenesulfonic acid monohydrate and 0.495 g of 10% Pd on carbon. The mixture was shaken under hydrogen at 37 psi for 2 h; the Pd/C catalyst was then filtered off, and the filtrate was concentrated to a volume of about 70 mL to give a mixture of **4b** and **5a**. An additional 0.15 g of *p*-toluenesulfonic acid monohydrate was added, and the solution was heated at 60 °C for 1 h. After cooling, the solid was collected, washed with MeOH, and dried to give 2.63 g (76%) of **6a**: mp 231–232 °C; MS *m/z* 202; IR 1701, 1672, 1395, 1712, 1504, 1599, 1432, 771 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (m, 4H), 4.41 (t, J = 8 Hz, 1H), 6.93 (m, 1H), 7.14 (m, 2H), 8.10 (d, J = 9 Hz, 1H), 8.55 (br s, 1H). Anal. ($C_{11}H_{10}N_2O_2$) C, H, N.

(*S*)-3,3a-Dihydropyrrolo[1,2-*a*]quinoxaline-1,4(2*H*,5*H*)-dione (6b). In the same manner as for **6a**, 3.75 g (12.6 mmol) of **3c** afforded 1.19 g (47%) of **6b**: mp 248–250 °C dec; $[\alpha]_D$ = −65.4° (0.772, MeOH); MS *m/z* 202; IR 1699, 1684, 1505, 1431 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.6 (m, 4H), 4.40 (t, J = 8.1 Hz, 1H), 6.92 (m, 1H), 7.14 (m, 2H), 8.09 (m, 1H). Anal. ($C_{11}H_{10}N_2O_2$) H, N; C: calcd, 65.34; found, 64.82.

(*R*)-3,3a-Dihydropyrrolo[1,2-*a*]quinoxaline-1,4(2*H*,5*H*)-dione (6c). In the same manner as for **6a**, *N*-(2-nitrophenyl)-D-glutamic acid diethyl ester (5.10 g, 17.2 mmol) afforded 1.79 g (51%) of **6c**; mp 248–250 °C dec; $[\alpha]_D$ = +65.9° (0.699, MeOH); MS *m/z* 202; IR 1671, 1706, 1394, 1433, 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.4–2.8 (m, 4H), 4.41 (t, J = 8.2 Hz, 2H), 6.92 (m, 1H), 7.13 (m, 2H), 8.08 (m, 1H). Anal. ($C_{11}H_{10}N_2O_2$) C, H, N.

1,2,3,4-Tetrahydro-3-(hydroxymethyl)quinoxalin-2-one (5d). A mixture of 4.30 g (17.9 mmol) of **3e** and 0.506 g of 10% Pd/C in 150 mL of methanol was shaken on a Parr hydrogenator at 40 psi for 3.5 h. The catalyst was removed by filtration and the filtrate concentrated. The residue was chromatographed on silica gel (400 mL) using MeOH/dichloromethane (6/94) to give 2.73 g (86%) of **5d**: mp 140–141 °C; MS *m/z* 178; IR 1682, 1675, 3295, 1044, 3156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (m, 1H), 3.90 (m, 1H), 4.10 (m, 3H), 6.73 (m, 3H), 6.92 (dt, J = 1.5, 7.5 Hz, 1H), 8.23 (br s, 1H). Anal. ($C_9H_{10}N_2O_2$) C, H, N.

3,3a-Dihydro-1*H*-oxazolo[3,4-*a*]quinoxaline-1,4(5*H*)-dione (6d). A solution of 1.35 g (5.61 mmol) of **5d**, 1.00 g (6.17 mmol) of carbonyldiimidazole, and 1.64 mL (11.8 mmol) of triethylamine was stirred in 30 mL of THF at room temperature for 6 h and then at 80 °C overnight. An additional 0.11 g of carbonyldiimidazole was added, and the mixture was heated for an additional 6 h. The solvent was then removed and the residue partitioned between dichloromethane and water. The organic layers were filtered through sodium sulfate and taken to dryness. The crude product was crystallized from methanol and dichloromethane to give 1.02 g (88%) of **6d**: mp 230–231 °C; MS *m/z* 204; IR 1745, 1701, 1688, 1509, 3281 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.59 (t, J = 8.4 Hz, 1H), 4.77 (dd, J = 2.2, 8.1 Hz, 2H), 6.94 (m, 1H), 7.19 (m, 2H), 7.81 (m, 1H), 8.4 (br s, 1H). Anal. ($C_{10}H_8N_2O_3$) C, H, N.

(*RS*)-1-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-12,12a-dihydroimidazo[1,5-*a*]pyrrolo[2,1-*c*]quinoxalin-10(11*H*)-one (1a). Compound **6a** (0.520 g, 2.57 mmol) was stirred in 6.5 mL of DMF and cooled to 0 °C. To this was added 2.70 mL (2.70 mmol) of 1 M potassium *tert*-butoxide in THF. After 10 min the ice bath was removed. Ten minutes later an additional 6 mL of DMF was added to aid in stirring. After 30 min had elapsed, the mixture was cooled in an ice/MeOH bath, and 0.39 mL (2.70 mmol) of diethyl chlorophosphate was added. The mixture was stirred for 10 min, after which time the ice/MeOH bath was removed. After a total of 45 min had passed, the mixture was cooled at −78 °C and 0.403 g (2.70 mmol) of 5-cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole[11] was added, followed by 2.70 mL (2.7 mmol) of 1 M potassium *tert*-butoxide in THF added dropwise over 10 min. After stirring at −78 °C for 1.5 h, the cooling bath was removed and the mixture was allowed to warm to room temperature (over about 30 min). Water was added, and the reaction mixture was partitioned between ethyl acetate and water, followed by a brine wash of the organic layers. The organic layers were dried over magnesium sulfate and concentrated, and the residue was chromatographed on silica gel (200 mL) using ethyl acetate/hexane (75/25) to give 0.404 g (47%) of product. Recrystallization from dichloromethane/ethyl acetate/hexane gave 0.329 g of **1a**: mp 180–183 °C dec; MS *m/z* 333 (M^+); IR 1701, 1574, 1509, 1477, 766 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (m, 2H), 1.36 (m, 2H), 2.27 (m, 2H), 2.60 (m, 1H), 2.78 (m, 1H), 3.38 (m, 1H), 5.29 (dd, J = 6.6, 9.5 Hz, 1H), 7.26 (dd, J = 1.5, 8 Hz, 1H), 7.33 (dt, J = 1.6, 8 Hz, 1H), 7.57 (dd, J = 1.5, 8 Hz, 1H), 8.17 (s, 1H), 8.37 (dd, J = 1.5, 8.1 Hz, 1H). Anal. ($C_{18}H_{15}N_5O_2$) C, H, N.

(*S*)-1-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-12,12a-dihydroimidazo[1,5-*a*]pyrrolo[2,1-*c*]quinoxalin-10(11*H*)-one (1b). In the same manner as for **1a**, 1.00 g (4.94 mmol) of **6b** afforded 0.758 g (46%) of **1b**. Crystallization from dichloromethane and ethyl acetate gave a first crop of 0.573 g and a second crop of 0.132 g: mp 181.5–183 °C dec; $[\alpha]_D$ = −197° (0.98, CH_2Cl_2); MS *m/z* 333; IR 1708, 1511, 761, 1204, 1403 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (m, 2H), 1.35 (m, 2H), 2.25 (m, 2H), 2.56 (m, 1H), 2.76 (m, 1H), 3.35 (m, 1H), 5.30 (dd, J = 1.8, 6.6 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.34 (m, 1H), 7.57 (d, J = 7.9 Hz, 1H), 8.18 (s, 1H), 8.34 (dd, J = 1.3, 8.1 Hz, 1H). Anal. ($C_{18}H_{15}N_5O_2$) C, H, N.

(*R*)-1-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-12,12a-dihydroimidazo[1,5-*a*]pyrrolo[2,1-*c*]quinoxalin-10(11*H*)-one (1c). In the same manner as for **1a**, **6c** (1.00 g, 4.94 mmol) afforded 0.755 g (46%) of **1c**: mp 181.5–183 °C dec; $[\alpha]_D$ = +154° (0.98, CH_2Cl_2); MS *m/z* 333; IR 1707, 1511, 1499, 761, 1403 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (m, 2H), 1.37 (m, 2H), 2.27 (m, 2H), 2.58 (m, 1H), 2.77 (m, 1H), 3.37 (m, 1H), 5.30 (dd, J = 6.6, 9.6 Hz, 1H), 7.30 (m, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.57 (d, J = 6.5 Hz, 1H), 8.17 (s, 1H), 8.36 (d, J = 8.1 Hz, 1H). Anal. ($C_{18}H_{15}N_5O_2$) C, H, N.

12-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-1,12b-dihydroimidazo[5,1-*a*]oxazolo[4,3-*c*]quinoxalin-3(3*H*)-one (1d). In the same manner as for **1a**, 0.485 g (2.38 mmol) of **6d** afforded 0.083 g (10%) of **1d** after chromatography on silica gel using ethyl acetate/dichloromethane (20/80) and crystallization from dichloromethane/ethyl acetate/hexane; mp 228–230 °C; MS *m/z* 335; IR 1749, 1570, 1511, 1213, 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (m, 4H), 2.28 (m, 1H), 4.63 (t, J = 9.5 Hz, 1H), 5.35 (m, 1H), 5.57 (m, 1H), 7.31 (dd, J = 1,4, 7.9 Hz, 1H), 7.41 (dt, J = 1.2, 7.6 Hz, 1H), 7.61 (dd, J = 1.3, 8 Hz, 1H), 8.11 (dd, J = 1.3, 8.1 Hz, 1H), 8.23 (s, 1H). Anal. ($C_{17}H_{13}N_5O_3$) C, H, N.

***tert*-Butyl (*S*)-12,12a-Dihydroimidazol[1,5-*a*]pyrrolo[2,1-*c*]quinoxaline-1-carboxylate (1e).** In the same manner as for **1a**, 0.74 g (3.67 mmol) of **6b** and 0.62 g (4.40 mmol) of *tert*-butyl isocyanoacetate afforded 0.57 g (48%) of **1e**: mp 202–207 °C dec; MS *m/z* 325; IR 1719, 1363, 1700, 1507, 1161, 1293 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (s, 9H), 2.32 (m, 1H), 2.55–2.75 (m, 2H), 3.36 (m, 1H), 5.26 (dd, J = 2.9, 6.7 Hz, 1H), 7.28 (m, 1H), 7.36 (m, 1H), 7.52 (dd, J = 1.4, 8 Hz, 1H), 8.06 (s, 1H), 8.34 (dd, J = 1.4, 8.2 Hz, 1H). Anal. ($C_{18}H_{18}N_3O_3$) C, H, N.

1,2,3,4-Tetrahydroquinoxalin-2-one (10a). A mixture of 12.30 g (87.2 mmol) of 1-fluoro-2-nitrobenzene, 12.17 g (87.2 mmol) of glycine ethyl ester hydrochloride, 15.2 mL (87.2 mmol) of diisopropylethylamine, and 50 mL of acetonitrile was stirred at room temperature for 60 h, after which an additional 20 mL of diisopropylethylamine and 3 g of glycine ethyl ester hydrochloride were added. The mixture was stirred an additional 20 h and then partitioned between dichloromethane and water. The organic layers were filtered through sodium sulfate, concentrated, and chromatographed on silica gel (500 mL) using ethyl acetate/hexane (5/95), followed by hexane/ethyl acetate/dichloromethane (8:1:1) to give 16.73 g (85%) of *N*-(2-nitrophenyl)glycine ethyl ester as a yellow solid: mp 79.0–79.5 °C; MS *m/z* 224; ^1H NMR ($CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3H), 4.09 (d, J = 5.3 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 6.72 (m, 2H), 7.47 (t, J = 7.7 Hz, 1H), 8.21 (d, J = 8.5 Hz, 1H), 8.42 (br s, 1H). Anal. ($C_{10}H_{12}N_2O_4$) C, H, N. A mixture of 16.65 g (74.2 mol) of the above ester and 0.906 g of 10% Pd/C in 500 mL of methanol was shaken under H_2 at 35 psi for 1.5 h. The catalyst was then filtered off and the filtrate concentrated. The residue was chromatographed on silica gel (500 mL) using MeOH/dichloromethane (2/98) to give 9.71 g (88%) of **10a**: mp 136–138 °C (from ethyl acetate/dichloromethane); MS *m/z* 148; IR 1692, 1508, 748, 3369, 1307 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (br s, 1H), 4.00 (d, J = 2 Hz, 2H), 6.67 (d, J = 7.8 Hz, 1H), 6.76 (m, 2H), 6.88 (m, 1H), 8.8 (br s, 1H). Anal. ($C_8H_8N_2O$) C, H, N.

Alternatively, **10a** could be prepared by treating a solution of 2.32 g (21.4 mmol) of *o*-phenylenediamine, 3.9 mL (27.9 mmol) of triethylamine, 5 mL of dichloromethane, and 5 mL of THF (not dried) with 3.1 mL (27.9 mmol) of ethyl 2-bromoacetate in 11 mL of THF (not dried) over 2 h. The mixture was stirred

overnight at room temperature and then heated at 60 °C for 3 h. After cooling, the solvent was removed under reduced pressure. Approximately 30 mL each of water and hexane were added to the residue, and the slurry was stirred for several minutes. The hexane layer (which contains the less polar, dialkylated side product) was decanted and discarded. The aqueous slurry was washed a second time with hexane, after which the solid was collected and washed with several aliquots of water. The solid was dried under reduced pressure to give 1.97 g (62%) of **10a**, mp 133–134 °C.

6-Fluoro-1,2,3,4-tetrahydroquinoxalin-2-one (10b). To a mixture of 19.20 g (0.1207 mol) of 2,4-difluoronitrobenzene, 16.52 g (0.1207 mol) of glycine ethyl ester hydrochloride, and 50 mL of acetonitrile was added 42 mL (0.241 mol) of diisopropylethylamine. A mild exotherm ensued, and the mixture was stirred (without cooling) for 2 h. Acetonitrile was removed, and the residue was partitioned between dichloromethane and water. The organic layers were dried over sodium sulfate and concentrated to give 28.60 g (98%) of *N*-(5-fluoro-2-nitrophenyl)glycine ethyl ester as a yellow solid, mp 114.0–114.5 °C. This material (28.60 g, 0.118 mol), 1.01 g of 10% Pd/C, and 500 mL of methanol were shaken at 45 psi under H_2. After 2 h an additional 0.54 g of catalyst was added. The mixture was shaken for 1 h at 42 psi, and then the catalyst was removed by filtration. To the filtrate was added 0.314 g of *p*-TsOH. The solution was concentrated to a volume of about 250 mL and then stirred at room temperature overnight. The mixture was then further concentrated, and dichloromethane was added. The solid was collected and chromatographed on silica gel using MeOH/dichloromethane (2/98) as eluent. The product fractions were combined, concentrated, and triturated with a small amount of dichloromethane. The solids were collected, triturated a second time with dichloromethane, and then dried to afford 12.15 g of **10b** as an amber solid: mp 176.0–177.5 °C; MS *m/z* 166; IR 1682, 1515, 1304, 1159, 3397 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (br s, 1H), 3.99 (d, *J* = 1.8 Hz, 2H), 6.41 (dd, *J* = 3.3, 9.4 Hz, 1H), 6.46 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.63 (dd, *J* = 5, 8.3 Hz, 1H), 8.33 (br s, 1H). Anal. ($C_8H_7FN_2O$) C, H, N.

3,3-Dimethyl-1,2,3,4-tetrahydroquinoxalin-2-one (11). A mixture of 7.55 g (69.8 mmol) of *o*-phenylenediamine, 12.8 mL (87.3 mmol) of ethyl 2-bromoisobutyrate, 15.5 mL (87.3 mmol) of diisopropylethylamine, and 30 mL of DMF was heated at 110 °C for 5 h, after which an additional 0.5 mL of ethyl bromoisobutyrate and 0.8 mL of diisopropylethylamine was added. After being heated for an additional 2 h, the mixture was cooled and DMF was removed under reduced pressure. The residue was partitioned between ethyl acetate, water, and brine. The organic layers were dried over magnesium sulfate, and the product was crystallized from dichloromethane/hexane to give 9.335 g (76%) of **11**: mp 173–174 °C (lit.[13] mp 179–181 °C); ^1H NMR ($CDCl_3$) δ 1.41 (s, 6H), 3.72 (br s, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.76 (m, 2H), 6.87 (dt, *J* = 2, 7.6 Hz, 1H), 8.50 (br s, 1H). Anal. ($C_{10}H_{12}N_2O$) C, H, N.

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydro-4,4-dimethylimidazo[1,5-*a*]quinoxaline (12a). In the same manner as for **13a**, 1.200 g (6.81 mmol) of **11** afforded 1.551 g (74%) of **12a**: mp 166–169 °C (from MeOH/CH_2Cl_2/hexane); MS *m/z* 307; ^1H NMR ($CDCl_3$) δ 1.23 (m, 2H), 1.37 (m, 2H), 2.27 (m, 1H), 3.78 (br s, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.85 (t, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 8 Hz, 1H), 8.09 (s, 1H). Anal. ($C_{17}H_{17}N_5O$) C, H, N.

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydroimidazo[1,5-*a*]quinoxaline (12b). Using the same reaction conditions as for **13a** but substituting a quench into water and aqueous NH_4Cl and collection of the resulting solid for the partitioning and chromatography steps, 1.01 g (6.82 mmol) of **10a** afforded 1.41 g (74%) of **12b**: mp 235–239 °C; MS *m/z* 279; ^1H NMR ($CDCl_3$) δ 1.23 (m, 2H), 1.37 (m, 2H), 2.28 (m, 1H), 4.08 (br s, 1H), 4.81 (s, 2H), 6.83 (m, 2H), 7.10 (dt, *J* = 1.2, 7.7 Hz, 1H), 7.42 (dd, *J* = 1.3, 8.0 Hz, 1H), 8.07 (s, 1H). Anal. ($C_{15}H_{13}N_5O$) C, H, N.

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-7-fluoro-4,5-dihydroimidazo[1,5-*a*]quinoxaline (12c). In the same manner as for **13a**, 2.186 g (13.15 mmol) of **10b** afforded 2.44 g (64%) of **12c**: mp 263–265 °C; MS *m/z* 297; IR 1206, 1530, 1272, 1638, 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (m, 2H), 1.32 (m, 2H), 2.26 (m, 1H), 4.78 (s, 2H), 6.55 (m, 2H), 7.38 (m, 1H), 8.07 (s, 1H). Anal. ($C_{15}H_{12}FN_5O$) C, H, N.

4-[(*tert*-Butyloxy)carbonyl]-1,2,3,4-tetrahydroquinoxalin-2-one (15a). A mixture of 1.08 g (7.29 mmol) of **10a**, 1.59 g (7.29 mmol) of di-*tert*-butyl dicarbonate, 1.01 g (7.29 mmol) of potassium carbonate, and 10 mL of THF was stirred at 60 °C overnight. An additional 0.93 g of di-*tert*-butyl dicarbonate and 1 mL of water were then added, and the reaction mixture was stirred at 65 °C for 5.5 h. After a final addition of 0.24 g of di-*tert*-butyl dicarbonate and stirring for 2 more hours, the mixture was cooled, the solvent removed under reduced pressure, and the residue partitioned between dichloromethane and water, followed by a brine wash. The crude product was chromatographed on silica gel using MeOH/dichloromethane (2/98). Recrystallization from ethyl acetate and hexane gave 1.08 g (59%) of **15a**: mp 143–144 °C; MS *m/z* 248; IR 1685, 1703, 1504, 753, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 9H), 4.40 (s, 2H), 6.88 (m, 1H), 7.09 (m, 2H), 7.63 (br m, 1H), 8.58 (br s, 1H). Anal. ($C_{13}H_{16}N_2O_3$) C, H, N.

4-Benzoyl-1,2,3,4-tetrahydroquinoxalin-2-one (15b). A mixture of 0.593 g (4.0 mmol) of **10a** and 0.725 mL (5.2 mmol) of triethylamine in 5 mL of THF was cooled at 0 °C. To this was added 0.56 mL (4.8 mmol) of benzoyl chloride. After the addition was complete, the ice bath was removed and an additional 5 mL of THF was added. The reaction mixture was stirred for 30 min and then partitioned between ethyl acetate, aqueous sodium bicarbonate, and brine. The organic layers were dried over magnesium sulfate and concentrated. The crude product was recrystallized from methanol/dichloromethane/hexane to give 0.894 g (89%) of **15b**: mp 208.0–208.5 °C; MS *m/z* 252; IR 1684, 1666, 1502, 757, 1362 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.60 (s, 2H), 6.7 (br s, 1H), 6.78 (t, *J* = 7 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.33 (m, 2H), 7.41 (m, 3H), 8.77 (br s, 1H). Anal. ($C_{15}H_{12}N_2O_2$) C, H, N.

4-Acetyl-1,2,3,4-tetrahydroquinoxalin-2-one (15c). In the same manner as for **15b**, 0.676 g (4.56 mmol) of **10a** and 0.36 mL (5.02 mmol) of acetyl chloride afforded 0.735 g (84%) of **15c**: mp 164–165 °C; ^1H NMR ($CDCl_3$) δ 2.28 (br s, 3H), 4.54 (br s, 2H), 7.00 (d, *J* = 8.5 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.21 (m, 2H), 9.19 (br s, 1H). Anal. ($C_{10}H_{10}N_2O_2$) H, N; C: calcd, 63.15; found, 62.69.

4-(2-Chlorophenyl)-1,2,3,4-tetrahydroquinoxalin-2-one (15d). In the same manner as for **15b**, **10a** (2.11 g, 14.2 mmol) and 2-chlorobenzoyl chloride (2.99 g, 17.1 mmol) afforded 2.74 g (67%) of **15d**: mp 222.5–224 °C; MS *m/z* 286; IR 1687, 1665, 1500, 755, 1154 cm^{-1}. Anal. ($C_{15}H_{11}ClN_2O_2$) C, H, N.

5-[(*tert*-Butyloxy)carbonyl]-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydroimidazo[1,5-*a*]quinoxaline (13a). A solution of 1.031 g (4.15 mmol) of **15a** in 5 mL of THF was cooled at 0 °C. To this was added 4.6 mL (4.57 mmol) of 1 M potassium *tert*-butoxide (in THF). After the addition the ice bath was removed, and the reaction mixture was allowed to warm to room temperature over 45 min. The reaction mixture was then cooled at −78 °C, and 0.66 mL (4.57 mmol) of diethyl chlorophosphate was added. The reaction mixture was stirred at −78 °C for 15 min and then allowed to warm over the next 45 min. The reaction mixture was again cooled to −78 °C, and 0.68 g (4.57 mmol) of 5-cyclopropyl-3-(isocyanomethyl)-1,2,4-oxadiazole[11] was added, followed by 4.6 mL of 1 M potassium *tert*-butoxide. The reaction mixture was stirred for 2 h at −78 °C and then allowed to warm for 30 min, after which it was partitioned between ethyl acetate and water, followed by two brine washes. The organic layers were dried over magnesium sulfate, concentrated, and chromatographed on silica gel (200 mL) using MeOH/dichloromethane (2/98) to give 1.50 g (95%) of **13a** as a solid. Recrystallization from MeOH/EtOAc/hexane gave 1.07 g of product: mp 203.5–204.5 °C; MS *m/z* 379; IR 1706, 1509, 1574, 1308, 1214 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (m, 2H), 1.37 (m, 2H), 1.52 (s, 9H), 2.28 (m, 1H), 5.23 (s, 2H), 7.29 (m, 2H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.76 (br d, *J* = 8 Hz, 1H), 8.10 (s, 1H). Anal. ($C_{20}H_{21}N_5O_3$) C, H, N.

5-Benzoyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydroimidazo[1,5-*a*]quinoxaline (13b). In the same manner as for **13a**, with the addition of 0.25 mL of DMF after the addition of diethyl chlorophosphate, 0.6703 g (2.66 mmol) of **15b** afforded 0.530 g (52%) of **13b**: mp 198–199 °C (from dichloromethane/ethyl acetate/hexane); MS *m/z* 383; IR 1663, 1506, 1574, 762,

1481 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 4H), 2.25 (m, 1H), 5.40 (br s, 2H), 7.05 (m, 2H), 7.3–7.45 (m, 6H), 7.59 (d, J = 8.5 Hz, 1H), 8.20 (s, 1H). Anal. ($C_{22}H_{17}N_5O_2$) H, N; C: calcd, 68.92; found, 68.32.

5-Acetyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydroimidazo[1,5-*a*]quinoxaline (13c). In the same manner as for **13a**, 0.5054 g (2.66 mmol) of **15c** afforded 0.456 g (53%) of product, which was recrystallized from dichloromethane/ethyl acetate/hexane to give 0.368 g (43%) of **13c**: mp 187–188 °C; MS m/z 321; IR 1576, 1654, 1505, 1387, 1355 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 2H), 1.38 (m, 2H), 2.3 (br m, 4H), 5.30 (br s, 2H), 7.37 (m, 2H), 7.60 (m, 1H), 8.13 (s, 1H). The signal for H_6 is very broadened in the aromatic region. Anal. ($C_{17}H_{15}N_5O_2$) C, H, N.

5-Acetyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydro-4,4-dimethylimidazo[1,5-*a*]quinoxaline (13d). A mixture of 0.294 g (0.956 mmol) of **12a** and 4 mL of acetic anhydride was stirred at 110 °C for 3 days. Excess acetic anhydride was then removed under reduced pressure, and the residue was partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layers were filtered through sodium sulfate and evaporated to dryness. The residue was crystallized from dichloromethane/ethyl acetate to give 0.279 g (83%) of **13d**: mp 162–163 °C; MS m/z 349; IR 1567, 1512, 1281, 1671, 1319 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 2H), 1.35 (m, 2H), 1.90 (s, 6H), 2.15 (s, 3H), 2.27 (m, 1H), 7.17 (dd, J = 1.9, 7.8 Hz, 1H), 7.32 (m, 2H), 7.51 (dd, J = 2.1, 6.9 Hz, 1H), 8.12 (s, 1H). Anal. ($C_{19}H_{19}N_5O_2$) C, H, N.

5-(2-Chlorobenzoyl)-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydroimidazo[1,5-*a*]quinoxaline (13e). A slurry consisting of 0.492 g (1.76 mmol) of **12b**, 0.268 mL (2.11 mmol) of 2-chlorobenzoyl chloride, 0.0538 g (0.44 mmol) of (dimethylamino)pyridine, 0.368 g (2.11 mmol) of diisopropylethylamine, and 9 mL of THF was stirred at room temperature for 1.5 h. The mixture was then partitioned between ethyl acetate, aqueous sodium bicarbonate, and brine. The product was poorly soluble in both the organic and aqueous phases; filtration of the extraction solvents yielded additional material. The crude product was then triturated with ethyl ether and dried to give 0.53 g (72%) of **13e**: mp 254–256 °C; MS m/z 417, 419; IR 1659, 1576, 1508, 765, 1394 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H). The remaining peaks are extremely broadened. Anal. ($C_{22}H_{16}ClN_5O_2$) H; C: calcd, 63.24; found, 62.58; N: calcd 16.76; found, 16.30.

***tert*-Butyl 5-(2-Chlorobenzoyl)-7-fluoro-4,5-dihydroimidazo[1,5-*a*]quinoxaline-3-carboxylate (13f).** In the same manner as for **13a**, 0.997 g (3.71 mmol) of **15d** and 0.628 g (4.45 mmol) of *tert*-butyl isocyanoacetate afforded 0.720 g (47%) of **13f** after chromatograpy and crystallization from dichloromethane/ethyl ether/hexane: mp 199–200.5 °C; MS m/z 409; IR 1659, 1700, 1143, 1295, 1509, 1493 cm^{-1}; ^{1}H NMR ($CDCl_3$) diffuse peaks for all but the C-1 proton at 8.06 (s, 1H). Anal. ($C_{22}H_{20}ClN_3O_3$) C, H, N.

***tert*-Butyl 5-[(*tert*-Butyloxy)carbonyl]-4,5-dihydroimidazo[1,5-*a*]quinoxaline-3-carboxylate (13g).** In the same manner as for **13a**, **15a** (0.938 g, 3.78 mmol) and *tert*-butyl isocyanoacetate (0.64 g, 4.54 mmol) afforded 0.808 g (57%) of **13g**: mp 178–180 °C; MS m/z 371; IR 1711, 1367, 1154, 1509, 1300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 9H), 1.63 (s, 9H), 5.17 (s, 2H), 7.28 (m, 2H), 7.50 (dd, J = 1.6, 7.7 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 8.00 (s, 1H). Anal. ($C_{20}H_{25}N_3O_4$) C, H, N.

***tert*-Butyl 5-Acetyl-4,5-dihydroimidazo[1,5-*a*]quinoxaline-3-carboxylate (13h).** In the same manner as for **13a**, **15c** (0.555 g, 2.92 mmol) and *tert*-butyl isocyanoacetate (0.495 g, 3.50 mmol) afforded 0.462 g (50%) of **13h**: mp 150–152 °C; MS m/z 313; IR 1691, 1669, 1502, 1154, 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 9H), 2.28 (bs, 3H), 5.27 (bs, 2H), 7.25 (m, 1H), 7.37 (m, 1H), 8.03 (s, 1H). The signal for H_6 is very broadened near δ 7.3. Anal. ($C_{17}H_{19}N_3O_3$) C, H, N.

5-Acetyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-7-fluoro-4,5-dihydroimidazo[1,5-*a*]quinoxaline (13k). A mixture of 0.340 g (1.14 mmol) of **12c**, 0.5 mL of acetic anhydride, and 1 mL of THF was heated at 80 °C for 4 h. An additional 1 mL of acetic anhydride was added, and the temperature was increased to 100 °C, allowing the THF to evaporate. After 10–15 min **12c** went into solution, and the reaction mixture was heated an additional 1 h and then cooled. Chromatography on silica gel (150 mL) using methanol/dichloromethane (2/98), followed by crystallization from dichloromethane and hexane, gave 0.259 g (67%) of **13k**: mp 180.5–182.5 °C; MS m/z 339; IR 1512, 1577, 1669, 1221, 1622 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (m, 2H), 2.36 (m, 2H), 2.28 (m, 1H), 2.35 (br s, 3H), 5.28 (br s, 2H), 7.09 (m, 1H), 7.26 (m, 1H), 7.58 (m, 1H), 8.08 (s, 1H). Anal. ($C_{17}H_{14}FN_5O_2$) H; C: calcd, 60.17; found, 59.57; N: calcd, 20.64; found 20.08.

5-Benzoyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-7-fluoro-4,5-dihydroimidazo[1,5-*a*]quinoxaline (13l). To 0.5526 g (1.86 mmol) of **12c**, 0.250 g (2.04 mmol) of (dimethylamino)pyridine, and 20 mL of THF was added 0.24 mL (2.04 mmol) of benzoyl chloride. After 50 min, 6 mL of DMF was added. After stirring overnight, TLC showed some **12c** still remaining. An additional 0.24 mL of benzoyl chloride was added, followed by 0.36 mL (2.04 mmol) of diisopropylethylamine. The mixture was stirred for 24 h and then partitioned between ethyl acetate, water, and brine. The organic layers were dried over magnesium sulfate, and the crude product was chromatographed on silica gel (300 mL) using a 1:10 mixture of ethyl acetate and MeOH/dichloromethane (2/98). The product was crystyallized from dichloromethane and hexane to give 0.388 g (52%) of **13l**: mp 190–193 °C; MS m/z 401; IR 1367, 1672, 1515, 1499, 1577 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 4H), 2.20 (m, 1H), 5.35 (s, 2H), 6.89 (br d, 1H), 7.00 (m, 1H), 7.35–7.60 (m, 6H), 8.14 (s, 1H). Anal. ($C_{22}H_{16}FN_5O_2$) C, H, N.

2-Fluoro-6-nitrobenzamide (22). A mixture of 5.01 g (27.06 mmol) of **21**[21] and 20 mL of thionyl chloride was stirred at reflux for 2 h. After cooling, the excess thionyl chloride was removed and the residue was stirred at 0 °C in 5 mL of dichloromethane. Ammonium hydroxide (30%) was added cautiously (exotherm!) until no acid chloride remained. The solid was collected, washed with water and a small amount of dichloromethane, and dried to give 4.29 g (86%) of **22**: mp 161–162 °C; MS m/z 184; IR 1517, 1676, 3443, 1599, 1358 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.0 (br d, 2H), 7.48 (m, 1H), 7.59 (m, 1H), 7.95 (d, J = 8.2 Hz, 1H). Anal. ($C_7H_5FN_2O_3$) C, H, N.

***N*-[(*tert*-Butyloxy)carbonyl]-2-fluoro-6-nitroaniline (23).** To a slurry of 4.29 g (23.3 mmol) of **22** in 50 mL of dry *tert*-butyl alcohol was added 11.08 g (25.0 mmol) of lead tetraacetate which had been stored under high vacuum for several hours to remove acetic acid. After being stirred at reflux for 1.5 h, the mixture was cooled and excess *tert*-butyl alcohol was removed. Acetone was added to dissolve the product, and the slurry was filtered through Celite. The filtrate was concentrated, and the residue was chromatographed on silica gel (350 mL) using ethyl acetate/hexane (5/95) to give 3.67 g of product. Recrystallization from ethyl ether and hexane gave 3.25 g (62%) of **23**: mp 100–101 °C; MS m/z 256; IR 1703, 1547, 1353, 1269, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H), 7.26 (dt, J = 5.1, 8.4 Hz, 1H), 7.42 (m, 2H), 7.83 (dt, J = 1.4, 8.4 Hz, 1H). Anal. ($C_{11}H_{13}FN_2O_4$) C, H, N.

***N*-[(*tert*-Butyloxy)carbonyl]-*N*-(2-fluoro-6-nitrophenyl)-glycine Ethyl Ester (24).** To an ice-cooled solution of 1.85 g (8.25 mmol) of **23** in 15 mL of THF was added (dropwise, over 5 min) 8.67 mL (8.67 mmol) of 1 M potassium *tert*-butoxide in THF. After 20 min, 0.96 mL (8.67 mmol) of ethyl bromoacetate was added dropwise over several minutes. The ice bath was removed, and the mixture was stirred for 2 h, after which time it was partitioned between ethyl acetate, aqueous sodium bicarbonate/brine, and brine. The organic layers were dried over magnesium sulfate to give 2.06 g (73%) of **24**: mp 80–81.5 °C; IR 1535, 1752, 1715, 1200, 1192 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2:1 mixture of rotamers, δ 1.26, 1.30 (t, J = 7.1 Hz, 3H), 1.35, 1.50 (s, 6H), 1.50 (s, 3H), 3.94–4.27 (m, 3H), 4.44, 4.45 (d, J = 15 Hz, 1H), 7.42 (m, 2H), 7.39 (m, 1H). Anal. ($C_{15}H_{19}FN_2O_6$) C, H, N.

4-[(*tert*-Butyloxy)carbonyl]-5-fluoro-1,2,3,4-tetrahydroquinoxalin-2-one (25). A mixture of 2.06 g (6.02 mmol) of **24** and 0.19 g of 10% Pd/C in 150 mL of methanol was shaken under hydrogen on a Parr apparatus at 37 psi for 1 h. The catalyst was then filtered off, and 0.016 g (0.08 mmol) of *p*-toluenesulfonic acid was added. The solution was stirred at 80 °C for 1 h and then at room temperature overnight. The solvent was then removed, and the residue was chromatographed on silica gel (200 mL) using ethyl acetate/dichloromethane (5/95) to give 1.64 g (100%) of **25**: mp 155–156 °C; MS m/z 266; IR 1717, 1698, 1332, 1162, 1498 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 6.69 (dd, J = 1, 8.1 Hz, 1H), 6.84 (dt, J = 1, 9.8 Hz, 1H), 7.12 (dt, J = 5.2, 8.2

Hz, 1H), 8.61 (br s, 1H). Anal. ($C_{13}H_{15}FN_2O_3$) H, N; C: calcd, 58.64; found, 57.75.

5-[(*tert*-Butyloxy)carbonyl]-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-6-fluoro-4,5-dihydroimidazo[1,5-*a*]quinoxaline (26). In the same manner as for **13a**, 1.64 g (6.16 mmol) of **25** afforded 1.14 g (47%) of **26**. In the workup step, the product was a suspension in the organic phase, so the organic phases were collected without filtration through drying agent. Chromatography was performed on 250 mL of silica gel using methanol/dichloromethane (2/98): mp 199–200 °C; MS *m/z* 397; IR 1715, 1494, 1505, 1226, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (m, 2H), 1.36 (m, 2H), 1.45 (s, 9H), 2.27 (m, 1H), 7.10 (t, J = 9 Hz, 1H), 7.32 (m, 2H), 8.12 (s, 1H). The C-4 proton signals are extremely broadened in the region of δ 5. Anal. Calcd ($C_{20}H_{20}FN_5O_3$) C, H, N.

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-6-fluoro-4,5-dihydroimidazo[1,5-*a*]quinoxaline (27). A mixture of 3.39 g (8.53 mmol) of **26** and 50 mL of HCl/MeOH was stirred at room temperature overnight. The solvent was then removed in vacuo, and the residue was partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layers were dried over sodium sulfate and taken to dryness to give 2.62 g (theoretical, 2.54 g) of **27** which was used without further purification: mp 201.5–202.5 °C; MS *m/z* 297; IR 1577, 1206, 1520, 1410, 1214 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (m, 2H), 1.35 (m, 2H), 2.26 (m, 1H), 4.32 (br s, 1H), 4.86 (d, J = 1.6 Hz, 2H), 6.78 (dt, J = 5.5, 8.3 Hz, 1H), 6.95 (t, J = 10 Hz, 1H), 7.22 (d, J = 8.1 Hz, 1H), 8.06 (s, 1H). Anal. ($C_{15}H_{12}FN_5O$) C, H, N.

5-Acetyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-6-fluoro-4,5-dihydroimidazo[1,5-*a*]quinoxaline (13l). A solution of 0.504 g (2.70 mmol) of **27**, 0.03 g (0.24 mmol) of (dimethylamino)-pyridine, and 12 mL of acetic anhydride was stirred at 100 °C for 1 h. After cooling, excess acetic anhydride was removed and the residue was partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layers were dried over sodium sulfate and concentrated. Chromatography on silica gel (320 mL) using methanol/dichloromethane (2/98) gave a poor separation of the product from the imine byproduct. The imine impurity was successfully removed by taking up the mixture in dichloromethane and allowing the imine to precipitate. The solids were removed by filtration, the filtrate was concentrated, and the product was crystallized from dichloromethane and hexane to give 0.349 g (61%) of **13l**: mp 208.5–210.0 °C; MS *m/z* 339; IR 1671, 1503, 1254, 879, 1204 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (m, 2H), 2.38 (m, 2H), 2.13 (br s, 3H), 2.29 (m, 1H), 7.16 (m, 1H), 7.41 (m, 2H), 8.13 (s, 1H). The C-4 proton signals are broadened into the baseline. Anal. ($C_{17}H_{14}FN_5O_2$) C, H, N.

5-Benzoyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-6-fluoro-4,5-dihydroimidazo[1,5-*a*]quinoxaline (13j). In the same manner as for **13l**, 0.438 g (1.47 mmol) of **27** afforded 0.481 g (82%) of **13j**: mp 234.5–235.5 °C (from dichloromethane/hexane); MS *m/z* 401; IR 1660, 1502, 1366, 786, 1247 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (m, 4H), 2.20 (m, 1H), 5.32 (v br s), 6.98 (br t, 1H), 7.3–7.5 (m, 7H), 8.19 (s, 1H). Anal. ($C_{22}H_{16}FN_5O_2$) C, H, N.

5-(Chlorocarbonyl)-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydro-4,4-dimethylimidazo[1,5-*a*]quinoxaline (16a). To a mixture of 0.647 g (2.10 mmol) of **12b**, 0.55 mL (3.15 mmol) of diisopropylethylamine, and 10 mL of THF was added 3.3 mL (3.15 mmol) of phosgene (1.09 M in toluene). After 2.5 h an additional 0.33 mL of diisopropylethylamine and 2.0 mL of phosgene solution were added. The mixture was stirred for 2 more hours, and a final addition of 0.15 mL of diisopropylethylamine and 0.5 mL of phosgene solution were added. The mixture was stirred a final 30 min and then poured onto ice/aqueous sodium bicarbonate. (Caution: gas evolution.) The mixture was extracted with ethyl ether and washed with brine. The organic layers were dried with magnesium sulfate and concentrated to give 0.651 g (84%) of **16a** as a solid which could be stored in the refrigerator for several weeks: MS *m/z* 369, 371; IR 1754, 1575, 1182, 1508, 1478 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (m, 2H), 1.35 (m, 2H), 1.90 (s, 6H), 2.29 (m, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.54 (t, J = 9 Hz, 2H), 8.15 (s, 1H). Anal. ($C_{18}H_{16}ClN_5O_2$) C, H, N.

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydro-4,4-dimethyl-5-(methoxycarbonyl)imidazo[1,5-*a*]quinoxaline (17a). Sodium metal (0.0136 g, 0.593 mmol) was added to 20 mL of MeOH, and the reaction mixture was stirred until the metal was consumed. To this was added 0.209 g (0.565 mmol) of **16a** as a suspension in MeOH. After 25 min the solvent was removed under reduced pressure and the residue was partitioned between dichloromethane, water, and aqueous sodium bicarbonate. The organic layers were filtered through sodium sulfate and concentrated. The crude product was crystallized from dichloromethane and hexane to give 0.198 g (96%) of **17a**: mp 183–184 °C; MS *m/z* 365; IR 1725, 1296, 1569, 1256, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (m, 2H), 1.36 (m, 2H), 1.88 (s, 6H), 2.28 (m, 1H), 3.68 (s, 3H), 7.28 (m, 2H), 7.36 (m, 1H), 7.48 (m, 1H), 8.09 (s, 1H). Anal. ($C_{18}H_{16}N_5O_3$) C, H, N.

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-4,5-dihydro-4,4-dimethyl-5-(isopropoxycarbonyl)imidazo[1,5-*a*]quinoxaline (17b). Sodium metal (0.0137 g, 0.616 mmol) was stirred in 2-propanol until the metal was consumed. To this was added 0.207 g (0.560 mmol) of **16a** as a suspension in isopropanol. After stirring for 4 h, the solvent was removed under reduced pressure, and the residue was partitioned between dichloromethane, water, and aqueous sodium bicarbonate. The organic layers were filtered through sodium sulfate and concentrated. The crude product was crystallized from dichloromethane and hexane to give 0.195 g (88%) of **17b**: mp 172.5–173.0 °C; MS *m/z* 393; IR 1716, 1252, 1288, 1510, 1291 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, J = 6.2 Hz, 6H), 1.25 (m, 2H), 1.35 (m, 2H), 1.88 (s, 6H), 2.28 (m, 1H), 4.98 (sept, J = 6.2 Hz, 1H), 7.25 (m, 2H), 7.38 (m, 1H), 7.47 (m, 1H), 8.09 (s, 1H). Anal. ($C_{21}H_{23}N_5O_3$) C, H, N.

Ethyl 4,5-Dihydroimidazo[1,5-*a*]quinoxaline-3-carboxylate (18). In the same manner as for **13a**, 1.01 g (6.81 mmol) of **10a** and 0.82 mL (7.50 mmol) of ethyl isocyanoacetate afforded 1.009 g (61%) of **18**: mp 248–250 °C; MS *m/z* 243; IR 1717, 1174, 745, 3252, 1619 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (t, J = 7.2 Hz, 3H), 4.08 (br s, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.83 (d, J = 1.8 Hz, 2H), 6.80 (dd, J = 1.2, 8.0 Hz, 1H), 6.85 (dt, J = 1.2, 7.7 Hz, 1H), 7.11 (dt, J = 1.3, 7.7 Hz, 1H), 7.39 (dd, J = 1.3, 8.0 Hz, 1H), 7.99 (s, 1H). Anal. ($C_{13}H_{13}N_3O_2$) C, H, N.

3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dihydroimidazo[1,5-*a*]quinoxaline (19). Sodium hydride (60% in oil; 0.142 g, 3.55 mmol) was washed three times with pentane. THF (30 mL) was added, followed by 0.356 g (3.55 mmol) of cyclopropyl carboxamide oxime.[11] After 10 min, 0.786 g (3.23 mmol) of **18** was added, followed by an additional 5 mL of THF. After an hour, 14 mL of DMF was added. The reaction mixture was stirred an additional 4 h, after which the solvents were removed. Water was added to the residue, and the solid was collected, washed with a small amount of ethyl ether, and dried under vacuum to give 0.480 g (53%) of **19**: mp 248–250 °C; MS *m/z* 279; IR 1636, 1521, 1595, 1570, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (m, 2H), 1.15 (m, 2H), 1.93 (NH and H_2O), 2.15 (m, 1H), 4.85 (d, J = 1.5 Hz, 2H), 6.84 (dd, J = 1.2, 8.0 Hz, 2H), 7.14 (dt, J = 1.3, 7.8 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H).

5-Acetyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dihydroimidazo[1,5-*a*]quinoxaline (20). A mixture of 0.201 g (0.720 mmol) of **19**, 3 mL of acetic anhydride, and 0.7 mL of THF was heated at 80 °C for 45 min. The mixture was then cooled, concentrated, and partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layers were filtered through sodium sulfate and concentrated. The crude product was crystallized from dichloromethane and hexane and then recrystallized from ethyl ether/ethyl acetate/hexane to give 0.20 g (87%) of **20**: mp 202.0–202.5 °C; MS *m/z* 321; IR 1674, 1639, 1501, 1358, 1401 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (m, 2H), 1.19 (m, 2H), 2.18 (m, 1H), 2.29 (br s, 3H), 5.32 (br s, 2H), 7.27 (m, 1H), 7.41 (m, 2H), 7.62 (m, 1H), 8.15 (s, 1H). Anal. ($C_{17}H_{15}N_5O_2$) C, H, N.

$GABA_A$ Receptor Expression. DNA manipulations and general baculovirus methods (Sf-9 cell cultivation, infection and isolation, and purification of recombinant viruses) were performed as described elsewhere.[22] The Sf-9 cells were infected at a multiplicity of infection of three plaque-forming units of viruses: AcNPV-α1 or -α6, AcNPV-β2 and AcNPV-γ2. Infected cells were used for electrophysiological measurements at 48 h postinfection or for membrane preparations at 60 h postinfection. The stable cell lines expressing α1 or α6, β2, and γ2 subunits of $GABA_A$ were derived by transfection of plasmids containing cDNA and a plasmid encoding G418 resistance into human kidney cells (A293

cells) as described elsewhere.[23] After 2 weeks of selection in 1 mg/mL G418, cells positive for all three $GABA_A$ receptor mRNAs by Northern blotting were used for electrophysiology to measure GABA-induced Cl^- currents. For equilibrium binding measurements, Sf-9 cells infected with baculovirus-carrying cDNAs for $\alpha 1$ or $\alpha 6$, $\beta 2$, and $\gamma 2$ subunits were harvested in 2-L batches 60 h postinfection. The membranes were prepared following the procedure above[22] and were stored at −80 °C in a solution containing 300 mM sucrose, 5 mM Tris/HCl, pH 7.5, and glycerol to a final concentration of 20%. Equilibrium binding of [^{3}H]-flunitrazepam or [^{3}H]Ro-4513 to the cloned $GABA_A$ receptors was measured in a 500-μL volume of normal saline containing 6 nM of [^{3}H]flunitrazepam or [^{3}H]Ro-4513, varying concentrations of test ligands and 50 μg of membrane protein. The mixture was incubated for 60 min at 4 °C, filtered over a Whatman glass fiber filter, and washed four times with cold normal saline. The filter was then counted for radioactivity in the presence of a scintillation cocktail (Insta Gel).

Cerebellar (A1) and Spinal Cord (A2) Regional Binding. Rat spinal cord neuronal or cerebellar membranes freshly prepared are suspended in 300 mM sucrose, 10 mM Hepes/Tris, pH 7.4. Typically, the reaction medium contains 6 nM [^{3}H]-flunitrazepam, 50 μg of membrane protein, test drugs at various concentrations, or vehicle in 200 μL, 118 mM NaCl, 10 mM Hepes/Tris, pH 7.4, and 1 mM $MgCl_2$. The mixtures are incubated for 60 min at 4 °C. The amount of binding is determined with rapid filtration techniques using Whatman GF/B filters.

[^{35}S]-*tert*-Butylbicyclophosphorothionate ([^{35}S]TBPS) Binding and Measurements of $^{36}Cl^-$ Uptake. Measurements of [^{35}S]TBPS binding and chloride-36 uptake were performed as described elsewhere.[24]

Metrazole Antagonism. Compounds were tested for their ability to antagonize metrazole-induced convulsions in rats after ip injection as described elsewhere.[25]

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