values and 95% confidence limits.

Cisplatin-Induced Emesis in Ferrets and Dogs. A modified procedure reported by Gylys et al.[20] was followed. The inhibitory activity of the test compounds toward emesis induced by iv administration of cisplatin in ferrets (14 mg/kg) or in dogs (5 mg/kg) was studied. For iv evaluation, animals were pretreated with two doses of the compound intravenously 30 min prior to and 60 min after challenge with cisplatin and then the number of emetic episodes and retches was monitored for 5 h (**44a** and **54a**), or animals were pretreated with one dose of the compound intravenously right before challenge with cisplatin, and then the number of emetic episodes and retches was monitored for 5 h (**64**). For po evaluation, animals were pretreated with the compound orally 60 min prior to challenge with cisplatin, and then the number of emetic episodes and retches was monitored for 5 h (**44a** and **64**). Drugs were prepared daily in saline for iv administration or distilled water for po administration before use. The results were expressed as mean ± SE. Statistical analysis was performed using Student's *t* test.

Acknowledgment. We thank Director Akiyoshi Kawasaki of Research Headquarters of Ono Pharmaceutical Co., Ltd. for his warm encouragement throughout this work. We are also grateful to Professor Hisashi Yamamoto of Nagoya University for his helpful advice and stimulating discussions.

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Synthesis and Excitatory Amino Acid Pharmacology of a Series of Heterocyclic-Fused Quinoxalinones and Quinazolinones

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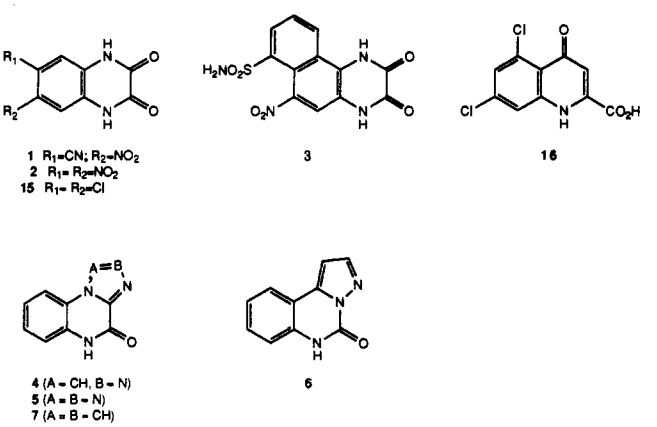
As part of our program aimed at the development of potent excitatory amino acid antagonists, we synthesized and evaluated a series of substituted 1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-ones, **4**, tetrazolo[1,5-*a*]quinoxalin-4(5*H*)-ones, **5**, and pyrazolo[1,5-*c*]quinazolin-5(6*H*)-ones, **6**, and an imidazo[1,2-*a*]quinoxalin-4(5*H*)-one, **7**. In general, the same heterocycles which demonstrated the best affinity for the AMPA receptor also demonstrated the best affinity for the glycine site on the NMDA receptor complex. 1-Propyl-7,8-dichloro-1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-one, **4d**, was found to bind with the greatest affinity to the AMPA receptor with an IC_{50} of 0.83 μM and antagonized 40 μM AMPA-induced depolarization in the cortical slice preparation with an IC_{50} of 44 μM. 7,8-Dichloro-1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-one, **4a**, and 7,8-dichloroimidazo[1,2-*a*]quinoxalin-4(5*H*)-one, **7**, possessed the best affinity for the glycine site with IC_{50} values of 0.63 and 1.26 μM, respectively. It is noteworthy that the SAR for the heterocyclic compounds did not directly parallel that of known quinoxalinediones (e.g. DNQX, **2**, and DCQX, **15**) at the AMPA receptor nor that of the kynurenic acids at the glycine site on the NMDA receptor complex.

Glutamate neurotoxicity is thought to play a role in a number of pathophysiological conditions including ischemia,[1] brain[2] and spinal cord trauma,[3] and a variety of neurodegenerative disorders.[4] Excitatory amino acid antagonists may have important therapeutic potential in the treatment of these disease states. Although molecular biologist's cloning efforts are in the process of further defining glutamate receptors, at least three ionotropic glutamate receptors have been identified by classical methodology. These ionotropic receptors are named for the agonists which activate them: *N*-methyl-D-aspartic acid (NMDA), 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA), and kainic acid (KA). Several modulatory sites have been identified for the NMDA receptor-ion channel complex including a glutamate recognition site, a glycine recognition site, and an ion channel site to which compounds such as phencyclidine (PCP) and MK-801 (dizocilpine) bind.[5]

A number of quinoxalinediones, including 6-cyano-7-nitroquinoxaline-2,3-dione (**1**, CNQX), 6,7-dinitroquinoxaline-2,3-dione (**2**, DNQX), and 6-nitro-7-sulfamoylbenzo[*f*]quinoxaline-2,3-dione (**3**, NBQX) are potent antagonists of the AMPA receptor (Chart I).[6]

Chart I



CNQX and DNQX were found to also have affinity for the glycine binding site on the NMDA receptor.[7] As part of

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† Royal Veterinary College.

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(3) Faden, A. I.; Ellison, J. A.; Noble, L. J. Effects of competitive and noncompetitive NMDA receptor antagonists in spinal cord injury. *Eur. J. Pharmacol.* **1990**, *175*, 165–174.

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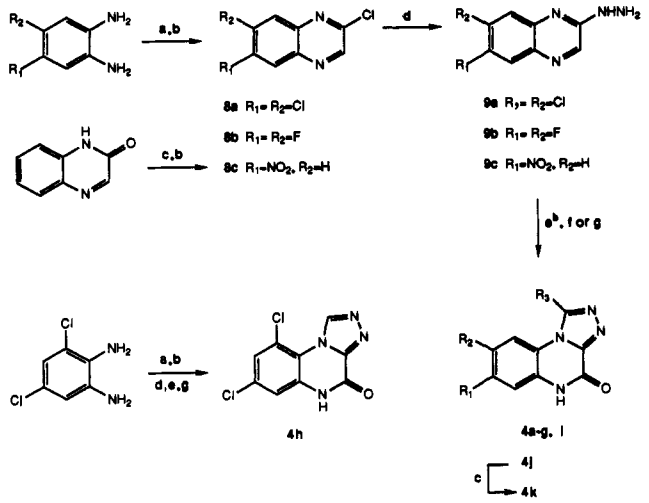
Scheme I.[a] Synthesis of Triazolo Compounds



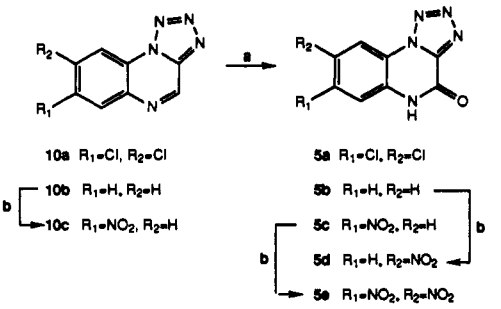
[a] (a) HCOCOOH; (b) $POCl_3$; (c) KNO_3, H_2SO_4; (d) NH_2NH_2; (e) $R^3C(OR)_3$; (f) H_2O_2; (g) MMPP. [b] CF_3COOH used in the case of **4g**.

our program aimed at the development of potent excitatory amino acid antagonists, we synthesized and evaluated a series of substituted 1,2,4-triazolo[4,3-*a*]quinoxalin-4-(5*H*)-ones, **4**, tetrazolo[1,5-*a*]quinoxalin-4(5*H*)-ones, **5**, and pyrazolo[1,5-*c*]quinazolin-5(6*H*)-ones, **6**, and an imidazo-[1,2-*a*]quinoxalin-4(5*H*)-one, **7** (Chart I).

Chemistry

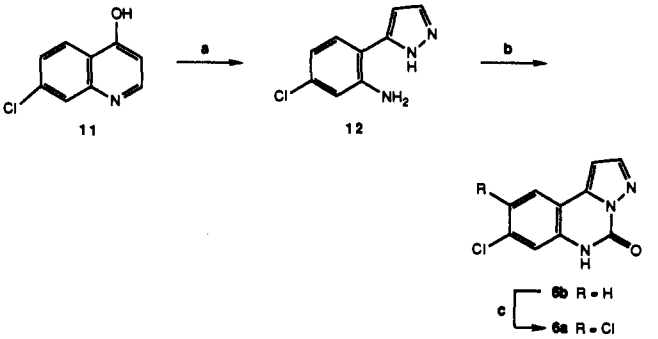
The substituted 1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-ones, **4a–k**, were prepared using established methodology as shown in Scheme I.[8] Condensation of 4,5-dichlorophenylenediamine with glyoxylic acid hydrate followed by chlorination with phosphorus oxychloride afforded 2,6,7-trichloroquinoxaline, **8a**. Treatment of **8a** with hydrazine yielded the corresponding 2-hydrazino compound **9a** which was condensed with a variety of ortho esters and oxidized using hydrogen peroxide in acetic acid to give **4a–f**. The trifluoromethyl analog, **4g**, was prepared in a similar manner except that the condensation step utilized trifluoroacetic acid instead of an ortho ester.

Scheme II.[a] Synthesis of Tetrazolo Compounds



[a] (a) H_2O_2; (b) KNO_3, H_2SO_4.

Scheme III.[a] Synthesis of Pyrazolo Compounds



[a] (a) NH_2NH_2; (b) $Cl_3COCOOCl_3$, K_2CO_3; (c) SO_2Cl_2, AcOH.

Using the unsymmetrical 3,5-dichlorophenylenediamine, we obtained a 7:1 mixture of 2,6,8-trichloroquinoxaline and 2,5,7-trichloroquinoxaline. This mixture was treated as described above except that the oxidation of the triazoloquinoxalines to the triazoloquinoxalinones was accomplished using the magnesium salt of monoperoxyphthalic acid (MMPP). We have found this to be an excellent way to accomplish the general conversion of quinoxalines to quinoxalinones. Recrystallization of the product mixture afforded the desired product, **4h**, contaminated with less than 2% of the 6,8-dichloro isomer by ^{1}H-NMR analysis. The difluoro analog, **4i**, was prepared from the corresponding 4,5-difluorophenylenediamine as described for **4h**.

The nitro analogs, **4j** and **4k**, were obtained using standard nitration chemistry. The 2-chloro-6-nitroquinoxaline, **8c**, was obtained by nitration of quinoxalin-2-one with KNO_3 in concentrated H_2SO_4 at 0 °C followed by chlorination with $POCl_3$. Conversion of **8c** to **4j** was accomplished as described above for **4a–f**. More vigorous nitration conditions (KNO_3/H_2SO_4 at 60 °C) were used to convert the mononitro compound **4j** to the dinitro analog **4k**.

7,8-Dichlorotetrazolo[1,5-*a*]quinoxalin-4(5*H*)-one, **5a**, was prepared using similar chemistry to that employed in constructing the triazolo series (Scheme II).[8b,9] Treatment of 2,6,7-trichloroquinoxaline, **8a**, with sodium azide afforded the tetrazoloquinoxaline, **10a**. Oxidation of **10a** with hydrogen peroxide yielded the corresponding dichlorotetrazoloquinoxalinone, **5a**. The unsubstituted quinoxaline, **10b**, and quinoxalinone, **5b**, were obtained using this methodology. Various nitro derivatives of the tetrazoloquinoxalinone series were prepared by taking

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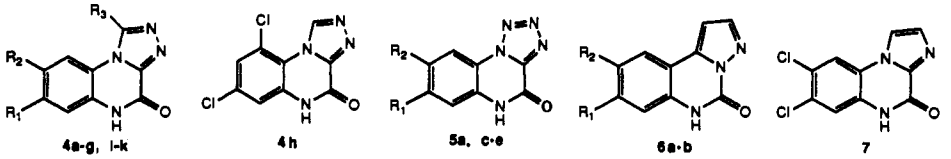
Table I. Displacement of [^{3}H]AMPA[a] and [^{3}H]Glycine Binding



compound	R_1	R_2	R_3	[^{3}H]AMPA[b] K_i[d] (μM)	[^{3}H]glycine[c] K_i[d] (μM)
4a	Cl	Cl	H	4.69 ± 0.69	0.63 ± 0.21
4b	Cl	Cl	Me	4.45 ± 1.41	>10
4c	Cl	Cl	Et	4.78 ± 1.13	4.58 ± 1.48
4d	Cl	Cl	*n*-Pr	0.83 ± 0.13	3.92 ± 0.19
4e	Cl	Cl	*n*-Bu	1.71 ± 1.20	1.48 ± 0.29
4f	Cl	Cl	Ph	>10	>10
4g	Cl	Cl	CF_3	>10	>10
4h				3.24 ± 1.07	2.85 ± 2.20
4i	F	F	H	>10	>10
4j	NO_2	H	H	0.99 ± 0.08	7.35 ± 0.21
4k	NO_2	NO_2	H	5.49 ± 0.92	5.12 ± 2.02
5a	Cl	Cl		>10	>10
5c	NO_2	H		>10	>10
5d	H	NO_2		>10	>10
5e	NO_2	NO_2		>10	>10
6a	Cl	Cl		>10	>10
6b	Cl	H		>10	>10
7				7.38 ± 1.16	1.26 ± 0.59
2				0.36 ± 0.07	0.39 ± 9.9
15				1.64 ± 0.79	0.21 ± 2.8
16				>10	0.04 ± 0.04

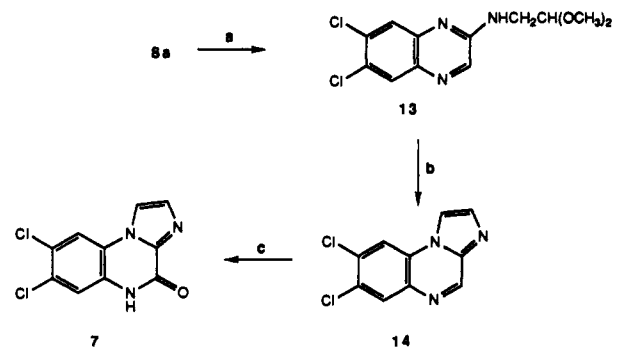
[a] 2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid. [b] K_i for displacement of [^{3}H]AMPA binding. Methodology described in Experimental Section. [c] K_i for displacement of [^{3}H]glycine binding. Methodology described in Experimental Section. [d] K_i values represent duplicate determinations performed in triplicate.

advantage of the different electrophilic substitution pattern of the quinoxalines versus the quinoxalinones. Mononitration of tetrazoloquinoxaline, **10b**, gave a mixture of the 7-nitro derivative, **10c**, and minor amount of another undetermined isomer. Compound **10c** was oxidized as before to provide 7-nitroquinoxalinone, **5c**. Compound **5c** was resubjected to nitrating conditions to give the 7,8-dinitro analog, **5e**. Mononitration of tetrazoloquinoxalinone, **5b**, gave rise to the 8-nitro analog, **5d**.

Synthesis of pyrazoloquinazolinones **6a** and **6b** employs a totally different strategy as shown in Scheme III.[10] 4-Hydroxy-7-chloroquinoline, **11**, was treated with hydrazine to give the anilino pyrazole, **12**, in an interesting rearrangement first reported by Alberti in 1957.[11] The quinazolinone ring was formed by reaction of **13** with triphosgene to afford the 8-chloropyrazoloquinazolinone, **6b**. We have found triphosgene to be of general utility in closing anilino heterocycles to the corresponding quinazolinone ring systems.[12] Conversion of the monochloride, **6b**, to the 8,9-dichloro compound, **6a**, was carried out employing sulfuryl chloride in acetic acid. When we attempted this transformation using *N*-chlorosuccinimide, the reaction did not proceed to completion.

8,9-Dichloroimidazo[1,2-*a*]quinoxalin-4(5*H*)-one, **7**, was prepared as described in Scheme IV.[13] Condensation of

Scheme IV.[a] Synthesis of 7,8-Dichloroimidazolo[1,2-*a*]quinoxalin-4(5*H*)-one



[a] (a) $H_2NCH_2CH(OCH_3)_2$; (b) HCl; (c) MMPP.

2,6,7-trichloroquinoxaline, **8a**, with aminoacetaldehyde dimethyl acetal resulted in the substituted quinoxaline, **13**, which was cyclized in methanolic HCl to give the imidazoquinoxaline, **14**. Oxidation of **14** with MMPP afforded the desired imidazoquinoxalinone, **7**.

Results and Discussion

The target compounds were evaluated for their ability to displace [^{3}H]AMPA, [^{3}H]glycine, [^{3}H]CGS 19755, and [^{3}H]kainate at a screening dose of 10 μM. K_i values were determined for those compounds which showed greater than 50% displacement at 10 μM (Table I). None of the compounds tested were found to affect significantly the binding of [^{3}H]kainate or [^{3}H]CGS 19755 at a concentration of 10 μM.

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In general, the triazolo[4,3-*a*]quinoxalin-4(5*H*)-ones, e.g. **4a**, showed the highest affinity for AMPA receptors among the four fused heterocyclic ring systems that we tested. A variety of C-1-substituted derivatives of **4a** were prepared in order to explore the effects of this substitution on receptor affinity. The highest affinity resided with those compounds possessing a linear, C_1 to C_4 *n*-alkyl chain, with the *n*-propyl- and *n*-butyl analogs **4d** and **4e** (K_i values of 0.83 ± 0.13 and 1.71 ± 1.20 μM, respectively) being somewhat preferred over the equipotent methyl- and ethyl-substituted compounds **4b** and **4c** (K_i values of 4.45 ± 1.41 and 4.78 ± 1.13 μM, respectively). Substitution at C-1 with phenyl or trifluoromethyl resulted in compounds whose AMPA receptor affinity (K_i) was greater than 10 μM. The difluoro analogue **4i** was significantly less active than the corresponding dichloro analogue **4a** with a K_i for the AMPA receptor greater than 10 μM.

Given the enhanced potency of **2** over 6,7-dichloroquinoxaline-2,3-dione, **15**, it might be expected that the 7,8-dinitro derivative, **4k**, would show enhanced receptor affinity for the AMPA receptor compared to the dichloro derivative, **4a**. Surprisingly, this was not the case as **4k** was equipotent to **4a**. However, the mononitro derivative, **4j**, had an K_i value of 0.99 ± 0.08 μM and was approximately 5 times more potent at displacing [^{3}H]AMPA binding than either the dichloro analog, **4a**, or the dinitro analog, **4k**. One possible explanation for this divergence might be that the additional fused heterocyclic ring imparts a significant change in the molecule's overall electronic nature. Another explanation may be that with the addition of the fused heterocyclic ring, there is now an unfavorable steric interaction for the dinitro compound **4k**.

Tetrazolo[1,5-*a*]quinoxalin-4(5*H*)-ones, **5a–d**, and pyrazolo[1,5-*c*]quinazolin-5(6*H*)-one, **6a**, did not significantly displace [^{3}H]AMPA binding at the screening concentration of 10 μM. The inactivity of **6a** may be due to insolubility problems experienced with this compound. However, the imidazo[1,2-*a*]quinoxalin-4(5*H*)-one, **7**, possessed reasonable affinity for the AMPA receptor with a K_i of 7.38 ± 1.16 μM.

In general, the same heterocycles which demonstrated the best affinity for the AMPA receptor also demonstrated the best affinity for the glycine site. Similar results for a limited number of these compounds (**4a**, **5a**, and **7**) have been reported recently by Jackson and co-workers.[14] However, there were differences in the structure–activity relationship (SAR) observed within the triazole class of compounds (**4**). For example, substituents in the 1-position of the triazolo compounds led to a modest reduction in glycine affinity whereas they improved AMPA binding. Another exception was the mononitro triazole, **4j**, which showed reduced affinity for the glycine site in contrast to the strong affinity observed for the AMPA receptor. Compound **4a** was the most potent displacer of [^{3}H]glycine having a K_i of 0.63 ± 0.21 μM. In addition, **4a** was found to inhibit [^{3}H]MK-801 binding significantly (85% inhibition at a concentration of 10 μM) which suggests that this compound acts as an antagonist at the glycine site. Given the structural similarity to 5,7-dichlorokynurenic acid, **16**, one might expect a similarly substituted triazolo compound such as **4h** would be more potent than **4a** at displacing [^{3}H]glycine, but that was not the case. Apparently the overall electronic topography is significantly altered by the introduction of the fused triazole ring such that kynurenic acid SAR is not a good predictor of heterocyclic analog affinity.

The activity of compounds exhibiting affinity for the AMPA receptor was examined in the cortical slice preparation.[15] The triazolo compounds were found to only weakly antagonize AMPA-induced depolarizations with IC_{50} values greater than 50 μM. However, **4d** and **4j** were reasonably potent AMPA antagonists with IC_{50} values of 44 ± 7 μM and 29 ± 3 μM, respectively. None of the compounds evaluated showed significant antagonism of 40 μM NMDA-induced depolarizations at a concentration of 100 μM.

Conclusions

A variety of heterocyclic fused quinoxalinones and quinazolinones were synthesized as potential excitatory amino acid receptor antagonists. Noteworthy was our ability to effectively utilize the oxidation state at the 4-position of the tetrazoloquinoxaline series (**5**) to control the regiochemistry of nitration. Nitration of the quinoxaline **10b** was directed to the 7-position, whereas nitration of the quinoxalinone **5b** was directed to the 8-position on the tricyclic ring system. In addition, we found that triphosphene serves as a convenient replacement for phosgene in the closure of the quinazoline ring system. Finally, the magnesium salt of monoperoxyphthalic acid (MMPP) is an excellent reagent for the oxidation of quinoxalines to the corresponding quinoxalinones.

Of the heterocyclic fused quinoxalinones and quinazolinones evaluated as antagonists of AMPA and of the glycine site on the NMDA receptor complex, the triazolo derivatives were found to bind with the greatest affinity for both sites, although the imidazo derivative **7** possessed noteworthy affinity for the glycine site. It was particularly interesting that the SAR for the heterocyclic compounds did not directly parallel that of known quinoxalinediones at either the AMPA receptor or at the glycine site on the NMDA receptor.

Experimental Section

General Experimental Procedures. All melting points were taken with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR were obtained on a GE QE 300 spectrometer. Chemical shift values are reported in ppm (δ) downfield from Me_4Si or DSS. Routine mass spectra were recorded on a Varian Mat 731 in the FD mode. Determination of exact mass was performed on a Zab 3F-VG Analytical spectrometer in the FAB mode. Elemental analyses were done either on a Perkin Elmer Elemental Analyzer 240 or on a Control Equipment Corp. 240-XA and are within 0.4% of the theoretical values.

General Method for the Preparation of Triazolo[4,3-*a*]quinoxalin-4(5*H*)-ones. The triazolo[4,3-*a*]quinoxalinones, **4a–f,j,k**, were prepared by the reaction of various ortho triesters with the appropriate 2-hydrazinoquinoxalines as described by Dreikorn et al.[8b] to give the triazolo[4,3-*a*]quinoxalines followed by oxidation to the corresponding quinoxalinones using either H_2O_2 or MMPP in acetic acid.

1-Methyl-7,8-dichloro-1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-one (4b). A suspension of 4,5-dichloro-1,2-phenylenediamine (25 g, 141.2 mmol) and glyoxylic acid monohydrate (13 g, 142.0 mmol) in 780 mL of EtOH was heated at reflux for 3 h and then cooled and filtered to yield 27.5 g (91%) of 6,7-dichloroquinoxalin-2-one. A mixture of the above product (25 g, 116.3 mmol) and phosphorus oxychloride (230 mL, 911.7 mmol) was stirred at reflux for 3 h and then cooled and carefully quenched with ice and water. The resulting precipitate was filtered and dried in vacuo (50 °C, 0.5 mmHg) to yield 25 g (92%) of **8a**. To

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a solution of **8a** in anhydrous EtOH (500 mL) was added anhydrous hydrazine (5.0 g, 156 mmol) dropwise, and then the red solution was heated at reflux for 1 h, cooled, and filtered. Recrystallization from 1500 mL of 95% EtOH gave 13.0 g (53%) of **9a**. A mixture of **9a** (1.0 g, 4.36 mmol) and triethyl orthoacetate (9.21 g, 56.7 mmol) was heated at reflux for 1 h, then cooled, and filtered to yield 0.85 g (77%) of 1-methyl-7,8-dichloro-1,2,4-triazolo[4,3-*a*]quinoxaline. To this product (0.5 g, 1.97 mmol) in 16 mL of acetic acid was added 5 mL of 30% hydrogen peroxide, and then the mixture was warmed to 50 °C for 17 h, cooled to room temperature, and filtered. The product was washed with water and dried in vacuo (50 °C, 0.5 mmHg) to afford 0.28 g (49%, 17% overall) of **4b**: mp > 250 °C; ^{1}H NMR (DMSO) δ 8.05 (s, 1 H), 7.51 (s, 1 H), 2.92 (s, 3 H). Anal. ($C_{10}H_6N_4OCl_2$) C, H, N.

1-(Trifluoromethyl)-7,8-dichloro-1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-one (4g). A mixture of **9a** (1.0 g, 4.4 mmol) and 5 mL of ice-cold trifluoroacetic acid (29.0 mmol) was heated to 100 °C for 3 h and then poured over ice/H_2O. The resultant precipitate was filtered and washed with water to yield 0.95 g (70%) of 1-(trifluoromethyl)-7,8-dichloro-1,2,4-triazolo[4,3-*a*]-quinoxaline. To the quinoxaline (0.80 g, 2.3 mmol) in 22 mL of HOAc was added 30% H_2O_2 (7 mL), and the mixture was heated to 55 °C for 16 h and then cooled to room temperature. The resultant precipitate was filtered and dried in vacuo to yield 0.33 g (44%) of **4g**: mp > 260 °C; ^{1}H NMR (DMSO) δ 7.75 (s, 1 H), 7.60 (s, 1 H); MS *m/e* 322 (M - 1), 324 (M + 1). Anal. ($C_{10}H_3N_4OCl_2F_2$) C, H, N.

7,9-Dichloro-1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-one (4h). A mixture of 3,5-dichloro-1,2-phenylenediamine (5.00 g, 28.2 mmol) and glyoxalic acid monohydrate (2.9 g, 31.0 mmol) in 120 mL of absolute EtOH was heated at reflux for 18 h, allowed to cool, and then filtered to yield 3.00 g (50%) of an approximately 7:1 mixture of 6,8-dichloroquinoxalin-2-one and 5,7-dichloroquinoxalin-2-one, respectively. This mixture (2.98 g, 13.9 mmol) and $POCl_3$ (30 mL) were stirred at reflux for 2.5 h, then cooled, and poured slowly onto H_2O, and the resultant precipitate was filtered to give 3.2 g (98%) of a mixture of 2,6,8-trichloroquinoxaline and 2,5,7-trichloroquinoxaline. The trichloroquinoxalines (1.40 g, 6.00 mmol) were treated with hydrazine (0.5 mL, 16 mmol) at reflux for 3 h, cooled, and filtered. This product mixture was heated in triethyl orthoformate (15 mL) at 100 °C for 5 h, then cooled, and diluted with Et_2O, and 0.96 g (65%) of an approximately 8:1 mixture of 7,9-dichloro-1,2,4-triazolo[4,3-*a*]quinoxaline and 6,8-dichloro-1,2,4-triazolo[4,3-*a*]quinoxaline was collected by filtration. This mixture was heated with 1.7 g (2.75 mmol) of 80% MMPP in 20 mL of glacial acetic acid at 60–70 °C for 18 h. Additional MMPP (0.85 g, 1.38 mmol) was added and the mixture heated for an additional 6 h. After cooling, the mixture was poured onto 300 mL of H_2O, and 0.47 g (87%) of a yellow precipitate was collected. Recrystallization from MeOH afforded 0.20 g (37%) of **4h**, which contained 2% or less of the 6,8-dichloro isomer: mp > 320 °C; ^{1}H NMR (DMSO) δ 12.3 (br s, 1 H), 10.16 (s, 1 H), 7.58 (d, J = 3 Hz, 1 H), 7.36 (d, J = 3 Hz, 1 H); MS *m/e* 254 (M - 1), 256 (M + 1), 258 (M + 3). Anal. ($C_9H_4N_4OCl_2$) C, H, N.

7-Nitro-1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-one (4j). Potassium nitrate (7.36 g, 72.7 mmol) was added in three portions to a solution of quinoxalin-2-one (10.62 g, 72.7 mmol) in 120 mL of concentrated sulfuric acid at 0 °C. The reaction mixture was stirred at room temperature for 2.5 h, then poured onto 1 L of ice/H_2O, and stirred for an additional 30 min. The precipitate was filtered, washed with water, and dried in vacuo (45 °C, 0.5 mmHg) for 1 h to yield 17.0 g of 6-nitroquinoxalin-2-one. This compound (6.9 g, 36.1 mmol) and PCl_5 (15 g, 72 mmol) in 70 mL of $POCl_3$ was heated at reflux for 4 h, then cooled to 45 °C, and slowly poured onto ice. The precipitate was filtered to yield 4.7 g (62%) of **8c**. Anhydrous hydrazine (0.46 g, 14.3 mmol) was added to 2.0 g of **8c** (9.5 mmol) in 50 mL of absolute EtOH, the mixture was heated at reflux for 1 h, then cooled, and filtered, and the product was washed with EtOH and dried in vacuo to yield 1.9 g (98%) of **9c**. A suspension of 1.5 g of **9c** (7.3 mmol) in 18 mL of triethyl orthoformate was heated at 110 °C for 3 h, then cooled, and filtered, and the product was washed with EtOH and dried in vacuo to yield 1.2 g (76%) of 7-nitro-1,2,4-triazolo-[4,3-*a*]quinoxaline. A mixture of 0.80 g (3.7 mmol) of this quinoxaline was oxidized as for **4b** in 35 mL of acetic acid with 11 mL of 30% H_2O_2 to yield 0.58 g (68%) of **4j**: mp > 260 °C; ^{1}H NMR (DMSO) δ 9.95 (s, 1 H), 8.35 (m, 1 H), 8.25 (m, 2 H); MS *m/e* 232 (M + 1). Anal. ($C_8H_5N_5O_3$) C, H, N.

7,8-Dinitro-1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-one (4k). Potassium nitrate (350 mg, 3.5 mmol) was added to a solution of 0.80 g (3.5 mmol) of **4j** in 6 mL of concentrated sulfuric acid at 0 °C, and the mixture was stirred at room temperature for 2 h and then heated at 50 °C for 40 h. The reaction mixture was poured onto 200 mL of ice and water, and the resultant product was collected by filtration, washed with water, and dried in vacuo (50 °C, 0.5 mmHg) to yield 0.54 g (56%) of **4k**: ^{1}H NMR (DMSO) δ 9.88 (s, 1 H), 9.01 (s, 1 H), 7.89 (s, 1 H); MS *m/e* 276 (M), Exact mass calcd for $C_8H_5N_6O_5$ (MH^+) 277.0321, found 277.0375.

7,8-Dichlorotetrazolo[1,5-*a*]quinoxalin-4(5*H*)-one (5a). **5a** was prepared as described by Dreikorn:[9] ^{1}H NMR (DMSO) δ 12.73 (br s, 1 H), 8.57 (s, 1 H), 7.66 (s, 1 H); MS *m/e* 257 (M + 1), 255 (M - 1). Anal. ($C_8H_3N_5OCl_2$) C, H, N.

7-Nitrotetrazolo[1,5-*a*]quinoxalin-4(5*H*)-one (5c). A mixture of 3.0 g (14.3 mmol) of **8c**, 5 mL of 1 N hydrochloric acid, and 1.1 g (17.2 mmol) of sodium azide in 60 mL of absolute EtOH was heated at reflux for 17 h, then cooled, filtered, and air-dried to give 3.8 g of **10c**. The product was slurried in H_2O and recollected to yield 2.8 g of **10c**. Recrystallization from 15 mL of 2:1 DMF/H_2O gave 0.79 g of **10c**. The nitrotetrazoloquinoxaline (1.84 g, 8.51 mmol) was added to a mixture of 15 mL of glacial AcOH and 20 mL of 30% H_2O_2 and heated at 85 °C for 16 h. Upon cooling, the mixture was diluted with H_2O (50 mL) and the precipitate collected by filtration. Recrystallization from 40 mL of 50% aqueous DMF gave 1.29 g of the 7-nitro product, **5c**: mp 266–268 °C; ^{1}H NMR (DMSO) δ 12.9 (br s, 1 H), 8.52 (d, J = 9 Hz, 1 H), 8.25 (m, 2 H). Anal. ($C_8H_4N_6O_3$) C, H, N.

8-Nitrotetrazolo[1,5-*a*]quinoxalin-4(5*H*)-one (5d). KNO_3 (0.83 g, 8.2 mmol) was added to a solution of tetrazolo[1,5-*a*]-quinoxalin-4(5*H*)-one,[9] **5b** (0.510 g, 2.72 mmol), in 15 mL of concentrated H_2SO_4 and the mixture stirred at 23 °C for 4 h before pouring onto ice/H_2O (100 mL). The precipitate was collected and recrystallized from 10 mL of 50% aqueous DMF to yield 0.361 g of the 8-nitro compound, **5d**. An analytical sample was prepared by drying in vacuo (55 °C, 0.5 mmHg) for 14 h: mp 273–275 °C; ^{1}H NMR (DMSO) δ 13.1 (br s, 1 H), 8.92 (d, J = 9 Hz, 1 H), 8.47 (dd, J = 9, 4 Hz, 1 H), 7.65 (d, J = 9 Hz, 1 H); MS *m/e* 232 (M). Anal. ($C_8H_4N_6O_3$) C, H, N.

7,8-Dinitrotetrazolo[1,5-*a*]quinoxalin-4(5*H*)-one (5e). The 7-nitrotetrazoloquinoxalinone, **5c** (3.00 g, 12.9 mmol), was added to concentrated H_2SO_4 (40 mL) and treated with KNO_3 (1.43 g, 14.1 mmol) with warming to 50 °C for 34 h. The mixture was cooled and poured onto 600 mL of ice/H_2O. The solid was collected by filtration and washed with H_2O to yield 3.16 g of the desired 7,8-dinitro derivative, **5e**, containing 10% of 6,7-dinitroquinoxalinedione. Analytical material was obtained by reverse-phase preparative HPLC (CH_3CN/H_2O) followed by recrystallization from absolute EtOH. mp 250–252 °C; ^{1}H NMR (CD_3OD) δ 9.07 (s, 1 H), 7.98 (s, 1 H); MS *m/e* 277 (M). Anal. ($C_8H_3N_7O_5$) C, H, N.

8-Chloropyrazolo[5,1-*c*]quinazolin-5(6*H*)-one (6b). A mixture of 7-chloro-4-hydroxyquinoline, **11** (20.08 g, 0.112 mol), and hydrazine hydrate (35 mL) was heated at 180–200 °C in ethylene glycol (150 mL) for 18 h. The mixture was poured onto 1.5 L of H_2O and stirred for 2 h. The precipitate was collected by filtration, washed with H_2O, and air-dried to afford 15.64 g of the pyrazole **12**.[11] Triphosgene (1.83 g, 6.17 mmol) was added to a mixture of **12** (1.00 g, 5.16 mmol) in 30 mL of THF. Solid K_2CO_3 was added and the suspension heated at reflux for 22 h. Upon cooling, H_2O was added and the precipitate collected by filtration to yield 1.07 g of the quinazolinone **6b**. Recrystallization from DMF afforded 0.638 g of crystalline material: mp > 320 °C; ^{1}H NMR (DMSO) δ 12.05 (br s, 1 H), 8.0 (m, 2 H), 7.3 (m, 2 H), 7.2 (m, 1 H); MS *m/e* 219 (M), 221 (M + 2). Anal. ($C_{10}H_6N_3OCl$) C, H, N.

8,9-Dichloropyrazolo[1,5-*c*]quinazolin-5(6*H*)-one (6a). The 8-chloropyrazoloquinazolinone, **6b** (1.00 g, 4.55 mmol), was added to glacial AcOH (20 mL) and treated with sulfuryl chloride (0.78 mL, 6.7 mmol). The mixture was heated at 75–85 °C for 6 h before additional SO_2Cl_2 (9.1 mmol) was added. After 15 h, the mixture was cooled and then added to 80 mL of H_2O. The resulting precipitate was collected, washed with H_2O, recrystallized from

DMF (150 mL), and dried in a vacuum oven (75 °C, 0.5 mmHg) for 23 h to yield the 8,9-dichloropyrazolo derivative, **6a**: mp > 330 °C; ^{1}H NMR (DMSO) δ 12.15 (br s, 1 H), 8.36 (d, J = 9 Hz, 1 H), 8.28 (s, 1 H), 7.4 (m, 2 H). Anal. ($C_{10}H_5N_3OCl_2$) C, H, N.

7,8-Dichloroimidazo[1,2-*a*]quinazolin-4(5*H*)-one (7). Aminoacetaldehyde dimethyl acetal (3.0 mL, 27.5 mmol) was added to a mixture of 2,6,7-trichloroquinoxaline, **8a** (4.20 g, 18.0 mmol), and triethylamine (3.0 mL, 21 mmol) in 120 mL of toluene and heated at reflux for 20 h. Upon cooling, the mixture was filtered to remove the salts, washed with EtOAc, and the filtrate concentrated in vacuo to give a black oil. Flash chromatography over silica gel (40–50% EtOAc/hexane) gave 3.02 g of **13**. A mixture of **13** (7.50 g, 24.8 mmol), in 100 mL of methanol containing 20 mL of concentrated HCl was heated at reflux for 6–12 h and then concentrated in vacuo, and the residue was neutralized by addition of dilute $NaHCO_3$. The resultant brown solid was collected by filtration, washed with H_2O, and air-dried to afford 4.23 g of **14**. To a solution of **14** (1.20 g, 5.04 mmol) in 20 mL of glacial acetic acid was added 80% monoperoxyphthalic acid magnesium salt hexahydrate (MMPP) (3.00 g, 4.85 mmol), and the mixture was heated at 55 °C for 18 h. Additional 1.0-g portions of MMPP were added daily as needed for 2 weeks until starting material was consumed as evidenced by ^{1}H NMR. The mixture was poured into 400 mL of H_2O and stirred for 1 h before collecting 0.52 g of **7** by filtration. An analytical sample of **7** was prepared by recrystallization from DMF followed by drying in a vacuum oven at 80–90 °C for 2 days: mp > 310 °C; ^{1}H NMR (DMSO) δ 11.95 (br s, 1 H), 8.59 (d, J = 2 Hz, 1 H), 8.54 (s, 1 H), 7.62 (d, J = 2 Hz, 1 H), 7.52 (s, 1 H); MS m/e 253 (M), 255 (M + 2). Anal. ($C_{10}H_5N_3OCl_2$) H, N; C: calcd, 47.27; found 46.84.

Radioligand Binding. For all binding assays, male Sprague-Dawley rats (150–175 g) were used. The binding of [^{3}H]AMPA (5 nM) was conducted with crude membranes of rat forebrain in the presence of 100 mM KSCN as described by Nielsen et al.[16] Nonspecific binding was determined with 10 μM nonlabeled AMPA. Displacement of the specific binding of [^{3}H]CGS 19755 (10 nM) to Triton-X-treated synaptosomal membranes of rat forebrain was used to determine NMDA receptor affinity as described by Murphy et al.[17] Nonspecific binding was determined using 10 μM L-glutamate. Samples were incubated in an ice bath for 30 min, and bound ligand was separated from the free ligand by rapid filtration through Whatman GF/B glass fiber filters. [^{3}H]Kainate binding was performed using washed synaptosomal membranes from the rat forebrain, prepared as described by Simon et al.[18] [^{3}H]Kainate (5 nM) was added to 50 mM Tris-HCl buffer (pH 7.4 at 4 °C0 containing 200–300 μg/mL of tissue protein. Samples were incubated for 30 min in an ice bath, and then rapidly filtered using a Brandel cell harvester and Whatman GF/C filters. Filters were washed twice with 3 mL of cold buffer. Nonspecific binding was determined using 100 μM nonlabeled kainate. [^{3}H]Glycine binding was performed on rat cortical membranes prepared by the freeze/thaw Triton extraction procedure developed for GABA-receptor binding with minor modifications.[19] Samples were incubated in the presence of 10 nM [^{3}H]glycine and 25 μg of membrane fragments on ice for 1 h and terminated by rapid filtration through Whatman GF/B filters. Nonspecific binding was determined in the presence of 100 μM D-serine. [^{3}H]MK-801 binding was performed in well-washed rat cortical membranes[20] with an added freeze/thaw procedure. The effect of compounds on [^{3}H]MK-801 binding (2.5 nM) was determined in the presence of glutamate (1 μM) and glycine (0.2 μM). Samples were incubated for 2 h at 27 °C and terminated by filtration. Nonspecific [^{3}H]MK-801 binding was determined in the presence of 0.5 μM MK-801.

Cortical Slice Electrophysiology. Depolarizations of rat 500-μm thick cortical wedges were performed using a grease-seal technique similar to that described previously by Harrison and Simmonds.[15] Briefly, 4-mL aliquots of NMDA (40 μM), quisqualate (40 μM), and kainic acid (10 μM) were superfused (2 mL/min) on the gray matter at intervals of 15–20 min until stable responses were attained. The tissue was then exposed for 15 min to various concentrations of the test compound before retesting the agonist. IC_{50} values were calculated from linear regression of log dose–response curves.

Acknowledgment. The authors gratefully acknowledge chemistry support from summer intern, Antonio Williams, and helpful chemistry discussions with Jim Wikel, Barry Dreikorn, Tom Thibault, Tim Shepherd, Frantz Victor, and Wayne Spitzer. The chromatographic expertise of Lyle Huckstep, Larry Sachs, and Reggie Thomas facilitated the separation of isomeric products. Finally, appreciation is extended to John Paschal and Juel DeHoniesto for assistance with ^{1}H NMR spectral analysis, and the Physical Chemistry department for structural verification.

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