Novel α-Amino-3-hydroxy-5-methylisoxazole-4-propionate Receptor Antagonists: Synthesis and Structure−Activity Relationships of 6-(1*H*-Imidazol-1-yl)-7-nitro-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione and Related Compounds

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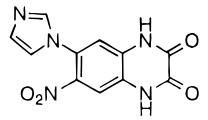
Received April 24, 1995[⊗]

We have synthesized and evaluated azaquinoxalinediones **3a**−**c** for their activity in inhibiting [^{3}H]AMPA binding from rat whole brain. It was found that the azaquinoxalinedione nucleus functions as a bioisostere for quinoxalinedione in AMPA receptor binding. The detailed structure−activity relationships of 6- and/or 7-substituted 2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione derivatives **4**, **7**−**10**, **13**, **15**, and **16** showed some differences in comparison with those of the corresponding substituted quinoxalinediones, including 6-(1*H*-imidazol-1-yl)-7-nitro-2,3-(1*H*,4*H*)-quinoxalinedione (**1**) (YM90K). The X-ray study exhibited that conformation of the 7-nitro group of **1**·HCl was nearly coplanar with the quinoxaline ring, whereas the 6-imidazol-1-yl group was rotated with respect to the aromatic ring. From the glycine site on NMDA receptor binding study, it is indicated that bulkiness of 6-substituents on pyridopyrazinediones may be responsible for the selectivity against the glycine site. Among the series of azaquinoxalinediones, 6-(1*H*-imidazol-1-yl)-7-nitro-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (**8c**) exhibited a combination of the best affinity to the AMPA receptors with a K_i value of 0.14 μM and selectivity against the glycine site (no affinity at 10 μM). *In vivo*, **8c** also protected against sound-induced seizure in DBA/2 mice (minimum effective dose, 10 mg/kg ip).

Excitatory amino acids (EAA), represented by L-glutamate (L-Glu), are major excitatory neurotransmitters in the mammalian central nervous system (CNS).[1−3] It has recently become clear that excess EAA stimulation causes degeneration of neurons, which is believed to link a number of CNS diseases such as epilepsy, after effects of cerebral ischemia, and Huntington's and Alzheimer's diseases.[4,5] Postsynaptic EAA receptors have been classified into four main subtypes,[6] namely, the *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), kainate (KA), and metabotropic glutamate receptor subtypes. AMPA and KA receptors may be grouped collectively as non-NMDA receptors.

During the design of new therapeutic agents for neurodegenerative diseases based on the EAA hypothesis, the NMDA subtype of the EAA receptors has been the subject of intensive study.[7−9] Within recent years, competitive AMPA receptor antagonists[10,11] have received considerable attention for their therapeutic potential in neurodegenerative disorders, based on their physiological and pharmacological activities.[12,13] Previously, we reported a potent and selective AMPA receptor antagonist, 6-(1*H*-imidazol-1-yl)-7-nitro-2,3-(1*H*,4*H*)-quinoxalinedione (**1**) (Figure 1),[14,15] which showed neuroprotective effects, i.e., anti-AMPA-induced toxicity in cultured neurons[16] and anticonvulsive activity and antiischemic effects in both global and focal ischemia models.[17−19] Compound **1** is now in clinical studies.



1 (YM90K)

Figure 1.

In a previous paper, we proposed the pharmacophore for the AMPA receptor based on the structure−activity relationships (SAR) of quinoxalinedione derivatives, including compound **1**,[14,15] namely, functional groups which possess moderately sized planar π-conjugation systems and appropriate hydrophobicity (such as imidazol-1-yl, nitro, or cyano group) are suitable for the 6-substituent of the 2,3(1*H*,4*H*)-quinoxalinedione nuclei, whereas electron-withdrawing groups such as nitro, trifluoromethyl, or cyano groups are suitable for the 7-substituent. Furthermore, it was revealed that 6,7-disubstitution by the appropriate combination of substituents provided synergistically improved affinity for AMPA receptors, whereas, 5,6- and 6,8-disubstitution showed no improvement.

As part of our program to explore the AMPA receptor pharmacophore, we have designed a series of azaquinoxalinediones (**3**, **4**, **7**−**10**, **13**, **15**, and **16**) and investigated the structure−activity relationships of these compounds in comparison with those of the corresponding quinoxalinediones. Some compounds were evaluated for selectivity against glycine sites on the NMDA receptors with respect to the binding affinity. To further investigate the pharmacophoric requirements for AMPA receptor binding, conformation studies of 6- and/or 7-, nitro- and/or imidazol-1-yl-substituted derivatives were carried out.

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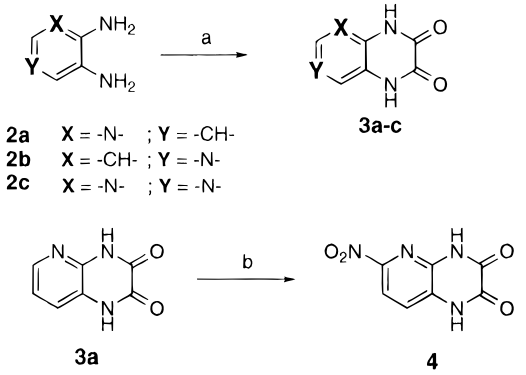
[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1996.

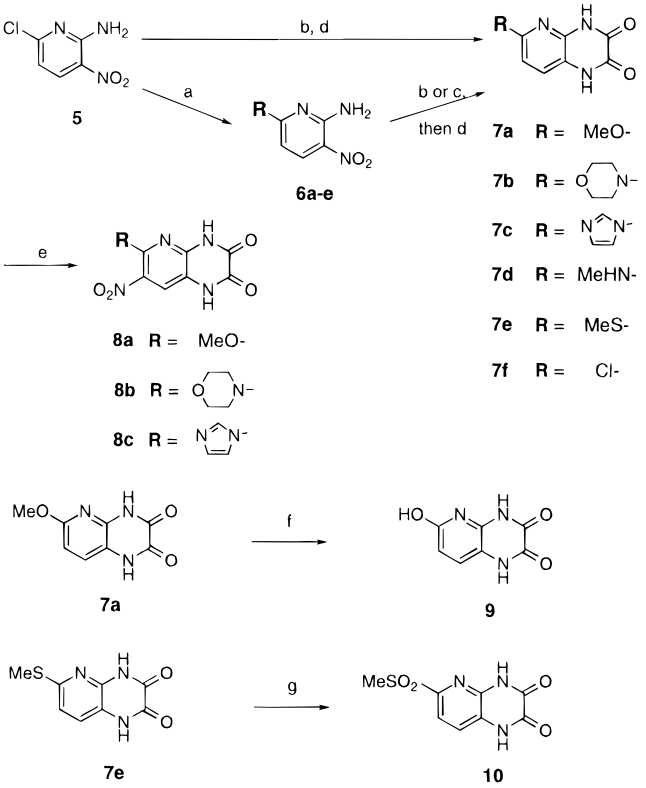
0022-2623/96/1839-1331$12.00/0

Scheme 1[a]



[a] (a) $(COOH)_2$, 4 N HCl; (b) $^fHNO_3$, AcOH, Ac_2O.

Scheme 2[a]



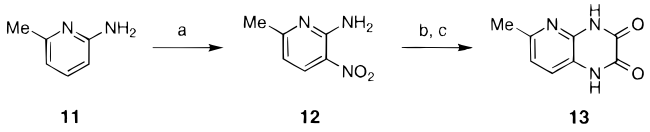
[a] (a) Nucleophile; (b) H_2, Pd−C (10%), HCl; (c) H_2, Ra Ni; (d) $(COOH)_2$, 4 N HCl; (e) nitration/$^fHNO_3$, Ac_2O, AcOH for **8a**; KNO_3, H_2SO_4 for **8b**; NO_2BF_4, tetramethylene sulfone for **8c**; (f) 48% HBr; (g) H_2O_2, AcOH.

Chemistry

Synthesis of the azaquinoxalinediones **3**, **4**, **7**−**10**, **13**, **15**, and **16** is described in Schemes 1−4. The corresponding diaminopyridines **2a**,**b** and pyrimidine **2c** were cyclized with oxalic acid in refluxing 4 N HCl to give the desired compounds **3a**−**c** (Scheme 1).[20] This reaction condition is commonly used in the following method for construction of the pyrazinedione portion. Nitration of compound **3a** with fuming HNO_3 in AcOH−Ac_2O gave the 6-nitro pyrazinedione **4** (Scheme 1).

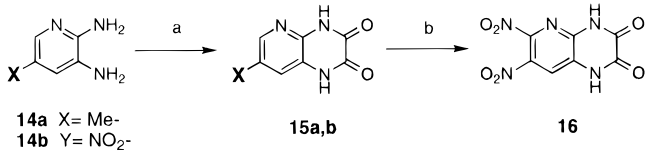
Most of our 6-substituted derivatives and their 7-nitro derivatives were prepared as shown in Scheme 2. The versatile starting material 2-amino-6-chloro-3-nitropyridine (**5**)[21] was treated with several nucleophiles to afford the corresponding derivatives **6a**−**e**. Hydrogenation of nitro derivatives **5** and **6e** with Raney nickel and **6a**−**d** with palladium on carbon followed by the cyclic condensation of the resulting diamines with oxalic acid gave the desired 6-substituted derivatives **7a**−**f**. The nitration of methoxy derivative **7a** with fuming HNO_3 in AcOH−Ac_2O gave the 6-methoxy-7-nitro derivative **8a**; nitration of morpholino derivative **7b** with KNO_3 in concentrated H_2SO_4 yielded the 6-morpholino-7-nitro derivative **8b**. The nitration of **7c**, however, was not complete in these conditions. The preparation of 6-(1*H*-imidazol-1-yl)-7-nitro derivative **8c** was accomplished by nitration with nitronium tetrafluoroborate[22] in tetramethylene sulfone at 120 °C. 6-Hydroxy derivative **9** was obtained by demethylation of methoxy derivative **7a** in 48% HBr. Methylsulfonyl derivative **10** was obtained by oxidation of methylthio derivative **7e** with hydrogen peroxide.

Scheme 3[a]



[a] (a) $^cHNO_3$, H_2SO_4; (b) H_2, Pd−C (10%); (c) $(COOH)_2$, 4 N HCl.

Scheme 4[a]



[a] (a) $(COOH)_2$, 4 N HCl; (b) NO_2BF_4, tetramethylene sulfone.

6-Methyl derivatives **13** were prepared in three steps, namely, nitration of aniline **11**, catalytic hydrogenation of resulting nitropyridine **12**, and subsequent cyclic condensation with oxalic acid (Scheme 3).

7-Methyl (**15a**) and 7-nitro (**15b**) derivatives were prepared by the cyclic condensation of appropriate diamines **14a**[23] and **14b**[24] (Scheme 4). The compound **15b** was nitrated with nitronium tetrafluoroborate in tetramethylene sulfone at 130 °C to give the 6,7-dinitro derivative **16**.

Structure−Activity Relationships. The structures of the azaquinoxalinediones and results of the radioreceptor assay for AMPA receptors[25] are summarized in Tables 1−4. The affinities are presented as K_i (μM) values or percent inhibition at 100 μM if the compounds had weak potency.

The nonsubstituted azaquinoxalinediones, 2,3-pyrido[2,3-*b*]pyrazinedione (**3a**) and 2,3-pyrido[2,3-*c*]pyrazinedione (**3b**), showed 22% and 32% inhibition of [^{3}H]AMPA binding at 100 μM, respectively. These are weak but similar affinities with the lead compound quinoxalinedione **17** (24% inhibition at 100 μM) (Table 1). The diazaquinoxalinedione, 6,7-pteridinedione (**3c**), exhibited moderately improved affinity (62% inhibition at 100 μM) compared to that of **17**. These results provide evidence that the introduction of a nitrogen atom in the benzo ring of quinoxalinedione is tolerated in AMPA receptor binding. In a previous paper, we have revealed that a combination of some 6- and 7-substitutions to the 2,3-quinoxalinediones is significantly effective in improving AMPA receptor binding potency.[15] Since 2,3-pyrido[2,3-*b*]pyrazinedione (**3a**) served in the modification of both 6- and 7-positions, we selected **3a** as a lead for the following further investigation.

Table 1. Azaquinoxalinediones and Quinoxalinedione

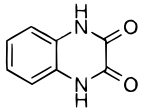
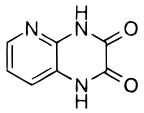
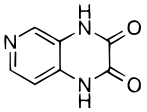
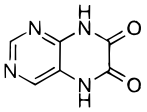
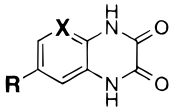
compd	structure	AMPA receptor affinity (inhibition at 100 μM)
17		24%
3a		22%
3b		32%
3c		62%

Table 2. 7-Substituted Pyridopyrazinedione and Quinoxalinedione Derivatives



compd	R	X	AMPA receptor affinity Ki (μM)[a]
15a	Me-	-N-	74% (100)[b]
15b	O_2N-	-N-	1.1 (1.05-1.10)
18	Me-	-CH-	28% (100)[b]
19	O_2N-	-CH-	2.0 (2.0-2.1)
20		-CH-	1.6 (1.6-1.7)

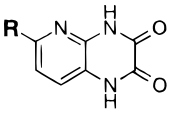
[a] K_i values were determined by double experiments performed in triplicate. Values in parentheses are 95% confindence intervals. [b] Inhibition at 100 μM.

Initially, monosubstituted analogues of pyridopyrazinedione were examined. The results of 7-substituted derivatives **15a**,**b** and corresponding quinoxalinediones **18**−**20** are listed in Table 2, and those of 6-substituted derivatives **4**, **7a**−**f**, **9**, **10**, and **13** are shown in Table 3.

As shown in Table 2, 7-nitro derivative **15b** exhibited a considerably enhanced potency, with a K_i value of 1.1 μM, similar to that of the corresponding nitroquinoxalinedione **19** (K_i = 2.0 μM). On the basis of percent inhibition of **3a** at 100 μM (see Table 1), the activity of **15b** was estimated as more than 100 times that of **3a**. 7-Methyl derivative **15a** showed moderately improved affinity (74% inhibition at 100 μM) compared to those of unsubstituted **3a** and the corresponding quinoxalinedione **18**.

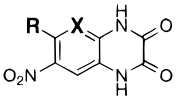
Among 6-substituted pyridopyrazinediones, only nitro derivative **4** (66% inhibition at 100 μM) and imidazol-1-yl derivative **7c** (76% inhibition at 100 μM, 25 (24−26) μM of K_i value) showed improved affinity; however, potency was less than that of the 7-substituted derivative **15b** and quinoxalinediones **20** and **19**, respectively (Table 3).

Table 3. 6-Substituted Pyridopyrazinedione Derivatives



compd	R	AMPA receptor affinity (inhibtion at 100 μM)
7f	Cl-	29%
7d	MeNH-	30%
13	Me-	31%
7b		32%
9	HO-	37%
7a	MeO-	41%
7e	MeS-	55%
10	$MeSO_2$-	56%
4	O_2N-	66%
7c		76%

Table 4. 7-Nitro-6-substituted Pyridopyrazinedione and Quinoxalinedione Derivatives



compd	R	X	AMPA receptor affinity (K_i : μM)[a]	glycine site affinity (K_i : μM)[a]
8a	MeO-	-N-	0.70 (0.63-0.77)	0.37 (0.31-0.44)
8b		-N-	0.92 (0.90-0.94)	14% (10)[b]
16	O_2N-	-N-	0.86 (0.79-0.95)	8.0 (7.1-9.2)
1		-CH-	0.084 (0.083-0.086)	16% (10)[b]
8c		-N-	0.14 (0.14-0.15)	0% (10)[b]

[a] See Table 1. [b] Inhibition at 10 μM.

From the results of the remarkably enhanced affinity of 7-nitro derivative **15b**, we next synthesized and evaluated 7-nitro-6-substituted pyridopyrazinediones (Table 4). Introduction of methoxy (**8a**), morpholino (**8b**), and nitro (**16**) groups at the 6-position resulted in little enhancement of potency. 6-(1*H*-Imidazol-1-yl)-7-nitro-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (**8c**) showed potent affinity (K_i value of 0.14 μM) which was 6-fold more than that of 6,7-dinitropyridopyrazinedione **16**,

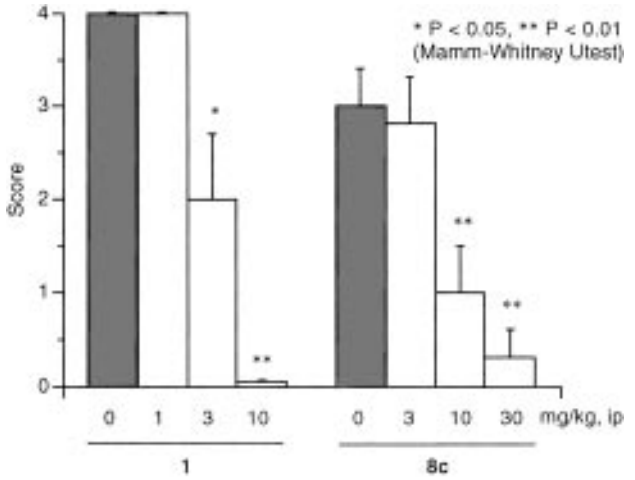


Figure 2. Anticonvulsant effects of **8c** and **1** on sound-induced seizure in DBA/2 mice. Vertical bars represent the mean ±SE ($N = 8$).

about 10 times that of **15b**, and close to that of the corresponding substituted quinoxalinedione **1** (K_i = 0.084 μM). In both the series, 2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinediones and 2,3(1*H*,4*H*)-quinoxalinediones, the combination of 6-(1*H*-imidazol-1-yl) group and 7-nitro group afforded the best affinity for AMPA receptors.

Although some quinoxaline derivatives are recognized as AMPA receptor antagonists, the general lack of specificity of most of them in distinguishing between AMPA receptor and glycine site on the NMDA receptor is known.[15,26,27] Thus we evaluated the selectivity of 7-nitro-6-substituted pyridopyrazinedione with respect to binding affinity (Table 4).[28] 6-Methoxypyridopyrazinedione **8a** displayed high affinity for both the glycine sites, with a K_i value of 0.37 μM, and AMPA receptors, with a K_i value of 0.70 μM. However, 6-nitro derivative **16**, 6-morpholino derivative **8b**, and 6-(1*H*-imidazol-1-yl) derivative **8c** showed little or no affinity for the glycine site. As the compounds which have bulkier 6-substituents showed less potent glycine site affinity, and as it is known that most quinoxalinediones and kynurenic acids which are glycine antagonists have small 5-, 6-, and 7-substituents,[26] selectivity for the glycine site may result from the bulkiness of 6-substituents on pyridopyrazinediones **16** and **8b**,**c**. Like the corresponding quinoxalinedione **1**,[15] compound **8c** showed a combination of the best affinity for the AMPA receptors (K_i value of 0.14 μM) and selectivity against the glycine site (no inhibition at 10 μM) in this series of pyridopyrazinediones. Thus, these findings verify that appropriate 6-substituents such as the 1*H*-imidazol-1-yl group in these classes of compounds not only function in improving AMPA receptor binding potency but also distinguish between AMPA receptor and glycine site.

In *in vivo* activity in preventing audiogenic seizure in the DBA/2 mouse,[29] the compound **8c** exhibited a minimum effective dose of 10 mg/kg ip when administered at 15 min prior to sound exposure, which is close to that of **1** (3 mg/kg ip) (Figure 2).

Conformation Study. In order to investigate the conformations of the 6-imidazolyl and 7-nitro groups to AMPA receptor binding in 6,7-disubstituted derivatives, X-ray crystallographic analysis of the hydrochloride salt of quinoxalinedione **1** was carried out. The solved crystalline structure of **1**·HCl is illustrated in Figure 3. Conformation of the 7-nitro group of **1** was

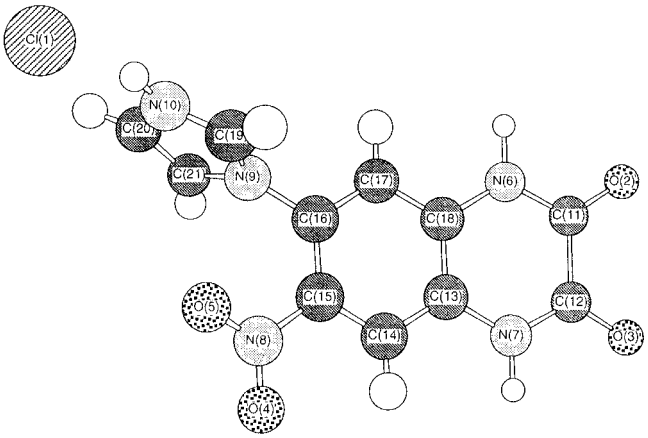


Figure 3. Conformation of **1**·HCl in the crystalline state as established by X-ray analysis.

nearlycoplanar with the quinoxaline ring (dihedral angle C16−C15−N8−O4: 167°), whereas the 6-imidazol-1-yl group was rotated with respect to the ring (dihedral angle C15−C16−N9−C19: 102°). This conformation probably reflects conjugational constraints in each substituent. The modification of **19** or **20** into **1** resulted in a synergistically improved affinity; the torsion of the 6-imidazolyl group is therefore at least tolerated in the AMPA receptor binding.

Since we were interested in the difference between 6- and 7-nitropyridopyrazinediones (**4** and **15b**) in AMPA receptor affinity, we modeled their molecular conformation utilizing MOPAC[30] and included 6-nitroquinoxaline **19**. The calculated optimum conformations of **4**, **15b**, and **19** are illustrated in Figure 4. The nitro group and the aromatic ring of compound **4** exhibited a dihedral angle of 130°, while those of **15b** and **19**, which showed more enhanced potency, were nearly horizontal (179° for **15b** and 177° for **19**), similar to the conformation of the nitro of **1**. These conformational differences can probably be accounted for as follows. The conjugation between the nitro group and aromatic ring constrains the conformation of **15b** and **19** into the coplanar, whereas coulombic repulsion between the lone pair of the pyridine nitrogen atom and the nitro group oxygen atom led to the twisted conformation of **4**.

Because of their different activities, we next focused our attention on the conformation of 6-imidazolylpyridopyrazinedione **7c** and 6-imidazolylquinoxalinedione **20**. The optimization of compound **20** by MOPAC calculation led to two planar conformations with the dihedral angles of 179° and 1° between the imidazolyl group and pyridopyrazinedione ring, respectively, and each showed the same internal energy. Since we observed little difference in the same two planar conformations (0° and 180°) and in internal energy (0.39 kcal difference), the different affinity between **7c** and **20** can not be explained by molecular planarity such as in the case of 6-nitropyridopyrazine **4** or 6-imidazolyl-7-nitroquionoxaline **1**.

On this basis, several interpretations of the SAR on AMPA affinity could be considered. First, the less improved affinity of 6-nitropyridopyrazine **4** may be caused by its twisted conformation. Because this torsional restriction is in contrast to the torsional tolerance of the imidazolyl group of 6,7-disubstituted **1** in improving the affinity, the SAR may reflect the different pharmacophore between the first and second substitu-

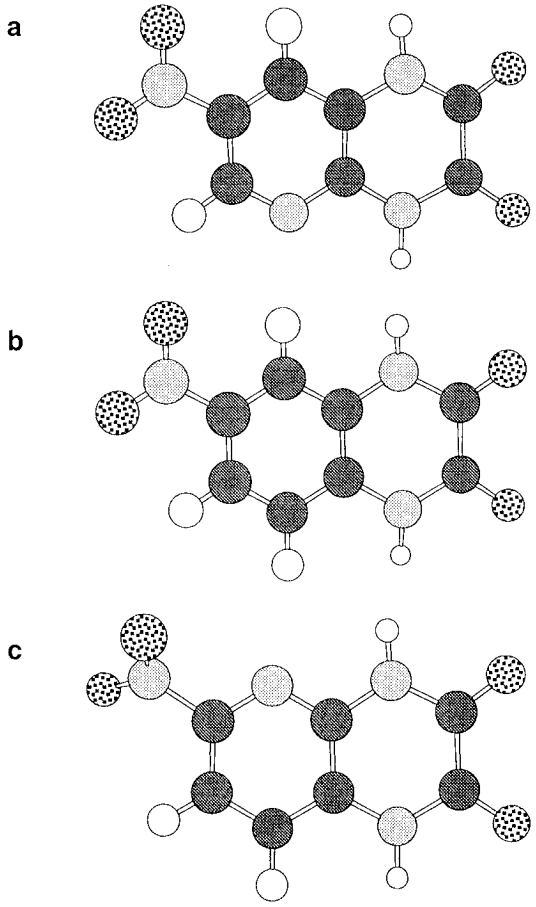


Figure 4. Conformations of nitro-substituted derivatives (a for **15b**, b for **19**, and c for **4**) calculated by MOPAC with PM3 Hamiltonian.

ents or between the nitro and imidazolyl group at the 6- or 7-position of the derivatives. The torsion of the nitro group certainly diminishes the conjugation system; it will also decrease the electron-withdrawing effects on the acidities of the amide proton of the ring and/or π-electron distribution on the aromatic ring, which may be favorable for the receptor binding. The assumption corresponds to the SAR, that is, the electron-withdrawing property of the 7-substituents improves AMPA receptor affinity.[15] Second, since neither substitution for **3a** with nitro, **4**, nor imidazolyl, **7c**, at the 6-position resulted in less improved affinity than those of **15b**, **19**, and **20**, the 6-substituents of monosubstituted pyridopyrazinediones may not be able to contribute to the favorable interaction with AMPA receptor, as compared to 7-substituents of monosubstituted pyridopyrazinediones and quinoxalinediones and 6-substituents of disubstituted derivatives. This may reflect the existence of a pyridine nitrogen atom at the ortho position which could cause Coulombic repulsion or affect the π-electron distribution on the aromatic nuclei. Possibly, the SAR on AMPA affinity may be caused by multiple reasons.

Conclusion

This study showed that the nitrogen atoms in the pyridine and pyrimidine rings of azaquinoxalinediones are tolerated in AMPA receptor binding. The detailed SAR of a series of 6- and/or 7-substituted pyrido[2,3-*b*]-pyrazinediones for the AMPA receptor binding showed some differences from that of the corresponding substituted quinoxalinediones. The X-ray study exhibited that conformation of the 7-nitro group of **1**·HCl was nearly coplanar with the quinoxaline ring, whereas the 6-imidazol-1-yl group was rotated with respect to the aromatic ring. Glycine site binding study of selected compounds indicated that bulkiness of 6-substituents on pyridopyrazinediones may be responsible for selectivity against the glycine site. Among this series of pyridopyrazinediones, 6-(1*H*-imidazol-1-yl)-7-nitro-2,3-(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (**8c**), an aza analogue of **1**, was found to combine potent affinity for AMPA-type non-NMDA EAA receptor and selectivity to the glycine binding site on the NMDA receptor.[31] *In vivo*, **8c** also showed protection against sound-induced seizure in DBA/2 mice.

Experimental Section

Chemistry. Melting points were measured on a Yanaco MP-3 melting point apparatus and are not corrected. Unless stated otherwise, ^{1}H NMR spectra were measured in DMSO-d_6 or $CDCl_3$ with either a JEOL FX90Q or FX100 spectrometer; chemical shifts are expressed in δ units using tetramethylsilane as the standard (in NMR description: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad peak). Mass spectra were recorded with a Hitachi M-80 or JEOL JMS-DX300 spectrometer. Where elemental analyses (C, H, Cl, N, S) are indicated only by symbols, analytical results obtained for these elements were within 0.4% of the theoretical values except where stated otherwise. All solutions were dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure.

The preparation of quinoxalinedione derivatives **1** and **17**−**20** has been reported previously.[15]

General Method for Preparation of Azaquinoxalinediones. 2,3(1*H*,4*H*)-Pyridopyrazinediones **3a**−**c** were prepared by reaction of the appropriate diamines with oxalic acid in 4 N HCl at reflux temperature.

2,3(1*H*,4*H*)-Pyrido[2,3-*b*]pyrazinedione (3a).[20] Diaminopyridine **2a** (3.7 g, 34.3 mmol) was treated with oxalic acid (3.4 g, 37.8 mmol) in 4 N HCl (20 mL) at reflux for 3 h. The resulting precipitate was collected and washed with water to give **3a** (3.9 g, 70%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 7.80 (dd, 1H), 7.24 (dd, 1H), 6.86 (dd, 1H); MS (EI) *m*/*z* 163 (M). Anal. ($C_7H_5N_3O_2$) C,H,N.

2,3(1*H*,4*H*)-Pyrido[2,3-*c*]pyrazinedione (3b): 48% from **2b**; mp >300 °C (H_2O); ^{1}H NMR δ 12.48 (brs, 2H), 8.48 (s, 1H), 8.36 (d, 1H), 7.42 (d, 1H); MS (EI) *m*/*z* 163 (M). Anal. ($C_7H_5N_3O_2$·0.9HCl) C,H,N.

6,7(5*H*,8*H*)-Pteridinedione (3c): 62% from **2c**; mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.64 (brs, 1H), 12.06 (brs, 1H), 8.61 (s, 1H), 8.37 (s, 1H); MS (EI) *m*/*z* 164 (M). Anal. ($C_7H_5N_3O_2$·0.1H_2O) C,H,N.

6-Nitro-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (4). To an ice-cold solution of **3a** (1.2 g, 7.48 mmol) in a mixture of acetic anhydride (12 mL) and acetic acid (2.4 mL) was added dropwise fuming HNO_3 (d = 1.52, 0.93 mL, 22.4 mmol). The reaction mixture was stirred at 50 °C for 1 h. The resulting precipitate was collected and washed with water to give **4** (0.49 g, 28%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.82 (brs, 1H), 12.44 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H); MS (EI) *m*/*z* 208 (M). Anal. ($C_7H_4N_4O_4$·0.1H_2O) C,H,N.

2-Amino-6-methoxy-3-nitropyridine (6a). Sodium (0.20 g, 8.70 mmol) was dissolved in methanol (20 mL). 2-Amino-6-chloro-3-nitropyridine (**5**)[21] (1.30 g, 7.49 mmol) was added to the solution and refluxed for 2 h. The resulting precipitate was collected and washed with a little methanol to give **6a** (0.89 g, 70%): mp 170−171 °C (methanol); ^{1}H NMR δ 8.26 (d, 1H), 8.16 (br, 2H), 6.15 (d, 1H), 3.91 (s, 3H); MS (EI) *m*/*z* 169 (M).

2-Amino-6-morpholino-3-nitropyridine (6b). A solution of **5** (2.00 g, 11.5 mmol) and morpholine (1.51 mL, 17.3 mmol) in methanol (20 mL) was stirred at room temperature overnight. The resulting precipitate was collected and washed with a little methanol to give **6b** (1.92 g, 74%): mp 155−158

°C (methanol); ^{1}H NMR δ 8.08 (d, 1H), 7.84 (br, 2H), 6.32 (d, 1H) 3.68 (s, 8H); MS (EI) *m/z* 244 (M).

2-Amino-6-(1*H*-imidazol-1-yl)-3-nitropyridine (6c). A solution of **5** (16.4 g, 94.6 mmol) was treated with imidazole (64.4 g, 946 mmol) in DMF (300 mL) at 120 °C for 1 h. The reaction mixture was cooled down to ambient temperature and poured in water (300 mL). The resulting precipitate was collected and washed with water to give **6c** (15.5 g, 80%): mp 235−236 °C (methanol); ^{1}H NMR δ 8.57 (d, 1H), 8.56 (d, 1H), 8.18 (brs, 2H), 7.95 (t, 1H), 7.16 (q, 1H), 7.16(d, 1H); MS (EI) *m/z* 205 (M).

2-Amino-3-nitro-6-(methylthio)pyridine (6e). A solution of **5** (2.00 g, 11.5 mmol) was treated with aqueous sodium mercaptan (15%, 5.92 mL, 6.51 mmol) in methanol (20 mL) at room temperature overnight. The resulting precipitate was collected and washed with methanol to give **6e** (1.72 g, 81%): mp 135−137 °C (methanol); ^{1}H NMR δ 8.17 (d, 1H), 8.10 (br, 2H), 6.64 (d, 1H), 2.56 (s, 3H); MS (EI) *m/z* 185 (M).

General Method for Preparation of 6-Substituted Pyridopyrazinediones. 6-Substituted-2,3(1*H*,4*H*)-pyrido-[2,3-*b*]pyrazinediones **7a**−**e** were prepared by hydrogenation of the appropriate 2-amino-3-nitropyridines under atmospheric pressure using Pd−C (**7a**−**d**) or Raney nickel (**7e,f**) to give the diamines followed by reaction with oxalic acid in 4 N HCl at reflux temperature to give the corresponding 6-substituted 2,3-(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinediones.

6-Methoxy-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (7a). A solution of **6a** (0.88 g, 5.20 mmol) in ethanol (20 mL) was hydrogenated under atmospheric pressure with 10% Pd−C as catalyst. The suspension was filtered, and the filtrate was evaporated. To a solution of this residue in 4 N HCl (12 mL) was added oxalic acid (0.47 g, 5.20 mmol), and the mixture was refluxed overnight. The resulting precipitate was collected and washed with water. The solid was recrystallized from DMF−water to give **7a** (0.57 g, 57%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.26 (s, 1H), 11.83 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 6.58 (d, J = 8.6 Hz, 1H), 3.83 (s, 3H); MS (FAB) *m/z* 194 (M + 1). Anal. ($C_8H_7N_3O_3$) C,H,N.

6-Morpholino-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (7b): 32% from **6b**; mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.01 (s, 1H), 11.71 (s, 1H), 7.33 (d, J = 8.6 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 3.65−3.75 (m, 4H), 3.35−3.41 (m, 4H); MS (FAB) *m/z* 249 (M + 1). Anal. ($C_{11}H_{12}N_4O_3\cdot0.6H_2O$) C,H,N.

6-(*N*-Methylamino)-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione hydrochloride (7d·HCl): 61% from 2-amino-6-(*N*-methylamino)-3-nitropyridine (**6d**);[21] mp >300 °C (DMF−H_2O); ^{1}H NMR δ 11.86 (br, 2H), 7.30 (d, J = 8.6 Hz, 1H), 6.96 (br, 1H), 6.36 (d, J = 8.6 Hz, 1H), 2.78 (s, 3H); MS (FAB) *m/z* 193 (M + 1). Anal. ($C_8H_7N_3O_2\cdot$HCl) C,H,N,Cl.

6-(Methylthio)-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (7e). A solution of **6e** (1.68 g, 9.07 mmol) in methanol (30 mL) was hydrogenated under atmospheric pressure with Raney nickel as catalyst. The suspension was filtered, and the filtrate was evaporated. To a solution of the residue in 4 N HCl (18 mL) was added oxalic acid (0.82 g, 9.07 mmol), and the mixture was refluxed overnight. The resulting precipitate was collected and washed with water. The solid was recrystallized from DMF−water to give **7e** (1.06 g, 56%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.31 (s, 1H), 11.90 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 3.32 (s, 3H); MS (FAB) *m/z* 210 (M + 1). Anal. ($C_8H_7N_3O_2S$) C,H,N,S.

6-Chloro-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (7f): 57% from **5**; mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.51 (s, 1H), 12.05 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H); MS (FAB) *m/z* 198 (M + 1). Anal. ($C_7H_4N_3O_2$-Cl·0.5DMF) C,H,N,Cl.

6-Methoxy-7-nitro-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (8a). To an ice-cold solution of **7a** (0.50 g, 2.59 mmol) in a mixture of acetic anhydride (5 mL) and acetic acid (5 mL) was added dropwise fuming HNO_3 (0.16 mL, 3.89 mmol), and the reaction mixture was stirred at 90 °C for 1 h. The solution was poured onto ice, and the resulting precipitate was collected and washed with water. The solid was recrystallized from DMF−water to give **8a** (0.38 g, 62%). The NOE was observed between the aromatic proton and the amide proton but not methoxy proton in NMR study of this compound: mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.82 (s, 1H), 11.98 (s, 1H), 8.08 (s, 1H), 4.00 (s, 3H); MS (FAB) *m/z* 239 (M + 1). Anal. ($C_8H_6N_4O_5\cdot0.1$DMF) C,H,N.

6-Morpholino-7-nitro-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (8b). To an ice-cold solution of **7b** (0.29 g, 1.17 mmol) in concentrated H_2SO_4 (3 mL) was added KNO_3 (0.12 g, 3.89 mmol) portionwise, and the reaction mixture was stirred at 90 °C for 1 h. The solution was poured onto ice, and the resulting precipitate was collected and washed with water. The solid was recrystallized from DMF−water to give **8b** (0.38 g, 65%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.57 (s, 1H), 11.86 (s, 1H), 8.01 (s, 1H), 3.70 (m, 4H), 3.33 (br, 4H); MS (FAB) *m/z* 294 (M + 1). Anal. ($C_{11}H_{11}N_5O_5$) C,H,N.

6-(1*H*-Imidazol-1-yl)-7-nitro-2,3(1*H*,4*H*)-pyrido[2,3-*b*]-pyrazinedione Hydrochloride (8c·HCl). A solution of **7c** (1.01 g, 3.56 mmol) and nitronium tetrafluoroborate[22] (85%, 1.35 g, 8.90 mmol) in tetramethylene sulfone (10 mL) was heated at 120 °C for 4 h. The solution was poured onto water (10 mL) and neutralized with 1 N NaOH. The resulting precipitate was collected and washed with hot water. The solid was suspended in water and mixed with 1 N HCl (3.6 mL). After the mixture was stirred for 0.5 h, the solid was collected and washed with water and ethanol followed by recrystallization with DMF−water to give **8c**·HCl (0.63 g, 57%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 13.16 (brs, 1H), 12.74 (brs, 1H), 9.53 (m, 1H), 8.46 (s, 1H), 8.07 (m, 1H), 7.87 (m, 1H); MS (FAB) *m/z* 275 (M + 1). Anal. ($C_{10}H_6N_6O_4\cdot$HCl·0.2H_2O) C,H,N,Cl.

6-Hydroxy-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione [2,3,6-(1*H*,4*H*,5*H*)-Pyrido[2,3-*b*]pyrazinetrione] (9). A solution of **7a** (0.25 g, 1.29 mmol) in aqueous HBr (48%, 5 mL) was refluxed for 4 h and then stirred at room temperature overnight. The reaction mixture was diluted with water (100 mL), and the resulting precipitate was collected and washed with water. Recrystalliaztion of the solid from DMF−water gave **9** (0.16 g, 70%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.69 (s, 1H), 11.77 (s, 1H), 10.65 (br, 1H), 7.38 (d, J = 8.6 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H); MS (FAB) *m/z* 180 (M + 1). Anal. ($C_7H_5N_3O_3\cdot0.1H_2O$) C,H,N.

6-(Methylsulfonyl)-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (10). To a solution of **7e** (0.20 g, 0.96 mmol) in acetic acid (2 mL) was added aqueous hydrogen peroxide (30%, 0.36 mL, 3.17 mmol), and the mixture was stirred at room temperature overnight. The solution was diluted with water (15 mL), and the resulting precipitate was collected and recrystallized from DMF−water to give **10** (0.12 g, 52%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.51 (br, 2H), 7.78 (d, 1H), 7.62 (d, 1H), 3.22 (s, 3H); MS (FAB) *m/z* 242 (M + 1). Anal. ($C_8H_7N_3O_4S$) C,H,N,S.

2-Amino-6-methyl-3-nitropyridine (12). To an ice-cold solution of **11** (23.0 g, 212 mmol) in concentrated H_2SO_4 (100 mL) was added dropwise concentrated HNO_3 (70%, d = 1.43, 13.4 mL, 212 mmol). The ice bath was removed, and the solution spontaneously heated to about 50 °C and then cooled. The reaction mixture was additionally stirred at room temperature for 2 h and poured onto ice. The solution was adjusted to pH 4−5 by aqueous NaOH, and the resulting precipitate was collected and washed with hot water to give **12** (15.4 g, 47%): ^{1}H NMR δ 8.64 (m, 2H), 8.25 (d, 1H), 6.64 (d, 1H), 2.71 (s, 3H); MS (GC−EI) *m/z* 153 (M).

6-Methylpyrido[2,3-*b*]pyrazine-2,3-dione (13). A solution of **12** (7.60 g, 49.7 mmol) in ethanol (80 mL) was hydrogenated under atmospheric pressure with 10% Pd−C as catalyst. The suspension was filtered, and the filtrate was evaporated. To a solution of this residue in 4 N HCl (54 mL) was added oxalic acid (4.30 g, 47.8 mmol), and the mixture was refluxed overnight. The resulting precipitate was collected and washed with water. The solid was recrystallized from DMF−water to give **13** (2.90 g, 33%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 11.98 (m, 2H), 7.36 (d, 1H), 6.99 (d, 1H), 2.40 (s, 3H); MS (EI) *m/z* 177 (M). Anal. ($C_8H_7N_3O_2$) C,H,N.

7-Methyl-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (15a). A solution of 2,3-diamino-5-methylpyridine (**14a**)[23] (4.60 g, 37.4 mmol) and oxalic acid (3.40 g, 37.8 mmol) in 4 N HCl (50 mL) was refluxed overnight. The resulting precipitate was collected and washed with water to give **15a** (4.9 g, 74%): mp

>300 °C; ^{1}H NMR δ 12.22 (s, 1H), 11.94 (s, 1H), 7.88 (m, 1H), 7.24 (m, 1H), 3.30 (s, 3H); MS (EI) *m/z* 177 (M). Anal. ($C_8H_7N_3O_2 \cdot 0.5H_2O$) C,H,N.

7-Nitro-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (15b): 81% from 2,3-diamino-5-nitropyridine (**14b**);[24] mp >300 °C; ^{1}H NMR δ 12.93 (br, 1H), 12.21 (br, 1H), 8.86 (d, J = 2.9 Hz, 1H), 8.40 (d, J = 2.9 Hz, 1H); MS (EI) *m/z* 208 (M). Anal. ($C_7H_4N_4O_4$) C,H,N.

6,7-Dinitro-2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinedione (16). A solution of **15b** (0.59 g, 2.83 mmol) and nitronium tetrafluoroborate[22] (85%, 0.53 g, 3.39 mmol) in tetramethylene sulfone (6 mL) was heated at 130 °C for 2 h. The solution was poured onto water (10 mL), and the resulting precipitate was collected. The solid was recrystallized from water to give **16** (0.32 g, 45%): mp 265 °C dec (H_2O); ^{1}H NMR δ 13.30 (s, 1H), 12.60 (s, 1H), 8.12 (s, 1H); MS (EI) *m/z* 253 (M). Anal. ($C_7H_3N_5O_6$) C,H,N.

Molecular Modeling. The conformation of the compounds was optimized by the PM3 method with MMOK parameter as implemented in the MOPAC[30] Ver. 6.0 program. For these computations, the molecular modeling package MOLGRAPH-MS (Daikin Industry Ltd., Japan) on an IRIS/INDIGO workstation (SiliconGraphics) was used.

X-ray Crystallographic Analysis of 1·HCl. Suitable crystals for X-ray diffraction studies formed from H_2O with space group symmetry of $P2_1/n$ and cell constants of a = 9.613(1) Å, b = 9.093(1) Å, c = 14.154(1) Å, β = 90.20(1)° for Z = 4, and a calculated density of 1.662 g/cm^3. A Rigaku AFC-5R automatic four-circle diffractometer equipped with graphite-monochromated Cu Kα radiation (λ = 1.541 84 Å) was used for data collection and $\theta - 2\theta$ scan technique. Of the 1831 reflections with $2\theta < 120°$ at a scanning rate of 8° (2θ) min^{-1}, 1727 were observed ($|F| > 3\sigma|F|$). Three reference reflections showed no significant intensity deterioration throughout the data collection. The intensities were corrected for Lorentz and polarization factors but not for absorption and secondary extinction.

The structure was solved by direct methods using the computer program SHELXS86.[31] All hydrogen atoms were located on a difference Fourier map. The structure was refined by block-diagonal least-squares calculations with anisotropic (isotropic for hydrogen atoms) thermal parameters to a final R value of 0.039 (R_W = 0.047).

Biology. Radiobinding Assay. Inhibition of the specific binding of [^{3}H]AMPA and strychnine-insensitive [^{3}H]Gly to brain membranes *in vitro* was evaluated using standard procedures. The binding of [^{3}H]AMPA was conducted with crude membranes of rat whole brain in the presence of 100 mM KSCN as described by Honore et al.[25] [^{3}H]Gly binding was examined using Triton X-100-treated membranes of whole brain except cerebellum.[28] Final ligand concentrations were as follows: [^{3}H]AMPA, 43 nM, and [^{3}H]Gly, 35 nM.

IC_{50} values were determined from logit−log analysis, and K_i values were determined using the Cheng−Prushoff relationship.

Audiogenic Seizures in DBA/2 Mice. Test compounds were given ip to groups of eight male DBA/2 mice (21−28 days old, weight 10−12 g) per dose level 15 min prior to challenge with auditory stimulation (12 kHz at 120 dB).[29] Seizure response was assessed on the following scale: 0 = no response, 1 = wild running, 1 = clonus, 1 = tonic, and 1 = respiratory arrest; maximum score = 4, and minimum score = 0.

Acknowledgment. We thank Professor H. Nohira of Saitama University and Drs. N. Inukai, K. Murase, T. Tamura, S. Usuda, and S. Tsukamoto of Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd., for their encouragement and helpful discussion. We also thank Dr. T. Furuya for X-ray analysis, Mr. J. Togami for AMPA binding assay, Mr. A. Kohara for glycine binding assay, and the staff of the Structure Analysis Department for measurement of NMR, mass spectra, and elemental analyses in Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd.

Supporting Information Available: Crystal data, fractional coordinates, bond lengths, bond angles, and torsional angles for compound **1** (4 pages). Ordering information is given on any current masthead page.

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JM950304+