Novel AMPA Receptor Antagonists: Synthesis and Structure−Activity Relationships of 1-Hydroxy-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione and Related Compounds

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As part of our study of novel antagonists at the α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) subtype of excitatory amino acid (EAA) receptors and the pharmacophoric requirements of the receptor, we designed and synthesized a series of 1-substituted 6-imidazolyl-7-nitro-, and 7-imidazolyl-6-nitroquinoxalinediones, as well as related compounds, **6a**−**j**, **7**, **11a**−**e**, **15**, and **17**, which are 1- and 4-substituted analogues of **1** (YM90K), and evaluated their activity to inhibit [^{3}H]AMPA binding from rat whole brain. On the basis of their structure−activity relationships (SAR), we deduced that the amide proton of the imidazolyl-near side of the quinoxalinedione nucleus is not essential for AMPA receptor binding, whereas that of the imidazolyl-far amide is. Further, the receptors possess size-limited bulk tolerance for their *N*-substituents on the imidazolyl-near amide portion. Moreover, we found that introduction of a hydroxyl group at the imidazolyl-near amide portion causes a severalfold improvement in AMPA receptor affinity over unsubstituted derivatives. Among the compounds, 1-hydroxy-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione (**11a**) showed high affinity for AMPA receptor with a K_i value of 0.021 μM, which is severalfold greater than that of **1** and NBQX (**2**) (**1**, $K_i = 0.084$ μM; **2**, $K_i = 0.060$ μM). Compound **11a** also showed over 100-fold selectivity for the AMPA receptor than for the *N*-methyl-D-aspartate (NMDA) receptor and the glycine site on NMDA receptor.

Introduction

Neurodegenerative disorders such as global and focal cerebral ischemia, Parkinson's, Huntington's, and Alzheimer's disease, and also epilespy often substantially impair the patient's ability to function in society.[1] In view of the lack of effective neuroprotective agents to treat these disorders, the underlying mechanisms leading to these disorders have been studied to identify novel target sites.[2] During the last decades, it has become clear that one of the main pathological processes of these disorders is excess stimulation of excitatory amino acid (EAA) receptors.[3−11]

Postsynaptic EAA receptors have been classified into four main subtypes,[12] 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. The cerebroprotective effects of the NMDA subtype of EAA receptor antagonists have been well documented in focal ischemia models[5,6] but have been questioned in global ischemia models.[13,14] More recently, the AMPA receptor has drawn much attention because of its implication in the above diseases,[7−11] especially in neurodegeneration after cerebral ischemia.[13−17] To date, selective and competitive AMPA receptor antagonists were reported as candidate for therapeutic agents include 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo[*f*]quinoxaline (**2**) (NBQX),[7] 6-(1*H*-imidazol-1-yl)-7-nitro-2,3-(1*H*,4*H*)-quinoxalinedione (**1**, YM90K),[18,19] and the others (Figure 1).[20−22] They have shown a variety of neuroprotective effects; compound **1**, for example, displayed anti-AMPA-induced toxicity in cultured neurons and anticonvulsive activity and antiischemic effects in both global and focal ischemia models.[15−18,23]

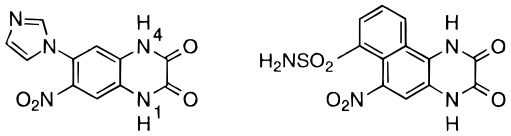

Figure 1.

We previously studied the structure−activity relationships (SAR) of imidazolylquinoxalinedione **1** and related compounds with regard to the effect of substituents on the benzene ring portion of the quinoxalinedione nucleus[19] and the pyridine ring portion of the pyridopyrazinedione nucleus[24] on binding activity for AMPA receptors. We concluded that functional groups which possess moderately sized π-conjugation systems and appropriate hydrophobicity are suitable for the 6-substituents, while electron-withdrawing groups are suitable for the 7-substituents. A combination of a 6-(1*H*-imidazol-1-yl) group and a 7-nitro group afforded the best affinity for AMPA receptors in both series, namely 2,3(1*H*,4*H*)-pyrido[2,3-*b*]pyrazinediones and 2,3-(1*H*,4*H*)-quinoxalinediones. As part of our program to discover potential AMPA receptor antagonists, we next focused on the pyrazine ring portion of the quinoxalinedione nucleus. In the present paper we report the synthesis of a series of 1-substituted 6-imidazolyl-7-nitro-, and 7-imidazolyl-6-nitroquinoxalinediones as well

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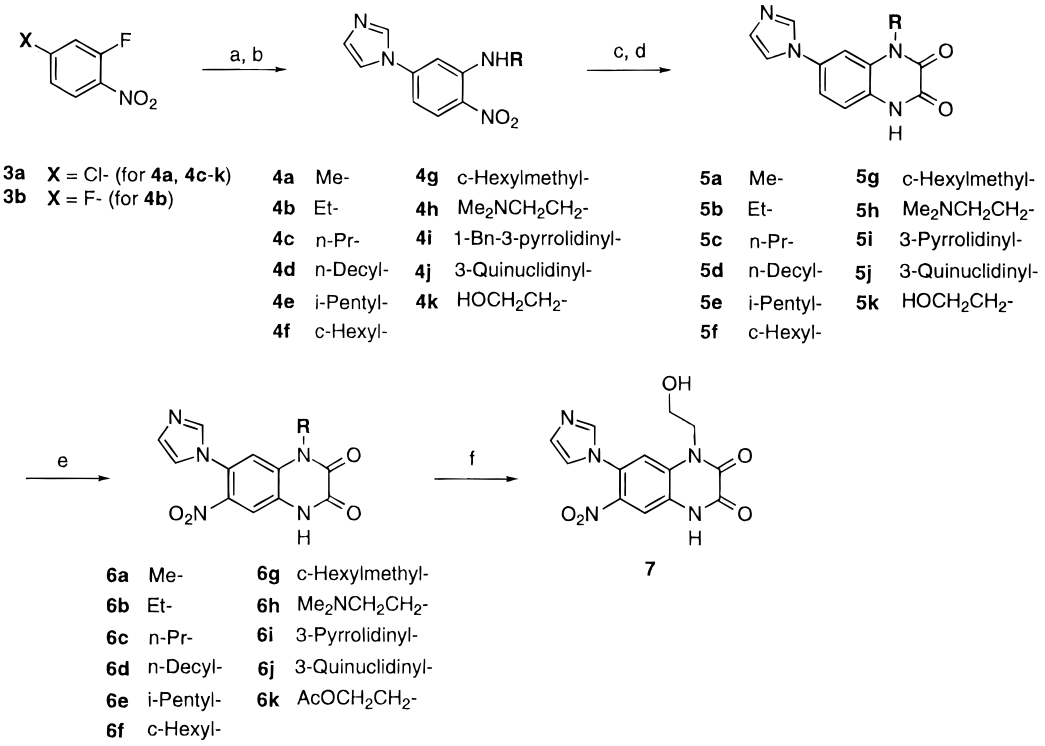
Scheme 1[a]



3a X = Cl- (for **4a**, **4c**-**k**)
3b X = F- (for **4b**)

4a	Me-	**4g**	c-Hexylmethyl-
4b	Et-	**4h**	$Me_2NCH_2CH_2$-
4c	n-Pr-	**4i**	1-Bn-3-pyrrolidinyl-
4d	n-Decyl-	**4j**	3-Quinuclidinyl-
4e	i-Pentyl-	**4k**	$HOCH_2CH_2$-
4f	c-Hexyl-		

5a	Me-	**5g**	c-Hexylmethyl-
5b	Et-	**5h**	$Me_2NCH_2CH_2$-
5c	n-Pr-	**5i**	3-Pyrrolidinyl-
5d	n-Decyl-	**5j**	3-Quinuclidinyl-
5e	i-Pentyl-	**5k**	$HOCH_2CH_2$-
5f	c-Hexyl-		

6a	Me-	**6g**	c-Hexylmethyl-
6b	Et-	**6h**	$Me_2NCH_2CH_2$-
6c	n-Pr-	**6i**	3-Pyrrolidinyl-
6d	n-Decyl-	**6j**	3-Quinuclidinyl-
6e	i-Pentyl-	**6k**	$AcOCH_2CH_2$-
6f	c-Hexyl-		

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[a] (a) RNH_2; (b) imidazole, KOH, DMSO for **4a**,**c**−**k**, imidazole, DMF for **4b**; (c) H_2, Pd−C, H^+; (d) $(COOH)_2$, H^+; (e) $^fHNO_3$, or NO_2BF_4; (f) 4 N HCl for **6k**.

as related compounds **6a**−**j**, **7**, **11a**−**e**, **15**, and **17** and the evaluation on their activity in inhibiting [^{3}H]AMPA binding from rat whole brain. We also discuss the pharmacophoric requirements of AMPA receptor with respect to the pyrazinedione portion of the quinoxalines on the basis of their SAR.

Chemistry

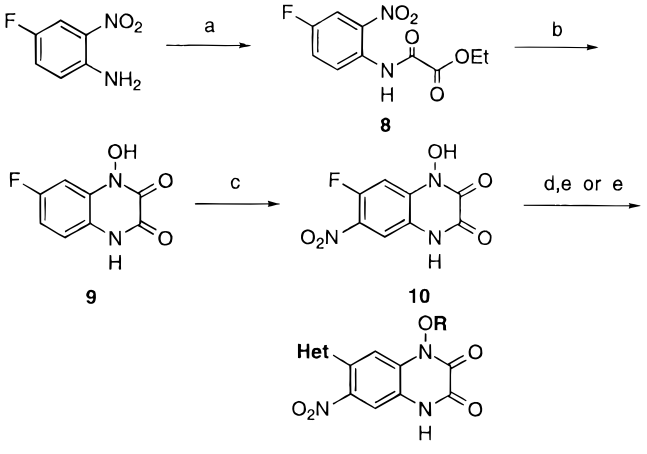
1-Alkyl-7-imidazolyl-6-nitro derivatives were prepared as shown in Scheme 1. Regiospecific nucleophilic substitution at the ortho position of 4-chloro-2-fluoronitrobenzene **3a** by treatment with various alkylamines in alcoholic solvents followed by substitution at the para position with imidazole in a presence of KOH in DMSO afforded the corresponding 2-(alkylamino)-4-(1*H*-imidazol-1-yl)nitrobenzenes **4a**,**c**−**k**. In the case of **3a** with 3-aminopyrrolidine, the reaction gave the desired *N*-(3-pyrrolidinyl)aniline with a substantial amount of undesired regioisomer, 2-(3-amino-1-pyrrolidinyl)benzene. To avoid formation of the byproduct, we utilized a 1-protected pyrrolidine, 3-amino-1-benzylpyrrolidine, as an amine component for the first substitution step and subsequent imidazole substitution of the resulting intermediate to yield benzylpyrrolidinylaniline **4i**. Next we attempted to examine the availability of 2,4-difluoronitrobenzene (**3b**) as a starting material. Treatment of **3b** with an excess equivalent of aqueous ethylamine in ethanol selectivity resulted in the ortho-substituted derivative, which was then reacted with imidazole in DMF, without KOH, to give *N*-ethyl-5-(1*H*-imidazol-1-yl)-2-nitroaniline, **4b**.

Hydrogenation of nitroaniline **4a**−**k** with palladium on carbon under atmospheric pressure followed by cyclic condensation of the resulting diamines with oxalic acid in refluxing 4 N HCl led to the formation of corresponding 1-substituted quinoxalinedione derivatives **5a**−**k**. In the case of the transformation from benzylpyrrolidinylaniline **4i** into quinoxaline **5i**, deprotection of its benzyl group occurred simultaneously in the reduction step. The nitration of **5a**−**k** in a concentrated H_2SO_4 or Ac_2O−AcOH−H_2SO_4 system gave 1-alkyl-7-(1-imidazolyl)-6-nitroquinoxalinediones **6a**−**c**,**e**−**k**. The reaction of **5k** in Ac_2O−AcOH−H_2SO_4 led ot nitration of the 6-position on the quinoxaline nucleus as well as acetylation of the 1-hydroxylethyl group at the same time. The resulting compound **6k** was hydrolyzed by acidic treatment to give the desired 1-hydroxyethyl derivative **7**. The nitration of **5d**, however, was sluggish in these conditions. *n*-Decyl deriative **6d** was obtained by nitration with nitronium tetrafluoroborate[25] in tetramethylene sulfone at 100 °C in low isolated yield (14%).

As shown in Scheme 2, 1-hydroxy- or 1-alkoxy-6-nitro-7-imidazolyl deriatives **11a**−**e** were prepared as follows. 2-Amino-5-fluoronitrobenzene was treated with ethyloxalyl chloride to give ethoxalyl derivative **8**. Contrary to our expectations, catalytic hydrogenation of **8** with palladium on carbon until the consumption of 2 equiv of hydrogen followed by workup[26] resulted in a mixture of desired 1-hydroxy-7-fluoroquinoxalinedione (**9**), starting material **8**, and an over-reduced 7-fluoroquinoxalinedione. On the other hand, **9** was prepared by catalytic hydrogenation with iridium on carbon[27] in excellent yield without the byproduct. Compound **9** was nitrated, and subsequent nucleophilic substitution of the fluorine atom of **10** with imidazoles or triazole gave 1-hydroxyquinoxalinediones **11a**,**d**,**e**. 1-Alkoxyquinoxalines **11b**,**c** were prepared by alkylation of the 1-hydroxy gruop of **10** under basic condition, followed by the treatment with imidazole.

Ethoxalylation of 3-fluoroaniline followed by nitration yielded a mixture of nitrobenzene **12** with two regio isomers, which were separated by silica gel chromatography. Reduction of the nitro group of **12** into hydroxylamine by Zn−NH_4Cl treatment under Zinin's condi-

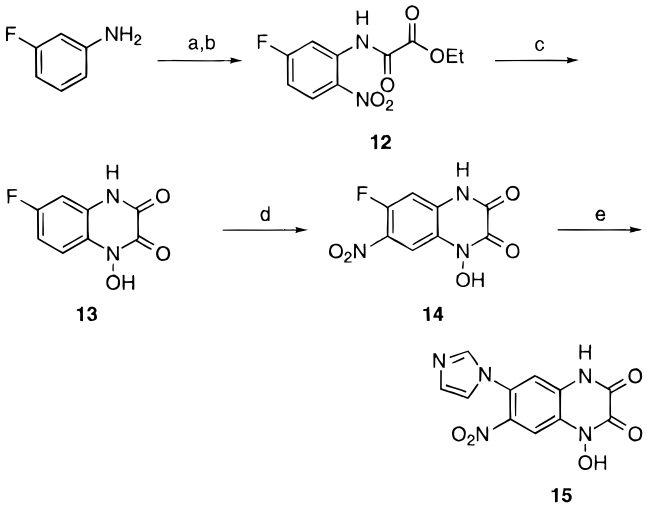
Scheme 2[a]



11a	**R** = H-	**Het** = 1-Imidazolyl-
11b	**R** = Me-	**Het** = 1-Imidazolyl-
11c	**R** = Et-	**Het** = 1-Imidazolyl-
11d	**R** = H-	**Het** = 4-Methyl-1-imidazolyl-
11e	**R** = H-	**Het** = 1,2,4-Tetrazol-1-yl-

[a] (a) EtOCOCOCl, Et_3N; (b) H_2, Ir−C; (c) KNO_3, H_2SO_4; (d) M_2SO_4−K_2CO_3 for **11b**, EtI−NaH for **11c**; (e) imidazole for **11a**−**c**, 4-methylimidazole for **11d**, and triazole−NaH for **11e**.

Scheme 3[a]



[a] (a) EtOCOCOCl, Et_3N; (b) $^fHNO_3$; (c) Zn, NH_4Cl; (d) KNO_3, H_2SO_4; (e) imidazole.

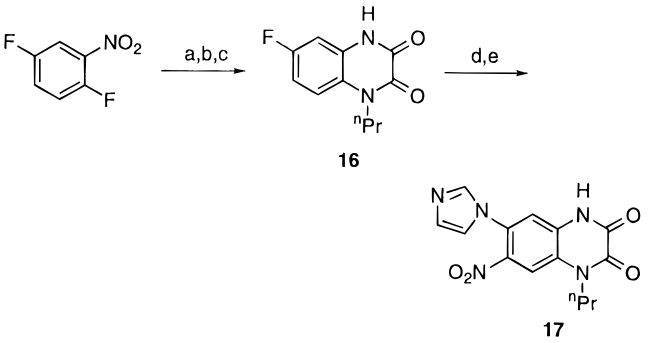
tion[28] and following workup led to formation of cyclized compound **13**, which was purified, nitrated, and then treated with imidazole to give 1-hydroxy-6-imidazolyl-7-nitroquinoxalinedione, **15** (Scheme 3).

The preparation of 1-*n*-propyl-6-imidazolyl-7-nitroquinoxaline (**17**) was carried out as follows. 2,5-Difluoronitrobenzene was ortho substituted with *n*-propylamine. The product was hydrogenated with palladium on carbon under atmospheric pressure, and then cyclic-condensed with oxalic acid to afford 1-propyl-6-fluoroquinoxaline (**16**). Subsequent nitration with KNO_3 and nucleophilic substitution with imidazole gave compound **17** (Scheme 4).

Results and Discussion

The structure of the 1-substituted quinoxalinediones and the results of radiobinding assays for AMPA receptor[29] are summarized in Tables 1 and 2. Affinities are presented as K_i (μM) values. Initially we investigated 1-alkyl-7-imidazolyl-6-nitroquinoxalinediones, namely 4-alkyl derivatives of compound **1** (Table 1). 1-Methyl-

Scheme 4[a]



[a] (a) *n*-$PrNH_2$; (b) H_2, Pd−C; (c) $(COOH)_2$, H^+; (d) KNO_3, H_2SO_4; (e) imidazole.

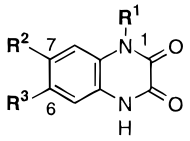
(**6a**), 1-ethyl- (**6b**), and 1-*n*-propylquinoxalinediones (**6c**) showed AMPA receptor affinity (K_i = 0.33, 0.19, and 0.14 μM, respectively) equipotent to or slightly less than that of unsubstituted **1** (K_i = 0.084 μM). To explore the bulk tolerance of AMPA receptor for the substituents, 1-branched-alkyl (**6e**) and 1-cycloalkyl (**6f**) derivatives were examined; these also showed affinity similar to that of **1** (K_i = 0.23 and 0.11 μM). In contrast, the binding activity of the more lengthened analogues 1-(cyclohexylmethyl)quinoxalinedione (**6g**) and 1-*n*-decylquinoxalinedione (**6d**) had about 1/10 and 1/100 times the affinity of **1**, respectively. These results indicated that the imidazolyl-near amide proton on the quinoxaline nucleus is not essential for AMPA receptor binding and that the receptor possesses size-limited bulk tolerance for the 1-substituents. We thus speculated that the imidazolyl-near amide act as a hydrogen bond acceptor, shown as a_1 in the pharmacophore model in Figure 2, rather than as a hydrogen donor.

We next focused on the effect of a heteroatom at the substituents for AMPA receptor binding. 1-Methoxy (**11b**) and 1-ethoxy (**11c**) derivatives exhibited only a severalfold decrease in AMPA affinity (K_i = 0.38, 0.30 μM, respectively) compared to that of **1**. Their binding activity is closely similar to that of the topologically corresponding alkyl analogues **6b** and **6c**. Compounds **6h** and **7**, which possess dimethylamino and hydroxy groups at the end of 1-alkyl substituents, respectively, displayed 5−10-fold less AMPA affinity than **1**, these values being even less than those of the corresponding 1-alkyl analogues **6e** and **6c**. The 1-(3-pyrrolidinyl) (**6i**), 1-(3-quinuclidinyl) (**6j**) derivatives also exhibited less affinity than compound **1** and the 1-cyclohexyl derivative **6f**. Thus, it can be speculated that the inner part of the suggested bulk tolerate pocket of the AMPA receptor for the substituents may be, at least in part, a hydrophobic environment.

It is interesting that 1-hydroxy-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione **11a**, in which the hydroxyl group is directly attached to the quinoxalinedione nucleus, showed AMPA receptor affinity with a K_i value of 0.021 μM, which is 3−4-fold greater than those of compounds **1** and **2** (**1**, K_i = 0.084 μM; NBQX (**2**), K_i = 0.060 μM). To our knowledge, compound **11a** possesses one of the highest AMPA receptor affinities among existing ligands for this receptor.

We then examined 1-substituted 6-imidazolyl-7-nitroquinoxaline derivatives **15** and **17**, namely 1-substituted derivatives of compound **1**. Both 1-hydroxyl (**15**) and 1-*n*-propyl (**17**) derivatives displayed affinity 20−30-fold weaker than that of the corresponding 7-imida-

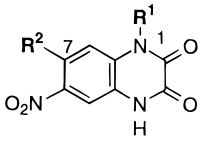
Table 1. 1-Substituted 6- or 7-Imidazolylquinoxalinedione Derivatives



compd	R^1	R^2	R^3	AMPA receptor affinity K_i (μM)[a]
6a	Me	1-imidazolyl	NO_2	0.33 (0.33−0.34)
6b	Et	1-imidazolyl	NO_2	0.19 (0.19−0.19)
6c	*n*-Pr	1-imidazolyl	NO_2	0.14 (0.13−0.14)
6d	*n*-decyl	1-imidazolyl	NO_2	8.9 (8.8−9.0)
6e	isopentyl	1-imidazolyl	NO_2	0.23 (0.22−0.25)
6f	cyclohexyl	1-imidazolyl	NO_2	0.11 (0.10−0.12)
6g	cyclohexylmethyl	1-imidazolyl	NO_2	0.79 (0.77−0.81)
7	$HOCH_2CH_2$	1-imidazolyl	NO_2	0.42 (0.41−0.44)
6h	$Me_2NCH_2CH_2$	1-imidazolyl	NO_2	0.84 (0.80−0.88)
6i	3-pyrrolidinyl	1-imidazolyl	NO_2	0.55 (0.51−0.59)
6j	3-quinuclidinyl	1-imidazolyl	NO_2	1.0 (1.0−1.1)
11a	HO	1-imidazolyl	NO_2	0.021 (0.019−0.023)
11b	MeO	1-imidazolyl	NO_2	0.38 (0.36−0.40)
11c	EtO	1-imidazolyl	NO_2	0.30 (0.29−0.32)
15	HO	NO_2	1-imidazolyl	0.44 (0.39−0.51)
17	*n*-Pr	NO_2	1-imidazolyl	4.5 (4.2−4.7)
1 (YM90K)				0.084 (0.083−0.086)
2 (NBQX)				0.060 (0.058−0.061)

[a] K_i values were determined by double experiments performed in triplicate. Values in parentheses are 95% confidence intervals.

Table 2. 1-Hydroxyquinoxalinedione Derivatives



compd	R^1	R^2	AMPA receptor affinity K_i (μM)[a]
11d	HO	4-methyl-1-imidazolyl	0.050 (0.049−0.052)
11e	HO	1,2,4-triazol-1-yl	0.18 (0.17−0.18)
18	H	4-methyl-1-imidazolyl	0.18 (0.17−0.19)
19	H	1,2,4-triazol-1-yl	0.24 (0.23−0.25)

[a] See Table 1.

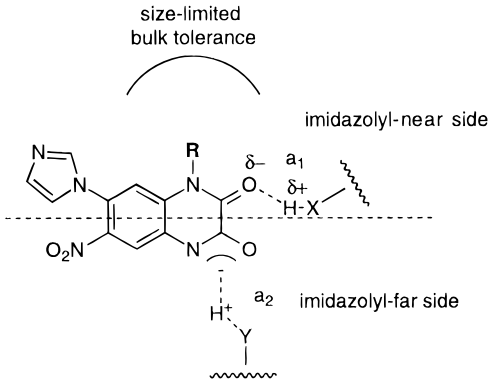


Figure 2. Suggested pharmacophore model of AMPA receptors for the binding of quinoxalinediones with respect to pyrazine ring portion.

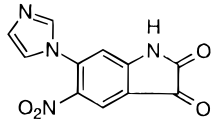


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Figure 3.

zolyl-6-nitroquinoxalines **11a** and **6c**. We previously reported that 6-(1*H*-imidazol-1-yl)-5-nitro-2,3(1*H*)-indolinedione (**20**) possesses no or negligible affinity for the AMPA receptor (K_i > 100 μM) (Figure 3).[30] These results indicated that the imidazolyl-far amide proton is essential for AMPA receptor binding. On the basis of the experimental observation that 1-substituted-7-imidazolyl-6-nitroquinoxalinedione **11b** forms a salt with imidazole, as stated in the Experimental Section, we deduced that the amide might act as a proton donor in a Coulombic interaction such as a_2 as shown in Figure 2. The hypothetical anionic site on the receptor in the above interaction could be a basic amino acid residue such as a histidine or lysine residue. The slight affinity compound **15** and **17** showed for the AMPA receptor deserves an explanation. In previous papers, we suggested that the AMPA receptor requires different structural features between 6- and 7-substituents of quinoxalinediones for their binding to the receptors.[19,24] Moreover, the ratios of the affinity of **15** versus **11a** and **17** versus **6c** are similar (1/20 and 1/30, respectively). Therefore, **15** and **17** probably bind to the receptors in an upside-down mode, in which 6- and 7-substituents are less favorable.

These SAR clearly indicated that the pyrazinedione portion of the quinoxalinedione nucleus plays an important role in AMPA receptor binding and that the receptor requires different structural features with respect to the imidazolyl-near and the imidazolyl-far amide of the pyrazine portion of quinoxalinedione nucleus, respectively.

The pharmacophore model of the pyrazine portion of the quinoxalinedione described in Figure 2 possesses some similarity to that of kynurenic acids, quinoxalinediones, and tetramic acids for the glycine site on the NMDA receptor suggested by Leeson et al.[31−33] This similarity may explain why most known quinoxaline derivatives have at least some affinity for both the AMPA receptor and glycine site. Different pharmacophoric requirements of substituents on the benzene portion of the quinoxaline nucleus may confer selectivity to selected ligands such that they can bind the AMPA receptor and glycine site on the NMDA receptor with different affinity.[19,22,24]

Since 1-hydroxyquinoxaline **11a** exhibited better affinity than **1**, we prepared and evaluated 1-hydroxy-7-(1,2,4-triazolyl)- (**11e**) and 1-hydroxy-7-(4-methylimi-

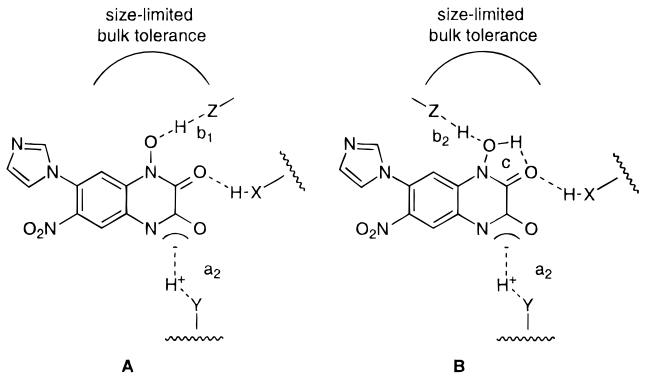

Figure 4. Suggested pharmacophore model of AMPA receptors for the binding of 1-hydroxyquinoxalinediones with respect to pyrazine ring portion.

dazolyl)quinoxalinediones (**11d**) (Table 2). In the case of triazolyl derivative **11e**, its affinity was equipotent to that of the corresponding 1-unsubstituted derivative **19**. In contrast, 4-methylimidazolyl derivative **11d** exhibited 4-fold greater affinity than unsubstituted **18**, giving a relation similar to that between **11a** and **1**. These results indicate that the introduction of a hydroxyl group to the nitrogen atom of imidazolyl-near amide results in a severalfold improvement in affinity for AMPA receptors, at least in the imidazolylquinoxalinedione derivatives.[34]

The effects of the hydroxy group probably result from its acting as a supplementary interaction site for AMPA receptor binding, because the acidic proton at the imidazolyl-near amide portion is not essential for AMPA receptor binding and the introduction of a hydroxy into the amide induced only a modest improvement in the affinity. Such interactions are probably not as strong as a Coulombic interaction. On these bases, several explanations can be speculated for the effect of the hydroxy group. First, the 1-hydroxyl group may contribute to hydrogen bonding or another dipole−dipole interaction such as hypothetical interaction b_1 (Figure 4A) or b_2 (Figure 4B). If the hydroxy group acts as a hydrogen bond donor as b_1, the distance between the hydroxy group and the nucleus may be critical for the interaction, since 1-hydroxyethyl derivative **7** displayed less affinity than **1**.[22] On the other hand, compounds **6h**−**j**, which have amino substituents at the 1-position, possess weaker affinity than **1**, and 1-alkoxy derivatives **11b**,**c** showed no improvement over **1**. Therefore, if the hydroxy group acts as a hydrogen bond acceptor as b_2, it may be important that the direction of the lone pair of the hydroxy group be constrained by intramolecular hydrogen bonding as seen in Figure 4B. Second, the expanded π-conjugation ring system of the quinoxalinedione nucleus by formation of pseudoring c in model **B** (Figure 4) may contribute to the receptor binding mediated by $\pi-\pi$ or $\pi-\sigma$ interaction. The favorable effects of the hydroxyl group may have multiple causes.

Among the compounds, 1-hydroxy-7-imidazolyl-6-nitroquinoxalinedione (**11a**), which showed the best affinity for AMPA receptor, was further characterized by its affinity for some another EAA receptor subtypes, high-affinity KA binding site,[35] NMDA binding site,[36] and strychnine-insensitive glycine site on NMDA receptor [37] (Table 3). Compound **11a** showed affinity severalfold greater than that for **1** and **2** for both non-NMDA receptors, AMPA receptor, and KA site, with AMPA selectivity 30-fold greater than KA selectivity (K_i of **11a** for KA site = 0.63 μM). Selectivity of **11a** between AMPA receptor and both binding sites on NMDA receptors was less than those of **1** and **2** but was nevertheless largely retained ($K_{i,NMDA}/K_{i,AMPA}$ = 570, $K_{i,glycine}/K_{i,AMPA}$ = 200, respectively).

Table 3. Affinities of **11a**, **1**, and **2** for EAA Receptor Subtypes

	K_i (μM)[a]			
	non-NMDA receptor affinity		NMDA receptor affinity	
compd	AMPA receptor	high-affinity KA site	NMDA binding site	glycine binding site
11a	0.021	0.63 (0.61−6.65)	12 (7.8−19)	4.2 (3.6−4.9)
1	0.084	2.2 (2.1−2.2)	>100	37 (34−40)
2	0.060	4.1 (3.9−4.3)	>100	>100

[a] See Table 1.

Conclusion

We synthesized a series of 1-substituted quinoxalinedione derivatives and evaluated their affinity for AMPA receptors. On the basis of their SAR, we deduced that the pyrazinedione portion of the quinoxalinedione nucleus play an important role in AMPA receptor binding. Further, the receptor requires different structural features with respect to the imidazolyl-near and imidazolyl-far amide of the pyrazine portion of quinoxalinedione nucleus; namely, the amide proton of the imidazolyl-near side of the quinoxalinedione nucleus is not essential for the receptor binding whereas that of the imidazolyl-far amide is. Further, the receptors possess size-limited bulk tolerance for their *N*-substituents on the imidazolyl-near amide portion. Moreover, we found that introduction of a hydroxyl group at the imidazolyl-near amide portion causes a severalfold improvement in AMPA receptor affinity over that of unsubstituted derivatives. Among the compounds, 1-hydroxy-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione (**11a**) showed high affinity for the AMPA receptor with a K_i value of 0.021 μM, which is severalfold greater than that of **1** and NBQX (**2**).

Experimental Section

Chemistry. Melting points were measured on a Yanaco MP-3 melting point apparatus and are uncorrected. Unless stated otherwise, ^{1}H NMR spectra were measured with a JEOL FX90Q, FX100, EX400, or GX500 spectrometer in DMSO-d_6 except where stated otherwise; chemical shifts are expressed in δ units using tetramethylsilane as the standard (in NMR description, s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, se = sextet, 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 of the elements, analytical results obtained for these elements were within 0.4% of the theoretical values except where stated otherwise. All solvents were evaporated in vacuo, and precipitates were dried under reduced pressure. The preparation of quinoxalinedione derivatives **1** and **18**−**20** has been reported previously.[19]

General Method for Preparation of 3-Imidazolylaniline 4a−**k.** The compounds were prepared by treatment of **3a** or **3b** with alkylamines followed by imidazole.

5-(1*H*-Imidazol-1-yl)-*N*-methyl-2-nitroaniline (4a). To an ice-cold solution of 4-chloro-2-fluoronitrobenzene (**3a**) (3.00 g, 17.1 mmol) in ethanol (6 mL) was added dropwise aqueous methylamine (40%, 6 mL). The reaction mixture was stirred at same temperature for 1 h, allowed to warm to room temperature, and then poured into water (50 mL). The resulting precipitate was collected, washed with a small amount of chilled ethanol−water solution, and then recrystallized from methanol to give 3-chloro-*N*-methyl-5-nitroaniline

(1.04 g, 33%). This orange-colored intermediate was added to a solution of imidazole (3.76 g, 55.2 mmol) and KOH (85%, 0.54 g, 83.1 mmol) in DMSO (10 mL). The mixture was heated at 120 °C for 2 h and then poured onto ice−water (60 g). The resulting precipitate was collected and washed with water to give **4a** (1.11 g, 93%): ^{1}H NMR δ 8.48 (s, 1H), 8.33 (br m, 1H), 8.19 (d, 1H), 7.94 (t, 1H), 7.15 (t, 1H), 7.08 (dd, 1H), 6.95 (d, 1H), 3.05 (d, 3H); MS (EI) *m*/*z* 218 (M).

5-(1*H*-Imidazol-1-yl)-2-nitro-*N*-propylaniline (4c): 3 equiv of *n*-propylamine was used in a place of aqueous methylamine; 90% from **3a** (two steps); ^{1}H NMR δ 8.48 (s, 1H), 8.32 (br s, 1H), 8.19 (d, 1H), 7.94 (s, 1H), 7.16 (s, 2H), 7.01 (dd, 1H), 3.44 (q, 2H), 1.69 (se, 2H), 0.98 (t, 3H); MS (EI) *m*/*z* 246 (M).

***N*-Decyl-5-(1*H*-imidazol-1-yl)-2-nitroaniline (4d):** 3 equiv of *n*-decylamine was used in a place of aqueous methylamine; 89% from **3a** (two steps); ^{1}H NMR δ 8.48 (s, 1H), 8.26 (br d, 1H), 8.19 (d, 1h), 7.93 (t, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 7.01 (dd, 1H), 3.45 (q, 2H), 1.24−1.74 (m, 16H), 0.85 (t, 3H); MS (EI) *m*/*z* 344 (M).

5-(1*H*-Imidazol-1-yl)-*N*-isopentyl-2-nitroaniline (4e): 5 equiv of isopentylamine was used in a place of aqueous methylamine; 99% from **3a** (two steps); ^{1}H NMR δ 8.48 (s, 1H), 8.19 (d, 1H), 8.19 (br s, 1H), 7.93 (t, 1H), 7.17 (m, 2H), 7.01 (dd, 1H), 3.46 (dd, 2H), 1.43−1.90 (m, 3H), 0.96 (d, 6H); MS (EI) *m*/*z* 274 (M).

***N*-Cyclohexyl-5-(1*H*-imidazol-1-yl)-2-nitroaniline (4f):** 3 equiv of cyclohexylamine at 60 °C was used in a place of aqueous methylamine at ambient temperature; 91% from **3a** (two steps); ^{1}H NMR δ 8.48 (t, 1H), 8.19 (d, 2H), 7.93 (t, 1H), 7.16−7.22 (m, 2H), 7.00 (dd, 1H), 3.92 (m, 1H), 1.37−2.00 (m, 10H); MS (EI) *m*/*z* 286 (M).

***N*-(Cyclohexylmethyl)-5-(1*H*-imidazol-1-yl)-2-nitroaniline (4g):** 3 equiv of cyclohexylmethylamine was used in a place of aqueous methylamine; 85% from **3a** (two steps); ^{1}H NMR δ 8.48 (s, 1H), 8.19 (d, 1H) 8.19 (br s, 1H), 7.93 (t, 1H), 7.17 (m, 2H), 7.01 (dd, 1H), 3.32 (t, 2H), 0.97−1.83 (m, 11H); MS (EI) *m*/*z* 300 (M).

***N*-[2-(Dimethylamino)ethyl]-5-(1*H*-imidazol-1-yl)-2-nitroaniline (4h):** 3 equiv of *N*,*N*-dimethylethylenediamine was used in a place of aqueous methylamine; 84% from **3a** (two steps); ^{1}H NMR δ 8.49 (s, 1H), 8.45 (t, 1H), 8.19 (d, 1H), 7.95 (s, 1H), 7.17 (d, 1H), 7.16 (s, 1H), 7.03 (dd, 1H), 3.50 (dd, 2H), 3.33 (d, 1H), 2.53 (d, 1H), 2.24 (s, 6H); MS (EI) *m*/*z* 275 (M).

5-(1*H*-Imidazol-1-yl)-2-nitro-*N*-(1-benzyl-3-pyrrolidinyl)aniline (4i): 2 equiv of 1-benzyl-3-aminopyrrolidine was used in a place of aqueous methylamine; 97% from **3a** (two steps). Spectral data for 3-chloro-2-nitroaniline intermediate: ^{1}H NMR δ 8.25 (br d, 1H), 8.14 (d, 1H), 7.27−7.48 (m, 5H), 7.18 (d, 1H), 6.79 (dd, 1H), 4.33 (m, 1H), 3.72 (s, 2H), 2.30−2.92 (m, 6H); MS (EI) *m*/*z* 331 (M).

5-(1*H*-Imidazol-1-yl)-2-nitro-*N*-(3-quinuclidinyl)aniline (4j): 2 equiv of 3-aminoquinuclidine dihydrochloride with 10 equiv of triethylamine was used in a place of aqueous methylamine; 65% from **3a** (two steps); ^{1}H NMR δ 8.52 (br d, 1H), 8.48 (s, 1H), 8.21 (dd, 1H), 7.93 (t, 1H), 7.16 (t, 1H), 6.97−7.09 (m, 2H), 4.02 (m, 1H), 3.41−3.56 (m, 2H), 2.41−2.77 (m, 4H), 1.96−2.06 (m, 1H), 1.44−2.06 (m, 4H); MS (EI) *m*/*z* 313 (M).

***N*-(2-Hydroxylethyl)-5-(1*H*-imidazol-1-yl)-2-nitroaniline (4k):** 2 equiv of ethanolamine was used in a place of aqueous methylamine; 91% from **3a** (two steps); ^{1}H NMR δ 8.48 (s, 1H), 8.36 (br d, 1H), 8.18 (d, 1H), 7.93 (t, 1H), 7.16 (m, 2H), 7.00 (dd, 1H), 5.02 (t, 1H), 3.50−3.73 (m, 4H); MS (FAB) *m*/*z* 249 (M + 1).

***N*-Ethyl-5-(1*H*-imidazol-1-yl)-2-nitroaniline (4b).** To an ice-cold solution of ethanol (10 mL) and aqueous ethylamine (70%, 10 mL, excess equivalent) was added portionwise 2,4-difluoronitrobenzene (**3b**) (3.00 g, 18.9 mmol). The reaction mixture was stirred at same temperature for 30 min, allowed to warm to room temperature, and then poured into water (100 mL). The resulting precipitate was collected and washed with a small amount of chilled ethanol−water solution to give *N*-ethyl-5-fluoro-2-nitroaniline (3.32 g, 96%). (Note: The aniline was sublimed under reduced pressure.) This intermediate (1.70 g, 9.23 mmol) was dissolved in a solution of imidazole (6.28 g, 92.2 mmol) in DMF (20 mL). The mixture was heated at 140 °C for 3 h and then poured into water (100 mL). The resulting precipitate was collected and washed with water to give **4a** (2.09 g, 97%): ^{1}H NMR δ 8.31 (d, 1H), 8.14 (br m, 1H), 7.94 (t, 1H), 7.25−7.35 (m, 2H), 6.78 (d, 1H), 6.68 (dd, 1H), 3.39 (m, 2H), 1.42 (t, 3H); MS (EI) *m*/*z* 232 (M).

General Method for Preparation of 1-Substituted-7-imidazolyl-6-nitroquinoxalinediones 6a−k. The compounds were prepared by hydrogenation of the appropriate *o*-nitroanilines **4a**−**k** under atmospheric pressure using Pd−C, followed by reaction with oxalic acid in 4 N HCl at reflux temperature and then nitration by fuming HNO_3 (**6a**−**c**,**e**−**k**) or nitronium tetrafluoroborate (**6d**).

7-(1*H*-Imidazol-1-yl)-1-methyl-2,3(1*H*,4*H*)-quinoxalinedione Hydrochloride (5a·HCl). Imidazolylaniline **4a** (1.08 g, 4.95 mmol) was hydrogenated in a solution of methanol (50 mL) and concentrated HCl (1.5 mL) under atmospheric pressure using 10% palladium on carbon (0.11 g), filtered, and evaporated to give suitably substituted phenylenediamine, which was treated with oxalic acid (0.45 g, 4.95 mmol) in 4 N HCl (15 mL) at reflux overnight. The resulting precipitate was collected and washed with water to give **5a**·HCl (1.20 g, 87%): mp >300 °C; ^{1}H NMR δ 12.26 (br s, 1H), 9.64 (s, 1H), 8.29 (s, 1H), 7.98 (s, 1H), 7.76 (s, 1H), 7.59 (d, 1H), 7.34 (d, 1H), 3.58 (s, 3H); MS (FAB) *m*/*z* 243 (M + 1).

1-Ethyl-7-(1*H*-imidazol-1-yl)-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (5b·HCl): 89% from **4b**; ^{1}H NMR δ 12.40 (br s, 1H), 9.87 (s, 1H), 8.35 (d, 1H), 7.94 (d, 1H), 7.83 (d, 1H), 7.61 (dd, 1H), 7.44 (d, 1H), 4.24 (q, 2H), 1.26 (t, 3H); MS (FAB) *m*/*z* 257 (M + 1).

7-(1*H*-Imidazol-1-yl)-1-propyl-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (5c·HCl): 93% from **4c**; mp > 300 °C (H_2O); ^{1}H NMR δ 12.35 (br s, 1H), 9.79 (s, 1H), 8.31 (s, 1H), 7.92 (s, 1H), 7.78 (d, 1H), 7.59 (dd, 1H), 7.40 (d, 1H), 4.15 (t, 2H), 1.70 (se, 2H), 0.96 (t, 3H); MS (FAB) *m*/*z* 271 (M + 1).

1-Decyl-7-(1*H*-imidazol-1-yl)-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (5d·HCl): 78% from **4d**; mp 183−186 °C (H_2O−HCl); ^{1}H NMR δ 12.37 (br s, 1H), 9.82 (s, 1H), 8.32 (t, 1H), 7.93 (t, 1H), 7.71 (dd, 1H), 7.56 (d, 1H), 7.41 (d, 1H), 4.19 (t, 2H), 1.24−1.64 (m, 16H), 0.85 (t, 3H); MS (FAB) *m*/*z* 369 (M + 1).

7-(1*H*-Imidazol-1-yl)-1-isopentyl-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (5e·HCl): 50% from **4e**; mp >300 °C; ^{1}H NMR δ 12.39 (br s, 1H), 9.83 (s, 1H), 8.33 (s, 1H), 7.94 (s, 1H), 7.56−7.69 (m, 2H), 7.42 (d, 1H), 4.20 (m, 2H), 1.57 (m, 3H), 0.96 (d, 6H); MS (FAB) *m*/*z* 299 (M + 1).

1-Cyclohexyl-7-(1*H*-imidazol-1-yl)-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (5f·HCl): 30% from **4f**; mp >300 °C; ^{1}H NMR δ 12.31 (br s, 1H), 9.81 (s, 1H), 8.28 (s, 1H), 7.92 (s, 1H), 7.90 (d, 1H), 7.56 (dd, 1H), 7.39 (d, 1H), 4.50 (m, 1H), 2.32−2.44 (br m, 2H), 1.36−1.77 (br m, 8H); MS (FAB) *m*/*z* 311 (M + 1).

1-(Cyclohexylmethyl)-7-(1*H*-imidazol-1-yl)-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (5g·HCl): 87% from **4g**; mp >300 °C (H_2O−HCl); ^{1}H NMR δ 12.34 (br s, 1H), 9.72 (s, 1H), 8.28 (s, 1H), 7.92 (s, 1H), 7.75 (d, 1H), 7.57 (dd, 1H), 7.39 (d, 1H), 4.10 (d, 2H), 1.59−1.86 (m, 6H), 1.01−1.14 (m, 5H); MS (FAB) *m*/*z* 325 (M + 1).

1-[2-(Dimethylamino)ethyl]-7-(1*H*-imidazol-1-yl)-2,3-(1*H*,4*H*)-quinoxalinedione Dihydrochloride (5h·2HCl): 86% from **4h**; mp 249−252 °C (H_2O−HCl−iPrOH); ^{1}H NMR δ 12.43 (s, 1H), 10.86 (br s, 1H), 10.04 (s, 1H), 8.48 (s, 1H), 8.05 (d, 1H), 7.94 (s, 1H), 7.67 (dd, 1H), 7.46 (d, 1H), 4.65 (t, 2H), 3.46 (s, 2H), 2.90 (s, 6H); MS (FAB) *m*/*z* 300 (M + 1).

7-(1*H*-Imidazol-1-yl)-1-(3-pyrrolidinyl)-2,3(1*H*,4*H*)-quinoxalinedione dihydrochloride (5i·2HCl): 97% from **4i** (the deprotection of benzyl group occurred simultaneously in the reduction step); ^{1}H NMR δ 12.38 (br s, 1H), 9.95 (s, 1H), 8.43 (s, 1H), 7.92 (s, 1H), 7.37−7.69 (m, 3H), 5.71 (m, 1H), 4.55 (br m, 2H), 3.64 (br m, 4H); MS (FAB) *m*/*z* 297 (M + 1).

7-(1*H*-Imidazol-1-yl)-1-(3-quinuclidinyl)-2,3(1*H*,4*H*)-quinoxalinedione dihydrochloride (5j·2HCl): 36% from **4j**; ^{1}H NMR δ 12.23 (br s, 1H), 9.00 (s, 1H), 8.05 (s, 1H), 7.31−7.53 (m, 4H), 5.15−5.30 (m, 2H), 4.27−4.42 (m, 1H), 3.28−3.77 (s, 5H), 1.68−2.31 (s, 4H); MS (FAB) *m*/*z* 338 (M + 1).

1-(2-Hydroxyethyl)-7-(1*H*-imidazol-1-yl)-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (5k·HCl): 49% from **4k**; mp >300 °C (H_2O−HCl); ^{1}H NMR δ 12.31 (br s, 1H), 9.87 (s, 1H),

8.36 (s, 1H), 7.98 (d, 1H), 7.92 (s, 1H), 7.62 (dd, 1H), 7.20 (d, 1H), 4.32 (t, 2H), 3.71 (t, 2H); MS (FAB) *m/z* 273 (M + 1).

Sodium 7-(1*H*-Imidazol-1-yl)-1-methyl-6-nitro-2,3-(1*H*,4*H*)-quinoxalinedionate (Na Salt of 6a). To an ice-cold solution of **5a** (0.70 g, 2.51 mmol) in concentrated H_2SO_4 (7 mL) was added dropwise fumin gHNO_3 (d = 1.52, 0.11 mL, 2.64 mmol) with the temperature maintained below 10 °C. After 2 h of stirring at ambient temperature, the reaction mixture was poured onto ice−water and then made basic by addition of aqueous NaOH (20%). The resulting precipitate was collected and recrystallized with ethanol−water to give the Na salt of **6a** (0.29 g, 37%): mp >300 °C (H_2O); ^{1}H NMR δ 7.82 (s, 1H), 7.60 (s, 1H), 7.35 (t, 1H), 7.19 (s, 1H), 7.04 (t, 1H), 3.52 (s, 3H); MS (FAB) *m/z* 310 (M + Na + 1). Anal. ($C_{12}H_8N_5O_4$·Na·2H_2O) C, H, N.

Sodium 7-(1*H*-Imidazol-1-yl)-1-isopentyl-6-nitro-2,3-(1*H*,4*H*)-quinoxalinedionate (Na salt of 6e): 32% from **5e**; mp 280−282 °C (H_2O); ^{1}H NMR δ 7.94 (s, 1H), 7.92 (s, 1H), 7.52 (s, 1H), 7.44 (s, 1H), 7.10 (s, 1H), 4.16 (t, 2H), 1.67 (qu, 1H), 1.50 (dd, 2H), 0.94 (d, 6H); MS (FAB) *m/z* 366 (M + Na + 1). Anal. ($C_{16}H_{16}N_5O_4$·Na) C, H, N.

1-(Cyclohexylmethyl)-7-(1*H*-imidazol-1-yl)-6-nitro-2,3-(1*H*,4*H*)-quinoxalinedione (6g). The reaction mixture was poured onto ice−water and then neutralized by addition of aqueous NaOH (20%). The resulting precipitate was collected and recrystallized with DMF−water to give **6g**: 41% from **5g**; mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.39 (br s, 1 H), 7.95 (s, 1H), 7.89 (s, 1H), 7.64 (s, 1H), 7.41 (s, 1H), 7.10 (s, 1H), 4.06 (d, 2H), 1.07−1.68 (m, 11H); MS (EI) *m/z* 369 (M). Anal. ($C_{18}H_{18}N_5O_4$·0.75H_2O) C, H; N: calcd, 18.34; found, 18.76.

7-(1*H*-Imidazol-1-yl)-6-nitro-1-(3-pyrrolidinyl)-2,3-(1*H*,4*H*)-quinoxalinedione (6i): 18% from **5i**; mp 272−275 °C dec (H_2O); ^{1}H NMR δ 8.22 (s, 1H), 7.92 (s, 1H), 7.89 (s, 1H), 7.40 (s, 1H), 7.08 (s, 1H), 5.47 (m, 1H), 2.81−3.21 (m, 4H), 2.14 (m, 2H); MS (FAB) *m/z* 343 (M + 1). Anal. ($C_{15}H_{14}N_6O_4$·2H_2O) C, H, N.

7-(1*H*-Imidazol-1-yl)-6-nitro-1-(3-quinuclidinyl)-2,3-(1*H*,4*H*)-quinoxalinedione (6j): 12% from **5j**; mp >300 °C (H_2O); ^{1}H NMR δ 7.96 (s, 1H), 7.93 (s, 1H), 7.46 (s, 1H), 7.36 (s, 1H), 7.10 (s, 1H), 4.65 (m, 1H), 3.97 (m, 1H), 2.99 (m, 2H), 2.80 (m, 2H), 2.15 (d, 1H), 1.90−2.00 (m, 2H), 1.61 (m, 1H), 1.35 (m, 1H), 1.24 (s, 1H); MS (FAB) *m/z* 383 (M + 1). Anal. ($C_{18}H_{18}N_6O_4$·2H_2O) C, H, N.

1-Ethyl-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione Hydrochloride (6b·HCl). The crude **6b** was heated under reflux with 1 N HCl and then recrystallized from water−ethanol to give **6b·HCl**: 46% from **5b**; mp >300 °C (H_2O−EtOH); ^{1}H NMR δ 12.71 (br s, 1H), 9.57 (s, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 8.00 (s, 1H), 7.91 (s, 1H), 4.15 (q, 2H), 1.22 (t, 3H); MS (FAB) *m/z* 302 (M + 1). Anal. ($C_{13}H_{11}N_5O_4$·HCl·H_2O) C, H, N, Cl.

7-(1*H*-Imidazol-1-yl)-6-nitro-1-propyl-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (6c·HCl): 78% from **5c**; mp >300 °C (H_2O−HCl); ^{1}H NMR δ 12.81 (br s, 1H), 9.57 (s, 1H), 8.31 (s, 1H), 8.06 (d, 1H), 8.00 (s, 1H), 7.92 (d, 1H), 4.07 (t, 2H), 1.67 (se, 2H), 0.94 (t, 3H); MS (FAB) *m/z* 316 (M + 1). Anal. ($C_{14}H_{13}N_5O_4$·HCl) C, H, N, Cl.

1-(2-Acetoxyethyl)-7-(1*H*-imidazol-1-yl)-6-nitro-2,3-(1*H*,4*H*)-quinoxalinedione hydrochloride (6k·HCl): an Ac_2O−AcOH−H_2SO_4 (5:1:1) solution was used in place of a concentrated H_2SO_4 solvent; 54% from **5k**; mp 248−250 °C (H_2O); ^{1}H NMR δ 12.43 (br s, 1H), 7.95 (d, 1H), 7.92 (s, 1H), 7.76 (s, 1H), 7.43 (s, 1H), 7.11 (s, 1H), 4.45 (t, 2H), 4.28 (t, 2H), 1.87 (s, 3H); MS (FAB) *m/z* 360 (M + 1).

1-[2-(Dimethylamino)ethyl]-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione dihydrochloride (6h·2HCl): an Ac_2O−AcOH−H_2SO_4 (5:1:1) solution was used in place of a concentrated H_2SO_4 solvent; 29% from **5h**; mp 284−287 °C (H_2O−HCl); ^{1}H NMR δ 12.56 (br s, 1H), 9.28 (s, 1H), 8.11 (s, 1H), 8.05 (d, 1H), 7.99 (s, 1H), 7.75 (d, 1H), 4.54 (t, 2H), 3.46 (m, 2H), 2.88 (m, 6H); MS (FAB) *m/z* 345 (M + 1). Anal. ($C_{15}H_{16}N_6O_4$·2HCl·0.25H_2O) C, H, N, Cl.

1-Cyclohexyl-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione Sulfate (6f·H_2SO_4). To an ice-cold solutionof **5f** (0.70 g, 2.02 mmol) in concentrated H_2SO_4 (7 mL) was added dropwise fuming HNO_3 (d = 1.52, 0.10 mL, 2.41 mmol) with the temperature maintained below 10 °C. After being stirred at ambient temperature for 2 h, the reaction mixture was poured onto ice−water to give a precipitate which was collected and recrystallized with DMF−water to give **6f·H_2SO_4** (0.15 g, 16%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.46 (br s, 1H), 9.51 (s, 1H), 8.11 (s, 1H), 8.06 (s, 2H), 7.92 (s, 1H), 4.41 (t, 1H), 2.37 (br m, 2H), 1.38−1.76 (br m, 8H); MS (FAB) *m/z* 356 (M + 1). Anal. ($C_{17}H_{17}N_5O_4$·H_2SO_4·0.5H_2O) C, H, N, S.

1-Decyl-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione Hydrochloride (6d·HCl). A solution of **5d** (1.00 g, 2.47 mmol) and nitronium tetrafluoroborate[25] (85%, 0.56 g, 3.58 mmol) in tetramethylene sulfone (8 mL) was heated at 100 °C for 30 min. After cooling, the reaction mixture was poured onto ice−water and then neutralized by addition of aqueous 1 N NaOH. The resulting precipitate was collected, dissolved in 4 N HCl−MeOH, and then concentrated to give crude product which was recrystallized from water−ethanol to give **6d·HCl** (0.15 g, 14%): mp 188−192 °C (MeOH); ^{1}H NMR δ 12.66 (br s, 1H), 9.51 (s, 1H), 8.20 (s, 1H), 8.05 (s, 1H), 7.94 (s, 1H), 7.91 (s, 1H), 4.08 (t, 2H), 1.62 (m, 2H), 1.24 (s, 14H), 0.85 (t, 3H); MS (FAB) *m/z* 414 (M + 1). Anal. ($C_{21}H_{27}N_5O_4$·HCl) C, H, N; Cl: calcd, 7.88; found, 8.29.

1-(2-Hydroxyethyl)-7-(1*H*-imidazol-1-yl)-6-nitro-2,3-(1*H*,4*H*)-quinoxalinedione Hydrochloride (7·HCl). (Acetoxyethyl)quinoxaline **6k** (0.25 g, 0.63 mmol) was treated with 4 N HCl at 100 °C for 30 min. After cooling, the reaction mixture was evaporated, and the residue was recrystallized-from *i*-PrOH to give **7·HCl** (0.20 g, 72%): mp >300 °C (*i*-PrOH); ^{1}H NMR δ 12.77 (br s, 1H), 9.56 (s, 1H), 8.28 (s, 1H), 8.15 (s, 1H), 8.06 (s, 1H), 7.91 (s, 1H), 4.25 (t, 2H), 3.67 (t, 2H); MS (FAB) *m/z* 318 (M + 1). Anal. ($C_{13}H_{11}N_5O_5$·HCl) C, H, Cl; N: calcd, 19.80; found, 19.25.

4-(Ethoxalylamino)-1-fluoro-3-nitrobenzene (8). The title compound was obtained in 71% yield from 2-amino-5-fluoronitrobenzene by following the procedure described for 1-chloro-4-(ethoxalylamino)-3-nitrobenzene:[26] ^{1}H NMR ($CDCl_3$) δ 11.78 (br, 1H), 8.87 (dd, 1H), 8.01 (dd, 1H), 7.47 (ddd, 1H), 4.47 (q, 2H), 1.46 (t, 3H); MS (EI) *m/z* 256 (M).

1-Hydroxy-7-fluoro-2,3(1*H*,4*H*)-quinoxalinedione (9). (Ethoxalylamino)benzene **8** (10.0 g, 39.0 mmol) was hydrogenated in DMF (200 mL) under atmospheric pressure in a presence of 5% iridium on carbon (0.50 g)[27] until the consumption of 2 equiv of hydrogen. The reaction mixture was filtered and evaporated at 60 °C to give crude product which was washed with solution of water and ethanol to give **9** (7.64 g, quantitative): mp 138−140 °C dec (EtOH−H_2O); ^{1}H NMR δ 12.13 (br s, 1H), 11.82 (br s, 1H), 7.12−7.31 (m, 2H), 6.99 (dd, 1H); MS (FAB) *m/z* 197 (M + 1).

1-Hydroxy-7-fluoro-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione (10). To an ice-cold solution of **9** (4.00 g, 20.4 mmol) in concentrated H_2SO_4 (40 mL) was added portionwise KNO_3 (2.27 g, 22.5 mmol) with the temperature maintained below 10 °C; the mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. The reaction mixture was poured onto ice−water (200 g), and resulting precipitate was collected and washed with water to give **10** (3.64 g, 74%): mp 202 °C (H_2O); ^{1}H NMR δ 12.32 (br s, 1H), 12.19 (br, 1H), 7.92 (d, 1H, J = 7.0 Hz), 7.50 (d, 1H, J = 12.3 Hz); MS (FAB) *m/z* 242 (M + 1).

1-Hydroxy-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione (11a). A solution of **10** (2.61 g, 10.8 mmol) and imidazole (3.68 g, 54.1 mmol) in DMF (50 mL) was heated at 140 °C for 2 h, cooled to room temperature, and evaporated. The resulting crude solid was washed with small amount of water, methanol, and then chloroform and recrystallized from DMF to yield 1.23 g of imidazole salt of **11a**, which was suspended in a solution of water (10 mL) and 1 N HCl (3.5 mL) and stirred at room temperature for 1 h, and the suspension was collected and washed with water to afford **11a** (33%): mp 281−283 °C; ^{1}H NMR δ 12.58 (br s, 1H), 8.26 (s, 1H), 8.04 (s, 1H), 7.60 (s, 1H), 7.57 (t, 1H), 7.27 (s, 1H); MS (FAB) *m/z* 290 (M + 1). Anal. ($C_{11}H_7N_5O_5$·1.5H_2O) C, H, N.

Imidazolium 7-(1*H*-Imidazol-1-yl)-1-methoxy-6-nitro-2,3(1*H*,4*H*)-quinoxalinedionate (Imidazole Salt of 11b). The solution of **10** (0.25 g, 1.04 mmol), dimethyl sulfate (0.16 g, 1.24 mmol), and K_2CO_3 (0.17 g, 1.23 mmol) in DMSO (5 mL) was heated at 60 °C for 30 min. The reaction mixture was

poured into water, and the resulting precipitate was collected and washed with water to give 1-methoxyquinoxalinedione intermediate (0.10 g, 38%): mp >300 °C; ^{1}H NMR δ 7.79 (d, 1H, J = 7.5 Hz), 7.41 (d, 1H, J = 12.5 Hz), 3.97 (s, 3H). An NOE between the methyl group and H-8 was observed: MS (FAB) m/z 256 (M + 1).

The same procedure as described for **11a** was used for the preparation of **11b** from the intermediate, except the aqueous HCl treatment in the workup (66% from the intermediate): mp 212−215 °C (H_2O); ^{1}H NMR δ 12.25 (br s, 1H), 7.95 (s, 1H), 7.94 (s, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 7.46 (s, 1H), 7.10 (s, 1H), 7.02 (s, 2H), 4.00 (s, 3H); MS (FAB) m/z 304 (M + 1). Anal. ($C_{12}H_9N_5O_5 \cdot C_3H_3N_2 \cdot 0.5H_2O$) C, H, N.

1-Ethoxy-7-(1*H*-imidazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione (11c). Under argon atmosphere, sodium hydride [60% suspension in mineral oil (0.083 g, 2.07 mmol) from which the mineral oil was removed by extraction with *n*-hexane] was suspended in DMSO (5 mL). 1-Hydroxyquinoxaline **10** (0.50 g, 2.07 mmol) was added to the solution and stirred at room temperature for 30 min. To the reaction mixture was added dropwise ethyl iodide (0.32 g, 2.05 mmol), and then the mixture was gradually heated up to 120 °C, cooled to room temperature, diluted with water (10 mL), and acidified with 1 N HCl to pH 5−6. The resulting precipitate was collected and washed with boiling water to give a solid, which was purified by short column chromatography (methanol eluent) to give 1-ethoxyquinoxaline intermediate (0.23 g, 41%): mp 267−269 °C; ^{1}H NMR δ 12.29 (s, 1H), 7.91 (d, 1H, J = 6.5 Hz), 7.52 (d, 1H, J = 12.0 Hz), 4.23 (q, 2H), 1.37 (t, 3H). An NOE between the ethyl group and H-8 was observed: MS (FAB) m/z 270 (M + 1).

The same procedure as described for **11a** was used for preparation of **11c** from the intermediate (30% from the intermediate): mp 189−190 °C (DMF−H_2O); ^{1}H NMR δ 12.45 (s, 1H), 7.95 (s, 2H), 7.52 (s, 1H), 7.45 (s, 1H), 7.11 (s, 1H), 4.26 (q, 2H), 1.34 (t, 3H); MS (FAB) m/z 318 (M + 1). Anal. ($C_{13}H_{11}N_5O_5 \cdot 1.25H_2O$) C, H, N.

1-Hydroxy-7-(4-methyl-1*H*-imidazol-1-yl)-6-nitro-2,3-(1*H*,4*H*)-quinoxalinedione Hydrochloride (11d·HCl). The same procedure as described for **11a** was used except the product was recrystallized from excess 1 N HCl in the workup: 41% from **10**; mp >300 °C (HCl); ^{1}H NMR δ 12.78 (s, 1H), 12.37 (br s, 1H), 9.37 (s, 1H), 8.21 (s, 1H), 7.89 (s, 1H), 7.73 (s, 1H), 2.37 (s, 3H); MS (FAB) m/z 304 (M + 1). Anal. ($C_{12}H_9N_5O_5 \cdot HCl$) C, H, N, Cl.

1-Hydroxy-7-(1*H*-1,2,4-triazol-1-yl)-6-nitro-2,3(1*H*,4*H*)-quinoxalinedione (11e). Under argon atmosphere, sodium hydride [60% suspension in mineral oil (0.21 g, 5.25 mmol) from which the mineral oil was removed by extraction with *n*-hexane] was suspended in DMSO (5 mL). Triazole (0.14 g, 2.03 mmol) was added to the solution and stirred at room temperature for 30 min, and then **10** (0.40 g, 1.66 mmol) was added. The reaction mixture was heated at 150 °C overnight, cooled to room temperature, diluted with water (10 mL), and acidified with 1 N HCl to pH 4. The resulting precipitate was collected, washed with water and methanol, and recrystallized from DMF−water to give **11e** (0.19 g, 40%): mp >300 °C (DMF−H_2O); ^{1}H NMR δ 12.54 (s, 1H), 12.24 (s, 1H), 9.07 (s, 1H), 8.26 (s, 1H), 7.93 (s, 1H), 7.75 (s, 1H); MS (FAB) m/z 297 (M + 1). Anal. ($C_{10}H_6N_6O_5 \cdot 0.25H_2O$) C, H, N.

3-(Ethoxalylamino)-1-fluoro-4-nitrobenzene (12). 3-(Ethoxalylamino)-1-fluorobenzene was obtained in 62% yield from 3-fluoroaniline by following the procedure described for 1-chloro-4-(ethoxalylamino)-3-nitrobenzene:[26] ^{1}H NMR δ 10.96 (br s, 1H), 7.31−7.78 (m, 3H), 6.90−7.12 (m, 1H), 4.35 (q, 1H), 1.35 (t, 3H); MS (EI) m/z 211 (M).

To an ice-cold solution of the intermediate (7.90 g, 37.3 mmol) in AcOH−Ac_2O solution (1:1, 90 mL) was added dropwise fuming HNO_3 (d = 1.52, 10.0 mL, 241 mmol) with the temperature maintained below 20 °C. The solution was stirred at room temperature for 5 h and poured onto ice−water. The resulting precipitate was collected and washed with water to give a crude mixture, which was purified by column chromatography ($CHCl_3$ eluent) to give **12** (less polar isomer, 6.80 g, 71%), 5-(ethoxalylamino)-1-fluoro-2-nitrobenzene (more polar isomer, 0.034 g, 0.3%), and 3-(ethoxalylamino)-1-fluoro-2-nitrobenzene (most polar isomer, 2.31 g, 24%). **12**: ^{1}H NMR δ 11.56 (br s, 1H), 8.34 (dd, 1H, J = 5.7 Hz, J' = 9.4 Hz), 8.12 (dd, 1H, J = 2.9 Hz, J' = 10.9 Hz), 7.35 (ddd, 1H, J = 2.9 Hz, J' = 8.6 Hz, J'' = 10.3 Hz), 4.37 (q, 2H), 1.35 (t, 3H); MS (EI) m/z 256 (M). 5-(Ethoxalylamino)-1-fluoro-2-nitrobenzene: ^{1}H NMR δ 11.31 (br s, 1H), 7.42−7.84 (m, 3H), 4.33 (q, 2H), 1.35 (t, 3H); MS (EI) m/z 256 (M). 3-(Ethoxalylamino)-1-fluoro-2-nitrobenzene: ^{1}H NMR δ 11.44 (br s, 1H), 8.21 (t, 1H, J = 9.1 Hz), 7.98 (dd, 1H, J = 2.6 Hz, J' = 16.6 Hz), 7.85 (ddd, 1H, J = 1.1 Hz, J' = 2.6 Hz, J'' = 10.3 Hz), 4.37 (q, 2H), 1.35 (t, 3H); MS (EI) m/z 256 (M).

1-Hydroxy-6-fluoro-2,3(1*H*,4*H*)-quinoxalinedione (13). In a water bath, to a solution of **12** (6.20 g, 24.2 mmol) and NH_4Cl (5.64 g, 105 mmol) in water (40 mL) and DMF (120 mL) was added portionwise powdered zinc (5.70 g, 87.2 mmol) with the temperature maintained below 35 °C.[28] The reaction mixture was filtered and washed with hot DMF (100 °C), and the filtrate was allowed to cool to room temperature. The resulting precipitate was removed, and the solution was evaporated to afford crude solid, which was recrystallized from methanol−DMF to give **13** (2.73 g, 57%): ^{1}H NMR δ 12.28 (br s, 1H), 7.90 (dd, 1H, J = 5.7 Hz, J'= 10.9 Hz), 7.00−7.26 (m, 2H); MS (FAB, Neg) m/z 195 (M − 1).

1-Hydroxy-6-fluoro-7-nitro-2,3(1*H*,4*H*)-quinoxalinedione (14). The title compound was prepared by the method described for **10**: 16% from **13**; mp 208 °C dec; ^{1}H NMR δ 12.59 (br s, 1H), 12.12 (br s, 1H), 8.04 (d, 1H, J = 7.9 Hz), 7.16 (d, 1H, J = 13.0 Hz); MS (FAB) m/z 242 (M + 1).

1-Hydroxy-6-(1*H*-imidazol-1-yl)-7-nitro-2,3(1*H*,4*H*)-quinoxalinedione (15). The title compound was prepared by the method described for **11a**: 48% from **14**; mp 285 °C dec (H_2O); ^{1}H NMR δ 12.08 (br s, 1H), 8.13 (s, 1H), 7.92 (s, 1H), 7.43 (s, 1H), 7.20 (s, 1H), 7.13 (m, 1H); MS (FAB) m/z 290 (M + 1). Anal. ($C_{11}H_7N_5O_5 \cdot 0.5H_2O$) C, H, N.

6-Fluoro-1-propyl-2,3(1*H*,4*H*)-quinoxalinedione (16). The *N*-propylaniline intermediate was prepared by the method described for corresponding intermediate of **4b** using 2,5-difluoronitrobenzene in a place of 2,4-difluoronitrobenzene: 82% from starting material; ^{1}H NMR δ 7.95 (br, 1H), 7.88 (dd, 1H), 7.23−7.26 (m, 1H), 6.83 (dd, 1H), 3.26 (t, 2H), 1.76 (se, 2H), 1.06 (t, 3H); MS (EI) m/z 198 (M). The title compound was prepared by the method described for **5a**: 86% from the intermediate; ^{1}H NMR δ 12.07 (br s, 1H), 7.35−7.51 (m, 1H), 6.92−7.14 (m, 2H), 4.05 (t, 2H), 1.63 (se, 2H), 0.94 (t, 3H); MS (FAB) m/z 223 (M + 1).

6-(1*H*-Imidazol-1-yl)-7-nitro-1-propyl-2,3(1*H*,4*H*)-quinoxalinedione (17). The nitroquinoxaline intermediate was prepared by the method described for **10**: 95% from **16**; ^{1}H NMR δ 12.48 (br s, 1H), 8.00 (d, 1H, J = 6.8 Hz), 7.14 (d, 1H, J = 11.7 Hz), 4.09 (t, 2H), 1.67 (se, 2H), 0.96 (t, 3H); MS (FAB) m/z 268 (M + 1). The title compound was prepared by the method described for **11a**: 98% from the intermediate; mp 158−160 °C (H_2O); ^{1}H NMR δ 12.51 (br s, 1H), 8.13 (s, 1H), 7.91 (s, 1H), 7.42 (s, 1H), 7.21 (s, 1H), 7.10 (s, 1H), 4.14 (t, 2H), 1.70 (se, 2H), 0.97 (t, 3H); MS (FAB) m/z 316 (M + 1). Anal. ($C_{14}H_{13}N_5O_4 \cdot 1.25H_2O$) C, H, N.

Biology. Radiobinding Assay. Inhibition of the specific binding of [^{3}H]AMPA, [^{3}H]KA, NMDA-sensitive [^{3}H]Glu, and strychnine-insensitive [^{3}H]Gly to brain membraines in vivo 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.[29] [^{3}H]KA binding was performed using crude membranes from rat cortex.[35] [^{3}H]Glu and [^{3}H]-Gly bindings were examined using Triton X-100-treated membranes of whole brain except cerebellum.[36,37] Final ligand concentrations were as follows: [^{3}H]AMPA, 43 nM; [^{3}H]KA, 4 nM; [^{3}H]Glu, 10 nM; [^{3}H]Gly, 35 nM.

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

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