# 8-(1*H*-Imidazol-1-yl)-7-nitro-4(5*H*)-imidazo[1,2-*a*]quinoxalinone and Related Compounds: Synthesis and Structure−Activity Relationships for the AMPA-type Non-NMDA Receptor

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As a part of our program to discover novel antagonists for the AMPA subtype of EAA receptors, we designed and synthesized a series of heterocyclic-fused imidazolylquinoxalinones **5a**−**c**, **9**, **11**, **14a**−**e**, and **18** which led from 6-(1*H*-imidazol-1-yl)-7-nitro-2,3(1*H*,4*H*)-quinoxalinedione hydrochloride (**1a**·HCl, YM90K) by replacement of its amide with the imidazole and triazole rings. Their activity was evaluated by inhibiting [$^3$H]AMPA binding from rat whole brain. As a result, it appeared that 8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-imidazo[1,2-*a*]quinoxalinone (**5a**) and its [1,2,4]triazolo[4,3-*a*] analogue **14a** possessed high affinity for AMPA receptors with $K_i$ values of 0.057 and 0.19 $\mu$M, respectively, similar to the activity of **1a** and NBQX (**2**) (**1a**, $K_i$ = 0.084 $\mu$M; **2**, $K_i$ = 0.060 $\mu$M). In contrast, 8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-imidazo[1,5-*a*]quinoxalinone (**5b**) and 7-(1*H*-imidazol-1-yl)-8-nitro-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (**18**) showed no or weak affinity for the receptors. Hence, we deduced that the nitrogen atom of the fused heterocycles at the 3-position of **5a** and **14a** plays an essential role as hydrogen bond acceptors in binding to AMPA receptors, whereas their amides act as proton donors. From the SAR on 1-alkyl derivatives of **5a** and **14a**, it was indicated that introduction of suitable 1-alkyl substituents led to a severalfold improved AMPA affinity. A computational study on a model of water−quinoxaline complexes, a mimic of the putative hydrogen-bonding interaction between the receptors and quinoxalines, indicated that the different affinities of **5a**, **14a**, **1a**, and **19** for the AMPA receptor may depend on, at least in part, each stabilization energy for the interaction. On this basis, we propose a pharmacophore model of AMPA receptors for the binding of the imidazolylquinoxaline derivatives. The heterocyclic-fused quinoxalinones **5a**,**c** and **9** showed potent inhibitory activity in KA-induced toxicity for hippocampal cell culture with $IC_{50}$ values of 0.30, 0.32, and 0.30 $\mu$M, respectively (**1a**, 0.81 $\mu$M; **2**, 0.38 $\mu$M). Moreover **5a** possesses over 5000-fold AMPA selectivity against both the NMDA receptor and the glycine site on the NMDA receptor.

## Introduction

Neurotoxicity mediated by excessive excitatory amino acid (EAA) neurotransmission has been considered to be implicated in the pathology of disorders such as global and focal cerebral ischemia,[1−4] Parkinson's, Huntington's, and Alzheimer's disease,[5−7] and epilepsy.[8] In order to develop effective neuroprotective agents to treat these neurodegenerative disorders, many researchers have been working in this area.[9] Postsynaptic EAA receptors have been pharmacologically classified into four main subtypes:[10,11] namely, the *N*-methyl-D-aspartate (NMDA) receptor, the α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor, the kainate (KA) receptor subtypes, which are ligand-gated ionic channels, and the metabotropic glutamate receptor subtype, which is coupled to G-proteins. On the other hand, the AMPA receptor (also called AMPA/KA receptor) and the KA receptor (also called high-affinity KA receptor) may be collectively grouped as non-NMDA receptors. Recently, the blockade of AMPA-type non-NMDA receptor transmission has drawn much attention, because implication of the receptor subtype for the diseases, especially for neurodegeneration after cerebral ischemia,[2,4,12−14] has become clear. To date, potential, competitive, and selective AMPA receptor antagonists have been reported as candidates for the therapeutic agents which include 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo[*f*]quinoxaline (**2**) (NBQX),[2,6,8,12] 6-(1*H*-imidazol-1-yl)-7-nitro-2,3(1*H*,4*H*)-quinoxalinedione (**1a**) (YM90K),[4,14−16] and others[17−19] (Figure 1).

Previously, we discovered a novel series of imidazolylquinoxalinedione derivatives, represented by **1a**,[15,16] 1-hydroxyquinoxalinedione **1b**,[20] and pyrido[2,3-*b*]pyrazinedione **1c**,[21] which possess potent and selective AMPA antagonist activity. On the basis of their detailed structure−activity relationships (SAR), we deduced several pharmacophoric requirements for the compounds in binding to AMPA receptors. Herein we focused on our previous suggestions regarding the requirements for their pyrazinedione portion:[20] that is (1) the oxygen atom of their imidazolyl-near amide may function as an acceptor in the hydrogen-bonding interaction $a_1$ with the receptors in their keto form (Figure 2), and (2) the $\pi$-conjugation ring system of pseudoring structure b in **1b** (Figure 3) which is formed by its intramolecular hydrogen bonding[22] may cause its severalfold improved AMPA receptor affinity as compared to 1-unsubstituted **1a** by mediating a $\pi-\pi$ or $\pi-\sigma$ interaction with the receptor. In order to test these hypotheses, we designed heterocyclic-fused quinoxalinones[23] such as (imidazol-1-yl)imidazo- and [1,2,4]triazoloquinoxalinones **5a**,**b**, **14a**, and **18**. The fused heterocycles of **5a** and **14a** are expected to function as a bioisostere for the imidazolyl-near amide portion of **1a**−**c** by acting as both

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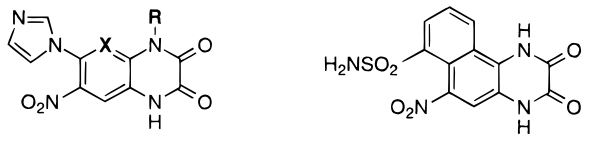


**1a** X = -CH- R = H YM90K
**1b** X = -CH- R = HO
**1c** X = -N- R = H

**2** NBQX

**Figure 1.**

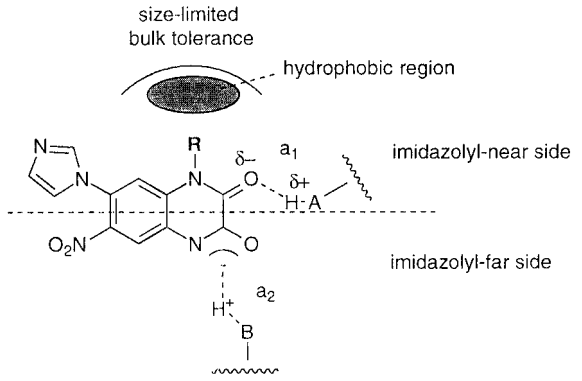



**Figure 2.** Suggested pharmacophore model of AMPA receptors for the binding of quinoxalinediones with respect to the pyrazine ring portion.

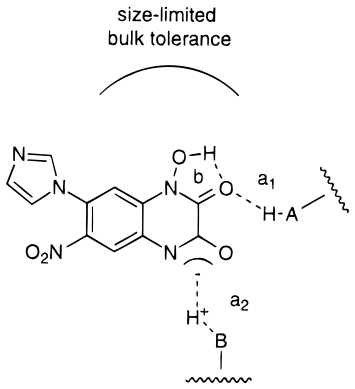



**Figure 3.** Suggested pharmacophore model of AMPA receptors for the binding of 1-hydroxyquinoxalinedione **1b** with respect to the pyrazine ring portion.

the acceptor for the putative hydrogen-bonding system and the expanded $\pi$-conjugation ring system.[22] On the other hand, **5b** and **18** were designed as two types of heterocyclic isomers of **5a** and **14a**.

In this paper, we describe the synthesis of **5a**,**b**, **14a**, and **18** as well as related compounds **5c**, **9**, **11**, and **14b**−**e** and SAR on their AMPA affinities in comparison with quinoxalinediones **1a**−**c**, **19**−**25**, and related compound **26**. On the basis of their SAR and a computational calculation, we discuss the pharmacophore model of the AMPA receptor for the binding of imidazolylquinoxalines. Moreover, with respect to the representative compounds, *in vitro* characterization was carried out.

## Chemistry

The synthesis of our heterocyclic-fused quinoxalinones **5a**−**c**, **9**, **11**, **14a**−**e**, and **18** is outlined in Schemes 1−4. The nucleophilic disubstitution of 2,4-difluoro-5-nitroaniline (**3a**)[25] with imidazole and 2-methylimidazole gave 2,4-di(1*H*-imidazol-1-yl)- (**4a**) and 2,4-bis(2-methyl-1*H*-imidazol-1-yl)-5-nitroaniline (**4b**), respectively. On the other hand, 2,4-di(1*H*-imidazol-1-yl)-5-(trifluoromethyl)aniline (**4c**) was obtained from 1,5-dichloro-2-nitro-4-(trifluoromethyl)benzene (**3b**) by disubstitution with imidazole followed by hydrogenation with palladium on carbon. Treatment of the resulting anilines **4a**−**c** with 1,1′-carbonyldiimidazole[26] in refluxing 1,2-dichlorobenzene led to the formation of the imidazole ring-fused quinoxalinones **5a**−**c** (Scheme 1).

1-Ethyl-8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-imidazo-[1,2-*a*]quinoxalinone **(9)** and its dihydro derivative **11** were prepared as shown in Scheme 2.[27] The chlorination of 6-fluoro-7-nitro-2,3(1*H*,4*H*)-quinoxalinedione by treatment with thionyl chloride provided 2,3-dichloro-6-fluoro-7-nitroquinoxaline (**6**). The nucleophilic substitution of **6** with 1 equiv of 1-amino-2-butanol at ambient temperature resulted in the 3-position selective monosubstitution on the quinoxaline nucleus. The resulting 3-chloro-7-fluoro-2-[(2-hydroxy-1-butyl)amino]-6-nitroquinoxaline (**7**) was oxidized under Swern's condition, intramolecular-cyclized by treatment with the trifluoroacetic anhydride−trifluoroacetic acid system, and then hydrolyzed by aqueous hydrochloric acid to give 1-ethyl-8-fluoro-7-nitro-4(5*H*)-imidazo[1,2-*a*]quinoxalinone (**8**), whereas 1,2-dihydro-1-ethyl-8-fluoro-7-nitro-4(5*H*)-imidazo[1,2-*a*]quinoxalinone (**10**) was synthesized from the intramolecular-cyclized condensation of **7** by treatment with thionyl chloride followed by acidic hydrolysis. Displacement of the fluorine atom of **8** and **10** with imidazole afforded the desired compounds **9** and **11**, respectively.

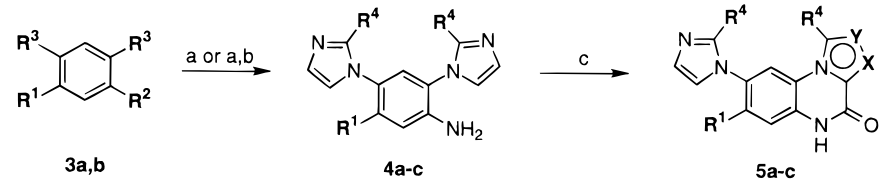
Compound **6** was utilized again as the starting material for the preparation of 8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone **(14a)** and its 1-alkyl derivatives **14b**−**e**. Namely, reaction of **6** with hydrazine provided (3-chloro-7-fluoro-6-nitroquinoxalin-2-yl)hydrazine (**12**), of which condensation with various ortho esters[28] followed by acidic hydrolysis of its chloroimine structure into amide produced the corresponding 8-fluoro-7-nitro-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinones **13a**−**e**. The substitution of **13a**−**e** with imidazole afforded the desired compounds **14a**−**e**, respectively (Scheme 3).

7-(1*H*-Imidazol-1-yl)-8-nitro-1-propyl-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (**18**) was prepared in four steps: namely, cyclic condensation of (6-fluoro-3-methoxyquinoxalin-2-yl)hydrazine[28] with tri-*n*-propyl orthoformate, acidic hydrolysis, nitration, and nucleophilic substitution with imidazole (Scheme 4).

## Results and Discussion

The heterocyclic-fused quinoxalinones were evaluated for their activity to inhibit [$^3$H]AMPA binding from rat whole brain.[29] The structures of the compounds and the results of the assay are summarized in Tables 1 and 2. Their affinities are presented as $K_i$ ($\mu$M) values. Initially, we examined 8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-imidazo[1,2-*a*]quinoxalinone (**5a**) and 8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (**14a**), which are the heteroaromatic-fused quinoxalinones designed from quinoxalinediones **1a**,**b** by replacement of their imidazole-near amide portion into imidazole and triazole rings (Figure 4). As predicted, it appeared that both **5a** and **14a** showed high affinity for AMPA receptors ($K_i$ = 0.057 and 0.19 $\mu$M) (Table 1) similar to the imidazolylquinoxalinedione derivatives **1a**−**c** ($K_i$ = 0.084, 0.021, and 0.14 $\mu$M, respectively) (Table 2).[16,20,21] In contrast, 1-methyl-8-(2-methyl-1*H*-

**Scheme 1**[a]



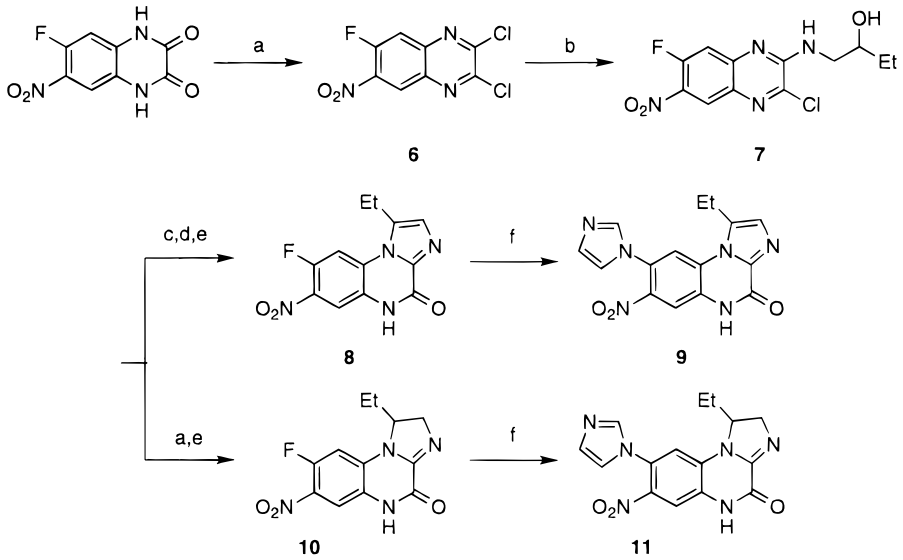

**3a** $R^1$ = $NO_2$- $R^2$ = $NH_2$- $R^3$ = F-
**3b** $R^1$ = $CF_3$- $R^2$ = $NO_2$- $R^3$ = Cl-

**4a** $R^1$ = $NO_2$- $R^4$ = H-
**4b** $R^1$ = $NO_2$- $R^4$ = Me-
**4c** $R^1$ = $CF_3$- $R^4$ = H-

**5a** $R^1$ = $NO_2$- $R^4$ = H- X = -N- Y = -CH-
**5b** $R^1$ = $NO_2$- $R^4$ = Me- X = -CH- Y = -N-
**5c** $R^1$ = $CF_3$- $R^4$ = H- X = -N- Y = -CH-

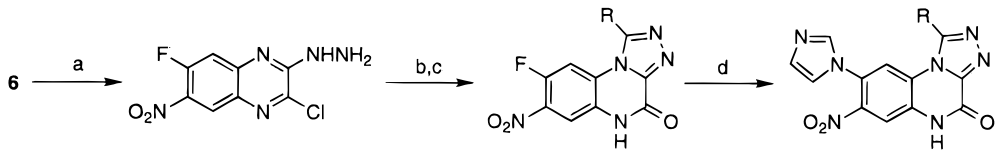
[a] (a) Imidazole or 2-methylimidazole; (b) $H_2$, Pd−C; (c) 1,1′-carbonyldiimidazole.

**Scheme 2**[a]




[a] (a) $SOCl_2$; (b) $C_2H_5CH(OH)CH_2NH_2$; (c) $(COCl)_2$, DMSO, $Et_3N$; (d) $(CF_3CO)_2O$, $CF_3COOH$; (e) 4 N HCl−MeOH; (f) imidazole, NaH.

**Scheme 3**[a]

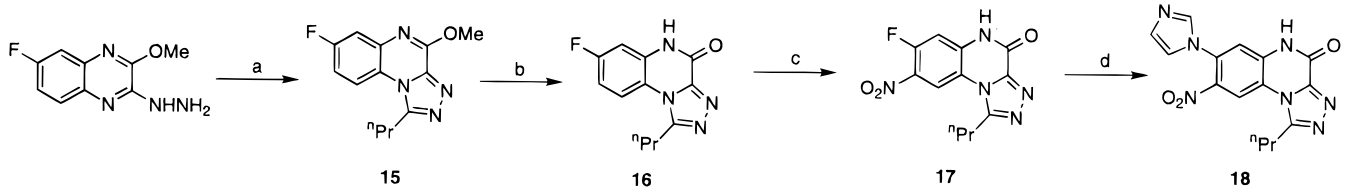



**13a** R = H-
**13b** R = Me-
**13c** R = Et-
**13d** R = *n*-Pr-
**13e** R = *n*-Bu-

**14a** R = H-
**14b** R = Me-
**14c** R = Et-
**14d** R = *n*-Pr-
**14e** R = *n*-Bu-

[a] (a) $NH_2NH_2$; (b) $RC(OEt)_3$; (c) 4 N HCl; (d) imidazole, NaH.

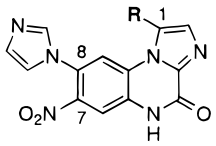
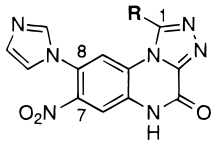
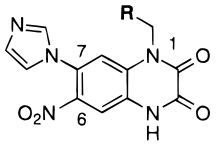
**Scheme 4**[a]




[a] (a) $RC(OEt)_3$; (b) 4 N HCl; (c) $KNO_3$, $^cH_2SO_4$; (d) imidazole, NaH.

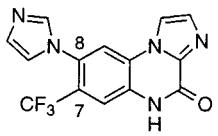
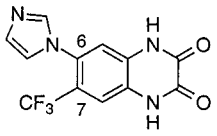
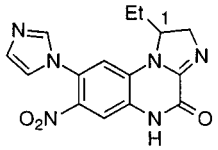
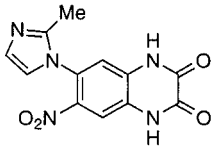
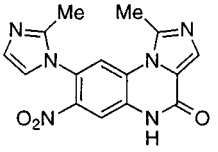
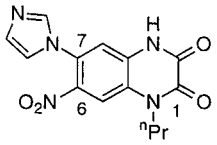
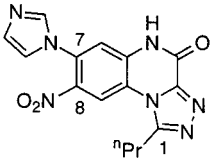
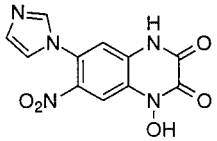
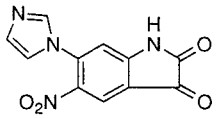
imidazol-1-yl)-7-nitro-4(5*H*)-imidazo[1,5-*a*]quinoxalinone (**5b**, X = carbon, Y = nitrogen, Figure 4), heterocyclic isomer of **5a** with respect to the position of the nitrogen atom which was a putative acceptor for the hypothesized hydrogen-bonding interaction with the AMPA receptor,[20] had no or negligible affinity for the receptors at a 10 $\mu$M dose (Table 2). Since 1-alkylimidazo[1,2-*a*]-quinoxalinone **9** and (2-methylimidazol-1-yl)quinoxalinedione **23** possess substantial AMPA affinity ($K_i$ = 0.020 and 0.39 $\mu$M, respectively) (Tables 1 and 2), the deprivation of AMPA affinity of **5b** should not be caused by its methyl substituents. The results clearly indicated that suitable heterorings, such as the imidazo[1,2-*a*] structure of **5a** and the [1,2,4]triazolo[4,3-*a*] structure of **14a**, function as a bioisostere for the imidazolyl-near amide portion of the imidazolylquinoxalinediones during

**Table 1.** Imidazo[1,2-*a*]- and [1,2,4]Triazolo[4,3-*a*]quinoxalinones and 1-Alkylquinoxalinediones

| Structure | R / | H- | Me- | Et | *n*-Pr- | *n*-Bu- |
|---|---|---|---|---|---|---|
|  | Compd. | **5a** | | **9** | | |
| | $K_i$ (μM)[a,b] | 0.057 (0.054-0.060) | | 0.020 (0.020-0.020) | | |
|  | Compd. | **14a** | **14b** | **14c** | **14d** | **14e** |
| | $K_i$ (μM)[a,b] | 0.19 (0.18-0.19) | 0.096 (0.094-0.098) | 0.048 (0.047-0.049) | 0.099 (0.097-0.10) | 0.070 (0.069-0.070) |
|  | Compd. | **19** | **20** | **21** | | |
| | $K_i$ (μM)[a,b] | 0.33 (0.33-0.34) | 0.19 (0.19-0.19) | 0.13 (0.13-0.14) | | |

[a] AMPA receptor affinity. [b] Data were determined by double experiments performed in triplicate. Values in parentheses are 95% confidence intervals.

**Table 2.** Alternative Imidazolylquinoxalines and Related Compounds

| Compd. | Structure | AMPA receptor affinity $K_i$ (μM)[b] | Compd. | Structure | AMPA receptor affinity $K_i$ (μM)[b] |
|---|---|---|---|---|---|
| **5c** |  | 0.066 (0.063-0.069) | **22** |  | 0.20 (0.20-0.21) |
| **11** |  | 0.15 (0.15-0.15) | **23** |  | 0.39 (0.35-0.43) |
| **5b** |  | >10 | **24** |  | 4.5 (4.2-4.7) |
| **18** |  | 6.6 (5.8-7.5) | **25** |  | 0.44 (0.39-0.51) |
| **1a** (YM90K) | | 0.084 (0.083-0.086) | | | |
| **1b** | | 0.021 (0.019-0.023) | **26** |  | >100 |
| **1c** | | 0.14 (0.14-0.15) | | | |
| **2** (NBQX) | | 0.060 (0.058-0.061) | | | |

[b] See corresponding footnote b in Table 1.

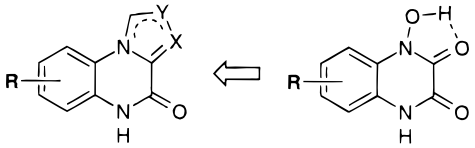


**Figure 4.** Design of heterocyclic-fused quinoxalinones.

AMPA receptor binding,[24] whereas an unsuitable heteroring, such as the imidazo[1,5-*a*] structure of **5b**, does not. We therefore deduced that (1) the heteroatom Z shown in Figure 5, which corresponds to the nitrogen atom of the fused heterocycle of **5a** and **14a** and the oxygen atom of the imidazolyl-near amide of quinoxalinediones **1a**−**c**, plays an essential role in binding to the AMPA receptor as an acceptor for the hypothetical hydrogen-bonding interaction $a_1$ and (2) the position of the heteroatom Z in the quinoxaline skeleton is a critical factor in expressing significant affinity for the receptor.

On the other hand, 7-(1*H*-imidazol-1-yl)-8-nitro-1-propyl-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (**18**), of which the fused triazole ring corresponds to the imidazolyl-far amide portion of **1a**−**c**, exhibited only about 1/70 time AMPA affinity compared to its 8-imidazolyl-7-nitro derivative **14d** ($K_i$ = 6.6 and 0.099 μM, respec-

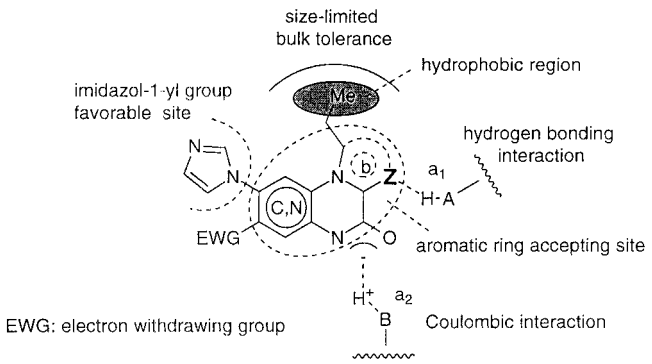



**Figure 5.** Suggested pharmacophore model of AMPA receptors for the binding of imidazolylquinoxaline derivatives.

tively) (Tables 1 and 2). This may be caused by the steric effect of the propyl substituent of **18**. However, a similar relationship was observed between the 1-substituted 7-imidazolyl-6-nitro- and 6-imidazolyl-7-nitroquinoxalinediones, i.e., **21** versus **24** ($K_i$ = 0.13 vs 4.5 $\mu$M) and **1b** versus **25** ($K_i$ = 0.021 vs 0.44 $\mu$M).[20] Moreover, 6-(1*H*-imidazol-1-yl)-5-nitro-2,3(1*H*)-indolinedione (**26**) possesses no or negligible affinity for the AMPA receptor.[20,30] Further, the ratios of the affinity between **14d** versus **18** (about 1/70) is largely similar to that of **21** versus **24** and **1b** versus **25** (about 1/30 and 1/20). On this basis, we suggest that the amide portion of the heterocyclic-fused quinoxalinones plays an essential role in the receptor binding as a proton donor site probably in a Coulombic interaction $a_2$ (Figures 5) in a similar manner with the imidazolyl-far amide of imidazolylquinoxalinediones (Figures 2 and 3).[20] This structural requirement is in contrast to that aforementioned for the imidazolyl-near side of the quinoxalinones and quinoxalinediones. On the other hand, we previously proposed that AMPA receptor binding requires different structural features for the 6- and 7-substituents on quinoxalinediones, respectively.[16,21] It is therefore speculated that the slight AMPA affinity of **18** probably results from its binding to the receptor in an upside-down mode, in which the positions of imidazolyl and nitro groups should be less favorable.[20]

From the previous results of SAR on 1-substituted quinoxalines,[20,31] we next evaluated 1-alkyl derivatives of **5a** and **9**. As shown in Table 1, compounds **9** and **14b**−**e** ($K_i$ = 0.020 and 0.048−0.099 $\mu$M, respectively) showed high affinity for the AMPA receptor with equipotent to 4-fold greater affinity than the corresponding unsubstituted **5a** and **14a** ($K_i$ = 0.057 and 0.19 $\mu$M, respectively). As a result, we found that compound **9** possesses one of the highest affinities for the AMPA receptor with a $K_i$ value of 0.020 $\mu$M among the heterocyclic-fused quinoxaline derivatives and the other existing AMPA ligands (for example, **1a**, 0.084; **1b**, 0.021; and **2**, 0.060 $\mu$M, respectively). A similar relationship was observed within the 1-alkyl quinoxalinediones, i.e., **20** and **21** versus **19** ($K_i$ = 0.19, 0.13 vs 0.33 $\mu$M). These findings agreed with our former suggestion[20] with respect to a hypothetical bulk tolerate pocket of the AMPA receptor for the 1-substituents; that is, the inner part of the pocket may be, at least in part, a hydrophobic environment (Figure 2). Because the ethyl substitution for the R group resulted in better affinity than the others (at least within the compounds in Table 1), there seems to be common favorable sizes or hydrophobicities for the 1-substituents on these quinoxalines.

In the case of the replacement of the nitro group of **5a** with trifluoromethyl, compound **5c** exhibited comparable AMPA affinity with **5a**, giving a similar relation to that between the corresponding quinoxalinediones **1a** and **22** (Table 2). Hence we speculated that electron-withdrawing groups would be appropriate for the 7-substituents on these heteroring-fused quinoxalinones for AMPA receptor binding like the corresponding position on the imidazolylquinoxalinediones.[19]

We also postulated that an expanded conjugated ring system of **1b** resulting from the pseudoring structure b (Figure 3) may contribute to AMPA receptor binding by mediating the $\pi-\pi$ or $\pi-\sigma$ interaction.[20] This hypothesis may deserve an explanation such that the 1,2-dihydroimidazo derivative **11**, in which the fused heterocycle is partially hydrogenated, possesses an AMPA affinity ($K_i$ = 0.15 $\mu$M) equipotent to that of the topologically corresponding 1-alkylquinoxalinedione derivative **21** ($K_i$ = 0.13 $\mu$M) and only 1/8 times that of the fully aromatized derivative **9** ($K_i$ = 0.020 $\mu$M) (Tables 1 and 2). On the other hand, the diminished AMPA affinity of **11** as compared to **9** may be caused by the steric effect of its 1-ethyl group and/or the existence of the enantio isomer. However, since imidazo[1,2-*a*]quinoxalinones **5a** and **9** displayed 6−7-fold greater affinities than the corresponding 1-alkylquinoxalinediones **19** and **21**, and since [1,2,4]triazolo[4,3-*a*]quinoxalinones **14a**−**c** exhibited equipotent to 3-fold greater affinities than the corresponding **19**−**21**, respectively (Table 1), it seems that (1) an expanded $\pi$-conjugated ring system, such as the pseudoring structure b of **1b** (Figure 3), and the imidazole and triazole rings of **5a**, **9**, and **14a**−**e** may contribute to, at least in part, AMPA receptor affinity and (2) the electronic topography of their fused heteroring may result in a different affinity in terms of **5a** and **9** versus **14a**,**c**.

These SAR indicated that the heterocyclic-fused imidazolylquinoxalinones **5a**,**c**, **9**, **11**, and **14a**−**e** probably bind to AMPA receptors in a similar manner to the imidazolylquinoxalinediones, the lead compounds. On the basis of these results, we propose the pharmacophore model of the AMPA receptor[18,32] for the binding of the imidazolylquinoxaline series as shown in Figure 5, which includes propositions from previous SAR.[16,20,21] In this model, other substituents possessing moderately sized $\pi$-conjugation systems and appropriate hydrophobicity, such as nitro and cyano groups, may also be conformed to the imidazol-1-yl group favorable site.[16]

Among the heterocyclic-fused quinoxalinone derivatives possessing high affinity for the AMPA receptor, **5a**,**c** and **9** were assessed functionally by examining their inhibitory activity in KA-induced toxicity for hippocampal cell primary culture, a putative predictor of antagonist activity to the AMPA receptor.[33] As shown in Table 3, **5a**,**c** and **9** exhibited potent inhibitory activity with $IC_{50}$ values of 0.30, 0.32, and 0.30 $\mu$M, respectively. Their activities are comparable with those of known AMPA antagonists **1a**,**b** and **2** ($IC_{50}$ = 0.81, 0.31, and 0.38 $\mu$M, respectively).[34,35]

Further, 8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-imidazo-[1,2-*a*]quinoxalinone (**5a**) was characterized by its affinity for the NMDA binding site and the strychnine-insensitive glycine site on the NMDA receptor[36,37] and showed no or negligible affinity for both sites (Table 3).

**Table 3.** *In Vitro* Characterization on Selected Compounds

| | receptor affinity $K_i$ ($\mu$M)[b] | | | |
|---|---|---|---|---|
| | | NMDA receptor | | |
| compd | AMPA receptor | NMDA binding site | glycine binding site | anti-KA toxicity $IC_{50}$ ($\mu$M)[b] |
| **5a** | 0.057 | >300 | >300 | 0.30 (0.016−0.59) |
| **5c** | 0.066 | NT | NT | 0.32 (0.064-0.58) |
| **9** | 0.020 | NT | NT | 0.30 (0.29−0.31) |
| **1a** | 0.084 | >100 | 37 (34-40) | 0.81 (0.23−1.4) |
| **1b** | 0.021 | 12 (7.8−19) | 4.2 (3.6−4.9) | 0.31 (0.18−0.44) |
| **2** | 0.060 | >100 | >100 | 0.38 (0.17−0.59) |

[b] See corresponding footnote b in Table 1.

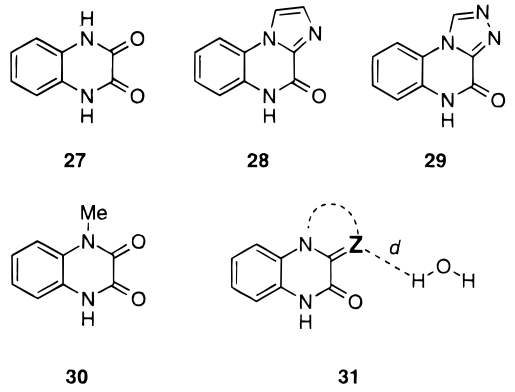



**Figure 6.** Structures of alternate compounds **27** (for **1a**), **28** (for **5a**), **29** (for **14a**), and **30** (for **19**) and model complex **31**.

Namely, we found that not only is **5a** one of the most potent AMPA antagonists among known compounds but it also possesses excellent AMPA selectivity against the NMDA and glycine sites (over 5000-fold, respectively), which is comparable to those of NBQX. Since another series of 4(5*H*)-imidazo[1,2-*a*]quinoxalinones having a non-imidazolyl substituent at the 8-position were reported as nonselective glycine/AMPA antagonists,[23] the AMPA selectivity of **5a** should not simply be caused by its three-ring system skeleton, like benzo[*f*]quinoxaline **2**. Although it is well-known that most of the known quinoxalines generally lack specificity in distinguishing the AMPA receptor from the glycine site,[23,31] imidazolylquinoxalinediones **1a**,**b** also possess AMPA selectivity.[16,20,21] We therefore deduced that a 1*H*-imidazol-1-yl group at that position should be an adequate substituent for these quinoxalines in distinguishing the AMPA receptor from the glycine site.

**Computational Study.** We have continuous interest in the discrepancy of AMPA affinity among 1-alkyl- and 1-unsubstituted quinoxalinediones, imidazo[1,2-*a*]-quinoxalinones, and [1,2,4]triazolo[4,3-*a*]quinoxalinones, such as **1a**, **19**, **5a**, and **14a**. As a hypothesis, we considered that the discrepancy may reflect the effect of respective structural features on the hydrogen-bonding interaction $a_1$ (Figure 5). To examine this hypothesis, we carried out a computational study on a model of the interaction utilizing MOPAC.[38] A water molecule was used as a mimic for the putative hydrogen bond donor site for the interaction $a_1$ in the receptor pocket (Figure 5), and quinoxaline−water complex **31** (Figure 6) was designed as a model for the interaction. For this study, in order to facilitate the computations, quinoxalines **27**−**30** were employed as alternates to **1a**, **5a**, **14a**, and **19**, respectively (Figure 6). In the present study, 1-hydroxyquinoxalinedione **1b** was excluded, because it is difficult to estimate the effect of its 1-hydroxy group which may contribute to the binding as a supplementary interaction site and may form an intramolecular hydrogen bond.[20]

First, each optimum structure of complex **31** for **27**−**30** was calculated. The results are shown in Figure 7. Values described in yellow letters show their hydrogen bond distance H−Z (*d*), the green letters show the degree for bond angle H−Z−C, and white letters show the degree for bond angle Z−C−C. Results are $d = 1.83$ Å, angle H−Z−C = 129°, angle Z-C-C = 125° for **27**, 1.84 Å, 129°, 130° for **28**, 1.89 Å, 124°, 131° for **29**, and 1.83 Å, 130°, 123° for **30**, respectively. The differences in bond distance *d* among them seems to not be significant (within 0.06 Å). In order to examine the effect of relative position between the quinoxaline and $H_2O$ molecule in each optimum complexes, a superimposition study was done on the complexes for **27** (red), **28** (blue), **29** (green), and **30** (cyan) based on the position of their $H_2O$ molecule (Figure 8). As see in Figure 8, the relative positions for **27**, **29**, and **30** are very similar, and a small difference was observed for **28**. Although this may be one reason for the different AMPA affinities of the respective parent compounds **1a**, **5a**, **14a**, and **19**, their relative position seems to be unrelated to the rank order of the affinity of the parent compounds.

Next, we calculated their stabilization energy ($\Delta E$) for the hydrogen bonding. The graph shown in Figure 9 describes the effect of varying distance *d* (optimum distance, 1.70, 1.80, 2.0, and 7.0 Å) along with the hydrogen bond axis (as illustrated in **31**, Figure 6) on $\Delta E$ for each complex. Their potential energy ($E_p$) was calculated as the final heat of formation. Since the hydrogen-bonding effect, when $d = 7.0$ Å, was considered to be negligibly small, each $\Delta E$ was determined as the discrepancy from $E_{p(d=7.0Å)}$. Values in the graph indicate $\Delta E_{max}$ ($E_{p(d=optimum)} - E_{p(d=7.0Å)}$) for **27**−**30**, and they are −2.78, −3.02, −1.37, and −1.32 kcal/mol, respectively. Their rank order correlates to the $K_i$ values of parent compounds **1a**, **5a**, **14a**, and **19**. Moreover, the maximum difference in $\Delta E_{max}$ among **27**−**30** is observed between **30** and **28**, and the discrepancy ($\Delta E_{max(compd\ 28)} - \Delta E_{max(compd\ 30)}$) is 1.70 kcal/mol. This nearly agrees with the discrepancy of free energy, 1.12 kcal, between the corresponding parent compounds **19** and **5a** calculated from their $K_i$ values for AMPA affinity eq a:

$$\begin{aligned}\Delta G_{\text{compd 19}} - \Delta G_{\text{compd 5a}} &= RT \ln(K_{i(\text{compd 19})}/K_{i(\text{compd 5a})}) \\ &= 1.99 \times 10^{-3}\ \text{kcal}\cdot\text{K}^{-1}\cdot\text{mol}^{-1} \times \\ &\quad 298\ \text{K} \times 2.30 \times -[(\log 0.38 \times \\ &\quad 10^{-6}\ \text{M}) - (\log 0.057 \times 10^{-6}\ \text{M})] \\ &= 1.12\ \text{kcal} \qquad \text{(eq a)}\end{aligned}$$

Although the range of the values is limited, the data support the hypothesis that the different AMPA affinities of **1a**, **5a**, **14a**, and **19** may depend on, at least in part, their stabilization energy $\Delta E_{max}$ for the hydrogen-bonding interaction $a_1$ resulting from the structural feature of the fused heterocycles and imidazolyl-near amides.

## Conclusion

This study shows that a novel series of heterocyclic-fused imidazolylquinoxalinones **5a**,**c**, **9**, **11**, and **14a**−**e**

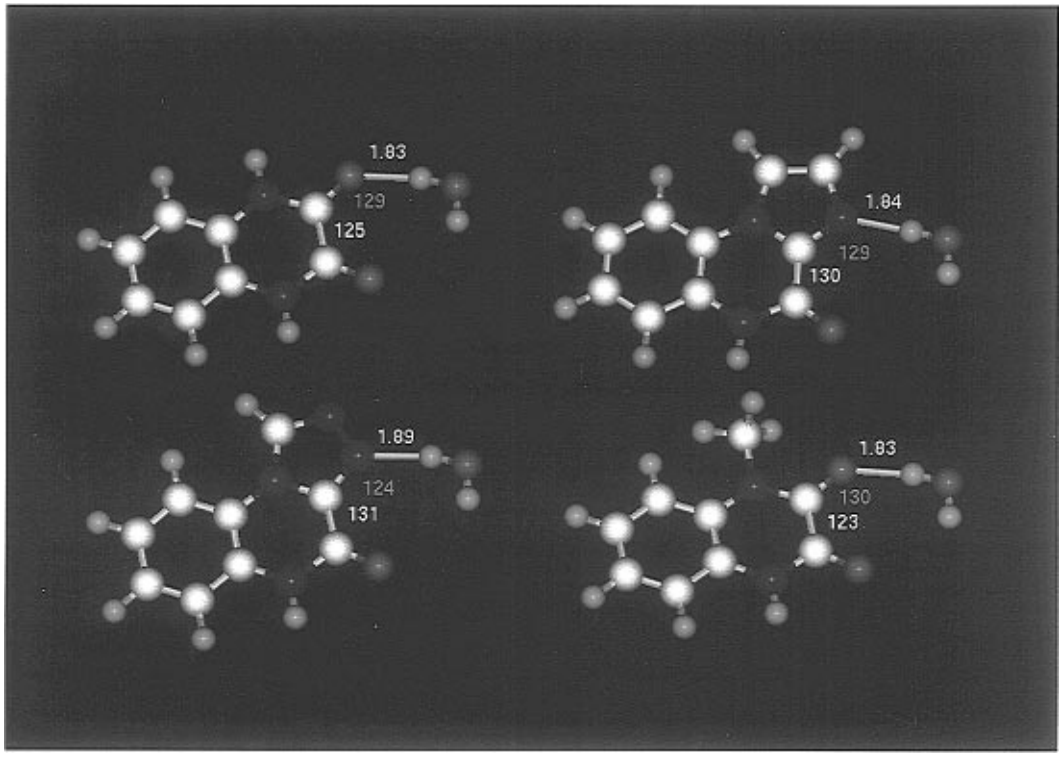



**Figure 7.** Model of hydrogen bonding of **27**−**30** with a $H_2O$ molecule. Molecular modeling and optimization were done with MOPAC using the PM3 Hamiltonian.

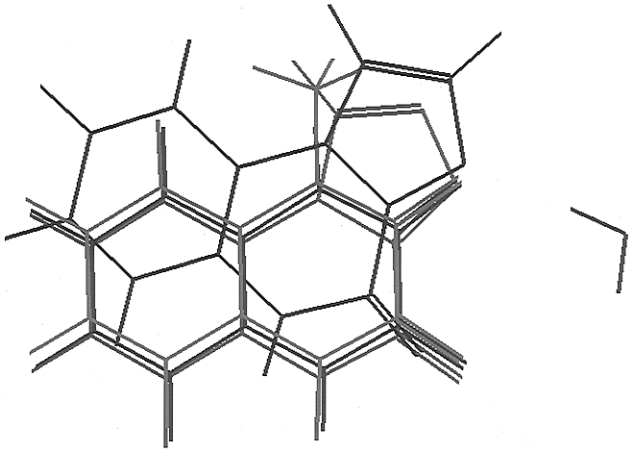


**Figure 8.** Superimposition of the model complex for quinoxalines **27** (red), **28** (blue), **29** (green), and **30** (cyan) with a $H_2O$ molecule.

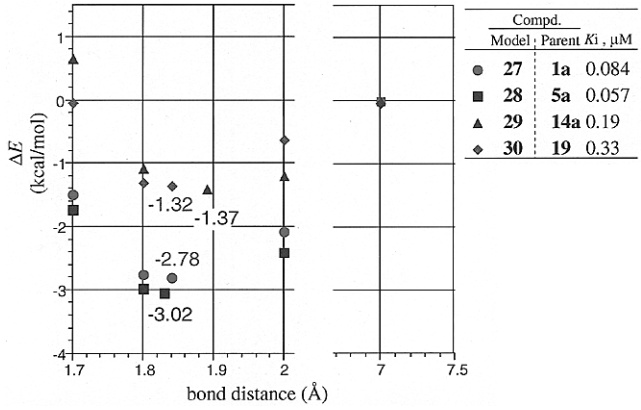



**Figure 9.** Effect of varying hydrogen bond distance on $\Delta E$ from $E_{p(d=7.0Å)}$ for **27**−**30**. Values in the graph are $\Delta E_{max}$ for each hydrogen bonding.

possess high affinity for AMPA receptors similar to known potential AMPA antagonists **1a**−**c** and **2**. On the basis of their SAR, we suggest that these heterocyclic-fused imidazolylquinoxalinones probably bind to the receptors in a similar manner as imidazolylquinoxalinediones **1a**−**c**. We also deduced that their heteroatom in the imidazolyl-near side (as Z shown in Figure 5) plays an essential role in AMPA receptor binding as a hydrogen bond acceptor, whereas their imidazolyl-far amide portion plays a critical role as a proton donor. Moreover, we propose a pharmacophore model of AMPA receptors for the binding of the imidazolylquinoxaline derivatives. Further, a computational study indicated that the different AMPA affinities of **1a**, **5a**, **14a**, and **19** may depend on, at least in part, their stabilization energy for the hypothetical hydrogen-bonding interaction. The heterocyclic-fused quinoxalinones **5a**,**c** and **9** showed potent inhibitory activity in KA-induced toxicity for hippocampal cell culture with $IC_{50}$ values of 0.30, 0.32, and 0.30 $\mu$M, respectively (**1a**, 0.81 $\mu$M; **2**, 0.38 $\mu$M), and **5a** possesses over 5000-fold AMPA selectivity against both the NMDA receptor and the glycine site on the NMDA receptor. We believe that this study could contribute to an understanding of the pharmacology of EAA receptors and the ligand−AMPA receptor interactions and to the design of novel AMPA receptor ligands.

## 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 $\delta$ 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, F, Cl, N) 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 **1a**−**c** and **19**−**26** has been reported previously.[16,20]

**2,4-Di(1*H*-imidazol-1-yl)-5-nitroaniline (4a).** The intermediate 2,4-difluoro-5-nitroaniline (**3a**) was prepared from 2,4-difluoroaniline by treatment with $^{f}HNO_3-H_2SO_4$ in the presence of a catalytic amount of urea in excellent yield.[25] Alternatively, **3a** was synthesized from 1,5-difluoro-2,4-dinitrobenzene performed by the application of selective hydrogenation using $PdCl_2$ and Fe in AcOH−EtOH (82%):[39] $^1$H NMR $\delta$ 7.52 (s, 1H), 7.43 (t, 1H), 5.66 (br, 2H); MS (EI) *m*/*z* 174 (M).

A solution of **3a** (0.50 g, 2.14 mmol) and imidazole (1.45 g, 21.4 mmol) in DMF (20 mL) was heated at 140 °C overnight. The reaction mixture was cooled to room temperature and then concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$−methanol = 8:1) and washed with boiling $H_2O$ to give the title compound as a brown solid (0.50 g, 64%): $^1$H NMR $\delta$ 7.92 (s, 1H), 7.78 (s, 1H), 7.59 (s, 1H), 7.47 (d, 1H), 7.44 (s, 1H), 7.31 (t, 1H), 7.16 (d, 1H), 7.02 (s, 1H), 6.00 (s, 2H); MS (EI) *m*/*z* 270 (M).

**2,4-Bis(2-methyl-1*H*-imidazol-1-yl)-5-nitroaniline (4b):** prepared by the same method described for **4a** using 2-methylimidazole; 30% from **3a**; $^1$H NMR $\delta$ 7.54 (s, 1H), 7.39 (s, 1H), 7.17 (d, 1H), 7.09 (d, 1H), 6.97 (d, 1H), 6.83 (d, 1H), 5.96 (brs, 1H), 2.18 (s, 3H), 2.12 (s, 3H); MS (EI) *m*/*z* 298 (M).

**2,4-Di(1*H*-imidazol-1-yl)-5-(trifluoromethyl)aniline (4c).** The intermediate, 1,5-di(1*H*-imidazol-1-yl)-2-nitro-5-(trifluoromethyl)benzene, was prepared from 1,5-dichloro-2-nitro-4-(trifluoromethyl)benzene (**3b**) using the same method described for **4a** from the intermediate (73%): $^1$H NMR $\delta$ 8.73 (s, 1H), 8.16 (s, 1H), 8.06 (s, 1H), 7.98 (s, 1H), 7.53 (s, 2H), 7.16 (s, 2H); MS (FAB) *m*/*z* 324 (M + 1).

The 1,5-di(1*H*-imidazol-1-yl)-2-nitro-5-(trifluoromethyl)benzene (2.00 g, 6.19 mmol) thus obtained was hydrogenated in methanol (100 mL) under 3 atm at 35 °C overnight using 10% palladium on carbon. The reaction mixture was filtered, evaporated, and recrystallized from ethyl acetate to give **4c** (1.40 g, 77%): $^1$H NMR $\delta$ 7.89 (s, 1H), 7.71 (s, 1H), 7.43 (s, 1H), 7.37 (s, 1H), 7.32 (s, 2H), 7.14 (s, 1H), 7.02 (s, 1H), 5.87 (s, 2H); MS (EI) *m*/*z* 293 (M).

The preparation of **5a**−**c** was performed by the application of a procedure described by Davey et al.[26]

**8-(1*H*-Imidazol-1-yl)-7-nitro-4(5*H*)-imidazo[1,2-*a*]quinoxalinone (5a).** A solution of **4a** (2.33 g, 8.62 mmol) and 1,1′-carbonyldiimidazole (4.19 g, 25.8 mmol) in 1,2-dichlorobenzene (25 mL) was heated at reflux for 4 h. After cooling, the resultant precipitate was collected and washed with boiled methanol to afford **5a** (1.23 g, 48%): mp >300 °C; $^1$H NMR $\delta$ 12.28 (br, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 8.13 (s, 1H), 7.97 (s, 1H), 7.67 (s, 1H), 7.48 (s, 1H), 7.14 (s, 1H); MS (FAB) *m*/*z* 297 (M + 1). Anal. ($C_{13}H_8N_6O_3$) C, H, N.

The following examples **5b**,**c** were prepared by the method described above.

**1-Methyl-8-(2-methyl-1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-imidazo[1,5-*a*]quinoxalinone Dihydrochloride (5b·2HCl).** The crude **5b** was treated with 1 N HCl, evaporated, and then washed with methanol−EtOAc to give **5b**·2HCl: 32% from **4b**; mp >300 °C; $^1$H NMR $\delta$ 12.33 (brs, 1H), 8.47 (s, 2H), 8.06 (s, 1H), 7.81 (s, 2H), 2.99 (s, 3H), 2.53 (s, 3H); MS (FAB) *m*/*z* 325 (M + 1). Anal. ($C_{15}H_{12}N_6O_3\cdot 2.1HCl\cdot 2H_2O$) C, H, N, Cl.

**8-(1*H*-Imidazol-1-yl)-7-(trifluoromethyl)-4(5*H*)-imidazo-[1,2-*a*]quinoxalinone (5c).** The crude **5c** was washed with methanol−water and then boiled DMF−water to afford **5c**: mp >300 °C; $^1$H NMR $\delta$ 12.19 (br, 1H), 8.66 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.83 (s, 1H), 7.65 (d, 1H), 7.45 (s, 1H), 7.13 (s, 1H); MS (FAB) *m*/*z* 320 (M + 1). Anal. ($C_{14}H_8N_5OF_3\cdot 0.3DMF$) C, H, N, F.

For the preparation of **9** and **11**, the procedure described by Lumma et al.[27] was applied.

**2,3-Dichloro-6-fluoro-7-nitroquinoxaline (6).** To a solution of 6-fluoro-7-nitro-2,3(1*H*,4*H*)-quinoxalinedione (25.0 g, 111 mmol) in thionyl chloride (250 mL) was added dropwise DMF (1 mL). The reaction mixture was refluxed for 4 h and then concentrated under vacuum. The resulting residue was coevaporated with chloroform several times, dissolved in chloroform (700 mL), and poured onto ice−water. The organic layer was collected, washed with saturated aqueous NaCl, dried over $Na_2SO_4$, and then evaporated to provide **6** as a brown solid (28.3 g, 97%), which was used without further purification in the next step: $^1$H NMR $\delta$ 8.94 (d, *J* = 7.29 Hz, 1H), 8.37 (d, *J* = 11.3 Hz, 1H); MS (EI) *m*/*z* 261 (M), 263 (M + 2).

**3-Chloro-7-fluoro-2-[(2-hydroxy-1-butyl)amino]-6-nitroquinoxaline (7).** In a water bath, to a solution of **6** (5.00 g, 19.1 mmol) in chloroform (50 mL) was added dropwise a solution of 1-amino-2-butanol (3.57 g, 40.1 mmol) in chloroform (2 mL) with the temperature maintained below 35 °C. The reaction mixture was stirred at room temperature for 4 h and then cooled to 0 °C. The resulting precipitate was collected and washed with *n*-hexane−EtOAc (1:1) to give **7** (4.38 g, 73%): $^1$H NMR $\delta$ 8.50 (d, *J* = 8.10 Hz, 1H), 8.02 (brt, 1H), 7.55 (d, *J* = 13.1 Hz, 1H), 4.84 (d, 1H), 3.64−3.87 (m, 1H), 3.37−3.56 (m, 2H), 1.34−1.54 (m, 2H), 0.93 (t, 3H); MS (EI) *m*/*z* 314 (M).

**1-Ethyl-8-fluoro-7-nitro-4(5*H*)-imidazo[1,2-*a*]quinoxalinone (8).** A solution of oxalyl chloride (6.15 g, 63.5 mmol) in dichloromethane (40 mL) was cooled to −60 °C. The mixture was added dropwise to a solution of DMSO (9.93 g, 127 mmol) in dichloromethane (10 mL) with the temperature maintained below −50 °C. After being stirred at the same temperature for 2 min, to the mixture was added dropwise a solution of **7** (4.00 g, 12.7 mmol) in DMSO (5 mL) and dichloromethane (5 mL); the mixture was stirred for 15 min and then added dropwise into triethylamine (10.9 g, 108 mmol) with the temperature maintained below −50 °C. After 5 min, the reaction mixture was allowed to warm to room temperature and then poured into water (70 mL). The solution was extracted with chloroform, and the organic layers were collected, washed with saturated aqueous NaCl, dried over $Na_2SO_4$, and evaporated. The residual brown solid was washed with water and then ethyl acetate to give 2.21 g (56%) of 4-chloro-7-fluoro-2-[(2-oxo-1-butyl)amino]-6-nitroquinoxaline as a yellowish brown solid: $^1$H NMR $\delta$ 8.55 (d, *J* = 7.92 Hz, 1H), 8.43 (brd, 1H), 7.56 (d, *J* = 12.9 Hz, 1H), 4.33 (d, 2H), 2.59 (q, 2H), 1.00 (t, 3H); MS (EI) *m*/*z* 312 (M).

A solution of the 4-chloro-7-fluoro-2-[(2-oxo-1-butyl)amino]-6-nitroquinoxaline (2.18 g, 6.97 mmol) in trifluoroacetic anhydride (20 mL), trifluoroacetic acid (0.50 mL), and chloroform (40 mL) was refluxed overnight. After cooling, the reaction mixture was evaporated, and the resulting residue was washed with *n*-hexane and then boiled in methanol to give 1.53 g of a yellow solid, 4-chloro-1-ethyl-8-fluoro-7-nitroimidazo[1,2-*a*]quinoxaline including a slight amount of **8**. Spectral data for the 4-chloroimidazo[1,2-*a*]quinoxaline: $^1$H NMR $\delta$ 8.73 (d, *J* = 7.74 Hz, 1H), 8.34 (d, *J* = 12.6 Hz, 1H), 7.75 (s, 1H), 3.30 (q, 2H), 1.44 (t, 3H); MS (FAB) *m*/*z* 295 (M + 1).

This obtained mixture was treated with a solution of 4 N HCl (12 mL) and methanol (12 mL) under reflux for 2 h. After cooling, the resulting precipitate was collected and washed with methanol and water to provide the title compound **8** (1.21 g, 63% from the 4-chloro-7-fluoro-2-[(2-oxo-1-butyl)amino]-6-nitroquinoxaline) as a slightly yellow solid: mp >300 °C; $^1$H NMR $\delta$ 12.09 (br, 1H), 8.14 (d, *J* = 7.33 Hz, 1H), 8.10 (d, *J* = 12.7 Hz, 1H), 7.43 (s, 1H), 3.25 (q, 2H), 1.39 (t, 3H); MS (FAB) *m*/*z* 277 (M + 1). Anal. ($C_{12}H_9N_4O_3F$) C, H, N, F.

**1-Ethyl-8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-imidazo[1,2-*a*]quinoxalinone (9).** Under an argon atmosphere, sodium hydride (60% suspension in mineral oil (0.46 g, 11.5 mmol) from which the mineral oil was removed by extraction with *n*-hexane) was suspended in DMF (10 mL). Imidazole (0.78 g, 11.5 mmol) was added to the solution and stirred at room temperature for 15 min, and then **8** (0.90 g, 3.26 mmol) was added. The reaction mixture was vigorously stirred at 50 °C for 1.5 h, diluted with water (100 mL), and filtered. The filtrate was neutralized with 1 N HCl. The resulting precipi-

tate was collected and washed with methanol to give **9** (0.67 g, 63%) as a slightly yellow solid: mp >300 °C; $^1$H NMR $\delta$ 12.28 (br, 1H), 8.16 (s, 1H), 8.09 (s, 1H), 8.00 (s, 1H), 7.51 (s, 1H), 7.45 (s, 1H), 7.12 (s, 1H), 3.26 (q, 2H), 1.38 (t, 3H); MS (FAB) *m*/*z* 325 (M + 1). Anal. ($C_{15}H_{12}N_6O_3 \cdot 1.25H_2O$) C, H, N.

**1,2-Dihydro-1-ethyl-8-fluoro-7-nitro-4(5*H*)-imidazo[1,2-*a*]quinoxalinone (10).** A solution of **7** in thionyl chloride (5 mL) and chloroform (5 mL) was heated under reflux for 2 h. After cooling, the reaction mixture was concentrated in vacuo, and the residue was coevaporated several times with chloroform and then ethyl acetate. The crude product thus obtained was washed with ethyl acetate to afford 1.08 g (57%) of 4-chloro-1,2-dihydro-1-ethyl-8-fluoro-7-nitroimidazo[1,2-*a*]quinoxaline as the intermediate: $^1$H NMR $\delta$ 8.54 (d, $J$ = 7.74 Hz, 1H), 7.85 (d, $J$ = 12.3 Hz, 1H), 5.1 (m, 1H), 3.75−4.40 (m, 2H), 1.83 (qu, 2H), 0.92 (t, 3H); MS (FAB) *m*/*z* 297 (M + 1).

The 4-chloro-1,2-dihydro-1-ethyl-8-fluoro-7-nitroimidazo[1,2-*a*]quinoxaline (1.08 g, 3.24 mmol) was treated with a mixture of 4 N HCl (12 mL) and methanol (12 mL) under reflux for 40 min. After cooling, the resulting precipitate was collected and washed with methanol and water to provide the title compound **10** (0.35 g, 34%): mp >300 °C; $^1$H NMR $\delta$ 13.16 (br, 1H), 8.24 (d, $J$ = 7.11 Hz, 1H), 7.80 (d, $J$ = 12.4 Hz, 1H), 5.08 (t, 1H), 4.22 (dd, 1H), 4.01 (dd, 1H), 1.76−1.88 (m, 2H), 0.92 (t, 3H); NOE between H-9 and 1-ethyl protons observed; MS (FAB) *m*/*z* 278 (M + 1). Anal. ($C_{12}H_{11}N_4O_3F \cdot 1.25H_2O$) C, N, F; H: calcd, 4.52; found, 3.89.

**1,2-Dihydro-1-ethyl-8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-imidazo[1,2-*a*]quinoxalinone (11):** prepared by the same method described for **9**; 58% from **10**; mp >300 °C; $^1$H NMR $\delta$ 11.93 (brs, 1H), 7.86 (s, 1H), 7.84 (s, 1H), 7.38 (s, 1H), 7.22 (s, 1H), 7.08 (s, 1H), 4.69−4.73 (m, 1H), 4.09 (dd, 1H), 3.85 (dd, 1H), 1.61−1.75 (m, 2H), 0.81 (qu, 3H); MS (FAB) *m*/*z* 327 (M + 1). Anal. ($C_{15}H_{14}N_6O_3 \cdot 1.5H_2O$) C, H, N.

**General Method for Preparation of 8-Imidazolyl-7-nitro[1,2,4]triazolo[4,3-*a*]quinoxalinones 14a−e.** The compounds were prepared by nucleophilic substitution of **6** with hydrazine followed by cyclic condensation with the appropriate ortho ester,[28] hydrolysis, and then nucleophilic substitution with imidazole.

**(3-Chloro-7-fluoro-6-nitroquinoxalin-2-yl)hydrazine (12).** In an ice−salt bath, to a solution of **6** (0.40 g, 1.52 mmol) in methanol (4 mL) was slowly added dropwise a solution of hydrazine monohydrate (0.098 g, 1.96 mmol) in methanol (1 mL). With stirring, the reaction mixture was allowed to gradually warm to 0 °C. After 30 min, the resulting precipitate was collected and washed with methanol to afford **12** (0.36 g, 92%): $^1$H NMR $\delta$ 8.30 (d, $J$ = 8.19 Hz, 1H), 7.34 (d, $J$ = 13.1 Hz, 1H), 6.80 (br, 3H); MS (EI) *m*/*z* 257 (M).

**8-Fluoro-7-nitro-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (13a).** A solution of **12** (0.70 g, 2.72 mmol) in triethyl orthoformate (3.56 g, 24.0 mmol) was stirred at 130 °C for 15 min. After cooling, the precipitate was collected and washed with methanol to provide 0.61 g (84%) of 4-chloro-8-fluoro-7-nitro[1,2,4]triazolo[4,3-*a*]quinoxaline as an intermediate: $^1$H NMR $\delta$ 10.20 (s, 1H), 8.84 (d, $J$ = 7.30 Hz, 1H), 8.81 (d, $J$ = 11.5 Hz, 1H); MS (FAB) *m*/*z* 268 (M + 1).

The same procedure as described for **8** from 4-chloro-1-ethyl-8-fluoro-7-nitroimidazo[1,2-*a*]quinoxaline was used for the preparation of **13a** from the intermediate: mp >300 °C; $^1$H NMR $\delta$ 12.29 (s, 1H), 9.88 (s, 1H), 8.56 (d, $J$ = 11.6 Hz, 1H), 8.10 (d, $J$ = 6.70 Hz, 1H); MS (FAB) *m*/*z* 250 (M + 1). Anal. ($C_9H_6N_5O_3F$) C, H, N.

**8-Fluoro-1-methyl-7-nitro-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (13b).** 4-Chloro-8-fluoro-1-methyl-7-nitro-[1,2,4]triazolo[4,3-*a*]quinoxaline: 73% from **12**; $^1$H NMR $\delta$ 8.79 (d, $J$ = 7.74 Hz, 1H), 8.44 (d, $J$ = 11.9 Hz, 1H), 3.13 (s, 1H); MS (FAB) *m*/*z* 282 (M + 1).

The title compound: 85% from the intermediate; mp >300 °C; $^1$H NMR $\delta$ 12.24 (brs, 1H), 8.19 (d, $J$ = 7.29 Hz, 1H), 8.08 (s, $J$ = 6.93 Hz, 1H), 3.01 (s, 3H); MS (FAB) *m*/*z* 264 (M + 1). Anal. ($C_{10}H_6N_5O_3F$) C, H, N, F.

**1-Ethyl-8-fluoro-7-nitro-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (13c).** 4-Chloro-1-ethyl-8-fluoro-7-nitro[1,2,4]-triazolo[4,3-*a*]quinoxaline: 82% from **12**; $^1$H NMR $\delta$ 8.79 (d, $J$ = 7.74 Hz, 1H), 8.39 (d, $J$ = 12.2 Hz, 1H), 3.51 (q, 2H), 1.50 (t, 3H); MS (FAB) *m*/*z* 296 (M + 1).

The title compound: 82% from the intermediate; mp >300 °C; $^1$H NMR $\delta$ 12.25 (s, 1H), 8.13 (d, $J$ = 9.54 Hz, 1H), 8.11 (d, $J$ = 9.90 Hz, 1H), 3.40 (q, 2H), 1.46 (t, 3H); MS (FAB) *m*/*z* 278 (M + 1). Anal. ($C_{11}H_8N_5O_3F$) H, N; C: calcd, 47.66; found, 47.13. F: calcd, 6.85; found, 7.30.

**8-Fluoro-7-nitro-1-propyl-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (13d).** 4-Chloro-8-fluoro-7-nitro-1-propyl-[1,2,4]triazolo[4,3-*a*]quinoxaline: 91% from **12**; $^1$H NMR $\delta$ 8.78 (d, $J$ = 7.74 Hz, 1H), 8.39 (d, $J$ = 12.0 Hz, 1H), 3.49 (t, 2H), 1.99 (se, 2H), 1.11 (t, 3H); MS (EI) *m*/*z* 309 (M).

The title compound: 79% from the intermediate; $^1$H NMR $\delta$ 12.22 (brs, 1H), 8.09 (d, $J$ = 7.30 Hz, 1H), 8.09 (d, $J$ = 11.6 Hz, 1H), 3.34 (t, 2H), 1.91 (se, 2H), 1.06 (t, 3H); MS (EI) *m*/*z* 291 (M). Anal. ($C_{12}H_{10}N_5O_3F$) C, H, N.

**1-Butyl-8-fluoro-7-nitro-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (13e).** 1-Butyl-4-chloro-8-fluoro-7-nitro[1,2,4]-triazolo[4,3-*a*]quinoxaline: 73% from **12**; $^1$H NMR $\delta$ 8.80 (d, 1H), 8.40 (d, 1H), 3.35 (t, 2H), 1.93 (qu, 2H), 1.54 (se, 2H), 0.99 (t, 3H); MS (FAB) *m*/*z* 324 (M + 1).

The title compound: 77% from the intermediate; mp 250−253 °C dec; $^1$H NMR $\delta$ 12.24 (brs, 1H), 8.17 (d, $J$ = 1.35 Hz, 1H), 8.06 (d, $J$ = 3.33 Hz, 1H), 3.34 (t, 2H), 1.90 (m, 2H), 1.50 (m, 2H), 0.98 (t, 3H); MS (FAB) *m*/*z* 306 (M + 1).

**8-(1*H*-Imidazol-1-yl)-7-nitro-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (14a):** prepared by the method described for **9**; 15% from **13a**; mp >300 °C; $^1$H NMR $\delta$ 12.40 (s, 1H), 9.90 (s, 1H), 8.62 (s, 1H), 8.11 (s, 1H), 7.97 (s, 1H), 7.48 (t, 1H), 7.15 (t, 1H); MS (FAB) *m*/*z* 298 (M + 1). Anal. ($C_{12}H_7N_7O_3 \cdot H_2O$) C, H, N.

**8-(1*H*-Imidazol-1-yl)-1-methyl-7-nitro-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (14b):** 88% from **13b**; mp >300 °C; $^1$H NMR $\delta$ about 12.00 (br, 1H), 8.13 (s, 1H), 8.11 (s, 1H), 8.02 (t, 1H), 7.52 (t, 1H), 7.13 (t, 1H), 3.04 (s, 3H); MS (FAB) *m*/*z* 312 (M + 1). Anal. ($C_{13}H_9N_7O_3 \cdot 1.5H_2O$) C, H, N.

**1-Ethyl-8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-[1,2,4]triazolo-[4,3-*a*]quinoxalinone (14c):** 81% from **13c**; mp >300 °C; $^1$H NMR $\delta$ 12.41 (br, 1H), 8.13 (s, 1H), 8.07 (s, 1H), 8.00 (t, 1H), 7.50 (t, 1H), 7.13 (t, 1H), 3.43 (q, 2H), 1.46 (t, 3H); MS (FAB) *m*/*z* 326 (M + 1). Anal. ($C_{14}H_{11}N_7O_3 \cdot 1.5H_2O$) C, H, N.

**8-(1*H*-Imidazol-1-yl)-7-nitro-1-propyl-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (14d):** 91% from **13d**; mp 294−295 °C dec; $^1$H NMR $\delta$ 12.43 (s, 1H), 8.13 (s, 1H), 8.05 (s, 1H), 8.01 (s, 1H), 7.51 (s, 1H), 7.14 (s, 1H), 2.50 (t, 2H), 1.93 (se, 2H), 1.05 (t, 3H); MS (FAB) *m*/*z* 340 (M + 1). Anal. ($C_{15}H_{13}N_7O_3 \cdot 0.75H_2O$) C, H, N.

**1-Butyl-8-(1*H*-imidazol-1-yl)-7-nitro-4(5*H*)-[1,2,4]triazolo-[4,3-*a*]quinoxalinone (14e):** 87% from **13e**; mp 178−180 °C dec; $^1$H NMR $\delta$ 12.34 (br, 1H), 8.13 (s, 1H), 8.04 (s, 1H), 8.00 (s, 1H), 7.51 (t, 1H), 7.14 (s, 1H), 3.41 (t, 2H), 1.85 (m, 2H), 1.45 (m, 2H), 0.94 (t, 3H); MS (FAB) *m*/*z* 354 (M + 1). Anal. ($C_{16}H_{15}N_7O_3 \cdot 0.5H_2O$) C, H, N.

**7-Fluoro-4-methoxy-1-propyl[1,2,4]triazolo[4,3-*a*]quinoxaline (15):** prepared from (6-fluoro-3-methoxyquinoxalin-2-yl)hydrazine[28] using the same method described for the intermediate of **13d**; 74% from starting material; $^1$H NMR $\delta$ 8.20 (dd, $J$ = 5.17, 9.35 Hz, 1H), 7.33−7.77 (m, 2H), 4.17 (t, 2H), 1.96 (se, 2H), 1.17 (t, 3H); MS (EI) *m*/*z* 260 (M).

**7-Fluoro-1-propyl-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (16):** prepared by the method described for **13d** from its intermediate; 82% from **15**; $^1$H NMR $\delta$ 12.08 (brs, 1H), 8.03 (dd, $J$ = 5.06, 10.1 Hz, 1H), 7.03−7.23 (m, 2H), 3.30 (t, 2H), 1.92 (se, 2H), 1.08 (t, 3H); MS (EI) *m*/*z* 246 (M).

**7-Fluoro-8-nitro-1-propyl-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (17).** To an ice-cold solution of **16** (0.51 g, 2.07 mmol) in concentrated $H_2SO_4$ (5 mL) was added portionwise $KNO_3$ (0.27 g, 2.67 mmol) with the temperature being maintained below 10 °C. After being stirred at ambient temperature for 2 h, the reaction mixture was poured onto ice−water. The resulting precipitate was collected and washed with water to give **17** (0.53 g, 88%): $^1$H NMR $\delta$ 12.56 (brs, 1H), 8.59 (d, $J$ = 6.70 Hz, 1H), 7.35 (d, $J$ = 12.2 Hz, 1H), 3.36

(t, 2H), 1.95 (se, 2H), 1.15 (t, 3H); MS (EI) *m*/*z* 291 (M). Anal. ($C_{12}H_{10}N_5O_3F \cdot H_2O$) C, H, N, F.

**7-(1*H*-Imidazol-1-yl)-8-nitro-1-propyl-4(5*H*)-[1,2,4]triazolo[4,3-*a*]quinoxalinone (18):** prepared by the same method described for **9**; 90% from **17**; mp 185−189 °C dec; $^1$H NMR $\delta$ 12.11 (brs, 1H), 8.66 (s, 1H), 8.00 (s, 1H), 7.51 (s, 1H), 7.43 (s, 1H), 7.14 (s, 1H), 3.40 (t, 2H), 1.96 (se, 2H), 1.12 (t, 3H); MS (FAB) *m*/*z* 340 (M + 1). Anal. ($C_{15}H_{13}N_7O_3 \cdot H_2O$) C, H, N.

**Molecular Modeling.** The structures and potential energies of the quinoxaline−$H_2O$ complexes were calculated using the PM3 method with the MMOK parameter as implemented in the MOPAC[38] version 5.0 program. For these computations including visualization, the molecular modeling package SYBYL on an Indigo2 R4400 workstation (SiliconGraphics) was used.

**Biology. 1. Radiobinding Assay.** Inhibition of the specific binding of [$^3$H]AMPA, NMDA-sensitive [$^3$H]Glu, 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.[29] [$^3$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]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.

**2. Anti-KA-Induced Neurotoxicity in Rat Primary Hippocampal Cultures.**[33] The hippocampal cell cultures were prepared from embryonic day 18−20 Wister rats. The cultures were used when 9−15 days *in vitro* and were treated overnight with compounds and 300 $\mu$M kainic acid. The cell viability was quantified by measuring the amount of released lactate dehydrogenase (LDH).

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