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TRICYCLIC QUINOXALINES AS LIGANDS FOR THE STRYCHNINE-INSENSITIVE GLYCINE SITE

Paul F. Jackson,* Timothy W. Davenport, James F. Resch, G. Scott Lehr, and Linda M. Pullan
Biomedical Research Department, ICI Pharmaceuticals Group, Wilmington, Delaware 19897

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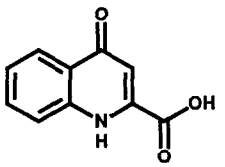
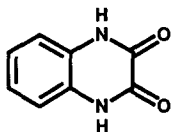
Abstract: The synthesis of a series of tricyclic quinoxalines is described. These compounds exhibit good affinity for both the strychnine-insensitive glycine site of the NMDA receptor and the AMPA receptor.

There is considerable interest in the modulation of excitatory amino acid receptors as a possible means of alleviating the neurological damage associated with disorders such as cerebral ischemia, Huntington's chorea, epilepsy, and Alzheimer's disease.[1] The N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors have attracted the most attention as possible therapeutic targets. Recently, it has been shown that glycine is required for activation of the NMDA receptor.[2] This has led to the identification of a strychnine-insensitive glycine site associated with the NMDA complex. There are several classes of antagonists which have been shown to bind at the glycine site, including kynurenic acid (1), quinoxalinedione (2), and HA-966 (3) derivatives.[3] These chemical series also show varying affinities for other excitatory amino acid receptors. It has recently been suggested by several laboratories that inhibition of both the NMDA receptor as well as a non-NMDA receptor may be necessary for maximal protection from cell death during an ischemic event.[4] As a result, a compound which shows activity at both the glycine site of the NMDA receptor and the AMPA receptor may have a higher level of protection in cerebral ischemia when compared to an agent which shows selectivity for only one receptor. We wish to report a new series of tricyclic quinoxaline compounds which exhibit good affinity for both the glycine and AMPA sites.



1



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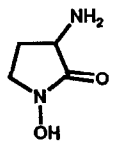
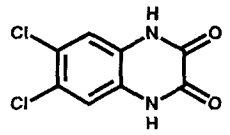
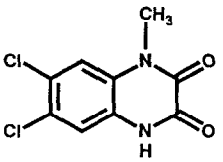
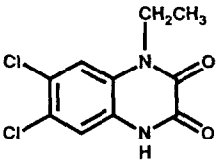
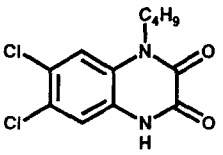


3

Initially, we prepared a series of quinoxalinediones to ascertain if it would be possible to place a substituent on one of the nitrogens and still retain activity at the glycine site. As can be seen in Table 1, placement of alkyl groups on the quinoxalinedione results in decreased binding. However, the methyl derivative (5) does still retain activity,[5] while the ethyl compound (6) decreases the inherent binding by a large factor.[6] This result implied that the glycine receptor would tolerate some substitution in the "northeastern" portion of a quinoxalinedione. The affinity for AMPA receptors, in contrast, was relatively unchanged in the molecules. As a result, we began to focus our efforts on a series of tricyclic quinoxalines.

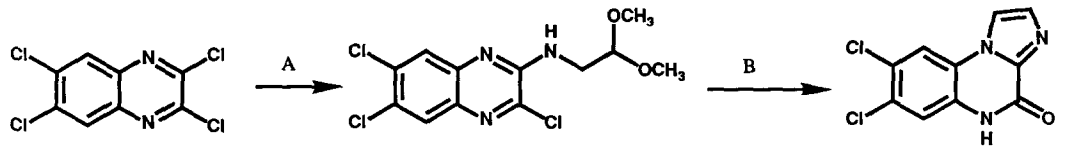
TABLE 1

	$IC_{50}(\mu M)$ [^{3}H] Gly (a) (n=3)	[^{3}H] AMPA (b) (n=3)	[^{3}H] CPP (c) (n=3)
 4 (DCQX)	4 ± 2	27 ± 13	>100
 5	17 ± 2	36 ± 15	>100
 6	96 ± 4	21 ± 12	>100
 7	>100	NT	NT

a) Reference 7 b) Reference 8 c) Reference 9

The synthesis of the imidazole derivative is outlined in Scheme 1. This route involves the reaction of the tetrachloroquinoxaline (8) with the amino acetal (9). This afforded the substituted trichloroquinoxaline (10). Treatment of this compound with 3N HCl then afforded the desired tricyclic quinoxaline (11). Although this strategy was attractive due to its brevity, the overall yield (15%) was disappointing.[10]

SCHEME 1

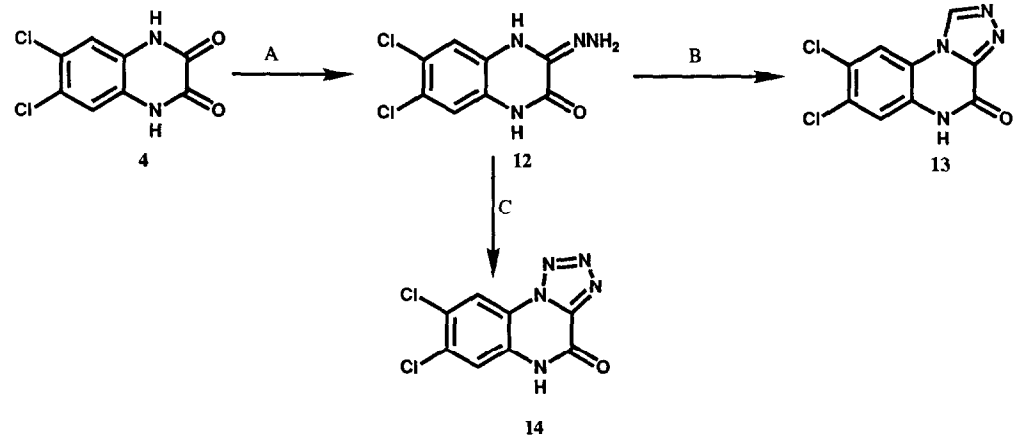


8 10 11

Conditions: A) Aminoacetaldehyde dimethyl acetal (9), dioxane. B) 3N HCl

The preparation of the triazole derivative (13) and the tetrazole derivative (14) is outlined in Scheme 2. Both routes begin with the reaction of the quinoxalenedione (4) with hydrazine hydrate.[11] This affords the hydrazide (12) which can be converted to the triazole (13) by reaction with triethyl orthoformate.[12] The tetrazole derivative (14) was prepared by reaction of the hydrazide (12) with nitrous acid. Several compounds made via these methods are shown in Table 2.

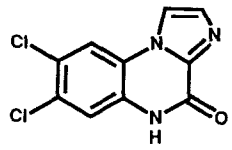
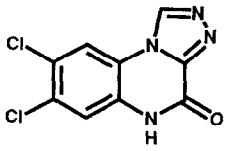
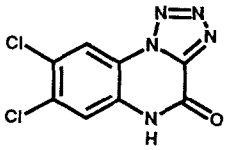
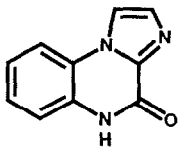
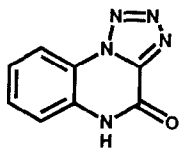
SCHEME 2



4 12 13 14

Conditions: A) Hydrazine hydrate, H2O. B) $HC(OEt)_3$ C)$NaNO_2$/HCl

TABLE 2

	$IC_{50}(\mu M)$		
	[^{3}H]Gly (n=3)	[^{3}H]AMPA (n=3)	[^{3}H]CPP (n=3)
 **11**	6 ± 3	7 ± 2	>100
 **13**	7 ± 4	8 ± 3	>100
 **14**	77 ± 15	>100	NT
 **15**	>100	NT	NT
 **16**	>100	NT	NT

As illustrated in Table 2, compounds (11) and (13) show binding activity at the glycine site comparable with DCQX (4). Furthermore, these compounds profile as glycine antagonists in the guinea pig myenteric plexus preparation, inhibiting L-glutamate induced contractions in a glycine-reversible manner.[13] The tetrazole derivative (14) did not show good affinity for the glycine site. This demonstrates that the strychnine-insensitive glycine receptor will allow only specific ring fusion strategies in the northeastern portion of a quinoxaline molecule. One possible explanation for this phenomena is based on electrostatic considerations. For example, preliminary results with electrostatic potential calculations on several molecules in Table 2 suggest that compounds (11) and (13) are more similar in nature to DCQX as opposed to compound (14). As a result, the receptor still recognizes the former two compounds as viable hydrogen bond acceptors much like DCQX.[14] With regard to the AMPA site, compounds (11) and (13) are more potent than DCQX. This implies that placement of a ring such as those shown in Table 2 onto a quinoxaline molecule increases the affinity of the molecule for the AMPA site.

In conclusion, we have described a series of quinoxaline compounds which show affinity for both the glycine and AMPA sites. As an AMPA antagonist alone has been shown to be beneficial in preventing neurodegeneration associated with an ischemic event,[7] an agent which shows affinity for the glycine site as well as the AMPA receptor may have additional benefits.

Acknowledgement: We wish to thank Maryann Britt and Kathy Paschetto for assistance in performing the binding assays.

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1 For a recent review, see: Lodge, D; Collinridge, G , Eds. The Pharmacology of Excitatory Amino Acids. A Special Report. *Trends in Pharmacological Sciences* **1991**.

2. Johnson, J.W.; Ascher, P. *Nature* **1987**, *325,* 529.

3. For leading references see: Leeson, P.D.; Baker, R.; Carling, R.W.; Curtis, N.R.; Moore, K.W.; Williams, B.J.; Foster, A.C.; Donald, A.E.; Kemp, J.A.; Marshall, G.R. *J. Med. Chem.* **1991**, *34*,1243.

4. a) Kaku, D.A.; Goldberg, M.P.; Choi, D.W. *Brain Res.* **1991**, *554*, 344 b) Mosinger, J. L.; Price, M.T.; Bai, H.Y.; Xiao, H.; Wozniak, D.F.; Olney, J.W. *Exp. Neurol.* **1991**, *113,* 10.

5. See reference 3 for a similarly substituted quinoxalinedione.

6. The N-substituted quinoxalinediones were prepared by alkylation of 4,5-dichloro-2-nitroaniline (1.HCO_2H, $(RCO)_2O$ 2.BH_3.DMS) followed by reduction of the nitro group ($SnCl_2.H_2O$/EtOH). This was subsequently reacted with diethyl oxalate to afford the substituted quinoxalinedione. See for example: Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315.

7. Radioligand receptor binding assays to rat brain synaptic membranes were as previously described for strychnine-insensitive [^{3}H] glycine binding: Pullan, L.M.; Britt, M.; Chapdelaine, M.J.; Keith, R.A.; LaMonte, D.; Mangano, T.J.; Patel, J.; Powel, R.J ; Stumpo, R.J.; Warwick, P.J.; Zinkand, W.C.; Salama, A I. *J. Neurochem.* **1990**, *55*,1346.

8. Binding to the AMPA receptor was determined as previously described: Sheardown, M.J ; Nielsen, E O.; Hansen, A.J.; Jacobsen, P.; Honore', T. *Science* **1990**, *247*, 571.

9. Binding with [^{3}H] CPP was determined as previously described: Pullan, L.M.; Powel, R J.; Stumpo, R.J., Britt, M.: Klika, A.B.; Meiners, B A.; Salama, A.I. *Eur.J.Pharmacol.-Mol. Pharmacol.Sect.* **1990**, *189*, 237

10 After our work was completed, an alternate method of preparing similar compounds appeared. See· Davey, D D., Europen Patent Application 400583. **1990.**

11 Cheeseman, G.W.H.; Rafiq, M. *J. Chem. Soc. (C)* **1971**, 452.

12 See for example: Makino, K.; Sakata, G.; Morimoto, K. *Heterocycles* **1985**, *23*, 2025.

13 For a description of this preparation, see: a) Luzzi,S.; Zilletti, L.; Franchi-Micheli, S.; Gori, A M.; Moroni, F. *Br. J. Pharmacol.* **1989**, *95*, 1271 b) See also reference 7.

14. Electrostatic potentials were calculated from the HF wavefunction with the 3-21G basis set using SPARTAN Carpenter, J.E.; Baker, J.; Hehre, W.J , Kahn, S.D. The SPARTAN System, **1990.** Baker, J.; Hehre, W.J. *J. Comp. Chem.* **1991**, *12*, 606. The electrostatic isopotential contours were displayed using ENIGMA. Loftus, P.; Waldman, M , Hout, R F. Chem. Design Automa News **1986.** The relationship of electrosatic potentials of glycine antagonists to the strychnine insensitive-glycine site is currently under investigation and will be reported in more detail at a later date.