Communications to the Editor

3′-(Arylmethyl)- and 3′-(Aryloxy)-3-phenyl-4-hydroxyquinolin-2(1*H*)-ones: Orally Active Antagonists of the Glycine Site on the NMDA Receptor

Janusz J. Kulagowski, Raymond Baker, Neil R. Curtis, Paul D. Leeson,* Ian M. Mawer, Angela M. Moseley, Mark P. Ridgill, Michael Rowley, Ian Stansfield, Alan C. Foster, Sarah Grimwood, Raymond G. Hill, John A. Kemp, George R. Marshall, Kay L. Saywell, and Mark D. Tricklebank

Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K.

Received February 16, 1994

Antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor have demonstrated promising potential for the treatment of a variety of neurological and neurodegenerative disorders.[1] Considerable attention has focused recently on the strychnine-insensitive glycine site present on the NMDA receptor, where glycine acts as an essential "coagonist" in the presence of the probable neurotransmitter, glutamic acid.[2] Current knowledge of the *in vivo* consequences of glycine-site blockade rests with studies of the low efficacy partial agonists (+)-HA-966 (**1**)[3] and L-687,414 (**2**),[4] which, despite having only micromolar affinities *in vitro*, are active *in vivo* after systemic administration and readily penetrate the blood–brain barrier. Experiments with these compounds have led to the important finding that the beneficial neuroprotective,[5] anticonvulsant,[6] and antipsychotic[7] activities mediated via glycine-site antagonism are not necessarily associated with the adverse side effects[8,9] of other types of NMDA receptor antagonists, particularly channel blockers such as dizocilpine (MK-801).[10]

Although several classes of glycine antagonists possessing high receptor affinity and selectivity have been found,[2] these compounds, exemplified by 5-iodo-7-chlorokynurenic acid (**3**),[11] L-689,560 (**4**),[12] and MDL 29,951 (**5**),[13] are severely compromised by a lack of activity *in vivo* following intraperitoneal or intravenous administration. Since effects on the central nervous system are seen following intracerebroventricular administration of **4**[14] and **5**,[15] it seems likely that these compounds, which contain highly polar carboxylic acid groups, do not readily cross the blood–brain barrier. In order to exploit the considerable therapeutic promise shown by the prototype partial agonists **1** and **2**, glycine antagonists with appreciable brain penetration are urgently needed. Herein, we disclose a new class of 3-substituted 4-hydroxyquinolin-2(1*H*)-ones,[16–18] which we show are selective glycine antagonists possessing potent *in vivo* activity following oral administration.

Our search for glycine antagonists with improved ability to cross the blood–brain barrier has focused[16] on a strategy of bioisosteric replacement of the 2-carboxylic acid group in **3** and **4**. This led to the synthesis of 3-substituted 4-hydroxyquinolin-2(1*H*)-ones **6**–**8**[16,18] as potent non-carboxylic glycine antagonists, with the 3-acyl series, exemplified by cyclopropyl ketone **7**, being the first glycine antagnists displaying significant *in vivo* activity after systemic administration.[18] These results showed that the enolic β-dicarbonyl moiety, within the 4-hydroxy-2-quinolone framework, may act as a brain-penetrating carboxyl bioisostere. Since affinity for the glycine site in this series is wholly dependent on the 3-substituent, the potent 3-phenyl derivative **6**, where the introduction of the phenyl group uniquely improves binding by >10³-fold,[16] became an obvious lead for further optimisation. Although activity may be improved by 4′-substitution of the 3-phenyl with electron-releasing groups,[17] our extensive studies[18] with the 3-acyl series, leading to the optimal arylpropargyl ester **8**, suggested an alternative approach. The 3-phenyl derivative **6** and the arylpropargyl ester **8** have equal *in vitro* affinities for the glycine site, with the arylpropargyl group in **8** improving affinity by 40-fold relative to the parent methyl ester.[18] Simple superimpositions of the 3-substituents in **6** and **8** (see Figure 1) imply that the activity of **6** might be improved by the introduction of 3′-hydrophobic substituents to mimic the bulky phenylpropargyl moiety of **8**. Several types of hydrophobic 3′-substituents were explored, and the optimal class which emerged possess 3′-arylmethyl and -aryloxy substituents, as illustrated by compounds **9**–**14**.

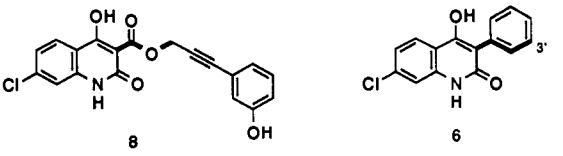
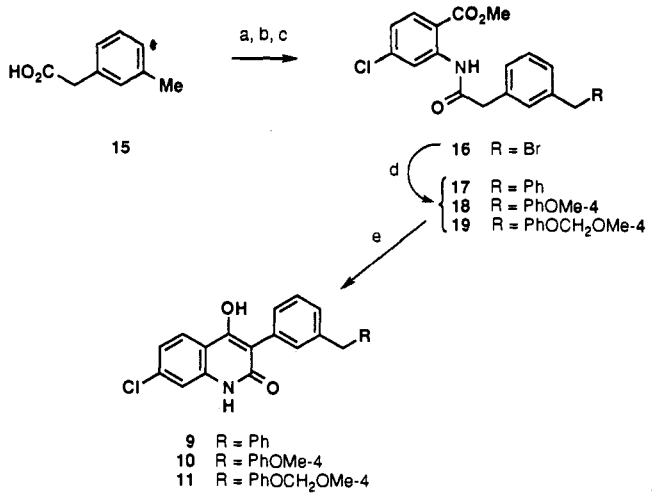


Figure 1. Phenylpropargyl ester **8** suggests substitution of the 3′-position of **6**.

Compounds **9**–**11** were prepared from 3-methylphenylacetic acid (**15**) (Scheme 1). Bromination of **15**, followed by conversion to the corresponding acid chloride and coupling with methyl 4-chloroanthranilate, provided the intermediate amide **16**. Displacement of the bromide from **16** with the appropriate (substituted phenyl) propylethynyl

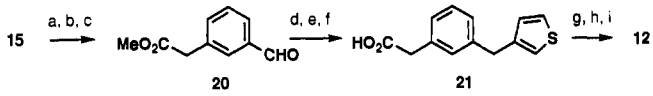
0022-2623/94/1837-1402$04.50/0 © 1994 American Chemical Society

Scheme 1[a]



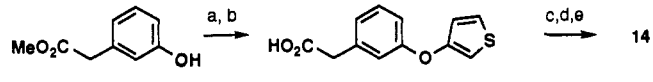
[a] Reagents: (a) NBS, AIBN, CCl_4, 80 °C; (b) $(COCl)_2$, CH_2Cl_2, 25 °C; (c) methyl 4-chloroanthranilate, CH_2ClCH_2Cl, 80 °C; (d) [RCuC≡CPr]Li, THF, −78 °C; (e) 2 equiv of KHMDS, THF, 25 °C, then TFA.

Scheme 2[a]



[a] Reagents: (a) NBS, AIBN, CCl_4, 80 °C; (b) HCl, MeOH, 0 °C; (c) $Me_3N^+O^-$, DMSO, 0 °C; (d) 3-lithiothiophene, THF, −78 °C; (e) Et_3SiH, TFA, CH_2Cl_2, 0 °C; (f) LiOH, THF, 25 °C, then H_3O^+; (g) $(COCl)_2$, CH_2Cl_2, 25 °C; (h) methyl 4-chloroanthranilate, CH_2ClCH_2Cl, 80 °C; (i) 2 equiv of KHMDS, THF, 25 °C, then TFA.

Scheme 3[a]

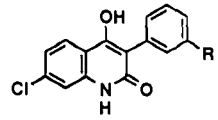


[a] Reagents: (a) 3-bromothiophene, K_2CO_3, CuO, pyridine, 115 °C; (b) LiOH, MeOH, H_2O, 25 °C, then H_3O^+; (c) $(COCl)_2$, CH_2Cl_2, 25 °C; (d) methyl 4-chloroanthranilate, CH_2ClCH_2Cl, 80 °C; (e) 2 equiv of KHMDS, THF, 25 °C, then TFA.

cuprate[19] formed benzyl derivatives **17–19**. Subsequent cyclization using potassium hexamethyldisilazide afforded the desired 3-aryl-4-hydroxyquinolin-2(1*H*)-ones. The efficient cyclization of **17–19** required 2 equiv of base to effect successive deprotonation of the amide NH and arylacetyl methylene groups. A modified sequence was used for the synthesis of the 3-thienyl derivative **12** (Scheme 2). The benzyl bromide derived from **15** was esterified and oxidized to aldehyde **20**. Reaction of **20** with 3-lithiothiophene, followed by deoxygenation of the resulting alcohol using ionic reduction, and then saponification, formed the carboxylic acid **21** which was converted to **12**. Diphenyl ether **13** was prepared from commercially available 3-phenoxyphenylacetic acid. The carboxylic acid **23**, used to prepare thienyl ether **14**, was synthesized by Ullmann coupling[20] of phenol **22** with 3-bromothiophene (Scheme 3).

Affinity for the glycine site *in vitro* was measured by displacement of [^{3}H]-L-689,560 ([^{3}H]-**4**) binding to rat brain membranes (IC_{50} values).[21] *In vitro* functional antagonist potencies were determined from blockade of NMDA-induced depolarizations on rat cortical slices (K_b values).[22] The primary *in vivo* test used was protection from audiogenic seizure in the DBA/2 mouse,[10,14] where compounds were administered intraperitoneally (ip) and orally (po) and ED_{50} values were determined 30 min after dosing. Other classes of NMDA receptor antagonists are effective in this model,[6,10] and activity in this test is considered to be the most sensitive available predictor of *in vivo* NMDA receptor antagonism. The results for compounds **9–14**, together with reference compounds **3–6**, are shown in Table 1.

Table 1. NMDA Receptor Activities of 3′-Substituted 3-Phenyl-4-hydroxy-2-quinolones



no.[a]	R	IC_{50} (nM)[b] [^{3}H]-L-689,560	K_b (nM)[c] NMDA	ED_{50} (mg/kg)[d] DBA/2 mouse ip	ED_{50} (mg/kg)[d] DBA/2 mouse po
6	H	170	880	4.5	7.6
9	CH_2Ph	4.1	87	1.3[e]	3.9
10	CH_2PhOMe-4	4.5	25	0.7	0.9
11	CH_2PhOCH_2OMe-4	2.2	3.2	0.5	0.9
12	CH_2(3-thienyl)	2.3	19	1.5	5.1
13	OPh	2.0	28	0.9	0.9
14	O(3-thienyl)	1.4	5.0	0.8	0.8
3		14	410	>250	
4		4.0	110	>100	
5		69	1320	>100	

[a] All compounds were characterized by proton NMR and mass spectra and provided satisfactory elemental analyses. [b] Inhibition of the binding of [^{3}H]-**4** to the strychnine-insensitive glycine site on rat brain membranes (ref 21). Values are the means from at least three experiments. [c] Block of NMDA-induced depolarizations on rat cortical slices (ref 22). Values are the means from at least three experiments. [d] Protection from audiogenic seizure in DBA/2 mice (21–23 days old, weighing 5–9 g); the end point was tonic seizure within 30 s (refs 10 and 14). Dosing solutions were 10% poly(ethylene glycol) 300 or 600, with the pH adjusted to 9–10 using 1 N sodium hydroxide. Potencies were measured 30 min after intraperitoneal (ip) or oral (po) administration. [e] Potency measured 10 min after administration.

Introduction of the 3′-arylmethyl and 3′-aryloxy substituents in compounds **9–14** results in up to 100-fold improved affinity for the glycine site relative to the unsubstituted derivative **6**, supporting the design hypothesis in Figure 1. Testing of homologues showed that a single atom methylene or oxygen spacer between the 3′-position and the aryl ring proved to be optimal (data not shown) and the aryl ring may be phenyl or 3-thienyl. Substitution of the 3′-phenyl ring is allowed, and 4″-derivatives such as **10** and **11** maintain high receptor affinity and functional antagonism *in vitro*. The most significant finding of this study is the potent *in vivo* activity of this series, with compounds **10** (L-703,717), **11** (L-708,541), **13** (L-701,324), and **14** (L-705,022) showing activity in the DBA/2 mouse model with ED_{50} values of below 1 mg/kg. The equivalent activities resulting from ip and po dosing of these compounds indicate high oral bioavailability. In addition, the behavioral stimulant and motor deficit properties seen with NMDA receptor channel blockers such as dizocilpine[10] were, as anticipated from earlier studies with 1 and 2,[3,6] absent at anticonvulsant doses. For example, the minimum effective oral doses of **12** and **13** for inducing motor deficits in mice, using the rotarod test,[3,6] are 100 and 30 mg/kg, respectively, demonstrating markedly improved therapeutic ratios relative to dizocilpine.

The pK_a values of the 3-aryl-4-hydroxyquinolin-2(1*H*)-ones (**10** is typical with a pK_a of 5.5) show that, in common with the carboxylic acids **3** and **4**, these molecules will be

highly (~99%) deprotonated at physiological pH. The enolic β-dicarbonyl system in **9–14** is therefore a bioisosteric, vinylogous carboxylic acid having improved oral absorption and blood–brain barrier permeability. The changed molecular properties which may underlie the improved systemic *in vivo* activity of the 4-hydroxy-2-quinolones relative to the carboxylic acids deserve comment in the context of current physicochemical models of blood–brain transfer. The activity of drugs in the central nervous system is usually associated with optimal hydrophobicity as estimated by 1-octanol/water partition coefficients ($\log P_{oct}$).[23] Although quinolones **9–14** are more hydrophobic than acid **4** (e.g., **10**, $\log P_{oct,pH7.4} = 2.9$; **4**, $\log P_{oct,pH7.4} = 1.1$), many derivatives of **4** with increased hydrophobicity retain affinity for the receptor[12] but are not active *in vivo*.[14] In general, we have found no obvious dependence of anticonvulsant activity on $\log P_{oct}$ in several classes of glycine antagonists derived from **3**, **4**,[14] **7**,[18] and **6**.[24] The presence of hydrogen bonding and dipolar groups has been proposed to reduce penetration of the blood–brain barrier,[25] and this model can qualitatively account for some of our results. Thus carboxylic acid **4**, which does not penetrate the brain, can form *seven* hydrogen bonds[26] to water (three amide NH donors, one hydroxyl donor + acceptor, and two carbonyl oxygen acceptors), whereas quinolone **9** penetrates the brain and can form *four* hydrogen bonds to water (one amide NH donor, one hydroxyl donor + acceptor, and one carbonyl oxygen acceptor), the fewest of any of the known classes of glycine antagonists. In addition, the polar 2- and 4-oxy groups of **9–14** are partially masked by the adjacent hydrophobic 3-phenyl. The ether oxygen atoms present in **10**, **11**, **13**, and **14** are relatively weak hydrogen-bond acceptors[27] and do not significantly influence *in vivo* activity. An additional factor is the ability of the 3-phenyl-4-hydroxyquinolin-2(1*H*)-one system to form an anion which is delocalized over five atoms. This may be relevant to brain penetration, since a related class of glycine antagonists which form similarly delocalized anions, the 3-nitro-3,4-dihydroquinolin-2(1*H*)-ones,[28] also possess *in vivo* activity. Finally, these non-carboxyl glycine antagonists may not readily efflux from the brain via carboxylic acid transporters.[29]

Compounds **10–14** proved to be highly selective for the glycine site, having no activity at amino acid receptors labeled by [^{3}H]AMPA, [^{3}H]kainate, and [^{3}H]strychnine at concentrations up to 100 μM. The class of 3′-(arylmethyl)- and 3′-(aryloxy)-3-phenyl-4-hydroxyquinolin-2(1*H*)-ones described here comprise the most potent glycine-site NMDA receptor antagonists yet described, both *in vitro* and *in vivo*, and are the first such compounds with significant activity in the central nervous system following oral dosing.

Acknowledgment. We thank Dr. Richard Herbert for NMR and mass spectroscopy and Alan Watt for measurement of log *P* and pK_a values.

References

(1) Meldrum, B., Ed. *Excitatory Amino Acid Antagonists*; Blackwell Scientific Publications: Oxford, 1991.
(2) (a) Kemp, J. A.; Leeson, P. D. The Glycine Site of the NMDA Receptor – Five Years On. *Trends Pharmacol. Sci.* **1993**, *14*, 20–25. (b) Leeson, P. D. Glycine-site N-Methyl-D-Aspartate Receptor Antagonists. In *Drug Design for Neuroscience*; Kozlkowski, A. P., Ed.; Raven Press: New York, 1993; pp 339–381.
(3) Singh, L.; Donald, A. E.; Foster, A. C.; Hutson, P. H.; Iversen, L. L.; Iversen, S. D.; Kemp, J. A.; Leeson, P. D.; Marshall, G. R.; Oles, R. J.; Priestley, T.; Thorn, L.; Tricklebank, M. D.; Vass, C. A.; Williams, B. J. Enantiomers of HA-966 (3-Amino-1-hydroxypyrrolidin-2-one) exhibit Distinct Central Nervous System Effects: (+) HA-966 is a Selective Glycine/N-methyl-D-aspartate Receptor Antagonist, but (–) HA-966 is a Potent γ-Butyrolactone-like Sedative. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 347–351.
(4) Leeson, P. D.; Williams, B. J.; Rowley, M.; Moore, K. W.; Baker, R.; Kemp, J. A.; Priestley, T.; Foster, A. C.; Donald, E. A. Derivatives of 1-Hydroxy-3-Aminopyrrolidin-2-one (HA-966). Partial Agonists at the Glycine Site of the NMDA Receptor. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 71–76.
(5) Gill, R.; Hargreaves, R.; Kemp, J. A. Neuroprotective Effects of the Glycine Site Antagonist (+)Cis-4-methyl-HA-966 (L-687,414) in a Rat Focal Ischaemia Model. *J. Cereb. Blood Flow Metab.* **1991**, *11*, Suppl. 2, S304.
(6) Saywell, K.; Singh, L.; Oles, R. J.; Vass, C.; Leeson P. D.; Williams, B. J.; Tricklebank, M. D. The Anticonvulsant Properties in the Mouse of the Glycine/NMDA Receptor Antagonist, L-687,414. *Br. J. Pharmacol.* **1991**, *102*, 66P.
(7) (a) Bristow, L. J.; Hutson, P. H.; Thorn, L.; Tricklebank, M. D. The Glycine/NMDA Receptor Antagonist, *R*-(+)-HA-966, Blocks Activation of the Mesolimbic Dopaminergic System Induced by Phencyclidine and Dizocilpine (MK-801) in Rodents. *Br. J. Pharmacol.* **1993**, *108*, 1156–1163. (b) Hutson, P. H.; Bristow, L. J.; Thorn, L.; Tricklebank, M. D. *R*-(+)-HA-966, a Glycine/NMDA Receptor Antagonist, Selectively Blocks the Activation of the Mesolimbic Dopamine System by Amphetamine. *Br. J. Pharmacol.* **1991**, *103*, 2037–2044.
(8) (a) Singh, L.; Menzies, R.; Tricklebank, M. D. The Discriminative Stimulus Properties of (+)-HA-966, an Antagonist at the Glycine/N-Methyl-D-aspartate Receptor. *Eur. J. Pharmacol.* **1990**, *186*, 129–132. (b) Smith, S. E.; Meldrum, B. S. The Glycine-site NMDA Receptor Antagonist, *R*-(+)-Cis-β-methyl-3-amino-1-hydroxypyrrolidin-2-one, L-687,414 is Anticonvulsant in Baboons. *Eur. J. Pharmacol.* **1992**, *211*, 109–111.
(9) Hargreaves, R. J.; Rigby, M.; Smith, D.; Hill, R. G. Lack of Effect of L-687,414 ((+)-*cis*-4-methyl-HA-966), an NMDA Receptor Antagonist acting at the Glycine Site, on Cerebral Glucose Metabolism and Cortical Neuronal Morphology. *Br. J. Pharmacol.* **1993**, *110*, 36–42.
(10) Tricklebank, M. D.; Singh, L.; Oles, R. J.; Preston, C.; Iversen, S. D. The Behavioral Effects of MK-801: a Comparison with Antagonists Acting Non-Competitively and Competitively at the NMDA Receptor. *Eur. J. Pharmacol.* **1989**, *167*, 127–135.
(11) 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. Kynurenic Acid Derivatives. Structure-Activity Relationships for Excitatory Amino Acid Antagonism and Identification of Potent and Selective Antagonists at the Glycine Site of the N-Methyl-D-aspartate Receptor. *J. Med. Chem.* **1991**, *34*, 1243–1252.
(12) Leeson, P. D.; Carling, R. W.; Moore, K. W.; Moseley, A. M.; Smith, J. D.; Stevenson, G.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Hoogsteen, K. 4-Amido-2-carboxytetrahydroquinolines. Structure-Activity Relationships for Antagonism at the Glycine Site of the NMDA Receptor. *J. Med. Chem.* **1992**, *35*, 1954–1968.
(13) Salituro, F. G.; Harrison, B. L.; Baron, B. M.; Nyce, P. L.; Stewart, K. T.; Kehne, J. H.; White, H. S.; McDonald, I. A. 3-(2-Carboxyindol-3-yl)propionic Acid-Based Antagonists of the N-Methyl-D-aspartic Acid Receptor Associated Glycine Binding Site. *J. Med. Chem.* **1992**, *35*, 1791–1799.
(14) Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Smith, J. D.; Saywell, K.; Tricklebank, M. D.; Kemp, J. A.; Marshall, G. R.; Foster, A. C.; Grimwood, S. Anticonvulsant Activity of Glycine-site NMDA Antagonists. 2. *Trans* 2-Carboxy-4-substituted Tetrahydroquinolines. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 65–70.
(15) Baron, B. M.; Harrison, B. L.; McDonald, A. A.; Meldrum, B. S.; Palfreyman, M. G.; Salituro, F. G.; Siegel, B. W.; Slone, A. L.; Turner, J. P.; White, H. S. Potent Indole- and Quinoline-Containing N-Methyl-D-aspartate Antagonists Acting at the Strychnine-insensitive Glycine Binding Site. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 947–956.
(16) Leeson, P. D.; Baker, R.; Carling, R. W.; Kulagowski, J. J.; Mawer, I. M.; Ridgill, M. P.; Rowley, M.; Smith, J. D.; Stansfield, I.; Stevenson, G. I.; Foster, A. C.; Kemp, J. A. Amino Acid Bioisosteres: Design of 2-Quinolone Derivatives as Glycine-site N-Methyl-D-aspartate Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 299–304.
(17) McQuaid, L. A.; Smith, E. C. R.; Lodge, D.; Pralong, E.; Wikel, J. H.; Calligaro, D. O.; O'Malley, P. J. 3-Phenyl-4-hydroxyquinolin-2(1H)-ones: Potent and Selective Antagonists at the Strychnine-Insensitive Glycine Site on the N-Methyl-D-aspartate Receptor Complex. *J. Med. Chem.* **1992**, *35*, 3423–3425.
(18) Rowley, M.; Leeson, P. D.; Stevenson, G. I.; Moseley, A. M.; Stansfield, I.; Sanderson, I.; Robinson, L.; Baker, R.; Kemp, J. A.; Marshall, G. R.; Foster, A. C.; Grimwood, S.; Tricklebank, M. D.; Saywell, K. L. 3-Acyl-4-hydroxyquinolin-2(1H)-ones. Systemically Active Anticonvulsants Acting by Antagonism at the Glycine Site of the N-Methyl-D-aspartate Receptor Complex. *J. Med. Chem.* **1993**, *36*, 3386–3396.

(19) Corey, E. J.; Beames, D. J. Mixed Cuprate Reagents of the Type R_1R_2CuLi which Allow Selective Group Transfer. *J. Am. Chem. Soc.* **1972**, *94*, 7210–7211.
(20) Evans, D. A.; Ellman, J. A. The Total Synthesis of the Isodityrosine-Derived Cyclic Tripeptides OF4949-III and K-13. Determination of the Absolute Configuration of K-13. *J. Am. Chem. Soc.* **1989**, *111*, 1063–1072.
(21) Grimwood, S.; Moseley, A. M.; Carling, R. W.; Leeson, P. D.; Foster, A. C. Characterization of the Binding of [^{3}H]L-689,560, anAntagonist for the Glycine Site on the N-Methyl-D-Aspartate Receptor, to Rat Brain Membranes. *Mol. Pharmacol.* **1992**, *41*, 923–930.
(22) Foster, A. C.; Kemp, J. A.; Leeson, P. D.; Grimwood, S.; Donald, A. E.; Marshall, G. R.; Priestley, T.; Smith, J. D.; Carling, R. W. Kynurenic Acid Analogues with Improved Affinity and Selectivity for the Glycine Site on the N-Methyl-D-Aspartate Receptor from Rat Brain. *Mol. Pharmacol.* **1992**, *41*, 914–922.
(23) Hansch, C.; Bjorkroth, J. P.; Leo, A. Hydrophobicity and Central Nervous System Agents: On the Principle of Minimal Hydrophobicity in Drug Design. *J. Pharm. Sci.* **1987**, *76*, 663–687.
(24) Unpublished results.
(25) (a) Young, R. C.; Mitchell, R. C.; Brown, T. H.; Ganellin, C. R.; Griffths, R.; Jones, M.; Rana, K. K.; Saunders, D.; Smith, I. R.; Sore, N. E.; Wilks, T. J. Development of a New Physicochemical Model for Brain Penetration and its Application to the Design of Centrally Acting H_2 Histamine Receptor Antagonists. *J. Med. Chem.* **1988**, *31*, 656–671. (b) van de Waterbeemd, H.; Kansy, M.Hydrogen-Bonding Capacity and Brain Penetration. *Chimia* **1992**, *46*, 299–303.
(26) Stein, W. D. *The Movement of Molecules Across Cell Membranes*; Academic Press: New York, 1967; pp 65–91.
(27) Abraham, M. H.; Duce, P. P.; Prior, D. V.; Barratt, D. G.; Morris, J. J.; Taylor, P. J. Hydrogen Bonding. Part 9. Solute Proton Donor and Proton Acceptor Scales for Use in Drug Design. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1355–1375.
(28) Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Moyes, C. R.; Mawer, I. M.; Thomas, S.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. 3-Nitro-3,4-dihydro-2(1H)-quinolones. Excitatory Amino Acid Antagonists acting at Glycine-site NMDA and (*RS*)-α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptors. *J. Med. Chem.* **1993**, *36*, 3397–3408.
(29) Hays, S. J.; Boxer, P. A.; Taylor, C. P.; Vartanian, M. G.; Robichaud, L. J.; Nielsen, E. O. N-Sulfonyl Derivatives of 6,7-Dichloro-3,4-dihydro-3-oxo-quinoxaline carboxylate as Glycine-site NMDA and AMPA Antagonists. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 77–80.