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TETRAMIC ACIDS AS NOVEL GLYCINE SITE ANTAGONISTS

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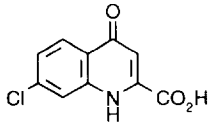
Abstract: Tetramic acids (**9**) have been designed as novel glycine site N-methyl-D-aspartate receptor antagonists.

It is well established that N-methyl-D-aspartate (NMDA) antagonists may be of use in the treatment of neurological diseases[1]. There are several sites on the NMDA receptor at which these antagonists may act; these include the glutamate recognition site, the ion channel, a polyamine site and a strychnine insensitive glycine site. There is increasing evidence[2] that antagonists acting at the glycine site may have a superior side effect profile over uncompetitive antagonists such as dizocilpine (MK-801). Several classes of compounds have been shown to be full antagonists at the glycine site including kynurenic acids (**1**)[3], 2-carboxytetrahydroquinolines (**2**)[4], 2-carboxyindoles[5], and 3-substituted 4-hydroxyquinolin-2(1H)-ones (**3**)[6,7].



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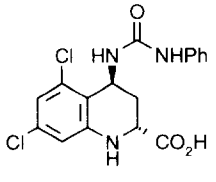

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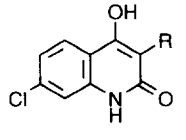
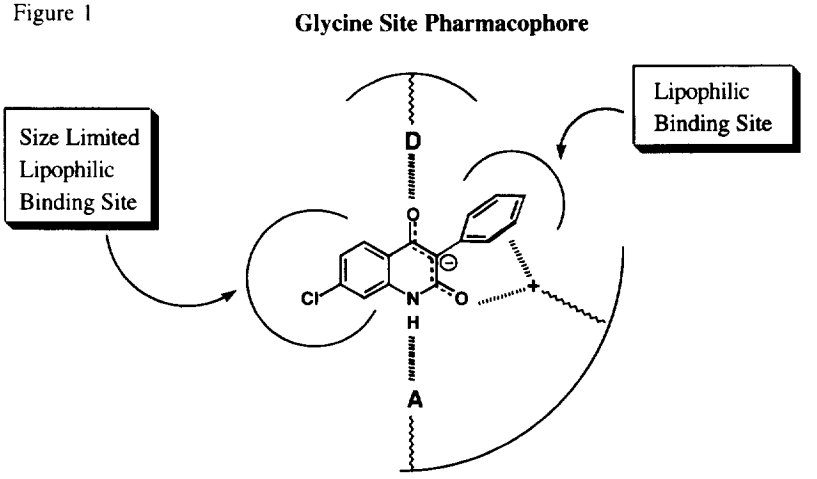


3a: R = H
3b: R = CO_2Me
3c: R=Ph

These compounds allowed a preliminary pharmacophore to be defined[6], proposing essential ionic and lipophilic interactions. With the discovery of the 4-hydroxy-3-phenylquinolin-2(1H)-ones[7] this model was further refined (Figure **1**). Based on other results it is proposed that the 3-phenyl group binds to the receptor *via* an electrostatic interaction between the π-electrons and a positive charge on the receptor, as has been observed in other biological systems[8]

Figure 1



D: Putative H-Bond donor; A: Putative H-bond acceptor; +: Coulombic interaction

It has been observed that 4-hydroxyquinolin-2(1H)-ones bearing a 3-phenyl substituent have a marked increase in potency over other functionality at this position[9,10]. Previously, we have reported that there are essential features required for activity: the 1-NH putatively involved in hydrogen bonding, an ionizable group to provide a charge interaction whose relative location is not critical, and a size limited lipophilic binding site occupied by a chlorophenyl moiety[9]. Thus we attempted to find alternative compounds that retained the electrostatic interactions whilst replacing the lipophilic chlorophenyl ring.

Based on this approach a series of tetramic acids (**4**) was targeted (Figure **2**) as these would have similar acidity to the hydroxyquinolones (*e.g.* tetramic acid pKa 6.4; **3a** pKa 5.8). Simple superposition of the tetramic acids with the 4-hydroxy-3-phenylquinolin-2(1H)-ones show that all groups involved in the charge interactions can be overlayed[11] (Figure **3**). It was noticed from the modelling that introduction of a substituent at the 5-position of the tetramic acid could be placed so that it occupied a similar region of space to the 7-chloro substituent (Figure **4**). A degree of conformational rigidity could be achieved by using an olefinic moiety at this position, which still placed the side chain in the correct region of space. Previous studies have shown strict spatial requirements of the chlorophenyl binding pocket, and the modelling study showed that only the (Z)-olefin could access this region, leading to the prediction that the (E)-isomer should be inactive.

The tetramic acids are readily synthesised, employing methyl 2-amino-2-(dimethoxyphosphinyl)acetate (**7**)[12] as a key intermediate. This is prepared (Scheme **1**) by condensation of glyoxylic acid and benzyl carbamate, followed by methylation, to yield the fully protected methoxy amino acid (**5**). Treatment of this methoxy glycine

Figure 2

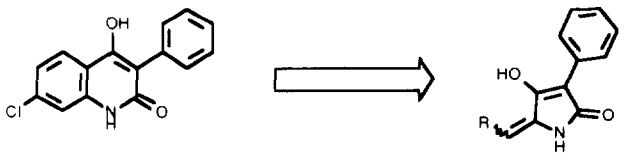


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Figure 3: Superposition of charged groups in tetramic acids and quinolinones

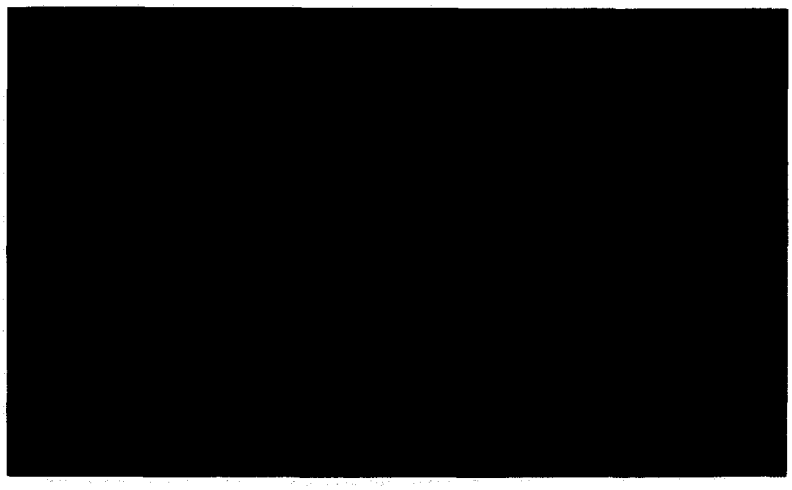
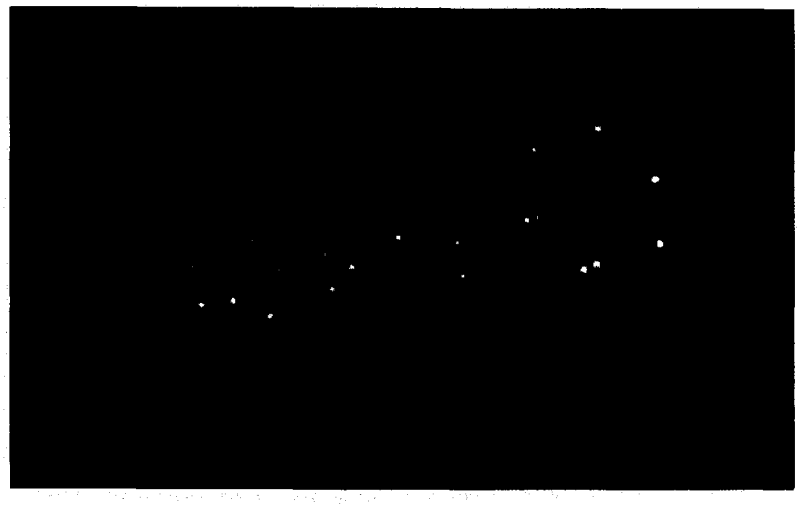
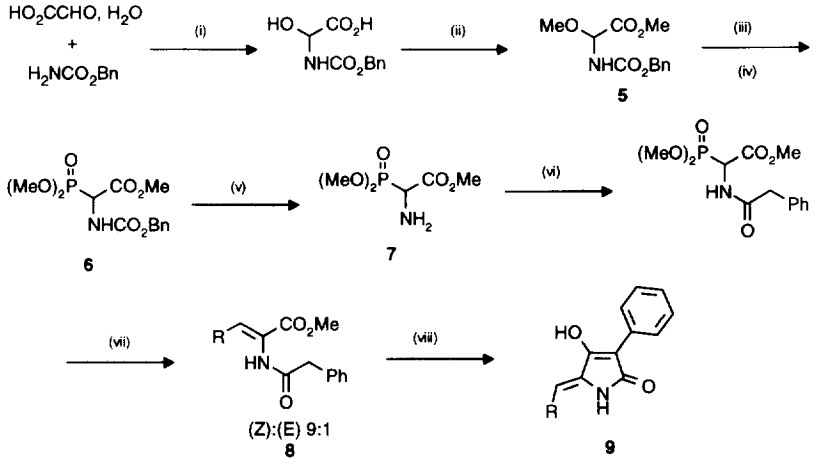


Figure 4: Overlay of lipophilic substituents in tetramic acids and quinolinones



derivative with phosphorus (III) chloride, followed by trimethyl phosphite gave the phosphonate (**6**), which was hydrogenolysed over palladium hydroxide to yield the amine (**7**). After forming the amide by coupling with phenylacetic acid, Horner-Emmons reaction with the appropriate aldehyde gave predominantly the desired (Z)-olefinic amide (**8**), which was separated from the (E)-isomer by chromatography. These amides were cyclised using potassium hexamethyldisilazide to yield the tetramic acids (**9**).

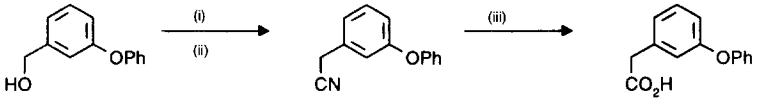
Scheme 1



Reagents: (i) Et_2O; (ii) MeOH, H_2SO_4; (iii) PCl_3; (iv) $(MeO)_3P$; (v) H_2, $Pd(OH)_2$, MeOH; (vi) $PhCH_2CO_2H$, DCC, CH_2Cl_2; (vii) RCHO, KO^tBu, CH_2Cl_2; (viii) KHMDS, THF

Use of a suitably substituted phenylacetic acid (*e.g.* Scheme **2**) allowed preparation of substituted phenyl derivatives (Scheme **3**).

Scheme 2

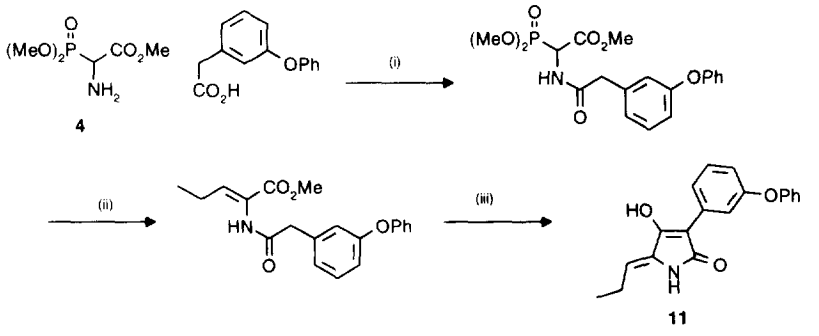


Reagents: (i) $SOCl_2$, DMF, CH_2Cl_2; (ii) KCN, DMSO; (iii) NaOH, EtOH

As expected the tetramic acids were acidic in nature (*e.g.* **9a** pKa 4.6; *c.f.* **3c** pKa 5.4), and the 1'-ethylmethylidene compound (**9a**) showed moderate affinity (IC_{50} 45.5μM, Table **1**) for the glycine site *in vitro*, as measured by displacement of [^{3}H]-L-689,560 to rat brain membranes [13]. Replacement of the ethyl group by phenyl (**9b**).propyl(**9c**) and cyclopropyl (**9d**) all gave increasingly potent compounds, and antagonism

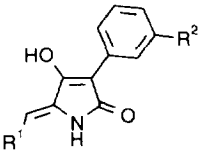
was shown by measuring NMDA depolarization in rat cortical slices [14] (Table 1). The modelling study had predicted that the (E)-isomer would be inactive. To test this hypothesis, the cyclopropyl (E)-substituted isomer (**10**) was prepared and this compound showed no activity for the glycine site, confirming the prediction and adding credence to the pharmacophore model being used.

Scheme 3



Reagents: (i) DCC, CH_2Cl_2, (ii) KO^tBu, CH_3CH_2CHO, CH_2Cl_2; (iii) KHMDS, THF

Table 1



No	R^1	R^2	IC_{50} (μM) vs [^{3}H]-L-689,560[a]	Kb (μM) vs NMDA[b]
9a	CH_3CH_2	H	45.5	115
9b	Ph	H	24.2	
9c	$CH_3CH_2CH_2$	H	15.7	154
9d	c-Pr	H	9.5	
10	*E*-c-Pr	H	18% @ 100	
11	CH_3CH_2	OPh	0.7	6.15
12	CH_3CH_2		3.0	15.8

[a] Inhibition of the binding of [^{3}H]-L-689,560 to the strychnine insensitive glycine site on rat brain membranes [13]

[b] Inhibition of NMDA-induced depolarizations in rat cortical slices [14]

In quinolinones derived from **3b** it has been demonstrated[10] that appropriate substitution of the 3-phenyl group leads to an increase in activity. Thus introduction of a phenoxy group at the 3-position of the phenyl group (**11**)

is accompanied by a 60-fold increase in activity. Other groups are also tolerated at this position, as is seen by the methallyl derivative (**12**), showing a similar trend as seen with the 4-hydroxy-3-phenylquinolin-2(1H)-ones.

Molecular modelling studies have been used to develop tetramic acids as novel glycine site antagonists in which for the first time the fused chlorophenyl moiety has been successfully replaced by a suitable acyclic lipophilic group[15]. These compounds have been shown to be antagonists possessing good affinity for the strychnine-insensitive glycine site, with compound **11** being the most potent (IC_{50} 0.7μM), as well as supporting the pharmacophore model that has been proposed to explain the interaction of glycine antagonists with the glycine receptor.

REFERENCES AND NOTES

1. Meldrum, B.S. (Ed.). *Excitatory Amino Acid Antagonists*, Blackwell, Oxford, **1991**.
2. (a) Kemp, J.A.; Leeson, P.D. *Trends Pharm. Sci.*, **1993**, *14*, 20.
   (b) Leeson, P. D.; Iversen, L. L. *J. Med. Chem.*, **1994**, *37*, 4053.
3. 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. Carling, R.W.; Leeson, P.D.; Moseley, A.M.; Baker, R.; Foster, A.C.; Grimwood, S., Kemp, J.A.; Marshall, G.R. *J. Med. Chem.*, **1992**, *35*, 1942.
5. Salituro, F.G; Harrison, B.L.; Baron, B.M.; Nyce, P.L.; Stewart, K.T.; Kehne, J.H.; White, H.S.; McDonald, I.A. *J. Med. Chem.*, **1990**, *33*, 2944.
6. 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. *J. Med. Chem.*, **1993**, *36*, 3386.
7. (a) McQuaid, L.A.; Smith, E.C.R.; Lodge, D.A.; Pralong, E.; Wikel, J.H.; Calligaro, D.O.; O'Malley, P.J. *J. Med. Chem.*, **1992**, *35*, 3423.
   (b) Leeson, P.D.; Carling, R.W.; Kulagowski, J.J.; Mawer, I.M.; Moore, K.W.; Moseley, A.M.; Rowley, M.; Smith, J.D.; Stevenson, G.I.; Williams, B.J.; Baker, R.; Foster, A.C.; Kemp, J.A.; Tricklebank, M.D. *Perspectives in Medicinal Chemistry*, (Ed. Testa, B.; Kyburz, E.; Fuhrer, W.; Giger, R.), Verlag Helvetica Chimica Acta, **1993**, 239.
8. Sussman, J.L.; Harel, M.; Frolow, F.; Oefner, C., Goldman, A.; Toker, L.; Silman, I. *Science*, **1991**, *253*, 872.
9. 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. *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 299.
10. Kulagowski, J.J.; Baker, R.; Curtis, N.R.; Leeson, P.D.; Mawer, I.M.; Moseley, A.M.; Ridgill, M.P.; Rowley, M.; Stansfield, I.; Foster, A.C.; Grimwood, S.; Kemp, J.A.; Marshall, G.R.; Saywell, K.L.; Tricklebank, M.D., *J. Med. Chem.* **1994**, *37*, 1402.
11. Structures were built and minimized using Sybyl, Tripos Associates Inc., St. Louis. Minimum energy conformations were used for all superpositions.
12. Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis*, **1984**, 53.
13. Grimwood, S., Moseley, A.M., Carling, R.W.; Leeson, P.D.; Foster, A.C. *Mol. Pharmacol.*, **1992**, *41*, 923.
14. 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., *Mol. Pharmacol.*, **1992**, *41*, 914.
15. Rowley, M., Leeson, P., Grimwood, S., Marshall, G., Saywell, K., *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 2089.

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