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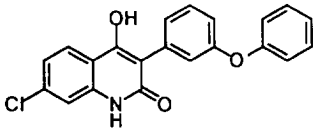
5,6,7,8-TETRAHYDROQUINOLONES AS ANTAGONISTS AT THE GLYCINE SITE OF THE NMDA RECEPTOR.

Michael Rowley,* Paul Leeson, Sarah Grimwood, George Marshall, and Kay Saywell
Merck Sharp and Dohme, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK.

Abstract The effect of reducing the benzo ring of a series of 4-hydroxyquinolone Glycine/NMDA antagonists is described. It is important that the ring be present, but not that it is aromatic. Provided that the correct lipophilic interactions are present, high affinity is found in 4-hydroxy-5,6,7,8-tetrahydroquinolones.

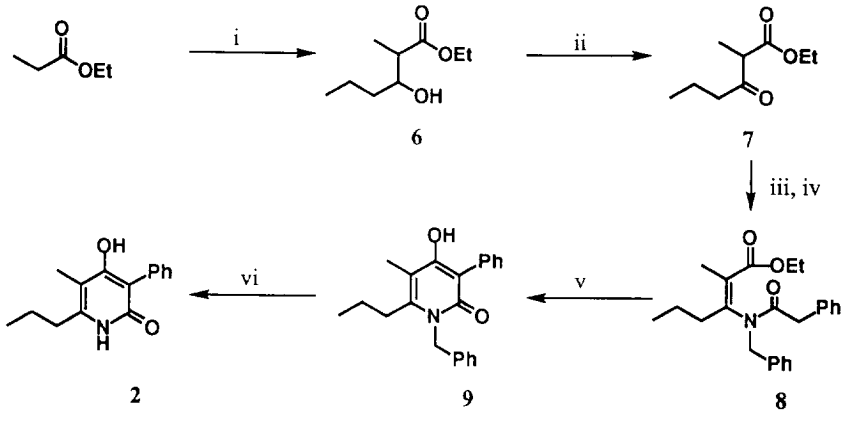
Over the last few years, a great deal of evidence has been accumulated that over-activation of the N-methyl-D-aspartate (NMDA) subtype of central excitatory amino acid receptor plays a role in a number of neurodegenerative disorders.[1,2] These include the delayed neuronal loss following cerebral ischaemia, epilepsy, Alzheimer's disease, and AIDS related dementia. NMDA antagonists may therefore be therapeutically useful, as they have been shown to be anticonvulsant and neuroprotective in animal models. We have been interested for some time in antagonists at the glycine binding site of this receptor, at which the binding of glycine is obligatory for receptor activation.[3] We have recently described[4,5] a series of 3-phenyl-4-hydroxyquinoline-2(1*H*)-ones typified by **L-701,324**, as potent, orally active antagonists at the glycine binding site of the NMDA receptor. We now describe the effect of removing the benzo ring of these quinolones, and replacing it with alkyl chains, or with a reduced ring that fills the same space as the benzo ring but lacks the aromatic character.



L-701,324

Pyridone (**2**) was made by the route shown in Scheme 1. Condensation of ethyl propionate with butyraldehyde gave the aldol product (**6**), which was oxidised to β-keto ester (**7**). The enamine was formed[6] by treatment with benzylamine in refluxing toluene, and acylated using phenylacetyl chloride without purification to give the amide (**8**). This was cyclised using sodium and a catalytic amount of ethanol, again in refluxing toluene. Removal of the benzyl group from the pyridone nitrogen of **9** required forcing conditions: hydrogenation on Pearlman's catalyst in ethanol at 50 psi and 100 °C completed the removal.

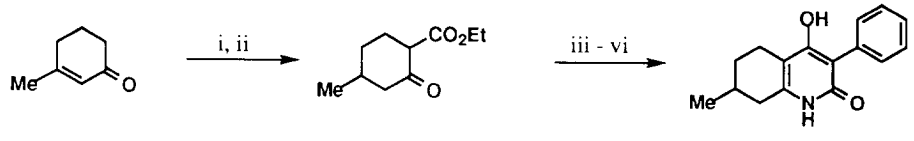
Scheme 1



Reagents: i) LDA, $CH_3CH_2CH_2CHO$, THF, -78°C, 99%; ii) PCC, CH_2Cl_2, rt, 60%; iii) $PhCH_2NH_2$, toluene, reflux; iv) $PhCH_2COCl$, CH_2Cl_2, rt, 14%; v) Sodium (1.1 equiv), EtOH (0.1 equiv), toluene, reflux, 26%; vi) H_2, $Pd(OH)_2$, EtOH, 50 psi, 100 °C, 2 h, 96%

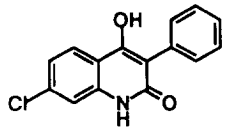
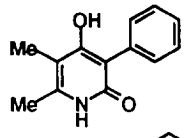
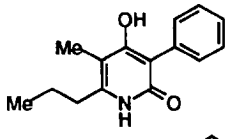
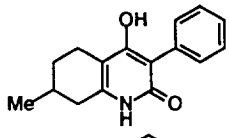
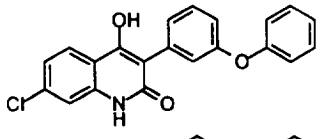
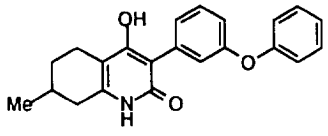
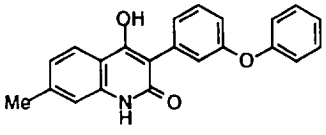
The tetrahydroquinolone (**3**) was synthesised using the route shown in Scheme 2 starting from 3-methyl-2-cyclohexenone (**10**). Carboxylation with lithium dicyclohexylamide and diethylpyrocarbonate, followed by hydrogenation gave the β-ketoester (**11**) largely as a single diastereoisomer. This was converted to the target compound (**3**) using the same conditions as above.

Scheme 2



Reagents: i) $(EtOCO)_2O$, $(c\text{-}C_6H_{11})_2NLi$, -78°C, 49%; ii) H_2 / Pd / C, 89%; iii) $PhCH_2NH_2$, toluene, reflux; iv) $PhCH_2COCl$, $ClCH_2CH_2Cl$, rt, 49 %; v) Na, cat. EtOH, toluene, reflux, 42%; vi) H_2 / $Pd(OH)_2$ / C 50 psi, 100 °C, 41%.

Other analogues (**1** and **4**) were made in a similar way. Compounds were evaluated for their ability to displace [^{3}H]-L-689,560 binding from rat cortical membranes[7] (IC_{50} values), antagonize NMDA induced responses in rat cortical slice[8] (apparent K_b values), and protect against audiogenic seizure in DBA/2 mice.[9]

Number	Structure	IC_{50} (μM) vs [^{3}H]-L-689,560	ED_{50} (mg/kg)[a] DBA/2 mouse or protected / tested[b]
L-698,532		0.17	4.5
1		> 100	
2		≈ 100	
3		3.5	8/8 @ 20 mg/kg 1/8 @ 10 mg/kg
L-701,324		0.002	0.88
4		0.057	1/8 @ 10 mg/kg
5		0.020	4/8 @ 10 mg/kg

a) Calculated ED_{50} (mg/kg ip) 30 min b) Number protected / number tested @ stated dose

Removal of the ring altogether (**1**) abolishes affinity. When a propyl group is introduced to the 6-position of the pyridone (**2**), which can access the lipophilic binding region used by the 7-chlorine atom in the quinolones, typified by **L-698,532**, there is some affinity (IC_{50} 100μM), although weak. This is improved when the chain is conformationally restrained into a six membered ring (**3**), and the methyl group is forced to

occupy the same space as the chlorine atom (assuming the methyl group is equatorial). In the 3-phenylquinolone series binding could be dramatically improved by addition of a 3' substituent on the benzene ring (**L-701,324**)[4]. This is also the case here, with the 3'-phenoxyphenyltetrahydroquinolone (**4**) having an affinity of 57 nM, comparable to the 7-methylquinolone (**5**, IC_{50} 20 nM). The reduction in affinity with replacement of a 7-chloro with a 7-methyl group is precedented for kynurenic acids.[10] This indicates that the aromatic and reduced series are binding in the same way to the glycine site.

These tetrahydroquinolones are antagonists at the NMDA receptor, with K_b's for **3** and **4** of 3.7 and 0.35 μM respectively in the cortical slice assay.

Although high affinity can be found with these tetrahydroquinolones, *in vivo* activity is poor. Despite having an affinity of 57 nM for the glycine binding site, **4** does not protect DBA/2 mice against audiogenic seizure when dosed at 10 mg/kg ip. There is a 30 fold reduction in affinity in moving from **L-701,324** to **4**, which plays a part in this loss of anticonvulsant activity, but other factors may well also be involved.

It is clear therefore that it is not the aromatic nature of the benzo ring of the quinolone Glycine/NMDA antagonists that is important for their binding to the receptor, but rather the lipophilicity of this portion of the molecule. By comparing **4** and **5** it can be seen that when the rest of the molecule is optimised, reduction of the benzo ring produces almost no lowering in binding affinity to the glycine site.

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