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2-CARBOXY INDOLINES AND INDOLES AS POTENTIAL GLYCINE/NMDA ANTAGONISTS: EFFECT OF FIVE-MEMBERED RING CONFORMATION ON AFFINITY.

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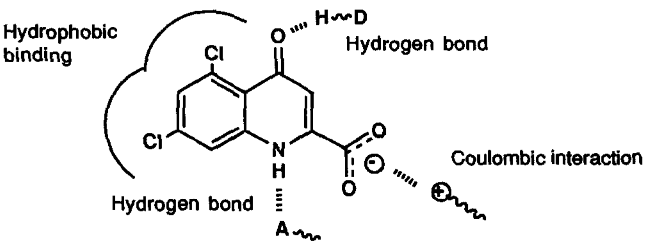
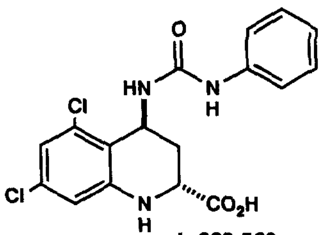
Abstract. 2-Carboxy indolines were synthesised as potential antagonists at the glycine site of the NMDA receptor, based on a pharmacophore developed from other series. None of the indolines had significant potency, possibly due to the lack of coplanarity of the carboxyl with the aromatic ring. The corresponding indoles are potent antagonists, as exemplified by **19**, IC_{50} 27 nM.

During the course of our work on the synthesis of glycine/NMDA site antagonists for the treatment of cerebral ischaemia,[1-3] we developed a pharmacophore model for kynurenic acid based compounds which is illustrated in Figure 1. The key features of this pharmacophore are size limited hydrophobic binding of the substituted benzene ring, the N-H as a hydrogen bond donor, a hydrogen bond accepting group in the 4-position, and a coulombic interaction with the 2-carboxylate.

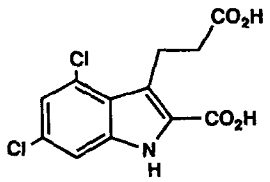
Figure 1



2-Carboxytetrahydroquinolines[1] (as exemplified by L-689,560), and indoles[4,5] (e.g.**1**) can be fitted to this pharmacophore. We have shown[3] that the unsaturation in the heterocyclic ring of kynurenic acids is not important for activity, and wished to explore the effect of hydrogenation of the C-2 C-3 bond of the indoles on conformation and affinity, whilst maintaining the key features of the pharmacophore, by making the corresponding indolines.



L-689,560



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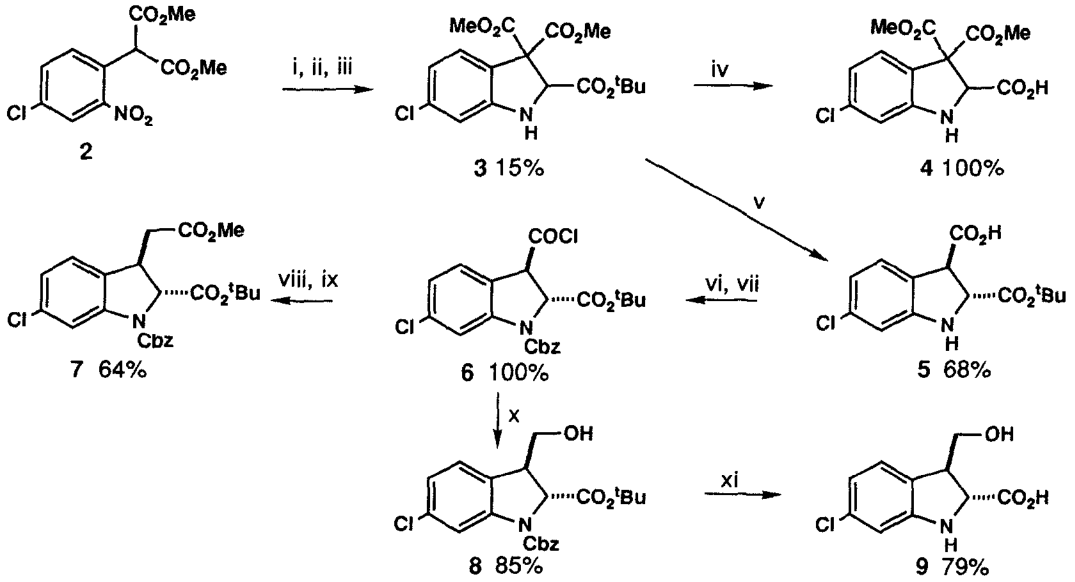
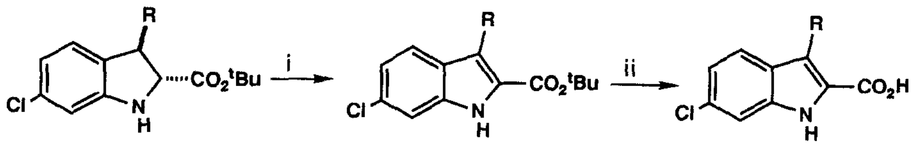
Compounds targetted were 2-carboxy-6-chloroindolines with a variety of hydrogen bond accepting groups attached to the 3-position. This type of compound was not known in the literature, so a route was devised starting from the nitroaryl malonate (**2**). Reduction of the nitro group with hydrogen, immediate formation of the imine with *t*-butyl glyoxalate, and *in situ* cyclisation gave the indoline triester (**3**). The *t*-butyl ester could be removed selectively with TFA to give the acid (**4**), or the methyl esters saponified with spontaneous decarboxylation, to give the *trans*[6] acid (**5**). After protection of the nitrogen as its benzyloxycarbamate, 5 could be converted to the acid chloride (**6**) and subjected to Arndt-Eistert homologation to the acetic ester (**7**). Alternatively, the acid chloride could be reduced to alcohol (**8**), followed by removal of both protecting groups with hydrogen bromide in acetic acid to give acid (**9**). Other compounds in Table 1 were made by routine manipulation of these intermediates.



Reagents i) H_2/Pd/C; ii) $OHCCO_2{}^tBu$; iii) NaOMe, MeOH; iv) CF_3CO_2H; v) LiOH, THF/H_2O; vi) $PhCH_2OCOCl$; vii) $(COCl)_2$; viii) CH_2N_2; ix) AgOCOPh, MeOH; x) Bu_4NBH_4; vi) HBr/AcOH

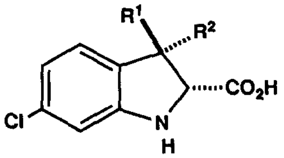
The indolines could be oxidised to the corresponding indoles with benzene selenenic anhydride.[7]



Reagents: i) $(PhSeO)_2O$; ii) CF_3CO_2H

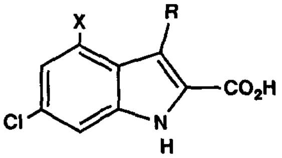
As can be seen from the results in Table 1, none of the indolines had significant affinity for the glycine/NMDA site, despite positioning of a carbonyl group as a hydrogen bond acceptor either directly attached to the 3-position (**4**, **10-12**) or with one (**13**) or two (**14**) atom spacers. Since the position of this hydrogen bonding group can be varied widely in other series,[1-5] it seem unlikely that this interaction is not accessed by one of the compounds in this series. A possible explanation for the lack of activity is suggested by molecular modelling: in the active series of compounds the 2-carboxylate can be coplanar with the benzene ring (Fig. 2)(in the tetrahydroquinolines the 4-substituent is axial and the carboxylate equatorial). Due to conformational effects of the five-membered ring the 2-carboxylate of the indolines is forced to be out of this plane (Fig. 3) and therefore cannot interact advantageously with the receptor. The best illustration of this is to compare the 3-carboxamides (**12** and **16**), where the former is not active, and the latter has submicromolar affinity.

Table 1 Indolines



No.	R^1	R^2	IC_{50} (μM)*
4	CO_2Me	CO_2Me	>100
9	CH_2OH	H	>100
10	CO_2Me	H	>300
11	CO_2H	H	>100
12	$CONH_2$	H	>100
13	CH_2CO_2H	H	>100
14	CH_2OCOPh	H	>100

Table 2 Indoles



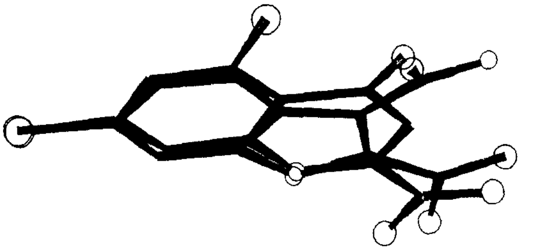
No.	R^1	X	IC_{50} (μM)*
15	CH_2OH	H	9.0
16	$CONH_2$	H	0.81
17	CH_2CO_2Me	H	1.78
1	$CH_2CH_2CO_2H$	Cl	0.07
18	$CH_2CH_2CONHPh$	Cl	0.036
19	$(CH_2)_2CONH(4\text{-}NH_2CH_2Ph)$	Cl	0.027

* Inhibition of [^{3}H]-L-689,560 binding[8] in rat cortical membranes

At the time this work was done Salituro[4] and Gray[5] had not published their work on indoles, and, as them, we found that acetic or propionic residues in the 3-position gave optimal affinity. In order to access the lipophilic binding seen in the tetrahydroquinolines we also synthesised aryl amides of the propionic acid. The 4-aminomethylphenyl amide (**19**) has a 2-3 fold improvement in the binding assay over the corresponding acid, showing that lipophilic binding can be found.

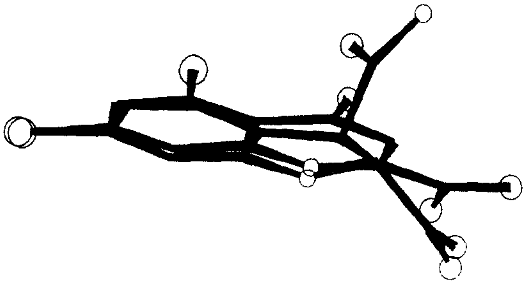
None of the acids had *in vivo* activity in the DBA/2 mouse audiogenic seizure model, probably due to their polar nature. The 2-ethyl esters of **1** and **19** were made as prodrugs, with the former protecting 6/8 animals when dosed at 100 mg/kg i.p. but 0/8 at 50 mg/kg, and the latter gave only 1/8 protected at 100 mg/kg i.p.

Figure 2



Overlay of **16** with 5,7-dichlorokynurenic acid.[9] The hydrogens have been removed for clarity.

Figure 3



Overlay of **12** with dichlorokynurenic acid.[9] The angle between the C-2 - carboxylate carbon bond and the plane of the aromatic ring is 39.9°.

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