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Unusual Synthesis of New Glycine Antagonists *via* Sequential Aldol Condensation-Lactonization-Elimination Reaction

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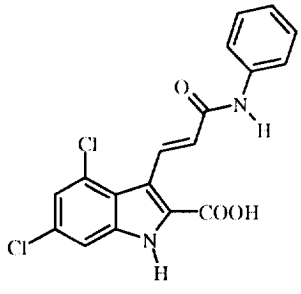
Abstract: Compounds **2** and **3** were designed in order to probe the North-East region of the strichnine-insensitive glycine binding site of the NMDA receptor. The two products were obtained readily by a tandem aldol condensation-lactonization-elimination step which affords the desired E isomer with complete regioselection.© 1998 Elsevier Science Ltd. All rights reserved.

Neurons are highly vulnerable to the very signaling mechanisms that support their ability to receive, process and relay information. Neuronal damage[1] can result from excessive exposure to excitatory amino acids (EAA) and from ingress of abnormally high amounts of Ca^{2+}. Indeed, several pathological conditions of the Central Nervous System, such as stroke[2], Huntingdon's desease[3], Alzheimer desease[4] and neurotrauma[5] seem to involve, among other factors, the over-activation of the receptor subtype responding to the exogenous agonist N-Methyl-D-Aspartic acid (NMDA)[6]. This receptor, and in particular the modulatory glycine binding site associated with it[7], is now widely recognized as being a potentially attractive target for curative as well as preventive therapy against stroke.



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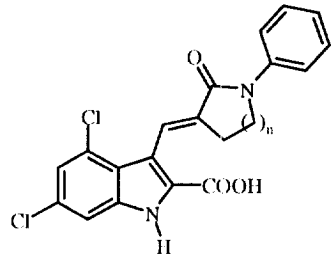

2 (n=1)
3 (n=2)

Figure 1

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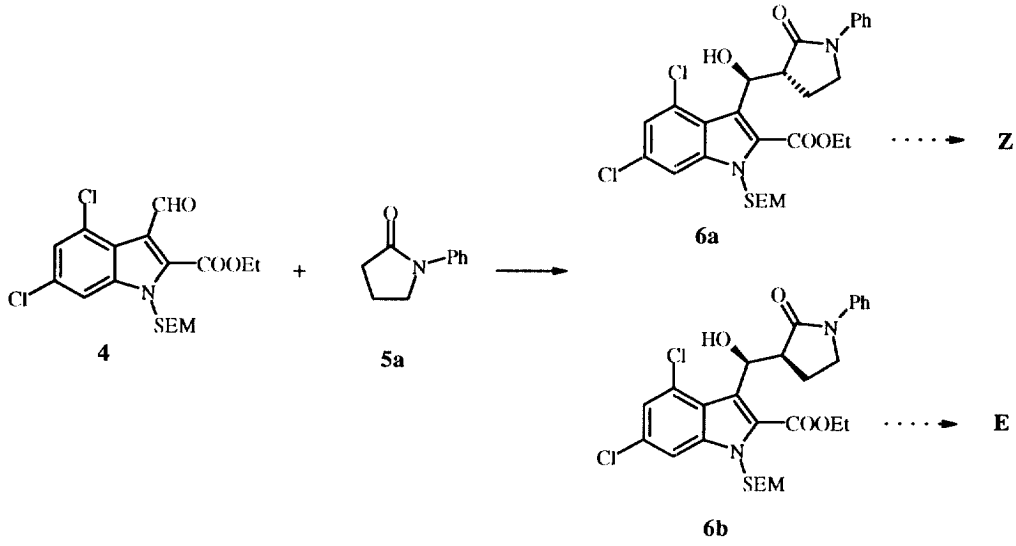
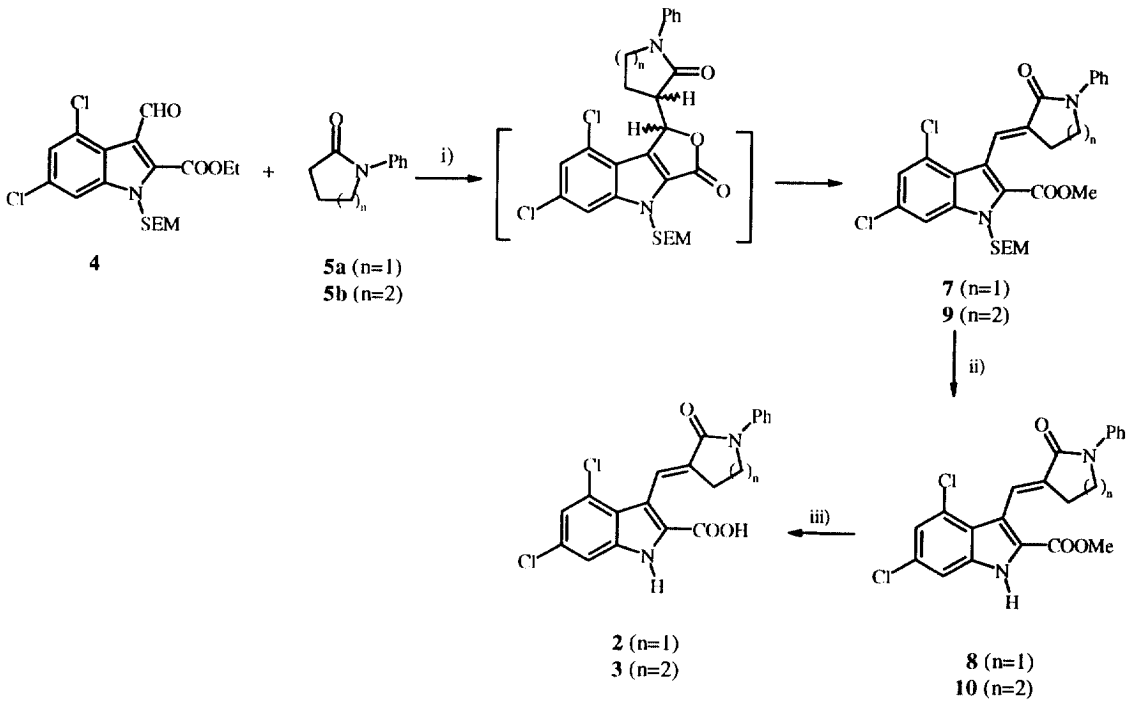
A long effort conducted in our laboratories[8] over the last few years has resulted in the identification of 2-carboxy indole derivative **1**[9] (GV150526) as a potent and selective antagonist acting at the glycine binding site associated with the NMDA receptor site. With the aim of better defining the shape of the "North-Eastern" region of the receptor binding pocket, compounds **2** and **3** (Figure 1) were synthesized as reported in Scheme 2. Our starting plan was to build the exocyclic double bond by way of an aldol condensation-elimination starting from known aldehyde **4**[10]. The choice of the protection of the indole nitrogen was crucial to the success of the synthesis: the SEM protecting group[11] was selected in view of its stability under basic conditions. In the first attempt, the Li enolate of N-phenylpyrrolidone, prepared by treatment of **5a** with a stoichiometric amount of t-BuLi for 1.5 h, was reacted with **4** in THF at -78°C, resulting in a 3/2 mixture of aldol products **6a** and **6b** in 60% cumulative yield (Scheme 1).



Scheme 1

When the condensation was repeated and the temperature was allowed to increase from -78°C to 20°C, a single, polar compound was produced, based on HPLC analysis. After treatment with $TMSCHN_2$ in CH_2Cl_2/MeOH 4:1 as solvent and purification by column chromatography, the product was identified as pure **7**[12], isolated in 57% overall yield. As shown in Scheme 2, the formation, after esterification, of derivative **7** can occur only if the intermediate aldol products **6a,b** cyclize during warm up to the corresponding lactones. As a matter of fact, these intermediates were observed on the HPLC between -50°C and 0°C. Following the cyclization, an elimination step leads to the olefin. This elimination may go either *via* a concerted mechanism or *via* a "benzylic-like" cation followed by proton abstraction by the LiOEt present in the reaction mixture. In the first case, a simple inspection of the Newman projections along the C^{α}-C^{β} bond showed that the *syn* lactone should afford the E double bond, whereas the *anti* lactone should give the Z double bond (Scheme 1). On the contrary, the second route could in principle give only one product if a conformational rearrangement occurs at the "cation" level. However, at this time we do not have any proof that supports either mechanism.

Starting from **7**, the first target product **2** was smoothly obtained by removal of the SEM protecting group under acidic conditions (HCl 6N, EtOH, 60% yield) followed by LiOH hydrolysis of the ester (83% yield).
The same reaction protocol was successfully followed for the preparation of **3**. Condensation of **4** with the Li enolate of N-phenyl-valerolactam **5b**[13] (prepared as described above) at -78°C gave a 3/1 mixture of anti/syn aldols, which upon warming afforded **9** in 65% isolated yield. As before, removal of the SEM protection (90% yield) and of the methyl ester (85% yield) gave the desired target **3**[14] in excellent overall yield.



i) **5a** or **5b**, t-BuLi, -78°C, THF, 3h; $(Me_3Si)CHN_2$, CH_2Cl_2/MeOH 4:1, 30 min, rt; ii) HCl. EtOH, reflux, 10h; iii) LiOH, EtOH, reflux, 1.5 h.

Scheme 2

The *in vitro* affinity of **2** and **3** for the glycinergic site was assessed by inhibition of the binding of [^{3}H]glycine.[15] Both compounds display nanomolar affinity (pKi=7.5 and 7.3 respectively, compared to pKi=8.5 for GV150526 **1**), thereby hinting that rigidification of the α,β–unsaturated side chain is tolerated.
In conclusion, a very simple and mechanistically novel reaction on an indole template has allowed us to prepare the first molecules belonging to a new class of conformationally restricted analogues of compound **1**.

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10. Aldehyde **4** is readily available from 3,5-dichloro-phenylhydrazine and ethyl pyruvate following a known procedure. See Shabica, C., et al. *J. Am. Chem. Soc.* **1946**, *68*, 1156.
11. Aldehyde **4** was converted into **4a** by treatment with NaH and SEMCl in DMF at 0°C.
12. ^{1}H NMR 300 MHz δ (DMSO) 13.6 (bs, 1H), 12.44 (s, 1H), 7.81 (d, 1H), 7.72 (t, 1H), 7.47 (d, 1H), 7.42 (t, 2H), 7.26 (d, 1H), 7.18 (tt, 1H), 3.88 (t, 1H), 2.67 (td, 1H); IR (Nujol) ν_{max} (cm^{-1}) 3281, 1682, 1630; MS (FAB) *m/z* (^{35}Cl) 401 [M+H]$^+$.
13. **5b** was obtained from commercially available δ-valerolactone by ring-opening with aniline (neat, 100°C) followed by bromination (CBr_4, PPh_3, DMF, 0°C) and ring closure (EtONa, EtOH, 60°C).
14. ^{1}H NMR 300 MHz δ (DMSO) 13.43 (bs, 1H), 12.36 (bs, 1H), 7.89 (bt, 1H), 7.43 (d, 1H), 7.37 (m, 4H), 7.24 (m, 1H), 7.21 (d, 1H), 3.71 (t, 2H), 2.39 (td, 2H), 1.85 (m, 2H); IR (Nujol) ν_{max} (cm^{-1}) 3294, 1670, 1645; MS (FAB) *m/z* (^{35}Cl) 415 [M+H]$^+$.
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