Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1689–1692

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

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

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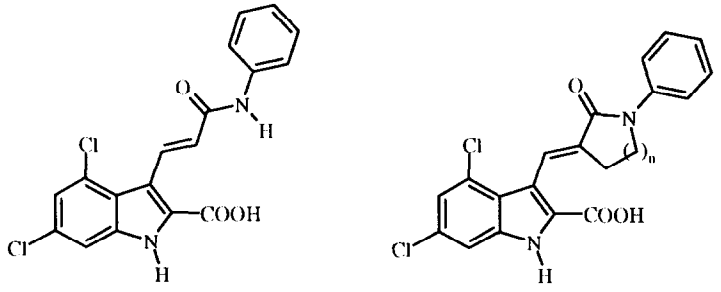
Received 3 April 1998; accepted 28 May 1998

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.

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.



1

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

Figure 1

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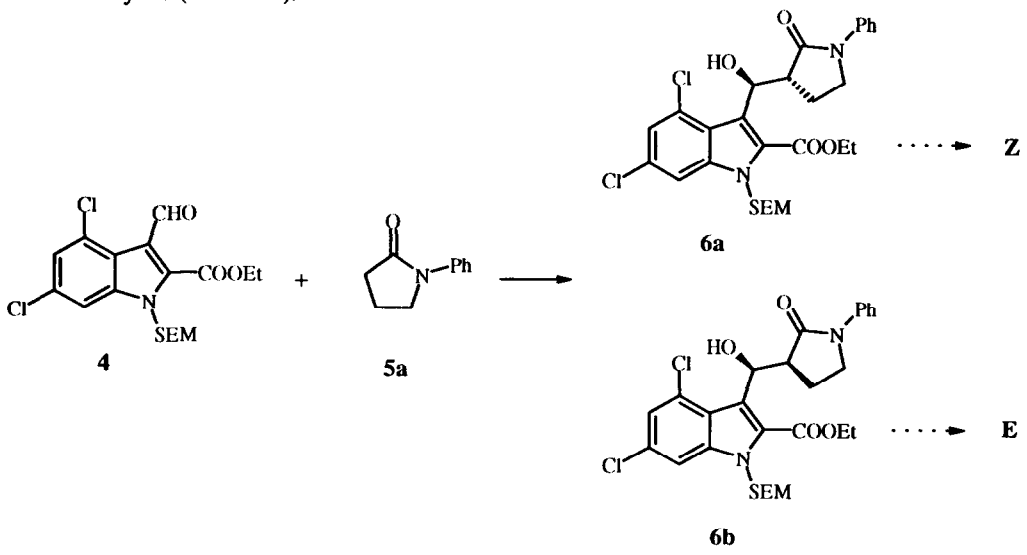
0960-894X/98/$19.00
PII: S0960-894X(98)00284-4

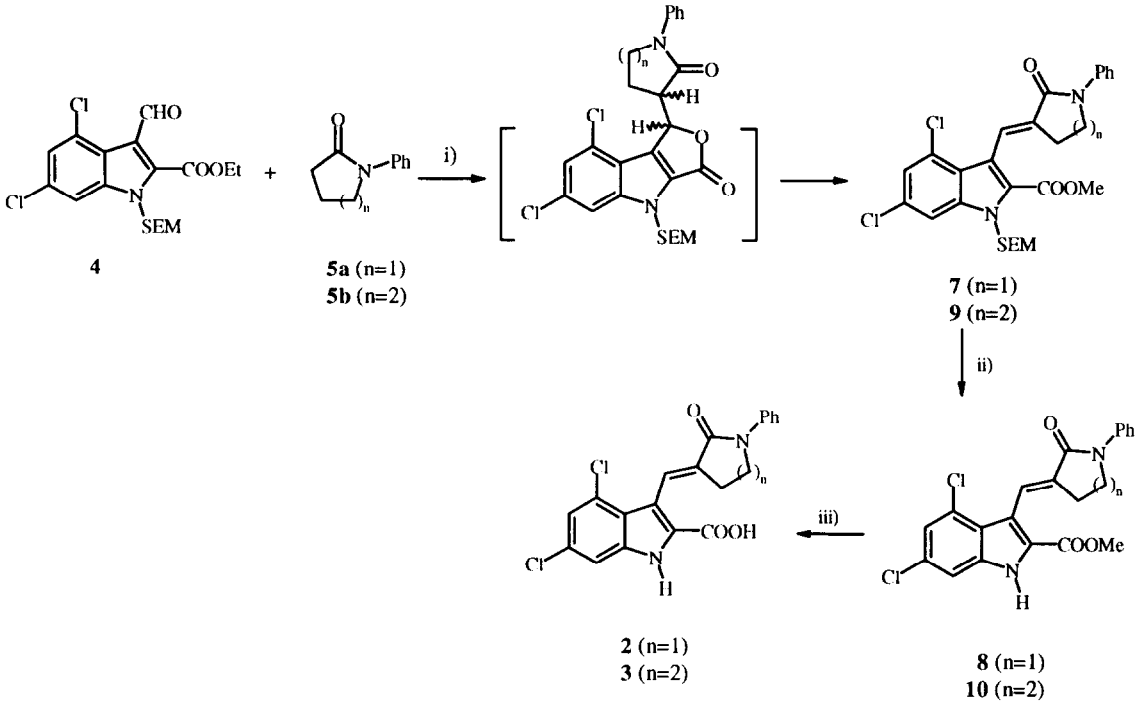
A long effort conducted in our laboratories[8] over the last few years has resulted in the identification of 2-carboxy indole derivative **1**[9] (GV150526) as a potent and selective antagonist acting at the glycine binding site associated with the NMDA receptor site. With the aim of better defining 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}-$C\beta$ 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**.

Acknowledgements: The authors would like to thank the personnel of the Mass Spectrometry Laboratory, the NMR Spectroscopy Laboratory and the Chemical Analysis Laboratory of GlaxoWellcome for spectral and other analytical data. We would also like to thank Dr Aldo Feriani for the Molecular Modeling studies.

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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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