Pergamon

Tetrahedron Letters 42 (2001) 3227–3230

TETRAHEDRON LETTERS

Efficient synthesis of novel benzo-[*e*]-[1,4]-diazepine derivatives

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Received 25 January 2001; revised 1 March 2001; accepted 8 March 2001

Abstract—Following two efficient synthetic routes a novel series of benzo-[*e*]-[1,4]-diazepine derivatives, bearing an unusual *Z exo*-methylencarbamoyl side chain at the C-5 position, have been prepared to identify new antagonists of the glycine binding site associated with NMDA receptor. © 2001 Published by Elsevier Science Ltd.

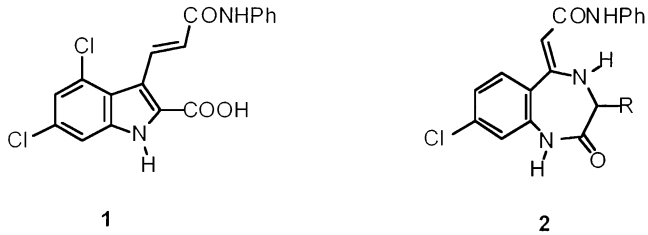
The role of excitatory amino acids (EAA) in pathological conditions, such as stroke, head trauma and neuronal spinal injury has been widely investigated.[1] In particular, the overstimulation of the *N*-methyl-D-aspartate (NMDA) receptor, through the modulation of the glycine binding site, has been proposed as a useful way forward to counteract excitotoxicity.[2] In this event, different classes of glycine antagonists[3] have been investigated in the last decade as potential neuroprotective agents. Our recent exploration of the indole-2-carboxylate template resulted in the identification of potent glycine antagonist compounds.[4,5] In particular, GV150526A **1**, shown in Fig. 1, reached phase III clinical trials in man as a potential anti-stroke agent.

To identify new glycine antagonists, novel benzodiazepine derivatives of general structure **2** (Fig. 1), bearing a *Z exo* α-β-unsaturated side chain in the position C-5, were designed by receptor mapping techniques based on the known pharmacophore model of the glycine binding site.[4b]

To prepare this novel template two synthetic strategies, shown in Schemes 1 and 3, respectively, were explored. In the first route (Scheme 1) the key intermediate **6** was obtained from the commercially available benzoic acid derivative **3** in a three-step sequence and high total yield. Reaction of the acyl chloride derived from **3** with the potassium salt of the mono ethyl malonate ester in the presence of $MgCl_2$ and TEA[7] gave compound **4**,[8] which was reacted with aniline in *m*-xylene at reflux to give the corresponding amide **5**. Finally, reduction of the nitro group afforded the desired aniline derivative **6** quantitatively.

To prepare the first compound of the series, the C-3 unsubstituted compound **2a**, reaction of **6** with bromoacetyl bromide in the presence of pyridine gave compound **8a** which was then transformed into the corresponding azido derivative **9a** in 50% yield. The crucial cyclization step was accomplished either by an *aza*-Wittig type reaction in the presence of PPh_3 or by catalytic hydrogenation, followed by the in situ cyclization of the amino intermediate to give, in both cases, **2a** in good yield as a chemically stable compound. Remarkably, the cyclization reaction proceeded with complete stereocontrol in the formation of the double bond, to give the desired *Z-exo*-2-carbamoylmethylene side chain only.[9]

To prepare C-3 substituted derivatives, the amidation reaction was repeated with racemic N-Cbz amino acids **7b–f**,[10] activated as acyl chlorides, affording derivatives **8b–f** in variable yields. The one-pot removal of the N-CBz protecting group, followed by cyclization of compounds **8b–f**, gave the *Z-exo* benzodiazepines **2b–f** in good yield, confirming the previous observation in terms of chemical stability of the *exo* derivatives with



1 2

Figure 1.

Keywords: glycine antagonists; synthesis; benzo-[*e*]-[1,4]-diazepines.

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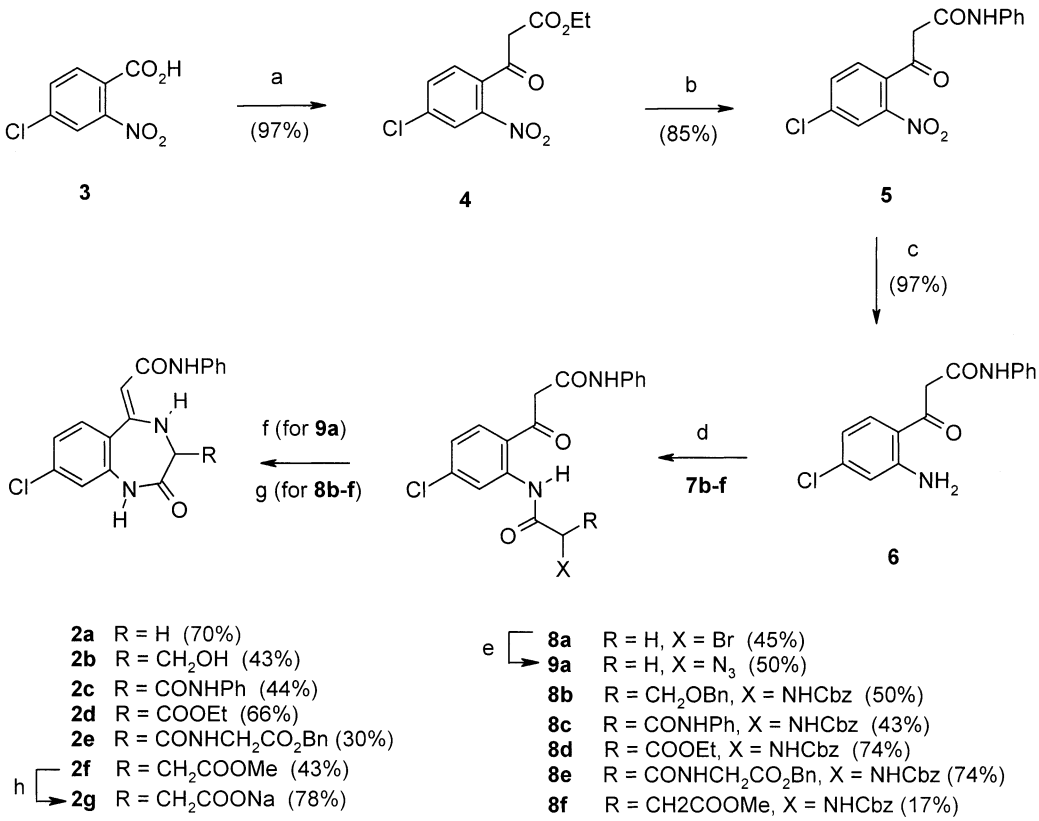
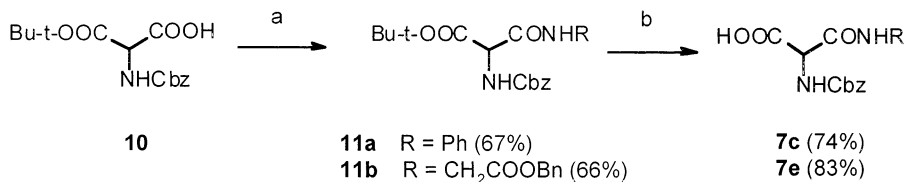
PII: S0040-4039(01)00402-6



Scheme 1. (a) $SOCl_2$, then $EtOOCCH_2COOK$, $MgCl_2$, Et_3N, CH_3CN; (b) $PhNH_2$, *m*-xylene, reflux; (c) Fe, $CaCl_2$, EtOH; (d) $BrCH_2COBr$, Et_2O (for **8a**) or RCHXCOOH (**7b–f**), PCl_5, THF/pyridine; (e) NaN_3, DMSO; (f) PPh_3, THF or $Pd/CaCO_3$, H_2 (1 atm), MeOH; (g) HBr/AcOH, CH_2Cl_2 or TMSBr, $PhSCH_3$; (h) Me_3SiONa, THF.[6]



Scheme 2. (a) RNH_2, EDCl, HOBT; (b) HCOOH (for **11a**) or TFA/CH_2Cl_2 (for **11b**).

respect to the corresponding *endo* analogues, which were never isolated.

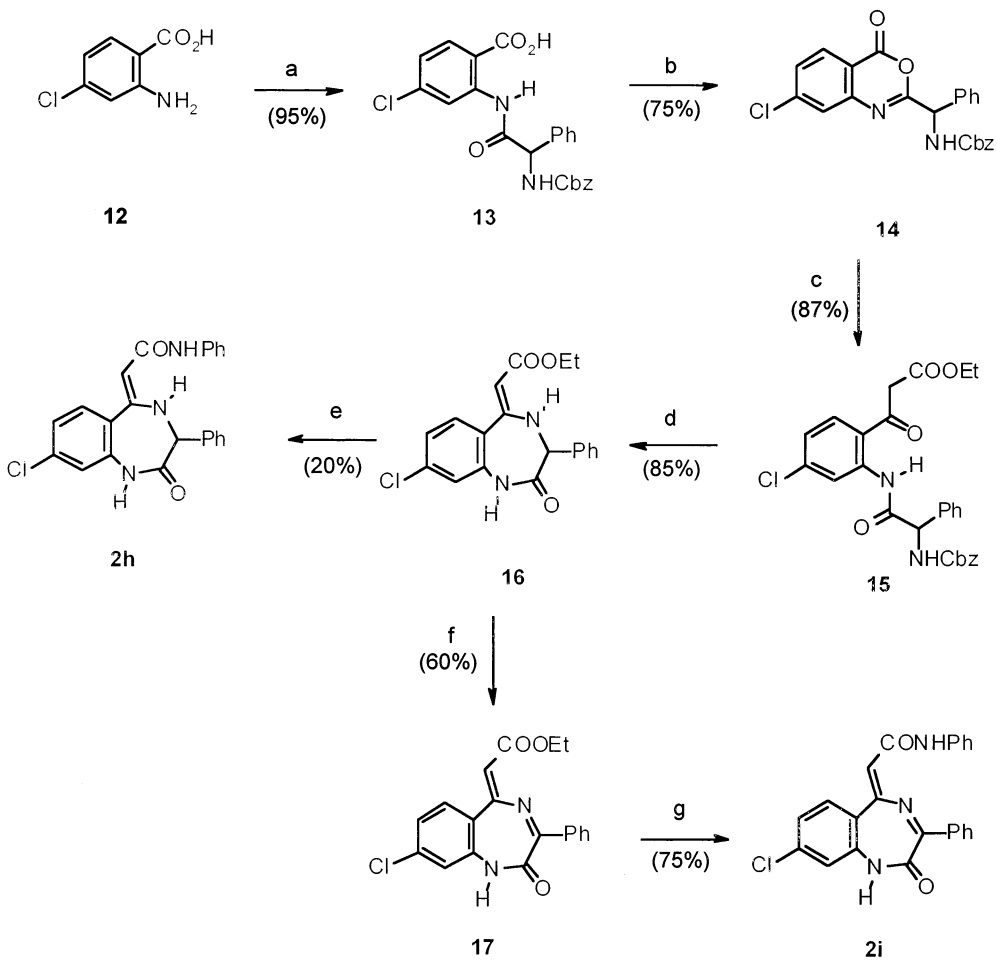
The synthesis of the unnatural aminoacids **7c** and **7e** is shown in Scheme 2. Thus, formation of the desired amides of aminomalonate monoester **10**,[11] followed by acid hydrolysis of the *t*-butyl ester afforded the final intermediates **7c** and **7e**.

A different approach for the synthesis of this novel class of benzodiazepine derivatives was also developed. As an example, the preparation of the C-3 phenyl derivative **2h** is described in Scheme 3. Commercially available 5-chloro-2-amino benzoic acid **12** was reacted with racemic N-Cbz-phenylglycine to obtain the amido derivative **13**. When this intermediate was heated in acetic anhydride, benzoxazinone intermediate **14** was obtained in high yield. Reaction with the potassium salt of the mono ethyl malonate ester in the presence of TEA and $MgCl_2$ gave the key β-ketoester derivative **15** in high yield.[12]

After deprotection of the amine moiety, the free amino derivative cyclized under mild acid conditions (AcOH or SiO_2) to yield the benzodiazepine derivative **16**, which was then converted into the desired *N*-phenyl amide **2h** in the presence of aniline and $Al(CH_3)_3$.

The corresponding unsaturated derivative **2i** was obtained from compound **16** in two steps: reaction with MnO_2 to give the ethyl ester intermediate **17** followed by treatment with aniline and $Al(CH_3)_3$. It is worth underlining that when the same oxidation reaction was carried out on compound **2h** a complex mixture of by-products was obtained.

In summary, two efficient synthetic routes have been developed to prepare a series of novel benzodiazepine derivatives,[13] bearing a chemically stable enamine *Z exo* double bond at position C-5, as compounds specifically designed to identify new classes of glycine antagonists.



Scheme 3. (a) PhCH(NHCbz)COCl, THF; (b) Ac_2O; (c) $EtOOCCH_2COOK$, $MgCl_2$, Et_3N, CH_3CN; (d) HBr/AcOH, CH_2Cl_2, then AcOH or SiO_2, EtOAC; (e) $PhNH_2$, $Al(CH_3)_3$, *m*-xylene/CH_2Cl_2; (f) MnO_2, toluene; (g) $PhNH_2$, $Al(CH_3)_3$, toluene.

Acknowledgements

The authors would like to thank Dr. C. Marchioro and her group for the ^1H NMR spectra and Dr. M. Hamdan and his group for MS spectra.

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13. (**2a**) ^{1}H NMR (300 MHz) δ (DMSO-d_6): 10.30 (bs, 1H); 9.64 (t, 1H); 9.47 (bs, 1H); 7.58 (d, 1H); 7.56 (d, 2H); 7.30 (m, 1H); 7.23 (t, 2H); 7.15 (bs, 1H); 6.92 (t, 1H); 4.85 (s, 1H); 3.79 (bs, 2H); $[M+H]^+$ (m/z): 328. (**2b**) ^{1}H NMR (300 MHz) δ (acetone-d_6): 10.05 (d, 1H); 9.43 (s, 1H); 8.75 (s, 1H); 7.67 (d, 2H); 7.64 (d, 1H); 7.31(m, 1H); 7.30 (s, 1H); 7.25 (t, 2H); 6.96 (m, 1H); 4.94 (s, 1H); 4.10 (m, 1H); 4.00 (m, 1H); 3.97 (m, 1H); 3.92 (m, 1H); $[M+H]^+$ (m/z): 358. (**2c**) ^{1}H NMR (300 MHz) δ (DMSO-d_6): 10.66 (bs, 1H); 10.18 (bs, 1H); 10.12 (bd, 1H); 9.52 (bs, 1H); 7.66–7.52 (m, 5H); 7.37 (m, 1H); 7.33 (m, 2H); 7.24 (m, 2H); 7.21 (bs, 1H); 7.08 (m, 1H); 6.94 (m, 1H); 4.93 (s, 1H); 4.75 (bs, 1H); $[M+H]^+$ (m/z): 447. (**2d**) ^{1}H NMR (300 MHz) δ (acetone-d_6): 10.37 (bd, 1H); 9.56 (s, 1H); 8.83 (s, 1H); 7.68 (dd, 2H); 7.62 (d, 1H); 7.26 (m, 4H); 6.98 (tt, 1H); 5.03 (s, 1H); 4.92 (bs, 1H); 4.30 (bs, 2H); 1.28 (bs, 3H). $[M+H]^+$ (m/z): 401. **2e)** ^{1}H NMR (300 MHz) δ (DMSO-d_6): 10.57 (bs, 1H); 9.99 (bd, 1H); 9.50 (bs, 1H); 8.55 (bs, 1H); 7.57 (m, 2H); 7.44–7.10 (m, 10H); 6.93 (m, 1H); 5.13 (s, 2H); 4.90 (s, 1H); 4.64 (bs, 1H); 4.20–3.94 (m, 2H). $[M+H]^+$ (m/z): 520. (**2g**) ^{1}H NMR (300 MHz) δ (DMSO-d_6): 10.33 (bs, 1H); 9.52 (d, 1H); 9.20 (s, 1H); 7.53 (d, 2H); 7.38 (d, 1H); 7.18 (t, 2H); 6.86 (m, 3H); 4.68 (s, 1H); 3.86 (m, 1H); 2.50 (m, 1H); 2.10 (m, 1H). $[M]^+$ (m/z): 407. (**2h**) ^{1}H NMR (300 MHz) δ (acetone-d_6): 10.49 (bs, 1H); 9.48 (bs, 1H); 8.82 (bs, 1H); 7.65 (d, 2H); 7.64–7.28 (m, 8H); 7.26 (t, 2H); 6.97 (t, 1H); 5.29 (bs, 1H); 5.03 (s, 1H); $[M+H]^+$ (m/z): 404. (**2i**) ^{1}H NMR (300 MHz) δ (DMSO-d_6): 11.37 (bs, 1H); 10.09 (bs, 1H); 7.89 (d, 2H); 7.54 (d, 1H); 7.55–7.45 (m, 3H); 7.33 (dd, 1H); 7.30 (t, 2H); 7.24 (d, 1H); 7.02 (tt, 1H); 6.61 (d, 2H); 5.64 (s, 1H). $[M+H]^+$ (m/z): 402.