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Synthesis of enantiomerically pure fused polyheterocyclic glycolurils based on (*S*)-α-amino acids

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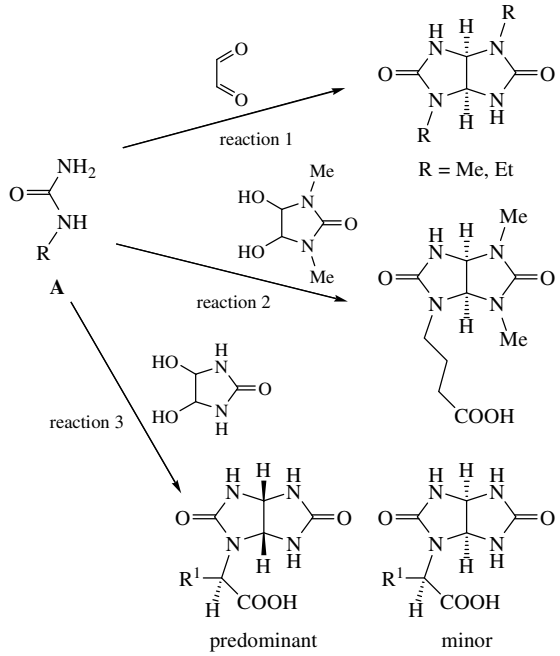
The synthesis of tetra- and pentacyclic fused heterocyclic systems based on the condensation of (*S*)-α-amino acids with achiral 2,4,6,8-tetra(hydroxymethyl)- and 1,5-butano-2,4,6,8-tetra(hydroxymethyl)glycolurils has been developed.

Previously, we found that optically pure glycolurils can be prepared by the conglomerate formation of 2,6-dimethyl-(diethyl)-[1,2] and 2-carboxypropylglycolurils[3] obtained by cyclocondensation of 1-methyl(ethyl)ureas with glyoxal[4] (reaction 1), by the α-ureidoalkylation of *N*-carbamoyl-γ-aminobutanoic acid involving 1,3-dimethyl-4.5-dihydroxyimidazolidin-2-one as an ureidoalkylating agent[3] (reaction 2), and using diastereoselective and diastereospecific syntheses from (*S*) or (*R*)-*N*-carbamoyl-α-amino acids and 4,5-dihydroxyimidazolidin-2-one[5,6] (reaction 3) (Scheme 1).†

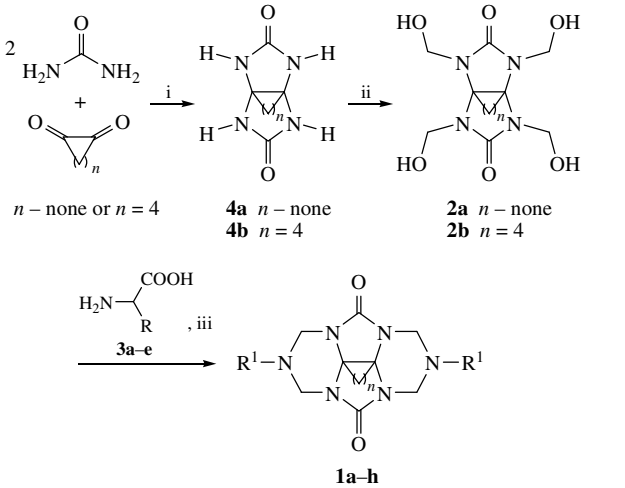
The addition of appropriate α-amino acid moieties to preformed achiral glycoluril moieties might be yet another method to obtain enantiomerically pure glycoluril derivatives. The purpose of this study was to develop a new method for the synthesis of enantiomerically pure fused tetra- and pentaheterocyclic compounds incorporating pharmacophoric moieties of glycoluril and (*S*)-α-amino acids by the condensation of achiral 2,4,6,8-tetra(hydroxymethyl)- and 1,5-tetramethyleno-2,4,6,8-tetra(hydroxymethyl)glycolurils with (*S*)-α-amino acids.

Similar reactions, which have been considered in the patent literature, are carried out by the condensation of 2,4,6,8-tetra(hydroxymethyl)- or 1,5-tetramethyleno-2,4,6,8-tetra(hydroxymethyl)glycolurils with achiral amino acids.[7–11] Therefore, in order to reach our goal, we studied the reactions of (*S*)-α-amino acids **3a–d** [Val (**3a**), Met (**3b**), *nor*-Val (**3c**), Trp (**3d**)] (as aqueous solutions of their potassium salts) with 2,4,6,8-tetra(hydroxymethyl)glycoluril **2a**, which was obtained similarly to a reported procedure[12] by N-hydroxymethylation of glycoluril **4a** synthesised from urea and glyoxal.[13] The syntheses of tetracyclic compounds **1a–d** were developed similarly to the reported procedure that we used previously;[11] the reaction time was varied from 1 to 2.5 h, and the temperature was 90 °C. The highest yields of tetracycles **1a–d** (45–82%) were obtained at a reaction time of 2 h (Scheme 2).



Scheme 1

† Only one of the possible enantiomers for reactions 1 and 2, as well as the diastereomers obtained from (*S*)-*N*-carbamoyl-α-amino acids (reaction 3) are shown in Scheme 1.



3a R = Pr^i
3b R = $(CH_2)_2SMe$
3c R = Pr
3d R = CH_2Ind
3e R = CH_2COOH

1a *n* – none, R^1 = (*S*)-CH(COOH)Pr^i
1b *n* – none, R^1 = (*S*)-CH(COOH)$(CH_2)_2SMe$
1c *n* – none, R^1 = (*S*)-CH(COOH)Pr
1d *n* – none, R^1 = (*S*)-CH(COOH)CH_2Ind
1e *n* = 4, R^1 = (*S*)-CH(COOH)Pr^i
1f *n* = 4, R^1 = (*S*)-CH(COOH)$(CH_2)_2SMe$
1g *n* = 4, R^1 = (*S*)-CH(COOH)Pr
1h *n* = 4, R^1 = (*S*)-CH(COOH)CH_2COOH

Scheme 2 *Reagents and conditions*: i, H_2O, H^+, reflux; ii, aq. CH_2O, pH 8.5, 90 °C, 1 h; iii, H_2O, KOH, 90 °C, 2 h.

It is well known that the annelation of a cyclohexane moiety to the molecule of a neurotropic compound expands the spectrum of its biological activity. For example, gabapentin, an analogue of GABA, is an efficient antiepilepsy drug also having an analgesic effect.[14,15] Furthermore, the cyclohexane moiety should increase the compound's lipophilicity, which, in turn, can result in a faster transfer of the compounds synthesised through various physiological barriers (*e.g.*, the hematoencephalic barrier).[14,15]

Therefore, using the procedure developed for derivatives **1a–d**, we synthesised pentacyclic compounds **1e–h** with preparative yields of 64–87%. Starting 1,5-tetramethyleno-2,4,6,8-tetra(hydroxymethyl)glycoluril **2b** was synthesised similarly to glycoluril **2a** by the exhaustive N-hydroxymethylation of 1,5-tetramethylenoglycoluril **4b**, which was obtained by the reaction of urea with cyclohexane-1,2-dione.[16] (*S*)-α-Amino acids **3a–c**,**e** [α-Ala, Met, *nor*-Val and Asp] were used in the condensation (Scheme 2).

The structures of compounds **1a–h** were confirmed by a combination of spectral characteristics including specific rotation.‡

Thus, the studies of the cyclocondensation of *N*-tetra(hydroxymethyl)glycolurils **2a**,**b** with (*S*)-α-amino acids resulted in the development of a new synthesis of enantiomerically pure glycoluril derivatives. This method was used to synthesise condensed tetra- and pentaheterocyclic compounds incorporating the pharmacophoric moieties of glycoluril and (*S*)-α-amino acids.

‡ All new compounds exhibited satisfactory elemental analyses, and their structures were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker WM-250 (250 MHz) and Bruker AM-300 (75.5 MHz) spectrometers, respectively. Chemical shifts were measured with reference to the residual protons of [$^2H_6$]DMSO as the solvent (δ 2.50).

General procedure for the synthesis of tetra- and pentacyclic glycoluril derivatives **1a–h**. A solution of the hydroxymethyl glycoluril derivative **2a** or **2b** (5 mmol) and the potassium salt of corresponding amino acid **3a–e** (10 mmol) in water (6 ml) prepared beforehand was kept for 2 h at 90 °C and cooled to room temperature; concentrated HCl (10 mmol) was added afterwards. The resulting precipitate of compound **1** was filtered off and crystallised from water.

*(*S,S*)-2-{6-(1-Carboxy-2-methylpropyl)-4,8-dioxotetrahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[def]fluoren-2-yl}-3-methylbutanoic acid* **1a**: yield 45%, mp 261–262 °C (decomp.), $[\alpha]_D^{20}$ +57.7° (*c* 1.6, H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.96 (br. t, 12H, 4Me), 1.70–1.78 (m, 2H, 2CH), 3.64–3.68 (m, 2H, 2CH), 3.82–3.94 (m, 4H, 2CH_2), 4.48–4.56 (m, 4H, 2CH_2), 5.22 (s, 2H, CHCH), 13.01 (br. s, 2H, 2COOH).

*(*S,S*)-2-{6-(1-Carboxy-3-methylthiopropyl)-4,8-dioxotetrahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[def]fluoren-2-yl}-4-methylthiobutanoic acid* **1b**: yield 65%, mp 195–197 °C (decomp.), $[\alpha]_D^{20}$ +77.7° (*c* 1.6, H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.89–2.03 (m, 4H, 2CH_2), 2.01 (s, 6H, 2Me), 2.29–2.42 (m, 4H, 2CH_2), 3.32–3.36 (m, 2H, 2CH), 4.10–4.25 (m, 4H, 2CH_2), 4.51–4.58 (m, 4H, 2CH_2), 5.53 (s, 2H, CHCH), 13.15 (br. s, 2H, 2COOH).

*(*S,S*)-2-{6-(1-Carboxybutyl)-4,8-dioxotetrahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[def]fluoren-2-yl}pentanoic acid* **1c**: yield 46%, mp 234–235 °C (decomp.), $[\alpha]_D^{20}$ +78.94° (*c* 1.6, H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.86–1.08 (m, 10H, 2Me + 2CH_2), 1.33–1.55 (m, 4H, 2CH_2), 3.20 (m, 2H, 2CH), 4.28–4.36 (m, 4H, 2CH_2), 4.66–4.75 (m, 4H, 2CH_2), 5.22 (s, 2H, CHCH), 13.20 (br. s, 2H, 2COOH).

*(*S,S*)-2-{(6-[1-Carboxy-2-(1*H*-indol-2-yl)ethyl]-4,8-dioxotetrahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[def]fluoren-2-yl}-3-(1*H*-indol-2-yl)-propanoic acid* **1d**: yield 82%, mp 276–277 °C (decomp.), $[\alpha]_D^{20}$ –109.9° (*c* 1.6, H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.93 (br. s, 4H, 2CH_2), 4.20 (br. s, 2H, 2CHCOO), 4.46 (br. s, 4H, 2CH_2), 5.27 (s, 2H, CHCH), 6.70 (br. s, 2H, 2CH_{Ind}), 6.99 (br. s, 2H, 2CH_{Ind}), 7.39 (br. s, 4H, 4CH_{Ind}), 7.83 (br. s, 2H, 2CH_{Ind}), 8.41 (br. s, 2H, 2NH_{Ind}), 10.68 (br. s, 2H, 2COOH).

*(*S,S*)-2-{8b,8c-Tetramethyleno-6-(1-carboxy-2-methylpropyl)-4,8-dioxotetrahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[def]fluoren-2-yl}-3-methylbutanoic acid* **1e**: yield 70%, mp 236–237 °C (decomp.), $[\alpha]_D^{20}$ –57.9° (*c* 1.6, H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.77–0.93 (m, 12H, 4Me), 1.03 (d, *J* 6.4 Hz), 1.47 (br. s, 4H, 2CH_{2cyc}), 2.00 (m, 6H, 2CH_{2cyc} + 2CH), 3.68–3.96 (m, 6H, 2CH_2 + 2CH), 4.43–4.62 (m, 4H, 2CH_2), 13.33 (br. s, 2H, 2COOH).

References

1 R. G. Kostyanovsky, K. A. Lyssenko, G. K. Kadorkina, O. V. Lebedev, A. N. Kravchenko, I. I. Chervin and V. R. Kostyanovsky, *Mendeleev Commun.*, 1998, 231

2 R. G. Kostyanovsky, K. A. Lyssenko, A. N. Kravchenko, O. V. Lebedev, G. K. Kadorkina and V. R. Kostyanovsky, *Mendeleev Commun.*, 2001, 134.

3 K. A. Lyssenko, D. G. Golovanov, A. N. Kravchenko, I. E. Chikunov, O. V. Lebedev and N. N. Makhova, *Mendeleev Commun.*, 2004, 105.

4 A. N. Kravchenko, A. S. Sigachev, E. Yu. Maksareva, G. A. Gazieva, N. S. Trunova, B. V. Lozhkin, T. S. Pivina, M. M. Il'in, K. A. Lyssenko, Yu. V. Nelyubina, V. A. Davankov, O. V. Lebedev, N. N. Makhova and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 680 (*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 691).

5 A. N. Kravchenko, K. Yu. Chegaev, I. E. Chikunov, P. A. Belyakov, E. Yu. Maksareva, K. A. Lyssenko, O. V. Lebedev and N. N. Makhova, *Mendeleev Commun.*, 2003, 269.

6 I. E. Chikunov, A. N. Kravchenko, P. A. Belyakov, K. A. Lyssenko, V. V. Baranov, O. V. Lebedev and N. N. Makhova, *Mendeleev Commun.*, 2004, 253.

7 A. Aumueller, P. Neumann and H. Trauth, *German Patent*, 3643892 (*Chem. Abstr.*, 1988, **109**, 232138).

8 D. Savostianoff, *French Patent*, 2291203 (*Chem. Abstr.*, 1977, **86**, 121377).

9 A. Aumueller, P. Neumann and H. Trauth, *German Patent* 3643889 (*Chem. Abstr.*, 1989, **110**, 96537).

10 S. G. Zlotin, I. V. Sharova and O. A. Luk'yanov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 777 (*Russ. Chem. Bull.*, 1996, **45**, 737).

11 Yu. B. Vikharev, L. V. Anikina, I. E. Chikunov, A. S. Sigachev, A. N. Kravchenko, Yu. V. Shklyaev and N. N. Makhova, *Voprosy Biologich. Meditsiny i Farm. Khimii*, 2006, (2), 12 (in Russian).

12 G. A. Gazieva, A. N. Kravchenko, K. Yu. Chegaev, Yu. A. Strelenko and O. V. Lebedev, *Mendeleev Commun.*, 2000, 28.

13 E. Grillon, R. Gallo, M. Pierrot, J. Boileau and E. Wimmer, *Tetrahedron Lett.*, 1988, **29**, 1015.

14 O. Sevcik and J. Mastik, *10th World Congress on Pain. International Association for the Study of Pain*, San Diego, California, USA, 2002. http://www.painstudy.ru/10wcp/anticonvulsants.htm

15 D. Hartmann, M. Baird and A. Souter, *10th World Congress on Pain. International Association for the Study of Pain*, San Diego, California, USA, 2002. http://www.painstudy.ru/10wcp/anticonvulsants.htm

16 D. F. Kutepov, A. A. Potashnik, D. N. Khokhlov and V. A. Tuzhilkina, *Zh. Obshch. Khim.*, 1959, **29**, 855 (in Russian).

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*(*S,S*)-2-{8b,8c-Tetramethyleno-6-(1-carboxy-2-methylthiopropyl)-4,8-dioxotetrahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[def]fluoren-2-yl}-4-methylthiobutanoic acid* **1f**: yield 87%, mp 209–211 °C (decomp.), $[\alpha]_D^{20}$ –63.6° (*c* 1.6, H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.49 (br. s, 4H, 2CH_{2cycl}), 1.74–2.16 (m, 14H, 2CH_{2cycl} + 2CH_2 + 2Me), 2.29–2.48 (m, 4H, 2CH_2 + [$^2H_6$]DMSO), 3.35–3.37 (br. t, 2H, 2CH), 4.09–4.23 (m, 4H, 2CH_2), 4.46–4.52 (m, 4H, 2CH_2), 12.51 (br. s, 2H, 2COOH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 14.61 (CH_2), 23.94 (CH_2), 28.54 (CH_2), 29.08 (*C*HCOO), 53.08 (SMe), 58.16 (SCH_2), 59.96 (C), 72.91 (CH_2), 158.99 (CO), 173.07 (COOH).

*(*S,S*)-2-{8b,8c-Tetramethyleno-6-(1-carboxybutyl)-4,8-dioxotetrahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[def]fluoren-2-yl}pentanoic acid* **1g**: yield 68%, mp 211–213 °C (decomp.), $[\alpha]_D^{20}$ –12.63° (*c* 1.6, H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.81 (m, 6H, 2Me), 1.19–1.34 (m, 4H, 2CH_2), 1.48 (br. s, 4H, 2CH_{2cycl}), 1.58–1.82 (m, 4H, 2CH_2), 2.02 (br. s, 4H, 2CH_{2cycl}), 3.23 (br. t, 2H, 2CH), 4.10–4.20 (m, 4H, 2CH_2), 4.50–4.56 (m, 4H, 2CH_2), 12.46 (br. s, 2H, 2COOH).

*(*S,S*)-2-{8b,8c-Tetramethyleno-6-(1,2-dicarboxyethyl)-4,8-dioxotetrahydro-2,3a,4a,6,7a,8a-hexaazacyclopenta[def]fluoren-2-yl}succinic acid* **1h**: yield 64%, mp 264–266 °C (decomp.), $[\alpha]_D^{20}$ –31.4° (*c* 1.6, H_2O). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.53 (br. s, 4H, 2CH_{2cycl}), 2.21 (br. s, 4H, 2CH_{2cycl}), 2.94 (br. s, 4H, 2CH_2COO), 3.66 (m, 2H, 2CH), 4.90 and 5.19 (dd, 8H, 4CH_2, *J* 11.0 Hz), 12.83 (br. s, 4H, 4COOH).