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Bioorganic & Medicinal Chemistry Letters 16 (2006) 6019–6023
Bioorganic & Medicinal Chemistry Letters

Synthesis and study of anti-inflammatory activity of some novel cyclophane amides

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Received 31 May 2006; revised 17 August 2006; accepted 30 August 2006
Available online 25 September 2006

Abstract—Macrocyclic di- and tetra-amides with thia- and oxylinkages were synthesized and screened for in vitro anti-inflammatory activity. Cyclophane diamide **15** showed a dose-dependent activity, while the other cyclophane amides **16**–**20** exhibited mild activity.

Synthesis of new supramolecules architecturally novel and of potential importance in the context of designing simple models for studying biomolecular interactions stimulates the imaginative skill of synthetic chemists. The basic crown ether has been modified by substituting the oxygen donor atom by sulfur and/or nitrogen atom and introducing functional groups, viz., amide, ester in the ring to use them as models of protein–metal binding sites in biological systems,[1] synthetic ionophores, therapeutic reagents in chelate therapy, cyclic antibiotics,[2] and to study host–guest interactions.[3] Cyclic amides play important role in various biological systems.[4] Cystine based cyclic peptide has the unique ability of forming double-helical structure.[5] Cyclic peptides with open pores are useful as transport vehicles for biologically important ions or neutral molecules.[6] The self-assembly of acyclic peptides and their ability to form β-sheet structures have been demonstrated.[7,8] Adamantane-based supramolecular systems also form double-helical cyclic structures.[8,9] Macrocyclic hexa-amides, which can effectively bind peptides, have been reported.[10] Supramolecular amides have been also used as molecular receptors and in molecular recognition of biologically interacting substrates[11] including anti-HIV active macrocyclic amides.[12] Copper complexes of macrocyclic compounds exhibit increased antibiotic and antifungal activity than the uncomplexed macrocyclic compounds.[13] Thus macrocyclic compounds containing amide linkages are found to be biologically active. Hence we are interested in the synthesis and study of anti-inflammatory activity of cyclophane amides.

Diamines **1**–**6** were synthesized and used for the preparation of cyclophane amides.

Diamine **1** and **2**[14] were prepared by the reaction of their corresponding dihalides **7** and **8** with 2-aminothiophenol in methanolic KOH at room temperature. Dichloride **8**[15] was obtained by the reaction of *o*-phenylenediamine with 2 equiv of chloroacetyl chloride in the presence of triethylamine in methylene chloride. Diamine **3** was prepared by the reaction of the corresponding dibromide[16] **9** with 2-aminothiophenol in toluene and aq KOH in the presence of tetrabutylammonium bromide at reflux. Nitro compounds **10** and **11** were obtained by the alkylation of 4-nitrobenzyl bromide and 1-(4-nitrophenoxy)-2-bromo ethane with 2-aminothiophenol, respectively. Reduction of the nitro compounds **10** and **11** with iron and dil HCl gave the diamine **4**[17] and **5** in 62% and 70% yields, respectively (Scheme 1).

In order to synthesize the cyclic tetra-amide with oxy linkages, diamine **6** was obtained in 65% yield by the reaction of diacid chloride **12** with 2 equiv of *N*-phenylethylenediamine (Scheme 2).

Diacid chloride **14**[18] was obtained by the reaction of the corresponding diacid **13** with excess thionyl chloride in

Keywords: Cyclophane; Anti-inflammatory; HRBC stabilization.
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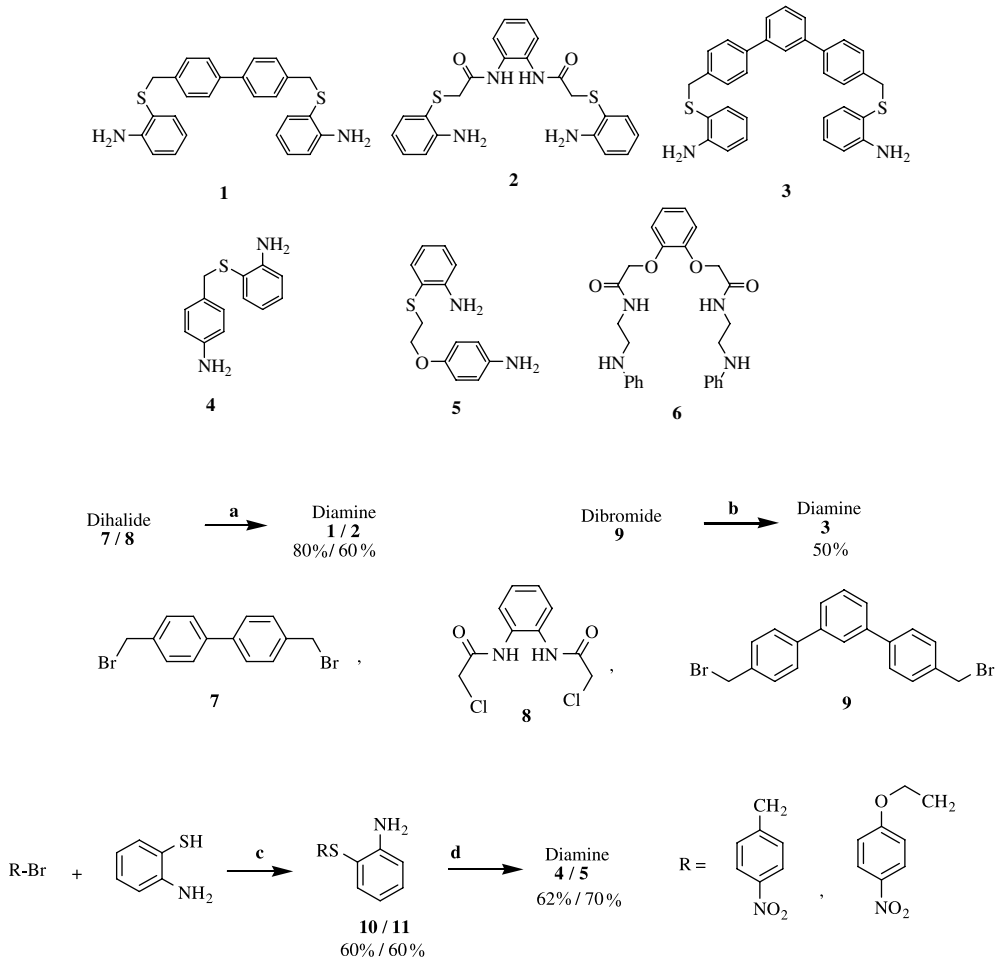
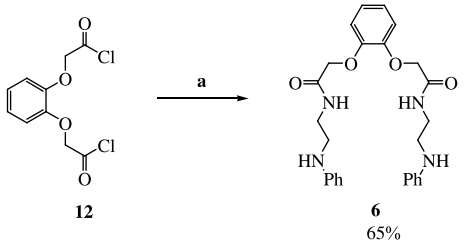
doi:10.1016/j.bmcl.2006.08.124



Scheme 1. Reagents and conditions: (a) 2-aminothiophenol (2 equiv), KOH, methanol, room temperature; (b) 2-aminothiophenol (2 equiv), aq KOH, toluene, TBAB, reflux, 4 h; (c) KOH, methanol, room temperature; (d) activated iron powder, dil HCl, reflux, 3 h.



Scheme 2. Reagents and conditions: (a) *N*-phenylethylenediamine (2 equiv), TEA, CH_2Cl_2, room temperature, 1 h.

the presence of triethyl amine in methylene chloride. Thus diacid chloride **14** was reacted with diamines **1**–**6** to give cyclophane amides **15**–**20** in 50%, 45%, 35%, 40%, 42%, and 40% yields, respectively (Scheme 3).

In ^{1}H NMR spectrum cyclophane amide **15**[19] displayed the aromatic methyl, SCH_2, and OCH_2 protons as singlets at δ 2.16, δ 3.95, and δ 4.80, respectively, in addition to aromatic protons. The protons attached to the amide nitrogen appeared at δ 9.68 as a broad singlet. In ^{13}C NMR spectrum aromatic methyl, SCH_2, OCH_2, and carbonyl carbons appeared at δ 19.4, 41.9, 67.9, and 164.0 in addition to the aromatic carbons. The molecular ion appeared at *m*/*z* 798 in the FAB mass spectrum for cyclophane amide **15**, which further confirms the proposed structure. Cyclophane amides **16**[20] and **17**[21] were also completely characterized by spectral and analytical data.

Cyclophane amide **18**[22] in ^{1}H NMR spectrum displayed the aromatic methyl protons as two singlets at δ 2.25 and δ 2.27, SCH_2 protons as singlet at δ 3.65, OCH_2 protons as two singlets at δ 5.08 and δ 5.17, and the amide protons as a broad singlet at δ 9.69 in addition to the aromatic protons. In ^{13}C NMR spectrum cyclophane amide **18** displayed two aromatic methyl carbons at δ 19.6 and δ 19.8, SCH_2 carbon at δ 43.3, OCH_2 carbons at δ 69.5 and δ 70.8, and carbonyl carbons at δ 162.8 and δ 165.7 in addition to the aromatic carbons. In the mass spectrum the molecular ion appeared at *m*/*z* 600.

Cyclophane amide **19**[23] in ^{1}H NMR spectrum displayed the aromatic methyl protons as two singlets at δ 2.25 and δ 2.33, SCH_2CH_2O protons as two triplet at δ 2.97 and δ 3.77 with $J = 4.8$ Hz, OCH_2 protons as two singlet at δ 5.01 and δ 5.06 in addition to the aromatic protons, and the amide protons as a broad singlet at δ 9.13. In ^{13}C NMR spectrum cyclophane amide **19**