Efficient Straightforward Synthesis of Amidopiperazinophanes as Versatile Novel Supramolecular Scaffolds

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Abstract  
A simple one-pot synthesis of amidopiperazinophanes with a combination of electron-deficient amide groups and electron-rich alkylene and piperazine functionalities has been achieved by using multi-component reaction (MCR) methodology with the Mannich reaction. Herein, we demonstrate the synthesis of macrocyclic amide structures in good yields. These macrocycles, with electron donor/acceptor sites, are versatile molecules for host–guest and binding.

Key words  
supramolecular, piperazine, host-guest, amide, Mannich reaction, multicomponent reaction

Molecular recognition and highly responsive signaling play an important role in host and guest interactions, which have been extensively studied in biological systems via supramolecular host–guest mechanisms.1 Generally, macrocyclic structures with heterocyclic ring systems possess numerous binding sites for metal ions2a that provide attractive cyclic structures with heterocyclic ring systems possess supramolecular host–guest mechanisms.1 Generally, macrocyclic backbone. 

Formation of macrocycles containing amide bonds can lead to a range of pharmaceutically interesting biological activities.2 Moreover, the presence of amide functionalities in supramolecular structures facilitates their use as molecular receptors4 for molecular recognition;5 for instance anti-HIV active macrocyclic amides.6 In addition, cyclic amides7 have structural rigidity, receptor selectivity, and biochemical stability. Recently, functionalized aza-oxo-thia macrocycles bearing tetra amides have been employed as potential antimicrobial and anticancer agents.8 The combination of a fluorophore-tag with cyclic peptides facilitates the selective detection of Hg(II).9 Furthermore, the possibility of intra- and intermolecular hydrogen bonding by the amide functionality may lead to compact conformations and functions.10 Cyclic amides have also been used as nanomaterial devices by the formation of tubular structures that lead to stacking and self-assembly.11 Moreover, transition-metal ions such as Ru(II), Pd(II), Ni(II), Co(II), Cu(II), and Fe(III)12 show selective metal ion complexation behavior with cyclic amides by formation of stable complexes. Conversely, cyclic amides have been found to be suitable neutral hosts for anionic guest systems.13 Earlier, we reported cyclophanes with intra-annular amide functionalities for selective ion transportation14 as well as for the development of bioactive compounds.15 Piperazine-containing cyclophanes have rarely been reported.16,17 The ability of piperazines to form hydrogen bonds with guests plays a pivotal role in biomedical and pharmaceutical fields. The presence of a piperazine in a cyclophane17 offers rigidity. Piperazine could act as an electron-donor group along with alkylenes in cyclic amides.18 In this sense, piperazine-amide macrocycles with a number of binding sites as well as with electron-rich heteroatoms such as N, S, and rigid alkylenes are of potential interest.19 Several attempts have been made to synthesize amide cyclophanes containing piperazines,20 but these have involved multi-step approaches, necessitating protection and deprotection strategies, extended reaction time for cyclization, and low reaction yields.21
Herein, we report a simple approach for the synthesis of novel amidopiperazinophanes 1–6 and 7–12 (Figure 1) of a 1:1 and 2:2 oligomeric nature, respectively, by using propargylamine and piperazine as skeletons through one-pot synthesis.

**Figure 1** Structures of piperazinoamide based 1:1 and 2:2 oligomeric forms of macrocycles 1–12.
multicomponent reaction (MCR) methodology. Moreover, this synthetic approach has advantages, including ease of manipulation, simple purification and intrinsic atom economy. These 1:1 monomeric and 2:2 dimeric forms of amidopiperazinophanes offer both π electron-rich donor (π = phenyl, ethynyl) and efficient hydrogen-bond acceptor systems (tertiary amine). Our observations suggest that these amide cyclophanes could be potential candidates for pharmaceutical applications. Moreover, our findings open up new perspectives to design and develop supramolecular scaffolds with amide functionalities in the macrocyclic ring by using this simple synthetic approach.

Amidopiperazinophanes can be obtained from the corresponding S-bispropargyloxy precyclophanes. The precyclophane bis-alkyne system can be constructed from the reaction of acid chlorides and S-propargyloxy-2-aminothiophenol. Mannich reaction methodology leads to the amide macrocycles in an effective manner by condensation of the terminal bisalkyne, piperazine, and formaldehyde through a multicomponent reaction (MCR).

To achieve target amide macrocycles 1–12, precyclophanes 13–18 with terminal bisalkynes were used as the main building blocks with S-propargyloxy-2-aminothiophenol 19 as the other starting precursor.

In this context, our initial aim focused on the synthesis of the precyclophanes using various aromatic diacid chlorides including phthaloyl chloride 20, isophthaloyl chloride 21, terephthaloyl chloride 22, pyridine-2,6-dicarboxylic acid chloride 23, 5-hydroxyisophthaloyl dichloride 24, and thiophene-2,5-dicarbonyl dichloride 25. Reaction of 1.0 equiv of each diacid chloride with 2.1 equiv of S-propargyloxy-2-aminothiophenol 19 at room temperature afforded the amide precyclophanes 13, 14, and 15 in 56, 65, and 59% yields, respectively. The synthesis was extended to incorporate hydroxyl and electron-rich heteroatoms such as N and S at the intra-annular position of the piperazinophanes, presenting features for hydrogen bonding and stacking along with binding sites for guest species. As a consequence, precyclophanes 16, 17, and 18 were prepared by treating S-propargyloxy-2-aminothiophenol 19 with freshly prepared pyridine-2,6-dicarbonyl dichloride 23, 5-hydroxyisophthaloyl dichloride 24, and thiophene-2,5-dicarbonyl dichloride 25 in the presence of triethylamine in dichloromethane at room temperature for 12 h to obtain 71, 67, and 78% yields, respectively (Scheme 1). The aromatic diacid chlorides 20–25 were synthesized according to the reported procedure.22

Scheme 1  Reagents and conditions: (i) NEt3, CH2Cl2 (dry), 12 h: (ii) piperazine, 37–41% aq. formaldehyde, CuCl, 90 °C, 2 h. 1 (31%); 2 (37%); 3 (30%); 4 (36%); 5 (32%); 6 (30%); 7 (23%); 8 (24%); 9 (27%); 10 (30%); 11 (18%); 12 (26%); 13 (56%); 14 (65%); 15 (59%); 16 (71%); 17 (67%); 18 (78%).
The structure of precyclophane 16 was confirmed by 1H NMR spectroscopic analysis by the appearance of long-range coupling between the two-proton triplet at $\delta = 1.91$ (t, J = 2.1 Hz, 2 H) for the acetylenic proton and a doublet at $\delta = 3.41$ (d, J = 2.4 Hz, 4 H) for S-methylene proton. The amide -NH proton appeared as a singlet at $\delta = 10.74$ in addition to the rest of the signals for eleven aromatic protons. In the 13C NMR spectrum, compound 16 presented signals from alkyne carbons, S-methylene and N-methylene carbons at $\delta = 24.4, 72.4, and 79.1$, respectively, the amide carbonyl carbon resonated at $\delta = 161.5$ and nine aromatic carbons were present. The amide carbonyl carbon of 16 was further evidenced by the appearance of a strong absorption band at 1656 cm$^{-1}$ in the IR spectrum. Finally, the precyclophane structure 16 was confirmed by the observation of a molecular ion peak at m/z 457 [M$^+$] in the mass spectrum.

The 1H NMR spectrum of precyclophane 18 contained signals at $\delta = 2.21$ (t, J = 2.7 Hz, 2 H), and $\delta = 3.49$ (d, J = 2.4 Hz, 4 H) for the acetylenic and S-methylene units, respectively, with a sharp singlet at $\delta = 0.47$ corresponding to the two amide NH protons, in addition to signals for ten aromatic protons. The 13C NMR spectrum of precyclophane 18 displayed resonances at $\delta = 25.3, 72.8, and 79.4$ for alkyne, S-CH$_2$, and N-CH$_2$ carbons, respectively, aromatic carbon signals at $\delta = 120.3-143.8$ and a resonance at $\delta = 158.8$ for the amide carbonyl carbon. A molecular ion peak of precyclophane 18 was observed at m/z 462 [M$^+$] in the mass spectrum. Further spectroscopic and analytical data matched with the structure of the precyclophane 18.

Our aim was to extend the study to various amidopiperazines with different heteroatoms and aromatic monomeric spacer units. Hence, coupling of 1.0 equiv of precyclophane 13–15 with 2.0 equiv of piperazine in the presence of a catalytic amount of CuCl in anhydrous dioxane at 90 °C for 2 h furnished functionalized 1:1 oligomeric amide cyclophanes 1, 2, and 3 with propargylamine and piperazine-containing skeletons in 31, 37, and 30%, yields, respectively, and 2:2 oligomeric cyclophane amides 7, 8, and 9 with propargylamine and piperazine skeletons in 24, 27, and 30% yields, respectively.

The proton NMR spectrum of monomeric macrocyclic amide 2 indicated the singlets at $\delta = 2.10, 2.87, 3.54$ for the piperazinyl, S-CH$_2$, and N-CH$_2$ protons, respectively, and the amide proton appeared as a sharp singlet at $\delta = 9.97$. The rest of the signals could be attributed to the aromatic protons. The 13C NMR spectrum showed four different signals for acetylene, piperazinyl and methylene carbons at $\delta = 26.2, 47.1, 51.6$ and 79.3, 80.5, respectively, and a signal at $\delta = 163.9$ for the amide carbonyl, in addition to the signals due to the aromatic carbons. Finally, the structure was confirmed by the appearance of a molecular ion at m/z 566.

The 1H NMR spectrum of 2:2 dimeric amidopiperazino- phane 8 showed a sharp singlet at $\delta = 2.23$ for the sixteen protons of piperazinyl units, an eight-proton singlet at $\delta = 2.99$ for S-CH$_2$ protons, a sharp singlet at $\delta = 3.55$ for the N-methylene protons, signals at $\delta = 7.13$ to 8.60 for the aromatic protons along with the four amide protons observed as a sharp singlet at $\delta = 9.68$. In the 13C NMR spectrum, signals at $\delta = 25.7, 46.8, 51.4, 79.5, 80.5$ and 120.7–140.2 corresponded to the piperazinyl, S-methylene, N-methylene, acetylenic carbons and the aromatic carbons, respectively. The amide carbonyl carbon was observed at $\delta = 164.0$. The structure of 2:2 oligomeric amidopiperazinophane 8 was confirmed by the appearance of a molecular ion at m/z 1132 [M$^+$] in the mass spectrum. Similarly, the structure of the remaining 1:1 oligomeric amide macrocycles 1, 3 and 2:2 oligomeric amidopiperazinophanes 5, 7 were confirmed by spectroscopic and analytical data.

The crystal structure of amidopiperazinophane 2 (Figure 2) showed a relatively planar bis(2-mercaptophe- nyl)-isophthalamide fragment linked to the tertiary amine of the piperazine unit. The mercaptophenyl unit is highly strained and turned away from the ring of isophthalamide by 8.18 (11) and 5.59 (10)°, at the same time these two rings are horizontally turned towards each another by 9.10 (12)°. Two intramolecular hydrogen bonds can be identified, generating S(5) ring motifs and the structure is further stabilized by hydrogen bonds of C–H···S and C–H···O. The oxygen atoms of the amide carbonyl linked to the isophthalamyl ring is disordered over two positions with an occupancy ratio of 0.41(6):0.59(6).21

Our strategy was extended to the synthesis of amide piperazinophanes containing two and four amide groups with different functional groups, as well as electron donor/acceptor heteroatoms at intra-annular positions by
introducing the pyridine-2,6-dicarbonyl, 5-hydroxyisophthaloyl and 2,5-thiophenedicarbonyl units. Thus, 1.0 equiv of precyclophane diynes 16, 17 and 18 were treated with 37–41%aq. formaldehyde (2.0 equiv) and piperazine (1.0 equiv), in the presence of a catalytic amount of CuCl in anhydrous dioxane at 90 °C for 2 h to form 1:1 oligomeric amide macrocycles 4, 5, 6 in 36, 32, and 30% yields, respectively, and 2:2 oligomeric amides macrocycles 10, 11 and 12 in 23, 18, and 26 yields, respectively.

The formation of 1:1 cyclophane 4 was confirmed by the appearance of an intense absorption band at 1664 cm⁻¹ in the FTIR spectrum for the amide carbonyl. The ¹H NMR spectrum displayed three sharp singlets at δ = 2.22, 3.11, and 3.66 for the protons of the piperazinyl, S-methylene, and N-methylene units, respectively, along with a sharp singlet at δ = 10.76 for the amide protons in the deshielded region in addition to the signals for the aromatic unit. In the ¹³C NMR spectrum, signals for the piperazine carbons, methylene carbons connected to sulfur, and nitrogen and the amide carbon at δ = 22.7, 46.8, 50.5, and 163.1, respectively, in addition to the aromatic carbons were observed. The molecular ion was found at m/z 567 [M⁺] in the mass spectrum and a satisfactory elemental analysis was obtained.

Similarly, the structure of 2:2 oligomeric cyclophane amide 10 was confirmed by ¹H NMR spectroscopy through the appearance of a sharp singlet at δ = 2.34 for sixteen protons of the piperazinyl skeleton, an eight proton singlet at δ = 3.02 for S-CH₂ group and a singlet at δ = 3.60 for the N-CH₂ protons with the rest of the signals at δ = 7.20–8.54 corresponding to the aromatic protons. The amide protons resonated at δ = 10.71. In the ¹³C spectrum, signals at δ = 24.7, and 46.9, 51.4, and 79.3, 80.5 could be assigned to the piperazinyl, acetylenic S-CH₂, and N-CH₂ groups, resonances between δ = 121.9 to 149.3 for the aromatic carbons and the amide carbons appeared at δ = 161.5. The FTIR spectrum showed an absorption band at 1656 cm⁻¹ for the amide carbonyl and a molecular ion was observed at m/z 1134 [M⁺] in the mass spectrum.

Analogously, the ¹H NMR spectrum of the dimeric amide macrocyclic receptor 12 displayed three sharp singlets at δ = 2.36, 3.10 and 3.56 for the piperazine, S-methylene and N-methylene protons, respectively. A sharp singlet was observed at δ = 9.53 for the four protons of the amide unit in addition to the signals for the aromatic protons. The ¹³C NMR spectrum displayed carbon signals at δ = 25.7, 46.8, 51.2, 79.0, and 80.9 for the S-CH₂, N-CH₂, piperazine and alkyne carbon, respectively, in addition to signals between δ = 120.5–143.8 assigned to the aromatic carbons. The amide carbonyl resonance was observed at δ = 158.8. A molecular ion was observed at m/z 1144 [M⁺] in the mass spectrum and its chemical composition was also evaluated by elemental analysis.

Similarly, other structures of 1:1 oligomeric and 2:2 oligomeric cyclophane amide 5, 6 and 11 bearing strong binding sites and electron-rich donor/acceptor units were completely characterized and confirmed by full spectroscopic and analytical analyses.

In summary, a simple approach to the synthesis of a family of amidopiperazinophane with an intra-annular amide unit with various spacer units has been achieved with good yields via Mannich reaction in a mild, straightforward, sequential, and rapid one-pot multicomponent reaction (MCR). All the amidopiperazinophane structures were completely characterized and confirmed by using standard spectroscopic and analytical methods. By taking account the merits of the synthetic strategy, our investigation will open new avenues for the design and synthesis of novel amidopiperazinophanes, with various binding sites with electron donor/acceptor units.

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Supporting Information

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(24) Synthesis of Precyclophane Amides; General Procedure A: A solution of the diacid chloride (3.0 g, 1.48 mmol) in anhydrous dichloromethane (100 mL) and a solution of the amine (4.82 g, 2.96 mmol) was added dropwise to dichloromethane (500 mL) over 6 h. The addition was complete, the reaction mixture was stirred for another 6 h. The solvent was removed under reduced pressure and the residue obtained was then dissolved in dichloromethane (300 mL), washed with water (2 × 100 mL) to remove triethylamine hydrochloride and then dried over anhydrous Na2SO4. Filtration and removal of the dichloromethane gave the crude precyclophane, which was purified by column chromatography (SiO2) using CHCl3/MeOH (97:3) as eluent.

Synthesis of Piperazinophanes/Cyclophane Amides by Mannich Reaction; General Procedure B: A mixture of precyclophane diyne (0.2 g, 3.98 mmol), piperazine (0.04 g, 0.49 g, 3.98 mmol), and formaldehyde (0.27 g, 7.96 mmol, from 37–41% of formaldehyde) and CuCl (0.04 g, 3.98 mmol) in dioxane (30 mL) was heated to reflux for 2 h under nitrogen. After the reaction was complete, the solvent was removed under reduced pressure, the residue was extracted with CHCl3 (3 × 100 mL), washed with water (2 × 100 mL), brine (150 mL) and dried over anhydrous Na2SO4. The solvent was removed and the crude product was purified by column chromatography on silica gel using CHCl3/MeOH (24:1) as eluent.

S-Propargyloxy-2-aminophenol 19: The S-propargyloxy-2-aminophenol (19) was prepared and obtained as dark-brown liquid, which was reported earlier from our laboratory.

Preparation of Diacid Chlorides: The diacid chlorides 20–25 were prepared from the corresponding diacids, as reported earlier by our group.

Representative Analytical Data

| Compound | Analytical Data |
|----------|-----------------|
| N3,N3-Bis-(2-(prop-2-ynylthio)phenyl)isophthalamide (14) | By following General Procedure A, the precyclophane amide diyne 14 was obtained as a brown solid from diacid chloride 21 (3.0 g, 1.48 mmol) and S-propargyloxy-2-aminophenol 19 (4.84 g, 2.97 mmol). Yield: 43.8 g (65%); mp 120 °C. |
Cyclophane Amide 1: The cyclophane amide 1 was afforded as a white solid from the precyclophane amide diyne 13 (0.4 g, 0.88 mmol), piperazine (0.08 g, 0.88 mmol), formaldehyde (0.05 g, 1.76 mmol, from 37–41% aq. formaldehyde) and CuCl (0.09 g, 0.88 mmol). Yield: 0.15 g (31%); mp 186 °C. 1H NMR (300 MHz, CDCl3): δ = 2.56 (s, 8 H), 3.04 (s, 4 H), 3.56 (s, 4 H), 7.14 (t, J = 7.5 Hz, 2 H), 7.45 (t, J = 7.8 Hz, 2 H), 7.64 (t, J = 7.5 Hz, 2 H), 7.68 (s, 4 H), 8.12 (d, J = 8.1 Hz, 2 H), 9.69 (s, 2 H). 13C NMR (75 MHz, CDCl3): δ = 25.6, 46.8, 51.4, 79.2, 80.2, 119.1, 120.3, 122.8, 124.6, 131.5, 136.3, 137.1, 140.3, 164.3. MS (EI-TOF): m/z = 566 [M+]. Anal. Calcd for C32H30N4O2S2: C, 67.89; H, 5.26; N, 9.97.

Cyclophane Amide 4: General Procedure B was followed for the synthesis of cyclophane amide 4 as a white solid from the precyclophane amide diyne 16 (0.4 g, 0.88 mmol), piperazine (0.08 g, 0.88 mmol), formaldehyde (0.05 g, 1.76 mmol, from 37–41% aq. formaldehyde) and CuCl (0.09 g, 0.88 mmol). Yield: 0.18 g (36%); mp 120 °C. 1H NMR (300 MHz, CDCl3): δ = 2.22 (s, 8 H), 3.11 (s, 4 H), 3.66 (s, 4 H), 7.29 (d, J = 7.8 Hz, 2 H), 7.38 (t, J = 7.8 Hz, 2 H), 7.63 (d, J = 7.8 Hz, 2 H), 8.01 (d, J = 6.3 Hz, 2 H), 8.12 (d, J = 7.8 Hz, 1 H), 8.39 (d, J = 7.8 Hz, 2 H), 10.76 (s, 2 H). 13C NMR (75 MHz, CDCl3): δ = 22.7, 46.8, 50.5, 78.2, 82.0, 123.4, 123.8, 125.5, 126.4, 129.5, 130.9, 138.6, 139.3, 150.5, 163.1. MS: m/z = 567 [M+]. Anal. Calcd for C31H29N5O2S2: C, 65.49; H, 5.26; N, 12.37.