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Synthesis of a Bile Acid-Based Click-Macrocycle and Its Application in Selective Recognition of Chloride Ion

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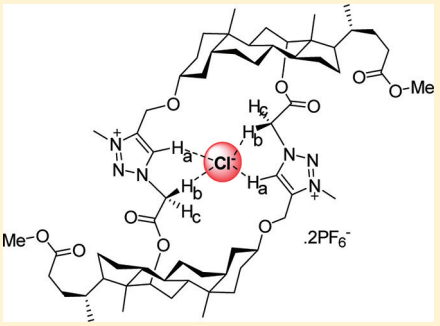
Supporting Information

ABSTRACT: A novel method for the synthesis of a bile acid-based macrocycle has been developed using click chemistry. The 1,2,3-triazolium derivative of the macrocycle shows remarkable selectivity in binding of chloride ion.



Design and synthesis of bile acid-based macrocycles has been a subject of considerable research interest because of their great potential applications in supramolecular chemistry. Their structural features, such as chiral, rigid, and amphiphilic frameworks possessing a well-defined hydrophilic interior due to the presence of convergent hydroxyl groups, make them suitable hosts for the binding of polar molecules in nonpolar solvents.[1−6] Consequently, several synthetic methods, involving macrolactonization, macrolactamization, ring-closing metathesis and Ugi-multi component macrocyclization, have been developed for the construction of bile acid-based macrocycles.[7−19] However, some drawbacks of these methods like low cyclization yield, lengthy synthesis, and in some cases, use of expensive reagents make them rather less attractive. Hence, it is desirable to develop more efficient and economical methods for the construction of these macrocycles. We previously reported a high-yielding synthetic procedure of head-to-head cholaphanes based on the use of Cs-salt methodology of macrocyclization.[20−23]

In recent years, click chemistry involving Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction of an azide and a terminal alkyne has been recognized as one of the most attractive methods for conjugate chemistry and has found its wide applications in the synthesis of a variety of interesting materials, polymers and peptides.[24−29] Besides, the unique property of the 1,4-disubstituted 1,2,3-triazole ring such as its ability to act as both a hydrogen bond acceptor and a hydrogen-bond donor has expanded its utility and attracted much recent interest for designing molecules of supramolecular interest.[30−35]

Lukashev and co-workers have used the click reaction for the synthesis of macrocyclic derivatives of bile acids.[36] However, the yields of these macrocycles have been found to be very low (9−25%), which may be due to the highly flexible nature of these macrocycles. Recently, Ju and co-workers have synthesized a cyclic dimer based on oleanolic acid using click chemistry in 24% yield (appeared after the submission of our manuscript).[37] This cyclic dimer binds fluoride ion in 1:2 stoichiometry through C--H--F^- interaction with methylene protons of acetyl groups.

Herein, we report an efficient synthesis of a bile acid-based bis-1,2,3-triazolium cyclodimer (cholaphane) using click reaction as described in Scheme 1 and its application in the recognition of chloride ion. Thus, the propargyl derivative of methyl deoxycholate **2** was synthesized by the reaction of deoxycholic acid **1** with propargyl bromide in the presence of sodium hydride in THF, followed by treatment with MeOH−H_2SO_4. Then, the monobromoacetyl derivative **3** was prepared by treatment of propargyl ether **2** with bromoacetyl bromide in the presence of K_2CO_3 in $CHCl_3$. Compound **3** on treatment with sodium azide in DMF gave its azido derivative **4**, which on click reaction in *t*-BuOH/H_2O (10:1) in the presence of $CuSO_4$ (10 mol %) and sodium ascorbate (20 mol %) gave deoxycholic acid based cholaphane **5** in 50% yield. The bismethiodide salt **6** of the cholaphane was obtained by methylation of **5** with methyl iodide, which was further anion exchanged with NH_4PF_6 in MeOH to give its PF_6^- salt **7**.

We have previously shown that the 1,2,3-triazolium moiety acts as a better hydrogen bond donor for anion recognition than the 1,2,3-triazole moiety itself presumably due to the increased acidity of the triazolium hydrogen.[38] Subsequently, 1,2,3-triazolium-based systems have been used by others also for anion recognition as well as for anion-templated synthesis of rotaxane and asymmetric catalysis.[39−41]

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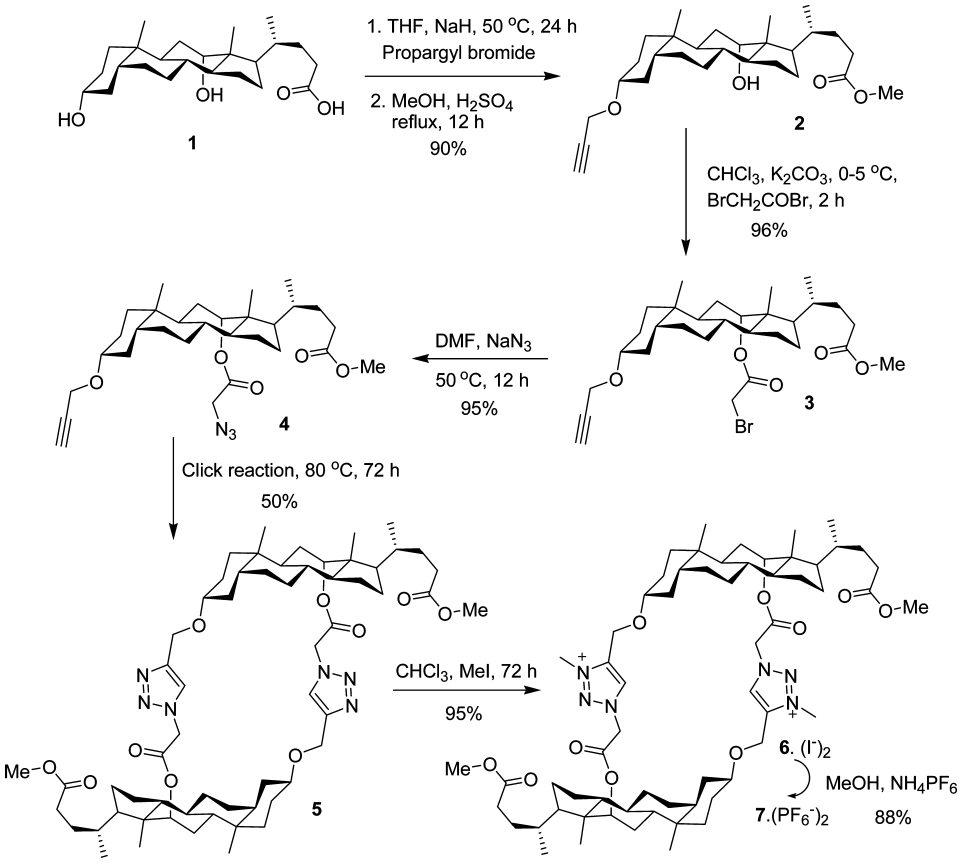
Scheme 1. Synthesis of Click-Macrocycle



This prompted us to examine the anion recognition behavior of the bis-1,2,3-triazolium cyclodimer **7**. The anion-binding property of **7** was studied by monitoring the ^{1}H NMR spectral changes caused by the addition of tetrabutylammonium salts of the anions to a $CDCl_3$ solution of the receptor. Upon addition of aliquots of the solution of Bu_4NX (X = F, Cl, Br, I, CH_3COO, H_2PO_4) to the solution of **7**−$(PF_6^-)_2$, significant downfield shifts were observed for the C(5)-H protons of both the triazolium groups suggesting the interaction of the anion with triazolium C(5)-protons (H_a) by forming C^+--H--X^- hydrogen bonds. In addition, appreciable downfield shifts were also observed for one of the methylene protons (H_b) of both the acetyl groups indicating their participation in hydrogen bonding with anions along with C-5 triazolium protons (Figure 1). Similar C--H--X^- interactions involving acetyl methylene protons have been observed earlier also in the binding of anions with our previously reported triazolium and imidazolium receptors.[38,42,43] The presence of these positively charged heterocycles at the methylene carbon of the acetyl group polarizes the methylene protons making them suitable for hydrogen bond interaction with anions (C--H--X^- interaction). In addition to these hydrogen-bond interactions, the electrostatic interactions between the anion and the triazolium groups also contribute to the binding of anions. The Job's plots analysis showed the formation of 1:1 complexes in all cases. The association constants were determined by using WinEQNMR software and are presented in Table 1. Receptor **7**−$(PF_6^-)_2$ was found to be highly selective for binding of chloride ion with binding constant *K*a = 3700 M^{-1}. The observed binding trend was Cl^- > HSO_4^- > $H_2PO_4^-$ > F^- > Br^- > CH_3COO^- > I^-. The high selectivity of this receptor toward chloride ion may be attributed to the appropriate cavity size of the receptor which brings about the most effective hydrogen-bonding interaction with this particular anion.

Previously, Davis and co-workers have reported the synthesis of a dimeric cyclocholamide which showed selective recognition of halide ions, particularly fluoride ion.[10] However, the lengthy and difficult synthesis of this cholaphane prevented its further applications. Later, they designed and synthesized various cholapods with urea and thiourea functionalities which were found to be highly effective anion receptors.[44,45] Interestingly, these cholapods exhibited remarkable capability to act as transmembrane chloride carriers.[46−48] Recently, they have synthesized the macrocyclic analogs of the cholapods (cholaphanes) and studied their transmembrane transport ability. These cholaphanes have been found to serve as better transmembrane anion carriers than the cholapods.[19] Some time ago, we also reported the syntheses and anion recognition properties of deoxycholic acid based cyclic bisimidazolium and bisbenzimidazolium receptors.[42,43] Although some of these receptors showed high binding affinities for chloride ion, their selectivities were very moderate. As compared to all of the above receptors, the present bistriazolium receptor seems to be more promising in terms of its simple and convenient synthesis and its much higher selectivity toward chloride ion. Hence, this system may prove to be an attractive chloride ion transporter. Chloride ion transporters are considered to have direct medical applications in the treatment of cystic fibrosis and other diseases caused by the deficiency in the chloride ion transport across biological membranes.[49]

In conclusion, we have developed a convenient synthesis of a bile acid based dimeric cholaphane using click chemistry. The

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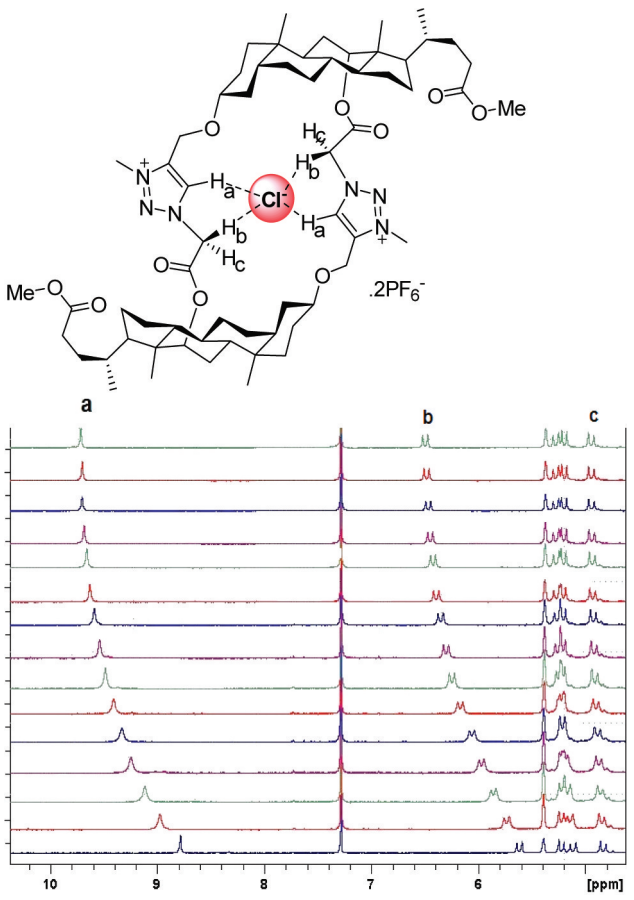

Figure 1. ^{1}H NMR titration of 7–$(PF_6^-)_2$ (10 mM, $CDCl_3$, 298 K) with increasing equivalents of TBACl (0–2.8 equiv) from bottom to the top.

Table 1. Association Constant (K_a)[a] for 1:1 Complexes of Receptor 7 with Anions in $CDCl_3$ at 298 K

anions[b]	receptor 7
F^-	400
Cl^-	3700
Br^-	90
I^-	50
$H_2PO_4^-$	650
CH_3COO^-	60
HSO_4^-	800

[a]Estimated error ≤12%. [b]Anions were used as tetrabutylammonium salts.

bistriazolium derivative of the cholaphane exhibits high selectivity in the recognition of chloride ion. We believe that this highly lipophilic and easily accessible macrocyclic receptor may attract considerable attention for its future applications in biology and medicine as a transmembrane chloride ion carrier.

EXPERIMENTAL SECTION

Methyl 3α-Propargyldeoxycholate (2). To a solution of **1** (2.0 g, 5.09 mmol) in 60 mL of dry THF was added sodium hydride (0.5 g, 20.8 mmol), and the solution was stirred at 50 °C for 1 h. To this solution was added 1.7 mL (14.2 mmol) of propargyl bromide. The solution was stirred at 50 °C for 24 h. The solution was allowed to cool to room temperature, 4–5 drops of water was added, and then the solution was evaporated under vacuum. The residue was dissolved in ether, a few drops of H_2SO_4 were added to bring the pH to 3, and then the solution was washed twice with water. The organic layer was dried over anhyd Na_2SO_4 and evaporated under vacuum to give a yellow solid, which was dissolved in 40 mL of methanol. After 3–4 drops of H_2SO_4 was added, the solution was refluxed for 12 h. The solution was cooled and then evaporated under vacuum. The residue was treated with hot hexane and filtered. The filtrate on keeping at room temperature for 10 min gave white crystals of **2**: yield 2.03 g, 90%; mp 79–80 °C; IR (KBr) ν_{max}/cm^{-1} 3509, 3224, 2935, 2867, 2113, 1725, 1447, 1377; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.67 (s, 3H), 0.91 (s, 3H), 0.96 (d, J = 6.0 Hz, 3H), 1.01–2.34 (b, 26H), 2.37 (bs, 1H), 3.49 (m, 1H), 3.66 (s, 3H), 3.96 (bs, 1H), 4.18 (d, J = 2.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 12.7, 18.7, 23.2, 23.6, 26.1, 26.7, 27.4, 27.7, 28.7, 30.9, 31.1, 31.6, 32.7, 33.6, 34.4, 35.1, 36.0, 42.0, 46.5, 47.2, 48.2, 51.5, 54.9, 73.0, 73.7, 78.0, 80.4, 174.6; HRMS (ES^+) 467.3130, $C_{28}H_{44}O_4Na$ requires 467.3137 $[M + Na]^+$.

Methyl 3α-Propargyl-12α-bromoacetyldeoxycholate (3). To a solution of compound **2** (1.0 g, 2.25 mmol) in 30 mL of dry $CHCl_3$ was added anhyd K_2CO_3 (0.62 g, 4.5 mmol). To this mixture at 0–5 °C was added bromoacetyl bromide (0.33 mL, 3.84 mmol) dropwise, and the reaction mixture was stirred for 2 h. After completion of the reaction, 20 mL of water was added. The chloroform layer was separated and washed with 5 mL of satd $NaHCO_3$ solution and then with brine (10 mL). The chloroform layer was dried over anhyd Na_2SO_4, filtered, and evaporated completely to give a yellow viscous liquid: yield 1.21 g, 96%; IR (KBr) ν_{max}/cm^{-1} 3296, 2937, 2865, 2113, 1733, 1446; ^{1}H NMR (300 MHz, $CDCl_3$,TMS) δ 0.75 (s, 3H), 0.85 (d, 3H, J = 6.3 Hz), 0.92 (s, 3H), 1.04–2.37 (b, 26H), 2.42 (bs, 1H), 3.47 (m, 1H), 3.68 (s, 3H), 3.87 (ABq, 2H, J = 10.8 Hz), 4.19 (d, 2H, J = 2.4 Hz), 5.17 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 12.3, 17.4, 23.0, 23.4, 25.5, 25.9, 26.1, 26.8, 27.1, 27.4, 30.7, 30.9, 32.8, 34.3, 34.8, 34.9, 35.7, 41.9, 45.2, 47.1, 49.2, 51.5, 55.0, 73.7, 78.1, 80.5, 166.7, 174.6; HRMS (ES^+) 603.2082, $C_{30}H_{45}BrKO_5$ requires 603.2087 $[M + K]^+$.

Methyl 3α-Propargyl-12α-azidoacetyldeoxycholate (4). To a solution of **3** (1.0 g, 1.77 mmol) in 20 mL of DMF was added sodium azide (0.57 g, 8.76 mmol), and the solution was stirred at 50 °C for 12 h. The solution was diluted with 40 mL of water and extracted with 30 mL of ethyl acetate twice. The organic layer was washed with water and then with brine solution, dried over anhyd Na_2SO_4, and evaporated under vacuum to give **4** as a white solid: yield (0.88 g, 95%); mp 58–60 °C; IR (KBr) ν_{max}/cm^{-1} 2942, 2866, 2107, 1740, 1451, 1374; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.74 (s, 3H), 0.80 (d, 3H, J = 6.3 Hz), 0.90 (bs, 3H), 1.03–2.34 (b, 26H), 2.41 (t, 1H, J = 2.1 Hz), 3.46 (m, 1H), 3.66 (s, 3H), 3.91 (s, 2H), 4.18 (d, 2H, J = 2.4 Hz), 5.22 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 12.4, 17.6, 23.1, 23.4, 25.7, 25.9, 26.9, 27.1, 27.3, 30.7, 30.9, 32.8, 34.3, 34.4, 34.6, 34.9, 35.7, 41.9, 45.1, 47.6, 49.4, 50.8, 51.5, 55.1, 73.8, 78.1, 80.2, 167.8, 174.5; HRMS (ES^+) 550.3308, $C_{30}H_{45}N_3O_5Na$ requires 550.3257 $[M + Na]^+$.

Cholaphane (5). To a solution of methyl 3α-propargyl-12α-azidoacetyldeoxycholate (**3**) (0.10 g, 0.18 mmol) in 120 mL of *t*-BuOH was added $CuSO_4$ (10 mol %) and sodium ascorbate (20 mol %) in 12 mL of H_2O. The solution was stirred at 80 °C for 72 h. The solution was evaporated under vacuum. The residue was dissolved in $CHCl_3$ and washed with water twice. The organic layer was dried over anhyd Na_2SO_4 and evaporated under vacuum. The column chromatography of the residue on silica gel column with chloroform–hexane (1:1) gave **5** as a white solid: yield 0.05 g, 50%; mp 38–40 °C; IR (KBr) ν_{max}/cm^{-1}, 2931, 2866, 1743, 1632, 1450, 1375, 1268; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.72 (s, 6H), 0.81 (s, 6H), 0.89 (d, 6H, J = 2.1), 1.02–2.41 (b, 52H), 3.68 (s, 6H), 3.83 (m, 2H), 4.89 (ABq, 4H, J = 14.4 Hz), 5.18 (ABq, 4H, J = 15.0 Hz), 5.31 (bs, 2H) 7.73 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 12.3, 17.9, 21.8, 23.5, 24.9, 26.4, 27.4, 27.3, 28.4, 29.7, 30.7, 31.0, 33.6, 33.6, 34.9, 34.9, 35.6, 41.5, 45.2, 47.6, 49.6, 51.5, 52.7, 57.5, 77.8, 123.9, 148.2, 164.1, 174.6; HRMS (ES^+) 1077.6611, C_{60} $H_{90}N_6O_{10}Na$ requires 1077.6616 $[M + Na^+]$.

Bis-1,2,3-triazolium Deoxycholaphane–dimethiodide Salt (6). To a solution of **5** (0.10 g, 0.09 mmol) in dry $CHCl_3$ (5 mL) was added MeI (1 mL). The solution was stirred at room temperature

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for 3 days. The solution was diluted with $CHCl_3$, washed with H_2O, dried over Na_2SO_4, and evaporated under vacuum to give methiodide salt **6**: yield 0.12 g, 95%; IR (KBr) ν_{max}/cm^{-1} 2933, 2866, 1743, 1632, 1448, 1375, 1268; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 0.78 (s, 6H), 0.83 (bs, 6H), 0.89 (s, 6H), 1.00−2.36 (b, 52H), 3.69 (s, 6H), 3.88 (m, 2H), 4.42 (s, 6H), 4.92 (d, 2H, J = 14.4 Hz), 5.23 (m, 4H), 5.40 (bs, 2H), 6.32 (d, 2H, J = 14.4 Hz), 9.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 12.5, 17.9, 21.7, 23.5, 25.2, 25.9, 26.2, 27.1, 28.2, 29.6, 30.5, 31.1, 33.5, 34.1, 34.9, 35.4, 39.1, 41.6, 45.3, 47.1, 49.2, 51.4, 53.2, 54.4, 55.9, 58.8, 78.9, 131.5, 143.5, 161.6, 174.6; HRMS (ES^+) 1211.6235, $C_{62}H_{96}N_6O_{10}I$ requires 1211.6227, $[M - I]^+$.

Bis-1,2,3-triazolium Deoxycholaphane−dimethylhexafluorophosphate Salt (7). Diiodide salt **6** (0.10 g, 0.07 mmol) was dissolved in MeOH (5 mL). This solution was added to a saturated methanolic solution of NH_4PF_6 (3 mL) and stirred for 1 h. The white precipitate obtained was filtered and washed with methanol and then dried under vacuum to give hexafluorophosphate salt **7**: yield 0.09 g, 88%; mp 98−100 °C; IR (KBr) ν_{max}/cm^{-1} 2932, 2868, 1746, 1449, 1374, 1270, 844; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 0.74 (s, 6H), 0.82 (s, 6H), 0.90 (d, J = 2.1, 6H), 1.02−2.40 (b, 52H), 3.68 (s, 6H), 3.78 (m, 2H), 4.38 (s, 6H), 4.84 (d, 2H, J = 15.6 Hz), 5.12 (d, 2H, J = 15.6 Hz), 5.22 (d, 2H, J = 14.4 Hz), 5.38 (bs, 2H), 5.67 (d, 2H, J = 15.6 Hz), 8.83 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 12.5, 17.9, 21.8, 23.5, 25.7, 25.8, 26.2, 26.2, 27.1, 28.1, 30.5, 31.1, 33.6, 34.2, 34.4, 34.8, 35.4, 35.7, 38.6, 41.6, 45.2, 45.3, 47.1, 49.2, 51.5, 52.5, 55.7, 78.3, 130.4, 143.7, 161.4, 174.7; HRMS (ES^+) 1229.6787, $C_{62}H_{96}N_6O_{10}PF_6$ requires 1229.6824 $[M - PF_6]^+$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra and binding isotherms. This material is available free of charge via the Internet at http://pubs.acs.org.

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