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Design and Synthesis of Novel Molecular Tweezers Derived from Chenodeoxycholic Acid

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Abstract: A novel type of chiral molecular tweezers has been designed and synthesized by using chenodeoxy cholic acid as spacer and the aromatic compounds as arm. Their structures were characterized by ^{1}HNMR, IR, MS spectra and elemental analysis. These chiral molecular tweezers showed good enantioselectivity for D-amino acid methyl esters.

Keywords: Molecular tweezers, synthesis, chenodeoxycholic acid, recognition.

The design and synthesis of artificial receptors which carry out molecular recognition using weak non-covalent interaction has been becoming one of the most challenging and attractive subjects in modern bioorganic chemistry[1-2]. In recent years, many interesting receptors have been developed. Among the various types of artificial receptors designed so far, a new class molecular tweezers has attracted more and more attention in molecular recognition, mimic enzyme catalysis, the resolution of racemates as well as molecular devices[3-6]. The natural rigid concave structure and inherent asymmetry of cholic acid pose it as ideal building blocks for the construction of molecular tweezers. The macrocyclic receptors based on cholic acid have been documented in the literature [7-8]. However, to our knowledge, the enantioselective recognition of molecular tweezers based on 3α, 7α-dihydroxy-5β-cholan-24-oic acid (chenodeoxycholic acid) has rarely been reported. In the previous paper, our research group reported the enantioselective recognition of molecular tweezers derived from 3α, 12α-dihydroxy-5β-cholan-24-oic acid (deoxycholic acid) for amino acid methyl esters [9-10]. These chiral molecular tweezers showed good enantioselectivity for D-amino acid methyl esters. Later, our research group synthesized a new type of chiral molecular tweezers based on 3α, 6α-dihydroxy-5β-cholan-24-oic acid (α-hyodeoxycholic acid). Their chiral recognition properties for amino acid methyl esters have been investigated. These chiral molecular tweezers demonstrated good enantioselectivity for L-amino acid methyl esters[11]. This fact reveals that the size of cleft and the change of microenvironment are important in molecular recognition. In order to further study the recognition mechanism of this kind of receptors for chiral compounds, we synthesized a novel type of chiral molecular tweezer

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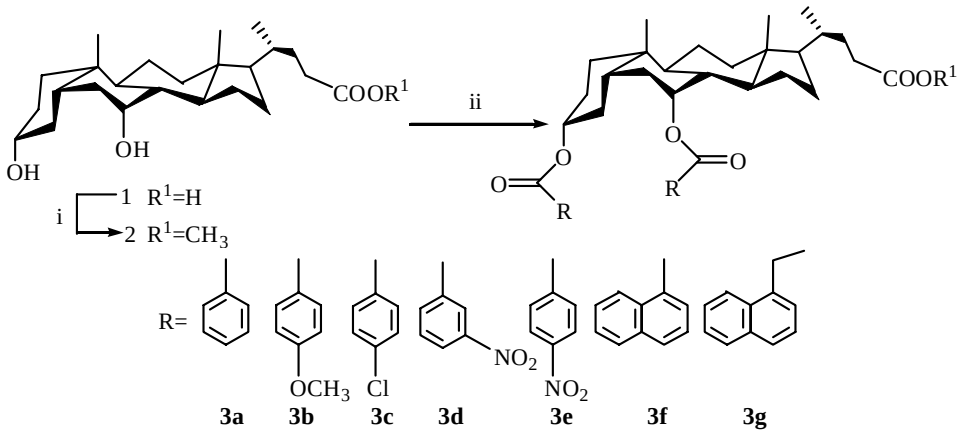
Scheme 1



Reagents and conditions: i. CH_3OH/TsOH; ii. $CHCl_3$/N $(C_2H_5)_3$ / RCOCl

receptors derived from 3α, 7α-dihydroxy-5β-cholan-24-oic acid (chenodeoxycholic acid). In this paper, we choose chenodeoxycholic acid methyl ester as spacer, and bridge different aromatic compounds in the 3α, 7α positions of chenodeoxycholic acid to get the molecular tweezer receptors **3a~g**. The synthetic route is shown in **Scheme 1**.

Chenodeoxycholic acid **1** was converted to chenodeoxycholic acid methyl ester according to the literature [12]. The reaction conditions significantly affect the yield of these receptors. The yields of compounds **3a~g** were poor when using toluene as solvent, CaH_2 as base and reacting for 22 h at 80℃. However, when these reactions were carried out in $CHCl_3$ at 70℃ for 20 h, the yields of the products were good.

All these molecular tweezers are new compounds, and their structures were confirmed by ^{1}HNMR, IR, MS spectra and elemental analysis.

The enantioselective recognition of molecular tweezers **3a~g** for some amino acid methyl esters have been investigated by UV-visible spectra titration. The preliminary results, as expected, showed that all these molecular tweezers possess the ability to complex with amino acid methyl esters examined. The association constants (Ka) and Gibbs free energy changes ($-\triangle G^o$) for inclusion complexation of molecular tweezers **3a~g** with all D-amino acid methyl esters are higher than that with all L-amino acid methy esters. The enantioselectivity K_D/K_L for **3e**, for example, is 7.91 to Phe-OMe, shows fairly good enantioselective recognition. The details of complexing experiments will be reported elsewhere.

Experimental

Melting points were determined on a micro-melting point apparatus and the thermometer was uncorrected. Infrared spectra were obtained on 1700 Perkin-Elmer FTIR using KBr disks. ^{1}HNMR spectra were recorded on a varian INOVA 400MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were determined on Finnigan LCQ^{DECA} instrument. Elemental analysis was performed on a Carlo-Erba-1106

autoanalyzer. All the solvents were used without further purification unless specified. $CHCl_3$ and $(C_2H_5)_3N$ were purified following standard purification procedures.

*General procedure of the preparation of molecular tweezers **3a~g**.*

To a solution of chenodeoxycholic acid methyl ester (0.203 g, 0.5 mmol) and newly prepared acyl chloride (2 mmol) in dry chloroform (10 mL) was added triethylamine (0.56 mL, 2 mmol). The reaction mixture was stirred at 70℃ for 20 h. After completion of the reaction, the mixture was cooled to room temperature, and then evaporated to dryness under reduced pressure, diluted with 20 mL ethyl acetate. The organic salt was filtrated off and washed with ethyl acetate (5 mL×2), then the combined filtrate was washed with saturated brine (15 mL×3), dried over anhydrous Na_2SO_4. The solvent was removed to yield the crude product, which was purified by column chromatography on silica gel H with dichloromethane/ethyl acetate/petroleum ether (50:1:20. V:V:V) as eluant to give pure product.

Compound 3a: white solid, yield 81%, m.p.: 82~84℃. IR (KBr, cm^{-1}): 2933, 2867, 1715, 1612, 1576, 1276. ^1H NMR ($CDCl_3$, 400MHz, δ ppm): 8.13~7.38 (m, 10H, Ar-H), 5.13 (s, 1H, H-7β), 4.82~4.85 (m, 1H, H-3β), 3.63 (s, 3H, $COOCH_3$), 1.03 (s, 3H, CH_3-19), 0.94 (d, J=6.4Hz, CH_3-21), 0.72 (s, 3H, CH_3-18). ESI-MS *m/z* (%): 637 (M^++23, 100). Anal. Calcd. for $C_{39}H_{50}O_6$: C 76.19, H 8.23; Found: C 76.14, H 8.28.

Compound 3b: white solid, yield 72%, m.p.: 76~78℃. IR (KBr, cm^{-1}) 2987, 2871, 1721, 1696, 1603, 1588, 1516, 1223, 1038. ^1H NMR ($CDCl_3$, 400MHz, δ ppm): 8.61~6.86 (m, 8H, Ar-H), 5.21 (s, 1H, H-7β), 4.78~4.84 (m, 1H, H-3β), 3.85 (s, 6H, Ph-OCH_3), 3.65 (s, 3H, $COOCH_3$), 1.02 (s, 3H, CH_3-19), 0.92 (d, J=6.4Hz, 3H, CH_3-21), 0.69 (s, 3H, CH_3-18). ESI-MS *m/z* (%): 697 (M^++23, 100). Anal. Calcd. for $C_{41}H_{54}O_8$: C 72.97, H 8.07; Found: C 72.82, H 8.11.

Compound 3c: white solid, yield 80%, m.p.: 94~96℃. IR (KBr, cm^{-1}) 2957, 2867, 1710, 1588, 1476, 1130. ^1H NMR ($CDCl_3$, 400MHz, δ ppm): 8.02~7.38 (m, 8H, Ar-H), 5.19 (s, 1H, H-7β), 4.81~4.86 (m, 1H, H-3β), 3.65 (s, 3H, $COOCH_3$), 1.02 (s, 3H, CH_3-19), 0.92 (d, J=6.4Hz, Hz, 3H, CH_3-21), 0.69 (s, 3H, CH_3-18). ESI-MS *m/z* (%): 683.71 (M^+, 100). Anal. Calcd. for $C_{39}H_{48}O_6Cl_2$: C 68.51, H 7.08; Found: C 68.43, H 7.12.

Compound 3d: pale yellow solid, yield 74%, m.p.: 152~154℃. IR (KBr, cm^{-1}) 2954, 2863, 1724, 1618, 1534, 1440, 1136. ^1H NMR ($CDCl_3$, 400MHz, δ ppm): 8.88~7.59 (m, 8H, Ar-H), 5.24 (s, 1H, H-7β), 4.87~4.91 (m, 1H, H-3β), 3.64 (s, 3H, $COOCH_3$), 1.05 (s, 3H, CH_3-19), 0.93 (d, J=6.4Hz, 3H, CH_3-21), 0.70 (s, 3H, CH_3-18). ESI-MS *m/z* (%): 727 (M^++23, 100). Anal. Calcd. for $C_{39}H_{48}N_2O_{10}$: C 66.46, H 6.86, N 3.97; Found: C 66.43, H 6.94, N 4.01.

Compound 3e: pale yellow solid, yield 77%, m.p.: 168~170℃. IR (KBr, cm^{-1}) 2942, 2875, 1718, 1603, 1528, 1458, 1260. ^1H NMR ($CDCl_3$, 400MHz, δ ppm): 8.29~8.06 (m, 8H, Ar-H), 5.21 (s, 1H, H-7β), 4.85~4.90 (m, 1H, H-3β), 3.63 (s, 3H, $COOCH_3$), 1.04 (s, 3H, CH_3-19), 0.94 (d, J=6.4Hz, 3H, CH_3-21), 0.71 (s, 3H, CH_3-18). ESI-MS *m/z* (%): 727 (M^++23, 100). Anal. Calcd. for $C_{39}H_{48}N_2O_{10}$: C 66.46, H 6.86, N 3.97; Found: C 66.33, H 6.95, N 4.03.

Compound 3f: white solid, yield 88%, m.p.: 88~90℃. IR (KBr, cm^{-1}) 2937, 2873, 1715, 1674, 1602, 1511, 1458, 1216. ^{1}H NMR ($CDCl_3$, 400MHz, δ ppm): 8.90~7.26 (m, 14H, Ar-H), 5.33 (s, 1H, H-7 β), 4.93~4.98 (m, 1H, H-3 β), 3.65 (s, 3H, $COOCH_3$), 1.06 (s, 3H, CH_3-19), 0.93 (d, J=6.4Hz, 3H, CH_3-21), 0.72 (s, 3H, CH_3-18). ESI-MS *m/z* (%): 737 (M^++23, 100). Anal. Calcd. for $C_{47}H_{54}O_6$: C 78.96, H 7.81; Found: C 78.82, H 7.92.

Compound 3g: white solid, yield 55%, m.p.: 60~62℃. IR (KBr, cm^{-1}) 2941, 2875, 1728, 1588, 1510, 1261, 1167. ^{1}H NMR ($CDCl_3$, 400MHz, δ ppm): 7.91~7.21 (m, 14H, Ar-H), 5.16 (s, 1H, H-7 β), 4.81~4.88 (m, 1H, H-3 β), 3.66 (s, 3H, $COOCH_3$), 1.08 (s, 3H, CH_3-19), 0.95 (d, J=6.4Hz, 3H, CH_3-21), 0.70 (s, 3H, CH_3-18). ESI-MS *m/z* (%): 765 (M^++23, 100). Anal. Calcd. for $C_{49}H_{58}O_6$: C 79.21, H 7.87; Found: C 78.98, H 7.96.

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