

## Design and Synthesis of Chiral Molecular Tweezers Based on Deoxycholic Acid

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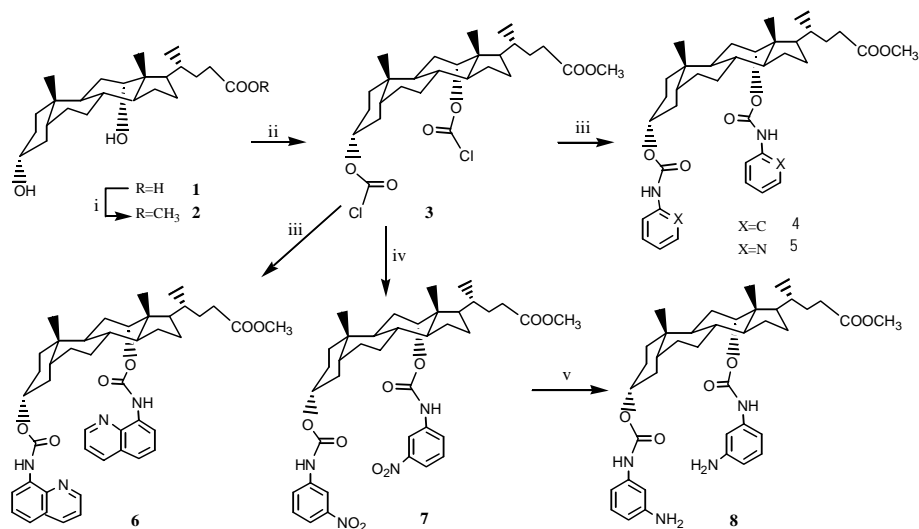
**Abstract:** A series of new chiral molecular tweezers have been designed and synthesized by using deoxycholic acid as spacer and aromatic amines as arms. Instead of using toxic phosgene, the triphosgene was employed in synthesis of the molecular tweezers receptors. These chiral molecular tweezers showed good enantioselectivity for *D*-amino acid methyl esters.

**Keywords:** Molecular tweezers, synthesis, deoxycholic acid, recognition.

Molecular tweezers is a novel type of artificial receptors, which not only offer the advantage of efficient construction but also their surfaces can be tailored for specific applications. The clefts of molecular tweezers are particularly effective in regard to complementarity with substrates since functional groups attached to the interior of the cleft converge on substrates held inside<sup>1</sup>. So, in recent years, the molecular tweezers receptors have attracted more and more attention in molecular recognition, mimic enzyme catalysis, the resolution of racemates, self-assembly of molecular structure as well as asymmetric phase-transfer catalysis study<sup>2-5</sup>. The design and synthesis of various types of molecular tweezers and study on their properties have been continually reported. The natural rigid concave structure and inherent asymmetry of cholic acid pose it as ideal building blocks for the construction of molecular tweezers. The co-directed 3 $\alpha$ , 7 $\alpha$ , 12 $\alpha$ -hydroxy groups in cholic acid can be modified to construct the various functional tweezers-type receptors. The steroidal guanidinium molecular tweezers based on cholic acid have been synthesized and showed the good enantioselective recognition for N-acyl- $\alpha$ -amino acids<sup>6</sup>. To our knowledge, however, the enantioselective recognition of molecular tweezers based on deoxycholic acid has rarely been reported. In the previous paper, we reported the enantioselective recognition of molecular tweezers derived from deoxycholic acid *via* ester chain for amino acid methyl esters<sup>7</sup>. In order to further study the recognition mechanism of this kind of receptors for chiral compounds, enhance the binding ability of receptors for substrates and develop their application in fields of biochemistry and supramolecular chemistry, we designed and synthesized a series of new tweezers-type receptors. The study of Hamilton showed that the more binding regions present, the stronger and the more stereo-selective recognition would be<sup>8</sup>. Viewed on this, in this paper, we choose deoxycholic acid **1** as a starting materials, and employ triphosgene to bridge the 3 $\alpha$ ,

12 $\alpha$ -hydroxy groups in **1** with different aromatic amines to synthesize the molecular tweezers receptors **4**~**8**. These new molecular tweezers contain more recognition regions compared with reported molecular tweezers<sup>7</sup>, and they are expected to have higher binding ability for amino acid methyl esters. In addition, avoiding the use of toxic phosgene, triphosgene was used in the synthetic process of these receptors. This provides a safe and convenient method for the synthesis of receptors *via* alkoxy-amides chain. The synthetic route is depicted in **scheme 1**.

Scheme 1



Reagents: i.  $\text{CH}_3\text{OH}/\text{CH}_3\text{COCl}$ ; ii.  $\text{CH}_2\text{Cl}_2/\text{Py}/\text{CO}(\text{OCCl}_3)_2$ ;  
iii.  $\text{CH}_2\text{Cl}_2/\text{pyridine}/40^\circ\text{C}/\text{aniline } \mathbf{4}$  or 2-aminopyridine **5** or 8-aminoquinoline **6**;  
iv.  $\text{CHCl}_3/\text{pyridine}/m\text{-nitroaniline}/70^\circ\text{C}$ ; v.  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}/\text{CH}_3\text{COOC}_2\text{H}_5$

Deoxycholic acid **1** was converted to methyl 3 $\alpha$ , 12 $\alpha$ -dihydroxy-7-deoxy-5 $\beta$ -cholan-24-oate **2** following a reported procedure<sup>9</sup>. Methyl deoxycholate **2** was reacted with triphosgene to give bis-chloroformate **3**, which was reacted directly with different aromatic amines to yield molecular tweezers **4**~**7**. The **7** was reduced with  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  in ethyl acetate to produce molecular tweezers **8**. The reaction conditions significantly affect the yield of the receptors. The only trace amounts of **7** could be detected by TLC analysis when using  $\text{CH}_2\text{Cl}_2$  as solvent and reacting for 24 h at  $40^\circ\text{C}$  whereas the **7** was obtained in yield of 30% when using 1,4-dioxane as solvent at  $80^\circ\text{C}$ . However, when reaction was carried out in  $\text{CHCl}_3$  at  $70^\circ\text{C}$  for 15 h, the **7** was produced in yield of 67%.

All these molecular tweezers are new compounds, and their structures were confirmed by IR spectra,  $^1\text{H}$ NMR spectra and elemental analysis.

The enantioselective recognition of molecular tweezers **4**~**8** for some amino acid methyl esters have been investigated by UV-Visible spectra titration and computer-aided molecular modeling. 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 ( $k_a$ ) and Gibbs free energy changes ( $-\Delta G^0$ ) for inclusion complexation of molecular tweezers **4**~**8** with all *D*-amino acid methyl esters are higher than with all *L*-amino acid methyl esters. The enantioselectivities  $K_D/K_L$  for **7**, for instance, is 3.31 for Phe-OMe and 3.11 for Leu-OMe, leading to fairly good enantioselective recognition.

Melting points were determined on a micro-melting point apparatus and the thermometer was uncorrected.  $^1\text{H}$  NMR spectra were recorded on AC-P400MHz spectrometer using  $\text{CDCl}_3$  or DMSO as solvent with TMS as references. IR spectra were recorded on a FT-IR 16PC spectrometer on KBr thin film. Elemental analysis was performed with a Carlo-Erba-1106 autoanalyzer. All solvents were purified before use.

#### **Preparation of molecular tweezers**

Typical procedure of preparation **4**: Triphosgene ( 0.1 g, 0.34 mmol ) was added to a solution of methyl deoxycholate **2** (0.2 g, 0.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (6 mL) and pyridine (0.2 mL ) at room temperature. The reaction mixture was stirred at 40°C for 4 h. **3** was formed, without separation aniline (0.1mL) was added directly to the mixture and reacted continually for 15 h at the same temperature. The solvent was removed and the residue was diluted with ethyl acetate (15 mL) and washed with 10% $\text{NaHCO}_3$  (10 mL $\times$ 3), brine (10 mL $\times$ 3) and finally dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The crude product was separated by column chromatography on silica gel with EtOAc- $\text{CH}_2\text{Cl}_2$  (2%, V/V) as eluant and then recrystallization from  $\text{CH}_2\text{Cl}_2$ /petroleum ether to yield **4** in 81% yield. The procedures of preparation **5** and **6** are the same as **4**.

Preparation of **7**: To unseparated **3**, *m*-nitroaniline (0.2 g, 1.5 mmol) was added and reacted continually for 15 h at 70°C. The solvent was removed and the residue was diluted with ethyl acetate (15 mL) and washed with 10% $\text{NaHCO}_3$  (10 mL $\times$ 3), brine (10 mL $\times$ 3) and finally dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The crude product was purified by column chromatography on silica gel with EtOAc- $\text{CH}_2\text{Cl}_2$  (2%, V/V) as eluant to produce the **7** in 67% yield.

Preparation of **8**: **7** (0.3 g, 0.4 mmol) was reacted with  $\text{SnCl}_2\cdot 2\text{H}_2\text{O}$  in EtOAc at 60°C with stirring under  $\text{N}_2$  atmosphere for 2 h. The mixture was then poured into 10% $\text{NaHCO}_3$  solution and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layer was washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was removed to yield the crude product, which was purified by column chromatography on silica gel with EtOAc- $\text{CH}_2\text{Cl}_2$  (30%, V/V) as eluant to give the **8** in 87 % yield.

$^1\text{H}$  NMR, IR and elemental analysis data of molecular tweezers **4**, **5**, **6**, **7** and **8** were listed in note 10. The details of enantioselective recognition of **4**~**8** are under further studies.

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## References and Notes

1. J. R. Julius Rebek, *Science*, **1987**, *235*, 1478.
2. Y. Habata, J. S. Bradshaw, X. X. Zhang, R. M. Izatt, *J. Am. Chem. Soc.*, **1997**, *119*, 7145.
3. N. I. Yoshio, T. Katsuki, *Tetrahedron Letters*, **1998**, *39*, 4325.
4. K. Manabe, *Tetrahedron Letters*, **1998**, *39*, 5807.
5. T. Tecilla, P. D. Robert, S. Gregory, S. A. David, H. W. David, D. H. Andrew, *J. Am. Chem. Soc.* **1990**, *112*, 9408.
6. A. P. Davis, J. L. Laurence, *Chem. Commun.*, **1999**, 9.
7. C. H. Xue, R. Hu, Q. M. Mu, F. Li, S. H. Chen, *Acta Chimica Sinica*, **2000**, *58*, 717.
8. A. D. Hamilton, *Bioorganic Chemistry Frontiers*. ed. by H. Dugas, Springer-Verlag, Berlin, Heidelberg, **1991**, Vol. 2, 117.
9. R. Hu, Z. M. Zhao, Z. X. Yang, S. H. Chen, *J. Sichuan University (Natural Science Edition)* (in Chinese), **1999**, *4*, 800.
10. Molecular tweezers **4**: white solid. mp: 136~138<sup>0</sup>C. IR( $\nu$ , cm<sup>-1</sup>): 3344 ( $\nu$ N-H); 2950, 2843 ( $\nu$ Csp<sup>3</sup>-H); 1741, 1720 ( $\nu$ C=O); 1602, 1540 ( $\nu$ Csp<sup>2</sup>-H); 1224, 1052, 1028 ( $\nu$ C-O). <sup>1</sup>H-NMR(CDCl<sub>3</sub>, 400MHz)  $\delta$  ppm: 6.51 (s, 1H, -N-H); 6.76 (s, 1H, -N-H); 7.01~7.46 (m, 10H, Ar-H); 5.11 (s, 1H, 12 $\beta$ -H); 4.68 (m, 1H, 3-H); 3.64 (s, 3H, -OCH<sub>3</sub>); 0.92 (s, 3H, 19-CH<sub>3</sub>); 0.89 (d, 3H, 21-CH<sub>3</sub>); 0.75 (s, 3H, 18-CH<sub>3</sub>). Analysis: Found C, 72.40%; H, 8.19%; N, 4.18%. C<sub>39</sub>H<sub>52</sub>N<sub>2</sub>O<sub>6</sub> requires C, 72.64%, H, 8.13%; N, 4.34%.  
Molecular tweezers **5**: white solid. mp: 156~157<sup>0</sup>C. IR ( $\nu$ , cm<sup>-1</sup>): 3154 ( $\nu$ N-H); 2942, 2879 ( $\nu$ Csp<sup>3</sup>-H); 1762, 1704 ( $\nu$ C=O); 1588, 1530 ( $\nu$ Csp<sup>2</sup>-H); 1216, 1058 ( $\nu$ C-O). <sup>1</sup>H-NMR(CDCl<sub>3</sub>, 400MHz)  $\delta$  ppm: 9.03 (s, 1H, -N-H); 8.58 (s, 1H, -N-H); 7.65~8.30 (m, 8H, Ar-H); 5.19 (s, 1H, 12 $\beta$ -H); 4.67 (m, 1H, 3 $\beta$ -H); 3.64 (s, 3H, -OCH<sub>3</sub>); 0.93 (d, 3H, 21-CH<sub>3</sub>); 0.85 (s, 3H, 19-CH<sub>3</sub>); 0.71 (s, 3H, 18-CH<sub>3</sub>). Analysis: Found C, 68.41%; H, 7.64%; N, 8.45%. C<sub>37</sub>H<sub>50</sub>N<sub>4</sub>O<sub>6</sub> requires C, 68.71%; H, 7.79%; N, 8.66%.  
Molecular tweezers **6**: white solid. mp: 212~213<sup>0</sup>C. IR ( $\nu$ , cm<sup>-1</sup>): 3374 ( $\nu$ N-H); 2946, 2823 ( $\nu$ Csp<sup>3</sup>-H); 1746, 1718 ( $\nu$ C=O); 1592, 1530 ( $\nu$ Csp<sup>2</sup>-H); 1242, 1206, 1030 ( $\nu$ C-O). <sup>1</sup>H-NMR(CDCl<sub>3</sub>, 400MHz)  $\delta$  ppm: 9.24 (s, 1H, -N-H); 9.02 (s, 1H, -N-H); 7.35~8.94 (m, 12H, Ar-H); 5.22 (s, 1H, 12 $\beta$ -H); 4.72 (m, 1H, 3 $\beta$ -H); 3.61 (s, 3H, -OCH<sub>3</sub>); 0.92 (d, 3H, 21-CH<sub>3</sub>); 0.97 (s, 3H, 19-CH<sub>3</sub>); 0.81 (s, 3H, 18-CH<sub>3</sub>). Analysis: Found C, 72.19%; H, 7.30%; N, 7.43%. C<sub>45</sub>H<sub>54</sub>N<sub>4</sub>O<sub>6</sub> requires C, 72.36%; H, 7.29%; N, 7.50%.  
Molecular tweezers **7**: yellow solid. mp: 128~130<sup>0</sup>C. IR ( $\nu$ , cm<sup>-1</sup>): 3374 ( $\nu$ N-H); 2943, 2864 ( $\nu$ Csp<sup>3</sup>-H); 1757, 1731, 1720 ( $\nu$ C=O); 1615, 1534 ( $\nu$ Csp<sup>2</sup>-H); 1596, 1350 ( $\nu$ NO<sub>2</sub>); 1222, 1050 ( $\nu$ C-O). <sup>1</sup>H-NMR(CDCl<sub>3</sub>, 400MHz)  $\delta$  ppm: 7.17 (s, 1H, -N-H); 7.67 (s, 1H, -N-H); 6.88~8.36 (m, 8H, Ar-H); 5.16 (s, 1H, 12 $\beta$ -H); 4.70 (m, 1H, 3 $\beta$ -H); 3.65 (s, 3H, -OCH<sub>3</sub>); 0.93 (s, 3H, 19-CH<sub>3</sub>); 0.89 (d, 3H, 21-CH<sub>3</sub>); 0.78 (s, 3H, 18-CH<sub>3</sub>). Analysis: Found C, 63.63%; H, 6.87%; N, 7.30%. C<sub>39</sub>H<sub>50</sub>N<sub>4</sub>O<sub>10</sub> requires C, 63.74%; H, 6.86%; N, 7.62%.  
Molecular tweezers **8**: white solid. mp: 114~116<sup>0</sup>C. IR ( $\nu$ , cm<sup>-1</sup>): 3456, 3370, 3254 ( $\nu$ N-H); 2946, 2865 ( $\nu$ Csp<sup>3</sup>-H); 1720, 1694 ( $\nu$ C=O); 1610, 1540 ( $\nu$ Csp<sup>2</sup>-H); 1220, 1052 ( $\nu$ C-O). <sup>1</sup>H-NMR(CDCl<sub>3</sub>, 400MHz)  $\delta$  ppm: 9.27(s, 1H, -N-H); 9.14 (s, 1H, -N-H); 6.15~6.89 (m, 8H, Ar-H); 4.99 (s, 4H, -NH<sub>2</sub>); 4.88 (s, 1H, 12 $\beta$ -H); 4.53 (m, 1H, 3 $\beta$ -H); 3.55 (s, 3H, -OCH<sub>3</sub>); 0.93 (s, 3H, 19-CH<sub>3</sub>); 0.78 (d, 3H, 21-CH<sub>3</sub>); 0.77 (s, 3H, 18-CH<sub>3</sub>). Analysis: Found C, 69.06%; H, 8.12%; N, 8.10%. C<sub>39</sub>H<sub>54</sub>N<sub>4</sub>O<sub>6</sub> requires C, 69.41%; H, 8.07%; N, 8.30%.

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