Synthesis of novel alkoxycarbonyl thiosemicarbazide molecular tweezers derived from deoxycholic acid under microwave irradiation

Yu Chen, ZhiGang Zhao*, XingLi Liu and ZhiChuan Shi

College of Chemistry and Environmental Protection Engineering, Southwest University for Nationalities, Chengdu 610041, P. R. China

A series of novel 12α-alkoxycarbonyl thiosemicarbazide molecular tweezers based on 3α-(1-naphthoyl) deoxycholic acid methyl ester were synthesised under microwave irradiation. Their structures were characterised by ^{1}H NMR, IR, MS spectra and elemental analysis. Their chiral recognition properties for the methyl esters of amino acids were investigated. The preliminary results showed that these molecular tweezers have good enantioselective recognition for *D/L*-amino acid methyl esters.

Keywords: molecular tweezers, deoxycholic acid, substituted thiosemicarbazide, molecular recognition, microwave irradiation

The study of the recognition of the amino acid components of proteins is an important aspect of various fields of the chemistry.[1,2] Among the various types of artificial receptors which have been designed are a new class of molecular tweezer derived from the steroid cholic acid. This is an ideal building block for the construction of molecular tweezers based its organized structural characteristics.[3–9] In recent years, some molecular tweezers based on steroidal cholic acid have been designed and synthesised.[10,11] To the best of our knowledge, however, the synthesis and recognition of molecular tweezers based on deoxycholic acid containing alkoxycarbonyl thiosemicarbazide unit in which three NH groups are directed towards the centre of the cavity, has not been reported. The NH group can hydrogen bond with substrates in the process of molecular recognition.

The application of microwave techniques for organic synthesis has attracted considerable interest in recent years.[12–14] It provides a unique chemical process with special attributes such as ease of manipulation, enhanced reaction rates, clean reaction outcomes and high yields. In view of this, we report a simple, safe and rapid synthetic method of artificial receptors based on deoxycholic acid containing alkoxycarbonyl thiosemicarbazide unit. In addition, avoiding the use of toxic phosgene, triphosgene was used in the synthetic process. This provides a safe and eco-friendly synthetic process for these molecular tweezers. The synthetic route is shown in Scheme 1.

Result and discussion

As shown in Scheme 1, deoxycholic acid **1** was converted to methyl 3α,12α-dihydroxy-7-deoxy-5β-cholan-24-oate **2** following a reported procedure.[15]

As shown in Scheme 2, intermediates **8a–l** were obtained following the previous method.[16]

The melting point of substituted thiosemicarbazides **8a–l**[17–28] is shown in Table 1.

We took the synthesis of **5a** and carried out several experiments under different conditions, such as microwave irradiation power, time and solvent to obtain the best results of this reaction. The typical results are shown in Tables 2–5.

As shown in Table 2, we irradiated the reaction using different powers for the same reaction time (12 min). As a result, 240 W was identified as the optimum power.

As shown in Table 3, we found that 12 min was the optimum reaction time when the yield was the highest under the same power (240 W). However, more byproducts were obtained when the reaction time was increased.

CH_2Cl_2, $CHCl_3$ and THF were compared to evaluate the solvent effect on the reaction. Different solvents were employed under the similar reaction conditions, and the results are shown in Table 4. Considering CH_2Cl_2 is less toxic than $CHCl_3$, THF and easily removed than the other two solvents, we conclude that CH_2Cl_2 is the best solvent in this reaction.

As shown in Table 5, we compared the synthesis of molecular tweezers **5a–l** by microwave irradiation and conventional heating. Compared to conventional thermal heating, microwave irradiation greatly decreased the reaction time from 300–540 min to 12–15 min. It was obvious that yields were increased from 65–85% to 89–94%. From these data, we conclude that microwave irradiation method is a rapid, efficient, and environmentally friendly methodology.

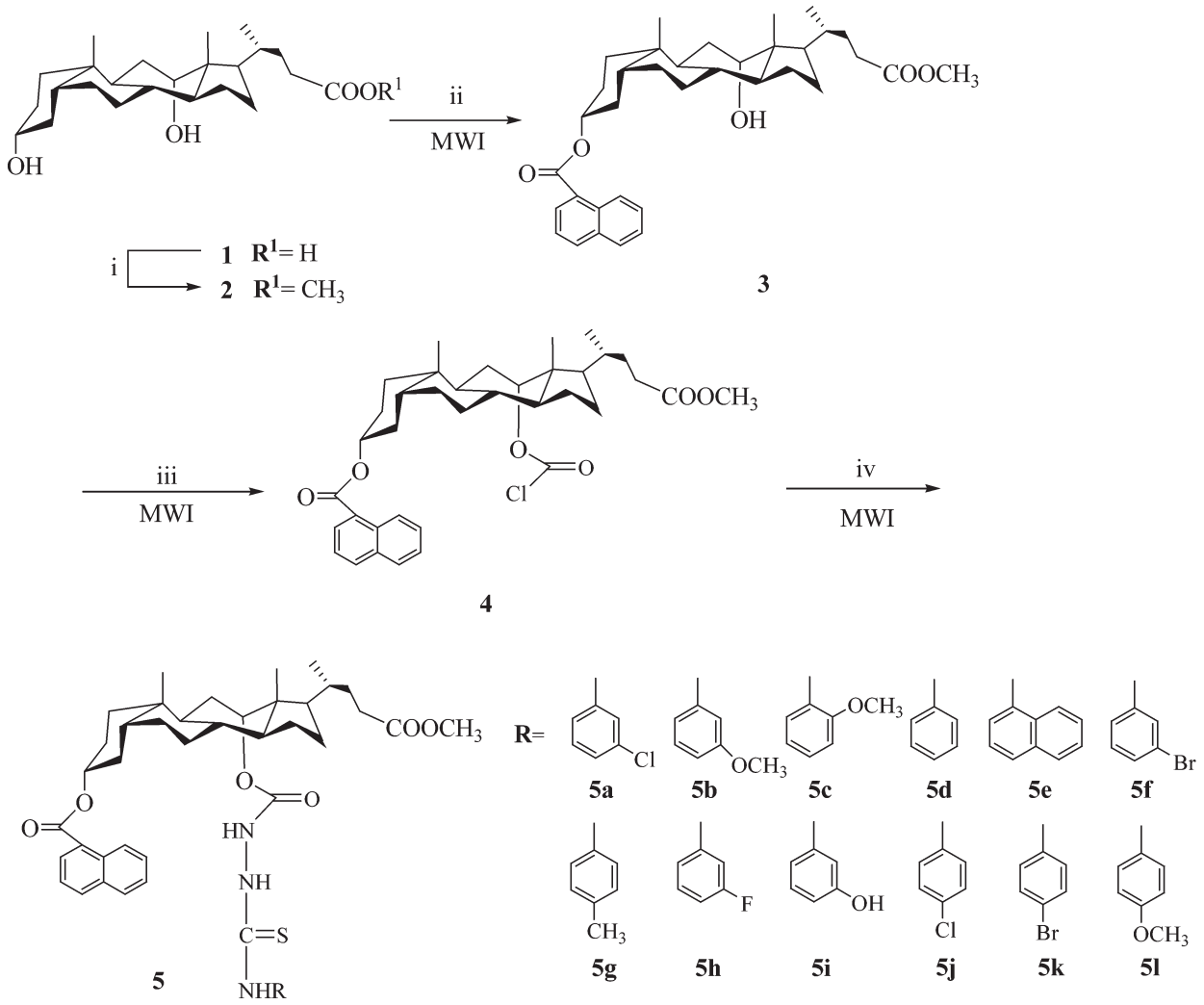
The recognition by the molecular tweezers **5h**, **5j** for some amino acid methyl esters has been investigated by UV-Vis spectra titration in $CHCl_3$ at 25 °C. The titration data were analysed by using the Hildebrand–Benesi equation.[29] The plot with $1/\Delta A$ versus the $1/[G_0]$ gave a straight line (Fig. 1), supporting the stoichiometry of 1:1 host–guest complexes. Using the linear fitting method, we obtained the associate constants of complex. The results indicate that molecular tweezers **5h**, **5j** not only recognise all amino acid methyl esters examined but also exhibit higher selectivity for *D*–amino acid methyl esters. The association constants of molecular tweezer **5h**, for instance, are 242.45, 253.04 L·mol^{-1} for *D*-Phe-OMe, *D*-Tyr-OMe, while the constants of **5h** are 98.05, 72.30 L·mol^{-1} for *L*-Phe-OMe, *L*-Tyr-OMe. The K_D/K_L is 2.47 and 3.50 respectively. The UV-Vis plot of **5h** for *D*-Tyr-OMe is shown in Fig. 2.

The enantioselective recognition of molecular tweezers **5h**, **5j** for some amino acid methyl esters has also been investigated by computer-aided molecular modelling using Chem 3D program. When the host **5h** at the minimum energy, its conformation is a tweezer type, which has the ability to form complex with guest molecules. The minimum energy conformation of **5h** is shown in Fig.3**.** The chiral recognition ability comes from the inherent asymmetry of deoxycholic acid, and the main recognition driving forces are the hydrogen bonding and π–π stacking interaction between the host and guest molecules. The details of molecular tweezers **5a–l** are under further studies.

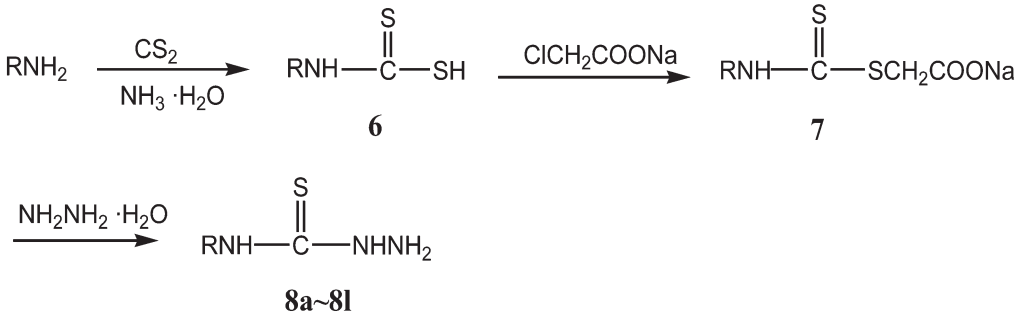
Experimental

Melting points were determined on a micro-melting point apparatus and are uncorrected. IR spectra were obtained on 1700 Perkin-Elmer FTIR using KBr disks. ^{1}H NMR spectra were recorded on a Varian INOVA 400 MHz 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. Microwave irradiation was carried out with a MCL-3 microwave oven at full power (700 W), which was modified from domestic microwave oven and tested to conform to the performance index before use. All the solvents were purified before use. Optical rotation was measured on a Wzz-2B polarimeter. All the solvents were purified before use.

* Correspondent. E-mail: zzg63129@yahoo.com.cn



Scheme 1 Synthetic route of molecular tweezers **5a–l**. Reagents: i, CH_3OH, CH_3COCl; ii, 1-naphthoyl chloride, K_2CO_3; iii, CH_2Cl_2, triphosgene, pyridine; iv, substituted thiosemicarbazide, pyridine.



Scheme 2 Synthetic route of substituted thiosemicarbazides **8a–l**.

Table 1 The melting point of substituted thiosemicarbazides **8a–l**

Product	Formula	M.p./°C	Lit. m.p./°C
8a	$C_7H_8N_3ClS$	126–127	125[17]
8b	$C_8H_{11}N_3OS$	157–158	161[18]
8c	$C_8H_{11}N_3OS$	155–156	159[19]
8d	$C_7H_{10}N_3S$	137–138	136–138[20]
8e	$C_{11}H_{11}N_3S$	135–136	138–139[21]
8f	$C_7H_8N_3BrS$	141–142	140[22]
8g	$C_8H_{11}N_3S$	135–136	137[23]
8h	$C_7H_8N_3FS$	137–138	138[24]
8i	$C_7H_9N_3OS$	160–162	160[25]
8j	$C_7H_8N_3ClS$	178–179	178[26]
8k	$C_7H_8N_3BrS$	165–168	163–165[27]
8l	$C_8H_{11}N_3OS$	147–148	152[28]

Table 2 The effect of microwave powers on yields

Power/W	100	150	200	240	300	350
Yield/%	64	70	85	93	89	80

Table 3 The effect of microwave irradiation time on yields

Time/min	10	11	12	14	18	20
Yield/%	76	87	93	90	85	81

Preparation of compound **3***; general procedure*

1-Naphthoic acid (1.2 mmol) was added to $SOCl_2$ (3 mL) and 1 drop of dry DMF at room temperature. 1-Naphthoyl chloride was obtained after refluxing 3 h in 65 °C. The excess $SOCl_2$ was removed under

Table 4 The effect of solvent on yields

Entry	Solvent	Yield/%	Volume of solvent/mL
1	THF	60	20
2	CH_2Cl_2	93	10
3	$CHCl_3$	90	10

Table 5 Synthetic comparison of molecular tweezers **5a–5l** between microwave irradiation and conventional heating

Comp.	Conventional method		Microwave method		t_C^a/t_{MW}^b
	t/min	Yield/%	t/min	Yield/%	
5a	480	**67**	**12.0**	**93**	**40**
5b	540	**80**	**12.0**	**92**	**45**
5c	480	**65**	**13.0**	**91**	**37**
5d	540	**70**	**12.0**	**92**	**45**
5e	360	**79**	**15.0**	**90**	**24**
5f	480	**81**	**12.0**	**90**	**40**
5g	480	**85**	**12.0**	**94**	**40**
5h	300	**79**	**14.0**	**92**	**21**
5i	300	**82**	**15.0**	**89**	**20**
5j	480	**78**	**12.0**	**92**	**40**
5k	540	**80**	**13.0**	**91**	**42**
5l	480	**76**	**12.0**	**92**	**40**

T_C^a, time of conventional heating method; T_{MW}^b, time of microwave irradiation method.

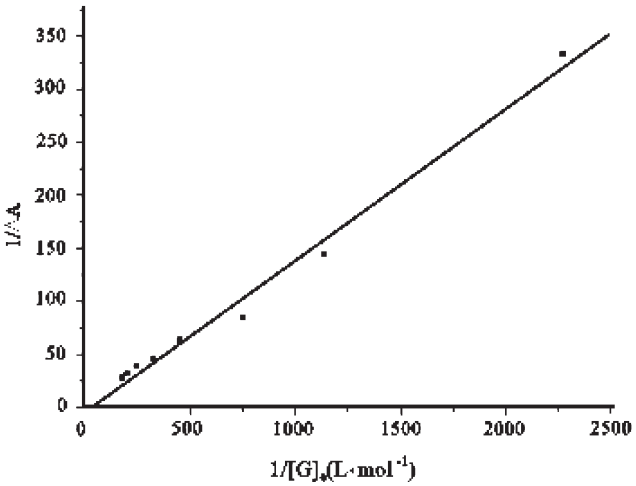


Fig. 1 Typical plot of $1/\Delta A$ *vs* the $1/[G_0]$ for the inclusion complexation of tweezer **5h** with *D*-Tyr-OMe in $CHCl_3$ at 25 °C.

reduced pressure, then mixed with the methyl 3α,12α-dihydroxy-7-deoxy-5β-cholan-24-oate (1 mmol). The reaction mixture was irradiated for 5 min at 460 W using solid K_2CO_3 as a support. The reaction was monitored by TLC until it was completed. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (10 mL×3). The organic layer was washed successively with 10% $NaHCO_3$ (10 mL×3), brine (10 mL×3), and finally dried over anhydrous Na_2SO_4. The solvent was evaporated to give the crude product. The crude product was purified by column chromatography on silica gel H with dichloromethane/ethyl acetate as eluant. The physical and spectra data of the compound **3** are as follows.

3: White crystals, yield 89%, m.p. 42–43 °C; $[\alpha]_D^{20}$ +21.4 (*c* 0.15, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.87 (d, *J* = 8.4 Hz, 1H, ArH), 8.20 (d, *J* = 7.2 Hz, 1H, ArH), 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.88 (d, *J* = 8.0 Hz, 1H, ArH), 7.62–7.46 (m, 3H, ArH), 5.14–5.06 (m, 1H, 3*β*-H), 4.01 (s, 1H, *12β*-H), 3.67 (s, 3H, $COOCH_3$), 0.93 (d, *J* = 6.8 Hz, 3H, 21-CH_3), 0.89 (s, 3H, 19-CH_3), 0.70 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3549, 2978, 2871, 1717, 1515, 1472, 1131; ESI–MS *m/z* (%): 561.4 $[(M+1)^+$, 100]. Anal. Calcd for $C_{36}H_{48}O_5$: C, 77.11; H, 8.63; Found: C, 76.98; H, 8.57%.

Microwave method for preparation of **5a–l**

Triphosgene (0.2 mmol) was added to a solution of compound **3** (0.5 mmol) in 10 mL dry CH_2Cl_2 and 0.1 mL dry pyridine at room temperature. The reaction mixture was irradiated for 9 min at 200 W to give compound **4**. The substituted thiosemicarbazide (0.5 mmol) and dry pyridine 0.2 mL were added directly to the mixture, which was then irradiated continually for 3–6 min at 240 W. The solvent was removed and the residue was diluted with ethyl acetate 20 mL and washed with 10% $NaHCO_3$ (10 mL×3), brine (10 mL×3), and finally dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel H with dichloromethane/ethyl acetate as eluant. The whole progress was monitored by TLC. The physical and spectra data of the compounds **5a–l** are as follows.

5a: White solid, yield 93%, m.p. 107–108 °C; $[\alpha]_D^{20}$ + 133.4 (c 0.15, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.85 (d, *J* = 8.8 Hz, 1H, ArNHCS), 8.42 (s, 1H, NH), 8.16 (d, *J* = 6.8 Hz, 1H, ArH), 8.02–7.96 (m, 2H, ArH), 7.89 (d, *J* = 8.4 Hz, 1H, ArH), 7.63–7.46 (m, 5H, ArH), 7.13–7.10 (m, 2H, ArH), 6.86 (s, 1H, CONH), 5.11 (s, 1H, 12*β*-H), 5.07–5.03 (m, 1H, 3*β*-H), 3.64 (s, 3H, $COOCH_3$), 0.96 (s, 3H, 19-CH_3), 0.87 (d, *J* = 6.0 Hz, 3H, 21-CH_3), 0.74 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3336, 2934, 2859, 1711, 1594, 1524, 1470, 1246, 1018, 777; ESI–MS *m/z* (%): 788.4 $[(M+1)^+$, 100]. Anal. Calcd for $C_{44}H_{54}ClN_3O_6S$: C, 67.03; H, 6.90; N, 5.33. Found: C, 66.95; H, 6.85; N, 5.29%.

5b: Pale yellow crystal, yield 92%, m.p. 102–103 °C; $[\alpha]_D^{20}$ +122.7 (c 0.10, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.87 (d, *J* = 9.2 Hz, 1H, ArNHCS), 8.18 (d, *J* = 7.6 Hz, 1H, ArH), 8.01 (d, *J* = 8.4 Hz, 2H, ArH+NH), 7.89 (d, *J* = 8.0 Hz, 1H, ArH), 7.62–7.47 (m, 4H, ArH), 7.21 (s, 1H, ArH), 7.00 (s, 1H, ArH), 6.88 (s, 2H, ArH), 6.75 (d, *J* = 6.8 Hz, 1H, CONH), 5.11 (s, 1H, 12*β*-H), 5.06 (s, 1H, 3*β*-H), 3.75 (s, 3H, $COOCH_3$), 3.64 (s, 3H, $COOCH_3$), 0.97 (s, 3H, 19-CH_3), 0.89 (d, *J* = 6.0 Hz, 3H, 21-CH_3), 0.75 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3320, 2942, 2859, 1715, 1603, 1453, 1246, 1006, 780; ESI–MS *m/z* (%): 784.4 $[(M+1)^+$, 100]. Anal. Calcd for $C_{45}H_{57}N_3O_7S$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.91; H, 7.29; N, 5.39%.

5c: White solid, yield 91%, m.p. 95–96 °C; $[\alpha]_D^{20}$ +114.9 (c 0.11, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.87 (d, *J* = 8.4 Hz, 1H, ArNHCS), 8.21 (d, *J* = 7.2 Hz, 1H, ArH), 8.01 (d, *J* = 8.0 Hz, 2H, ArH+NH), 7.89 (d, *J* = 8.4 Hz, 1H, ArH), 7.63–7.48 (m, 4H, ArH), 7.13–7.09 (m, 1H, ArH), 6.96–6.92 (m, 2H, ArH), 6.83–6.79 (m, 2H, ArH+CONH), 5.12 (s, 1H, 12*β*-H), 5.08–5.03 (m, 1H, 3*β*-H), 3.78 (s, 3H, $COOCH_3$), 3.64 (s, 3H, $COOCH_3$), 0.97 (s, 3H, 19-CH_3), 0.87 (d, *J* = 6.4 Hz, 3H, 21-CH_3), 0.74 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3316, 2943, 2869, 1717, 1595, 1541, 1449, 1242, 1014, 790; ESI–MS *m/z* (%): 784.5 $[(M+1)^+$, 100]. Anal. Calcd for $C_{45}H_{57}N_3O_7S$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.91; H, 7.29; N, 5.39%.

5d: White solid, yield 92%, m.p. 109–110 °C; $[\alpha]_D^{20}$ +78.4 (c 0.12, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.86 (d, *J* = 8.8 Hz, 1H, ArNHCS), 8.17 (d, *J* = 6.8 Hz, 2H, ArH+NH), 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.89 (d, *J* = 8.0 Hz, 1H, ArH), 7.63–7.46 (m, 4H, ArH), 7.35–7.26 (m, 4H, ArH), 7.19 (s, 1H, ArH), 6.87 (s, 1H, CONH), 5.11 (s, 1H, 12*β*-H), 5.08–5.05 (m, 1H, 3*β*-H), 3.64 (s, 3H, $COOCH_3$), 0.97 (s, 3H, 19-CH_3), 0.89 (d, *J* = 6.4 Hz, 3H, 21-CH_3), 0.75 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3411, 2934, 2859, 1711, 1599, 1512, 1445, 1246, 1014, 786; ESI–MS *m/z* (%): 754.4 $[(M+1)^+$, 100]. Anal. Calcd for $C_{44}H_{54}N_3O_6S$: C, 70.09; H, 7.35; N, 5.57. Found: C, 69.95; H, 7.28; N, 5.60%.

5e: Pale yellow crystal, yield 90%, m.p. 110–111 °C; $[\alpha]_D^{20}$ +136.3 (c 0.10, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.83 (d, *J* = 8.4 Hz, 1H, ArNHCS), 8.12 (d, *J* = 7.2 Hz, 2H, ArH+NH), 7.99 (d, *J* = 8.0 Hz, 2H, ArH), 7.87–7.85 (m, 3H, ArH), 7.60–7.43 (m, 8H, ArH), 6.94 (s, 1H, CONH), 5.10 (s, 1H, 12*β*-H), 5.02 (s, 1H, 3*β*-H), 3.60 (s, 3H, $COOCH_3$), 0.96 (s, 3H, 19-CH_3), 0.87 (d, *J* = 4.4 Hz, 3H, 21-CH_3), 0.74 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3432, 2938, 2859, 1711, 1653, 1508, 1466, 1242, 1018, 777; ESI–MS *m/z* (%): 804.5 $[(M+1)^+$, 100]. Anal. Calcd for $C_{48}H_{57}N_3O_6S$: C, 71.70; H, 7.15; N, 5.23. Found: C, 71.66; H, 7.18; N, 5.20%.

5f: White solid, yield 90%, m.p. 118–119 °C; $[\alpha]_D^{20}$ + 93.7 (c 0.10, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.85 (d, *J* = 8.8 Hz, 1H, ArNHCS), 8.37 (s, 1H, NH), 8.16 (d, *J* = 7.2 Hz, 1H, ArH), 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.89 (d, *J* = 8.0 Hz, 1H, ArH), 7.80 (s, 1H, ArH), 7.63–7.46 (m, 5H, ArH), 7.33–7.30 (m, 1H, ArH), 7.18–7.00 (m, 1H, ArH), 6.79 (s, 1H, CONH), 5.11 (s, 1H, 12*β*-H), 5.07–5.02 (m, 1H, 3*β*-H), 3.64 (s, 3H, $COOCH_3$), 0.96 (s, 3H, 19-CH_3), 0.87 (d, *J* = 6.4 Hz, 3H, 21-CH_3), 0.75 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3435, 2926, 2861, 1715, 1642, 1530, 1464, 1244, 1009, 781; ESI–MS *m/z* (%): 832.4 $[(M+1)^+$, 100]. Anal. Calcd for $C_{44}H_{54}BrN_3O_6S$: C, 63.45; H, 6.53; N, 5.05. Found: C, 63.41; H, 6.49; N, 5.01%.

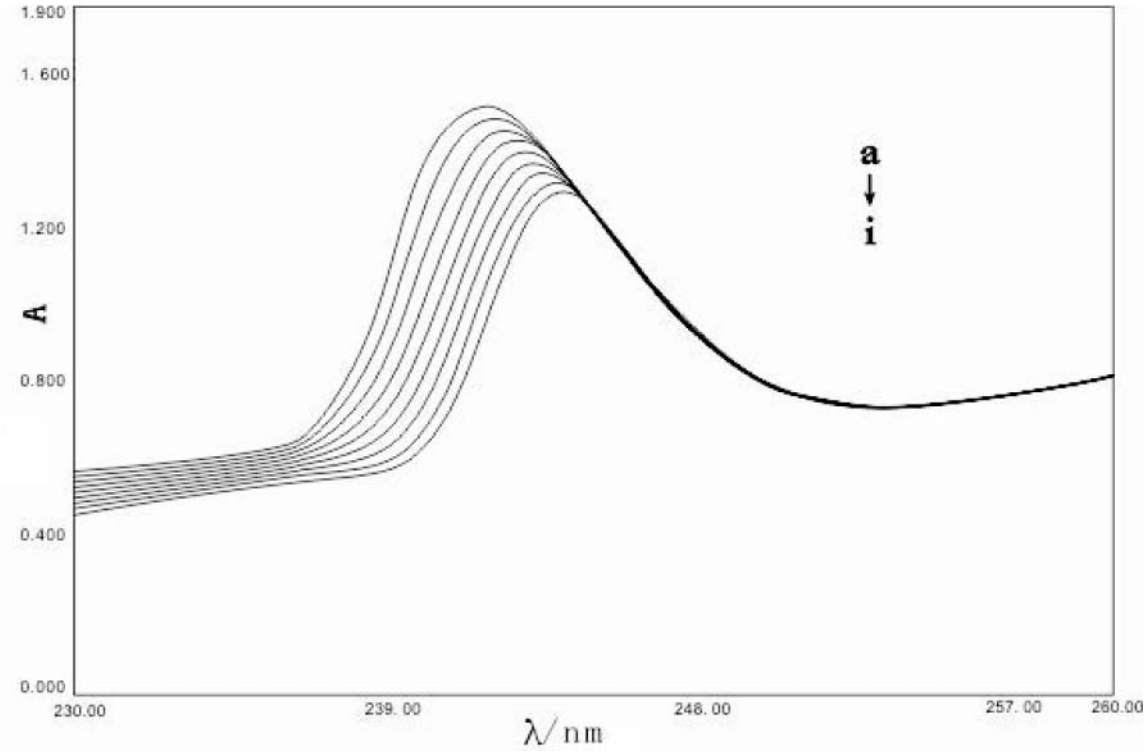


Fig. 2 UV-vis spectra of molecular tweezer **5h** (1.88×10^{-5}mol L^{-1}) in the presence of *D*-Tyr-OMe:(a) 0 mol L^{-1}; (b) 0.30×10^{-3}mol L^{-1}; (c) 0.60×10^{-3}mol L^{-1}; (d) 0.90×10^{-3}mol L^{-1}; (e) 1.20×10^{-3}mol L^{-1}; (f) 1.50×10^{-3}mol L^{-1}; (g) 1.80×10^{-3}mol L^{-1}; (h) 2.10×10^{-3}mol L^{-1}; (i) 2.40×10^{-3}mol L^{-1} with λ_{max} at 244.0 nm.

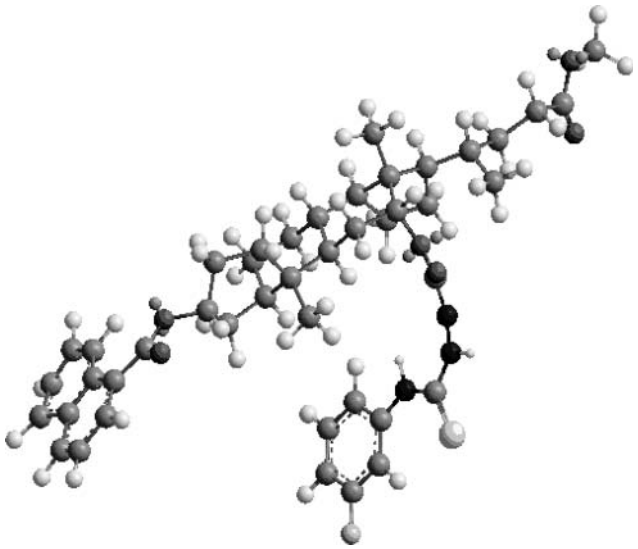


Fig. 3 Minimum energy conformation of molecular tweezer **5h**.

5g: Colourless crystals, yield 94%, m.p. 104–106 °C; $[\alpha]_D^{20}$ +77.2 (c 0.13, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.86 (d, *J* = 8.8 Hz, 1H, ArNHCS), 8.16 (d, *J* = 6.8 Hz, 1H, ArH), 8.01 (d, *J* = 8.0 Hz, 2H, ArH+NH), 7.89 (d, *J* = 8.0 Hz, 1H, ArH), 7.62–7.46 (m, 4H, ArH), 7.20–7.10 (m, 4H, ArH), 6.88 (s, 1H, CONH), 5.10 (s, 1H, 12β-H), 5.08–5.02 (m, 1H, 3*β*-H), 3.64 (s, 3H, $COOCH_3$), 0.97 (s, 3H, 19-CH_3), 0.89 (d, *J* = 6.4 Hz, 3H, 21-CH_3), 0.75 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3431, 2938, 2867, 1714, 1623, 1519, 1453, 1245, 1017, 785; ESI–MS *m/z* (%): 1558.6 $[(2M+23)^+$, 100]. Anal. Calcd for $C_{45}H_{57}N_3O_6S$: C, 70.37; H, 7.48; N, 5.47. Found: C, 70.31; H, 7.39; N, 5.44%.

5h: White solid, yield 92%, m.p. 103–104 °C; $[\alpha]_D^{20}$+157.8 (c 0.11, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.85 (d, *J* = 8.8 Hz, 1H, ArNHCS), 8.35 (s, 1H, NH), 8.16 (d, *J* = 7.2 Hz, 1H, ArH), 8.01 (d, *J* = 8.4 Hz, 1H, ArH), 7.89 (d, *J* = 8.0 Hz, 1H, ArH), 7.82 (s, 1H, ArH), 7.63–7.46 (m, 3H, ArH), 7.33–7.31 (m, 1H, ArH), 7.20–7.16 (m, 1H, ArH), 7.12–7.10 (m, 1H, ArH), 6.86–6.82 (m, 2H, ArH+CONH), 5.11 (s, 1H, 12*β*-H), 5.08–5.02 (m, 1H, 3*β*-H), 3.64 (s, 3H, $COOCH_3$), 0.97 (s, 3H, 19-CH_3), 0.88 (d, *J* = 6.4 Hz, 3H, 21-CH_3), 0.75 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3302, 2943, 2869, 1715, 1607, 1540, 1450, 1202, 1018, 781; ESI–MS *m/z* (%): 772.3 $[(M+1)^+$, 100]. Anal. Calcd for $C_{44}H_{54}FN_3O_6S$: C, 68.46; H, 7.05; N, 5.44. Found: C, 68.39; H, 7.08; N, 5.38%.

5i: Pale yellow crystal, yield 89%, m.p. 112–113 °C; $[\alpha]_D^{20}$ +94.1 (c 0.11, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.86 (d, *J* = 8.8 Hz, 1H, ArNHCS), 8.60 (s, 1H, NH), 8.19 (d, *J* = 6.4 Hz, 1H, ArH), 7.95 (d, *J* = 8.0 Hz, 1H, ArH), 7.85 (d, *J* = 8.4 Hz, 1H, ArH), 7.76 (s, 1H, OH), 7.63–7.45 (m, 4H, ArH), 7.19–7.15 (m, 1H, ArH), 7.06–6.82 (m, 3H, ArH), 6.71 (d, *J* = 7.2 Hz, 1H, CONH), 5.09 (s, 1H, 12*β*-H), 5.05–5.01 (m, 1H, 3β-H), 3.66 (s, 3H, $COOCH_3$), 0.95 (s, 3H, 19-CH_3), 0.84 (d, *J* = 5.6 Hz, 3H, 21-CH_3), 0.74 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3422, 3046, 2936, 2867, 1713, 1607, 1507, 1453, 1238, 1010, 786; ESI–MS *m/z* (%): 770.4 $[(M+1)^+$, 100]. Anal. Calcd for $C_{44}H_{55}N_3O_7S$: C, 68.63; H, 7.20; N, 5.46. Found: C, 68.60; H, 7.18; N, 5.44%.

5j: White solid, yield 92%, m.p. 114–115 °C; $[\alpha]_D^{20}$ + 98.2 (c 0.14, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.84 (d, *J* = 8.4 Hz, 1H, ArNHCS), 8.34 (s, 1H, NH), 8.15 (d, *J* = 7.2 Hz, 1H, ArH), 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 7.89 (d, *J* = 8.0 Hz, 1H, ArH), 7.82 (s, 1H, ArH), 7.63–7.46 (m, 3H, ArH), 7.34–7.19 (m, 4H, ArH), 6.86 (s, 1H, CONH), 5.10 (s, 1H, 12*β*-H), 5.07–5.02 (m, 1H, 3*β*-H), 3.64 (s, 3H, $COOCH_3$), 0.96 (s, 3H, 19-CH_3), 0.86 (d, *J* = 6.4 Hz, 3H, 21-CH_3), 0.75 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3436, 2942, 2872, 1711, 1632, 1516, 1458, 1238, 1010, 782; ESI–MS *m/z* (%): 1599.4 $[(2M+23)^+$, 100]. Anal. Calcd for $C_{44}H_{54}ClN_3O_6S$: C, 67.03; H, 6.90; N, 5.33. Found: C, 66.95; H, 6.83; N, 5.29%.

5k: White solid, yield 91%, m.p. 116–117 °C; $[\alpha]_D^{20}$+121.4 (c 0.11, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.90–8.83 (m, 1H, ArNHCS), 8.37 (s, 1H, NH), 8.21–8.14 (m, 1H, ArH), 8.01–7.82 (m, 3H, ArH), 7.63–7.46 (m, 3H, ArH), 7.34–7.26 (m, 4H, ArH), 6.89 (s, 1H, CONH), 5.09 (s, 1H, 12*β*-H), 5.06–5.02 (m, 1H, 3*β*-H), 3.64 (s, 3H, $COOCH_3$), 0.95 (s, 3H, 19-CH_3), 0.85 (d, *J* = 6.4 Hz, 3H, 21-CH_3), 0.74 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3436, 2940, 2864, 1714, 1520, 1503, 1449, 1242, 1014, 786; ESI–MS *m/z* (%): 832.4 $[(M+1)^+$,

100]. Anal. Calcd for $C_{44}H_{54}BrN_3O_6S$: C, 63.45; H, 6.53; N, 5.05. Found: C, 63.41; H, 6.49; N, 5.01%.

5l: White solid, yield 92%, m.p. 107–108 °C; $[\alpha]_D^{20}$ +145.6 (c 0.11, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.86 (d, J = 8.4 Hz, 1H, ArNHCS), 8.17 (d, J = 7.2 Hz, 1H, ArH), 8.01 (d, J = 8.4 Hz, 1H, ArH), 7.89 (d, J = 8.0 Hz, 2H, ArH+NH), 7.62–7.47 (m, 4H, ArH), 7.26 (s, 2H, ArH), 6.84–6.82 (m, 3H, ArH+CONH), 5.10 (s, 1H, 12β-H), 5.05 (s, 1H, 3β-H), 3.73 (s, 3H, $COOCH_3$), 3.64 (s, 3H, $COOCH_3$), 0.97 (s, 3H, 19-CH_3), 0.90 (d, J = 6.0 Hz, 3H, 21-CH_3), 0.75 (s, 3H, 18-CH_3); IR (KBr, cm^{-1}): 3411, 2942, 2868, 1716, 1618, 1515, 1457, 1244, 1025, 783; ESI–MS m/z (%): 784.4 [(M+1)$^+$, 100]. Anal. Calcd for $C_{45}H_{57}N_3O_7S$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.91; H, 7.29; N, 5.39%.

Conventional heating method for preparation of **5a–5l**

Triphosgene (0.2 mmol) was added to a solution of compound **3** (0.5 mmol) in 20 mL dry CH_2Cl_2 and 0.1 mL dry pyridine at room temperature. The solution was refluxed for 3 h, to give compound **4**. The substituted thiosemicarbazide (0.5 mmol) and dry pyridine 0.2 mL were added directly to the mixture which was refluxed for a further 2–6 h. The solvent was removed and the residue was diluted with ethyl acetate 20 mL and washed with 10% $NaHCO_3$ (10 mL×3), brine (10 mL×3), and finally dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel H with dichloromethane/ethyl acetate as eluant, in 65–5% yields.

We thank the Natural Science Foundation of the State Ethnic Affairs Commission of P.R. China (Project No.09XN08) for the financial support.

Received 21 March 2010; accepted 21 May 2010
Paper 1000019 doi: 10.3184/030823410X520732
Published online: 28 July 2010

References

1 A. Metzger, K. Gloe and H. Stephan, *J. Org. Chem.*, 1996, **61**, 2051.
2 Z.G. Zhao, X.L. Liu and S.H. Chen, *Chin. J. Org. Chem.*, 2009, **29**, 1336 (in Chinese).
3 K.S. Kim and H.S. Kim, *Tetrahedron*, 2005, **61**, 12366.
4 J.T. Luo, Y.L. Chen and X.X. Zhu, *Synlett*., 2007, **14**, 2201.
5 H.O. Jeung and T.C. Kui, *Tetrahedron.*, 2008, **64**, 6488.
6 S.Y. Liu, K.Y. Law, Y.B. He and W.H. Chan, *Tetrahedron Lett*., 2006, **47**, 7857.
7 H. Wang, W.H. Chan and W.M.A. Lee, *Org. Biomol. Chem*., 2008, **6**, 929.
8 C. Mamta, U. Shailesh and S.P. Pramod, *Tetrahedron*, 2007, **63**, 171.
9 H.K. Byeong, S.L. Chang, H.S. Jun and P.H. Him, *Talanta*, 2003, **61**, 393.
10 K.S. Kim, H.S. Jang and H.S. Kim, *J. Korean. Chem. Soc.*, 2006, **27**, 1445.
11 X.M. Wu, Z.G. Zhao and X.L. Liu, *Chin. J. Org. Chem.*, 2009, **29**, 956 (in Chinese).
12 H. Naeimi and L. Moradi, *Catalysis Commun.*, 2006, **7**, 1067.
13 V. Pollshettiwar and S.V. Rajender, *Acc. Chem. Res.*, 2008, **41**, 629.
14 E. Ramesh and R. Raghunathan, *Tetrahedron Lett*., 2008, **49**, 1812.
15 X.L. Liu, Z.G. Zhao and B.T. Zeng, *Chin. J. Org. Chem*., 2007, **27**, 994 (in Chinese).
16 C.Y. Liu, G.W. Ying, J. Qian, Z. Li and A.H. Yu, *Chem. Reag*., 2003, **25**, 160 (in Chinese).
17 A.J. Cowper, *J. Ind. Chem. Soc.*, 1981, **58**, 1087.
18 K. Joseph, *DE* 832891 1952.
19 M. Tisler, *Croatica Chem. Acta*, 1965, **28**, 147.
20 S.K. Chawla, *Polyhedron.*, 2006, **25**, 627.
21 M. Tisler, *Croatica Chem. Acta*, 1956, **28**, 147.
22 D.A. Benson, *Nucl. Acids Res.*, 2000, **28**, 15.
23 R.W. Bost, *J. Am. Chem. Soc.*, 1931, **53**, 652.
24 D.L. Klayman, *J. Med. Chem.*, 1979, **22**, 855.
25 A. Wahab, *Boll. Chim. Farm.*, 1978, **117**, 107.
26 M. Upalkanti, *Chem. Pharm. Bull.*, 2004, **52**, 178.
27 M. Upalkanti, *Chem. Pharm. Bull.*, 2004, **52**, 178.
28 R. Stanislav, *Colletc.Czech.Chem.Commun.*, 1986, **5**, 1692.
29 C.H. Xue, R. Hu, Q.M. Mu, F. Li and S.H. Chen, *Acta Chim. Sinica*, 2000, **58**, 717 (in Chinese).