Electronic Supplementary Material (ESI) for Chemical Communications

SUPPORTING INFORMATION

The Four-Step Total Synthesis of (–)-Chaetominine

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Contents

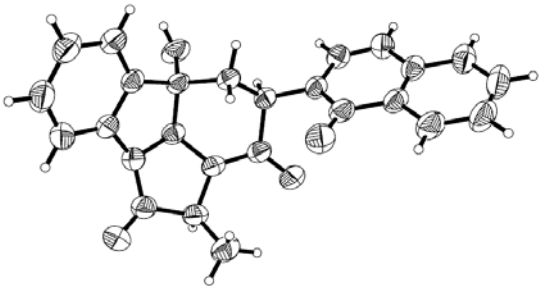


Figure 1 Single crystal X-ray structure of compound **1**

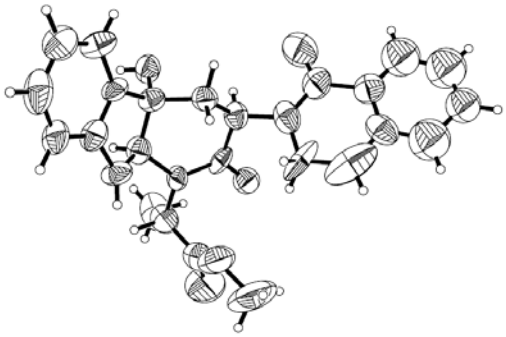


Figure 2 Single crystal X-ray structure of compound **5**

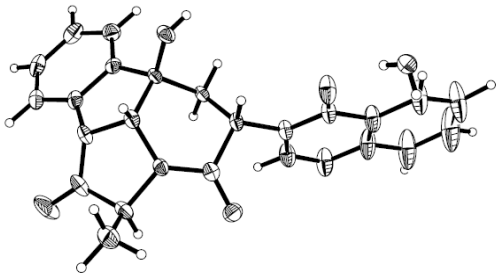


Figure 3 Single crystal X-ray structure of compound **7**

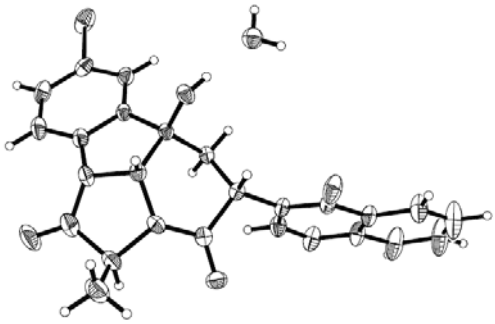
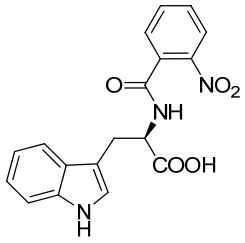


Figure 4 Single crystal X-ray structure of compound **8**

Experimental Section

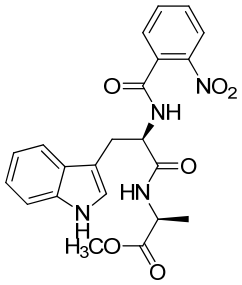
General Methods. Melting points were uncorrected. Infrared spectra were measured using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Silica gel (300-400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60-90°C) mixture. DMSO was pre-dried over calcium hydride. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

(*R*)-3-(1*H*-Indol-3-yl)-2-(2-nitrobenzamido)propanoic acid (4)



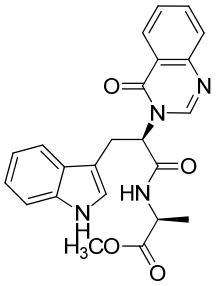
A mixture of 2-nitrobenzoic acid (1.25 g, 7.5 mmol) in thionyl chloride (1.63 mL, 22.5 mmol) was refluxed for 3 h. The excess thionyl chloride was removed under reduced pressure. The residue was dissolved in anhydrous THF (5 mL) and this solution was added dropwise to an ice-cooled solution of D-tryptophan (1.02 g, 5.0 mmol) in 15 mL of 1 *N* NaOH with vigorous stirring. After being stirred for 2 h, the reaction mixture was acidified with 1 *N* HCl until pH 3, and then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was crystallizd from EtOAc to give compound **4** (1.59 g, yield: 90%) as a yellow solid. Mp 204-206 °C (EtOAc); $[\alpha]_D^{20}$ −7.7 (*c* 1.1, CH_3OH); IR (film) ν_{max}: 3469, 3407, 1719, 1626, 1608, 1525, 1344, 1218, 741 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (br s, 1H), 10.91 (s, 1H), 9.17 (d, J = 7.9 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.75-7.60 (m, 3H), 7.50 (d, J = 7.3 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.30-7.25 (m, 1H), 7.12 (t, J = 7.3 Hz, 1H), 7.04 (t, J = 7.3 Hz, 1H), 4.77 (ddd, J = 8.6, 7.9, 5.2 Hz, 1H), 3.35 (dd, J = 14.8, 5.2 Hz, 1H), 3.23 (dd, J = 14.8, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.5, 166.0, 147.7, 136.7, 133.8, 132.5, 131.3, 129.7, 127.8, 124.5, 124.1, 121.6, 119.0, 118.7, 112.0, 110.4, 54.0, 27.5; MS (ESI) *m/z* 376 (M+Na$^+$, 100%); Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.12; H, 4.32; N, 11.58.

Methyl (*S*)-{2-[(*R*)-3-(1*H*-Indol-3-yl)-2-(2-nitrobenzamido)propanamido]propanoate} (3)



To a stirring solution of **4** (1.0 g, 2.83 mmol) in THF (10 mL) at –30 °C were added successively *N*-methylmorpholine (0.47 mL, 4.25 mmol) and ^{t}BuOCOC1 (0.40 mL, 3.11 mmol). After being stirred at –30 °C under N_2 for 60 min, the suspension was added slowly to a solution of L-alanine methyl ester hydrochloride (0.87 g, 5.66 mmol) and *N*-methylmorpholine (0.95 mL, 8.49 mmol) in THF (20 mL) at –78 °C, and the resulting mixture was stirred for 12 h at –20 °C. The reaction was quenched with a saturated aqueous NH_4Cl (10 mL) and diluted with water (30 mL). The aqueous phase was separated and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 3:2) to give compound **3** (1.16 g, yield: 91%) as a yellow solid. Mp 165-167 °C (EtOAc); $[\alpha]_D^{20}$ –32.8 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3299, 1739, 1651, 1530, 1348, 1213, 1159, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 7.96-7.92 (m, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.52-7.43 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.16-7.02 (m, 4H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 7.2 Hz, 1H), 4.99 (ddd, *J* = 7.8, 7.0, 6.5 Hz, 1H), 4.42 (dq, *J* = 7.2, 7.3 Hz, 1H), 3.64 (s, 3H), 3.41 (dd, *J* = 14.8, 6.5 Hz, 1H), 3.30 (dd, *J* = 14.8, 7.0 Hz, 1H), 1.18 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 170.3, 166.4, 146.2, 136.1, 133.8, 132.2, 130.5, 128.5, 127.5, 124.5, 123.3, 122.1, 119.6, 118.5, 111.3, 110.1, 54.2, 52.4, 48.2, 27.3, 17.4; MS (ESI) *m/z* 461 ($M+Na^+$, 100%); Anal. Calcd for $C_{22}H_{22}N_4O_6$: C, 60.27; H, 5.06; N, 12.78. Found: C, 59.85; H, 4.68; N, 12.50.

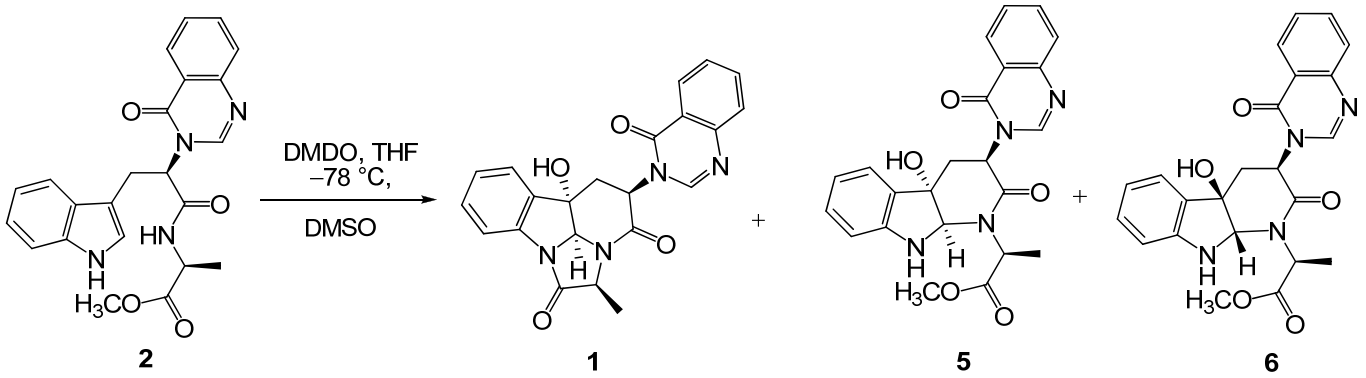
Methyl (*S*)-{2-[(*R*)-3-(1*H*-Indol-3-yl)-2-(4-oxoquinazolin-3(4*H*)-yl)propanamido]propanoate} (2)



To a suspension of zinc powder (200 mg, 3.08 mmol) in THF (5 mL) was added $TiCl_4$ (0.22 mL, 2.59 mmol). The resulting mixture was stirred at 50 °C for 1 h. After being cooled to 0 °C, a solution of compound **3** (186 mg, 0.42 mmol) in THF (2 mL) and trimethyl orthoformate (0.20 mL, 1.82 mmol) were added dropwise. The reaction mixture was stirred at 0 °C for 24 h before quenched with brine (5 mL) and stirred for another 2 h. The phases were separated, and the aqueous phase was extracted with EtOAc (3 ×

2 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 3:2) to give compound **2** (172 mg, yield: 97%) as a white solid. Mp 201-203 °C (EtOAc); $[\alpha]_D^{20}$ +52.8 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3319, 1743, 1660, 1609, 1547, 1476, 1456, 1216, 1159, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.23 (br s, 1H), 8.21-8.17 (m, 1H), 7.74-7.62 (m, 3H), 7.46-7.40 (m, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 7.04-7.01 (m, 1H), 6.96 (d, J = 7.3 Hz, 1H), 5.85 (dd, J = 8.7, 7.0 Hz, 1H), 4.48 (dq, J = 7.3, 7.2 Hz, 1H), 3.73 (dd, J = 14.5, 8.7 Hz, 1H), 3.59 (s, 3H), 3.41 (dd, J = 14.5, 7.0 Hz, 1H), 1.21 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 168.4, 161.1, 147.4, 144.2, 136.1, 134.5, 127.4, 127.2, 126.9, 126.8, 123.3, 122.3, 121.3, 119.8, 118.4, 111.3, 109.6, 56.3, 52.4, 48.4, 27.1, 17.5; MS (ESI) *m/z* 441 ($M+Na^+$, 100%); Anal. Calcd for $C_{23}H_{22}N_4O_4$: C, 66.02; H, 5.30; N, 13.39. Found: C, 65.77; H, 5.36; N, 13.14.

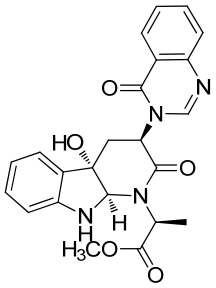
(–)-Chaetominine (**1**)



To a solution of compound **2** (200 mg, 0.48 mmol) in anhydrous acetone (2 mL) was added dropwise a solution of DMDO[1] in acetone (0.03 M, 32 mL, 0.96 mmol) at –78 °C. After being stirred for 1 h, DMSO (pre-dried over CaH_2 within 2 g/100 mL, 34 mL) was added. After being stirred for 48 h at rt, the solvent was removed under reduced pressure, and the residue cooled to 0 °C, and H_2O (100 mL) was added. The resulting mixture was extracted with Et_2O (10 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc: PE = 3:2 then CH_2Cl_2: CH_3OH = 30:1) to give chaetominine (**1**) (80 mg, yield: 42%), its precursor **5** (6 mg, yield: 3%), and compound **6** (105 mg, yield: 51%).

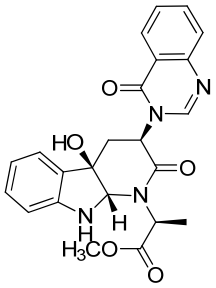
(–)-Chaetominine (**1**): colorless crystals. Mp 288-290 °C (MeOH) (lit. 161-163 °C;[2] 162-165 °C,[3] 164 °C;[4] 160-162 °C[5]); $[\alpha]_D^{20}$: –49.7 (*c* 0.48, MeOH) {lit. $[\alpha]_D^{20}$ –70 (*c* 0.48, MeOH);[2] –49.4 (*c* 0.26, MeOH);[3] –48 (*c* 0.45, MeOH);[4] –47.9 (*c* 0.25, MeOH)[5]}; IR (film) ν_{max}: 3424, 1726, 1662, 1609, 1478, 1325, 1277, 754 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.29 (br s, 1H), 8.18 (br d, J = 7.1 Hz, 1H), 7.86 (td, J = 7.6, 1.5 Hz, 1H), 7.69 (d, J = 6.9 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.43 (td, J = 7.6, 1.0 Hz, 1H), 7.25 (td, J = 7.6, 1.0 Hz, 1H), 6.68 (br s, 1H), 6.05-5.60 (br s, 1H), 5.61 (s, 1H), 4.61 (q, J = 6.9 Hz, 1H), 2.94 (dd, J = 12.8, 12.8 Hz, 1H), 2.54 (dd, J = 12.8, 3.0 Hz, 1H), 1.60 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 166.1 (br), 160.6, 148.0, 147.4 (br), 139.3, 137.3, 135.3, 130.5, 127.8 (2C), 127.0, 126.0, 125.5, 121.8, 115.1, 83.1, 77.0, 60.2, 50.8 (br), 38.7, 14.6; MS (ESI) *m/z* 425 ($M+Na^+$, 100%); Anal. Calcd for $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92. Found: C, 65.55; H, 4.75; N, 13.69.

Methyl (*S*)-{2-((3*R*,4a*S*,9a*R*)-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[*2,3-b*]indol-1-yl)propanoate} (5)



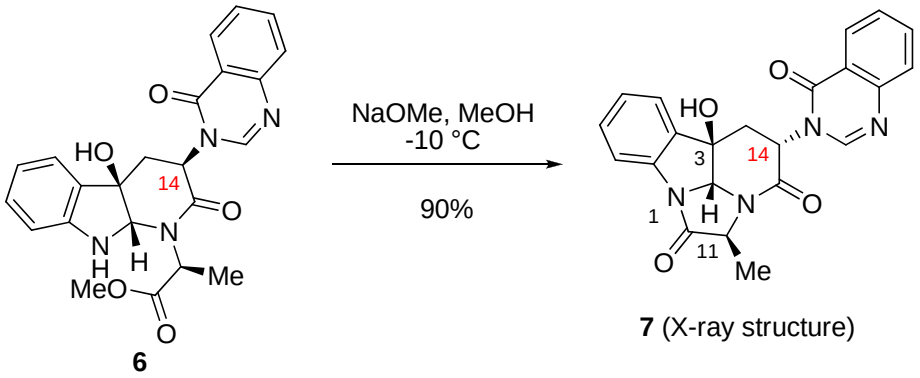
Compound **5**: Colorless crystals. Mp 154-157 °C (EtOAc); $[\alpha]_D^{20}$ –62.5 (*c* 0.36, $CHCl_3$); IR (film) ν_{max}: 3336, 1738, 1664, 1612, 1475, 1327, 1248, 1118, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.86 (br s, 1H), 7.77-7.70 (m, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.49-7.43 (m, 1H), 7.24-7.19 (m, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 5.43 (br s, 1H), 5.12 (s, 1H), 4.75 (br s, 1H), 3.75 (s, 3H), 2.90-2.70 (m, 1H), 2.34 (dd, *J* = 12.9, 5.0 Hz, 1H), 1.60 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 166.6, 160.7, 147.6, 145.9 (2C), 134.5, 131.7, 130.1, 127.4, 127.3, 126.8, 122.3, 121.9, 121.0, 111.8, 82.0, 77.8, 54.3, 52.6, 35.3, 15.1 (one amide carbonyl carbon was not observed due to slow rotation at the C_9-N bond);[4] MS (ESI) *m/z* 457 ($M+Na^+$, 100%); HRMS-ESI Calcd for $C_{23}H_{22}N_4O_5$ ($M+H^+$): 435.1668; found: 435.1689.

Methyl (*S*)-{2-((3*R*,4a*R*,9a*S*)-4a-hydroxy-2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)-2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[*2,3*]indol-1-yl)propanoate} (6)



Compound **6**: White solid. Mp 138-140 °C (EtOAc); $[\alpha]_D^{20}$ –184.2 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3374, 1740, 1674, 1612, 1474, 1243, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.73-7.66 (m, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.49-7.37 (m, 2H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.75 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 5.27 (d, *J* = 3.5 Hz, 1H), 5.22 (d, *J* = 3.5 Hz, 1H), 5.12 (q, *J* = 7.4 Hz, 1H), 5.04 (br s, 1H), 3.72 (s, 3H), 2.91 (br s, 1H), 2.45 (dd, *J* = 12.2, 4.0 Hz, 1H), 1.47 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.3, 160.4, 148.4, 146.9, 145.6, 134.4, 130.6, 129.4, 127.3, 126.9, 126.8, 123.7, 121.6, 120.0, 110.2, 80.5, 79.0, 52.4, 52.1, 40.1, 16.0 (one amide carbonyl carbon was not observed due to slow rotation at the C_9-N bond);[4] MS (ESI) *m/z* 457 ($M+Na^+$, 100%); Anal. Calcd for $C_{23}H_{22}N_4O_5$: C, 63.59; H, 5.10; N, 12.90. Found: C, 63.33; H, 4.94; N, 12.74.

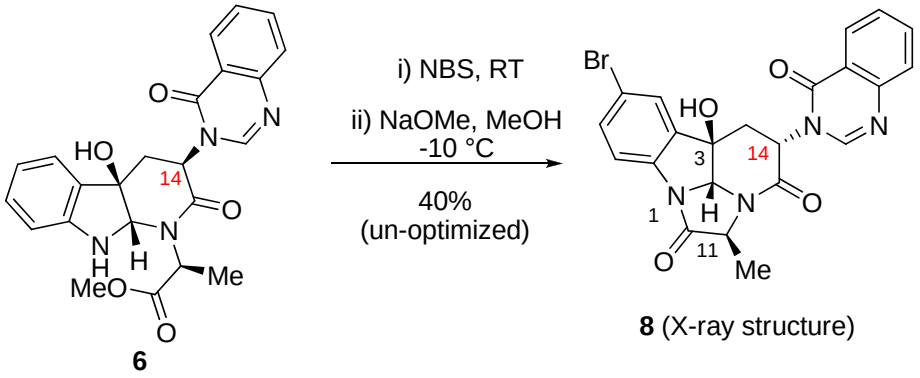
(+)-2,3,14-Tri-*epi*-chaetominine (7)



6 **7** (X-ray structure)

To a solution of compound **6** (37 mg, 0.09 mmol) in MeOH (1 mL) was added a solution of freshly prepared CH_3ONa (14 mg, 0.254 mmol) in CH_3OH (3.5 mL) at −10 °C. After being stirred for 24 h, the reaction mixture was acidified with 10% HCOOH until pH 7. The solvent was evaporated under reduced pressure, and the residue was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 3:2) to give compound **7** (34 mg, yield: 90%) as colorless crystals. Mp 205-208 °C (EtOAc); $[\alpha]_D^{20}$ +98.0 (*c* 0.50, CH_3OH); IR (film) ν_{max}: 3436, 1674, 1610, 1478, 1325, 1292, 1080, 773 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.21 (dd, J = 8.0, 0.8 Hz, 1H), 7.90-7.84 (m, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.59 (td, J = 8.0, 0.8 Hz, 1H), 7.53-7.46 (m, 2H), 7.42 (td, J = 7.5, 0.8 Hz, 1H), 7.25 (td, J = 7.5, 0.8 Hz, 1H), 6.79 (br s, 1H), 5.98-5.90 (m, 1H), 5.87 (s, 1H), 4.66 (q, J = 7.2 Hz, 1H), 2.96 (dd, J = 13.0, 13.0 Hz, 1H), 2.51 (dd, J = 13.0, 3.4 Hz, 1H), 1.50 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.5, 166.9, 160.6, 148.0, 147.3, 138.4, 138.2, 135.4, 130.4, 127.91, 127.88, 127.1, 126.1, 125.3, 121.7, 115.1, 83.6, 77.3, 60.3, 49.9, 39.0, 15.7; MS (ESI) *m/z* 425 ($M+Na^+$, 100%); Anal. Calcd for $C_{22}H_{18}N_4O_4 \cdot H_2O$: C, 62.85; H, 4.79; N, 13.33. Found: C, 62.75; H, 5.15; N, 13.22.

(2*R*,3*R*,11*S*,14*S*)-6-Bromo-4,5,5a,9c-tetrahydro-5a-hydroxy-2-methyl-4-(4-oxo-3(4*H*)-quinazolinyl)-3*H*-2a,9b-diazacyclopenta[*jk*]fluorene-1,3(2*H*)-dione (8)



6 **8** (X-ray structure)

To a solution of compound **6** (37 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise at rt a solution of *N*-bromosuccinimide (15 mg, 0.09 mmol) in CH_2Cl_2 (2 mL), and the resulting bright yellow solution was stirred for 30 minutes. The mixture was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over Na_2SO_4, filtered and concentrated. The residue was stirred in a solution of freshly prepared CH_3ONa (0.254 mmol) in CH_3OH (4.3 ml) at −10 °C for 24 h. The mixture was acidified with 10% of HCOOH until pH 7. The solvent was evaporated under reduced pressure, and the residue was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc: PE = 3:2) to give compound **8** (16 mg, yield: 40%) as a colorless crystals. Mp 182-185 °C (CH_3CN); $[\alpha]_D^{20}$ +250.0 (*c* 0.40, CH_3CN); IR (film) ν_{max}: 3354, 1725, 1672, 1611, 1477, 1324, 1261, 769 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 8.18-8.14 (m, 1H), 7.79 (s, 1H), 7.77-7.71 (m, 1H), 7.62-7.58 (m, 1H), 7.54-7.44 (m, 3H), 7.35 (d, J = 8.4 Hz, 1H), 5.85 (dd, J = 13.3, 3.6 Hz, 1H), 5.74 (s, 1H), 4.68 (br s, 1H), 4.63 (q, J = 7.2 Hz, 1H), 2.62 (dd, J = 13.3, 13.1 Hz, 1H), 2.49 (dd, J = 13.1, 3.6 Hz, 1H), 1.44 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 172.2, 166.6, 161.2, 148.4, 146.4, 139.5, 138.5, 135.3, 133.9, 128.4 (2C), 128.2, 128.0, 127.3, 122.3, 117.2, 84.1, 78.2, 60.2, 50.4, 39.2, 15.3; MS (ESI) *m/z* 481 ($M+H^+$, 100%); HRMS-ESI Calcd for $C_{22}H_{17}BrN_4O_4$: $(M+H)^+$ 481.0511; found: 481.0519.

References

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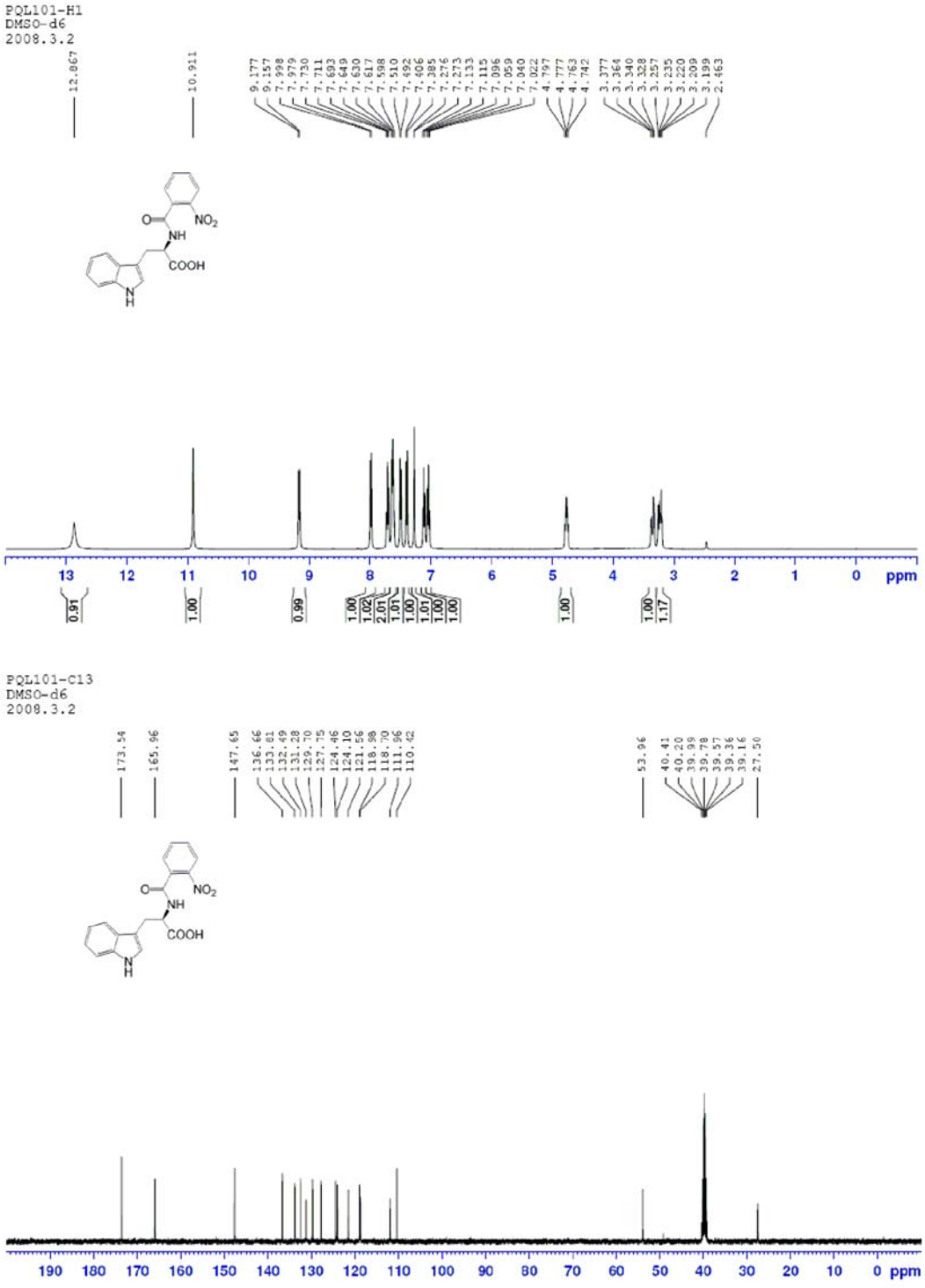
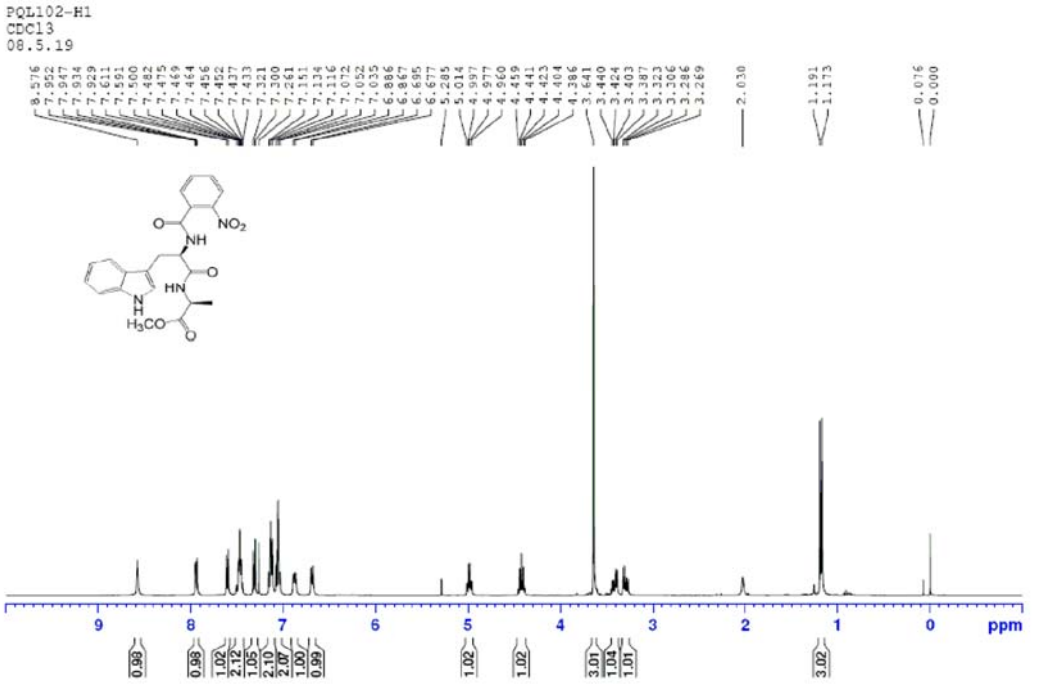
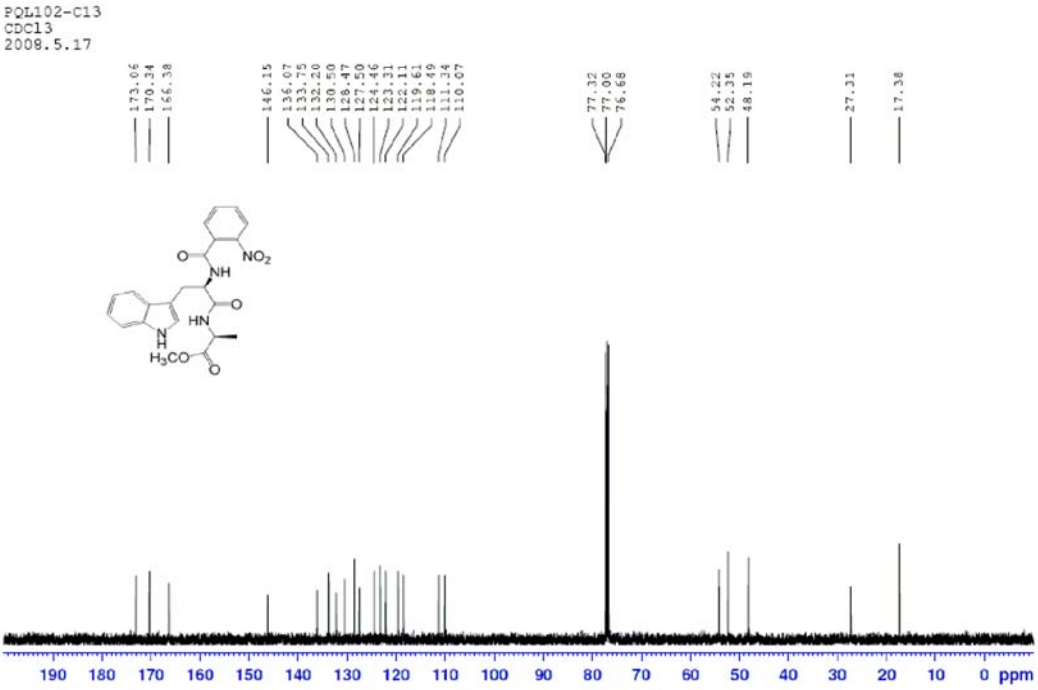
^{1}H and ^{13}C NMR spectra of compound **4**

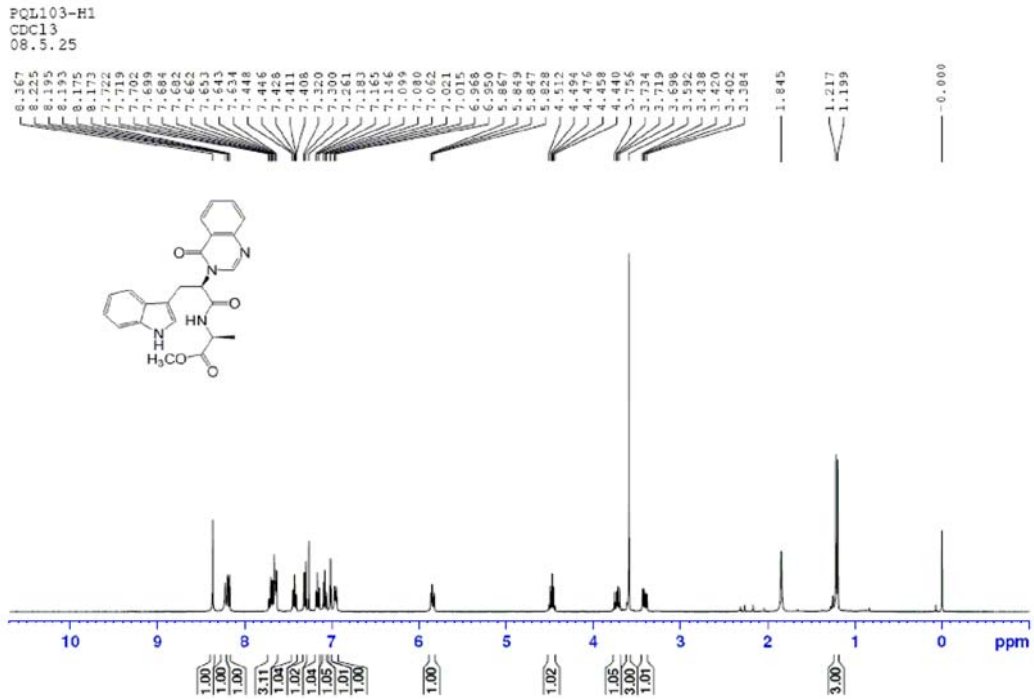


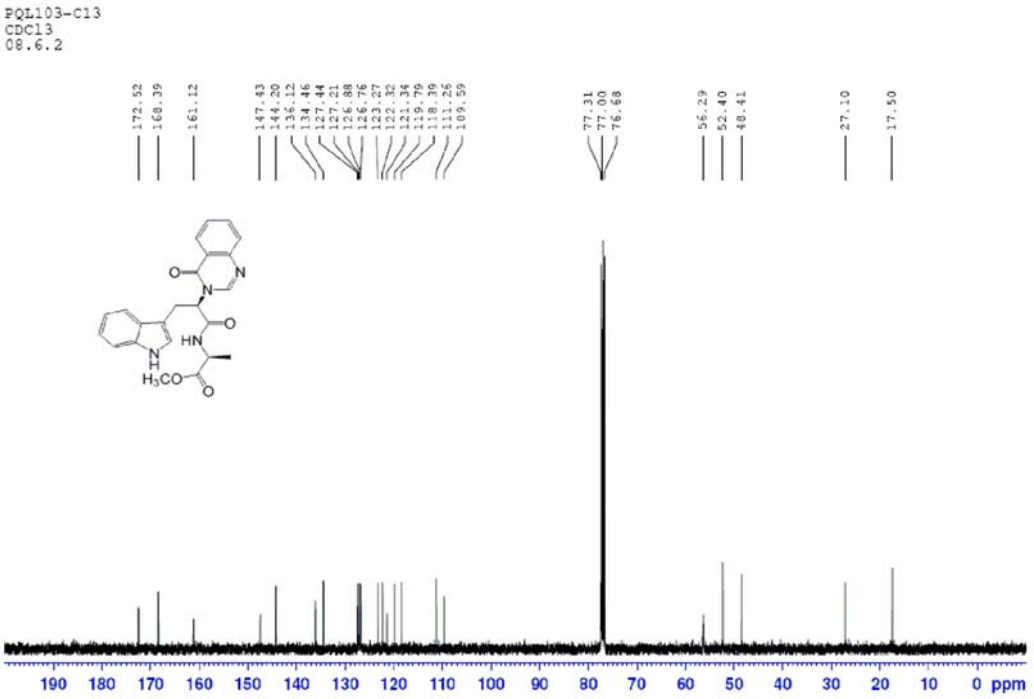
^{1}H and ^{13}C NMR spectra of compound **3**



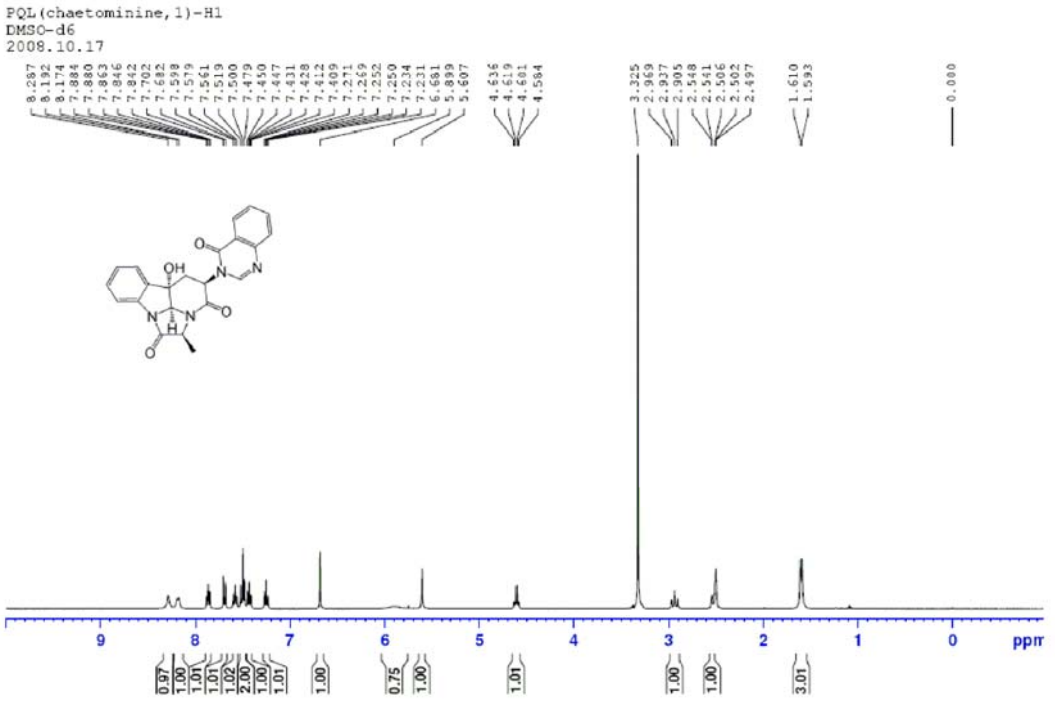


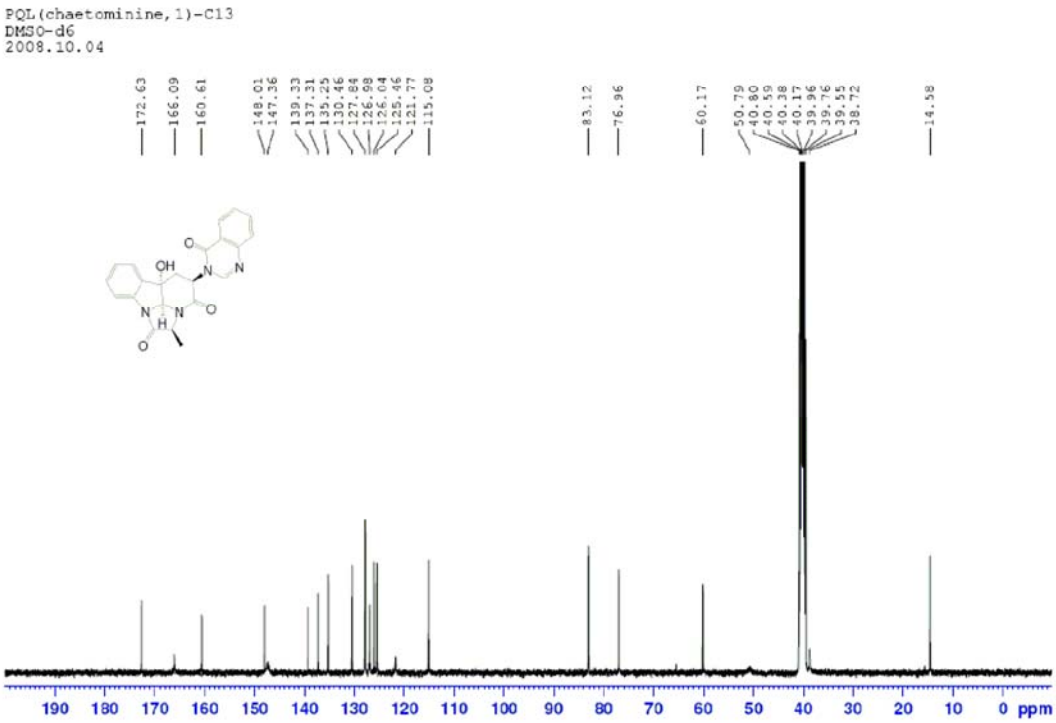
^{1}H and ^{13}C NMR spectra of compound **2**



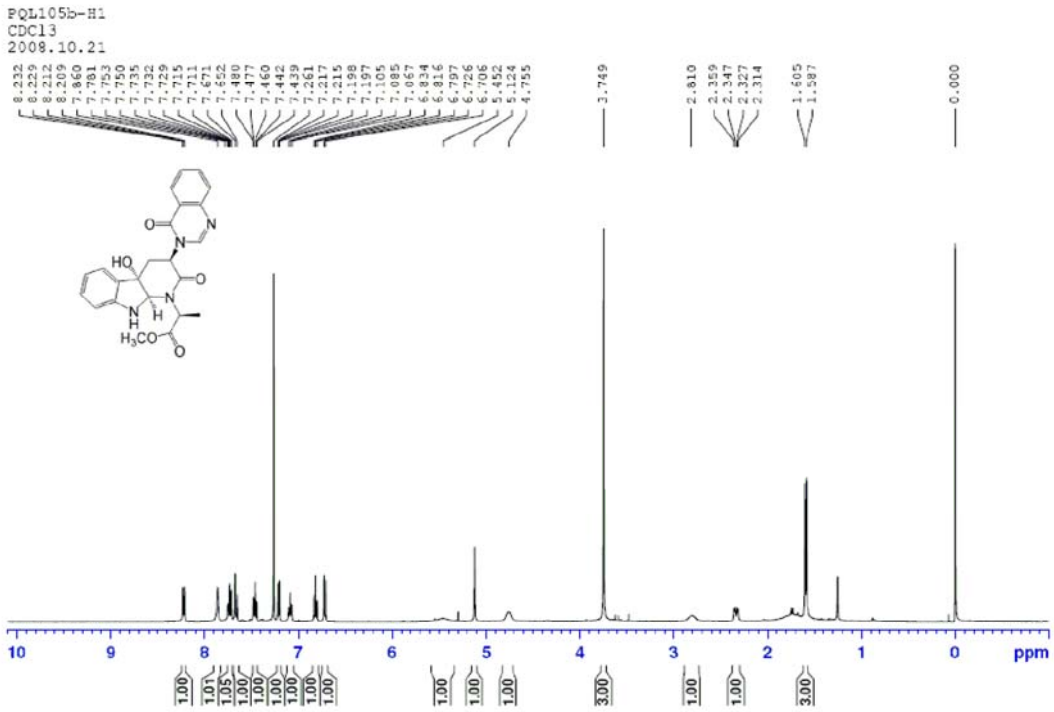


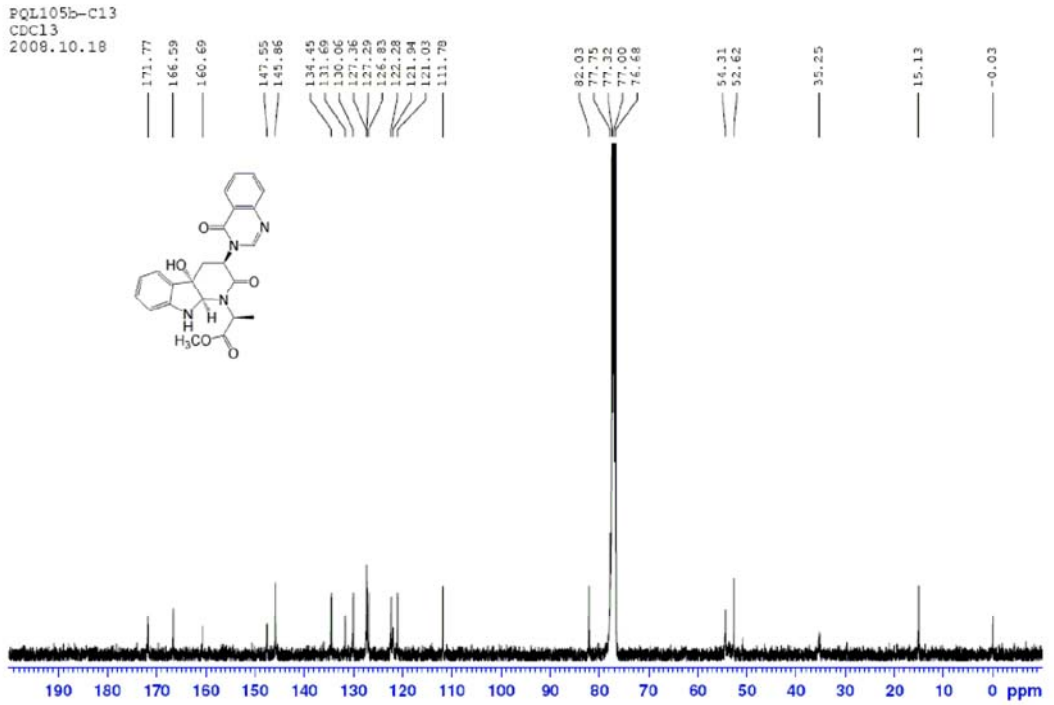
^{1}H and ^{13}C NMR spectra of (−)-chaetominine (**1**)



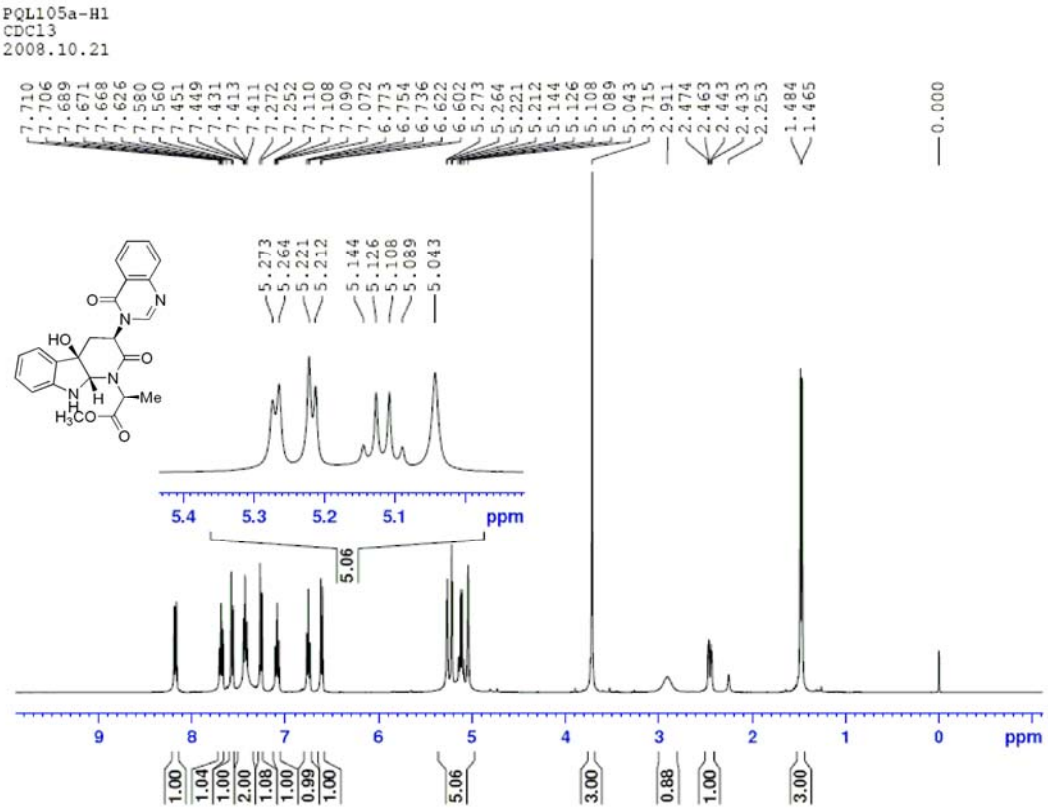


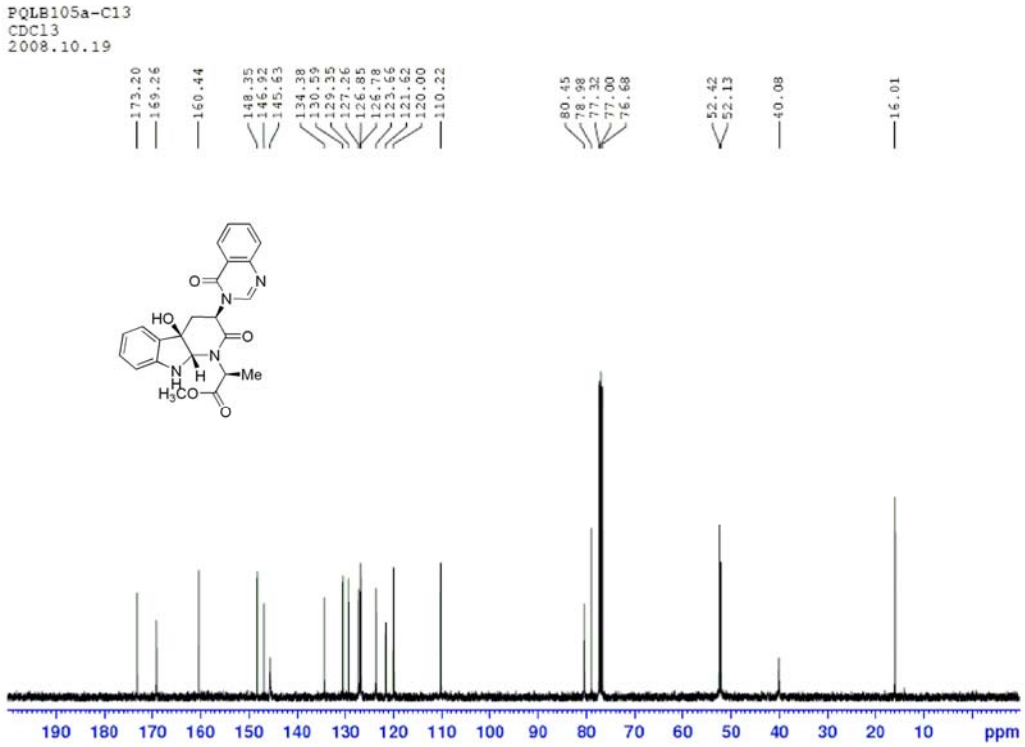
^{1}H and ^{13}C NMR spectra of compound **5**



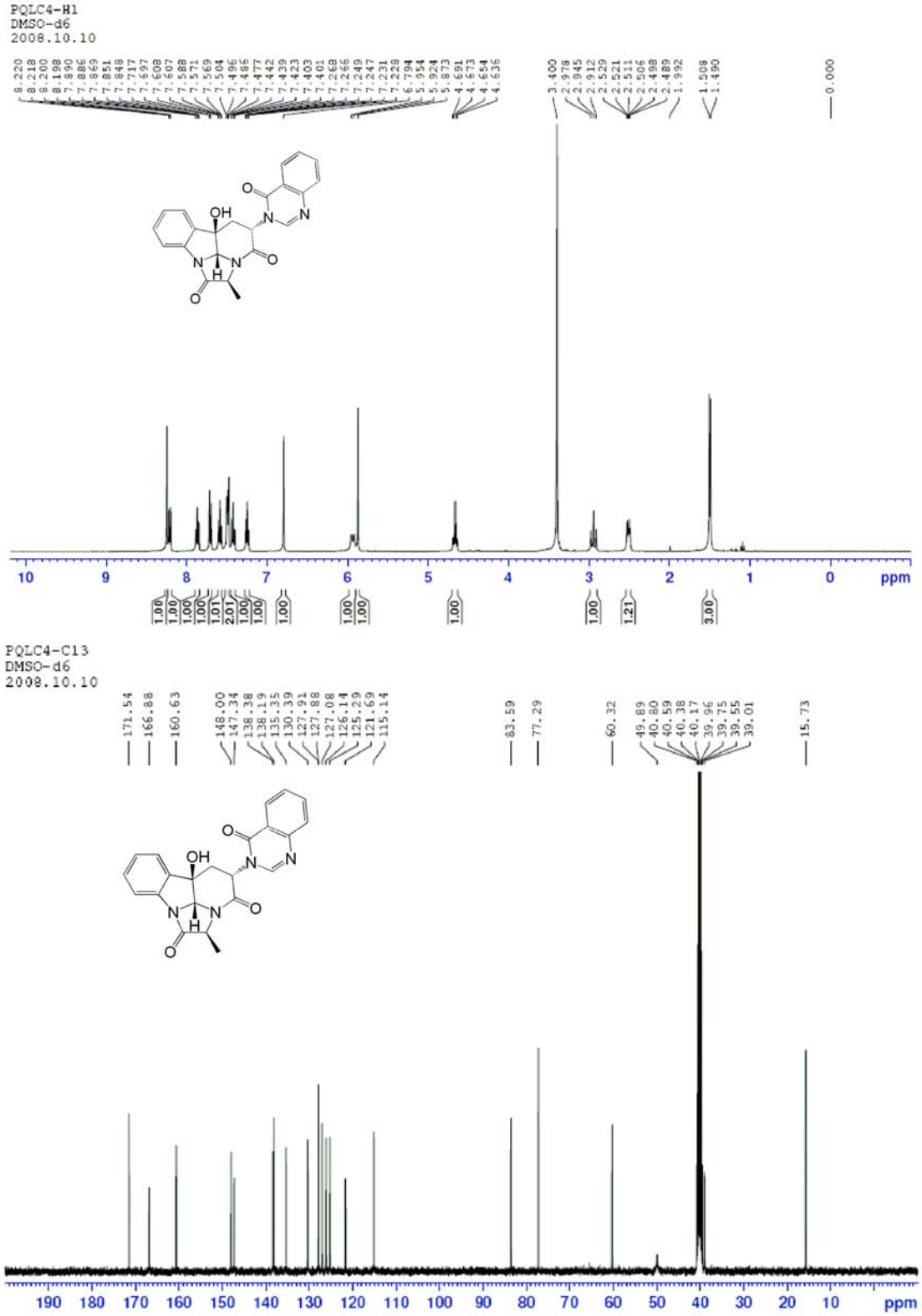


^{1}H and ^{13}C NMR spectra of compound **6**





^{1}H and ^{13}C NMR spectra of compound **7**



^{1}H and ^{13}C NMR spectra of compound **8**