Electronic Supplementary Information for

Complexity Generation by Chemical Synthesis: Five-Step Synthesis of (−)-Chaetominine from L-Tryptophan and its Biosynthetic Implications

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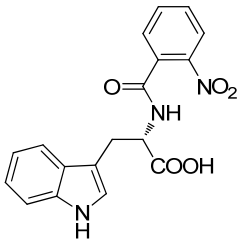
Contents

Experimental

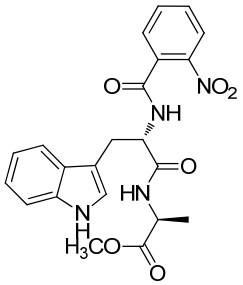
General Methods. Melting points were uncorrected. Infrared spectra were measured using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Silica gel (300-400 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.

(*S*)-3-(1*H*-Indol-3-yl)-2-(2-nitrobenzamido)propanoic acid (9).



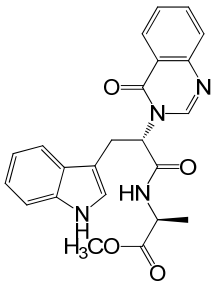
A mixture of 2-nitrobenzoic acid (6.14 g, 36.7 mmol) in thionyl chloride (8 mL, 110.1 mmol) was refluxed for 3 h. The excess thionyl chloride was removed under reduced pressure. The residue was dissolved in anhydrous THF (30 mL) and the solution was added dropwise to an ice-cooled solution of L-tryptophan (5.00 g, 24.5 mmol) in 73 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 × 50 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was crystallized from EtOAc to give compound **9** (7.87 g, yield: 91%) as a yellow solid. Mp 204-206 °C (EtOAc); $[\alpha]_D^{20}$ +7.6 (*c* 1.0, 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 12.90 (br s, 1H), 10.91 (s, 1H), 9.20 (d, *J* = 7.9 Hz, 1H), 8.20 (d, *J* = 7.9 Hz, 1H), 7.74 (t, *J* = 7.3 Hz, 1H), 7.70-7.62 (m, 2H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 4.80 (ddd, *J* = 8.6, 7.9, 5.1 Hz, 1H), 3.39 (dd, *J* = 14.8, 5.1 Hz, 1H), 3.23 (dd, *J* = 14.8, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 165.7, 147.4, 136.4, 133.6, 132.2, 131.0, 129.4, 127.5, 124.2, 123.8, 121.3, 118.7, 118.4, 111.7, 110.2, 53.7, 27.2; MS (ESI) *m/z* 376 (M+Na$^+$, 100%); HRMS-ESI Calcd for $C_{18}H_{15}N_3O_5$: 376.0909; found: 376.0906.

Methyl (*S*)-{2-[(*S*)-3-(1*H*-indol-3-yl)-2-(2-nitrobenzamido)propanamido]propanoate} (10).



To a stirring solution of **9** (1.8 g, 5.09 mmol) in THF (20 mL) at −30 °C were added successively *N*-methylmorpholine (0.84 mL, 7.63 mmol) and ^{i}BuOCOC1 (0.74 mL, 5.60 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 (1.42 g, 10.18 mmol) and *N*-methylmorpholine (1.68 mL, 15.28 mmol) in THF (36 mL) at −78 °C, and the resulting mixture was stirred for 12 h at −20 °C. The reaction was quenched with H_2O (5 mL) and brine (5 mL, and the resulting mixture was stirred for 15 min. The aqueous phase was extracted with EtOAc (3 × 40 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 = 1:2 to EtOAc: DCM = 1:4) to give compound **10** (2.07 g, 93%) as a yellow solid. Mp 75-77 °C (EtOAc); $[\alpha]_D^{20}$ +22.7 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3290, 1739, 1644, 1530, 1456, 1348, 1210, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50-8.44 (m, 1H), 7.98-7.93 (m, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.54-7.44 (m, 2H), 7.34-7.29 (m, 1H), 7.24-7.19 (m, 1H), 7.17-7.02 (m, 3H), 6.96 (dd, *J* = 7.6, 3.6 Hz, 1H), 6.62 (dd, *J* = 6.8, 3.6 Hz, 1H), 4.95 (ddd, *J* = 7.6, 7.3, 6.4 Hz, 1H), 4.38 (dq, *J* = 6.8, 7.2 Hz, 1H), 3.64 (s, 3H), 3.43 (dd, *J* = 14.8, 6.4 Hz, 1H), 3.26 (dd, *J* = 14.8, 7.3 Hz, 1H), 1.29 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.4, 166.3, 146.3, 136.1, 133.6, 132.2, 130.5, 128.6, 127.5, 124.4, 123.5, 122.0, 119.6, 118.6, 111.3, 110.1, 54.2, 52.4, 48.4, 27.6, 17.9; MS (ESI) *m/z* 461 (M+Na^+, 100%); HRMS-ESI Calcd for $C_{22}H_{22}N_4O_6$: $(M+Na)^+$ 461.1437; found: 461.1427.

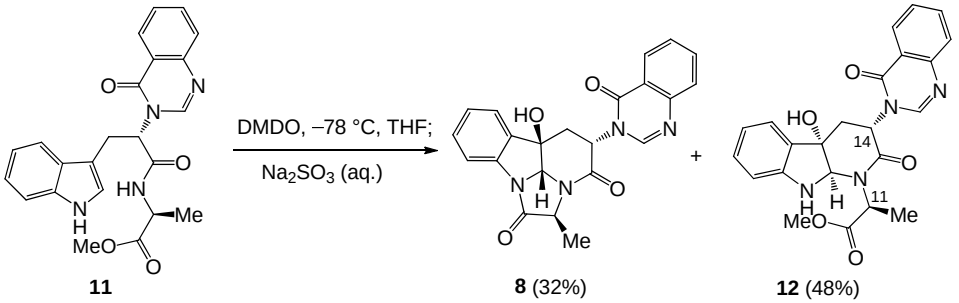
Methyl (*S*)-{2-[(*S*)-3-(1*H*-indol-3-yl)-2-(4-oxoquinazolin-3(4*H*)-yl)propanamido]propanoate} (11).



To a mixture of Zinc powder (388 mg, 5.97 mmol) and THF (30 mL) was added $TiCl_4$ (0.33 mL, 2.99 mmol) at 0 °C, and the reaction mixture were stirred for 1 h at 50 °C. To the resulting mixture, a THF (5 mL) solution of compound **10** (327 mg, 0.75 mmol) and triethyl orthoformate (0.33 mL, 2.99 mmol) were added. The resulting mixture was stirred for one day at 0 °C. To the reaction mixture were added brine (5 mL) and stirred for 2 h. After separating the phases, the aqueous phase was extracted with EtOAc (3 × 15

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 = 1:3 to DCM: MeOH = 40:1) to give compound **11** (298 mg, yield: 95%) as a yellow solid. Mp 203-205 °C (EtOAc); $[\alpha]_D^{20}$ +25.5 (*c* 1.0, THF); IR (film) ν_{max}: 3310, 1744, 1659, 1609, 1457, 1210, 1152, 743 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 10.0 (s, 1H), 8.42 (s, 1H), 8.15-8.09 (m, 2H), 7.77-7.68 (m, 2H), 7.60-7.57 (m, 1H), 7.48-7.43 (m, 1H), 7.32-7.29 (m, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.07-7.03 (m, 1H), 7.00-6.96 (m, 1H), 6.02 (dd, *J* = 10.3, 6.0 Hz, 1H), 4.51 (dq, *J* = 7.3, 7.3 Hz, 1H), 3.76 (ddd, *J* = 15.4, 6.0, 0.8 Hz, 1H), 3.70 (s, 3H), 3.63 (dd, *J* = 15.4, 10.3 Hz, 1H), 1.37 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 173.5, 170.1, 161.3, 148.8, 146.8, 137.6, 134.9, 128.2, 127.5, 127.3, 124.7, 122.6, 122.3, 119.7, 119.3, 112.2, 112.2, 110.2, 57.0, 52.4, 49.3, 27.9, 17.5; MS (ESI) *m/z* 419 ($M+H^+$, 100%), HRMS-ESI Calcd for $C_{23}H_{22}N_4O_4$: $(M+H)^+$ 419.1719; found: 419.1707.

(+)-2,3,14-Tri*epi*-chaetominine (6) and Methyl (α*S*,3*R*,4a*S*,9a*R*)-2,3,4,4a,9,9a-Hexahydro-4a-hydroxy-*α*-methyl-2-oxo-3-[4-oxo-3(4*H*)-quinazolinyl]-1*H*-pyrido[2,3]indole-1-ethanoate (12).



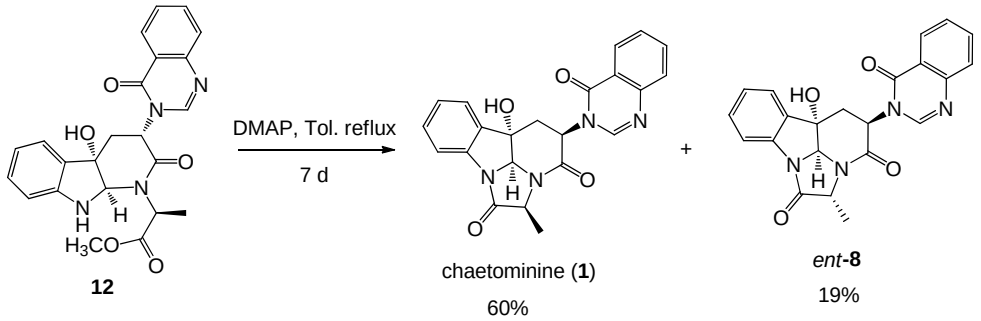
To a solution of **11** (200 mg, 0.48 mmol) in anhydrous acetone (2 mL) was added a solution of 0.05 M DMDO in acetone (19.2 mL, 0.96 mmol) at −78 °C. After being stirred for 1 h, Na_2SO_3 (sat.) (10 mL) was added and the mixture was stirred for 1.5 h at 0 °C. The solvent was evaporated under reduced pressure. To the residue was added a saturated NH_4Cl (10 mL) and the mixture 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 purified by column chromatography on silica gel (eluent: EtOAc: PE = 3:2) to give (+)-2,3,14-tri*epi*-chaetominine (**8**) (62 mg, yield: 32%) and compound **12** (100 mg, 48%).

The physical and spectral data of (+)-2,3,14-tri*epi*-chaetominine (**8**) are in agreement with those we obtained previously [1].

Compound **12**: white solid, Mp 146-148 °C (EtOAc); $[\alpha]_D^{20}$ +111.2 (*c* 1.0, THF); IR (film) ν_{max}: 3337, 2944, 1741, 1676, 1611, 1475, 1243, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.73-7.59 (m, 3H), 7.46-7.40 (m, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.17-7.12 (m, 1H), 6.87-6.81 (m, 1H), 6.64 (d, *J* = 7.3 Hz, 1H), 5.27 (br s, 1H), 5.21 (d, *J* = 4.0 Hz, 1H), 5.03 (q, *J* = 7.4 Hz, 1H), 4.72 (d, *J* = 4.0 Hz, 1H), 4.43 (s, 1H), 3.76 (s, 3H), 3.01-2.85 (m, 1H), 2.93 (dd, *J* = 12.1, 3.8 Hz, 1H), 1.49 (d, *J* =

7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 169.3, 160.6, 148.2, 147.2, 145.1, 134.4, 130.7, 128.8, 127.3, 127.2, 126.9, 123.9, 121.6, 120.7, 110.5, 81.9, 79.8, 52.9, 52.8, 51.5, 41.5, 15.7; MS (ESI) *m/z* 457 ($M+Na^+$, 100%); HRMS-ESI Calcd for $C_{23}H_{22}N_4O_5$: $(M+H)^+$ 435.1668; found: 435.1663.

(–)-Chaetominine (1) and (–)-11-*epi*-chaetominine (*ent*-8)

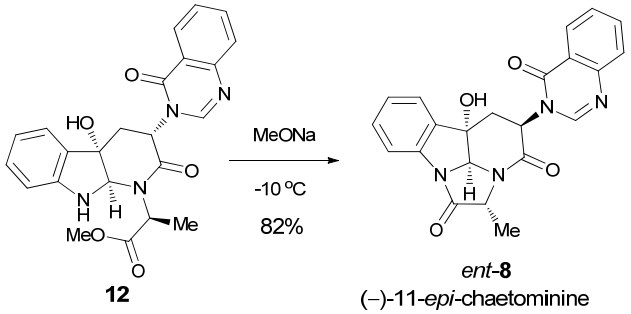


To a mixture of compound **12** (40 mg, 0.09 mmol) and DMAP (1.2 mg, 0.009 mmol) was added toluene (3 mL) under Ar. Then the mixture was stirred under reflux for 7 days. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/ hexane = 3: 2 to 2: 1) to give (–)-chaetominine (**1**) (22.2 mg, yield: 60%) and (–)-11-*epi*-chaetominine (*ent*-**8**) (7.0 mg, yield: 19%).

(–)-Chaetominine (**1**)**:** white solid, Mp 165-167 °C (after chromatography); Mp 196-198 °C (after recrystallization from EtOAc/ hexane); $[\alpha]_D^{20}$ –48.6 (*c* 0.21, MeOH). The spectral data are in agreement with those obtained previously [1].

(–)-11-*epi*-chaetominine (*ent*-**8**): white solid, 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}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.21 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.86 (td, *J* = 7.5, 1.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.58 (td, *J* = 7.5, 1.0 Hz, 1H), 7.50-7.45 (m, 2H), 7.41 (td, *J* = 7.5, 1.0 Hz, 1H), 7.24 (td, *J* = 7.5, 1.0 Hz, 1H), 6.76 (s, 1H), 5.98-5.88 (m, 1H), 5.85 (s, 1H), 4.65 (q, *J* = 7.3 Hz, 1H), 2.93 (dd, *J* = 13.0, 13.0 Hz, 1H), 2.51 (dd, *J* = 13.0, 3.4 Hz, 1H), 1.49 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8, 166.2, 159.9, 147.3, 146.6, 137.7, 137.5, 134.6, 129.7, 127.2, 127.2, 126.4, 125.4, 124.6, 121.0, 114.5, 82.9, 76.6, 59.6, 49.3, 38.3, 15.0; MS (ESI) *m/z* 425 ($M+Na^+$, 100%); HRMS-ESI Calcd for $C_{22}H_{18}N_4O_4$: 403.1406; found: 403.1403.

(2*R*,2a^1*S*,4*R*,5a*S*)-5a-Hydroxy-2-methyl-4-(4-oxoquinazolin-3(4*H*)-yl)-2a^1,4,5,5a-tetrahydro-1*H*-2a,9b-diazacyclopenta[*jk*]fluorene-1,3(2*H*)-dione (*ent*-8)



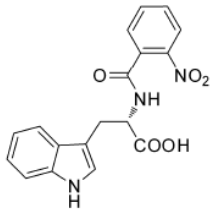
To a solution of compound **12** (43 mg, 0.1 mmol) in MeOH (1.5 mL) was added a solution of freshly prepared CH_3ONa (27 mg, 0.5 mmol) in CH_3OH (3.5 mL) at −10 °C. After stirring for 48 h, the reaction mixture was acidified with 10% HCOOH to reach pH = 7. The solvent was evaporated under reduced pressure, 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 *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent: EtOAc:PE = 3:2) to give *ent*-**8** (34 mg, 82%) as colorless crystals.

References

1. Q.-L. Peng, S.-P. Luo, X.-E. Xia, L.-X. Liu, P.-Q. Huang, *Chem. Commun*., 2014, **50**, 1986-1988.

^{1}H and ^{13}C NMR Spectra of compound (*S*)-9

XCPE101-H1
DMSO-d6
2012.6.28



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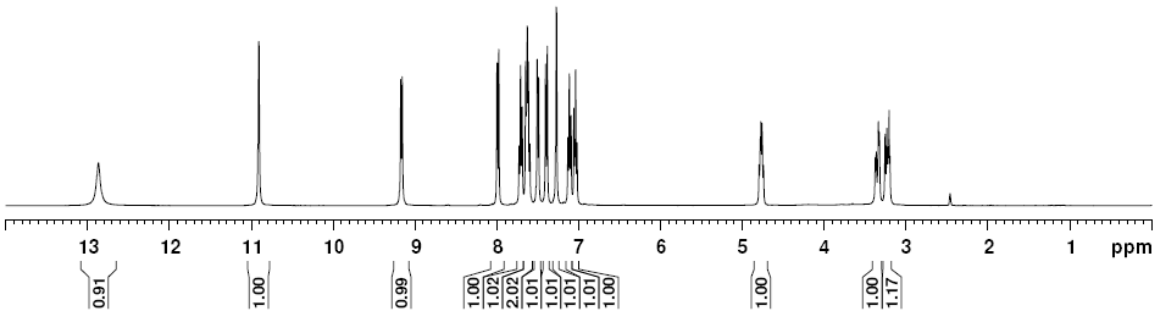

XCPE101-C13
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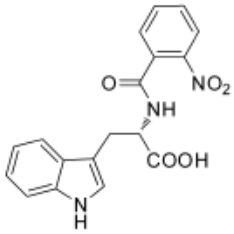

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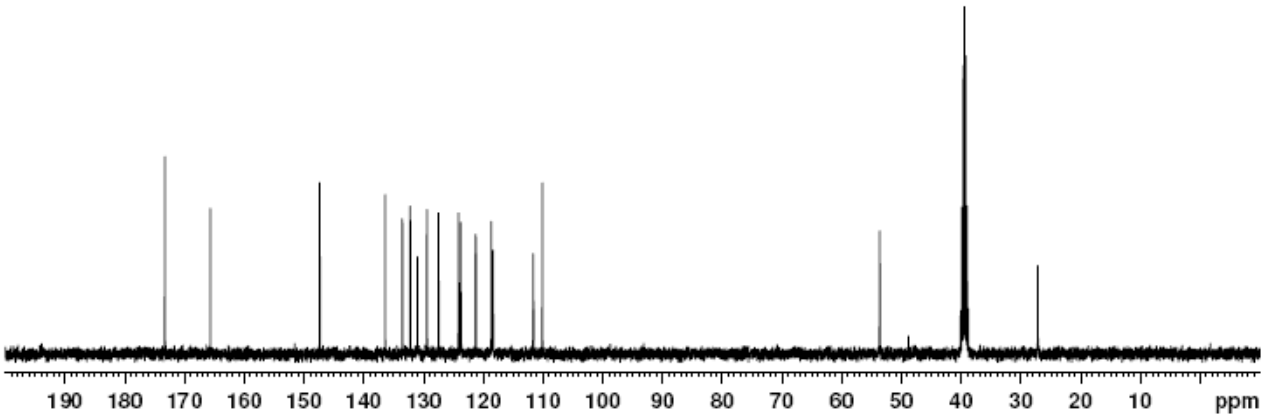
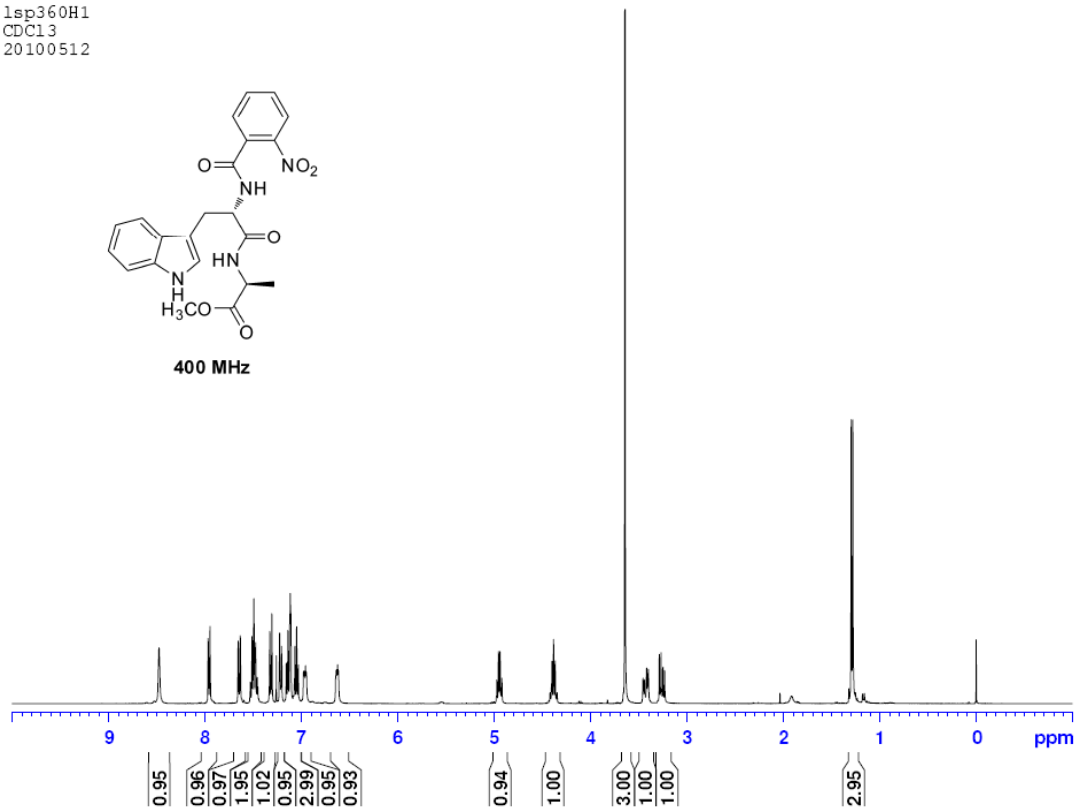
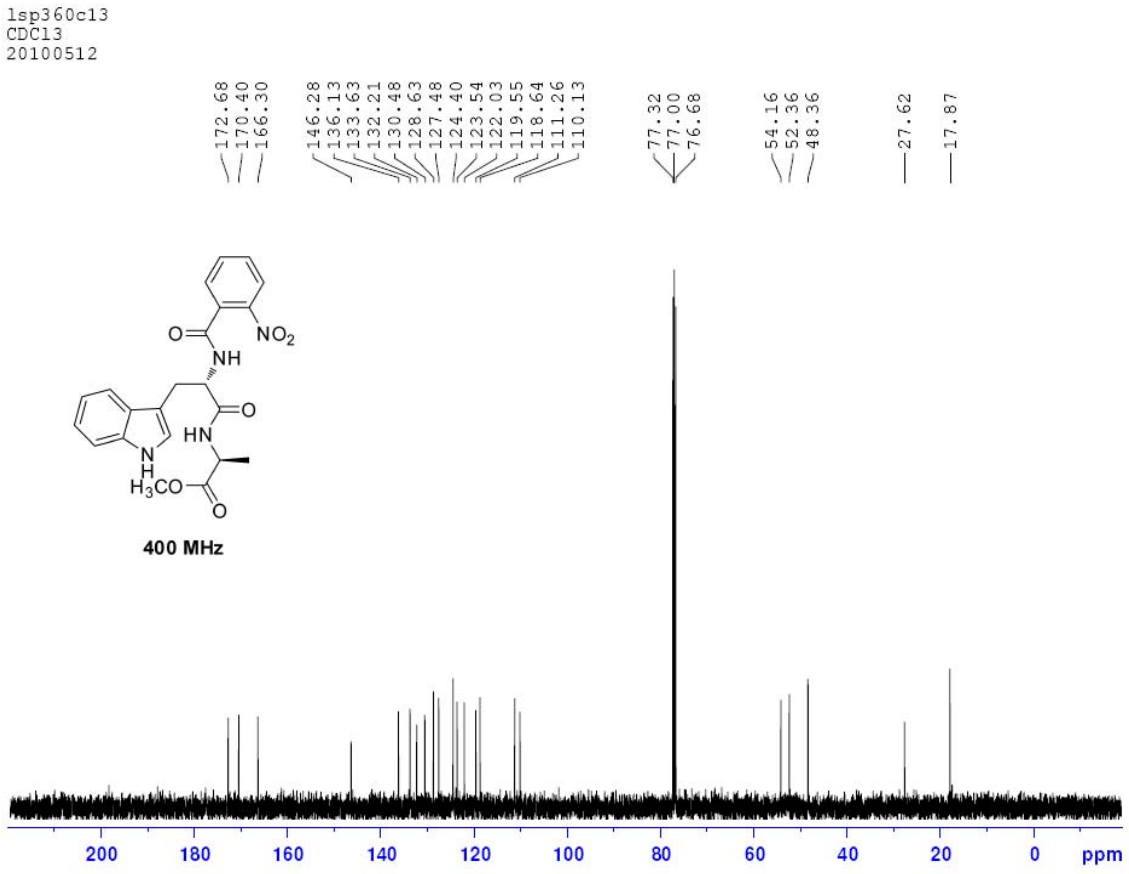


^{1}H and ^{13}C NMR Spectra of compound 10





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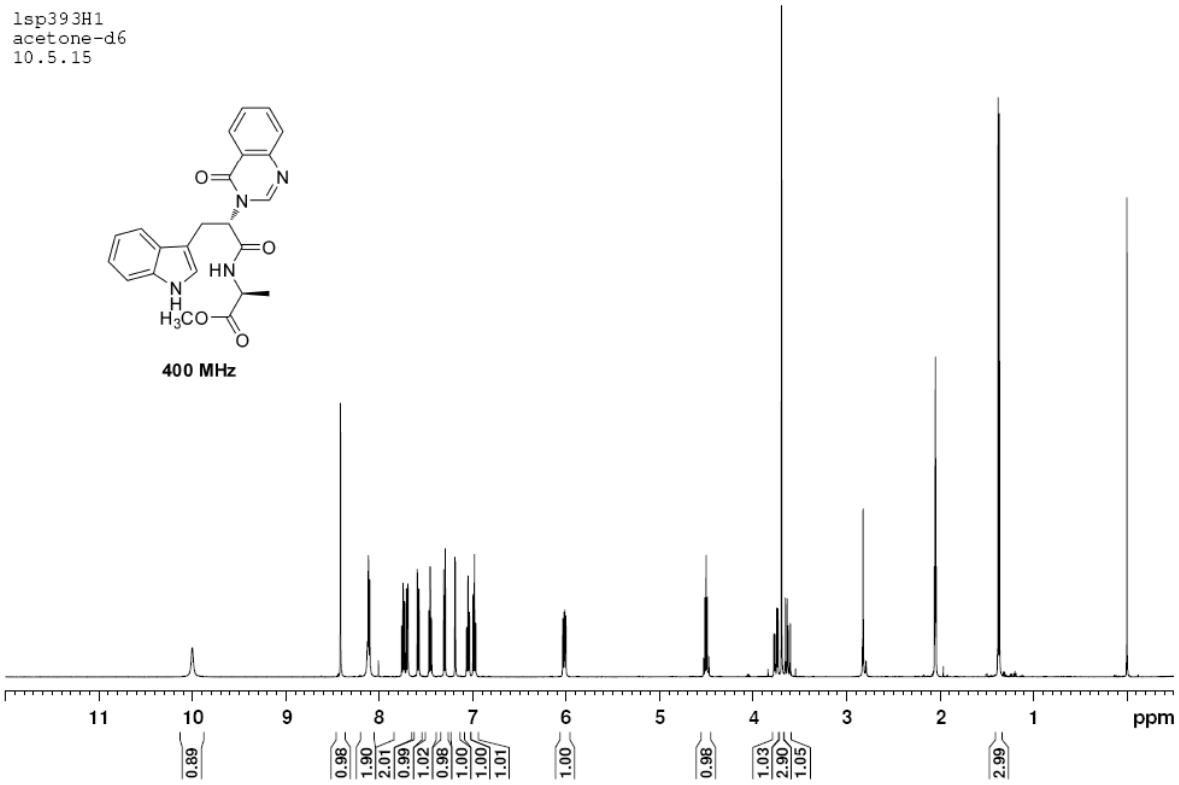
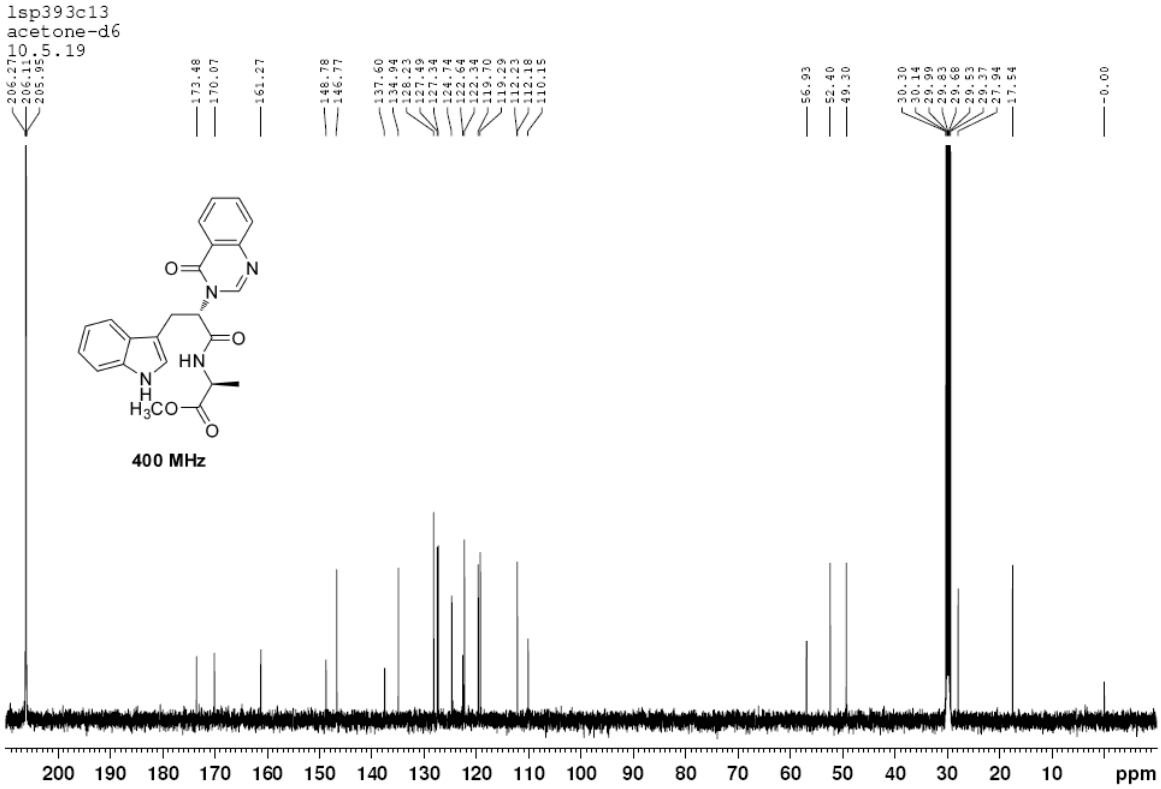
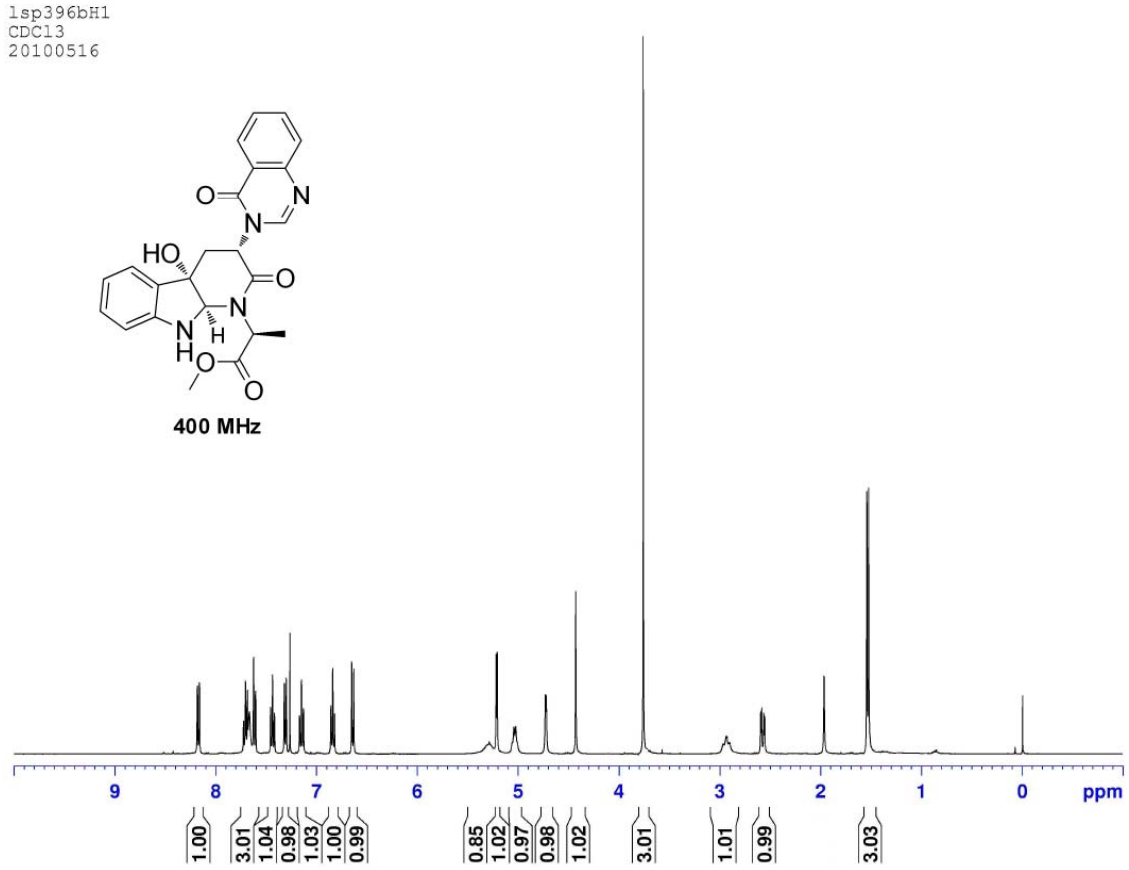
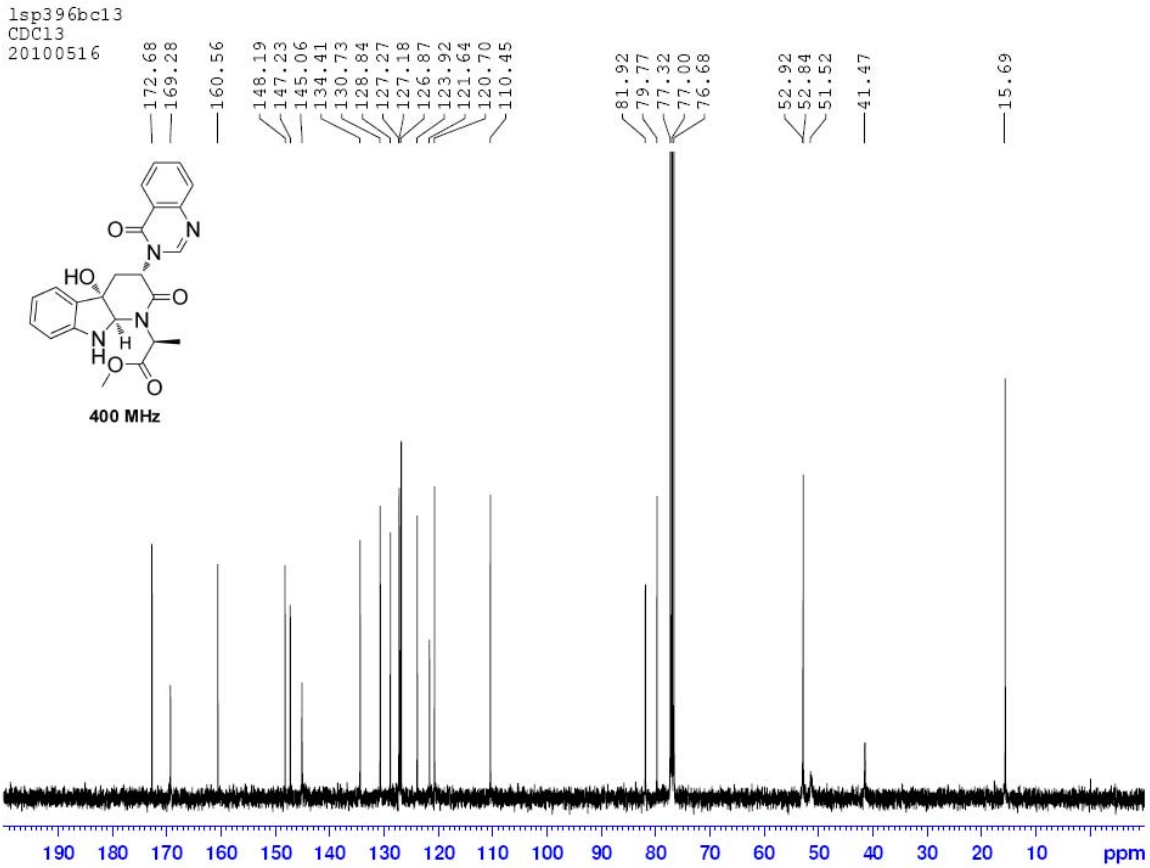




^{1}H and ^{13}C NMR Spectra of compound 12





^{1}H and ^{13}C NMR Spectra of compound *ent*-8