

Electronic Supplementary Information

Stereoselective synthesis of *N*-aryl proline amides by a biotransformation/Ugi-Smiles sequence

Anass Znabet,^a Sara Blanken,^a Elwin Janssen,^a Frans J. J. de Kanter,^a Madeleine Helliwell,^b Nicholas J. Turner,^c Eelco Ruijter^{a,*} and Romano V. A. Orru^{a,*}

^a Department of Chemistry & Pharmaceutical Sciences and Amsterdam Institute of Molecules, Medicines and Systems, VU University Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, the Netherlands

^b School of Chemistry, University of Manchester, Brunswick Street, Manchester, M13 9PL, UK

^c School of Chemistry, University of Manchester, Manchester Interdisciplinary Biocentre, 131 Princess Street, Manchester, UK M1 7DN

r.v.a.orr@vu.nl, e.ruijter@vu.nl

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General Information

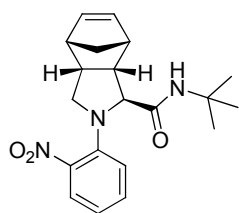
Starting materials and solvents were purchased from ABCR and Sigma-Aldrich and were used without treatment. 3-Azabicyclo[3,3,0]octane hydrochloride was purchased from AK Scientific. (1*R*,2*S*,6*R*,7*S*)-4-methyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene was prepared according to literature procedure.¹ Column chromatography was performed on silica gel. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 (400.13 MHz for ¹H and 100.61 MHz for ¹³C) or Bruker Avance 500 (500.23 MHz for ¹H and 125.78 MHz for ¹³C) in CDCl₃. Chemical shifts are reported in δ values (ppm) downfield from tetramethylsilane. Electrospray Ionisation (ESI) mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Thin Layer Chromatography was performed using TLC plates from Merck (SiO₂, Kieselgel 60) and was visualized by UV detection. Flash chromatography was performed using the indicated solvents and Silicycle Silia-P Flash Silica Gel (particle size 40-63 μ m, pore diameter 60 Å). Infrared (IR) spectra were recorded neat on a Shimadzu 6400s FTIR spectrometer and wavelengths are reported in cm⁻¹. Optical rotations were measured on an Optical Activity AA-10 and a Perkin Elmer 241 polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{20}$ (*c* = g/100 mL, solvent). Optical rotations were measured on a polarimeter with a sodium lamp. 1-Azido-2-isocyanoethane,² (isocyanomethyl)benzene,³ 3-(isocyanomethyl)pyridine³ and 2-bromo-4-nitrophenol⁴ were synthesized according to literature procedures.

General Procedure 1: Preparation of optically active imines (3*S*,7*R*)-8, azabicyclo-[3,3,0]oct-2-ene (32) and (3*S*,7*R*)-36

Unless stated otherwise: imines were synthesized according to literature procedure with minor adjustments. 0.7 g of freeze-dried MAO-N D5 *E. coli* were rehydrated for 30 min. in 20 ml of KPO₄ buffer (100 mM, pH = 8.0) at 37 °C. Subsequently 1 mmol of bridged amine or azabicyclo-[3,3,0]oct-2-ene in 30 ml of KPO₄ buffer (100 mM, pH = 8.0) was prepared. The pH of the solution was adjusted to 8.0 by addition of NaOH and then added to the rehydrated cells. After 16-17 h the reaction was stopped (conversions were > 95 %) and worked up. For workup the reaction mixture was centrifuged at 4000 rpm and 4 °C until the supernatant had clarified (40 – 60 minutes). The pH of the supernatant was then adjusted to 10-11 by addition of aq. NaOH and the supernatant was subsequently extracted with *t*-butyl methyl ether or dichloromethane (4 × 70 mL). The combined organic phases were dried with Na₂SO₄ and concentrated at the rotary evaporator.

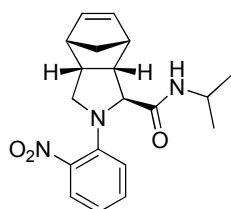
General procedure 2: Preparation of optically active Ugi-Smiles derivatives 10-32, 33-35

Unless stated otherwise: To a solution of optically imine (0.5 mmol, 2.0 equiv.) in 2 ml methanol nitrophenol or thiol (0.25 mmol, 1.0 equiv.) was added, followed by the isocyanide (0.375 mmol, 1.5 equiv.). The reaction mixture was stirred at 40°C for 24 h. The mixture was concentrated *in vacuo* and the crude product was purified by column chromatography (SiO₂, CHCl₃). After concentration *in vacuo* a bright colored oil or solid was obtained. Diastereomeric ratios were determined by ¹H NMR.



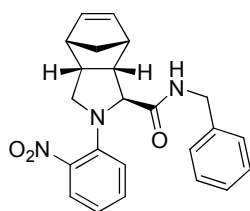
(1S,3aR,4S,7R,7aS)-N-(tert-butyl)-2-(2-nitrophenyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (11): General procedure 2 was followed using imine (3S,7R)-8 (60 mg, 0.45 mmol, 2.0 equiv.), 2-nitrophenol (31 mg, 0.22 mmol, 1.0 equiv.) and *tert*-butyl isocyanide (28 mg, 0.038 ml, 0.34 mmol, 1.5 equiv.) giving a yield of 57 mg (0.16 mmol, 73%) of a bright orange solid.

$[\alpha]_D^{20} = -1043.1^\circ$ ($c = 0.51$, CHCl_3); ^1H NMR (500.23 MHz, CDCl_3): $\delta = 7.65$ (dd, $J = 8.5$ Hz, $J = 1.5$ Hz, 1H), 7.29 (m, 1H), 6.91 (d, $J = 8.0$ Hz), 6.78 (m, 1H), 6.67 (bs, 1H), 6.14 (m, 1H), 5.79 (m, 1H), 4.00 (d, $J = 3.0$ Hz, 1H), 3.52 (dd, $J = 10.8$ Hz, $J = 9.0$ Hz, 1H), 3.17 (m, 1H), 3.02 (m, 1H), 2.89 (m, 1H), 2.79 (m, 1H), 2.20 (dd, $J = 3.0$ Hz, $J = 11.0$ Hz, 1H), 1.49 (d, $J = 8.5$ Hz, 1H), 1.37 (d, $J = 8.5$ Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 171.8$, 141.3, 139.3, 135.5, 135.3, 133.3, 126.4, 118.4, 117.4, 65.9, 54.7, 51.9, 51.1, 51.0, 50.8, 48.2, 47.7, 46.6, 54.4, 45.2, 45.0, 28.5, 28.5, 28.5; IR (neat): ν_{max} (cm^{-1}) = 3383, 2959, 2868, 1668, 1504, 852, 737; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 356.1969, found 356.1959;



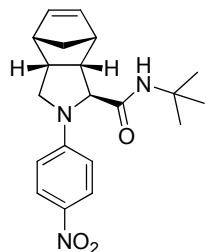
(1S,3aR,4S,7R,7aS)-N-isopropyl-2-(2-nitrophenyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide 12: General procedure 2 was followed using imine (3S,7R)-8 (67 mg, 0.5 mmol, 2.0 equiv.), 2-nitrophenol (35 mg, 0.25 mmol, 1.0 equiv.) and isopropyl isocyanide (26 mg, 0.035 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 51 mg (0.15 mmol, 60%) of a bright sticky orange oil.

$[\alpha]_D^{20} = -828.8^\circ$ ($c = 0.56$, CHCl_3); ^1H NMR (500.23 MHz, CDCl_3): $\delta = 7.65$ (dd, $J = 3.5$ Hz, $J = 9.75$ Hz, 1H), 7.29 (m, 1H), 6.91 (d, $J = 9.0$ Hz, 1H), 6.78 (m, 2H), 6.14 (m, 1H), 5.79 (m, 1H), 4.10 (m, 1H), 3.86 (m, 1H), 3.48 (m, 1H), 3.19 (m, 1H), 3.03 (m, 1H), 2.86 (m, 1H), 2.79 (m, 1H), 2.20 (dd, $J = 4.0$ Hz, $J = 11.0$ Hz, 1H), 1.48 (m, 1H), 1.36 (m, 1H), 1.07 (dd, $J = 2.0$ Hz, $J = 6.5$ Hz, 3H), 0.89 (dd, $J = 2.0$ Hz, $J = 6.5$ Hz, 3H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 171.6$, 141.2, 139.4, 135.6, 135.2, 133.3, 126.4, 118.5, 117.7, 65.4, 54.6, 51.8, 50.6, 47.7, 46.6, 45.1, 41.3, 22.4, 22.4; IR (neat): ν_{max} (cm^{-1}) = 3369, 2968, 2868, 1657, 1508, 741, 633, 493; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{19}\text{H}_{24}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 342.1812, found 342.1799.



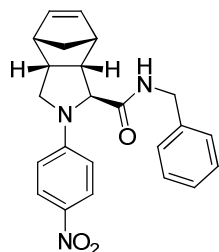
(1S,3aR,4S,7R,7aS)-N-benzyl-2-(2-nitrophenyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (13): General procedure 2 was followed using imine (3S,7R)-8 (67 mg, 0.5 mmol, 2.0 equiv.), 2-nitrophenol (35 mmol, 0.25 mmol, 1.0 equiv.) and benzyl isocyanide (44 mg, 0.046 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 49 mg (0.126 mmol, 51%) of a sticky orange oil.

$[\alpha]_D^{20} = -942.3^\circ$ ($c = 0.52$, CHCl_3); ^1H NMR (500.23 MHz, CDCl_3): $\delta = 7.61$ (dd, $J = 8.0$ Hz, $J = 1.5$ Hz, 1H), 7.30 (m, 1H), 7.16 (m, 4H), 7.14 (m, 2H), 6.94 (m, 1H), 6.17 (m, 1H), 5.84 (m, 1H), 4.35 (d, $J = 6.0$ Hz, 1H), 4.28 (d, 5.5 Hz, 1H), 4.17 (d, $J = 3.0$ Hz, 1H), 3.52 (dd, $J = 10.8$ Hz, $J = 8.5$ Hz, 1H), 3.22 (m, 1H), 3.07 (m, 1H), 2.90 (m, 1H), 2.80 (m, 1H), 2.22 (dd, $J = 11.0$ Hz, $J = 3.0$ Hz, 1H), 1.51 (d, $J = 8.5$ Hz, 1H), 1.38 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 172.7$, 141.1, 141.1, 137.9, 135.8, 135.3, 133.3, 128.6, 127.2, 126.4, 118.8, 117.7, 65.6, 54.6, 51.9, 50.9, 47.6, 46.6, 45.2, 43.2; IR (neat): ν_{max} (cm^{-1}) = 3377, 2962, 2866, 1664, 1506, 1259, 1014, 796; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 390.1812, found 390.1794.



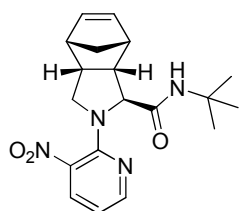
(1S,3aR,4S,7R,7aS)-N-(tert-butyl)-2-(4-nitrophenyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (14): General procedure 2 was followed using imine (3S,7R)-8 (67 mg, 0.5 mmol, 2.0 equiv.), 4-nitrophenol (35 mg, 0.25 mmol, 1.0 equiv.) and *tert*-butyl isocyanide (31 mg, 0.042 ml, 0.375 mmol 1.5 equiv.) giving a yield of 45 mg (0.13 mmol, 51%) of a yellow solid.

$[\alpha]_D^{20} = -42.7^\circ$ ($c = 0.52$, CHCl_3); ^1H NMR (500.23 MHz, CDCl_3): $\delta = 8.03$ (d, $J = 9.0$ Hz, 2H), 6.34 (d, $J = 9.0$ Hz, 2H), 6.08 (t, $J = 4.0$ Hz, 2H), 5.36 (bs, 1H), 3.56 (t, $J = 2.0$ Hz, 1H), 3.53 (s, 1H), 3.15 (s, 1H), 3.03 (m, 3H), 2.95 (s, 1H), 1.58 (d, $J = 8.5$ Hz, 1H), 1.44 (d, $J = 8.5$ Hz, 1H) 1.19 (s, 9H); ^{13}C NMR (100.61 MHz, CDCl_3): $\delta = 171.6$, 150.5, 138.3, 136.0, 135.9, 126.1, 126.1, 111.6, 111.6, 67.4, 52.7, 52.4, 52.0, 51.3, 47.4, 46.7, 44.1, 28.6, 28.6, 28.6; IR (neat): ν_{max} (cm^{-1}) = 3298, 2966, 2858, 1595, 1302, 1109, 823, 656; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 356.1969, found 356.1956.



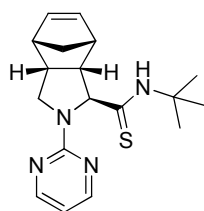
(1S,3aR,4S,7R,7aS)-N-benzyl-2-(4-nitrophenyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (15): General procedure 2 was followed using imine (3S,7R)-8 (67 mg, 0.5 mmol, 2.0 equiv.), 4-nitrophenol (35 mg, 0.25 mmol, 1.0 equiv.) and benzyl isocyanide (44 mg, 0.046 ml, 0.375 mmol and 1.5 equiv.) giving a yield of 56 mg (0.14 mmol, 58%) of a yellow solid.

$[\alpha]_D^{20} = -49.0^\circ$ ($c = 0.49$, CHCl_3); ^1H NMR (500.23 MHz, CDCl_3): $\delta = 8.00$ (d, $J = 9.5$ Hz, 2H), 7.18 (m, 3H), 7.02 (m, 2H), 6.34 (d, $J = 9.0$ Hz, 2H), 6.10 (m, 2H), 5.92 (s, 1H), 4.33 (d, $J = 6.0$ Hz, 2H), 3.74 (d, $J = 3.0$ Hz, 1H), 3.58 (m, 1H), 3.19 (s, 1H), 3.06 (m, 3H), 2.96 (s, 1H), 1.59 (d, $J = 8.5$ Hz, 1H), 1.45 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 172.4$, 150.4, 138.4, 137.7, 136.0, 135.9, 128.7, 128.7, 127.7, 127.5, 127.5, 126.1, 126.1, 111.7, 111.7, 66.8, 52.8, 52.5, 52.0, 47.4, 45.8, 44.1, 43.3; IR (neat): ν_{max} (cm^{-1}) = 3312, 2962, 2869, 1651, 1597, 1300, 1109, 825, 690; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 390.1812, found 390.1794.



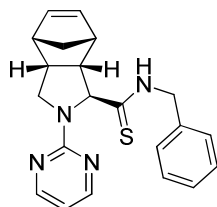
(1S,3aR,4S,7R,7aS)-N-(tert-butyl)-2-(3-nitropyridin-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (16): General procedure 2 was followed using imine (3S,7R)-8 (67 mg, 0.5 mmol, 2.0 equiv.), 3-nitropyridin-2-ol (35 mg, 0.25 mmol, 1.0 equiv.) and *tert*-butyl isocyanide (31 mg, 0.042 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 36 mg (0.10 mmol, 40%) of a dark yellow solid.

$[\alpha]_D^{20} = -474.6^\circ$ ($c = 0.51$, CHCl_3); ^1H NMR (500.23 MHz, CDCl_3): $\delta = 8.23$ (dd, $J = 2.0$ Hz, $J = 4.5$ Hz, 1H), 8.03 (dd, $J = 1.5$ Hz, $J = 8.0$ Hz, 1H), 6.69 (dd, $J = 4.5$ Hz, $J = 8.5$ Hz, 1H), 6.33 (bs, 1H), 5.94 (m, 1H), 5.56 (m, 1H), 5.03 (s, 1H), 3.49 (dd, $J = 8.5$, $J = 12$ Hz, 1H), 3.13 (m, 1H), 2.76 (m, 1H), 2.16 (dd, $J = 2.0$, $J = 12.0$ Hz, 1H), 1.39 (d, $J = 8.0$ Hz, 1H), 1.31 (d, $J = 8.5$ Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 171.5$, 151.7, 150.1, 150.1, 135.8, 134.7, 133.6, 113.1, 63.6, 53.8, 51.3, 51.0, 48.5, 47.8, 46.8, 44.8, 28.6; IR (neat): ν_{max} (cm^{-1}) = 3398, 2959, 2872, 1668, 1448, 716, 557; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_3$ ($[\text{M}+\text{H}]^+$): 357.1921, found 357.1905.



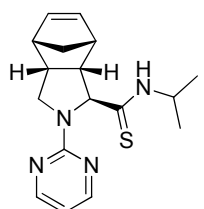
(1S,3aR,4S,7R,7aS)-N-(tert-butyl)-2-(pyrimidin-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carbothioamide (17): General procedure 2 was followed using imine (3S,7R)-8 (67 mg, 0.5 mmol, 2.0 equiv.), 2-mercaptopyrimidine (28 mg, 0.25 mmol, 1.0 equiv.) and *tert*-butyl isocyanide (31 mg, 0.042 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 50 mg (0.15 mmol, 61%) of a light yellow solid.

$[\alpha]_D^{20} = -80.8^\circ$ ($c = 0.495$, CHCl_3); ^1H NMR (500.23 MHz, CDCl_3): $\delta = 8.23$ (d, $J = 4.5$ Hz, 2H), 7.99 (bs, 1H), 6.48 (t, $J = 5.0$ Hz, 1H), 5.98 (t, $J = 7.0$ Hz, 2H), 4.39 (d, $J = 2.5$ Hz, 1H), 3.60 (dd, $J = 3.5$ Hz, $J = 11.5$ Hz, 1H), 3.50 (dd, $J = 8.5$ Hz, $J = 11.8$ Hz, 1H), 3.37 (m, 1H), 3.10 (m, 1H), 2.92 (m, 1H), 2.88 (m, 1H), 1.46 (d, $J = 8.5$ Hz, 1H), 1.38 (m, 10H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 202.6, 159.8, 157.7, 157.7, 135.6, 135.4, 110.6, 72.9, 55.0, 53.4, 51.7, 50.1, 47.5, 46.9, 44.2, 27.6, 27.6, 27.6$; IR (neat): ν_{max} (cm^{-1}) = 3303, 2964, 2856, 1680, 1377, 797, 719, 627; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{18}\text{H}_{25}\text{N}_4\text{S}$ ($[\text{M}+\text{H}]^+$): 329.1794, found 329.1783.



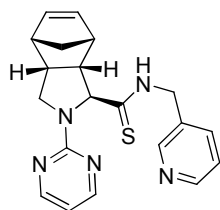
(1S,3aR,4S,7R,7aS)-N-benzyl-2-(pyrimidin-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carbothioamide (18): General procedure 2 was followed using imine (3S,7R)-8 (67 mg, 0.5 mmol, 2.0 equiv.), 2-mercaptopyrimidine (28 mg, 0.25 mmol, 1.0 equiv.) and benzyl isocyanide (44 mg, 0.046 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 57 mg (0.16 mmol, 63%) of a off-white solid.

$[\alpha]_D^{20} = -60.0^\circ$ ($c = 0.6$, CHCl_3); ^1H NMR (500.23 MHz, CDCl_3): $\delta = 8.38$ (bs, 1H), 8.17 (d, $J = 5.0$ Hz, 2H), 7.21 (m, 3H), 7.10 (t, $J = 5.5$ Hz, 2H), 6.45 (t, $J = 5.0$ Hz, 1H), 5.98 (s, 1H), 4.82 (m, 1H), 4.67 (m, 1H), 4.61 (s, 1H), 3.64 (m, 1H), 3.46 (m, 2H), 3.13 (s, 1H), 2.96 (m, 1H), 2.89 (s, 1H), 1.49 (d, $J = 8.5$ Hz, 1H), 1.41 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 203.7, 158.8, 156.7, 156.7, 135.2, 134.5, 134.4, 134.4, 127.7, 127.7, 127.7, 126.7, 126.7, 109.7, 70.2, 52.5, 50.6, 49.0, 48.4, 46.4, 45.9, 43.2$; IR (neat): ν_{max} (cm^{-1}) = 3175, 2966, 2870, 1585, 1493, 795, 696; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{21}\text{H}_{23}\text{N}_4\text{S}$ ($[\text{M}+\text{H}]^+$): 363.1638, found 363.1632.



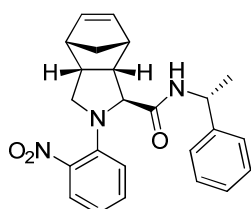
(1S,3aR,4S,7R,7aS)-N-isopropyl-2-(pyrimidin-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carbothioamide (19): General procedure 2 was followed using imine (3S,7R)-8 (67 mg, 0.5 mmol, 2.0 equiv.), 2-mercaptopyrimidine (28 mg, 0.25 mmol, 1.0 equiv.) and isopropyl isocyanide (26 mg, 0.035 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 54 mg (0.17 mmol, 68%) of light orange solid.

$[\alpha]_D^{20} = -173.7^\circ$ ($c = 0.50$, CHCl_3); ^1H NMR (500.23 MHz, CDCl_3): $\delta = 8.51$ (dd, $J = 5.0$ Hz, $J = 10.0$ Hz, 1 H), 8.22 (d, $J = 5.0$ Hz, 2H), 7.92 (bs, 1H), 6.47 (t, $J = 4.5$ Hz, 1H), 5.98 (m, 2H), 4.53 (m, 1H), 4.49 (d, $J = 2.5$ Hz, 1H), 3.64 (dd, $J = 3.0$ Hz, $J = 12$ Hz, 1H), 3.48 (dd, $J = 3.0$ Hz, $J = 12$ Hz, 1H), 3.40 (m, 1H), 3.11 (m, 1H), 2.94 (m, 1H), 2.89 (m, 1H), 1.47 (d, $J = 8.5$ Hz, 1H), 1.39 (d, $J = 8.5$ Hz, 1H), 1.07 (m, 6H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 202.5, 159.9, 157.7, 157.7, 135.4, 135.4, 110.6, 71.4, 53.3, 51.7, 50.0, 47.4, 46.9, 46.7, 44.2, 21.3, 21.1$; IR (neat): ν_{max} (cm^{-1}) = 3329, 2966, 2868, 1666, 1580, 1445, 804, 721; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{17}\text{H}_{23}\text{N}_4\text{S}$ ($[\text{M}+\text{H}]^+$): 315.1638, found 315.1634.



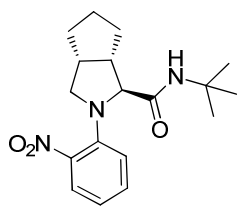
(1S,3aR,4S,7R,7aS)-N-(pyridin-3-ylmethyl)-2-(pyrimidin-2-yl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carbothioamide (20): General procedure A was followed using imine (3S,7R)-**8** (67 mg, 0.5 mmol, 2.0 equiv.), 2-mercaptopyrimidine (28 mg, 0.25 mmol, 1.0 equiv.) and 3-(isocyanomethyl)-pyridine (44 mg, 0.375 mmol, 1.5 equiv.) giving a yield of 34 mg (0.09 mmol, 37%) of an orange solid.

$[\alpha]_D^{20} = -106.1^\circ$ ($c = 0.51$, CHCl_3); $^1\text{H NMR}$ (400.16 MHz, CDCl_3): $\delta = 8.59$ (bs, 1H), 8.41 (m, 2H), 8.16 (d, $J = 4.4$ Hz, 2H), 7.47 (d, $J = 7.6$ Hz, 1H), 7.11 (dd, $J = 4.8$ Hz, $J = 7.8$ Hz, 1H), 6.46 (t, $J = 4.8$ Hz, 1H), 5.98 (m, 2H), 4.89 (dd, $J = 6.0$ Hz, $J = 15.2$ Hz, 1H), 4.70 (dd, $J = 6.0$ Hz, $J = 15.2$ Hz, 1H), 4.58 (d, $J = 2.4$ Hz, 1H), 3.63 (m, 1H), 3.42 (m, 2H), 3.11 (m, 1H), 2.94 (m, 2H), 1.48 (d, $J = 8.4$ Hz, 1H), 1.40 (d, $J = 8.4$ Hz, 1H); $^{13}\text{C NMR}$ (100.62 MHz, CDCl_3): $\delta = 204.7$, 158.9, 156.7, 148.1, 134.5, 134.3, 131.1, 122.5, 109.8, 70.3, 52.6, 50.7, 49.1, 46.4, 46.0, 43.2, 41.2; IR (neat): ν_{max} (cm^{-1}) = 3173, 2976, 2204, 1499, 922, 725, 642; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{20}\text{H}_{22}\text{N}_5\text{S}$ ($[\text{M}+\text{H}]^+$): 364.1590, found 364.1575.



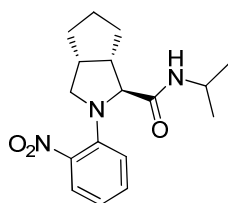
(1S,3aR,4S,7R,7aS)-2-(2-nitrophenyl)-N-((R)-1-phenylethyl)-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisoindole-1-carboxamide (21): General procedure A was followed using (3S,7R)-**8** (67 mg, 0.5 mmol, 2.0 equiv.), 2-nitrophenol (35 mg, 0.25 mmol, 1.0 equiv.) and (S)-(-)-methylbenzyl isocyanide (49 mg, 0.051 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 53 mg (0.13 mmol, 53%) of an orange solid.

$[\alpha]_D^{20} = -756.4^\circ$ ($c = 0.55$, CHCl_3); $^1\text{H NMR}$ (400.13 MHz, CDCl_3): $\delta = 7.63$ (d, $J = 8.0$ Hz, 1H), 7.26 (m, 2H), 7.02 (m, 3H), 6.88 (m, 3H), 6.79 (t, $J = 7.5$ Hz, 1H), 6.15 (m, 1H), 5.84 (m, 1H), 4.92 (m, 1H), 4.09 (s, 1H), 3.56 (dd, $J = 8.5$ Hz, $J = 10.5$ Hz, 1H), 3.20 (s, 1H), 3.09 (m, 1H), 2.95 (m, 1H), 2.81 (s, 1H), 2.26 (dd, $J = 3.0$, $J = 10.8$, 1H), 1.51 (m, 1H), 1.39 (m, 1H), 1.37 (d, $J = 7.0$ Hz); $^{13}\text{C NMR}$ (100.61 MHz, CDCl_3): $\delta = 171.7$, 143.4, 141.1, 139.7, 135.8, 135.3, 133.3, 128.3, 126.9, 126.3, 125.7, 125.7, 118.9, 117.9, 65.5, 54.5, 52.0, 50.7, 48.8, 47.6, 46.6, 45.2, 22.5; IR (neat): ν_{max} (cm^{-1}) = 3379, 3312, 2966, 1655, 1502, 739, 698; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 404.1969, found 404.1949.



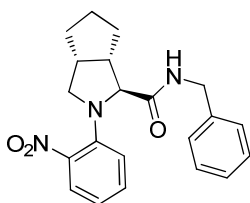
(1S,3aR,6aS)-N-(tert-butyl)-2-(2-nitrophenyl)octahydrocyclopenta[c]pyrrole-1-carboxamide (22): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 2-nitrophenol (35 mg, 0.25 mmol, 1.0 equiv.) and *tert*-butyl isocyanide (31 mg, 0.042 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 61 mg (0.18 mmol, 72%) of a bright sticky orange oil.

(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -734^\circ$ ($c = 0.52$, CHCl_3); $^1\text{H NMR}$ (500.23 MHz, CDCl_3): $\delta = 7.67$ (m, 2H), 7.33 (m, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 6.86 (m, 1H), 6.56 (bs, 1H), 3.88 (d, $J = 6.0$ Hz, 1H), 3.71 (m, 1H), 2.73 (m, 1H), 2.62 (m, 1H), 2.49 (dd, $J = 3.0$ Hz, $J = 10.3$ Hz, 1H), 1.88 (m, 2H), 1.70 (m, 2H), 1.66 (m, 1H), 1.21 (m, 1H), 1.18 (s, 9H); $^{13}\text{C NMR}$ (125.78 MHz, CDCl_3): $\delta = 171.7$, 142.1, 140.4, 135.5, 126.1, 119.5, 117.8, 69.6, 58.4, 50.8, 49.8, 43.2, 32.2, 31.7, 28.5, 28.5, 28.5, 24.9; $^1\text{H NMR}$ (500.23 MHz, CDCl_3): $\delta = 7.67$ (m, 2H), 7.33 (m, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 6.86 (m, 1H), 6.48 (bs, 1H), 4.36 (d, $J = 7.6$ Hz, 1H), 4.00 (m, 1H), 2.73 (m, 1H), 2.62 (m, 1H), 2.49 (dd, $J = 3.0$ Hz, $J = 10.3$ Hz, 1H), 1.88 (m, 2H), 1.70 (m, 2H), 1.66 (m, 1H), 1.21 (m, 1H), 1.18 (s, 9H); $^{13}\text{C NMR}$ (125.78 MHz, CDCl_3): $\delta = 171.7$, 142.1, 140.4, 135.2, 125.8, 119.8, 117.7, 70.1, 59.2, 50.8, 46.9, 42.8, 34.6, 29.7, 28.5, 28.5, 28.5, 25.9; IR (neat): ν_{max} (cm^{-1}) = 3689, 3352, 2957, 1655, 1506, 1265, 746, 710; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{18}\text{H}_{26}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 332.1969, found 332.1958;



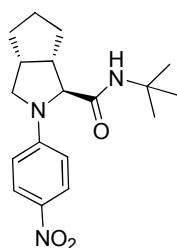
(1S,3aR,6aS)-N-isopropyl-2-(2-nitrophenyl)octahydrocyclopenta[c]pyrrole-1-carboxamide (23): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 2-nitrophenol (35 mg, 0.25 mmol, 1.0 equiv.) and isopropyl isocyanide (26 mg, 0.035 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 56 mg (0.18 mmol, 71%) of a sticky orange oil.

(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -722.9^\circ$ ($c = 0.55$, CHCl_3); ^1H NMR (400.13 MHz, CDCl_3): $\delta = 7.62$ (dd, $J = 1.5$ Hz, $J = 8.0$ Hz, 1H), 7.33 (m, 1H), 7.10 (m, 4H), 7.02 (d, $J = 8.5$ Hz, 1H), 6.96 (t, $J = 3.8$ Hz, 2H), 6.87 (t, $J = 7.5$ Hz, 1H), 4.30 (d, $J = 6.0$ Hz, 2H), 4.05 (d, $J = 6.5$ Hz, 1H), 3.72 (dd, $J = 7.5$ Hz, $J = 10.3$ Hz, 1H), 2.77 (m, 1H), 2.63 (m, 1H), 2.51 (dd, $J = 3.5$ Hz, $J = 10.0$ Hz, 1H), 1.91 (m, 2H), 1.72 (m, 2H), 1.61 (m, 1H), 1.21 (m, 1H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 170.5$, 141.0, 139.7, 132.5, 125.0, 119.1, 117.1, 68.2, 57.5, 48.7, 42.2, 40.0, 31.2, 30.8, 24.0, 21.4, 21.3; ^1H NMR (400.13 MHz, CDCl_3): $\delta = 7.66$ (dd, $J = 1.5$ Hz, $J = 8.0$ Hz, 1H), 7.33 (m, 1H), 7.00 (d, $J = 8.5$ Hz, 1H), 6.86 (t, $J = 7.5$ Hz, 1H), 6.50 (bs, 1H), 4.45 (d, $J = 7.6$ Hz, 2H), 3.88 (m, 1H), 3.70 (dd, $J = 7.0$ Hz, $J = 10.0$ Hz, 1H), 3.49 (m, 1H), 3.72 (m, 1H), 2.99 (m, 1H), 2.81 (m, 2H), 2.50 (dd, $J = 3.5$ Hz, $J = 10.0$ Hz, 1H), 1.88 (m, 1H), 1.62 (m, 1H), 1.21 (m, 1H), 1.12 (m, 3H), 0.79 (m, 3H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 170.5$, 141.0, 139.7, 132.2, 124.7, 118.7, 117.0, 65.6, 58.3, 45.8, 42.0, 40.0, 33.6, 29.0, 25.0, 21.7, 21.3; IR (neat): ν_{max} (cm^{-1}) = 3371, 2962, 2860, 1651, 1506, 1277, 773, 741; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{17}\text{H}_{24}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 318.1812, found 318.1799.



(1S,3aR,6aS)-N-benzyl-2-(2-nitrophenyl)octahydrocyclopenta[c]pyrrole-1-carboxamide (24): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 2-nitrophenol (35 mg, 0.25 mmol, 1.0 equiv.) and benzylisocyanide (44 mg, 0.046 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 69 mg (0.19 mmol, 76%) of a sticky orange oil.

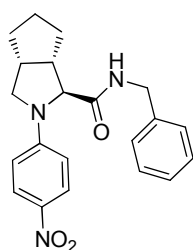
(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -650.9^\circ$ ($c = 0.55$, CHCl_3); ^1H NMR (500.23 MHz, CDCl_3): $\delta = 7.62$ (dd, $J = 1.5$ Hz, $J = 8.0$ Hz, 1H), 7.33 (m, 1H), 7.10 (m, 4H), 7.02 (d, $J = 8.5$ Hz, 1H), 6.96 (t, $J = 3.8$ Hz, 2H), 6.87 (t, $J = 7.5$ Hz, 1H), 4.30 (d, $J = 6.0$ Hz, 2H), 4.05 (d, $J = 6.5$ Hz, 1H), 3.72 (dd, $J = 7.5$ Hz, $J = 10.3$ Hz, 1H), 2.77 (m, 1H), 2.63 (m, 1H), 2.51 (dd, $J = 3.5$ Hz, $J = 10.0$ Hz, 1H), 1.91 (m, 2H), 1.72 (m, 2H), 1.61 (m, 1H), 1.21 (m, 1H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 171.5$, 140.9, 139.7, 137.0, 132.5, 127.5, 127.5, 126.3, 126.3, 126.2, 125.1, 118.9, 117.1, 68.2, 57.4, 48.9, 42.3, 41.9, 30.9, 30.6, 23.8; ^1H NMR (500.23 MHz, CDCl_3): $\delta = 7.62$ (dd, $J = 1.5$ Hz, $J = 8.0$ Hz, 1H), 7.33 (m, 1H), 7.10 (m, 4H), 7.02 (d, $J = 8.5$ Hz, 1H), 6.96 (t, $J = 3.8$ Hz, 2H), 6.87 (t, $J = 7.5$ Hz, 1H), 4.55 (d, $J = 7.6$ Hz, 2H), 4.05 (d, $J = 6.5$ Hz, 1H), 3.72 (dd, $J = 7.5$ Hz, $J = 10.3$ Hz, 1H), 3.17 (m, 1H), 3.01 (m, 1H), 2.51 (dd, $J = 3.5$ Hz, $J = 10.0$ Hz, 1H), 1.91 (m, 2H), 1.72 (m, 2H), 1.61 (m, 1H), 1.21 (m, 1H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 169.7$, 141.1, 139.7, 136.8, 132.3, 127.4, 127.4, 126.2, 126.2, 126.1, 124.8, 119.2, 116.9, 65.7, 58.3, 45.9, 42.3, 33.6, 28.9, 26.7, 24.9; IR (neat): ν_{max} (cm^{-1}) = 3373, 2945, 2868, 1655, 1508, 1277, 740, 598; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{21}\text{H}_{24}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 366.1812, found 366.1801.



(1S,3aR,6aS)-N-(tert-butyl)-2-(4-nitrophenyl)octahydrocyclopenta[c]pyrrole-1-carboxamide (25): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 4-nitrophenol (35 mg, 0.25 mmol, 1.0 equiv.) and *tert*-butyl isocyanide (31 mg, 0.042 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 80 mg (0.23 mmol, 90%) of a yellow solid.

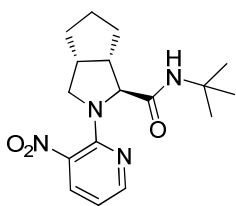
(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -67.4^\circ$ ($c = 0.48$, CHCl_3); ^1H NMR (400.13 MHz, CDCl_3): $\delta = 8.04$ (m, 2H), 6.46 (m, 2H), 5.61 (bs, 1H), 3.81 (m, 2H), 3.12

(dd, $J = 6.8$ Hz, $J = 10.4$ Hz, 1H), 2.83 (m, 1H), 2.73 (m, 1H), 2.01 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.63 (m, 1H), 1.53 (m, 2H), 1.21 (s, 9H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 170.3, 150.6, 137.6, 124.8, 124.8, 110.7, 110.7, 69.9, 54.7, 50.4, 49.2, 40.7, 31.6, 30.5, 27.6, 27.6, 23.8$; ^1H NMR (400.13 MHz, CDCl_3): $\delta = 8.04$ (m, 2H), 6.87 (m, 2H), 5.61 (bs, 1H), 4.12 (m, 2H), 3.34 (dd, $J = 6.8$ Hz, $J = 10.4$ Hz, 1H), 3.66 (m, 1H), 3.35 (m, 1H), 2.01 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.63 (m, 1H), 1.53 (m, 2H), 1.21 (s, 9H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 168.3, 150.6, 137.6, 124.6, 124.6, 111.4, 111.4, 66.7, 55.4, 50.4, 46.4, 41.5, 30.0, 28.7, 26.9, 26.9, 25.2$; IR (neat): ν_{max} (cm^{-1}) = 3298, 2957, 2864, 1597, 1296, 1109, 825, 752; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{18}\text{H}_{26}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 332.1969, found 332.1957.



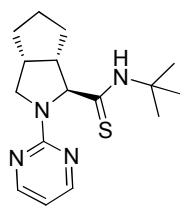
(1S,3aR,6aS)-N-benzyl-2-(4-nitrophenyl)octahydrocyclopenta[c]pyrrole-1-carboxamide (26): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 4-nitrophenol (35 mg, 0.25 mmol, 1.0 equiv.) and benzylisocyanide (44 mg, 0.046 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 69 mg (0.19 mmol, 76%) of a sticky yellow oil.

(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -90.9^\circ$ ($c = 0.55$, CHCl_3); ^1H NMR (400.13 MHz, CDCl_3): $\delta = 7.97$ (d, $J = 2.0$ Hz, 2H), 7.19 (m, 3H), 7.06 (t, $J = 5.6$ Hz, 2H), 6.42 (m, 2H), 6.25 (bs, 1H), 4.34 (m, 2H), 3.99 (d, $J = 2.4$ Hz, 1H), 3.80 (dd, $J = 8.4$ Hz, $J = 10.0$ Hz, 1H), 3.11 (dd, $J = 6.8$ Hz, $J = 10.0$ Hz, 1H), 2.80 (m, 1H), 2.04 (m, 1H), 1.83 (m, 1H), 1.75 (m, 1H), 1.64 (m, 1H), 1.55 (m, 3H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 172.0, 151.5, 138.6, 137.9, 128.7, 128.7, 127.9, 127.9, 127.7, 126.2, 126.2, 112.1, 112.1, 70.2, 55.6, 50.3, 43.3, 38.6, 32.4, 30.8, 24.8$; ^1H NMR (400.13 MHz, CDCl_3): $\delta = 7.97$ (d, $J = 2.0$ Hz, 2H), 7.19 (m, 3H), 7.06 (t, $J = 5.6$ Hz, 2H), 6.79 (m, 2H), 6.25 (bs, 1H), 4.34 (m, 2H), 3.99 (d, $J = 2.4$ Hz, 1H), 3.64 (dd, $J = 8.4$ Hz, $J = 10.0$ Hz, 1H), 3.32 (dd, $J = 6.8$ Hz, $J = 10.0$ Hz, 1H), 3.46 (m, 1H), 2.04 (m, 1H), 1.83 (m, 1H), 1.75 (m, 1H), 1.64 (m, 1H), 1.55 (m, 3H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 170.4, 152.0, 138.6, 137.7, 128.7, 127.7, 127.7, 127.5, 126.0, 126.0, 112.4, 112.4, 67.3, 56.3, 47.4, 43.4, 42.7, 30.8, 26.1, 24.9$; IR (neat): ν_{max} (cm^{-1}) = 3283, 2949, 2866, 1653, 1597, 1294, 1109, 750; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{21}\text{H}_{24}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 366.1812, found 366.1804.



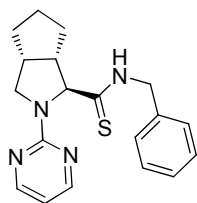
(1S,3aR,6aS)-N-(tert-butyl)-2-(3-nitropyridin-2-yl)octahydrocyclopenta[c]pyrrole-1-carboxamide (27): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 3-nitropyridin-2-ol (35 mg, 0.25 mmol, 1.0 equiv.) and *tert*-butyl isocyanide (31 mg, 0.042 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 61 mg (0.18 mmol, 73%) of a sticky orange oil.

(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -652.4^\circ$ ($c = 0.52$, CHCl_3); ^1H NMR (400.13 MHz, CDCl_3): $\delta = 8.25$ (dd, $J = 2.0$ Hz, $J = 4.6$, 1H), 8.04 (dd, $J = 1.6$ Hz, $J = 8.0$ Hz, 1H), 6.24 (bs, 1H), 4.86 (d, $J = 4.4$ Hz, 1H), 3.70 (dd, $J = 7.6$ Hz, $J = 11.2$ Hz, 1H), 2.82 (m, 1H), 2.68 (m, 1H), 2.54 (dd, $J = 2.8$ Hz, $J = 11.2$ Hz, 1H), 1.94 (m, 1H), 1.72 (m, 2H), 1.57 (m, 2H), 1.23 (s, 9H), 1.14 (m, 1H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 170.5, 150.9, 149.8, 133.7, 131.5, 112.5, 67.0, 56.1, 49.3, 46.7, 42.3, 31.7, 31.4, 31.1, 24.1, 24.1, 24.1$; ^1H NMR (400.13 MHz, CDCl_3): $\delta = 8.25$ (dd, $J = 2.0$ Hz, $J = 4.6$, 1H), 8.04 (dd, $J = 1.6$ Hz, $J = 8.0$ Hz, 1H), 6.07 (bs, 1H), 5.04 (d, $J = 7.6$ Hz, 1H), 3.70 (dd, $J = 7.6$ Hz, $J = 11.2$ Hz, 1H), 3.24 (m, 1H), 2.95 (m, 1H), 2.54 (dd, $J = 2.8$ Hz, $J = 11.2$ Hz, 1H), 1.94 (m, 1H), 1.72 (m, 2H), 1.57 (m, 2H), 1.23 (s, 9H), 1.14 (m, 1H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 169.0, 150.9, 149.8, 133.4, 131.5, 112.7, 64.6, 56.2, 49.3, 45.1, 42.6, 31.4, 28.7, 25.9, 25.9, 25.9, 24.32$; IR (neat): ν_{max} (cm^{-1}) = 3396, 2953, 2868, 1664, 1456, 763, 540; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{17}\text{H}_{25}\text{N}_4\text{O}_3$ ($[\text{M}+\text{H}]^+$): 333.1921, found 333.1907.



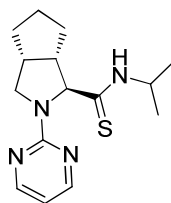
(1S,3aR,6aS)-N-(tert-butyl)-2-(pyrimidin-2-yl)octahydrocyclopenta[c]pyrrole-1-carbothioamide (28): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 2-mercaptopyrimidine (28 mg, 0.25 mmol, 1.0 equiv.) and *tert*-butyl isocyanide (31 mg, 0.042 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 61 mg (0.20 mmol, 80%) of a off-white solid.

(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -129.4^\circ$ ($c = 0.51$, CHCl_3); ^1H NMR (400.13 MHz, CDCl_3): $\delta = 8.28$ (d, $J = 4.8$ Hz, 2H), 8.07 (bs, 1H), 6.53 (t, $J = 4.8$ Hz, 1H), 4.67 (d, $J = 2.8$ Hz, 1H), 3.97 (dd, $J = 8.4$ Hz, $J = 11.4$ Hz, 1H), 3.58 (dd, $J = 6.4$ Hz, $J = 11.4$ Hz, 1H) 3.03 (m, 1H), 2.84 (m, 1H) 2.05 (m, 1H), 1.85 (m, 1H), 1.73 (m, 1H), 1.60 (m, 2H), 1.51 (m, 1H), 1.24 (s, 9H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 202.3$, 160.9, 157.7, 157.7, 111.1, 46.5, 54.1, 51.7, 41.6, 32.8, 31.5, 27.6, 27.6, 27.6, 25.1; ^1H NMR (400.13 MHz, CDCl_3): $\delta = 8.28$ (d, $J = 4.8$ Hz, 2H), 7.50 (bs, 1H), 7.08 (t, $J = 4.8$ Hz, 1H), 4.97 (d, $J = 2.8$ Hz, 1H), 4.28 (dd, $J = 8.4$ Hz, $J = 11.4$ Hz, 1H), 3.58 (dd, $J = 6.4$ Hz, $J = 11.4$ Hz, 1H) 3.30 (m, 1H), 3.16 (m, 1H) 2.05 (m, 1H), 1.85 (m, 1H), 1.73 (m, 1H), 1.60 (m, 2H), 1.51 (m, 1H), 1.24 (s, 9H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 199.5$, 160.9, 157.7, 157.7, 111.7, 75.3, 54.9, 49.5, 41.7, 29.7, 27.2, 27.6, 27.6, 27.6, 25.8; IR (neat): ν_{max} (cm^{-1}) = 3312, 2961, 2872, 1580, 1460, 1076, 798, 635; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{16}\text{H}_{25}\text{N}_4\text{S}$ ($[\text{M}+\text{H}]^+$): 305.1794, found 305.1780.



(1S,3aR,6aS)-N-benzyl-2-(pyrimidin-2-yl)octahydrocyclopenta[c]pyrrole-1-carbothioamide (29): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 2-mercaptopyrimidine (28 mg, 0.25 mmol, 1.0 equiv.) and benzyl isocyanide (44 mg, 0.046 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 49 mg (0.15 mmol, 58%) of a white solid.

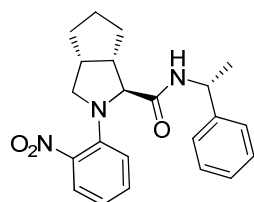
(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -66.7^\circ$ ($c = 0.48$, CHCl_3); ^1H NMR (400.13 MHz, CDCl_3): $\delta = 8.46$ (bs, 1H), 8.21 (d, $J = 4.8$ Hz, 2H), 7.18 (m, 3H), 7.11 (m, 2H), 6.50 (t, $J = 4.4$ Hz, 1H), 4.83 (m, 2H), 4.70 (dd, $J = 5.2$ Hz, $J = 15.2$, 1H), 3.79 (dd, $J = 8.4$ Hz, $J = 11.4$ Hz, 1H), 3.58 (dd, $J = 6.4$ Hz, $J = 11.4$ Hz, 1H) 3.04 (m, 1H), 2.81 (m, 1H) 2.05 (m, 1H), 1.80 (m, 1H), 1.59 (m, 2H), 1.50 (m, 2H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 204.4$, 160.9, 157.8, 157.8, 136.4, 128.7, 128.0, 127.8, 111.1, 74.8, 54.1, 51.8, 49.3, 41.7, 32.7, 31.4, 25.1; ^1H NMR (400.13 MHz, CDCl_3): $\delta = 7.87$ (bs, 1H), 8.27 (d, $J = 4.8$ Hz, 2H), 7.18 (m, 3H), 7.11 (m, 2H), 6.50 (t, $J = 4.4$ Hz, 1H), 5.15 (d, 1H), 4.83 (m, 1H), 4.98 (dd, $J = 5.2$ Hz, $J = 15.2$, 1H), 4.21 (dd, $J = 8.4$ Hz, $J = 11.4$ Hz, 1H), 4.04 (dd, $J = 6.4$ Hz, $J = 11.4$ Hz, 1H) 3.16 (m, 1H), 2.67 (m, 1H) 2.05 (m, 1H), 1.80 (m, 1H), 1.59 (m, 2H), 1.50 (m, 2H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 202.0$, 161.5, 157.7, 157.7, 136.4, 128.6, 127.8, 127.8, 111.7, 73.9, 54.8, 49.6, 48.8, 42.1, 29.5, 27.4, 25.7; IR (neat): ν_{max} (cm^{-1}) = 3196, 2947, 2862, 1491, 964, 744, 696; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{19}\text{H}_{23}\text{N}_4\text{S}$ ($[\text{M}+\text{H}]^+$): 339.1638, found 339.1626.



(1S,3aR,6aS)-N-isopropyl-2-(pyrimidin-2-yl)octahydrocyclopenta[c]pyrrole-1-carbothioamide (30): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 2-mercaptopyrimidine (28 mg, 0.25 mmol, 1.0 equiv.) and isopropyl isocyanide (26 mg, 0.035 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 62 mg (0.21 mmol, 85%) of a off-white sticky oil.

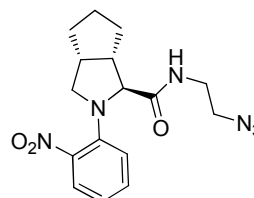
(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -102.9^\circ$ ($c = 0.51$, CHCl_3); ^1H NMR (400.13 MHz, CDCl_3): $\delta = 8.26$ (d, $J = 4.8$ Hz, 2H), 7.95 (bs, 1H), 6.53 (t, $J = 4.8$ Hz, 1H), 4.69 (d, $J = 2.8$ Hz, 1H), 4.57 (m, 1H), 3.82 (dd, $J = 8.4$ Hz, $J = 11.4$ Hz, 1H), 3.52 (dd, $J = 6.0$ Hz, $J = 11.4$ Hz, 1H) 2.98 (m, 1H), 2.79 (m, 1H) 2.00 (m, 1H), 1.79 (m, 1H), 1.57 (m, 2H), 1.50 (m, 2H), 1.05 (m, 6H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 202.2$, 160.9, 157.7, 157.7, 111.1, 75.0, 54.1, 51.6, 46.5, 41.7, 32.7, 31.4, 25.1, 20.9; ^1H NMR

(400.13 MHz, CDCl₃): δ = 8.26 (d, J = 4.8 Hz, 2H), 7.39 (bs, 1H), 7.02 (t, J = 4.8 Hz, 1H), 4.69 (d, J = 2.8 Hz, 1H), 4.24 (m, 1H), 3.82 (dd, J = 8.4 Hz, J = 11.4 Hz, 1H), 3.52 (dd, J = 6.0 Hz, J = 11.4 Hz, 1H), 3.24 (m, 1H), 3.11 (m, 1H), 2.00 (m, 1H), 1.79 (m, 1H), 1.57 (m, 2H), 1.50 (m, 2H), 1.05 (m, 6H); ¹³C NMR (100.62 MHz, CDCl₃): δ = 199.6, 161.5, 157.9, 157.9, 111.7, 73.8, 54.9, 49.5, 46.2, 41.9, 29.6, 27.1, 25.7, 21.5, 21.1; IR (neat): $\nu_{\max}$ (cm⁻¹) = 3190, 2961, 2866, 1583, 1499, 795; HR-MS (ESI, 4500 V): m/z calcd for C₁₅H₂₃N₄S ([M+H]⁺): 291.1638, found 291.1628.



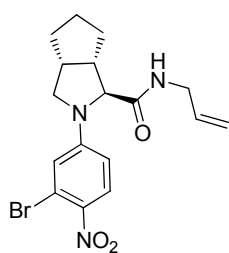
(1S,3aR,6aS)-2-(2-nitrophenyl)-N-((R)-1-phenylethyl)octahydrocyclopenta[c]-pyrrole-1-carboxamide (31): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 2-nitrophenol (35 mg, 0.25 mmol, 1.0 equiv.) and (S)-(-)- α -methylbenzyl isocyanide (49 mg, 0.051 ml, 0.375 mmol, 1.5 equiv.) giving a yield of 80 mg (0.23 mmol, 90%) of a sticky orange oil.

(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20}$ = -650.0° (c = 0.72, CHCl₃); ¹H NMR (400.13 MHz, CDCl₃): δ = 7.61 (d, J = 1.6 Hz, 1H), 7.22 (m, 2H), 6.98 (m, 1H), 6.85 (m, 5H), 4.91 (m, 1H), 3.96 (d, J = 6.0 Hz, 1H), 3.73 (dd, J = 7.2 Hz, J = 10.0 Hz, 1H), 2.77 (m, 1H), 2.65 (m, 1H), 2.51 (dd, J = 3.6 Hz, J = 10.0 Hz, 1H), 1.88 (m, 2H), 1.66 (m, 3H), 1.34 (d, J = 7.2 Hz, 3H), 1.21 (m, 2H); ¹³C NMR (100.62 MHz, CDCl₃): δ = 170.6, 142.3, 140.8, 140.1, 132.5, 127.2, 125.8, 124.8, 124.6, 119.0, 117.4, 68.2, 57.4, 48.8, 47.4, 42.3, 31.0, 30.7, 23.9, 21.2; ¹H NMR (400.13 MHz, CDCl₃): δ = 7.61 (d, J = 1.6 Hz, 1H), 7.36 (m, 2H), 6.98 (m, 1H), 6.85 (m, 5H), 4.91 (m, 1H), 4.49 (d, J = 6.0 Hz, 1H), 3.73 (dd, J = 7.2 Hz, J = 10.0 Hz, 1H), 3.16 (m, 1H), 2.94 (m, 1H), 2.51 (dd, J = 3.6 Hz, J = 10.0 Hz, 1H), 1.88 (m, 2H), 1.66 (m, 3H), 1.34 (d, J = 7.2 Hz, 3H), 1.21 (m, 2H); ¹³C NMR (100.62 MHz, CDCl₃): δ = 168.7, 142.3, 140.8, 140.1, 132.4, 127.7, 126.3, 125.1, 124.7, 119.3, 117.1, 65.6, 58.3, 47.4, 45.9, 42.0, 29.0, 28.7, 26.5, 20.1; IR (neat): $\nu_{\max}$ (cm⁻¹) = 3367, 2941, 2866, 1657, 1508, 741, 698; HR-MS (ESI, 4500 V): m/z calcd for C₂₂H₂₆N₃O₃ ([M+H]⁺): 380.1969, found 380.1953.



(1S,3aR,6aS)-N-(2-azidoethyl)-2-(2-nitrophenyl)octahydrocyclopenta[c]-pyrrole-1-carboxamide (33): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 1.3 equiv.), 2-nitrophenol (70 mg, 0.5 mmol, 1.3 equiv.) and 1-azido-2-isocyanoethane (36 mg, 0.375 mmol, 1.0 equiv.) giving a yield of 93 mg (0.27 mmol, 72%) of an orange solid.

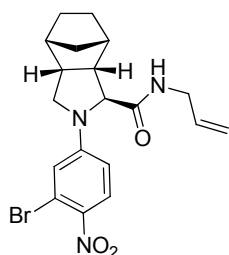
(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20}$ = -575.8° (c = 0.66, CHCl₃); ¹H NMR (400.13 MHz, CDCl₃): δ = 7.66 (d, J = 8.0 Hz, 1H), 7.33 (m, 1H), 7.02 (m, 1H), 6.87 (m, 1H), 4.04 (d, J = 5.6 Hz, 1H), 3.74 (m, 1H), 3.25 (m, 4H), 2.75 (m, 1H), 2.65 (m, 1H), 2.52 (dd, J = 3.6 Hz, J = 10.2 Hz, 1H), 1.89 (m, 2H), 1.65 (m, 3H), 1.26 (m, 2H); ¹³C NMR (100.62 MHz, CDCl₃): δ = 172.1, 140.9, 139.9, 132.6, 125.2, 119.1, 117.0, 68.2, 57.6, 49.6, 48.8, 42.5, 37.7, 30.9, 30.5, 24.7; ¹H NMR (400.13 MHz, CDCl₃): δ = 7.66 (d, J = 8.0 Hz, 1H), 7.21 (m, 1H), 7.02 (m, 1H), 6.87 (m, 1H), 4.52 (d, J = 5.6 Hz, 1H), 3.74 (m, 1H), 3.25 (m, 4H), 3.00 (m, 1H), 2.65 (m, 1H), 2.52 (dd, J = 3.6 Hz, J = 10.2 Hz, 1H), 1.89 (m, 2H), 1.65 (m, 3H), 1.26 (m, 2H); ¹³C NMR (100.62 MHz, CDCl₃): δ = 170.3, 141.0, 139.9, 132.3, 124.9, 119.4, 116.8, 65.6, 58.5, 49.7, 45.9, 42.0, 37.3, 28.9, 26.7, 25.0; IR (neat): $\nu_{\max}$ (cm⁻¹) = 3367, 2951, 2870, 2098, 1664, 1510, 1277, 729, 541; HR-MS (ESI, 4500 V): m/z calcd for C₁₆H₂₁N₆O₃ ([M+H]⁺): 345.1670, found 345.1654.



(1S,3aR,6aS)-N-allyl-2-(3-bromo-4-nitrophenyl)octahydrocyclopenta[c]-pyrrole-1-carboxamide (34): General procedure 2 was followed using 3-azabicyclo[3.3.0]oct-2-ene **32** (55 mg, 0.5 mmol, 2.0 equiv.), 4-nitro-3-bromophenol (54 mg, 0.25 mmol, 1.0 equiv.) and allyl isocyanide (27 mg, 0.4 mmol, 1.6 equiv.) giving a yield of 54 mg (0.14 mmol, 55%) of a sticky orange oil.

(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -122.1^\circ$ ($c = 0.48$, CHCl_3); ^1H NMR (400.13 MHz, CDCl_3): $\delta = 7.91$ (d, $J = 9.2$ Hz, 1H), 6.75 (d, $J = 2.8$ Hz, 1H), 6.40 (dd, $J = 2.8$ Hz, $J = 9.2$ Hz, 1H), 6.03 (bs, 1H), 5.69 (m, 1H), 5.03 (m, 2H), 3.94 (d, $J =$

2.4 Hz, 1H), 3.80 (m, 3H), 3.12 (dd, $J = 6.8$ Hz, $J = 10.2$ Hz, 1H), 2.75 (m, 2H), 2.04 (m, 1H), 1.75 (m, 2H), 1.60 (m, 3H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 170.5$, 149.5, 137.7, 132.5, 127.4, 117.2, 116.9, 115.7, 110.3, 69.1, 54.6, 49.3, 40.7, 40.7, 31.4, 30.5, 23.8; ^1H NMR (400.13 MHz, CDCl_3): $\delta = 7.85$ (d, $J = 9.2$ Hz, 1H), 7.09 (d, $J = 2.8$ Hz, 1H), 6.40 (dd, $J = 2.8$ Hz, $J = 9.2$ Hz, 1H), 7.30 (bs, 1H), 5.69 (m, 1H), 5.03 (m, 2H), 4.27 (d, $J = 2.4$ Hz, 1H), 3.66 (m, 3H), 3.12 (dd, $J = 6.8$ Hz, $J = 10.2$ Hz, 1H), 3.33 (m, 2H), 2.04 (m, 1H), 1.75 (m, 2H), 1.60 (m, 3H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 169.0$, 149.9, 137.7, 132.6, 127.3, 117.6, 116.7, 116.0, 110.5, 66.0, 55.4, 46.4, 41.7, 33.6, 29.8, 27.1, 24.5; IR (neat): ν_{max} (cm^{-1}) = 3286, 2951, 2866, 1589, 1302, 727, 646; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{17}\text{H}_{21}\text{BrN}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 394.0761, found 394.0754.



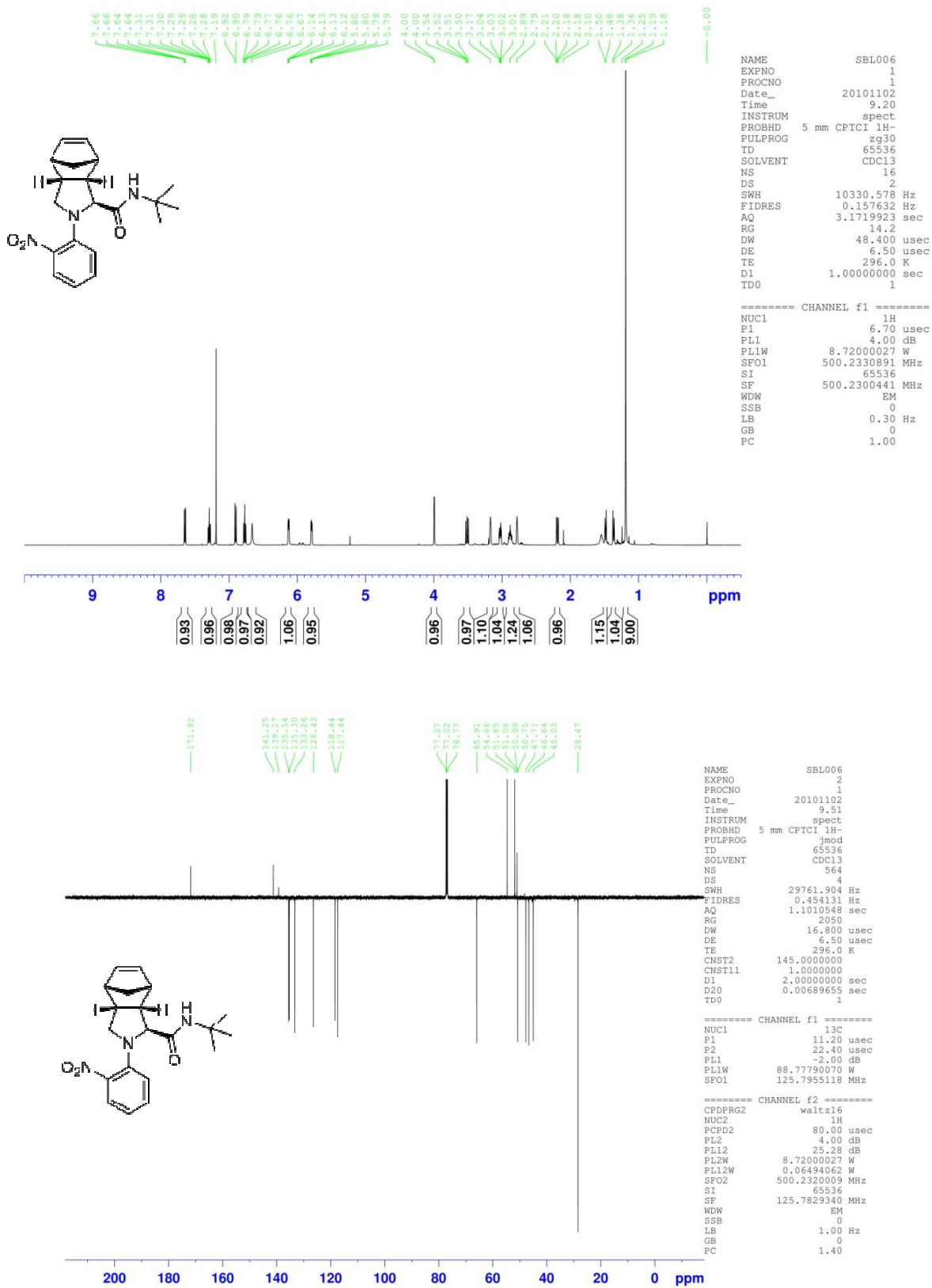
(1S,3aR,4R,7S,7aS)-N-allyl-2-(3-bromo-4-nitrophenyl)octahydro-1H-4,7-methanoisindole-1-carboxamide (35): General procedure 2 was followed using saturated bridged (3S,7R)-**36** (68 mg, 0.5 mmol, 2.0 equiv.), 3-bromo-4-nitrophenol (54 mg, 0.25 mmol, 1.0 equiv.) and allyl isocyanide (27 mg, 0.040 ml, 0.4 mmol, 1.5 equiv.), giving a yield of 35 mg (0.08 mmol, 34%) of a yellow solid.

$[\alpha]_D^{20} = -90.6^\circ$ ($c = 0.53$, CHCl_3); ^1H NMR (400.13 MHz, CDCl_3): $\delta = 7.95$ (d, $J = 9.2$ Hz, 1H), 6.83 (d, $J = 2.8$ Hz, 1H), 6.49 (dd, $J = 2.8$ Hz, $J = 9.2$ Hz, 1H), 5.70 (m, 2H), 5.03 (m, 3H), 4.14 (s, 1H), 3.78 (m, 2H), 3.56 (d, $J = 1.6$ Hz, 1H), 3.47 (m, 1H), 2.74 (m, 1H), 2.41 (m, 1H), 2.24 (m, 1H), 1.51 (m, 2H), 1.14 (m, 4H); ^{13}C NMR (100.62 MHz, CDCl_3): $\delta = 172.0$, 149.6, 138.3, 133.6, 128.9, 118.3, 117.8, 116.6, 110.9, 63.5, 50.5, 49.3, 42.5, 42.0, 41.8₂, 41.8, 41.2, 22.8, 22.1; IR (neat): ν_{max} (cm^{-1}) = 3283, 2953, 2869, 1651, 1589, 1304, 837, 744; HR-MS (ESI, 4500 V): m/z calcd for $\text{C}_{19}\text{H}_{23}\text{BrN}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 420.0917, found 420.0897.

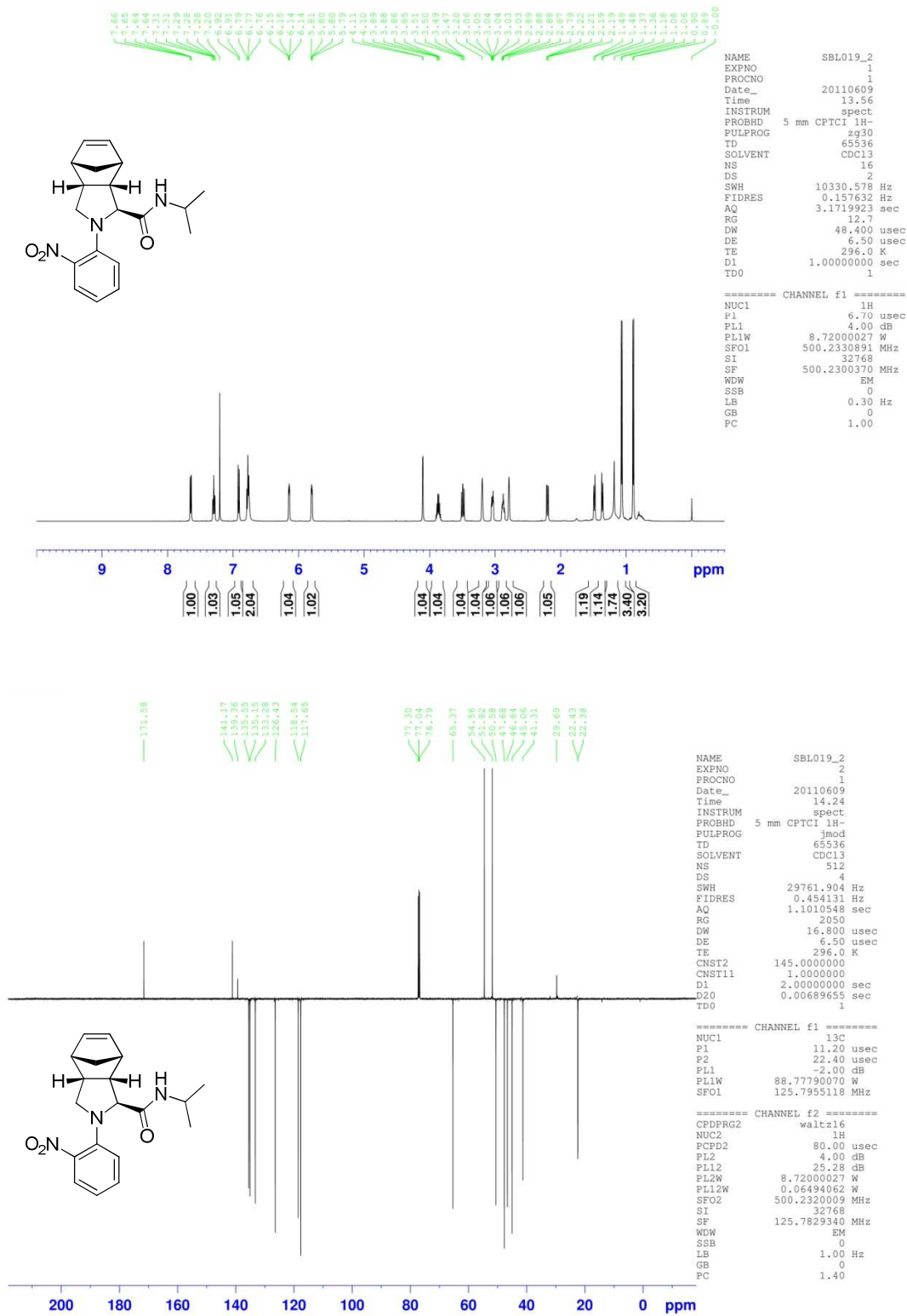
References:

- (1) S. Michaelis and S. Blechert, *Chem. Eur. J.* 2007, **13**, 2358–2368.
- (2) F. E. Hahn, V. Langenhahn and T. Pape, *Chem. Comm.* 2005, **43**, 5390-5392.
- (3) J. Zhu, X. Wu and S. J. Danishefsky, *Tetrahedron Lett.* 2009, **50**, 577–579.
- (4) K. Hornberger, M. Cheung, M. A. Pobanz, K. A. Emmitte, K. W. Kuntz and J. G. Badiang, WO2007/30366 A1, 2007.
- (5) Optical rotation determined for diastereomeric mixture. Value is reported for comparative purposes.

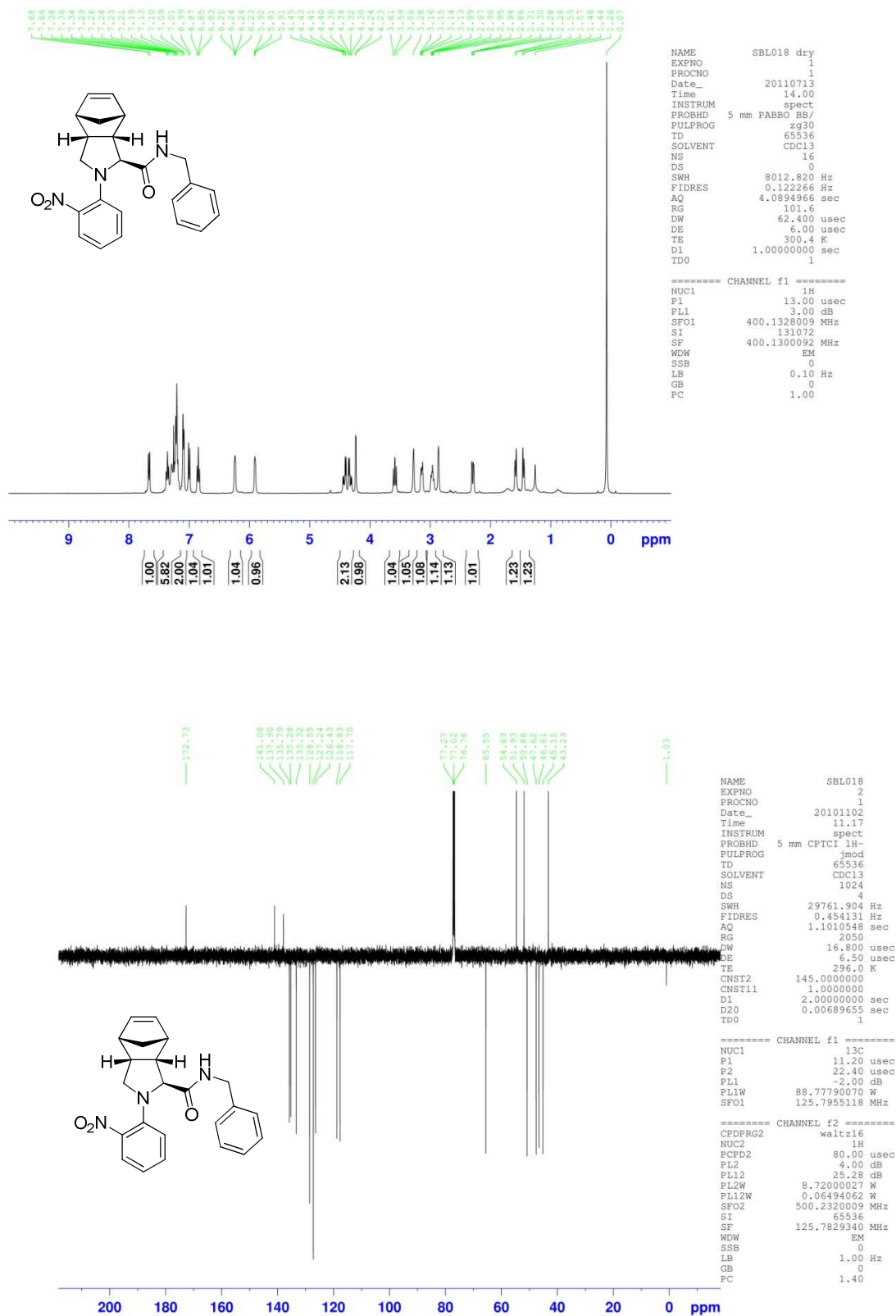
Compound 11



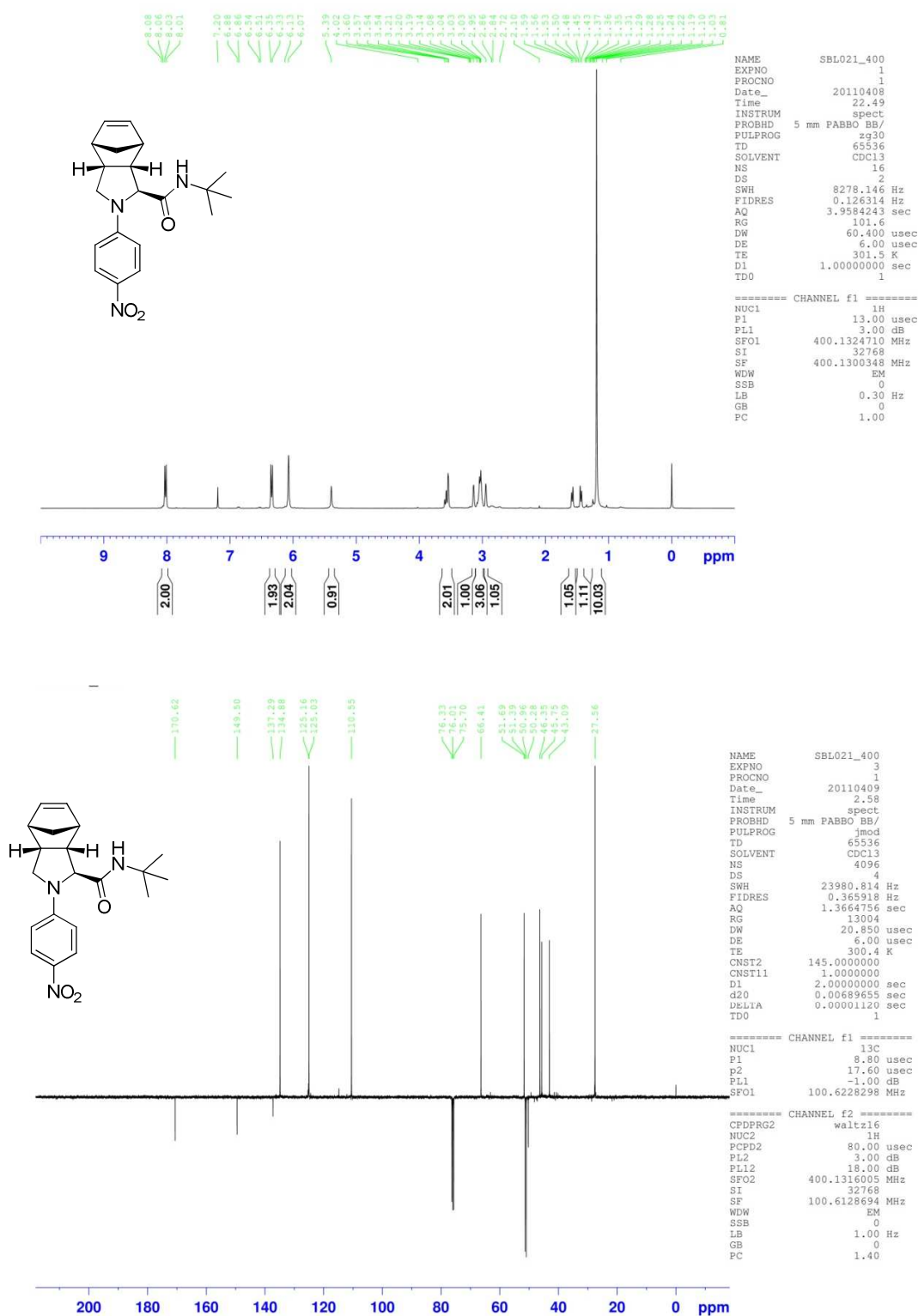
Compound 12



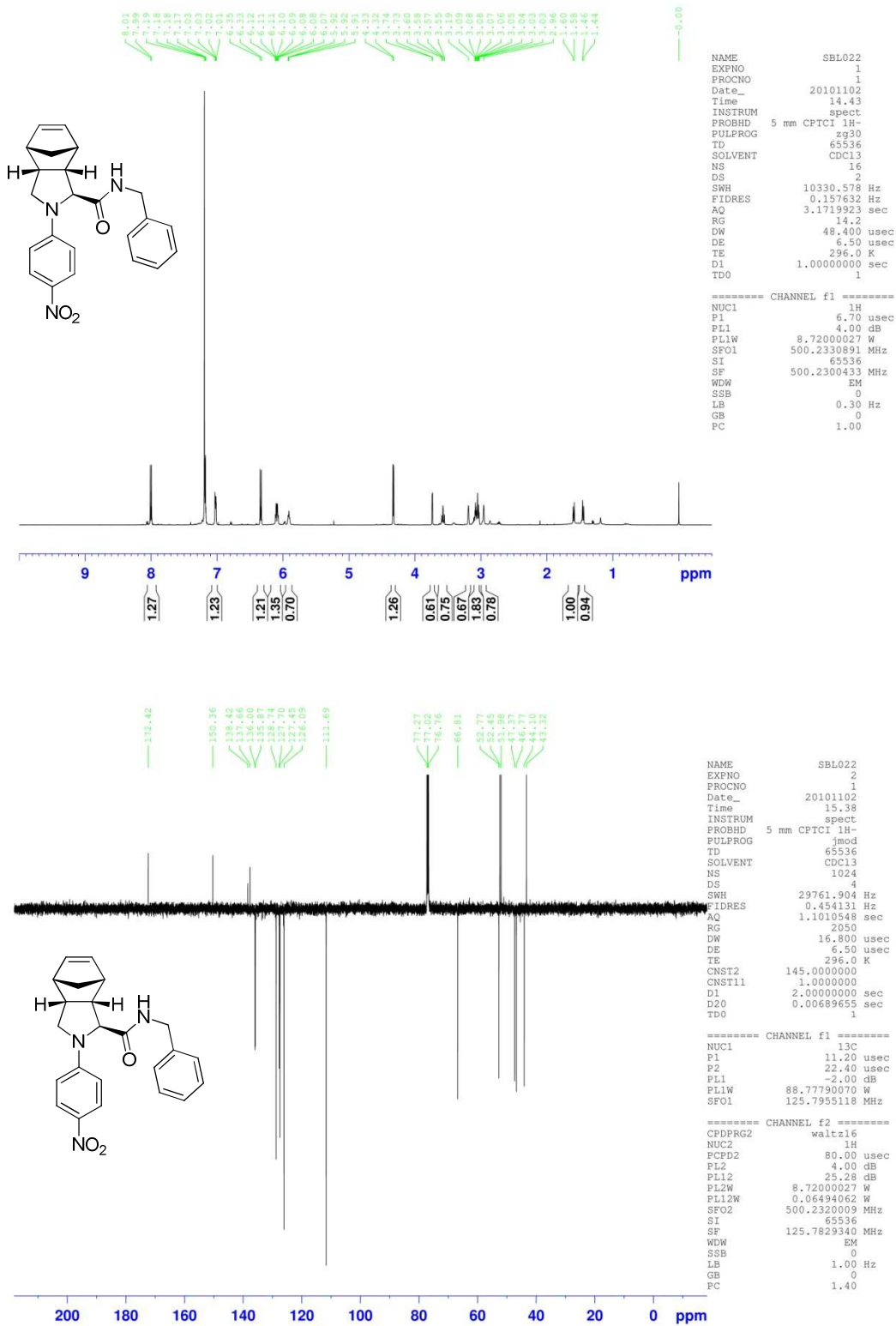
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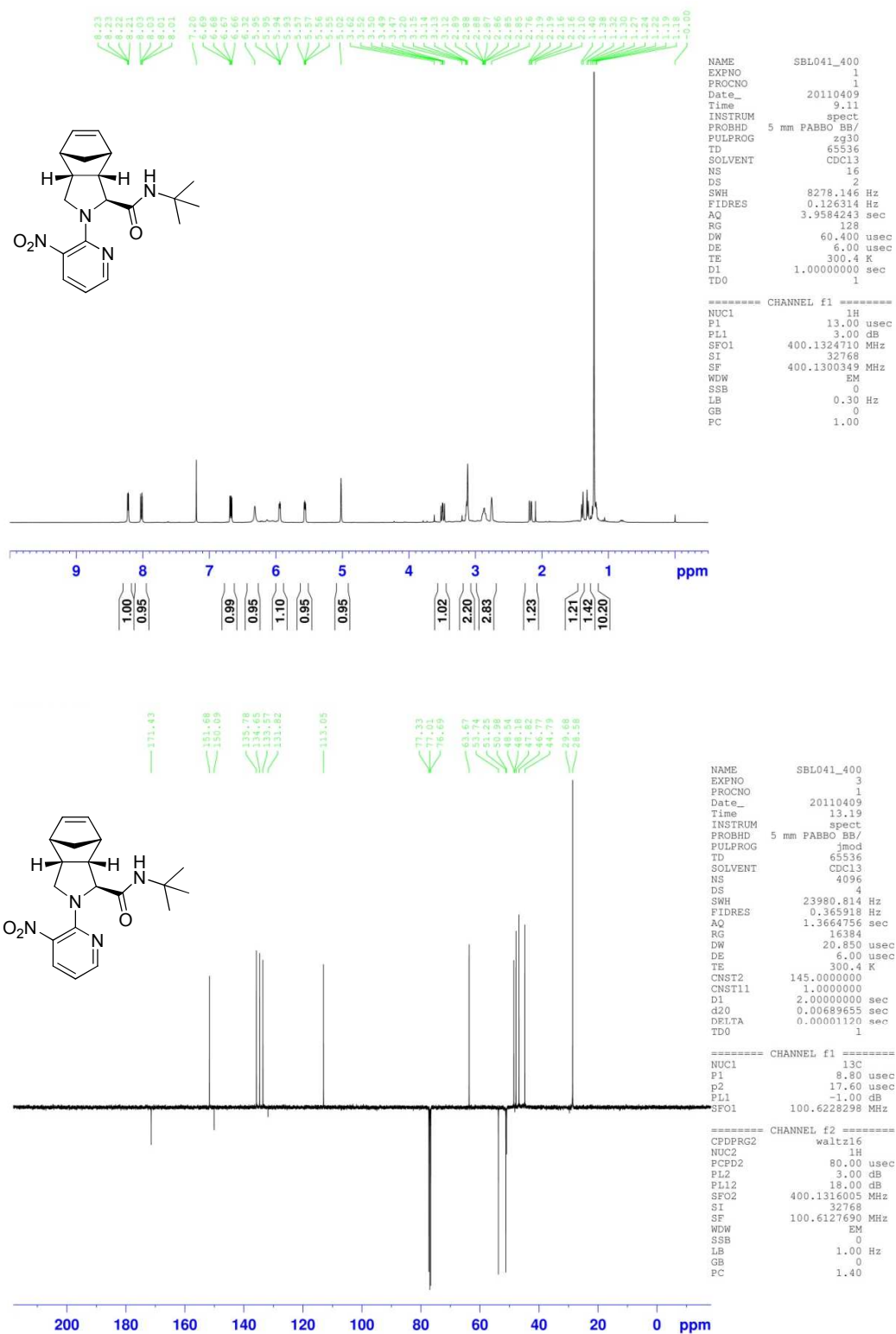
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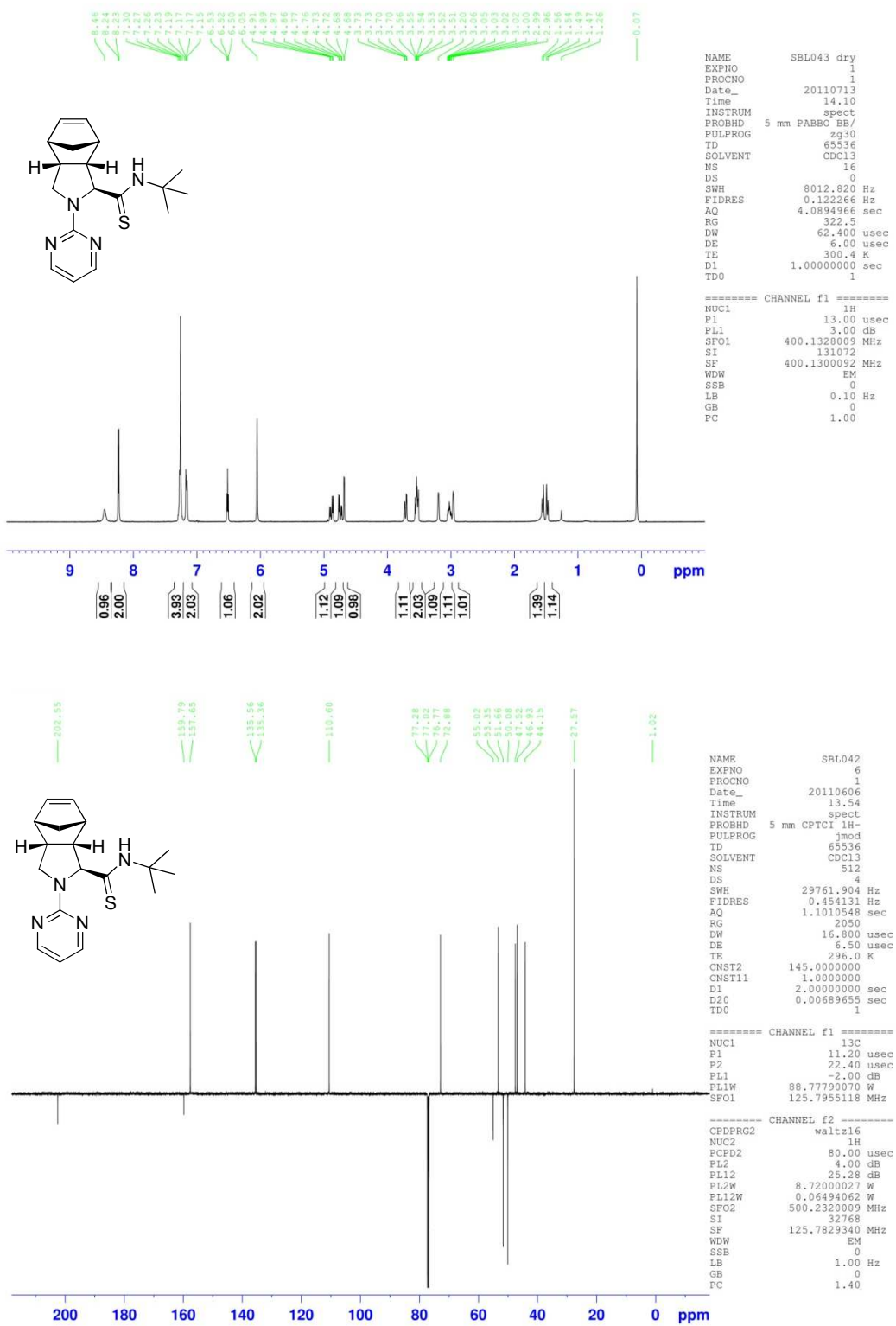
Compound 15



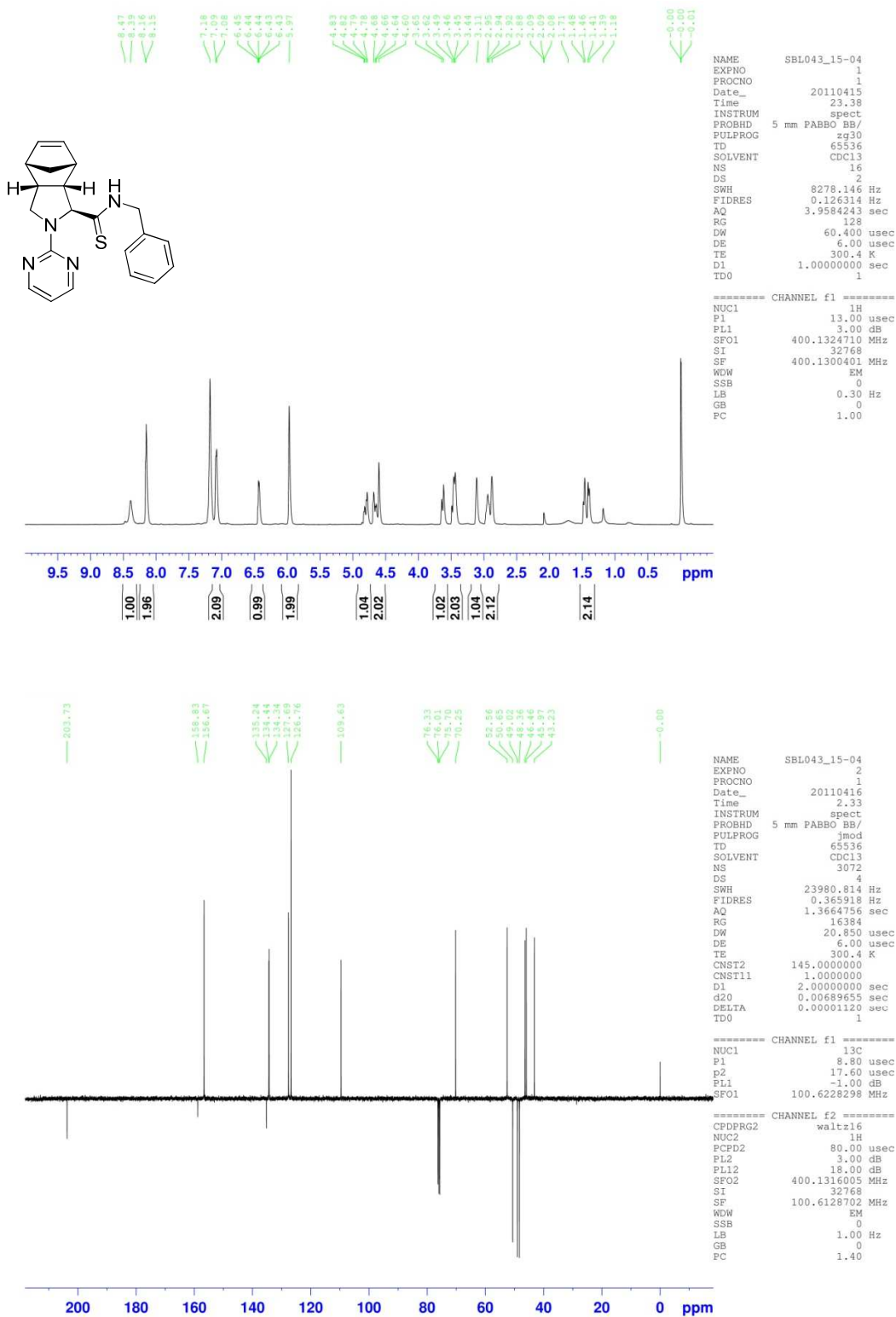
Compound 16



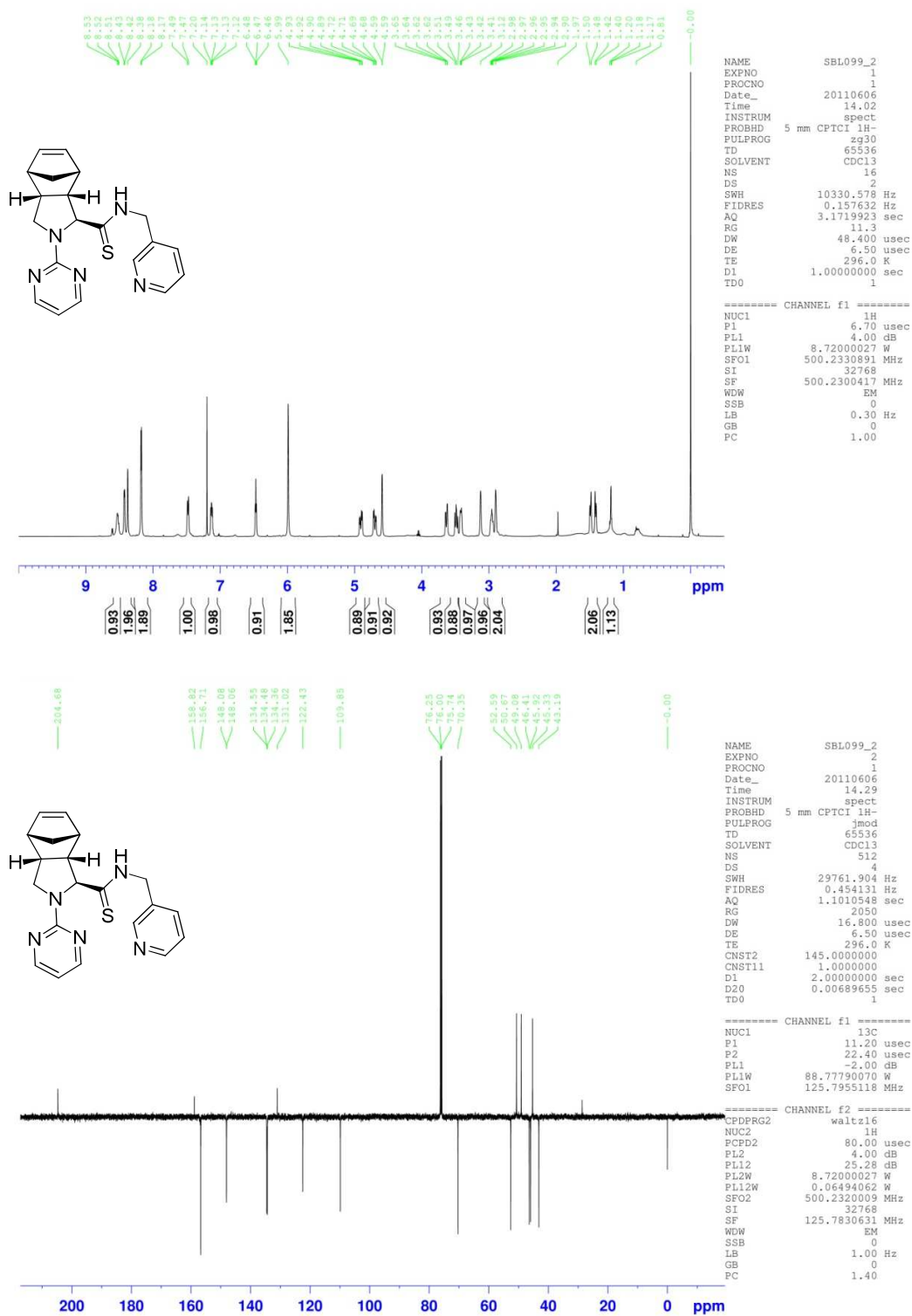
Compound 17



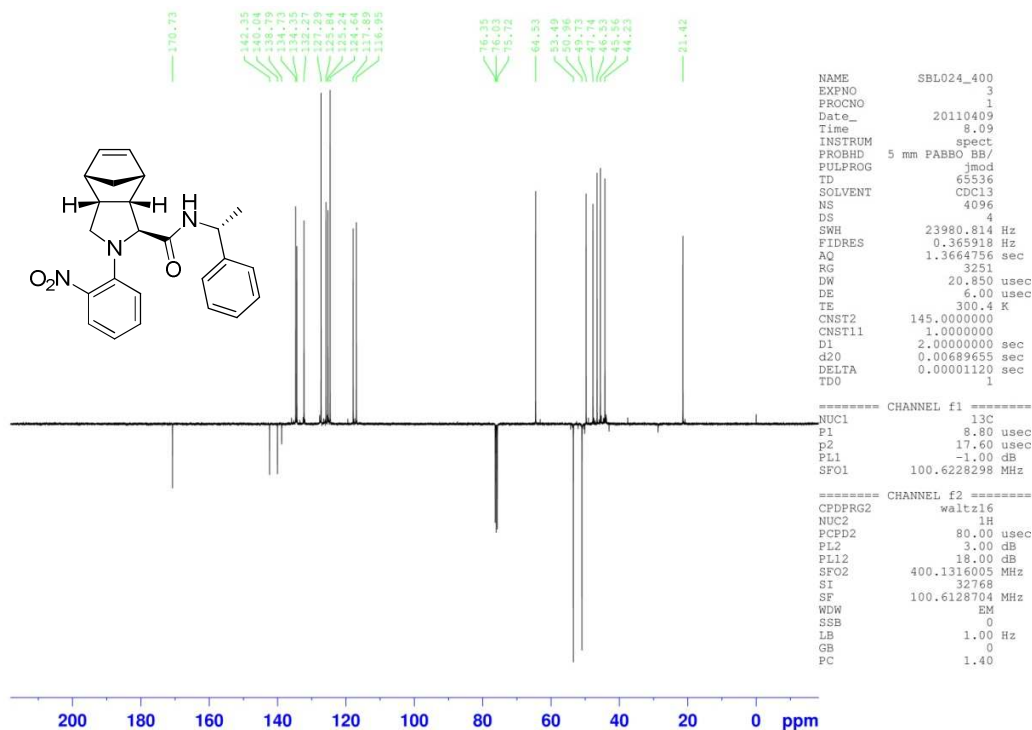
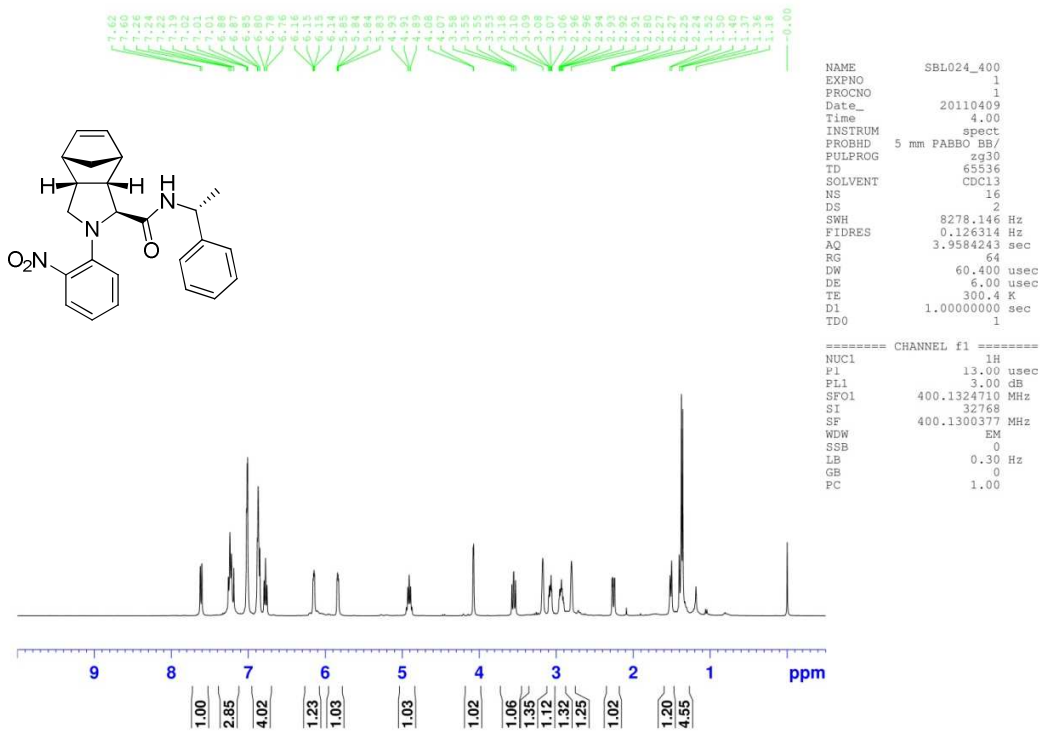
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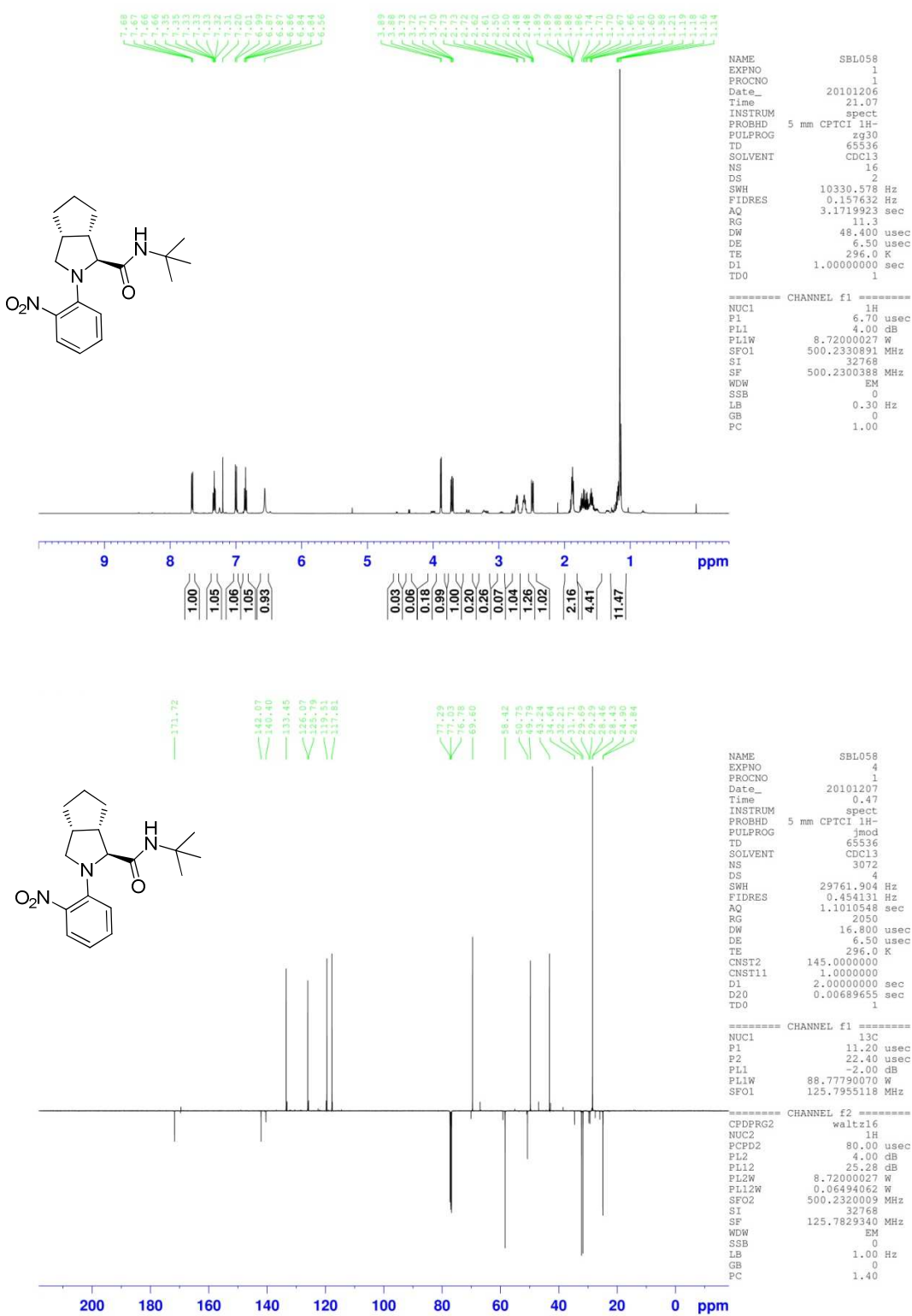
Compound 20



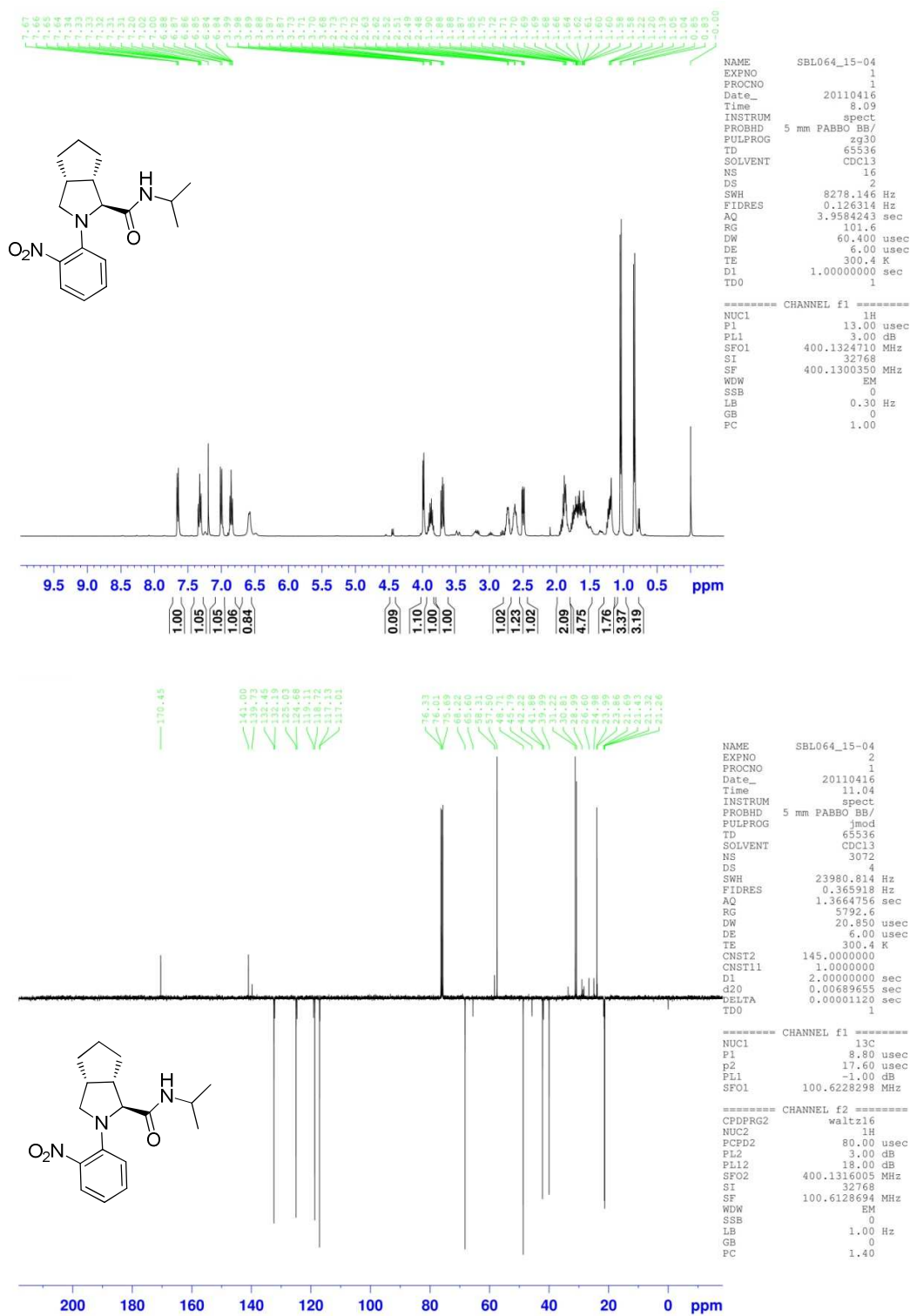
Compound 21



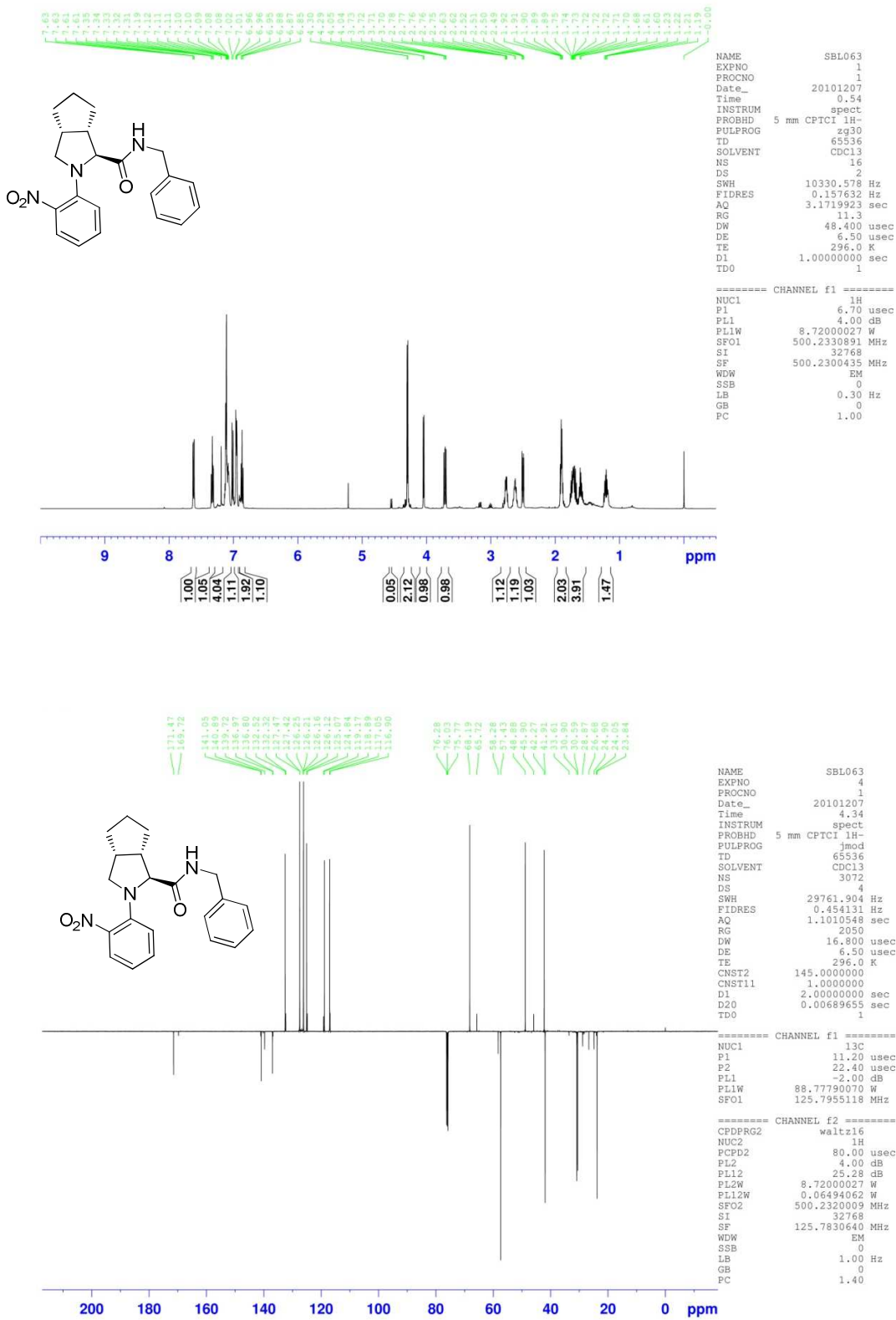
Compound 22



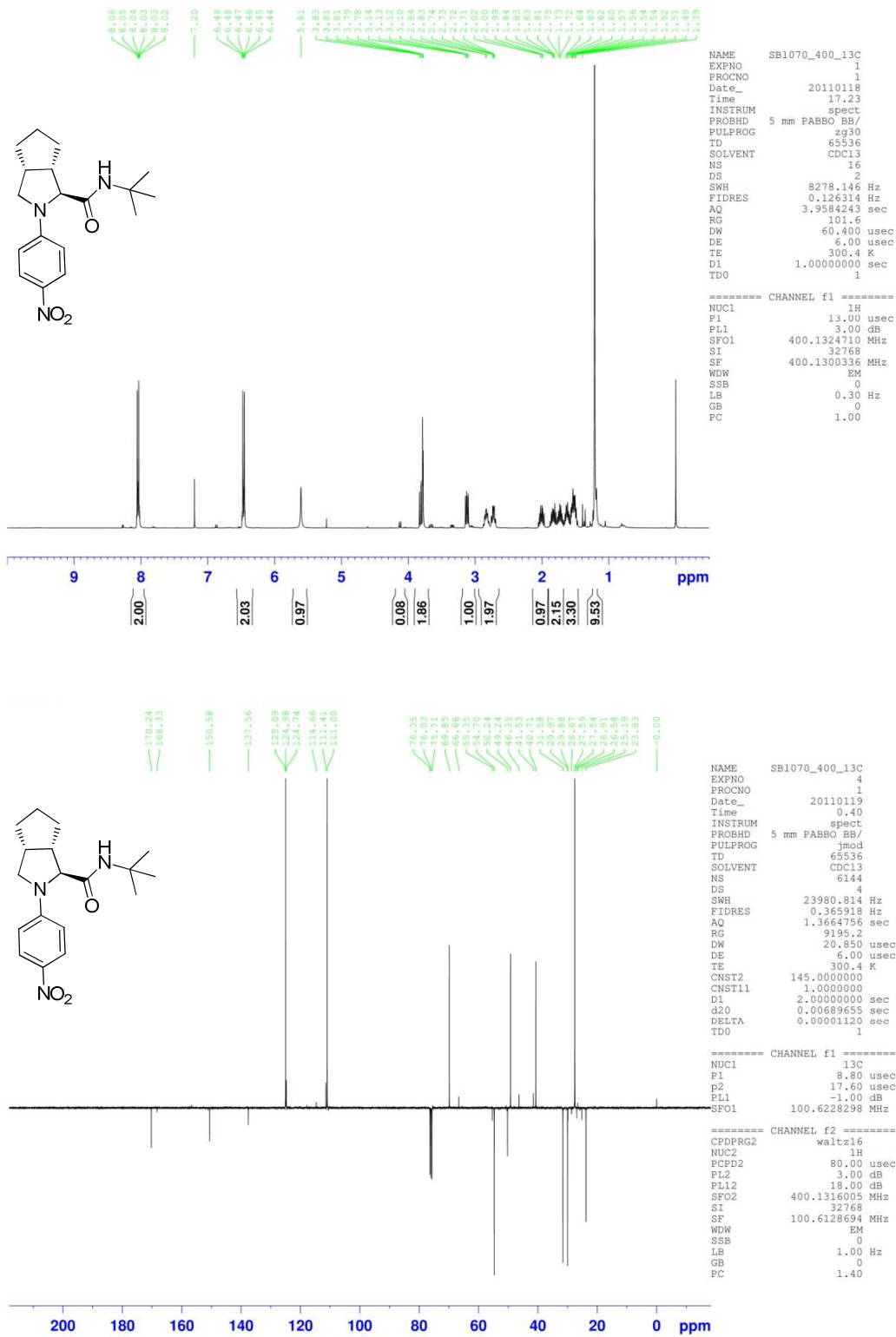
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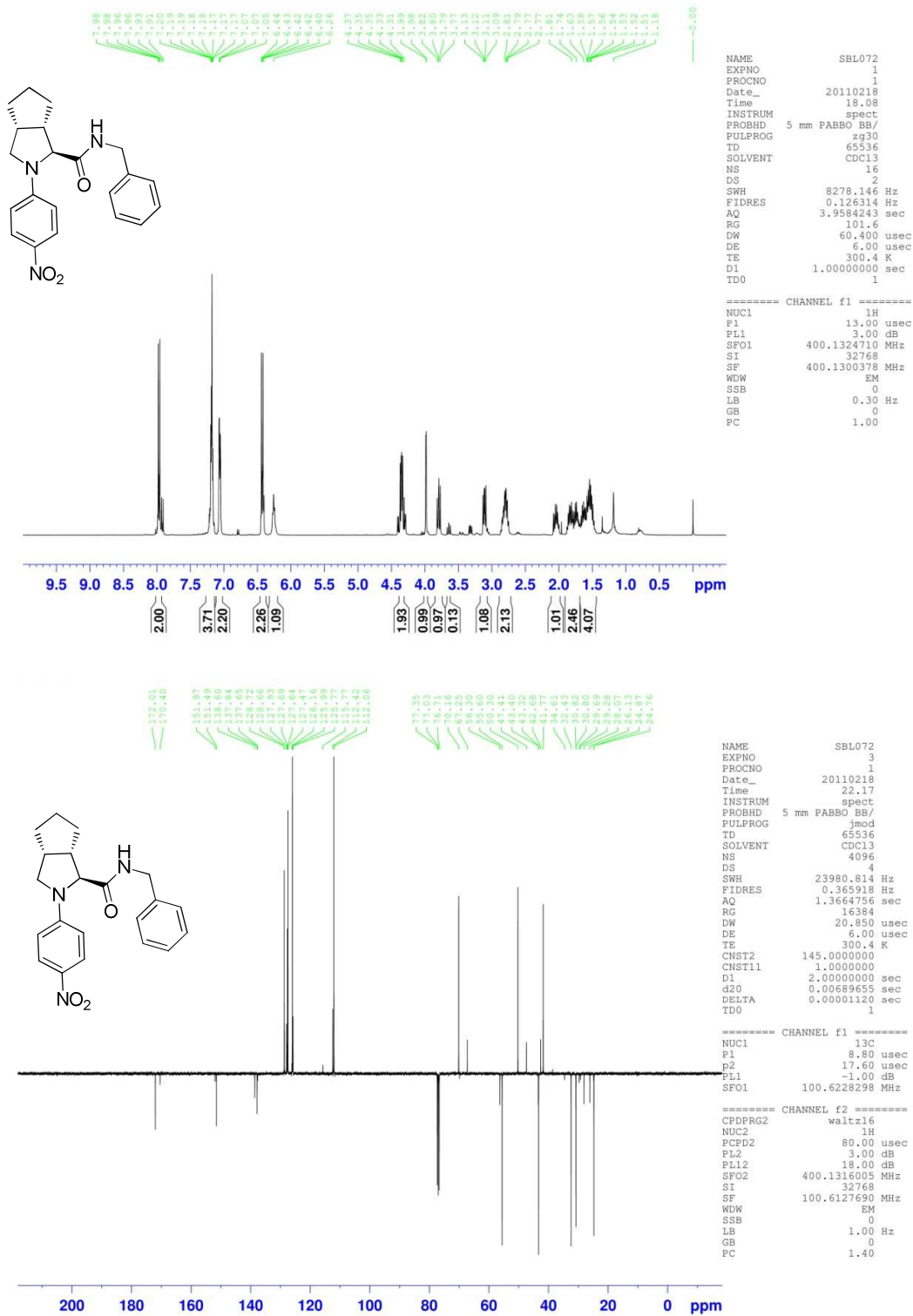
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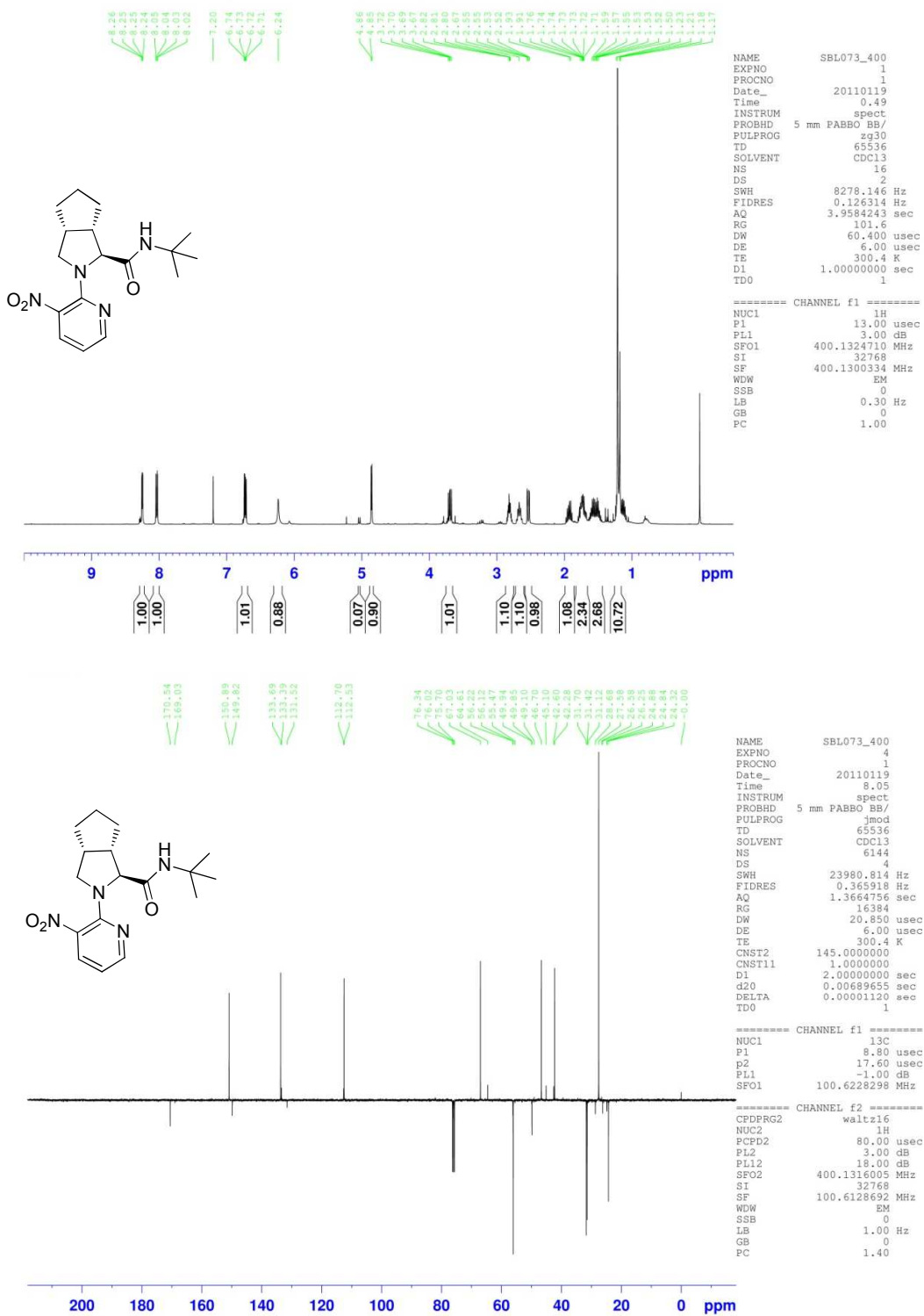
Compound 25



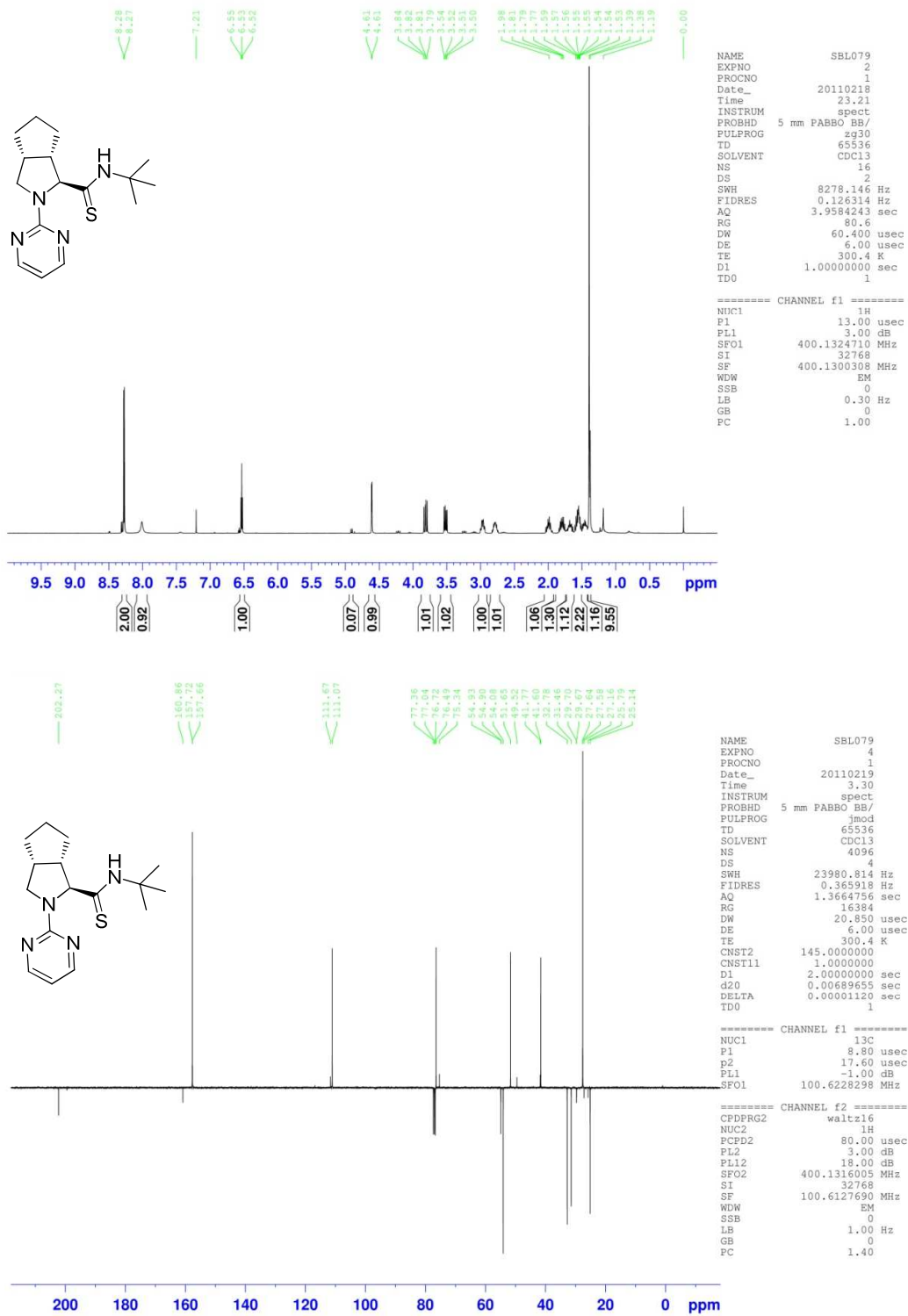
Compound 26



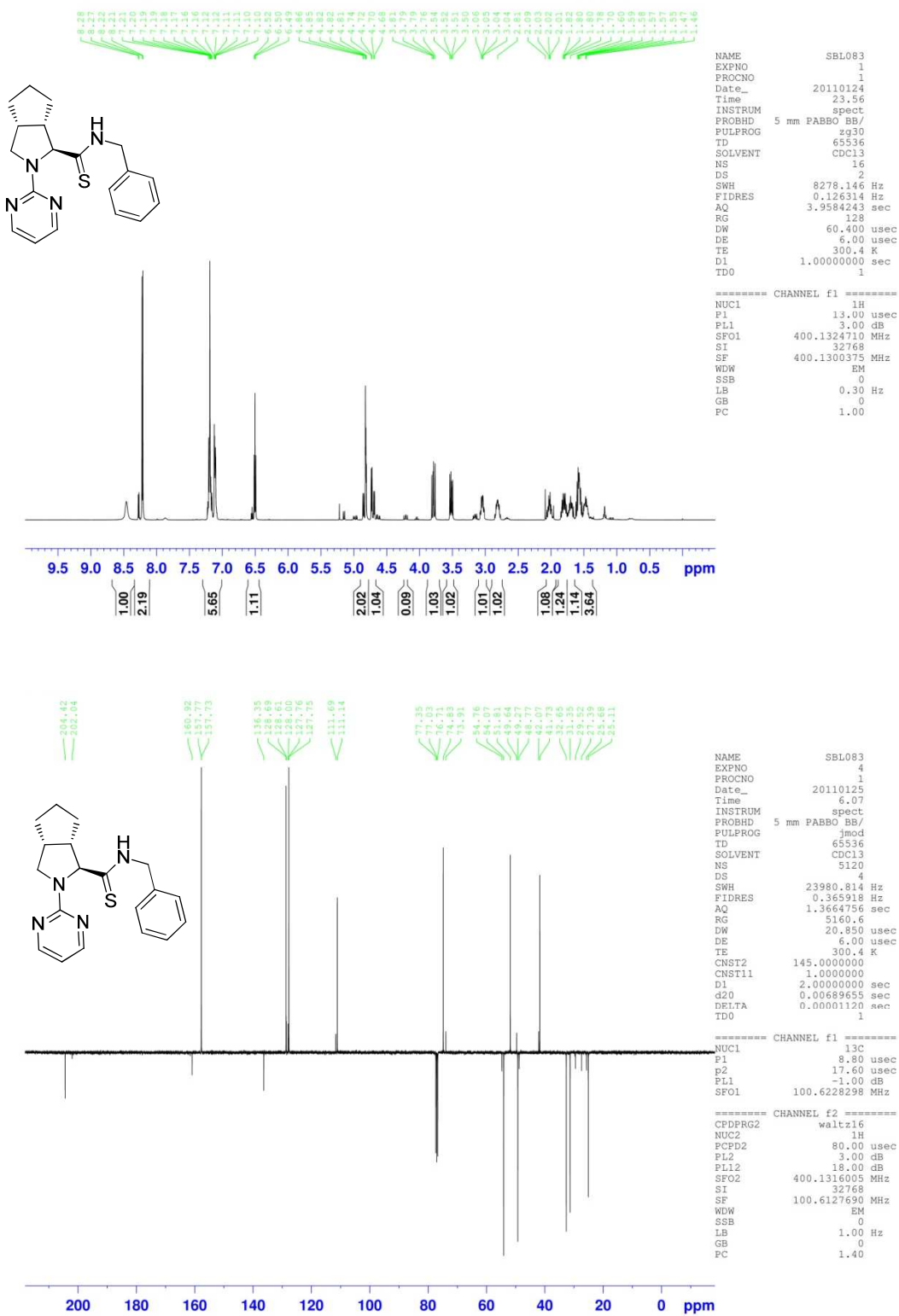
Compound 27



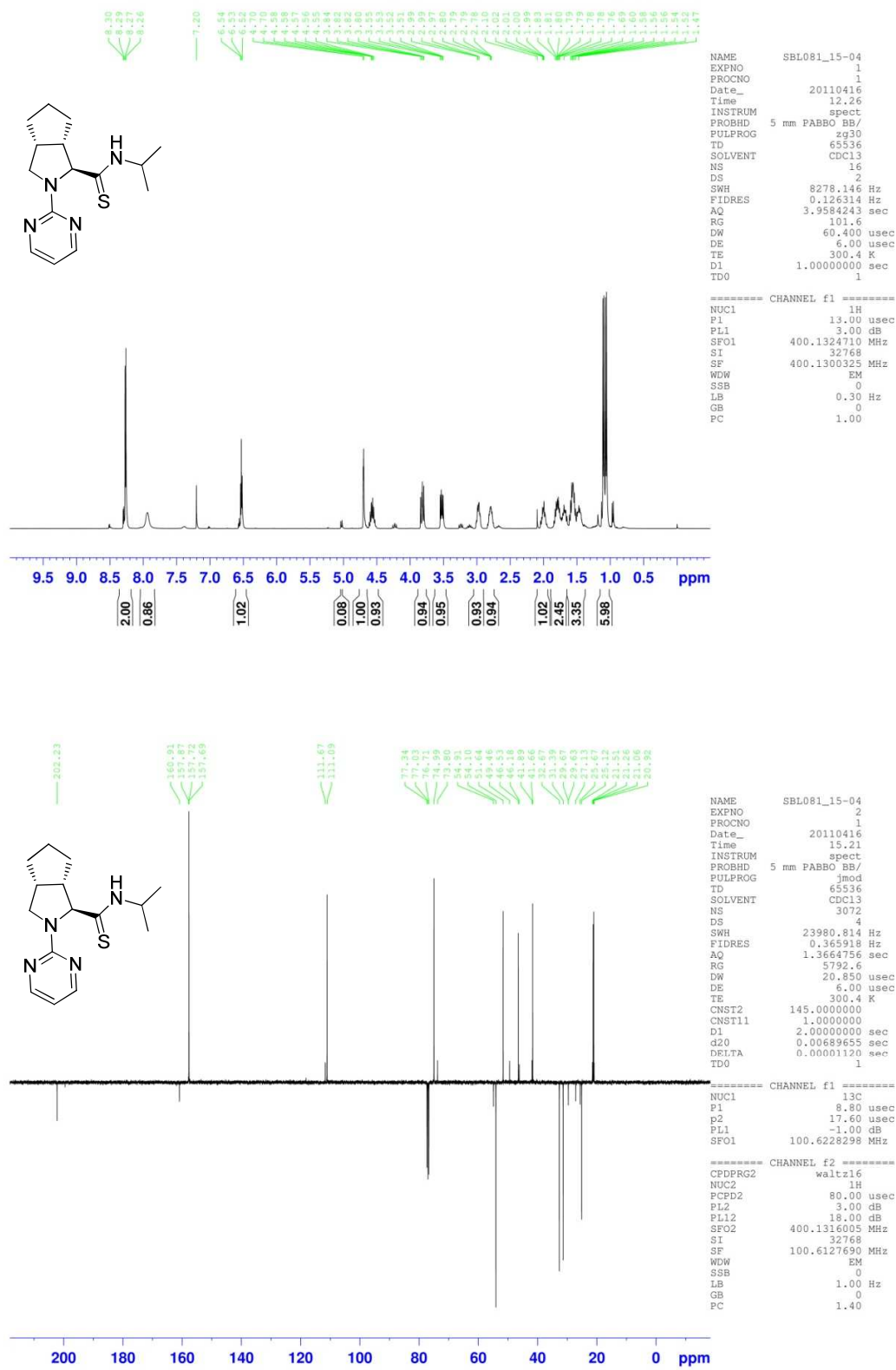
Compound 28



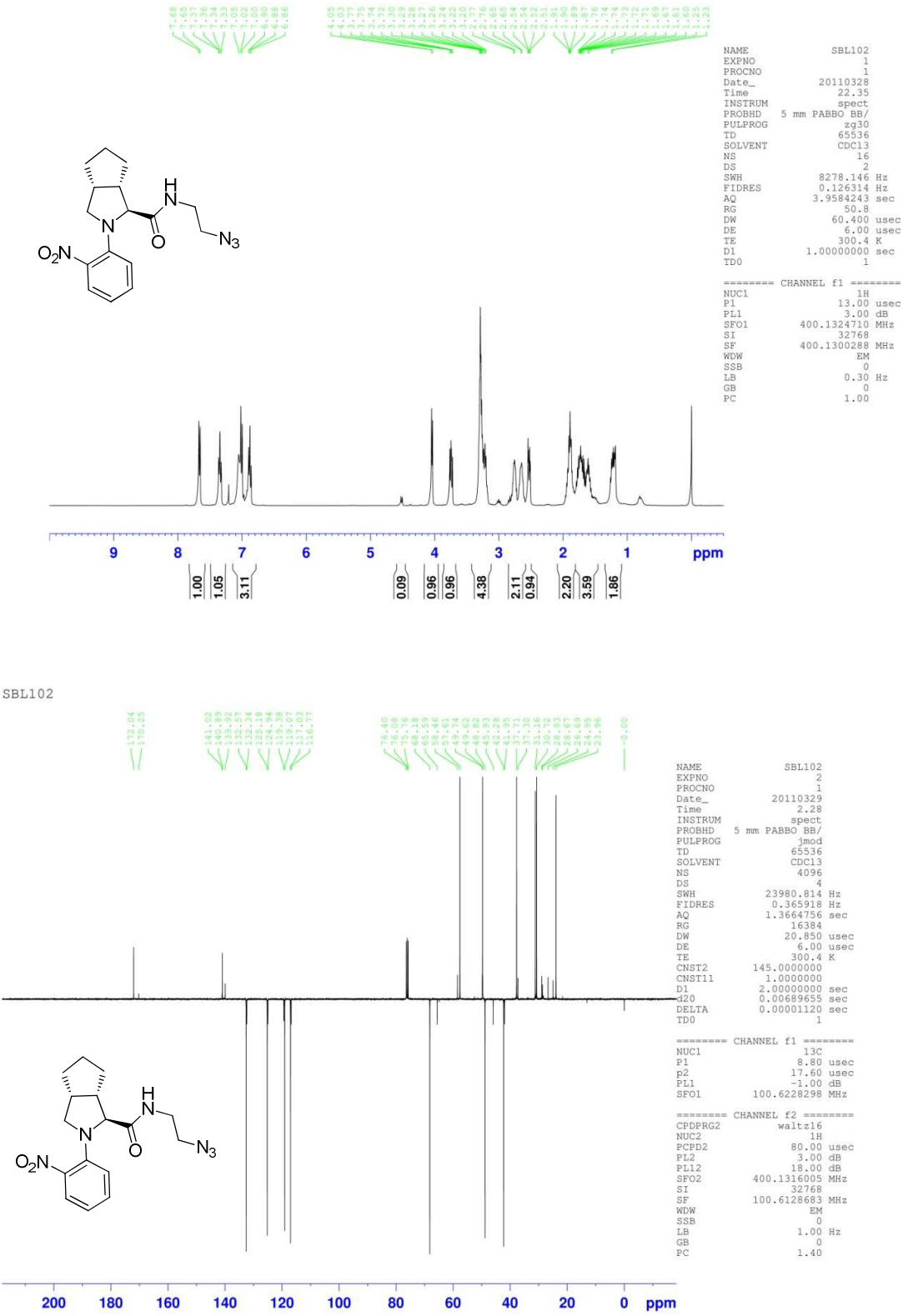
Compound 29



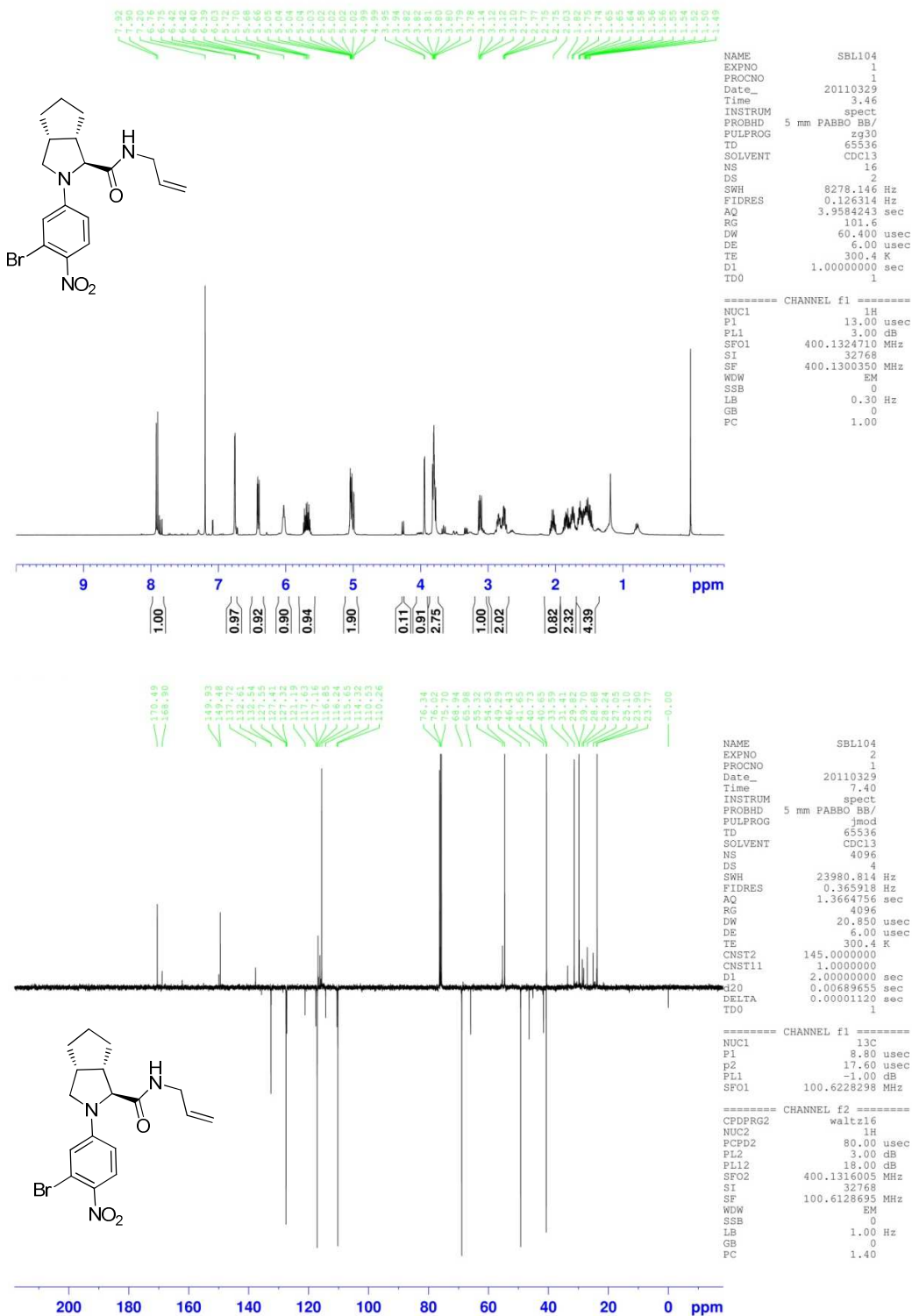
Compound 30



Compound 33



Compound 34



Compound 35

