Electronic Supplementary Information

Synthesis and biological evaluation of *N*-arylated-lactam-type iminosugars as new immunosuppressive agents

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Experimental

1. Chemistry

1.1. General

Solvents were dried according to standard methods. Analytical thin-layer chromatography (TLC) was carried out on 0.25 mm silica gel 60 F-254 plates (Merck), employing ultraviolet light and/or staining with ceric ammonium molybdate for visualization. Column chromatography was performed employing 200–300 mesh silica gel or C-18 reversed-phase silica gel (Merck). Optical rotations were measured on the Rudolph Research Analytical Autopol IV automatic polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE III-400 or III-600 spectrometers at ambient temperature. Chemical shifts (in ppm) were referenced to the residual proton signal of the solvent. High resolution mass spectrometry (HRMS) was performed on a Thermo Scientific LTQ Orbitrap Discovery. Matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) MS was performed on an AB SCIEX 5800 spectrometer.

1.2. General procedure for deprotection of the 3,4-*O*-isopropylidene group.

The substrate (0.074 mmol) was dissolved in a combined solvent of CH_2Cl_2/TFA (3:1, 2.0 mL), and the mixture was stirred at room temperature until TLC analysis showed the disappearance of the starting material. The solvent was evaporated in *vacuo.* The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH) to yield the product.

1.3. General procedure for borinic acid-catalyzed alkylation of carbohydrate substrates

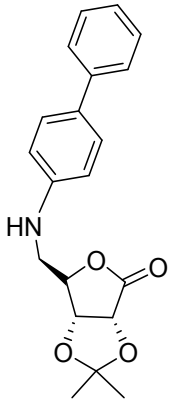
The carbohydrate substrate (1.0 equiv.), 2-aminoethyl diphenylborinate **A** (10 mol %), KI (1.5 equiv.) and K_2CO_3 (1.5 equiv.) were weighed into a one dram vial, and dissolved in dry acetonitrile (0.033 M). The alkyl halide (3.0 equiv.) was then added, and the reaction vessel was capped with a septum and purged with argon. The mixture was stirred overnight at 60 °C. The resulting mixture was diluted with ethyl acetate and washed with water and brine. The organic layers were combined, dried (Na_2SO_4),

filtered and concentrated to dryness. The resulting crude material was purified by column chromatography on silica gel using the stated eluent system.

1.4. General hydrogenation procedure

To the mixture of reactant (0.1 mmol) in THF (1.0 mL) placed in a glass autoclave, Pd/C catalyst (5% palladium on carbon) was added. Upon substitution of air with hydrogen (4 times), the solution was stirred at room temperature under hydrogen pressure of 0.4 MPa for 2 days. The mixture was filtered through Celite. The solution was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel.

(3aR, 6R, 6aR)-6-((1,1'-Biphenyl-4-ylamino)methyl)-2, 2-dimethyldihydrofuro[3, 4-d][1, 3]dioxol-4(3aH)-one (35)

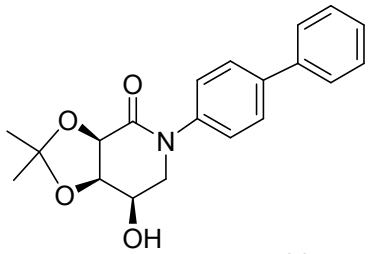


35

To a stirred solution of compound **33** (16 mg, 0.085 mmol) in CH_2Cl_2 (3.0 mL**)** was added Dess-Martin periodinane (46.9 mg, 0.11 mmol) at room temperature under argon. After 30 min., Et_2O (10 mL) was added to the reaction mixture, and the mixture was filtered on Celite. The filtrate was concentrated in *vacuo* and the residue was dissolved in MeOH (3.0 mL**)** and 1,1-biphenyl-4-amine (15.8 mg 0.09 mmol), AcOH (5.8 µL, 0.102 mmol) were added and the mixture was stirred at 45 ^oC for 4 h. The mixture was cooled to room temperature, followed by addition of $NaCNBH_3$ (10.68 mg, 0.17 mmol) and the stirring was continued overnight. The reaction was quenched with saturated $NaHCO_3$. After removal of the solvent, the residue was dissolved in ethyl

acetate and washed with brine twice. The organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate 5:1) on silica gel to provide compound **35** as a pale yellow solid, yield: 65%. $[\alpha]_D^{25}$ = -16 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2H), 7.48-7.46 (m, 2H), 7.43-7.39 (m, 2H), 7.30 (d, *J* = 7.4 Hz, 1H), 6.77-6.75 (m, 2H), 4.81-4.77 (m, 2H), 4.72 (d, *J* = 5.8 Hz, 1H), 3.84 (br, 1H), 3.59 (dd, *J* = 14.5, 3.6 Hz, 1H), 3.50 (dd, *J* = 14.5, 4.1 Hz, 1H), 1.49 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 146.6, 140.9, 132.2, 128.8, 128.3, 126.6, 126.5, 113.9, 113.7, 82.6, 78.5, 75.2, 46.1, 26.8, 25.7; HRMS (ESI): Calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$, 340.1549; Found, 340.1549.

(3aR, 7R, 7aR)-5-(1,1'-Biphenyl-4-yl)-7-hydroxy-2, 2-dimethyltetrahydro-[1,3]dioxolo[4, 5-c]pyridin-4(3aH)-one (36)

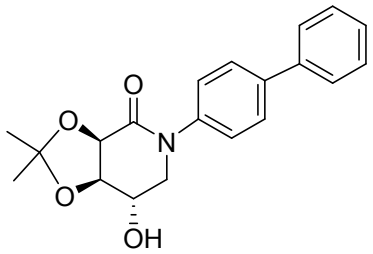


36

To a solution of compound **35** (339 mg, 0.1 mmol) in anhydrous MeOH was added MeONa (1.08 mg, 0.02 mmol). The mixture was stirred at room temperature until TLC indicated the disappearance of the starting material. The reaction was quenched with AcOH. After removal of the solvent, the residue was dissolved in ethyl acetate and washed with water and brine. The inorganic phase was extracted twice with ethyl acetate. The combined organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate 1:2) on silica gel to afford compound **36** as a yellow solid, yield: 92%. $[\alpha]_D^{25}$ = 4.8 (c 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.55 (m, 4H), 7.45-7.33 (m, 5H), 4.73 (d, *J* = 7.6 Hz, 1H), 4.65 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.19 (br, 1H), 3.92 (dd, *J* = 12.7, 7.7 Hz, 1H), 3.69 (dd, *J* = 12.7, 2.9 Hz, 1H), 2.66 (br, 1H), 1.61 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6,

141.5, 140.5, 140.1, 128.9, 128.0, 127.6, 127.3, 126.0, 111.2, 74.9, 74.7, 65.1, 51.2, 26.3, 24.5; HRMS (ESI): Calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$, 340.1549; Found, 340.1546.

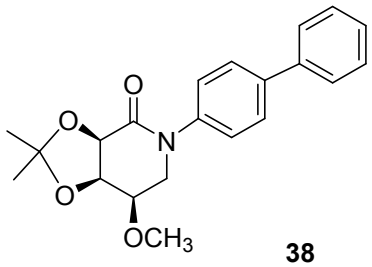
(3aR, 7S, 7aR)-5-(1,1'-Biphenyl]-4-yl)-7-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-c]pyridin-4(3aH)-one (37)



37

To an ice-cooled solution of compound **36** (267 mg, 0.79 mmol), triphenylphosphine (620 mg, 2.36 mmol) and *p*-nitrobenzoic acid (394 mg, 2.36 mmol) in anhydrous tetrahydrofuran (10 mL) under an atmosphere of argon, was added a solution of diethyl azodicarboxylate (DEAD) (374 μL, 2.36 mmol) in anhydrous tetrahydrofuran (1 mL) dropwise slowly. The resulting solution was warmed to ambient temperature and stirred overnight and the volatiles removed in *vacuo*. The residue was then dissolved in anhydrous methanol and a catalytic amount of MeONa was added. The mixture was stirred for 1h. The solvent was removed in *vacuo*. The residue was then dissolved in ethyl acetate and washed by water and brine. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 1:2) to afford the required product (136 mg) as a white solid, yield 51%. $[\alpha]_D^{25}$ = -38 (c 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.53 (m, 4H), 7.44-7.32 (m, 5H), 4.74 (d, *J* = 6.9 Hz, 1H), 4.46 (br, 1H), 4.11 (br, 1H), 4.03 (d, *J* = 13.1 Hz, 1H), 3.63 (dd, *J* = 12.9, 4.0 Hz, 1H), 2.83 (br, 1H), 1.55 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 141.7, 140.5, 140.1, 128.9, 128.0, 127.6, 127.3, 126.1, 110.7, 77.7, 74.9, 67.7, 52.1, 26.9, 24.6; HRMS (ESI): Calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$, 340.1549; Found, 340.1548.

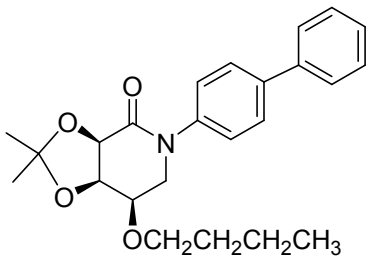
(3aR, 7R, 7aR)-5-(1,1'-Biphenyl-4-yl)-7-methoxy-2,2-dimethyltetrahydrobenzo[d][1,3]dioxol-4(3aH)-one (38)



38

To an ice-cold solution of compound **36** (44 mg, 0.13 mmol) and CH_3I (16 μL) in anhydrous DMF was added 60% NaH (7.8 mg, 0.195 mmol). After stirring for 1 h, the mixture was warmed to room temperature and the stirring was continued until TLC indicated the disappearance of the starting material. The solvent was evaporated in *vacuo.* The residue was dissolved in ethyl acetate, washed with water and brine. The organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo*. Column chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) gave the desired product as a white solid in 92% yield (42 mg). $[\alpha]_D^{25}$ = -74 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.56 (m, 4H), 7.46-7.34 (m, 5H), 4.79-4.77 (m, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.07 (dd, *J* = 11.6, 9.9 Hz, 1H), 3.84 (ddd, *J* = 11.6, 4.1, 2.9 Hz, 1H), 3.66 (ddd, *J* = 11.6, 4.1, 1.2 Hz, 1H), 3.53 (s, 3H), 1.59 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 141.4, 140.4, 140.2, 129.0, 128.1, 127.6, 127.3, 125.8, 111.4, 75.4, 74.7, 73.6, 57.8, 47.8, 26.8, 25.1; HRMS (ESI): Calcd for $C_{21}H_{24}NO_4$ $[M+H]^+$, 354.1705; Found, 354.1697.

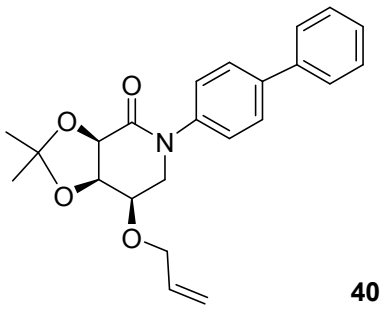
(3aR, 7R, 7aR)-5-(1,1'-Biphenyl-4-yl)-7-butoxy-2,2-dimethyltetrahydrobenzo[d][1,3]dioxol-4(3aH)-one (39)



39

Compound **39** was prepared from compound **36** (50 mg, 0.15 mmol), C_4H_9I (35 μL, 0.3 mmol) and 60% NaH (11 mg, 0.225 mmol) by the same procedure as described for the preparation of **38**. Yield 65% as a pale yellow solid after column chromatography (petroleum ether/ethyl acetate, 2:1). $[\alpha]_D^{25}$ = -42.9 (c 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.55 (m, 4H), 7.46-7.42 (m, 2H), 7.37-7.33 (m, 3H), 4.75-4.73 (m, 1H), 4.67 (d, *J* = 6.4 Hz, 1H), 4.09 (dd, *J* = 11.5, 9.8 Hz, 1H), 3.91 (ddd, *J* = 9.7, 4.0, 2.7 Hz, 1H), 3.68-3.57 (m, 3H), 1.67-1.59 (m, 2H), 1.58 (s, 3H), 1.48 (s, 3H), 1.45-1.35 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 141.5, 140.5, 140.2, 129.0, 128.1, 127.6, 127.3, 125.8, 111.5, 75.4, 74.3, 73.2, 70.4, 48.4, 32.0, 27.0, 25.3, 19.3, 14.0; HRMS (ESI): Calcd for $C_{24}H_{30}NO_4$ $[M+H]^+$, 396.2175; Found, 396.2171.

(3aR, 7R, 7aR)-5-(1,1'-Biphenyl-4-yl)-7-(allyloxy)-2,2-dimethyltetrahydrobenzo[d][1,3]dioxol-4(3aH)-one (40)

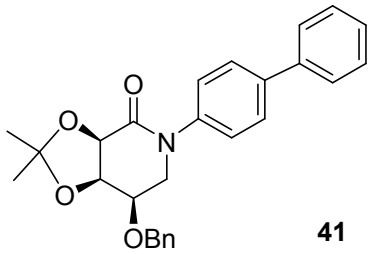


40

Compound **40** was prepared from compound **36** (76 mg, 0.224 mmol), allyl bromide (40 μL, 0.448 mmol) and 60% NaH (15 mg, 0.336 mmol) by the same procedure as described for the preparation of **38**. Yield 80% as a pale yellow solid after column chromatography (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = -53.3 (c 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.56 (m, 4H), 7.46-7.34 (m, 5H), 6.00-5.90 (m, 1H), 5.36-5.32 (m, 1H), 5.28-5.25 (m, 1H), 4.74-4.72 (m, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 4.20-4.19 (m, 2H), 4.10 (dd, *J* = 11.4, 9.9 Hz, 1H), 3.99 (ddd, *J* = 9.7, 3.7, 2.9 Hz, 1H), 3.62 (ddd, *J* = 11.5, 3.9, 1.0 Hz, 1H), 1.58 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 141.4, 140.5, 140.2, 134.2, 129.0, 128.1, 127.6, 127.3, 125.8,

118.6, 111.5, 75.4, 74.3, 72.1, 71.3, 48.4, 26.9, 25.2; HRMS (ESI): Calcd for $C_{23}H_{26}NO_4$ $[M+H]^+$, 380.1862; Found, 380.1855.

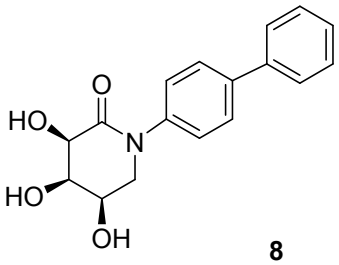
(3aR, 7R, 7aR)-5-(1,1'-Biphenyl-4-yl)-7-(benzyloxy)-2,2-dimethyltetrahydrobenzo[d][1,3]dioxol-4(3aH)-one (41)



41

Compound **41** was prepared from compound **36** (32 mg, 0.094 mmol), BnBr (23 μL, 0.189 mmol) and 60% NaH (5.7 mg, 0.142 mmol) by the same procedure as described for the preparation of **38**. Yield 70% as a white solid after column chromatography (petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = -668 (c 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.55 (m, 4H), 7.46-7.42 (m, 2H), 7.38-7.29 (m, 8H), 4.73-4.70 (m, 3H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.10 (dd, *J* = 11.5, 9.9 Hz, 1H), 3.97 (dt, *J* = 9.6, 3.1 Hz, 1H), 3.58 (dd, *J* = 11.7, 3.2 Hz, 1H), 1.59 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 141.4, 140.5, 140.2, 137.4, 129.0, 128.8, 128.4, 128.10, 128.07, 127.6, 127.3, 125.8, 111.5, 75.5, 74.3, 72.0, 71.9, 48.4, 26.9, 25.2; HRMS (ESI): Calcd for $C_{27}H_{28}NO_4$ $[M+H]^+$, 430.2018; Found, 430.2012.

(2R, 3R, 4R)-6-(1,1'-Biphenyl-4-yl)-2, 3,4-trihydroxycyclohexan-1-one (8)

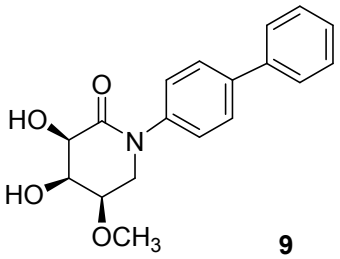


8

Compound **8**: a pale yellow solid, yield 65%. $[\alpha]_D^{25}$ = 45.0 (c 0.2, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 7.69-7.61 (m, 4H), 7.46-7.32 (m, 5H), 4.30-4.26 (m, 3H), 3.92-3.87 (m, 1H), 3.62 (dd, *J* = 11.5, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.0,

142.7, 141.6, 141.4, 129.9, 128.8, 128.6, 128.0, 127.6, 72.7, 71.3, 66.4, 54.0; HRMS (ESI): Calcd for $C_{17}H_{18}NO_4$ $[M+H]^+$, 300.1236; Found, 300.1231.

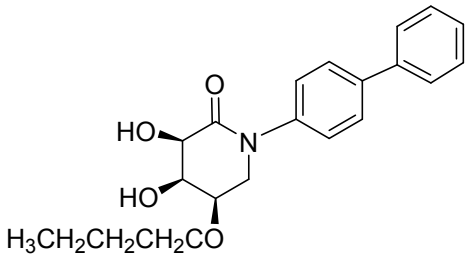
(2R, 3S, 4R)-6-(1,1'-Biphenyl-4-yl)-2, 3-dihydroxy-4-methoxycyclohexan-1-one (9)



9

Compound **9**: a white solid, yield 75%. $[\alpha]_D^{25}$ = 29.4 (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.56 (m, 4H), 7.46-7.42 (m, 2H), 7.38-7.33 (m, 3H), 4.61 (br, 1H), 4.23 (br, 1H), 4.03 (t, *J* = 9.9 Hz, 1H), 3.90-3.86 (m, 1H), 3.75 (dd, *J* = 11.1, 6.0 Hz, 1H), 3.51 (s, 3H), 2.90 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 140.6, 140.5, 140.4, 129.0, 128.2, 127.7, 127.3, 125.9, 74.0, 69.9, 67.3, 57.4, 50.6; HRMS (ESI): Calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$, 314.1392; Found, 314.1389.

(3R, 4S, 5R)-1-(1,1'-Biphenyl-4-yl)-5-butoxy-3,4-dihydroxypiperidin-2-one (10)

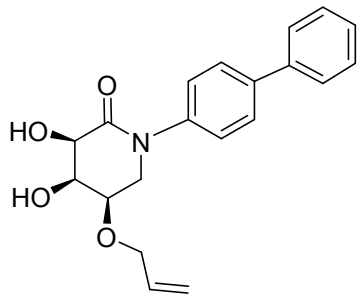


10

Compound **10**: a white solid, yield 92%. $[\alpha]_D^{25}$ = 18.6 (c 0.5, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2H), 7.57-7.56 (m, 2H), 7.45-7.42 (m, 2H), 7.37-7.33 (m, 3H), 4.56 (br, 1H), 4.23 (br, 2H), 4.01 (t, *J* = 9.8 Hz, 1H), 3.94-3.92 (m, 1H), 3.71 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.67-3.63 (m, 1H), 3.54-3.51 (m, 1H), 2.99 (br, 1H), 1.63-1.58 (m, 2H), 1.42-1.36 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 140.6, 140.44, 140.39, 129.0, 128.2, 127.7, 127.3, 125.9, 72.6, 70.0,

69.9, 68.0, 50.9, 31.9, 29.9, 19.4, 14.0; HRMS (ESI): Calcd for $C_{21}H_{26}NO_4$ $[M+H]^+$, 356.1862; Found, 356.1862.

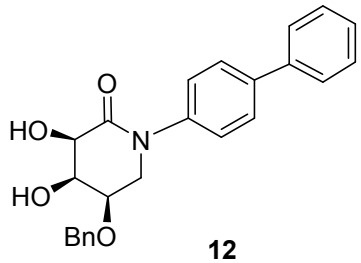
(3R, 4S, 5R)-1-(1,1'-Biphenyl-4-yl)-5-(allyloxy)-3,4-dihydroxypiperidin-2-one (11)



11

Compound **11**: a white solid, yield 55%. $[\alpha]_D^{25}$ = 33.1 (c 0.7, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.56 (m, 4H), 7.46-7.43 (m, 2H), 7.38-7.34 (m, 3H), 5.99-5.89 (m, 1H), 5.34 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dd, *J* = 10.3, 1.0 Hz, 1H), 4.57 (br, 1H), 4.23-4.01 (m, 5H), 3.85 (br, 1H), 3.76-3.68 (m, 1H), 2.83 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 140.6, 140.5, 140.4, 134.1, 129.0, 128.2, 127.7, 127.3, 125.9, 118.5, 71.6, 70.8, 69.9, 68.0, 50.8; HRMS (ESI): Calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$, 340.1549; Found, 340.1551.

(3R, 4S, 5R)-1-(1,1'-Biphenyl-4-yl)-5-(benzyloxy)-3,4-dihydroxypiperidin-2-one (12)

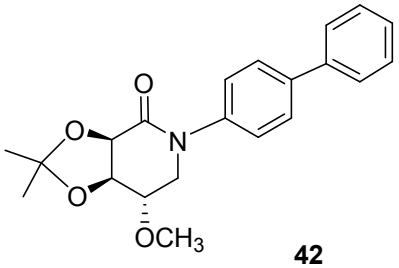


12

Compound **12**: a white solid, yield 65%. $[\alpha]_D^{25}$ = 23.3 (c 0.3, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.55 (m, 4H), 7.46-7.31 (m, 10H), 4.74 (d, *J* = 12.2 Hz, 1H), 4.66 (d, *J* = 12.2 Hz, 1H), 4.59 (br, 1H), 4.18 (br, 1H), 4.12-4.03 (m, 2H), 3.68 (dd, *J* = 10.2, 5.3 Hz, 1H), 2.96 (br, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 140.6, 140.5,

140.4, 137.3, 128.8, 128.7, 128.3, 128.0, 127.8, 127.5, 127.1, 125.7, 71.4, 71.2, 69.7, 67.7, 50.7; HRMS (ESI): Calcd for $C_{24}H_{24}NO_4$ $[M+H]^+$, 390.1705; Found, 390.1702.

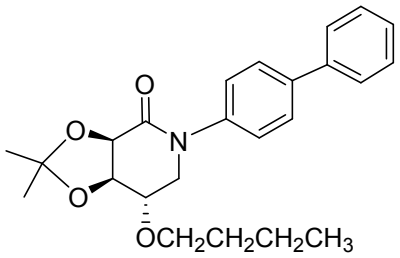
(3aR, 7S, 7aR)-5-(1,1'-Biphenyl-4-yl)-7-methoxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4, 5-c]pyridin-4(3aH)-one (42)



42

Compound **42** was prepared from compound **37** (44 mg, 0.13 mmol), CH_3I (16 μL, 0.26 mmol) and 60% NaH (7.8 mg, 0.195 mmol) by the same procedure as described for the preparation of **38**. Yield 96% as a white solid after column chromatography (petroleum ether/ethyl acetate, 2:1). $[\alpha]_D^{25}$ = -51.6 (c 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.56 (m, 4H), 7.46-7.33 (m, 5H), 4.73 (d, *J* = 7.1 Hz, 1H), 4.54-4.53 (m, 1H), 4.03 (dd, *J* = 13.1, 1.4 Hz, 1H), 3.72 (dd, *J* = 13.4, 3.9 Hz, 1H), 3.66 (br, 1H), 3.46 (s, 3H), 1.57 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 141.9, 140.6, 140.0, 129.0, 128.1, 127.6, 127.3, 126.1, 110.6, 76.4, 75.7, 75.2, 57.4, 48.8, 26.8, 24.6; HRMS (ESI): Calcd for $C_{21}H_{24}NO_4$ $[M+H]^+$, 354.1705; Found, 354.1696.

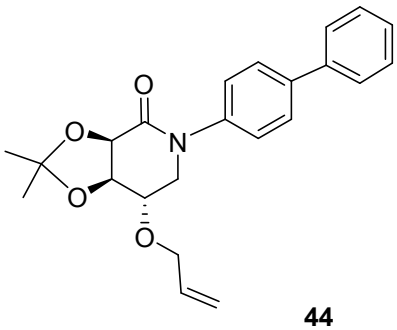
(3aR, 7S, 7aR)-5-(1,1'-Biphenyl]-4-yl)-7-butoxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4, 5-c]pyridin-4(3aH)-one (43)



43

Compound **43** was prepared from compound **37** (50 mg, 0.15 mmol), C_4H_9I (35 μL, 0.3 mmol) and 60% NaH (11 mg, 0.225 mmol) by the same procedure as described for the preparation of **38**. Yield 65% as a white solid after column chromatography (petroleum ether/ethyl acetate, 3:1). $[\alpha]_D^{25}$ = -64.0 (c 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 4H), 7.45-7.33 (m, 5H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.54-4.51 (m, 1H), 4.03 (d, *J* = 12.8 Hz, 1H), 3.74-3.67 (m, 2H), 3.55 (t, *J* = 6.4 Hz, 2H), 1.61-1.54 (m, 5H), 1.43-1.33 (m, 5H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 142.0, 140.6, 139.9, 128.9, 128.0, 127.5, 127.3, 126.1, 110.5, 76.0, 75.2, 74.7, 69.6, 49.2, 32.0, 26.8, 24.6, 19.4, 14.0; HRMS (ESI): Calcd for $C_{24}H_{30}NO_4$ $[M+H]^+$, 396.2175; Found, 396.2167.

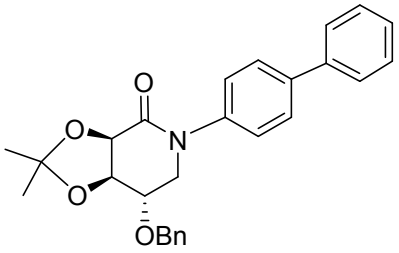
(3aR, 7S, 7aR)-5-(1,1'-Biphenyl-4-yl)-7-(allyloxy)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-c]pyridin-4(3aH)-one (44)



44

Compound **44** was prepared from compound **37** (50 mg, 0.15mmol), allyl bromide (26 μL, 0.3 mmol) and 60% NaH (13 mg, 0.22 mmol) by the same procedure as described for the preparation of **38**. Yield 80% as a pale yellow solid after column chromatography (petroleum ether/ ethyl acetate, 2:1). $[\alpha]_D^{25}$ = -29.2 (c 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 4H), 7.45-7.33 (m, 5H), 5.95-5.85 (m, 1H), 5.30 (d, *J* = 16.9 Hz, 1H), 5.22 (d, *J* = 10.3 Hz, 1H), 4.74 (d, *J* = 6.9 Hz, 1H), 4.55-4.54 (m, 1H), 4.12 (d, *J* = 5.2 Hz, 2H), 4.04 (d, *J* = 13.2 Hz, 1H), 3.82 (br, 1H), 3.70 (dd, *J* = 13.2, 3.3 Hz, 1H), 1.56 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 141.9, 140.6, 140.0, 134.0, 128.9, 128.0, 127.6, 127.3, 126.1, 117.9, 110.6, 76.0, 75.2, 74.1, 70.5, 49.3, 26.8, 24.6; HRMS (ESI): Calcd for $C_{20}H_{26}NO_4$ $[M+H]^+$, 380.1862; Found, 380.1859.

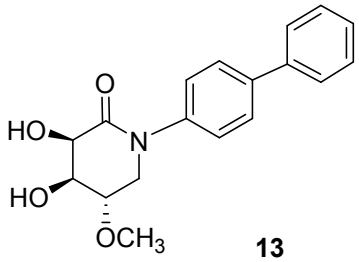
(3aR, 7S, 7aR)-5-(1,1'-Biphenyl-4-yl)-7-(benzyloxy)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-c]pyridin-4(3aH)-one (45)



45

Compound **45** was prepared from compound **37** (32 mg, 0.094 mmol), benzyl bromide (23 μL, 0.189 mmol) and 60% NaH (10 mg, 0.142 mmol) by the same procedure as described for the preparation of **38**. Yield 78% as a white solid after column chromatography (petroleum ether/ethyl acetate, 2:1). $[\alpha]_D^{25}$ = -22.8 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 4H), 7.46-7.42 (m, 2H), 7.38-7.33 (m, 8H), 4.76 (d, *J* = 7.1 Hz, 1H), 4.67 (d, *J* = 12.5 Hz, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 4.59-4.57 (m, 1H), 4.04 (dd, *J* = 13.2, 1.0 Hz, 1H), 3.87 (br, 1H), 3.73 (dd, *J* = 13.3, 3.7 Hz, 1H), 1.55 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 141.9, 140.6, 140.0, 137.5, 129.0, 128.7, 128.2, 128.0, 127.8, 127.6, 127.3, 126.1, 110.6, 76.1, 75.2, 74.1, 71.5, 49.3, 26.8, 24.6; HRMS (ESI): Calcd for $C_{27}H_{28}NO_4$ $[M+H]^+$, 430.2018; Found, 430.2015.

(3R, 4S, 5S)-1-(1,1'-Biphenyl-4-yl)-3,4-dihydroxy-5-methoxypiperidin-2-one (13)

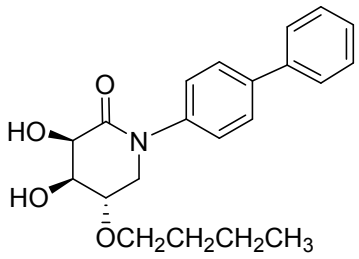


13

Compound **13**: a white solid, yield 62%. $[\alpha]_D^{25}$ = 50.0 (c 0.6, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (m, 4H), 7.45-7.42 (m, 2H), 7.37-7.33 (m, 3H), 4.47 (s, 1H), 4.42 (s, 1H), 4.11 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.81 (d, *J* = 2.5 Hz, 1H), 3.67 (dd, *J*

= 13.2, 3.3 Hz, 1H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 140.7, 140.4, 140.3, 129.0, 128.1, 127.7, 127.3, 126.0, 76.6, 69.0, 68.9, 57.5, 51.1; HRMS (ESI): Calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$, 314.1392; Found, 314.1392.

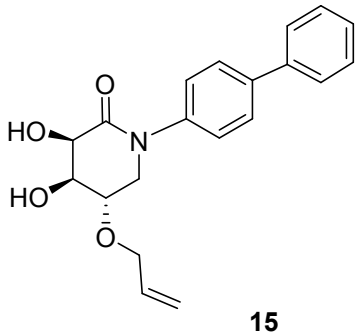
(3R, 4S, 5S)-1-(1,1'-Biphenyl-4-yl)-5-butoxy-3,4-dihydroxypiperidin-2-one (14)



14

Compound **14**: a white solid, yield 84%. $[\alpha]_D^{25}$ = 13.0 (c 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.61 (m, 2H), 7.59-7.56 (m, 2H), 7.46-7.43 (m, 2H), 7.38-7.34 (m, 3H), 4.49 (d, *J* = 3.6 Hz, 1H), 4.41 (t, *J* = 3.5 Hz, 1H), 4.12 (dd, *J* = 13.0, 4.5 Hz, 1H), 3.91-3.88 (m, 2H), 3.67 (dd, *J* = 13.0, 4.3 Hz, 1H), 3.63-3.58 (m, 2H), 2.87 (br, 1H), 1.63-1.56 (m, 2H), 1.45-1.35 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 140.9, 140.5, 140.3, 129.0, 128.1, 127.7, 127.3, 125.9, 74.9, 69.9, 69.3, 68.7, 51.3, 32.0, 19.5, 14.0; HRMS (ESI): Calcd for $C_{21}H_{26}NO_4$ $[M+H]^+$, 356.1862; Found, 356.1854.

(3R, 4S, 5S)-1-(1,1'-Biphenyl-4-yl)-5-(allyloxy)-3,4-dihydroxypiperidin-2-one (15)

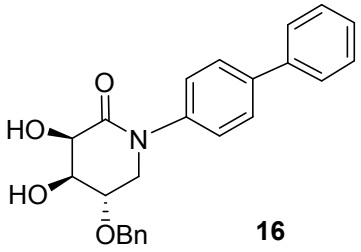


15

Compound **15**: a white solid, yield 83%. $[\alpha]_D^{25}$ = 27.6 (c 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (m, 4H), 7.45-7.41 (m, 2H), 7.36-7.34 (m, 3H), 5.96-5.87 (m, 1H), 5.34-5.30 (m, 1H), 5.24-5.22 (m, 1H), 4.51 (br, 1H), 4.41 (br, 1H), 4.19-

4.10 (m, 3H), 3.96 (d, J = 3.2 Hz, 1H), 3.66 (dd, J = 13.0, 3.8 Hz, 1H), 3.33 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 140.8, 140.5, 140.3, 134.1, 129.0, 128.1, 127.7, 127.3, 125.9, 118.0, 74.3, 70.8, 69.3, 68.8, 51.4; HRMS (ESI): Calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$, 340.1549; Found, 340.1548.

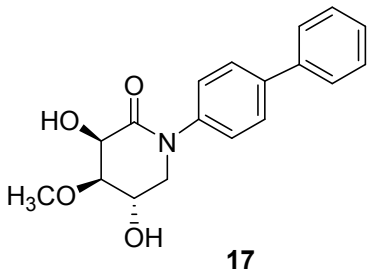
(3R, 4S, 5S)-1-(1,1'-Biphenyl-4-yl)-5-(benzyloxy)-3,4-dihydroxypiperidin-2-one (16)



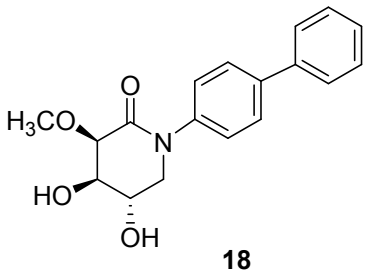
16

Compound **16**: a white solid, yield 64%. $[\alpha]_D^{25}$ = 90.0 (c 0.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.54 (m, 4H), 7.45-7.25 (m, 10H), 4.71 (d, J = 11.9 Hz, 1H), 4.65 (d, J = 11.9 Hz, 1H), 4.56 (br, 1H), 4.46 (br, 1H), 4.11 (dd, J = 13.1, 4.3 Hz, 1H), 4.02 (d, J = 3.5 Hz, 1H), 3.69 (dd, J = 13.0, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 140.8, 140.5, 140.3, 137.5, 129.0, 128.8, 128.3, 128.1, 127.9, 127.7, 127.3, 125.9, 74.4, 71.9, 69.3, 68.8, 51.3; HRMS (ESI): Calcd for $C_{24}H_{24}NO_4$ $[M+H]^+$, 390.1705; Found, 390.1709.

(3R,4R,5S)-1-(1,1'-Biphenyl-4-yl)-3,5-dihydroxy-4-methoxypiperidin-2-one (17) and (3R,4R,5S)-1-(1,1'-biphenyl-4-yl)-4,5-dihydroxy-3-methoxypiperidin-2-one (18)



17



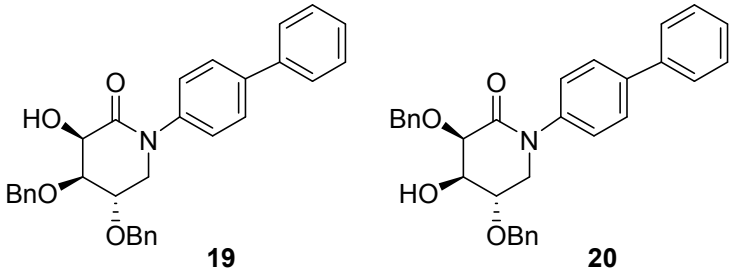
18

Compounds **17** and **18** were prepared from compound **7** and methyl iodide in a yield of 55% with a ratio of 1:1.

Compound **17**: a colorless oil. $[\alpha]_D^{25}$ = 22.9 (c 0.7, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.37-7.35 (m, 3H), 4.66 (s, 1H), 4.34 (s, 1H), 4.12 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.93 (s, 1H), 3.66 (s, 1H), 3.62 (s, 3H), 3.59 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.22 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 140.7, 140.3, 140.1, 128.8, 128.0, 127.5, 127.1, 125.9, 80.5, 68.9, 66.2, 59.8, 54.2; HRMS (ESI): Calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$, 314.1392; Found, 314.1391.

Compound **18**: a colorless oil. $[\alpha]_D^{25}$ = 43.1 (c 0.3, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.68-7.61 (m, 4H), 7.46-7.42 (m, 2H), 7.37-7.32 (m, 3H), 4.28-4.26 (m, 1H), 4.16-4.08 (m, 3H), 3.63 (s, 3H), 3.50 (dd, *J* = 12.0, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.8, 142.8, 141.7, 141.4, 129.9, 128.8, 128.6, 128.0, 127.8, 79.3, 71.2, 68.4, 59.8, 55.5; HRMS (ESI): Calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$, 314.1392; Found, 314.1390.

(3R,4R,5S)-1-(1,1'-Biphenyl-4-yl)-4,5-bis(benzyloxy)-3-hydroxypiperidin-2-one (19) and (3R,4R,5S)-1-(1,1'-biphenyl-4-yl)-3,5-bis(benzyloxy)-4-hydroxypiperidin-2-one (20)



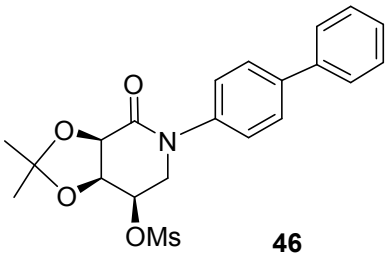
Compounds **19** and **20** were prepared from compound **16** and benzyl bromide in a yield of 78% with a ratio of 1:1.

Compound **19**: a white solid. $[\alpha]_D^{25}$ = -1.0 (c 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 4H), 7.46-7.28 (m, 15H), 4.97 (d, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 12.1 Hz, 1H), 4.69 (t, *J* = 2.9 Hz, 2H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.26 (t, *J* = 3.2 Hz, 1H), 4.07 (dd, *J* = 13.1, 5.1 Hz, 1H), 3.92-3.89 (m, 1H), 3.78 (d, *J* = 2.8 Hz, 1H), 3.66 (dd, *J* = 13.0, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 141.0, 140.6, 140.2, 138.5, 137.4, 129.0, 128.8, 128.6, 128.3, 128.1, 128.0,

127.9, 127.8, 127.6, 127.3, 126.0, 76.3, 74.1, 73.9, 71.7, 69.8, 52.1; HRMS (ESI): Calcd for $C_{31}H_{30}NO_4$ $[M+H]^+$, 480.2175; Found, 480.2184.

Compound **20**: a white solid. $[\alpha]_D^{25}$ = 74.7 (c 0.9, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 4H), 7.46-7.29 (m, 15H), 5.23 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 12.3 Hz, 1H), 4.63 (d, *J* = 12.3 Hz, 1H), 4.34-4.32 (m, 2H), 4.09 (dd, *J* = 12.9, 4.0 Hz, 1H), 4.00-3.98 (m, 1H), 3.64 (dd, *J* = 12.9, 4.0 Hz, 1H), 2.86 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 141.4, 140.7, 140.1, 137.9, 137.6, 129.0, 128.8, 128.7, 128.5, 128.23, 128.19, 128.1, 127.8, 127.6, 127.3, 126.4, 75.1, 74.5, 74.5, 72.0, 70.6, 51.0; HRMS (ESI): Calcd for $C_{31}H_{30}NO_4$ $[M+H]^+$, 480.2175; Found, 480.2168.

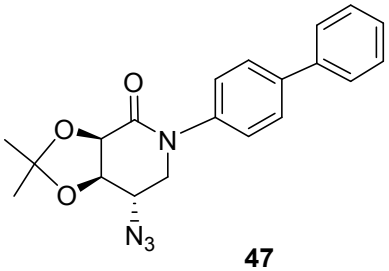
(3aR, 7R, 7aS)-5-(1,1'-Biphenyl-4-yl)-2,2-dimethyl-4-oxohexahydro-[1,3]dioxolo[4,5-c]pyridin-7-yl methanesulfonate (46)



46

To an ice-cooled solution of compound **36** (20 mg, 0.059 mmol), DMAP (1.4 mg, 0.012 mmol) and Et_3N (17.1 μL, 0.12 mmol) in anhydrous CH_2Cl_2 (3 mL) was added MsCl (9.1 μL, 0.12 mmol). After stirring for 2 h, water (15 mL) was added. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated in *vacuo.* Column chromatography on silica gel (petroleum ether/ethyl acetate, 1:2) gave compound **46** (23.1 mg) as a white solid, yield 94%. $[\alpha]_D^{25}$ = -18.8 (c 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.56 (m, 4H), 7.47-7.43 (m, 2H), 7.37-7.35 (m, 3H), 5.17 (d, *J* = 8.3 Hz, 1H), 4.78 (s, 2H), 4.22 (dd, *J* = 12.5, 8.6 Hz, 1H), 3.86 (dd, *J* = 12.5, 3.3 Hz, 1H), 3.16 (s, 3H), 1.61 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 140.7, 140.6, 140.4, 129.0, 128.3, 127.7, 127.3, 126.0, 112.0, 74.9, 73.6, 71.8, 49.2, 39.1, 26.6, 25.0; HRMS (ESI): Calcd for $C_{21}H_{24}NO_6S$ $[M+H]^+$, 418.1324; Found, 418.1316.

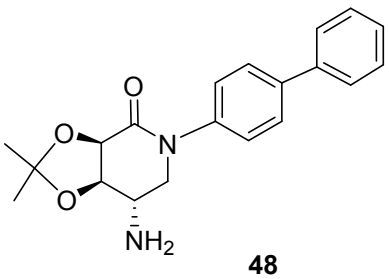
(3aR, 7S, 7aR)-5-(1,1'-Biphenyl-4-yl)-7-azido-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-c]pyridin-4(3aH)-one (47)



47

To a solution of compound **46** (89 mg, 0.213 mmol) in anhydrous DMF (5 mL) was added NaN_3 (69 mg, 1.07 mmol). The mixture was stirred at 90 °C overnight. After cooling to room temperature, ethyl acetate (30 mL) was added to the mixture. The mixture was washed with brine and the inorganic phase was extracted with ethyl acetate (20 mL×2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 3:1) on silica gel to afford compound **47** (67 mg) as a yellow solid, yield 87%**.** $[\alpha]_D^{25}$ = -8.7 (c 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (m, 2H), 7.58-7.56 (m, 2H), 7.46-7.43 (m, 2H), 7.39-7.34 (m, 3H), 4.80 (d, *J* = 6.9 Hz, 1H), 4.55-4.52 (m, 1H), 4.10 (dd, *J* = 13.3, 2.5 Hz, 1H), 4.03-4.00 (m, 1H), 3.66 (ddd, *J* = 13.3, 5.3, 1.0 Hz, 1H), 1.59 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 141.0, 140.5, 140.4, 129.0, 128.2, 127.7, 127.3, 126.1, 111.2, 75.8, 74.7, 59.0, 49.5, 26.8, 24.6; HRMS (ESI): Calcd for $C_{20}H_{21}N_4O_3$ $[M+H]^+$, 365.1614; Found, 365.1614.

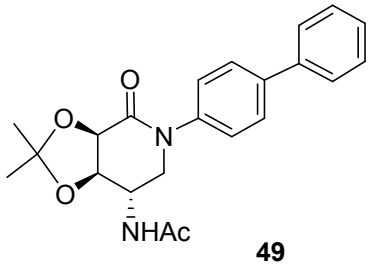
(3aR, 7S, 7aR)-5-(1,1'-Biphenyl-4-yl)-7-amino-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-c]pyridin-4(3aH)-one (48)



48

To a solution of compound **47** (13.0 mg, 0.036 mmol) in THF (2.0 mL) was added Ph_3P (14.0 mg, 0.054 mmol) and 4 drops of water. After stirring for 48 h at room temperature, the solvent was evaporated in *vacuo*. The residue was dissolved in ethyl acetate (50 mL), washed with brine (20 mL×3), dried over Na_2SO_4, filtered and concentrated in *vacuo*. Column chromatography on silica gel (petroleum ether/acetone, 1:2) gave compound **48** (10.0 mg) as a white solid, yield 83%. $[\alpha]_D^{25}$ = -56.0 (c 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.56 (m, 4H), 7.46-7.33 (m, 5H), 4.75 (d, *J* = 7.1 Hz, 1H), 4.31 (dd, *J* = 6.9, 5.5 Hz, 1H), 3.94 (dd, *J* = 12.7, 2.8 Hz, 1H), 3.56 (dd, *J* = 12.8, 6.4 Hz, 1H), 3.38 (br, 1H), 1.57 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 141.6, 140.5, 140.0, 129.0, 128.0, 127.6, 127.3, 125.9, 110.6, 79.1, 74.7, 52.8, 50.5, 27.0, 24.8; HRMS (ESI): Calcd for $C_{20}H_{23}N_2O_3$ $[M+H]^+$, 339.1709; Found, 339.1701.

_N_-((3aR, 7S, 7aR)-5-(1,1'-Biphenyl-4-yl)-2,2-dimethyl-4-oxohexahydro-[1,3]dioxolo[4,5-c]pyridin-7-yl)acetamide (49)

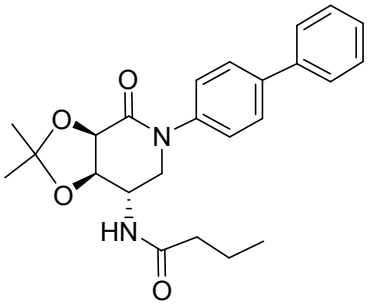


49

To an ice-cooled solution of compound **48** (45.0 mg, 0.13 mmol) in anhydrous pyridine (3 mL) was added DMAP (3.1 mg, 0.025 mmol) and acetic anhydride (24 μL, 0.254 mmol). After stirring for 0.5 h, the mixture was warmed to room temperature and the stirring was continued until TLC showed the reaction was complete. The reaction was quenched with saturated sodium bicarbonate. The reaction mixture was extracted with ethyl acetate (50 mL×2). The organic layer was combined and washed with water (15 mL×2), dried over Na_2SO_4, filtered and concentrated in *vacuo*. Column chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) gave compound **49** (43.0 mg) as a white solid, yield 87%. $[\alpha]_D^{25}$ = 21.2 (c 0.6, $CHCl_3$); ^1H NMR (400 MHz,

$CDCl_3$) δ 7.54-7.51 (m, 4H), 7.46-7.36 (m, 3H), 7.20-7.16 (m, 2H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.38-4.36 (m, 1H), 4.10-4.05 (m, 1H), 3.60 (d, *J* = 12.0 Hz, 1H), 1.77 (s, 3H), 1.57 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 167.00, 141.1, 140.5, 140.1, 129.1, 128.1, 127.9, 127.2, 126.3, 110.8, 76.1, 75.2, 50.4, 47.8, 26.6, 24.4, 22.8; HRMS (ESI): Calcd for $C_{22}H_{25}N_2O_4$ $[M+H]^+$, 381.1814; Found, 381.1813.

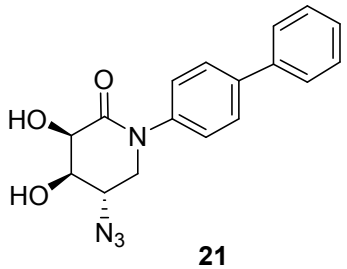
***N*-((3aR, 7S, 7aR)-5-(1,1'-Biphenyl-4-yl)-2,2-dimethyl-4-oxohexahydro-[1,3]dioxolo[4,5-c]pyridin-7-yl)butyramide (50)**



50

Compound **50** was prepared from compound **48** and butyric anhydride by the same procedure as described in the synthesis of **49** as a white solid, yield: 70%. $[\alpha]_D^{25}$ = -16.0 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.52 (m, 4H), 7.45-7.34 (m, 3H), 7.26-7.23 (m, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.55-4.54 (m, 1H), 4.37 (br, 1H), 4.12 (d, *J* = 13.1 Hz, 1H), 3.62 (dd, *J* = 13.0, 3.7 Hz, 1H), 2.07-2,02 (m, 2H), 1.62-1.58 (m, 5H), 1.43 (s, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 166.6, 141.2, 140.3, 140.2, 129.1, 128.1, 127.8, 127.2, 126.0, 110.8, 76.3, 75.2, 50.2, 48.4, 38.2, 26.7, 24.4, 19.1, 13.9; HRMS (ESI): Calcd for $C_{24}H_{29}N_2O_4$ $[M+H]^+$, 409.2127; Found, 409.2129.

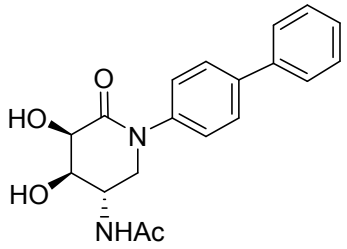
(3R, 4R, 5S)-1-(1,1'-Biphenyl-4-yl)-5-azido-3,4-dihydroxypiperidin-2-one (21)



21

Compound **21** was synthesized from compound **47** as a yellow solid, yield: 93%. $[\alpha]_D^{25}$ = 68.0 (c 0.6, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.55 (m, 4H), 7.46-7.42 (m, 2H), 7.38-7.32 (m, 3H), 4.45 (br, 1H), 4.38 (br, 1H), 4.26-4.17 (m, 3H), 3.61 (dd, *J* = 13.0, 3.7 Hz, 1H), 3.37 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 140.8, 140.33, 140.29, 129.0, 128.3, 127.8, 127.3, 126.0, 69.1, 68.3, 58.2, 50.7; HRMS (ESI): Calcd for $C_{17}H_{17}N_4O_3$ $[M+H]^+$, 325.1301; Found, 325.1302.

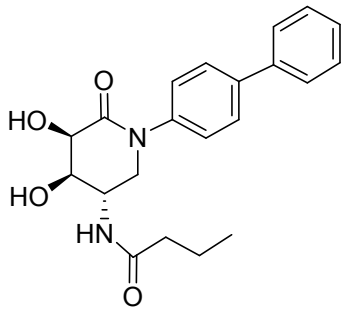
_N_-((3S, 4R, 5R)-1-(1,1'-Biphenyl-4-yl)-4,5-dihydroxy-6-oxopiperidin-3-yl)acetamide (22)



22

Compound **22** was synthesized from compound **49** as a white solid, yield: 70%. $[\alpha]_D^{25}$ = 1.8 (c 1.4, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.68-7.60 (m, 4H), 7.46-7.42 (m, 4H), 7.36-7.33 (m, 1H), 4.53 (d, *J* = 3.6 Hz, 1H), 4.36-4.32 (m, 1H), 4.25 (t, *J* = 3.8 Hz, 1H), 4.12 (dd, *J* = 13.0, 5.9 Hz, 1H), 3.60 (dd, *J* = 13.0, 6.0 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.4, 173.1, 142.4, 141.5, 141.3, 129.9, 128.7, 128.6, 127.9, 127.4, 72.3, 70.7, 52.1, 50.8, 22.7; HRMS (ESI): Calcd for $C_{19}H_{21}N_2O_4$ $[M+H]^+$, 341.1501; Found, 341.1496.

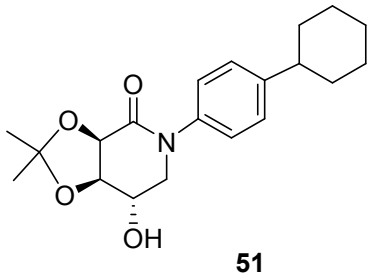
_N_-((3S, 4R, 5R)-1-(1,1'-Biphenyl-4-yl)-4,5-dihydroxy-6-oxopiperidin-3-yl)butyramide (23)



23

Compound **23** was synthesized from compound **50** as a white solid, yield: 88%. $[\alpha]_D^{25}$ = 23.2 (c 0.5, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.67-7.60 (m, 4H), 7.45-7.40 (m, 4H), 7.36-7.32 (m, 1H), 4.51 (d, *J* = 3.4 Hz, 1H), 4.36-4.32 (m, 1H), 4.24 (t, *J* = 3.7 Hz, 1H), 4.13 (dd, *J* = 13.0, 5.9 Hz, 1H), 3.58 (dd, *J* = 13.0, 5.9 Hz, 1H), 2.25 (t, *J* = 7.1 Hz, 2H), 1.72-1.62 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.3, 173.1, 142.4, 141.6, 141.4, 129.9, 128.7, 128.6, 128.0, 127.3, 72.2, 70.8, 52.2, 50.7, 38.8, 20.3, 14.0; HRMS (ESI): Calcd for $C_{21}H_{25}N_2O_4$ $[M+H]^+$, 369.1814; Found, 369.1813.

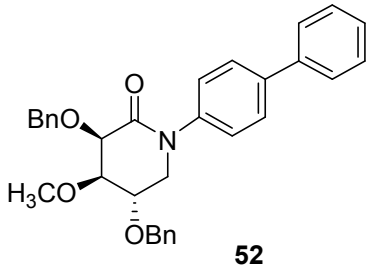
(3aR, 7S, 7aR)-5-(4-Cyclohexylphenyl)-7-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-c]pyridin-4(3aH)-one (51)



51

Compound **51** was synthesized from compound **37** by hydrogenation in a yield of 92% as a white solid. $[\alpha]_D^{25}$ = -22.0 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.15 (m, 4H), 4.68 (d, *J* = 6.9 Hz, 1H), 4.42 (ddd, *J* = 6.9, 3.0, 0.9 Hz, 1H), 4.03-4.02 (m, 1H), 3.93 (dd, *J* = 13.2, 2.3 Hz, 1H), 3.52 (ddd, *J* = 13.4, 4.8, 1.0 Hz, 1H), 3.35 (d, *J* = 4.0 Hz, 1H), 2.49-2.45 (m, 1H), 1.85-1.73 (m, 5H), 1.51 (s, 3H), 1.43-1.32 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 147.0, 140.1, 127.6, 125.7, 110.5, 74.8, 67.3, 52.2, 44.3, 34.5, 27.0, 26.9, 26.2, 24.7; HRMS (ESI): Calcd for $C_{20}H_{28}NO_4$ $[M+H]^+$, 346.2018; Found, 346.2018.

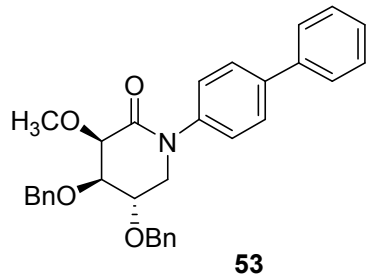
(3R, 4R, 5S)-1-(1,1'-Biphenyl]-4-yl)-3,5-bis(benzyloxy)-4-methoxypiperidin-2-one (52)



52

Compound **52** was prepared from compound **20** and methyl iodide by the same procedure as described for the synthesis of compound **38** as a white solid, yield: 75%. $[\alpha]_D^{25}$ = 143.6 (c 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.55 (m, 4H), 7.46-7.27 (m, 15H), 5.10 (d, *J* = 12.1 Hz, 1H), 4.77 (d, *J* = 12.1 Hz, 1H), 4.62 (br, 2H), 4.42 (d, *J* = 3.0 Hz, 1H), 4.09 (dd, *J* = 13.0, 4.7 Hz, 1H), 4.00 (dd, *J* = 7.8, 4.4 Hz, 1H), 3.88 (dd, *J* = 4.1, 3.2 Hz, 1H), 3.62 (dd, *J* = 13.0, 3.2Hz, 1H), 3.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 141.4, 140.7, 139.9, 138.3, 137.7, 128.9, 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.5, 127.3, 126.4, 80.6, 76.0, 74.3, 73.9, 71.8, 59.2, 51.9; HRMS (ESI): Calcd for $C_{32}H_{32}NO_4$ $[M+H]^+$, 494.2331; Found, 494.2329.

(3R, 4R, 5S)-1-(1,1'-Biphenyl-4-yl)-4,5-bis(benzyloxy)-3-methoxypiperidin-2-one (53)

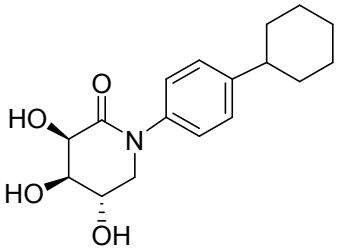


53

Compound **53** was prepared from compound **19** and methyl iodide by the same procedure as described for the synthesis of compound **38** as a white solid, yield: 85%. $[\alpha]_D^{25}$ = 41.4 (c 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.55 (m, 4H), 7.45-7.28 (m, 15H), 4.90 (d, *J* = 12.3 Hz, 1H), 4.69 (d, *J* = 12.3 Hz, 1H), 4.59 (s, 2H), 4.20 (d, *J* = 2.9 Hz, 1H), 4.13 (dd, *J* = 4.3, 3.1 Hz, 1H), 4.08 (dd, *J* = 13.0, 4.9 Hz, 1H), 3.97

(dd, J = 8.4, 4.3 Hz, 1H), 3.67 (s, 3H), 3.62 (dd, J = 13.1, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 141.4, 140.7, 139.9, 138.3, 137.7, 128.9, 128.7, 128.6, 128.2, 128.1, 128.0, 127.8, 127.5, 127.3, 126.3, 79.1, 74.6, 73.2, 72.0, 60.1, 52.0; HRMS (ESI): Calcd for $C_{32}H_{32}NO_4$ $[M+H]^+$, 494.2331; Found, 494.2328.

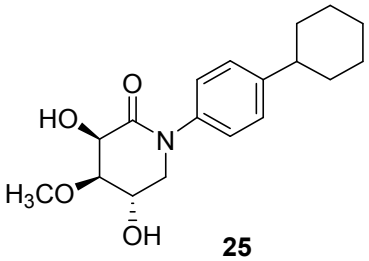
(3R, 4R, 5S)-1-(4-Cyclohexylphenyl)-3,4,5-trihydroxypiperidin-2-one (24)



24

Compound **24** was prepared by hydrolysis of compound **51** as a white solid. Yield: 83%. $[\alpha]_D^{25}$ = 35.8 (c 0.6, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.27-7.25 (m, 2H), 7.19-7.17 (m, 2H), 4.53 (d, J = 3.3 Hz, 1H), 4.19-4.06 (m, 3H), 3.48-3.44 (m, 1H), 2.56-2.51 (m, 1H), 1.86-1.75 (m, 5H), 1.50-1.29 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.4, 148.5, 141.2, 128.7, 127.2, 72.7, 69.8, 68.5, 55.9, 45.6, 35.7, 28.0, 27.2; HRMS (ESI): Calcd for $C_{17}H_{24}NO_4$ $[M+H]^+$, 306.1705; Found, 306.1698.

(3R, 4R, 5S)-1-(4-Cyclohexylphenyl)-3,5-dihydroxy-4-methoxypiperidin-2-one (25)

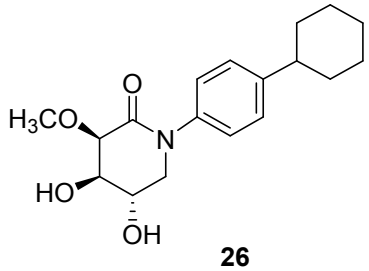


25

Compound **25** was prepared by hydrogenation of compound **52** as a white solid. Yield: 75%. $[\alpha]_D^{25}$ = 55.0 (c 0.3, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.16 (m, 4H), 4.61 (s, 1H), 4.28 (br, 1H), 4.04 (dd, J = 13.0, 4.0 Hz, 1H), 3.89 (br, 1H), 3.73-3.68 (m, 1H), 3.59 (s, 3H), 3.52 (d, J = 12.7 Hz, 1H), 2.50 (br, 1H), 1.85-1.69 (m, 5H), 1.45-1.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 147.2, 139.4, 127.8, 125.6,

80.8, 69.0, 66.4, 63.0, 59.9, 54.5, 44.4, 34.6, 27.0, 26.3; HRMS (ESI): Calcd for $C_{18}H_{26}NO_4$ $[M+H]^+$, 320.1862; Found, 320.1859.

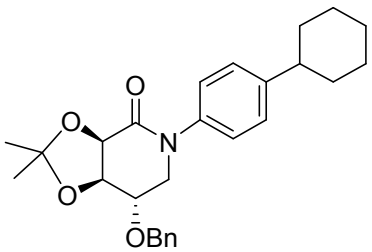
(3R, 4R, 5S)-1-(4-Cyclohexylphenyl)-4,5-dihydroxy-3-methoxypiperidin-2-one (26)



26

Compound **26** was prepared by hydrogenation of compound **53** as a white solid. Yield: 63%. $[\alpha]_D^{25}$ = 35.3 (c 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.22 (m, 2H), 7.17-7.15 (m, 2H), 4.26-4.20 (m, 1H), 4.05-4.02 (m, 2H), 3.92 (dd, *J* = 12.5, 5.0 Hz, 1H), 3.72 (s, 3H), 3.49 (dd, *J* = 12.4, 6.8 Hz, 1H), 2.78 (d, *J* = 5.7 Hz, 1H), 2.52-2.48 (m, 1H), 2.37 (d, *J* = 2.9 Hz, 1H), 1.88-1.73 (m, 5H), 1.45-1.33 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.9, 147.2, 139.5, 127.8, 125.8, 78.3, 72.2, 67.1, 60.5, 53.6, 44.3, 34.5, 34.5, 27.0, 26.3; HRMS (ESI): Calcd for $C_{18}H_{26}NO_4$ $[M+H]^+$, 320.1862; Found, 320.1860.

(3aR, 7S, 7aR)-7-(Benzyloxy)-5-(4-cyclohexylphenyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-c]pyridin-4(3aH)-one (54)

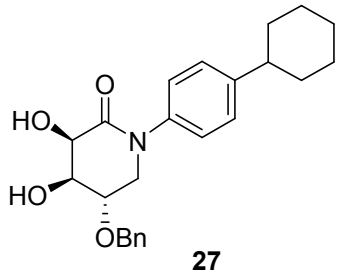


54

Compound **54** was prepared from compound **51** and benzyl bromide by the same procedure as described for the synthesis of compound **38** as a white solid, yield: 85%. $[\alpha]_D^{25}$ = -10.0 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 7.23-7.18 (m, 4H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H), 4.62 (d, *J* = 11.9 Hz,

1H), 4.56 (ddd, *J* = 7.0, 3.4, 1.1 Hz, 1H), 3.98 (dd, *J* = 13.3, 2.1 Hz, 1H), 3.85-3.82 (m, 1H), 3.67 (ddd, *J* = 13.3, 4.8, 1.1 Hz, 1H), 2.51-2.47 (m, 1H), 1.87-1.73 (m, 5H), 1.53 (s, 3H), 1.45 (s, 3H), 1.41-1.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 146.2, 140.3, 137.5, 128.7, 128.2, 127.8, 127.7, 125.6, 110.5, 76.1, 75.2, 74.1, 71.5, 49.3, 44.3, 34.6, 27.0, 26.8, 26.3, 24.6; HRMS (ESI): Calcd for $C_{27}H_{34}NO_4$ $[M+H]^+$, 436.2488; Found, 436.2484.

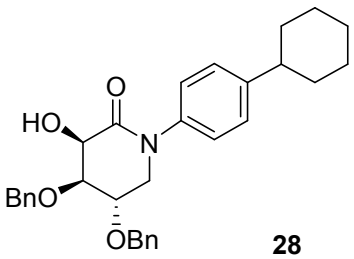
(3R, 4S, 5S)-5-(Benzyloxy)-1-(4-cyclohexylphenyl)-3,4-dihydroxypiperidin-2-one (27)



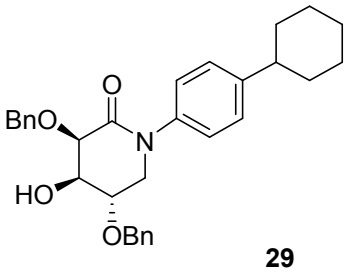
27

Compound **27** was prepared by removal of the 3,4-isopropylidene group in compound **54** as a white solid. Yield: 80%. $[\alpha]_D^{25}$ = 25.8 (c 0.3, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 7.23-7.14 (m, 4H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 4.52 (d, *J* = 3.5 Hz, 1H), 4.43 (t, *J* = 3.4 Hz, 1H), 4.04 (dd, *J* = 13.0, 4.5 Hz, 1H), 3.99 (dd, *J* = 7.6, 3.9 Hz, 1H), 3.65 (dd, *J* = 12.9, 4.0 Hz, 1H), 2.49 (br, 1H), 1.84-1.73 (m, 5H), 1.44-1.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 147.3, 139.2, 137.5, 128.8, 128.2, 127.83, 127.79, 125.4, 74.4, 71.8, 69.3, 68.7, 51.4, 44.3, 34.5, 34.5, 27.0, 26.2; HRMS (ESI): Calcd for $C_{24}H_{30}NO_4$ $[M+H]^+$, 396.2175; Found, 396.2173.

(3R,4R,5S)-4,5-Bis(benzyloxy)-1-(4-cyclohexylphenyl)-3-hydroxypiperidin-2-one (28) and (3R,4R,5S)-3,5-bis(benzyloxy)-1-(4-cyclohexylphenyl)-4-hydroxypiperidin-2-one (29)



28



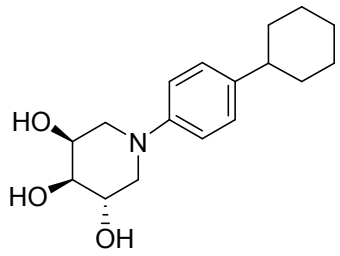
29

Compounds **28** and **29** were prepared from compound 27 and benzyl bromide in a yield of 87% with a ratio of 1:1.

Compound **28**: a white solid. $[\alpha]_D^{25}$ = 4.6 (c 0.4, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ7.36-7.28 (m, 8H), 7.22-7.20 (m, 2H), 7.16-7.14 (m, 2H), 4.95 (d, *J* = 12.1 Hz, 1H), 4.70 (d, *J* = 12.1 Hz, 1H), 4.64 (t, *J* = 2.57 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.23 (t, *J* = 3.2 Hz, 1H), 4.00(dd, *J* = 13.2, 5.1 Hz, 1H), 3.88-3.86 (m, 1H), 3.79 (br, 1H),3.61 (dd, *J* = 13.2, 3.9 Hz, 1H), 2.50-2.47 (m, 1H), 1.86-1.83 (m, 4H), 1.74(d, *J* = 12.7 Hz, 1H) 1.43-1.37 (m, 4H),1.27-1.23(m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 146.9, 139.3, 138.3, 137.3, 128.6, 128.4, 128.1, 127.74, 127.67, 127.6, 125.4, 76.2, 73.8, 73.7, 71.4, 69.5, 52.0, 44.2, 34.39, 34.38, 26.8, 26.1; HRMS (ESI): Calcd for $C_{31}H_{36}NO_4$ $[M+H]^+$, 486.2644; Found, 486.2632.

Compound **29**: a white solid. $[\alpha]_D^{25}$ = 53.9 (c 0.8, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43-7.42 (m, 2H), 7.36-7.27 (m, 8H), 7.22-7.20 (m, 2H), 7.16-7.14 (m, 2H), 5.20 (d, *J* = 11.7 Hz, 1H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.29 (br, 2H), 4.01 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.94-3.92 (m, 1H), 3.57 (dd, *J* = 13.0, 4.1 Hz, 1H), 2.95 (s, 1H), 2.51-2.47 (m, 1H), 1.87-1.73 (m, 5H), 1.43-1.23 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ169.3, 146.9, 139.8, 137.9, 137.6, 128.7, 128.6, 128.5, 128.1, 128.1, 127.8, 127.7, 125.9, 75.1, 74.5, 74.4, 71.8, 70.6, 51.0, 44.3, 34.5, 27.0, 26.1; HRMS (ESI): Calcd for $C_{31}H_{36}NO_4$ $[M+H]^+$,486.2644; Found,.486.2634.

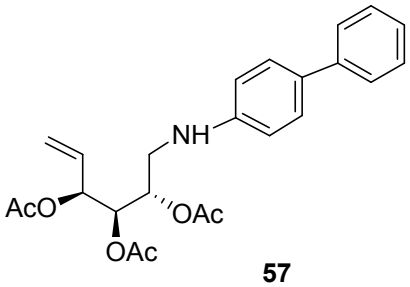
(3S, 5S)-1-(4-Cyclohexylphenyl)piperidine-3,4,5-triol (30)



30

BH_3·THF (1 M, 0.35 mL, 0.35 mmol) was added dropwise to the solution of **24** (46.0 mg, 0.151 mmol) in anhydrous THF (2 mL) at 0 °C under argon. After stirring for 20 min at room temperature, the solution was refluxed for 4 h. Then the mixture was cooled to 0 °C, 6N HCl was added dropwise until no further evolution of gas occurred. After refluxing 30 min, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 15:1) on silica gel to provide compound **30** (33.4 mg, 76%) as a colorless solid. $[\alpha]_D^{25}$ = 2.9 (c 0.4, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.08-7.06 (m, 2H), 6.93-6.91 (m, 2H), 4.01 (dt, *J* = 5.8, 2.9 Hz, 1H), 3.91 (td, *J* = 7.7, 4.1 Hz, 1H), 3.52 (dd, *J* = 7.5, 3.3 Hz, 1H), 3.44 (ddd, *J* = 11.8, 4.0, 1.4 Hz, 1H), 3.37 (dd, *J* = 12.2, 2.7 Hz, 1H), 2.96 (dd, *J* = 12.2, 2.8 Hz, 1H), 2.74 (dd, *J* = 11.8, 7.9 Hz, 1H), 2.44-2.41 (m, 1H), 1.82-1.73 (m, 5H), 1.47-1.34 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.1, 141.3, 128.2, 118.7, 75.0, 69.8, 69.3, 55.4, 55.3, 45.2, 35.9, 28.1, 27.3; HRMS (ESI): Calcd for $C_{17}H_{26}NO_3$ $[M+H]^+$, 292.1913; Found, 292.1912.

(2S, 3S, 4S)-1-(1,1'-Biphenyl-4-yl-amino)hex-5-ene-2,3,4-triyl triacetate (57)

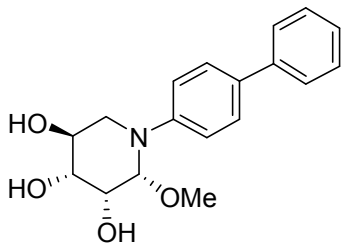


57

To a deoxygenated mixture of zinc (304 mg, 0.465 mmol), NH_4Cl (249 mg, 4.65 mmol) and VB_{12} (126 mg, 0.009 mmol) in MeOH (4.0 mL) was added methyl 6-iodo-2,3,4-tri-*O*-acetyl-6-deoxy-α-D-galactopyranoside (**55**) under argon. The mixture was stirred at room temperature for 1 h, then filtered, and concentrated in *vacuo*. The residue

was dissolved in ethyl acetate and washed with H_2O and brine, dried (Na_2SO_4), filtered. The filtrate was concentrated in *vacuo* and the residue was dissolved in MeOH (3.0 mL**)**, 1,1'-biphenyl-4-amine (86.6 mg, 0.512 mmol) and AcOH (31 µL, 0.558 mmol) were added and the mixture was stirred at 45 °C for 4 h. Then $NaCNBH_3$ (58.4 mg, 0.93 mmol) was added to the mixture and the stirring was continued overnight. The reaction was quenched with saturated $NaHCO_3$. After removal of the solvent, the residue was dissolved in ethyl acetate and washed with brine twice. The organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate 8:1) on silica gel to provide compound **57** as a pale yellow syrup, yield: 65%. $[\alpha]_D^{25}$ = +2.8 (c 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.3 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.5 (t, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 2H), 5.79-5.71 (m, 1H), 5.40-5.28 (m, 5H), 4.11 (br, 1H), 3.40 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.17 (dd, *J* = 12.7, 6.8 Hz, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.7, 169.7, 146.9, 141.3, 132.7, 130.9, 128.8, 128.2, 126.4, 126.3, 120.7, 113.2, 71.7, 71.6, 69.0, 43.8, 21.1, 21.0, 20.9; HRMS (ESI): Calcd for $C_{24}H_{28}NO_6$ $[M+H]^+$, 426.1917; Found, 426.1909.

(2R, 3R, 4R, 5S)-1-(1,1'-Biphenyl-4-yl)-2-methoxypiperidine-3,4,5-triol (31)



31

A mixture of compound **57** (37.0 mg, 0.087 mmol), MeOH (1.5 mL), water (0.5 mL), osmium tetroxide (1% in water, 10 µL) was stirred for 10 minutes during which time the mixture became pale pink. A total of 38.0 mg (0.174 mmol) of finely powdered sodium metaperiodate was added in portions over a period of 30 min. The reaction mixture was then stirred for an additional 2 h. The mixture was extracted thoroughly with ethyl acetate and the combined organic layers were dried over anhydrous sodium

sulfate and filtered. The filtrate was concentrated. The residue was dissolved in anhydrous MeOH (3.0 mL) and a catalytic amount of NaOMe was added. The mixture was stirred until TLC showed the reaction was complete. The MeOH was evaporated in *vacuo.* Column chromatography on silica gel (CH_2Cl_2/MeOH, 15:1) gave compound **31** as a yellow solid in 60% yield. $[\alpha]_D^{25}$ = -62.4 (c 0.5, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.57-7.50 (m, 4H), 7.40-7.36 (m, 2H), 7.27-7.23 (m, 1H), 7.12-7.10 (m, 2H), 5.10 (d, *J* = 2.5 Hz, 1H), 4.01 (t, *J* = 3.2 Hz, 1H), 3.91 (td, *J* = 10.1, 5.7 Hz, 1H), 3.72 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.54 (ddd, *J* = 11.5, 5.7, 0.7 Hz, 1H), 3.17 (s, 3H), 3.10 (t, *J* = 10.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.5, 142.1, 134.1, 129.8, 128.5, 127.5, 127.3, 118.7, 93.5, 93.4, 73.2, 71.48, 71.46, 68.7, 56.9; HRMS (ESI): Calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$, 316.1549; Found, 316.1546.

Biology

All laboratory animal experiments were performed according to the national guidelines and approved by the Institutional Animal Care and Use Committee of Peking University.

Preparation of mouse splenocytes suspension

Splenocytes suspensions were prepared from male BALB/c mouse. Mouse splenocytes were plated on 96-well microplates at a density of 5×10^5 cells/well and cultured in RPMI-1640 media (Hyclone) containing 10% fetal bovine serum (FBS), 2.5 μg/mL of concanavalin A alone or along with 50 μM of synthetic iminosugar compounds at 37 °C, 5% CO_2 for 48 h.

Proliferation assays

Cell proliferation was measured by the cell-counting kit-8 (CCK-8) method in 48 h after culture. CCK-8 (10 mL, Dojindo) was added to each well and the plates were incubated for 4 h at 37 °C. Optical density was measured using a Microplate Reader at 450 nm. All data were presented as means ± SEM.

Cytokine measurement

The 96-well microplates were incubated for 48 h in 5% CO_2 at 37 °C, and the plates were centrifuged at 4 °C, 1500×g for 15 min to precipitate the cells. The supernatant was taken, and stored at −20 °C before the measurement of the cytokines. The samples, which had been frozen, were thawed to room temperature before the measurements of IL-4 and INF-γ were taken. The amounts of cytokines were measured with enzyme-linked immunosorbent assay (IL-4 ELISA kit, Bender MedSystems, Vienna, Austria; INF-γ ELISA kit, San Diego, USA) procedures according to the manufacturer's directions.

Table S1. Inhibitory rates of all synthetic compounds on spleen proliferation[a]

Compound	Mean (%)	SEM (%)	Compound	Mean (%)	SEM (%)	Compound	Mean (%)	SEM (%)
CSA	96.6	0.07	**15**	17.3	6.25	**24**	59.3	8.48
7	81.3	4.18	**16**	20.5	4.17	**25**	78.5	4.79
8	-6.8	4.69	**17**	26.1	7.14	**26**	58.1	6.01
9	-30.4	11.29	**18**	-5.2	0.94	**27**	9.4	2.39
10	17.3	3.83	**19**	96.1	0.31	**28**	99.4	0.09
11	-6.4	3.62	**20**	97.5	0.30	**29**	99.6	0.07
12	28.7	3.19	**21**	1.3	4.61	**30**	69.3	3.37
13	1.2	1.38	**22**	6.0	3.63	**31**	94.7	0.77
14	63.3	5.84	**23**	7.8	4.60			

[a]Values are mean values of three independent experiments. Concentration of CSA was 1 μM and concentration of **8**-**31** were 50 μM.

Table S2. Inhibitory rates on IFN-γ secretion of the tested compounds[a]

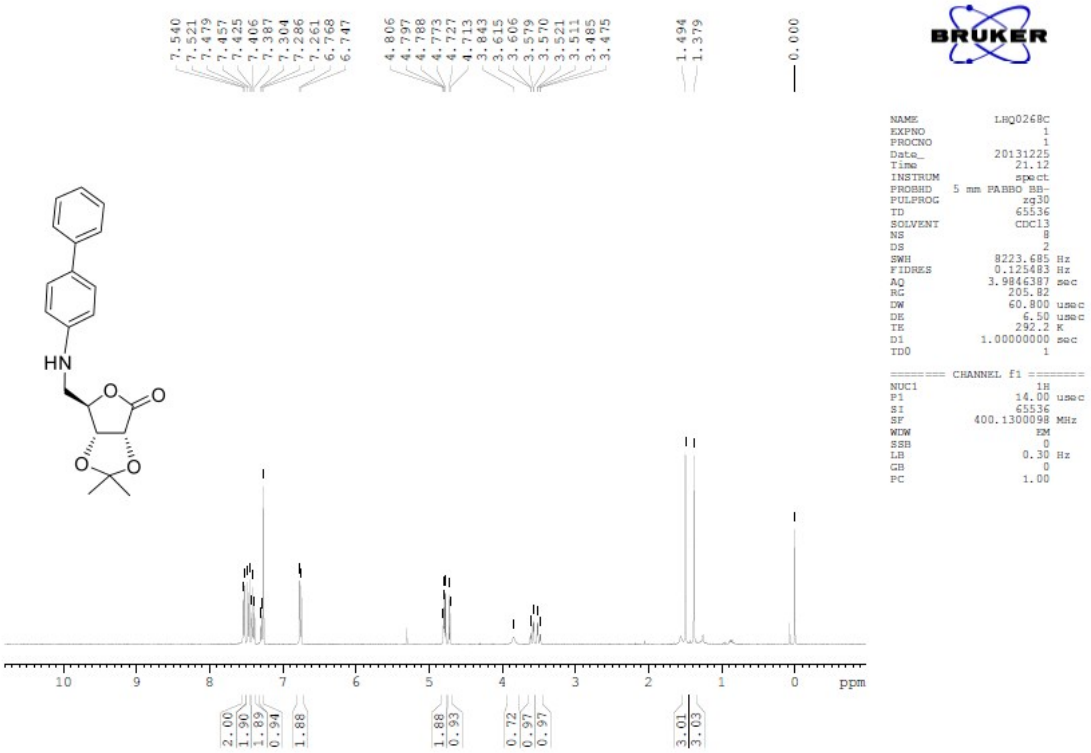
Compound	12.5 μM (%)	SEM (%)	25 μM (%)	SEM (%)
19	19.55	9.30	91.34	3.19
20	33.16	10.90	104.37	1.35
25	5.60	12.62	7.00	7.83
28	14.25	9.87	24.39	6.72
29	25.54	9.93	96.51	2.63
31	6.19	11.56	29.70	8.63
CSA	104.61	1.73		

[a]Each compound was tested at two different concentrations: 12.5 and 25 μM. Concentration of CSA was 1 μM. Data are means ± SEM of at least three independent experiments.

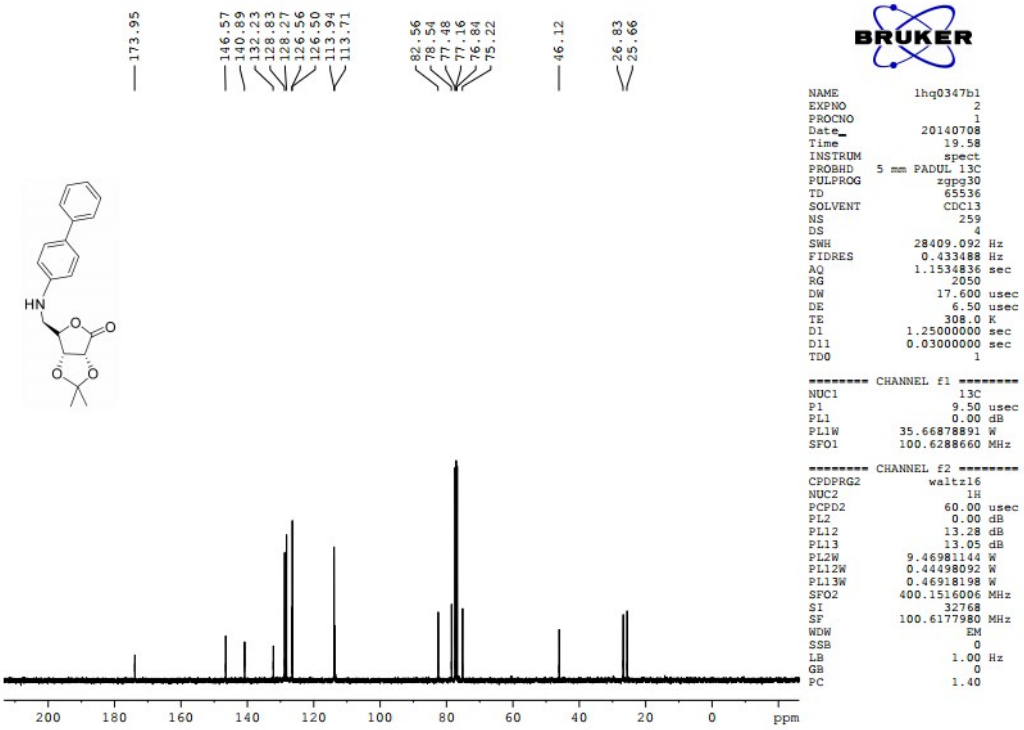
Table S3. Inhibitory rates on IL-4 secretion of the tested compounds[a]

Compound	12.5 μM (%)	SEM (%)	25 μM (%)	SEM (%)
19	42.33	10.74	100.64	1.21
20	74.90	2.55	105.91	2.57
25	1.68	1.72	24.19	8.29
28	12.80	8.02	1.85	14.92
29	1.56	8.16	99.92	2.09
31	-26.56	6.90	11.21	7.23
CSA	106.7	2.71		

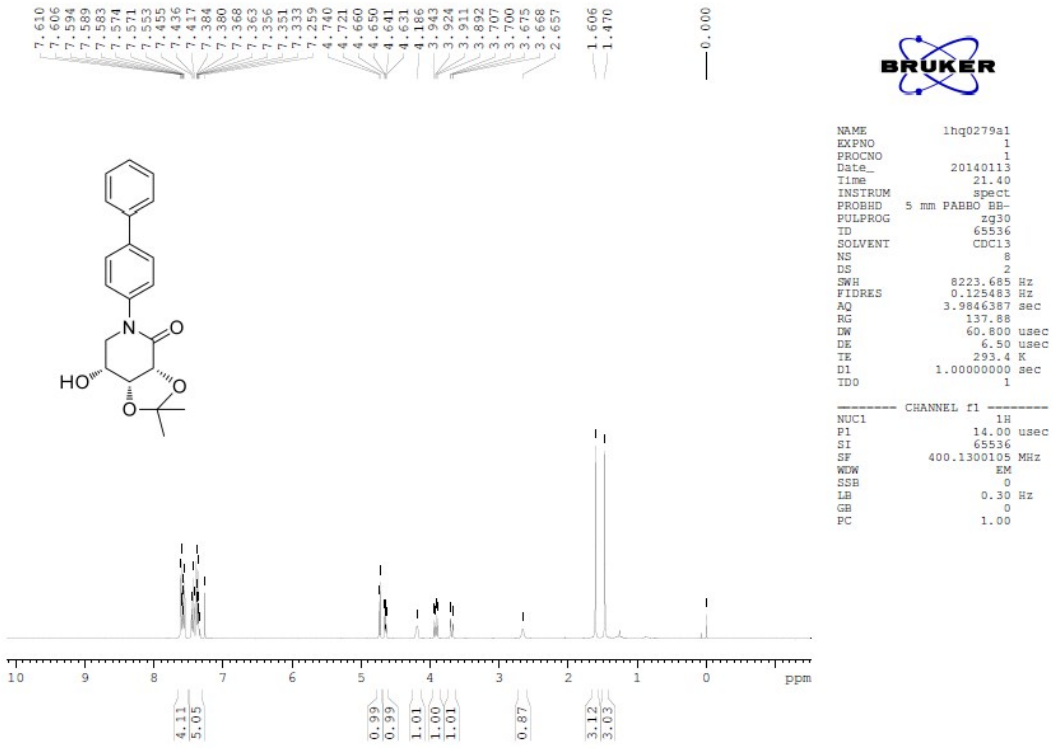
[a]Each compound was tested at two different concentrations: 12.5 and 25 μM. Concentration of CSA was 1 μM. Data are means ± SEM of at least three independent experiments.



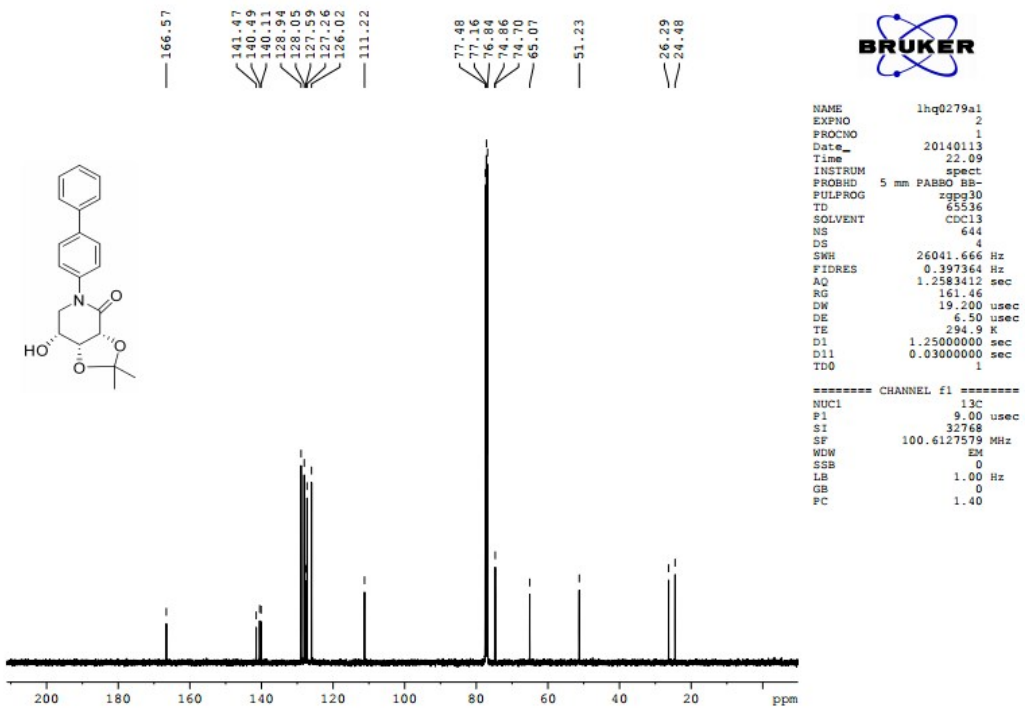
^{1}H NMR spectrum of **35**



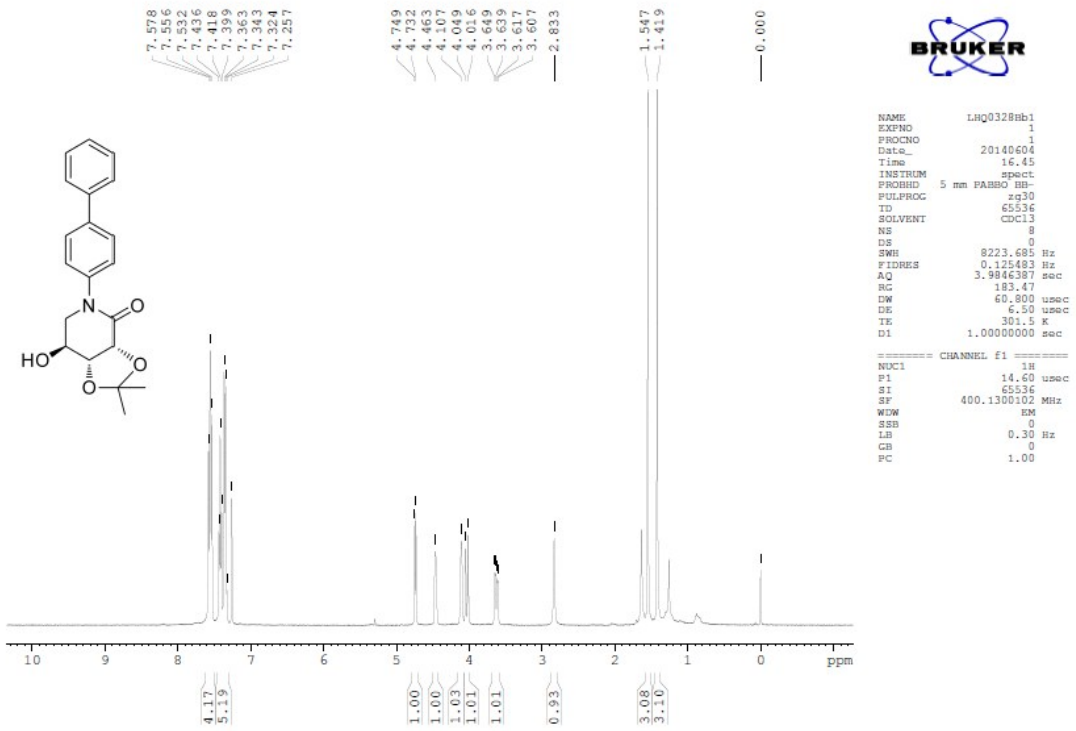
^{13}C NMR spectrum of **35**



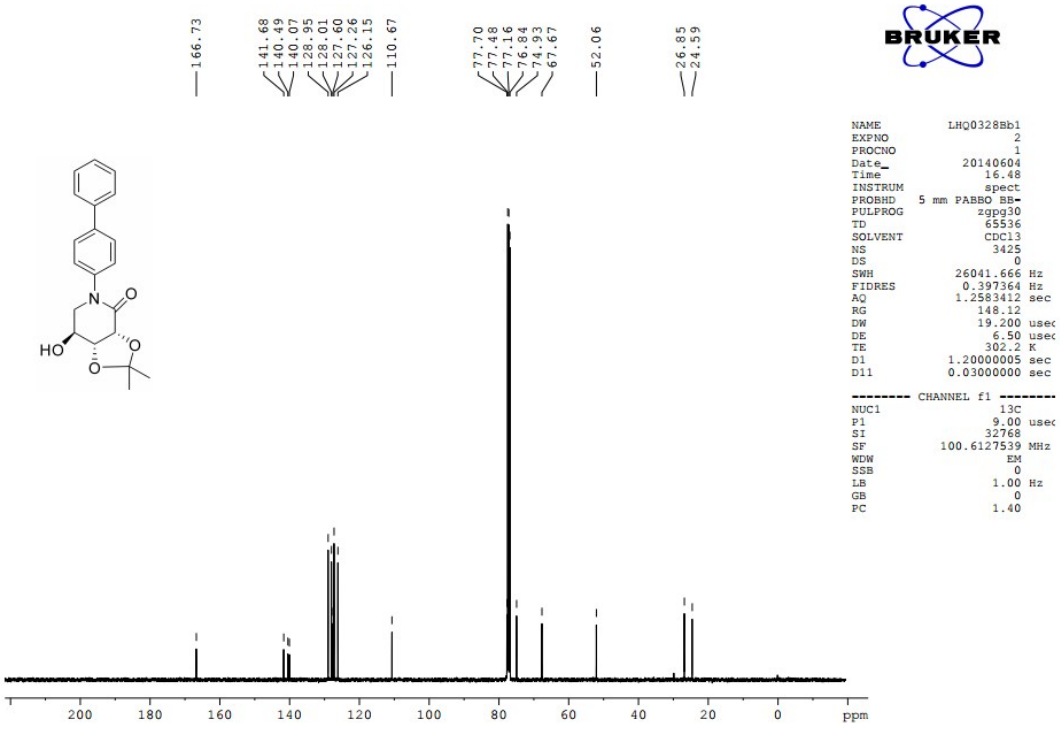
^{1}H NMR spectrum of **36**



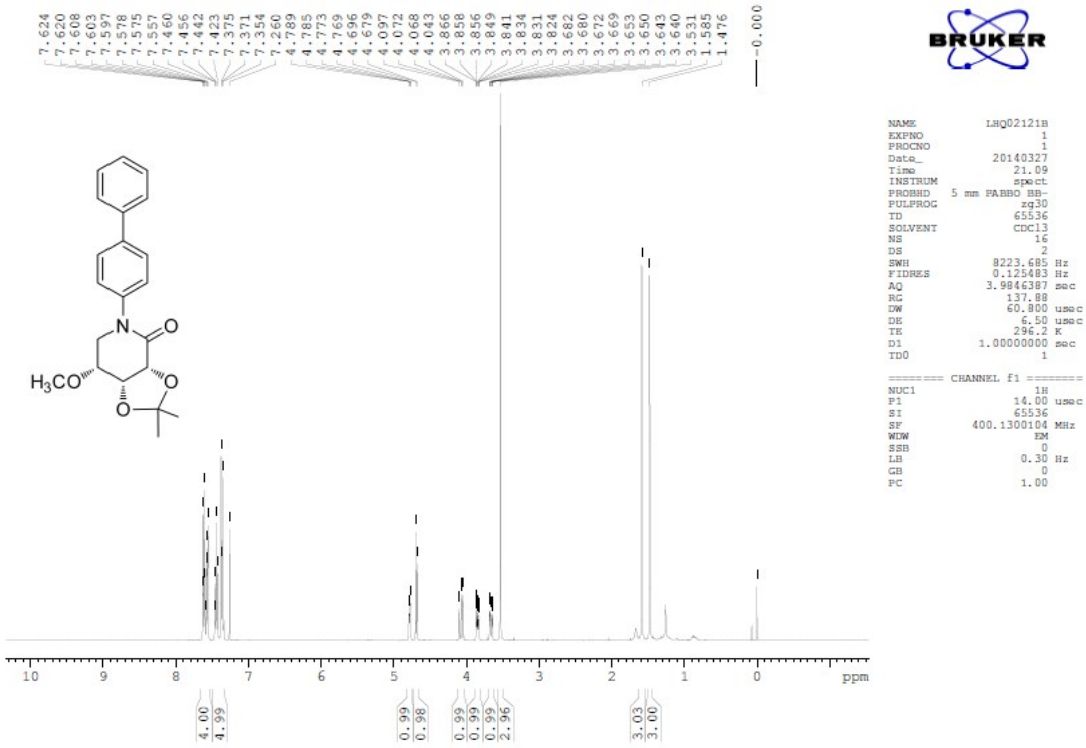
^{13}C NMR spectrum of **36**



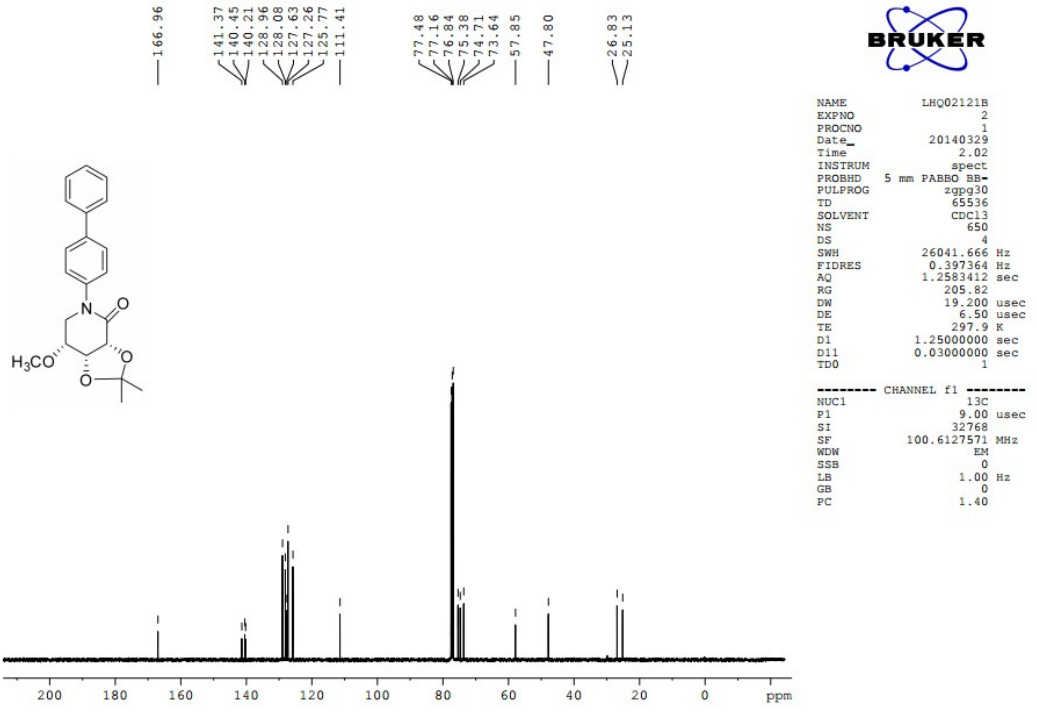
^{1}H NMR spectrum of **37**



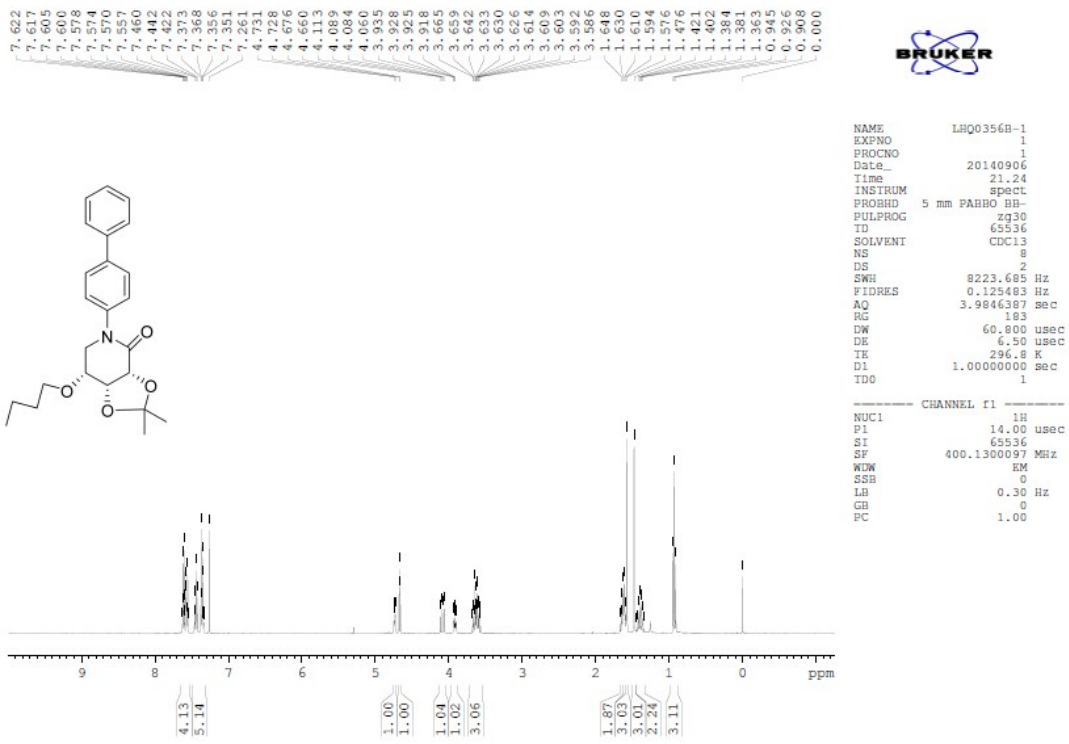
^{13}C NMR spectrum of **37**



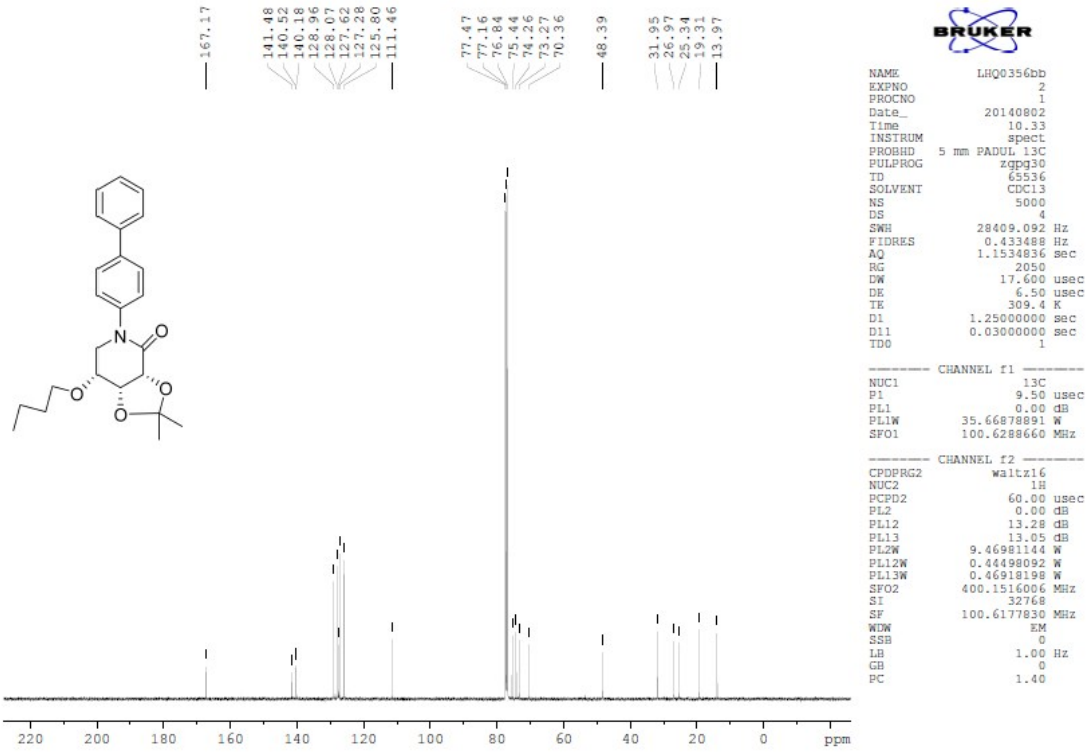
^{1}H NMR spectrum of **38**



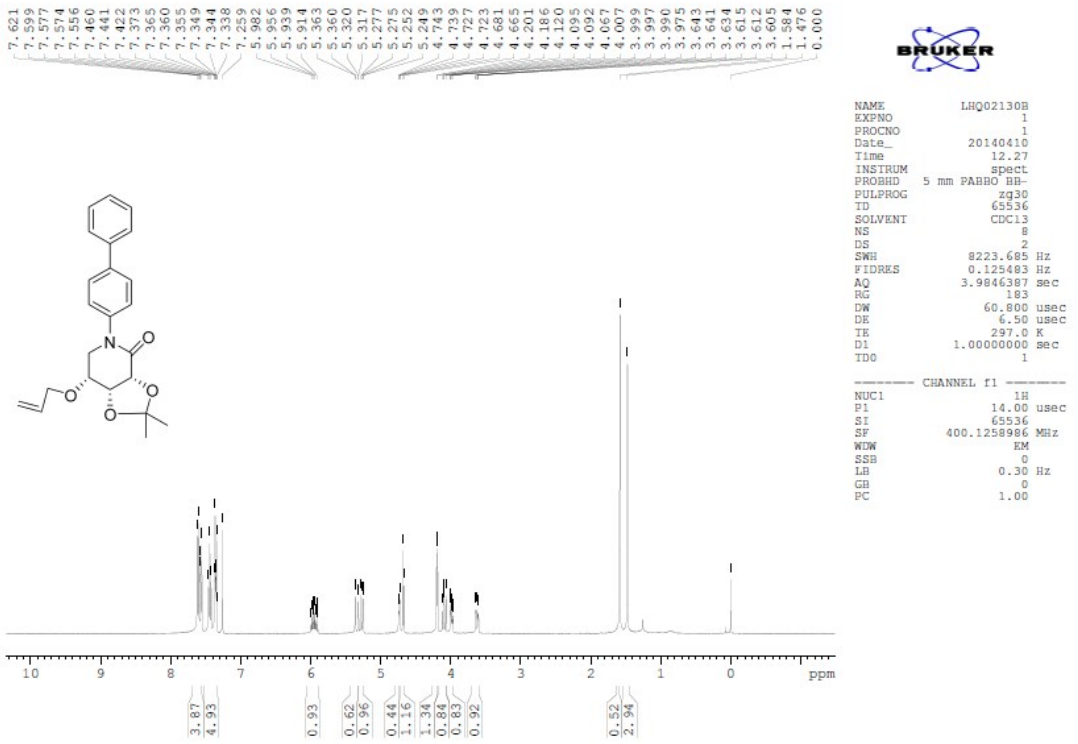
^{13}C NMR spectrum of **38**



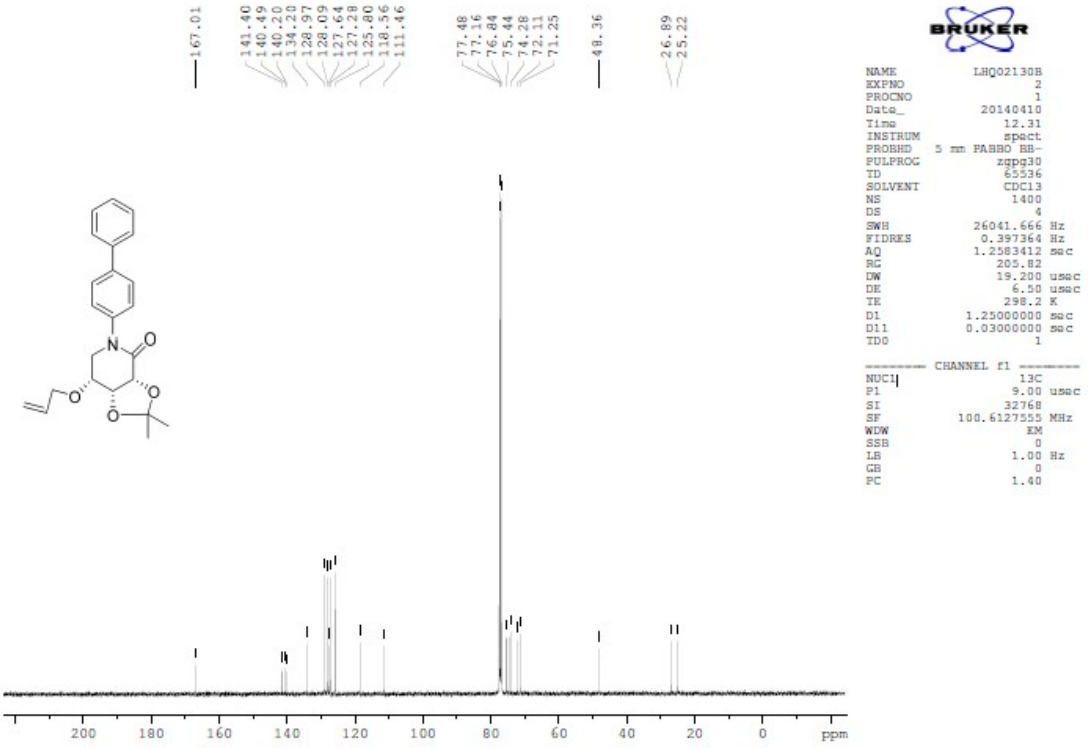
^{1}H NMR spectrum of **39**



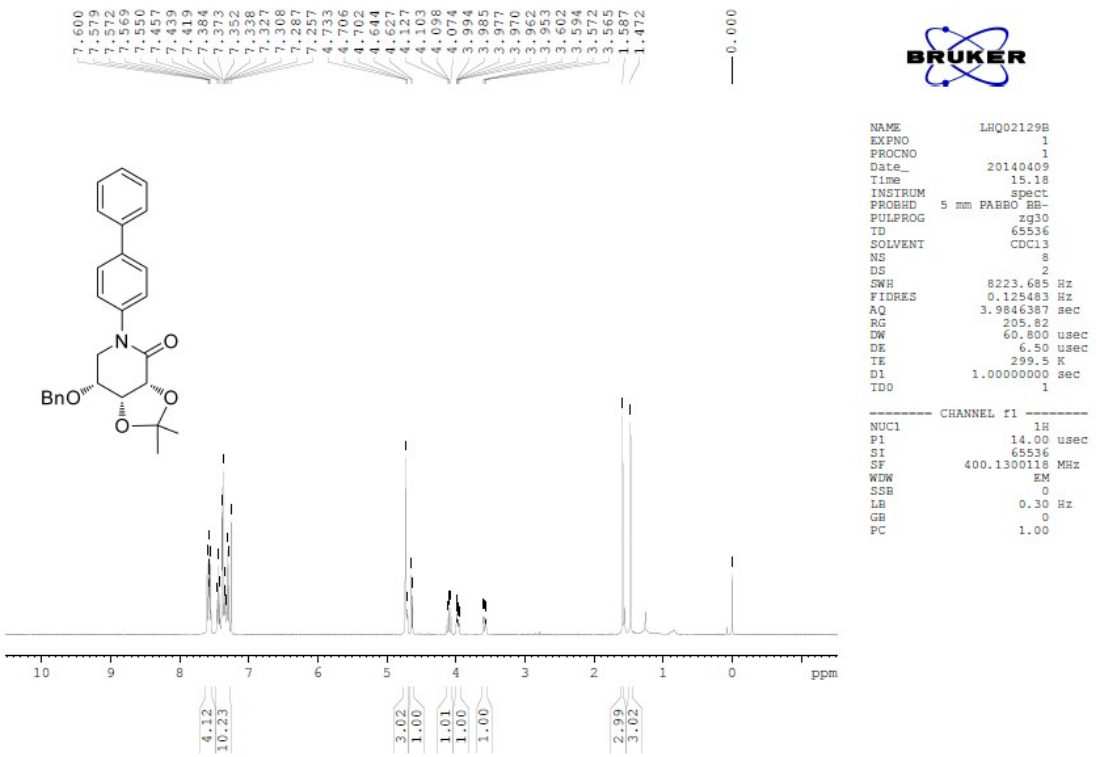
^{13}C NMR spectrum of **39**



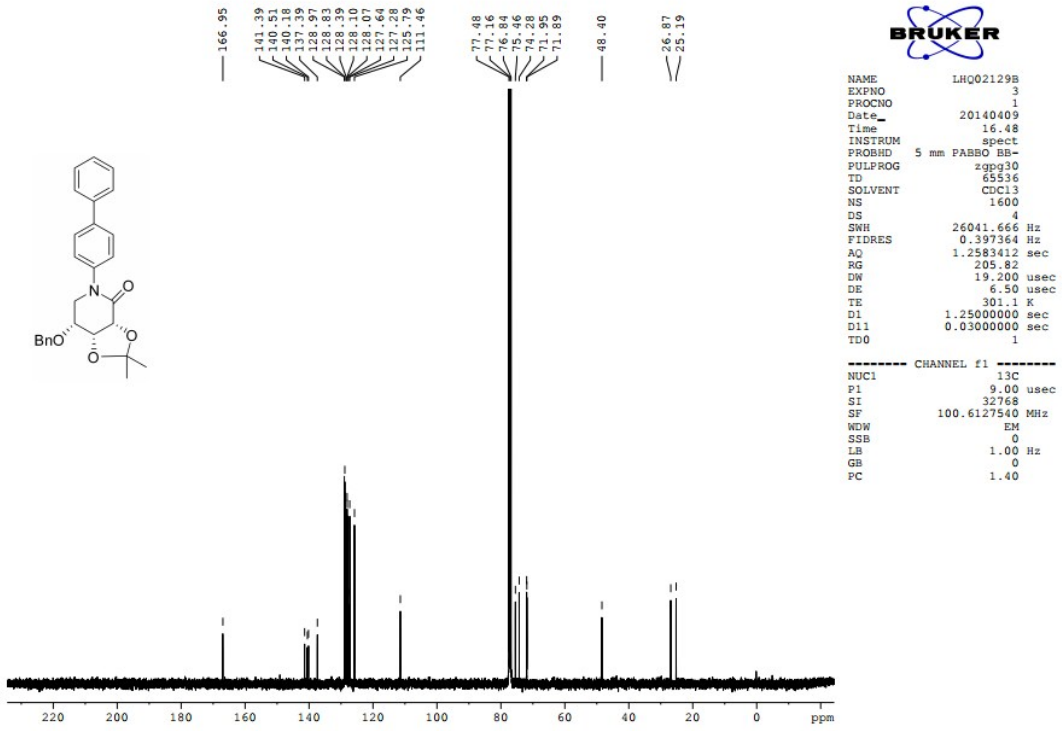
^{1}H NMR spectrum of **40**



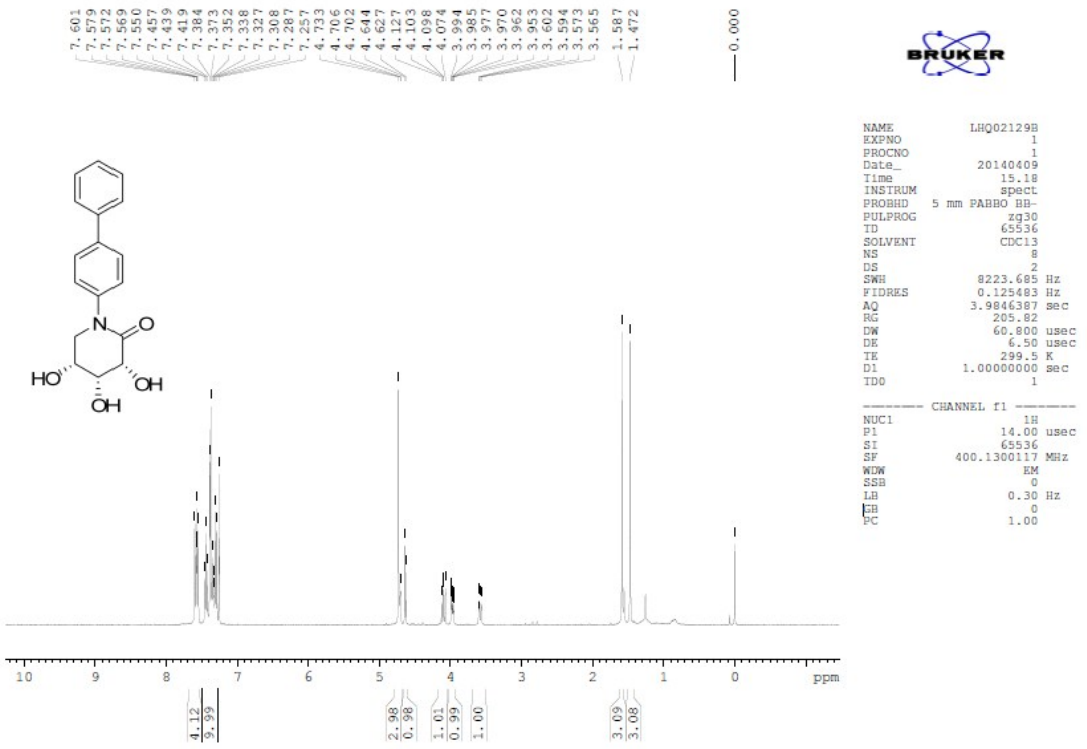
^{13}C NMR spectrum of **40**



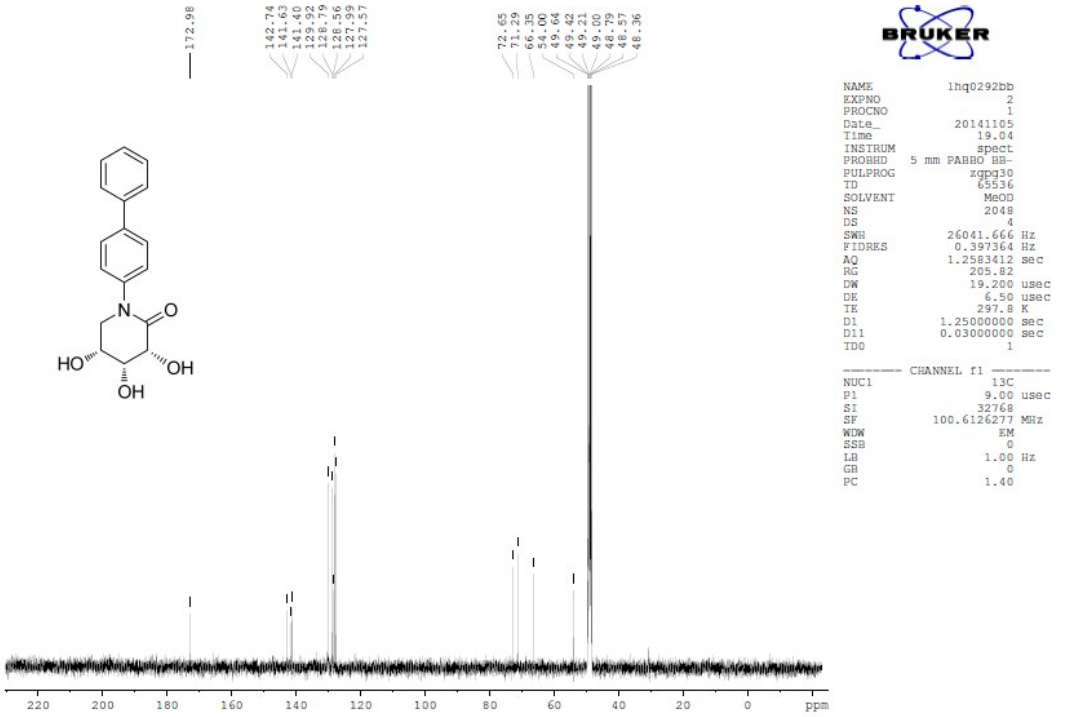
^{1}H NMR spectrum of **41**



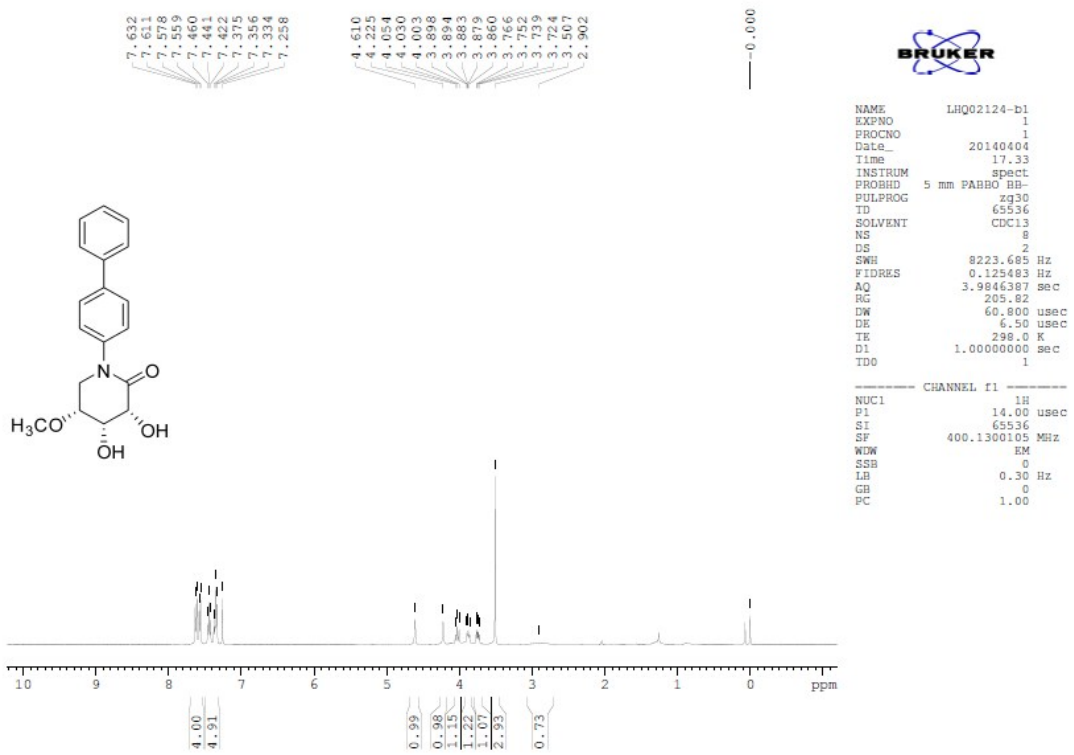
^{13}C NMR spectrum of **41**



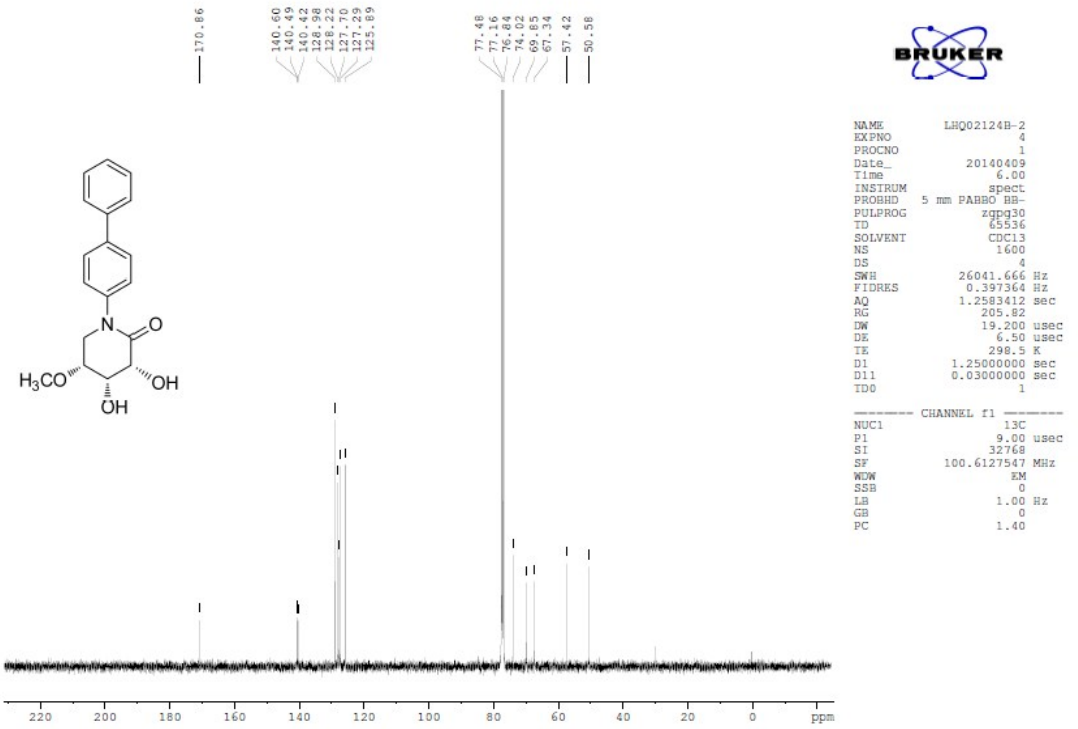
^{1}H NMR spectrum of **8**



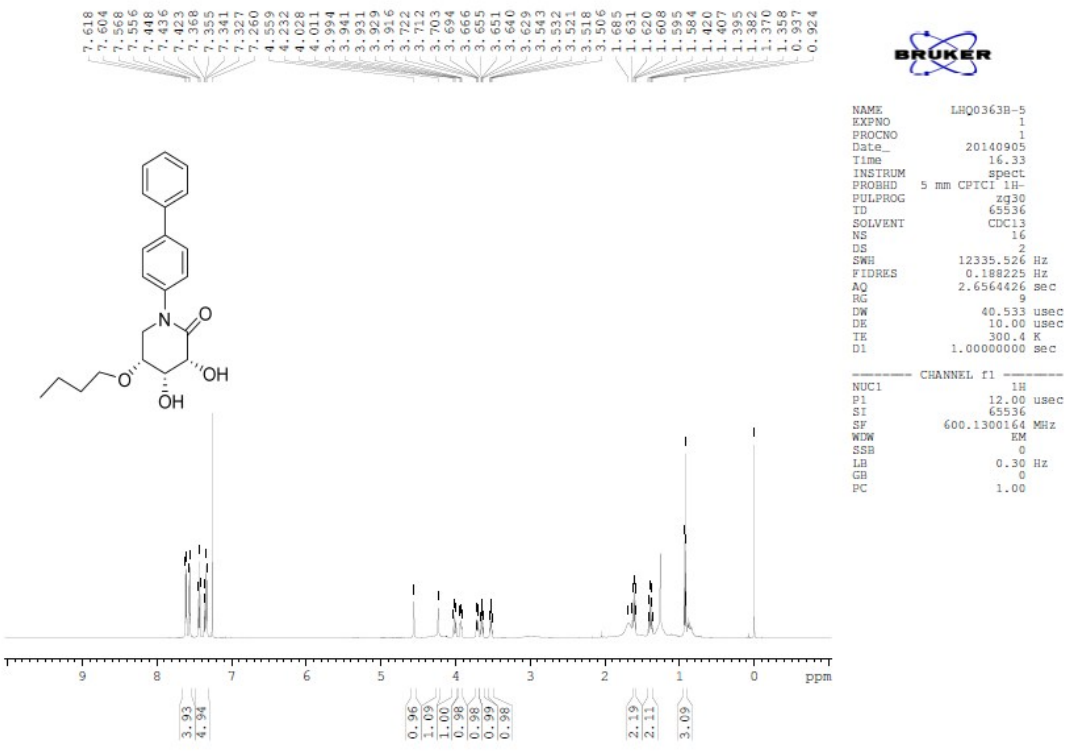
^{13}C NMR spectrum of **8**



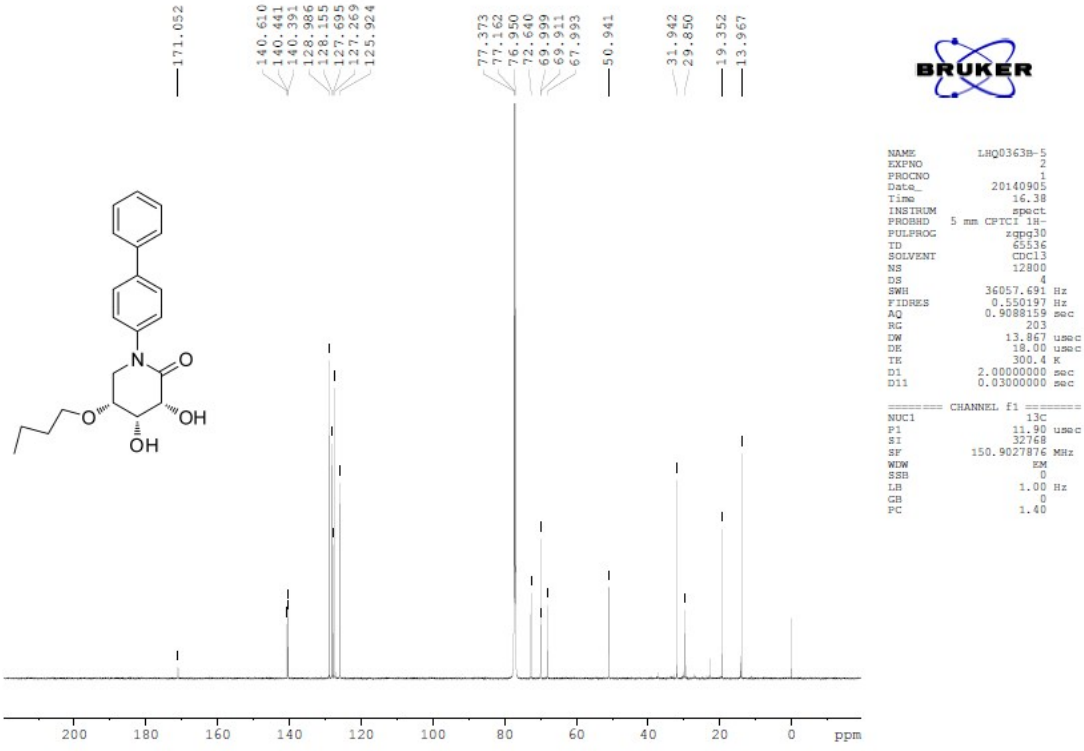
^{1}H NMR spectrum of **9**



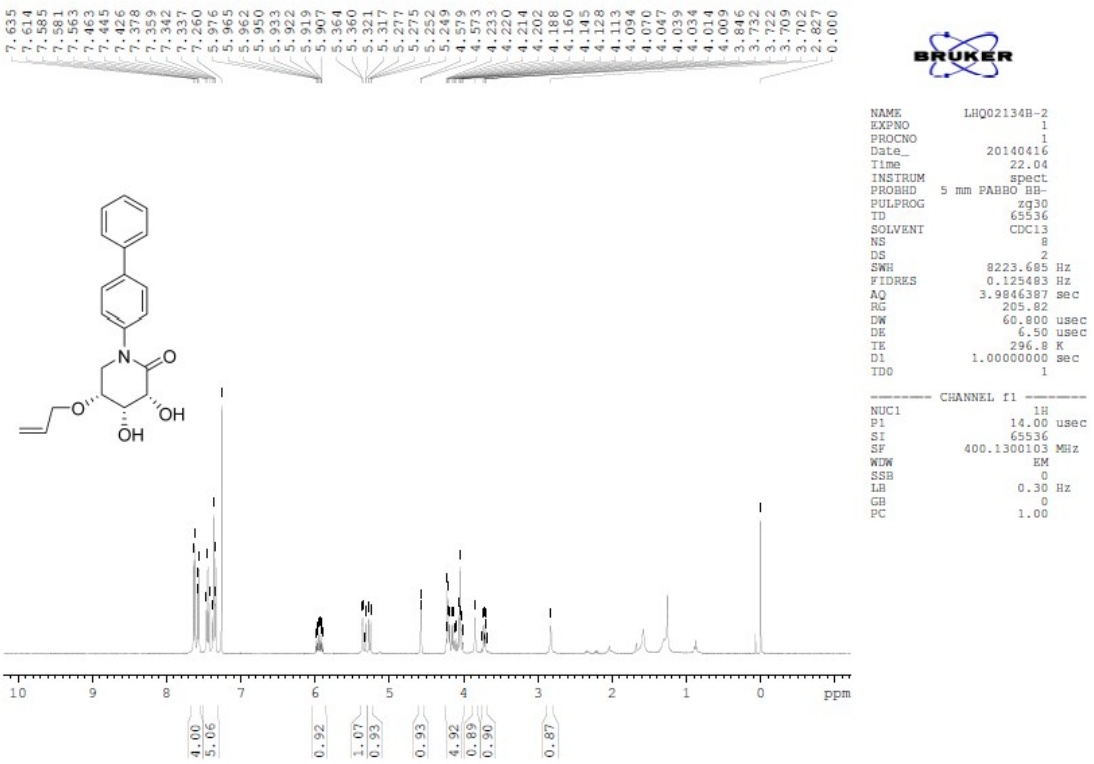
^{13}C NMR spectrum of **9**



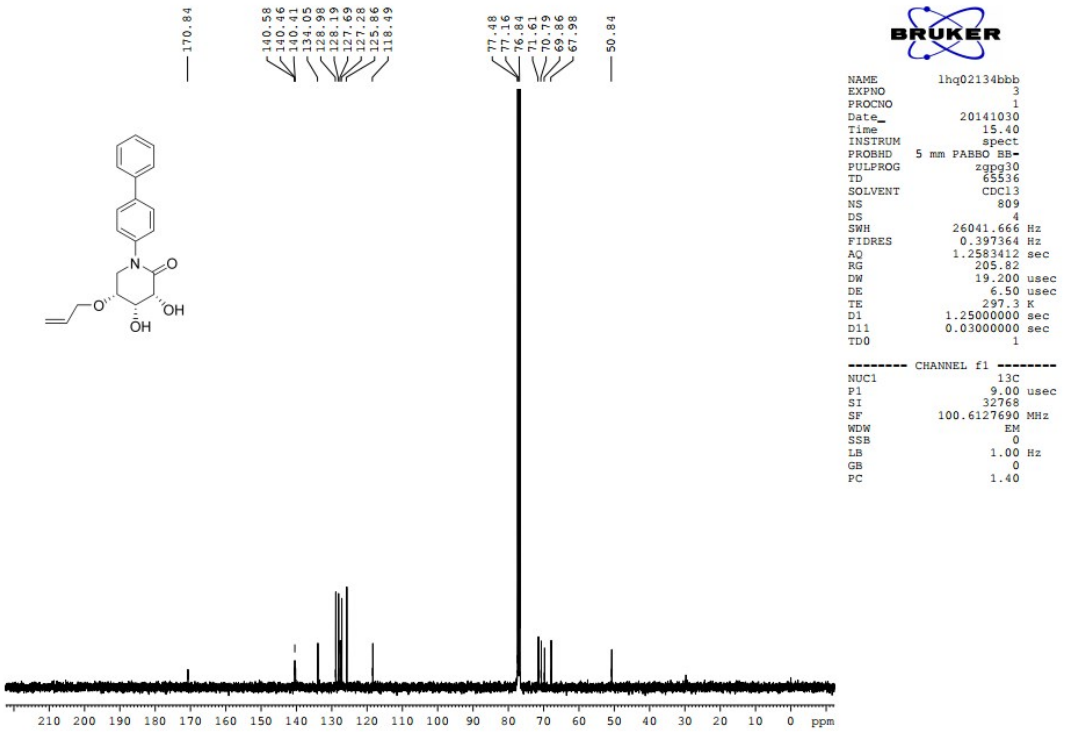
^{1}H NMR spectrum of **10**



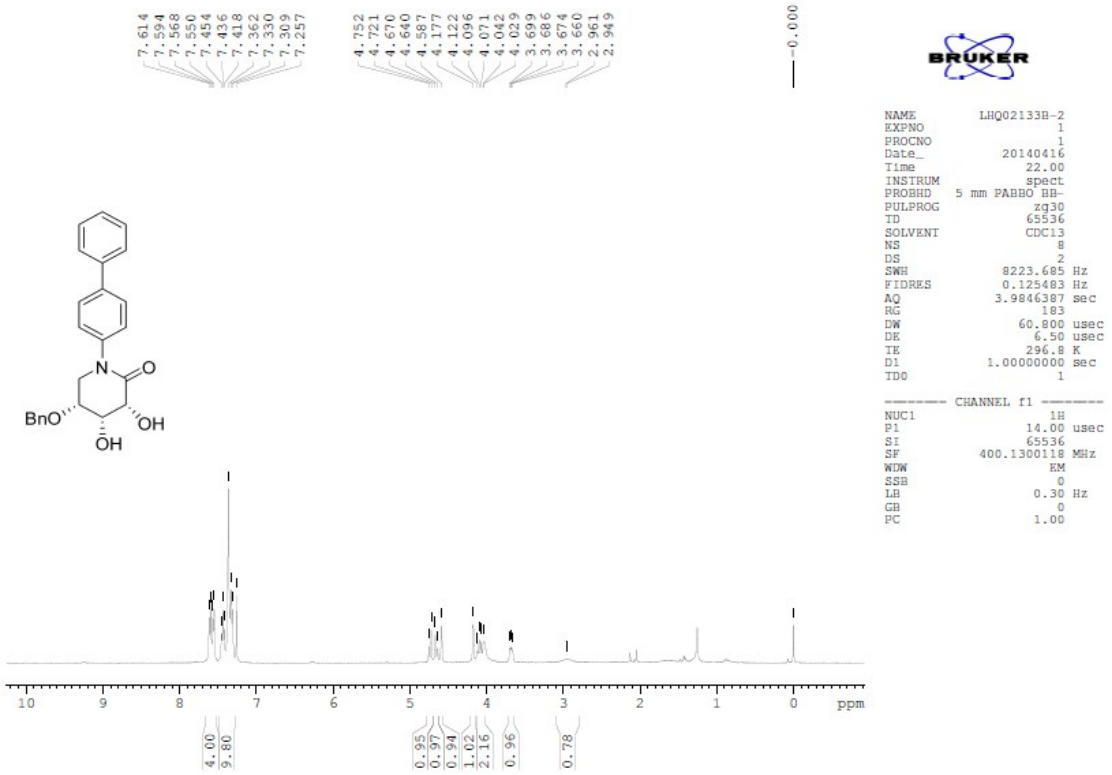
^{13}C NMR spectrum of **10**



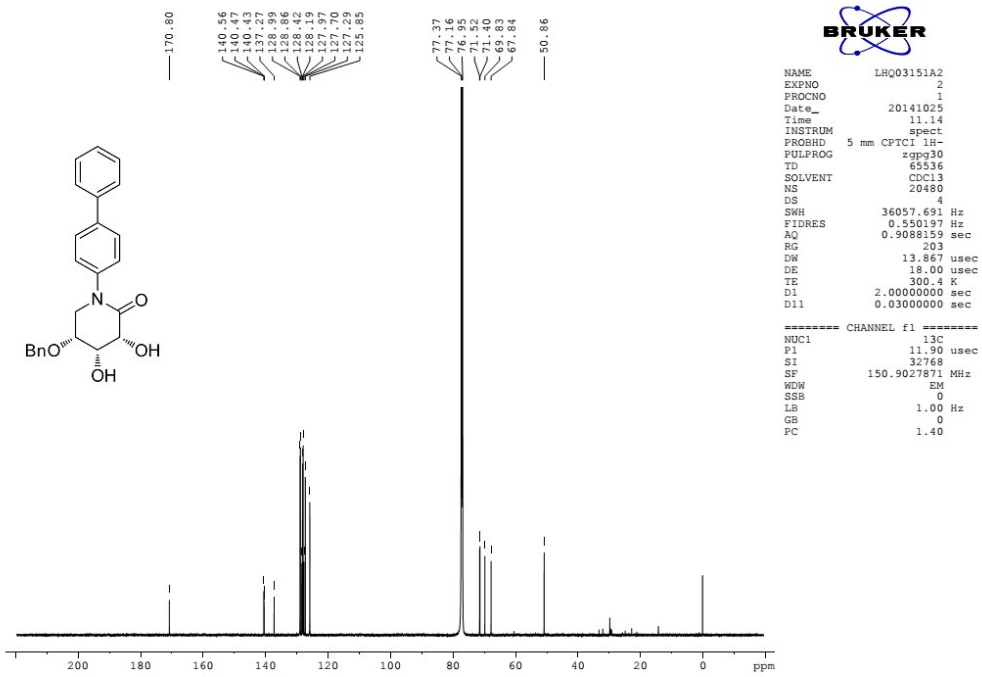
^{1}H NMR spectrum of **11**



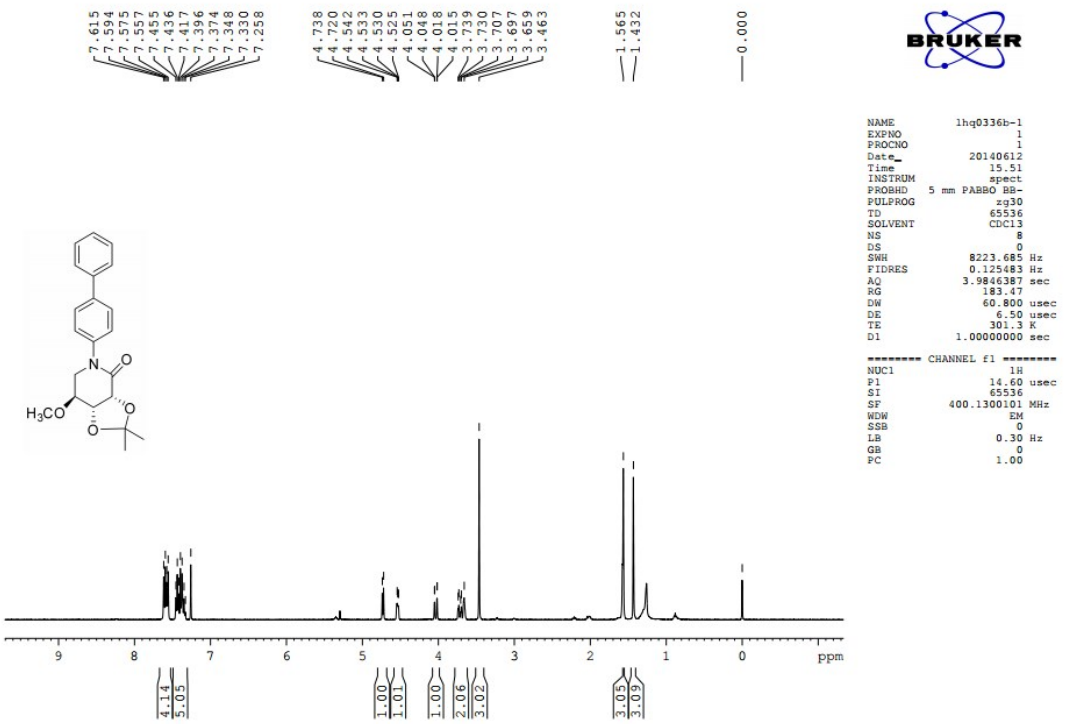
^{13}C NMR spectrum of **11**



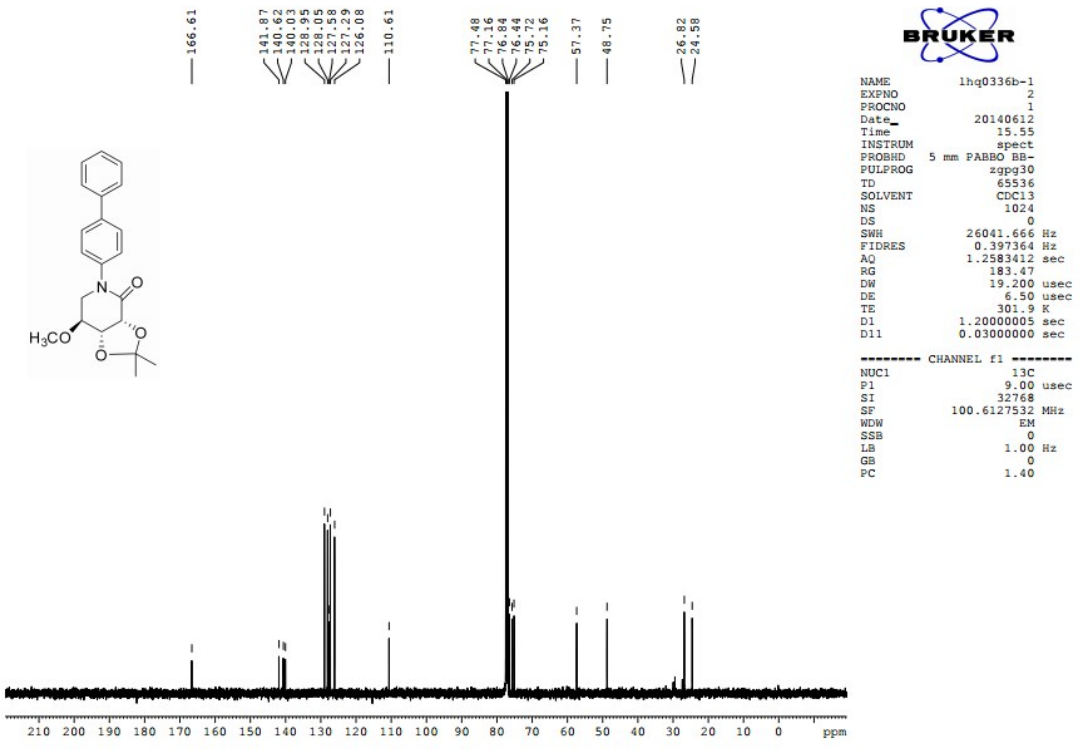
^{1}H NMR spectrum of **12**



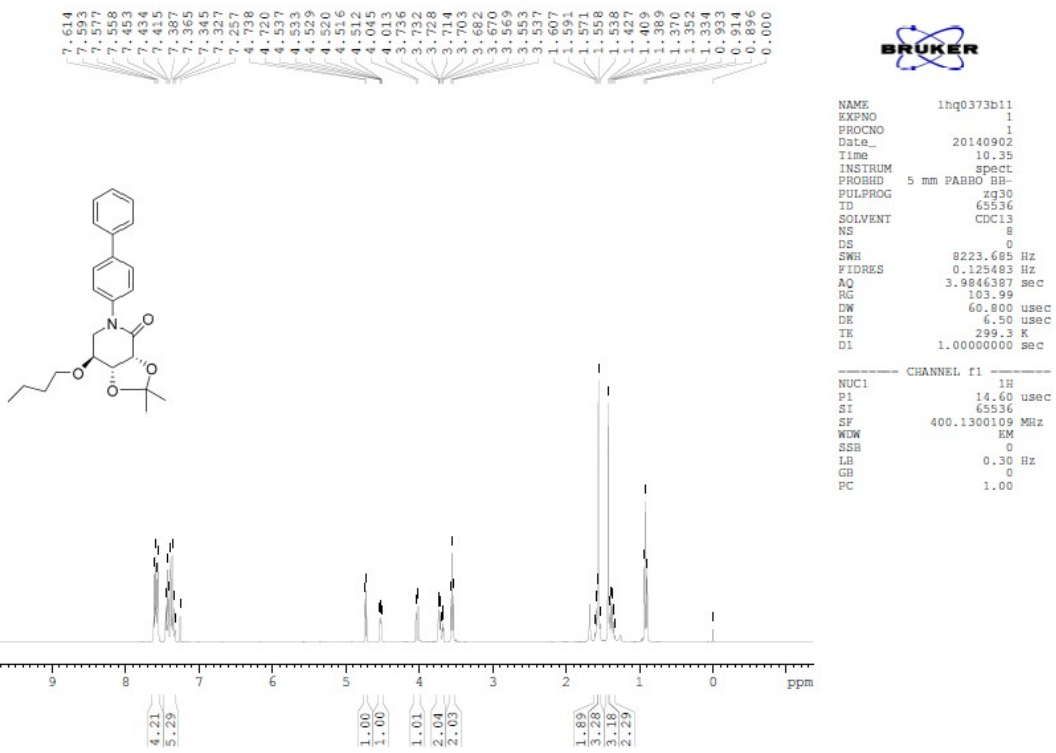
^{13}C NMR spectrum of **12**



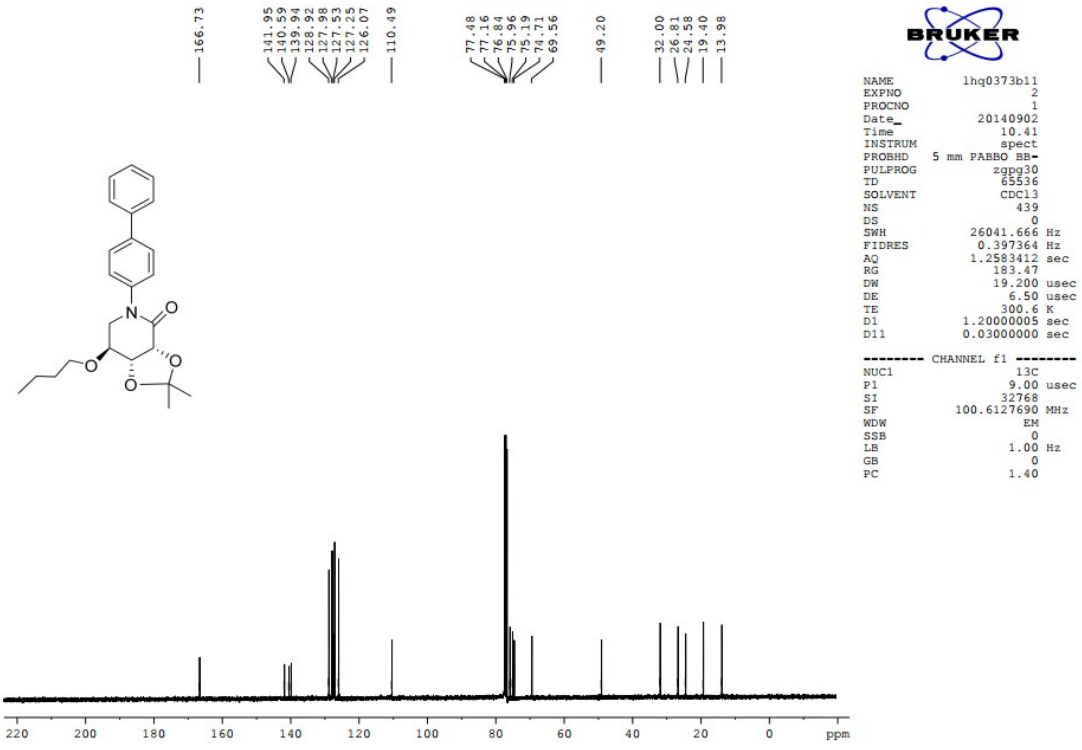
^{1}H NMR spectrum of **42**



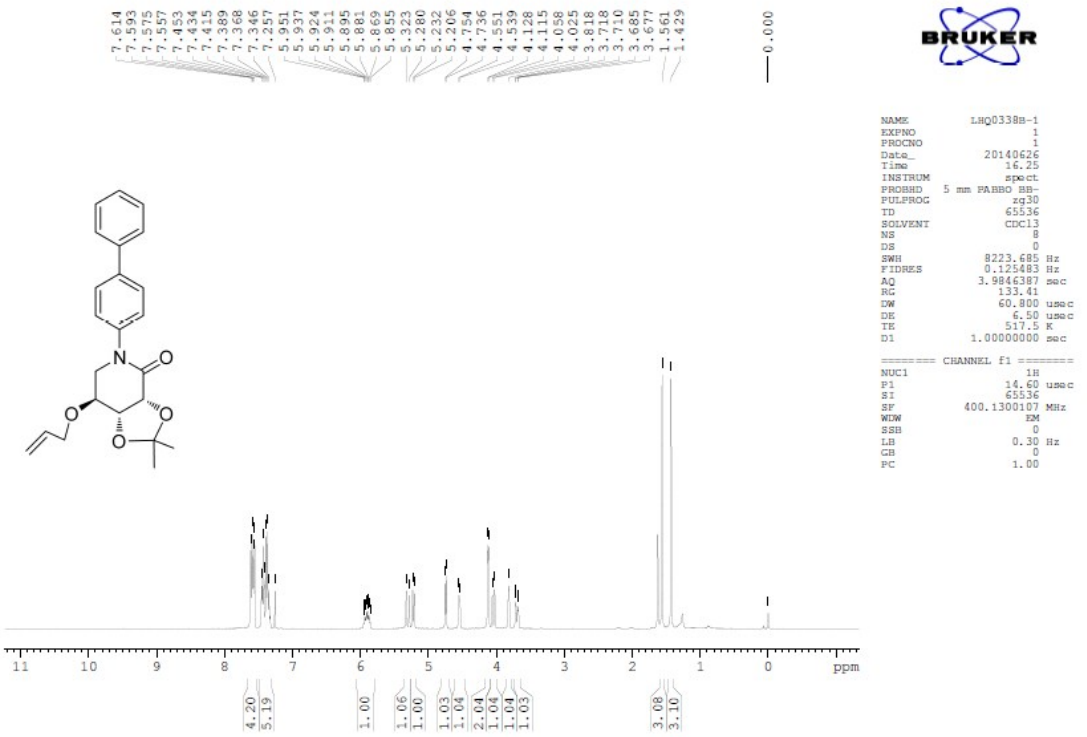
^{13}C NMR spectrum of **42**



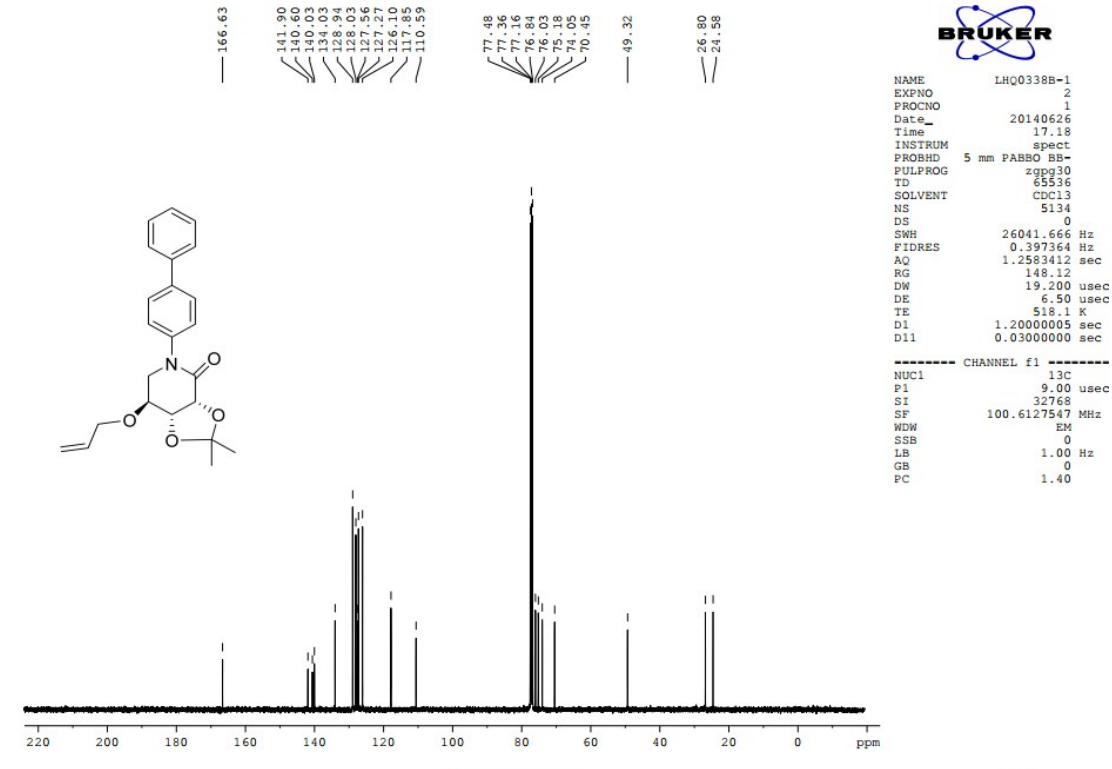
^{1}H NMR spectrum of **43**



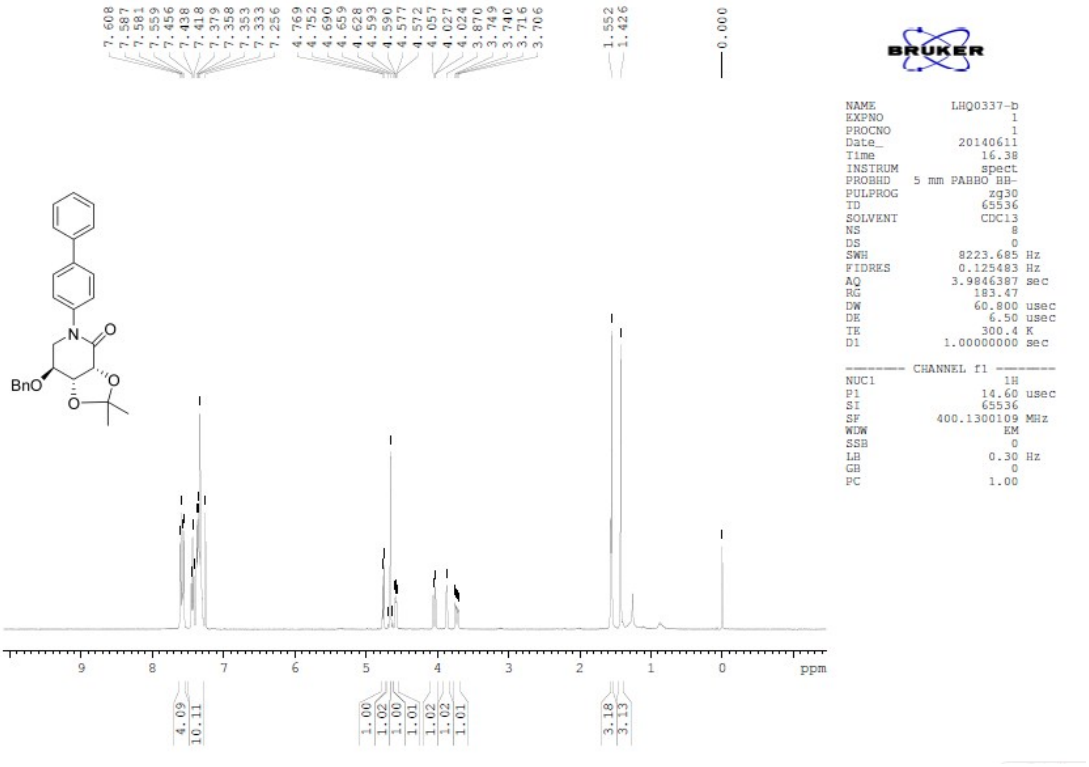
^{13}C NMR spectrum of **43**



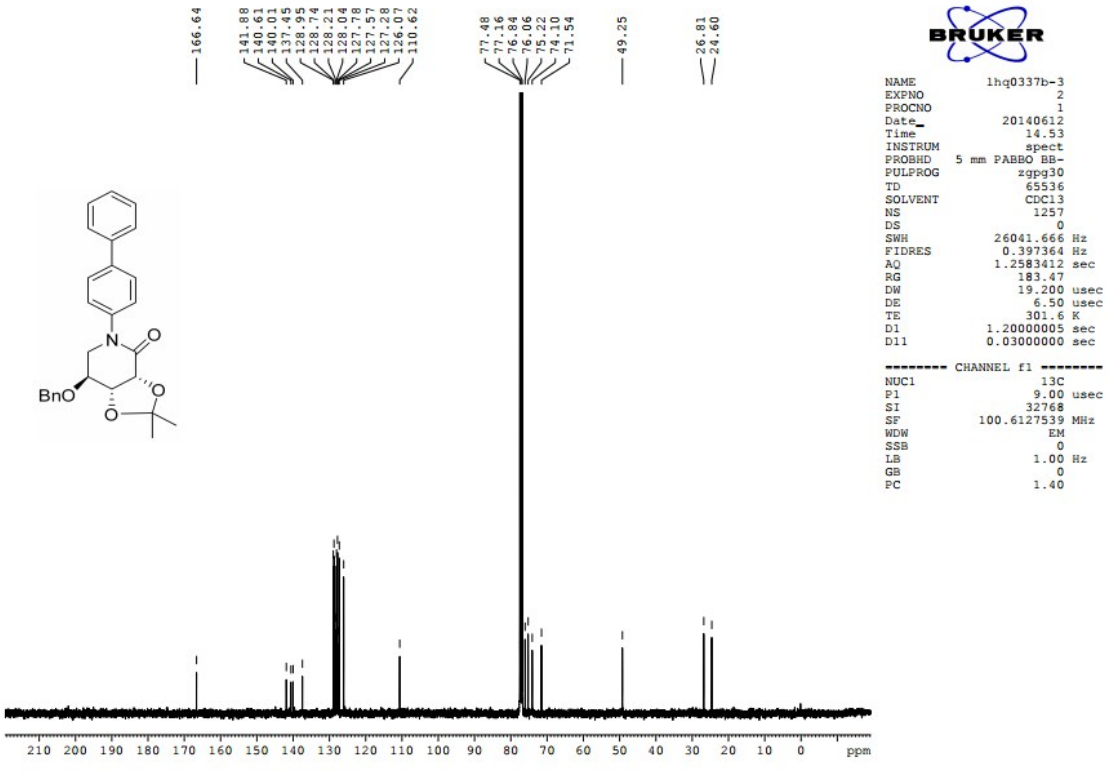
^{1}H NMR spectrum of **44**



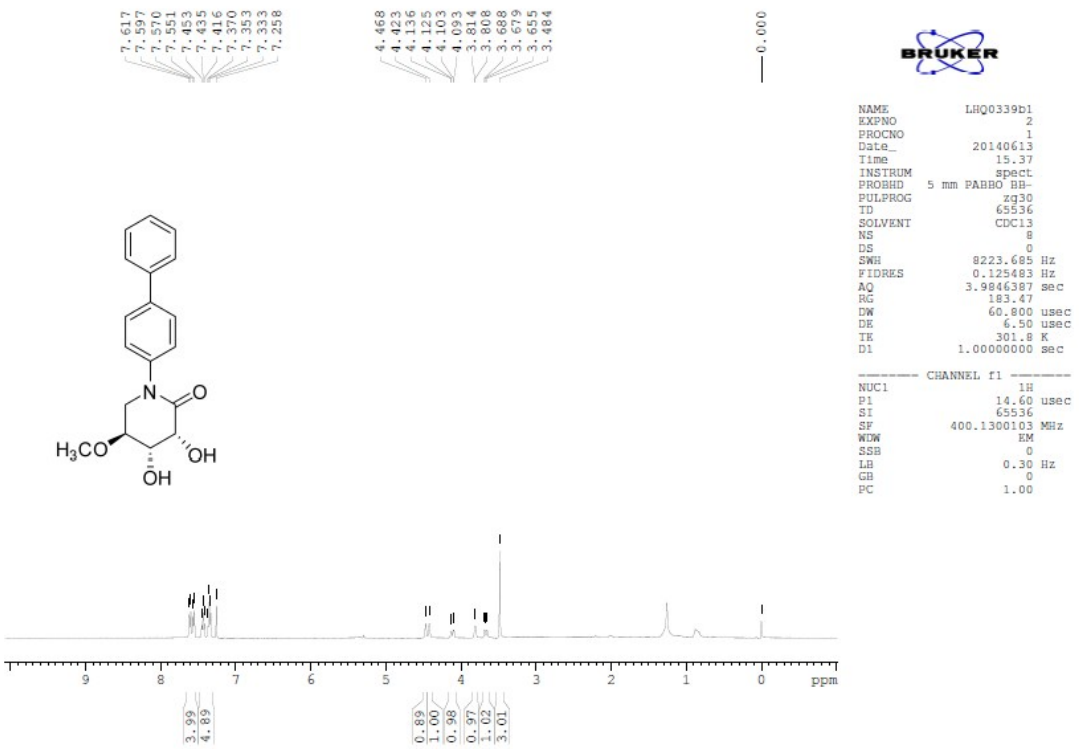
^{13}C NMR spectrum of **44**



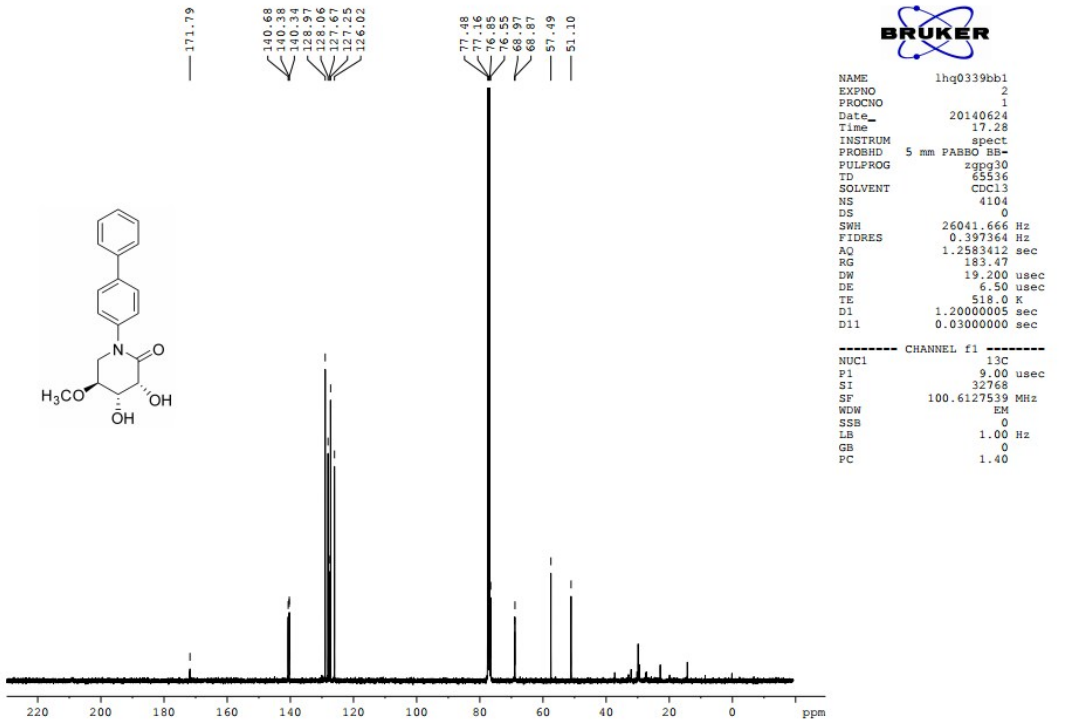
^{1}H NMR spectrum of **45**



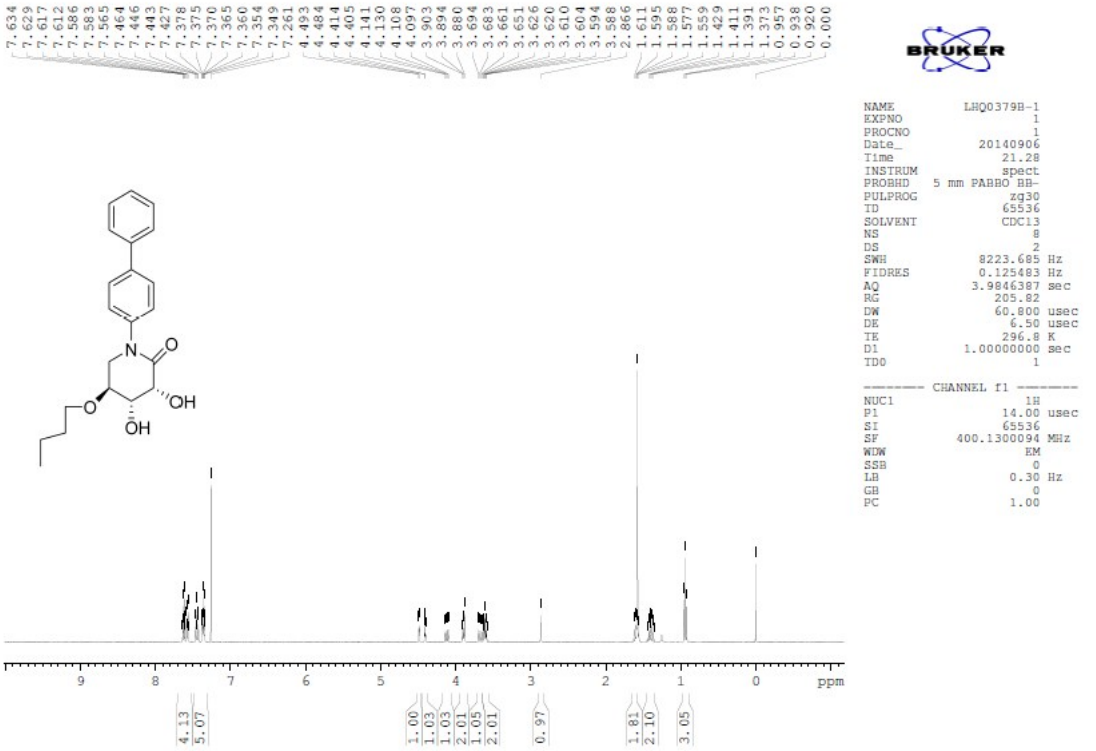
^{13}C NMR spectrum of **45**



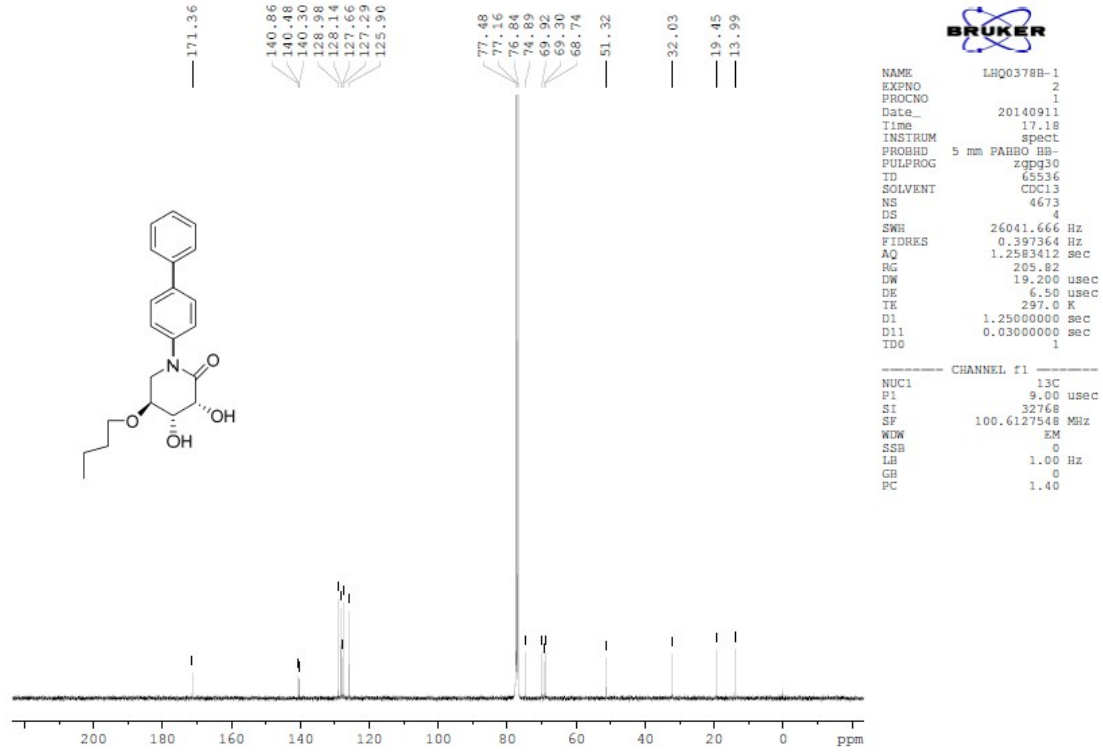
^{1}H NMR spectrum of **13**



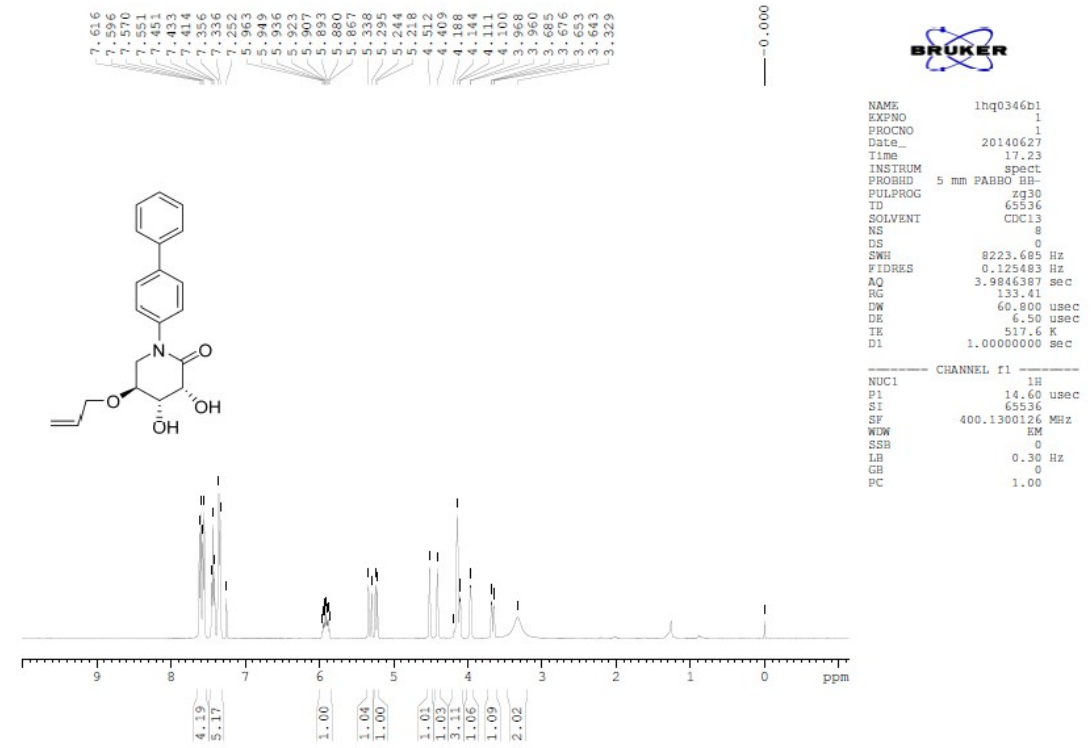
^{13}C NMR spectrum of **13**



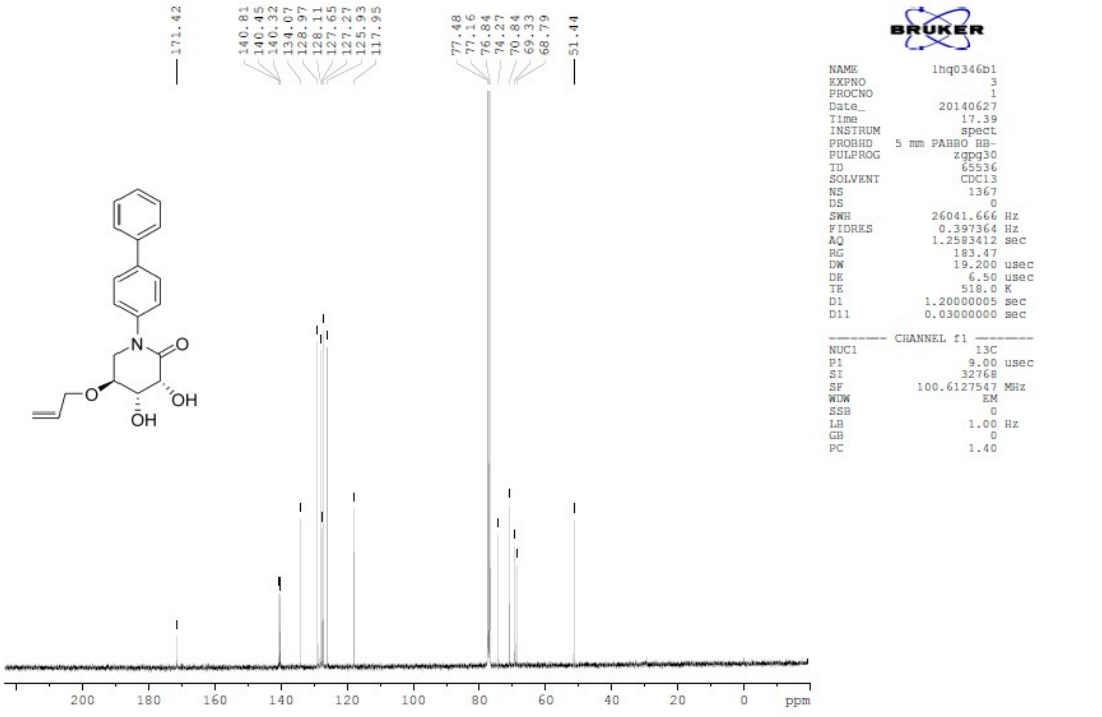
^{1}H NMR spectrum of **14**



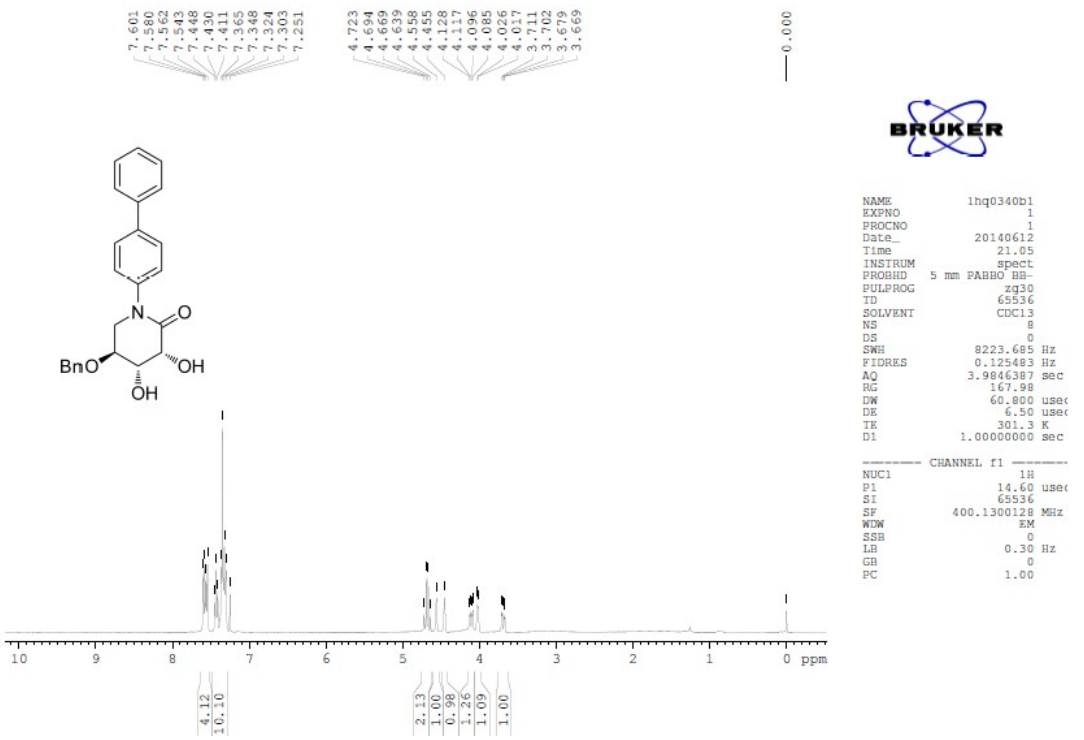
^{13}C NMR spectrum of **14**



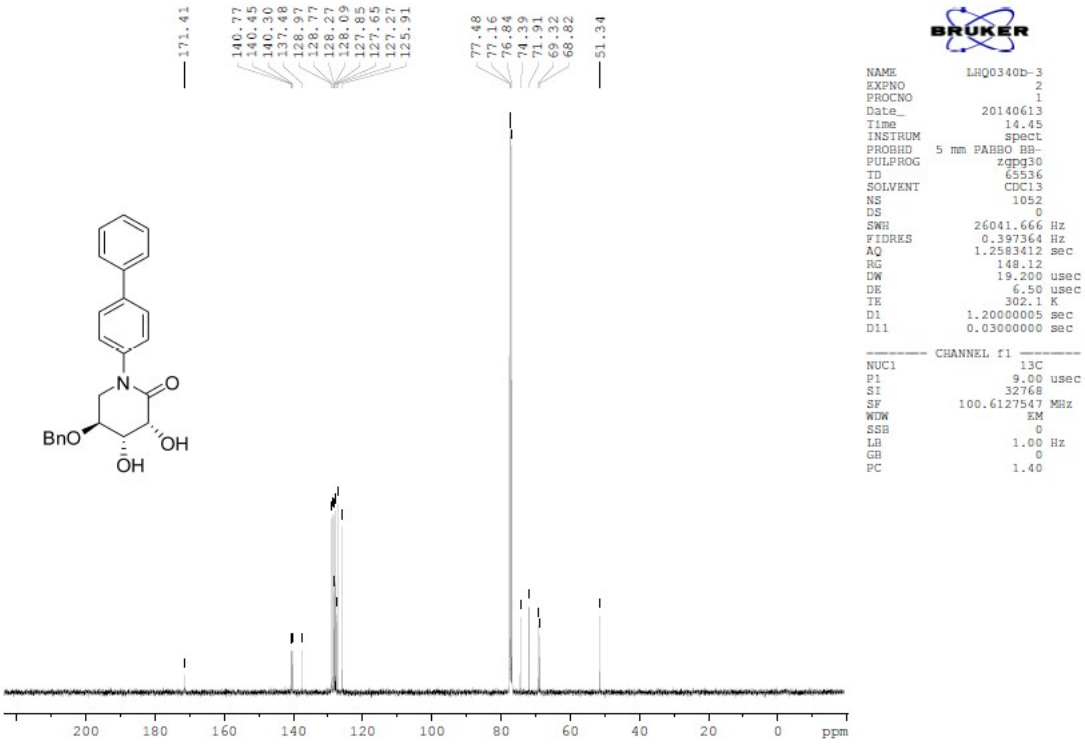
^{1}H NMR spectrum of **15**



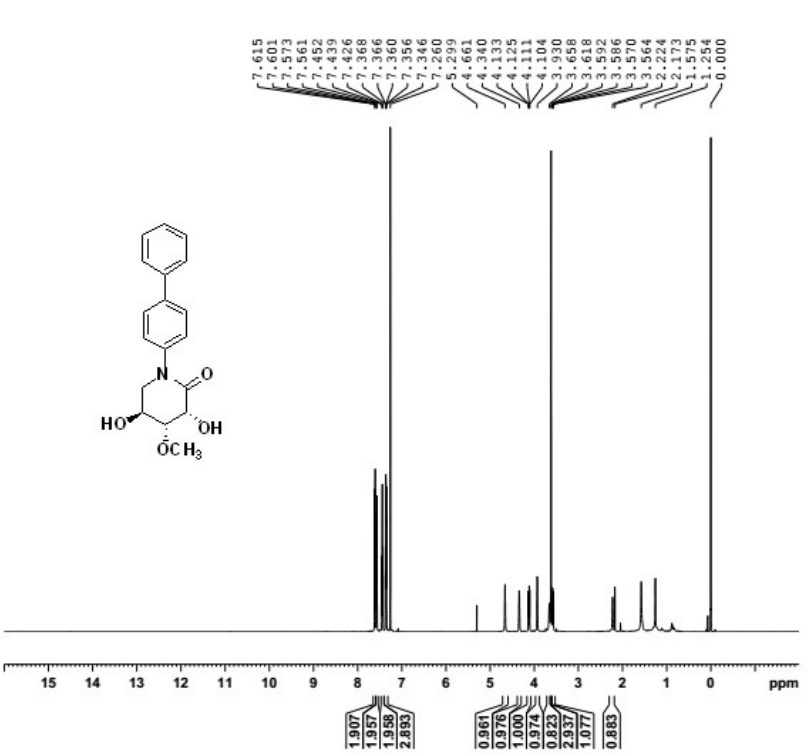
^{13}C NMR spectrum of **15**

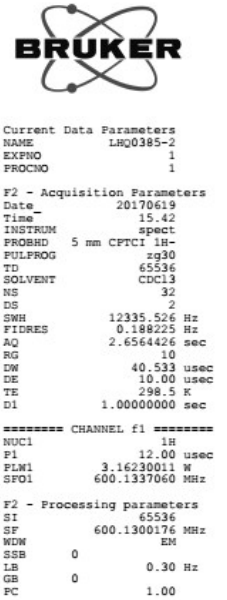


^{1}H NMR spectrum of **16**

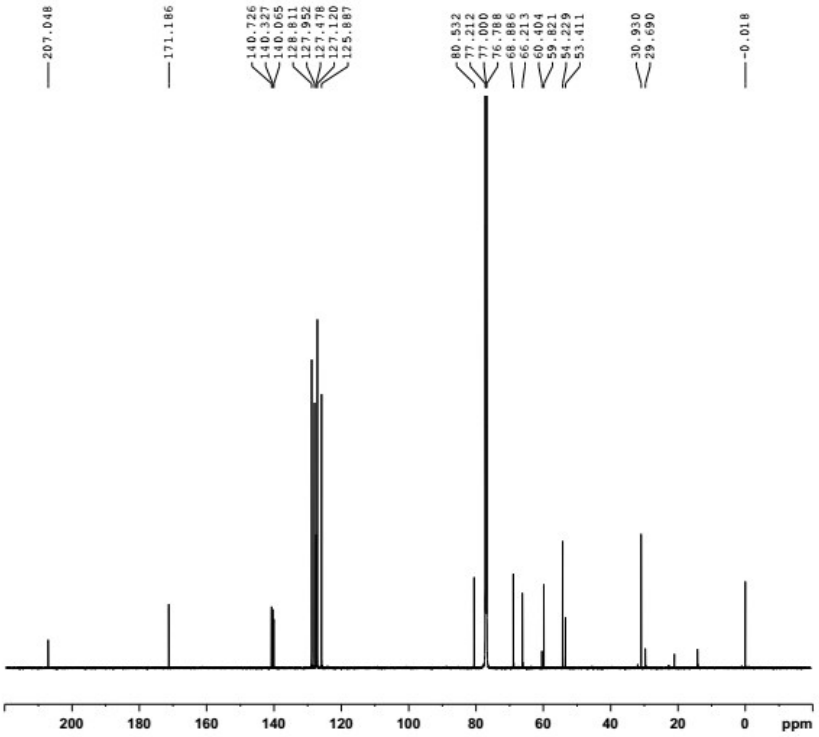


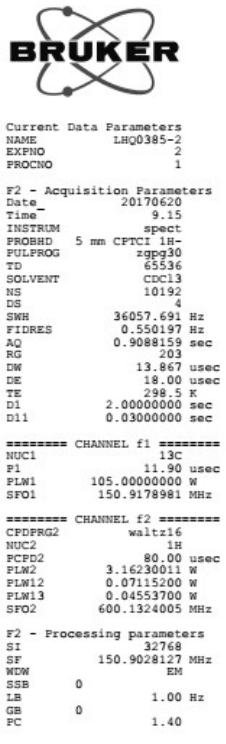
^{13}C NMR spectrum of **16**



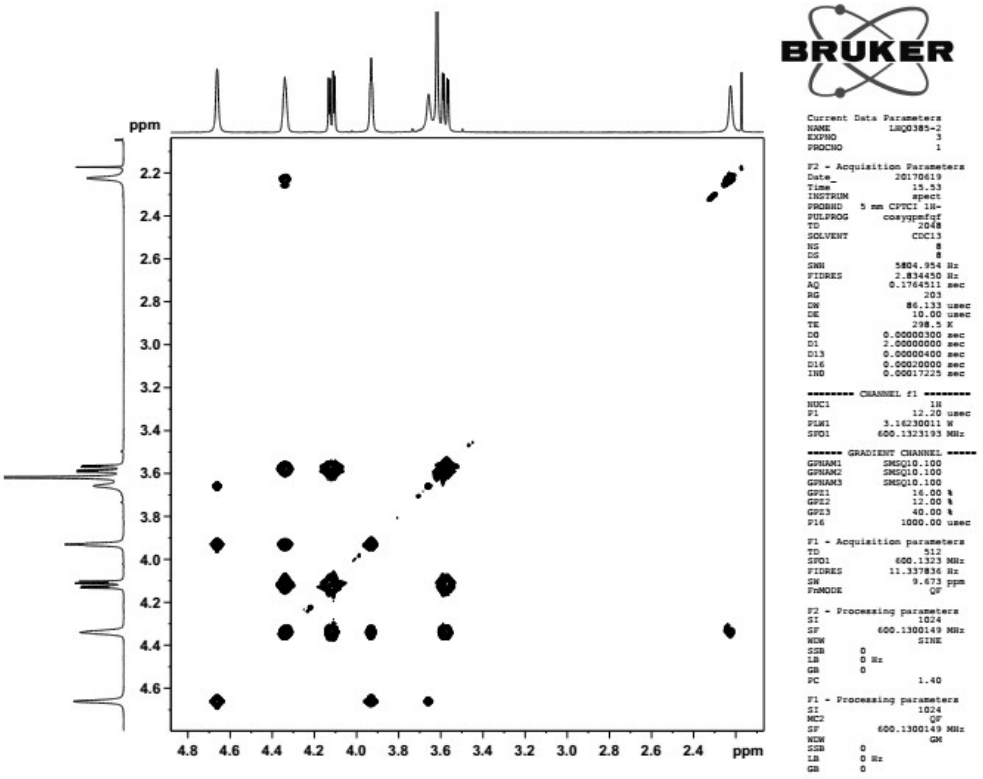


^{1}H NMR spectrum of **17**

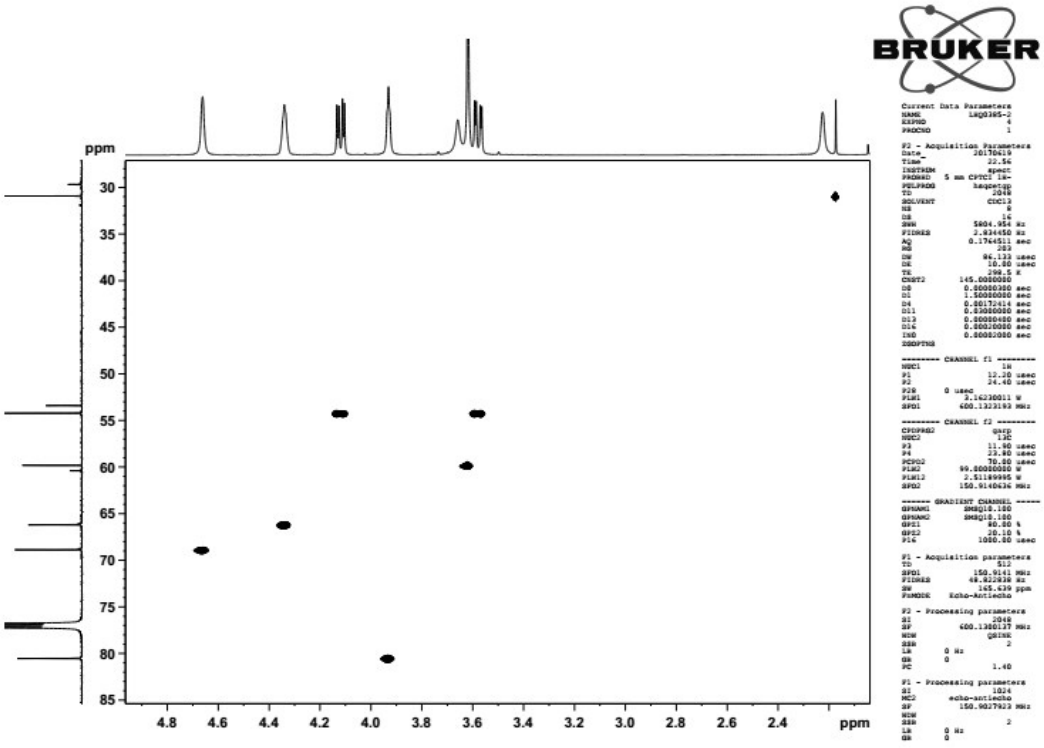




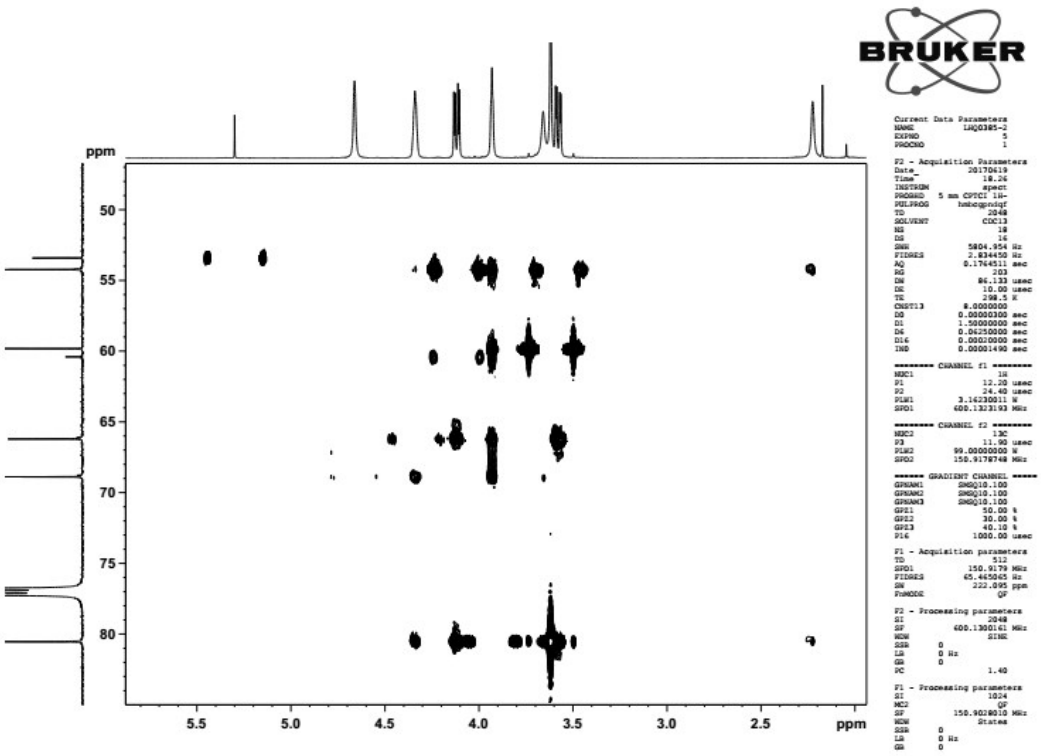
^{13}C NMR spectrum of **17**



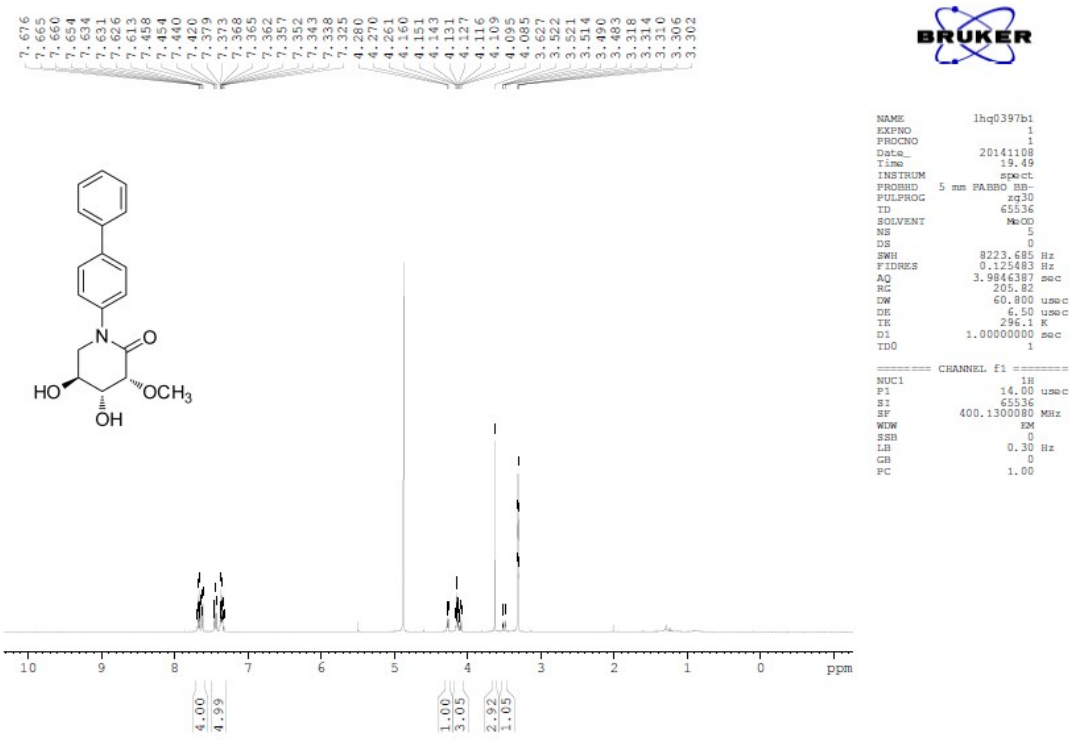
expanded ^{1}H-^{1}H COSY spectrum of **17**



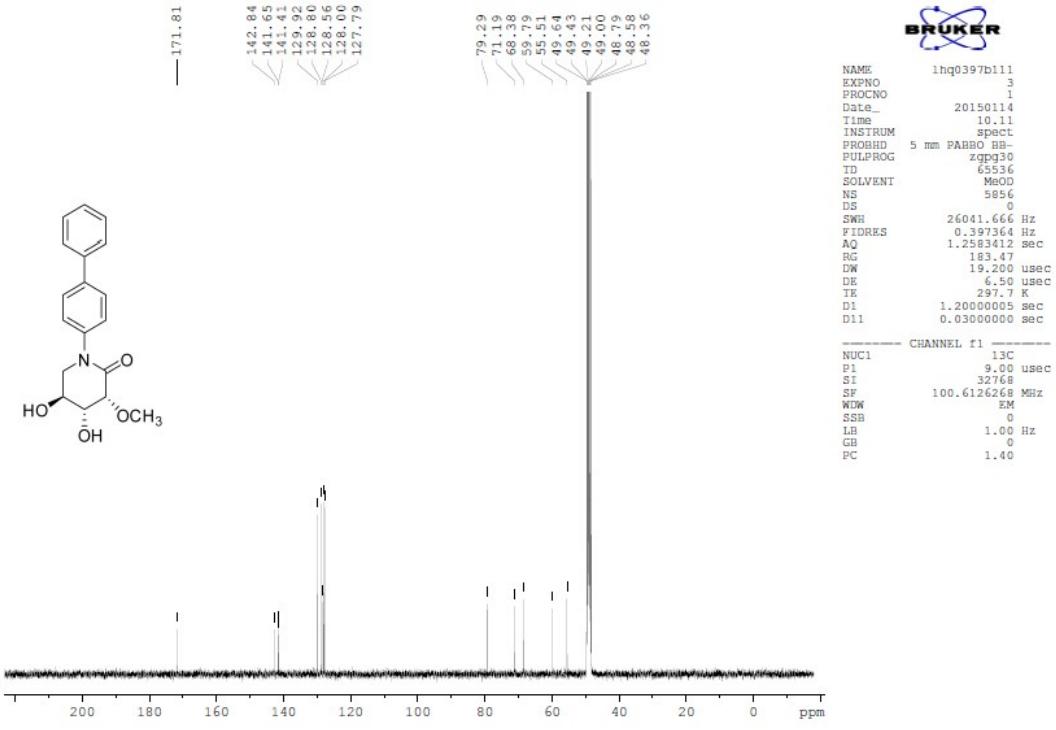
expanded HSQC spectrum of **17**



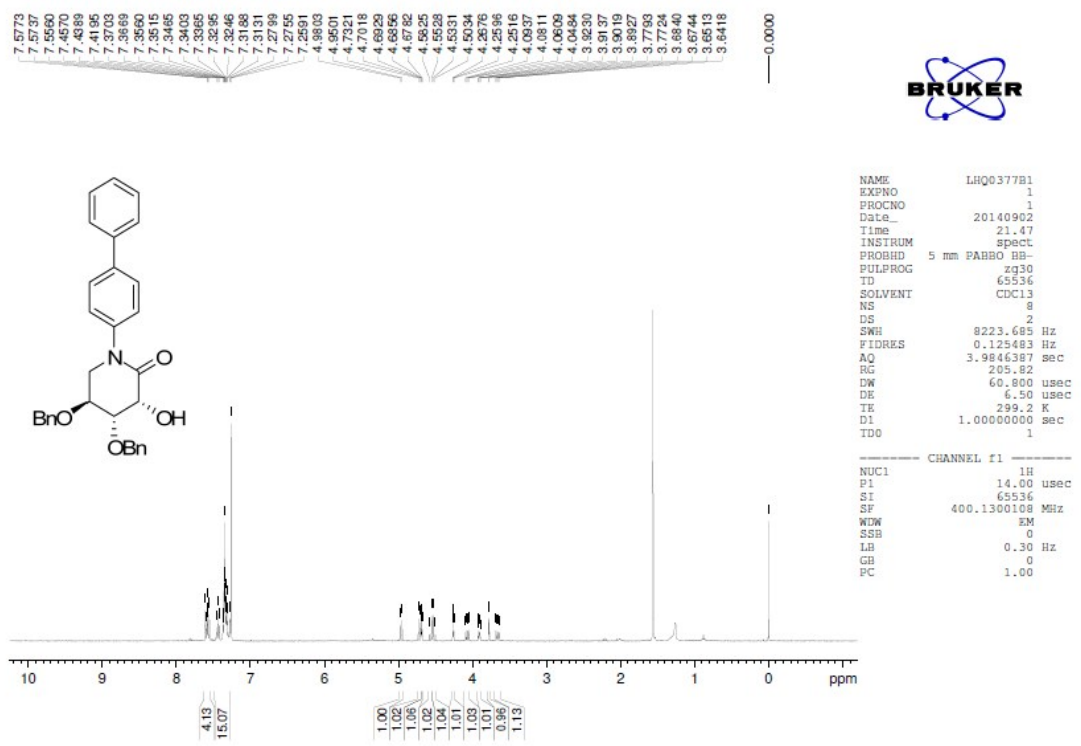
expanded HMBC spectrum of **17**



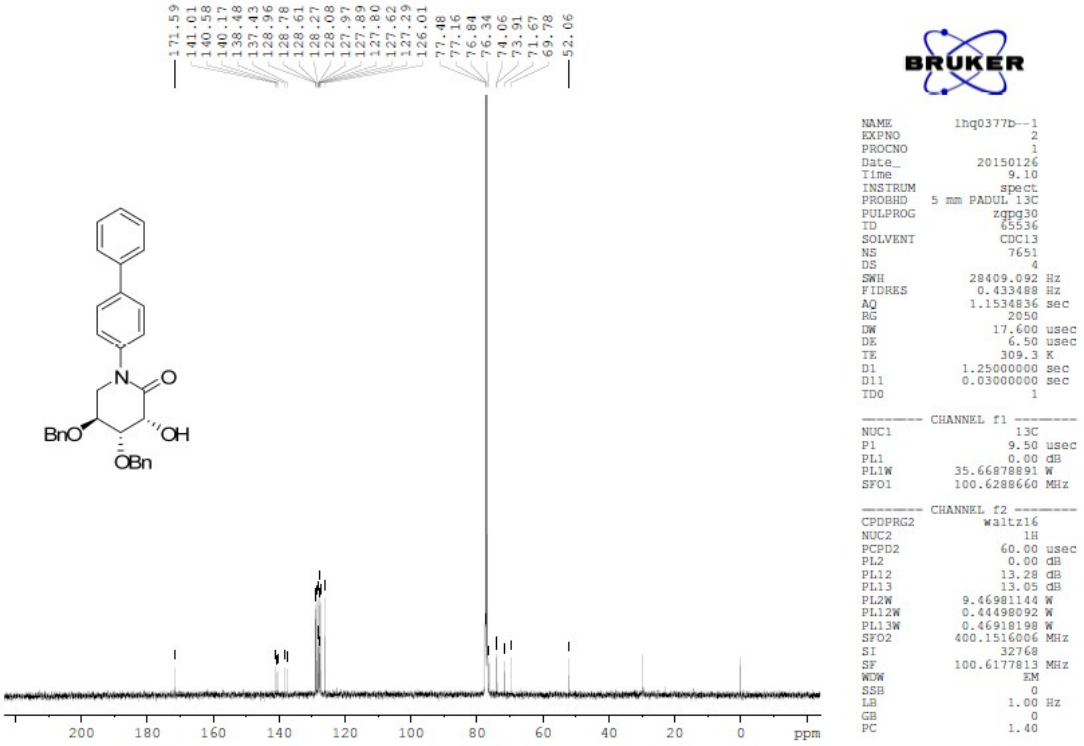
^{1}H NMR spectrum of **18**



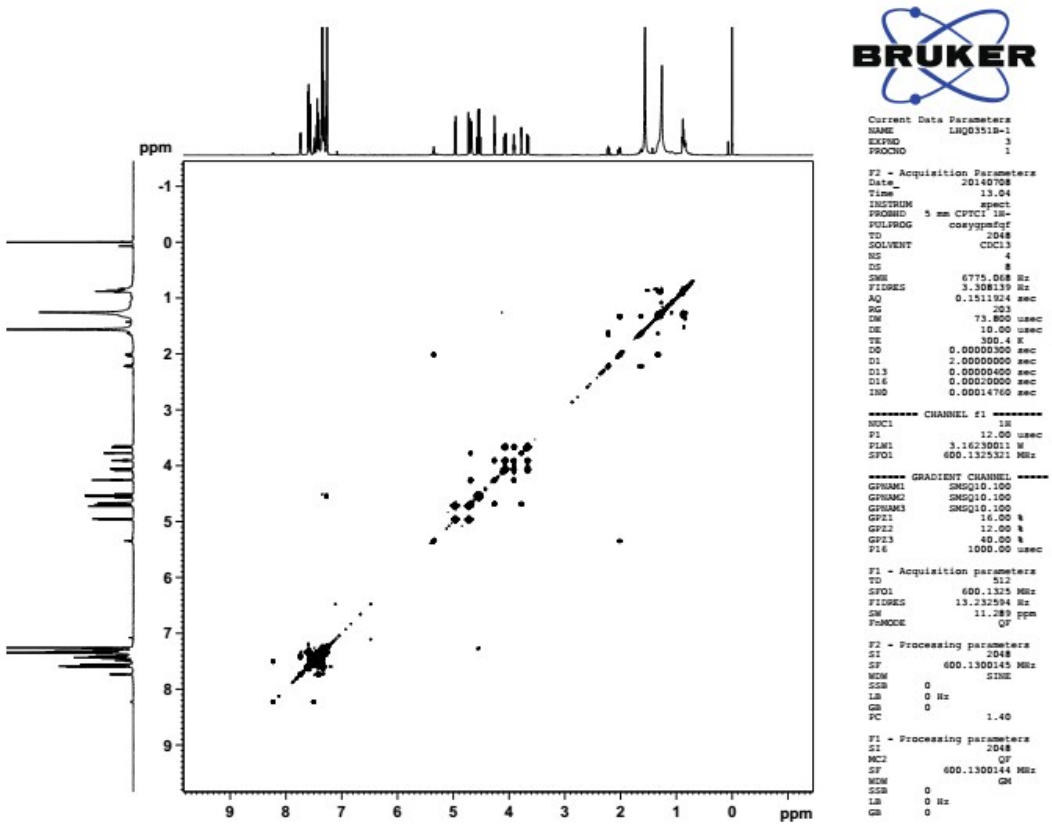
^{13}C NMR spectrum of **18**



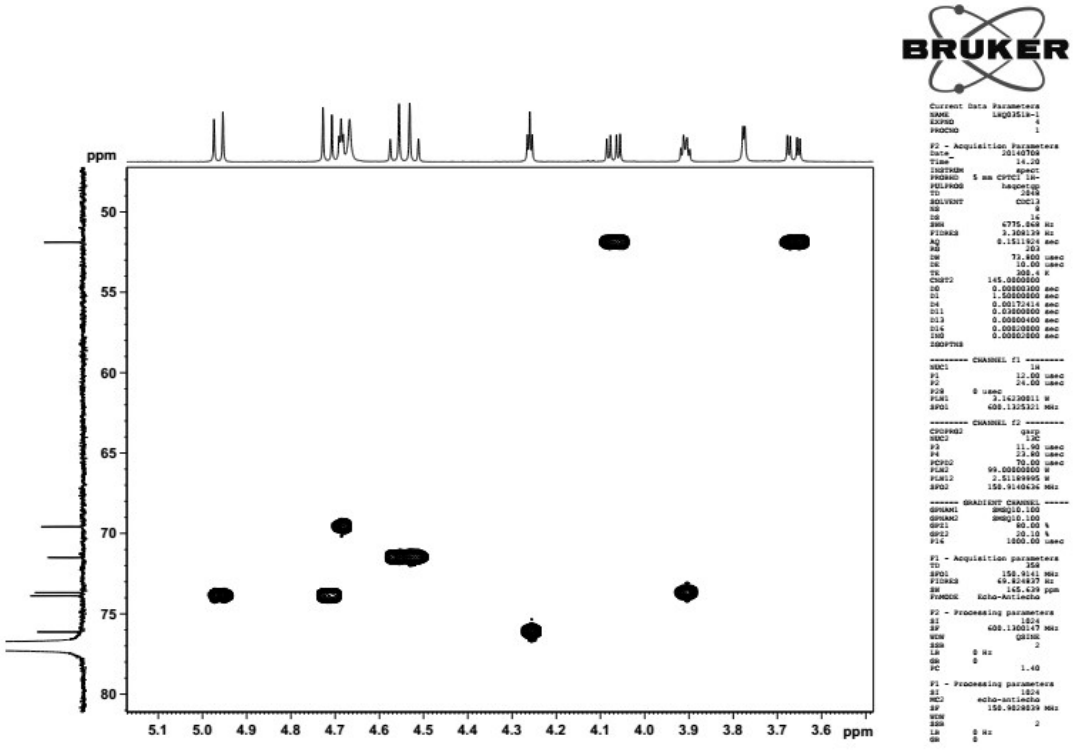
^{1}H NMR spectrum of **19**



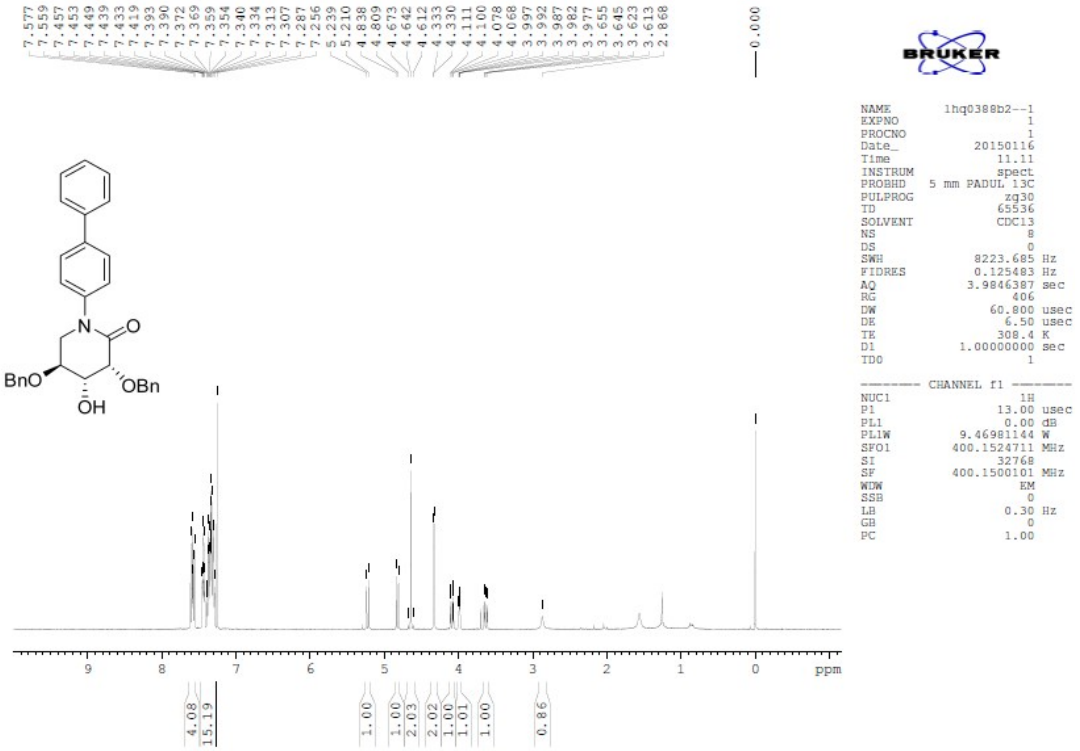
^{13}C NMR spectrum of **19**



^{1}H-^{1}H COSY spectrum of **19**



expanded HSQC spectrum of **19**



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EXPNO 1
PROCNO 1
Date_ 20150116
Time 11.11
INSTRUM spect
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TD 65536
SOLVENT CDC13
NS 8
DS 0
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 406
DW 60.800 usec
DE 6.50 usec
TE 308.4 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
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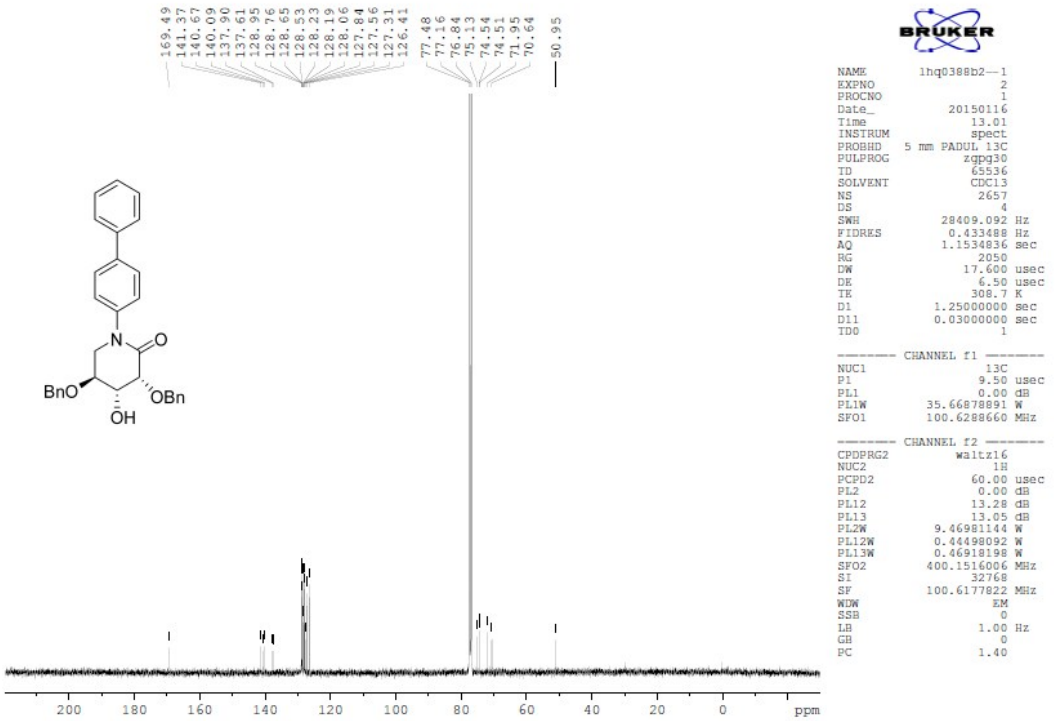
P1 13.00 usec
PL1 0.00 dB
PL1W 9.46981144 W
SFO1 400.1524711 MHz
SI 32768
SF 400.1500101 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

^{1}H NMR spectrum of **20**



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PROCNO 1
Date_ 20150116
Time 13.01
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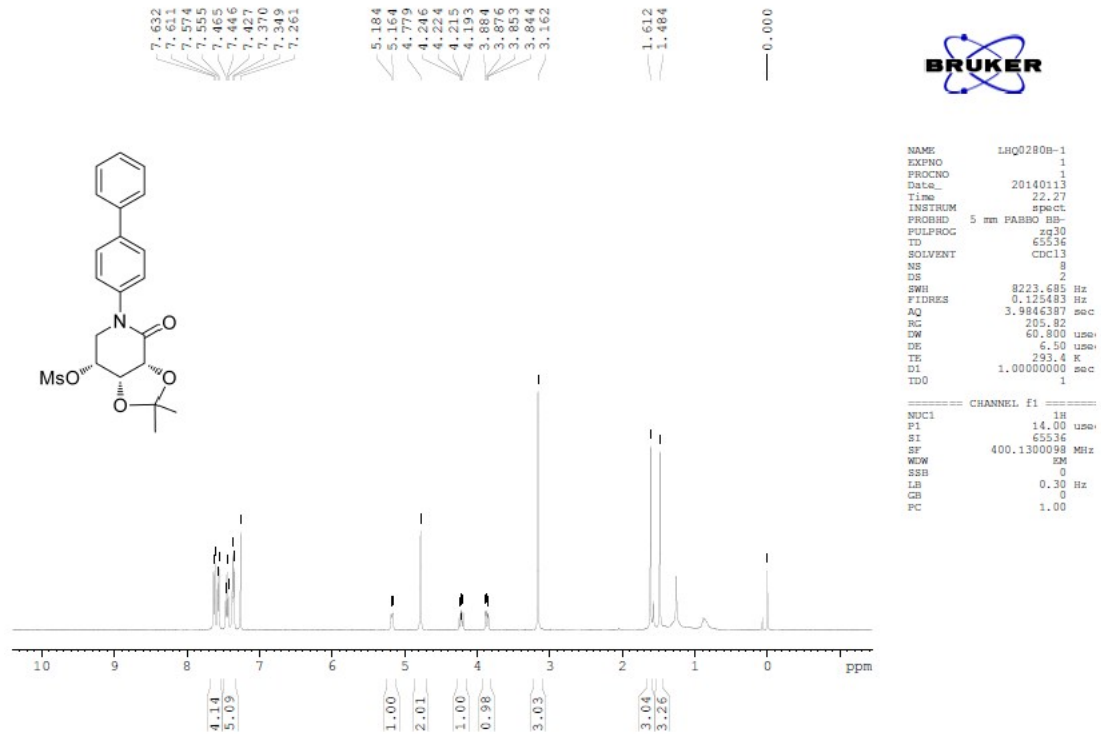
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 2657
DS 4
SWH 28409.092 Hz
FIDRES 0.433488 Hz
AQ 1.1534836 sec
RG 2050
DW 17.600 usec
DE 6.50 usec
TE 308.7 K
D1 1.25000000 sec
D11 0.03000000 sec
TD0 1

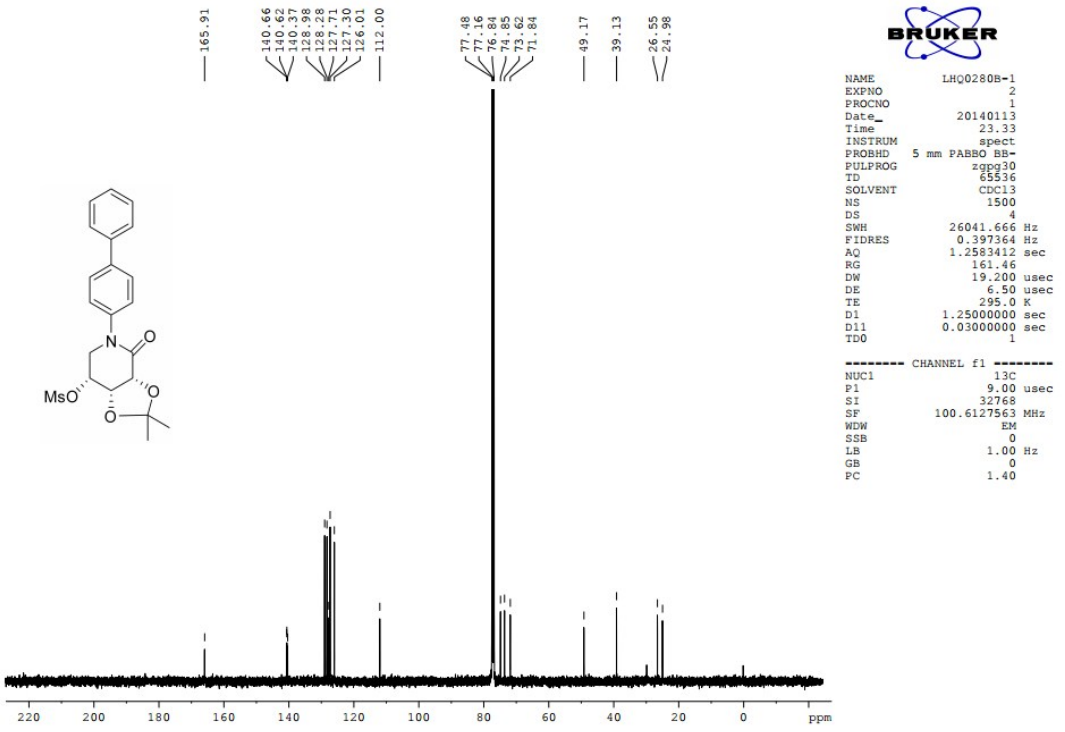
======== CHANNEL f1 ========
NUC1 13C
P1 9.50 usec
PL1 0.00 dB
PL1W 35.66878891 W
SFO1 100.6288660 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 60.00 usec
PL2 0.00 dB
PL12 13.28 dB
PL13 13.05 dB
PL2W 9.46981144 W
PL12W 0.44198092 W
PL13W 0.46918198 W
SFO2 400.1516006 MHz
SI 32768
SF 100.6177822 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

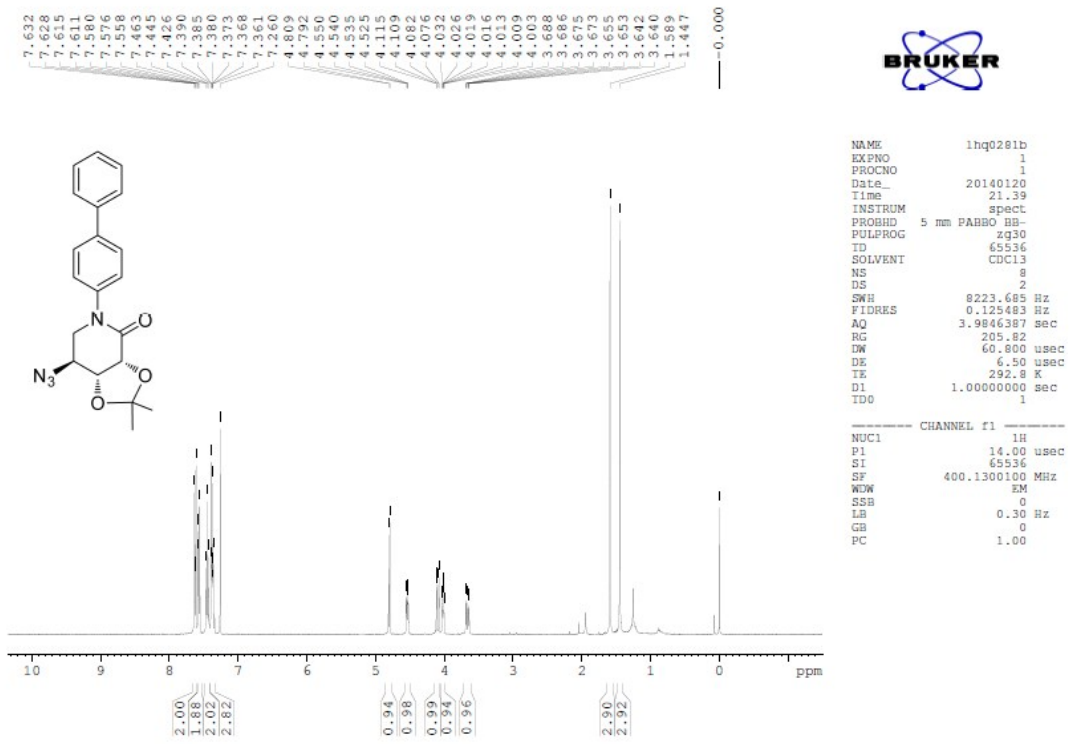
^{13}C NMR spectrum of **20**



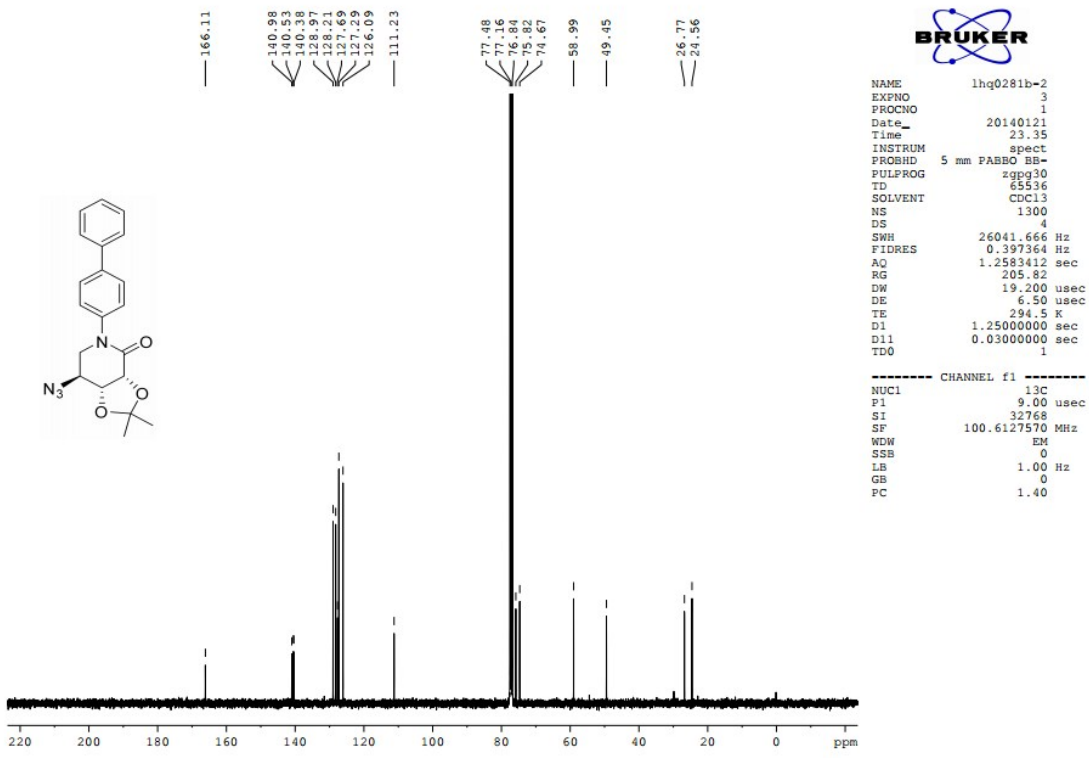
^{1}H NMR spectrum of **46**



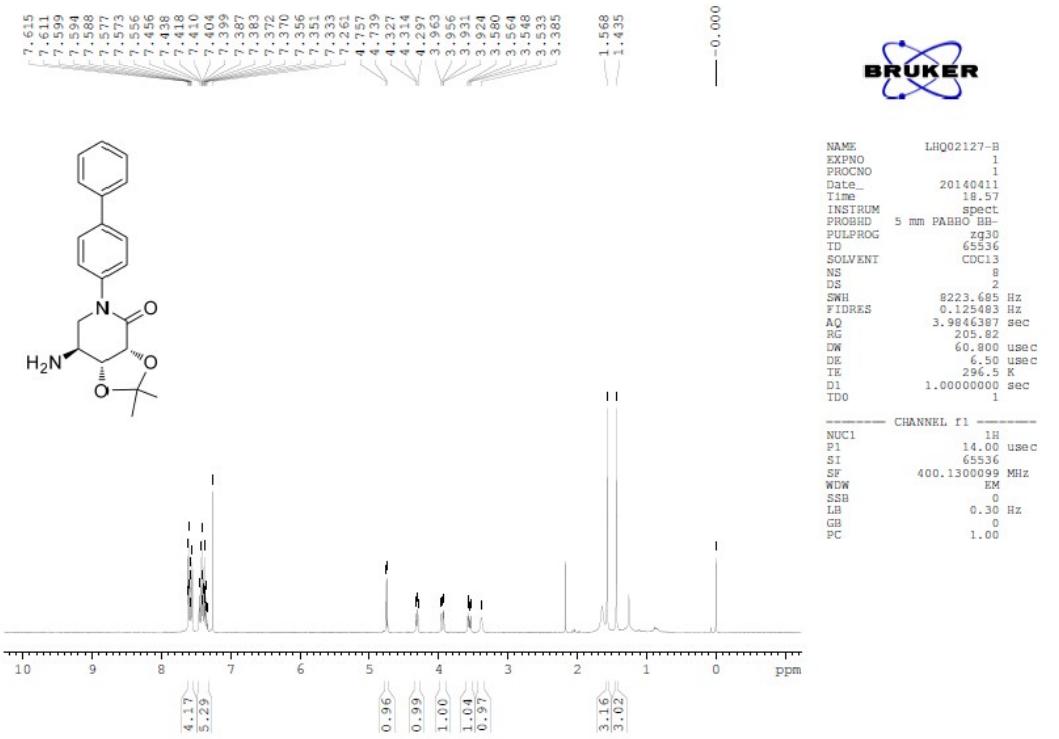
^{13}C NMR spectrum of **46**



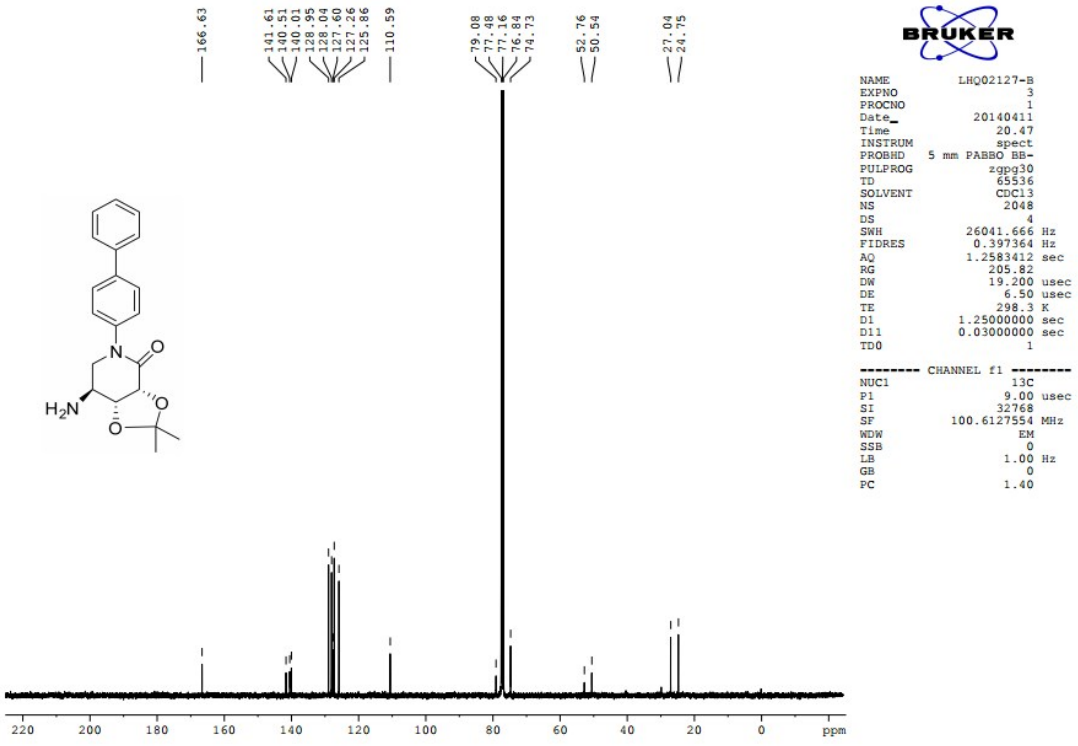
^{1}H NMR spectrum of **47**



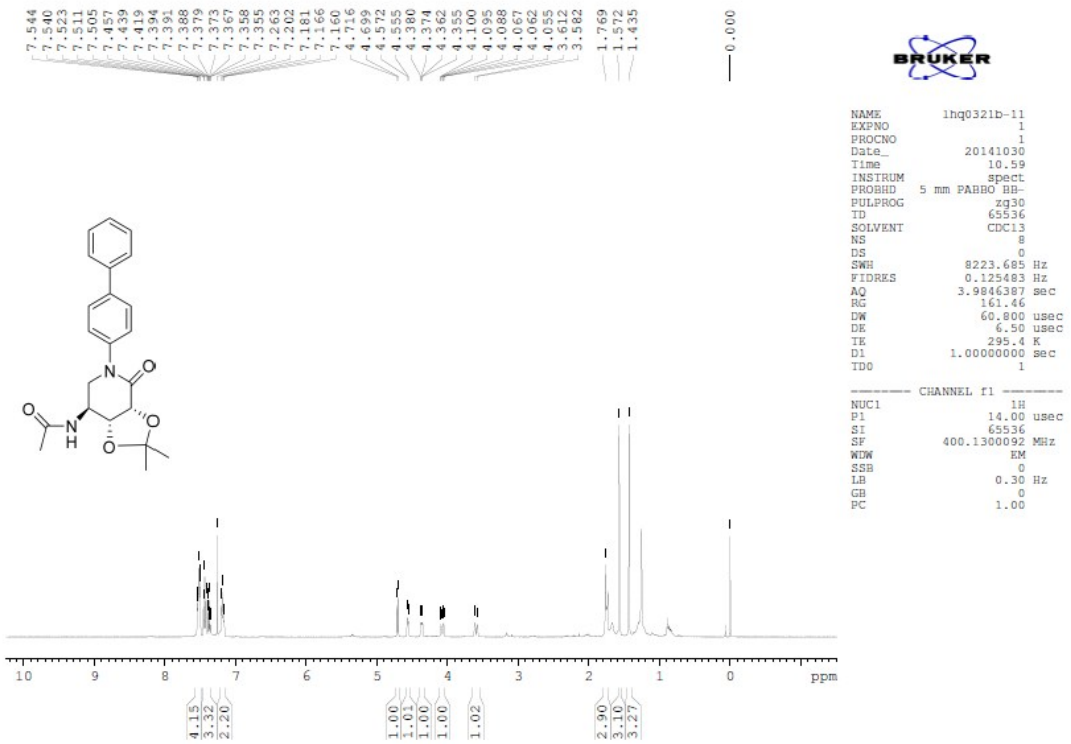
^{13}C NMR spectrum of **47**



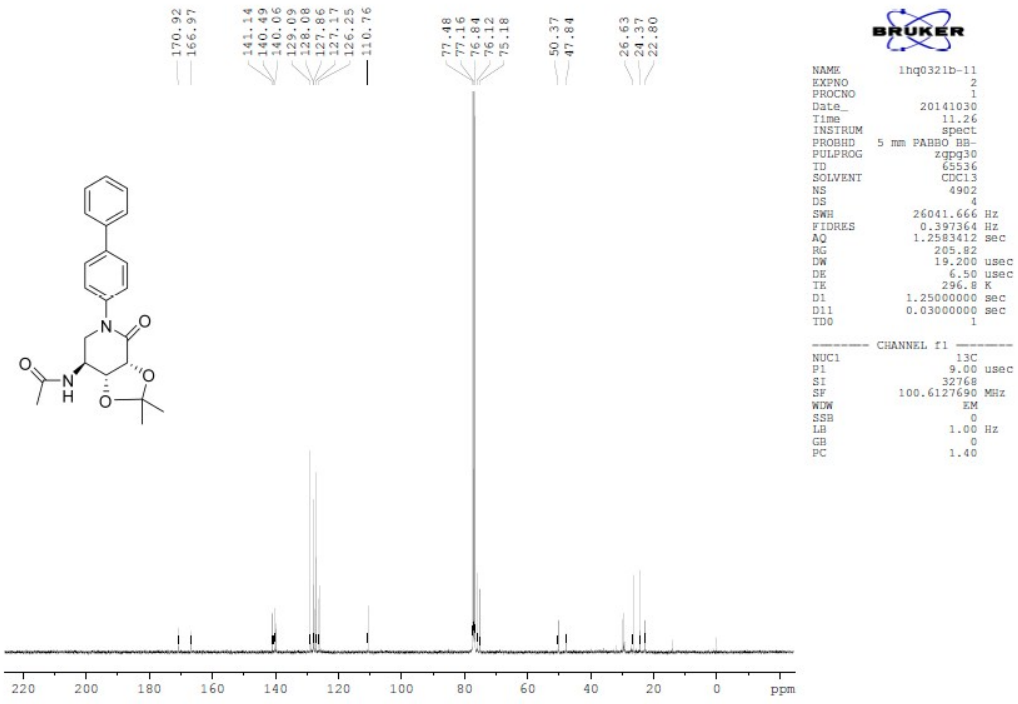
^{1}H NMR spectrum of **48**



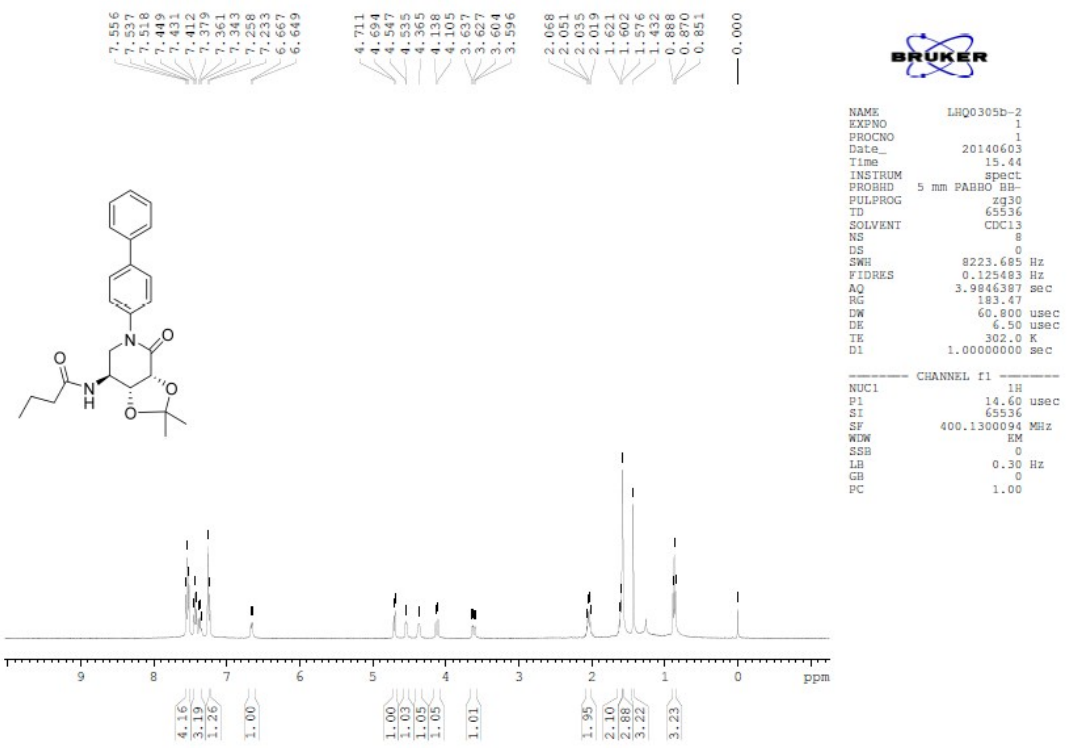
^{13}C NMR spectrum of **48**



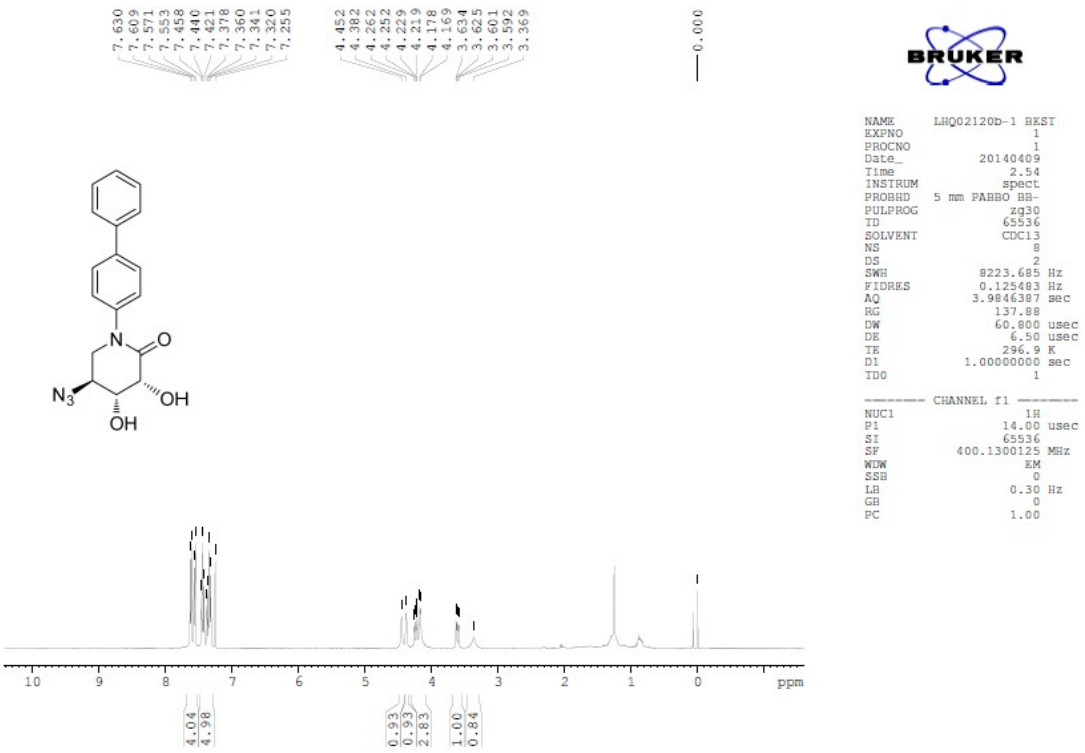
^{1}H NMR spectrum of **49**



^{13}C NMR spectrum of **49**



^{1}H NMR spectrum of **50**

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PROCNO              1
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Time             2.54
INSTRUM         spect
PROBHD   5 mm PABBO BB-
PULPROG          zg30
TD              65536
SOLVENT          CDC13
NS                  8
DS                  2
SWH           8223.685 Hz
FIDRES        0.125483 Hz
AQ            3.9846387 sec
RG              137.88
DW               60.800 usec
DE                6.50 usec
TE               296.9 K
D1           1.00000000 sec
TD0                 1

======== CHANNEL f1 ========
NUC1               1H
P1              14.00 usec
SI              65536
SF         400.1300125 MHz
WDW               EM
SSB                0
LB              0.30 Hz
GB                 0
PC              1.00
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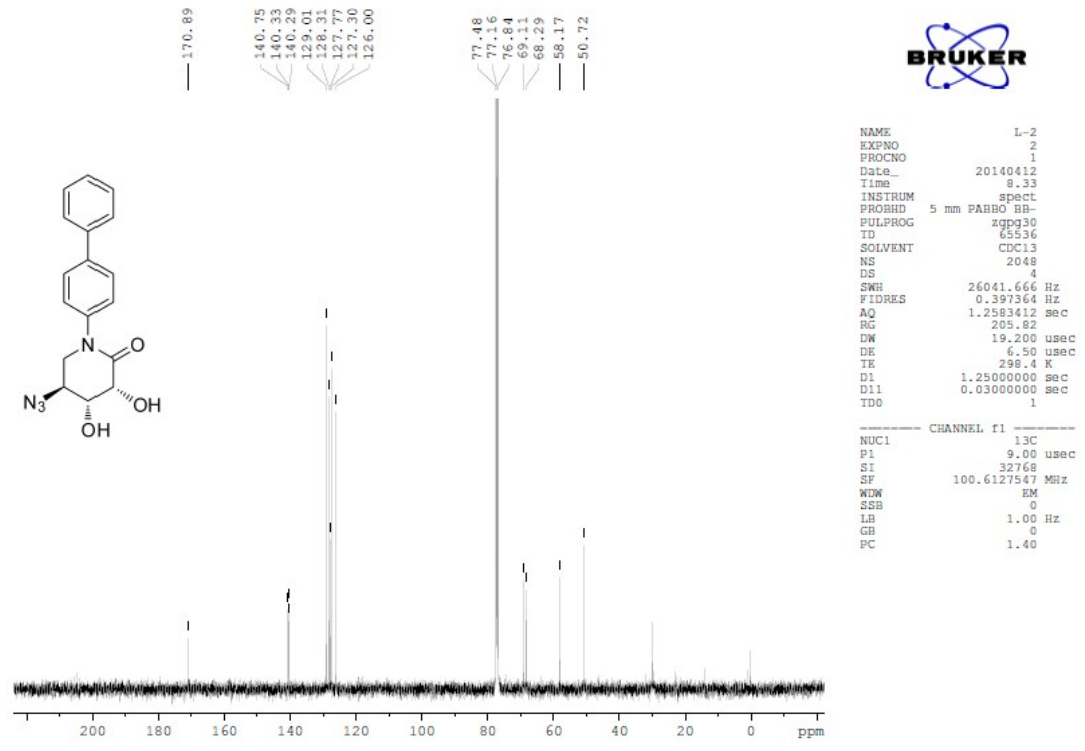
^{1}H NMR spectrum of **21**

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PROCNO              1
Date_        20140412
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TD              65536
SOLVENT          CDC13
NS               2048
DS                  4
SWH          26041.666 Hz
FIDRES        0.397364 Hz
AQ            1.2583412 sec
RG              205.82
DW               19.200 usec
DE                6.50 usec
TE               298.4 K
D1           1.25000000 sec
D11          0.03000000 sec
TD0                 1

======== CHANNEL f1 ========
NUC1               13C
P1               9.00 usec
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SSB                0
LB              1.00 Hz
GB                 0
PC              1.40
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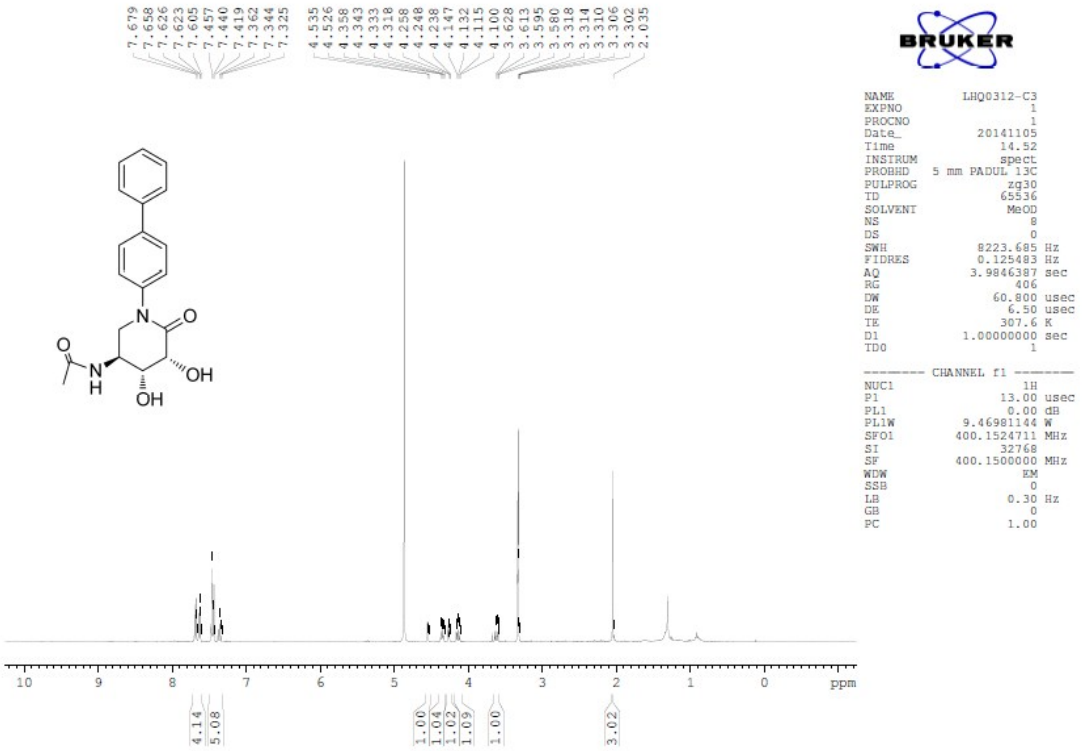
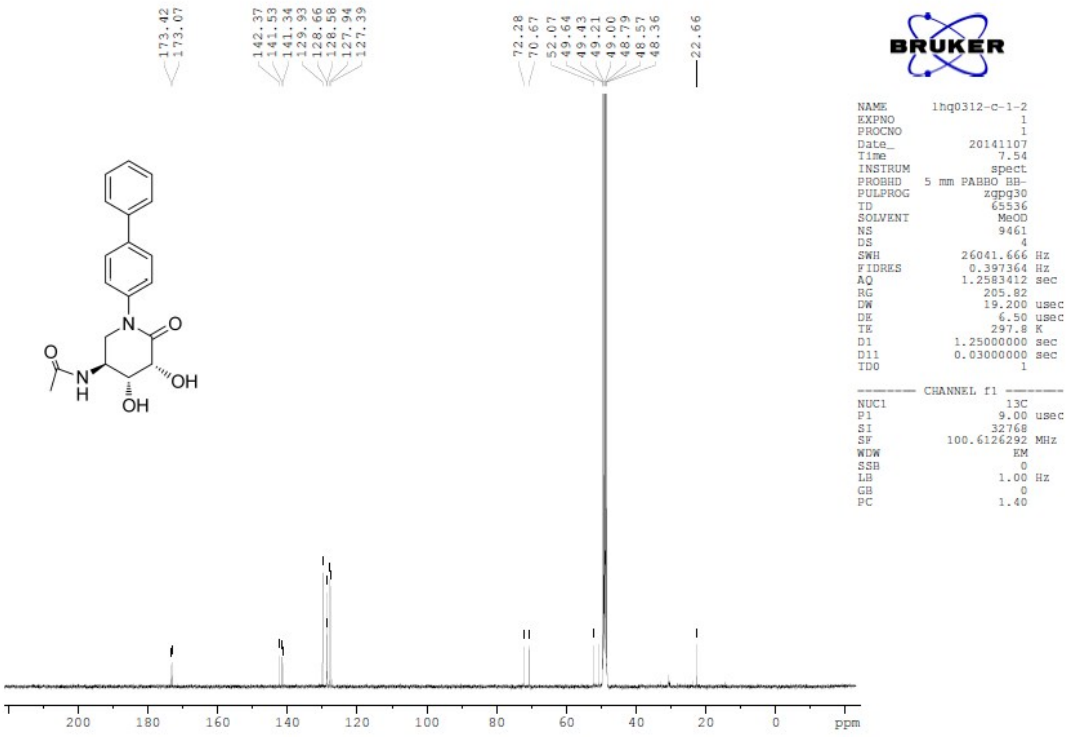
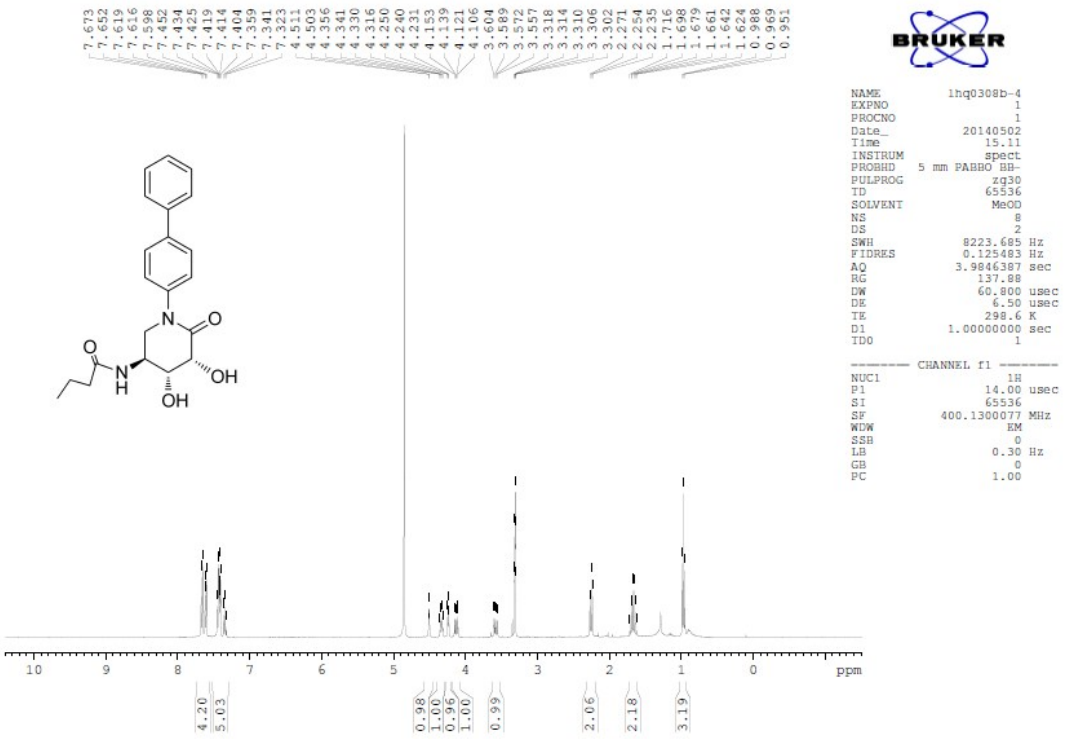
^{13}C NMR spectrum of **21**



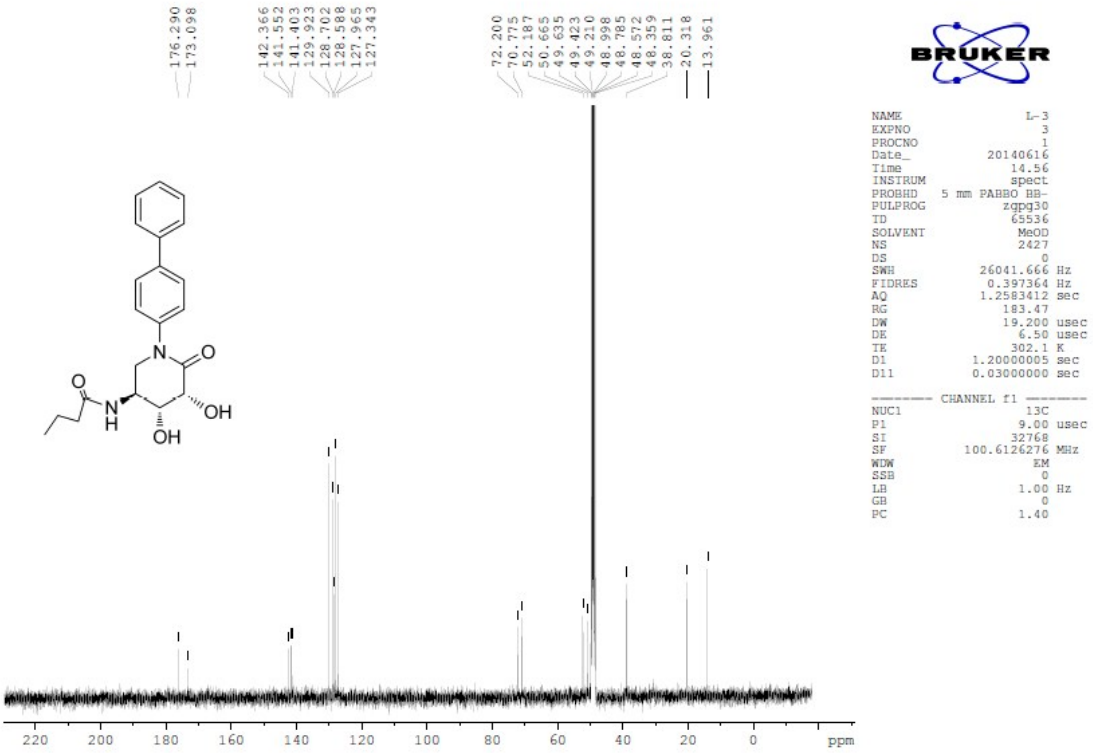
^{1}H NMR spectrum of **22**



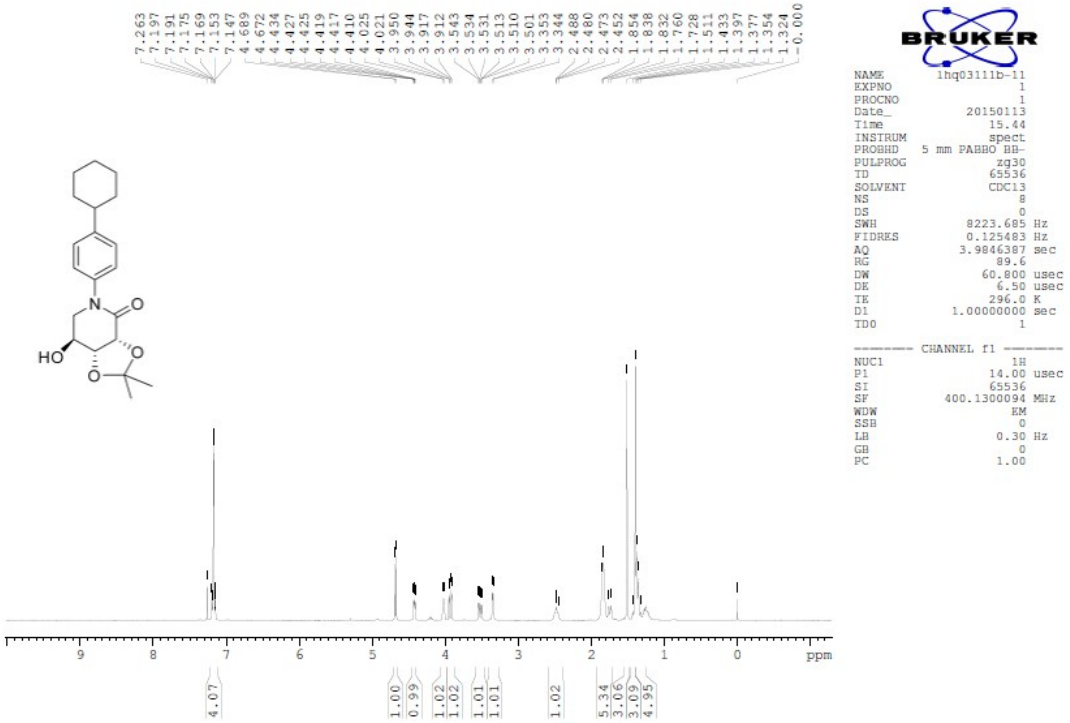
^{13}C NMR spectrum of **22**



^{1}H NMR spectrum of **23**



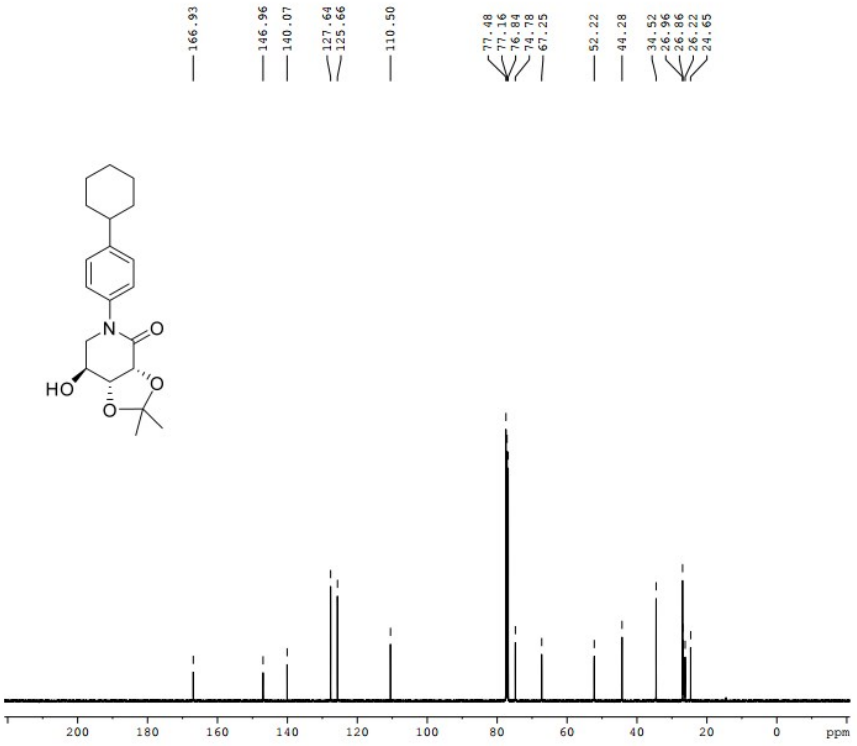
^{13}C NMR spectrum of **23**



BRUKER

NAME	1hq03111b-11
EXPNO	1
PROCNO	1
Date_	20150113
Time	15.44
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	0
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	89.6
DW	60.800 usec
DE	6.50 usec
TE	296.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	14.00 usec
SI	65536
SF	400.1300094 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

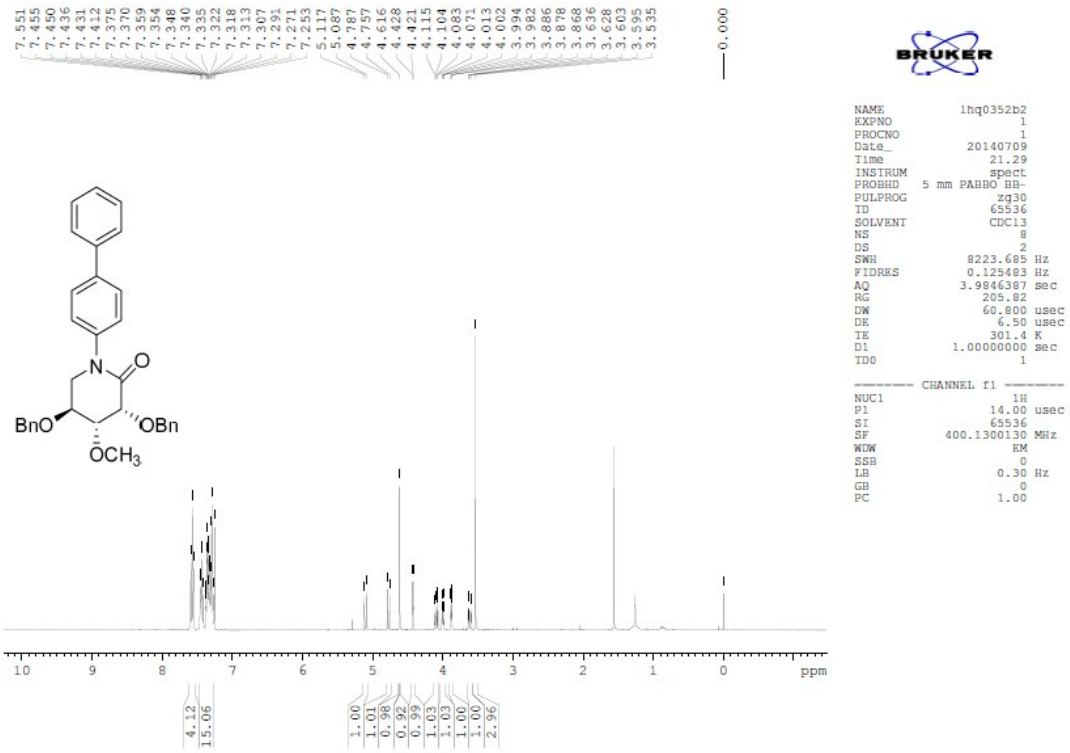
^{1}H NMR spectrum of **51**



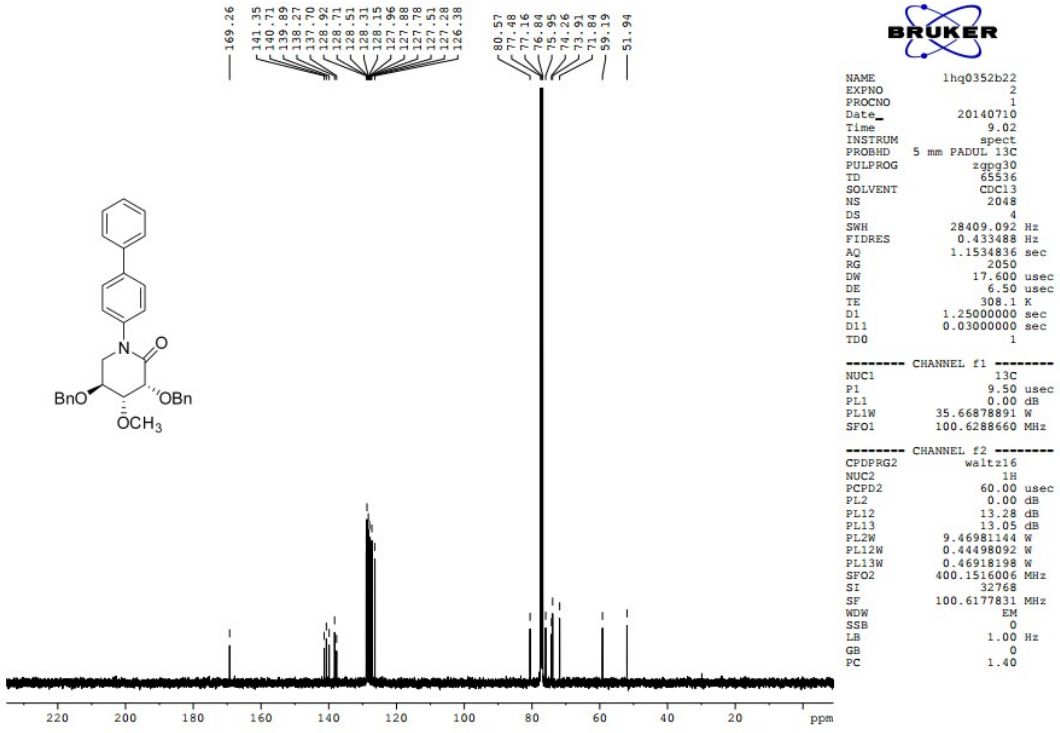
BRUKER

NAME	1hq03111b-11
EXPNO	3
PROCNO	1
Date_	20150113
Time	15.49
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1133
DS	4
SWH	26041.666 Hz
FIDRES	0.397364 Hz
AQ	1.2583412 sec
RG	205.82
DW	19.200 usec
DE	6.50 usec
TE	296.5 K
D1	1.25000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	9.00 usec
SI	32768
SF	100.6127579 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

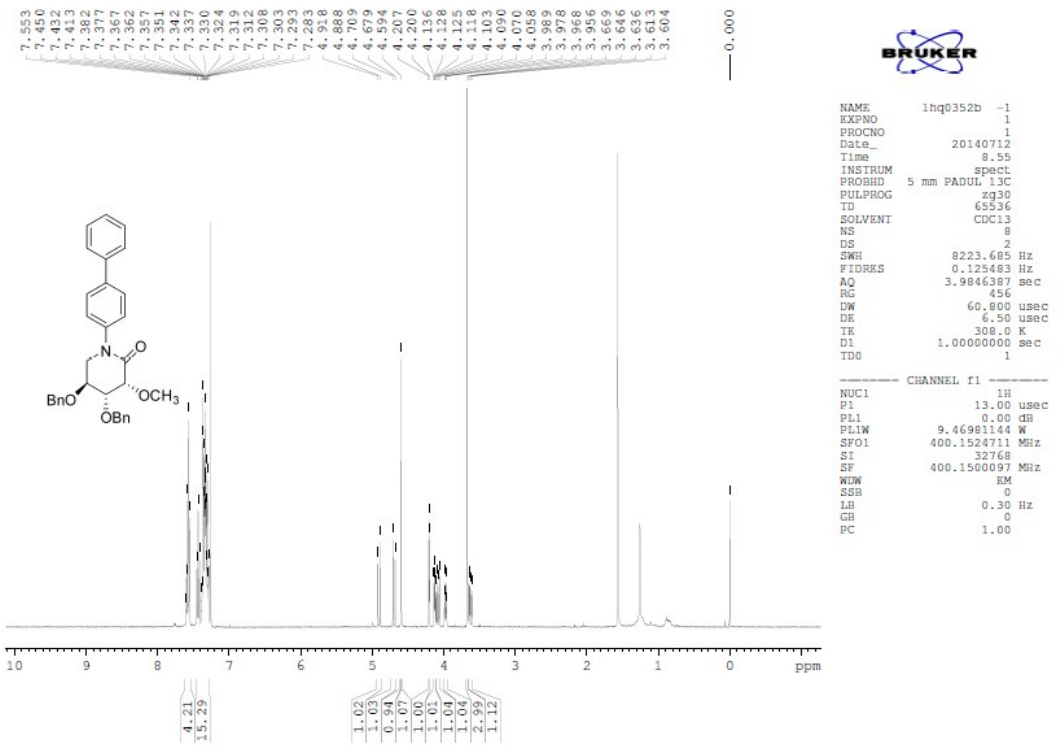
^{13}C NMR spectrum of **51**



^{1}H NMR spectrum of **52**



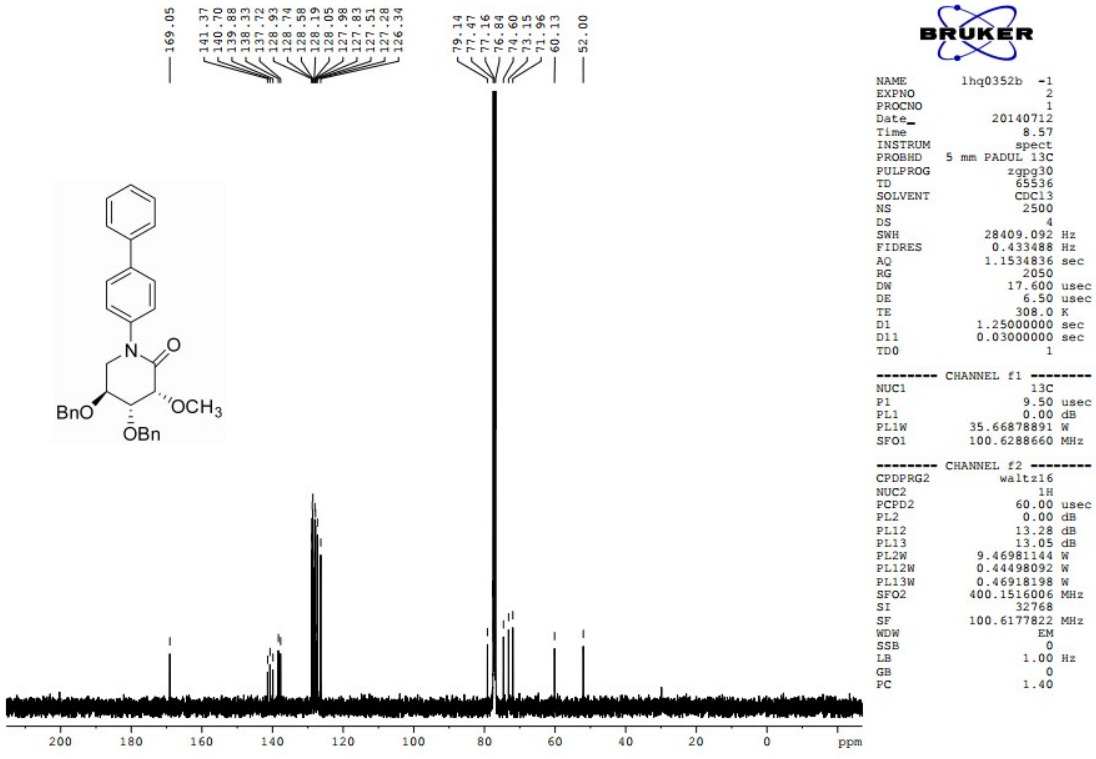
^{13}C NMR spectrum of **52**



BRUKER

```
NAME          1hq0352b  -1
EXPNO                  1
PROCNO                 1
Date_           20140712
Time                8.55
INSTRUM            spect
PROBHD   5 mm PADUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ              3.9846387 sec
RG                   456
DW                60.800 usec
DE                 6.50 usec
TE                308.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.00 usec
PL1                0.00 dB
PL1W           9.46981144 W
SFO1         400.1524711 MHz
SI                 32768
SF           400.1500097 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
```

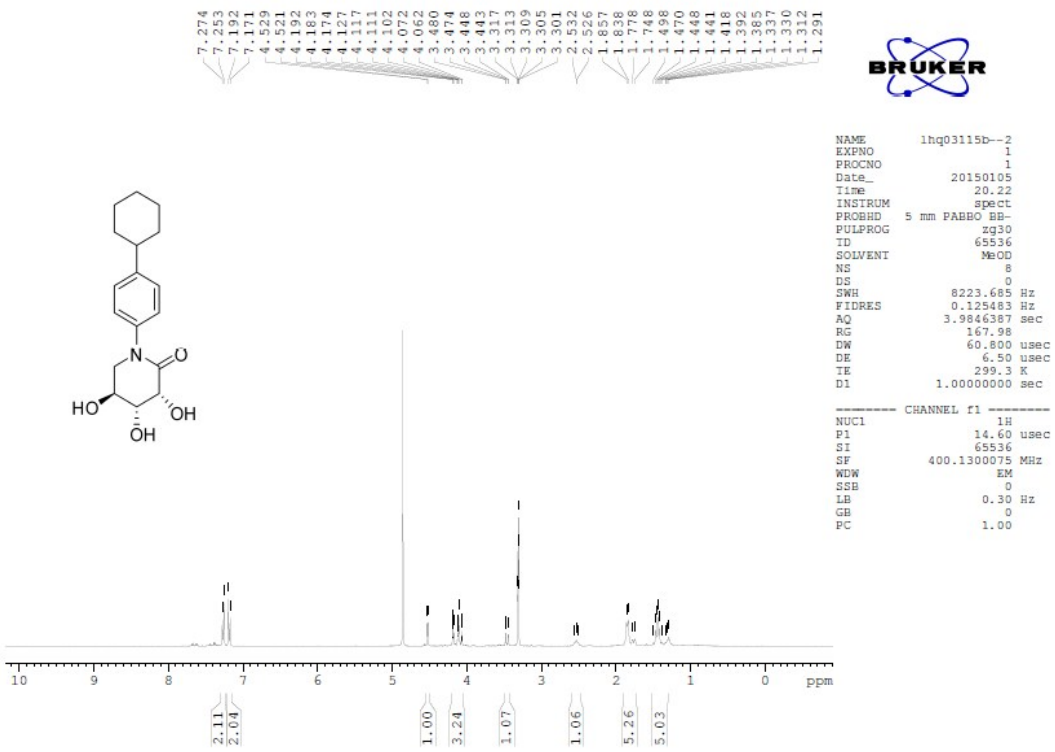
^{1}H NMR spectrum of **53**



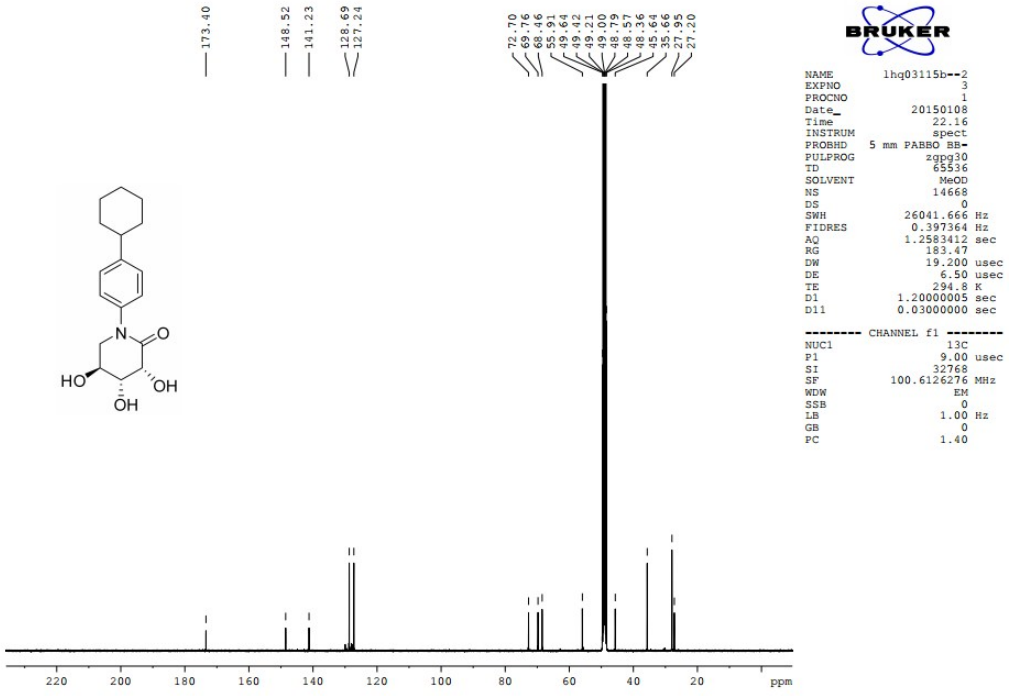
BRUKER

```
NAME          1hq0352b  -1
EXPNO                  2
PROCNO                 1
Date_           20140712
Time                8.57
INSTRUM            spect
PROBHD   5 mm PADUL 13C
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  2500
DS                     4
SWH            28409.092 Hz
FIDRES          0.433488 Hz
AQ              1.1534836 sec
RG                  2050
DW                17.600 usec
DE                 6.50 usec
TE                308.0 K
D1             1.25000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.50 usec
PL1                0.00 dB
PL1W          35.66878891 W
SFO1         100.6288660 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              60.00 usec
PL2                0.00 dB
PL12              13.28 dB
PL13              13.05 dB
PL2W           9.46981144 W
PL12W          0.44498092 W
PL13W          0.46918198 W
SFO2         400.1516006 MHz
SI                 32768
SF           100.6177822 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```

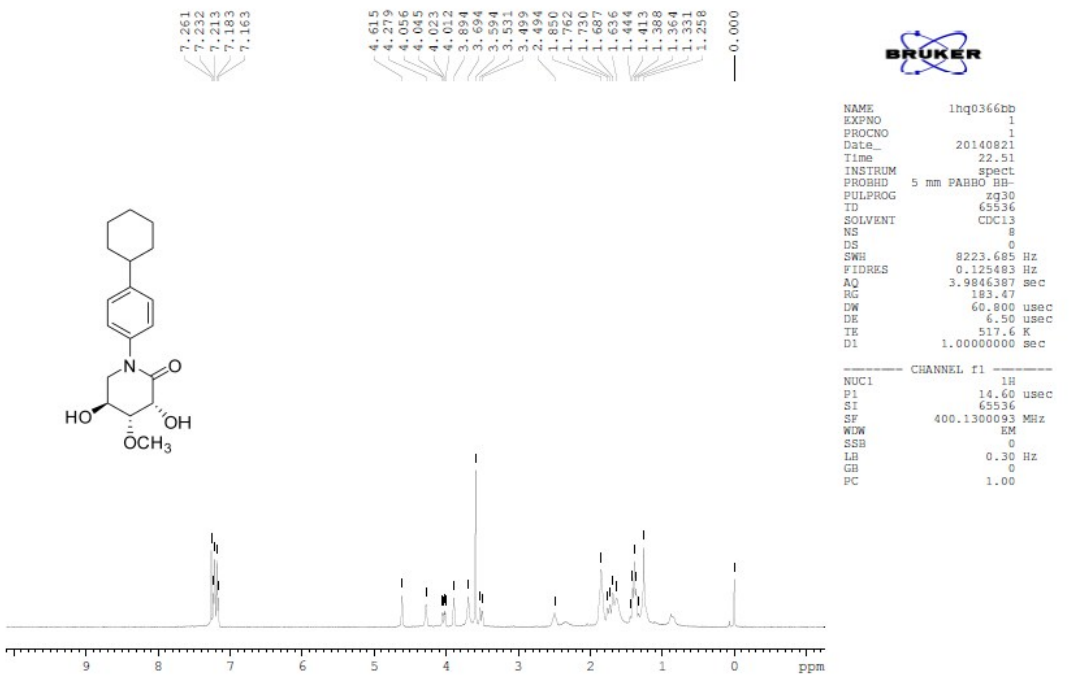
^{13}C NMR spectrum of **53**



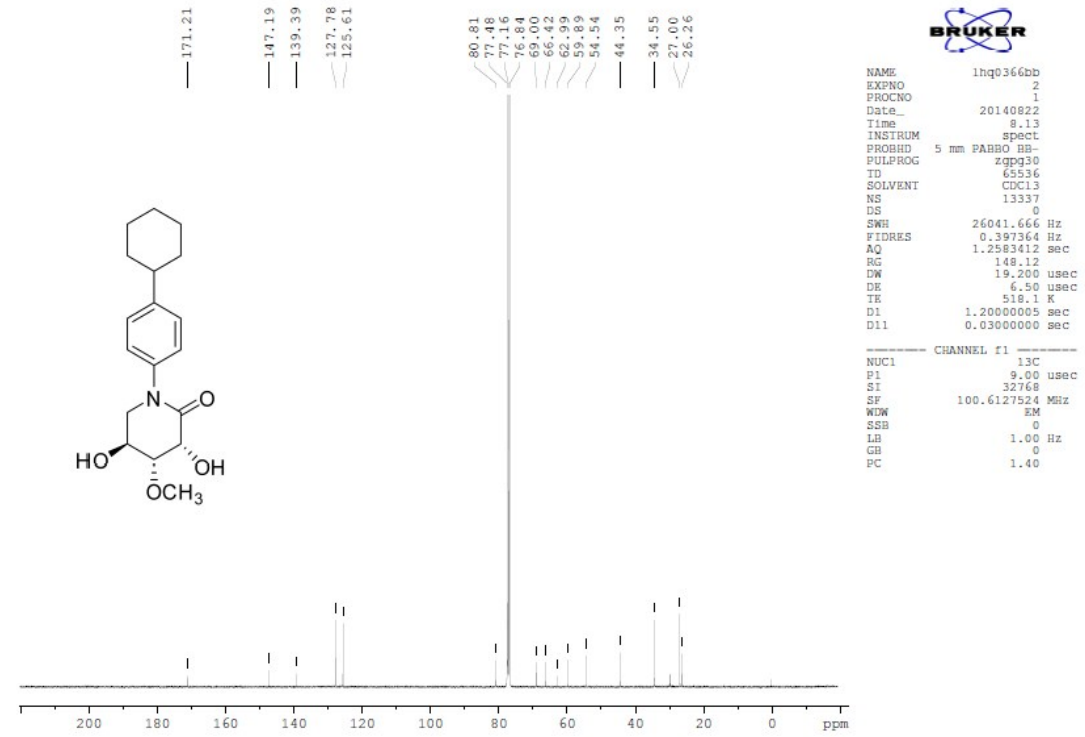
^{1}H NMR spectrum of **24**



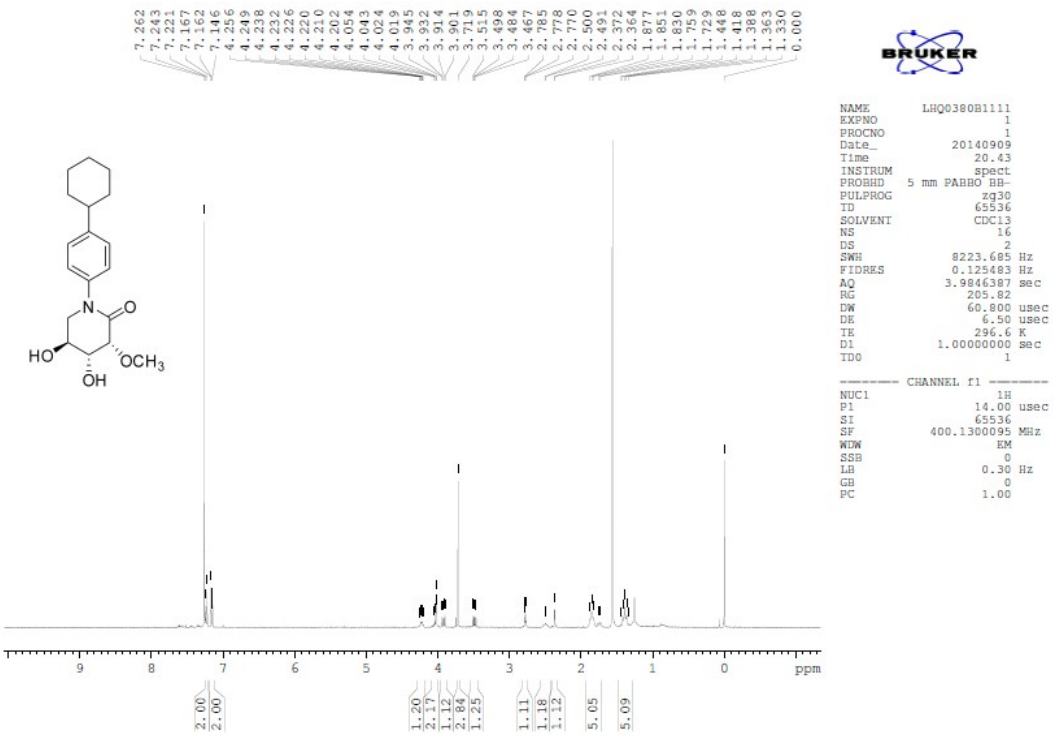
^{13}C NMR spectrum of **24**



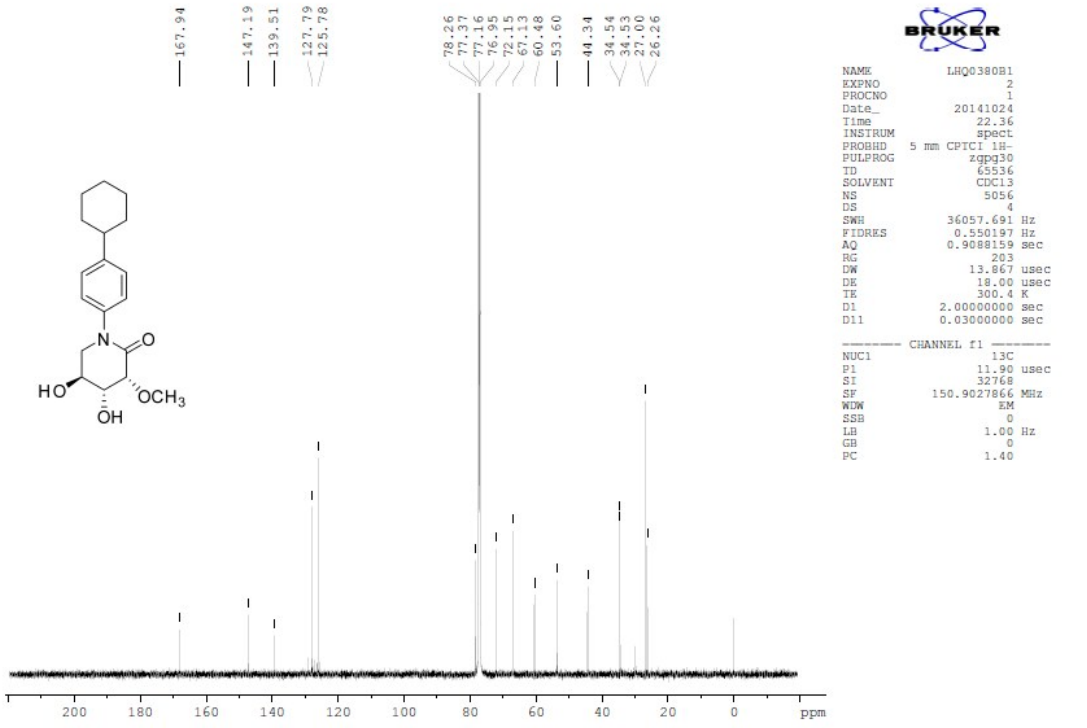
^{1}H NMR spectrum of **25**



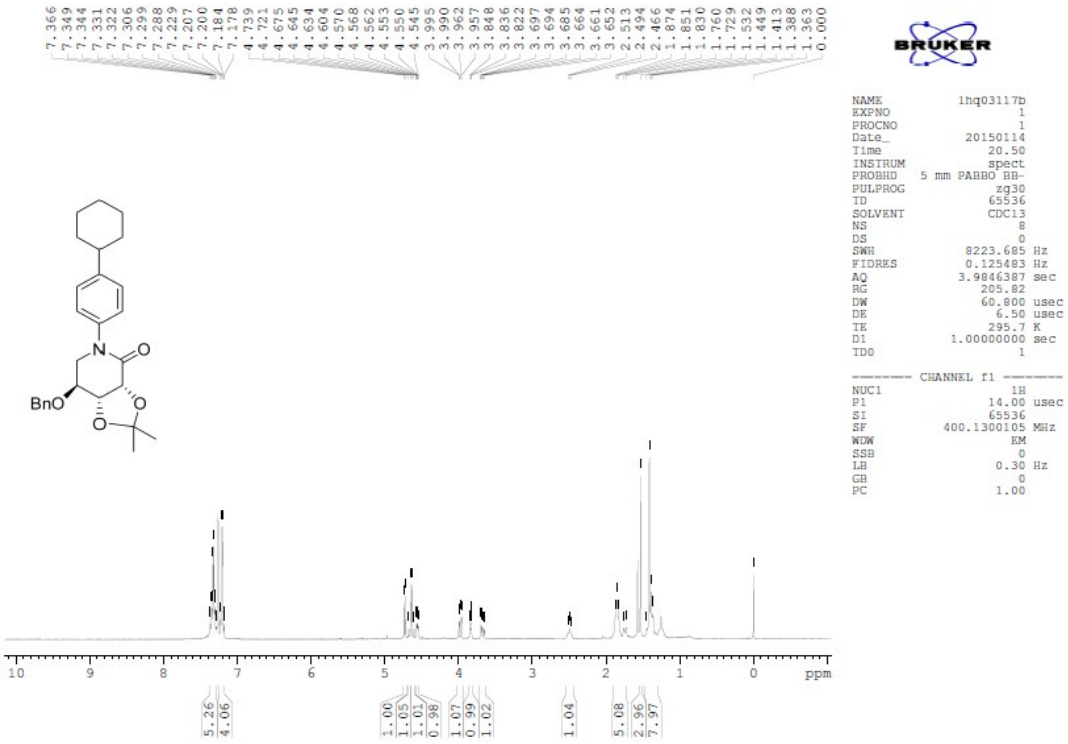
^{13}C NMR spectrum of **25**



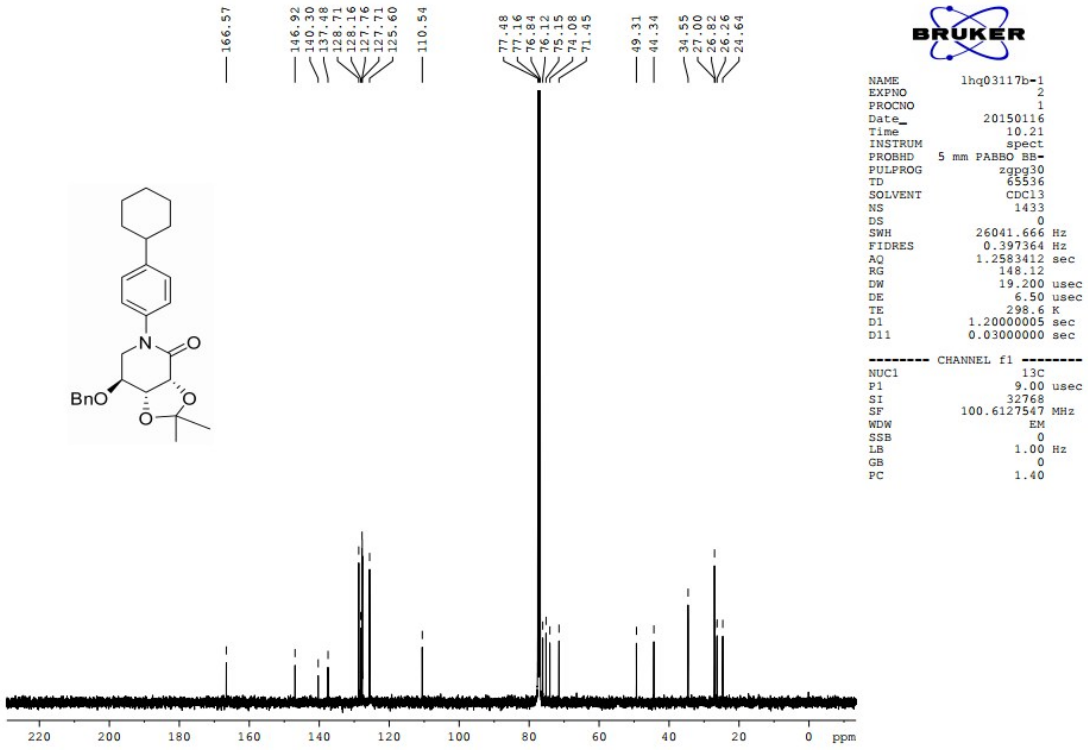
^{1}H NMR spectrum of **26**



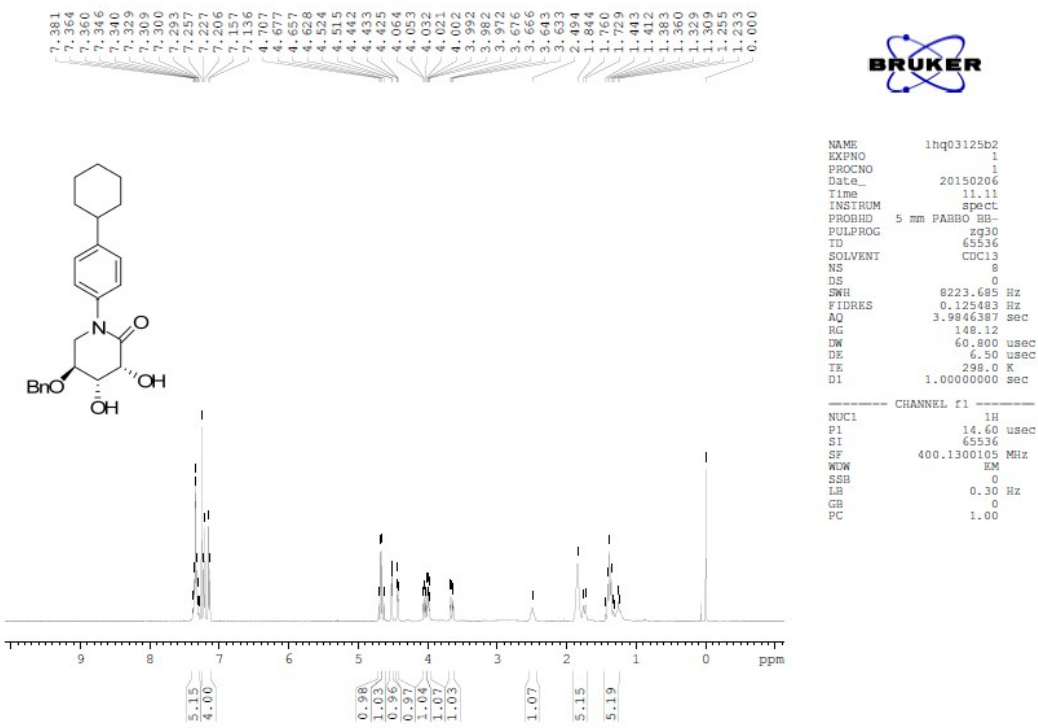
^{13}C NMR spectrum of **26**



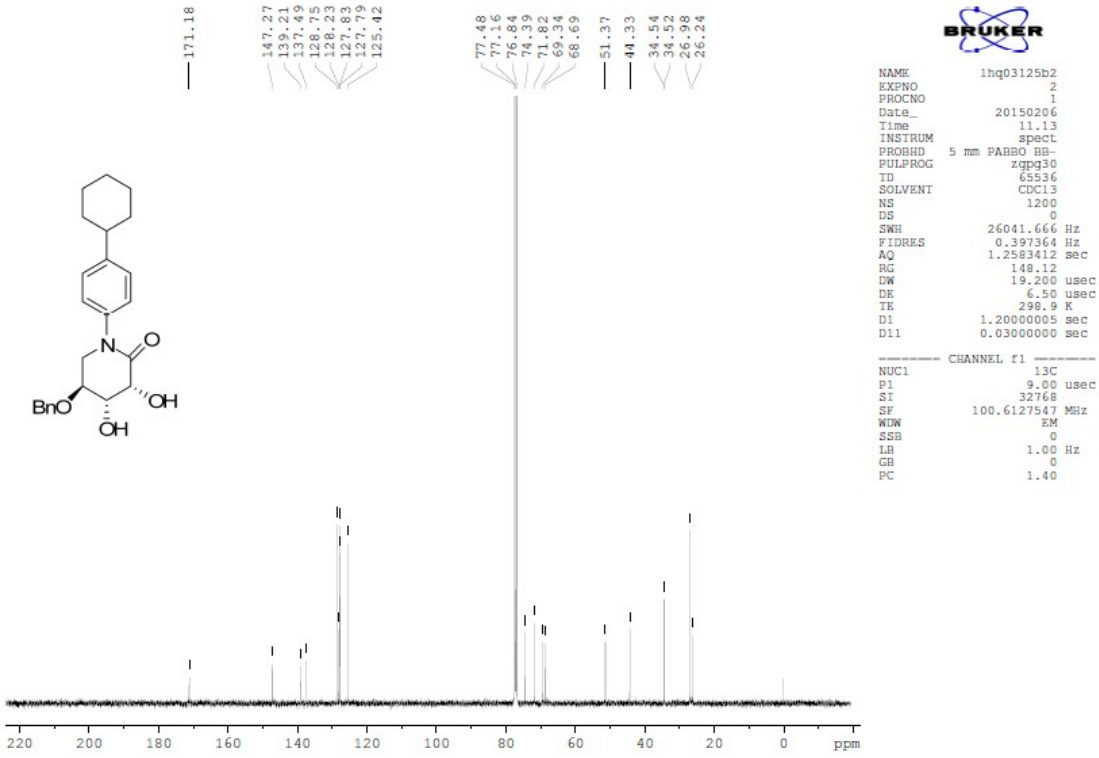
^{1}H NMR spectrum of **54**



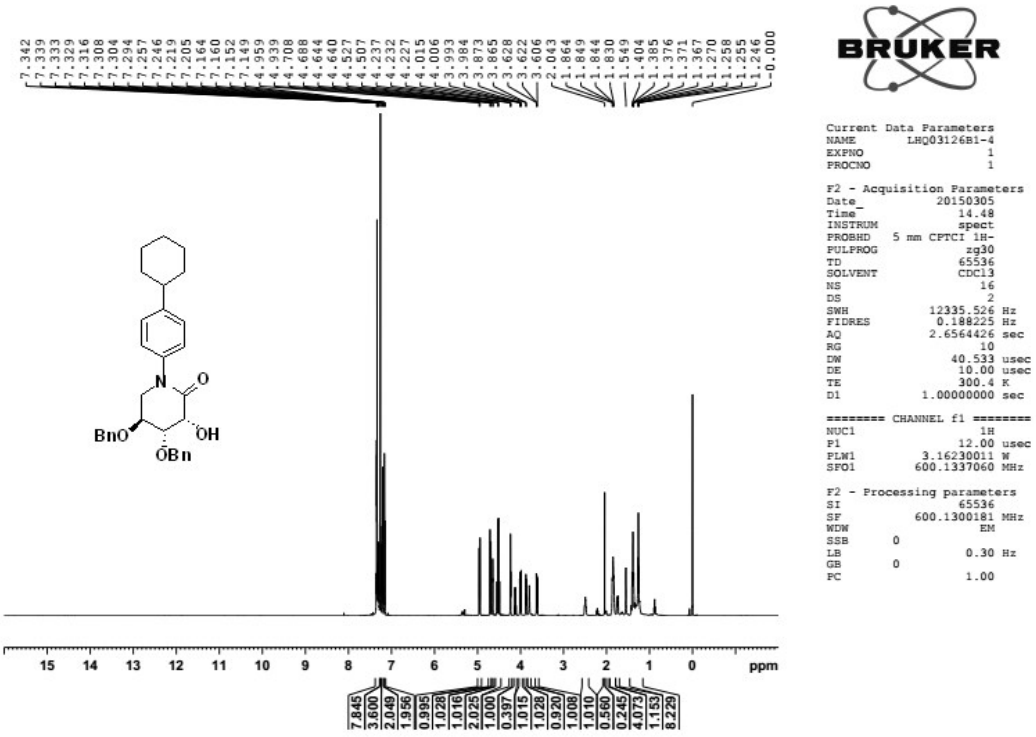
^{13}C NMR spectrum of **54**



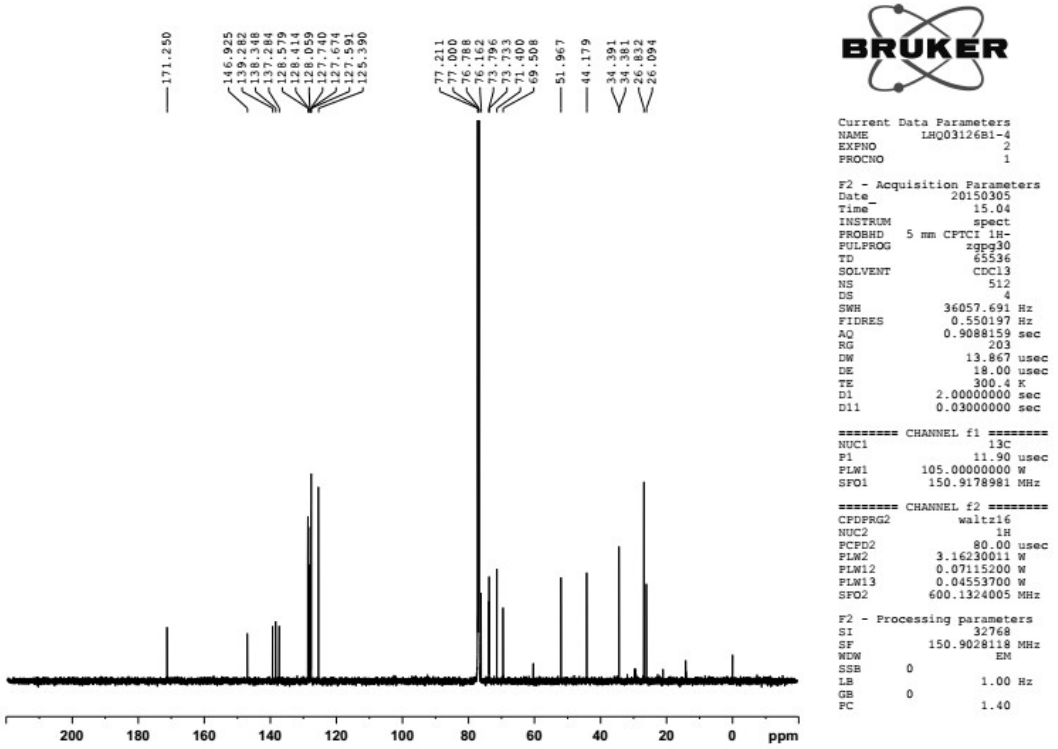
^{1}H NMR spectrum of **27**



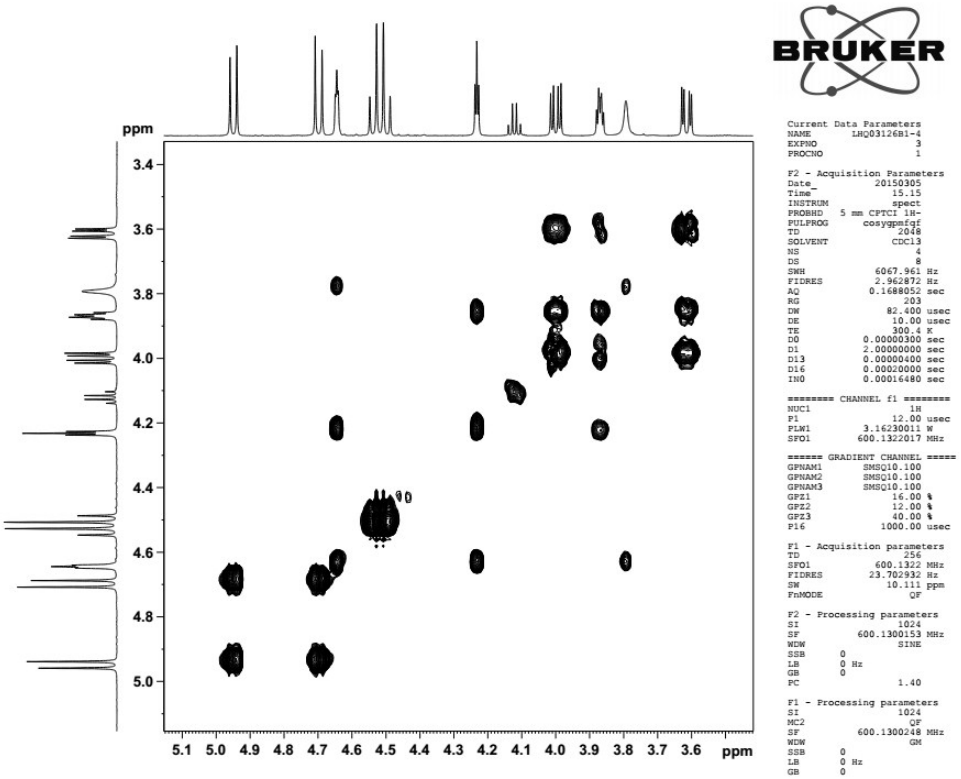
^{13}C NMR spectrum of **27**



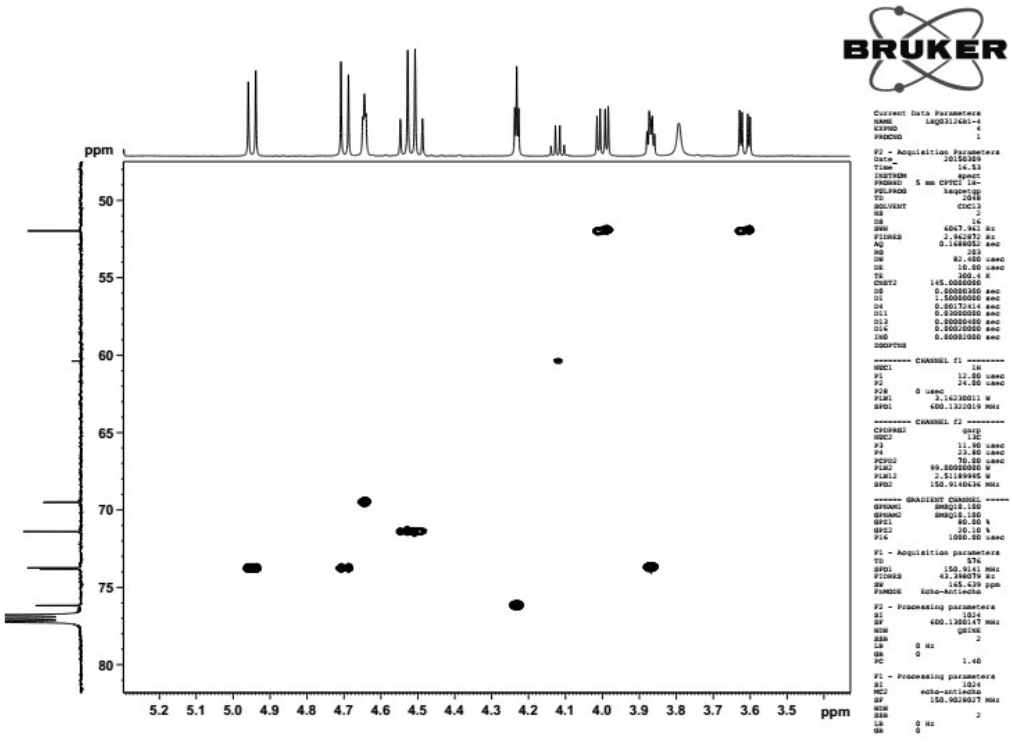
^{1}H NMR spectrum of **28**



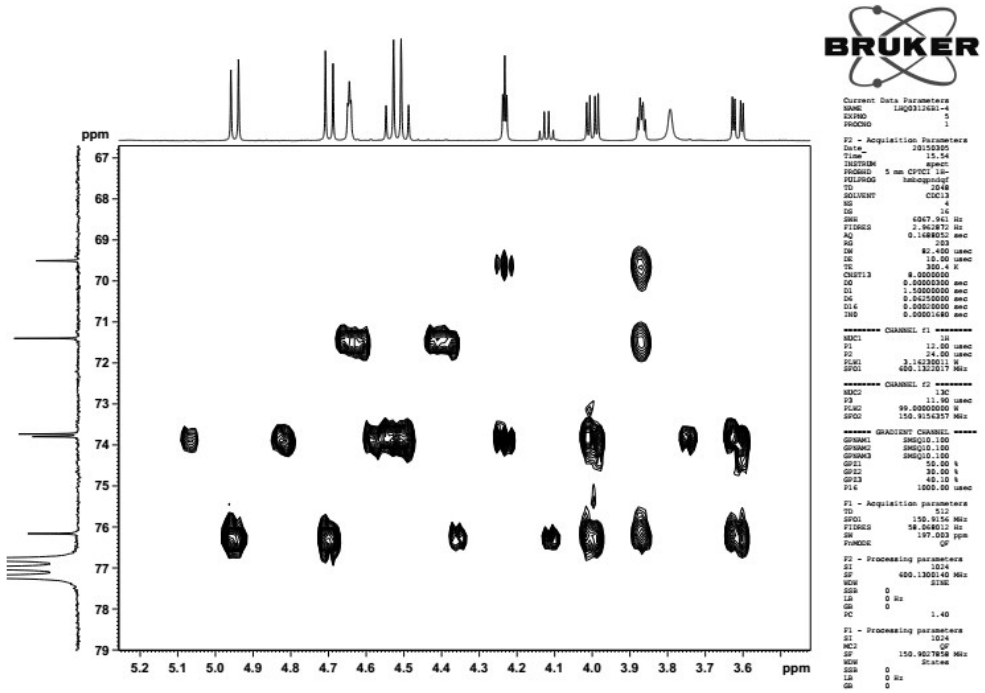
^{13}C NMR spectrum of **28**



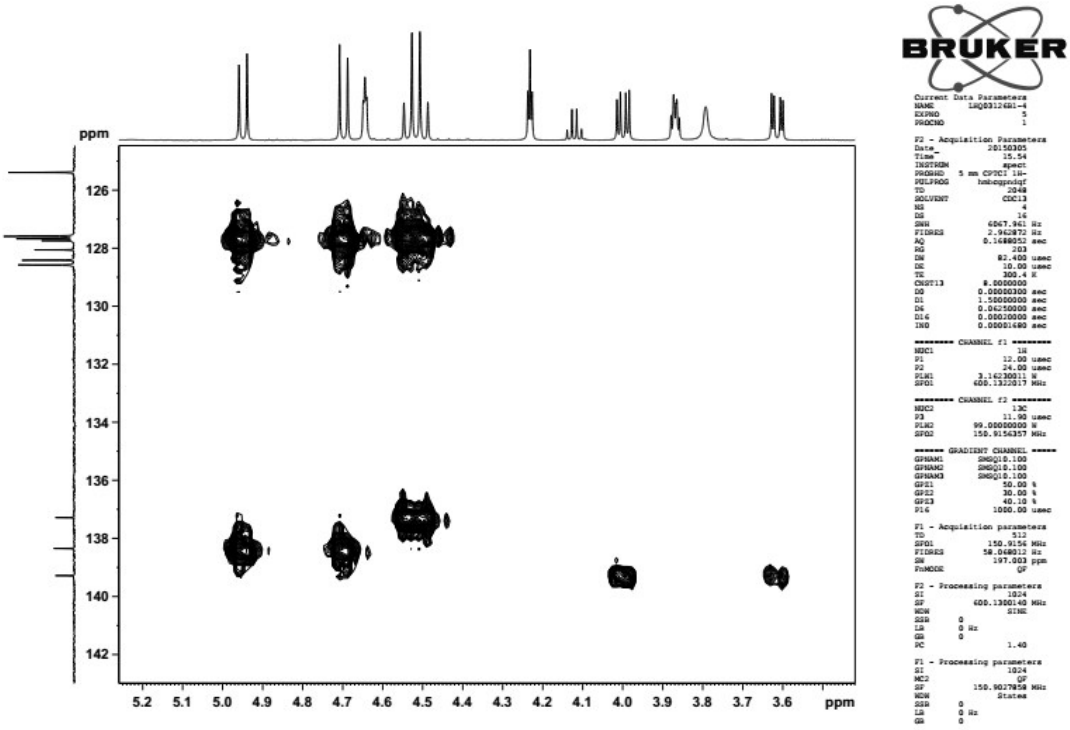
expanded ^{1}H-^{1}H COSY spectrum of **28**



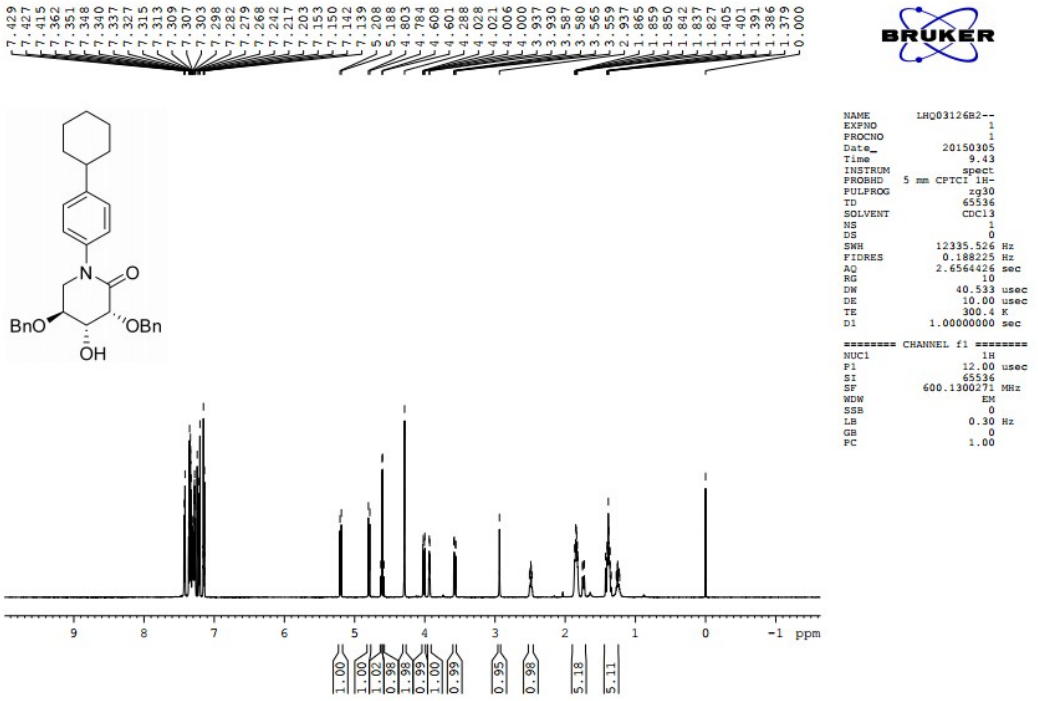
expanded HSQC spectrum of **28**



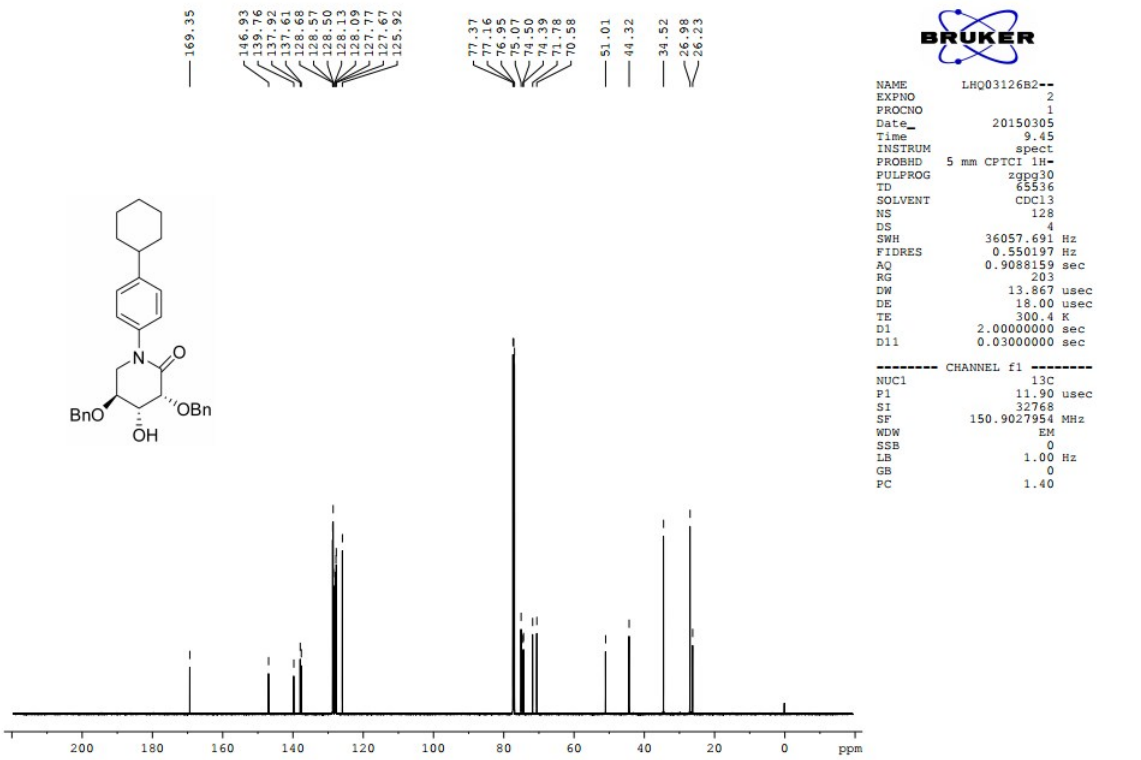
expanded HMBC spectrum of **28**



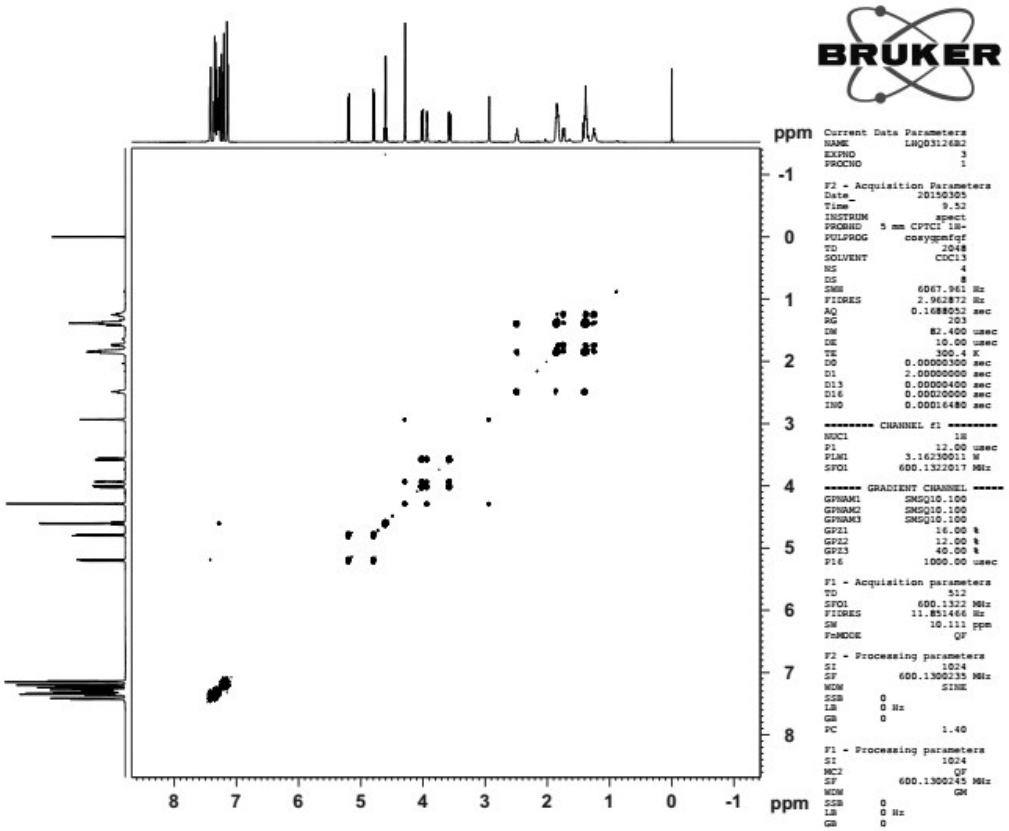
expanded HMBC spectrum of **28**



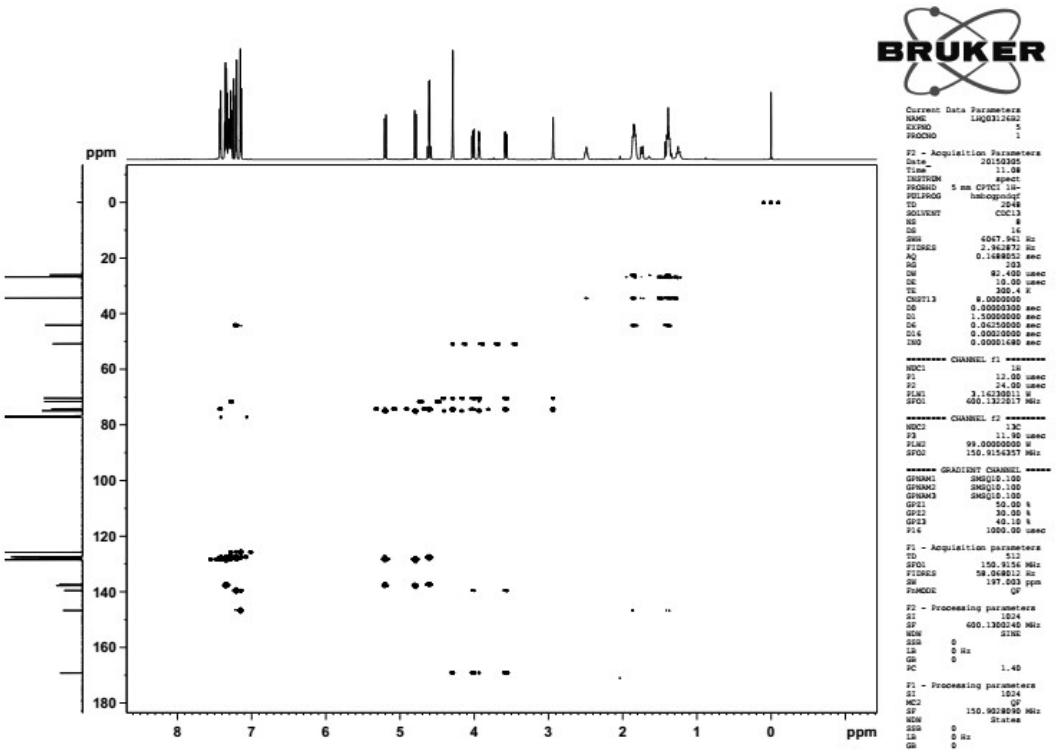
^{1}H NMR spectrum of **29**



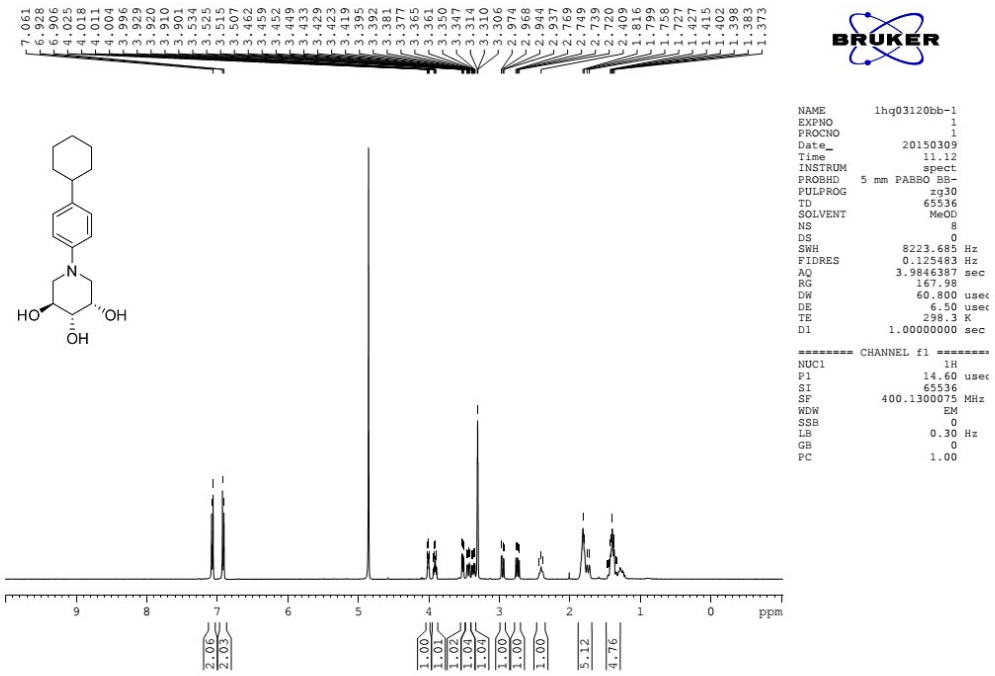
^{13}C NMR spectrum of **29**



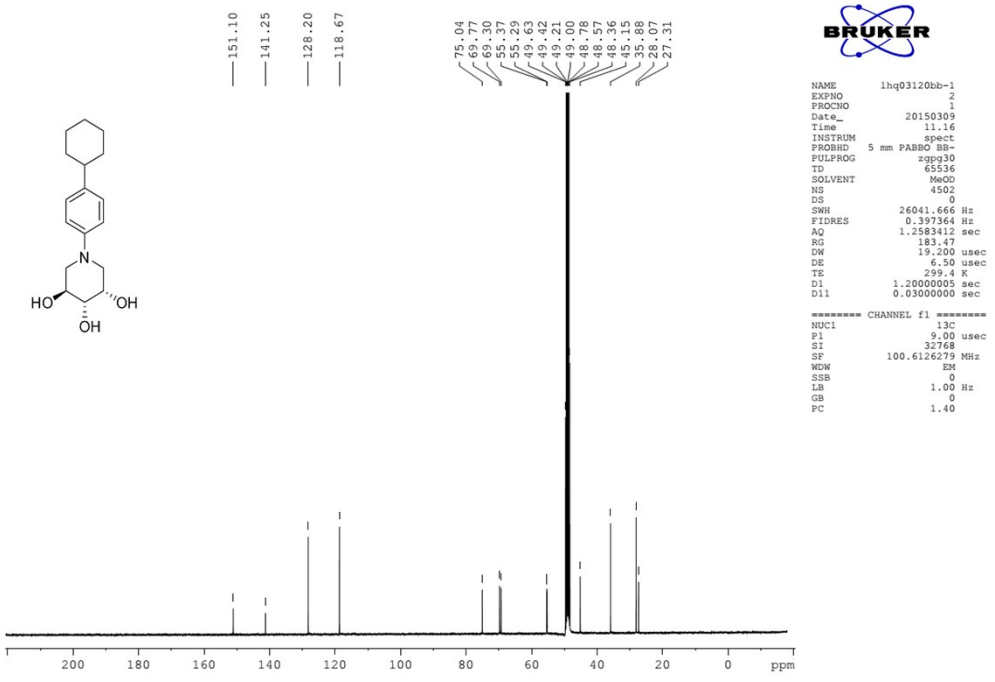
^{1}H-^{1}H COSY spectrum of **29**



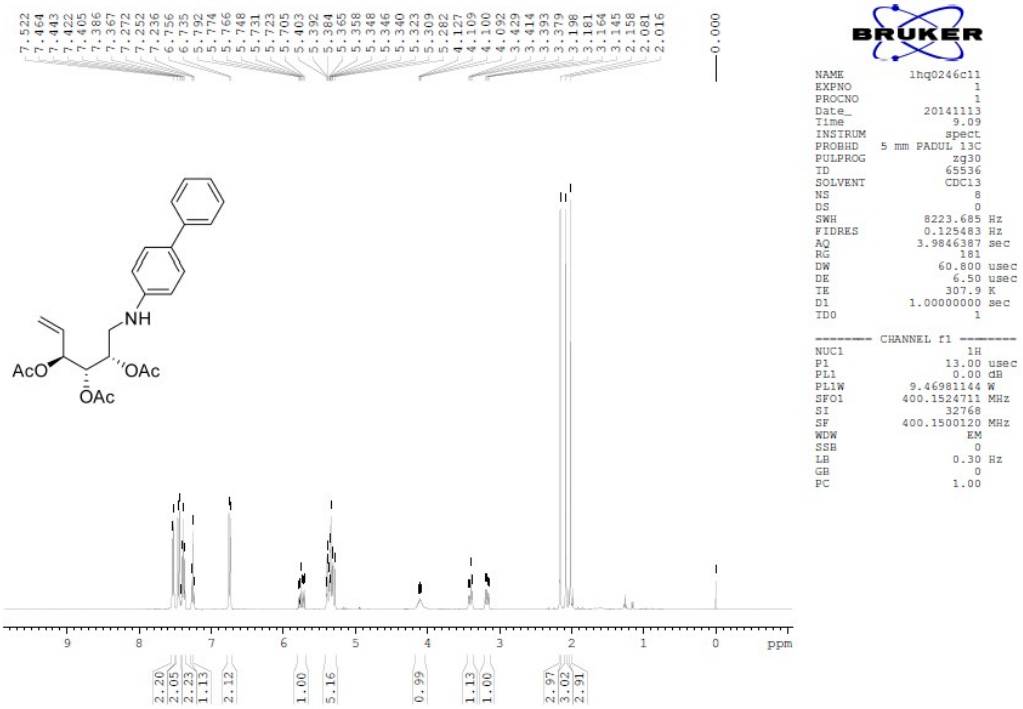
HMBC spectrum of **29**



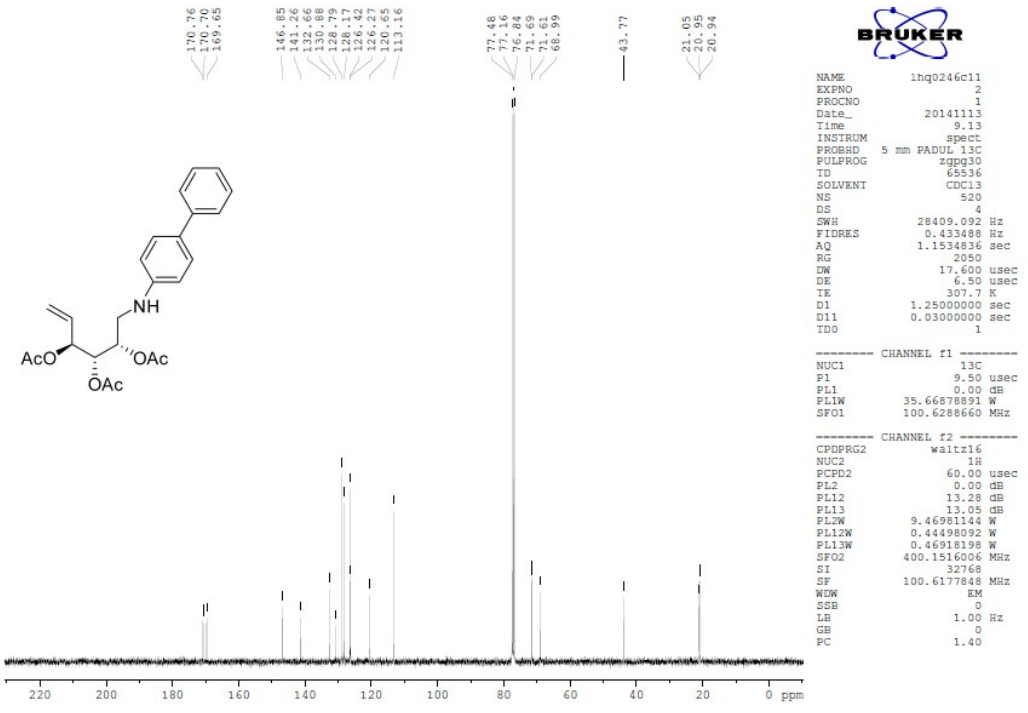
^{1}H NMR spectrum of **30**



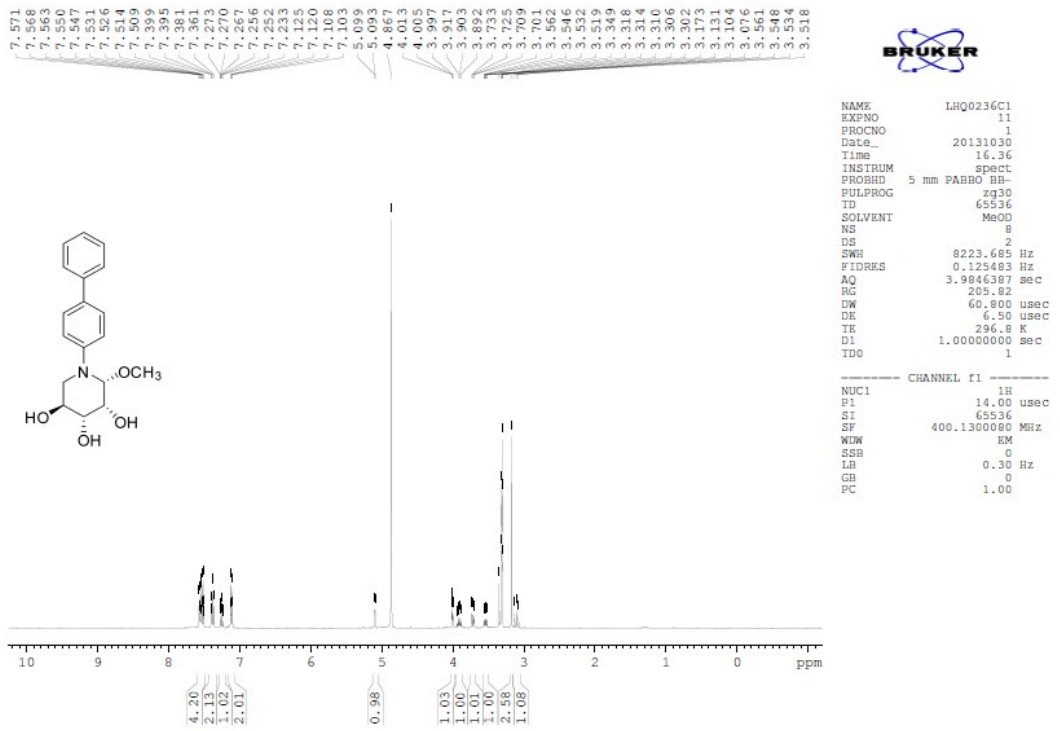
^{13}C NMR spectrum of **30**



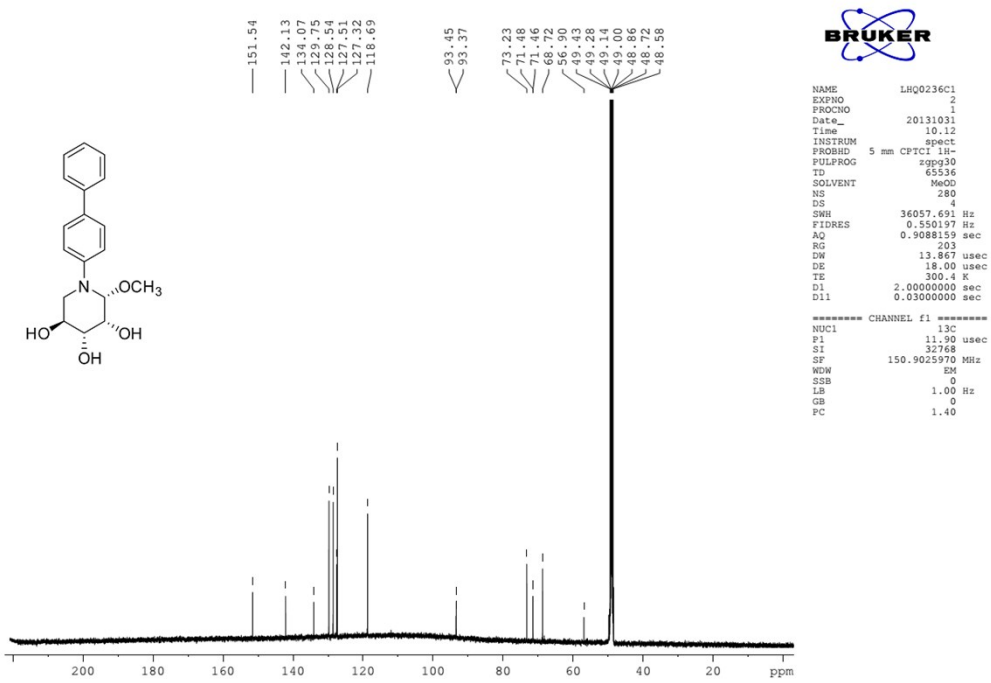
^{1}H NMR spectrum of **57**



^{13}C NMR spectrum of **57**



^{1}H NMR spectrum of **31**



^{13}C NMR spectrum of **31**