Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Insights into the Structural Patterns of the Antileishmanial Activity of Bi- and Tricyclic *N*-Heterocycles

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General Procedures

Materials and methods: Dichloromethane was dried and purified under an argon atmosphere using an LC technology Solutions' SP-1 Solvent Purifier All oximes were synthesized according to the literature procedure.[1] All heterocyclic *N*-oxides were synthesized according to reported procedures.[2] N'-(2-chloro-1-phenylethylidene)-4-methylbenzenesulfonohydrazide was synthesized according to literature procedure.[3] All other reagents were purchased and used without further purification.

Purification: Column chromatography was performed using CombiFlash Rf-200 (Teledyne-Isco) automated flash chromatography system.

Characterization: ^{1}H, ^{13}C, ^{19}F NMR spectra were recorded at 500 (^{1}H), 125 (^{13}C), and 282 MHz (^{19}F) on Varian Mercury VX 300 and Agilent Inova 500 instruments in $CDCl_3$ solutions. Chemical shifts (δ) are reported in parts per million (ppm) from the residual

solvent peak and coupling constants (*J*) in Hz. Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (quart.), quintet (quint.), septet (sept.), multiplet (m), broad (br).

Infrared measurements were carried out neat on a Brüker Vector 22 FT-IR spectrometer fitted with a Specac diamond attenuated total reflectance (ATR) module.

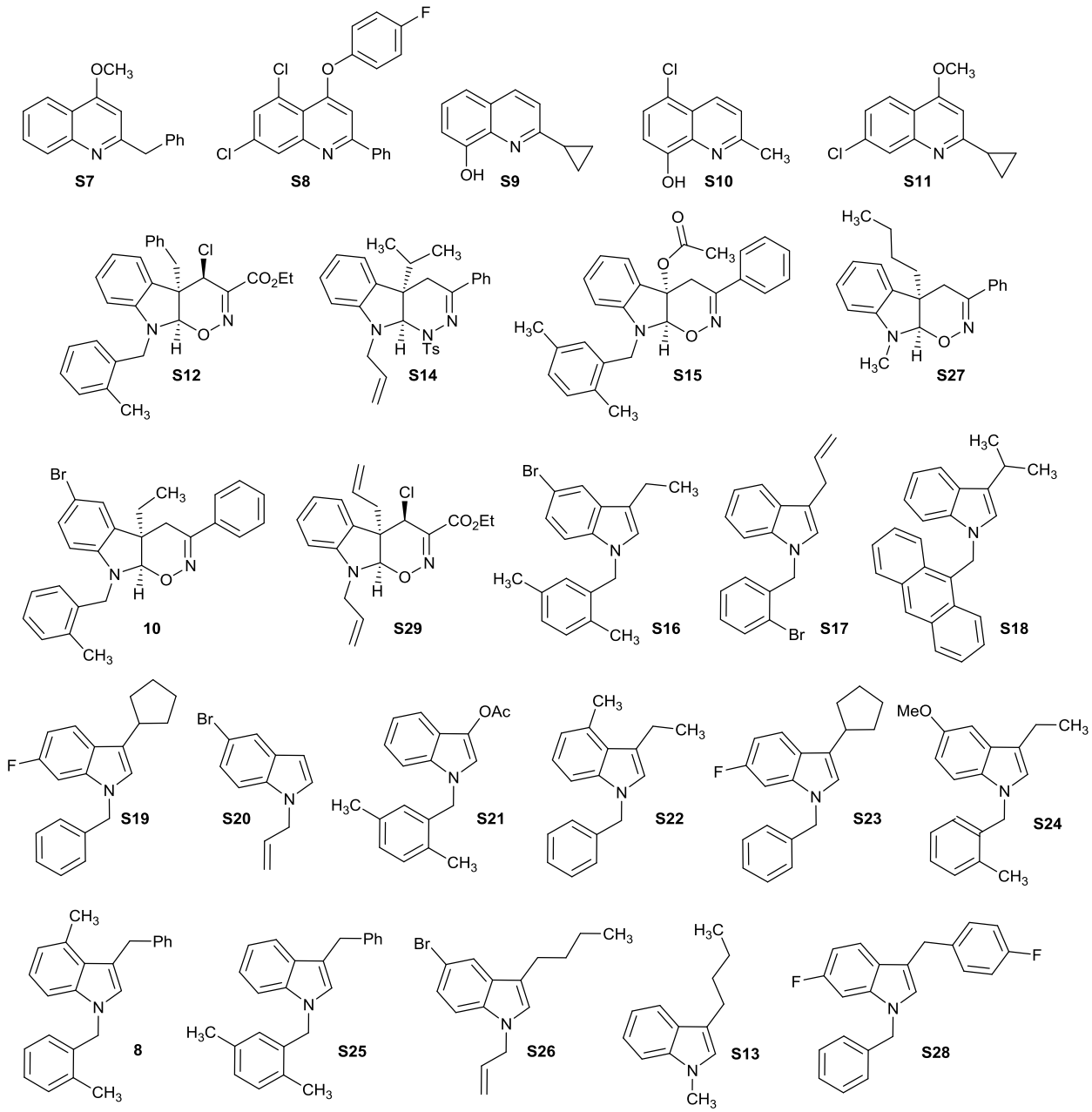
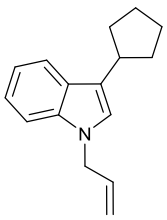


Figure S1. Tested compounds that are inactive against promastigotes and intracellular amastigotes of *L. major* and *L. panamensis*.

General Procedure 1 (GP1) for the synthesis of 1,2-oxazines 9-11, 13, 14, 16, 18-20, S15, S19, S29:

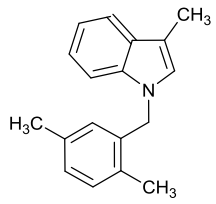
To an oven dried flask was added 3Å MS (5 scoops), CuOTf ½ PhMe (10-20 mol%), *rac*-BINAP or (*S*)-DM-BINAP (10-20 mol%) and dichloromethane (0.1-0.2M). The reaction stirred for 15 min before being cooled to -78 °C under argon and indole (1 equiv.), oxime (1 equiv.) and silver carbonate (3 equiv.) were added sequentially. The reaction was allowed to warm to either –20 or –15 °C and stirred for the specified time. The reaction mixtures were then filtered, concentrated under reduced pressure, and purified by column chromatography [hexanes/EtOAc, silica gel] to yield the desired products.

1-Allyl-3-cyclopentyl-1*H*-indole (S1)



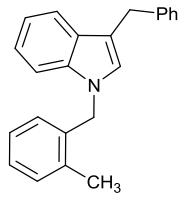
3-Cyclopentyl-1*H*-indole[4] (300 mg, 1.62 mmol, 1 equiv.) in dimethylacetamide (8 mL) was reacted with sodium hydride (130 mg, 3.24 mmol, 2 equiv., 60% in mineral oil). After 15 min allyl bromide (295 mg, 2.43 mmol, 1.5 equiv.) was added and the reaction stirred for 12 h. The reaction was diluted with a 1M aqueous solution of potassium hydrogen sulfate (20 mL) and the aqueous layer extracted with EtOAc (5 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography [hexanes, silica gel] to yield indole **S1** (289 mg, 79 %). – ^{1}H NMR (500 MHz): 1.69–1.83 (6 H, m), 2.14–2.19 (2 H, m), 3.22–3.31 (1 H, m), 4.68–4.70 (2 H, m), 5.10–5.21 (2 H, m), 5.96–6.05 (1 H, m), 6.88 (1 H, s), 7.10 (1 H, dt, *J* = 1, 7 Hz), 7.20 (1 H, dt, *J* = 1.5, 7.5 Hz), 7.28–7.30 (1 H, m), 7.66 (1 H, td, *J* = 1, 7.5 Hz) ppm. – ^{13}C NMR (125 MHz): 25.3, 33.4, 37.0, 48.7, 109.5, 117.1, 118.6, 119.8, 120.3, 121.4, 123.5, 128.0, 133.8, 136.8 ppm. – IR: 1084, 1255, 1331, 1466, 1613, 2867, 2954, 3047 cm^{-1}. – MS (ESI): 226.0, HRMS: 226.1598, calcd: 226.1590 [M+H^{+}].

1-(2,5-Dimethylbenzyl)-3-methyl-1*H*-indole (S2)



3-Methylindole (1.00 g, 7.63 mmol, 1 equiv.) in dimethylacetamide (20 mL) was reacted with sodium hydride (458 mg, 11.44 mmol, 1.5 equiv., 60 % in mineral oil) at 0 °C. After 15 min, 2,5-dimethylbenzyl chloride (1 mL, 6.86 mmol, 0.9 equiv.) was added and the reaction warmed to 23 °C. After 12 h, the reaction was diluted with a 1M aqueous solution of potassium hydrogen sulfate (30 mL), and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield indole **S2** (1.21 g, 64 %). – ^{1}H NMR (500 MHz): 2.24 (3 H, s), 2.27 (3 H, s), 2.35 (3 H, s), 5.19 (2 H, s), 6.73 (1 H, s), 6.77 (1 H, s), 7.04 (1 H, d, *J* = 8 Hz), 7.10-7.16 (2 H, m), 7.21 (1 H, t, *J* = 8.5 Hz), 7.26-7.30 (1 H, m), 7.62 (1 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 9.7, 18.7, 21.0, 47.8, 109.3, 110.7, 118.7, 119.0, 121.5, 125.4, 128.4, 128.4, 128.8, 130.4, 132.8, 135.2, 135.9, 136.8 ppm. – IR: 1014, 1127, 1240, 1332, 1467, 1502, 1614, 2856, 2917, 3045 cm^{-1}. – MS (ESI): 250.1, 251.1, HRMS: 250.1591, calcd: 250.1590 [M+H^{+}].

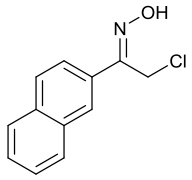
3-Benzyl-1-(2-methylbenzyl)-1*H*-indole (S3)



To a solution of 1-(2-methylbenzyl)-1*H*-indole[1] (300 mg, 1.36 mmol, 1 equiv.) and benzaldehyde (145 mg, 1.36 mmol, 1 equiv.) in dichloromethane (13.60 mL) was added triethylsilane (607 μL, 3.81 mmol, 2.8 equiv.) and trifluoroacetic acid (210 μL, 2.72 mmol, 2 equiv.) sequentially at 0 °C. After 2 h the crude reaction was concentrated under reduced pressure and purified by column chromatography [hexanes/EtOAc, silica gel] to yield indole **S3** (412 mg, 97 %). – ^{1}H NMR (500 MHz): 2.32 (3 H, s), 4.12 (2 H, s), 5.25 (2 H, s), 6.75 (1 H, d, *J* = 8 Hz), 6.79 (1 H, s), 7.07–7.11 (2 H, m), 7.16–7.21 (4 H, m), 7.25–7.30 (6 H, m), 7.54 (1 H, td, *J* = 1, 8 Hz) ppm. – ^{13}C NMR (125 MHz): 19.4 (CH_3), 32.0 (CH_2), 48.2 (CH_2), 110.0 (CH), 115.2 (C), 119.6 (CH), 122.2 (CH), 126.3 (CH), 126.8 (CH), 126.8 (CH), 127.6 (C), 128.0 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 130.8 (CH), 135.9 (C), 137.4 (C), 141.8 (C) ppm. – IR: 1013, 1172, 1288, 1374, 1481, 1558,

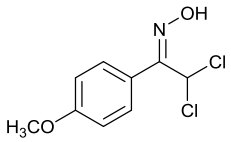
1604, 2855, 2921, 2954 cm^{-1}. – MS (ESI): 312.0, HRMS: 312.1741, calcd: 312.1747 $[M+H^+]$.

2-Chloro-1-(naphthalen-2-yl)ethan-1-one oxime (S4)



To a solution of 2-chloro-1-(2-naphthyl)ethanone (1 g, 4.90 mmol, 1 equiv.) in MeOH (25 mL) and water (5 mL) was added hydroxylamine hydrochloride (1.01 g, 14.70 mmol, 3 equiv.) at 23 °C. After 12 h the reaction was concentrated and the aqueous layer extracted with chloroform (5 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield oxime **S4** (823 mg, 76 %). – m.p.: 90–92 °C. – ^{1}H NMR (500 MHz): 4.74 (2 H, s), 7.53-7.54 (2 H, m), 7.86-8.13 (6 H, m) ppm. – ^{13}C NMR (125 MHz): 31.8, 123.2, 126.4, 126.6, 127.1, 127.7, 128.5, 129.9, 130.6, 133.1, 134.0, 154.3 ppm. – IR: 1058, 1156, 1239, 1321, 1430, 1505, 2926, 3055 cm^{-1}.

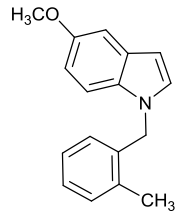
2,2-Dichloro-1-(4-methoxyphenyl)ethan-1-one oxime (S5)



To a pre-dried container was added copper(II) chloride (402 mg, 3.00 mmol, 3 equiv.), lithium chloride (126 mg, 3.00 mmol, 3 equiv.) and dimethylformamide (5 mL). The solution was heated with argon bubbling through twice before 2-chloro-1-(4-methoxyphenyl)ethan-1-one (184 mg, 1.00 mmol, 1 equiv.) was added and the reaction heated to 90 °C with a reflux condenser. After 12 h the reaction was diluted with a 1M aqueous solution of potassium hydrogen sulfate (50 mL) and the aqueous layer was extracted with EtOAc (10 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography [hexanes, silica gel] to yield 2,2-dichloro-1-(4-methoxyphenyl)ethan-1-one.[5] The purified product was dissolved in MeOH (2.5 mL) and water (250 µL) before hydroxylamine hydrochloride (100 mg, 1.37 mmol, 3 equiv.) was added and the reaction stirred at 23 °C. After 12 h the reaction was concentrated and the aqueous layer extracted with chloroform (5 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield oxime **S5** (107 mg, 73 %). – ^{1}H NMR (300 MHz): 4.55

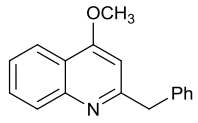
(3 H, s), 7.64 (1 H, d, *J* = 8.5 Hz), 7.69 (1 H, d, *J* = 8.5 Hz), 8.27 (1 H, d, *J* = 8.5 Hz), 8.43 (1 H, d, *J* = 8.5 Hz), 13.41 (1 H, br s) ppm. – ^{13}C NMR (75 MHz): 55.23, 70.6, 120.7, 123.4, 153.7, 154.7, 160.6 ppm. – IR: 1025, 1314, 1460, 1595, 2848, 2938, 3014 cm^{-1}. – MS (ESI): 235.0, HRMS: 235.0141, calcd: 235.0156 [M+2H^{+}].

5-Methoxy-1-(2-methylbenzyl)-1*H*-indole (S6)



To a solution of 5-methoxyindole (300 mg, 2.0 mmol) in dimethylacetamide (10 mL) was added sodium hydride (120 mg, 3.0 mmol, 1.5 equiv.) at 23 °C. After 15 min, 2-methylbenzyl chloride (252 mg, 1.80 mmol, 0.9 equiv.) was added. After 12 h the reaction was diluted with a 1M aqueous solution of potassium hydrogen sulfate (15 mL), and the aqueous layer extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography [hexanes, silica gel] to yield indole **S6** (401 mg, 89 %). – ^{1}H NMR (500 MHz): 2.37 (3 H, s), 3.93 (3 H, s), 5.27 (2 H, s), 6.55 (1 H, d, *J* = 3 Hz), 6.82 (7.5 Hz), 6.95 (1 H, dd, *J* = 2.5, 8.5 Hz), 7.06 (1 H, d, *J* = 3 Hz), 7.15–7.19 (1 H, m), 7.22–7.28 (5 H, m) ppm. – ^{13}C NMR (125 MHz): 19.1 (CH_3), 48.3 (CH_2), 55.9 (CH_3), 101.2 (CH), 102.7 (CH), 110.4 (CH), 112.1 (CH), 126.4 (CH), 127.4 (CH), 127.8 (CH), 128.7 (CH), 129.1 (C), 130.5 (CH), 131.9 (C), 135.4 (C), 135.8 (C), 154.2 (C) ppm. – IR: 1133, 1239, 1345, 1487, 1577, 1622, 2833, 2918, 3018 cm^{-1}. – MS (ESI): 251.9, 252.9, HRMS: 252.1387, calcd: 252.1383 [M+H^{+}].

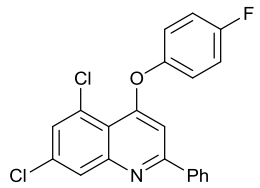
2-Benzyl-4-methoxyquinoline[14] (S7)



4-Methoxyquinoline 1-oxide[14] (70 mg, 0.4 mmol) was reacted with copper(I) chloride (4 mg, 0.04 mmol, 10 mol %), magnesium chloride (80 mg, 0.80 mmol, 2 equiv), and benzylmagnesium bromide (800 μL, 0.80 mmol, 2 equiv, 1M in tetrahydrofuran) in diethyl ether (2 mL). The crude product was purified by column chromatography to yield quinoline **S7** (60 mg, 61 %). – ^{1}H NMR (500 MHz): 3.93 (3 H, s), 4.72 (2 H, s), 6.56 (1 H, s), 7.24–7.49 (6 H, m), 7.70 (1 H, dt, *J* = 1, 8 Hz), 8.04 (1 H, d, *J* = 8.5 Hz), 8.14 (1 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (125

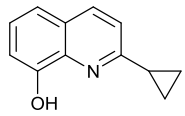
MHz): 46.0, 55.3, 100.1, 120.1, 121.7, 125.2, 126.5, 127.6, 128.3, 129.1, 129.9, 139.3, 148.6, 162.4, 162.6 ppm. – IR: 1113, 1233, 1362, 1446, 1569, 1619, 2867, 2957, 3049 cm^{-1}.

5,7-Dichloro-4-(4-fluorophenoxy)-2-phenylquinoline[14] (S8)



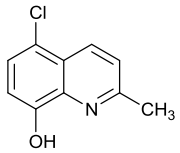
5,7-Dichloro-4-(4-fluorophenoxy)quinoline 1-oxide (25 mg, 0.077 mmol) was reacted with copper(I) chloride (1 mg, 0.008 mmol, 10 mol %), magnesium chloride (14 mg, 0.144 mmol, 2 equiv), and phenylmagnesium bromide (78 μL, 0.233 mmol, 3 equiv, 3.2M in diethyl ether) in diethyl ether (400 μL). The crude product was purified by column chromatography to yield quinoline **S8** (20 mg, 68 %). – ^{1}H NMR (500 MHz): 7.09 (1 H, s), 7.19–7.20 (4 H, m), 7.39–7.48 (3 H, m), 7.57 (1 H, d, *J* = 2 Hz), 7.94–7.96 (2 H, m), 8.10 (1 H, d, *J* = 2 Hz) ppm. – ^{13}C NMR (125 MHz): 104.7, 117.2 (d, *J* = 23 Hz), 122.2 (d, *J* = 8.5 Hz), 127.4, 128.1, 128.9, 129.2, 130.0, 130.1, 135.2, 138.3, 150.1, 151.7, 159.0, 159.6, 160.9, 162.9 ppm. – IR: 1109, 1259, 1340, 1482, 1527, 2978, 3021, 3046 cm^{-1}.

2-Cyclopropylquinolin-8-ol[14] (S9)



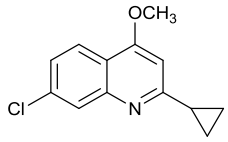
8-Hydroxyquinoline 1-oxide (28 mg, 0.177 mmol) was reacted with copper(I) chloride (2 mg, 0.017 mmol, 10 mol %), magnesium chloride (26 mg, 0.265 mmol, 1.5 equiv.), and cyclopropylmagnesium chloride (1.4 mL, 0.708 mmol, 4 equiv., 0.5M in tetrahydrofuran) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield quinoline **S9** (27 mg, 84 %). – ^{1}H NMR (500 MHz): 1.09–1.13 (2 H, m), 1.18–1.21 (2 H, m), 2.17–2.23 (1 H, m), 7.11 (1 H, dd, *J* = 1, 7.5 Hz), 7.26 (1 H, dd, *J* = 1 H, 8.5 Hz), 7.30–7.35 (2 H, m), 7.99 (1 H, d, *J* = 8.5 Hz) 8.04–8.22 (1 H, br s) ppm. – ^{13}C NMR (75 MHz): 11.19, 17.53, 109.67, 117.61, 121.31, 126.10, 126.72, 135.80, 137.62, 151.32, 161.49 ppm. – IR: 1238, 1318, 1474, 1572, 1697, 2913, 2999, 3034 cm^{-1}.

5-Chloro-2-methylquinolin-8-ol[14] (S10)



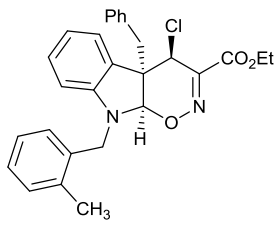
5-Chloro-8-hydroxyquinoline 1-oxide[14] (60 mg, 0.31 mmol) was reacted with copper(I) chloride (3 mg, 0.031 mmol, 10 mol %), magnesium chloride (92 mg, 0.92 mmol, 3 equiv), and methylmagnesium bromide (387 μL, 1.22 mmol, 4 equiv, 3.2M in diethyl ether) in diethyl ether (1.5 mL). The crude product was purified by column chromatography to yield quinoline **S10** (57 mg, 96 %). – ^{1}H NMR (500 MHz): 2.76 (3 H, s), 7.07 (1 H, d, *J* = 8.5 Hz), 7.41–7.45 (2 H, m), 8.39 (1 H, d, *J* = 9 Hz) ppm. – ^{13}C NMR (125 MHz): 24.8, 109.8, 120.3, 123.5, 124.5, 126.4, 133.4, 138.1, 150.8, 157.7 ppm. – IR: 1042, 1204, 1368, 1471, 1624, 3065, 3124, 3206 cm^{-1}.

7-Chloro-2-cyclopropyl-4-methoxyquinoline[14] (S11)



7-Chloro-4-methoxyquinoline 1-oxide[14] (42 mg, 0.20 mmol) was reacted with copper(I) chloride (2 mg, 0.02 mmol, 10 mol %), magnesium chloride (30 mg, 0.30 mmol, 1.5 equiv), and cyclopropylmagnesium bromide (800 μL, 0.40 mmol, 2 equiv, 0.5M in tetrahydrofuran) in diethyl ether (1 mL). The crude product was purified by column chromatography to yield quinoline **S11** (32 mg, 68 %). – ^{1}H NMR (500 MHz): 0.85–1.45 (4 H, m), 1.89–2.18 (1 H, m), 4.05 (3 H, s), 6.64 (1 H, s), 7.38 (1 H, d, *J* = 8.5 Hz), 7.99 (1 H, s), 8.07 (1 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 26.0, 33.5, 49.3, 55.6, 98.8, 118.6, 123.1, 125.6, 127.5, 135.5, 149.1, 162.3, 168.8 ppm. – IR: 906, 1072, 1161, 1237, 1342, 1429, 1550, 1607, 3037, 3094 cm^{-1}.

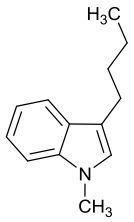
Ethyl (4*R**,4a*R**,9a*R**)-4a-benzyl-4-chloro-9-(2-methylbenzyl)-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole-3-carboxylate (S12)



According to GP5, **S3** (75 mg, 0.24 mmol, 1 equiv.) was reacted with ethyl 3,3-dichloro-2-(hydroxyimino)propanoate (48 mg, 0.24 mmol, 1 equiv.) and *rac*-BINAP (31 mg, 0.05 mmol, 20 mol%) at –15 °C for 56 h to yield 1,2-oxazine **S12** (47 mg, 41 %). – ^{1}H NMR (500 MHz): 1.34 (3 H, t, *J* = 7 Hz), 2.24 (1 H, s), 3.02 (1 H, d, *J* = 14 Hz), 3.11 (1 H, d, *J* = 14 Hz), 4.30–4.37 (2 H, m), 4.43 (1 H, d, *J* = 16 Hz), 4.52

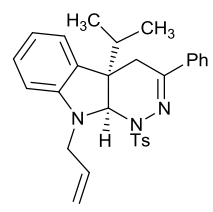
(1 H, d, *J* = 16 Hz), 5.10 (1 H, s), 5.15 (1 H, s), 6.39 (1 H, d, *J* = 7.5 Hz), 6.79–6.86 (3 H, m), 7.04–7.30 (7 H, m), 7.36–7.39 (3 H, m) ppm. – ^{13}C NMR (125 MHz): 14.0, 19.1, 44.1, 45.3, 46.6, 57.0, 62.7, 98.9, 106.4, 118.4, 125.9, 126.2, 127.4, 127.8, 128.0, 128.3, 128.6, 129.5, 130.3, 134.2, 136.1, 149.9, 160.9, 163.9 ppm. – IR: 1014, 1153, 1289, 1354, 1453, 1553, 1605, 2906, 3025, 3053 cm^{-1}. – MS (ESI): 474.8, 475.9, 476.9, HRMS: 475.1782, calcd: 475.1783 [M+H$^+$].

3-Butyl-1-methyl-1*H*-indole[6] (S13)



To a solution of 1-methyl-1*H*-indole[7] (1.0 g, 7.63 mmol,1 equiv.) and *n*-butyraldehyde (0.69 mL, 7.63 mmol, 1 equiv.) in dichloromethane (76 mL) at 0 °C was added triethylsilane (3.41 mL, 21.36 mmol, 2.8 equiv.) and trifluoroacetic acid (1.17 mL, 15.26 mmol, 2 equiv.). The reaction was allowed to warm to 23 °C over 2 h before being diluted with H_2O (100 mL). The aqueous layer was extracted with dichloromethane (5 × 15 mL), and the combined organic layers dried over anhydrous sodium sulfate. The organic layers were concentrated, and the crude product purified by column chromatography [hexanes, silica gel] to yield indole **S13** (962 mg, 67 %). – ^{1}H NMR (500 MHz): 0.99–1.03 (3 H, m), 1.44–1.49 (2 H, m), 1.71–1.74 (2 H, m), 2.79 (2 H, t, *J* = 8 Hz), 3.77 (3 H, s), 6.85 (1 H, s), 7.13 (1 H, dt, *J* = 1, 7 Hz), 7.21-7.32 (2 H, m), 7.63 (1 H, d, *J* = 8.5 Hz) ppm. – ^{13}C NMR (125 MHz): 14.0, 22.7, 24.8, 32.5, 32.7, 109.1, 115.7, 118.4, 119.1, 121.4, 126.0, 128.0, 137.1 ppm. – IR: 1013, 1130, 1248, 1376, 1471, 1614, 2857, 2926, 3056 cm^{-1}. – MS (ESI): 188.1, calcd: 188.1 [M+H$^+$].

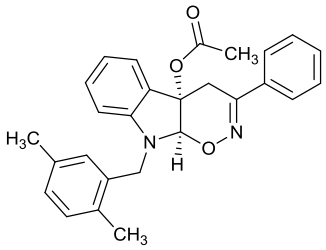
(4a*S**,9a*R**)-9-allyl-4a-isopropyl-3-phenyl-1-tosyl-4,4a,9,9a-tetrahydro-1*H*-pyridazino[3,4-*b*]indole (S14)



To a solution of 1-allyl-3-isopropyl indole (100 mg, 0.5 mmol, 1 equiv.) and *N*'-(2-chloro-1-phenylethylidene)-4-methylbenzenesulfonohydrazide[8] (162 mg, 0.5 mmol, 1 equiv.) in dichloromethane (5 mL) was added sodium bicarbonate (420 mg, 5.0 mmol, 10 equiv.) at 23 °C. The reaction was allowed to stir for 23 h before being concentrated under reduced

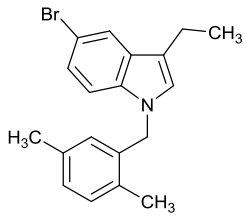
pressure and purified by column chromatography to yield 1,2-pyridazine **S14** (152 mg, 63 %). – ^{1}H NMR (500 MHz): 0.97 (3 H, d, *J* = 15 Hz), 2.40 (3 H, s), 2.44 (1 H, dd, *J* = 2, 14.5 Hz), 2.88 (1 H, dd, *J* = 2, 14.5 Hz), 4.09 (2 H, d, *J* = 5.5 Hz), 5.18 (1 H, dd, *J* = 1 , 10 Hz), 5.33 (1 H, d, *J* = 17 Hz), 5.76–5.87 (1 H, m), 5.89 (1 H, d, *J* = 2.5 Hz), 6.38 (1 H, d, *J* = 8 Hz), 6.61 (1 H, t, *J* = 7.5 Hz), 6.97–7.01 (2 H, m), 7.25–7.32 (5 H, m), 7.50 (2 H, d, *J* = 7.5 Hz), 7.91 (2 H, d, *J* = 7.5 Hz) ppm. – ^{13}C NMR (125 MHz): 17.4, 17.5, 34.5, 35.1, 47.8, 54.7, 107.4, 107.7, 117.7, 122.7, 125.9, 126.6, 128.0, 128.2, 128.6, 129.1, 130.2, 131.2, 133.0, 135.7, 143.7, 150.1, 162.8 ppm. – IR: 1095, 1224, 1370, 1464, 1604, 2873, 2960, 3060 cm^{-1}. – MS (ESI): 486.2, HRMS: 486.2186, calcd: 486.2210 [M+H^{+}].

(4a*S*,9a*R*)-9-(2,5-Dimethylbenzyl)-3-phenyl-9,9a-dihydro-[1,2]oxazino[6,5-*b*]indol-4a(4*H*)-yl acetate[1] (S15)



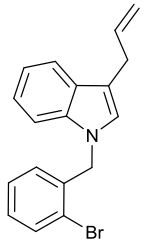
According to GP1, 1-(2,5-dimethylbenzyl)-1*H*-indol-3-yl acetate (42 mg, 0.142 mmol) was reacted with 2-chloro-1-phenylethan-1-one oxime (23 mg, 0.142 mmol, 1 equiv.) for 48 h to yield 1,2-oxazine **S15** (52 mg, 85 %). 96% *ee*. – $[\alpha]_D^{24}$ +110° (*c* 0.11, $CHCl_3$). – ^{1}H NMR (500 MHz): 2.08 (3 H, s), 2.29 (3 H, s), 2.34 (3 H, s), 3.24 (1 H, d, *J* = 14 Hz), 3.76 (1 H, d, *J* = 14 Hz), 4.53 (1 H, d, *J* = 16.5 Hz), 4.67 (1 H, d, *J* = 16.5 Hz), 5.66 (1 H, s), 6.31 (1 H, d, *J* = 7.5 Hz), 6.66 (1 H, ddd, *J* = 1, 7.5, 7.5 Hz), 7.02 (1 H, d, *J* = 7.5 Hz), 7.06–7.10 (2 H, m), 7.16–7.20 (2 H, m), 7.25–7.30 (2 H, m), 7.34–7.43 (3 H, m), 7.58–7.59 (2 H, m) ppm. – ^{13}C NMR (75 MHz): 18.8 (CH_3), 21.2 (CH_3), 21.5 (CH_3), 21.8 (CH_3), 32.1 (CH_2), 46.1 (CH_2), 88.1 (C), 97.0 (CH), 106.0 (CH), 117.7 (CH), 124.4 (CH), 125.2 (CH), 125.7 (CH), 126.1 (CH), 127.6 (CH), 128.1 (CH), 128.5 (CH), 128.9 (CH), 130.0 (CH), 130.4 (CH), 130.8 (CH), 132.6 (C), 133.5 (C), 134.6 (C), 135.3 (C), 151.9 (C), 168.1 (C), 169.2 (C) ppm. – IR: 813, 910, 1019, 1087, 1170, 1319, 1398, 1444, 1490, 1609, 1714, 2915, 3052 cm^{-1}.

5-Bromo-1-(2,5-dimethylbenzyl)-3-ethyl-1*H*-indole[1] (S16)



To a solution of 5-Bromo-1-(2,5-dimethylbenzyl)-1*H*-indole[1] (1.2 g, 3.82 mmol) in dichloromethane (38 mL) was added acetaldehyde (213 μL, 3.82 mmol, 1 equiv.), triethylsilane (1.70 mL, 10.69 mmol, 2.8 equiv.), and trifluoroacetic acid (589 μL, 7.64 mmol, 2 equiv.) at 0 °C sequentially. After 12 h the reaction was diluted with water (20 mL), and the organic layer separated. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography [hexanes, silica gel] to yield indole **S16** (1.03 g, 80 %). – m.p.: 81–84 °C. – ^{1}H NMR (300 MHz): 1.29 (3 H, dt, *J* = 1.45), 2.21 (6 H, s), 2.65–2.78 (2 H, m), 5.15 (2 H, d, *J* = 5 Hz), 6.58 (1 H, s), 6.76 (1 H, d, *J* = 5 Hz), 6.96–7.04 (1 H, m), 7.05–7.14 (2 H, m), 7.25–7.35 (1 H, m), 7.72 (1 H, d, *J* = 4 Hz) ppm. – ^{13}C NMR (75 MHz): 15.11, 18.70. 19.11, 21.52, 48.47, 111.26, 112.4, 117.8, 122.0, 124.6, 125.9, 128.5, 128.8, 130.7, 132.9, 135.0, 136.2 ppm. – IR: 1183, 1469, 2249, 2966 cm^{-1}.

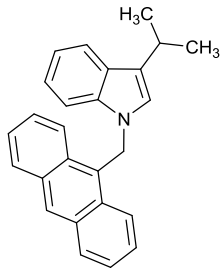
3-Allyl-1-(2-bromobenzyl)-1*H*-indole (S17)



To a solution of 3-allyl-1*H*-indole[9] (314 mg, 2.0 mmol, 1 equiv.) in dimethylacetamide (10 mL) was added sodium hydride (160 mg, 4.0 mmol, 2 equiv., 60% in mineral oil). After 15 min 1-bromo-2-(chloromethyl)benzene (385 mg, 1.9 mmol, 0.9 equiv.) was added. After 12 h the reaction was diluted with a 1M aqueous solution of potassium hydrogen sulfate (50 mL). The aqueous layer was extracted with EtOAc (5 x 20 mL), and the combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography [hexanes, silica gel] to yield indole **S17** (589 mg, 95 %). – ^{1}H NMR (500 MHz): 3.69 (2 H, d, *J* = 5.5 Hz), 5.23–5.35 (2 H, m), 5.42 (2 H, s), 6.20–6.28 (1 H, m), 6.66–6.69 (1 H, m), 7.01 (1 H, s), 7.18–7.22 (2 H, m), 7.25–7.35 (4 H, m), 7.70–7.72 (1 H, m), 7.79 (1 H, d, *J* = 7.5 Hz) ppm. – ^{13}C NMR (125 MHz): 30.0 (CH_2), 50.1 (CH_2), 109.8 (CH), 114.2 (C), 115.4 (CH_2), 119.4 (CH), 119.5 (CH), 122.2 (CH), 122.3 (C), 126.1 (CH), 128.0 (CH), 128.2 (CH), 128.3 (C), 129.1 (CH), 132.8 (CH), 137.0 (C), 137.1 (C), 137.4 (CH)

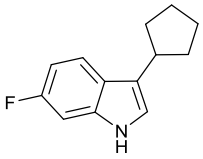
ppm. – IR: 1014, 1106, 1268, 1349, 1441, 1555, 1614, 2852, 2924, 3055 cm^{-1}. – MS (ESI): 326.0, 326.9, HRMS: 326.0548, calcd: 326.0538 [$M+H^+$].

1-(Anthracen-9-ylmethyl)-3-isopropyl-1*H*-indole (S18)



To a solution of 3-isopropyl-1*H*-indole[4] (78 mg, 0.49 mmol, 1 equiv.) in dimethylacetamide (2.5 mL) was added sodium hydride (39 mg, 0.98 mmol, 2 equiv.) at 23 °C. After 15 min, 9-(chloromethyl)anthracene (100 mg, 0.44 mmol, 0.9 equiv.) was added and the reaction was stirred for 12 h. The reaction was diluted with a 1M aqueous solution of potassium hydrogen sulfate (25 mL), and the aqueous layer extracted with EtOAc (5 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the crude product purified by column chromatography [hexanes, silica gel] to yield indole **S18** (89 mg, 58 %). – m.p.: 146–149 °C. – ^{1}H NMR (500 MHz): 1.18 (6 H, d, *J* = 6.5 Hz), 3.07 (1 H, sext., *J* = 6.5 Hz), 6.08 (2 H, s), 6.33 (1 H, s), 7.24 (1 H, d, *J* = 7.5 Hz), 7.41 (1 H, t, *J* = 7 Hz), 7.50-7.55 (4 H, m), 7.75 (2 H, t, *J* = 8.5 Hz), 8.11 (2 H, dd, *J* = 3, 7.5 Hz), 8.20 (2 H, dd, *J* = 1.5, 8.4 Hz), 8.59 (1 H, s) ppm. – ^{13}C NMR (125 MHz): 14.2, 22.8, 23.3, 25.6, 29.8, 32.0, 42.0, 109.3, 118.9, 119.9, 121.6, 121.9, 122.8, 123.9, 125.3, 126.2, 127.0, 127.6, 128.9, 129.3, 131.4, 131.5, 137.1 ppm. – IR: 1142, 1240, 1460, 1578, 1642, 2854, 2927, 2957, 3057 cm^{-1}. – MS (ESI): 350.1, HRMS: 350.1908, calcd: 350.1903 [$M+H^+$].

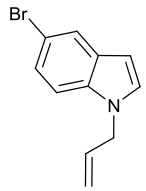
3-Cyclopentyl-6-fluoro-1*H*-indole[1] (S19)



In an oven dried flask, triethylsilane (1.41 mL, 8.88 mmol, 2.4 equiv.) and trichloroacetic acid (904 mg, 5.55 mmol, 1.5 equiv.) were dissolved in toluene (4 mL) and the resulting solution was heated to 70 °C. A solution of 6-fluoroindole (500 mg, 3.70 mmol) and cyclopentanone (0.360 mL, 4.07 mmol, 1.1 equiv.) in toluene (4 mL), was added over 1 h. After an additional 20 min at 70 °C the solution was quenched with a 10% aqueous solution of sodium carbonate. The organic layer was separated, dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by column

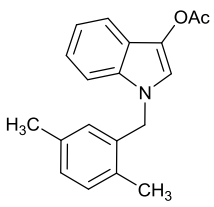
chromatography [hexanes, silica gel] to afford the disubstituted indole **S19** (500 mg, 67%). – m.p.: 57 °C. – ^{1}H NMR: 1.65–1.86 (6 H, m), 2.13–2.21 (2 H, m), 3.22–3.28 (1 H, m), 6.89 (1 H, dt, *J* = 2, 9 Hz), 6.96 (1 H, s), 7.05 (1 H, dd, *J* = 2, 9 Hz), 7.55–7.58 (1 H, m), 7.55–7.95 (1 H, br s) ppm. – ^{13}C NMR: 25.2, 33.2, 36.9, 97.1, 108.3, 108.7, 119.7, 124.4, 136.4, 158.1 ppm. – ^{19}F NMR: –121.98 ppm. – IR: 832, 1026, 1136, 1303, 1493, 1548, 1622, 1867, 2868, 2951 cm^{-1}. – MS (ESI): 204.0 [M + H^{+}].

1-Allyl-5-bromo-1*H*-indole[10] (S20)



To a solution of 5-bromoindole (500 mg, 2.55 mmol) in dimethylacetamide (13 mL) was added sodium hydride (204 mg, 5.10 mmol, 1.5 equiv.) at 23 °C. The reaction stirred for 15 min before allyl bromide (330 μL, 5.10 mmol, 2 equiv.) was added. After 12 h the reaction was diluted with a 1M aqueous solution of potassium hydrogen sulfate (20 mL), and the aqueous layer extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and the crude product purified by column chromatography [hexanes, silica gel] to yield indole **S20** (479 mg, 80 %). – ^{1}H NMR (500 MHz): 4.71–4.73 (2 H, m), 5.07 (1 H, dd, *J* = 1, 17.5 Hz), 5.22 (1 H, dd, *J* = 1, 10.5 Hz), 5.95–6.02 (1 H, m), 6.46 (1 H, d, *J* = 3.5 Hz), 7.10 (1 H, d, *J* = 3 Hz), 7.19 (1 H, d, *J* = 8 Hz), 7.27–7.30 (1 H, m), 7.76 (1 H, s) ppm. – ^{13}C NMR (125 MHz): 49.0, 101.0, 111.1, 112.8, 117.5, 123.4, 124.4, 129.1, 130.4, 133.1, 134.8 ppm. – IR: 1035, 1151, 1239, 1329, 1419, 1506, 2852, 2924, 3083 cm^{-1}.

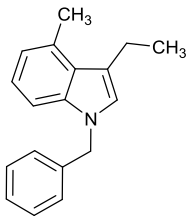
1-(2,5-Dimethylbenzyl)-1*H*-indol-3-yl acetate[1] (S21)



1-(2,5-dimethylbenzyl)-1*H*-indole[1] was added to a oven dried pressure vessel cooled under argon with $Pd(OAc)_2$ (28 mg, 0.127 mmol, 0.03 equiv.), $PhI(OAc)_2$ (2.74 g, 8.50 mmol, 2 equiv.), potassium hydroxide (238 mg, 4.25 mmol, 1 equiv.), in acetonitrile (15 mL). The solution was heated to 70 °C over 12 h. The solution was concentrated and the crude product was purified by column chromatography [hexanes/EtOAc, silica gel] to yield indole **S21** (800 mg, 65 %). – m.p.: 114–115 °C. – ^{1}H NMR (300 MHz): 2.21

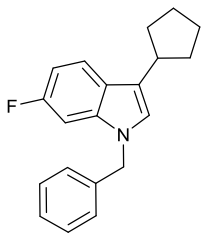
(3H, s), 2.23 (3 H, s), 2.34 (3 H, s), 5.19 (2 H, s), 6.70 (1 H, s), 7.01 (1 H, dd, *J* = 0.5, 8.5 Hz), 7.08 (1 H, d, *J* = 7.5 Hz), 7.13 (1 H, td, *J* = 1, 7.4 Hz), 7.16 (2 H, s), 7.11 (1 H, td, *J* = 1, 7.5 Hz), 7.57 (1 H, dt, *J* = 1, 8 Hz) ppm. – ^{13}C NMR (75 MHz): 18.6 (CH_3), 20.9 (CH_3), 48.1 (CH_2), 109.5 (CH), 116.9 (CH), 117.6 (CH), 119.5 (CH), 120.3 (C), 122.4 (CH), 128.4 (C), 128.5 (CH), 129.6 (C), 130.4 (CH), 132.7 (C), 132.5 (C), 134.5 (C), 135.9 (C), 168.5 (C) ppm. – IR: 1205, 1368, 1466, 1744, 2251 cm^{-1}.

1-Benzyl-3-ethyl-4-methyl-1*H*-indole (S22)



To a solution of 1-benzyl-4-methyl-1*H*-indole[11] (500 mg, 2.26 mmol, 1 equiv.) and acetaldehyde (100 mg, 2.26 mmol, 1 equiv.) in dichloromethane (23 mL) was added triethylsilane (1.01 mL, 6.32 mmol, 2.8 equiv.) and trifluoroacetic acid (0.35 mL, 4.52 mmol, 2 equiv.) sequentially at 0 °C. After 2 h the reaction was concentrated under reduced pressure and purified by column chromatography [hexanes/EtOAc, silica gel] to yield indole **S22** (401 mg, 71 %). – ^{1}H NMR (300 MHz): 1.50 (3 H, t, *J* = 7.5 Hz), 2.91 (3 H, s), 3.18 (2 H, quart., *J* = 7.5 Hz), 5.35 (2 H, s), 7.01–7.45 (9 H, m). ppm. – ^{13}C NMR (75 MHz): 15.7, 20.5, 20.7, 49.9, 107.7, 119.1, 120.7, 121.8, 125.1, 126.78, 126.9, 127.6, 128.8, 131.4, 137.3, 138.1 ppm. – IR: 1223, 1333, 1430, 1574, 2878, 3028 cm^{-1}. – MS ESI: 250.0, HRMS: 250.1599, calcd: 250.1590 [M+H^{+}].

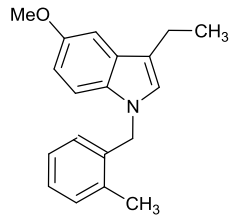
1-Benzyl-3-cyclopentyl-6-fluoro-1*H*-indole[1] (S23)



According to GP1, indole **S19** (242 mg, 1.30 mmol) in DMF (2.6 mL) was reacted with sodium hydride (78 mg, 1.95 mmol, 1.5 equiv., 60% in mineral oil) and benzyl chloride (220 μL, 1.95 mmol, 1.5 equiv.). The product was purified by column chromatography [hexanes/EtOAc, silica gel] to yield indole **S23** (248 mg, 65 %). – ^{1}H NMR (500 MHz): 1.88–2.10 (6 H, m), 2.34–2.44 (2 H, m), 3.47 (1 H, quint, *J* = 8 Hz), 5.29 (2 H, s), 7.07–7.13 (3 H, m), 7.28 (2 H, dd, *J* = 1.5, 6.5 Hz), 7.40–7.50 (3 H, m), 7.79 (1 H, dd, *J* = 6, 9 Hz) ppm. – ^{13}C NMR (125 MHz): 25.2, 33.2, 36.9, 49.8, 95.9 (d, $J_{C\text{-}F}$ = 26.5 Hz), 107.3 (d, $J_{C\text{-}F}$ = 24.5 Hz), 120.4 (d, $J_{C\text{-}F}$ = 10 Hz), 120.6, 124.2 (d, $J_{C\text{-}F}$ = 4 Hz), 124.6, 126.6,

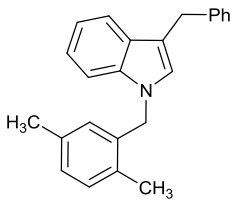
127.5, 128.6, 128.7, 136.9 (d, J_{C-F} = 12 Hz), 137.3, 158.8, 160.7 ppm. – IR: 908, 1173, 1332, 1453, 1486, 1557, 1620, 2867, 2951, 3030 cm^{-1}.

3-Ethyl-5-methoxy-1-(2-methylbenzyl)-1*H*-indole (S24)



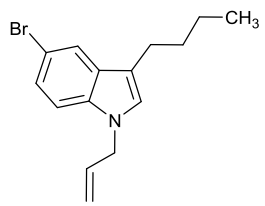
To a solution of **S6** (251 mg, 1.00 mmol, 1 equiv.) and acetaldehyde (45 mg, 1.00 mmol, 1 equiv.) in dichloromethane (10 mL) was added triethylsilane (325 mg, 2.80 mmol, 2.8 equiv.) and trifluoroacetic acid (228 mg, 2.00 mmol, 2 equiv.) sequentially at 0 °C. After 2 h the reaction was concentrated under reduced pressure and purified by column chromatography [hexanes/EtOAc, silica gel] to yield indole **S24** (184.5 mg, 66 %). – m.p.: 64–68 °C. – ^{1}H NMR (500 MHz): 1.34 (3 H, t, *J* = 7 Hz), 2.33 (3 H, s), 2.78 (2 H, quart., *J* = 7 Hz), 3.90 (3 H, s), 5.22 (2 H, s), 6.76–6.87 (3 H, m), 7.10–7.22 (5 H, m) ppm. – ^{13}C NMR (125 MHz): 14.5, 18.4, 19.1, 48.1, 56.0, 101.1, 110.3, 111.7, 117.4, 125.3, 126.3, 127.3, 127.6, 128.3, 130.3, 132.2, 135.6, 135.7, 153.7 ppm. – IR: 1041, 1176, 1266, 1350, 1461, 1579, 1621, 2842, 2917, 2961 cm^{-1}. – MS (ESI): 280.1, HRMS: 280.1686, calcd: 280.1696 [$M+H^{+}$].

3-Benzyl-1-(2,5-dimethylbenzyl)-1*H*-indole (S25)



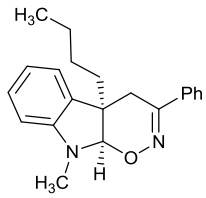
To a solution of 1-(2,5-dimethylbenzyl)-1*H*-indole[1] (300 mg, 1.37 mmol, 1 equiv.) and benzaldehyde (145 mg, 1.36 mmol, 1 equiv.) in dichloromethane (13.6 mL) was added triethylsilane (0.61 mL, 3.81 mmol, 2.8 equiv.) and trifluoroacetic acid (0.21 mL, 2.72 mmol, 2 equiv.) at 0 °C. The reaction was allowed to warm to 23 °C, and concentrated under reduced pressure after 2 h. The crude product was purified by column chromatography [hexanes, silica gel] to yield indole **S25** (404 mg, 91 %). –^{1}H NMR (300 MHz): 2.22 (3 H, s), 2.26 (3 H, s), 4.14 (2 H, s), 5.20 (2 H, s), 6.64 (1 H, s), 6.80 (1 H, s), 7.01–7.29 (10 H, m), 7.54 (1 H, dd, *J* = 1, 7.5 Hz) ppm. – ^{13}C NMR (75 MHz): 18.8, 21.2, 48.0, 109.7, 114.7, 119.2, 119.5, 121.8, 125.9, 126.5, 128.2, 128.3, 128.4, 128.7, 130.5, 132.7, 135.3, 135.9, 137.1, 141.6 ppm. – IR: 1096, 1251, 1350, 1466, 1494, 1554, 1612, 2917, 3024 cm^{-1}. – MS (ESI): 326.0, HRMS: 316.1903, calcd: 326.1903 [$M+H^{+}$].

1-Allyl-5-bromo-3-butyl-1*H*-indole (S26)



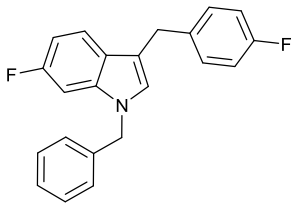
To a solution of **S20** (150 mg, 0.64 mmol, 1 equiv.) and *n*-butyraldehyde (46 mg, 0.64 mmol, 1 equiv.) in dichloromethane (6.5 mL) was added triethylsilane (208 mg, 1.79 mmol, 2.8 equiv.) and trifluoroacetic acid (100 μL, 1.28 mmol, 2 equiv.) sequentially at 0 °C. After 2 h the reaction was concentrated under reduced pressure and the crude product purified by column chromatography [hexanes/EtOAc, silica gel] to yield indole **S26** (161 mg, 87 %). – ^{1}H NMR (500 MHz): 0.96 (3 H, t, *J* = 7.5 Hz), 1.39–1.44 (2 H, m), 1.64–1.70 (2 H, m), 2.70 (2 H, t, *J* = 7.5 Hz), 4.66 (2 H, d, *J* = 5.5 Hz), 5.06 (1 H, dd, *J* = 1, 17 Hz), 5.19 (1 H, dd, *J* = 1, 10.5 Hz), 5.93–6.00 (1 H, m), 6.87 (1 H, s), 7.14 (1 H, d, *J* = 8.5 Hz), 7.25–7.27 (1 H, m), 7.71 (1 H, s) ppm. – ^{13}C NMR (125 MHz): 14.3 (CH_3), 21.1 (CH_2), 29.8 (CH_2), 49.0 (CH_2), 60.4 (CH_2), 101.0 (CH), 111.1 (CH), 112.9 (C), 117.5 (CH_2), 123.4 (CH), 124.4 (CH), 129.1 (CH), 130.4 (C), 133.1 (CH), 134.8 (C) ppm. – IR: 1152, 1210, 1331, 1419, 1467, 2854, 2923, 2953 cm^{-1}. – MS (ESI): 291.0 [M-], HRMS: 292.0697, calcd: 292.0695 [M+H^{+}].

4a-Butyl-9-methyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (S27)



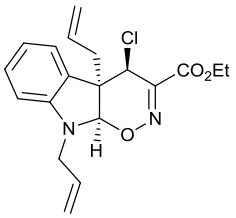
According to GP5, **S13** (75 mg, 0.40 mmol, 1 equiv.) was reacted with 2-chloro-1-phenylethan-1-one oxime (68 mg, 0.40 mmol, 1 equiv.) and BINAP (50 mg, 0.08 mmol, 20 mol%) at –15 °C for 56 h to yield 1,2-oxazine **S27** (77 mg, 59 %). – ^{1}H NMR (500 MHz): 0.90 (3 H, t, *J* = 7.5 Hz), 1.31–1.36 (4 H, m), 1.85–1.90 (2 H, m), 2.71 (1 H, d, *J* = 14 Hz), 3.00 (1 H, d, *J* = 14 Hz), 3.05 (3 H, s), 5.33 (1 H, s), 6.33 (1 H, d, *J* = 8 Hz), 6.60 (1 H, dt, *J* = 1, 8.5 Hz), 6.99 (1 H, dd, *J* = 1, 7.5 Hz), 7.03 (1 H, dt, *J* = 1, 7.5 Hz), 7.30–7.36 (3 H, m), 7.44–7.49 (2 H, m) ppm. – ^{13}C NMR (125 MHz): 14.0, 23.1, 25.8, 30.3, 32.7, 39.7, 51.4, 99.4, 104.6, 117.2, 122.2, 126.2, 128.4, 128.5, 130.1, 131.5, 134.8, 151.0, 170.9 ppm. – IR: 1015, 1124, 1225, 1333, 1466, 1608, 2858, 2928, 2955, 3053 cm^{-1}. – MS (ESI): 321.0, 322.1, HRMS: 321.1959, calcd: 321.1961 [M+H^{+}].

1-Benzyl-6-fluoro-3-(4-fluorobenzyl)-1*H*-indole (S28)



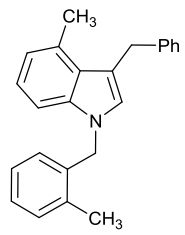
To a solution of 1-benzyl-6-fluoro-1*H*-indole[12] (100 mg, 0.44 mmol, 1 equiv.) and 4-fluorobenzaldehyde (55 mg, 0.44 mmol, 1 equiv.) in dichloromethane (5 mL) was reacted with triethylsilane (142 mg, 1.23 mmol, 2.8 equiv.) and trifluoroacetic acid (100 mg, 0.88 mmol, 2 equiv.) at 0 °C for 2 h. The reaction was diluted with water (5 mL), and the aqueous layer extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure, and purified by column chromatography [hexanes, silica gel] to yield indole **S28** (101 mg, 69 %). – m.p.: 65–67 °C. – ^{1}H NMR (500 MHz): 4.10 (2 H, s), 5.23 (2 H, s), 6.84–7.40 (12 H, m) ppm. – ^{13}C NMR (125 MHz): 30.8, 50.1, 96.1, 96.2 (d), 107.9 (d), 115.2 (d), 120.1 (d), 124.6, 126.7, 126.8, 127.6, 128.9, 129.9 (m), 137.0 (m), 159.1, 160.4, 161.0, 162.4 ppm. – ^{19}F NMR (282 MHz): –117.5, –120.6 ppm. – IR: 1116, 1254, 1357, 1487, 1508, 1622, 2899, 2938, 3031 cm^{-1}. – MS (ESI): 334.1, HRMS: 334.1390, calcd: 334.1402 [M+H^{+}].

Ethyl (4*R*,4a*R*,9a*R*)-4a,9-diallyl-4-chloro-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole-3-carboxylate[1] (S29)



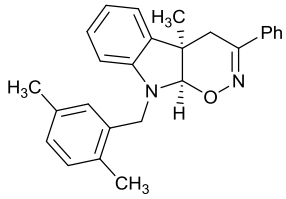
According to GP1, 1,3-diallyl-1*H*-indole[1] (28 mg, 0.142 mmol) was reacted with ethyl 3,3-dichloro-2-(hydroxyimino)propanoate[1] (28 mg, 01.42 mmol, 1 equiv.) and (*S*)-*DTBM*-Segphos (16.7 mg, 14.2 μmol, 10 mol%) for 64 h to yield 1,2-oxazine **S29** (32 mg, 63 %). – 91% *ee*. – $[\alpha]_D^{24}$ +103° (*c* 0.13, $CHCl_3$) – ^{1}H NMR (500 MHz): 1.35 (3 H, t, *J* = 7.5 Hz), 2.42–2.53 (2 H, m), 4.03–4.08 (2 H, m), 4.30–4.41 (2 H, m), 4.94 (1 H, s), 5.12–5.23 (4 H, m), 5.27–5.32 (1 H, m), 5.49–5.76 (1 H, m), 5.82–5.92 (1 H, m), 6.51 (1 H, d, *J* = 8 Hz), 6.78 (1 H, ddd, *J* = 1, 7.5, 7.5 Hz), 7.16–7.23 (2 H, m) ppm. – ^{13}C NMR (125 MHz): 14.1, 43.2, 47.2, 48.0, 55.7, 62.8, 98.7, 106.4, 117.6, 118.3, 120.7, 125.1, 128.1, 129.1, 130.9, 132.7, 149.0, 160.8, 163.7 ppm. – IR: 873, 920, 1004, 1176, 1243, 1439, 1489, 1606, 1719, 2905, 2980, 3055 cm^{-1}.

3-Benzyl-4-methyl-1-(2-methylbenzyl)-1*H*-indole[1] (8)



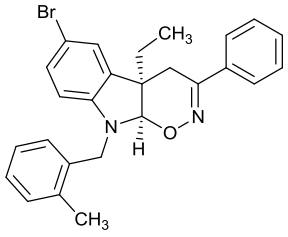
To a solution of 4-methyl-1-(2-methylbenzyl)-1*H*-indole[1] (1.68 g, 7.14 mmol) in dichloromethane (71 mL) was added benzaldehyde (727 μL, 7.14 mmol, 1 equiv.), triethylsilane (3.18 mL, 19.99 mmol, 2.8 equiv.), and trifluoroacetic acid (1.09 mL, 14.28 mmol, 2 equiv.) at 0 °C sequentially. After 3 h the reaction was concentrated under reduced pressure and purified by column chromatography [hexanes/EtOAc, silica gel] to yield indole **8** (1.5 g, 65 %). – m.p.: 115–116 °C. – ^{1}H NMR (500 MHz): 2.34 (3 H, s), 2.58 (3 H, s), 4.32 (2 H, s), 5.24 (2 H, s), 6.70 (1 H, s), 6.72 (1 H, d, *J* = 7.5 Hz), 6.84 (1 H, d, *J* = 6.5 Hz), 7.05–7.15 (3 H, m), 7.18–7.23 (5 H, m), 7.27–7.36 (2 H, m) ppm. – ^{13}C NMR (125 MHz): 18.96, 20.10, 33.09, 47.72, 107.45, 114.64, 120.69, 121.80, 125.66, 126.12, 126.60, 126.82, 127.27, 127.39, 128.20, 128.38, 130.18, 131.17, 135.27, 135.34, 137.33, 142.03 ppm. – IR: 993, 1173, 1231, 1331, 1396, 1425, 1492, 1570, 1603, 2912, 3023 cm^{-1}.

(4a*R*,9a*R*)-9-(2,5-Dimethylbenzyl)-4a-methyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (9)



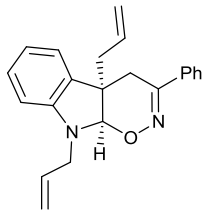
According to GP1, **S2** (100 mg, 0.40 mmol, 1 equiv.) was reacted with 2-chloro-1-phenylethan-1-one oxime (68 mg, 0.40 mmol, 1 equiv.) and (*S*)-Tol-BINAP (54 mg, 0.08 mmol, 20 mol%) for 56 h at –15 °C to yield 1,2-oxazine **9** (43 mg, 28 %). – ^{1}H NMR (500 MHz): 1.57 (3 H, s), 2.29 (3 H, s), 2.33 (3 H, s), 2.68 (1 H, d, *J* = 14 Hz), 3.11 (1 H, d, *J* = 14 Hz), 4.50 (1 H, d, *J* = 16 Hz), 4.67 (1 H, d, *J* = 16 Hz), 5.25 (1 H, s), 6.31 (1 H, d, *J* = 8 Hz), 6.62 (1 H, t, *J* = 7 Hz), 6.97–7.15 (5 H, m), 7.33–7.39 (3 H, m), 7.52 (2 H, d, *J* = 1, 7 Hz) ppm. – ^{13}C NMR (125 MHz): 14.1, 18.8, 27.1, 31.6, 33.5, 47.2, 98.9, 105.2, 117.6, 121.9, 126.1, 127.8, 128.4, 128.5, 130.2, 130.3, 132.7, 133.1, 134.6, 135.1, 135.4, 149.9, 170.5 ppm. – IR: 1039, 1102, 1206, 1318, 1445, 1490, 1608, 2863, 2957, 3047 cm^{-1}. – MS ESI: 383.2, HRMS: 383.2121, calcd: 383.2118 [M+H^{+}].

(4a*R*,9a*R*)-6-Bromo-4a-ethyl-9-(2-methylbenzyl)-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole[1] (10)



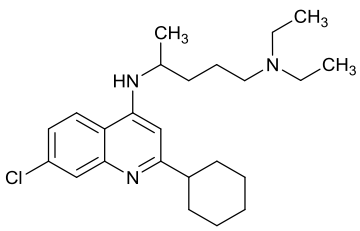
According to GP1, 5-bromo-3-ethyl-1-(2-methylbenzyl)-1*H*-indole[1] (49 mg, 0.142 mmol) was reacted with 2-chloro-1-phenylethan-1-one oxime (23 mg, 0.142 mmol, 1 equiv.) for 48 h to yield 1,2-oxazine **10** (53 mg, 78%). – 92% *ee*. – $[\alpha]_D^{24}$ +134° (*c* 0.15, $CHCl_3$). – ^{1}H NMR (500 MHz): 0.88 (3 H, t, *J* = 7.5 Hz), 1.94 (2 H, q, *J* = 2.5 Hz), 2.30 (3 H, s), 2.32 (3 H, s), 2.69 (1 H, d, *J* = 14 Hz), 3.01 (1 H, d, *J* = 14 Hz), 4.44 (1 H, d, *J* = 16 Hz), 4.67 (1 H, d, *J* = 16 Hz), 5.30 (1 H, s), 6.18 (1 H, d, *J* = 8.5 Hz), 7.03–7.16 (5 H, m), 7.36–7.43 (3 H, m), 7.52–7.54 (2 H, m) ppm. – ^{13}C NMR (75 MHz): 8.3, 18.8, 21.2, 32.6, 32.6, 45.0, 51.7, 96.7, 106.3, 108.6, 125.3, 126.0, 127.7, 128.3, 128.4, 128.5, 128.8, 130.2, 130.2, 131.0, 132.8, 133.0, 134.1, 134.3, 135.3, 139.6, 170.7 ppm. – IR: 1039, 1219, 1279, 1382, 1444, 1489, 1600, 1706, 2913, 2967, 3057 cm^{-1}.

(4a*R*,9a*R*)-4a,9-Diallyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole[1] (11)



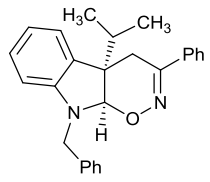
According to GP1, 1,3-diallyl-1*H*-indole[1] (28 mg, 0.142 mmol) was reacted with 2-chloro-1-phenylethan-1-one oxime (24 mg, 0.142 mmol, 1 equiv.) and BINAP (9 mg, 0.01 mmol, 10 mol%) for 48 h at 0 °C to yield 1,2-oxazine **11** (30 mg, 82 %). – ^{1}H NMR (500 MHz): 2.58 (1 H, dd, *J* = 1, 8.5 Hz), 2.62 (1H, dd, *J* = 1, 8.5 Hz), 2.73 (1 H, d, *J* = 14 Hz), 3.01 (1 H, d, *J* = 14 Hz), 3.75 (1 H, dd, *J* = 1.5, 6.5 Hz), 4.10 (1 H, dd, *J* = 1.5, 6.5 Hz), 5.12–5.20 (3 H, m), 5.40 (1 H, s), 5.30 (1 H, s), 5.61–5.70 (1 H, m), 5.87–5.94 (1 H, m), 6.32 (1 H, d, *J* = 7.5 Hz), 6.58 (1 H, ddd, *J* = 1, 7.5, 7.5 Hz), 6.97–7.01 (2 H, m), 7.28–7.36 (3 H, m), 7.45–7.49 (2 H, m) ppm. – ^{13}C NMR (75 MHz): 32.0 (CH_2), 44.2 (CH_2), 46.2 (CH_2), 50.7 (C), 97.3 (CH), 105.1 (CH), 116.6 (CH_2), 117.2 (C), 119.1 (CH_2), 122.3 (CH), 125.9 (CH), 128.2 (CH), 128.3 (CH), 129.9 (CH), 130.8 (C), 132.4 (CH), 133.3 (CH), 134.4 (C), 149.8 (C), 170.3 (C) ppm. – IR: 873, 914, 1076, 1164, 1313, 1442, 1489, 1607, 1640, 2905 cm^{-1}.

N^4-(7-Chloro-2-cyclohexylquinolin-4-yl)-N^1,N^1-diethylpentane-1,4-diamine[14] (12)



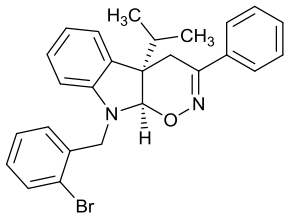
To solution of 4,7-dichloro-2-cyclohexylquinoline[14] (50 mg, 0.179 mmol) in 2-amino-5-diethylaminopentane (1 mL) was added samarium triflate (11 mg, 0.018, 10 mol %) and heated to 140 °C. After 12 h the reaction was concentrated under reduced pressure and purified by column chromatography [dichloromethane /methanol] to yield quinoline **12** (44 mg, 61 %). – ^{1}H NMR (300 MHz): 1.00 (6 H, t, *J* = 7 Hz), 1.24–2.01 (16 H, m), 2.44–2.57 (7 H, m), 2.68–2.77 (1 H, m), 3.72 (1 H, t, *J* = 5 Hz), 5.12 (1 H, d, *J* = 5.5 Hz), 6.31 (1 H, s), 7.24–7.27 (1 H, m), 7.61 (1 H, d, *J* = 8.5 Hz), 7.91 (1 H, d, *J* = 2 Hz) ppm. – ^{13}C NMR (75 MHz): 11.28, 20.21, 23.72, 26.12, 26.59, 29.71, 32.90, 32.93, 34.55, 46.71, 48.01, 52.49, 97.02, 116.38, 120.8, 124.12, 128.32, 128.88, 134.55, 149.09, 168.72 ppm. – IR: 1147, 1227, 1289, 1379, 1449, 1532, 1609, 2850, 2926, 2957 cm^{-1}.

(4a*S*,9a*R*)-9-Benzyl-4a-isopropyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (13)



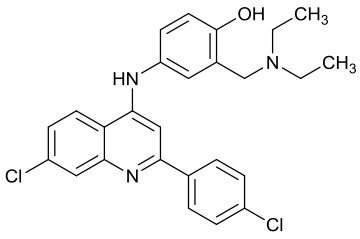
According to GP1, 1-benzyl-3-isopropyl-1*H*-indole[13] (130 mg, 0.52 mmol, 1 equiv.) was reacted with 2-chloro-1-phenylethan-1-one oxime (89 mg, 0.52 mmol, 1 equiv.) and (*S*)-Tol-BINAP (71 mg, 0.10 mmol, 20 mol%) for 48 h to yield 1,2-oxazine **13** (146 mg, 73 %) – 90 % ee. – $[\alpha]_D^{24}$ +87° (*c* 0.13, $CHCl_3$). – ^{1}H NMR (500 MHz): 0.96 (3 H, d, *J* = 7 Hz), 0.99 (3 H, d, *J* = 7 Hz), 2.14 (1 H, sept., *J* = 7 Hz), 2.77 (1 H, d, *J* = 14 Hz), 3.05 (1 H, d, *J* = 14 Hz), 4.55 (1 H, d, *J* = 16 Hz), 4.76 (1 H, d, *J* = 16 Hz), 5.40 (1 H, s), 6.27 (1 H, d, *J* = 8 Hz), 6.56 (1 H, dt, *J* = 1, 7.5 Hz), 6.95 (1 H, dt, *J* = 1, 8 Hz), 7.01 (1 H, dd, *J* = 1, 7 Hz), 7.27–7.46 (10 H, m) ppm. – ^{13}C NMR (125 MHz): 17.4, 17.4, 31.2, 36.1, 47.3, 55.2, 96.1, 105.0, 117.2, 123.1, 126.2, 127.1, 127.5, 128.4, 128.5, 130.0, 134.8, 138.1, 151.1, 171.6 ppm. – IR: 1083, 1140, 1233, 1445, 1505, 2880 3014 cm^{-1}. – MS ESI: 383.0, 383.9, HRMS: 383.2119, calcd: 383.2118 [M+H$^+$].

(4a*S*,9a*R*)-9-(2-Bromobenzyl)-4a-isopropyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole[1] (14)



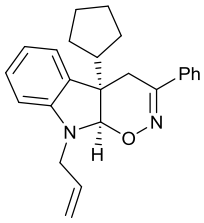
According to GP1, 1-(2-bromobenzyl)-3-isopropyl-1*H*-indole[1] (47 mg, 0.142 mmol) was reacted with 2-chloro-1-phenylethan-1-one oxime (23 mg, 0.142 mmol, 1 equiv.) for 64 h at -15 °C to yield 1,2-oxazine **14** (50 mg, 76%). 90% *ee*. – $[\alpha]_D^{24}$ +82° (*c* 0.15, $CHCl_3$). – ^{1}H NMR (300 MHz): 1.01 (3 H, d, *J* = 6.5 Hz), 1.03 (3 H, d, *J* = 6.5 Hz), 2.17 (1 H, sept, *J* = 7 Hz), 2.79 (1 H, d, *J* = 14 Hz), 3.09 (1 H, d, *J* = 14 Hz), 4.56 (1 H, d, *J* = 17 Hz), 4.85 (1 H, d, *J* = 17 Hz), 5.41 (1 H, s), 6.23 (1 H, d, *J* = 7.5 Hz), 6.60 (1 H, td, *J* = 1, 7.5 Hz), 6.96 (1 H, td, *J* = 1, 7.5 Hz), 7.03 (1 H, dd, *J* = 1, 7.5 Hz), 7.14 (1 H, m), 7.24–7.36 (4 H, m), 7.40–7.49 (3 H, m), 7.65 (1 H, dd, *J* = 1, 7.5 Hz) ppm. – ^{13}C NMR (75 MHz): 17.4 (CH_3), 17.6 (CH_3), 31.2 (CH_2), 36.1 (CH), 48.3 (CH_2), 55.2 (C), 96.4 (CH), 105.2 (CH), 117.4 (C), 123.0 (CH), 126.0 (CH), 127.3 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 129.2 (CH), 129.9 (CH), 130.0 (CH), 132.6 (CH), 134.5 (C), 136.5 (C), 150.5 (C), 171.4 (C) ppm. – IR: 1025, 1094, 1252, 1348, 1440, 1489, 1567, 1605, 2874, 2931, 2963, 3054 cm^{-1}.

5-((7-Chloro-2-(4-chlorophenyl)quinolin-4-yl)amino)-2-((diethylamino)methyl)phenol[14] (15)



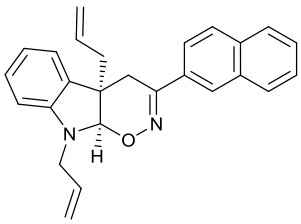
To a solution of 4,7-dichloro-2-(4-chlorophenyl)quinoline[14] (50 mg, 0.163 mmol) in ethanol (2 mL) was added 5-amino-2-((diethylamino)methyl)phenol hydrochloride[15] (43 mg, 0.163 mmol, 1 equiv.) and heated to 100 °C. After 48 h, the reaction was concentrated under reduced pressure and purified by column chromatography [dichloromethane/methanol] to yield quinoline **15** (63 mg, 84 %). – ^{1}H NMR (500 MHz): 1.16 (6 H, d, *J* = 7.5 Hz), 2.68 (4 H, quart, *J* = 7.5 Hz), 3.82 (2 H, s), 6.70–6.78 (3 H, m), 7.00 (1 H, d, *J* = 8 Hz), 7.17–7.59 (4 H, m), 7.80 (1 H, d, *J* = 9 Hz), 7.90 (2 H, d, *J* = 8 Hz), 8.08 (1 H, s) ppm. – ^{13}C NMR (125 MHz): 11.2, 46.3, 56.6, 100.4, 110.0, 112.57, 117.3, 118.7, 121.1, 125.8, 128.6, 128.8, 128.8, 129.0, 129.3, 135.4, 135.6, 138.3, 139.9, 148.1, 149.1, 158.0, 159.8 ppm.

(4a*S,9a*R**)-9-Allyl-4a-cyclopentyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (16)**



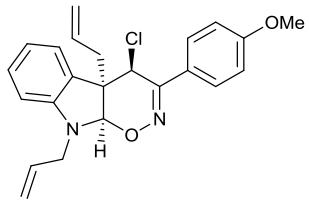
According to GP1, **S1** (50 mg, 0.22 mmol, 1 equiv.) was reacted with 2-chloro-1-phenylethan-1-one oxime (37 mg, 0.22 mmol, 1 equiv.) and *rac*-BINAP (31 mg, 0.05 mmol, 20 mol%) at -15 °C for 56 h to yield 1,2-oxazine **16** (67 mg, 86%). – ^{1}H NMR (500 MHz): 1.35–1.85 (8 H, m), 2.37–2.42 (1 H, m), 2.78 (1 H, d, *J* = 9 Hz), 3.03 (1 H, d, *J* = 9 Hz), 3.96–4.00 (1 H, m), 4.12–4.17 (1 H ,m), 5.22 (1 H, dquart., *J* = 1.5, 10.5 Hz), 5.32 (1 H, dquart., *J* = 1.5, 10.5 Hz), 5.43 (1 H, s), 5.91–5.98 (1 H, m), 6.32 (1 H, d, *J* = 8 Hz), 5.65 (1 H, dt, *J* = 1, 7.5 Hz), 6.99 (1 H, dt, *J* = 1.5, 8 Hz), 7.01 (1 H, d, *J* = 7.5 Hz), 7.29–7.36 (3 H, m), 7.46 (2H, dd, *J* = 1.5, 8.5 Hz), ppm. – ^{13}C NMR (125 MHz): 25.3, 25.4, 27.2, 31.9, 46.3, 48.7, 53.7, 96.8, 105.1, 116.8, 117.2, 122.9, 126.2, 128.2, 130.0, 131.1, 133.7, 134.8, 150.4, 171.1 ppm. – IR: 1174, 1317, 1464, 1492, 1607, 2872, 2958 cm^{-1}. – MS (ESI): 359.1, HRMS: 359.2106, calcd: 359.2118 [M+H^{+}].

(4a*R,9a*R**)-4a,9-Diallyl-3-(naphthalen-2-yl)-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (18)**



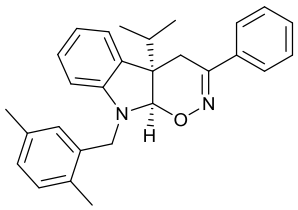
According to GP1, 1,3-diallyl-1*H*-indole[1] (100 mg, 0.51 mmol, 1 equiv.) was reacted with **S4** (111 mg, 0.51 mmol, 1 equiv.) and *rac*-BINAP (68 mg, 0.10 mmol, 20 mol%) for 56 h at -15 °C to yield 1,2-oxazine **18** (109 mg, 56 %). – ^{1}H NMR (500 MHz): 2.60-2.71 (2 H, s), 2.86 (1 H, d, *J* = 14 Hz), 3.17 (1 H, d, *J* = 14 Hz), 4.02 (1 H, dd, *J* = 4.5, 16.5 Hz), 4.16 (1 H, dd, *J* = 4.6, 16.5 Hz), 5.17–5.24 (3 H, m), 5.33 (1 H, dd, *J* = 1.5, 17 Hz), 5.46 (1 H, s), 5.68–5.78 (1 H, m), 5.91–5.99 (1 H, m), 6.35 (1 H, d, *J* = 7.5 Hz), 6.60 (1 H, t, *J* = 7.5 Hz), 7.00 (1 H, t, *J* = 7.5 Hz), 7.07 (1 H, d, *J* = 7 Hz), 7.48–7.51 (2 H, m), 7.72–7.86 (4 H, m), 7.93 (1 H, s) ppm. – ^{13}C NMR (125 MHz): 31.7, 44.3, 46.4, 50.9, 97.6, 105.4, 116.8, 117.5, 119.4, 122.5, 123.2, 126.1, 126.5, 127.1, 127.7, 128.5, 131.1, 132.0, 132.7, 132.9, 133.6, 134.1, 150.1, 170.4 ppm. – IR: 1114, 1215, 1354, 1465, 2890, 2990, 3045 cm^{-1}. – MS (ESI): 380.9, 381.9, HRMS: 381.1961, calcd: 381.1961 [M+H^{+}].

(4*R,4a*R**,9a*R**)-4a,9-Diallyl-4-chloro-3-(4-methoxyphenyl)-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (19)**



According to GP1, 1,3-diallyl-1*H*-indole[1] (100 mg, 0.51 mmol, 1 equiv.) was reacted with **S5** (118 mg, 0.51 mmol, 1 equiv.) and *rac*-BINAP (62 mg, 0.10 mmol, 20 mol%) at 0 °C for 48 h to yield 1,2-oxazine **19** (123 mg, 61 %). – ^{1}H NMR (500 MHz): 3.79 (3 H, s), 4.00 (1 H, dd, *J* = 4.5, 16.5 Hz), 4.08–4.16 (2 H, m), 5.18–5.23 (5 H, m), 5.48 (1 H, s), 5.62–5.67 (1 H, m), 5.88–5.94 (1 H, m), 6.43 (1 H, d, *J* = 8 Hz), 6.68 (1 H, t, *J* = 7.5 Hz), 6.82 (2 H, d, *J* = 8.5 Hz), 7.10 (2 H, d, *J* = 8.5 Hz), 7.14 (1 H, t, *J* = 7.5 Hz), 7.36 (1 H, d, *J* = 7.5 Hz) ppm. – ^{13}C NMR (125 MHz): 42.0 (CH_2), 46.4 (CH_2), 55.3 (CH_3), 56.7 (CH), 57.0 (C), 98.3 (CH), 105.6 (CH), 113.5 (CH), 117.1 (CH_2), 117.5 (CH), 120.3 (CH_2), 124.6 (C), 125.3 (CH), 127.8 (C), 129.5 (CH), 131.8 (CH), 133.3 (CH), 150.5 (C), 161.0 (C), 172.6 (C) ppm. – IR: 1032, 1178, 1322, 1418, 1492, 1514, 1607, 2838, 2909, 3006, 3070 cm^{-1}. – MS (ESI): 395.0, HRMS: 395.1517, calcd: 395.1521 [$M+H^+$].

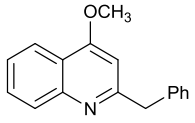
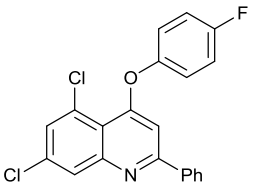
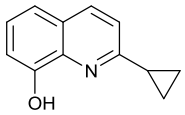
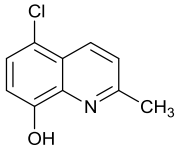
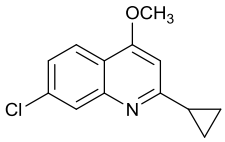
(4a*S*,9a*R*)-9-(2,5-Dimethylbenzyl)-4a-isopropyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole[1] (20)



According to GP1, 1-(2,5-dimethylbenzyl)-3-isopropyl-1*H*-indole (40 mg, 0.142 mmol) was reacted with 2-chloro-1-phenylethan-1-one oxime (23 mg, 0.142 mmol, 1 equiv.) for 56 h at –15 °C to yield 1,2-oxazine **20** (43 mg, 73%). 95% *ee*. – $[\alpha]_D^{24}$ +127° (*c* 0.16, $CHCl_3$). – ^{1}H NMR (500 MHz): 0.96 (3 H, d, *J* = 7 Hz), 1.00 (3 H, d, *J* = 7 Hz), 2.20 (1 H, sept, *J* = 7 Hz), 2.27 (3 H, s), 2.32 (3 H, s), 2.76 (1 H, d, *J* = 13.5 Hz), 3.06 (1 H, d, *J* = 13.5 Hz), 4.45 (1 H, d, *J* = 16 Hz), 4.68 (1 H, d, *J* = 16 Hz), 5.32 (1 H, s), 6.28 (1 H, d, *J* = 16 Hz), 6.57 (1 H, ddd, *J* = 1, 7.5, 7.5 Hz), 7.04 (1 H, ddd, *J* = 1.5, 7.5, 7.5 Hz), 7.08 (1 H, dd, *J* = 1, 7.5 Hz), 7.13–7.18 (1 H, m), 7.20–7.25 (4 H, m), 7.29–7.42 (2 H, m), 7.49–7.53 (1 H, m) ppm. – ^{13}C NMR (75 MHz): 17.4 (CH_3), 17.5 (CH_3), 18.8 (CH_3), 21.1 (CH_3), 31.4 (CH_2), 36.0 (CH), 44.9 (CH_2), 55.1 (C), 95.6 (CH), 104.7 (CH), 116.9 (CH), 123.0 (CH), 125.2 (CH), 126.0 (CH), 127.5 (CH), 128.1 (CH),

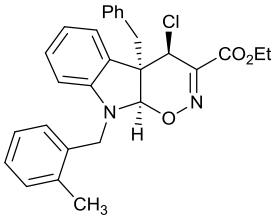
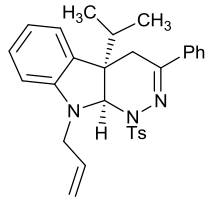
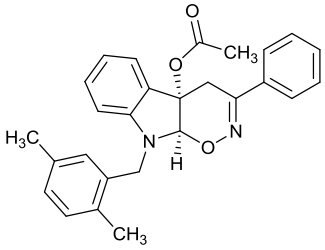
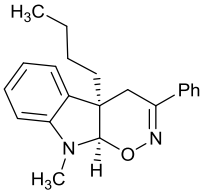
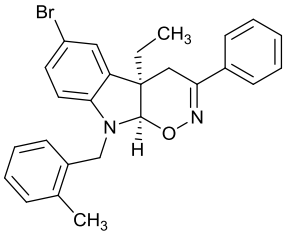
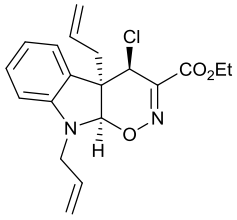
128.6 (CH), 128.9 (CH), 129.8 (CH), 129.9 (CH), 130.0 (CH), 132.9 (C), 134.6 (C), 134.9 (C), 135.1 (C), 137.7, (C), 151.0 (C), 171.4 (C) ppm. – IR: 904, 1024, 1122, 1222, 1278, 1312, 1387, 1444, 1489, 1606, 1704, 2872, 2921, 2963, 3050 cm^{-1}.

Table S1: Screening of quinolines against promastigotes and intracellular amastigotes of *L. major* and *L. panamensis*.[a]

Compound	Structure	IC_{50} (μM)±SD			
		Intracellular *L. major* amastigotes	Intracellular *L. panamensis* amastigotes	*L. major* promastigotes	*L. panamensis* promastigotes
S7		NA	NA	NA	NA
S8		NA	NA	NA	NA
S9		NA	NA	NA	NA
S10		NA	NA	NA	NA
S11		NA	NA	NA	NA

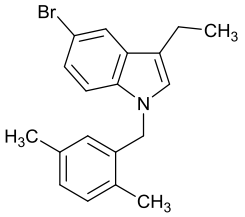
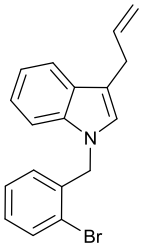
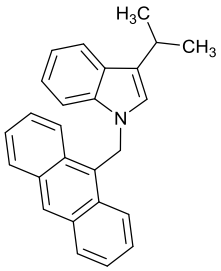
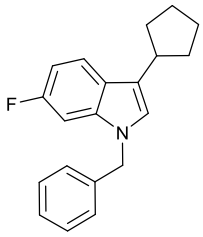
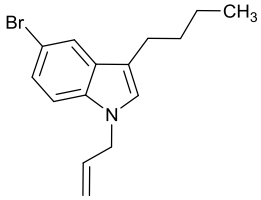
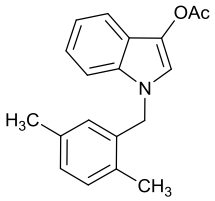
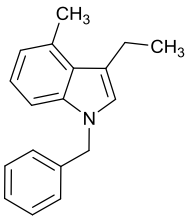
[a] NA: non-active. IC_{50} values are mean± standard deviation of two independent experiments. The control drug was amphotericin B, with an IC_{50} value for intracellular amastigotes of 0.103 μM for *L. panamensis* and 0.157 μM for *L. major*. The amphotericin B IC_{50} for promastigotes was 0.1 μM for *L. panamensis* and 0.243 μM for *L. major*.

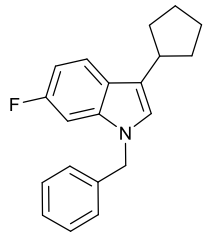
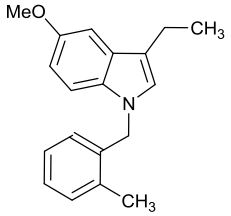
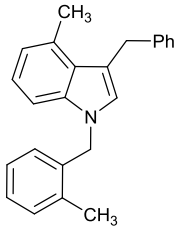
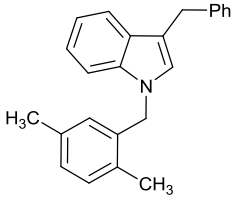
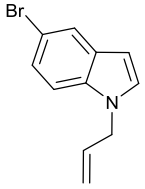
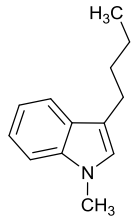
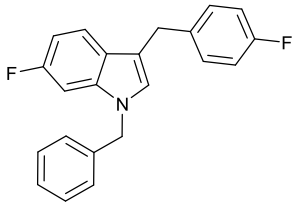
Table S2: Tetrahydrooxazinoindoles (TOIs) that are inactive against promastigotes and intracellular amastigotes of *L. major* and *L. panamensis*.[a]

Compound	Structure	IC_{50} (μM)±SD			
		Intracellular *L. major* amastigotes	Intracellular *L. panamensis* amastigotes	*L. major* promastigotes	*L. panamensis* promastigotes
S12		NA	NA	NA	NA
S14		NA	NA	NA	NA
S15		NA	NA	NA	NA
S27		NA	NA	NA	NA
10		NA	NA	NA	NA
S29		NA	NA	NA	NA

[a] NA: non-active. IC_{50} values are mean± standard deviation of two independent experiments. The control drug was amphotericin B, with an IC_{50} value for intracellular amastigotes of 0.103 μM for *L. panamensis* and 0.157 μM for *L. major*. The amphotericin B IC_{50} for promastigotes was 0.1 μM for *L. panamensis* and 0.243 μM for *L. major*.

Table S3: Screening of indoles against promastigotes and intracellular amastigotes of *L. major* and *L. panamensis*.[a]

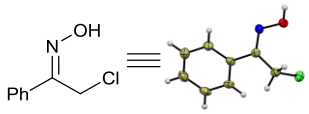
Compound	Structure	IC_{50} (μM)±SD			
		Intracellular *L. major* amastigotes	Intracellular *L. panamensis* amastigotes	*L. major* promastigotes	*L. panamensis* promastigotes
S16		NA	NA	NA	NA
S17		NA	NA	NA	NA
S18		NA	NA	NA	NA
S19		NA	NA	NA	NA
S26		NA	NA	NA	NA
S21		NA	NA	NA	NA
S22		NA	NA	NA	NA

S23		NA	NA	NA	NA
S24		NA	NA	NA	NA
8		NA	NA	NA	NA
S25		NA	NA	NA	NA
S20		NA	NA	NA	NA
S13		NA	NA	NA	NA
S28		NA	NA	NA	NA

[a] NA: non-active. IC_{50} values are mean± standard deviation of two independent experiments. The control drug was amphotericin B, with an IC_{50} value for intracellular amastigotes of 0.103 μM for *L. panamensis* and 0.157 μM for *L. major*. The amphotericin B IC_{50} for promastigotes was 0.1 μM for *L. panamensis* and 0.243 μM for *L. major*.

X-Ray Crystallographic Data

(*Z*)-2-Chloro-1-phenylethan-1-one oxime (7)



7

CCDC 1457714

Bond precision: C-C = 0.0019 A Wavelength=0.71075

Cell: a=11.461(3) b=18.171(5) c=7.917(2)

alpha=90 beta=106.770(4) gamma=90

Temperature: 98 K

	Calculated	Reported
Volume	1578.7(7)	1578.7(7)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C8 H8 Cl N O	C8 H8 Cl N O
Sum formula	C8 H8 Cl N O	C8 H8 Cl N O
Mr	169.60	169.60
Dx,g cm-3	1.427	1.427
Z	8	8
Mu (mm-1)	0.419	0.419
F000	704.0	704.0
F000'	705.44	
h,k,lmax	14,23,10	14,23,10
Nref	3629	3617
Tmin,Tmax	0.920,0.920	0.916,1.000
Tmin'	0.920	

Correction method= # Reported T Limits:

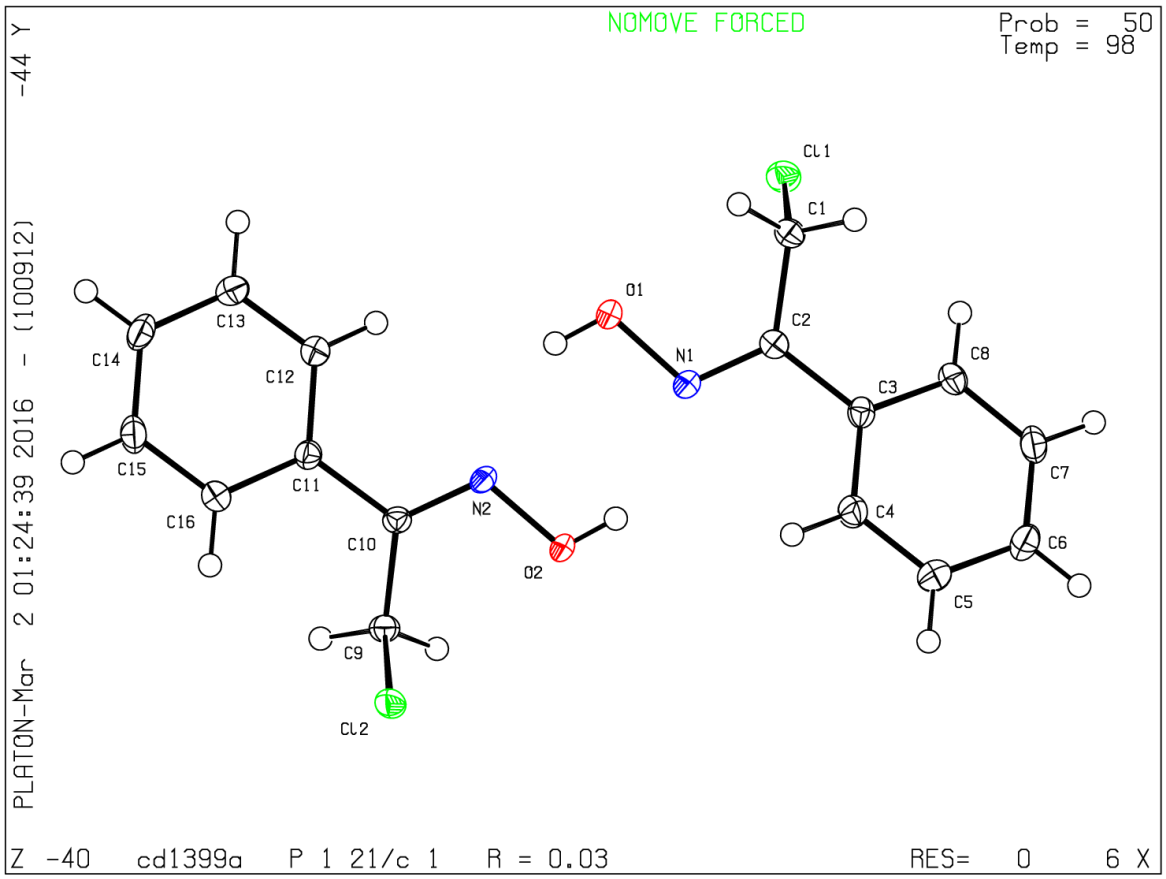
Tmin=0.916 Tmax=1.000 AbsCorr = MULTI-SCAN

Data completeness= Theta(max)= 27.499

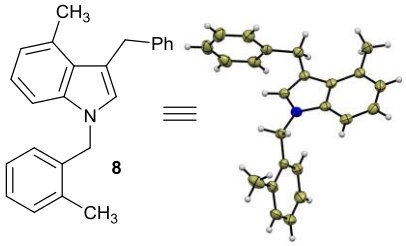
0.997

R(reflections)= 0.0328(3489) wR2(reflections)= 0.0816(3617)

S = 1.057 Npar= 201



3-Benzyl-4-methyl-1-(2-methylbenzyl)-1*H*-indole (8)



CCDC 1457713

Bond precision: C-C = 0.0016 A Wavelength=0.71075

Cell: a=8.9502(6) b=9.1881(5) c=11.6731(8)

alpha=83.963(6) beta=70.783(5) gamma=77.642(5)

Temperature: 98 K

	Calculated	Reported
Volume	884.82(10)	884.82(10)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C24 H23 N	C24 H23 N
Sum formula	C24 H23 N	C24 H23 N
Mr	325.43	325.43
Dx,g cm-3	1.222	1.221
Z	2	2
Mu (mm-1)	0.070	0.070
F000	348.0	348.0
F000'	348.12	
h,k,lmax	11,11,15	11,11,15
Nref	4067	4038
Tmin,Tmax	0.973,0.993	0.829,1.000
Tmin'	0.966	

Correction method= # Reported T Limits:

Tmin=0.829 Tmax=1.000 AbsCorr = MULTI-SCAN

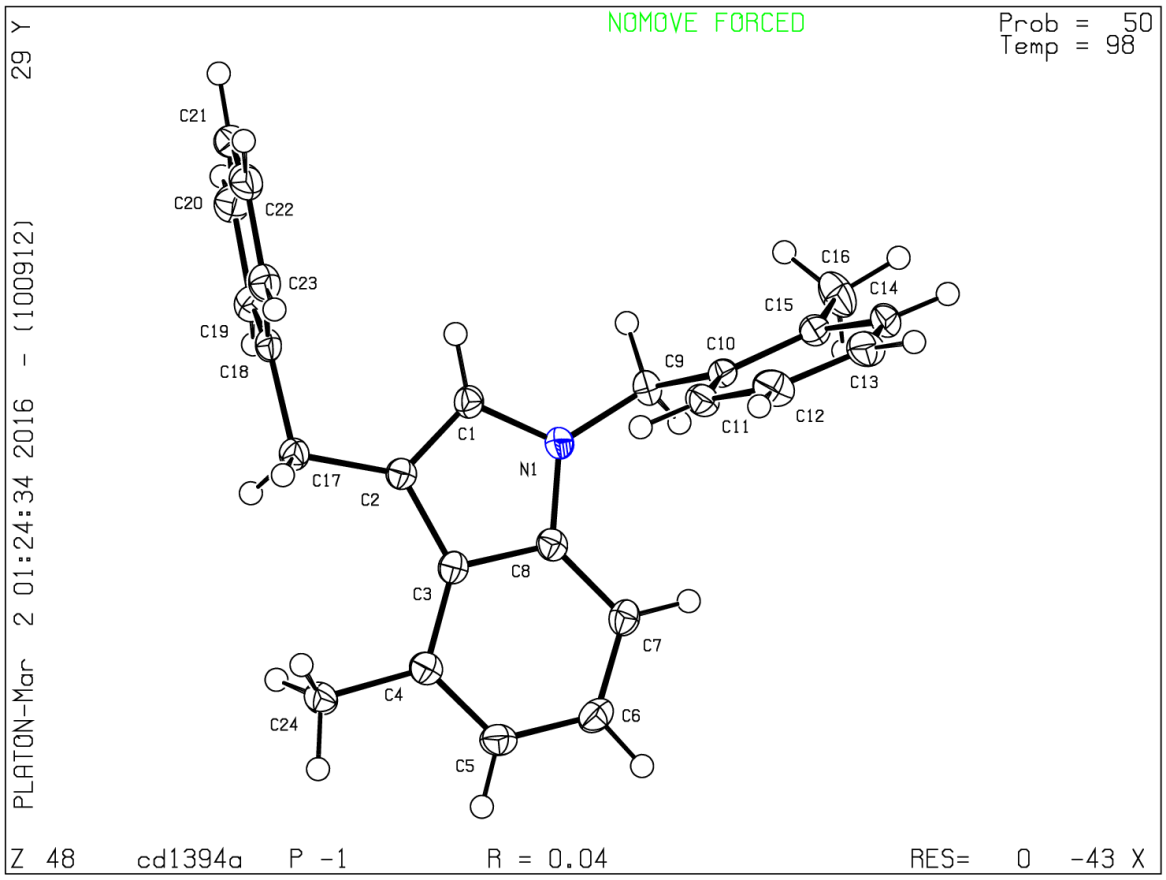
Data completeness= Theta(max)= 27.485

0.993

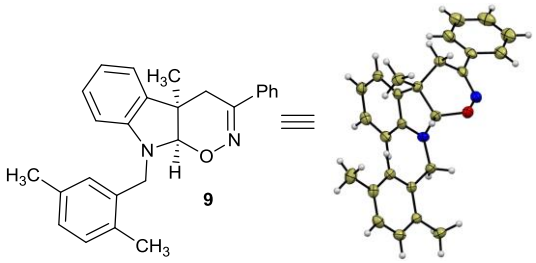
R(reflections)= 0.0410(wR2(reflections)= 0.1105(

3573) 4038)

S = 1.039 Npar= 228



(4a*R*,9a*R*)-9-(2,5-Dimethylbenzyl)-4a-methyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (9)



CCDC 1457715

Bond precision: C-C = 0.0018 A Wavelength=0.71075

Cell: a=6.8190(12) b=8.4731(15) c=17.387(3)

alpha=91.130(4) beta=90.978(5) gamma=96.993(4)

Temperature: 98 K

	Calculated	Reported
Volume	996.7(3)	996.8(3)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C26 H26 N2 O	C26 H26 N2 O
Sum formula	C26 H26 N2 O	C26 H26 N2 O
Mr	382.49	382.49
Dx,g cm-3	1.275	1.274
Z	2	2
Mu (mm-1)	0.078	0.078
F000	408.0	408.0
F000'	408.15	
h,k,lmax	8,11,22	8,11,22
Nref	4566	4525
Tmin,Tmax	0.972,0.992	0.876,1.000
Tmin'	0.964	

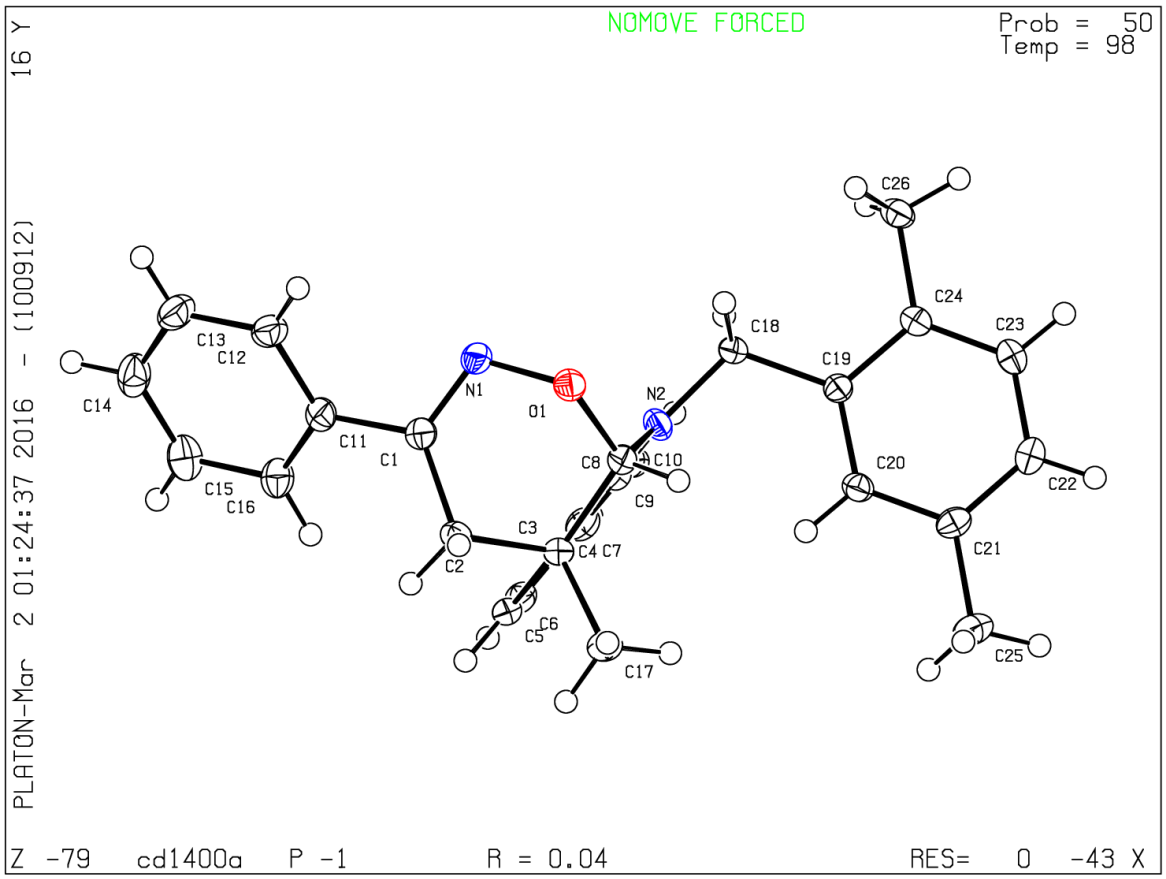
Correction method= # Reported T Limits:

Tmin=0.876 Tmax=1.000 AbsCorr = MULTI-SCAN

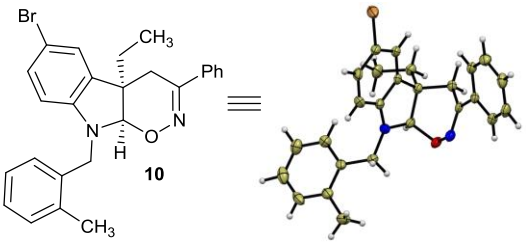
Data completeness= 0.991 Theta(max)= 27.494

R(reflections)= 0.0448(4124) wR2(reflections)= 0.1168(4525)

S = 1.029 Npar= 265



(4aR*,9aR*)-6-bromo-4a-ethyl-9-(2-methylbenzyl)-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-b]indole (10)



CCDC 1481256

Bond precision: C-C = 0.0032 A Wavelength=0.71073

Cell: a=9.1842(15) b=10.542(2) c=11.953(2)

alpha=84.992(11) beta=72.078(11) gamma=74.256(11)

Temperature: 98 K

	Calculated	Reported
Volume	1059.8(3)	1059.8(3)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C26 H25 Br N2 O	C26 H25 Br N2 O
Sum formula	C26 H25 Br N2 O	C26 H25 Br N2 O
Mr	461.38	461.39
Dx,g cm-3	1.446	1.446
Z	2	2
Mu (mm-1)	1.960	1.960
F000	476.0	476.0
F000'	475.58	
h,k,lmax	11,13,15	11,13,15
Nref	4879	4879
Tmin,Tmax	0.602,0.907	0.364,1.000
Tmin'	0.452	

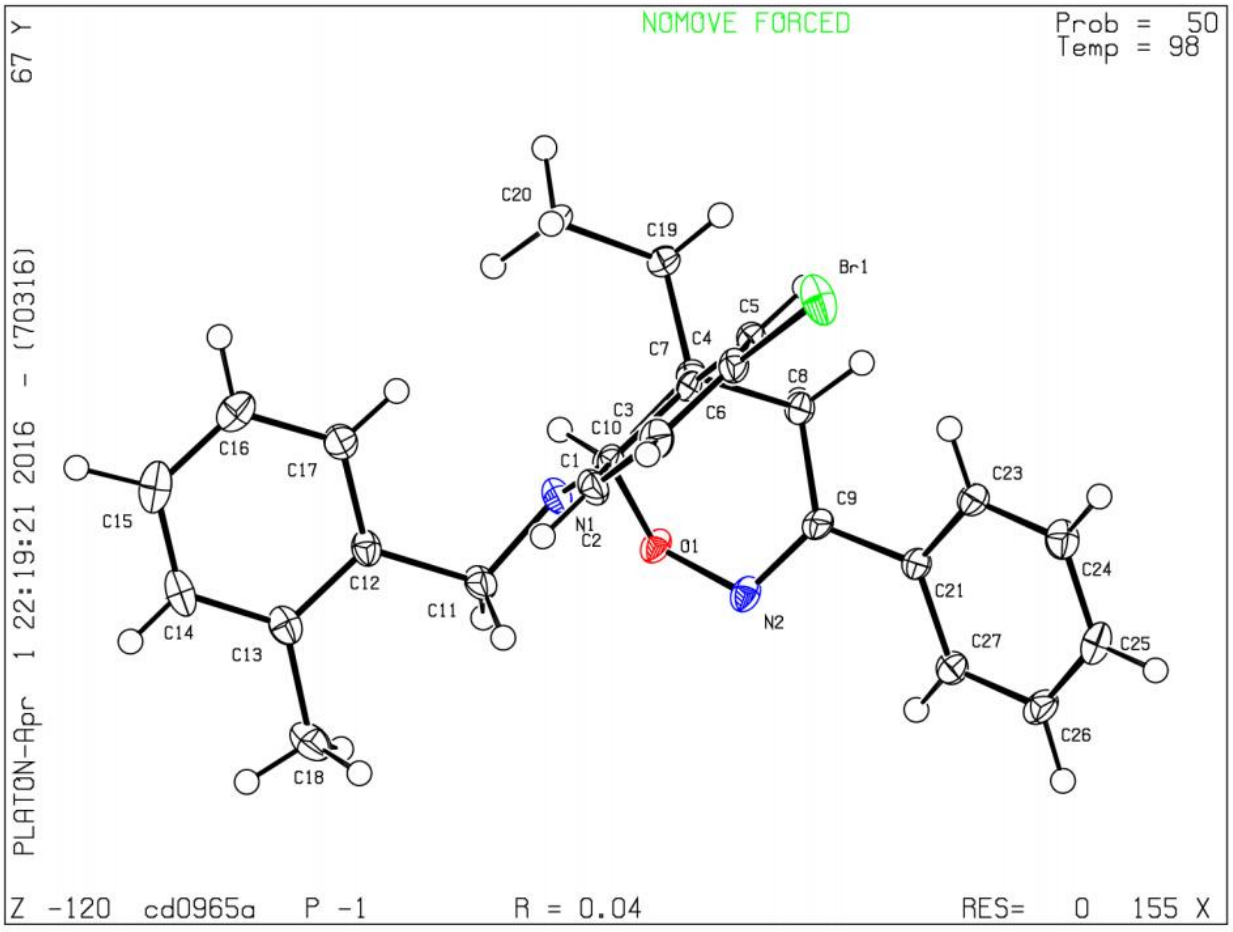
Correction method= # Reported T Limits: Tmin=0.364

Tmax=1.000 AbsCorr = MULTI-SCAN

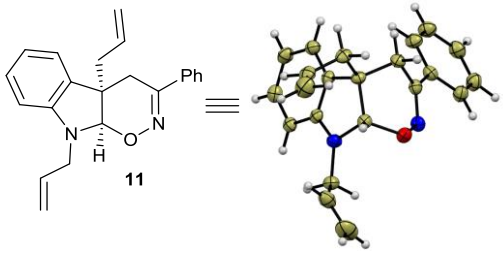
Data completeness= 0.985 Theta(max)= 27.499

R(reflections)= 0.0377(4223) wR2(reflections)= 0.0885(4807)

S = 1.021 Npar= 346



(4a*R*,9a*R*)-4a,9-Diallyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (11)



CCDC 1457716

Bond precision: C-C = 0.0019 A Wavelength=0.71073

Cell: a=9.059(2) b=9.9601(19) c=11.1789(18)

alpha=114.934(8) beta=101.127(13) gamma=92.311(14)

Temperature: 98 K

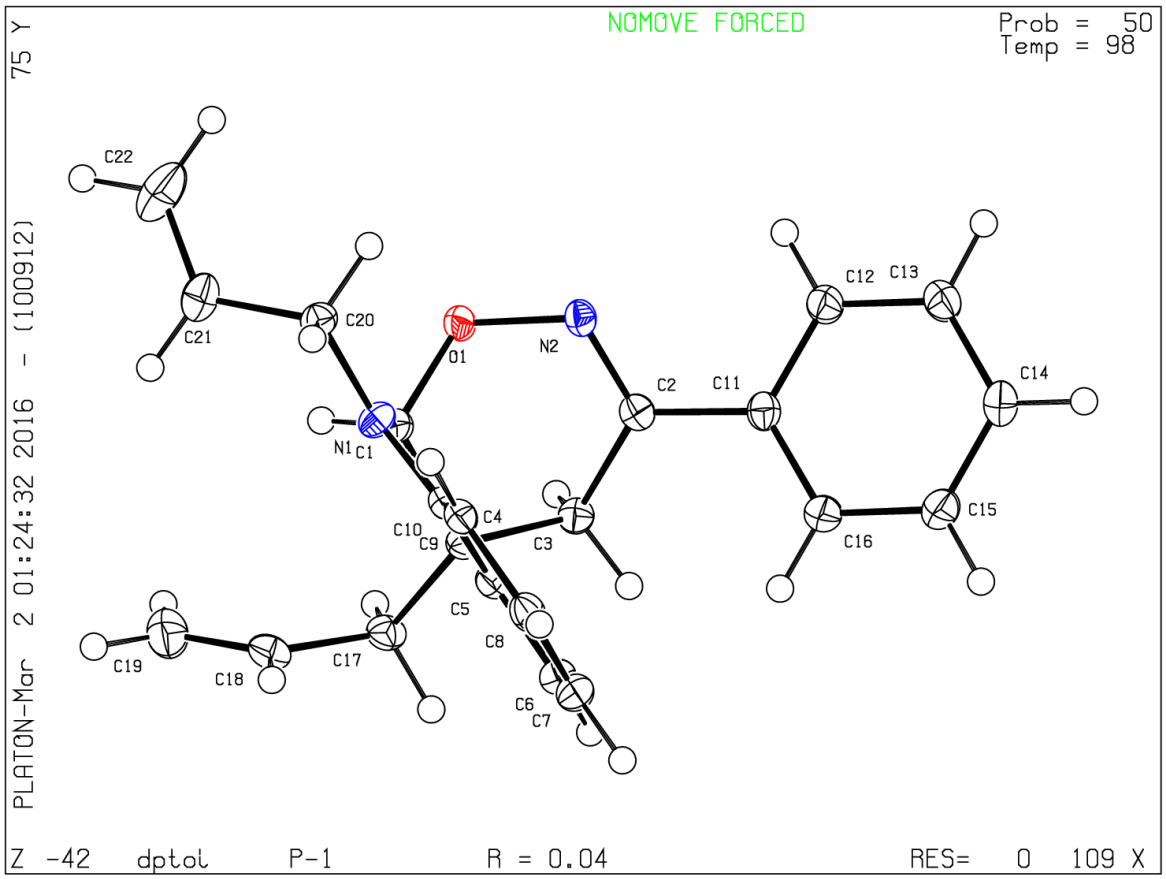
	Calculated	Reported
Volume	889.0(3)	889.0(3)
Space group	P -1	P-1
Hall group	-P 1	-P 1
Moiety formula	C22 H22 N2 O	C22 H22 N2 O
Sum formula	C22 H22 N2 O	C22 H22 N2 O
Mr	330.42	330.42
Dx,g cm-3	1.234	1.234
Z	2	2
Mu (mm-1)	0.076	0.076
F000	352.0	352.0
F000'	352.13	
h,k,lmax	11,12,14	11,12,14
Nref	4078	4043
Tmin,Tmax	0.986,0.995	0.891,1.000
Tmin'	0.960	

Correction method= # Reported T Limits: Tmin=0.891 Tmax=1.000 AbsCorr = MULTI-SCAN

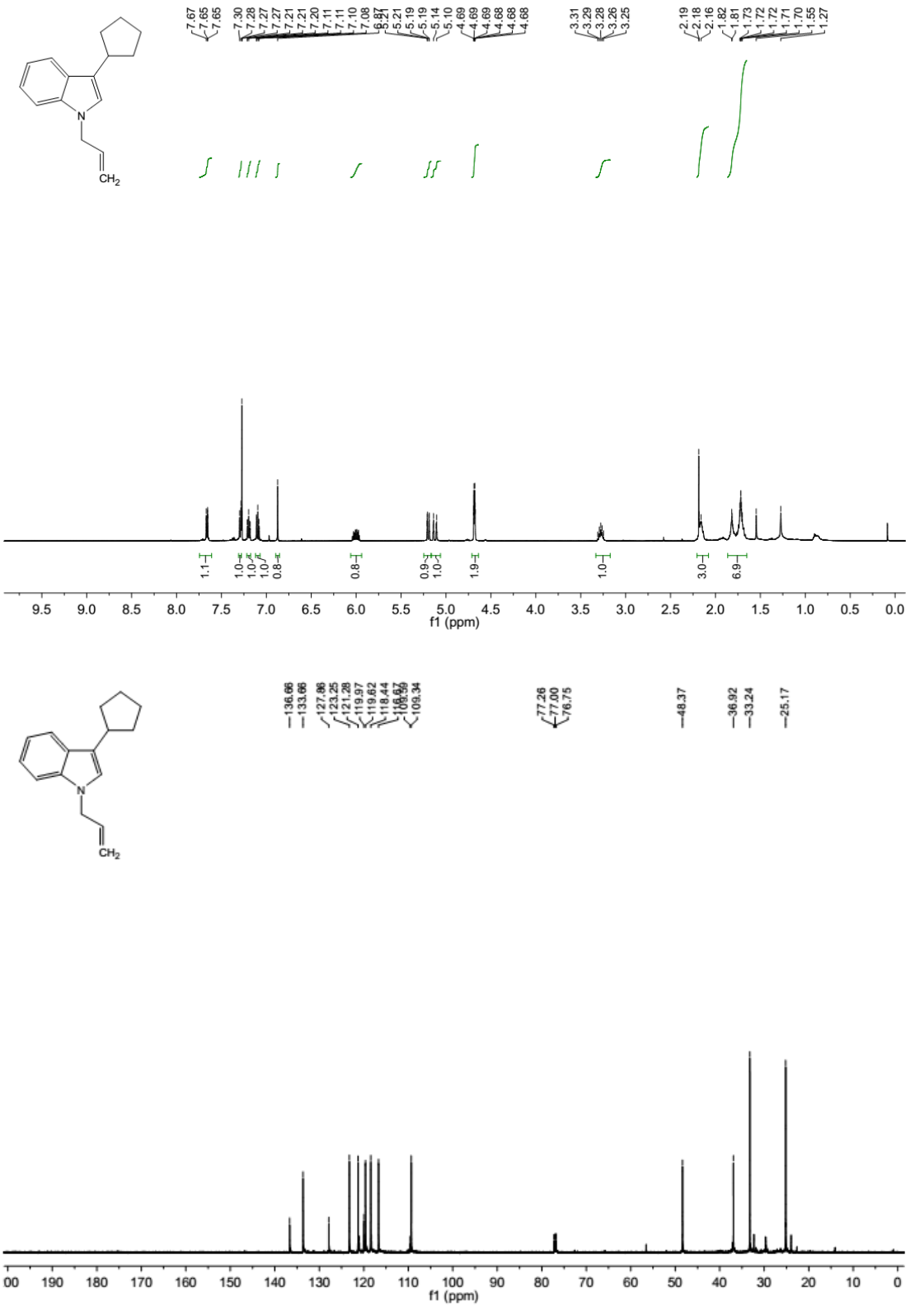
Data completeness= 0.991 Theta(max)= 27.500

R(reflections)= 0.0438(3675) wR2(reflections)= 0.0931(4043)

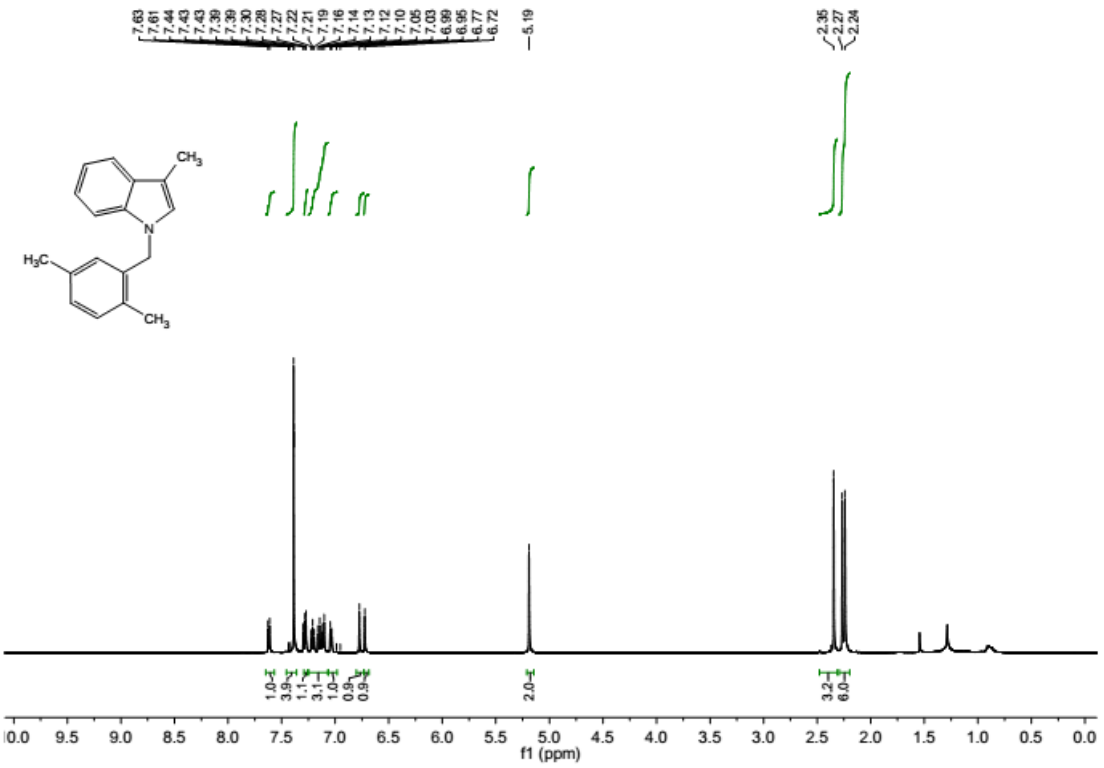
S = 1.019 Npar= 292

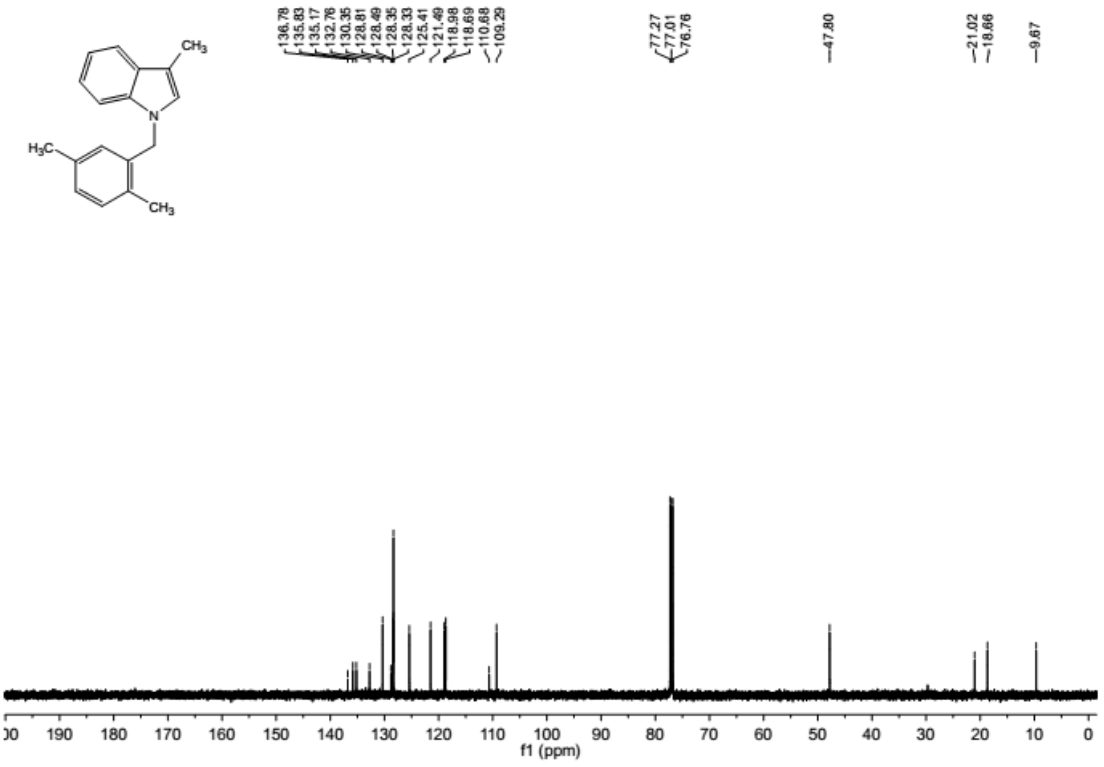


1-Allyl-3-cyclopentyl-1*H*-indole (S1)

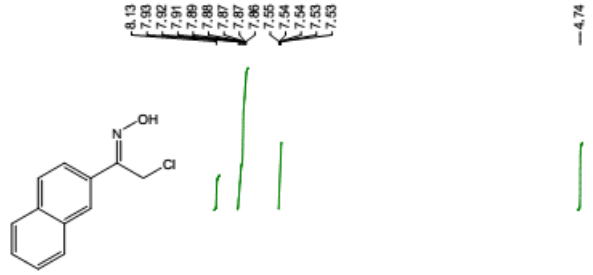


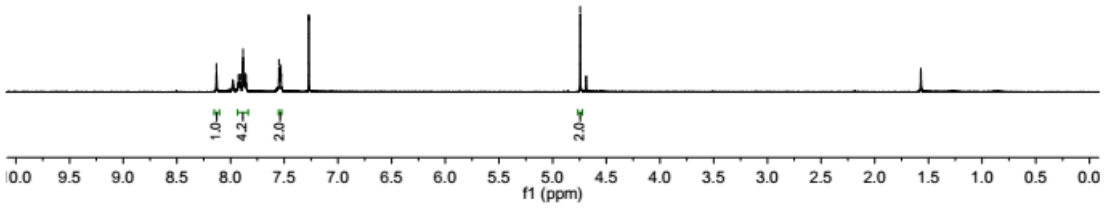
1-(2,5-Dimethylbenzyl)-3-methyl-1*H*-indole (S2)

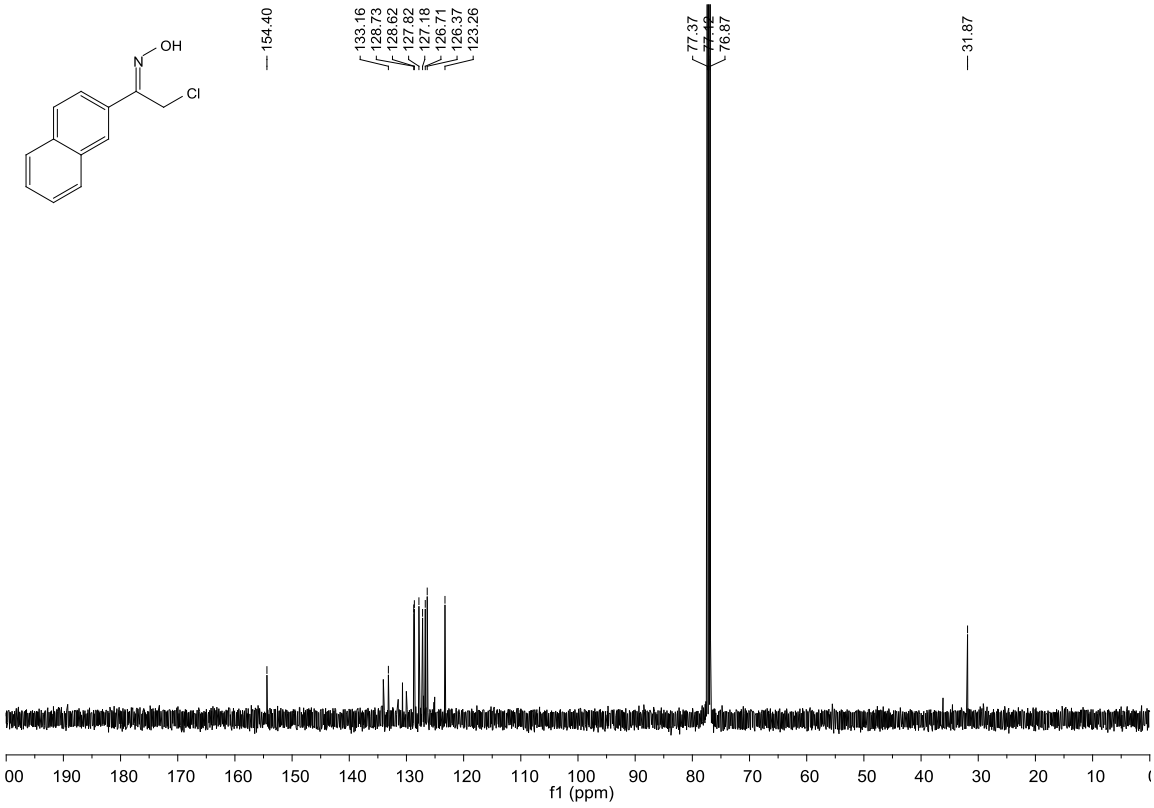




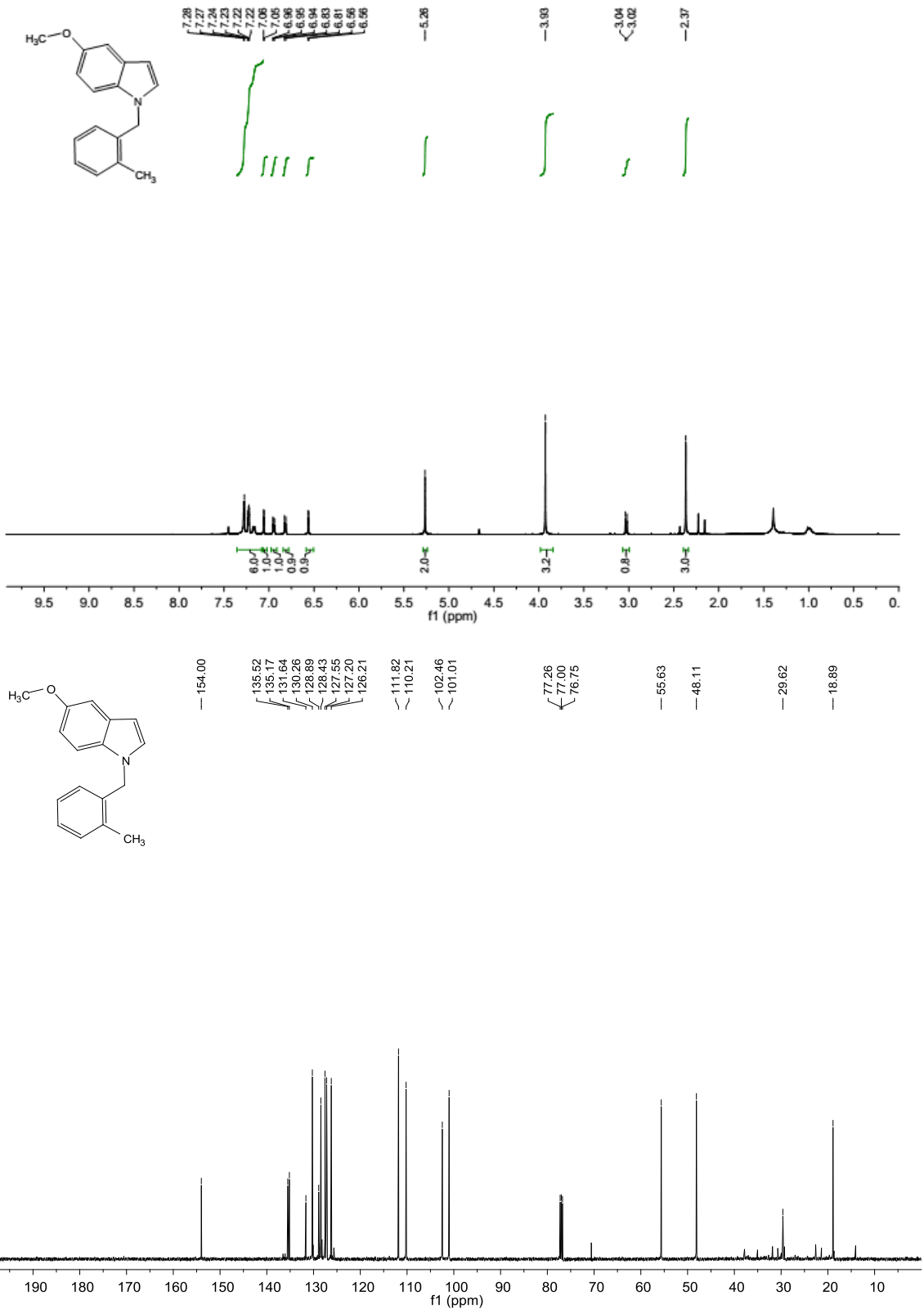
2-Chloro-1-(naphthalen-2-yl)ethan-1-one oxime (S4)



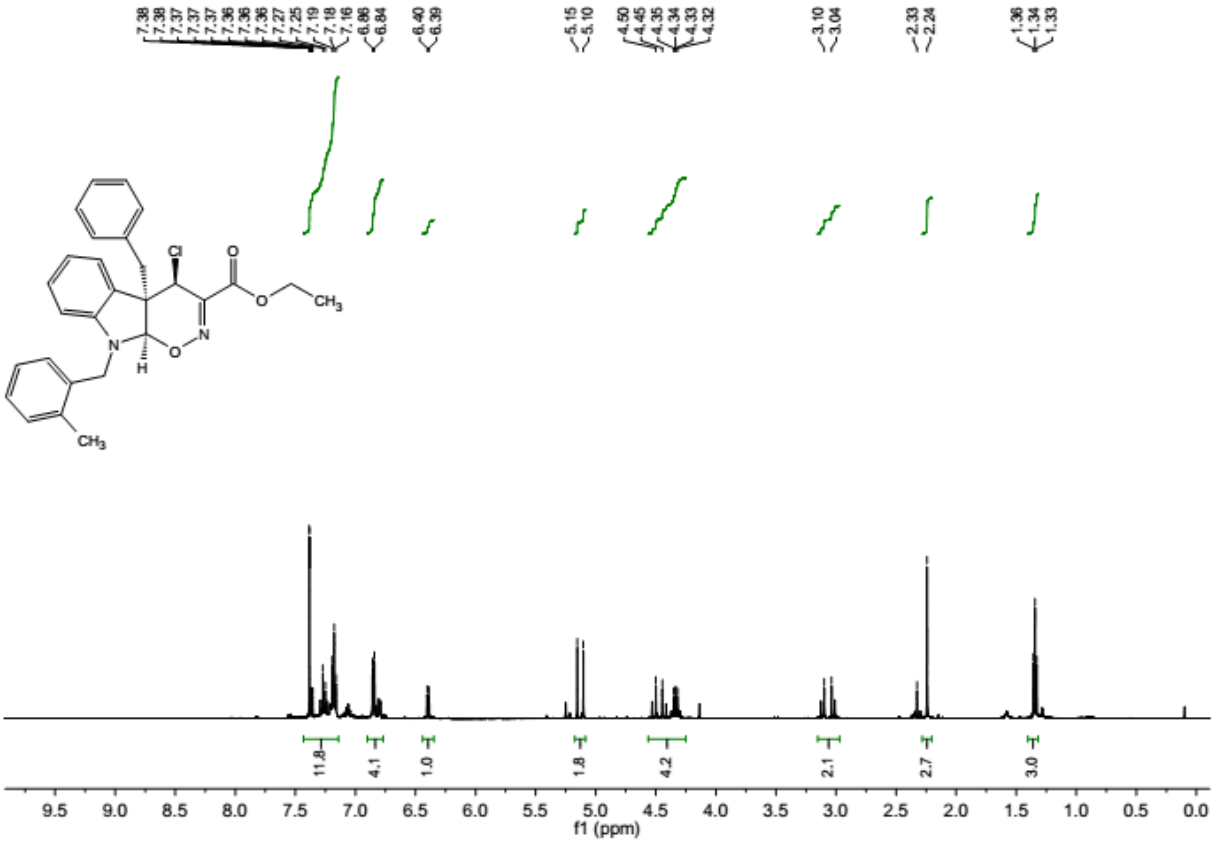


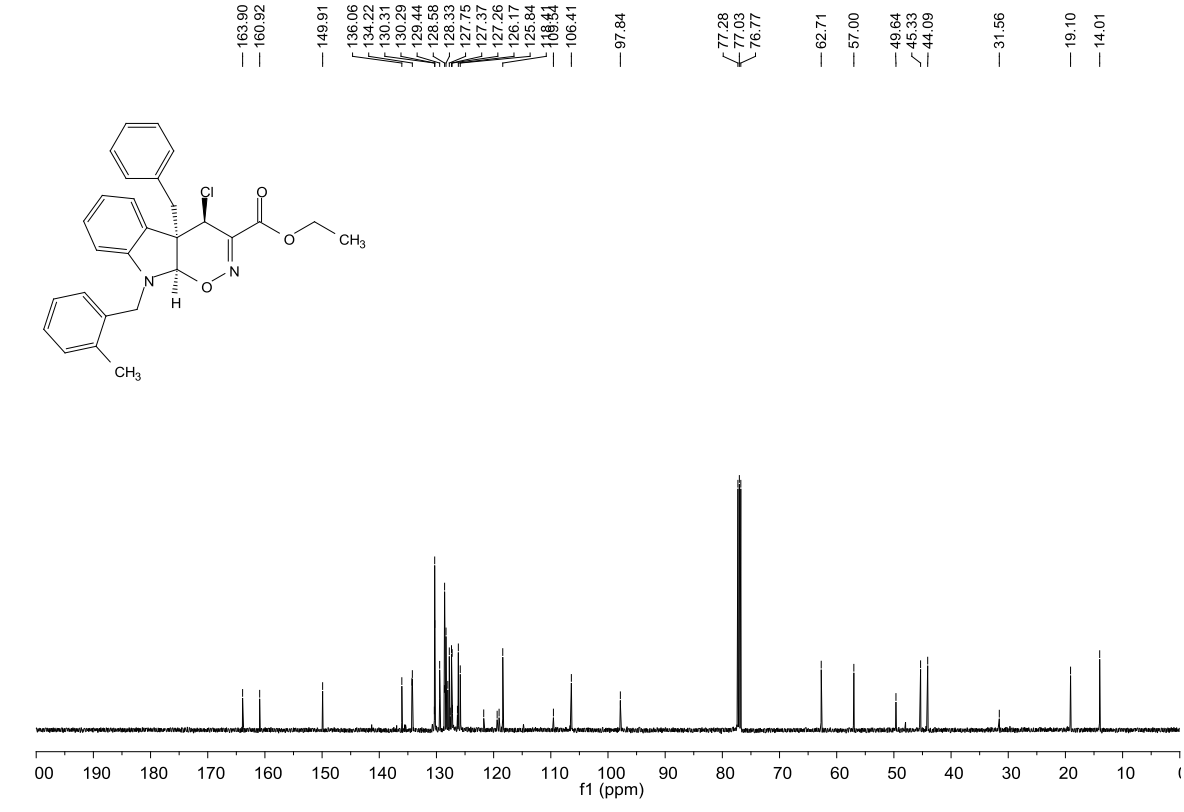


5-Methoxy-1-(2-methylbenzyl)-1*H*-indole (S6)

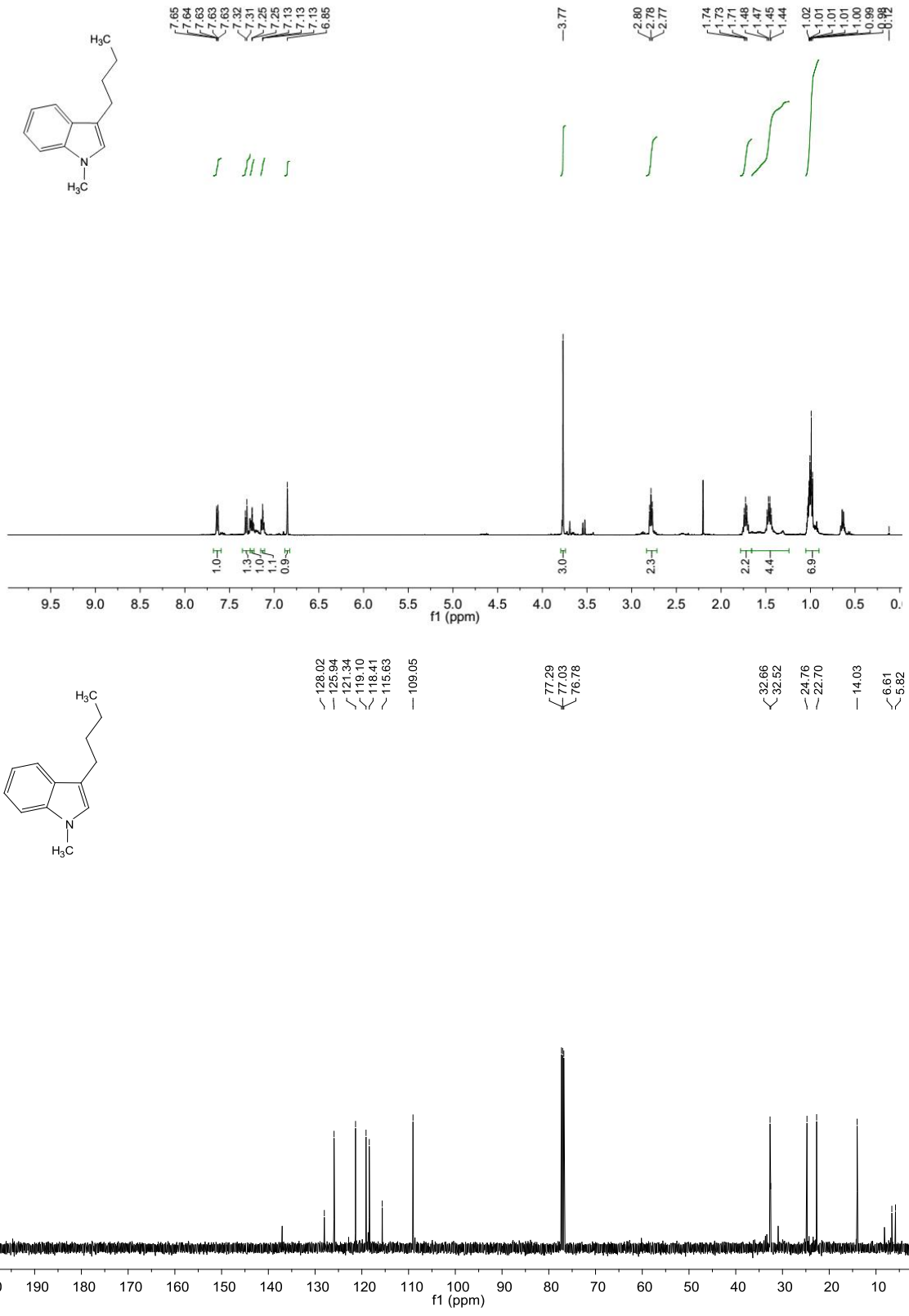


Ethyl (4*R*,4a*R*,9a*R*)-4a-benzyl-4-chloro-9-(2-methylbenzyl)-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole-3-carboxylate (S12)

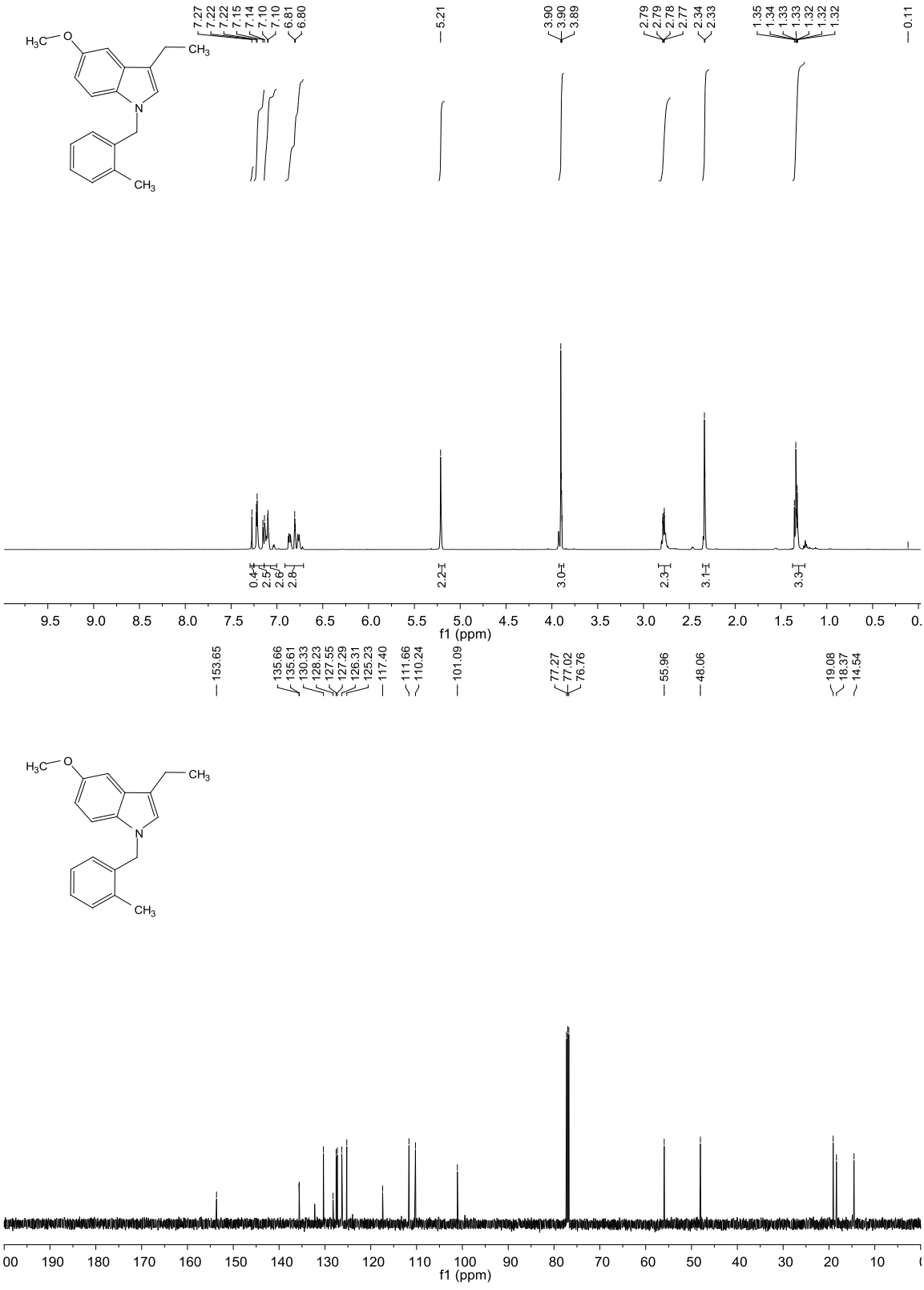




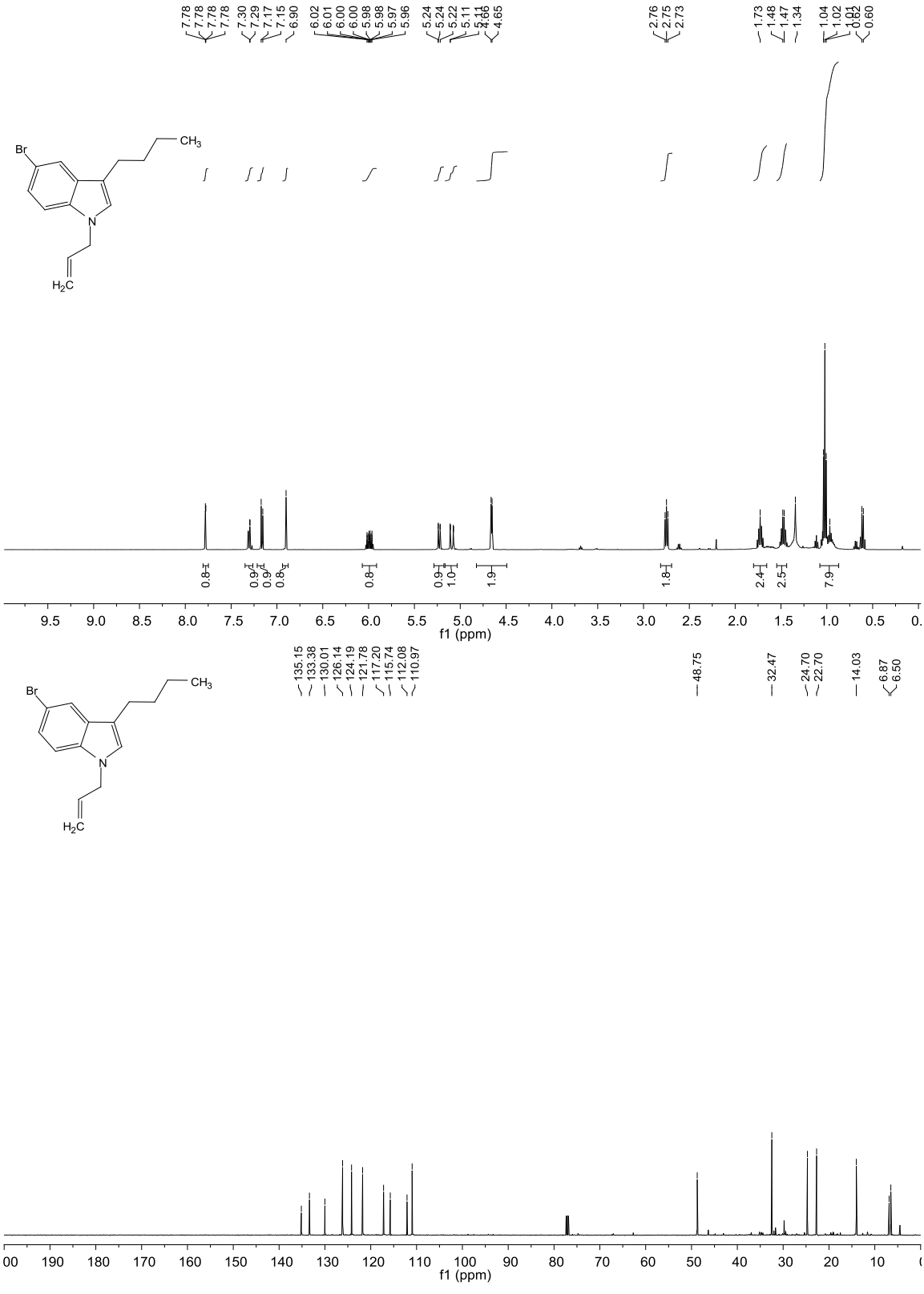
3-Butyl-1-methyl-1*H*-indole (S13)



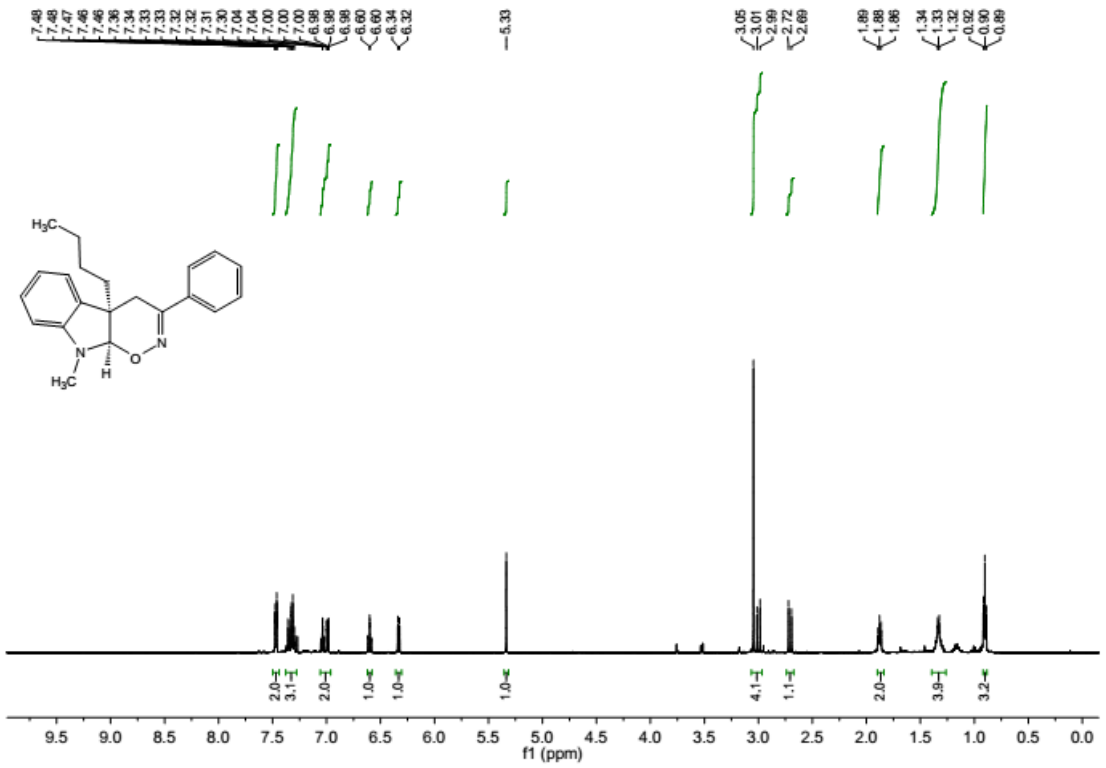
3-Ethyl-5-methoxy-1-(2-methylbenzyl)-1*H*-indole (S24)

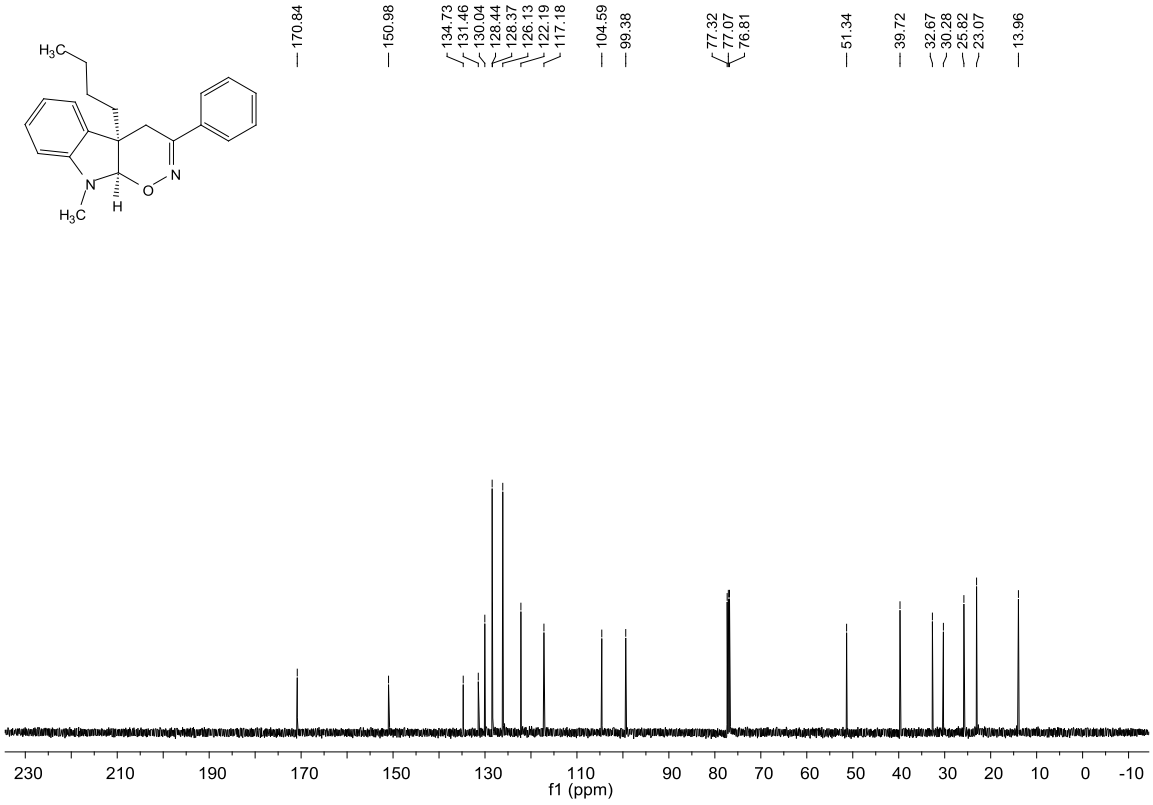


1-Allyl-5-bromo-3-butyl-1*H*-indole (S26)

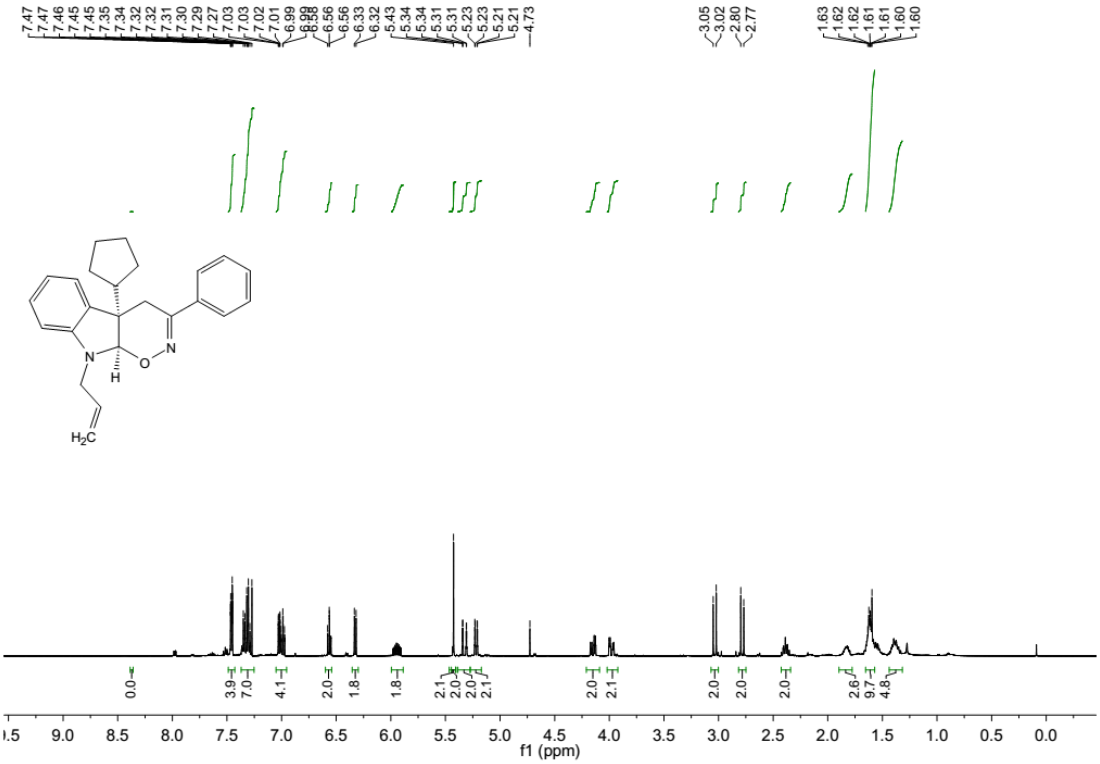


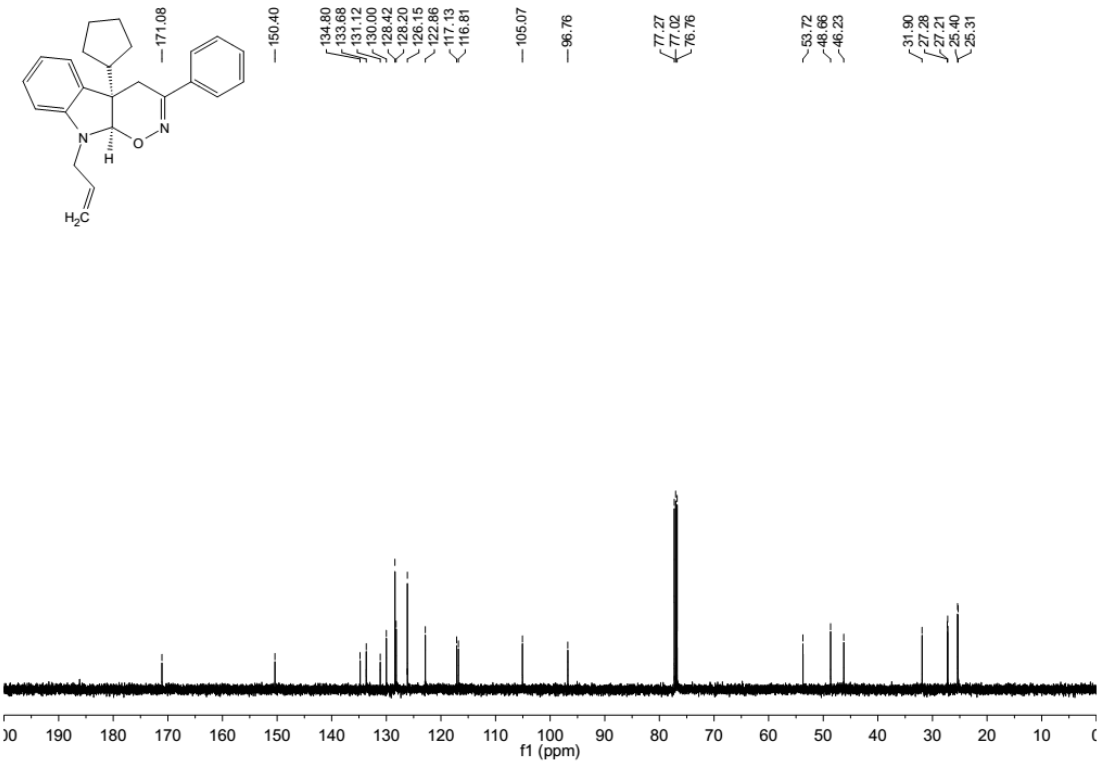
4a-Butyl-9-methyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (S27)



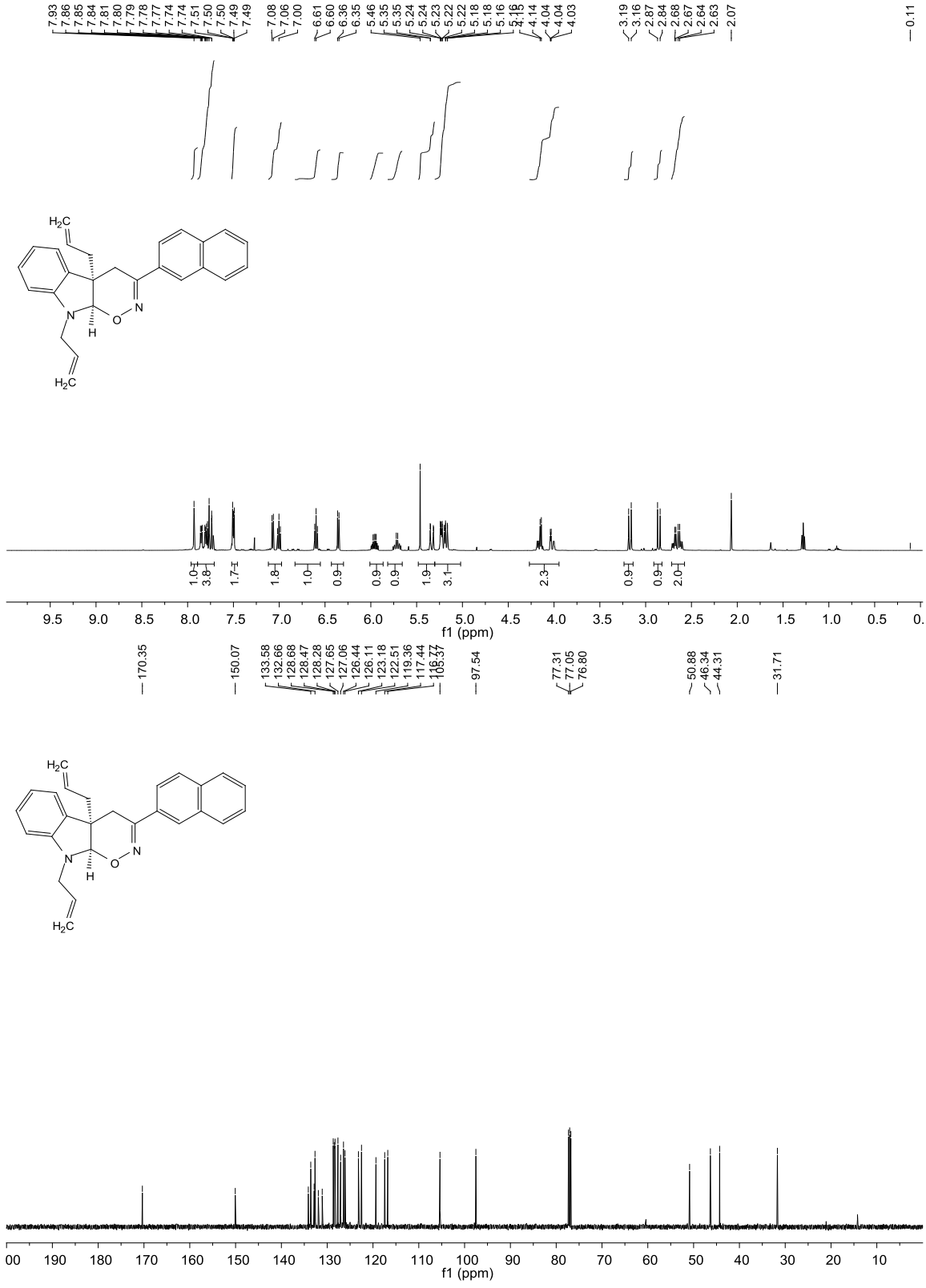


(4a*S*,9a*R*)-9-Allyl-4a-cyclopentyl-3-phenyl-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (16)

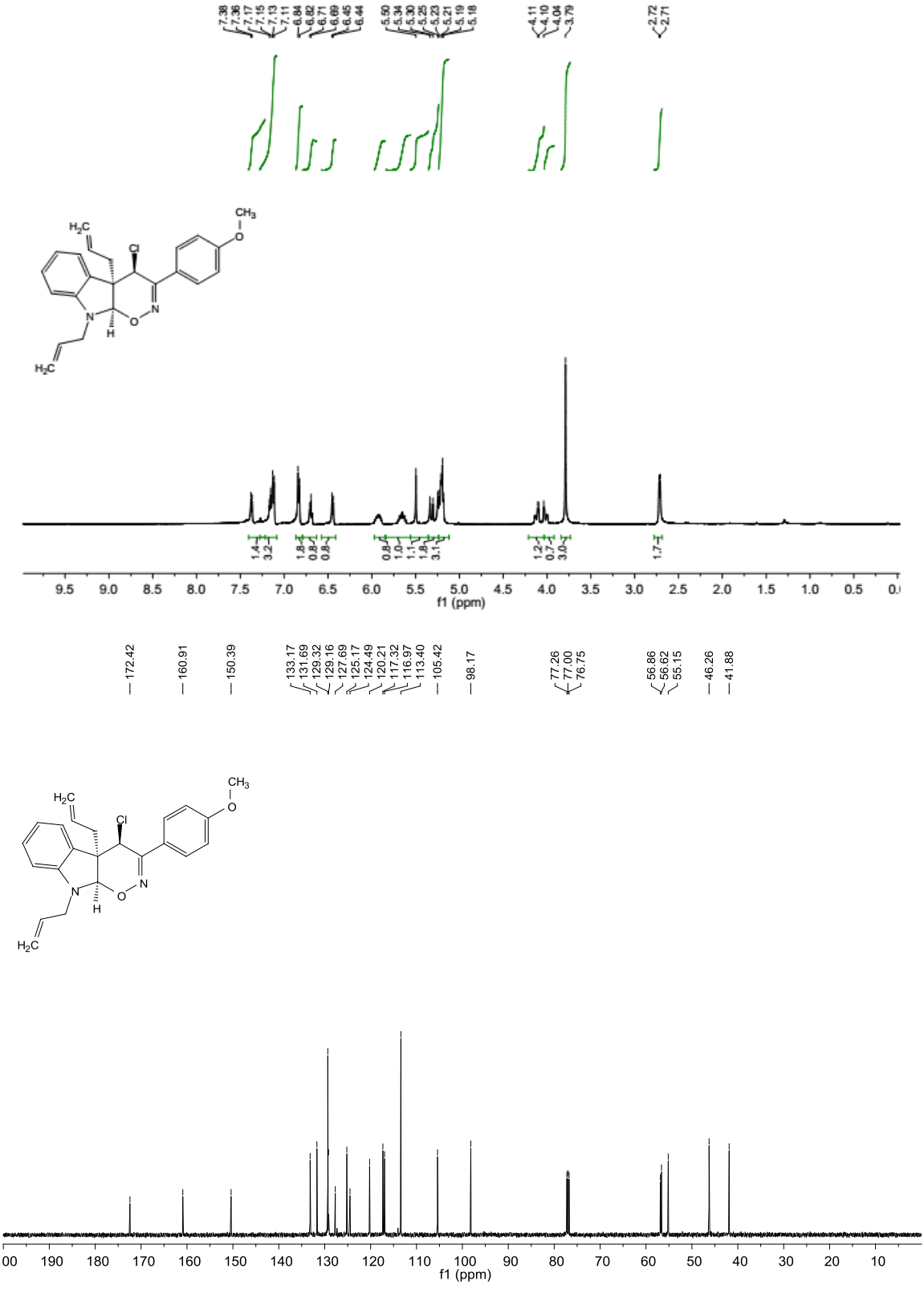




(4a*R*,9a*R*)-4a,9-Diallyl-3-(naphthalen-2-yl)-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (18)



(4*R*,4a*R*,9a*R*)-4a,9-Diallyl-4-chloro-3-(4-methoxyphenyl)-4,4a,9,9a-tetrahydro-[1,2]oxazino[6,5-*b*]indole (19)



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[1] Zhang, Y.; Stephens, D.; Hernandez, G.; Mendoza, R.; Larionov, O. V. *Chem. Eur. J.* **2012***, 18*, 16612–16615.

[2] Larionov, O.V.; Stephens, D.; Mfuh, A.M.; Arman, H.D.; Naumova, A.S.; Chavez, G.; Skenderi, B. *Org. Biomol. Chem.* **2014***, 12*, 3026–3036.

[3] Hatcher, J. M.; Coltart, D.M. *J. Am. Chem. Soc.* **2010,** *132,* 4546–4547.

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