Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Asymmetric synthesis of pyrazole derivative using *tert*-butansulfoneamide as a chiral auxiliary

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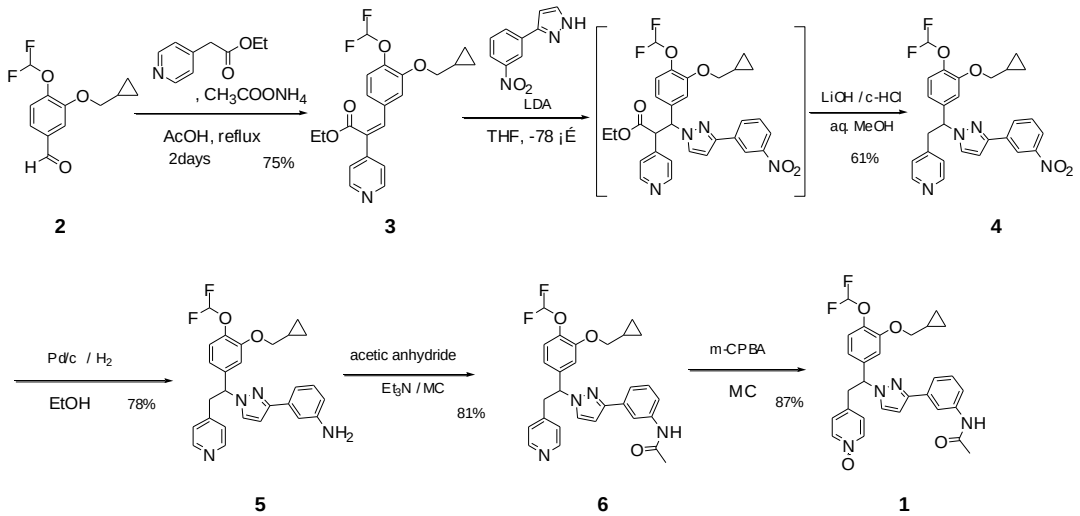
General methods

^{1}H NMR and ^{13}C NMR were recorded on Varian Gemini 200 (200 MHz ^{1}H)and 500 (500 MHz ^{1}H) spectrometer, and Brucker AM-300 spectrometer (^{13}C). Tetramethylsilane was used as an internal standard. IR spectra were recorded on Travel IR Portable (ATR-FT IR Spectrometer System, Sens IR) spectrometers. Peaks are reported in units of cm^{-1}. Mass spectra (LMS) were recorded on a JEOL JMS-01 mass spectrometer, and HRMS were recorded on Autospec Mass spectrometer a DX-300 mass spectrometer (Micromass) under electron impact (EI) conditions. Optical rotations were recorded on Rudolph Autopol Ⅲ (Automatic polarimeter) in the solvent indicated. Analytical HPLC was performed on a Jasco 880-PU Intelligent HPLC Pump or Lasco BIPP-1 HPLC Pump equiped with Jasco UVDEC-100-IV UV Spectrometer or Jasco UVDEC-100-UVV Spectrometer. The columns used were Waters Optipak-XC, Daicel OD-H and Daicel AD. Reaction were monitered by thin-layer chromatography carried out on 0.25 mm Merck silicagel plates (60F-254) with UV light, ethanolic phosphomolybdic acid, or *p*-anisaldehyde solution and heat as the developing agent. Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. Solvent were distilled. For anhydrous reactions, THF, ether, DME, and toluene were distilled from sodium metal benzophenone ketyl.

Synthetic procedure for racemic *N*-(3-{1-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-(1-oxypyridin-4-yl)ethyl]-1*H*-pyrazol-3-yl}phenyl)acetamide



Synthesis of 3-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-yl-acrylic acid ethyl ester (3)

Ethyl 4-pyridylacetate (10.23 g, 61.93 mmol) and ammonium acetate (6.36 g, 82.57 mmol) were added to a solution of **2** (10 g, 41.28 mmol) in acetic acid. The mixture was refluxed for 18 h. The reaction was allowed to cool to ambient temperature and the solvent was removed in vacuo and diluted with ethyl acetate and washed with saturated $NaHCO_3$ water solution and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (n-Hexane/EA, 7/1) to give **3** (12.0 g, 75%).

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.66 ~ 8.27 (2H, m, Ar), 7.83 (1H, s, -CH=), 7.18 (2H, d, *J*= 6.2 Hz, Ar), 7.04 ~ 6.97 (1H, m, Ar), 6.74 (1H, d, *J* = 8.2 Hz, Ar), 6.60 (1H, t, *J* = 62 Hz, -

CHF_2-), 6.50 (1H, d, *J* = 2 Hz, Ar), 4.32 ~ 4.22 (2H, m, -CH_2-), 3.42 (2H, d, *J* = 7 Hz, -OCH_2-), 1.29 (3H, t, *J* = 7.2 Hz, -CH_3), 1.12 ~ 1.05 (1H, m, -CH-), 0.63 ~ 0.54 (2H, m, -CH_2-), 0.28 ~ 0.23 (2H, m, -CH_2-).

Synthesis of 4-{2-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-[3-(3-nitrophenyl)pyrazol-1-yl]-ethyl}pyridine (4)

To a stirred solution of 3-(3-nitrophenyl)pyrazole (5.83 g, 30.82 mmol) in THF was added LDA (20.5 ml, 30.82 mmol) dropwise at – 78 °C and the reaction mixture was stirred for 0.5 h at rt. After cooling to -78 °C, **3** (4 g 10.27 mmol) solution in THF was added slowly to the reaction mixture. After 5 min, the cooling bath was removed, and the mixture was stirred for 6 h. the reaction solution was quenched with saturated aq-NH_4Cl at 0℃, diluted with ethyl acetate (100 mL) and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (n-Hexane/EA, 1/2) to give **4** (2.75 g, 61 %).

^{1}H NMR (300 MHz, $CDCl_3$) *δ*8.69 (1H, s, Ar), 8.44 (2H, d, *J* = 5.7 Hz, Ar), 8.14 ~ 8.11 (2H, m, Ar), 7.60 ~ 7.57(1H, m, Ar), 7.34~ 7.33 (1H, m, Ar), 7.14 ~ 6.92 (5H, m, Ar), 6.61 (1H, t, *J* = 75.3 Hz, -CHF_2-), 6.58 (1H, d, J = 2.4 Hz, Ar), 5.42 ~ 5.37 (1H, m, -CH-), 3.96 ~ 3.89 (1H, m, dd, -CH_2-), 3.85 (2H, d, *J* = 6.9 Hz, -OCH_2-), 3.43 ~ 3.36 (1H, m, dd, -CH_2), 1.28~ 1.19 (1H, m, -CH-), 0.62 ~ 0.58 (1H, m, -CH_2-), 0.35 ~ 0.30 (1H, m, -CH_2-).

Synthesis of 3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethyl]-1*H*-pyrazol-3-yl}phenylamine (5)

To a stirred solution of **4** (0.07 g, 0.13 mmol) in EtOH was added 10% Pd/C followed by charged with hydrogen gas. The resulting mixture was stirred at ambient temperature for 5h before it was fillered. The filterate was diluted with ethyl acetate and washed water and

brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2 / MeOH, 20 / 1) to give **5** (0.054 g, 78 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ8.49 ~ 8.41 (2H, m, Ar), 7.24 ~ 6.67 (10H, m, Ar), 6.59 (1H, t, J = 76.9 Hz, -CHF_2), 6.45 (1H, m, Ar), 5.36 ~ 5.33 (1H, m, -CH-), 3.91 ~ 3.78 (3H, m, dd, -OCH_2-, -CH_2-), 3.38 ~ 3.33 (1H, m, dd, -CH_2-), 1.28 ~ 1.19 (1H, m, -CH-), 0.64 ~ 0.57 (2H, m, -CH_2-), 0.35 ~ 0.30 (2H, m, -CH_2-).

Synthesis of *N*-(3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethyl]-1*H*-pyrazol-3-yl}phenyl)acetamide (6)

To a stirred solution of **5** (0.17 g, 0.36 mmol) in CH_2Cl_2 was added Et_3N (0.054 g, 0.54 mmol) and followed by dropwise acetic anhydride (0.044 g, 0.43 mmol). The reaction mixture was stirred for 6 h at rt. The reaction solution was quenched with saturated aq-NH_4Cl, diluted with CH_2Cl_2 and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2 / MeOH, 20 / 1) to give **6** (0.15 g, 81 %).

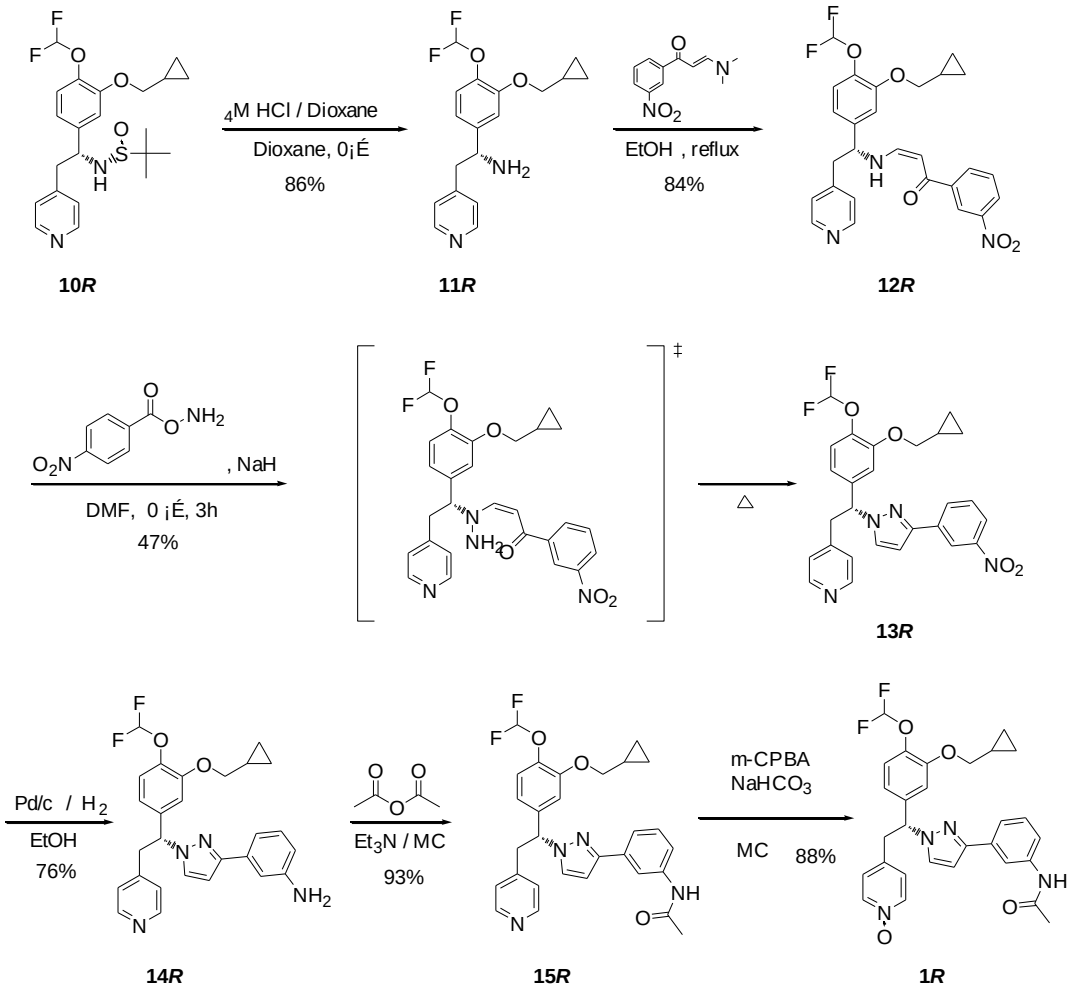
^{1}H NMR (200 MHz, $CDCl_3$) δ8.43 (2H, d, J = 5.6 Hz, Ar), 7.96 (1H, s, Ar), 7.59 ~ 6.90 (9H, m, Ar), 6.60 (1H, t, J = 75.2 Hz, -CHF_2), 6.50 (1H, s, Ar), 5.40 ~ 5.33 (1H, m, -CH-), 3.97 ~ 3.86 (1H, m, -CH_2-), 3.82 (2H, d, J = 7 Hz, -OCH_2-), 3.40 ~ 3.30 (1H, m, -CH_2-), 2.20 (3H, s, -CH_3), 1.26 ~ 1.22 (1H, m, -CH-), 0.65 ~ 0.55 (2H, m, -CH_2-), 0.35 ~ 0.28 (2H, m, -CH_2-).

Synthesis of *N*-(3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl) -2-(1-oxypyridin-4-yl)-ethyl]-1*H*-pyrazol-3-yl}phenyl)acetamide (1)

To a stirred solution of **6** (0.02 g, 0.039 mmol) in CH_2Cl_2 was added mcpba (0.016 g, 0.058 mmol) slowely. The reaction mixture was stirred for 3 h at rt. The reaction solution was quenched with saturated aq- $NaHCO_3$, diluted with CH_2Cl_2 and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2 / MeOH, 20 / 1) to give **1** (0.017 g, 87 %).

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.04 (2H, d, J = 7 Hz, Ar), 7.89 (1H, s, Ar), 7.67 (1H, s, Ar), 7.51 ~ 6.91 (8H, m, Ar), 6.62 (1H, t, J = 75.4 Hz, -CHF_2), 6.48 (1H, m, Ar), 5.35 ~ 5.28 (1H, m, -CH-), 3.94 ~ 3.82 (3H, m, dd, -OCH_2-, -CH_2-), 3.37 ~ 3.27 (1H, m, -CH_2-), 2.21 (3H, s, -CH_3), 1.72 ~ 1.20 (1H, m, -CH-), 0.66 ~ 0.56 (2H, m, -CH_2-), 0.36 ~ 0.28 (2H, m, -CH_2-).

Synthetic procedure for chiral *N*-(3-{1-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-(1-oxypyridin-4-yl)ethyl]-1*H*-pyrazol-3-yl}phenyl)acetamide



10*R* **11*R*** **12*R***

13*R*

14*R* **15*R*** **1*R***

(*R*)-2-Methylpropane-2-sulfinic acid 3-cyclopropylmethoxy-4-difluoromethoxylbenzylideneamide (9*R*)

To a stirred solution of **2** (2.0 g, 8.2 mmol) in THF was added $Ti(OEt)_4$ (37.0 g, 33.0 mmol) and followed by dropwise (*R*)-(+)-2-methyl-2-propanesulfinamide (1.0 g, 8.2 mmol). The reaction mixture was stirred for 12 h at rt. The reaction solution was quenched with saturated aq-NH_4Cl, diluted with ethyl acetate and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (n-Hexane / EA, 5 / 1) to give **9*R*** (2.85 g, 99.8 %).

$[\alpha]^{23}_D$ -204.6° (*c* 0.025, EtOH); IR (neat) ν_{max} 3085, 3013, 2983, 2901, 2873, 1737, 1598 1580, 1509, 1430, 1270, 1111, 1077, 1047, 1024, 1008, 906.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.50 (1H, s, -NCH), 7.47 (1H, d, J = 1.8 Hz, Ar), 7.41 ~ 7.39 (1H, m, Ar), 7.27 ~ 7.25 (1H, m, Ar), 6.72 (1H, t, *J* = 74.9 Hz, $-CHF_2$), 3.95 (2H, d, J = 6.9 Hz, $-OCH_2-$), 1.32 ~ 1.27 (1H, m, -CH-), 1.26 (9H, s, 3 $-CH_3$), 0.69 ~ 0.66 (2H, m, $-CH_2-$), 0.41 ~ 0.38 (2H, m, $-CH_2-$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 161.6, 150.8, 132.3, 123.4, 122.5, 117.8, 115.8, 113.7, 74.0, 57.9, 22.6, 10.0, 3.2; MS m/z (%) 289 (M+, 98), 288 (5), 272 (4), 241 (20), 240 (22), 212 (7), 187 (11), 184 (5), 167 (8), 149 (3), 97 (2), 84 (7), 71 (4), 55 (90); HRMS calcd for $C_{16}H_{21}F_2NO_3S$: 345.1210, found: 345.1213

(*S*)-2-Methylpropane-2-sulfinic acid 3-cyclopropylmethoxy-4-difluoromethoxylbenzylideneamide (9*S*)

Prepared as described for compound **9*R*** (8.2 mmol scale, 98.8% yield)

$[\alpha]^{23}_D$ -206.0° (*c* 0.025, EtOH); All spectra was identical to the compound **9*R***.

(*Rs, R*)-2-Methylpropane-2-sulfinic acid [1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-yl-ethyl]amide (10*R*)

To a stirred solution of 4-methylpyridine (1.1 g, 11.2 mmol) in THF was added n-BuLi (6.1 ml, 9.8 mmol) dropwise at – 78 °C and the reaction mixture was stirred for 0.5 h at 0 °C.

After cooling to -78 °C, **9*R*** (2.6 g, 7.5 mmol) solution in THF was added dropwise to the reaction mixture and stirred for 3 h at -78 °C. The reaction solution was quenched with saturated aq-NH_4Cl, diluted with ethyl acetate (100 mL) and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (n-Hexane/EA, 2/1) to give **10*R*** (2.78 g, 83 %).

$[\alpha]^{23}_{D}$ -30.0° (*c* 0.025, EtOH); IR (neat) ν_{max} 3206, 2955, 2927, 2871, 1735, 1602, 1562, 1509, 1467, 1413, 1386, 1215, 1116, 1045, 915, 835, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.42~ 8.41 (2H, m, Ar), 7.08 (1H, d, *J* = 8.2 Hz, Ar), 6.97 ~ 6.96 (2H, m, Ar), 6.85 ~ 6.83 (1H, m, Ar), 6.80 (1H, d, *J* = 1.9 Hz, Ar), 6.60 (1H, t, *J* = 75.4 Hz, $-CHF_2$), 4.58 (1H, d, *J* = 4.6 Hz, -CH-), 3.76 (2H, d, *J* = 6.9 Hz, $-OCH_2-$), 3.73 (1H, d, *J* = 4.6 Hz, -NH-), 3.29 ~ 3.25 (1H, m, dd, $-CH_2-$), 3.01 ~ 2.97 (1H, m, dd, $-CH_2$), 1.18~ 1.15 (1H, m, -CH-), 1.15 (9H, s, $-CH_3$, $-CH_3$, $-CH_3$), 0.61 ~ 0.59 (1H, m, $-CH_2-$), 0.32~ 0.31 (1H, m, $-CH_2-$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.4, 149.6, 146,4, 140.1, 139.7, 124.9, 122.7, 119.3, 118.2, 116.1, 114.1, 113.8, 73.8, 59.8, 56.1, 42.7, 22.5, 10.0, 3.1; MS m/z (%) 438 (M+, 40), 391 (11), 383 (92), 346 (37), 320 (80), 291 (77), 288 (75), 265 (100), 242 (80), 213 (72), 188 (97), 166 (77), 147 (83), 141 (25), 106 (68), 92 (42), 56 (49); HRMS calcd for $C_{22}H_{28}F_2N_2O_3S$: 438.1789, found: 438.1782.

(*Ss, S*)-2-Methylpropane-2-sulfinic acid [1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-yl-ethyl]amide (10*S*)

Prepared as described for compound **10*R*** (8.2 mmol scale, 82% yield)

$[\alpha]^{23}_{D}$ +30.6° (*c* 0.025, EtOH); All spectra was identical to the compound **10*R***.

(*R*)-1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethylamine (11*R*)

4*N*-HCl (4.1 ml, 16.4 mmol) were added slowly to a solution of **10*R*** (1.8 g, 4.1 mmol) in dioxane at 0 °C. After 5 min, the cooling bath was removed. The reaction was allowed to ambient temperature and stirred for 4h. The solid formed during the reaction was filtered up and added to saturated aq- $NaHCO_3$, extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2 / MeOH, 20 / 1) to give **11*R*** (1.2 g, 85.6%).

$[\alpha]^{23}_D$ -316.8 ° (*c* 0.03, EtOH); IR (neat) ν_{max} 3073, 3016, 2926, 2874, 1734, 1666, 1600, 1562, 1506, 1469, 1422, 1411, 1380, 1269, 1207, 1112, 1016, 897, 822, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ8.48 (2H, d, *J* = 5.8 Hz, Ar), 7.10 (1H, d, *J* = 8.2 Hz, Ar), 7.06 ~ 7.05 (2H, m, Ar), 6.91 (1H, d, *J* = 1.9 Hz, Ar), 6.86 ~ 6.84 (1H, m, Ar), 6.61 (1H, t, *J* = 75.6 Hz, -CHF_2), 4.21 ~ 4.18 (1H, m, -CH-), 3.84(2H, d, *J* = 3.6Hz, -OCH_2-), 2.93 ~ 2.90 (1H, m, dd, -CH_2-), 2.84 ~ 2.81 (1H, m, dd, -CH_2), 1.68 (2H, s, -NH_2), 1.24~ 1.20 (1H, m, -CH-), 0.64~ 0.61 (1H, m, -CH_2-), 0.35~ 0.33(1H, m, -CH_2-); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.5, 149.7, 147,6, 143.4, 139.5, 124.6, 122.6, 118.9, 116.2, 112.4, 73.9, 56.5, 45.7, 10.1, 3.1; MS m/z (%) 334 (M+, 12), 306 (7), 296 (60), 268 (60), 243 (100), 242 (45), 214 (22), 188 (80), 168 (25), 147 (87), 121 (48), 107 (40), 88 (70) 57 (55); HRMS calcd for $C_{18}H_{20}F_2N_2O_2$: 334.1493, found: 334.1486.

(*S*)-1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethylamine (11*S*)

Prepared as described for compound **11*R*** (3.1 mmol scale, 82% yield)

$[\alpha]^{23}_D$ +314.8 ° (*c* 0.03, EtOH); All spectra was identical to the compound **11*R***.

(*R*)-3-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethylamino]-1-(3-nitrophenyl)propenone (12*R*)

Compound **11*R*** (1.0 g, 2.8 mmol) and *(E)*-3-(*N*,*N*-Dimethylamino-1-(4-nitrophenyl)-2-

propen-1-one (0.6 g, 2.8 mmol) were refluxed in ethanol for 12h. The reaction was allowed to cool to the ambient temperature and was quenched by adding water and concentrated in vaccuo. The mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (CH_2Cl_2 / MeOH, 80 / 1) to afford **12*R*** (1.2 g, 84.2 %).

$[\alpha]^{23}_D$ -120.8° (*c* 0.025, EtOH); IR (neat) ν_{max} 3232, 3078, 3018, 2928, 1733, 1626, 1585, 1525, 1500, 1427, 1380, 1347, 1267, 1109, 1044, 1021, 1005, 911, 810, 782, 724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ8.67 (1H, d, *J* = 1.8 Hz, Ar), 8.53 ~ 8.52 (2H, m, Ar), 8.31 ~ 8.28 (1H, m, Ar), 8.18 ~ 8.16 (1H, m, Ar), 7.62 ~ 7.58 (1H, m, Ar), 7.17 (1H, d, *J* = 8.2 Hz, olefinic-H), 7.09 ~ 7.08 (1H, m, Ar), 6.86 ~ 6.79 (3H, m, Ar) 6.62 (1H, t, *J* = 75.3 Hz, $-CHF_2$), 5.70 (1H, d, *J* = 7.5 Hz, olefinic-H), 4.54 ~ 4.49 (1H, m, -CH-), 3.84 (2H, d, *J* = 6.9Hz, $-OCH_2-$), 3.16 (1H, d, *J* = 7.2Hz, $-CH_2$), 1.65 (1H, s, -NH-), 1.27~ 1.21 (1H, m, -CH-), 0.66~ 0.62 (1H, m, $-CH_2-$), 0.36~ 0.33 (1H, m, $-CH_2-$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 187.3, 153.7, 151.0, 150.1, 148.3, 145,5, 140.8, 138.9, 132.8, 129.4, 125.5, 124.6, 123.2, 122.1, 119.1, 116.0, 113.9, 112.6, 91.1, 74.1, 63.7, 43.5, 10.0, 3.2; MS m/z (%) 509 (M+, 10), 479 (4), 417 (100), 387 (38), 363 (25), 333 (40), 318 (12), 296 (4), 264 (5), 242 (6), 212 (3), 196 (7), 167 (8), 150 (22), 147 (13), 93 (48), 92 (5), 55 (75); HRMS calcd for $C_{27}H_{25}F_2N_3O_5$: 509.1762, found: 509.1763.

(*S*)-3-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethylamino]-1-(3-nitrophenyl)propenone (12*S*)

Prepared as described for compound **12*R*** (2.2 mmol scale, 89% yield)

$[\alpha]^{23}_D$ +121.8° (*c* 0.025, EtOH); All spectra was identical to the compound **12*R***.

(*R*)-4-{2-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-[3-(3-nitrophenyl)-pyrazol-1-yl]-ethyl}pyridine (13*R*)

To a stirred solution of **12*R*** (1.1g, 2.1 mmol) in DMF was added NaH (0.2 g, 4.2 mmol) slowly at 0 °C and the reaction mixture was stirred for 1 h at 0 °C. *O*-(4-Nitrobenzoyl)hydroxylamine (0.9 g, 4.2 mmol)was added slowly to the reaction mixture and stirred for 3 h at 0 °C and followed by heating for 10 min. The reaction was allowed to ambient temperature and was quenched with saturated aq-NH_4Cl, diluted with ethyl acetate and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (n-Hexane/EA, 1/2) to give **13*R*** (0.5 g, 47.4 %). $[\alpha]^{23}_{D}$ -191.0° (*c* 0.015, EtOH); IR (neat) ν_{max} 3078, 3017, 2927, 1732, 1602, 1531, 1512, 1432, 1411, 1379, 1346, 1215, 1115, 1047, 1019, 907, 862, 808, 763, 732, 673 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 ~ 8.69 (1H, m, Ar), 8.45 (2H, d, *J* = 5.7 Hz, Ar), 8.17 ~ 8.15(1H, m, Ar), 8.13 (1H, d, *J* = 7.8 Hz, Ar), 7.59 ~ 7.56 (1H, m, Ar), 7.34 (1H, d, *J* = 2.3 Hz, Ar), 7.13 (1H, d, *J* = 8.2 Hz, Ar), 7.08 (1H, d, *J* = 1.9 Hz, Ar), 6.99 (2H, d, *J* = 5.6 Hz, Ar), 6.94 ~ 6.92 (1H, m, Ar), 6.61 (1H, t, *J* = 75.3 Hz, $-CHF_2$), 6.58 (1H, d, *J* = 2.3 Hz, Ar), 5.41 ~ 5.38 (1H, m, -CH-), 3.93 ~ 3.90 (1H, m, dd, $-CH_2$-), 3.86 (2H, d, *J* = 4.6Hz, $-OCH_2$-), 3.42 ~ 3.39 (1H, m, dd, $-CH_2$), 1.26~ 1.23 (1H, m, -CH-), 0.62~ 0.60 (1H, m, $-CH_2$-), 0.34~ 0.33(1H, m, $-CH_2$-); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.8, 150.0, 149.6, 148.9, 146,6, 140.5, 138.0, 135.4, 131.4, 129.7, 124.4, 122.9, 122.4, 120.5, 119.6, 118.2, 116.2, 113.5, 103.6, 74.1, 67.0, 41.5, 10.2, 3.4; MS m/z (%) 506 (M+, 75) 476 (25), 452 (24), 451 (6), 414 (99), 384 (30), 360 (35), 359 (6), 317 (65), 297 (25), 263 (24), 251 (42), 243 (10), 212 (6), 197 (13), 167 (15), 149(9), 147 (5), 97 (7), 71 (11), 55 (100); HRMS calcd for $C_{27}H_{24}F_2N_4O_4$: 506.1766, found: 509.1753.

(*S*)-4-{2-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-[3-(3-nitrophenyl)-pyrazol-1-yl]-ethyl}-pyridine (13*S*)

Prepared as described for compound **13*R*** (1.7 mmol scale, 47% yield)

$[\alpha]^{23}_{D}$ +195.0° (*c* 0.015, EtOH); All spectra was identical to the compound **13*R***.

(*R*)-3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethyl]-1*H*-pyrazol-3-yl}phenylamine (14*R*)

To a stirred solution of **13*R*** (0.4 g, 0.79 mmol) in EtOH was added 10% Pd/C followed by charged with hydrogen gas. The resulting mixture was stirred at ambient temperature for 5h and fillered. The filterate was diluted with ethyl acetate and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2 / MeOH, 20 / 1) to give **14*R*** (0.29 g, 76 %).

$[\alpha]^{23}_{D}$ -89.0° (*c* 0.015, EtOH);); IR (neat) ν_{max} 3215, 3026, 2927, 1729, 1604, 1561, 1510, 1477, 1449, 1432, 13829, 1347, 1267, 1206, 1112, 1047, 1025, 907, 807, 786, 757, 727, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ8.49 (2H, d, *J* = 5.9 Hz, Ar), 7.32 ~ 7.31 (1H, m, Ar), 7.26 ~ 7.25 (3H, m, Ar), 7.17 (1H, d, *J* = 8.2 Hz, Ar), 7.08 (1H, d, *J* = 2.0 Hz, Ar), 7.03 (1H, d, *J* = 5.9 Hz, Ar), 6.98 (2H, d, *J* = 2.0 Hz, Ar), 6.96 (1H, d, *J* = 2.0 Hz, Ar), 6.73 ~ 6.72 (1H, m, Ar), 6.65 (1H, t, *J* = 75.4 Hz, -CHF_2), 6.73 ~ 6.71 (1H, m, Ar), 5.44 ~ 5.41 (1H, m, -CH-), 4.00 ~ 3.95 (1H, m, dd, -CH_2-), 3.87 (2H, d, *J* = 6.9Hz, -OCH_2-), 3.42 ~ 3.38 (1H, m, dd, -CH_2), 1.32~ 1.26 (1H, m, -CH-), 0.67~ 0.65 (1H, m, -CH_2-), 0.39~ 0.37 (1H, m, -CH_2-); ^{13}C NMR (500 MHz, $CDCl_3$) δ 152.0, 150.8, 149.9, 146,8, 140.3, 138.6, 134.7, 130.7, 129.7, 124.5, 122.8, 119.5, 118.3, 116.3, 116.2, 114.8, 113.5, 112.3 103.2, 74.0, 66.6, 41.5, 10.2, 3.3; MS m/z (%) 476 (M+, 90), 421 (7), 414 (3), 384 (99), 356 (3), 318 (30), 317 (12), 297 (5), 263 (23), 243 (8), 207 (15), 197 (13), 170 (15), 149 (16), 147 (15), 135 (12), 84 (100), 55 (60); HRMS calcd for $C_{27}H_{26}F_2N_4O_2$: 476.2024, found: 476.2021.

(*S*)-3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethyl]-1*H*-pyrazol-3-yl}phenylamine (14*S*)

Prepared as described for compound **14*R*** (0.6 mmol scale, 77% yield) $[\alpha]^{23}_{D}$ +86.3° (*c* 0.015, EtOH); All spectra was identical to the compound **14*R***.

(*R*)-*N*-(3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-yl-ethyl]-1*H*-pyrazol-3-yl}phenyl)acetamide (15*R*)

To a stirred solution of **14*R*** (0.15 g, 0.31 mmol) in CH_2Cl_2 was added acetic anhydride (0.038 g, 0.38 mmol) and Et_3N (0.047 g, 0.47 mmol). After the reaction was stirred for 12 h at rt, quenched with saturated aq-$NaHCO_3$, diluted with ethyl acetate and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2 / MeOH, 40 / 1) to give **15*R*** (0.15 g, 93.3 %).

$[\alpha]^{23}_{D}$ -149.7° (*c* 0.018, EtOH); IR (neat) ν_{max} 3091, 2365, 2329, 2129, 1986, 1794, 1606, 1554, 1507, 1466, 1415, 1375, 1271, 1119, 1111, 1043, 999, 855, 796, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ8.41 (2H, d, *J* = 5.5 Hz, Ar), 7.99 (1H, s, Ar), 7.55 ~ 7.50 (2H, m, Ar), 7.34 ~ 7.31 (1H, m, Ar), 7.26 ~ 7.25 (1H, m, Ar), 7.09 (1H, d, *J* = 8.2 Hz, Ar), 7.01 (1H, d, *J* = 1.9 Hz, Ar), 6.96 (2H, d, *J* = 5.7 Hz, Ar), 6.90 ~ 6.88 (1H, m, Ar), 6.59 (1H, t, *J* = 75.4 Hz, -CHF_2), 6.46 (1H, d, *J* = 2.2 Hz, Ar), 5.37 ~ 5.34 (1H, m, -CH-), 3.90 ~ 3.86 (1H, m, dd, -CH_2-), 3.80 (2H, d, *J* = 6.9Hz, -OCH_2-), 3.50 ~ 3.24 (1H, m, dd, -CH_2), 2.16 (3H, s, -CH_3) 1.25~ 1.17 (1H, m, -CH-), 0.60~ 0.56 (1H, m, -CH_2-), 0.31~ 0.28 (1H, m, -CH_2-); ^{13}C NMR (500 MHz, $CDCl_3$) δ 168.7, 151.4, 150.7, 149.9, 146,9, 140.3, 138.6, 138.5, 134.4, 130.9, 129.4, 124.5, 122.8, 121.6, 119.5, 117.1 116.2, 114.2, 113.5, 103.2, 74.0, 66.6, 41.5, 24.7, 10.2, 3.3; MS m/z (%) 518 (M+, 64), 464 (7), 463 (7), 426 (100), 398 (6), 372 (12), 334 (6), 317 (40), 297 (13), 263 (22), 251 (18), 243 (10), 197 (16), 159 (26), 154 (5), 130 (10), 93 (5), 77 (4), 55 (80); HRMS calcd for $C_{29}H_{28}F_2N_4O_3$: 518.2129, found: 518.2115.

(*S*)-*N*-(3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-

pyridin-4-yl-ethyl]-1*H*-pyrazol-3-yl}phenyl)acetamide (15*S*)

Prepared as described for compound **15*R*** (0.25 mmol scale, 96% yield) $[\alpha]^{23}_{D}$ +148.8° (*c* 0.018, EtOH); All spectra was identical to the compound **15*R***.

(*R*)-*N*-(3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-(1-oxypyridin-4-yl)-ethyl]-1*H*-pyrazl-3-yl-phenyl)acetamide (1*R*)

To a stirred solution of **15*R*** (0.10 g, 0.19 mmol) in CH_2Cl_2 was added mcpba (0.071 g, 0.028 mmol) and $NaHCO_3$ (0.024 g, 0.028 mmol). After stirring for 12 h at rt, the reaction was quenched with saturated aq-$NaHCO_3$, diluted with ethyl acetate and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2 / MeOH, 20 / 1) to give **1*R*** (0.089 g, 88.7 %).
$[\alpha]^{23}_{D}$ -122.0° (*c* 0.018, EtOH); IR (neat) ν_{max} 3010, 2167, 2036, 1541, 1276, 1261, 764, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ8.03~ 8.01 (2H, m, Ar), 7.93 (1H, s, Ar), 7.52 ~ 7.48 (2H, m, Ar), 7.34 ~ 7.31 (1H, m, Ar), 7.24 (1H, d, *J* = 2.2 Hz, Ar), 7.13 (1H, d, *J* = 8.2 Hz, Ar), 7.05 (1H, d, *J* = 1.9 Hz, Ar), 6.96 ~ 6.91 (3H, m, Ar), 6.61 (1H, t, *J* = 75.3 Hz, -CHF_2), 6.47 (1H, d, *J* = 2.3 Hz, Ar), 5.33 ~ 5.29 (1H, m, -CH-), 3.87 ~ 3.86 (1H, m, dd, -CH_2-), 3.84 (2H, d, *J* = 6.9Hz, -OCH_2-), 3.33 ~ 3.29 (1H, m, dd, -CH_2), 2.18 (3H, s, -CH_3) 1.25~ 1.20 (1H, m, -CH-), 0.62~ 0.58 (1H, m, -CH_2-), 0.33~ 0.30 (1H, m, -CH_2-); ^{13}C NMR (500 MHz, $CDCl_3$) δ 168.9, 151.6, 150.9, 140.4, 139,0, 138.9, 138.0, 134.2, 131.0, 129.4, 127.0, 122.9, 121.4, 119.5, 119.4, 117.1 116.1, 114.2, 113.4, 103.6, 74.1, 66.4, 40.6, 24.6, 10.2, 3.3; MS m/z (%) 534 (M+, 52), 518 (72), 464 (5), 426 (100), 372 (12), 317 (32), 297 (10), 263 (30), 251 (18), 243 (7), 197 (12), 184 (8), 159 (25), 130 (8), 104 (3), 93 (10), 92 (7), 55 (78); HRMS calcd for $C_{29}H_{28}F_2N_4O_4$: 534.2079 found: 534.2065.

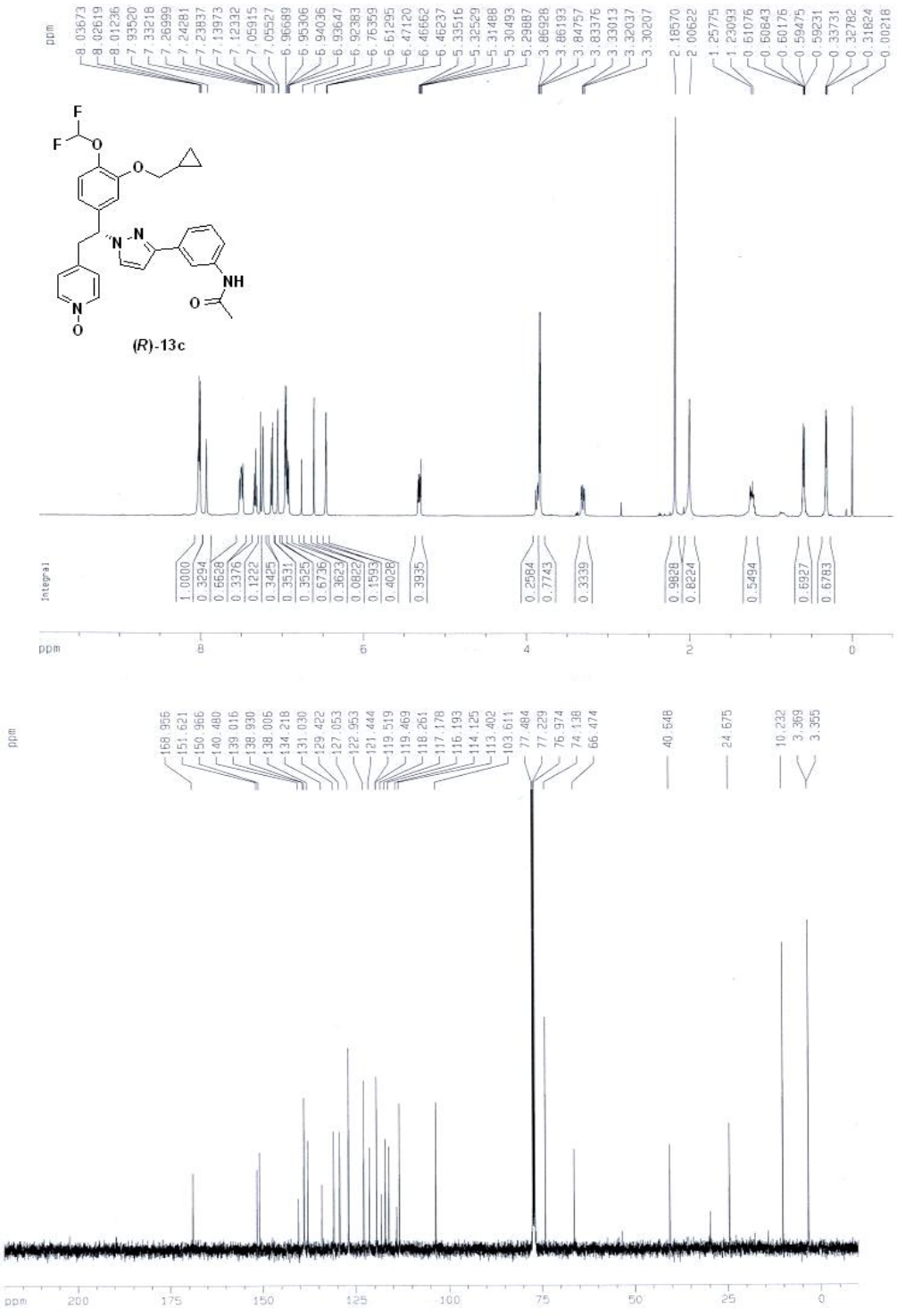
(*S*)-*N*-(3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-

(1-oxypyridin-4-yl)-ethyl]-1*H*-pyrazl-3-yl-phenyl)acetamide (1*S*)

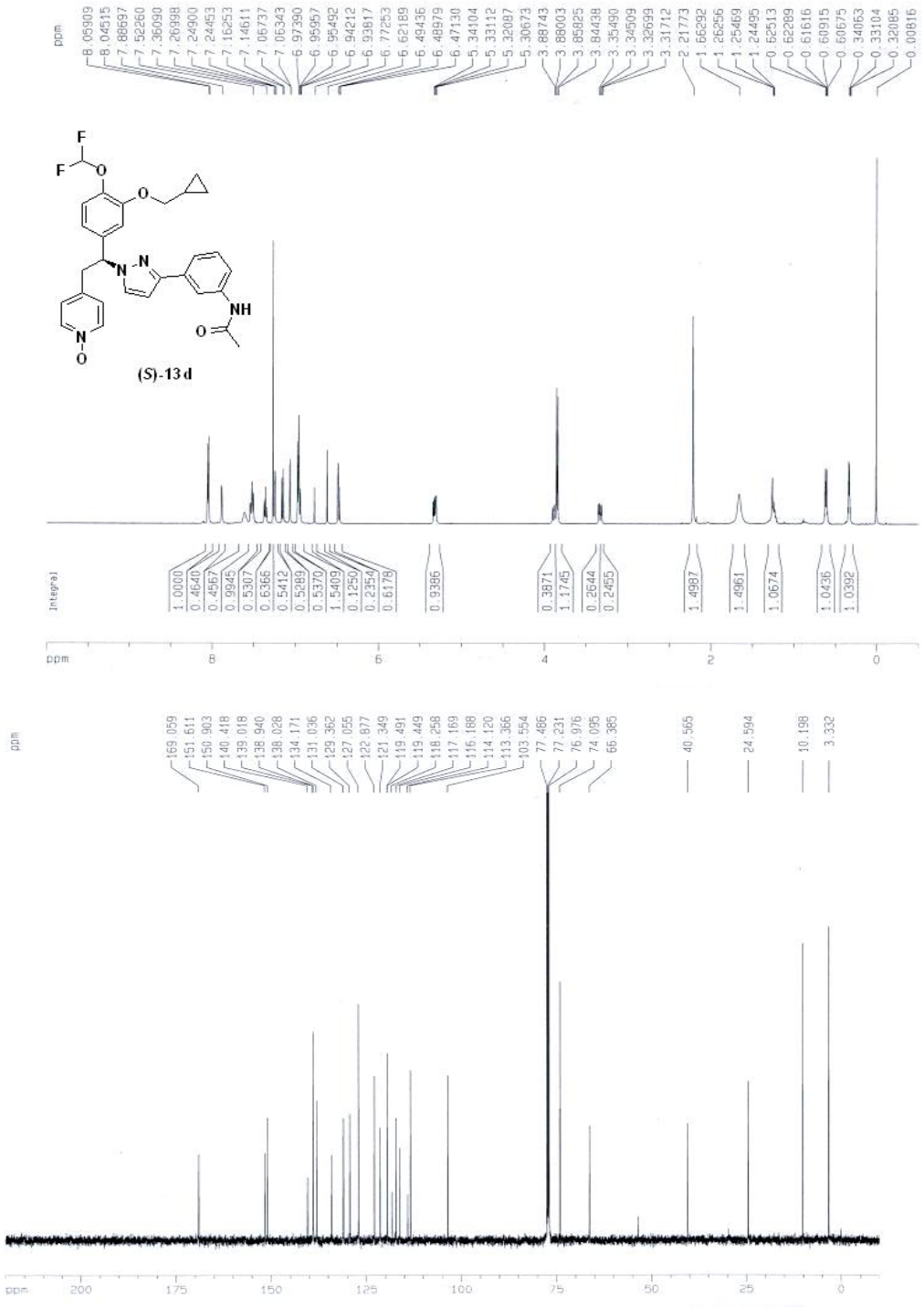
Prepared as described for compound **1*R*** (0.15 mmol scale, 85% yield)

$[\alpha]_D^{23}$ +120.85° (*c* 0.018, EtOH); All spectra was identical to the compound **1*R***.

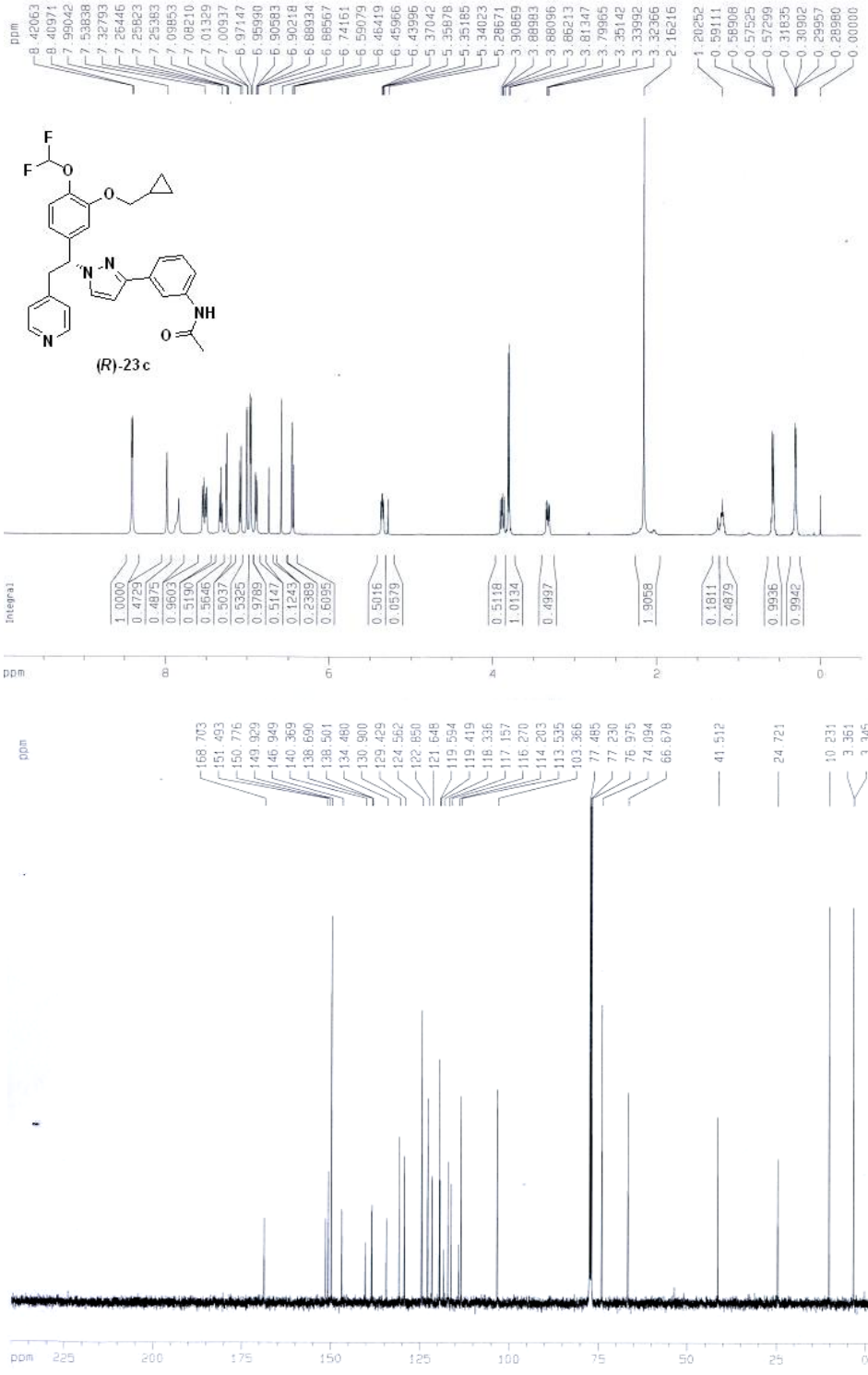
^{1}H and ^{13}C NMR of 1*R*



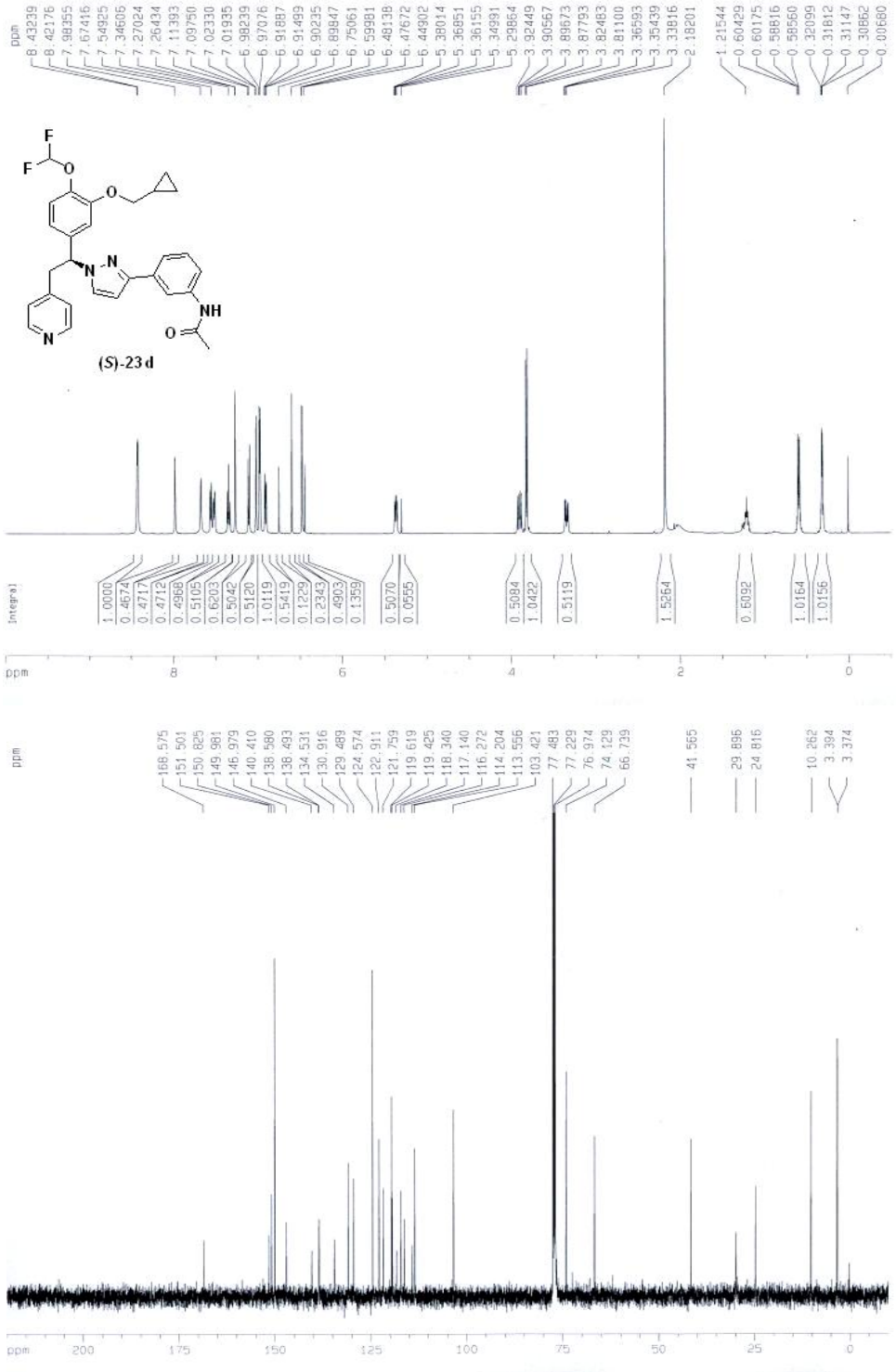
^{1}H and ^{13}C NMR of 1*S*



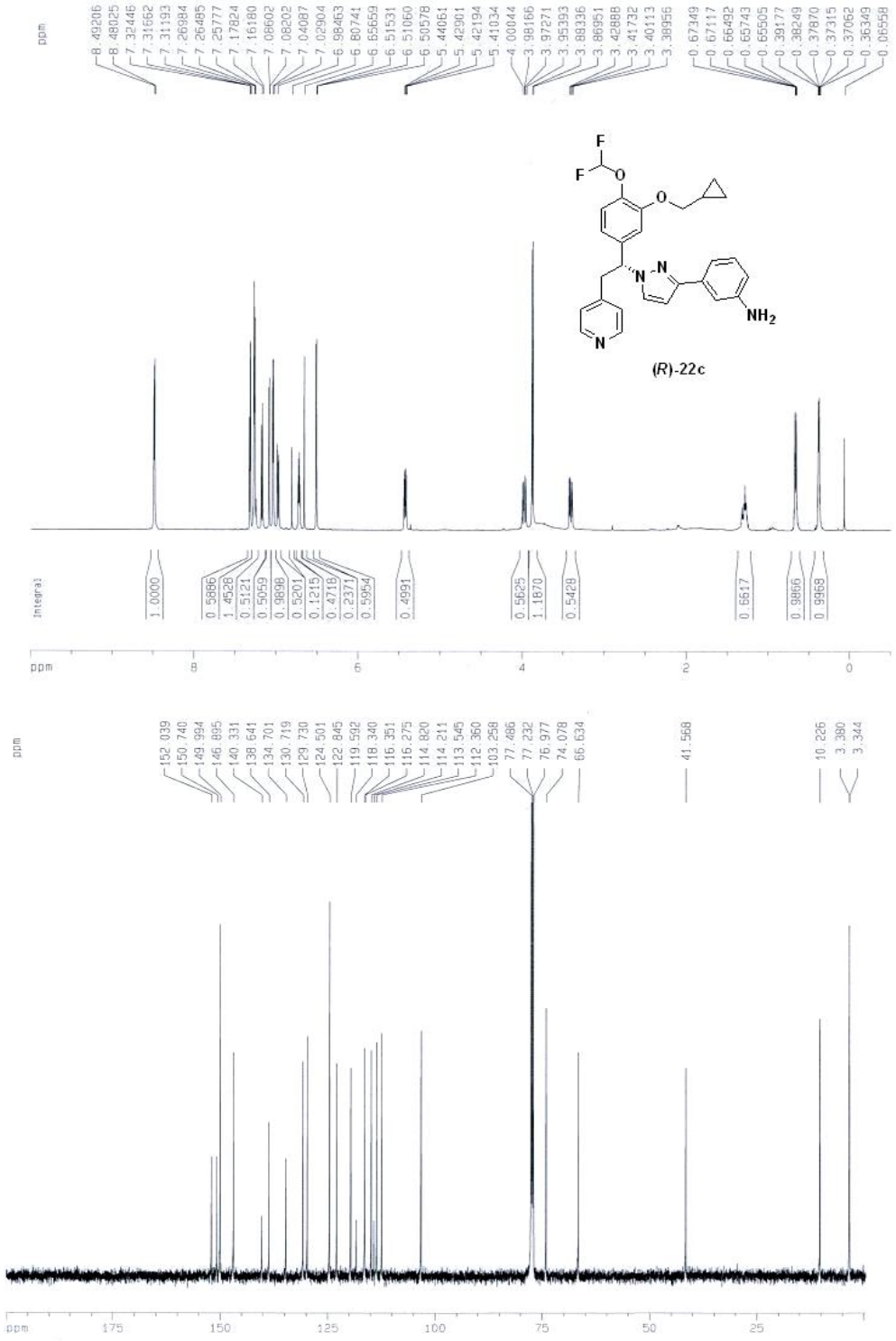
^{1}H and ^{13}C NMR of 15*R*



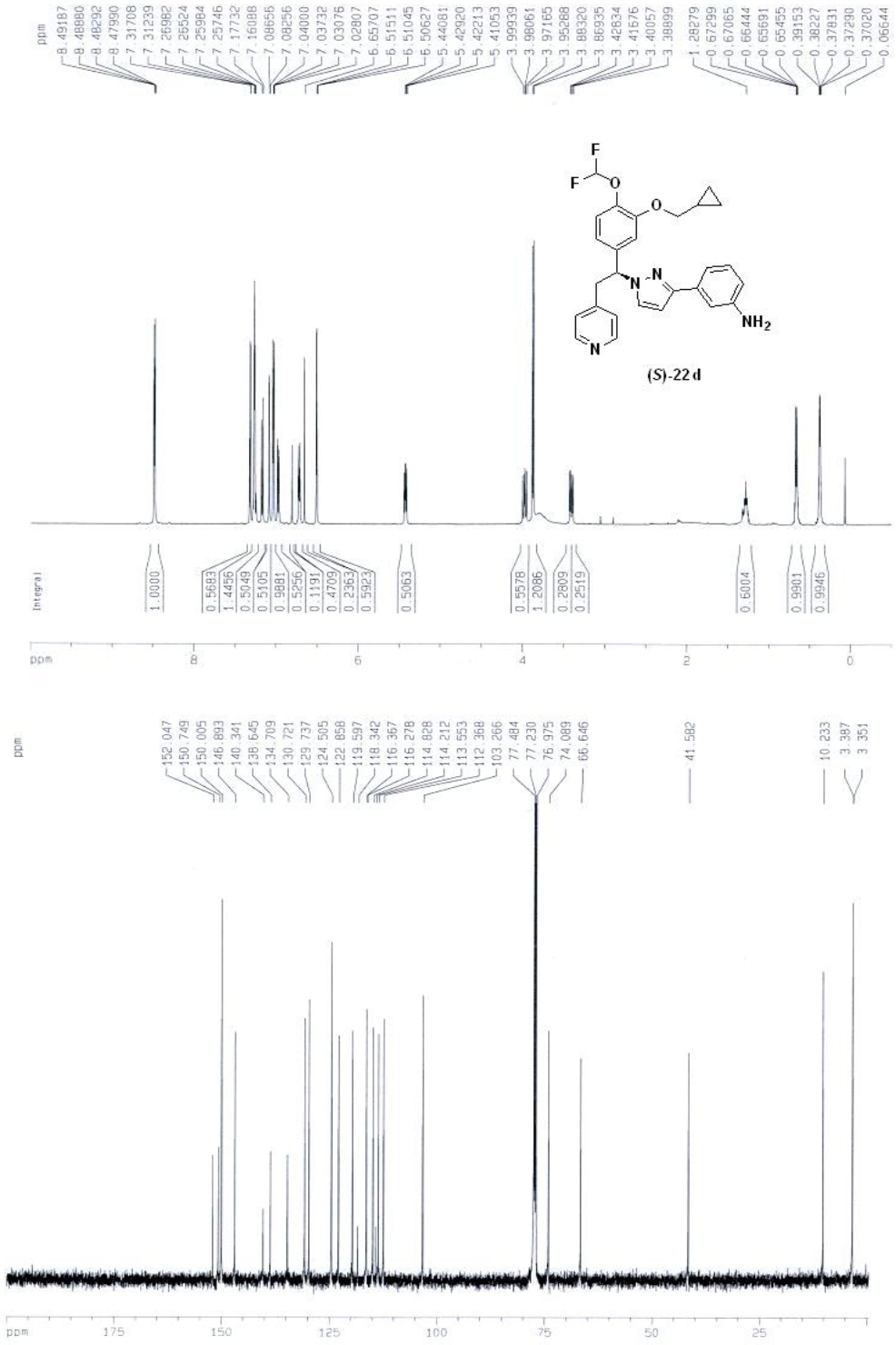
^{1}H and ^{13}C NMR of 15*S*



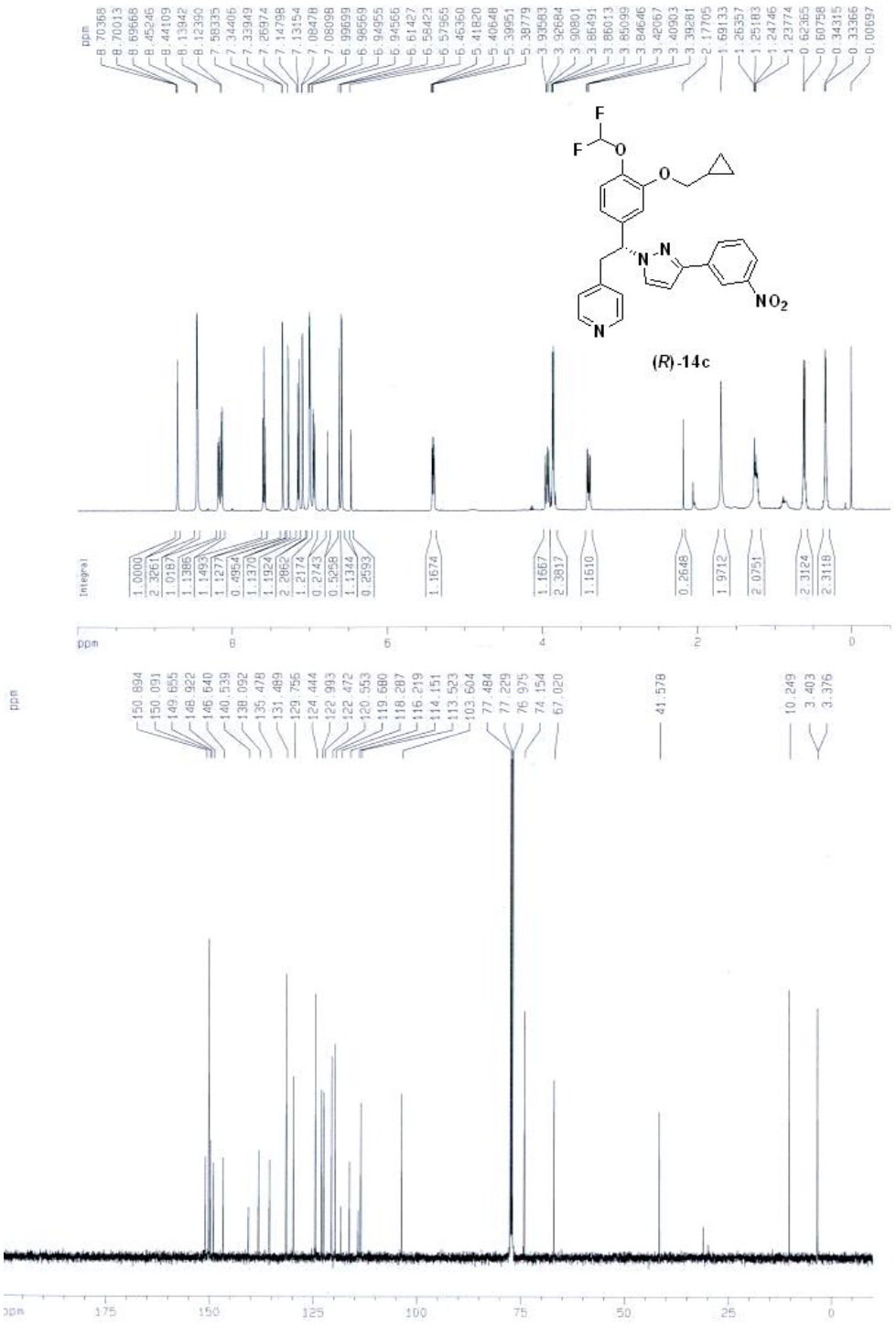
^{1}H and ^{13}C NMR of 14*R*



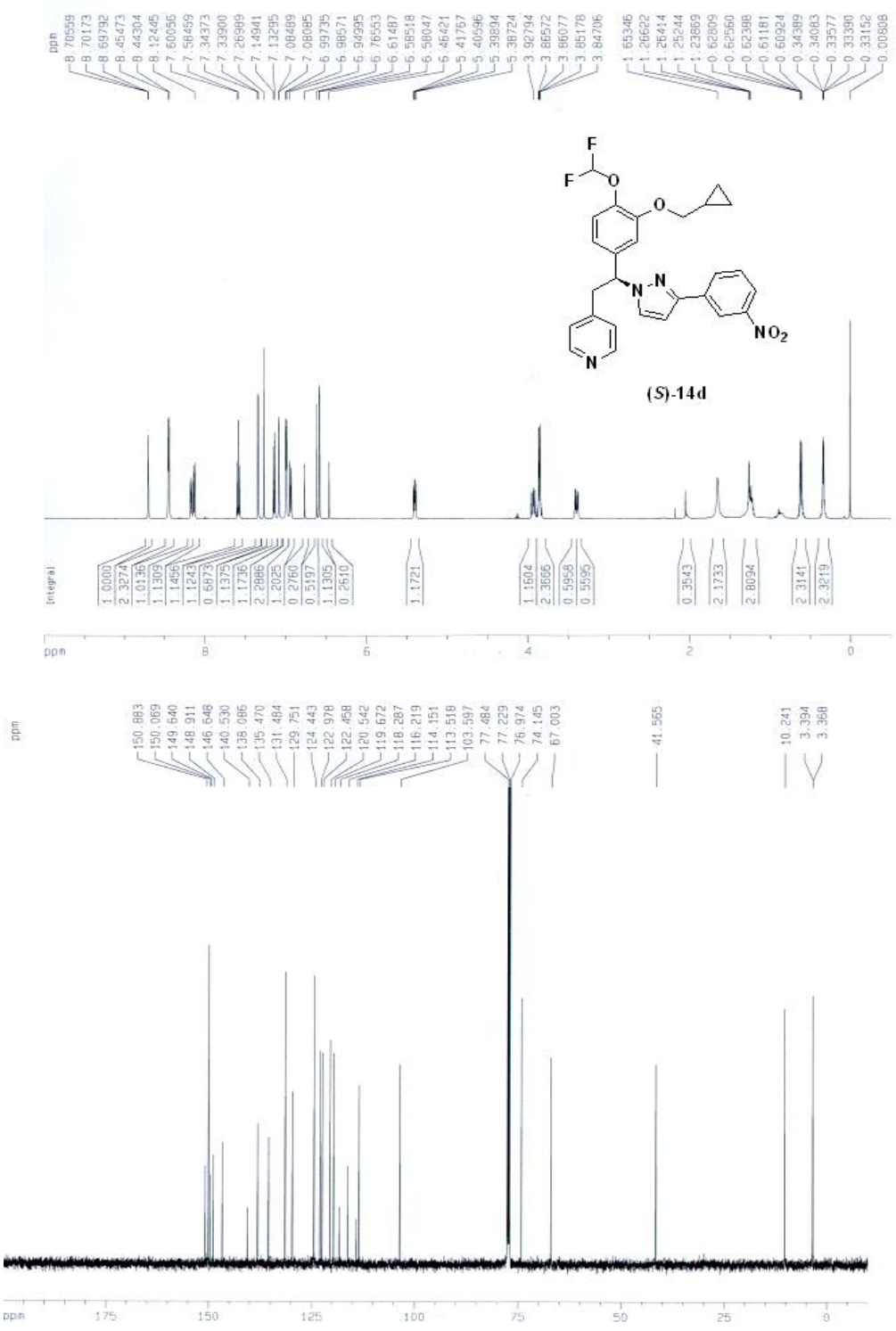
^{1}H and ^{13}C NMR of 14*S*



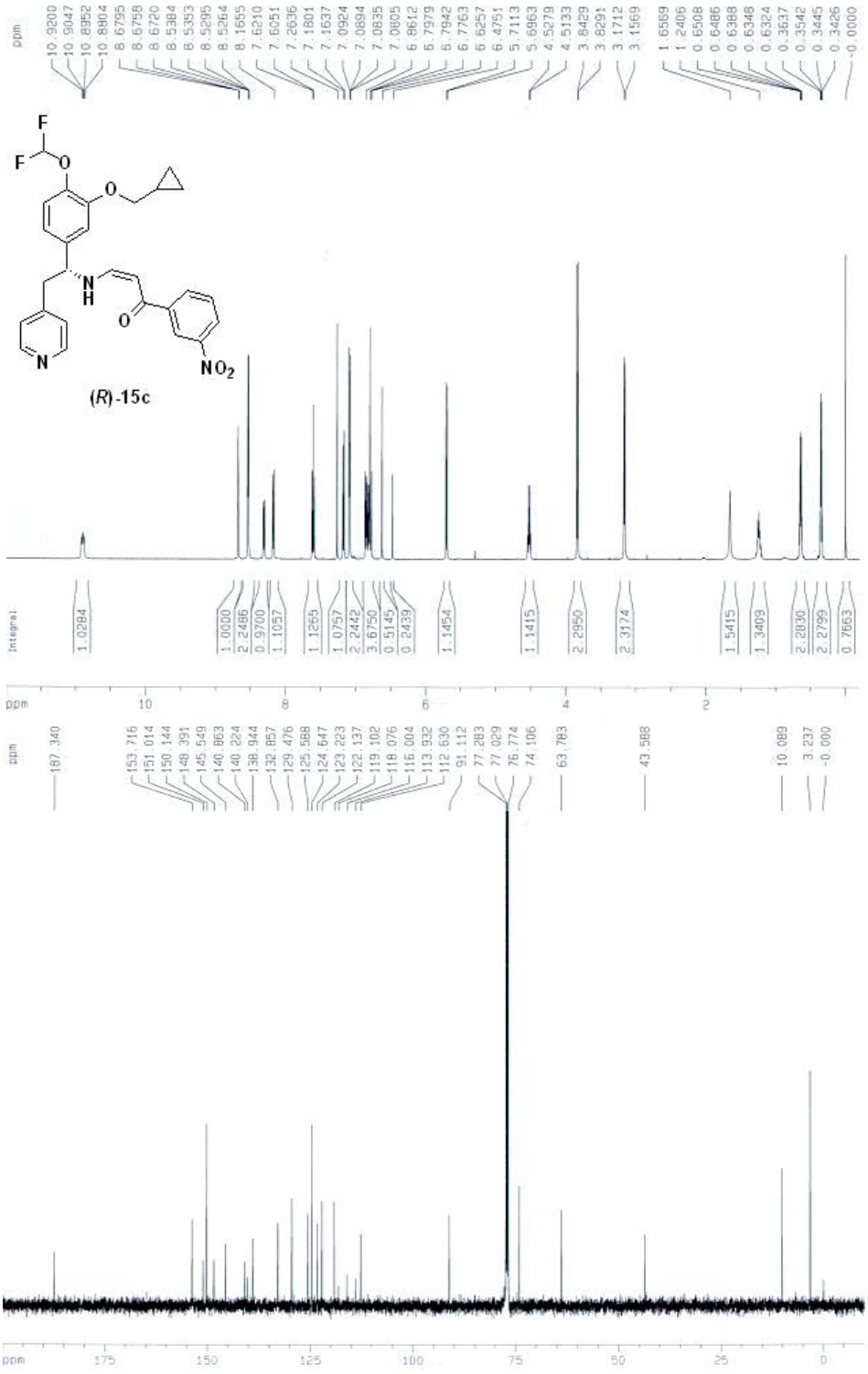
^{1}H and ^{13}C NMR of 13*R*



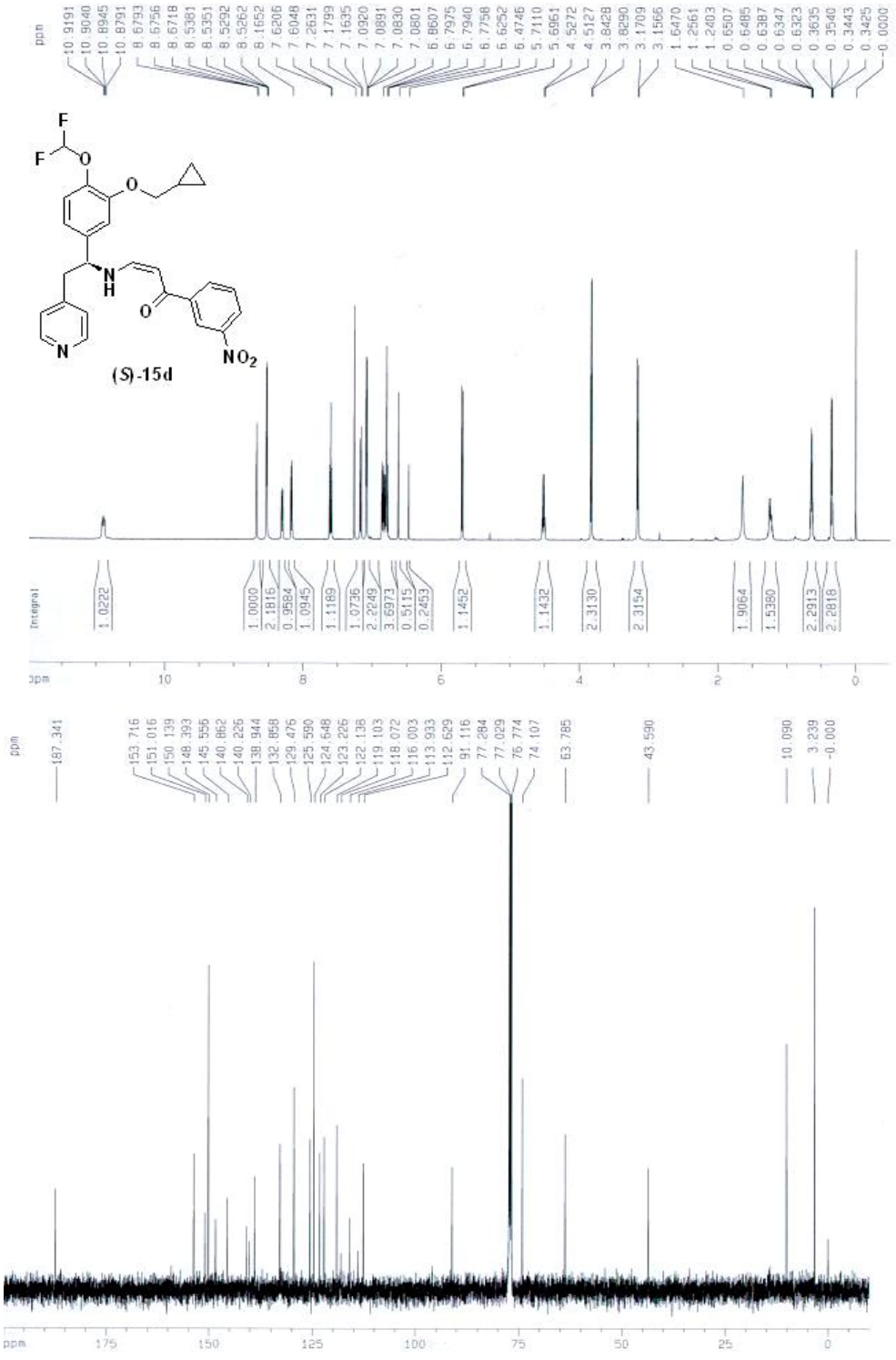
^{1}H and ^{13}C NMR of 13*S*



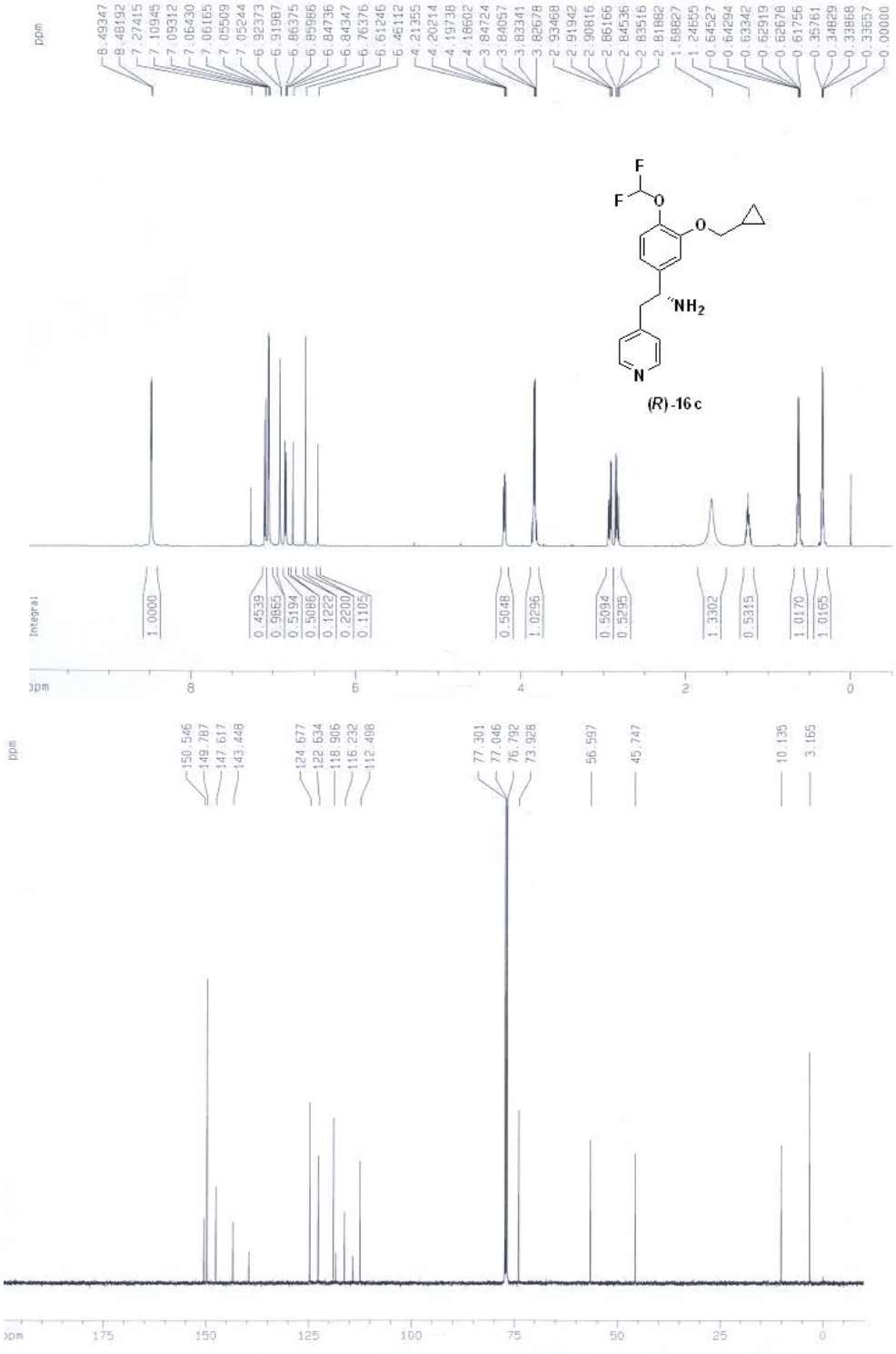
^{1}H and ^{13}C NMR of 12*R*



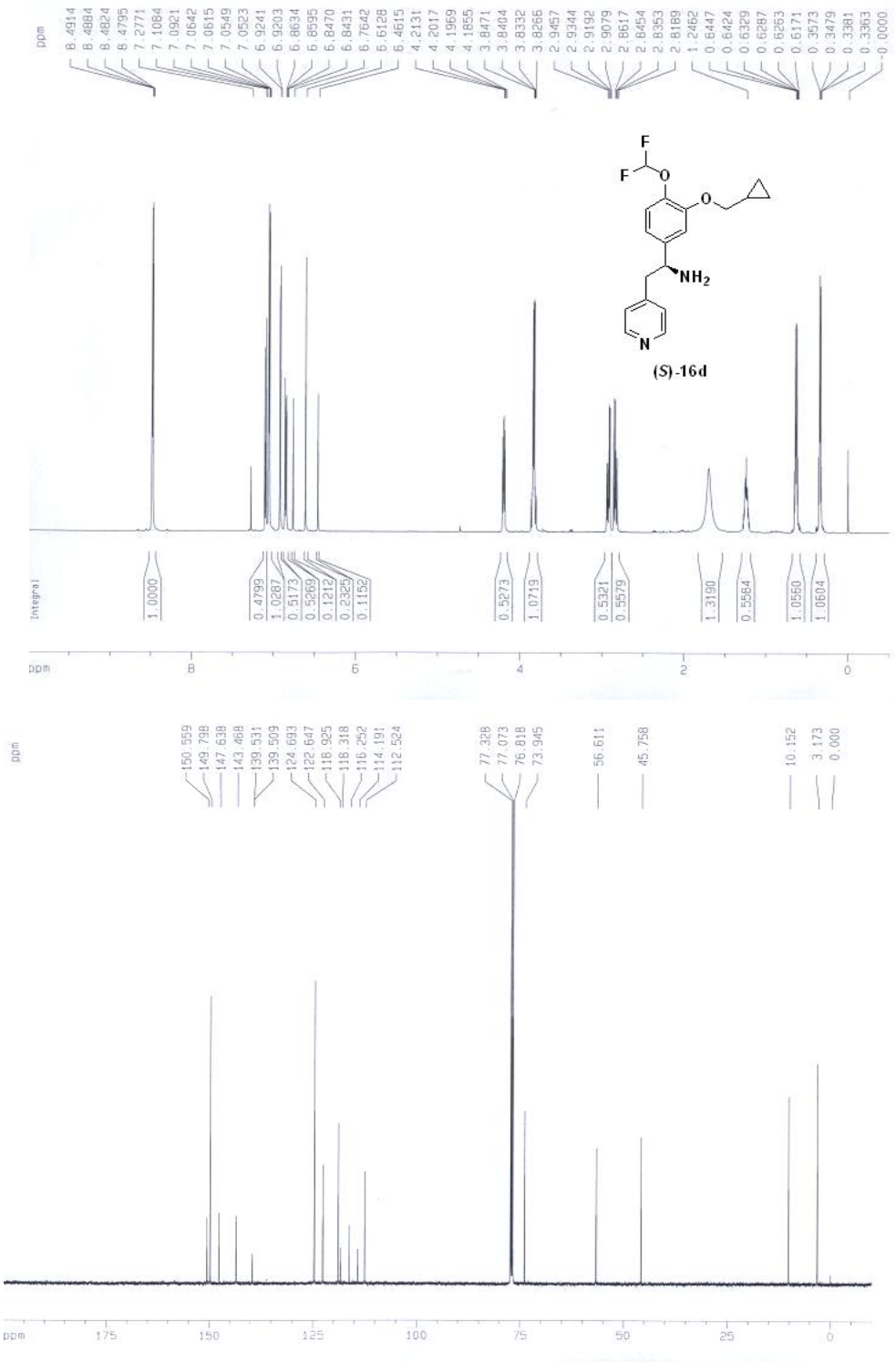
^{1}H and ^{13}C NMR of 12*S*



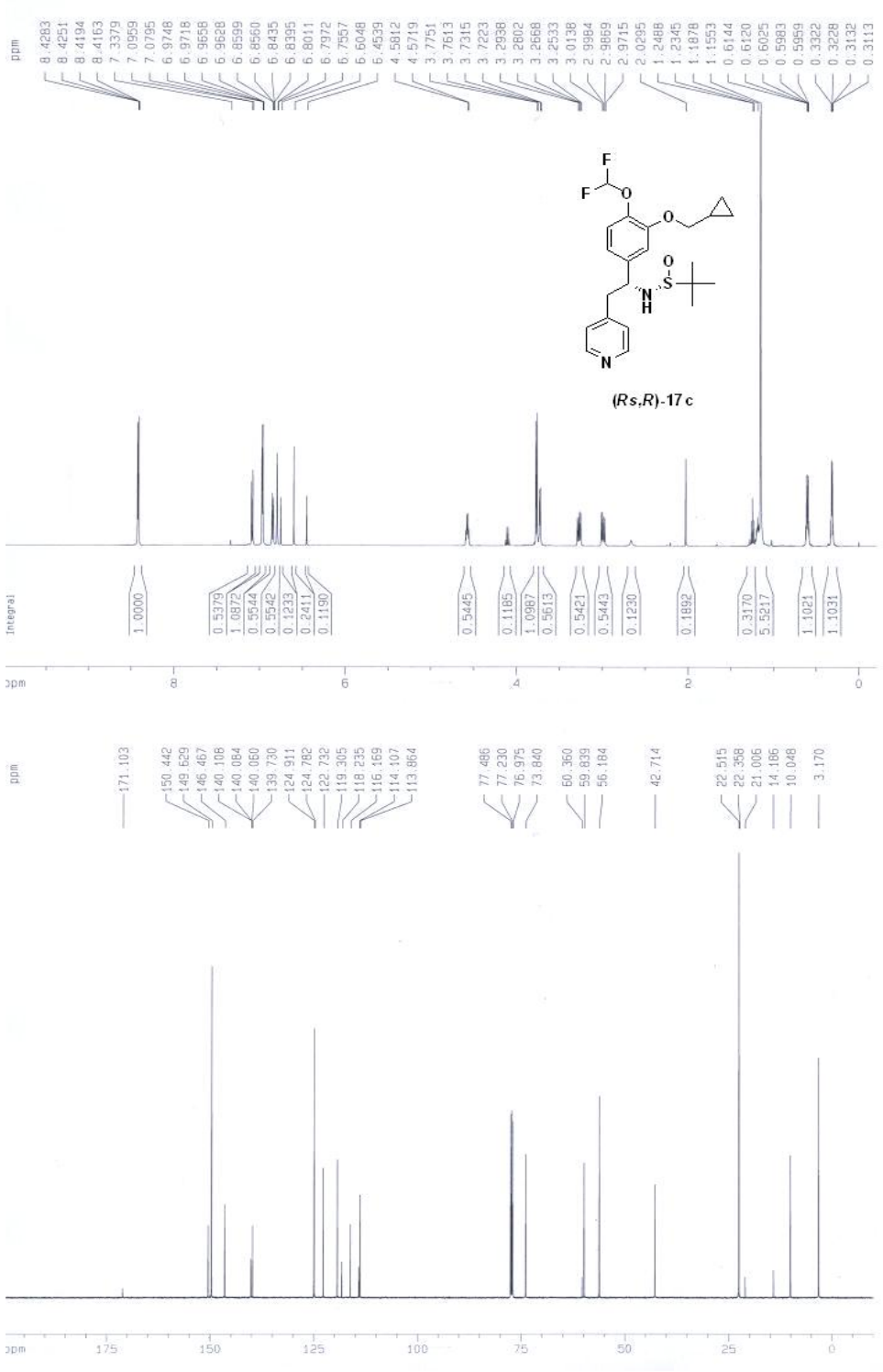
^{1}H and ^{13}C NMR of 11*R*



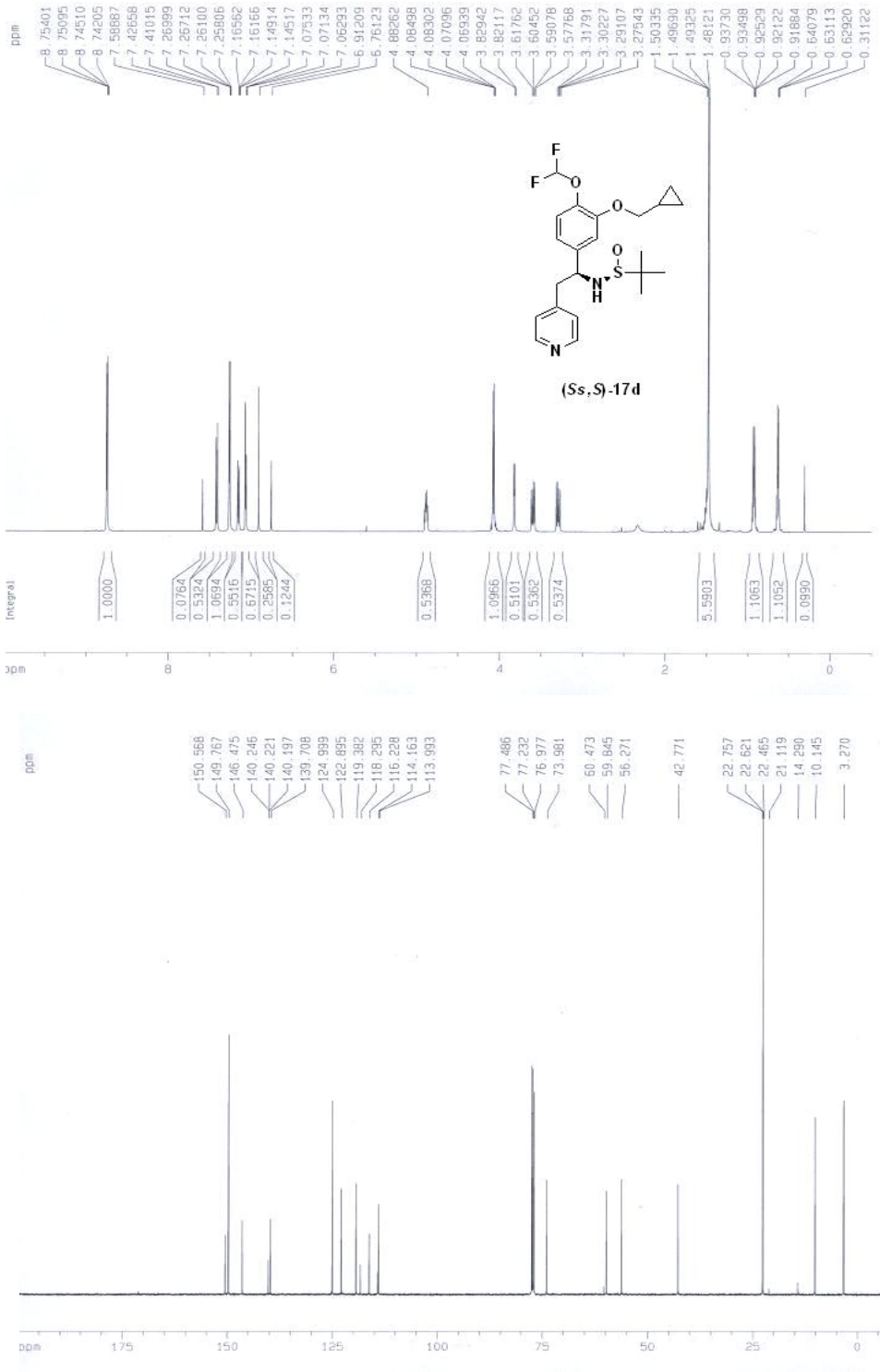
^{1}H and ^{13}C NMR of 11*S*



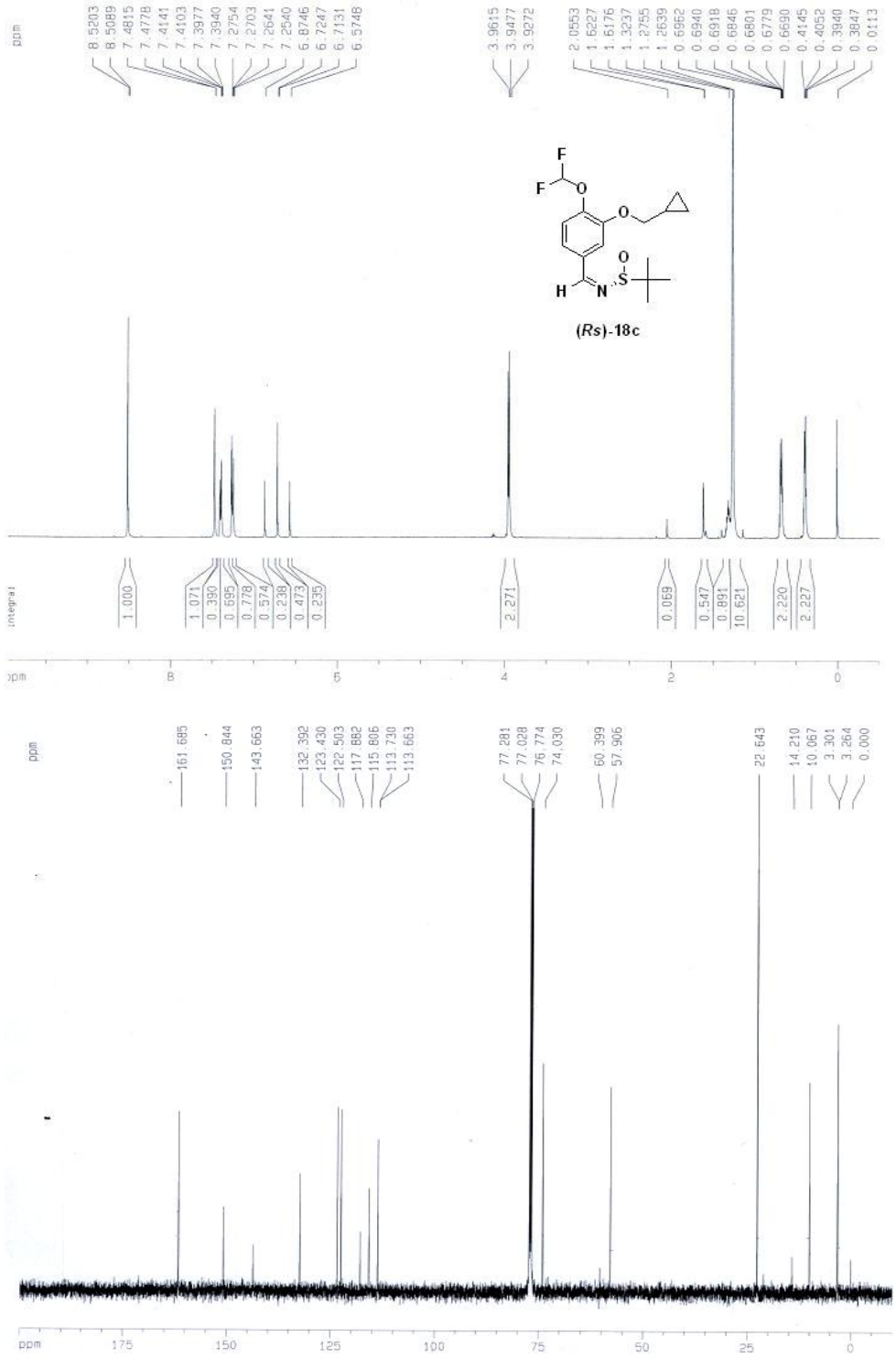
^{1}H and ^{13}C NMR of 10*R*



^{1}H and ^{13}C NMR of 10*S*



^{1}H and ^{13}C NMR of 9*R*



^{1}H and ^{13}C NMR of 9*S*