Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Electronic Supplementary Information

Chemoselective Direct Reductive Trifluoromethylation of Amides: A Flexible Access to Functionalized α-Trifluoromethylamines

Hang Chen,[a] Jian-Liang Ye,*[a] and Pei-Qiang Huang*[ab]

[a] *Department of Chemistry, Fujian Provincial Key Laboratory of Chemical Biology, iChEM (Collaborative Innovation Center of Chemistry for Energy Materials), College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, P. R. China*

[b] *State Key Laboratory of Applied Organic Chemistry Lanzhou University, Lanzhou 730000, P. R. China*

Fax: 86-592-2189959; pqhuang@xmu.edu.cn

Contents

1. General methods and General procedure

General methods

^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on a spectrometer at 400, 376 and 100 MHz, respectively. Chemical shifts (δ) of ^{1}H NMR and ^{13}C NMR respectively referenced to an internal standard (Me_4Si, 0 ppm for ^{1}H NMR and $CDCl_3$, 77.0 ppm for ^{13}C NMR). ^{19}F NMR used $PhCF_3$ as external standard. Mass spectra were obtained on a mass spectrometer in the ESI mode. Silicagel (300-400 mesh) was used for flash column chromatography (FC), eluting (unless otherwise stated) with ethyl acetate/ hexane mixture. Trifluoromethanesulfonic anhydride (Tf_2O) was distilled over phosphorous pentoxide and was stored for no more than a week before re-distillation. Dry dichloromethane and acetonitrile were distilled over calcium hydride under argon. Dimethylformamide was distilled under vacuum from P_2O_5 and stored over 4Å MS. Other commercially available chemicals were used without further purification. All reactions were carried out under an argon atmosphere.

General procedure A: One-pot Preparation of Trifluoromethylated Amines from Secondary Amides by Direct Reductive Nucleophilic Trifluoromethylation

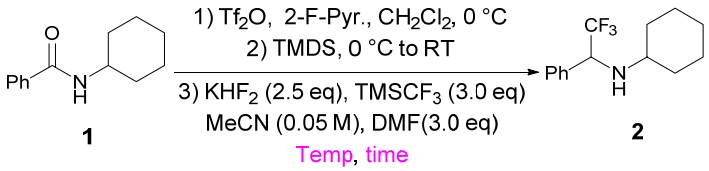
To a solution of secondary amide (0.25 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL, 0.25 M), 2-fluoropyridine (24 μL, 0.28 mmol, 1.1 equiv) and trifluoromethanesulfonic anhydride (Tf_2O) (47 μL, 0.28 mmol, 1.1 equiv) was successively added dropwise via a syringe at 0 °C under Ar atmosphere, and the reaction was stirred for 30 min. To the resulting mixture, 1,1,3,3-tetramethyldisiloxane [$(Me_2SiH)_2O$] (31 μL, 0.18 mmol, 0.7 equiv) was added dropwise at 0 °C, and the reaction mixture was stirred for 30 min. Then, the reaction was allowed to warm up to room temperature and continually stirred for 5 h. CH_2Cl_2 was evaporated under reduced pressure. To the residue, KHF_2 (49 mg, 0.63 mmol, 2.5 equiv) and 4 Å MS powder (1.0 g/mmol) was added. Then MeCN (5.0 mL, 0.05 M) and DMF (60 uL, 0.75 mmol, 3.0 equiv) was added at –78 °C under Ar atmosphere, and the mixture was warmed up to room temperature and stirred for 10 mins. Again the reaction mixture was cooled to –78 °C. $TMSCF_3$ (120 ul, 0.75 mmol, 3.0 equiv) was added via a syringe The mixture was allowed to warmed up to room temperature and stirred for 18 h. The reaction was quenched with a saturated aqueous Na_2CO_3 (1.0 mL) and the mixture was stirred for 3 min, diluting with water (8.0 mL), and extracted with diethyl ether/hexane (1:3, 3×15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give the corresponding trifluoromethylated amine.

General procedure B: One-pot Preparation of Trifluoromethylated Amines from Secondary Amides by Direct Reductive Nucleophilic Trifluoromethylation

To a solution of secondary amide (0.25 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL, 0.25 M), 2-fluoropyridine (24 μL, 0.28 mmol, 1.1 equiv) and trifluoromethanesulfonic anhydride (Tf_2O) (47 μL, 0.28 mmol, 1.1 equiv) was successively added dropwise via a syringe at 0 °C under Ar atmosphere, and the reaction was stirred for 30 min. To the resulting mixture, 1,1,3,3-tetramethyldisiloxane [$(Me_2SiH)_2O$] (31 μL, 0.18 mmol, 0.7 equiv) was

added dropwise at 0 °C, and the reaction mixture was stirred for 30 min. Then, the reaction was allowed to warm up to room temperature and continually stirred for 5 h. CH_2Cl_2 was evaporated under reduced pressure. To the residue, KHF_2 (68 mg, 0.88 mmol, 3.5 equiv) and 4 Å MS powder (1.0 g/mmol) was added. Then MeCN (5.0 mL, 0.05 M), DMF (100 uL, 1.25 mmol, 5.0 equiv) and TFA (19 uL, 0.25 mmol, 1.0 equiv) was added at –78 °C under Ar atmosphere, and the mixture was warmed up to room temperature and stirred for 10 mins. Again the reaction mixture was cooled to –78 °C. $TMSCF_3$ (185 uL, 1.25 mmol, 5.0 equiv) was added via a syringe The mixture was allowed to warmed up to room temperature and stirred for 18 h. The reaction was quenched with a saturated aqueous Na_2CO_3 (1.0 mL) and the mixture was stirred for 3 min, diluting with water (8.0 mL), and extracted with diethyl ether/hexane (1:3, 3×15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give the corresponding trifluoromethylated amine.

2. Table S1. Optimization of reaction temperature and time.[a]

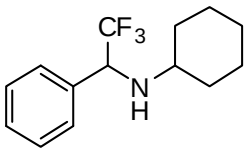


Entry	Temp	Time	Yield (%)[b]
1	–78 °C to RT	3 h	61
2	–78 °C to RT	6 h	67
3	–78 °C to RT	12 h	84
4	–78 °C to RT	18 h	86
5	–78 °C to RT	36 h	86
6	–78 °C to –40 °C	18 h	65
7	0 °C to RT	18 h	80
8	–10 °C to RT	18 h	82
9	0 °C	18 h	0
10	–78 °C to 0 °C	18 h	0

[a] Reaction conditions: i) **1a**-**i** (0.25 mmol), Tf_2O (0.28 mmol), 2-F-Pyr. (0.28 mmol), CH_2Cl_2 (0.25 M); ii) TMDS (0.18 mmol); iii) KHF_2 (0.63 mmol), $TMSCF_3$ (0.75 mmol), 4 Å MS (1.0 g/mmol), MeCN (0.05 M), DMF (0.75 mmol). [b] Yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

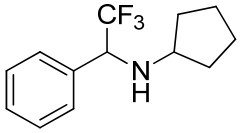
3. Data of α-trifluoromethylamines 2a–2i and 2l-2w

N-(2,2,2-Trifluoro-1-phenylethyl)cyclohexanamine (2a)



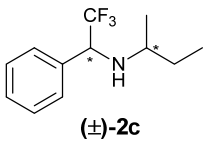
Following general procedure, the reductive trifluoromethylation of amide **1a** (51 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), trifluoromethylated amine **2a** (53 mg, yield: 82%) as a light yellow oil. IR (film): 3344, 3067, 3033, 2929, 2855, 1496, 1453, 1373, 1264, 1168, 1121, 890, 875, 845, 781, 709, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.00-1.23 (m, 5H), 1.45-1.60 (m, 2H), 1.63-1.78 (m, 3H), 1.91-1.99 (m, 1 H), 2.31-2.43 (m, 1H), 4.26 (q, J = 7.7 Hz, 1H), 7.33-7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 24.9, 25.9, 32.7, 34.2, 53.8, 61.5 (q, J = 28.5 Hz), 125.5 (q, J = 280.0 Hz), 128.4 (2C), 128.6 (2C), 128.7, 135.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.2 (d, J = 8.2 Hz). HRMS-ESI calcd for $[C_{14}H_{19}F_3N]^+$ ($M+H^+$): 258.1464; found: 258.1473.

N-(2,2,2-Trifluoro-1-phenylethyl)cyclopentanamine (2b)



Following general procedure, the reductive trifluoromethylation of amide **1b** (47 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), trifluoromethylated amine **2b** (49 mg, 81%) as a light yellow oil. IR (film): 3337, 3062, 3030, 2956, 2870, 1696, 1472, 1456, 1363, 1262, 1164, 1107, 863, 845, 761, 703, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26-1.44 (m, 3H), 1.44-1.57 (m, 2H), 1.68-1.74 (m, 1H), 1.67 (br s, 1H), 1.74-1.85 (m, 2H), 2.98-3.07 (m, 1H), 4.17 (q, J = 7.7 Hz, 1H), 7.38-7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.70, 23.72, 32.5, 33.6, 57.2, 63.4 (q, J = 28.7 Hz), 125.5 (q, J = 281.6 Hz), 128.4 (2C), 128.6 (2C), 128.8, 135.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.3 (d, J = 7.0 Hz). HRMS-ESI calcd for $[C_{13}H_{17}F_3N]^+$ ($M+H^+$): 244.1308; found: 244.1312.

N-(2,2,2-Trifluoro-1-phenylethyl)butan-2-amine (±2c)

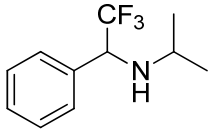


(±)-2c

Following general procedure, the reductive trifluoromethylation of amide **1c** (44 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), trifluoromethylated amine (±)-**2c** (38 mg, 66%) as a mixture containing two inseparable diastereomers (d.r. = 1.6:1,

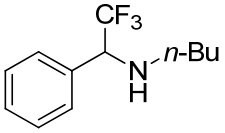
determined by ^{1}H NMR). IR (film): 3349, 3068, 3034, 2966, 2932, 2977, 1498, 1456, 1379, 1332, 1166, 1171, 1117, 1031, 860, 850, 761, 703, 607, 601 cm^{-1}; Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.4 Hz, 3H), 1.10 (d, J = 6.3 Hz, 3H), 1.35-1.53 (m, 3H), 2.49-2.59 (m, 1H), 4.28 (q, J = 7.7 Hz, 1 H), 7.39-7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.2, 19.2, 30.4, 51.5, 62.1 (q, J = 28.8 Hz), 125.7 (q, J = 281.0 Hz), 128.5 (2C), 128.61 (2C), 128.8, 135.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.2 (d, J = 7.8 Hz). Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 7.4 Hz, 3H), 1.07 (d, J = 6.4 Hz, 3H), 1.53-1.62 (m, 3H), 2.63-2.73 (m, 1H), 4.32 (q, J = 7.5 Hz, 1H), 7.46-7.51 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.4, 20.4, 28.5, 52.0, 62.2 (q, J = 28.5 Hz), 125.8 (q, J = 281.0 Hz), 128.4 (2C), 128.64 (2C), 128.76, 135.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.1 (d, J = 7.6 Hz). HRMS-ESI calcd for $[C_{12}H_{17}F_3N]^+$ ($M+H^+$): 232.1308; found: 232.1309.

N-(2,2,2-Trifluoro-1-phenylethyl)propan-2-amine (2d)



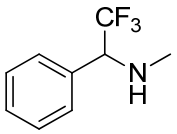
Following general procedure, the reductive trifluoromethylation of amide **1d** (41 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), trifluoromethylated amine **2d** (36 mg, 67%) as a light yellow oil (volatile). IR (film): 3337, 3068, 3034, 2966, 2931, 2871, 1497, 1456, 1375, 1358, 1264, 1179, 1115, 882, 851, 761, 703, 627 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01-1.18 (m, 6H), 1.53 (br s, 1H), 2.73-2.85 (m, 1H), 4.25 (q, J = 7.5 Hz, 1H), 7.34-7.52 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 23.7, 46.0, 62.1 (q, J = 28.6 Hz), 125.6 (q, J = 281.3 Hz), 128.4 (2C), 128.6 (2C), 128.8, 135.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.2 (d, J = 7.9 Hz). HRMS-ESI calcd for $[C_{11}H_{15}F_3N]^+$ ($M+H^+$): 218.1146; found: 218.1153.

N-(2,2,2-Trifluoro-1-phenylethyl)butan-1-amine (2e)



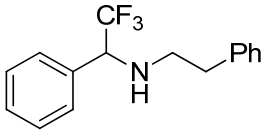
Following general procedure, the reductive trifluoromethylation of amide **1e** (44mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), the trifluoromethylated amine **2e** (36 mg, 62%) as a light yellow oil. IR (film): 3347, 3067, 3034, 2960, 2931, 2861, 1496, 1380, 1357, 1263, 1171, 1116, 1030, 878, 847, 760, 704, 608, 601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 7.3 Hz，3H), 1.26-1.37 (m, 2H), 1.39-1.51 (m, 2H), 1.58 (br s, 1H), 2.55 (m, 2H), 4.11 (q, J =7.6 Hz, 1H), 7.32-7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 20.2, 32.1, 47.5, 64.8 (q, J = 28.6 Hz), 125.3 (q, J = 281.4 Hz), 128.5 (2C), 128.6 (2C), 128.9, 134.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.5 (d, J = 7.2 Hz). HRMS-ESI calcd for $[C_{12}H_{17}F_3N]^+$ ($M+H^+$): 232.1308; found: 232.1313.

2,2,2-Trifluoro-*N*-methyl-1-phenylethanamine (2f)



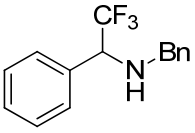
Following general procedure, the reductive trifluoromethylation of amide **1f** (34 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20), trifluoromethylated amine **2f** (27 mg, 57%) as a light yellow oil (volatile). IR (film): 3349, 2959, 2925, 2854, 1730, 1600, 1461, 1379, 1262, 1206, 1153, 1119, 1070, 1021, 801, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.69 (br s, 1H), 2.29 (s, 3H), 3.92 (q, J = 7.5 Hz, 1H), 7.14-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.6, 66.5 (q, J = 28.6 Hz), 125.4 (q, J = 281.7 Hz), 128.5 (2C), 128.7 (2C), 129.0, 134.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.2 (d, J = 7.0 Hz). HRMS-ESI calcd for $[C_9H_{11}F_3N]^+$ ($M+H^+$): 190.0838; found: 190.0846.

2,2,2-Trifluoro-*N*-phenethyl-1-phenylethanamine (2g)



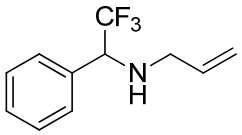
Following general procedure B, the reductve trifluoromethylation of amide **1g** (56 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), the known trifluoromethylated amine **2g** (70 mg, 71%) as a yellow oil. IR (film): 3341, 3064, 3030, 2927, 2852, 1506, 1473, 1455, 1355, 1264, 1167, 1122, 1065, 752, 701, 630, 551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.68 (br s, 1H), 2.73-2.92 (m, 4H), 4.14 (q, J = 7.4 Hz，1H), 7.12-7.41 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.2, 48.8, 64.6 (q, J =28.8 Hz), 125.3 (q, J = 281.4 Hz), 126.3, 128.46 (2C), 128.52 (2C), 128.64 (2C), 128.68 (2C), 128.9, 134.4, 139.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.2 (d, J = 7.3 Hz). HRMS-ESI calcd for $[C_{16}H_{16}F_3N]^+$ ($M+H^+$): 280.1303; found: 280.1308.

2,2,2-Trifluoro-*N*-phenethyl-1-phenylethanamine (2h)



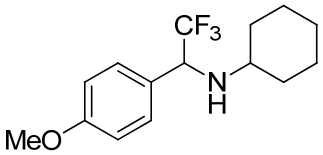
Following general procedure B, the reductive trifluoromethylation of amide **1h** (53 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), the known trifluoromethylated amine **2h**[1] (66 mg, 46%) as a light yellow oil. IR (film): 3345, 3088, 3065, 3031, 2925, 2852, 1604, 1496, 1455, 1375, 1339, 1263, 1172, 1124, 1029, 973, 880, 851, 739, 701, 637, 566, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.93 (br s, 1H), 3.74 (d, J = 13.5 Hz, 1H), 3.90 (q, J = 13.5 Hz, 1H), 4.22 (q, J = 7.6 Hz , 1H), 7.31-7.58 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.1, 64.5 (q, J = 28.8 Hz), 125.5 (q, J = 281.4 Hz), 127.4, 128.2 (2C), 128.6 (2C), 128.7 (2C), 128.8 (2C), 129.0, 134.3, 139.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.8 (d, J = 7.3 Hz). MS(ESI) *m/z* 265 ($M+H^+$).

N-(2,2,2-Trifluoro-1-phenylethyl)prop-2-en-1-amine (2i)



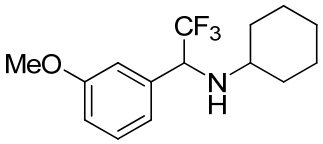
Following general procedure B, the reductive trifluoromethylation of amide **1i** (40 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/30), trifluoromethylated amine **2i** (54 mg, 60%) as a yellow oil (volatile). IR (film): 3343, 3069, 3034, 2925, 2851, 1645, 1456, 1365, 1264, 1171, 1123, 994, 925, 845, 761, 704, 626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (br s, 1H), 3.10-3.15 (m, 2H), 4.09-4.25 (m, 1H), 5.09-5.25 (m, 2H), 5.78-5.95 (m, 1H), 7.29-7.53 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.8, 63.5 (q, J = 28.7 Hz), 117.0, 125.5 (q, J = 282.0 Hz), 128.6 (2C), 128.7 (2C), 129.0, 134.5, 135.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.0 (d, J = 7.0 Hz). HRMS-ESI calcd for $[C_{11}H_{12}F_3NNa]^+$ ($M+Na^+$): 238.1587; found: 238.1594.

N-(2,2,2-Trifluoro-1-(4-methoxyphenyl)ethyl)cyclohexanamine (2l)



Following general procedure, the reductive trifluoromethylation of amide **1l** (58 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/30), the trifluoromethylated amine **2l** (58 mg, 81%) as a light yellow oil. IR (film): 3335, 2930, 2854, 1613, 1586, 1515, 1465, 1451, 1374, 1305, 1251, 1171, 1121, 1035, 857, 825, 695, 612, 584, 530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.00-1.21 (m, 5H), 1.51-1.61 (m, 1H), 1.47 (br s, 1H), 1.63-1.80 (m, 3H), 1.88-1.98 (m, 1H), 2.32-2.42 (m, 1H), 3.82 (s, 3H), 4.23 (q, J = 7.8 Hz, 1H), 6.89-6.94 (m, 2H), 7.29-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 24.9, 25.9, 32.7, 34.2, 53.8, 55.2, 61.4 (q, J = 28.6 Hz), 114.0, 114.2, 121.4, 125.5 (q, J = 281.8 Hz), 129.6, 137.0, 159.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.8 (d, J = 7.8 Hz). HRMS-ESI calcd for $[C_{15}H_{21}F_3NO]^+$ ($M+H^+$): 288.1570; found: 288.1573.

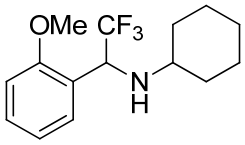
N-(2,2,2-Trifluoro-1-(3-methoxyphenyl)ethyl)cyclohexanamine (2m)



Following general procedure, the reductive trifluoromethylation of amide **1m** (58 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/30), the trifluoromethylated amine **2m** (57 mg, 80%) as a light yellow oil. IR (film): 3337, 3003, 2929, 2854, 1603, 1588, 1491, 1467, 1453, 1438, 1350 1306, 1259, 1170, 1120, 1049, 937, 890, 851, 786, 714, 625, 568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.00-1.22 (m, 5H), 1.51 (br s, 1H), 1.53-1.63 (m, 1H), 1.63-1.79 (m, 3H), 1.89-1.97 (m, 1H), 2.34-2.44 (m, 1H), 3.83 (s, 3H), 4.23 (q, J = 7.7 Hz, 1H), 6.88-6.99 (m, 2H), 7.27-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.7, 25.1,

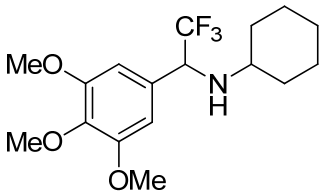
26.1, 32.8, 34.3, 53.9, 55.4, 61.5 (q, J = 28.6 Hz), 114.1, 114.3, 120.8, 129.7, 137.1, 125.7 (q, J = 281.4 Hz), 160.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.1 (d, J = 7.6 Hz). HRMS-ESI calcd for $[C_{15}H_{21}F_3NO]^+$ (M+H$^+$): 288.1570; found: 288.1569.

N-(2,2,2-Trifluoro-1-(2-methoxyphenyl)ethyl)cyclohexanamine (2n)



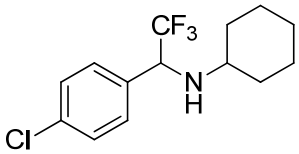
Following general procedure, the reductive trifluoromethylation of amide **1n** (58 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/30), the trifluoromethylated amine **2n** (59 mg, 82%) as a light yellow oil. IR (film): 3342, 3005, 2930, 2854, 1603, 1580, 1493, 1466, 1438, 1372, 1328, 1246, 1166, 1125, 1096, 1029, 891, 859, 793, 756, 698, 618 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02-1.22 (m, 5H), 1.49-1.58 (m, 1H), 1.61-1.75 (m, 4H), 1.87-1.97 (m, 1H), 2.32-2.41 (m, 1H), 3.83 (s, 3H), 4.87 (q, J = 8.1 Hz, 1H), 6.91 (dd, J = 8.3, 0.8 Hz, 1H), 6.98 (td, J = 7.5, 1.0 Hz, 1H), 7.27-7.33 (m, 1H); 7.37 (d, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 24.9, 26.0, 32.8, 34.1, 53.7 (q, J = 29.3 Hz), 54.1, 55.7, 111.1, 120.9, 124.2, 125.9 (q, J = 281.4 Hz), 128.2, 129.6, 157.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.2 (d, J = 7.6 Hz). HRMS-ESI calcd for $[C_{15}H_{20}F_3NNaO]^+$ (M+Na$^+$): 310.1389; found: 310.1388.

N-(2,2,2-Trifluoro-1-(3,4,5-trimethoxyphenyl)ethyl)cyclohexanamine (2o)



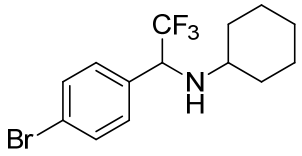
Following general procedure, the reductive trifluoromethylation of amide **1o** (73 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/5), the trifluoromethylated amine **2o** (72 mg, 83%) as a light yellow oil. IR (film): 3327, 2930, 2854, 1593, 1508, 1484, 1423, 1327, 1242, 1152, 1130, 1009, 824, 713, 660, 535 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00-1.23 (m, 5H), 1.47 (br s, 1H), 1.53-1.60 (m, 1H), 1.62-1.80 (m, 3H), 1.88-1.97 (m, 1H), 2.34-2.43 (m, 1H), 3.86 (s, 3H), 3.87 (s, 6H), 4.18 (q, J = 7.5 Hz, 1H), 6.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 25.0, 25.9, 32.8, 34.3, 53.8, 56.2 (2C), 60.8, 61.7 (q, J = 28.5 Hz), 105.5 (2C), 125.5 (q, J = 281.5 Hz), 130.8, 138.4, 153.3 (2C); ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.2 (d, J = 7.5 Hz). HRMS-ESI calcd for $[C_{17}H_{25}F_3NNaO_3]^+$ (M+H$^+$): 370.1600; found: 370.1604.

N-(2,2,2-Trifluoro-1-(3-methoxyphenyl)ethyl)cyclohexanamine (2p)



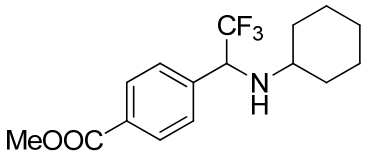
Following general procedure, the reductive trifluoromethylation of amide **1p** (59 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), the trifluoromethylated amine **2p** (36 mg, 50%) as a yellow oil. IR (film): 3339, 2929, 2655, 1588, 1493, 1450, 1412, 1351, 1261, 1169, 1123, 1093, 1016, 890, 853, 817, 730, 689, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99-1.21 (m, 5H), 1.49 (br s, 1H), 1.52-1.62 (m, 1H), 1.62-1.79 (m, 3H), 1.85-1.99 (m, 1H), 2.30-2.42 (m, 1H), 4.28 (q, J = 7.5 Hz, 1H), 7.33-7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 24.9, 25.9, 32.6, 34.2, 53.7, 60.9 (q, J = 28.7 Hz), 125.3 (q, J = 281.3 Hz), 128.8 (2C), 129.8 (2C), 133.8, 134.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.4 (d, J = 7.5 Hz). HRMS-ESI calcd for $[C_{14}H_{18}ClF_3N]^+$ ($M+H^+$): 292.1074; found: 292.1080.

N-(1-(4-Bromophenyl)-2,2,2-trifluoroethyl)cyclohexanamine (2q)



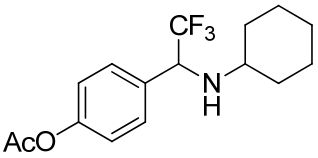
Following general procedure, the reductive trifluoromethylation of amide **1q** (71 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), the trifluoromethylated amine **2q** (59 mg, 70%) as a yellow oil. IR (film): 3334, 2929, 2855, 1593, 1490, 1407, 1351, 1261, 1173, 1123, 1074, 1012, 890, 852, 814, 727, 685, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99-1.21 (m, 5H), 1.50 (br s, 1H), 1.53-1.62 (m, 1H), 1.62-1.79 (m, 3H), 1.85-1.94 (m, 1H), 2.28-2.39 (m, 1H), 4.25 (q, J = 7.5 Hz, 1H), 7.23-7.32 (m, 2H), 7.47-7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 24.9, 25.9, 32.6, 34.2, 53.7, 61.0 (q, J = 28.8 Hz), 122.9, 125.2 (q, J = 281.7 Hz), 130.1 (2C), 131.8 (2C), 134.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.4 (d, J = 7.5 Hz). HRMS-ESI calcd for $[C_{14}H_{18}BrF_3N]^+$ ($M+H^+$): 336.0569; found: 336.0573.

Methyl 4-(1-(cyclohexylamino)-2,2,2-trifluoroethyl)benzoate (2r)



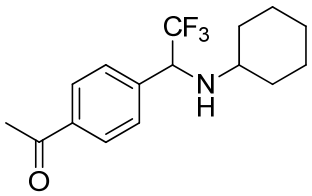
Following general procedure B, the reductive trifluoromethylation of amide **1r** (65 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), the trifluoromethylated amine **2r** (55 mg, 70%) as a yellow oil. IR (film): 3338, 2930, 1727, 1614, 1579, 1450, 1437, 1418, 1350, 1283, 1169, 1116, 1021, 971, 890, 862, 842, 820, 771, 717, 686, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.00-1.19 (m, 5H), 1.50-1.58 (m, 1H), 1.60 (br s, 1H), 1.63-1.77 (m, 3H), 1.86-1.94 (m, 1H), 2.29-2.39 (m, 1H), 3.92 (s, 3H), 4.33 (q, J = 7.5 Hz, 1H), 7.46-7.51 (m, 2H), 8.03-8.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 24.8, 25.9, 32.6, 34.2, 52.1, 53.9, 61.3 (q, J = 28.8 Hz), 125.3 (q, J = 281.7 Hz), 128.5 (2C), 129.8 (2C), 130.7, 140.4, 166.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.2 (d, J = 7.4 Hz). HRMS-ESI calcd for $[C_{16}H_{20}F_3NNaO_2]^+$ ($M+H^+$): 338.1339; found: 338.1340.

4-(1-(Cyclohexylamino)-2,2,2-trifluoroethyl)phenyl acetate (2s)



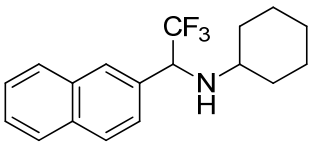
Following general procedure, the reductive trifluoromethylation of amide **1s** (65 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/10), the trifluoromethylated amine **2s** (51 mg, 65%) as a light yellow oil. IR (film): 3340, 3040, 2930, 2855, 1762, 1609, 1509, 1474, 1450, 1422, 1371, 1309, 1262, 1205, 1121, 1018, 914, 863, 839, 691, 664, 612, 526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99-1.29 (m, 5H), 1.49 (br s, 1H), 1.52-1.66(m, 1H), 1.62-1.78 (m, 3H), 1.91-2.01 (m, 1H), 2.34 (s, 3H), 2.38-2.47 (m, 1H), 4.32 (q, J = 7.6 Hz, 1H); 7.13-7.19 (m, 2H), 7.43-7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 24.5, 24.9, 25.9, 32.7, 34.2, 53.6, 60.8 (q, J = 28.6 Hz), 121.7 (2C), 125.4 (q, J = 280.9 Hz), 129.5 (2C), 151.0, 169.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.4 (d, J = 7.6 Hz). HRMS-ESI calcd for $[C_{16}H_{21}F_3NO_2]^+$ ($M+H^+$): 316.1519; found: 316.1522.

1-(4-(1-(Cyclohexylamino)-2,2,2-trifluoroethyl)phenyl)ethanone (2t)



Following general procedure B, the reductive trifluoromethylation of amide **1t** (61 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/10), the trifluoromethylated amine **2t** (46 mg, 61%) as a yellow oil. IR (film): 3343, 2929, 2855, 1687, 1610, 1560, 1450, 1416, 1360, 1265, 1166, 1124, 1017, 958, 890, 858, 822, 694, 617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.03-1.25 (m, 5H), 1.50-1.57 (m, 2H), 1.65-1.78 (m, 3H), 1.89-1.97 (m, 1H), 2.32-2.42 (m, 1H), 2.64 (s, 3H), 4.37 (q, J = 7.6 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 8.00 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 24.8, 25.9, 26.6, 32.7, 34.2, 53.9, 61.3 (q, J = 28.6 Hz), 125.2 (q, J = 281.3 Hz), 128.6 (2C), 128.7 (2C), 137.5, 140.5, 197.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.4 (d, J = 7.9 Hz). HRMS-ESI calcd for $[C_{16}H_{20}F_3NNaO]^+$ ($M+Na^+$): 322.1389; found: 322.1389.

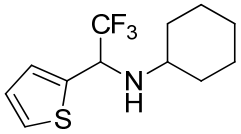
N-(2,2,2-Trifluoro-1-(naphthalen-2-yl)ethyl)cyclohexanamine (2u)



Following general procedure, the reductive trifluoromethylation of amide **1u** (63 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), the trifluoromethylated amine **2u** (53 mg, 69%) as a light yellow oil. IR (film): 3336, 3058, 2929, 2854, 1510, 1499, 1371, 1350, 1267, 1164, 1120, 816, 747, 709; ^1H NMR (400 MHz, $CDCl_3$): δ 1.05-1.26 (m, 5H), 1.47-1.56 (m, 1H), 1.62 (br s, 1H), 1.63-1.79 (m, 3H), 1.95-2.09 (m, 1H), 2.32-2.48 (m, 1H), 4.43 (q, J = 7.7 Hz, 1H); 7.46-7.54 (m, 3H), 7.81-7.88 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 25.0, 26.0, 32.7, 34.3, 53.8, 61.7 (q, J = 28.7 Hz), 125.5, 125.8 (q, J = 280.5 Hz), 126.4, 126.5,

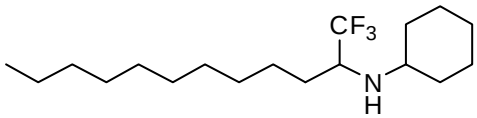
127.8, 128.1, 128.2, 128.6, 132.8, 133.2, 133.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ −73.9 (d, J = 7.6 Hz). HRMS-ESI calcd for $[C_{18}H_{20}F_3N]^+$ ($M+H^+$): 308.1621; found: 308.1626.

N-(2,2,2-Trifluoro-1-(thiophen-2-yl)ethyl)cyclohexanamine (2v)



Following general procedure B, the reductive trifluoromethylation of amide **1v** (52 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), the known trifluoromethylated amine **2v**[9c] (66 mg, 62%) as a yellow oil. IR (film): 3340, 2929, 2855, 1473, 1450, 1374, 1264, 1221, 1166, 1121, 858, 829, 705, 637 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02-1.38 (m, 5H), 1.50 (br s, 1H), 1.53-1.64 (m, 1H), 1.66-1.81 (m, 3H), 1.89-1.97 (m, 1H), 2.47-2.57 (m, 1H), 4.55 (q, J = 7.3 Hz, 1H); 6.99-7.12 (m, 2H), 7.30-7.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.5, 24.9, 25.9, 32.7, 34.0, 54.0, 57.2 (q, J = 30.3 Hz), 125.0 (q, J = 281.1 Hz), 125.9, 126.89, 126.92, 138.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.0 (d, J = 7.3 Hz). MS(ESI) *m/z* 264 ($M+H^+$).

N-(1,1,1-Trifluorotridecan-2-yl)cyclohexanamine (2w)

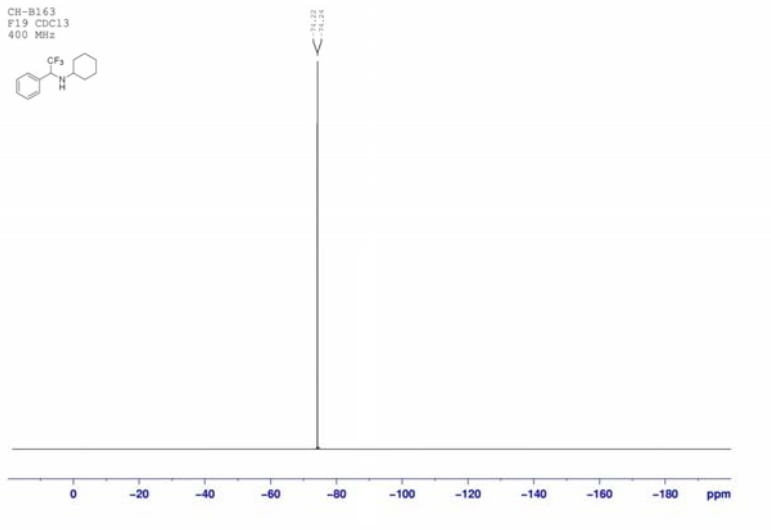


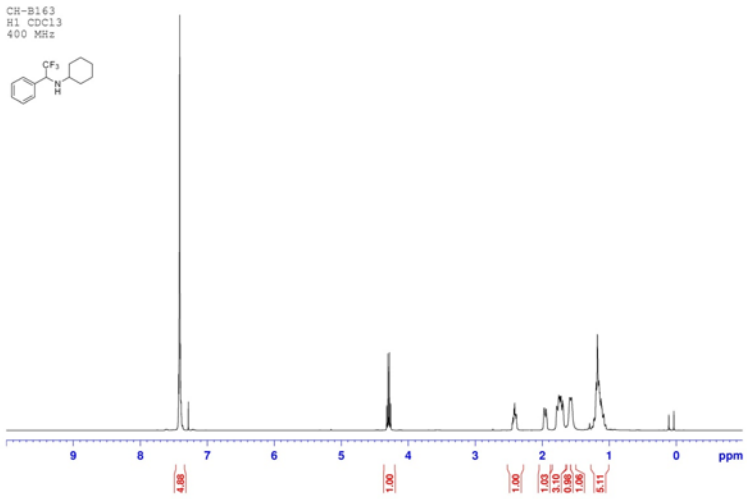
Following general procedure B, the reductive trifluoromethylation of amide **1w** (67 mg, 0.25 mmol) gave, after flash column chromatography on silica gel (eluent: hexane), the trifluoromethylated amine **2w** (80 mg, 61%) as a light yellow oil. IR (film): 3441, 2927, 2855, 1640, 1466, 1451, 1377, 1263, 1147, 1110, 846, 700, 595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 0.94-1.41 (m, 22H), 1.44-1.55 (m, 1H), 1.56-1.63 (m, 1H), 1.63-1.77 (m, 3H), 1.78-1.91 (m, 2H), 2.52-2.63 (m, 1H), 2.95-3.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 25.0, 25.1, 25.8, 26.2, 29.5, 29.58, 29.64, 29.7, 30.06 (2C), 32.1, 33.7, 34.6, 55.5, 56.7 (q, J = 27.2 Hz), 127.3 (q, J = 283.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.8 (d, J = 7.0 Hz). HRMS-ESI calcd for $[C_{18}H_{35}F_3N]^+$ ($M+H^+$): 322.2716; found: 322.2719.

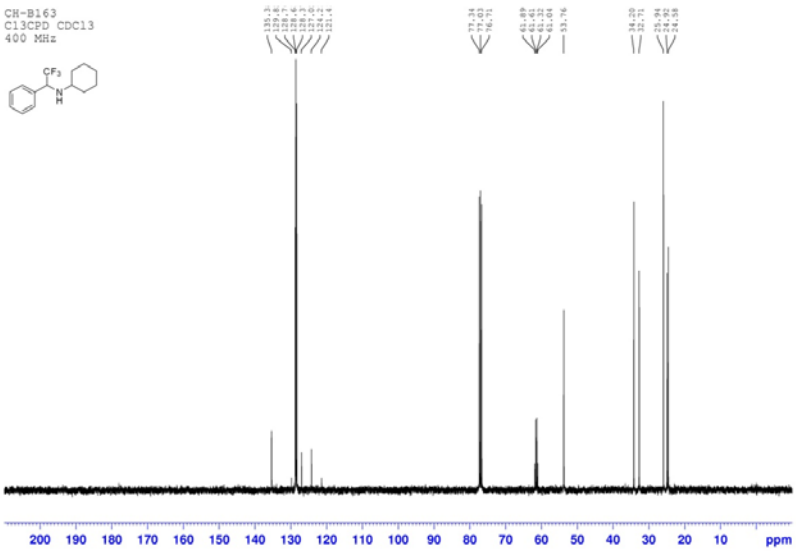
References

1. V. V. Levin, A. D. Dilman, P. A. Belyakov, M. I. Struchkova and V. A. Tartakovsky, *Eur. J. Org. Chem.*, 2008, 5226.

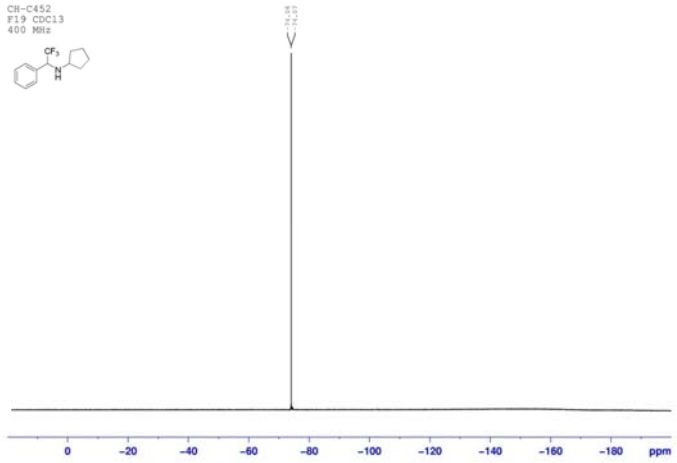
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2a

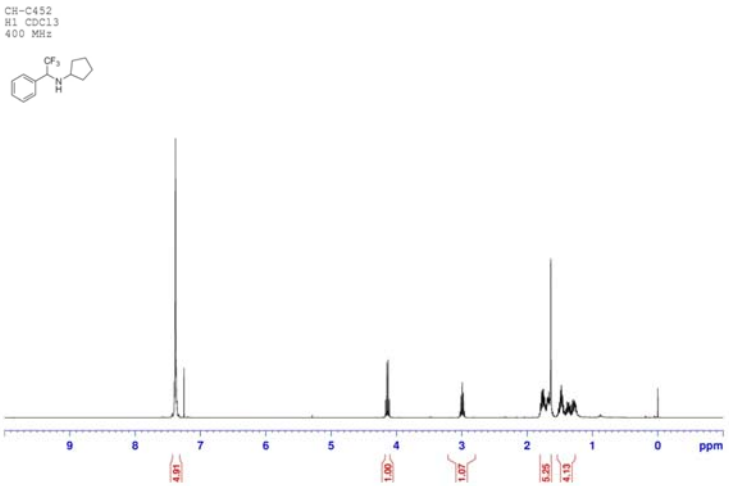


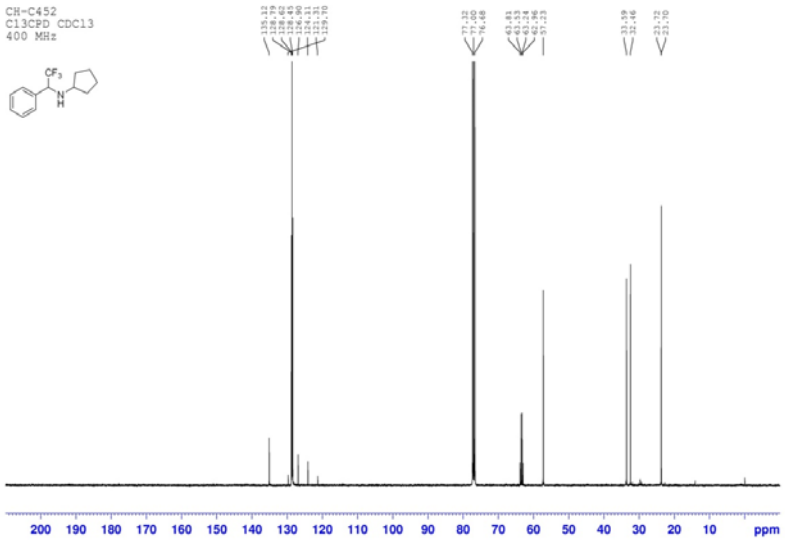




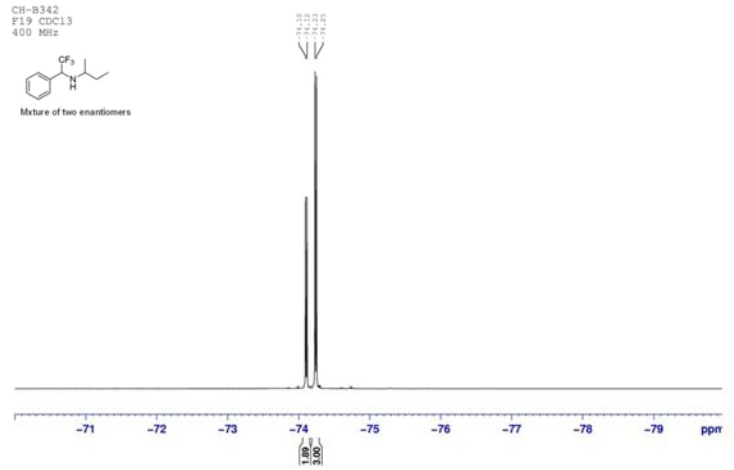
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2b

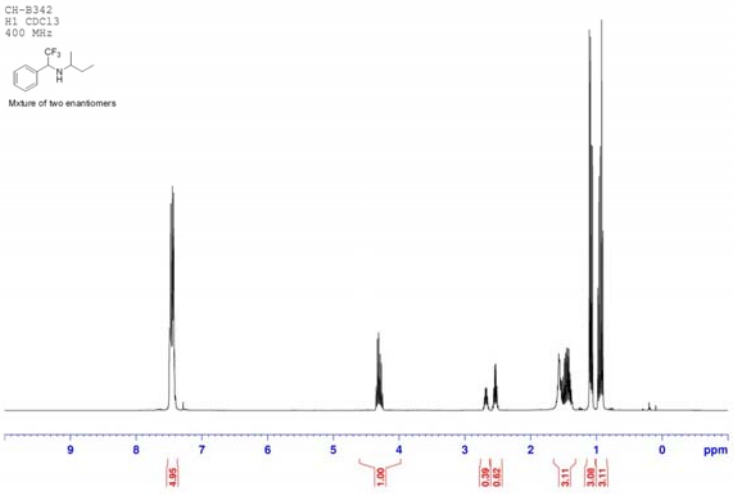


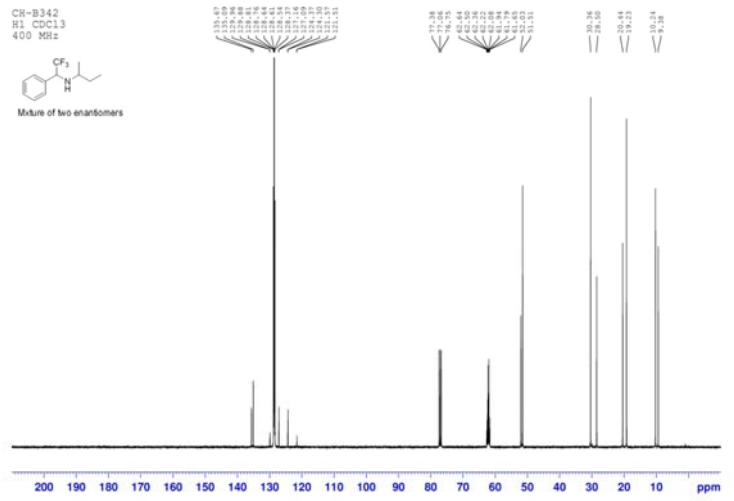




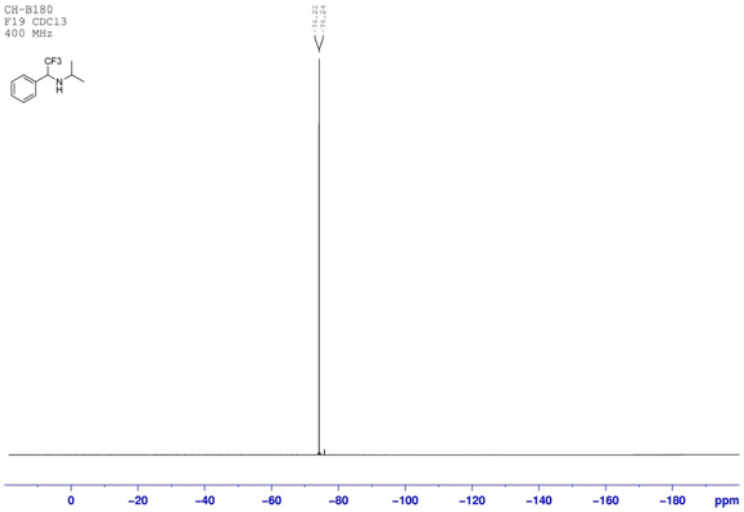
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2c

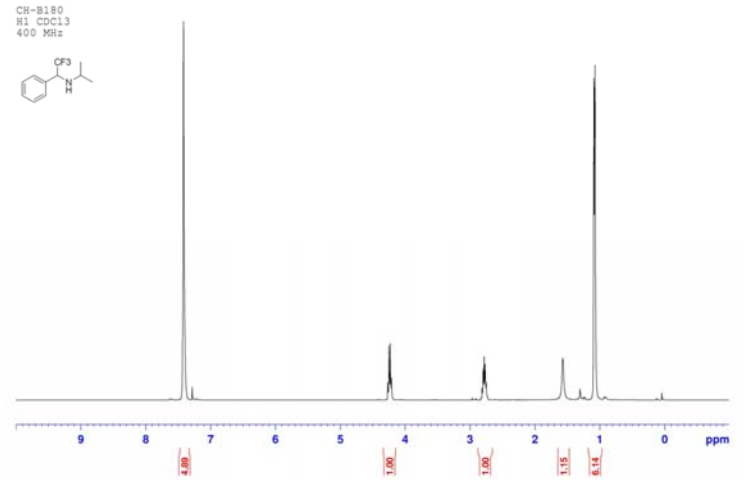


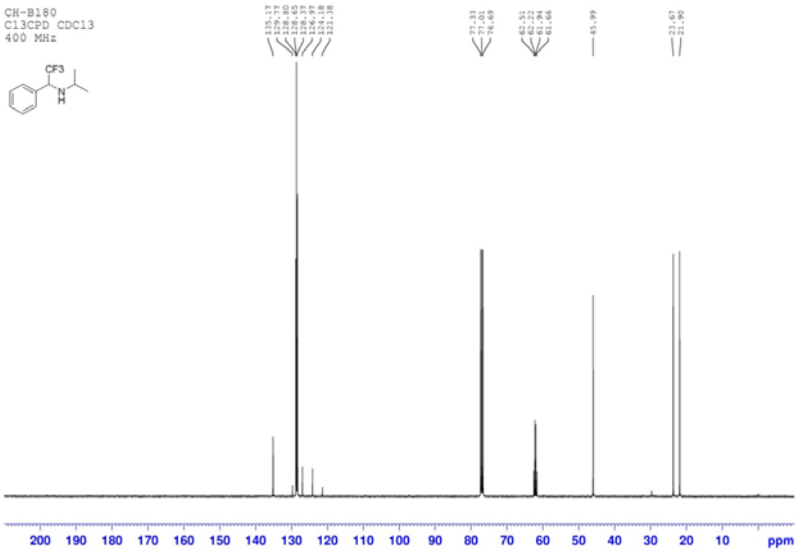




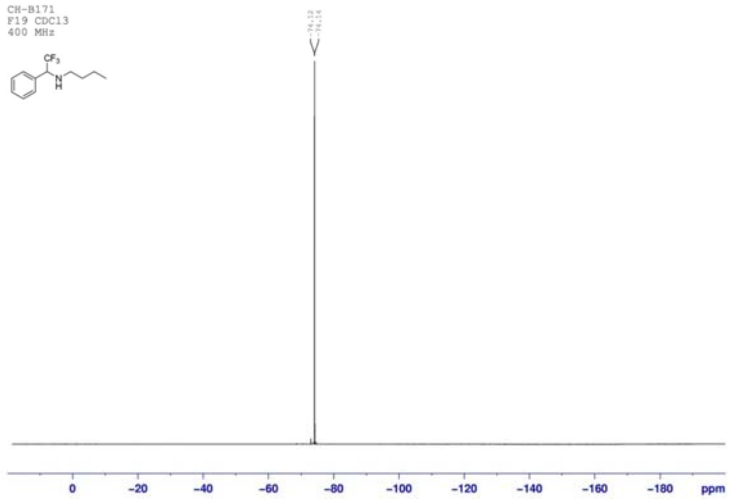
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2d

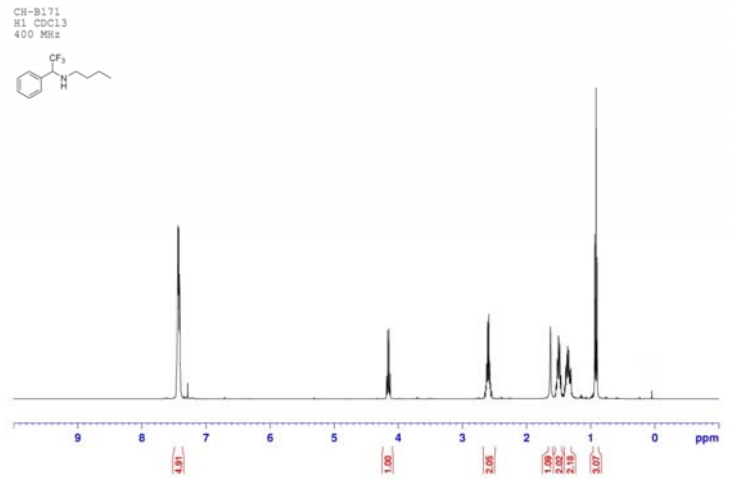


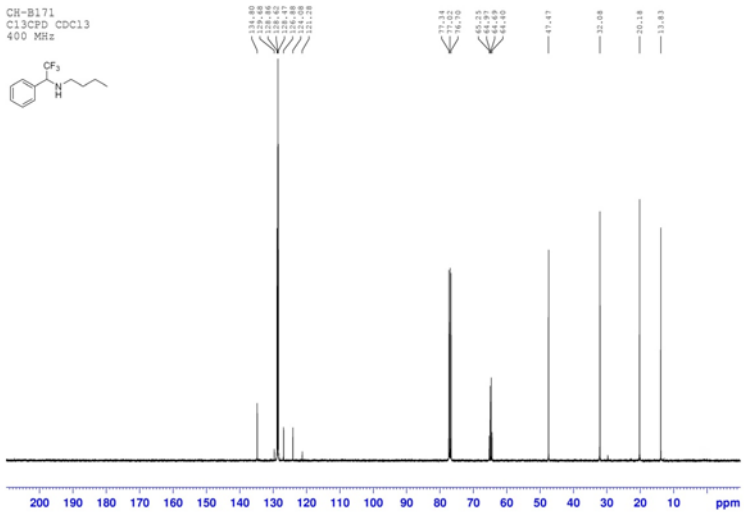




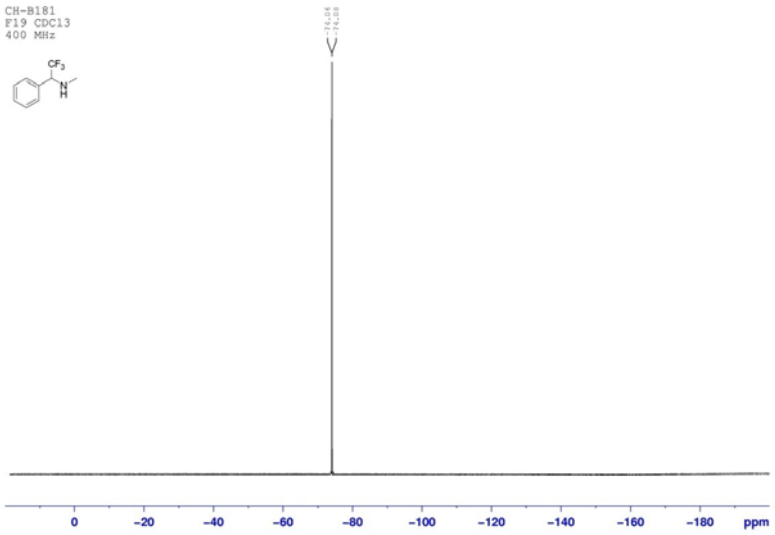
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2e

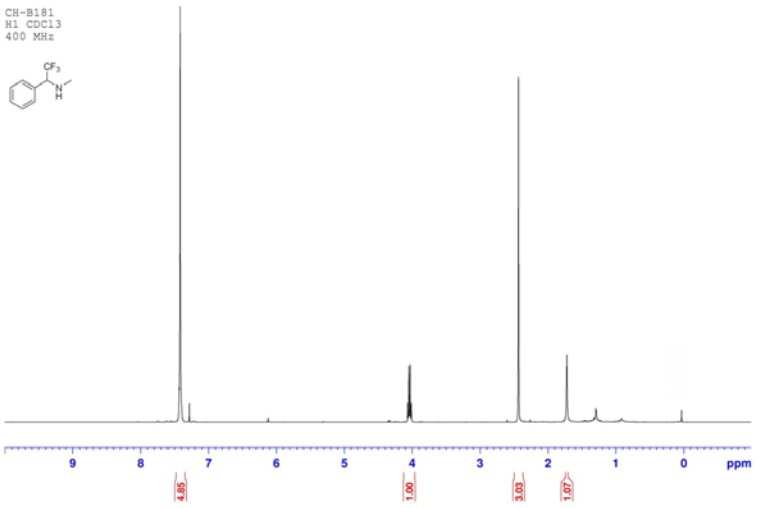


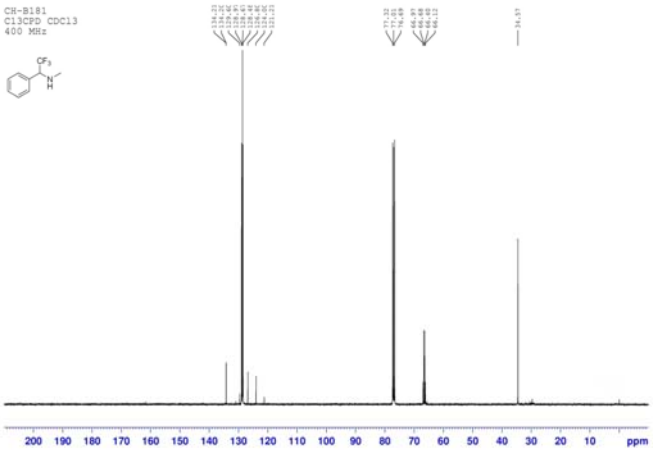




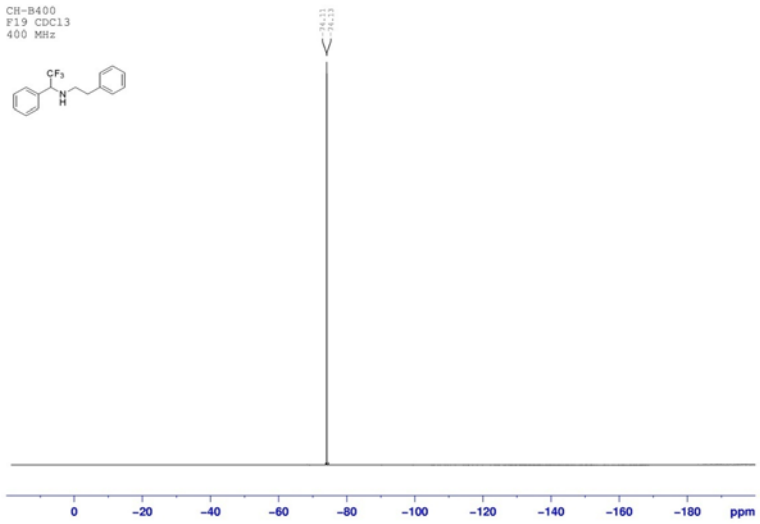
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2f

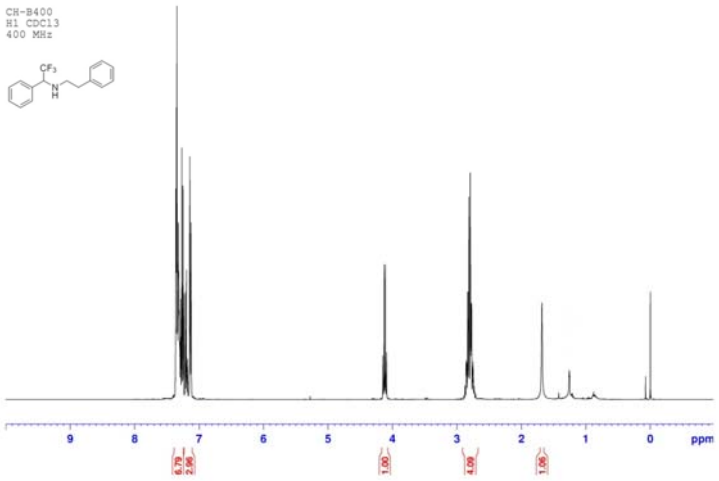


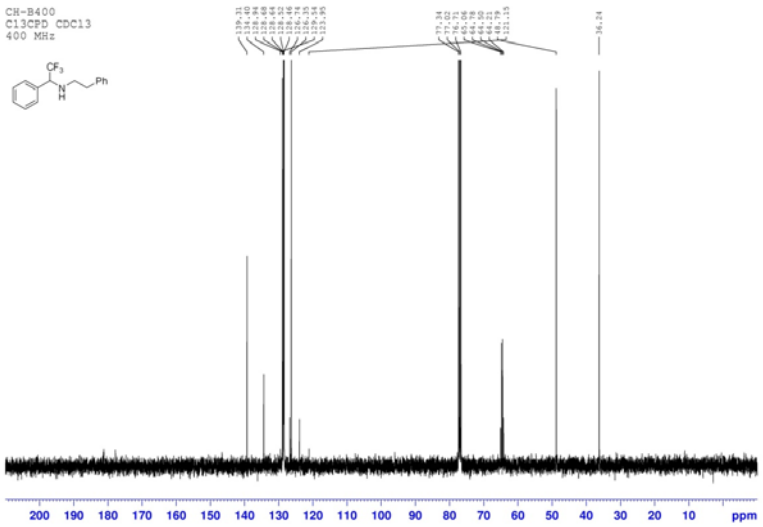




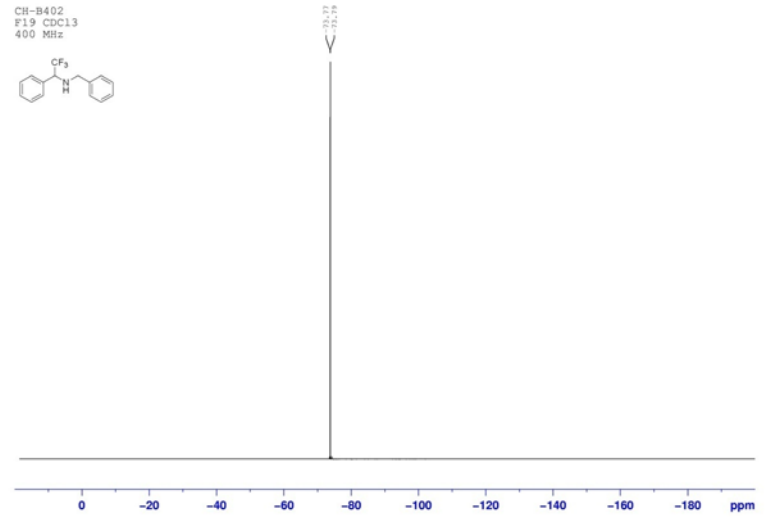
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2g

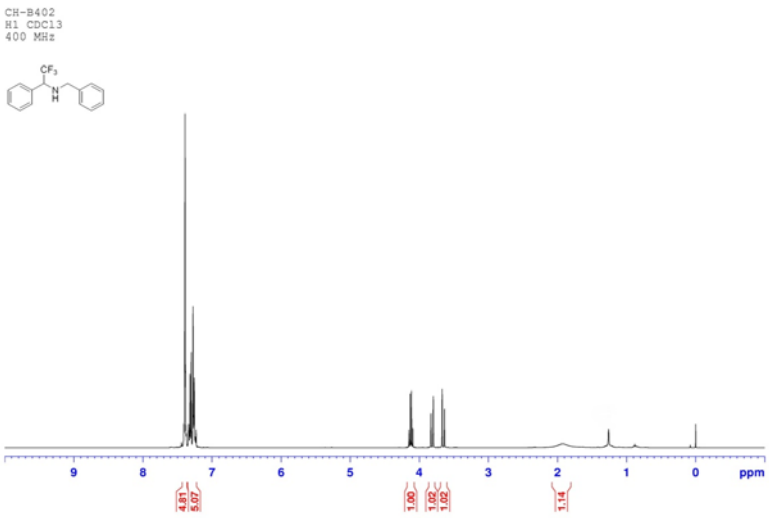


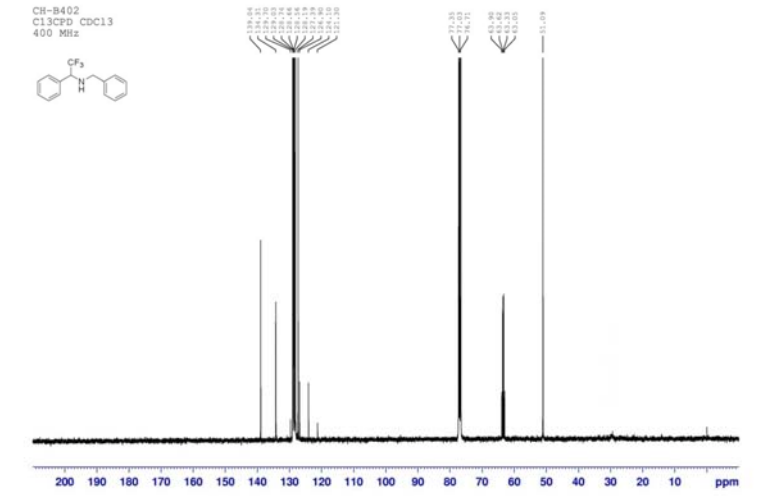




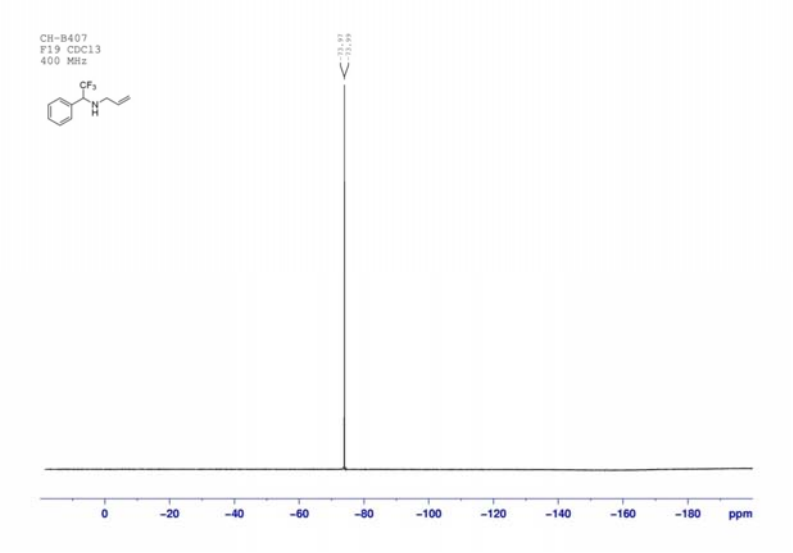
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2h

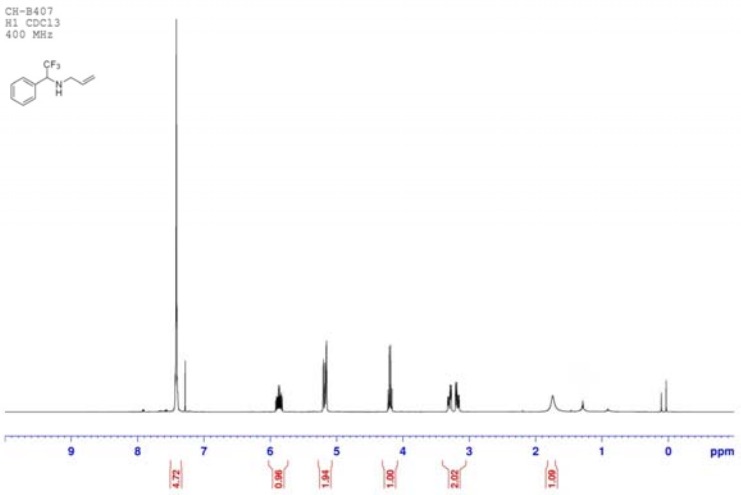


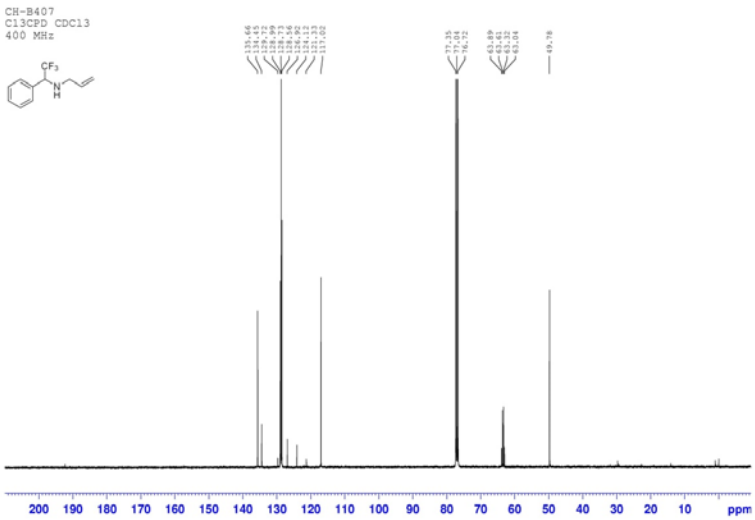




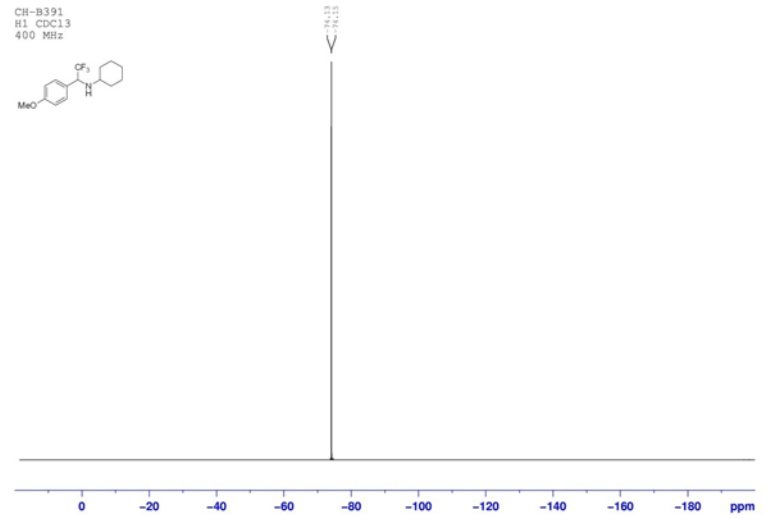
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2i

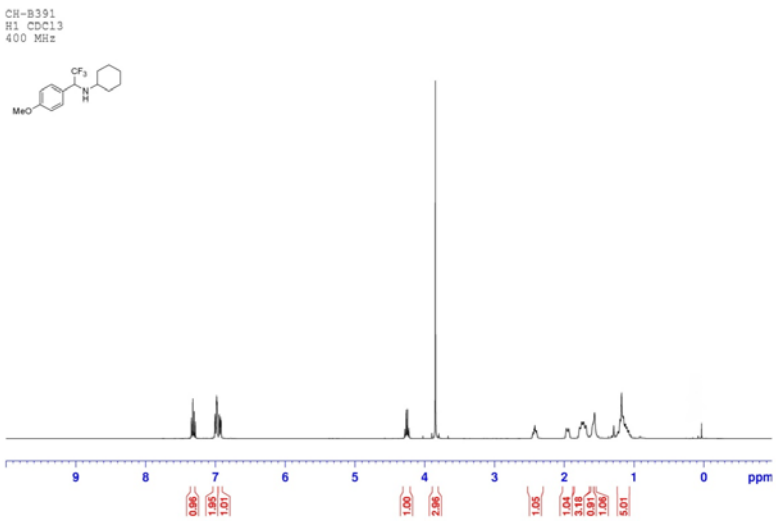


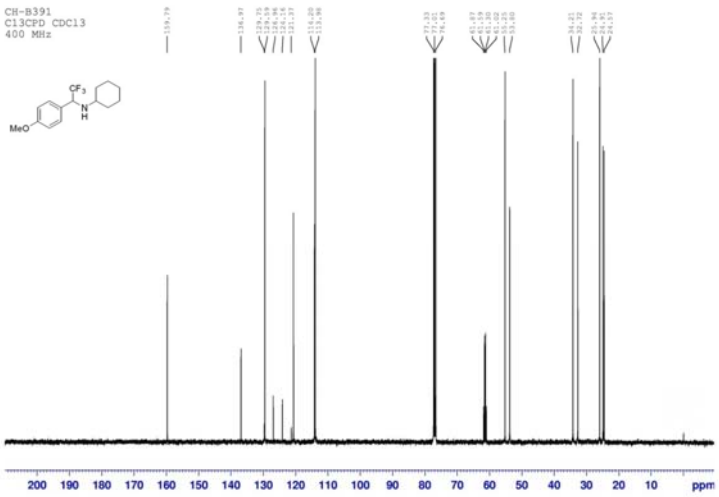




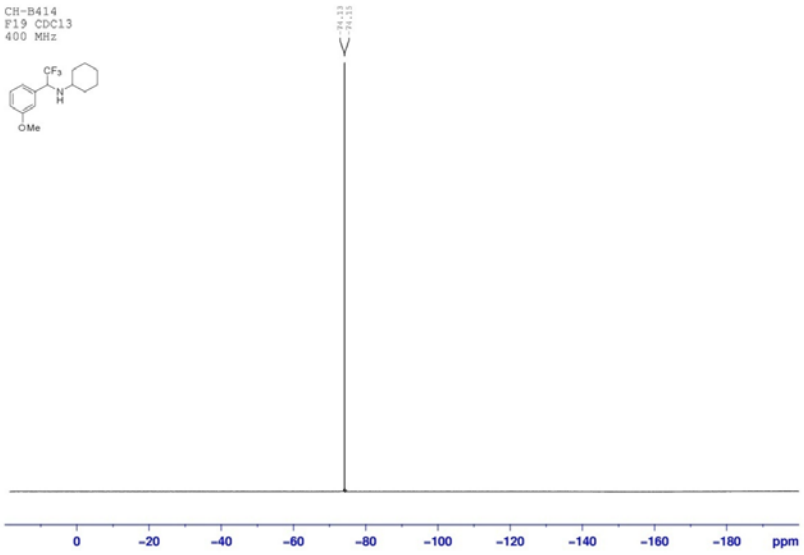
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2j

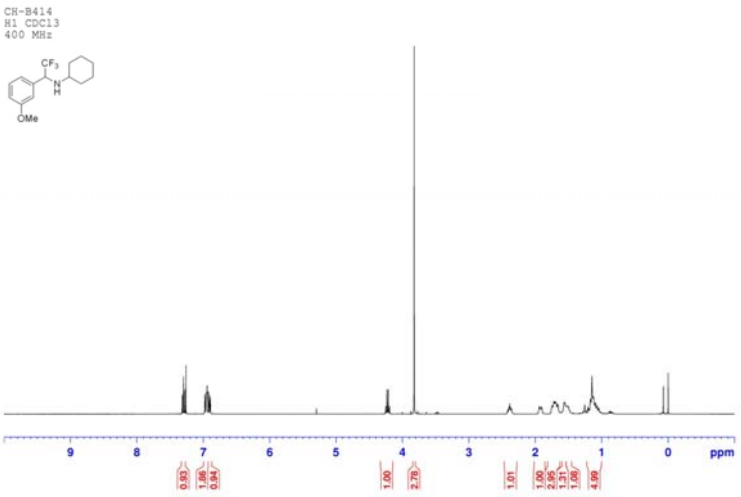


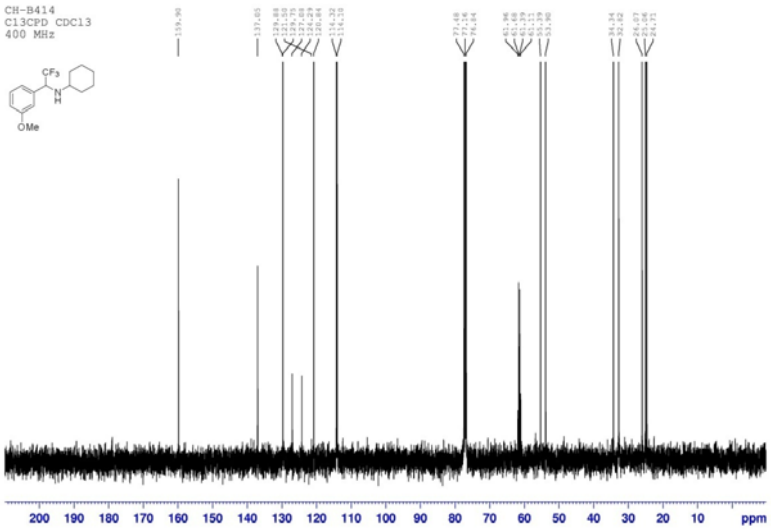




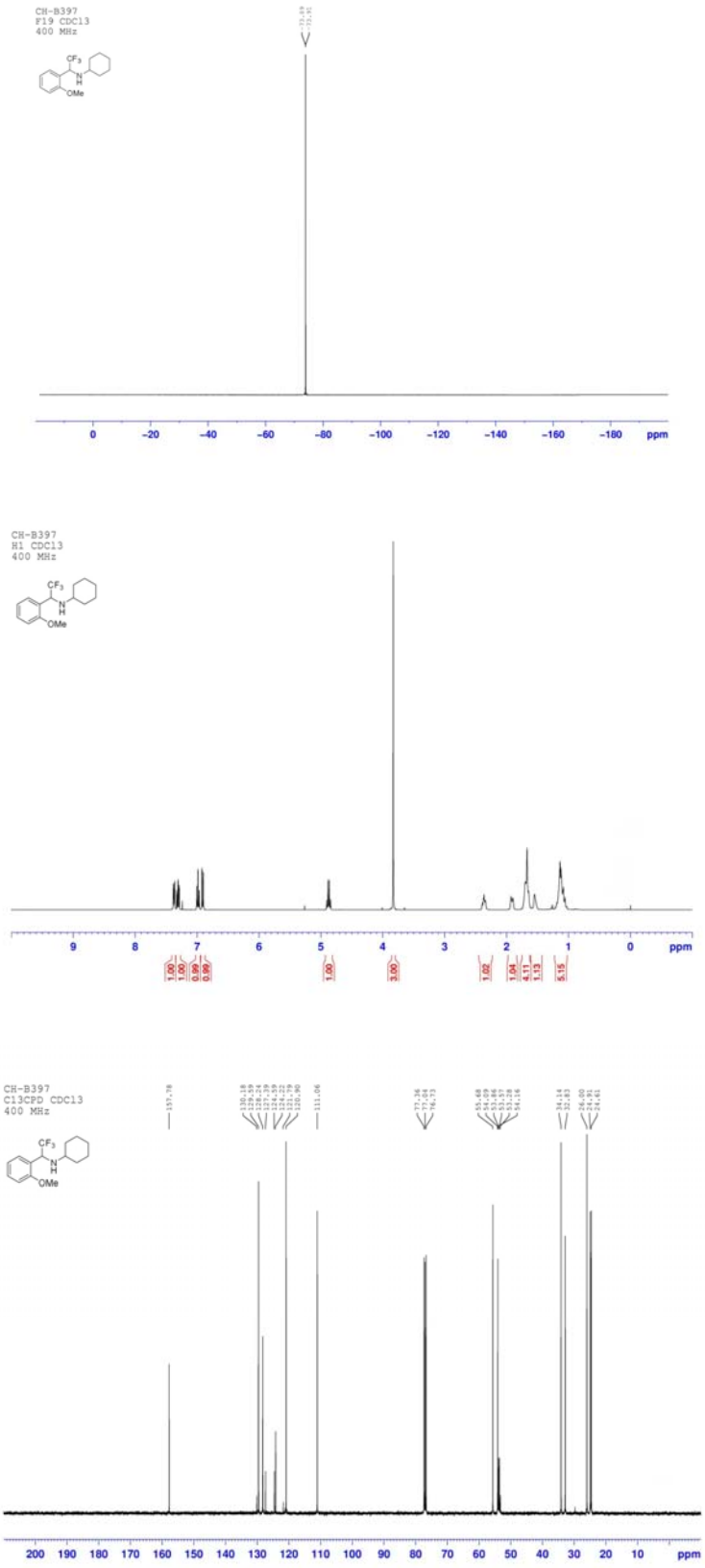
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2k



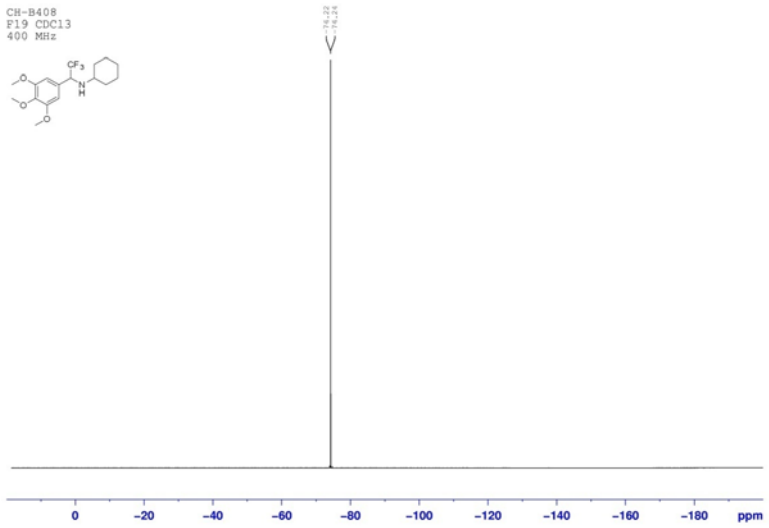


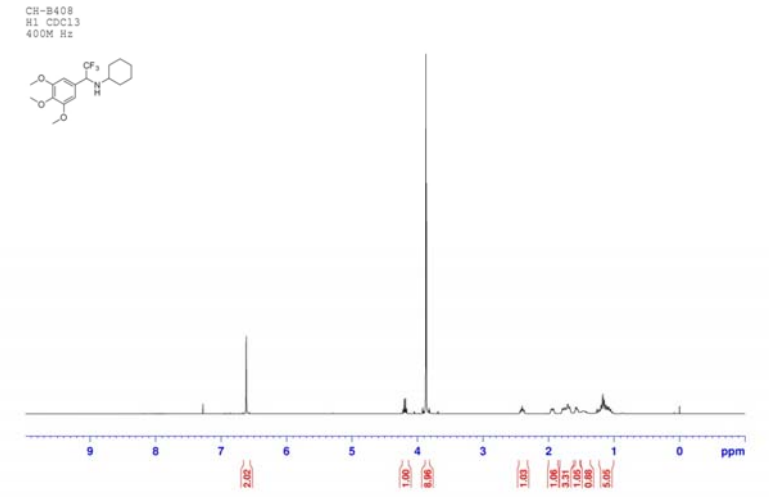


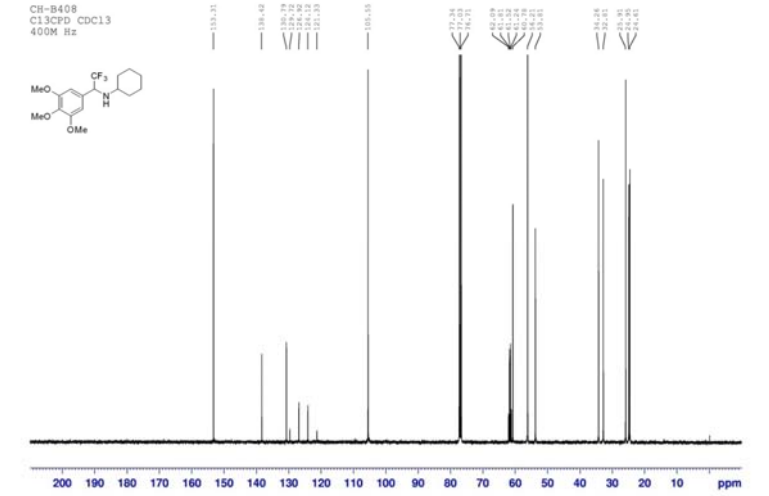
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2l



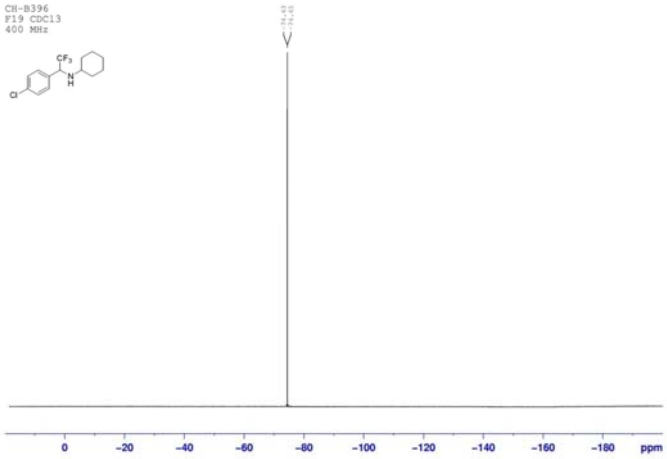
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2m

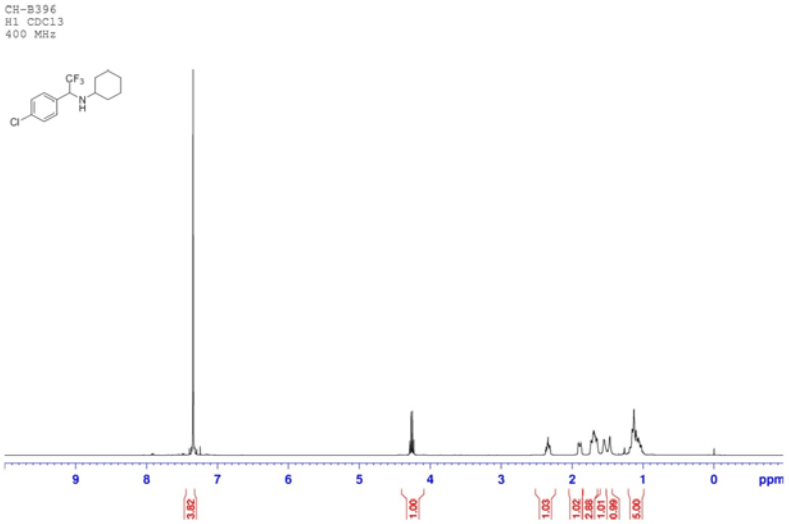


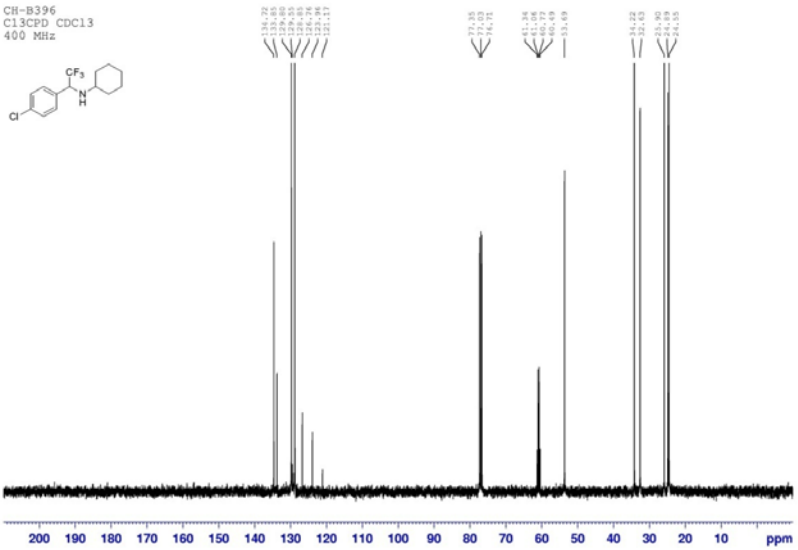




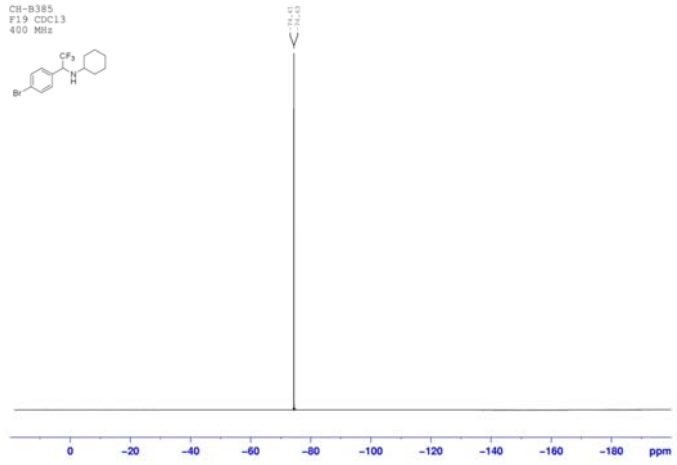
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2n

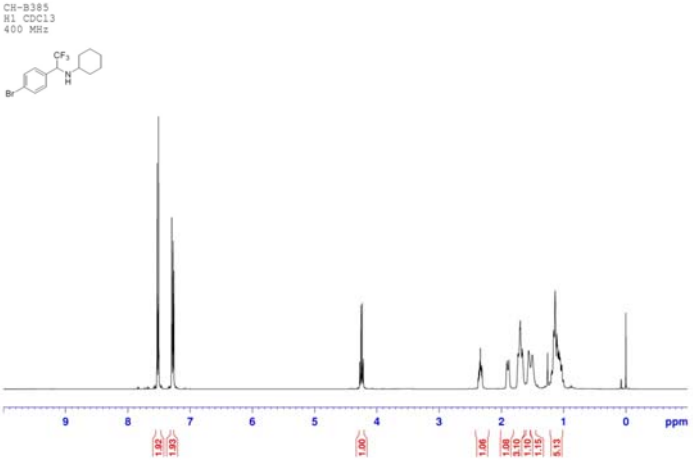


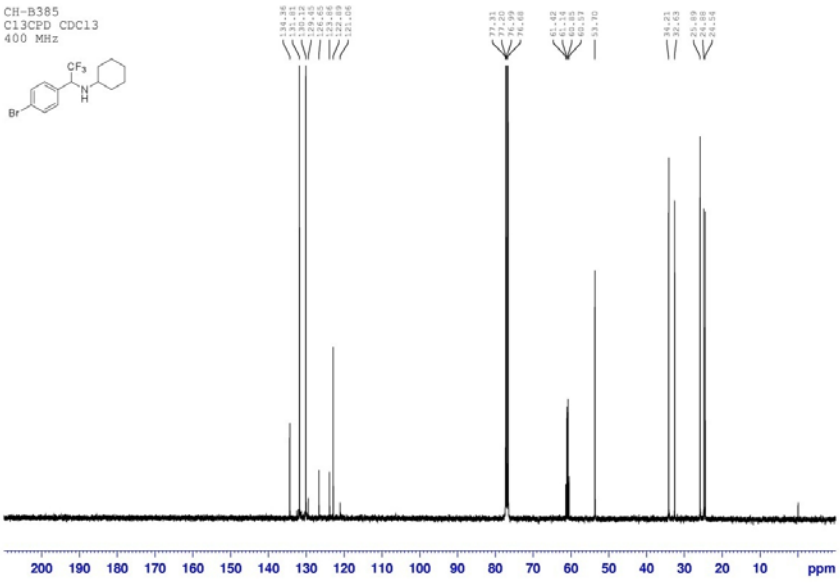




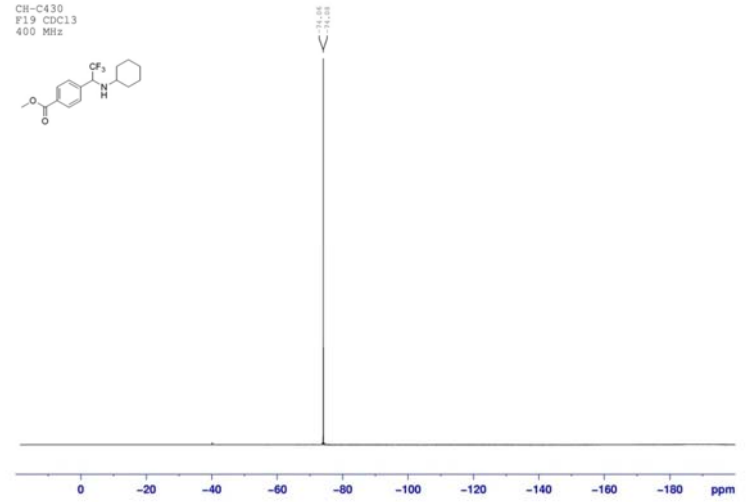
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2o

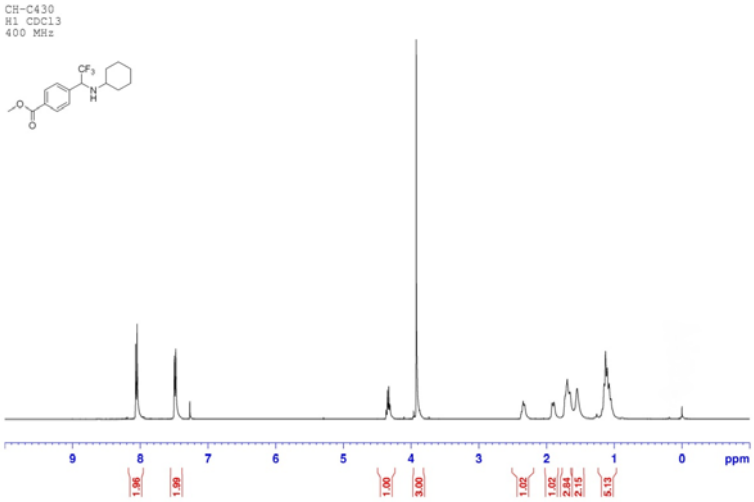


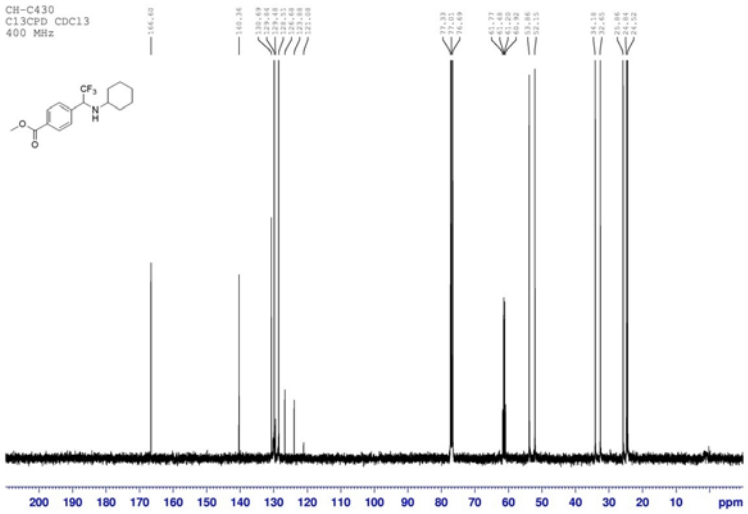




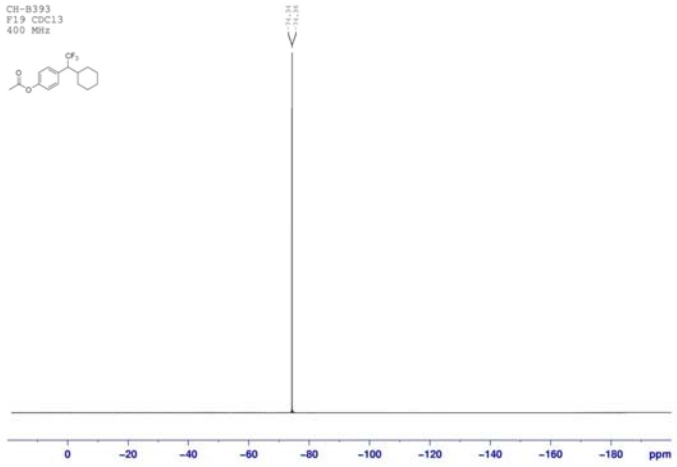
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2p

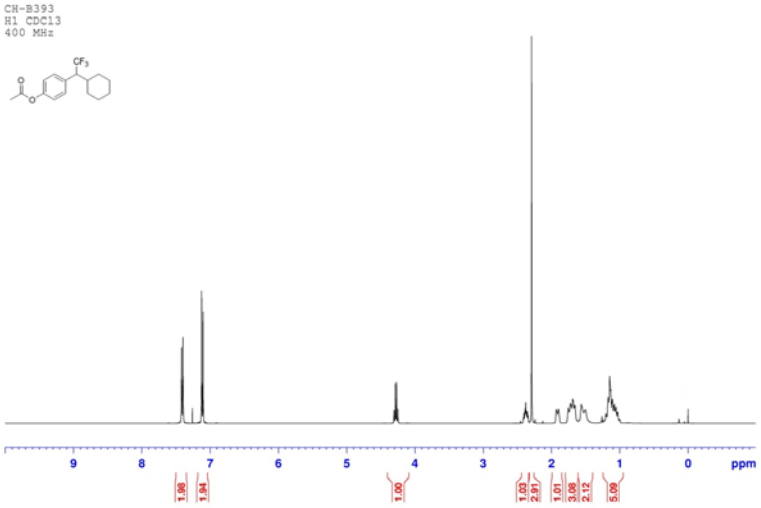


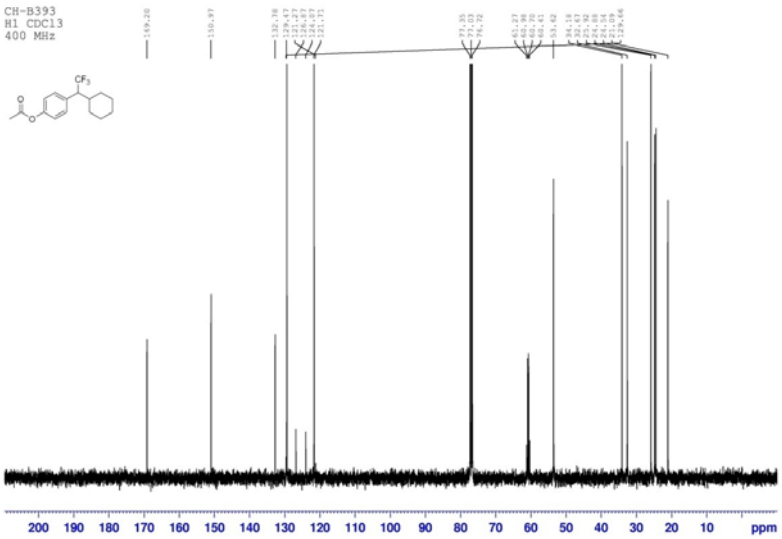




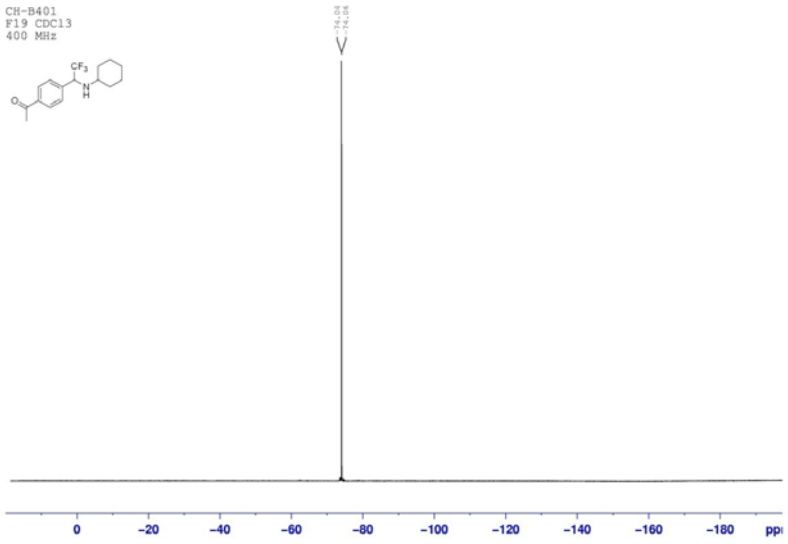
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2q

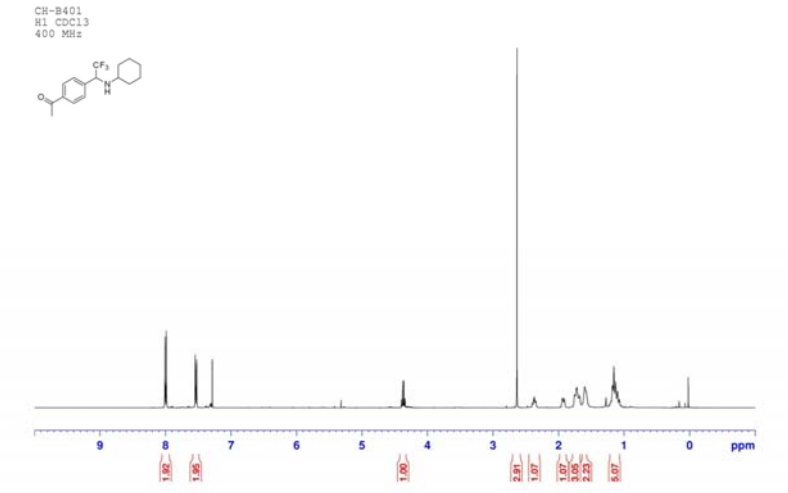


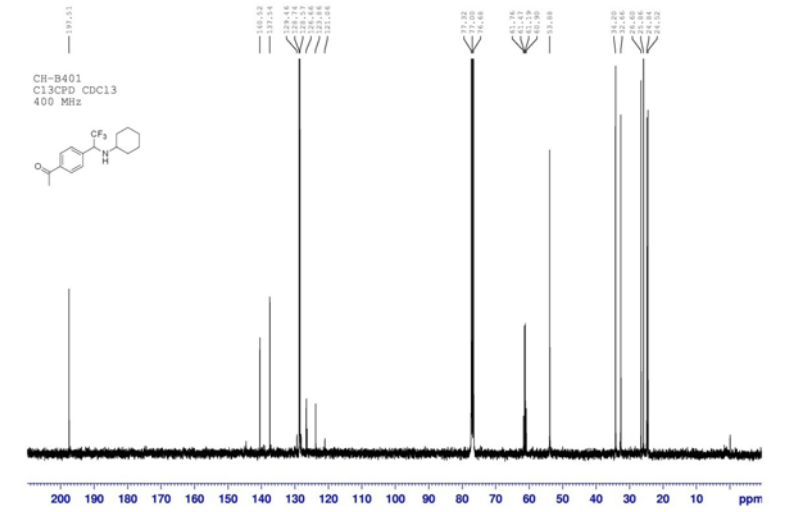




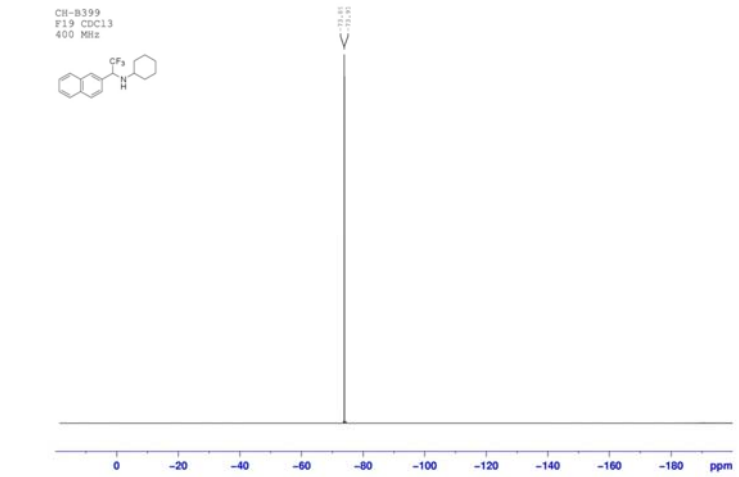
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2r

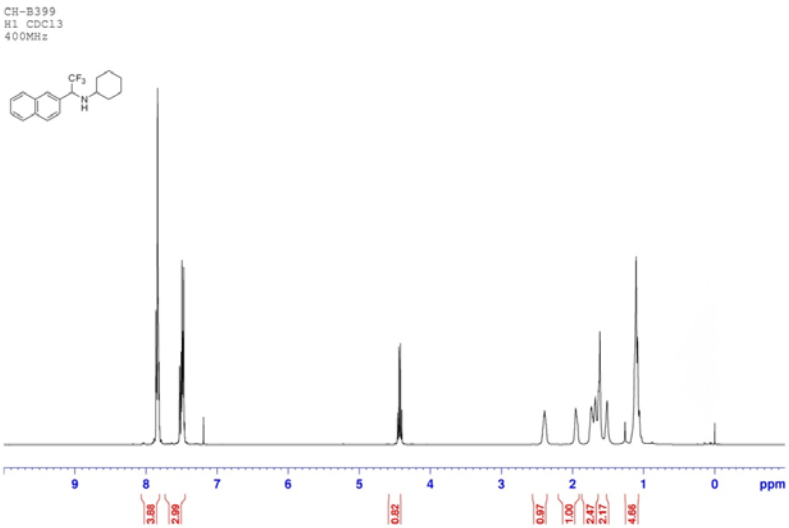


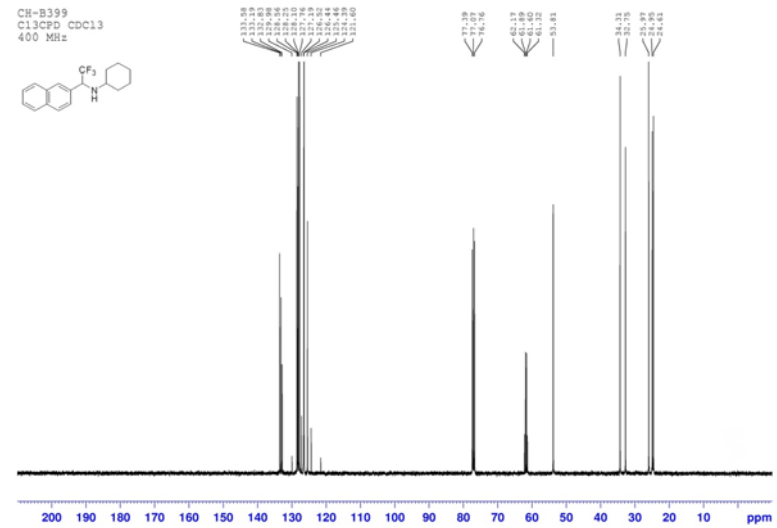




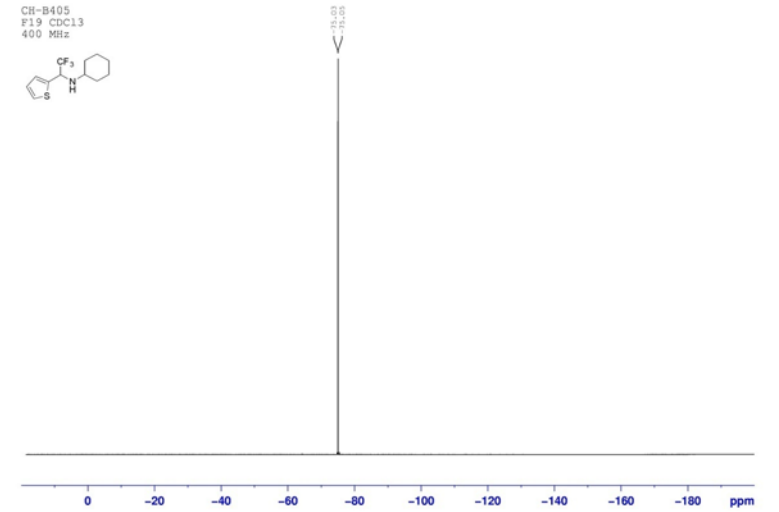
^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2s

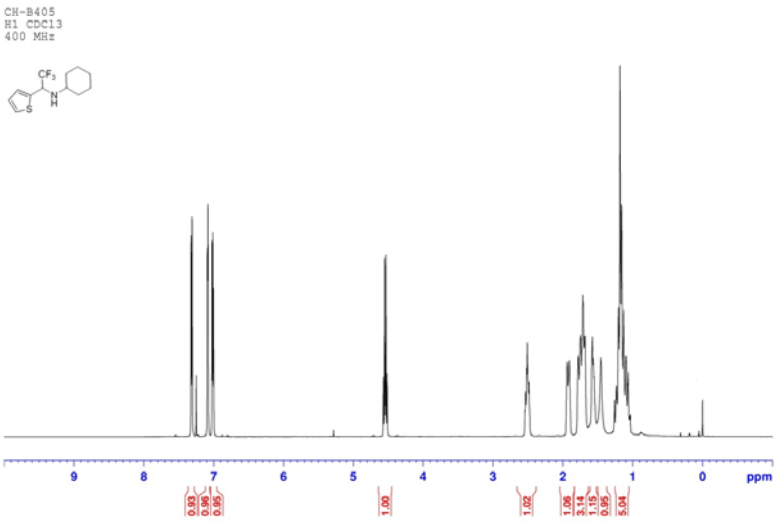


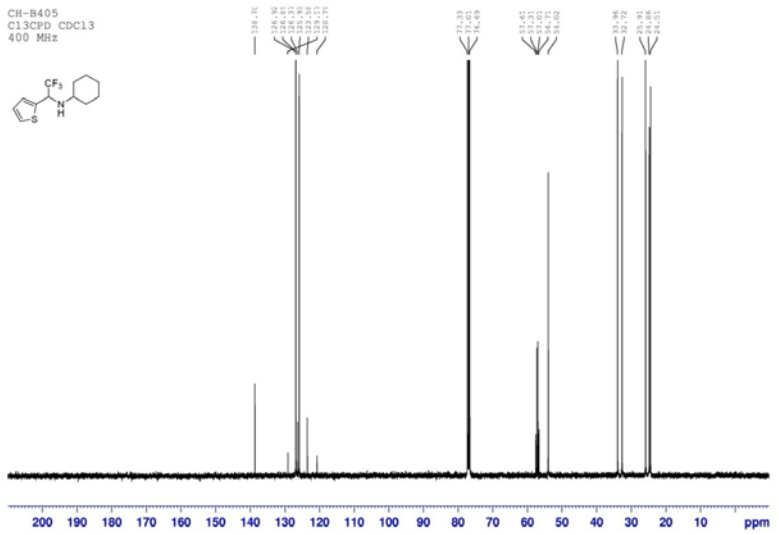




^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2t







^{19}F, ^{1}H and ^{13}C NMR spectra of compound 2u