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Regioselectivity of S_NAr reactions in the synthesis of isomeric difluorinated 4- and 6-piperidino-5-azaindoles

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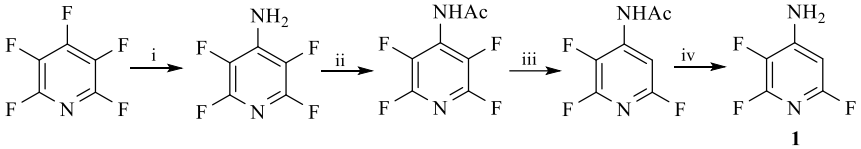
Contents

General Information

NMR spectra were recorded on a Bruker Avance-300 (300.13 MHz for ^{1}H; 282.37 MHz for ^{19}F), Avance-400 (400.13 MHz for ^{1}H; 100.62 MHz for ^{13}C; 376.46 MHz for ^{19}F), DRX-500 (125.76 MHz for ^{13}C) and Bruker Avance 600 (600.18 MHz for ^{1}H; 150.93 MHz for ^{13}C) instruments. $CDCl_3$, acetone-d_6 and CD_3CN were used as solvents, with residual $CHCl_3$ (δ_H = 7.24 ppm) or $CDCl_3$ (δ_C = 77.0 ppm) residual CH_3CN, (δ_H = 1.94 ppm), CD_3CN (δ_C = 1.3, 118.3 ppm) and acetone-d_6 with residual acetone (δ_H = 2.04 ppm) or acetone-d_6 (δ_C = 29.80, 206.0 ppm) being employed as internal standards. C_6F_6 (δ_F = –163.0 ppm) was used as external reference for recording the ^{19}F NMR spectra, in experimental part the chemical shifts in the ^{19}F NMR spectra are given relative to $CFCl_3$. ^{13}C NMR spectra were recorded with C–H spin decoupling. The structure of **5** and **7** was determined using two-dimensional NOESY and HOESY experiments. Masses of molecular ions were determined by HRMS on a DFS Thermo scientific instrument (EI, 70 eV). Melting points were recorded on a Mettler-Toledo FP81 Thermosystem apparatus. The IR spectra were recorded on a Bruker Vector 22 spectrometer (KBr).

Et_3N, MeCN and THF were distilled and kept over CaH_2 before use. Other solvents were purified using standard procedures. Zinc dust was treated with hydrochloric acid (5%, twice), distilled water (twice), acetone (twice) and air dried. KOH flakes (90%) were grounded into powder before use. $PdCl_2(PPh_3)_2$ was synthesized according to the known method [H. Itatani, J. C. Bailar Jr., *J Am. Oil Chem. Soc.*, 1967, **44**, 147; https://doi.org/10.1007/BF02558176]. Other chemicals were commercial grade and used without further purification.

Experimental procedures



Scheme S1 *Reagents and conditions*: i, 25% aq. NH_3, THF, reflux, 2 h; ii, Ac_2O, conc. $HClO_4$ (0.1 ml), benzene, reflux, 5 min; iii, zinc powder, $CuCl_2$, 25% aq. NH_3, room temperature, 24 h; iv, 25% aq. NH_3, reflux, 1 h.

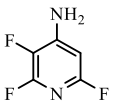
4-Amino-2,3,5,6-tetrafluoropyridine

3,4,5,6-Pentafluoropyridine (25 g, 148 mmol) was dissolved in THF (175 ml), and 25% aq. NH_3 (ρ = 0.88 g/ml, 125 ml) was added. The mixture was refluxed for 2 h, poured into H_2O (500 ml) and extracted with Et_2O (3×75 ml). The extract was dried over $MgSO_4$ and solvents were evaporated to give a pale cream solid. Recrystallization of the crude product from hexane gave target compound. Yield: 20 g (80%). Lit. data: [I. Raache, L. Sekhri, A. Tabchouche, *Orient. J. Chem.*, 2016, **32**, 1799; http://dx.doi.org/10.13005/ojc/320408].

N-(Perfluoropyridin-4-yl)acetamide

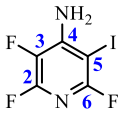
4-Amino-2,3,5,6-tetrafluoropyridine (1.03 g, 6.22 mmol) and Ac_2O (0.76 g, 7.46 mmol) were dissolved in benzene (5 ml) with stirring. To the formed solution, a drop of $HClO_4$ was added. The reaction mixture was refluxed with stirring for 5 min. After cooling, hexane (7 ml) was added to the mixture. The formed crystals were filtered off, washed with hexane (2×5 ml) and dried. Yield: 1.08 g (83%). Lit. data: [S. S. Laev, V. U. Evtefeev, V. D. Shteingarts, *J. Fluor. Chem.*, 2001, **110**, 43; https://doi.org/10.1016/S0022-1139(01)00404-3].

*2,3,6-Trifluoropyridin-4-amine (**1**)*



To a cold (~5 °C) solution of $CuCl_2×2H_2O$ (0.3276 g, 1.92 mmol) in aqueous ammonia (17 ml) was added zinc dust (acid treated, 1.5616 g, 24.02 mmol), and this was stirred for 3 min. *N*-(Perfluoropyridin-4-yl)acetamide (0.5 g, 2.40 mmol) was then added and the resulting mixture, and this was stirred for 24 h at r. t. The aqueous solution was decanted and the metal residue was washed with ammonia (3×3 ml). The combined aqueous-ammonia solution was refluxed for 1 h. After cooling the mixture was extracted with CH_2Cl_2 (4×12 ml). The combined organic solution was dried over $MgSO_4$ and the solvent was evaporated. The target compound was isolated using silica gel column chromatography (eluent: CH_2Cl_2 : hexane 1:1 – 1:0). Yield 0.2 g (56%). The NMR data are consistent with the known ones [S. S. Laev, V. U. Evtefeev, V. D. Shteingarts, *J. Fluor. Chem.*, 2001, **110**, 43; https://doi.org/10.1016/S0022-1139(01)00404-3].

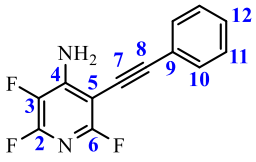
*2,3,6-Trifluoro-5-iodopyridin-4-amine (**2**)*



Compound **1** (0.26 g, 1.75 mmol), I_2 (0.2138 g, 0.84 mmol) and HIO_3 (0.2963 g, 0.96 mmol) were added to 1,4-dioxane (15 ml) and H_2O (1.5 ml), and the mixture was refluxed for 5 h. After cooling the mixture was diluted with brine (15 ml) and extracted with CH_2Cl_2 (4×15 ml). The organic layers were washed with saturated Na_2SO_3 solution (10 ml) and dried over $MgSO_4$. After evaporation of the solvents, the target compound was isolated.

Ligt yellow solid, yield 0.46 g (97%), mp = 111.9 °C (with decomposition). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.11 (s, 2 H, NH_2). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –58.8 (dd, J (F^6,F^3) = 20 Hz, J (F^6,F^2) = 12, Hz, 1 F, F^6), –92.7 (dd, J (F^2,F^3) ≈ 20 Hz, J (F^2,F^6) = 12 Hz, 1 F, F^2), –165.2 (t, J (F^3,F^6) ≈ J (F^3,F^2) = 20 Hz, 1 F, F^3). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 154.8 (ddd, ^1J (C^6,F^6) = 233 Hz, ^2J (C^6,F^2) = 16 Hz, ^3J (C^6,F^3) = 2.5 Hz , C^6), 149.1 (ddd, ^1J (C^2,F^2) ≈ 230 Hz, ^2J (C^2,F^3) = 18 Hz, ^3J (C^2,F^6) = 13 Hz, C^2), 148.0 (m, C^4), 129.4 (ddd, ^1J (C^3,F^3) = 249 Hz, ^2J (C^3,F^2) = 29 Hz, ^2J (C^3,F^6) = 6 Hz, C^3), 58.1 (dm, ^2J (C^5,F^6) = 49 Hz, ^3J (C^5,F^3) = 5 Hz, C^5). IR (KBr), ν, cm^{-1}: 3494 (m), 3356 (s), 1697 (w), 1626 (vs), 1606 (s), 1576 (m), 1498 (s), 1448 (s), 1398 (w), 1385 (m), 1371 (m), 1319 (m), 1225 (s), 1092 (s), 1010 (w), 949 (w), 887 (w), 816 (m), 731 (w), 667 (w), 642 (w), 420 (w). HRMS (EI): *m/z* $[M]^+$ calcd for $C_5H_2N_2F_3I$: 273.9209; found: 273.9215.

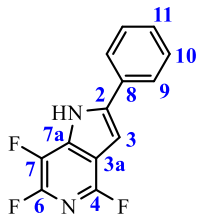
*2,3,6-Trifluoro-5-(phenylethynyl)pyridin-4-amine (**3**)*



A solution of aminoaryl iodide **2** (0.540 g, 1.97 mmol), phenylacetylene (0.403 mg, 3.94 mmol), CuI (0.019 mg, 0.0985 mmol) in NEt_3 (20 ml) was bubbled with argon for 30 min. Then $PdCl_2(PPh_3)_2$ (0.069 mg, 0.0985 mmol) was added, and the mixture was stirred at 78 °C for 2 h in an argon atmosphere. After cooling, the reaction mixture was filtered, the precipitate was washed with warm EtOAc (4×5 ml), and the solvents were evaporated from the combined filtrate. The crude product was purified by column chromatography on silica gel using hexane and CH_2Cl_2 (sequentially) as eluents and additional crystallization from a mixture of CH_2Cl_2 and hexane to obtain compound **3**.

Light beige crystals, yield 0.388 g (79%), mp = 161.6–161.8 °C ($CHCl_3$/petroleum ether (40-70)). ^{1}H NMR (300 MHz, acetone-d_6), δ: 7.51–7.48 (m, 2 H, H^{10}), 7.33–7.31 (m, 3 H, H^{11}, H^{12}), 6.31 (s, 2 H, NH_2). ^{19}F NMR (282 MHz, acetone-d_6), δ: –72.3 (dd, J (F^6,F^3) = 21 Hz, J (F^6,F^2) = 13 Hz, 1 F, F^6), –94.6 (dd, J (F^2,F^3) = 21 Hz, J (F^2,F^6) = 13 Hz, 1 F, F^2), –172.8 (t, J (F^3,F^6) ≈ J (F^3,F^2) = 21 Hz, 1 F, F^3). ^{13}C NMR (151 MHz, acetone-d_6), δ: 155.0 (dd, ^1J (C^6,F^6) = 240 Hz, ^2J (C^6,F^2) = 16 Hz, C^6), 148.5 (m, C^4), 147.4 (ddd, ^1J (C^2,F^2) = 237 Hz, ^2J (C^2,F^3) = 19 Hz, ^3J (C^2,F^6) = 14 Hz, C^2), 130.8 (s, C^{10}), 129.7 (ddd, ^1J (C^3,F^3) = 244 Hz, ^2J (C^3,F^2) = 28 Hz, ^3J (C^3,F^6) = 5 Hz, C^3), 128.3 (s, C^{12}), 127.7 (s, C^{11}), 121.5 (s, C^9), 99.0 (m, C^7), 88.8 (dm, ^2J (C^5,F^6) = 37 Hz, C^5), 75.5 (s, C^8). IR (KBr), ν, cm^{-1}: 3460 (m), 3327 (s), 3236 (w), 3201 (m), 3082 (w), 1668 (m), 1635 (vs), 1612 (m), 1593 (m), 1504 (s), 1489 (vs), 1462 (vs), 1444 (m), 1398 (m), 1338 (m), 1321 (s), 1288 (w), 1225 (w), 1115 (s), 1095 (s), 1070 (w), 1024 (w), 997 (w), 906 (m), 779 (w), 756 (s), 690 (m), 648 (w), 609 (w), 507 (w), 480 (w), 470 (w), 436 (w), 411 (w). HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_7N_2F_3$: 248.0556; found: 248.0553.

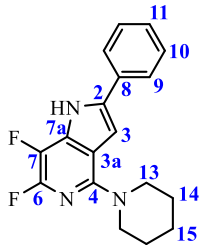
*4,6,7-Trifluoro-2-phenyl-1H-pyrrolo[3,2-c]pyridine (**4**)*



A solution of compound **3** (0.040 g, 0.16 mmol) and KOH (0.027 g, 0.48 mmol) in dry MeCN (11 ml) was refluxed with stirring for 2 h. After cooling, the reaction mixture was filtered, the precipitate was washed with warm MeCN (3×5 ml), and the solvents were evaporated from the combined filtrate. The crude product was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to obtain compound **4**.

White solid, yield 0.035 g (88%), mp = 183.1–183.2 °C (from EtOAc/hexane). ^{1}H NMR (300 MHz, CD_3CN), δ: 10.67 (s, 1 H, NH), 7.74 (m, 2 H, H^9), 7.51–7.37 (m, 3 H, H^{10}, H^{11}), 6.88 (d, J (H^3,F^7)= 2.9 Hz, 1 H, H^3). ^{19}F NMR (282 MHz, CD_3CN), δ: –78.2 (dd, J (F^4,F^7) = 29.5 Hz, J (F^4,F^6) = 14, Hz, 1 F, F^4), –105.7 (dd, J (F^6,F^7) = 20 Hz, J (F^6,F^4) = 14 Hz, 1 F, F^6), –167.9 (m, J (F^7,F^4) = 29.5 Hz, J (F^7,F^6) = 20 Hz, J (F^7,H) = 3 Hz, 1 F, F^7). ^{13}C NMR (101 MHz, CD_3CN), δ: 147.4 (dd, ^1J (C^4,F^4) = 240 Hz, ^2J (C^4,F^6) = 16 Hz, C^4), 143.4 (dt, ^1J (C^6,F^6) = 227 Hz, ^2J (C^6,F^7) ≈ ^3J (C^6,F^4) = 15 Hz, C^6), 143.0 (s, C^2), 136.1 (m, C^{7a}), 131.3 (s, C^8), 130.8 (ddd, ^1J (C^7,F^7) = 249 Hz, ^2J (C^7,F^6) = 30 Hz, ^3J (C^7,F^4) = 8 Hz, C^7), 129.9 (s, C^{10}), 129.7 (s, C^{11}), 126.6 (s, C^9), 114.0 (dm, ^2J (C^{3a},F^4) = 40 Hz, C^{3a}), 96.9 (d, ^3J (C^3,F^4) = 6 Hz, C^3). IR (KBr), ν, cm^{-1}: 3292 (m), 3282 (m), 3128 (w), 3074 (w), 3036 (w), 3014 (w), 2956 (w), 2924 (m), 2852 (w), 1647 (s), 1624 (w), 1558 (m), 1495 (vs), 1454 (s), 1412 (m), 1379 (s), 1358 (s), 1317 (s), 1284 (s), 1217 (w), 1190 (w), 1163 (w), 1151 (w), 1107 (s), 1047 (w), 1030 (w), 1001 (w), 985 (s), 930 (w), 906 (w), 798 (w), 762 (m), 740 (s), 686 (m), 634 (w), 617 (w), 604 (m), 447 (w). HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_7N_2F_3$: 248.0556; found: 248.0557.

*6,7-Difluoro-2-phenyl-4-(piperidin-1-yl)-1H-pyrrolo[3,2-c]pyridine (**5**)*

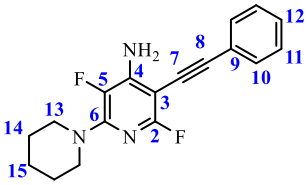


A solution of compound **4** (0.030 g, 0.12 mmol), piperidine (0.051 g, 0.60 mmol) in dry MeCN (1.5 ml) was refluxed with stirring for 22 h. After cooling, the volatiles of the reaction mixture were evaporated, the crude product was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to obtain compound **5** as a viscous oil.

Brown solid, yield 0.035 g (92%), mp = 118.6–121.7 °C ($CHCl_3$/hexane). ^{1}H NMR (600.18 MHz, CD_3CN), δ: 10.16 (s, 1 H, NH), 7.73–7.71 (dm, 2 H, H^9), 7.44–7.41 (tm, 2 H, H^{10}), 7.32 (tm, 1 H, H^{11}), 6.89 (dd, J (H^3,F^7) = 3.1 Hz, J (H^3,F^6) = 2.4 Hz, 1 H, H^3), 3.54 (m, 4 H, H^{13}), 1.67–1.61 (m, 6 H, H^{14}, H^{15}). ^{19}F NMR (376 MHz, CD_3CN), δ: –106.0 (d, J (F^6,F^7) = 26 Hz, 1 F, F^6), –179.2 (dd, J (F^7,F^6) = 26 Hz, J (F^7,H^3) = 3 Hz, 1 F, F^7). ^{13}C NMR (151 MHz, CD_3CN), δ: 148.3 (dd, ^1J (C^4,F^6) = 16.5 Hz, ^2J (C^4,F^7) = 1 Hz, C^4), 145.4 (dd, ^1J (C^6,F^6) = 217 Hz, ^2J (C^6,F^7) = 11.5 Hz, C^6), 138.9 (m, C^2), 134.9

(dd, ^1J (C^{7a},F^7) = 11 Hz, ^2J (C^{7a},F^6) = 6 Hz, C^{7a}), 132.3 (s, C^8), 129.9 (s, C^{10}), 128.9 (s, C^{11}), 126.8 (dd, ^1J (C^7,F^7) = 243 Hz, ^2J (C^7,F^6) = 34 Hz, C^7), 126.2 (s, C^9), 115.7 (m, C^{3a}), 101.2 (s, C^3), 49.9 (s, C^{13}), 26.7 (s, C^{14}), 25.5 (s, C^{15}). IR (KBr), ν, cm^{-1}: 3471 (w), 3271 (w), 3232 (w), 2931 (m), 2854 (w), 2837 (w), 2820 (w), 1616 (s), 1558 (w), 1489 (vs), 1464 (s), 1450 (s), 1417 (s), 1371 (m), 1344 (m), 1321 (m), 1298 (m), 1275 (s), 1259 (s), 1226 (m), 1176 (w), 1159 (w), 1026 (m), 999 (w), 980 (m), 956 (w), 931 (w), 912 (w), 870 (w), 852 (w), 796 (w), 766 (m), 752 (m), 729 (m), 692 (m), 669 (w), 640 (w), 629 (w), 621 (w), 517 (w), 501 (w), 478 (w). HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{17}N_3F_2$: 313.1385; found: 313.1383.

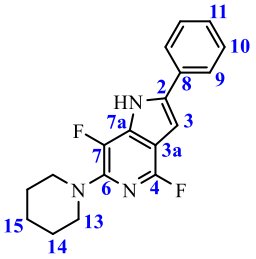
*2,5-Difluoro-3-(phenylethynyl)-6-(piperidin-1-yl)pyridin-4-amine (**6**)*



A solution of compound **3** (0.060 g, 0.24 mmol), piperidine (0.102 g, 1.21 mmol) in dry MeCN (2.0 ml) was refluxed with stirring for 2 h. After cooling, the volatiles of the reaction mixture were evaporated, the crude product was purified by column chromatography on silica gel using the mixture of CH_2Cl_2 and hexane (1:2) as eluent to obtain compound **6**.

Beige solid, yield 0.069 g (79%), mp = 127.1–127.2 °C ($CHCl_3$/hexane). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.51–7.46 (m, 2 H, H^{10}), 7.34–7.31 (m, 3 H, H^{11}, H^{12}), 4.68 (s, 2 H, NH_2), 3.48 (m, 4 H, H^{13}), 1.62 (m, 6 H, H^{15}). ^{19}F NMR (282 MHz, $CDCl_3$), δ: –67.6 (d, J (F^2,F^5) = 24.5 Hz, 1 F, F^2), –159.4 (d, J (F^5,F^2) = 24.5 Hz, 1 F, F^5). ^{13}C NMR (126 MHz, $CDCl_3$), δ: 156.8 (d, ^1J (C^2,F^2) = 232 Hz, C^2), 145.4 (m, ^2J (C^4,F^5) = 14 Hz, C^4), 145.3 (m, ^2J (C^6,F^5) = 19 Hz, C^6), 133.5 (dd, ^1J (C^5,F^5) = 236.5 Hz, ^2J (C^5,F^2) = 5 Hz, C^5), 131.4 (s, C^{11}), 128.3 (s, C^{10}), 122.9 (s, C^{12}), 97.8 (s, C^9), 82.6 (d, ^1J (C^3,F^2) = 41 Hz, C^3), 78.3 (s, C^7), 78.3 (s, C^8), 48.2 (d, ^1J (C^{13},F^5) = 7 Hz, C^{13}), 25.9 (s, C^{14}), 24.7 (s, C^{15}). IR (KBr), ν, cm^{-1}: 3502 (w), 3383 (s), 3018 (w), 2933 (m), 2852 (m), 2204 (w), 1632 (vs), 1608 (s), 1597 (s), 1550 (m), 1498 (s), 1464 (m), 1450 (s), 1404 (m), 1390 (m), 1379 (s), 1321 (m), 1286 (m), 1261 (m), 1201 (m), 1174 (m), 1163 (w), 1118 (s), 1076 (m), 1063 (m), 1034 (w), 1012 (m), 976 (w), 964 (w), 931 (w), 904 (m), 858 (w), 850 (w), 804 (w), 771 (w), 746 (m), 708 (w), 686 (m), 648 (w), 629 (w), 538 (w), 463 (w). HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{17}N_3F_2$: 313.1385; found: 313.1388.

*4,7-Difluoro-2-phenyl-6-(piperidin-1-yl)-1H-pyrrolo[3,2-c]pyridine (**7**)*

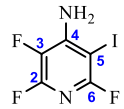


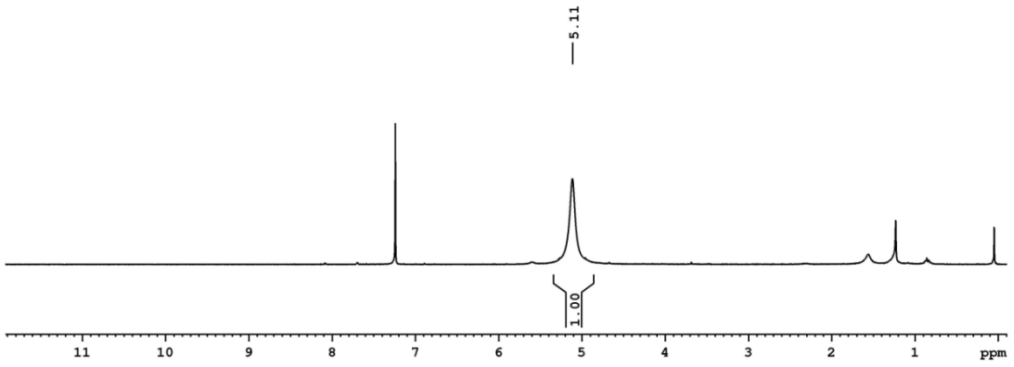
A solution of compound **6** (0.030 g, 0.10 mmol) and KOH (0.016 g, 0.29 mmol) in dry MeCN (1.5 ml) was refluxed with stirring for 2 h. After cooling, the reaction mixture was filtered, the precipitate was washed with warm MeCN (3×0.5 ml), and the solvents were evaporated from the combined filtrate. The crude product was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to obtain compound **7**.

White solid, yield 0.026 g (88%), mp = 139.3–140.4 °C ($CHCl_3$/hexane). ^{1}H NMR (600 MHz, CD_3CN), δ: 10.10 (s, 1 H, NH), 7.73 (dm, 2 H, H^9), 7.44 (t, 2 H, H^{10}), 7.34 (tm, 1 H, H^{11}), 6.75 (d, J (H^3,F^7) = 3.0 Hz, 1 H, H^3), 3.27 (m, 4 H, H^{13}), 1.65 (m, 4 H, H^{14}), 1.58 (m, 2 H, H^{15}). ^{19}F NMR (376 MHz, CD_3CN), δ: –78.5 (d, J (F^4,F^7) = 33 Hz, 1 F, F^4), –158.9 (dd, J (F^7,F^4) = 33 Hz, J (F^7,H^3) = 3 Hz, 1 F, F^7). ^{13}C NMR (151 MHz, CD_3CN), δ: 149.3 (d, ^1J (C^4,F^4) = 232 Hz, C^4), 141.6 (dd, ^2J (C^6,F^7) = 16 Hz, ^3J (C^6,F^4) = 7.5 Hz, C^6), 140.6 (s, C^2), 136.7 (dd, ^2J (C^{7a},F^7) ≈ ^3J (C^{7a},F^4) = 14 Hz, C^{7a}), 135.5 (dd, ^1J (C^7,F^7) = 243 Hz, ^4J (C^7,F^4) = 8 Hz, C^7), 132.0 (s, C^8), 130.0 (s, C^{10}), 129.3 (s, C^{11}), 126.4 (s, C^9), 109.8 (dd, ^1J (C^{3a},F^4) = 45 Hz, ^2J (C^{3a},F^7) = 4 Hz , C^{3a}), 96.7 (d, ^3J (C^3,F^4) = 5.5 Hz, C^3), 50.7 (d, ^4J (C^{13},F^7) = 4 Hz, C^{13}), 26.8 (s, C^{14}), 25.4 (s, C^{15}). IR (KBr), ν, cm^{-1}: 3143 (m), 3064 (m), 3035 (m), 2985 (m), 2947 (m), 2935 (m), 2916 (m), 2842 (m), 2704 (w), 2667 (w), 2511 (w), 1645 (s), 1604 (m), 1589 (m), 1552 (w), 1491 (vs), 1462 (s), 1450 (s), 1412 (m), 1388.5 (s), 1361.5 (s), 1350 (s), 1317 (m), 1288 (s), 1265 (s), 1255 (s), 1223 (m), 1196 (m), 1168 (m), 1155 (m), 1118 (m), 1105 (s), 1072 (m), 1039 (m), 1028 (m), 997 (w), 980 (s), 930 (w), 912 (w), 860 (m), 798 (m), 766 (s), 744 (s), 692 (s), 669 (w), 650 (w), 632 (w), 621 (w), 575 (w), 503 (w), 470 (w). HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{17}N_3F_2$: 313.1385; found: 313.1381.

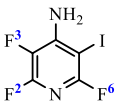
Copies of NMR and IR spectra

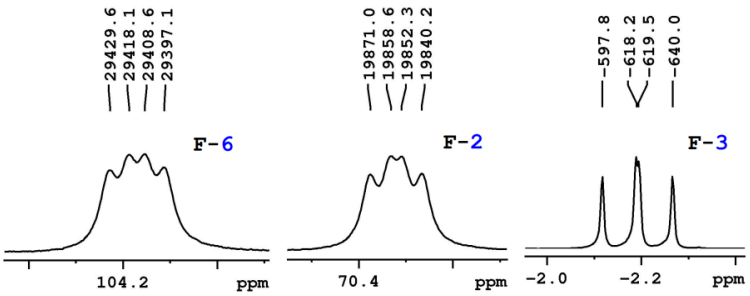
^{1}H NMR spectrum ($CDCl_3$, residual $CHCl_3$ δ_H = 7.24 ppm) Bruker Avance 300 (300.13 MHz) of **2**

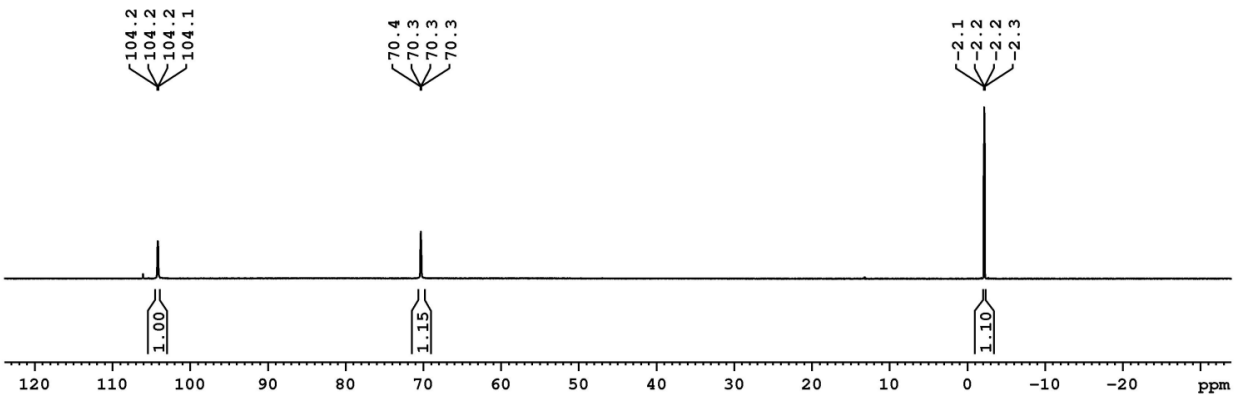




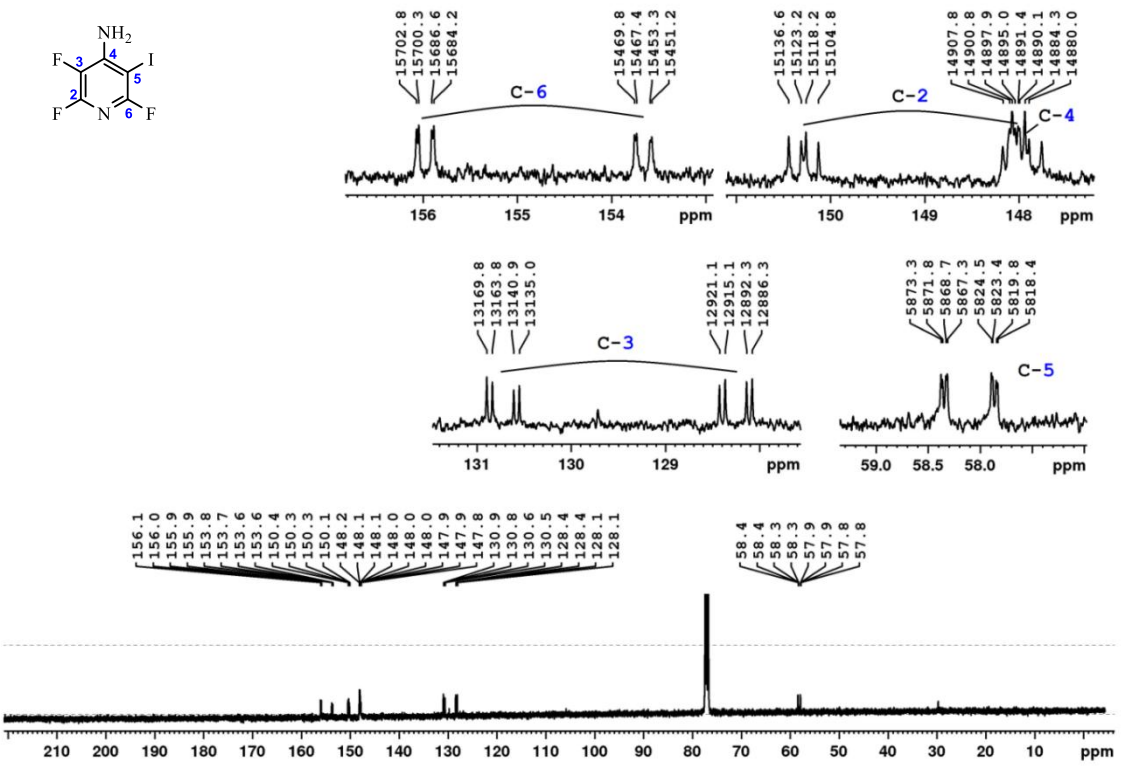
^{19}F NMR spectrum ($CDCl_3$, C_6F_6, δ_F = –163.0 ppm) Bruker Avance 300 (282.4 MHz) of **2**



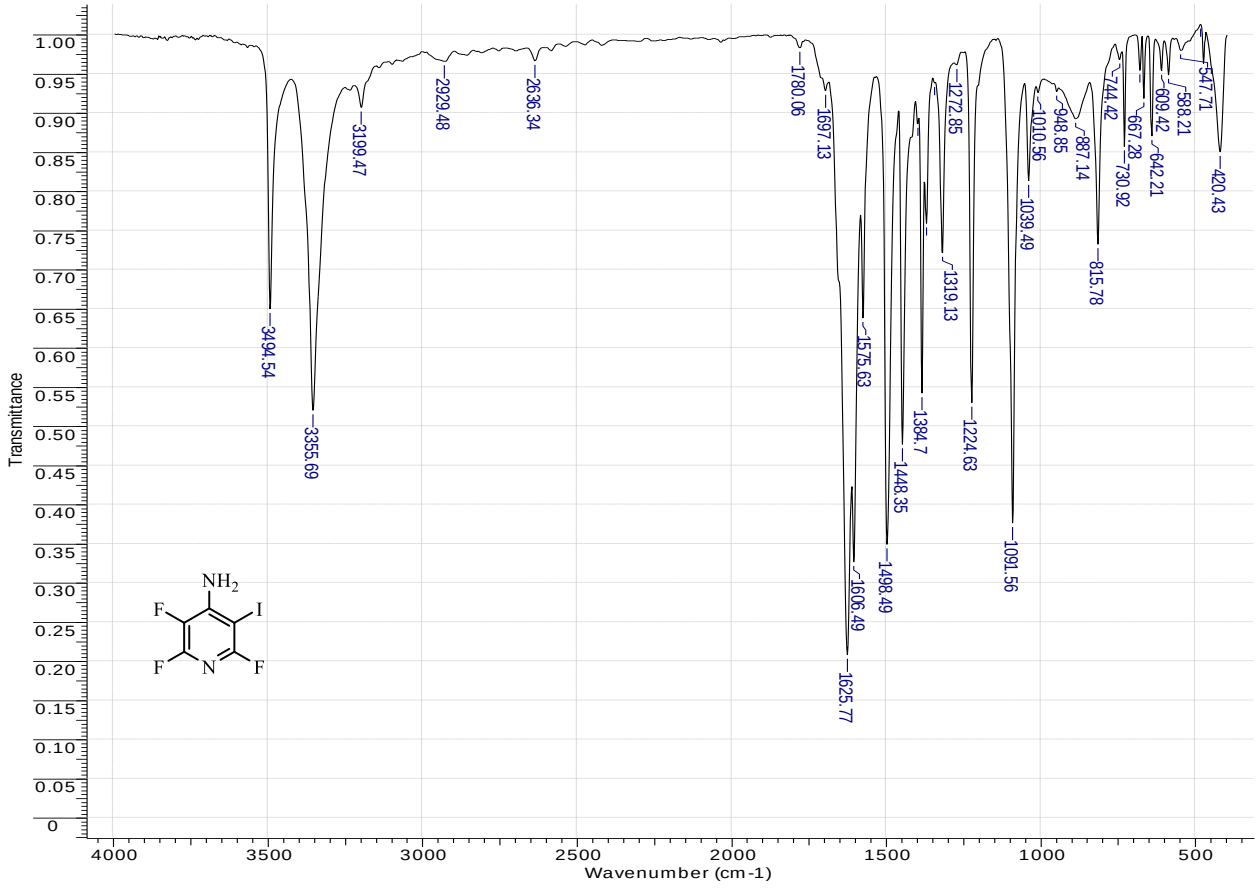




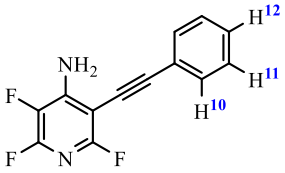
^{13}C NMR spectrum ($CDCl_3$, δ_C = 77.0 ppm) Bruker Avance 400 (100.6 MHz) of **2**

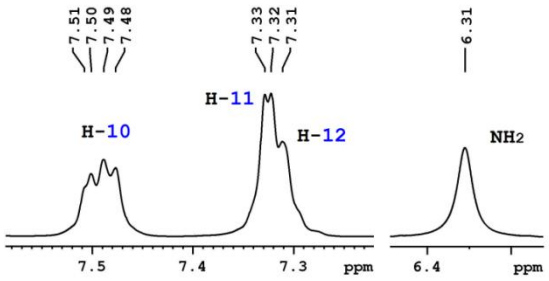


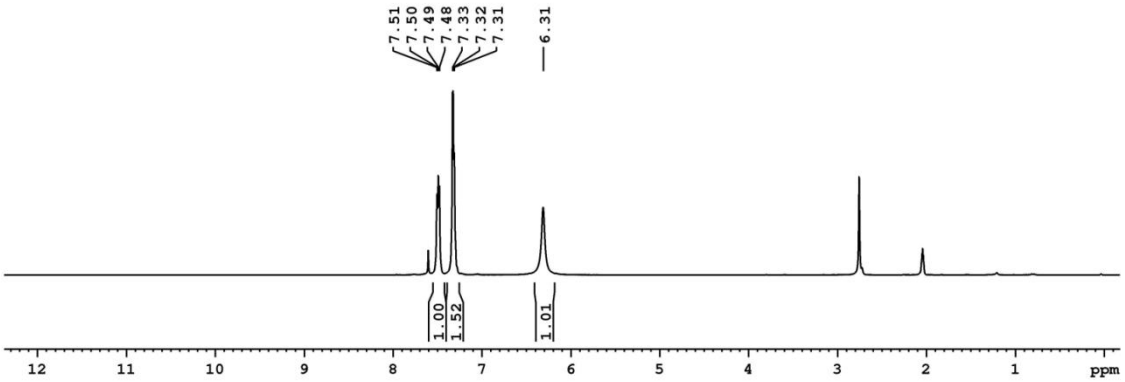
IR (KBr) for **2**



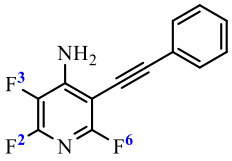
^{1}H NMR spectrum (acetone-d_6, residual acetone, δ_H = 2.04 ppm) Bruker Avance 300 (300.13 MHz) of **3**

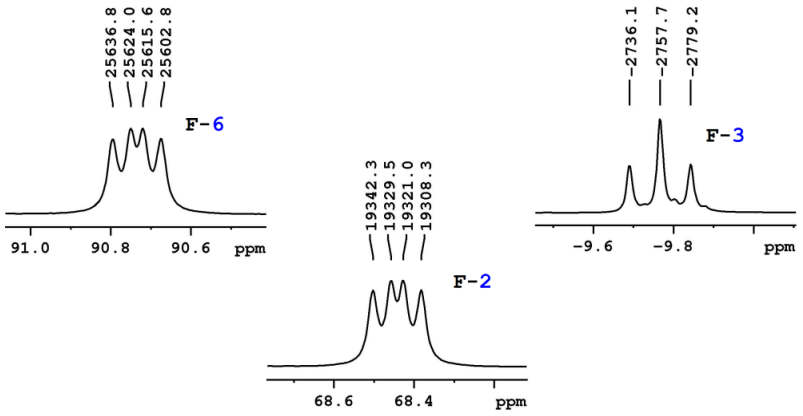


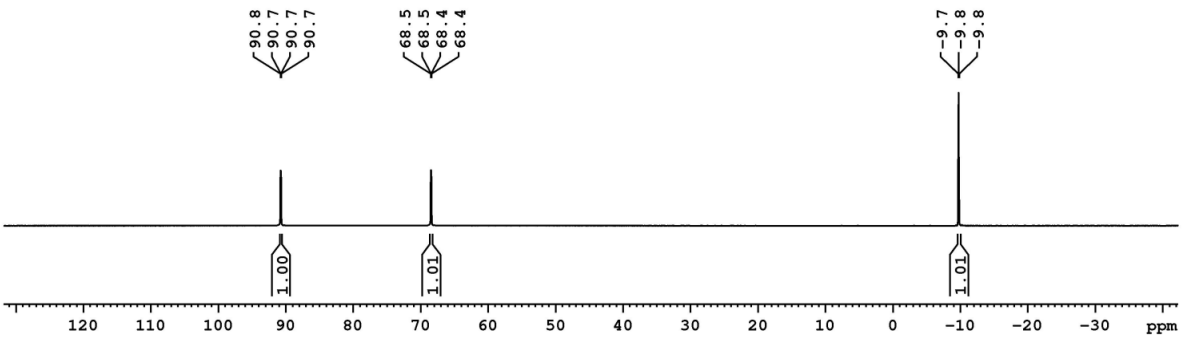




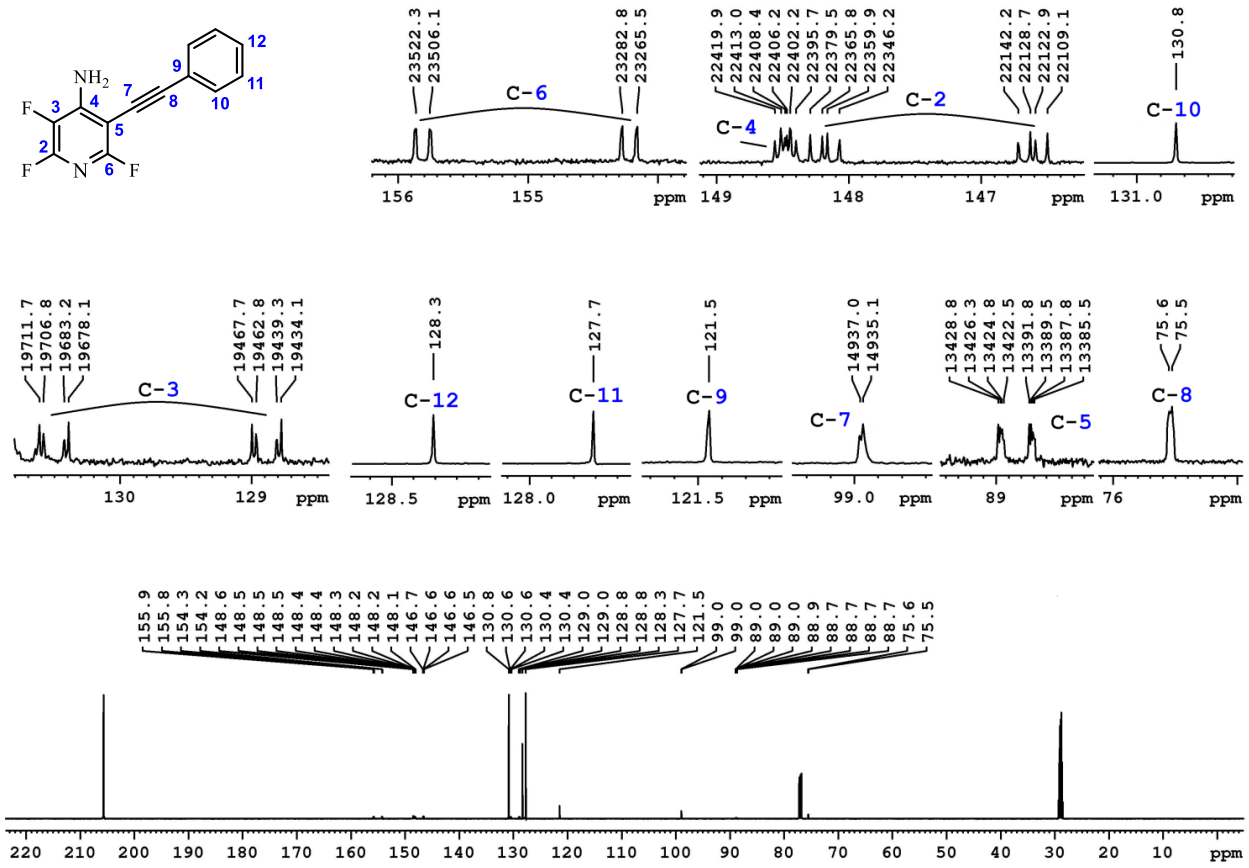
^{19}F NMR spectrum (acetone-d_6, C_6F_6, δ_F = –163.0 ppm) Bruker Avance 300 (282.4 MHz) of **3**



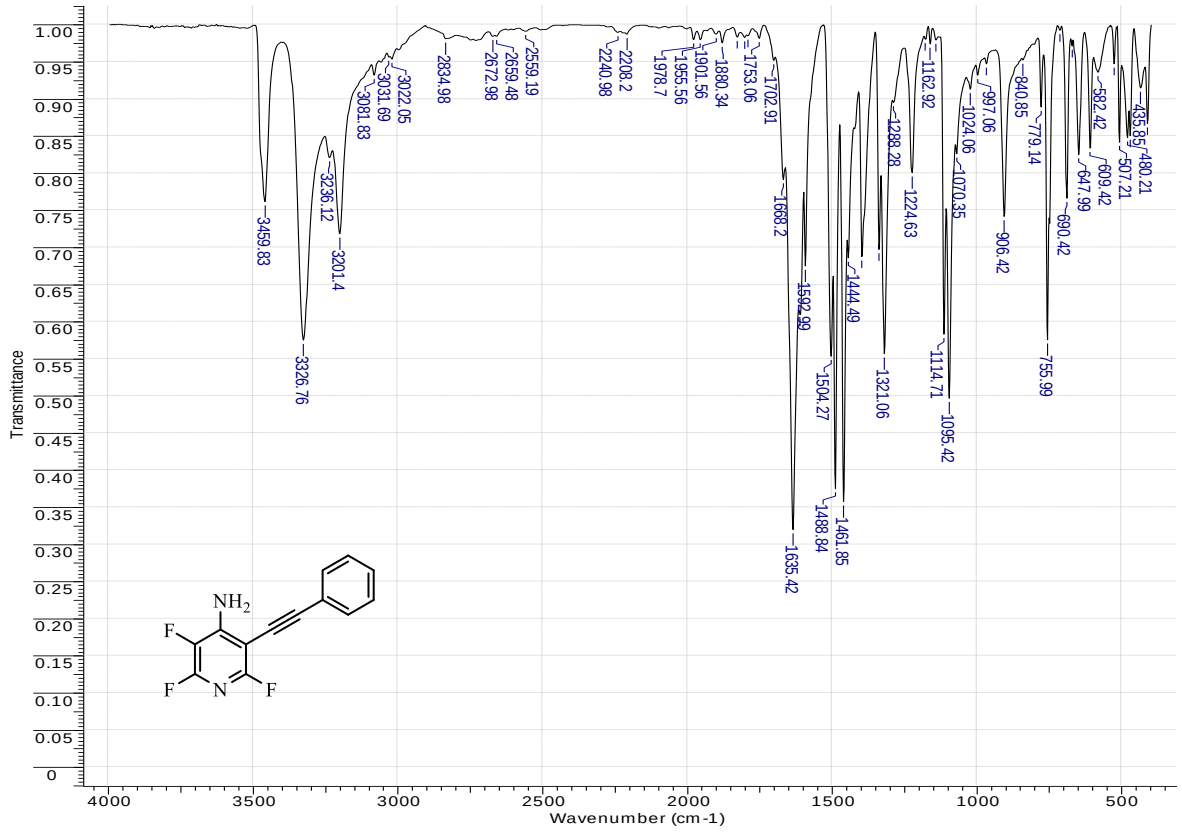




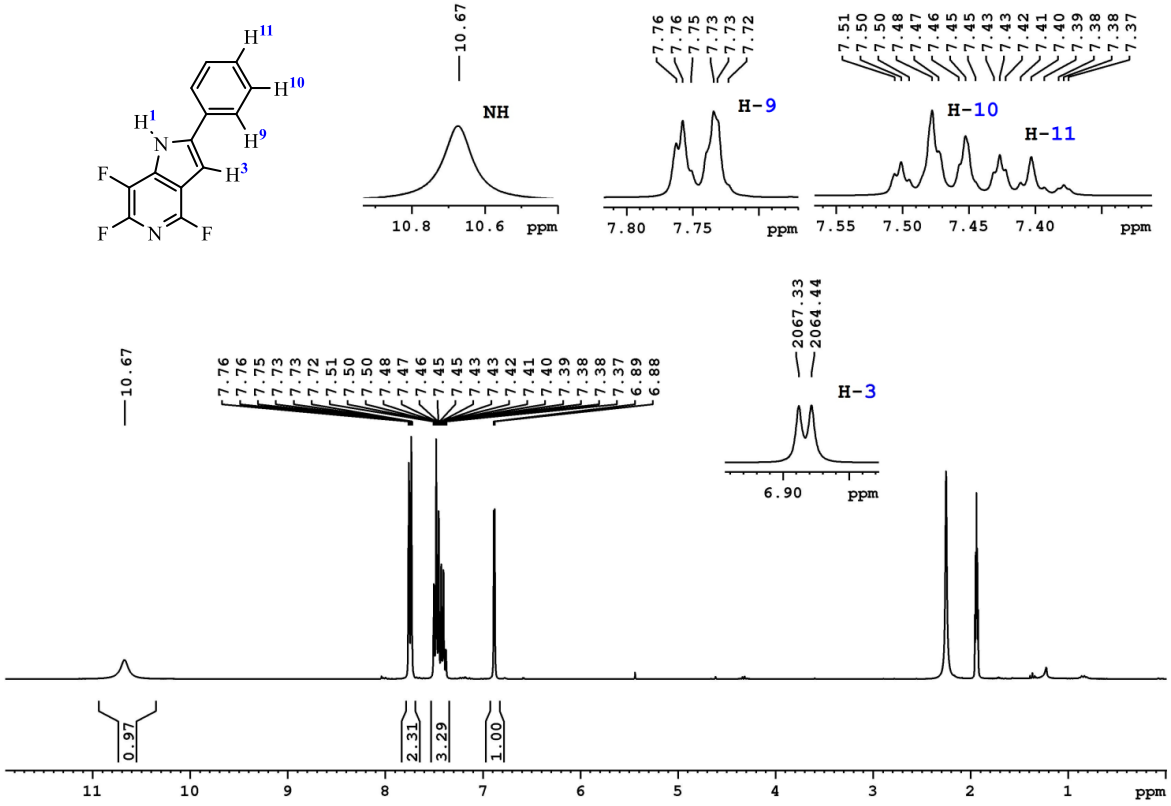
^{13}C NMR spectrum ($CDCl_3$, acetone-d_6, δ_C ($CDCl_3$) = 77.0 ppm) Bruker Avance 600 (150.9 MHz) of **3**



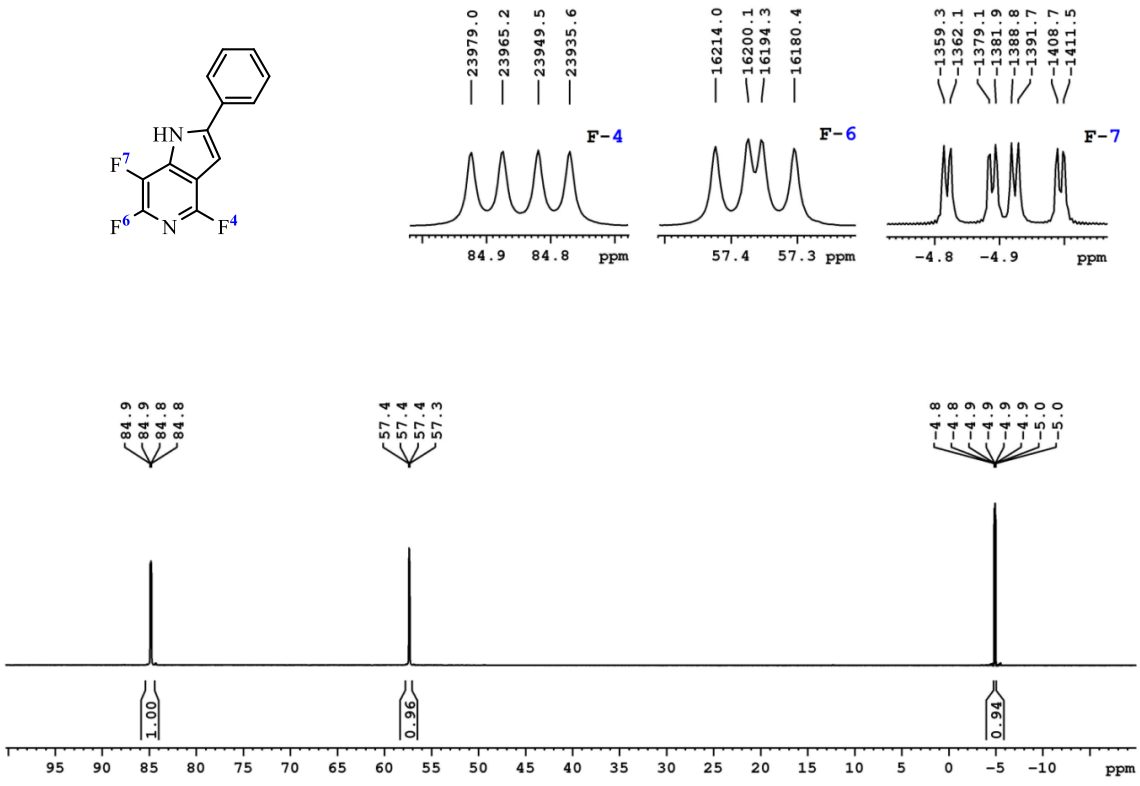
IR (KBr) for **3**



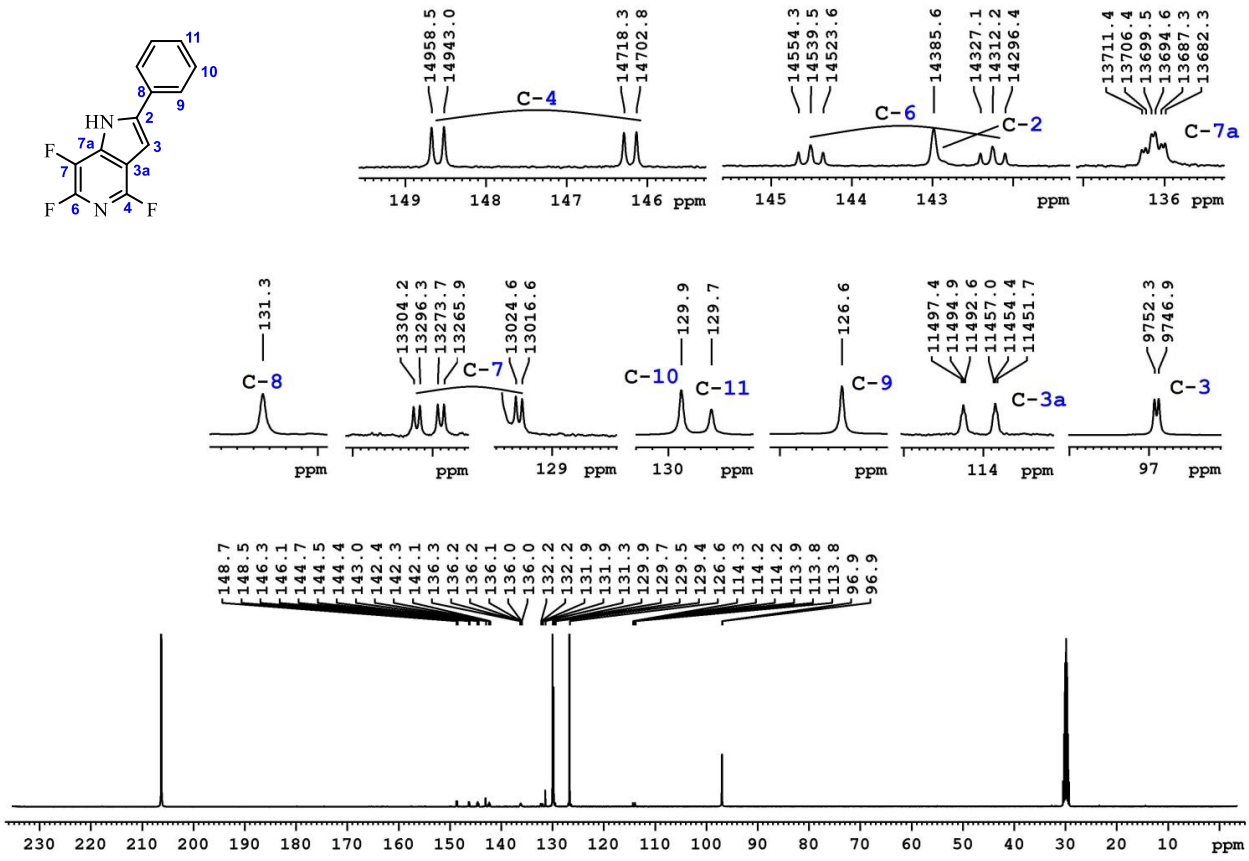
^{1}H NMR spectrum (CD_3CN, residual CH_3CN, δ_H = 1.94 ppm) Bruker Avance 300 (300.13 MHz) of **4**



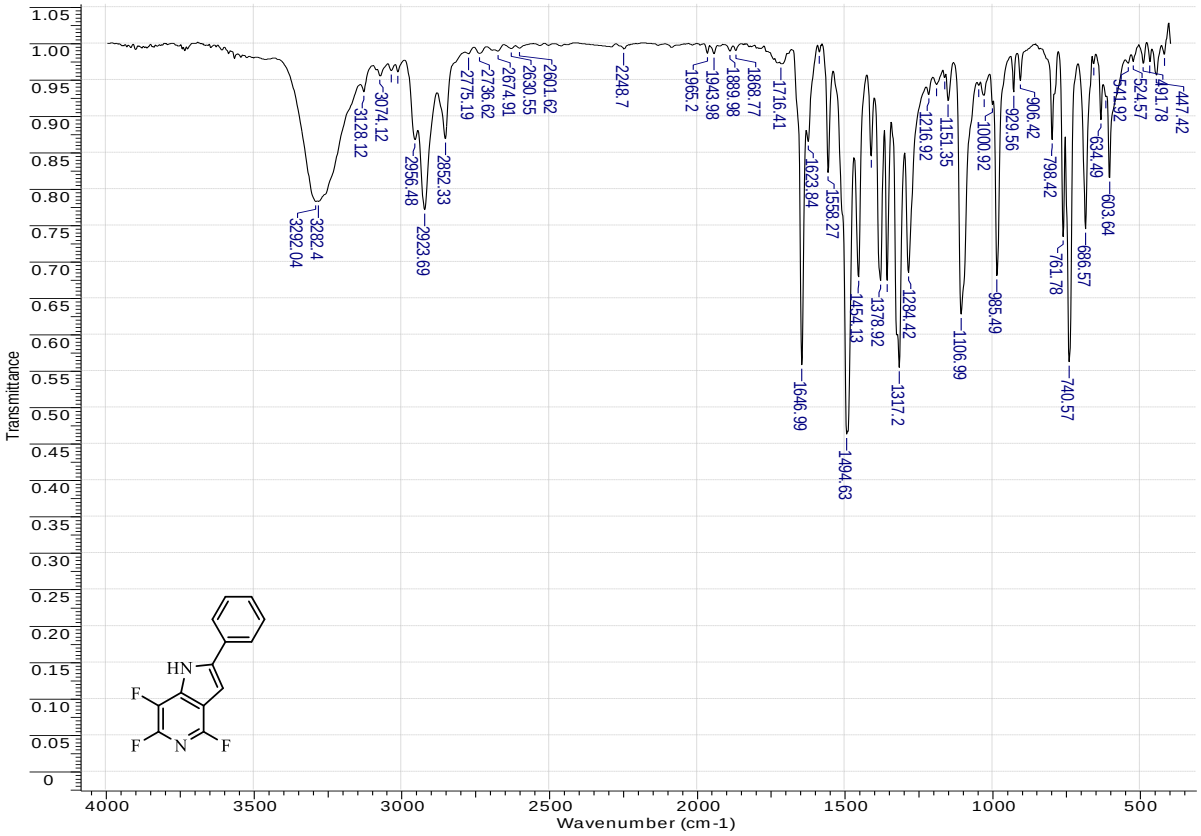
^{19}F NMR spectrum (CD_3CN, C_6F_6, δ_F = –163.0 ppm) Bruker Avance 300 (282.4 MHz) of **4**



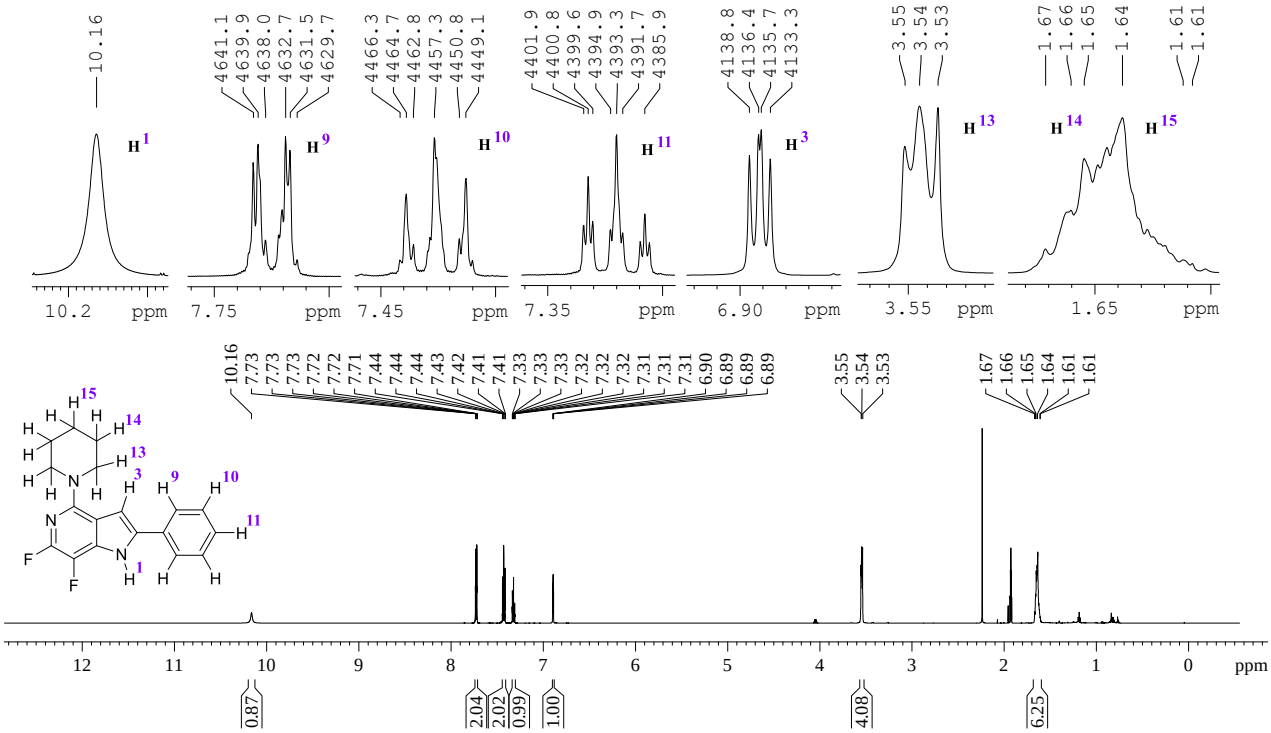
^{13}C NMR spectrum (acetone-d_6, δ_C = 29.8, 206.0 ppm) Bruker Avance 400 (100.6 MHz) of **4**



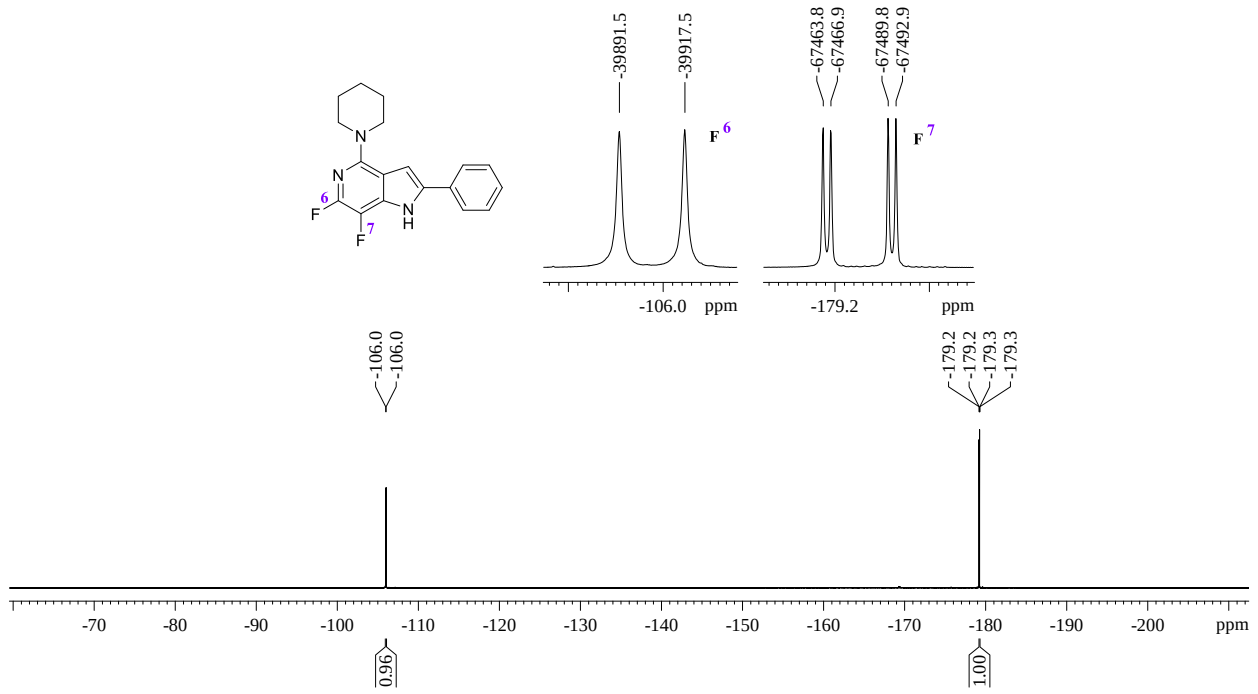
IR (KBr) for **4**



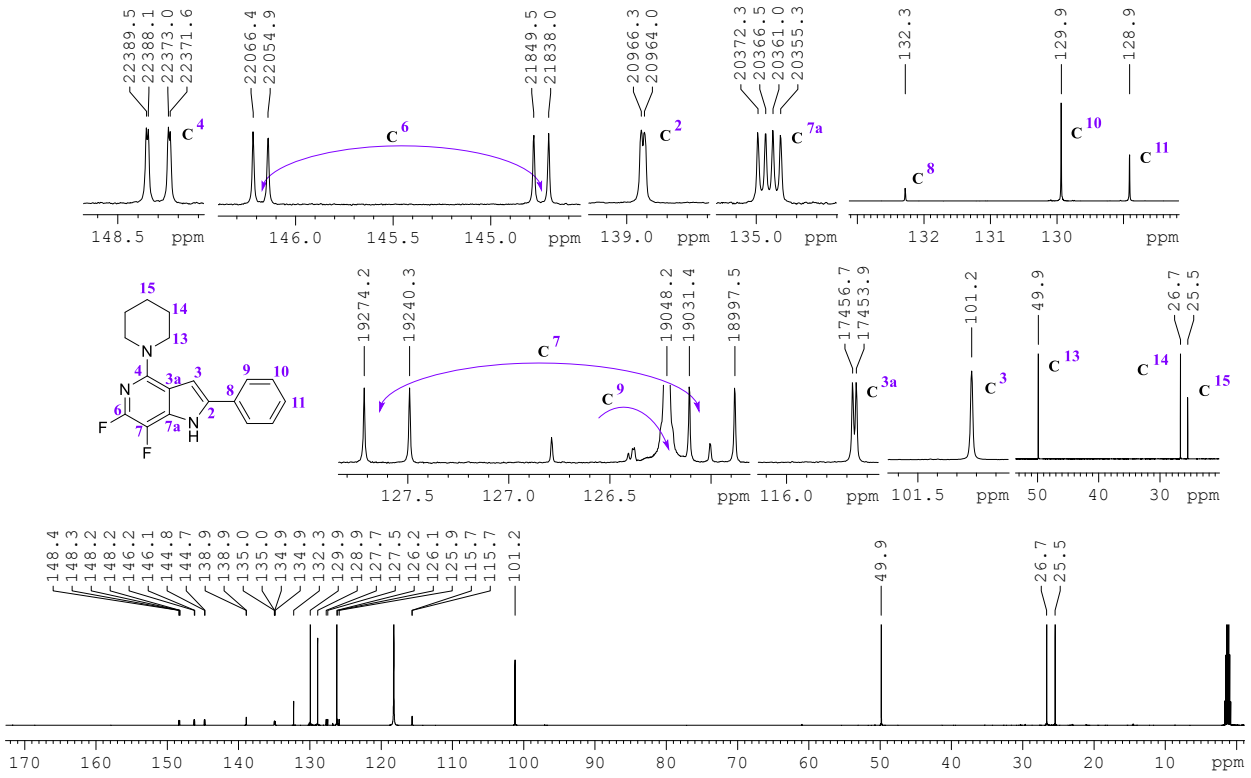
^{1}H NMR spectrum (CD_3CN, residual CH_3CN, δ_H = 1.94 ppm) Bruker Avance-600 (600.18 MHz) of **5**



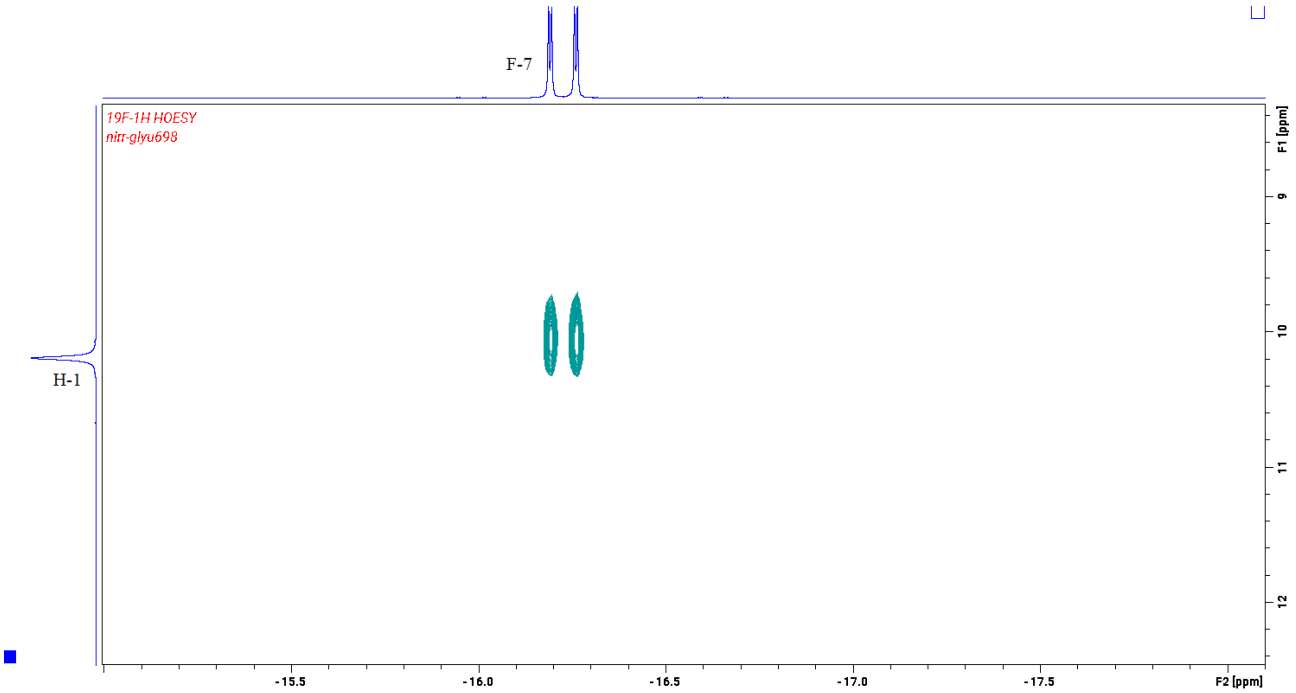
^{19}F NMR spectrum (CD_3CN) Bruker Avance-400 (376.46 MHz) of **5**



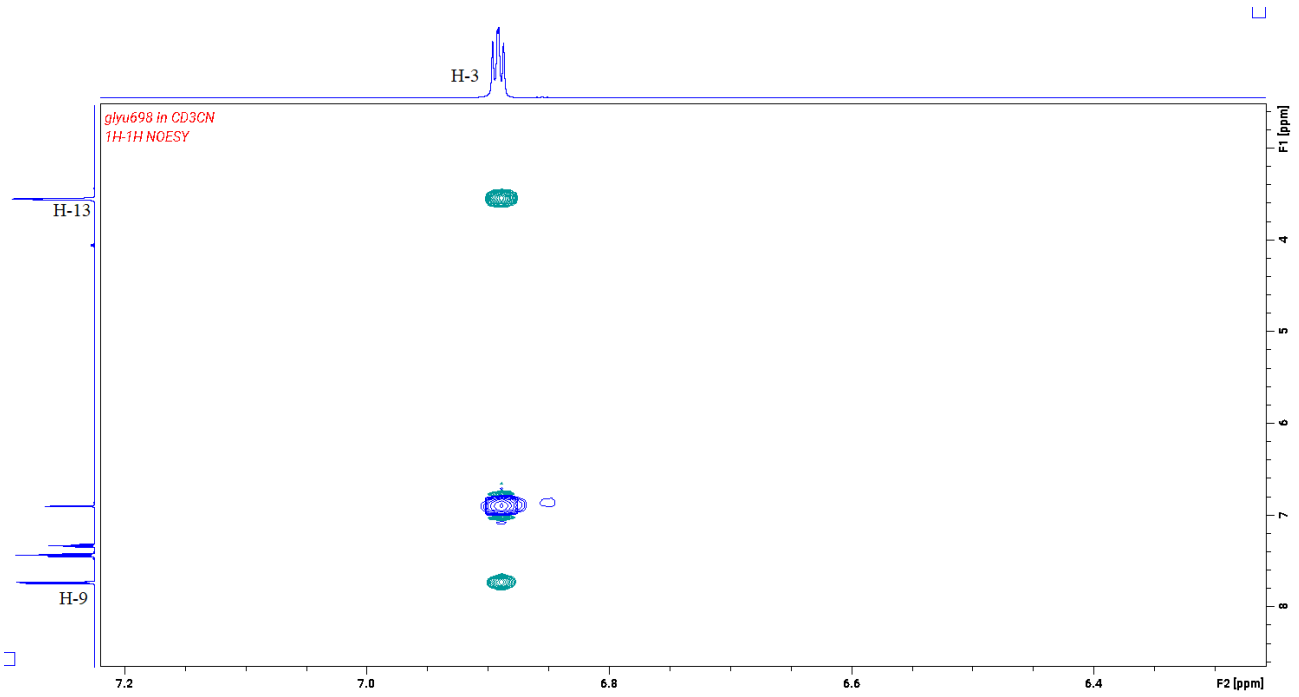
^{13}C NMR spectrum (CD_3CN, δ_C = 118.3, 1.3 ppm) Bruker Avance-600 (150.93 MHz) of **5**



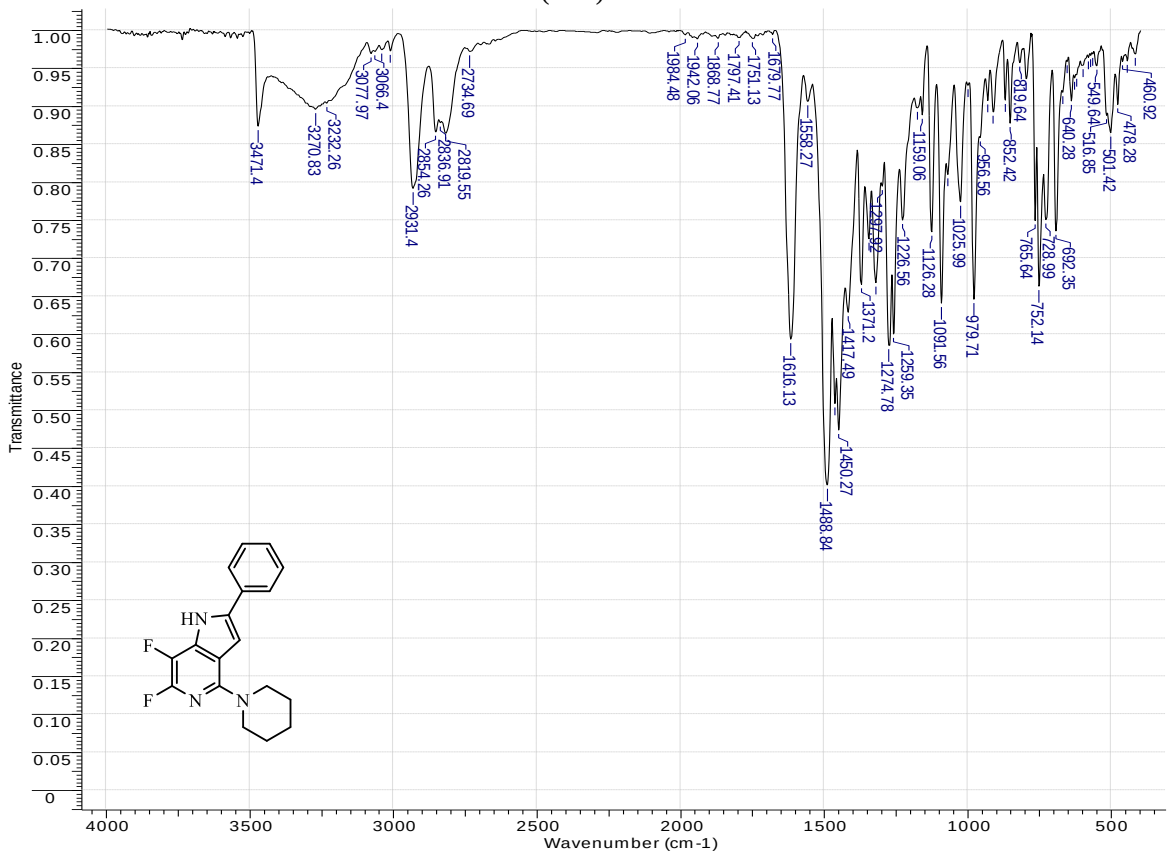
NMR HOESY ^{19}F-^{1}H spectrum fragment for **5**



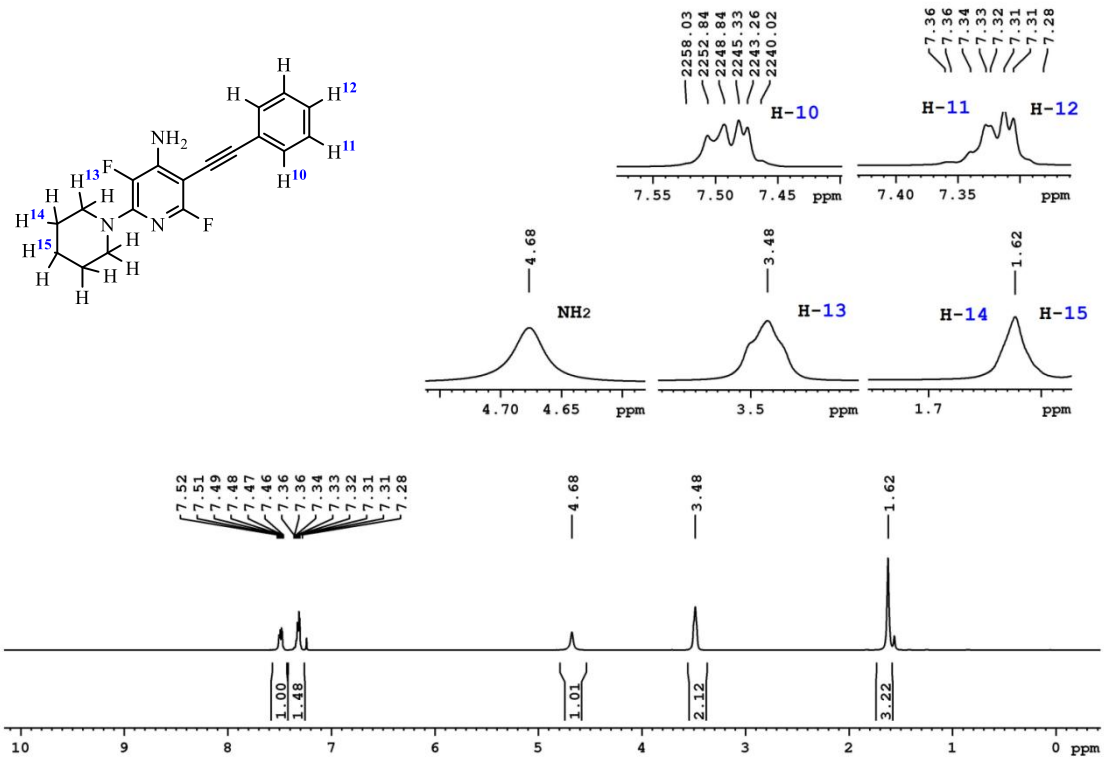
NMR NOESY ^{1}H – ^{1}H spectrum fragment for **5**



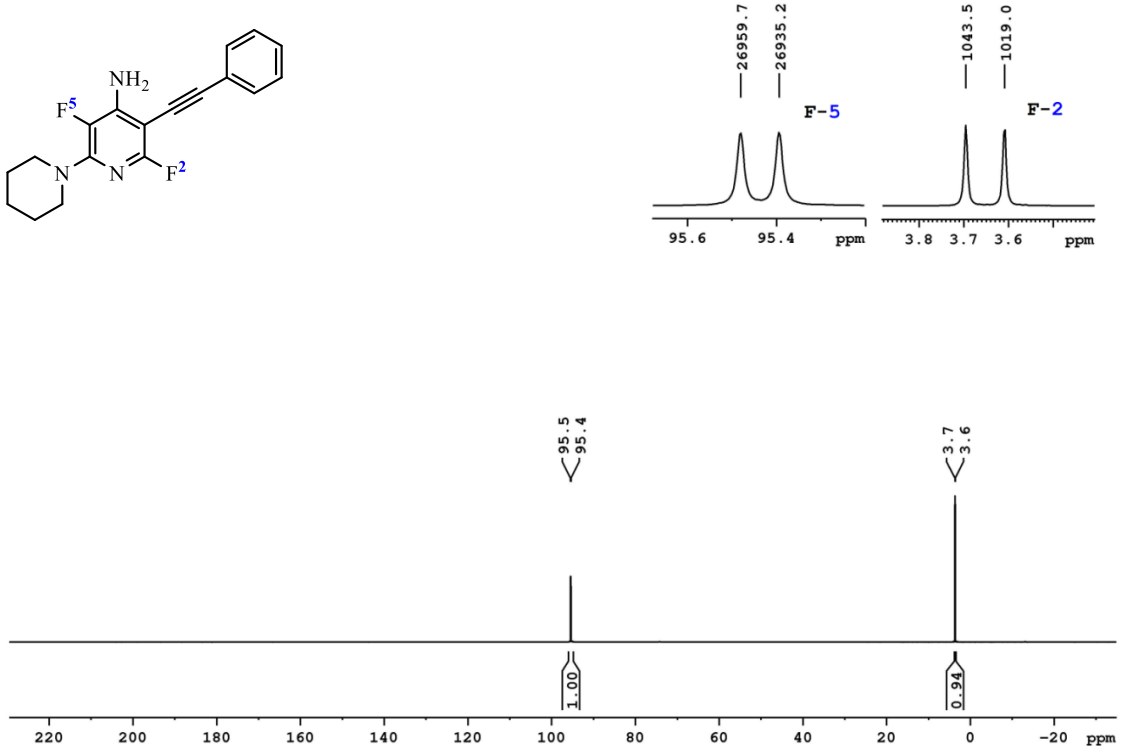
IR (KBr) for **5**



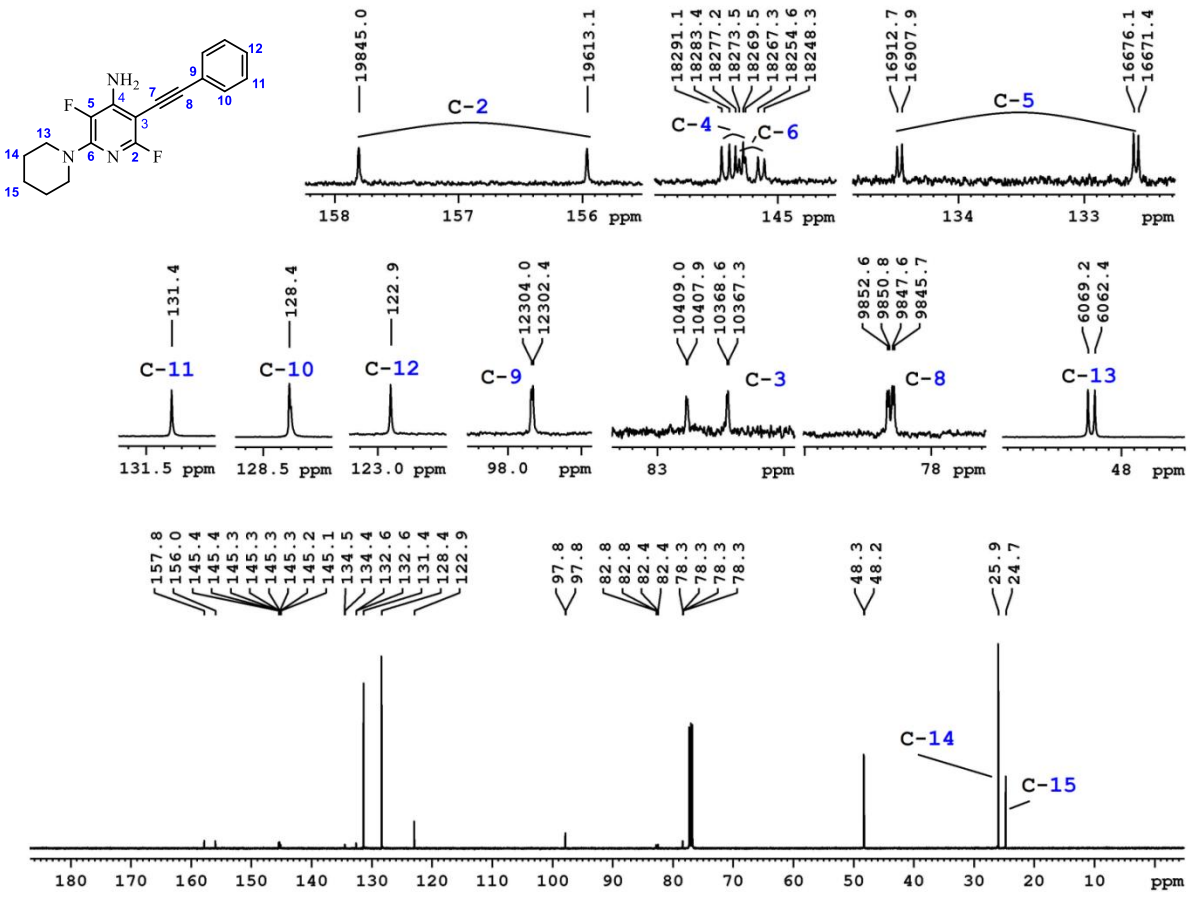
^{1}H NMR spectrum ($CDCl_3$, residual $CHCl_3$ δ_H = 7.24 ppm) Bruker Avance 300 (300.13 MHz) of **6**



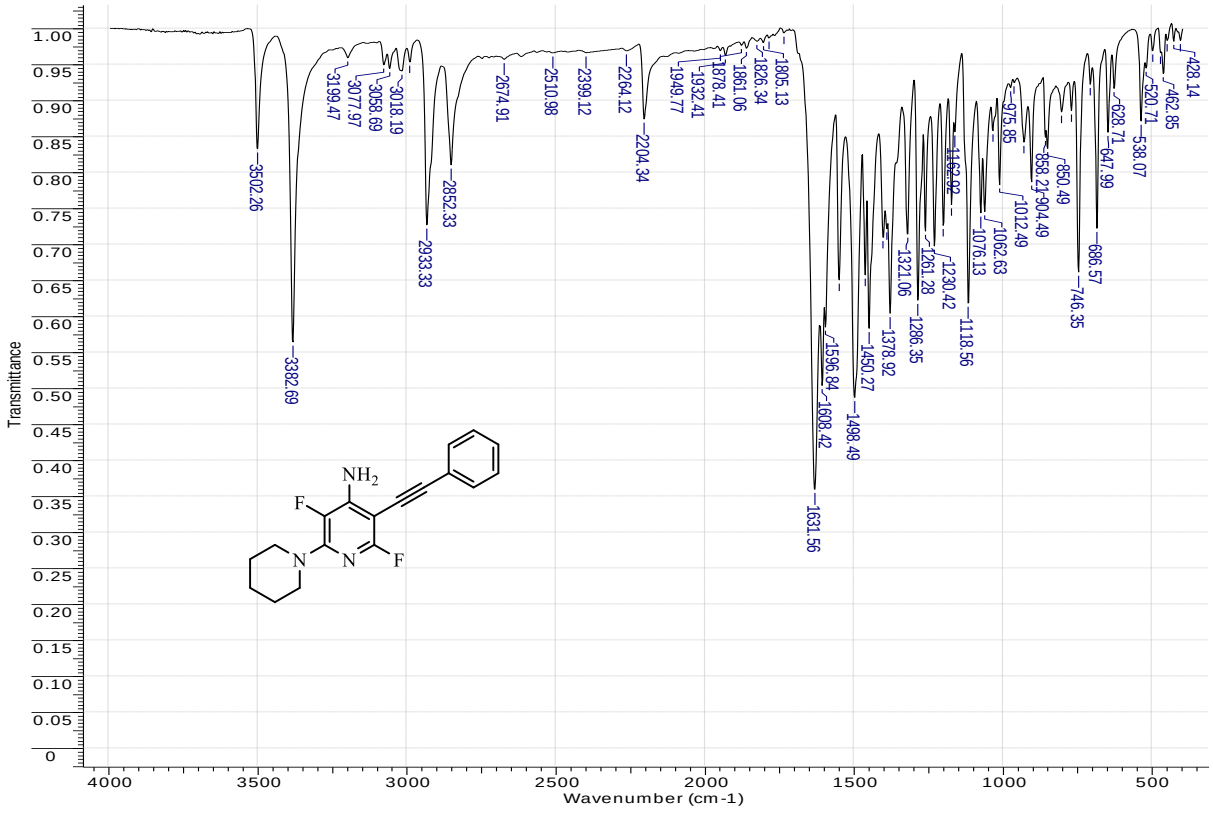
^{19}F NMR spectrum ($CDCl_3$, C_6F_6, δ_F = –163.0 ppm) Bruker Avance 300 (282.4 MHz) of **6**



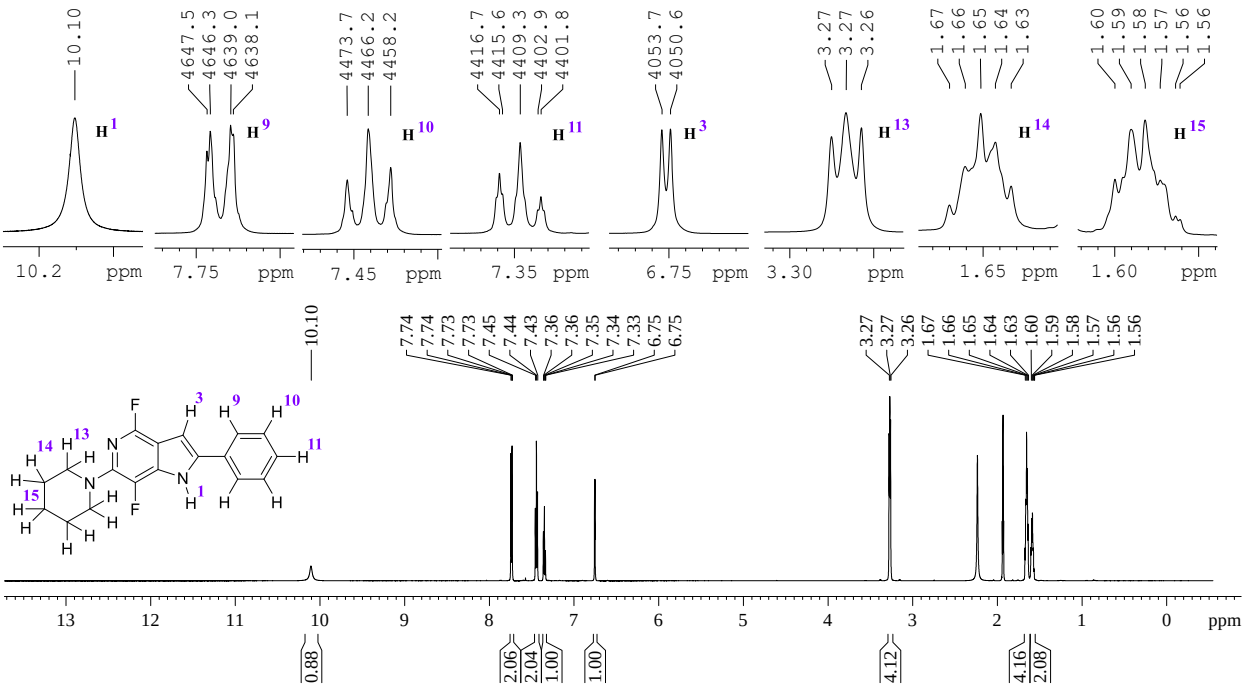
^{13}C NMR spectrum ($CDCl_3$, δ_C = 77.0 ppm) Bruker DRX-500 (125.8 MHz) of **6**



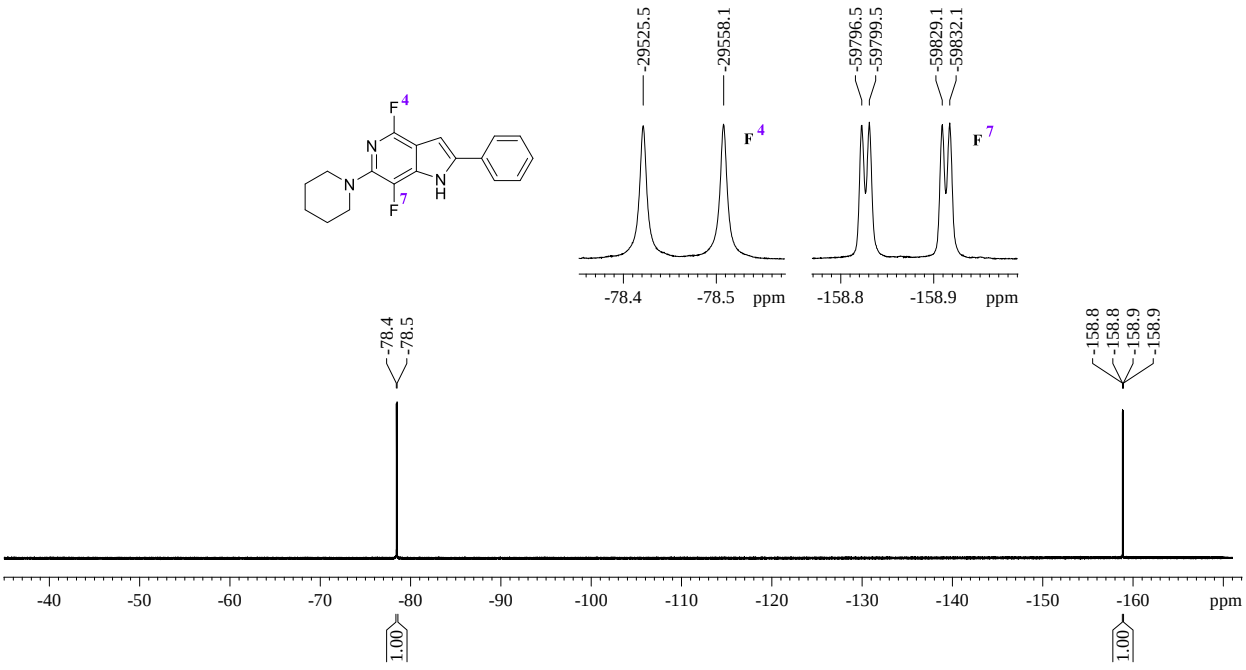
IR (KBr) for **6**



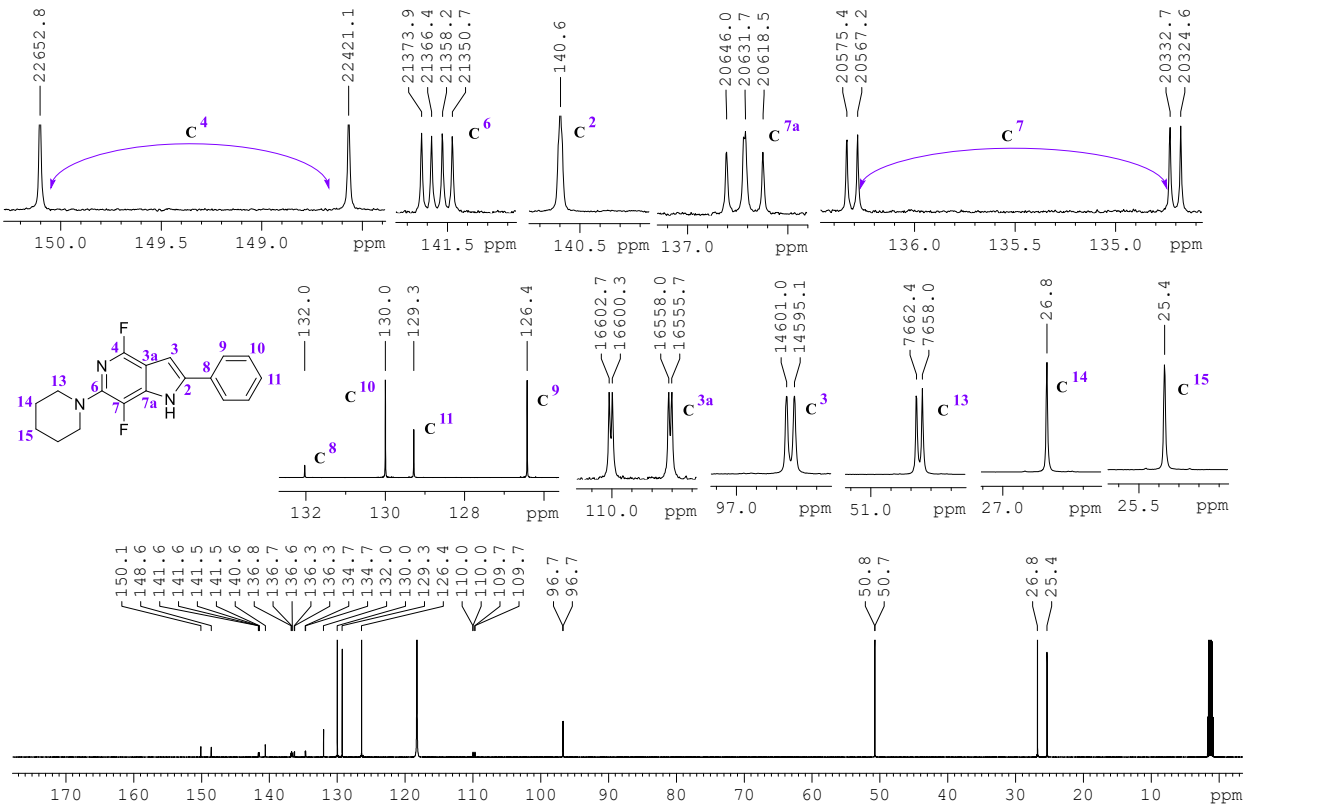
^{1}H NMR spectrum (CD_3CN, residual CH_3CN, δ_H = 1.94 ppm) Bruker Avance-600 (600.18 MHz) of **7**



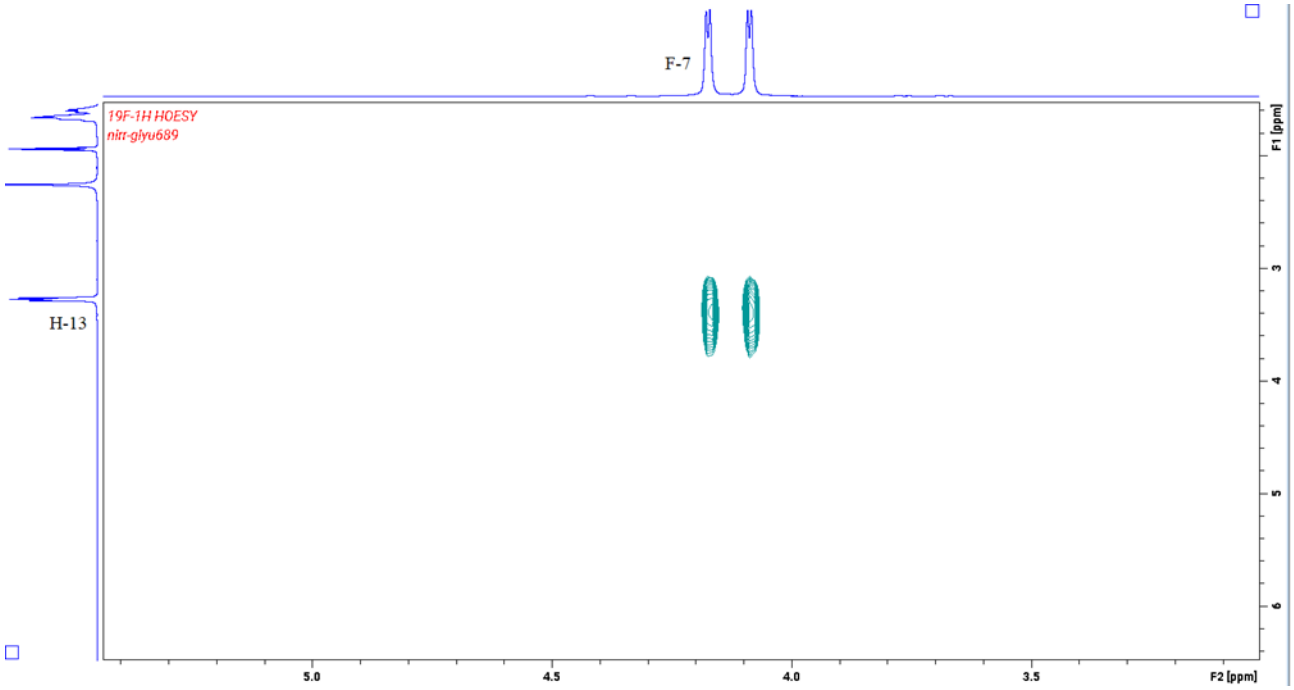
^{19}F NMR spectrum (CD_3CN) Bruker Avance-400 (376.46 MHz) of **7**



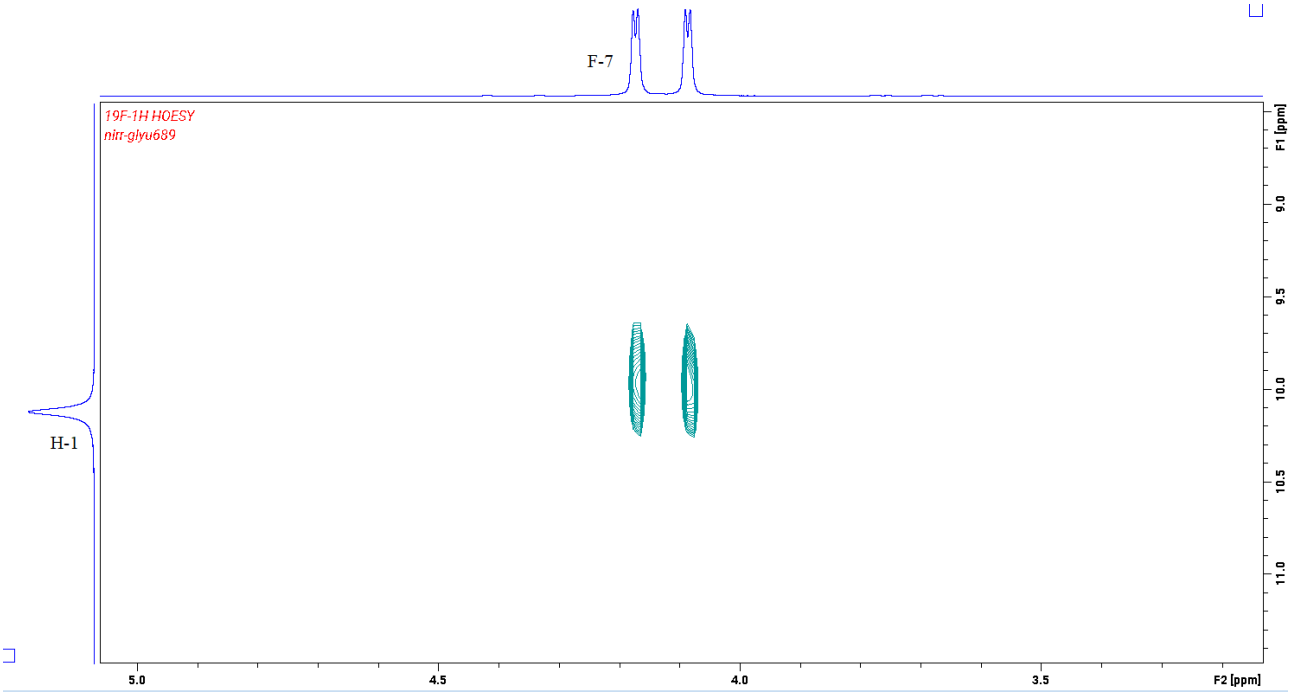
^{13}C NMR spectrum (CD_3CN, δ_C = 118.3, 1.3 ppm) Bruker Avance-600 (150.93 MHz) of **7**



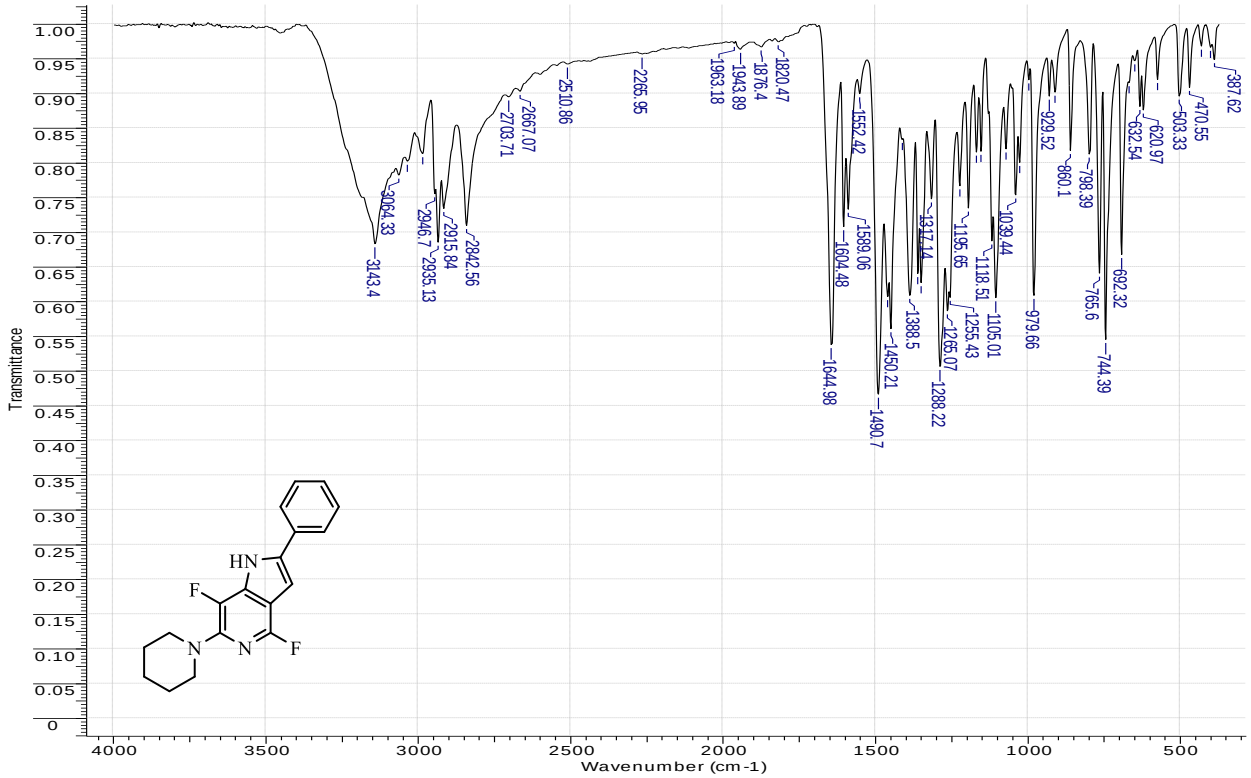
NMR HOESY ^{19}F-^{1}H spectrum fragment for **7**



NMR HOESY ^{19}F-^{1}H spectrum fragments for **7**



IR (KBr) for **7**



Data of quantum chemical calculations

***Methods*.** Potential energy curves for the reactions of nucleophilic substitution of the fluorine atom in polyfluoroarenes **3** and **4** were calculated using the density functional theory, the CAM-B3LYP/6-31G(d) method. Stationary points of the potential energy surfaces corresponding to the pre-reaction complex, the transition state of the reaction, and the post-reaction complex were located. The assignment was confirmed by IRC (Intrinsic Reaction Coordinate) calculations. All these calculations were performed using the GAMESS software package [M.W. Schmidt, K.K. Baldridge, J.A. Boatz, S.T. Elbert, M.S. Cordon, J.J. Jensen, S. Koseki, N. Matsunaga, K.A. Nguyen, S. Su, T.L. Windus, M. Dupuis, J.A. Montgomery. *J. Comput. Chem*., 1993, **14**, 1347; https://doi.org/10.1002/jcc.540141112], calculation parameters were chosen 'by default'. The low level of computations we chose turned out to be sufficient for solving a qualitative problem: interpreting experimental data. The energetic preference of the formation of the structures with N-H···N hydrogen bonding compared to the nucleophilic substitution of fluorine atoms (see Figure 1 (*b*, *c*) in the main text) is so obvious that it is unlikely to disappear with an increase in the level of calculations.

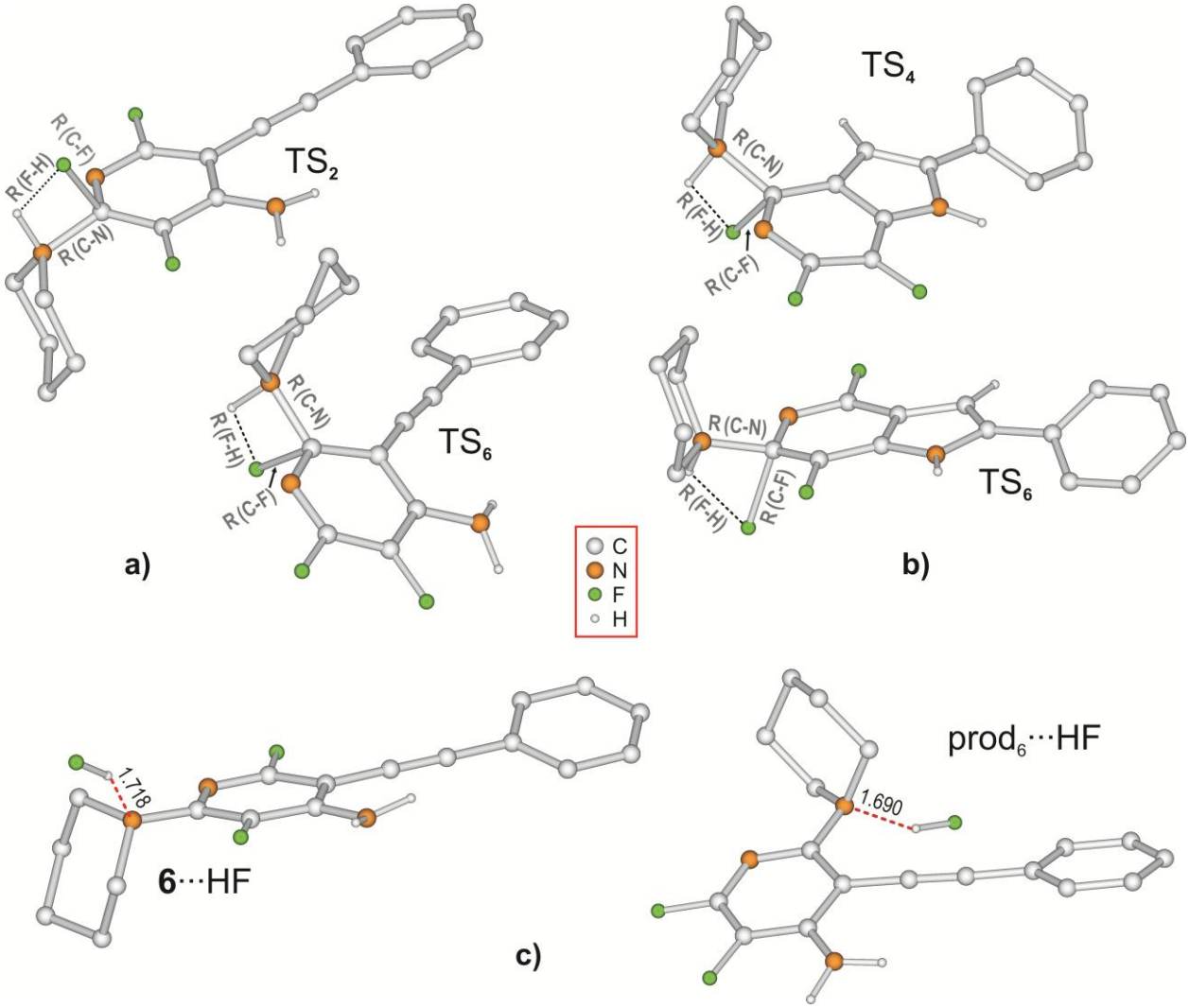


Figure S1 Structures of the transition states (TS_i, *i* is the position under consideration) of nucleophilic substitution of fluorine atoms in the interaction of compounds (*a*) **3** and (*b*) **4** with piperidine. Designations of the characteristic interatomic distances, the numerical values of which are given in Table S1. (*c*) Post-reaction complexes for **3**. C–H bonds are shown only in pyrrole rings.

Table S1 Relative energies (ΔE)[a)] and characteristic interatomic distances (R)[b)] for stationary structures of potential curves of the reaction of nucleophilic substitution of fluorine atoms in the interaction of compounds **3** and **4** with piperidine

Compound	**3**					
E (**3**+pip) a.u.	-908.164949 + (-1251.756137) = -1159.921131 (0)[c)]					
position	2			6		
structure	min_2	TS_2	**6** ··· HF	min_6	TS_6	$prod_6$ ··· HF
ΔE kcal/mol	-5.0	29.2	-12.9	-3.6	34.0	-13.3
R (C-F) Å	1.331	1.863	-	1.332	1.853	-
R (C-N) Å	3.149	1.523	1.404	3.024	1.541	1.416
R (F-H) Å	2.470	1.604	0.959	2.564	1.556	0.969
Compound	**4**					
E (**4**+pip) a.u.	-908.225584 + (-251.756137) = -1159.981721 (0)[c)]					
position	4			6		
structure	min_4	TS_4	**5** ··· HF	min_6	TS_6	**7** ··· HF
ΔE kcal/mol	-3.4	34.0	-12.1	-4.8	32.5	-10.7
R (C-F) Å	1.337	1.840	-	1.337	1.806	-
R (C-N) Å	3.053	1.541	1.421	3.216	1.535	1.411
R (F-H) Å	2.475	1.636	0.973	2.397	1.721	0.960
Compound	**4** ··· pip					
E (**4** ··· pip +pip) a.u.	-1160.002788 + (-251.756137) = -1411.758925 (0)[c)]					
position	4			6		
structure	min_4	TS_4	pip ··· **5** ··· HF	min_6	TS_6	pip ··· **7** ··· HF
ΔE kcal/mol	-3.0	32.4	-11.6	-4.5	34.5	-10.0
R (C-F) Å	1.338	1.854	-	1.342	1.790	-
R (C-N) Å	3.149	1.515	1.422	3.395	1.543	1.415
R (F-H) Å	2.727	1.713	0.973	2.224	1.747	0.961

[a)] The sum of the total energies of a molecular of the polyfluoroarene and a piperidine molecule was taken as zero; see footnote [c)].

[b)] Designations of the characteristic interatomic distances are given in Fig. S1 on the images of structures TS_i.

[c)] Calculation of the energy defined as zero value.

Total energy and Cartesian coordinates of structure TS_{nhn}

This structure corresponds to the transition state of transformation of min_6 into the structure with a hydrogen bond N–H···N.

E = -1159.988052 a.u.

C	-1.9087797404	1.3182091261	-3.4673355033
C	-2.1428560464	0.5385754045	-2.3303551706
C	-2.6714919989	-0.7458817848	-2.4929766326
C	-2.9542617321	-1.2390814372	-3.7598880701
C	-2.7220397550	-0.4543399293	-4.8833101177
C	-2.2019971455	0.8275400963	-4.7313636213
C	-1.8413427057	1.0664348434	-0.9969147195
N	-1.5367016539	0.2086637921	0.0574023518
C	-1.2847951767	0.9433758410	1.1739513970
C	-1.4680564634	2.3010720788	0.8492655266
C	-1.8226061669	2.3545636757	-0.5367759357
C	-0.9206313654	0.5700214073	2.4632061549
C	-0.7163374331	1.5902956984	3.3602642961
N	-0.8839295118	2.8772036362	3.0891630178
C	-1.2523918896	3.2123110189	1.8840139468
F	-0.7468490577	-0.7168149195	2.7967295600
F	-0.3107647235	1.2772608540	4.5939578834
F	-1.4165344459	4.5134303782	1.6374683048
C	2.3637492128	-0.7815648413	2.6901199916
N	2.1033260147	0.0774770060	1.5373087835
C	3.0041554137	-0.2103411487	0.4265004786
C	2.7790982620	-1.6413258736	-0.0538820158
C	2.9733376434	-2.6306605190	1.0979070960
C	2.1162842764	-2.2369450067	2.3034622765
H	-1.2958078222	-0.7651055284	-0.0434854130
H	-1.4770339533	2.3075619570	-3.3548242174
H	-2.8941047143	-1.3547231578	-1.6214189872
H	-3.3675561762	-2.2371289394	-3.8676207253
H	-2.9453913667	-0.8389552021	-5.8732964906
H	-2.0130401855	1.4449596019	-5.6039653922
H	-2.0720602516	3.2380118755	-1.1043845508
H	2.1925159838	1.0521792572	1.8091317745
H	1.6952236546	-0.4842725178	3.5027034694
H	3.4022415408	-0.6783292551	3.0583733836
H	2.3268609939	-2.8908416765	3.1568711697
H	4.0676223796	-0.0941430027	0.7105203890
H	2.8026975945	0.5014474511	-0.3806709209
H	1.7555834817	-1.7213786806	-0.4410841180
H	3.4601205383	-1.8707236062	-0.8810037203
H	2.7389735351	-3.6507086451	0.7735020378
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H	1.0540617325	-2.3466613938	2.0593909078