Supporting Information

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1. General Considerations

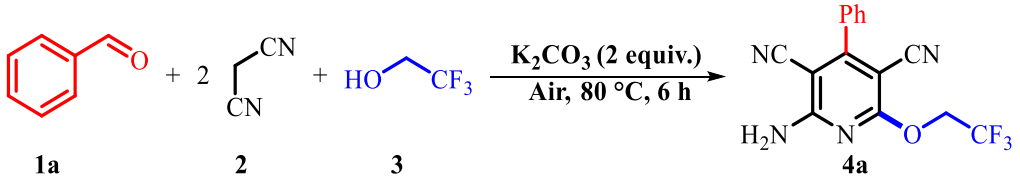
1.1.1 Reagent Information:

Unless otherwise stated, all the catalytic reactions were carried out in screw cap reaction tube with magnetic stirring under air atmosphere. All the chemicals like benzaldehyde, malononitrile, TFE utilized in the experiments were purchased from commercial source and used as received. For column chromatography silica gel (100-200 mesh) was obtained from SRL Co. During elution petroleum ether and ethyl acetate mixture was used.

1.1.2 Analytical Information:

^{1}H NMR, ^{13}C NMR spectroscopy and HRMS were used to characterize all the isolated compounds. Copies of the ^{1}H NMR, ^{13}C NMR and HRMS spectra were attached in this supporting information. All NMR spectra were recorded on a BRUKER 400 MHz to 700 MHz instrument. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to residual $CHCl_3$ (7.26 ppm) or DMSO-d_6 (2.5 ppm) in the deuterated solvent, unless otherwise stated. All ^{13}C NMR spectra were reported in ppm relative to $CDCl_3$ (77.23 ppm) or DMSO-d_6 (39.65 ppm). High-resolution mass spectra (HRMS) were recorded using an Agilent TOF/6500 series Q-TOF mass spectrometer.

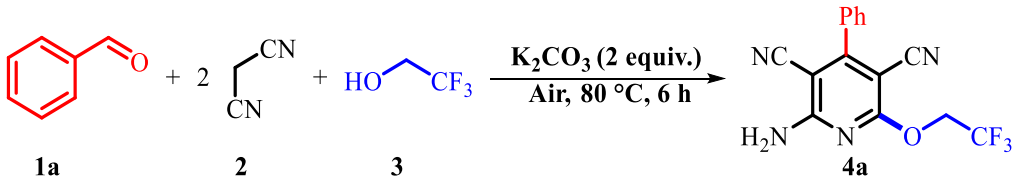
1.1.3. General Procedure for synthesis of α-(OCH_2CF_3) substituted pyridines



1a **2** **3** **4a**

To perform the reaction, benzaldehyde (0.125 mmol), malononitrile (0.25mmol), TFE (1.0 ml), and K_2CO_3 (2 equiv.) were added to a sealed reaction tube. The reaction mixture was stirred vigorously at 80 °C for 6h, during which time the progress of the reaction was monitored using TLC visualized under short-UV. Upon completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (EtOAc, 25 mL). The mixture was then filtered to remove any solid impurities. The filtrate was washed with distilled water (3 × 20 mL) to eliminate residual salts and other contaminants. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography, using petroleum ether/ethyl acetate as the eluent, to produce the desired product as a yellow solid in 92% yield (36.58 mg).

1.1.4. General procedure for scale-up reaction:

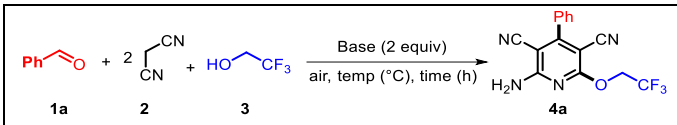


1a **2** **3** **4a**

A round-bottomed flask was charged with benzaldehyde (510 µL, 5 mmol), malononitrile (555.12 µL, 10 mmol) and K_2CO_3 (2 equiv.) were then added. The mixture was dissolved in 10 mL of TFE (required TFE = 359 µL) and refluxed at 80 °C for 6h under ambient conditions. Upon completion, the reaction mixture was cooled to room temperature. It was then diluted with ethyl acetate (EtOAc). The mixture was then filtered to remove any solid impurities. The filtrate was washed with distilled water (3 × 20 mL) to eliminate residual salts and other contaminants. The organic layer was dried over anhydrous sodium sulphate (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (100-200 mesh) using a

gradient eluent system of petroleum ether and ethyl acetate produced desired product as a yellow solid in 70% yield (1.11 gm).

2. Table S1: Optimization of reaction conditions[a]



1a 2 3 4a

Entry	Base (equiv.)	T (°C)	Time (h)	Yield (%)
1	K_2CO_3	80	12	92
2	**K_2CO_3**	**80**	**6**	**92**
3	K_2CO_3	100	6	86
4	K_2CO_3	110	6	82
5	Cs_2CO_3	80	6	80
6	Na_2CO_3	80	6	60
7	NaOH	80	6	87
8	KOH	80	6	90
9	DBU	80	6	N.D
10	DABCO	80	6	N.D
11	^{t}BuONa	80	6	50
12	^{t}BuOLi	80	6	53
13	^{t}BuOK	80	6	49
14	K_2CO_3	RT	6	68
15	-	80	6	N.D

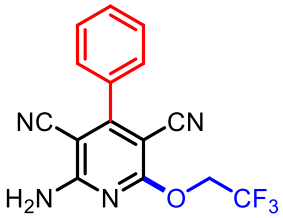
[a]Reaction conditions: **1a** (0.125 mmol), **2** (0.25 mmol), TFE (1 mL), Base (2 equiv.), temp. (80 °C), time (6 h), under air atm.

Table S2: Summary of the electronic effect of substituents on reaction yield

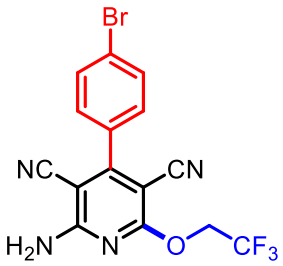
Substituent category	Substituents	Electronic effect	Yield (%)
EWG (para)	–F (4c), $-NO_2$ (4e), –CN (4f), –Br (4b), –Cl (4d)	–I / –M	85–95%
EWG (meta)	–Cl (4g) and –Br (4h)	–I	86% and 82%
EWG (Ortho-substituted)	–Br (4i), –F (4j), –Cl (4k), 2–F–3–Cl (4l)	Steric + electronic	73-80%
EDG (para)	–Me (4m), –OMe (4n), $-OCH_2C_6H_5$ (4o), –propargyloxy (4p)	+M/+I	64-76%
EDG (meta and para)	3,4–OMe (4q), 3–OH–4–OMe (4r), 3,4,5–OMe (4s)	(+M)	62-72%

EDG (meta)	$-OCH_2C_6H_5$ (4t) and –OPh (4u)	Partial effect of -I	70% and 73%
EDG (ortho)	–Me (4v) and 4–Br–2–Me (4w)	Steric + electronic	59% and 69%
Heteroaryl	Thiophene–3–CHO	π-rich heteroarene	~54%

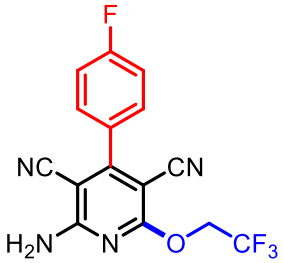
3. Characterization data



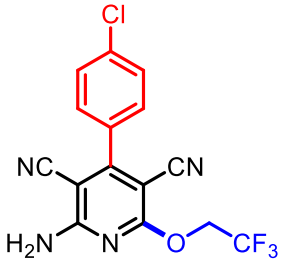
2-amino-4-phenyl-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, entry 4a): Yellow solid (**Isolated yield**: 92 %, 36.58 mg), mp: 208-209 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (m, 5H), 5.73 (s, 2H), 4.85 (q, *J* = 8.1 Hz, 2H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.6, 161.9, 160.5, 131.5, 129.5, 129.4, 128.7, 122.0, 115.2, 113.6, 87.1, 86.4, 63.5 (q, *J* = 37.3 Hz), **^{19}F NMR** (565 MHz, $CDCl_3$) δ -73.39. **HRMS (ESI)** calculated for $C_{15}H_{10}F_3N_4O$ [(M+H)+] is 319.0810 and found 319.0811.



2-amino-4-(4-bromophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, entry 4b): yellow solid (**Isolated yield**: 85%, 41.65 mg), mp: 204-206 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.81 – 7.64 (m, 2H), 7.42 – 7.26 (m, 2H), 5.79 (s, 2H), 4.84 (d, *J* = 8.1 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.2, 160.2, 160.1, 132.4, 129.9, 125.9, 123.4, 121.6, 114.6, 113.0, 86.4, 85.6, 63.1 (q, *J* = 37.2 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.42. **HRMS (ESI)** calculated for $C_{15}H_9BrF_3N_4O$ [(M+H)+] is 396.8465 and found 396.8464.

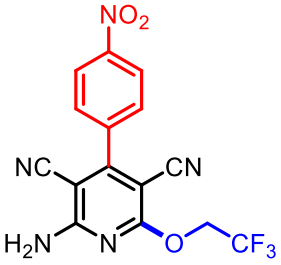


2-amino-4-(4-fluorophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4c): yellow solid (**Isolated yield**: 95%, 39.91 mg), mp: 192-194 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.30 – 7.21 (m, 2H), 5.85 (s, 2H), 4.84 (q, *J* = 8.1 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.2, 164.4, 163.5, 160.5 (d, *J* = 20.6 Hz), 132.0, 130.8 (d, *J* = 8.9 Hz), 123.6, 116.5 (d, *J* = 22.1 Hz), 114.9, 113.4, 86.6, 85.9, 63.2 (q, *J* = 37.2 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.83, -108.39. **HRMS (ESI)** calculated for $C_{15}H_9F_4N_4O$ [(M+H)+] is 337.0772 and found 337.0771.

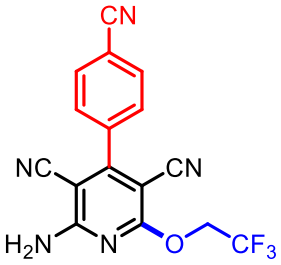


2-amino-4-(4-chlorophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4d): yellow solid (**Isolated yield**: 89%, 39.22 mg), mp: 198-200 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 – 7.52 (m, 2H), 7.50 – 7.44 (m, 2H), 5.82 (s, 2H), 4.84 (q, *J* = 8.1 Hz, 2H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.2, 160.22, 160.20, 137.5, 131.1,

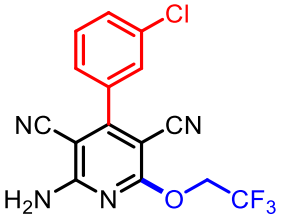
129.7, 129.4, 129.3, 114.6, 113.0, 86.4, 85.6, 63.3 (q, *J* = 37.3 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.90. **HRMS (ESI)** calculated for $C_{15}H_9ClF_3N_4O$ [(M+H)+] is 353.2705 and found 353.2706 .



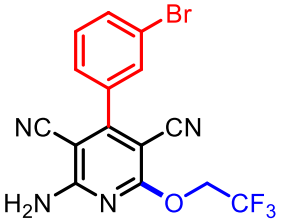
2-amino-4-(4-nitrophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4e): Orange solid (**Isolated yield**: 94%, 42.66 mg,), mp: 191-193 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.61 – 8.28 (m, 2H), 7.83 – 7.64 (m, 2H), 5.92 (s, 2H), 4.87 (q, *J* = 8.1, 2H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.3, 160.3, 159.1, 149.4, 139.0, 129.9, 124.5, 121.7, 114.3, 112.8, 86.7, 85.8, 63.4 (q, *J* = 37.5 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.78. **HRMS (ESI)** calculated for $C_{15}H_8F_3N_5O_3$ [(M+NH_4)+] is 381.3026 and found 381.3027.



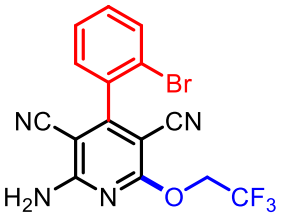
2-amino-4-(4-cyanophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4f): White solid **(Isolated yield:** 93%, 39.88 mg), mp: 195-197 °C**; ^{1}H NMR** (700 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.12 – 8.06 (m, 2H), 7.84 – 7.76 (m, 2H), 5.13 (q, *J* = 8.8 Hz, 2H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ 163.7, 161.0, 160.2, 138.9, 133.2, 130.0, 124.6, 118.6, 115.1, 114.3, 113.6, 85.2, 83.5, 62.6 (q, *J* = 35.5 Hz). **^{19}F NMR** (377 MHz, DMSO) δ -73.90. **HRMS (ESI)** calculated for $C_{16}H_9F_3N_5O$ [(M+H)+] is 344.2215 and found 344.2214.



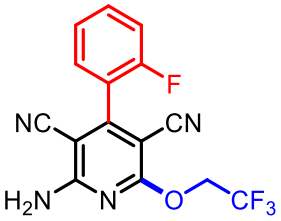
2-amino-4-(3-chlorophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4g): yellow solid (**Isolated yield**: 86%, 37.90 mg), mp: 193-195 °C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 7.47 (m, 3H), 7.41 (dt, *J* = 7.4, 1.5 Hz, 1H), 5.79 (s, 2H), 4.85 (q, *J* = 8.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.2, 160.2, 159.9, 135.1, 134.5, 131.3, 130.5, 128.4, 126.5, 121.2, 114.4, 112.8, 86.7, 85.9, 63.2 (q, *J* = 37.3 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.42. **HRMS (ESI)** calculated for $C_{15}H_8ClF_3N_4O$ [(M+Na)+] is 375.0310 and found 375.0311.



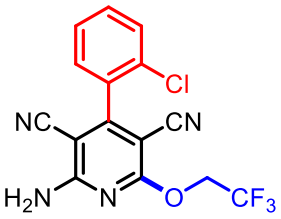
2-amino-4-(3-bromophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4h): yellow solid (**Isolated yield**: 82%, 40.18 mg), mp: 200-202 °C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.1, 2.0 Hz, 1H), 7.72 (t, *J* = 1.8 Hz, 1H), 7.53 – 7.46 (m, 2H), 5.83 (s, 2H), 4.90 (q, *J* = 8.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.3, 160.3, 159.9, 134.8, 134.3, 131.3, 130.8, 127.1, 124.1, 123,2, 114.6, 112.9, 86.9, 86.1, 63.3 (q, *J* = 37.2 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.42. **HRMS (ESI)** calculated for $C_{15}H_8BrF_3N_4O$ [(M+Na)+] is 418.9792 and found 418.9791.



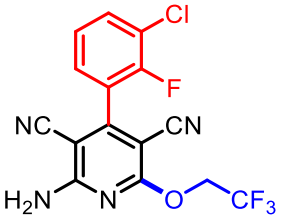
2-amino-4-(2-bromophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4i): yellow solid (**Isolated yield**: 76%, 37.24 mg), mp: 201-203 °C **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.49 (td, *J* = 7.6, 1.2 Hz, 1H), 7.41 (td, *J* = 7.8, 1.8 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.75 (s, 2H), 4.97 – 4.70 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8, 160.9, 159.8, 134.3, 133.6, 132.0, 129.4, 128.0, 124.0, 121.2, 113.9, 112.4, 87.9, 87.2, 62.93 (q, *J* = 35.1 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.74. **HRMS (ESI)** calculated for $C_{15}H_8BrF_3N_4O$ [(M+Na)+] is 418.9792 and 418.9791.



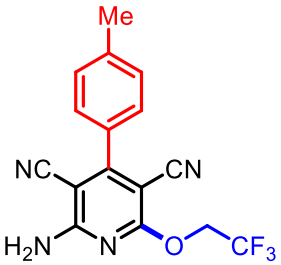
2-amino-4-(2-fluorophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4j): White solid **(Isolated yield:** 80%, 33.61 mg), mp: 188-200 °C; **^{1}H NMR** (700 MHz, DMSO-d_6) δ 8.28 (d, 2H), 7.71 – 7.63 (m, 1H), 7.58 (td, *J* = 7.5, 1.8 Hz, 1H), 7.47 (ddd, *J* = 9.7, 8.4, 1.0 Hz, 1H), 7.42 (td, *J* = 7.5, 1.1 Hz, 1H), 5.17 – 5.07 (m, 2H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ 163.6, 160.9, 157.8, 156.2, 133.5 (d, *J* = 8.3 Hz), 131.1, 125.5 (d, *J* = 3.2 Hz), 123.0, 121.9 (d, *J* = 15.3 Hz), 116.7 (d, *J* = 21.0 Hz)114.9, 114.1, 86.1, 84.3, 62.7 (q, *J* = 35.3 Hz). **^{19}F NMR** (377 MHz, DMSO) δ -73.42, -114.37. **HRMS (ESI)** calculated for $C_{15}H_9F_4N_4O$ [(M+H)+] is 337.0794 and 337.0793.



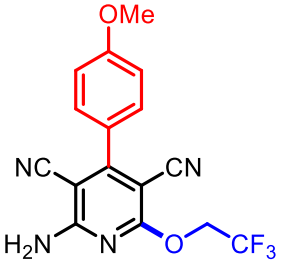
2-amino-4-(2-chlorophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4k): yellow solid (**Isolated yield**: 73%, 32.17 mg), mp: 197-199 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.53 – 7.41 (m, 2H), 7.32 (dd, *J* = 7.5, 1.8 Hz, 1H), 5.72 (s, 2H), 4.96 – 4.73 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$**)** δ 163.8, 159.8, 159.5, 132.2, 132.0, 130.5, 129.6, 127.5, 123.5, 121.7, 114.0, 112.4, 87.9, 87.2, 62.7 (q, *J* = 35.3 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.41. **HRMS (ESI)** calculated for $C_{15}H_9ClF_3N_4O$ [(M+H)+] is 353.0463 and found 353.0462.



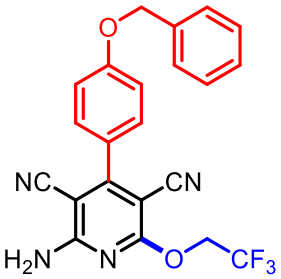
2-amino-4-(3-chloro-2-fluorophenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4l): yellow solid (**Isolated yield**: 77%, 35.31 mg), mp: 194-196 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.49 (m, 1H), 7.32 – 7.18 (m, 2H), 5.77 (s, 2H), 4.95 – 4.66 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.0, 159.9, 155.4 (d, *J* = 67.6 Hz), 153.2, 133.6, 128.3, 125.4, 123.9, 122.6 (dd, *J* = 32.2, 16.2 Hz), 121.2, 113.9, 112.4, 87.7, 86.9, 63.3 (q, *J* = 37.3 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.77, -114.72. **HRMS (ESI)** calculated for $C_{15}H_7ClF_4N_4O$ [(M+Na)+] is 393.0198 and 393.0199 .



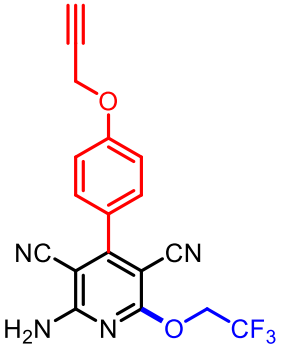
2-amino-4-(p-tolyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4m): yellow solid (**Isolated yield**: 76%, 31.55 mg), mp: 216-218 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.37 – 7.33 (m, 2H), 5.72 (s, 2H), 4.84 (q, *J* = 8.2 Hz, 2H), 2.43 (s, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.4, 161.8, 160.4, 130.2, 130.1, 129.9, 128.5, 123.7, 115.2, 113.6, 86.8, 86.0, 63.2 (q, *J* = 37.3 Hz), 21.6. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.97 **HRMS (ESI)** calculated for $C_{16}H_{12}F_3N_4O$ [(M+H)+] is 333.1013 and found 333.1012.



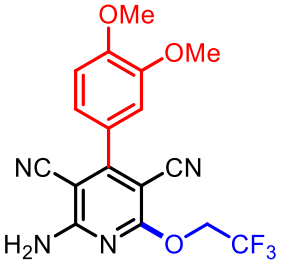
2-amino-4-(4-methoxyphenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4n): yellow semi solid (**Isolated yield**: 70%, 30.46 mg), mp: 215-217 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 2H), 7.09 – 7.00 (m, 2H), 5.74 (s, 2H), 4.83 (q, *J* = 8.1 Hz, 2H), 3.87 (s, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.4, 161.9, 161.2, 160.4, 130.2, 129.2, 125.0, 115.3, 114.5, 113.7, 86.3, 85.7, 63.1 (q, *J* = 37.1 Hz), 55.4. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.77. **HRMS (ESI)** calculated for $C_{16}H_{12}F_3N_4O_2$ [(M+H)+] is 349.0887 and found 349.0886.



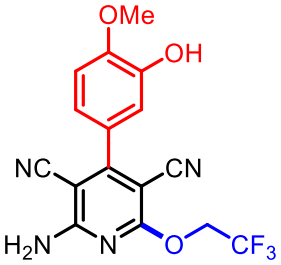
2-amino-4-(4-(benzyloxy)phenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4o): white solid (**Isolated yield**: 64%, 33.93 mg), mp: 218-220 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.6, 1.6 Hz, 2H), 7.48 – 7.39 (m, 4H), 7.39 – 7.32 (m, 1H), 7.16 – 7.08 (m, 2H), 5.74 (s, 2H), 5.12 (s, 2H), 4.91 – 4.77 (m, 2H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.5, 161.2, 160.4, 136.3, 130.4, 129.3, 128.8, 128.7, 128.4, 127.7, 121.9, 115.6, 115.45, 115.43, 86.5, 85.8, 70.3, 63.2 (q, *J* = 37.2 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.90. **HRMS (ESI)** calculated for $C_{22}H_{16}F_3N_4O_2$ [(M+H)+] is 425.1298 and found 425.1297.



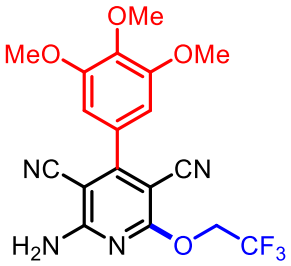
2-amino-4-(4-(prop-2-yn-1-yloxy)phenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile(Scheme 1, 4p): Green solid (**Isolated yield**: 68%, 31.62 mg), mp: 213-215 °C; **^{1}H NMR** (400 MHz,) δ 7.57 – 7.49 (m, 2H), 7.17 – 7.09 (m, 2H), 5.72 (s, 2H), 4.84 (q, *J* = 8.1 Hz, 2H), 4.76 (d, *J* = 2.4 Hz, 2H), 4.71 (d, *J* = 2.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.5, 161.1, 160.4, 160.0, 131.5, 130.3, 129.4, 125.9, 115.5, 115.3, 86.6, 85.9, 77.9, 76.3, 63.2 (q, *J* = 37.2 Hz), 56.0. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.39. **HRMS (ESI)** calculated for $C_{18}H_{11}F_3N_4O_2$ [$(M+Na)^+$]. is 395.0798 and found 395.0799.



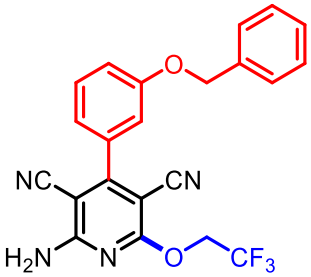
2-amino-4-(3,4-dimethoxyphenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4q): White solid **(Isolated yield:** 72%, 34.03 mg), mp: 219-221 °C; **^{1}H NMR** (700 MHz, DMSO-d_6) δ 7.21 (d, *J* = 1.8 Hz, 1H), 7.16 – 7.11 (m, 2H), 5.12 (q, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ 163.9, 161.5, 161.2, 150.9, 148.8, 126.1, 123.1, 122.0, 115.8, 115.0, 112.7, 112.0, 85.2, 83.6, 62.5 (q, *J* = 35.6 Hz), 56.0, 55.9. **^{19}F NMR** (377 MHz, DMSO) δ -73.77. **HRMS (ESI)** calculated for $C_{17}H_{14}F_3N_4O_3$ [(M+H)+] is 379.1116 and found 379.1115.



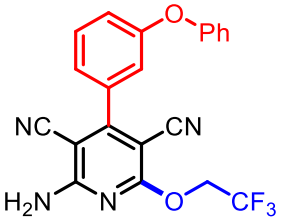
2-amino-4-(3-hydroxy-4-methoxyphenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4r): Yellow **(Isolated yield:** 67%, 30.48 mg), mp: 214-216 °C; **^{1}H NMR** (700 MHz, DMSO-d_6) δ 9.45 (s, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.98 – 6.93 (m, 2H), 5.10 (q, *J* = 8.8 Hz, 2H), 3.86 (s, 3H). **^{13}C NMR** (176 MHz, DMSO-d_6) δ 163.9, 161.2, 160.2, 159.0, 149.9, 146.8, 126.4, 120.4, 116.2, 115.9, 114.9, 112.4, 83.7, 83.5, 61.8 (q, *J* = 35.0 Hz), 56.0. **^{19}F NMR** (377 MHz, DMSO) δ -73.77. **HRMS (ESI)** calculated for $C_{16}H_{12}F_3N_4O_3$ [(M+H)+] is 365.0863 and found 365.0862.



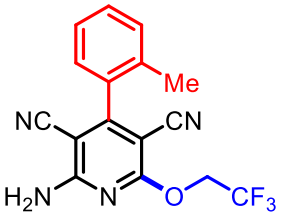
2-amino-6-(2,2,2-trifluoroethoxy)-4-(3,4,5-trimethoxyphenyl)pyridine-3,5-dicarbonitrile (Scheme 1, 4s): White solid (**Isolated yield**: 62%, 31.62 mg), mp: 220-222 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.78 (s, 2H), 5.85 (s, 2H), 4.83 (q, *J* = 8.1 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.4, 161.1, 160.4, 153.4, 140.3, 127.8, 121.3, 115.2, 113.6, 106.2, 86.2, 85.7, 63.1 (q, *J* = 37.1 Hz), 61.0, 56.4. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.78. **HRMS (ESI)** calculated for $C_{18}H_{15}F_3N_4O_4$ [$(M+Na)^+$] is 431.1025and found 431.1026.



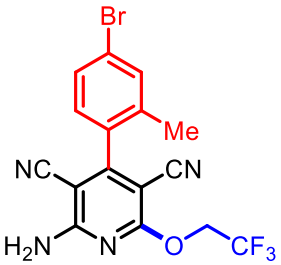
2-amino-4-(3-(benzyloxy)phenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4t): yellow solid (**Isolated yield**: 70%, 37.11 mg), mp: 217-219 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.30 (m, 6H), 7.19 – 7.08 (m, 3H), 5.73 (s, 2H), 5.11 (s, 2H), 4.84 (q, *J* = 8.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.2, 161.3, 160.2, 159.0, 136.4, 134.1, 130.3, 128.6, 128.1, 127.5, 124.0, 120.9, 117.9, 114.8, 114.6, 113.2, 86.7, 86.0, 70.4, 63.1 (q, *J* = 37.1 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.77. **HRMS (ESI)** calculated for $C_{22}H_{15}F_3N_4O_2$ [(M+Na)$^+$] is 447.1135 and found 447.1134.



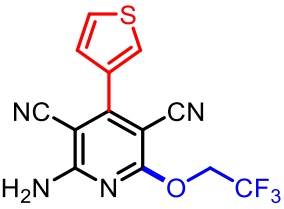
2-amino-4-(3-phenoxyphenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4u): Colorless liquid (**Isolated yield**: 73%, 37.44 mg), mp: 218-220 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (t, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.39 – 7.26 (m, 1H), 7.26 – 7.06 (m, 6H), 5.72 (s, 2H), 4.82 (q, *J* = 8.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.2, 160.9, 160.1, 157.9, 156.0, 134.3, 130.6, 129.9, 129.0, 127.1, 124.1, 122.7, 121.1, 119.6, 117.9, 114.7, 113.0, 86.0, 63.1 (q, *J* = 37.2 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.77. **HRMS (ESI)** calculated for $C_{21}H_{13}F_3N_4O_2$ [(M+Na)$^+$] is 433.0980 and found 433.0981.



2-amino-4-(o-tolyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4v): White solid (**Isolated yield**: 59%, 24.49 mg), mp: 215-217 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.26 (d, *J* = 1.9 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 5.75 (s, 2H), 4.93 – 4.73 (m, 2H), 2.26 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.8, 162.6, 159.8, 134.9, 132.9, 130.9, 130.5, 127.8, 126.3, 123.5, 114.2, 112.7, 87.7, 86.9, 63.1 (q, *J* = 37.2 Hz), 19.2. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.94. **HRMS (ESI)** calculated for $C_{16}H_{12}F_3N_4O$ [(M+H)+] is 333.1003 and found 333.1002.



2-amino-4-(4-bromo-2-methylphenyl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4w): White solid (**Isolated yield**: 69%, 37.18 mg), mp: 212-214 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 2.0 Hz, 1H), 7.48 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 5.79 (s, 2H), 4.88 – 4.79 (m, 2H), 2.25 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.9, 161.4, 159.9, 137.3, 134.0, 131.8, 129.8, 129.4, 125.0, 124.0, 114.1, 112.6, 87.6, 86.7, 63.2 (q, *J* = 37.2 Hz),19.2. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.87. **HRMS (ESI)** calculated for $C_{16}H_{10}BrF_3N_4O$ [(M+Na)$^+$] is 432.9959 and found 432.9958.

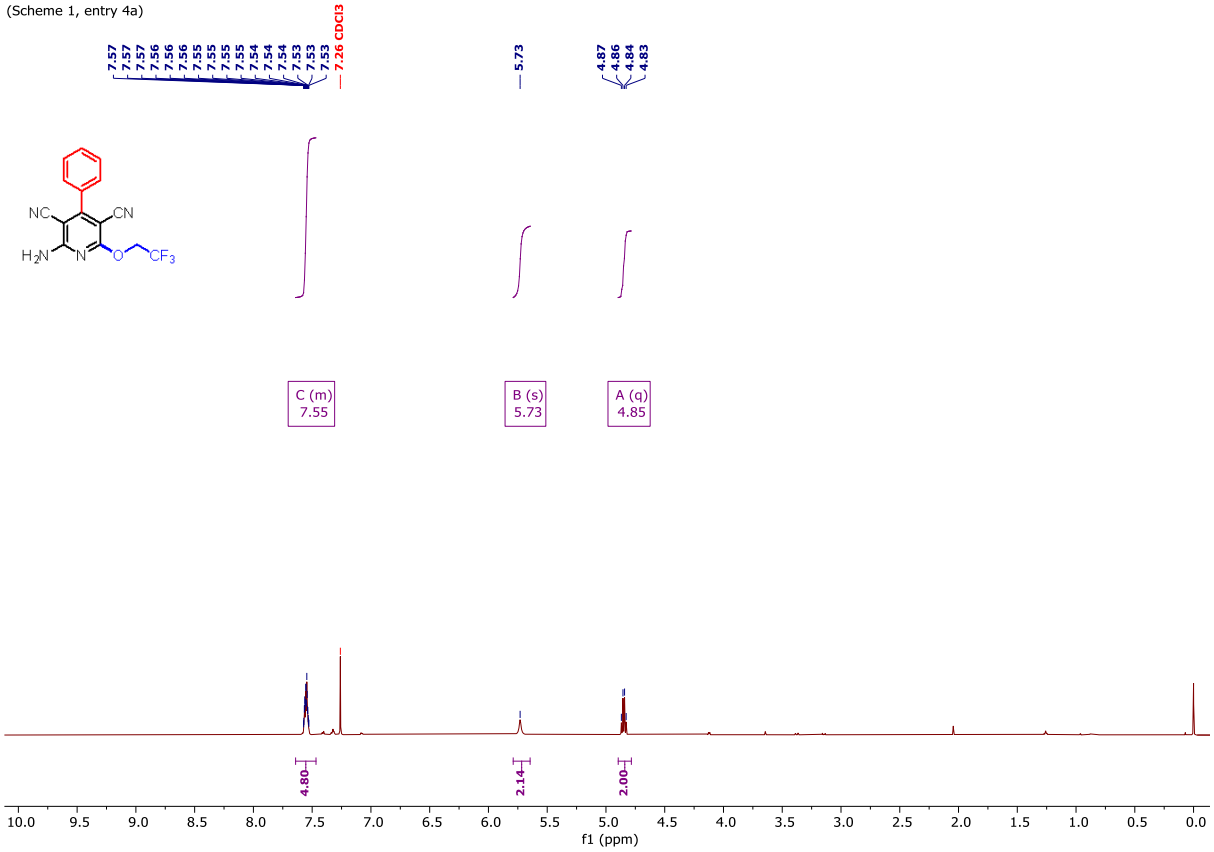


2-amino-4-(thiophen-3-yl)-6-(2,2,2-trifluoroethoxy)pyridine-3,5-dicarbonitrile (Scheme 1, 4x): Pink solid (**Isolated yield**: 54%, 21.60mg), mp: 211-213 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 – 7.34 (m, 3H), 5.75 (s,

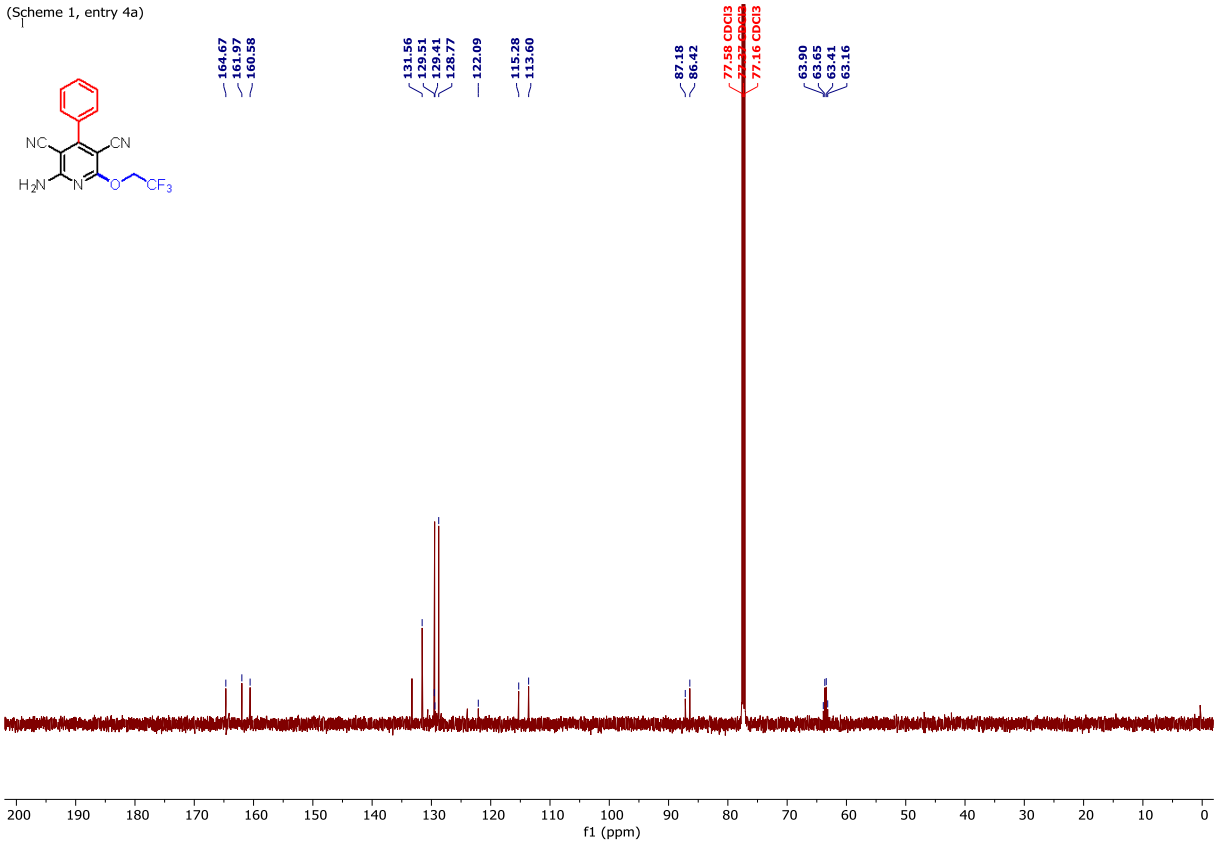
2H), 4.85 (q, *J* = 8.1 Hz, 2H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.6, 160.5, 155.4, 129.0, 127.3, 127.2, 124.0, 121.3, 115.3, 113.6, 85.9, 85.1, 63.1 (q, *J* = 37.4 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -73.97. **HRMS (ESI)** calculated for $C_{13}H_8F_3N_4OS$ [(M+H)+] is 325.0471 and found 325.0472.

4. NMR Spectra of the Synthesized Compounds

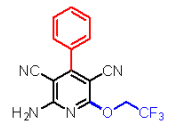
(Scheme 1, entry 4a)

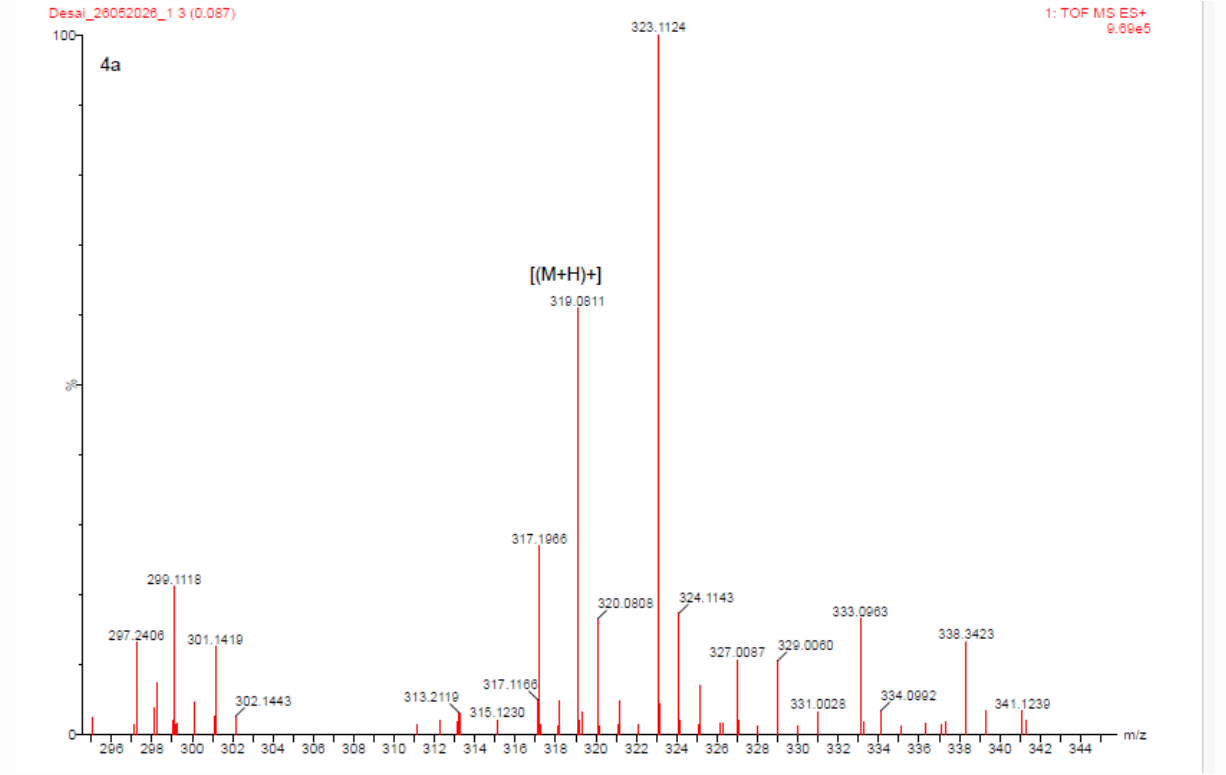


(Scheme 1, entry 4a)

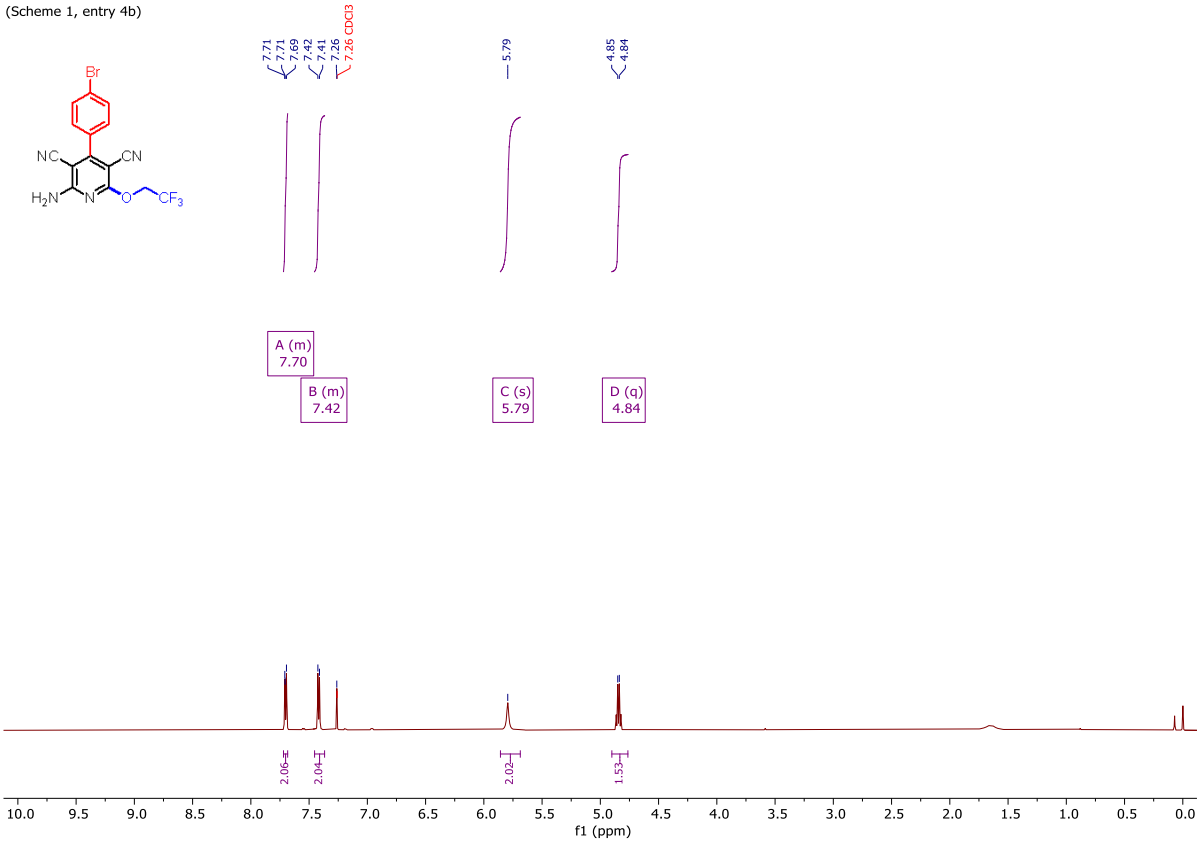


(Scheme 1, entry 4a)

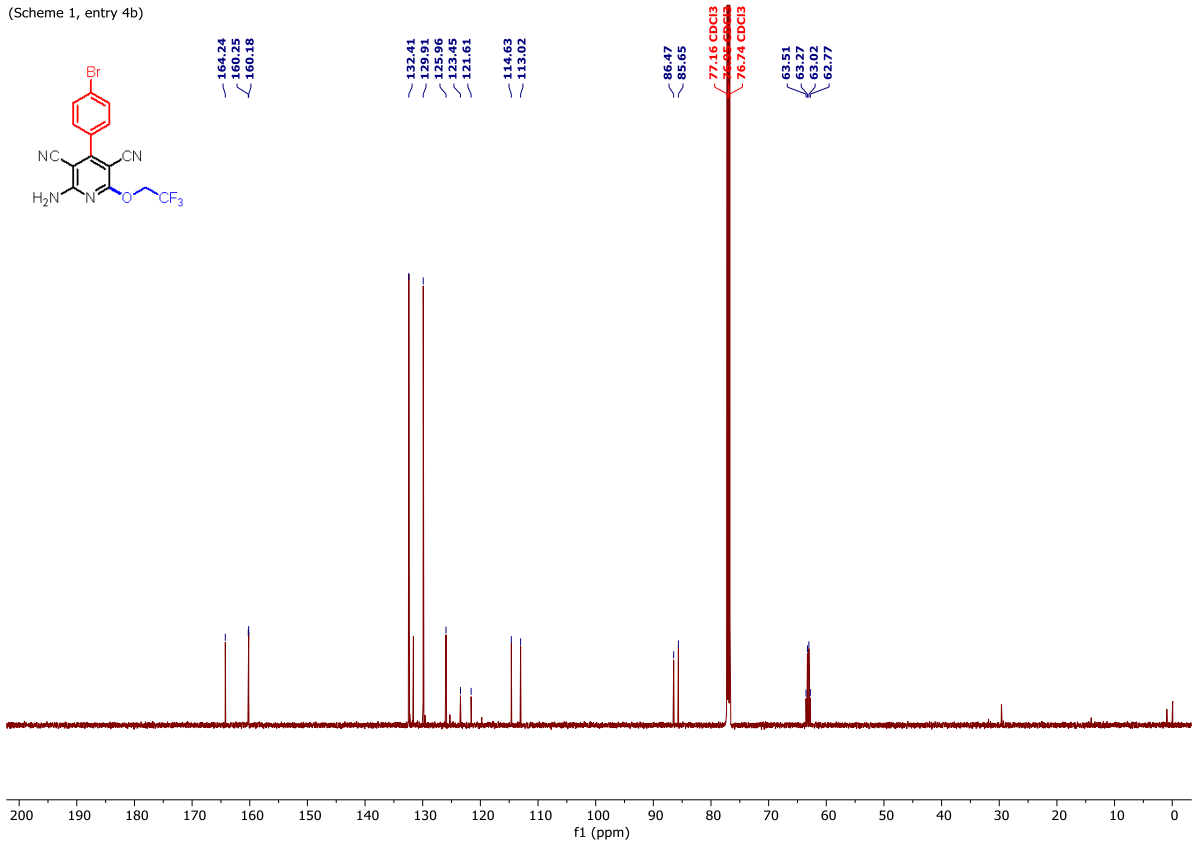




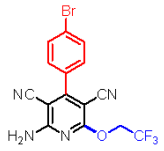
(Scheme 1, entry 4b)

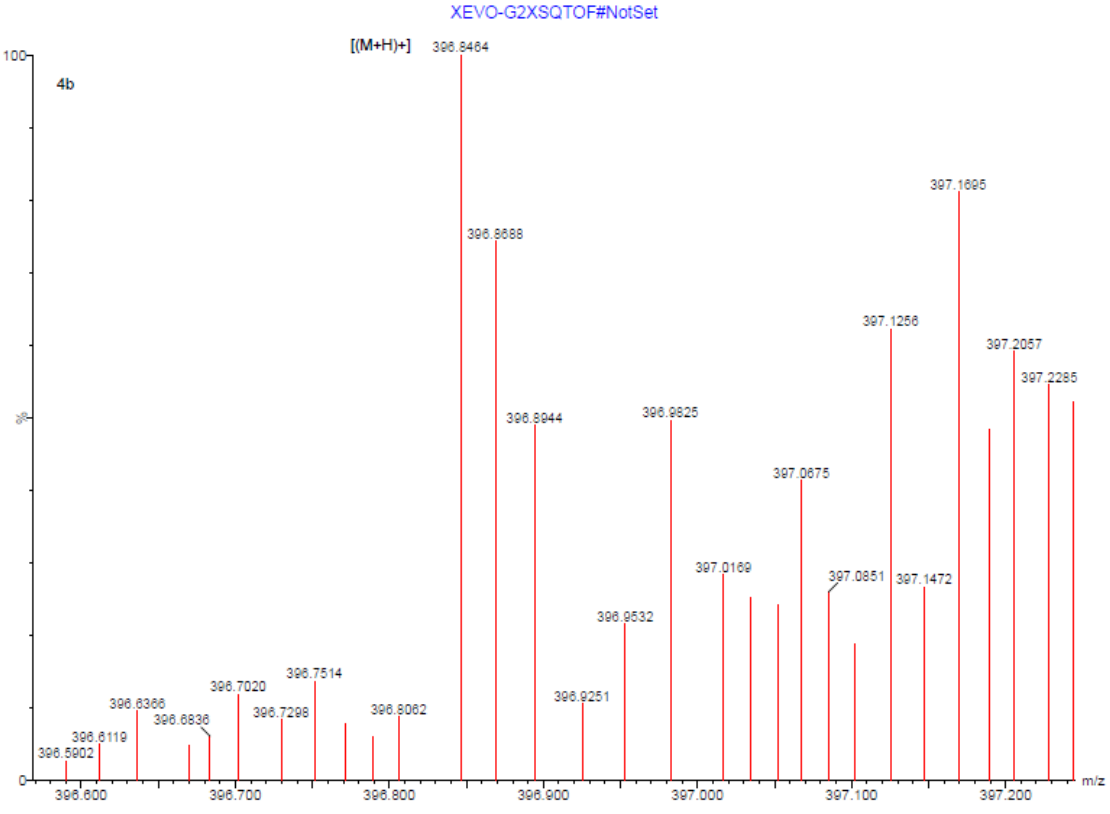


(Scheme 1, entry 4b)

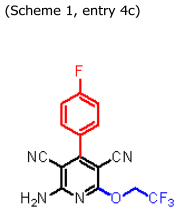


(Scheme 1, entry 4b)

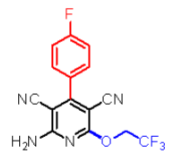




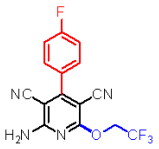
(Scheme 1, entry 4c)



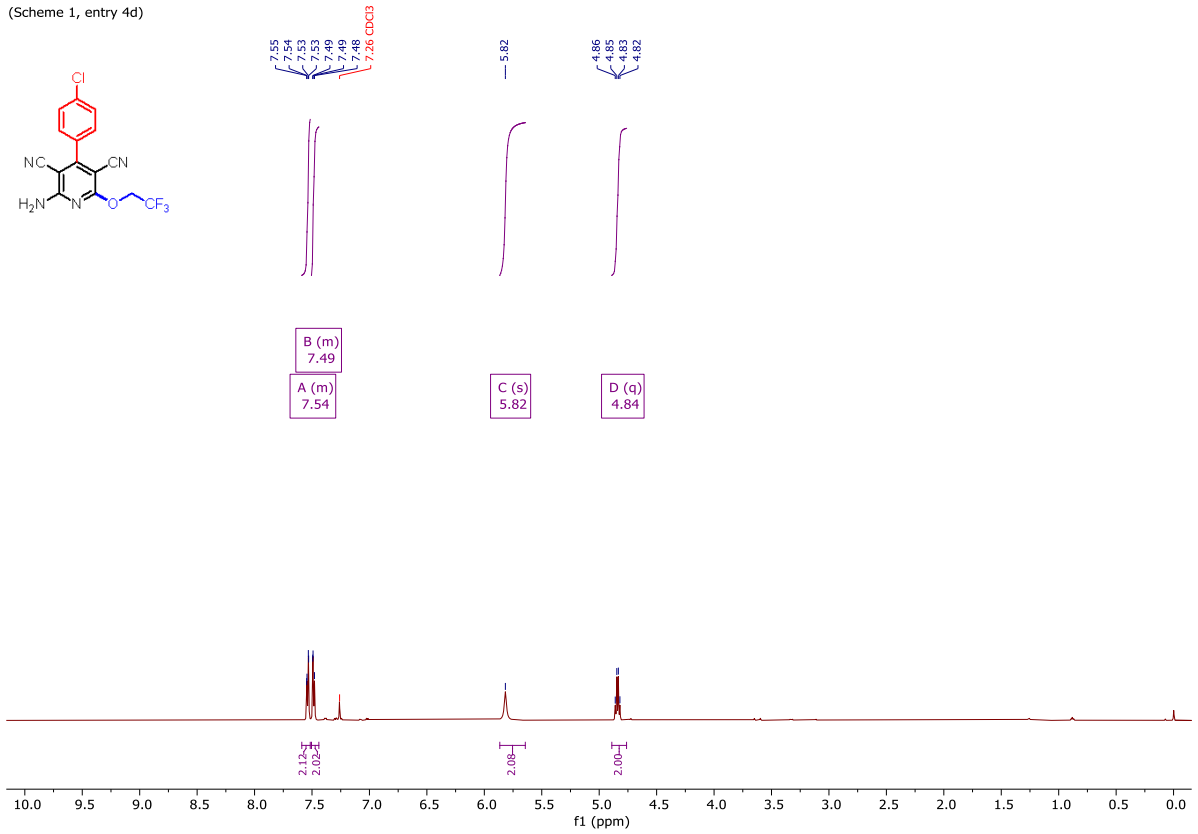
(Scheme 1, entry 4c)



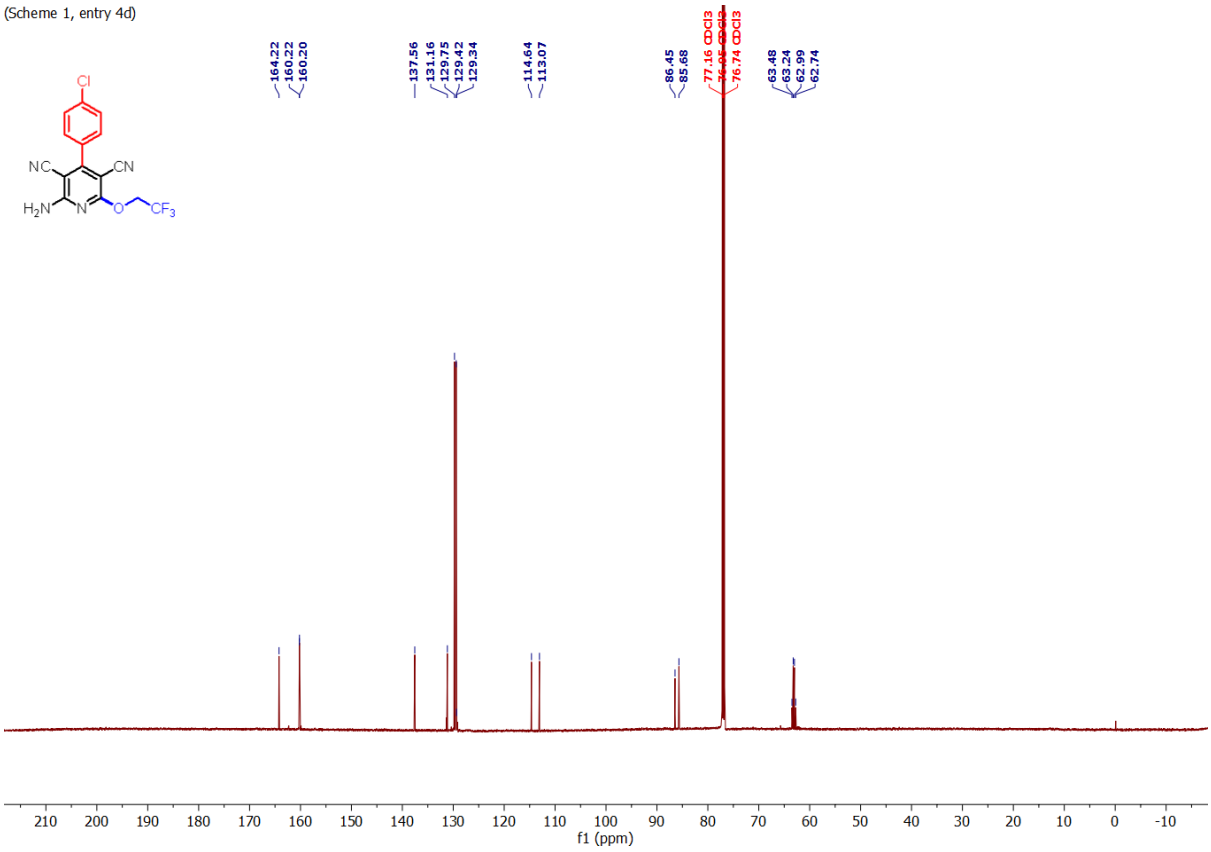
(Scheme 1, entry 4c)



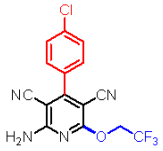
(Scheme 1, entry 4d)

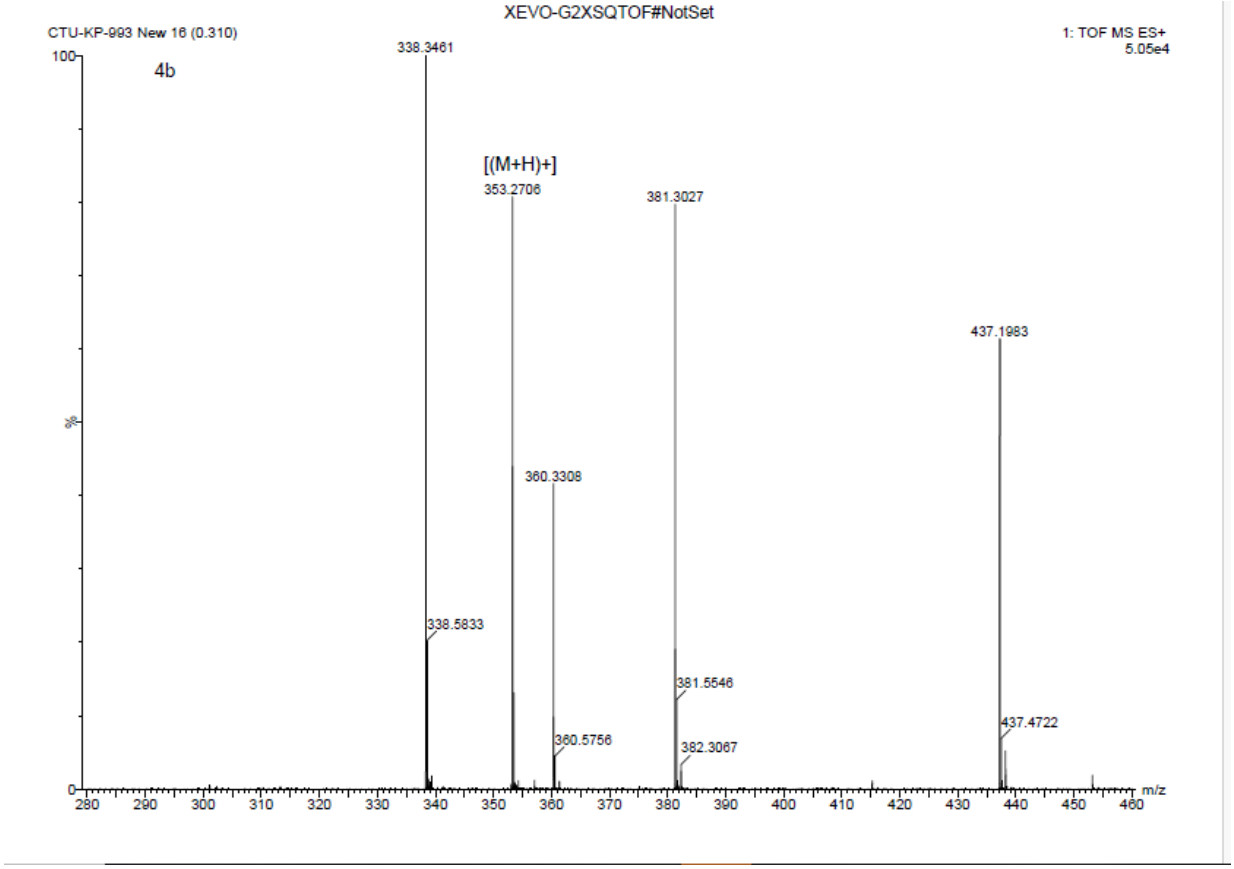


(Scheme 1, entry 4d)

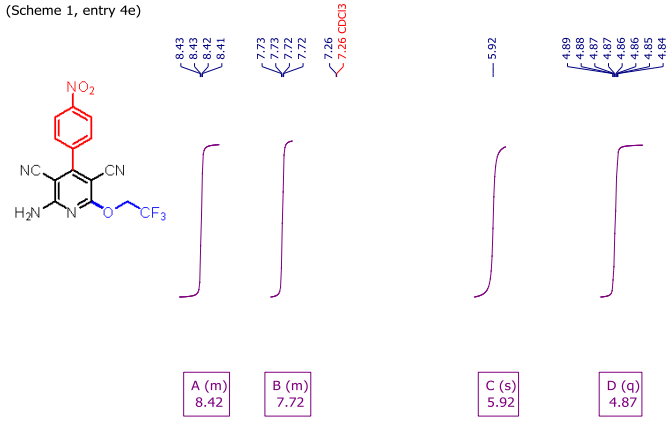


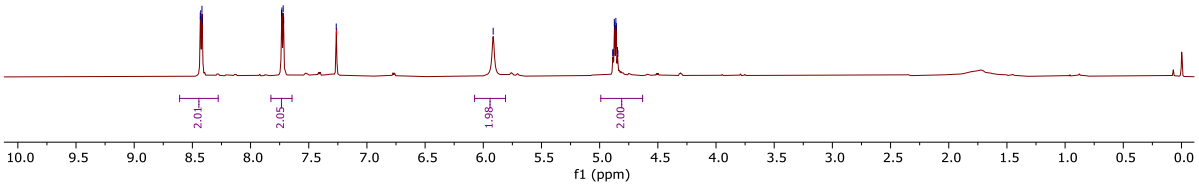
(Scheme 1, entry 4d)



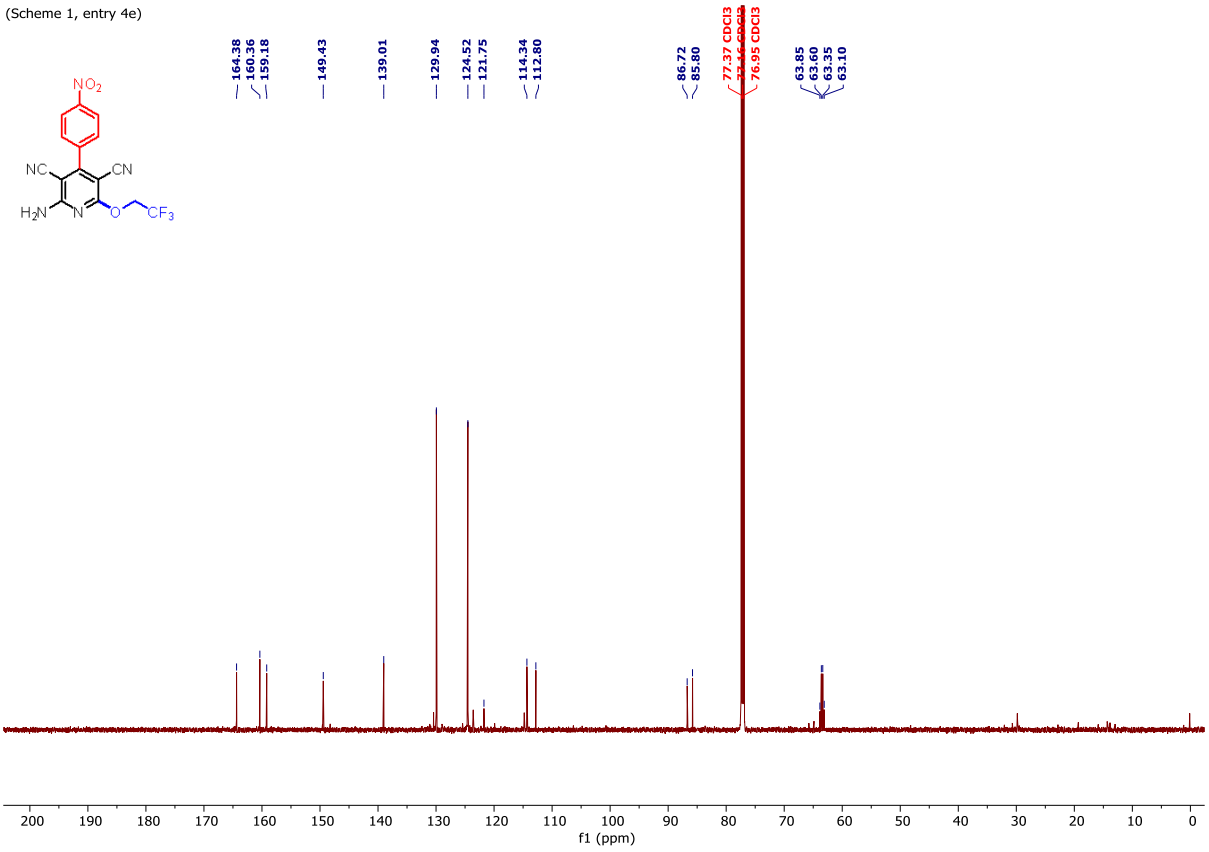


(Scheme 1, entry 4e)

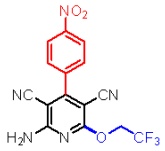


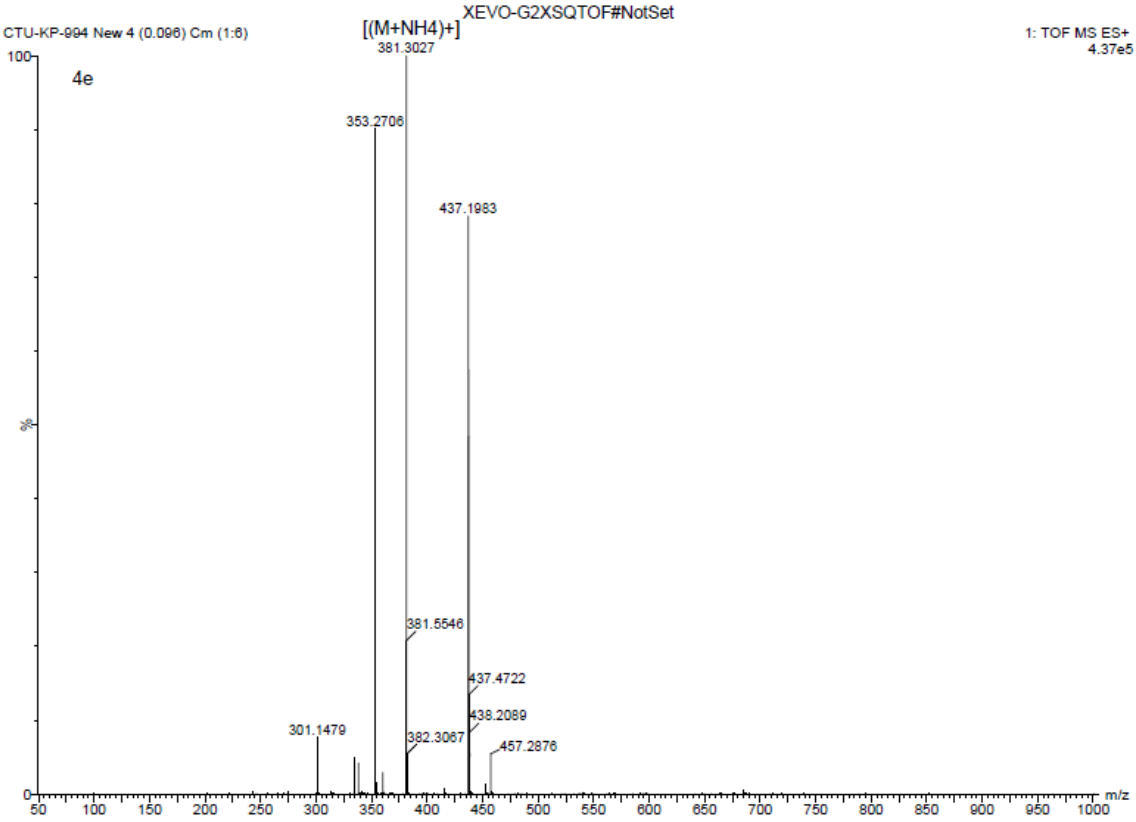


(Scheme 1, entry 4e)

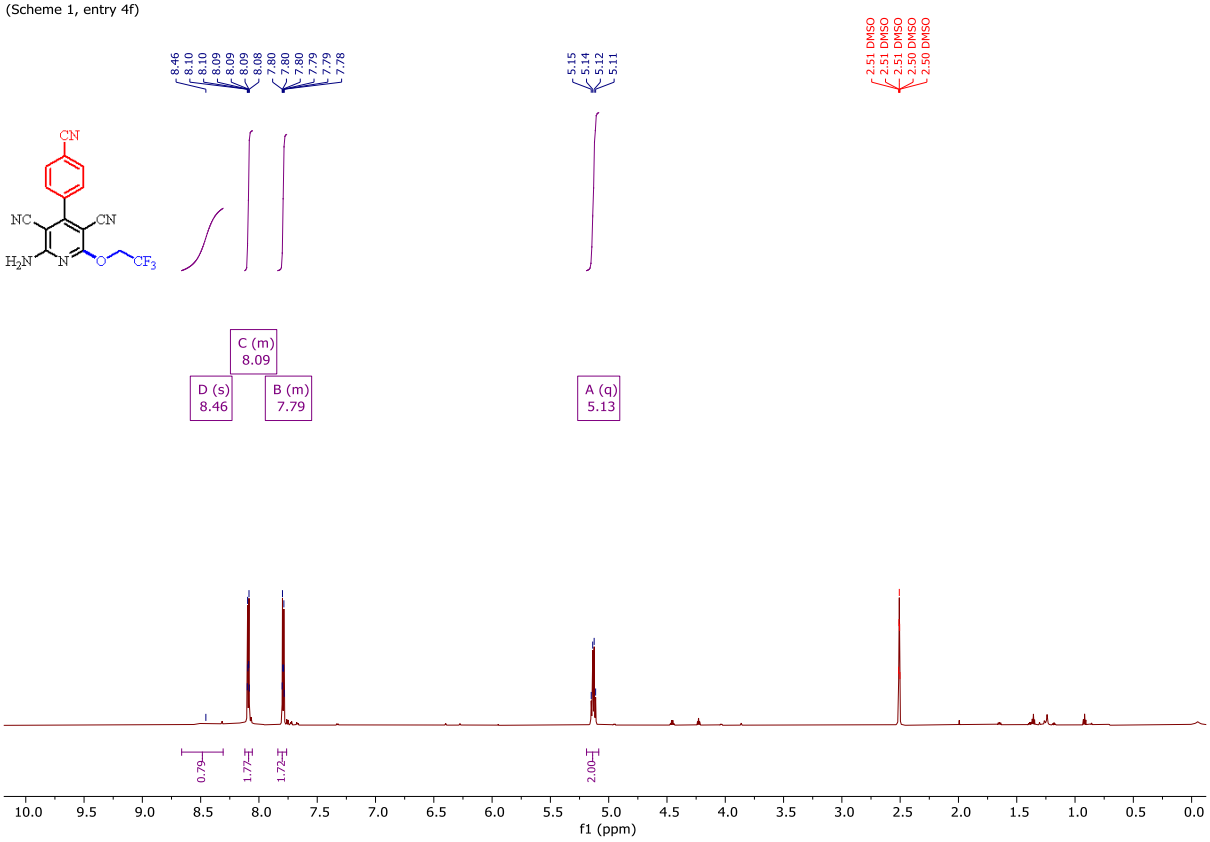


(Scheme 1, entry 4e)

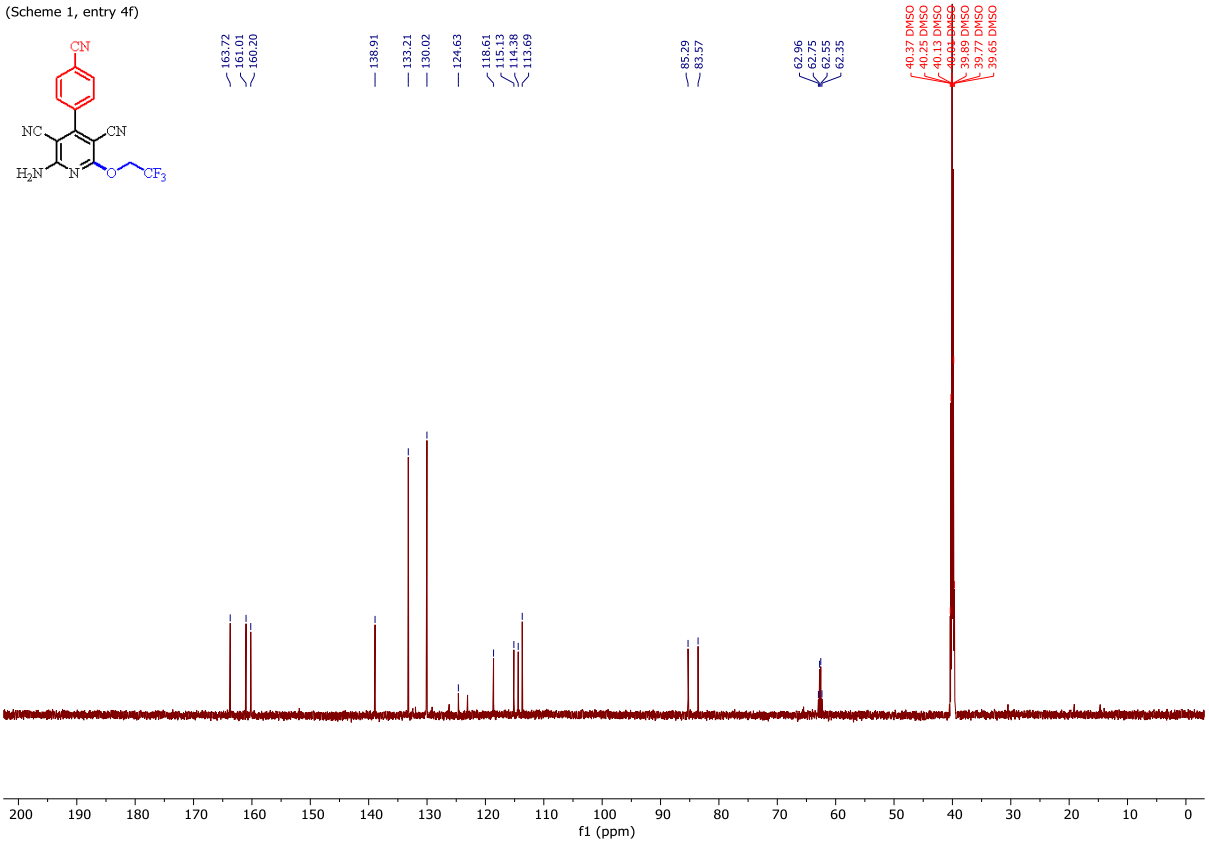




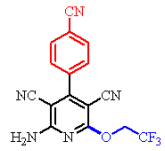
(Scheme 1, entry 4f)

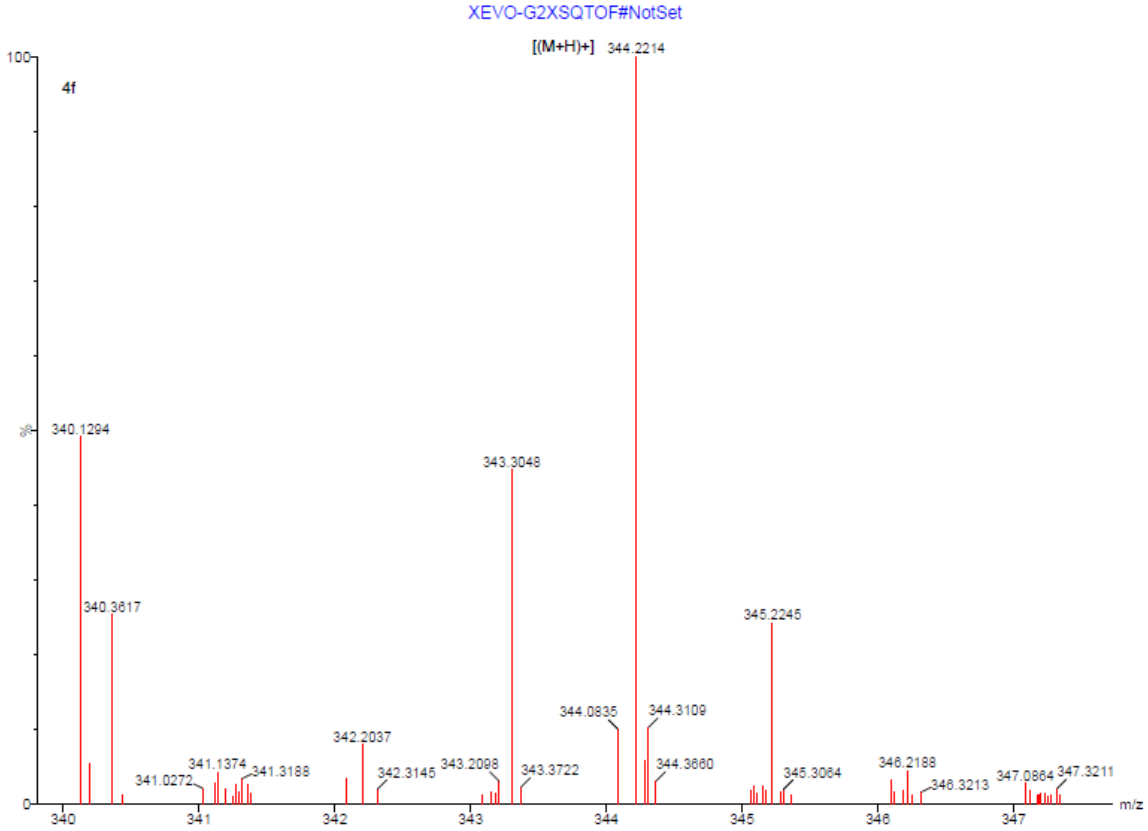


(Scheme 1, entry 4f)

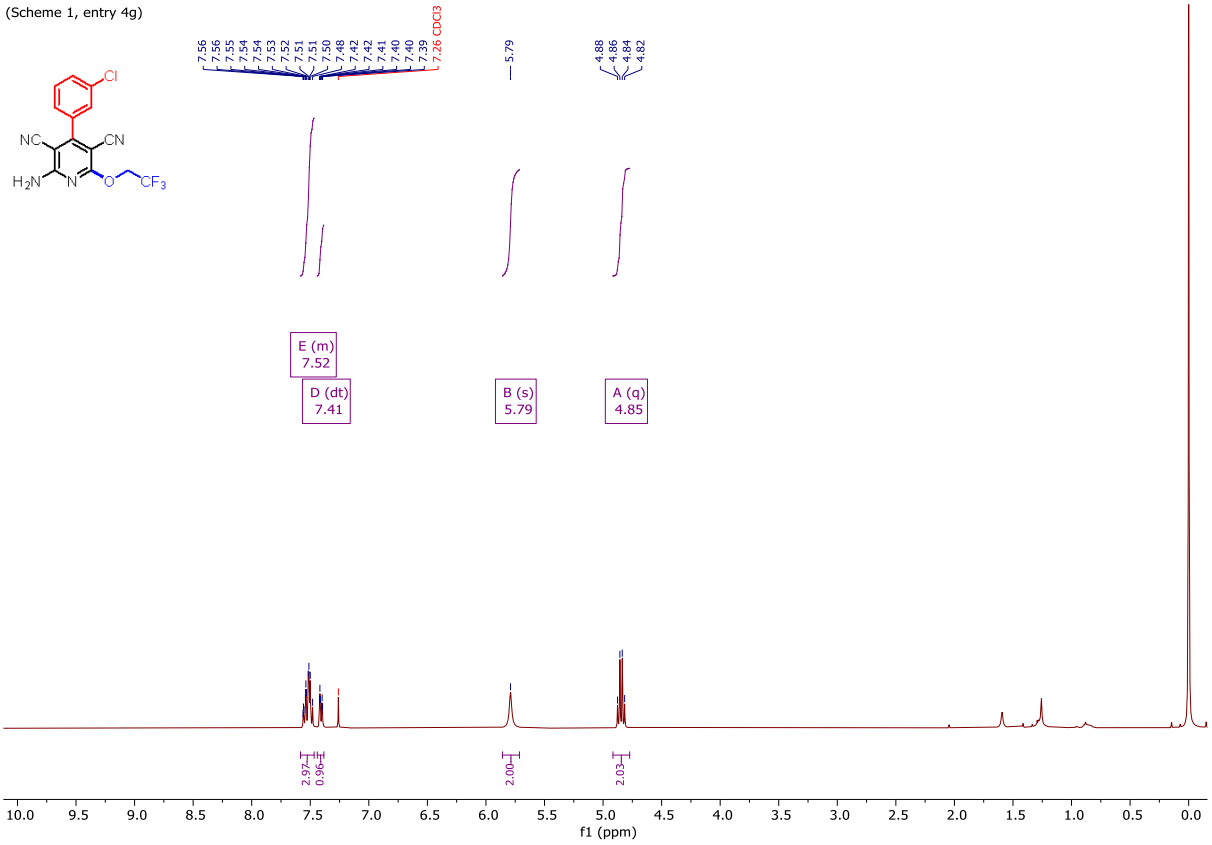


(Scheme 1, entry 4f)

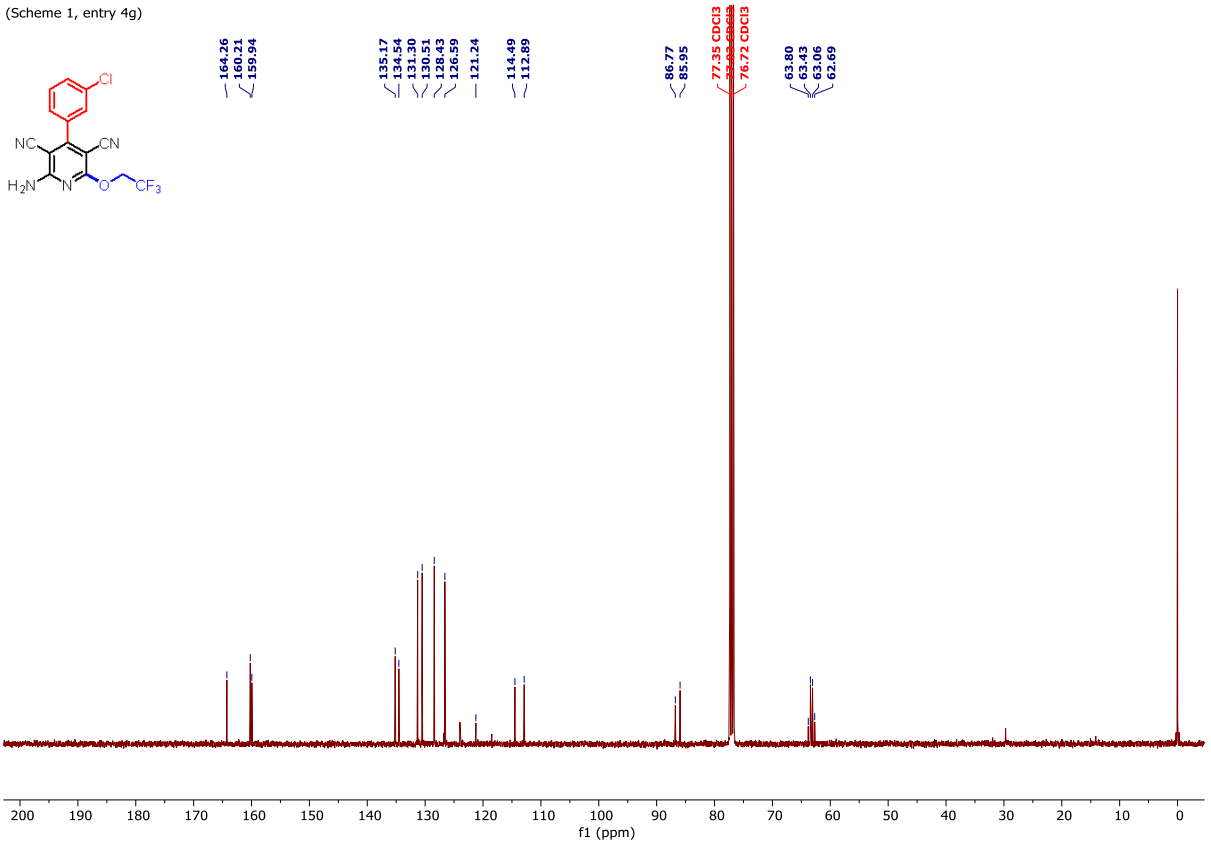




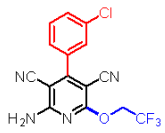
(Scheme 1, entry 4g)

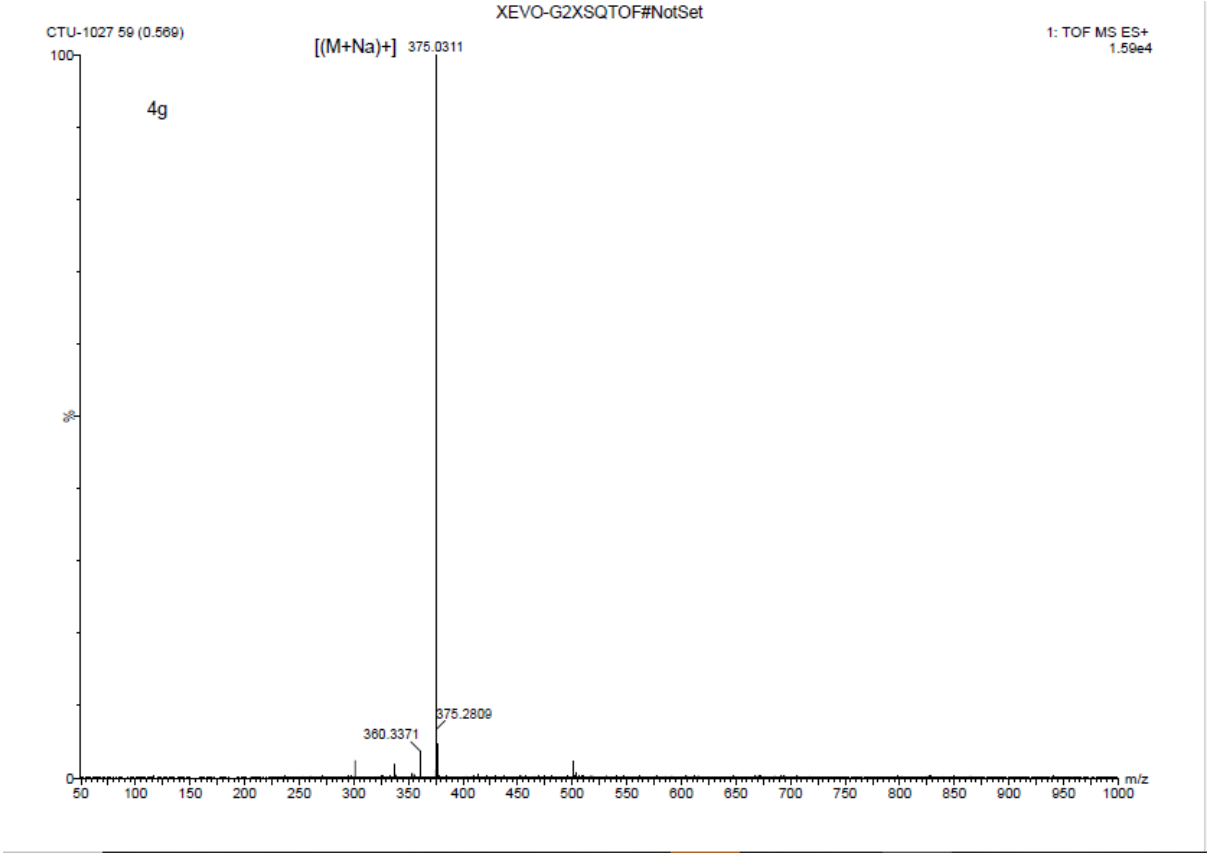


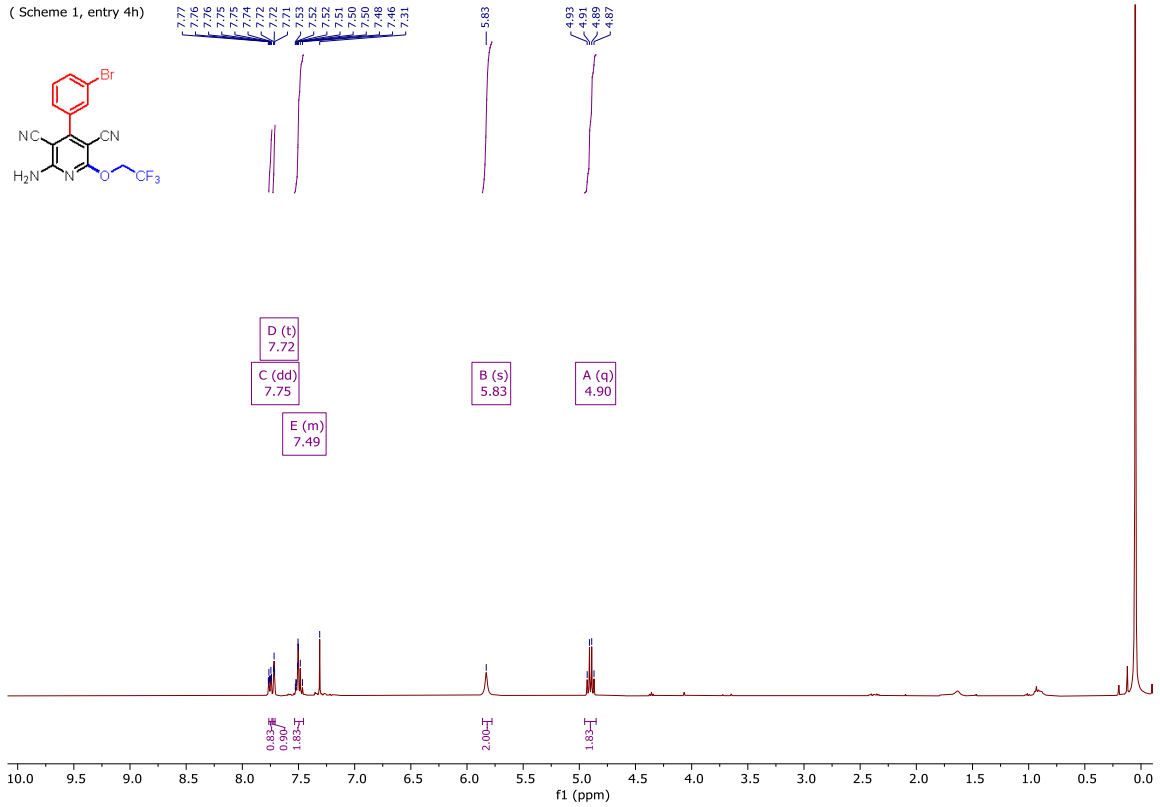
(Scheme 1, entry 4g)

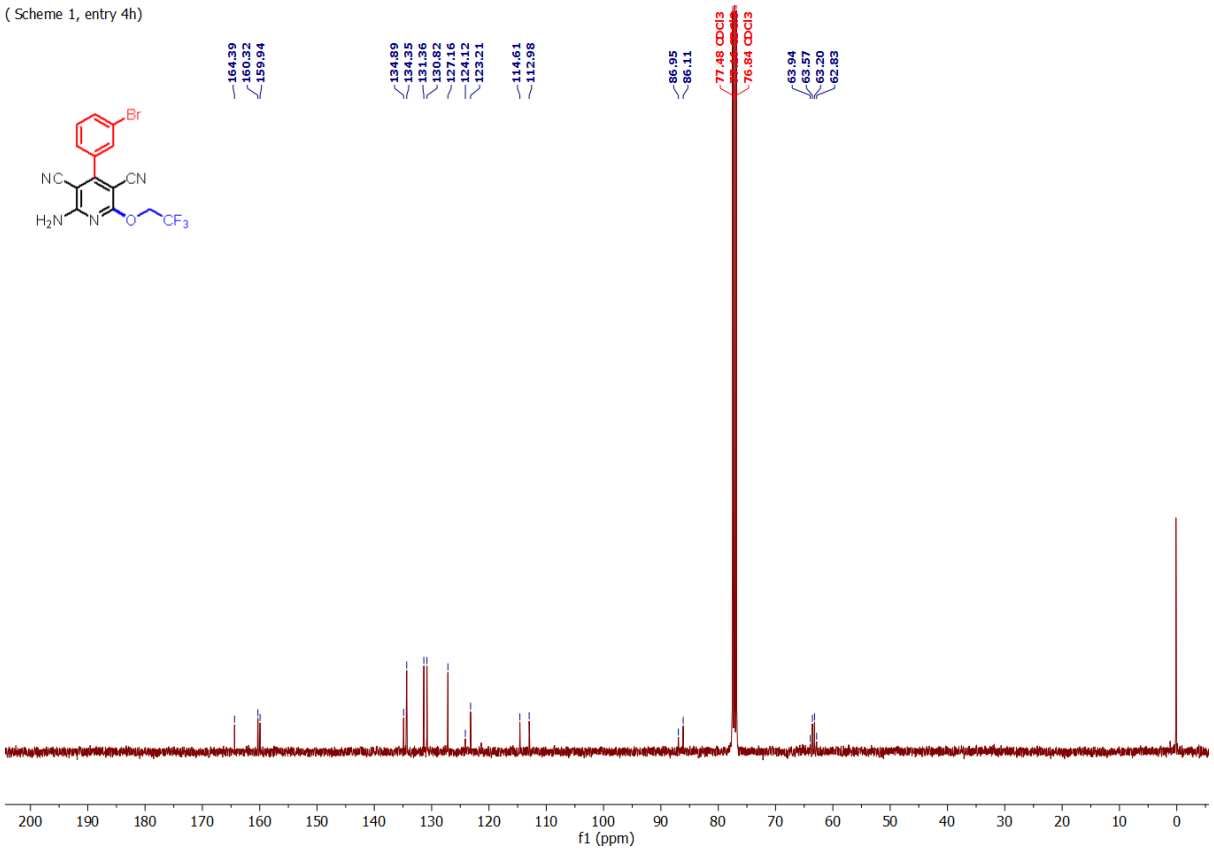


(Scheme 1, entry 4g)

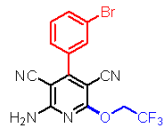


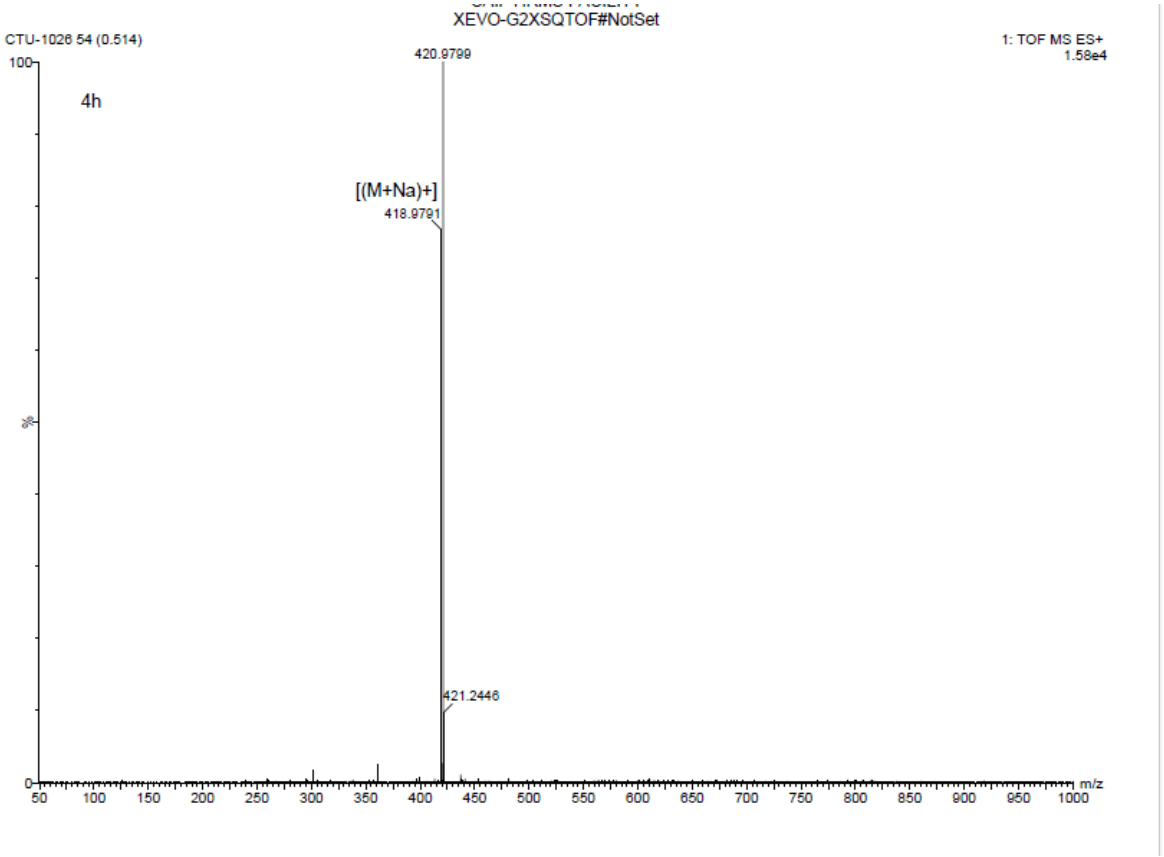



(Scheme 1, entry 4h)
7.77
7.76
7.76
7.75
7.75
7.74
7.72
7.72
7.71
7.53
7.52
7.52
7.51
7.50
7.50
7.48
7.46
7.31
5.83
4.93
4.91
4.89
4.87
Br
NC
CN
H2N
N
O
CF3
D (t)
7.72
C (dd)
7.75
E (m)
7.49
B (s)
5.83
A (q)
4.90
0.83
0.90
1.83
2.00
1.83
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

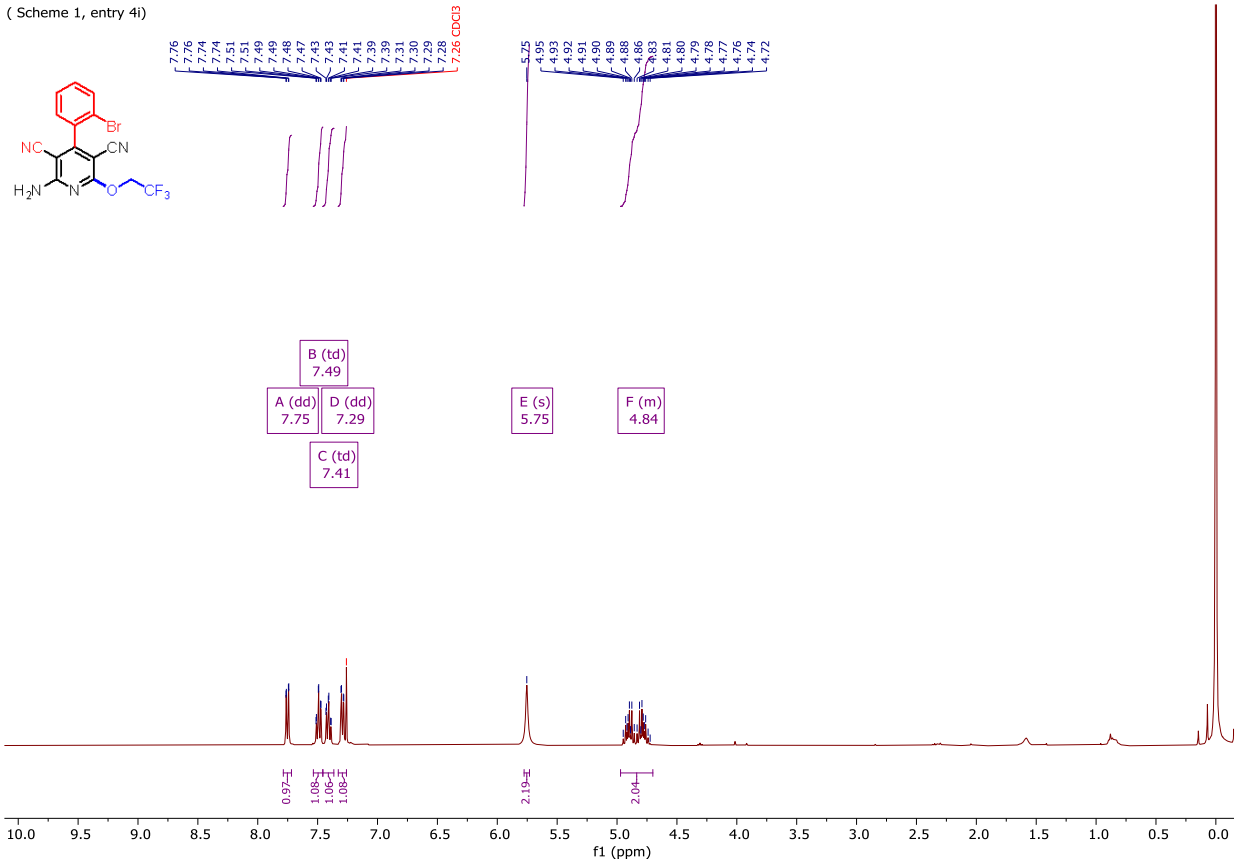

(Scheme 1, entry 4h)
164.39
160.32
159.94
134.89
134.35
131.36
130.82
127.16
124.12
123.21
114.61
112.98
86.95
86.11
77.48 CDCl3
76.84 CDCl3
63.94
63.57
63.20
62.83
Br
NC
CN
H2N
N
O
CF3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(Scheme 1, entry 4h)

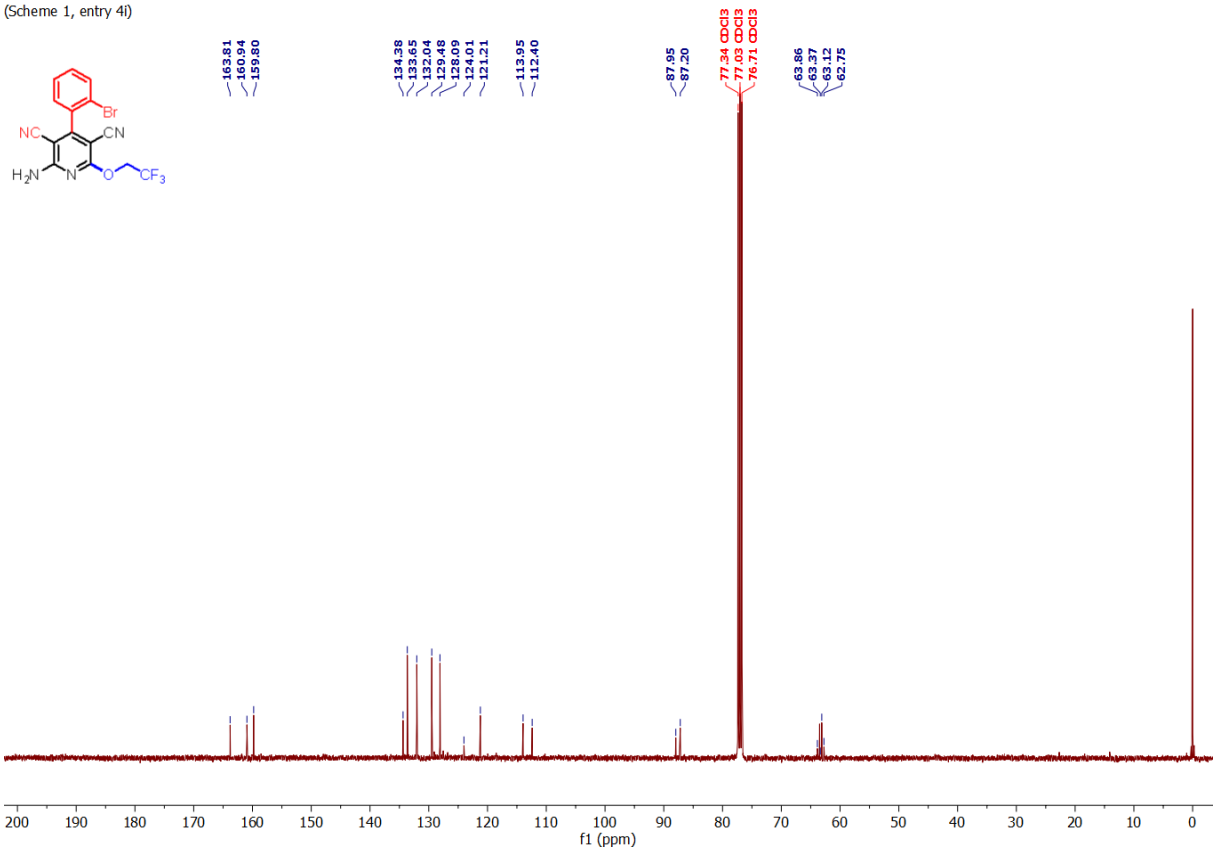




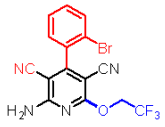
(Scheme 1, entry 4i)

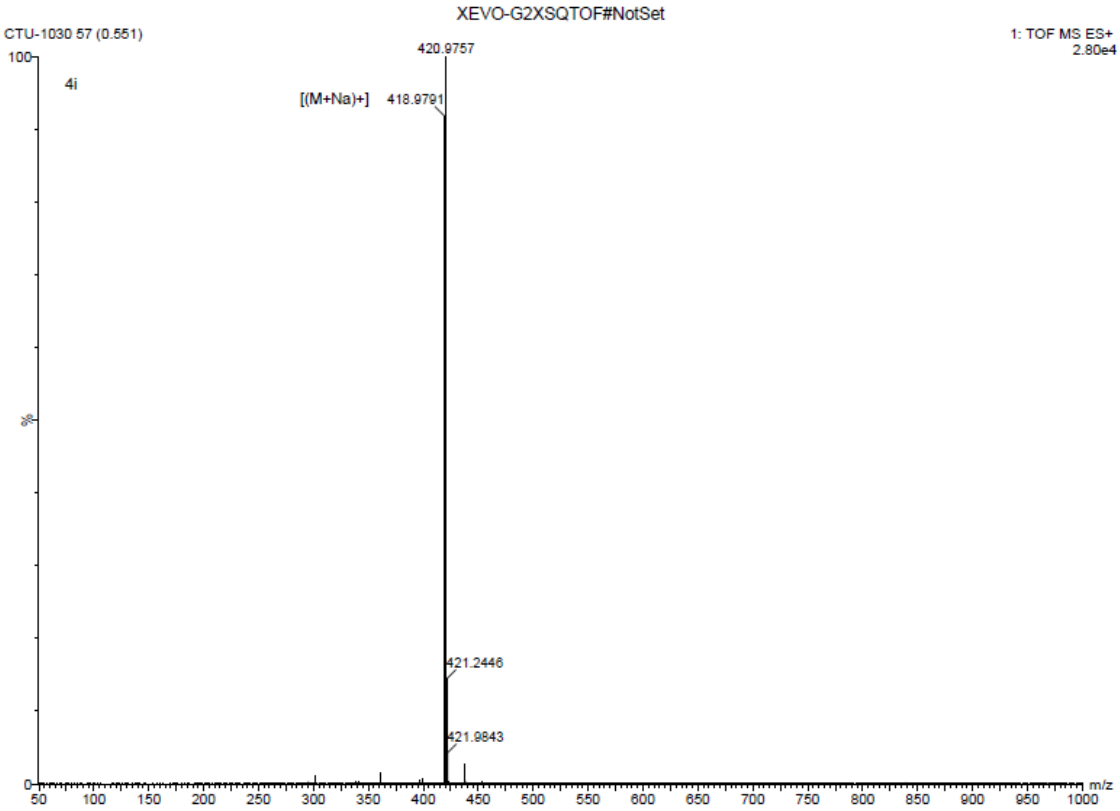


(Scheme 1, entry 4i)

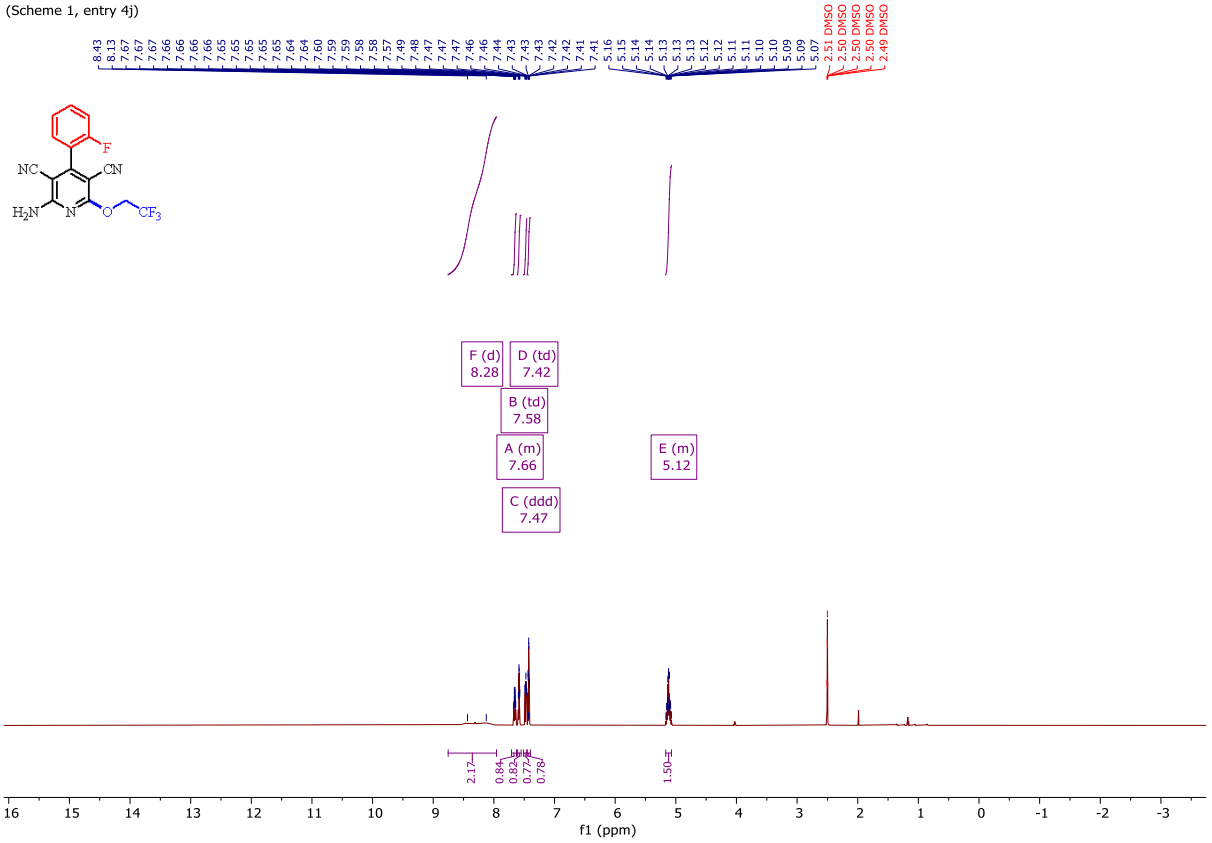


(Scheme 1, entry 4i)

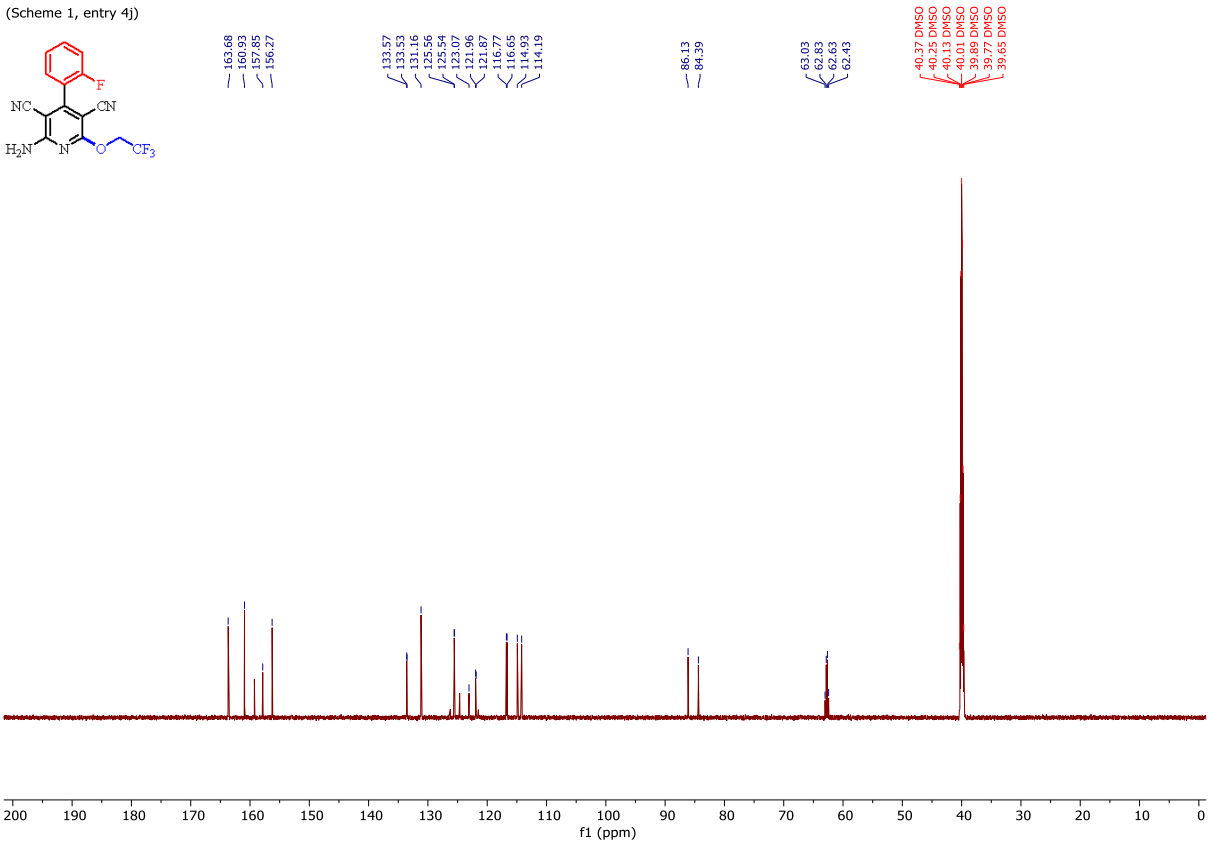




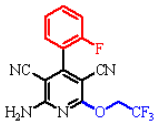
(Scheme 1, entry 4j)

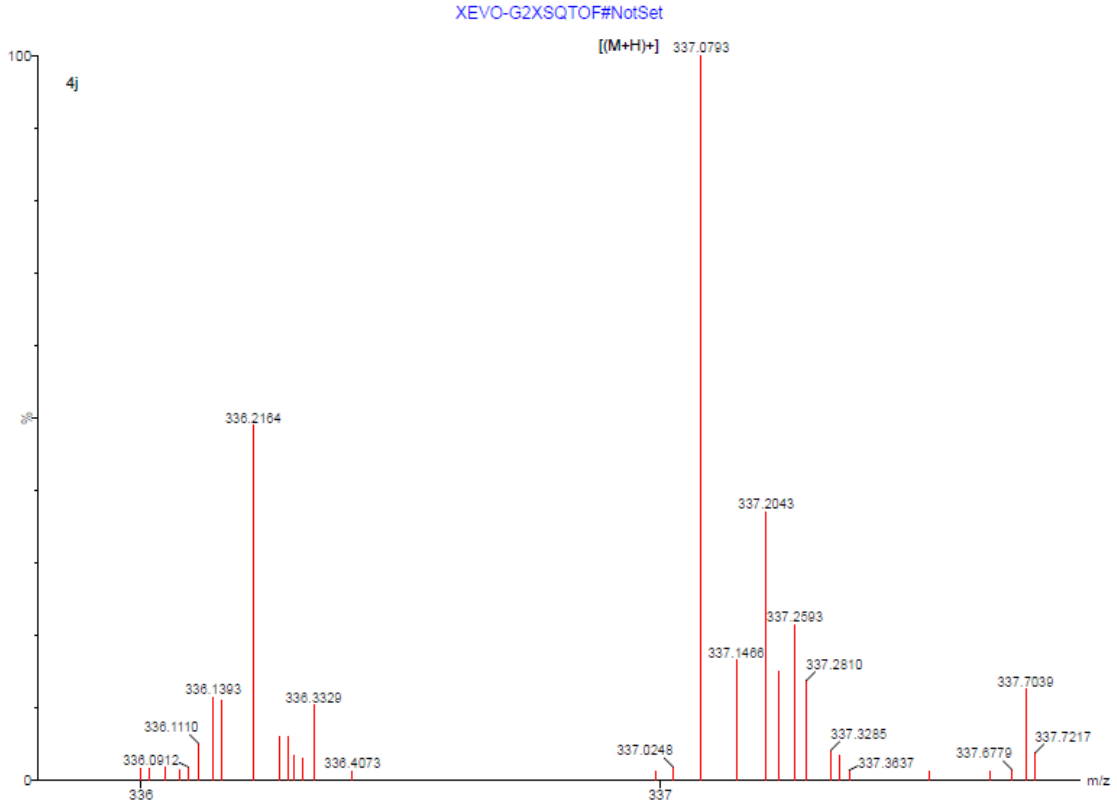


(Scheme 1, entry 4j)

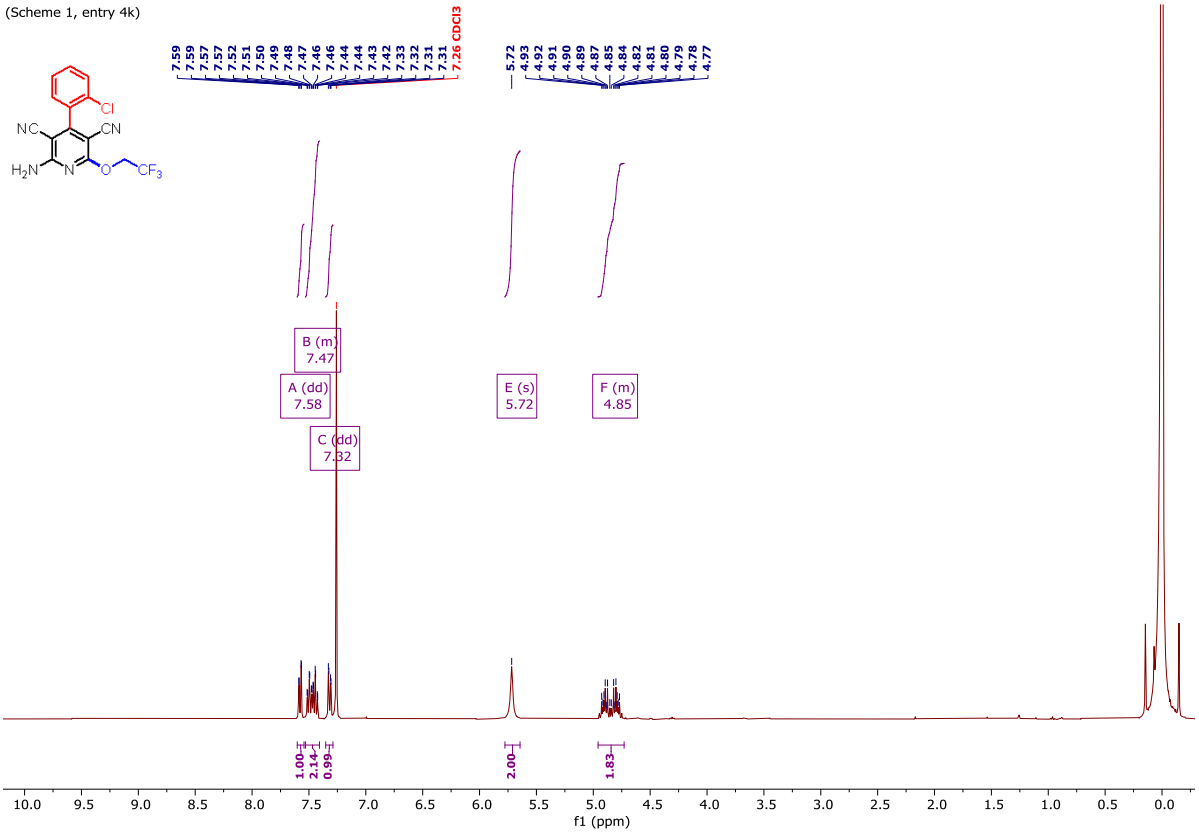


(Scheme 1, entry 4j)

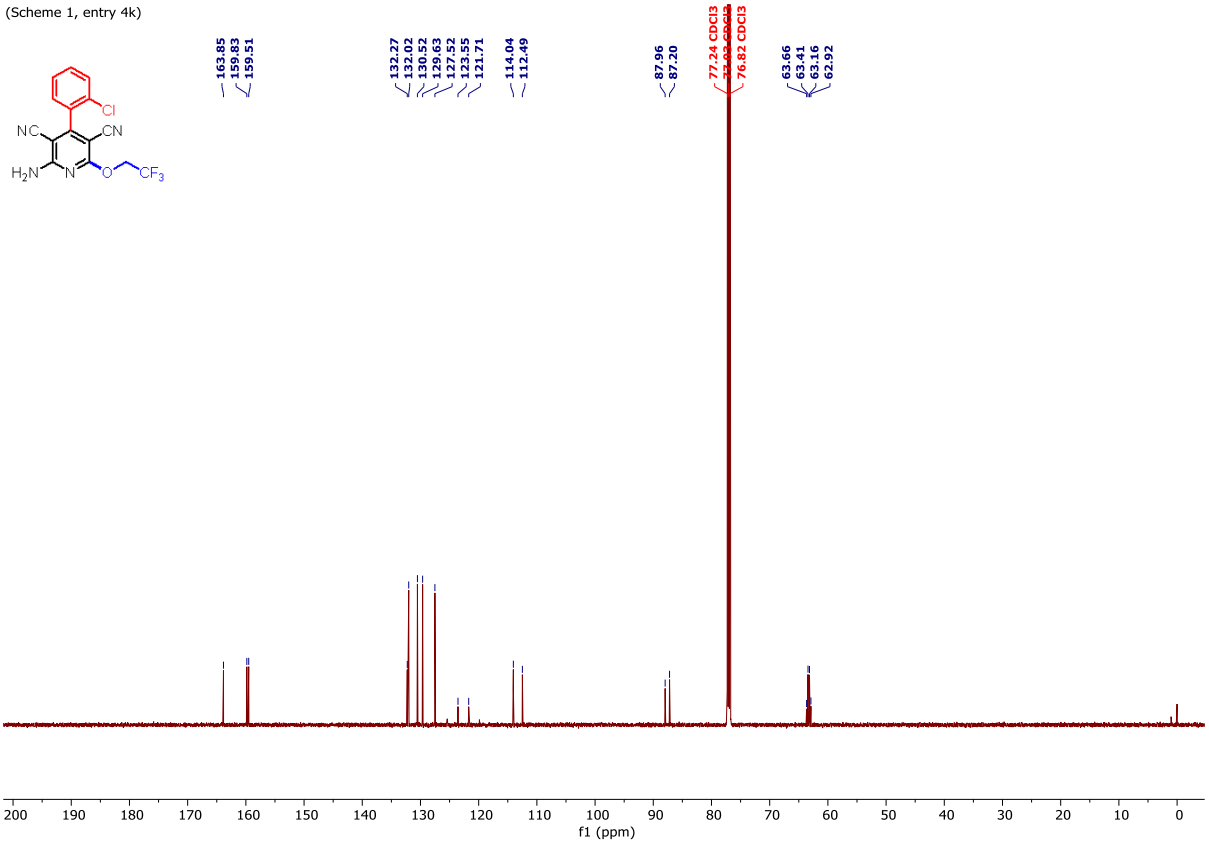




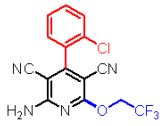
(Scheme 1, entry 4k)

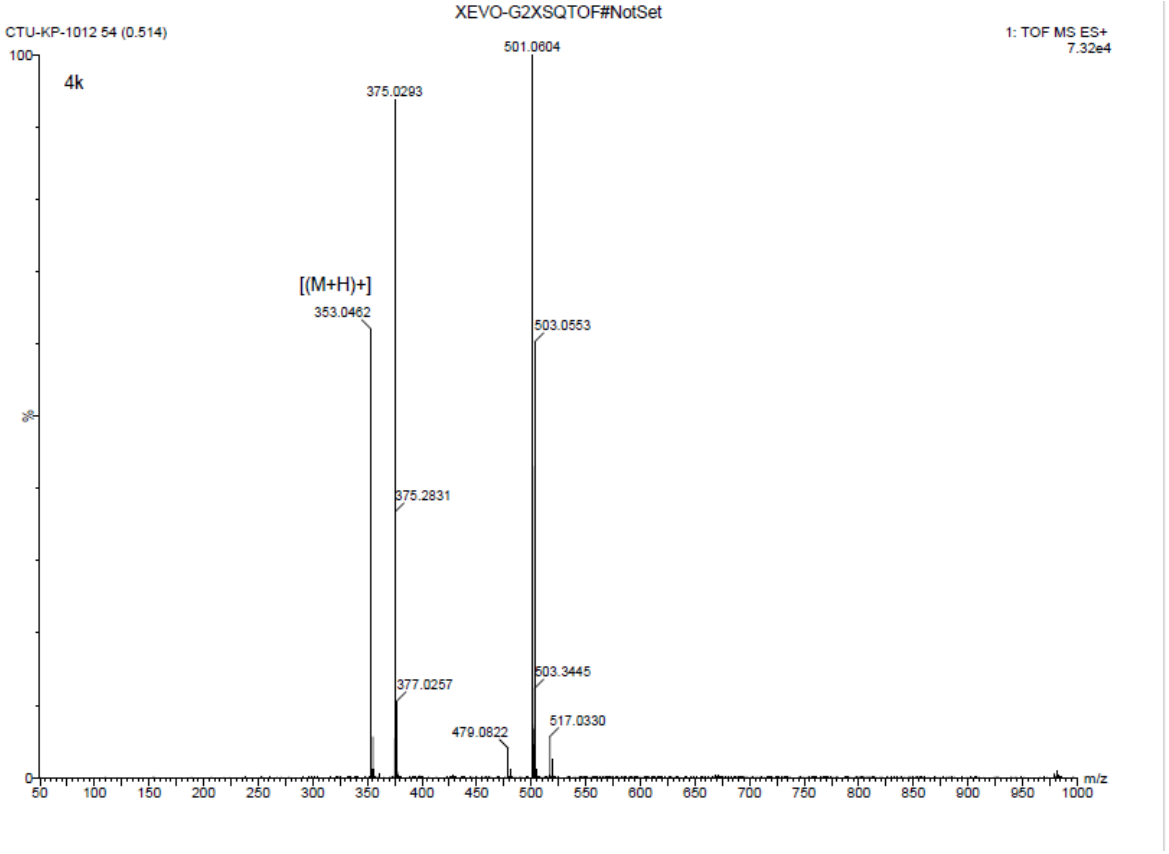


(Scheme 1, entry 4k)

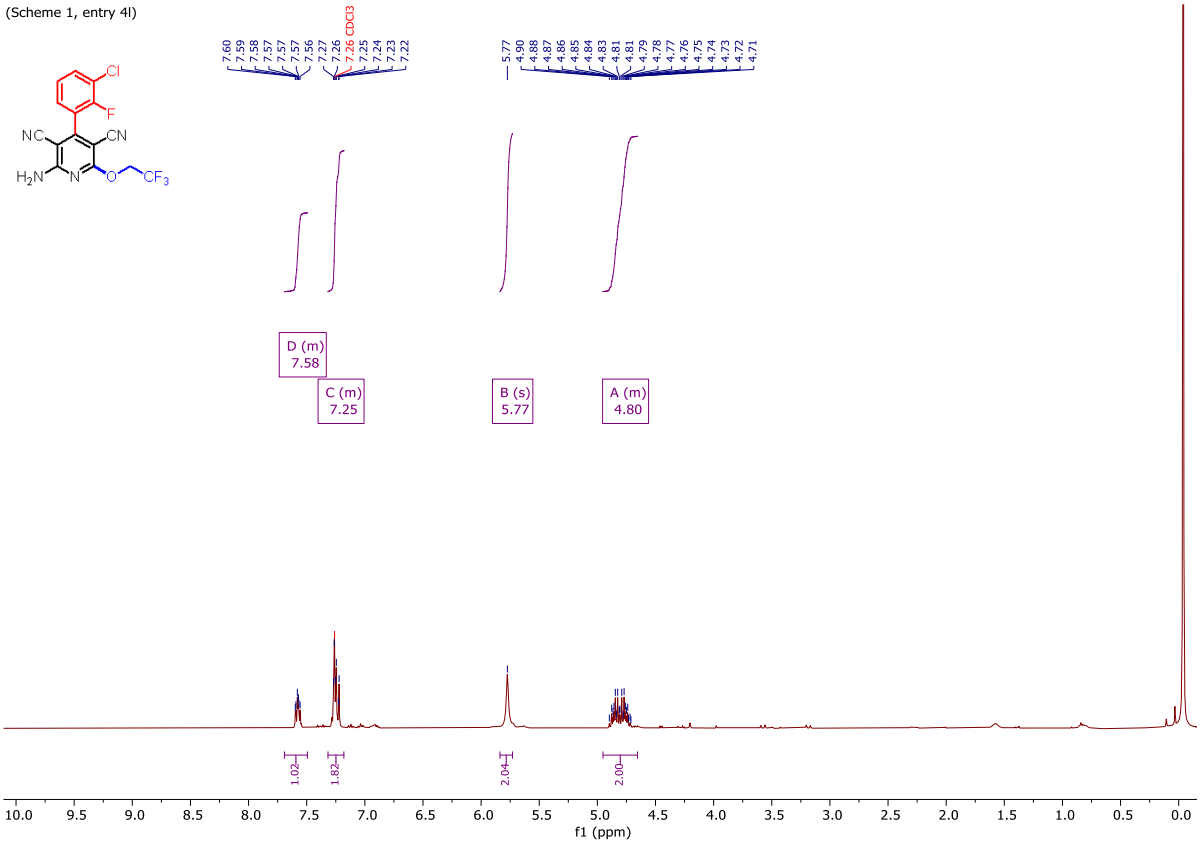


(Scheme 1, entry 4k)

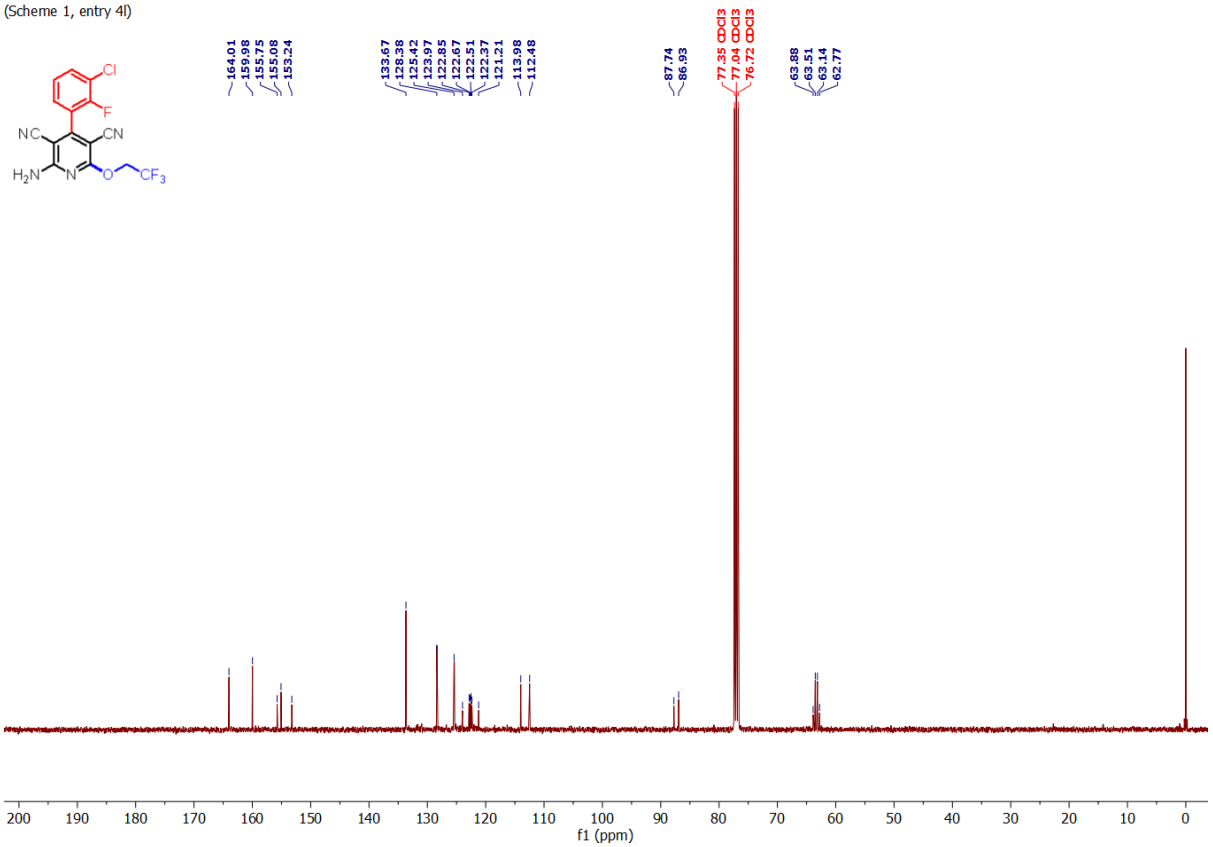




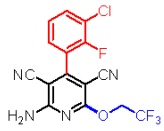
(Scheme 1, entry 4l)

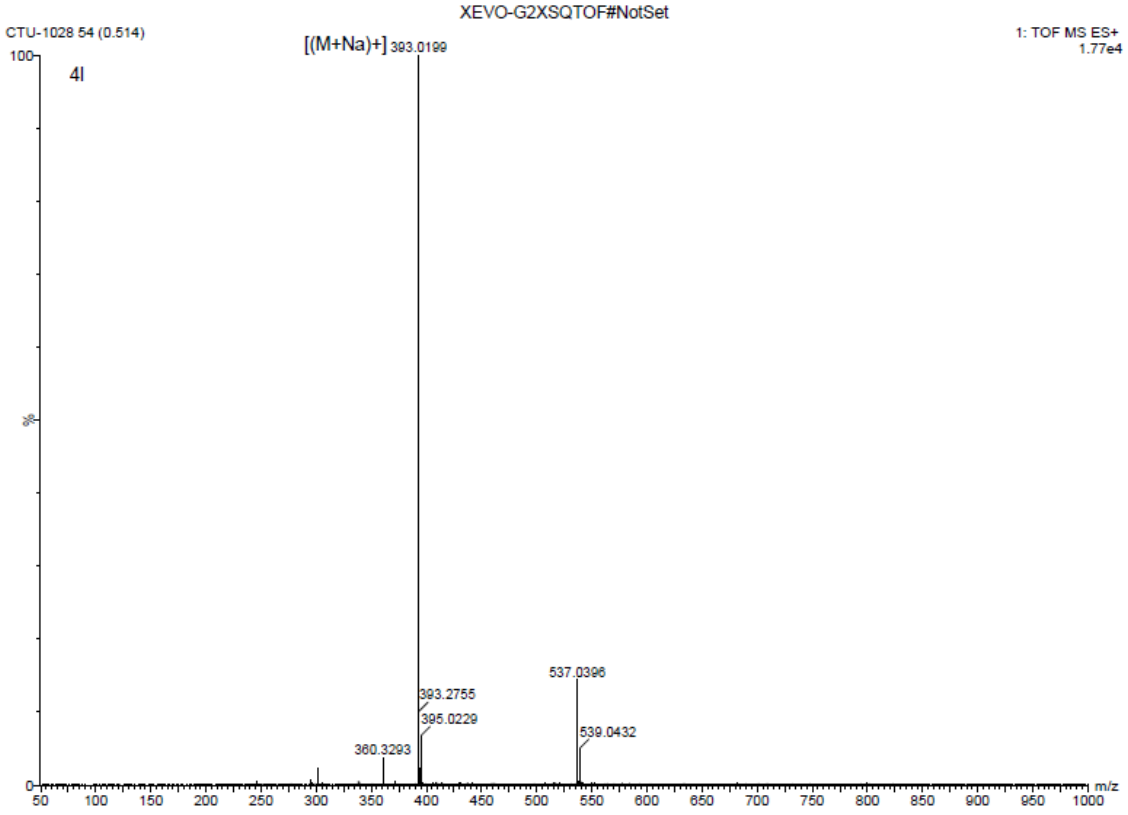


(Scheme 1, entry 4l)

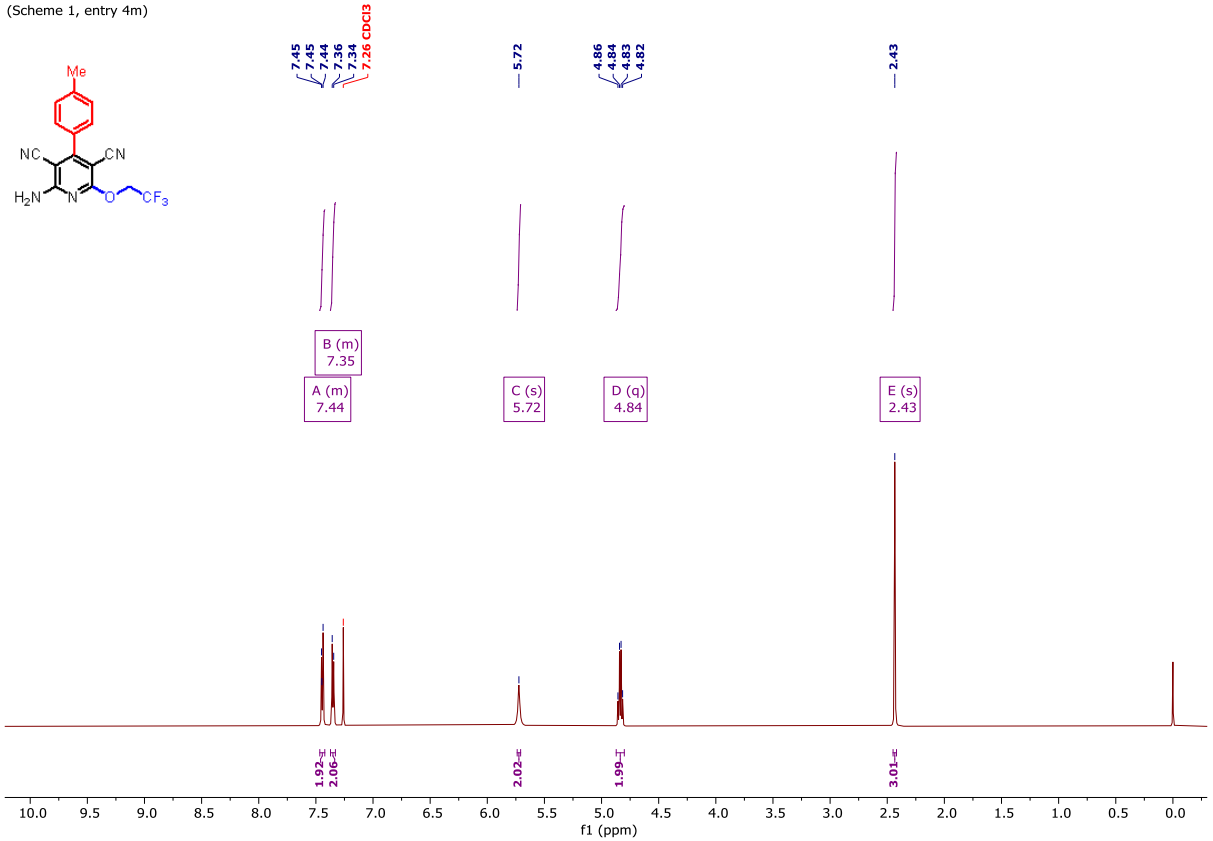


(Scheme 1, entry 4l)

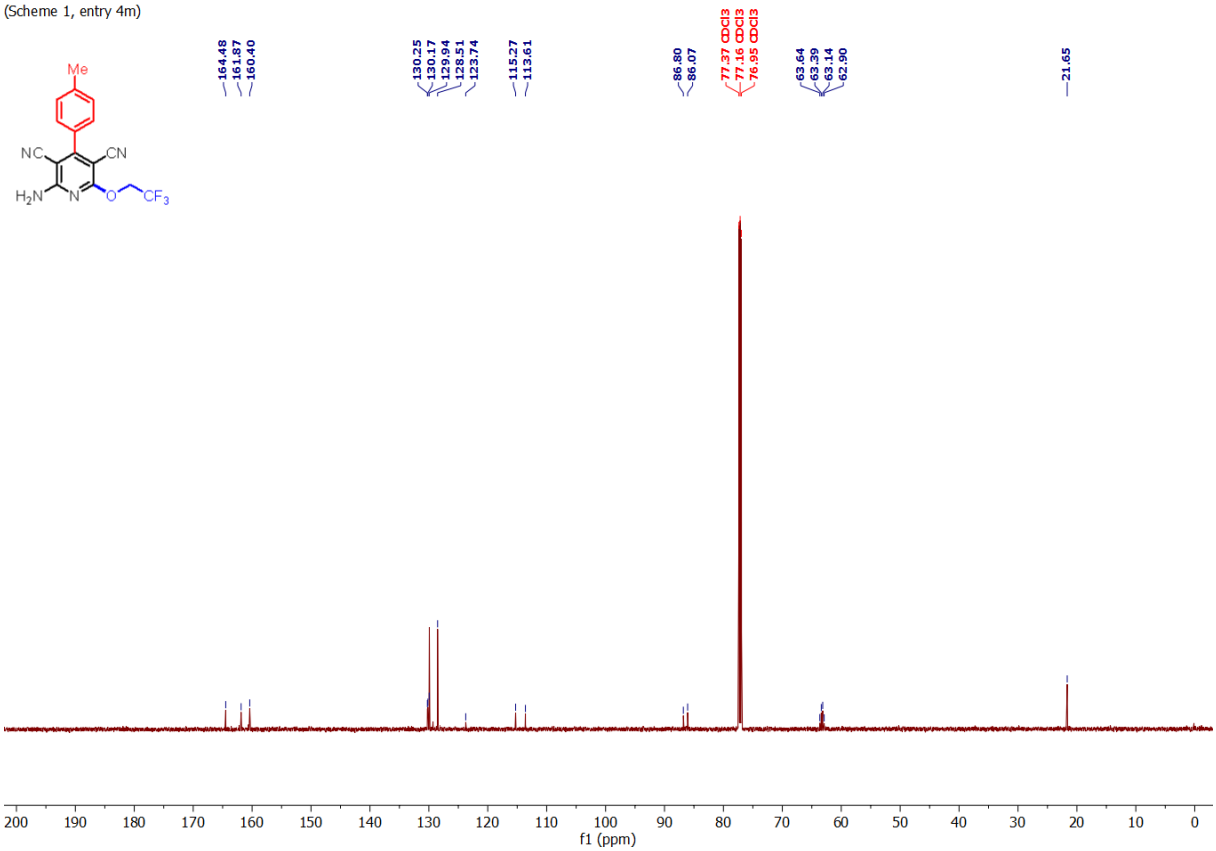




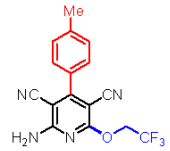
(Scheme 1, entry 4m)

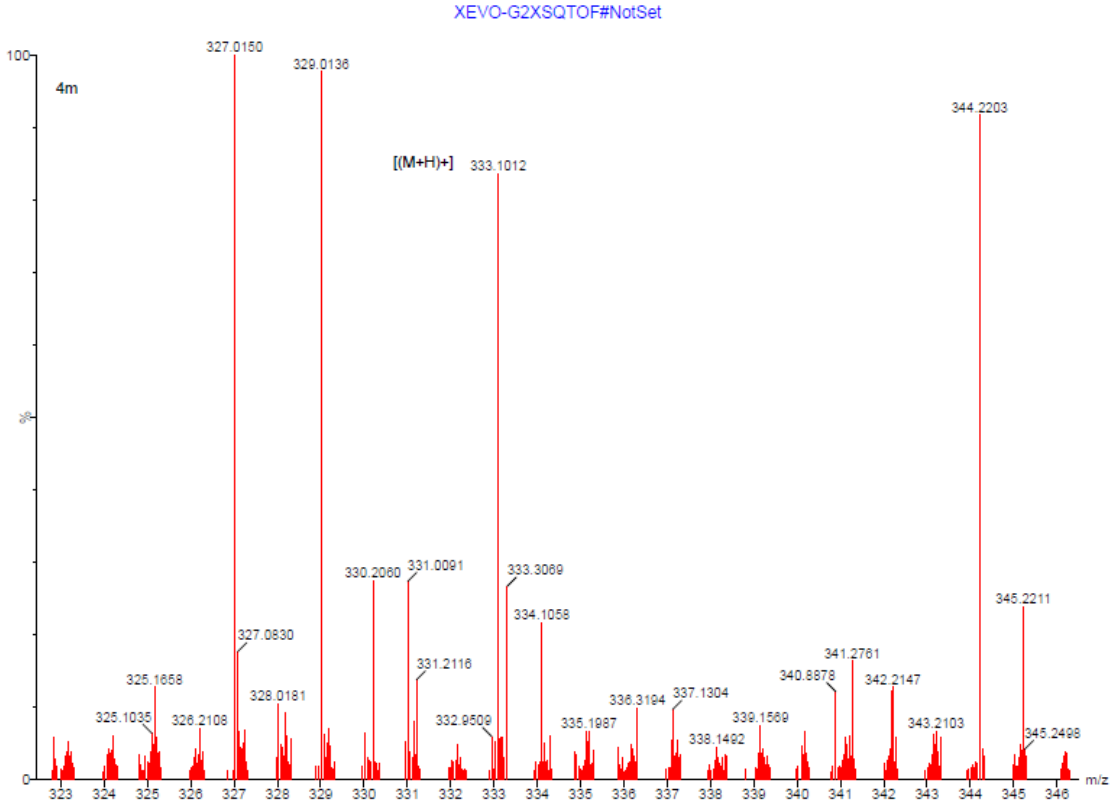


(Scheme 1, entry 4m)

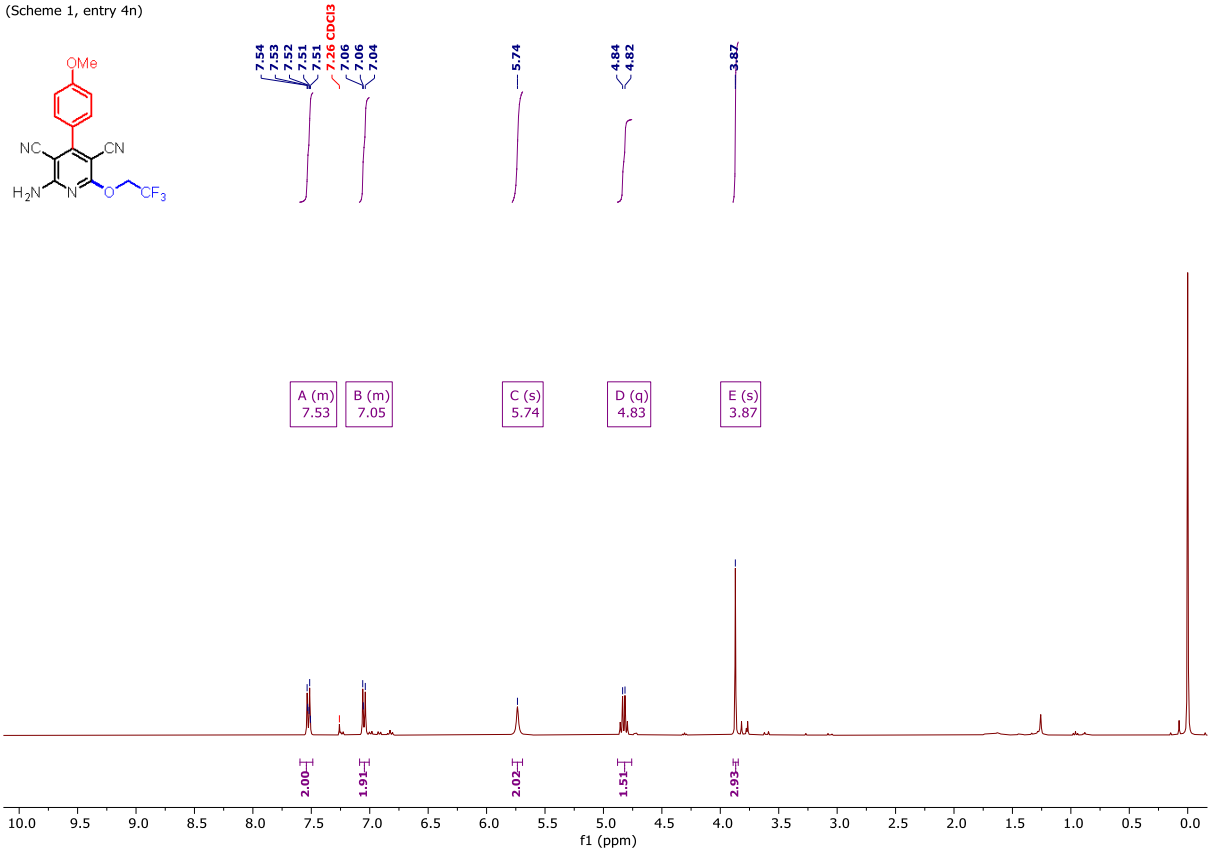


(Scheme 1, entry 4m)

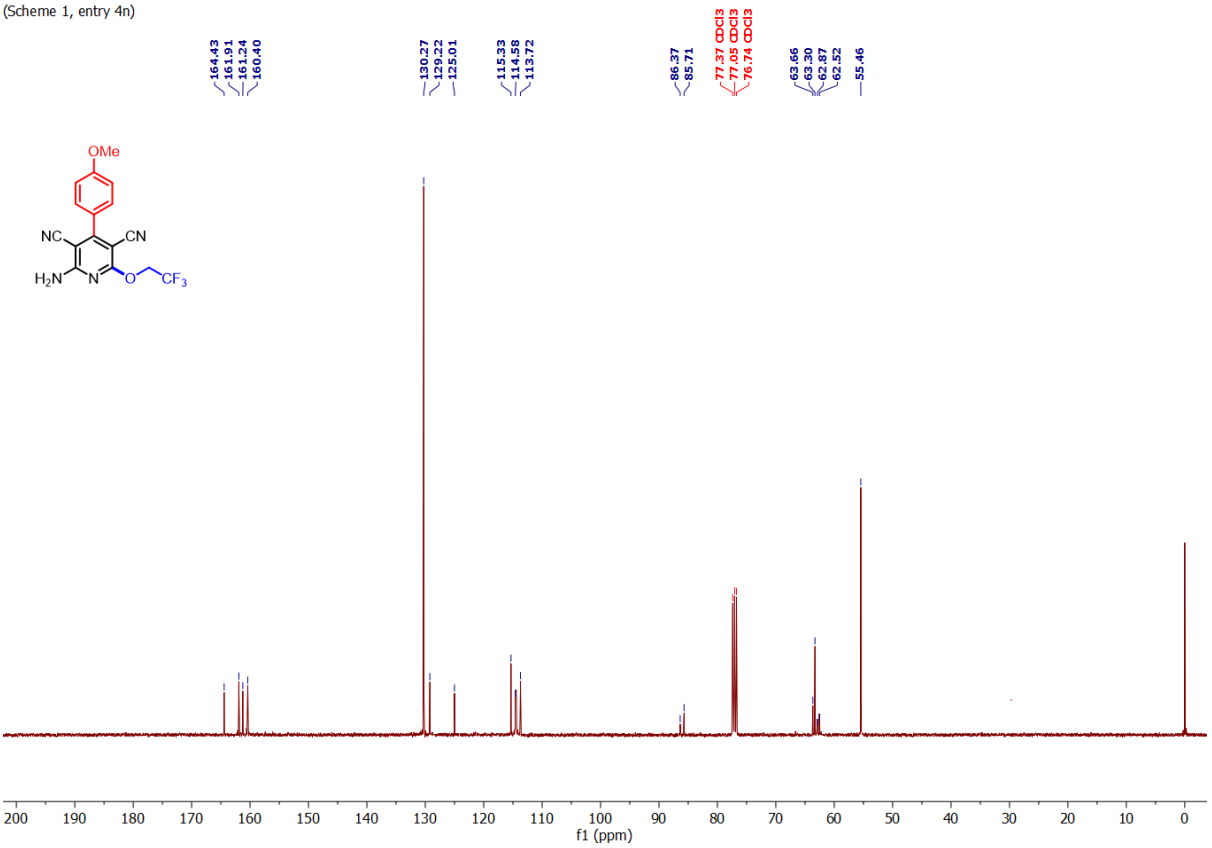




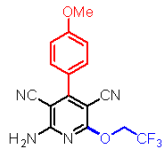
(Scheme 1, entry 4n)

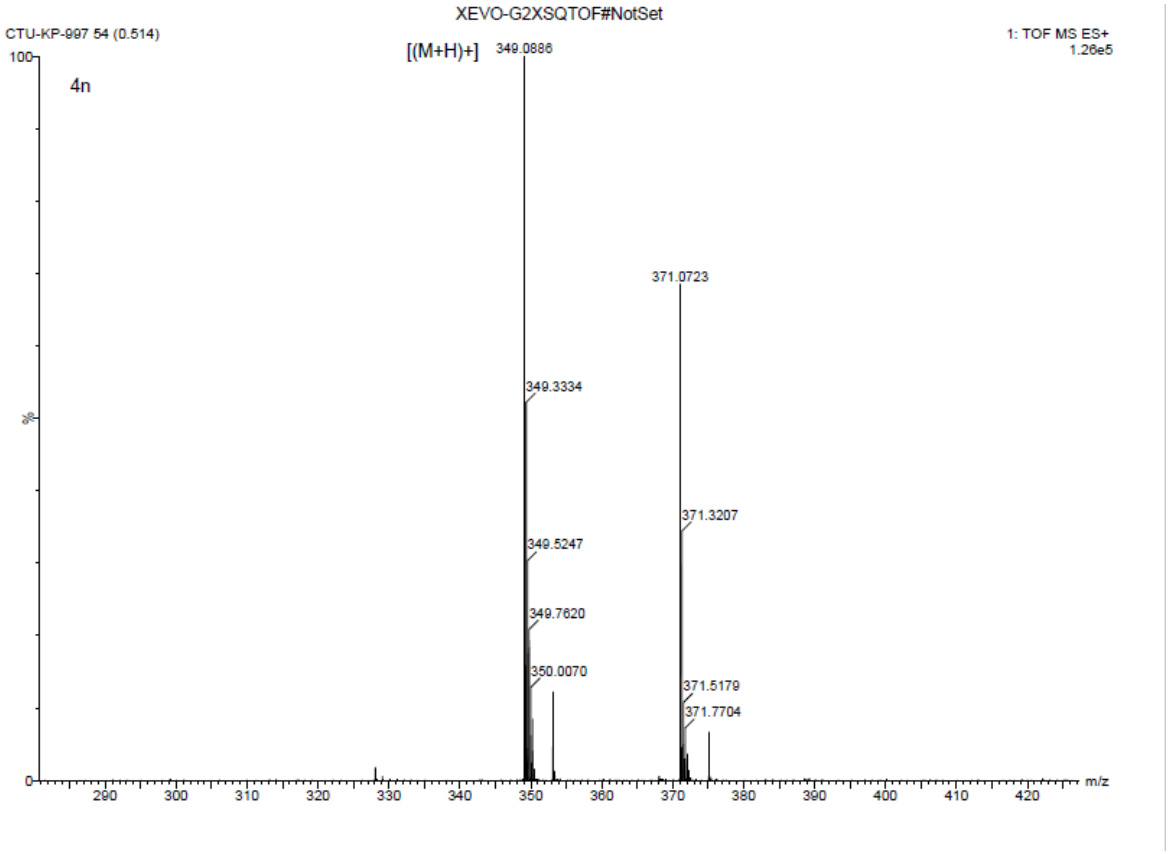


(Scheme 1, entry 4n)

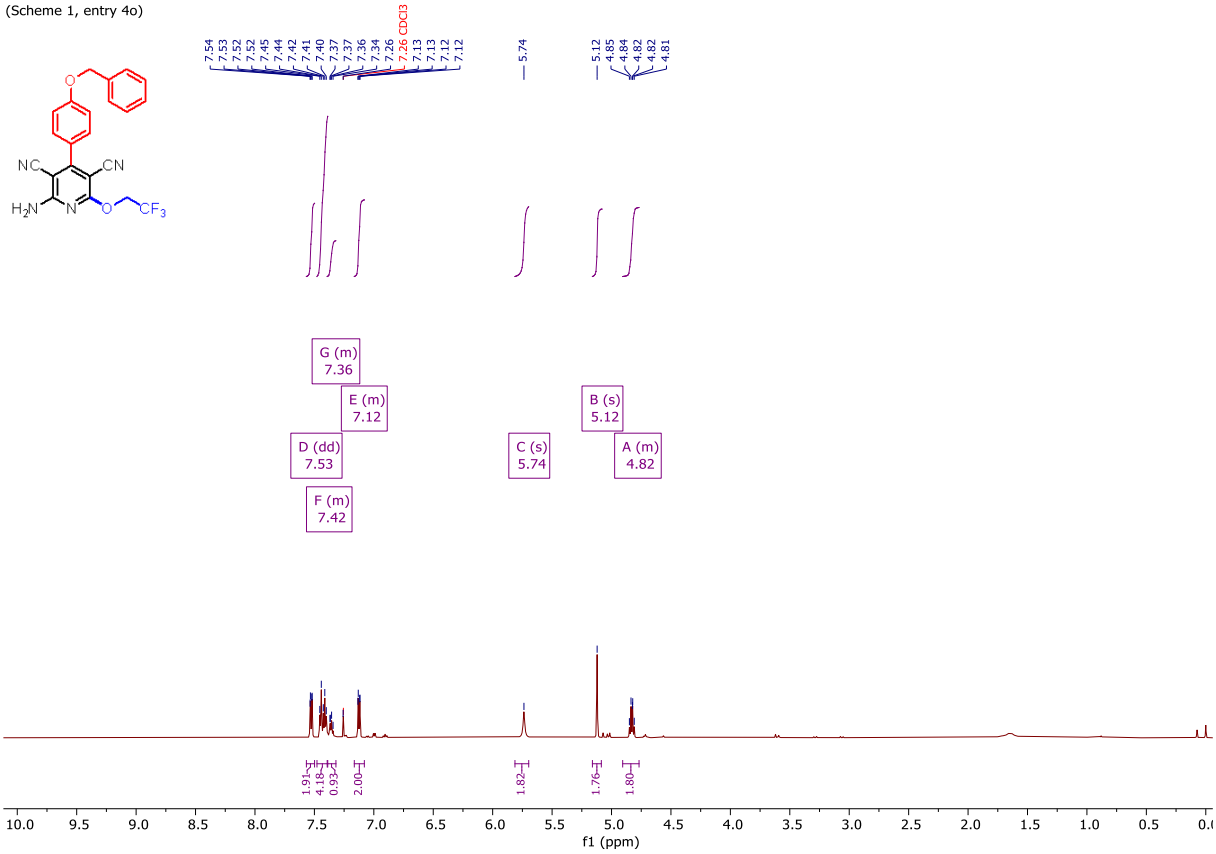


(Scheme 1, entry 4n)

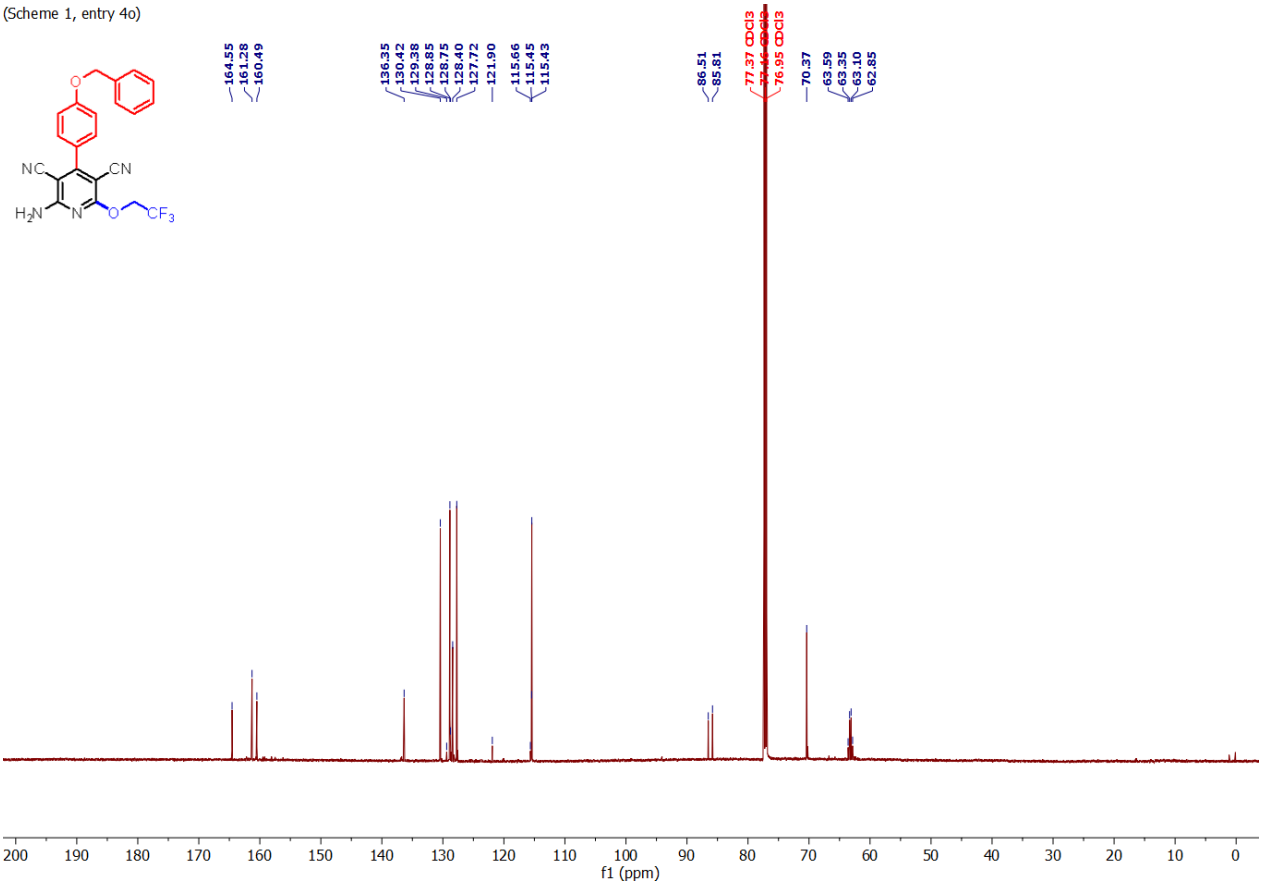




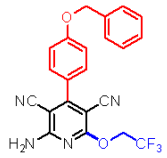
(Scheme 1, entry 4o)

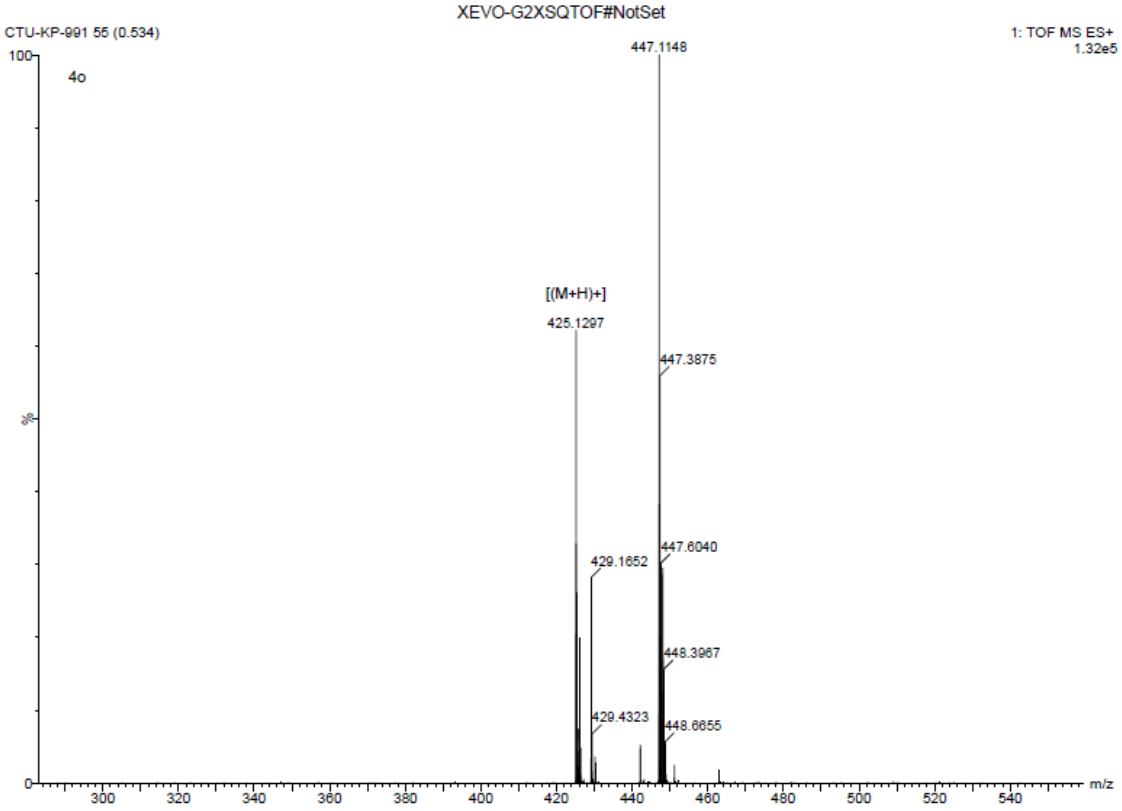


(Scheme 1, entry 4o)

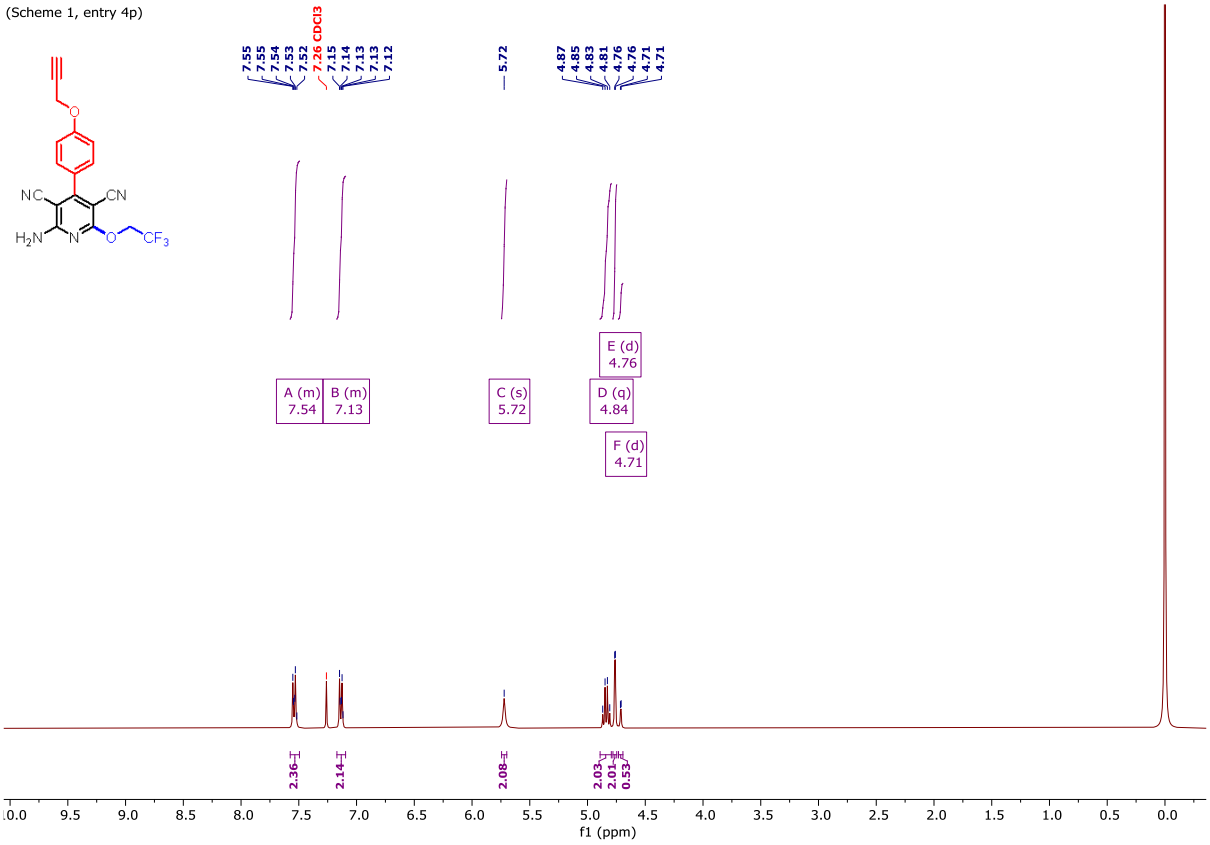


(Scheme 1, entry 4o)

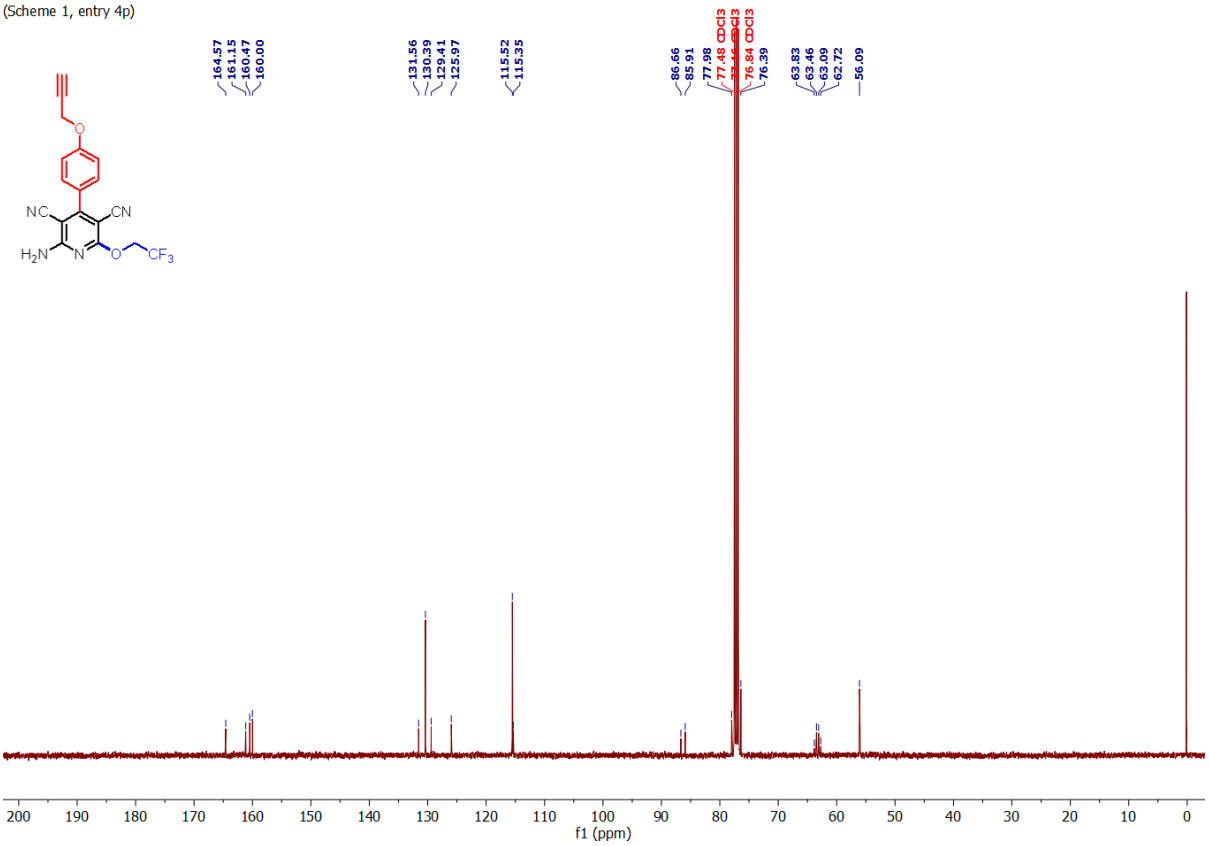




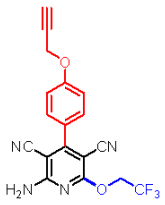
(Scheme 1, entry 4p)

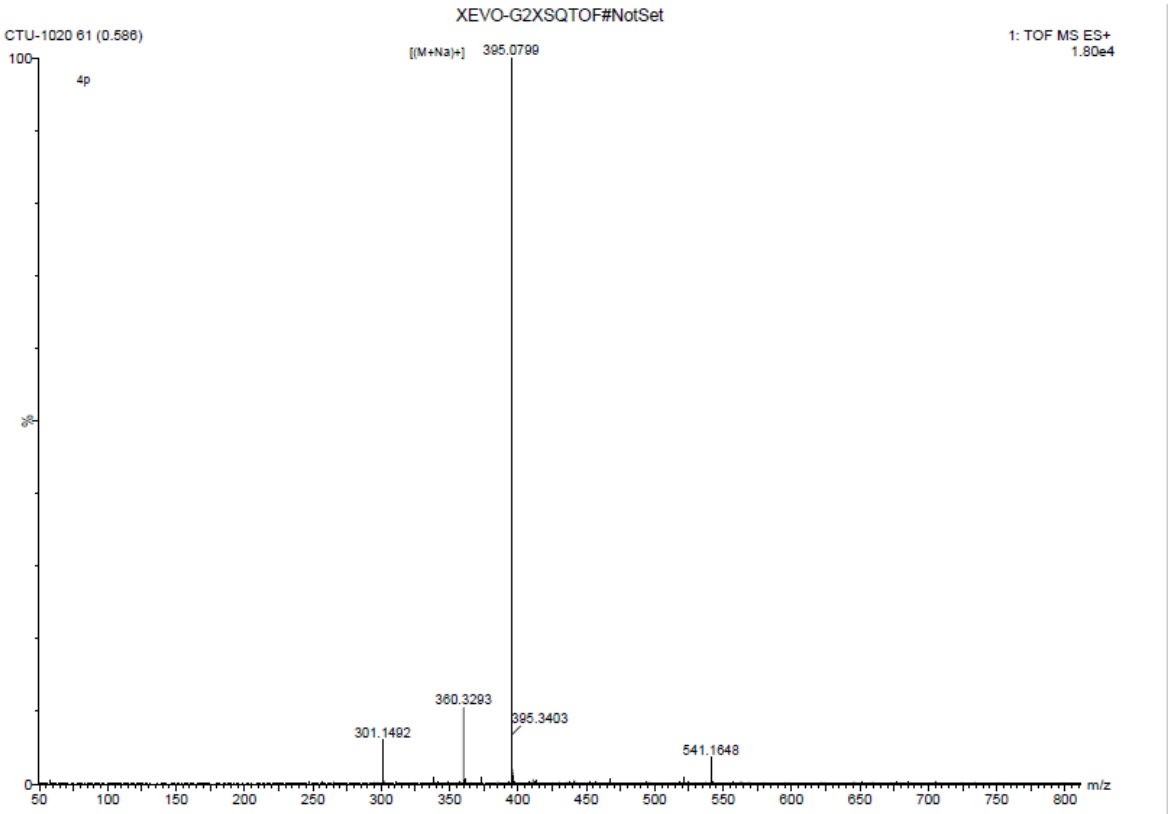


(Scheme 1, entry 4p)

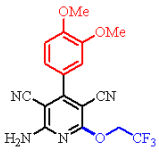


(Scheme 1, entry 4p)

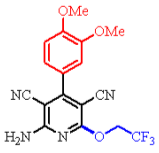




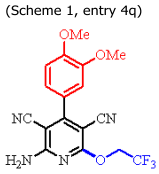
(Scheme 1, entry 4q)

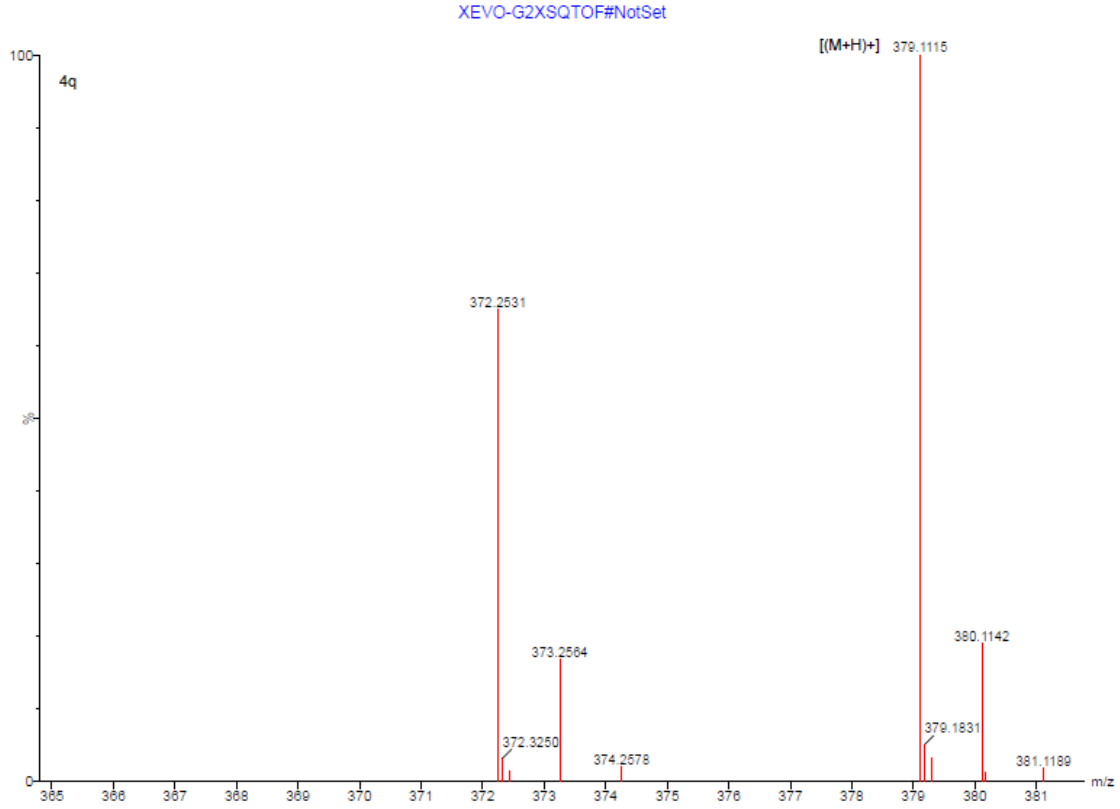


(Scheme 1, entry 4q)

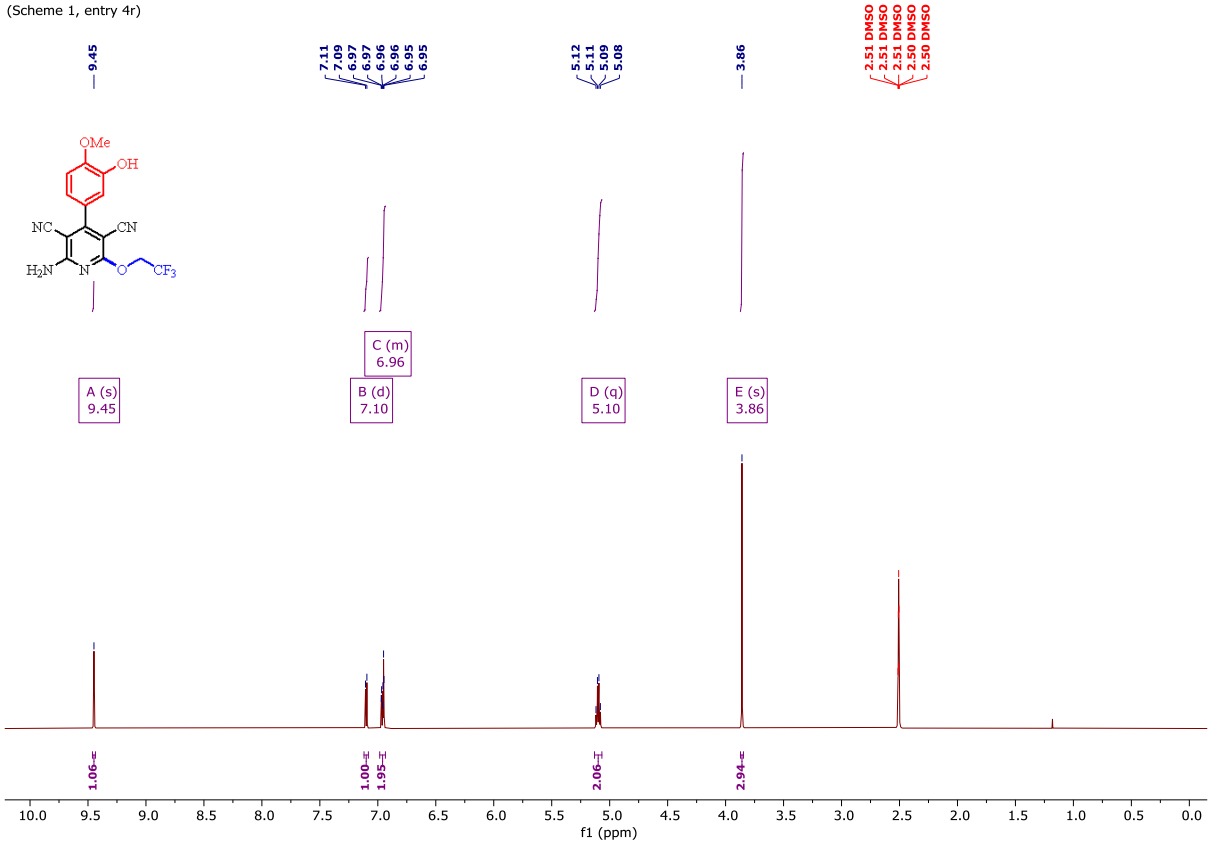


(Scheme 1, entry 4q)

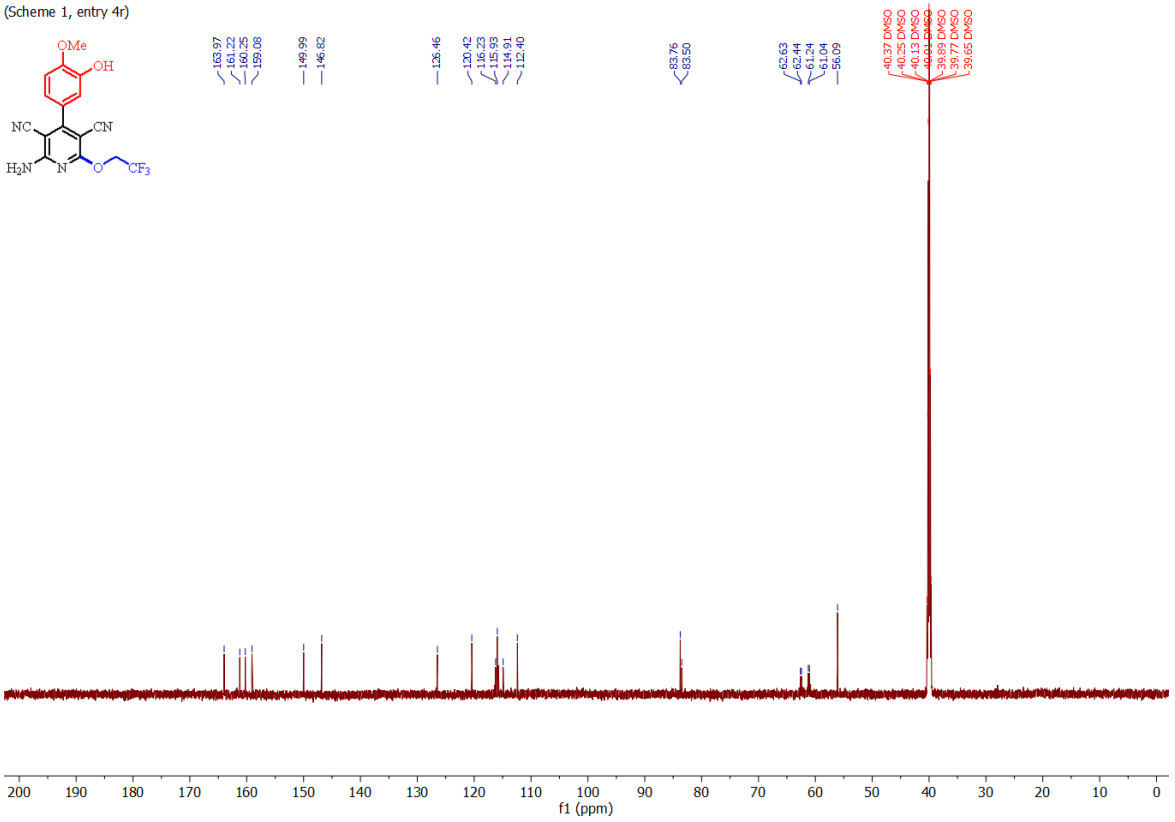




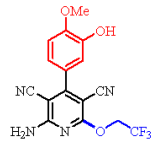
(Scheme 1, entry 4r)

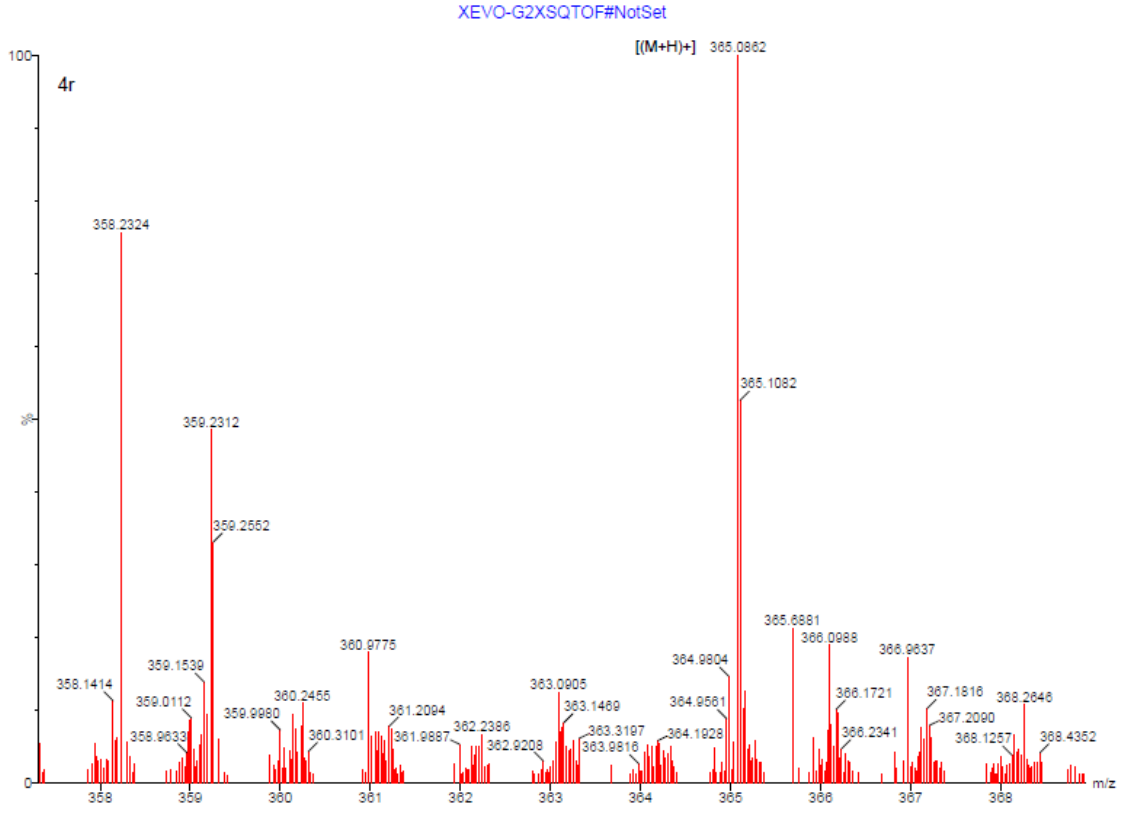


(Scheme 1, entry 4r)

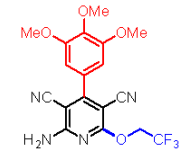


(Scheme 1, entry 4r)

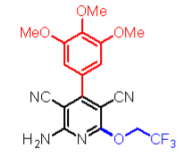




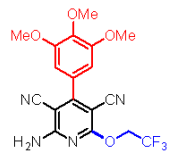
(Scheme 1, entry 4s)

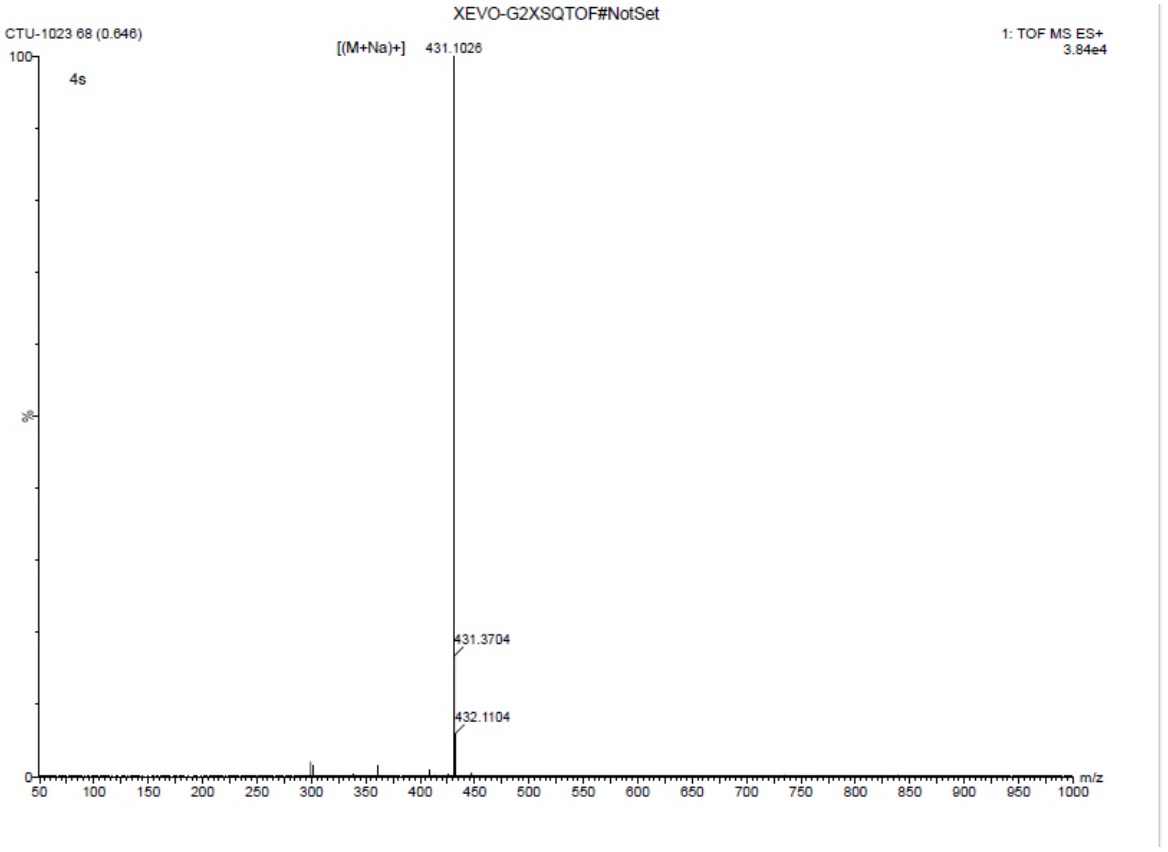


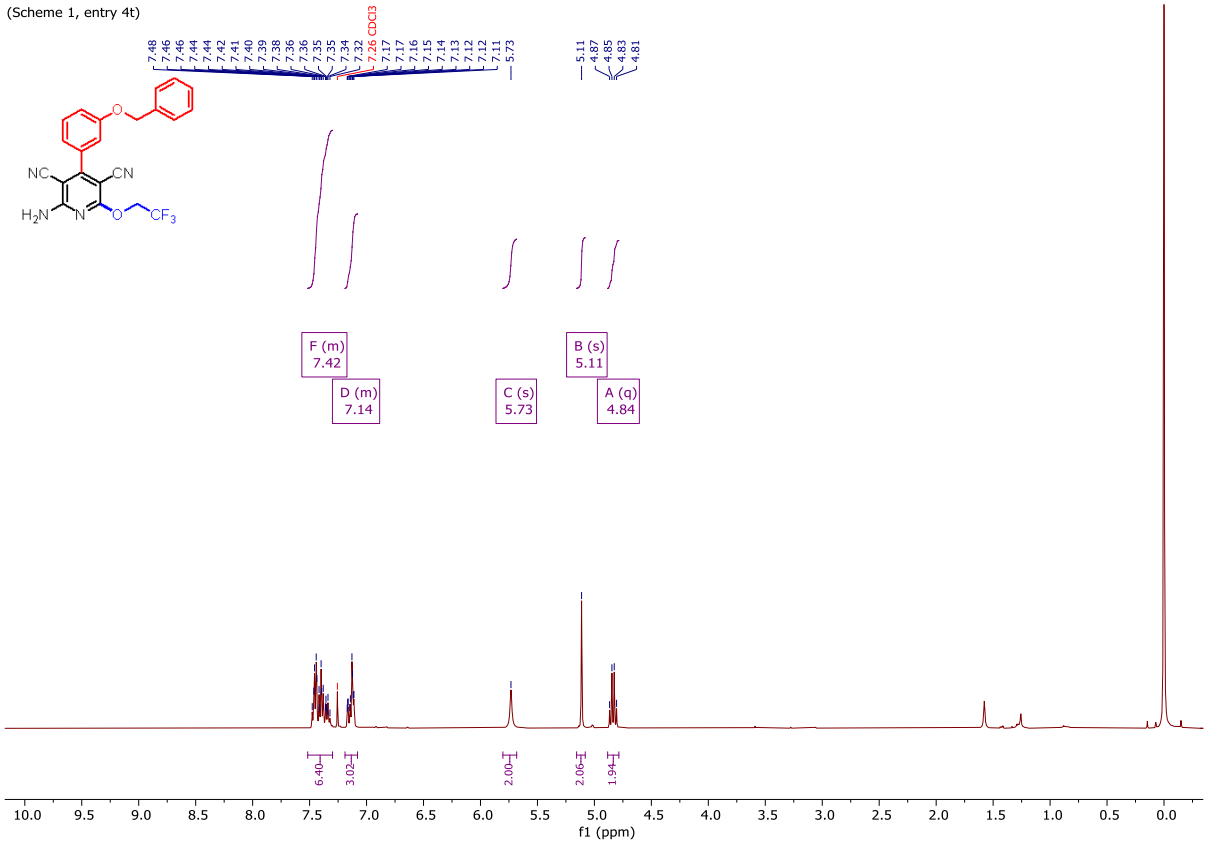
(Scheme 1, entry 4s)

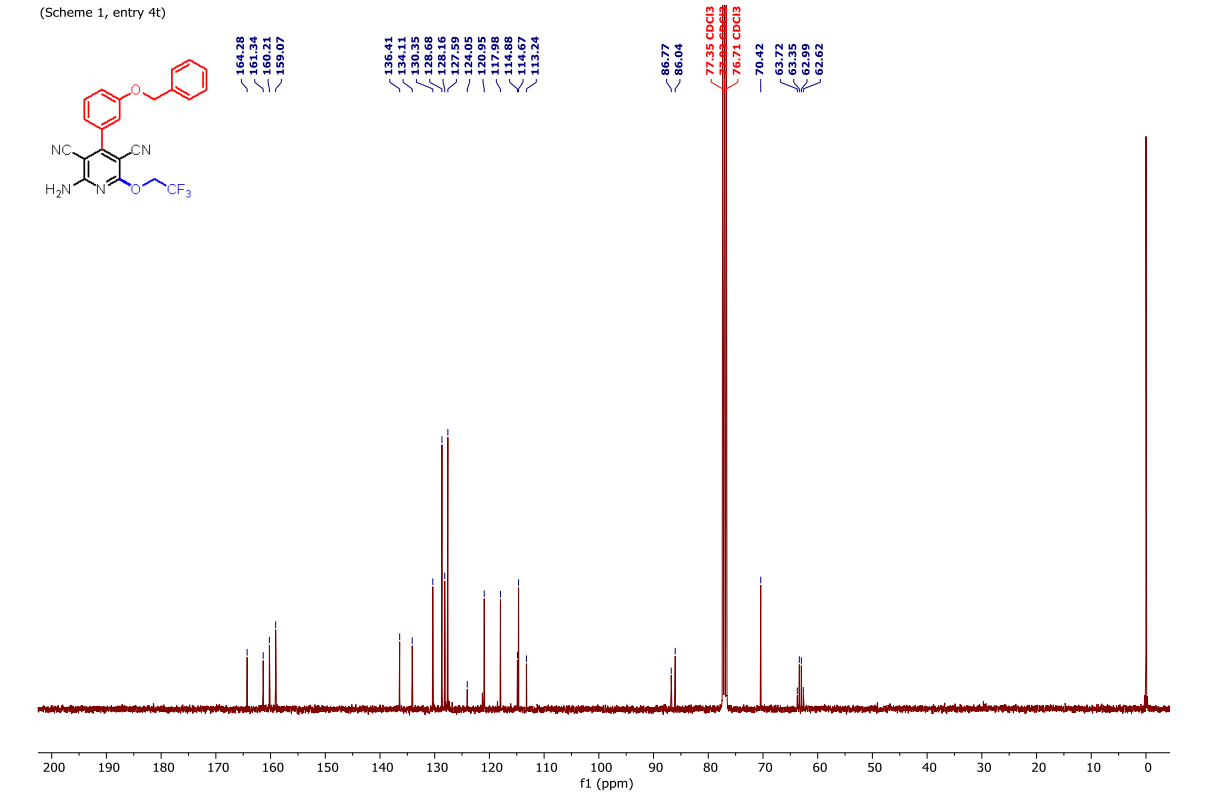


(Scheme 1, entry 4s)

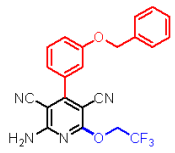


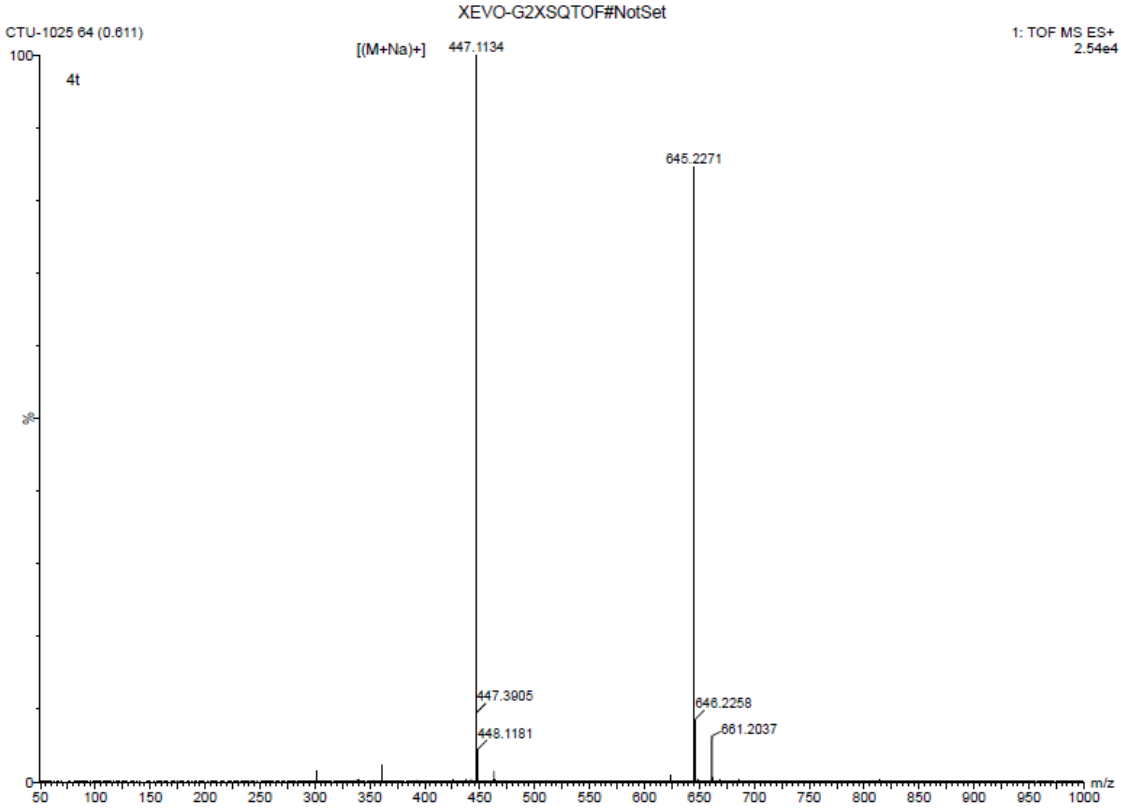



(Scheme 1, entry 4t)
7.48 7.46 7.46 7.44 7.44 7.42 7.41 7.40 7.39 7.38 7.36 7.36 7.35 7.35 7.34 7.32 7.26 CDCl3 7.17 7.17 7.16 7.15 7.14 7.13 7.12 7.12 7.11 5.73
5.11 4.87 4.85 4.83 4.81
NC CN
H2N N O CF3
F (m) 7.42
D (m) 7.14
C (s) 5.73
B (s) 5.11
A (q) 4.84
6.40 3.02 2.00 2.06 1.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

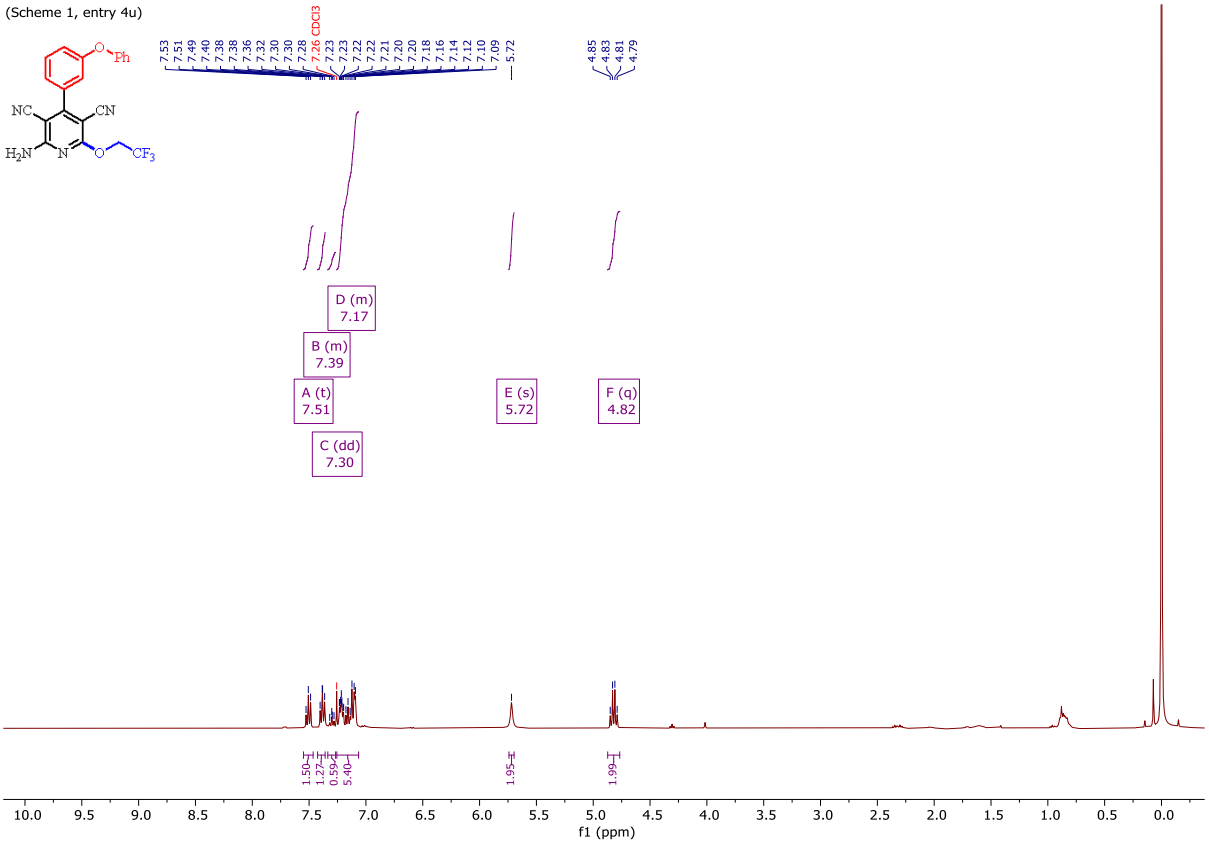

(Scheme 1, entry 4t)
164.28 161.34 160.21 159.07
136.41 134.11 130.35 128.68 128.16 127.59 124.05 120.95 117.98 114.88 114.67 113.24
86.77 86.04
77.35 CDCl3 76.71 CDCl3
70.42
63.72 63.35 62.99 62.62
NC CN
H2N N O CF3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(Scheme 1, entry 4t)

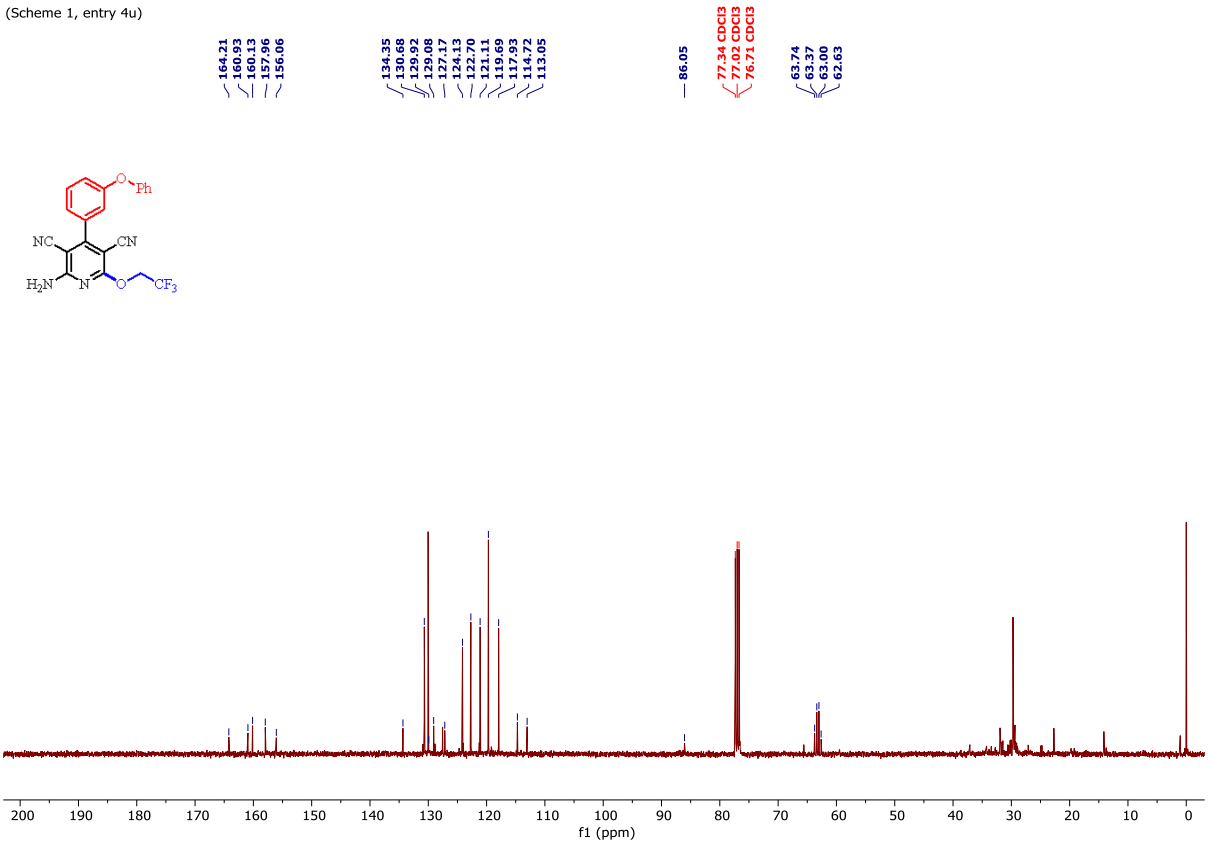




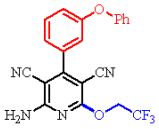
(Scheme 1, entry 4u)

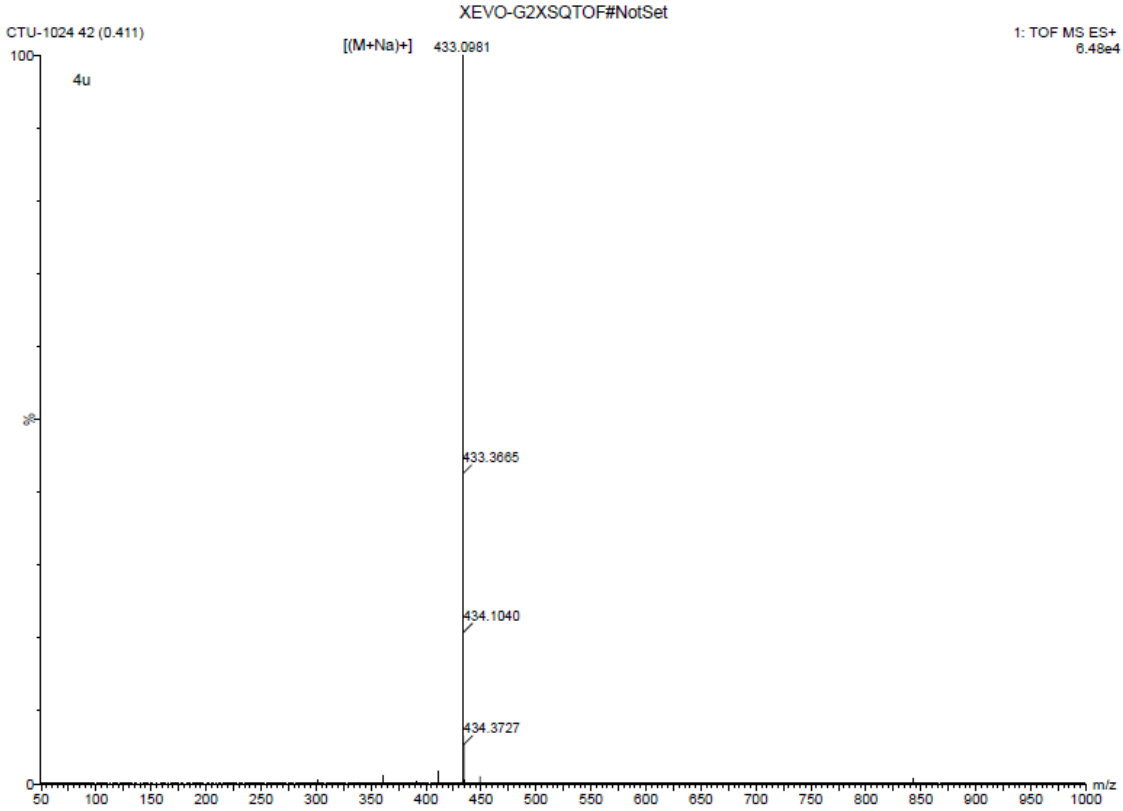


(Scheme 1, entry 4u)

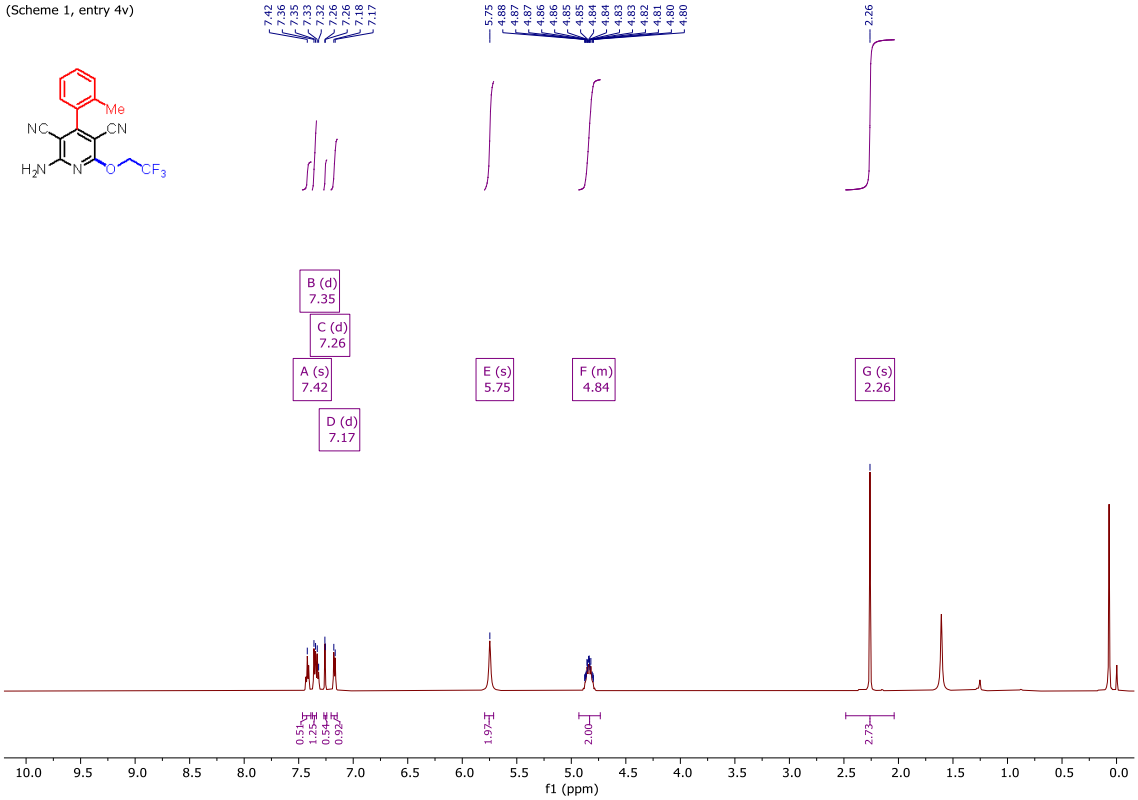


(Scheme 1, entry 4u)

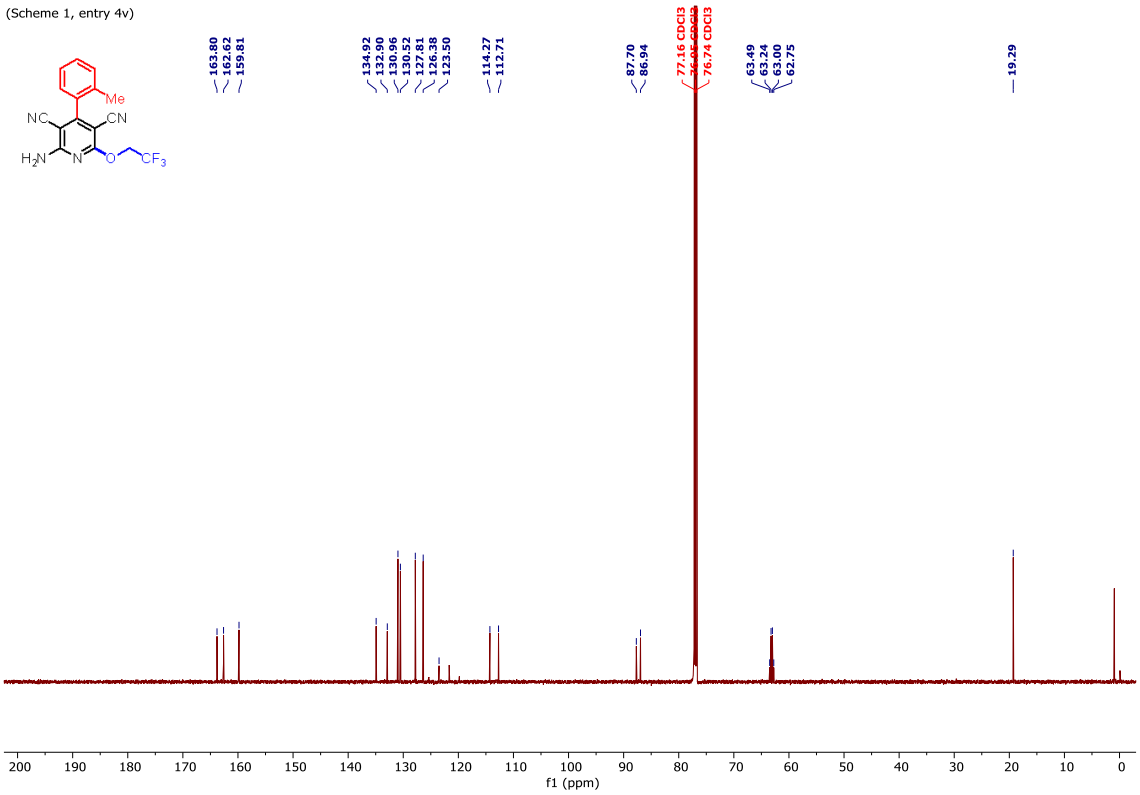




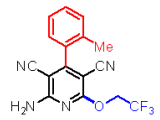
(Scheme 1, entry 4v)

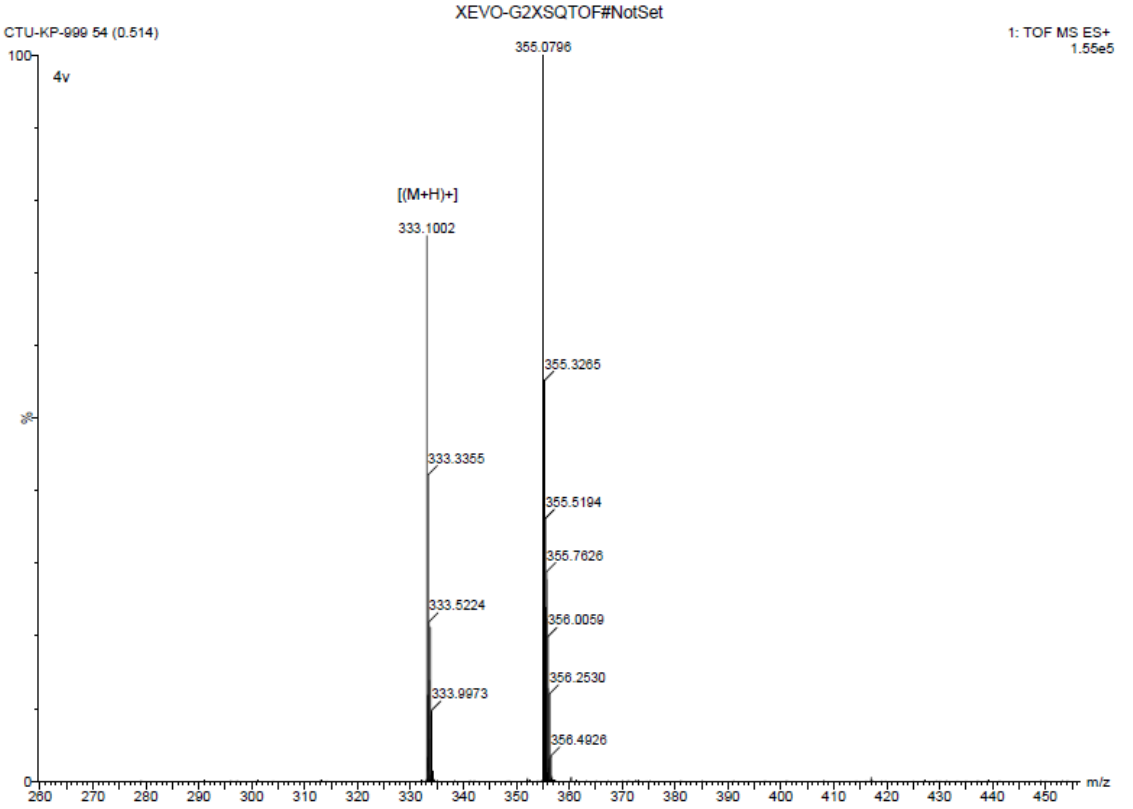


(Scheme 1, entry 4v)

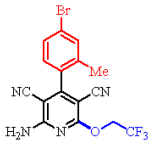


(Scheme 1, entry 4v)

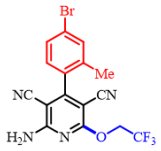




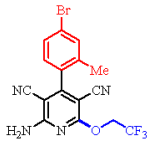
(Scheme 1, entry 4w)

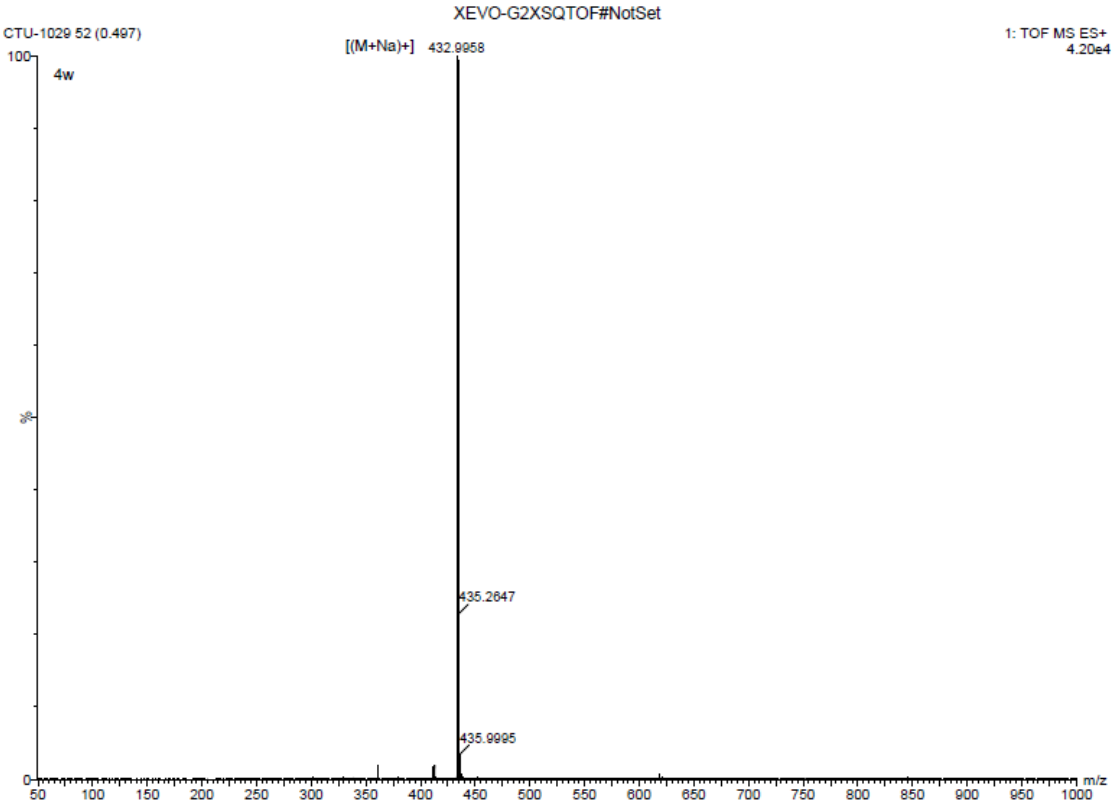


(Scheme 1, entry 4w)

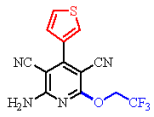


(Scheme 1, entry 4w)





(Scheme 1, entry 4x)



(Scheme 1, entry 4x)

(Scheme 1, entry 4x)