SAR Based Optimization of a 4-Quinoline Carboxylic Acid Analog with Potent Anti-Viral Activity

Supporting Information

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Contents:

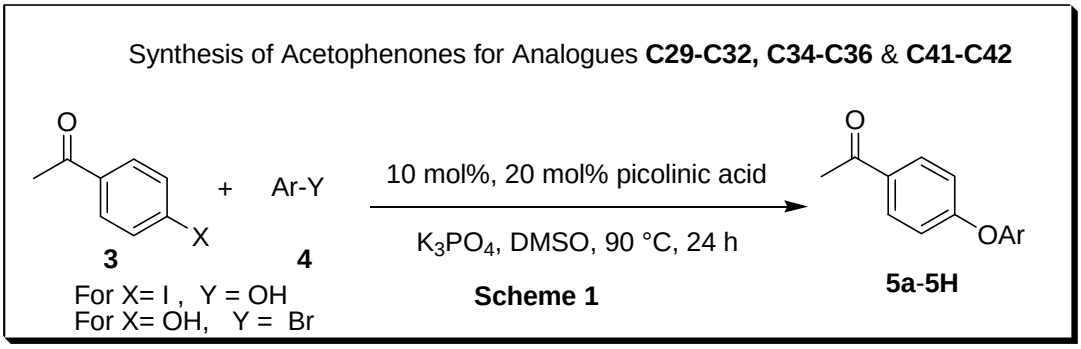
General Experimental:

Unless otherwise noted, commercially available materials were used without further purification. All solvents were of HPLC or ACS grade. Anhydrous DMSO and EtOH were purchased from commercial sources. Reactions were performed under an atmosphere of argon with magnetic stirring unless noted otherwise. Flash chromatography (FC) was performed using *E Merck* silica gel 60 (240–400 mesh). Thin layer chromatography was performed using pre-coated plates purchased from *E. Merck* (silica gel 60 PF254, 0.25 mm) that were visualized using a $KMnO_4$ or Ce (IV)stain. Nuclear magnetic resonance (NMR) spectra were recorded on a *Varian Inova*-400, *Varian Inova*-500 spectrometer at operating frequencies of 400/500 MHz (^{1}H NMR) or 125/100 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to residual solvent and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplate. Electrospray ionization mass spectra (ESI-MS) were recorded on a Shimadzu 2010-LCMS and/or on a Micromass Q-Tof Ultima spectrometer. All compounds were at least 95% pure.

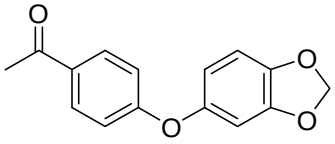
Synthetic Procedures:

Compounds **C2-C44** were synthesized according to a modified literature procedure.[1] All the substituted isatins were commercially available. Most of the substituted acetophenones were commercially available except for analogues **C30-C33**, **C34-C36** and **C41-C42** for which appropriate acetophenones were synthesized via a modified Buchwald type C-O bond formation methodology.[2] However, for analogues **C43** and **C44**, the corresponding acetophenones were synthesized via a Chan-Lam type C-O bond formation methodology.[3]

(1) Mueller, G. P.; Stobaugh, R. E. Steric hindrance in the Pfitzinger reaction. *J. Am. Chem. Soc.* **1950**, *72*, 1598.
(2) Maiti, D.; Buchwald, S. L. Cu catalyzed arylation of phenols: synthesis of sterically hindered and heteroaryl diaryl ethers. *J. Org. Chem.* **2010**, *75*, 1791.
(3) Qiao, J. X.; Lam, P. Y. S. Copper-promoted carbon-heteroatom bond cross-coupling with boronic acids and derivatives. *Synthesis* 2011, *6*, 829.



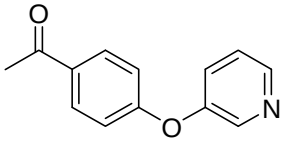
1-(4-(benzo[d][1,3]dioxol-6-yloxy)phenyl)ethanone (5a):



An oven-dried schlenk tube was charged with a magnetic stir bar, 4-iodoacetophenone (1.0 g, 4.06 mmol), benzo[d][1,3]dioxol-5-ol (560.3 mg, 4.06 mmol), Copper (I) iodide (77.3 mg, 0.41 mmol), picolinic acid (99.9 mg, 0.81 mmol) and potassium phosphate (tribasic) (1.72 g, 8.12 mmol). The tube was then evacuated and back filled with nitrogen. The protocol was repeated two times. Under a counter flow of nitrogen, 8 mL of DMSO was added via a syringe. The tube was placed in a preheated oil bath at 90 ºC and the reaction slurry was stirred vigorously for 24 h. The reaction mixture was cooled to room temperature. Ethyl acetate (60 mL) and water (5 mL) were added and the reaction mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted three more times with ethyl acetate (60 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered through a small pad of silica gel. The filtrate was concentrated and the resulting residue was purified by column chromatography (15% EA in Hex) to yield the title compound, 351.0 mg (33.7%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.53 (s, 3H), 5.97 (s, 2H), 6.51 (dd, J = 8.2, 2.0 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz,

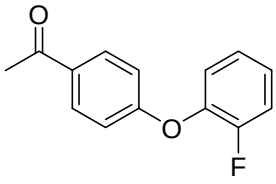
2H); ^{13}C NMR (100 MHz, $CDCl_3$): 26.4, 101.7, 102.9, 108.4, 113.0, 116.5, 130.5, 131.6, 144.7, 148.6, 149.6, 162.2, 196.6. ESI-MS calcd for $C_{15}H_{13}O_4$ (M+H), 257.1; found, 256.9.

1-(4-(pyridin-3-yloxy)phenyl)ethanone (5b):



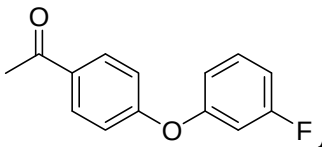
An oven-dried schlenk tube was charged with a magnetic stir bar, 4-iodoacetophenone (1.0 g, 4.06 mmol), 3-hydroxypyridine (386.1 mg, 4.06 mmol), Copper (I) iodide (77.3 mg, 0.41 mmol), picolinic acid (99.9 mg, 0.81 mmol) and potassium phosphate (tribasic) (1.72 g, 8.12 mmol). The tube was then evacuated and back filled with nitrogen. The protocol was repeated two times. Under a counter flow of nitrogen, 8 mL of DMSO was added via a syringe. The tube was placed in a preheated oil bath at 90 ºC and the reaction slurry was stirred vigorously for 24 h. The reaction mixture was cooled to room temperature. Ethyl acetate (60 mL) and water (5 mL) were added and the reaction mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted three more times with ethyl acetate (60 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered through a small pad of silica gel. The filtrate was concentrated and the resulting residue was purified by column chromatography (60% EA in Hex) to yield the title compound, 259.7 mg (30%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.54 (s, 3H), 6.98 (d, J = 8.2 Hz, 2H), 7.34 (m, 2H), 7.92 (d, J = 8.2 Hz, 2H), 8.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 26.5, 117.5, 124.4, 127.0, 130.7, 132.6, 142.4, 145.6, 152.3, 160.9, 196.6. ESI-MS calcd for $C_{13}H_{12}NO_2$ (M+H), 214.1; found, 214.0.

1-(4-(2-fluorophenoxy)phenyl)ethanone (5c):



An oven-dried schlenk tube was charged with a magnetic stir bar, 4-iodoacetophenone (1.0 g, 4.06 mmol), 2-fluorophenol (455.1 mg, 4.06 mmol), Copper (I) iodide (77.3 mg, 0.41 mmol), picolinic acid (99.9 mg, 0.81 mmol) and potassium phosphate (tribasic) (1.72 g, 8.12 mmol). The tube was then evacuated and back filled with nitrogen. The protocol was repeated two times. Under a counter flow of nitrogen, 8 mL of DMSO was added via a syringe. The tube was placed in a preheated oil bath at 90 ºC and the reaction slurry was stirred vigorously for 24 h. The reaction mixture was cooled to room temperature. Ethyl acetate (60 mL) and water (5 mL) were added and the reaction mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted three more times with ethyl acetate (60 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered through a small pad of silica gel. The filtrate was concentrated and the resulting residue was purified by column chromatography (20% EA in Hex) to yield the title compound, 350.0 mg (38%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.53 (s, 3H), 6.95 (d, J = 8.8 Hz, 2H), 7.15 (m, 4H), 7.91 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 26.6, 116.0, 117.3 (d, J = 18.0 Hz), 123.0, 125.0 (d, J = 3.0 Hz), 126.1 (d, J = 7.0 Hz), 126.2, 132.0, 142.0, 154.5 (d, J = 249.0 Hz), 161.6, 196.2. ESI-MS calcd for $C_{14}H_{18}FO_2$ (M+H), 231.1; found, 231.0.

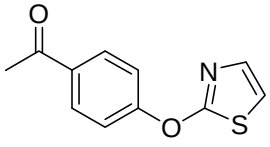
1-(4-(3-fluorophenoxy)phenyl)ethanone (5d):



An oven-dried schlenk tube was charged with a magnetic stir bar, 4-iodoacetophenone (1.0 g, 4.06 mmol), 3-fluorophenol (455.1 mg, 4.06 mmol), Copper (I) iodide

(77.3 mg, 0.41 mmol), picolinic acid (99.9 mg, 0.81 mmol) and potassium phosphate (tribasic) (1.72 mg, 8.12 mmol). The tube was then evacuated and back filled with nitrogen. The protocol was repeated two times. Under a counter flow of nitrogen, 8 mL of DMSO was added via a syringe. The tube was placed in a preheated oil bath at 90 ºC and the reaction slurry was stirred vigorously for 24 h. The reaction mixture was cooled to room temperature. Ethyl acetate (60 mL) and water (5 mL) were added and the reaction mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted three more times with ethyl acetate (60 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered through a small pad of silica gel. The filtrate was concentrated and the resulting residue was purified by column chromatography (20% EA in Hex) to yield the title compound, 368.0 mg (40%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.54 (s, 3H), 6.73 (dt, *J* = 9.8, 2.4 Hz, 1H), 6.84 (m, 2H), 7.0 (d, *J* = 8.3 Hz, 2H), 7.30 (dt, *J* = 8.3, 6.6 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 26.4, 107.4 (d, *J* = 24.0 Hz), 111.2 (d, *J* = 21.0 Hz), 115.2 (*J* = 3.0 Hz), 117.8, 130.6, 130.8 (*J* = 10.0 Hz), 132.5, 157.0 (d, *J* = 10.0 Hz), 160.9, 163.0 (d, *J* = 247.0 Hz), 196.6. ESI-MS calcd for $C_{14}H_{18}FO_2$ (M+H), 231.1; found, 230.9.

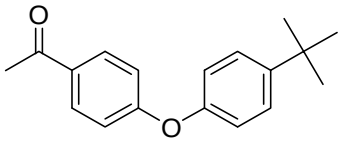
1-(4-(thiazol-2-yloxy)phenyl)ethanone (5e):



An oven-dried schlenk tube was charged with a magnetic stir bar, 4-hydroxyacetophenone (500.0 mg, 3.67 mmol), 2-bromothiazole (221 µL, 2.45 mmol), Copper (I) iodide (47.0 mg, 0.24 mmol), picolinic acid (60.0 mg, 0.49 mmol) and potassium phosphate (tribasic) (1.04 g, 4.88 mmol). The tube was then evacuated and back filled with nitrogen. The protocol was repeated two times. Under a counter flow of nitrogen, 4mL of DMSO was added via a syringe. The tube was placed in a preheated oil bath at 90 ºC and the reaction slurry was

stirred vigorously for 24 h. The reaction mixture was cooled to room temperature. Ethyl acetate (30 mL) and water (3 mL) were added and the reaction mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted three more times with ethyl acetate (40 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered through a small pad of silica gel. The filtrate was concentrated and the resulting residue was purified by column chromatography (50% EA in Hex) to yield the title compound, 161.0 mg (30%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.60 (s, 3H), 6.90 (d, J = 4.1 Hz, 1H), 7.25 (d, J = 4.1 Hz, 1H), 7.35 (d, J = 8.6 Hz, 2H), 8.01 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 26.6,114.0, 119.4, 130.4, 134.2, 137.6, 158.9, 172.0, 196.6. ESI-MS calcd for $C_{11}H_{10}NO_2S$ (M+H), 220.0; found, 219.9.

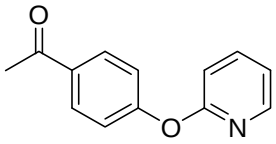
1-(4-(4-tert-butylphenoxy)phenyl)ethanone (**5f**):



An oven-dried schlenk tube was charged with a magnetic stir bar, 4-iodoacetophenone (250.0 mg, 1.02 mmol), 4-*tert*-butylphenol (183.2 mg, 1.22 mmol), Copper (I) iodide (9.71 mg, 0.05 mmol), picolinic acid (13.5 mg, 0.11 mmol) and potassium phosphate (tribasic) (433.0 mg, 2.04 mmol). The tube was then evacuated and back filled with nitrogen. The protocol was repeated two times. Under a counter flow of nitrogen, 2 mL of DMSO was added via a syringe. The tube was placed in a preheated oil bath at 90 ºC and the reaction slurry was stirred vigorously for 24 h. The reaction mixture was cooled to room temperature. Ethyl acetate (25 mL) and water (5 mL) were added and the reaction mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted three more times with ethyl acetate (20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered through a small pad of silica gel. The filtrate was concentrated and the resulting residue

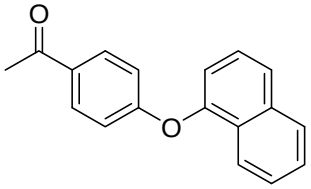
was purified by column chromatography (15% EA in Hex) to yield the title compound, 218.9 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): 1.32 (s, 9H), 2.55 (s, 3H), 6.97 (d, J = 9.6 Hz, 4H), 7.38 (d, J = 8.7 Hz 2H), 7.91 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 26.4, 31.5, 34.4, 117.0, 119.7, 126.8, 130.5, 131.6, 147.5, 152.9, 162.3, 196.7. ESI-MS calcd for $C_{18}H_{21}O_2$ (M+H), 269.2 found, 269.0.

1-(4-(pyridin-2-yloxy)phenyl)ethanone (**5g**):

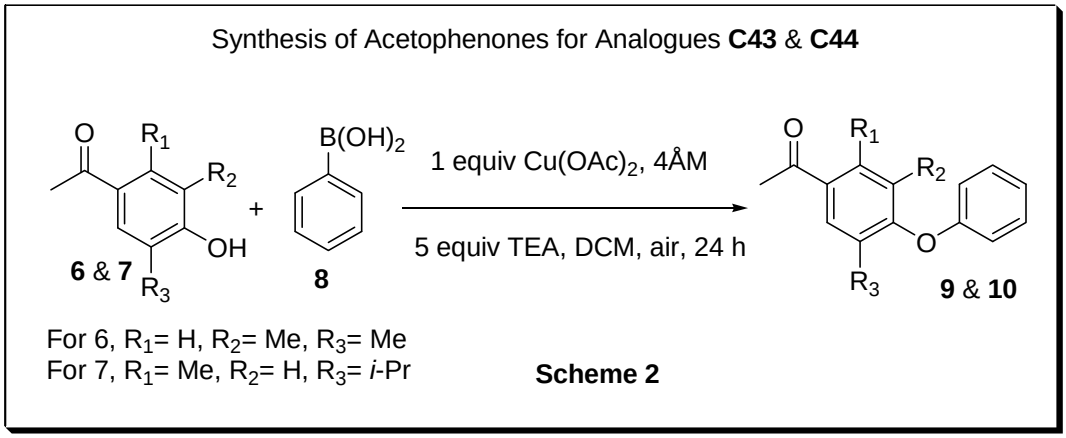


An oven-dried schlenk tube was charged with a magnetic stir bar, 4-hydroxyacetophenone (500.0 mg, 3.67 mmol), 2-bromopyridine (239 µL, 2.45 mmol), Copper (I) iodide (47.0 mg, 0.24 mmol), picolinic acid (60.0 mg, 0.49 mmol) and potassium phosphate (tribasic) (1.04 g, 4.88 mmol). The tube was then evacuated and back filled with nitrogen. The protocol was repeated two times. Under a counter flow of nitrogen, 4mL of DMSO was added via a syringe. The tube was placed in a preheated oil bath at 90 ºC and the reaction slurry was stirred vigorously for 24 h. The reaction mixture was cooled to room temperature. Ethyl acetate (30 mL) and water (3 mL) were added and the reaction mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted three more times with ethyl acetate (40 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered through a small pad of silica gel. The filtrate was concentrated and the resulting residue was purified by column chromatography (60% EA in Hex) to yield the title compound, 472.2 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.49 (s, 3H), 6.89 (d, J = 8.2 Hz, 1H), 6.97 (dd, J = 7.3, 5.1 Hz, 1H), 7.10 (d, J = 8.6 Hz, 2H), 7.64 (m, 1H), 7.91 (d, J = 8.6 Hz, 2H), 8.12 (dd, J = 5.0, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 26.5, 112.4, 119.4, 120.4, 120.5, 130.3, 133.2, 147.6, 158.4, 162.6, 196.8. ESI-MS calcd for $C_{13}H_{12}NO_2$ (M+H), 214.1; found, 214.0.

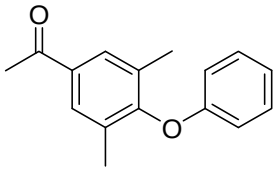
1-(4-(naphthalen-2-yloxy)phenyl)ethanone (5h):



An oven-dried schlenk tube was charged with a magnetic stir bar, 4-iodoacetophenone (1.0 g, 4.06 mmol), 2-napthol (585.3 mg, 4.06 mmol), Copper (I) iodide (77.3 mg, 0.41 mmol), picolinic acid (99.9 mg, 0.81 mmol) and potassium phosphate (tribasic) (1.72 g, 8.12 mmol). The tube was then evacuated and back filled with nitrogen. The protocol was repeated two times. Under a counter flow of nitrogen, 8 mL of DMSO was added via a syringe. The tube was placed in a preheated oil bath at 90 ºC and the reaction slurry was stirred vigorously for 24 h. The reaction mixture was cooled to room temperature. Ethyl acetate (60 mL) and water (5 mL) were added and the reaction mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted three more times with ethyl acetate (60 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered through a small pad of silica gel. The filtrate was concentrated and the resulting residue was purified by column chromatography (25% EA in Hex) to yield the title compound, 511.2 mg (48%). ^{1}H NMR (500 MHz, $CDCl_3$): 2.60 (s, 3H), 7.06 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 1H), 7.48 (m, 3H), 7.76 (d, J = 8.8 Hz, 1H), 7.87 (m, 2H), 7.96 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 26.8, 116.5, 116.5, 117.8, 120.6, 125.6, 127.1, 128.1, 130.5, 130.9, 131.0, 132.3, 134.5, 153.4, 162.2, 197.1. ESI-MS calcd for $C_{18}H_{15}O_2$ (M+H), 263.10; found, 263.0.

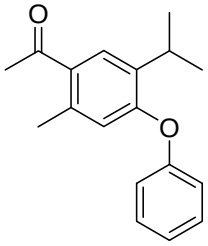


1-(3,5-dimethyl-4-phenoxyphenyl)ethanone (**9**):



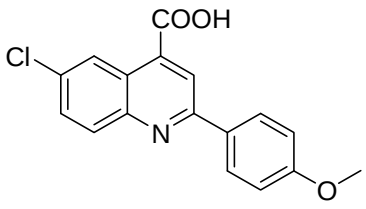
Into a flame dried round-bottomed flask was weighed 1-(4-hydroxy-3,5-dimethylphenyl)ethanone (328.0 mg, 2.0 mmol), phenyl boronic acid (488.0 mg, 4.0 mmol), copper acetate (726.5 mg, 4.0 mmol). 10 mL of dichloromethane was added to the flask before the addition of triethylamine (837 µL, 6.0 mmol). The flask was stirred at room temperature for 24 h. The solvent was removed using a rotary evaporator. Ethyl acetate (150 mL) and water (50 mL) were added and the reaction mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted three more times with ethyl acetate (300 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered through a small pad of silica gel. The filtrate was concentrated and the resulting residue was purified by column chromatography (25% EA in Hex) to yield the title compound, 432.5 mg (90%). ^{1}H NMR (500 MHz, $CDCl_3$): 2.16 (s, 6H), 2.58 (s, 3H), 6.73 (d, J = 7.7 Hz, 2H), 6.97 (t, J = 7.4 Hz, 1H), 7.20 (m, 2H), 7.71 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 16.5, 26.7, 114.6, 121.8, 129.5, 129.8, 131.9, 134.0, 155.2, 157.2,197.5. ESI-MS calcd for $C_{16}H_{17}O_2$ (M+H), 241.1; found, 241.0

1-(5-isopropyl-2-methyl-4-phenoxyphenyl)ethanone (10):



Into a flame dried round-bottomed flask was weighed 1-(4-hydroxy-5-isopropyl-2-methylphenyl)ethanone (384.5 mg, 2.0 mmol), phenyl boronic acid (387.7 mg, 4.0 mmol), copper acetate (726.5 mg, 4.0 mmol). 10 mL of dichloromethane was added to the flask before the addition of triethylamine (837 μL, 6.0 mmol). The flask was stirred at room temperature for 24 h. The solvent was removed using a rotary evaporator. Ethyl acetate (150 mL) and water (50 mL) were added and the reaction mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted three more times with ethyl acetate (300 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered through a small pad of silica gel. The filtrate was concentrated and the resulting residue was purified by column chromatography (25% EA in Hex) to yield the title compound, 461.4 mg (86%). ^{1}H NMR (500 MHz, $CDCl_3$): 1.30 (d, J = 4.4 Hz, 6H), 2.45 (s, 3H), 2.62 (s, 3H), 3.36 (m, 1H), 6.66 (s, 1H), 7.00 (d, J = 4.4 Hz, 2H), 7.15 (t, J = 4.4 Hz, 1H), 7.37 (t, J = 4.4 Hz, 2H), 7.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 22.0, 23.1, 27.3, 29.7, 119.1, 121.6, 123.8, 129.4, 130.1, 133.0, 136.6, 138.9, 157.1, 200.7. ESI-MS calcd for $C_{18}H_{21}O_2$ (M+H), 269.15; found, 269.0.

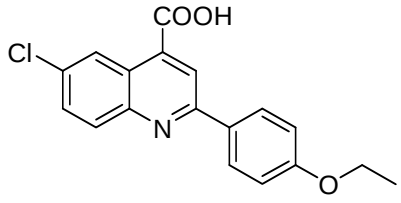
6-chloro-2-(4-methoxyphenyl)quinoline-4-carboxylic acid (C2):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-chloroisatin (501.0 mg, 2.76 mmol). 5.5 mL of ethanol was added to

the flask. An ethanolic solution of 4-methoxyacetophenone (434.3 mg, 2.90 mmol) was added into the flask followed by the gradual addition of KOH (447.0 mg dissolved in 500 μL of H_2O, 8.0 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light yellow powder; yield 344.9 mg (40%). ^{1}H NMR (500 MHz, DMSO-d_6): 3.84 (s, 3H), 7.10 (d, J = 8.3 Hz, 2H), 7.82 (d, J = 8.9 Hz, 1H), 8.11 (d, J = 9.0 Hz, 1H), 8.24 (d, J = 8.3 Hz, 2H), 8.47 (s, 1H), 8.73 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 56.0, 115.0, 120.8, 124.6, 125.0, 129.4, 130.5, 131.0, 132.2, 132.5, 136.4, 147.6, 156.5, 161.7, 167.8. HRMS (ESI$^-$) calcd for $C_{17}H_{11}ClNO_3$ (M-H), 312.0433; found, 312.0439.

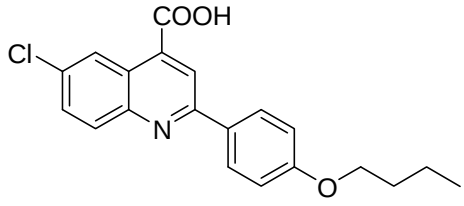
6-chloro-2-(4-ethoxyphenyl)quinoline-4-carboxylic acid (**C3**):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-chloroisatin (501.0 mg, 2.76 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-ethoxyacetophenone (474.0 mg, 2.90 mmol) was added into the flask followed by the gradual addition of KOH (447.0 mg dissolved in 500 μL of H_2O, 8.0 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light yellow powder; yield 452.3 mg (50%). ^{1}H NMR (500

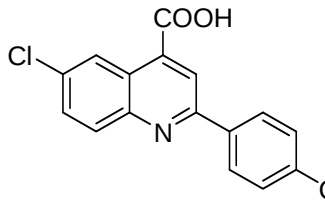
MHz, DMSO-d_6): 1.38 (d, J = 8.1 Hz, 3H), 4.14 (q, J = 8.3 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 9.1 Hz, 1H), 8.09 (d, J = 8.3 Hz, 1H), 8.21 (d, J = 8.3 Hz, 2H), 8.46 (s, 1H), 8.71 (d, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 15.3, 64.0, 115.5, 120.7, 124.8, 125.1, 129.4, 130.6, 131.3, 132.2, 132.4, 137.2, 147.6, 156.6, 161.0, 168.0. HRMS (ESI$^-$) calcd for $C_{18}H_{13}ClNO_3$ (M-H), 326.0589; found, 326.0593.

2-(4-butoxyphenyl)-6-chloroquinoline-4-carboxylic acid (C4):



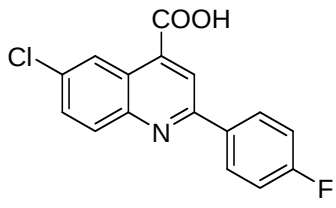
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-chloroisatin (501.0 mg, 2.76 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-butoxyacetophenone (555.6 mg, 2.90 mmol) was added into the flask followed by the gradual addition of KOH (447.0 mg dissolved in 500 μL of H_2O, 8.0 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light yellow powder; yield 587.1 mg (60%). ^{1}H NMR (400 MHz, DMSO-d_6): 0.93 (t, J = 7.4 Hz, 3H), 1.45 (m, 2H), 1.70 (m, 2H), 4.04 (t, J = 6.5 Hz, 2H), 7.08 (d, J = 8.3 Hz, 2H), 7.82 (dd, J = 9.0, 2.4 Hz, 1H), 8.11 (d, J = 9.0 Hz, 1H), 8.22 (d, J = 8.3 Hz, 2H), 8.47 (s, 1H), 8.72 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.2, 19.2, 40.4, 67.8, 115.3, 120.6, 124.4, 124.7, 129.2, 130.1, 131.0, 132.0, 132.3, 136.4, 147.4, 156.4, 161.0, 167.6. HRMS (ESI$^-$) calcd for $C_{20}H_{17}ClNO_3$ (M-H), 354.0902; found, 354.0903.

6-chloro-2-(4-(trifluoromethoxy)phenyl)quinoline-4-carboxylic acid (C5):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-chloroisatin (501.0 mg, 2.76 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-trifluoromethoxyacetophenone (463 μL, 2.90 mmol) was added into the flask followed by the gradual addition of KOH (447.0 mg dissolved in 500 μL of H_2O, 8.0 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light pink powder; yield 416.1 mg (41%). ^{1}H NMR (500 MHz, DMSO-d_6): 7.50 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 9.1 Hz, 1H), 8.03 (d, J = 9.1 Hz, 1H), 8.35 (d, J = 8.4 Hz, 2H), 8.40 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 119.7, 120.5 (d, J = 255.0 Hz), 121.6, 125.3, 125.6, 129.7, 130.8, 132.0, 132.2, 137.5, 141.8, 147.2, 150.0, 155.3, 168.2. HRMS (ESI$^-$) calcd for $C_{17}H_8ClF_3NO_3$ (M-H), 366.0150; found, 366.0154.

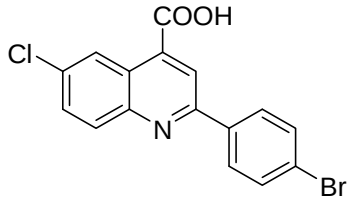
6-chloro-2-(4-fluorophenyl)quinoline-4-carboxylic acid (C6):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-chloroisatin (501.0 mg, 2.76 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-fluoroacetophenone (350 μL, 2.90 mmol) was added into the flask

followed by the gradual addition of KOH (447.0 mg dissolved in 500 μL of H_2O, 8.0 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 349.0 mg (42%). ^{1}H NMR (500 MHz, DMSO-d_6): 7.40 (t, J = 8.8 Hz, 2H), 7.85 (dd, J = 9.1, 2.3 Hz, 1H), 8.13 (d, J = 8.9 Hz, 1H), 8.34 (dd, J = 8.5, 5.7 Hz, 2H), 8.50 (s, 1H), 8.77 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 116.4 (d, J = 16.5 Hz), 120.7, 124.9, 125.2, 130.1 (d, J = 7.1 Hz), 131.1, 132.3, 132.8, 134.7, 138.0, 147.4, 155.8, 164.2 (d, J = 241.0 Hz), 167.9. HRMS (ESI$^-$) calcd for $C_{16}H_8ClFNO_2$ (M-H), 300.0233; found, 300.0244.

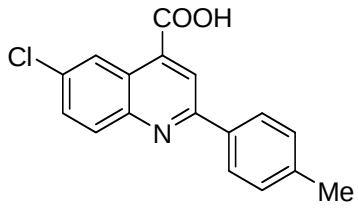
2-(4-bromophenyl)-6-chloroquinoline-4-carboxylic acid (C7):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-chloroisatin (501.0 mg, 2.76 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-bromoacetophenone (575.3 mg, 2.90 mmol) was added into the flask followed by the gradual addition of KOH (447.0 mg dissolved in 500 μL of H_2O, 8.0 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 446.7 mg (45%). ^{1}H NMR (400 MHz, DMSO-d_6):

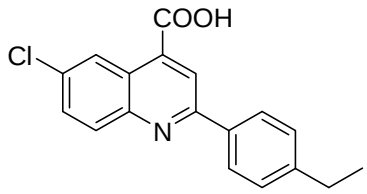
7.75 (d, J = 8.6 Hz, 2H), 7.86 (dd, J = 9.2, 2.5 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 8.24 (d, J = 8.6 Hz, 2H), 8.52 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 120.8, 124.5, 124.8, 129.7, 131.3, 132.3, 132.4, 133.1, 136.9, 137.0, 147.3, 155.6, 167.4. HRMS (ESI$^-$) calcd for $C_{16}H_8BrClNO_2$ (M-H), 359.9432; found, 359.9422.

6-chloro-2-p-tolylquinoline-4-carboxylic acid (C8):



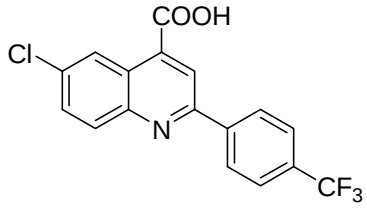
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-chloroisatin (501.0 mg, 2.76 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-methylacetophenone (388.0 mg, 2.90 mmol) was added into the flask followed by the gradual addition of KOH (447.0 mg dissolved in 500 μL of H_2O, 8.0 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: yellow powder; yield 434.5 mg (53%). ^{1}H NMR (500 MHz, DMSO-d_6): 2.41 (s, 3H), 7.35 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 9.0 Hz, 1H), 8.11 (d, J = 9.0 Hz, 1H), 8.15 (d, J = 8.5, 5.7 Hz, 2H), 8.48 (s, 1H), 8.72 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 21.6, 121.0, 124.8, 125.0, 127.8, 130.3, 131.2, 132.4, 132.8, 135.4, 136.5, 140.7, 147.6, 156.9, 167.7. HRMS (ESI$^-$) calcd for $C_{17}H_{11}ClNO_2$ (M-H), 296.0484; found, 296.0498.

6-chloro-2-(4-ethylphenyl)quinoline-4-carboxylic acid (C9):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-chloroisatin (501.0 mg, 2.76 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-ethylacetophenone (428.5 mg, 2.90 mmol) was added into the flask followed by the gradual addition of KOH (447.0 mg dissolved in 500 μL of H_2O, 8.0 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: yellow powder; yield 581.7 mg (68%). ^{1}H NMR (500 MHz, DMSO-d_6): 1.23 (t, J = 7.6 Hz, 3H), 2.70 (q, J = 7.7 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.86 (dd, J = 9.1, 2.3 Hz, 1H), 8.16 (d, J = 9.0 Hz, 1H), 8.21 (d, J = 7.9 Hz, 2H), 8.52 (s, 1H), 8.77 (d, J = 2.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 16.0, 28.7, 121.1, 124.9, 125.0, 127.9, 129.1, 131.3, 132.4, 132.8, 135.7, 136.8, 146.9, 147.6, 157.0, 167.8. HRMS (ESI$^-$) calcd for $C_{18}H_{13}ClNO_2$ (M-H), 310.0640; found, 310.0629

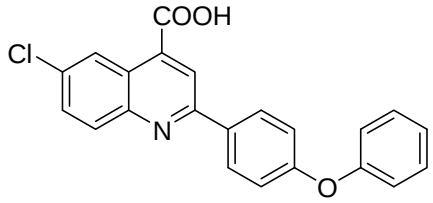
6-chloro-2-(4-(trifluoromethyl)phenyl)quinoline-4-carboxylic acid (C10):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-chloroisatin (501.0 mg, 2.76 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-trifluoromethylacetophenone (389.0 mg, 2.90 mmol) was

added into the flask followed by the gradual addition of KOH (447.0 mg dissolved in 500 μL of H_2O, 8.0 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: yellow powder; yield 386.9 mg (40%). ^{1}H NMR (500 MHz, DMSO-d_6): 7.73 (dd, J = 8.2, 2.5 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H), 8.06 (d, J = 9.0 Hz, 1H), 8.30 (s, 1H), 8.44 (d, J = 8.2 Hz, 2H), 9.02 (d, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 118.5, 124.7 (d, J = 216.0 Hz), 126.2 (d, J = 3.0 Hz), 126.5, 127.0, 128.3, 129.9 (d, J = 26.0 Hz), 130.2, 131.1, 131.7, 142.9, 147.2, 149.4, 155.1, 168.9. ESI-MS calcd for $C_{17}H_8ClF_3NO_2$ (M-H), 350.03 found, 349.8.

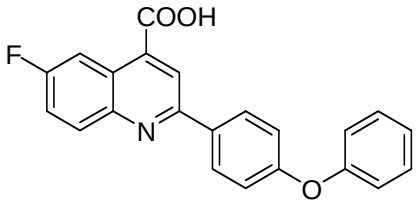
6-chloro-2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C11):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-chloroisatin (501.0 mg, 2.76 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoixyacetophenone (613.7 mg, 2.90 mmol) was added into the flask followed by the gradual addition of KOH (447.0 mg dissolved in 500 μL of H_2O, 8.0 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: yellow powder; yield 485.5 mg (47%). ^{1}H NMR (500 MHz,

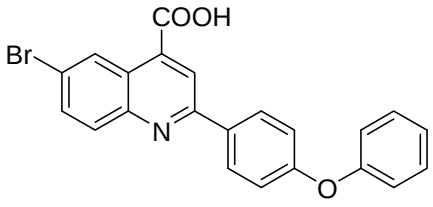
DMSO-d_6): 7.13 (m, 4H), 7.21 (m, 1H), 7.44 (m, 2H), 7.82 (m, 1H), 8.11 (m, 1H), 8.29 (m, 2H), 8.49 (m, 1H), 8.75 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 119.0, 120.1, 120.9, 124.8, 124.9, 125.0, 129.8, 130.9, 131.3, 132.3, 132.8, 133.0, 136.9, 147.6, 156.3, 156.5, 159.5, 168.8. ESI-MS calcd for $C_{22}H_8ClF_3NO_2$ (M-H), 374.1 found, 373.8.

6-fluoro-2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C12):



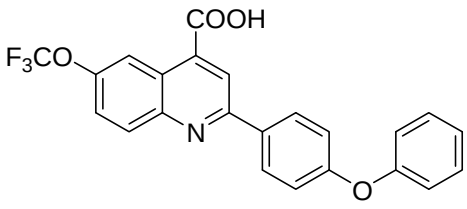
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (500.0 mg, 3.03 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoxyacetophenone (665.3 mg, 3.18 mmol) was added into the flask followed by the gradual addition of KOH (494.0 mg dissolved in 500 μL of H_2O, 8.8 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 468.2 mg (43%). ^{1}H NMR (500 MHz, DMSO-d_6): 7.13 (m, 4H), 7.21 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.72 (dt, J = 8.5, 2.8 Hz, 1H), 8.16 (dd, J = 9.3, 5.9 Hz, 1H), 8.27 (d, J = 8.7 Hz, 2H), 8.47 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): 110.1 (d, J = 28.2 Hz), 119.0, 120.0, 120.5, 120.6 (d, J = 26.0 Hz), 125.1, 125.2 (d, J = 12.5 Hz), 129.6, 130.9, 132.9 (d, J = 12.1 Hz), 133.4, 146.4, 155.3, 156.6, 159.2, 160.9 (d, J = 244.3 Hz), 168.3. HRMS (ESI$^-$) calcd for $C_{22}H_{13}FNO_3$ (M-H), 358.0885; found, 358.0891.

6-bromo-2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C13):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-bromoisatin (452.0 mg, 2.0 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoxyacetophenone (424.5 mg, 2 mmol) was added into the flask followed by the gradual addition of KOH (326.0 mg dissolved in 350 μL of H_2O, 5.8 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 397.0 mg (47%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.13 (m, 4H), 7.18 (t, J = 7.9 Hz, 1H), 7.42 (t, J = 7.9 Hz, 2H), 7.90 (dd, J = 9.0, 2.2 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 8.26 (d, J = 9.0 Hz, 2H), 8.45 (s, 1H), 8.88 (d, J = 2.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 118.9, 119.9, 120.7, 121.4, 124.6, 125.0, 128.0, 129.6, 130.7, 132.2, 132.8, 133.6, 136.4, 147.5, 156.1, 156.2, 159.3, 167.5. ESI-MS calcd for $C_{22}H_{15}BrNO_3$ (M+H), 420.02; found, 419.8.

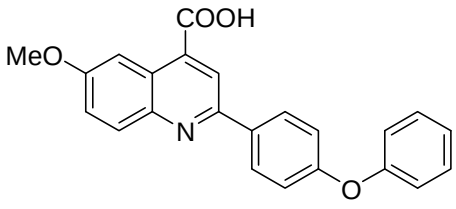
2-(4-phenoxyphenyl)-6-(trifluoromethoxy)quinoline-4-carboxylic acid (C14):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-trifluoromethoxyisatin (100.0 mg, 0.43 mmol). 1.5 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoxyacetophenone (91.9 mg, 0.43 mmol) was added into the flask followed by the gradual addition of KOH (70.8 mg dissolved in 100 μL of

H_2O, 1.26 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 121.5 mg (66%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.14 (m, 4H), 7.18 (m, 1H), 7.76 (dd, J = 9.1, 2.7 Hz, 1H), 8.19 (d, J = 9.1 Hz, 1H), 8.27 (d, J = 8.4 Hz, 2H), 8.50 (s, *1*H), 8.67 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 116.5, 118.7, 119.9, 120.6 (d, J = 256 Hz), 121.0, 124.2, 124.3, 124.6, 129.7, 130.7, 132.7, 137.0, 147.1, 147.2, 147.3, 156.2, 156.4, 159.4, 167.4. ESI-MS calcd for $C_{23}H_{15}F_3NO_4$ (M+H), 426.09; found, 425.9.

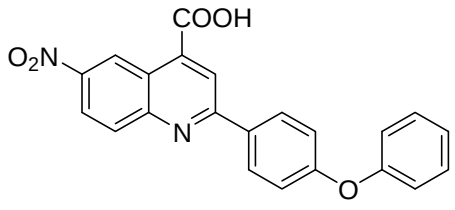
6-methoxy-2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C15):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-methoxyisatin (354.0 mg, 2.0 mmol). 3 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoxyacetophenone (424.5 mg, 2.0 mmol) was added into the flask followed by the gradual addition of KOH (325.7 mg dissolved in 400 μL of H_2O, 5.8 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 282.3 mg (38%). ^{1}H NMR (400 MHz, DMSO-d_6): 3.34 (s, 3H), 7.10 (m, 4H), 7.18 (m, 1H), 7.40 (m, 3H), 7.95 (d, J = 9.2 Hz,

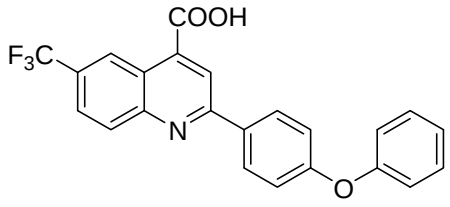
1H), 8.14 (m, J = 8.4 Hz, 1H), 8.20 (s, 1H), 8.22 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): 55.8, 105.0, 118.5, 118.8, 119.6, 122.4, 124.4, 125.6, 129.0, 130.6, 131.2, 134.1, 145.0, 153.0, 156.5, 157.8, 158.4, 169.2, 172.6. ESI-MS calcd for $C_{23}H_{18}NO_4$ (M+H), 372.1; found, 371.9.

6-nitro-2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C16):



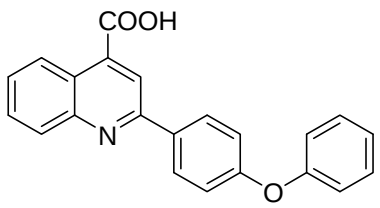
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-nitroisatin (500.0 mg, 2.60 mmol). 5 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoxyacetophenone (552.4 mg, 2.60 mmol) was added into the flask followed by the gradual addition of KOH (423.4 mg dissolved in 500 μL of H_2O, 7.54 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 301.2 mg (30%). ^{1}H NMR (500 MHz, DMSO-d_6): 7.15 (m, 4H), 7.25 (m, 1H), 7.48 (m, 2H), 8.24 (d, J = 5.1 Hz, 1H), 8.34 (d, J = 5.1 Hz, 2H), 8.47 (d, J = 5.1 Hz, 1H), 8.58 (s, 1H), 9.63 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 118.5, 120.0, 121.4, 122.7, 122.9, 123.6, 124.8, 130.0, 130.7, 131.6, 132.0, 138.6, 145.6, 150.7, 155.9, 158.8, 161.0, 173.6. HRMS (ESI$^-$) calcd for $C_{22}H_{13}N_2O_5$ (M-H), 385.0825; found, 385.0830.

6-(trifluoromethyl)-2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C17):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-trifluoromethylisatin (100.0 mg, 0.47 mmol). 1 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoxyacetophenone (100.0 mg, 0.47 mmol) was added into the flask followed by the gradual addition of KOH (77.0 mg dissolved in 100 μL of H_2O, 1.36 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 25.0 mg (13%). ^{1}H NMR (500 MHz, DMSO-d_6): 7.14 (m, 4H), 7.21 (m, 1H), 7.45 (t, J = 6.8 Hz, 2H), 7.82 (d, J = 8.6 Hz, 1H), 8.34 (d, J = 7.7 Hz, 2H), 8.57 (s, 1H), 8.73 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 116.9, 118.0 (d, J = 282.0 Hz), 118.8, 119.3, 119.9, 120.6, 121.9, 124.3 (d, J = 14.0 Hz), 125.2, 129.7, 130.7, 132.8 (d, J = 29.0 Hz), 138.8, 147.0, 147.3, 156.2, 156.4, 159.3, 167.7. ESI-MS calcd for $C_{23}H_{13}F_3NO_3$ (M-H), 408.1 found, 407.8.

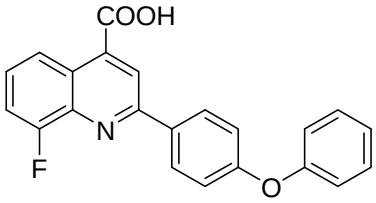
2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C18):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed isatin (500.0 mg, 3.40 mmol). 5 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoxyacetophenone (721.0 mg, 3.40 mmol) was added into the

flask followed by the gradual addition of KOH (553.7 mg dissolved in 500 μL of H_2O, 9.90 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 656.3 mg (50%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.12 (m, 4H), 7.17 (m, 1H), 7.41 (m, 2H), 7.64 (ddd, J = 8.5, 6.8, 1.3 Hz, 1H), 7.79 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.27 (d, J = 8.1 Hz, 2H), 8.39 (s, 1H), 8.62 (d, J = 8.5, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 118.9, 119.3, 119.8, 123.7, 124.6, 125.8, 128.0, 129.5, 130.1, 130.6, 133.2, 138.0, 148.8, 155.6, 156.3, 159.3, 159.1, 168.1. HRMS (ESI$^-$) calcd for $C_{22}H_{13}FNO_3$ (M-H), 358.0879; found, 358.0883.

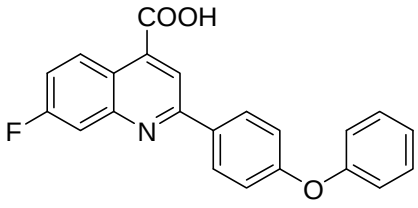
8-fluoro-2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C19):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 7-fluoroisatin (100.0 mg, 0.61 mmol). 1 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoxyacetophenone (128.5 mg, 0.61 mmol) was added into the flask followed by the gradual addition of KOH (99.3 mg dissolved in 100 μL of H_2O, 1.77 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 184.1 mg (84%). ^{1}H NMR (400

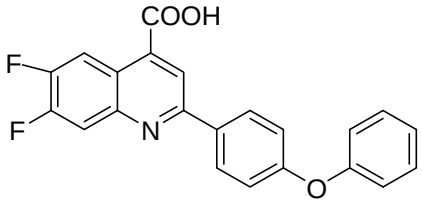
MHz, DMSO-d_6): 7.09 (m, 4H), 7.16 (m, 1H), 7.39 (dd, J = 8.5, 7.3 Hz, 2H), 7.59 (m, 2H), 8.26 (d, J = 8.1 Hz, 2H), 8.40 (dd, J = 6.5, 3.4 Hz, 1H), 8.45 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 114.6 (d, J = 19.0 Hz), 118.7, 119.8, 120.3, 121.8 (d, J = 5.0 Hz), 124.5, 125.3, 127.8 (d, J = 8.0 Hz), 129.7, 130.6, 132.9, 137.9 (d, J = 3.0 Hz), 138.9 (d, J = 10.0 Hz), 155.7, 156.2, 157.8 (d, J = 254.0 Hz), 159.3, 167.7. ESI-MS calcd for $C_{22}H_{15}FNO_3$ (M+H), 360.1; found, 359.9.

7-fluoro-2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C20):



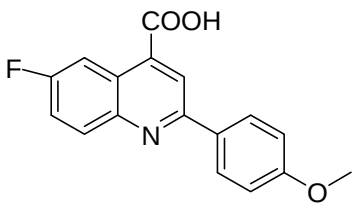
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 6-fluoroisatin (200.0 mg, 1.21 mmol). 1.5 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoxyacetophenone (257.0 mg, 1.21 mmol) was added into the flask followed by the gradual addition of KOH (197.0 mg dissolved in 200 μL of H_2O, 3.51 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 108.6 mg (25%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.12 (m, 4H), 7.12 (m, 1H), 7.40 (m, 2H), 7.57 (td, J = 8.8, 2.7 Hz, 1H), 7.81 (dd, J = 10.2, 2.7 Hz, 1H), 8.27 (d, J = 8.2 Hz, 2H), 8.38 (s, 1H), 8.71 (dd, J = 9.4 , 6.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 113.3 (d, J = 20.0 Hz), 117.9 (d, J = 25.0 Hz), 118.7, 118.9, 119.9, 121.0, 124.6, 124.7, 128.6 (d, J =10.0 Hz), 130.7, 132.8, 137.9, 150.0 (d, J = 13.0 Hz), 156.2, 156.8, 159.3, 163.0 (d, J = 248.0 Hz), 167.9. ESI-MS calcd for $C_{22}H_{15}FNO_3$ (M+H), 360.1; found, 359.9.

6,7-difluoro-2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C21):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5,6-difluoroisatin (200.0 mg, 1.09 mmol). 1.5 mL of ethanol was added to the flask. An ethanolic solution of 4-phenoxyacetophenone (231.4 mg, 1.09 mmol) was added into the flask followed by the gradual addition of KOH (178.0 mg dissolved in 200 μL of H_2O, 3.17 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: off white powder; yield 205.5 mg (50%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.12 (m, 4H), 7.19 (m, 1H), 7.40 (m, 2H), 7.43 (t, J = 7.9 Hz, 1H), 7.96 (dd, J = 11.9, 8.1 Hz, 1H), 8.24 (m, 3H), 8.90 (dd, J = 11.9 , 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 113.7 (d, J = 19.0 Hz), 115.4 (d, J = 15.0 Hz), 118.3, 118.6, 118.7, 119.8, 122.4 (d, J = 9.0 Hz), 124.5, 129.4, 130.7, 133.7, 146.3, 148.8 (d, J = 250 Hz), 150.1, 151.5 (d, J = 233.0 Hz), 156.3, 158.9, 172.5. ESI-MS calcd for $C_{22}H_{12}F_2NO_3$ (M-H), 376.1; found, 375.8.

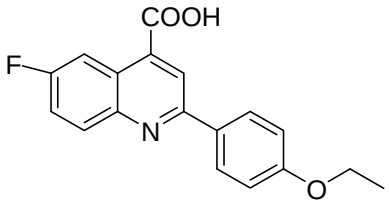
6-fluoro-2-(4-methoxyphenyl)quinoline-4-carboxylic acid (C22):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (500.0 mg, 3.03 mmol). 5 mL of ethanol was added to the flask. An ethanolic solution of 4-methoxyacetophenone (478.0 mg, 3.03 mmol) was added into

the flask followed by the gradual addition of KOH (494.0 mg dissolved in 500 μL of H_2O, 8.80 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 377.8 mg (40%). ^{1}H NMR (400 MHz, DMSO-d_6): 3.79 (s, 3H), 7.02 (d, J = 8.3 Hz, 2H), 7.65 (td, J = 8.7, 2.9 Hz, 1H), 8.08 (dd, J = 9.3, 5.8 Hz, 1H), 8.14 (d, J = 8.3 Hz, 2H), 8.37 (dd, J = 11.0, 3.0 Hz, 1H), 8.41 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 55.7,109.4 (d, J = 25.0 Hz), 114.7, 120.4 (d, J = 26.0 Hz), 120.5, 124.4 (d, J = 11.0 Hz), 129.0, 130.4, 132.7 (d, J = 9.0 Hz), 136.3 (d, J = 6.0 Hz), 146.2, 155.4, 160.7 (d, J = 244.0 Hz), 161.3, 167.6. ESI-MS calcd for $C_{17}H_{11}FNO_3$ (M-H), 296.1; found, 295.9.

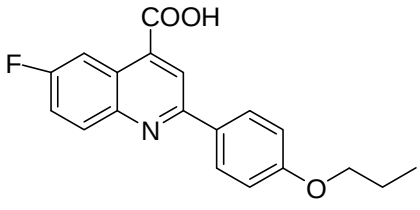
2-(4-ethoxyphenyl)-6-fluoroquinoline-4-carboxylic acid (C23):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (500.0 mg, 3.03 mmol). 5 mL of ethanol was added to the flask. An ethanolic solution of 4-ethoxyacetophenone (521.4 mg, 3.18 mmol) was added into the flask followed by the gradual addition of KOH (494.0 mg dissolved in 500 μL of H_2O, 8.80 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via

recrystallization from acetic acid: light brown powder; yield 462.2 mg (49%). ^{1}H NMR (500 MHz, DMSO-d_6): 1.41 (t, J = 6.8 Hz, 3H), 4.15 (q, J = 6.6 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.77 (td, J = 8.4, 2.9 Hz, 1H), 8.20 (dd, J = 9.2, 5.5 Hz, 1H), 8.24 (d, J = 8.3 Hz, 2H), 8.48 (dd, J = 10.9, 2.8 Hz, 1H), 8.52 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 15.0, 63.7,109.6 (d, J = 25.0 Hz), 115.2, 120.4 (d, J = 26.0 Hz), 120.5, 124.4 (d, J = 10.0 Hz), 129.1, 130.3, 132.8 (d, J = 5.0 Hz), 136.5 (d, J = 6.0 Hz), 146.2, 155.5, 160.6, 160.7 (d, J = 244.0 Hz), 167.6. ESI-MS calcd for $C_{18}H_{13}FNO_3$ (M-H), 324.1; found, 323.9.

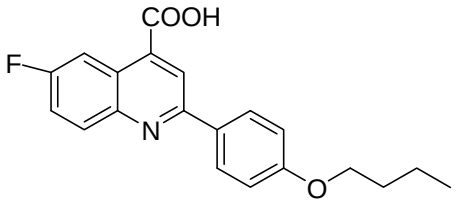
6-fluoro-2-(4-propoxyphenyl)quinoline-4-carboxylic acid (C24):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (500.0 mg, 3.03 mmol). 5 mL of ethanol was added to the flask. An ethanolic solution of 4-propoxyacetophenone (539.8 mg, 3.03 mmol) was added into the flask followed by the gradual addition of KOH (494.0 mg dissolved in 500 μL of H_2O, 8.80 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 591.4 mg (60%). ^{1}H NMR (400 MHz, DMSO-d_6): 0.97 (t, J = 7.4 Hz, 3H), 1.74 (q, J = 7.0 Hz, 2H), 3.98 (t, J = 6.5 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 7.54 (td, J = 8.6, 2.9 Hz, 1H), 7.99 (dd, J = 9.2, 5.8 Hz, 1H), 8.13 (m, 3H), 8.58 (dd, J = 11.4, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 10.1, 22.5, 69.5, 111.0 (d, J = 23.0 Hz), 115.1, 118.2, 119.4 (d, J = 26.0 Hz), 125.7, 128.8, 131.3, 131.9 (d, J = 9.0 Hz), 146.1,

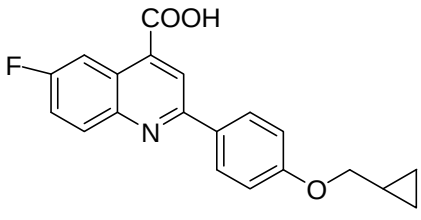
155.4, 159.7 (d, J = 235.0 Hz), 160.4, 168.8. ESI-MS calcd for $C_{19}H_{17}FNO_3$ (M+H), 326.1; found, 325.9.

2-(4-butoxyphenyl)-6-fluoroquinoline-4-carboxylic acid (C25):



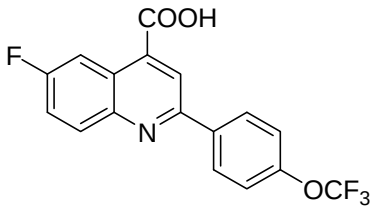
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (500.0 mg, 3.03 mmol). 5 mL of ethanol was added to the flask. An ethanolic solution of 4-butoxyacetophenone (611.4 mg, 3.03 mmol) was added into the flask followed by the gradual addition of KOH (494.0 mg dissolved in 500 μL of H_2O, 8.80 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: light brown powder; yield 411.3 mg (40%). ^{1}H NMR (400 MHz, DMSO-d_6): 0.90 (t, J = 7.4 Hz, 3H), 1.41 (h, J = 7.4Hz, 2H), 1.68 (dq, J = 8.4, 6.5 Hz, 2H), 4.02 (t, J = 6.5 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 7.72 (td, J = 8.7, 2.9 Hz, 1H), 8.17 (m, 3H), 8.40 (d, J = 8.3, 1H), 8.45(s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 14.2, 19.2, 31.2, 67.8, 109.6 (d, J = 25.0 Hz), 115.3, 120.6, 120.8 (d, J = 25.0 Hz), 124.4 (d, J = 11.0 Hz), 129.2, 129.9, 132.4 (d, J = 9.0 Hz), 136.9 (d, J = 6.0 Hz), 145.8, 155.4, 160.7 (d, J = 248.0 Hz), 161.0, 167.6. ESI-MS calcd for $C_{20}H_{19}FNO_3$ (M+H), 340.1; found, 339.9.

2-(4-(cyclopropylmethoxy)phenyl)-6-fluoroquinoline-4-carboxylic acid (C26):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (200.0 mg, 1.21 mmol). 2 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(cyclopropylmethoxy)phenyl)ethanone (230.0 mg, 1.21 mmol) was added into the flask followed by the gradual addition of KOH (197.1 mg dissolved in 300 μL of H_2O, 3.51 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light brown powder; yield 221.3 mg (52%). ^{1}H NMR (400 MHz, DMSO-d_6): 0.32 (dd, J = 6.0, 4.3 Hz, 2H), 0.56 (m, 2H), 0.93 (ddt, J = 10.4, 7.3, 3.7 Hz, 1H), 3.88 (d, J = 7.0 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 7.71 (td, J = 8.7, 2.9 Hz, 1H), 8.17 (m, 3H), 8.38 (m, 1H), 8.45(s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 3.6, 10.6, 72.7, 109.6 (d, J = 25.0 Hz), 115.3, 120.4, 120.5 (d, J = 10.0 Hz), 129.0, 130.3, 132.8, 132.9, 136.8, 146.3, 155.5, 160.7 (d, J = 244.0 Hz), 160.8, 167.7. ESI-MS calcd for $C_{20}H_{15}FNO_3$ (M-H), 336.1 found, 335.9.

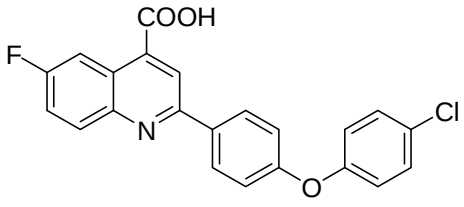
6-fluoro-2-(4-(trifluoromethoxy)phenyl)quinoline-4-carboxylic acid (C27):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (500.0 mg, 3.03 mmol). 5 mL of ethanol was added to the

flask. An ethanolic solution of 4-trifluoromethoxyacetophenone (618.6 mg, 3.03 mmol) was added into the flask followed by the gradual addition of KOH (494.0 mg dissolved in 500 μL of H_2O, 8.8 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: off white powder; yield 372.5 mg (35%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.50 (d, J = 8.4 Hz, 2H), 7.74 (td, J = 8.7, 2.9 Hz, 1H), 8.18 (dd, J = 9.3, 5.7 Hz, 1H), 8.35 (d, J = 8.4 Hz, 2H), 8.41 (dd, J = 11.0, 2.9 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 109.6 (d, J = 24.0 Hz), 120.5 (d, J = 256.0 Hz), 120.8 (d, J = 25.0 Hz), 120.9, 121.7, 125.0 (d, J = 11.0 Hz), 129.7, 133.1 (d, J = 9.0 Hz), 137.0 (d, J = 6.0 Hz), 137.1, 146.1, 150.0, 154.4, 161.7 (d, J = 246.0 Hz), 167.5. ESI-MS calcd for $C_{17}H_8F_4NO_3$ (M-H), 350.05 found, 349.8.

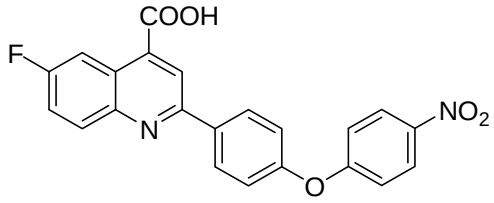
2-(4-(4-chlorophenoxy)phenyl)-6-fluoroquinoline-4-carboxylic acid (C28):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (67.1 mg, 0.41 mmol). 0.5 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(4-chlorophenoxy)phenyl)ethanone (100.0 mg, 0.41 mmol) was added into the flask followed by the gradual addition of KOH (66.1 mg dissolved in 60 μL of H_2O, 1.18 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was

collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: off white powder; yield 87.9 mg (55%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.15 (m, 4H), 7.47 (d, J = 8.3 Hz, 2H), 7.76 (td, J = 8.7, 2.9 Hz, 1H), 8.19 (d, J = 9.3, 5.7 Hz, 1H), 8.30 (d, J = 8.3 Hz, 2H), 8.43 (dd, J = 11.0, 2.9 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 109.6 (d, J = 24.0 Hz), 119.1, 120.6 (d, J = 25.0 Hz), 120.7, 121.4, 124.7 (d, J = 11.0 Hz), 128.3, 129.6, 130.5, 133.0 (d, J = 10.0 Hz), 133.4, 136.9 (d, J = 5.0 Hz), 146.3, 155.1, 155.4, 156.7, 160.9 (d, J = 245.0 Hz), 167.6. ESI-MS calcd for $C_{22}H_{14}FClNO_3$ (M+H), 394.1 found, 393.8.

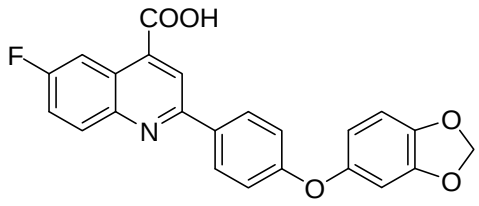
2-(4-(4-nitrophenoxy)phenyl)-6-fluoroquinoline-4-carboxylic acid (C29):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (64.3 mg, 0.389 mmol). 0.5 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(4-nitrophenoxy)phenyl)ethanone (100.0 mg, 0.39 mmol) was added into the flask followed by the gradual addition of KOH (63.5 mg dissolved in 60 μL of H_2O, 1.13 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light brown powder; yield 95.9 mg (61%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.22 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.58 (td, J = 8.7, 2.9 Hz, 1H), 8.04 (dd, J = 9.2, 5.8 Hz, 1H), 8.21 (s, 1H), 8.25 (d, J = 8.6 Hz, 2H), 8.30 (d, J = 8.6 Hz, 2H), 8.64 (dd, J = 11.5, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 111.3

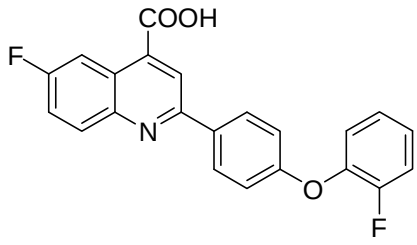
(d, J = 22.0 Hz), 118.1, 119.5 (d, J = 26.0 Hz), 119.6, 121.0, 126.7, 129.6, 132.0, 132.1, 136.3, 143.0, 146.0, 154.7, 156.0, 160.3 (d, J = 252.0 Hz), 162.9, 166.6. ESI-MS calcd for $C_{22}H_{14}FN_2O_5$ (M+H), 405.1 found, 404.8.

2-(4-(benzo[d][1,3]dioxol-6-yloxy)phenyl)-6-fluoroquinoline-4-carboxylic acid (C30):



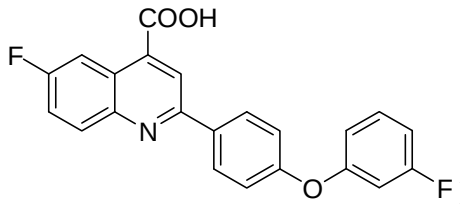
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (90.8 mg, 0.55 mmol). 0.5 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(benzo[d][1,3]dioxol-6-yloxy)phenyl)ethanone (140.0 mg, 0.55 mmol) was added into the flask followed by the gradual addition of KOH (89.1 mg dissolved in 60 μL of H_2O, 1.59 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: yellow powder; yield 110.9 mg (50%). ^{1}H NMR (400 MHz, DMSO-d_6): 6.04 (s, 2H), 6.57 (dd, J = 8.3, 2.4 Hz, 1H), 6.80 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 8.3 Hz, 2H), 7.72 (td, J = 8.7, 2.9 Hz, 1H), 8.15 (dd, J = 8.9, 5.8 Hz, 1H), 8.17 (d, J = 8.3 Hz, 2H), 8.41 (dd, J = 11.0, 3.0 Hz, 1H), 8.46 (s, 1H); ^{13}C NMR (120 MHz, DMSO-d_6): 102.1, 103.0, 109.0, 109.6 (d, J = 25.0 Hz), 112.9, 117.7, 120.6, 120.7 (d, J = 26.0 Hz), 124.5 (d, J = 11.0 Hz), 129.4, 132.4, 132.9 (d, J = 9.0 Hz), 136.7 (d, J = 5.0 Hz), 144.5, 146.2, 148.7, 150.2, 155.2, 160.2, 160.8 (d, J = 245.0 Hz), 167.6. ESI-MS calcd for $C_{23}H_{13}FNO_5$ (M-H), 402.9 found, 401.8.

2-(4-(2-fluorophenoxy)phenyl)-6-fluoroquinoline-4-carboxylic acid (C31):



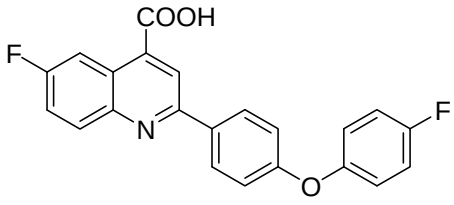
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (99.1 mg, 0.60 mmol). 0.5 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(2-fluorophenoxy)phenyl)ethanone (138.0 mg, 0.60 mmol,) was added into the flask followed by the gradual addition of KOH (97.8 mg dissolved in 60 μL of H_2O, 1.73 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: off white powder; yield 181.9 mg (80%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.05 (d, J = 8.4 Hz, 2H), 7.25 (m, 3H), 7.38 (m, 1H), 7.64 (td, J = 8.7, 2.9 Hz, 1H), 8.07 (dd, J = 8.8, 5.8 Hz, 1H), 8.18 (d, J = 8.4 Hz, 2H), 8.39 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): 109.6 (d, J = 35.0 Hz), 117.1, 117.7 (d, J = 18.0 Hz), 120.3, 120.6, 123.2, 124.6 (d, J = 11.0 Hz), 126.0 (d, J = 4.0 Hz), 126.6 (d, J = 7.0 Hz), 129.4, 132.8 (d, J = 9.0 Hz), 133.0, 136.5 (d, J = 6.0 Hz), 142.5 (d, J = 11.0 Hz), 146.1, 154.0 (d, J = 246.0 Hz), 155.0, 159.1, 160.8 (d, J = 244.0 Hz), 172.5. ESI-MS calcd for $C_{22}H_{14}FNO_3$ (M+H), 378.0 found, 377.9.

2-(4-(3-fluorophenoxy)phenyl)-6-fluoroquinoline-4-carboxylic acid (C32):



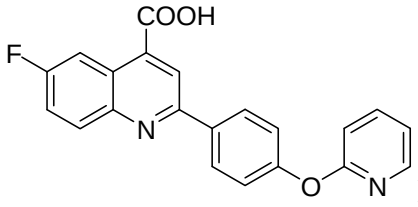
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (93.3 mg, 0.57 mmol). 0.5 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(3-fluorophenoxy)phenyl)ethanone (130.0 mg, 0.56 mmol) was added into the flask followed by the gradual addition of KOH (92.0 mg dissolved in 60 μL of H_2O, 1.64 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: off white powder; yield 44.7 mg (21%). ^{1}H NMR (400 MHz, DMSO-d_6): 6.92 (dd, J = 8.2, 2.4 Hz, 1H), 7.00 (m, 2H), 7.20 (d, J = 8.2 Hz,2H), 7.44 (m, 1H), 7.75 (dd, J = 8.6, 2.9 Hz, 1H), 8.19 (dd, J = 9.3, 5.7 Hz, 1H), 8.30 (d, J = 8.2 Hz, 2H), 8.42 (dd, J = 11.0, 3.0 Hz, 1H), 8.50 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 107.0 (d, J = 24.0 Hz), 109.6 (d, J = 24.0 Hz), 111.2 (d, J = 21.0 Hz), 115.0 (d, J = 3.0 Hz), 119.7, 120.6, 120.7 (d, J = 22.0 Hz), 124.7 (d, J = 10.0 Hz), 129.6, 131.9 (d, J = 10.0 Hz), 133.0 (d, J = 10.0 Hz), 133.7, 137.0, 146.2, 155.2, 158.0, 158.8 (d, J = 182.0 Hz), 159.7, 163.3 (d, J = 244.0 Hz), 167.6. ESI-MS calcd for $C_{22}H_{12}FNO_3$ (M-H), 376.1 found, 375.8.

2-(4-(4-fluorophenoxy)phenyl)-6-fluoroquinoline-4-carboxylic acid (C33):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (71.8 mg, 0.44 mmol). 0.5 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(4-fluorophenoxy)phenyl)ethanone (100.0 mg, 0.44 mmol) was added into the flask followed by the gradual addition of KOH (70.8 mg dissolved in 60 μL of H_2O, 1.26 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: off white powder; yield 82.1 mg (50%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.10 (d, J = 8.3 Hz, 2H), 7.16 (m, 2H), 7.26 (m, 2H), 7.73 (td, J = 8.7, 2.9 Hz, 1H), 8.17 (dd, J = 9.3, 5.8 Hz, 1H), 8.26 (d, J = 8.3 Hz, 2H), 8.41 (dd, J = 11.0, 2.9 Hz, 1H), 8.47 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 109.6 (d, J = 25.0 Hz), 110.0, 117.2 (d, J = 23.0 Hz), 118.3, 120.6, 120.8, 121.9 (d, J = 9.0 Hz), 124.6 (d, J = 10.0 Hz), 129.5, 132.9, 136.9, 146.2, 152.2, 155.2, 159.1 (d, J = 239.0 Hz), 159.5, 160.9 (245.0 Hz), 167.6. ESI-MS calcd for $C_{22}H_{12}FNO_3$ (M-H), 376.1 found, 375.8.

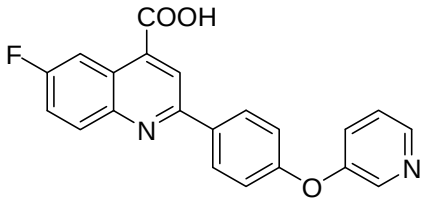
6-fluoro-2-(4-(pyridin-2-yloxy)phenyl)quinoline-4-carboxylic acid (C34):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (274.5 mg, 1.66 mmol). 2.0 mL of ethanol was added to

the flask. An ethanolic solution of 1-(4-(pyridin-2-yloxy)phenyl)ethanone (354.0 mg, 1.66 mmol) was added into the flask followed by the gradual addition of KOH (270.4 mg dissolved in 300 μL of H_2O, 4.81 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light brown powder; yield 454.2 mg (76%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.11 (d, J = 8.3 Hz, 1H), 7.14 (m, 1H), 7.25 (d, J = 8.2 Hz, 2H), 7.70 (td, J = 8.6, 2.9 Hz, 1H), 7.85 (td, J = 7.7, 2.0 Hz, 1H), 8.15 (m, 2H), 8.26 (d, J = 8.3 Hz, 2H), 8.41 (dd, J = 11.0, 3.0 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 109.6 (d, J = 25.0 Hz), 112.4, 119.9, 120.5, 120.7, 121.8, 124.7 (d, J = 11.0 Hz), 129.1, 133.0 (d, J = 19.0 Hz), 134.2, 136.7, 140.8, 146.2, 147.9, 155.2, 156.1, 161.4 (d, J = 245.0 Hz), 163.1, 167.6. ESI-MS calcd for $C_{21}H_{12}FN_2O_3$ (M-H), 359.1 found, 358.9.

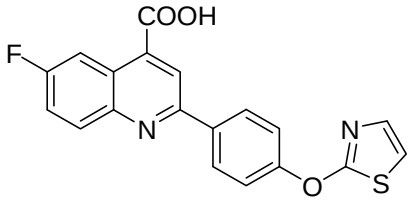
6-fluoro-2-(4-(pyridin-3-yloxy)phenyl)quinoline-4-carboxylic acid (C35):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (77.5 mg, 0.47 mmol). 2.0 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(pyridin-3-yloxy)phenyl)ethanone (100.0 mg, 0.47 mmol) was added into the flask followed by the gradual addition of KOH (76.5 mg dissolved in 200 μL of H_2O, 1.36 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was

collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light brown powder; yield 42.3 mg (25%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.21 (d, J = 8.4 Hz, 2H), 7.47 (dd, J = 8.5, 4.6 Hz, 1H), 7.57 (dd, J = 8.2, 2.9 Hz, 1H), 7.76 (td, J = 8.7, 2.9 Hz, 1H), 8.20 (dd, J = 9.2, 5.6 Hz, 1H), 8.32 (d, J = 8.6 Hz, 2H), 8.44 (m, 3H), 8.51 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 109.5 (d, J = 25.0 Hz), 119.0, 120.7, 120.8 (d, J = 26.0 Hz), 124.9 (d, J = 10.0 Hz), 125.3, 127.0, 129.7, 133.1 (d, J = 11.0 Hz), 133.7, 137.4, 142.0, 145.6, 146.2, 155.2, 158.5, 159.9, 163.5 (d, J = 245.0 Hz), 167.6. ESI-MS calcd for $C_{21}H_{12}FN_2O_3$ (M-H), 359.1 found, 358.9.

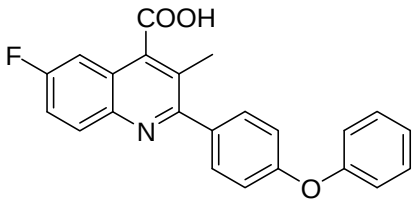
6-fluoro-2-(4-(thiazol-2-yloxy)phenyl)quinoline-4-carboxylic acid (C36):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (135.4 mg, 0.82 mmol). 1.5 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(thiazol-2-yloxy)phenyl)ethanone (180.0 mg, 0.82 mmol) was added into the flask followed by the gradual addition of KOH (134.0 mg dissolved in 200 μL of H_2O, 2.38 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light brown powder; yield 204.0 mg (68%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.26 (d, J = 3.9 Hz, 1H), 7.32 (d, J = 4.5 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.73 (t, J = 8.7 Hz, 1H), 8.18 (dd, J = 9.4, 5.6 Hz, 1H), 8.32 (d, J = 8.1 Hz, 2H), 8.41 (d, J = 11.6 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 109.6 (d, J = 25.0 Hz),

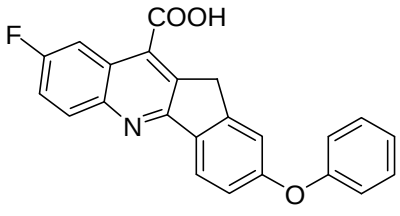
115.7, 116.3, 120.6 (d, J = 4.0 Hz), 120.7, 120.9, 124.8 (d, J = 11.0 Hz), 129.1 (d, J = 10.0 Hz), 129.5, 133.0, 135.6, 138.0, 146.2, 154.8, 156.9, 161.0 (d, J = 245.0 Hz), 167.7. ESI-MS calcd for $C_{19}H_{12}FN_2SO_3$ (M+H), 367.1 found, 366.8.

6-fluoro-3-methyl-2-(4-phenoxyphenyl)quinoline-4-carboxylic acid (C37):



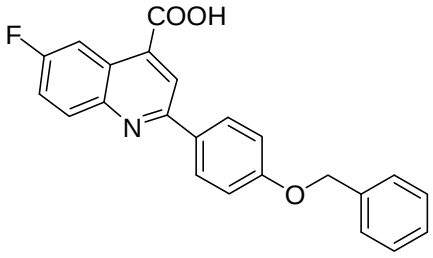
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (163.0 mg, 0.99 mmol). 2.0 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-phenoxyphenyl)propan-1-one (223.0 mg, 0.99 mmol) was added into the flask followed by the gradual addition of KOH (161.0 mg dissolved in 300 μL of H_2O, 2.87 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light brown powder; yield 120.2 mg (34%). ^{1}H NMR (400 MHz, DMSO-d_6): 2.41 (s, 3H), 7.12 (m, 4H), 7.20 (m, 1H), 7.46 (m, 3H), 7.66 (m, 3H), 8.10 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 18.2, 108.5 (d, J = 25.0 Hz), 118.2, 119.6, 119.8 (d, J = 25.0 Hz), 123.6 (d, J = 10.0 Hz), 124.3, 125.3, 130.6, 131.4, 132.5 (d, J = 9.0 Hz), 135.3, 143.3, 156.6, 157.5, 159.5, 160.5 (d, J = 245.0 Hz), 169.1. ESI-MS calcd for $C_{23}H_{15}FNO_3$ (M-H), 372.1 found, 371.9.

8-fluoro-2-phenoxy-11H-indeno[1,2-b]quinoline-10-carboxylic acid (C38):



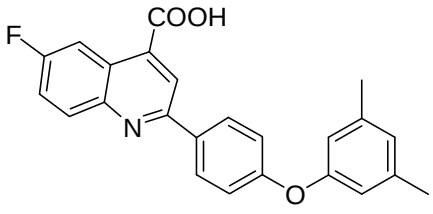
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (165.0 mg, 1.00 mmol). 2.0 mL of ethanol was added to the flask. An ethanolic solution of 2,3-dihydro-5-phenoxyinden-1-one (224.0 mg, 1.00 mmol) was added into the flask followed by the gradual addition of KOH (163.0 mg dissolved in 300 μL of H_2O, 2.90 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light brown powder; yield 185.5 mg (50%). ^{1}H NMR (400 MHz, DMSO-d_6): 4.30 (s, 2H), 7.14 (m, 3H), 7.24 (m, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.47 (m, 2H), 7.72 (td, J = 8.7, 2.9 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 8.20 (dd, J = 9.3, 5.8 Hz, 1H), 8.29 (dd, J = 11.3, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 35.8, 109.9 (d, J = 25.0 Hz), 115.4, 118.1, 119.3 (d, J = 26.0 Hz), 120.0, 123.4, 124.2 (d, J = 11.0 Hz), 124.7, 130.7, 130.9, 131.7 (d, J = 5.0 Hz), 132.0 (d, J = 5.0 Hz), 134.1, 136.7, 145.6, 148.1, 156.3, 160.0, 160.1 (d, J = 243.0 Hz), 167.6. ESI-MS calcd for $C_{23}H_{15}FNO_3$ (M+H), 372.1 found, 371.9.

2-(4-(benzyloxy)phenyl)-6-fluoroquinoline-4-carboxylic acid (C39):



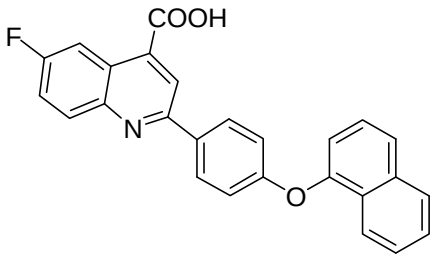
Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (500.0 mg, 3.03 mmol). 5.0 mL of ethanol was added to the flask. An ethanolic solution of 4-benzyloxyacetophenone (686.0 mg, 3.03 mmol) was added into the flask followed by the gradual addition of KOH (493.6 mg dissolved in 500 μL of H_2O, 8.79 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light brown powder; yield 678.0 mg (60%). ^{1}H NMR (400 MHz, DMSO-d_6): 5.14 (s, 2H), 7.13 (d, J = 8.2 Hz, 2H), 7.34 (t, J = 7.0 Hz, 1H), 7.40 (t, J = 7.3 Hz, 2H), 7.48 (t, J = 7.5 Hz, 2H), 7.67 (t, J = 8.5 Hz, 1H), 8.10 (dd, J = 8.8, 5.9 Hz, 1H), 8.18 (d, J = 8.2 Hz, 2H), 8.41 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): 69.8, 109.7 (d, J = 24.0 Hz), 115.6, 120.3, 120.4 (d, J = 26.0 Hz), 124.5 (d, J = 11.0 Hz), 128.2, 128.3, 128.9, 129.0, 130.7, 132.7 (d, J = 10.0 Hz), 137.2, 146.2, 155.4, 160.4, 160.6 (d, J = 246.0 Hz), 167.8. ESI-MS calcd for $C_{23}H_{15}FNO_3$ (M+H), 372.1 found, 371.9.

2-(4-(3,5-dimethylphenoxy)phenyl)-6-fluoroquinoline-4-carboxylic acid (C40):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (137.2 mg, 0.83 mmol). 1.5 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(3,5-dimethylphenoxy)phenyl)ethanone (200.0 mg, 0.83 mmol) was added into the flask followed by the gradual addition of KOH (135.2 mg dissolved in 150 μL of H_2O, 2.4 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light brown powder; yield 161.0 mg (50%). ^{1}H NMR (400 MHz, DMSO-d_6): 2.28 (s, 6H), 6.74 (s, 2H), 6.85 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.77 (td, J = 8.4, 2.7 Hz, 1H), 8.20 (dd, J = 9.3, 5.7 Hz, 1H), 8.29 (d, J = 8.4 Hz, 2H), 8.48 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): 21.3, 109.9 (d, J = 24.0 Hz), 117.9, 117.7, 118.8, 120.1, 120.4 (d, J = 26.0 Hz), 124.9 (d, J = 11.0 Hz), 126.1, 129.4, 131.1, 133.1, 140.0, 146.2, 155.2, 156.3, 159.2, 160.6 (d, J = 244.0 Hz), 167.9. HRMS (ESI$^-$) calcd for $C_{24}H_{17}FNO_3$ (M-H), 386.1192 found, 386.1202.

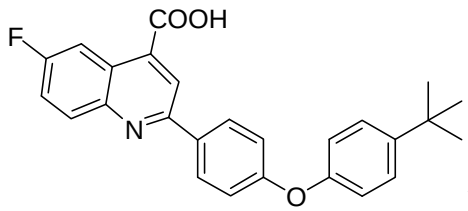
6-fluoro-2-(4-(naphthalen-1-yloxy)phenyl)quinoline-4-carboxylic acid (C41):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (126.0 mg, 0.76 mmol). 1.5 mL of ethanol was added to

the flask. An ethanolic solution of 1-(4-(naphthalen-1-yloxy)phenyl)ethanone (200.0 mg, 0.76 mmol) was added into the flask followed by the gradual addition of KOH (124.0 mg dissolved in 150 μL of H_2O, 2.2 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light brown powder; yield 62.0 mg (20%). ^{1}H NMR (400 MHz, DMSO-d_6): 7.26 (d, J = 8.2 Hz, 2H), 7.39 (dd, J = 8.9, 2.5 Hz, 1H), 7.51 (m, 2H), 7.57 (d, J = 2.4 Hz, 1H), 7.79 (td, J = 8.7, 3.0 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 8.9 Hz, 1H), 8.22 (dd, J = 9.3, 5.7 Hz, 1H), 8.35 (d, J = 8.3 Hz, 2H), 8.47 (dd, J = 10.9, 3.0 Hz, 1H), 8.54 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 109.6 (d, J = 25.0 Hz), 115.2, 119.2, 120.4, 120.6, 120.7, 120.8, 124.6 (d, J = 11.0 Hz), 125.6, 127.2, 128.2, 129.6, 130.5, 130.7, 132.9 (d, J = 10.0 Hz), 133.2, 137.0 (d, J = 6.6 Hz), 146.2, 154.2, 155.2 (d, J = 3.0 Hz), 159.0, 160.9 (d, J = 244.0 Hz), 167.6. HRMS (ESI$^-$) calcd for $C_{26}H_{15}FNO_3$ (M-H), 408.1030 found, 408.1031.

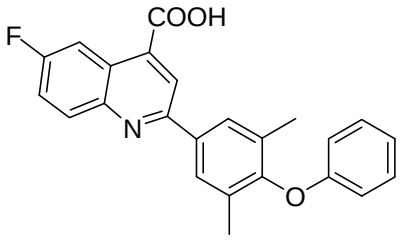
2-(4-(4-tert-butylphenoxy)phenyl)-6-fluoroquinoline-4-carboxylic acid (C42):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (55.5 mg, 0.34 mmol). 1.0 mL of ethanol was added to the flask. An ethanolic solution of 1-(4-(4-tert-butylphenoxy)phenyl)ethanone (90.0 mg, 0.34 mmol) was added into the flask followed by the gradual addition of KOH (54.7 mg dissolved in 100 μL of H_2O, 0.98 mmol, 2.9 equiv). The flask was refluxed under an atmosphere of argon for 48 h. It

was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light yellow powder; yield 28.2 mg (20%). ^{1}H NMR (400 MHz, DMSO-d_6): 1.26 (s, 9H), 7.01 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.73 (ddd, J = 9.3, 8.2, 2.9 Hz, 1H), 8.16 (dd, J = 9.3, 5.8 Hz, 1H), 8.24 (d, J = 8.3 Hz, 2H), 8.41 (dd, J = 11.0, 2.9 Hz, 1H), 8.46 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 31.7, 34.6, 109.6 (d, J = 24.0 Hz), 118.5, 119.4, 120.5, 120.7 (d, J = 21.0 Hz), 124.6 (d, J = 12.0 Hz), 127.3, 129.5, 132.8, 132.9 (d, J = 9.0 Hz), 136.9 (d, J = 8.0 Hz), 146.2, 146.9, 153.8, 155.2, 159.4, 160.8 (d, J = 244.0 Hz), 167.6. ESI-MS calcd for $C_{26}H_{21}FNO_3$ (M-H), 414.2 found, 413.9.

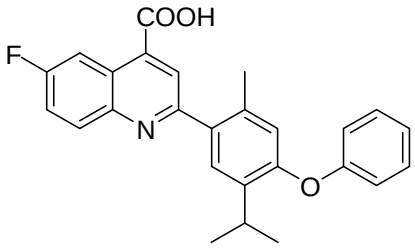
6-fluoro-2-(3,5-dimethyl-4-phenoxyphenyl)quinoline-4-carboxylic acid (C43):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (62.0 mg, 0.38 mmol). 1.0 mL of ethanol was added to the flask. An ethanolic solution of 1-(3,5-dimethyl-4-phenoxyphenyl)ethanone (90.0 mg, 0.38 mmol) was added into the flask followed by the gradual addition of KOH (61.2 mg dissolved in 100 μL of H_2O, 1.09 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from hot ethanol: light yellow powder; yield 34.2 mg (24%). ^{1}H

NMR (400 MHz, DMSO-d_6): 2.19 (s, 6H), 6.81 (d, J = 8.1 Hz, 2H), 7.03 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.79 (td, J = 8.8, 3.0 Hz, 1H), 8.12 (s, 2H), 8.25 (dd, J = 9.3, 5.8 Hz, 1H), 8.48 (dd, J = 11.0, 2.9 Hz, 1H), 8.57 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 16.6, 109.8 (d, J = 24.0 Hz), 114.8, 120.6, 120.7 (d, J = 23.0 Hz), 120.9, 124.7 (d, J = 11.0 Hz), 128.5, 130.5, 132.0, 132.5, 133.0 (d, J = 10.0 Hz), 135.0, 146.3, 152.6, 155.5, 159.7, 160.9 (d, J = 245.0 Hz), 167.7. HRMS (ESI$^-$) calcd for $C_{24}H_{17}FNO_3$ (M-H), 386.1192 found, 386.1195.

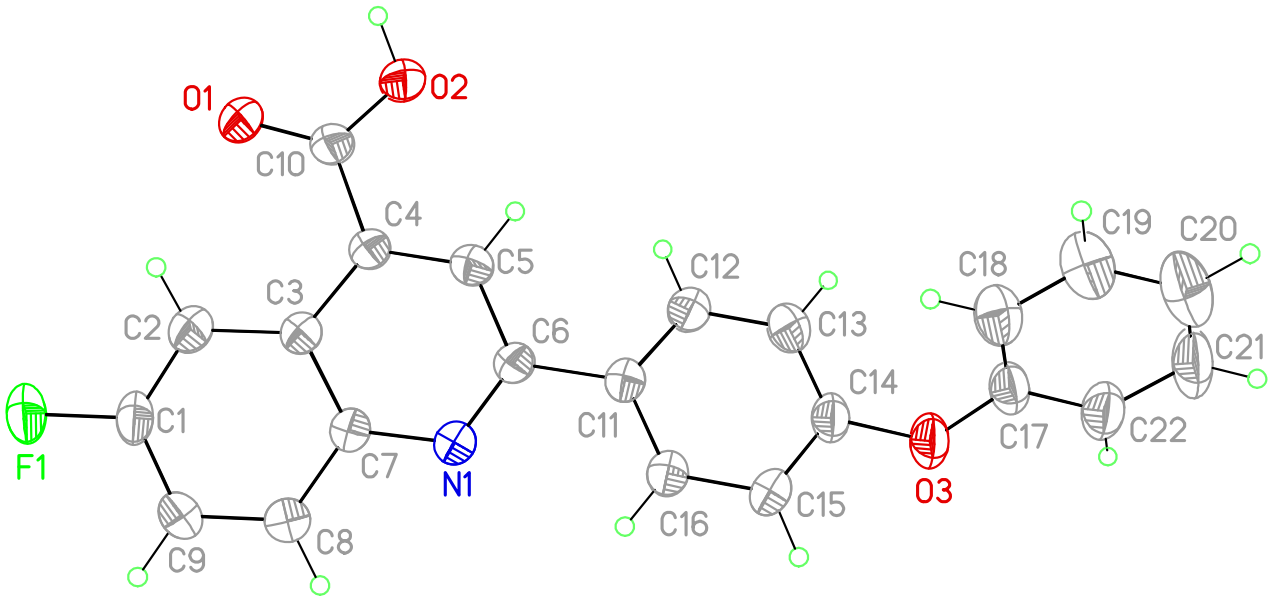
6-fluoro-2-(5-isopropyl-2-methyl-4-phenoxyphenyl)quinoline-4-carboxylic acid (C44):



Into a flame dried round-bottomed flask fitted with a reflux condenser was weighed 5-fluoroisatin (500.0 mg, 3.03 mmol). 5.5 mL of ethanol was added to the flask. An ethanolic solution of 1-(5-isopropyl-2-methyl-4-phenoxyphenyl)ethanone (675.0 mg, 3.18 mmol) was added into the flask followed by the gradual addition of KOH (494.0 mg dissolved in 500 μL of H_2O, 8.8 mmol). The flask was refluxed under an atmosphere of argon for 48 h. It was then cooled to room temperature, and ethanol was removed using a rotary evaporator. Into the residue was added 1M aqueous hydrochloride acid until the pH becomes 2.0. The precipitate was collected by filtration, washed with brine and dried under vacuum. The crude product was purified via recrystallization from acetic acid: off white powder; yield 591.2 mg (47%). ^{1}H NMR (500 MHz, DMSO-d_6): 1.22 (d, J = 6.8 Hz, 6H), 2.31 (s, 3H), 3.22 (m, 1H), 6.87 (s, 1H), 7.00 (d, J = 8.3 Hz, 2H), 7.12 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.56 (s, 1H), 7.80 (td, J = 8.5, 2.1 Hz, 1H), 8.15 (s, 1H), 8.22 (dd, J = 9.0, 5.8 Hz, 1H), 8.52(d, J = 10.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 20.5, 23.5, 27.4, 109.8 (d, J = 23.4 Hz), 118.1, 120.8

(d, J = 26.3 Hz), 122.4, 123.5, 124.6 (d, J = 11.3 Hz), 124.8, 129.3, 130.7, 133.2 (d, J = 10.0 Hz), 135.9, 136.0, 136.2, 137.8, 146.2, 154.0, 158.3, 159.0, 161.3 (d, J = 245.0 Hz), 167.8. HRMS (ESI$^-$) calcd for $C_{22}H_{13}FNO_3$ (M-H), 414.1505; found, 414.1512.

X-ray structure of **C12**:



X-ray Experimental for **C12**: Crystals grew as pale yellow prisms by slow evaporation from acetic acid. The data crystal was cut from a larger crystal and had approximate dimensions; 0.33 x 0.23 x 0.08 mm. The data were collected on a Rigaku SCX-Mini diffractometer with a Mercury CCD using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 1800 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 19 seconds per frame. The data were collected at 223 K using a Rigaku Tech50 low

temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The acidic hydrogen atoms on O2 and O2a were observed in a ΔF amp and refined with isotropic displacement parameters. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0611*P)^2 + (0.5767*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.167, with R(F) equal to 0.0626 and a goodness of fit, S, = 1.02. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were corrected for secondary extinction. The correction takes the form: $F_{corr} = kF_c/[1 + (1.5(6)x10^{-6})* F_c^2 \lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

References

1) CrystalClear 1.40 (2008). Rigaku Americas Corporation, The Woodlands, TX.
2) SIR97. (1999). A program for crystal structure solution. Altomare A., Burla M.C., Camalli M., Cascarano G.L., Giacovazzo C. , Guagliardi A., Moliterni A.G.G., Polidori G.,Spagna R. J. Appl. Cryst. 32, 115-119.
3) Sheldrick, G. M. (1994). SHELXL97. Program for the Refinement of Crystal Structures. University of Gottingen, Germany.
4) $R_w(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ where w is the weight given each reflection.
   $R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\sigma(F_o))$.
   $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.
5) International Tables for X-ray Crystallography (1992). Vol. C, Tables 4.2.6.8 and 6.1.1.4, A. J. C. Wilson, editor, Boston: Kluwer Academic Press.
6) Sheldrick, G. M. (1994). SHELXTL/PC (Version 5.03). Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.

Crystallographic Material for **C12**.

X-ray Experimental.

Table 1. Crystallographic Data for **C12**.

Table 2. Fractional coordinates and equivalent isotropic thermal parameters (Å2) for the non-hydrogen atoms of **C12**.

Table 3. Bond Lengths (Å) and Angles (o) for the non-hydrogen atoms of **C12**.

Table 4. Anisotropic thermal parameters for the non-hydrogen atoms of **C12**.

Table 5. Fractional coordinates and isotropic thermal parameters (Å2) for the hydrogen atoms of **C12**.

Table 6. Torsion Angles (o) for the non-hydrogen atoms of **C12**.

Table 7. H-Bond Lengths (Å) and Angles (o) for **C12**.

Table 1. Crystal data and structure refinement for **C12**.

Empirical formula	C22 H14 F N O3	
Formula weight	359.34	
Temperature	233(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.2245(12) Å	α= 108.572(3)°.
	b = 11.7731(15) Å	β= 90.821(3)°.
	c = 16.368(2) Å	γ = 98.631(4)°.
Volume	1662.3(4) Å3	
Z	4	
Density (calculated)	1.436 Mg/m3	
Absorption coefficient	0.104 mm-1	
F(000)	744	
Crystal size	0.33 x 0.23 x 0.08 mm	
Theta range for data collection	3.09 to 27.48°.	

Index ranges	-11<=h<=11, -15<=k<=15, -21<=l<=21
Reflections collected	29575
Independent reflections	7602 [R(int) = 0.0637]
Completeness to theta = 27.48°	99.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	7602 / 0 / 496
Goodness-of-fit on F2	1.023
Final R indices [I>2sigma(I)]	R1 = 0.0626, wR2 = 0.1392
R indices (all data)	R1 = 0.1240, wR2 = 0.1669
Extinction coefficient	1.5(6)x10-6
Largest diff. peak and hole	0.261 and -0.234 e.Å-3

Table 2. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103)for **C12**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
F1	8443(2)	9436(1)	5019(1)	64(1)
O1	10991(2)	6143(2)	4685(1)	60(1)
O2	11587(2)	4577(2)	3663(1)	64(1)
O3	8941(2)	1904(2)	-1711(1)	52(1)
N1	8484(2)	6014(2)	1849(1)	37(1)
C1	8501(3)	8579(2)	4238(1)	43(1)
C2	9283(3)	7680(2)	4194(2)	43(1)
C3	9321(2)	6766(2)	3390(1)	33(1)
C4	10083(2)	5745(2)	3225(1)	35(1)
C5	10034(3)	4953(2)	2412(1)	37(1)
C6	9227(2)	5102(2)	1720(1)	33(1)
C7	8532(2)	6838(2)	2658(1)	34(1)
C8	7753(3)	7817(2)	2757(2)	43(1)
C9	7736(3)	8682(2)	3535(2)	46(1)
C10	10932(3)	5512(2)	3922(2)	38(1)
C11	9172(2)	4238(2)	831(1)	34(1)
C12	10110(3)	3386(2)	580(2)	47(1)
C13	10029(3)	2597(2)	-251(2)	55(1)

C14	9006(3)	2639(2)	-857(1)	39(1)
C15	8100(3)	3493(2)	-634(1)	40(1)
C16	8179(3)	4281(2)	202(1)	39(1)
C17	8548(3)	657(2)	-1917(2)	42(1)
C18	8057(3)	88(2)	-1322(2)	52(1)
C19	7657(3)	-1142(3)	-1597(2)	63(1)
C20	7705(4)	-1829(3)	-2441(2)	72(1)
C21	8186(3)	-1264(3)	-3030(2)	68(1)
C22	8620(3)	-2(2)	-2761(2)	54(1)
F1A	4294(2)	9091(1)	5416(1)	64(1)
O1A	6761(2)	5764(2)	5145(1)	54(1)
O2A	7470(2)	4263(2)	4117(1)	54(1)
O3A	4906(2)	1441(2)	-1242(1)	49(1)
N1A	4256(2)	5572(2)	2282(1)	37(1)
C1A	4306(3)	8194(2)	4649(1)	44(1)
C2A	5049(3)	7277(2)	4623(1)	38(1)
C3A	5078(2)	6349(2)	3824(1)	33(1)
C4A	5828(2)	5333(2)	3683(1)	32(1)
C5A	5762(2)	4506(2)	2872(1)	34(1)
C6A	4957(2)	4639(2)	2175(1)	32(1)
C7A	4312(3)	6418(2)	3085(1)	36(1)
C8A	3558(3)	7409(2)	3166(2)	45(1)
C9A	3552(3)	8289(2)	3933(2)	47(1)
C10A	6728(2)	5142(2)	4380(1)	34(1)
C11A	4889(2)	3751(2)	1291(1)	33(1)
C12A	5503(3)	2697(2)	1107(2)	45(1)
C13A	5448(3)	1902(2)	274(2)	48(1)
C14A	4807(3)	2163(2)	-391(1)	40(1)
C15A	4174(3)	3185(2)	-232(2)	52(1)
C16A	4216(3)	3972(2)	605(2)	48(1)
C17A	3893(3)	388(2)	-1593(1)	38(1)
C18A	2668(3)	75(2)	-1195(2)	47(1)
C19A	1697(3)	-971(3)	-1625(2)	62(1)
C20A	1956(4)	-1683(2)	-2438(2)	63(1)
C21A	3188(4)	-1365(2)	-2822(2)	58(1)

C22A	4167(3)	-335(2)	-2402(2)	47(1)

Table 3. Bond lengths [Å] and angles [°] for **C12**.

F1-C1	1.361(2)	C15-H15	0.94
O1-C10	1.228(3)	C16-H16	0.94
O2-C10	1.291(3)	C17-C22	1.360(3)
O2-H2O	1.00(4)	C17-C18	1.393(4)
O3-C14	1.386(3)	C18-C19	1.363(4)
O3-C17	1.386(3)	C18-H18	0.94
N1-C6	1.322(3)	C19-C20	1.367(4)
N1-C7	1.365(3)	C19-H19	0.94
C1-C2	1.351(3)	C20-C21	1.378(4)
C1-C9	1.390(3)	C20-H20	0.94
C2-C3	1.415(3)	C21-C22	1.401(4)
C2-H2	0.94	C21-H21	0.94
C3-C7	1.426(3)	C22-H22	0.94
C3-C4	1.436(3)	F1A-C1A	1.361(2)
C4-C5	1.355(3)	O1A-C10A	1.230(2)
C4-C10	1.493(3)	O2A-C10A	1.288(3)
C5-C6	1.417(3)	O2A-H2OA	0.85(3)
C5-H5	0.94	O3A-C17A	1.387(3)
C6-C11	1.482(3)	O3A-C14A	1.394(3)
C7-C8	1.415(3)	N1A-C6A	1.323(3)
C8-C9	1.355(3)	N1A-C7A	1.368(3)
C8-H8	0.94	C1A-C2A	1.354(3)
C9-H9	0.94	C1A-C9A	1.397(3)
C11-C16	1.387(3)	C2A-C3A	1.414(3)
C11-C12	1.389(3)	C2A-H2A	0.94
C12-C13	1.374(3)	C3A-C7A	1.423(3)
C12-H12	0.94	C3A-C4A	1.429(3)
C13-C14	1.377(3)	C4A-C5A	1.368(3)
C13-H13	0.94	C4A-C10A	1.495(3)
C14-C15	1.367(3)	C5A-C6A	1.414(3)
C15-C16	1.381(3)	C5A-H5A	0.94

C6A-C11A	1.486(3)	C15A-H15A	0.94
C7A-C8A	1.417(3)	C16A-H16A	0.94
C8A-C9A	1.351(3)	C17A-C18A	1.373(3)
C8A-H8A	0.94	C17A-C22A	1.379(3)
C9A-H9A	0.94	C18A-C19A	1.383(4)
C11A-C16A	1.388(3)	C18A-H18A	0.94
C11A-C12A	1.389(3)	C19A-C20A	1.374(4)
C12A-C13A	1.381(3)	C19A-H19A	0.94
C12A-H12A	0.94	C20A-C21A	1.368(4)
C13A-C14A	1.371(3)	C20A-H20A	0.94
C13A-H13A	0.94	C21A-C22A	1.371(4)
C14A-C15A	1.368(3)	C21A-H21A	0.94
C15A-C16A	1.385(3)	C22A-H22A	0.94

C10-O2-H2O	115(2)	N1-C7-C3	123.8(2)
C14-O3-C17	119.63(19)	C8-C7-C3	119.3(2)
C6-N1-C7	119.11(18)	C9-C8-C7	121.4(2)
C2-C1-F1	118.5(2)	C9-C8-H8	119.3
C2-C1-C9	124.1(2)	C7-C8-H8	119.3
F1-C1-C9	117.4(2)	C8-C9-C1	118.0(2)
C1-C2-C3	119.0(2)	C8-C9-H9	121.0
C1-C2-H2	120.5	C1-C9-H9	121.0
C3-C2-H2	120.5	O1-C10-O2	122.2(2)
C2-C3-C7	118.2(2)	O1-C10-C4	123.1(2)
C2-C3-C4	126.6(2)	O2-C10-C4	114.7(2)
C7-C3-C4	115.25(19)	C16-C11-C12	117.2(2)
C5-C4-C3	119.6(2)	C16-C11-C6	119.9(2)
C5-C4-C10	118.0(2)	C12-C11-C6	122.9(2)
C3-C4-C10	122.36(19)	C13-C12-C11	121.5(2)
C4-C5-C6	121.3(2)	C13-C12-H12	119.3
C4-C5-H5	119.4	C11-C12-H12	119.3
C6-C5-H5	119.4	C12-C13-C14	120.1(2)
N1-C6-C5	121.0(2)	C12-C13-H13	119.9
N1-C6-C11	117.65(19)	C14-C13-H13	119.9
C5-C6-C11	121.4(2)	C15-C14-C13	119.6(2)
N1-C7-C8	116.98(19)	C15-C14-O3	118.3(2)

C13-C14-O3	121.9(2)	C7A-C3A-C4A	115.85(19)
C14-C15-C16	120.1(2)	C5A-C4A-C3A	119.29(19)
C14-C15-H15	120.0	C5A-C4A-C10A	117.7(2)
C16-C15-H15	120.0	C3A-C4A-C10A	122.95(18)
C15-C16-C11	121.5(2)	C4A-C5A-C6A	121.0(2)
C15-C16-H16	119.3	C4A-C5A-H5A	119.5
C11-C16-H16	119.3	C6A-C5A-H5A	119.5
C22-C17-O3	115.7(2)	N1A-C6A-C5A	121.33(19)
C22-C17-C18	120.7(2)	N1A-C6A-C11A	117.30(19)
O3-C17-C18	123.6(2)	C5A-C6A-C11A	121.36(19)
C19-C18-C17	118.9(2)	N1A-C7A-C8A	116.92(19)
C19-C18-H18	120.5	N1A-C7A-C3A	123.6(2)
C17-C18-H18	120.5	C8A-C7A-C3A	119.50(19)
C18-C19-C20	121.8(3)	C9A-C8A-C7A	121.2(2)
C18-C19-H19	119.1	C9A-C8A-H8A	119.4
C20-C19-H19	119.1	C7A-C8A-H8A	119.4
C19-C20-C21	119.1(3)	C8A-C9A-C1A	118.1(2)
C19-C20-H20	120.4	C8A-C9A-H9A	121.0
C21-C20-H20	120.4	C1A-C9A-H9A	121.0
C20-C21-C22	120.1(3)	O1A-C10A-O2A	122.2(2)
C20-C21-H21	119.9	O1A-C10A-C4A	123.2(2)
C22-C21-H21	119.9	O2A-C10A-C4A	114.58(19)
C17-C22-C21	119.3(3)	C16A-C11A-C12A	117.4(2)
C17-C22-H22	120.4	C16A-C11A-C6A	119.9(2)
C21-C22-H22	120.4	C12A-C11A-C6A	122.7(2)
C10A-O2A-H2OA	112(2)	C13A-C12A-C11A	121.2(2)
C17A-O3A-C14A	119.19(18)	C13A-C12A-H12A	119.4
C6A-N1A-C7A	118.95(18)	C11A-C12A-H12A	119.4
C2A-C1A-F1A	118.4(2)	C14A-C13A-C12A	119.9(2)
C2A-C1A-C9A	124.2(2)	C14A-C13A-H13A	120.1
F1A-C1A-C9A	117.4(2)	C12A-C13A-H13A	120.1
C1A-C2A-C3A	118.7(2)	C15A-C14A-C13A	120.4(2)
C1A-C2A-H2A	120.7	C15A-C14A-O3A	119.4(2)
C3A-C2A-H2A	120.7	C13A-C14A-O3A	119.9(2)
C2A-C3A-C7A	118.4(2)	C14A-C15A-C16A	119.5(2)
C2A-C3A-C4A	125.74(19)	C14A-C15A-H15A	120.3

C16A-C15A-H15A	120.3	C20A-C19A-H19A	119.8
C15A-C16A-C11A	121.5(2)	C18A-C19A-H19A	119.8
C15A-C16A-H16A	119.2	C21A-C20A-C19A	120.0(3)
C11A-C16A-H16A	119.2	C21A-C20A-H20A	120.0
C18A-C17A-C22A	120.7(2)	C19A-C20A-H20A	120.0
C18A-C17A-O3A	124.1(2)	C20A-C21A-C22A	120.4(3)
C22A-C17A-O3A	115.2(2)	C20A-C21A-H21A	119.8
C17A-C18A-C19A	118.9(2)	C22A-C21A-H21A	119.8
C17A-C18A-H18A	120.5	C21A-C22A-C17A	119.6(3)
C19A-C18A-H18A	120.5	C21A-C22A-H22A	120.2
C20A-C19A-C18A	120.4(3)	C17A-C22A-H22A	120.2

Table 4. Anisotropic displacement parameters (Å2x 103) for **C12**. The anisotropic displacement factor exponent takes the form: -2π2[h2 a*2U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
F1	84(1)	58(1)	38(1)	-9(1)	-3(1)	33(1)
O1	88(1)	56(1)	33(1)	2(1)	-17(1)	34(1)
O2	92(2)	64(1)	38(1)	6(1)	-14(1)	47(1)
O3	78(1)	39(1)	32(1)	2(1)	4(1)	9(1)
N1	43(1)	36(1)	31(1)	8(1)	-2(1)	9(1)
C1	52(2)	41(1)	29(1)	-2(1)	2(1)	13(1)
C2	47(2)	45(2)	32(1)	7(1)	-5(1)	11(1)
C3	35(1)	33(1)	30(1)	8(1)	-1(1)	7(1)
C4	39(1)	33(1)	32(1)	8(1)	-6(1)	8(1)
C5	41(1)	34(1)	37(1)	9(1)	-3(1)	12(1)
C6	35(1)	31(1)	31(1)	8(1)	-4(1)	5(1)
C7	39(1)	33(1)	29(1)	7(1)	0(1)	7(1)
C8	54(2)	41(1)	35(1)	11(1)	-1(1)	16(1)
C9	58(2)	41(1)	40(1)	9(1)	5(1)	24(1)
C10	43(1)	36(1)	36(1)	9(1)	-7(1)	10(1)
C11	37(1)	33(1)	31(1)	7(1)	-1(1)	6(1)
C12	56(2)	49(2)	35(1)	5(1)	-4(1)	23(1)

C13	70(2)	51(2)	41(2)	2(1)	2(1)	33(2)
C14	52(2)	32(1)	29(1)	4(1)	4(1)	6(1)
C15	45(2)	41(1)	30(1)	6(1)	-6(1)	6(1)
C16	43(2)	38(1)	33(1)	5(1)	-2(1)	11(1)
C17	41(2)	36(1)	41(1)	-1(1)	1(1)	10(1)
C18	57(2)	45(2)	46(2)	6(1)	10(1)	9(1)
C19	66(2)	47(2)	67(2)	9(2)	9(2)	6(1)
C20	72(2)	43(2)	84(2)	0(2)	7(2)	2(2)
C21	77(2)	50(2)	54(2)	-16(2)	-1(2)	12(2)
C22	61(2)	50(2)	40(2)	-1(1)	-1(1)	11(1)
F1A	100(1)	53(1)	33(1)	-3(1)	0(1)	36(1)
O1A	79(1)	54(1)	27(1)	2(1)	-13(1)	31(1)
O2A	78(1)	54(1)	32(1)	5(1)	-14(1)	35(1)
O3A	61(1)	43(1)	31(1)	-3(1)	6(1)	1(1)
N1A	44(1)	36(1)	28(1)	5(1)	-5(1)	10(1)
C1A	61(2)	37(1)	29(1)	-1(1)	4(1)	17(1)
C2A	48(2)	40(1)	26(1)	7(1)	-4(1)	12(1)
C3A	36(1)	32(1)	29(1)	9(1)	-1(1)	6(1)
C4A	35(1)	33(1)	27(1)	9(1)	-3(1)	4(1)
C5A	42(1)	29(1)	30(1)	7(1)	-4(1)	10(1)
C6A	36(1)	31(1)	29(1)	8(1)	-2(1)	7(1)
C7A	42(1)	33(1)	29(1)	4(1)	-3(1)	10(1)
C8A	56(2)	46(2)	33(1)	7(1)	-8(1)	23(1)
C9A	59(2)	43(2)	41(1)	9(1)	0(1)	26(1)
C10A	39(1)	30(1)	31(1)	7(1)	-6(1)	6(1)
C11A	38(1)	32(1)	27(1)	6(1)	-3(1)	6(1)
C12A	62(2)	44(2)	33(1)	11(1)	-2(1)	21(1)
C13A	68(2)	39(1)	37(1)	7(1)	5(1)	21(1)
C14A	47(2)	36(1)	29(1)	0(1)	-1(1)	3(1)
C15A	67(2)	52(2)	31(1)	1(1)	-15(1)	23(1)
C16A	62(2)	44(2)	34(1)	2(1)	-14(1)	25(1)
C17A	50(2)	28(1)	33(1)	4(1)	-8(1)	13(1)
C18A	46(2)	42(2)	48(2)	5(1)	3(1)	14(1)
C19A	47(2)	51(2)	83(2)	17(2)	0(2)	4(1)
C20A	74(2)	38(2)	63(2)	1(1)	-22(2)	1(2)
C21A	90(2)	39(2)	38(2)	4(1)	-10(2)	11(2)

C22A	69(2)	37(1)	32(1)	5(1)	-1(1)	13(1)

Table 5. Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2x 10 3) for **C12**.

	x	y	z	U(eq)
H2	9793	7662	4689	51
H5	10545	4293	2305	45
H8	7236	7868	2274	52
H9	7222	9333	3596	55
H12	10815	3349	986	57
H13	10673	2027	-405	66
H15	7423	3544	-1051	48
H16	7544	4860	348	47
H18	8002	546	-739	62
H19	7340	-1529	-1194	75
H20	7415	-2676	-2618	87
H21	8222	-1727	-3613	81
H22	8957	386	-3160	64
H2A	5537	7257	5125	46
H5A	6259	3838	2775	41
H8A	3054	7454	2677	54
H9A	3054	8947	3984	56
H12A	5965	2521	1558	54
H13A	5850	1184	164	57
H15A	3714	3351	-688	62
H16A	3778	4672	712	57
H18A	2492	563	-639	56
H19A	854	-1195	-1360	74
H20A	1287	-2388	-2729	76
H21A	3365	-1855	-3377	69
H22A	5019	-123	-2665	56
H2OA	7970(40)	4180(30)	4530(20)	92(12)

H2O	12300(40)	4500(30)	4100(20)	121(13)

Table 6. Torsion angles [°] for **C12**.

F1-C1-C2-C3	178.4(2)	C5-C6-C11-C12	-13.1(4)
C9-C1-C2-C3	-1.1(4)	C16-C11-C12-C13	-1.8(4)
C1-C2-C3-C7	0.2(4)	C6-C11-C12-C13	180.0(2)
C1-C2-C3-C4	-179.6(2)	C11-C12-C13-C14	0.2(4)
C2-C3-C4-C5	-178.9(2)	C12-C13-C14-C15	1.9(4)
C7-C3-C4-C5	1.3(3)	C12-C13-C14-O3	176.5(2)
C2-C3-C4-C10	1.4(4)	C17-O3-C14-C15	-119.1(2)
C7-C3-C4-C10	-178.4(2)	C17-O3-C14-C13	66.3(3)
C3-C4-C5-C6	-0.9(4)	C13-C14-C15-C16	-2.2(4)
C10-C4-C5-C6	178.8(2)	O3-C14-C15-C16	-177.0(2)
C7-N1-C6-C5	1.8(3)	C14-C15-C16-C11	0.5(4)
C7-N1-C6-C11	-178.9(2)	C12-C11-C16-C15	1.5(4)
C4-C5-C6-N1	-0.7(4)	C6-C11-C16-C15	179.7(2)
C4-C5-C6-C11	-180.0(2)	C14-O3-C17-C22	-175.2(2)
C6-N1-C7-C8	178.2(2)	C14-O3-C17-C18	6.9(4)
C6-N1-C7-C3	-1.4(3)	C22-C17-C18-C19	0.4(4)
C2-C3-C7-N1	180.0(2)	O3-C17-C18-C19	178.1(2)
C4-C3-C7-N1	-0.2(3)	C17-C18-C19-C20	-1.0(4)
C2-C3-C7-C8	0.4(3)	C18-C19-C20-C21	0.7(5)
C4-C3-C7-C8	-179.7(2)	C19-C20-C21-C22	0.1(5)
N1-C7-C8-C9	-179.9(2)	O3-C17-C22-C21	-177.5(2)
C3-C7-C8-C9	-0.3(4)	C18-C17-C22-C21	0.4(4)
C7-C8-C9-C1	-0.5(4)	C20-C21-C22-C17	-0.6(4)
C2-C1-C9-C8	1.2(4)	F1A-C1A-C2A-C3A	-179.3(2)
F1-C1-C9-C8	-178.3(2)	C9A-C1A-C2A-C3A	0.1(4)
C5-C4-C10-O1	-176.7(2)	C1A-C2A-C3A-C7A	-0.5(3)
C3-C4-C10-O1	3.0(4)	C1A-C2A-C3A-C4A	178.9(2)
C5-C4-C10-O2	2.2(3)	C2A-C3A-C4A-C5A	-179.8(2)
C3-C4-C10-O2	-178.1(2)	C7A-C3A-C4A-C5A	-0.4(3)
N1-C6-C11-C16	-10.5(3)	C2A-C3A-C4A-C10A	-1.6(4)
C5-C6-C11-C16	168.8(2)	C7A-C3A-C4A-C10A	177.8(2)
N1-C6-C11-C12	167.6(2)	C3A-C4A-C5A-C6A	-0.4(3)

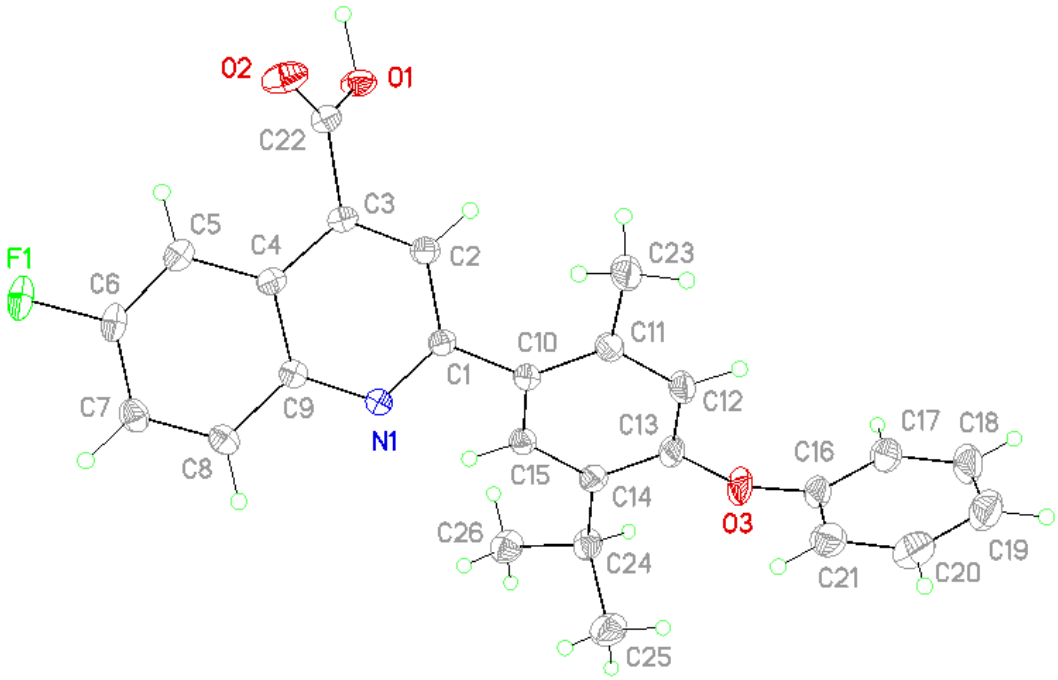
C10A-C4A-C5A-C6A	-178.7(2)	C5A-C6A-C11A-C12A	5.2(4)
C7A-N1A-C6A-C5A	-0.2(3)	C16A-C11A-C12A-C13A	0.2(4)
C7A-N1A-C6A-C11A	-179.1(2)	C6A-C11A-C12A-C13A	-178.6(2)
C4A-C5A-C6A-N1A	0.7(3)	C11A-C12A-C13A-C14A	1.5(4)
C4A-C5A-C6A-C11A	179.5(2)	C12A-C13A-C14A-C15A	-2.3(4)
C6A-N1A-C7A-C8A	179.3(2)	C12A-C13A-C14A-O3A	172.3(2)
C6A-N1A-C7A-C3A	-0.6(3)	C17A-O3A-C14A-C15A	-100.3(3)
C2A-C3A-C7A-N1A	-179.6(2)	C17A-O3A-C14A-C13A	85.0(3)
C4A-C3A-C7A-N1A	0.9(3)	C13A-C14A-C15A-C16A	1.6(4)
C2A-C3A-C7A-C8A	0.5(3)	O3A-C14A-C15A-C16A	-173.1(2)
C4A-C3A-C7A-C8A	-179.0(2)	C14A-C15A-C16A-C11A	0.1(4)
N1A-C7A-C8A-C9A	180.0(2)	C12A-C11A-C16A-C15A	-0.9(4)
C3A-C7A-C8A-C9A	-0.1(4)	C6A-C11A-C16A-C15A	177.8(2)
C7A-C8A-C9A-C1A	-0.3(4)	C14A-O3A-C17A-C18A	8.6(3)
C2A-C1A-C9A-C8A	0.3(4)	C14A-O3A-C17A-C22A	-173.3(2)
F1A-C1A-C9A-C8A	179.7(2)	C22A-C17A-C18A-C19A	-1.0(4)
C5A-C4A-C10A-O1A	-173.4(2)	O3A-C17A-C18A-C19A	176.9(2)
C3A-C4A-C10A-O1A	8.4(4)	C17A-C18A-C19A-C20A	0.0(4)
C5A-C4A-C10A-O2A	6.3(3)	C18A-C19A-C20A-C21A	0.6(4)
C3A-C4A-C10A-O2A	-171.9(2)	C19A-C20A-C21A-C22A	-0.3(4)
N1A-C6A-C11A-C16A	5.3(3)	C20A-C21A-C22A-C17A	-0.7(4)
C5A-C6A-C11A-C16A	-173.5(2)	C18A-C17A-C22A-C21A	1.4(4)
N1A-C6A-C11A-C12A	-176.0(2)	O3A-C17A-C22A-C21A	-176.8(2)

Table 7. Hydrogen bonds for **C12** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O2A-H2OA...O1#1	0.85(3)	1.76(4)	2.610(2)	174(3)
O2-H2O...O1A#1	1.00(4)	1.63(4)	2.625(2)	170(3)

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,-y+1,-z+1

X-ray structure of **C44**:



Crystallographic summary for **C44**. Thin, colorless lathes were grown by slow evaporation from hot ethanol, Orthorhombic, $Pca2_1$, Z=4 in a cell of dimensions: a = 39.877(3), b = 7.5843(11), c = 6.7766(10)Å, V = 2049.5(5)Å^3, ρ_{calc} = 1.35 g-cm^{-3}, F(000) = 872. A total of 28855 reflections were measured, 2540 unique (R_{int} = 0.102), on a Rigaku AFC-12 with a Saturn 724+

CCD using graphite monochromatized Mo Kα radiation (λ = 0.71075Å) at -173 ˚C. The structure was refined on F^2 to an R_W = 0.125, with a conventional R = 0.0527 (2220 reflections with $F_O > 4[\sigma(F_O)]$), and a goodness of fit = 1.10 for 288 refined parameters.

X-ray Experimental for **C44**: Crystals grew as thin, colorless plates by slow evaporation hot ethanol. The data crystal had approximate dimensions; 0.14 x 0.12 x 0.04 mm. The data were collected on a Rigaku AFC12 diffractometer with a Saturn 724+ CCD using a graphite monochromator with MoKα radiation (λ = 0.71075Å). A total of 1590 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 28 seconds per frame. The data were collected at 100 K using a Rigaku XStream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] Structure analysis was aided by use of the programs PLATON98[4] and WinGX.[5] The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.0717*P)^2 + (0.4615*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_W(F^2)$ refined to 0.125, with R(F) equal to 0.0527 and a goodness of fit, S, = 1.12. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[6] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_C/[1 + (4.0(4)x10^{-5})* F_C^2 \lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[7] All figures were generated using SHELXTL/PC.[8] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

References

1) CrystalClear 1.40 (2008). Rigaku Americas Corportion, The Woodlands, TX.
2) SIR97. (1999). A program for crystal structure solution. Altomare A., Burla M.C., Camalli M., Cascarano G.L., Giacovazzo C. , Guagliardi A., Moliterni A.G.G., Polidori G.,Spagna R. J. Appl. Cryst. 32, 115-119.
3) Sheldrick, G. M. (2008). SHELXL97. Program for the Refinement of Crystal Structures. Acta Cryst., A64, 112-122.
4) Spek, A. L. (1998). PLATON, A Multipurpose Crystallographic Tool. Utrecht University, The Netherlands.
5) WinGX 1.64. (1999). An Integrated System of Windows Programs for the Solution, Refinement and Analysis of Single Crystal X-ray Diffraction Data. Farrugia, L. J. J. Appl. Cryst. 32. 837-838.
6) $R_W(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ where w is the weight given each reflection. $R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\sigma(F_o))$. $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.
7) International Tables for X-ray Crystallography (1992). Vol. C, Tables 4.2.6.8 and 6.1.1.4, A. J. C. Wilson, editor, Boston: Kluwer Academic Press.
8) Sheldrick, G. M. (1994). SHELXTL/PC (Version 5.03). Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.

Material and methods for Co-crystal structure of **C44-hDHODH**:

Gene cloning of human *DHODH*. The truncated $hDHODH_{30-396}$ gene was subcloned into pET28b to generate the expression plasmid pET28b-$hDHODH_{30-396}$ using plasmid pET22b-$hDHODH_{30-396}$[1] as the PCR template and primers AACCATGGCCACGGGAGATGAG and AACTCGAGCCTCCGATGATCTGC, containing restriction endonuclease sites NcoI and XholI. In order to facilitate crystallization, a new construct pET28b-$hDHODH_{33-396}$ was then created by deletion mutagenesis PCR (stratagene site-directed mutagenesis protocol) using 125 ng each of primers GGAGATATACCATGGGAGATGAGCGTTTC and GAAACGCTCATCTCCCATGGTATATCTCC, 20ng of plasmid pET28b-$hDHODH_{30-396}$ was used as the template with the addition of 2.5 unit of Pfu polymerase (stratagene) and 1µl of 10mM dNTP mixture (Roche). The final reaction volume is 50 µl and was performed 15

thermal cycles (95 °C for 30s, 58 °C for 1 min, and 72 °C for 8 min). The reaction was treated with Dpn1 for 1 hour and then transformed into Top10 competent cell.

Protein expression and purification. $hDHODH_{33\text{-}396}$ was expressed in *E.coli* BL21 phage-resistant cells (Novagen) grown in Terrific Broth medium containing kanamycin (50 μg/ml). Cells were grown to 0.8 OD_{600} at 37 ^{o}C, 0.2 mM isopropyl-β-D-thiogalactoside (IPTG) was added to induce protein expression and cells were grown overnight at 16^{o}C before harvesting by centrifugation (4000 g). The pellet was resuspended in lysis buffer (50 mM HEPES pH8.0, 300 mM NaCl, 10% Glycerol, 10 mM imidazole, and 0.05% THESIT detergent (Fluka)), containing protease-inhibitor cocktail for His-tag protein (Sigma) and cells were lysed by three passes through an EmulsiFlex-C5 high pressure homogenizer (Avestin Inc.). The lysate was clarified by centrifugation (20,000 g) and the result supernatant was applied on 5 ml HisTrap HP column (GE Healthcare) precharged with Ni^{+2}. The column was sequentially washed with lysis buffer and lysis buffer containing 40 mM imidazole. $hDHODH_{33\text{-}396}$ was eluted from the column in lysis buffer containing 200 mM imidazole. Fractions containing $hDHODH_{33\text{-}396}$ were pooled, concentrated with Amicon Ultra concentrator (Millipore) to 2-4 ml and then purified by gel filtration column chromatography on a HiLoad 16/60 superdex 200 column (GE Healthcare) equilibrated with gel filtration buffer (20 mM Hepes, pH 7.8, 300 mM NaCl, 10% Glycerol, 1 mM DTT). The fractions containing $hDHODH_{33\text{-}396}$ were pooled, with addition of 40 mM Zwittergent3-10 (Affymetrix) and 200 mM Hega 8 (Affymetrix), and then concentrated to 20 mg/ml.

Crystallization and data collection. Random crystallization screen kit Ammonium sulfate suite (Nextal) and detergent screen kits (Hampton Research) were utilized to determine preliminary crystallization conditions, subsequent refinement of precipitant concentration,

detergent concentration, pH and protein concentration were then done to find the optimal conditions. Detergent screens showed that Zwittergent3-10 and Hega-8 improved crystallization of *h*DHODH and the 2 detergents were subsequently added to the pool fractions after the Gel filtration purification step. Crystal of $hDHODH_{33-396}$–C44 complex was grown by vapor diffusion in hanging drop at 20°C under the condition of 1.72 M Ammonium sulfate, 0.1 M Sodium Acetate, pH 5.4, 1.5 M NaCl, and 10 mM DTT. The protein solution was mixed with 2 mM L-DHO, 1mM C44 then incubated on ice for 2 h. The crystallization drop was a 1 to 1 ratio of protein solution and reservoir solution. Crystals typically grew in 10-15 days.

Crystals were flashed frozen with liquid nitrogen using oil (Hampton Research) as cryoprotectant agent. Diffraction data were collected at 100K on beamline 19ID at Advanced Photon Source (APS) using an ADSC Q315 detector. The best crystal diffracted to a resolution of 1.22 Å and has a space group of $P3_221$ with the cell dimension $a=b=90.87$, $c=122.19$. Diffraction data were integrated and intensities were scaled with HKL2000 package [2] (Table S1).

Structure determination and refinement. Crystallographic phases of $hDHODH_{33-396}$–C44 complex were solved by molecular replacement with Phaser [3] using the previously reported structure of *h*DHODH bound to brequinar (PDB ID 1D3G[4], polypeptide only) as a search model with bound ligands removed from prior to use as the search model. The $hDHODH_{33-396}$–C44 structure has one molecule in the asymmetric unit. The inhibitor C44 in addition to L-DHO and FMN showed up clearly on the difference Fourier map (Fo-Fc) (Figure S1A). Structures were rebuilt with COOT[5] and refined with REFMAC [6] and phases were improved with DM[7] (Table S1 and Figure S1B). Water molecules were added if the density was stronger than 3.4 σ and they were removed if the density was weaker than 1 σ in the

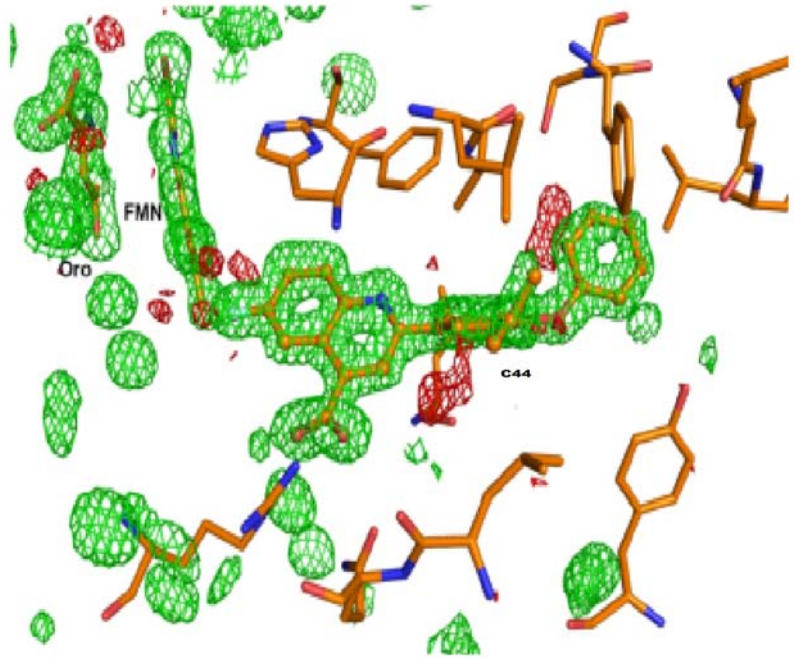
density map with ARP/WARP[8] .The final structure contains residues Asp34 – Arg396, with the exception that density was not observed for a loop formed by residues 71-73 and 222-225. Cofactor FMN, substrate L-DHO, inhibitor C44, 300 water molecules and a bound Zwittergent3-10 detergent molecule were also present in the structure.

Table S1

*C44-h*DHODH diffraction data and refinement statistics

Data collection		**Refinement**	
Resolution (Å)	50.0-1.22	Solvent (%)	66.7
Space group	$P3_221$	R_{factor} (%)	14.0
Cell dimensions	a=b=90.87, c=122.19	R_{free} (%)	16.1
	$\alpha=\beta=90^o$, $\gamma=120^o$	No. of atoms	6463
Unique reflections	172,407	No. of water atoms	300
Completeness (%)	99.7 (100)	rms deviations	
Redundancy	7.1 (7)	Bond length (Å)	0.026
I/σ	27 (2)	Bond angles (deg.)	2.5
R_{sym} (%)	6.6 (93.7)	Ramachandran plot	
		Most favored (%)	96.9
		Allowed region (%)	3.1

A.



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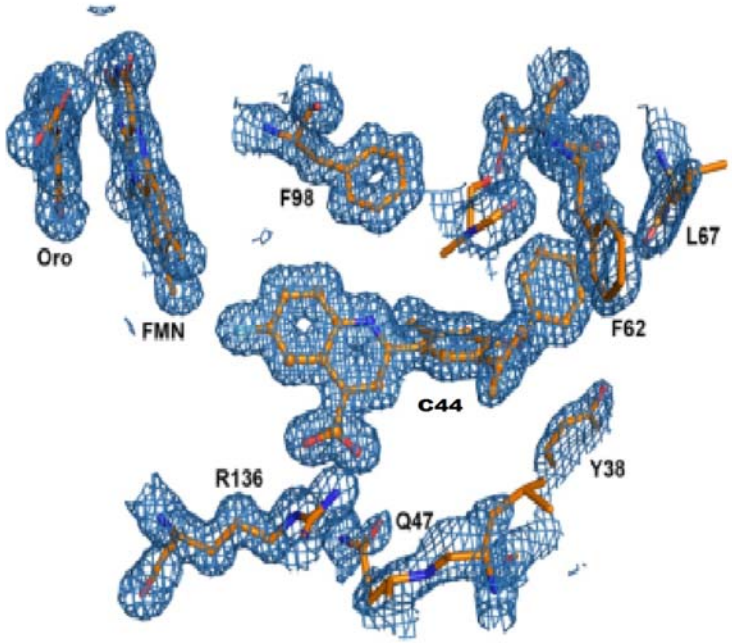

Figure S1. Difference maps for the structure determination of C44 in complex with human DHODH. A. Initial difference map (fo-fc). The map was calculated with Refmac using the S67

initial molecular replacement solution prior to refinement. Orange: protein coordinator; ball: C44; Green: map contoured at 3 sigma; red: map contoured at -3 sigma. B. Refined 2fofc map. The map was calculated with final refined model using Refmac. Orange: protein coordinator; ball: C44; Blue: map contoured at 1 sigma.

Reference:

1. Baldwin, J., et al., *Malarial dihydroorotate dehydrogenase. Substrate and inhibitor specificity.* J Biol Chem, 2002. **277**(44): p. 41827-34.
2. Zbyszek Otwinowski, W.M., *Processing of X-ray Diffraction Data Collected in Oscillation Mode*, in *Methods in Enzymology*. 1997. p. 307-326.
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5. Emsley, P. and K. Cowtan, *Coot: model-building tools for molecular graphics.* Acta Crystallogr D Biol Crystallogr, 2004. **60**(Pt 12 Pt 1): p. 2126-32.
6. Murshudov, G.N., A.A. Vagin, and E.J. Dodson, *Refinement of macromolecular structures by the maximum-likelihood method.* Acta Crystallogr D Biol Crystallogr, 1997. **53**(Pt 3): p. 240-55.
7. Cowtan, K., *Modified phased translation functions and their application to molecular-fragment location.* Acta Crystallogr D Biol Crystallogr, 1998. **54**(Pt 5): p. 750-6.
8. Lamzin, V.S. and K.S. Wilson, *Automated refinement of protein models.* Acta Crystallogr D Biol Crystallogr, 1993. **49**(Pt 1): p. 129-47.

Material and Methods for Viral Replication Studies:

Reagents

Vesicular stomatitis expressing GFP (VSV-GFP) was kindly provided by Dr. G. Barber from University of Miami School of Medicine. A/WSN/1933 was a gift from Dr. A. García-Sastre from Mount Sinai School of Medicine.

Cell Culture

MDCK cells and BHK cells were obtained from the American Type Culture Collection and cultured in DMEM (Invitrogen) containing 10% fetal bovine serum and 1% penicillin (Invitrogen).

Influenza virus replication

MDCK cells were infected with A/WSN/1933 at an MOI of 0.001. After 1 h infection, virus was removed and diluted compounds were added to cells. After 48 h incubation, culture supernatant was collected and viral titers were determined by plaque assay. Culture supernatant was serially diluted and added to MDCK cells. After 1 h infection, virus was removed and MDCK cells were covered by agar and incubated at 37℃ for 48 h. Cells were fixed in 2.5% (v/v) paraformaldehyde for 1 h before the agar layer was removed. Cells were stained with crystal violet and plaques were counted and subsequently used to calculate virus titers.

VSV replication assay

MDCK cells were infected with VSV-GFP at MOI of 0.001. After 1 h infection, virus was removed and diluted compounds were added to cells. After 48 h incubation, culture supernatant was collected and viral titers were determined by plaque assay. Culture supernatants were serially diluted and added to BHK cells. After 1 h infection, virus was

removed and BHK cells were covered with agar and incubated at 37℃ for 24 h. The number of plaques showing GFP expression were counted by fluorescence microscopy and subsequently used to calculate virus titers.

Calculations

Viral titer in the presence of compound (Vc) relative to viral titer in the absence of compound (V0) was determined ((logVc/logV0)×100). Data were fitted to the log (I) versus response equation in Prism (GraphPad Software) to determine the IC50.

Minimal cytotoxicity of compound C44 in human bronchial epithelial cells

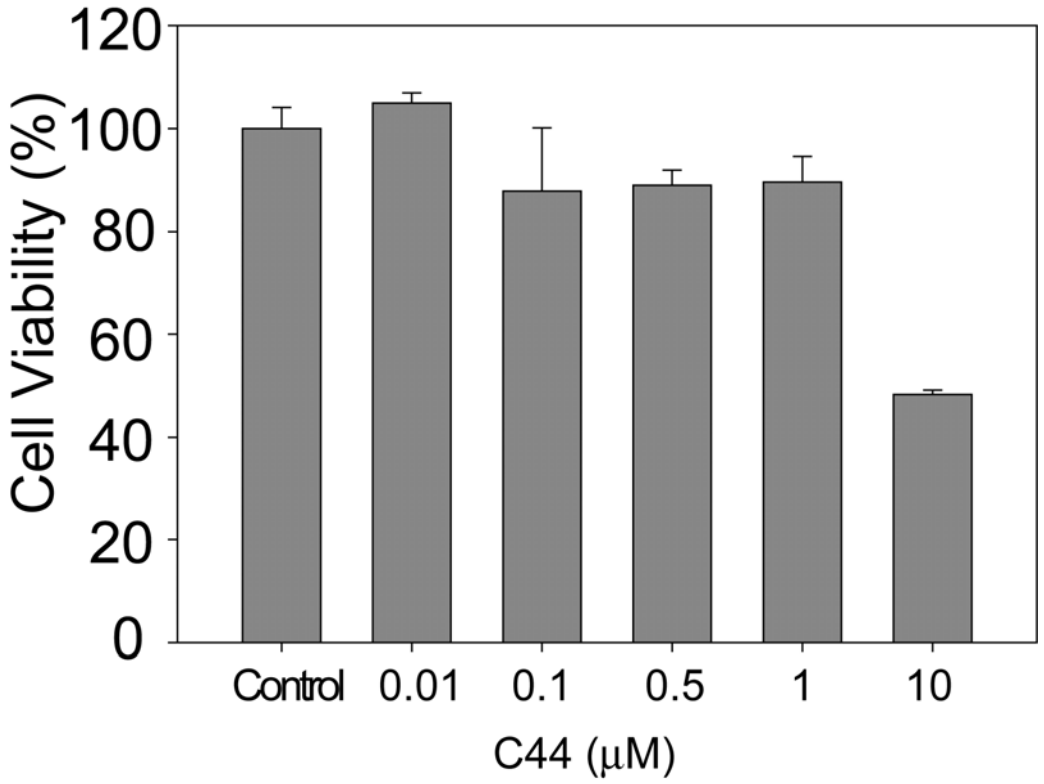


Figure S2: Minimal cytotoxicity of compound C44 in human bronchial epithelial cells. The cytotoxicity assay was performed in Human Bronchial Epithelial Cells (HBEC). Compound was dissolved in sterile DMSO (Sigma) at a stock concentration of 10 mM and then diluted in culture medium (keratinocyte-SFM from GIBCO) to final concentrations depicted in the figure. Cells were treated for 48 h with compounds at various depicted

concentrations, and control cells were treated with 0.01% DMSO (Control). Cells were then lysed and ATP levels measured by luminescence using the CellTiter-Glo kit (Promega), following the manufacturer's instructions.

Minimal cytotoxicity of compound C44 in Caco-2 cells

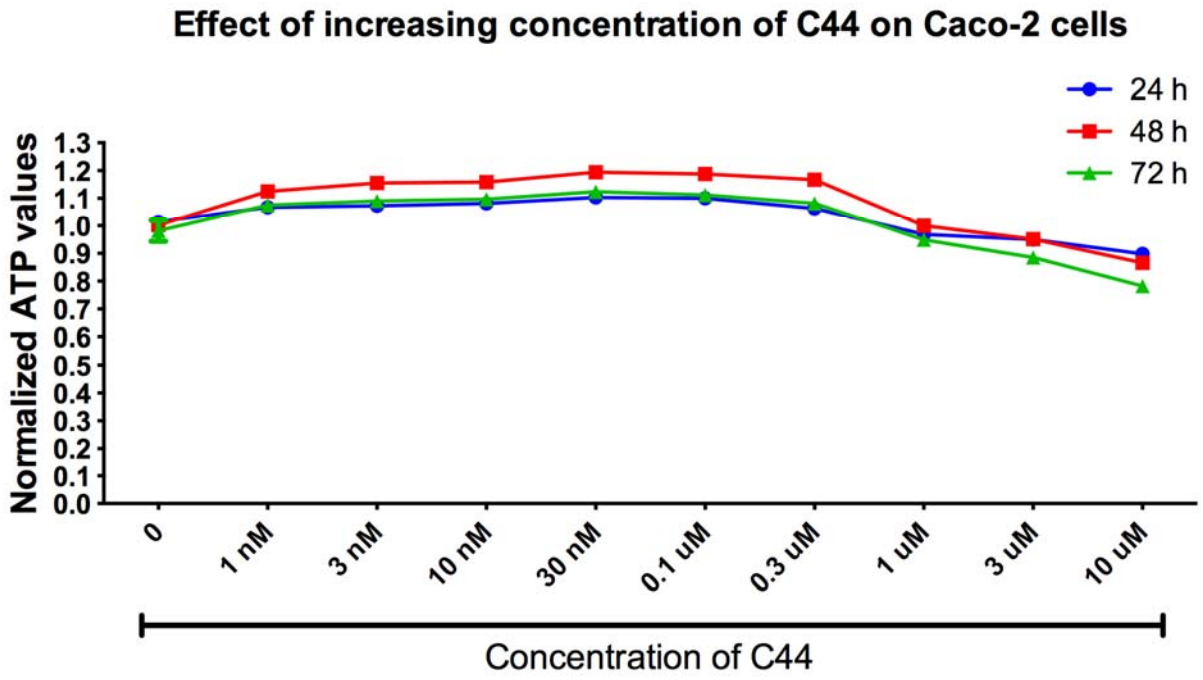
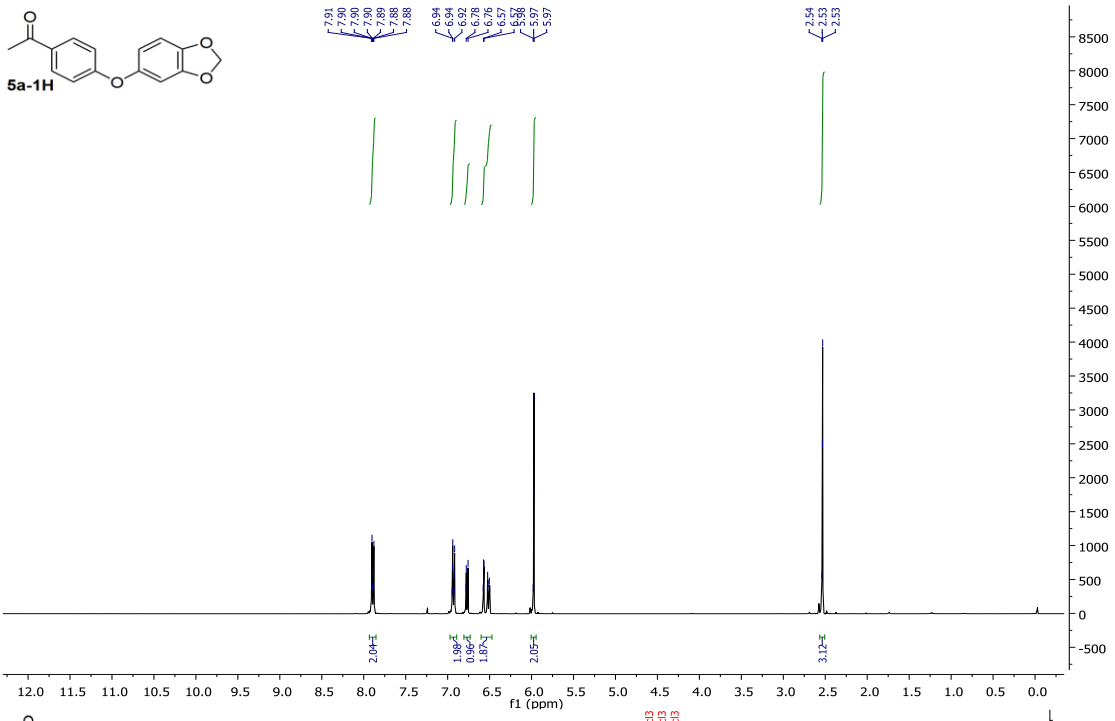


Figure S3: Minimal cytotoxicity of compound C44 in Caco-2 cells. Cells were plated in 96-well plates at 40,000 cells/well and allowed to grow until confluency. The confluent cells were treated with the indicated concentrations of **C44**, with six replicates for each concentration. After the indicated times, cells were lysed with CellTiter-Glo Luminescent Cell Viability Assay reagent (Promega) and luminescence was read using the Envision plate reader. The ATP values were normalized to those of the untreated cells. Average values with standard deviations were graphed. Error bars were smaller than the symbols for most data points.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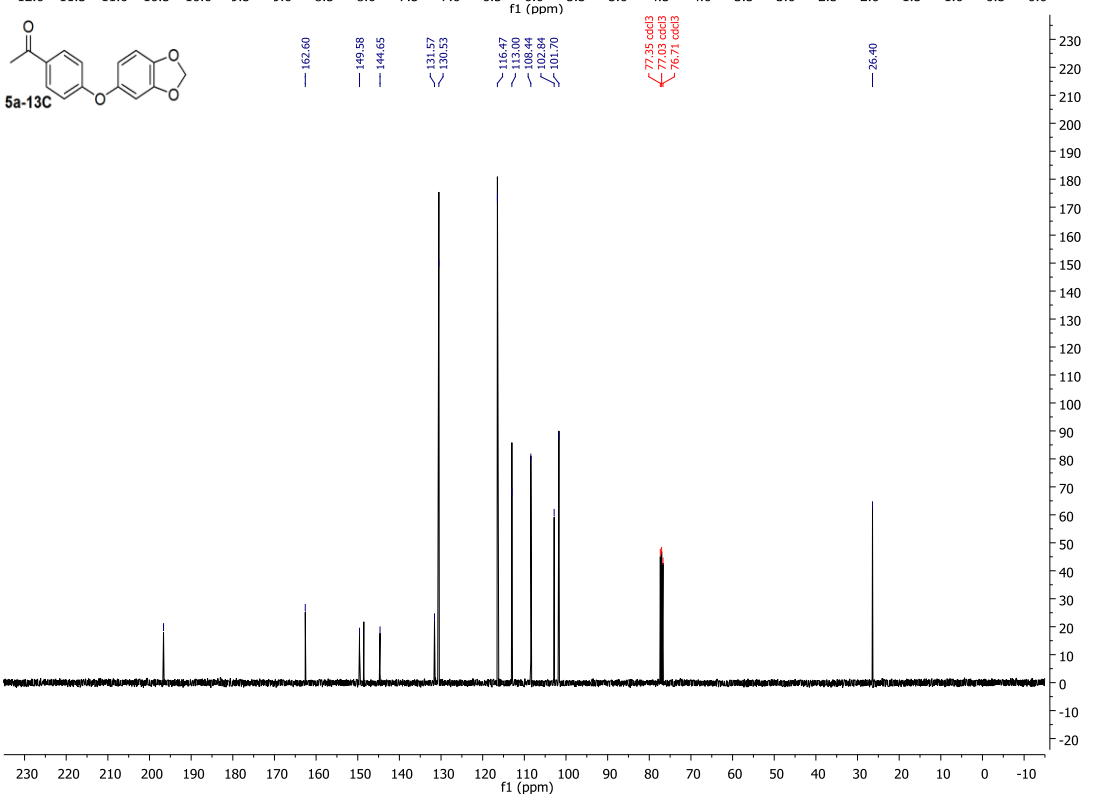
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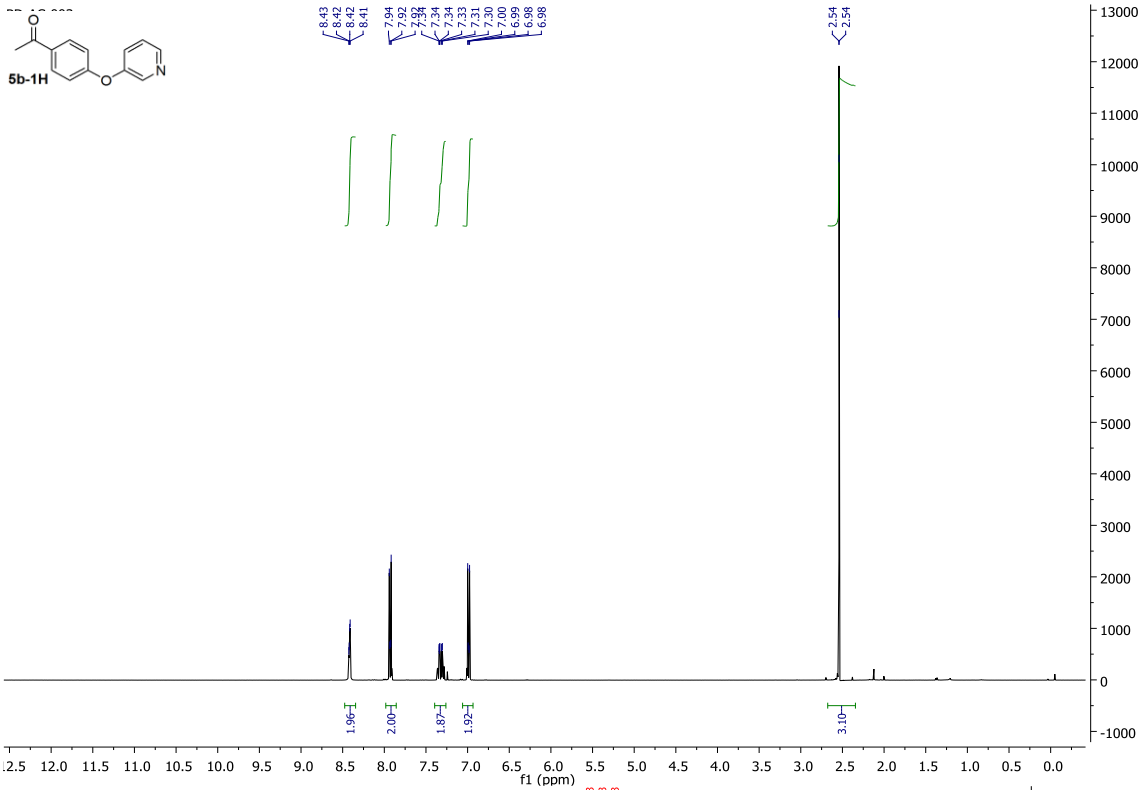
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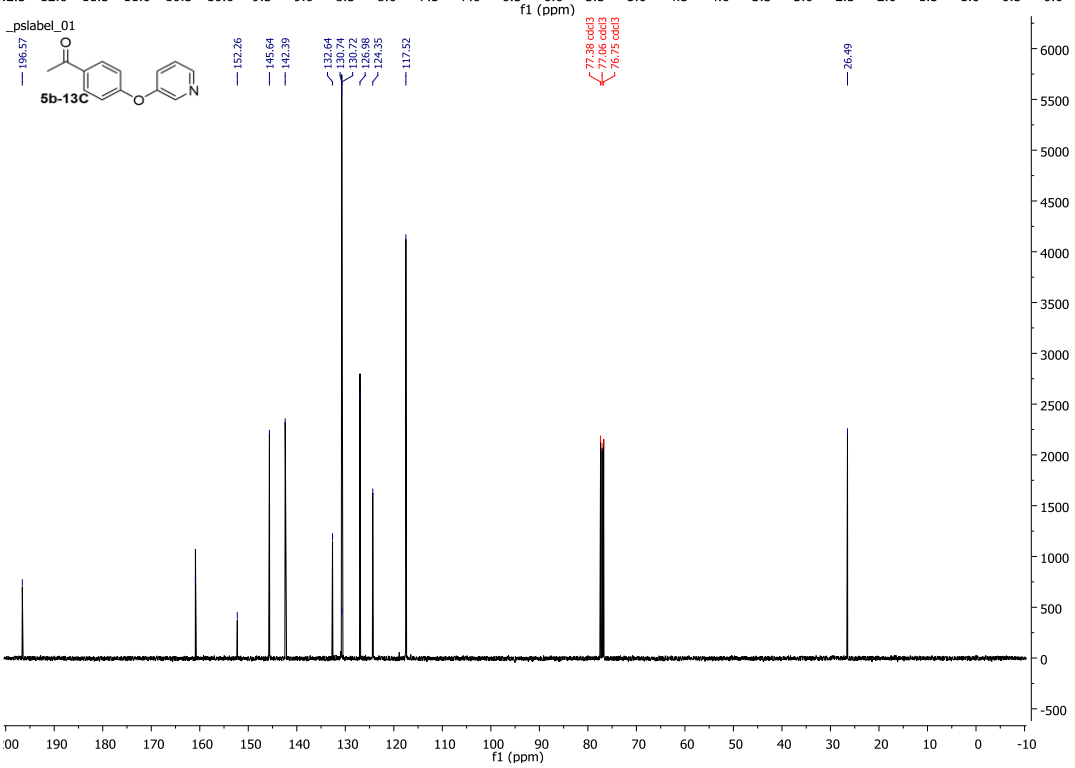
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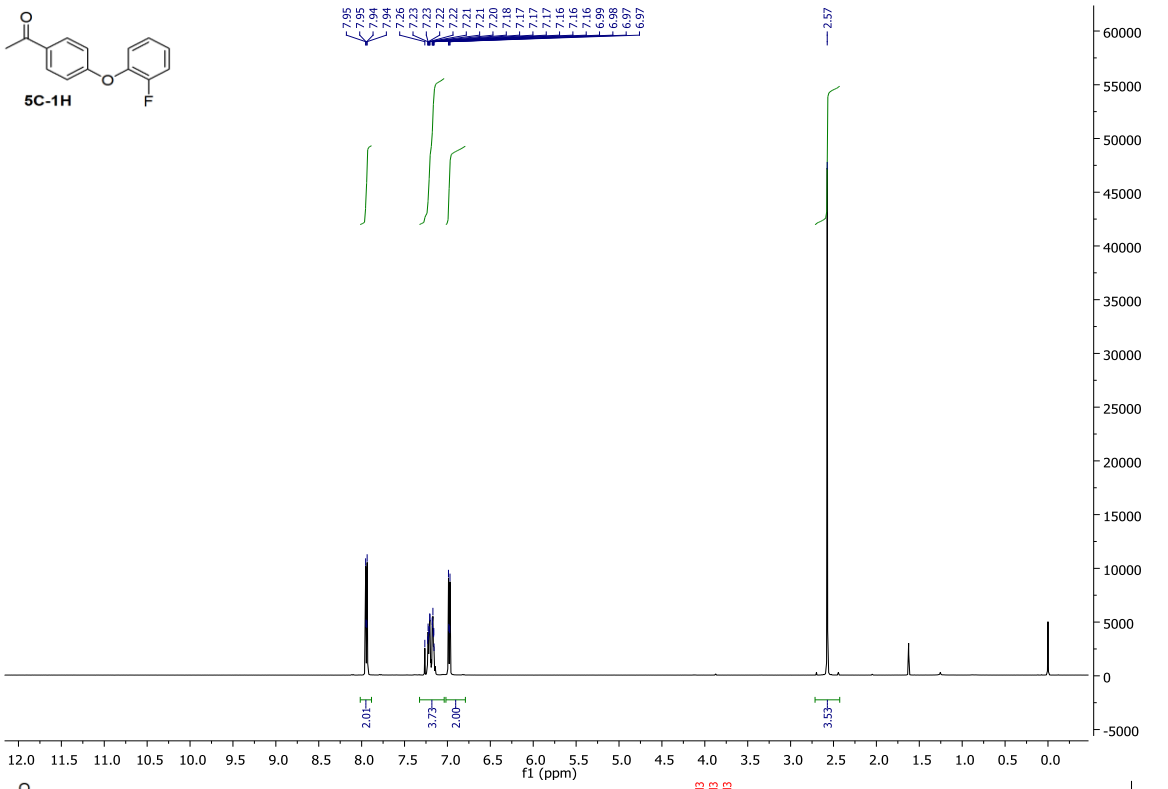
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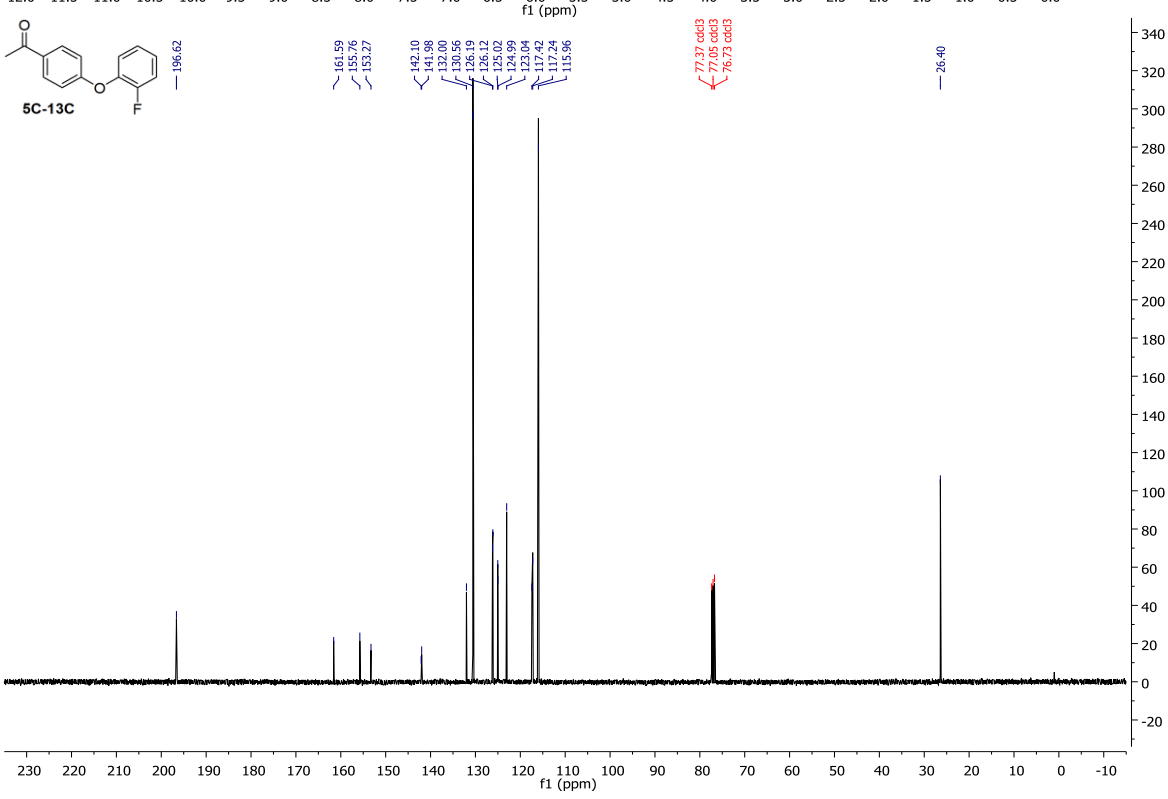
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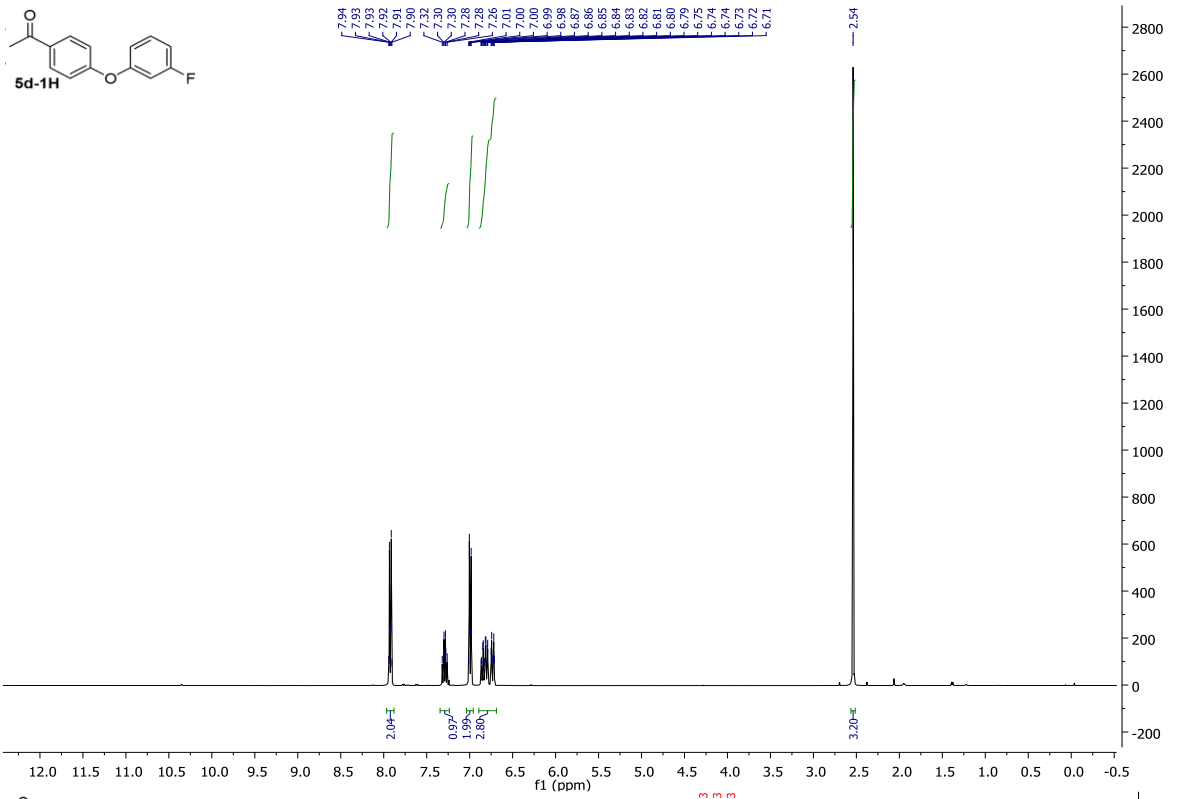
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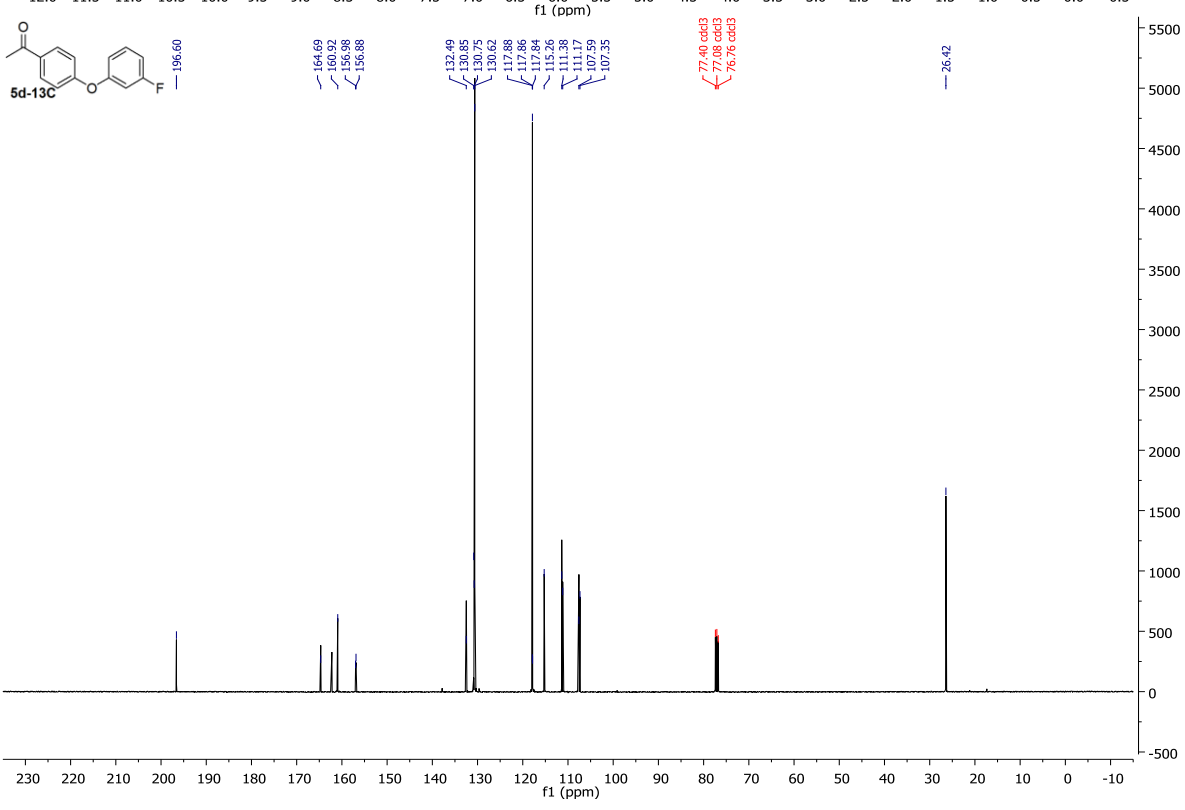
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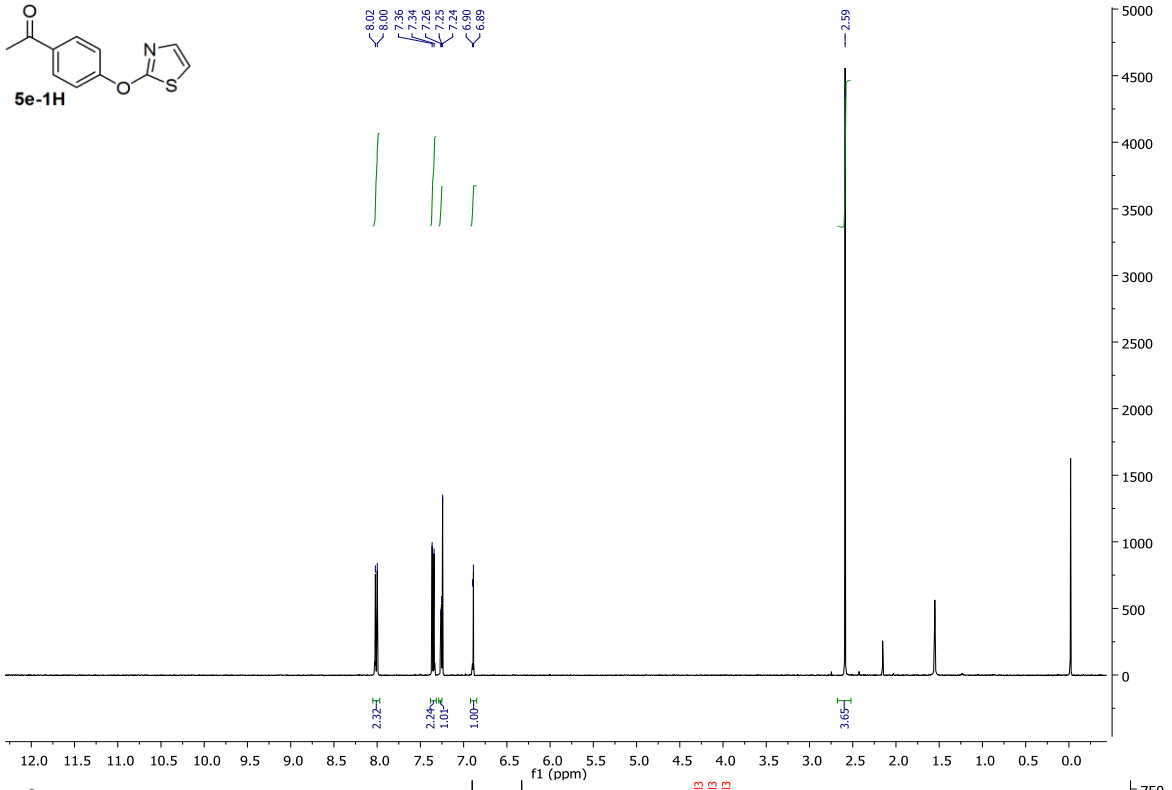
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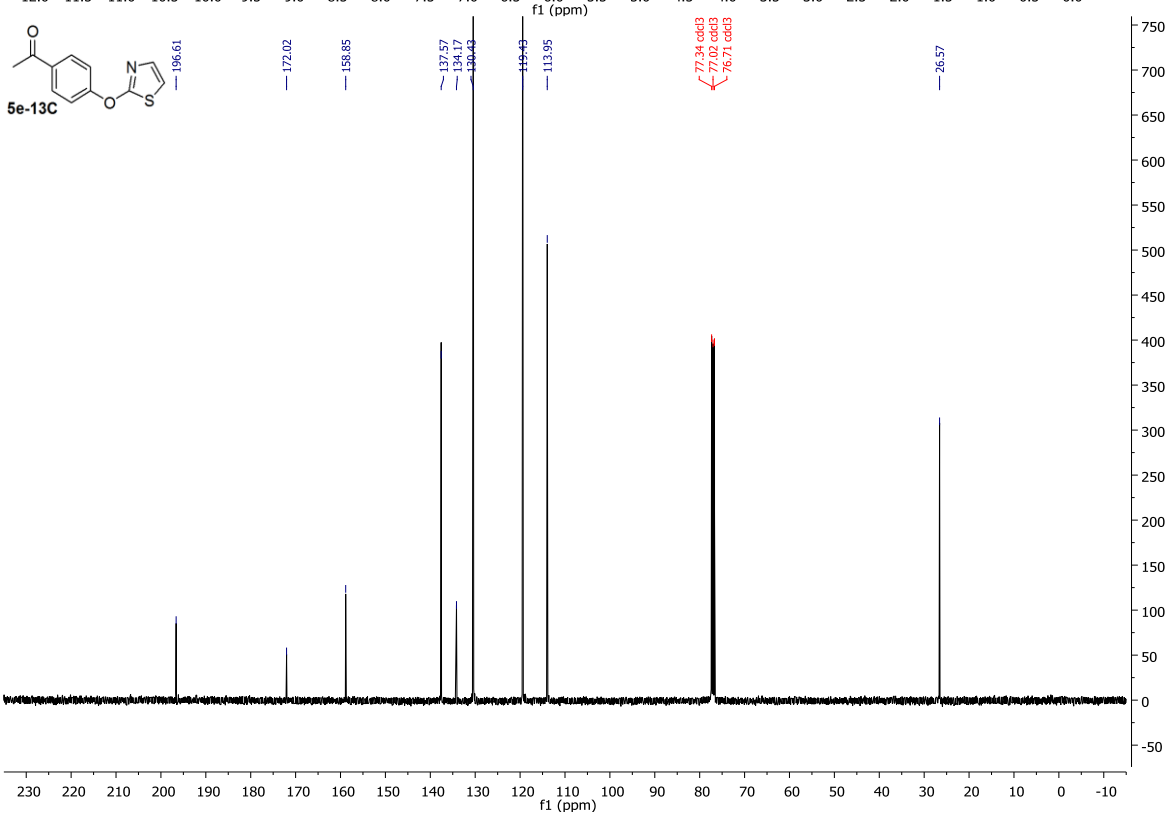
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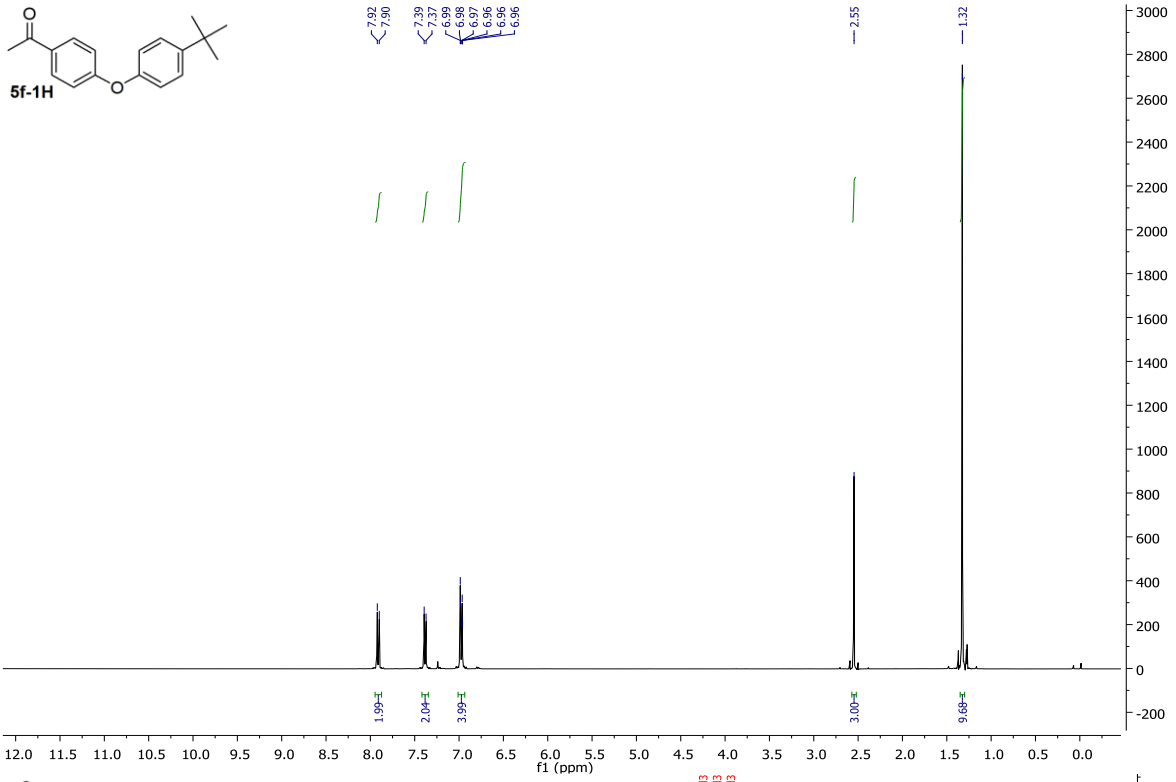
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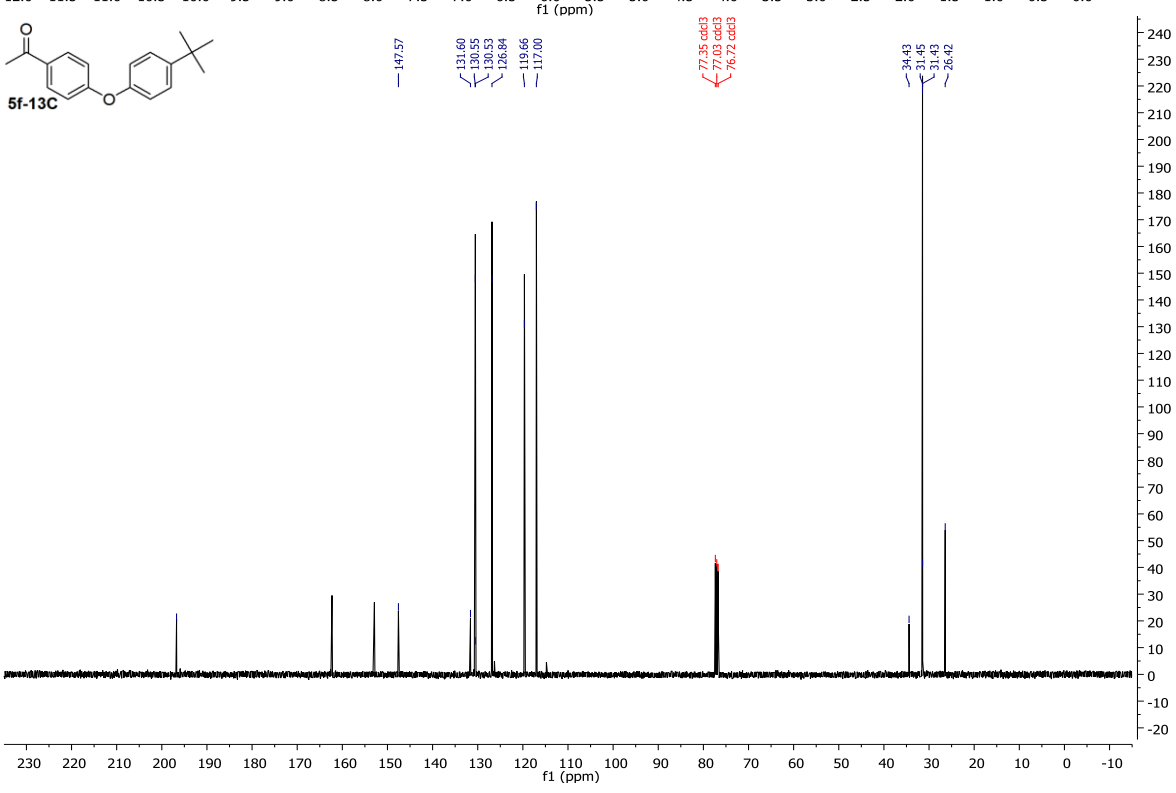
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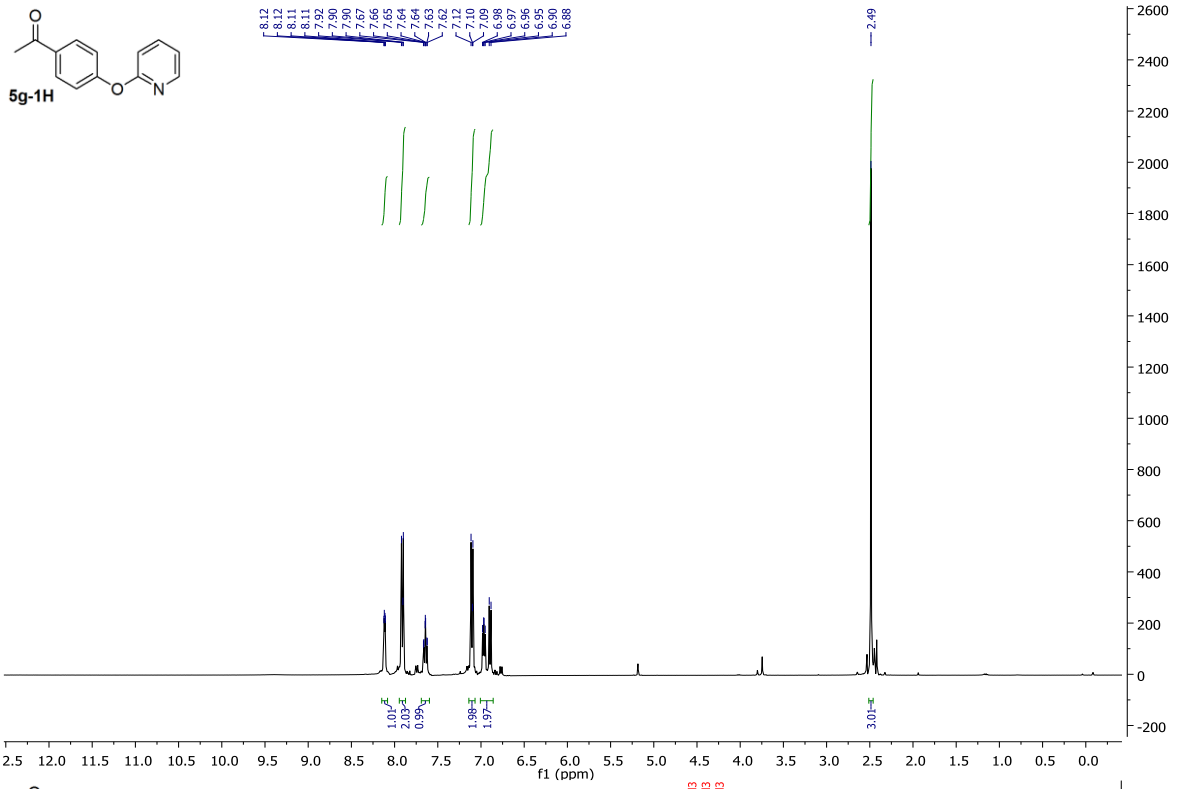
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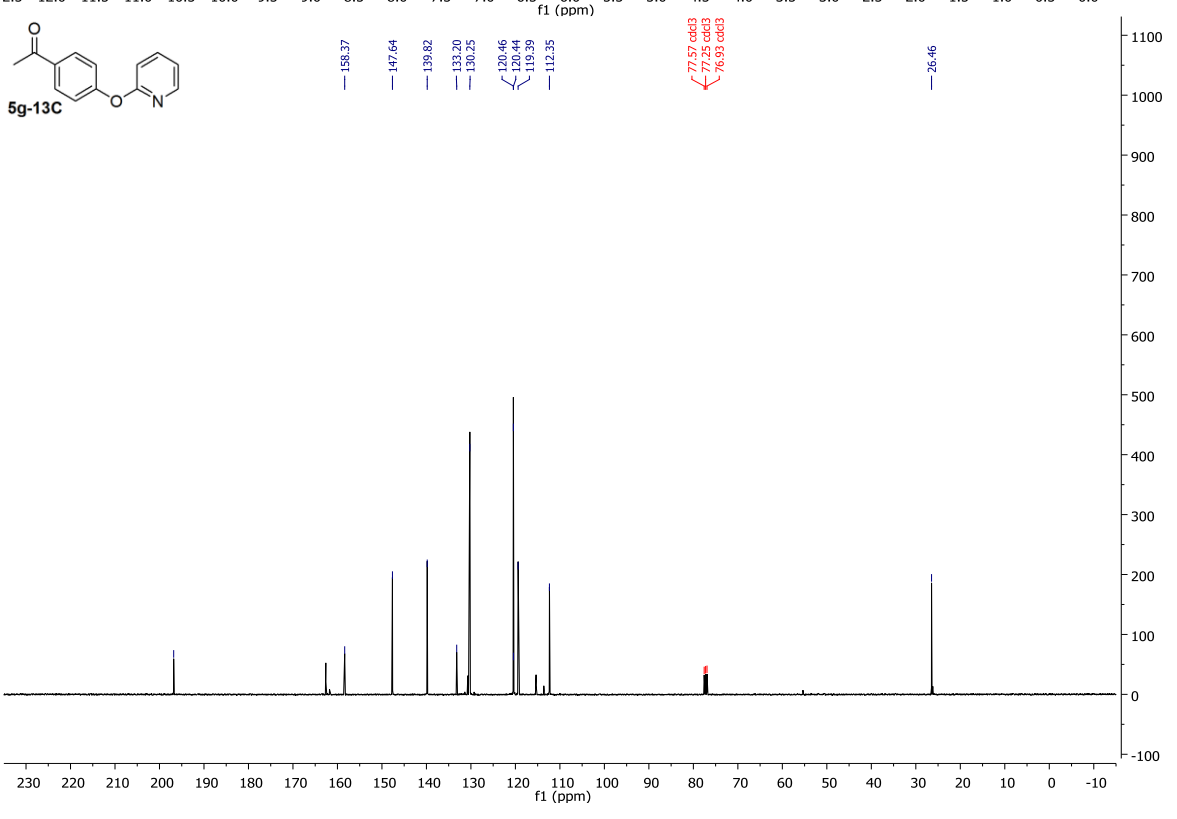
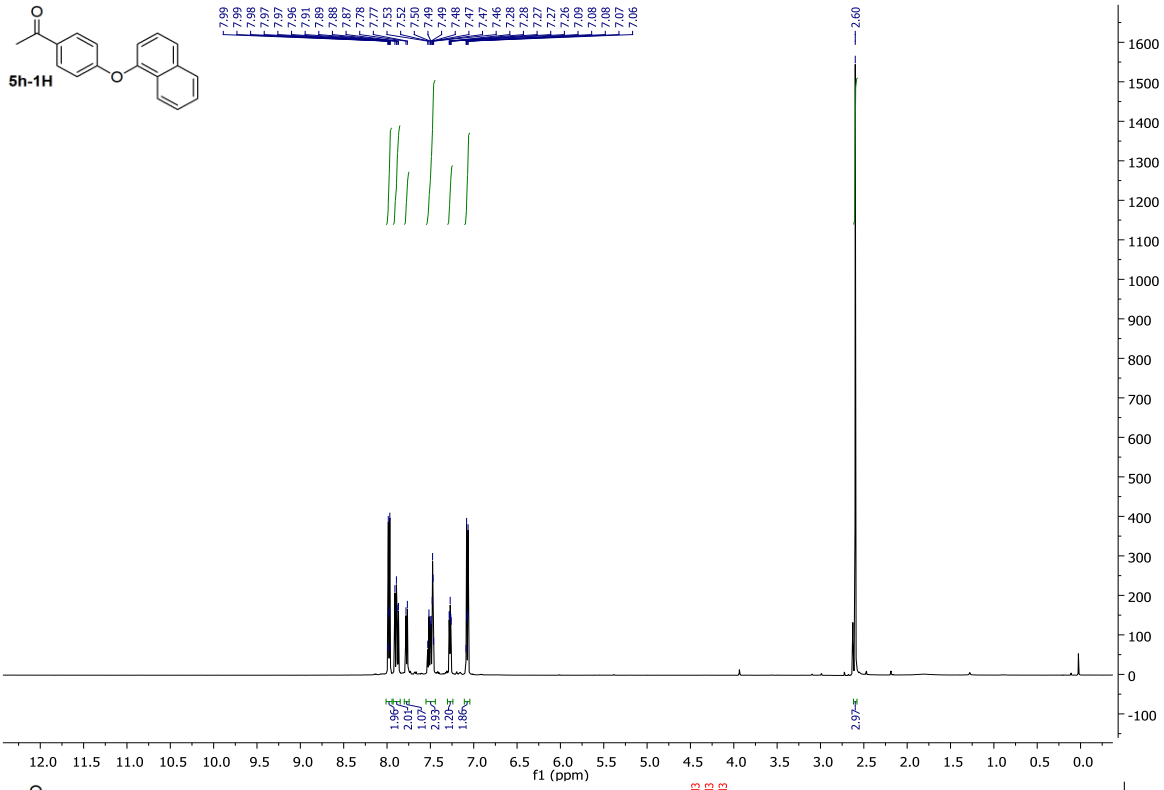
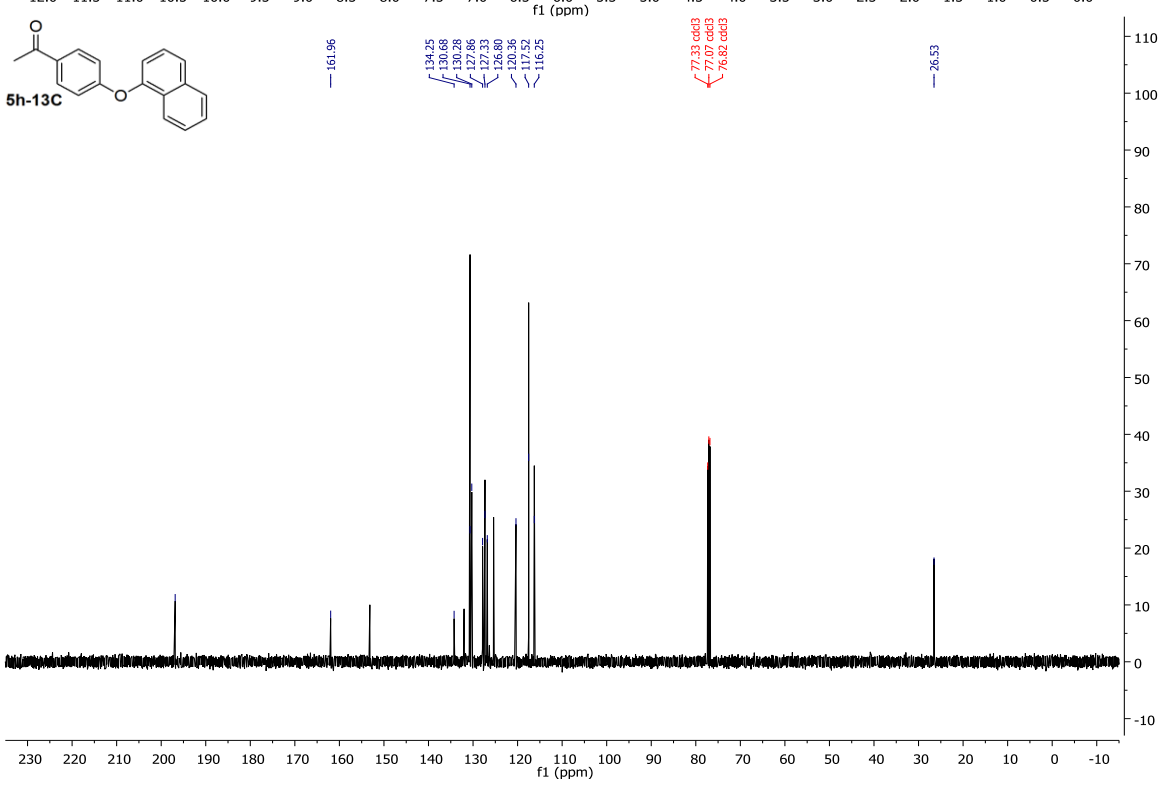
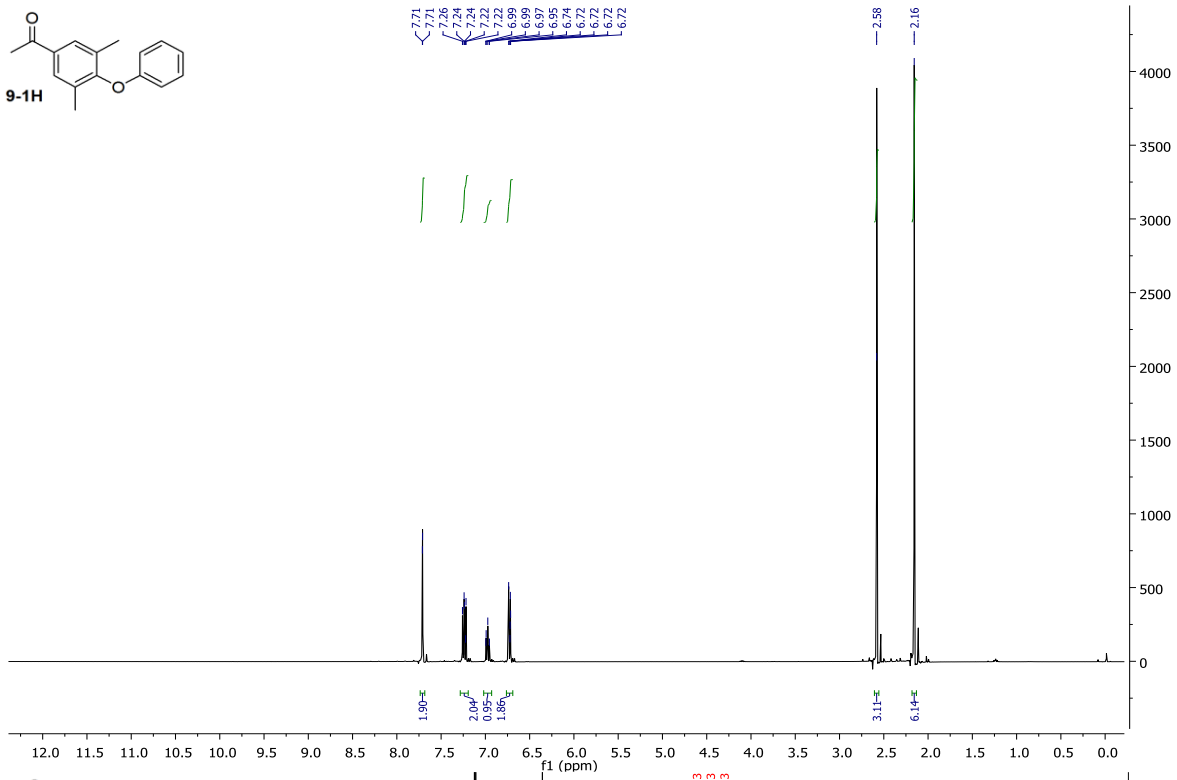
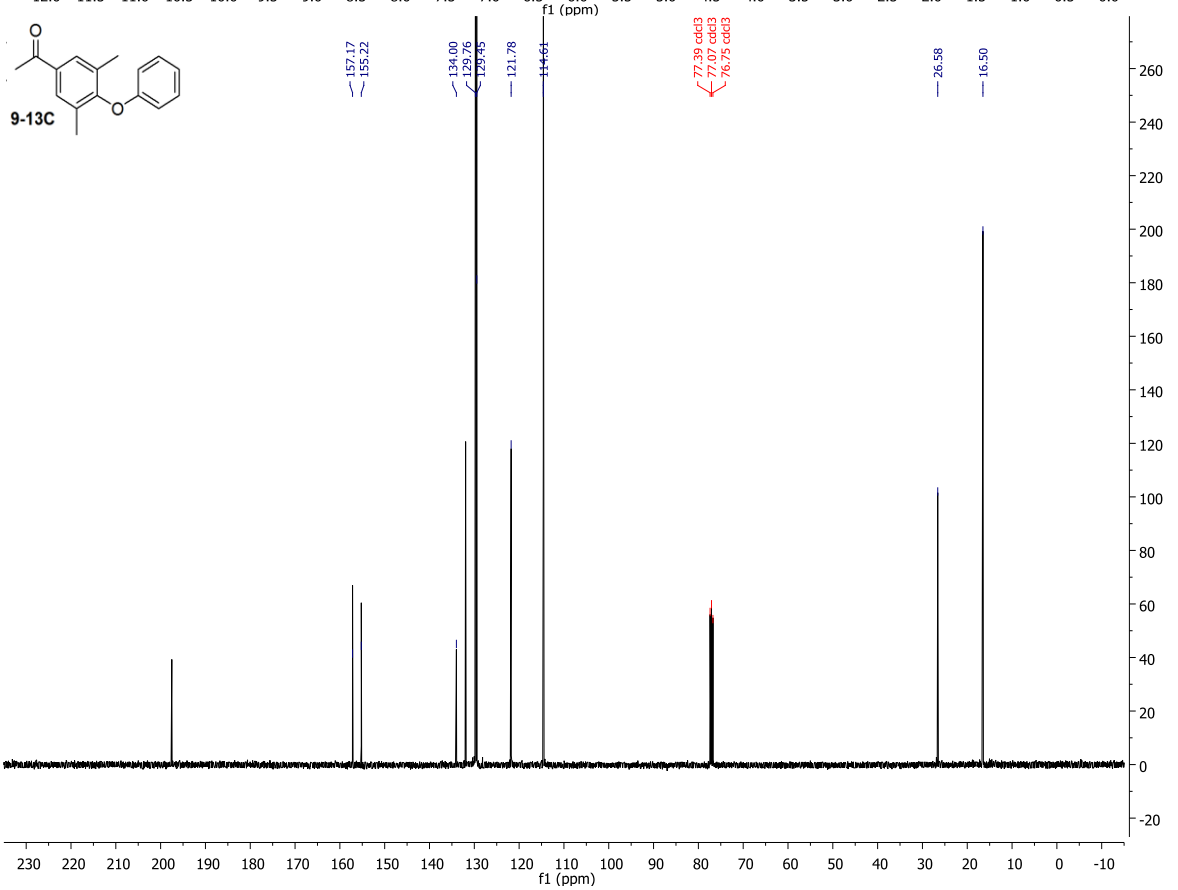
7.09
6.98
6.97
6.96
6.95
6.90
6.88
2.49
1.01
2.03
0.99
1.98
1.97
3.01
f1 (ppm)

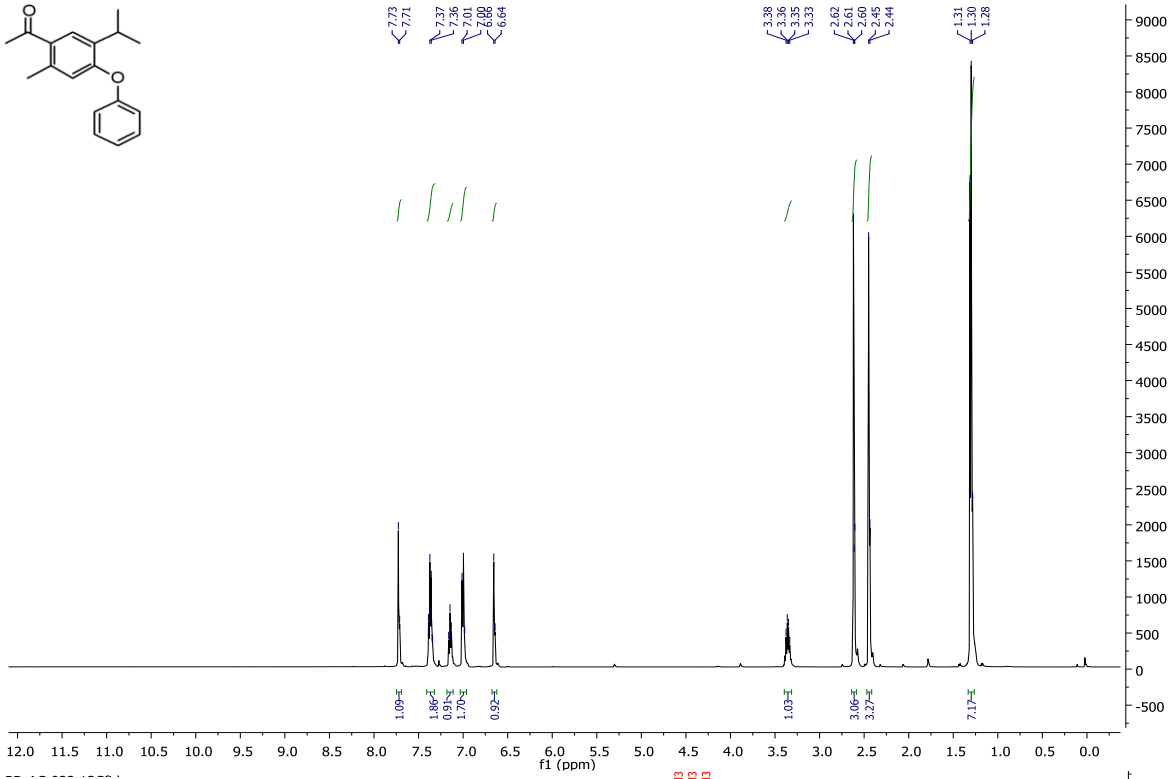

5g-13C
158.37
147.64
139.82
133.20
130.25
120.46
120.44
119.39
112.35
77.57 cdcl3
77.25 cdcl3
76.93 cdcl3
26.46
f1 (ppm)

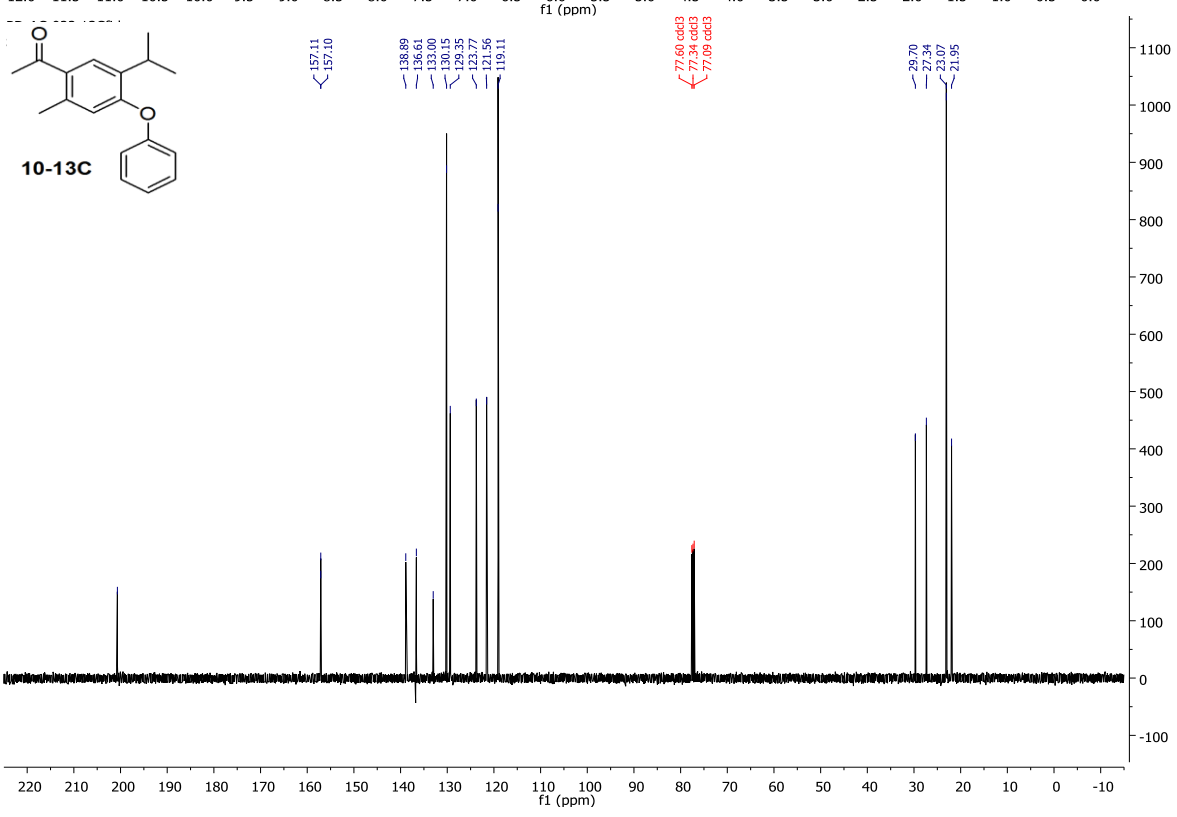

5h-1H
7.99
7.99
7.98
7.97
7.97
7.96
7.91
7.89
7.88
7.87
7.78
7.77
7.53
7.52
7.50
7.49
7.49
7.48
7.47
7.47
7.46
7.28
7.28
7.27
7.27
7.26
7.09
7.08
7.08
7.07
7.06
2.60
1.96
2.01
1.07
2.93
1.20
1.86
2.97
f1 (ppm)

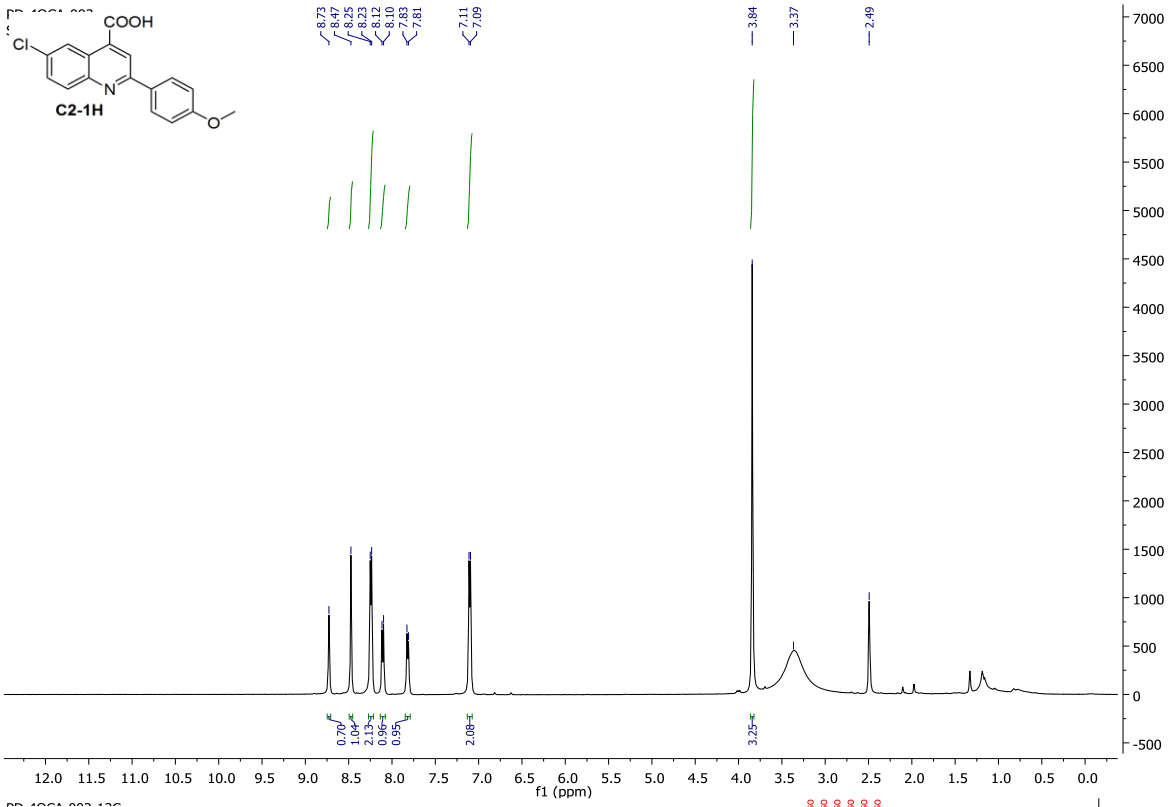

5h-13C
161.96
134.25
130.68
130.28
127.86
127.33
126.80
120.36
117.52
116.25
77.33 cdcl3
77.07 cdcl3
76.82 cdcl3
26.53
f1 (ppm)

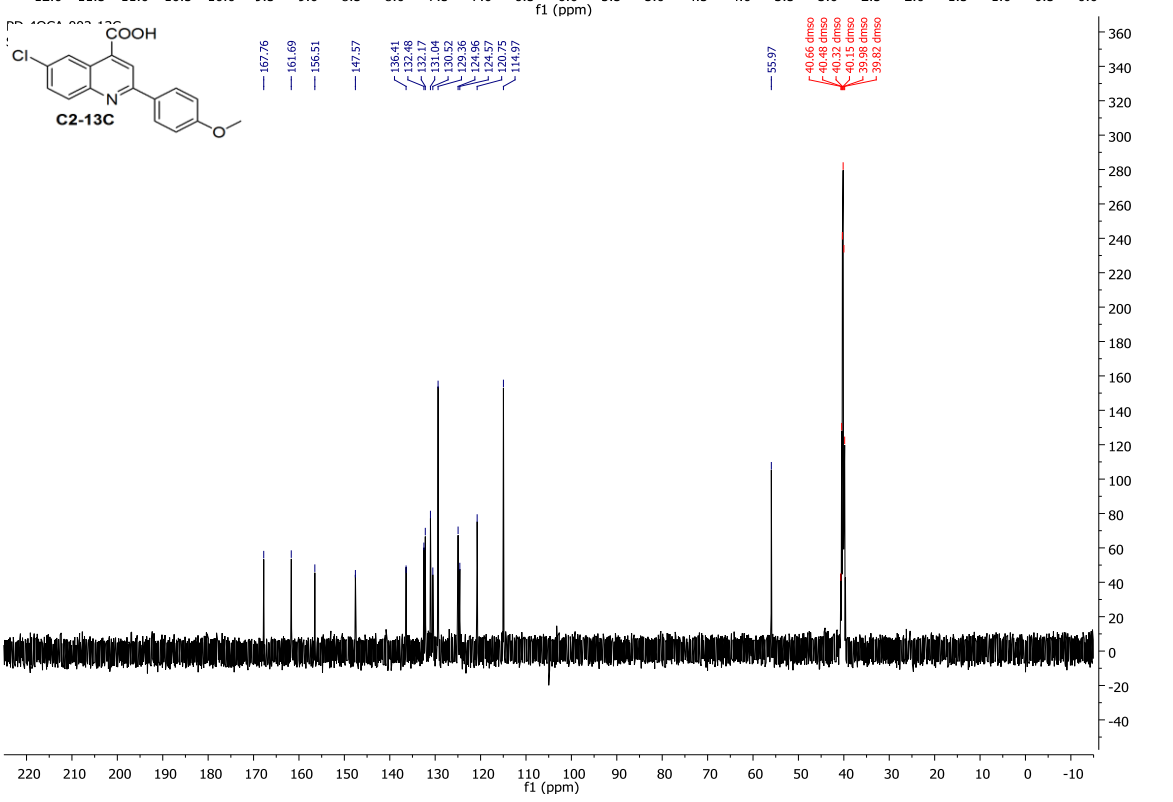

9-1H
7.71
7.71
7.26
7.24
7.24
7.22
7.22
6.99
6.99
6.97
6.95
6.74
6.72
6.72
6.72
6.72
2.58
2.16
1.90
2.04
0.95
1.86
3.11
6.14
f1 (ppm)

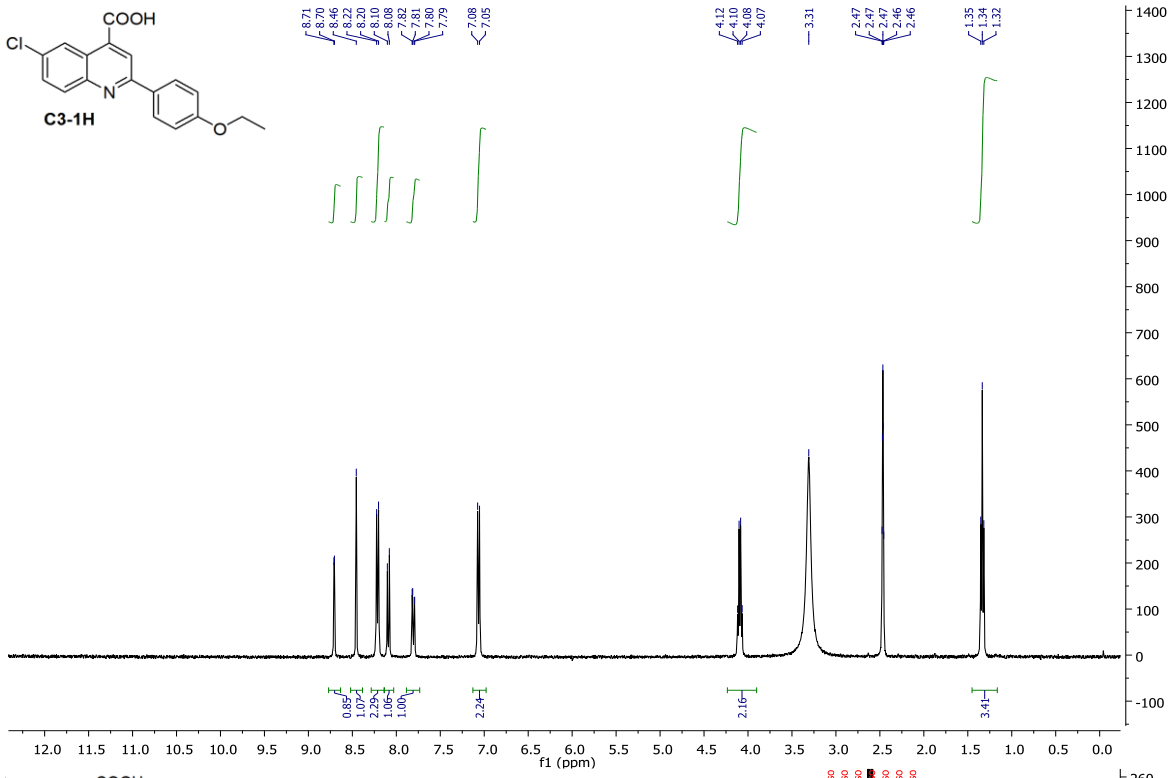

9-13C
157.17
155.22
134.00
129.76
129.45
121.78
114.61
77.39 cdcl3
77.07 cdcl3
76.75 cdcl3
26.58
16.50
f1 (ppm)

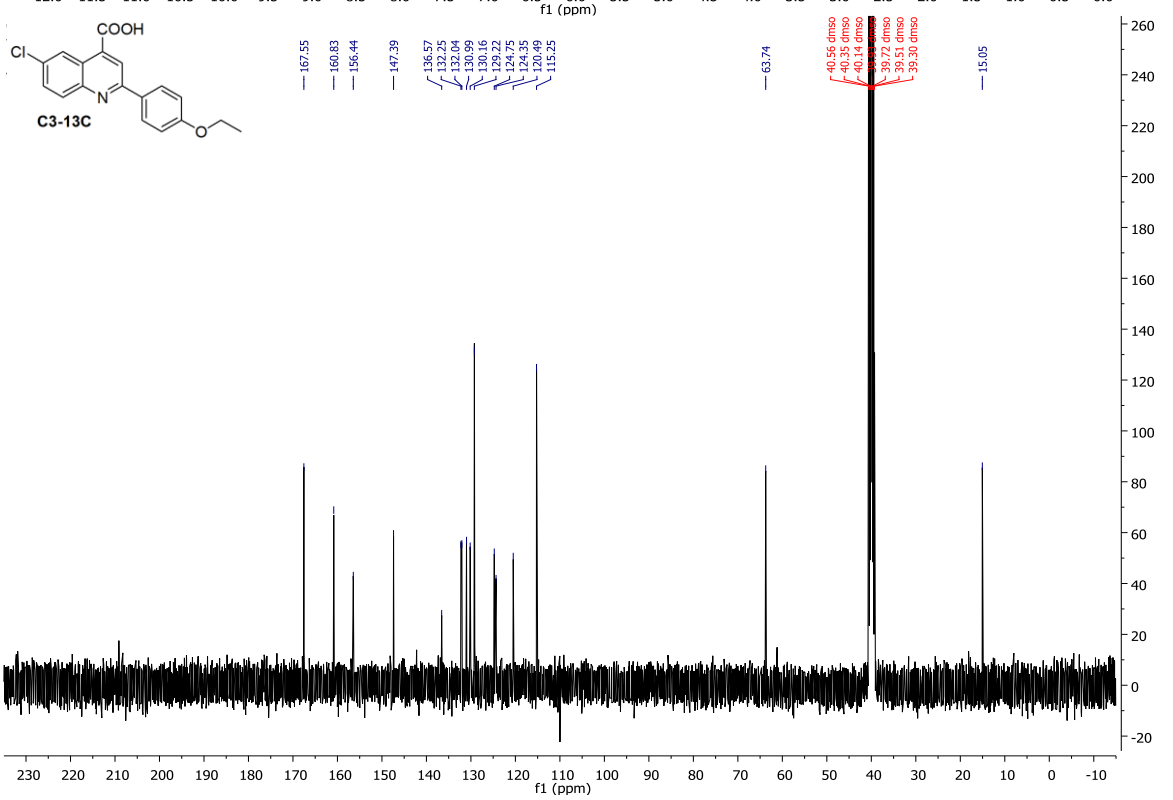

7.73
7.71
7.37
7.36
7.01
6.88
6.64
3.38
3.36
3.35
3.33
2.62
2.61
2.60
2.45
2.44
1.31
1.30
1.28
1.09
1.86
0.91
1.70
0.92
1.03
3.06
3.27
7.17
f1 (ppm)

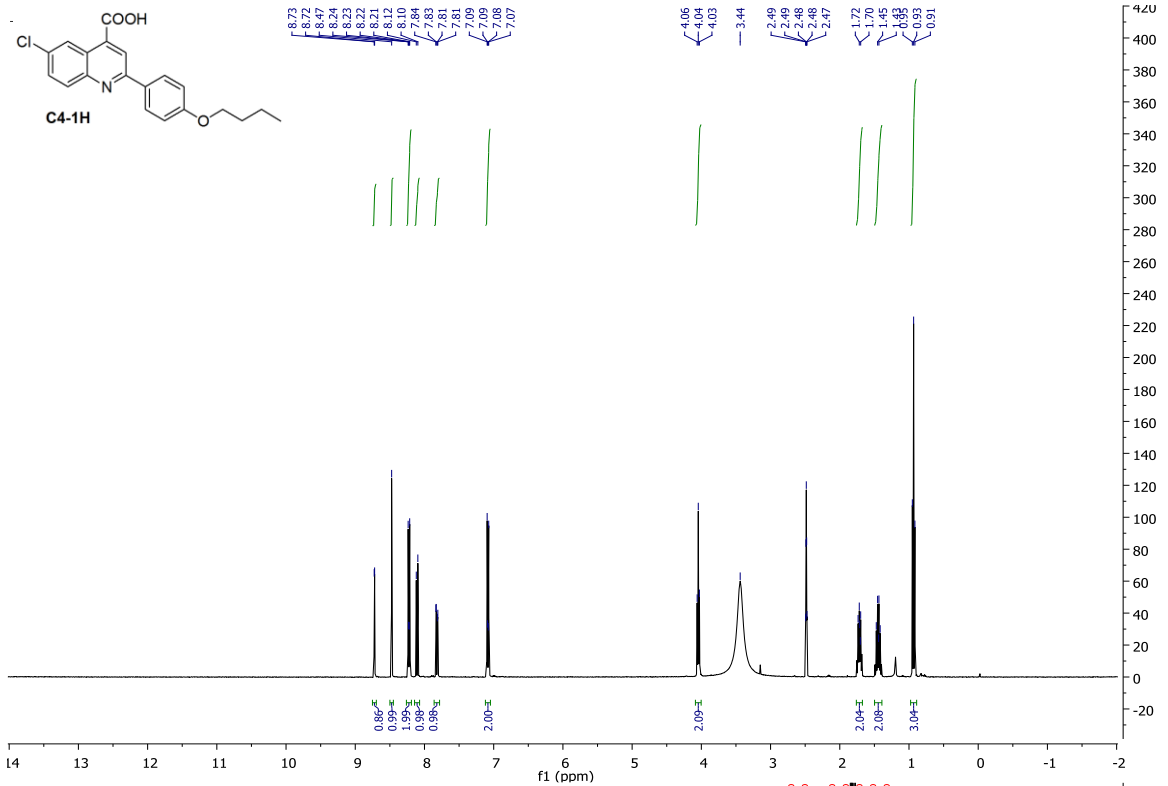

10-13C
157.11
157.10
138.89
136.61
133.00
130.15
129.35
123.77
121.56
119.11
77.60 cdcl3
77.34 cdcl3
77.09 cdcl3
29.70
27.34
23.07
21.95
f1 (ppm)

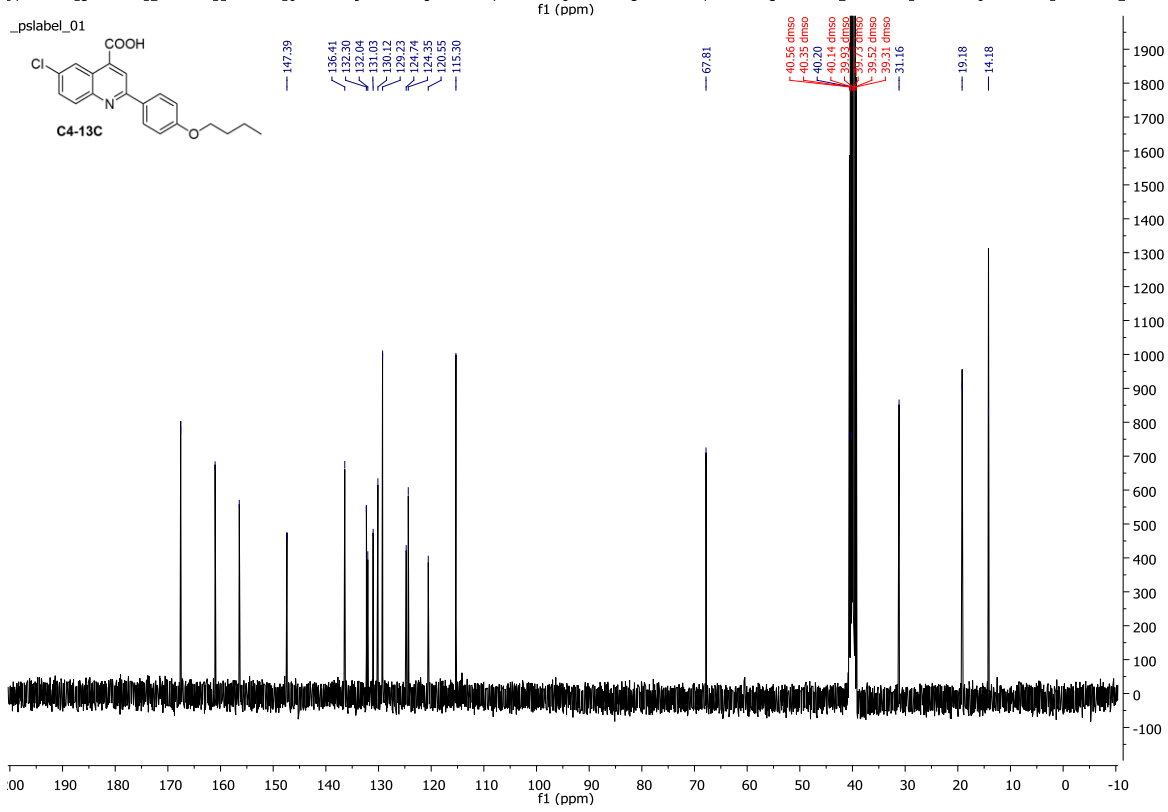

COOH
Cl
N
O
C2-1H
8.73
8.47
8.25
8.23
8.12
8.10
7.83
7.81
7.11
7.09
3.84
3.37
2.49
0.70
1.04
2.13
0.96
0.95
2.08
3.25
f1 (ppm)

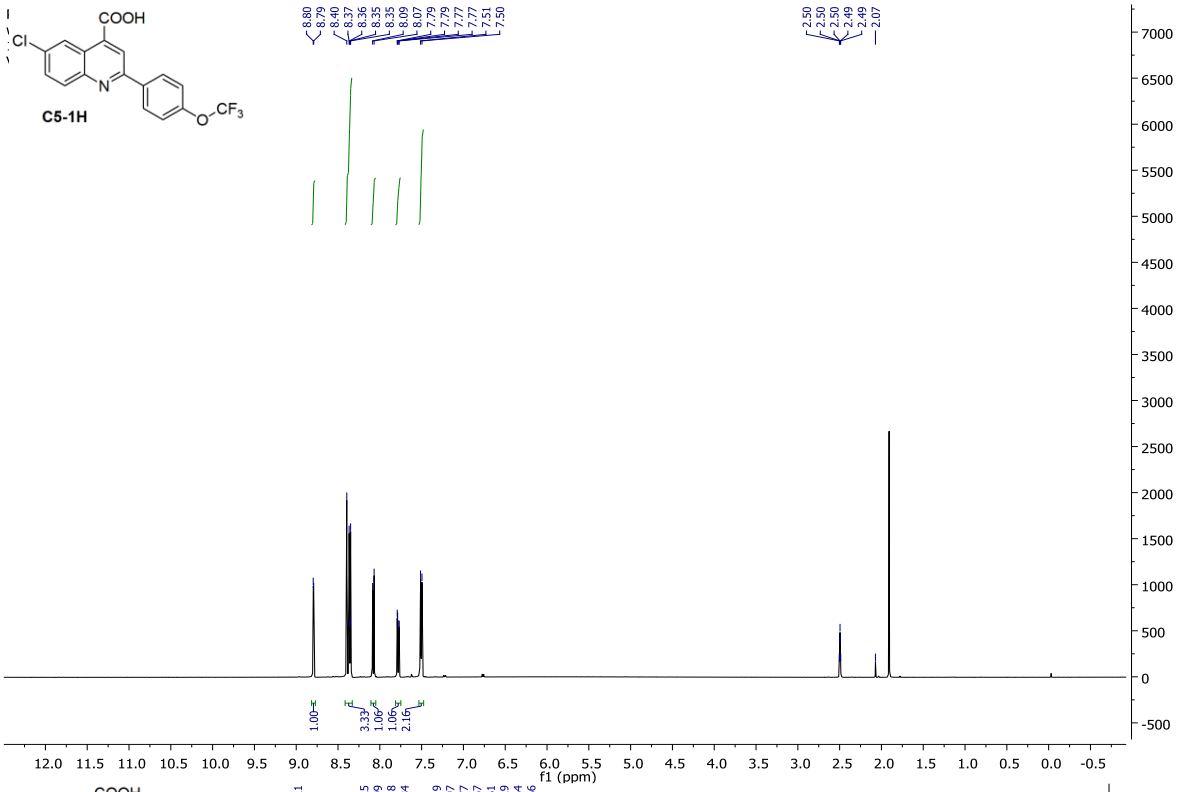

COOH
Cl
N
O
C2-13C
167.76
161.69
156.51
147.57
136.41
132.48
132.17
131.04
130.52
129.36
124.96
124.57
120.75
114.97
55.97
40.66 dmso
40.48 dmso
40.32 dmso
40.15 dmso
39.98 dmso
39.82 dmso
f1 (ppm)

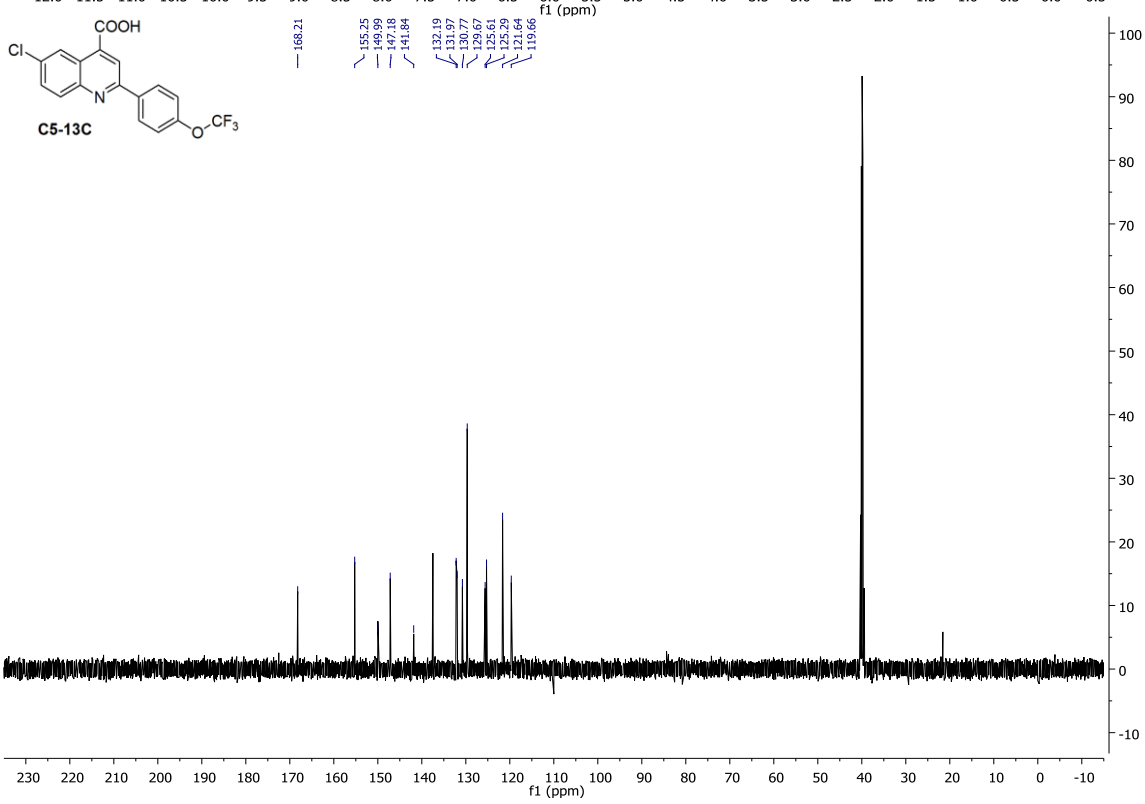

COOH
Cl
N
O
C3-1H
8.71
8.70
8.46
8.22
8.20
8.10
8.08
7.82
7.81
7.80
7.79
7.08
7.05
4.12
4.10
4.08
4.07
3.31
2.47
2.47
2.47
2.46
2.46
1.35
1.34
1.32
0.85
1.07
2.29
1.06
1.00
2.24
2.16
3.41
f1 (ppm)

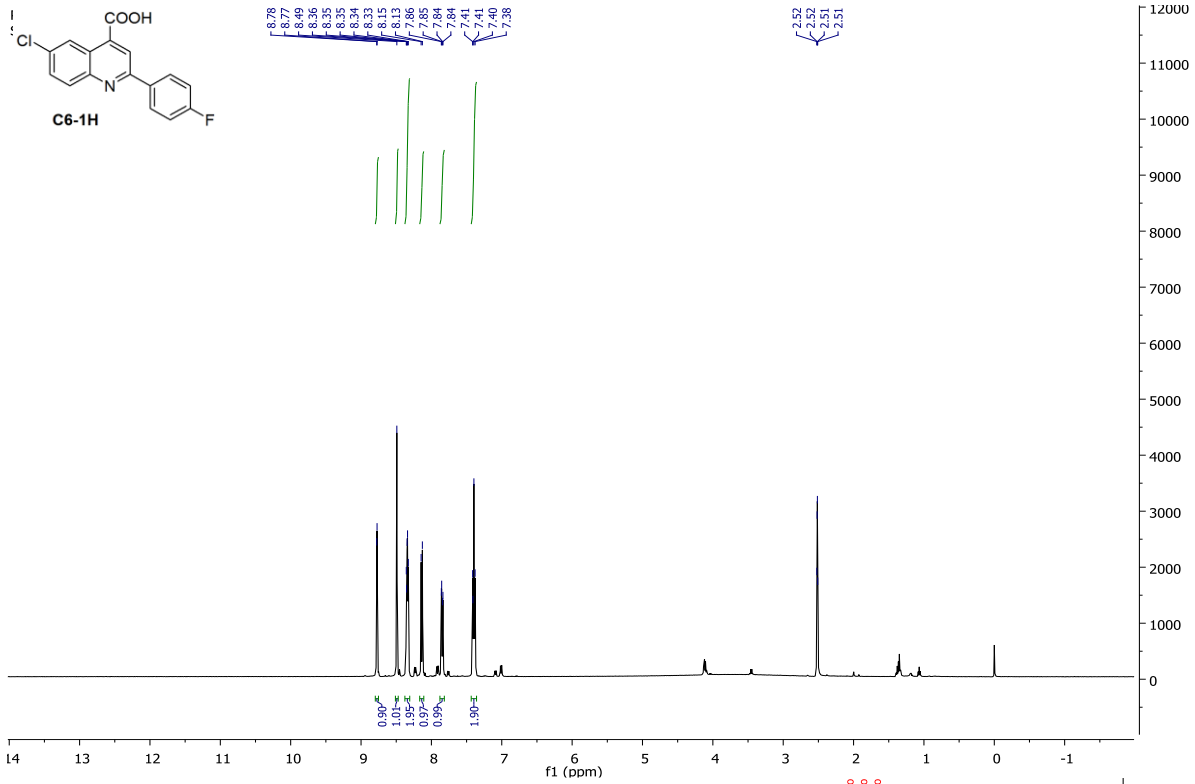

COOH
Cl
N
O
C3-13C
167.55
160.83
156.44
147.39
136.57
132.25
132.04
130.99
130.16
129.22
124.35
124.25
120.49
115.25
63.74
40.56 dmso
40.35 dmso
40.14 dmso
39.72 dmso
39.51 dmso
39.30 dmso
15.05
f1 (ppm)

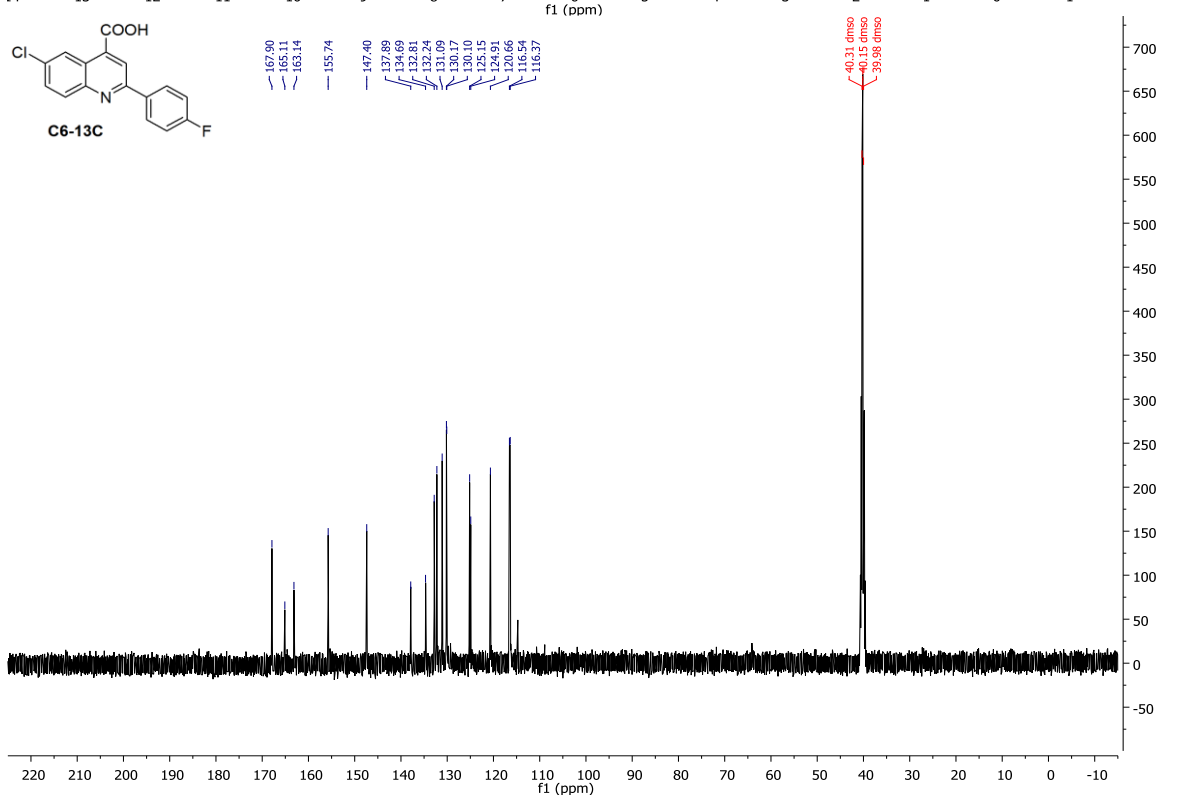

COOH
Cl
N
O
C4-1H
8.73
8.72
8.47
8.24
8.23
8.22
8.21
8.12
8.10
7.84
7.83
7.81
7.81
7.09
7.09
7.08
7.07
4.06
4.04
4.03
3.44
2.49
2.49
2.48
2.48
2.47
1.72
1.70
1.45
1.43
0.95
0.93
0.91
0.86
0.99
1.99
0.98
0.98
2.00
2.09
2.04
2.08
3.04
f1 (ppm)

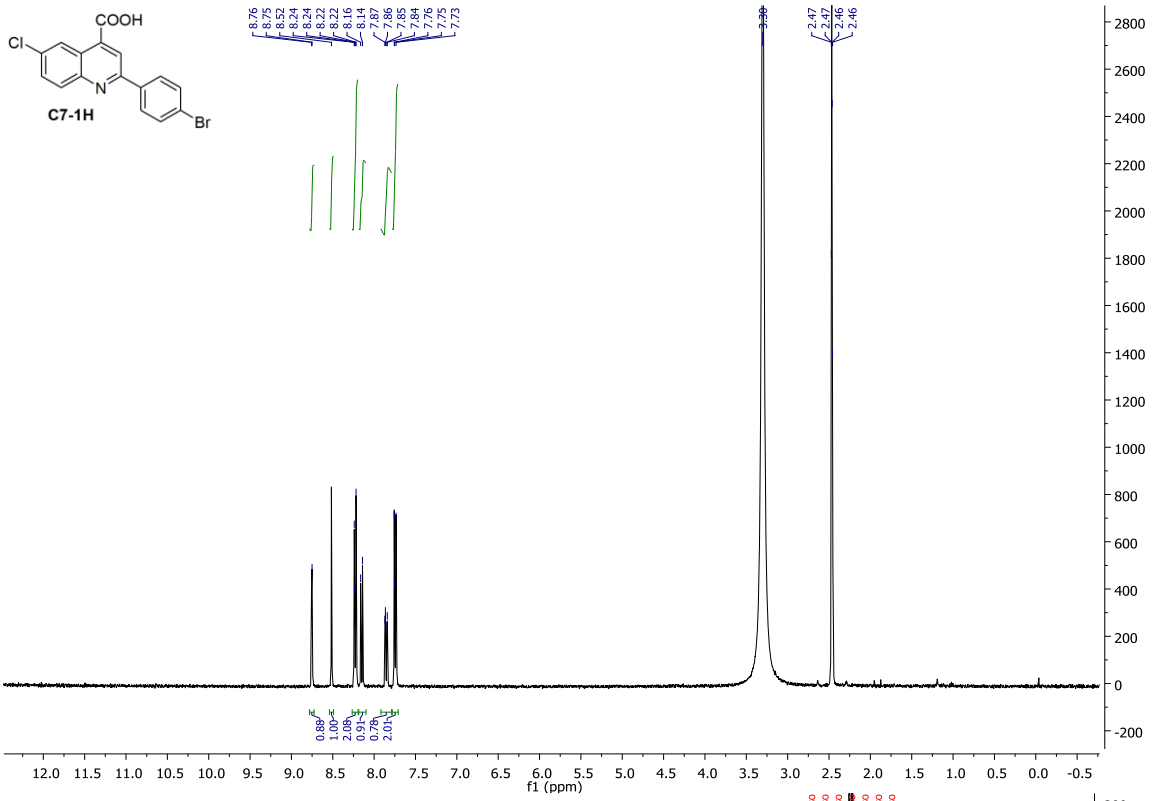

_pslabel_01
COOH
Cl
N
O
C4-13C
147.39
136.41
132.30
131.04
131.03
130.12
129.23
124.74
124.35
120.55
115.30
67.81
40.56 dmso
40.35 dmso
40.20
40.14 dmso
39.93 dmso
39.73 dmso
39.52 dmso
39.31 dmso
31.16
19.18
14.18
f1 (ppm)


COOH
Cl
N
O
CF3
C5-1H
8.80
8.79
8.40
8.37
8.36
8.35
8.35
8.09
8.07
7.79
7.79
7.77
7.77
7.51
7.50
2.50
2.50
2.50
2.49
2.49
2.07
1.00
3.33
1.06
1.06
2.16
f1 (ppm)


COOH
Cl
N
O
CF3
C5-13C
168.21
155.25
149.99
147.18
141.84
132.19
131.97
130.77
129.67
125.61
125.29
121.64
119.66
f1 (ppm)


COOH
Cl
N
F
C6-1H
8.78
8.77
8.49
8.36
8.35
8.35
8.34
8.33
8.15
8.13
7.86
7.85
7.84
7.84
7.41
7.41
7.40
7.38
2.52
2.52
2.51
2.51
0.90
1.01
1.95
0.97
0.99
1.90
f1 (ppm)


COOH
Cl
N
F
C6-13C
167.90
165.11
163.14
155.74
147.40
137.89
134.69
132.81
132.24
131.09
130.17
130.10
125.15
124.91
120.66
116.54
116.37
40.31 dmso
40.15 dmso
39.98 dmso
f1 (ppm)


COOH
Cl
N
Br
C7-1H
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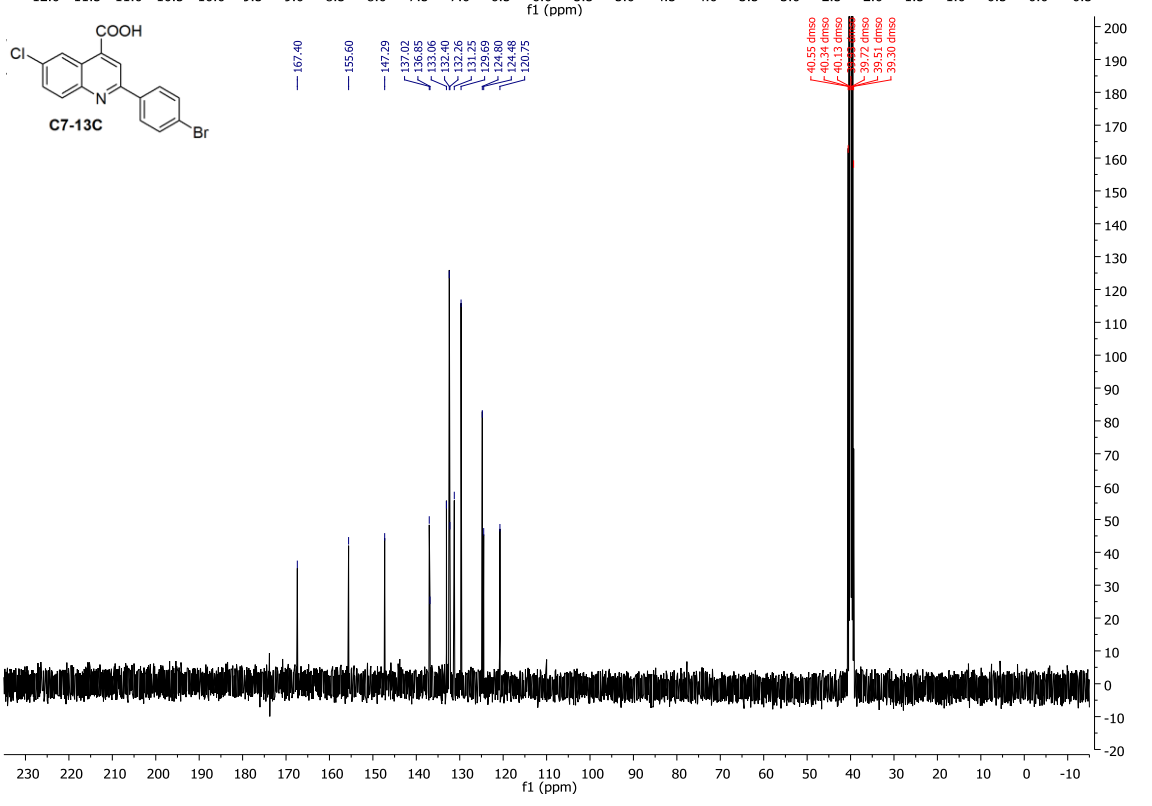
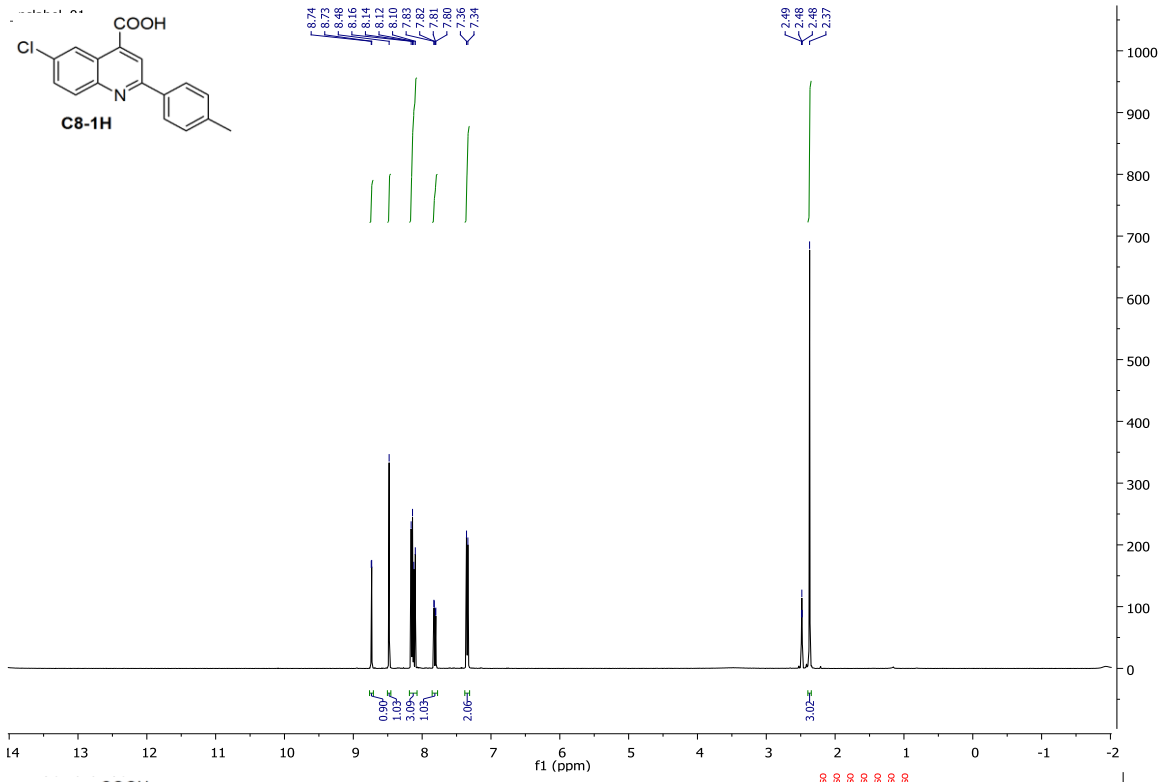
8.52
8.24
8.24
8.22
8.22
8.16
8.14
7.87
7.86
7.85
7.84
7.76
7.75
7.73
3.36
2.47
2.47
2.46
2.46
0.88
1.00
2.08
0.91
0.78
2.01
f1 (ppm)


COOH
Cl
N
Br
C7-13C
167.40
155.60
147.29
137.02
136.85
133.06
132.40
132.26
131.25
129.69
124.80
124.48
120.75
40.55 dmso
40.34 dmso
40.13 dmso
39.72 dmso
39.51 dmso
39.30 dmso
f1 (ppm)


COOH
Cl
N
C8-1H
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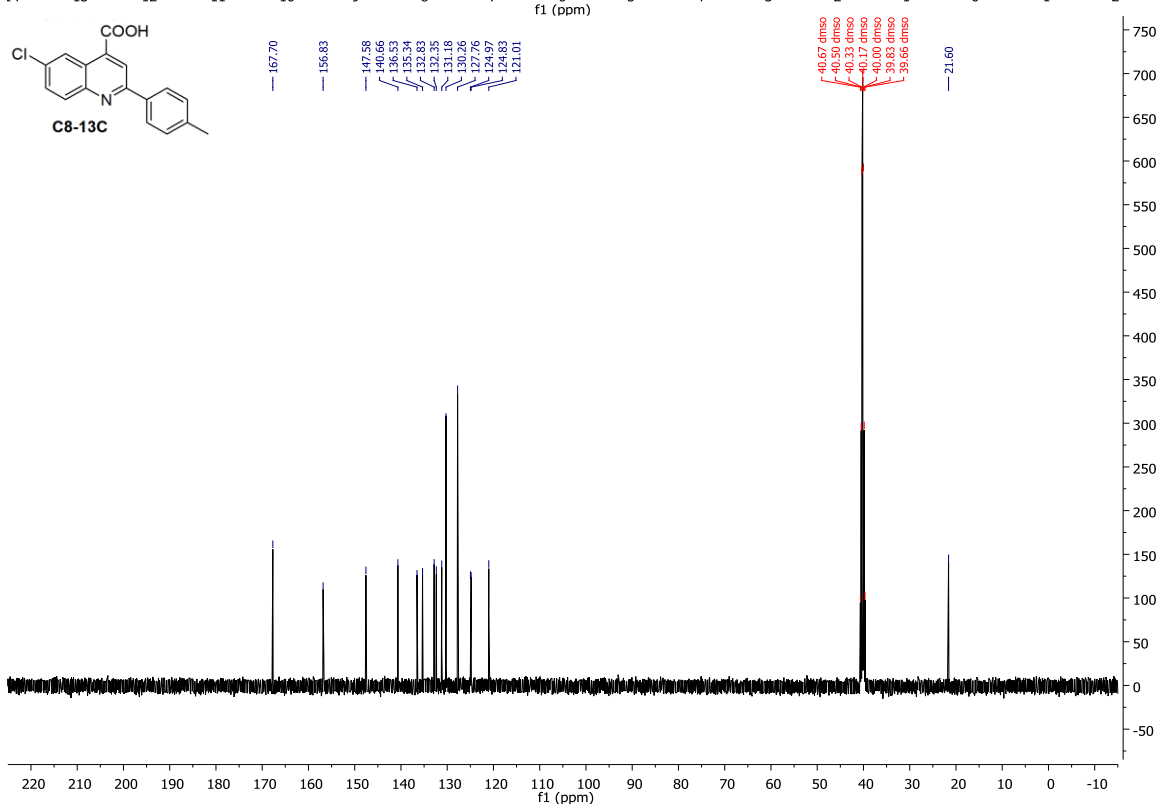
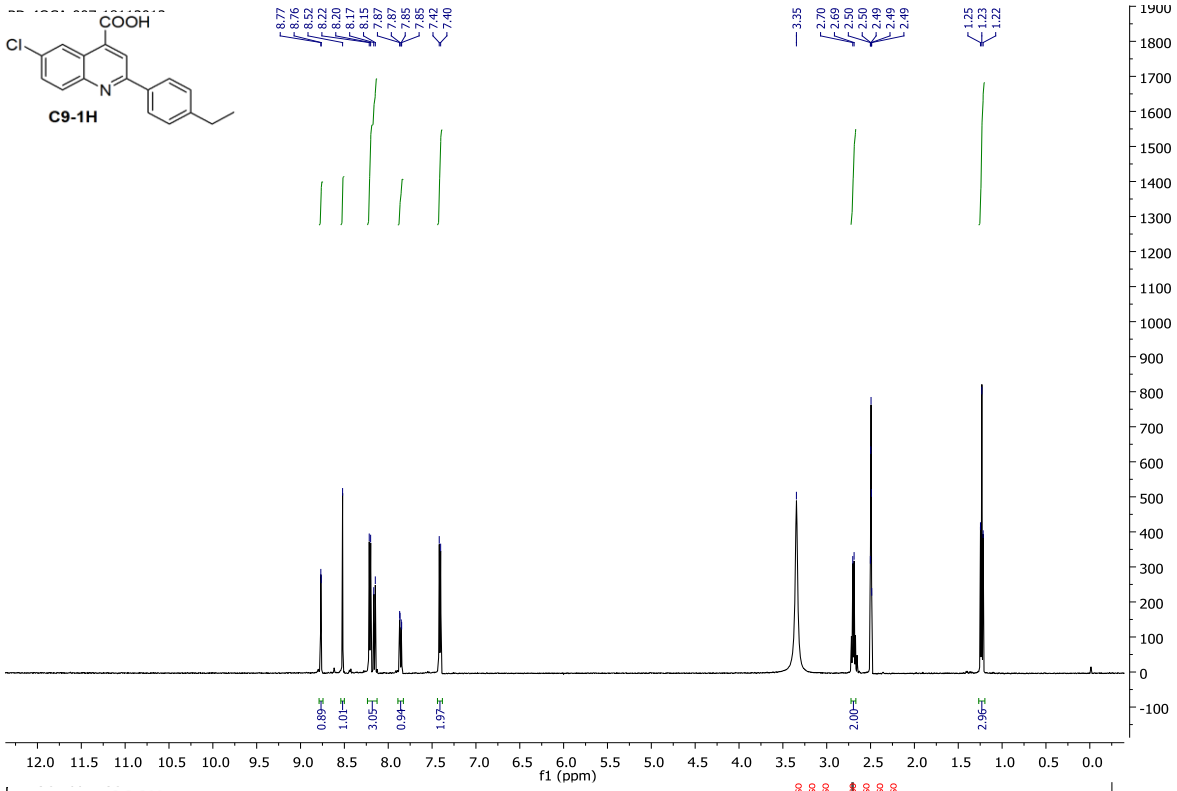
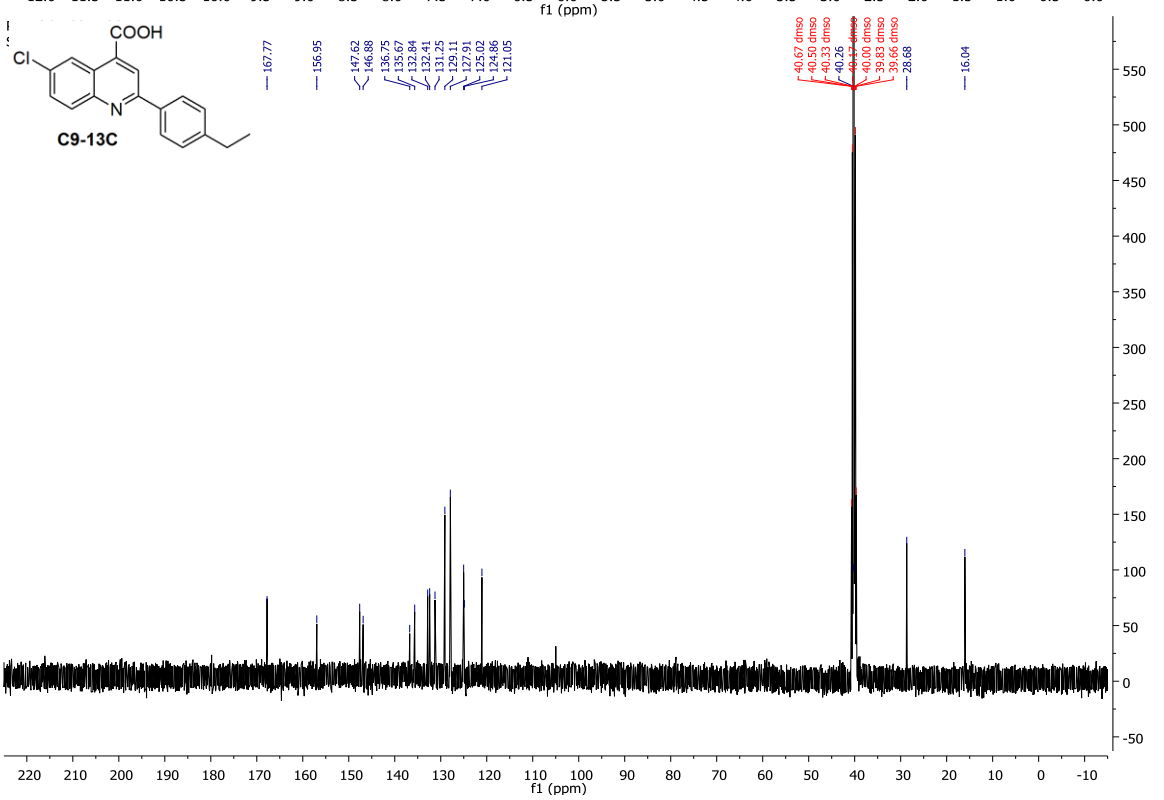
8.73
8.48
8.16
8.14
8.12
8.10
7.83
7.82
7.81
7.80
7.36
7.34
2.49
2.48
2.48
2.37
0.90
1.03
3.09
1.03
2.06
3.02
f1 (ppm)


COOH
Cl
N
C8-13C
167.70
156.83
147.58
140.66
136.53
135.34
132.83
132.35
131.18
130.26
127.76
124.97
124.83
121.01
40.67 dmso
40.50 dmso
40.33 dmso
40.17 dmso
40.00 dmso
39.83 dmso
39.66 dmso
21.60
f1 (ppm)


COOH
Cl
N
C9-1H
8.77
8.76
8.52
8.22
8.20
8.17
8.15
7.87
7.87
7.85
7.85
7.42
7.40
3.35
2.70
2.69
2.50
2.50
2.49
2.49
2.49
1.25
1.23
1.22
0.89
1.01
3.05
0.94
1.97
2.00
2.96
f1 (ppm)


COOH
Cl
N
C9-13C
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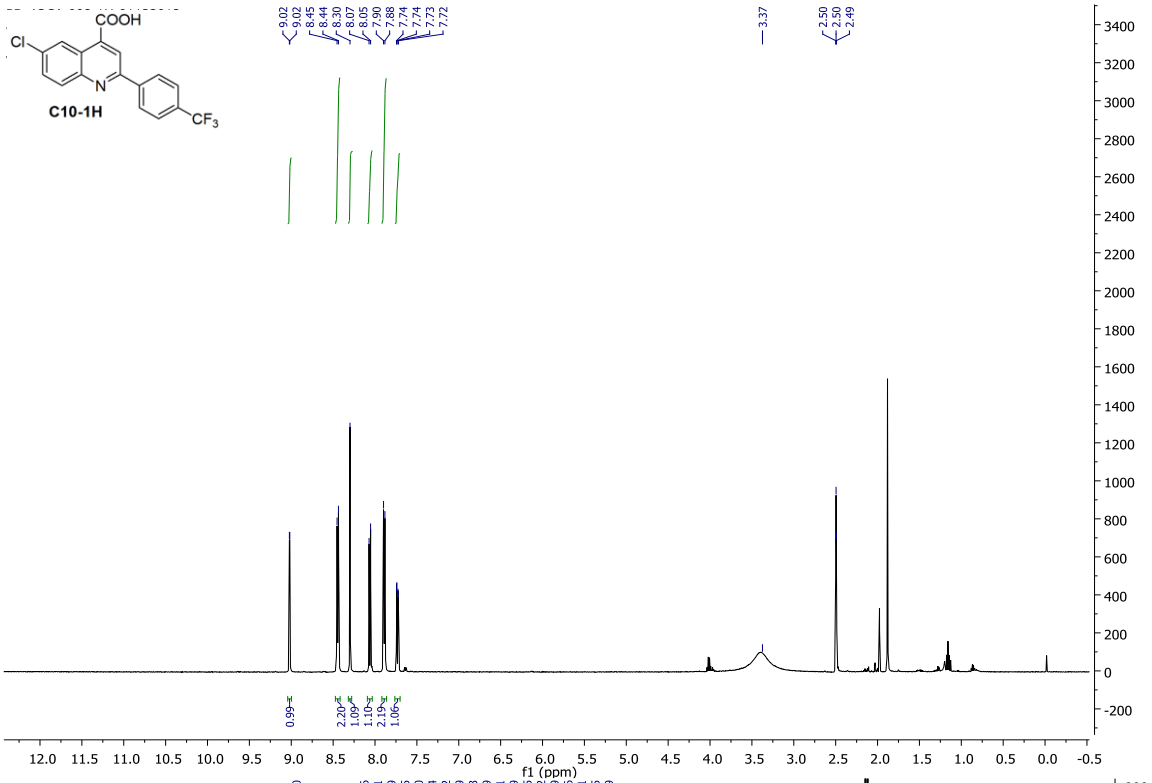
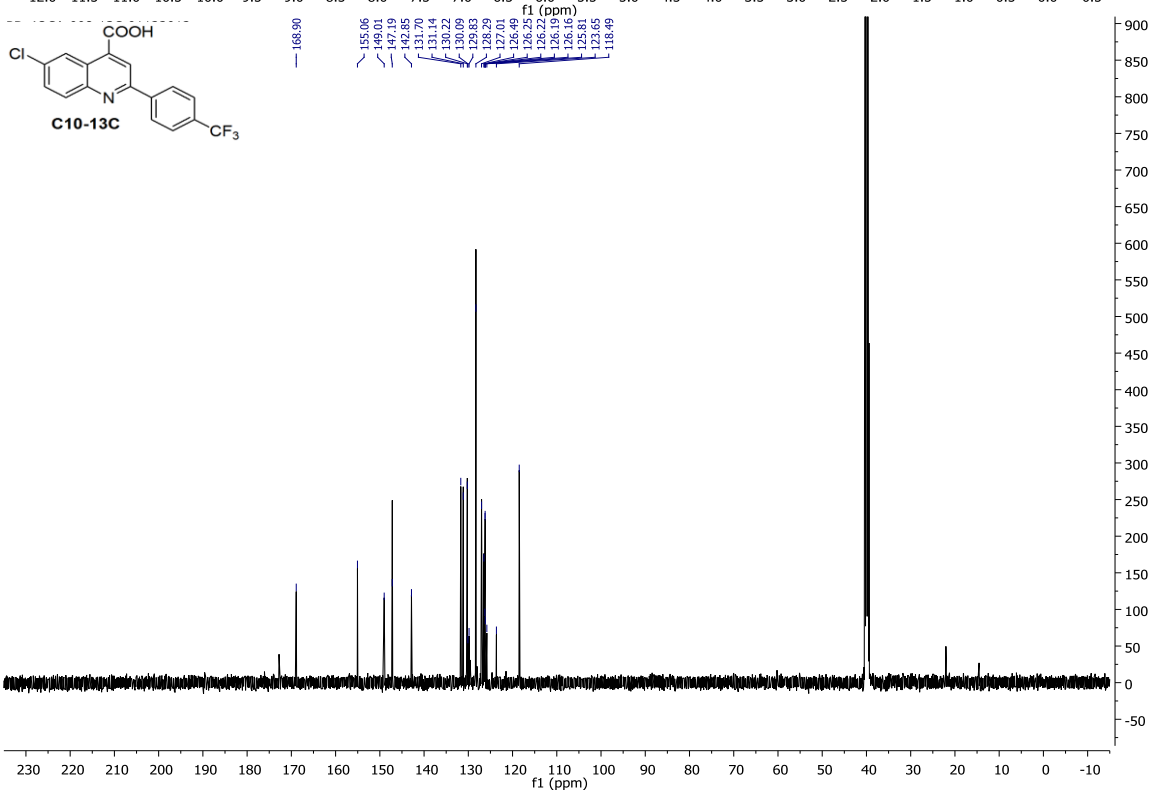
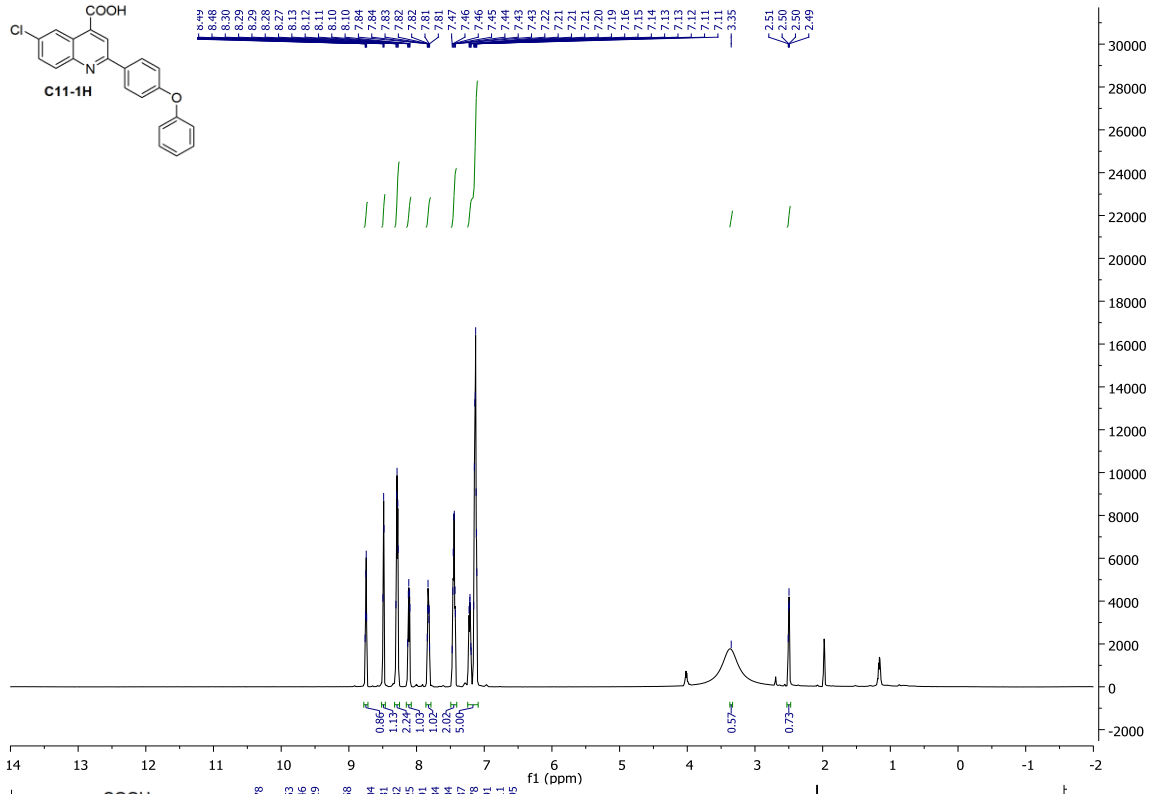
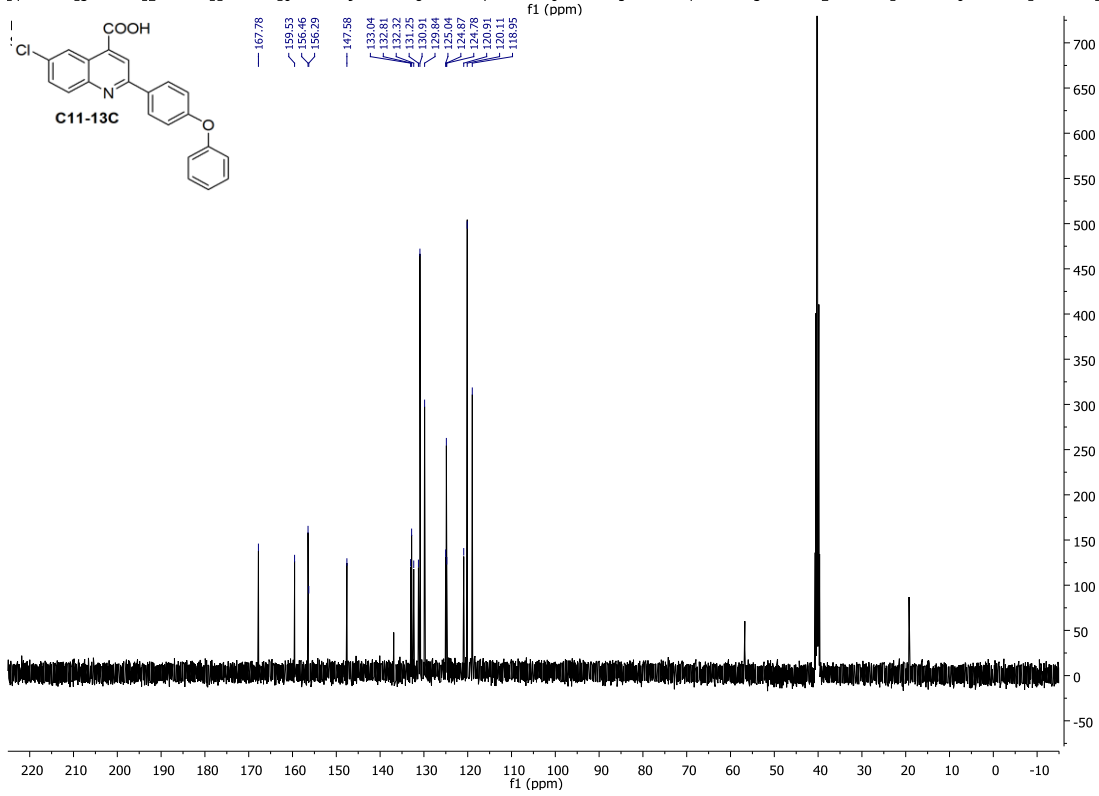
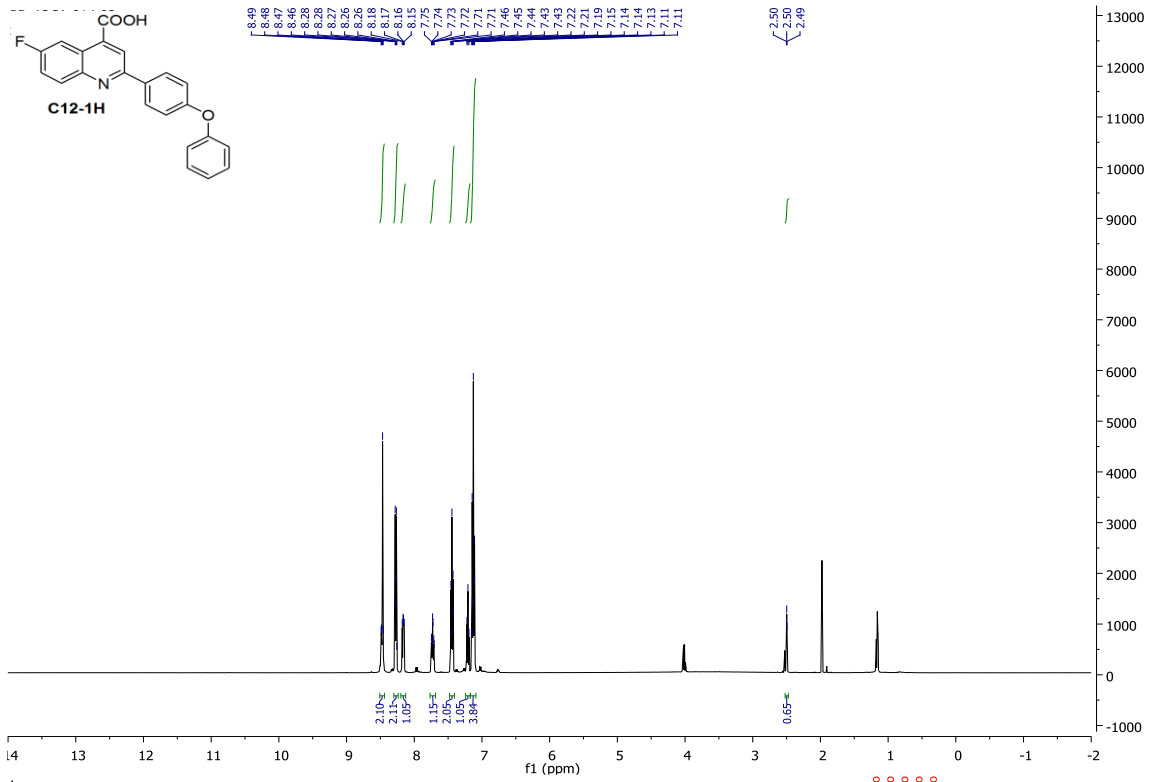
147.62
146.88
136.75
135.67
132.84
132.41
131.15
129.11
127.91
125.02
124.86
121.05
40.67 dmso
40.50 dmso
40.33 dmso
40.26
40.00 dmso
39.83 dmso
39.66 dmso
28.68
16.04
f1 (ppm)

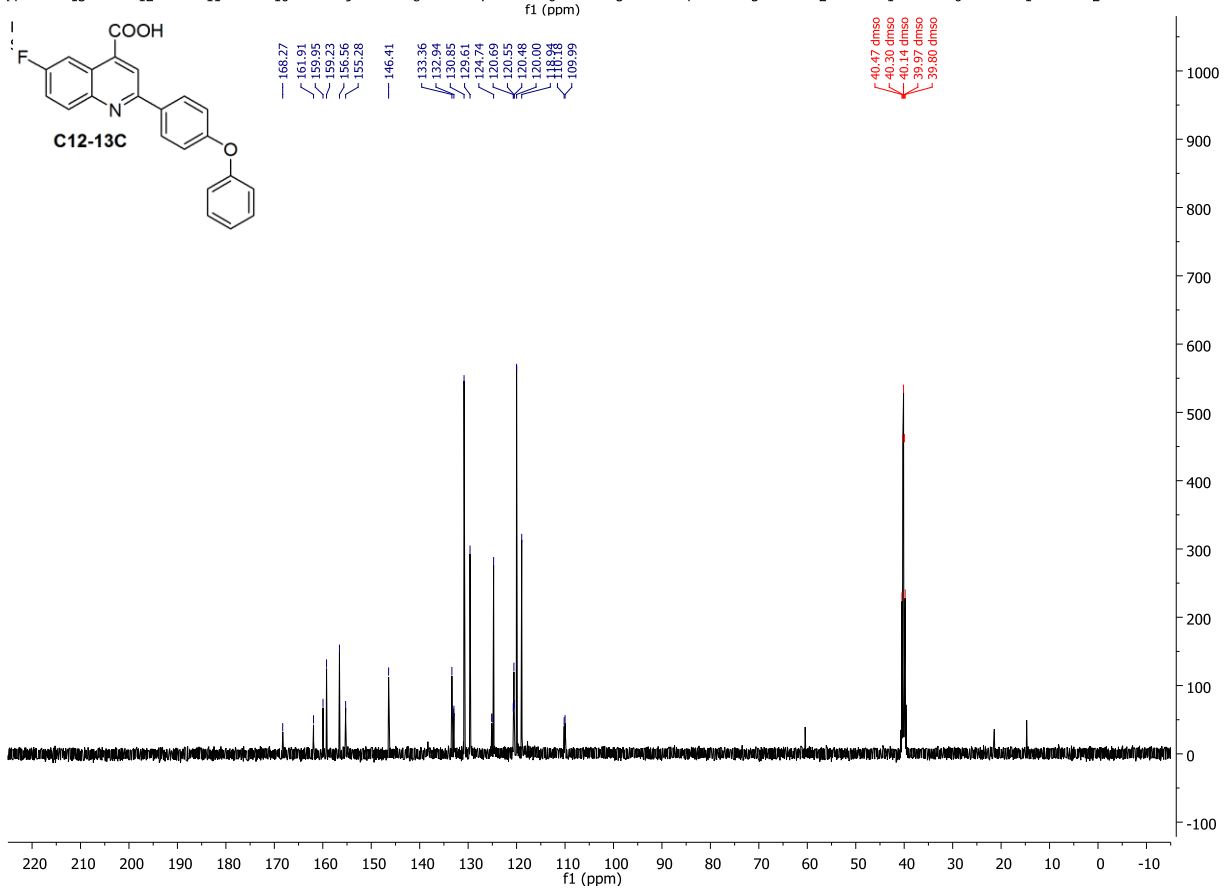

COOH
Cl
N
CF3
C10-1H
9.02
9.02
8.45
8.44
8.30
8.07
8.05
7.90
7.88
7.74
7.74
7.73
7.72
3.37
2.50
2.50
2.49
0.99
2.20
1.09
1.10
2.19
1.06
f1 (ppm)

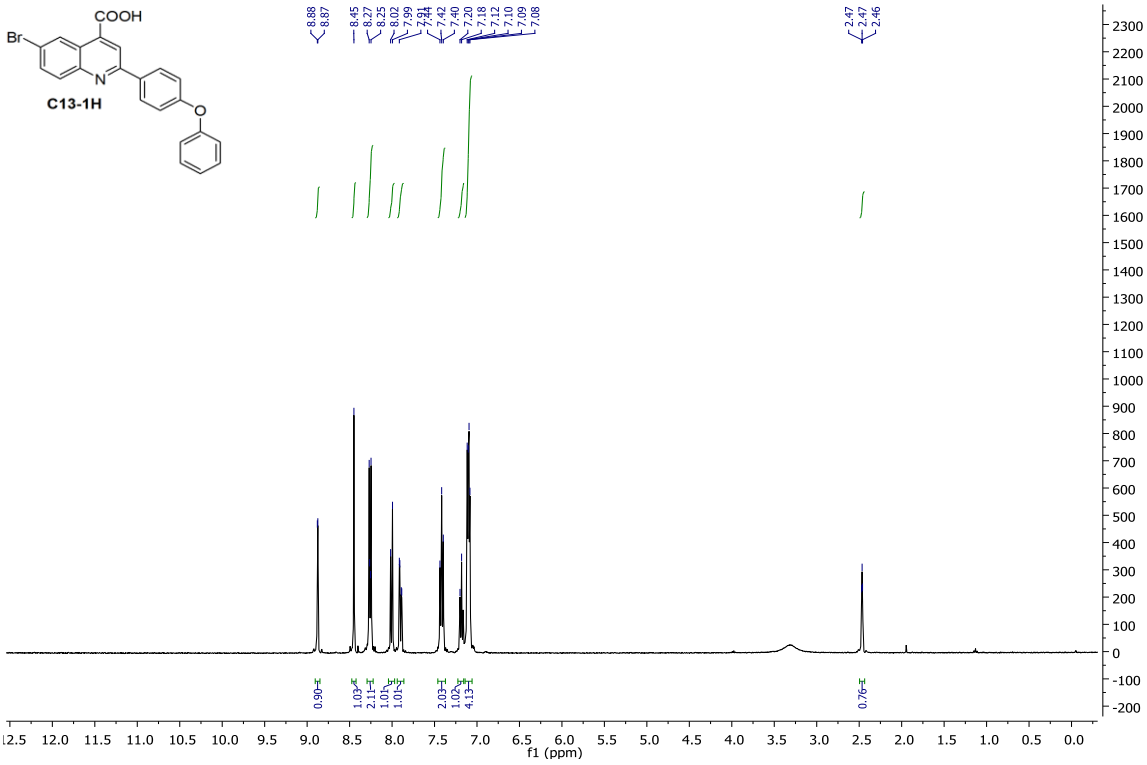

COOH
Cl
N
CF3
C10-13C
168.90
155.06
149.01
147.19
142.85
131.70
131.14
130.22
130.09
129.83
128.29
127.01
126.49
126.25
126.22
126.19
126.16
125.81
123.65
118.49
f1 (ppm)

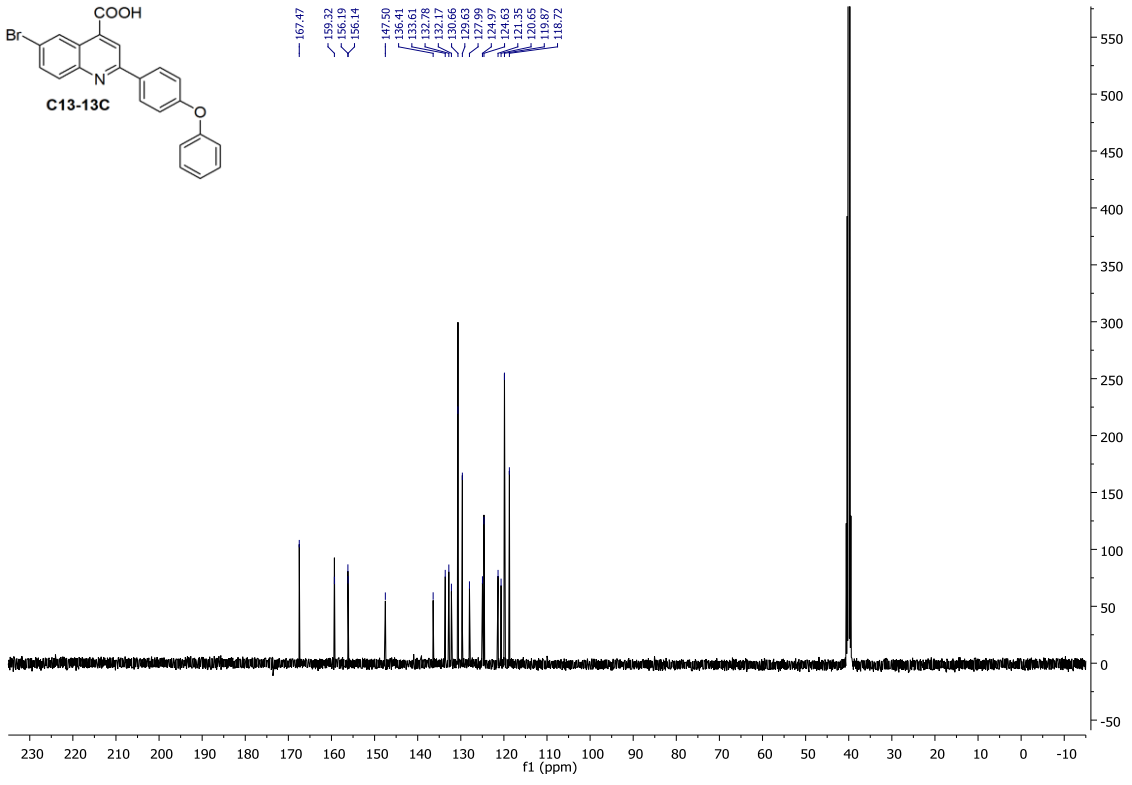

COOH
Cl
N
O
C11-1H
f1 (ppm)

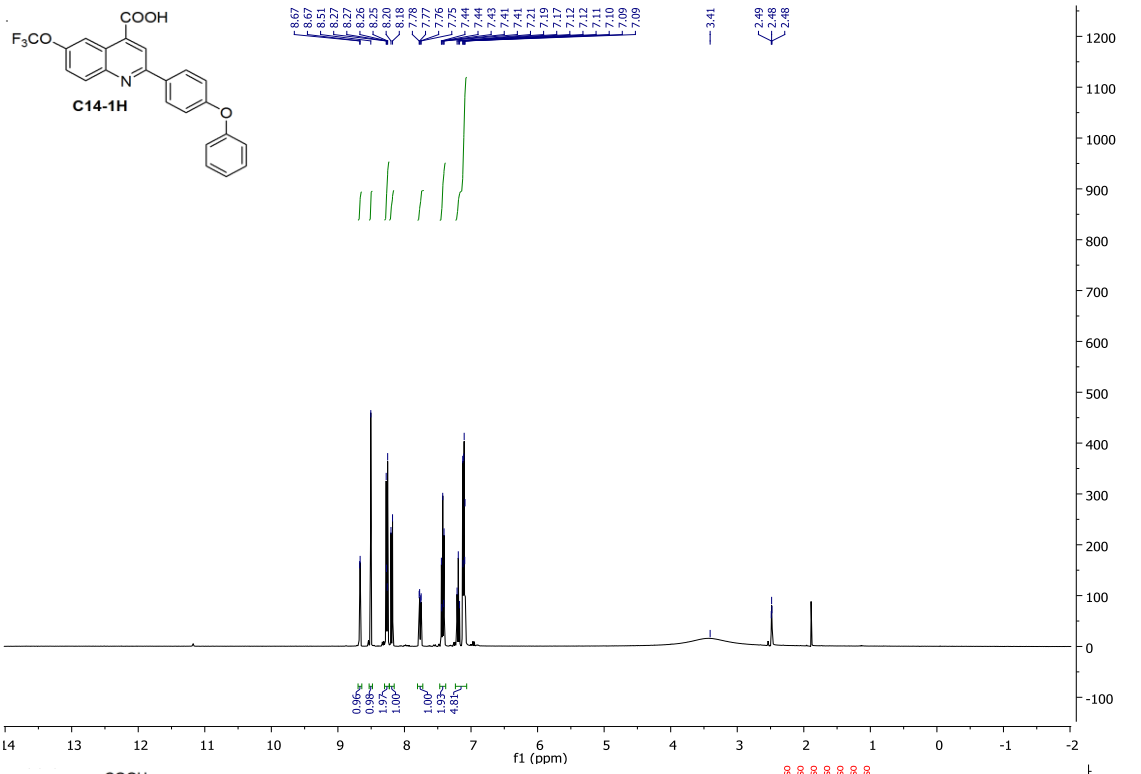

COOH
Cl
N
O
C11-13C
f1 (ppm)

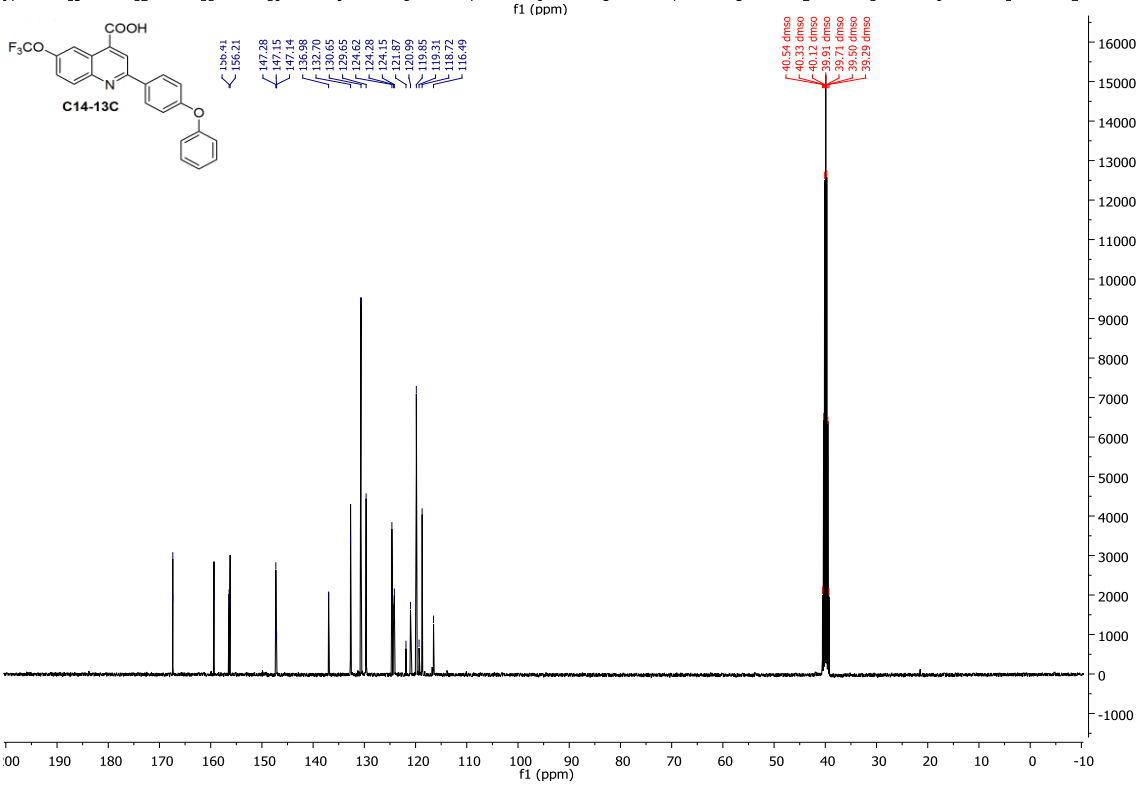

COOH
F
N
O
C12-1H
8.49
8.48
8.47
8.46
8.28
8.28
8.27
8.26
8.26
8.18
8.17
8.16
8.15
7.75
7.74
7.73
7.72
7.71
7.71
7.46
7.45
7.44
7.43
7.43
7.22
7.21
7.19
7.15
7.14
7.14
7.13
7.11
7.11
2.50
2.50
2.49
2.10
2.11
1.05
1.15
2.06
1.05
3.84
0.65
f1 (ppm)

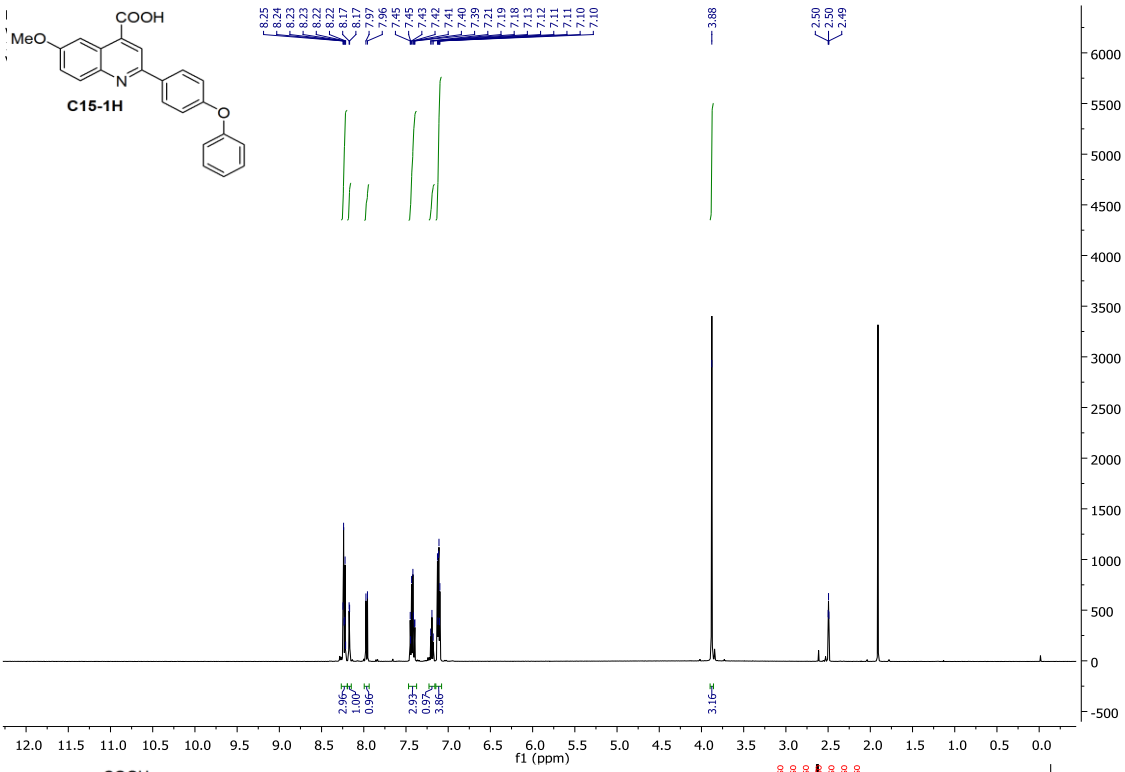

COOH
F
N
O
C12-13C
168.27
161.91
159.95
159.23
156.56
155.28
146.41
133.36
132.94
130.85
129.61
124.74
120.69
120.55
120.48
120.00
118.94
118.18
109.99
40.47 dmso
40.30 dmso
40.14 dmso
39.97 dmso
39.80 dmso
f1 (ppm)

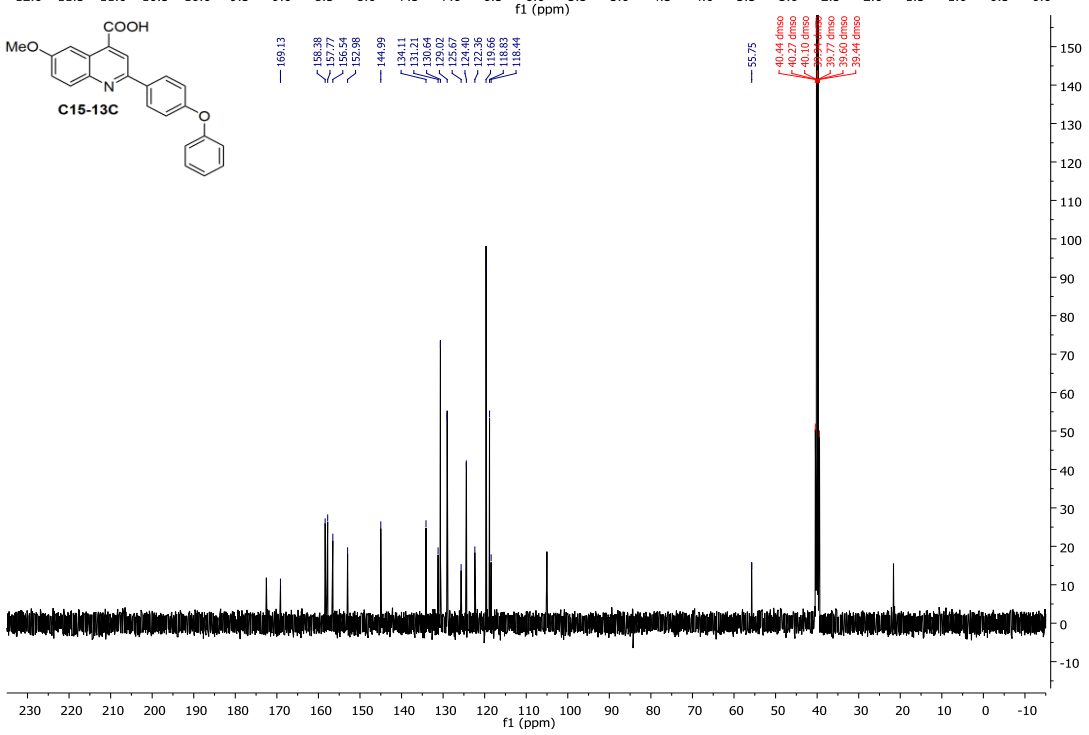

COOH
Br
N
O
C13-1H
8.88
8.87
8.45
8.27
8.25
8.02
7.99
7.91
7.44
7.42
7.40
7.20
7.18
7.12
7.10
7.09
7.08
2.47
2.47
2.46
0.90
1.03
2.11
1.01
1.01
2.03
1.02
4.13
0.76
f1 (ppm)

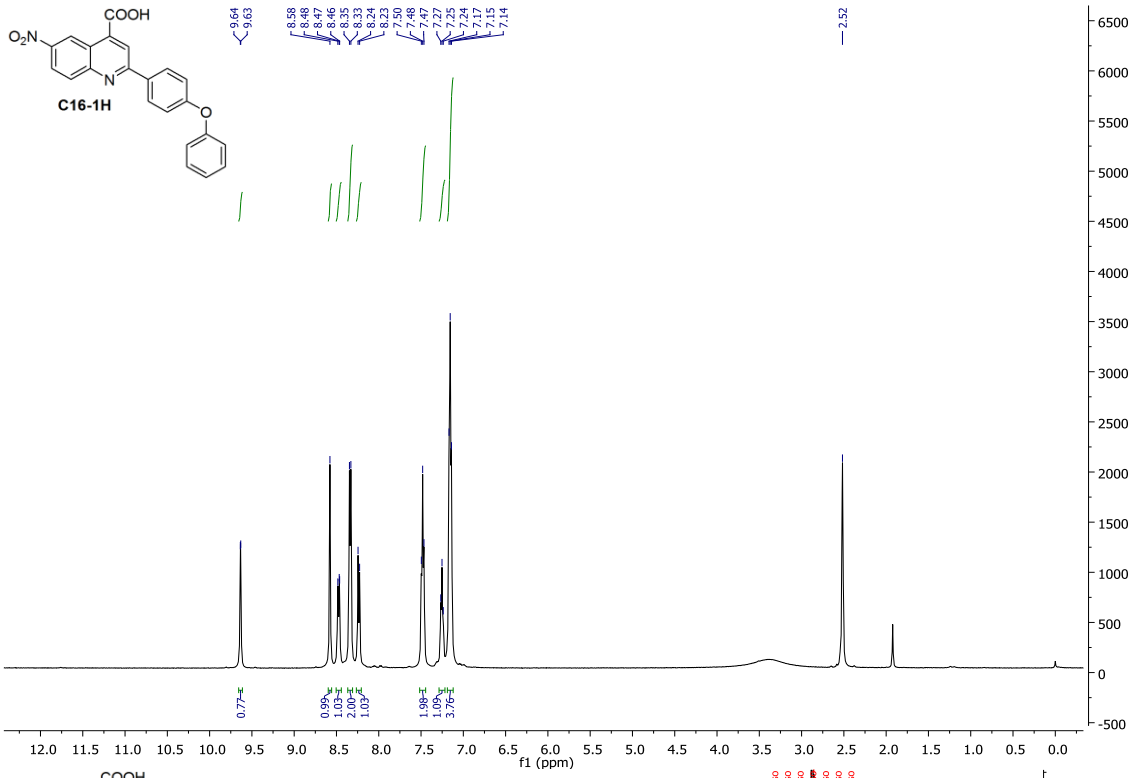

COOH
Br
N
O
C13-13C
167.47
159.32
156.19
156.14
147.50
136.41
133.61
132.78
131.77
130.66
129.63
127.99
124.97
124.63
121.35
120.65
119.87
118.72
f1 (ppm)

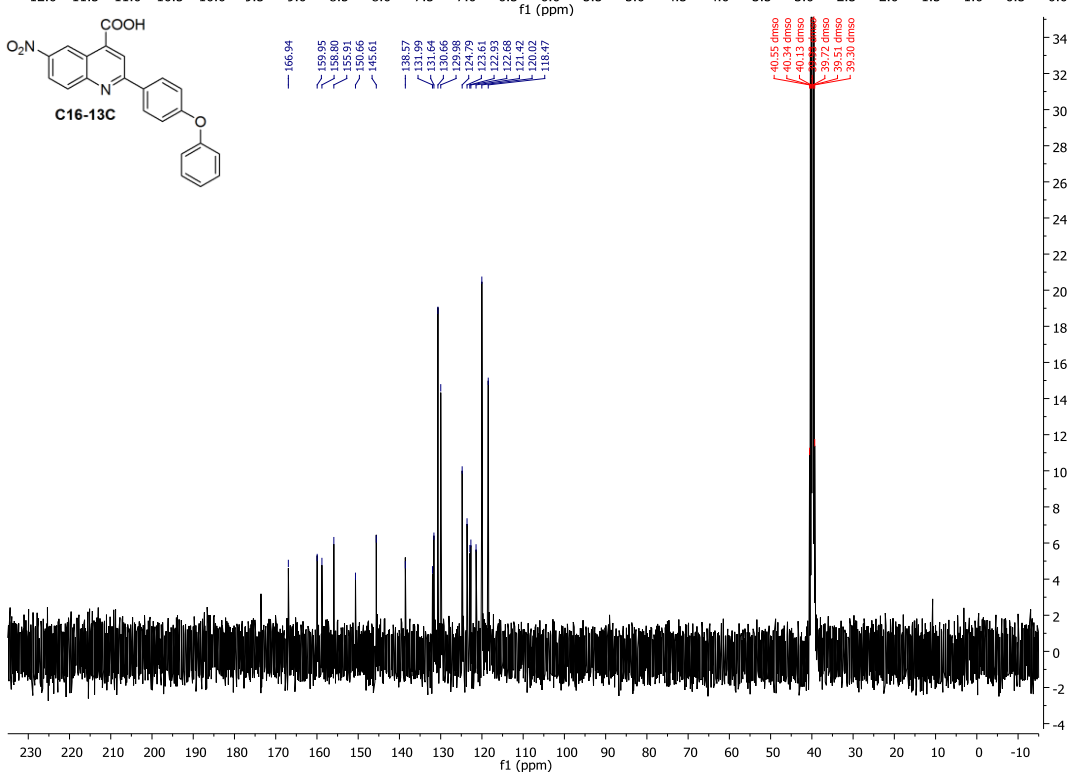

COOH
F3CO
N
O
C14-1H
8.67
8.67
8.51
8.27
8.27
8.26
8.25
8.20
8.18
7.78
7.77
7.76
7.75
7.44
7.44
7.43
7.41
7.41
7.21
7.19
7.17
7.12
7.12
7.11
7.10
7.09
7.09
3.41
2.49
2.48
2.48
0.96
0.96
0.97
1.00
1.00
1.99
4.81
f1 (ppm)

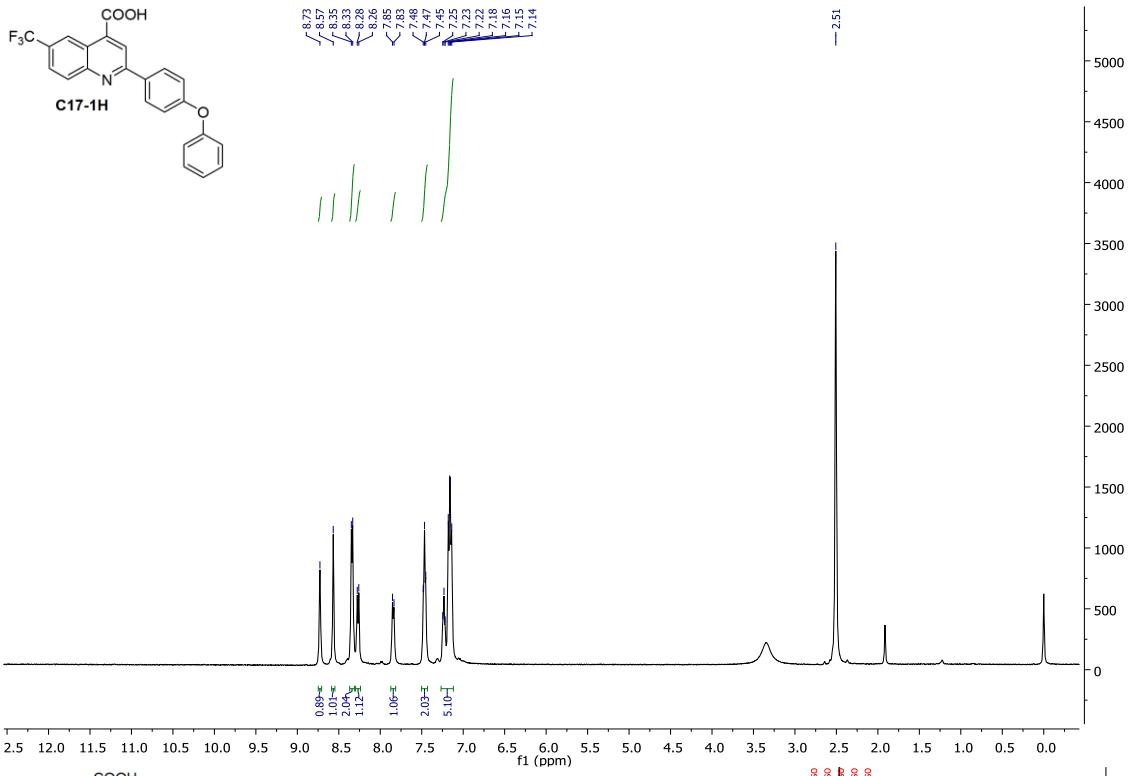

COOH
F3CO
N
O
C14-13C
136.41
156.21
147.28
147.15
147.14
136.98
132.70
130.65
129.65
124.62
124.28
124.15
121.87
120.99
119.85
119.31
118.72
116.49
40.54 dmso
40.33 dmso
40.12 dmso
39.91 dmso
39.71 dmso
39.50 dmso
39.29 dmso
f1 (ppm)

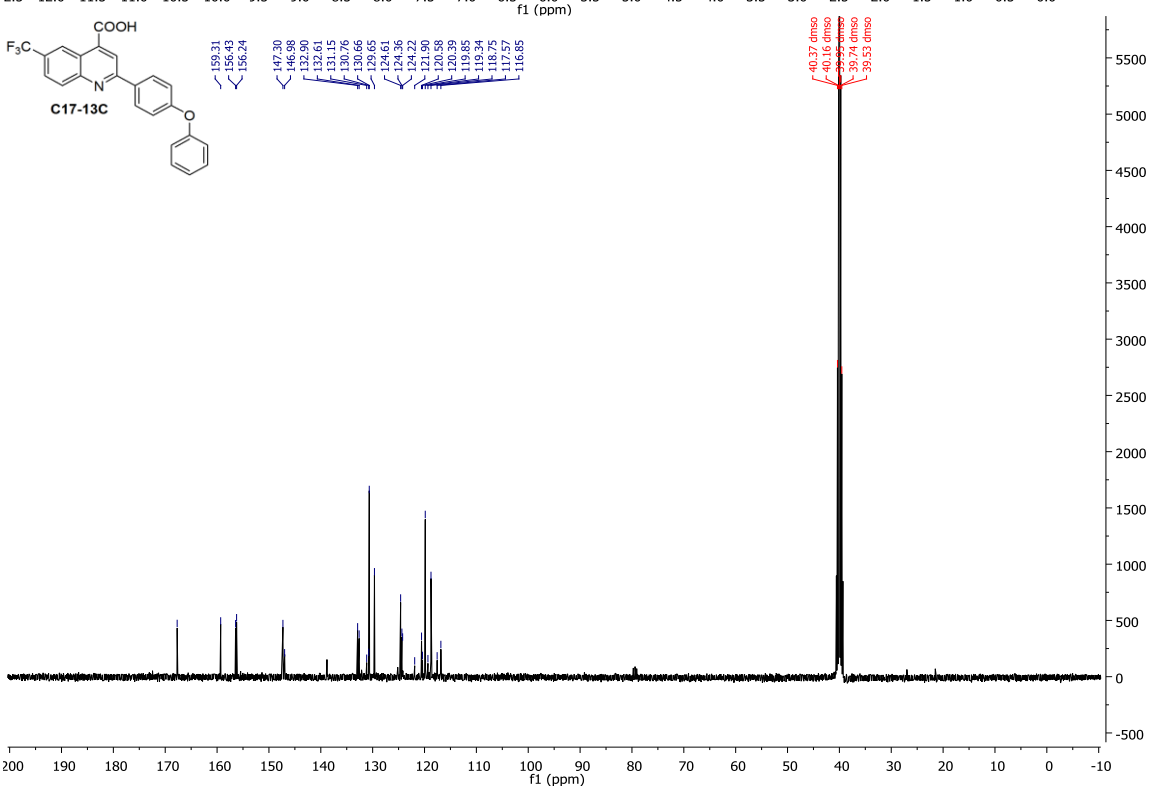

COOH
MeO
N
O
C15-1H
8.25
8.24
8.23
8.23
8.22
8.22
8.17
8.17
7.97
7.96
7.45
7.43
7.42
7.41
7.40
7.39
7.21
7.19
7.18
7.13
7.12
7.11
7.11
7.10
7.10
3.88
2.50
2.50
2.49
2.96
1.00
0.96
2.93
0.97
3.86
3.16
f1 (ppm)

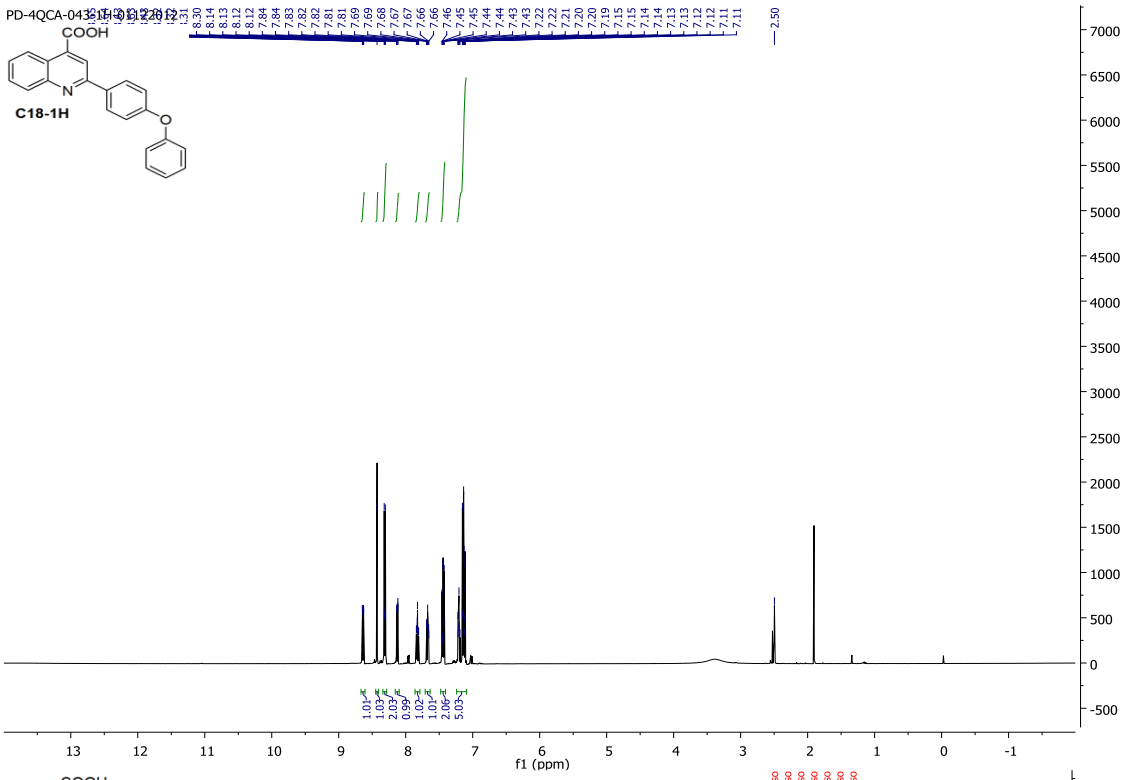

COOH
MeO
N
O
C15-13C
169.13
158.38
157.77
156.54
152.98
144.99
134.11
131.21
130.64
129.02
125.67
124.40
122.36
119.66
118.83
118.44
55.75
40.44 dmso
40.27 dmso
40.10 dmso
39.77 dmso
39.60 dmso
39.44 dmso
f1 (ppm)

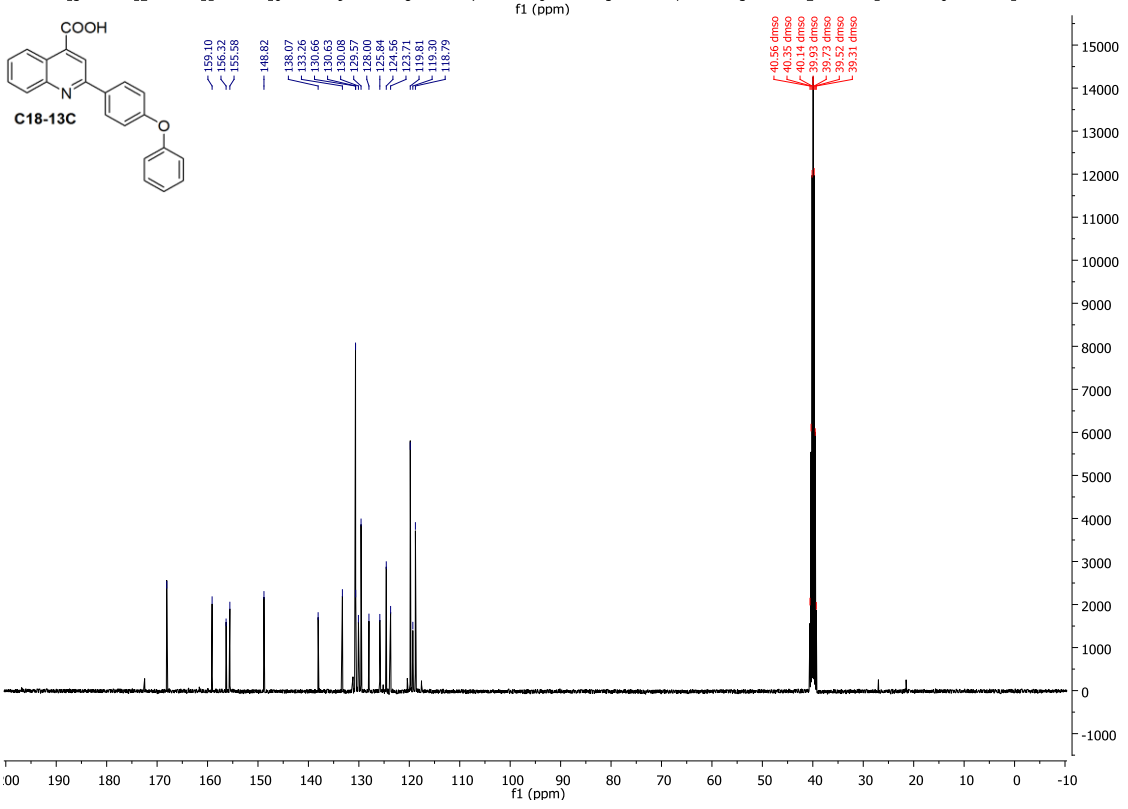

COOH
O2N
N
O
C16-1H
9.64
9.63
8.58
8.48
8.47
8.46
8.35
8.33
8.24
8.23
7.50
7.48
7.47
7.27
7.25
7.24
7.17
7.15
7.14
2.52
0.77
0.99
1.03
2.00
1.03
1.98
1.09
3.76
f1 (ppm)

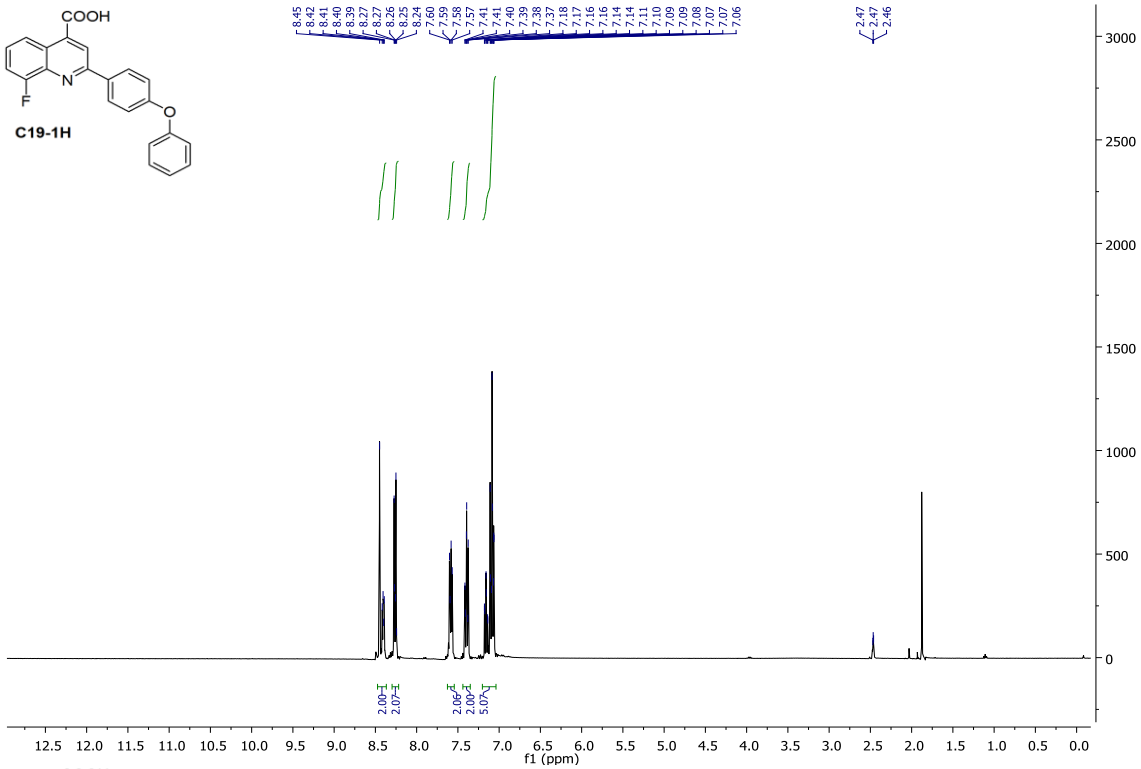

COOH
O2N
N
O
C16-13C
166.94
159.95
158.80
155.91
150.66
145.61
138.57
131.99
131.64
130.66
129.98
124.79
123.61
122.93
122.68
121.42
120.02
118.47
40.55 dmso
40.34 dmso
40.13 dmso
39.72 dmso
39.51 dmso
39.30 dmso
f1 (ppm)


COOH
F3C
N
O
C17-1H
8.73
8.57
8.35
8.33
8.28
8.26
7.85
7.83
7.48
7.47
7.45
7.25
7.23
7.22
7.18
7.16
7.15
7.14
2.51
0.89
1.01
2.04
1.12
1.06
2.03
5.10
f1 (ppm)


COOH
F3C
N
O
C17-13C
159.31
156.43
156.24
147.30
146.98
132.90
132.61
131.15
130.76
130.66
129.65
124.61
124.36
124.22
121.90
120.58
120.39
119.85
119.34
118.75
117.57
116.85
40.37 dmso
40.16 dmso
39.95 dmso
39.74 dmso
39.53 dmso
f1 (ppm)


PD-4QCA-043-1H-01122012
COOH
N
O
C18-1H
8.30
8.14
8.13
8.12
7.84
7.83
7.82
7.81
7.69
7.68
7.67
7.66
7.46
7.45
7.44
7.43
7.22
7.21
7.20
7.19
7.15
7.14
7.13
7.12
7.11
2.50
1.01
1.03
2.03
0.99
1.02
1.01
2.06
5.03
f1 (ppm)


COOH
N
O
C18-13C
159.10
156.32
155.58
148.82
138.07
133.26
130.66
130.63
130.08
129.57
128.00
125.84
124.56
123.71
119.81
119.30
118.79
40.56 dmso
40.35 dmso
40.14 dmso
39.93 dmso
39.73 dmso
39.52 dmso
39.31 dmso
f1 (ppm)


COOH
N
F
O
C19-1H
8.45
8.42
8.41
8.40
8.39
8.27
8.27
8.26
8.25
8.24
7.60
7.59
7.58
7.57
7.41
7.41
7.40
7.39
7.38
7.37
7.18
7.17
7.16
7.16
7.14
7.14
7.11
7.10
7.09
7.09
7.08
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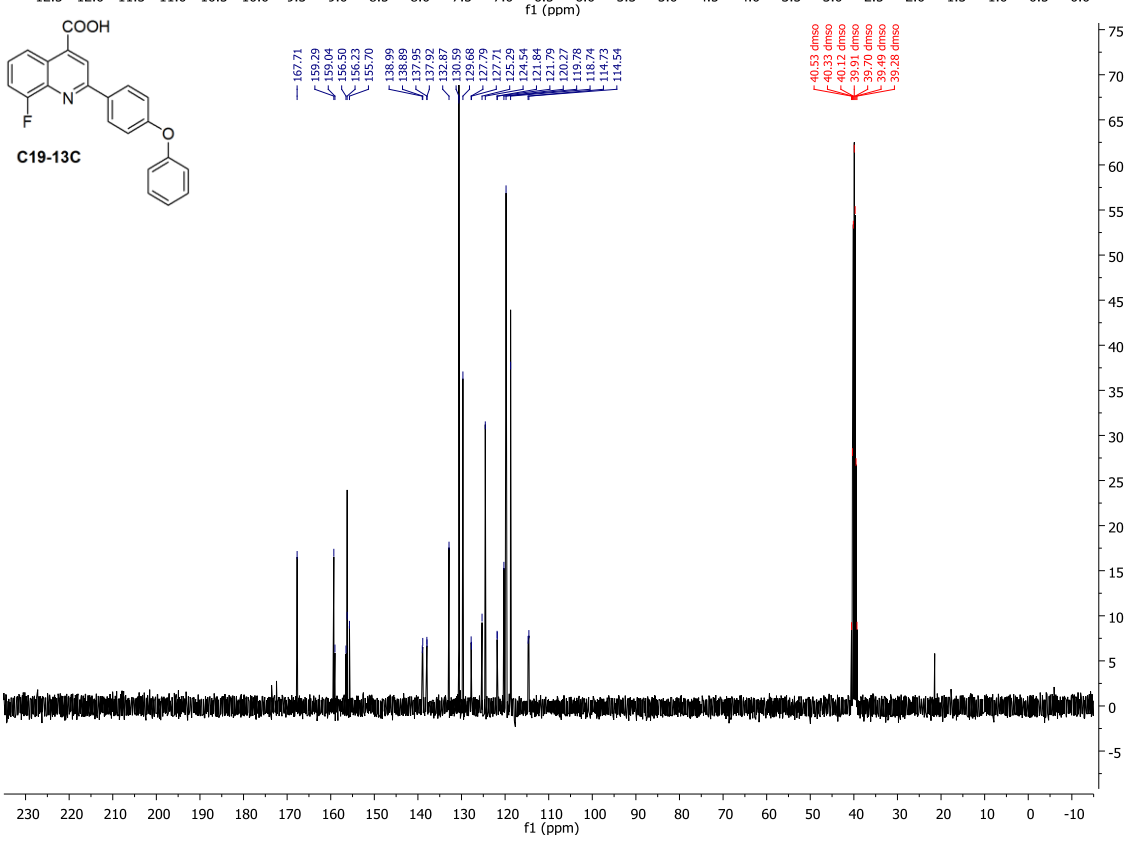
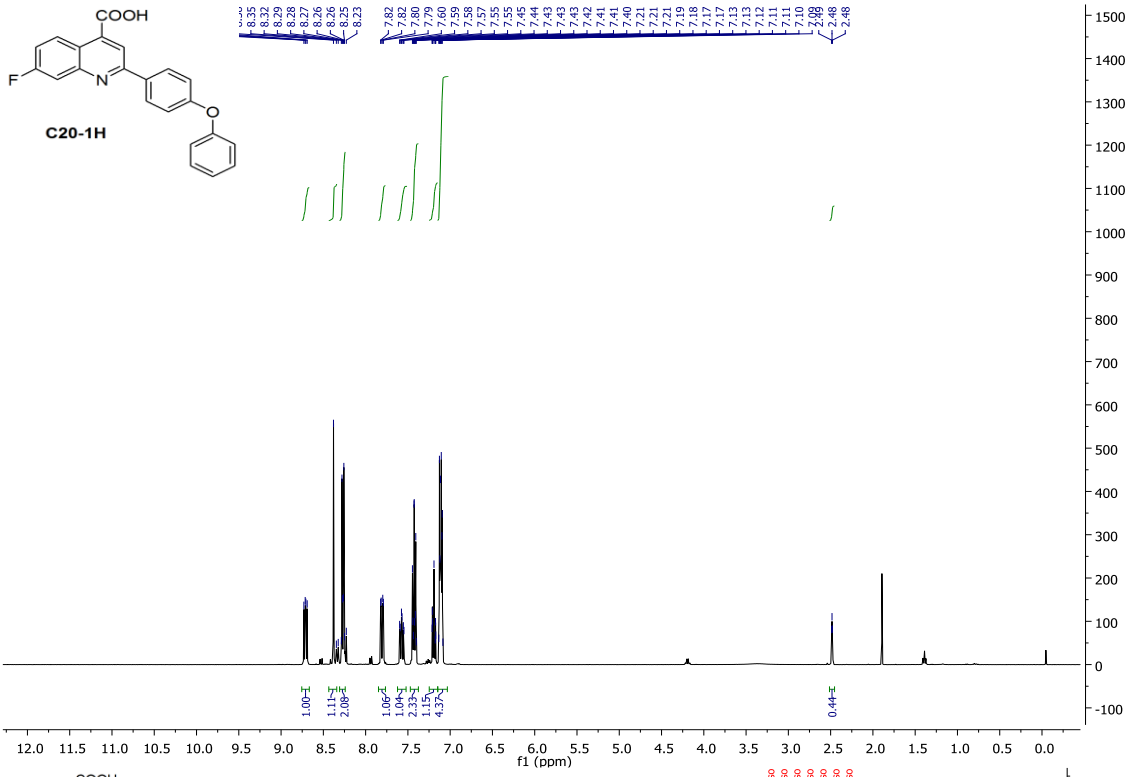
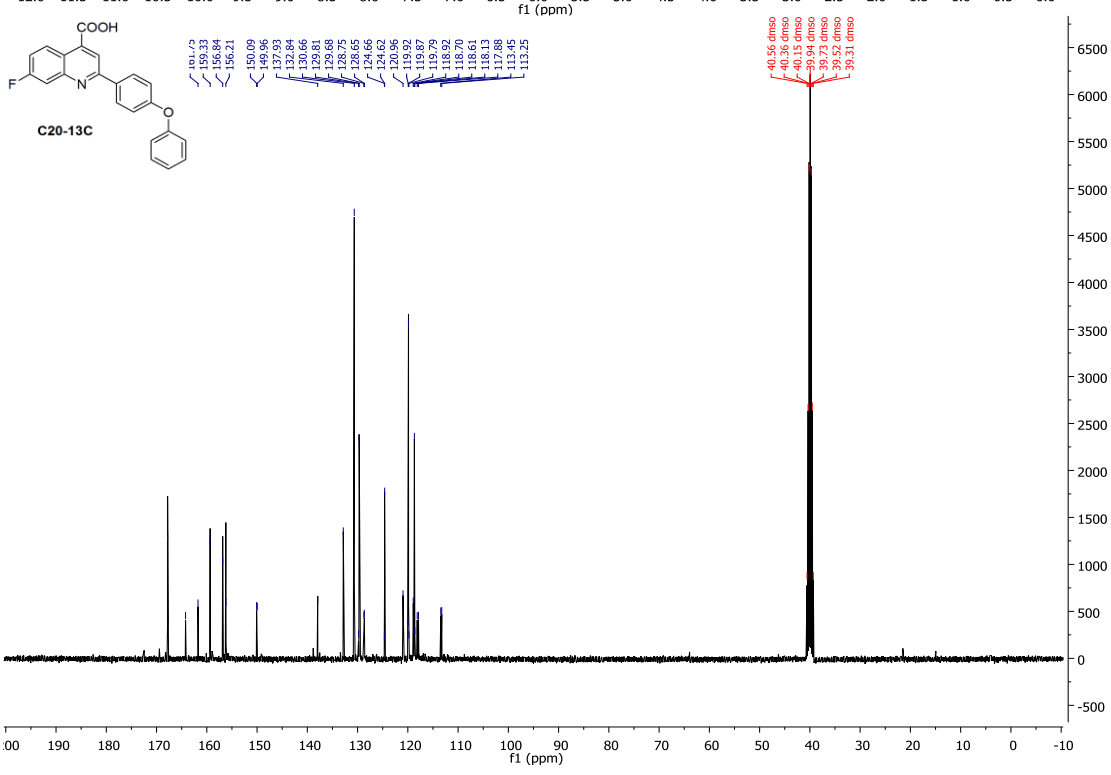
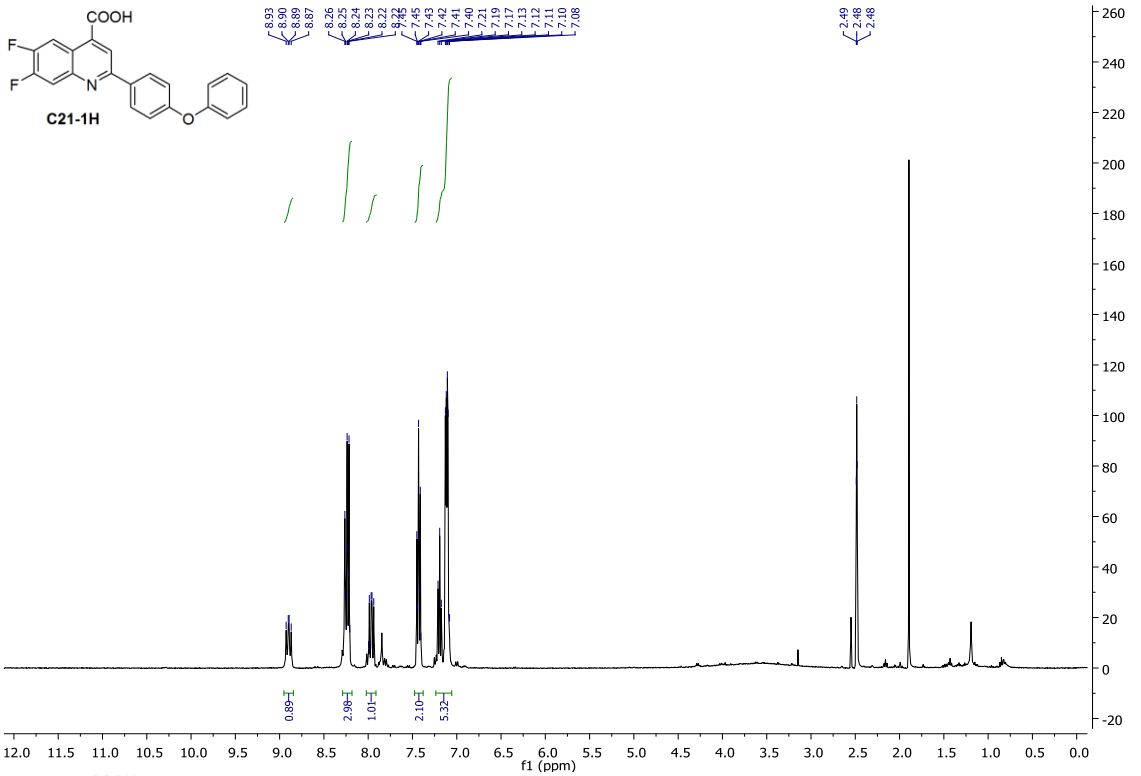
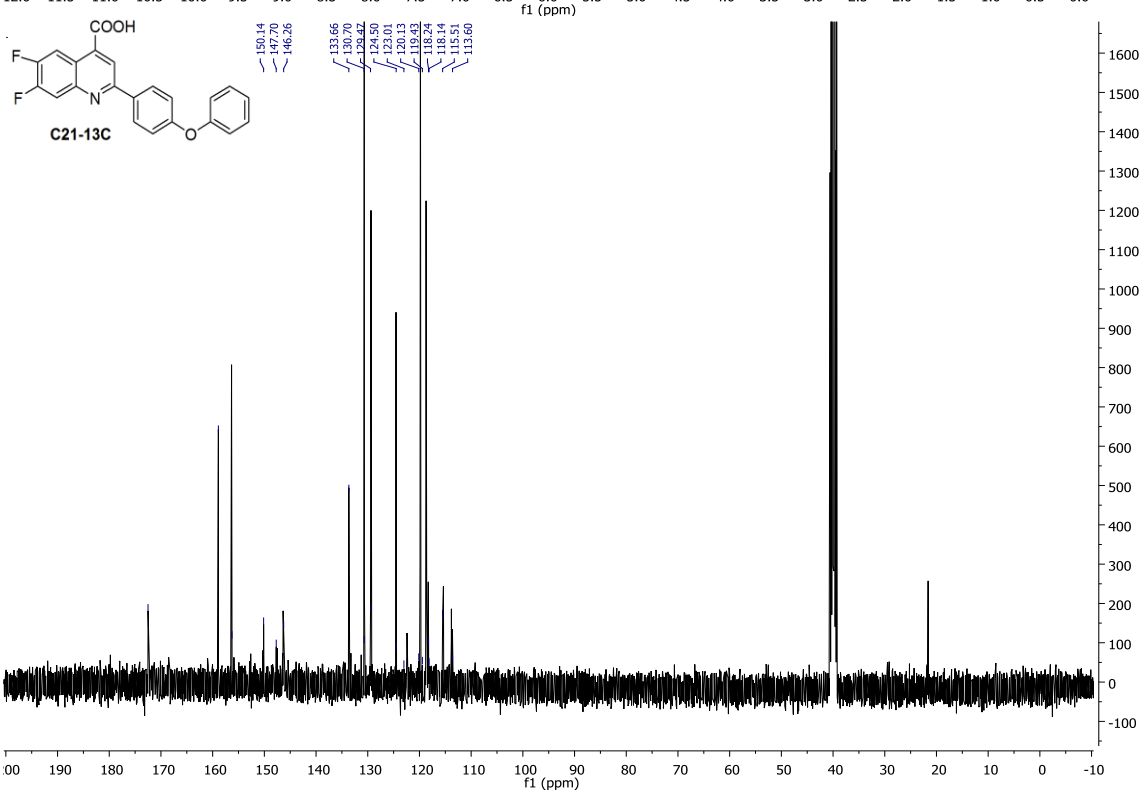
2.00
2.07
2.06
2.00
5.07
f1 (ppm)

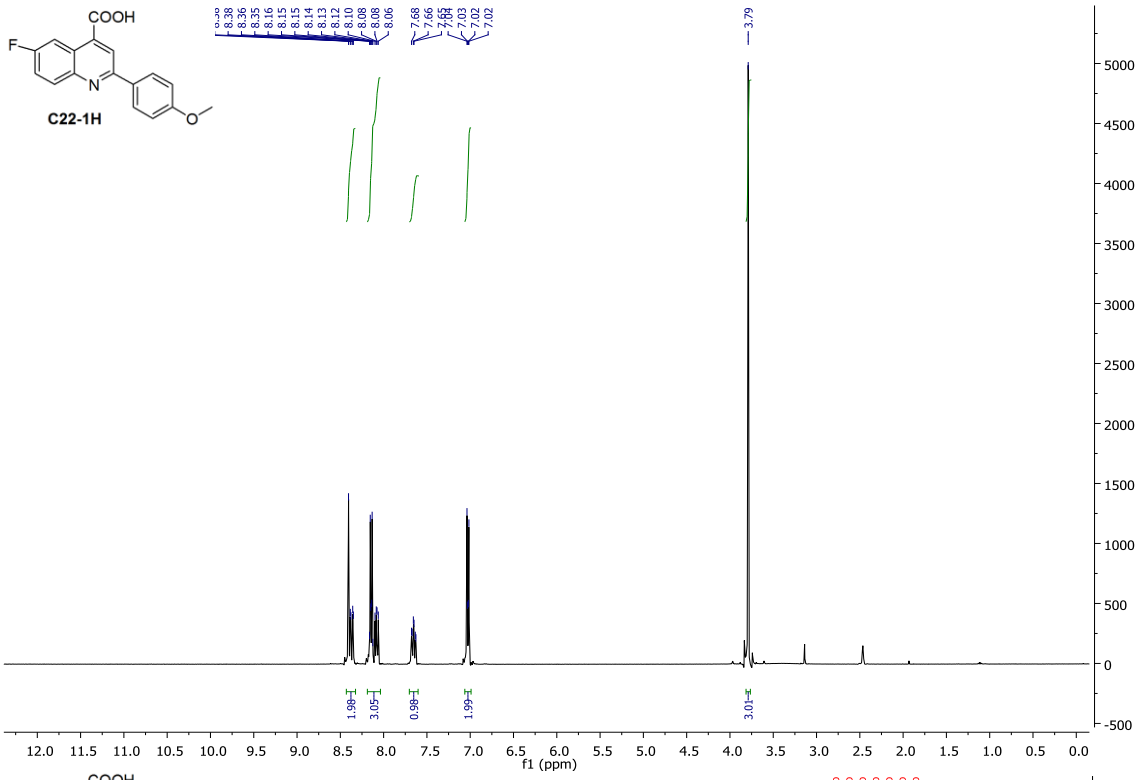

COOH
N
F
O
C19-13C
167.71
159.29
159.04
156.50
156.23
155.70
138.99
138.89
137.95
137.92
132.87
130.59
129.68
127.79
127.71
127.59
124.54
121.84
121.79
120.27
119.78
118.74
114.73
114.54
40.53 dmso
40.33 dmso
40.12 dmso
39.91 dmso
39.70 dmso
39.49 dmso
39.28 dmso
f1 (ppm)

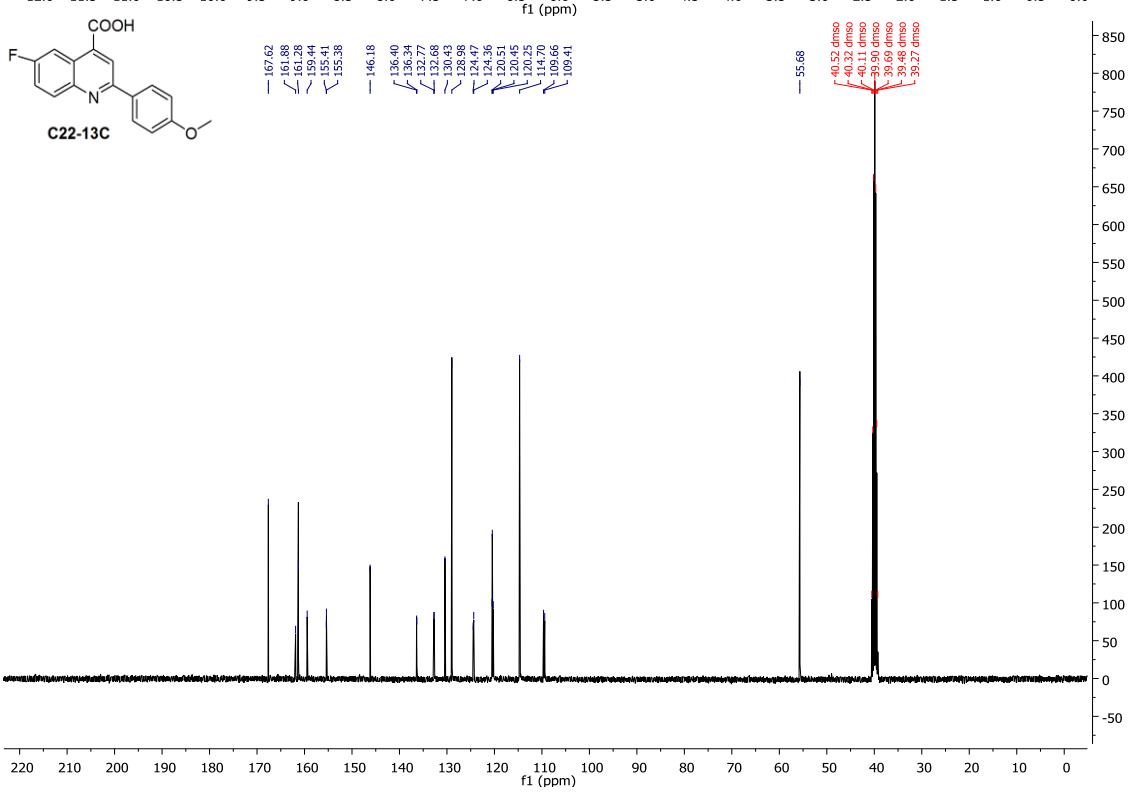

COOH
F
N
O
C20-1H
f1 (ppm)

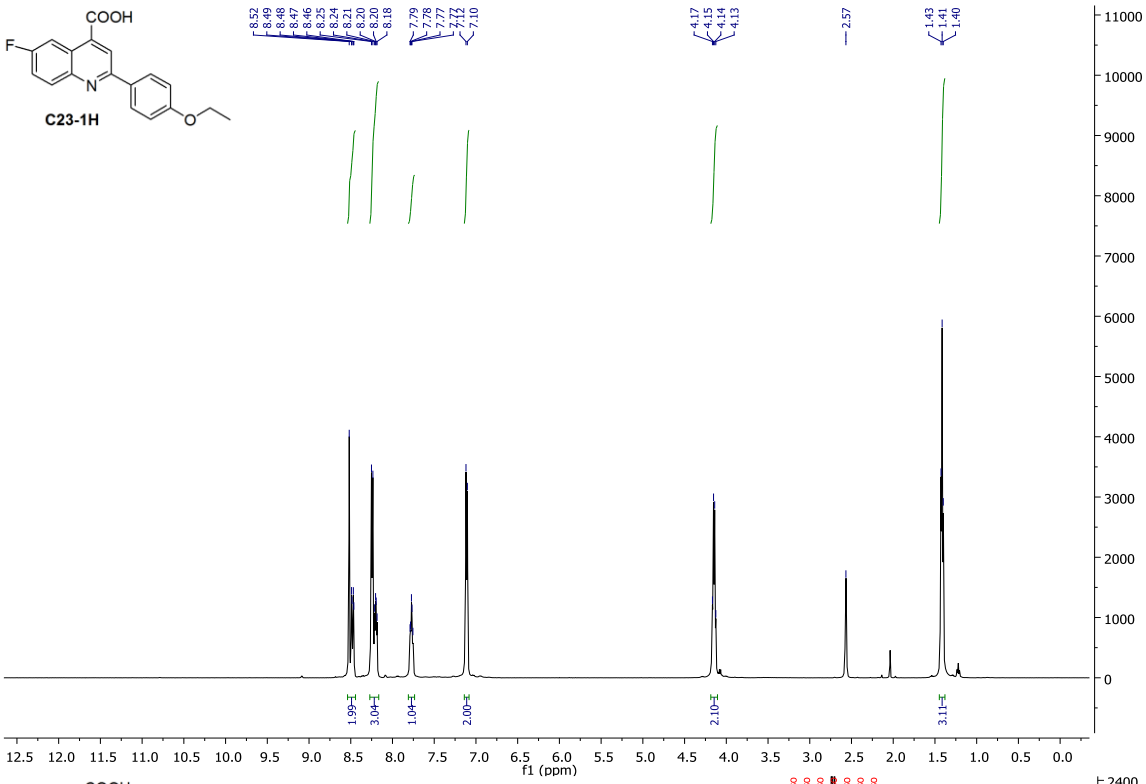

COOH
F
N
O
C20-13C
f1 (ppm)

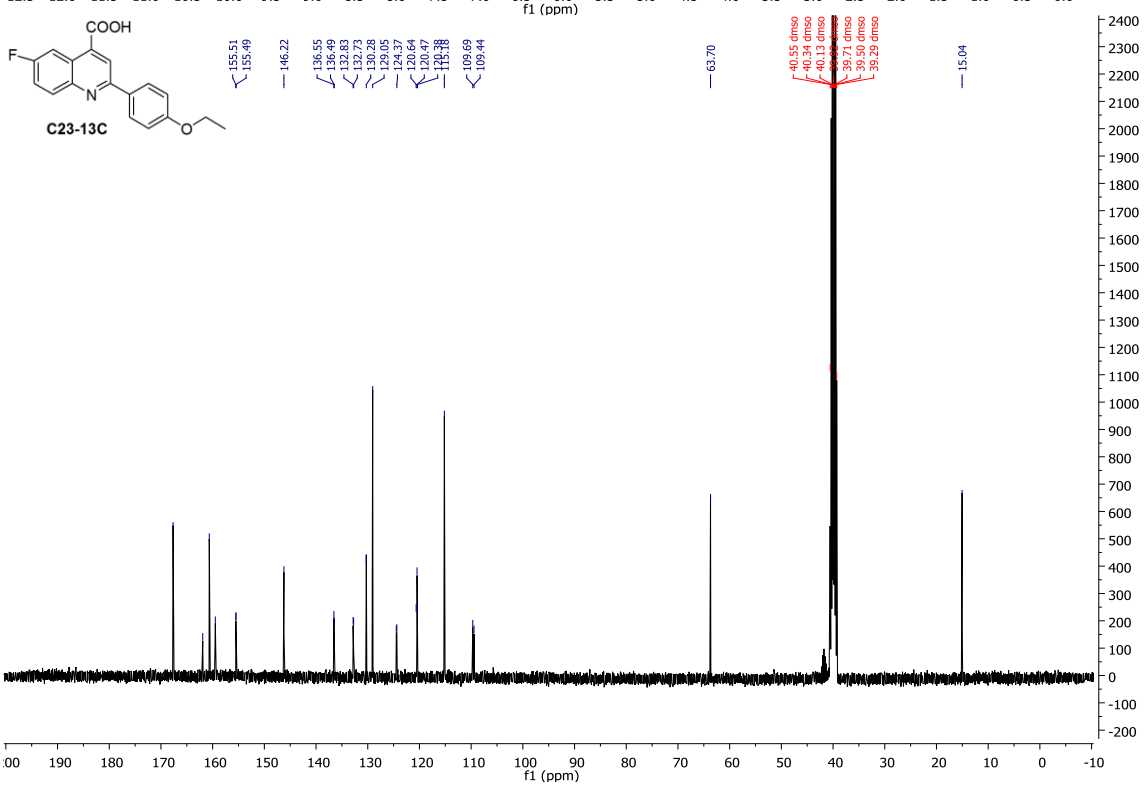

COOH
F
F
N
O
C21-1H
8.93
8.90
8.89
8.87
8.26
8.25
8.24
8.23
8.22
7.45
7.43
7.42
7.41
7.40
7.21
7.19
7.17
7.13
7.12
7.11
7.10
7.08
2.49
2.48
2.48
0.89
2.98
1.01
2.10
5.32
f1 (ppm)

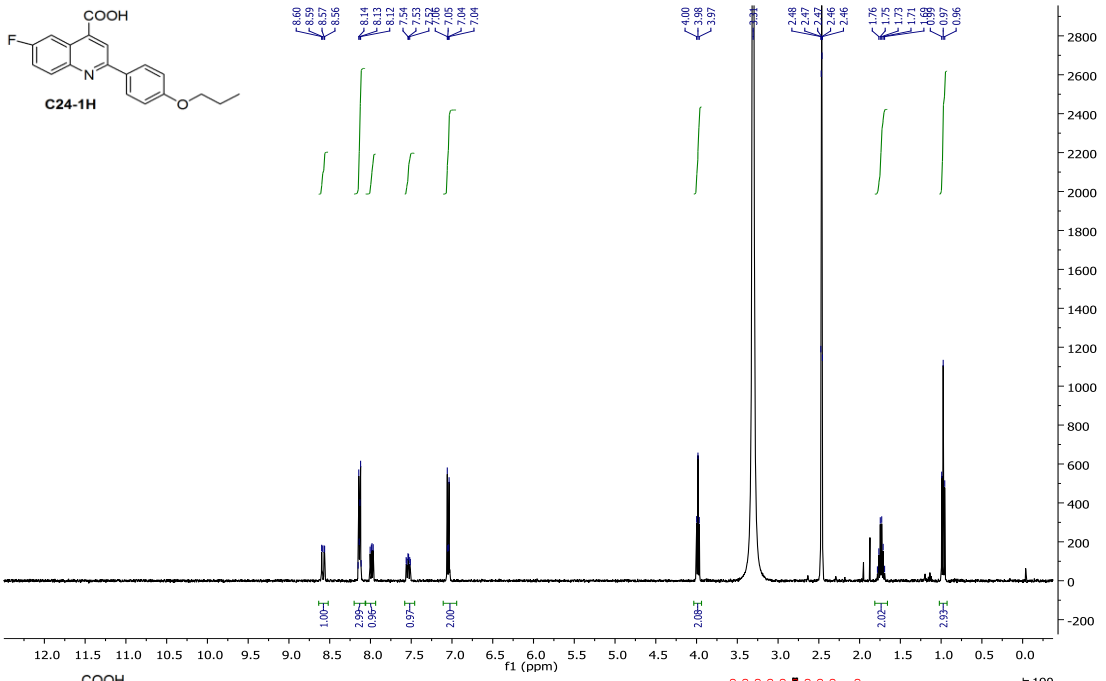

COOH
F
F
N
O
C21-13C
150.14
147.70
146.26
133.66
130.70
129.47
124.50
123.01
120.13
119.43
118.24
118.14
115.51
113.60
f1 (ppm)

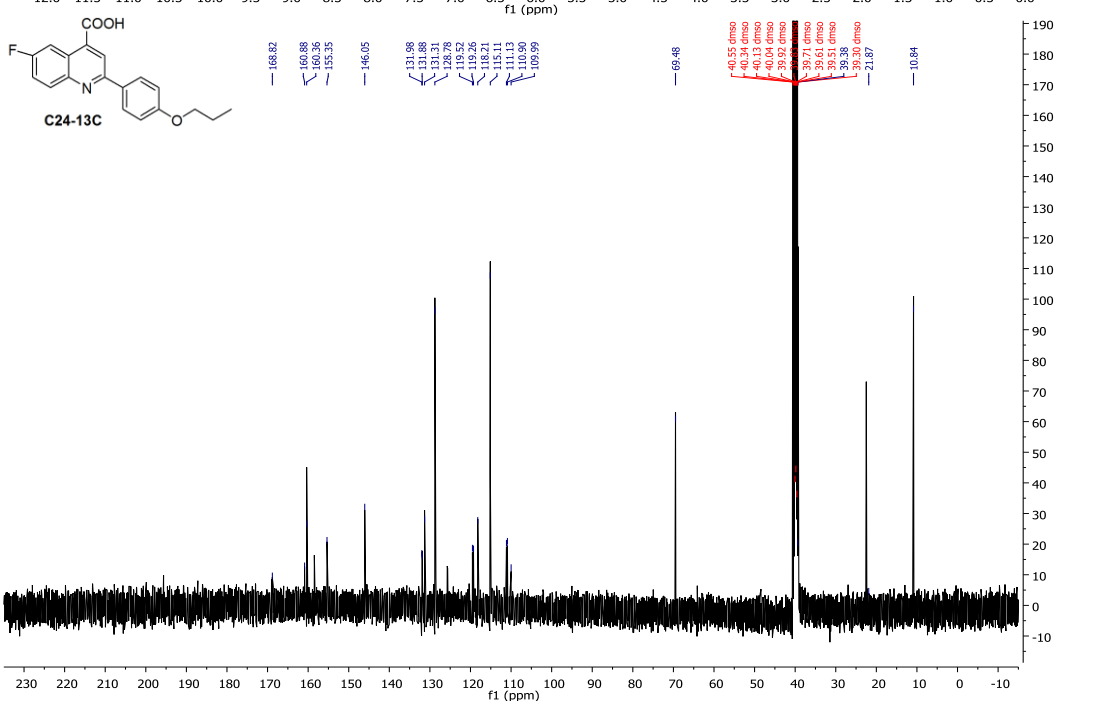

COOH
F
N
O
C22-1H
8.38
8.36
8.35
8.16
8.15
8.15
8.14
8.13
8.12
8.10
8.08
8.08
8.06
7.68
7.66
7.65
7.64
7.03
7.02
7.02
3.79
1.00
3.05
0.98
1.99
3.01
f1 (ppm)

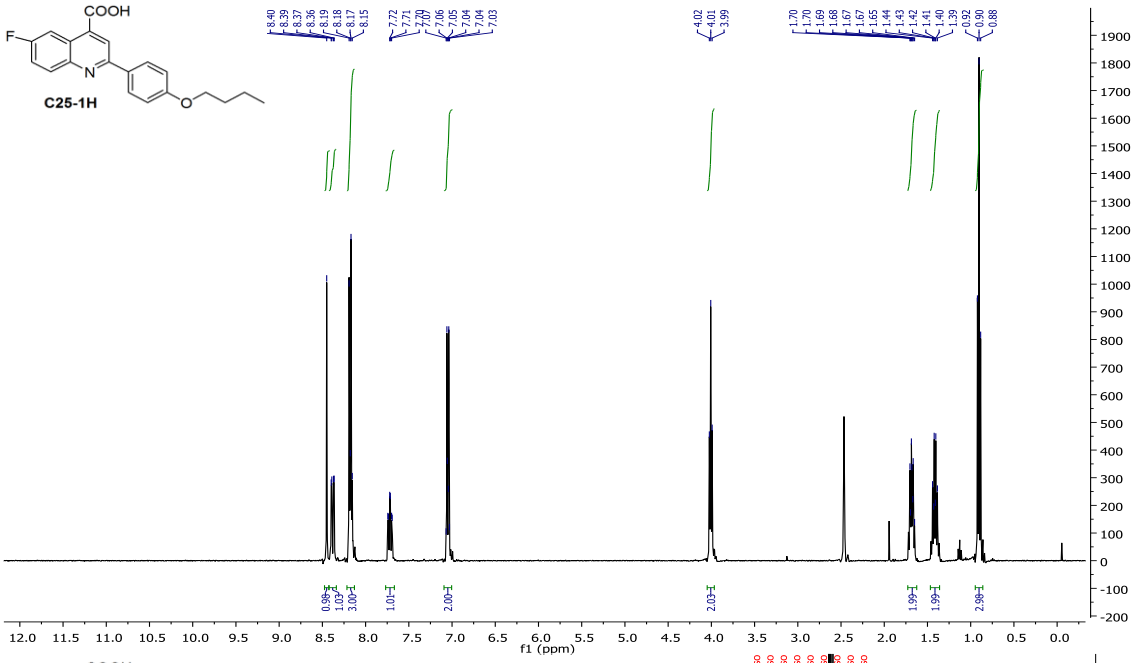

COOH
F
N
O
C22-13C
167.62
161.88
161.28
159.44
155.41
155.38
146.18
136.40
136.34
132.77
132.68
130.43
128.98
124.47
124.36
120.51
120.45
120.25
114.70
109.66
109.41
55.68
40.52 dmso
40.32 dmso
40.11 dmso
39.90 dmso
39.69 dmso
39.48 dmso
39.27 dmso
f1 (ppm)

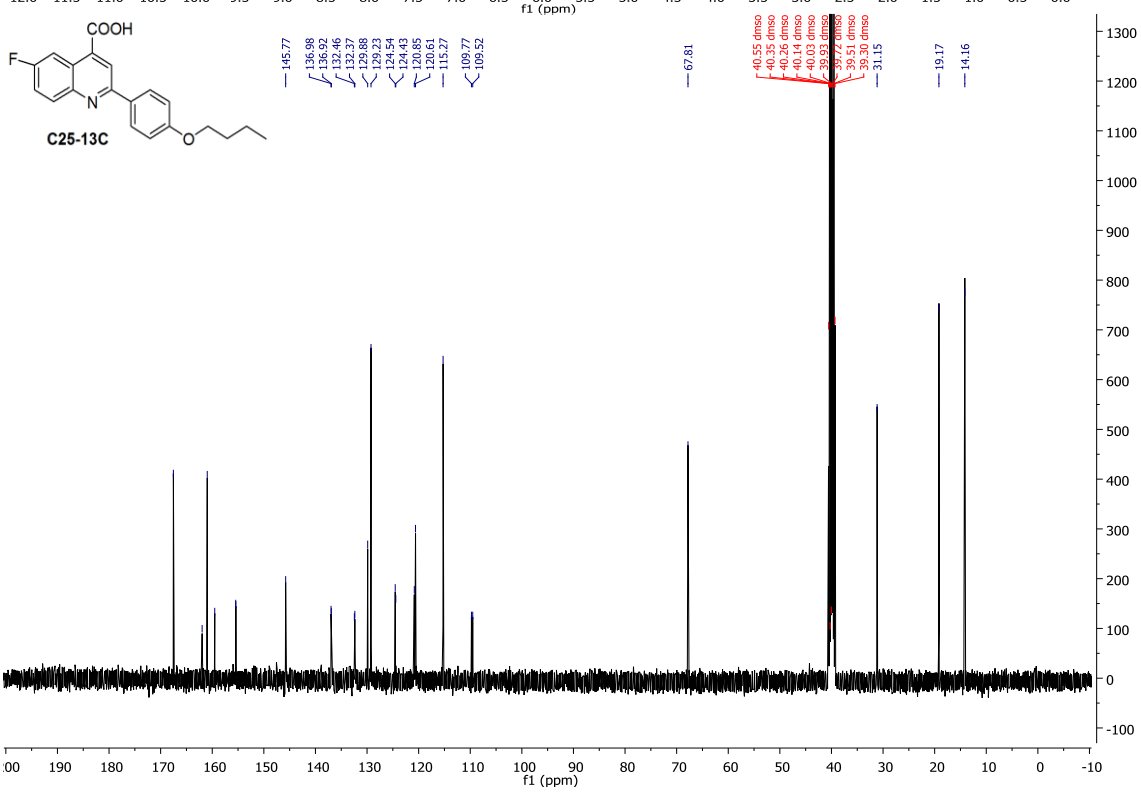

COOH
F
N
O
C23-1H
8.52
8.49
8.48
8.47
8.46
8.25
8.24
8.21
8.20
8.20
8.18
7.79
7.78
7.77
7.77
7.12
7.10
4.17
4.15
4.14
4.13
2.57
1.43
1.41
1.40
1.99
3.04
1.04
2.00
2.10
3.11
f1 (ppm)

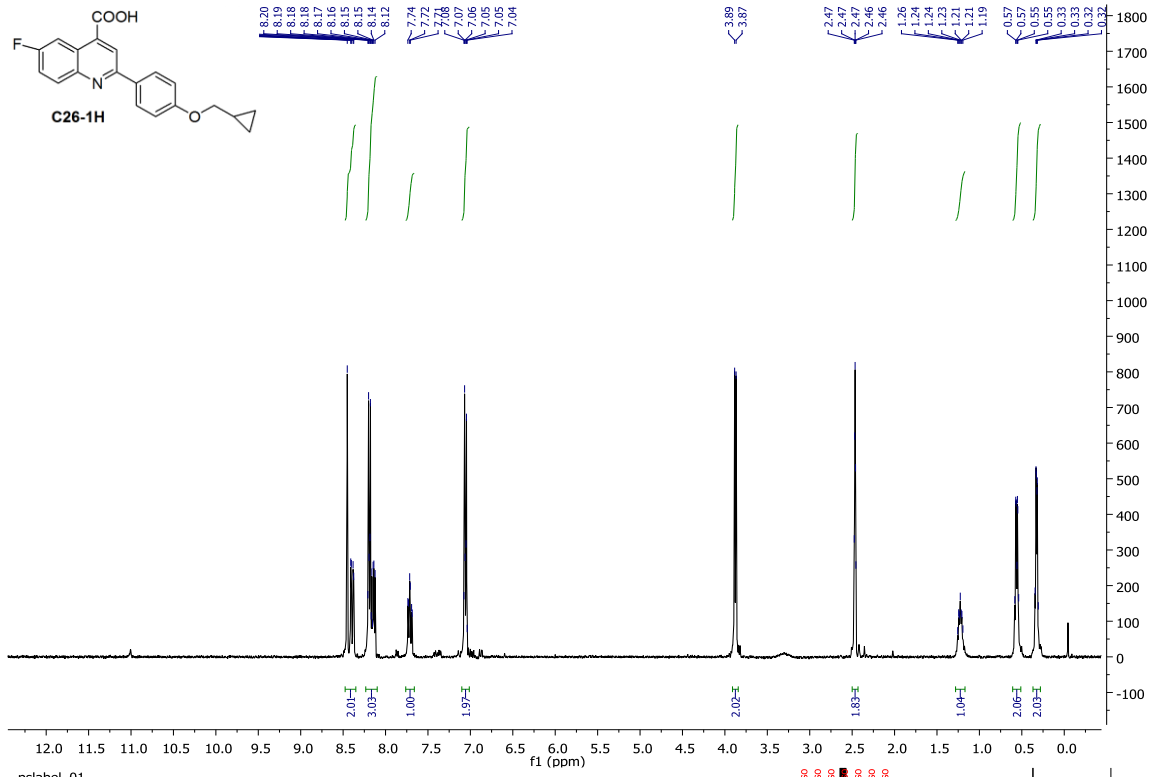

COOH
F
N
O
C23-13C
155.51
155.49
146.22
136.55
136.49
132.83
132.73
130.28
129.05
124.37
120.64
120.47
120.38
115.18
109.69
109.44
63.70
40.55 dmso
40.34 dmso
40.13 dmso
39.71 dmso
39.50 dmso
39.29 dmso
15.04
f1 (ppm)

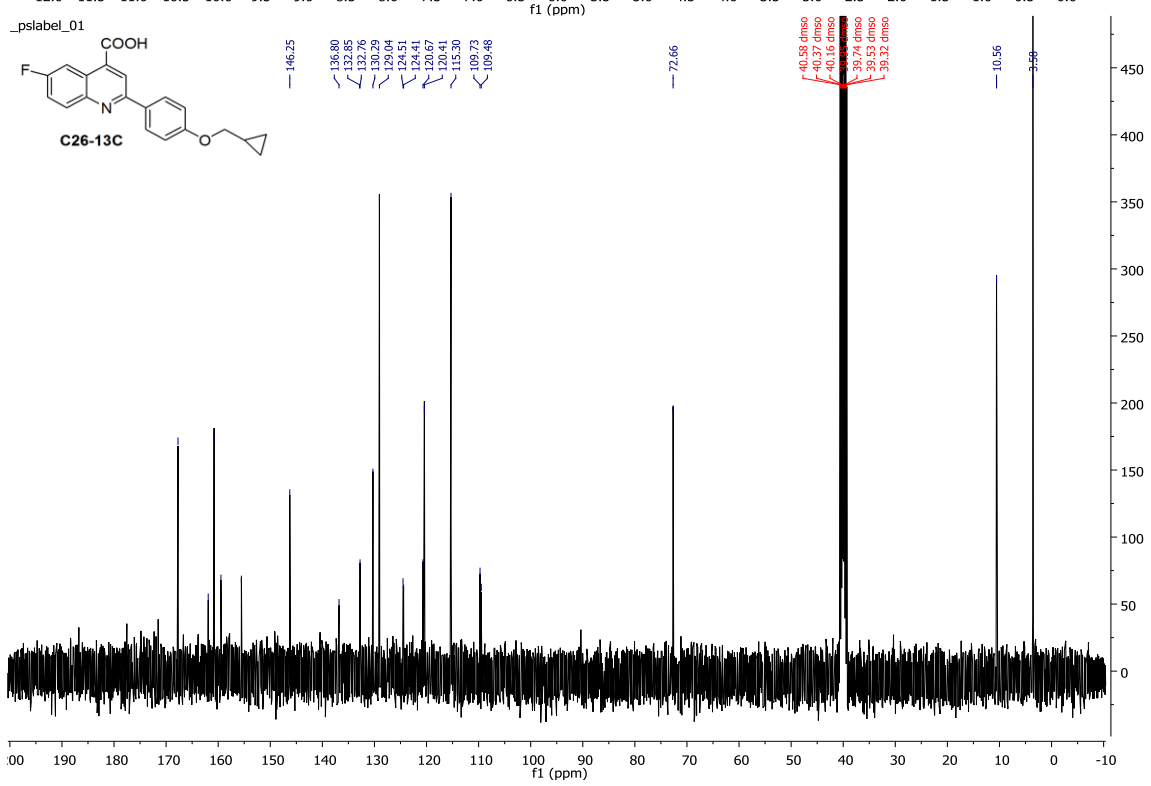

COOH
F
N
O
C24-1H
8.60
8.59
8.57
8.56
8.14
8.13
8.12
7.54
7.53
7.06
7.05
7.04
7.04
4.00
3.98
3.97
3.33
2.48
2.47
2.46
2.46
1.76
1.75
1.73
1.71
0.99
0.97
0.96
1.00
2.99
0.96
0.97
2.00
2.08
2.02
2.93
f1 (ppm)

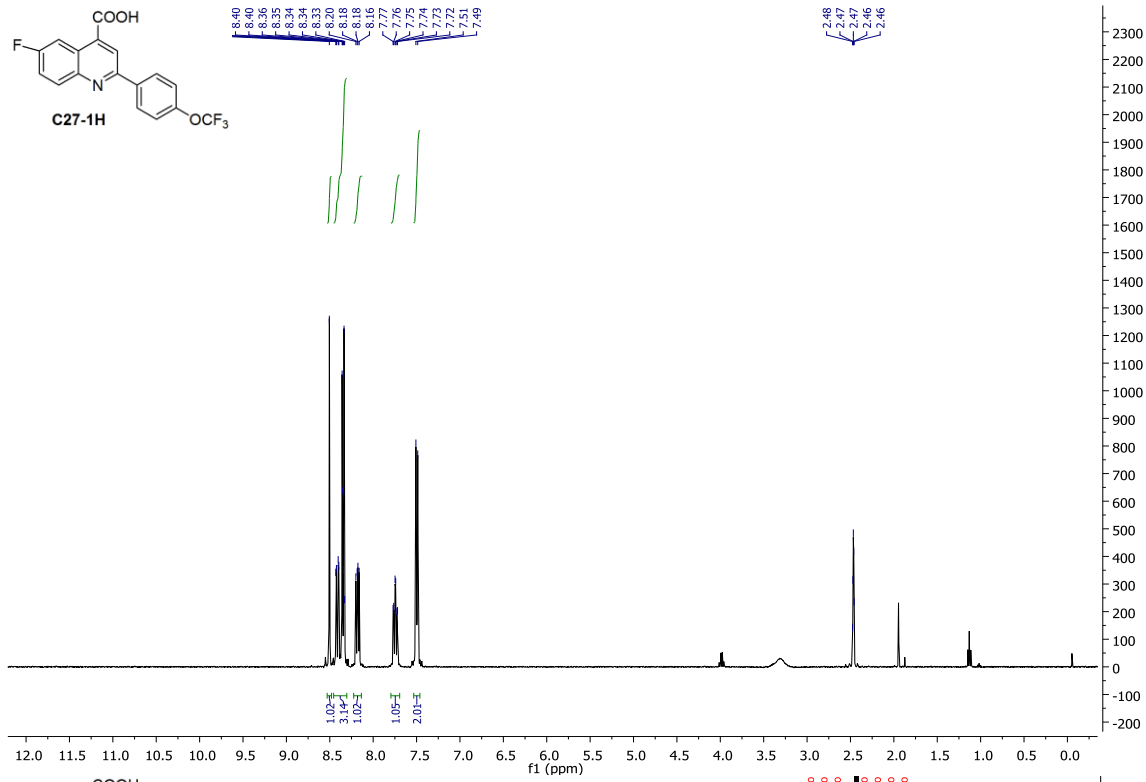

COOH
F
N
O
C24-13C
168.82
160.88
160.36
155.35
146.05
131.98
131.88
131.31
128.78
119.52
119.26
118.21
115.11
111.13
110.90
109.99
69.48
40.55 dmso
40.34 dmso
40.13 dmso
40.04 dmso
39.92 dmso
39.71 dmso
39.61 dmso
39.51 dmso
39.38
39.30 dmso
21.87
10.84
f1 (ppm)


COOH
F
N
O
C25-1H
8.40
8.39
8.37
8.36
8.19
8.18
8.17
8.15
7.72
7.71
7.70
7.07
7.06
7.05
7.04
7.04
7.03
4.02
4.01
3.99
1.70
1.70
1.69
1.68
1.67
1.67
1.65
1.44
1.43
1.42
1.41
1.40
1.39
0.92
0.90
0.88
0.99
1.03
3.00
1.01
2.00
2.03
1.99
1.99
2.98
f1 (ppm)


COOH
F
N
O
C25-13C
145.77
136.98
136.92
132.46
132.37
129.88
129.23
124.54
124.43
120.85
120.61
115.27
109.77
109.52
67.81
40.55 dmso
40.35 dmso
40.26 dmso
40.14 dmso
40.03 dmso
39.93 dmso
39.72 dmso
39.51 dmso
39.30 dmso
31.15
19.17
14.16
f1 (ppm)


COOH
F
N
O
C26-1H
8.20 8.19 8.18 8.18 8.17 8.16 8.15 8.15 8.14 8.12
7.74 7.72 7.71 7.08 7.07 7.06 7.05 7.04
3.89 3.87
2.47 2.47 2.47 2.46 2.46
1.26 1.24 1.24 1.23 1.21 1.21 1.19
0.57 0.57 0.55 0.55 0.33 0.33 0.32 0.32
2.01 3.03 1.00 1.97 2.02 1.83 1.04 2.06 2.03
f1 (ppm)


_pslabel_01
COOH
F
N
O
C26-13C
146.25
136.80
132.85
132.76
130.29
129.04
124.51
124.44
120.67
120.41
115.30
109.73
109.48
72.66
40.58 dmso
40.37 dmso
40.16 dmso
39.95 dmso
39.74 dmso
39.53 dmso
39.32 dmso
10.56
3.58
f1 (ppm)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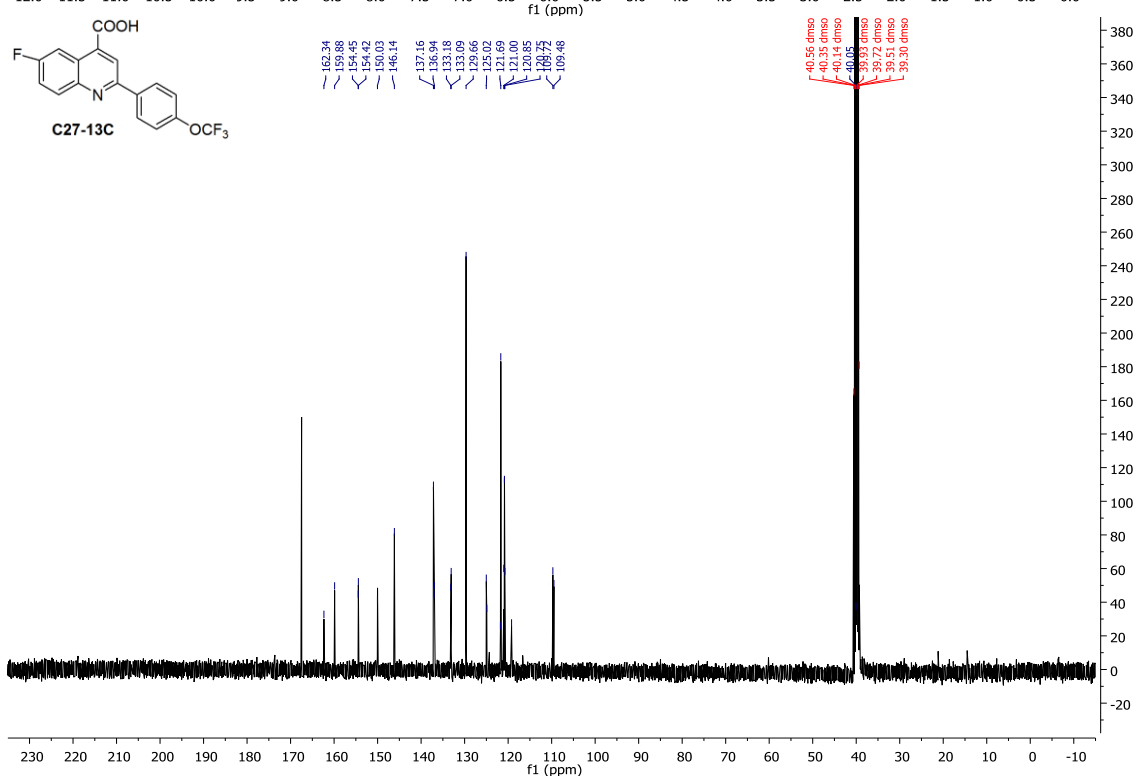
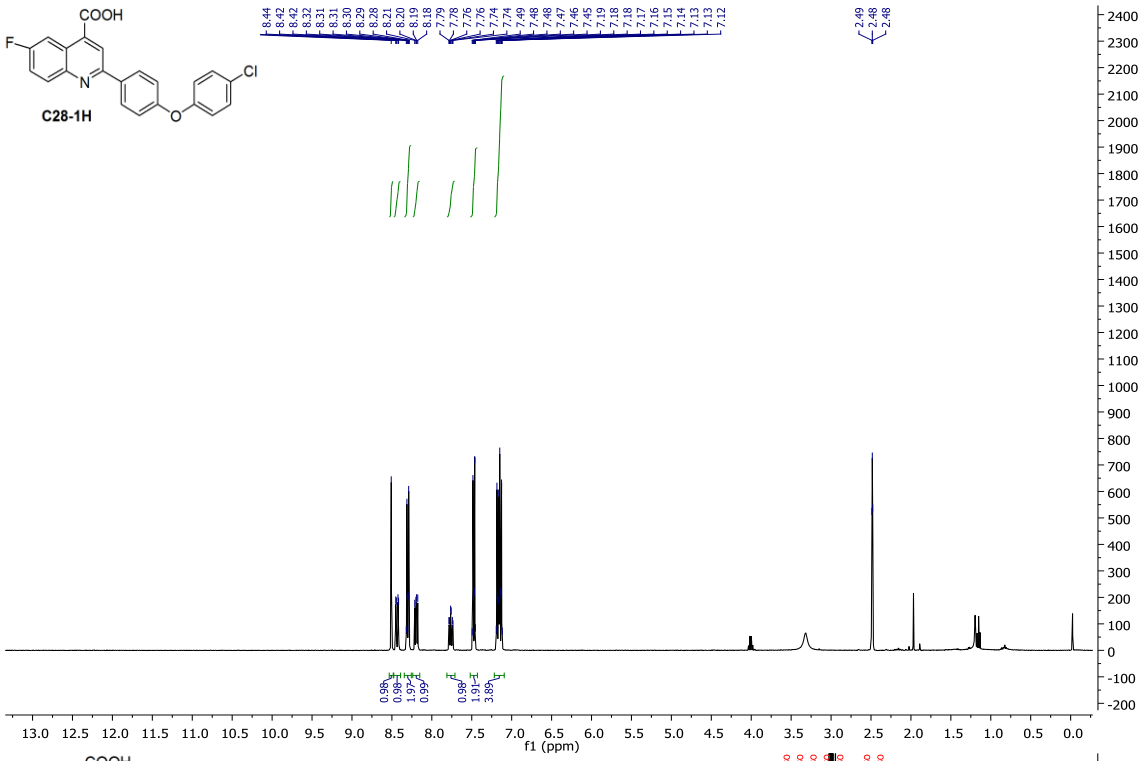
F
N
OCF3
C27-1H
8.40
8.40
8.36
8.35
8.34
8.34
8.33
8.20
8.18
8.18
8.16
7.77
7.76
7.75
7.74
7.73
7.72
7.51
7.49
2.48
2.47
2.47
2.46
2.46
1.02
3.14
1.02
1.05
2.01
f1 (ppm)


COOH
F
N
OCF3
C27-13C
162.34
159.88
154.45
154.42
150.03
146.14
137.16
136.94
133.18
133.09
129.66
125.02
121.69
121.00
120.85
109.72
109.48
40.56 dmso
40.35 dmso
40.14 dmso
39.93 dmso
39.72 dmso
39.51 dmso
39.30 dmso
f1 (ppm)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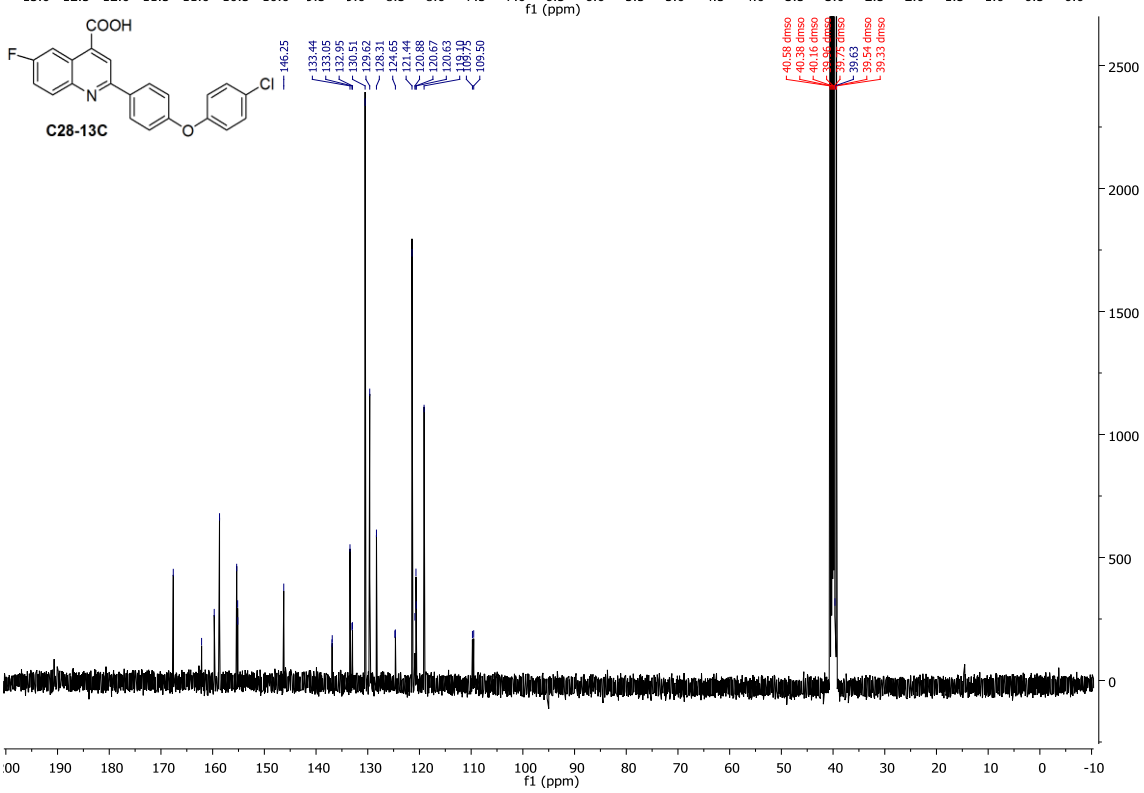
F
N
Cl
O
C28-1H
8.44
8.42
8.42
8.32
8.31
8.31
8.30
8.29
8.28
8.21
8.20
8.19
8.18
7.79
7.78
7.76
7.76
7.74
7.74
7.49
7.48
7.48
7.47
7.46
7.45
7.19
7.18
7.18
7.17
7.16
7.15
7.14
7.13
7.13
7.12
2.49
2.48
2.48
0.98
0.98
1.97
0.99
0.98
1.91
3.89
f1 (ppm)


COOH
F
N
Cl
O
C28-13C
146.25
133.44
133.05
132.95
130.51
129.62
128.31
124.65
121.44
120.88
120.67
120.63
109.50
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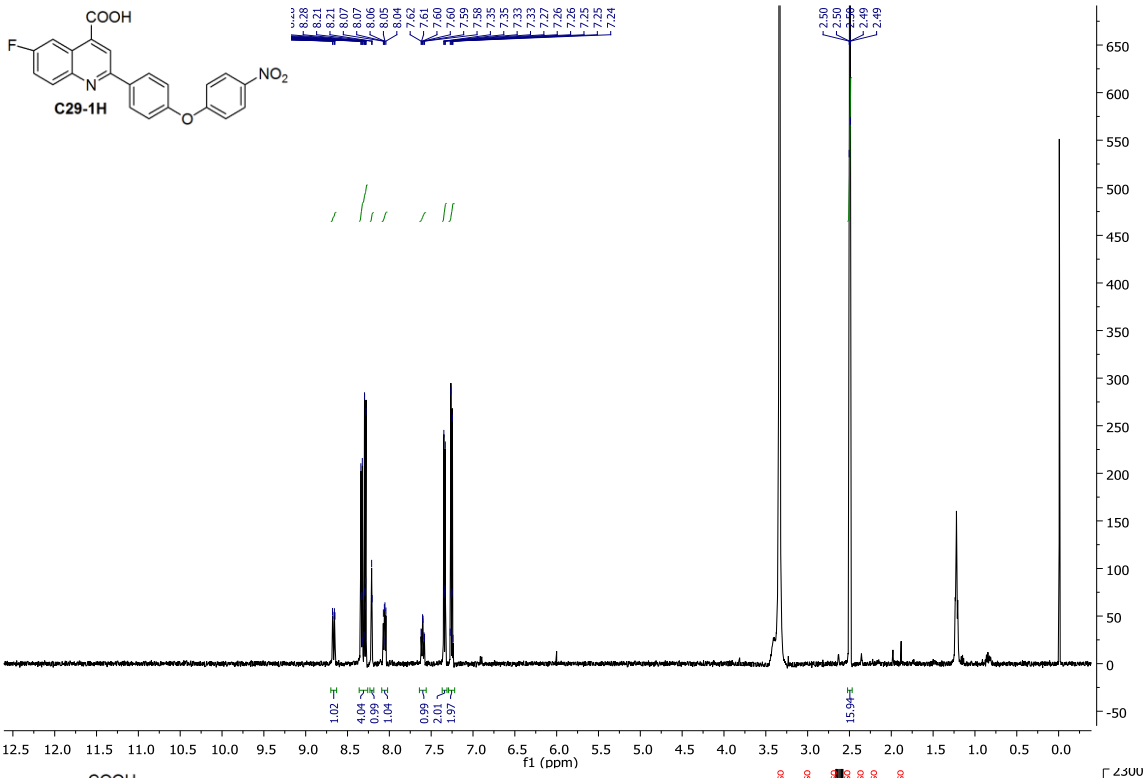
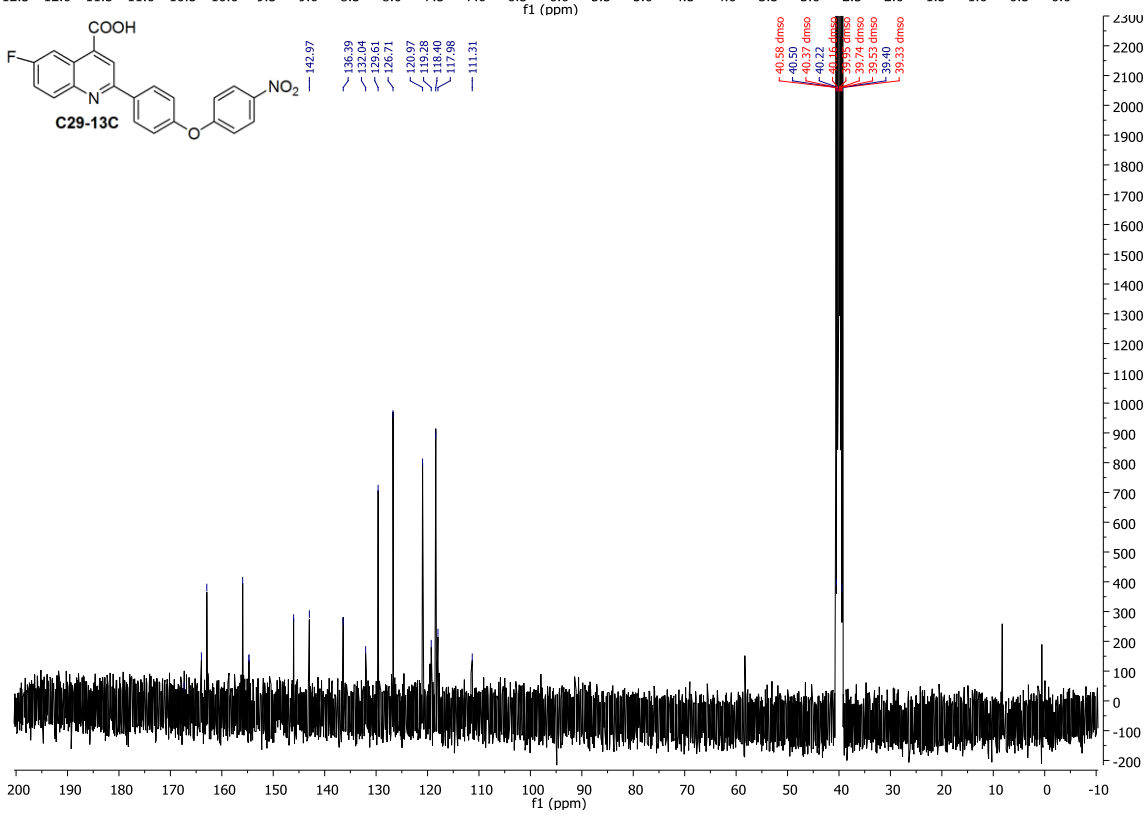
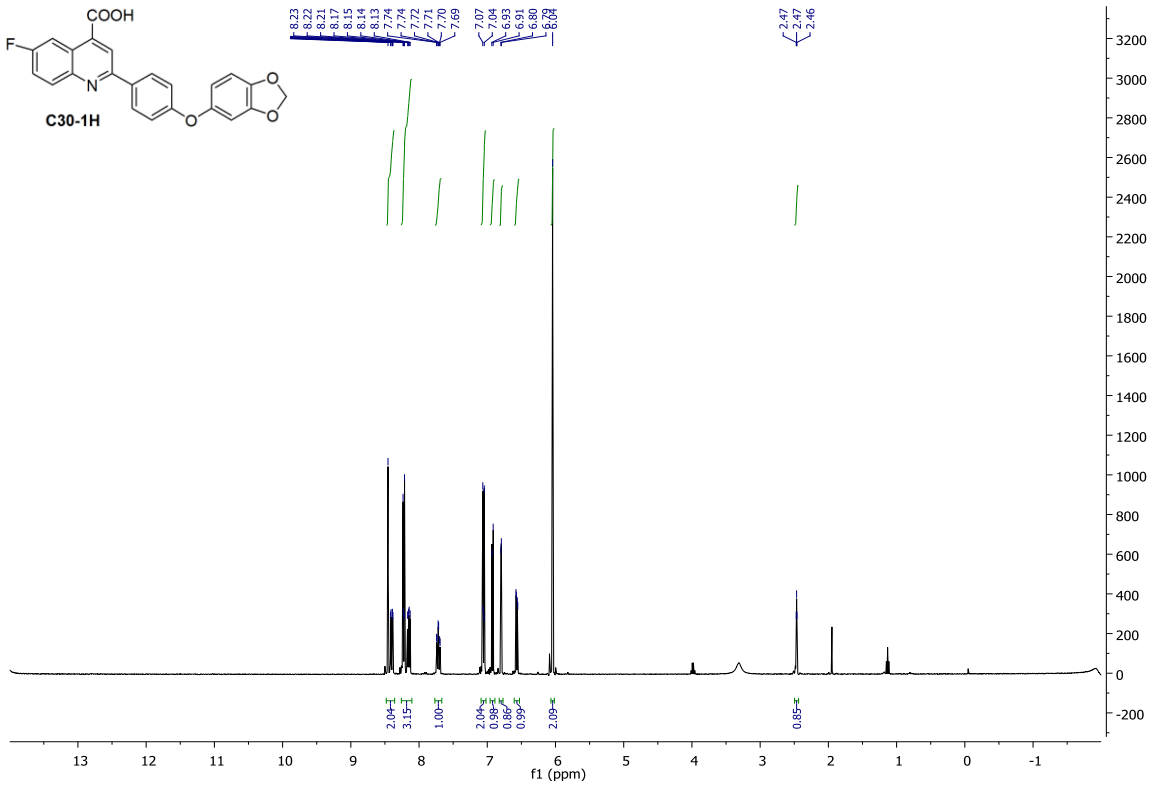
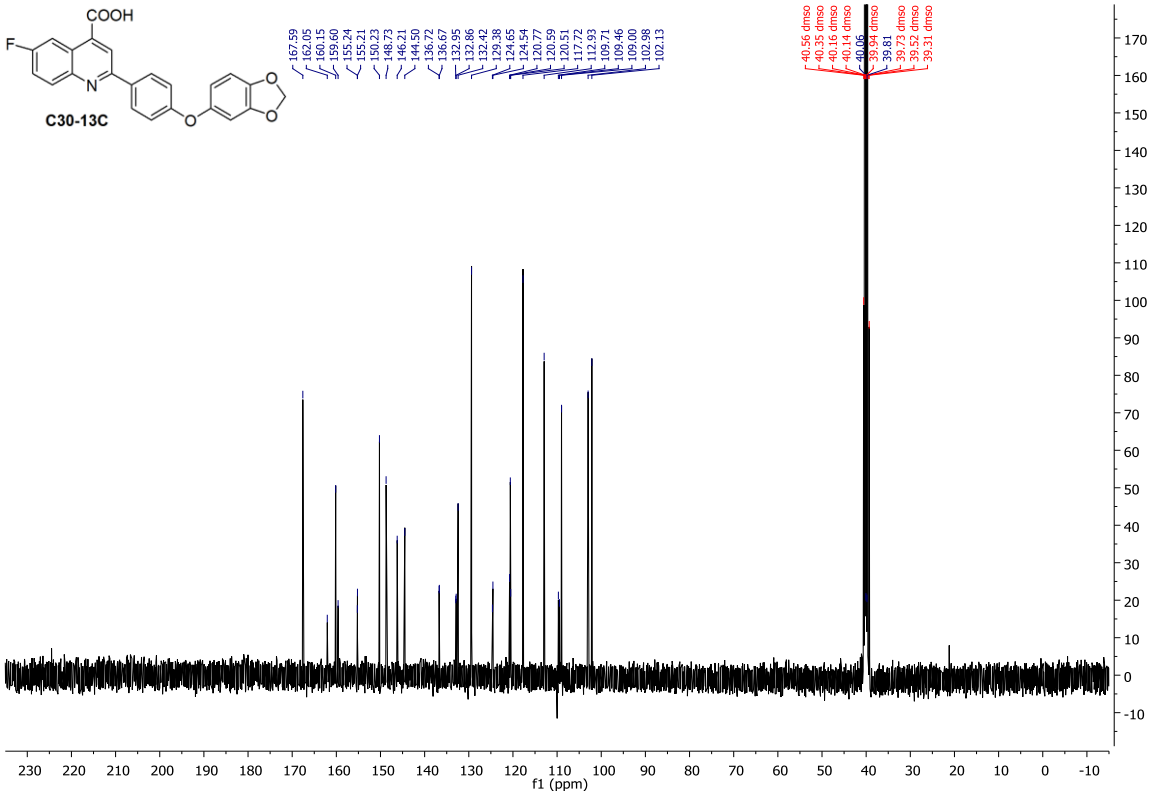
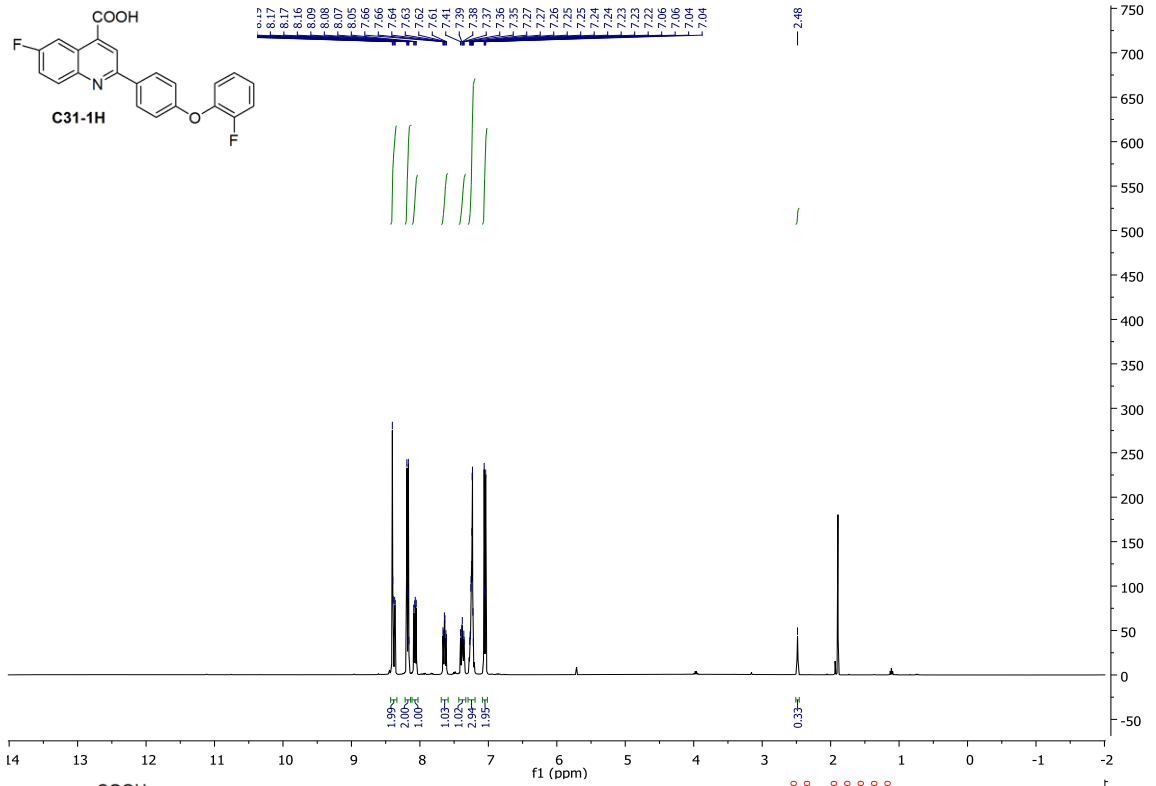
40.38 dmso
40.16 dmso
39.75 dmso
39.63
39.54 dmso
39.33 dmso
f1 (ppm)

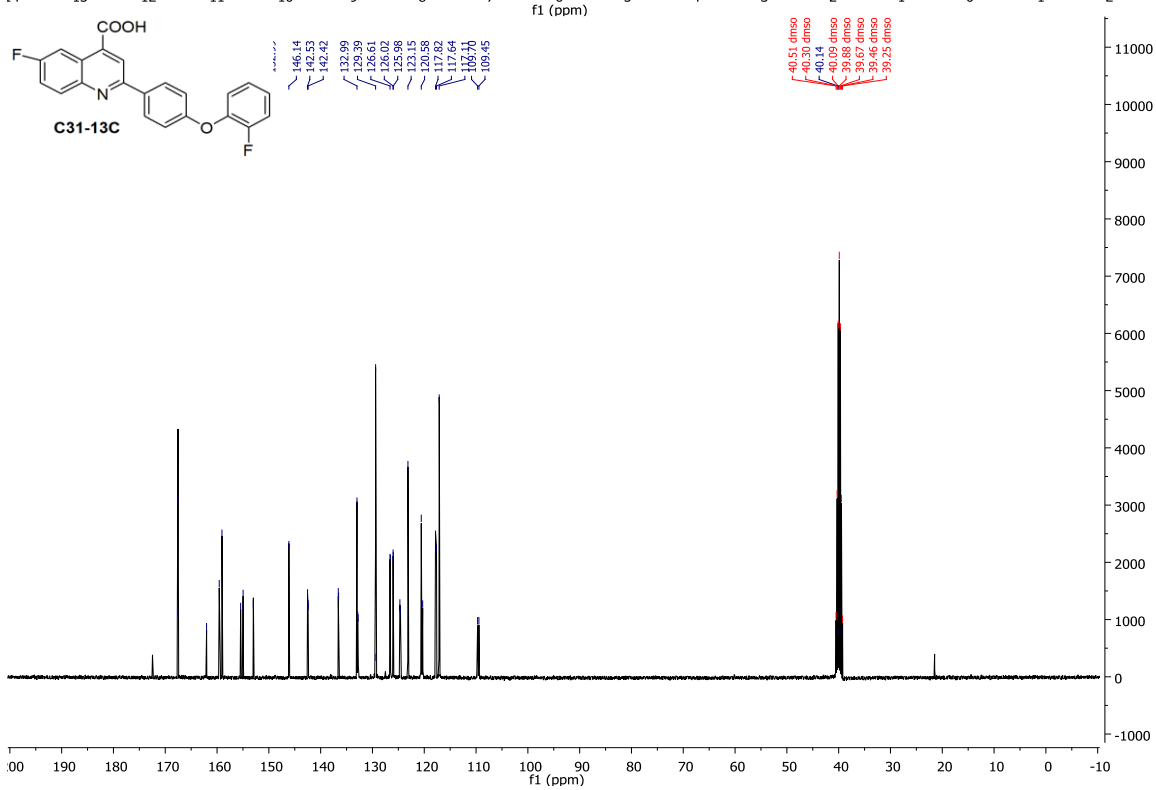

COOH
F
N
O
NO2
C29-1H
8.28
8.21
8.21
8.07
8.07
8.06
8.05
8.04
7.62
7.61
7.60
7.60
7.59
7.58
7.35
7.35
7.33
7.33
7.27
7.26
7.26
7.25
7.25
7.24
2.50
2.50
2.50
2.49
2.49
1.02
4.04
0.99
1.04
0.99
2.01
1.97
15.94
f1 (ppm)


COOH
F
N
O
NO2
C29-13C
142.97
136.39
132.04
129.61
126.71
120.97
119.28
118.40
117.98
111.31
40.58 dmso
40.50
40.37 dmso
40.22
39.95 dmso
39.74 dmso
39.53 dmso
39.40
39.33 dmso
f1 (ppm)


COOH
F
N
O
O
O
C30-1H
8.23
8.22
8.21
8.17
8.15
8.14
8.13
7.74
7.74
7.72
7.71
7.70
7.69
7.07
7.04
6.93
6.91
6.80
6.79
6.04
2.47
2.47
2.46
2.04
3.15
1.00
2.04
0.98
0.86
0.99
2.09
0.85
f1 (ppm)


COOH
F
N
O
O
O
C30-13C
167.59
162.05
160.15
159.60
155.24
155.21
150.23
148.73
146.21
144.50
136.72
136.67
132.95
132.86
132.42
129.38
124.65
124.54
120.77
120.59
120.51
117.72
112.93
109.71
109.46
109.00
102.98
102.13
40.56 dmso
40.35 dmso
40.16 dmso
40.14 dmso
40.06
39.94 dmso
39.81
39.73 dmso
39.52 dmso
39.31 dmso
f1 (ppm)


COOH
F
N
O
F
C31-1H
8.17
8.16
8.09
8.08
8.07
8.05
7.66
7.64
7.63
7.62
7.61
7.41
7.39
7.38
7.37
7.36
7.35
7.27
7.26
7.25
7.24
7.23
7.22
7.06
7.04
2.48
1.99
2.00
1.00
1.03
1.02
2.04
1.95
0.33
f1 (ppm)


COOH
F
N
O
F
C31-13C
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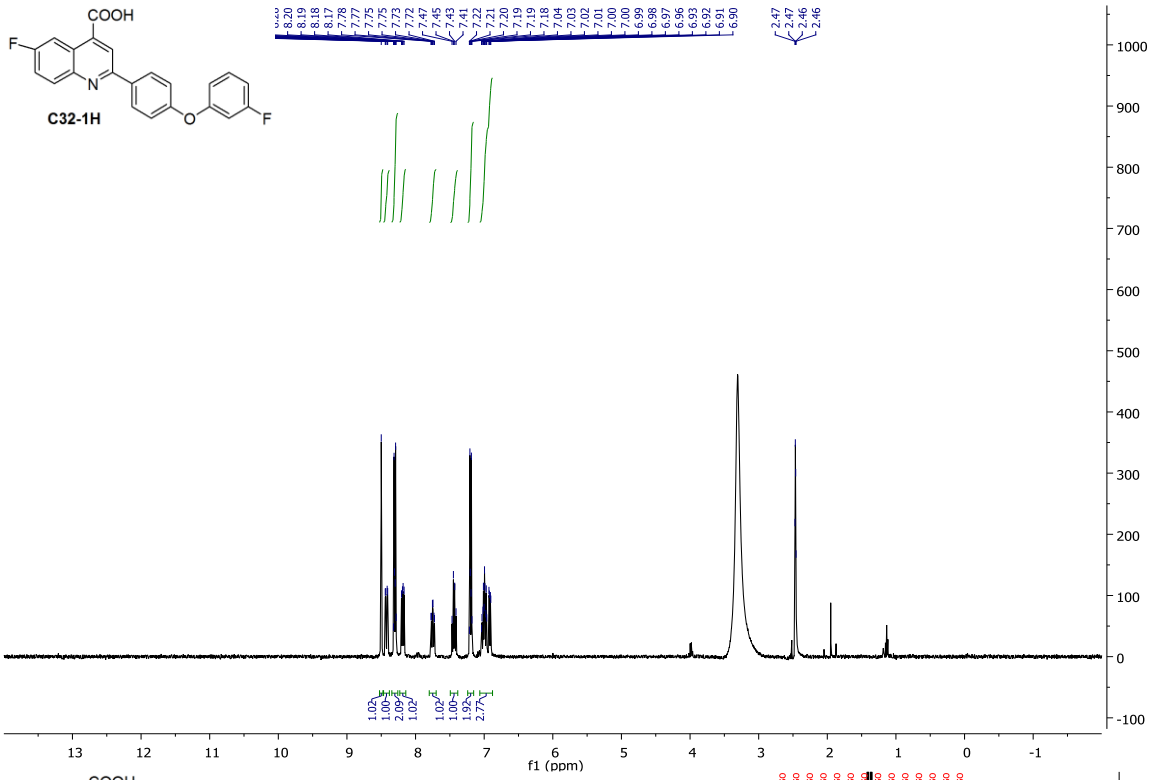
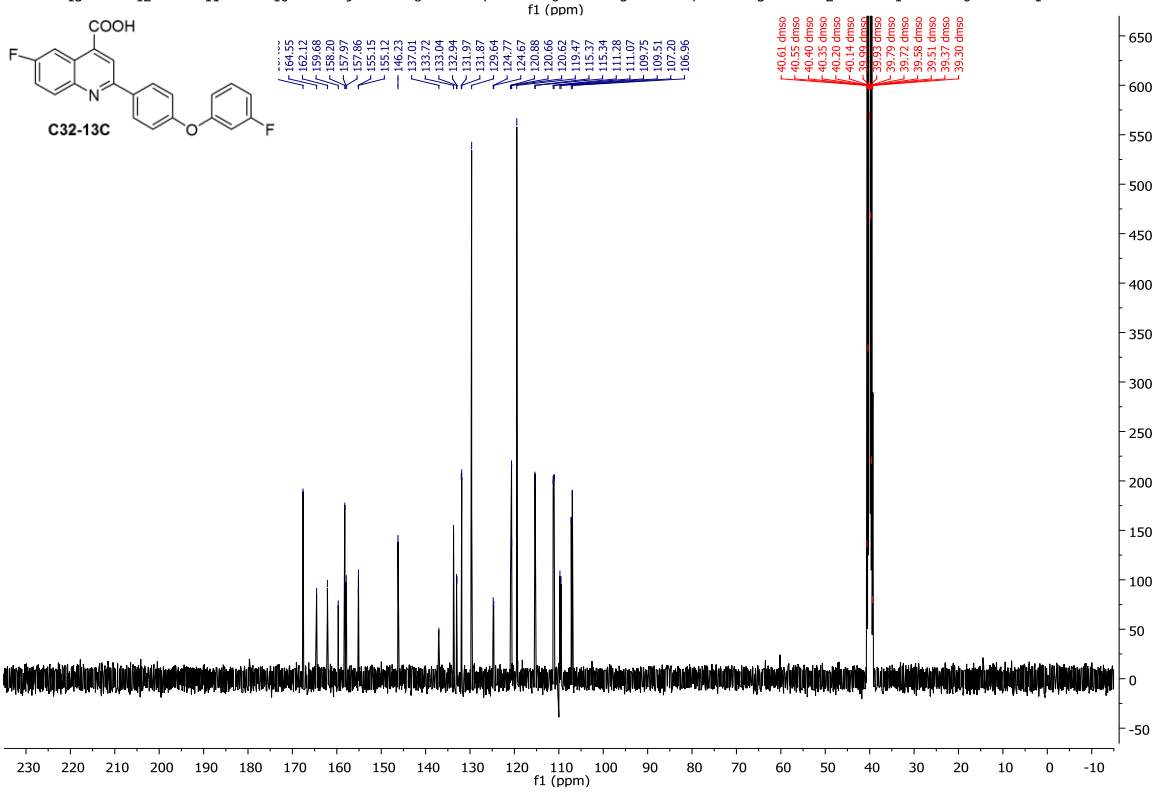
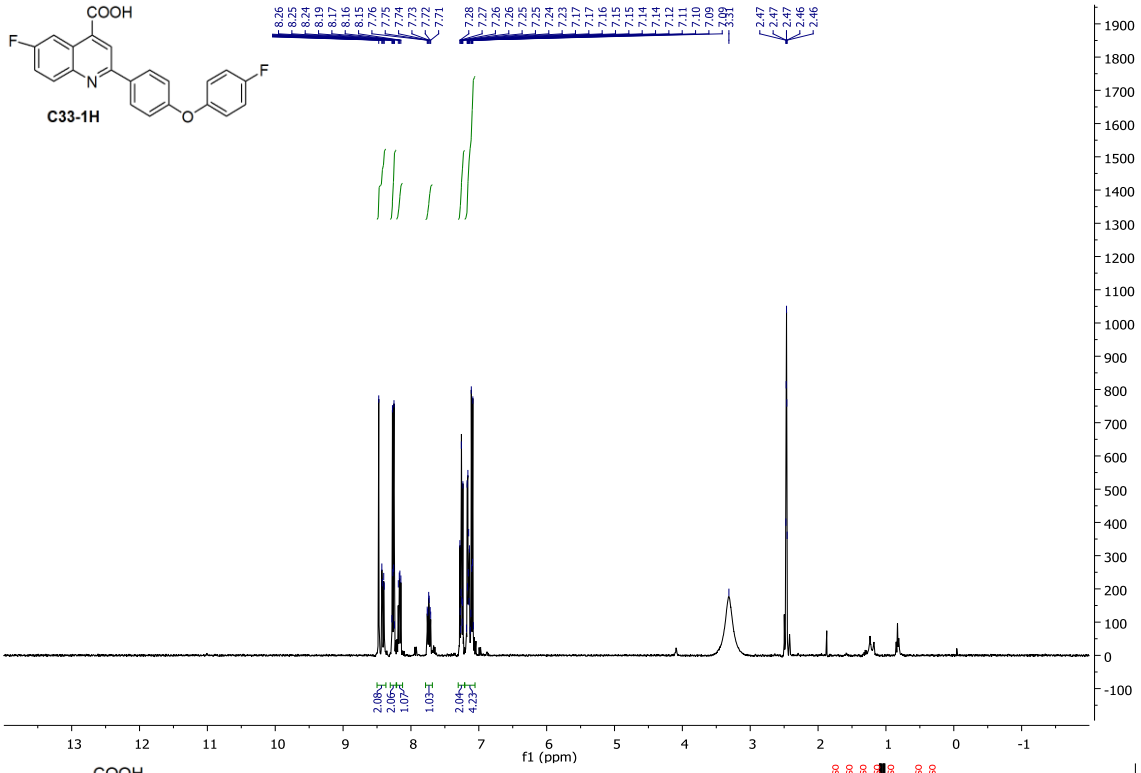
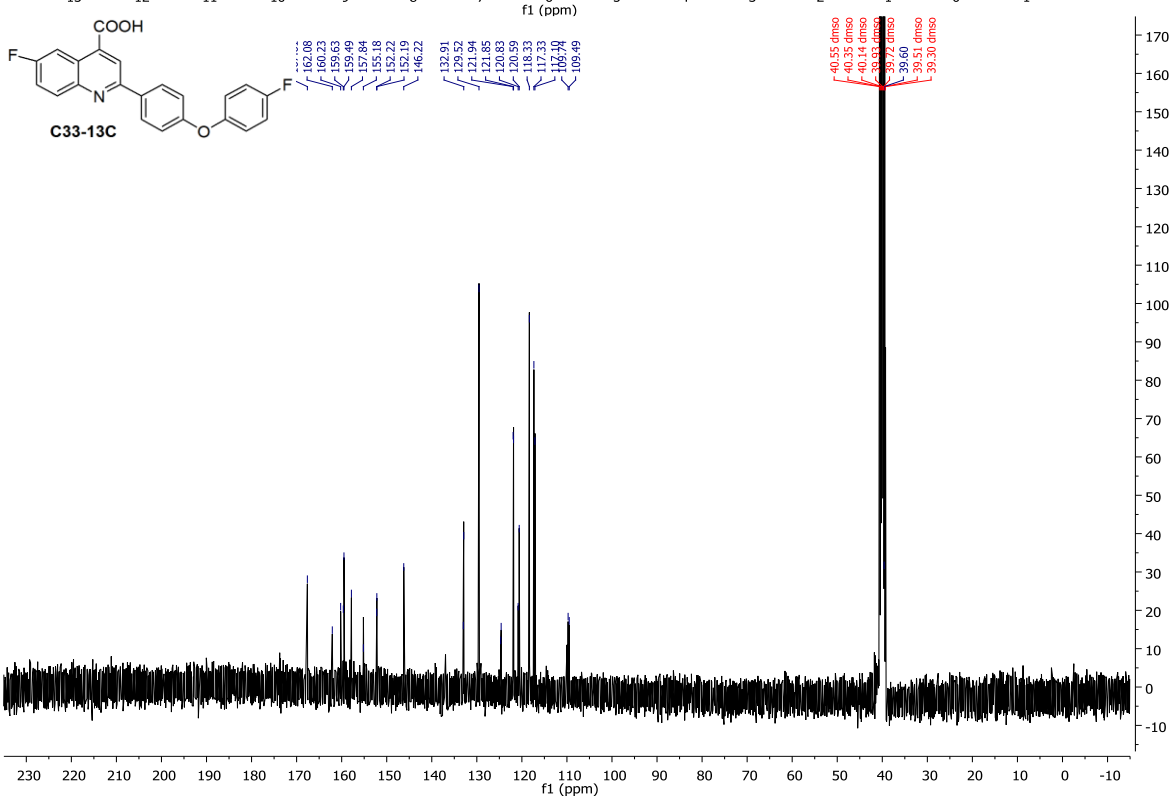
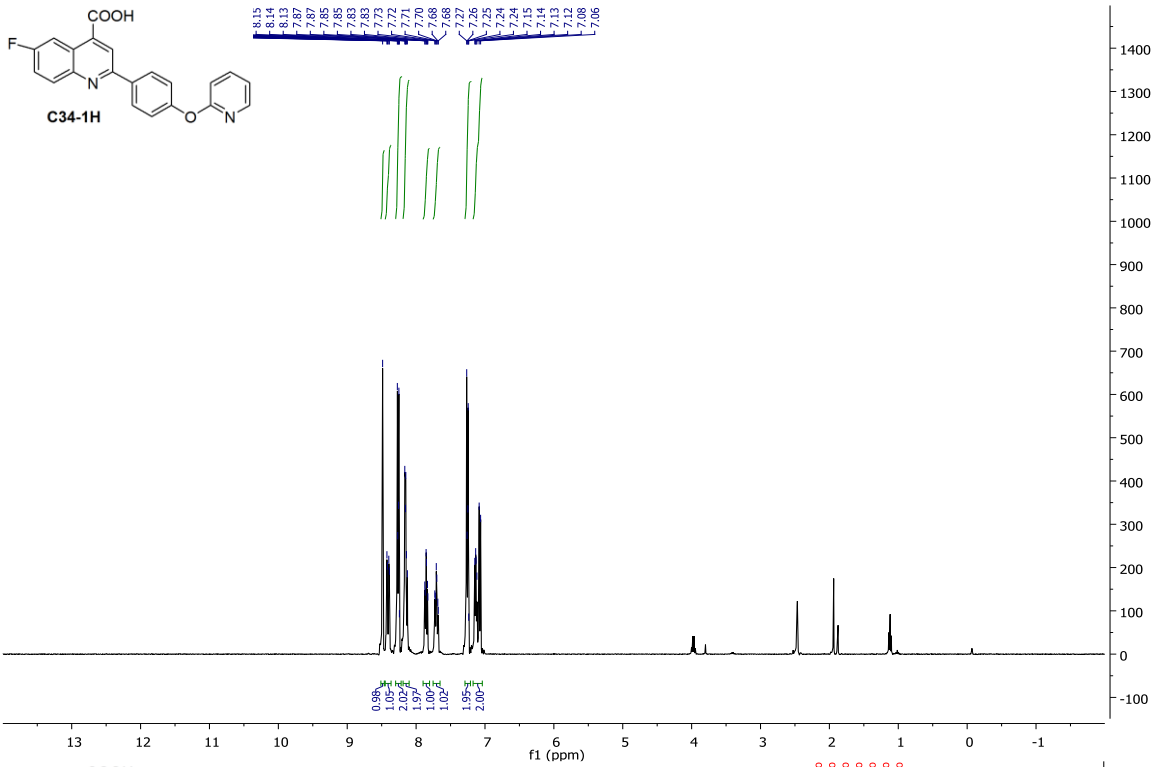
142.53
142.42
132.99
129.39
126.61
126.02
125.98
123.15
120.58
117.82
117.64
109.45
40.51 dmso
40.30 dmso
40.14
40.09 dmso
39.88 dmso
39.67 dmso
39.46 dmso
39.25 dmso
f1 (ppm)


COOH
F
N
O
F
C32-1H
f1 (ppm)


COOH
F
N
O
F
C32-13C
f1 (ppm)


COOH
F
N
O
F
C33-1H
8.26
8.25
8.24
8.19
8.17
8.16
8.15
7.76
7.75
7.74
7.73
7.72
7.71
7.28
7.27
7.26
7.26
7.25
7.25
7.24
7.23
7.17
7.17
7.16
7.15
7.15
7.14
7.14
7.12
7.11
7.10
7.09
3.33
2.47
2.47
2.47
2.46
2.46
2.08
2.06
1.07
1.03
2.04
4.23
f1 (ppm)


COOH
F
N
O
F
C33-13C
162.08
160.23
159.63
159.49
157.84
155.18
152.22
152.19
146.22
132.91
129.52
121.94
121.85
120.83
120.59
118.33
117.33
109.49
40.55 dmso
40.35 dmso
40.14 dmso
39.93 dmso
39.72 dmso
39.60
39.51 dmso
39.30 dmso
f1 (ppm)


COOH
F
N
O
N
C34-1H
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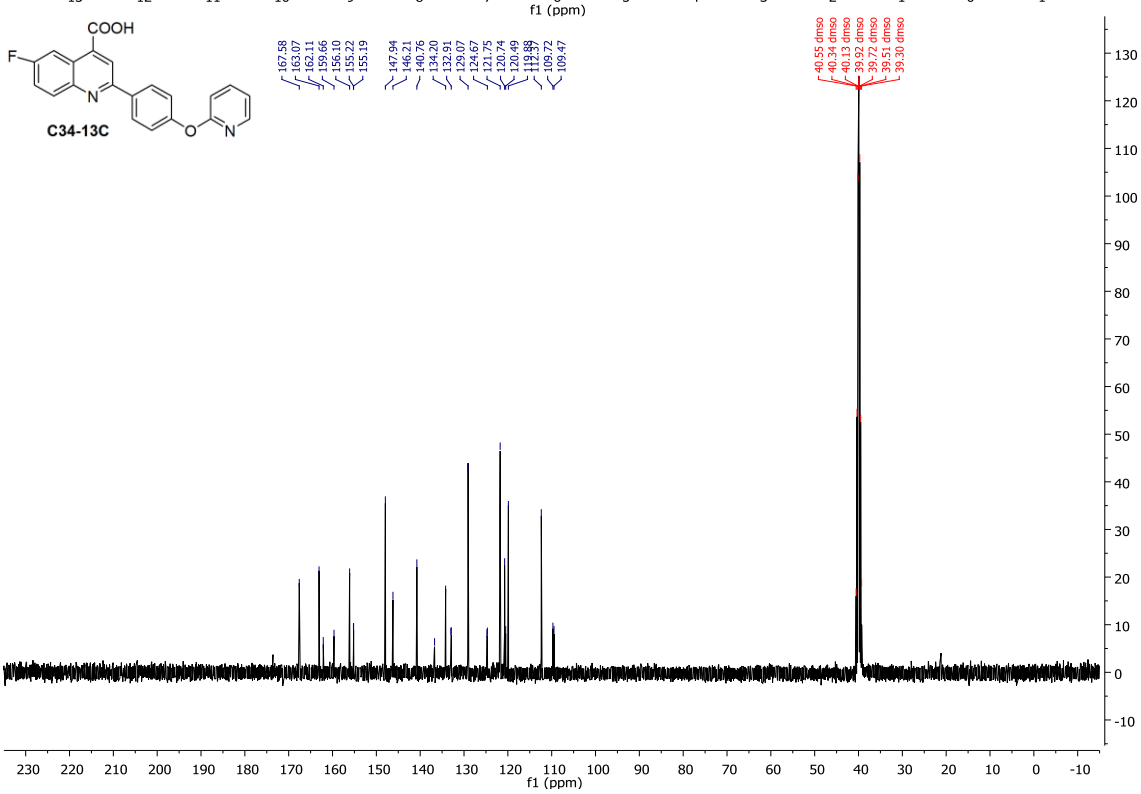
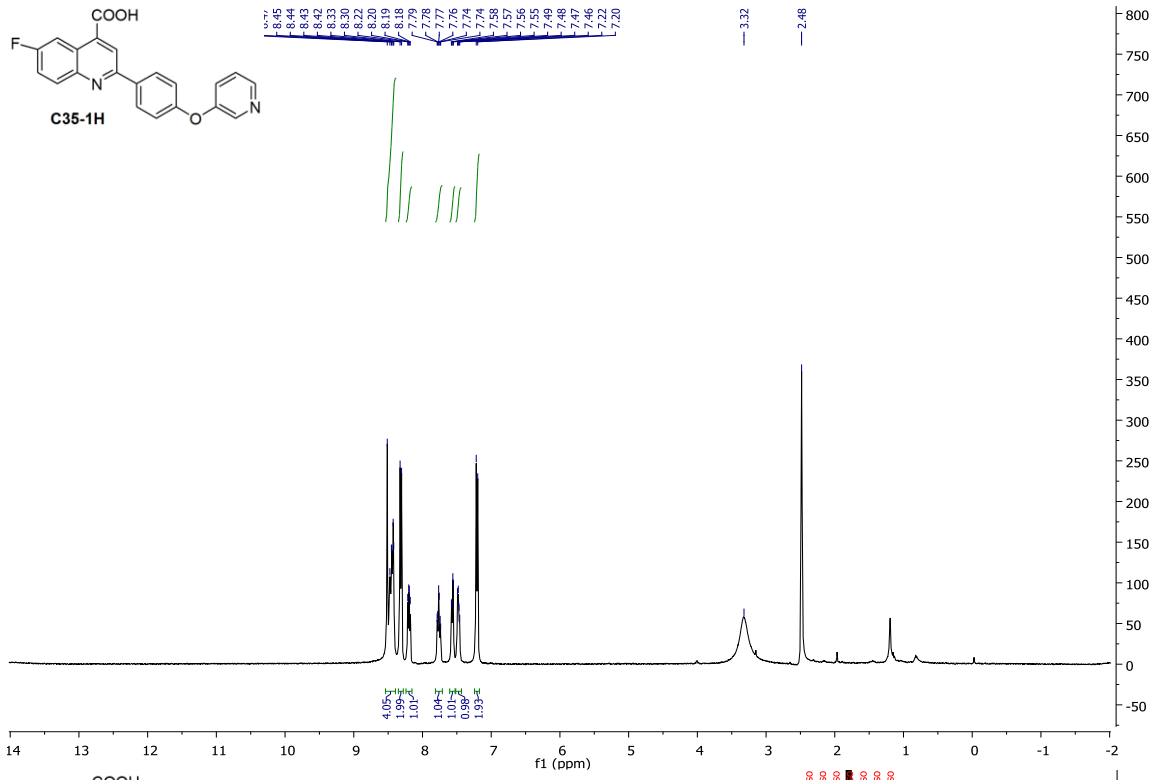
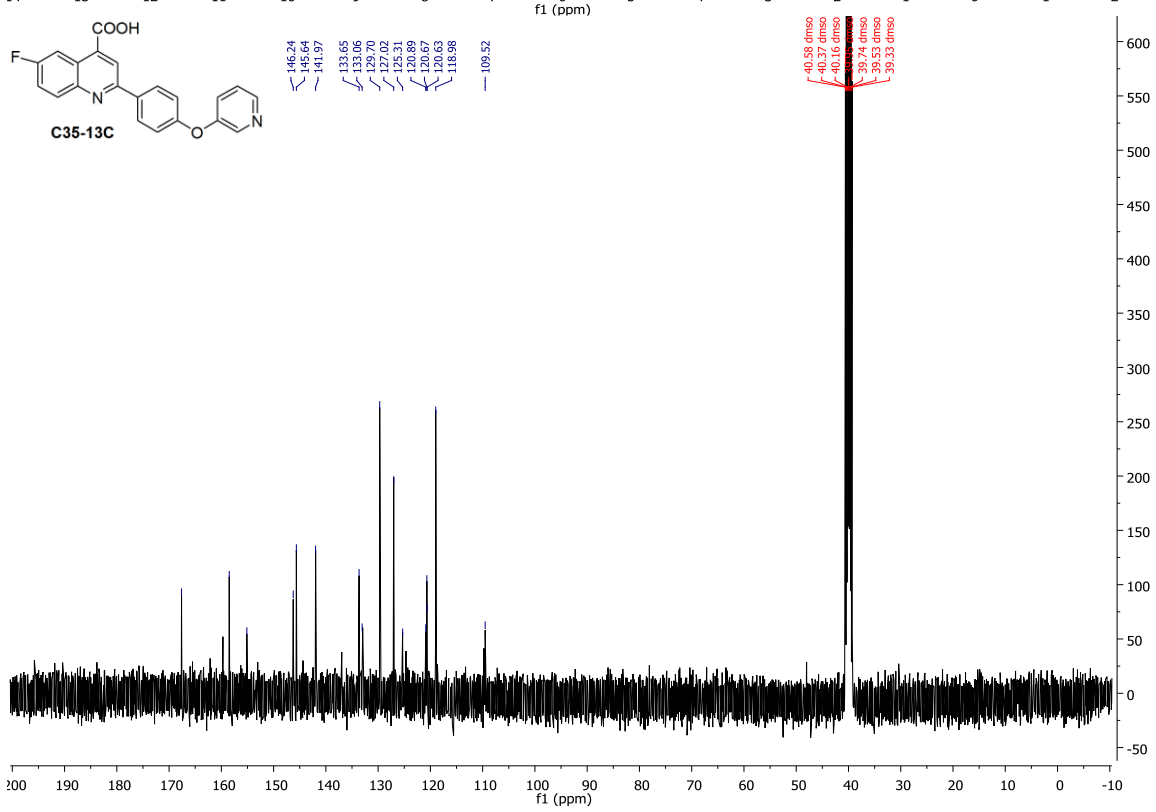
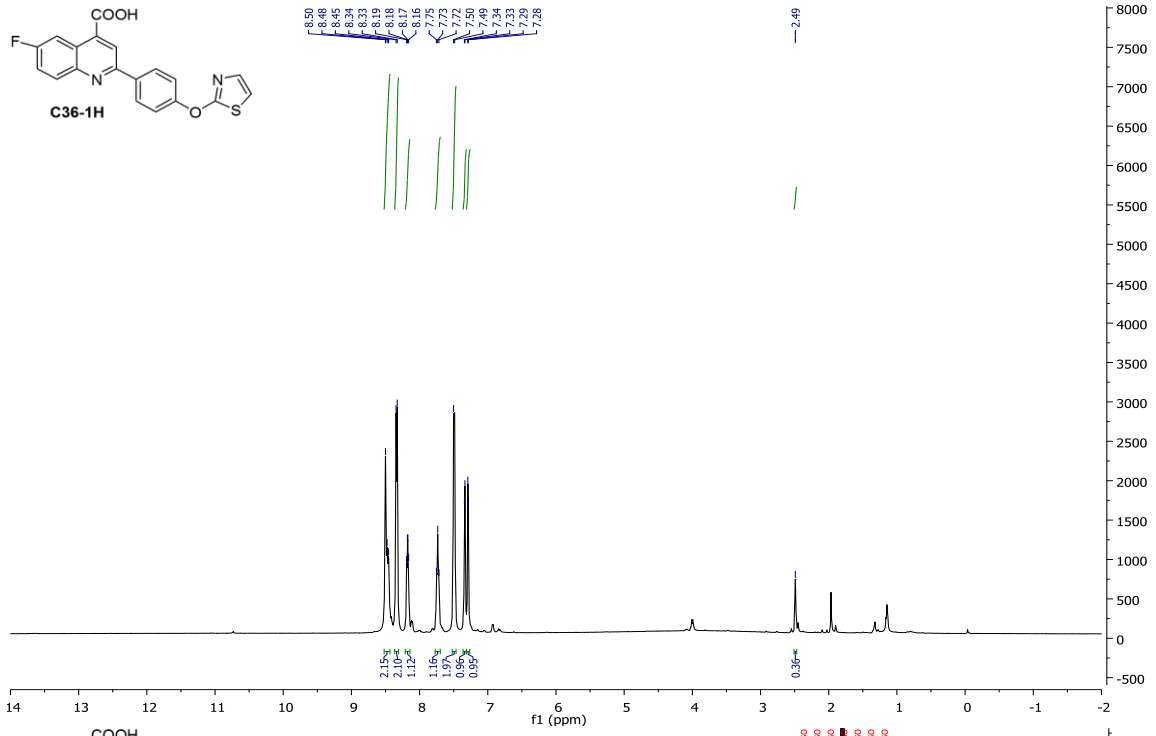
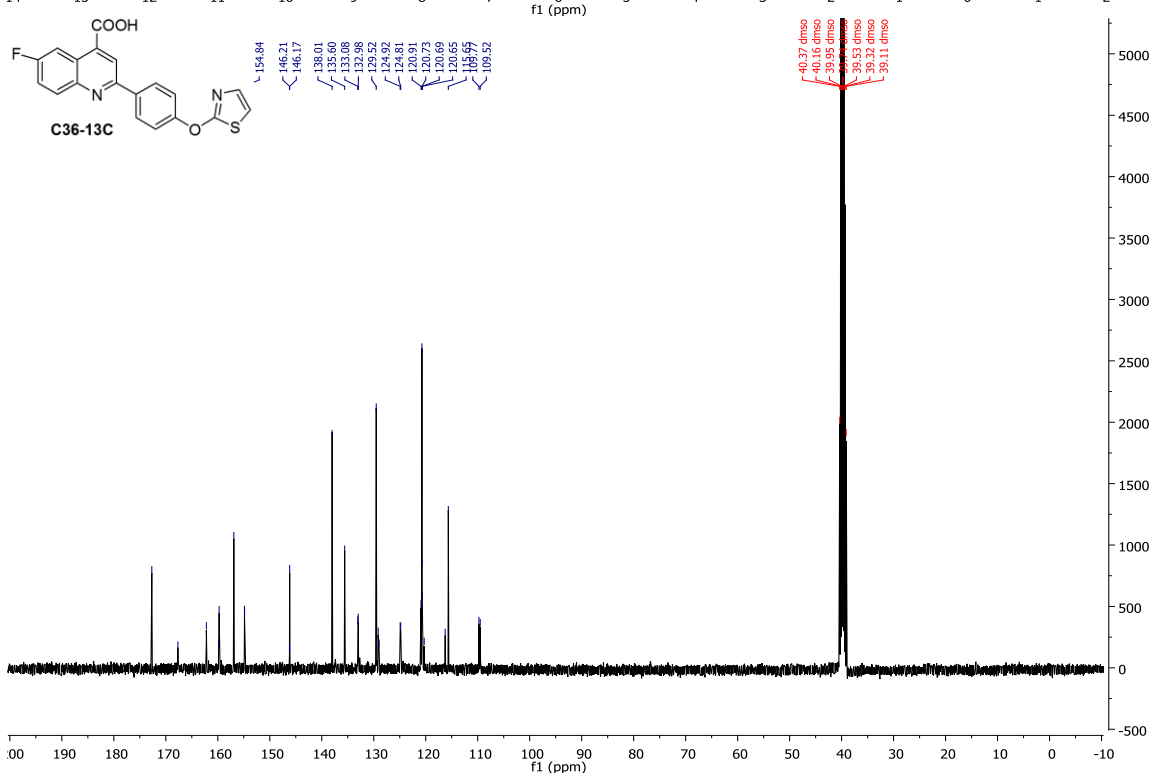
8.14
8.13
7.87
7.87
7.85
7.85
7.83
7.83
7.73
7.72
7.71
7.70
7.68
7.68
7.27
7.26
7.25
7.24
7.24
7.15
7.14
7.13
7.12
7.08
7.06
0.98
1.05
2.02
1.97
1.00
1.02
1.95
2.00
f1 (ppm)

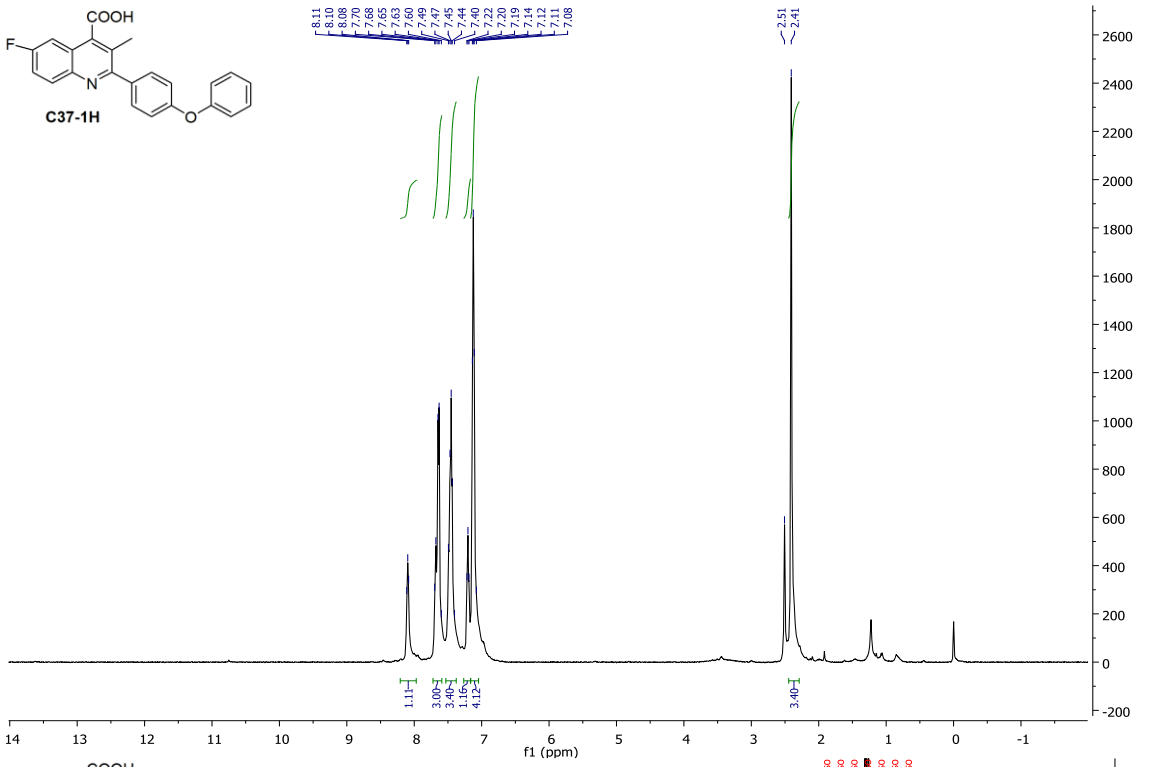

COOH
F
N
O
N
C34-13C
167.58
163.07
162.11
159.66
156.10
155.22
155.19
147.94
146.21
140.76
134.20
132.91
129.07
124.67
121.75
120.74
120.49
109.72
109.47
40.55 dmso
40.34 dmso
40.13 dmso
39.92 dmso
39.72 dmso
39.51 dmso
39.30 dmso
f1 (ppm)

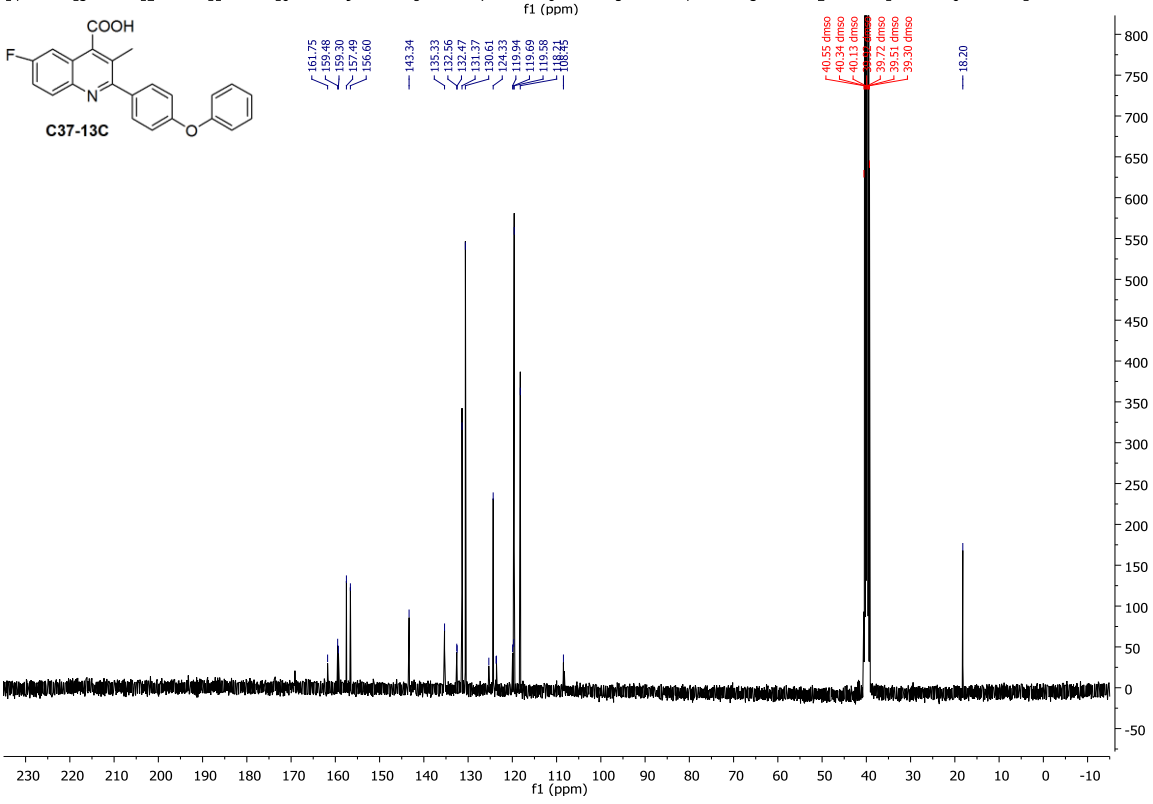

COOH
F
N
O
N
C35-1H
8.45
8.44
8.43
8.42
8.33
8.30
8.22
8.20
8.19
8.18
7.79
7.78
7.77
7.76
7.74
7.74
7.58
7.57
7.56
7.55
7.49
7.48
7.47
7.46
7.22
7.20
3.32
2.48
4.05
1.99
1.01
1.04
1.01
0.98
1.93
f1 (ppm)

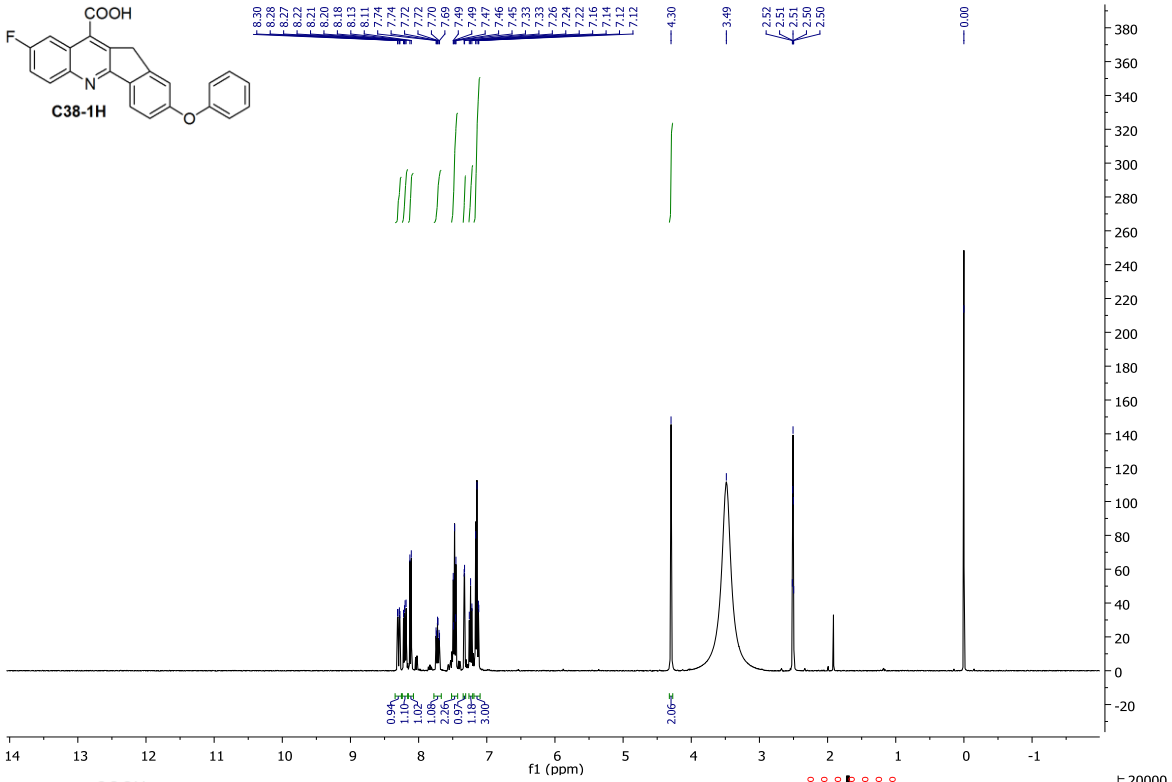

COOH
F
N
O
N
C35-13C
146.24
145.64
141.97
133.65
133.06
129.70
127.02
125.31
120.89
120.67
120.63
118.98
109.52
40.58 dmso
40.37 dmso
40.16 dmso
39.95 dmso
39.74 dmso
39.53 dmso
39.33 dmso
f1 (ppm)


COOH
F
N
O
N
S
C36-1H
8.50
8.48
8.45
8.34
8.33
8.19
8.18
8.17
8.16
7.75
7.73
7.72
7.50
7.49
7.34
7.33
7.29
7.28
2.49
2.15
2.10
1.12
1.16
1.97
0.96
0.99
0.36
f1 (ppm)


COOH
F
N
O
N
S
C36-13C
154.84
146.21
146.17
138.01
135.60
133.08
132.98
129.52
124.92
124.81
120.91
120.73
120.69
120.65
115.65
115.55
109.77
109.52
40.37 dmso
40.16 dmso
39.95 dmso
39.74 dmso
39.53 dmso
39.32 dmso
39.11 dmso
f1 (ppm)


COOH
F
N
O
C37-1H
8.11
8.10
8.08
7.70
7.68
7.65
7.63
7.60
7.49
7.47
7.45
7.44
7.40
7.22
7.20
7.19
7.14
7.12
7.11
7.08
2.51
2.41
1.11
3.00
3.40
1.16
4.12
3.40
f1 (ppm)


COOH
F
N
O
C37-13C
161.75
159.48
159.30
157.49
156.60
143.34
135.33
132.56
132.47
131.37
130.61
124.33
119.94
119.69
119.58
40.55 dmso
40.34 dmso
40.13 dmso
39.72 dmso
39.51 dmso
39.30 dmso
18.20
f1 (ppm)


COOH
F
N
O
C38-1H
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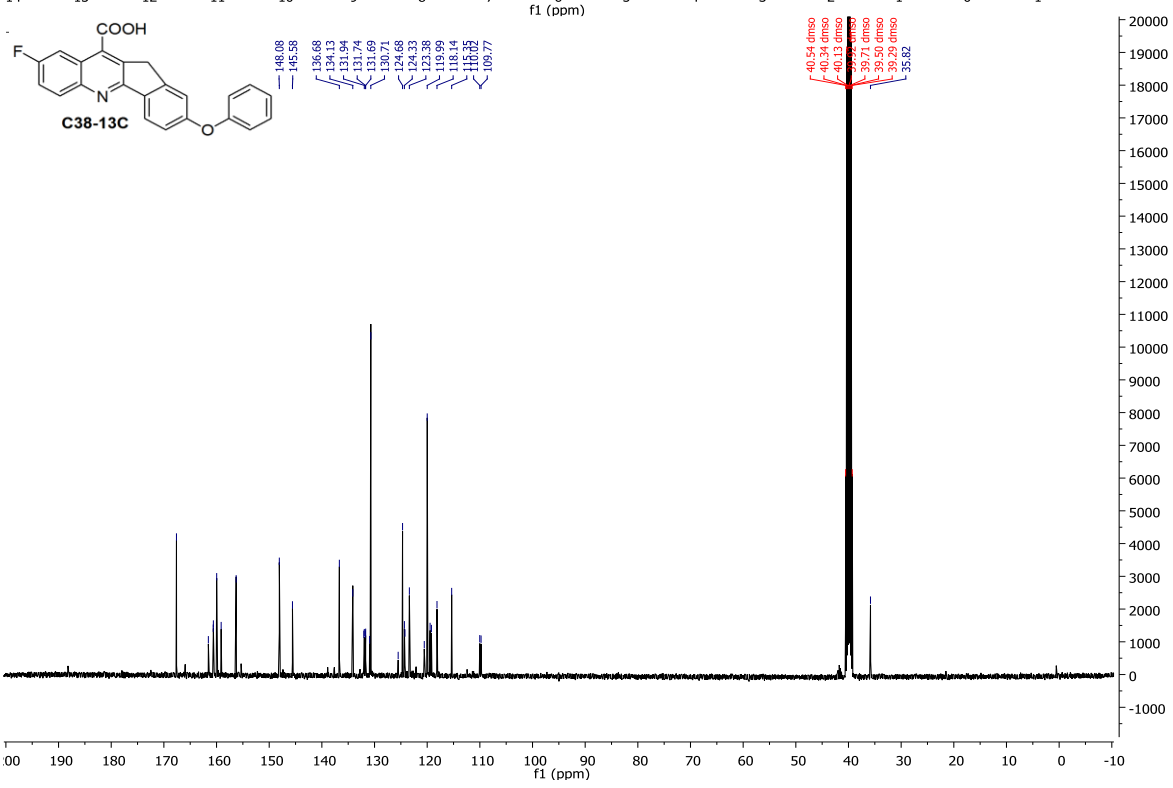
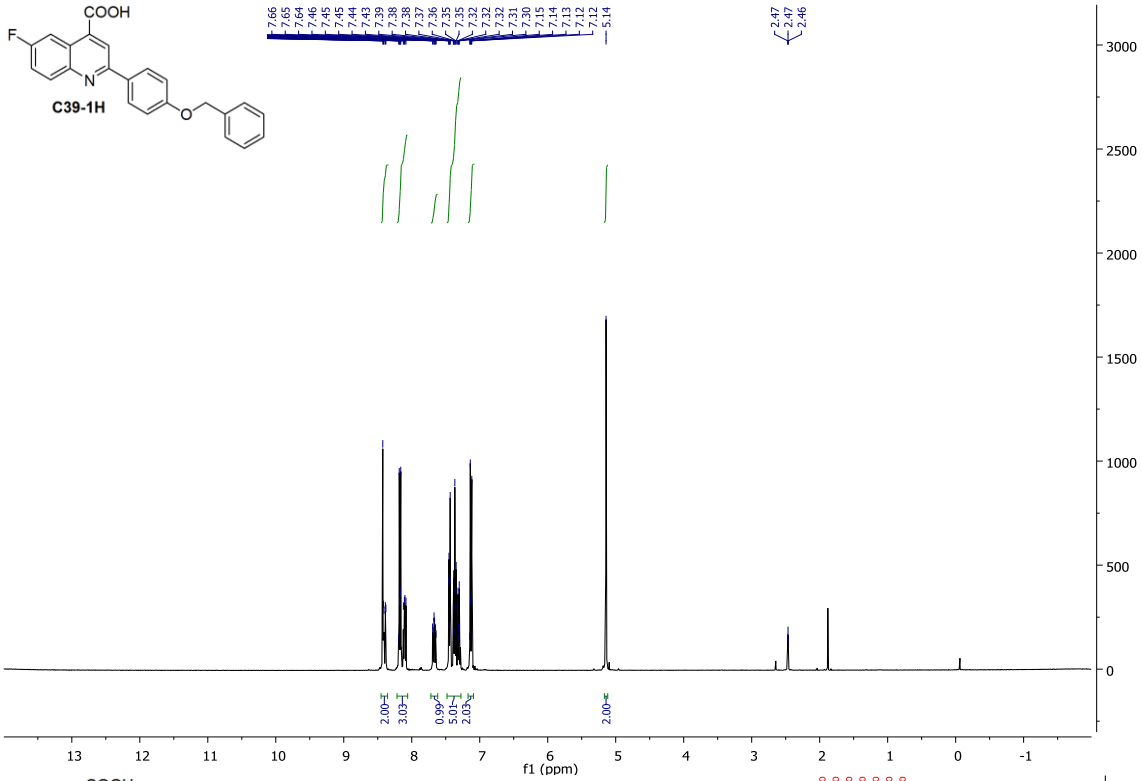
8.28
8.27
8.22
8.21
8.20
8.18
8.13
8.11
7.74
7.74
7.72
7.72
7.70
7.69
7.49
7.49
7.47
7.46
7.45
7.33
7.26
7.24
7.22
7.16
7.14
7.12
7.12
4.30
3.49
2.52
2.51
2.51
2.50
2.50
0.00
0.94
1.10
1.02
1.08
2.26
0.97
1.18
3.00
2.06
f1 (ppm)


COOH
F
N
O
C38-13C
148.08
145.58
136.68
134.13
131.94
131.74
131.69
130.71
124.68
124.33
123.38
119.99
118.14
116.15
110.02
109.77
40.54 dmso
40.34 dmso
40.13 dmso
39.92 dmso
39.71 dmso
39.50 dmso
39.29 dmso
35.82
f1 (ppm)


COOH
F
N
O
C39-1H
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7.65
7.64
7.46
7.45
7.45
7.44
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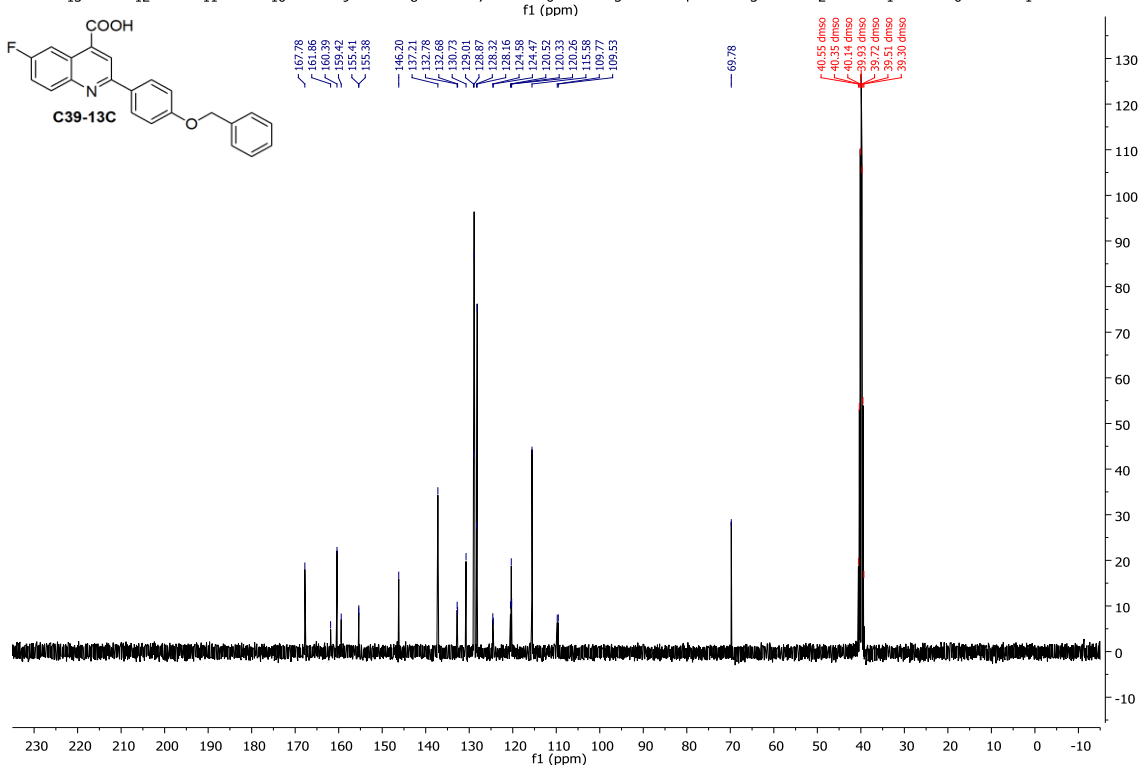
7.39
7.38
7.38
7.37
7.36
7.35
7.35
7.32
7.32
7.32
7.31
7.30
7.15
7.14
7.13
7.12
7.12
5.14
2.47
2.47
2.46
2.00
3.03
0.99
5.01
2.05
2.00
f1 (ppm)


COOH
F
N
O
C39-13C
167.78
161.86
160.39
159.42
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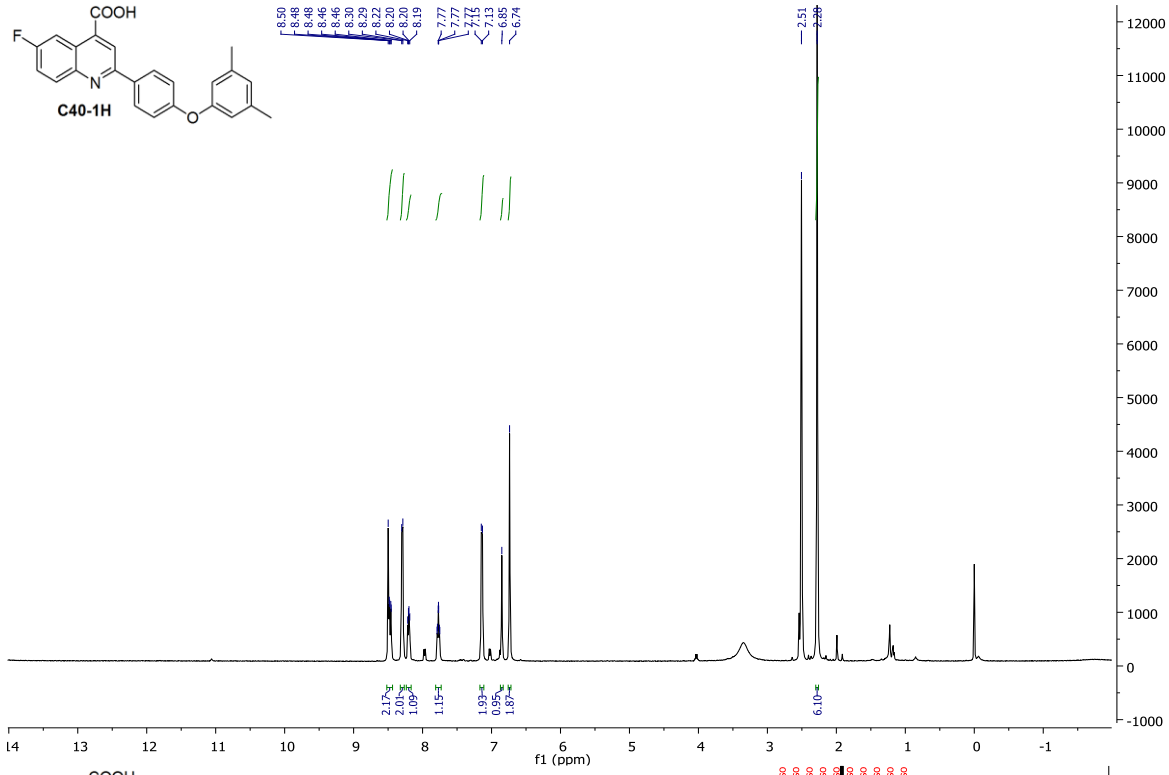
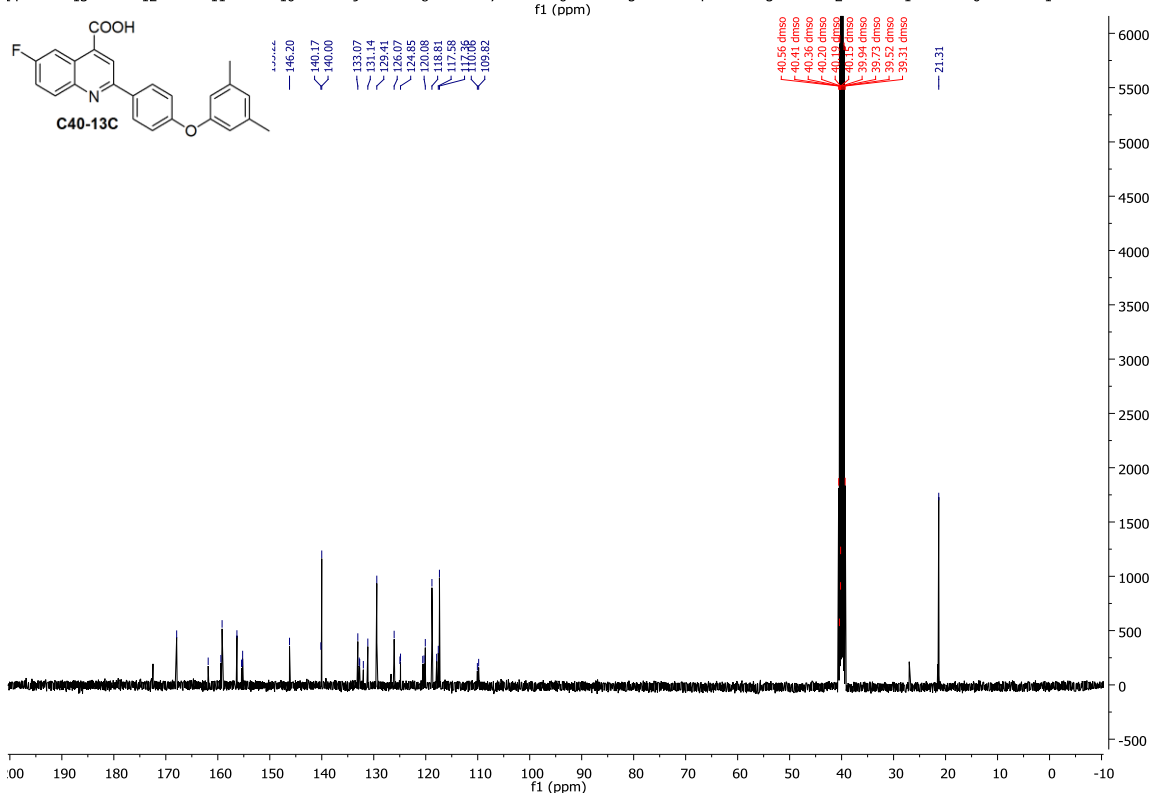
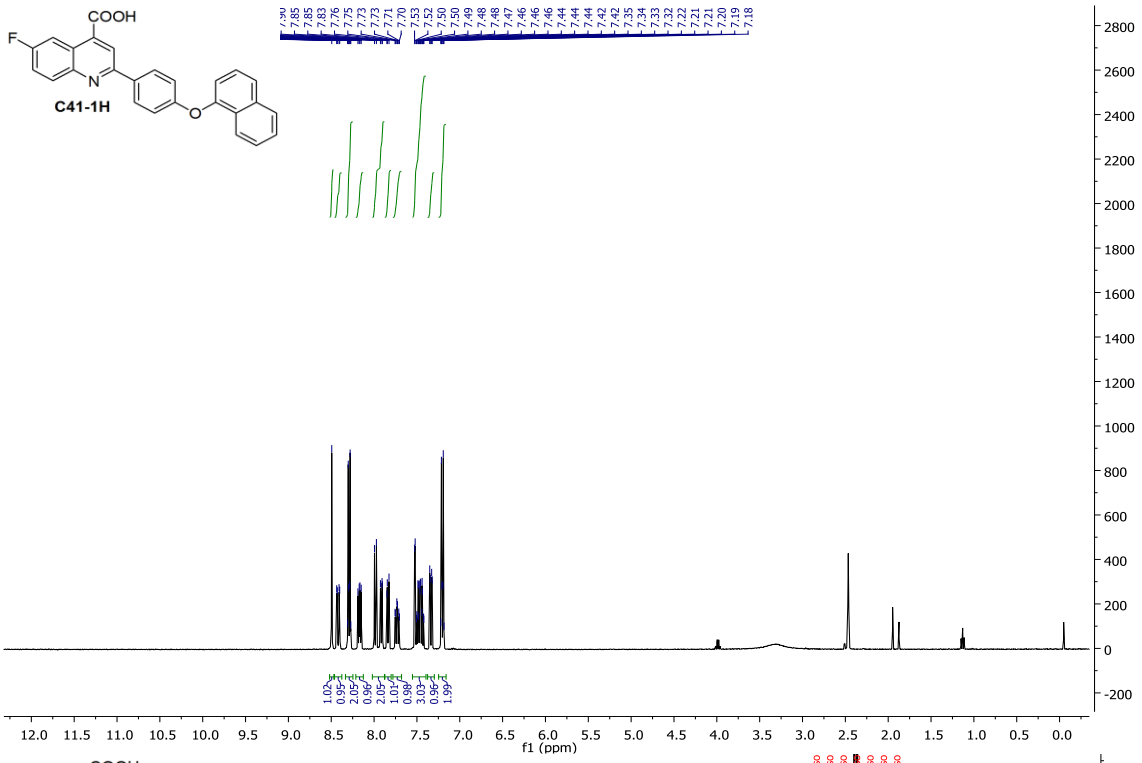
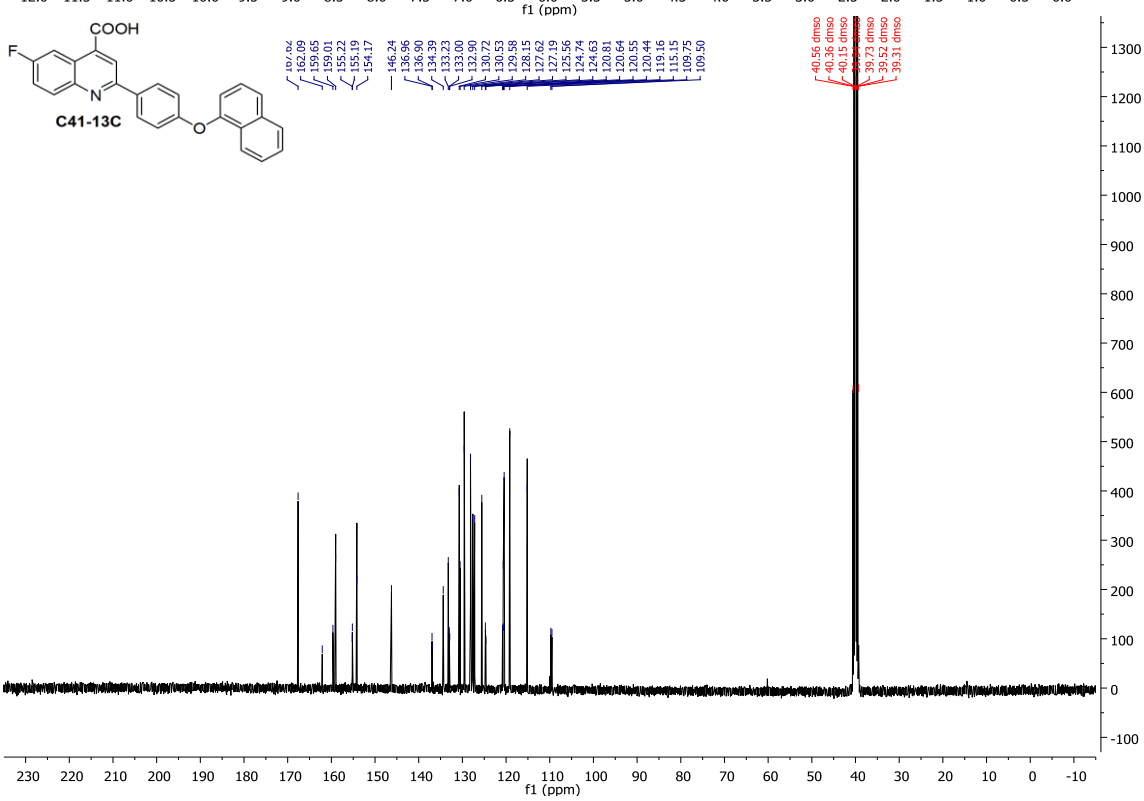
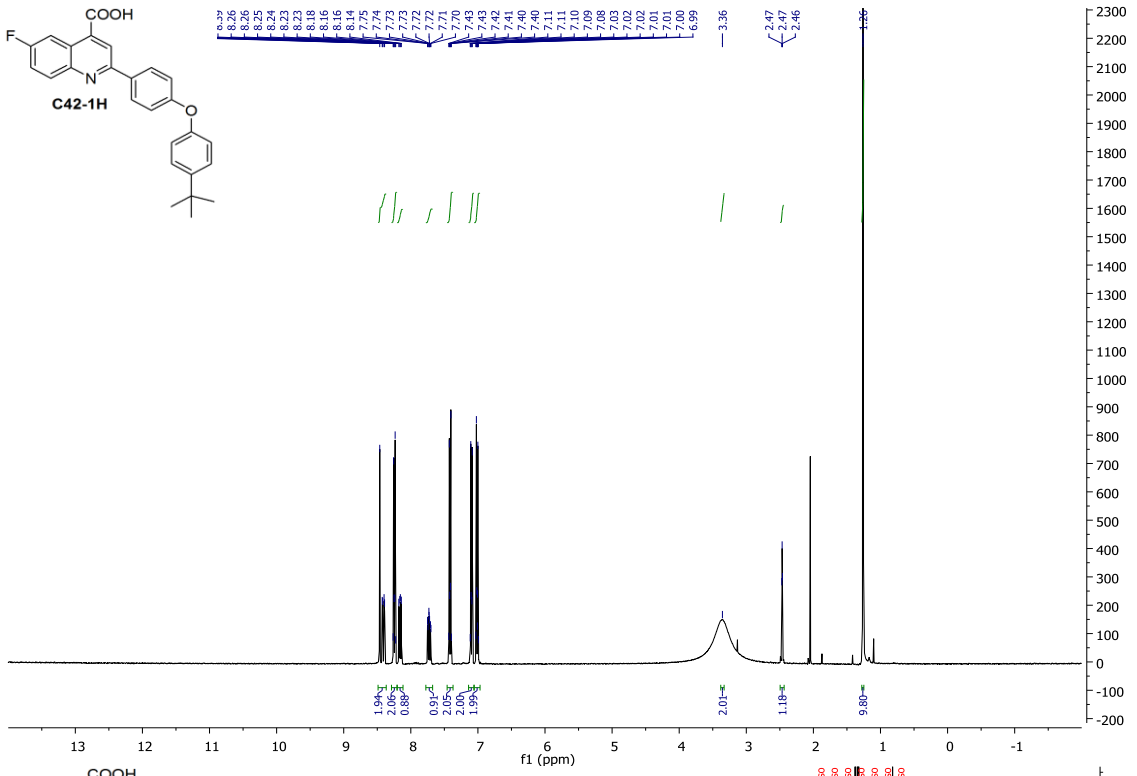
155.38
146.20
137.21
137.08
132.68
130.73
129.01
128.87
128.32
128.16
124.58
124.47
120.52
120.33
120.26
115.58
109.77
109.53
69.78
40.55 dmso
40.35 dmso
40.14 dmso
39.93 dmso
39.72 dmso
39.51 dmso
39.30 dmso
f1 (ppm)

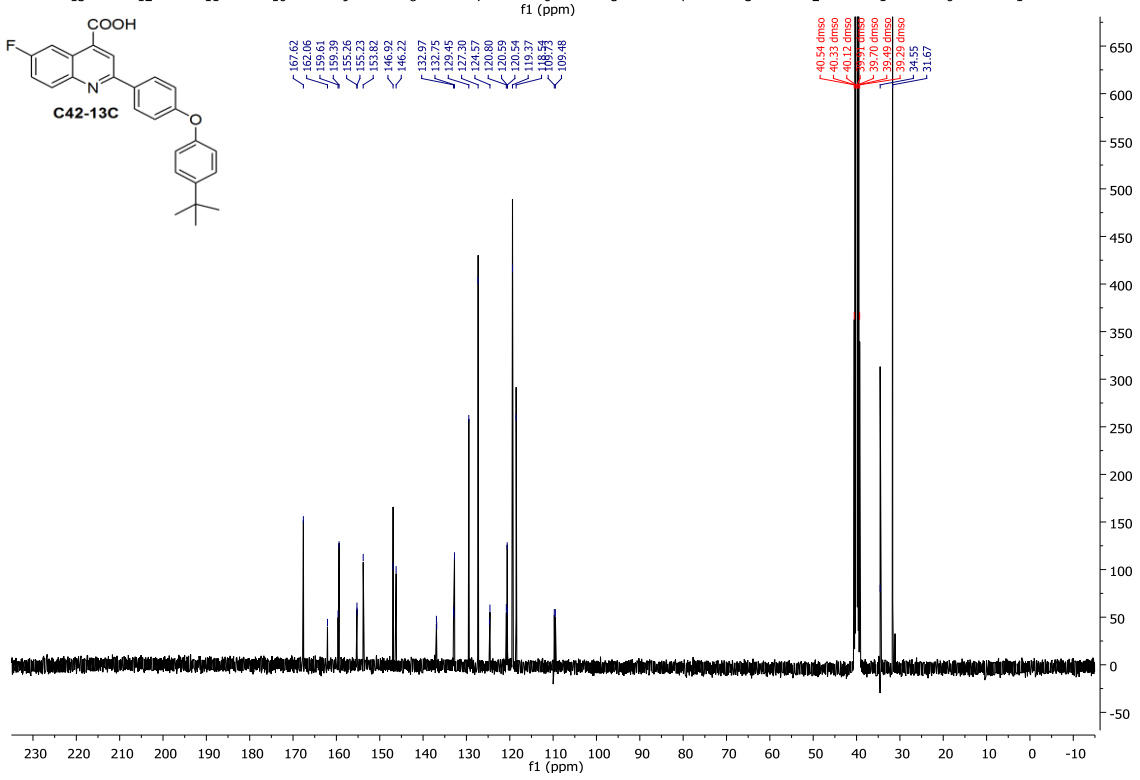

COOH
F
N
O
C40-1H
8.50
8.48
8.48
8.46
8.46
8.30
8.29
8.22
8.20
8.20
8.19
7.77
7.77
7.72
7.15
7.13
6.85
6.74
2.51
2.28
2.17
2.01
1.09
1.15
1.93
0.95
1.87
6.10
f1 (ppm)

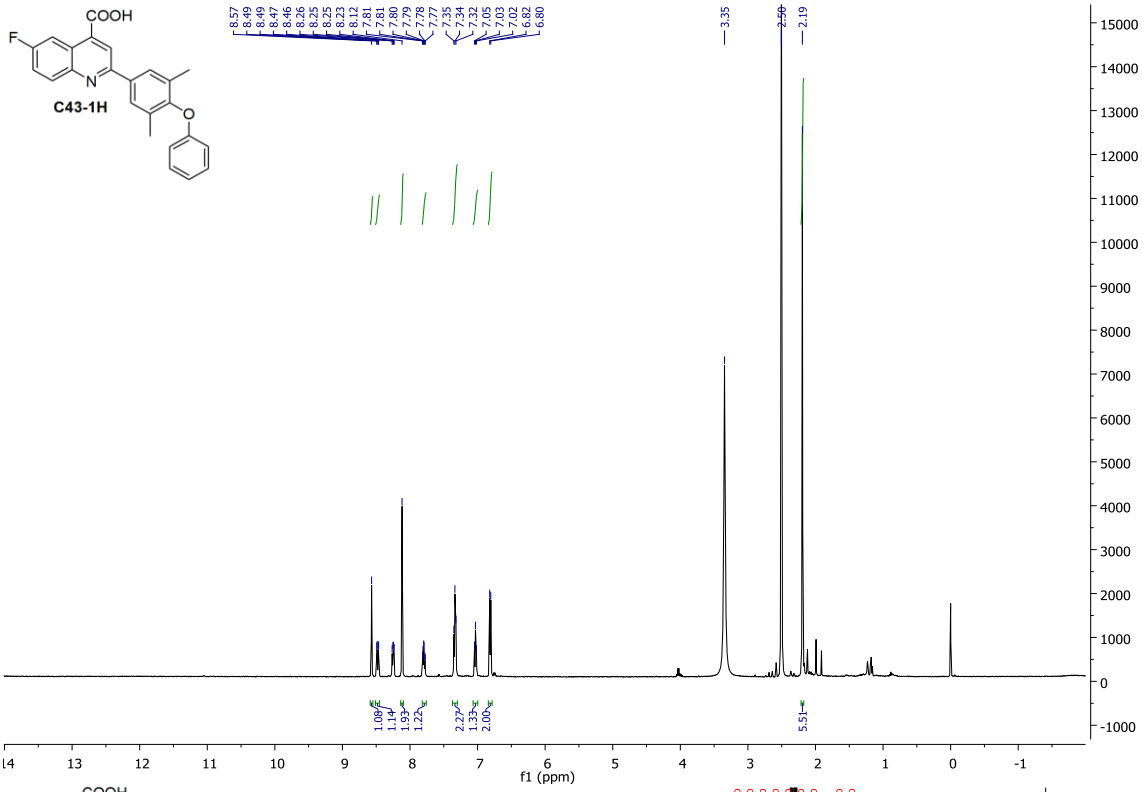

COOH
F
N
O
C40-13C
146.20
140.17
140.00
133.07
131.14
129.41
126.07
124.85
120.08
118.81
117.58
109.82
40.56 dmso
40.41 dmso
40.36 dmso
40.20 dmso
40.04 dmso
39.94 dmso
39.73 dmso
39.52 dmso
39.31 dmso
21.31
f1 (ppm)

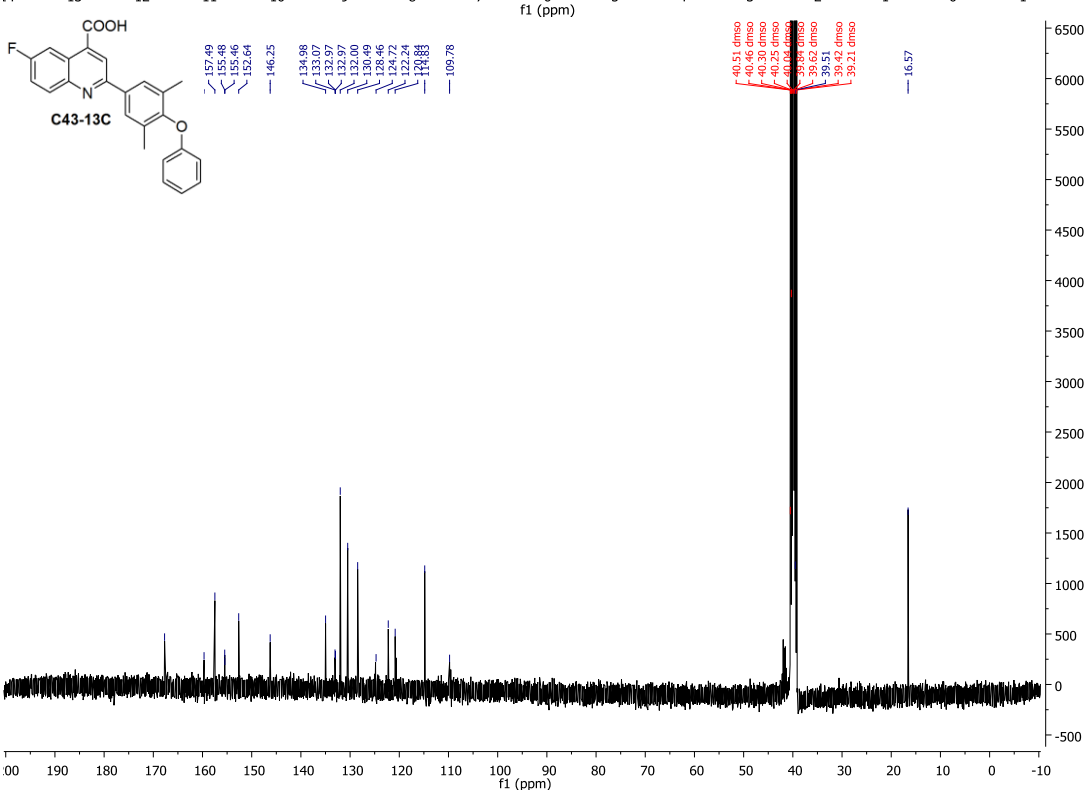

COOH
F
N
O
C41-1H
f1 (ppm)

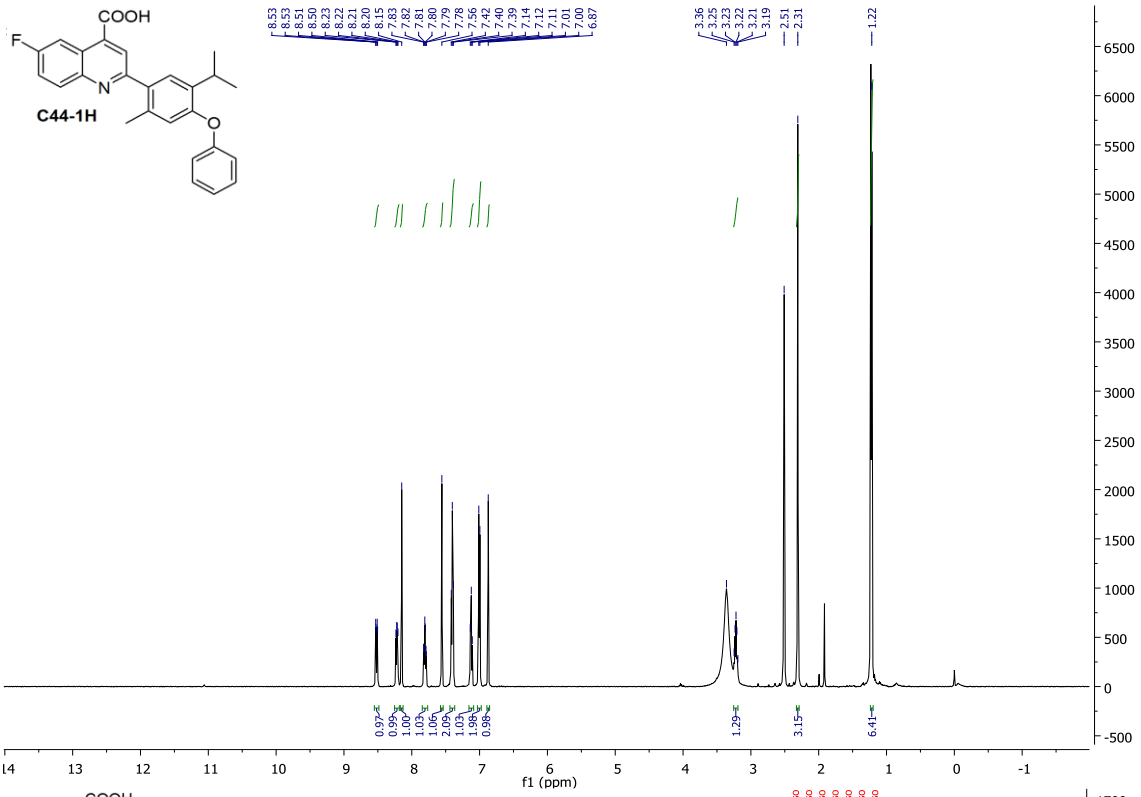

COOH
F
N
O
C41-13C
f1 (ppm)

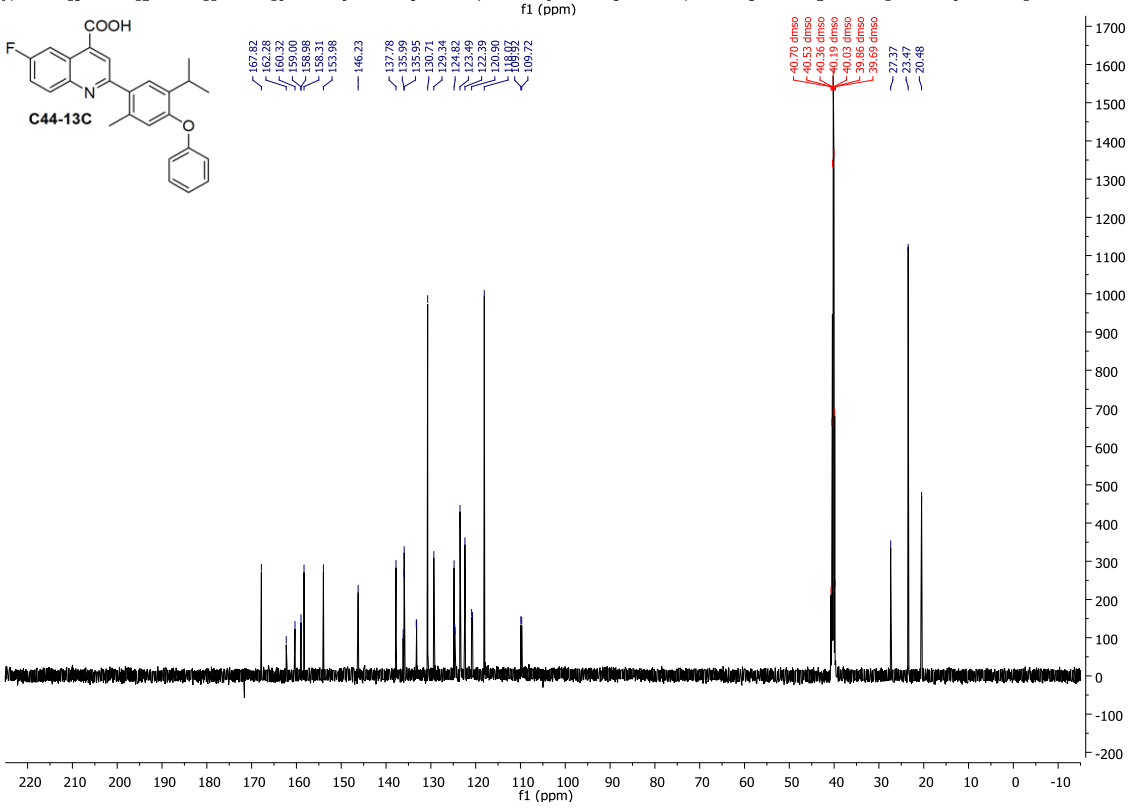

COOH
F
N
O
C42-1H
f1 (ppm)


COOH
F
N
O
C42-13C
f1 (ppm)


COOH
F
N
O
C43-1H
8.57
8.49
8.49
8.47
8.46
8.26
8.25
8.23
8.12
7.81
7.81
7.80
7.79
7.78
7.77
7.35
7.34
7.32
7.05
7.03
7.02
6.82
6.80
3.35
2.50
2.19
1.08
1.14
1.93
1.22
2.27
1.33
2.00
5.51
f1 (ppm)


COOH
F
N
O
C43-13C
157.49
155.48
155.46
152.64
146.25
134.98
133.07
132.97
132.07
132.00
130.49
128.46
124.72
122.24
120.84
114.83
109.78
40.51 dmso
40.46 dmso
40.30 dmso
40.25 dmso
40.04 dmso
39.83 dmso
39.62 dmso
39.51
39.42 dmso
39.21 dmso
16.57
f1 (ppm)


COOH
F
N
O
C44-1H
8.53
8.53
8.51
8.50
8.23
8.22
8.21
8.20
8.15
7.83
7.82
7.81
7.80
7.79
7.78
7.56
7.42
7.40
7.39
7.14
7.12
7.11
7.01
7.00
6.87
3.36
3.25
3.23
3.22
3.21
3.19
2.51
2.31
1.22
0.97
0.99
1.00
1.03
1.06
2.09
1.03
1.98
0.98
1.29
3.15
6.41
f1 (ppm)


COOH
F
N
O
C44-13C
167.82
162.28
160.32
159.00
158.98
158.31
153.98
146.23
137.78
135.99
135.95
130.71
129.34
124.82
123.49
123.39
120.90
109.97
109.72
40.70 dmso
40.53 dmso
40.36 dmso
40.19 dmso
40.03 dmso
39.86 dmso
39.69 dmso
27.37
23.47
20.48
f1 (ppm)