Electronic Supplementary Material (ESI) for Molecular Systems Design & Engineering.

Supplementary Material (ESI)

Nitro Sulfonyl Fluorides are a new pharmacophore for the development of antibiotics

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Materials: All the chemicals used in the synthesis of NSFs were purchased from Sigma-Aldrich. 0.1 M phosphate buffered saline (PBS), syringes, needles, pipette tips, microcentrifuge tubes, and nuclear magnetic resonance (NMR) tubes were purchased from VWR. ^{1}H-NMR spectra were recorded in $CDCl_3$, in a Bruker 300 MHz and 400 MHz spectrometers at 300K. TMS (δ (ppm) H = 0.00) was used as the internal reference. ^{13}C-NMR spectra were recorded in $CDCl_3$ at a 100MHz on a Bruker 400 MHz spectrometer, using the central resonances of $CDCl_3$ (δ (ppm) C = 77.23). Chemical shifts are reported in ppm and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), and m (multiplet). Coupling constants, *J*, are reported in hertz (Hz). High-resolution mass spectra (HRMS) were obtained on an AB SCIEX TOF/TOF 5800 system and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M^+) or a suitable fragment ion. Chemicals were purchased from Aldrich or VWR and used without further purification. All solvents were purified using standard methods. Flash chromatography was carried out using silica gel (230-400 mesh). All reactions were performed under anhydrous conditions under N_2 or Argon and monitored by TLC on Kieselgel 60 F254 plates (Merck). Macrophage RAW 264.7 cells were obtained from the UCB Cell Culture Facility, which is supported by The University of California Berkeley.

A. The structures of the initial library

A library of SF-containing compounds were screened for their antibacterial activity of against *E.coli* to determine if SFs had any intrinsic antibacterial activity. The library contained a variety of chemical structures including aliphatic, aromatic, and heterocyclic SFs, such as thiophene and imidazole SFs, as well as Michael acceptors, such as etheneslfonyl fluoride (ESF). We also included two known serine protease inhibitors, 4-(2-aminoethyl)benzenesulfonyl fluoride (AEBSF) and phenylmethylsulfonyl fluoride (PMSF). All compounds were tested against a Kanamycin-resistant strain of *E. coli* (plasmid transfected BL21) at an initial concentration of 100 μM.

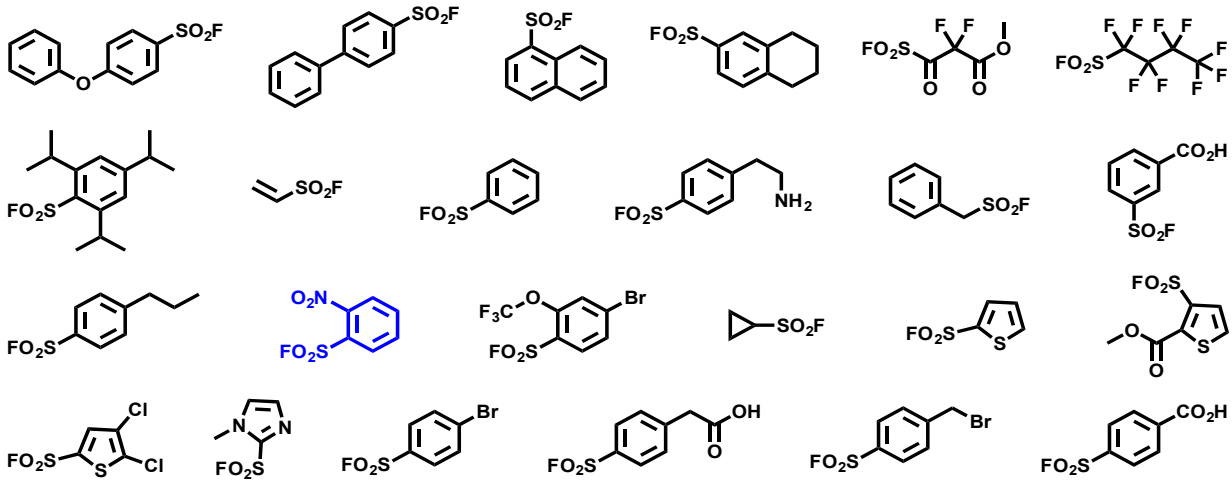


Figure S1 Structures of sulfonyl fluorides for Initial library screening

B. MTT assay for Cytotoxicity

The cytotoxicity of the compounds was tested against RAW cells using MTT assay (MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). RAW cells were obtained from Cell Culture Facility at University of California, Berkeley. The cells were grown in DMEM media supplemented with 5 % FBS and 1 % Penn Strip and incubated at 37 °C in a humidified incubator with 5 % CO_2. The cells were washed with DPBS and dissociated using TrypLe. The cells were incubated at 37 °C until the cells were detached from the plate, transferred to centrifuge vial and pelleted via centrifugation at 1000 rpm for 5 min. The cells were counted per 2 mL media. The desired amount of media was added to the cell solution so that 10,000 cells can be added to each well of a 96-well plate in 200 μM aliquots. After the addition, the cells were incubated at 37 °C for 1-2 days. A serial dilution of the sulfonyl fluorides dissolved in sterile DMSO was prepared by the addition of fully-supplemented DMEM. The residual medium in each well was aspirated and the different compounds concentrations were added to each well of every column of the 96-well plate in 100 μL aliquots. After the addition of the solution, the cells were incubated at 37 °C for 24 hours. After the incubation period, the medium was aspirated and then 40 μL of 0.5 mg/mL MTT (3-(4,5-dimethylthizol-2-yl)-2,5-diphenyltetrazolium bromide) in DPBS was added to each well. The cells were then incubated at 37 °C for 4 hours. After the incubation period, 40 μL of 1.0 M HCl solution were added to dissolve the remaining crystals. The plates were shaken for 5 minutes to assure that all of the crystals are dissolved. The optical density was determined from the resulting solutions using the optical density reader.

Each experiment was run in triplicate. The optical density data was used to calculate IC_{50} values for each compound on RAW cells using the Hill slope equation. The IC_{50} values and their standard errors were calculated from the viability-concentration curve using the Four Parameter Logistic Model of Sigmaplot. The concentration of DMSO per well was ≤ 1 % in all cases. The control experiment, i.e., adding 1 % DMSO to the cells, indicated that 1 % DMSO was not cytotoxic, and thus, all the cells treated remained virtually 100% positive.

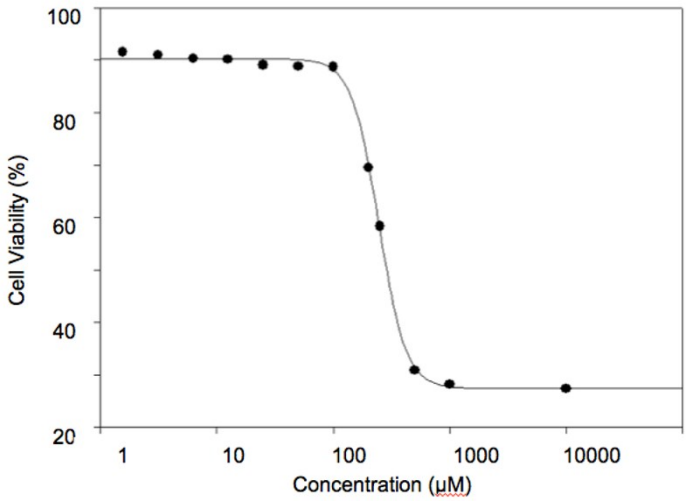


Figure S2. *In vitro* cytotoxicty of compound 1 determined via the MTT assay.

C. Further NSFs for SAR study

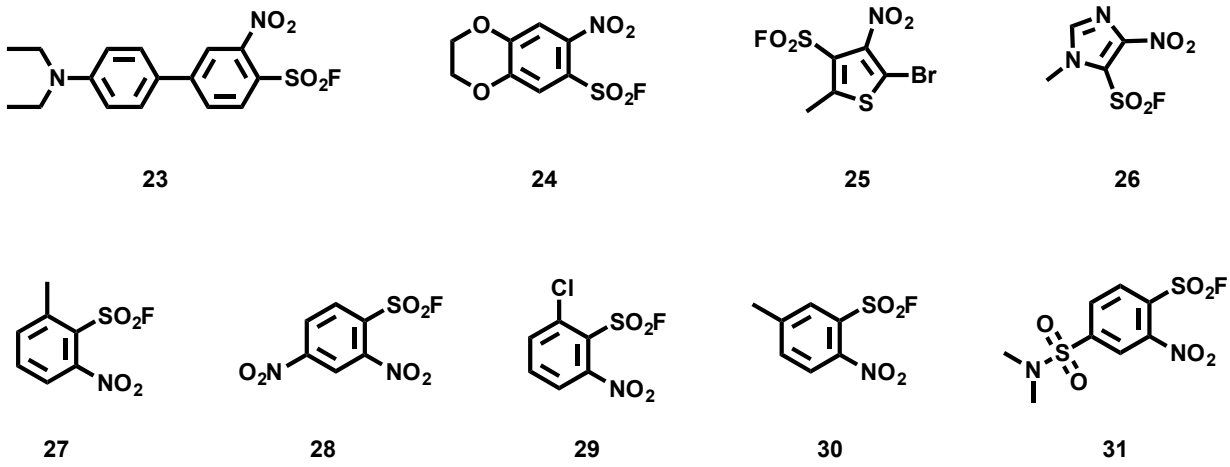
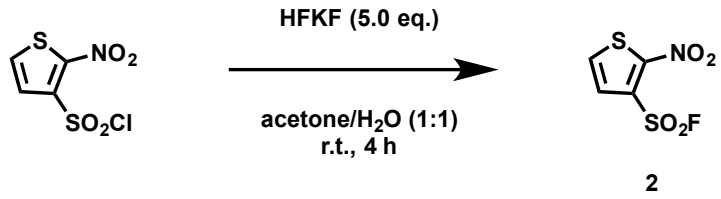


Figure S3 Structures of sulfonyl fluorides for further SAR study

D. Synthesis of compound 2 and NSFs



Scheme S1. Synthetic scheme for compound 2

General procedure: A 25 mL round bottom flask was charged with 2-nitrothiophene-3-sulfonyl chloride and an excess amount of KFHF in a 1:1 mixture of acetone and water. The reaction was stirred for 3 hours at room temperature. Upon completion, the solvents were removed under vacuum and the resulting crude product was purified via flash column chromatography to furnish 36.5 mg (31%) of compound **2** as a pale white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.59 (d, 1 H, *J* = 5.68 Hz), 7.69-7.70 (d, 1 H, *J* = 5.6 Hz); ^{19}F NMR (400 MHz, $CDCl_3$) δ 63.7; HRMS (ESI) m/z calculated for Chemical Formula: $C_4H_2FNO_4S_2$ 210.9409 Found: 210.9411 (Δ = 0.95 ppm)

In a similar manner, compound **18-22** and **24-31** were synthesized and characterized.

2-(2-nitrophenyl)oxirane (14)
Procedure: To a 25 mL round bottom flask was added 2-bromo-2'-nitroacetophenone (1.237g, 4.1 mmol, 1 equiv) in dry 1,2-dioxane (7 mL). To a separate round bottom flask was added dry MeOH (4 mL) and $NaBH_4$ (0.501 g, 12.7 mmol, 3.1 equiv) under nitrogen. Both flasks were cool to 0 °C and the $NaBH_4$/MeOH solution was pipetted into the stirring solution of acetophenone/dioxane. After the addition, the reaction solution was briefly sonicated and allowed to stir under nitrogen at room temperature for 18h. The solution was then cooled to 0 °C, added 10% NaOH in water, and allowed to stir for 30 min. The solvents were removed under vacuum, redissolved in CH_2Cl_2, (10 mL), washed with water (10 mL), dried over Na_2SO_4, and concentrated to yield 68% of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.12 (d, 1H, *J* = 7.7 Hz), 7.65 (t, 1H, *J* = 6.8 Hz), 7.58 (d, 1H, *J* = 7.4 Hz), 7.46 (t, 1H, *J* = 6.6 Hz), 4.43-4.47 (m, 1H), 3.24-3.20 (m, 1H), 2.62-2.66 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) *δ* 147.7, 134.5, 134.2, 128.4, 126.8, 124.5, 50.5, 50.4. HRMS (EI) m/z calculated for: $C_8H_7NO_3$: 165.1480. Found: 165.0426 (Δ 0.1054).

4-methyl-2-nitrobenzenesulfonyl fluoride (18)
89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.06 (d, 2H, J = 8.1 Hz), 7.80 (s, 1H), 7.64 (d, 1H, *J* = 8.1 Hz), 2.57 (s, 1H). ^{19}F NMR (400 MHz, $CDCl_3$) *δ* 65.92. HRMS (EI) m/z calculated for: $C_7H_6FNO_4S$: 219.1864. Found: 219.2448 (Δ 0.0584).

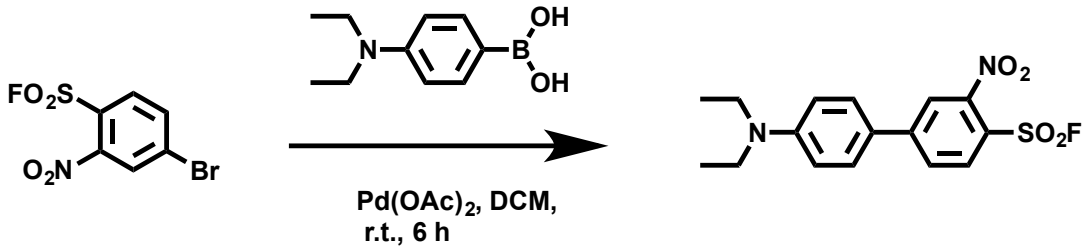
4-chloro-2-nitrobenzenesulfonyl fluoride (19)
47% yield. ^{1}H NMR (100 MHz, $CDCl_3$) *δ* 7.80-7.82 (dd ,1 H, *J* =), 7.87 (d, 1 H), 8.19-8.21 (d, 1 H, *J* =); ^{19}F NMR(100 MHz, $CDCl_3$) *δ* 65.67.

5-chloro-2-nitrobenzenesulfonyl fluoride (20)
78% yield. ^{1}H NMR (100 MHz, $CDCl_3$) *δ* 7.89-7.91 (dd ,1 H, *J* =), 8.04-8.06 (d, 1 H), 8.22 (d, 1 H, *J* =); ^{19}F NMR (100 MHz, $CDCl_3$) *δ* 65.56.

5-bromo-2-nitrobenzenesulfonyl fluoride (21)
60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.32 (s, 1H), 8.07 (d, 1H, *J* = 8.4 Hz), 7.94 (d, 1H, *J* = 8.5 Hz). ^{19}F NMR (400 MHz, $CDCl_3$) *δ* 65.73. HRMS (EI) m/z calculated for: $C_6H_3BrFNO_4S$: 284.0554. Found: 284.8932 (Δ 0.8378).

4-bromo-2-nitrobenzenesulfonyl fluoride (22)
74% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.07 (d, 1H, J = 8.5 Hz), 8.00 (d, 1H, J = 8.5 Hz). ^{19}F NMR (400 MHz, $CDCl_3$) δ 66.40. HRMS (EI) m/z calculated for: $C_6H_3BrFNO_4S$: 284.0554. Found: 283.9873 (Δ 0.0681).

4'-(diethylamino)-3-nitro-[1,1'-biphenyl]-4-sulfonyl fluoride (23)



Scheme S2. Synthetic scheme for compound 23

Procedure: 4-bromo-2-nitrobenzenesulfonyl fluoride (1.0 eq.), boronic acid (1.5 eq), $Pd(OAc)_2$ (1.0 mol %), triethylamine (3.0 eq.) in DCM were added to a round-bottomed flask. The resulting reaction mixture was stirred at room temperature for 6 hours. Upon completion, the reaction mixture was diluted with DCM and washed with water, followed by brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. 69 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.07 (d, 1H, J = 8.5 Hz), 8.00 (d, 1H, J =8.5 Hz). ^{19}F NMR (400 MHz, $CDCl_3$) δ 66.40.

7-nitro-2,3-dihydrobenzo[b][1,4]dioxine-6-sulfonyl fluoride (24)
78 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.11 (m, 2H), 7.90-7.88 (m, 1H), 3.44 (d, 4H, J = 8.5 Hz). ^{19}F NMR (400 MHz, $CDCl_3$) δ 71.98.

5-bromo-2-methyl-4-nitrothiophene-3-sulfonyl fluoride (25)
69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (s, 3H).^{19}F NMR (400 MHz, $CDCl_3$) δ 70.26. HRMS (EI) m/z calculated for: $C_5H_3BrFNO_4S_2$: 304.1044. Found: 304.8665 (Δ 0.7621).

1-methyl-4-nitro-1H-imidazole-5-sulfonyl fluoride (26)
77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 3.73 (s, 3H), .^{19}F NMR (400 MHz, $CDCl_3$) δ 64.27. HRMS (EI) m/z calculated for: $C_4H_4FN_3O_4S$: 209.1514. Found: 209.1229 (Δ 0.0285).

2-methyl-6-nitrobenzenesulfonyl fluoride (27)
45% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (t,1H, J = 8.3 Hz), 7.60 (d, 1H J = 7.8 Hz), 7.52 (d, 1 H, J = 8.1 Hz), 2.76 (1H, s). ^{19}F NMR (400 MHz, $CDCl_3$) δ 67.92. HRMS (EI) m/z calculated for: $C_7H_6FNO_4S$: 219.1864. Found: 219.0000 (Δ 0.1864).

2,4-dinitrobenzenesulfonyl fluoride (28)
98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 2.0 Hz, 1H), 8.70 (dd, 1H, J = 8.8, 2.4 Hz), 8.50 (d, 1 H, J = 10.3 Hz). ^{19}F NMR (400 MHz, $CDCl_3$) δ 66.40. HRMS (EI) m/z calculated for: $C_6H_3FN_2O_6S$: 250.1564. Found: 249.9697 (Δ 0.1867).

2-chloro-6-nitrobenzenesulfonyl fluoride (29)
61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.33 (m, 2H), 7.20-7.12 (m, 1H). ^{19}F NMR (400 MHz, $CDCl_3$) δ 68.89. HRMS (EI) m/z calculated for: $C_6H_3ClFNO_4S$: 239.6014. Found: 238.9456 (Δ 0.6558).

5-methyl-2-nitrobenzenesulfonyl fluoride (30)
78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.94 (d, 1H, J = 8.9 Hz), 7.71 (d, 1H, J = 8.1 Hz), 2.56 (s, 3H). ^{19}F NMR (400 MHz, $CDCl_3$) δ 66.71. HRMS (EI) m/z calculated for: $C_7H_6FNO_4S$: 219.1864. Found: 219.0003 (Δ 0.1861).

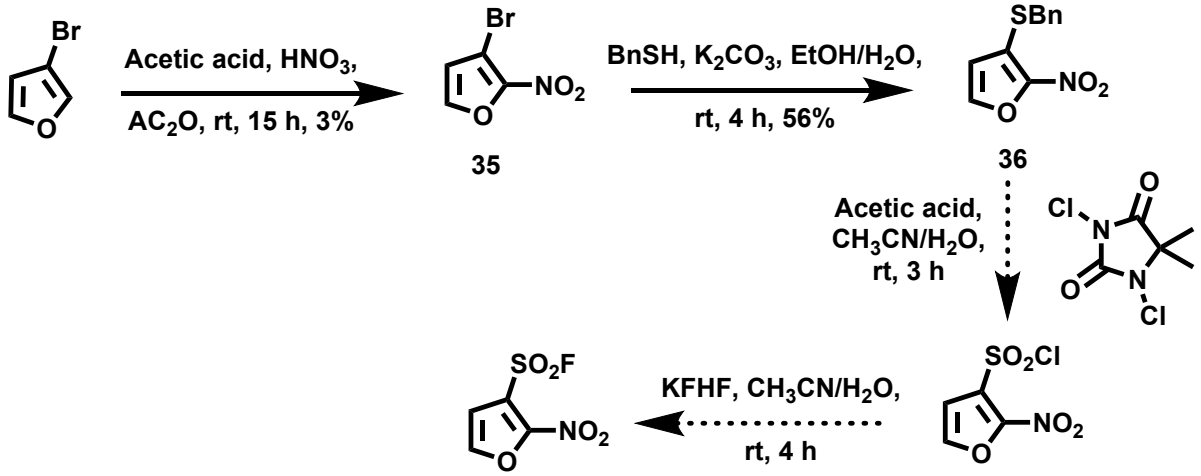
4-(N,N-dimethylsulfamoyl)-2-nitrobenzenesulfonyl fluoride (31)
91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, 1H, J = 7.5 Hz), 8.33 (s, 1H), 8.19, (d, 1H, J = 7.6 Hz). ^{19}F NMR (400 MHz, $CDCl_3$) δ 66.38. HRMS (EI) m/z calculated for: $C_8H_9FN_2O_6S_2$: 312.2864. Found: 312.2694 (Δ 0.0170).

5-chloro-4-nitrothiophene-2-sulfonyl fluoride (32)
56% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H). ^{19}F NMR (400 MHz, $CDCl_3$) δ 72.38. HRMS (EI) m/z calculated for: $C_4HClFNO_4S_2$: 245.6234. Found: 244.9024 (Δ 0.721).
MIC for compound **32** againt KAN-resistant *e. Coli* (see section G for procedural details); 50 uM.

5-methyl-2-nitrothiophene-3-sulfonyl fluoride (33)
79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 2.63 (s, 3H). ^{19}F NMR (400 MHz, $CDCl_3$) δ 63.14. HRMS (EI) m/z calculated for: $C_5H_5FNO_4S_2$: 225.2084. Found: 225.8004 (Δ 0.592). MIC for compound **33** againt KAN-resistant *e. Coli* (see section G for procedural details); 10 uM (2 ug/mL).

E. Attempted Substrate Scope Expansion

Attempts to make both furan and pyrrole derivatives were envisioned to result in 4 overall steps, however, all failed at the third step (Scheme S3). For example, 2-nitrofuran-3-sulfonyl fluoride could be synthesized by nitration of 3-bromofuran followed by aromatic substitution of benzyl mercaptan, oxidative chlorination to the sulfonyl chloride, and final transformation to the sulfonyl fluoride.



Scheme S3. Attempted synthesis of 2-nitrofuran-3-sulfonyl fluoride

3-bromo-2-nitrofuran (35)
To a 100 mL round-bottomed flask was added acetic anhydride (2.5 mL, 26.5 mmol, 2.6 equiv) and nitric acid (468 µL, 11.2 mmol, 1.1 equiv). To an addition funnel was added acetic acid (18 mL, 316.2 mmol, 31 equiv) and 3-bromofuran (1.51 g, 10.2 mmol, 1 equiv) and this was added dropwise to the stiring nitric acid/acetic anhydride solution at rt. After complete addition, the reaction was allowed to stir for 15 hours and was then poured over 50 g ice, added ethyl acetate (40 mL), added to a separatory funnel and the phases were separated. The aqueous phase was washed with more ethyl acetate (1 x 30 mL), and the combined organic layers were rinsed with brine (1 x 40 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purfied via column chromatography (4:1 hexanes: ethyl acetate) to yield 50 mg (0.26 mmol, 3% yield) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 2.5 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H). HRMS (EI) m/z calculated for: $C_4H_2BrNO_3$: 191.9680. Found: 192.0430 (Δ 0.075).

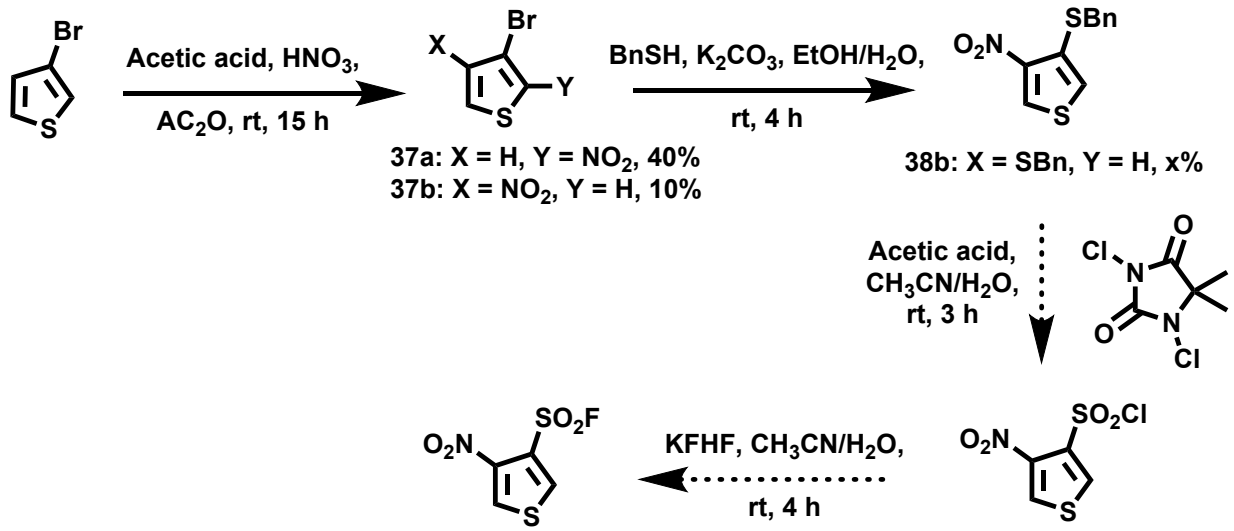
3-(benzylthio)-2-nitrofuran (36)
A 25 mL round-bottomed flask was charged with 3-bromo-2-nitrofuran **35** (50 mg, 0.26 mmol, 1 equiv), K_2CO_3 (0.0447 g, 0.29 mmol, 1.1 equiv), water (130 µL), and ethanol (600 µL) under a nitrogen atmosphere. Benzyl mercaptan (31 µL, 0.26 mmol, 1 equiv) dissolved in ethanol (55 µL) was then added via syringe and continued to stir at rt for 4 hours. The reaction solution was then concentrated and purified by column chromatography (2:1 hexanes: ethyl acetate) to yield 34 mg (0.145 mmol, 56% yield) of an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.23 (m,

7H), 3.65 (s, 2H). ^{13}C (400 MHz, $CDCl_3$) δ 137.4, 129.5, 128.5, 127.5, 43.3. HRMS (EI) m/z calculated for: $C_{11}H_9NO_3S$: 235.2570. Found: 235.0112 (Δ 0.2458).

Additional attempts to expand the substrate scope on the thiophene core via iodination followed by Suzuki coupling would enable the introduction of various aromatic rings at the 5-position using commercially-available boronic acids (scheme S4). All iodination reagents, including the use of LDA as a base, led to recovery of starting material or decomposition products only. Furthermore, the iodination was attempted on intermediate **36** to avoid any interference with the sulfonyl fluoride moeity, though no desired product was isolated.

Scheme S4. Attempted synthesis of 5-aryl-substituted 2-nitrothiophene-3-sulfonyl fluorides

Utilizing the 4-step route generated for the attempted pyrrole and furan derivatives was applied to the thiophene core (Scheme S5). Commercially-available 3-bromothiophene led to two nitration products; 3-bromo-2-nitrothiophene (**37a**) and 3-bromo-4-nitrothiophene (**37b**). Carrying on **37b** led to successful substitution, however, the oxidative chlorination was unsuccessful.



Scheme S5. Attempted synthesis of 4-nitrothiophene-3-sulfonyl fluoride

3-bromo-2-nitrothiophene (37a)

See experimental for compound **35**. 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 1.8 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H). HRMS (EI) m/z calculated for: $C_4H_2BrNO_2S$: 208.0290. Found: 208.0629 (Δ 0.0338).

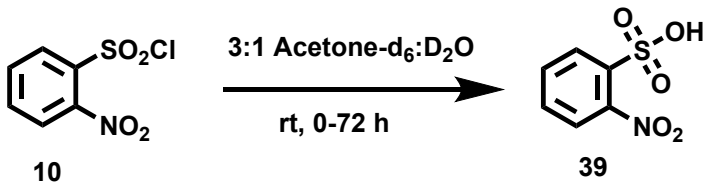
3-bromo-4-nitrothiophene (37b)

See experimental for compound **35**. 10% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 5.5 Hz, 1H), 7.11 (d, J = 5.9 Hz, 1H). HRMS (EI) m/z calculated for: $C_4H_2BrNO_2S$: 208.0290. Found: 208.1147 (Δ 0.0857).

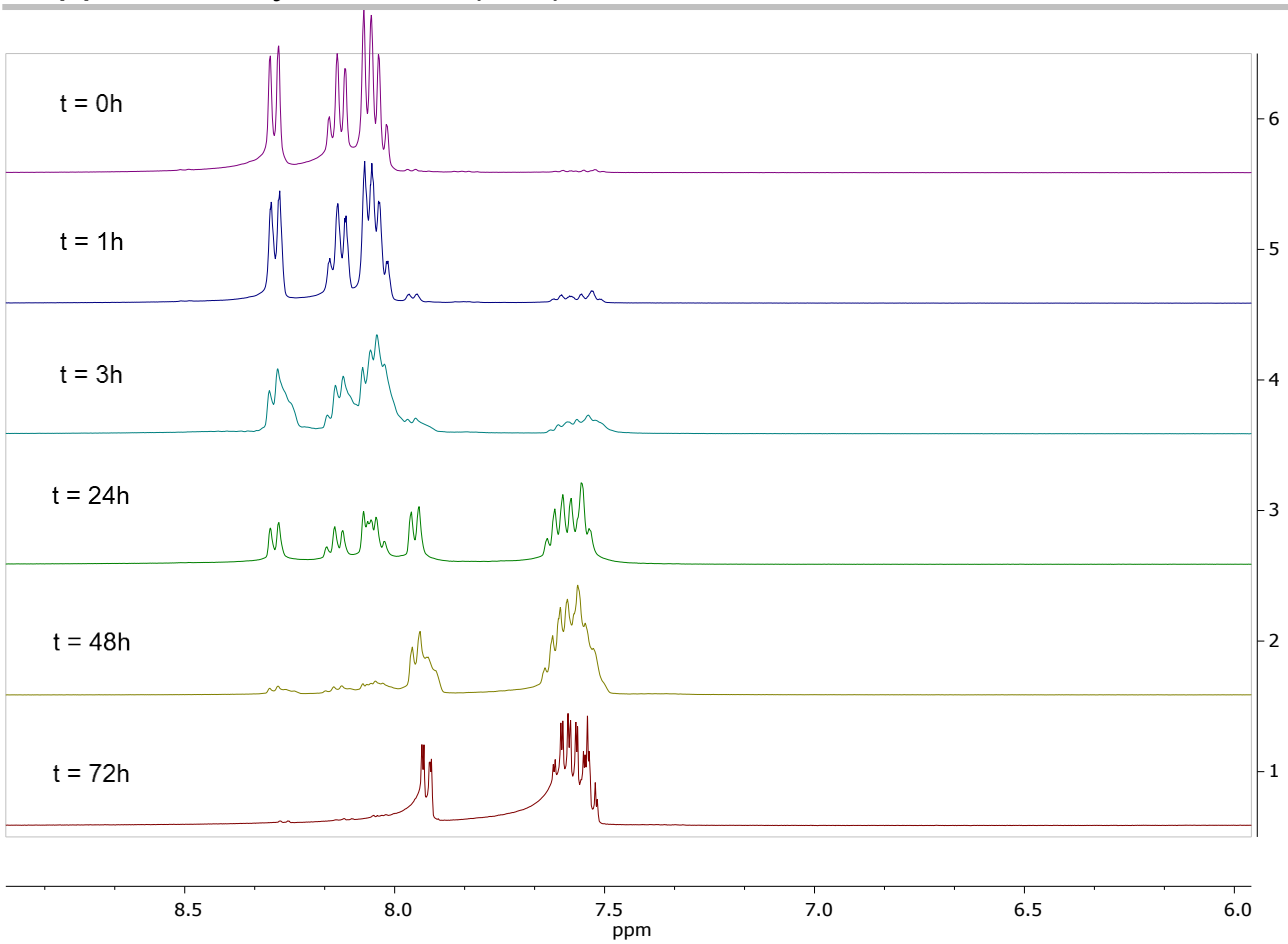
F. Rate of Hydrolysis

The aryl sulfonyl chloride moeity is much more succeptible to hydrolysis than an aryl sulfonyl fluoride, as demonstrated by the ^{1}H NMR time trial of 2-nitrosulfonyl chloride in 2:1 acetone-d_6:D_2O compared to 2-nitrosulfonyl fluoride in the same solvent (See Scheme S6 and S7, respectively). After 48 h, the sulfonyl chloride is almost completely hydrolyzed compared to the sulfonyl fluoride, which shows no new peaks corresponding to the hydrolysis product. As a reference, the hydrolyzed compound **39** was synthesized.

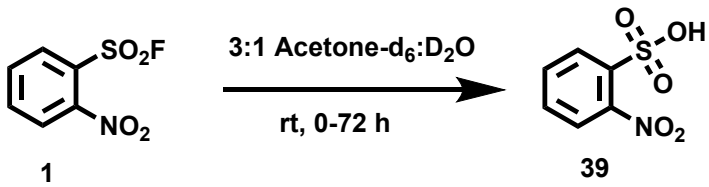
2-nitrobenzenesulfonic acid (39)
To a solution of 2-nitrobenzenesulfonyl chloride **10** (19.9 mg, 0.090 mmol) in acetone (300 µL) was slowly added water (100 µL) and sonicated briefly. After 72 h of stirring at rt, the reaction solution was concentrated under reduced pressure to yield 20.4 mg (0.100 mmol, 99% yield) of a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.81-7.65 (m, 4H). HRMS (EI) m/z calculated for: $C_6H_5NO_5S$: 203.1680. Found: 201.9816 (Δ 1.1864).



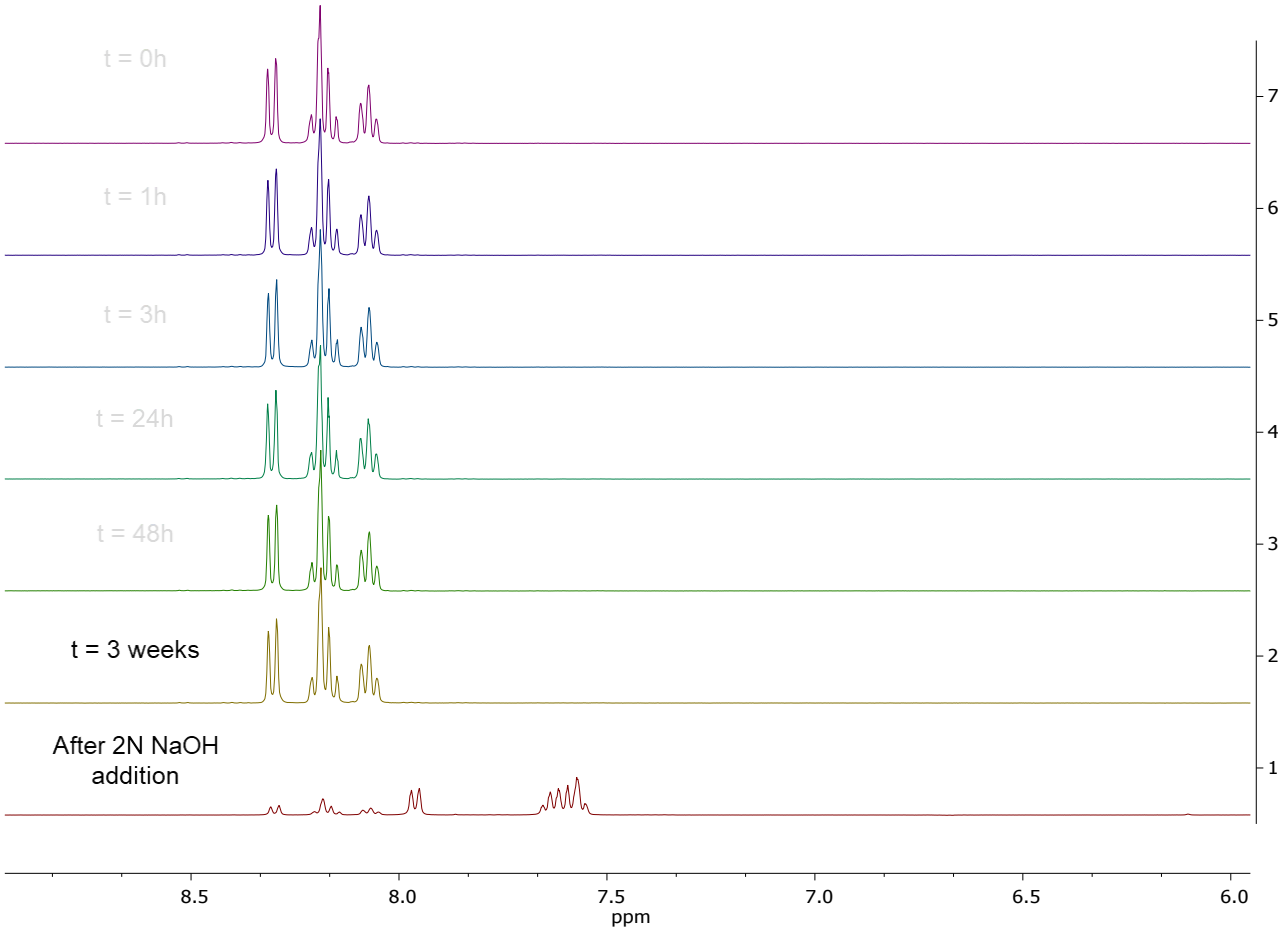
10 **39**



Scheme S6. ^{1}H NMR of 2-nitrobenzenesulfonyl chloride **10** hydrolysis from 0-72 h.

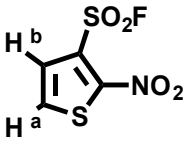


1 **39**



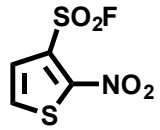
Scheme S7. ^{1}H NMR of 2-nitrobenzenesulfonyl fluoride **1** hydrolysis from 0-72 h.

^{1}H NMR for compound 2

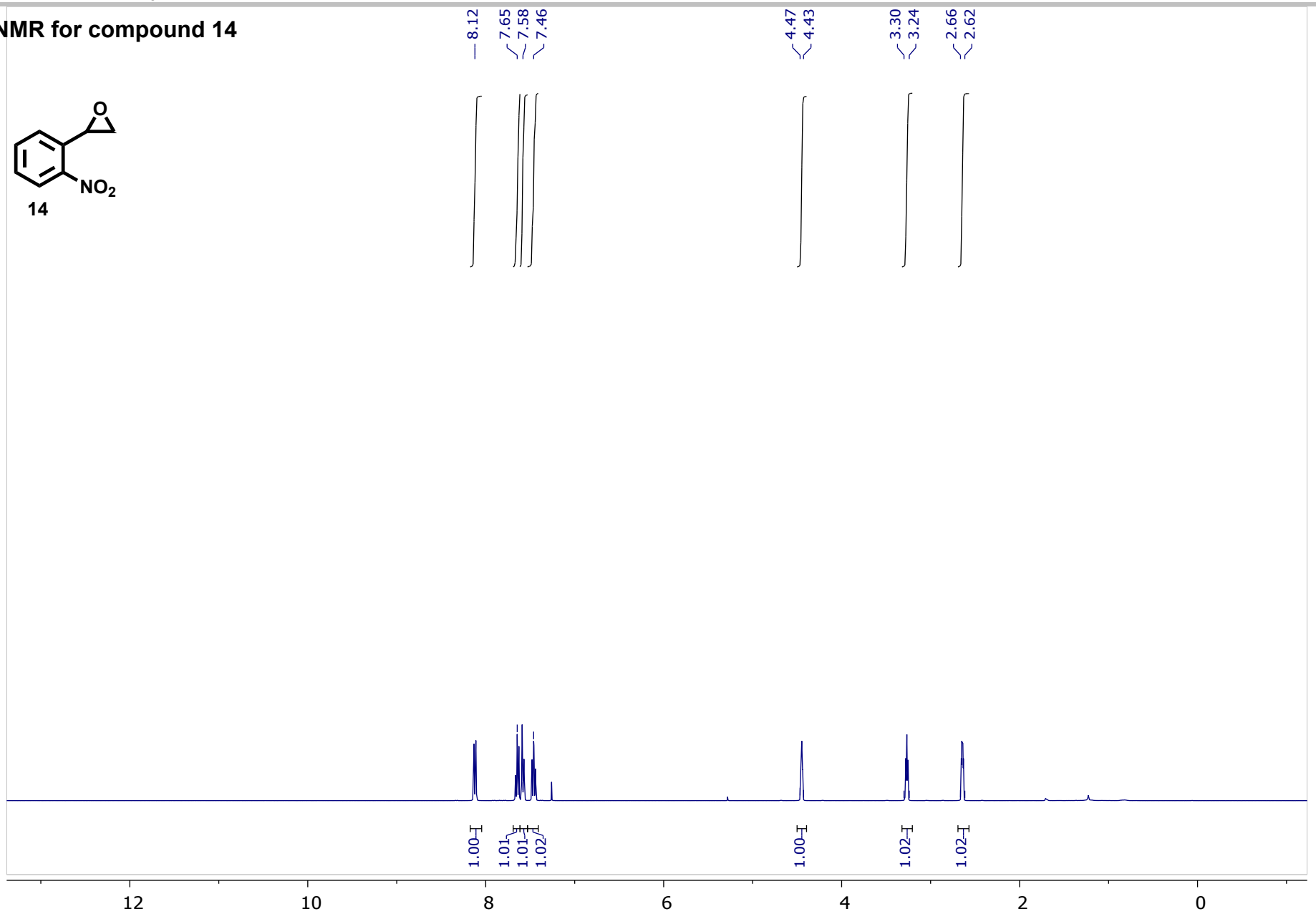


^{19}F NMR for compound 2

^{13}C NMR for compound 2



^{1}H NMR for compound 14



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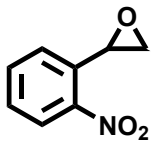
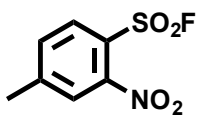
^{13}C NMR for compound 14



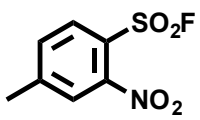
14

^{1}H NMR for compound 18



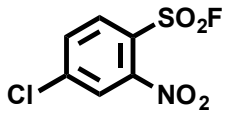
18

^{19}F NMR for compound 18



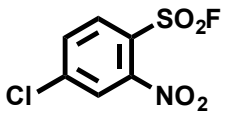
18

^{1}H NMR for compound 19



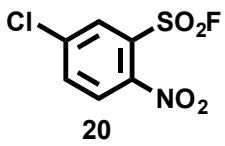
19

^{19}F NMR for compound 19



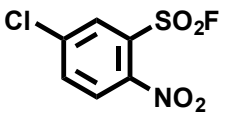
19

^{1}H NMR for compound 20



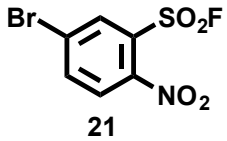
20

^{19}F NMR for compound 20



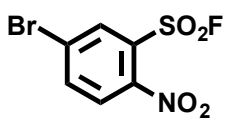
20

^{1}H NMR for compound 21



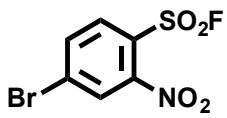
21

^{19}F NMR for compound 21



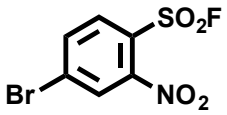
21

^{1}H NMR for compound 22



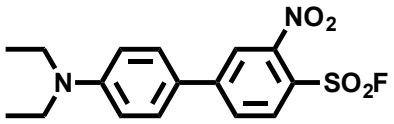
22

^{19}F NMR for compound 22



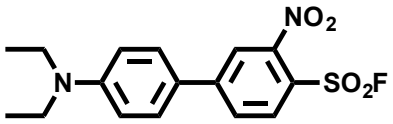
22

^{1}H NMR for compound 23



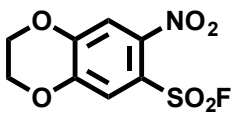
23

^{19}F NMR for compound 23



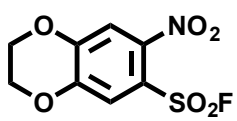
23

^{1}H NMR for compound 24



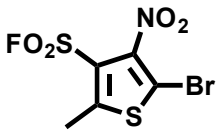
24

^{19}F NMR for compound 24



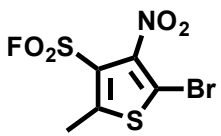
24

^{1}H NMR for compound 25



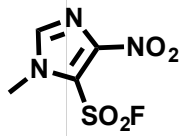
25

^{19}F NMR for compound 25



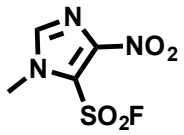
25

^{1}H NMR for compound 26



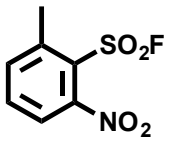
26

^{19}F NMR for compound 26



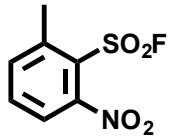
26

^{1}H NMR for compound 27



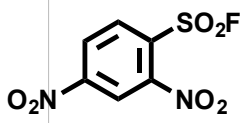
27

^{19}F NMR for compound 27



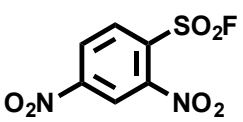
27

^{1}H NMR for compound 28

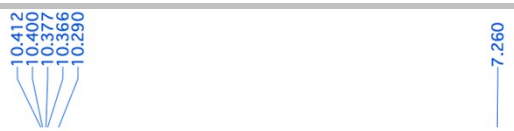


28

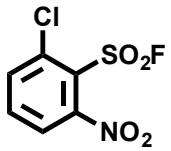
^{19}F NMR for compound 28



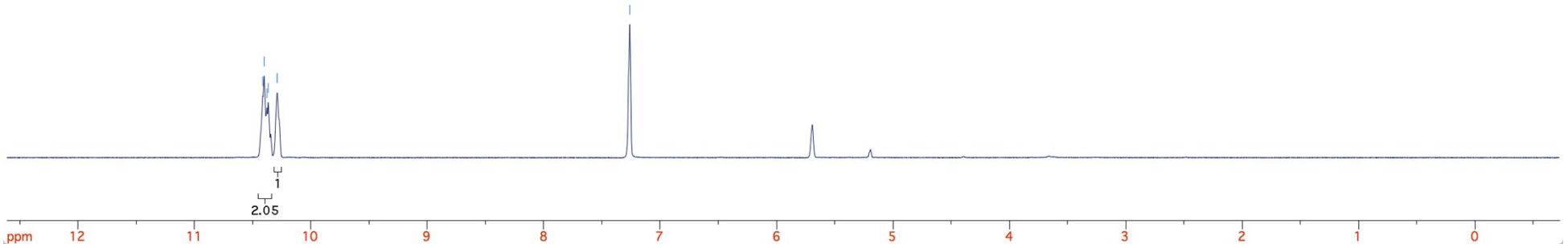
28



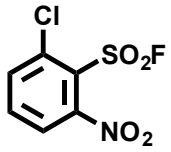
^{1}H NMR for compound 29



29

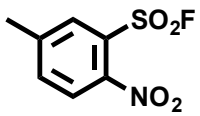


^{19}F NMR for compound 29



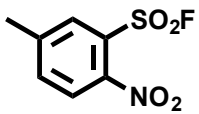
29

^{1}H NMR for compound 30



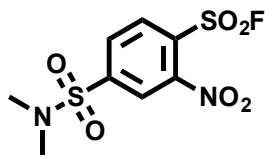
30

^{19}F NMR for compound 30



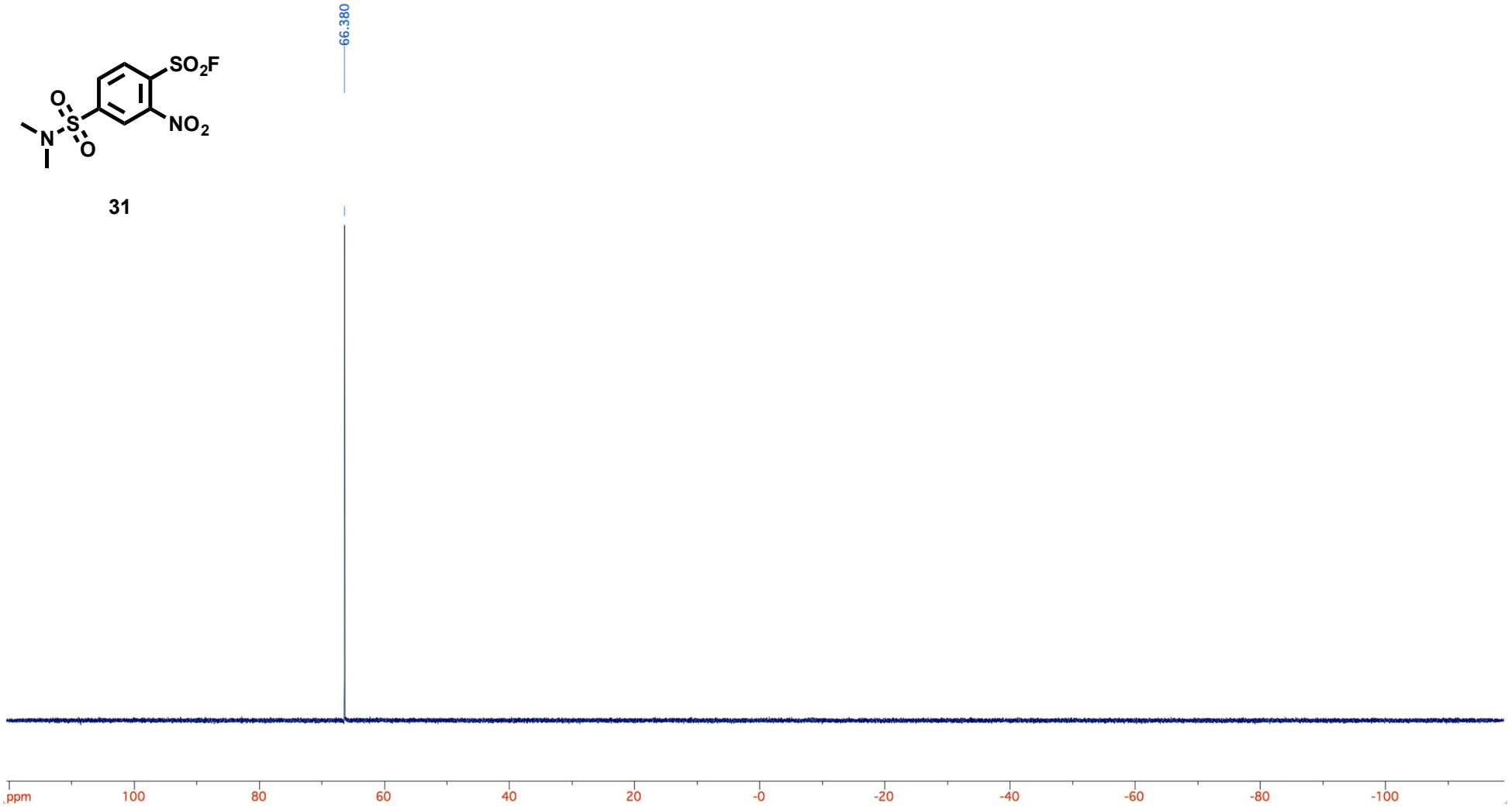
30

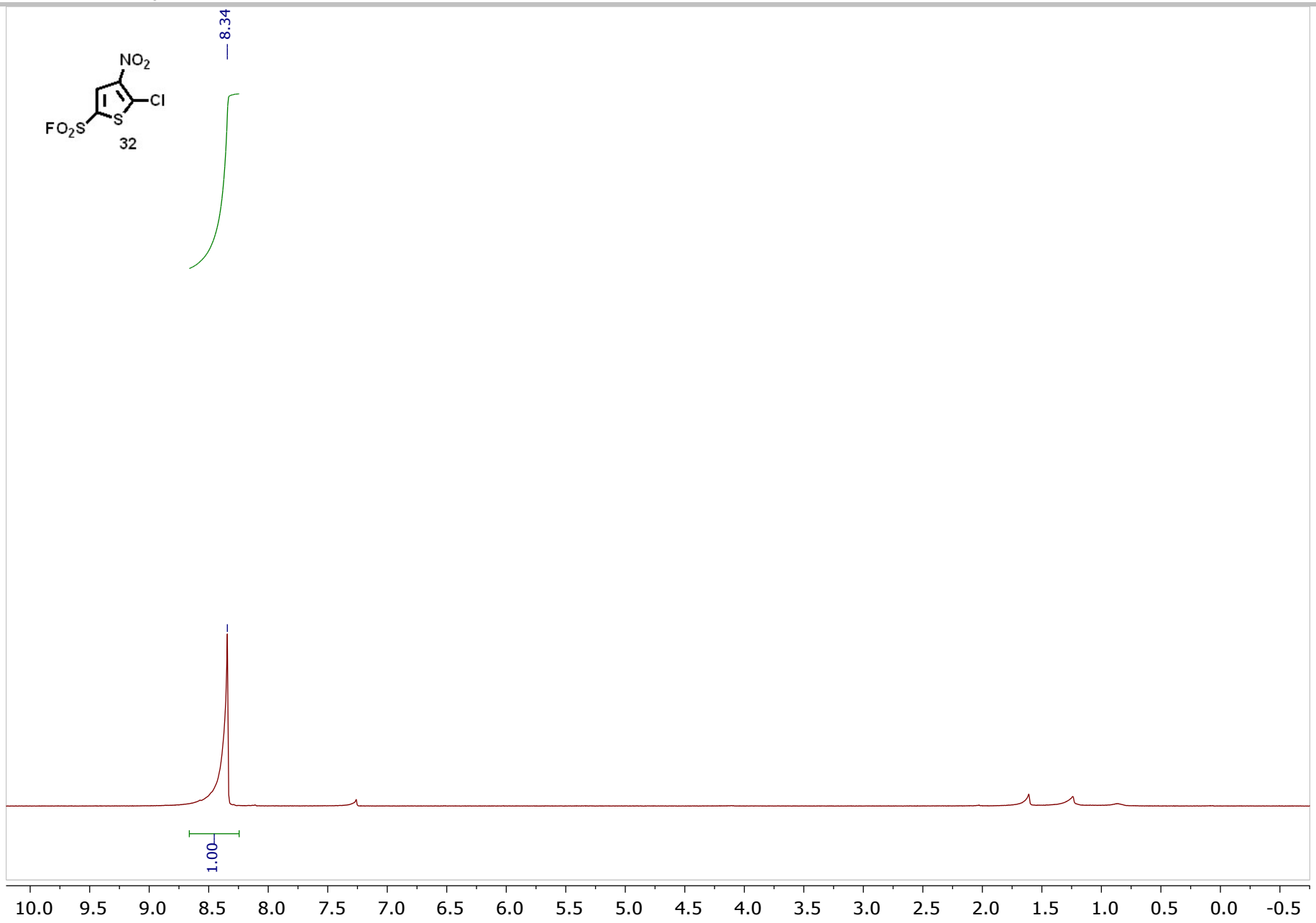
^{1}H NMR for compound 31

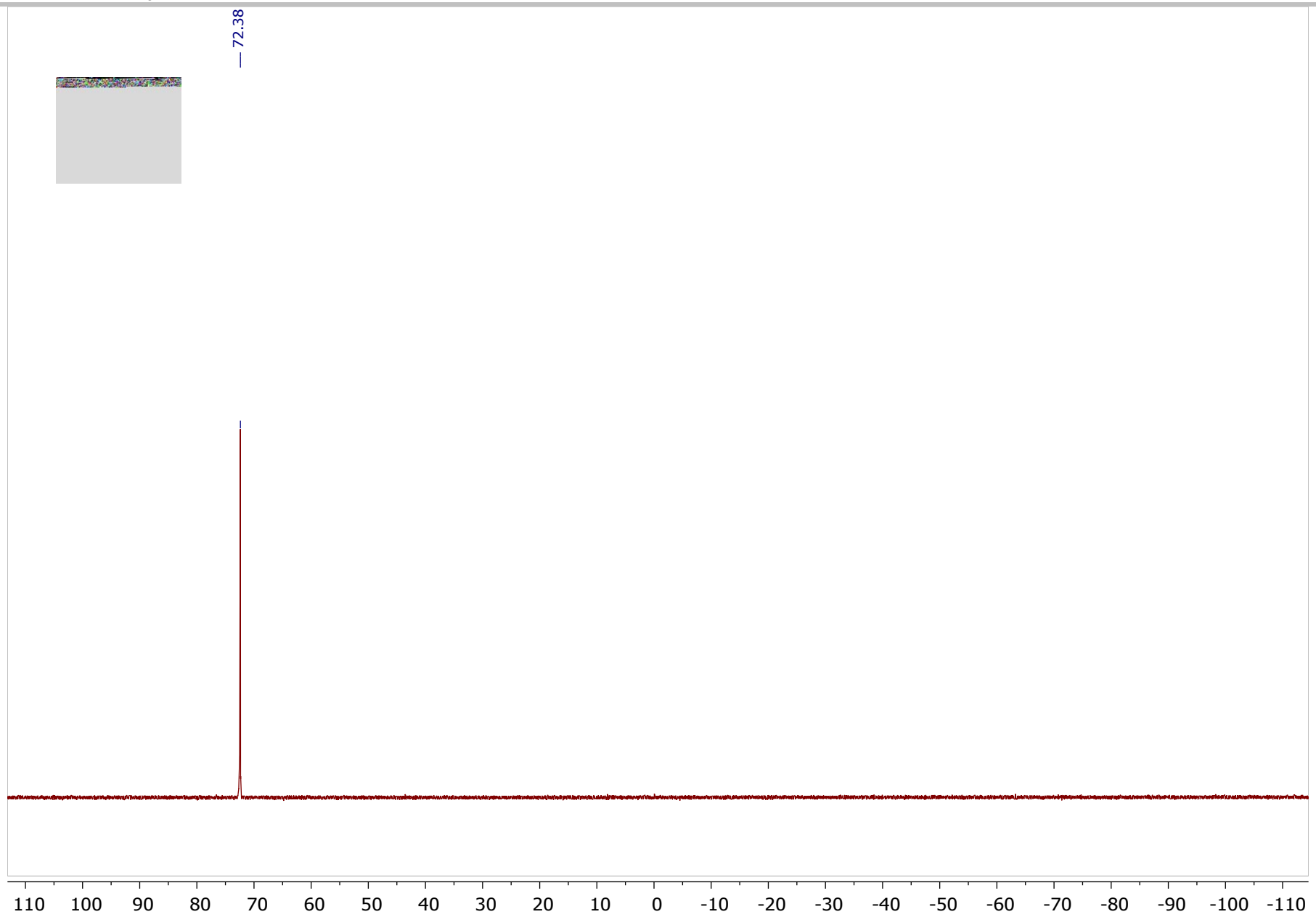


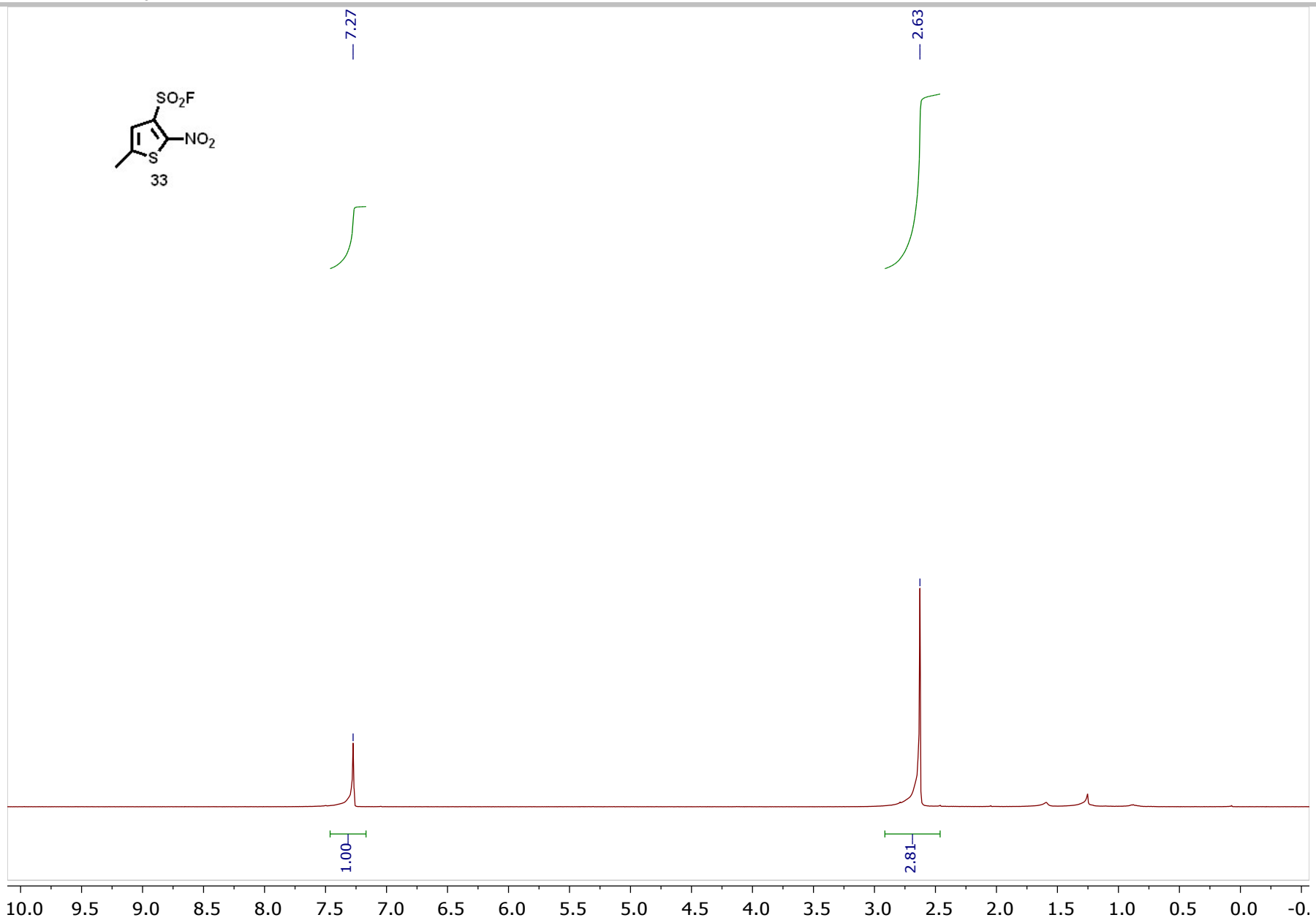
31

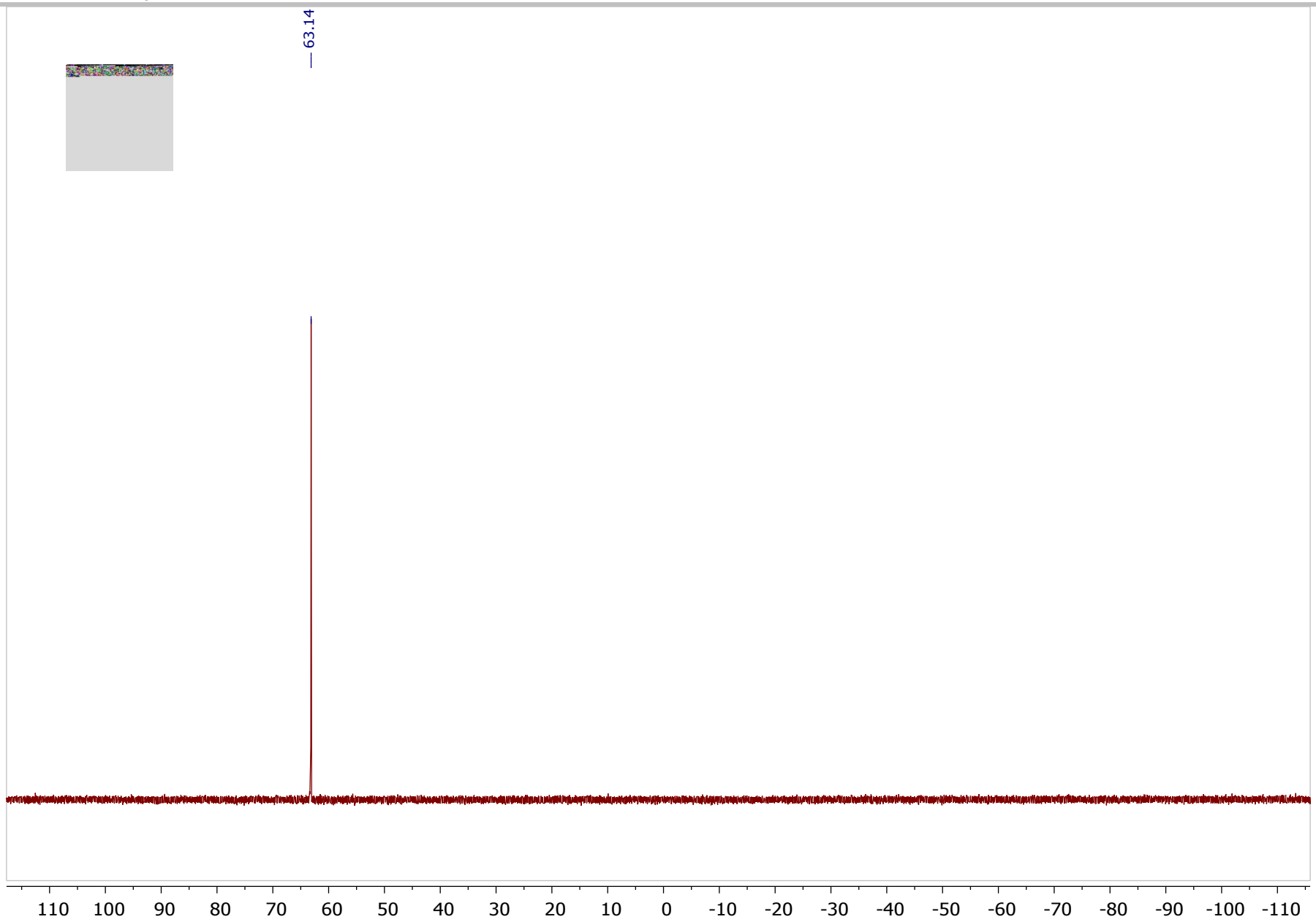
^{19}F NMR for compound 31

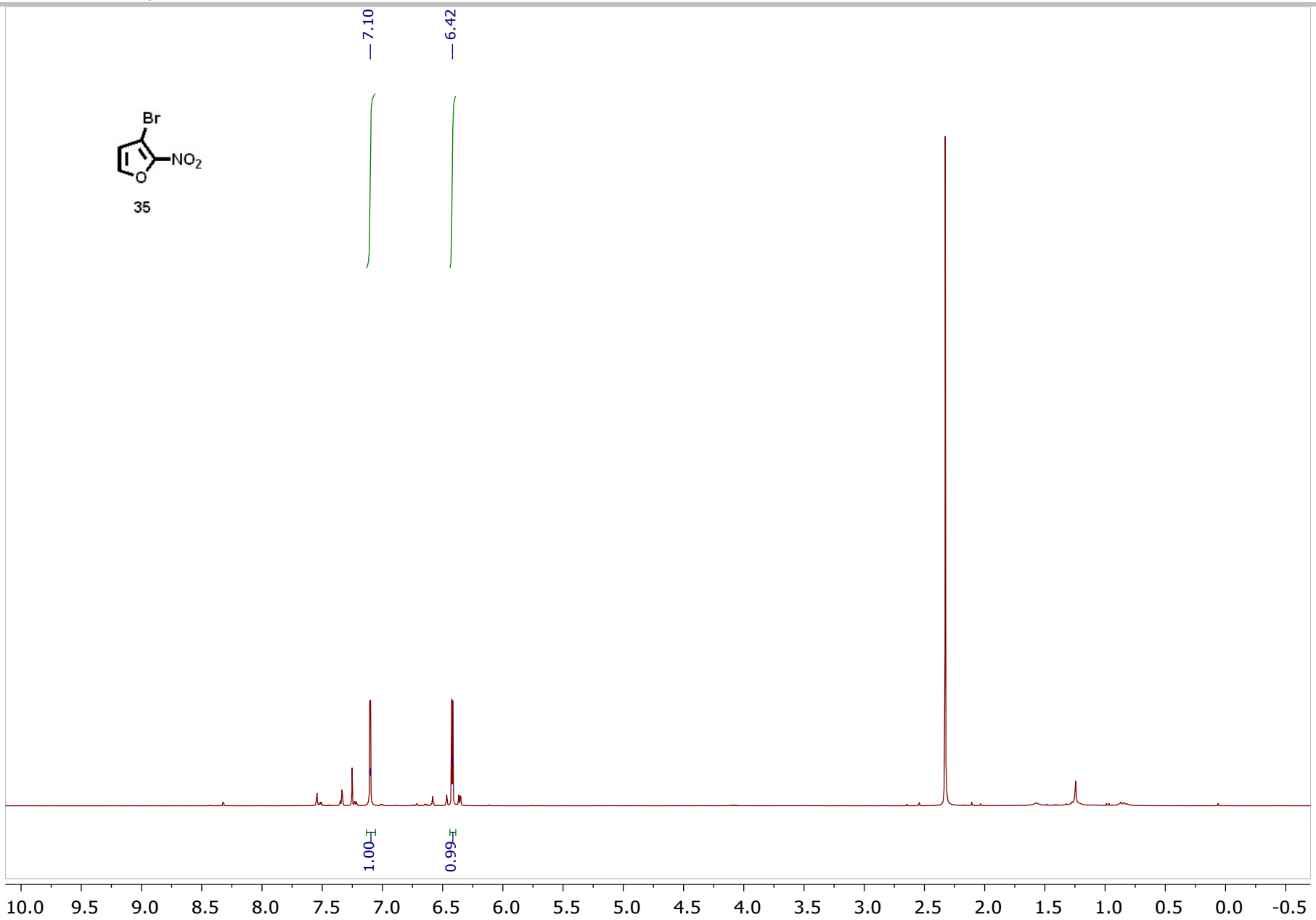

66.380
SO2F
O
S
N
O
NO2
31
ppm
100
80
60
40
20
-0
-20
-40
-60
-80
-100

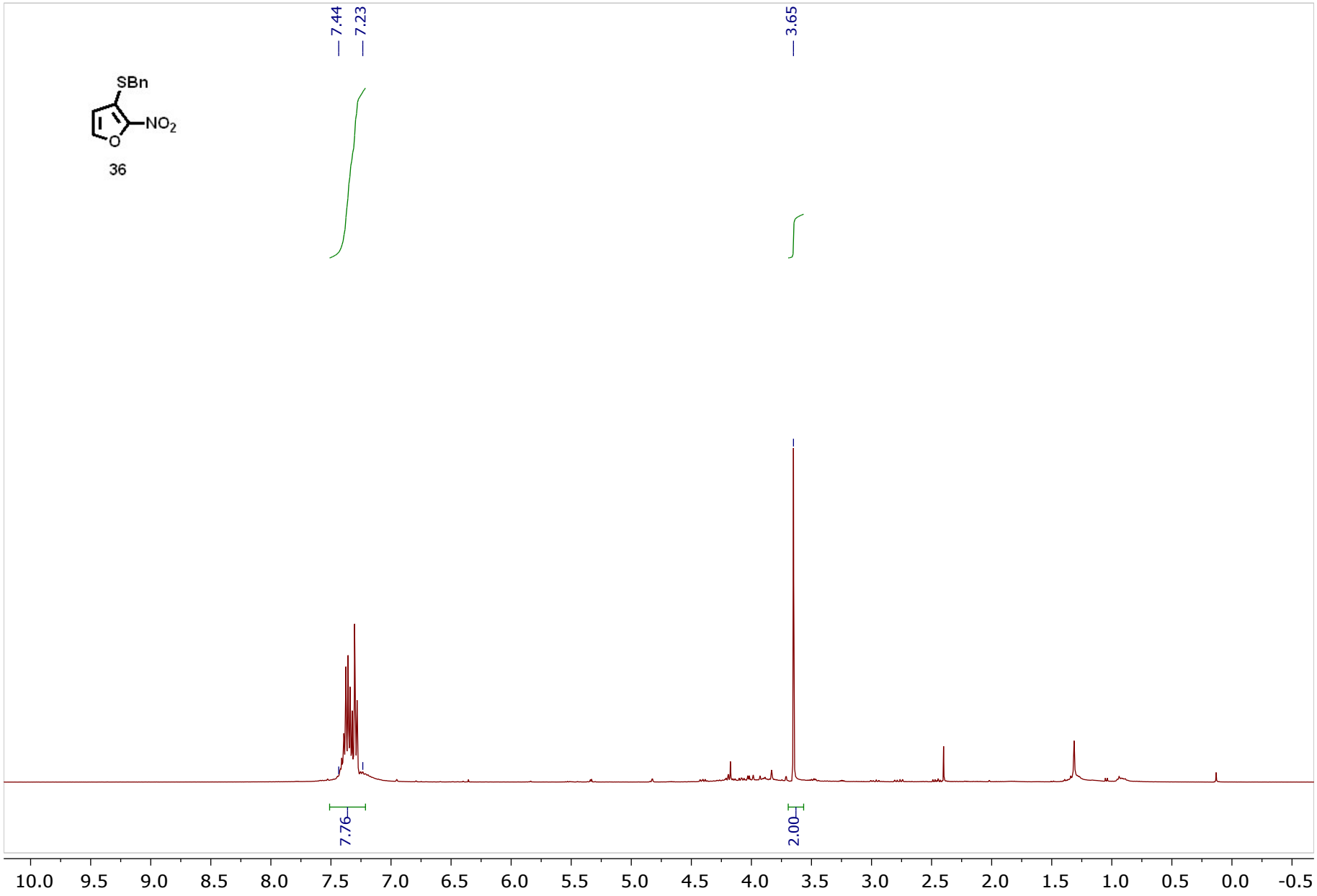

8.34
NO2
Cl
FO2S
S
32
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

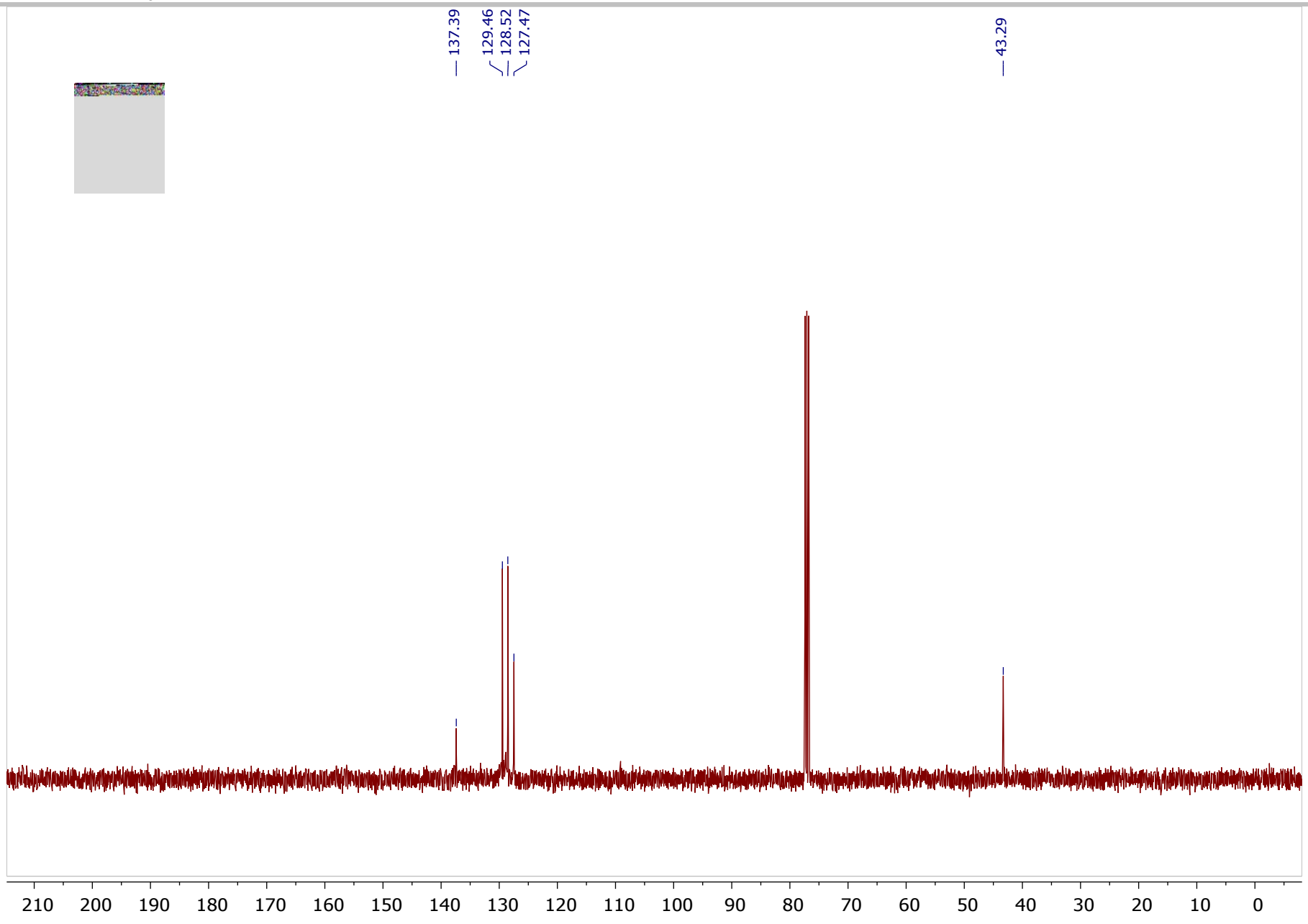

72.38
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110

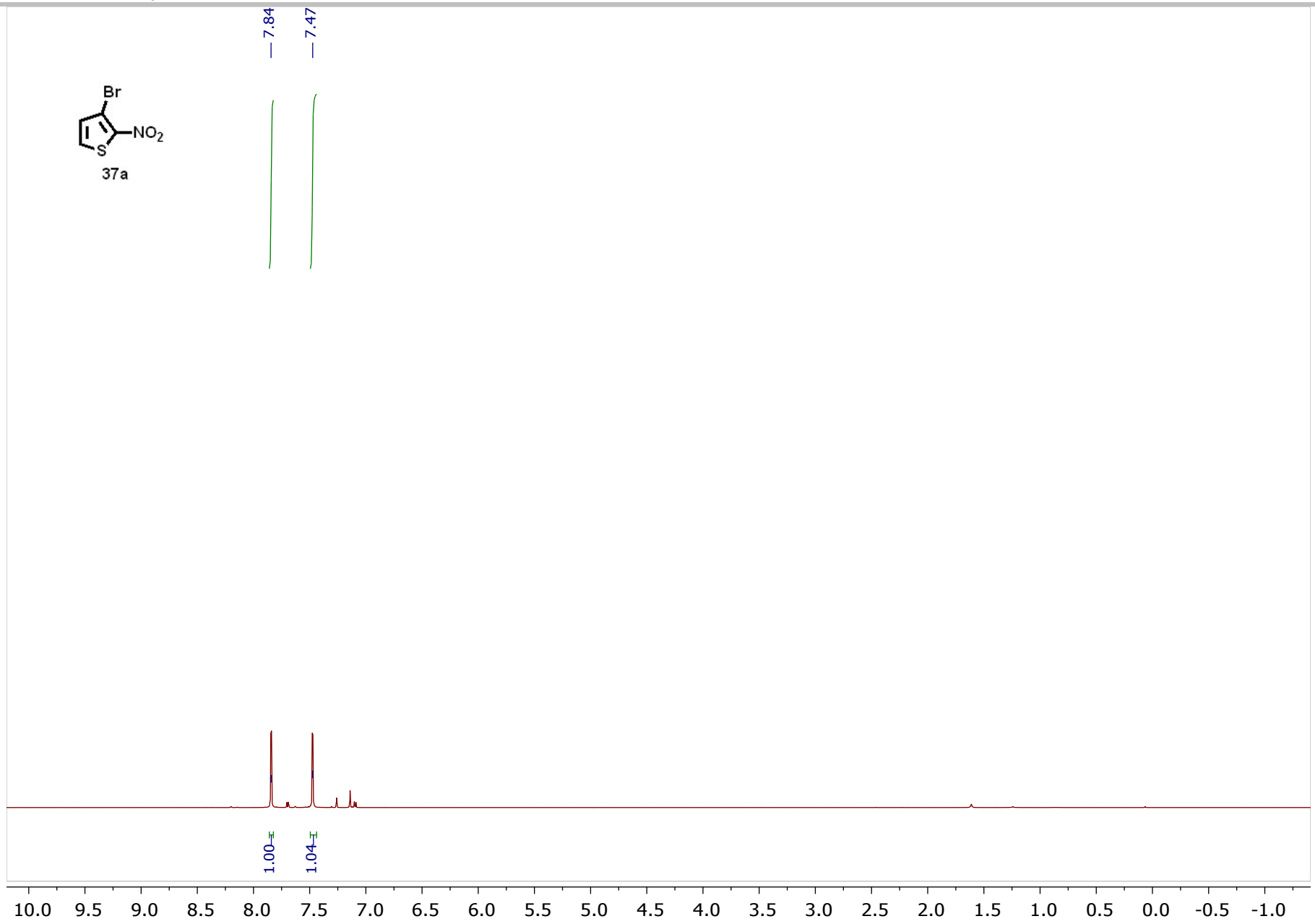

7.27
2.63
SO2F
NO2
S
33
1.00
2.81
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.

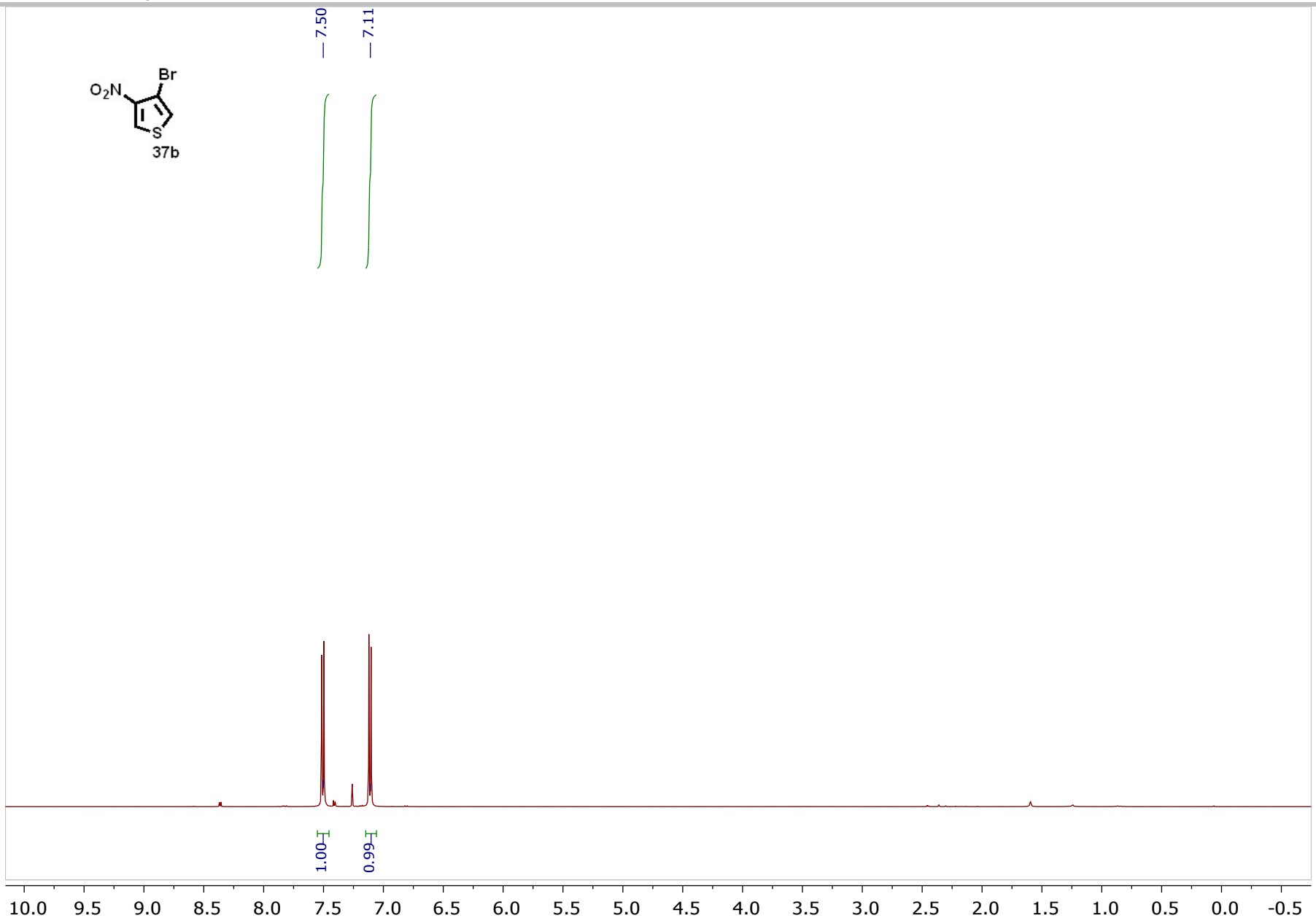

63.14
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110


7.10
6.42
Br
NO2
O
35
1.00
0.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


7.44
7.23
3.65
SBn
NO2
O
36
7.76
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


137.39
129.46
128.52
127.47
43.29
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.84
7.47
Br
NO2
S
37a
1.00
1.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0


7.50
7.11
Br
O_2N
S
37b
1.00
0.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

G. Antibacterial Activity Determination

E. coli or other bacteria strains were grown on Mueller Hinton agar plates for 1-2 days until colonies were obtained. 10 mL Mueller Hinton Broth was inoculated with one colony of bacteria in a sterile tube and grew until mid log phase (OD_{600} 0.5 to 0.9: about 15 h). The cells were diluted to OD_{600} 0.08- 0.10 with media for addition to 96 plates. 20 µL of the diluted cells were added in 20 mL of media. Stock solutions of the compounds were prepared in DMSO. 198 µL cells were added to each well of the 96 well plates, and 2 µL of different concentration of compounds were added to the 96 well plates. The plates were incubated for an additional 16 h at 37 ^{o}C, and the OD was measured and the MIC_{99} was determined. Each concentration was measured in triplicate.