Supporting Information

Discovery of Novel Small Molecule Dual Inhibitors Targeting Toll-like Receptor 7 and 8

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GENERAL CELL CULTURE CONSIDERATIONS

THP-1 cells were sourced from ATCC and were not further authenticated. The human embryonic kidney (HEK)-Blue Nulll1, TLR2-, TLR4-, TLR7-, and TLR9-overexpressing HEK-Blue cells were purchased (InvivoGen) and were not further authenticated. Stable TLR3-and TLR5- overexpressing HEK-Blue cells were generated by lentiviral infection of HEK-Blue Null1 cells and functionally authenticated in our laboratory as previously described.[1–3] The stable TLR8-overexpressing HEK-Blue cells were authenticated by confocal microscopy and functional validation.[4,5] All cultured cells were grown at 37 °C in a humidified incubator containing 5% CO_2. HEK-Blue TLR cells were cultured in complete culture medium: Dulbecco's modified Eagle's medium (DMEM), 10% (v/v) FBS, 50 U/mL penicillin, 50 mg/mL streptomycin, 100 mg/mL normocin, and 2 mM L-glutamine. THP-1 were cultured in Roswell Park Memorial Institute (RPMI) 1640 medium supplemented with 10% (v/v) FBS, 2 mM L-glutamine, 100 μg/mL streptomycin and 100 U/mL penicillin and 0.05 mM 2-mercaptoethanol. The cultures were checked periodically and found to be free of mycoplasma contamination.

CELL CULTURE AND SECRETED EMBRYONIC ALKALINE PHOSPHATASE (SEAP) ASSAY

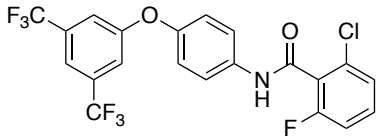
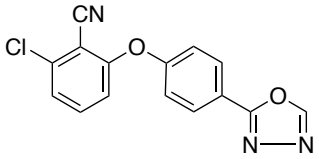
Commercially available or prepared (Dr. Shuting Zhang) Hek 293 cells transfected with appropriate hTLR gene and an inducible secreted embryonic alkaline phosphatase (SEAP) reporter gene were used to evaluate compound potency and TLR specificity. The SEAP reporter gene is fused to five NF-κB and AP-1 sites. Stimulation of hTLRs is induced with natural ligand or small molecule chemical ligand (R848). This activates NF-κβ and AP-1, which induces the production of SEAP protein. Growth media for cell maintenance was prepared using DMEM media with 10% FBS, 1% L-glutamine, 1% penicillin/streptomycin and supplemental antibiotics (10 μg/mL blasticidin and 100 μg/mL zeocin) per manufacturer's recommendations to select for TLR and reporter expression. Unsupplemented test media was prepared using DMEM media with 10% FBS (deactivated), 1% L-glutamine, and 1% penicillin/streptomycin (note supplemental antibiotics were not added). 100,000 cells/well or 70,000 cells/well were plated in a tissue culture treated 96-well (Costar 3596) in unsupplemented DMEM test media. Cells were then treated with appropriate concentration of compound, natural TLR ligand (1 μg/mL R848, 1 μg/mL R848 or ssRNA/LyoVec, purchased from Invivogen). The cells were incubated for 18–20 hours and assayed for NF-κB signaling using a SEAP assay. Quanti-Blue (Invivogen) medium for quantification of alkaline phosphatase was used was used to monitor expression of SEAP via detection of SEAP reporter protein secreted by cells. The compounds were considered active if they decreased SEAP levels as indicated by a decrease in absorbance at 620 nm. The data were normalized with 100% untreated cells as the negative control and 100% cells treated with TLR ligand (1 μg/mL R848) as the positive control. All data for cell-based assays is represented as the average and standard deviation of three biological replicates.

CELL-BASED HIGH THROUGHPUT SCREENING (HTS)

Hits **1** and **2** were manually identified from an HTS targeting TLR8, see Table S1. We used the Maybridge HitFinder library, which contained 14,400 small molecules. The library compounds follow the Lipinski guidelines for "drug-likeness" and have properties that include: no more than 5 hydrogen bond donors, no more than 10 hydrogen acceptors, a molecular weight less than 500, and an octanol-water partition coefficient log P less than 5. The HTS protocol and results have been published for the development of the first selective TLR8 inhibitor.[4,5]

For this project, hit **1** and **2** were first re-tested at 4, 8, and 16 μM concentrations for potency validation and cell toxicity. Both compounds decreased inhibited TLR8 signaling in a dose-dependent manner to down regulate TLR8 induced SEAP levels with IC_{50} values of 2.88 ±0.25 μM (TLR7) and 1.64 ±0.40 μM (TLR8) for **1** and IC_{50}= 1.40 ±0.06 μM (TLR8) for **2**, see Figure S1. and Figure S2. For specificity test, no obvious inhibition was observed on other TLRs. Interestingly, compound **1** was the only inhibitor that down-regulated TLR7 induced SEAP levels. Compounds **1** and **2** share structural similarities that revealed come structure-activity relationship (SAR) information. Both compounds contained a diaryl ether linkage and the aromatic tricyclic ring core scaffold indicating those motifs are important for target selectivity. Differences such as the amide functional group and the 1,3,5-oxadiazole motif suggested those motifs could be modified to modulate TLR7/8 selectivity. Thus, we purchased **1** and **2** compounds (two different scaffold families) from Maybridge for further evaluation and potency optimization via SAR.

Table S1. Chemical structures of the hits identified from the cell-based HTS of the Maybridge Hit Finder library.

Compound ID	Chemical Structure
1	
2	

REPRESENTATIVE PROTOCOL FOR PREPARATION OF COMPOUND SOLUTIONS FOR CELL-BASED ASSAYS

Compound stock solutions were prepared by dissolving compounds in 100% DMSO to obtain a final concentration of 20 mM. The intermediate compound stock solutions (i.e. 10 mM, 100 µM) used for compound serial dilutions were prepared by diluting the appropriate volume of 20 mM compound stock solution in test media. The final DMSO content in the final compound solution was < 5%. Ten or 50 µL of a sample solution were dispensed per well using Eppendorf multichannel pipette. Subsequently, 90 µL or 50 µL of ligand or 100% test media was added to each well. Prior to addition of compound or ligand, 100 µL of 100% cells were dispensed per well, final volume of test well was 200 µL.

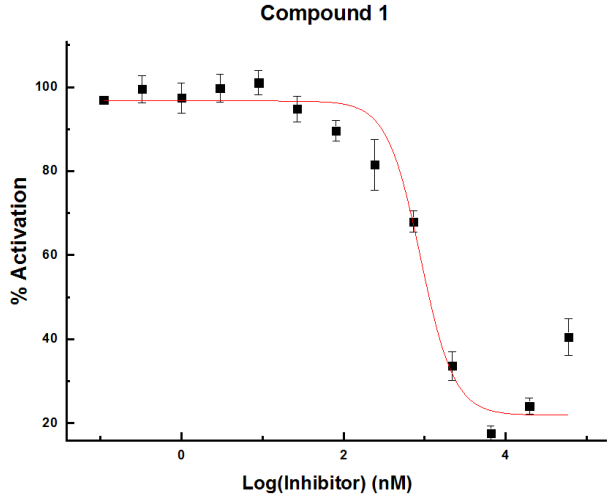


Figure S1. Dose-response curve for compound **1** using the Hek-Blue-human TLR8 (hTLR8) is a gene reporter assay. The assay co-expresses hTLR8 gene with an inducible secreted embryonic alkaline phosphatase (SEAP reporter gene, which is fused to five NF-κβ and AP-1 sites. Stimulation of the hTLR8 is induced with R848, a known TLR8 agonist. This activates NF-κβ and AP-1, which induces the production of SEAP. IC_{50} was derived from dose-response curve in HEK-Blue TLR8 cell line for the measurement of the production of SEAP. Serial dilutions of compounds in DMSO and R848 ligand were added to the cells, incubated at 37 °C for 16 h. HEK-blue detection cell culture medium was used to monitor expression of SEAP via detection of SEAP reporter protein secreted by cells. The data was normalized as (well raw data – untreated cells)/(ligand + solvent control – untreated cells) such that ligand (1 µg/mL R848) + solvent is 100% activation, and untreated cells are 0% activation. The experiment was conducted with a minimum of three biological replicates, in triplicate. The IC_{50} values were obtained by using Origin Pro 9 to calculate the dose-response curve.

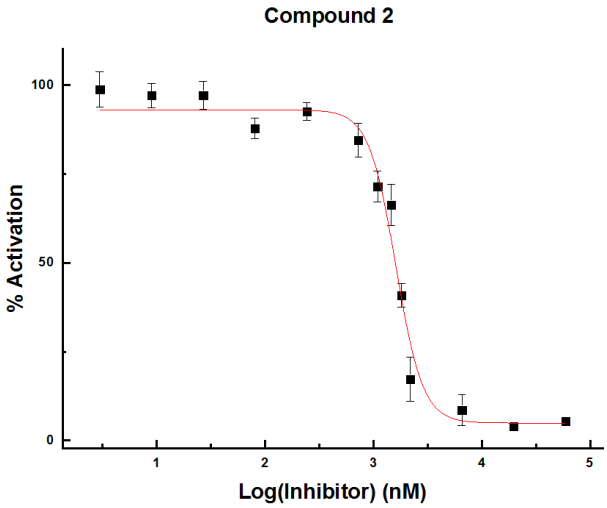


Figure S2. Dose-response curve for compound **2** using the Hek-Blue-human TLR8 (hTLR8) is a gene reporter assay. The assay co-expresses hTLR8 gene with an inducible secreted embryonic alkaline phosphatase (SEAP reporter gene, which is fused to five NF-κβ and AP-1 sites. Stimulation of the hTLR8 is induced with R848, a known TLR8 agonist. This activates NF-κβ and AP-1, which induces the production of SEAP. IC_{50} was derived from dose-response curve in HEK-Blue TLR8 cell line for the measurement of the production of SEAP. Serial dilutions of compounds in DMSO and R848 ligand were added to the cells, incubated at 37 °C for 16 h. HEK-blue detection cell culture medium was used to monitor expression of SEAP via detection of SEAP reporter protein secreted by cells. The data was normalized as (well raw data – untreated cells)/(ligand + solvent control – untreated cells) such that ligand (1 μg/mL R848) + solvent is 100% activation, and untreated cells are 0% activation. The experiment was conducted with a minimum of three biological replicates, in triplicate. The IC_{50} values were obtained by using Origin Pro 9 to calculate the dose-response curve.

TOLL-LIKE RECEPTOR (TLR) SELECTIVITY STUDY

The selectivity of compounds against the TLR family was examined in HEK-Blue cells overexpressing a specific TLR and accessory proteins. The assay was performed in the same manner as "SEAP reporter assay," except that polyriboinosinic:polyribocytidylic acid (poly(I:C)) (5 μg/mL), LPS (lipopolysaccharide) (20 ng/mL), Pam3CSK4 (*N*-palmitoyl-*S*-[2,3-bis(palmitoyloxy)-(2*RS*)-propyl]-[*R*]-cysteinyl-[*S*]-seryl-[*S*]-lysyl-[*S*]-lysyl-[*S*]-lysyl-[*S*]-lysine3HCl) (100 ng/mL), Pam2CSK4 (*S*-[2,3-bis(palmitoyloxy)-(2*RS*)-propyl]-[*R*]-cysteinyl-[*S*]-seryl-[*S*]-lysyl-[*S*]-lysyl-[*S*]-lysyl-[*S*]-lysine3CF_3COOH) (10 ng/mL), Flagellin (50 ng/mL), R848 (1 μg/mL), and ODN2006 (0.15 μM) were used to selectively activate HEK-Blue hTLR3, hTLR4, hTLR1/2, hTLR2/6, hTLR5, hTLR7, and hTLR9 cells, respectively.

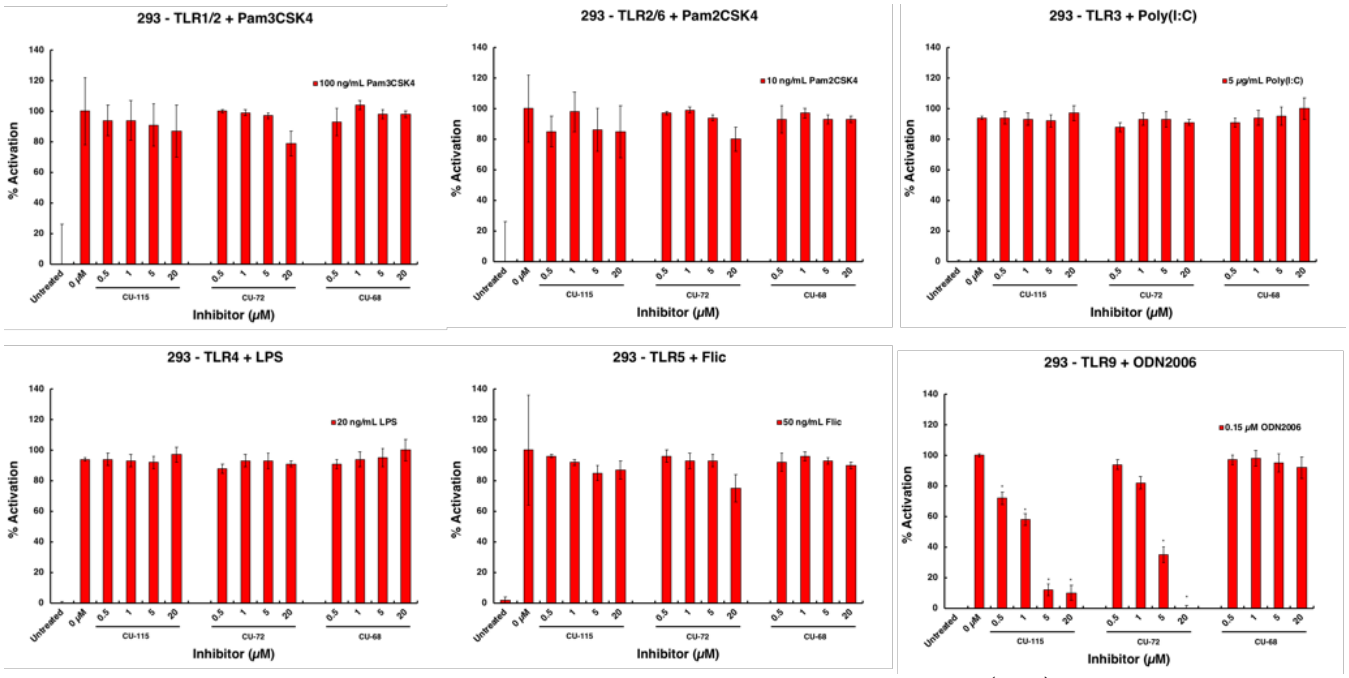


Figure S3. Effect of **CU-115**, **CU-72**, and **CU-68** on Toll-like receptor pathways. Human embryonic kidney (HEK) 293 cells expressing human toll-like receptor (hTLR) gene and an inducible secreted embryonic alkaline phosphatase (SEAP) reporter gene were incubated with **CU-115**, **CU-72**, or **CU-68** for 16 h. Ligand-induced TLR activation was determined by measuring absorbance at 620 nm for the SEAP protein and comparing wells treated with sample to 50% DMSO treated and untreated cells. The data was normalized as [(raw data – untreated cells)/(ligand + solvent control – untreated

cells)]. Ligand + solvent is 100% activation, and untreated cells are 0% activation. The result of one representative biological replicate for three independent days is plotted with the error bars representing the standard deviation of three technical replicates for one independent biological replicate. At 0.5, 1, 5, and 20 μM **CU-115**, **CU-72**, or **CU-68** do not modulate the NF-κB inhibition induced by Pam2CSK4, Pam3CSK4, Poly(I:C), LPS, R848, and Flic in HEK-293 TLR1/2, TLR2/6, TLR3, and TLR4 cells. Both **CU-115** and **CU-72** inhibited TLR9 signaling at 1, 5, and 20 μM and ~10–25% inhibition. **CU-72** was least active (~10% inhibition) in TLR9 cells and CU-68 displayed 0% inhibitory activity in TLR9 cells.

WST-1 CELL VIABILITY ASSAY

Cellular toxicity was determined using the established Roche Cell Proliferation WST-1 assay purchased from Sigma Aldrich. The WST-1 reagent was diluted (1:10) into cell-containing media and incubated for 30 minutes. The sample well was assayed with absorbance at 430 nm. The data point represents the average and standard deviation of three biological replicates. The data were normalized as (raw data – 100% DMSO)/(untreated cells – 100% DMSO) such that untreated cells are 100% survival and 100% DMSO is 0% survival.

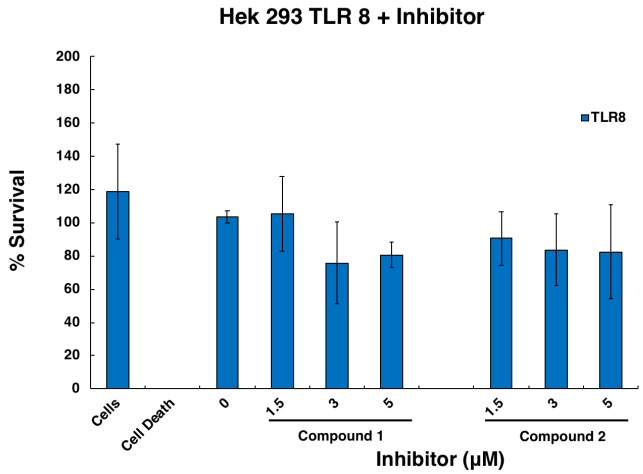


Figure S4. Cellular toxicity studies for compound **1** and **2** are nontoxic. The toxicity was examined by treating HEK 293 TLR8 with sample compound at 1.5, 3, and 5 μM in DMSO (1% final concentration) for 16 hours. Cell survival rate was determined by measuring absorbance at 430 nm and comparing wells treated with sample to 50% DMSO treated and untreated cells. Compound **1** and **2** were nontoxic at low concentrations to HEK 293 cells at 1.5, 3, and 5 μM.

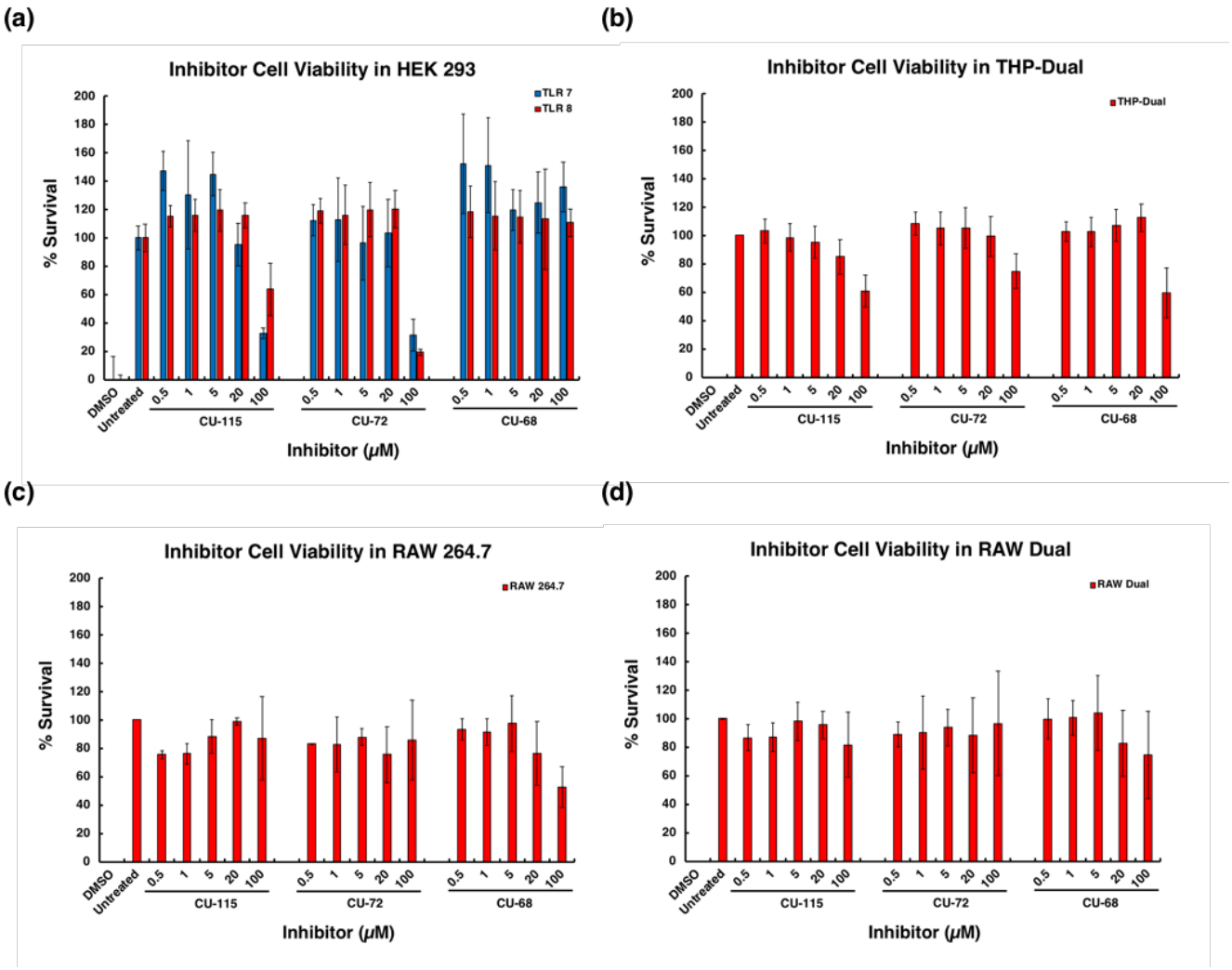
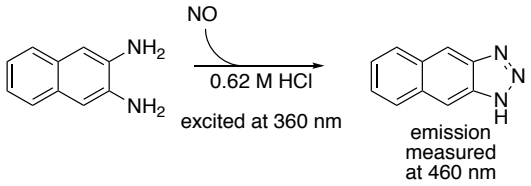


Figure S5. The toxicity was examined by treating Hek-293 TLR7, Hek-293 TLR8, THP-Dual, Raw 264.7, and RAW Dual cell lines with sample compound at 0.5, 1.0, 5, and 20 μM in DMSO (1% final concentration) for 16 hours. Cell survival rate was determined by measuring absorbance at 430 nm and comparing wells treated with sample to 50% DMSO treated and untreated cells. **CU-115**, **CU-72**, and **CU-68** inhibitors were nontoxic at low concentrations (0.5 and 20 μM). **CU-115** and **CU-72** are toxic to Hek 293 cells at 100 μM and **CU-68** displayed partial toxicity at 100 μM in THP-Dual cells.

NITRIC OXIDE (NO) ASSAY[6]

Raw 264.7 cells were plated on day one at 375,000 cells/mL in a tissue culture treated 96-well plate. The cells were plated in supplemented RPMI medium (10% fetal bovine serum, 1% L-glutamine, 1% penicillin/streptomycin) and incubated at 37 °C. On day two, supplemented media was removed from the cells, and the unsupplemented RPMI was added (100 μL). The cells were treated with 1 μg/mL R848 (90 μL) (Invivogen) and varying concentrations of the appropriate organic compound (10 μL). The final volume in each well was 200 μL. The 96-well plate was incubated with the organic compound for 18–24 hours at 37 °C. On day three, a solution of 0.05 mg/mL 2,3-diaminonapthalene (DAN, Sigma Aldrich) in 0.62 M HCl was prepared. The 96-well plate was removed from the incubator and 90 μL of media from each well was transferred to a black 96-well plate (Thermo-Scientific) respectively. This was followed by the addition of DAN/HCl solution (10 μL/well) to each well. The plate was covered with aluminum foil and shaken at room temperature for 15–20 minutes. The plate was quenched with 3 M aqueous NaOH (5 μL/ well). A Beckman Coulter DTX 880 Multimode Detector was used to quantify the results. Samples were excited at 360 nm and emission was measured at 430 nm. The data were normalized as (well raw data – untreated cells)/(ligand + solvent control – untreated cells) such that ligand + solvent is 100% activation, and untreated cells are 0% activation. The experiment was conducted with a minimum of three biological replicates, in triplicate. The IC_{50} values were obtained by using Origin Pro 9 to calculate the dose-response curve.



The NO assay uses a Sandmeyer-like reaction to convert 2,3-diaminonaphthalene to fluorescent 1(H)-naphthotriazole in the presence of NO. Activation of TLR7 results in the activation of NO synthase and the production of NO in RAW 264.7 macrophage cells.[6,7] We monitored the NO level as an indicator of R848-induced TLR7 activation to evaluate the compound inhibitory activity.

CYTOSOLIC NUCLEIC ACID SENSING PATHWAY SELECTIVITY ASSAYS

INTERFERON REGULATORY FACTOR (IRF)-LUCIA ASSAY IN RAW 264.7 CELLS:

Commercially available Raw-Dual cells (Invivogen) transfected with IRF-Luc/KI-[macrophage inflammatory protein-2 (MIP-2)]-secreted embryonic alkaline phosphatase (SEAP) reporter genes and an inducible Lucia luciferase gene (Luc) were used to evaluate compound potency for murine macrophages. The Lucia luciferase gene is under the control of an ISG54 minimal promoter with IFN-stimulated response elements. Stimulation of cGAS was induced with G3YSD, a cGAS agonist (Invivogen). This activates the IRF pathway, which induces the production of the Luciferase protein. Growth media for cell maintenance was prepared using DMEM media with 10 % FBS 1% L-glutamine, 1% penicillin/streptomycin and supplemental antibiotics (100 µg/mL normocin and 200 µg/mL zeocin) per manufacturer's recommendations to select for cGAS and IRF-Lucia/KI-[MIP-2]SEAP reporter expression.

Unsupplemented test media was prepared using DMEM media with 10% FBS (heat deactivated), 1% L-glutamine, and 1% penicillin/streptomycin (**note:** supplemental antibiotics were not added). 100,000 cells/well were plated in a tissue culture treated 96-well (Costar 3596) in unsupplemented DMEM test media. Cells were then treated with appropriate concentration of compound, and 1 µg/mL G3YSD ligand. The cells were incubated for 18–20 hours and assayed for IRF signaling using a Lucia luciferase assay. Quanti-Luc (Invivogen) medium for quantification of luciferase was used to monitor the luciferase expression by detection of Lucia luciferase reporter protein secreted by cells. The compounds were considered active if they decreased luciferase levels as indicated by a decrease in luminescence relative light units (RLU). The data were normalized with 100% untreated cells as the negative control and 100% cells treated with cGAS ligand (1 µg/mL G3YSD) as the positive control. All data for cell-based assays are represented as the average and standard deviation of three biological replicates, unless otherwise noted.

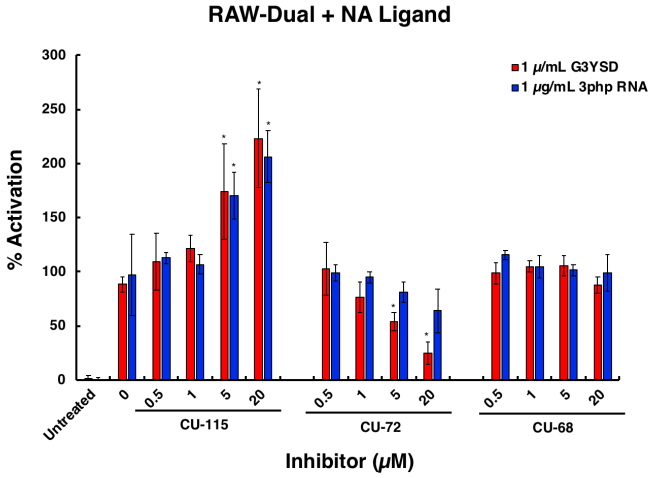


Figure S6. Effects of **CU-68**, **CU-115**, and **CU-72** treatment on IFN-I inhibition mediated by human cGAS and RIG-I cytosolic sensors. Raw-Dual cells transfected with IRF-Luc/KI-[macrophage inflammatory protein-2 (MIP-2)]-secreted embryonic alkaline phosphatase (SEAP) reporter gene and an inducible Lucia luciferase gene (Luc). The RAW-Dual cells were stimulated 3p-hpRNA, a known RIG-I agonist in the presence or absence of the inhibitors and to activate the cGAS pathway we used Y-form dsDNA (G3-YSD), a known cGAS agonist. The cells were incubated for 18–20 h and assayed for IRF signaling using a Lucia luciferase assay. Quanti-Luc (Invivogen) medium for quantification of luciferase was used to monitor the expression of luciferase via detection of Lucia luciferase reporter protein secreted by cells. The compounds were considered active if they decreased luciferase levels as indicated by a decrease in luminescence relative light units (RLU). The data were normalized as [(raw data – untreated cells)/(ligand + solvent control – untreated cells)]. Ligand + solvent is 100% activation, and untreated cells are 0% activation. The average result of three biological replicates for three independent days is plotted with the error bars representing the standard deviation of three independent biological replicates. At

0.5, 1, 5 and 20 μM **CU-115** and **CU-68** do not modulate type-1 IFN transcription mediated by cGAS-STING or the RIG-I pathways in RAW-Dual cells. **CU-72** displayed an off-target effect for both the cGAS-STING and RIG-I pathway at 5 and 20 μM.

INTERFERON REGULATORY FACTOR (IRF)-LUCIA ASSAY IN THP1-DUAL CELLS:

Commercially available THP-1 cells (Invivogen) transfected with IRF-Luc/KI-[macrophage inflammatory protein-2 (MIP-2)]-secreted embryonic alkaline phosphatase (SEAP) reporter genes and an inducible Lucia luciferase gene (Luc) were used to evaluate compound potency for THP-1 cells. The Lucia luciferase gene is under the control of an ISG54 minimal promoter with IFN-stimulated response elements. Stimulation of cGAS was induced with G3YSD, a cGAS agonist (Invivogen), and stimulation of RIG-I was induced with 3p-hpRNA, a known RIG-I agonist (Invivogen). This activates the IRF pathway, which induces the production of the Luciferase protein. Growth media for cell maintenance was prepared using RPMI medium (10% fetal bovine serum, 1% L-glutamine, 1% penicillin/streptomycin) and 100 μg/mL Normocin per manufacture's recommendations to select for cGAS and IRF-Lucia/KI-[MIP-2]SEAP reporter expression.

PHORBOL 12-MYRISTATE 13-ACETATE (PMA)-INDUCED THP-1 DIFFERENTIATION PROTOCOL:

Day 1: THP-1 cells with phorbol-12-myristate-13-acetate (PMA; 50 ng/mL final concentration) treatment were seeded at ~100,000 cells per well in 200 μL supplemented RPMI medium (10% (v/v) FBS, 2 mM L-glutamine, 100 μg/mL streptomycin and 100 U/mL penicillin and 0.05 mM 2-mercaptoethanol) in 96-well plates and incubated at 37 °C in a humidified 5% CO2 atmosphere. After 24 h, the cells were adhered to the surface of the dish and gently washed with pre-warmed PBS and 200 μL growth medium.

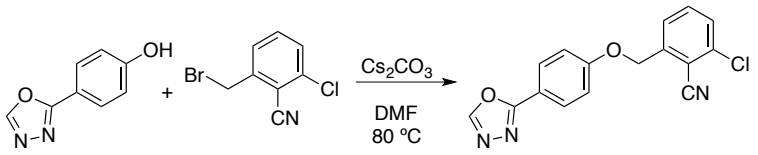
Day 4: The medium was replaced with unsupplemented RPMI, and the cells were treated with G3YSD (1 μg/mL) and various concentrations of compounds or left untreated. The cells were incubated for 18–20 hours and assayed for IRF signaling using a Lucia luciferase assay. Quanti-Luc (Invivogen) medium for quantification of luciferase was used to monitor the expression of luciferase via detection of Lucia luciferase reporter protein secreted by cells. The compounds were considered active if they decreased luciferase levels as indicated by a decrease in luminescence relative light units (RLU). The data were normalized with 100% untreated cells as the negative control and 100% cells treated with cGAS ligand (1 μg/mL G3YSD) as the positive control. All data for cell-based assays are represented as the average and standard deviation of three biological replicates, unless otherwise noted.

For evaluating inhibition of the retinoic acid-inducible gene I (RIG-I) receptor, the same protocol described above was used. The RIG-I pathway is activated using 1 μg/mL of 3p-hpRNA (Invivogen), a known RIG-I agonist. Quanti-Luc (Invivogen) medium for quantification of luciferase was used to monitor the expression of luciferase via detection of Lucia luciferase reporter protein secreted by cells as described above.

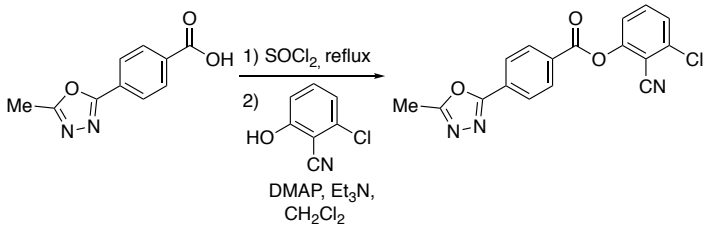
HUMAN TNF-α AND IL-1β ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA):

Levels of TNF-α or IL-1β were determined using Anti-human TNF or Anti-human IL-1β respectively with an ELISA Kit following manufacturer's instructions. THP-1 cells with phorbol-12-myristate-13-acetate (PMA; 50 ng/mL) treatment were seeded at 2×10^6 per well in 2 mL supplemented RPMI medium (10% (v/v) FBS, 2 mM L-glutamine, 100 μg/mL streptomycin and 100 U/mL penicillin and 0.05 mM 2-mercaptoethanol) in 6-well plates and incubated at 37 °C in a humidified 5% CO_2 atmosphere. After 24-48 h, the cells were adhered to the surface of the dish. The medium was replaced with unsupplemented RPMI, and the cells were treated with R848 (1 μg/mL) and various concentrations of compounds or left untreated in 3 mL un-supplemented RPMI. After 24 h, supernatants of the culture media were collected, and the levels of TNF-α were determined using human TNF-α ELISA Set (BD Biosciences) according to the manufacturer's instructions.

Scheme S1. Synthesis of 37.



Scheme S2. Synthesis of 38.



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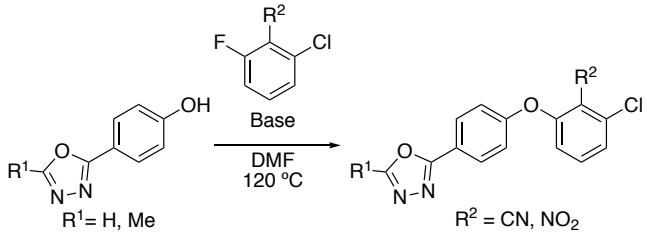
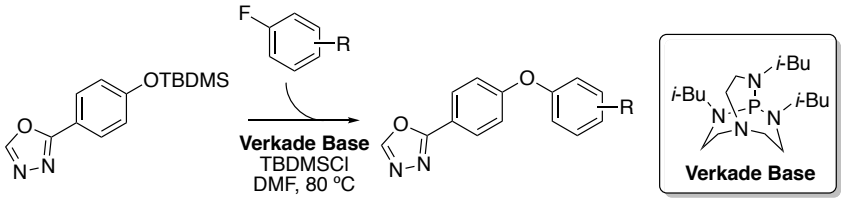
Scheme S3. General S_NAr routes.

(a)

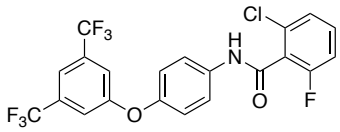


(b)



SPECTRAL DATA

Compound 1:



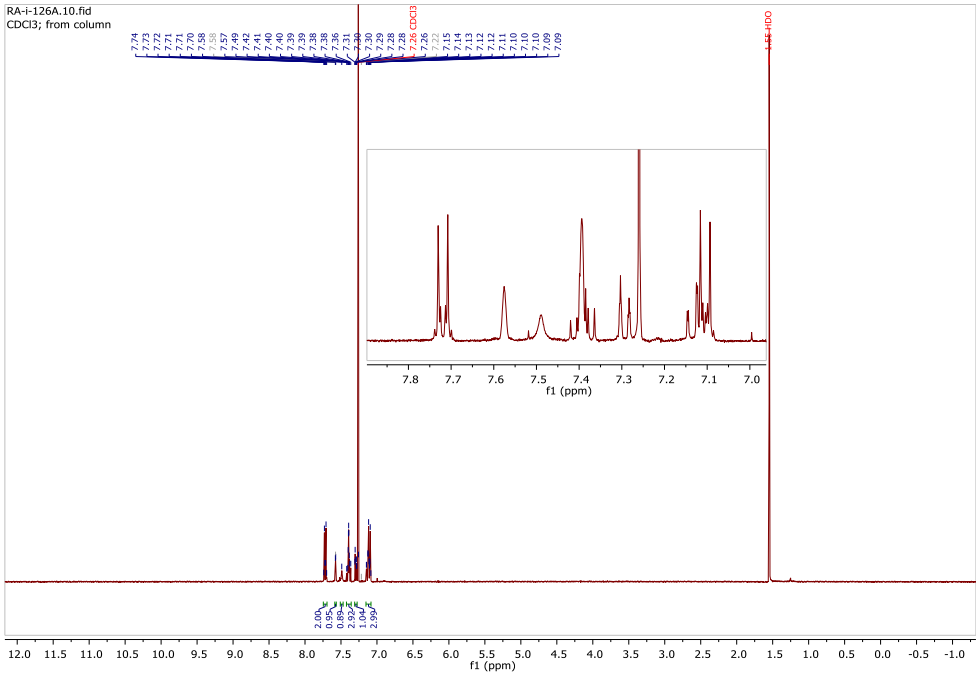


Figure S7. ^{1}H NMR Spectrum of Compound 1 (400 MHz, $CDCl_3$).

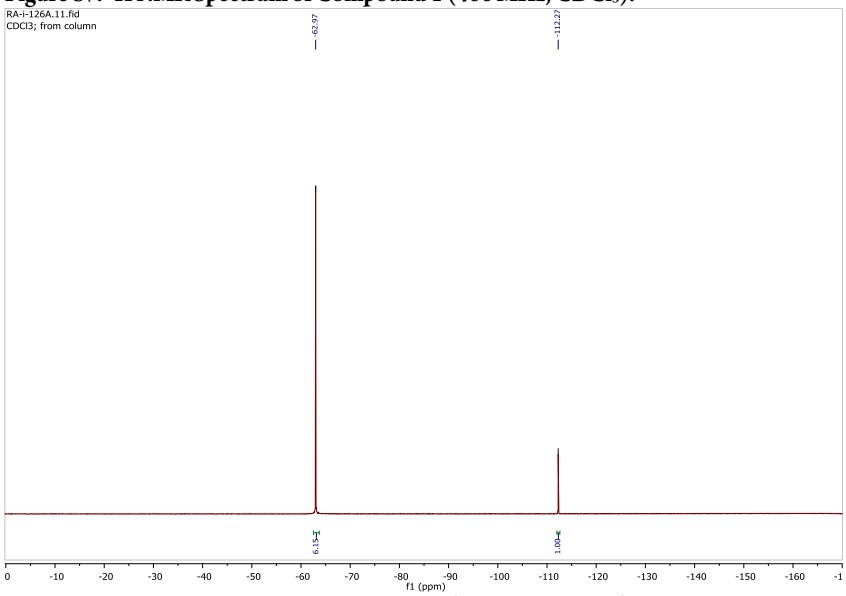


Figure S8. ^{19}F NMR Spectrum of Compound 1 (376 MHz, $CDCl_3$).

Compound 3:

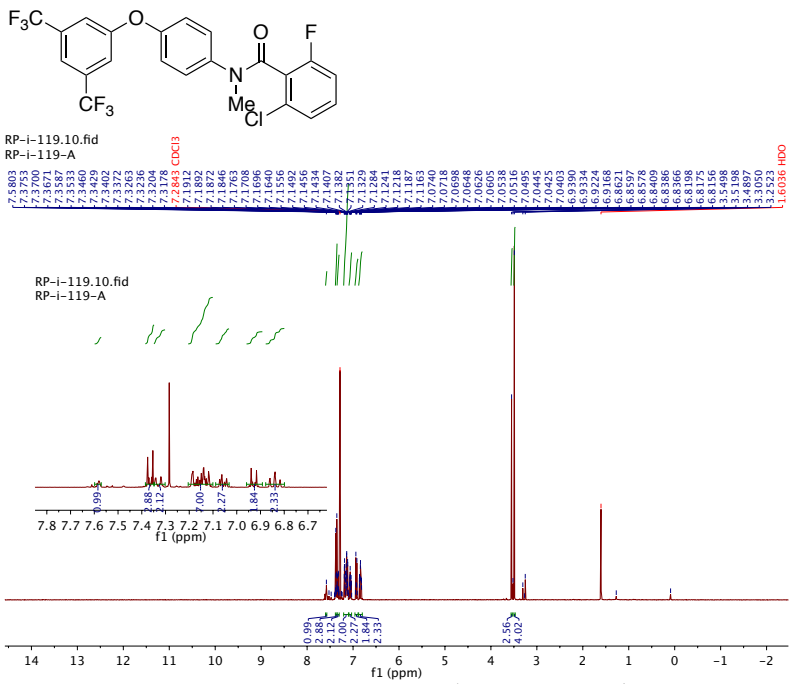


Figure S9. ^{19}F NMR Spectrum of Compound 3 (365 MHz, $CDCl_3$).

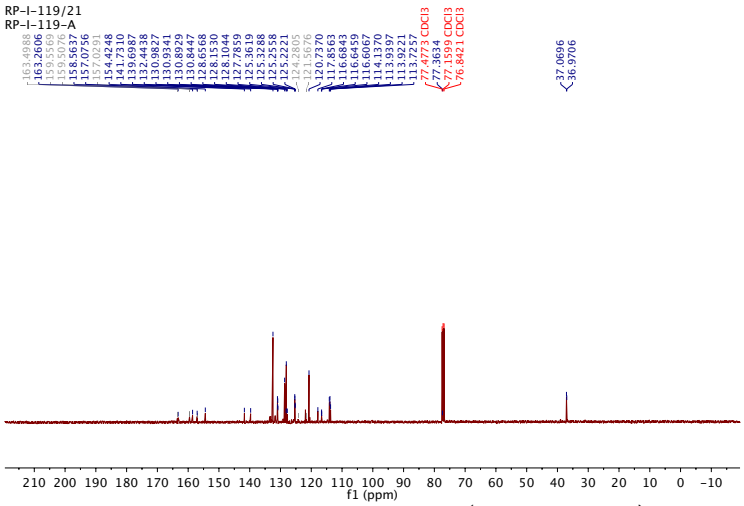


Figure S10. ^{13}C NMR Spectrum of Compound 3 (101 MHz, $CDCl_3$).

Compound 3:

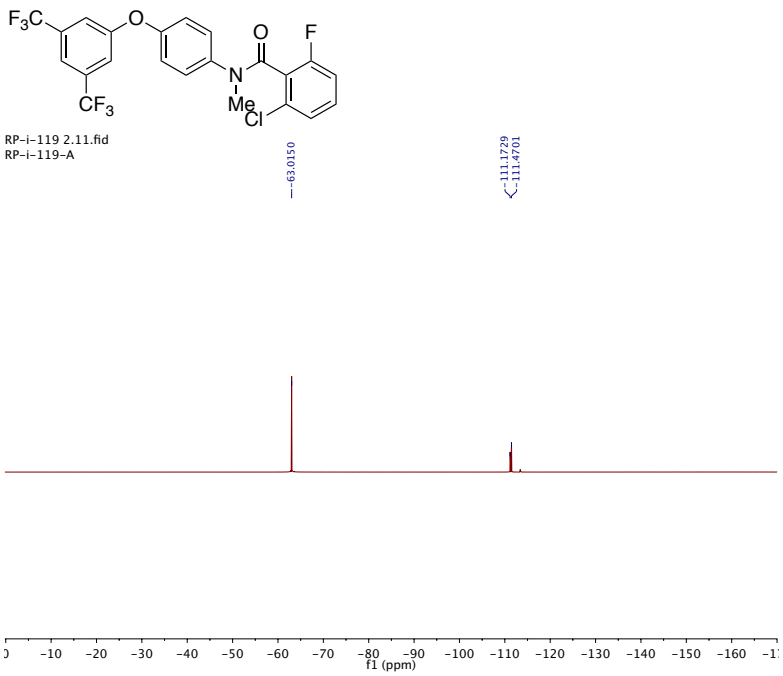


Figure S11. ^{19}**F NMR Spectrum of Compound 3 (365 MHz, $CDCl_3$).**

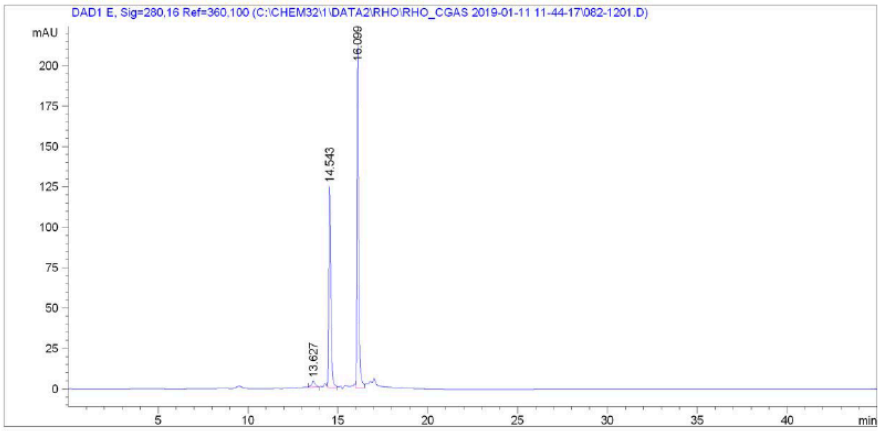
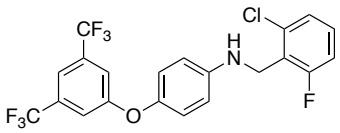


Figure S12. HPLC Chromatogram of Compound 3.

Compound 4:



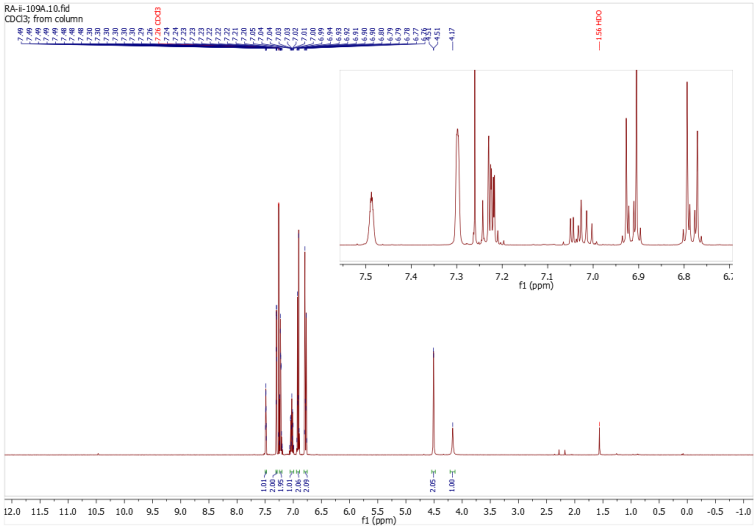


Figure S13. ^{1}H NMR Spectrum of Compound 4 (400 MHz, $CDCl_3$).

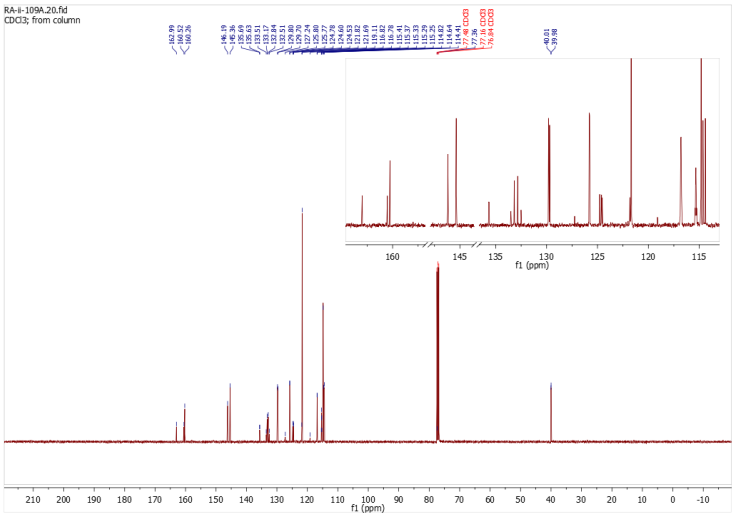
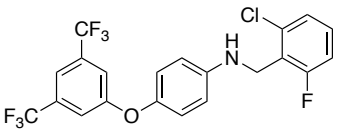


Figure S14. ^{13}C NMR Spectrum of Compound 4 (101 MHz, $CDCl_3$).

Compound 4:



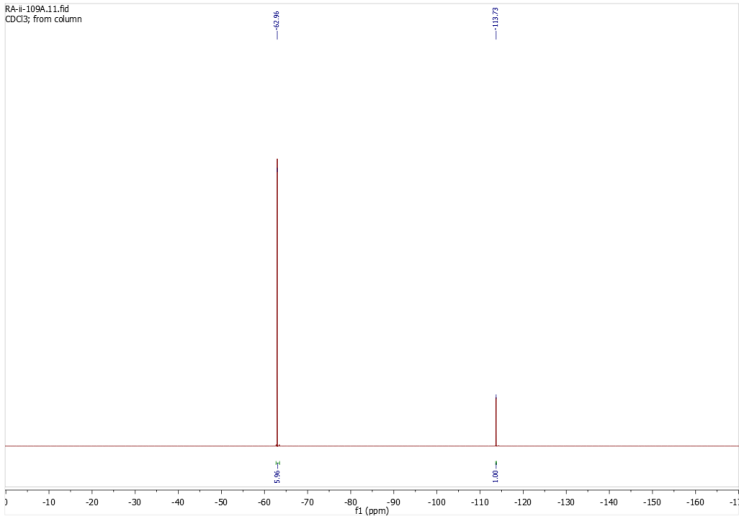


Figure S15. ^{19}F NMR Spectrum of Compound 4 (365 MHz, $CDCl_3$).

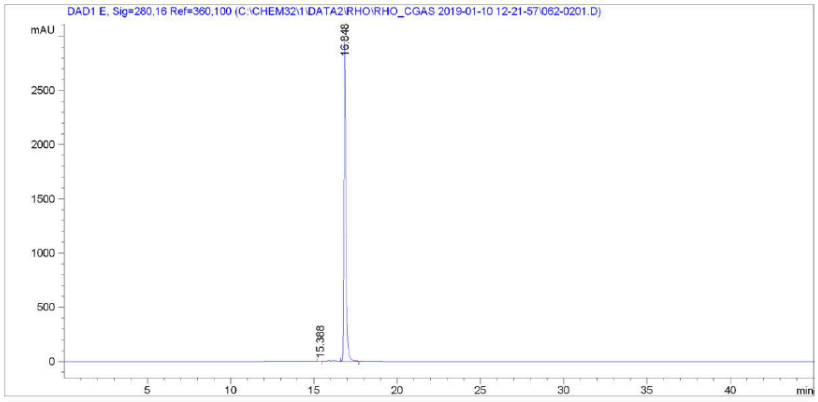
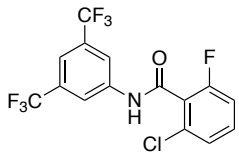


Figure S16. HPLC Chromatogram of Compound 4.

Compound 5:



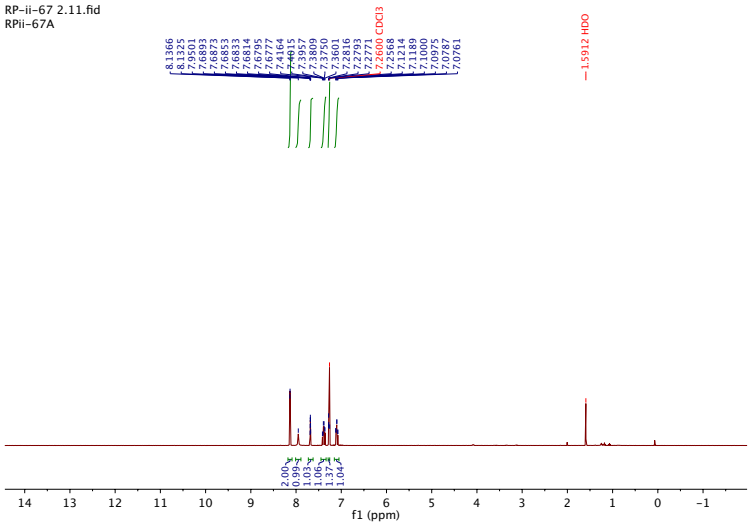


Figure S17. ^{1}H NMR Spectrum of Compound 5 (400 MHz, $CDCl_3$).

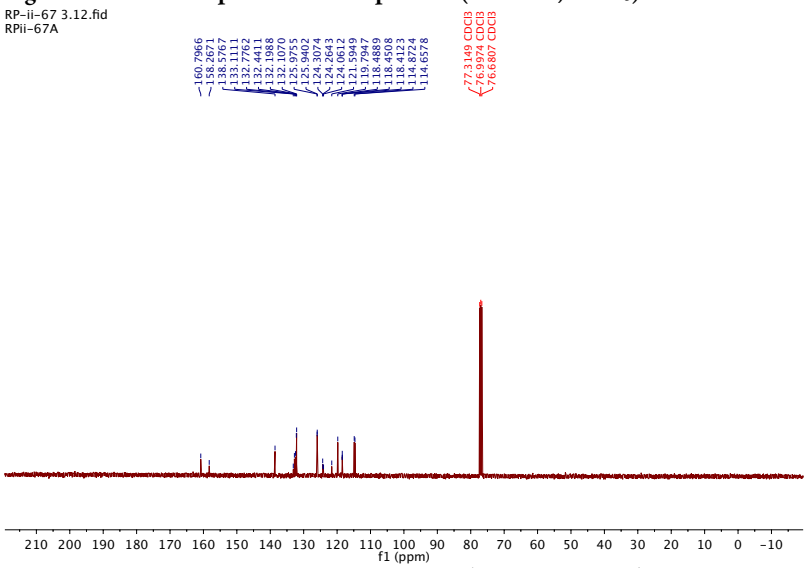


Figure S18. ^{13}C NMR Spectrum of Compound 5 (101 MHz, $CDCl_3$).

Compound 5:

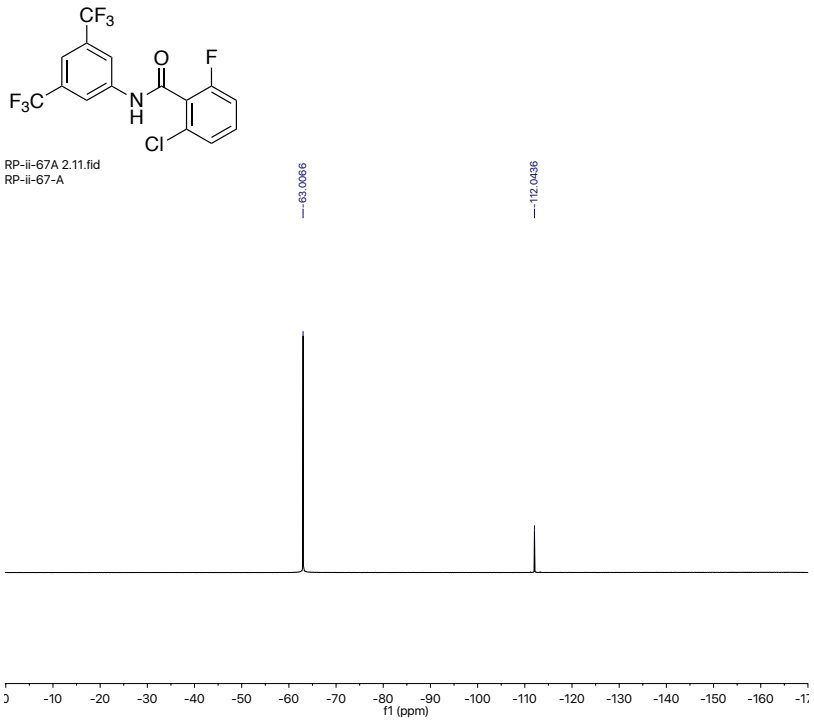


Figure S19. ^{19}F NMR Spectrum of Compound 5 (365 MHz, $CDCl_3$).

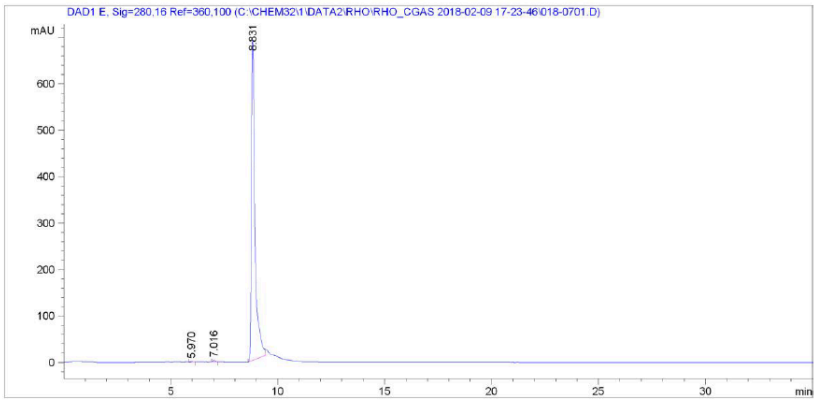
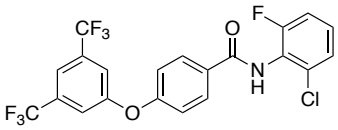


Figure S20. HPLC Chromatogram of Compound 5.

Compound 6:



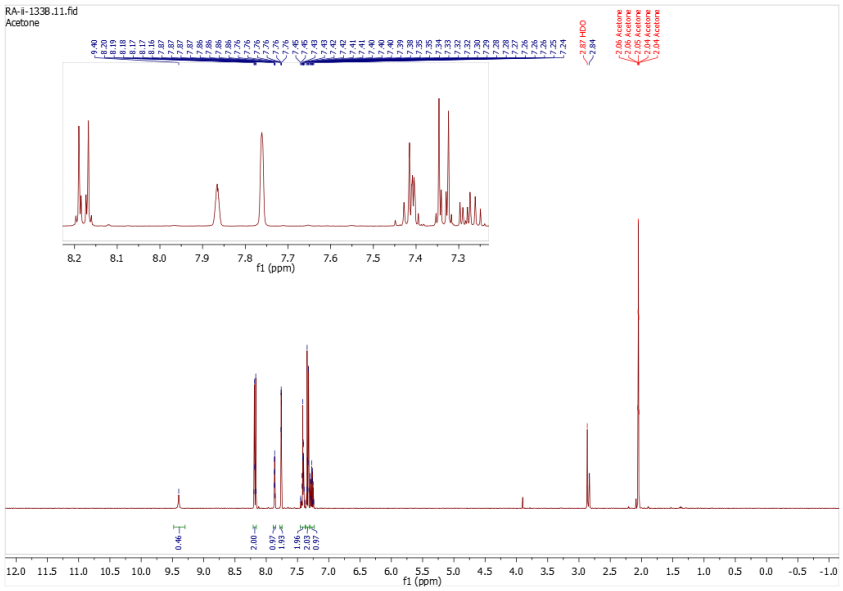


Figure S21. ^{1}H NMR Spectrum of Compound 6 (400 MHz, Acetone-d_6).

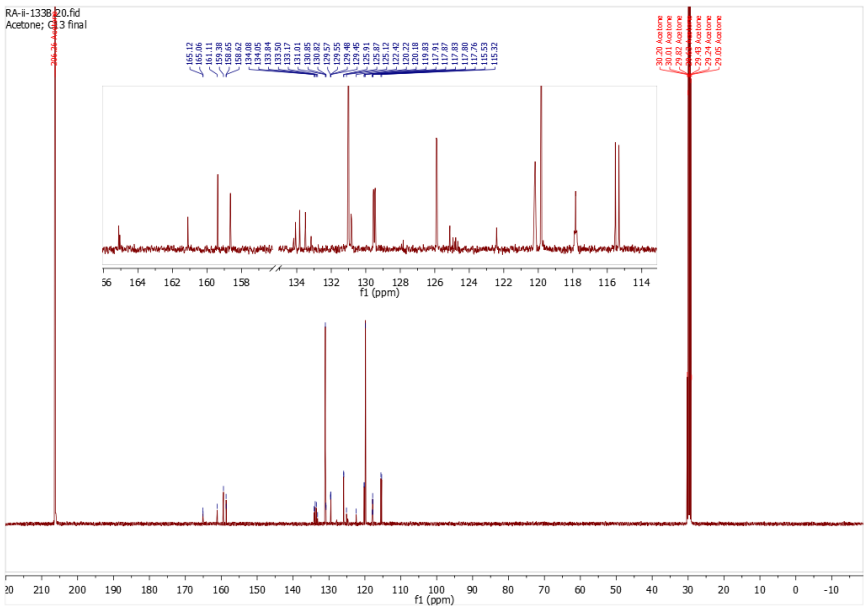
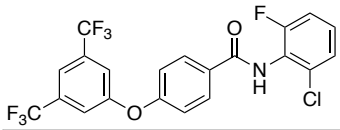


Figure S22. ^{13}C NMR Spectrum of Compound 6 (101 MHz, Acetone-d_6).

Compound 6:



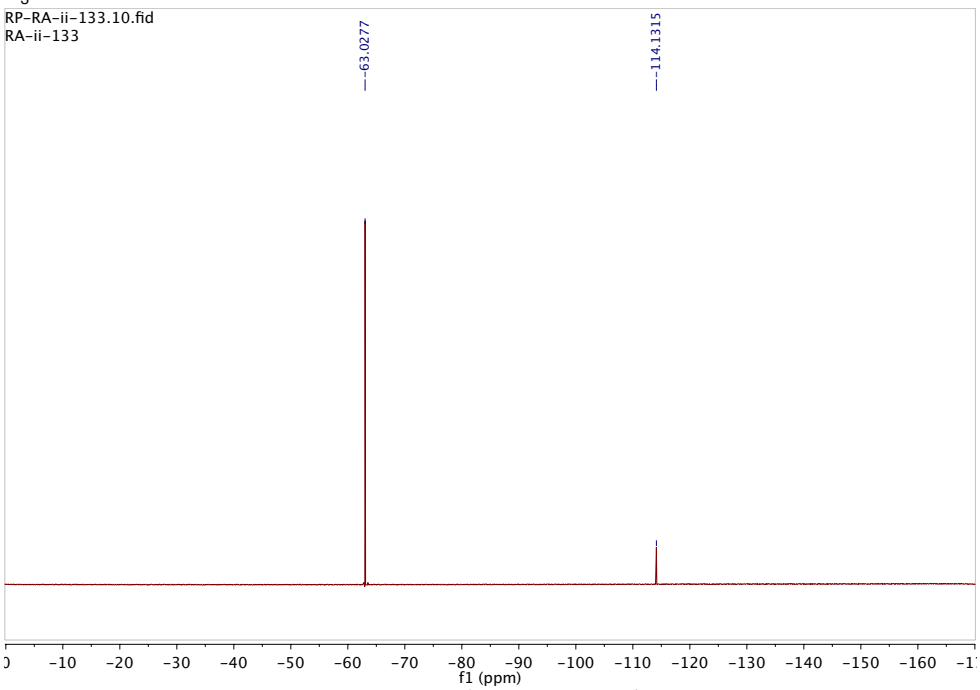


Figure S23. ^{19}F NMR Spectrum of Compound 6 (376 MHz, $CDCl_3$).

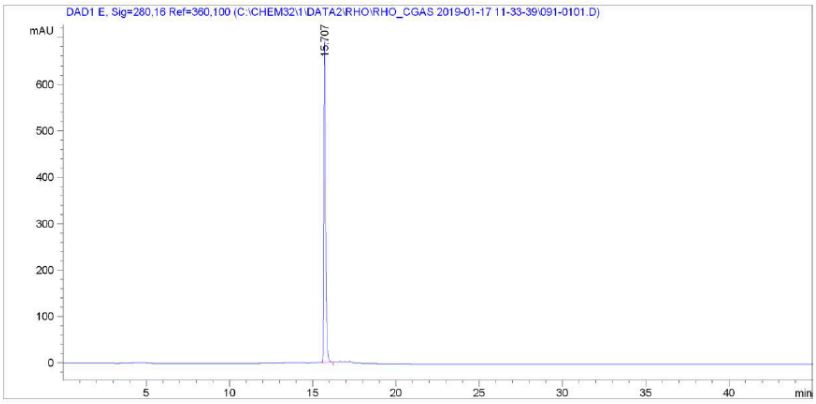
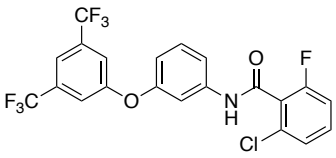


Figure S24. HPLC Chromatogram of Compound 6.

Compound 7:



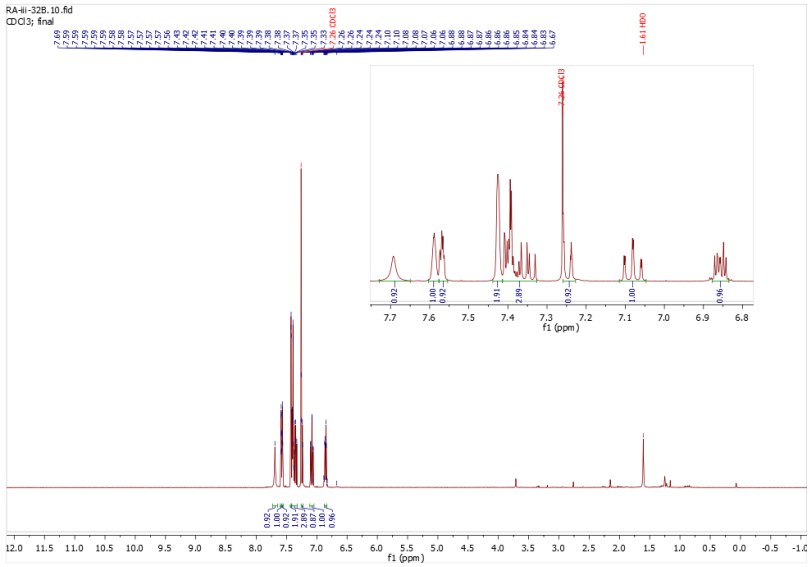


Figure S25. ^{1}H NMR Spectrum of Compound 7 (400 MHz, $CDCl_3$).

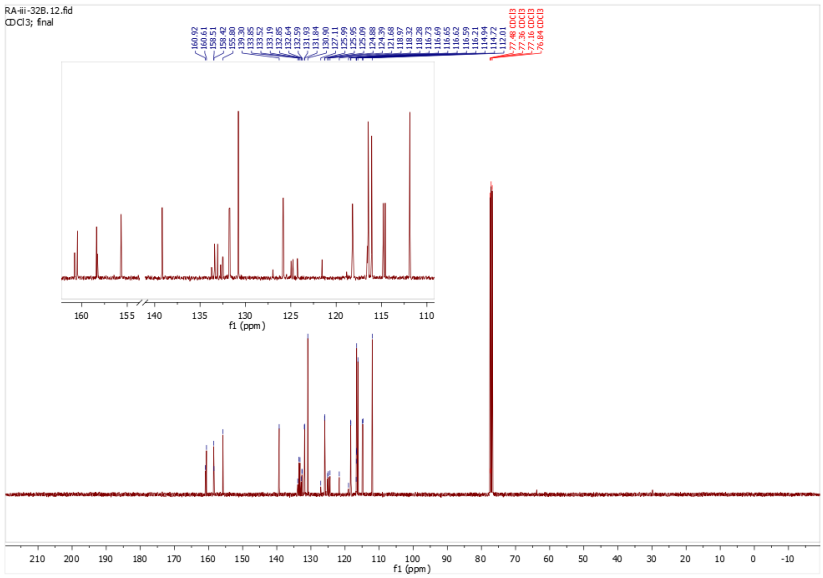


Figure S26. ^{13}C NMR Spectrum of Compound 7 (101 MHz, $CDCl_3$).

Compound 7:

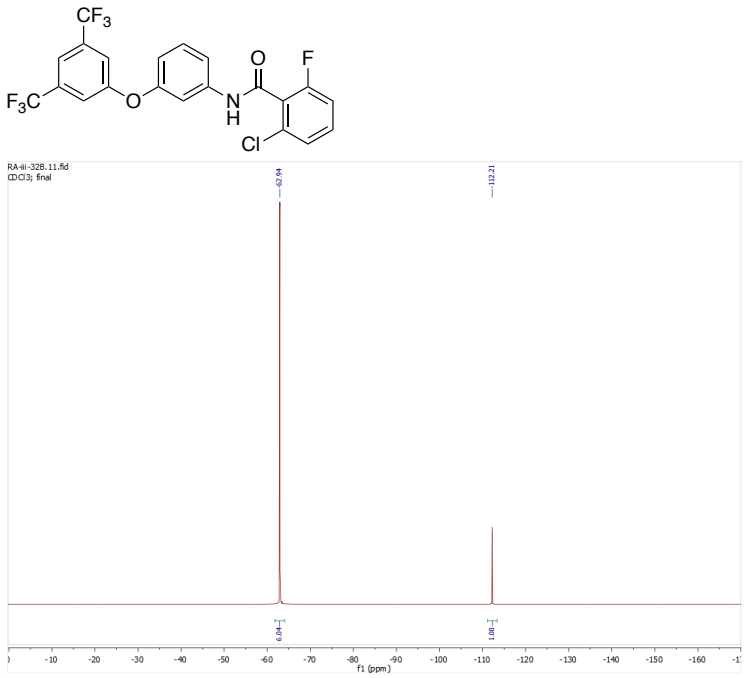


Figure S27. ^{19}F NMR Spectrum of Compound 7 (376 MHz, $CDCl_3$).

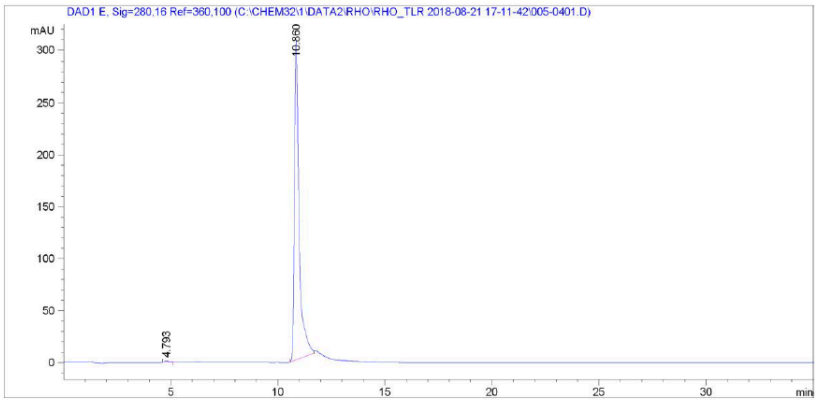
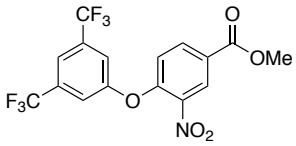


Figure S28. HPLC Chromatogram of Compound 7.

Compound 9:



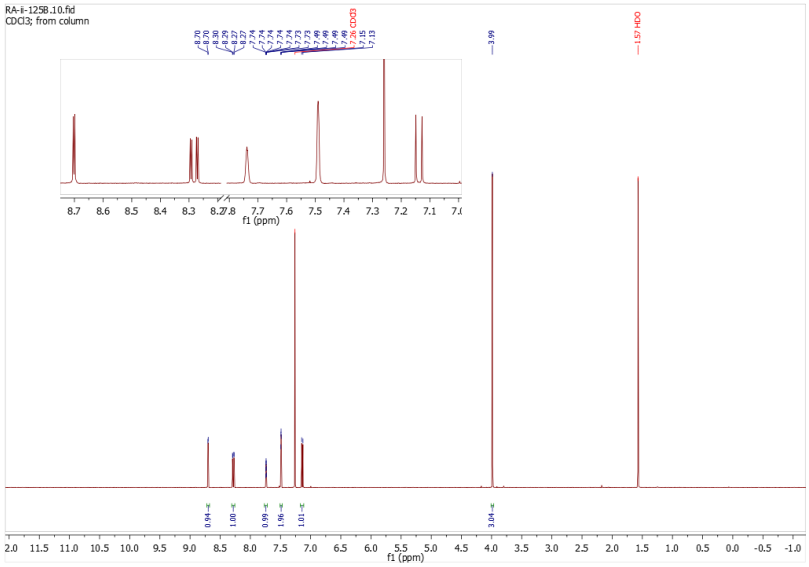


Figure S29. ^{1}H NMR Spectrum of Compound 9 (400 MHz, $CDCl_3$).

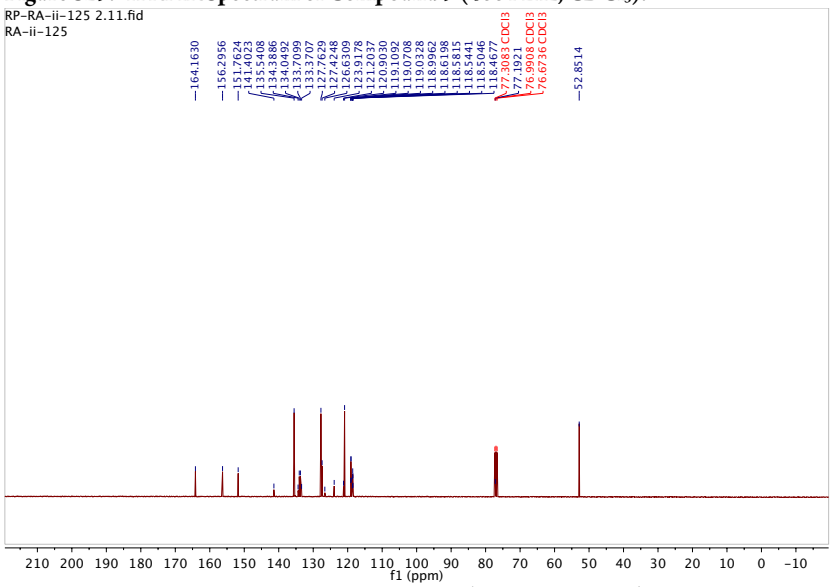
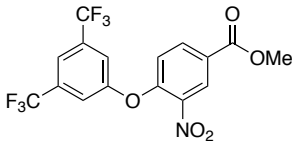


Figure S30. ^{13}C NMR Spectrum of Compound 9 (101 MHz, $CDCl_3$).

Compound 9:



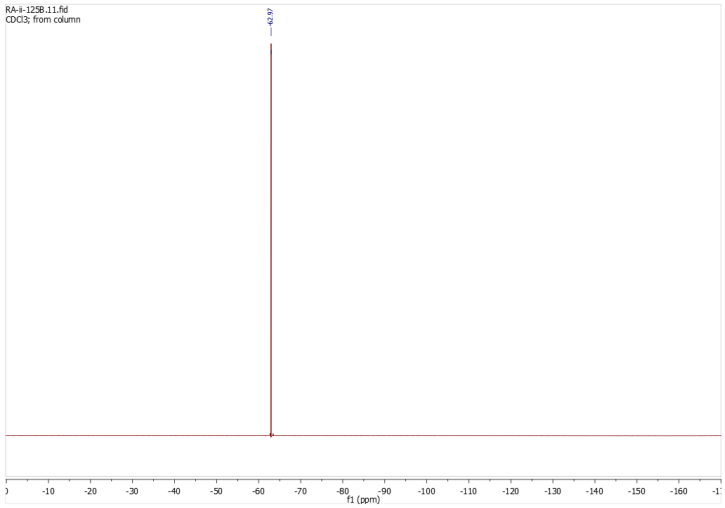
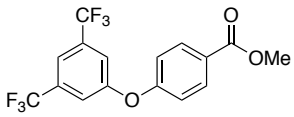


Figure S31. ^{19}F NMR Spectrum of Compound 9 (376 MHz, $CDCl_3$).

Compound 10:



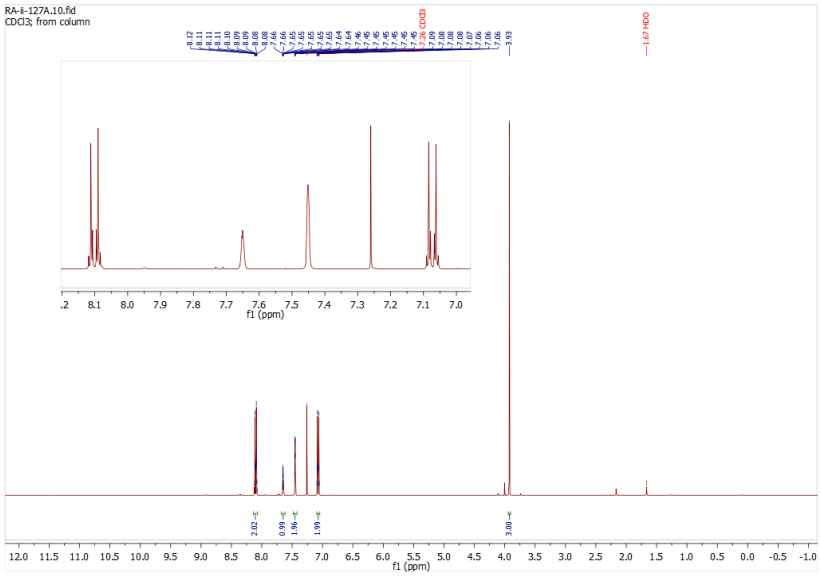


Figure S32. ^{1}H NMR Spectrum of Compound 10 (400 MHz, $CDCl_3$).

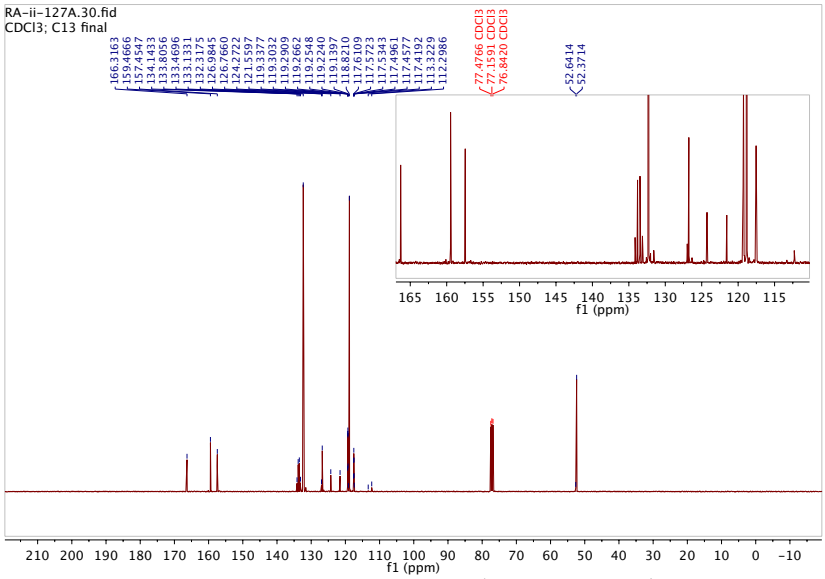


Figure S33. ^{13}C NMR Spectrum of Compound 10 (101 MHz, $CDCl_3$).

Compound 10:

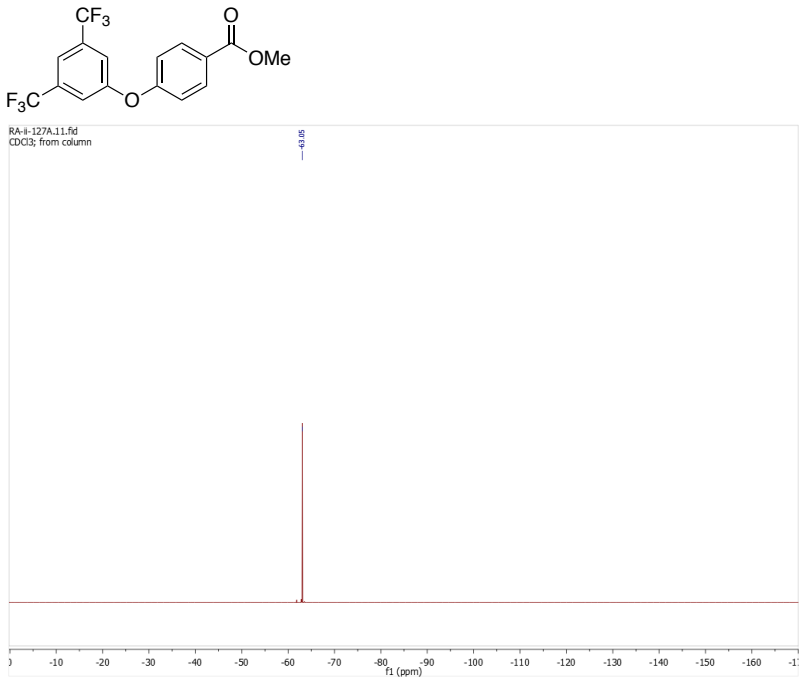
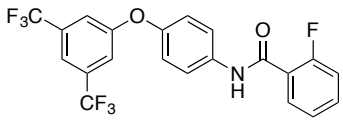


Figure S34. ^{19}F NMR Spectrum of Compound 10 (376 MHz, $CDCl_3$).

Compound 14a:



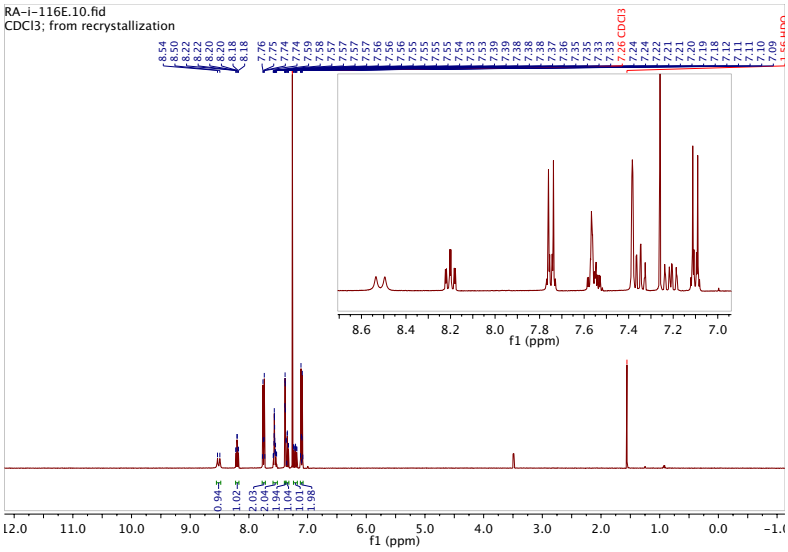


Figure S35. ^{1}H NMR Spectrum of Compound 14a (400 MHz, $CDCl_3$).

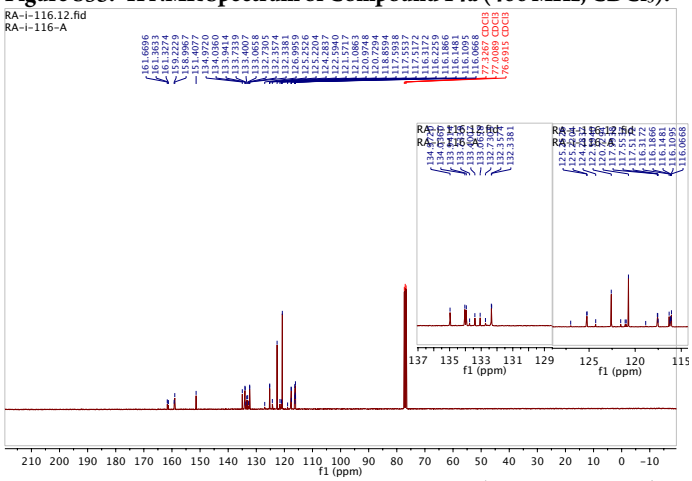
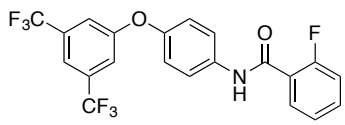


Figure S36. ^{1}H NMR Spectrum of Compound 14a(400 MHz, $CDCl_3$).

Compound 14a:



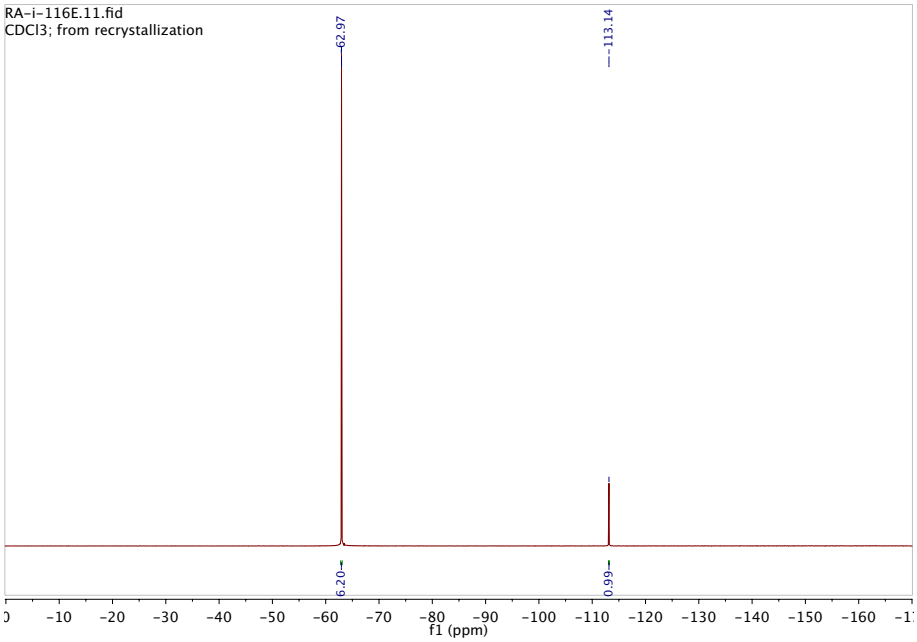


Figure S37. ^{19}F NMR Spectrum of Compound 14a (376 MHz, $CDCl_3$).

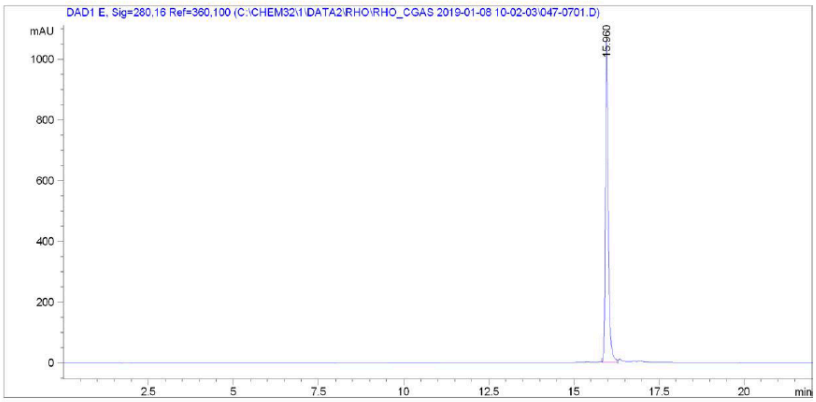
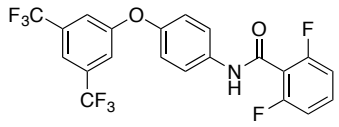


Figure S38. HPLC Chromatogram of Compound 14a.

Compound 14b:



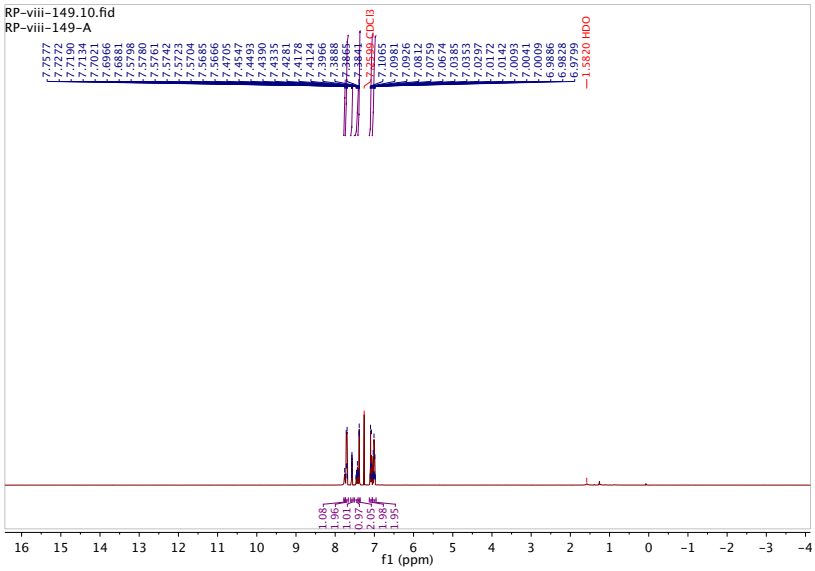


Figure S39. ^{1}H NMR Spectrum of Compound **14b** (400 MHz, $CDCl_3$).

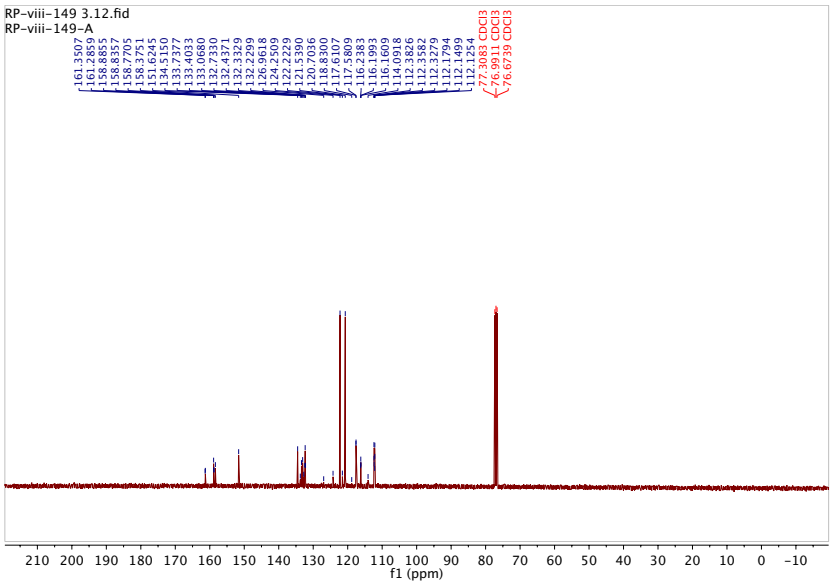
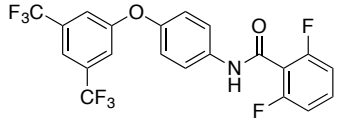


Figure S40. ^{13}C NMR Spectrum of Compound **14b** (101 MHz, $CDCl_3$).

Compound 14o:

Compound 14b:



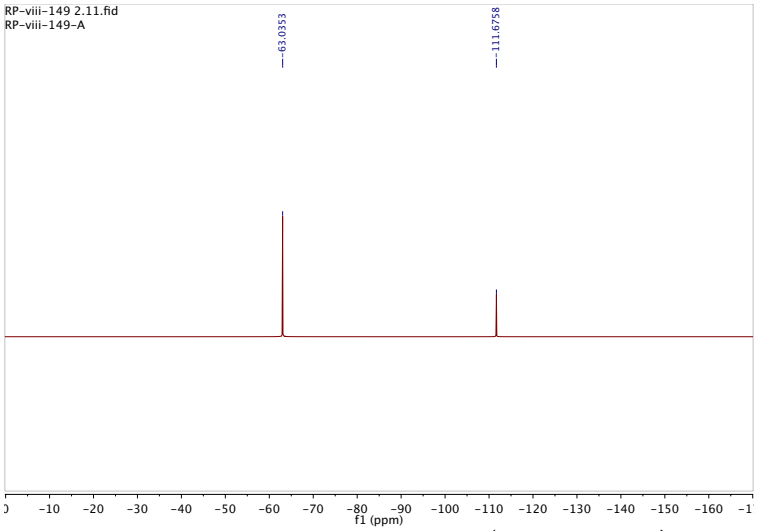


Figure S41. ^{19}F NMR Spectrum of Compound 14b (376 MHz, $CDCl_3$).

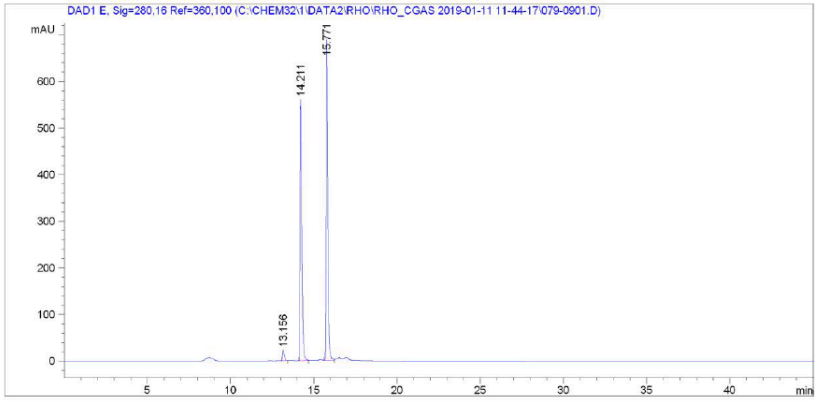
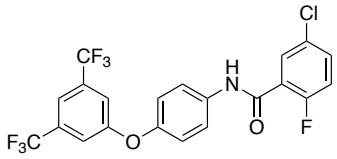


Figure S42. HPLC Chromatogram of Compound 14b.

Compound 14d:



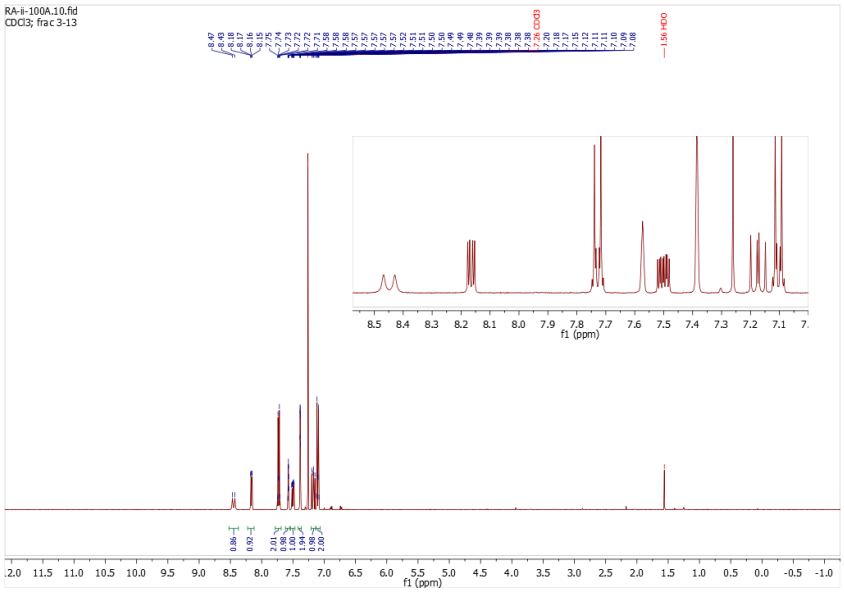


Figure S43. ^{1}H NMR Spectrum of Compound 14d (400 MHz, $CDCl_3$).

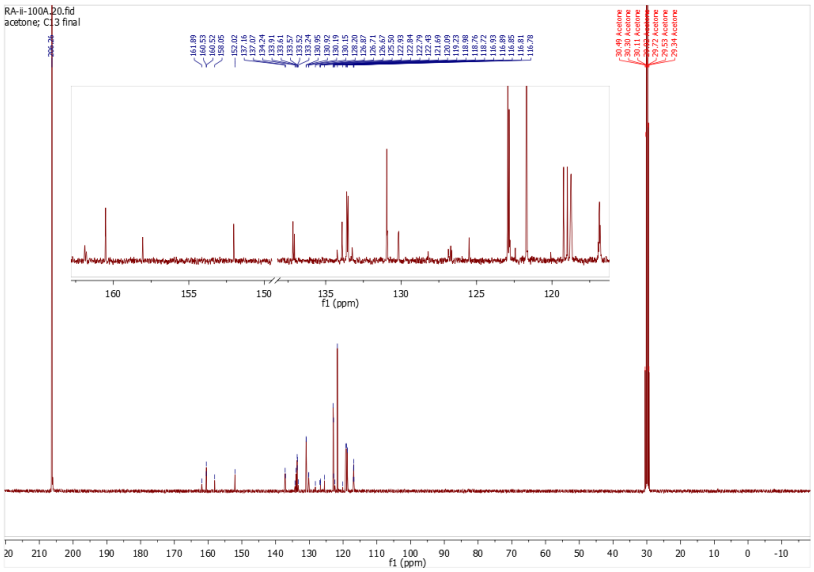
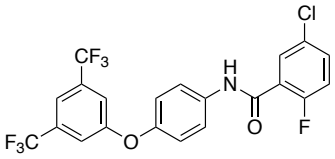


Figure S44. ^{13}C NMR Spectrum of Compound 14d (101 MHz, $CDCl_3$).

Compound 14d:



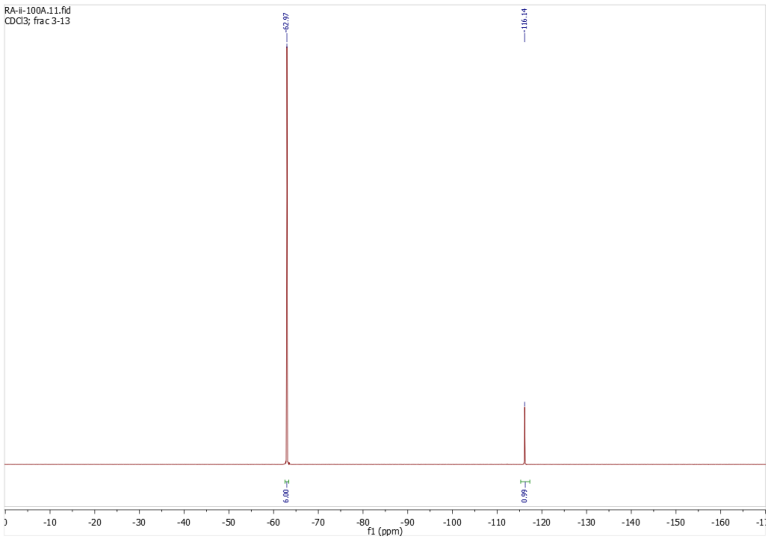


Figure S45. ^{19}F NMR Spectrum of Compound 14d (376 MHz, $CDCl_3$).

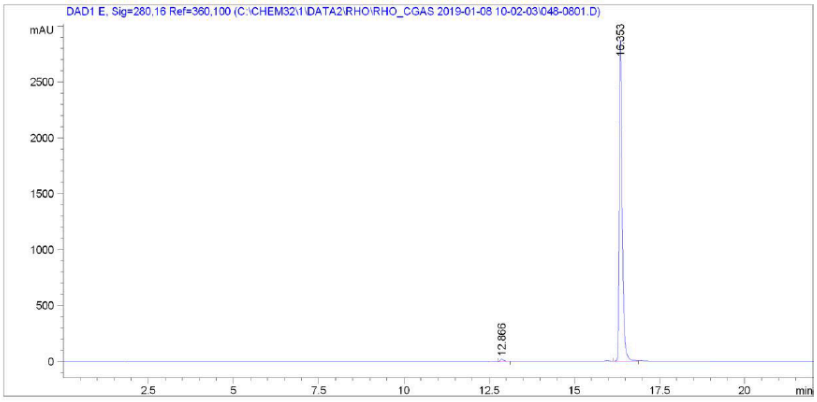
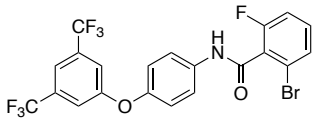


Figure S46. HPLC Chromatogram of Compound 14d.

Compound 14e:



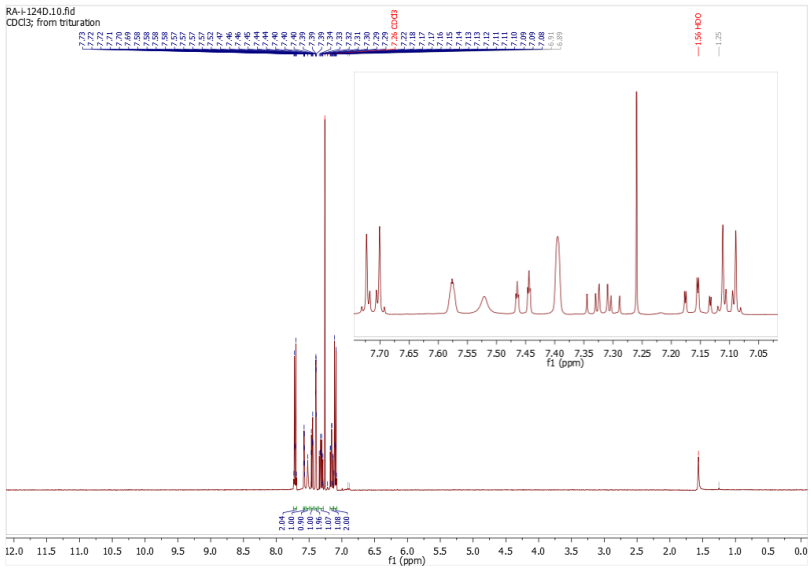


Figure S47. ^{1}H NMR Spectrum of Compound 14e (400 MHz, $CDCl_3$).

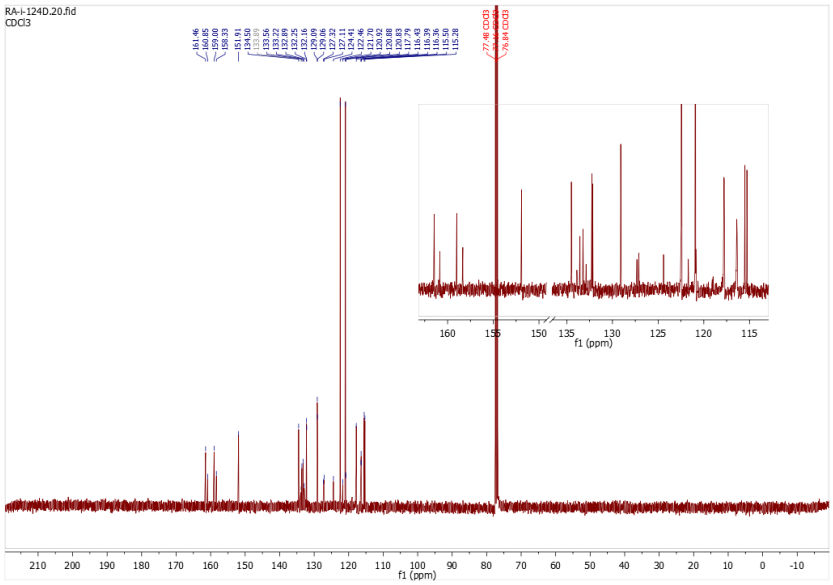


Figure S48. ^{13}C NMR Spectrum of Compound 14e (101 MHz, $CDCl_3$).

Compound 14e:

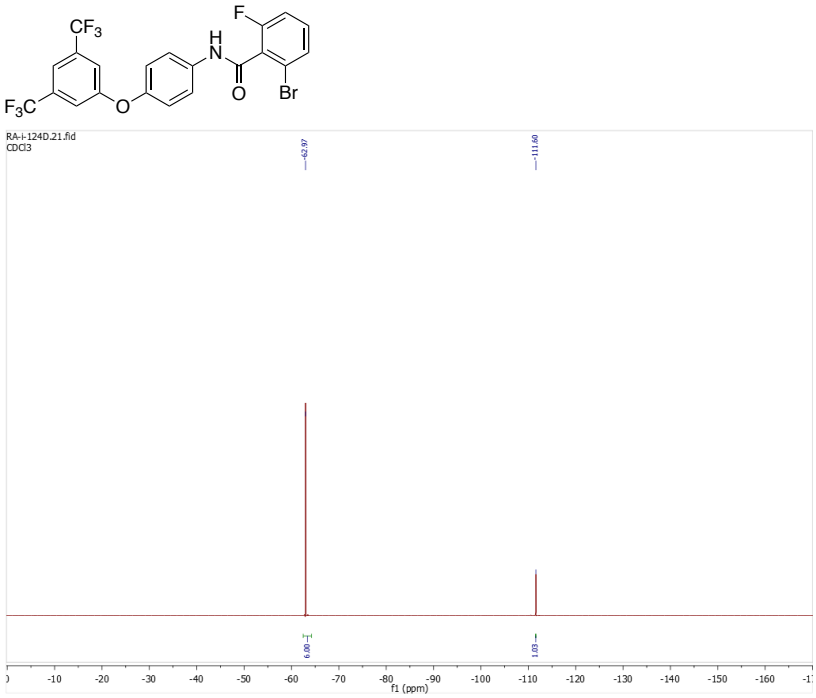


Figure S49. ^{19}F NMR Spectrum of Compound 14e (376 MHz, $CDCl_3$).

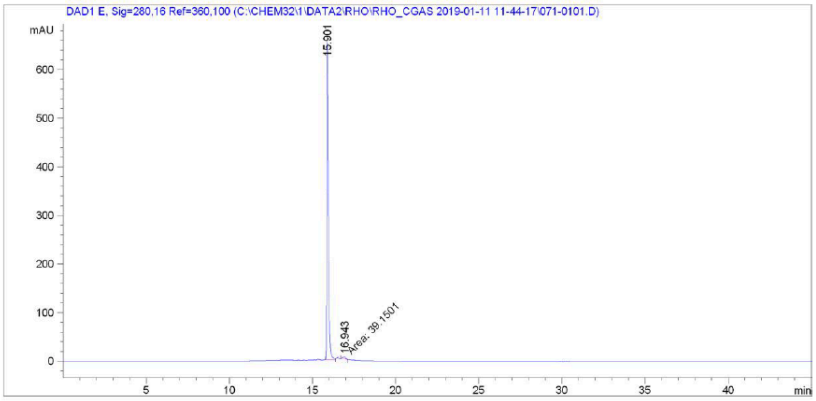
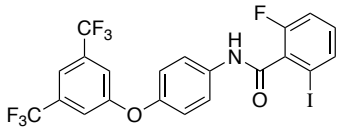


Figure S50. HPLC Chromatogram of Compound 14e.

Compound 14f:



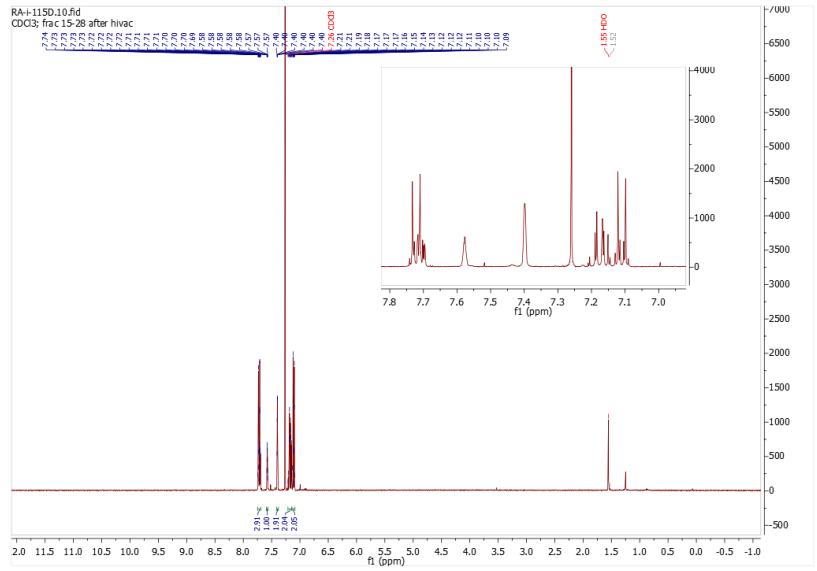


Figure S51. ^{1}H NMR Spectrum of Compound 14f (400 MHz, $CDCl_3$).

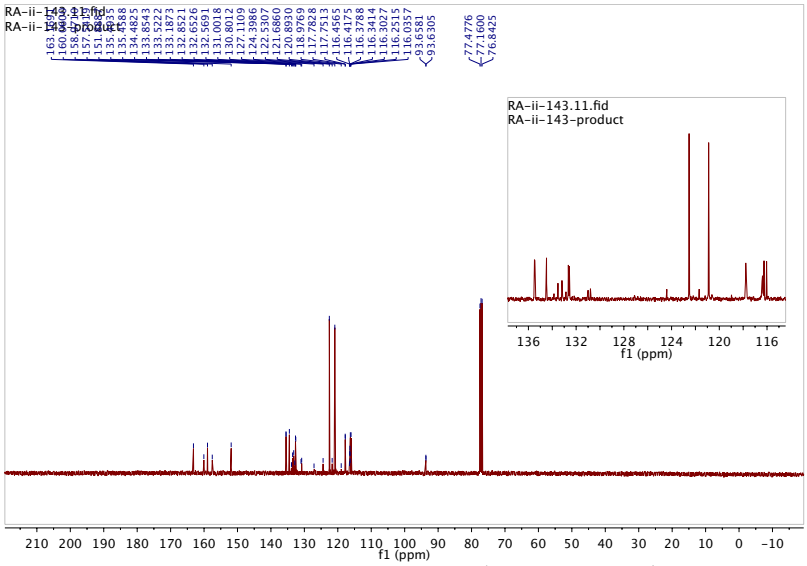
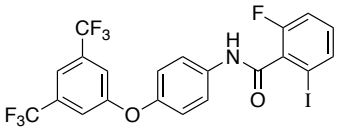


Figure S52. ^{1}H NMR Spectrum of Compound 14f (400 MHz, $CDCl_3$).

Compound 14f:



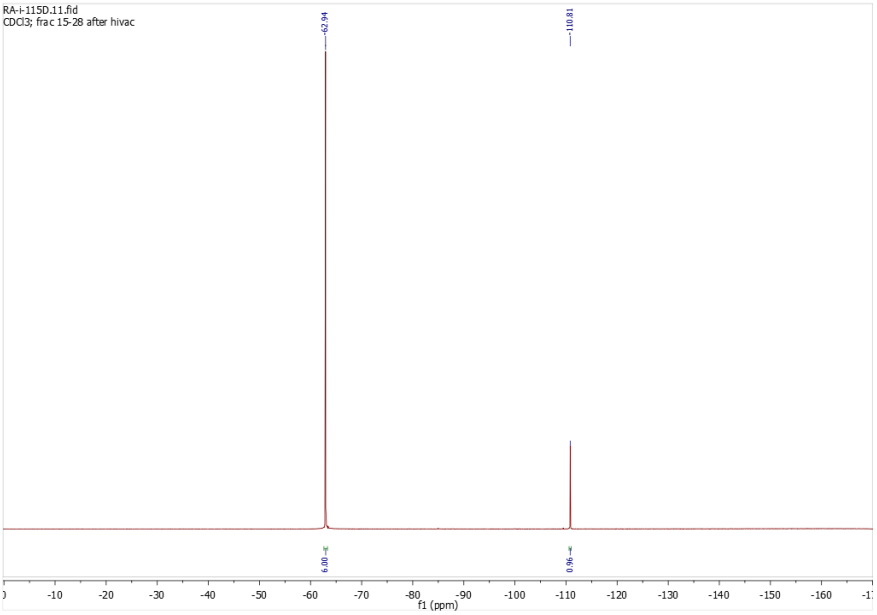


Figure S53. ^{19}F NMR Spectrum of Compound 14f (376 MHz, $CDCl_3$).

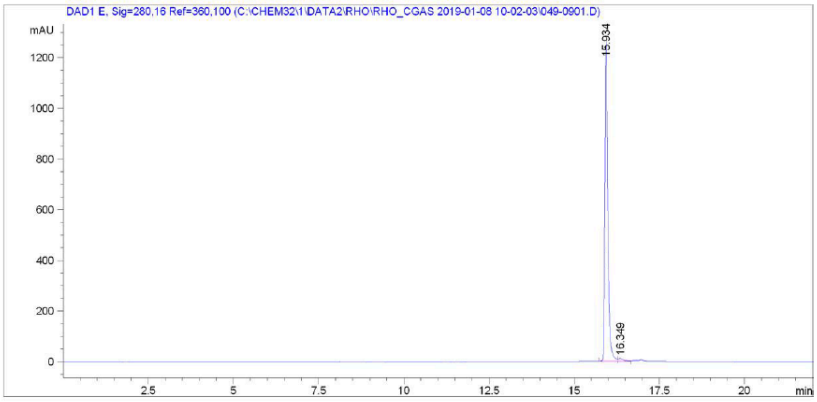
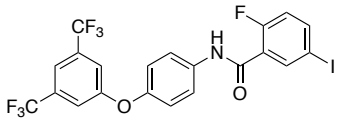


Figure S54. HPLC Chromatogram of Compound 14f.

Compound 14g:



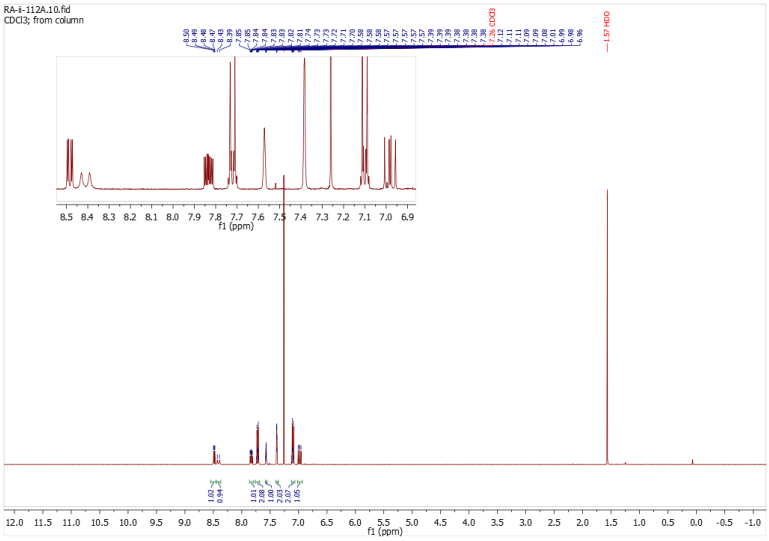


Figure S55. ^{1}H NMR Spectrum of Compound 14g (400 MHz, $CDCl_3$).

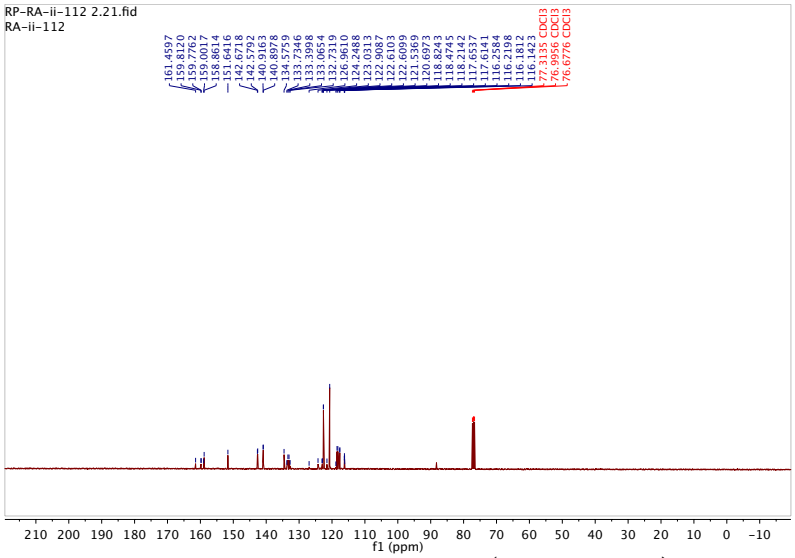


Figure S56. ^{13}C NMR Spectrum of Compound 14g (101 MHz, $CDCl_3$).

Compound 14g:

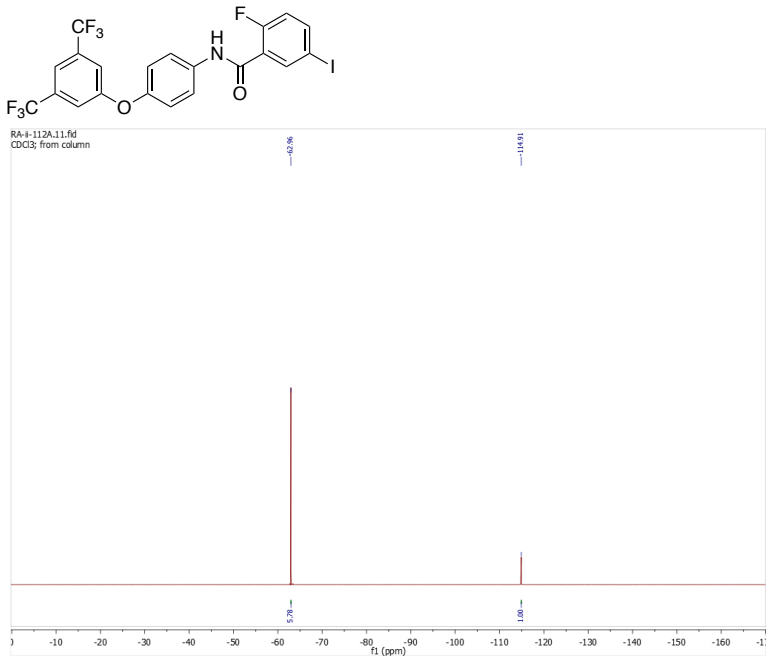


Figure S57. ^{19}F NMR Spectrum of Compound 14g (376 MHz, $CDCl_3$).

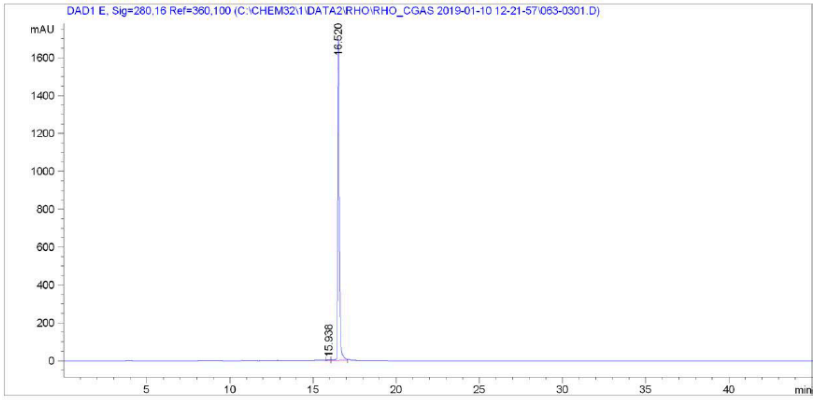
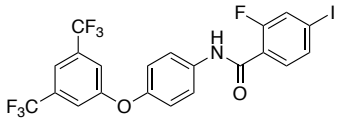


Figure S58. HPLC Chromatogram of Compound 14g.

Compound 14h:



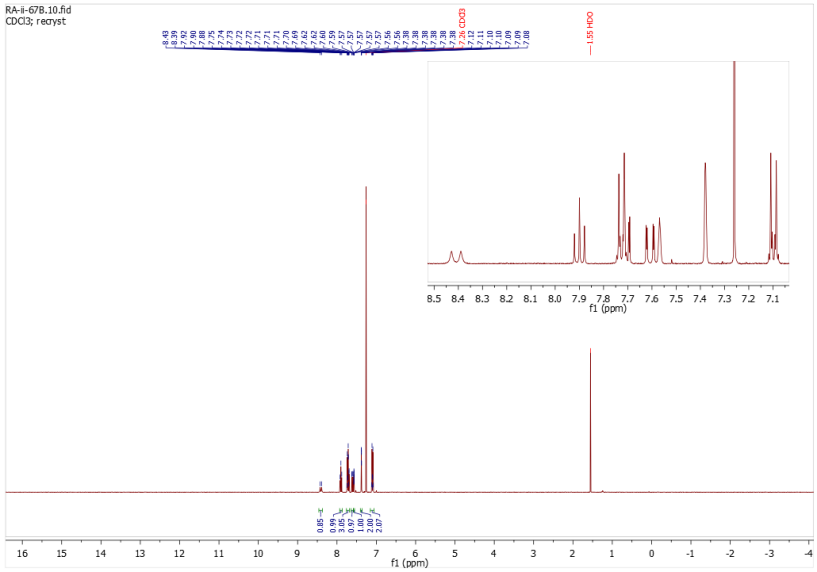


Figure S59. ^{1}H NMR Spectrum of Compound 14h (400 MHz, $CDCl_3$).

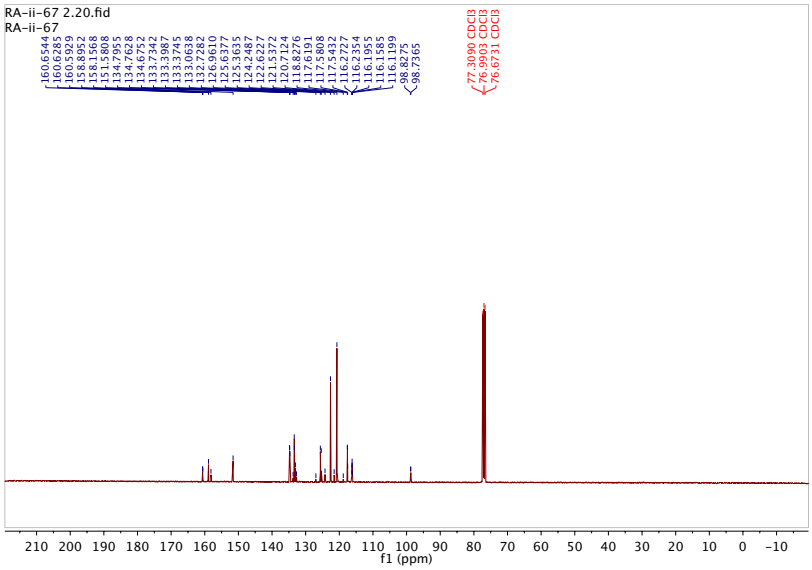


Figure S60. ^{13}C NMR Spectrum of Compound 14h (101 MHz, $CDCl_3$).

Compound 14h:

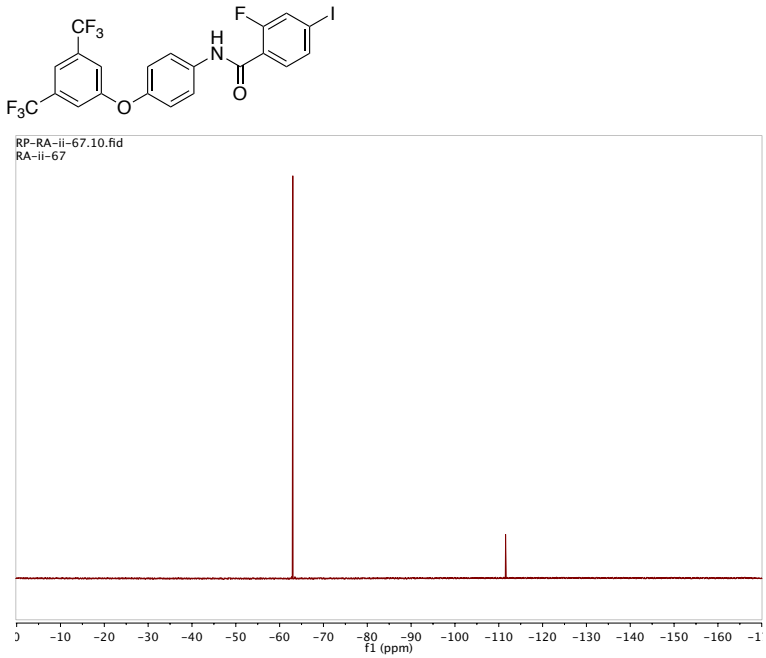


Figure S61. ^{19}F NMR Spectrum of Compound 14h (376 MHz, $CDCl_3$).

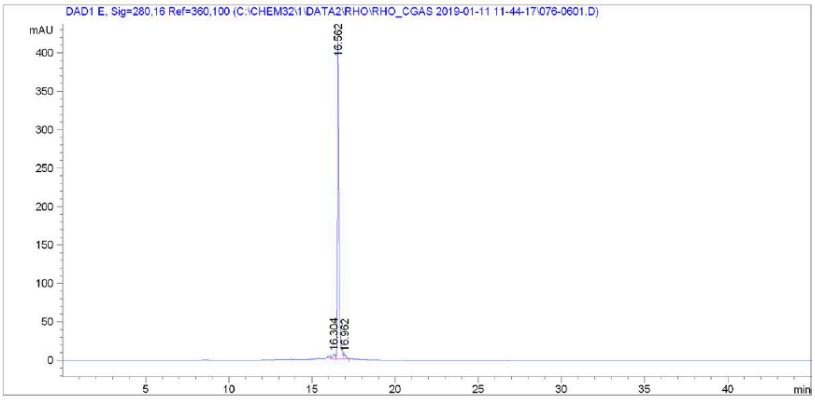
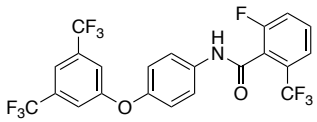


Figure S62. HPLC Chromatogram of Compound 14h.

Compound 14i:



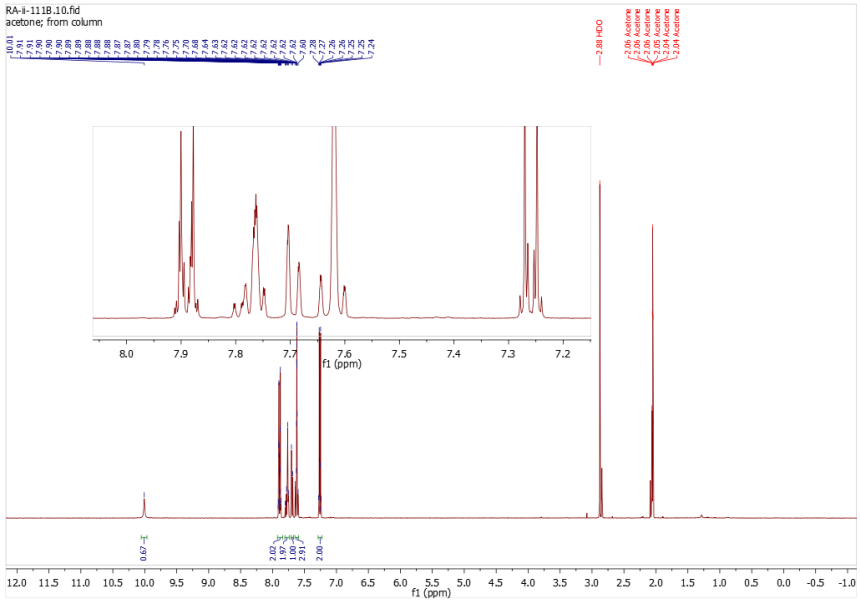


Figure S63. ^{1}H NMR Spectrum of Compound 14i (400 MHz, Acetone-d$_6$).

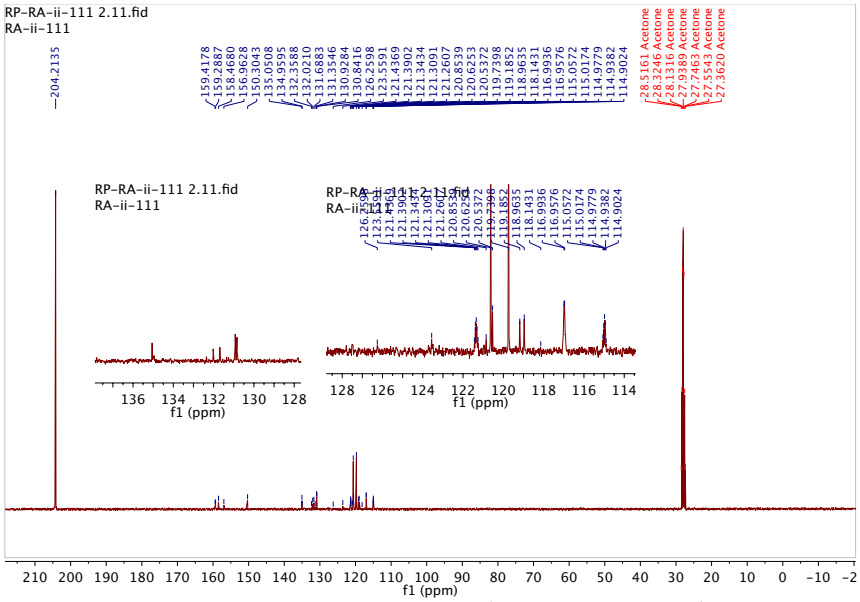
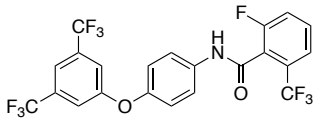


Figure S64. ^{13}C NMR Spectrum of Compound 14i (101 MHz, Acetone-d$_6$).

Compound 14i:



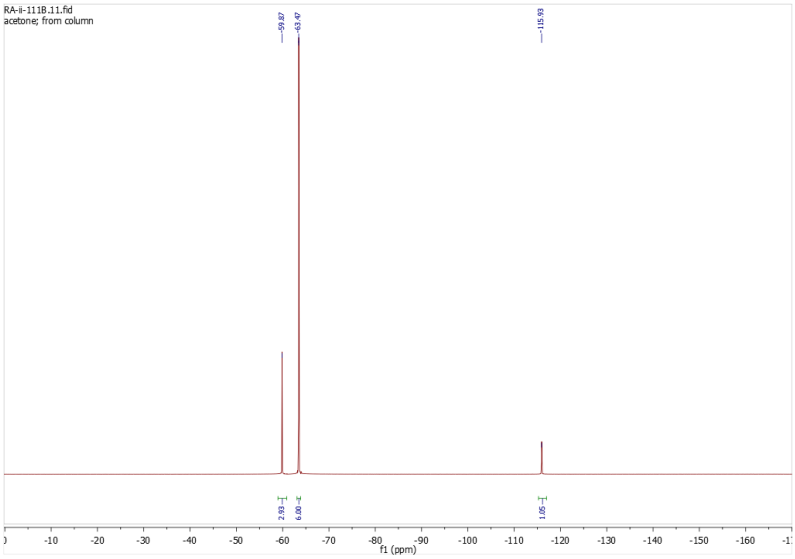


Figure S65. ^{19}F NMR Spectrum of Compound 14i (376 MHz, Acetone-d_6).

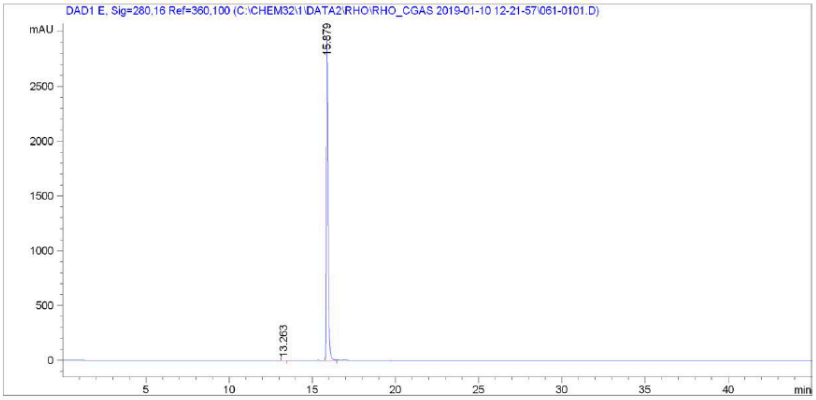
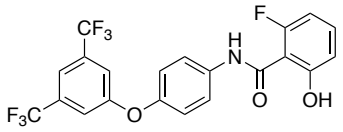


Figure S66. HPLC Chromatogram of Compound 14i.

Compound 14j:



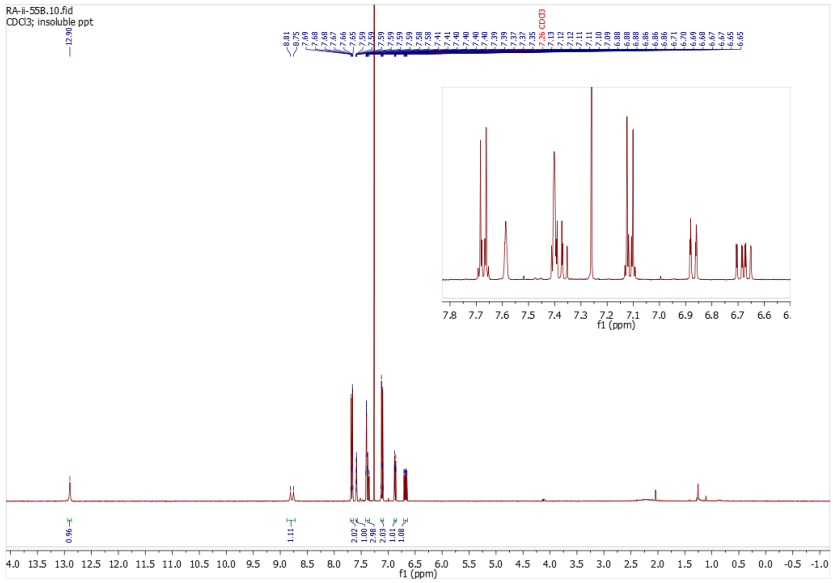


Figure S67. ^{1}H NMR Spectrum of Compound 14j (400 MHz, $CDCl_3$).

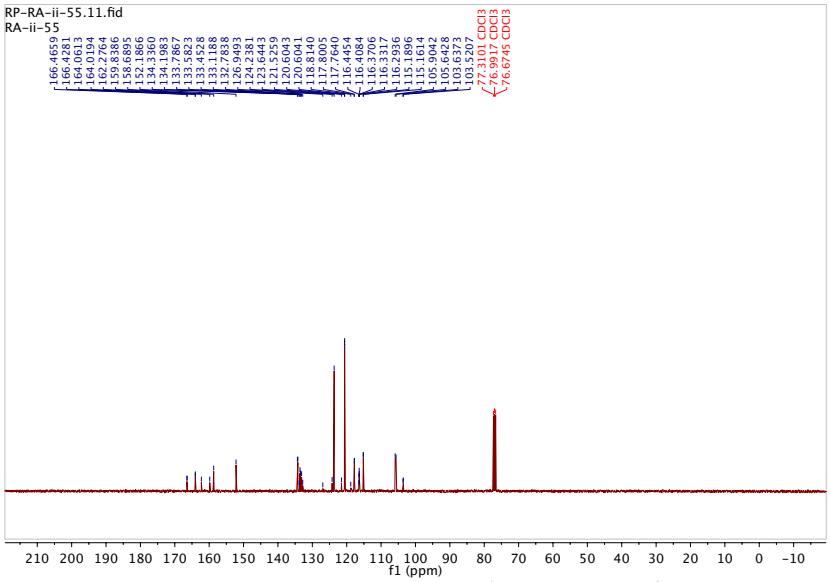
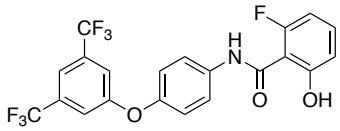


Figure S68. ^{13}C NMR Spectrum of Compound 14j (101 MHz, $CDCl_3$).

Compound 14j:



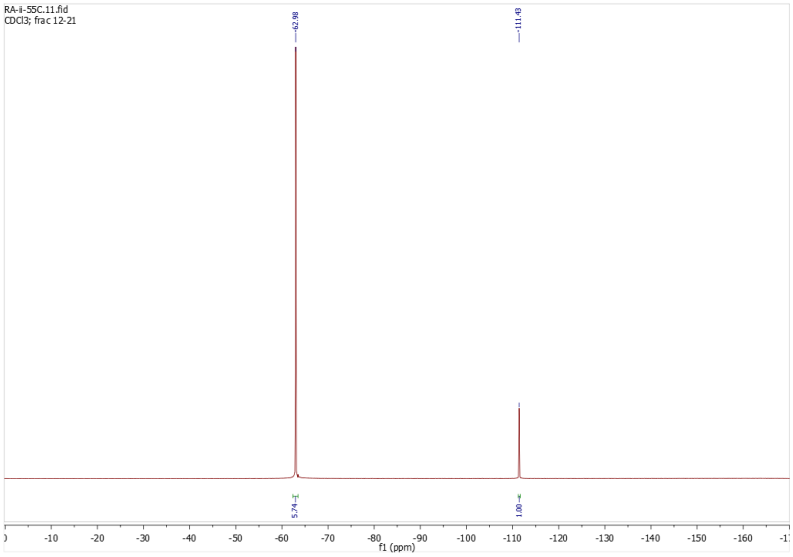


Figure S69. ^{19}F NMR Spectrum of Compound 14j (376 MHz, $CDCl_3$).

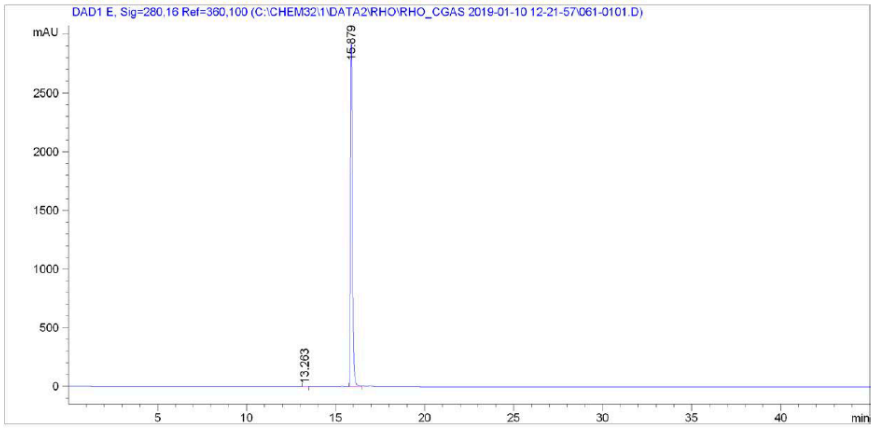
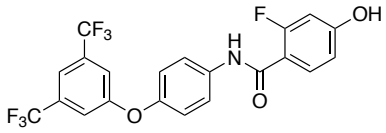


Figure S70. HPLC Chromatogram of Compound 14j.

Compound 14k:



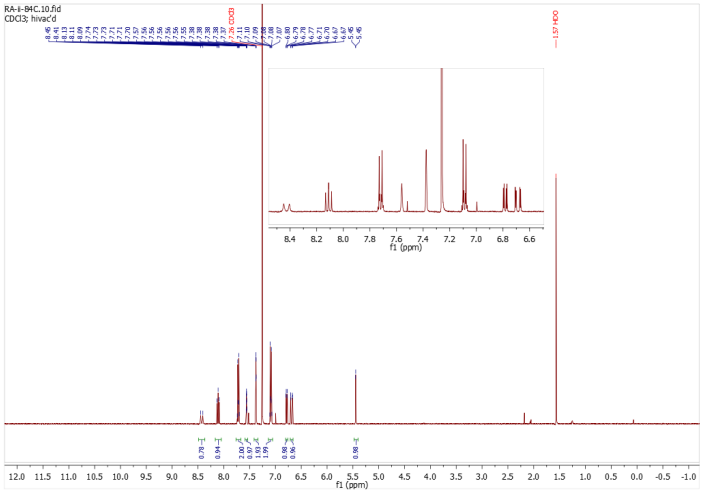


Figure S71. ^{1}H NMR Spectrum of Compound 14k (400 MHz, Acetone-d$_6$).

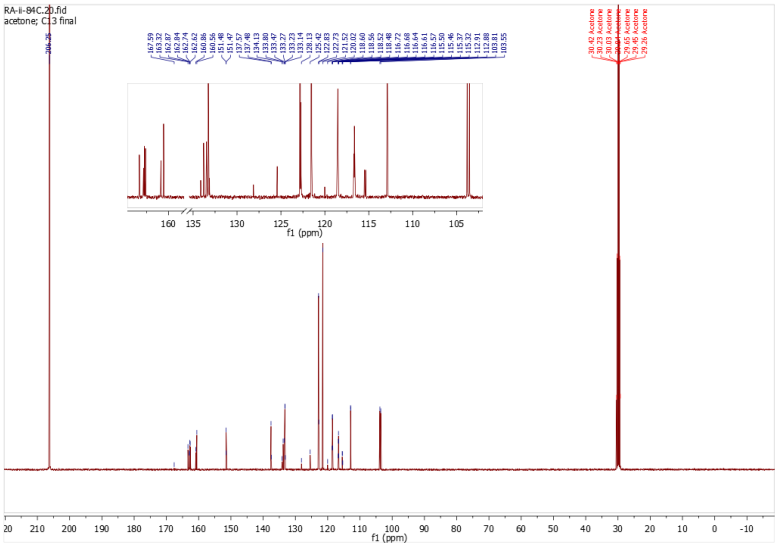
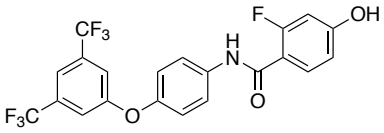


Figure S72. ^{13}C NMR Spectrum of Compound 14k (101 MHz, Acetone-d$_6$).

Compound 14k:



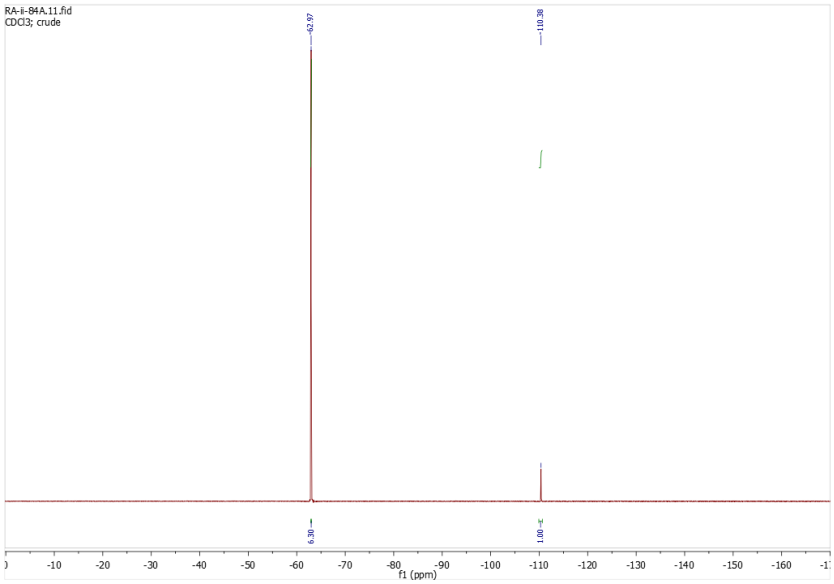


Figure S73. ^{19}F NMR Spectrum of Compound 14k (376 MHz, Acetone-d_6).

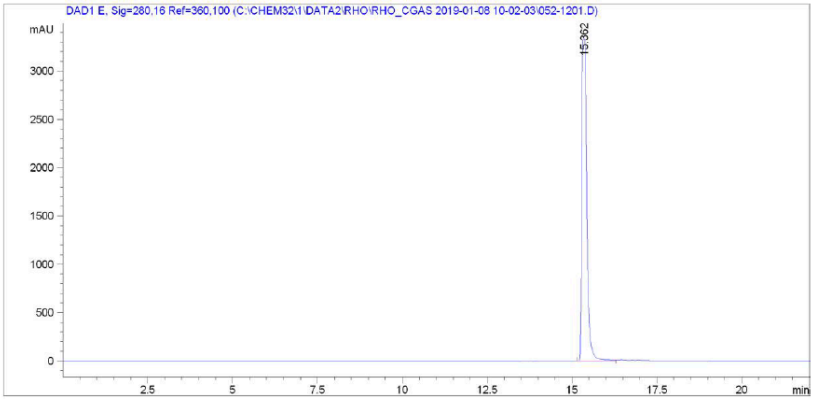
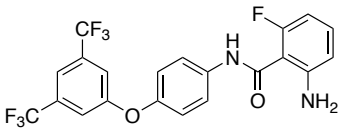


Figure S74. HPLC Chromatogram of Compound 14k.

Compound 14l:



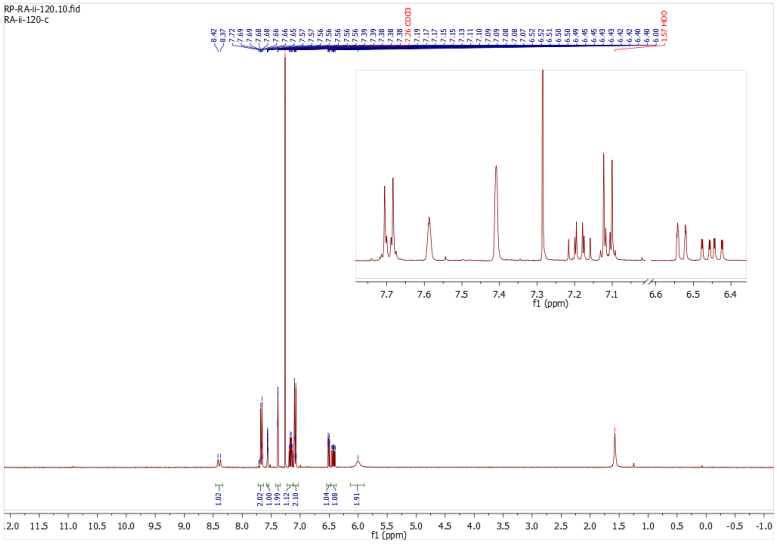


Figure S75. ^{1}H NMR Spectrum of Compound 14l (400 MHz, $CDCl_3$).

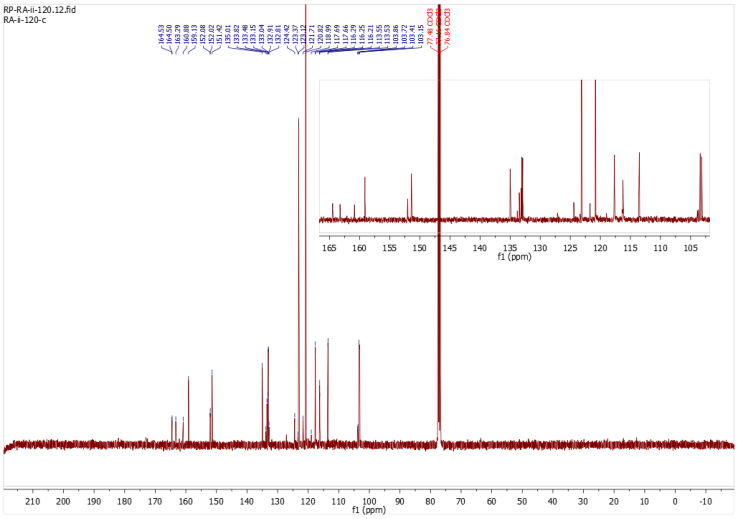
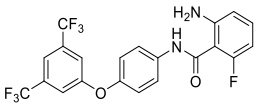


Figure S76. ^{13}C NMR Spectrum of Compound 14l (101 MHz, $CDCl_3$).

Compound 14l:



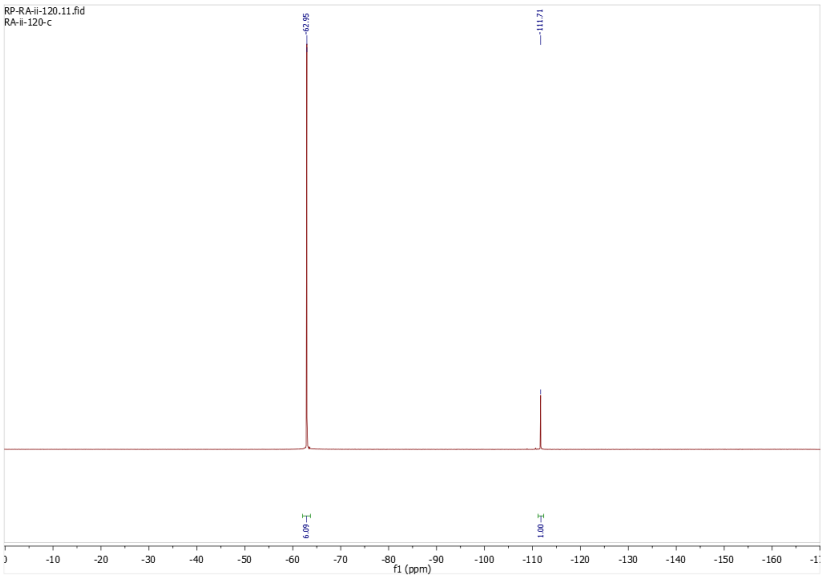


Figure S77. ^{19}F NMR Spectrum of Compound 14l (376 MHz, $CDCl_3$).

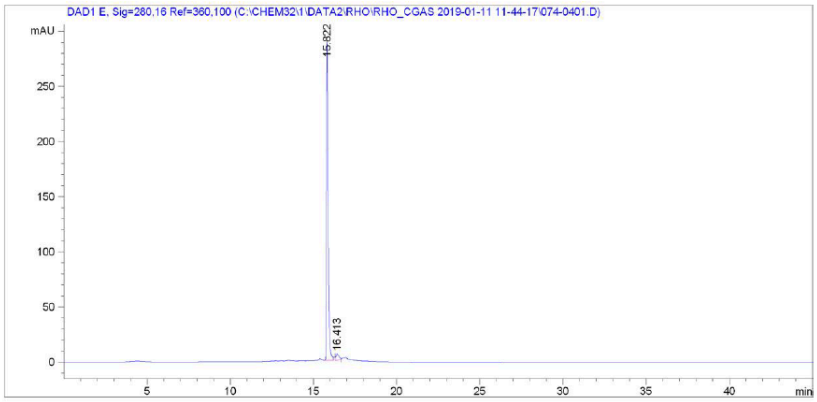
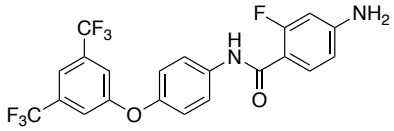


Figure S78. HPLC Chromatogram of Compound 14l.

Compound 14m:



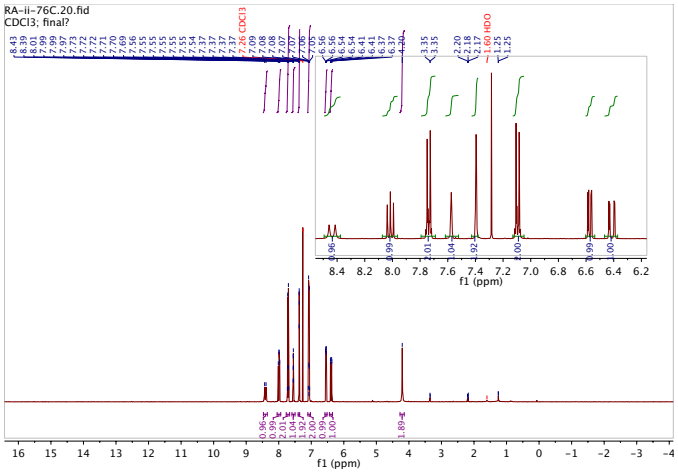


Figure S79. ^{1}H NMR Spectrum of Compound 14m (400 MHz, $CDCl_3$).

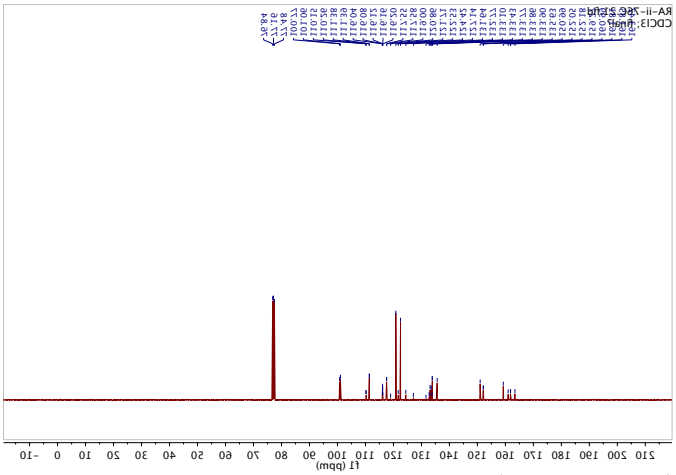
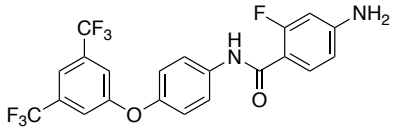


Figure S80. ^{13}C NMR Spectrum of Compound 14m (101 MHz, $CDCl_3$).

Compound 14m:



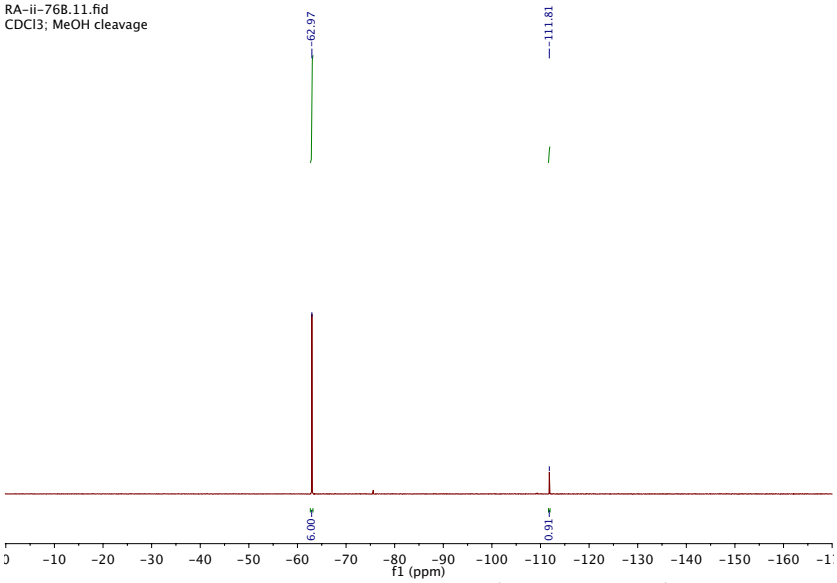


Figure S81. ^{19}F NMR Spectrum of Compound 14m (376 MHz, $CDCl_3$).

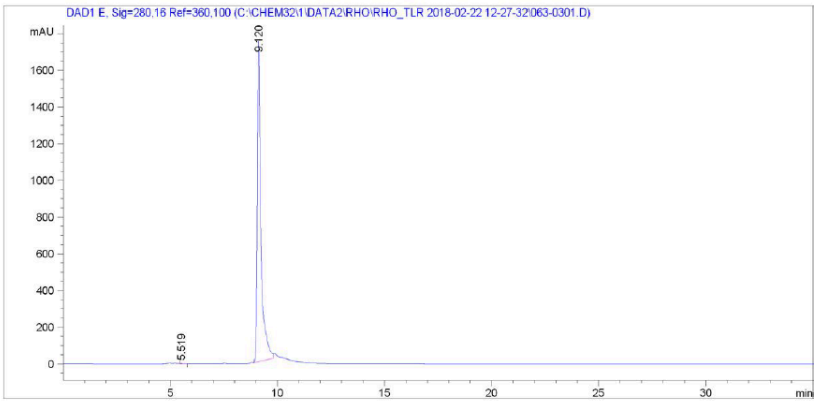
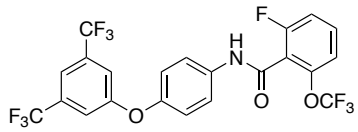


Figure S82. HPLC Chromatogram of Compound 14m.

Compound 14n:



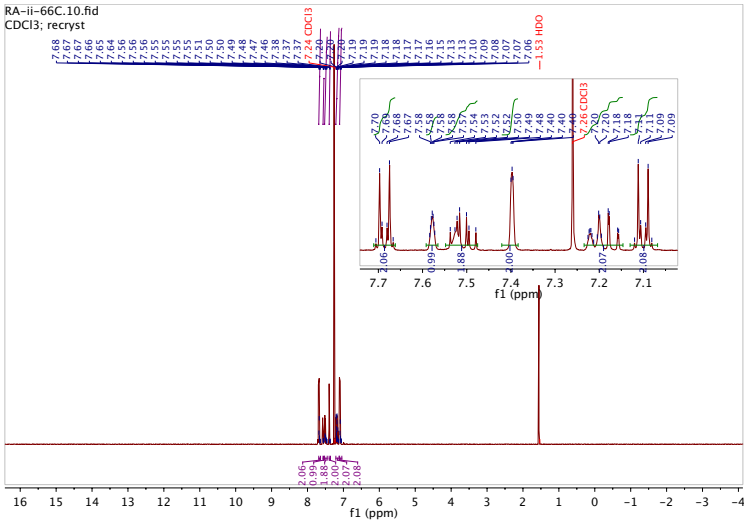


Figure 83. ^{1}H NMR Spectrum of Compound 14n (400 MHz, $CDCl_3$).

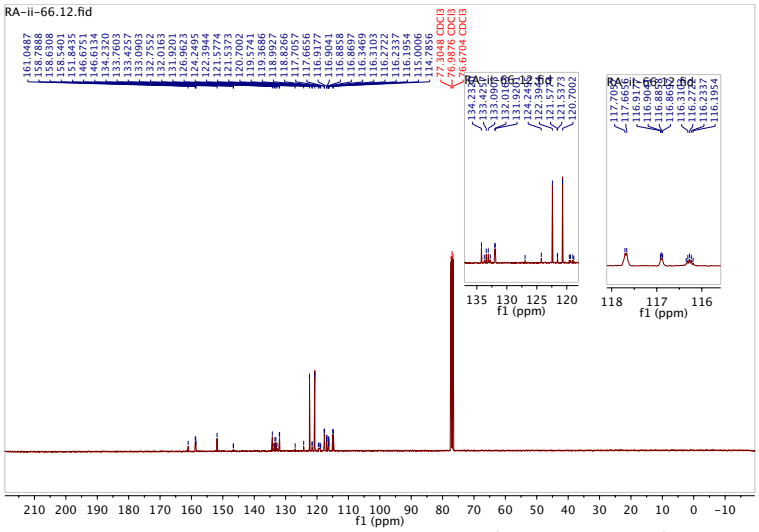
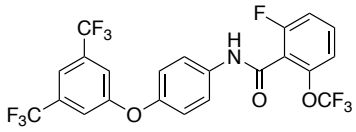


Figure S84. ^{13}C NMR Spectrum of Compound 14n (101 MHz, $CDCl_3$).

Compound 14n:



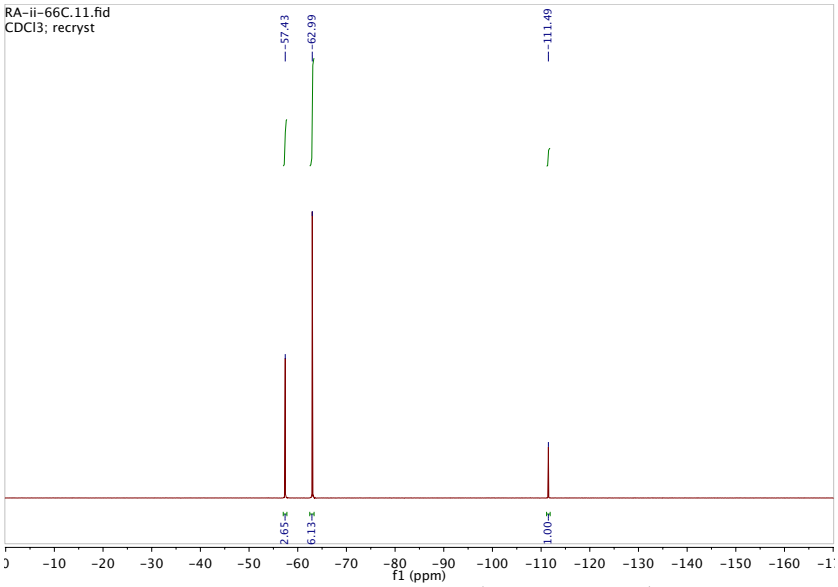


Figure 85. ^{19}F NMR Spectrum of Compound 14n (376 MHz, $CDCl_3$).

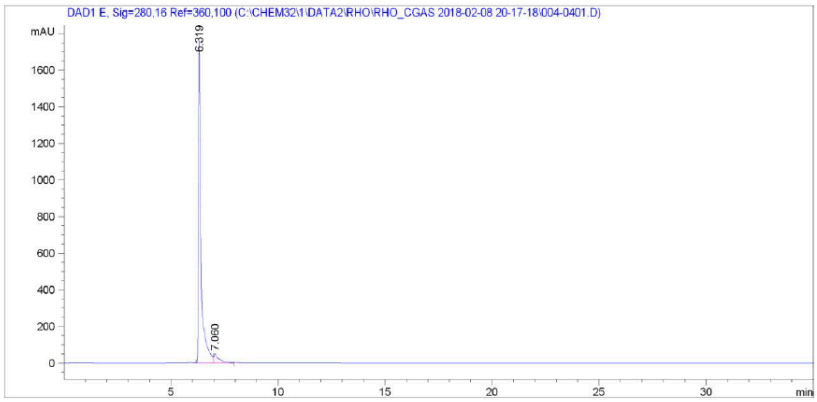


Figure S86. HPLC Chromatogram of Compound 14n.

Compound 14o:

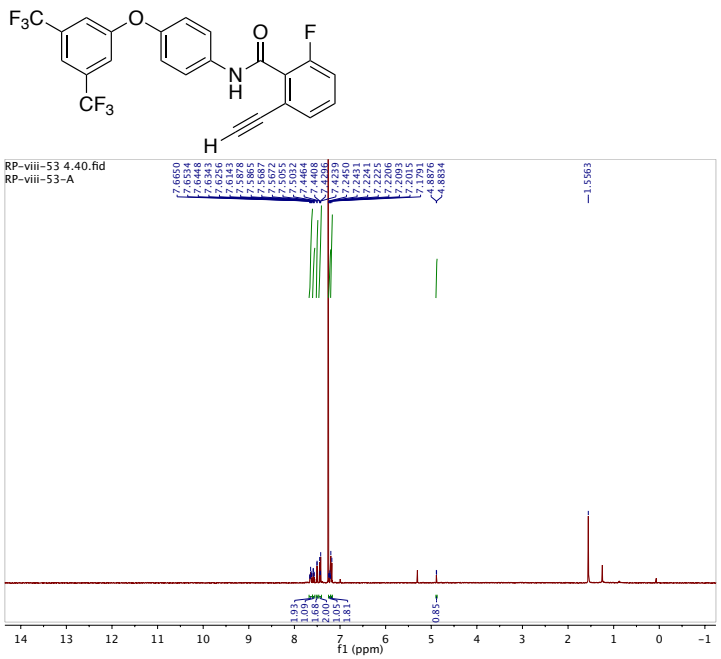


Figure S87. ^{1}H NMR Spectrum of Compound 14o (400 MHz, $CDCl_3$).

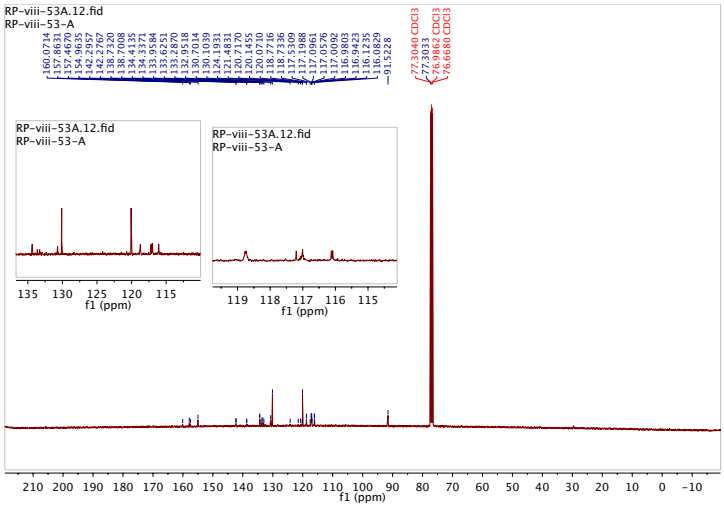
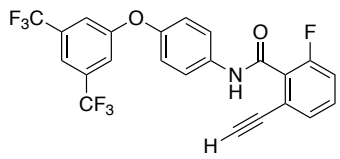


Figure S88. ^{13}C NMR Spectrum of Compound 14o (101 MHz, $CDCl_3$).

Compound 14o:



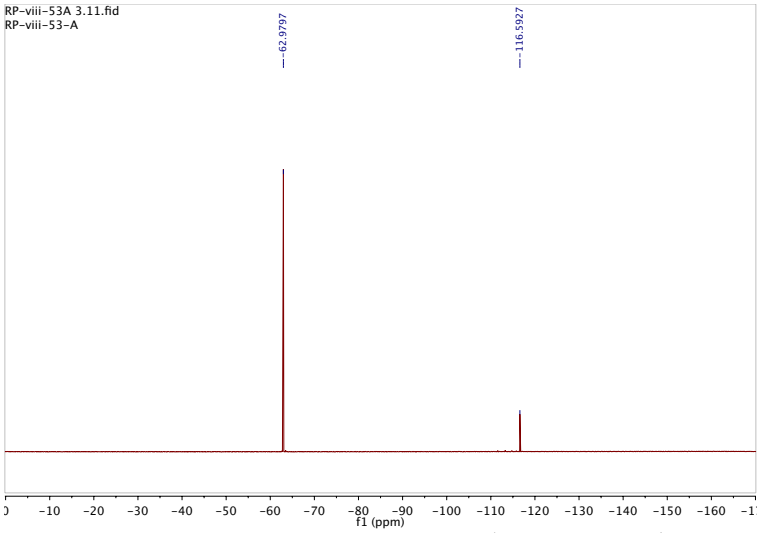


Figure S89. ^{19}F NMR Spectrum of Compound 14o (376 MHz, $CDCl_3$).

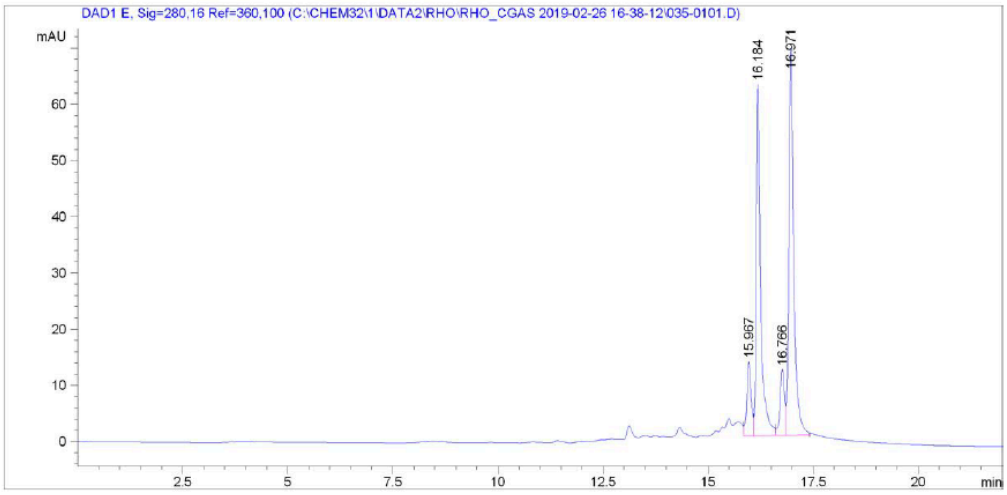
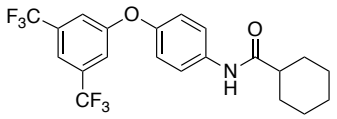


Figure S90. HPLC Chromatogram of Compound 14o.

Compound 15a:



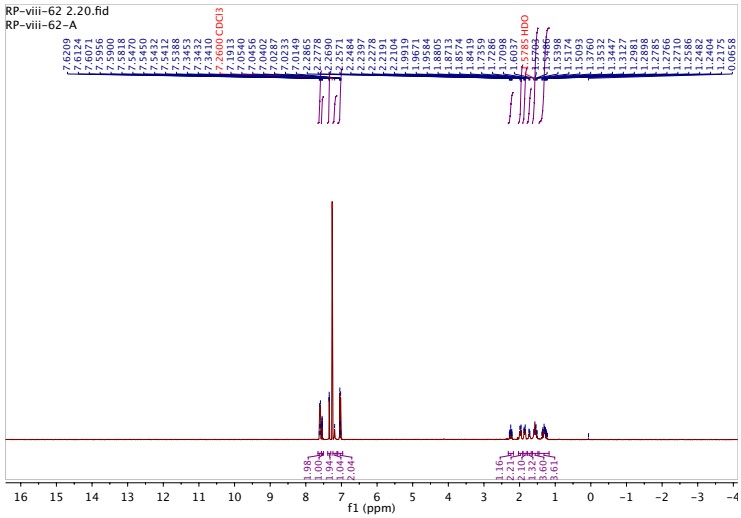


Figure S91. ^{1}H NMR Spectrum of Compound 15a (400 MHz, $CDCl_3$).

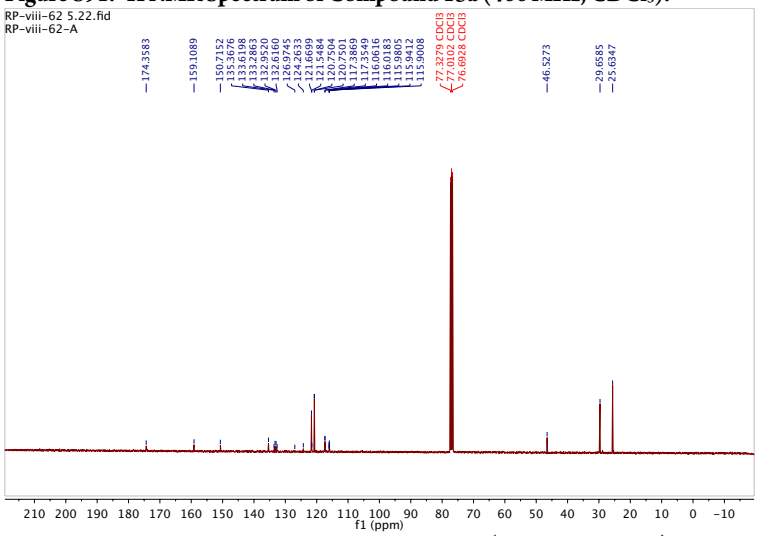


Figure S92. ^{13}C NMR Spectrum of Compound 15a (101 MHz, $CDCl_3$).

Compound 15a:

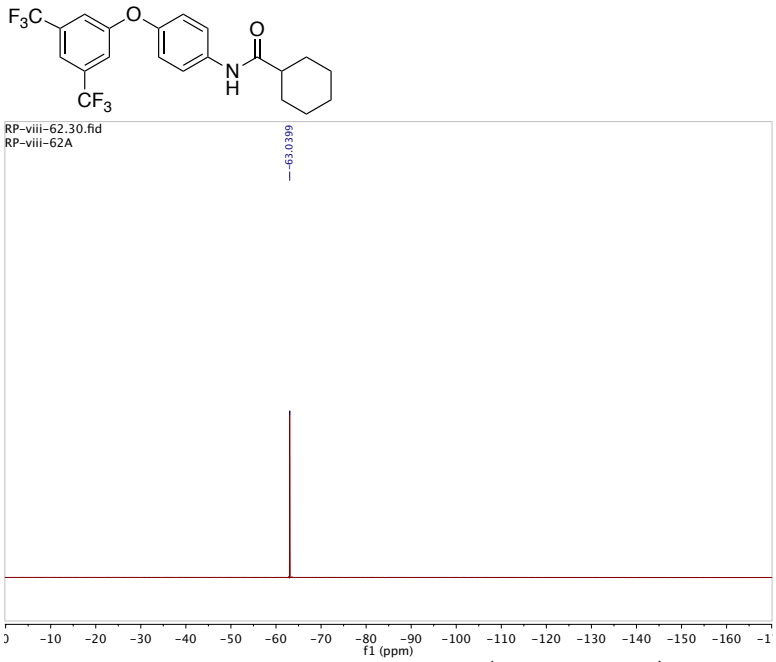


Figure S93. ^{19}F NMR Spectrum of Compound 15a (376 MHz, $CDCl_3$).

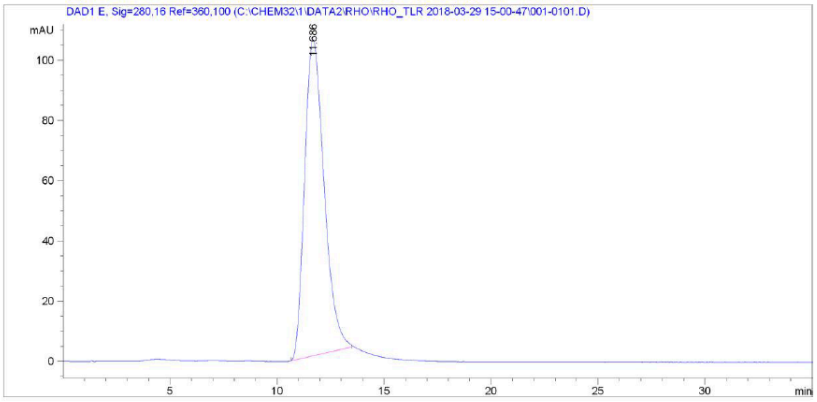
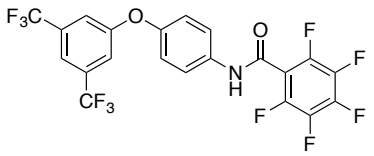


Figure S94. HPLC Chromatogram of Compound 15a.

Compound 15b:



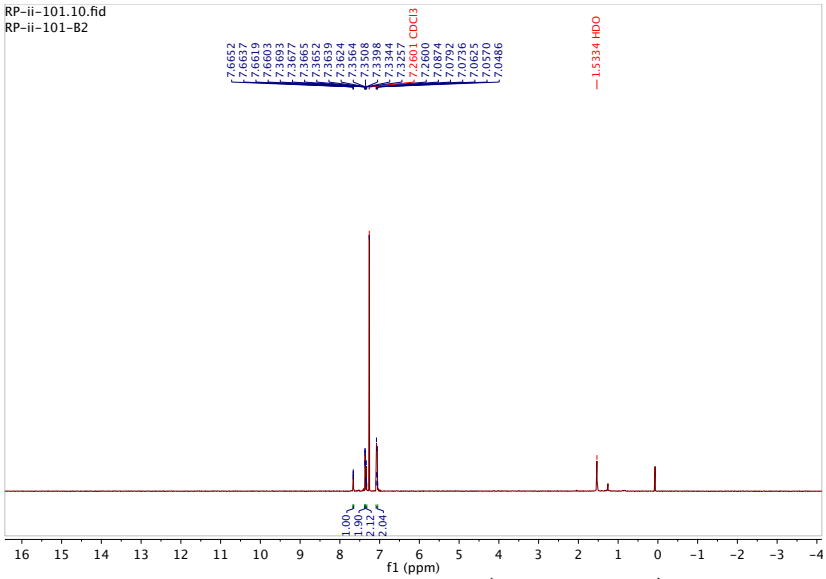


Figure S95. ^{1}H NMR Spectrum of Compound 15b (400 MHz, $CDCl_3$).

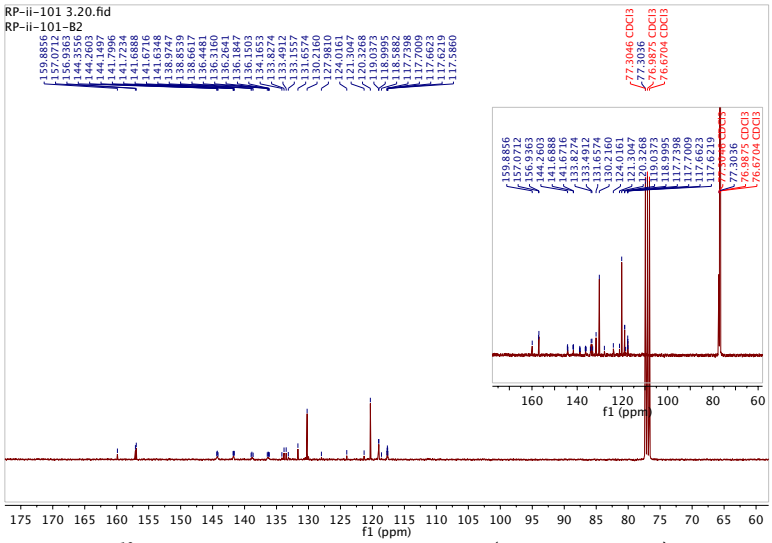
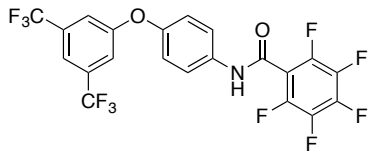


Figure S96. ^{13}C NMR Spectrum of Compound 15b (101 MHz, $CDCl_3$).

Compound 15b:



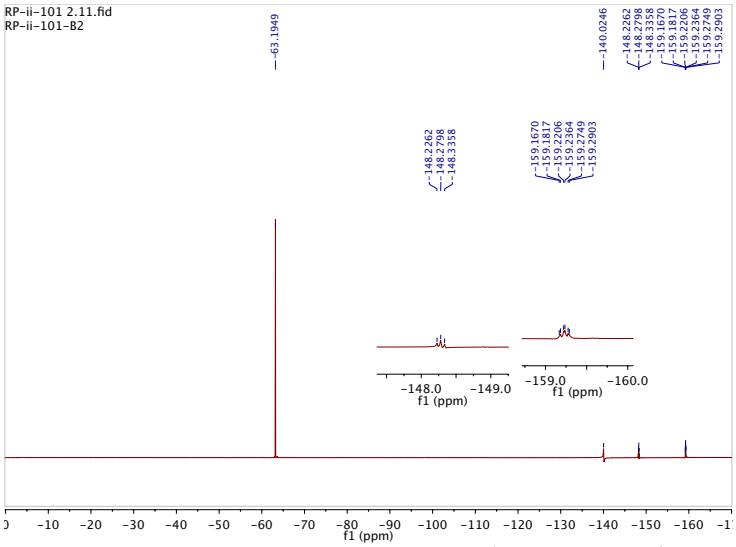


Figure S97. ^{19}F NMR Spectrum of Compound 15b (376 MHz, $CDCl_3$).

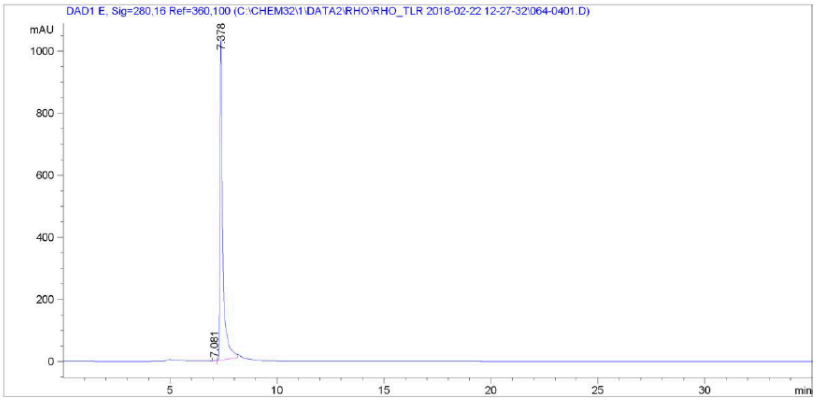
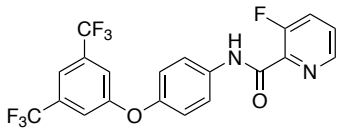


Figure S98. HPLC Chromatogram of Compound 15b.

Compound 15c:



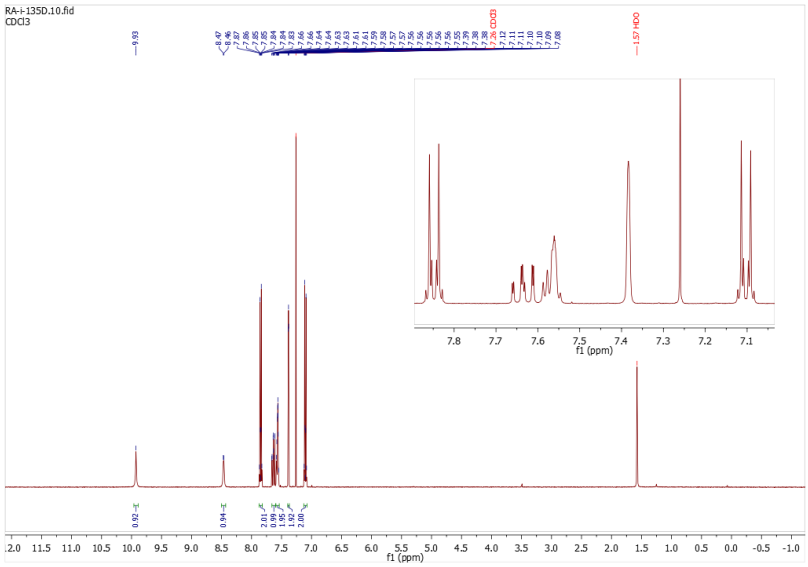


Figure S99. ^{1}H NMR Spectrum of Compound 15c (400 MHz, $CDCl_3$).

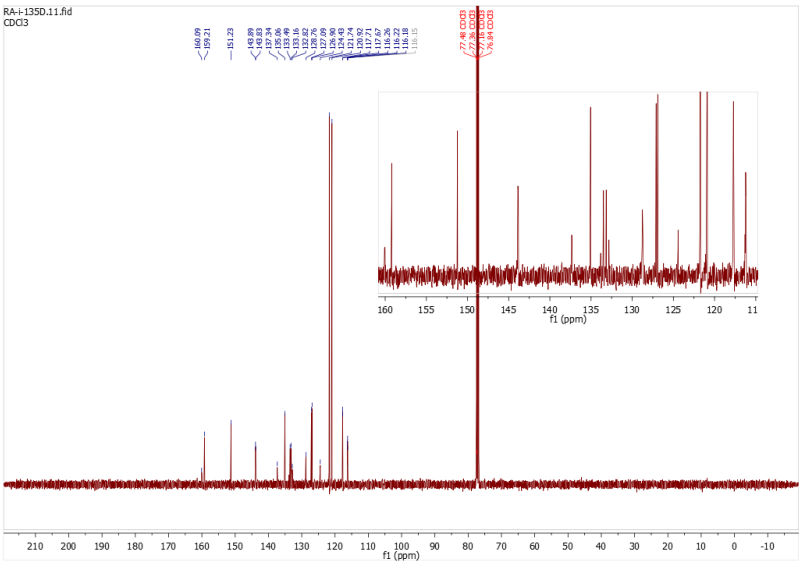
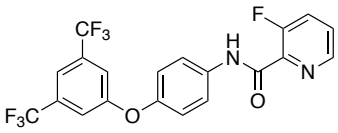


Figure S100. ^{13}C NMR Spectrum of Compound 15c (101 MHz, $CDCl_3$).

Compound 15c:



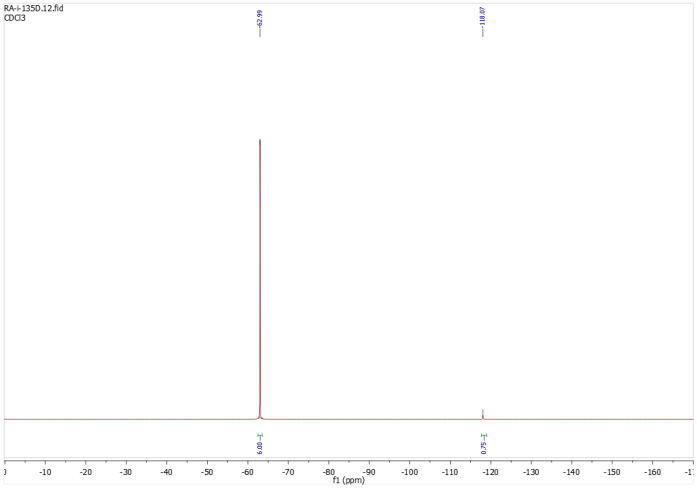


Figure S101. ^{19}F NMR Spectrum of Compound 15c (376 MHz, $CDCl_3$).

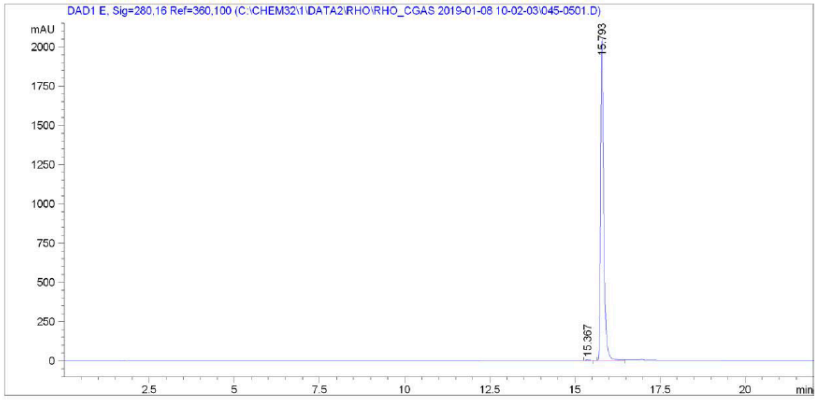


Figure S102. HPLC Chromatogram of Compound 15c.

Compound 15d:

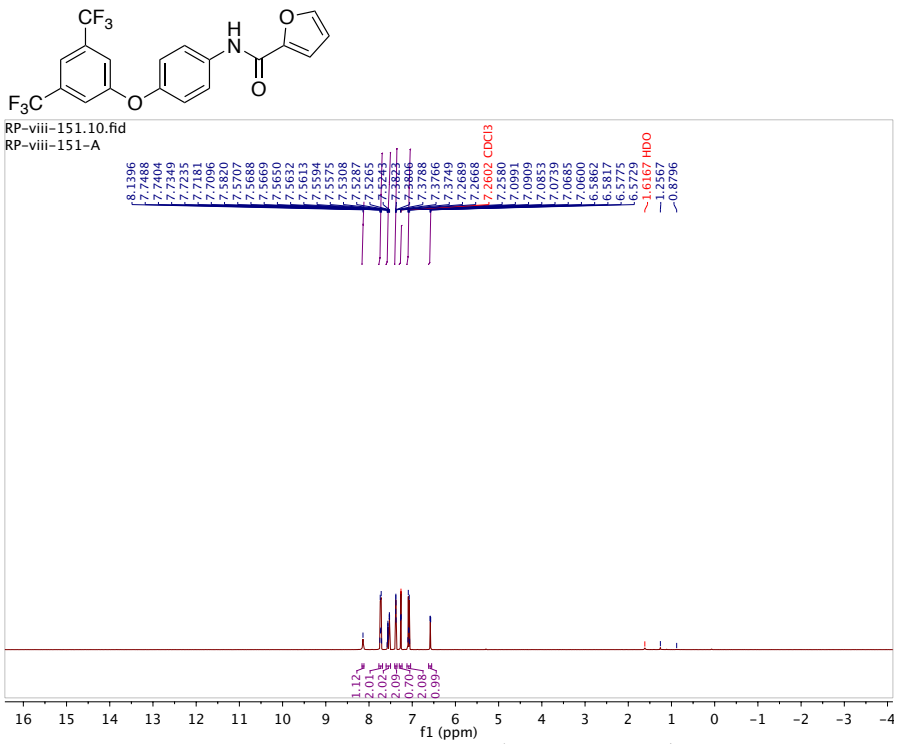


Figure S103. ^{1}H NMR Spectrum of Compound 15d (400 MHz, $CDCl_3$).

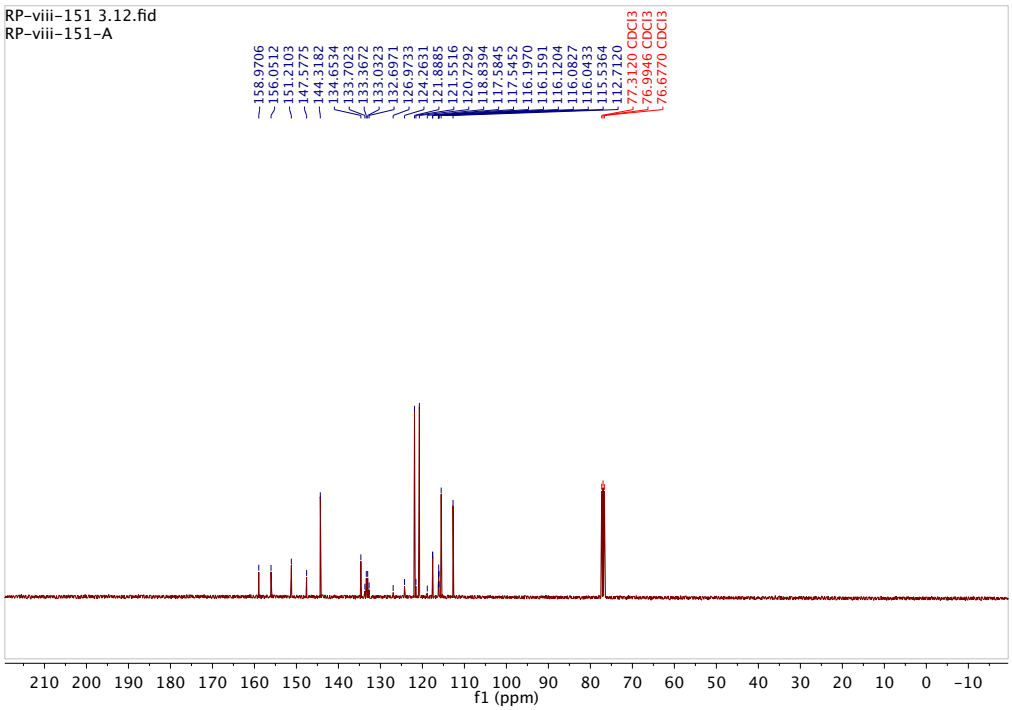


Figure S104. ^{13}C NMR Spectrum of Compound 15d (101 MHz, $CDCl_3$).

Compound 15d:

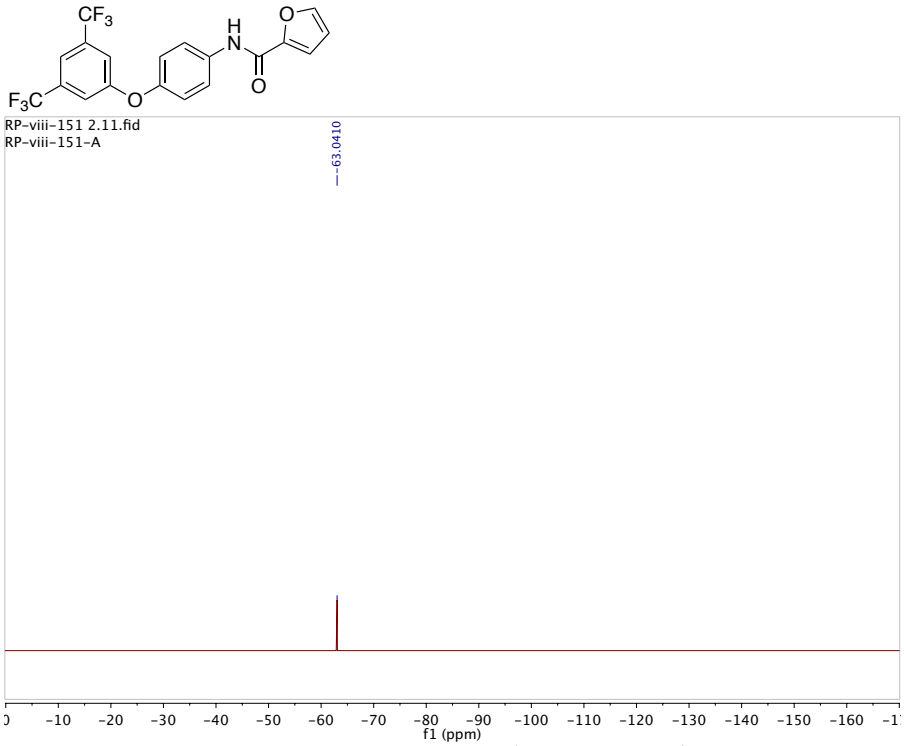


Figure S105. 19F NMR Spectrum of Compound 15d (376 MHz, $CDCl_3$).

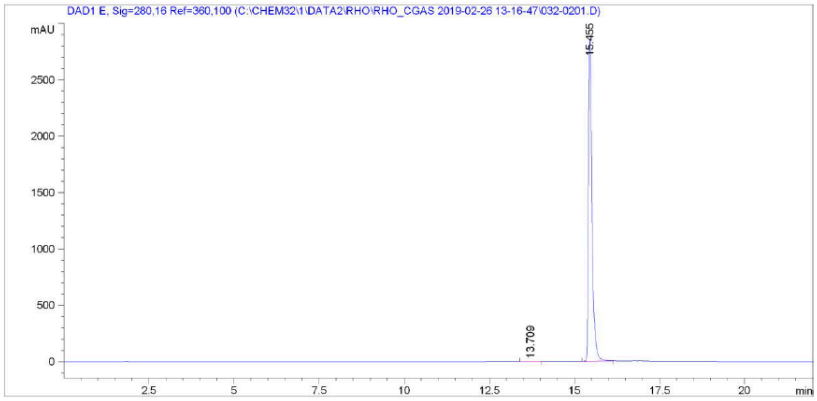
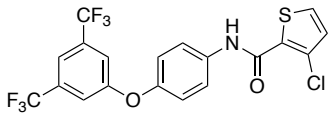


Figure S106. HPLC Chromatogram of Compound 15d.

Compound 15e:



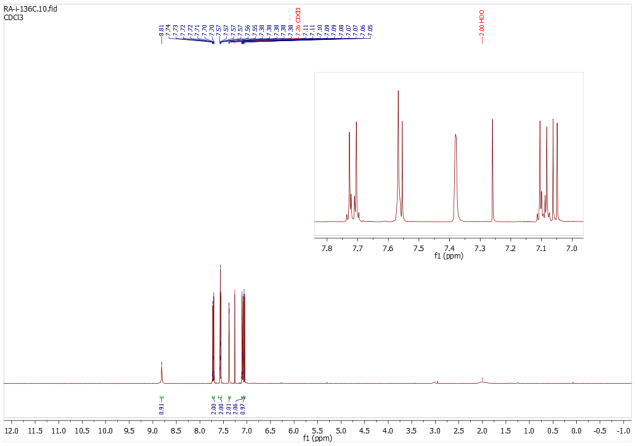


Figure S107. ^{1}H NMR Spectrum of Compound 15e (400 MHz, $CDCl_3$).

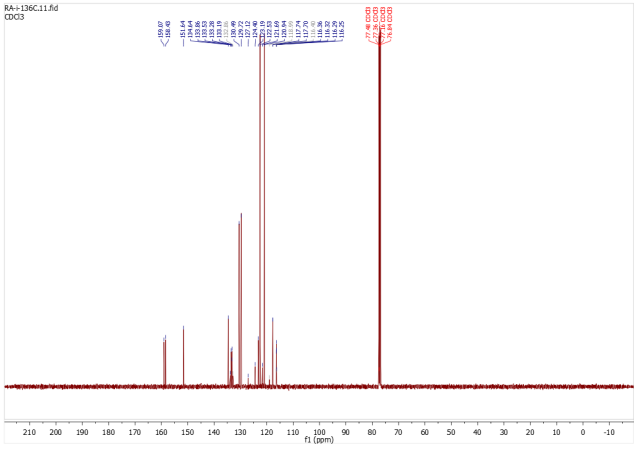


Figure S108. ^{13}C NMR Spectrum of Compound 15e (101 MHz, $CDCl_3$).

Compound 15e:

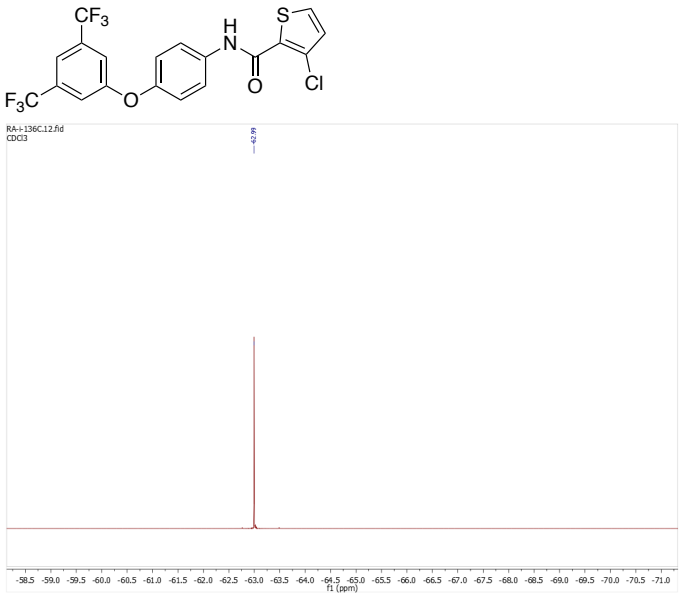


Figure S109. ^{19}F NMR Spectrum of Compound 15e (376 MHz, $CDCl_3$).

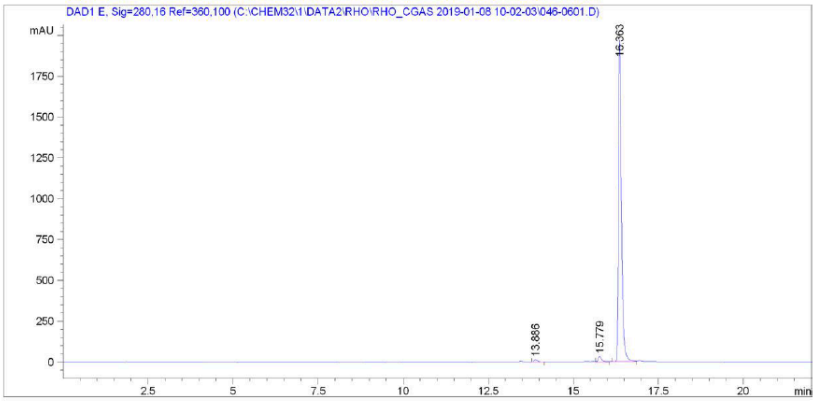
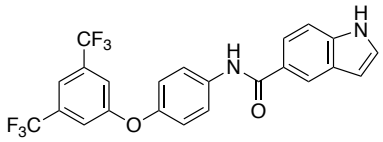


Figure S110. HPLC Chromatogram of Compound 15e.

Compound 15f:



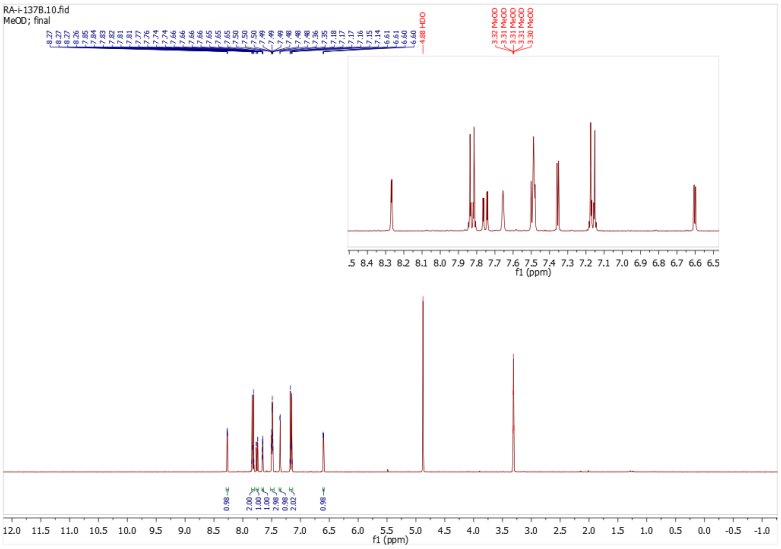


Figure S111. ^{1}H NMR Spectrum of Compound 15f (400 MHz, MeOD).

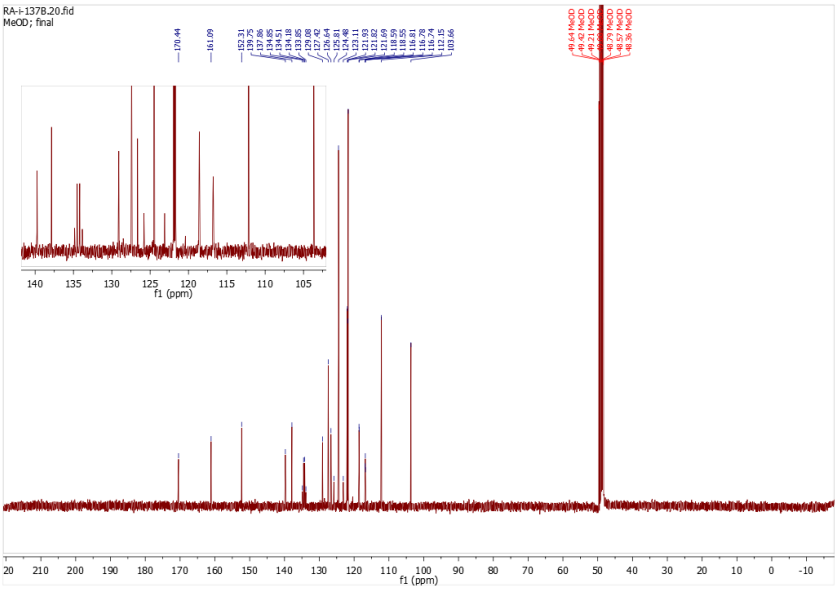
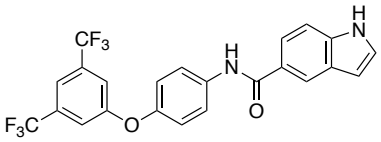


Figure S112. ^{13}C NMR Spectrum of Compound 15f (101 MHz, MeOD).

Compound 15f:



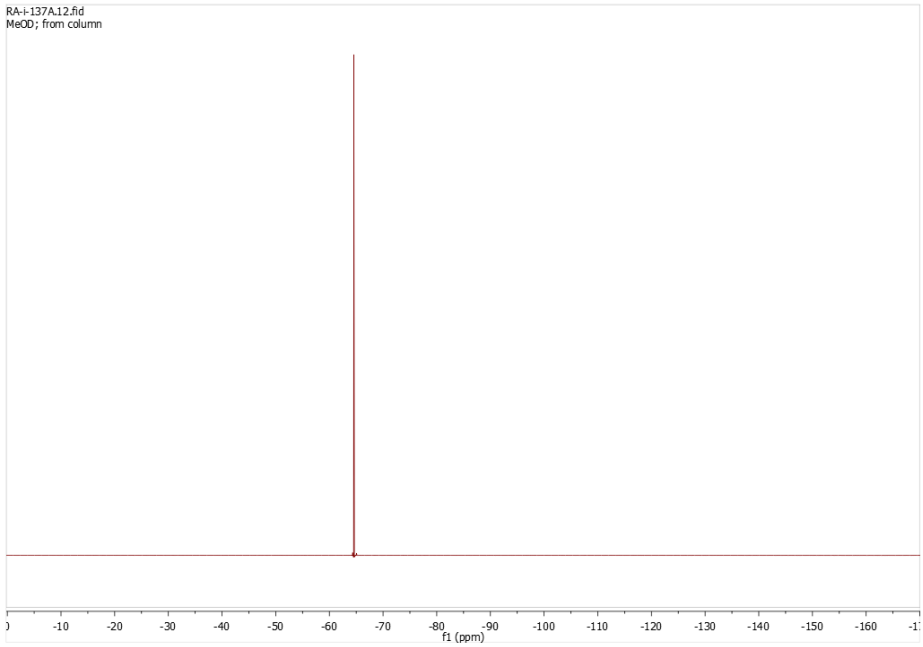


Figure S113. ^{19}F NMR Spectrum of Compound 15f (376 MHz, MeOD).

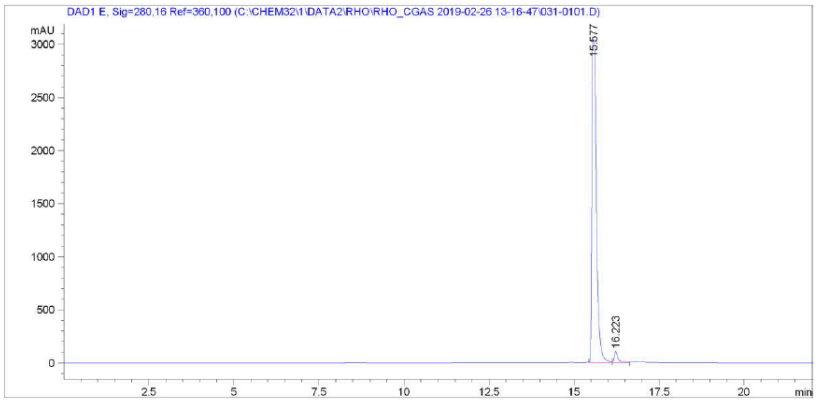


Figure S114. HPLC Chromatogram of Compound 15f.

Compound 15g:

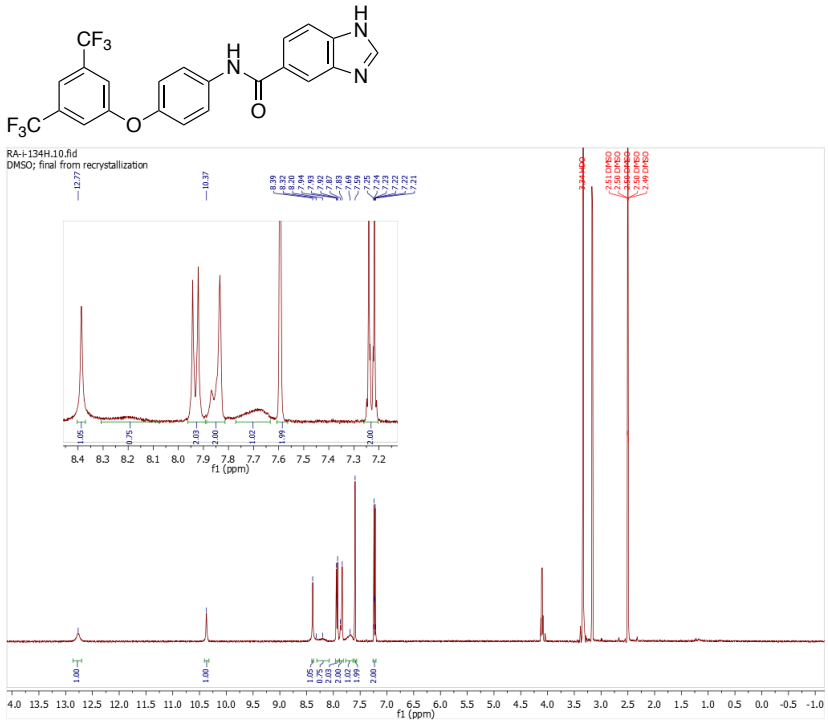


Figure S115. ^{1}H NMR Spectrum of Compound 15g (400 MHz, Acetone-d_6).

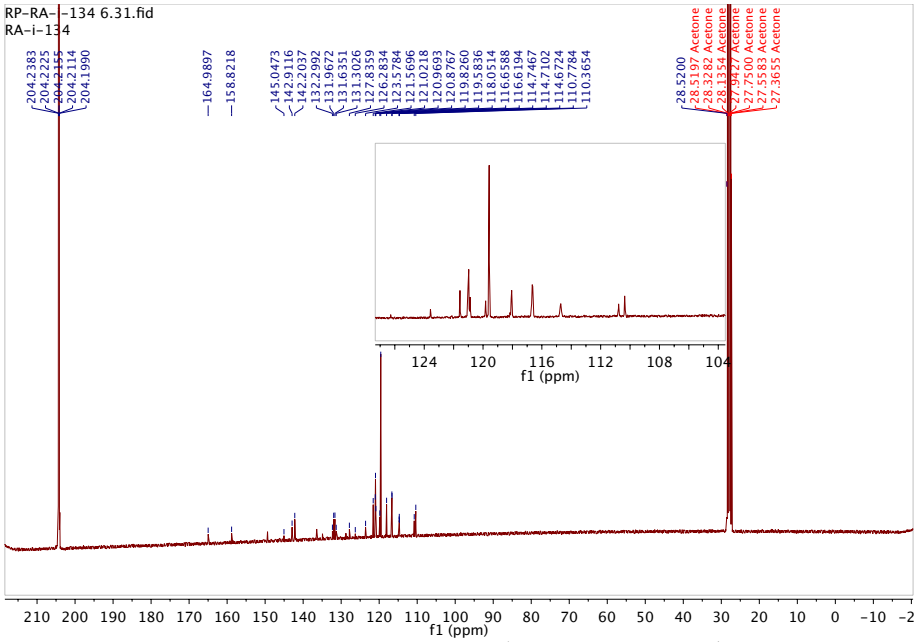
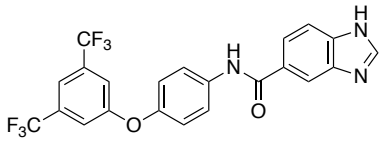


Figure S116. ^{13}C NMR Spectrum of Compound 15g (101 MHz, Acetone-d_6).

Compound 15g:



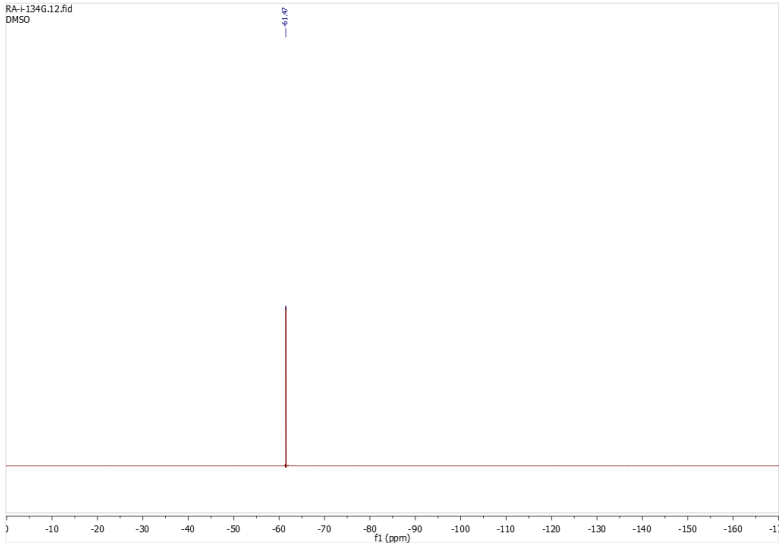


Figure S117. ^{19}F NMR Spectrum of Compound 15g (376 MHz, $CDCl_3$).

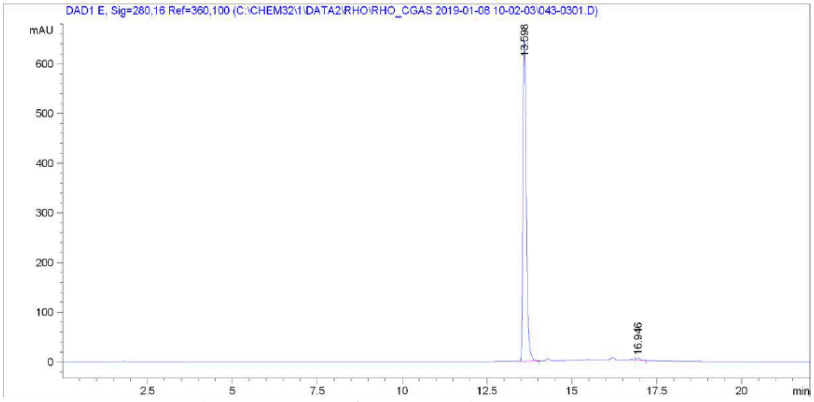


Figure S118. HPLC Chromatogram of Compound 15g.

Compound 16:

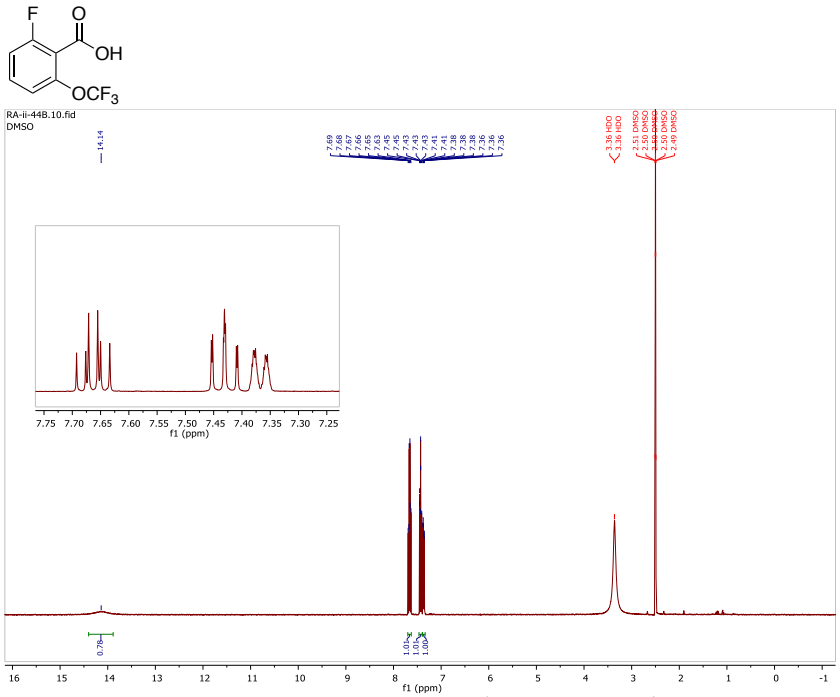


Figure S119. ^{1}H NMR Spectrum of Compound 16(400 MHz, $CDCl_3$).

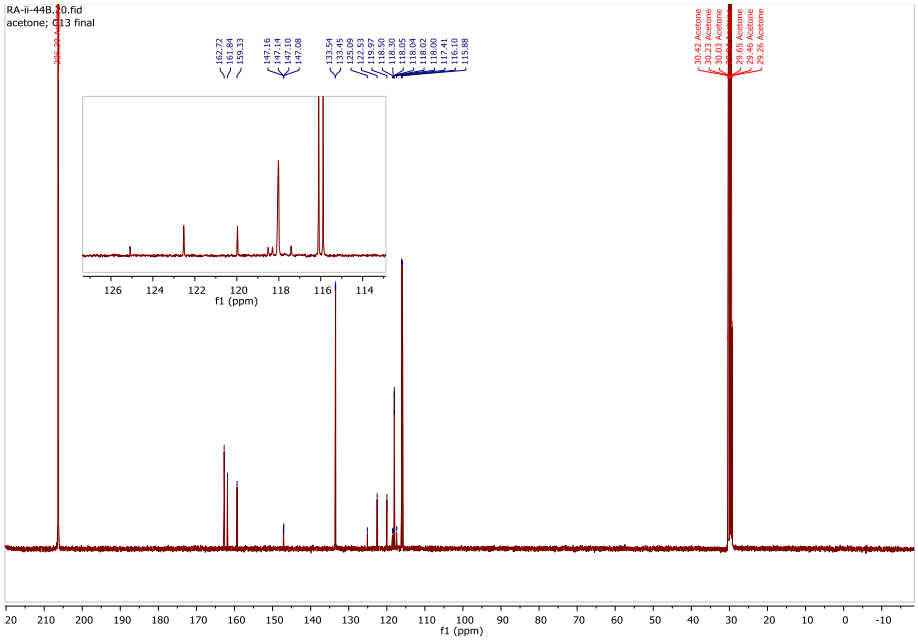
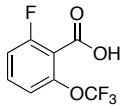


Figure S120. ^{13}C NMR Spectrum of Compound 16(101 MHz, $CDCl_3$).

Compound 16:



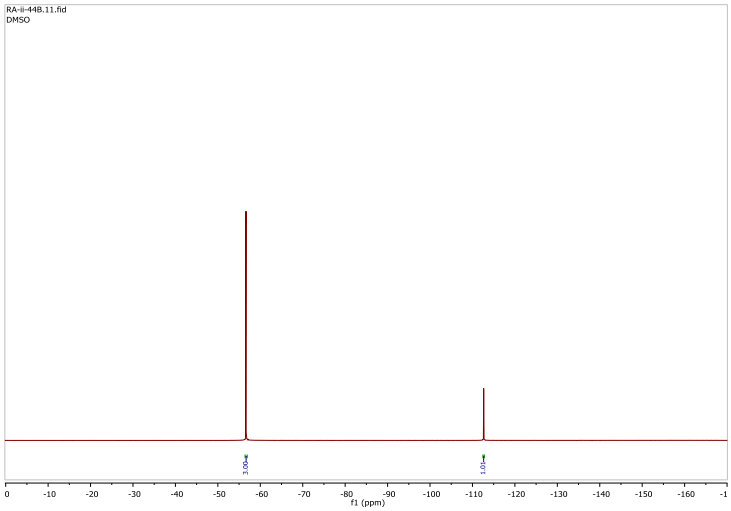
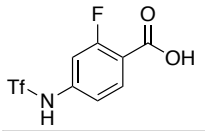


Figure S121. ^{19}F NMR Spectrum of Compound 16 (376 MHz, $CDCl_3$).

Compound 17:



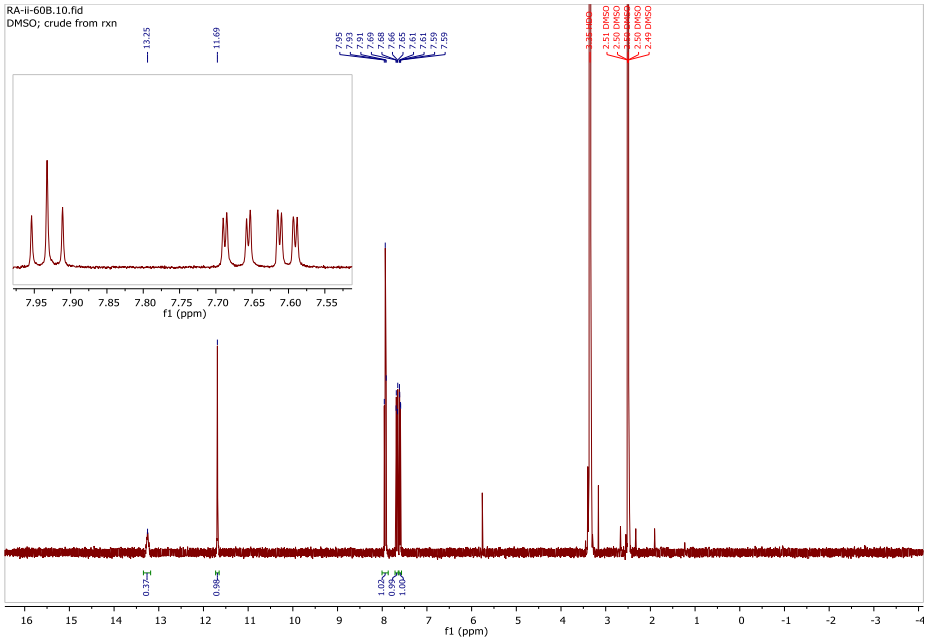


Figure S122. ^{1}H NMR Spectrum of Compound 17 (400 MHz, DMSO).

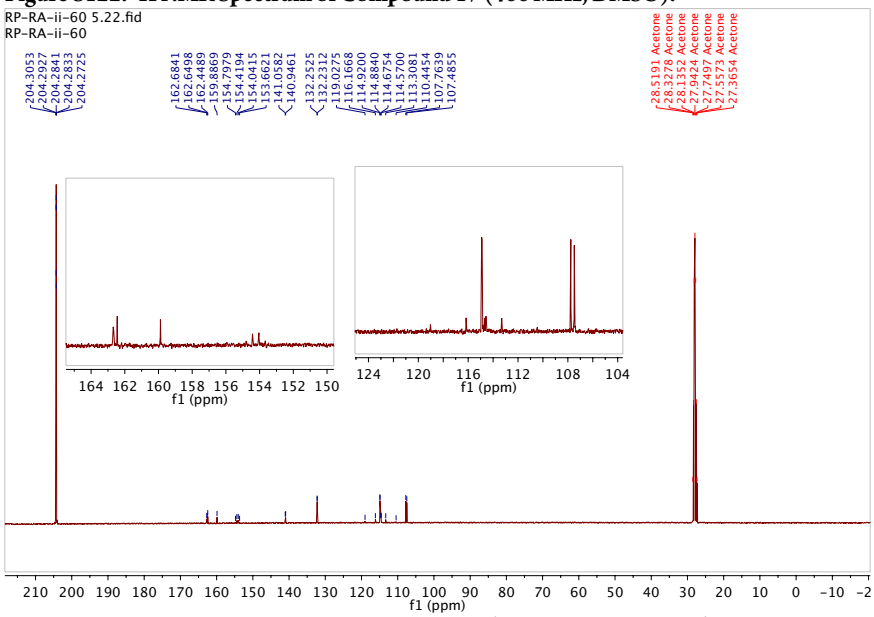


Figure S123. ^{13}C NMR Spectrum of Compound 17 (101 MHz, Acetone-d_6).

Compound 17:

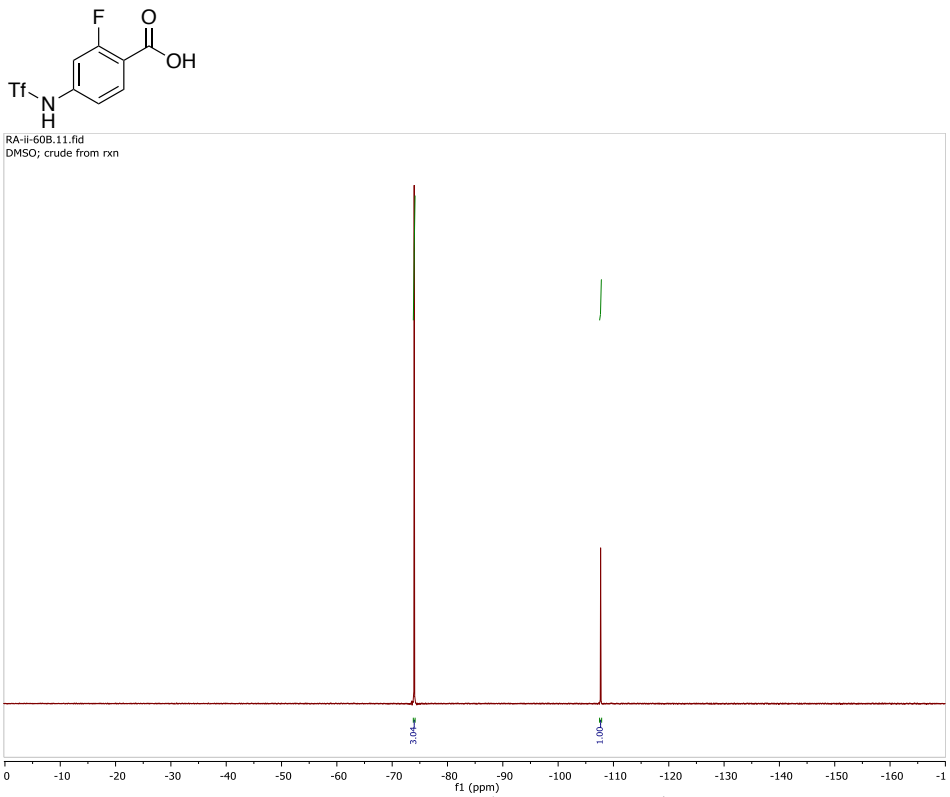
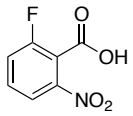


Figure S124. ^{19}F NMR Spectrum of Compound 17 (376 MHz, DMSO).

Compound 18:



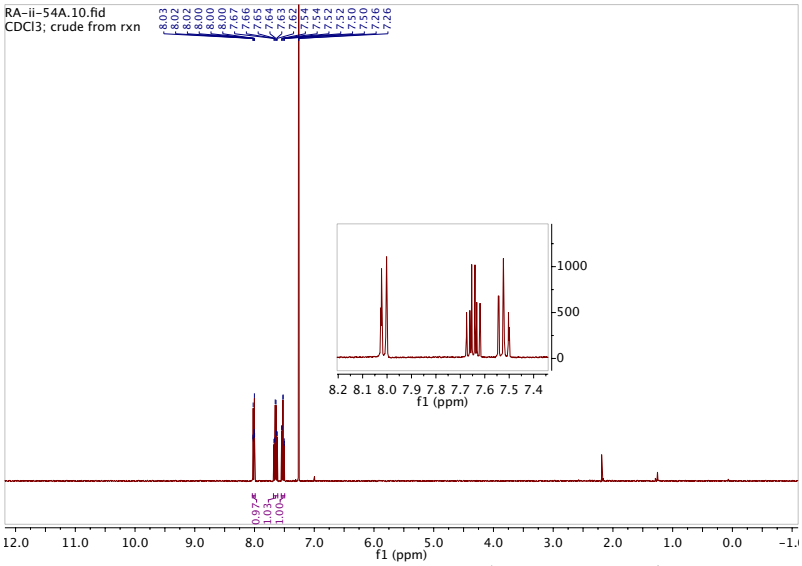


Figure S125. ^{1}H NMR Spectrum of Compound 18 (400 MHz, $CDCl_3$).

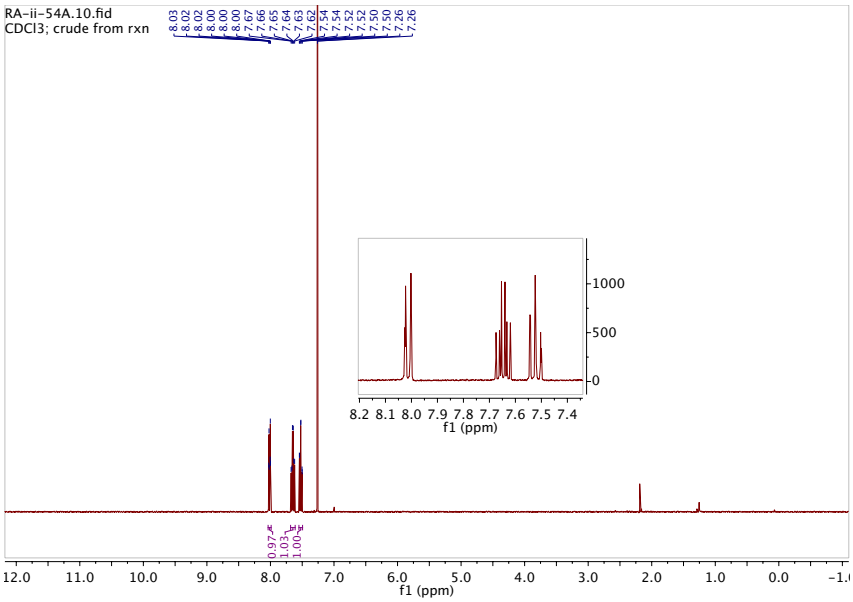
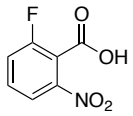


Figure S126. ^{13}C NMR Spectrum of Compound 18 (101 MHz, Acetone-d_6).

Compound 18:



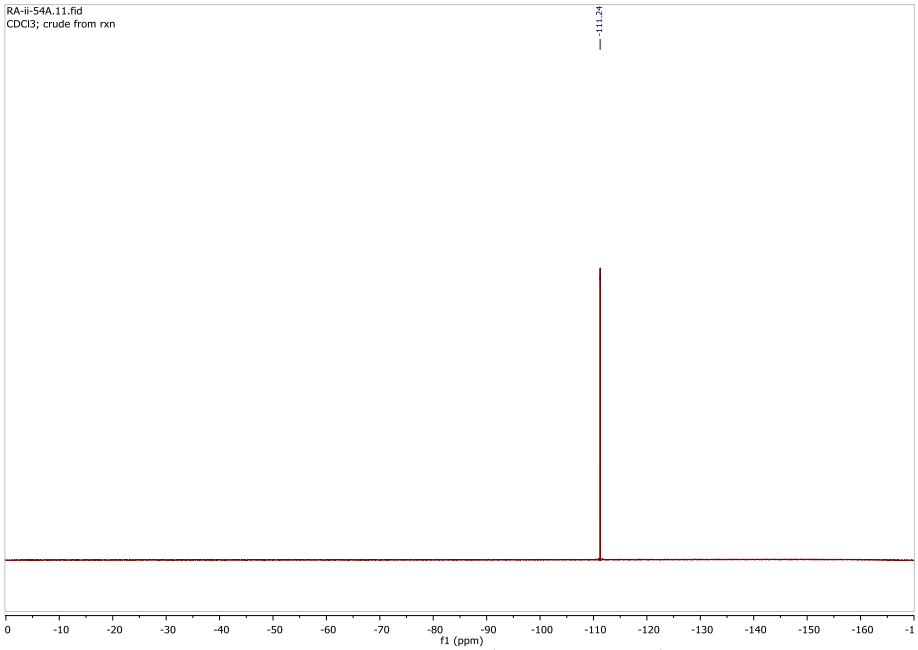
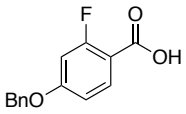


Figure S127. ^{19}F NMR Spectrum of Compound 18 (376 MHz, $CDCl_3$).

Compound 19:



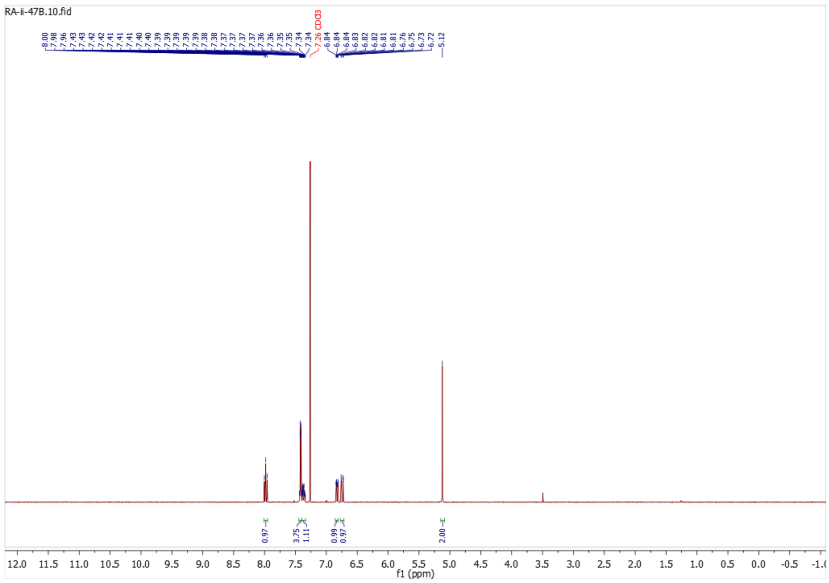


Figure S128. ^{1}H NMR Spectrum of Compound 19 (400 MHz, $CDCl_3$).

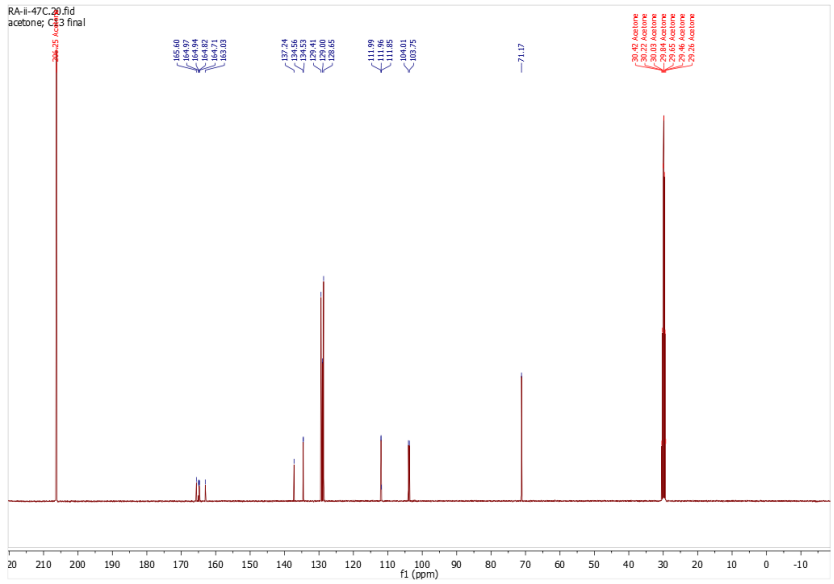


Figure S129. ^{13}C NMR Spectrum of Compound 19 (101 MHz, $CDCl_3$).

Compound 29:

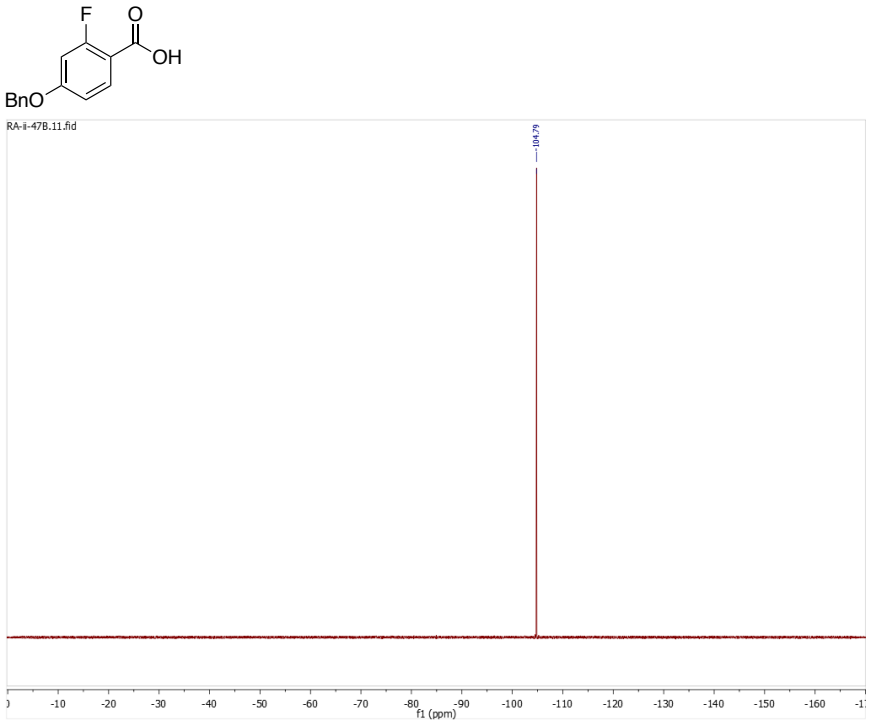


Figure S130. ^{19}F NMR Spectrum of Compound 19 (376 MHz, $CDCl_3$).

Compound 22:

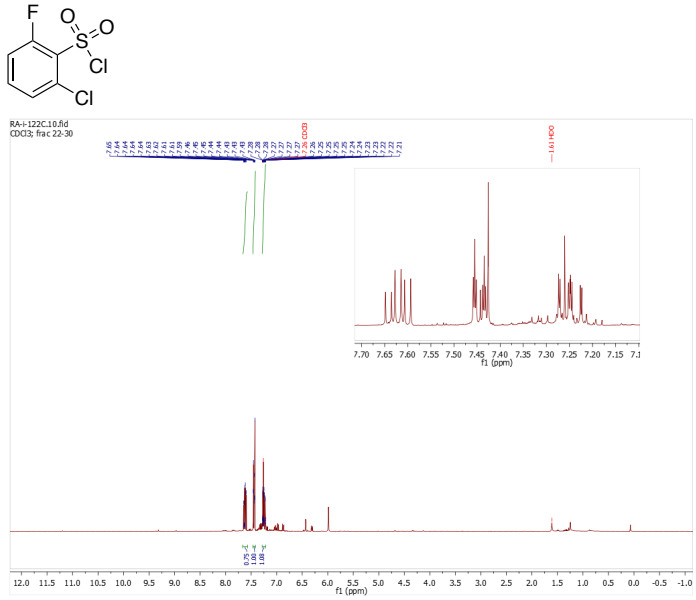
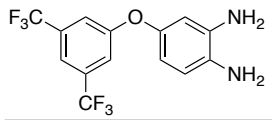


Figure S131. ^{1}H NMR Spectrum of Compound 22 (400 MHz, $CDCl_3$).

Compound 23:



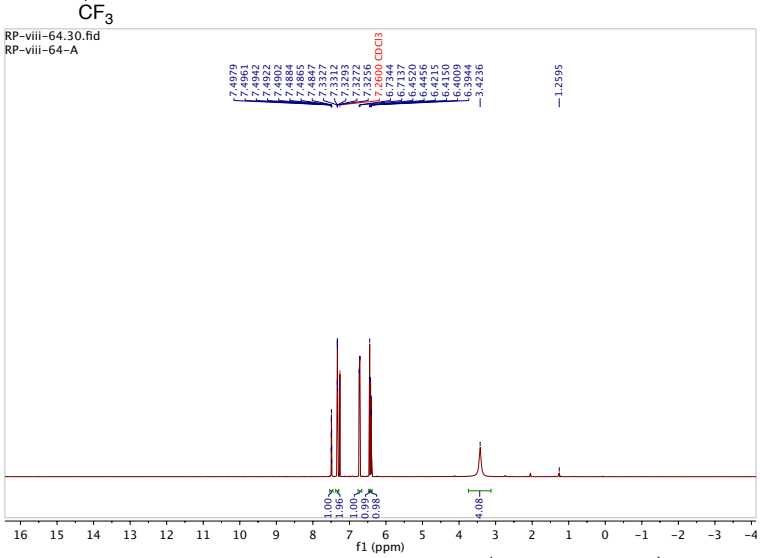


Figure S132. ^{1}H NMR Spectrum of Compound 23 (400 MHz, $CDCl_3$).

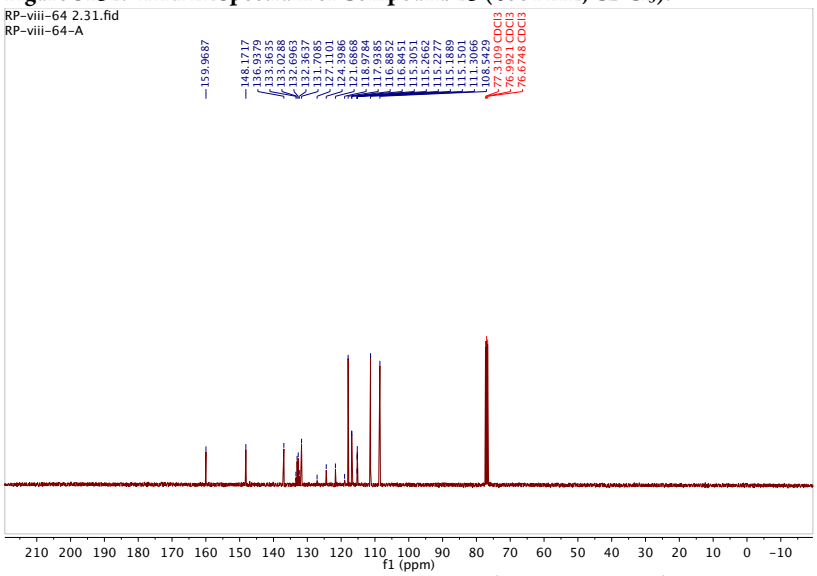


Figure S133. ^{13}C NMR Spectrum of Compound 23 (101 MHz, $CDCl_3$).

Compound 23:

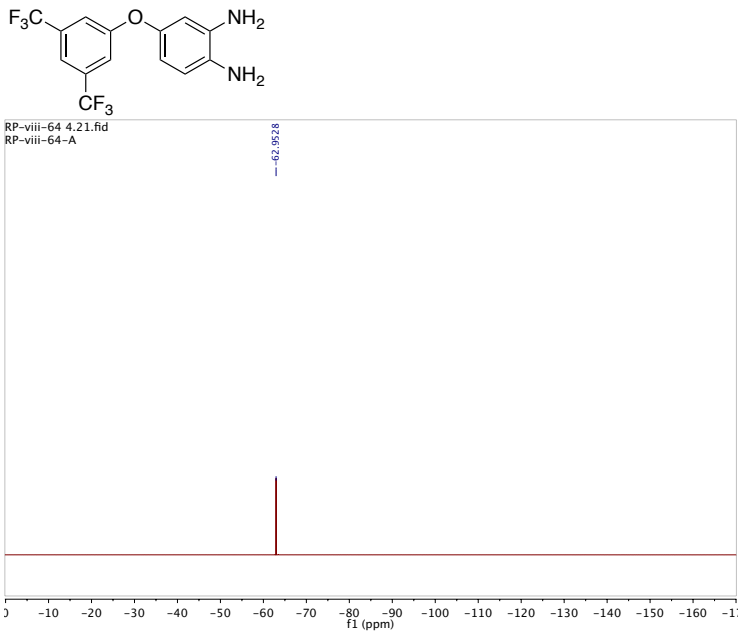
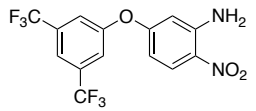


Figure S134. ^{19}F NMR Spectrum of Compound 23 (376 MHz, $CDCl_3$).

Compound 24:



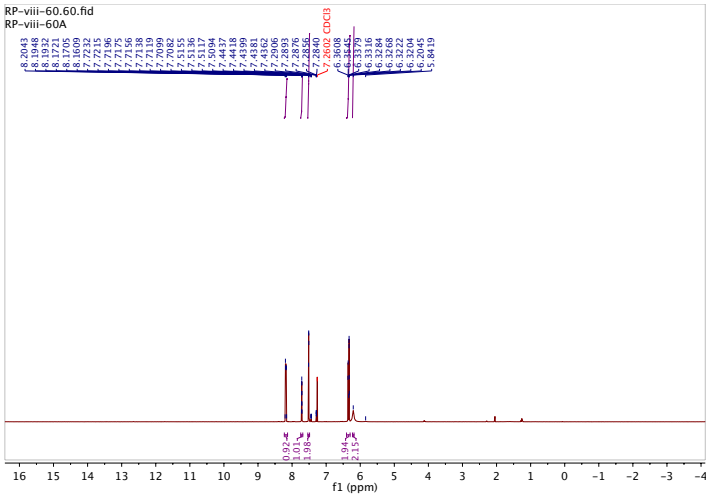


Figure S135. ^{1}H NMR Spectrum of Compound 24 (400 MHz, $CDCl_3$).

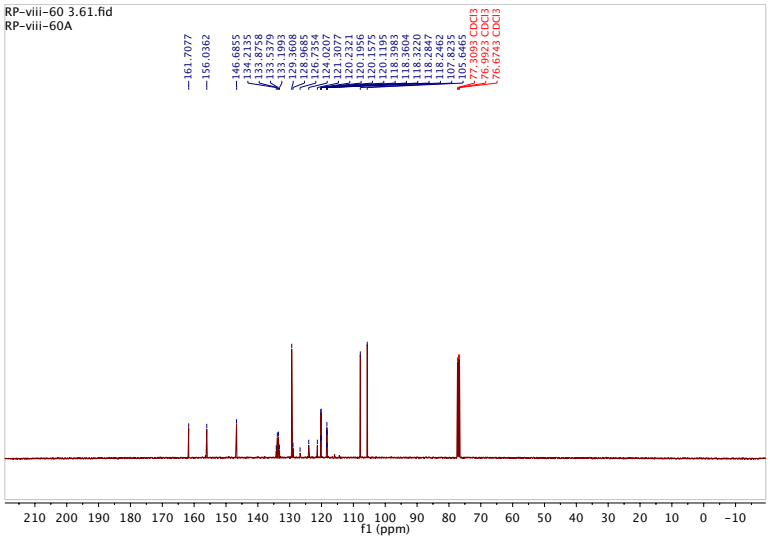
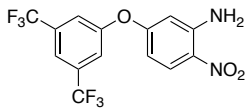


Figure S136. ^{13}C NMR Spectrum of Compound 24 (101 MHz, $CDCl_3$).

Compound 24:



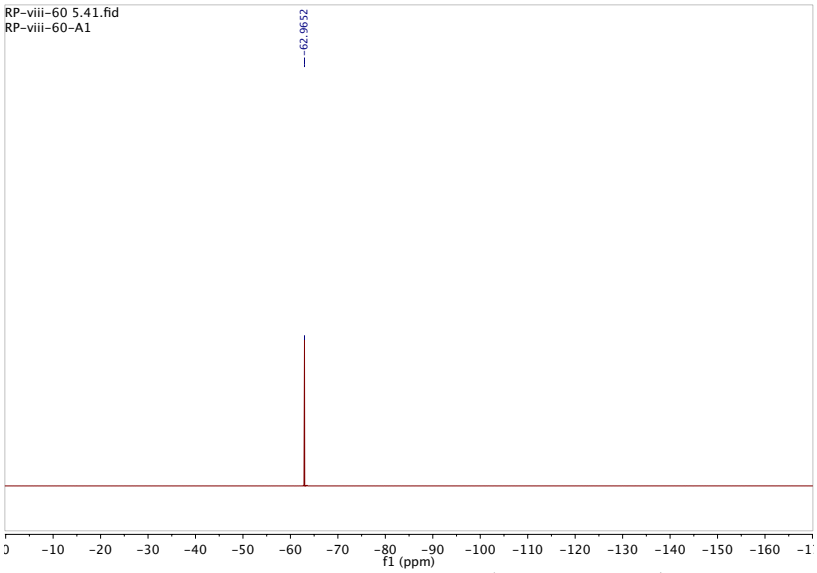
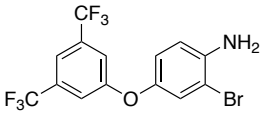


Figure S137. ^{19}F NMR Spectrum of Compound 24 (376 MHz, $CDCl_3$).

Compound 25:



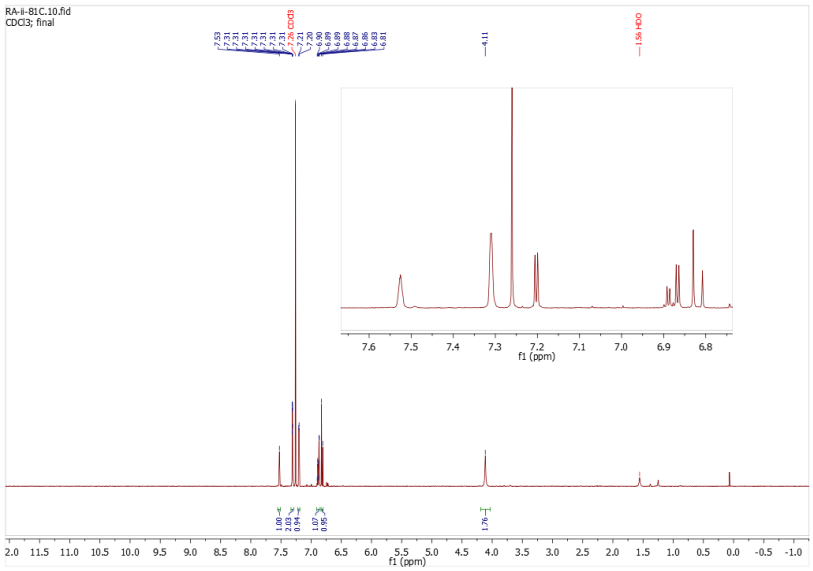


Figure S138. ^{1}H NMR Spectrum of Compound 25 (400 MHz, $CDCl_3$).

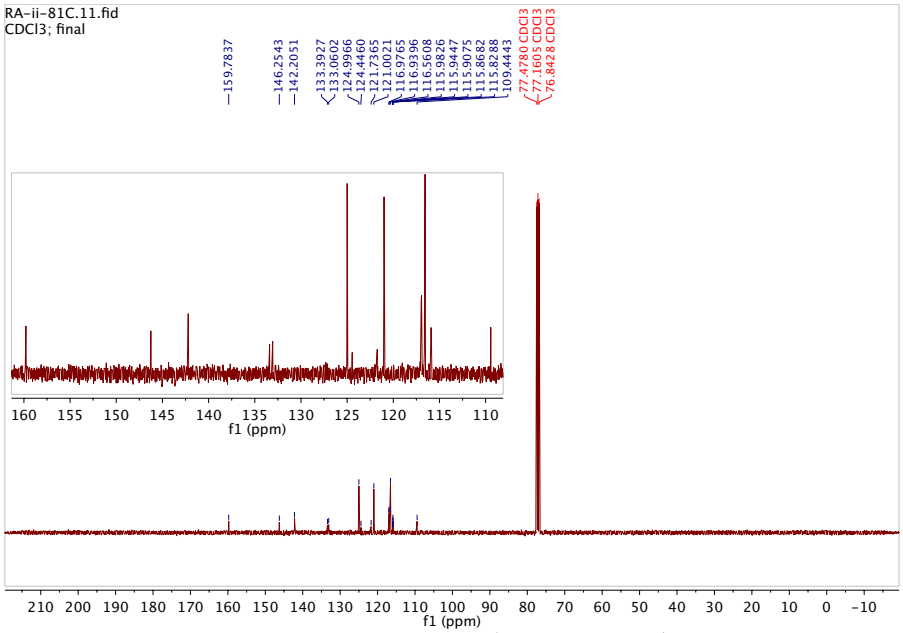


Figure S139. ^{13}C NMR Spectrum of Compound 25 (101 MHz, $CDCl_3$).

Compound 25:

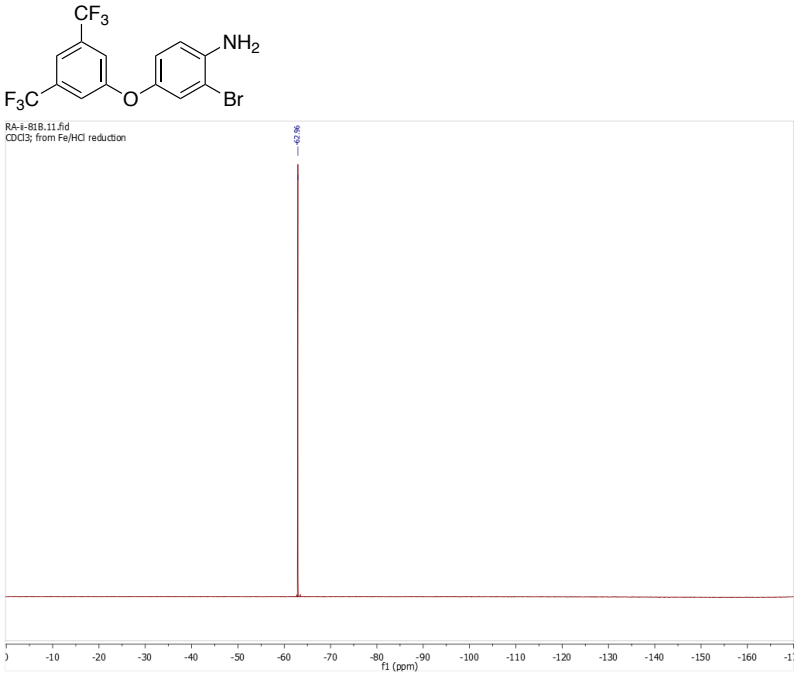
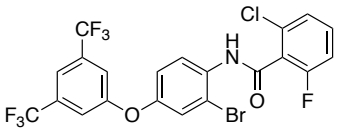


Figure S140. ^{19}F NMR Spectrum of Compound 25 (376 MHz, $CDCl_3$).

Compound 26:



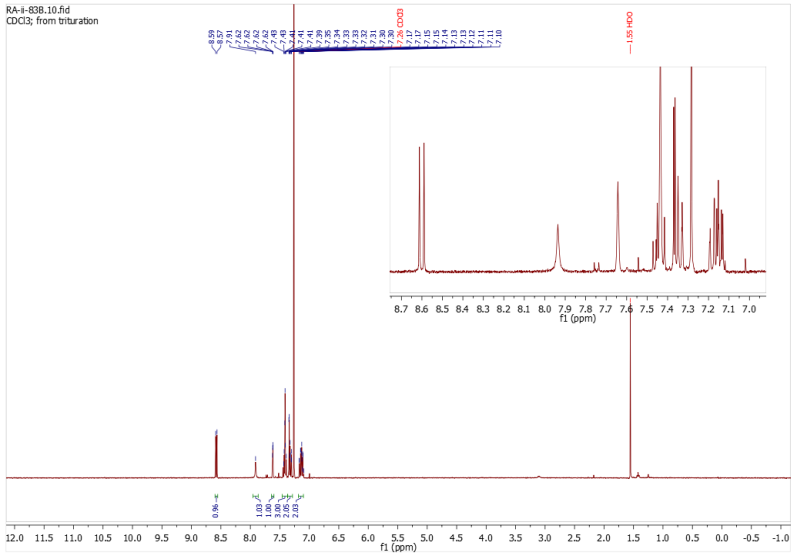


Figure S141. ^{1}H NMR Spectrum of Compound 26 (400 MHz, $CDCl_3$).

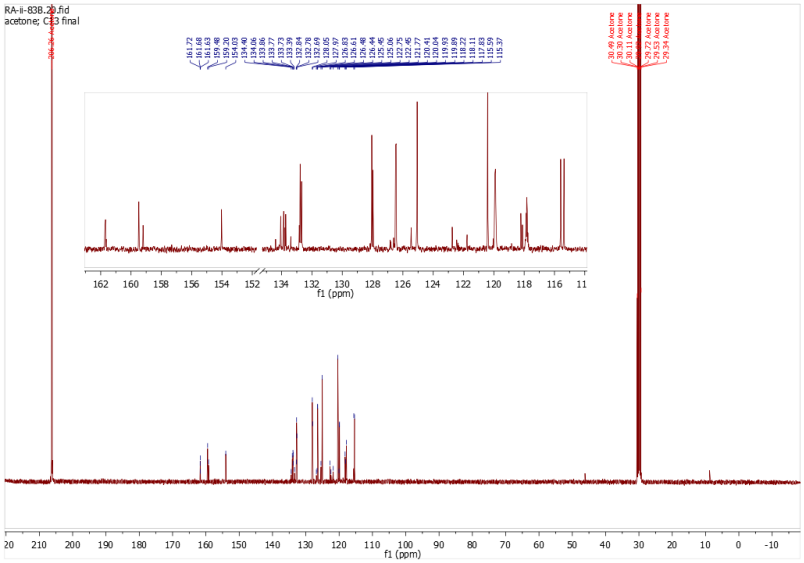
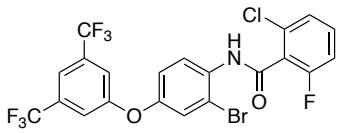


Figure S142. ^{13}C NMR Spectrum of Compound 26 (101 MHz, $CDCl_3$).

Compound 26:



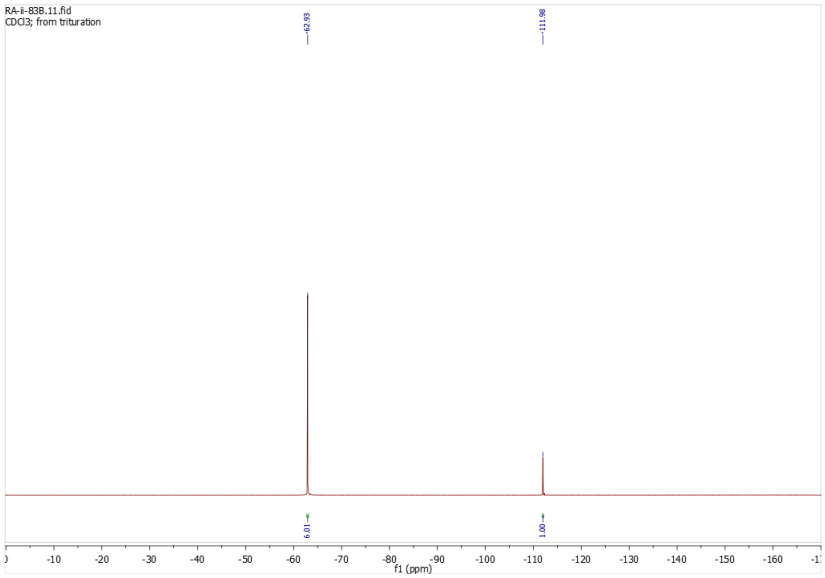


Figure S143. ^{19}F NMR Spectrum of Compound 26 (376 MHz, $CDCl_3$).

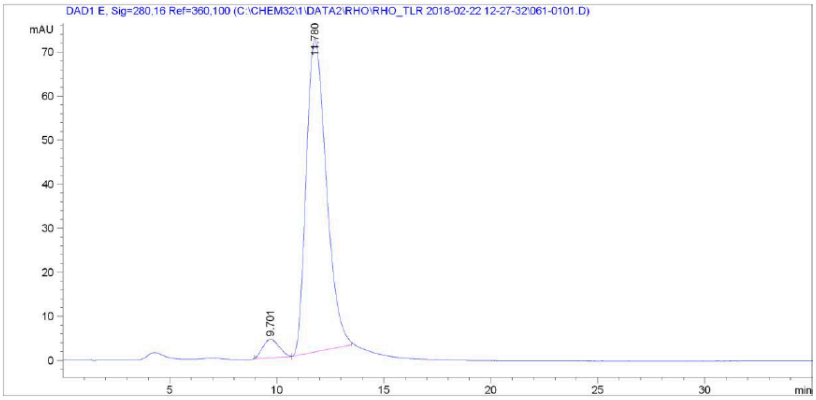
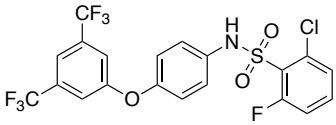


Figure S144. HPLC Chromatogram of Compound 26.

Compound 27a:



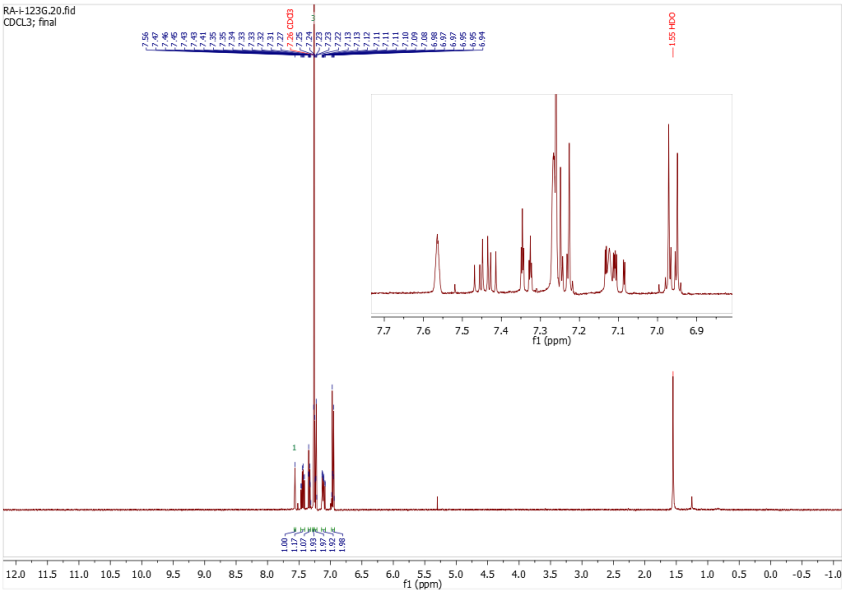


Figure S145. ^{1}H NMR Spectrum of Compound 27a (400 MHz, $CDCl_3$).

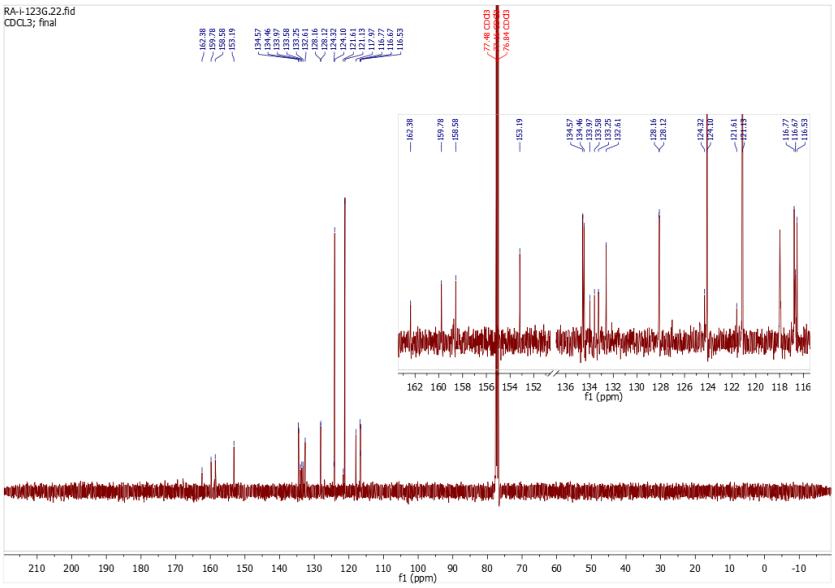


Figure S146. ^{13}C NMR Spectrum of Compound 27a (101 MHz, $CDCl_3$).

Compound 27a:

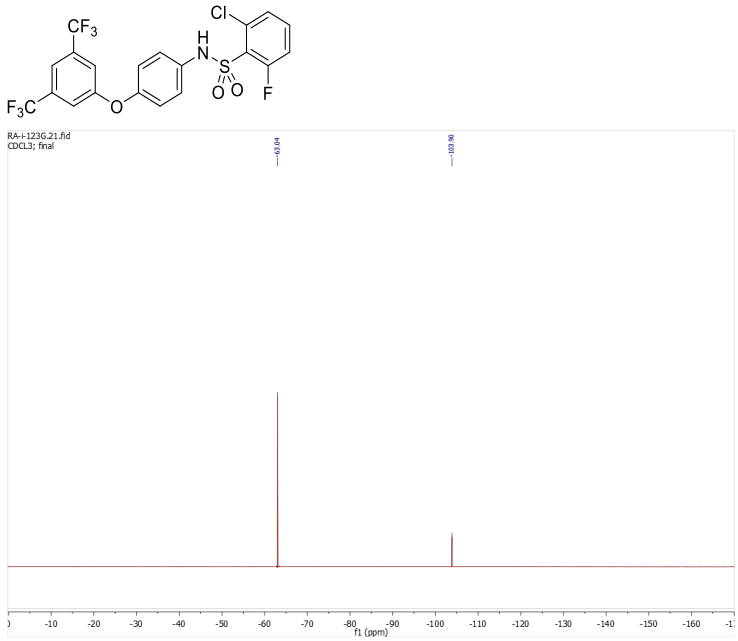


Figure S147. ^{19}F NMR Spectrum of Compound 27a (376 MHz, $CDCl_3$).

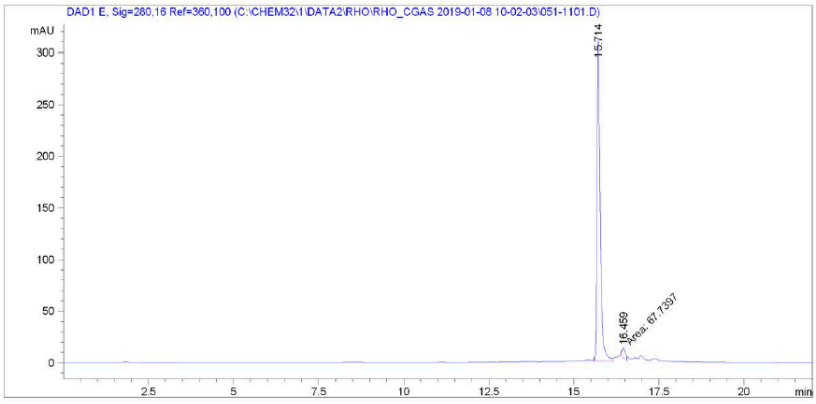
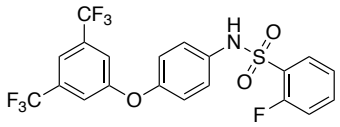


Figure S148. HPLC Chromatogram of Compound 27a.

Compound 27b:



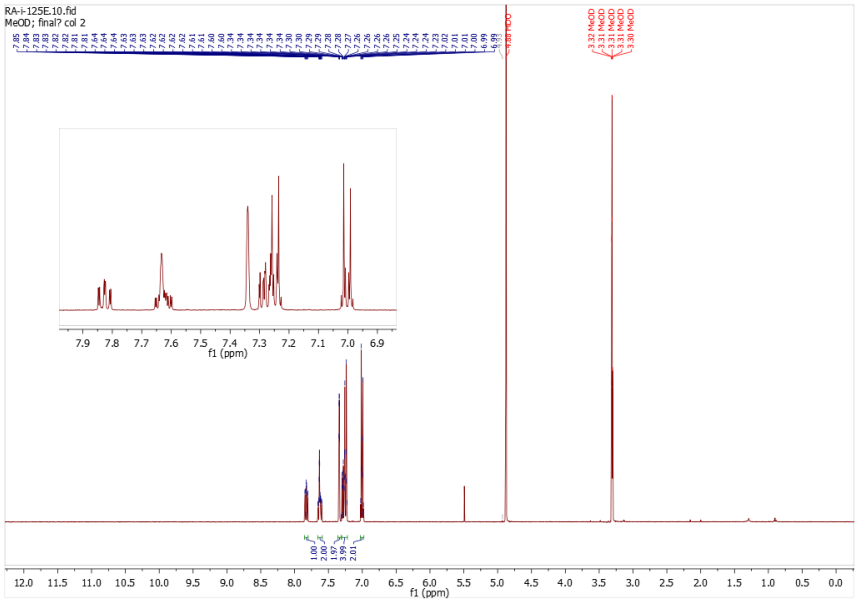


Figure S149. ^{1}H NMR Spectrum of Compound 27b (400 MHz, MeOD).

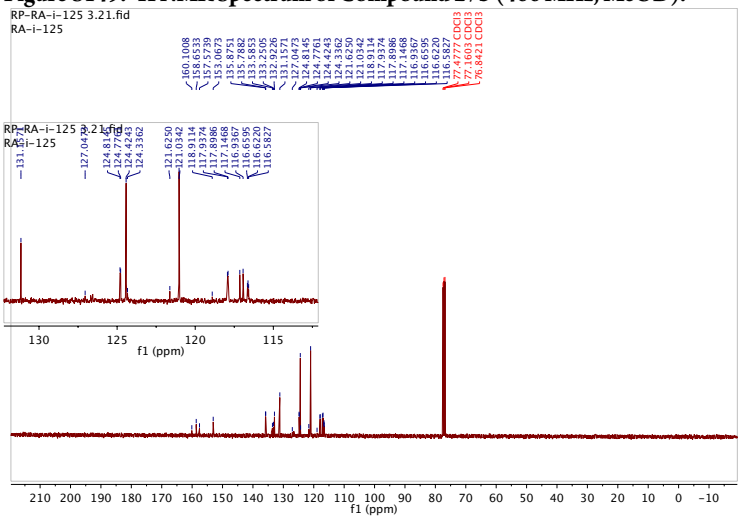
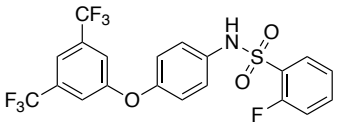


Figure S150. ^{13}C NMR Spectrum of Compound 27b (101 MHz, $CDCl_3$).

Compound 27b:



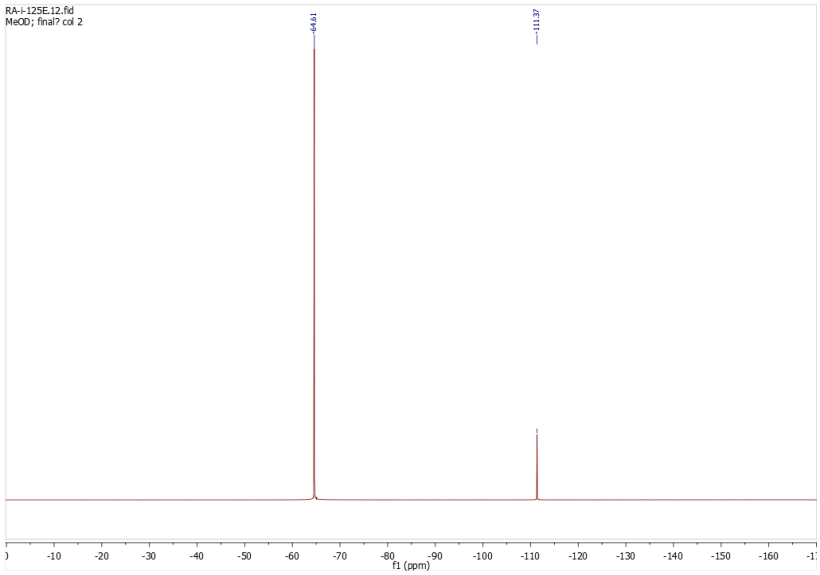


Figure S151. ^{19}F NMR Spectrum of Compound 27b (376 MHz, MeOD).

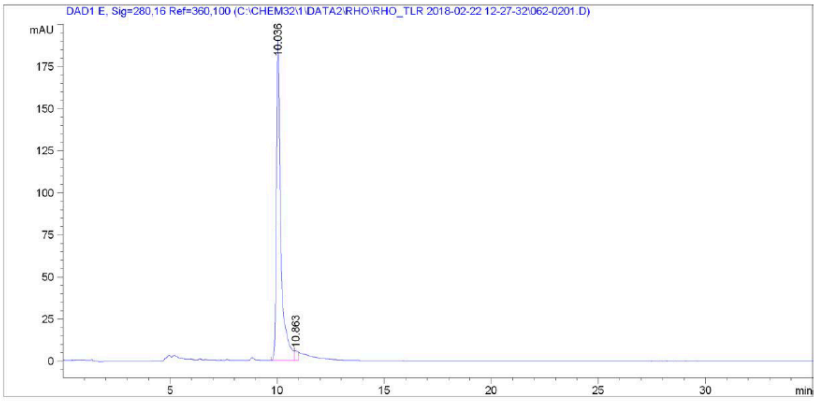


Figure S152. HPLC Chromatogram of Compound 27b.

Compound 28:

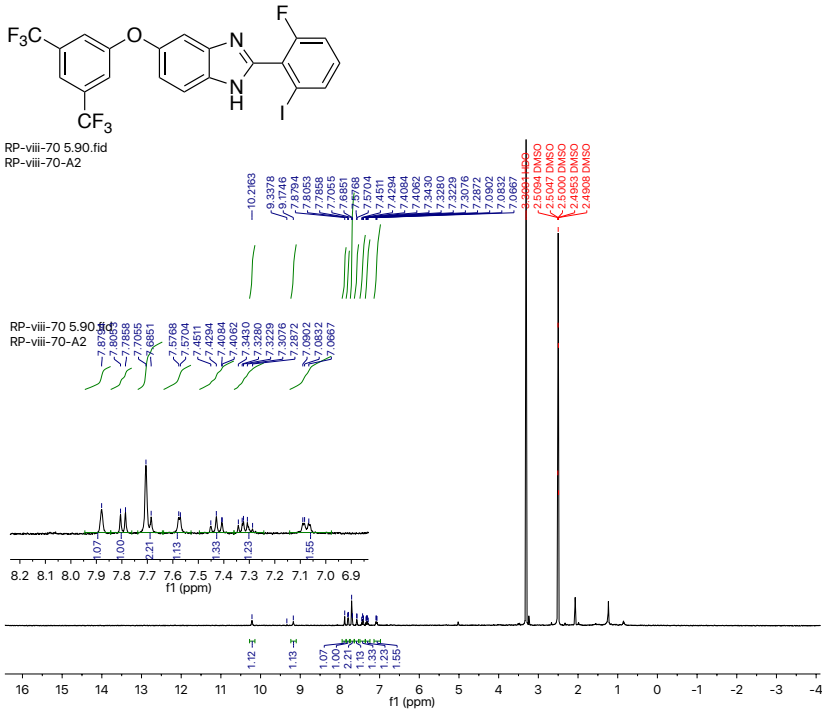
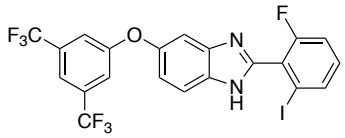


Figure S153. ^{1}H NMR Spectrum of Compound 28 (400 MHz, DMSO-d_6).

Compound 28:



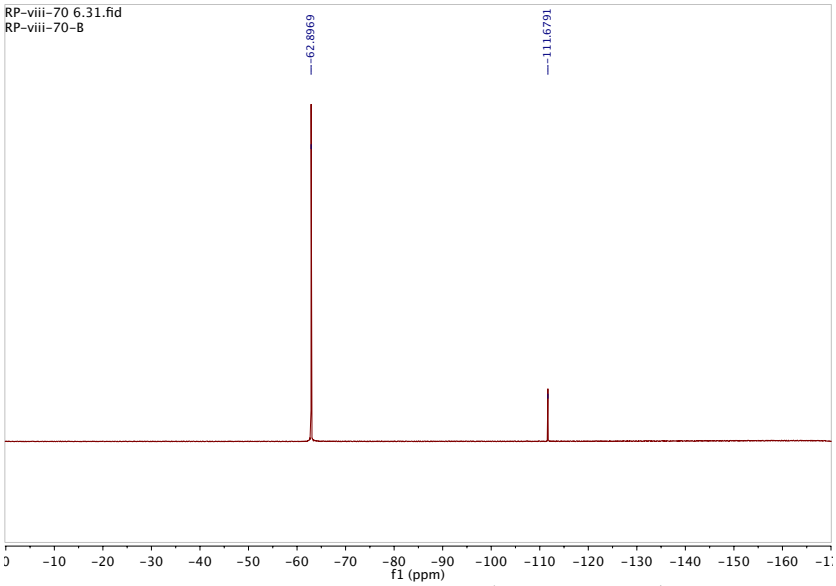


Figure S154. ^{19}F NMR Spectrum of Compound 28 (376 MHz, $CDCl_3$).

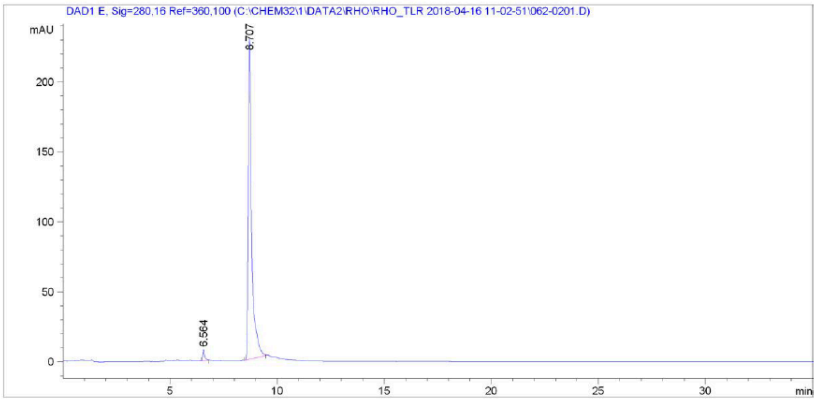
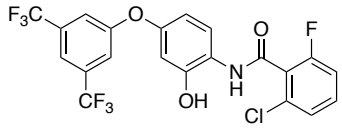


Figure S155. HPLC Chromatogram of Compound 28.

Compound 29:



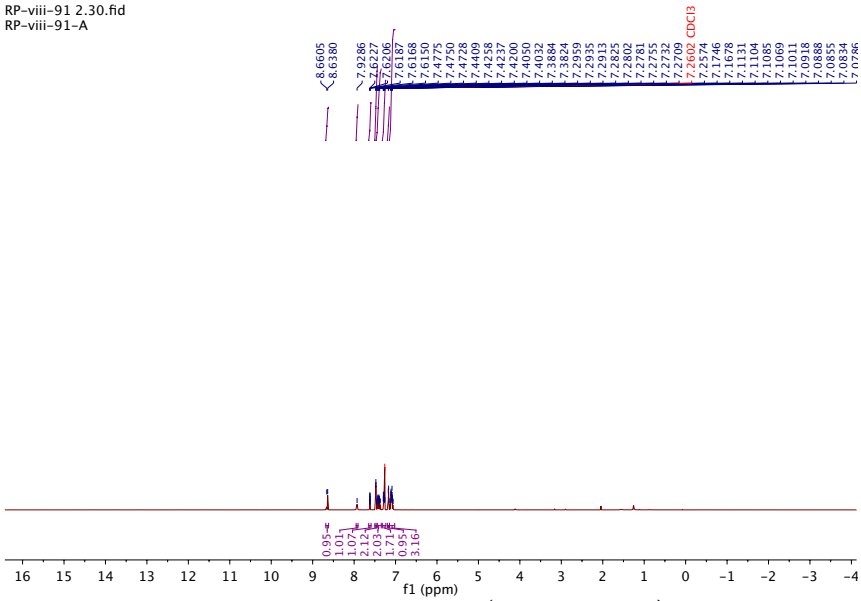


Figure S156. ^{1}H NMR Spectrum of Compound 29 (400 MHz, $CDCl_3$).

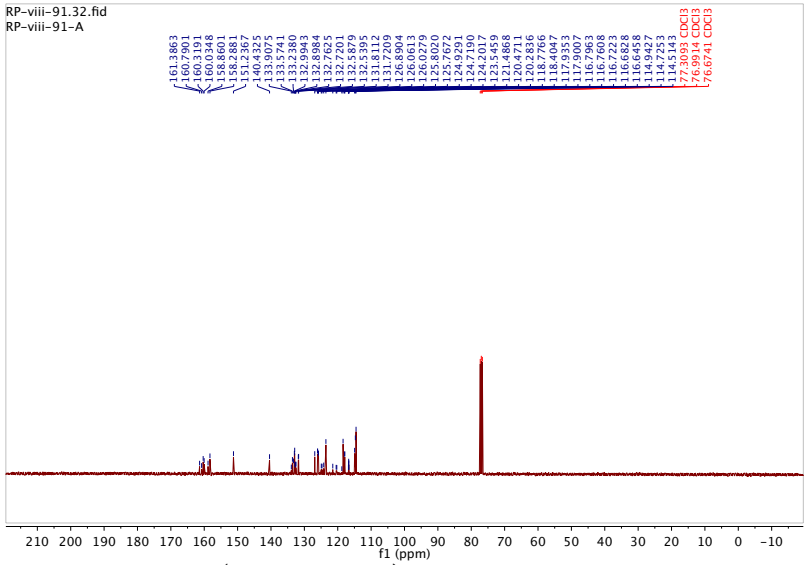


Figure S157. ^{13}C NMR Spectrum of Compound 29 (101 MHz, $CDCl_3$).

Compound 29:

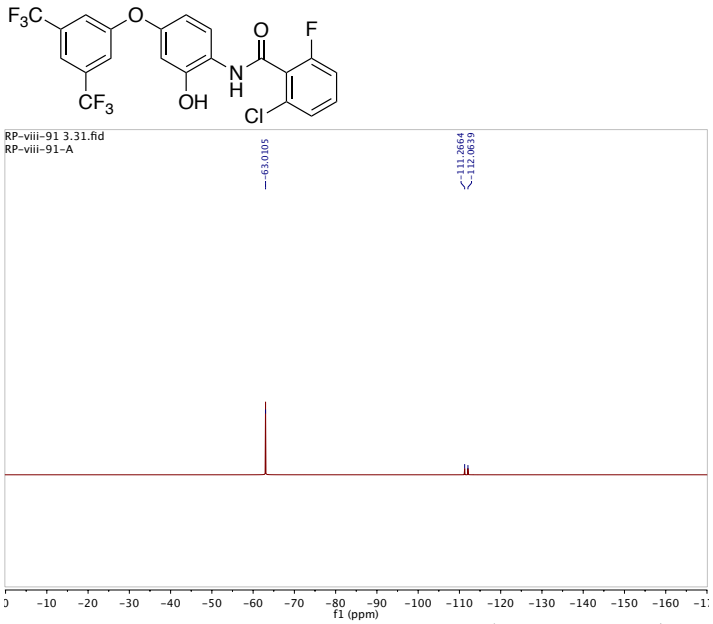


Figure S158. ^{19}F NMR Spectrum of Compound 29 (376 MHz, $CDCl_3$).

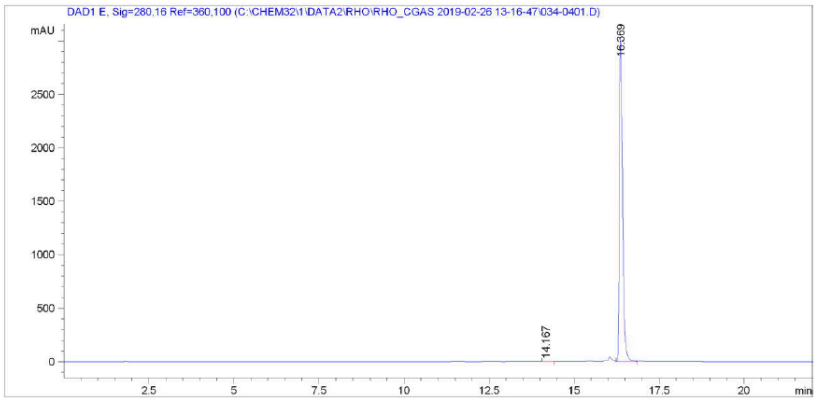


Figure S159. HPLC Chromatogram of Compound 29.

Compound 30:

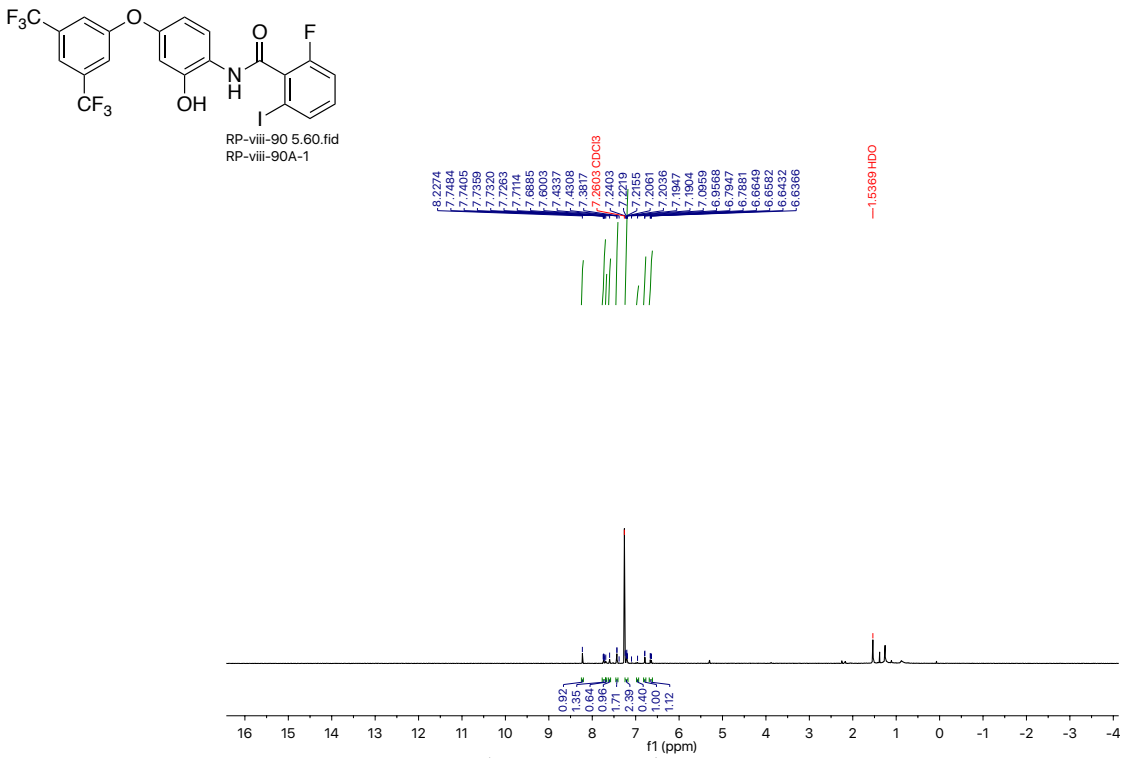


Figure S160. ^{1}H NMR Spectrum of Compound 30 (400 MHz, $CDCl_3$).

Compound 30:

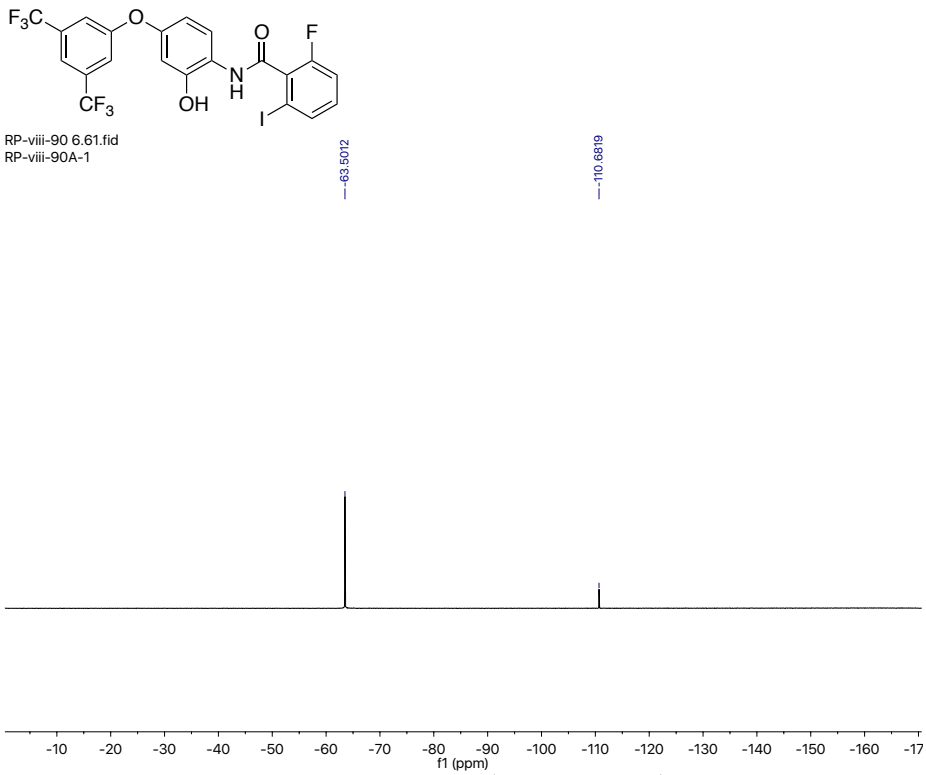


Figure S161. ^{19}F NMR Spectrum of Compound 30 (376 MHz, $CDCl_3$).

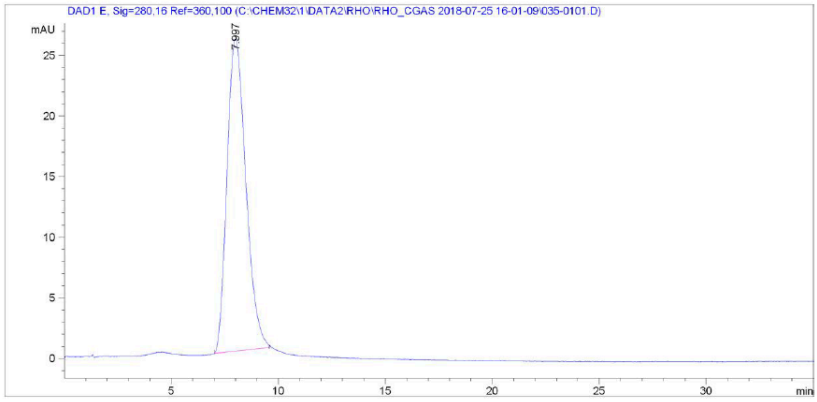
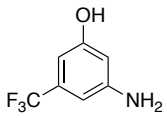


Figure S162. HPLC Chromatogram of Compound 30.

Compound 31:



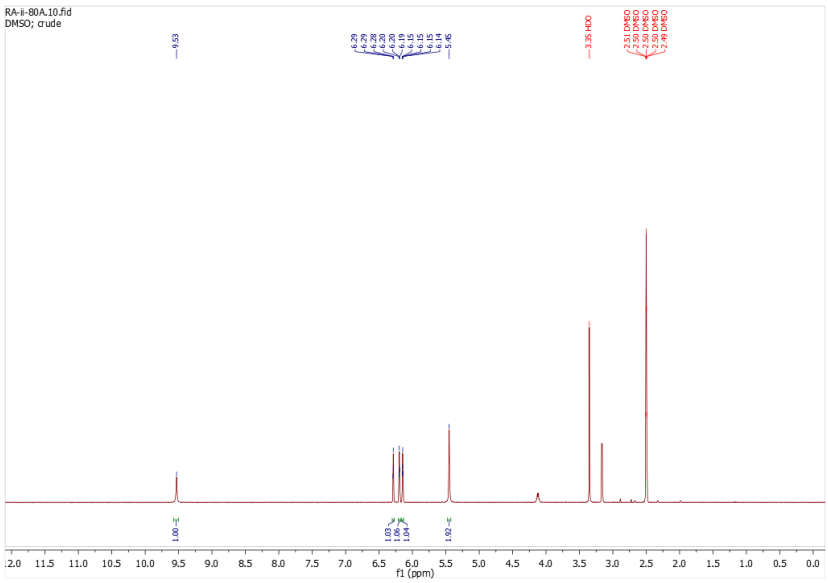


Figure S163. ^{1}H NMR Spectrum of Compound 31 (400 MHz, DMSO.

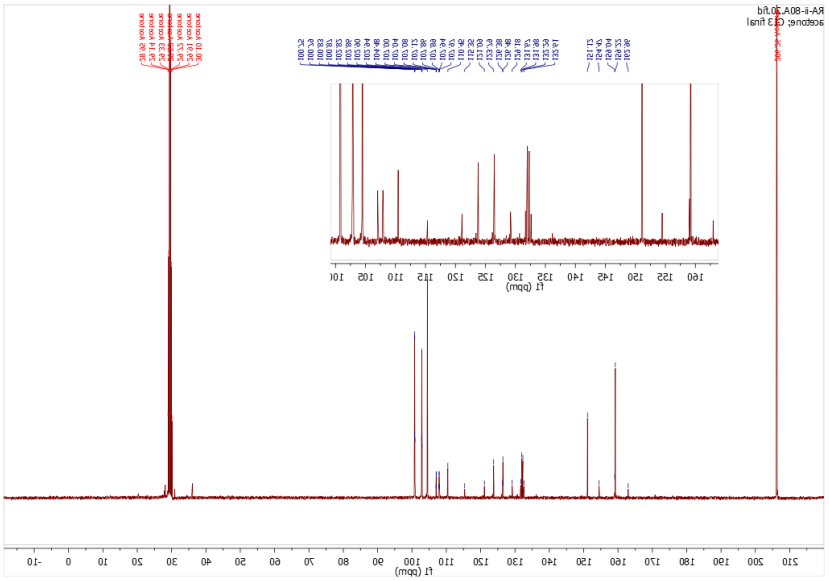
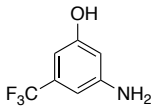


Figure S164. ^{13}C NMR Spectrum of Compound 31 (101 MHz, Acetone-d_6).

Compound 31:



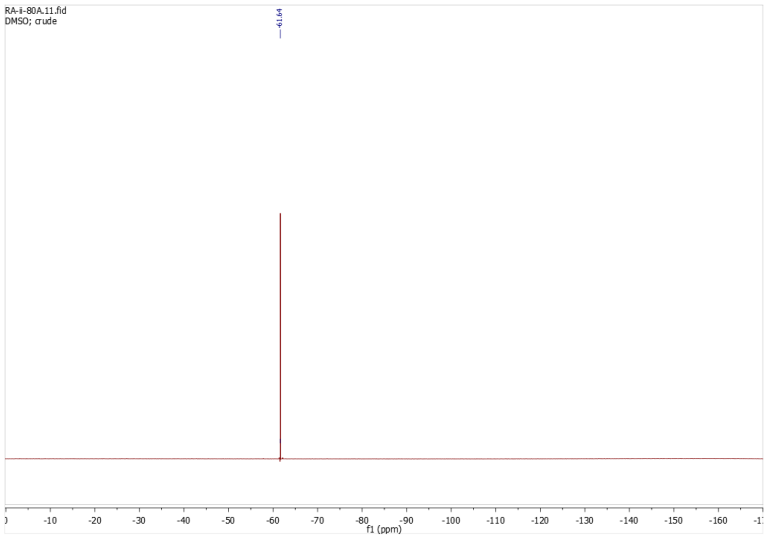
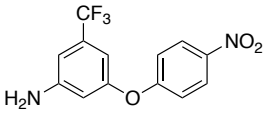


Figure S165. ^{19}F NMR Spectrum of Compound 31 (376 MHz, DMSO).

Compound 32:



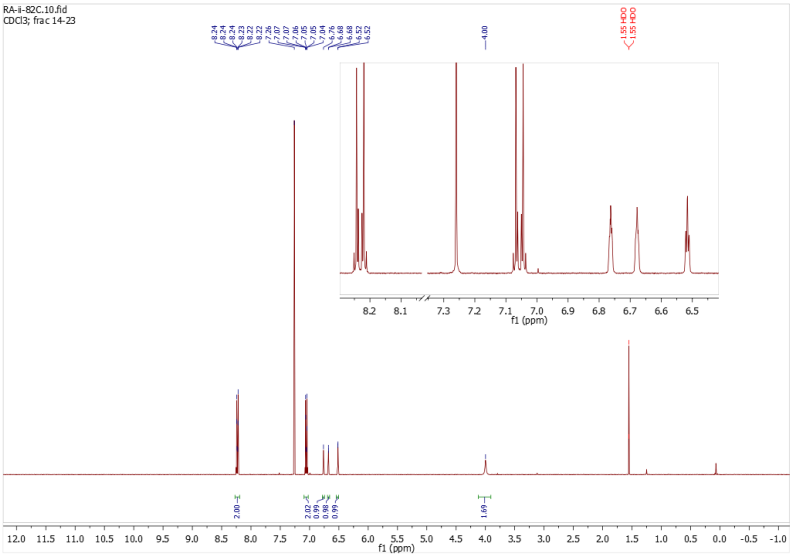


Figure S166. ^{1}H NMR Spectrum of Compound 32 (400 MHz, $CDCl_3$).

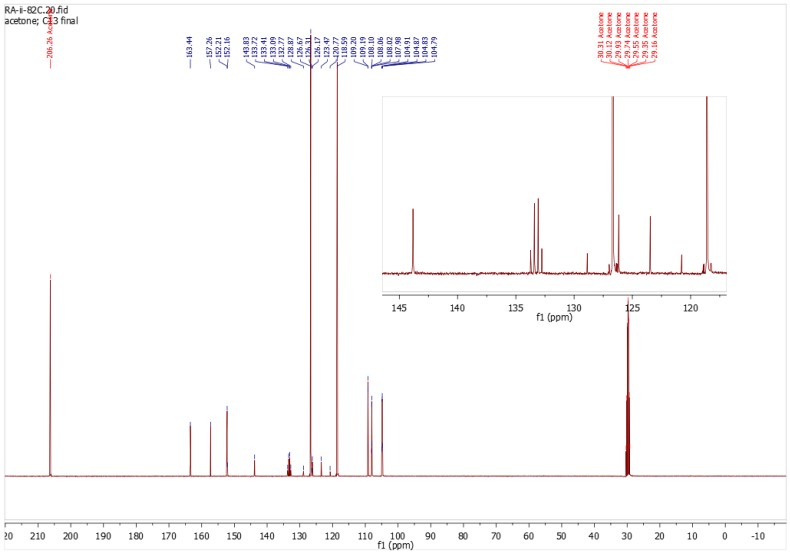


Figure S167. ^{13}C NMR Spectrum of Compound 32 (101 MHz, Acetone-d_6).

Compound 32:

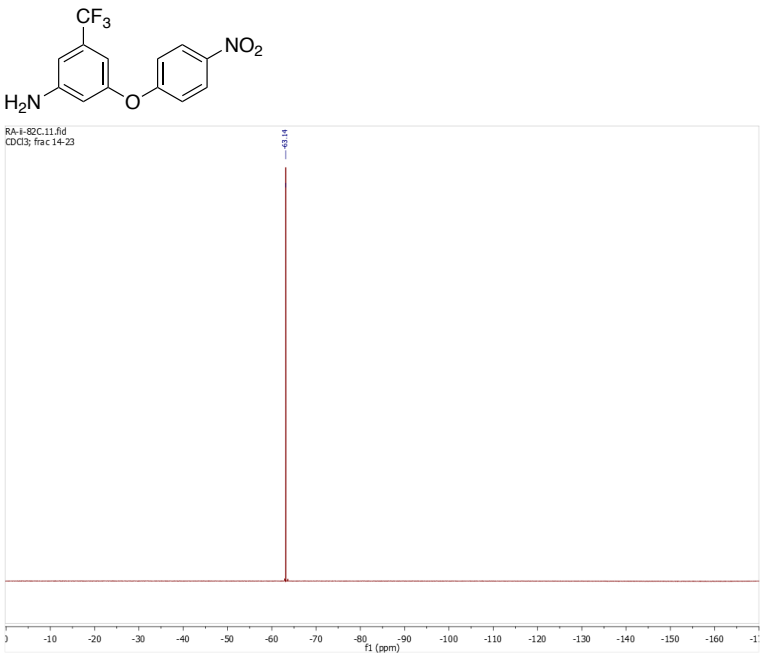
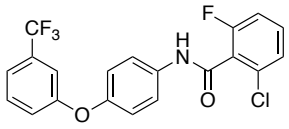


Figure S168. ^{19}F NMR Spectrum of Compound 32 (376 MHz, $CDCl_3$).

Compound 35a:



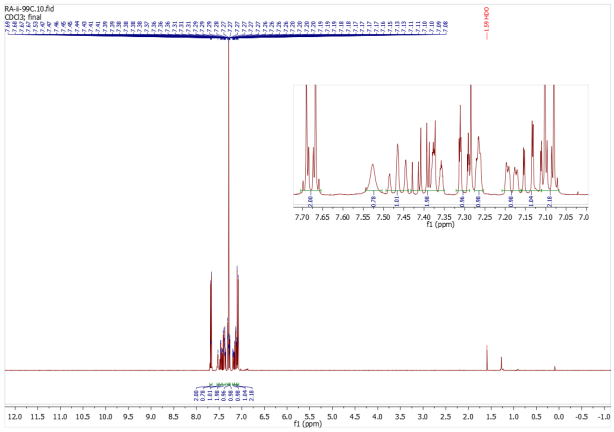


Figure S169. ^{1}H NMR Spectrum of Compound 35a (400 MHz, $CDCl_3$).

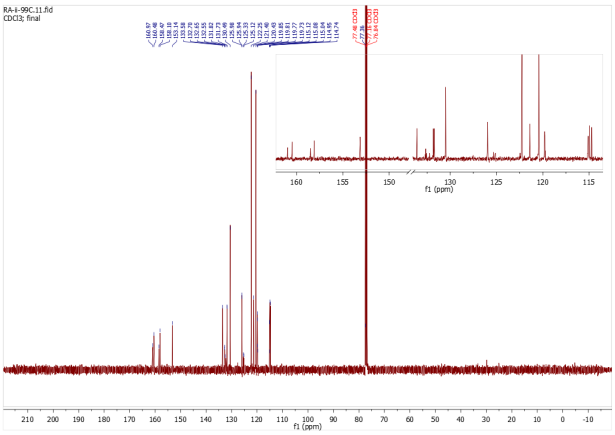


Figure S170. ^{13}C NMR Spectrum of Compound 35a (101 MHz, $CDCl_3$).

Compound 35a:

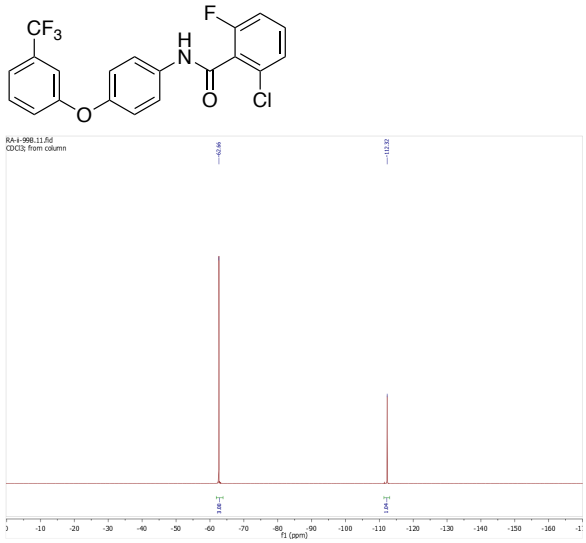


Figure S171. ^{19}F NMR Spectrum of Compound 35a (376 MHz, $CDCl_3$).

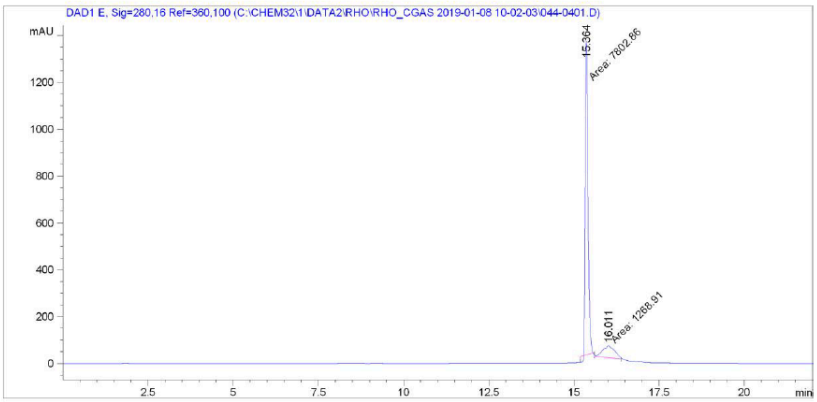
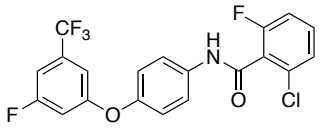


Figure S172. HPLC Chromatogram of Compound 35a.

Compound 35b:



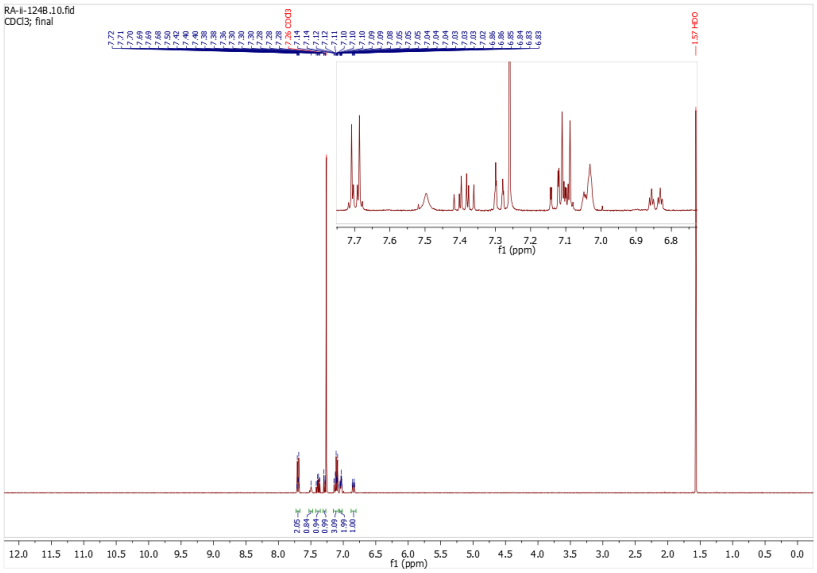


Figure S173. ^{1}H NMR Spectrum of Compound 35b (400 MHz, $CDCl_3$).

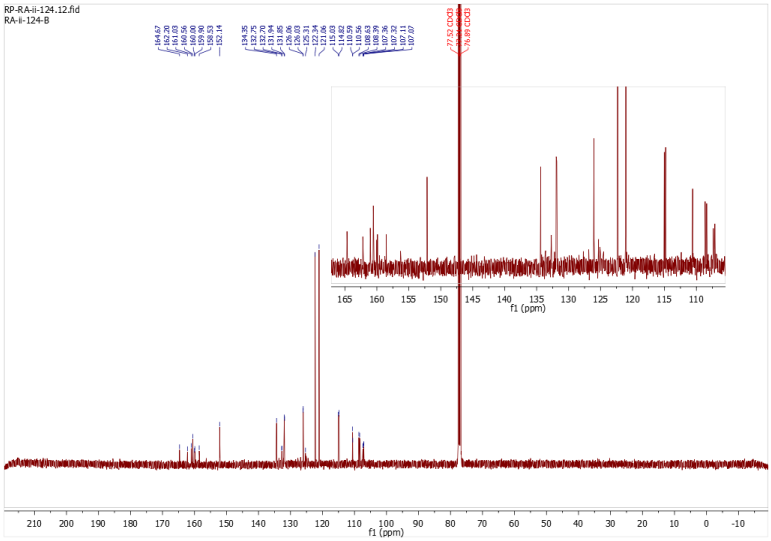


Figure S174. ^{13}C NMR Spectrum of Compound 35b (101 MHz, $CDCl_3$).

Compound 35b:

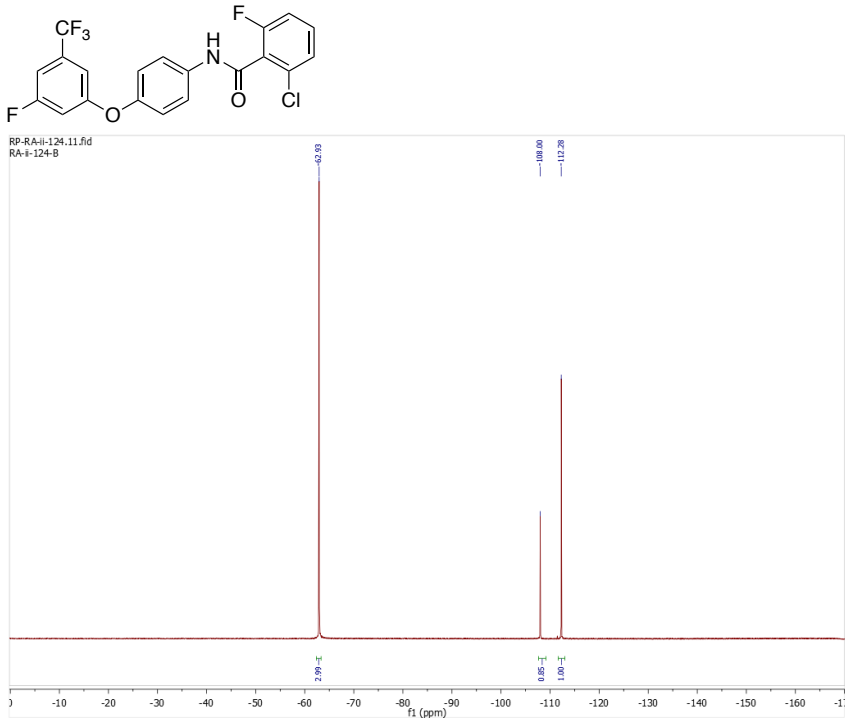


Figure S175. ^{19}F NMR Spectrum of Compound 35b (376 MHz, $CDCl_3$).

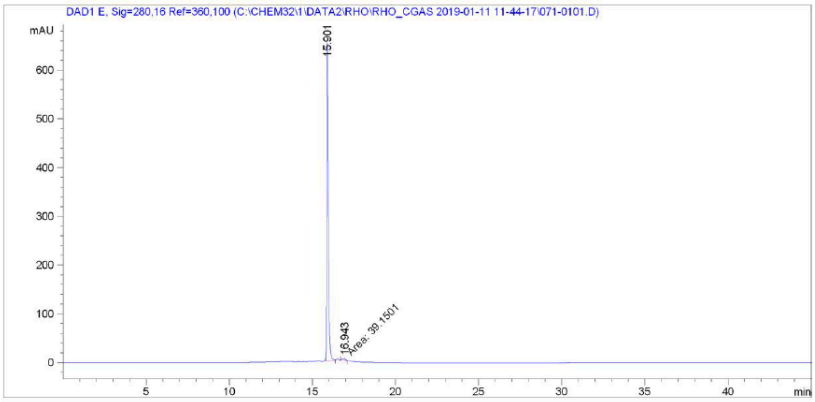
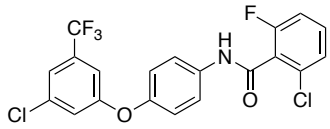


Figure S176. HPLC Chromatogram of Compound 35b.

Compound 35c:



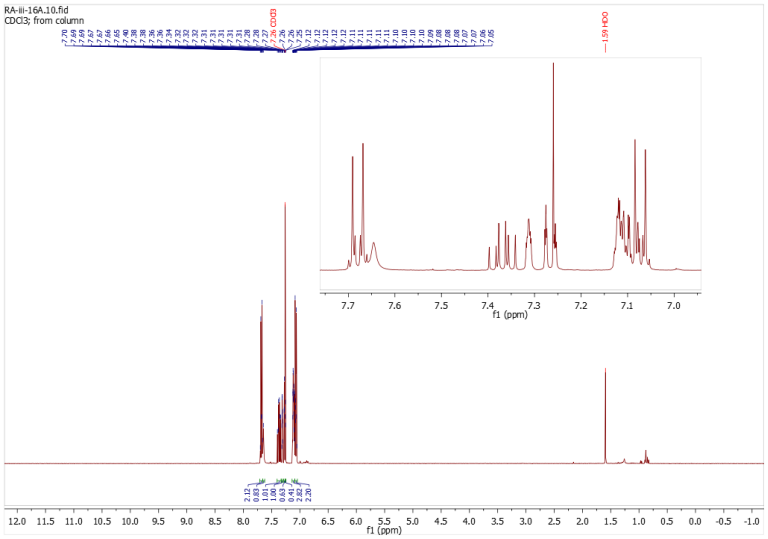


Figure S177. ^{1}H NMR Spectrum of Compound 35c (400 MHz, $CDCl_3$).

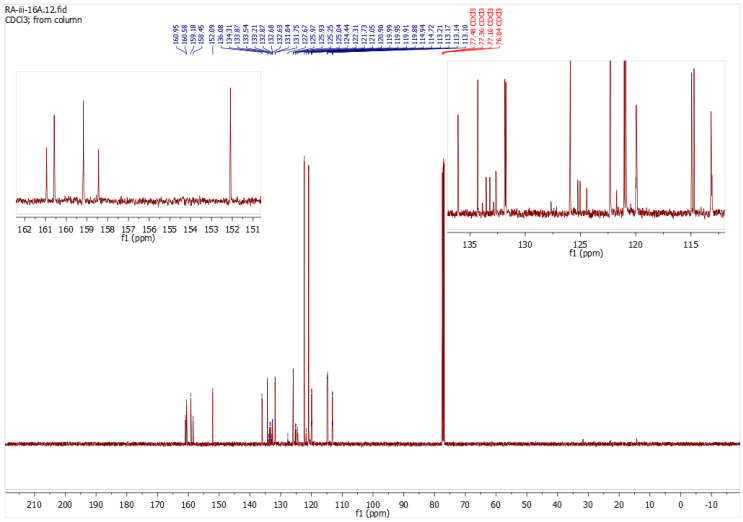
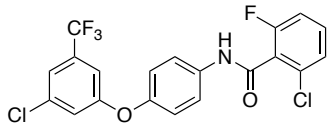


Figure S178. ^{13}C NMR Spectrum of Compound 35c (101 MHz, $CDCl_3$).

Compound 35c:



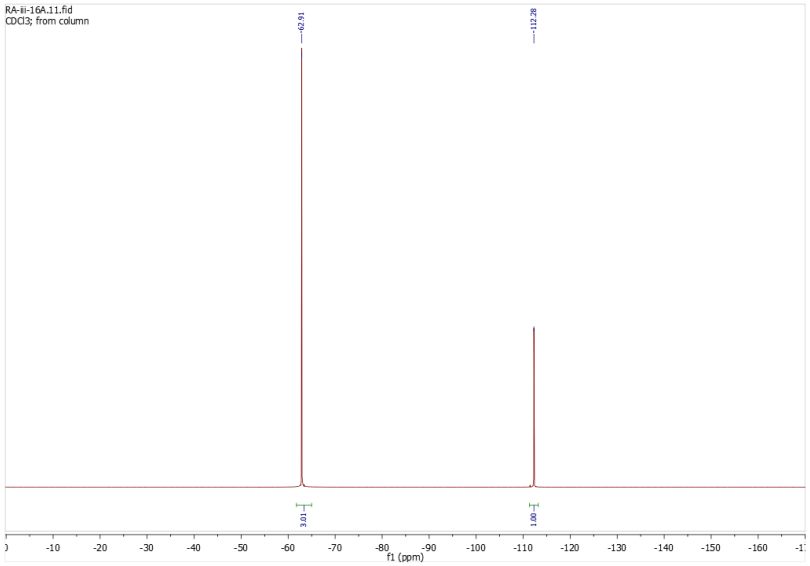


Figure S179. ^{19}F NMR Spectrum of Compound 35c (376 MHz, $CDCl_3$).

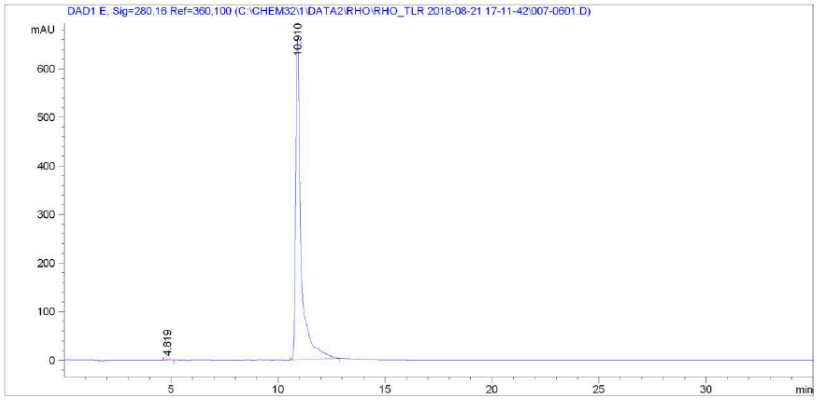
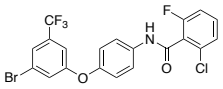


Figure S180. HPLC Chromatogram of Compound 35c.

Compound 35d:



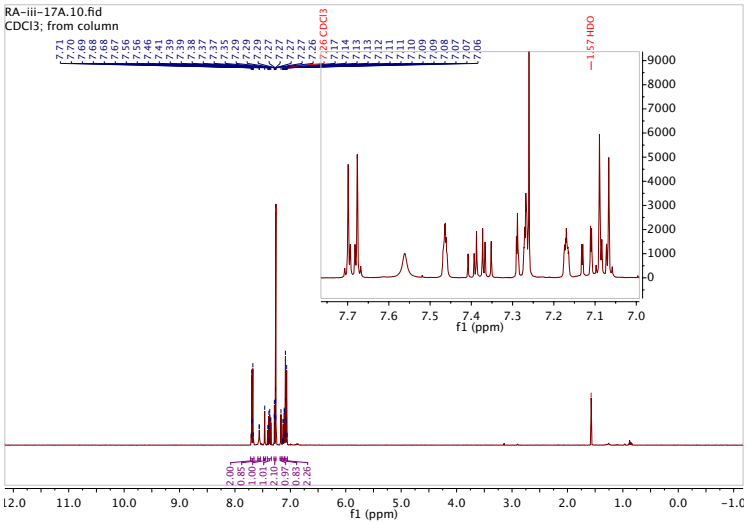


Figure S181. ^{1}H NMR Spectrum of Compound 35d (400 MHz, $CDCl_3$).

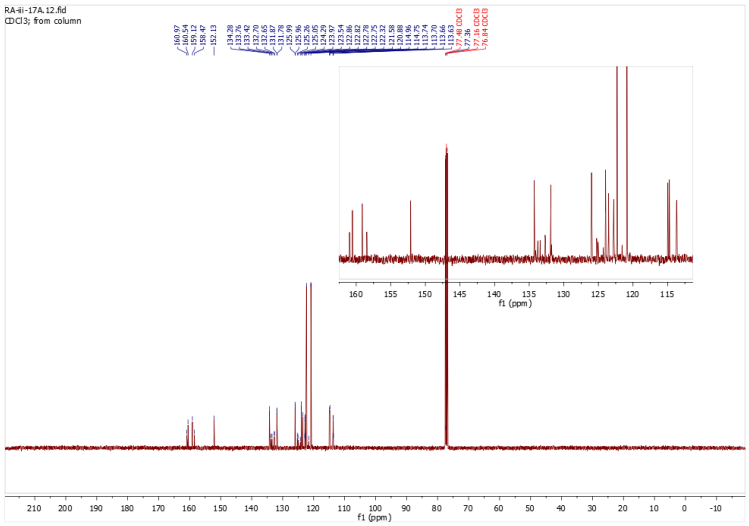
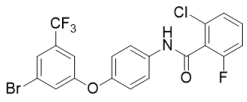


Figure S182. ^{13}C NMR Spectrum of Compound 35d (101 MHz, $CDCl_3$).

Compound 35d:



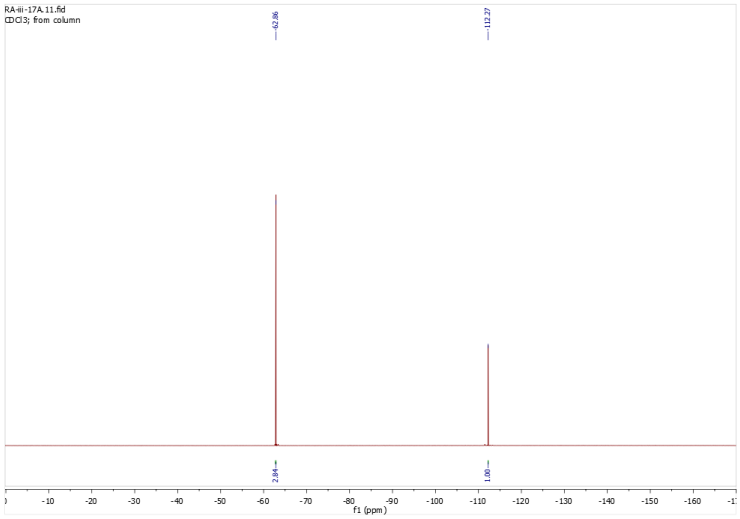


Figure S183. ^{19}F NMR Spectrum of Compound 35d (376 MHz, $CDCl_3$).

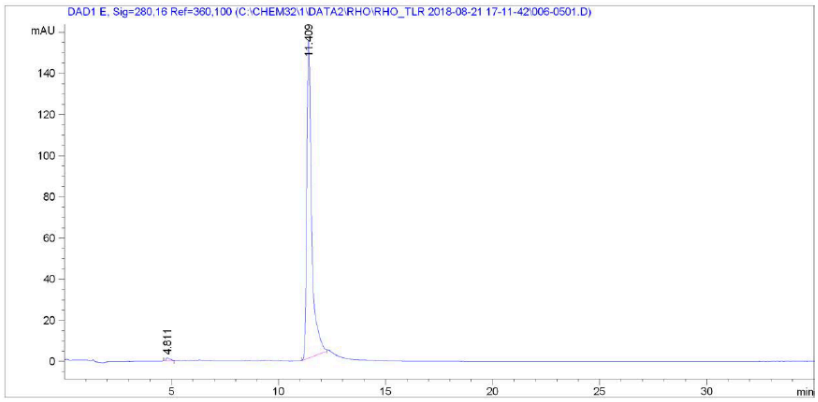
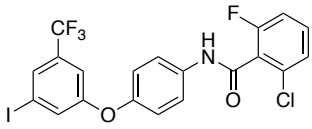


Figure S184. HPLC Chromatogram of Compound 35d.

Compound 35e:



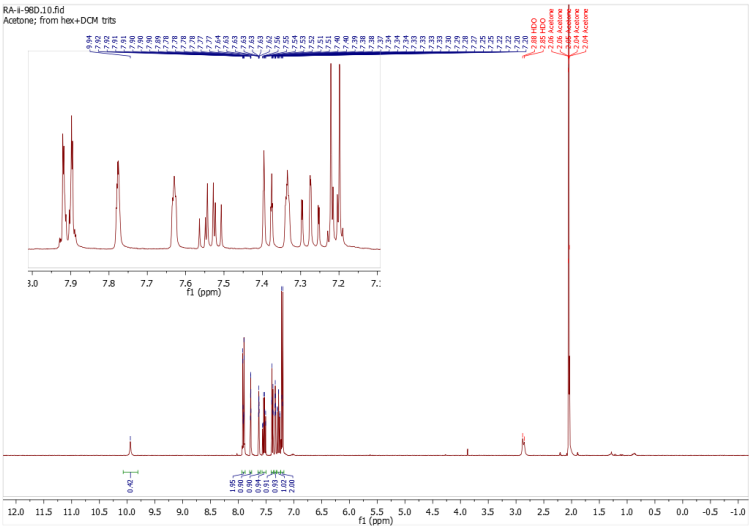


Figure S185. ^{1}H NMR Spectrum of Compound 35e (400 MHz, $CDCl_3$).

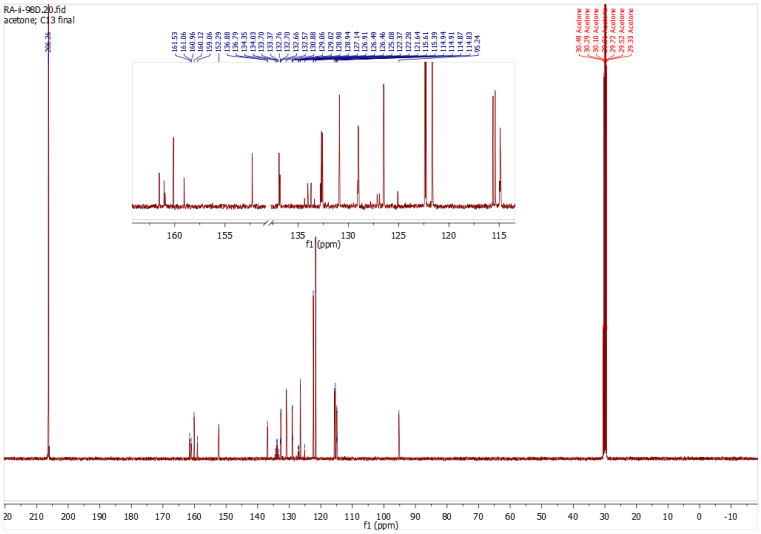
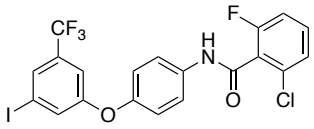


Figure S186. ^{13}C NMR Spectrum of Compound 35e (101 MHz, $CDCl_3$).

Compound 35e:



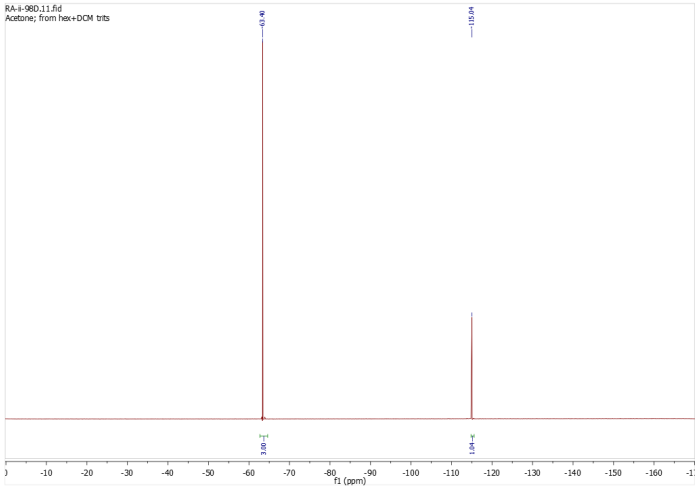


Figure S187. ^{19}F NMR Spectrum of Compound 35e (376 MHz, $CDCl_3$).

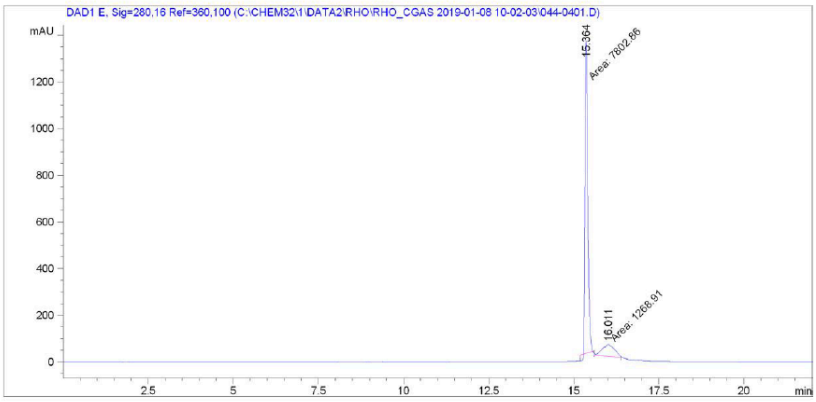
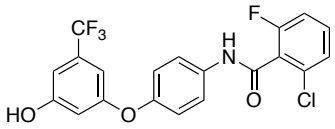


Figure S188. HPLC Chromatogram of Compound 35e.

Compound 35f:



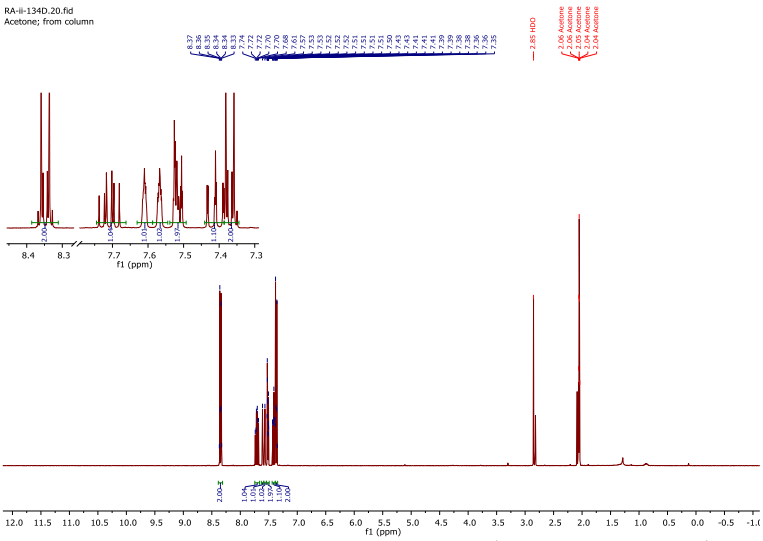


Figure S189. ^{1}H NMR Spectrum of Compound 35f (400 MHz, Acetone-d_6).

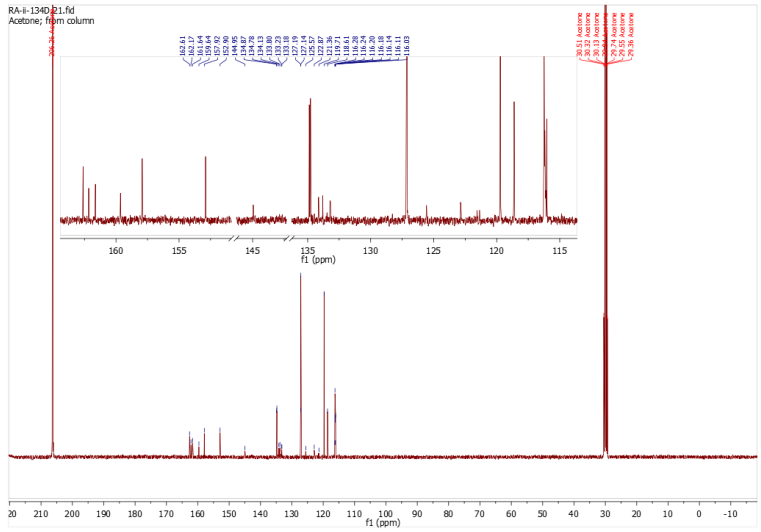


Figure S190. ^{13}C NMR Spectrum of Compound 35f (101 MHz, Acetone-d_6).

Compound 35f:

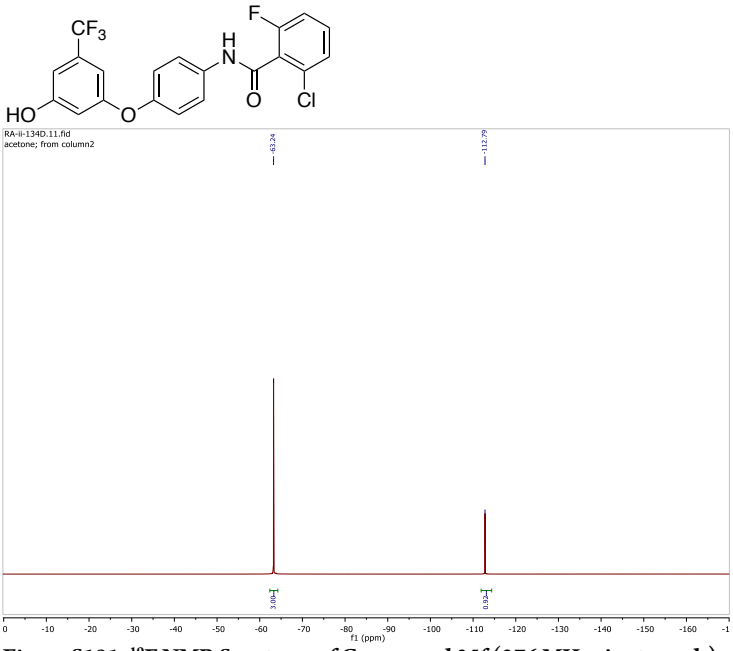


Figure S191. ^{19}F NMR Spectrum of Compound 35f (376 MHz, Acetone-d_6).

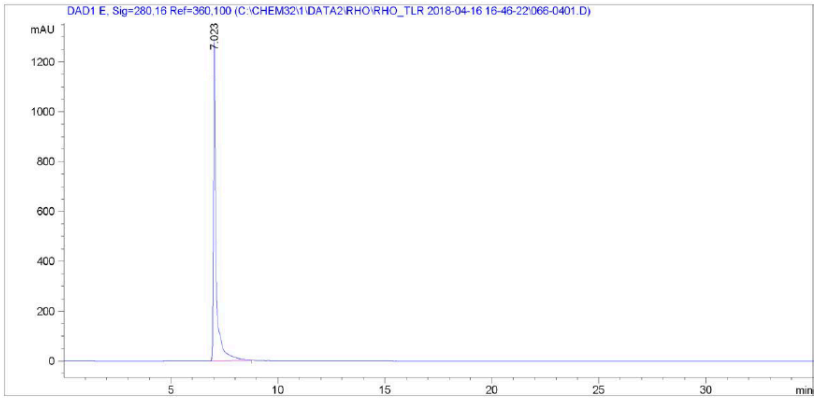


Figure S192. HPLC Chromatogram of Compound 35f.

Compound 35g:

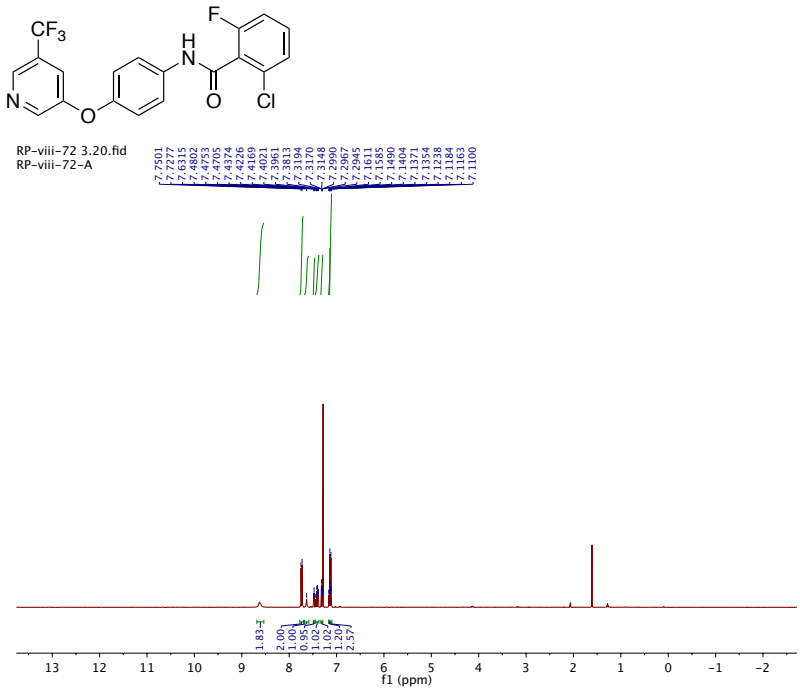


Figure S193. ^{1}H NMR Spectrum of Compound 35g (400 MHz, $CDCl_3$).

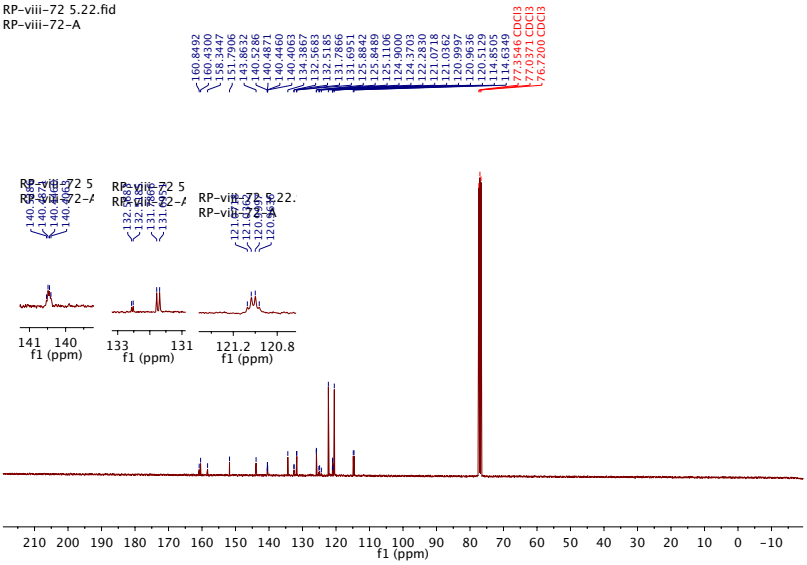
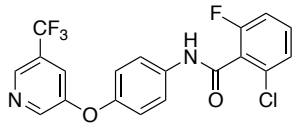


Figure S194. ^{13}C NMR Spectrum of Compound 35g (101 MHz, $CDCl_3$).

Compound 35g:



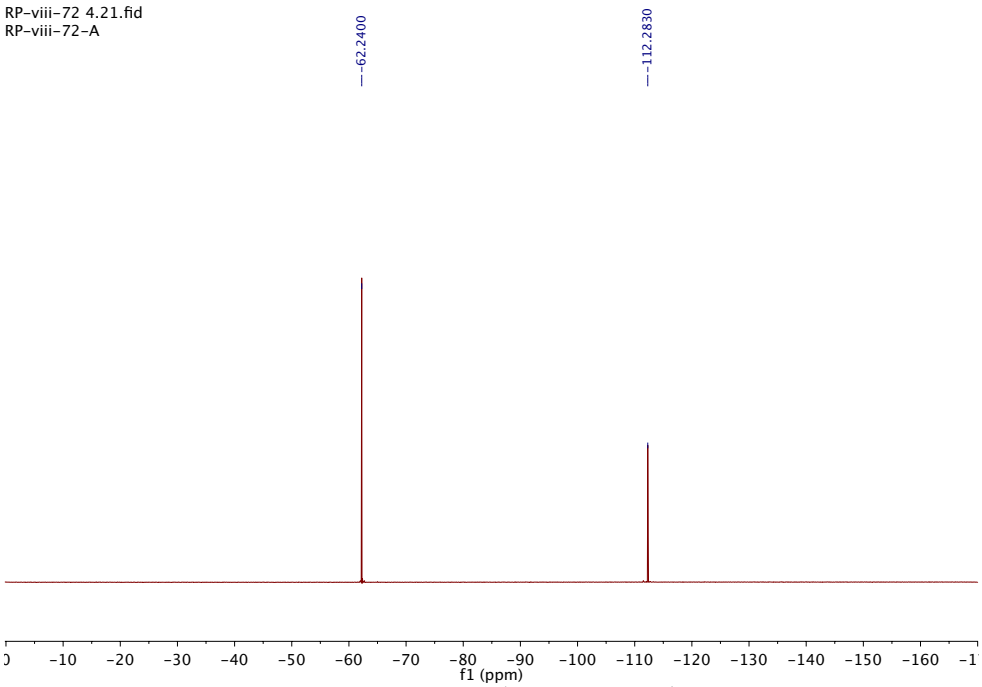


Figure S195. ^{19}F NMR Spectrum of Compound 35g (376 MHz, $CDCl_3$).

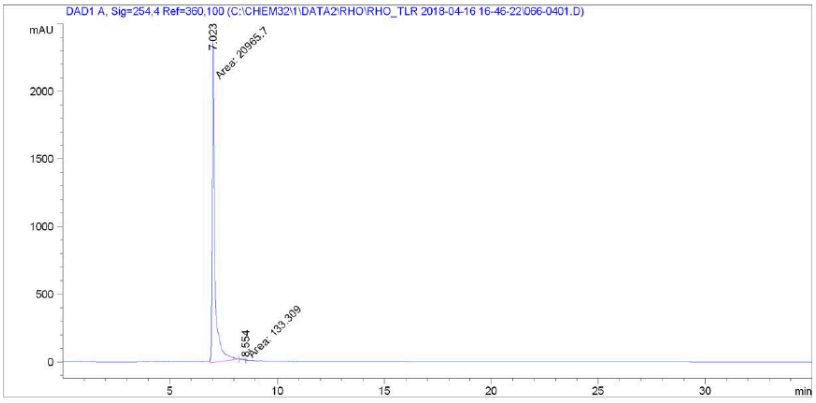
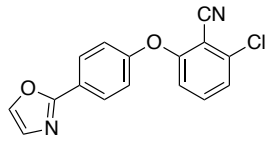


Figure S196. HPLC Chromatogram of Compound 35g.

Compound 36:



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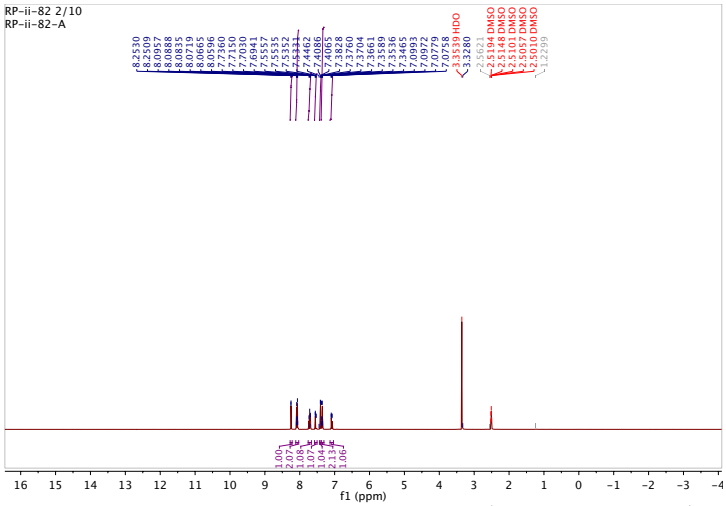


Figure S197. ^{1}H NMR Spectrum of Compound 36 (400 MHz, DMSO-d$_6$).

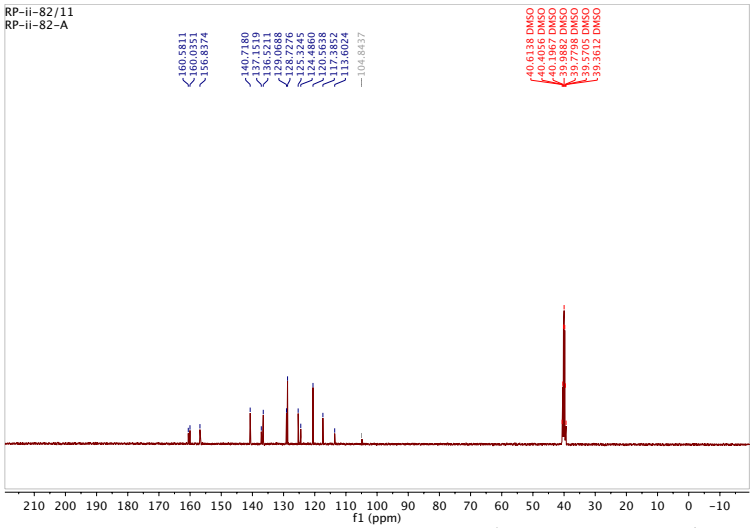


Figure S198. ^{13}C NMR Spectrum of Compound 36 (101 MHz, DMSO-d$_6$).

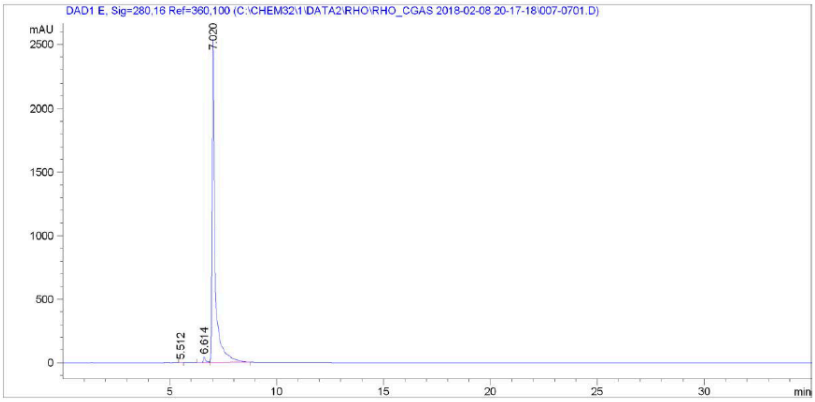


Figure S199. HPLC Chromatogram of Compound 36.

Compound 37:

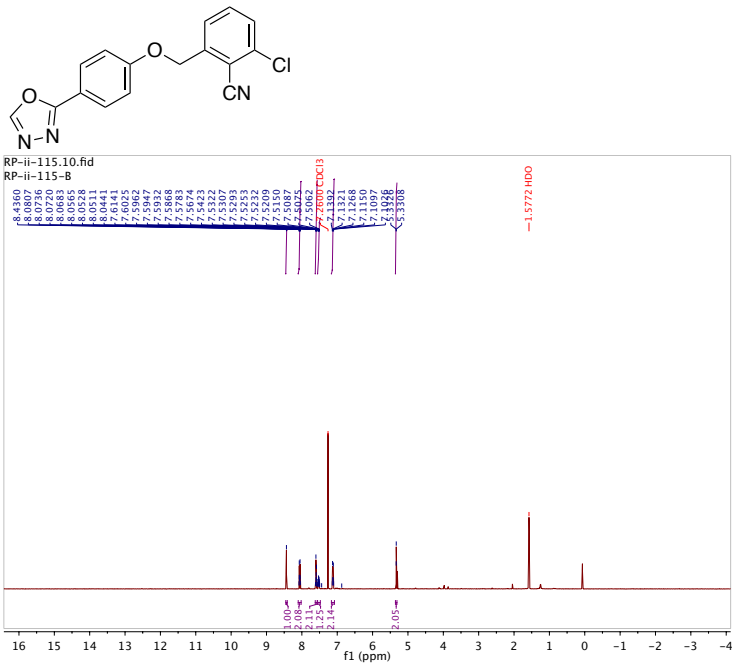


Figure S200. ^{1}H NMR Spectrum of Compound 37 (400 MHz, $CDCl_3$).

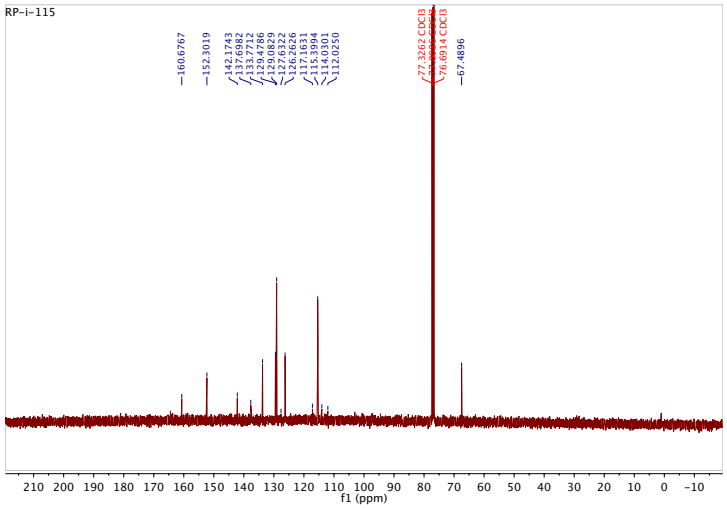


Figure S201. ^{13}C NMR Spectrum of Compound 37 (101 MHz, $CDCl_3$).

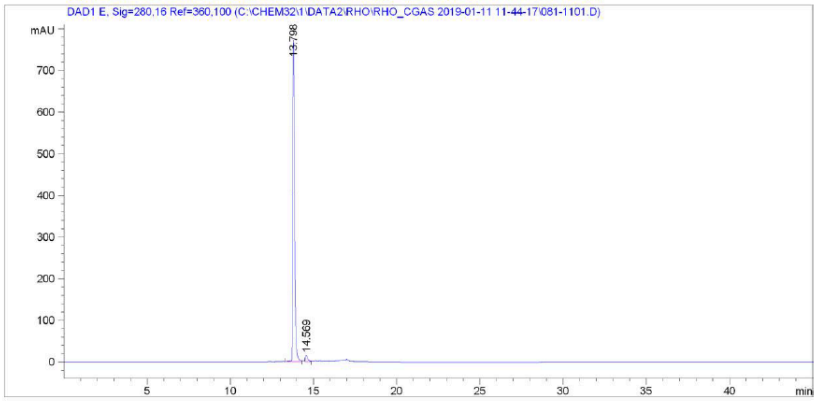
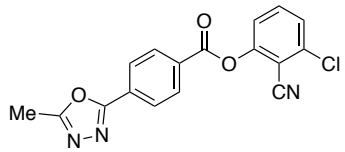


Figure S202. HPLC Chromatogram of Compound 37.

Compound 38:



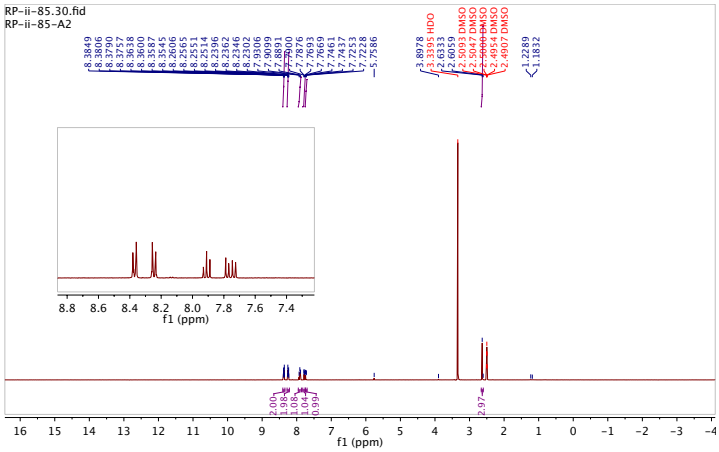


Figure S203. ^{1}H NMR Spectrum of Compound 38 (400 MHz, DMSO).

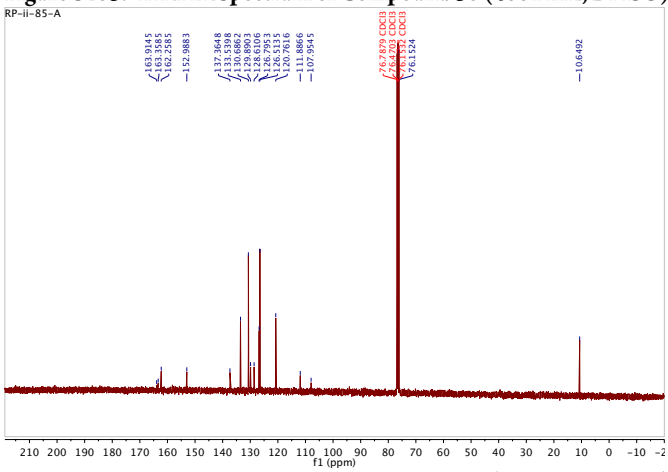


Figure S204. ^{13}C NMR Spectrum of Compound 38 (101 MHz, $CDCl_3$).

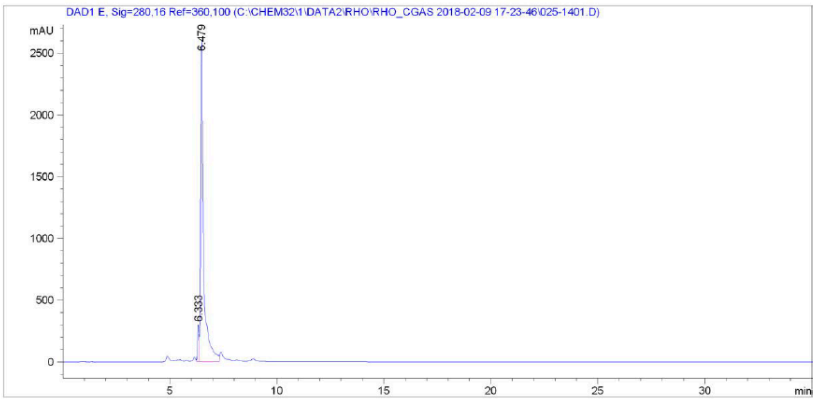


Figure S205. HPLC Chromatogram of Compound 38.

Compound 39a:

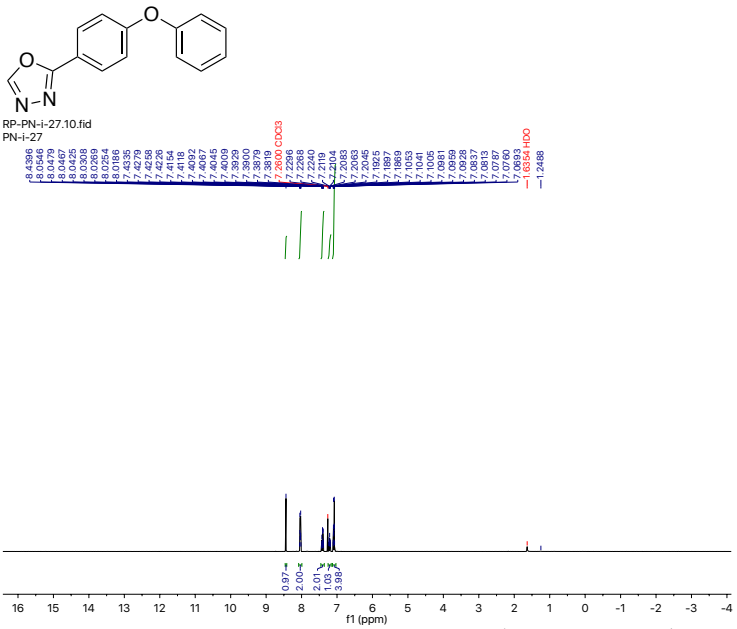


Figure S206. 1H NMR Spectrum of Compound 39a (400 MHz, $CDCl_3$).

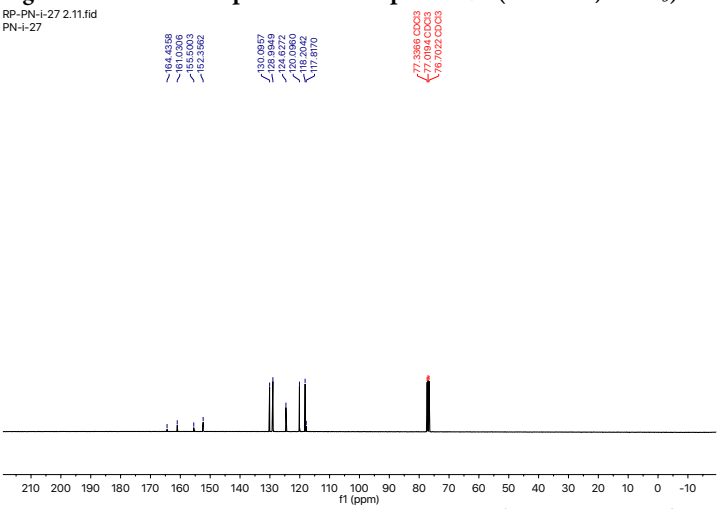


Figure S207. ^{13}C NMR Spectrum of Compound 39a (101 MHz, $CDCl_3$).

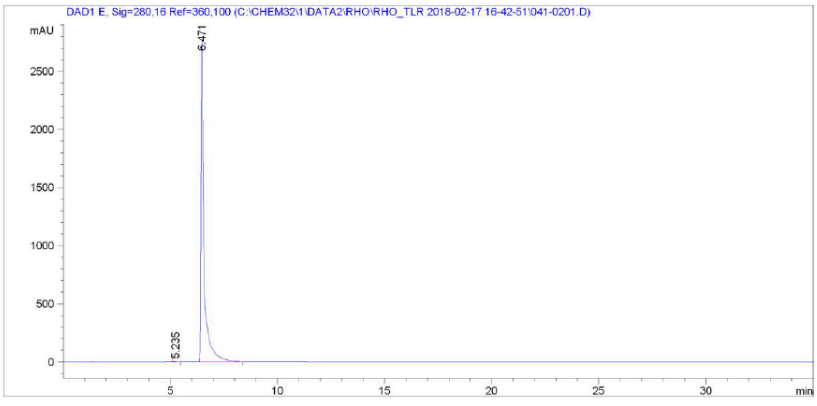


Figure S208. HPLC Chromatogram of Compound 39a.

Compound 39b:

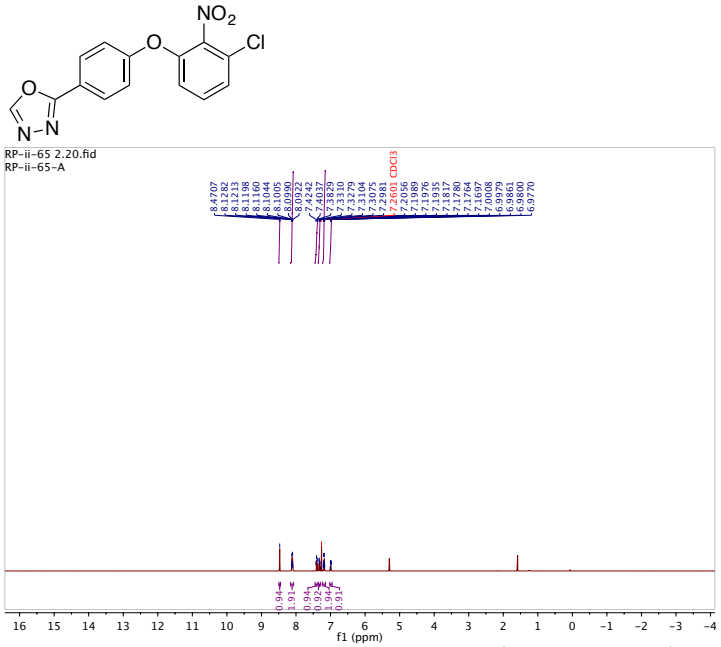


Figure S209. ^{1}H NMR Spectrum of Compound 39b (400 MHz, $CDCl_3$).

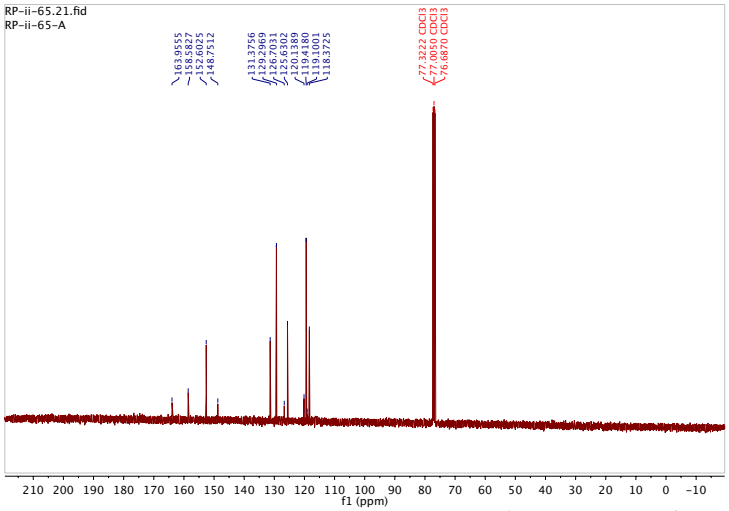


Figure S210. ^{13}C NMR Spectrum of Compound 39b (101 MHz, $CDCl_3$).

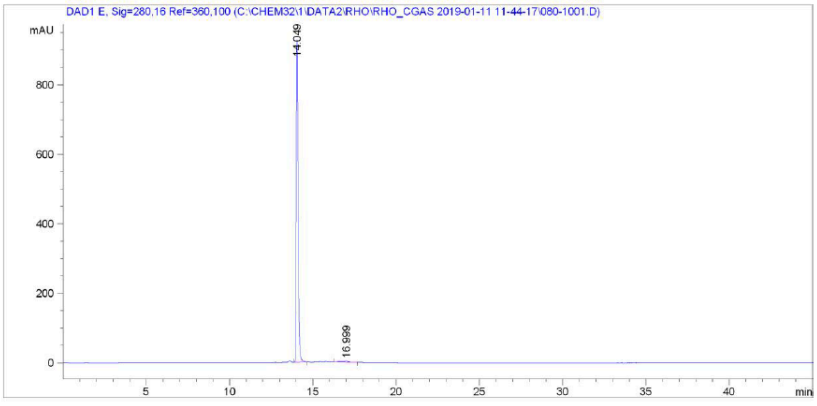


Figure S211. HPLC Chromatogram of Compound 39b.

Compound 39c:

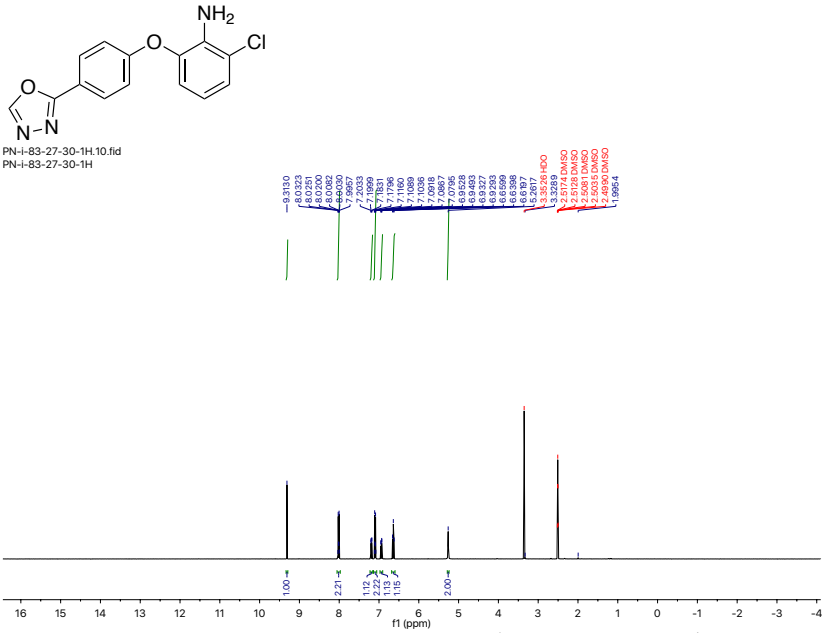


Figure S212. ^{1}H NMR Spectrum of Compound 39c (400 MHz, DMSO-d_6).

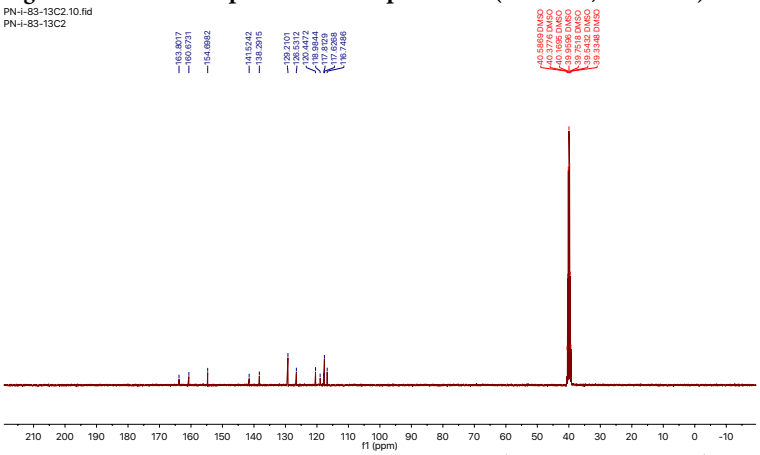


Figure S213. ^{13}C NMR Spectrum of Compound 39c (101 MHz, DMSO-d_6).

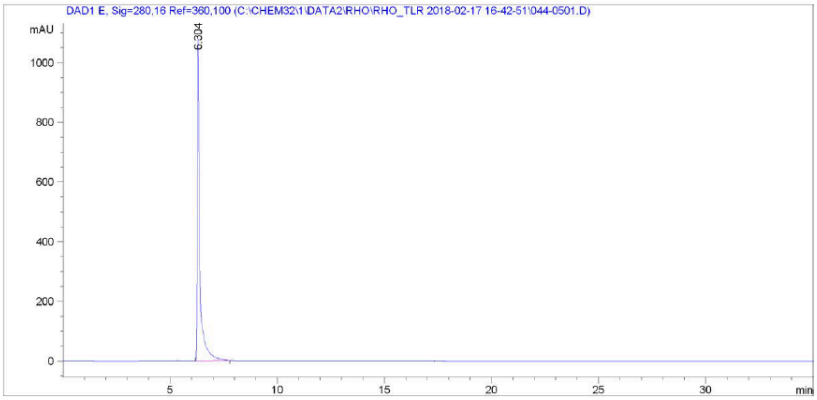


Figure S214. HPLC Chromatogram of Compound 39c.

Compound 39d:

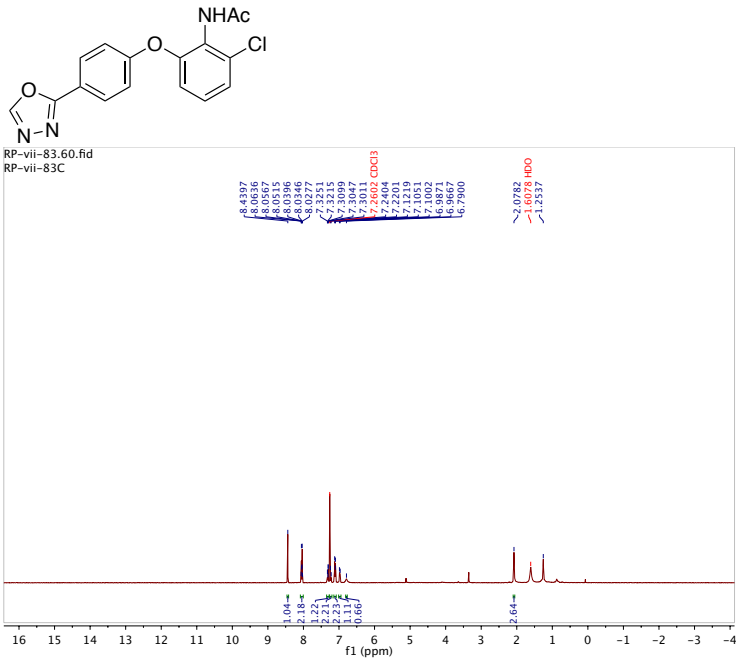


Figure S215. ^{1}H NMR Spectrum of Compound 39d (400 MHz, $CDCl_3$).

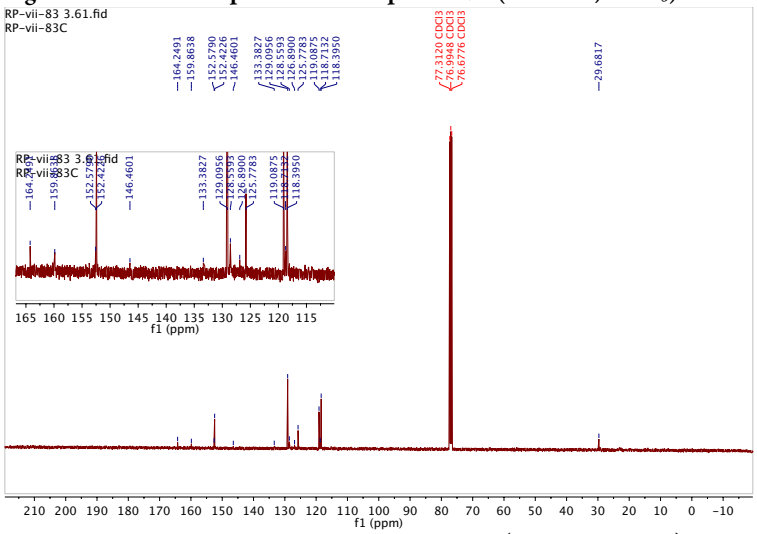


Figure S216. ^{13}C NMR Spectrum of Compound 39d (101 MHz, $CDCl_3$).

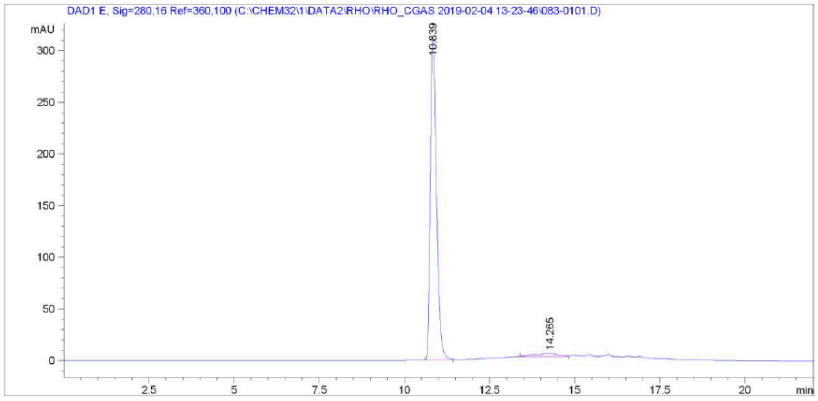
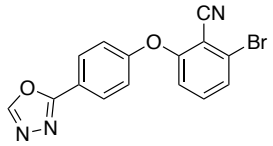


Figure S217. HPLC Chromatogram of Compound 39d.

Compound 39e:



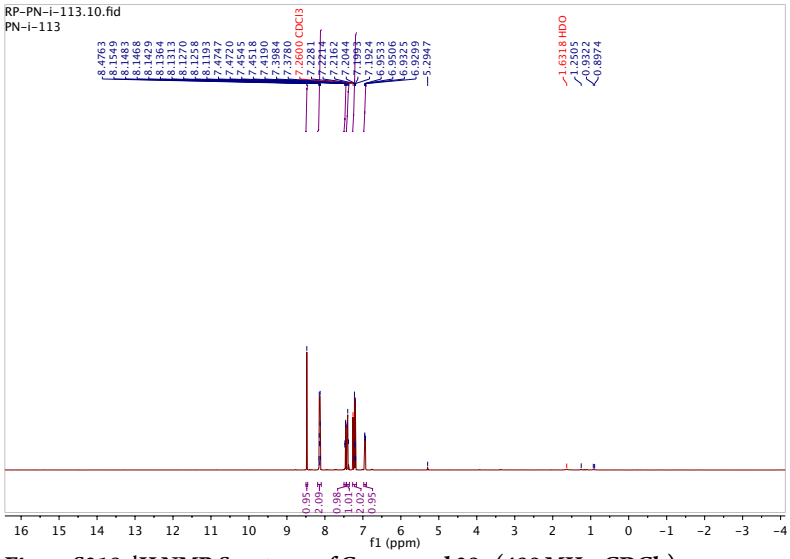


Figure S218. ^{1}H NMR Spectrum of Compound 39e (400 MHz, $CDCl_3$).

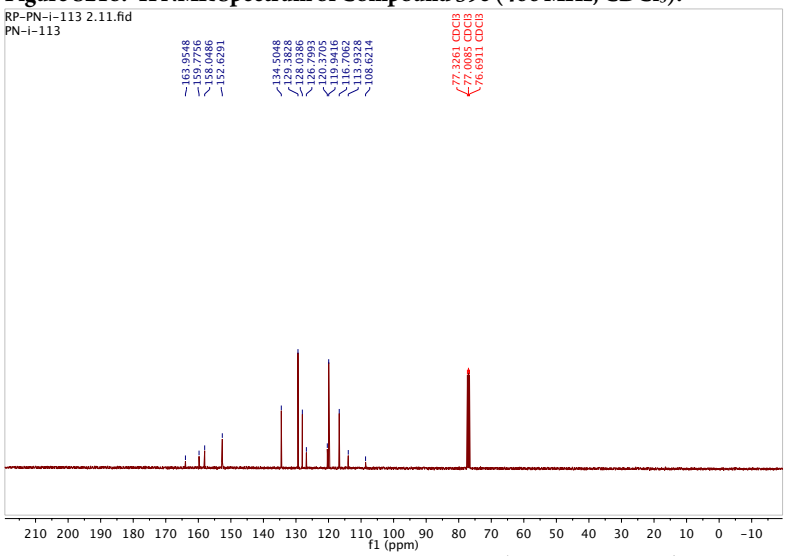


Figure S219. ^{13}C NMR Spectrum of Compound 39e (101 MHz, $CDCl_3$).

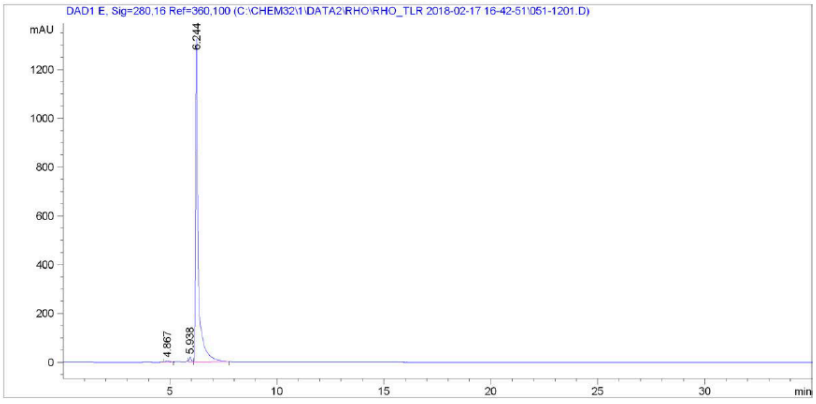
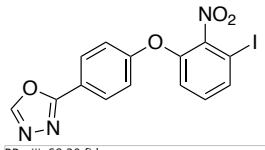


Figure S220. HPLC Chromatogram of Compound 39e.

Compond 39f:



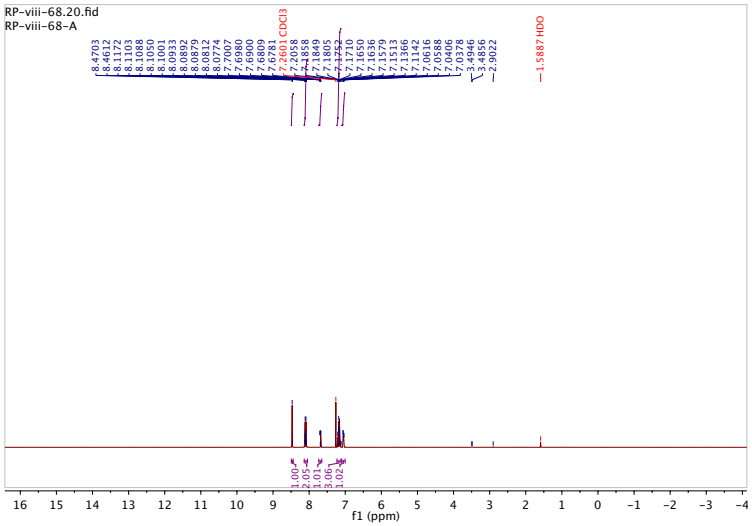


Figure S221. ^{1}H NMR Spectrum of Compound 39f (400 MHz, $CDCl_3$).

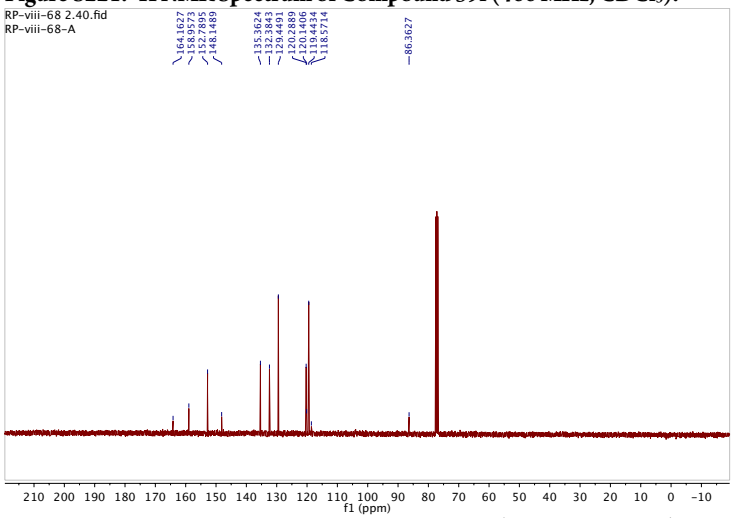


Figure S222. ^{13}C NMR Spectrum of Compound 39f (101 MHz, $CDCl_3$).

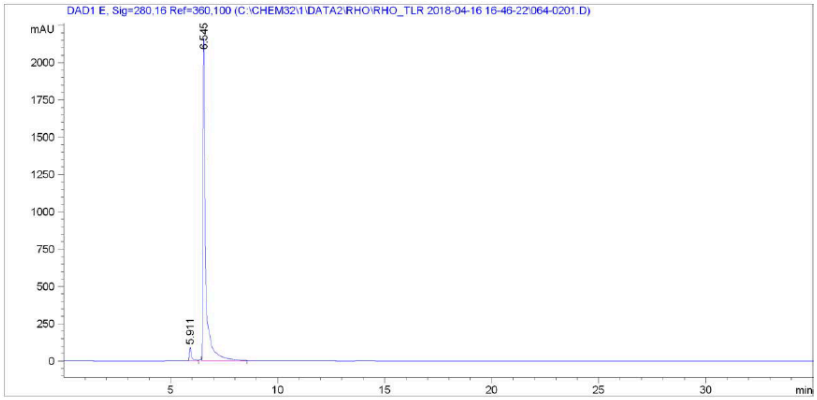
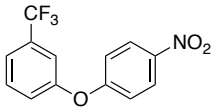


Figure S223. HPLC Chromatogram of Compound 39f.

Compound 40a:



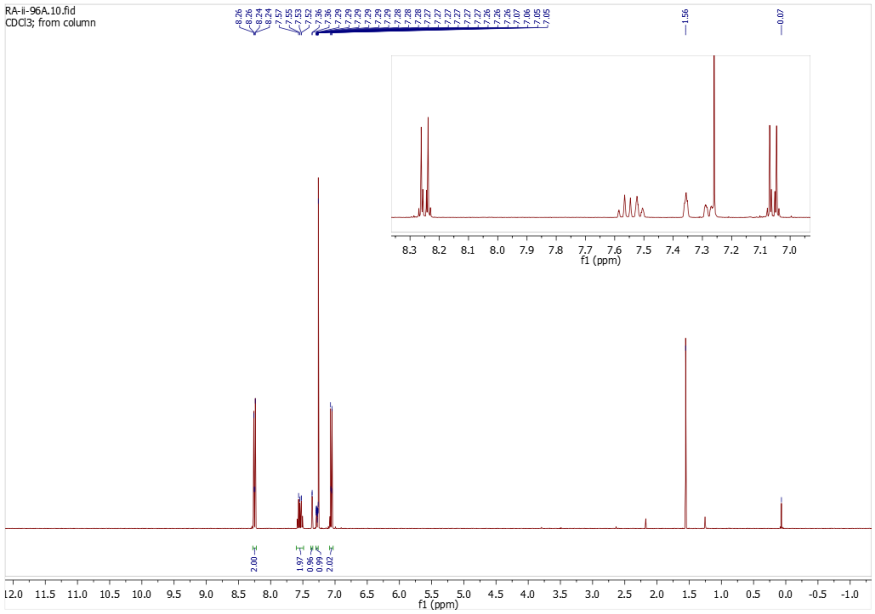


Figure S224. ^{1}H NMR Spectrum of Compound 40a (400 MHz, $CDCl_3$).

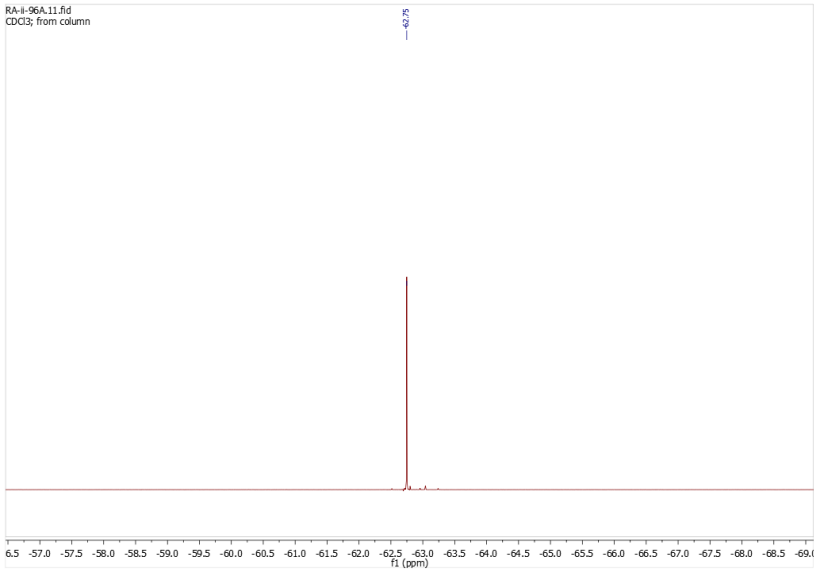
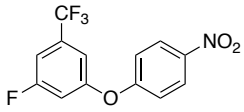


Figure S225. ^{19}F NMR Spectrum of Compound 40a (376 MHz, $CDCl_3$).

Compound 40b:



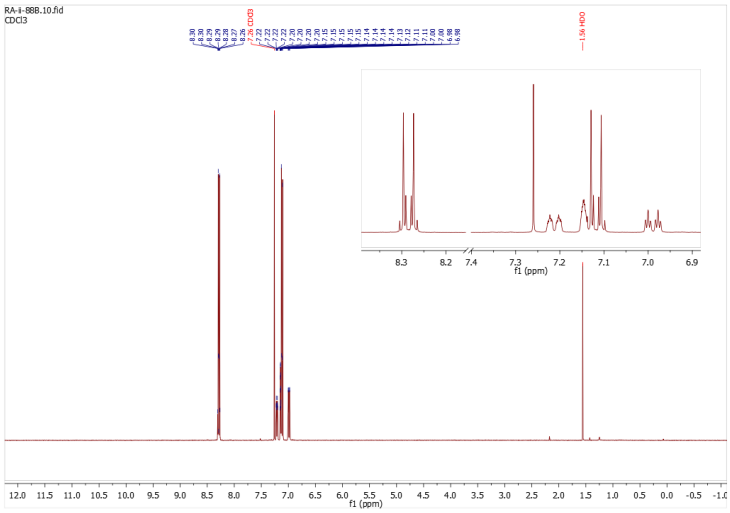


Figure S226. ^{1}H NMR Spectrum of Compound 40b (400 MHz, $CDCl_3$).

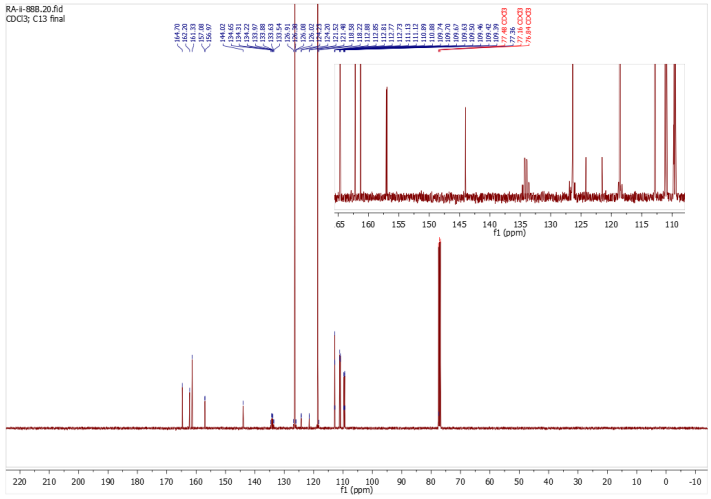
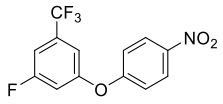


Figure S227. ^{13}C NMR Spectrum of Compound 40b (101 MHz, Acetone-d_6).

Compound 40b:



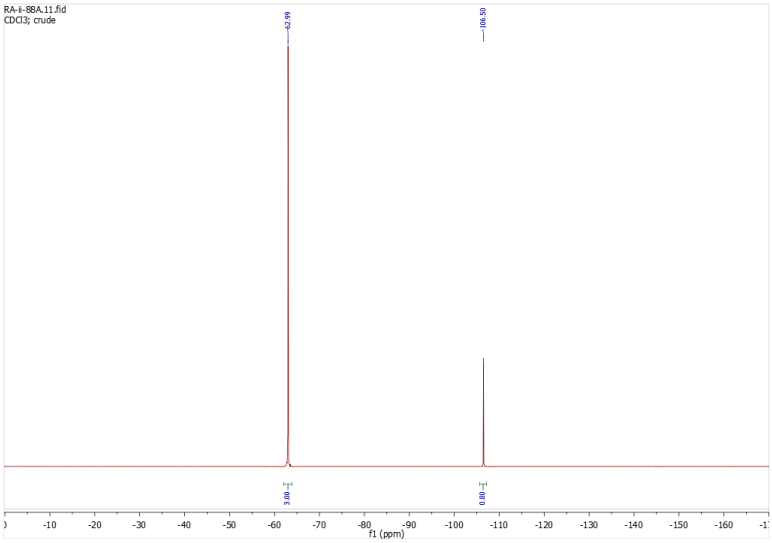
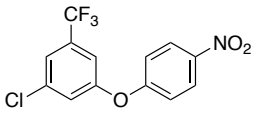


Figure S228. ^{19}F NMR Spectrum of Compound 40b (376 MHz, $CDCl_3$).

Compound 40c:



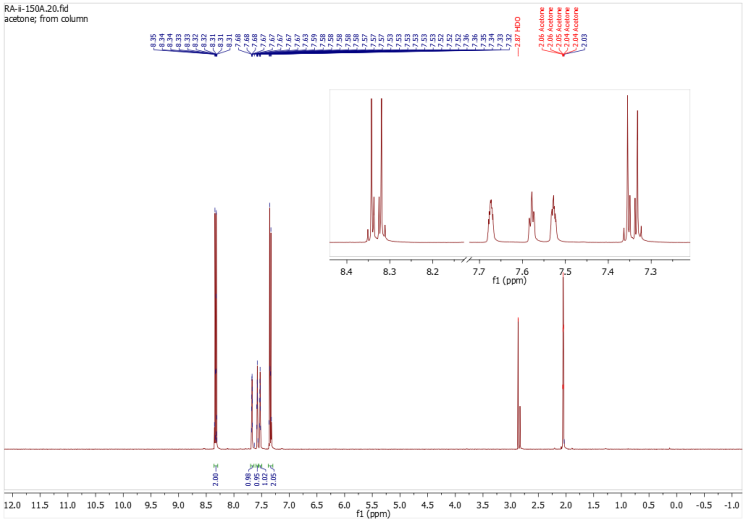


Figure S229. ^{1}H NMR Spectrum of Compound 40c (400 MHz, $CDCl_3$).

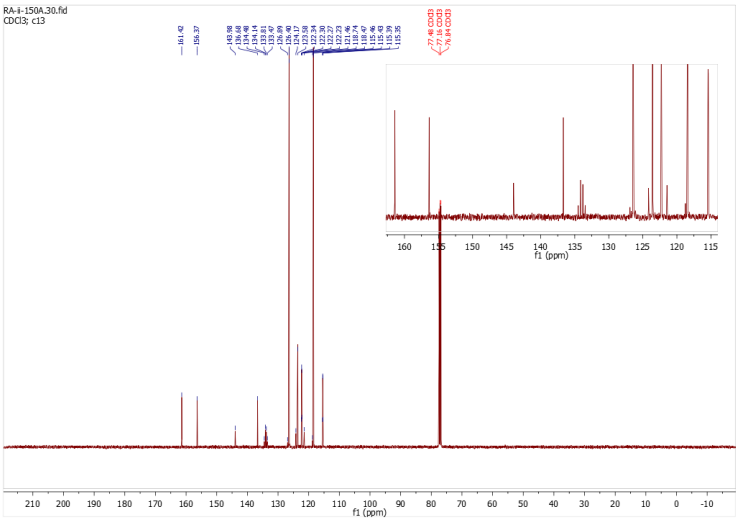


Figure S230. ^{13}C NMR Spectrum of Compound 40c (101 MHz, $CDCl_3$).

Compound 40c:

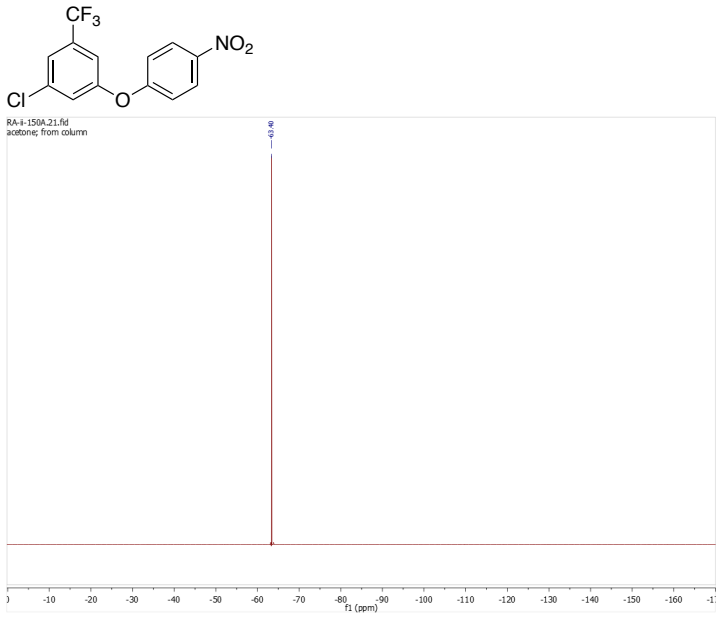
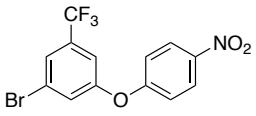


Figure S231. ^{19}F NMR Spectrum of Compound 40c (376 MHz, $CDCl_3$).

Compound 40d:



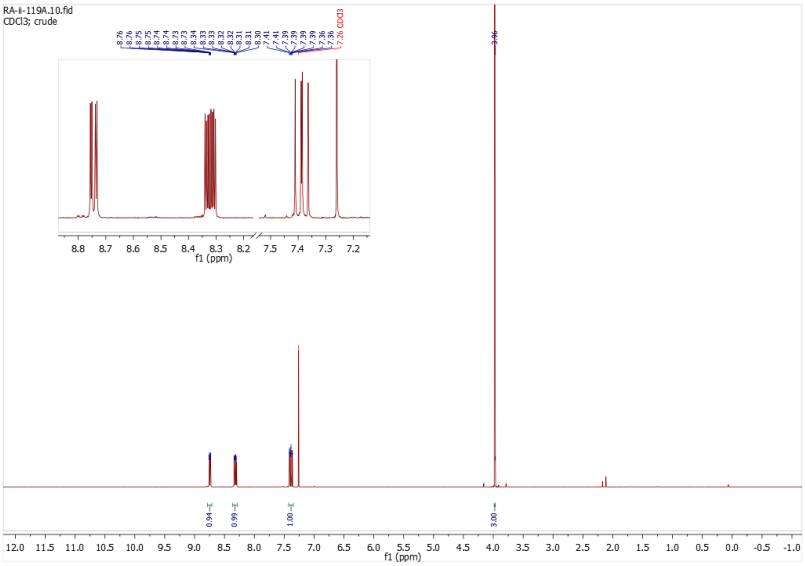


Figure S232. ^{1}H NMR Spectrum of Compound 40d (400 MHz, $CDCl_3$).

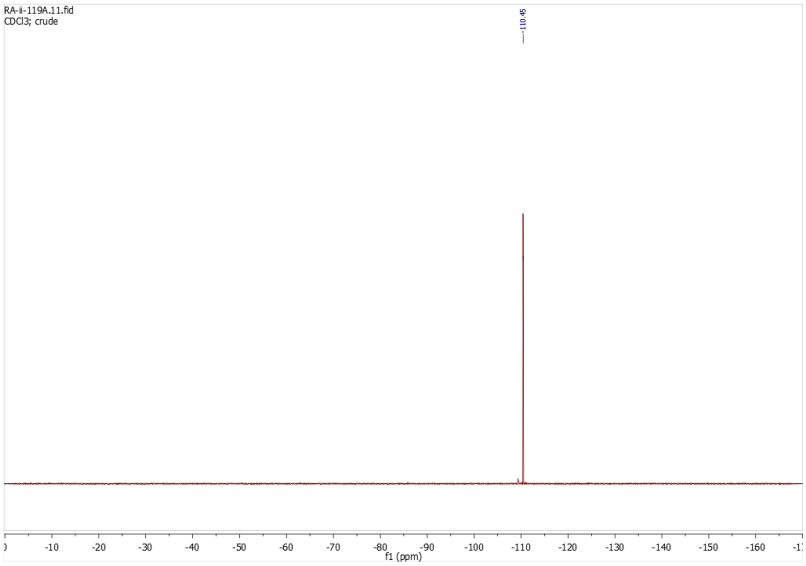
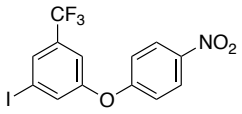


Figure S233. ^{19}F NMR Spectrum of Compound 40d (376 MHz, $CDCl_3$).

Compound 40e:



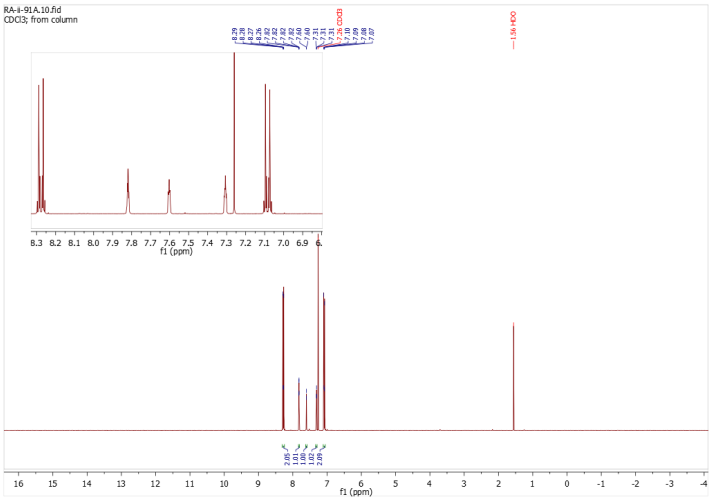


Figure S234. ^{1}H NMR Spectrum of Compound 40e (400 MHz, $CDCl_3$).

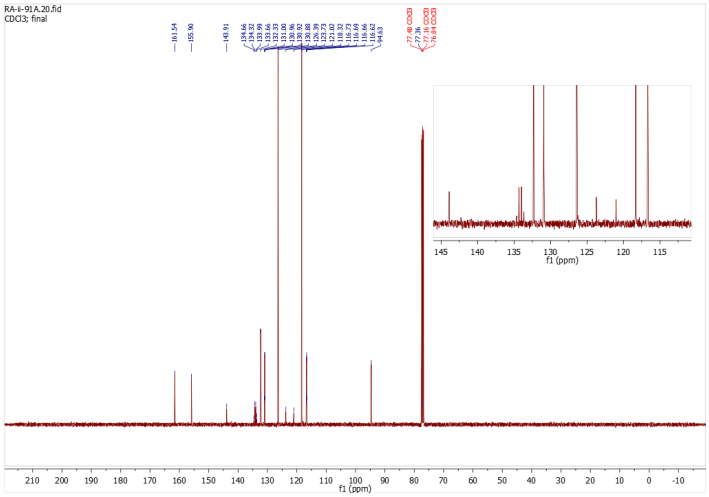
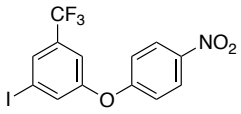


Figure S235. ^{13}C NMR Spectrum of Compound 40e (101 MHz, $CDCl_3$).

Compound 40e:



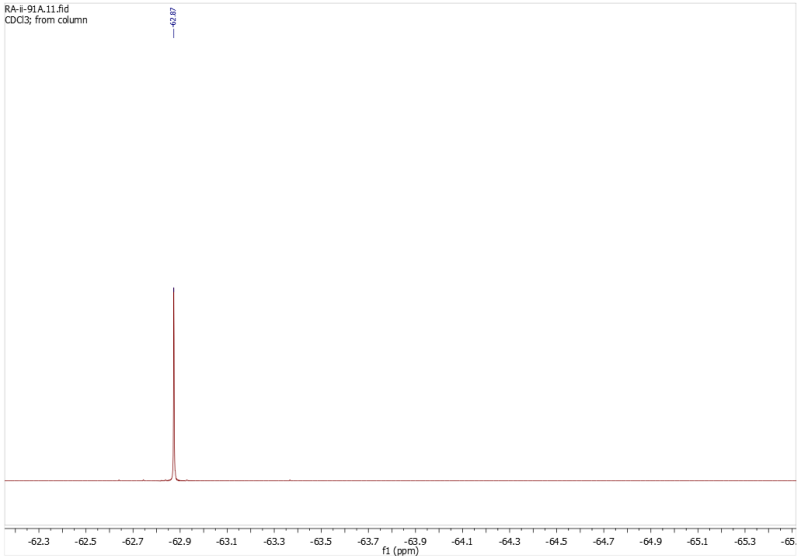
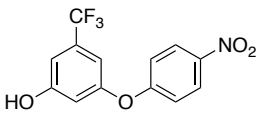


Figure S236. ^{19}F NMR Spectrum of Compound 40e (376 MHz, $CDCl_3$).

Compound 40f:



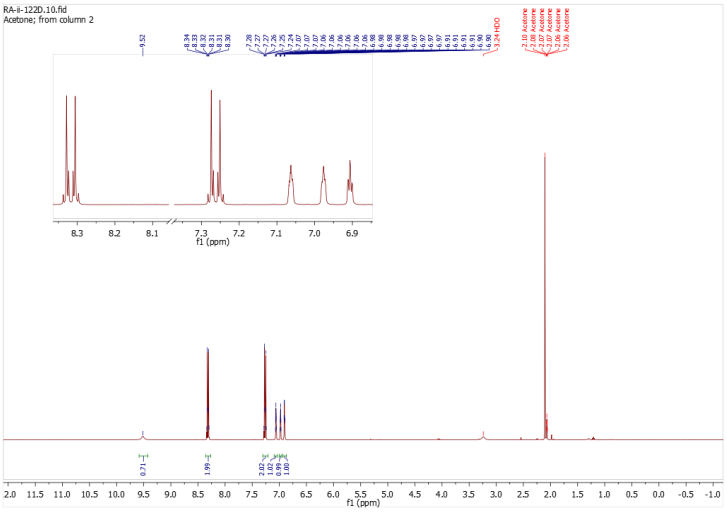


Figure S237. ^{1}H NMR Spectrum of Compound 40f (400 MHz, $CDCl_3$).

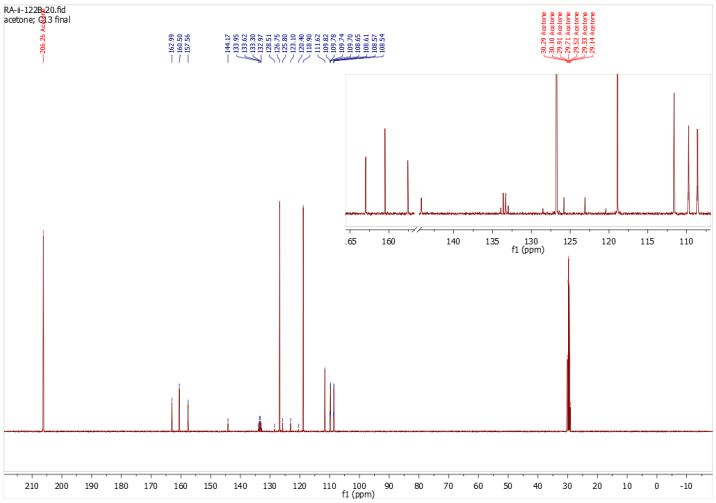


Figure S238. ^{13}C NMR Spectrum of Compound 40f (101 MHz, Acetone-d_6).

Compound 40f:

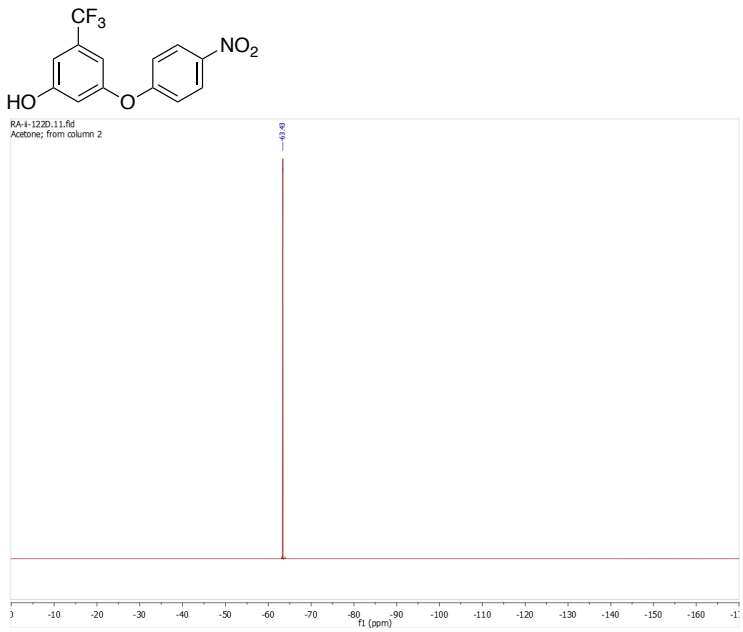
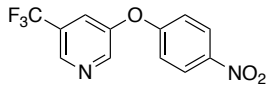


Figure S239. ^{19}F NMR Spectrum of Compound 40f (376 MHz, $CDCl_3$).

Compound 40g:



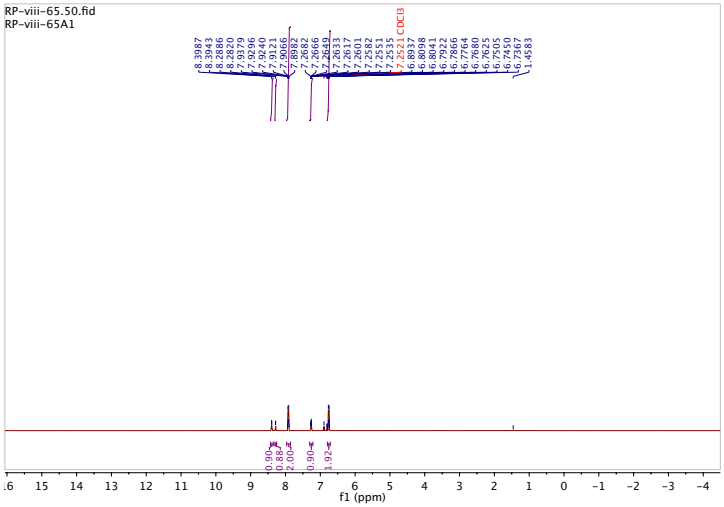


Figure S240. ^{1}H NMR Spectrum of Compound 40g (400 MHz, $CDCl_3$).

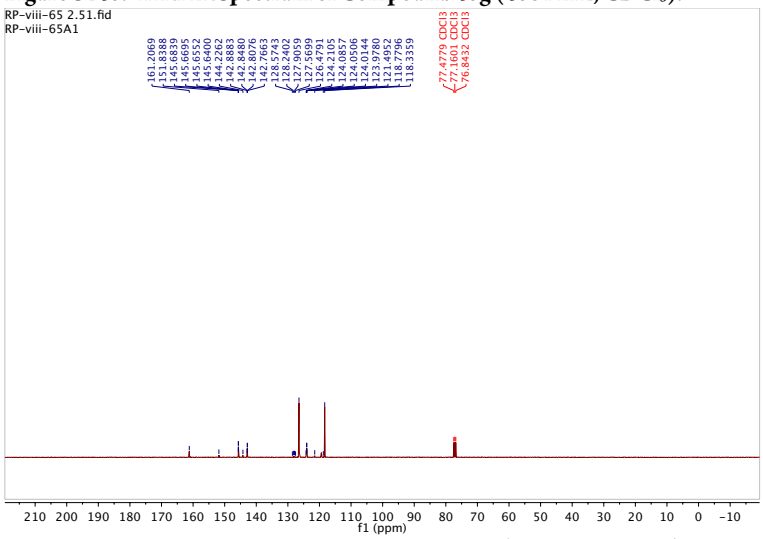
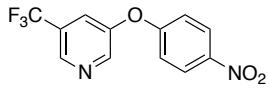


Figure S241. ^{13}C NMR Spectrum of Compound 40g (101 MHz, $CDCl_3$).

Compound 40g:



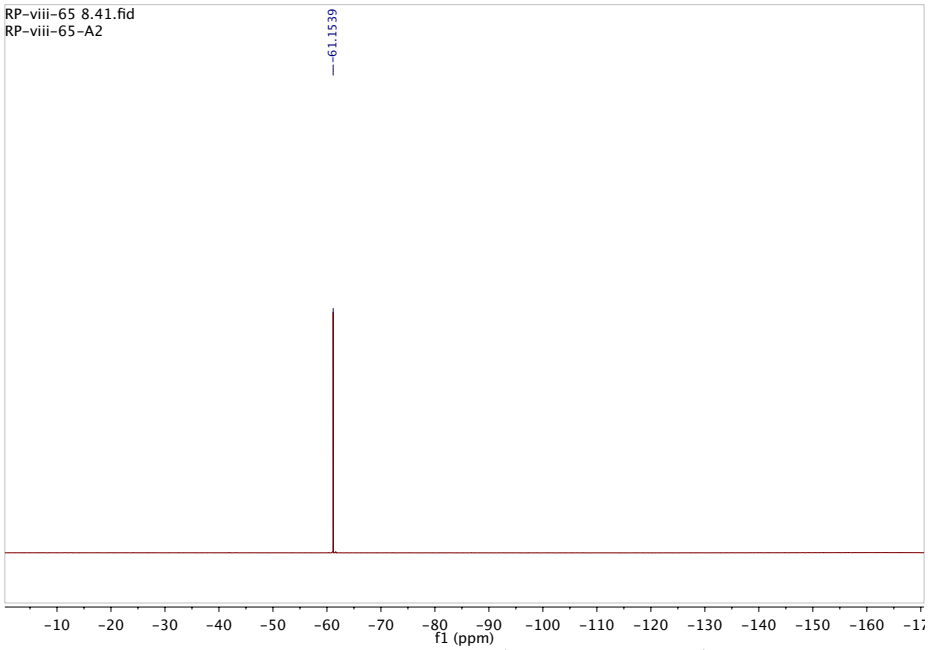
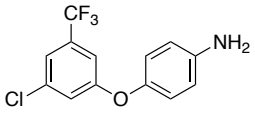


Figure S242. ^{19}F NMR Spectrum of Compound 40g (376 MHz, DMSO-d_6).

Compound 41a:



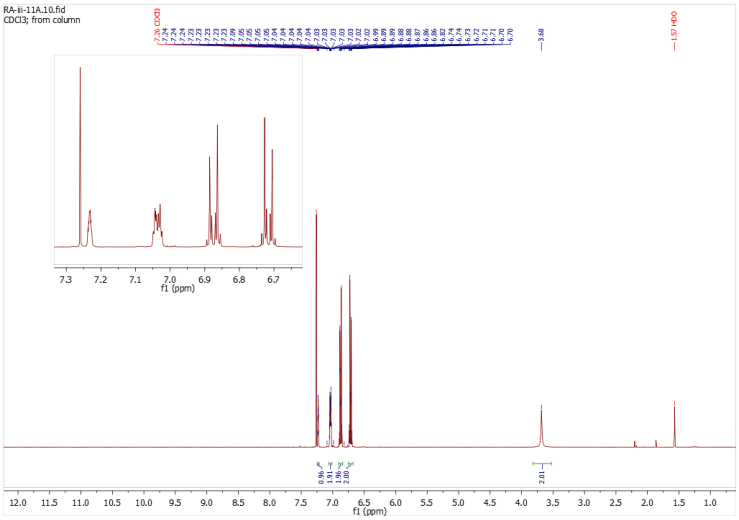


Figure S243. ^{1}H NMR Spectrum of Compound 41a (400 MHz, $CDCl_3$).

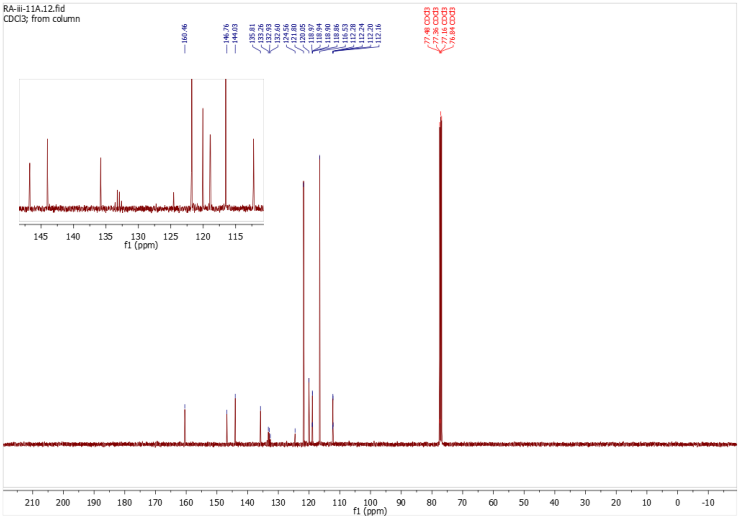


Figure S244. ^{13}C NMR Spectrum of Compound 41a (101 MHz, $CDCl_3$).

Compound 41a:

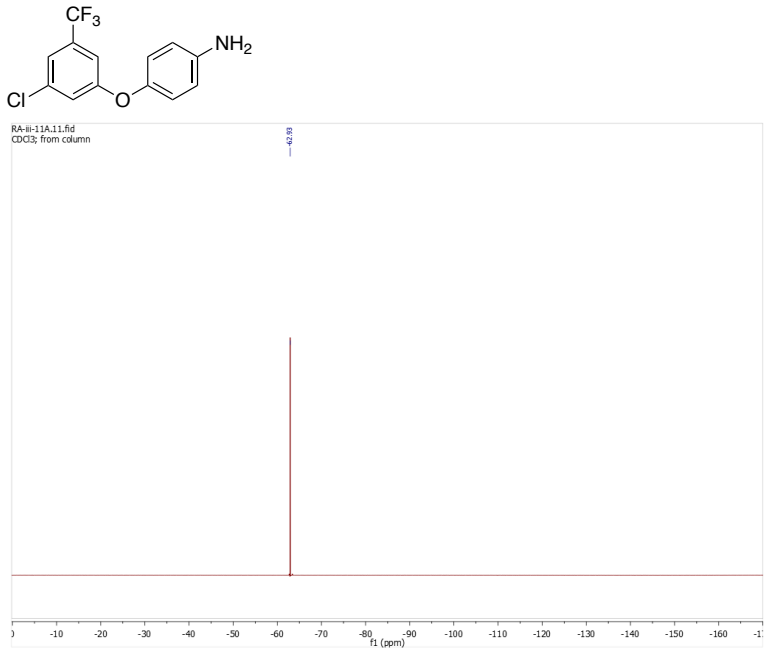
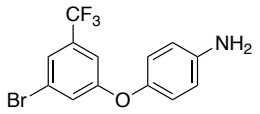


Figure S245. ^{19}F NMR Spectrum of Compound 41a (376 MHz, $CDCl_3$).

Compound 41b:



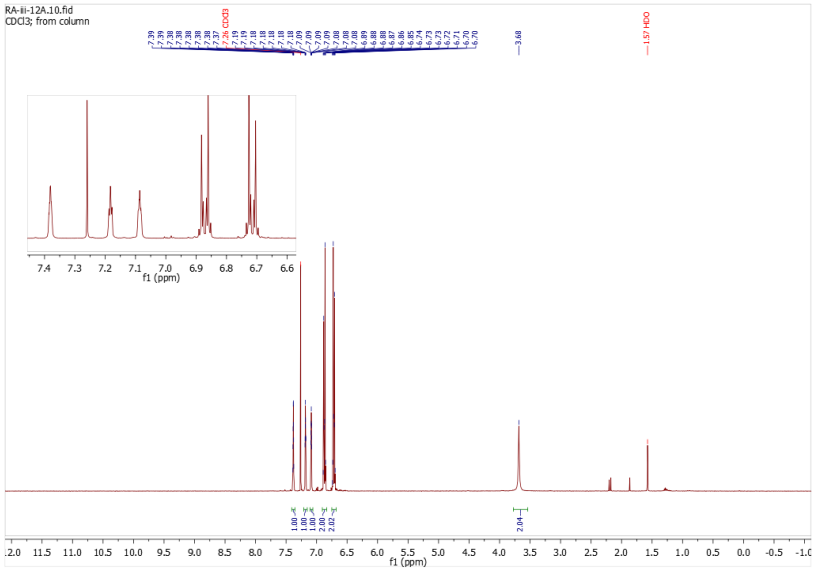


Figure S246. ^{1}H NMR Spectrum of Compound 41b (400 MHz, $CDCl_3$).

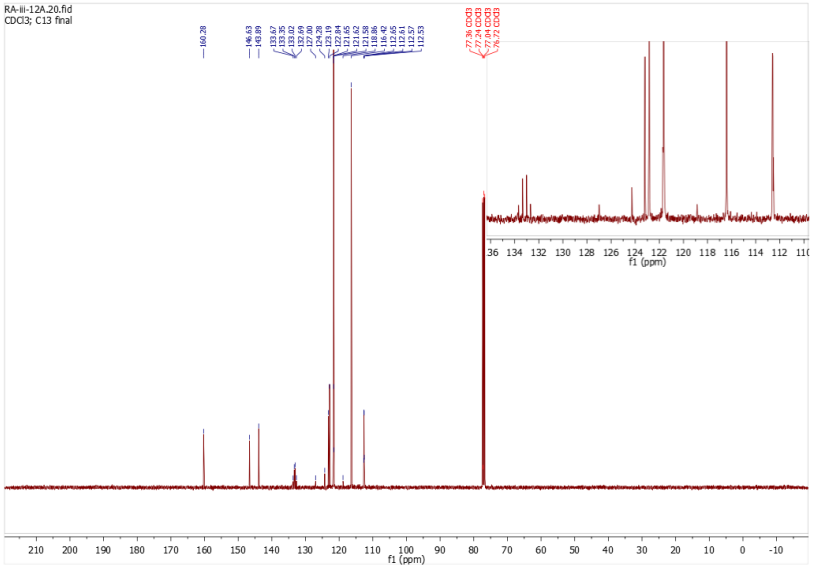
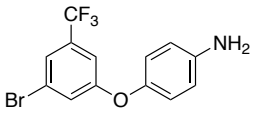


Figure S247. ^{13}C NMR Spectrum of Compound 41b (101 MHz, $CDCl_3$).

Compound 41b:



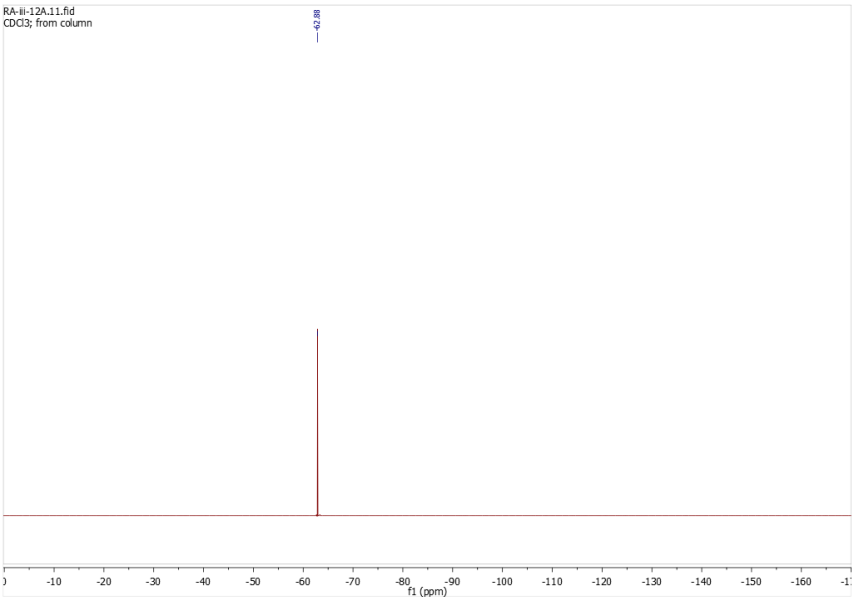
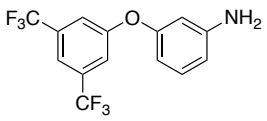


Figure S248. ^{19}F NMR Spectrum of Compound 41b (376 MHz, $CDCl_3$).

Compound 41c:



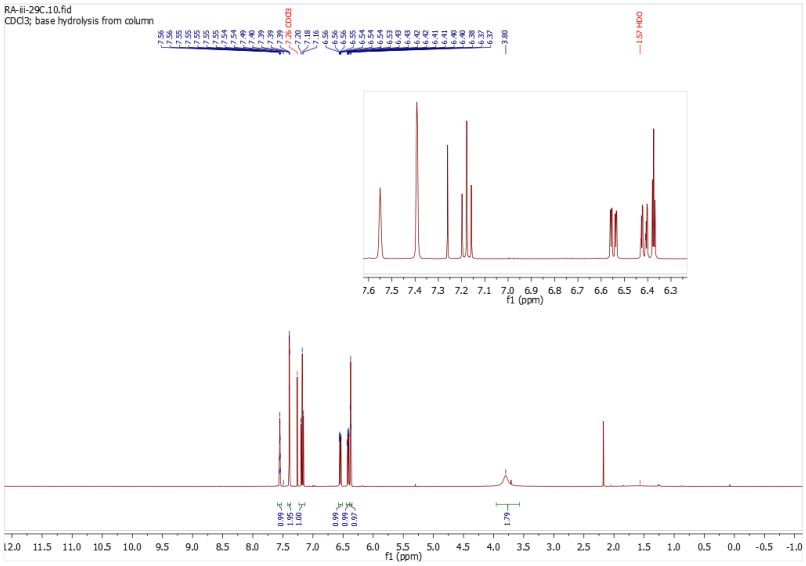


Figure S249. ^{1}H NMR Spectrum of Compound 41c (400 MHz, $CDCl_3$).

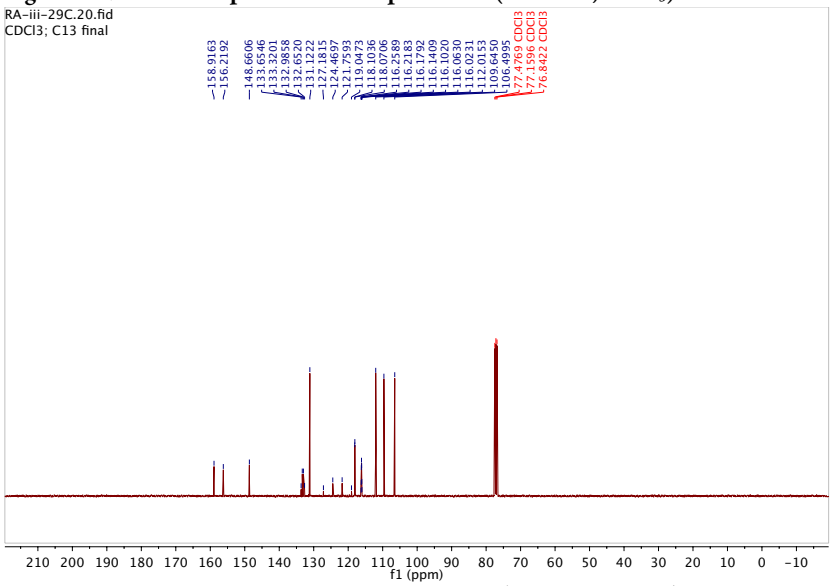
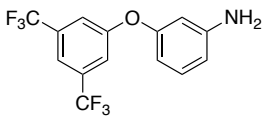


Figure S250. ^{13}C NMR Spectrum of Compound 41c (101 MHz, $CDCl_3$).

Compound 41c:



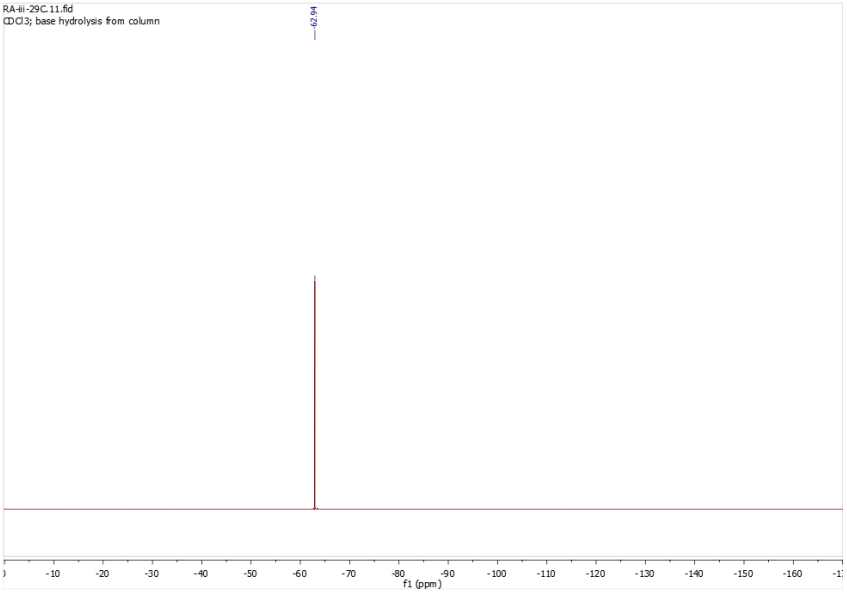
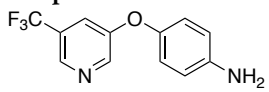


Figure S251. ^{19}F NMR Spectrum of Compound 41c (376 MHz, $CDCl_3$).

Compound 41:



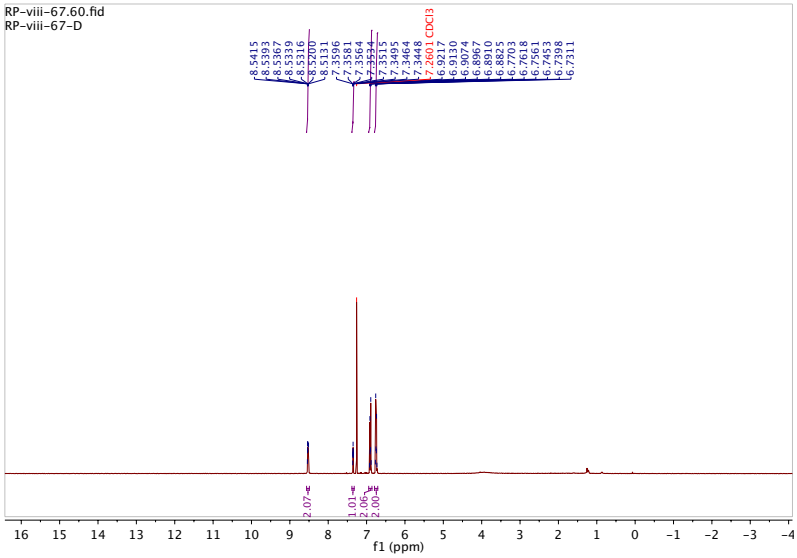


Figure S252. ^{1}H NMR Spectrum of Compound **41d** (400 MHz, $CDCl_3$).

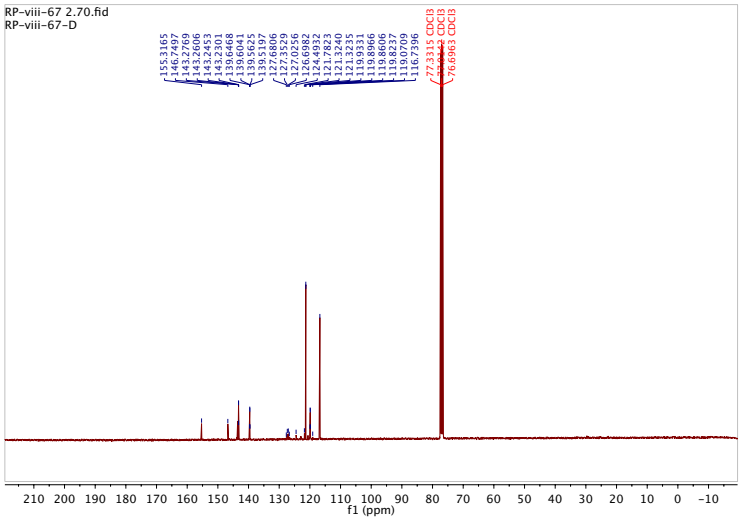
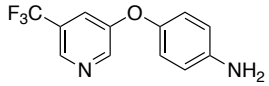


Figure S253. ^{13}C NMR Spectrum of Compound **41d** (101 MHz, $CDCl_3$).

Compound 41d:



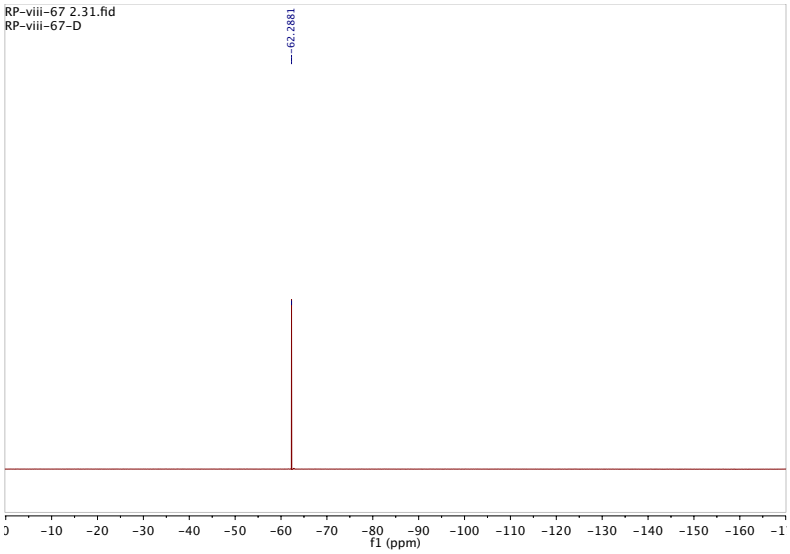
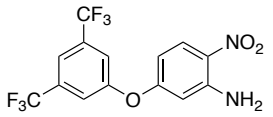


Figure S254. ^{19}F NMR Spectrum of Compound **41d** (376 MHz, $CDCl_3$).

Compound 32:



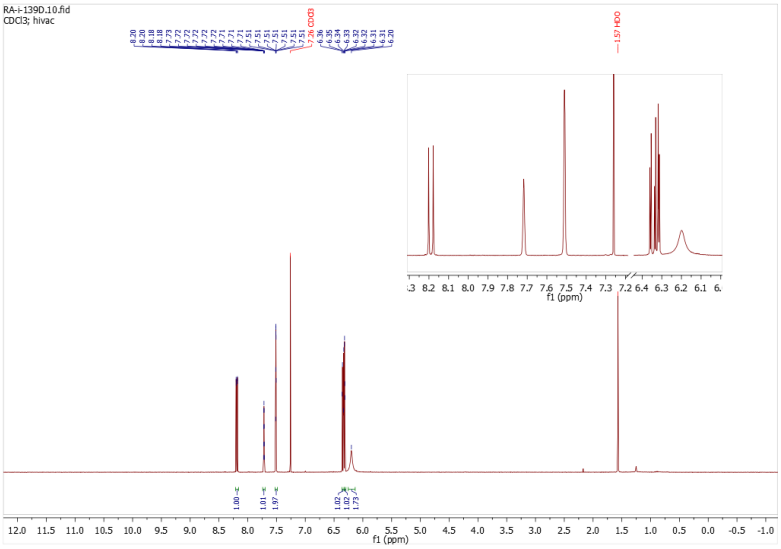


Figure S255. ^{1}H NMR Spectrum of Compound 32 (400 MHz, $CDCl_3$).

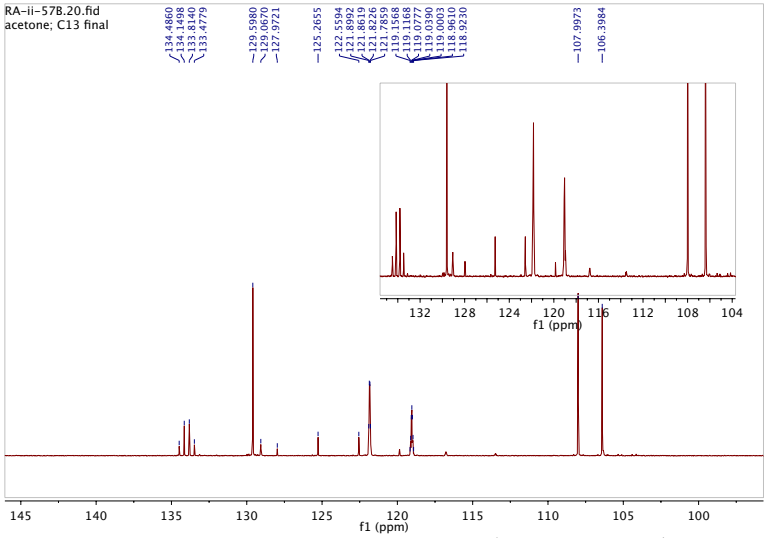


Figure S256. ^{13}C NMR Spectrum of Compound 32 (101 MHz, $CDCl_3$).

Compound 32:

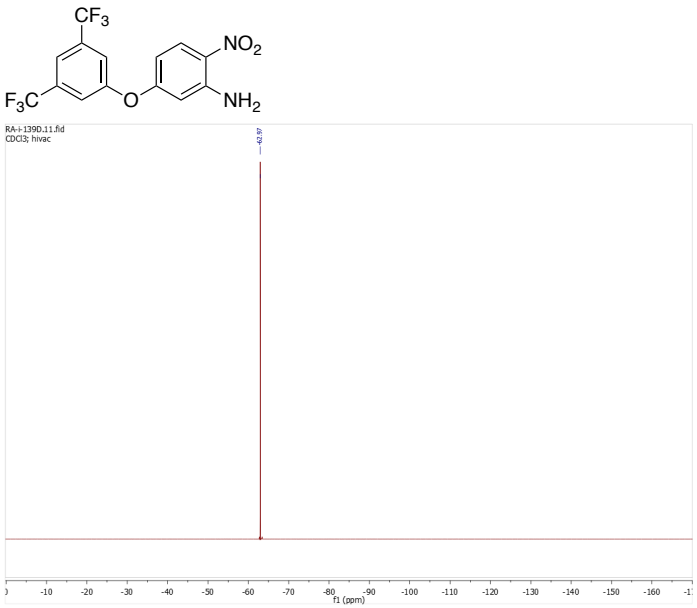
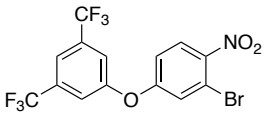


Figure S257. ^{19}F NMR Spectrum of Compound 32 (376 MHz, $CDCl_3$).

Compound 43:



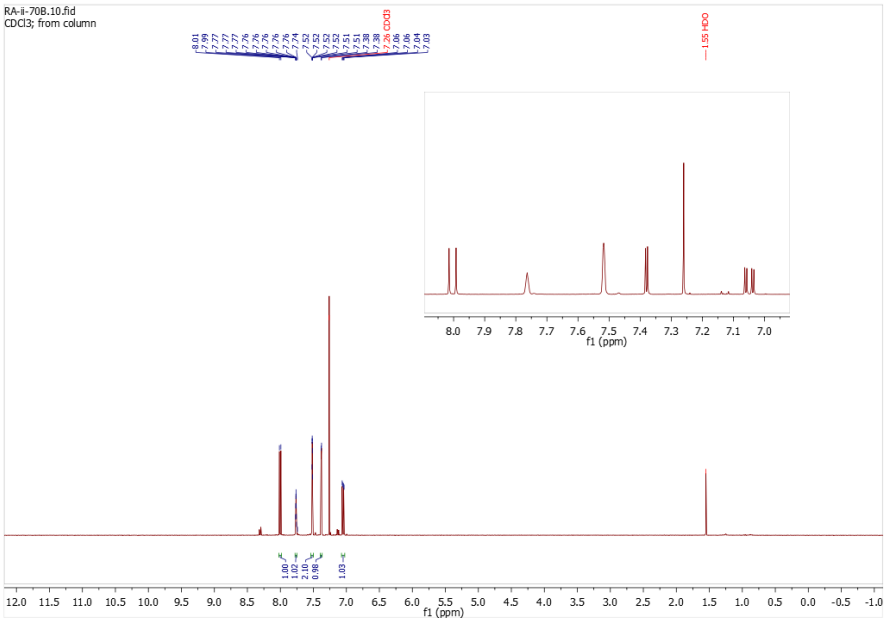


Figure S258. ^{1}H NMR Spectrum of Compound 43 (400 MHz, $CDCl_3$).

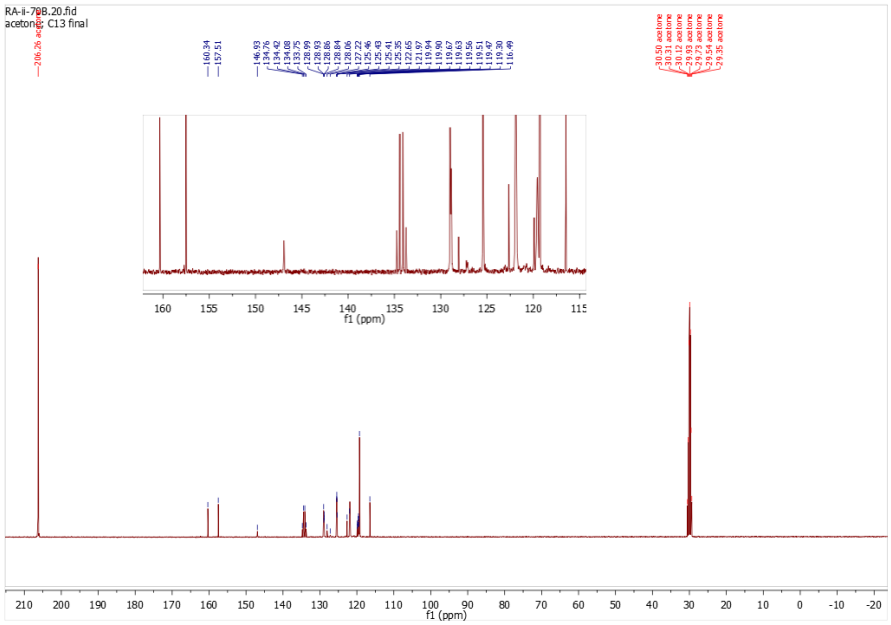
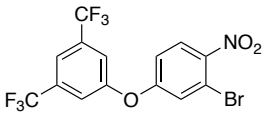


Figure S259. ^{13}C NMR Spectrum of Compound 43 (101 MHz, Acetone-d_6).

Compound 43:



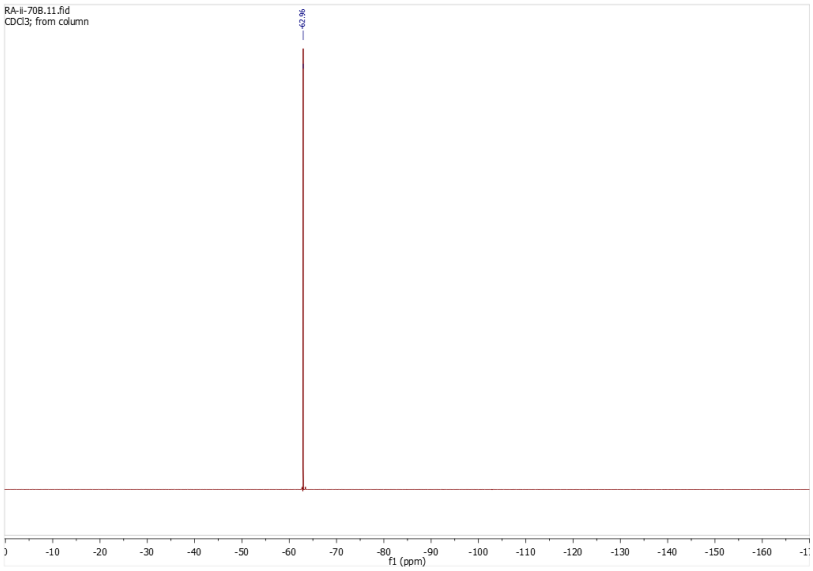


Figure S260. ^{19}F NMR Spectrum of Compound 43 (376 MHz, $CDCl_3$).

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