Contents: **P #**

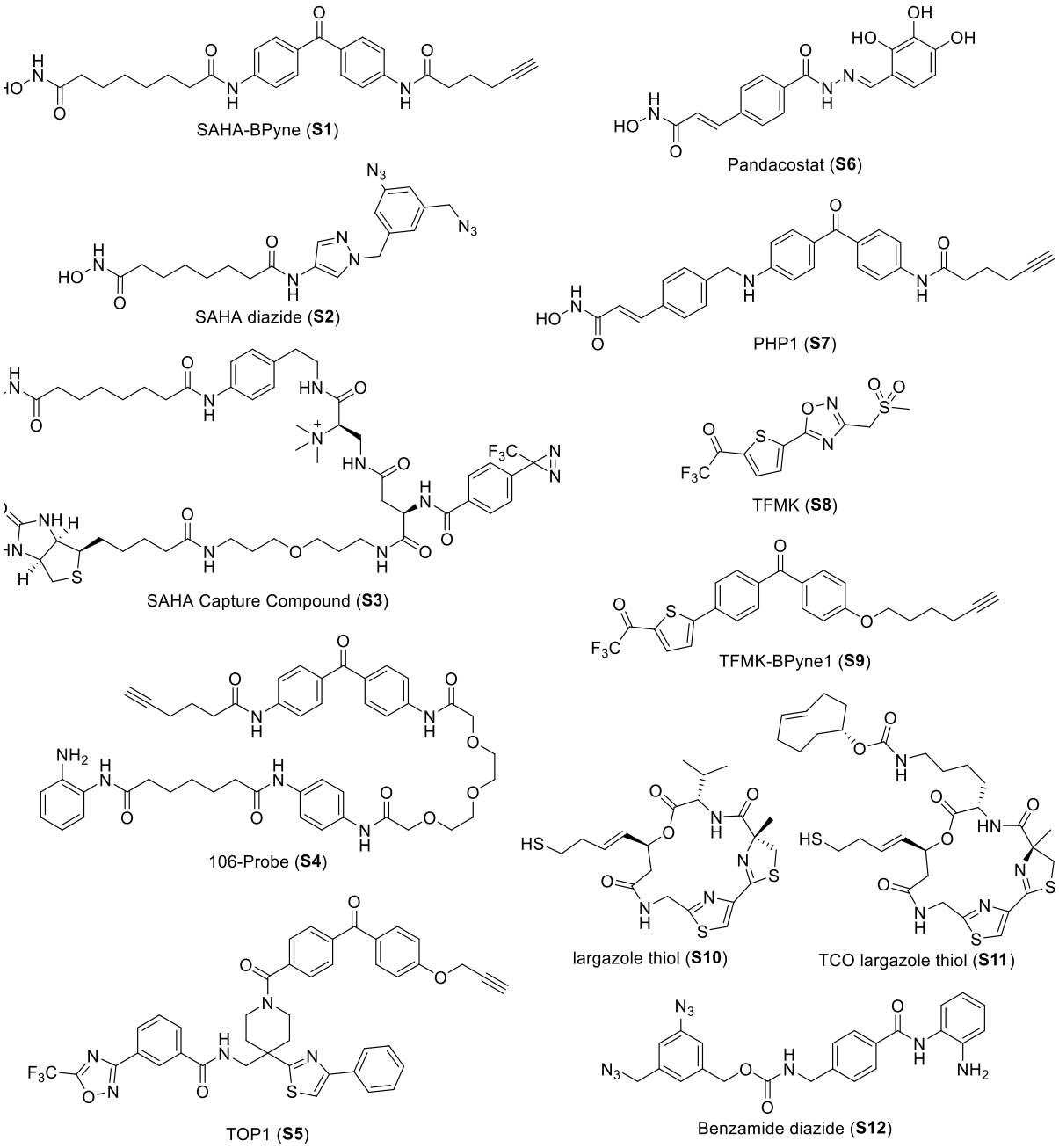
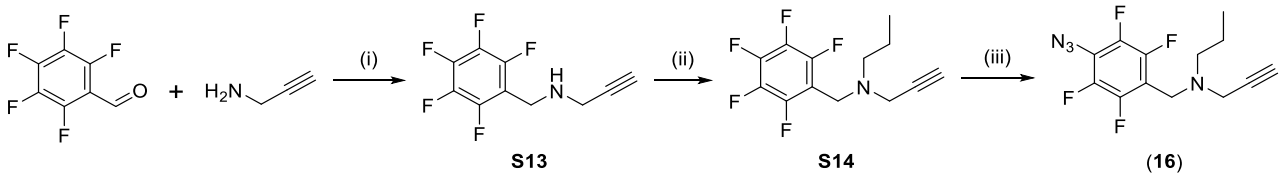


Figure S1. Structures of representative examples of HDAC PRPs reported in the literature

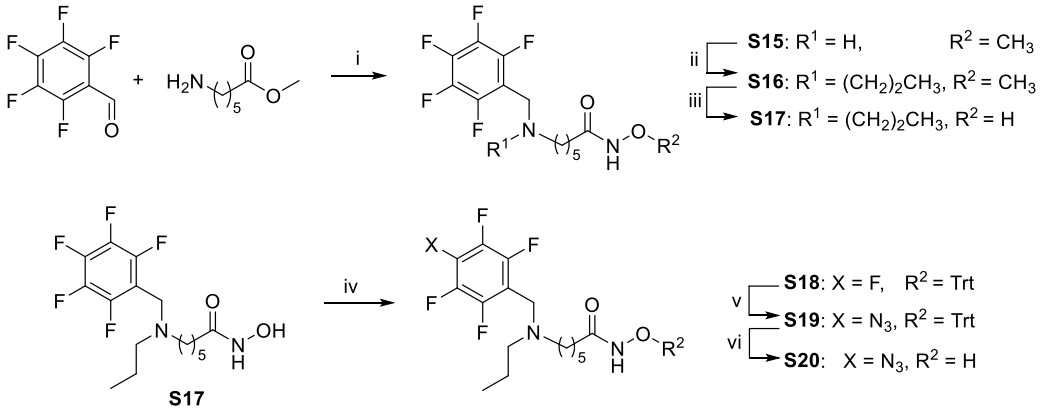
Table S1. *In silico* physicochemical properties of PRPs in comparison to their parent HDACi calculated in MOE.

Compound name (#)[Ref][a]	M.W.[b]	TPSA[c]	ASA_H[d]	SlogP[e]	logS[f]	MR[g]	Drug-like[h]	Lipiniski violation[i]
SAHA (**1**)	264.3	78.4	379	2.5	-2.9	7.5	1	0
PRP **8**	387.3	77.3	404	4.0	-4.1	9.1	1	0
PRP **9**	534.5	106.4	561	6.1	-6.8	13.5	0	2
SAHA-BPyne (**S1**)[1]	477.6	124.6	629	4.4	-6.3	13.6	1	0
SAHA-diazide (**S2**)[2]	440.5	145.7	394	5.0	-3.3	11.6	0	2
SAHA-capture compound (**S3**)[3]	1104.3	299.0	883	3.8	-8.8	28.5	0	3
PDA-106 (**6**)	339.4	84.2	508	4.1	-4.5	10.1	1	0
PRP **14**	609.6	112.2	677	7.9	-8.4	16.1	0	2
106-PRP (**S4**)[4]	847.0	216.3	1050	6.8	-10.3	23.8	0	4
TMP-269 (**7**)	514.5	90.1	515	5.7	-7.8	13.2	0	2
PRP **15**	541.4	96.0	459	5.7	-8.3	12.0	0	2
TOP1 (**S5**)[5]	775.8	127.5	808	8.0	-12.5	20.9	0	2
Panobinostat (**2**)	349.4	77.2	459	3.6	-4.1	10.4	1	0
PRP **10**	433.4	77.3	437	4.9	-5.9	10.6	1	0
Pandacostat (**S6**)	357.3	151.5	302	1.1	-3.0	9.2	1	1
PHP1 (**S7**)[5]	481.6	107.5	634	5.1	-7.0	14.1	1	1
PCI-34051 (**4**)	296.3	63.5	354	3.1	-3.4	8.5	1	0
PRP **12**	460.4	82.2	420	4.9	-5.6	11.2	1	0
TFMK (**S8**)	340.3	90.1	234	2.4	-4.4	7.0	1	0
TFMK-BPyne (**S9**)[5]	456.5	43.4	546	6.6	-8.6	12.1	1	1
Largazole-thiol (**S10**)	496.7	148.6	468	2.6	-5.0	13.1	1	0
TCO largazole thiol (**S11**)[6]	677.9	186.9	602	4.7	-6.5	18.2	0	2
Entinostat (**5**)	376.4	177	513	3.9	-3.8	10.7	1	0
PRP **13**	547.6	333	515	6.2	-7.0	12.3	1	1
Benzamide-diazide (**S12**)	482.4	209	560	8.2	-7.8	15.4	0	3
Givinostat (**3**)	421.5	77	377	4.5	-5.4	9.7	1	1
PRP **11**	407.3	91	496	5.1	-5.9	12.1	1	0

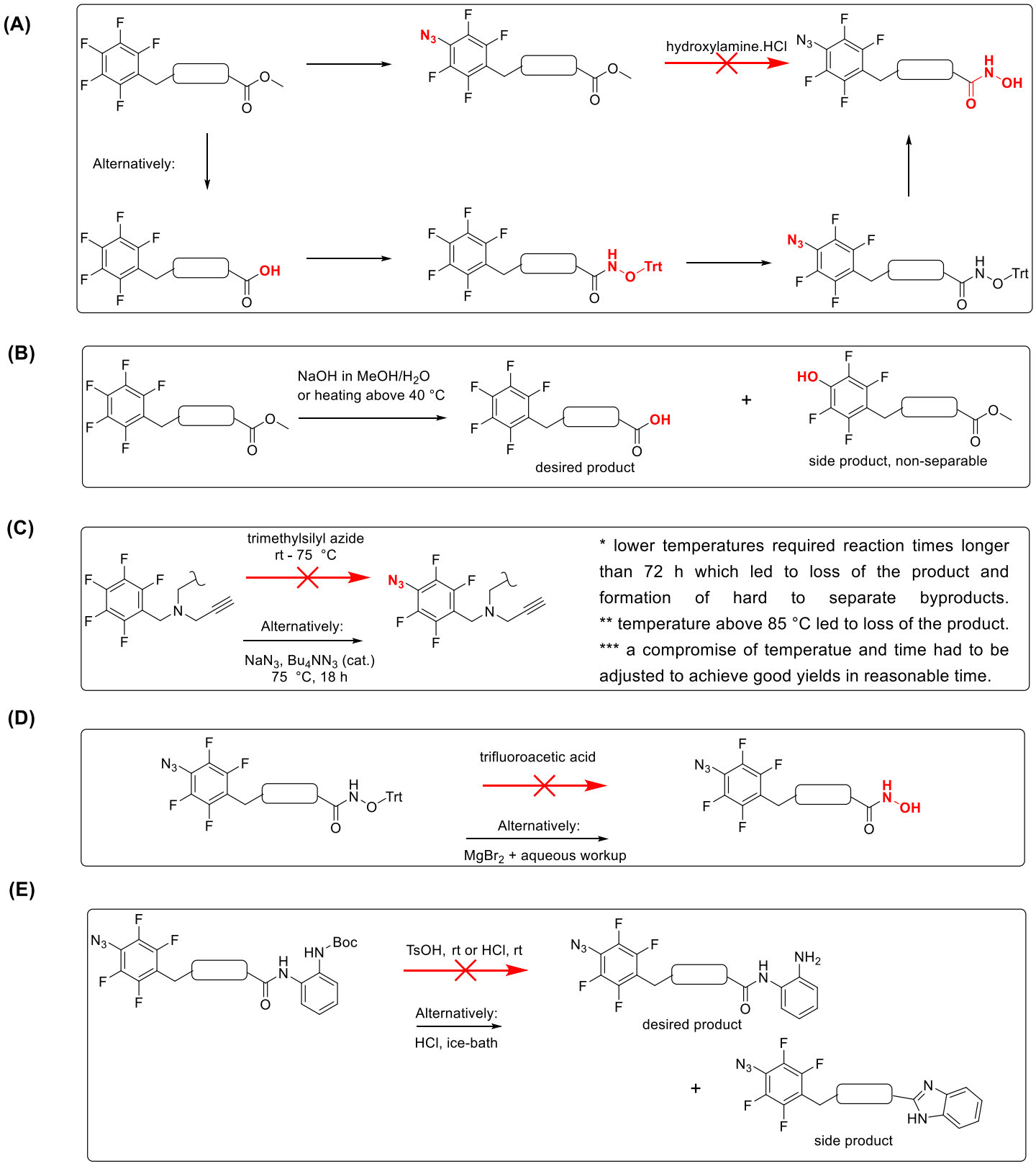
[a]Compound numbers: corresponding to structures in Figures 1 & 2 of the manuscript, and PRPs from previous studies shown in Figure S1 below, rows of parent HDACi are highlighted in grey.
[b]M.W.: Molecular weight
[c]TPSA: Topological Polar surface area (Å^2)
[d]ASA_H: water accessible surface area of all hydrophobic atoms (Å^2)
[e]SlogP: Log of the octanol/water partition coefficient (including implicit hydrogens).
[f]logS: Log of the aqueous solubility (mol/L).
[g]MR: Molecular refractivity (including implicit hydrogens).
[h]Drug-like: Lipiniski drug-likeness test, 1 for pass (<2 in violation of lipiniski).
[i]Lipiniski violation: The number of violations of Lipinski's Rule of Five.



Scheme S1. Synthesis of the TFPA control **16**. Reagents and Conditions: (i) a. DCM,18 h, b. $NaBH_4$, CH_3OH, 0 °C-rt, (ii) propyl bromide, K_2CO_3, CH_3CN, reflux, 20 h; (iii) NaN_3, Bu_4NN_3, DMF, 80 °C, 18 h.



Scheme S2. Synthesis of tag-free competitor **S20**. Reagents and conditions: (i) $NaBH_4$, CH_3OH, 0 °C→rt, 24 h (ii) propyl bromide, CH_3CN, K_2CO_3, 12 h; (iii) LiOH, THF/H_2O (1:1), 18 h; (iv) *O*-tritylhydroxylamine, EDC•HCl, HOBt, DMAP, Et_3N, $CHCl_3$, 18 h; (v) NaN_3, Bu_4NN_3, DMF, 75 °C, 18 h; (vi) $MgBr_2$, DCM, 30 min.



Scheme S3. Optimization of synthetic strategy.

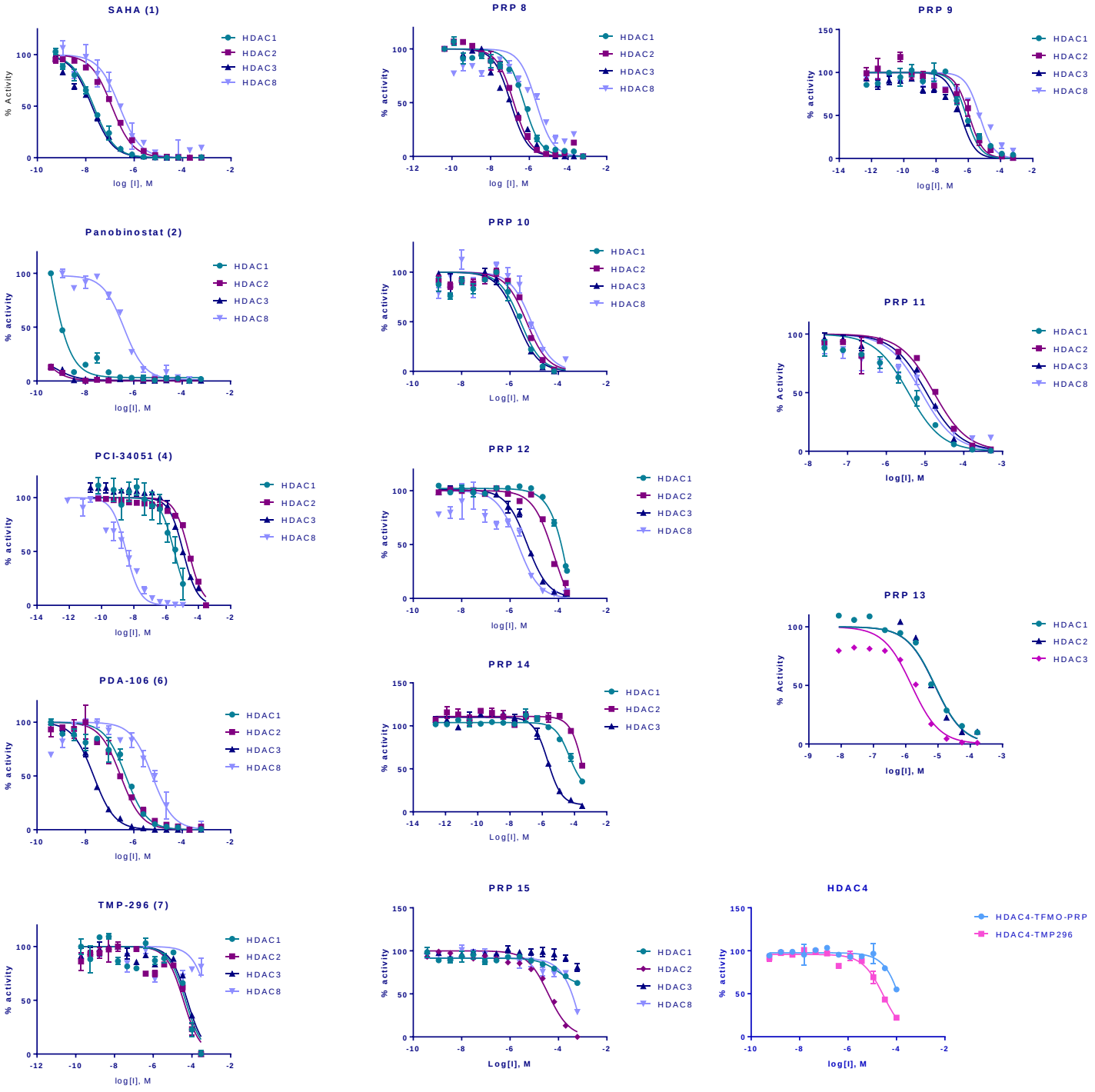


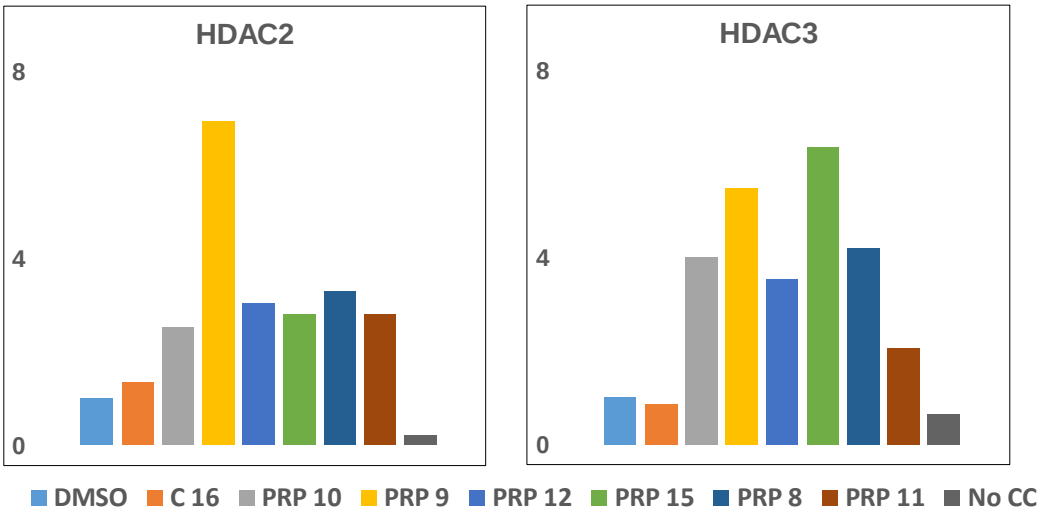
Figure S2. Representative Dose-response curves for TFPA HDAC PRPs (8-15) and their parent HDACi (1, 2, 4, 6, and 7). Data points represent the mean of inhibition at each concentration from at least two duplicate data sets. HDAC pIC_{50} values were calculated by fitting the data using non-linear regression dose-response curve variable slope (four parameters).

Table S2 Percentage inhibition of recombinant HDAC4 for PRPs and their parent compounds

	HDAC4% inhibition ± SD					
Compound	**10 μM**			**100 μM**		
SAHA (1)	33	±	3.8	77	±	0.5
8	46	±	0.9	92	±	0.12
9	7	±	2.5	18	±	0.7
Panobinostat (2)	27	±	6.6	83	±	18.5
10	6	±	1.5	19	±	0.0
PDA-106 (6)	8	±	0.9	9	±	5.9
14	9	±	3.5	12	±	4.7
PCI-34051(4)	ND*			ND		
12	5	±	3.1	ND		

*ND; not determined.

(a) SET-2



(b) SET-2

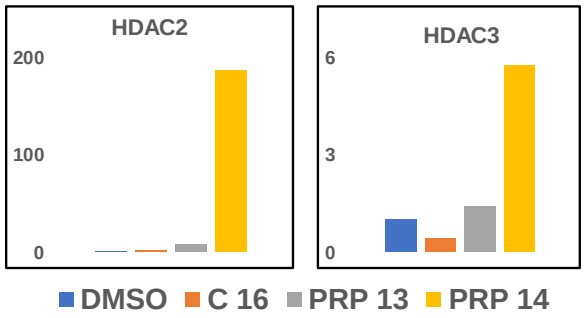


Figure S3 Densitometric analysis of HDAC2 and HDAC3 photolabeling in SET-2 cells by (a) PRPs **9**-**12** and **15** (Figure 4a, manuscript) and (b) PRPs **13** and **14** (Figure 4b, manuscript). Photolabeling signal (800 nm) was normalized to the antibody signal (700 nm) of corresponding isoform and GAPDH and calculated as a fold change relative to DMSO signal.

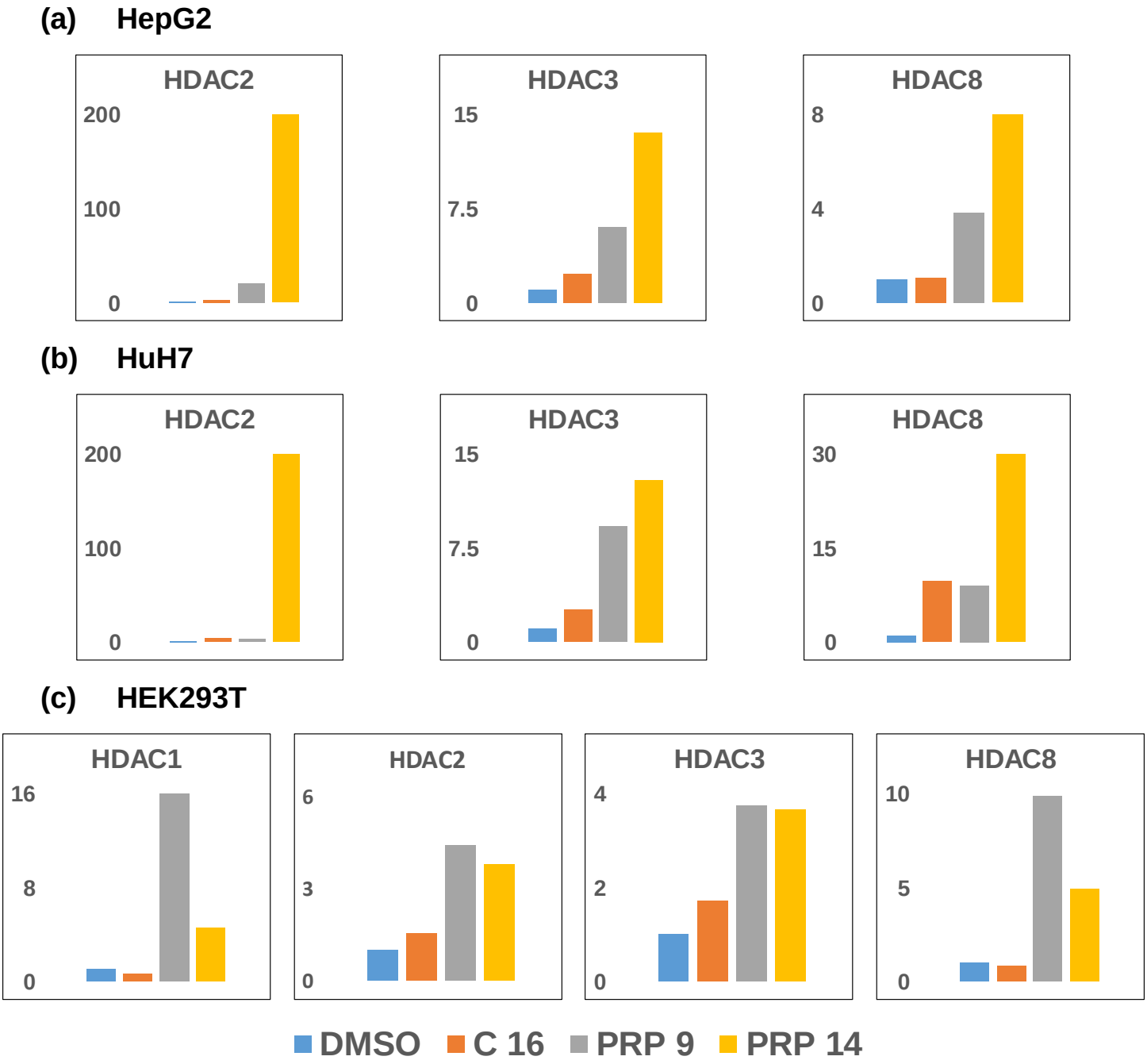


Figure S4 Densitometric analysis of HDAC photolabeling in (a) HepG2 cells (Figure 5a, manuscript), (b) HuH7 cells (Figure 5b, manuscript) and (c) HEK293T cells (Figure 5c, manuscript) by PRPs **9** and **14**. HDAC1 analysis was only done in HEK293T cells where a labeling band for HDAC1 was detected. Photolabeling signal (800 nm) was normalized to the antibody signal (700 nm) of corresponding isoform and GAPDH and calculated as a fold change relative to DMSO signal.

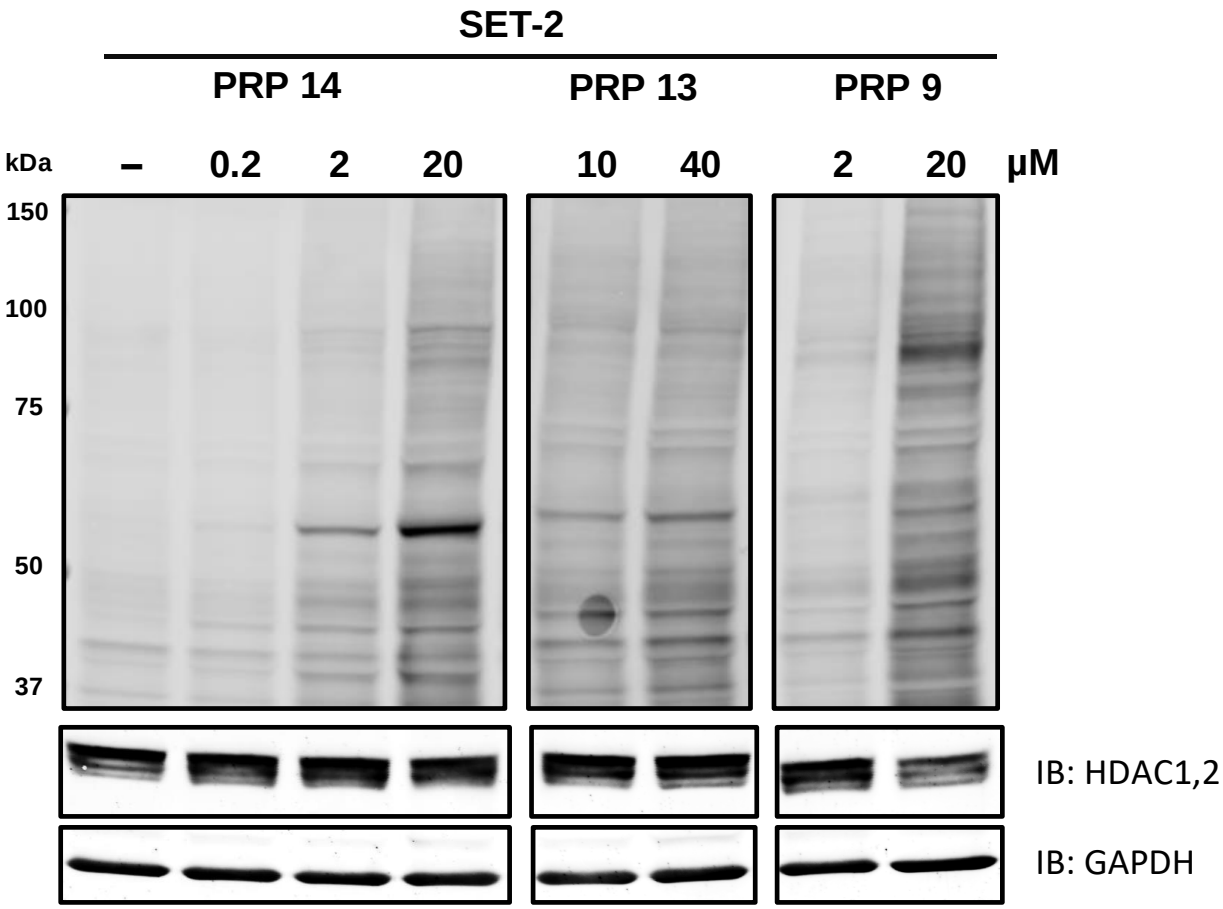


Figure S5. Concentration dependent labeling with PRPs **14**, **13** and **9** in live SET-2 cells.

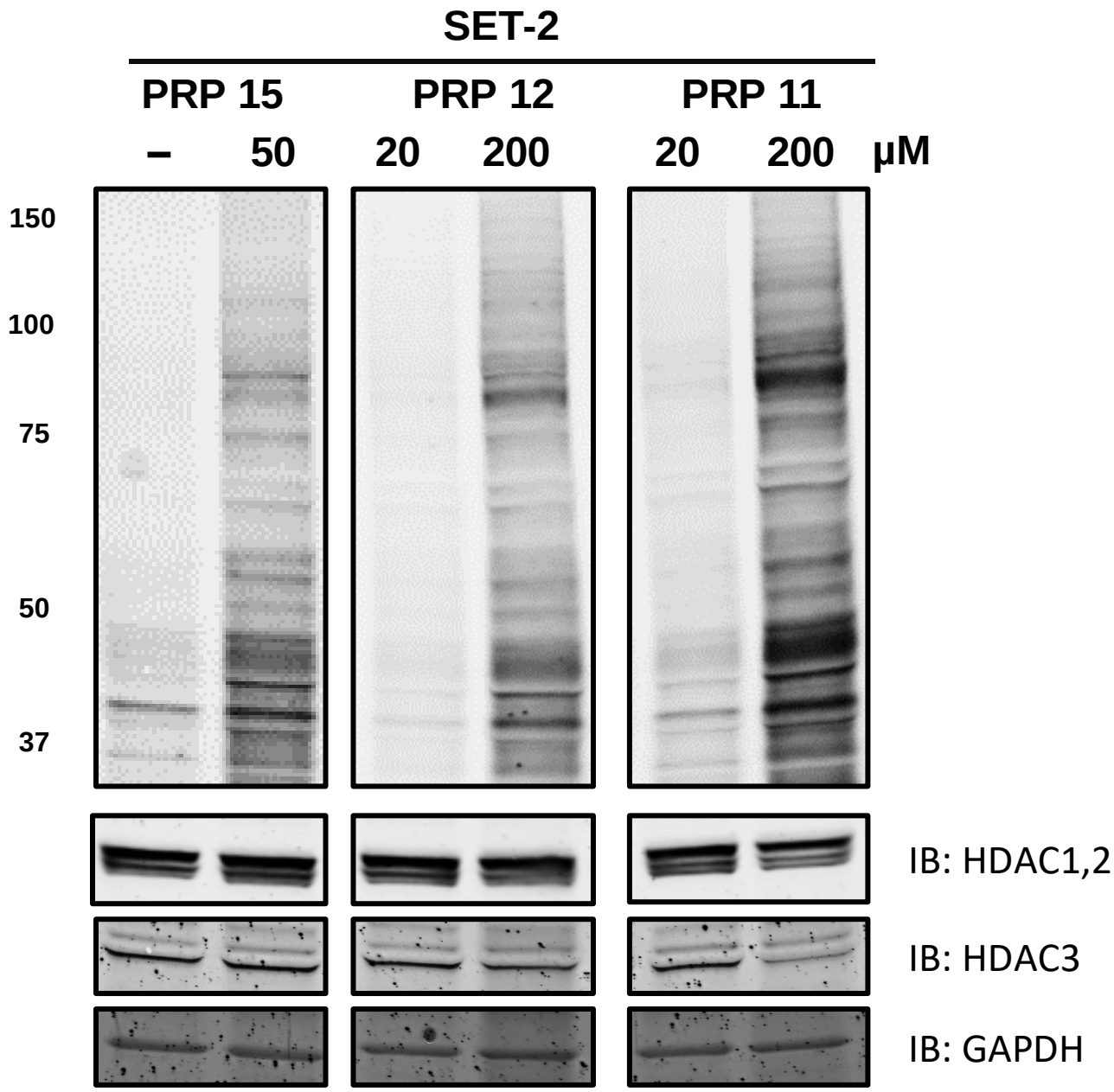


Figure S6. Concentration dependent labeling with PRPs **15**, **12** and **11** in live SET-2 cells.

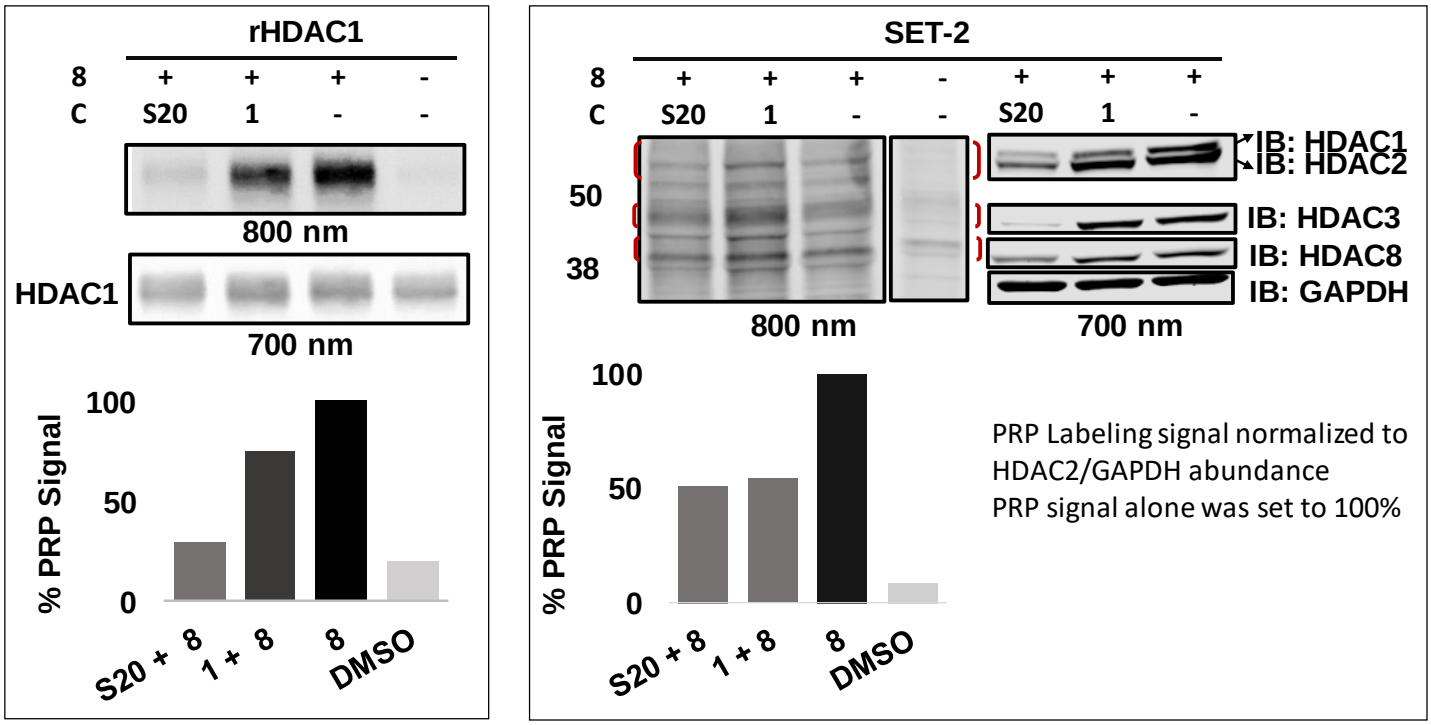
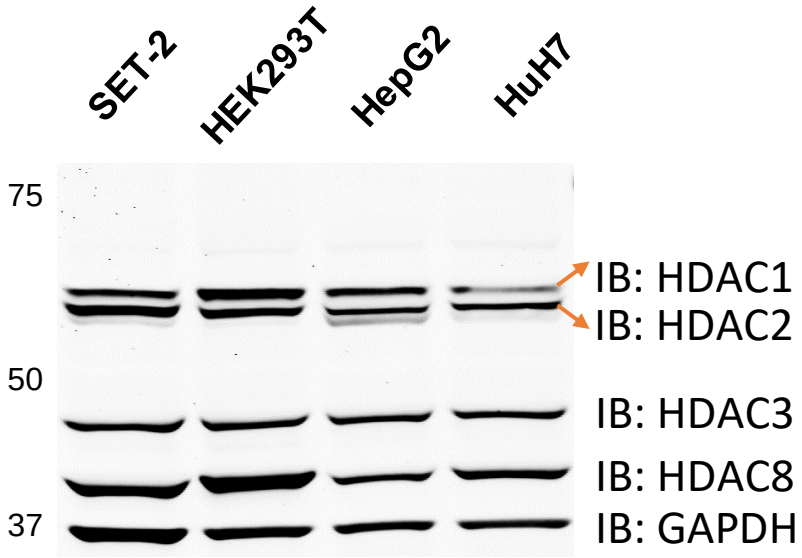


Figure S7. Competition of PRP **8** with **S20** compared to SAHA **1** in rHDAC1 and live SET-2 cells. Densitometry analysis of labeling bands is indicated below each gel section.

Left: Labeling of rHDAC1with PRP **8**. Labeling signal was normalized to HDAC1 immunoblotting signal. Densitometric analysis shows that **S20** is a better competitor (signal is 25% of PRP alone) for **8** than **1** (signal is 75% of PRP alone).

Right: Labeling of live SET-2 cells with PRP **8**. HDAC2 Labeling signal was normalized to HDAC2/GAPDH abundance detected by immunoblotting. Densitometric analysis shows insignificant difference was between **1** and **S20** in SET-2 cells. A decline in HDAC1-3 abundance was observed in case of **S20** competition.

(a)



(b)

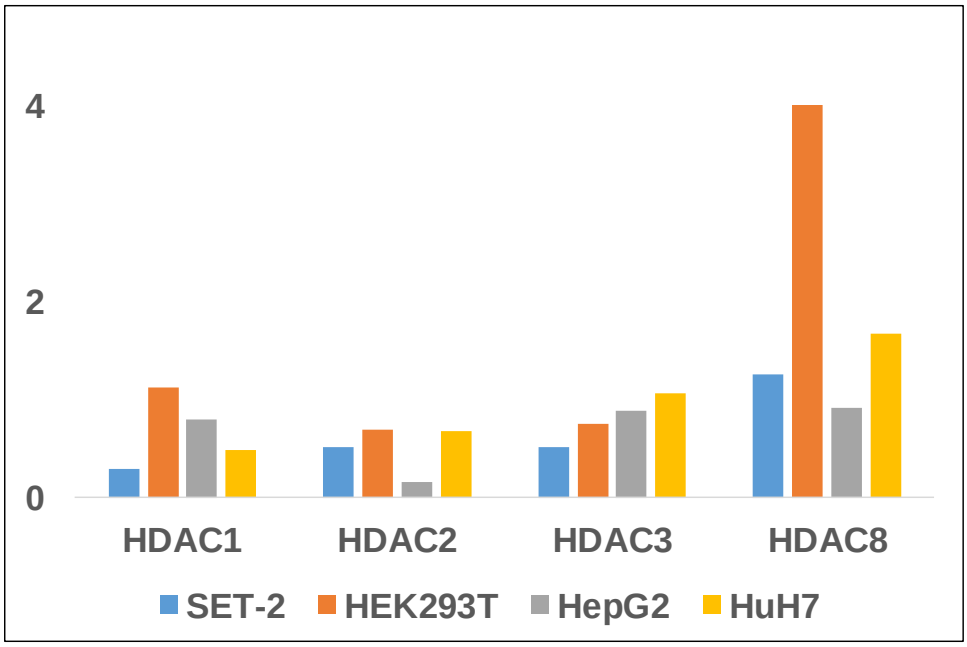


Figure S8 (a) Western blot analysis of HDAC1, 2, 3 and 8 in the four cell lines SET-2, HepG2, HuH7 and HEK293T.

(b) Densitometric analysis of (a), Immunoblotting signal of corresponding isoform normalized to GAPDH signal for each cell line.

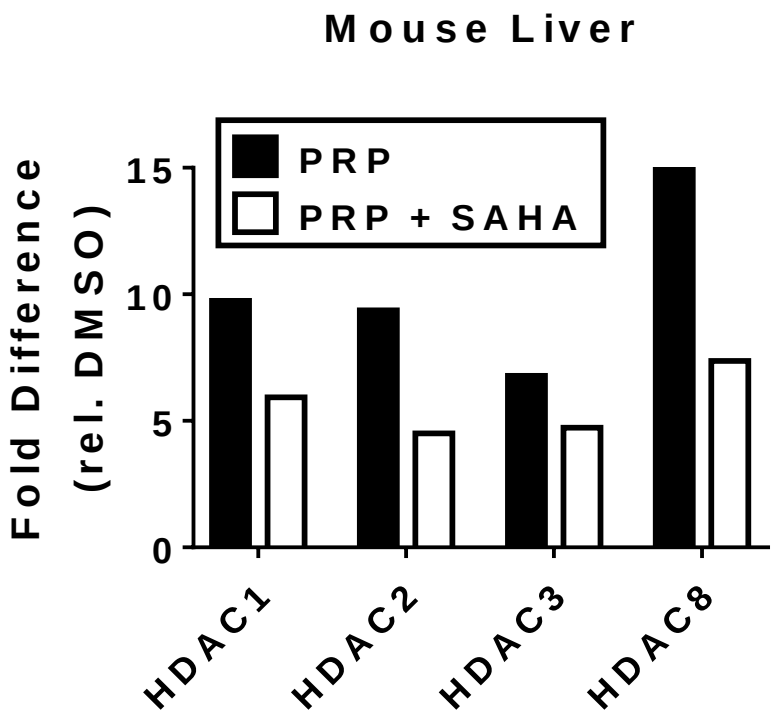


Figure S9 Densitometric analysis of HDACs1-3 and 8 photolabeling in mouse liver tissue (Figure 6, manuscript) calculated as a fold change relative to DMSO signal.

Molecular Modeling Procedure

Coordinates of X-ray models of class I HDAC2 (4LXZ)[7], HDAC8 (1T69)[8] and class II HDAC7 (3ZNR)[9] were downloaded from the protein data bank (PDB). All molecular modeling studies were performed in Molecular Operating Environment (MOE). The proteins were subjected to the “structure preparation” procedure. Hydrogen atoms were added using the Protonate3D algorithm. The structures were aligned and the ligands were replaced with SAHA. The energy of the resulting protein-SAHA complexes was minimized utilizing AMBER12EHT forcefield.[10] The ligands for docking were assigned MMFF94x charges and minimized using the MMFF94x forcefield until the RMS gradient was less than 0.001 kcal/mol/Å^2. The MOE docking module “Dock” was used for docking/scoring using the default parameters and settings. SAHA was used to define the binding site. Docking was performed using the “induced fit” and the “rigid receptor” algorithms, “Triangle Matcher” for placement, “London dG” for scoring of the binding poses after placement, and “GBVI/WSA dG” for rescoring of the resulting poses. The hydroxamic acid portion of SAHA was used as a template for placement.

Water/octanol partition coefficients SlogP and logD, solubility logS, and topological surface area (TPSA) parameters were calculated in MOE software.

Synthesis Procedure and Compounds Characterization:

General Procedure (A) for reductive amination: A solution of the aldehyde (1 equivalent) in anhydrous DCM (5 mL/mmol) was added to a solution of the amine (1 equivalent) in anhydrous DCM (5 mL/mmol) in a round bottom flask containing oven–dried 4 Å molecular sieves (0.1 g/10 mL) and stirred at room temperature (rt) for 6–18 h under nitrogen atmosphere until complete formation of imine on as monitored by TLC. Then, the reaction mixture was placed in an ice bath, diluted with anhydrous methanol (10 mL/mmol), and sodium tetrahydroborate (4 equivalents) was added portionwise with 10 min intervals over 30 min and stirred for an additional 3–6 h. Molecular sieves were filtered under vacuum and the solvent was evaporated. Water (10 mL/mmol) was added to the residue and pH adjusted to ca. 10–12 and extracted 3 times with equal volume of EtOAc. Combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by silica gel chromatography eluting 10–50% EtOAc/hexanes to give the secondary amine.

General Procedure (B) for amide coupling: To a stirred solution of the acid (1 equivalent) in anhydrous chloroform (10 mL/mmol) in a round bottom flask was added EDC.HCl (1.5 equivalent), HOBt (1.1 equivalent), DMAP (1.1 equivalent) and triethylamine (1.5 equivalent) then stirred for 30 min at rt under nitrogen atmosphere. Then, the amine (1.25 equivalent) was added and reaction mixture was stirred for 6–18 h until completion as verified by TLC. The solvent was then evaporated in vacuo, water was added to the residue and pH adjusted as necessary then extracted 3 times with DCM or EtOAc (10 mL/mmol). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography using 10–35% EtOAc/hexanes to afford the amide product.

General Procedure (C) for alkylation: To a solution of the secondary amine (1 equivalent) in anhydrous acetonitrile (10 mL/mmol) in a round bottom flask, oven–dried potassium carbonate (3 equivalents) was added and the suspension was stirred for 30 min at rt under nitrogen. Then, the alkyl bromide (3 equivalents) was added portionwise and the reaction mixture was stirred, monitored for completion by TLC and more potassium carbonate and/or alkyl bromide was added as necessary. The solvent was evaporated, the residue was diluted with water (10 mL/mmol) and pH adjusted to ca. 10–12 and extracted with DCM (3×10 mL/mmol). The combined DCM layers were concentrated, washed with saturated sodium bicarbonate solution (15 mL/mmol) and brine (5 mL/mmol) sequentially then dried over anhydrous sodium sulfate and solvent evaporated in vacuo. The crude product was purified by silica gel chromatography if needed eluting a gradient of EtOAc/hexanes.

General Procedure (D) for ester hydrolysis:

D–1: To a solution of the ester (1 equivalent) in tetrahydrofuran (20 mL/mmol), lithium hydroxide (5 equivalent) in water (10 mL/mmol ester) was added and stirred at rt for 4–120 h. After complete hydrolysis as monitored by TLC, the reaction mixture was concentrated in vacuo, acidified with 2N hydrochloric acid to pH ca. 1–5 by 1 M HCl, placed on ice-bath and diluted with ice-cooled water. The precipitated acid was filtered, and the residue washed with ice-cooled EtOAc and the aqueous solution was extracted with EtOAc (3×10 mL/mmol). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to afford the corresponding carboxylic acid that was used in the next steps without further purification.

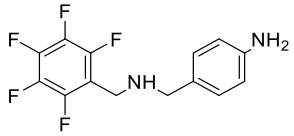
N.B. Esters **39** and **47** were poorly soluble in THF/water, so dioxane was added to give a THF/water/dioxane mixture in a ratio of 6:3:1 to ensure their solubility.

D–2: To a solution of the ester (1 equivalent) in methanol (20 mL/mmol), sodium hydroxide (5 equivalent) in water (10 mL/mmol ester) was added and stirred in a round bottom flask at rt for 4–10 h. After complete hydrolysis as monitored by TLC, the reaction mixture was concentrated in vacuo, acidified with 2N hydrochloric acid to pH ca. 1–5, diluted with brine and extracted with EtOAc (2×10 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to afford the corresponding carboxylic acid that was used in next steps without further purification.

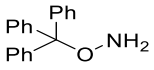
General Procedure (E) for azidation: To a solution of the pentafluorophenyl derivative (1 equivalent) in anhydrous dimethylformamide (5 mL/mmol), sodium azide (2 equivalent) and tetrabutylammonium azide (0.1 equivalent) were added in a sealed pressure vessel and protected from light by tin foil wrap. The reaction mixture was stirred at 50–80 °C for 17–22 h. After completion as monitored by LC–MS (both product and starting material have the same retention factor (R_f) on TLC and time of retention (RT) on LC), reaction mixture was allowed to cool to rt, poured in an ice/water mixture and extracted with EtOAc (2×10 mL). The organic extract was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude was purified immediately by short silica gel column if necessary eluting 30±10% EtOAc/hexanes isocratically. The product was stored under nitrogen in an air-tight container at –20 °C untill the next step.

General Procedure (F) for detritylation: To a stirred solution of the tritylhydroxamate (1 equivalent) in anhydrous DCM (20 mL/mmol), magnesium bromide (10 equivalent) was added and stirred at rt under nitrogen in a tin foil wrapped round bottom flask for 0.5–6 h. After completion as monitored by TLC, the reaction mixture was poured to an ice–cooled water (20 mL/mmol), pH adjusted to ca. 7–9 and extracted with EtOAc (3×20 mL). Combined organic extracts were dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was purified either by silica–gel chromatography eluting 0–10% methanol in DCM or C_{18}–modified silica eluting 0–10% methanol in water to yield the hydroxamate.

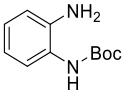
- **N.B.** Extra peaks in the ^{19}F-NMR spectrum arise from residual starting material of azidation reaction which is not separable from the azide product
- **N.B.** ^{1}H NMRs of the *o*-aminoanilide PRPs **14**, **13** and intermediates of their synthesis indicate presence of ca. 10/90 E*/Z* isomers around the C-N amide bond.



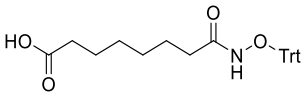
4-((((Perfluorophenyl)methyl)amino)methyl)aniline (18). Following general procedure (A), perfluorobenzaldehyde (1.0 g, 5.1 mmol) was reacted with 4-(aminomethyl)aniline **18** (0.62 g, 5.1 mmol) for 18 h then with sodium tetrahydroborate (0.77 g, 20.4 mmol) for 4 h. Reaction workup pH was adjusted to ca. 12 and the aqueous layer was extracted with EtOAc (3×25 mL). The crude product was purified by silica gel chromatography eluting 10–50% EtOAc/hexanes to give **18** as a yellow solid (0.93 g, 60% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 6.95 (s, 2H), 6.49 (s, 2H), 4.89 (s, 2H), 3.74 (s, 2H), 3.50 (s, 2H), 2.40 (s, 1H). The amine peaks were confirmed by D_2O exchange. ^{13}C NMR (101 MHz, DMSO–d_6) δ 147.68, 146.47, 138.24, 135.94, 129.00, 127.37, 114.64, 113.96, 52.19, 52.13. ^{19}F NMR (376 MHz, DMSO–d_6) δ –143.73 (d, J = 23.9 Hz, 2F), –157.32 (t, J = 21.9 Hz, 1F), –163.39 (t, J = 23.1 Hz, 2F).



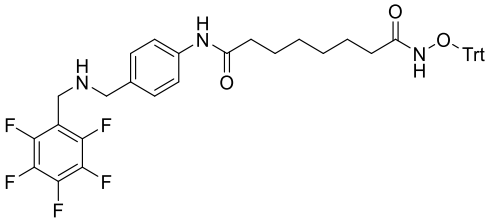
***O*-tritylhydroxylamine (19).** Following a previously reported procedure[11] in two step synthesis: reaction of trityl chloride (8.4 g, 30 mmol) and *N*-hydroxyphthalimide (4.9 g, 30 mmol) gave the *N*-trityloxyphthaimide (10 g, 24.7 mmol) that was reacted in the next step with hydrazine hydrate (2.6 mL, 51.2 mmol). Final product was purified by recrystallization from isopropanol to give **19** as yellowish white crystals (6 g, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.3 Hz, 6H), 7.41–7.29 (m, 9H), 4.95 (bs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.30, 128.88, 127.90, 127.27, 90.85. ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.30, 128.88, 127.90, 127.27, 90.85.



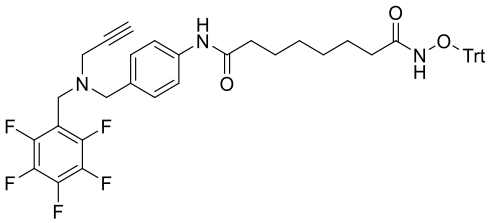
***tert*–butyl (2–aminophenyl)carbamate (20).** di–*tert*–butyl dicarbonate (2.22 g, 10.19 mmol) solution in methanol (10 mL) was added dropwise to *O*–phenylenediamine (1 g, 9.26 mmol) solution in methanol (10 mL) over 45 min. The reaction was stirred at rt for 24 h. The solvent was evaporated in vacuo and the crude product purified by silica gel chromatography eluting 10–50% EtOAc/hexanes to afford the desired product **20** as white shiny crystals (1.8 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.80 (dd, *J* = 12.4, 7.8 Hz, 2H), 6.26 (bs, 1H), 3.76 (bs, 2H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.86, 139.95, 126.16, 124.80, 119.65, 117.63, 80.54, 28.34.



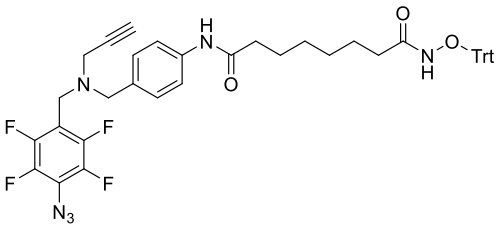
8–oxo–8-((trityloxy)amino)octanoic acid (21). Step 1: Following general procedure (B), suberic acid monomethyl ester (0.72 mL, 4 mmol) was coupled with **19** (1.37 g, 5 mmol) to give methyl 8–oxo–8-((trityloxy)amino)octanoate (**21a)** as a white solid (1.5 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (bs, 1H), 7.60–7.40 (m, 3H), 7.36 (s, 12H), 3.68 (s, 3H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.71–1.46 (m, 4H), 1.36–1.10 (m, 4H), 1.11–0.99 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.23, 170.39, 141.19, 129.07, 128.15, 93.48, 51.46, 33.99, 28.74, 24.71. **Step 2:** Following general procedure (D–2), **21a** (1.47 g, 3.3 mmol) was hydrolyzed to the corresponding acid **21** which was purified as a white solid (1.3 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (bs, 1H), 7.61–7.39 (m, 3H), 7.36 (s, 12H) 2.30 (t, *J* = 7.4 Hz, 2H), 1.57 (dt, *J* = 15.2, 7.0 Hz, 4H), 1.37–1.14 (m, 4H), 1.07 (d, *J* = 6.1 Hz, 2H).



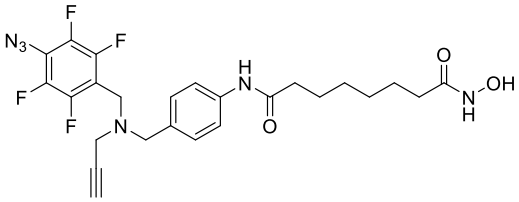
***N*^{1}-(4-((((perfluorophenyl)methyl)amino)methyl)phenyl)-*N*^{8}-(trityloxy)octanediamide (23).** Following general procedure (B), the acid **21** (0.6 g, 1.35 mmol) was coupled in 8 h reaction to the amine **19** (0.42 g, 1.39 moles) to produce **23** as a white solid (0.48 g, 50% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.16 (s, 1H), 9.78 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.33 (s, 15H), 7.22 (d, *J* = 8.5 Hz, 2H), 3.76 (s, 2H), 3.62 (s, 2H), 2.23 (t, *J* = 7.4 Hz, 2H), 1.78 (t, *J* = 7.0 Hz, 2H), 1.49 (dt, *J* = 15.0, 7.5 Hz, 2H), 1.17 (dd, *J* = 12.4, 5.3 Hz, 4H), 1.06–0.91 (m, 2H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 192.88, 142.96, 138.45, 129.44, 128.56, 127.98, 119.22, 95.34, 91.49, 74.18, 64.08, 52.04, 36.81, 28.82, 25.15, 19.98. LC–MS (ESI) for $C_{41}H_{38}F_5N_3O_3$ *m/z*: 714.3 $[M-H]^-$.



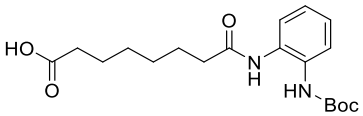
***N*^{1}-(4-((((perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)methyl)phenyl)-*N*^{8}-(trityloxy)octanediamide (25).** Following general procedure (C), **23** (460 mg, 0.64 mmol) was alkylated with propargyl bromide (0.42 mL, 1.9 mmol) for 48 h at rt and the crude product was purified by silica–gel chromatography eluting 25–50% EtOAc/hexanes to give **25** as a yellowish white solid (240 mg, 60% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.16 (s, 1H), 9.82 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.32 (s, 15H), 7.19 (d, J = 8.5 Hz, 2H), 3.76 (s, 2H), 3.61 (s, 2H), 3.28–3.18 (m, 3H), 2.23 (t, J = 7.4 Hz, 2H), 1.77 (t, J = 7.0 Hz, 2H), 1.55–1.39 (m, 2H), 1.16 (dt, J = 14.3, 6.8 Hz, 4H), 0.99 (dd, J = 19.7, 12.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 171.60, 170.76, 142.95, 138.97, 132.70, 129.43, 127.97, 119.26, 92.18, 78.46, 76.90, 60.22, 56.98, 44.61, 41.59, 36.81, 32.44, 28.81, 28.63, 25.43, 25.15. ^{19}F NMR (376 MHz, DMSO–d_6) δ –142.14 (dd, J = 23.8, 7.9 Hz, 2F), –156.31 (t, J = 22.1 Hz, 1F), –163.28 (dd, J = 23.0, 8.6 Hz, 2F). HRMS (ESI–TOF) for $C_{44}H_{40}F_5N_3O_3$ *m/z* [M–H]$^-$ calcd: 752.2917, found: 752.2925.



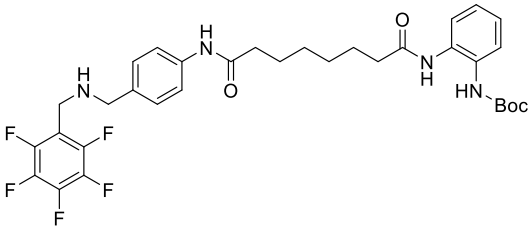
***N*^{1}-(4-(((4–Azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)methyl)phenyl)-*N*^{8}-(trityloxy)octanediamide (27)**. Following general procedure (E), **25** (156 mg, 0.2 mmol) was subject to azidation for 17 h at 75 °C to afford **27** as a yellow oil (70 mg, 45% yield) after purification on a short silica gel column eluting 25% EtOAc/hexanes. ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.16 (s, 1H), 9.82 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.30 (dd, J = 8.7, 5.7 Hz, 15H), 7.18 (d, J = 8.5 Hz, 2H), 3.75 (s, 2H), 3.60 (s, 2H), 3.25 (t, J = 2.2 Hz, 1H), 3.23 (d, J = 2.0 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.77 (t, J = 6.9 Hz, 2H), 1.49 (dt, J = 15.0, 7.5 Hz, 2H), 1.16 (dt, J = 14.5, 6.6 Hz, 4H), 0.99 (dt, J = 15.5, 7.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 171.59, 170.76, 142.95, 138.94, 132.73, 129.43, 127.97, 119.27, 92.18, 78.48, 76.89, 56.93, 44.75, 41.67, 36.81, 32.44, 28.82, 28.63, 25.43, 25.15. ^{19}F NMR (376 MHz, DMSO–d_6) δ –143.02 (dd, J = 22.6, 9.8 Hz, 2F), –152.94 (dd, J = 22.6, 9.8 Hz, 2F). MS (ESI) *m/z*: 775.25 [M−H]$^-$.



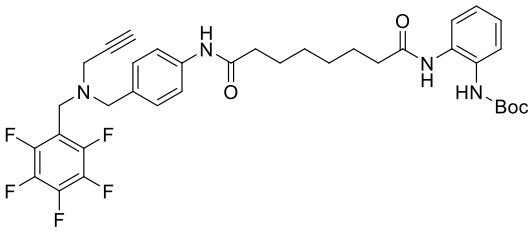
***N*^{1}-(4-(((4–Azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)methyl)phenyl)-*N*^{8}–hydroxyoctanediamide (9)**. Following general procedure (F), **27** (70 mg, 0.09 mmol) was detritylated to give PRP **9** as a light brown solid (20 mg, 42% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.33 (s, 1H), 9.85 (s, 1H), 8.65 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 3.75 (s, 2H), 3.60 (s, 2H), 3.25 (d, J = 2.0 Hz, 1H), 3.23 (s, 2H), 2.28 (t, J = 7.4 Hz, 2H), 1.94 (t, J = 7.4 Hz, 2H), 1.52 (ddd, J = 30.9, 13.8, 6.8 Hz, 4H), 1.27 (dd, J = 9.9, 6.8 Hz, 4H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 171.60, 169.52, 138.94, 132.74, 129.45, 119.28, 78.48, 76.89, 56.93, 44.75, 41.67, 36.81, 32.70, 28.89, 25.51. ^{19}F NMR (376 MHz, DMSO–d_6) δ –143.03 (dd, J = 22.6, 9.7 Hz, 2F), –152.95 (dd, J = 22.5, 9.8 Hz, 2F). HRMS (ESI–TOF) for $C_{25}H_{26}F_4N_6O_3$ *m/z* [M+H]$^+$ calcd: 535.2076, found: 535.2077.



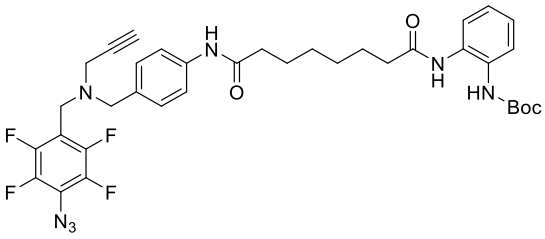
8-((2-((*tert*–butoxycarbonyl)amino)phenyl)amino)-8–oxooctanoic acid (22). Step 1: Following general procedure (B), suberic acid monomethyl ester (0.36 mL, 2 mmol) was coupled with **20** (0.46 g, 2.2 mmol) to give methyl 8-((2-((*tert*–butoxycarbonyl)amino)phenyl)amino)-8–oxooctanoate **(22a)** as a colorless oil (0.76 g, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (bs, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 6.8 Hz, 1H), 7.16 (quint, *J* = 7.9 Hz, 2H), 6.93 (bs, 1H), 3.68 (s, 3H), 2.35 (dt, *J* = 17.6, 7.4 Hz, 4H), 1.74 (dd, *J* = 14.5, 7.2 Hz, 2H), 1.65 (dd, *J* = 13.8, 6.9 Hz, 2H), 1.53 (s, 9H), 1.40 (dd, *J* = 4.6, 1.4 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.21, 172.13, 154.23, 130.62, 130.14, 126.16, 125.50, 125.41, 124.52, 80.91, 51.50, 37.19, 33.97, 28.75, 28.30, 25.48, 24.73. **Step 2:** Following general procedure (D–2), **22a** (0.76 g, 2.7 mmol) was hydrolyzed to the corresponding acid **22** which was purified as a sticky solid (0.7 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (bs, 1H), 7.58 (bs, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 10.3, 4.7 Hz, 2H), 2.46 – 2.32 (m, 4H), 1.77 (t, J = 7.6 Hz, 2H), 1.66 (dd, J = 14.3, 7.6 Hz, 2H), 1.53 (s, 9H), 1.46 – 1.35 (m, 4H).



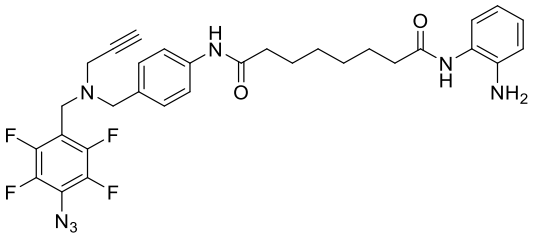
***tert*–butyl (2-(8–oxo–8-((4-((((perfluorophenyl)methyl)amino)methyl)phenyl)amino)octanamido)phenyl)carbamate (24).** Following general procedure (B), the acid **22** (0.45 g, 1.2 mmol) was coupled in 16 h reaction to the amine **19** (0.37 g, 1.25 mmol) to produce the **24** as a viscous oil (0.42 g, 55% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.81 (s, 1H), 9.45 (s, 1H), 8.31 (s, 1H), 7.52 (t, *J* = 8.1 Hz, 3H), 7.41 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.11 (dtd, *J* = 25.6, 7.5, 1.6, 2H), 5.77 (s, 1H), 3.79–3.74 (m, 2H), 3.63 (s, 2H), 2.33 (dt, *J* = 22.3, 7.3 Hz, 4H), 1.71–1.55 (m, 4H), 1.45 (s, 9H), 1.36 (dd, *J* = 7.6, 3.6 Hz, 4H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 172.25, 171.49, 153.53, 138.45, 135.09, 131.56, 130.16, 128.55, 125.51, 125.33, 124.37, 124.16, 119.22, 79.80, 52.03, 36.84, 36.41, 28.98, 28.84, 28.51, 25.57. ^{19}F NMR (376 MHz, DMSO–d_6) δ –143.65 (dd, *J* = 24.1, 8.1 Hz, 2F), –157.13 (t, *J* = 22.1 Hz, 1F), –163.29 (td, *J* = 23.8, 8.0 Hz, 2F). MS (ESI) *m/z*: 649.25 $[M+H]^+$.



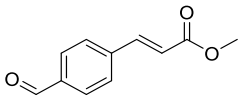
***tert*–butyl (2-(8–oxo–8-((4-((((perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)methyl)phenyl)amino)octanamido)phenyl)carbamate (26).** Following general procedure (C), **24** (0.42 g, 0.65 mmol) was alkylated with propargyl bromide (0.42 mL, 1.9 mmol) for 48 h at rt and the crude product was purified by silica–gel chromatography eluting 25–50% EtOAc/hexanes to give **26** as a yellowish white solid (0.45 g, 65% yield). ^{1}H NMR (400 MHz, DMS–d_6) δ 9.85 (s, 1H), 9.45 (s, 1H), 8.31 (s, 1H), 7.53 (d, *J* = 7.0 Hz, 3H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.23–7.00 (m, 4H), 3.77 (s, 2H), 3.61 (s, 2H), 3 3.27–3.17 (m, 3H), 2.42–2.22 (m, 4H), 1.68–1.55 (m, 4H), 1.44 (d, *J* = 14.9 Hz, 9H), 1.35–1.14 (m, 4H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 172.21, 171.55, 153.46, 144.52, 132.66, 129.47, 125.49, 124.34, 119.24, 79.78, 76.89, 56.99, 44.59, 41.57, 36.83, 28.50, 25.59. MS (ESI) *m/z*: 687.3 $[M+H]^+$ and 685.2 $[M-H]^-$.



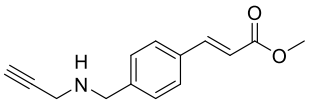
***tert*–butyl (2-(8-((4-(((4–azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)methyl)phenyl)amino)-8–oxooctanamido)phenyl)carbamate (28).** Following general procedure (E), **26** (200 mg, 0.29 mmol) was subject to azidation for 17 h at 75 °C to afford **27** as a yellow oil (50 mg, 25% yield) after purification on a short column eluting 35% EtOAc/Hexanes isocratically. ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.85 (bs, 1H), 9.44 (bs, 1H), 8.30 (bs, 1H), 7.52 (d, *J* = 8.4 Hz, 3H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.13 (td, *J* = 7.8, 1.4 Hz, 1H), 7.07 (td, *J* = 7.6, 1.5 Hz, 1H), 3.75 (s, 2H), 3.60 (s, 2H), 3.25 (t, *J* = 2.1 Hz, 1H), 3.23 (s, 2H), 2.32 (dt, *J* = 20.6, 7.3 Hz, 4H), 1.61 (d, *J* = 5.5 Hz, 4H), 1.45 (s, 9H), 1.39–1.28 (m, 4H) . ^{13}C NMR (101 MHz, DMSO–d_6) δ 172.24, 171.52, 153.53, 146.90, 138.95, 132.73, 131.56, 130.15, 129.44, 125.50, 124.36, 119.27, 79.79, 78.47, 76.89, 60.22, 56.93, 44.75, 36.83, 36.41, 28.97, 28.83, 28.50, 25.54. ^{19}F NMR (376 MHz, DMSO–d_6) δ –143.03 (dd, *J* = 22.6, 9.8 Hz, 2F), –152.95 (dd, *J* = 22.5, 9.7 Hz, 2F). MS (ESI) *m/z*: 710.3 $[M+H]^+$ and 708.1 $[M-H]^-$.



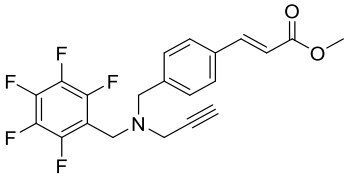
***N*^{1}-(2–aminophenyl)-*N*^{8}-(4-(((4–azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)methyl)phenyl)octanediamide (14).** To a stirred solution of **28** (20 mg, 0.03 mmol) in 1,4–dioxane, 4M hydrochloric acid in 1,4–dioxane (0.5 mL) was added dropwise and stirred for 2 h in an ice–bath. The solvent was evaporated in vacuo and residue was diluted in EtOAc, washed with saturated sodium bicarbonate then 10% NaOH added to pH ca. 9. The EtOAc layer was dried over anhydrous sodium sulfate, solvent evaporated under vacuo and the crude was purified by preparative TLC eluting with 40% EtOAc/hexanes (R_f = 0.2) then extracted with EtOAc and dried in vacuo to give **14** as a yellowish white solid (10 mg, 56% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.34 (s, 1H), 9.53 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 2H), 7.49 (dd, *J* = 14.3, 7.9 Hz, 3H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 4.98 (s, 2H), 3.86 (s, 2H), 3.70 (s, 2H), 3.32 (d, *J* = 6.3 Hz, 3H), 2.33 (dd, *J* = 13.4, 6.7 Hz, 4H), 1.58 (bs, 4H), 1.31 (bs, 4H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 171.62, 142.36, 138.96, 132.75, 129.46, 126.15, 125.76, 124.07, 119.30, 116.65, 116.36, 78.50, 76.90, 56.95, 44.77, 41.68, 36.86, 36.24, 29.00, 25.71, 25.56. ^{19}F NMR (376 MHz, DMSO–d_6) δ –143.01 (dd, *J* = 22.6, 9.6 Hz, 2F), –152.93 (dd, *J* = 22.5, 9.6 Hz, 2F). HRMS (ESI–TOF) *m/z* calcd for $C_{31}H_{31}F_4N_7O_2$ $[M+H]^+$: 610.2548; found: 610.2545.



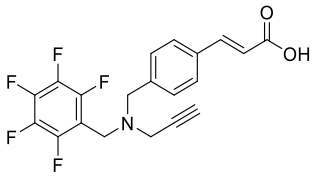
(*E*)-methyl 3-(4–formylphenyl)acrylate (31). To a solution of anhydrous sodium acetate, NaOAc (2.7 g, 33.0 mmol), *p*–bromobenzaldehyde, **29** (5.55 g, 30.0 mmol) and palladium acetate, $Pd(OAc)_2$ (2.6 mg, 0.04% mol) in anhydrous *N*–methyl–2–pyrrolidone, NMP (40 mL), methyl acrylate, **30** (3.9 mL, 43.3 mmol) was introduced via a syringe and the reaction mixture was heated at 120 °C for 60 min under nitrogen. The resulting red solution containing a white precipitate was diluted with water (100 mL) and extracted with EtOAc (2×70 mL). The combined organic layers were washed twice with water, once with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated in vacuo to give **31** as a yellow solid (5.63 g, 99%) which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.04 (s, 1H), 8.02–7.88 (m, 4H), 7.74 (d, *J* = 16.1 Hz, 1H), 6.83 (d, *J* = 16.1 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 193.11, 166.78, 143.52, 140.04, 137.46, 130.32 (2C), 129.42 (2C), 121.39, 52.15.



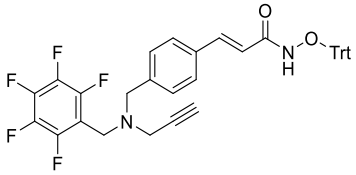
Methyl (*E*)-3-(4-(prop–2–yn–1–ylamino)phenyl)acrylate (32). To a solution of **31** (5.6 g, 29.6 mmol) in anhydrous dichloroethane (70 mL), propargyl amine (2.6 mL, 32.6 mmol) was added. The reaction mixture was stirred under nitrogen at rt for 1 h. Sodium triacetoxyborohydride (12.6 g, 59.3 mmol) was added, reaction was stirred for 16 h. The reaction mixture was concentrated in vacuo, diluted with water (100 mL) and extracted with DCM (3×100 mL). The combined DCM extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by silica gel chromatography eluting 10–70% EtOAc/hexanes to give **32** as a yellow solid (3.6 g, 70%). ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.74–7.60 (m, 3H), 7.37 (d, *J* = 7.7 Hz, 2H), 6.61 (d, *J* = 16.0 Hz, 1H), 3.77 (s, 2H), 3.73 (s, 3H), 3.09 (s, 1H), 2.09 (s, 2H), 1.94–1.88 (m, 1H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 167.20, 144.91, 143.44, 132.92, 128.94 (2C), 128.71 (2C), 117.60, 83.16, 74.29, 51.89, 37.18, 31.15. HRMS (ESI–TOF) *m/z* calcd for $C_{14}H_{15}NO_2$ $[M+H]^+$: 230.1176, found: 230.1167.



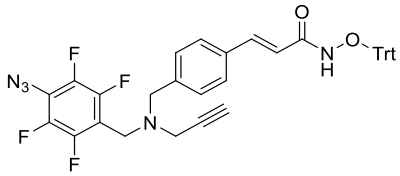
Methyl (*E*)-3-(4-((((perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)methyl)phenyl)acrylate (33). Following general procedure (C), **32** (3.6 g, 16 mmol) was reacted with pentafluorobenzyl bromide (2.5 mL, 16 mmol) for 14 h. The crude product was purified by silica gel chromatography eluting 5–25% EtOAc/hexanes to give **33** as a yellowish white solid (6.41 g, 98%). ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.65 (t, *J* = 12.1 Hz, 3H), 7.34 (d, *J* = 8.1 Hz, 2H), 6.61 (d, *J* = 16.0 Hz, 1H), 3.79 (s, 2H), 3.73 (s, 3H), 3.71 (s, 2H), 3.29–2.25 (m, 3H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 167.13, 144.69, 141.19, 133.52, 129.54 (2C), 128.72 (2C), 117.95, 78.38, 76.97, 57.09, 51.90, 44.76, 41.95. HRMS (ESI–TOF) *m/z* calcd for $C_{21}H_{16}F_5NO_2$ $[M+H]^+$: 410.1174, found: 410.1158.



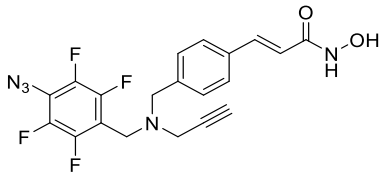
(*E*)-3-(4-((((perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)methyl)phenyl)acrylic acid (34). Following general procedure (D–1), **33** (6.41 g, 15.68 mmol) was hydrolyzed for 20 h. During the aqueous workup, pH was adjusted to ca. 5. The carboxylic acid **34** was obtained as a white solid (6.13 g, 99%). ^{1}H NMR (400 MHz, DMSO–d_6) δ 12.37 (s, 1H), 7.63 (d, 2H, J = 8.0 Hz), 7.56 (d, J = 16.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 6.49 (d, J = 16.0 Hz, 1H), 3.78 (s, 2H), 3.69 (s, 2H), 3.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 168.04, 144.05, 140.87, 133.76, 129.54 (2C), 128.55 (2C), 119.39, 114.93, 87.19, 78.40, 76.97, 57.10, 41.94. HRMS (ESI–TOF) *m/z* calcd for $C_{20}H_{14}F_5NO_2$ $[M+H]^+$: 396.1017, found: 396.0994.



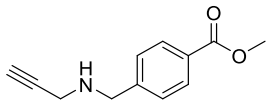
(*E*)-3-(4-((((perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)methyl)phenyl)-*N*-(trityloxy)acrylamide (35). Following general procedure (B), **34** (6.13 g, 15.52 mmol), was coupled to **19** (5.34 g, 19.4 mmol) in a 6 h reaction. The crude product was then purified by silica gel chromatography eluting 0–35% EtOAc/hexanes to give **35** as a white solid (4.45 g, 75%). ^{1}H NMR (400 MHz, DMSO–d_6) δ 10.40 (bs, 1H), 7.62–6.76 (m, 20H), 6.45 (d, J = 14.6 Hz, 1H), 3.76 (s, 2H), 3.66 (s, 2H), 3.25 (s, 3H).^{13}C NMR (101 MHz, DMSO–d_6) δ 170.79, 129.53 (2C), 129.34 (12C), 128.07 (5C), 78.39, 76.95, 60.21, 57.09, 44.75, 41.90. HRMS (ESI–TOF) *m/z* calcd for $C_{39}H_{29}F_5N_2O_2$ $[M–H]^-$: 651.2076, found: 651.2078.



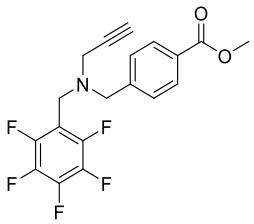
(*E*)-3-(4-(((4–azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)methyl)phenyl)-*N*-(trityloxy)acrylamide (36). Following general procedure (E) at 80 °C for 15 h, **35** (4.45 g, 6.8 mmol) was azidated to **36**. The brown crude product was purified by short silica gel column eluting with 20% EtOAc/ hexanes to give **36** as a shiny yellow solid (0.86 g, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 16.8 Hz, 1H), 7.61–7.03 (m, 19H), 6.10 (d, J = 15.8 Hz, 1H), 3.84 (s, 2H), 3.72 (s, 2H), 3.29 (s, 2H), 2.32 (s, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 170.60, 142.15, 142.09, 141.52, 141.18, 140.01, 139.96, 129.15 (2C), 128.96 (12C), 128.19 (3C), 128.04 (2C), 93.65, 77.59, 73.81, 57.01, 45.07, 41.71. HRMS (ESI–TOF) *m/z* calcd for $C_{39}H_{29}F_4N_5O_2$ $[M–H]^-$: 674.2184, found: 674.2206.



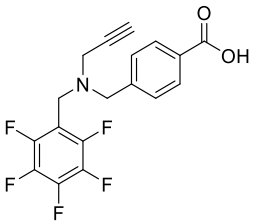
(*E*)-3-(4-(((4–azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)methyl)phenyl)-*N*–hydroxyacrylamide (10). Following general procedure (F) for 30 min, **36** (0.70 g, 1.03 mmol) was detritylated. Upon completion, reaction mixture was concentrated under vacuum, diluted with water, pH adjusted to ca. 8, the precipitate was filtered, washed with 20% EtOAc/hexanes (5×5 mL) and purified by recrystallization from 20% EtOAc/Hexanes. The product was dried under vacuum to yield a **10** as a light brown solid (0.2 g, 50%). The solubility of **10** was limited in DMSO-d_6, CDCl3, acetone-d_6 , MeOD and mixtures thereof. Purity was confirmed by HPLC analysis to be ca. 97%**.** ^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 15.8 Hz, 1H), 7.50 (d, *J* = 7.0 Hz, 2H), 7.37 (d, *J* = 7.7 Hz, 2H), 6.47 (d, *J* = 15.7 Hz, 1H), 5.12 (s, 2H), 3.86 (s, 2H), 3.38 – 3.35 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.82, 146.39, 143.96, 141.23, 138.57, 129.05, 128.86, 127.73, 127.48, 126.88, 126.60, 118.97, 112.04, 77.91, 76.45, 56.55, 48.56, 44.36.^{19}F NMR (376 MHz, DMSO–d_6) δ –143.00 (dd, *J* = 22.3, 9.2 Hz, 2F), –152.91 (dd, *J* = 22.4, 9.5 Hz, 2F). HRMS (ESI–TOF) *m/z* calcd for $C_{20}H_{15}F_4N_5O_2$ $[M+H]^+$: 434.1235, found: 434.1236.



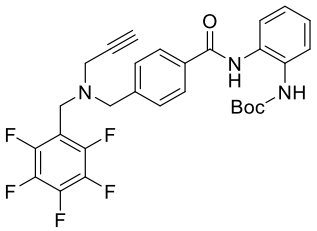
methyl 4-((prop–2–yn–1–ylamino)methyl)benzoate (38). Following general procedure (A), the aldehyde **37** (0.5 g, 3.04 mmol) was reacted with propargylamine (0.2 mL, 3.05 mmol) and after reduction of the imine, the crude product was filtered, washed with 10% sodium bicarbonate then ice–cooled EtOAc (3×5 mL) to give **38** as a white solid (0.5 g, 81% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.92 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 2H), 3.30 (d, *J* = 2.4 Hz, 2H), 3.12–3.05 (m, 1H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 166.66, 146.52, 129.54 (2C), 128.64 (2C), 128.48, 83.12, 74.37, 52.49, 51.36, 37.19. MS (ESI) *m/z*: 204.0 $[M+H]^+$.



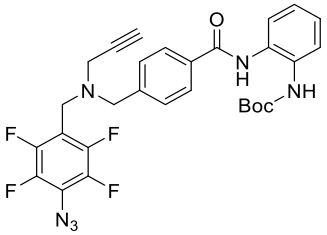
methyl 4-((((perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)methyl)benzoate (39). Following general procedure (C), **38** (0.63 g, 3.1 mmol) was alkylated with perfluorobenzylbromide (0.39 g, 4.6 mmol) for 48 h at rt to give **39** as a white solid (1.00 g, 84% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 2H), 3.76 (s, 2H), 3.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 166.54, 147.06, 144.61, 144.28, 138.52, 129.59 (2C), 129.32 (2C), 129.08, 112.29, 78.31, 77.07, 57.03, 52.54, 44.79, 42.00. ^{19}F NMR (376 MHz, DMSO–d_6) δ –142.10 (dd, *J* = 23.8, 8.6 Hz, 2F), –156.18 (t, *J* = 22.0 Hz, 1F), –163.18 (td, *J* = 23.1, 8.6 Hz, 2F). MS (ESI) *m/z*: 384.1 $[M+H]^+$.



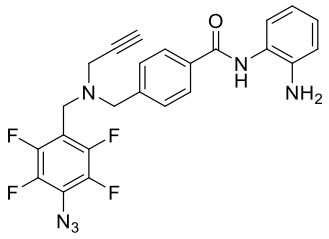
4-((((perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)methyl)benzoic acid (40). Following general procedure (D–1), **39** (1 g, 2.61 mmol) was hydrolyzed in 6:3:1 THF:water:dioxane to **40** after 48 h reaction. Product was obtained as a yellowish white solid (0.98 g, quantitative). ^{1}H NMR (400 MHz, DMSO–d_6) δ 7.88 (d, J = 7.4 Hz, 2H), 7.39 (d, J = 7.5 Hz, 2H), 3.80 (s, 2H), 3.74 (s, 2H), 3.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 167.81, 143.22, 129.69 (2C), 129.02 (2C), 78.36, 77.02, 57.09, 44.81, 41.97. MS (ESI) *m/z*: 370.0 $[M+H]^+$, MS 368.0 $[M-H]^-$.



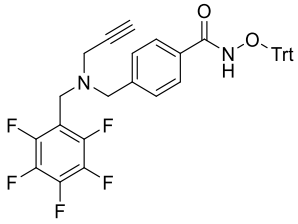
tert–butyl (2-(4-((((perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)methyl)benzamido)phenyl)carbamate (43). Following general procedure (B), **40** (0.4 mg, 1.08 mmol) was reacted with **20** (0.27 g, 1.3 mmol), the crude mixture was purified on silica–gel column eluting 20–40% EtOAc/hexanes to give **43** as yellowish–white solid (0.43 g, 71% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.82 (bs, 1H), 8.69 (bs, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.54 (ddd, J = 9.6, 7.8, 1.6 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.18 (dtd, J = 18.5, 7.4, 1.7 Hz, 2H), 3.81 (s, 2H), 3.78 (s, 2H), 3.31 (d, J = 2.0 Hz, 2H), 3.28 (t, J = 2.2 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 165.49, 153.97, 147.09, 144.66, 142.63, 136.06, 133.69, 132.16, 130.29, 129.12 (2C), 128.01 (2C), 126.48, 126.05, 124.62, 124.37, 112.28, 80.11, 78.36, 77.00, 57.08, 44.70, 41.94, 28.46 (9C). ^{19}F NMR (376 MHz, DMSO–d_6) δ –142.02 (dd, J = 23.9, 7.9 Hz, 2F), –156.13 (t, J = 22.1 Hz, 1F), –163.16 (td, J = 23.6, 7.9 Hz, 2F). MS (ESI) *m/z*: 560.2 $[M+H]^+$ and 558.2 $[M-H]^-$. HRMS (ESI–TOF) *m/z* calcd for $C_{29}H_{26}F_5N_3O_3$ $[M+H]^+$: 560.1967, found: 560.1974.



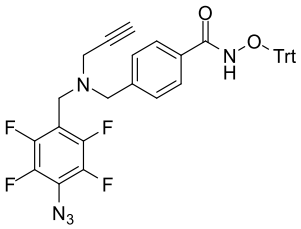
***tert*–butyl (2-(4-(((4–azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)methyl)benzamido)phenyl)carbamate (44).** Following general procedure (E) at 80 °C, **43** (0.3 g, 0.5 mmol) was azidated and the crude product was purified on a short column eluting 20% EtOAc/hexanes to give **44** as a yellow oil (0.17, 59% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.80 (bs, 1H), 8.68 (bs, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.53 (t, J = 8.6 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.23–7.10 (m, 2H), 3.79 (s, 2H), 3.76 (s, 2H), 3.28 (s, 3H), 1.48–1.38 (m, 9H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 165.49, 153.95, 142.65, 133.68, 132.15, 130.27, 129.07 (2C), 128.01 (2C), 126.48, 126.05, 124.61, 124.35, 80.11, 78.37, 77.01, 57.00, 44.80, 41.94, 28.46 (9C). ^{19}F NMR (376 MHz, DMSO–d_6) δ –142.94 (dd, J = 22.6, 9.7 Hz, 2F), –152.85 (dd, J = 22.5, 9.8 Hz, 2F). MS (ESI) *m/z*: 583.2 $[M+H]^+$ and 581.2 $[M-H]^-$.



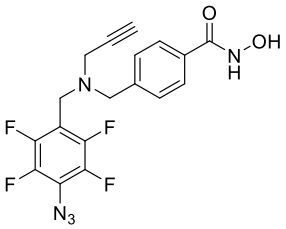
***N*-(2–aminophenyl)-4-(((4–azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)methyl)benzamide (13).** To a stirred solution of **44** (20 mg, 0.03 mmol) in 1,4–dioxane, 4M hydrochloric acid in 1,4–dioxane (0.5 mL) was added dropwise and stirred for 6 h in an ice–bath. The solvent was evaporated in vacuo and the residue was diluted in EtOAc, washed with saturated sodium bicarbonate then 10% NaOH added to pH ca. 9. The EtOAc layer was dried over anhydrous sodium sulfate, solvent evaporated under vacuo and the crude was purified by preparative TLC running 25% EtOAc/hexanes (R_f = 0.15) then extracted with EtOAc and dried in vacuo to give **13** as a yellowish white solid (5 mg, 35% yield). ^{1}H NMR (400 MHz, CDCl3) δ 8.12 (d, *J* = 7.1 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.13 (td, *J* = 7.6, 1.6 Hz, 1H), 6.94 – 6.86 (m, 2H), 4.71 (t, *J* = 4.5 Hz, 1H), 3.87 (t, *J* = 1.6 Hz, 2H), 3.82 (s, 1H), 3.32 (d, *J* = 2.3 Hz, 2H), 2.34 (t, *J* = 2.4 Hz, 1H). ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 9.70 (bs, 1H), 7.98 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 7.1 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 3.83 (s, 2H), 3.79 (s, 2H), 3.61 (s, 2H), 3.31 (s, 3H). ^{13}C NMR (101 MHz, DMSO–*d*$_6$) δ 165.53, 146.96, 144.52, 142.10, 134.03, 130.07, 128.91 (2C), 128.26 (2C), 127.19, 126.97, 124.06, 117.11, 116.86, 78.39, 77.04, 57.00, 44.90, 41.86. ^{19}F NMR (376 MHz, $CDCl_3$) δ –142.02 (dd, *J* = 21.0, 10.2 Hz, 2F), –152.07 (dd, *J* = 21.2, 10.4 Hz, 2F). HRMS (ESI–TOF) *m/z* calcd for $C_{24}H_{18}F_4N_6O$ $[M+H]^+$: 483.1551, found: 483.15590.



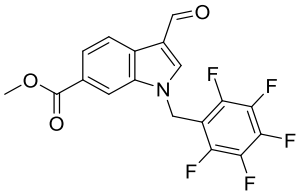
4-((((perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)methyl)-N-(trityloxy)benzamide (41). Following general procedure (B), the reaction of **40** (0.4 mg, 1.08 mmol) and **19** (0.42 g, 1.39 moles) gave **41** as a white solid (0.43 mg, 64% yield). ^{1}H NMR (400 MHz, DMSO–*d*$_6$) δ 10.86 (bs, 1H), 7.50-7.40 (m, 5H), 7.40–7.21 (m, 14H) 3.77 (s, 2H), 3.67 (s, 2H), 3.27–3.20 (m, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.56 (d, J = 6.1 Hz, 5H), 7.45 – 7.29 (m, 13H), 3.83 (s, 2H), 3.72 (s, 2H), 3.24 (d, J = 2.1 Hz, 2H), 2.30 (t, J = 2.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO–*d*$_6$) δ 143.00, 129.62 (6C), 129.36 (2C), 128.70 (2C), 127.95 (6C), 127.87 (3C), 92.87, 78.28, 77.02, 56.89, 44.76, 41.65. ^{19}F NMR (376 MHz, DMSO–*d*$_6$) δ –142.10 (dd, *J* = 23.6, 7.3 Hz, 2F), –156.04 (t, *J* = 22.3 Hz, 1F), –163.08 (td, *J* = 23.4, 7.5 Hz, 2F). MS (ESI) *m/z*: 627.2 $[M+H]^+$ and 625.1 $[M-H]^-$. HRMS (ESI–TOF) *m/z* calcd for $C_{37}H_{27}F_5N_2O_2$ $[M+H]^+$: 627.2065, found: 627.20710.



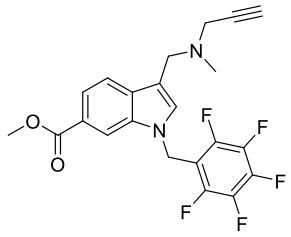
4-(((4–azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)methyl)-*N*-(trityloxy)benzamide (42). Following general procedure (E) at 80 °C for 18 h, **41** (60 mg, 0.1 mmol) was azidated and the crude product was purified on a short column eluting 20% EtOAc/hexanes to give **42** as a yellow oil (30 mg, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.34 (m, 19H), 3.81 (s, 2H), 3.71 (s, 2H), 3.29 (s, 2H), 2.47–2.22 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.77, 131.44, 129.16, 128.93 (8C), 128.06 (8C), 127.87 (3C), 127.60, 127.15, 77.34, 77.02, 76.70, 73.88, 56.82, 45.09, 41.56. ^{19}F NMR (376 MHz, $CDCl_3$) δ -142.13 (dd, *J* = 21.2, 10.3 Hz, 2F), -152.12 (dd, *J* = 21.2, 10.4 Hz, 2F). MS (ESI) *m/z*: 648.2s $[M-H]^-$.



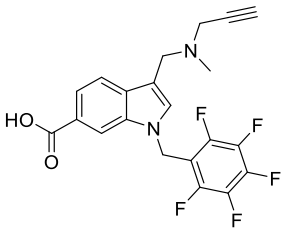
4-(((4–azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)methyl)-*N*–hydroxybenzamide (11). Following general procedure (F) for 30 min, **42** (30 mg, 0.046 mmol) was detritylated to give **11** as a brown solid (6 mg, 32% yield). ^{1}H NMR (400 MHz, DMSO–d_6) δ 11.18 (bs, 1H), 9.00 (bs, 1H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 3.77 (s, 2H), 3.71 (s, 2H), 3.31 (s, 2H), 3.16 (s, 1H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 164.49, 141.79, 132.23, 128.94 (2C), 127.30 (2C), 78.37, 77.01, 56.91, 44.89, 41.84. ^{19}F NMR (376 MHz, DMSO–d_6) δ –143.03 (dd, *J* = 22.9, 9.6 Hz, 2F), –152.85 (dd, *J* = 22.5, 9.2 Hz, 2F). MS (ESI) *m/z*: 408.1 $[M+H]^+$. HRMS (ESI–TOF) *m/z* calcd for $C_{18}H_{13}F_4N_5O_2$ $[M+H]^+$: 408.1078, found: 408.10910.



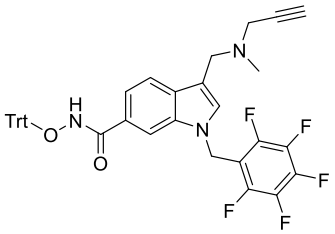
Methyl 3–formyl–1-((perfluorophenyl)methyl)-1*H*–indole–6–carboxylate (46). To a solution of methyl 3–formyl–1*H*–indole–6–carboxylate, **45** (230 mg, 1.13 mmol) and pentafluorobenzylbromide (0.17 mL, 1.13 mmol) in anhydrous dimethylformamide (3 mL) was added sodium hydride (60% mineral oil suspension, 67.9 mg, 1.69 mmol) and stirred at rt for 18 h. Upon completion, the reaction mixture was diluted with water (30 mL), extracted with EtOAc (3×30 mL). The combined organic extracts were washed with dilute sodium bicarbonate (30 mL) and brine (30 mL) then dried over anhydrous sodium sulfate, filtered and solvent removed in vacuo. The product **46** was obtained as orange–yellow solid (430 mg, 99%) and used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.42–8.21 (m, 2H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.94 (s, 1H), 5.52 (s, 2H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.99, 166.75, 146.25, 143.74, 139.31, 138.61, 136.04, 128.33, 126.11, 123.93, 121.62, 118.82, 111.31, 99.59, 51.93, 37.63. HRMS (ESI–TOF) *m/z* calcd for $C_{18}H_{10}F_5NO_3$ $[M+H]^+$: 384.0654, found: 384.0655.



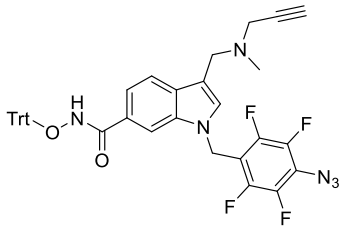
Methyl 3-((methyl(prop–2–yn–1–yl)amino)methyl)-1-((perfluorophenyl)methyl)-1*H*–indole–6–carboxylate (47). To a solution of **46** (360 mg, 0.94 mmol) in dichloroethane (3 mL) was added *N*–methylpropargylamine (0.237 mL, 2.8 mmol) and sodium triacetoxyborohydride (398.3 mg, 1.88 mmol). The reaction mixture was stirred at rt under nitrogen for 5 h then concentrated, diluted with water (3 mL), pH adjusted by 1N sodium hydroxide to ca. 9 and extracted with DCM (3×3mL). The DCM extracts were combined, dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo to yield **47** as an orange oil (400 mg, 97%) which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.88–7.80 (m, 1H), 7.77 (dd, *J* = 7.7, 5.1 Hz, 1H), 7.28 (s, 1H), 5.42 (s, 2H), 3.98 (s,3H), 3.75 (s, 2H), 3.33 (s, 2H), 2.38 (s, 3H), 2.31 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.53, 146.13, 143.72, 136.02, 135.27, 131.44, 129.77, 123.80, 120.54, 119.11, 113.54, 110.94, 109.91, 78.23, 73.01, 51.66, 49.79, 44.32, 41.39, 36.74.



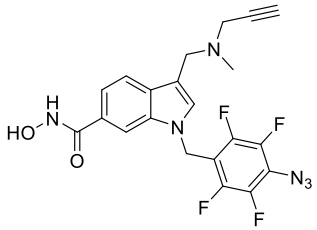
3-((Methyl(prop–2–yn–1–yl)amino)methyl)-1-((perfluorophenyl)methyl)-1*H*–indole–6–carboxylic acid (48). Following general procedure (D–1), **47** (400 mg, 0.92 mmol) was hydrolyzed in 30 mL 6:3:1 THF/water/dioxane using lithium hydroxide (110 mg, 4.6 mmol) in a 120 h reaction to give **48** as an orange brown solid (380 mg, 98%) that was employed for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.69 (d, *J* = 6.5 Hz, 1H), 7.33 (s, 1H), 5.33 (s, 2H), 3.81 (s, 2H), 3.40–3.22 (m, 2H), 2.40 (s, 3H), 2.31 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.21, 146.15, 143.70, 142.31, 139.77, 138.49, 135.96, 135.17, 131.38, 130.90, 124.94, 121.10, 118.59, 111.36, 111.07, 109.84, 76.79, 74.48, 48.68, 43.38, 40.39, 36.70. HRMS (ESI–TOF) *m/z* calcd for $C_{21}H_{15}F_5N_2O_2$ $[M–H]^-$: 421.0981, found: 421.0967.



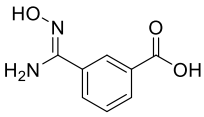
3-((Methyl(prop–2–yn–1–yl)amino)methyl)-1-((perfluorophenyl)methyl)-*N*-(trityloxy)-1*H*–indole–6–carboxamide (49). Following general procedure (B), **48** (400 mg, 1.0 mmol) and **19** (326 mg, 1.2 mmol) were coupled in 6 h reaction. The crude product was purified by silica gel chromatography eluting a gradient of 10–80% EtOAc/hexanes to give **49** as white solid (300 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.76 (s, 1H), 7.66–7.53 (m, 7H), 7.42–7.19 (m, 12H), 7.10 (d, *J* = 7.3 Hz, 1H), 5.33 (s, 2H), 3.70 (s, 2H), 3.28 (s, 2H), 2.33 (s, 3H), 2.28 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.39, 147.25, 143.63, 141.60 (3C), 139.86, 135.27, 130.56, 129.30, 128.52 (6C), 127.63 (6C), 127.39 (3C), 125.89, 119.40, 117.44, 113.39, 108.75, 92.83, 78.16, 78.16, 73.03, 49.75, 44.24, 41.34, 36.75. HRMS (ESI–TOF) *m/z* calcd for $C_{40}H_{30}F_5N_3O_2$ $[M+H]^+$: 680.2331, found: 680.2312.



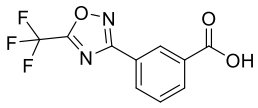
1-(4–Azido–2,3,5,6–tetrafluorobenzyl)-3-((methyl(prop–2–yn–1–yl)amino)methyl)-*N*-(trityloxy)-1*H*–indole–6–carboxamide (50). Following general procedure (E), **49** (300 mg, 0.442 mmol) was azidated at 50 °C for 22 h. After the workup, **50** was given as a brown solid (305 mg, 98%) which was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.75 (s, 1H), 7.60 (s, 5H), 7.43–7.20 (m, 12H), 7.11 (s, 1H), 5.31 (s, 2H), 3.70 (s, 2H), 3.28 (s, 2H), 2.33 (s, 3H), 2.29 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.70, 141.61 (3C), 135.24, 130.57, 129.43, 128.54 (6C), 127.64 (6C), 127.39 (3C), 125.84, 119.35, 117.46, 113.15, 108.76, 92.83, 78.11, 73.10, 49.70, 44.19, 41.29, 36.85. ^{19}F NMR (376 MHz, $CDCl_3$) δ –139.96—140.95 (m, 2F), –149.04 (d, *J* = 21.2 Hz, 2F). HRMS (ESI–TOF) *m/z* calcd for $C_{40}H_{30}F_4N_6O_2$ $[M–H]^-$: 701.2293, found: 701.2295.



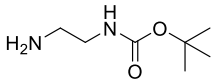
1-(4–Azido–2,3,5,6–tetrafluorobenzyl)-*N*–hydroxy–3-((methyl(prop–2–yn–1–yl)amino)methyl)-1*H*–indole–6–carboxamide (12). Following general procedure (F), **50 (**210 mg, 0.3 mmol) was detritylated in 3 h at rt under nitrogen atmosphere to give **12** as a brown solid (50 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.77 (s, 1H), 7.41 (s, 1H), 7.29 (s, 1H), 5.39 (s, 2H), 3.76 (s, 2H), 3.33 (s, 2H), 2.38 (s, 3H), 2.32 (s, 1H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (bs, 1H), 8.97 (bs, 1H), 7.96 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.5 –7.38 (m, 2H), 5.57 (s, 2H), 3.64 (s, 2H), 3.25 (s, 2H), 3.19 (s, 1H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, DMSO–*d6*) δ 165.78, 135.82, 130.65, 130.35, 126.88, 119.58, 118.13, 112.68, 111.24, 109.47, 79.62, 76.34, 50.40, 44.73, 41.45, 37.59. ^{19}F NMR (376 MHz, DMSO–d_6) δ –143.36 (dd, *J* = 22.3, 9.1 Hz, 2F), –151.78 (dd, *J* = 22.3, 9.2 Hz, 2F). HRMS (ESI–TOF) *m/z* calcd for $C_{21}H_{16}F_4N_6O_2$ $[M–H]^-$: 459.1198, found: 459.1196.



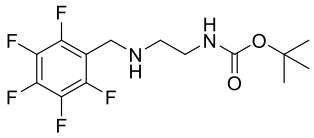
(*Z*)-3-(*N*'–hydroxycarbamimidoyl)benzoic acid (52). To a solution of 3–cyanobenzoic acid **51** (1.00 g, 6.8 mmol) in ethanol (50 mL), 8–hydroxyquinoline (5 mg, 0.03 mmol) was added. A solution of hydroxylamine hydrochloride (0.95 g, 13.6 mmol) in water (8 mL) and sodium carbonate (1.20 g, 10.9 mmol) in water (12 mL) were added successively. The reaction was refluxed for 4 h (85 °C). Upon completion, ethanol was removed under vacuum, the residue was diluted with water and set in an ice–bath. The cooled mixture pH was adjusted to ca. 3.5 using 1 N HCl, the precipitate was filtered, washed with iced water and dried in vacuo to give **52** as a greyish–white solid (500 mg, 41%),. ^{1}H NMR (400 MHz, DMSO–d_6) δ 9.73 (bs, 1H), 8.27 (s, 1H), 7.93 (d, *J* = 6.9 Hz, 1H), 7.88 (d, *J* = 6.9 Hz, 1H), 7.49 (t, *J* = 7.0 Hz, 1H), 5.89 (bs, 2H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 159.26, 150.36, 133.70, 129.63, 129.44, 128.42, 128.39, 126.41. HRMS (ESI–TOF) *m/z* calcd for $C_8H_8N_2O_3$ $[M+H]^+$: 181.0608, found: 181.0603.



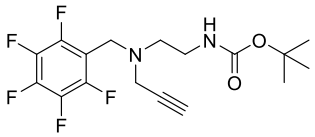
3-(5-(Trifluoromethyl)-1,2,4–oxadiazol–3–yl)benzoic acid (53). A suspension of the benzamidoxime **52** (500 mg, 2.8 mmol) in anhydrous pyridine (8 mL) was cooled in an ice bath. Trifluoroacetic anhydride, TFAA (1.62 mL, 8.34 mmol) was added dropwise over 20 min. The reaction was slowly warmed to rt and further heated to 50 °C for 3 h. The reaction mixture was poured into ice–water and pH adjusted to ca. 4 by 10% hydrochloric acid. The product was extracted by EtOAc and the solvent was removed under reduced pressure. The crude was purified by silica gel chromatography eluting 3–20% EtOAc/hexanes to give **53** as white crystals (200 mg, 25%). ^{1}H NMR (400 MHz, DMSO–d_6) δ 13.42 (bs, 1H), 8.57 (s, 1H), 8.30 (d, J = 7.8 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 168.49, 167.97, 166.35, 133.12, 132.11, 131.44, 130.27, 128.00, 124.99, 120.81. HRMS (ESI–TOF) *m/z* calcd for $C_{10}H_5F_3N_2O_3$ $[M–H]^-$: 257.0179, found: 257.0191.



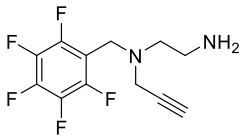
***tert*–Butyl (2–aminoethyl)carbamate (55).** A solution of di–*tert*–butyl dicarbonate (2.5 g, 12 mmol) in 60 mL chloroform was added dropwise to a solution of 1,2–diamimoethane **54** (8.3 mL, 125 mmol) in 125 mL of chloroform over 3 h with vigorous stirring and cooling in an ice bath. The reaction mixture was stirred for additional 16 h at rt. The reaction mixture was concentrated in vacuo then washed with (6×60 mL) of water. The chloroform layer was dried over anhydrous sodium sulfate and evaporated to give **55** as a colorless oil (1.5 g, 80%) which was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (bs, 1H), 3.27–3.11 (m, 2H), 2.80 (dd, J = 7.8, 3.7 Hz, 2H), 1.46 (s, 9H), 1.35 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.19, 79.22, 41.89, 28.40 (9C), 28.37. HRMS (ESI–TOF) *m/z* calcd for $C_7H_{16}N_2O_2$ $[M+H]^+$: 161.1285, found: 161.1284.



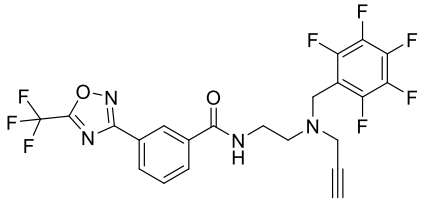
***tert*–Butyl (2-(((perfluorophenyl)methyl)amino)ethyl)carbamate (56)**. Following general procedure (A), pentafluorobenzaldehyde (1.53 g, 7.81 mmol) and **55** (1.4 g, 8.72 mmol) were reacted, then the crude product was purified by silica gel chromatography eluting with 20–50% EtOAc/hexanes to give **56** as a colorless viscous oil (1.5 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (bs, 1H), 3.93 (s, 2H), 3.34–3.15 (m, 2H), 2.80–2.63 (m, 2H), 2.06 (bs, 1H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.65, 143.66, 143.02, 142.67, 104.76, 78.95, 47.66 (2C), 39.72, 27.96 (9C). HRMS (ESI–TOF) *m/z* calcd for $C_{14}H_{17}F_5N_2O_2$ $[M+H]^+$: 341.1283, found: 341.1254.



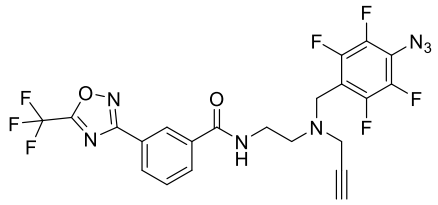
***tert*–Butyl (2-(((perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)ethyl)carbamate (57).** Following general procedure (C), **56** (500 mg, 1.47 mmol) was alkylated with propargyl bromide (80% w/v in toluene, 0.48 mL, 4.41 mmol) in 24 h reaction. After the workup, **57** was obtained an orange solid (550 mg, 98%) which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (s, 1H), 3.86–3.76 (m, 2H), 3.37 (d, *J* = 2.5 Hz, 2H), 3.24 (t, *J* = 5.6 Hz, 2H), 2.72 (t, *J* = 5.3 Hz, 2H), 2.25 (d, *J* = 2.4 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.91, 148.30, 148.03, 130.49, 108.67, 79.22, 77.45, 73.64, 52.24, 44.68, 41.88, 37.70, 28.34 (9C). HRMS (ESI–TOF) *m/z* calcd for $C_{17}H_{19}F_5N_2O_2$ $[M+H]^+$: 379.1439, found: 379.1426.



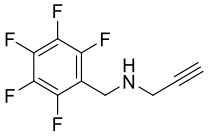
***N*^{1}-((perfluorophenyl)methyl)-*N*^{1}-(prop–2–yn–1–yl)ethane–1,2–diamine (58).** To a solution of **57** (550 mg, 1.45 mmol) in 1,4–dioxane (6 mL) was added 4M hydrochloric acid in 1,4–dioxane (10 mL) and stirred for 3 h at rt. The solvent was then evaporated under vacuo to yield a brown sticky solid (453 mg, 99%). The amine hydrochloride salt was converted into the free amine base by adding trimethylamine (0.2 mL) to a DCM suspension till complete dissolution then the solvent was evaporated yielding **58** as a light brown solid (400 mg). ^{1}H NMR (400 MHz, DMSO–d_6) δ 4.37 (bs, 2H), 3.84 (s, 2H), 3.48 (s, 2H), 3.29 (s, 1H), 2.91 (dd, *J* = 11.3, 5.6 Hz, 2H), 2.79 (t, *J* = 6.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO–d_6) δ 110.93, 77.63, 76.91, 49.18, 44.44, 41.55, 36.10. HRMS (ESI–TOF) *m/z* calcd for $C_{12}H_{11}F_5N_2$ $[M+H]^+$: 279.0915, found: 279.0907.



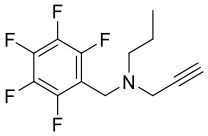
***N*-(2-(((Perfluorophenyl)methyl)(prop–2–yn–1–yl)amino)ethyl)-3-(5-(trifluoromethyl)-1,2,4–oxadiazol–3–yl)benzamide (59).** Following general procedure (B), **53** (200 mg, 0.8 mmol) and **58** (214 mg, mmol) were coupled in 20 h. During the workup pH was made ca. 9, extracted with DCM (3×10 mL). The crude product was purified by silica gel chromatography eluting 5–35% EtOAc/hexanes to give **59** as a white solid (220 mg, 55%). ^{1}H NMR (400 MHz, CDCl3) δ 8.47 (s, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 6.74 (bs, 1H), 3.89 (s, 2H), 3.63 (dd, *J* = 11.0, 5.3 Hz, 2H), 3.43 (d, *J* = 2.2 Hz, 2H), 2.94 (t, *J* = 5.7 Hz, 2H), 2.34 (t, *J* = 2.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.61, 166.01, 135.56, 130.90, 130.44, 129.65, 125.76, 125.41, 77.22, 74.05, 51.65, 44.89, 41.68, 36.99.^{19}F NMR (376 MHz, $CDCl_3$) δ -65.39 (s, 3F), -142.42 (dd, *J* = 22.0, 8.1 Hz, 2F), -154.12 (t, *J* = 20.7 Hz, 1F), -161.62 (dt, *J* = 22.2, 8.1 Hz, 2F). HRMS (ESI–TOF) *m/z* calcd for $C_{22}H_{14}F_8N_4O_2$ $[M+H]^+$: 519.1062, found: 519.1048.



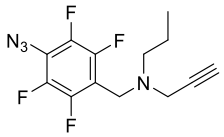
***N*-(2-((4–Azido–2,3,5,6–tetrafluorobenzyl)(prop–2–yn–1–yl)amino)ethyl)-3-(5-(trifluoromethyl)-1,2,4–oxadiazol–3–yl)benzamide (15).** Following general procedure (E), **59** (200 mg, 0.38 mmol) was azidated at 80 °C for 18 h. The crude was purified by a short silica gel column eluting 25% EtOAc/hexanes to give **15** as a white solid (50 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.29 (d, *J* = 7.7 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 6.76 (bs, 1H), 3.88 (s, 2H), 3.63 (dd, *J* = 10.8, 5.2 Hz, 2H), 3.43 (d, *J* = 2.0 Hz, 2H), 2.93 (t, *J* = 5.6 Hz, 2H), 2.34 (t, *J* = 2.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.64, 165.97, 135.57, 130.87, 130.43, 129.63, 125.82, 125.43, 77.22, 74.01, 51.59, 45.00, 41.77, 37.00. ^{19}F NMR (376 MHz, $CDCl_3$) δ –65.37 (s, 3F), –142.81 (dd, *J* = 21.1, 10.3 Hz, 2F), –151.67 (dd, *J* = 21.1, 10.3 Hz, 2F). HRMS (ESI–TOF) *m/z* calcd for $C_{22}H_{14}F_7N_7O_2$ $[M+H]^+$: 542.1170, found: 542.1166.



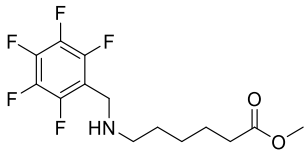
***N*-((perfluorophenyl)methyl)prop-2-yn-1-amine** (**S13**). Following general procedure (A), pentafluorobenzaldehyde (0.89 g, 4.5 mmol) and propargylamine (0.32 mL, 4.9 mmol) were reacted to give **S13** as colorless oil (0.8 g, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (t, *J* = 1.5 Hz, 2H), 3.47 (d, *J* = 2.4 Hz, 2H), 2.26 (t, *J* = 2.4 Hz, 1H), 1.64 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.68, 136.18, 112.89, 81.03, 71.97, 39.47, 37.68. ^{19}F NMR (376 MHz, $CDCl_3$) δ -143.91 (dd, *J* = 22.4, 8.6 Hz, 2F), -155.26 (t, *J* = 20.7 Hz, 1F), -162.08 (dt, *J* = 22.7, 8.8 Hz, 2F). MS (ESI) *m/z*: 236.0 $[M+H]^+$.



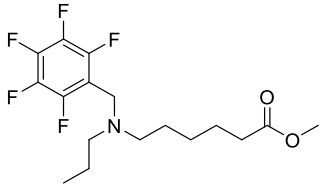
***N*-((perfluorophenyl)methyl)-*N*-propylprop-2-yn-1-amine** (**S14**)**.** Following general procedure (C), **S13** (0.24 g, 1 mmol) was alkylated with propyl bromide (0.27 mL, 3 mmol) and refluxed for 20 h. The crude product was purified on a silica column eluting 0-10% EtOAc/hexanes to give **S14** as a colorless oil (0.15 g, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 2H), 3.40 (d, *J* = 2.3 Hz, 2H), 2.58–2.50 (m, 2H), 2.23 (t, *J* = 2.4 Hz, 1H), 1.58–1.45 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.04, 144.58, 112.16, 78.01, 73.11, 54.98, 44.88, 41.94, 20.56, 11.63. ^{19}F NMR (376 MHz, $CDCl_3$) δ -142.05 (dd, *J* = 22.3, 8.5 Hz, 2F), -155.41 (t, *J* = 20.8 Hz, 1F), -162.48 (td, *J* = 22.7, 8.7 Hz, 2F). MS (ESI) *m/z*: 278.1 $[M+H]^+$.



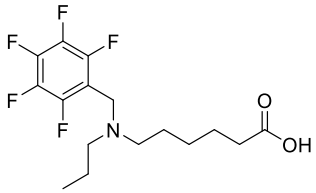
***N*-(4-azido-2,3,5,6-tetrafluorobenzyl)-*N*-propylprop-2-yn-1-amine (16).** Following general procedure (E), SA-02-175 (0.10 g, 0.36 mmol) was azidated to give **SA-02-179** (**16**) as colorless oil (60 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (t, *J* = 1.5 Hz, 2H), 3.39 (d, *J* = 2.3 Hz, 2H), 2.57–2.50 (m, 2H), 2.23 (t, *J* = 2.4 Hz, 1H), 1.57–1.46 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -142.34 (dd, *J* = 21.4, 10.4 Hz, 2F), -152.35 (dd, *J* = 21.3, 10.4 Hz, 2F). MS (ESI) *m/z*: 301.10 $[M+H]^+$. HRMS (ESI–TOF) *m/z* calcd for $C_{13}H_{12}F_4N_4$ $[M+H]^+$: 301.1071, found: 301.1065.



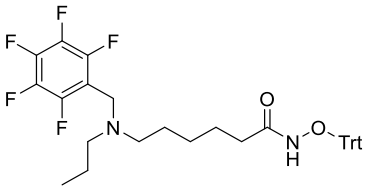
Methyl 6-(((perfluorophenyl)methyl)amino)hexanoate (S15). Following general procedure (A), pentafluorbenzaldehyde, (1.96 g, 10 mmol) and methyl 6-aminohexanoate hydrochloride (1.54 g, 10.6 mmol) were reacted for 16 h then reduced with sodium tetrahydroborate (0.60 g, 16 mmol) for 18 h. The crude product was purified by silica gel chromatography eluting 0-40% EtOAc/hexanes to give **S15** as a colorless liquid (2.6 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 2H), 3.66 (s, 3H), 2.56 (t, *J* = 7.0 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.70–1.56 (m, 2H), 1.48 (m, 2H), 1.40–1.29 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.05, 51.47, 48.57, 40.50, 33.92, 29.54, 26.71, 24.74. ^{19}F NMR (376 MHz, $CDCl_3$) δ -144.78 (dd, *J* = 22.8, 8.7 Hz, 2F), -156.24 (t, *J* = 20.7 Hz, 1F), -162.62 (td, *J* = 22.6, 8.8 Hz, 2F). HRMS (ESI-TOF) *m/z* for $C_{14}H_{16}F_5NO_2$ $[M+H]^+$ calcd: 326.1174, found: 326.1193.



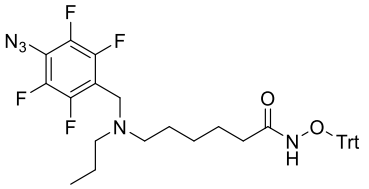
Methyl 6-(((perfluorophenyl)methyl)(propyl)amino)hexanoate (S16). The secondary amine **S15** (0.88 g, 2.7 mmol) was alkylated with propyl bromide (2 mL, 20 mmol) in a sealed pressure vessel for 48 h. The crude product was purified with silica gel chromatography eluting 5-35% EtOAc/hexanes to give **S16** as a glassy solid (0.88 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (d, *J* = 9.6 Hz, 5H), 2.37 (d, *J* = 36.7 Hz, 6H), 1.49 (t, *J* = 59.0 Hz, 8H), 0.87 (s, 3H). MS (ESI) *m/z*: 368.1 $[M+H]^+$.



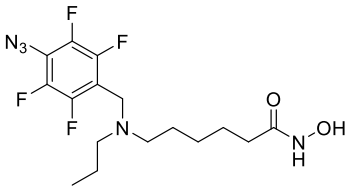
6-(((Perfluorophenyl)methyl)(propyl)amino)hexanoic acid (S17). The tertiary amine **S16** (0.87 g, 2.4 mmol) was hydrolyzed following general procedure (D-1). Upon completion, as monitored by TLC, the reaction was brought to pH ca. 4.5 with 10% hydrochloric acid and extracted with DCM (3×30 mL). The crude product was obtained as white solid and used in the next reaction without further purification (0.76 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 2H), 2.24 (m, 8H), 1.64–1.12 (m, 6H), 0.78 (t, *J* = 6.8 Hz, 3H).



6-(((Perfluorophenyl)methyl)(propyl)amino)-*N*-(trityloxy)hexanamide (S18). Following general procedure (B), **S17** (0.70 g, 2 mmol) was coupled with **19** (0.68 g, 2.5 mmol) The crude product was then purified by silica gel chromatography eluting 5-35% EtOAc/hexanes to give **19** as a white solid (0.91 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.49 (s, 3H), 7.36 (s, 12H), 3.69 (s, 4H), 2.39–2.30 (m, 4H), 1.47 (dd, *J* = 14.3, 7.3 Hz, 2H), 1.35 (s, 2H), 1.27 (d, *J* = 6.8 Hz, 2H), 1.04 (s, 2H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -141.91 (dd, *J* = 22.6, 7.6 Hz, 2F), -155.76 (t, *J* = 20.9 Hz, 1F), -162.24–-162.76 (m, 2F). MS (ESI) *m/z*: 611.3 $[M+H]^+$ and 609.2 $[M-H]^-$.

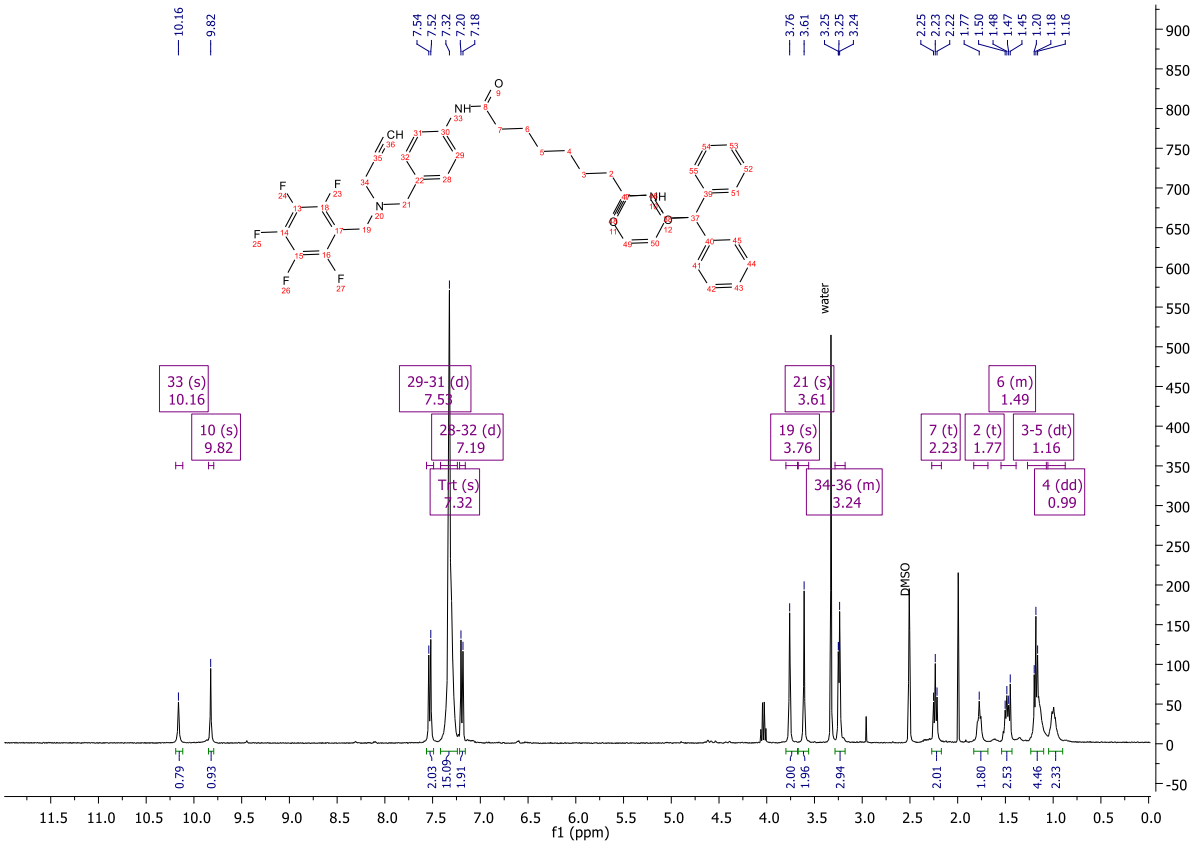


6-((4-Azido-2,3,5,6-tetrafluorobenzyl)(propyl)amino)-*N*-(trityloxy)hexanamide (S19). Following general procedure (E), **S18** (0.45 g, 0.75 mmol) was azidated with sodium azide (0.91 g, 1.5 mmol), tetrabutylammonium azide (0.02 g, 0.077 mmol) at 75 °C for 18 h. The crude brown solid was then passed through a short silica gel column eluting 35% EtOAc/hexanes to give **S19** as a colorless sticky solid (0.19 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.49 (s, 3H), 7.36 (s, 12H), 3.68 (s, 4H), 2.33 (s, 4H), 1.47 (dd, *J* = 13.3, 6.8 Hz, 2H), 1.35 (s, 2H), 1.28 (s, 2H), 1.04 (s, 2H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.05, 128.12, 55.40, 53.28, 44.99, 31.21, 26.80, 26.68, 20.12, 11.77. ^{19}F NMR (376 MHz, $CDCl_3$) δ -142.15 (d, *J* = 11.6 Hz, 2F), -152.39 (d, *J* = 11.4 Hz, 2F). MS (ESI) *m/z*: 634.25 $[M-H]^+$ and 632.15 $[M-H]^-$.

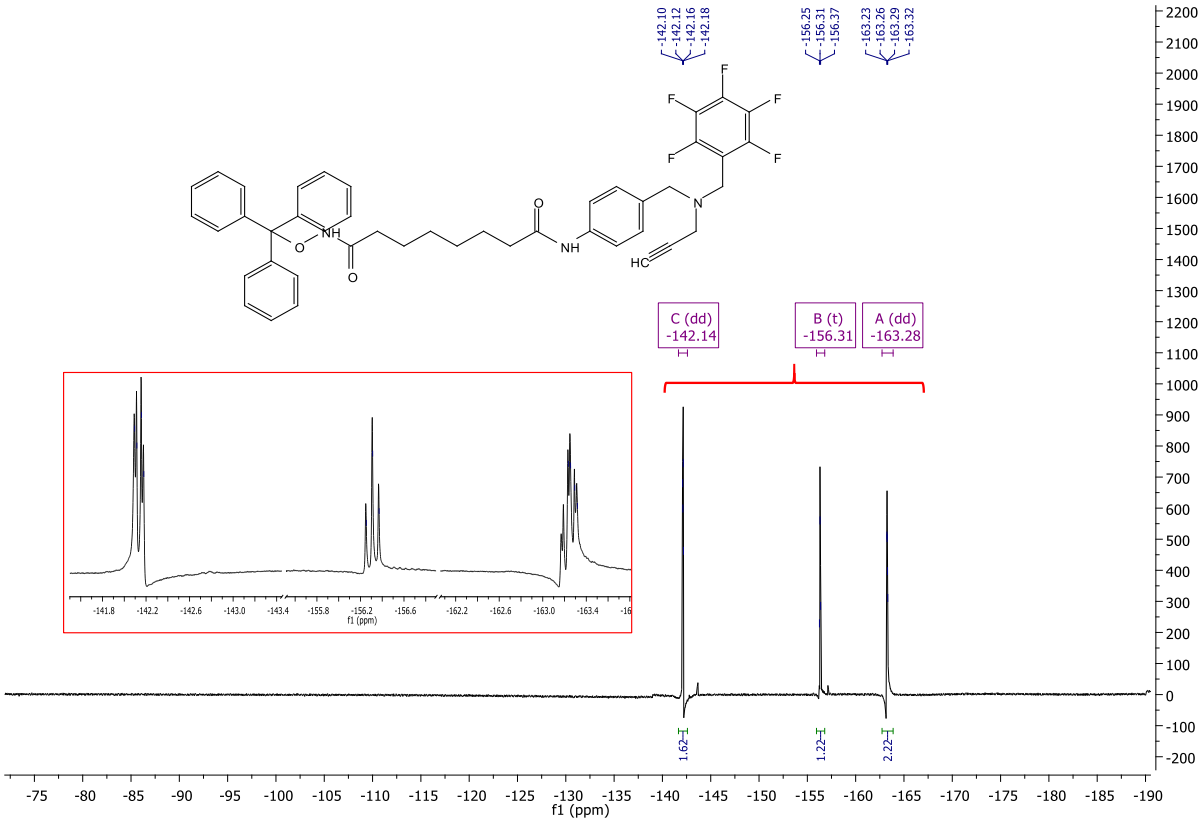


6-((4-Azido-2,3,5,6-tetrafluorobenzyl)(propyl)amino)-*N*-hydroxyhexanamide (S20). Following general procedure (F), **S19** (0.19 g, 0.3 mmol) in DCM was detritylated to give **S20** as a sticky colorless solid (0.09 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.65 (s, 1H), 3.67 (s, 2H), 2.33 (s, 4H), 1.91 (s, 2H), 1.42 (s, 4H), 1.22 (s, 2H), 0.81 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.49, 146.72, 141.72, 139.08, 129.43, 128.00, 113.09, 55.25, 53.15, 45.21, 32.75, 26.77, 26.60, 25.46, 20.11, 12.10. ^{19}F NMR (376 MHz, DMSO-d_6) δ -143.34 (dd, *J* = 22.9, 9.3 Hz, 2F), -152.75 (dd, *J* = 22.9, 9.1 Hz, 2F). HRMS (ESI–TOF) *m/z* calcd for $C_{16}H_{21}F_4N_5O_2$ $[M+H]^+$: 392.1704, found: 392.1705.

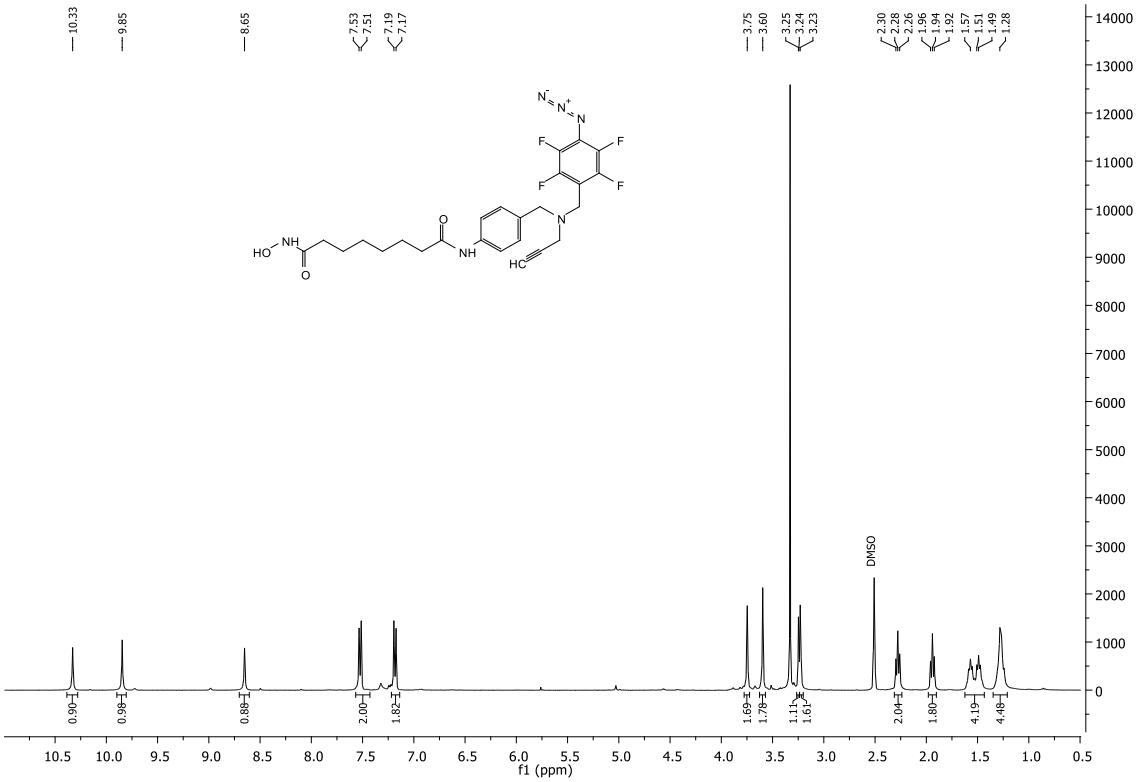
^{1}H NMR for intermediate **25**



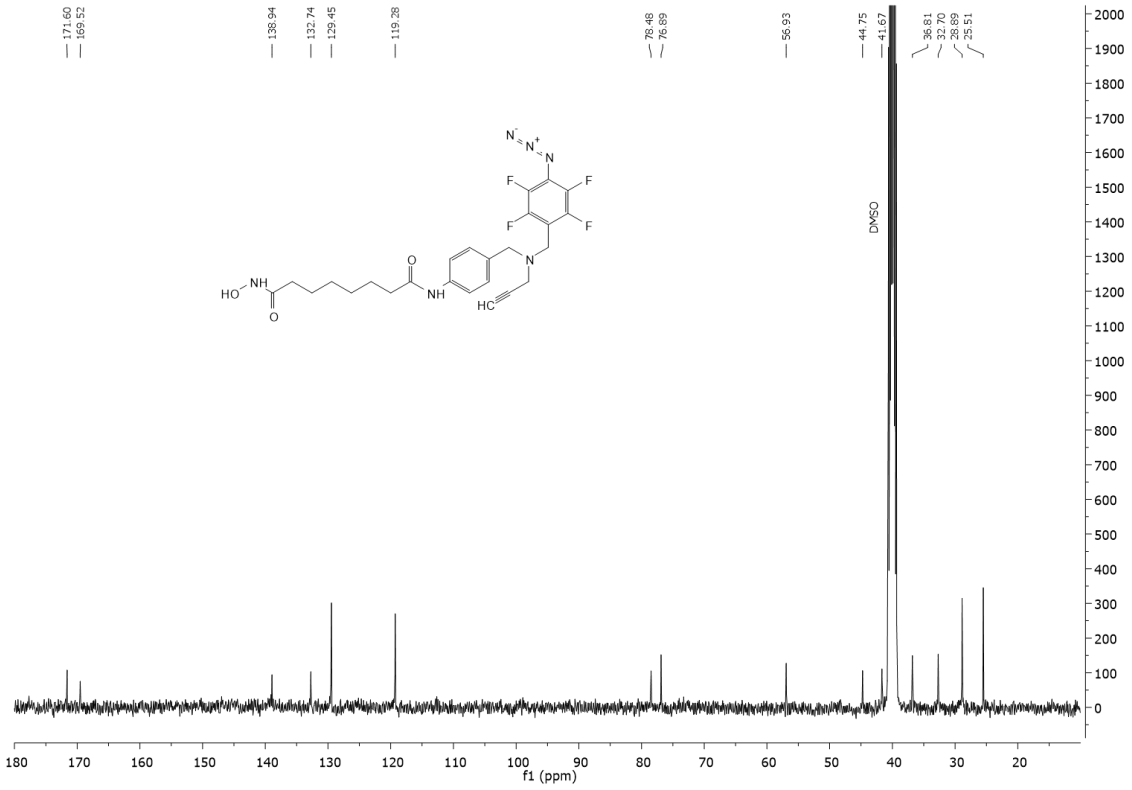
^{19}F NMR for intermediate **25**



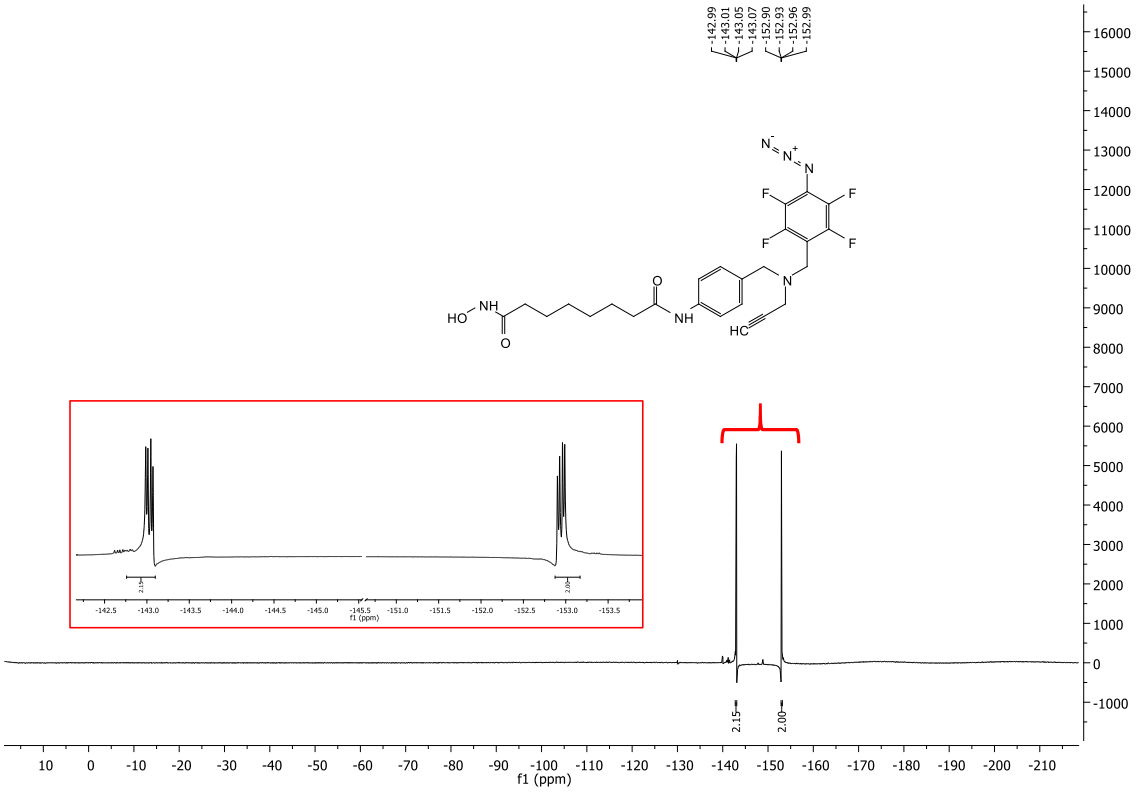
^{1}H-NMR for PRP **9**



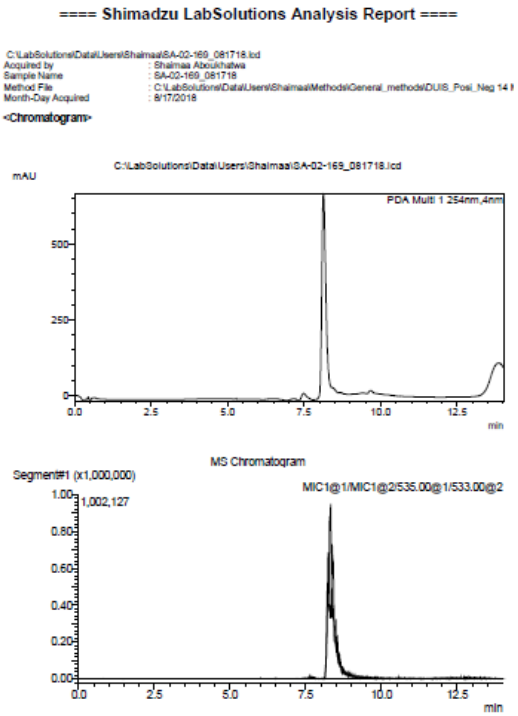
^{13}C-NMR for PRP **9**



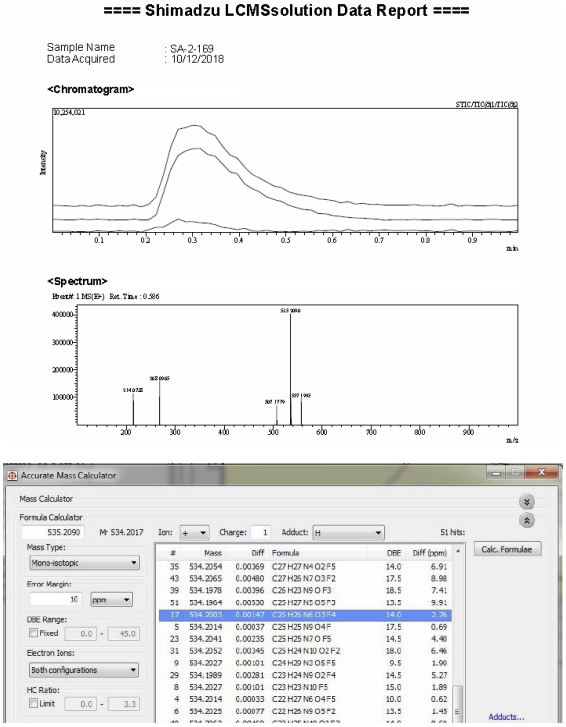
^{19}F-NMR for PRP **9**



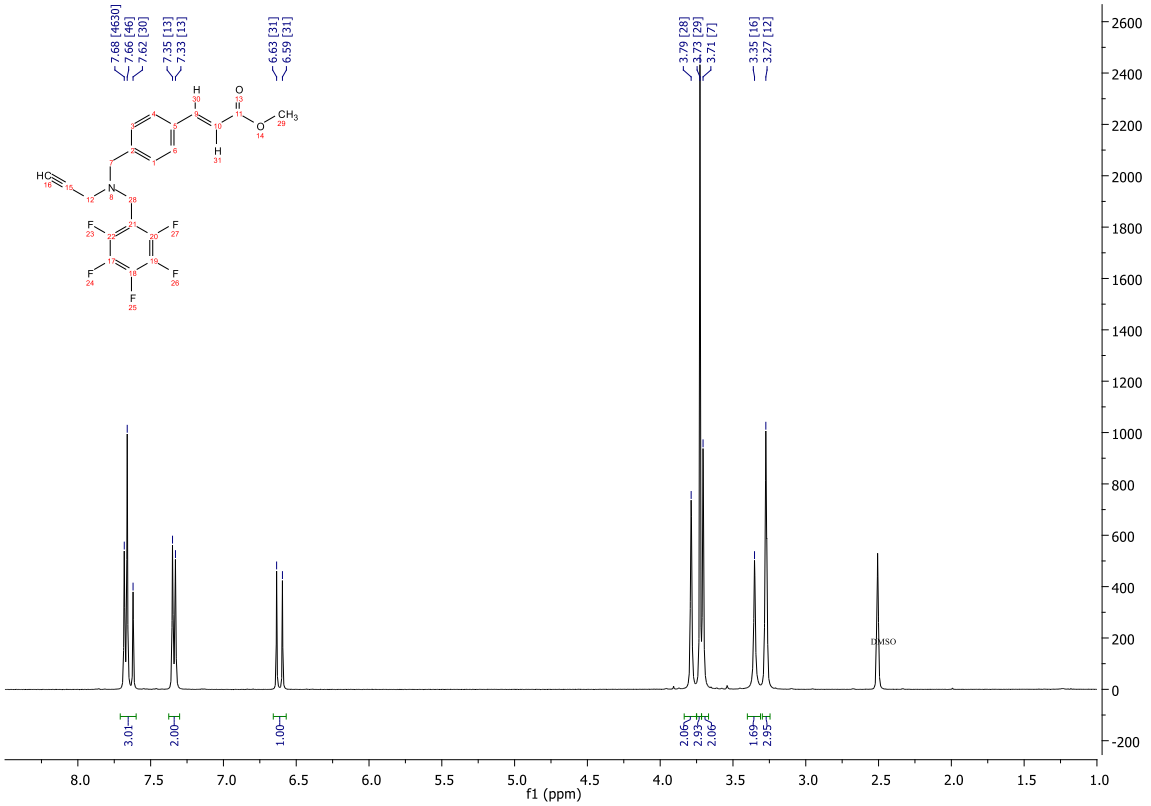
LC-MS analysis of PRP **9**



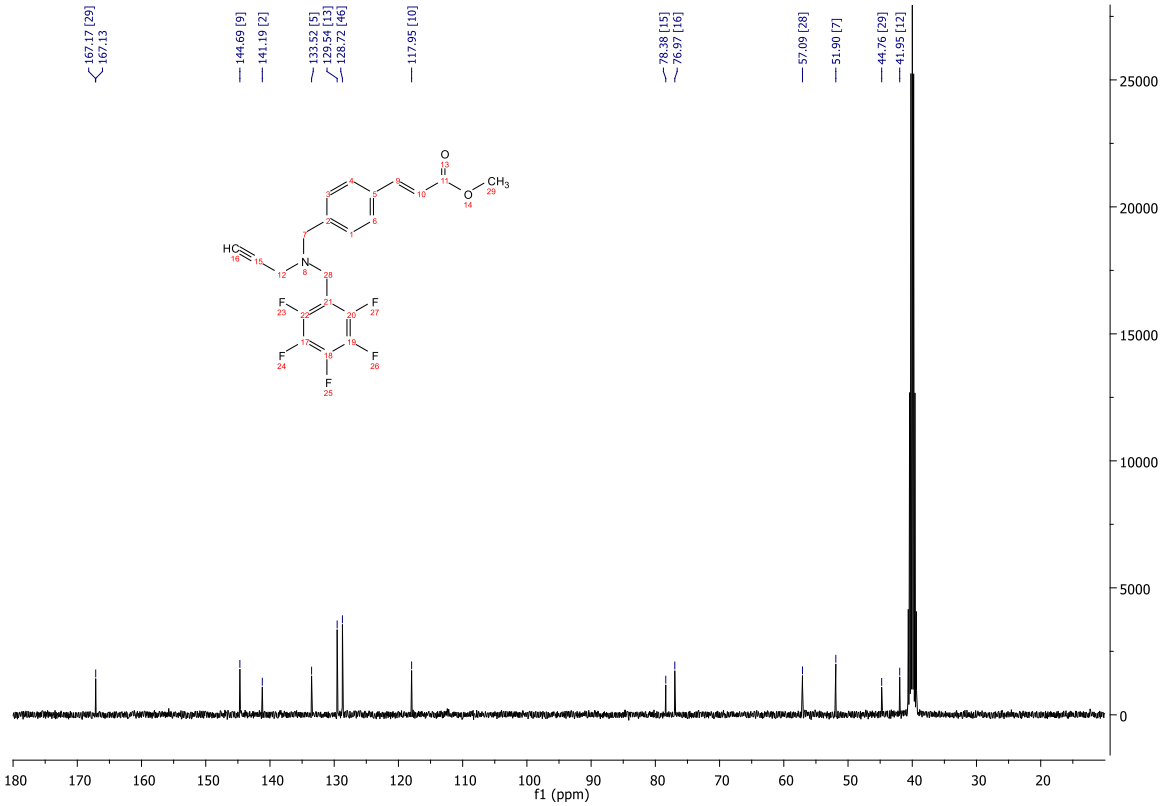
HRMS report for PRP **9**



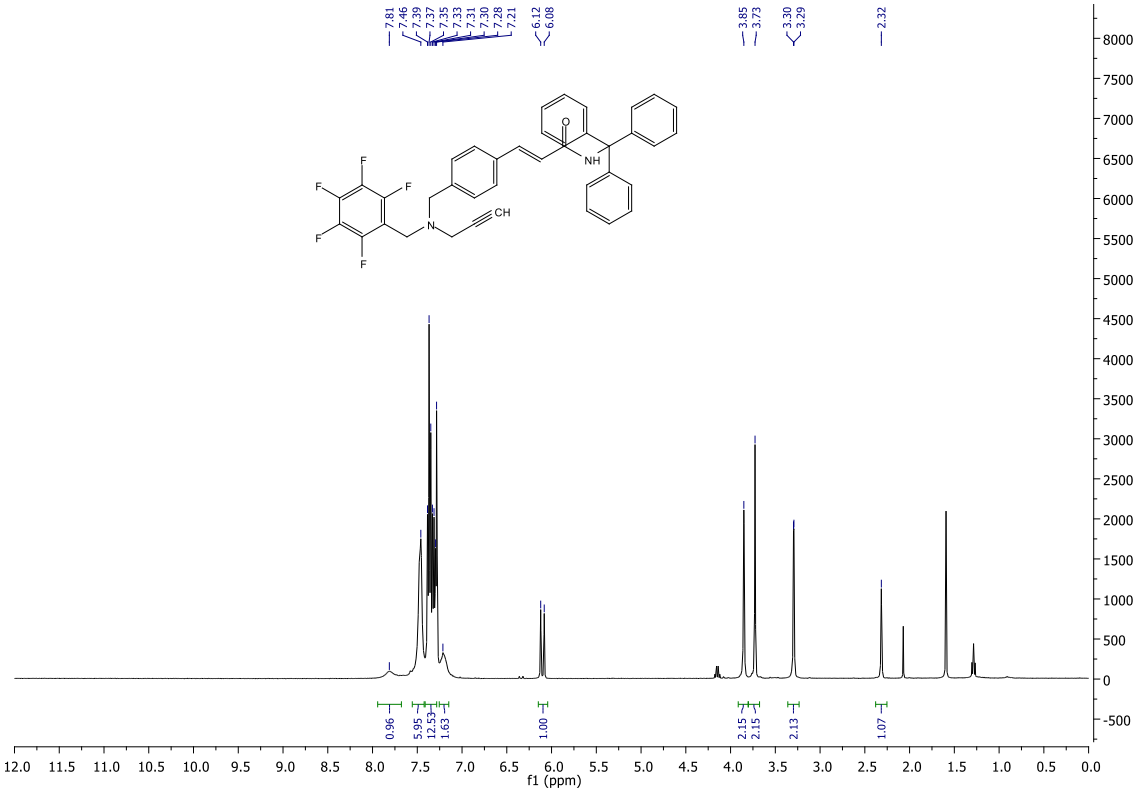
^{1}H NMR for intermediate **33**



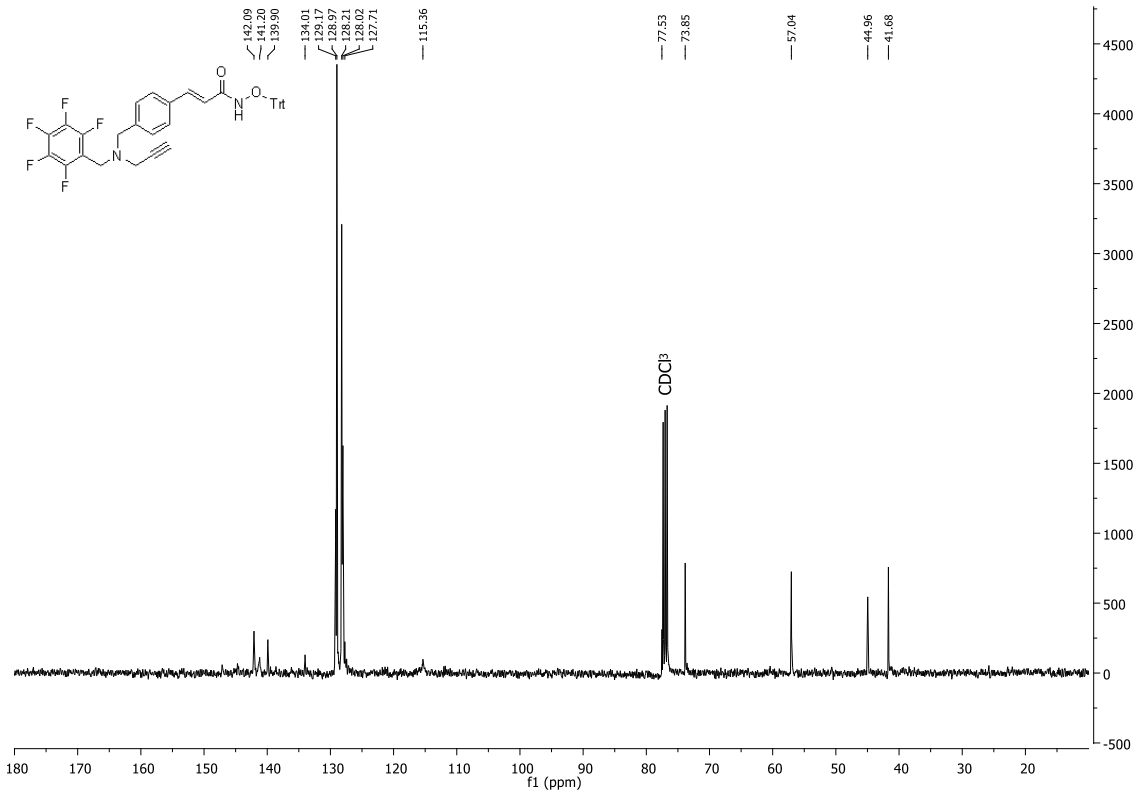
^{13}C NMR for intermediate **33**



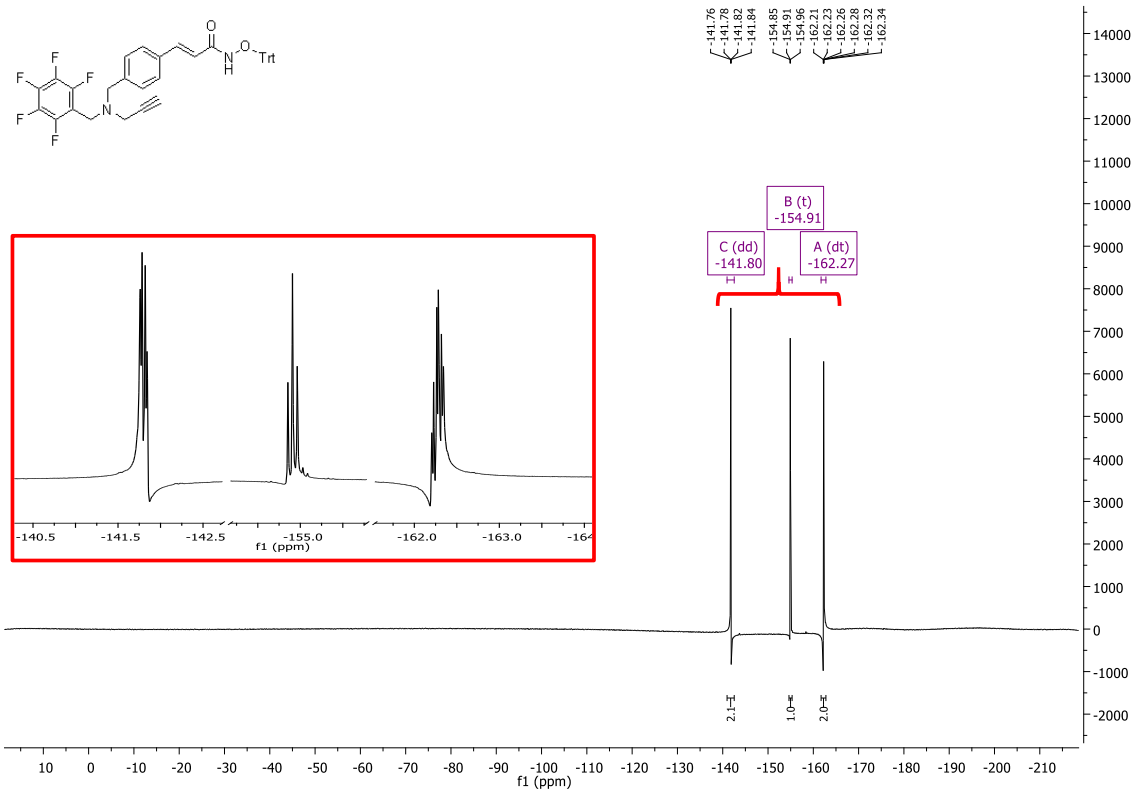
^{1}H NMR for intermediate **35**



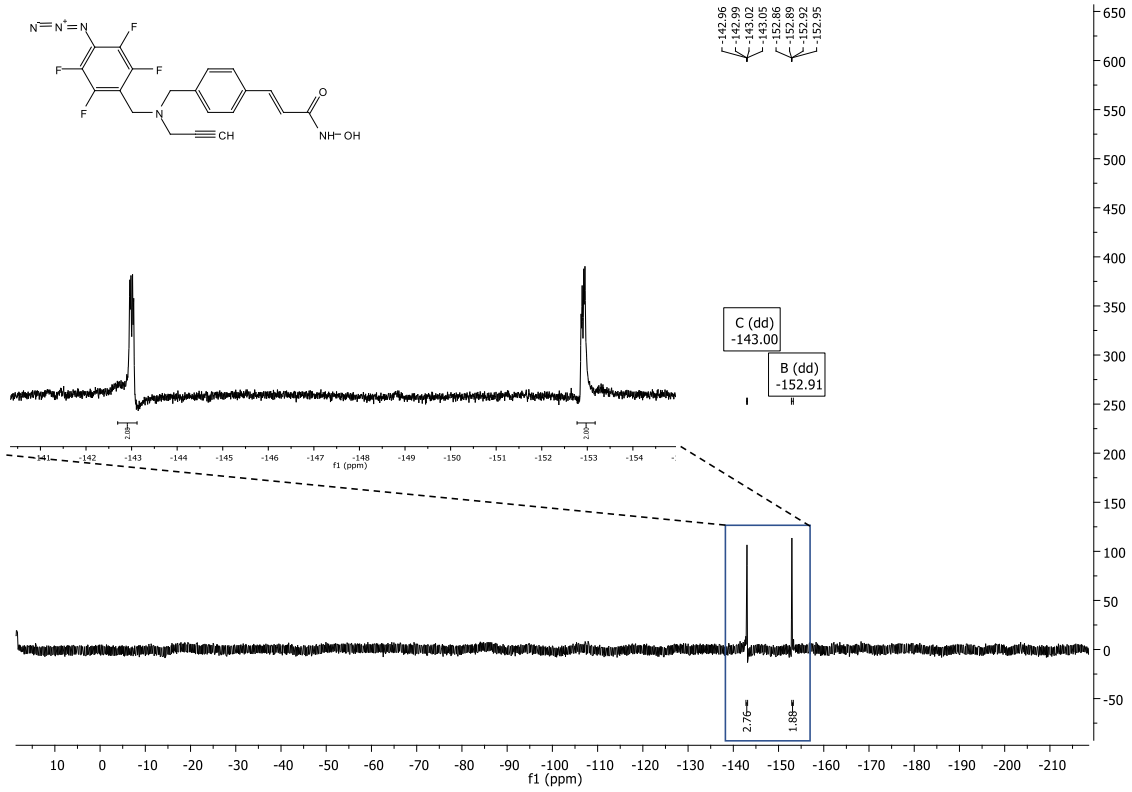
^{13}C NMR for intermediate **35**



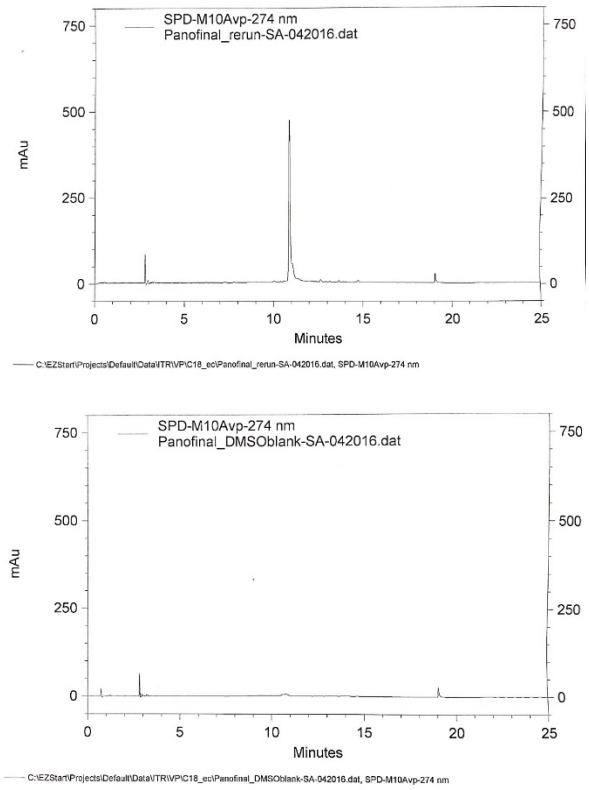
^{19}F-NMR for intermediate **35**



^{19}F-NMR for PRP **10**



HPLC analysis of PRP **10**



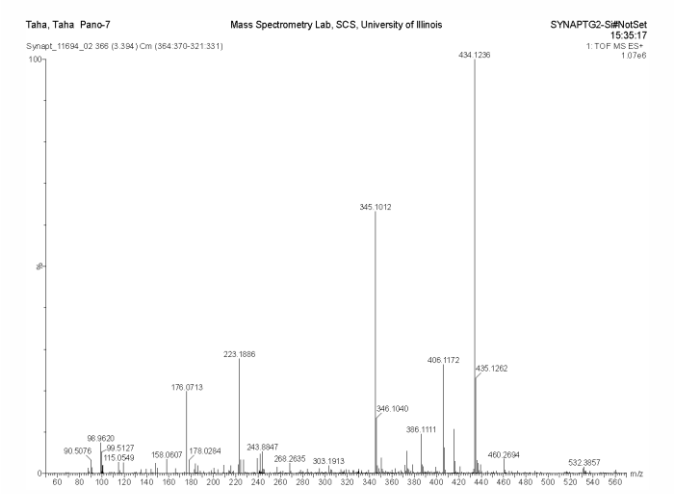
HRMS report for PRP **10**

Elemental Composition Report

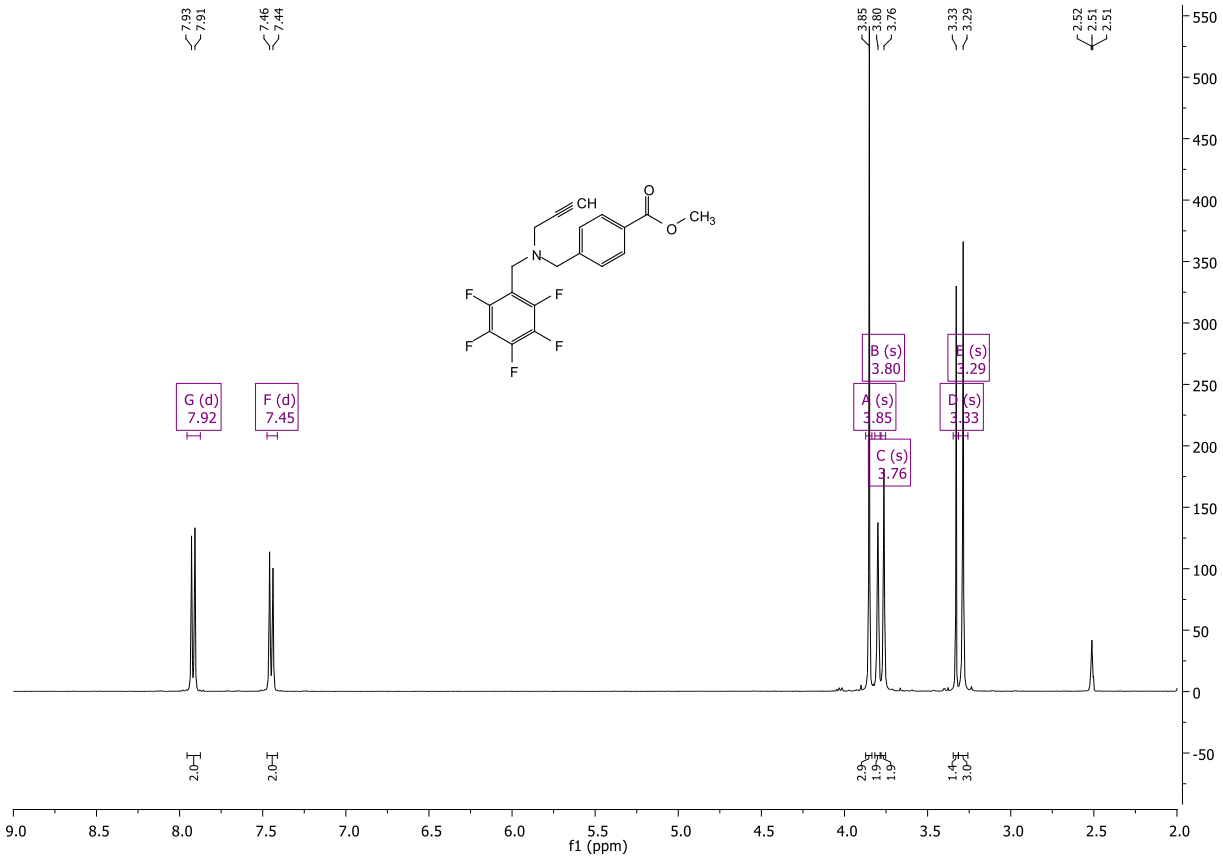
Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -50.0, max = 150.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 9

Monoisotopic Mass, Even Electron Ions
98 formula(e) evaluated with 1 results within limits (up to 10 closest results for each mass)
Elements Used:
C: 0-100 H: 0-150 N: 4-6 O: 1-3 F: 4-4

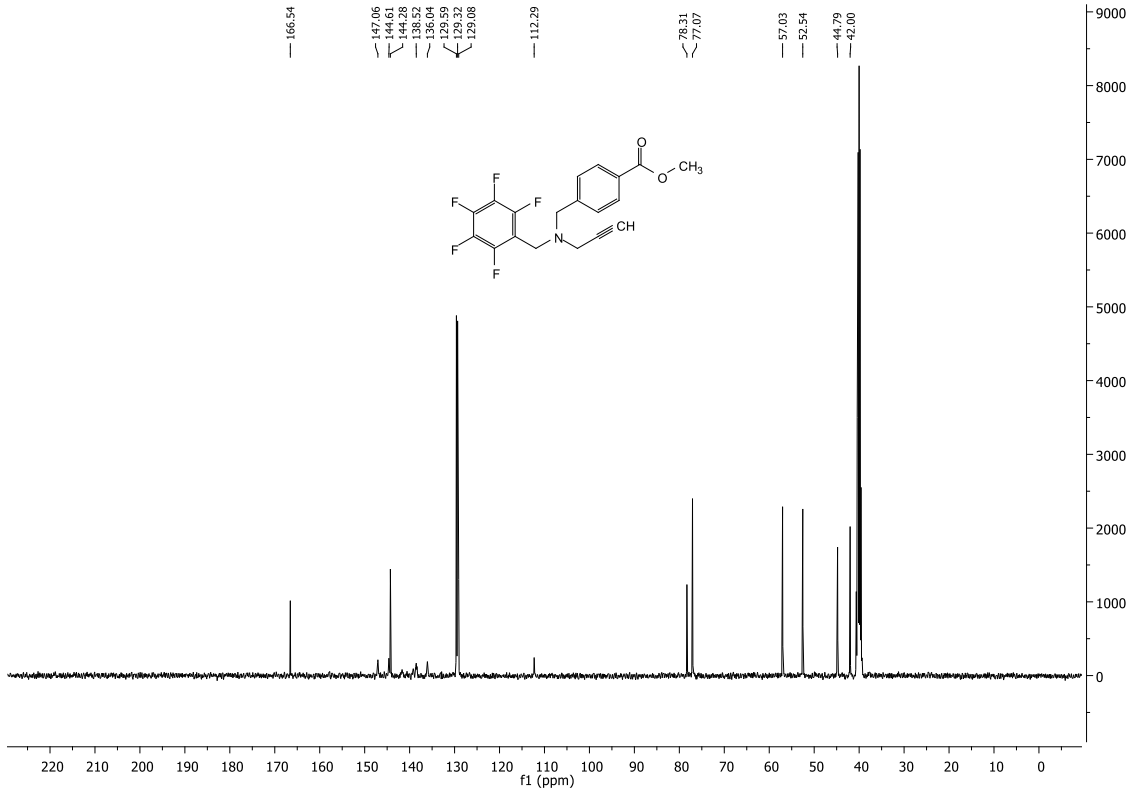
Minimum:				-50.0				
Maximum:		5.0	5.0	150.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
434.1236	434.1240	-0.4	-0.9	13.5	668.0	n/a	n/a	C20 H16 N5 O2 F4



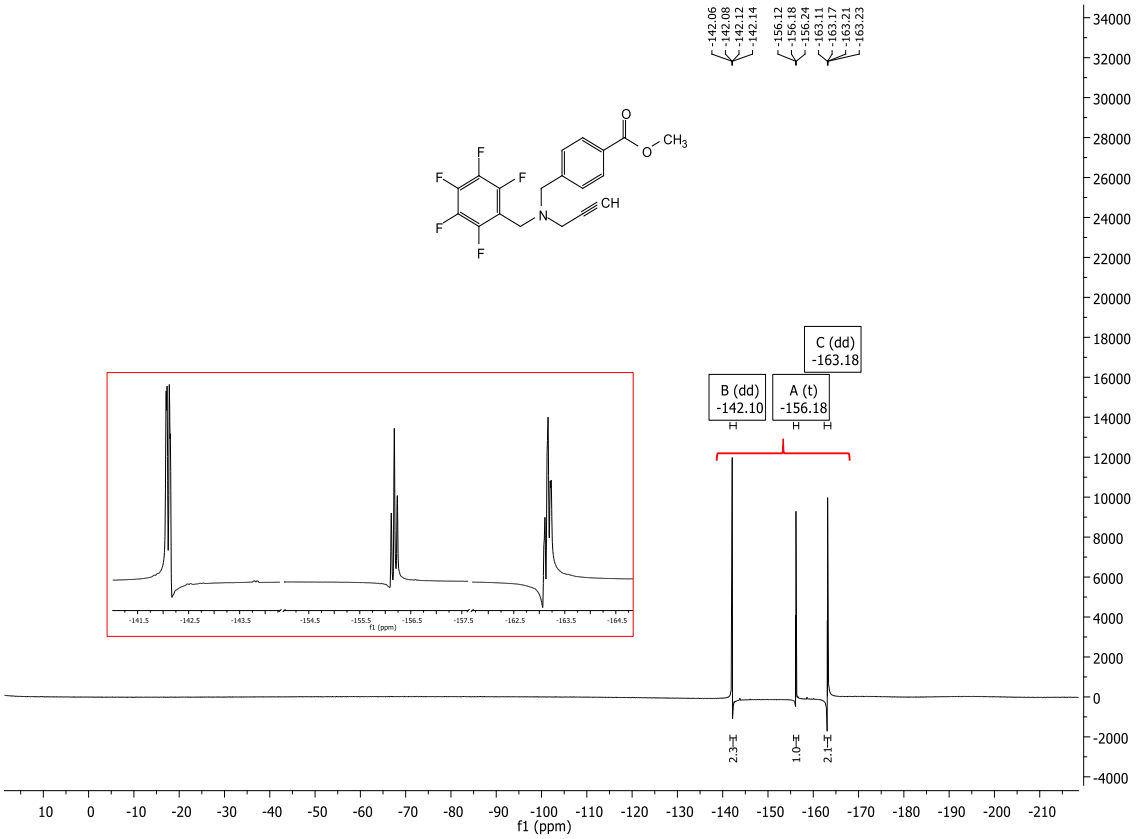
^{1}H NMR for intermediate **39**



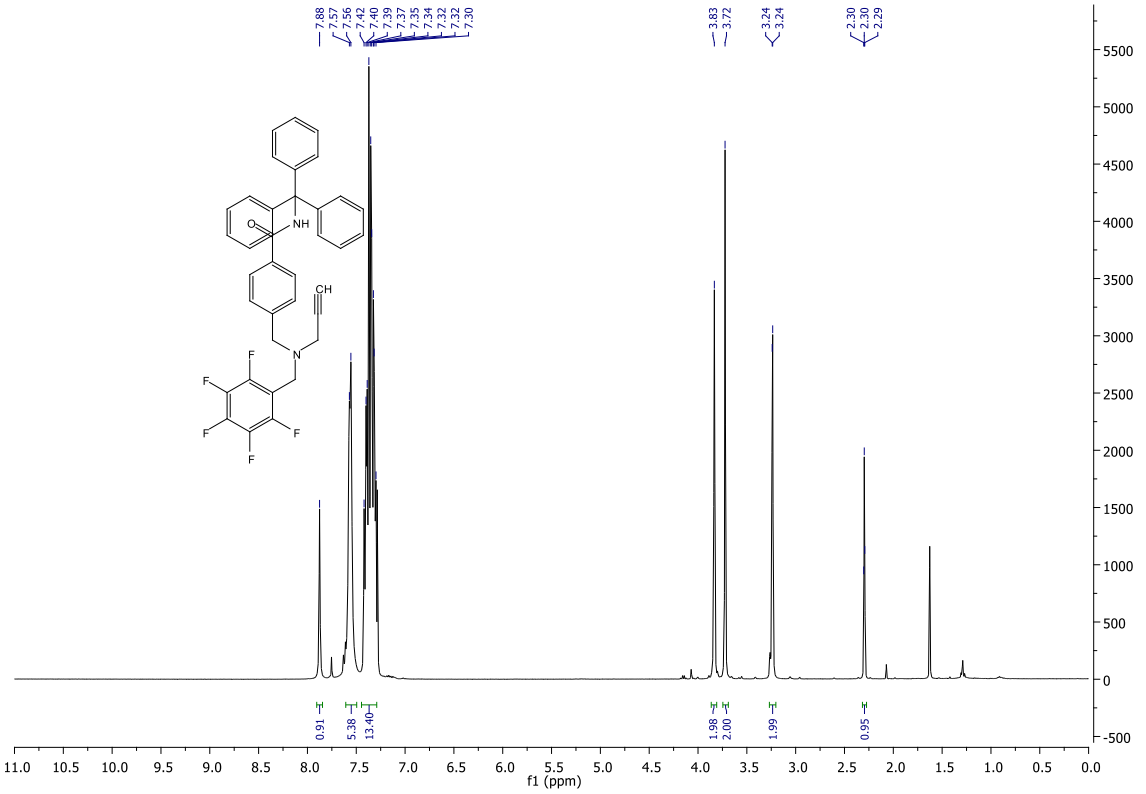
^{13}C NMR for intermediate **39**



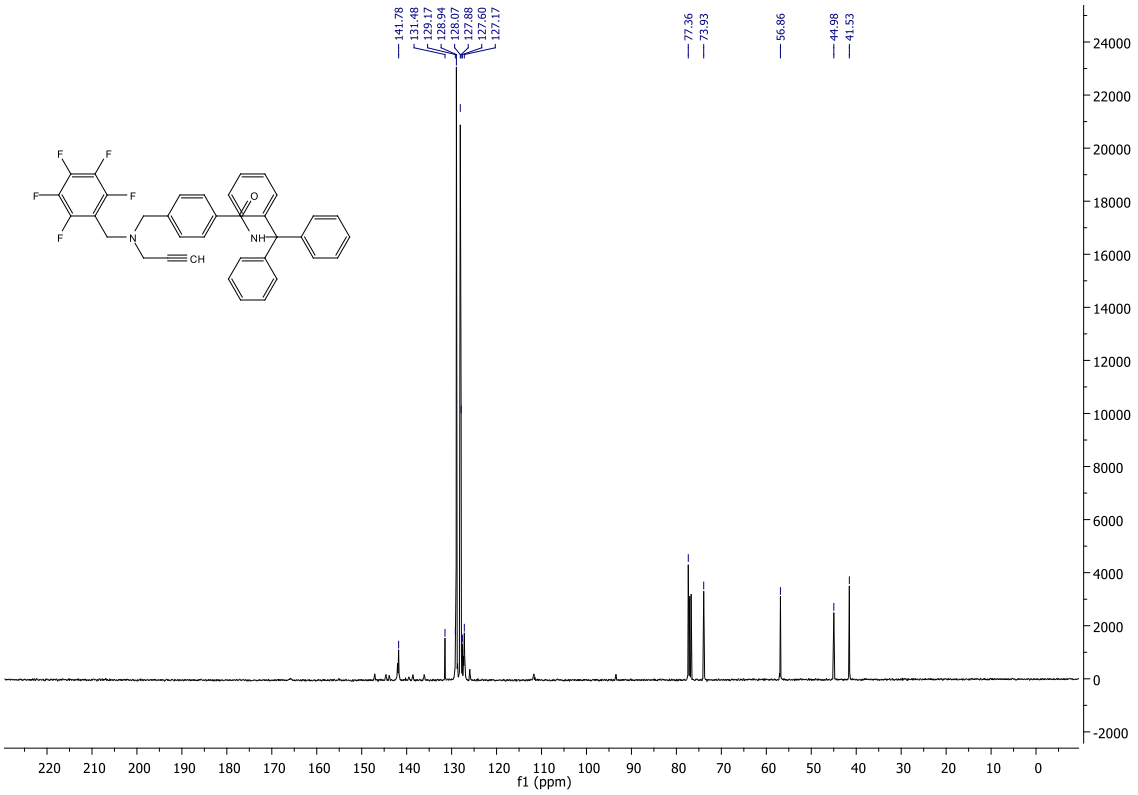
^{19}F NMR for intermediate **39**



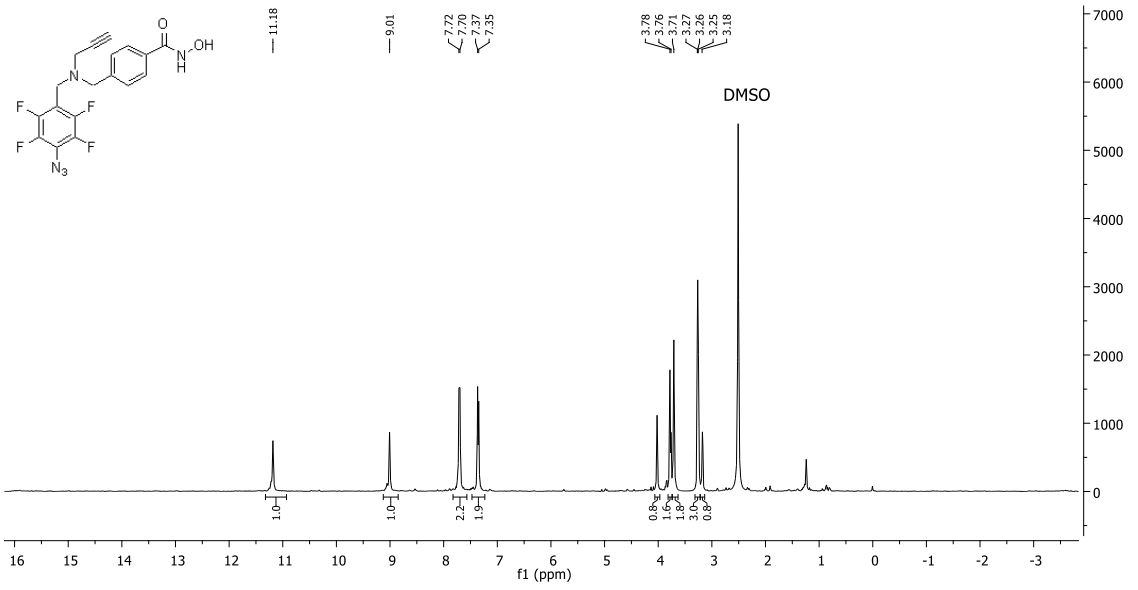
^{1}H NMR for intermediate **41**



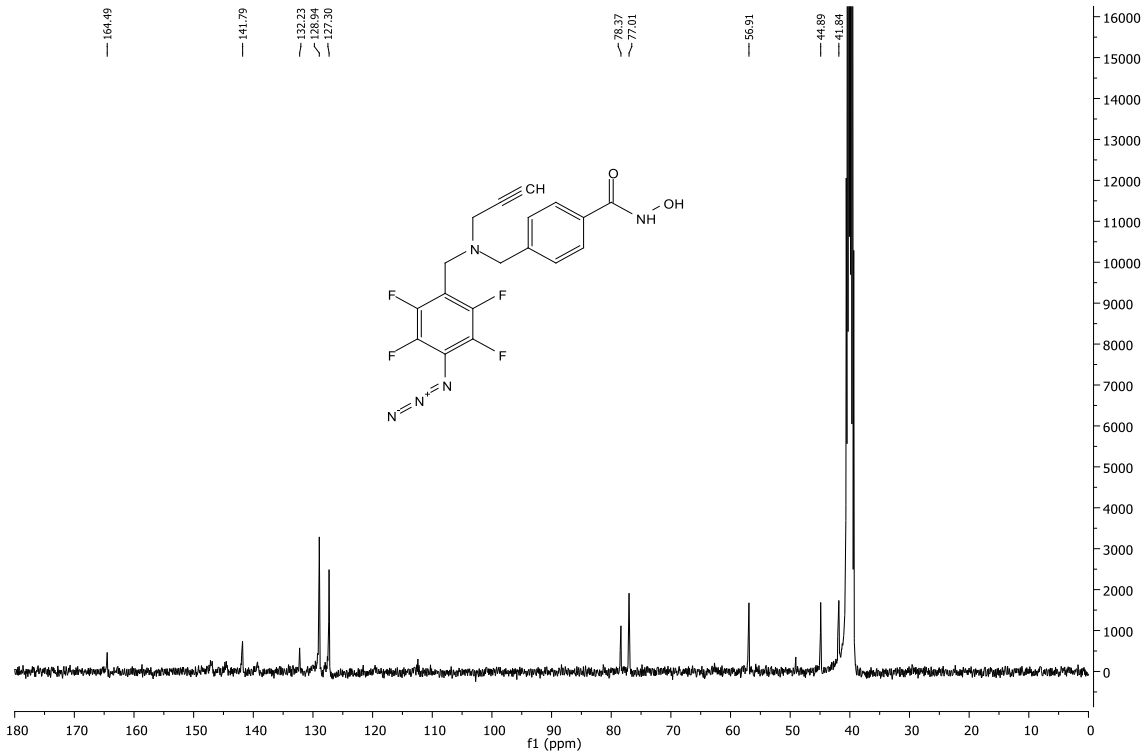
^{13}C NMR for intermediate **41**



^{1}H NMR for PRP **11**



^{13}C NMR for PRP **11**



LC-MS analysis for PRP **11**

==== Shimadzu LabSolutions Analysis Report ====

C:\LabSolutions\Data\Users\Shaimaa\SA-02-127_082318_re.lcd
Acquired by : Shaimaa Aboukhatwa
Sample Name : SA-02-127_082318_re
Method File : C:\LabSolutions\Data\Users\Shaimaa\Methods\General_methods\DUIS_Posi_Neg 14 I
Month-Day Acquired : 8/23/2018

<Chromatogram>

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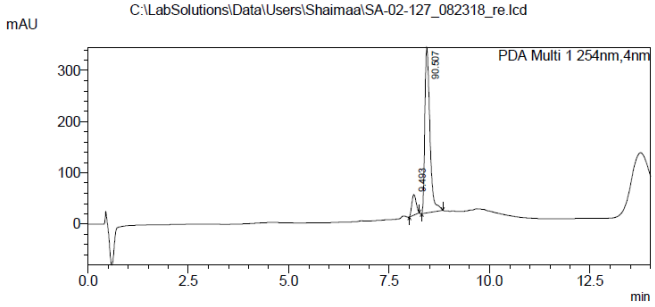
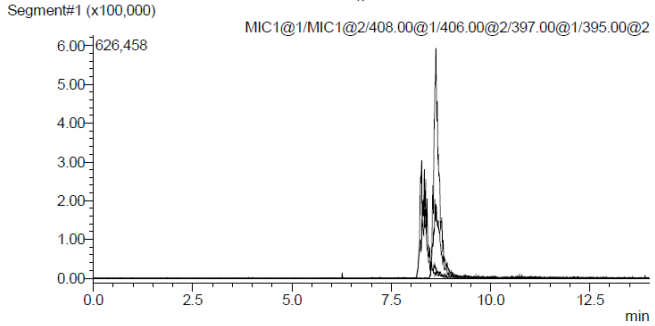


MS Chromatogram

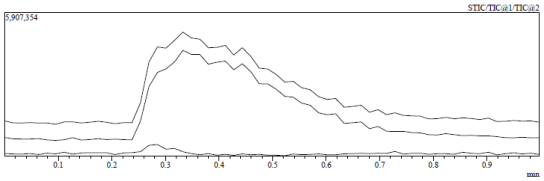


HRMS report for PRP **11**

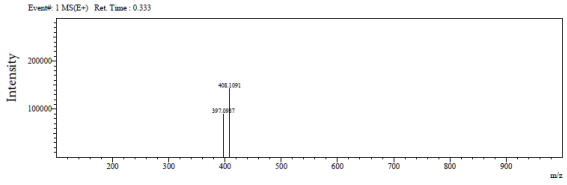
==== Shimadzu LCMSsolution Data Report ====

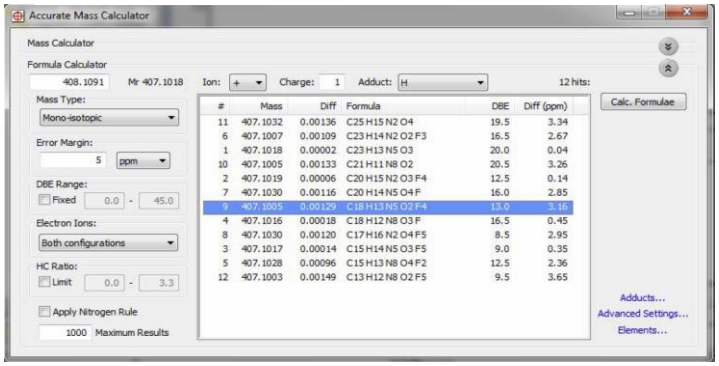
<Chromatogram>

Sample Name : SA-2-127
Data Acquired : 10/16/2018



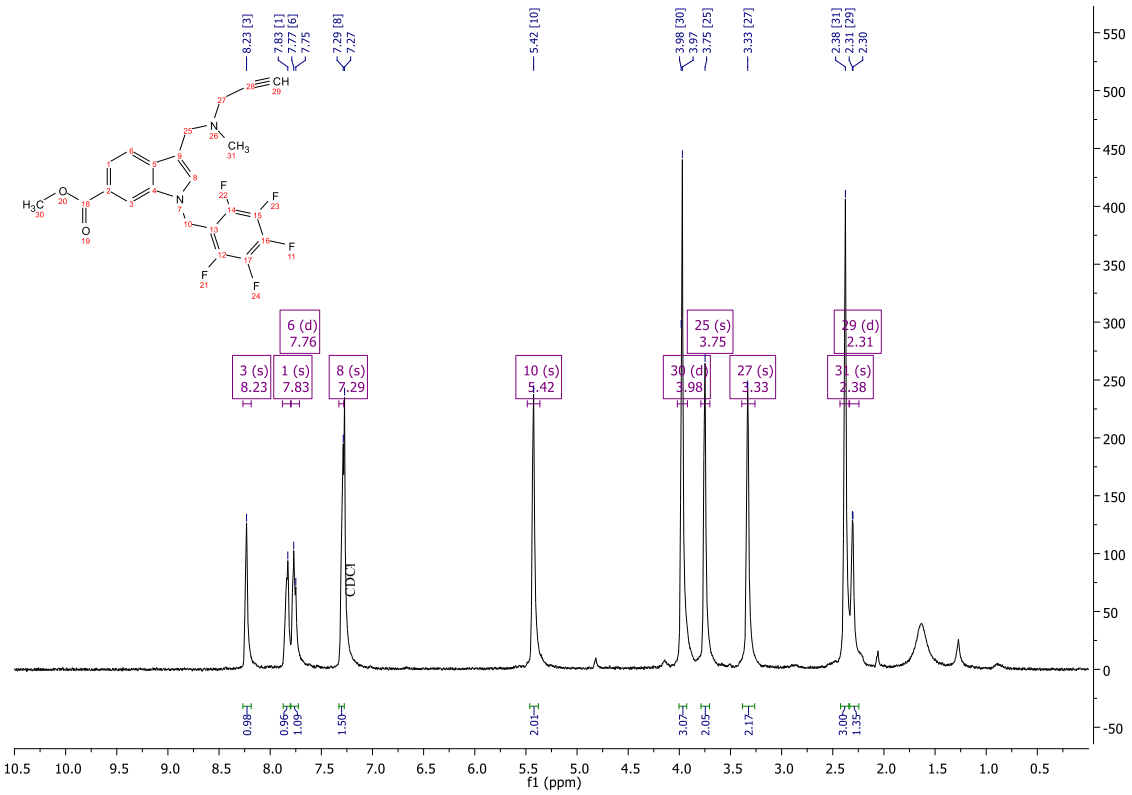
<Spectrum>



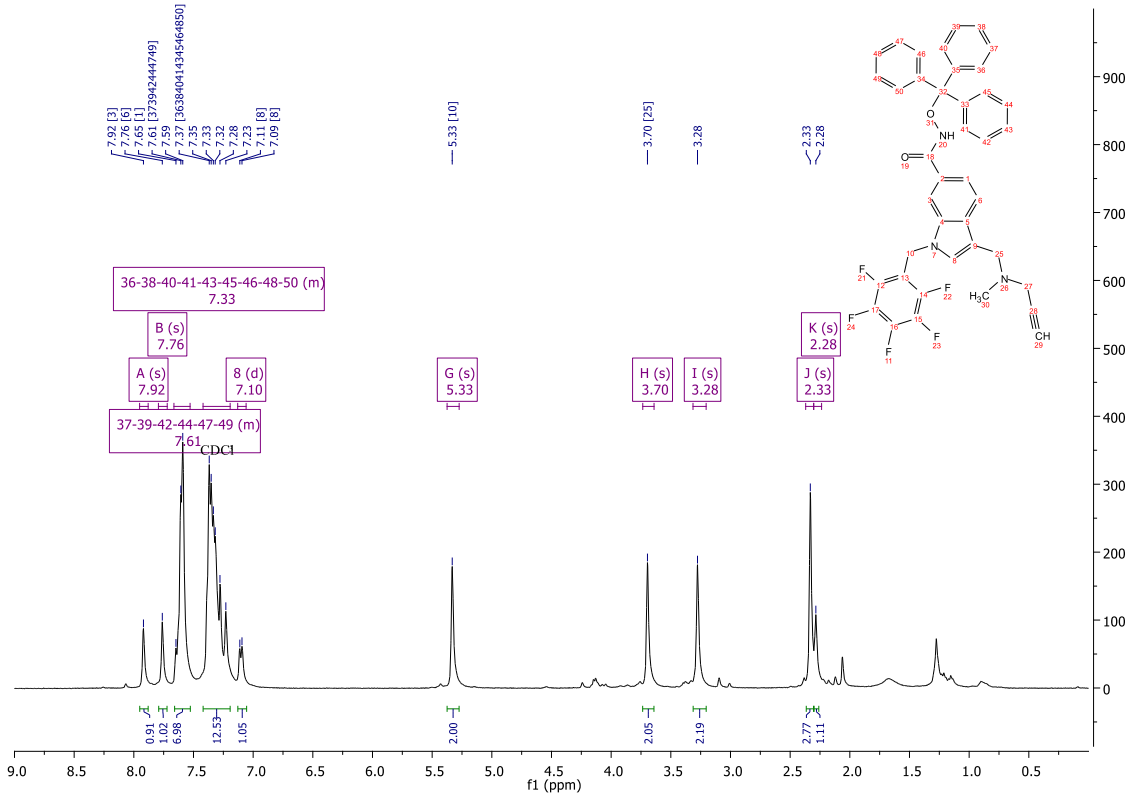


#	Mass	Diff	Formula	DBE	Diff (ppm)
11	407.1032	0.00136	C25 H15 N2 O4	19.5	3.34
6	407.1007	0.00109	C23 H14 N2 O2 F3	16.5	2.67
1	407.1018	0.00002	C23 H13 N5 O3	20.0	0.04
10	407.1005	0.00133	C21 H11 N8 O2	20.5	3.26
2	407.1019	0.00006	C20 H15 N2 O3 F4	12.5	0.14
7	407.1030	0.00116	C20 H14 N5 O4 F	16.0	2.85
9	407.1005	0.00129	C18 H13 N5 O2 F4	13.0	3.16
4	407.1016	0.00018	C18 H12 N8 O3 F	16.5	0.45
8	407.1030	0.00120	C17 H16 N2 O4 F5	8.5	2.95
3	407.1017	0.00014	C15 H14 N5 O3 F5	9.0	0.35
5	407.1028	0.00096	C15 H13 N8 O4 F2	12.5	2.36
12	407.1003	0.00149	C13 H12 N8 O2 F5	9.5	3.65

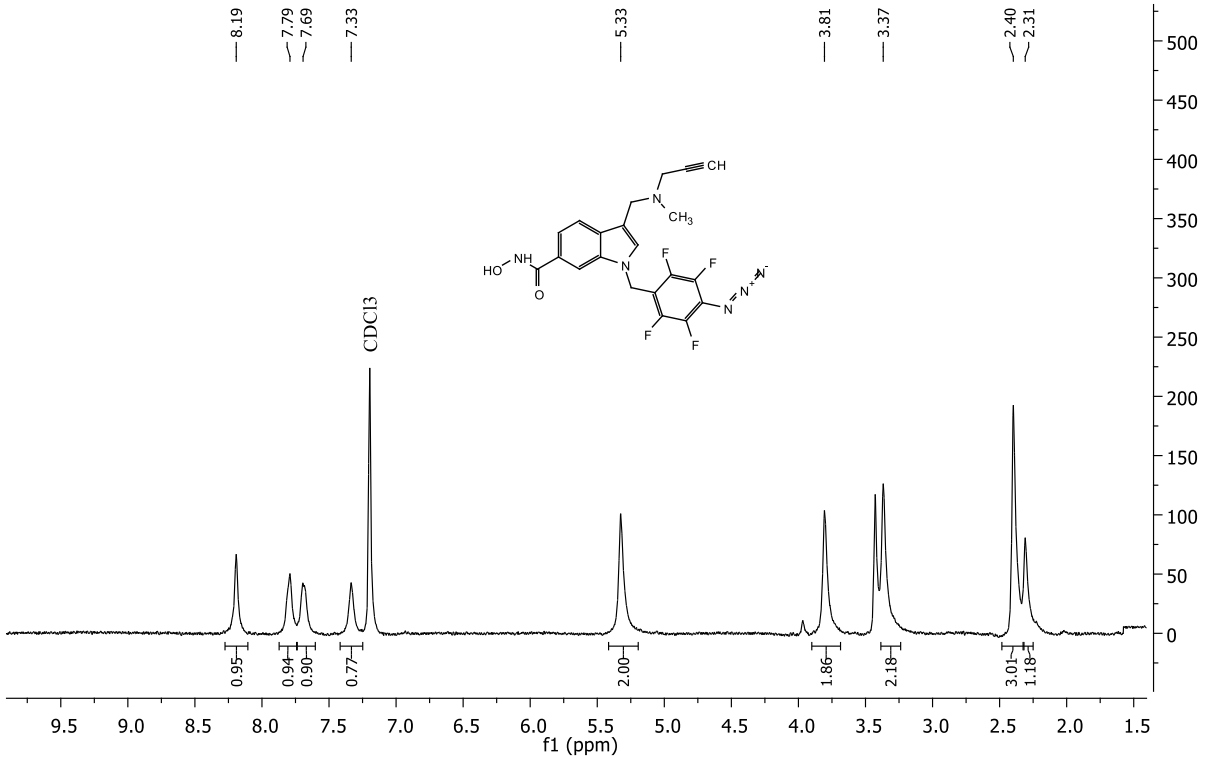
^{1}H NMR for intermediate **47**



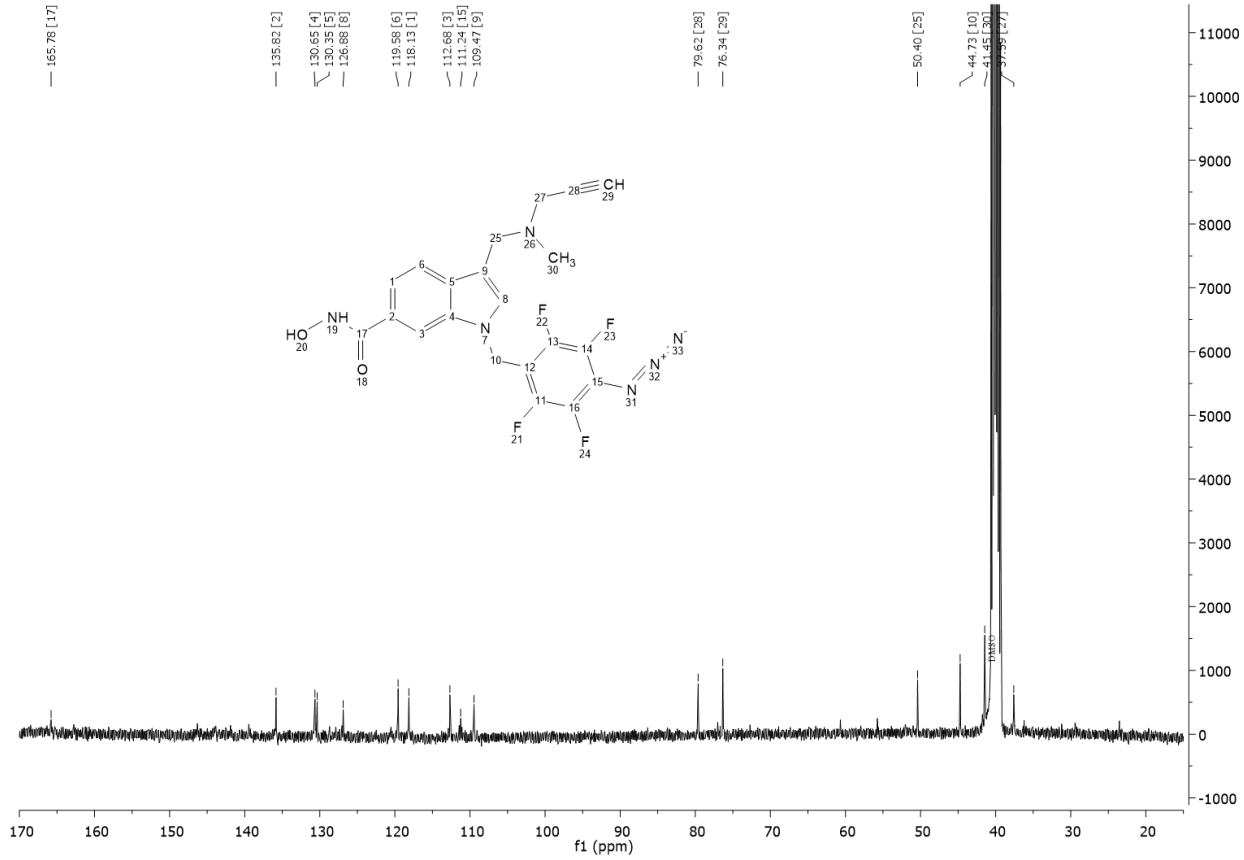
^{1}H NMR for intermediate **49**



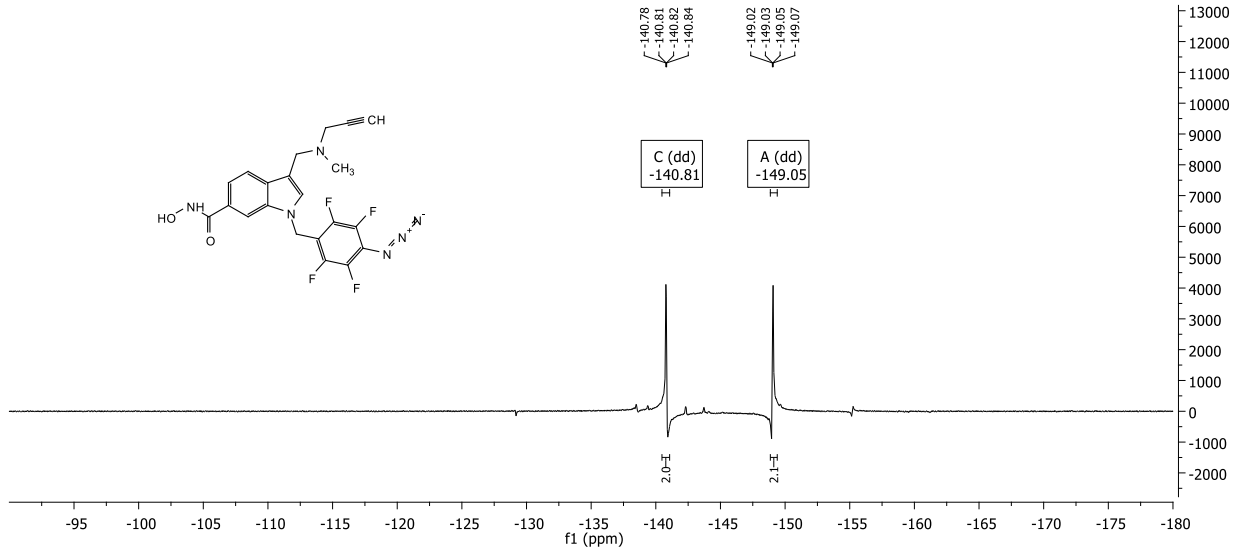
^{1}H NMR spectrum for PRP **12**



^{13}C NMR spectrum for PRP **12**



^{19}F NMR spectrum for PRP **12**

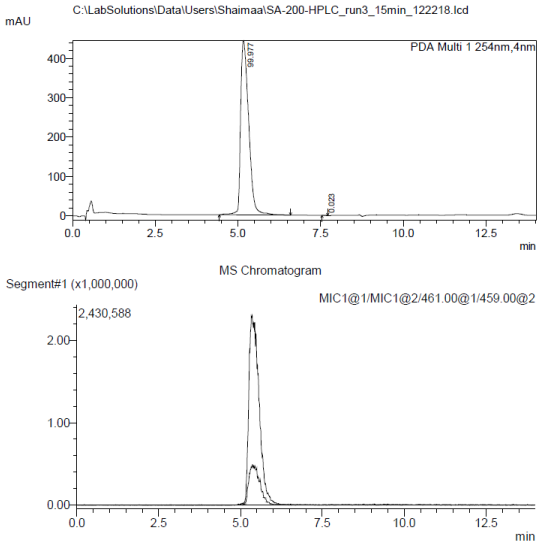


LC-MS analysis of PRP **12**

==== Shimadzu LabSolutions Analysis Report ====

C:\LabSolutions\Data\Users\Shaimaa\SA-200-HPLC_run3_15min_122218.lcd
Acquired by : Shaimaa Aboukhatwa
Sample Name : SA-200-HPLC_run3_15min_122218
Method File : C:\LabSolutions\Data\Users\Shaimaa\Methods\General_methods\DUIS_Posi_Neg 14 M
Month-Day Processed : 12/23/2018

<Chromatogram>

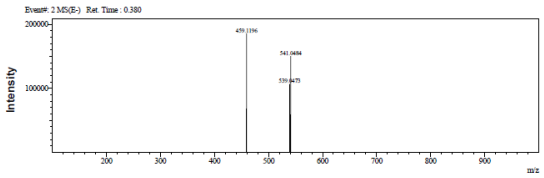


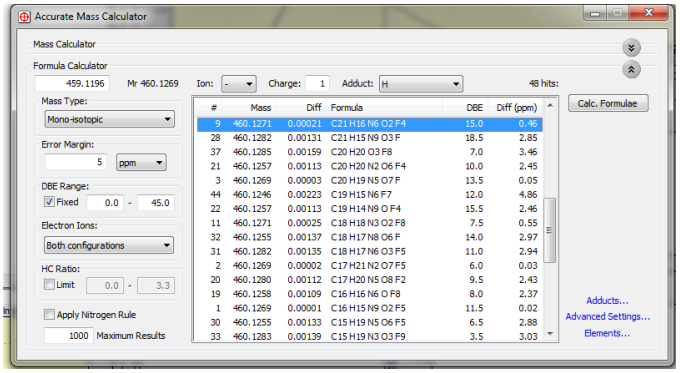
HRMS report for PRP **12**

==== Shimadzu LCMSsolution Data Report ====

Sample Name : SA-200
Data Acquired : 12/15/2016

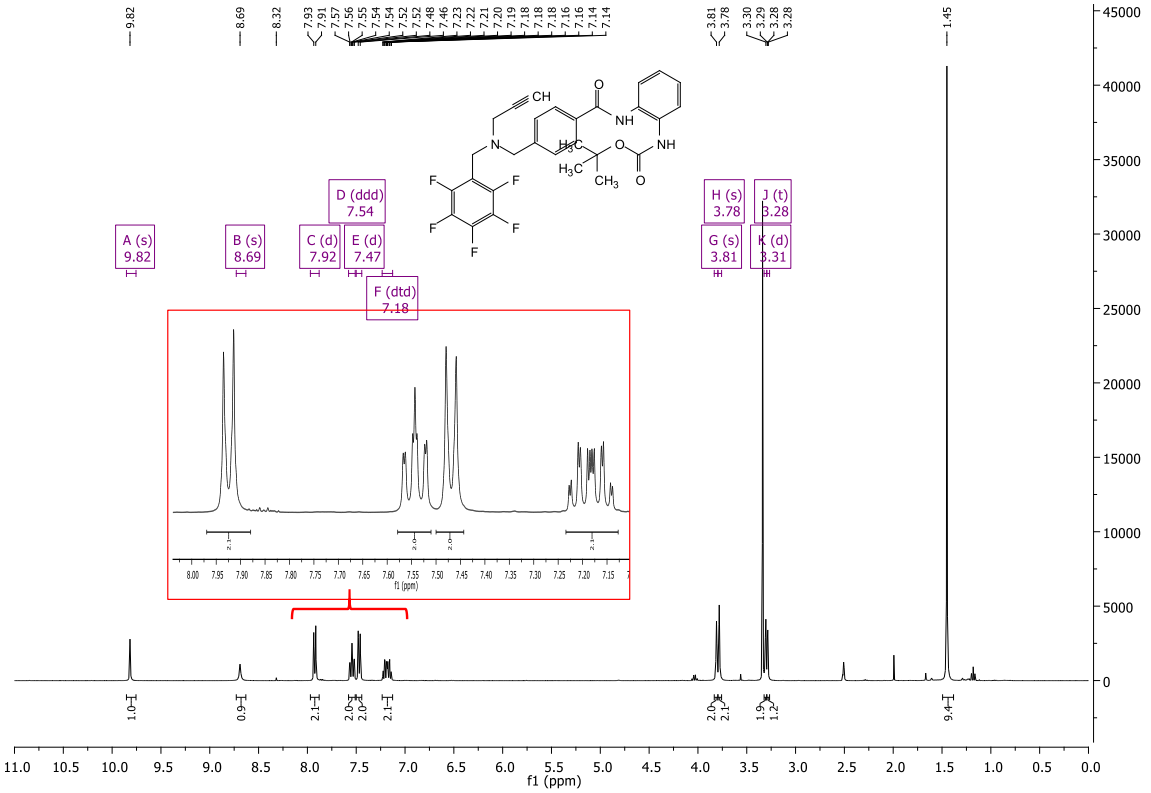
<Spectrum>



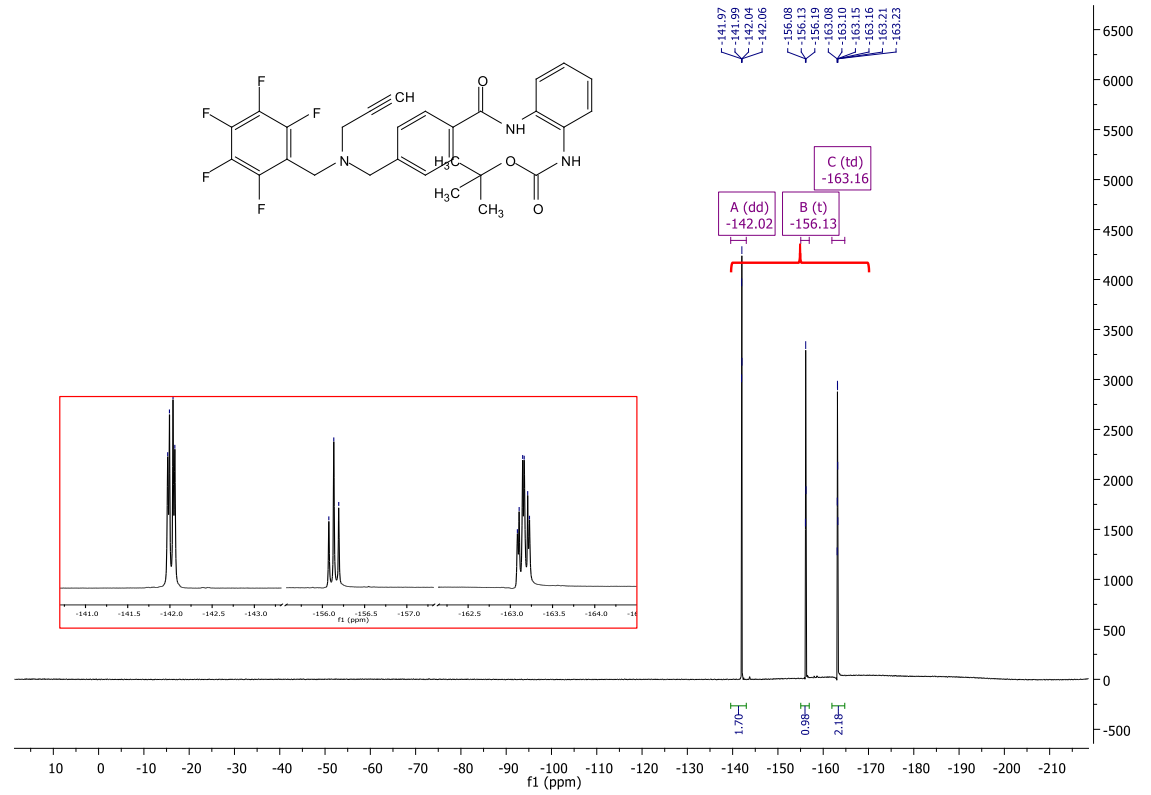


#	Mass	Diff	Formula	DBE	Diff (ppm)
9	460.1271	0.00021	C21 H16 N6 O2 F4	15.0	0.46
28	460.1282	0.00131	C21 H15 N9 O3 F	18.5	2.85
37	460.1285	0.00159	C20 H20 O3 F8	7.0	3.46
21	460.1257	0.00113	C20 H20 N2 O6 F4	10.0	2.45
3	460.1269	0.00003	C20 H19 N5 O7 F	13.5	0.05
44	460.1246	0.00223	C19 H15 N6 F7	12.0	4.86
22	460.1257	0.00113	C19 H14 N9 O F4	15.5	2.46
11	460.1271	0.00025	C18 H18 N3 O2 F8	7.5	0.55
32	460.1255	0.00137	C18 H17 N8 O6 F	14.0	2.97
31	460.1282	0.00135	C18 H17 N6 O3 F5	11.0	2.94
2	460.1269	0.00002	C17 H21 N2 O7 F5	6.0	0.03
20	460.1280	0.00112	C17 H20 N5 O8 F2	9.5	2.43
19	460.1258	0.00109	C16 H16 N6 O F8	8.0	2.37
1	460.1269	0.00001	C16 H15 N9 O2 F5	11.5	0.02
30	460.1255	0.00133	C15 H19 N5 O6 F5	6.5	2.88
33	460.1283	0.00139	C15 H19 N3 O3 F9	3.5	3.03

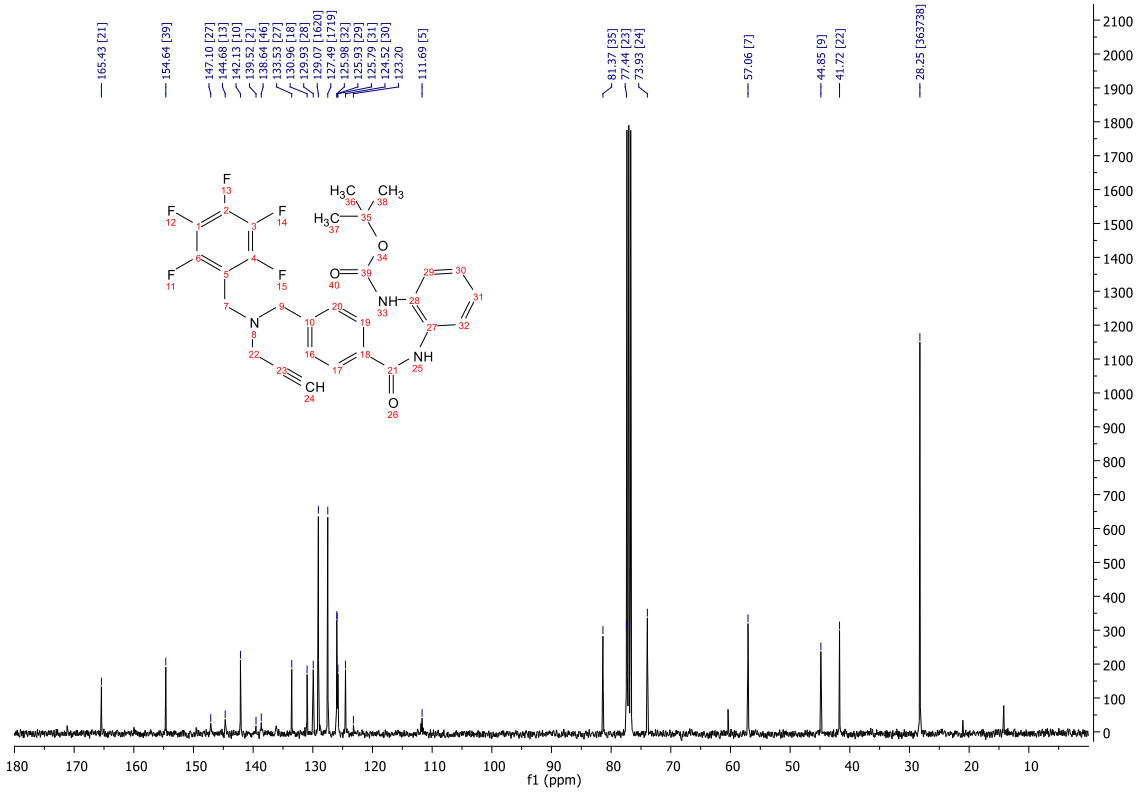
^{1}H NMR for intermediate **43**



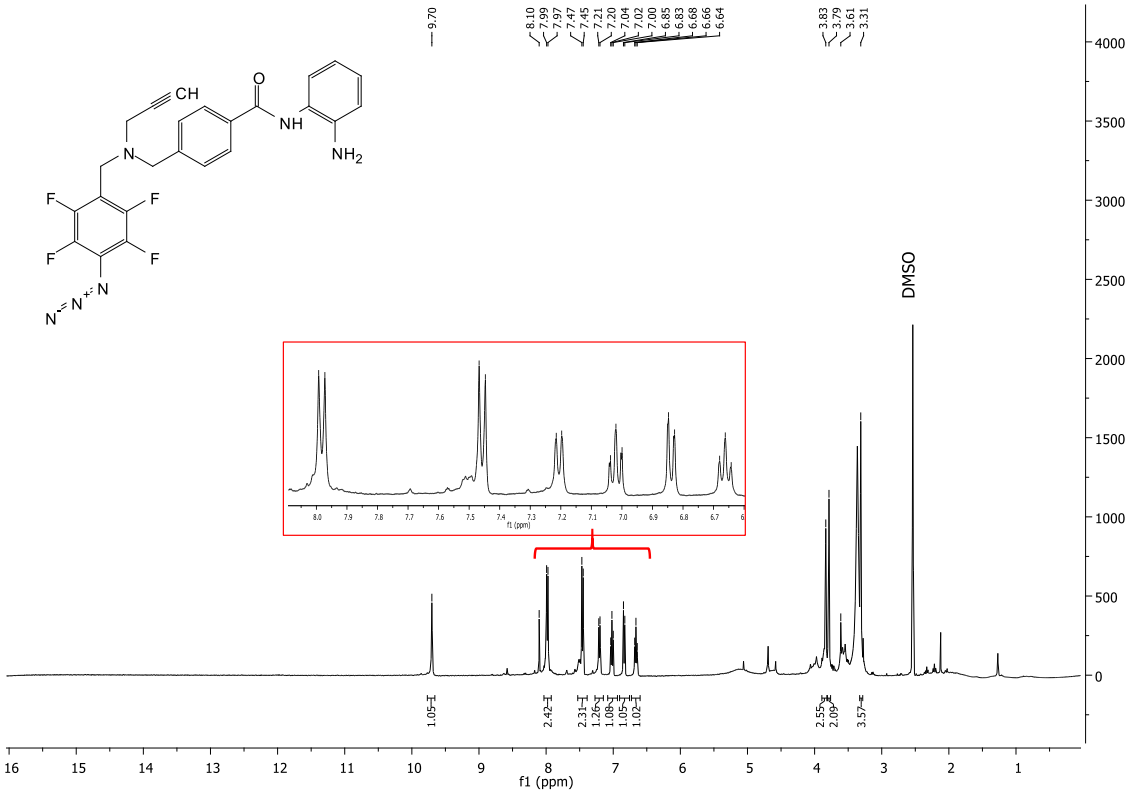
^{19}F NMR for intermediate **43**



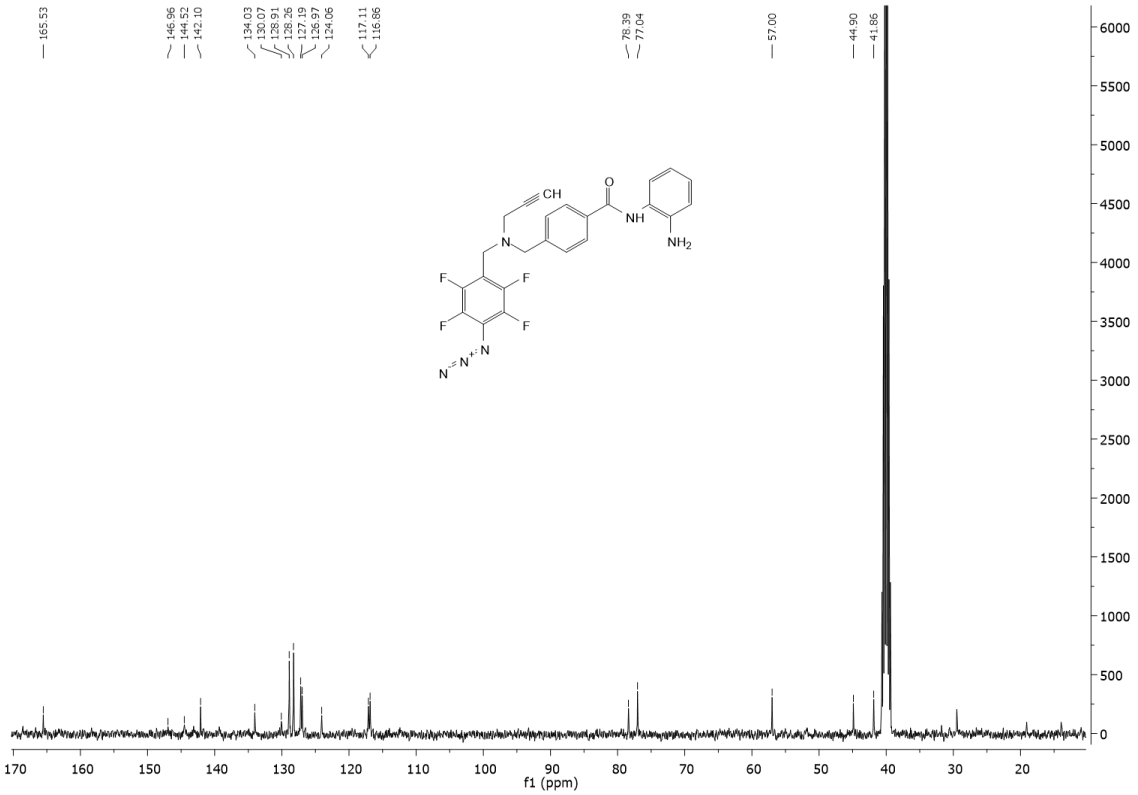
^{13}C NMR for intermediate **43**



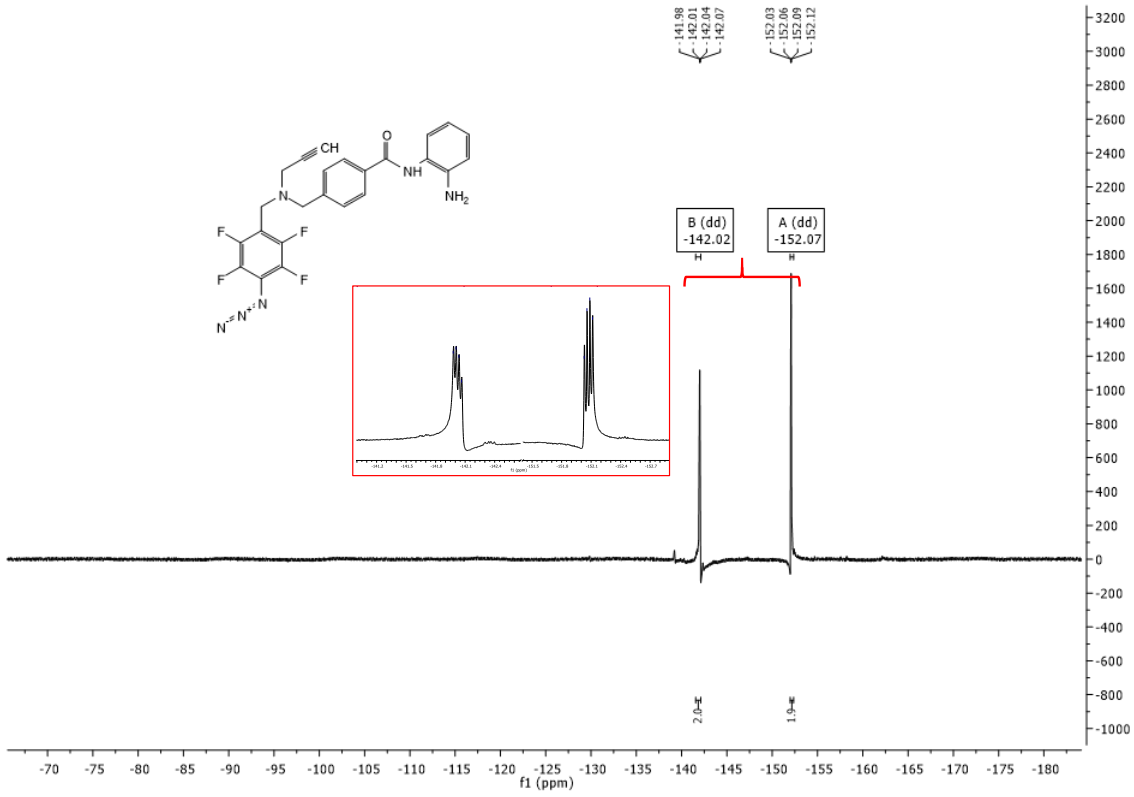
^{1}H NMR for PRP **13**



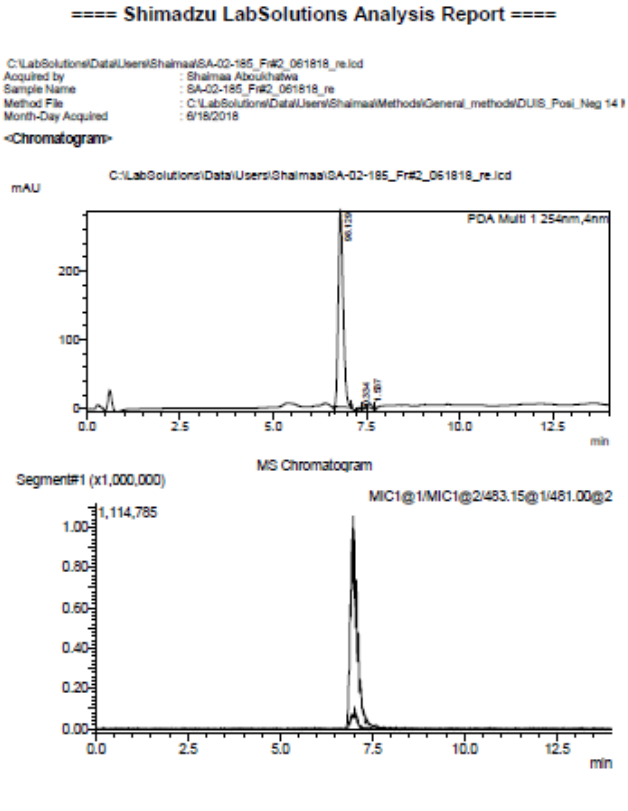
^{13}C NMR for PRP **13**



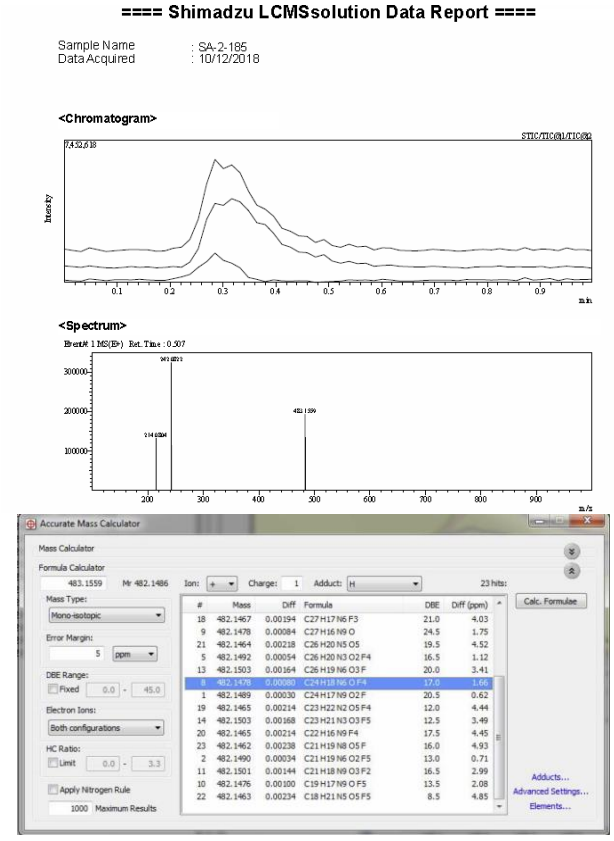
^{19}F NMR for PRP **13**



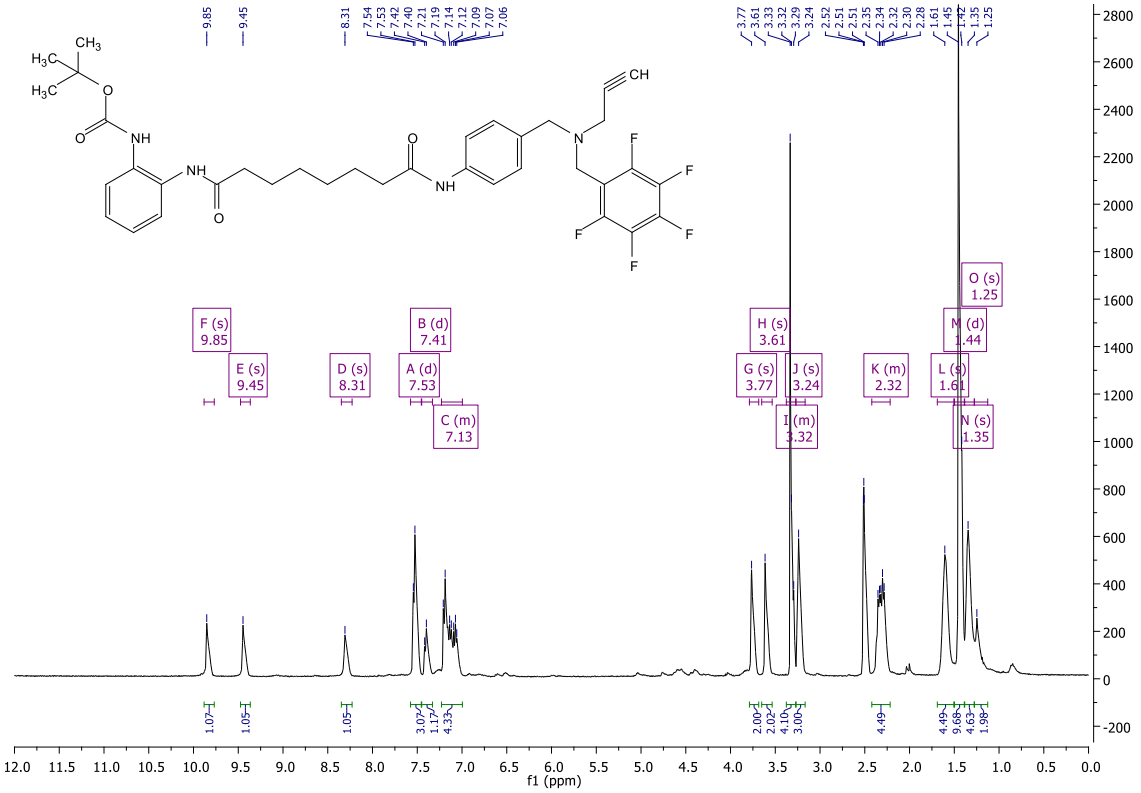
LC-MS analysis of PRP **13**



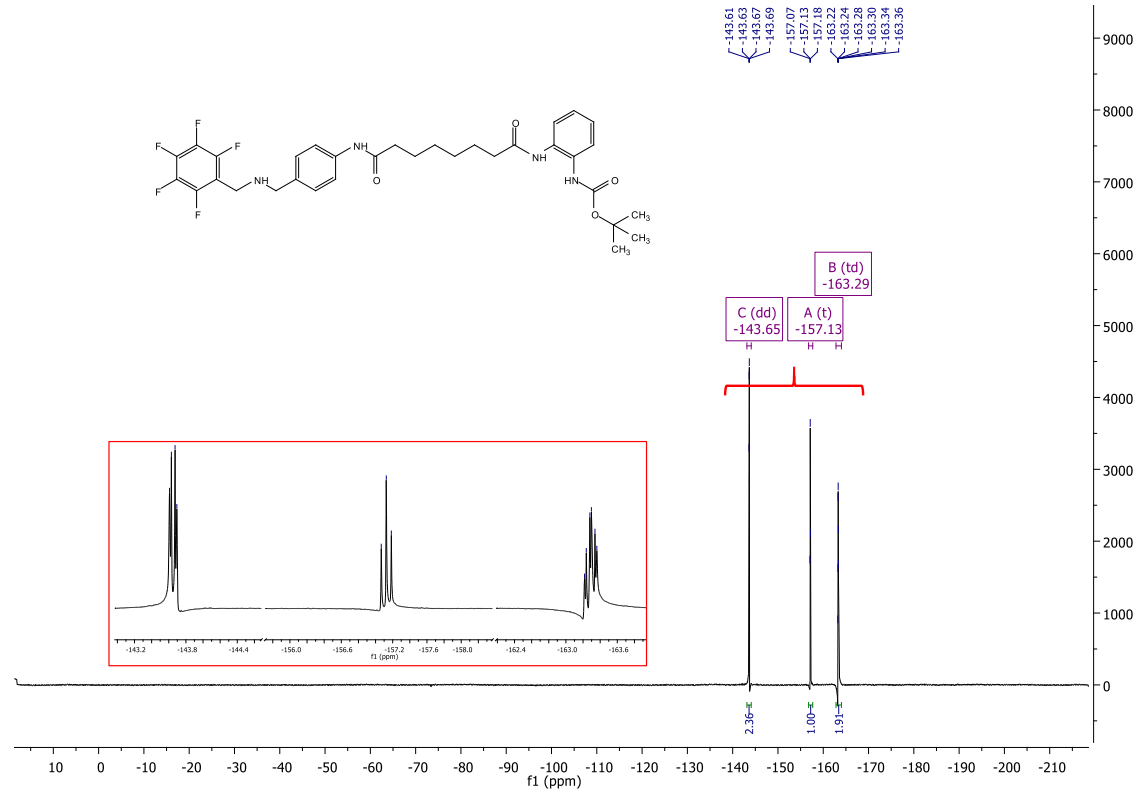
HRMS report for PRP **13**



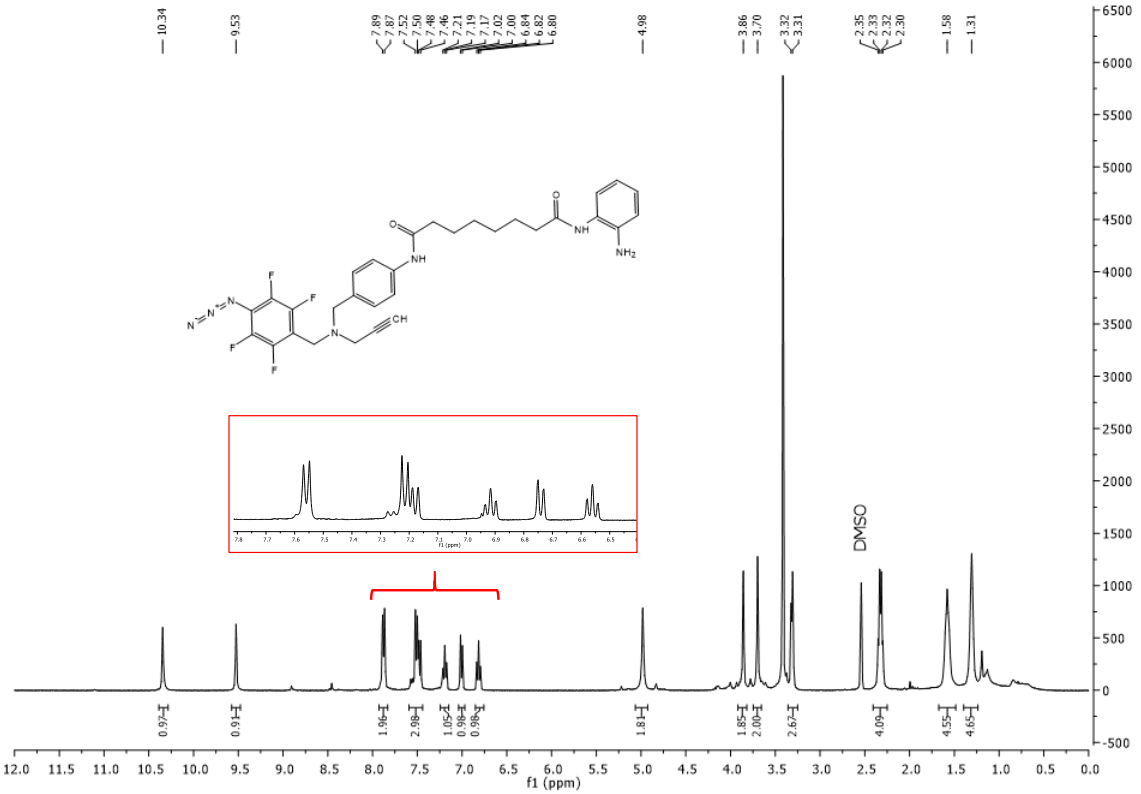
^{1}H NMR for intermediate **26**



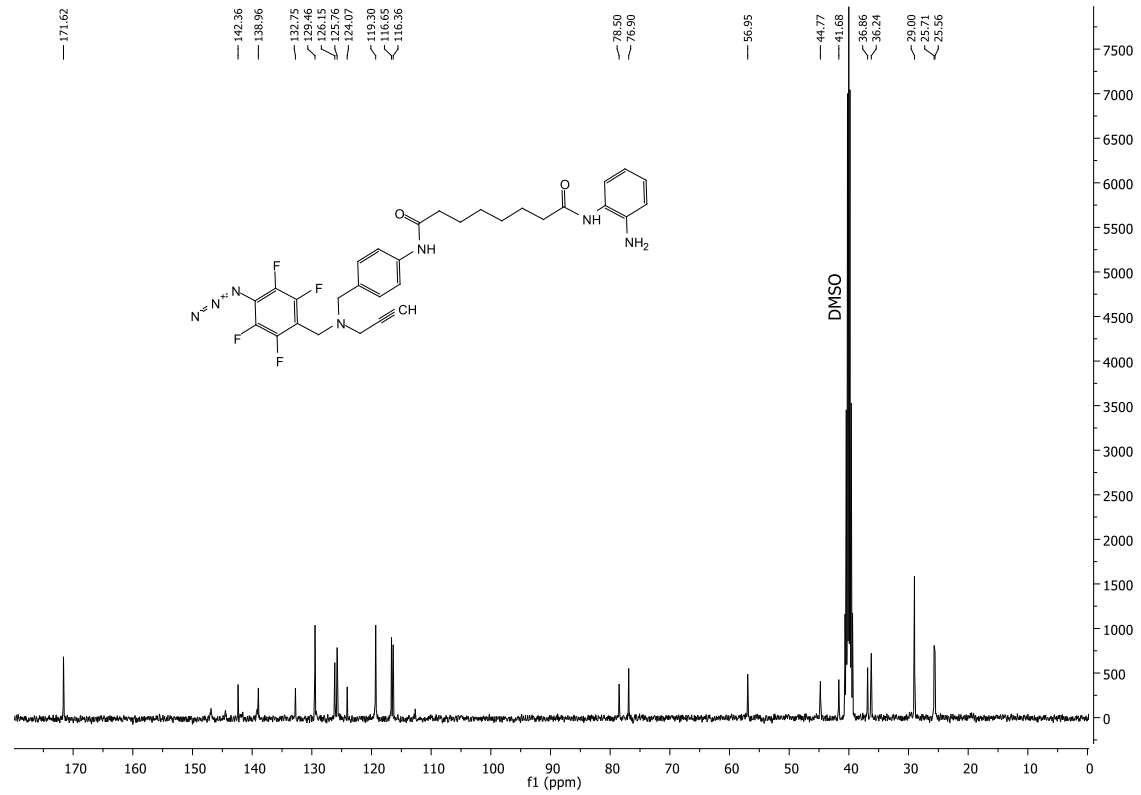
^{19}F NMR for intermediate **26**



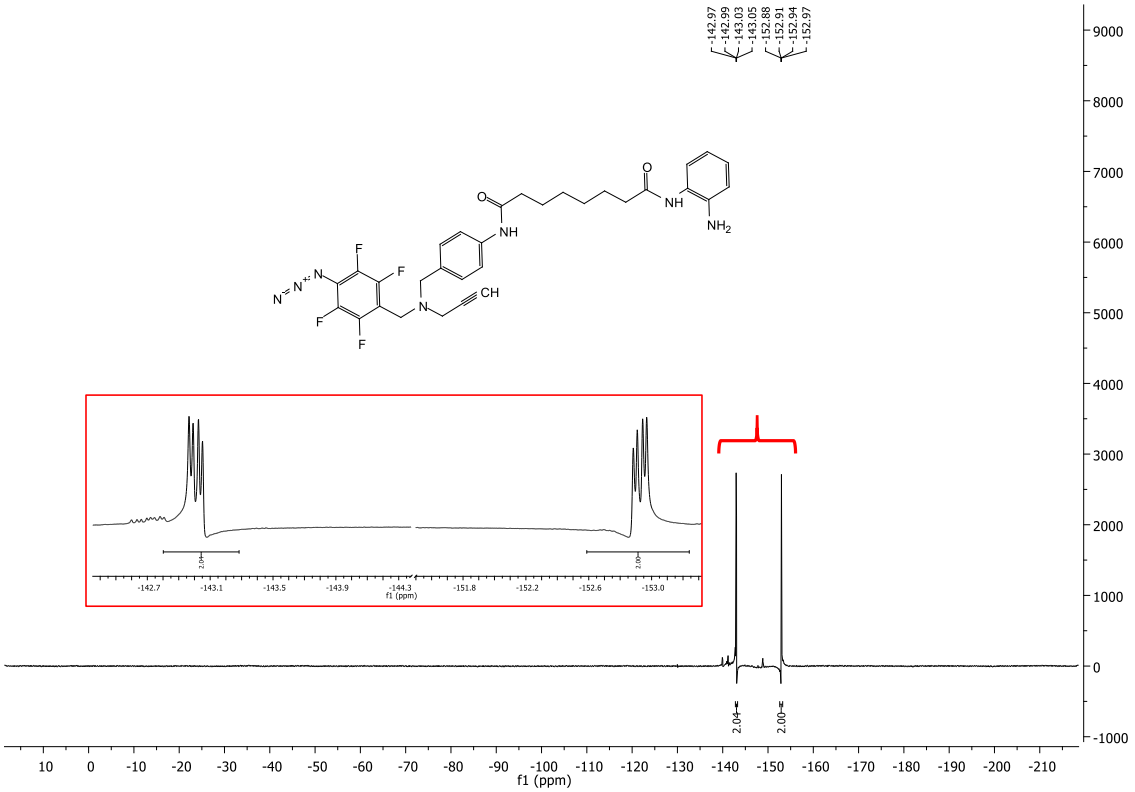
^{1}H-NMR for PRP **14**



^{13}C-NMR for PRP **14**



^{19}F-NMR for PRP 14

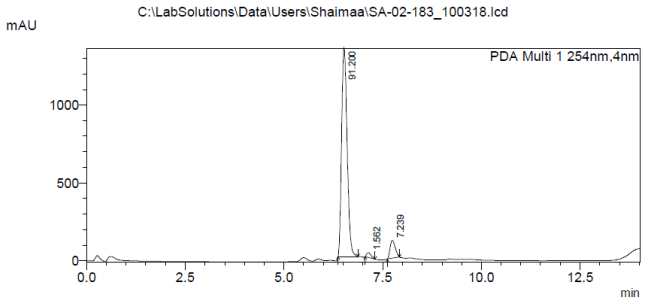


LC-MS analysis of PRP **14**

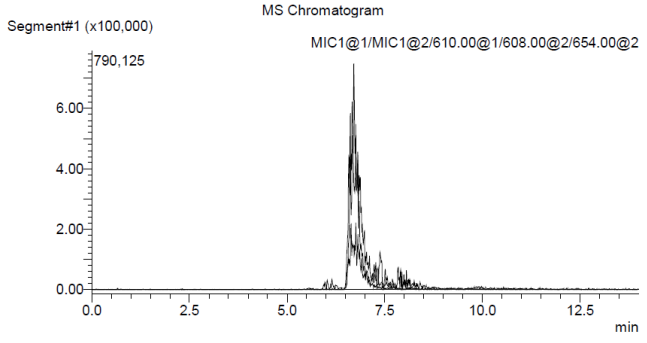
==== Shimadzu LabSolutions Analysis Report ====

C:\LabSolutions\Data\Users\Shaimaa\SA-02-183_100318.lcd
Acquired by : Shaimaa Aboukhatwa
Sample Name : SA-02-183_100318
Method File : C:\LabSolutions\Data\Users\Shaimaa\Methods\General_methods\DUIS_Posi_Neg 14 f
Month-Day Acquired : 10/3/2018

<Chromatogram>



MS Chromatogram

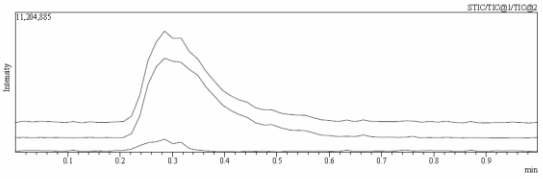


HRMS report for PRP **14**

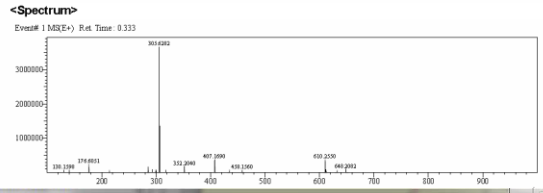
==== Shimadzu LCMSsolution Data Report ====

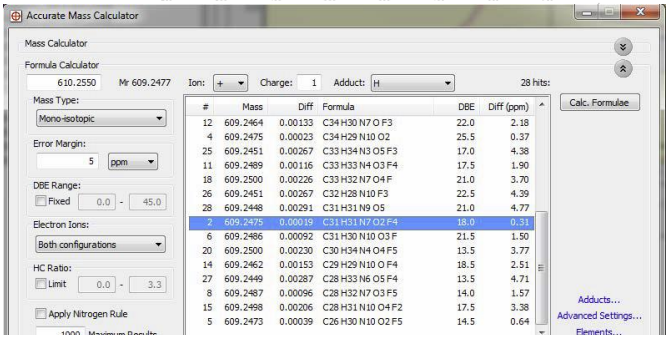
Sample Name : SA-2-183
Data Acquired : 10/12/2018

<Chromatogram>

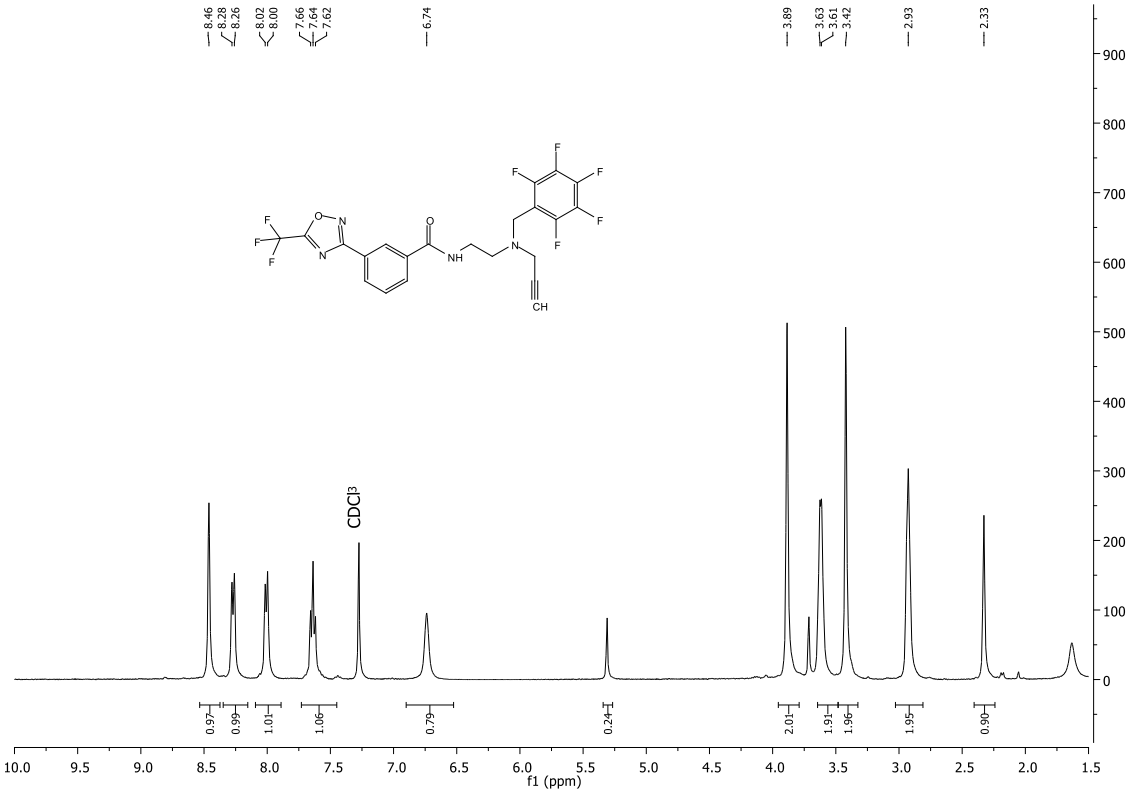


<Spectrum>

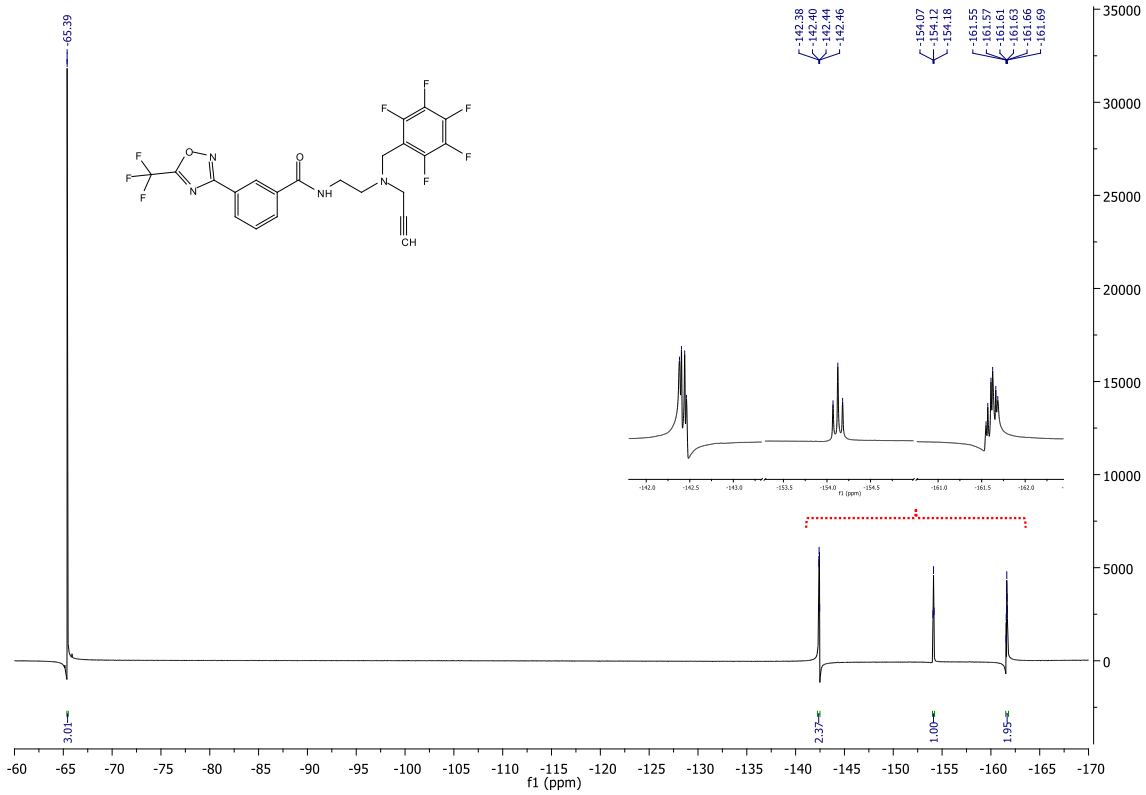




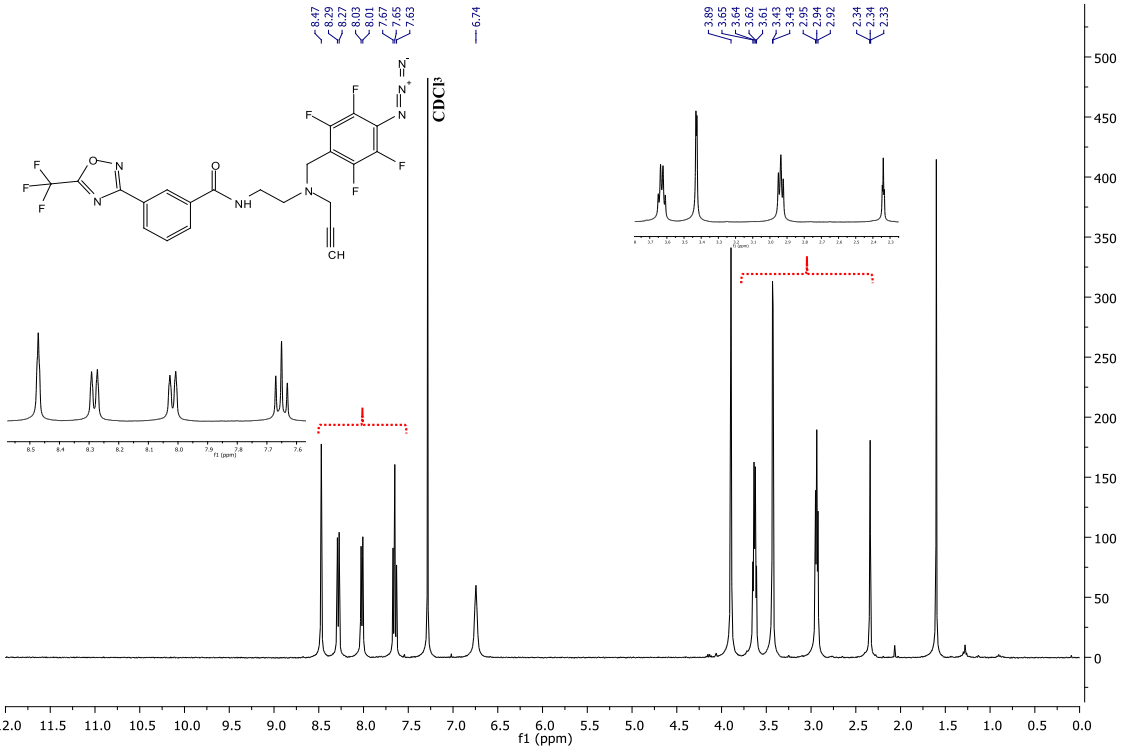
^{1}H NMR for intermediate **59**



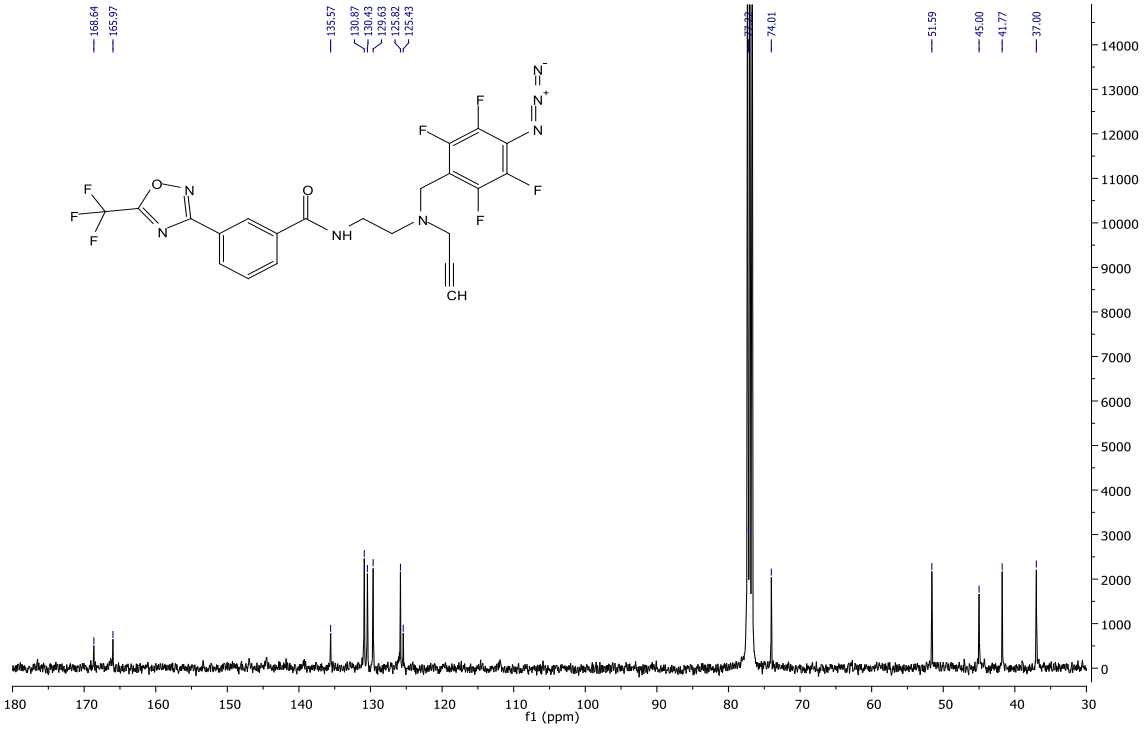
^{19}F NMR for intermediate **59**



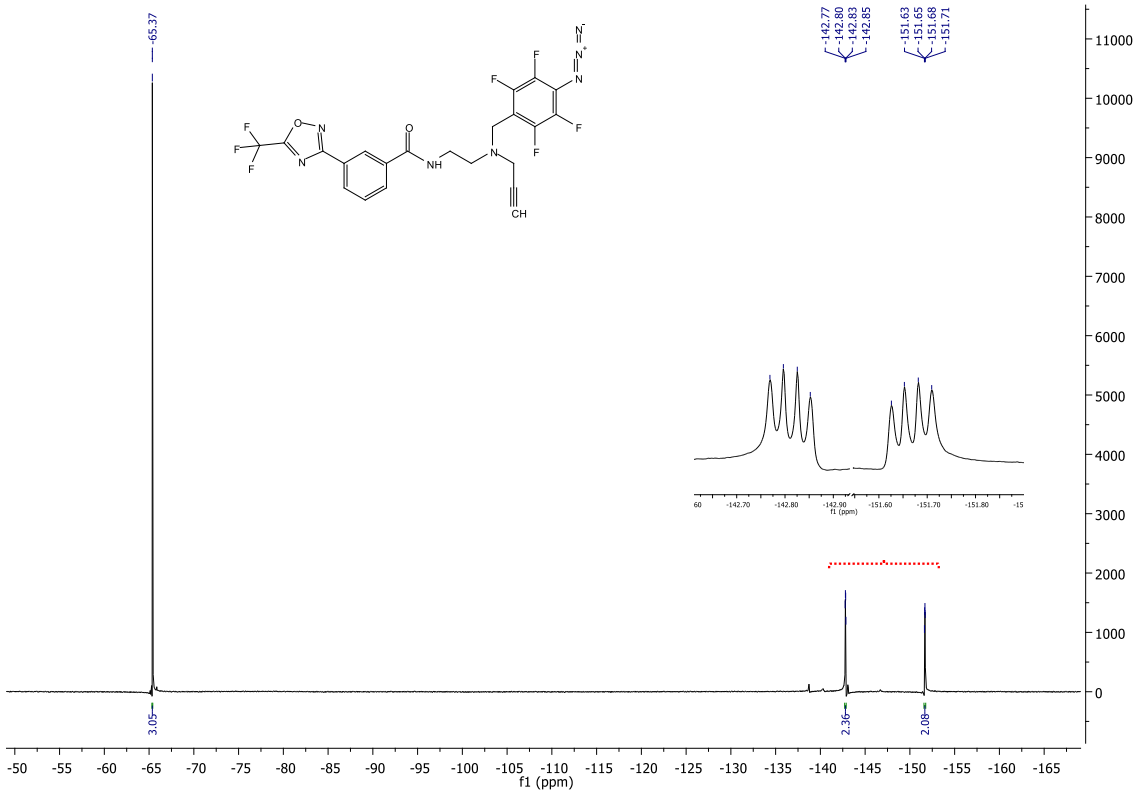
^{1}H NMR spectrum for PRP **15**



^{13}C NMR spectrum for PRP **15**



^{19}F NMR spectrum for PRP **15**

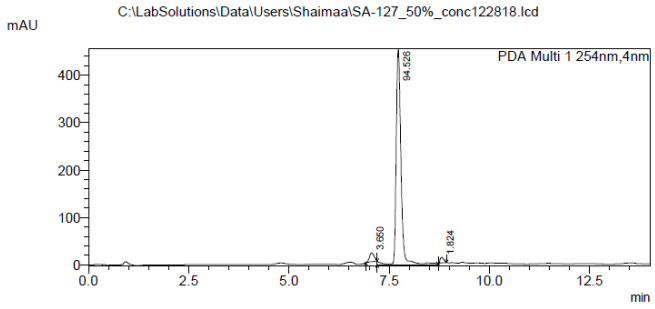


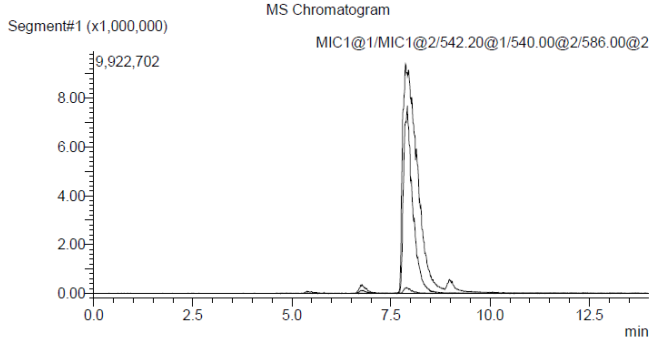
LCMS PRP **15**

==== Shimadzu LabSolutions Analysis Report ====

C:\LabSolutions\Data\Users\Shaimaa\SA-127_50%_conc122818.lcd
Acquired by : Shaimaa Aboukhatwa
Sample Name : SA-127_50%_conc122818
Method File : C:\LabSolutions\Data\Users\Shaimaa\Methods\General_methods\DUIS_Posi_Neg 14
Month-Day Processed : 12/28/2018

<Chromatogram>



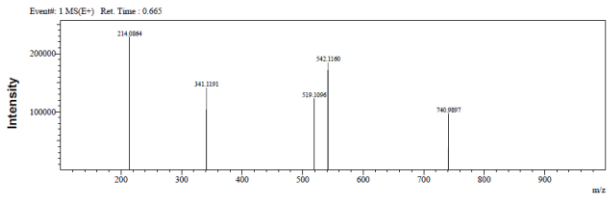


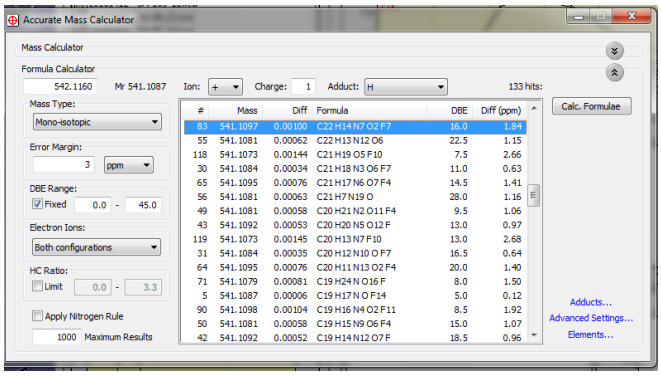
HRMS report for PRP **15**

==== Shimadzu LCMSsolution Data Report ====

Sample Name : SA-127
Data Acquired : 12/15/2016

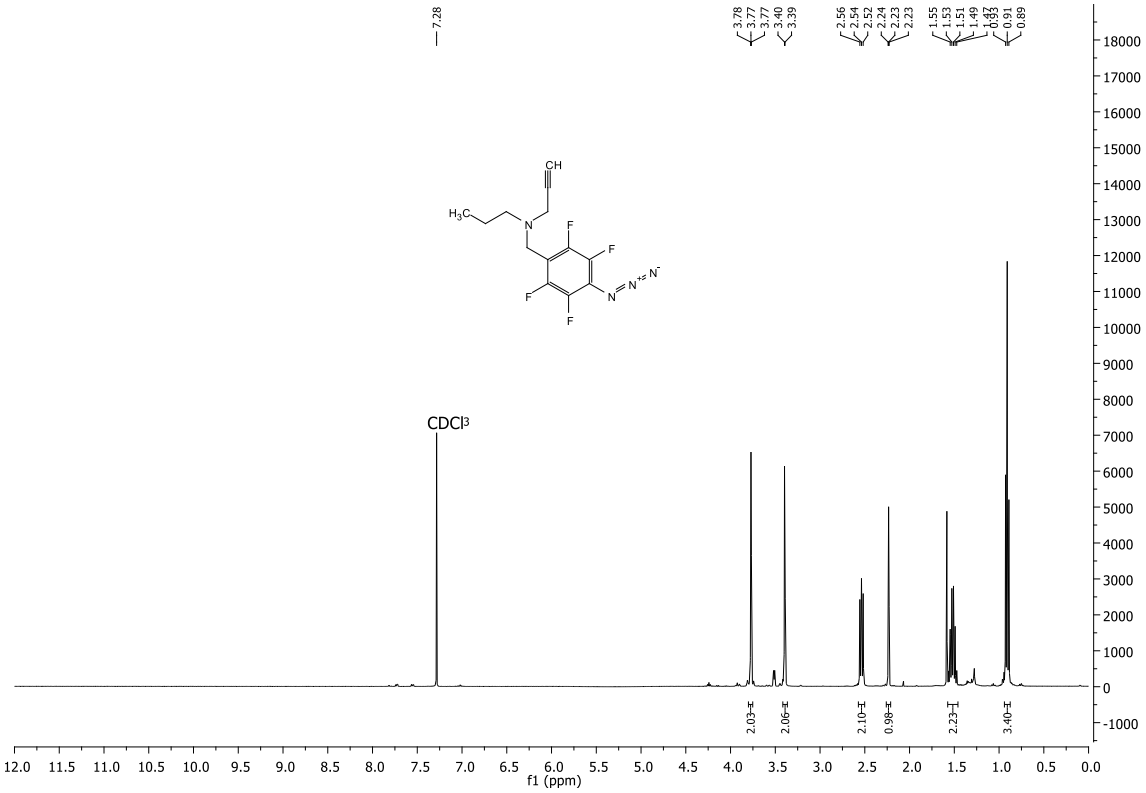
<Spectrum>



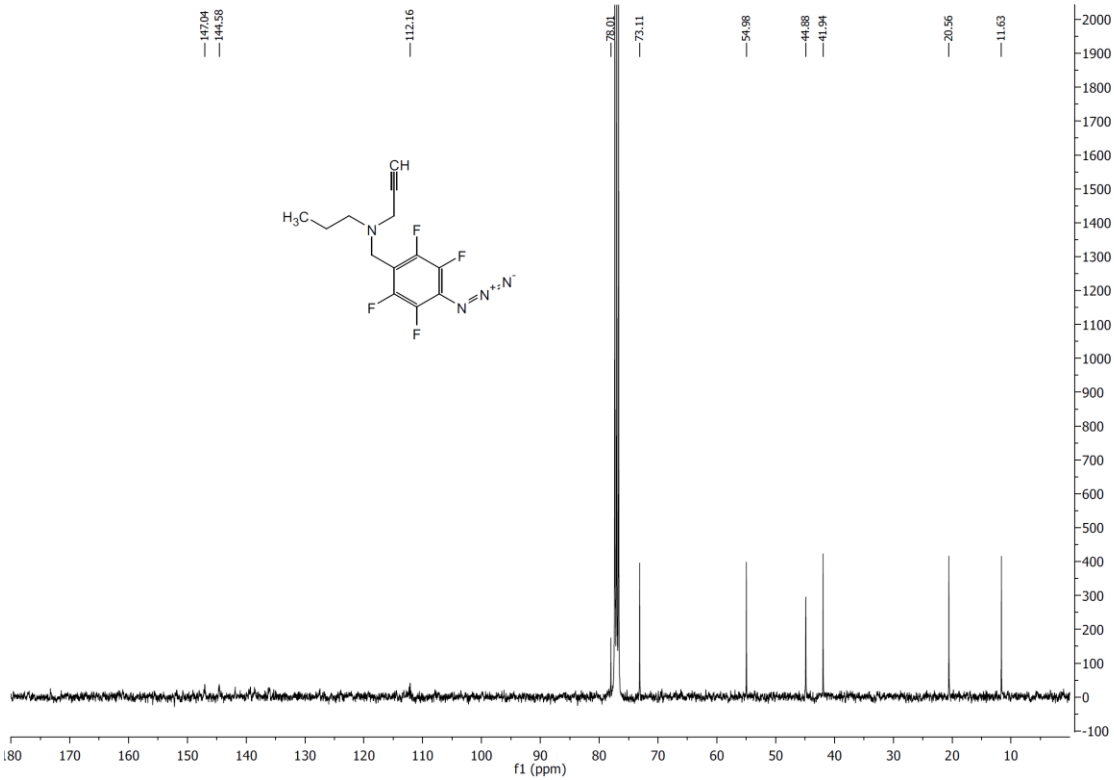


#	Mass	Diff	Formula	DBE	Diff (ppm)
83	541.1097	0.00100	C22 H14 N7 O2 F7	16.0	1.84
55	541.1081	0.00062	C22 H13 N12 O6	22.5	1.15
118	541.1073	0.00144	C21 H19 O5 F10	7.5	2.66
30	541.1084	0.00034	C21 H18 N3 O6 F7	11.0	0.63
65	541.1095	0.00076	C21 H17 N6 O7 F4	14.5	1.41
56	541.1081	0.00063	C21 H7 N19 O	28.0	1.16
49	541.1081	0.00058	C20 H21 N2 O11 F4	9.5	1.06
43	541.1092	0.00053	C20 H20 N5 O12 F	13.0	0.97
119	541.1073	0.00145	C20 H13 N7 F10	13.0	2.68
31	541.1084	0.00035	C20 H12 N10 O F7	16.5	0.64
64	541.1095	0.00076	C20 H11 N13 O2 F4	20.0	1.40
71	541.1079	0.00081	C19 H24 N O16 F	8.0	1.50
5	541.1087	0.00006	C19 H17 N O F14	5.0	0.12
90	541.1098	0.00104	C19 H16 N4 O2 F11	8.5	1.92
50	541.1081	0.00058	C19 H15 N9 O6 F4	15.0	1.07
42	541.1092	0.00052	C19 H14 N12 O7 F	18.5	0.96

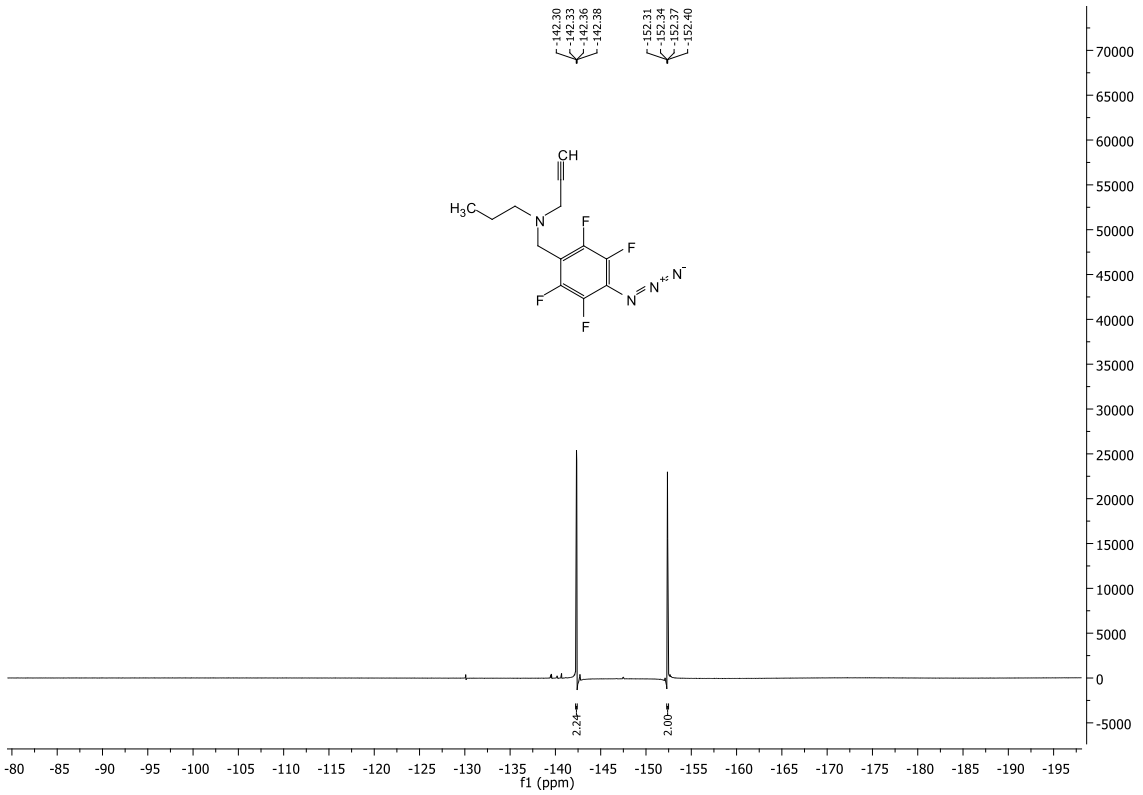
^{1}H NMR for **16**



^{13}C NMR for **16**



^{19}F NMR for **16**

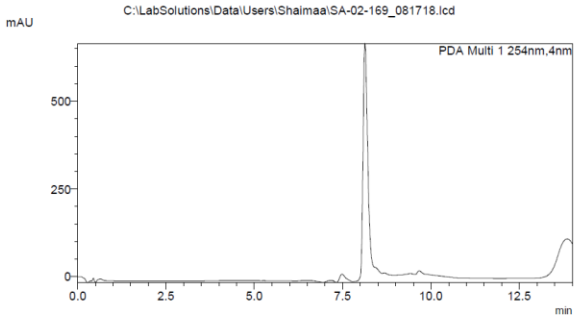


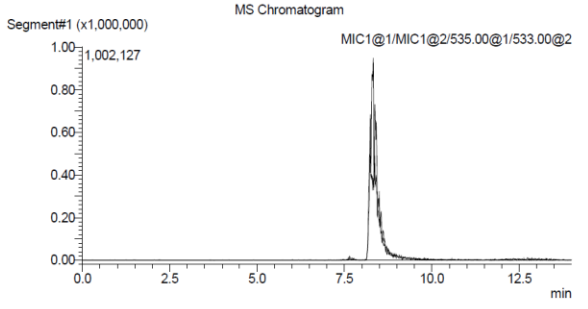
LC-MS analysis of **16**

==== Shimadzu LabSolutions Analysis Report ====

C:\LabSolutions\Data\Users\Shaimaa\SA-02-169_081718.lcd
Acquired by : Shaimaa Aboukhatwa
Sample Name : SA-02-169_081718
Method File : C:\LabSolutions\Data\Users\Shaimaa\Methods\General_methods\DUIS_Posi_Neg 14 f
Month-Day Acquired : 8/17/2018

<Chromatogram>



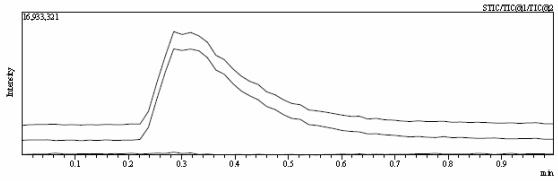


HRMS report for **16**

==== Shimadzu LCMSsolution Data Report ====

Sample Name : SA-2-179
Data Acquired : 10/12/2018

<Chromatogram>



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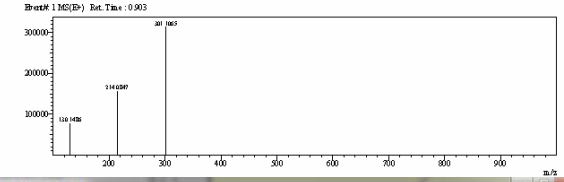
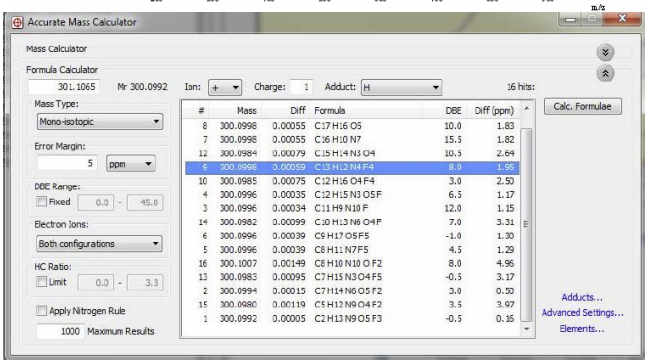
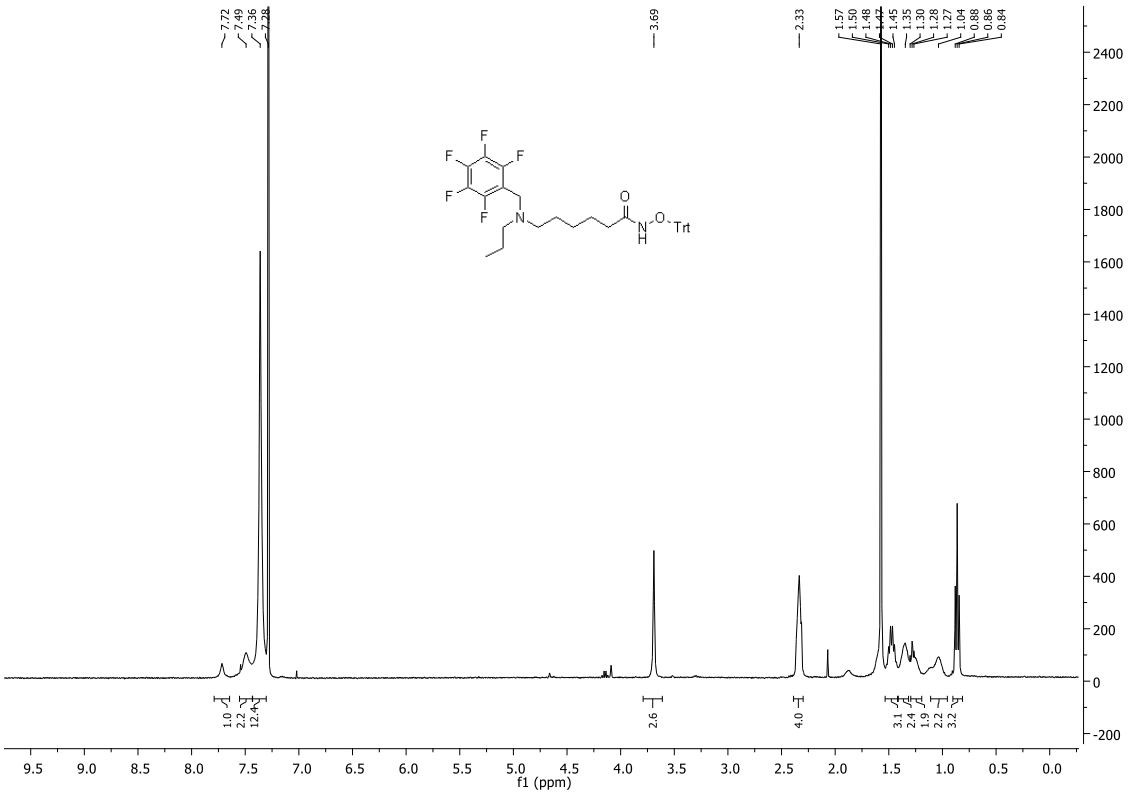


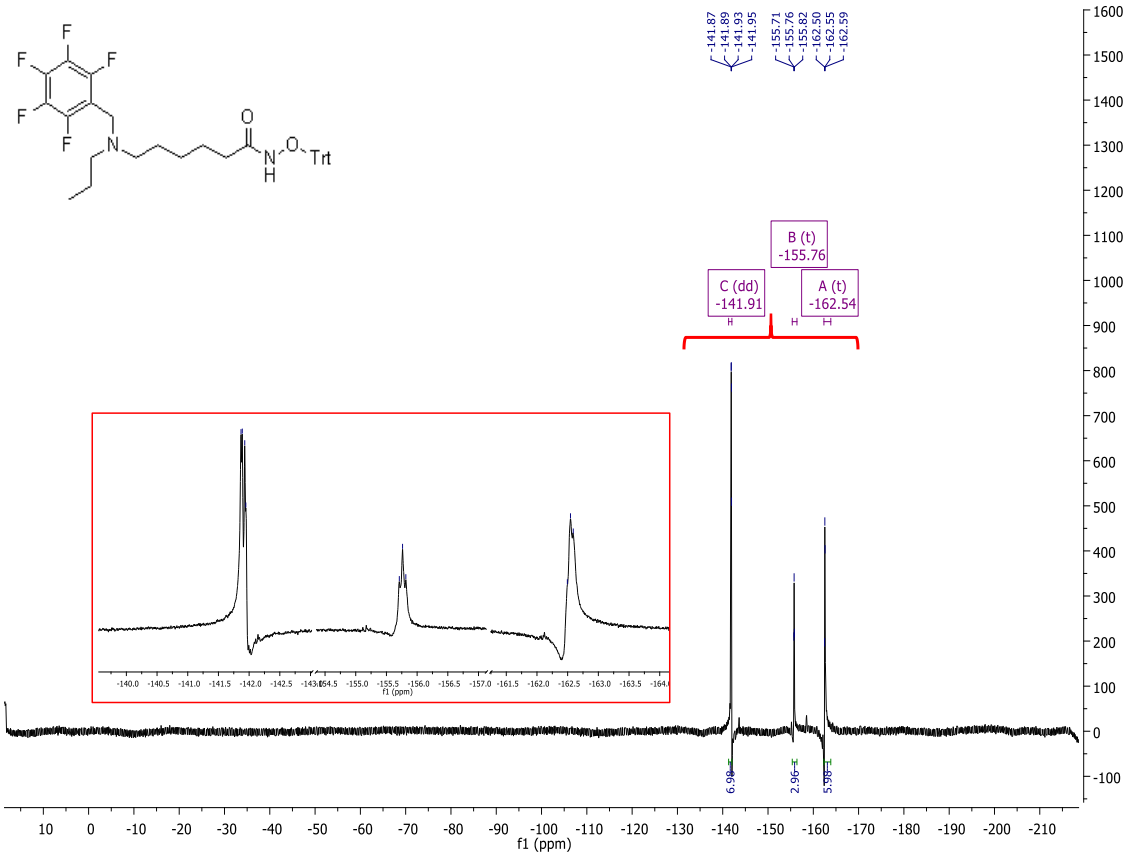


#	Mass	Diff	Formula	DBE	Diff (ppm)
8	300.0998	0.00055	C17 H16 O5	10.0	1.83
7	300.0998	0.00055	C16 H10 N7	15.5	1.82
12	300.0984	0.00079	C15 H14 N3 O4	10.5	2.64
9	300.0998	0.00059	C13 H12 N4 F4	8.0	1.95
10	300.0985	0.00075	C12 H16 O4 F4	3.0	2.50
4	300.0996	0.00035	C12 H15 N3 O5 F	6.5	1.17
3	300.0996	0.00034	C11 H9 N10 F	12.0	1.15
14	300.0982	0.00099	C10 H13 N6 O4 F	7.0	3.31
6	300.0996	0.00039	C9 H17 O5 F5	-1.0	1.30
5	300.0996	0.00039	C8 H11 N7 F5	4.5	1.29
16	300.1007	0.00149	C8 H10 N10 O F2	8.0	4.96
13	300.0983	0.00095	C7 H15 N3 O4 F5	-0.5	3.17
2	300.0994	0.00015	C7 H14 N6 O5 F2	3.0	0.50
15	300.0980	0.00119	C5 H12 N9 O4 F2	3.5	3.97
1	300.0992	0.00005	C2 H13 N9 O5 F3	-0.5	0.16

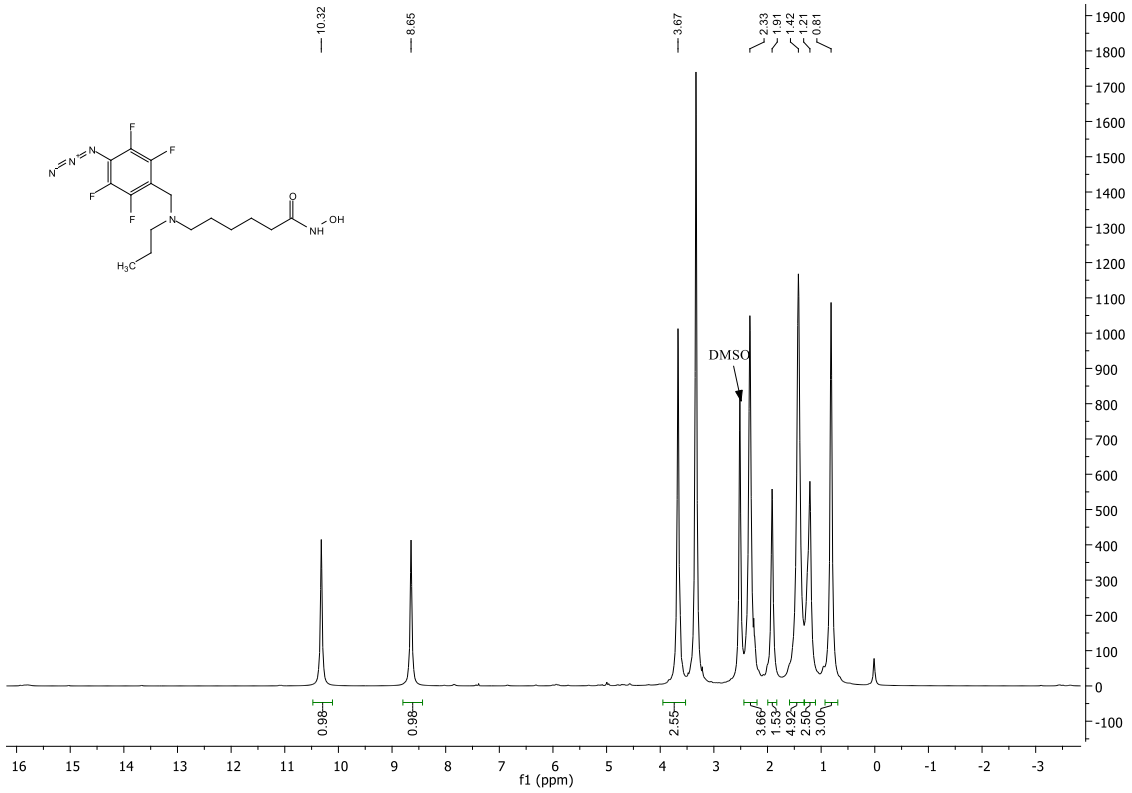
^{1}H NMR for intermediate **S18**



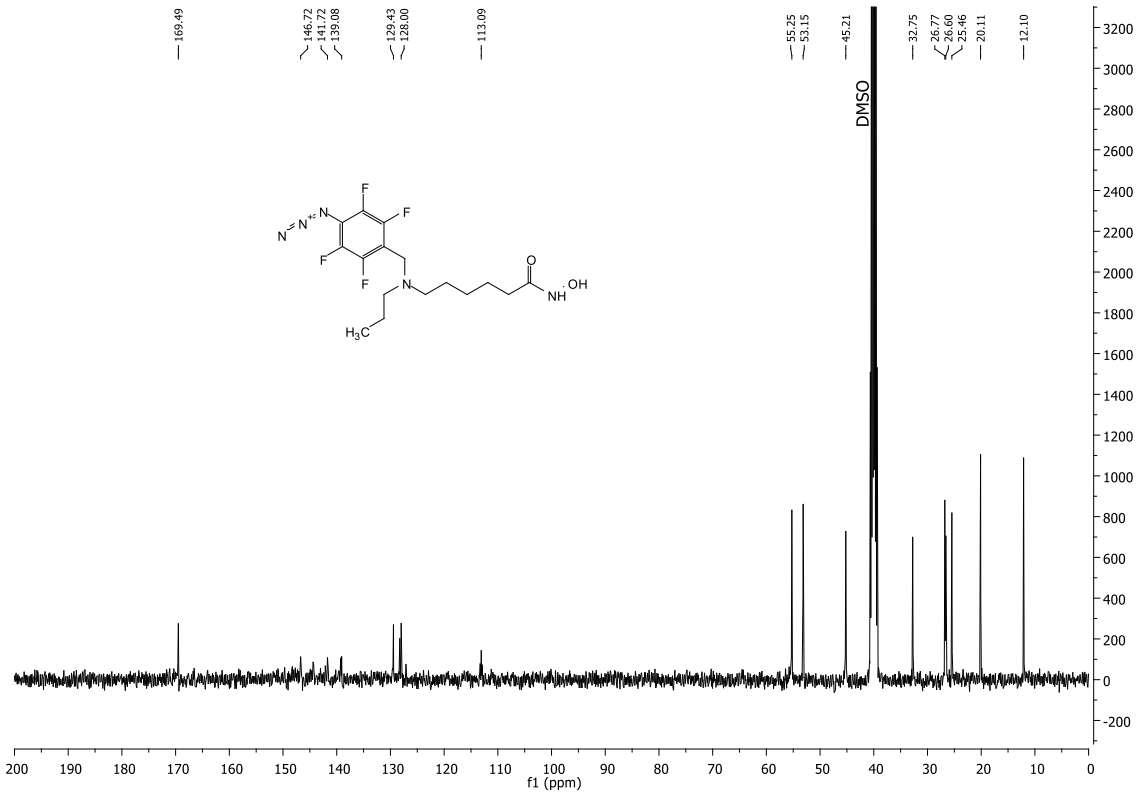
^{19}F NMR for intermediate **S18**



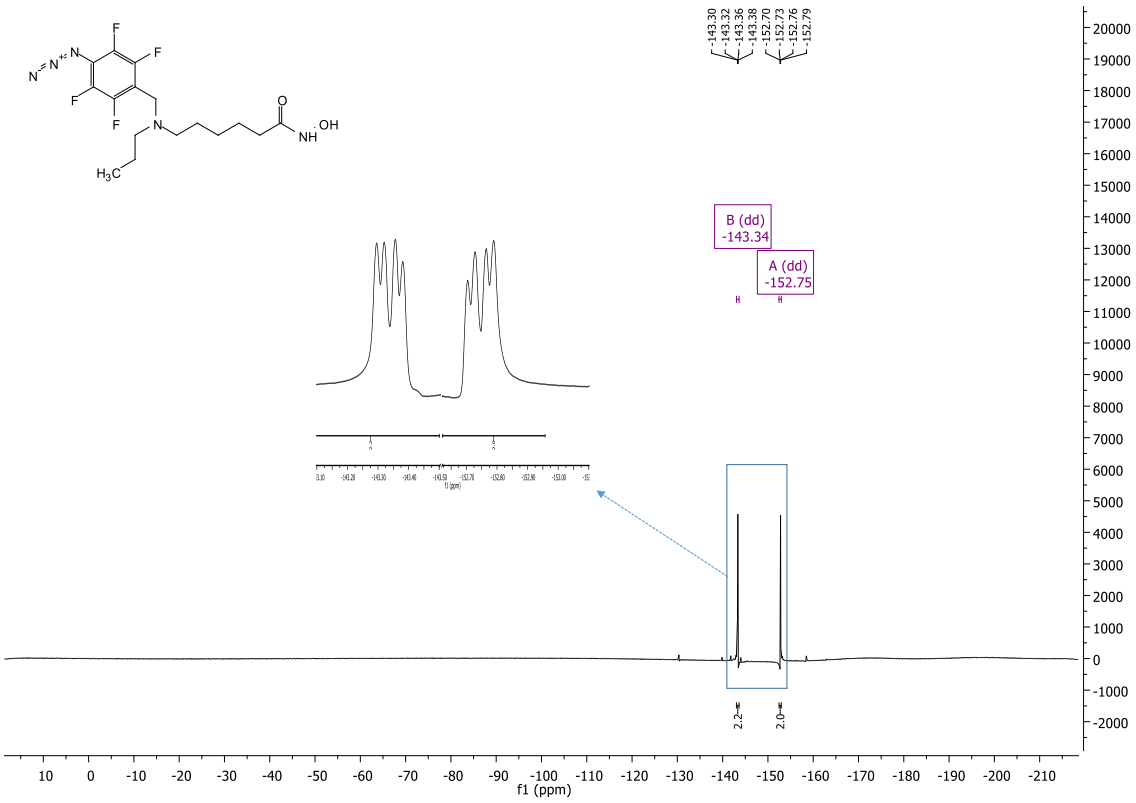
^{1}H NMR for **S20**



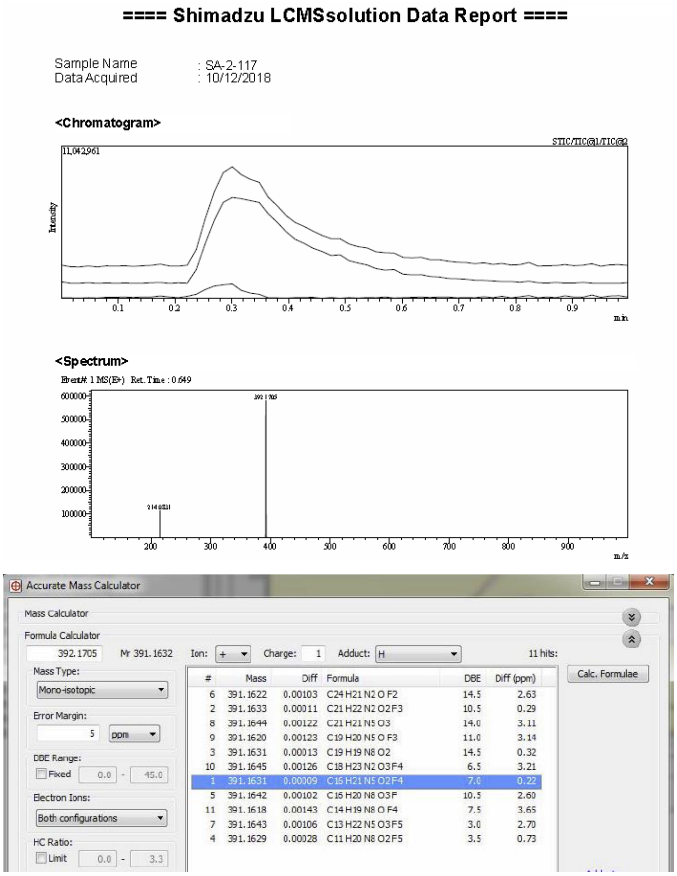
^{13}C NMR for **S20**



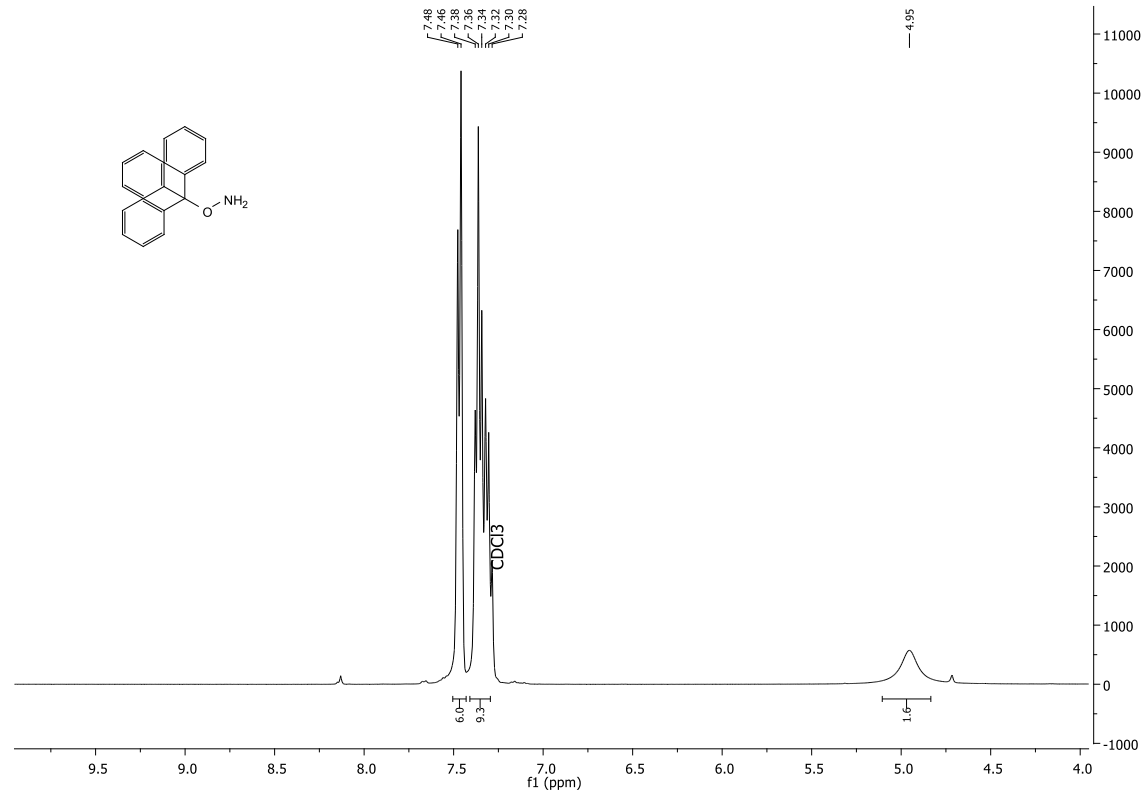
^{19}F NMR for **S20**



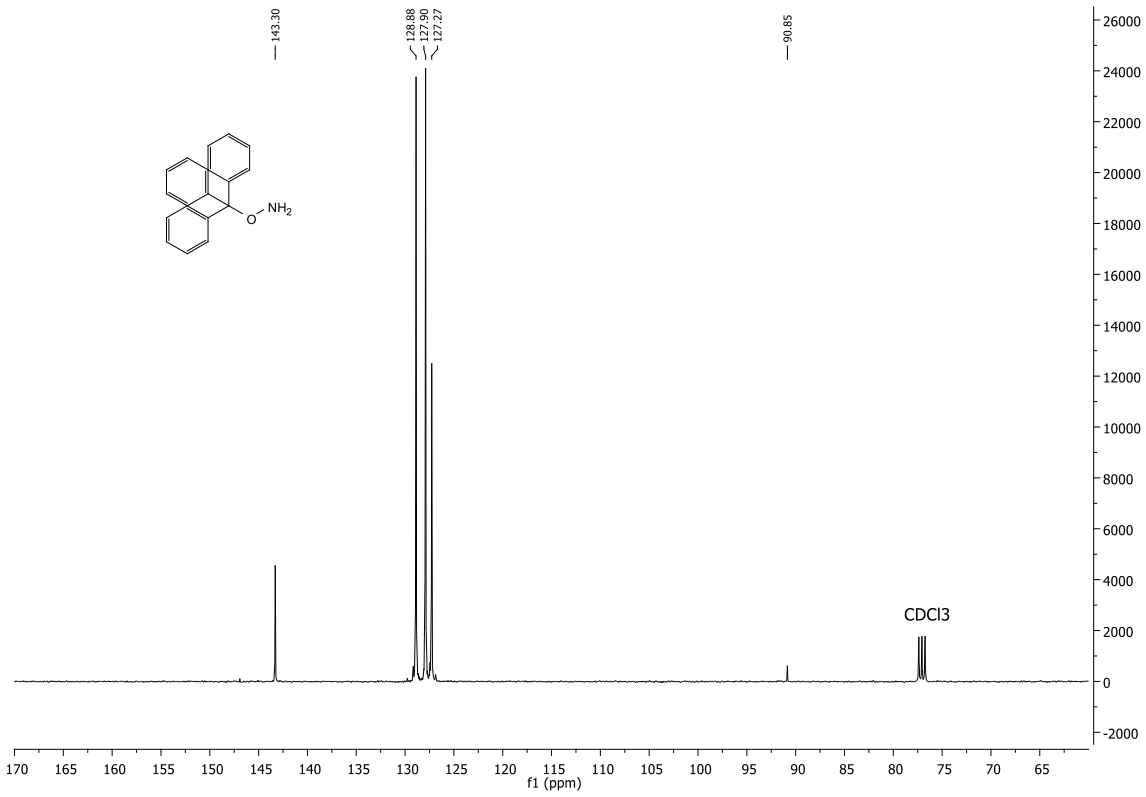
HRMS report for **S20**



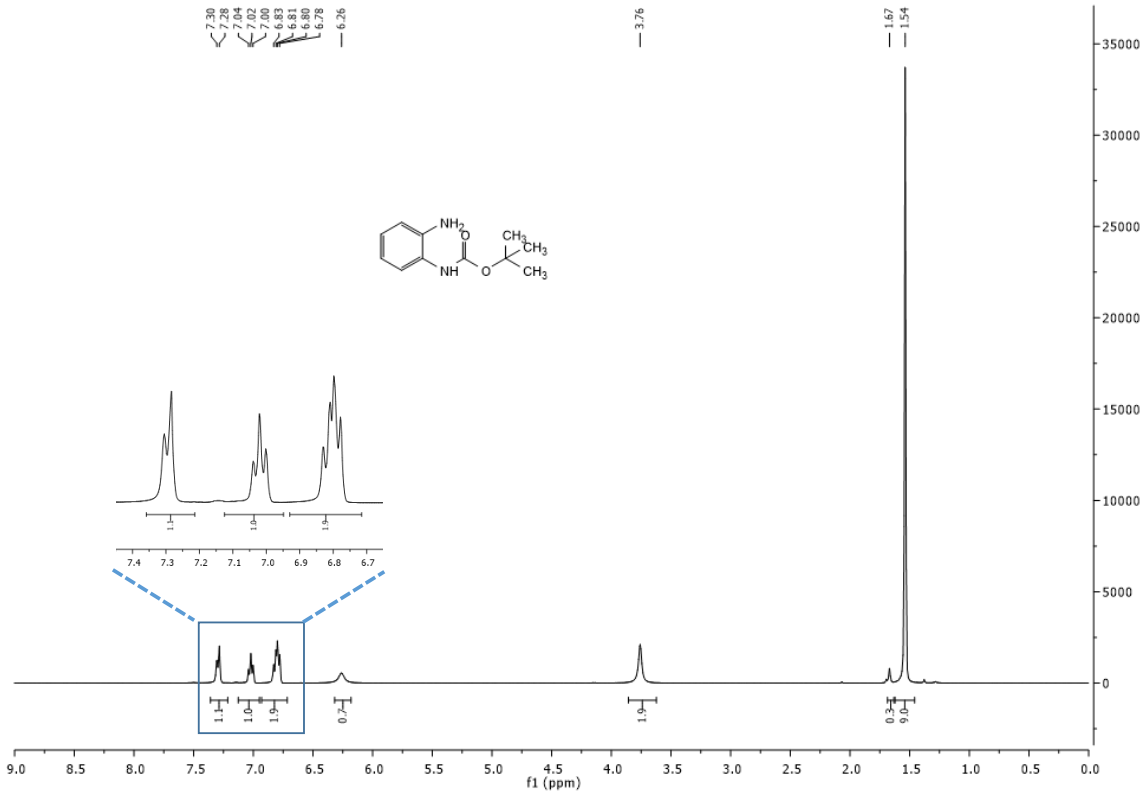
^{1}H NMR for **19**



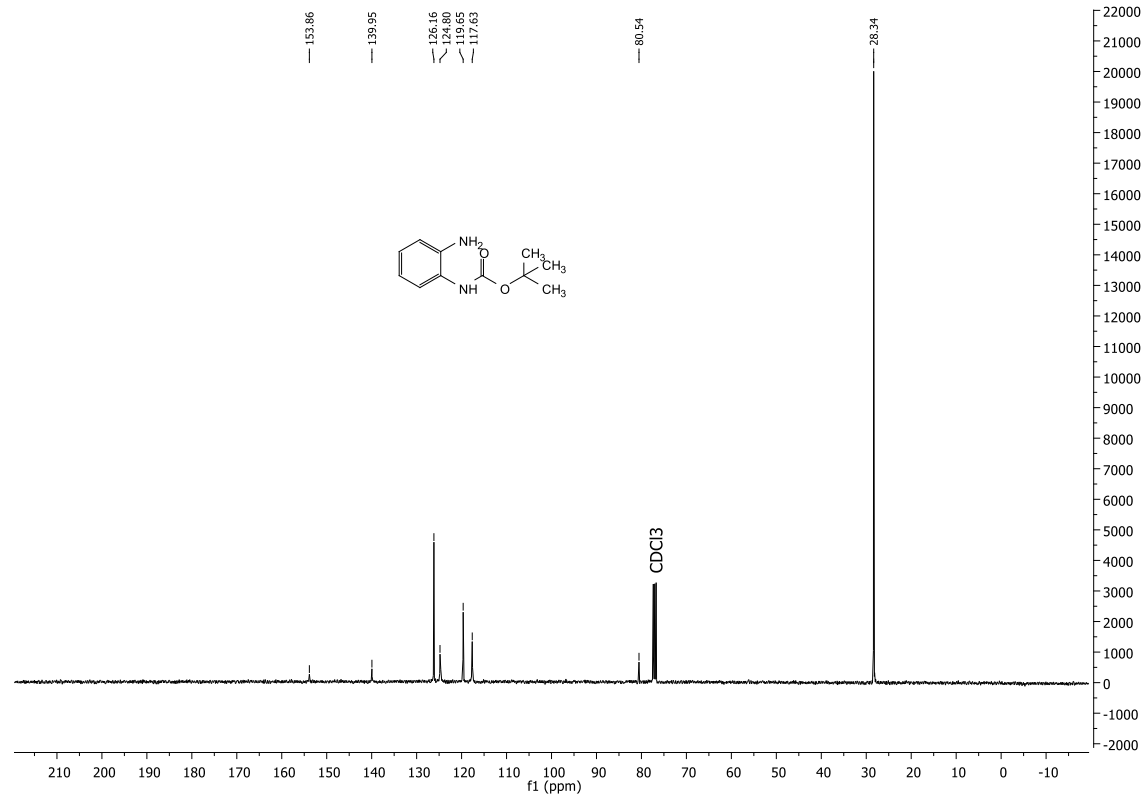
^{13}C NMR for **19**



^{1}H NMR for **20**



^{13}C NMR for **20**



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