Supporting Information

Improved Synthesis of the Nav1.7 Inhibitor GDC-0276 via a Highly Regioselective S_NAr Reaction

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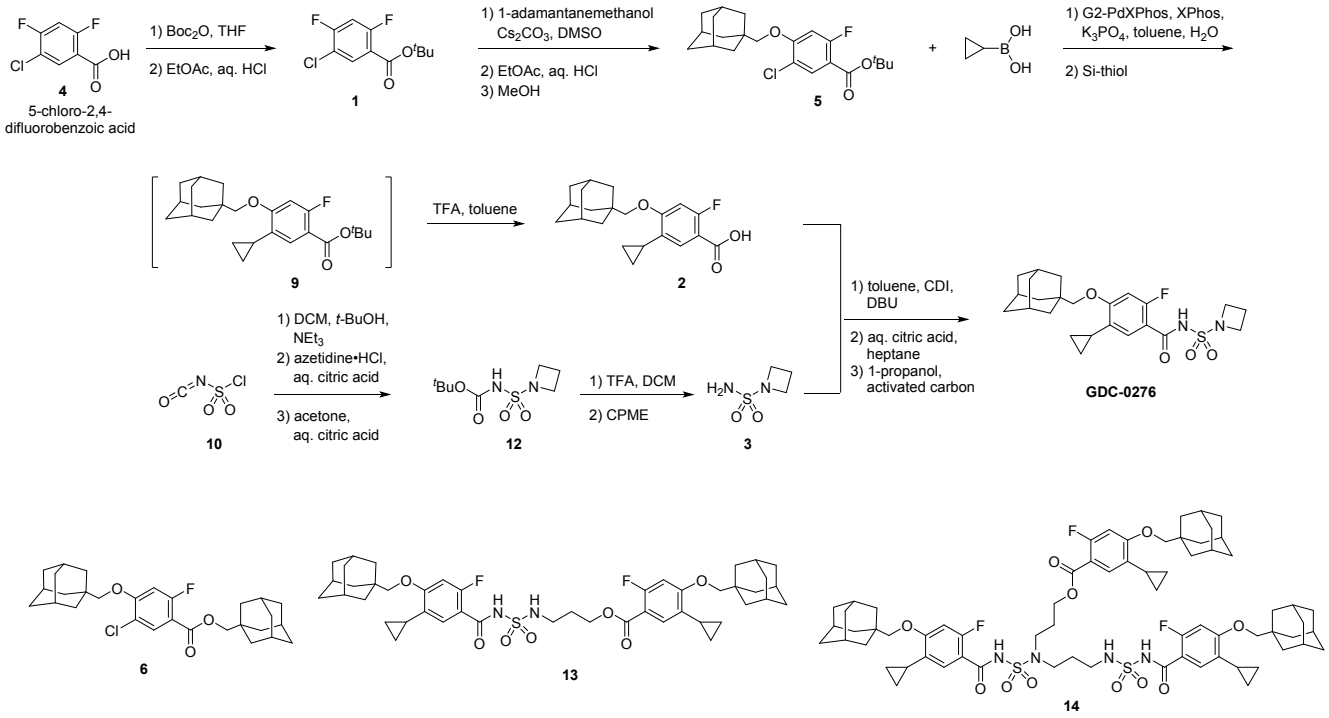
Scheme S1. *GDC-0276 Synthetic Scheme 1st Generation*



Scheme S2. *GDC-0276 Synthetic Scheme 2nd Generation*

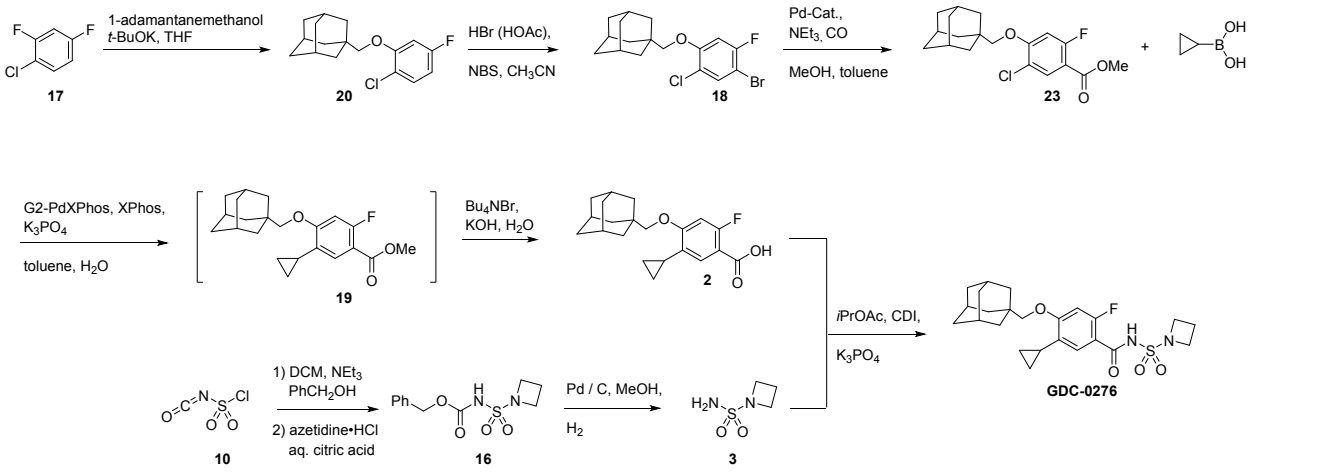


Figure S-1.1. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of *t-butyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **5**.

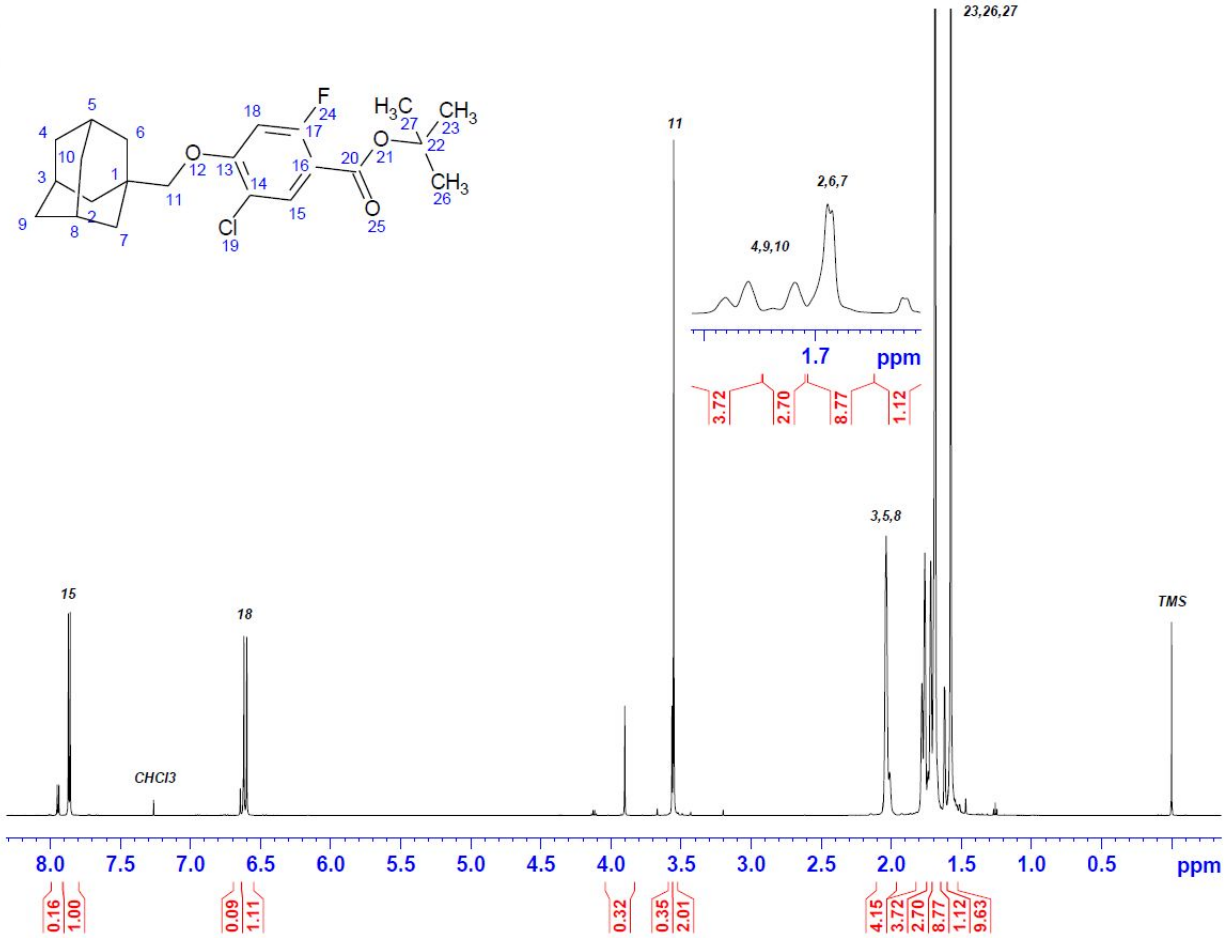


Figure S-1.2. ^{13}C NMR (150 MHz, $CDCl_3$) spectrum of *t-butyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **5**.

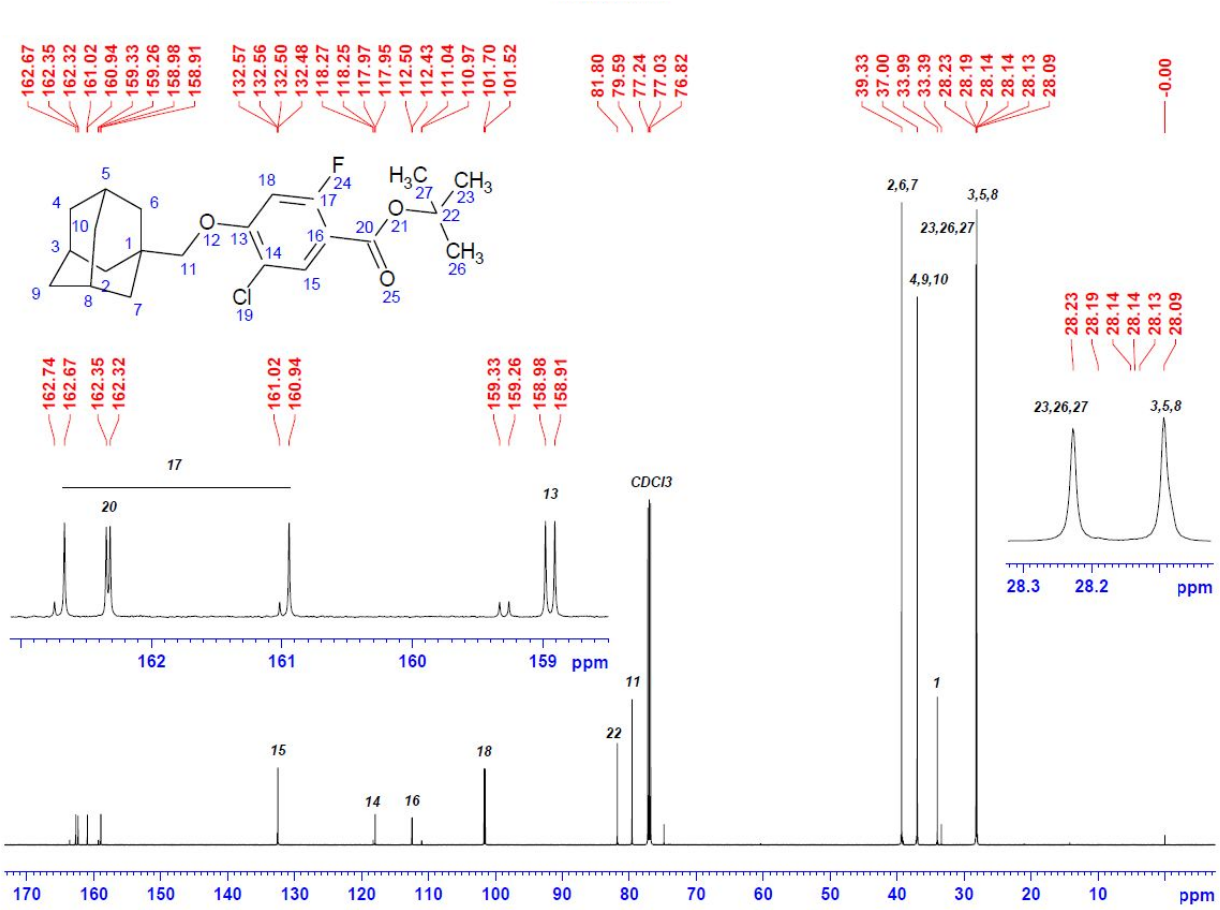


Figure S-1.3. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid* **2**.

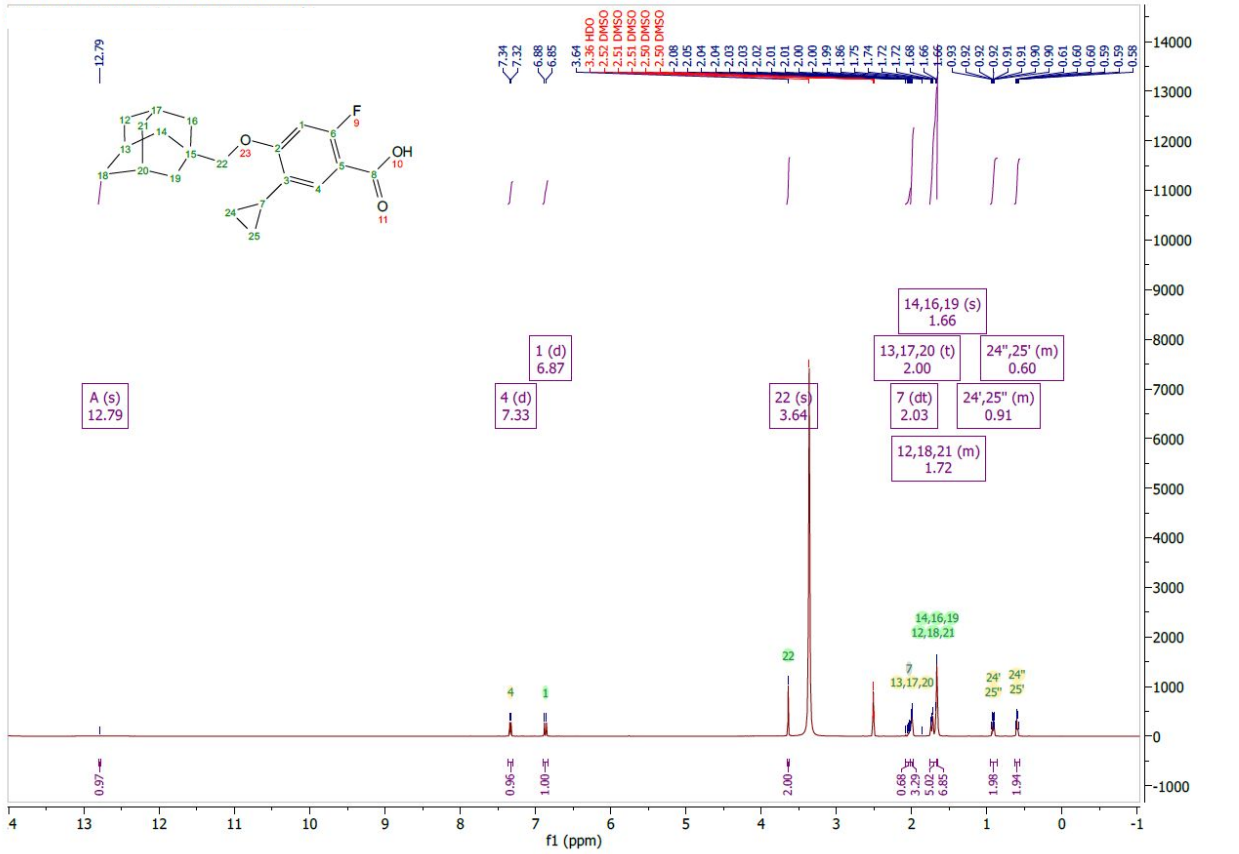


Figure S-1.4. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of *4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid* **2**.

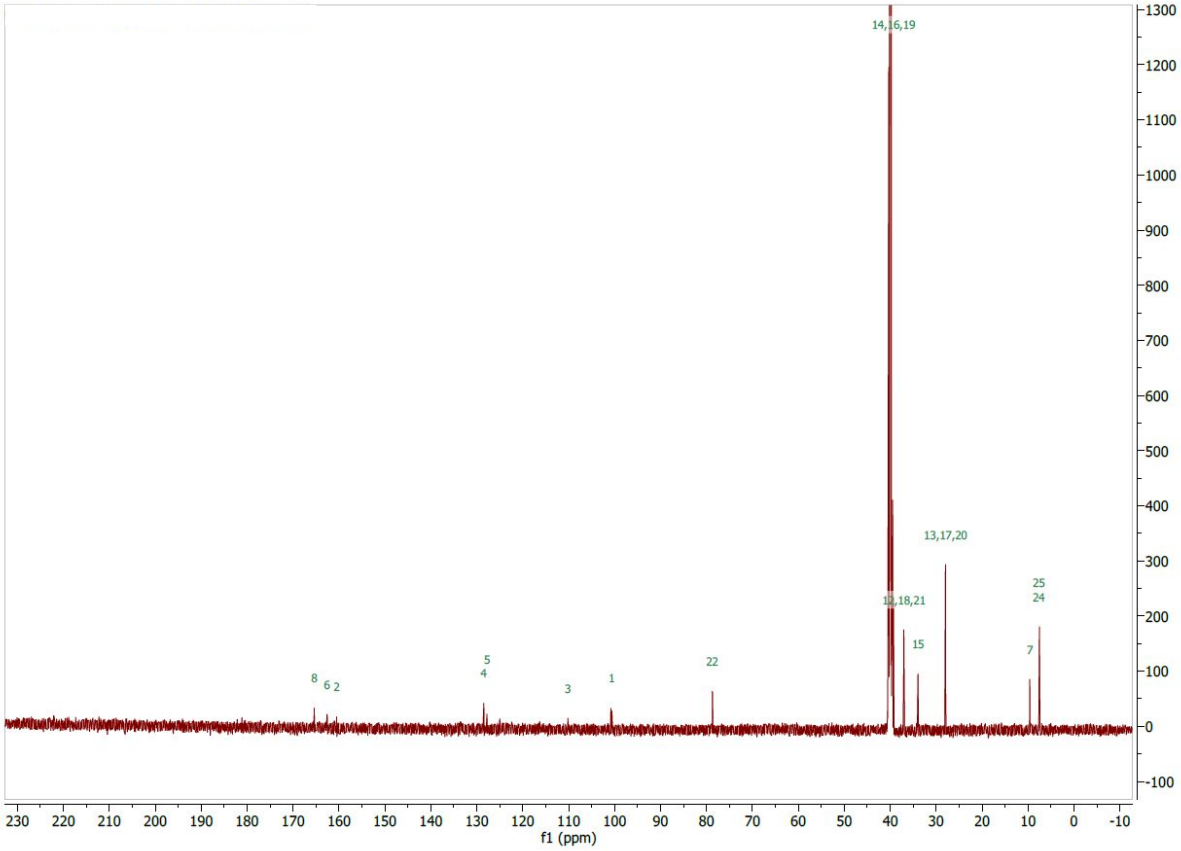


Figure S-1.5. HSQC spectrum of *4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid* **2**.

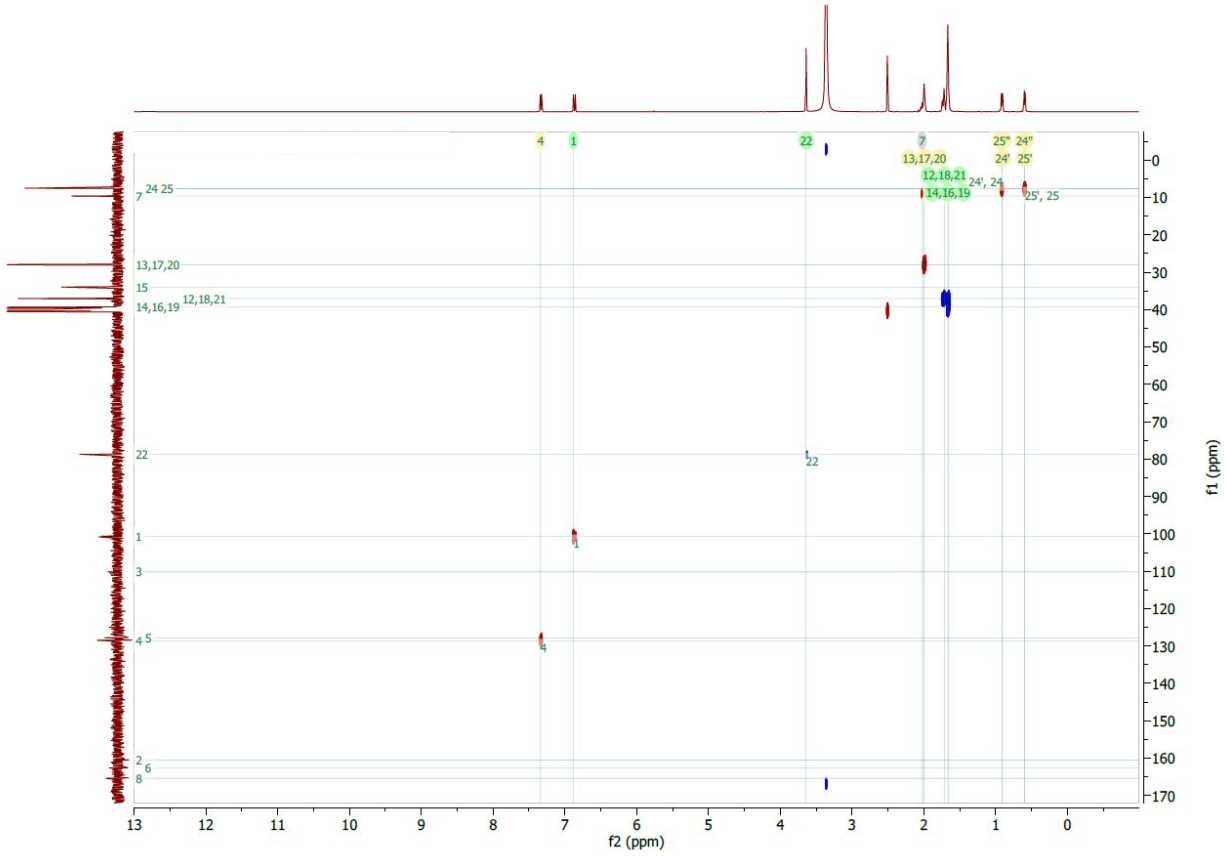


Figure S-1.6. HMBC spectrum of *4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid* **2**.

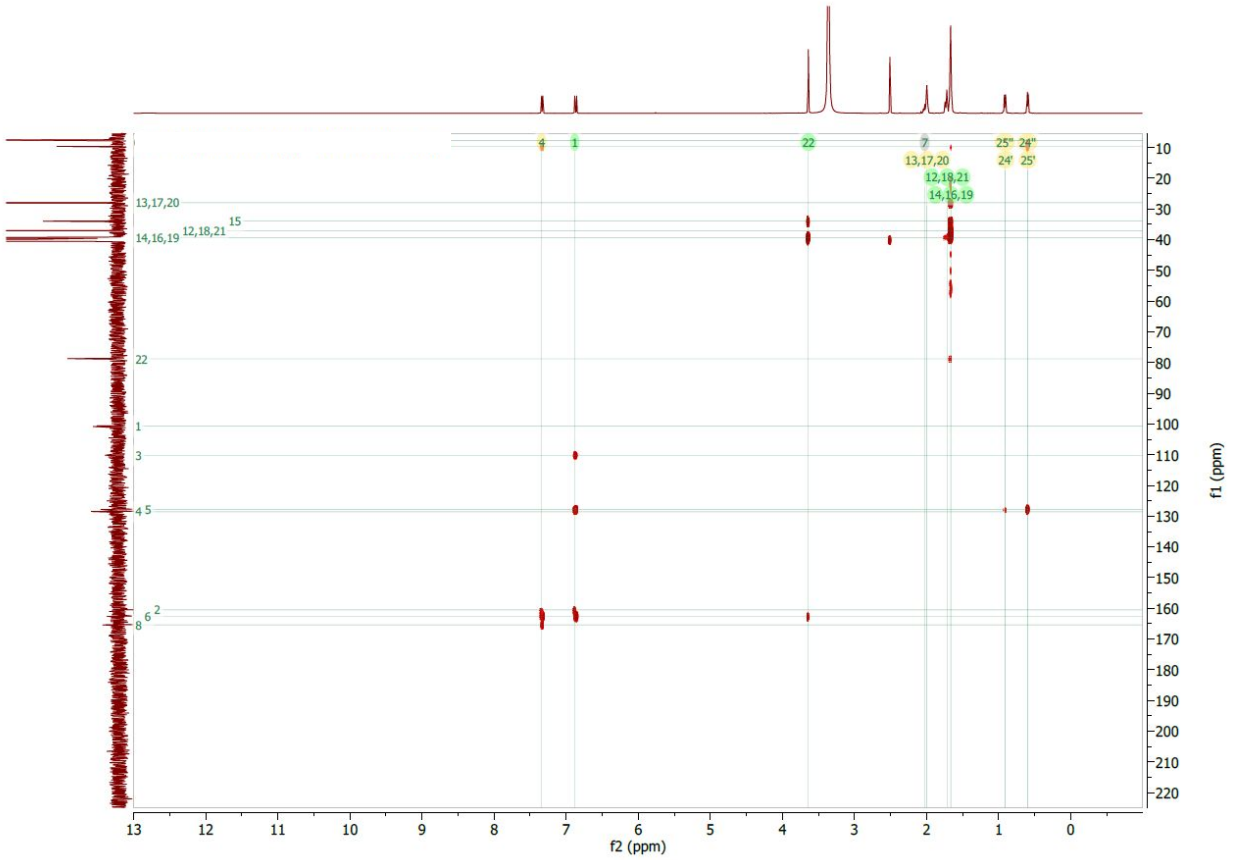


Figure S-1.7. COSY spectrum of *4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid* **2**.

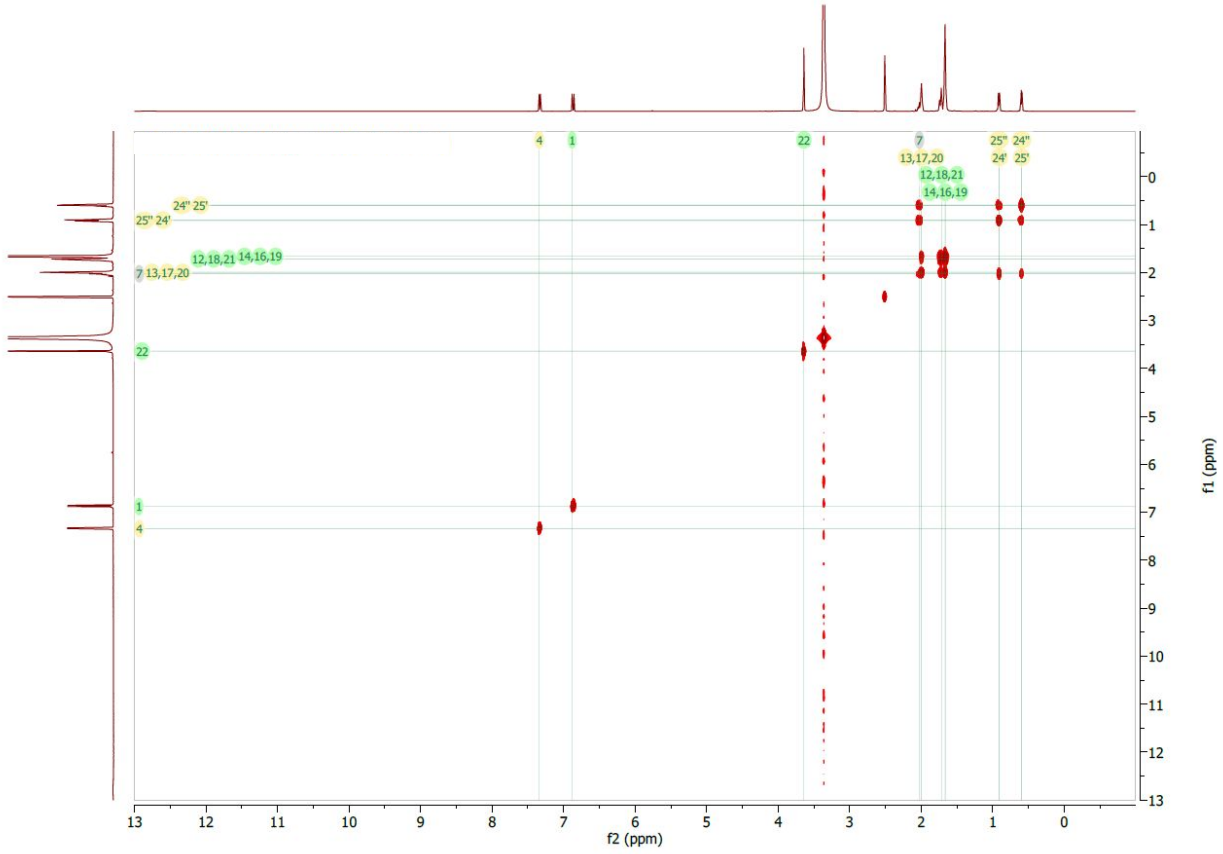


Figure S-1.8. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *t-butyl (azetidin-1-ylsulfonyl)carbamate* **12**.

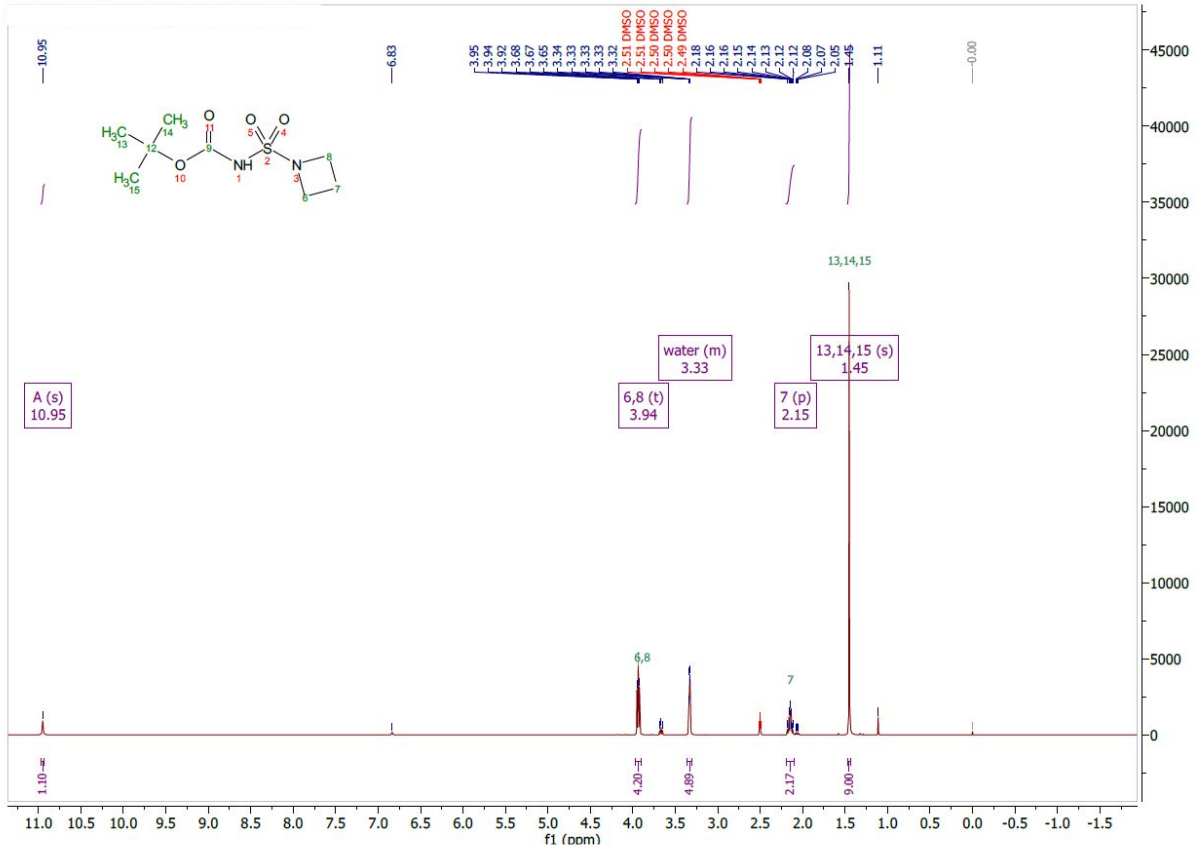


Figure S-1.9. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of *t-butyl (azetidin-1-ylsulfonyl)carbamate* **12**.

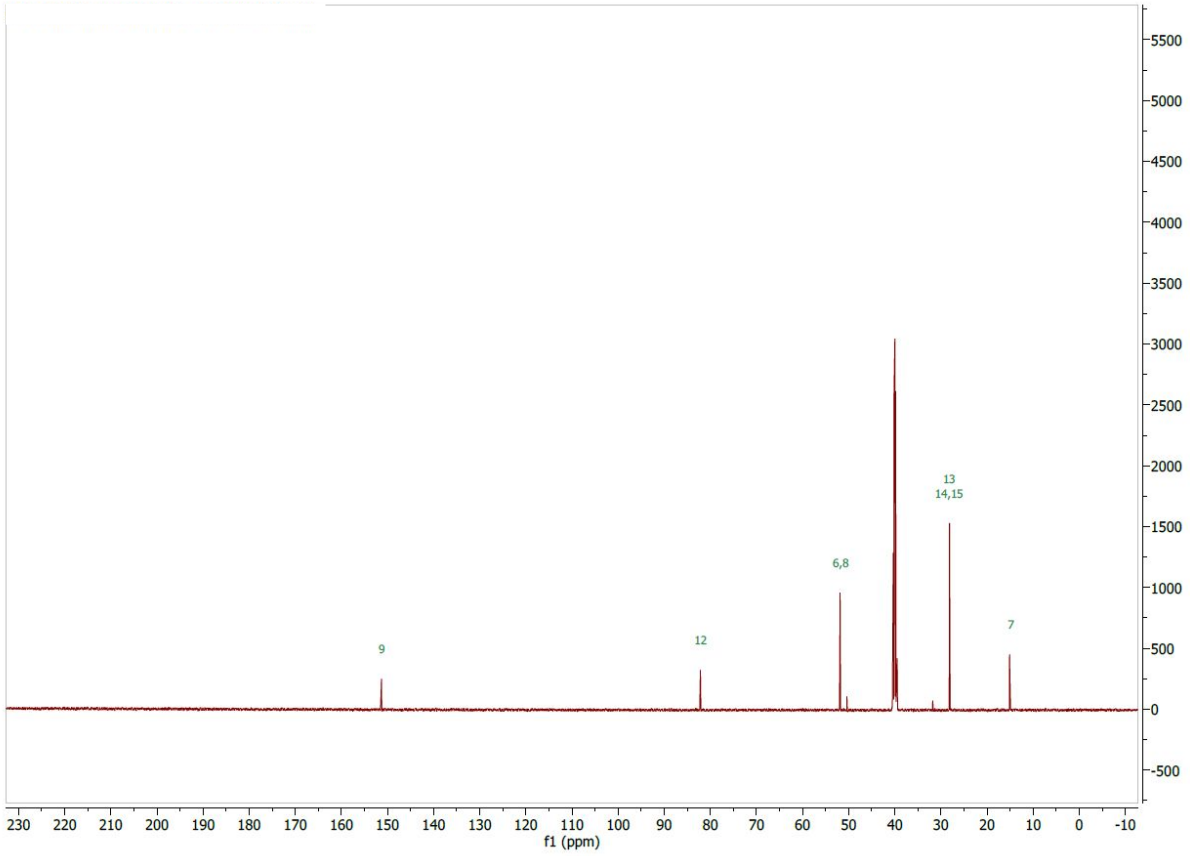


Figure S-1.10. HSQC spectrum of *t-butyl (azetidin-1-ylsulfonyl)carbamate* **12**.

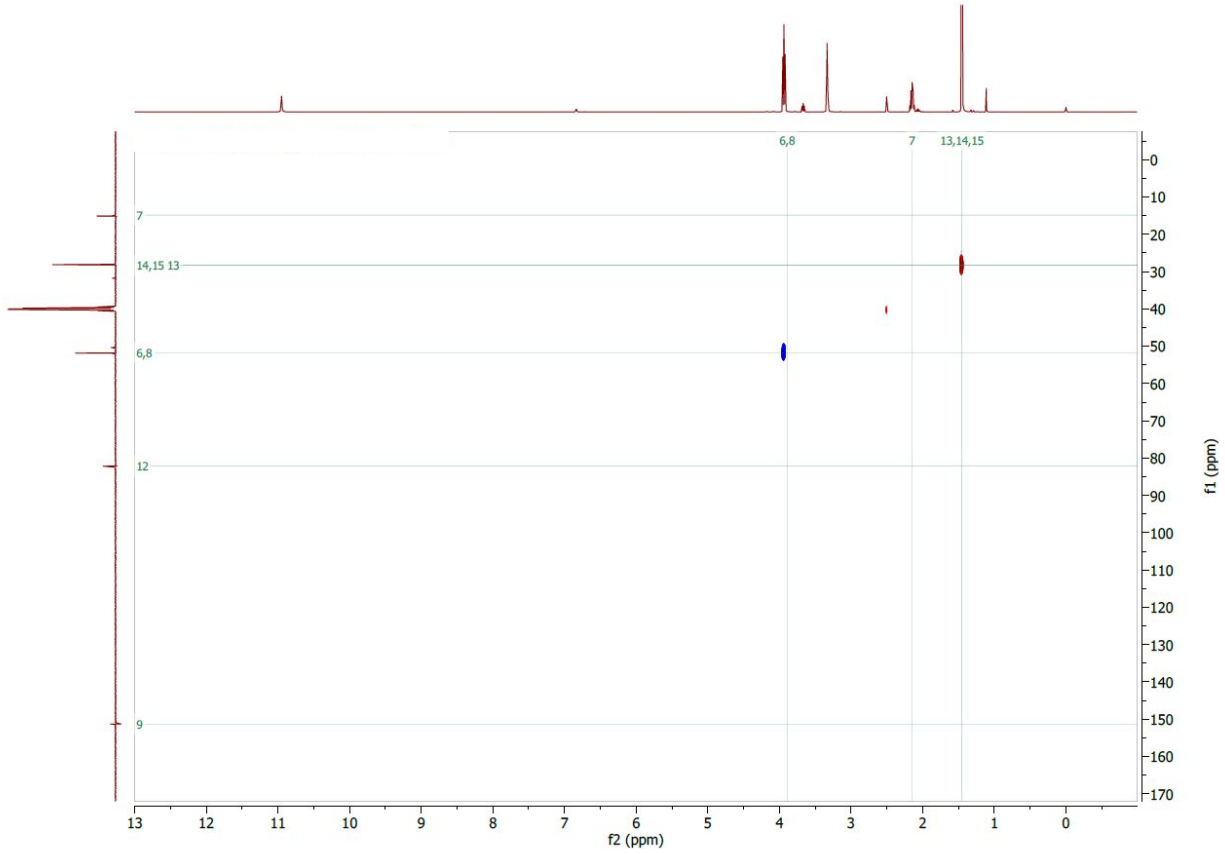


Figure S-1.11. HMBC spectrum of *t-butyl (azetidin-1-ylsulfonyl)carbamate* **12**.

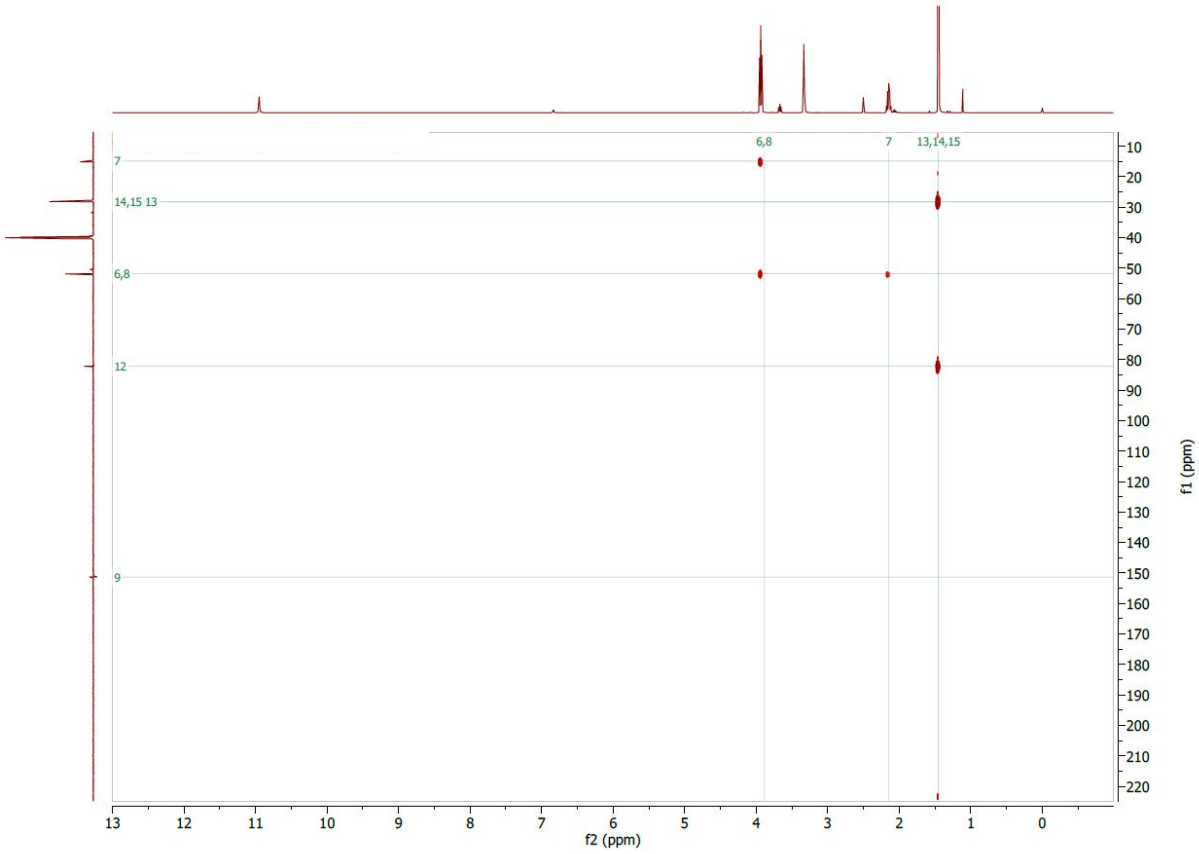


Figure S-1.12. COSY spectrum of *t-butyl (azetidin-1-ylsulfonyl)carbamate* **12**.

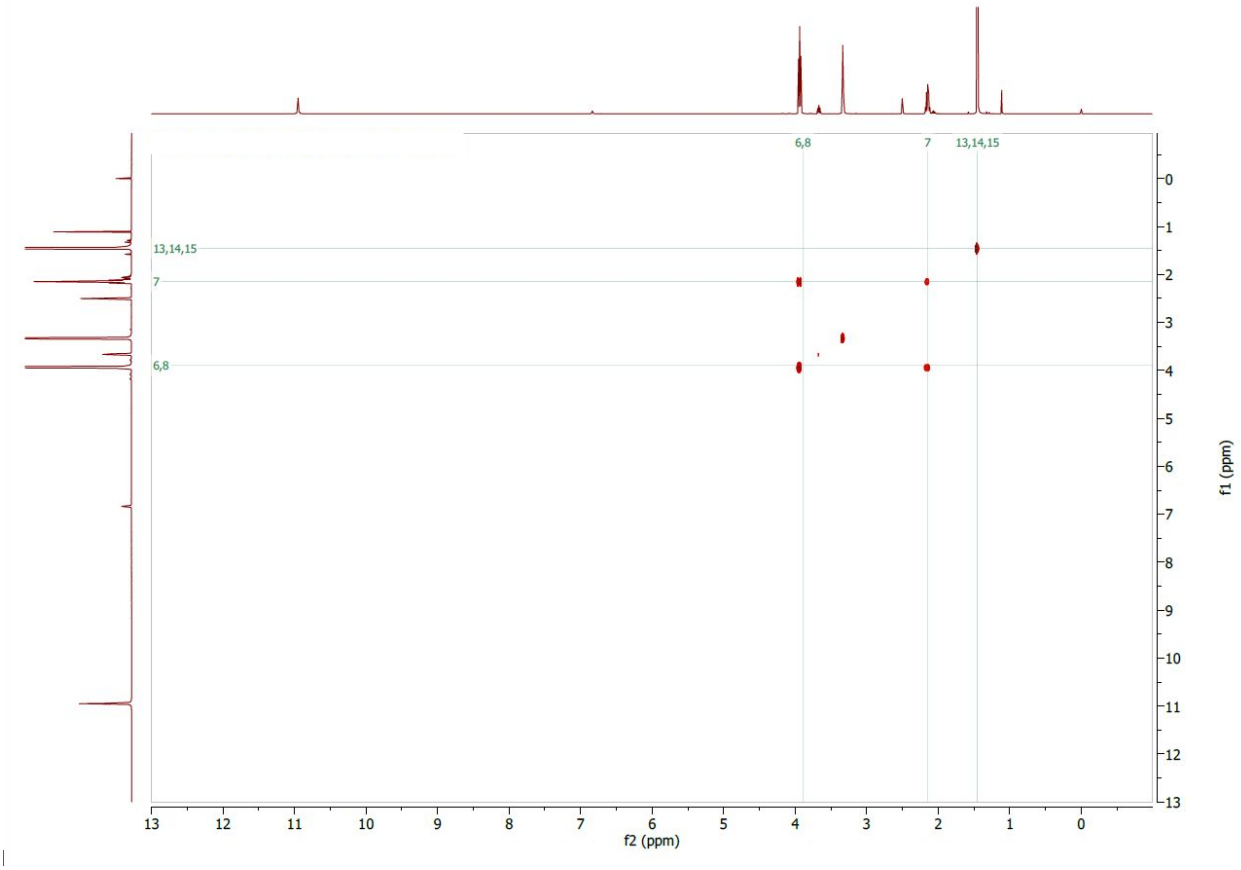


Figure S-1.13. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *azetidine-1-sulfonamide* **3**.

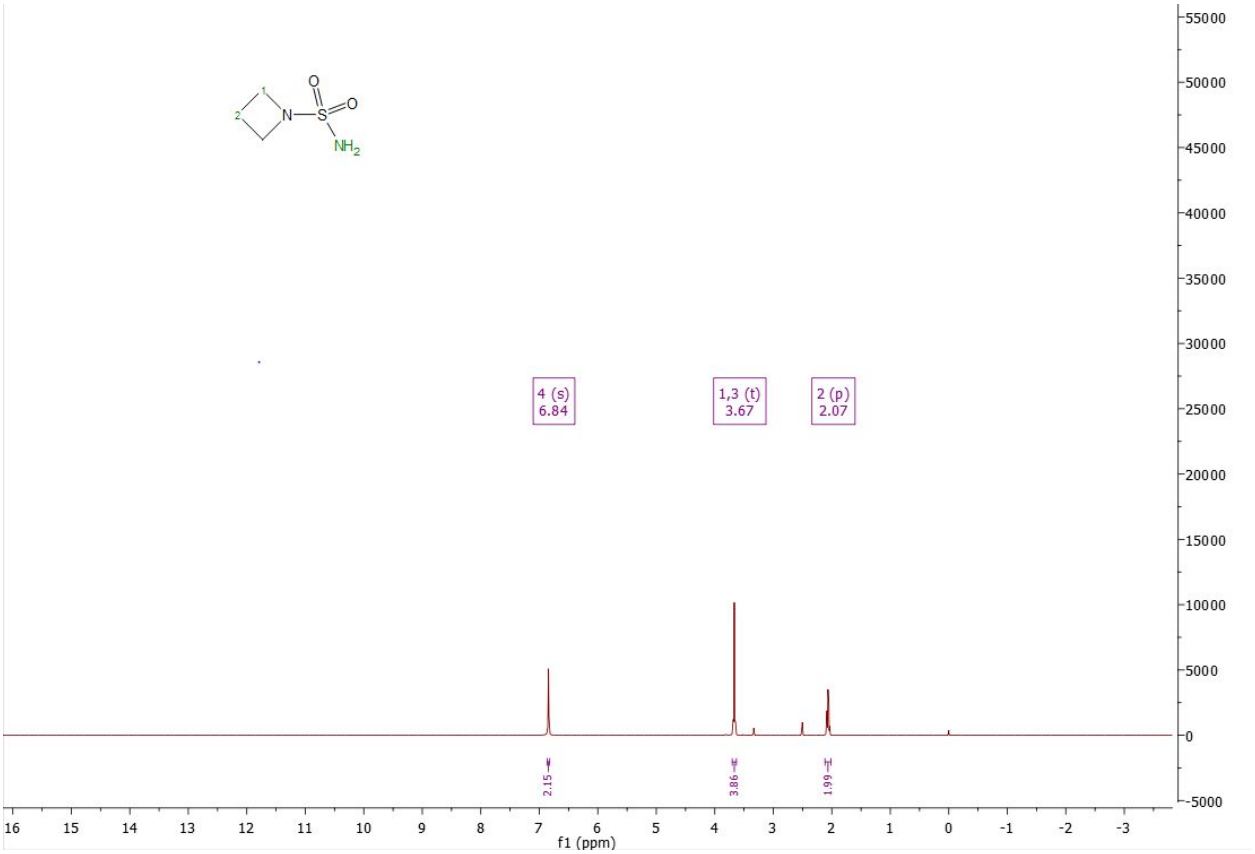


Figure S-1.14. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of *azetidine-1-sulfonamide* **3**.

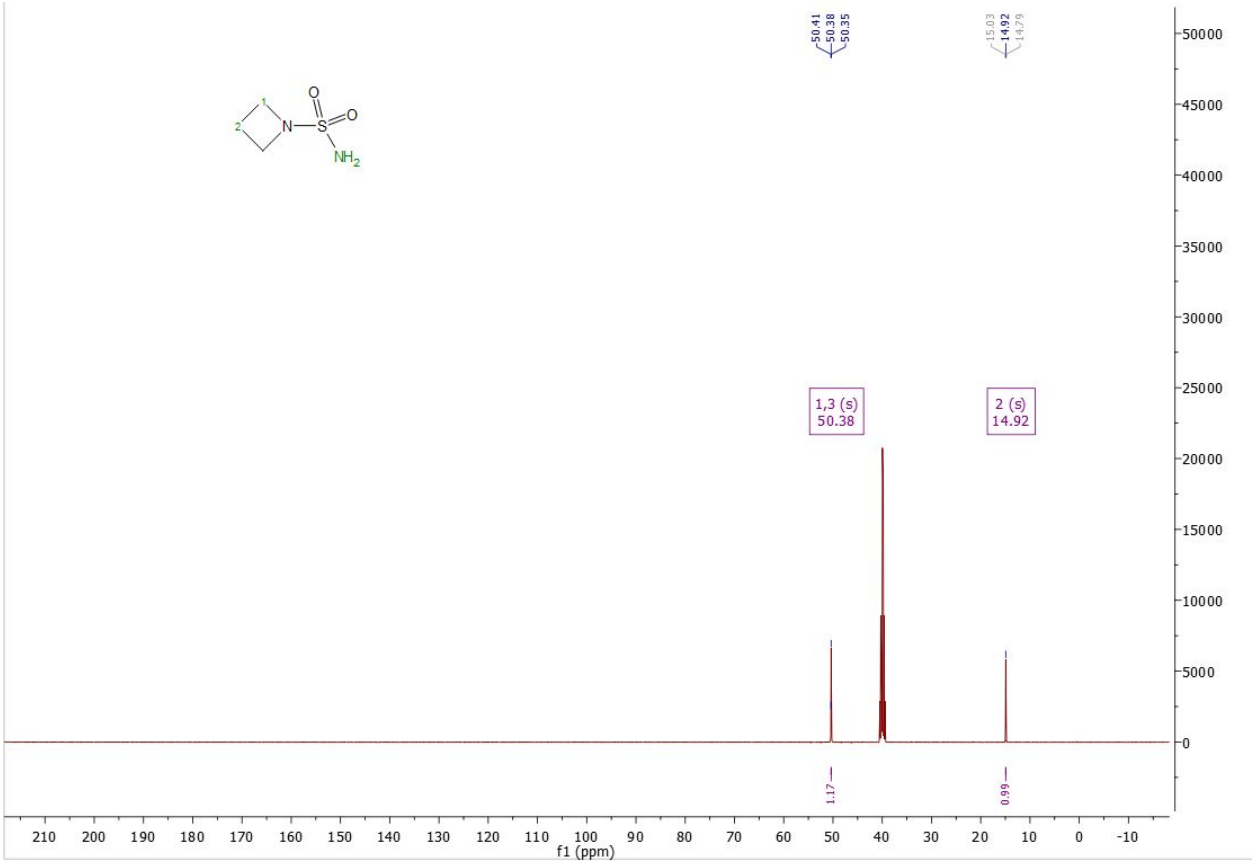


Figure S-1.15. ^{1}H NMR (500 MHz, DMSO-D6) spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **13**.

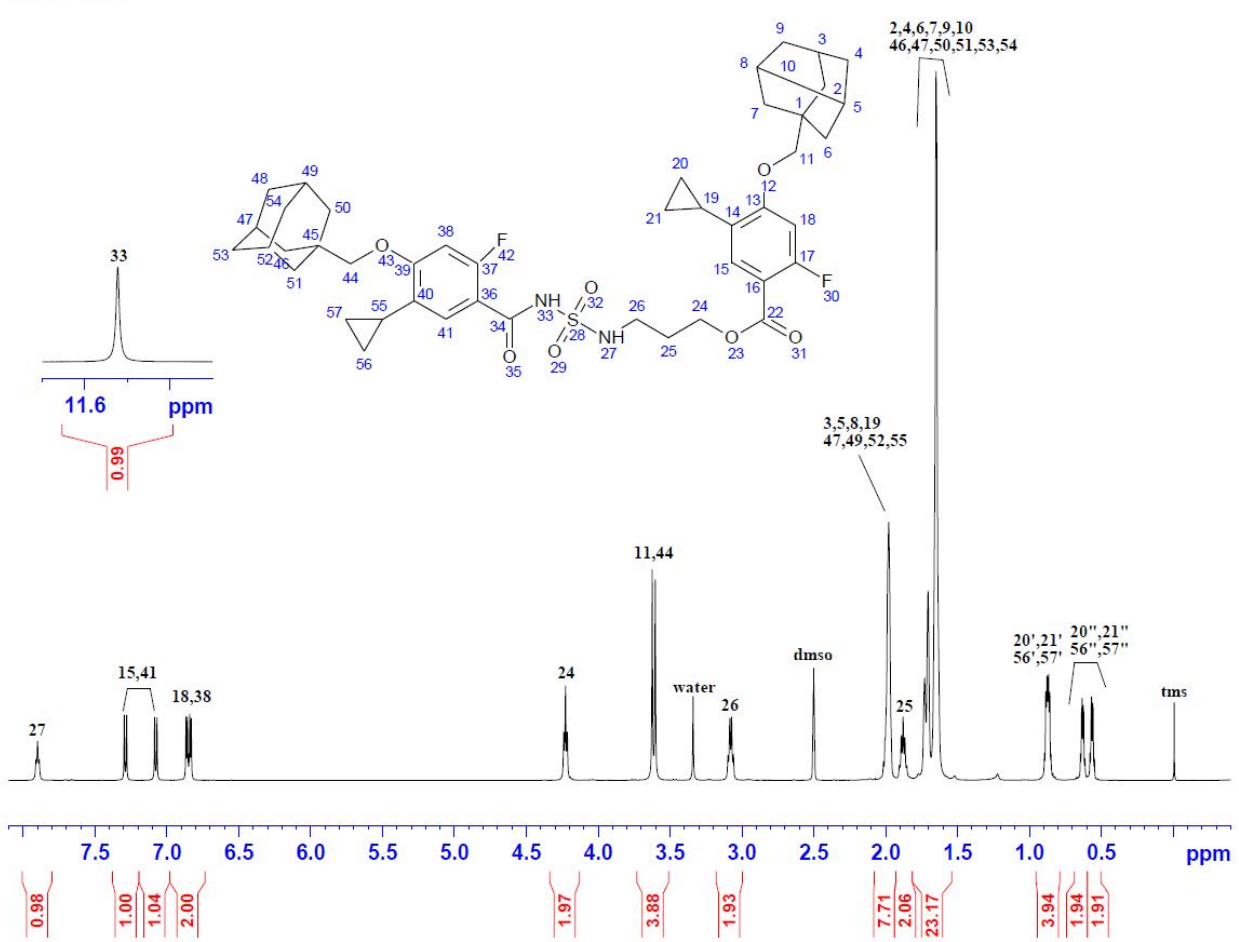


Figure S-1.16. ^{13}C NMR (125 MHz, DMSO-D6) spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **13**.

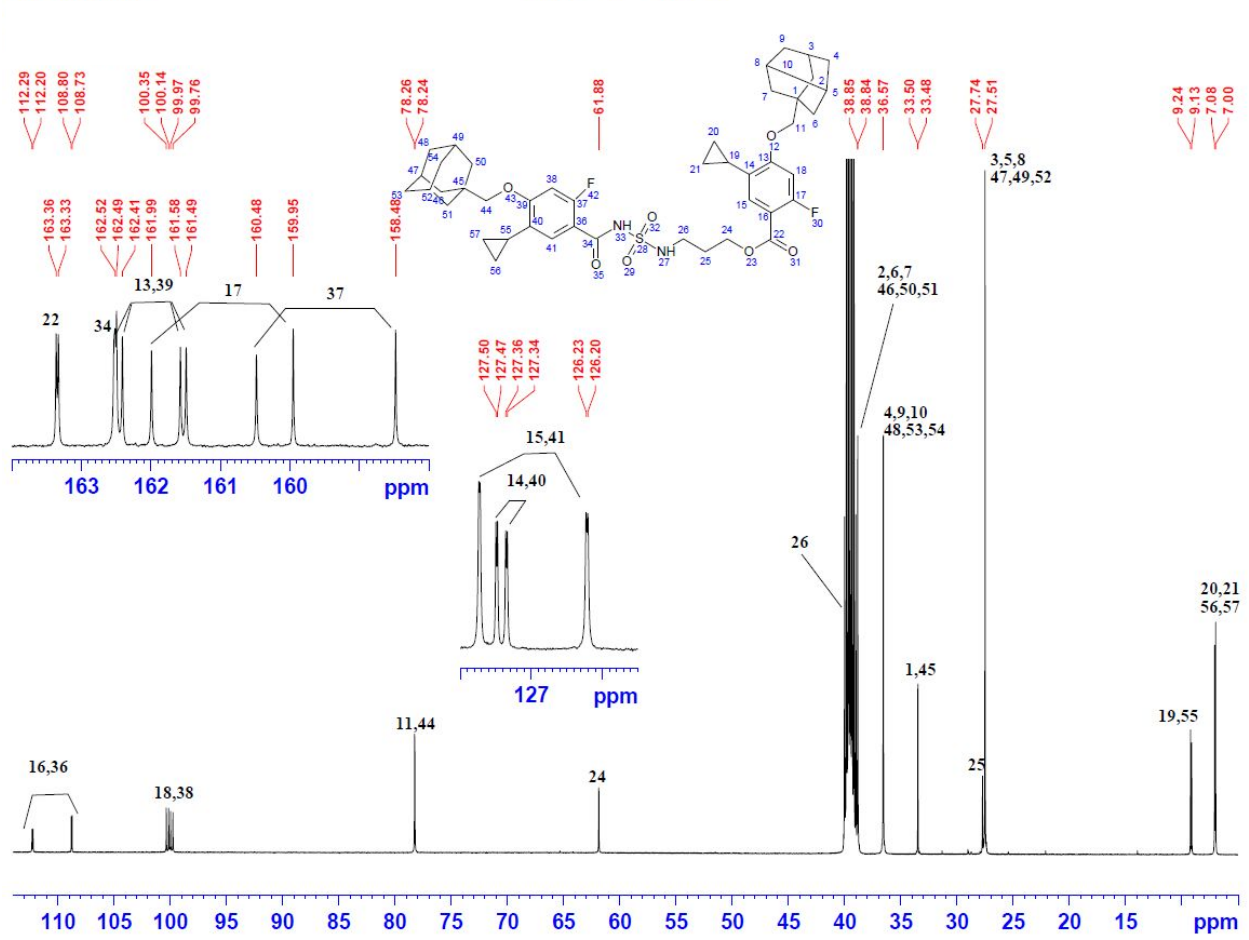


Figure S-1.17. HSQC spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **13**.

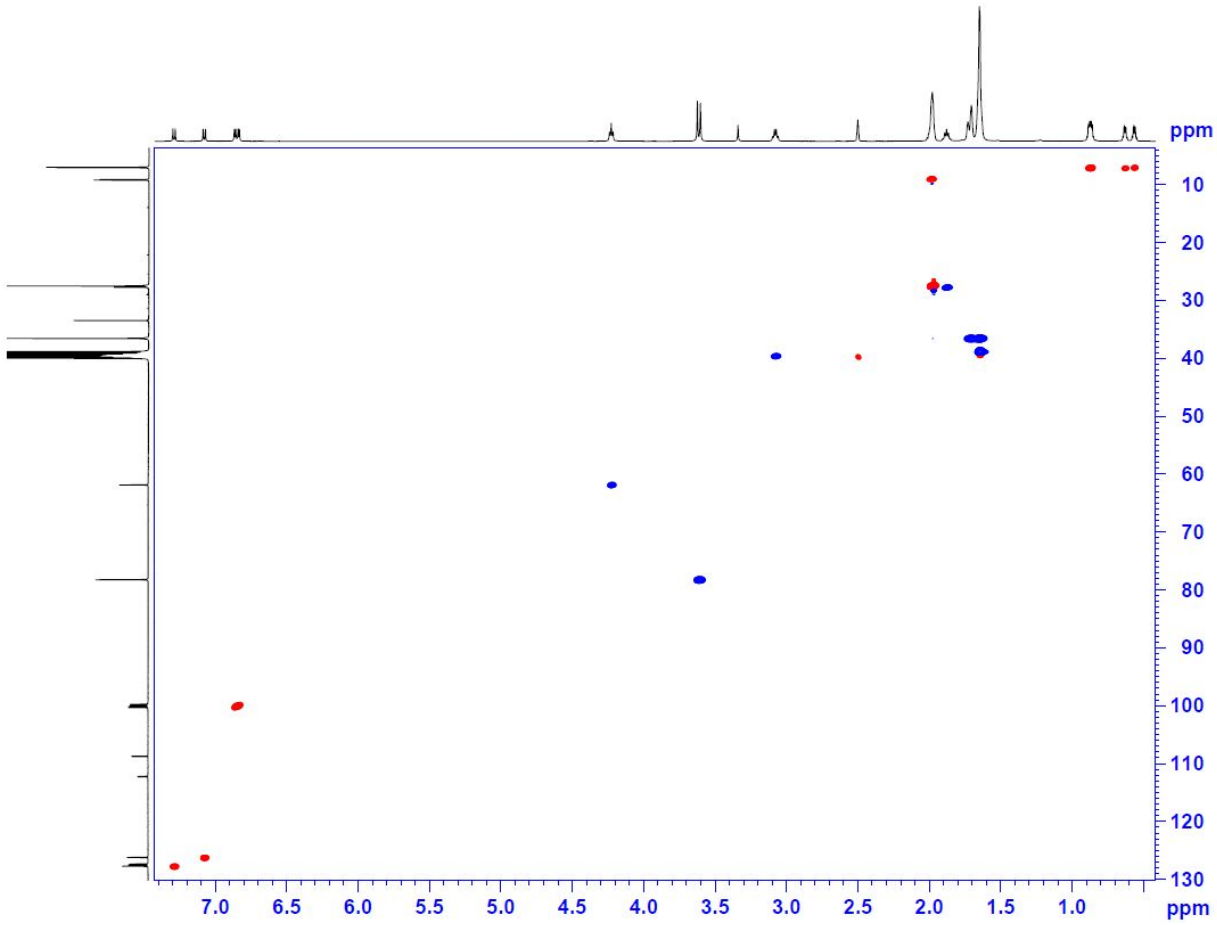


Figure S-1.18. HMBC spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **13**.

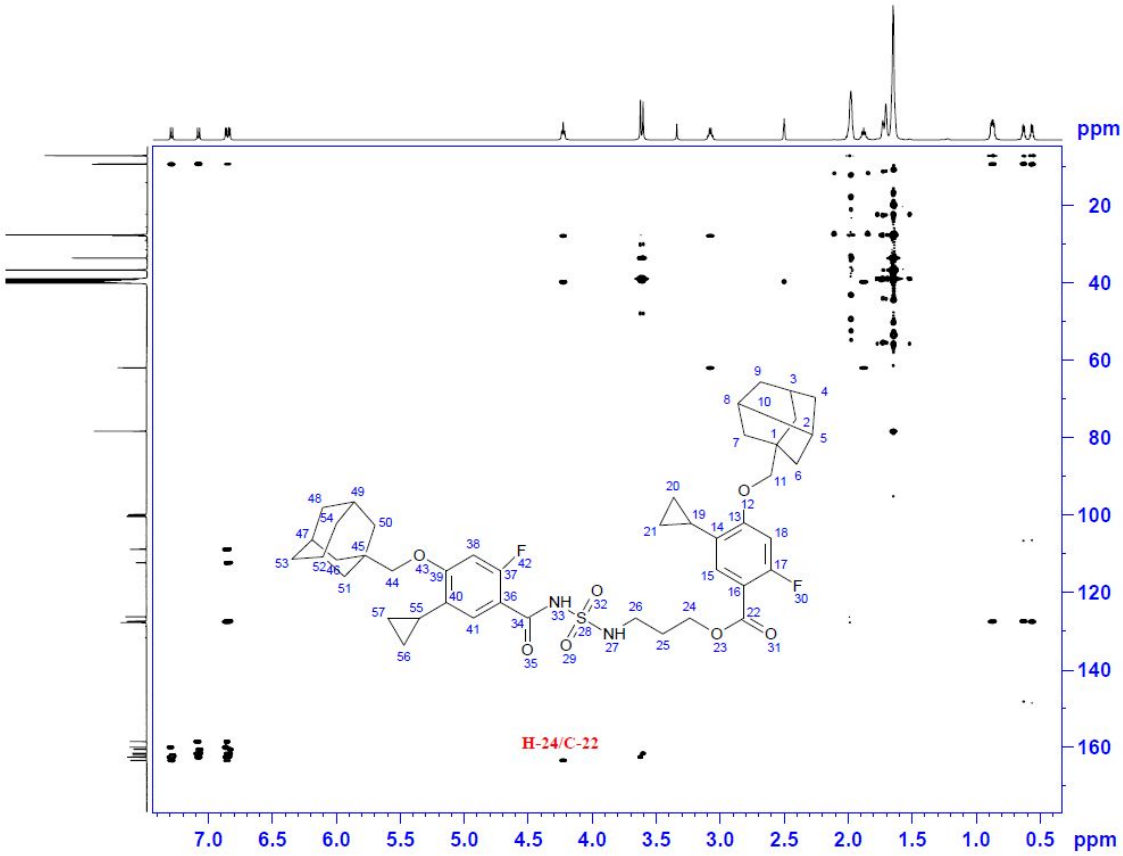


Figure S-1.19. H-N HSQC spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **13**.

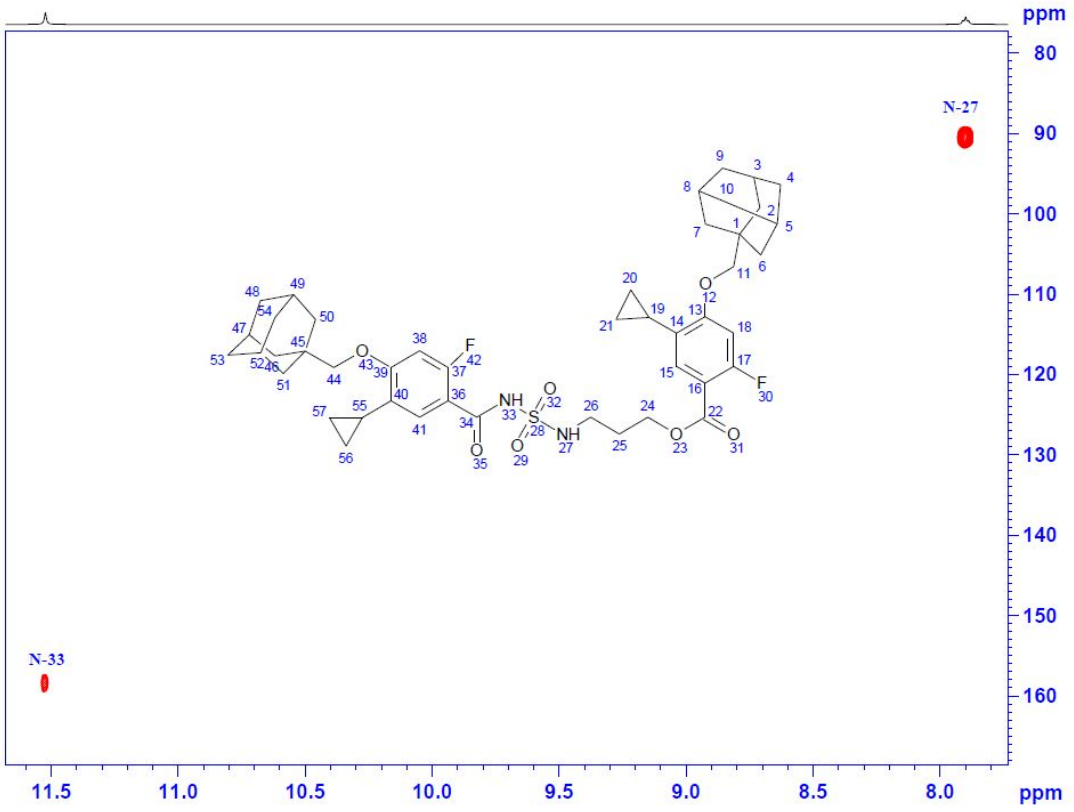


Figure S-1.20. H-N HMBC spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **13**.

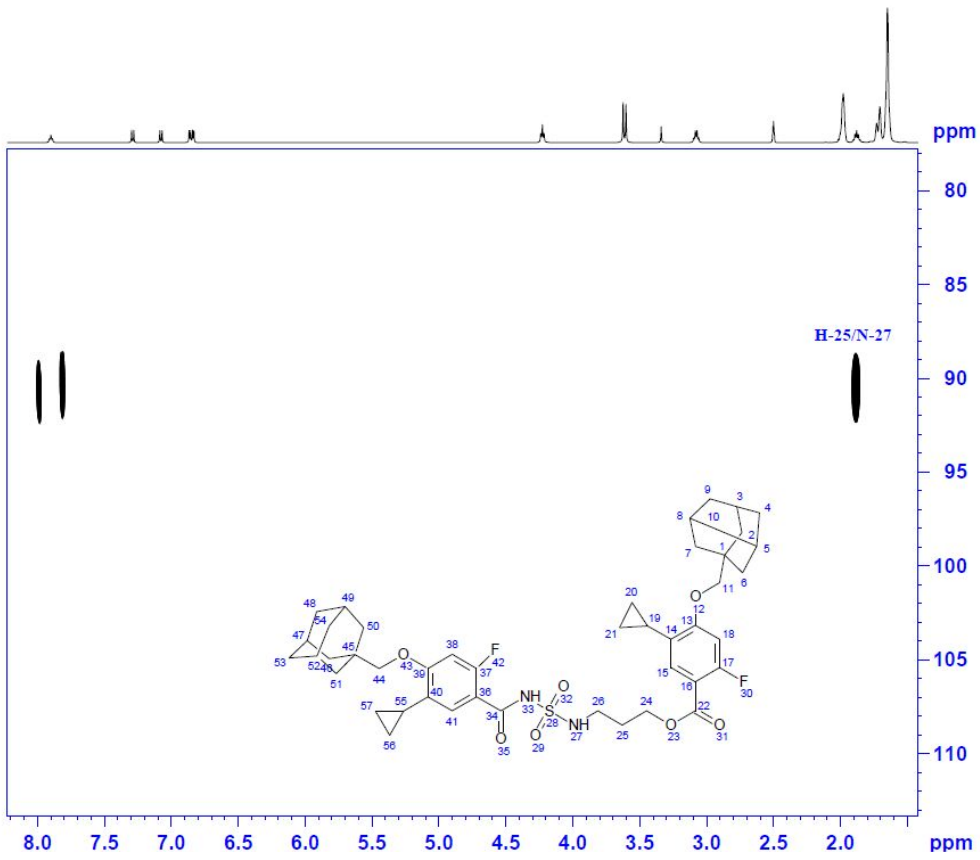


Figure S-1.21. DFQ-COSY spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **13**.

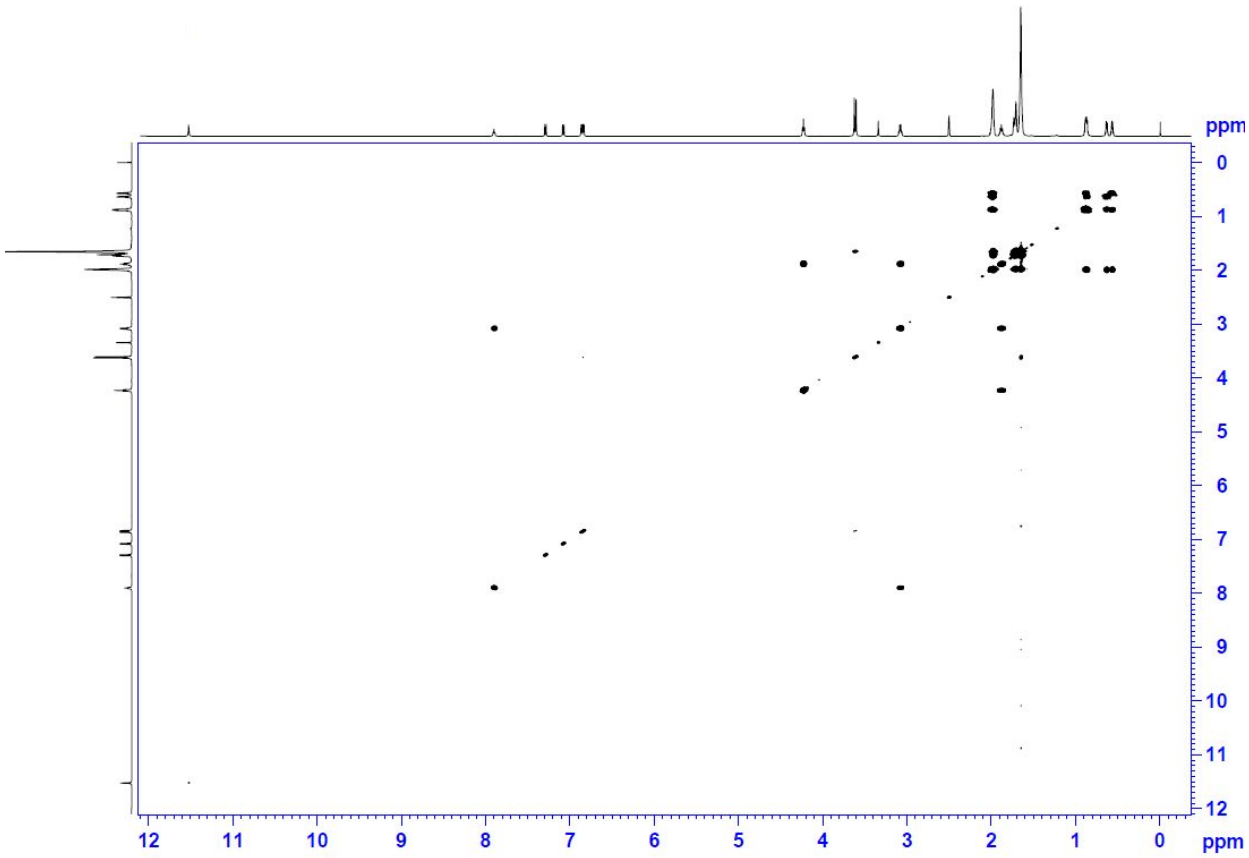


Figure S-1.22. ^{1}H NMR (500 MHz, DMSO-D6) spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)(3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **14**.

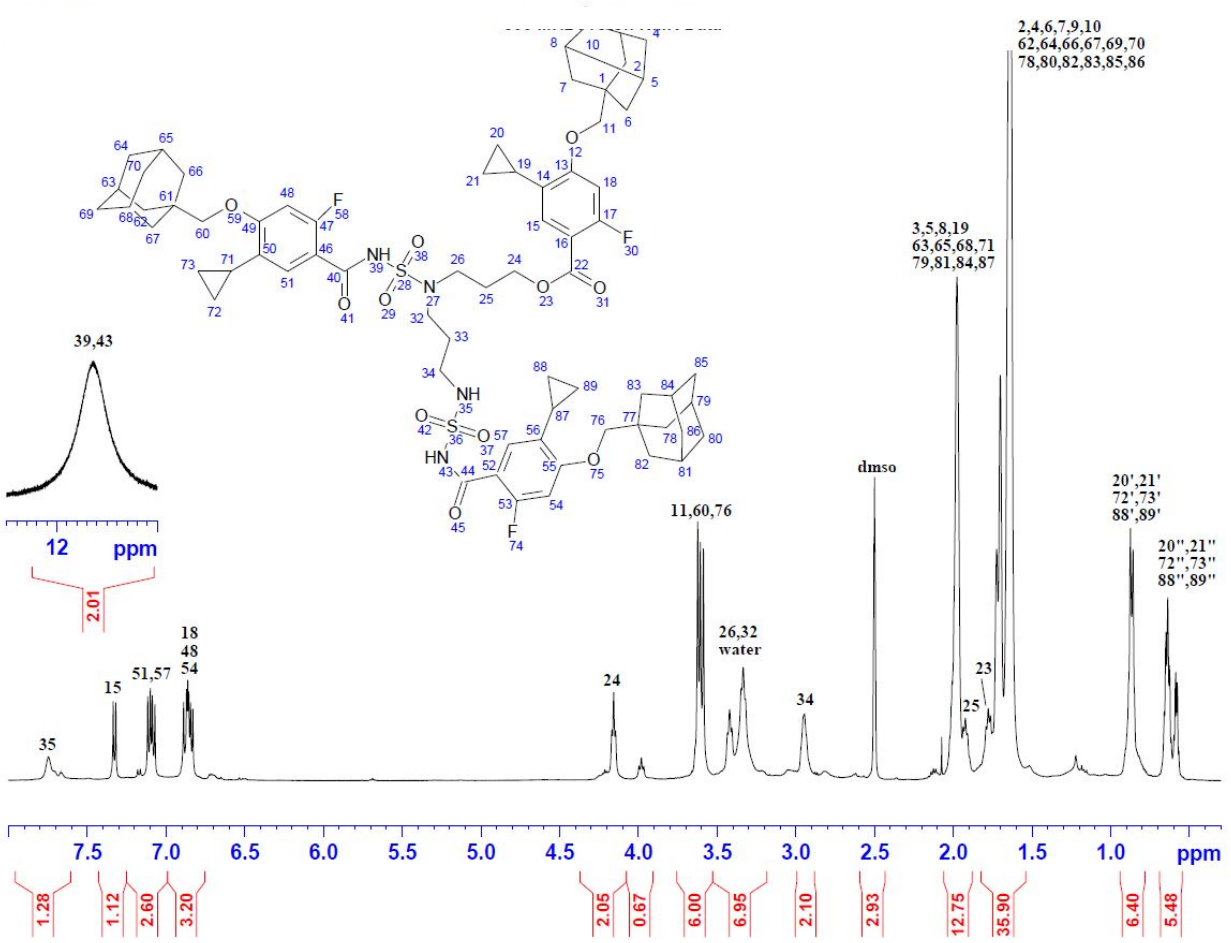


Figure S-1.23. ^{13}C NMR (125 MHz, DMSO-D6) spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)(3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **14**.

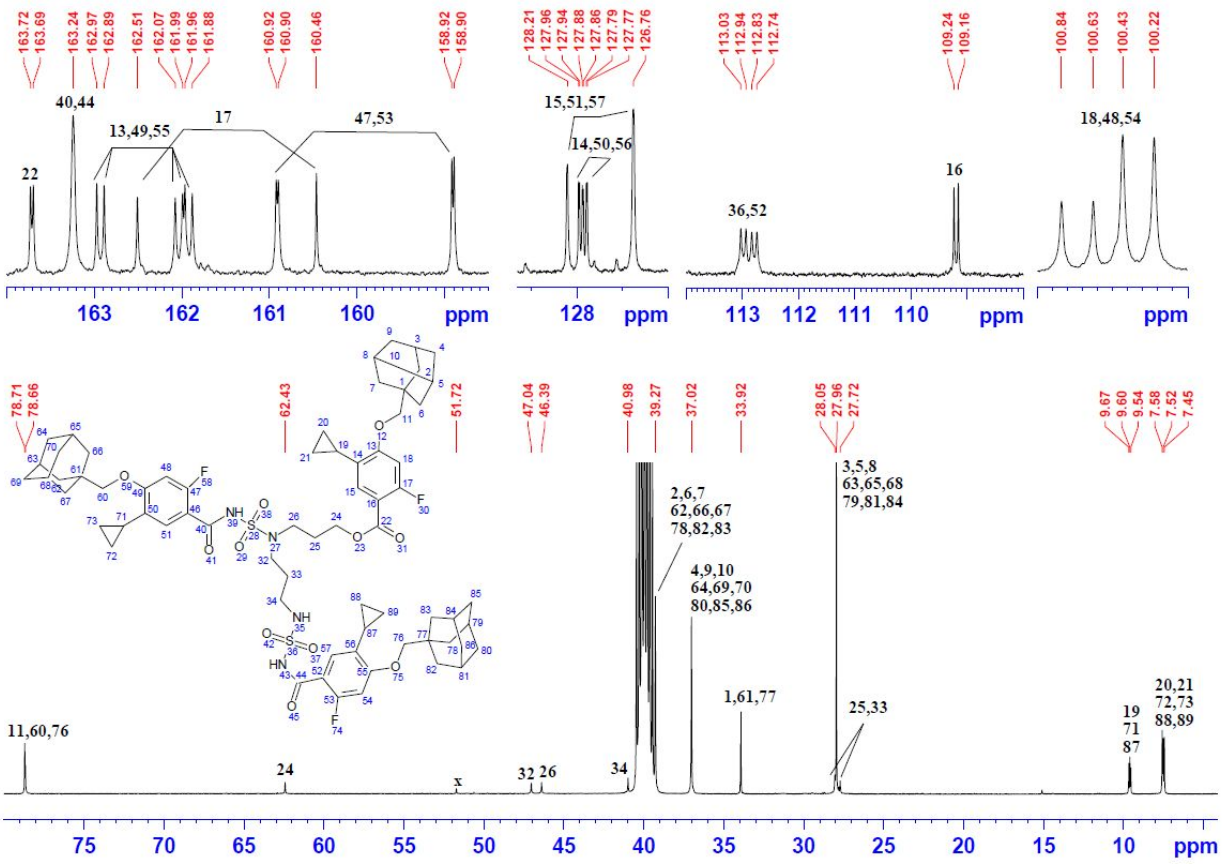


Figure S-1.24. HSQC spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)(3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **14**.

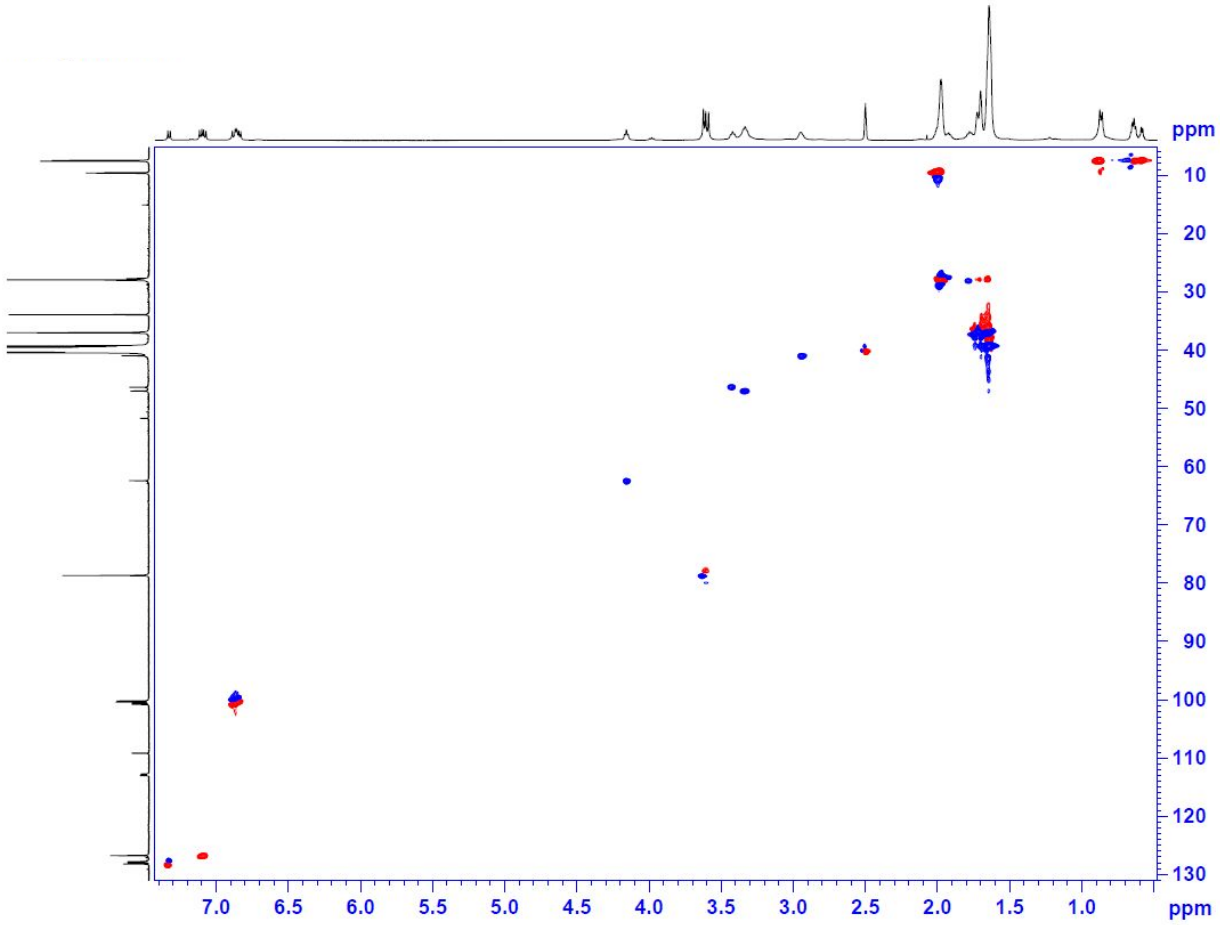


Figure S-1.25. HMBC spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)(3-((N-(4-(((3r,5r,7r)-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **14**.

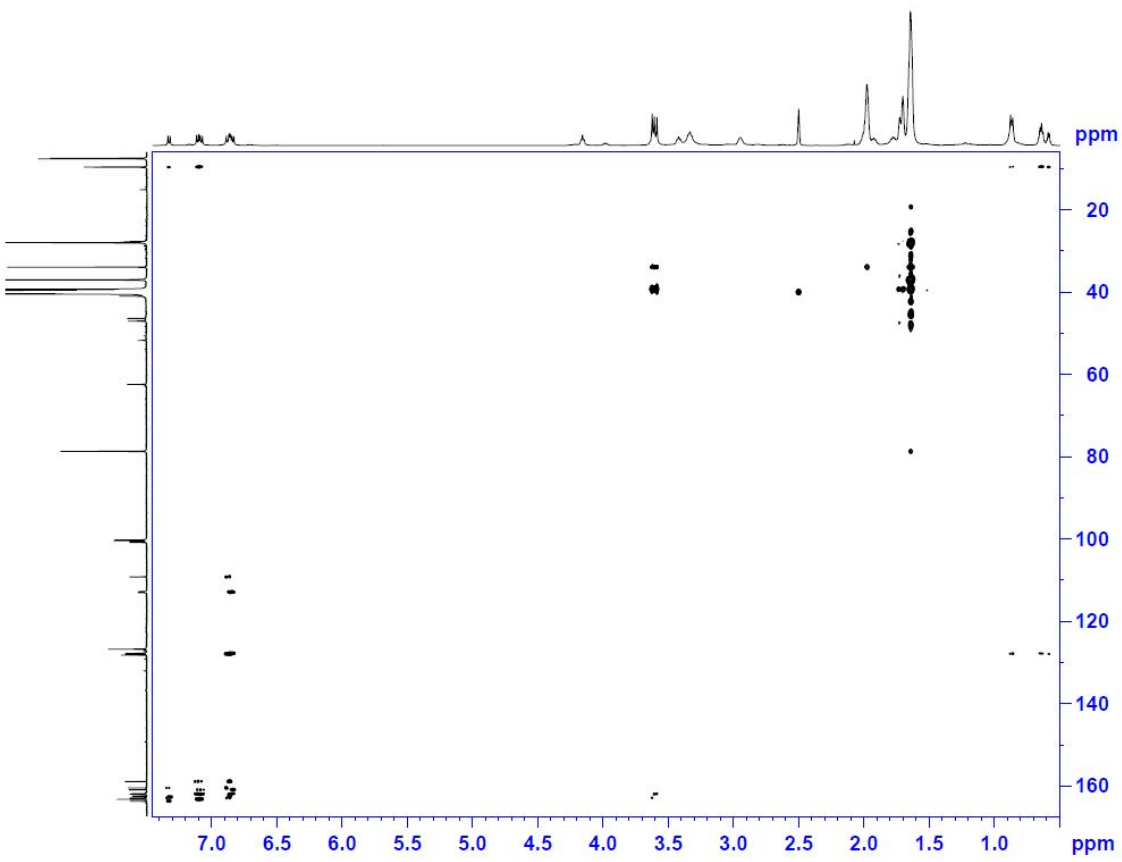


Figure S-1.26. DFQ-COSY spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)(3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **14**.

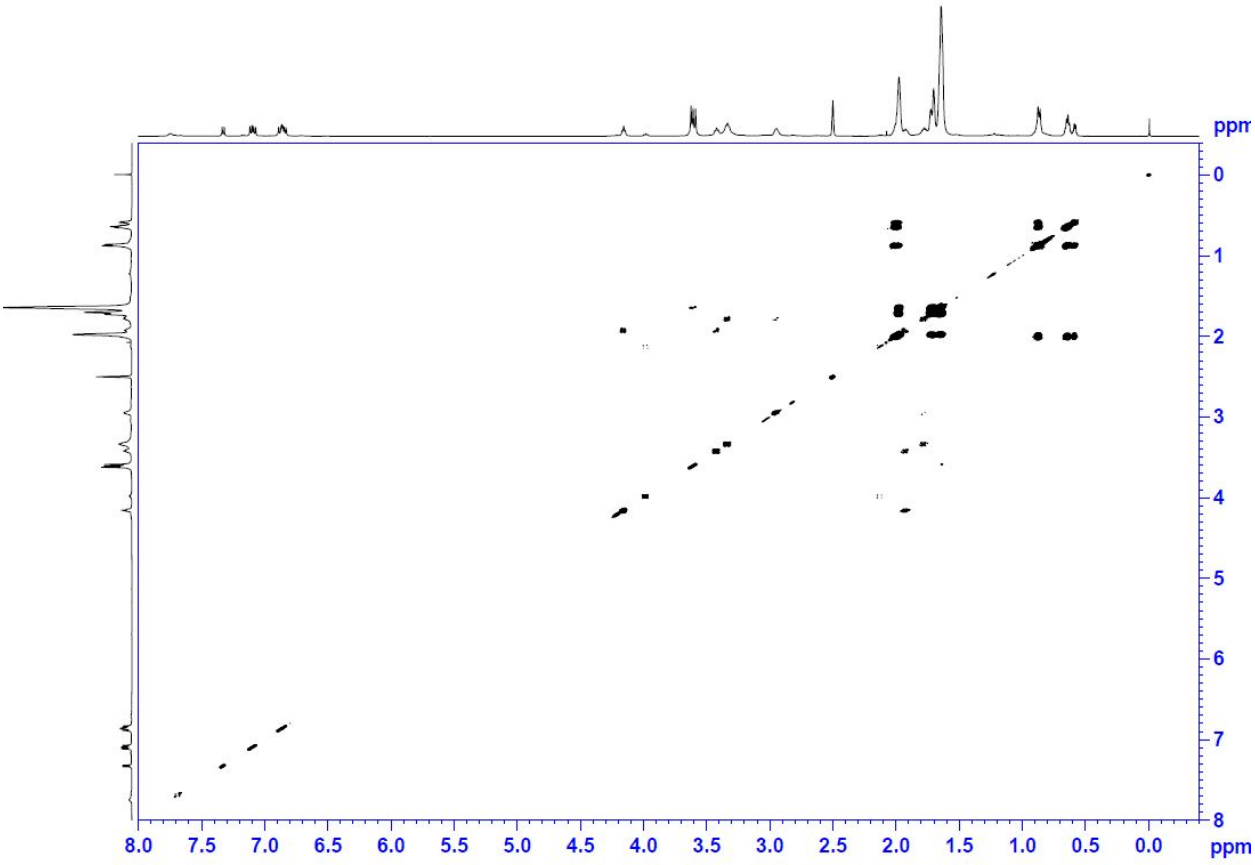


Figure S-1.27. HRMS spectrum of *3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)(3-((N-(4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)amino)propyl)amino)propyl 4-((-adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoate* **14**.

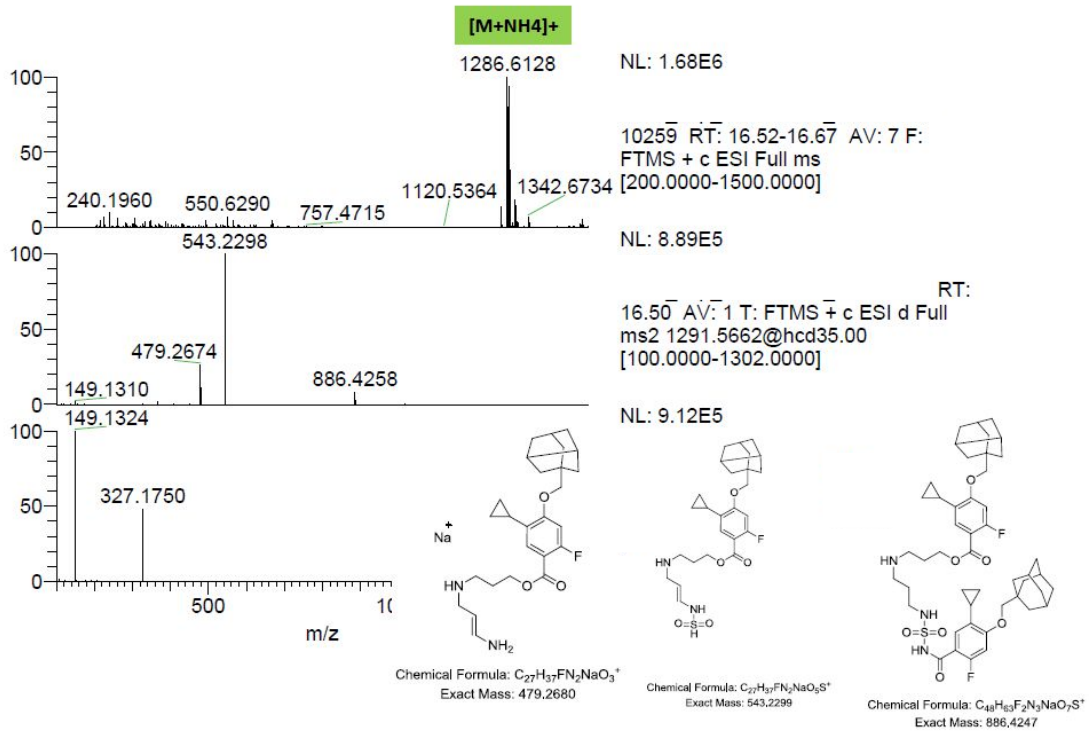


Figure S-1.28. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *(adamantan-1-yl)methyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **6**.

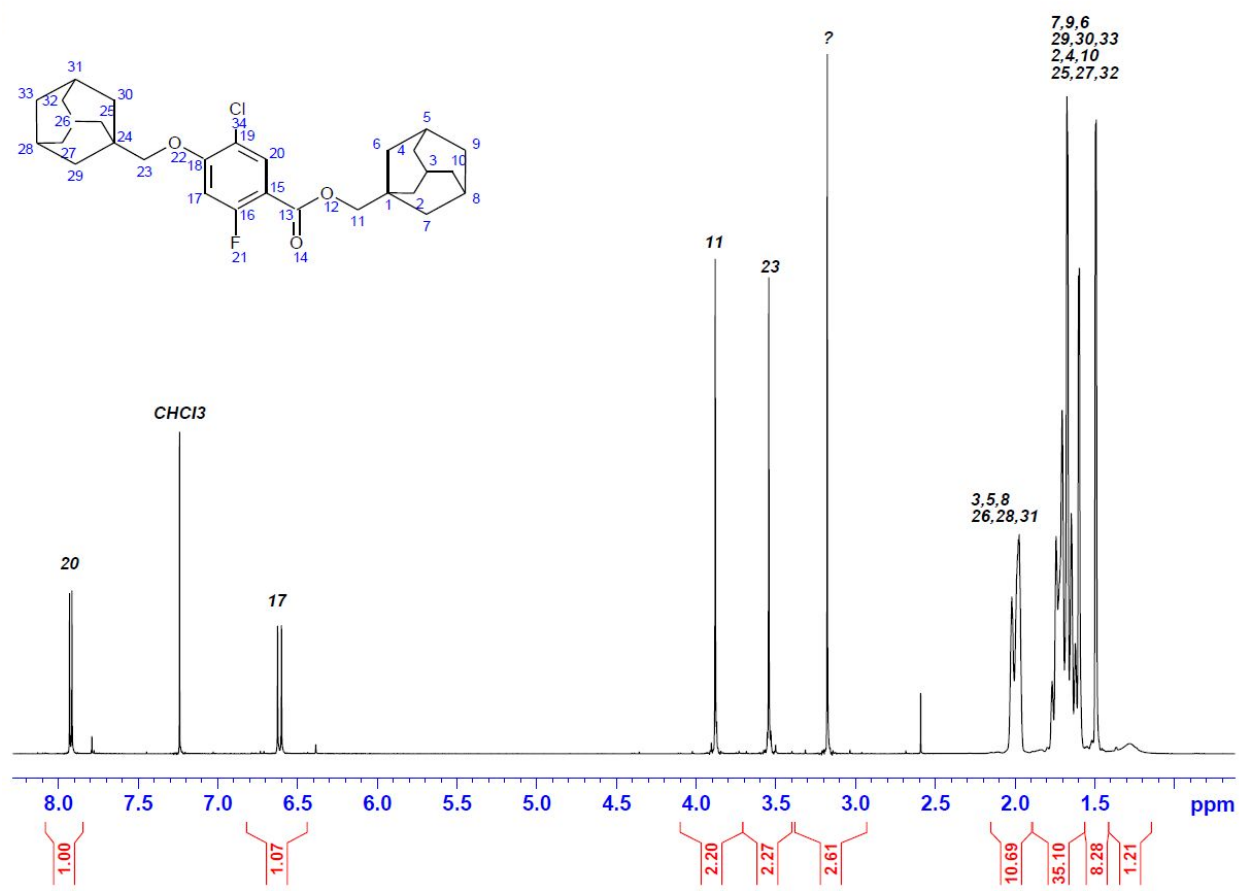


Figure S-1.29. ^{13}C NMR (150 MHz, $CDCl_3$) spectrum of *(adamantan-1-yl)methyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **6**.

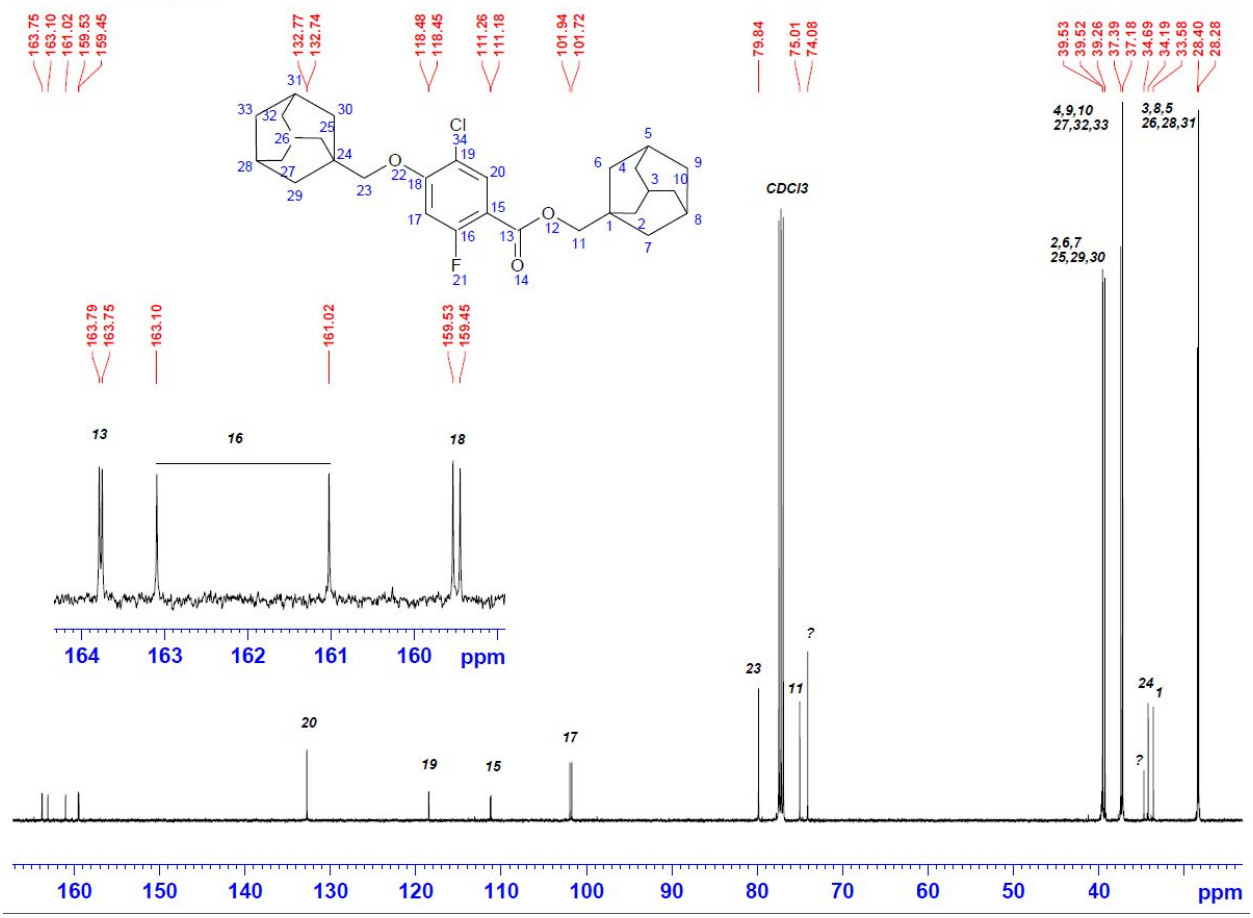


Figure S-1.30. HSQC spectrum of *(adamantan-1-yl)methyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **6**.

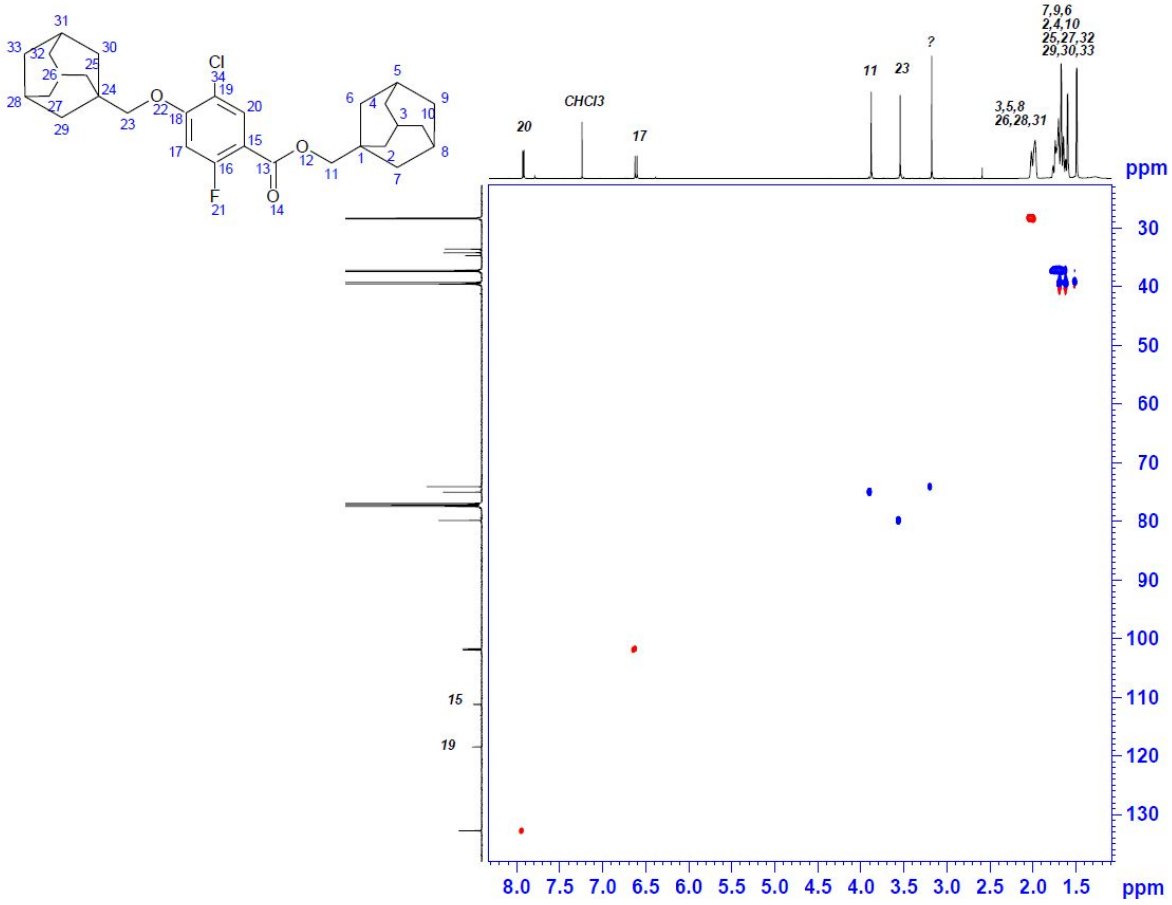


Figure S-1.31. HMBC spectrum of *(adamantan-1-yl)methyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **6**.

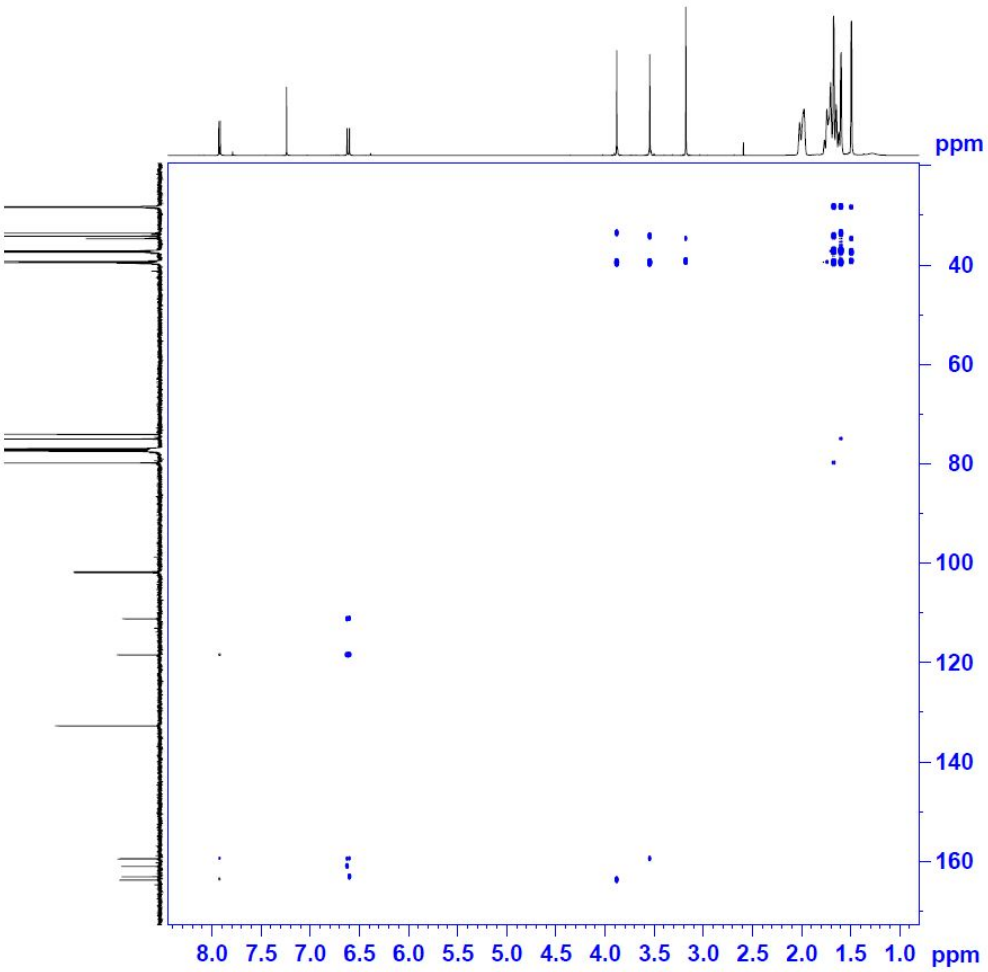


Figure S-1.32. DQF-COSY spectrum of *(adamantan-1-yl)methyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **6**.

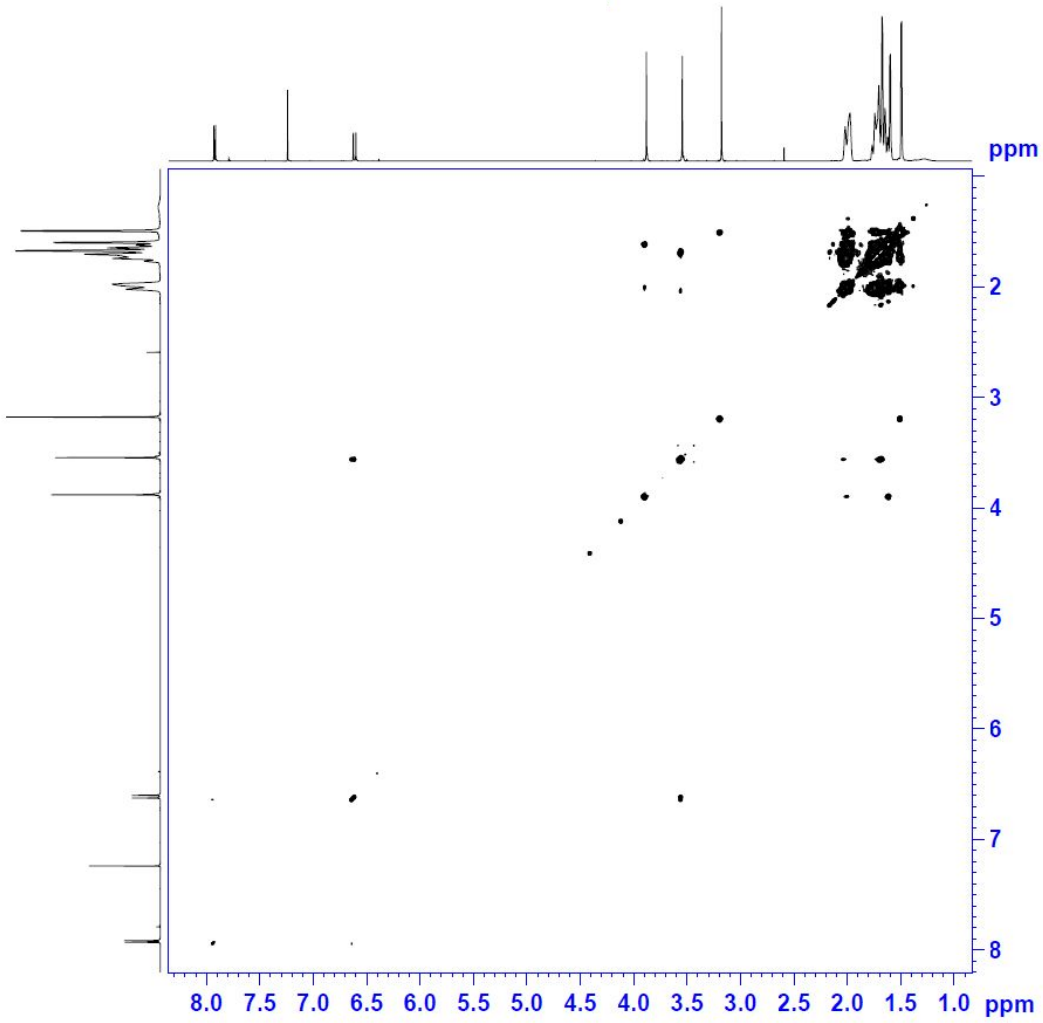
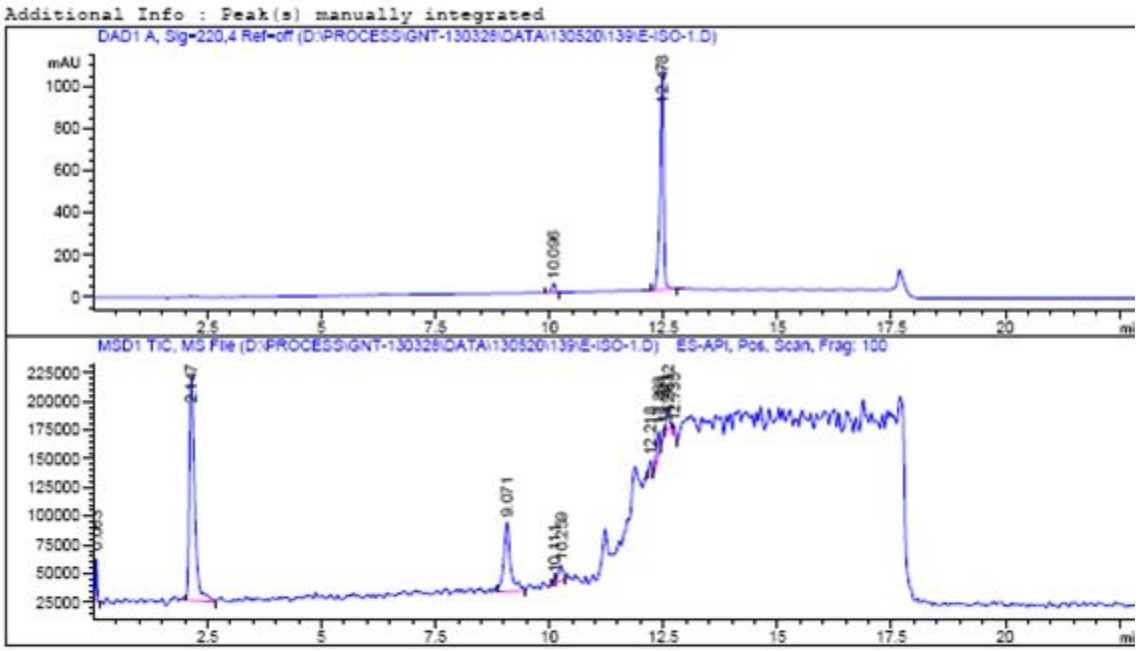


Figure S-1.33. LCMS data for **6**.



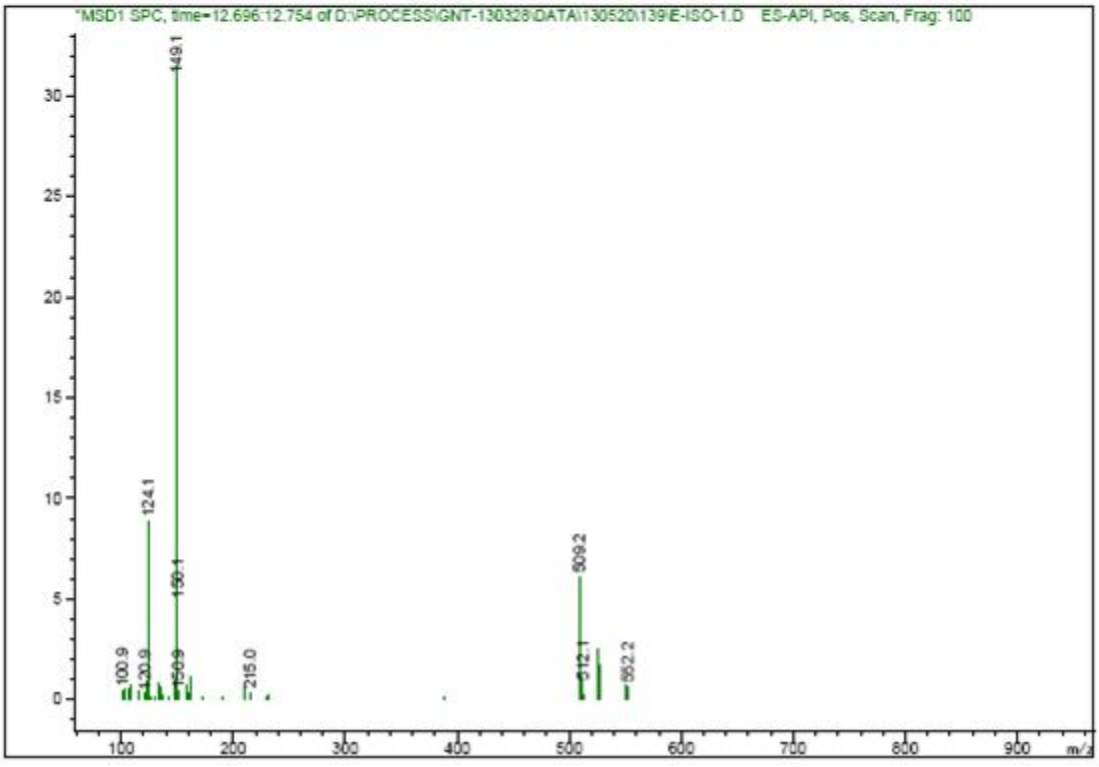


Figure S-2.1. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *1-((2-chloro-5-fluorophenoxy)methyl)adamantane* **20**.

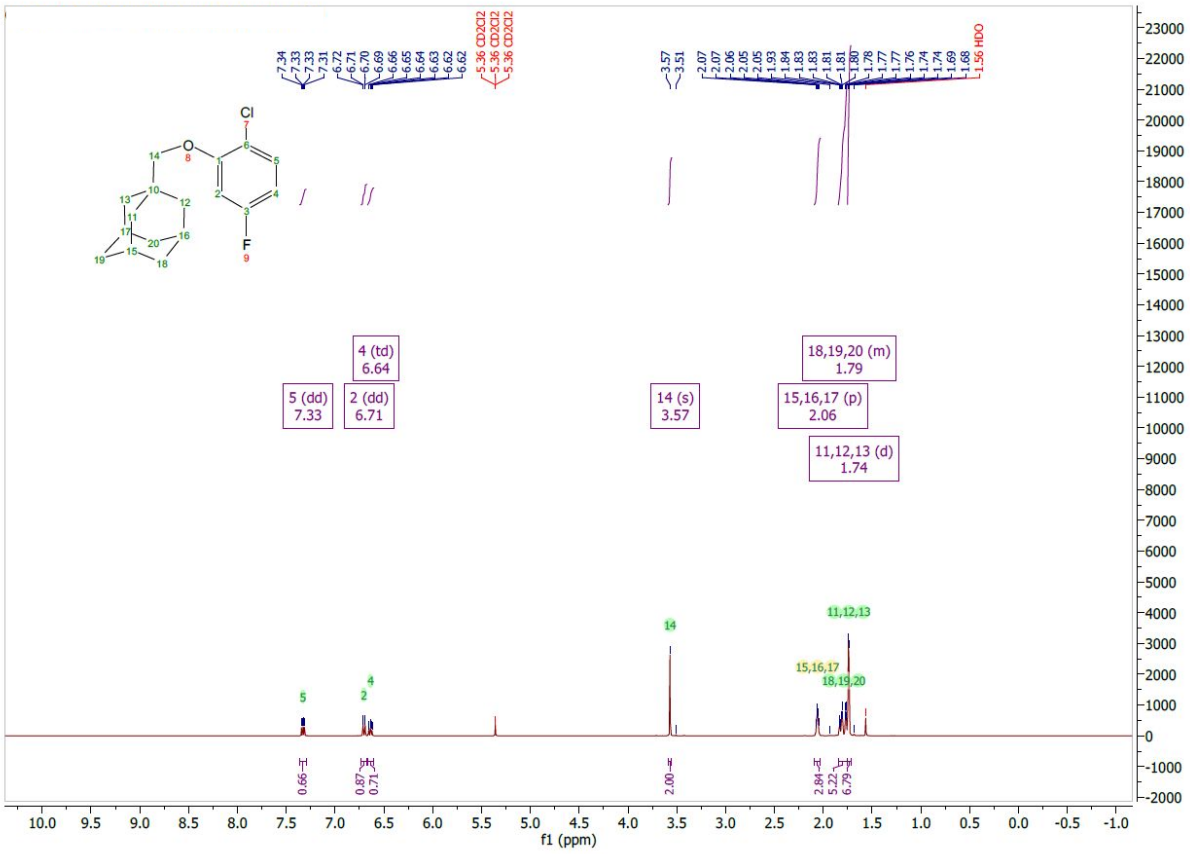


Figure S-2.2. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of *1-((2-chloro-5-fluorophenoxy)methyl)adamantane* **20**.

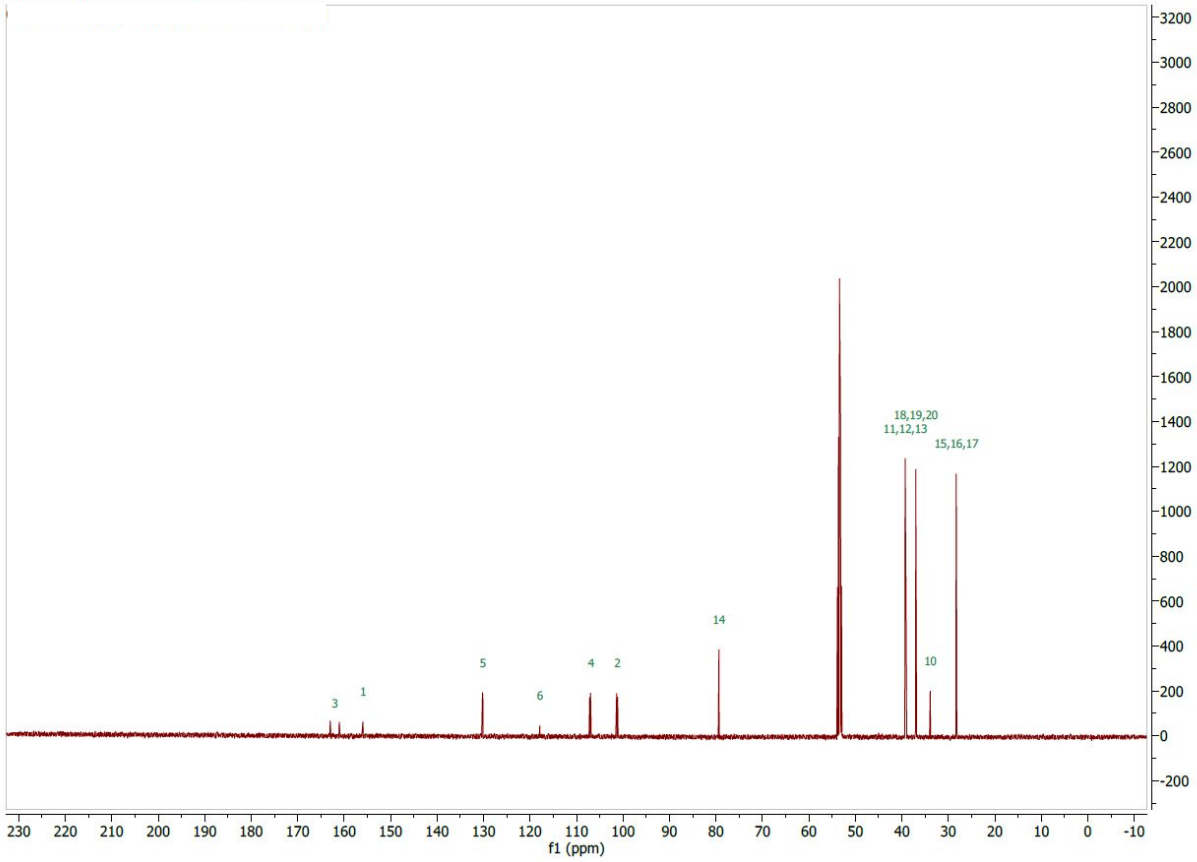


Figure S-2.3. HSQC spectrum of *1-((2-chloro-5-fluorophenoxy)methyl)adamantane* **20**.

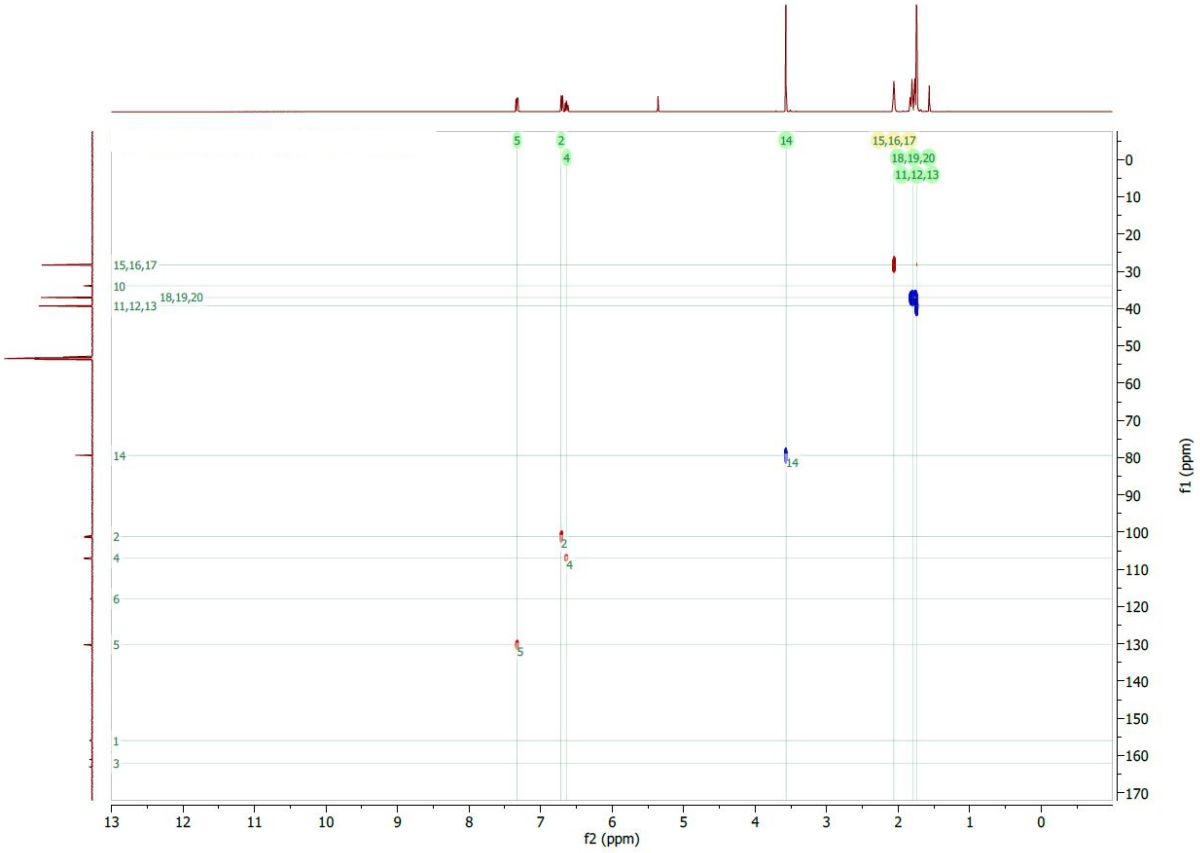


Figure S-2.4. HMBC spectrum of *1-((2-chloro-5-fluorophenoxy)methyl)adamantane* **20**.

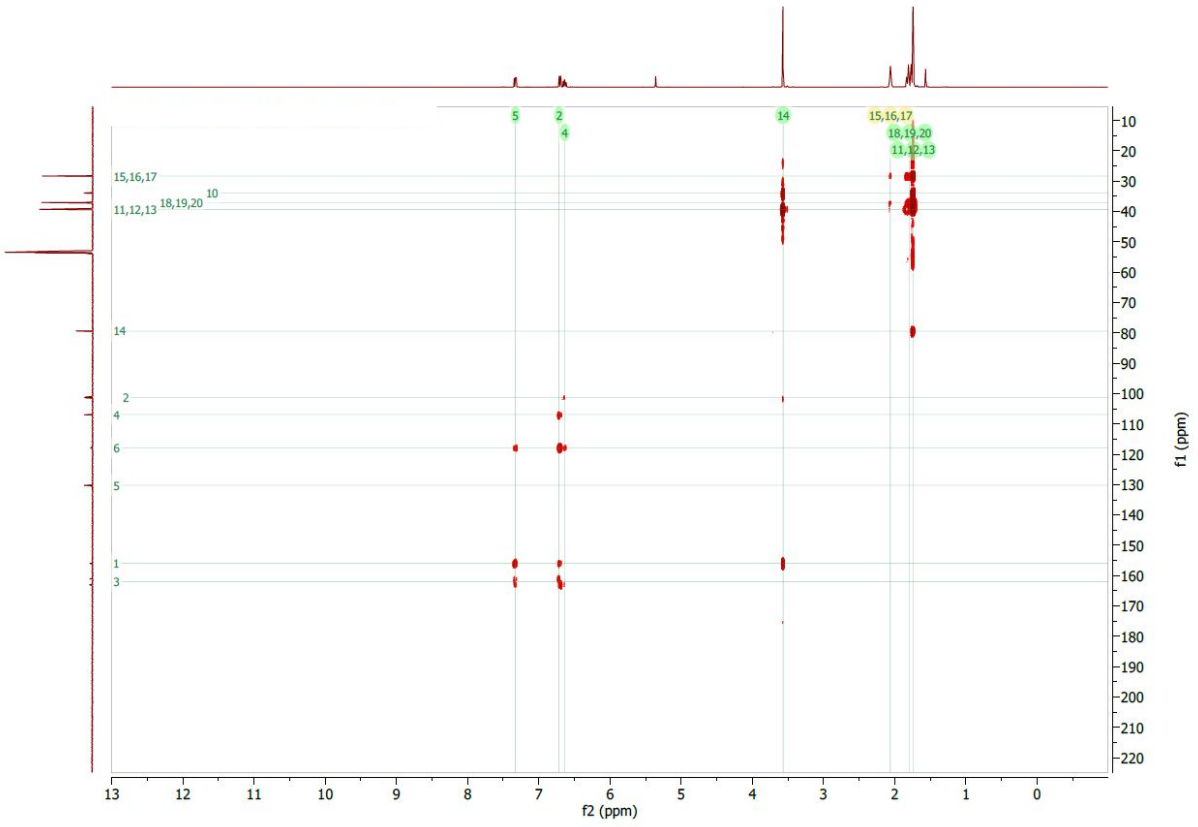


Figure S-2.5. COSY spectrum of *1-((2-chloro-5-fluorophenoxy)methyl)adamantane* **20**.

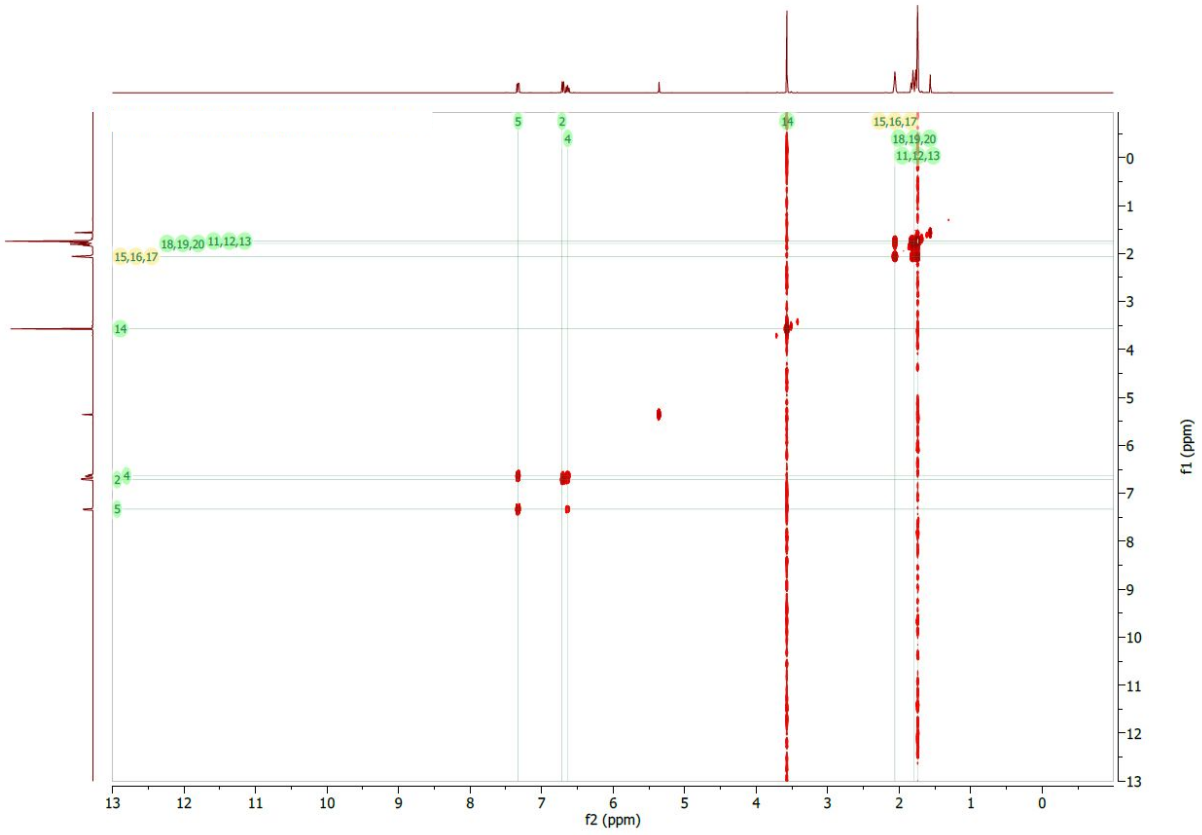


Figure S-2.6. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *1-((4-bromo-2-chloro-5-fluorophenoxy)methyl)adamantane* **18**.

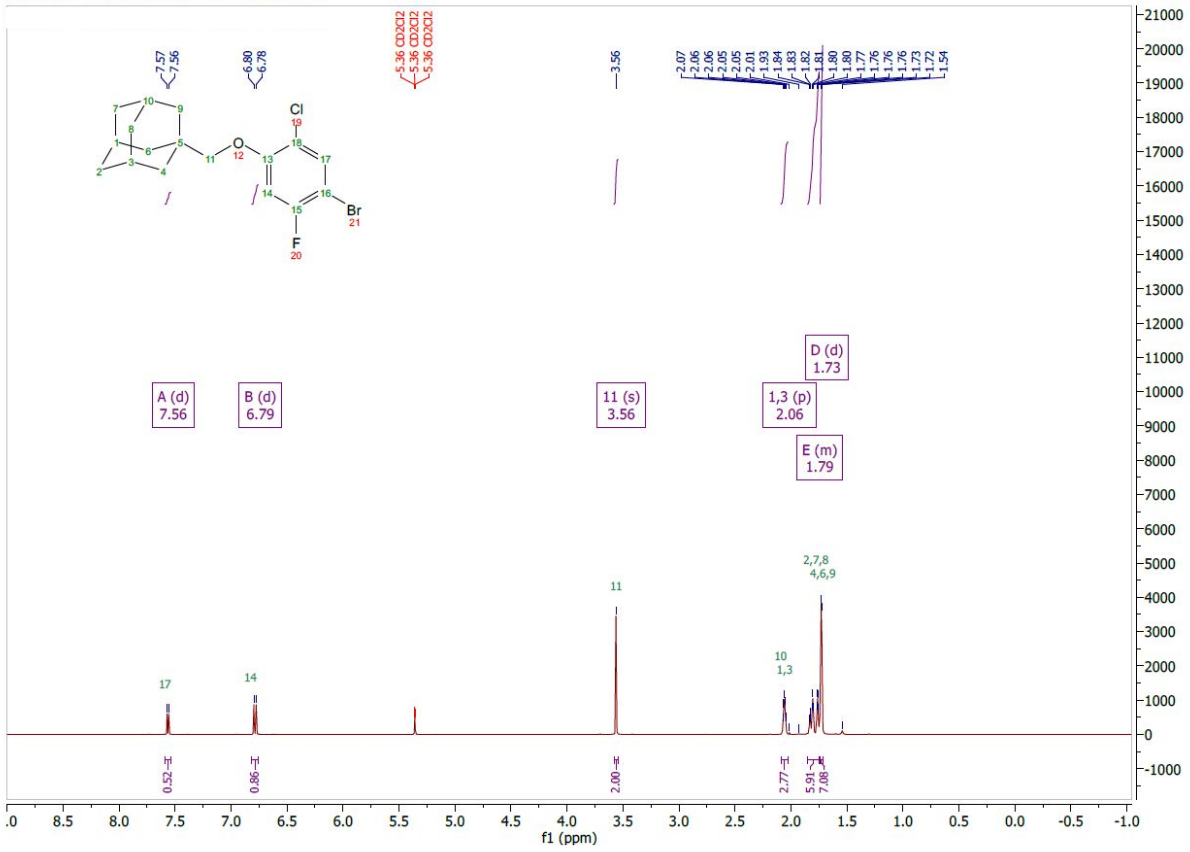


Figure S-2.7. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of *1-((4-bromo-2-chloro-5-fluorophenoxy)methyl)adamantane* **18**.

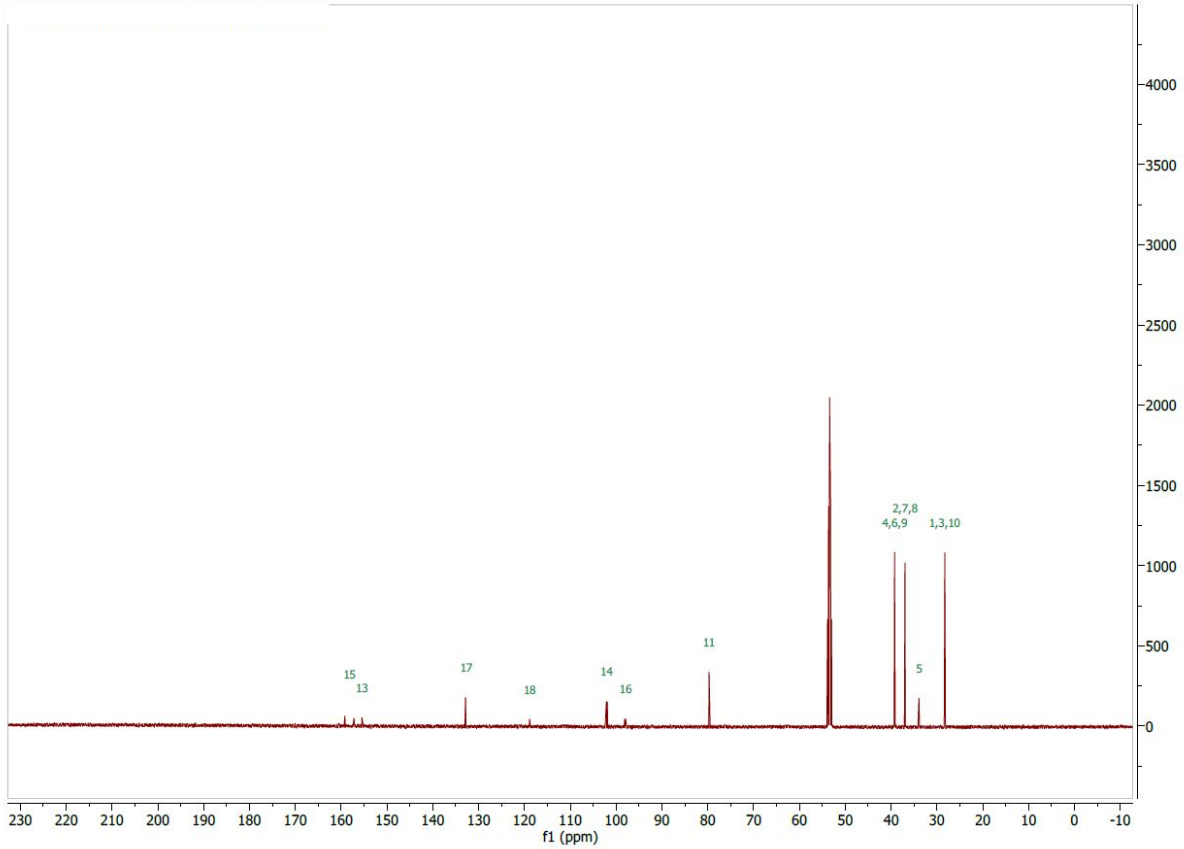


Figure S-2.8. HSQC spectrum of *1-((4-bromo-2-chloro-5-fluorophenoxy)methyl)adamantane* **18**.

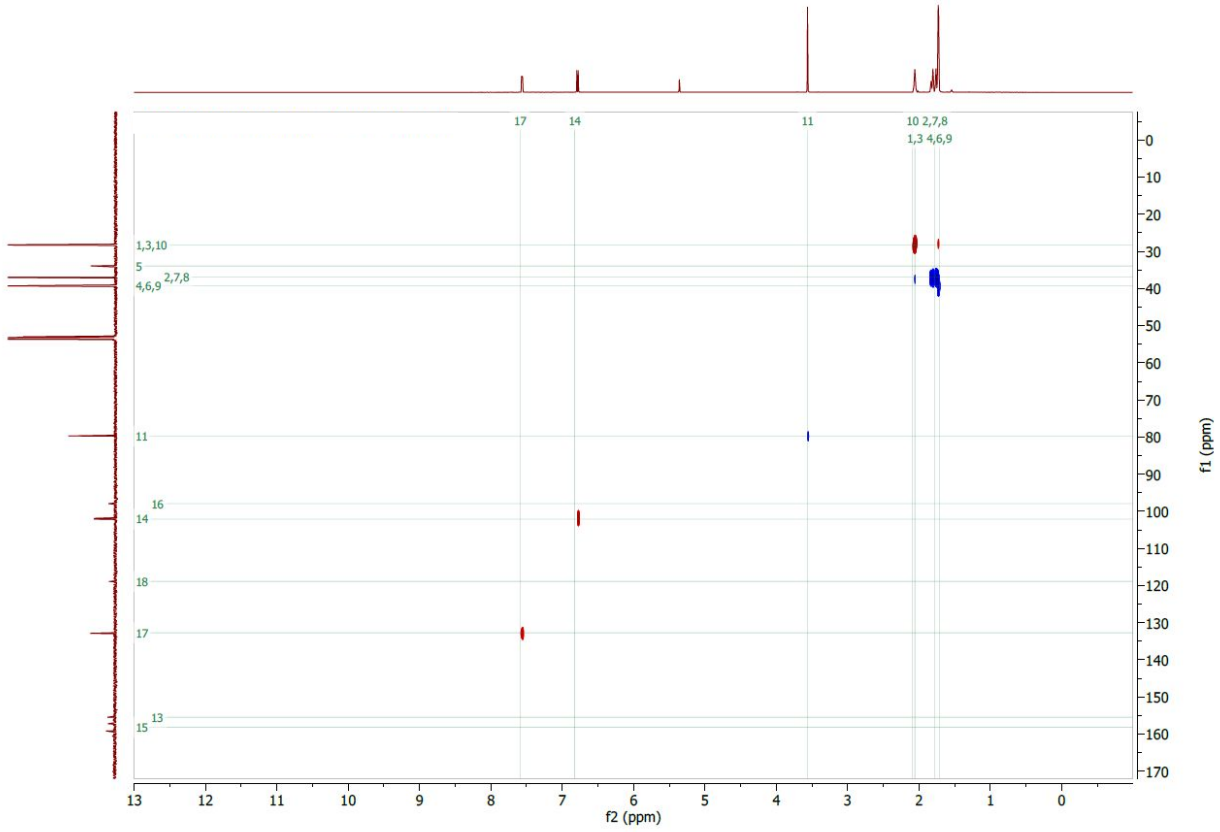


Figure S-2.9. HMBC spectrum of *1-((4-bromo-2-chloro-5-fluorophenoxy)methyl)adamantane* **18**.

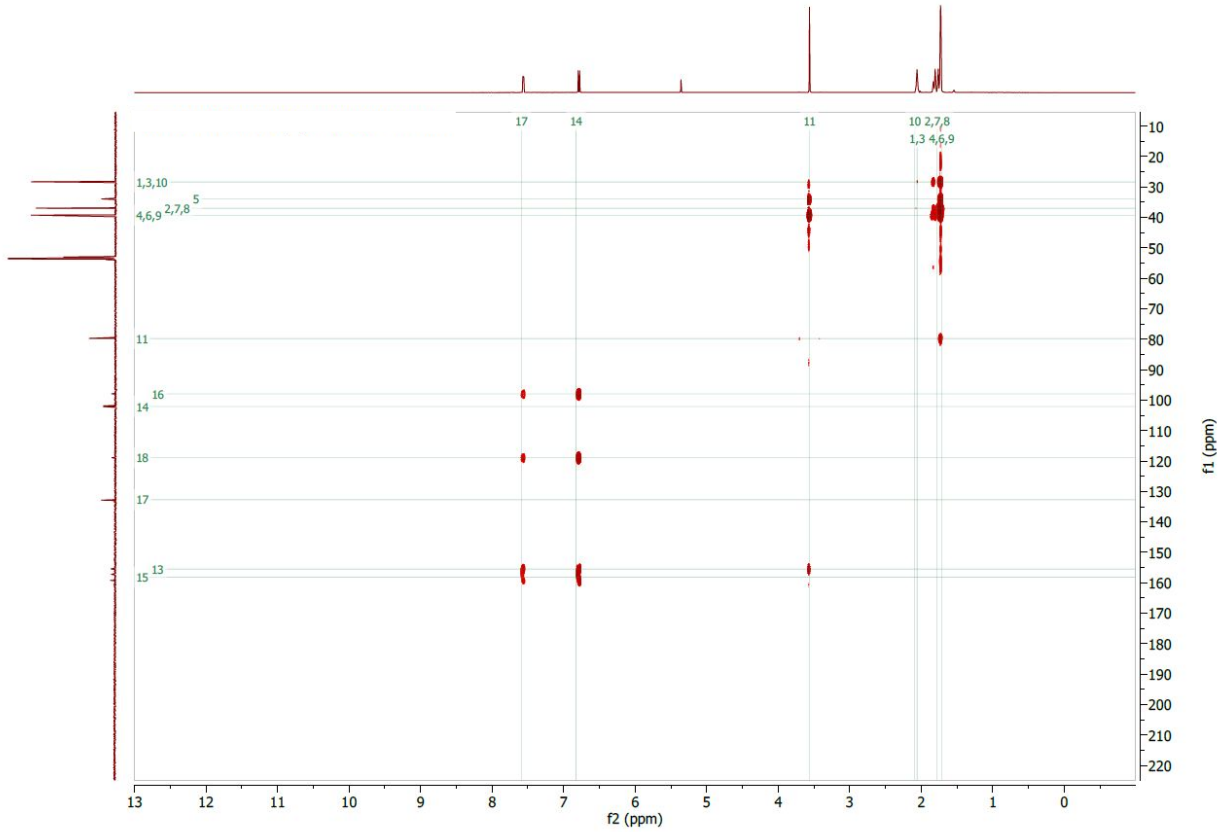


Figure S-2.10. COSY spectrum of *1-((4-bromo-2-chloro-5-fluorophenoxy)methyl)adamantane* **18**.

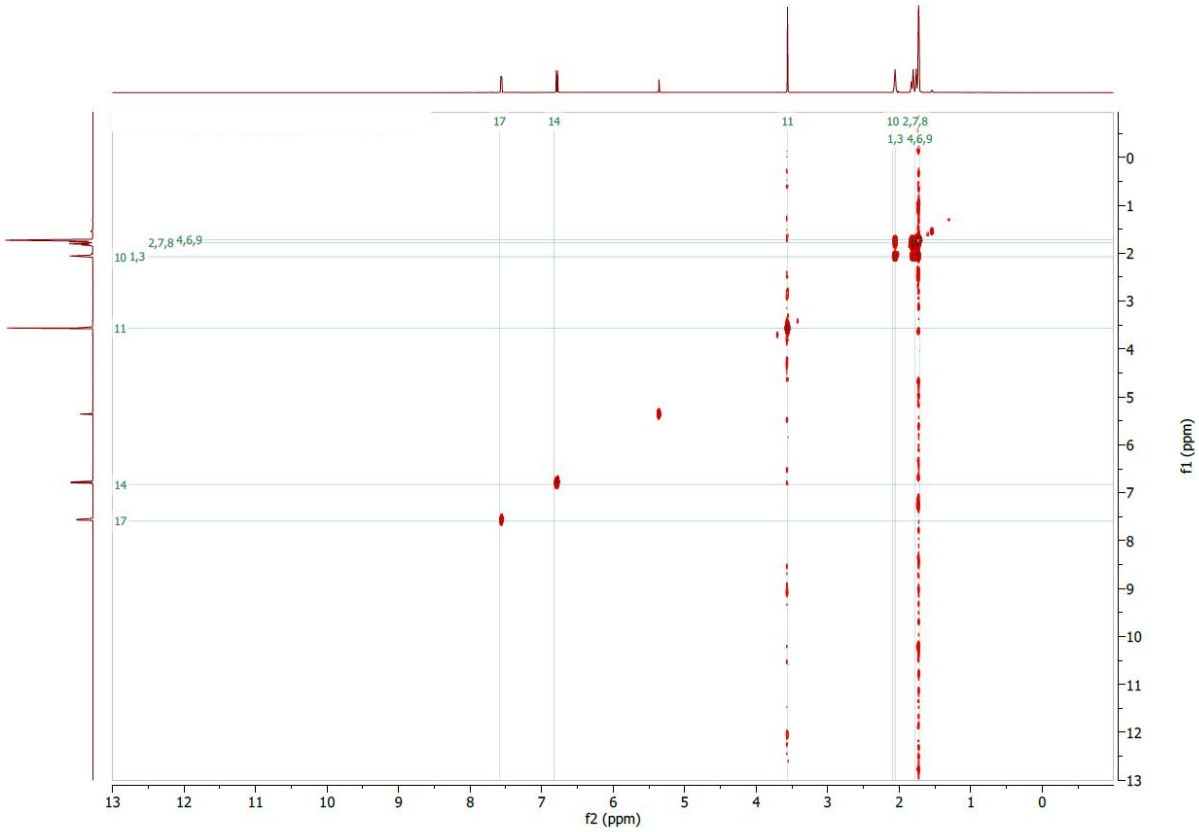


Figure S-2.11. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *methyl 4-(()-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **23**.

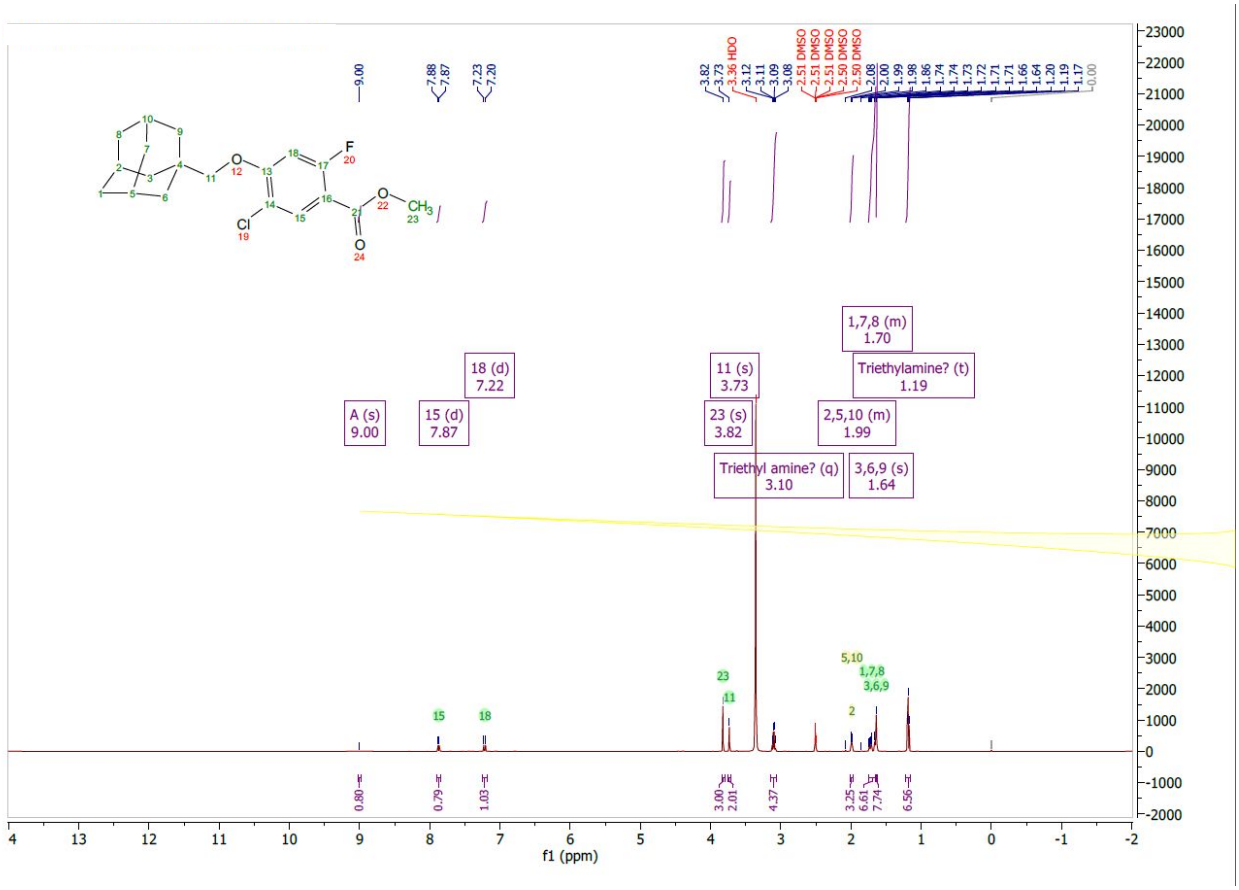


Figure S-2.12. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of *methyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **23**.

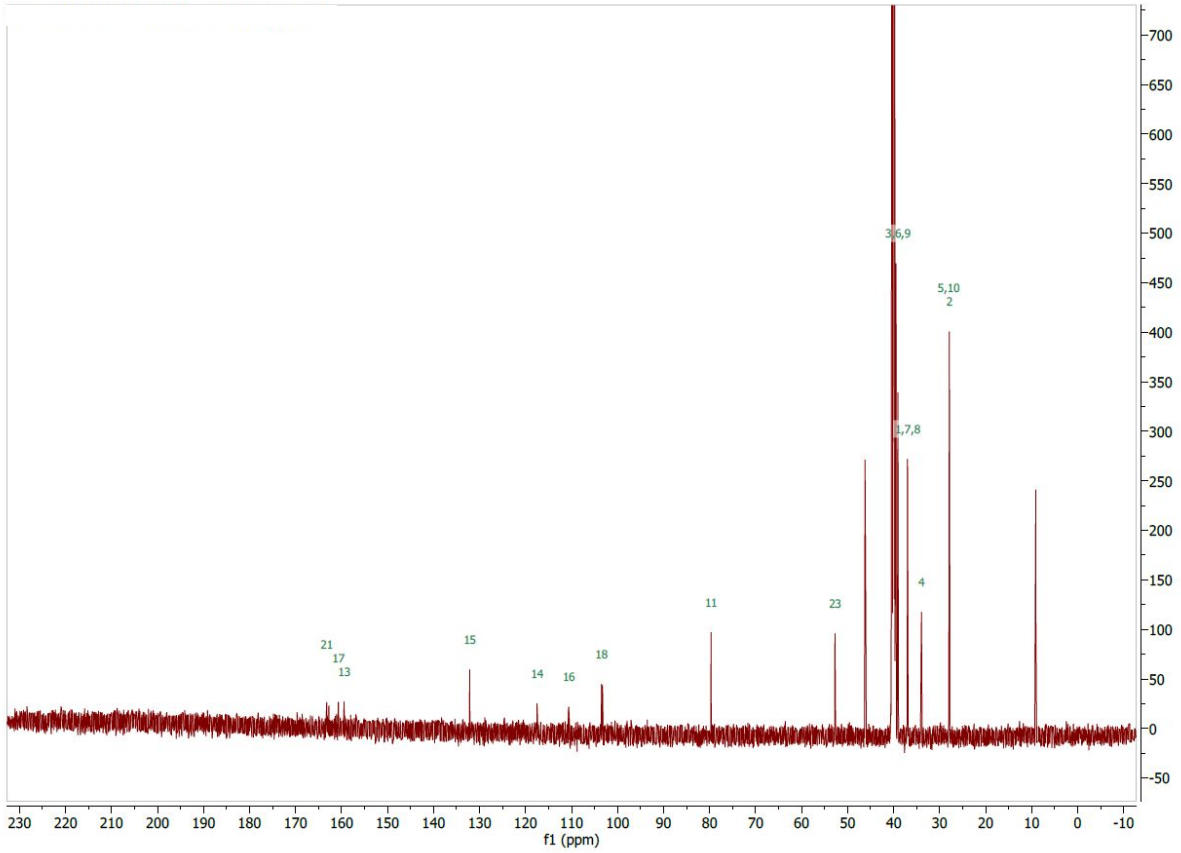


Figure S-2.13. HSQC spectrum of *methyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **23**.

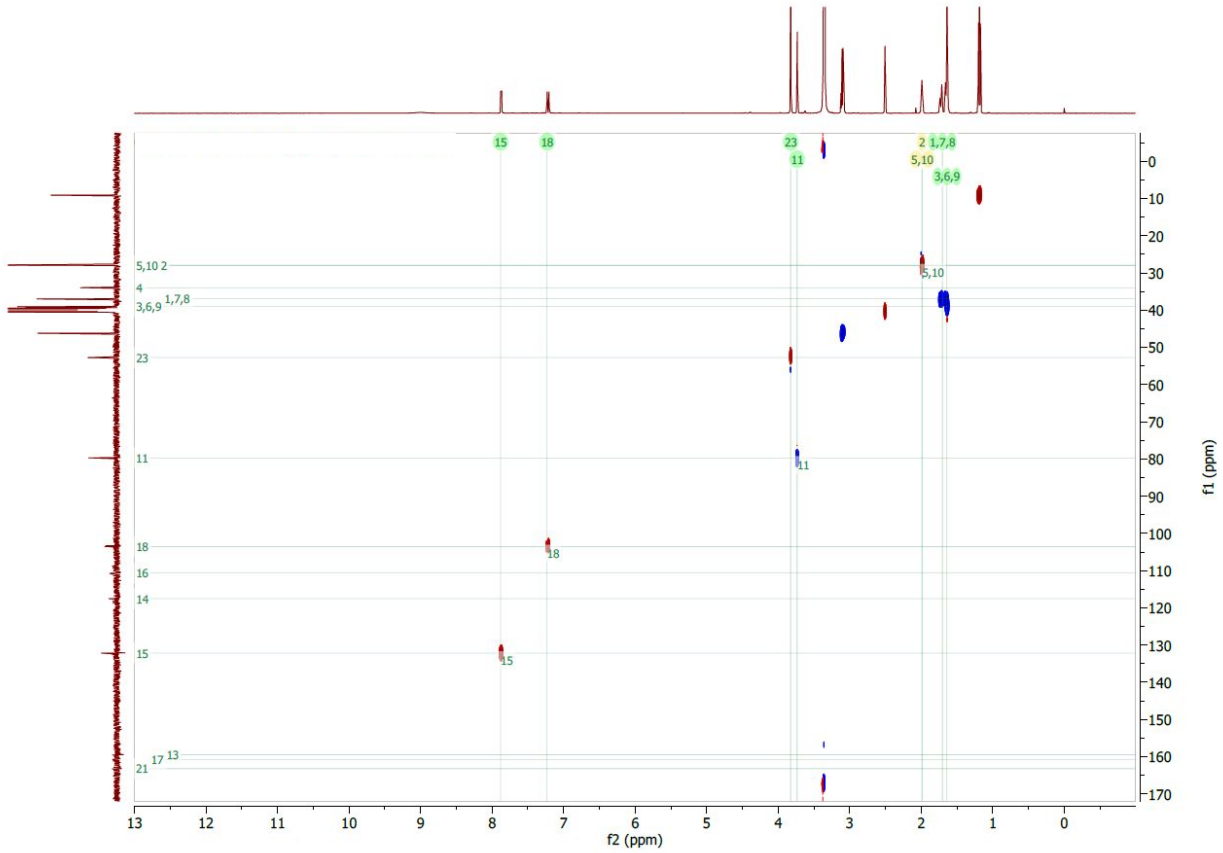


Figure S-2.14. HMBC spectrum of *methyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **23**.

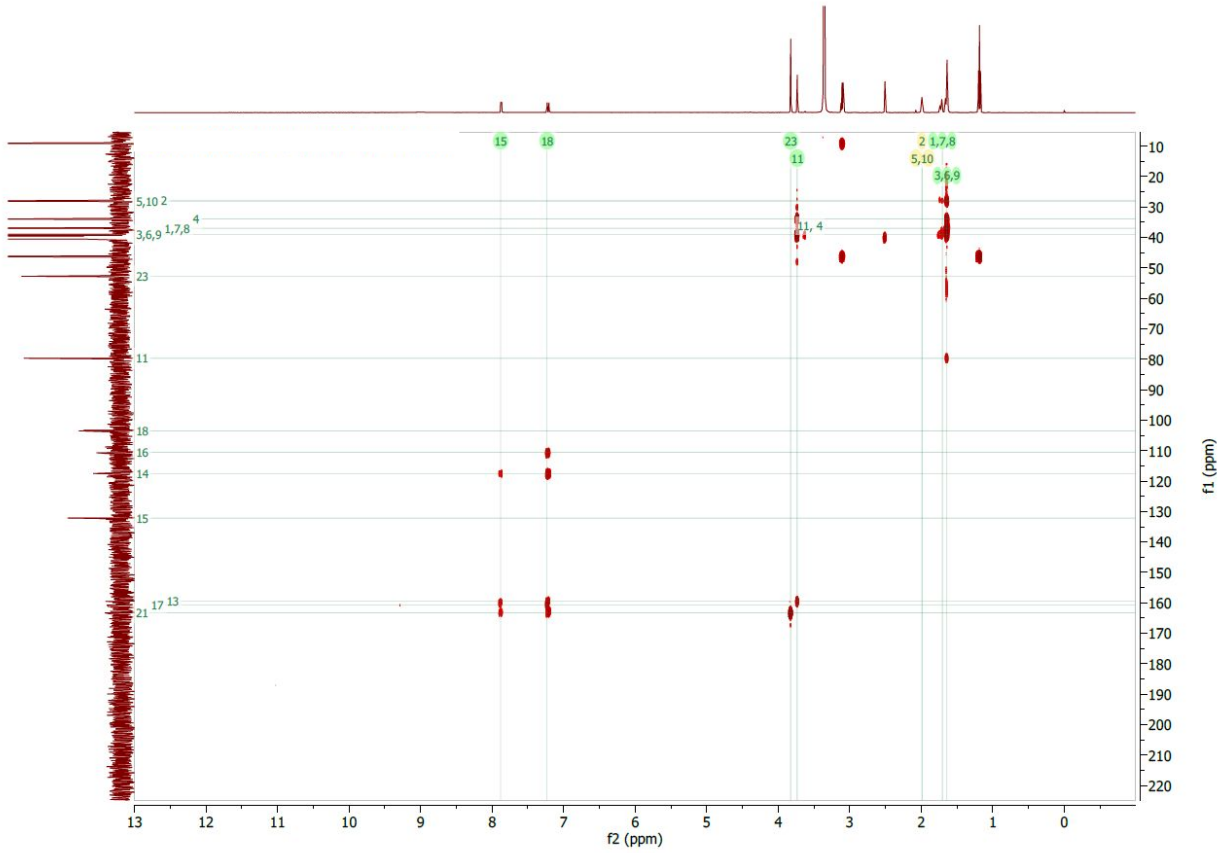


Figure S-2.15. COSY spectrum of *methyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate* **23**.

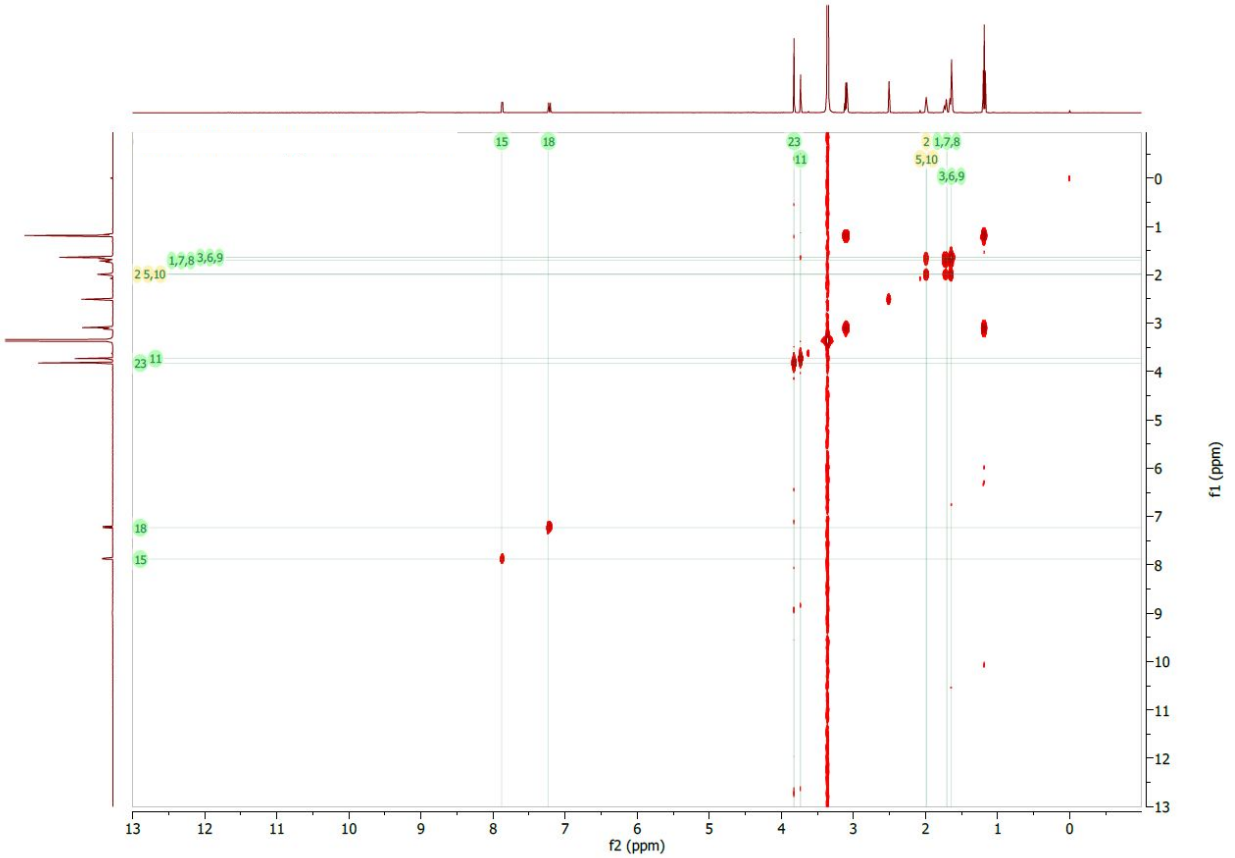


Figure S-2.16. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *benzyl (azetidin-1-ylsulfonyl)carbamate* **16**.

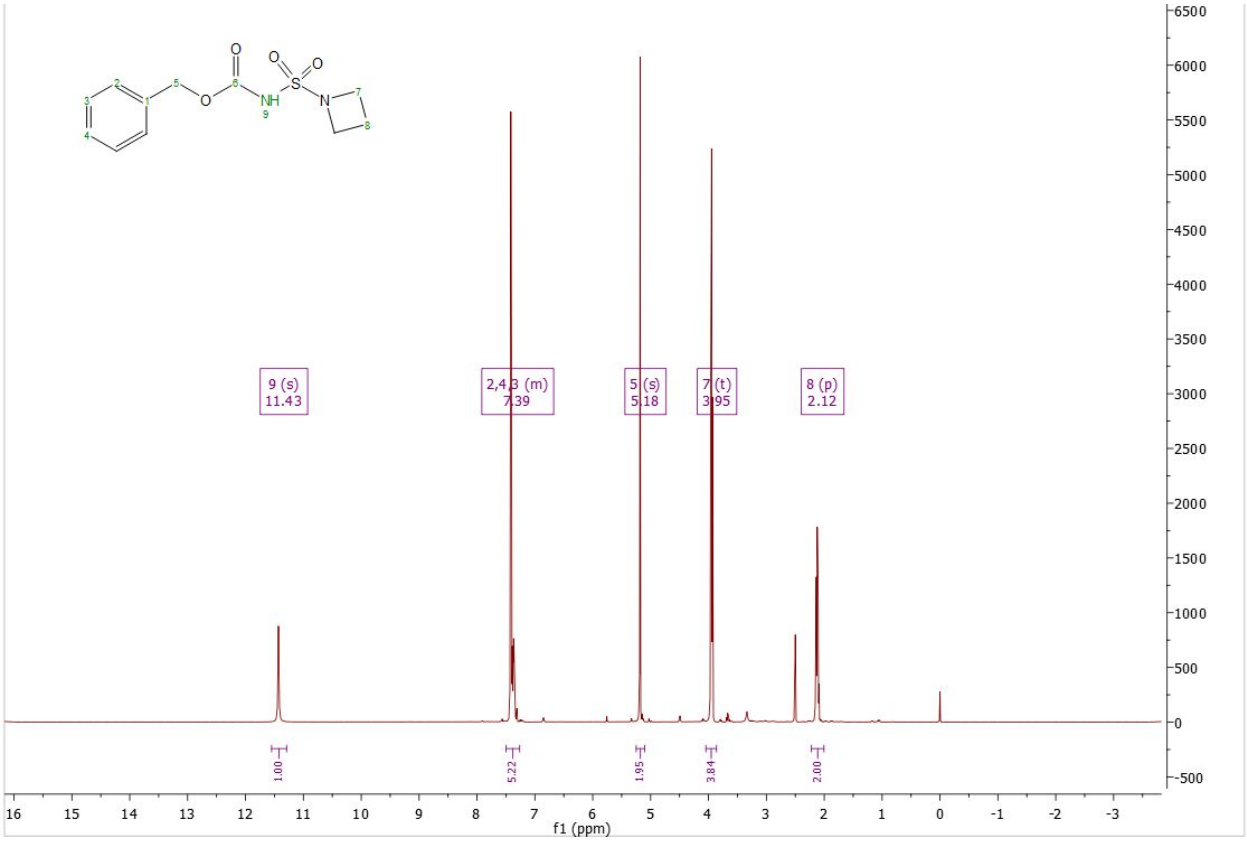


Figure S-2.17. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of *benzyl (azetidin-1-ylsulfonyl)carbamate* **16**.

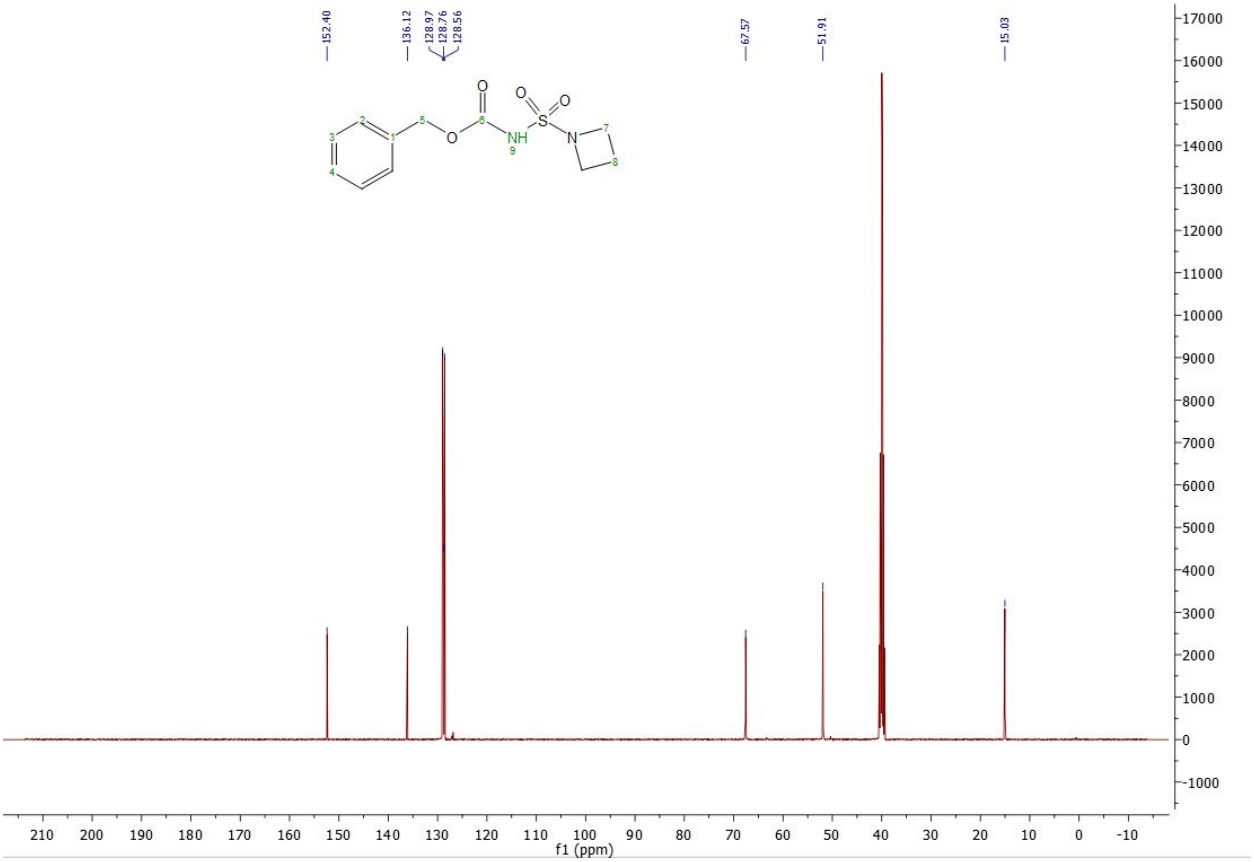


Figure S-2.18. ^{1}H NMR (600 MHz, C_6D_6) spectrum of *4-((-adamantan-1-yl)methoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluorobenzamide GDC-0276*.

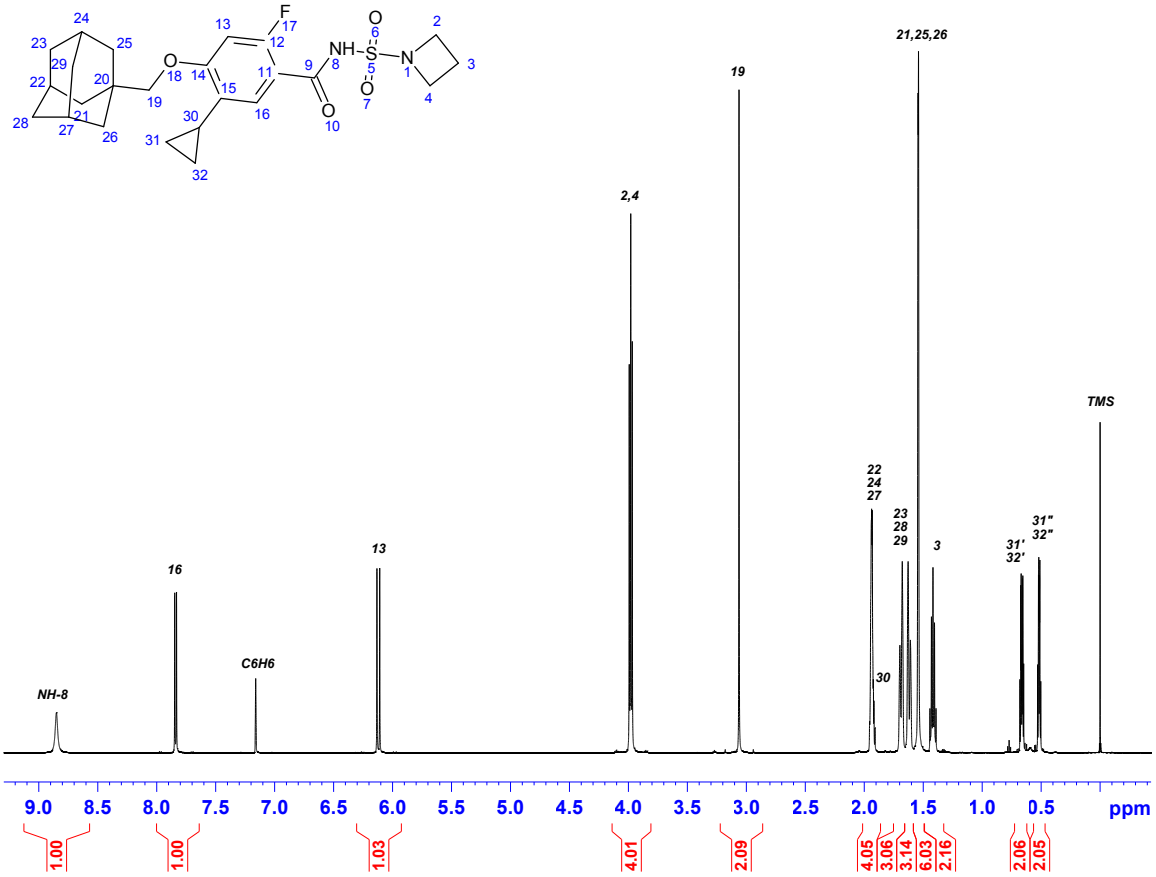


Figure S-2.19. ^{13}C NMR (150 MHz, C_6D_6) spectrum of *4-((-adamantan-1-yl)methoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluorobenzamide GDC-0276*.

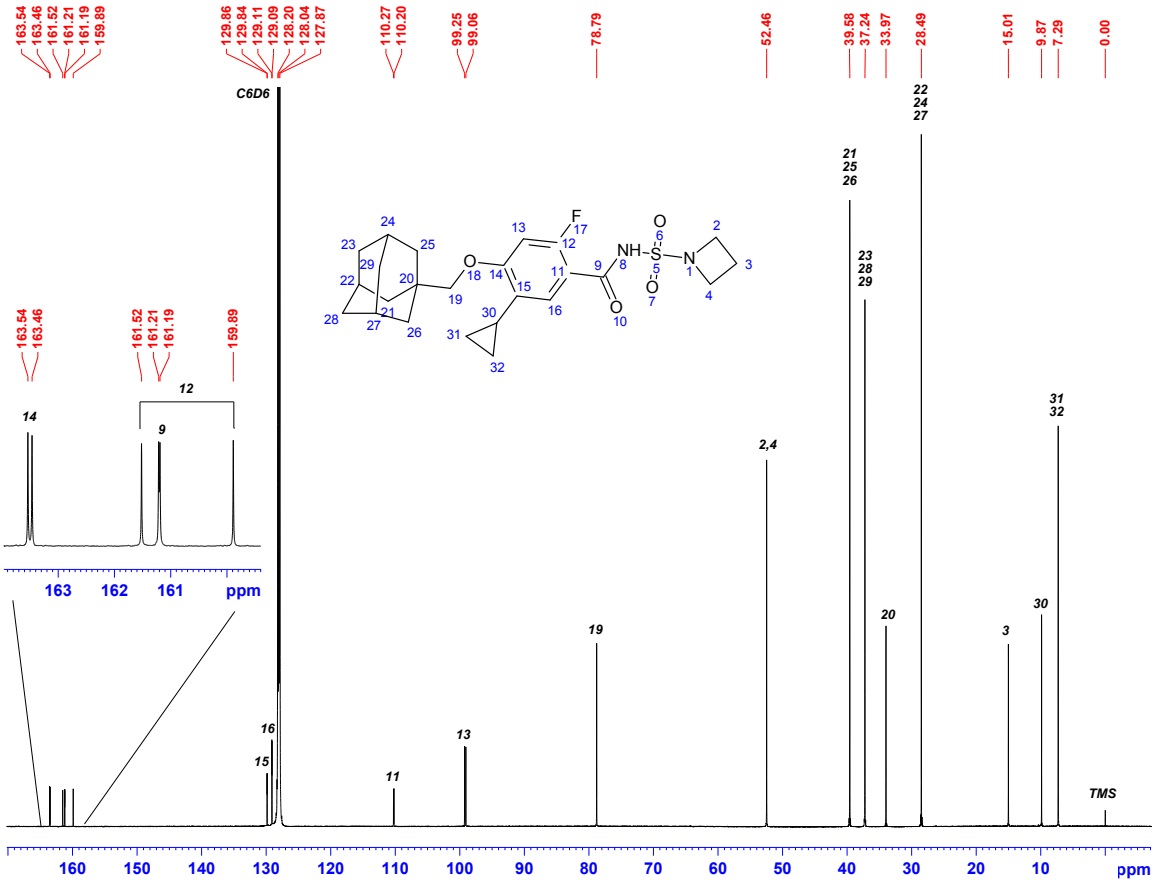


Figure S-2.20. HSQC spectrum of *4-((-adamantan-1-yl)methoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluorobenzamide GDC-0276*.

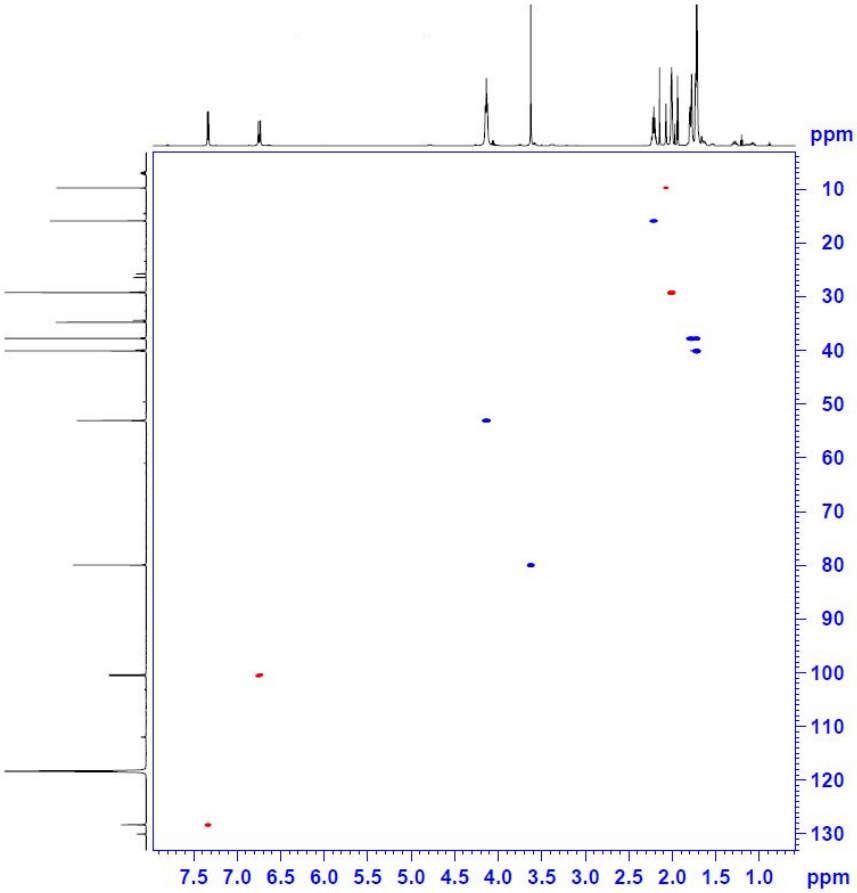


Figure S-2.21. HMBC spectrum of *4-((-adamantan-1-yl)methoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluorobenzamide GDC-0276*.

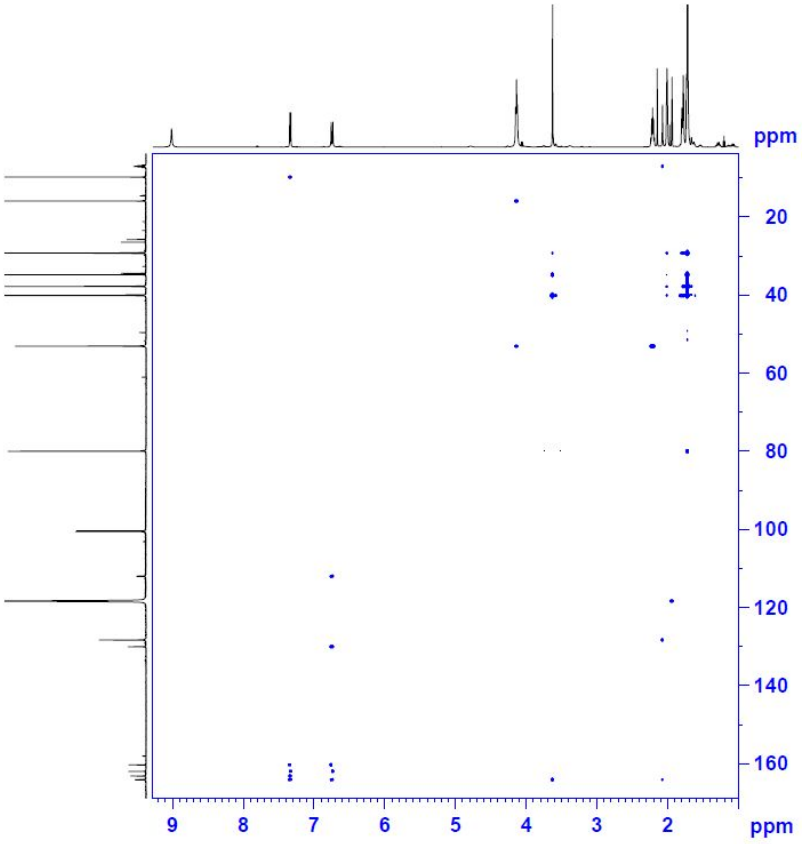


Figure S-2.22. DQF-COSY spectrum of *4-((-adamantan-1-yl)methoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluorobenzamide GDC-0276*.

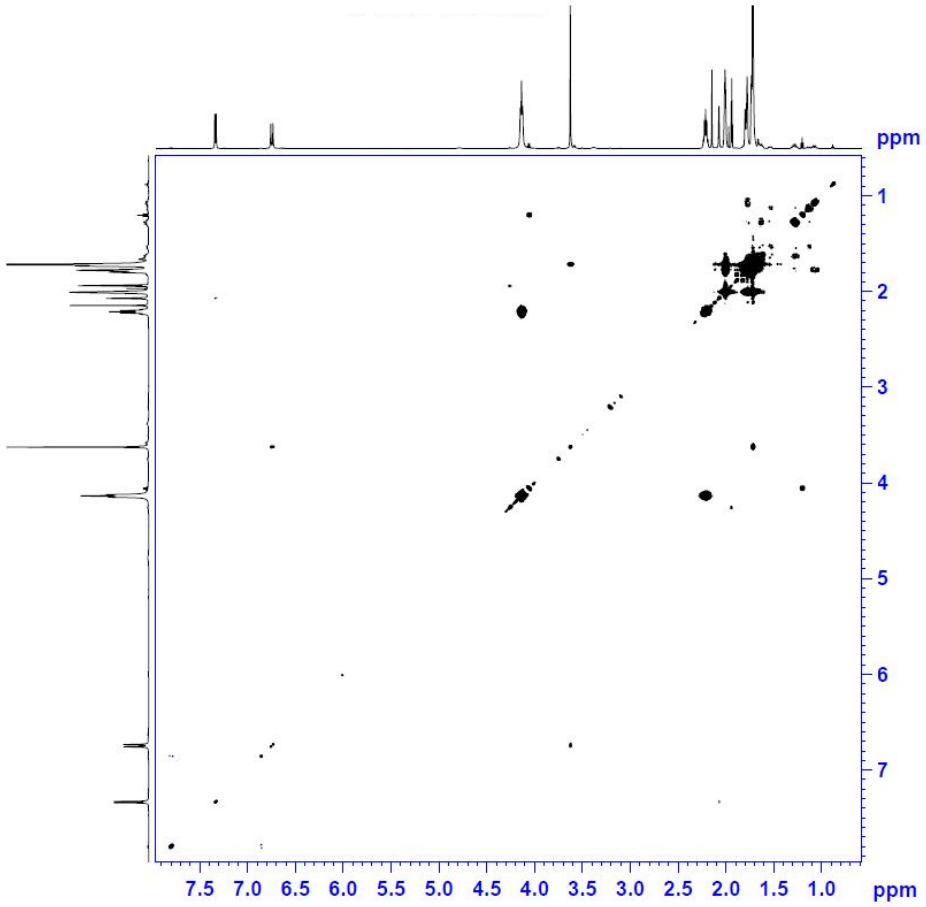
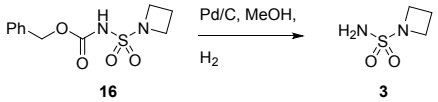


Table S1. Solubility Data for *Cbz Sulfamide* **16** and *Sulfamide* **3**



16 **3**

Entry[a]	Solvent	Solubility of **16** at 15 ºC (mg / g)	Solubility of **3** at 15 ºC (mg/g)
1	2-propanol	27.6	20.9
2	EtOH	71.1	43.1
3	*i*PrOAc	72.5	12.5
4	MeOH	285.0	108.4
5	2-MeTHF	387.1	28.3
6	Acetone	450.0	512.3

[a] Solubility experiments were conducted by mixing substrates in closed vials with stir bars in solvent (2 mL, saturated mixtures) at 15 ºC and stirring for 2 h. Then samples were taken from the vials and filtered. The clear solution was analyzed by HPLC to calculate the assay of substrates.

Figure S-2.23. *DSC for cycloproyplboronic acid*

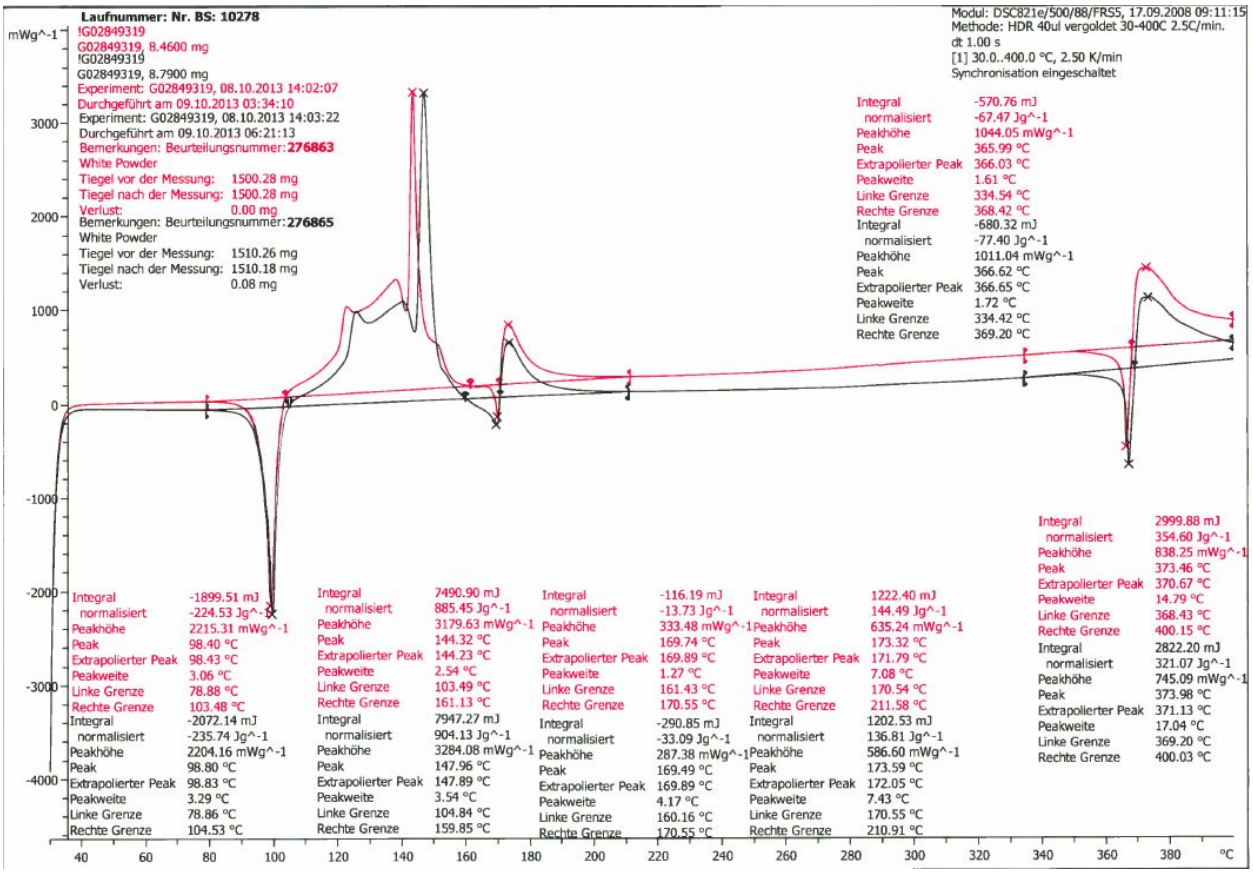
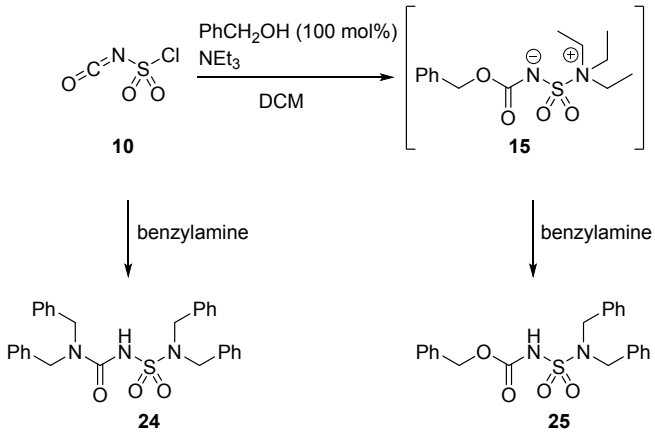
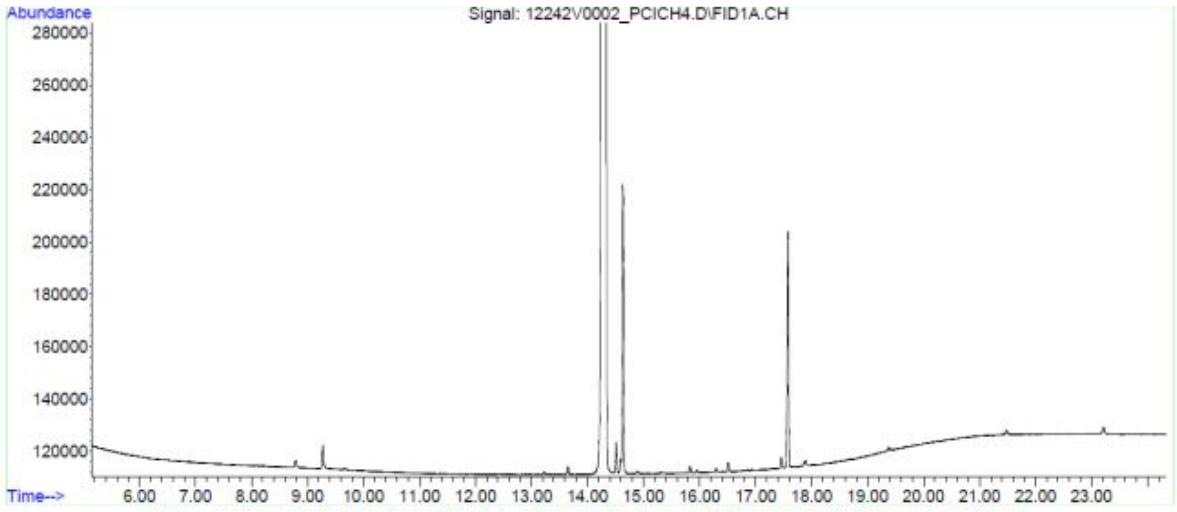


Figure S-2.24. Derivatization of *CSI* **(10)** *and* **15**



Dibenzylamine was added to the reaction and stirred for 5 min, then analyzed by HPLC for derivatives **24** and **25**.

Figure S-2.25. *LCMS Data of* **21** *and* **22**.



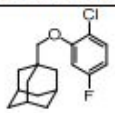
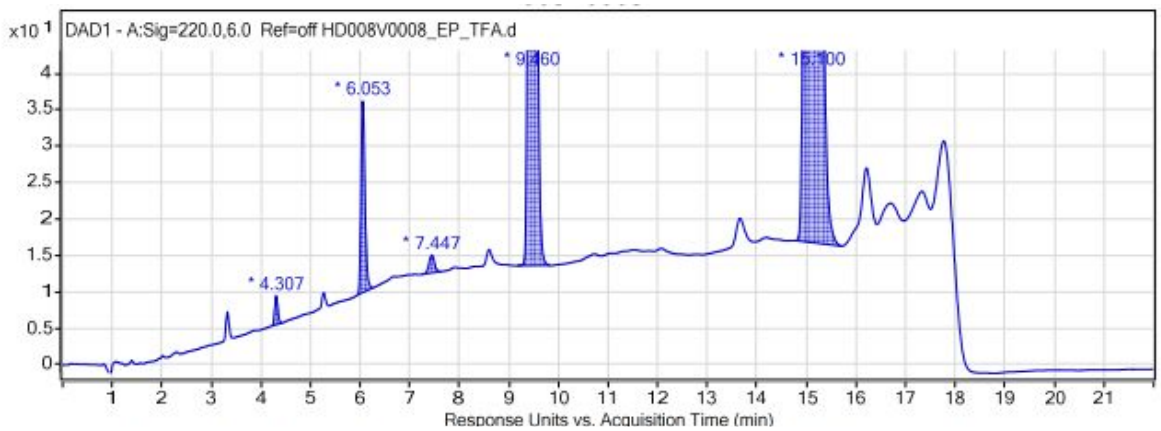
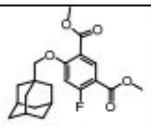
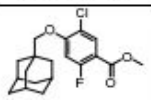
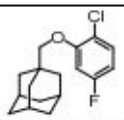
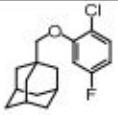
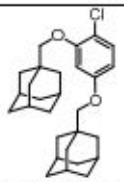
Proposed structure	M	MS	Frag-ments	remarks
 Exact Mass: 294.119	294 Da	$_{EI}[M]^+$ = 294 Da $_{PCI,CH4}[M-H]^+$ = 293 Da $_{PCI,CH4}[M+ C_2H_5]^+$ = 321 Da $_{PCI,CH4}[M+ C_3H_5]^+$ = 333 Da	149, 159 149, 159, 175, 259, 275  Exact Mass: 149.133  Exact Mass: 159.001  Exact Mass: 259.150  Exact Mass: 275.120	
		$_{PCI,C4H10}[M-H]^+$ = 293 Da $_{PCI,C4H10}[M+ C_2H_5]^+$ = 321 Da	149	

Figure S-2.26. *LCMS Data of* **24**.



RT [min]	Sub-stance	Proposed structure	M	MS	MS/MS	remarks
4.3	NK		429.252 Da	ESI$[M+H]^+$ = 430.2594 Da ESI$[2M+Na]^+$ = 881.4935 Da	149.13, 218.08, 250.11, 282.13, 398.23	No isotopes Cl / Br
6.1	NK		405.207 Da	ESI$[M+H]^+$ = 406.2139 Da	149.13, 226.06, 258.09, 374.19	1x Cl
7.5	NK		518.204 Da	ESI$[M+H]^+$ = 519.2108 Da ESI$[M+Na]^+$ = 541.1889 Da ESI$[2M+H]^+$ = 1037.4118 Da ESI$[2M+Na]^+$=1059.3952 Da		No isotopes Cl / Br
9.5	NK	 Exact Mass: 376.169	376.170 Da	ESI$[M+Na]^+$ = 399.1589 Da ESI$[2M+Na]^+$ = 775.3289 Da		No isotopes Cl / Br
15.1		 Exact Mass: 352.124	352.125 Da	ESI$[M+Na]^+$ = 375.1137 Da ESI$[2M+Na]^+$ = 727.2393 Da	149.13, 181.07, 332.16, 344.17, 352.59	1x Cl

14.5		 Exact Mass: 294.119	294 Da	$_{EI}[M]^+$ = 294 Da $_{PCI,CH4}[M-H]^+$ = 293 Da $_{PCI,CH4}[M+ C_2H_5]^+$ = 321 Da $_{PCI,C4H10}[M-H]^+$ = 293 Da $_{PCI, C4H10}[M+ C_2H_5]^+$ = 321 Da $_{PCI, C4H10}[M+ C_3H_5]^+$ = 333 Da	149, 159 149, 159, 163, 173, 259, 275 149	
14.6		 Exact Mass: 294.119	294 Da	$_{EI}[M]^+$ = 294 Da $_{PCI,CH4}[M-H]^+$ = 293 Da $_{PCI,CH4}[M+ C_2H_5]^+$ = 321 Da $_{PCI,C4H10}[M]^+$ = 294 Da	149, 159 149, 163, 275 149	
17.6		 Exact Mass: 440.248	440 Da	$_{EI}[M]^+$ = 440 Da $_{PCI,CH4}[M+H]^+$ = 439 Da $_{PCI,C4H10}[M-H]^+$ = 439 Da	203, 239, 295 135, 147, 175, 295, 135, 295	

Side product **24** could not be traced back to the corresponding dibromo side product in the starting material for the carbonylation, as this species was absent.