

SUPPORTING INFORMATION FOR

2-Oxaadamant-1-yl ureas as soluble epoxide hydrolase inhibitors: *in vivo* evaluation in a murine model of acute pancreatitis

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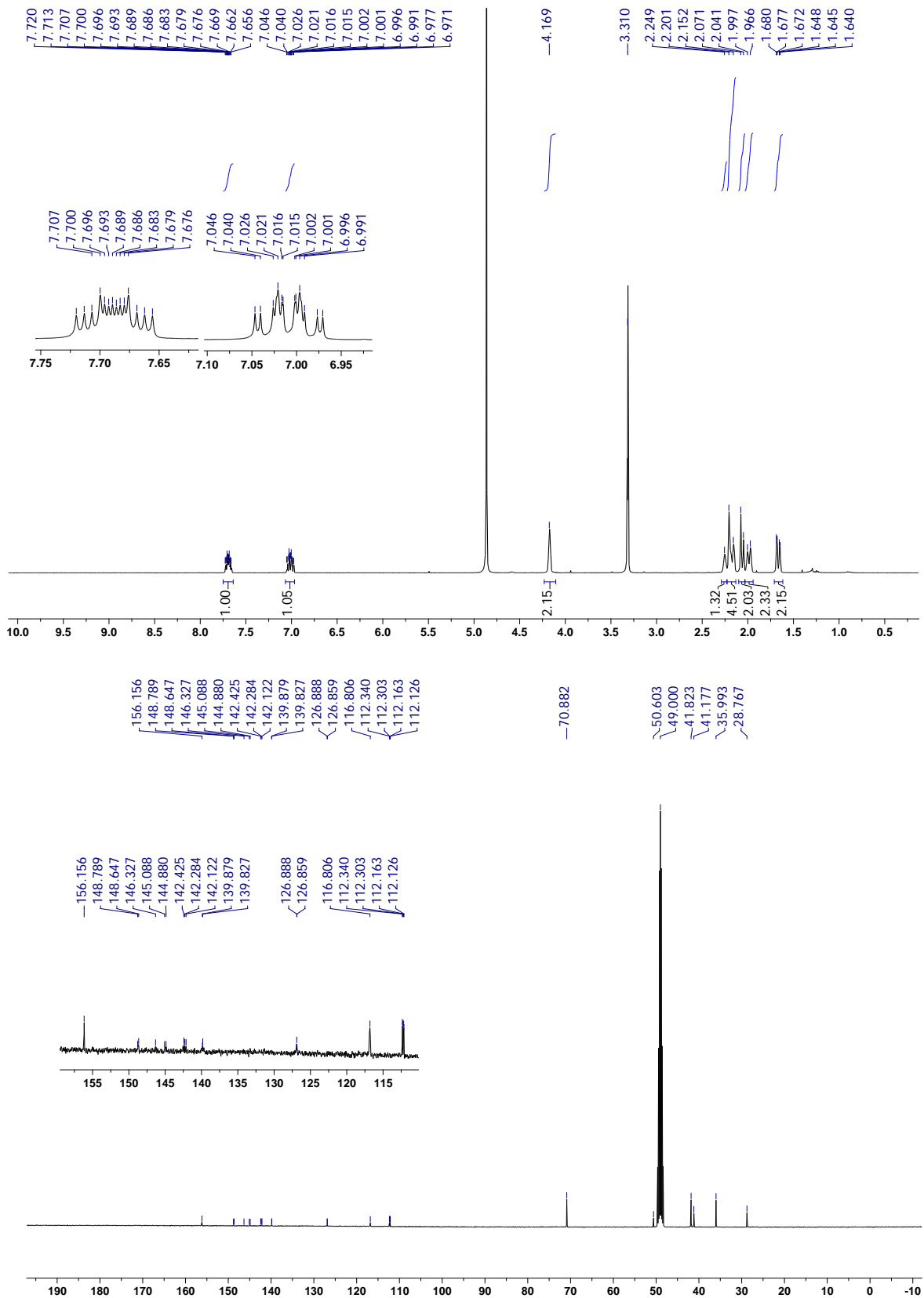
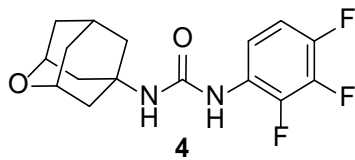
¹⁰Institució Catalana de Recerca i Estudis Avançats (ICREA), 08010 Barcelona, Spain.

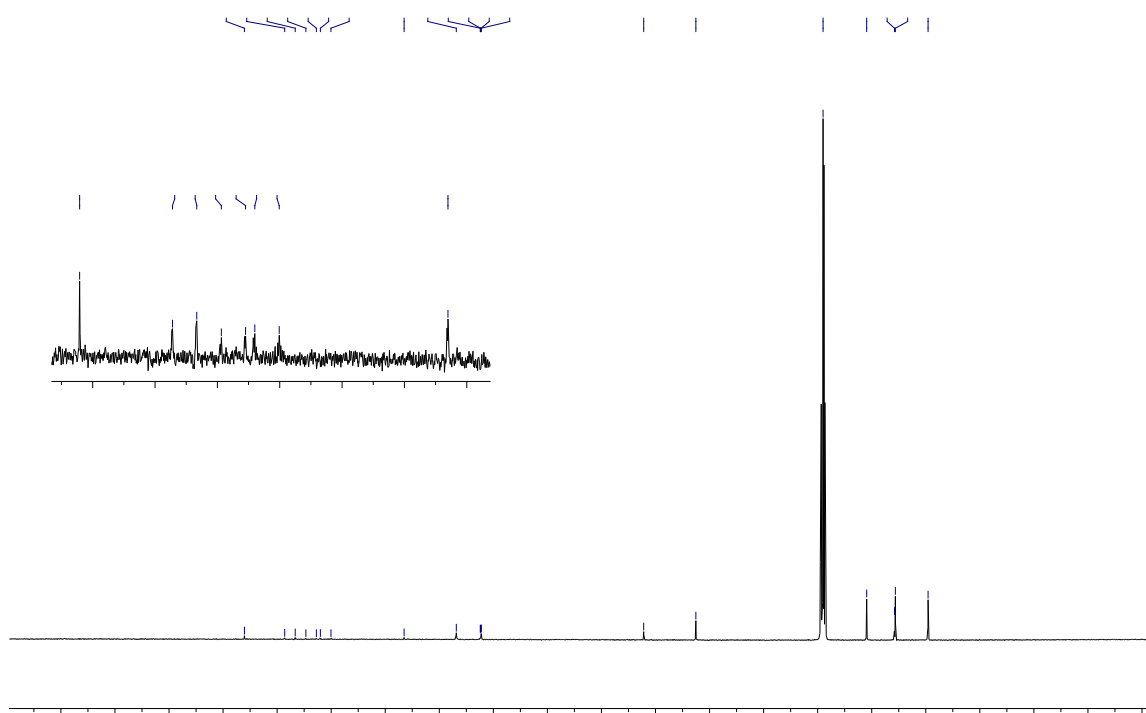
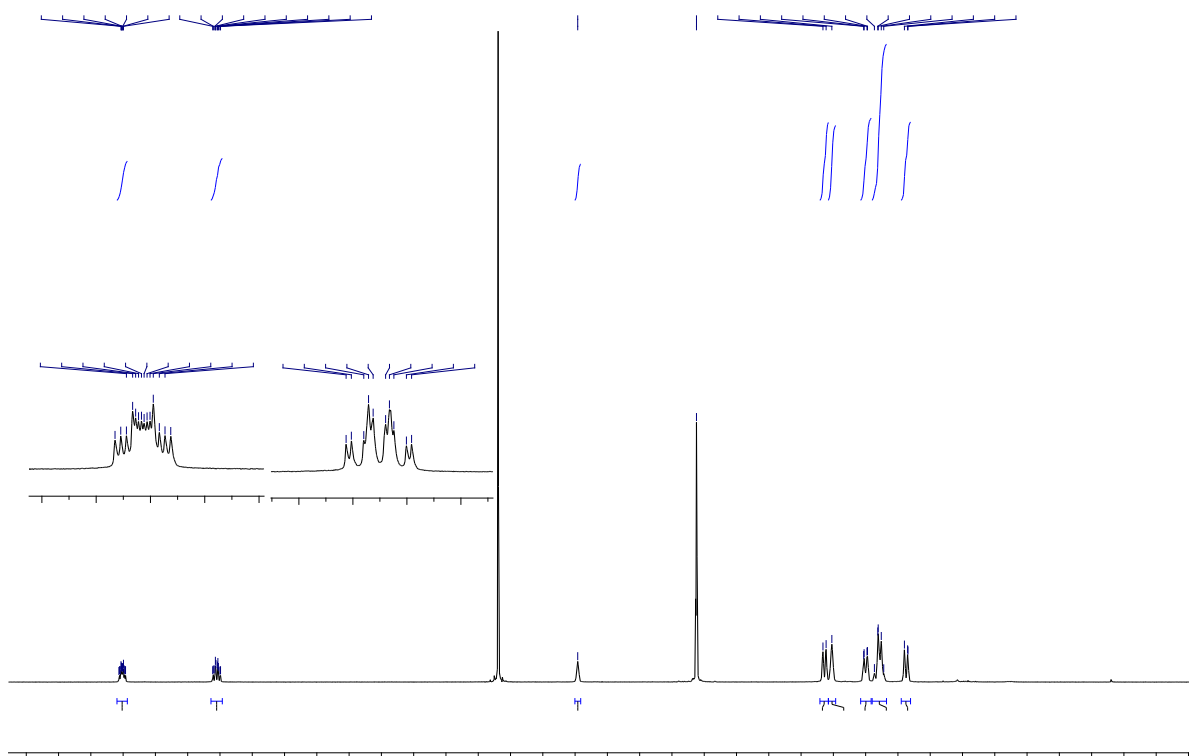
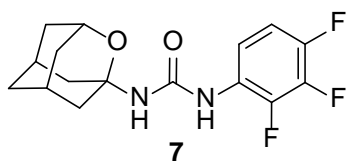
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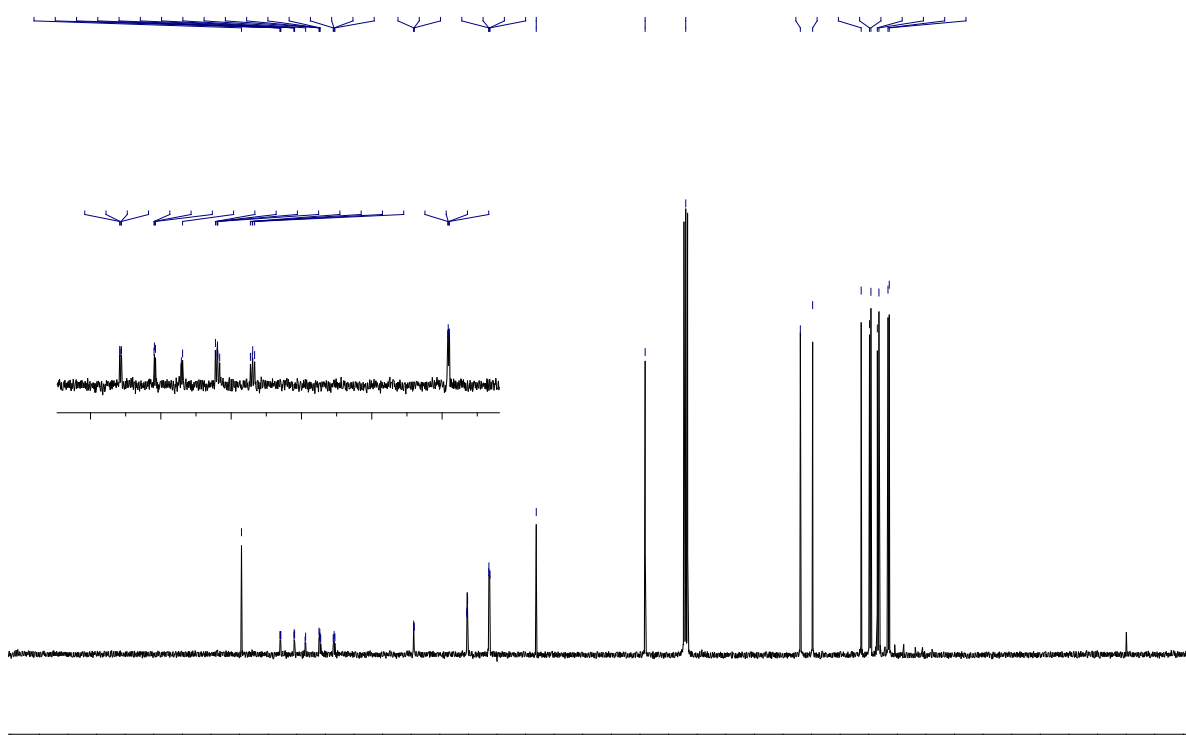
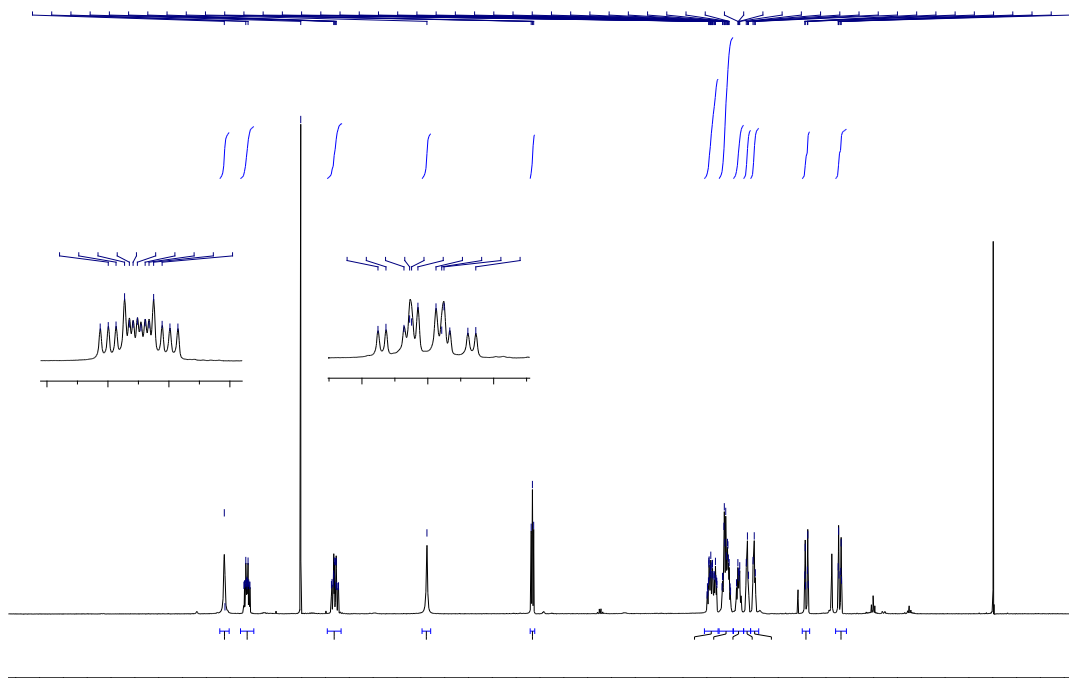
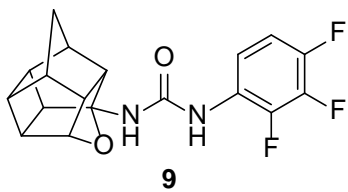
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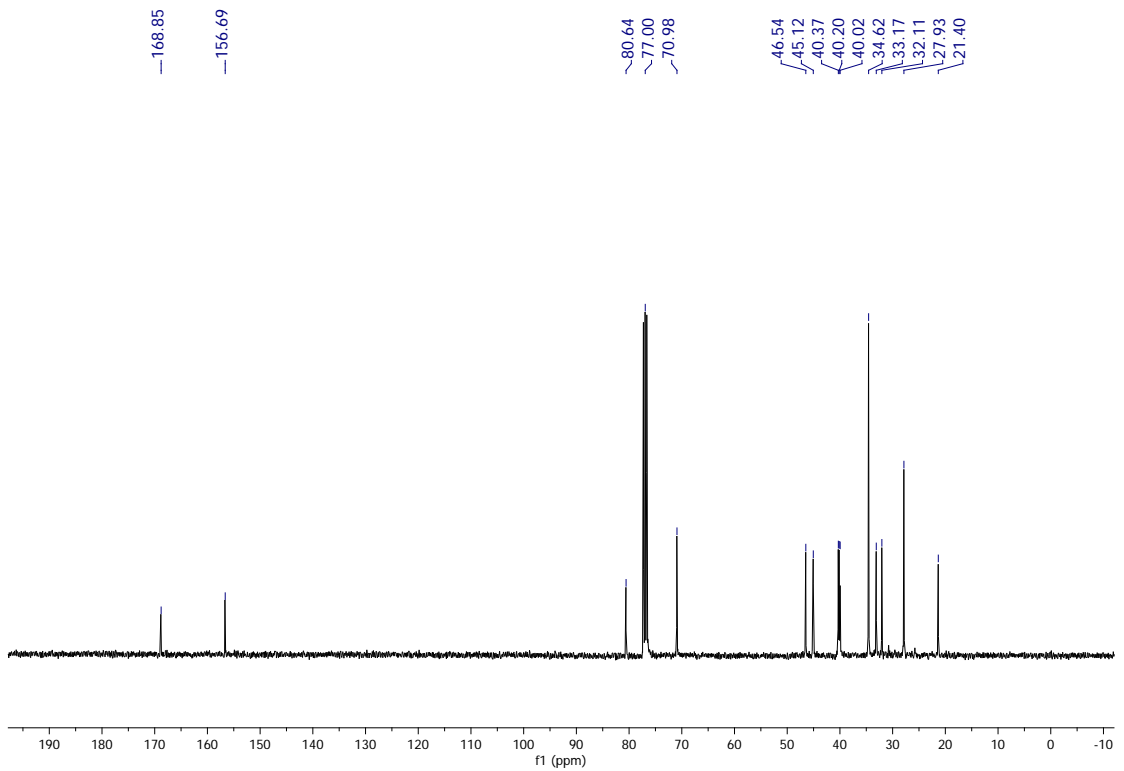
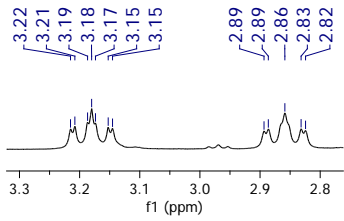
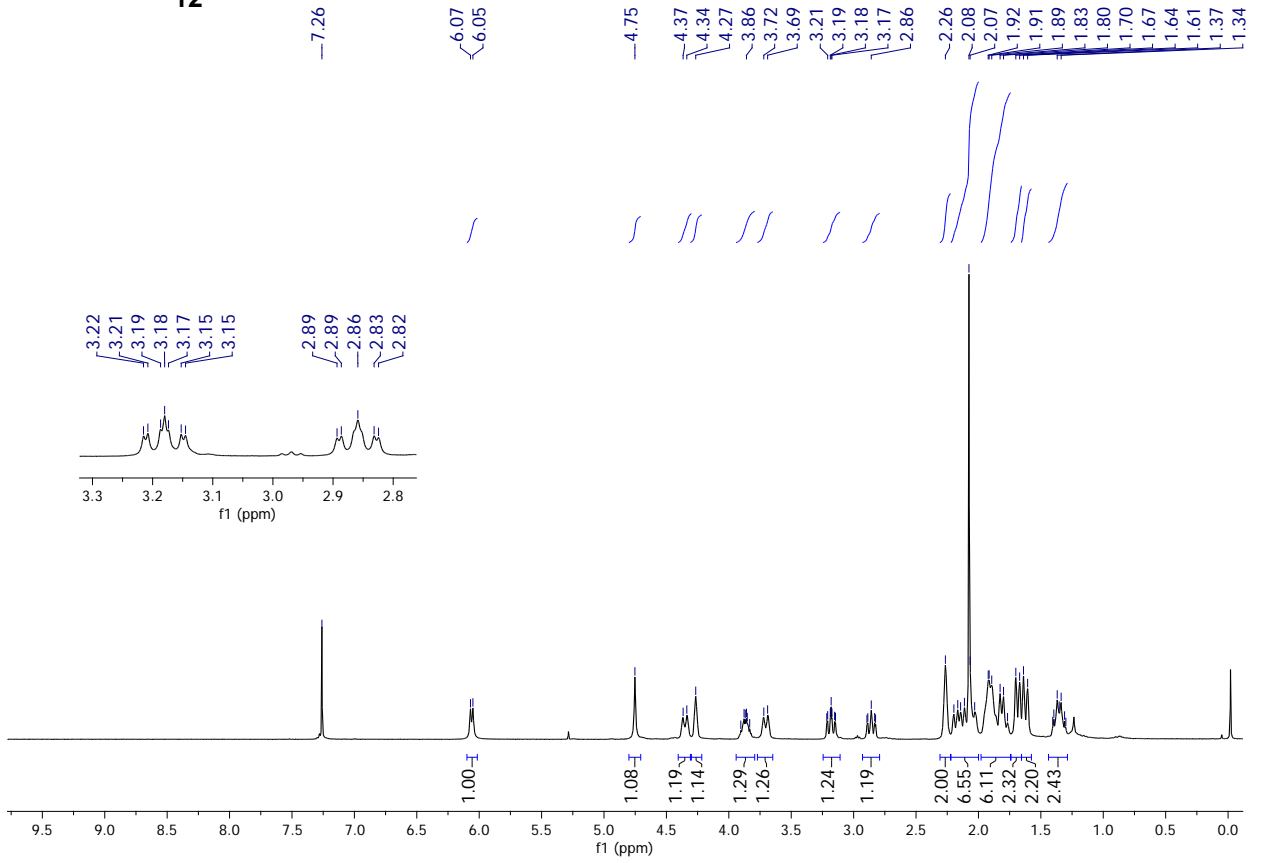
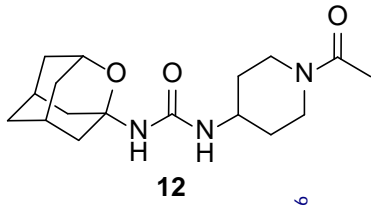
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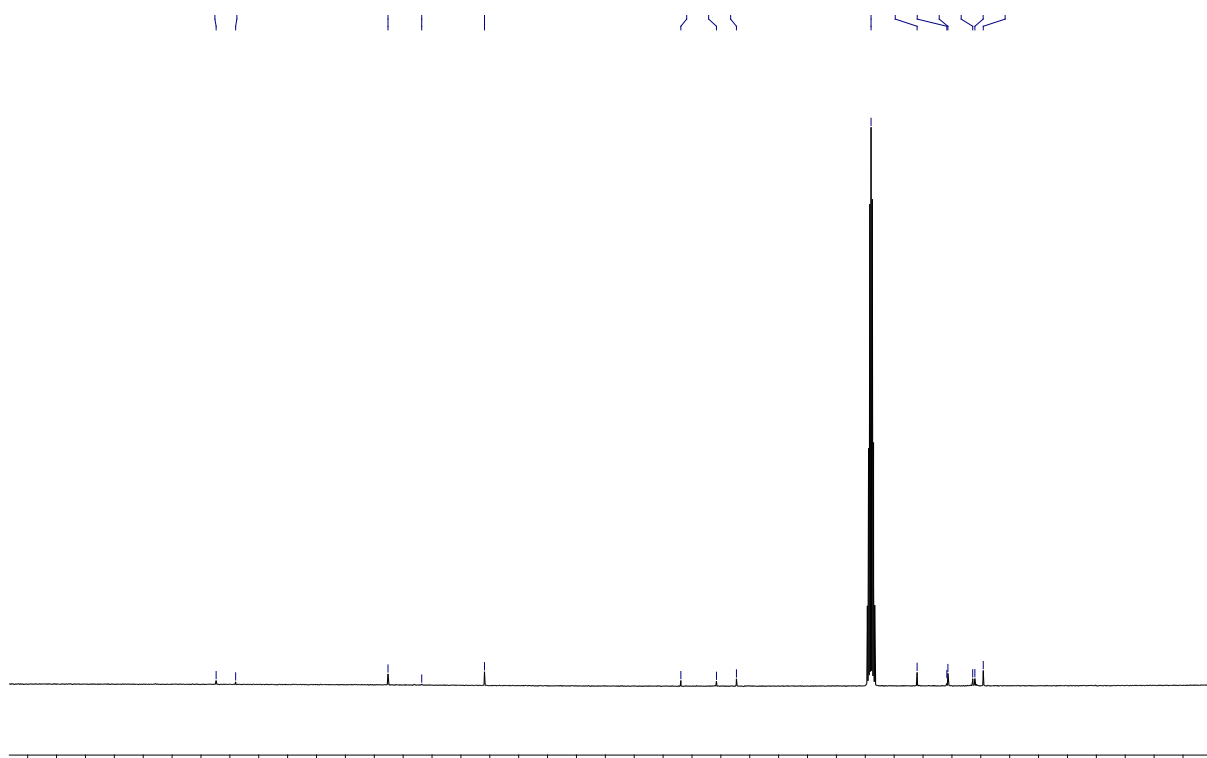
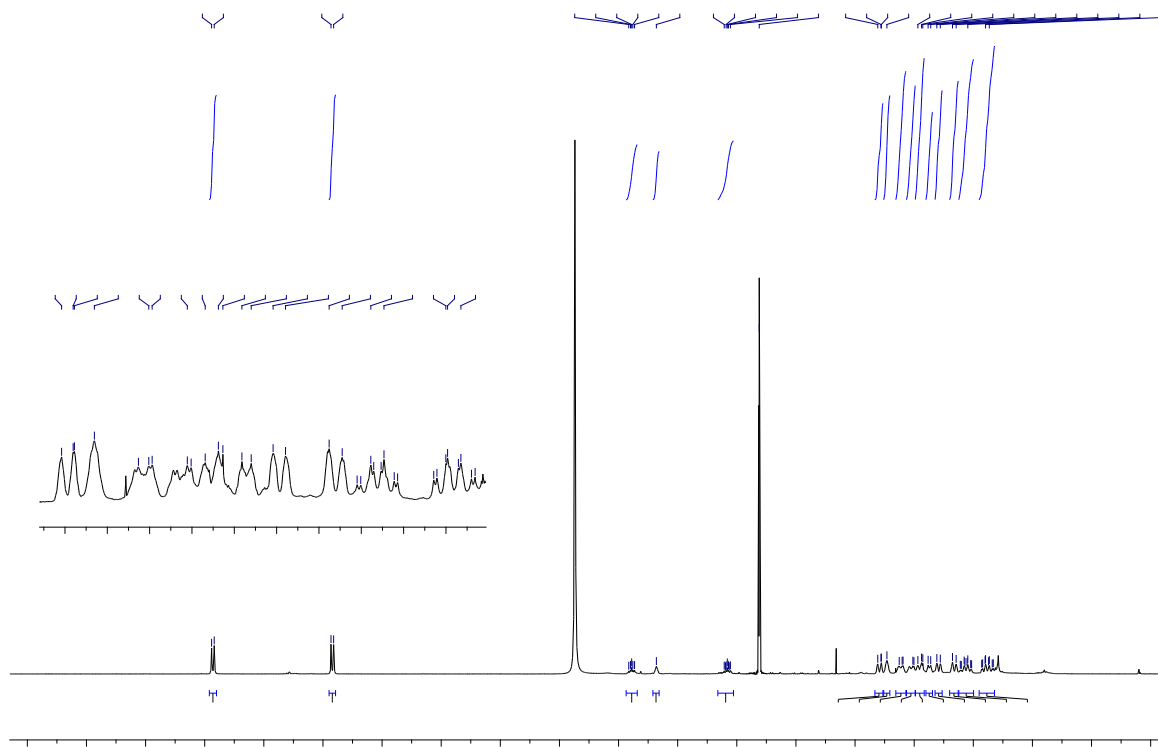
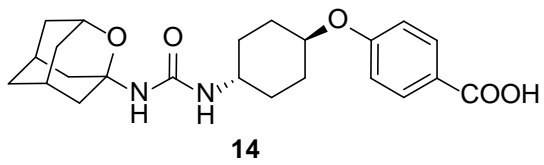
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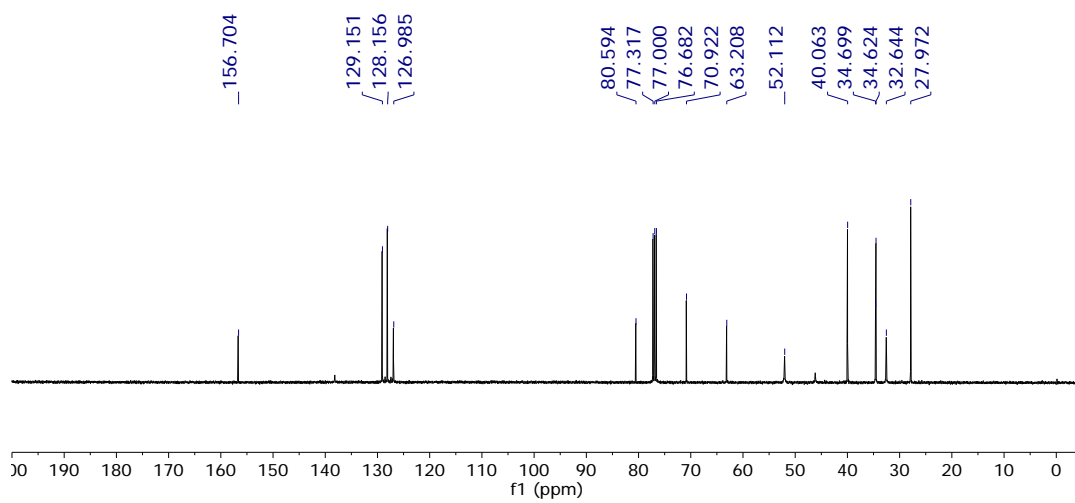
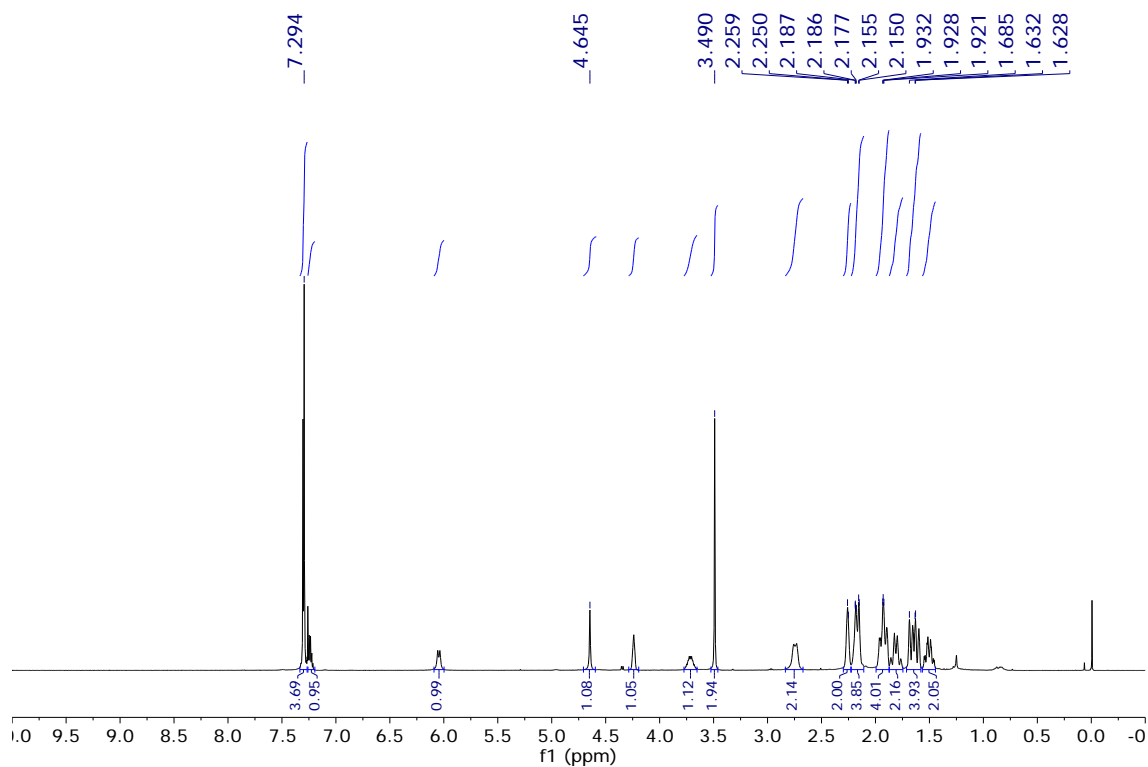
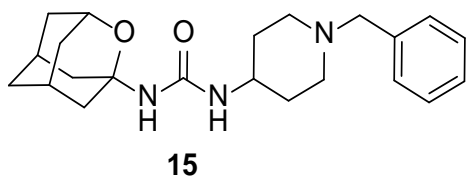


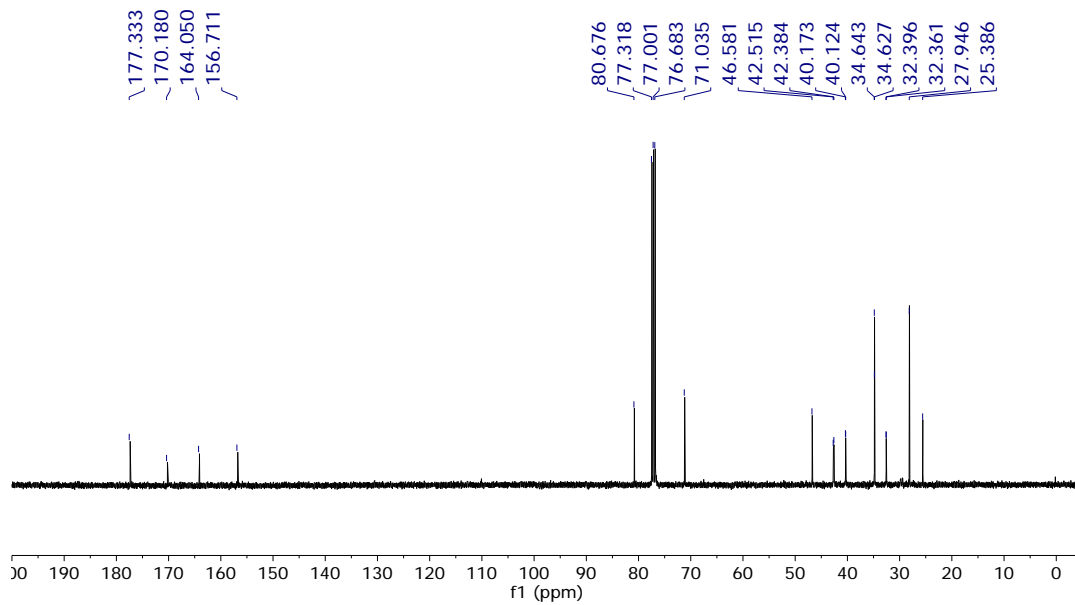
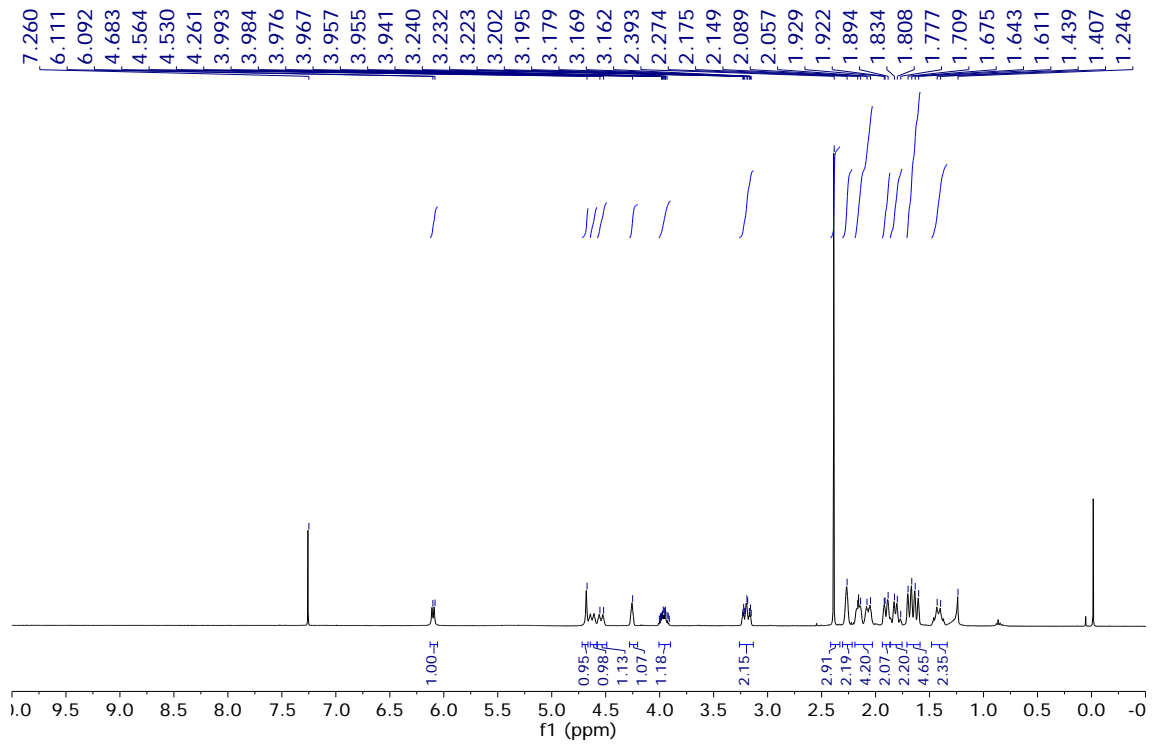
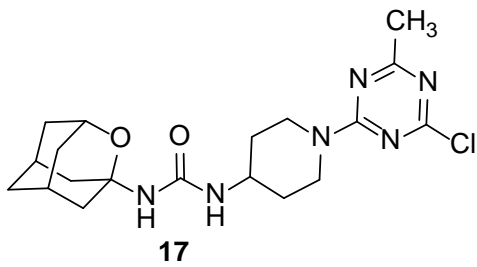


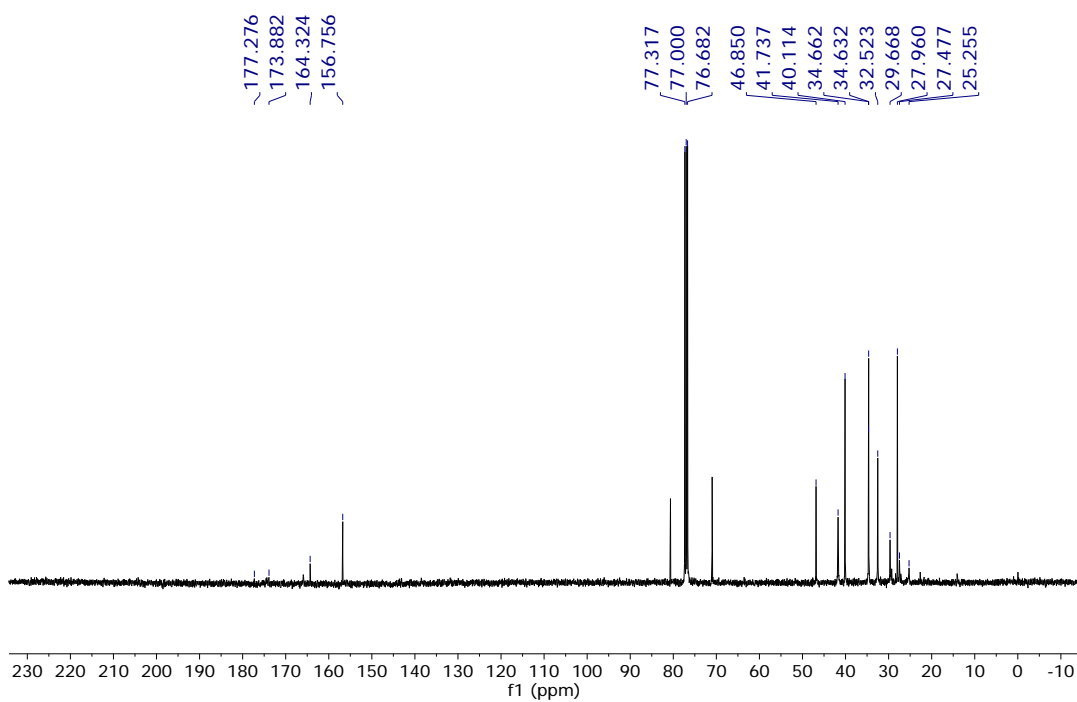
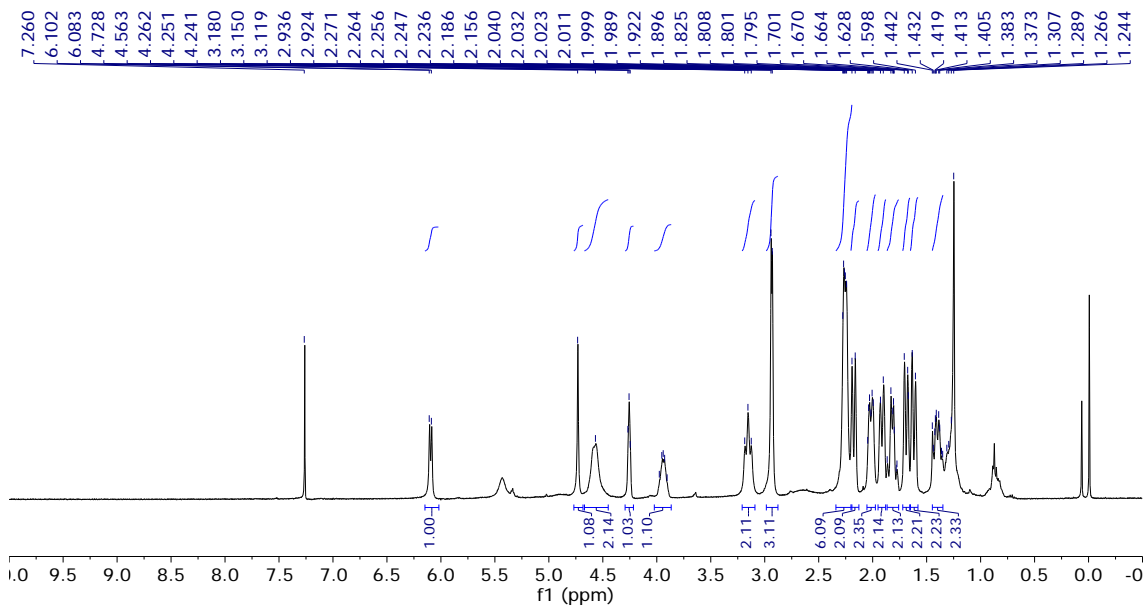
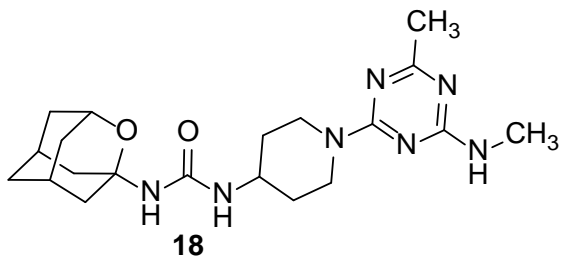


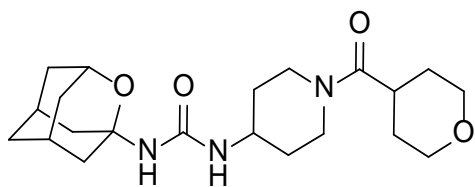




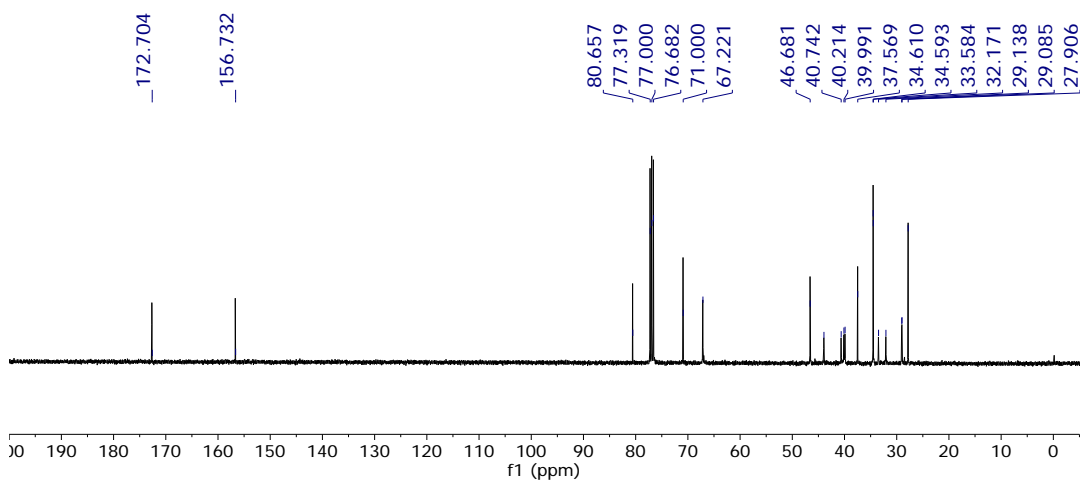
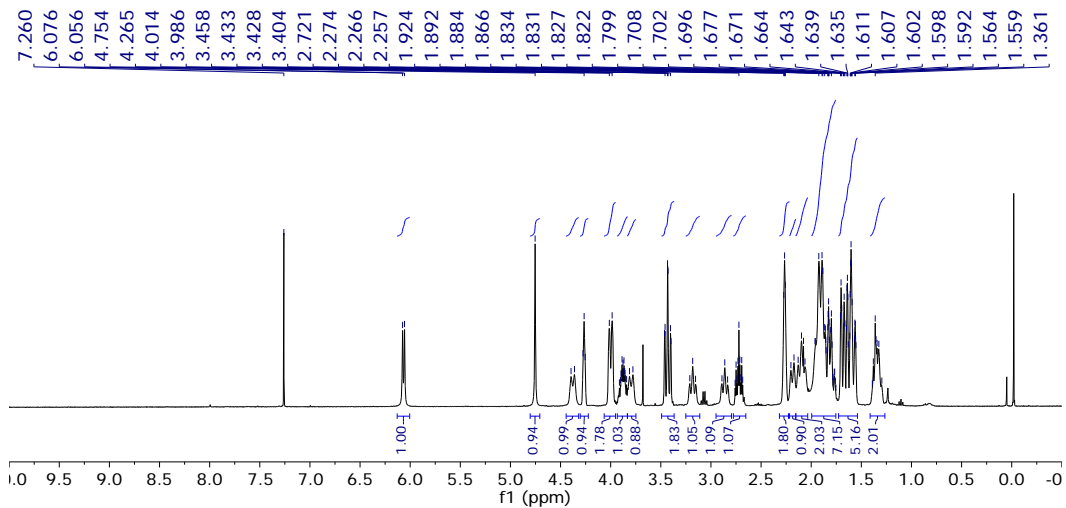


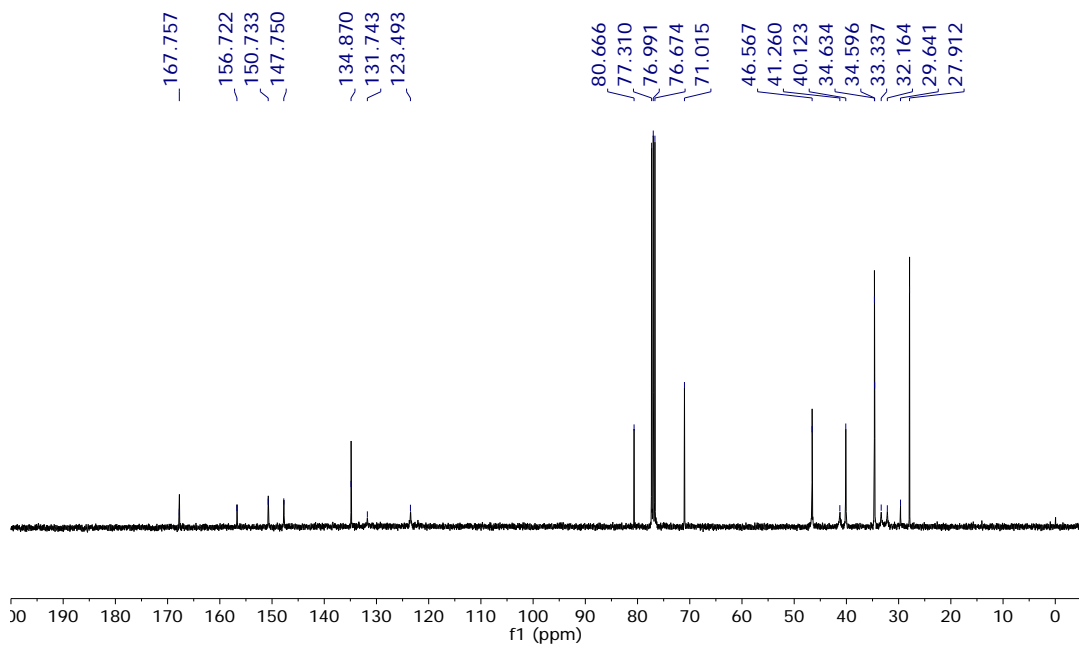
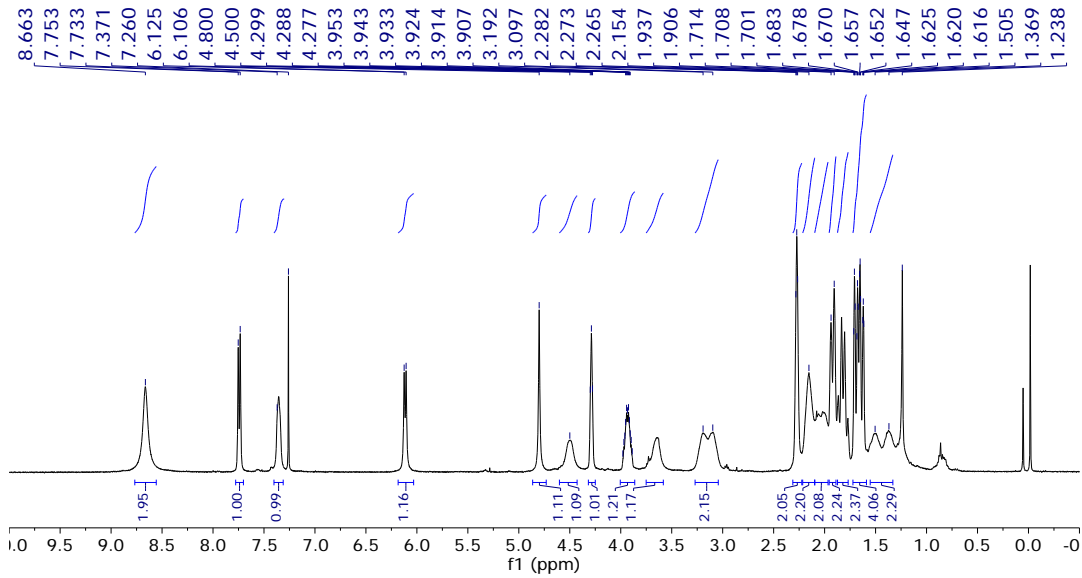
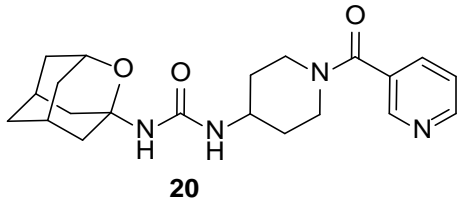


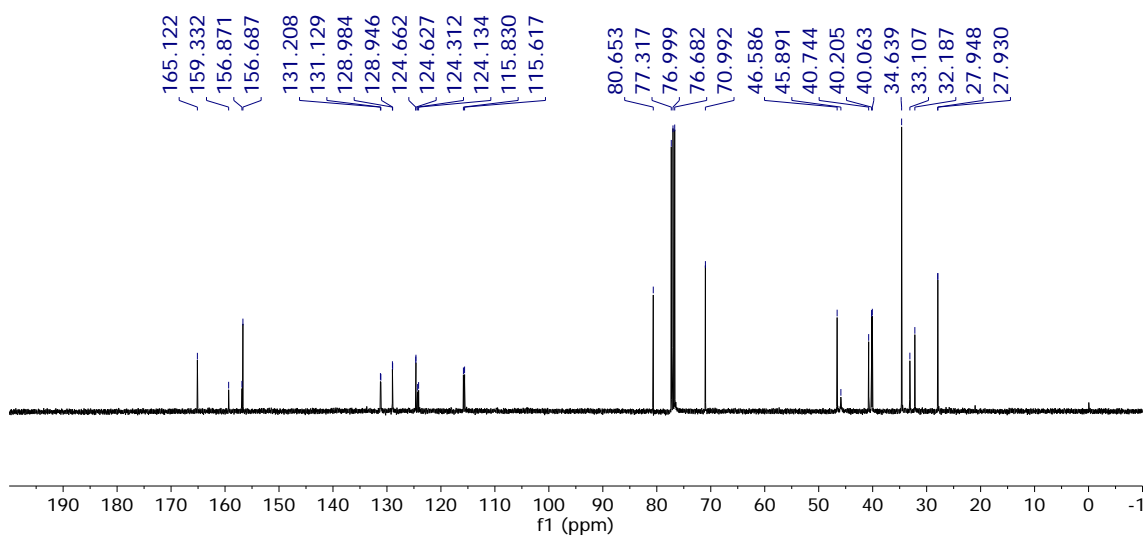
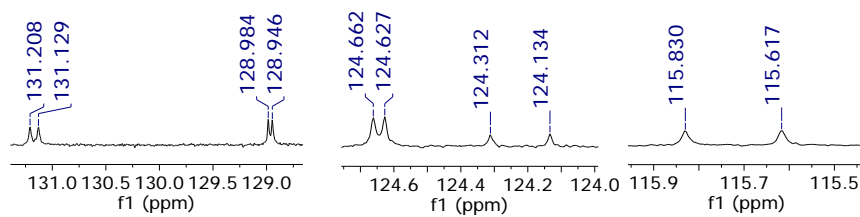
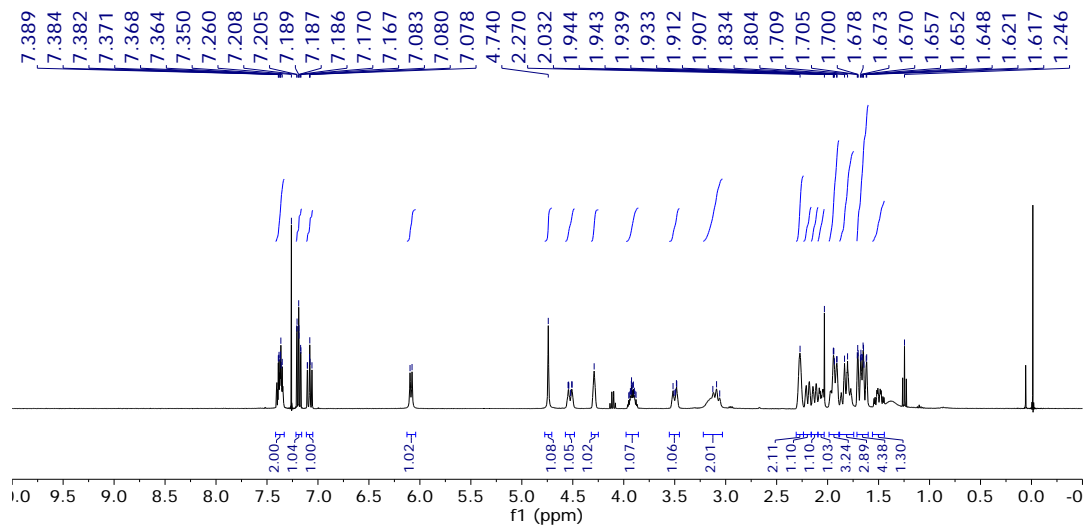
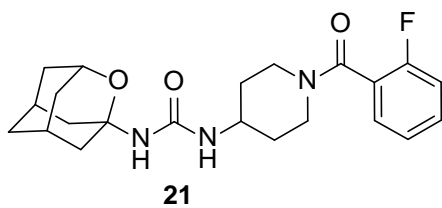


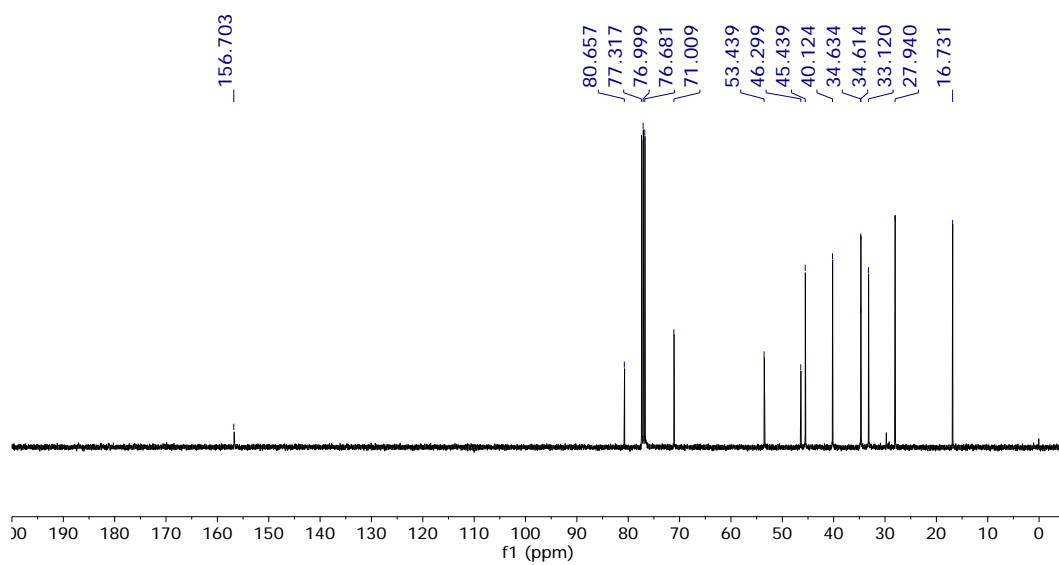
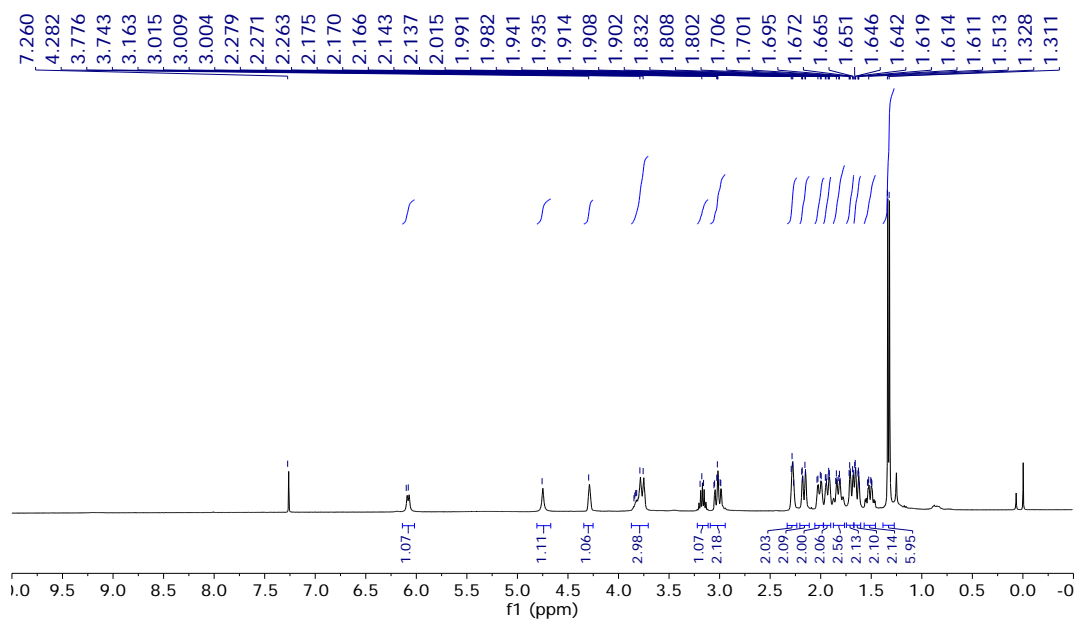
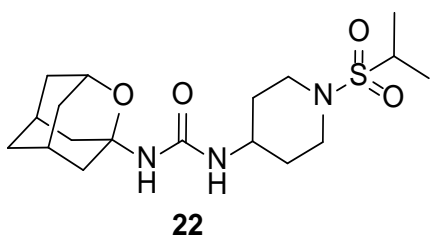


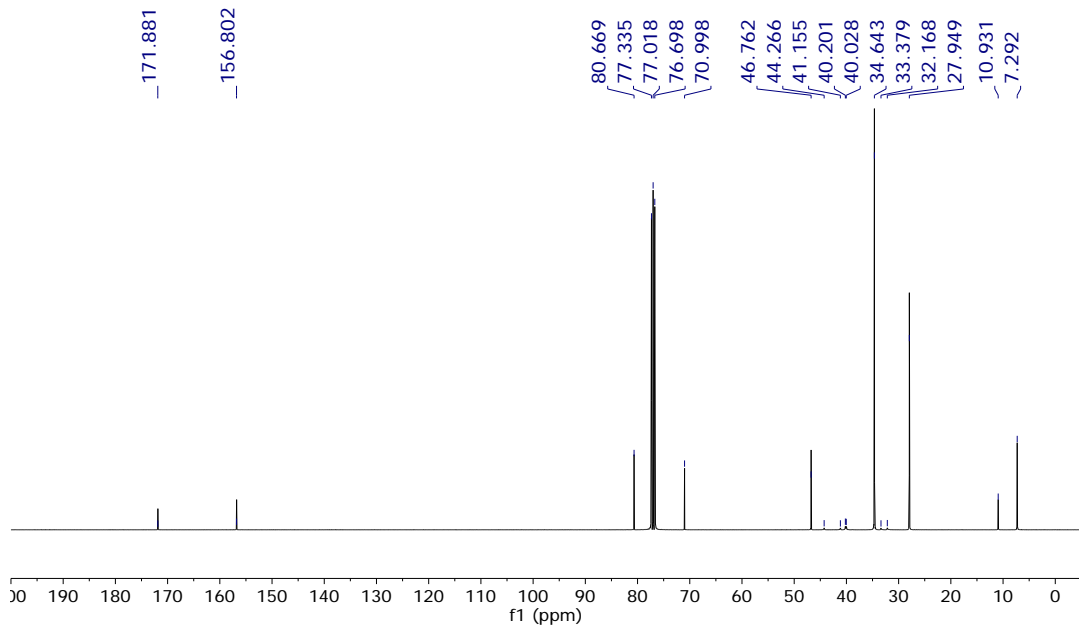
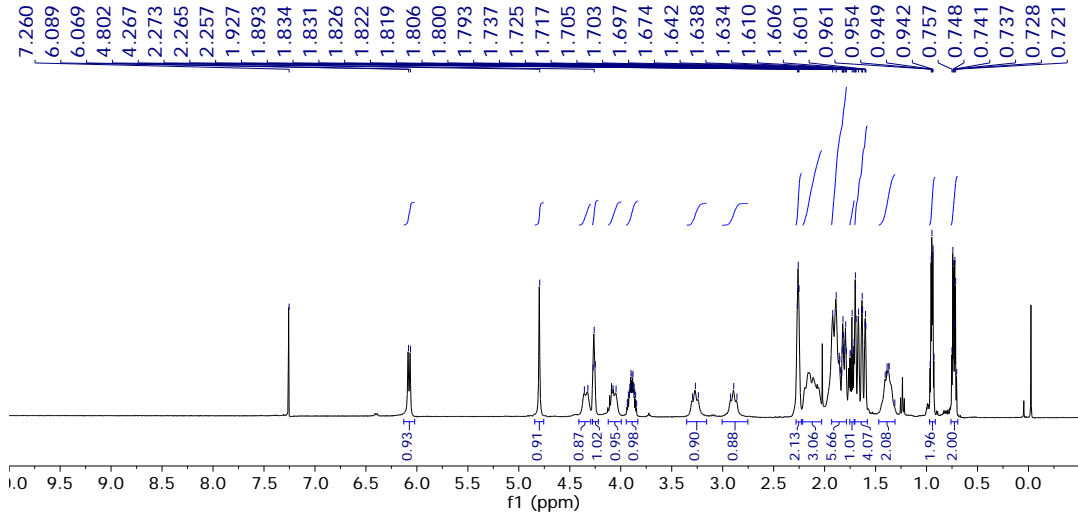
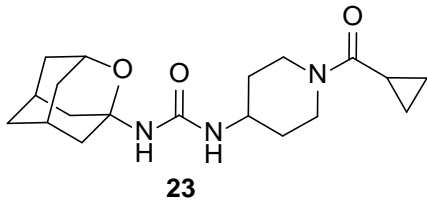
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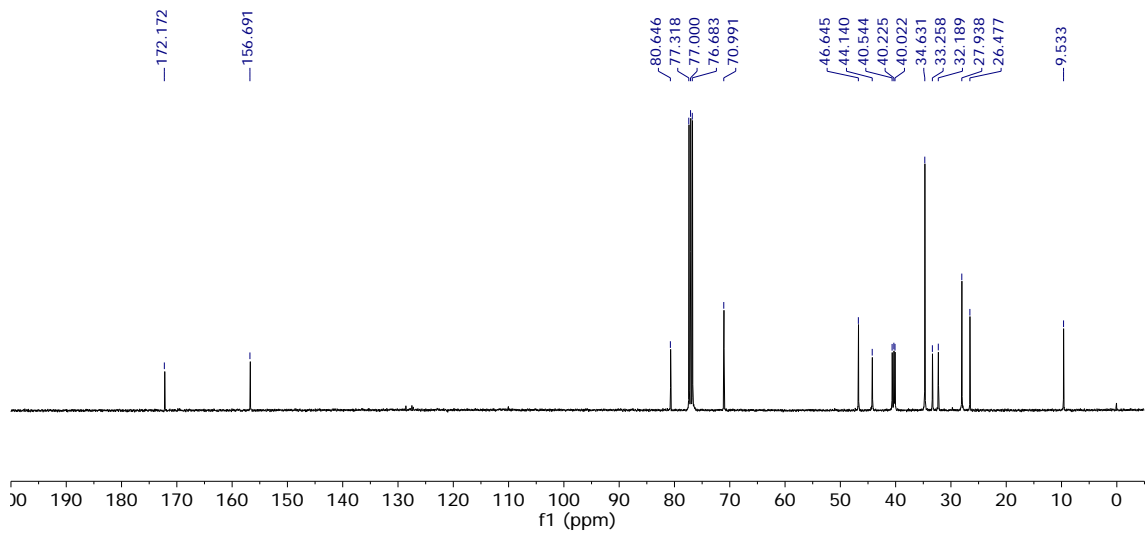
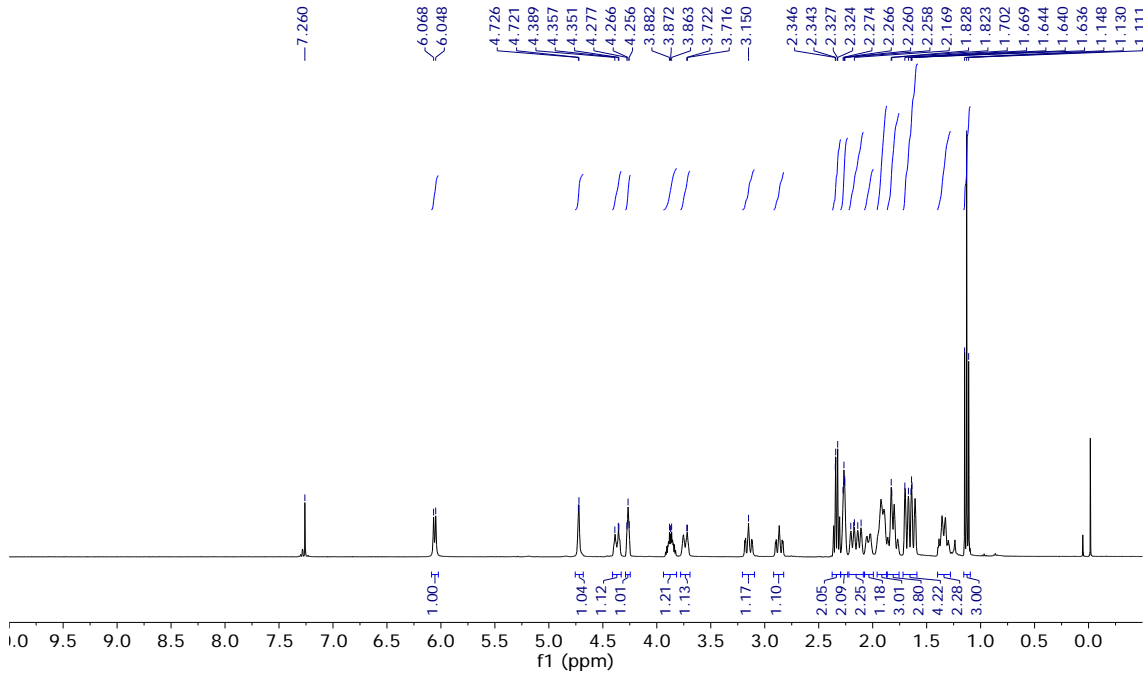
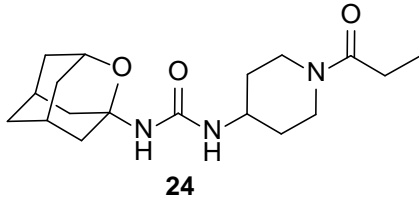


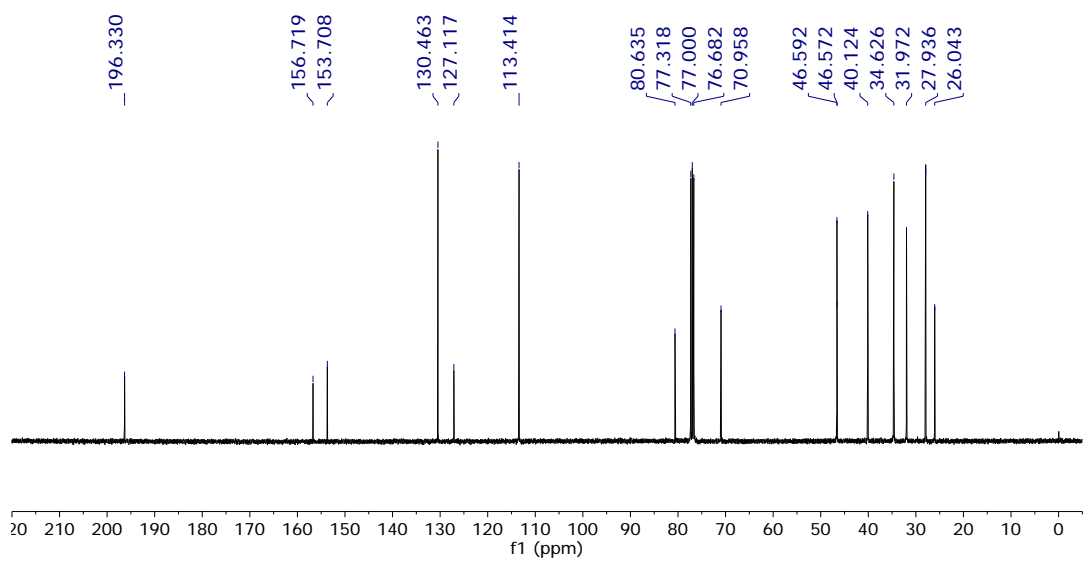
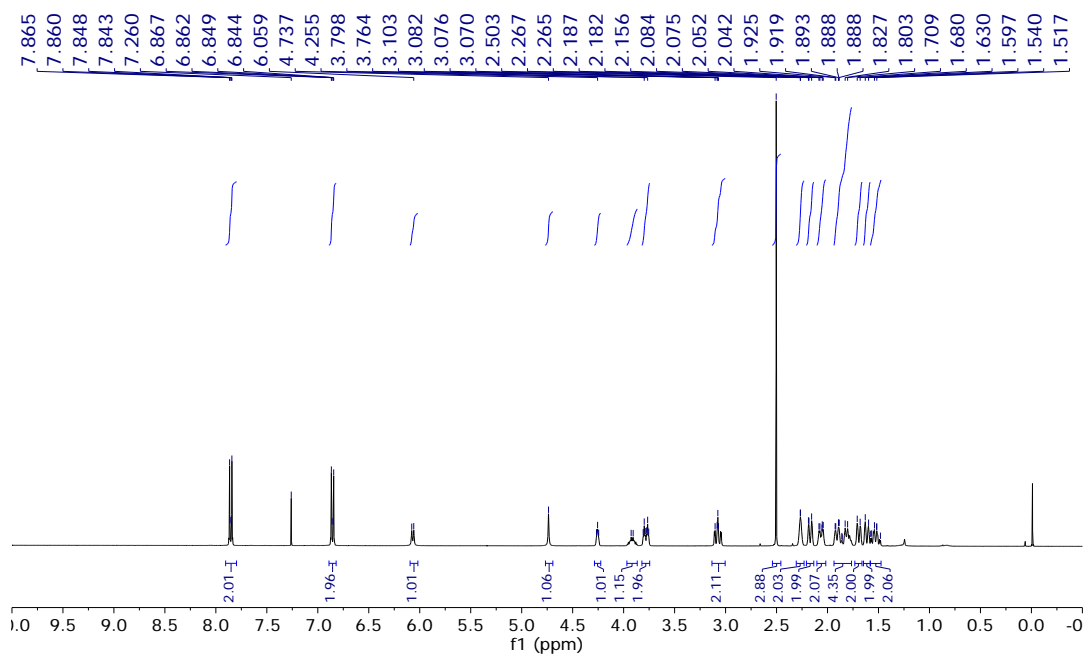
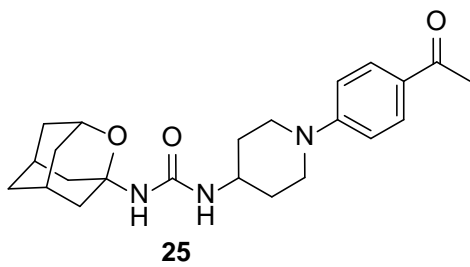


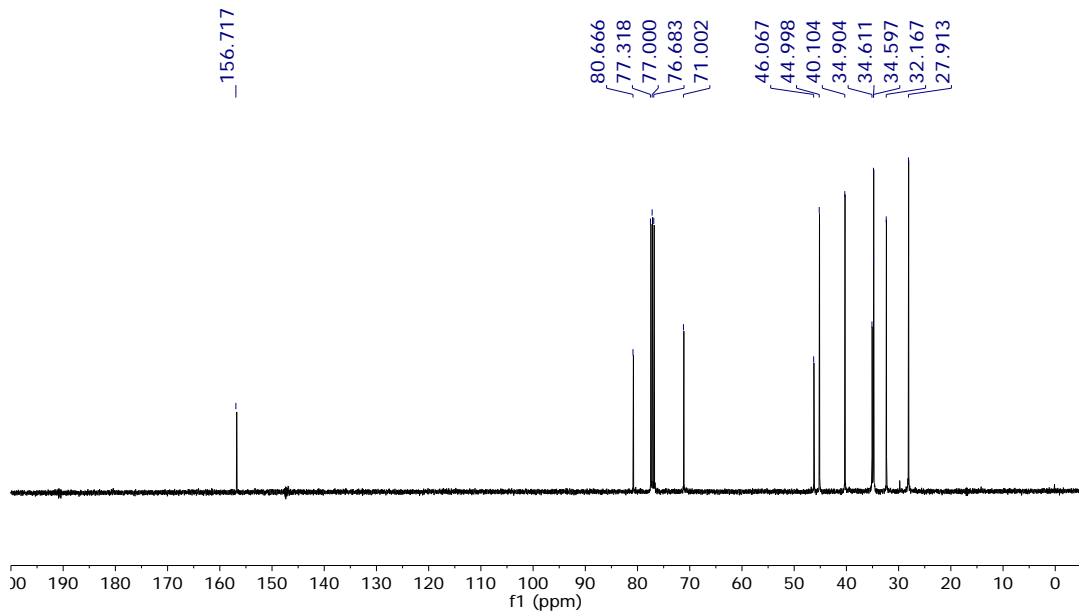
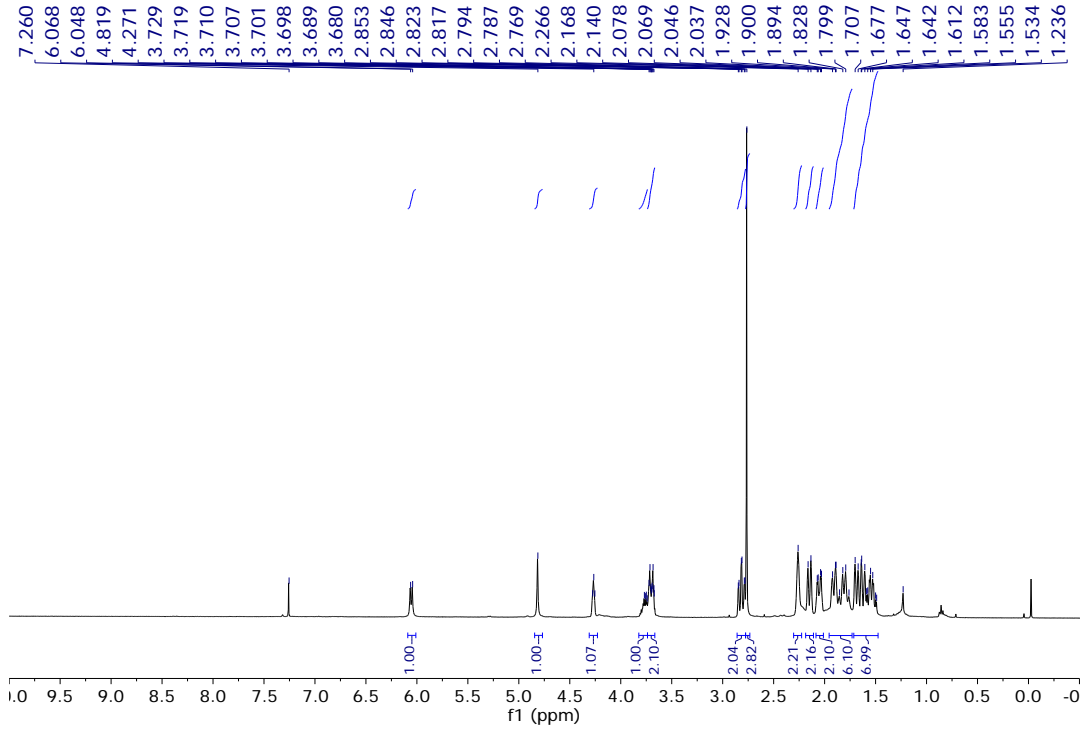
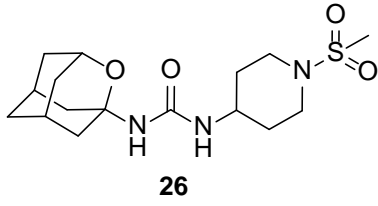


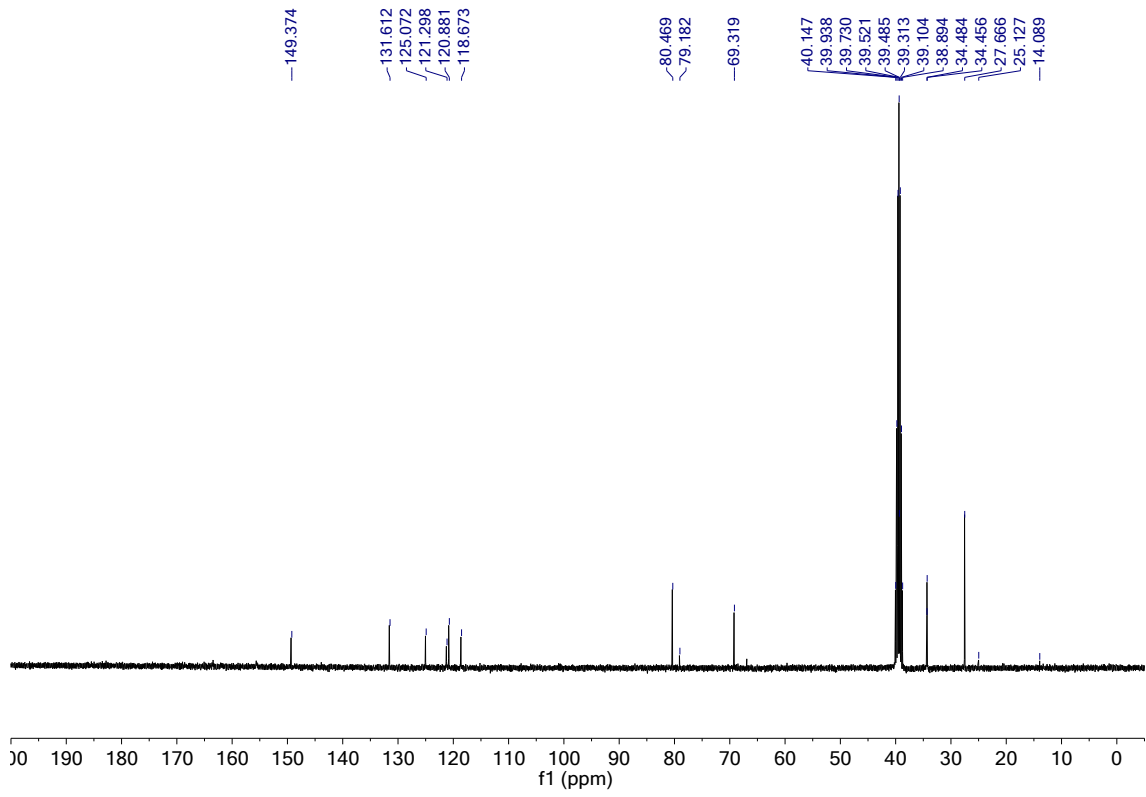
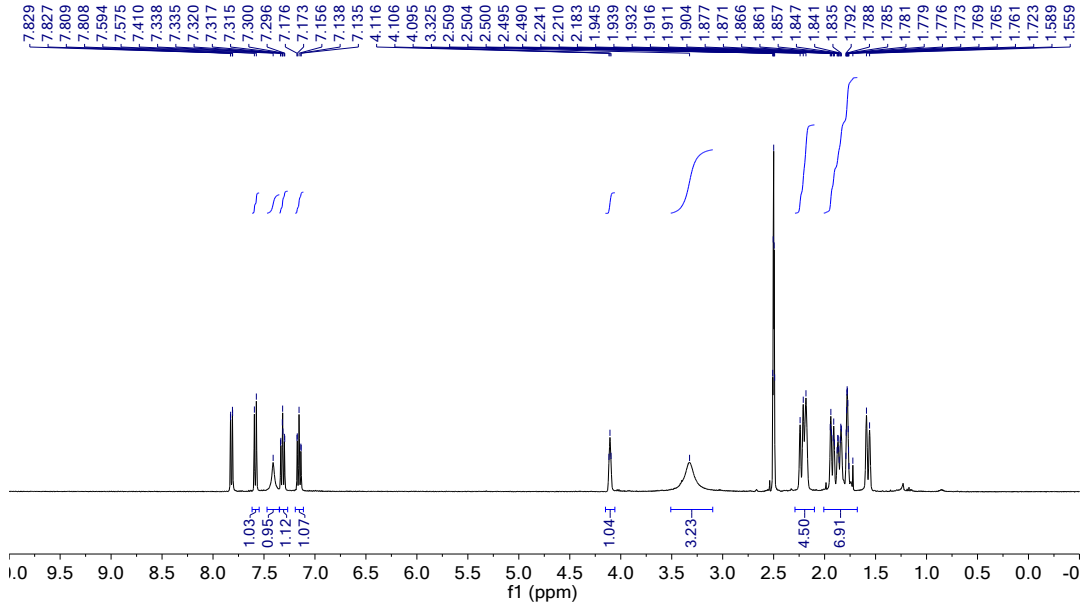
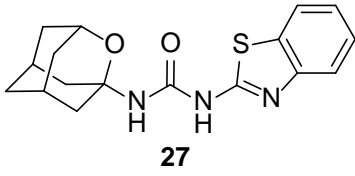


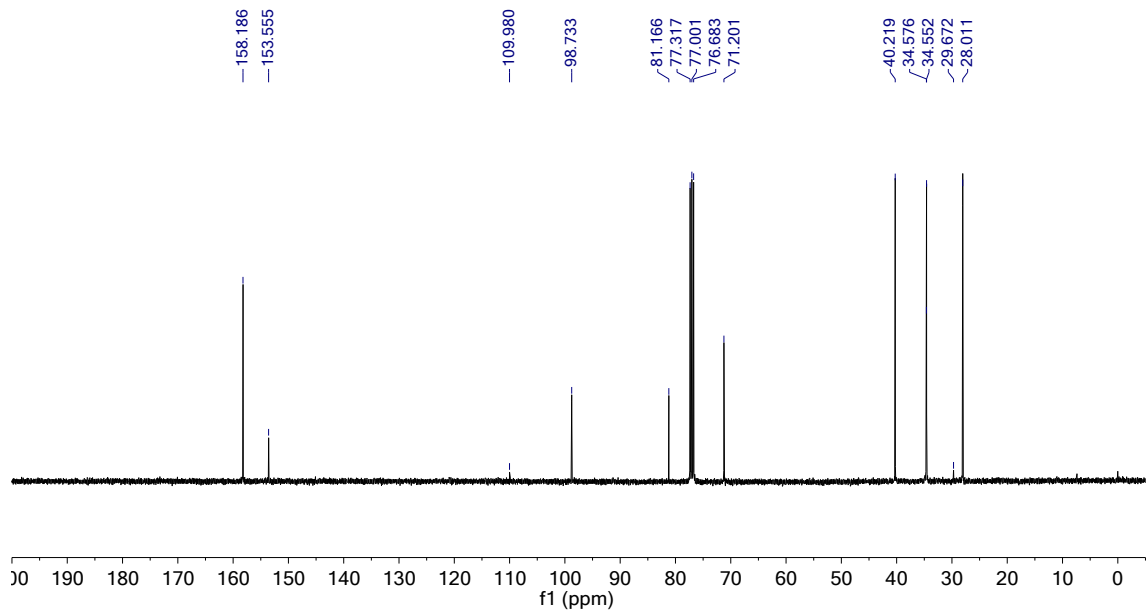
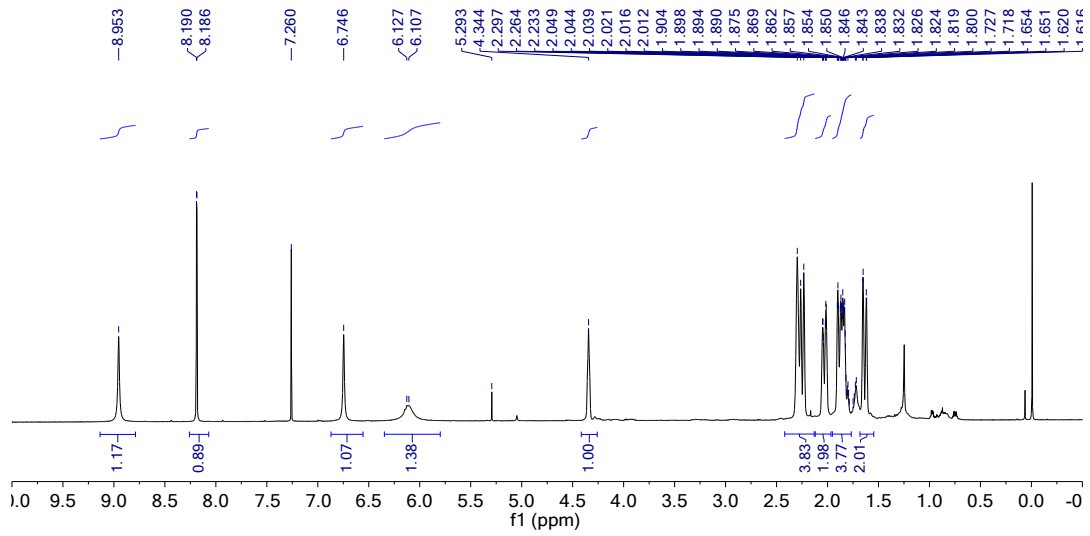
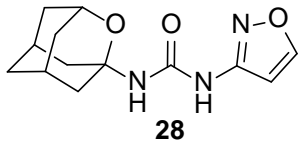


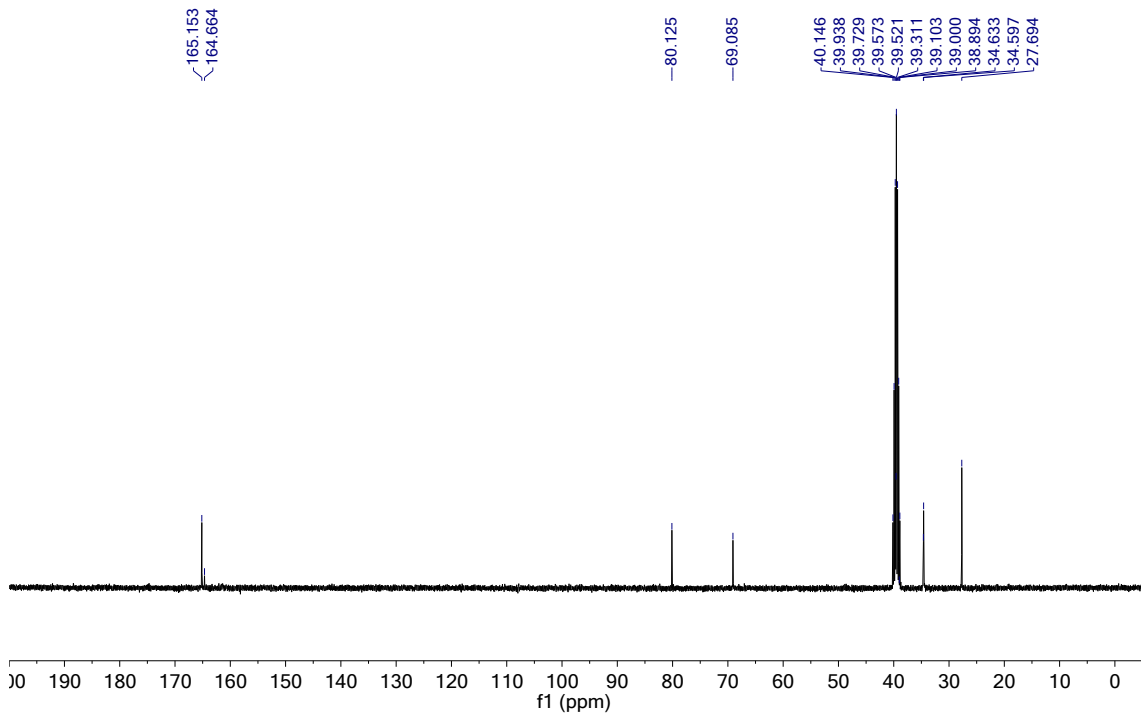
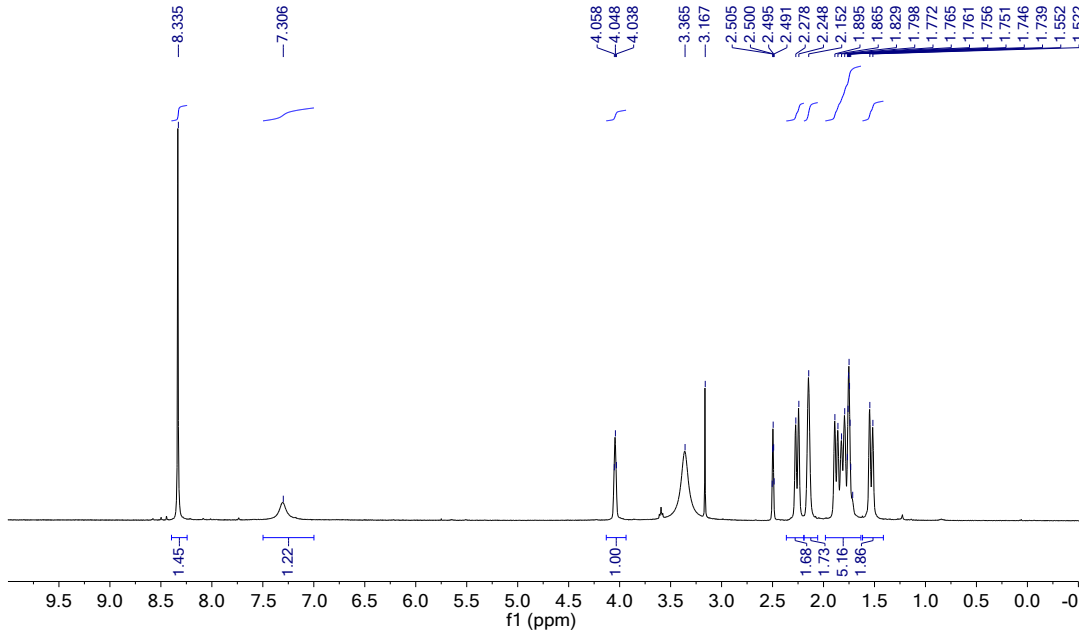
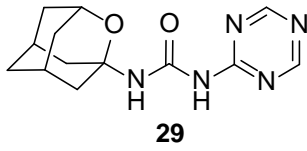


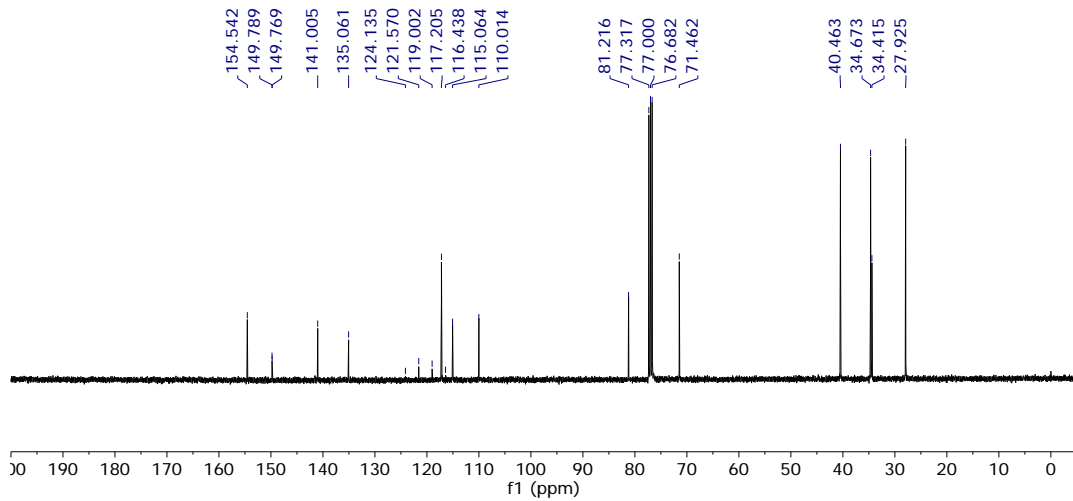
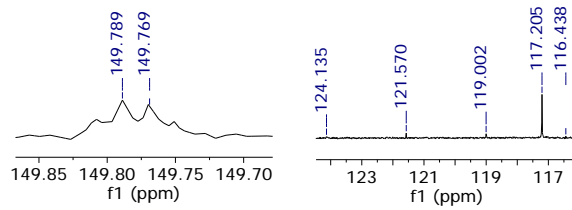
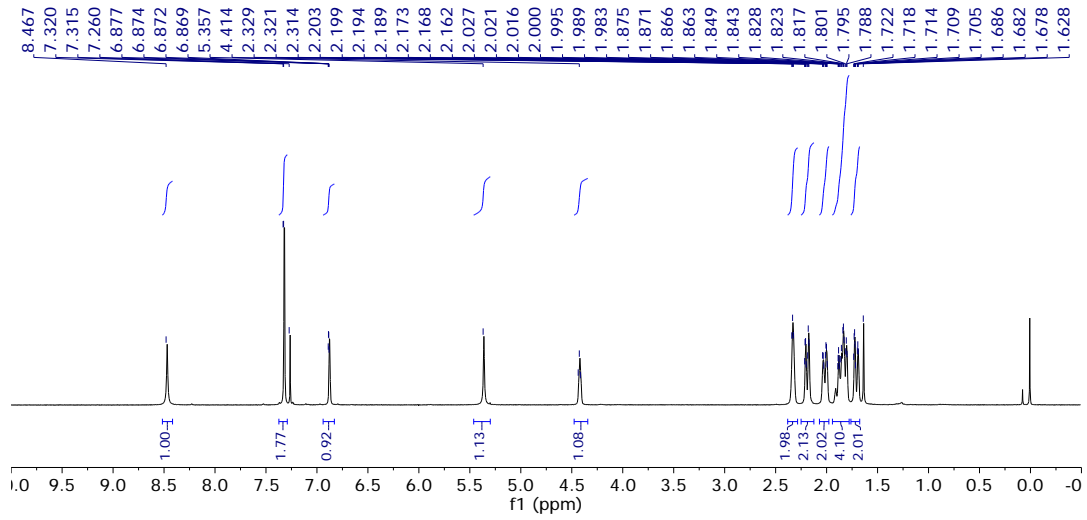
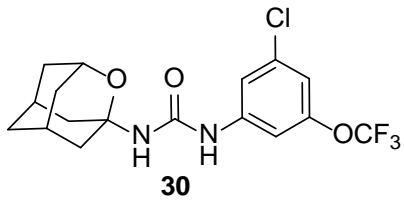


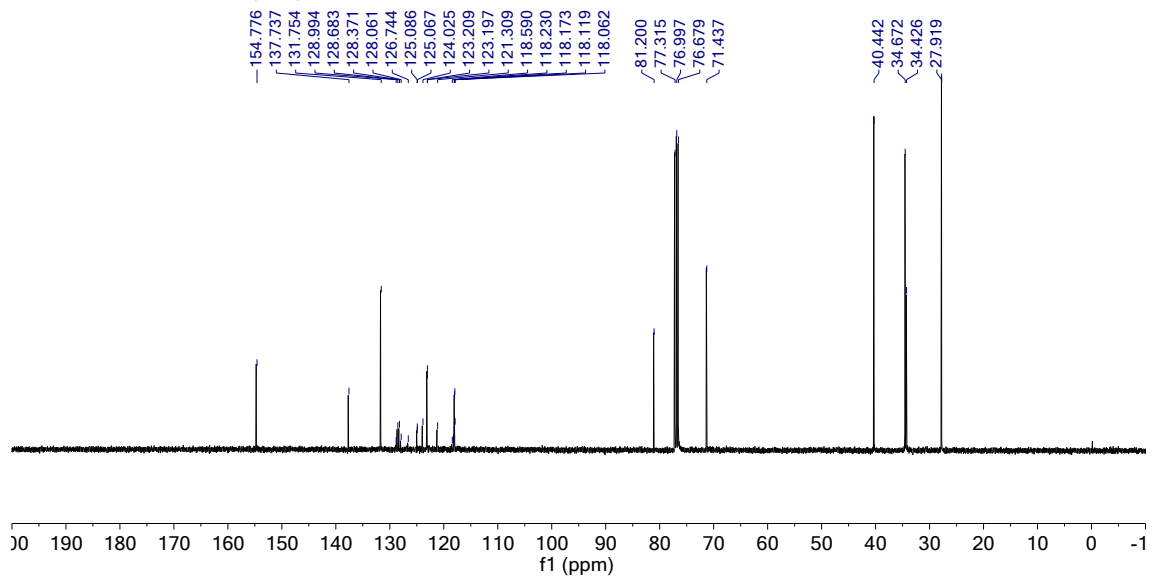
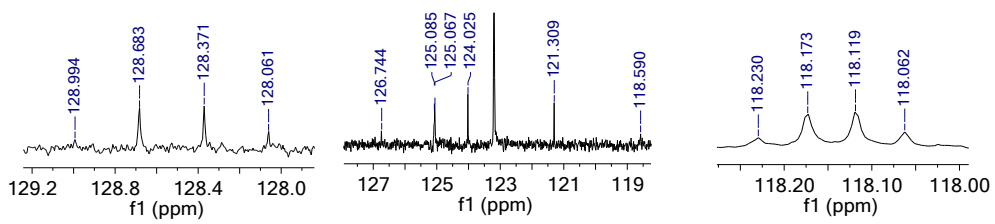
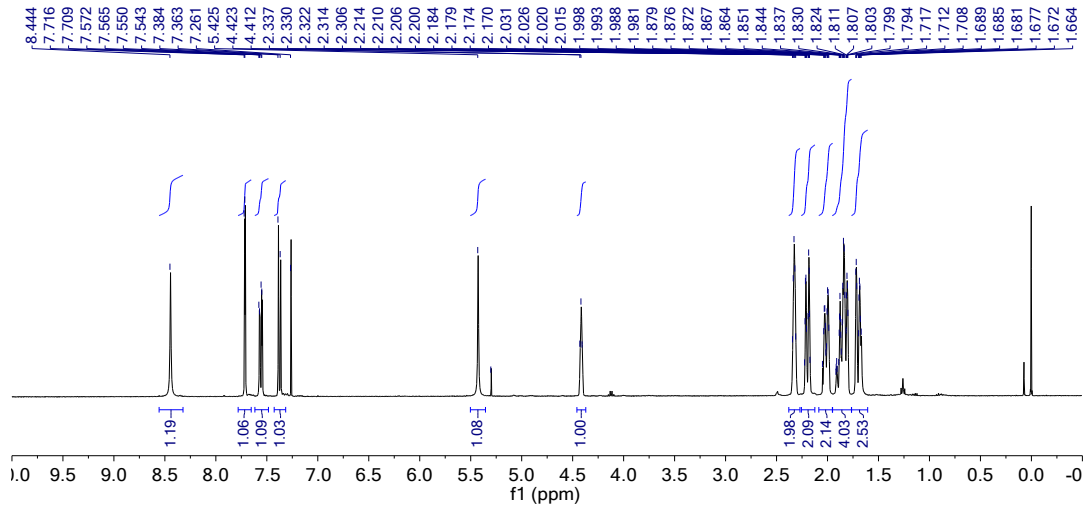
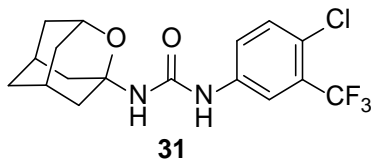


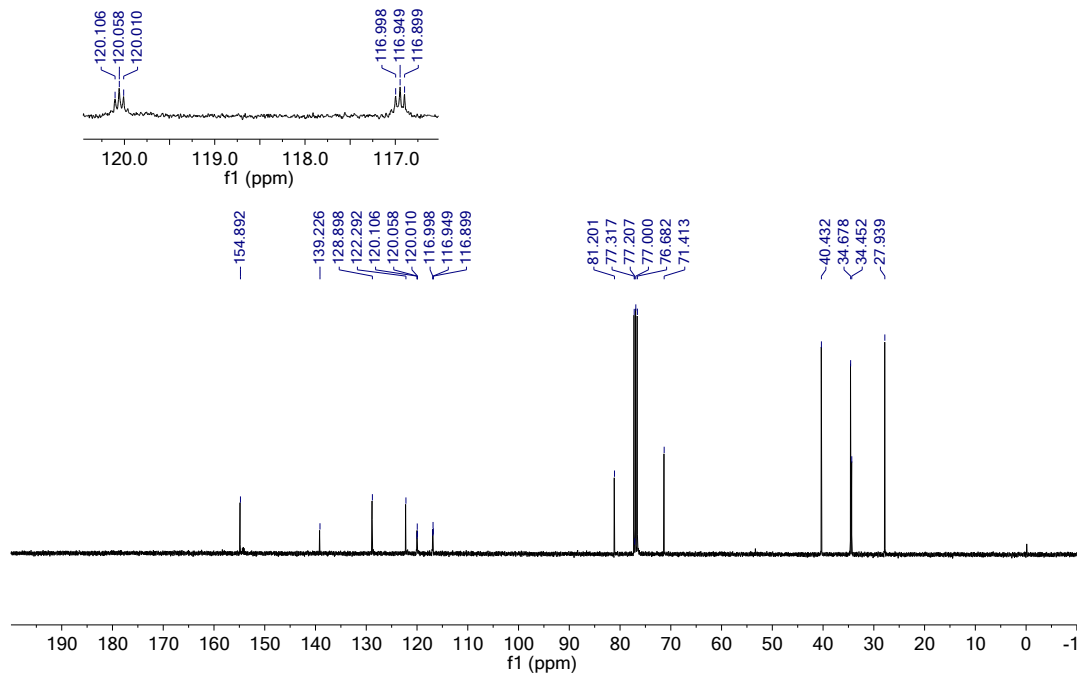
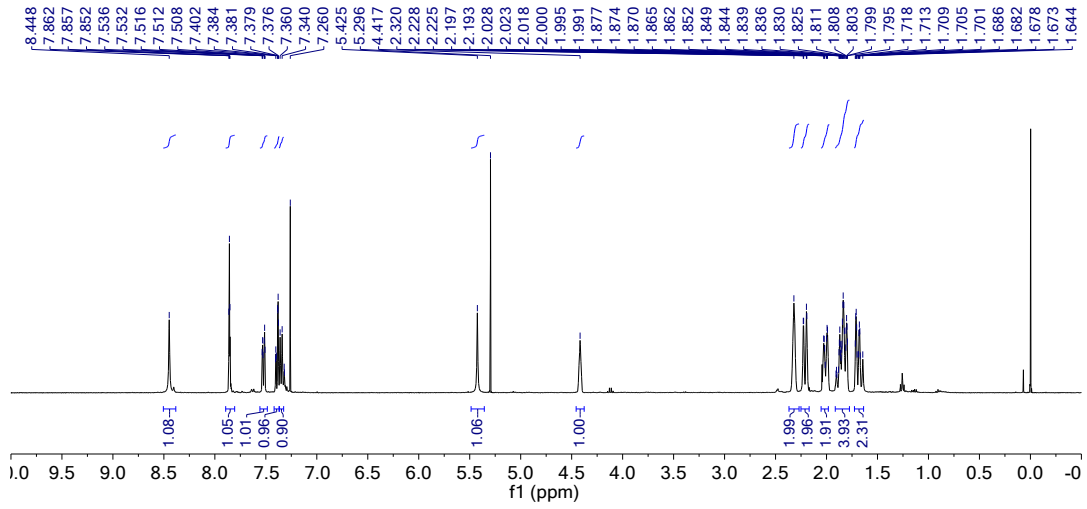
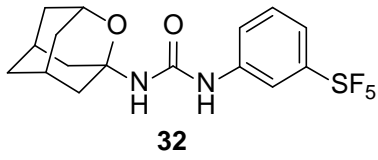




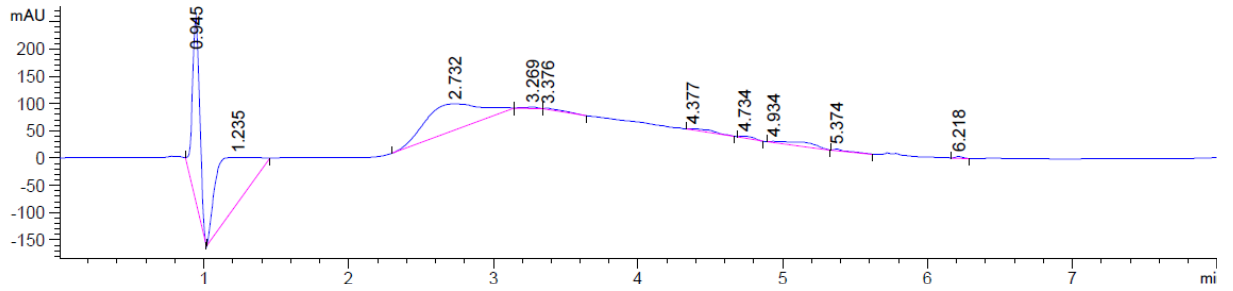




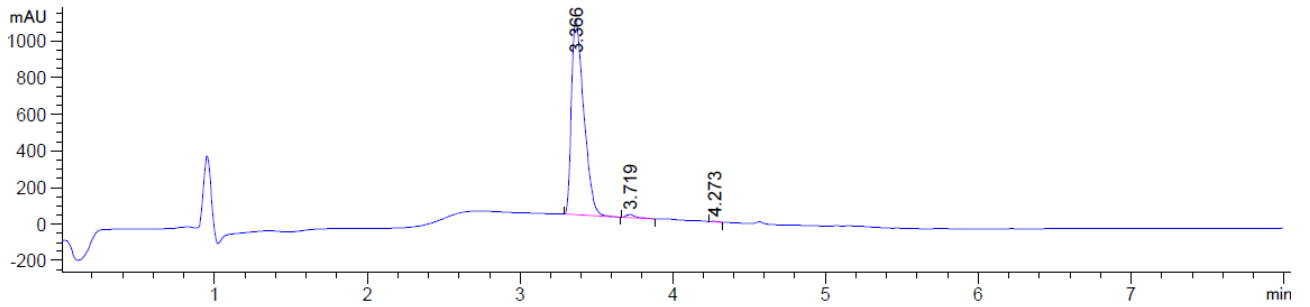




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Compound 15

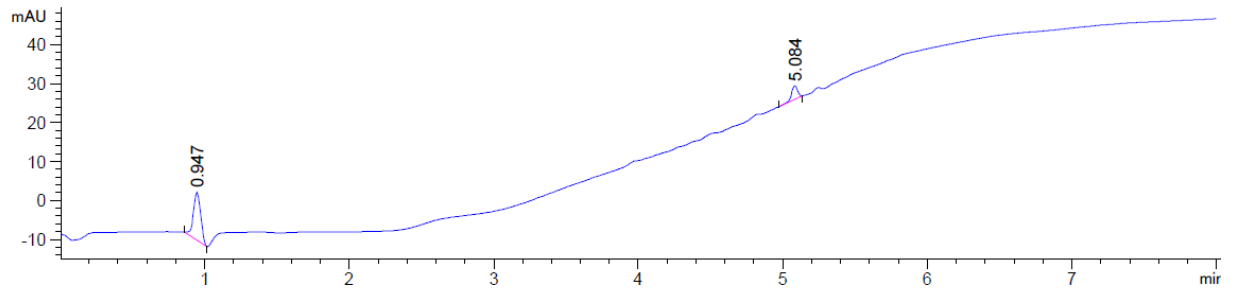


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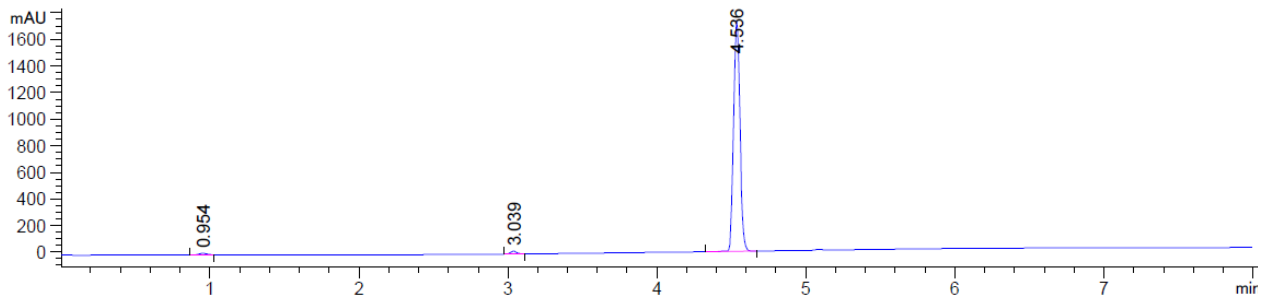
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2	3.719	BB	0.0618	71.82229	17.53464	1.1886
3	4.273	BB	0.0426	7.26377	2.76769	0.1202

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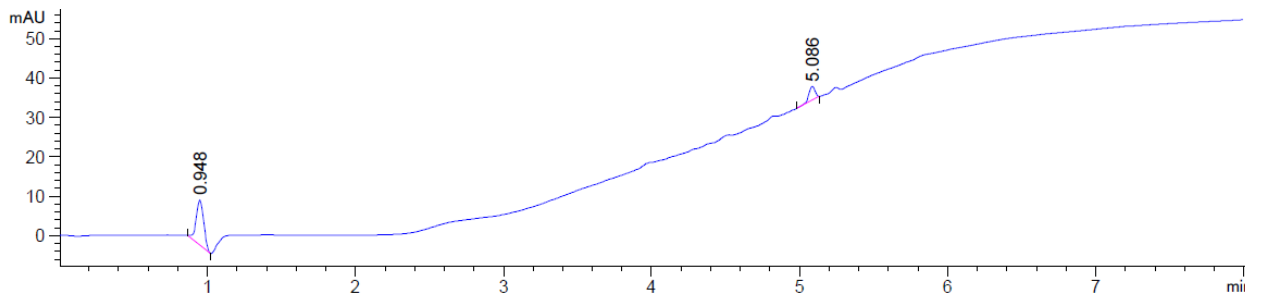


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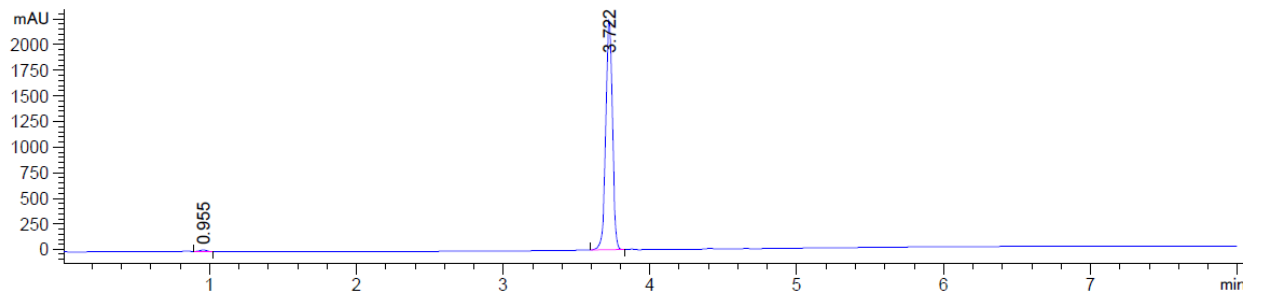
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2	3.039	BB	0.0472	61.01562	20.20074	1.1552
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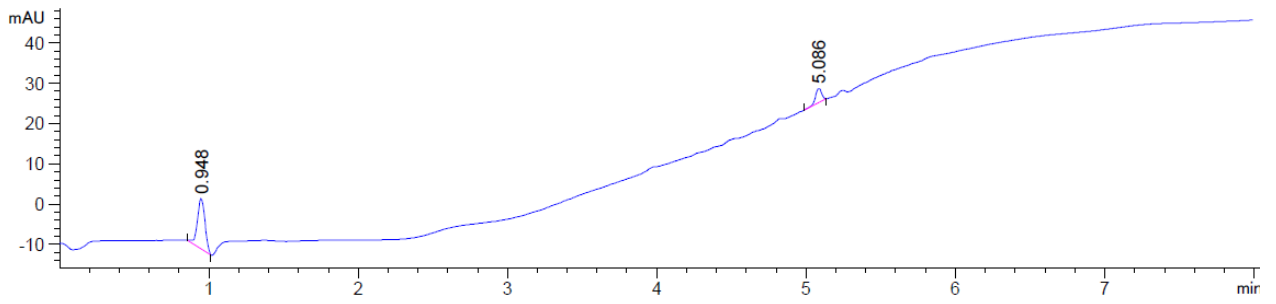


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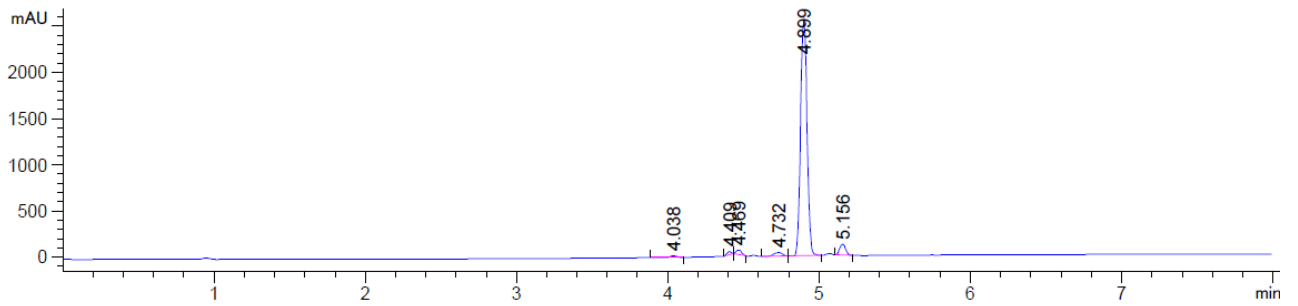
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2	3.722	BB	0.0488	7110.12598	2253.27002	99.2341

Totals : 7165.00344 2268.67728

Blank test



Compound 32



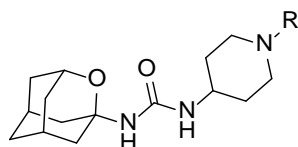
Signal 1: DAD1 A, Sig=245,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.038	BB	0.0495	54.91798	17.09327	0.6652
2	4.409	BB	0.0349	67.59186	31.65423	0.8187
3	4.469	BB	0.0404	115.69170	47.56844	1.4013
4	4.732	BB	0.0697	158.29762	38.69275	1.9173
5	4.899	BB	0.0465	7533.47803	2546.79443	91.2457
6	5.156	BB	0.0443	326.27591	117.92603	3.9519

Totals : 8256.25310 2799.72915

Compound	Molecular Formula	Calculated			Found		
		C	H	N	C	H	N
4	$C_{16}H_{17}F_3N_2O_2 \cdot 0.5H_2O$	57.31	5.41	8.35	57.46	5.70	8.22
7	$C_{16}H_{17}F_3N_2O_2$	58.89	5.25	8.58	59.00	5.60	8.57
9	$C_{18}H_{15}F_3N_2O_2$	62.07	4.34	8.04	62.04	4.43	7.98
12	$C_{17}H_{27}N_3O_3 \cdot 0.25H_2O$	62.65	8.50	12.89	62.64	8.61	12.74
14	$C_{23}H_{30}N_2O_5 \cdot 0.1H_2O$	66.36	7.31	6.73	66.13	7.32	6.64
17	$C_{19}H_{27}ClN_6O_2 \cdot 0.7C_3H_6O$	56.62	7.03	18.78	56.22	6.74	18.53
18	$C_{20}H_{31}N_7O_2 \cdot 0.2C_5H_{12} \cdot 1.1C_3H_6O$	60.83	8.40	20.43	61.01	8.15	20.30
19	$C_{21}H_{33}N_3O_4 \cdot 1H_2O$	61.59	8.61	10.26	62.20	8.55	10.38
20	$C_{21}H_{28}N_4O_3 \cdot 0.25C_6H_{14} \cdot 0.1 CH_2Cl_2$	65.49	7.71	13.52	65.42	7.61	13.54
21	$C_{22}H_{28}FN_3O_3$	65.82	7.03	10.47	65.88	7.25	10.36
22	$C_{18}H_{31}N_3O_4S \cdot 0.5H_2O$	54.80	8.18	10.65	55.03	7.93	10.46
23	$C_{19}H_{29}N_3O_3 \cdot 1H_2O$	62.44	8.55	11.50	62.81	8.54	11.07
24	$C_{18}H_{29}N_3O_3 \cdot 0.6C_4H_8O_2$	63.10	8.77	10.82	62.94	8.96	10.97
25	$C_{23}H_{31}N_3O_3 \cdot 0.25H_2O$	68.72	7.90	10.45	68.96	7.78	10.21
26	$C_{16}H_{27}N_3O_4S \cdot 0.2C_5H_{12} \cdot 0.15C_3H_6O$	55.07	8.02	11.04	55.48	7.57	10.60
28	$C_{13}H_{17}N_3O_3$	59.30	6.51	15.96	59.46	6.70	14.31
30	$C_{17}H_{18}ClF_3N_2O_3$	52.25	4.64	7.17	52.05	4.80	7.02
31	$C_{17}H_{18}ClF_3N_2O_2$	54.48	4.84	7.47	54.57	4.84	7.64

Table S1: Elemental analysis data.



Compound	R	Cytochrome inhibition ^[a]						hERG inhibition ^[c]
		CYP 1A2	CYP 2C9	CYP 2C19	CYP 2D6	CYP 3A4 ^[b]		
						(BFC)	(DBF)	
12		6 ± 2	2 ± 2	3 ± 3	3 ± 1	20 ± 4	17 ± 1	2 ± 2
22		1 ± 1	1 ± 1	1 ± 1	1 ± 1	37 ± 3	2 ± 2	2 ± 2

Table S2. Inhibition (expressed as % of inhibition) of recombinant human cytochrome P450 enzymes and of hERG channel by selected inhibitors. ^aThe cytochrome inhibition was tested at 10 μM for compound **12** and at 1 μM for compound **22**. ^bFor the study of CYP3A4, two different substrates were used: benzyloxytrifluoromethylcoumarin (BFC) and dibenzylfluorescein (DBF). ^cThe hERG inhibition was tested at 10 μM. All the values represent the mean ± SD of three measurements (n = 3).

Compound	IC ₅₀ <i>h</i> LOX-5	<i>h</i> COX-2 (10 μM)
21	> 100 μM	11.4 %
22	> 100 μM	3.8 %
24	> 100 μM	13.6 %

Table S3: IC₅₀ in human LOX-5 (*h*LOX-5) and inhibition (expressed as % of inhibition) of human COX-2 (*h*COX-2) at 10 μM for compounds **21**, **22** and **24**. Inhibition of *h*COX-2 was performed at Eurofins (catalogue reference 4186).

Time	ID	Total Concentration (ng/mL)	Mean (ng/mL)	SD (ng/mL)
0 h	Mouse 1	0	0	0
	Mouse 2	0		
	Mouse 3	0		
0.16 h	Mouse 1	140	117.33	32.58
	Mouse 2	132		
	Mouse 3	80		
0.5 h	Mouse 1	5.61	5.85	0.22
	Mouse 2	6.05		
	Mouse 3	5.9		
1 h	Mouse 1	1.41	2.71	2.12
	Mouse 2	5.16		
	Mouse 3	1.56		
2 h	Mouse 1	0.4	0.30	0.09
	Mouse 2	0.23		
	Mouse 3	0.27		
4 h	Mouse 1	0.13	0.14	0.01
	Mouse 2	0.15		
	Mouse 3	0.14		
6 h	Mouse 1	0.23	0.12	0.12
	Mouse 2	0		
	Mouse 3	0.13		
24 h	Mouse 1	0	0.00	0.00
	Mouse 2	0		
	Mouse 3	0		

Table S4: Mean of concentrations of **22** in mouse plasma at different times after ip administration at 1 mg/kg.

Time	ID	Total Concentration (ng/mL)	Mean (ng/mL)	SD (ng/mL)
0 h	Mouse 1	0	0	0
	Mouse 2	0		
	Mouse 3	0		
0.16 h	Mouse 1	94.22	108.39	12.43
	Mouse 2	113.52		
	Mouse 3	117.44		
0.5 h	Mouse 1	37.55	20.75	14.69
	Mouse 2	10.30		
	Mouse 3	14.40		
1 h	Mouse 1	2.67	4.66	3.30
	Mouse 2	8.47		
	Mouse 3	2.83		
2 h	Mouse 1	0.18	0.35	0.19
	Mouse 2	0.31		
	Mouse 3	0.56		
4 h	Mouse 1	0.13	0.14	0.02
	Mouse 2	0.14		
	Mouse 3	0.16		
6 h	Mouse 1	0.13	0.13	0.00
	Mouse 2	0.13		
	Mouse 3	0.13		
24 h	Mouse 1	0.00	0.00	0.00
	Mouse 2	0.00		
	Mouse 3	0.00		

Table S5: Mean of concentrations of **22** in mouse plasma at different times after iv administration at 1 mg/kg.

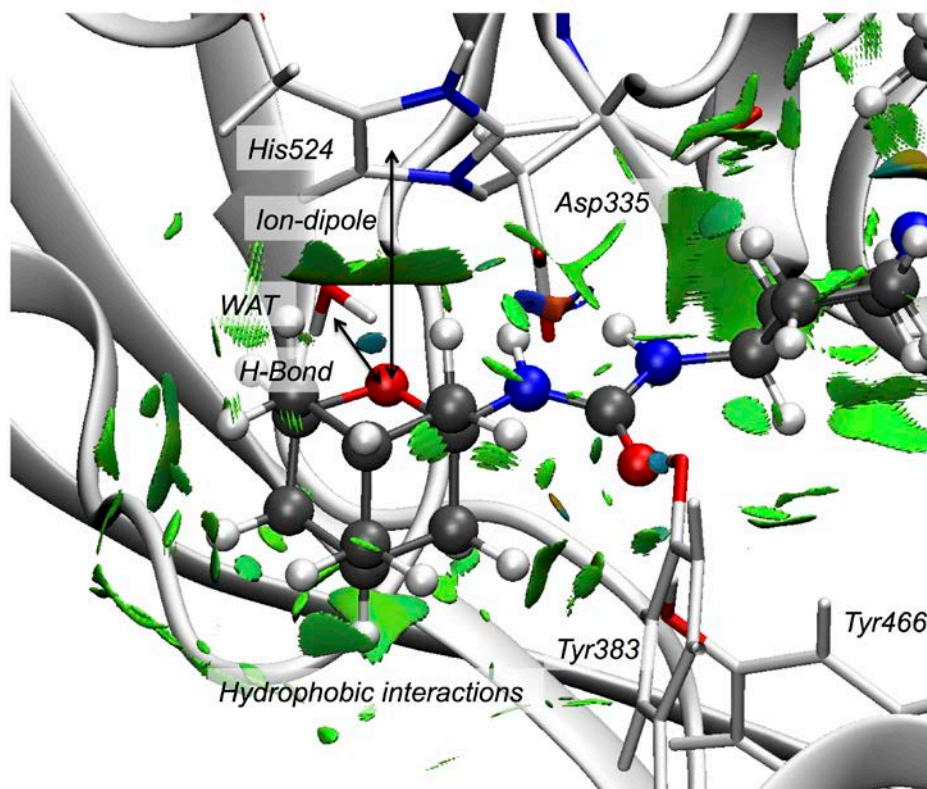


Figure S1. Representation of the noncovalent interactions (computed with NCIPLOT) at the active site of sEH in the presence of compound **22**. The weak interactions are shown as green surfaces, hydrogen-bonds are depicted in blue, and repulsive interactions in red. The interaction surfaces of the hydrogen-bond between the oxygen atom of compound **22** and the active site water molecule and the ion-dipole interaction between protonated His524 and the oxygen atom of compound **22** are highlighted. Additionally, several hydrophobic interactions between the adamantane group and residues Phe267, Tyr383, Leu408, Leu417, Met419, and Trp525 are observed.

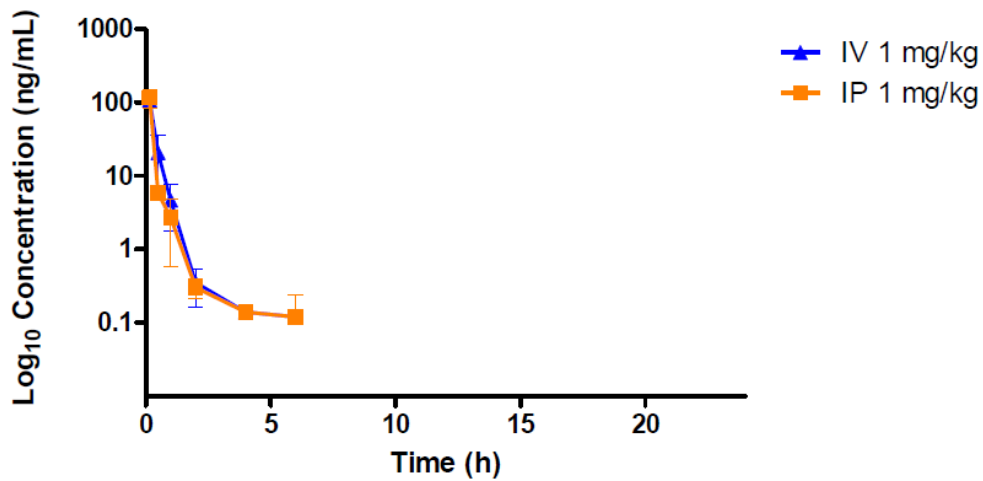


Figure S2: Concentration (scale log 10) vs time for ip and iv administration at 1 mg/kg of compound 22.

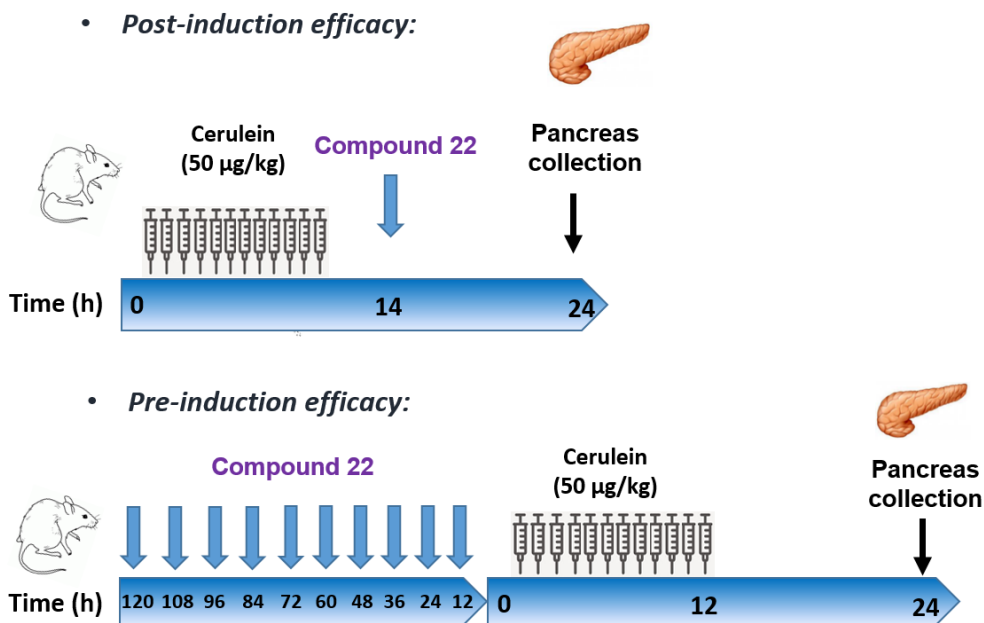


Figure S3: Experimental procedures of the two *in vivo* efficacy experiments of compound 22.