Supporting Information

A Modular, One-pot, Sequential Aziridine Ring Opening–S_NAr Strategy to 7-, 10- and 11-membered Benzofused Sultams

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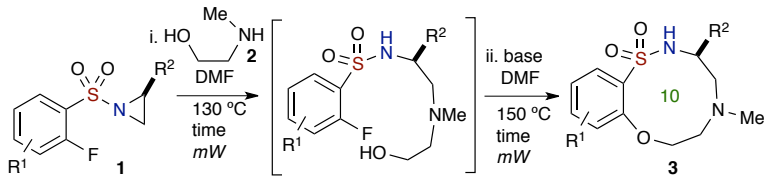
Table 1. *Optimization of reaction conditions*



entry[h]	R^1, R^2	conc (i to ii M)	time (i, ii mins)	base	yield (%)[a]
1	F, ^{i}Bu	1.0 to 0.3	20, 60	Cs_2CO_3	23[b]
2	F, ^{i}Bu	0.8 to 0.3	20, 60	Cs_2CO_3	43[b]
3	F, ^{i}Bu	0.5 to 0.3	20, 60	Cs_2CO_3	40[b]
4	F, ^{i}Bu	1.0 to 0.3	5 d[c], 60	Cs_2CO_3	23
5	F, ^{i}Pr	0.8 to 0.3	20, 60	CsF	3[d]
6	F, ^{i}Pr	0.8 to 0.3	20, 60	K_2CO_3	18[e]
7	F, ^{i}Pr	0.8 to 0.3	20, 60	K_3PO_4	11[d]
8	F, ^{i}Pr	0.8 to 0.3	20, 60	DBU	4[f]
9	F, ^{i}Pr	0.8 to 0.3	20, 60	NaH	11[g]

[a]Final isolated yield over 2 reactions after flash chromatography. [b]**Aziridine-opening**: **1** (1.0 equiv) and **2** (1.05–1.3 equiv) in DMF at 130 ºC. **S_NAr**: Cs_2CO_3 (2.5 equiv) in DMF at 150 ºC. [c]Aziridine-opening: reaction stirred at rt for 5 days. [d]CsF or K_3PO_4 (2.0 equiv). [e]K_2CO_3 (3.0 equiv). [f]DBU (0.3 equiv). [g]NaH (2.2 equiv). [h]Reactions were monitored by TLC.

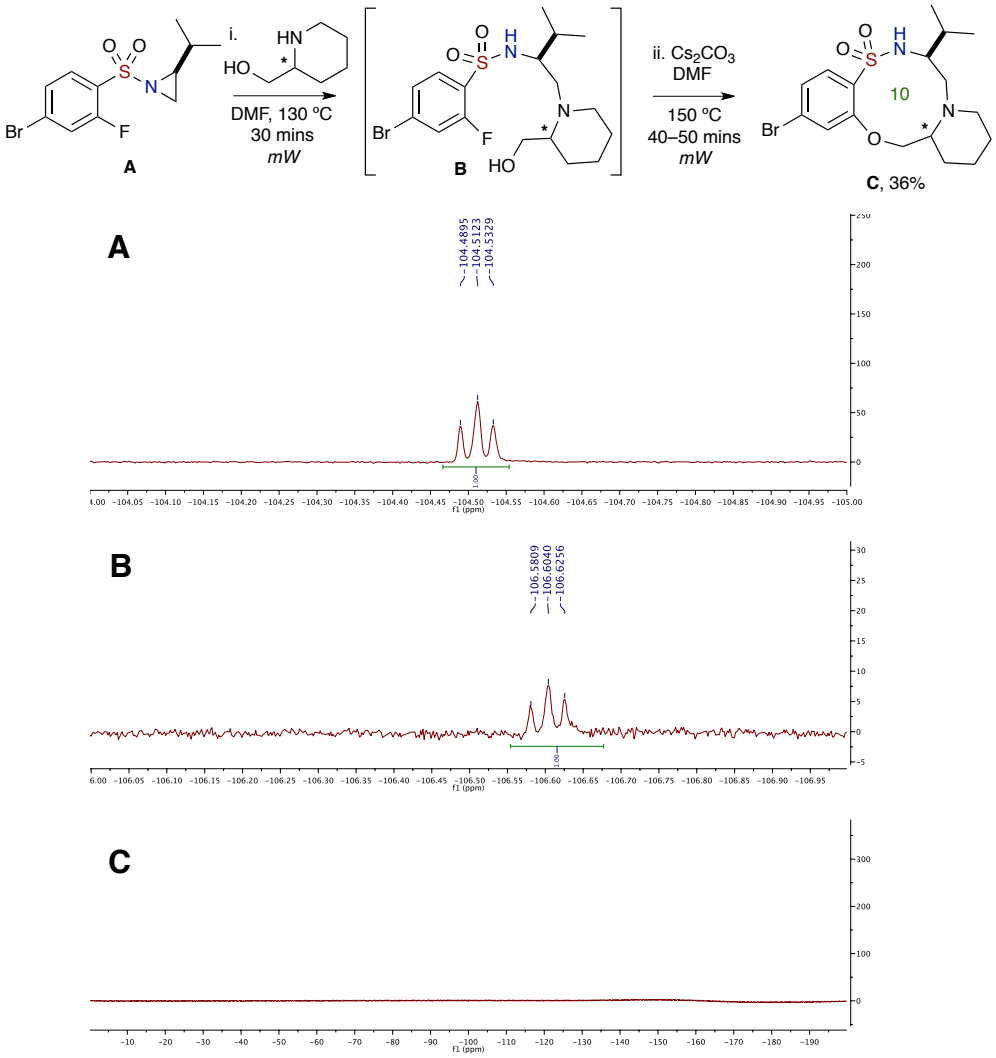
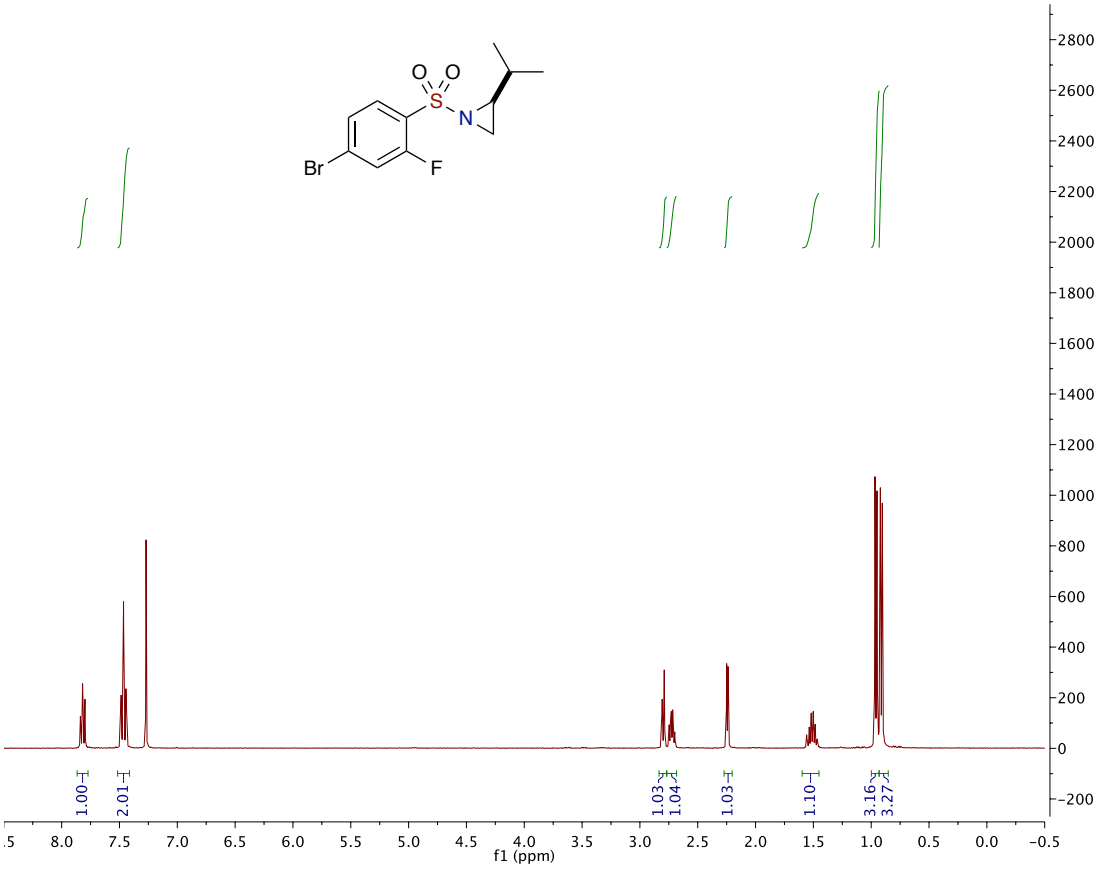
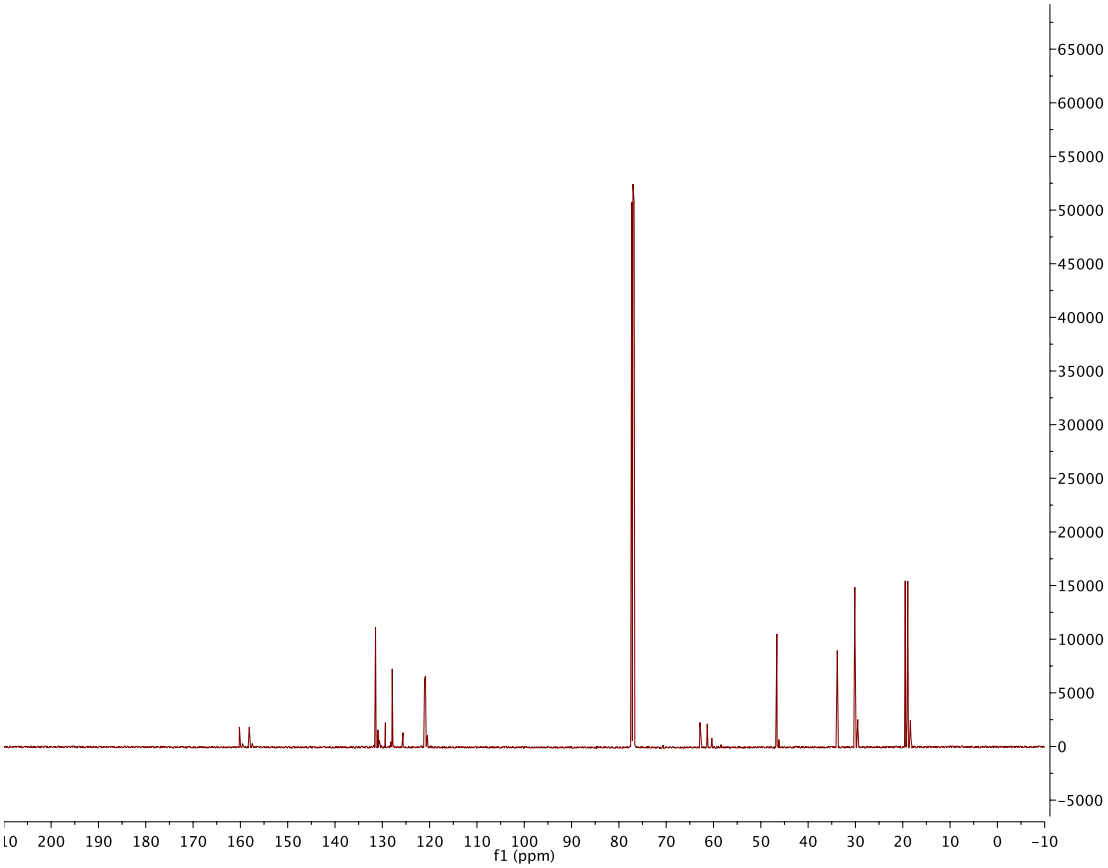


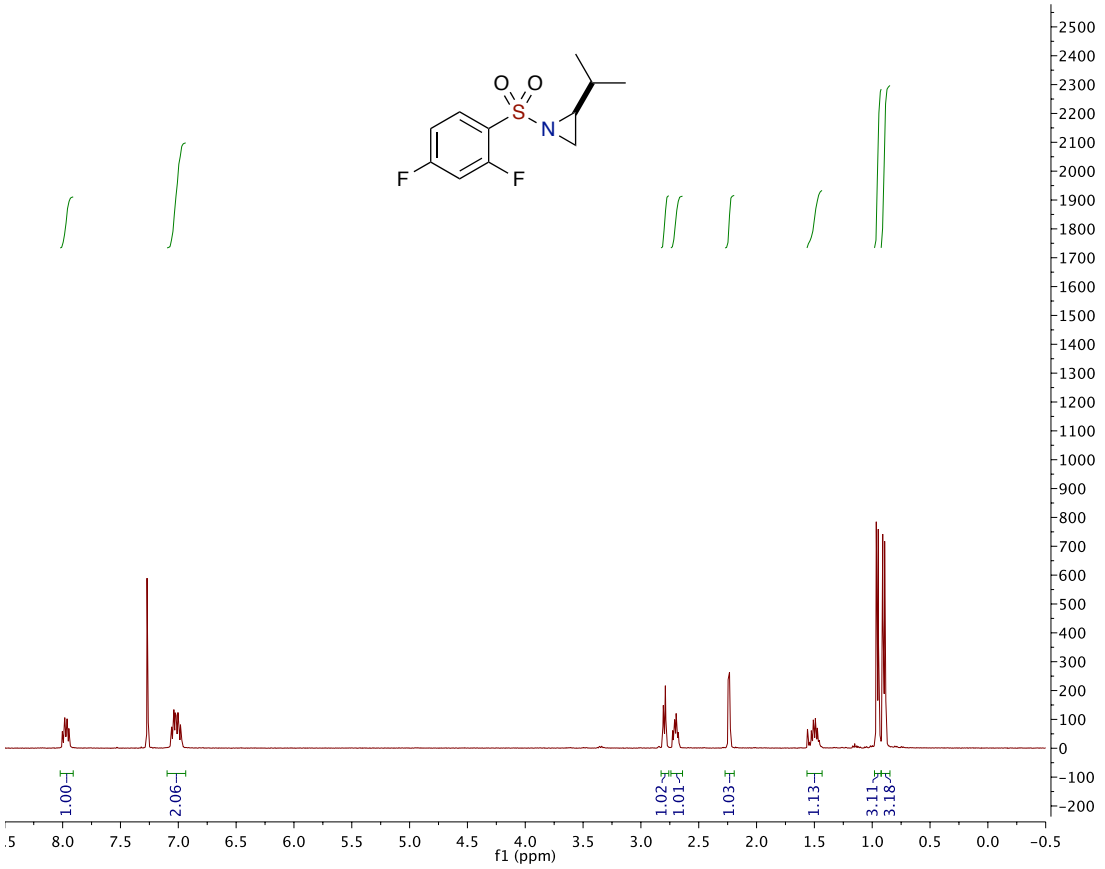
Figure 1. *^{19}F NMR studies: comparison between sulfonamide **A**, ring opened **B** and product **C**.*

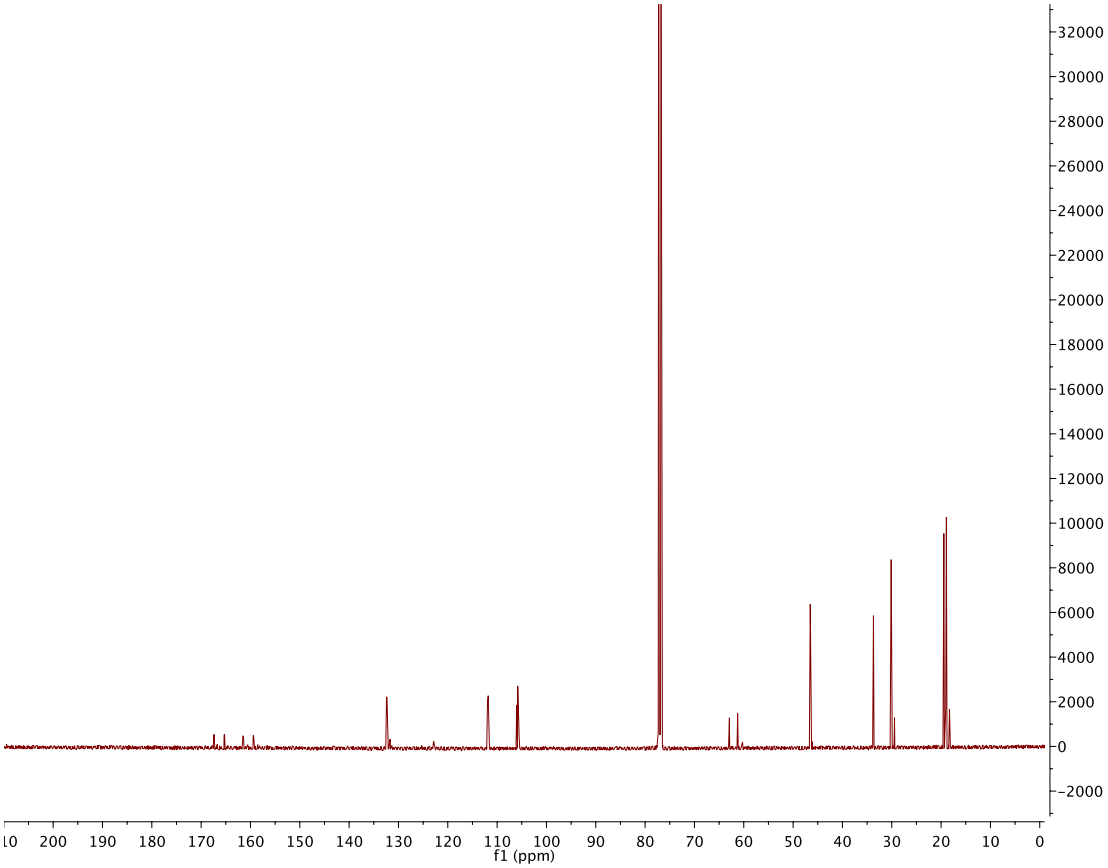
(*S*)-1-((4-bromo-2-fluorophenyl)sulfonyl)-2-isopropylaziridine (4b)



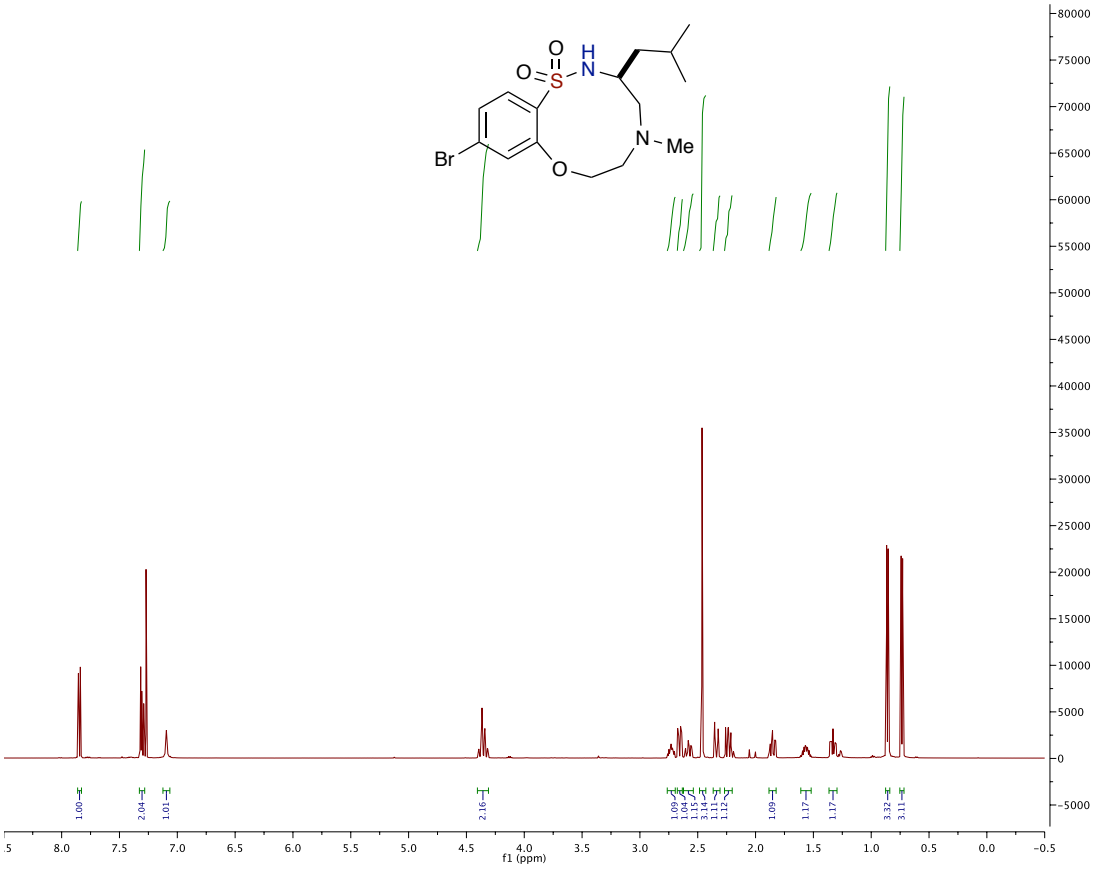


(*S*)-1-((2,4-difluorophenyl)sulfonyl)-2-isopropylaziridine (4d)





(*S*)-10-bromo-3-isobutyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathiadiazecine 1,1-dioxide (6a)



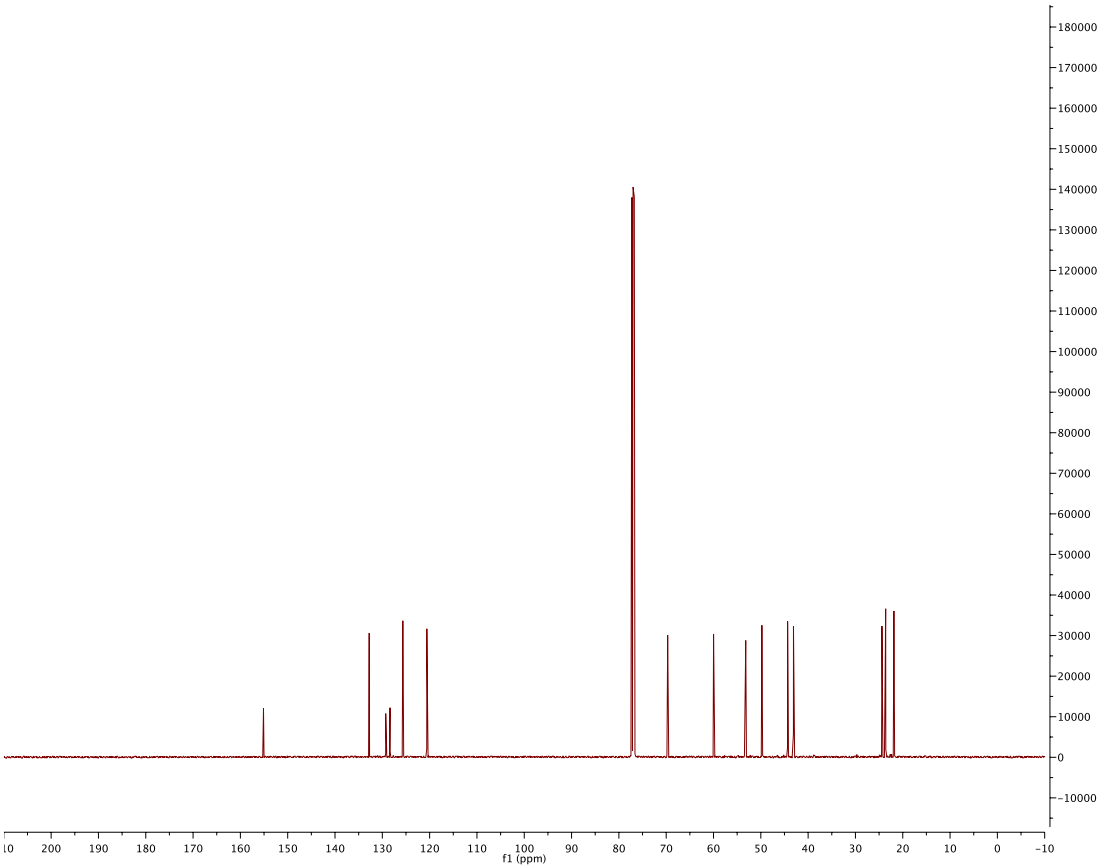
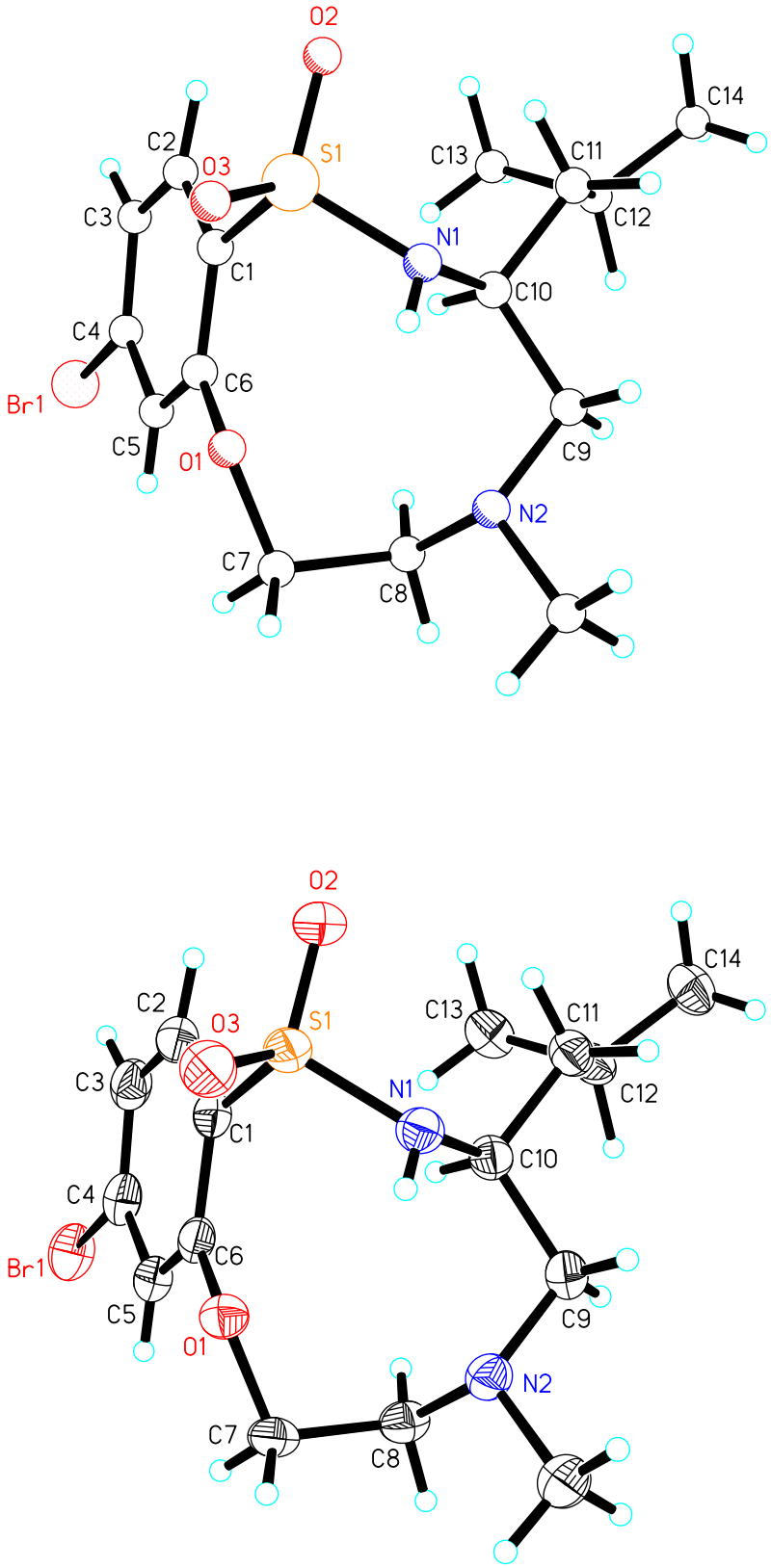
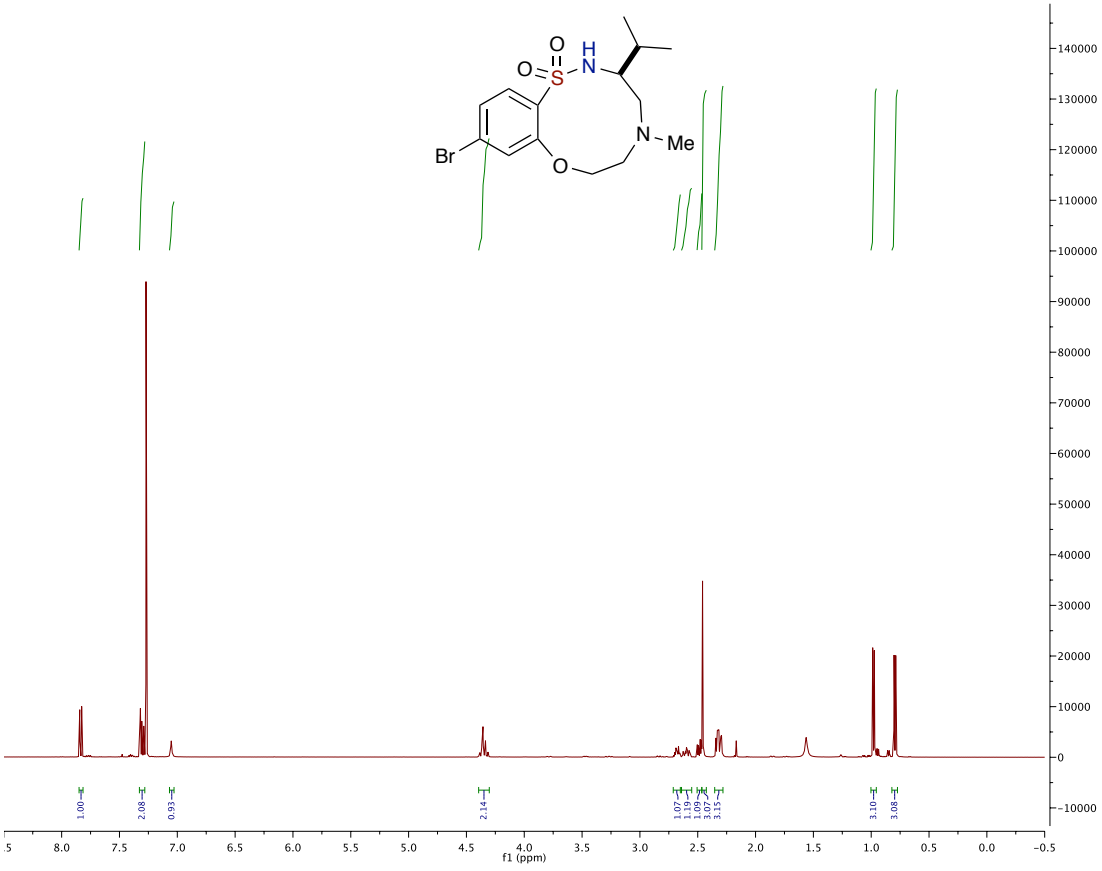
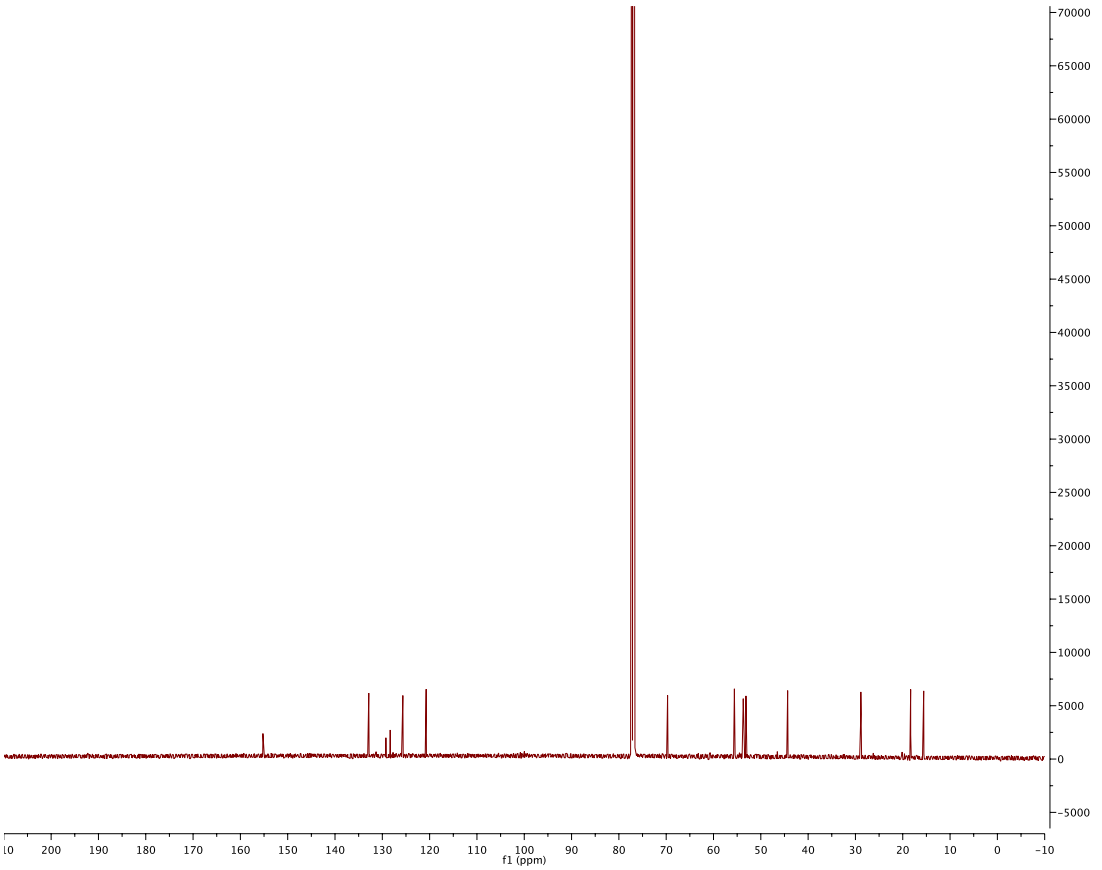


Figure 1. X-ray crystal structure of sultam **6a** where the thermal ellipsoids are set at a 50% probability level.

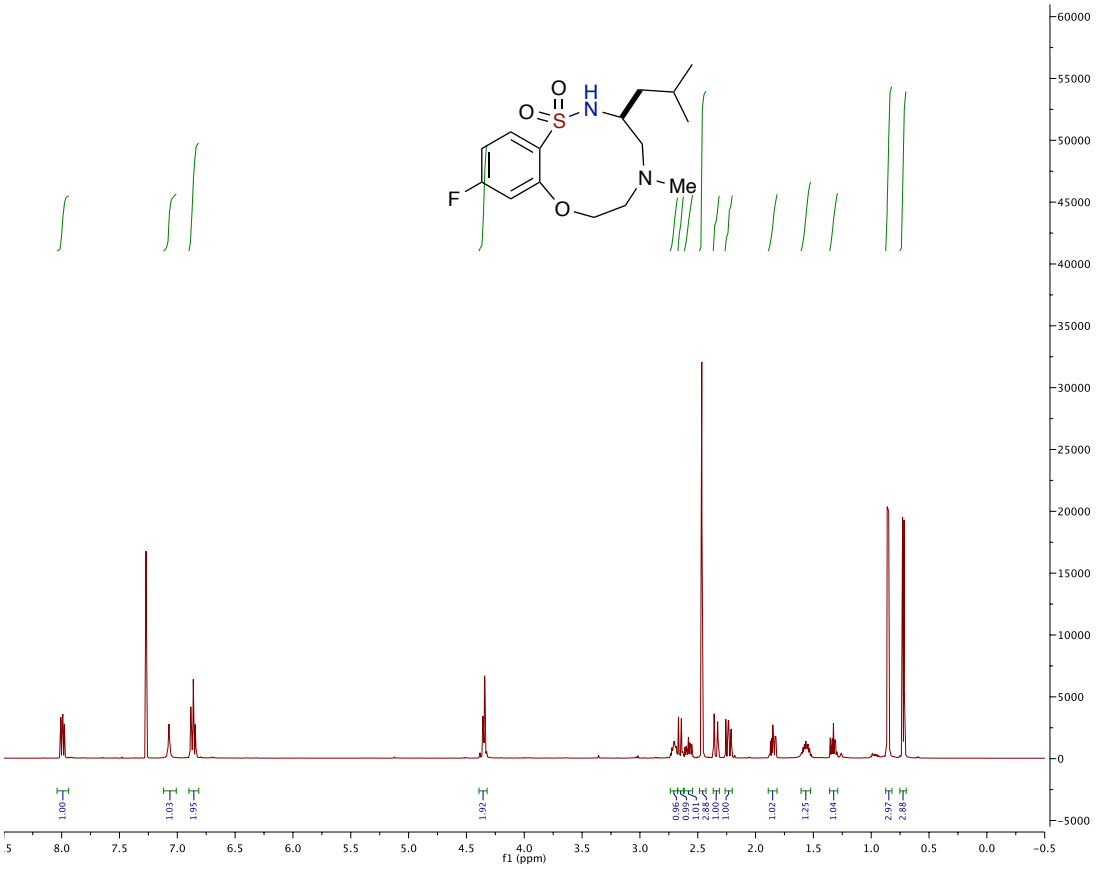


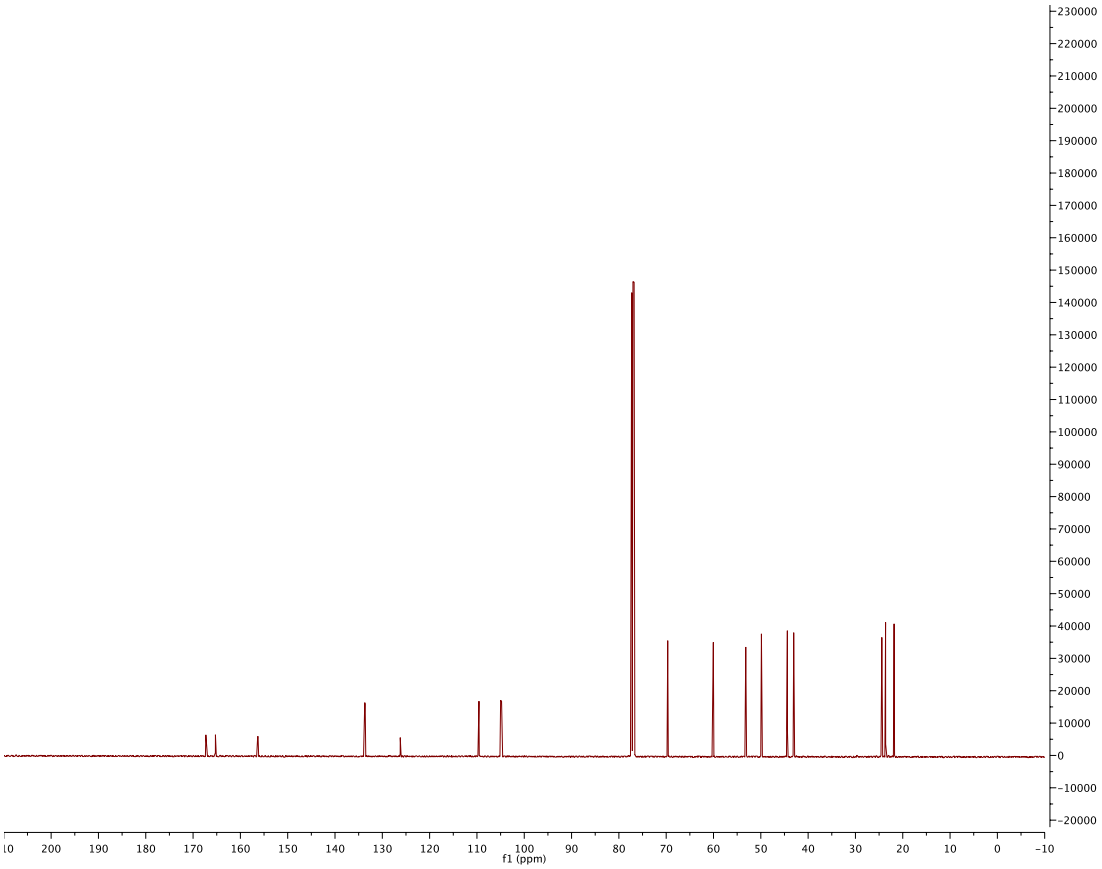
(*S*)-10-bromo-3-isopropyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathiadiazecine-1,1-dioxide (6b)



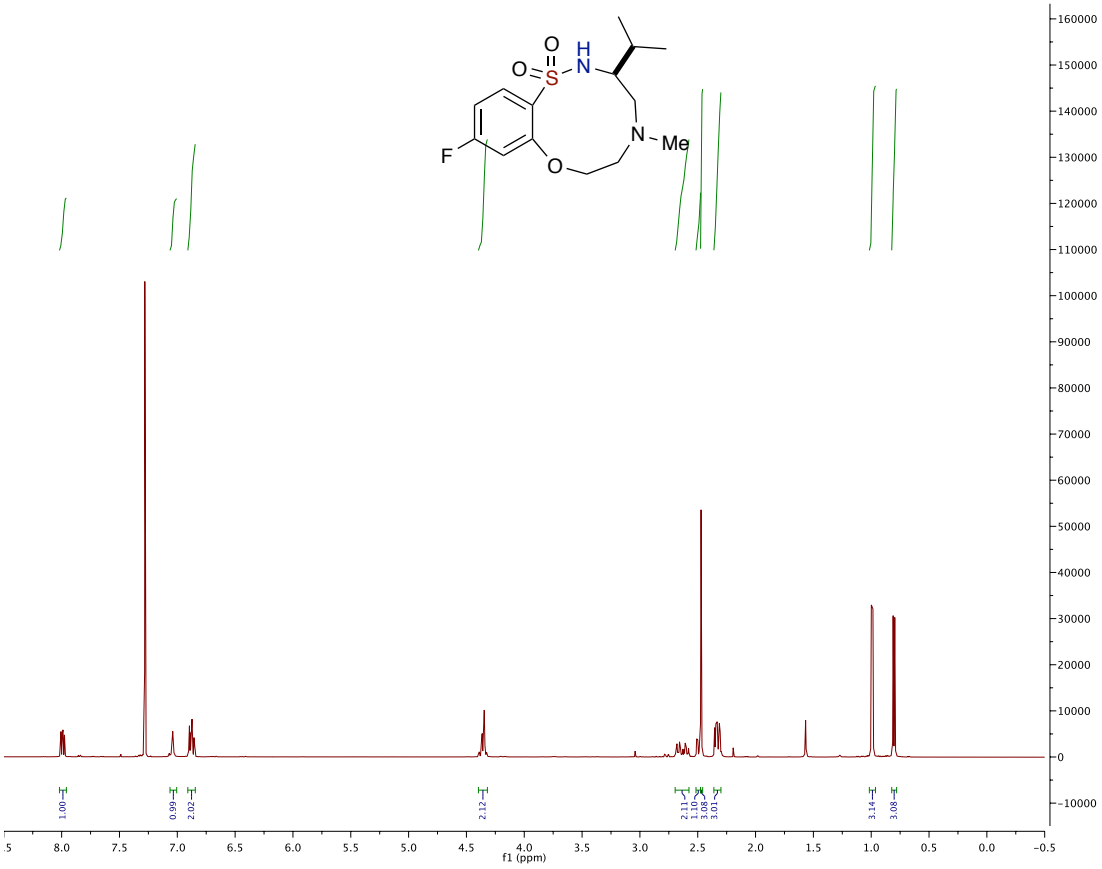


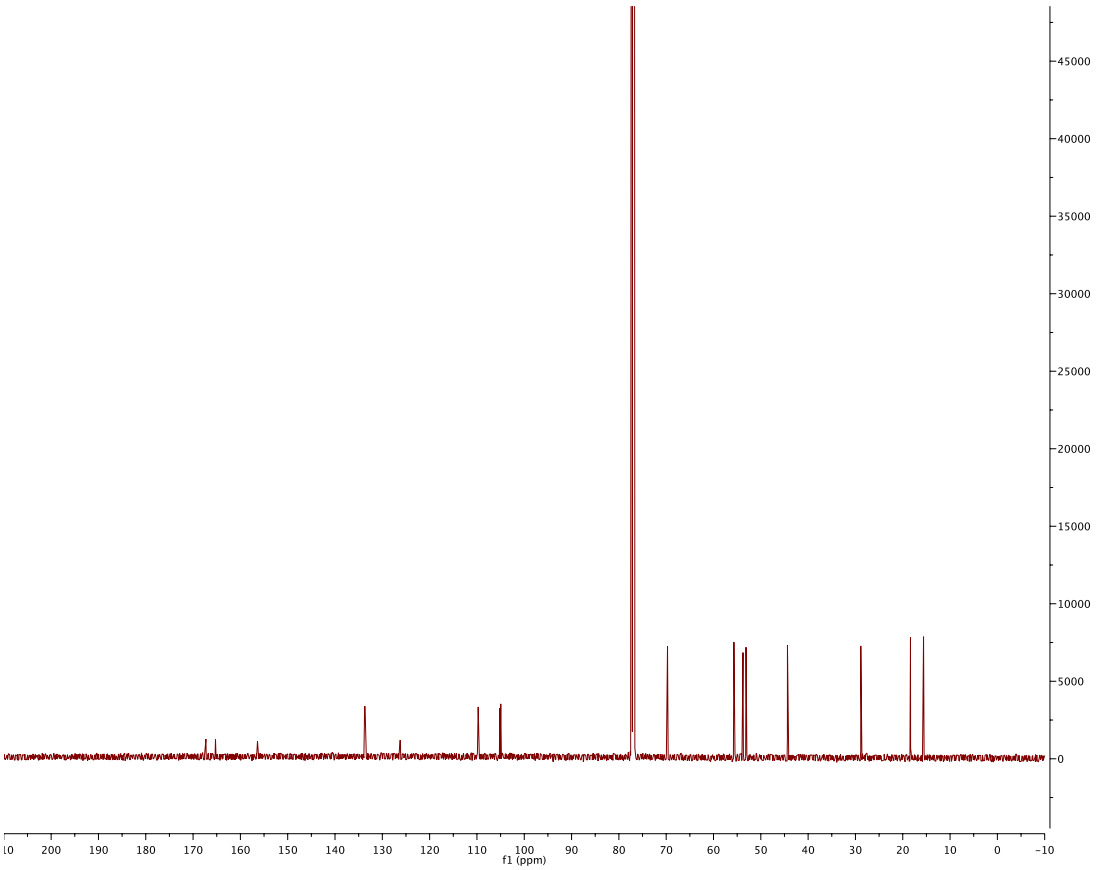
(*S*)-10-fluoro-3-isobutyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathiadiazecine 1,1-dioxide (6c)



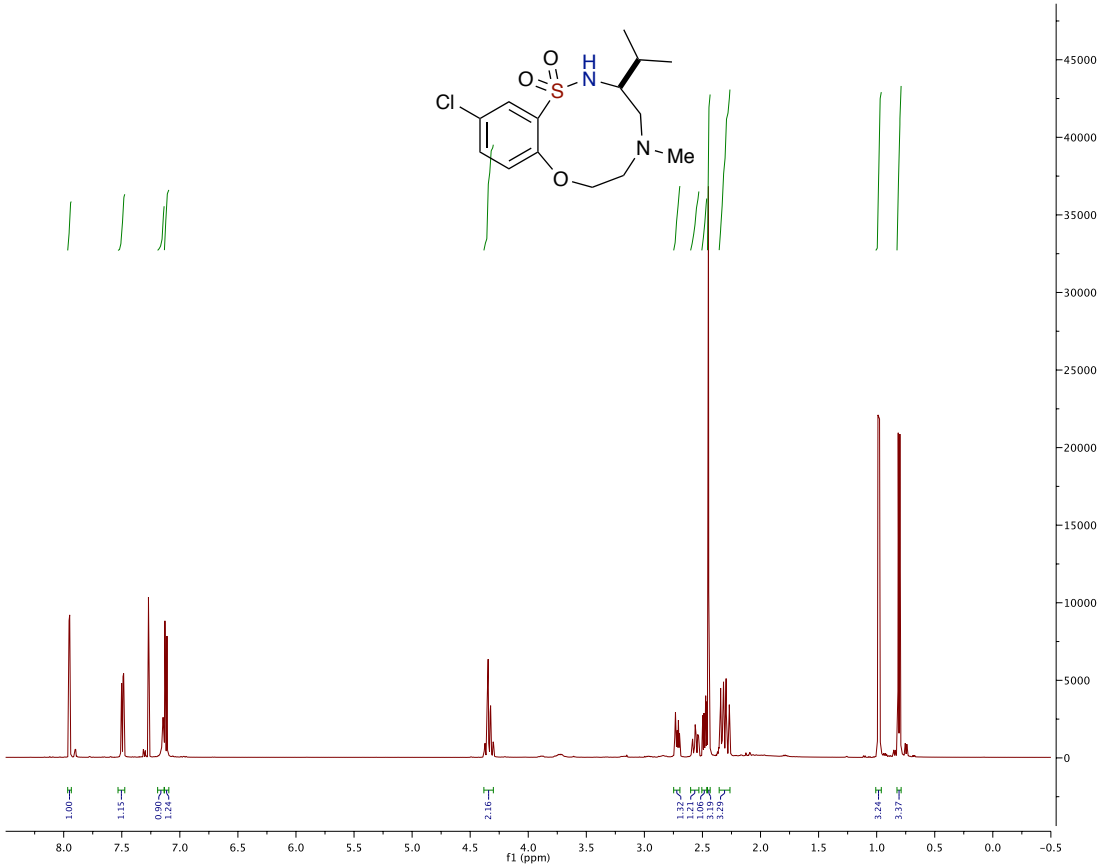


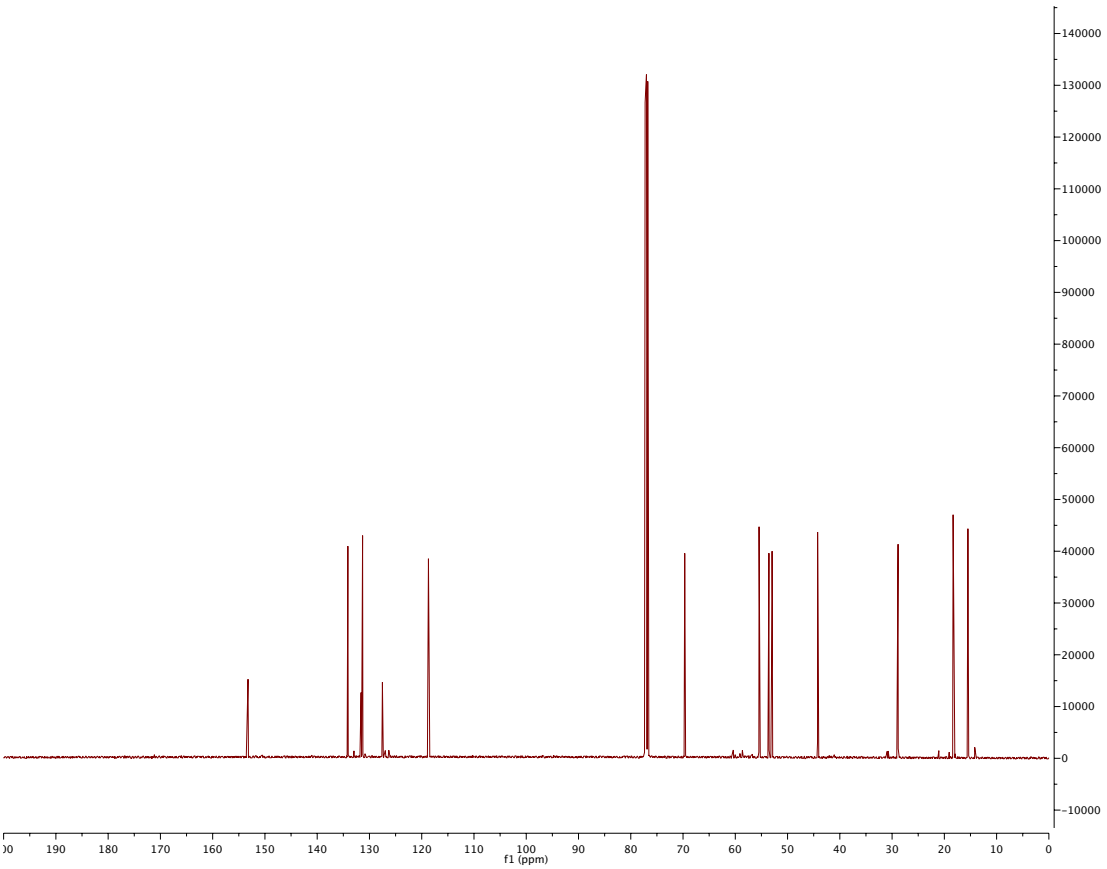
(*S*)-10-fluoro-3-isopropyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathiadiazecine-1,1-dioxide (6d)



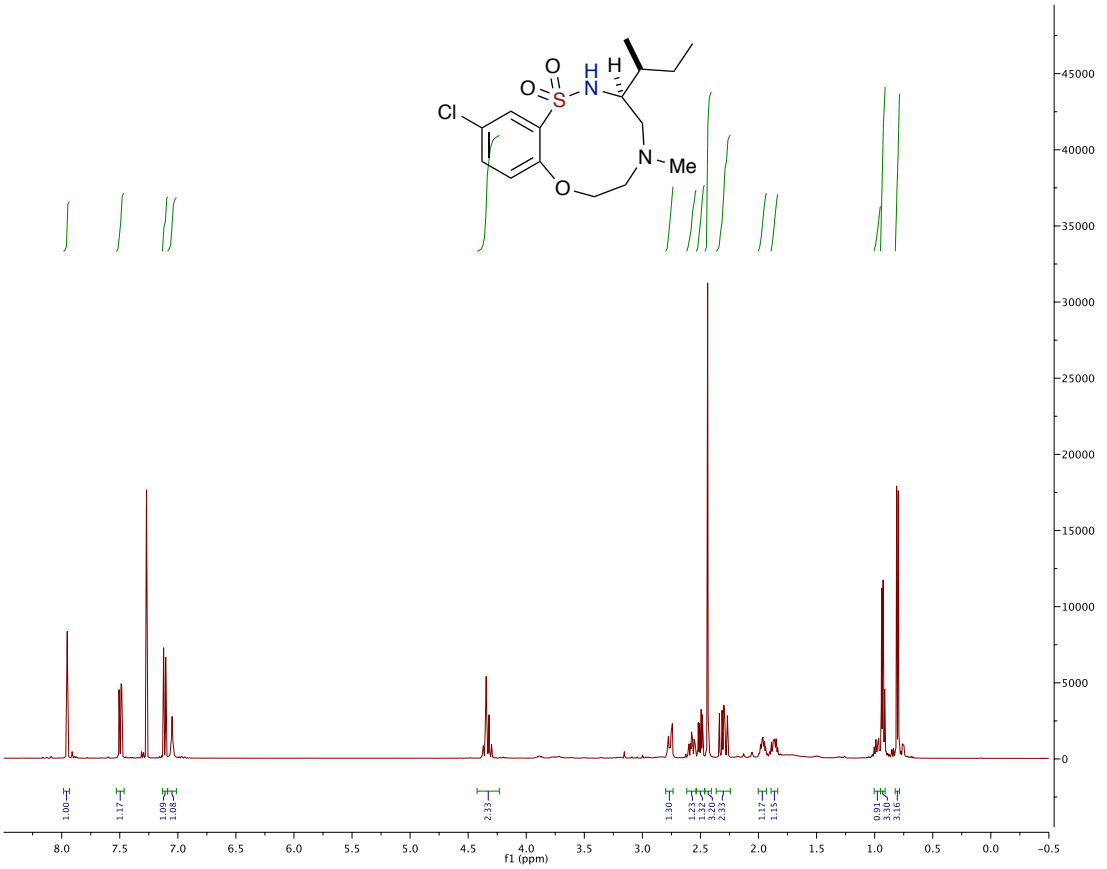


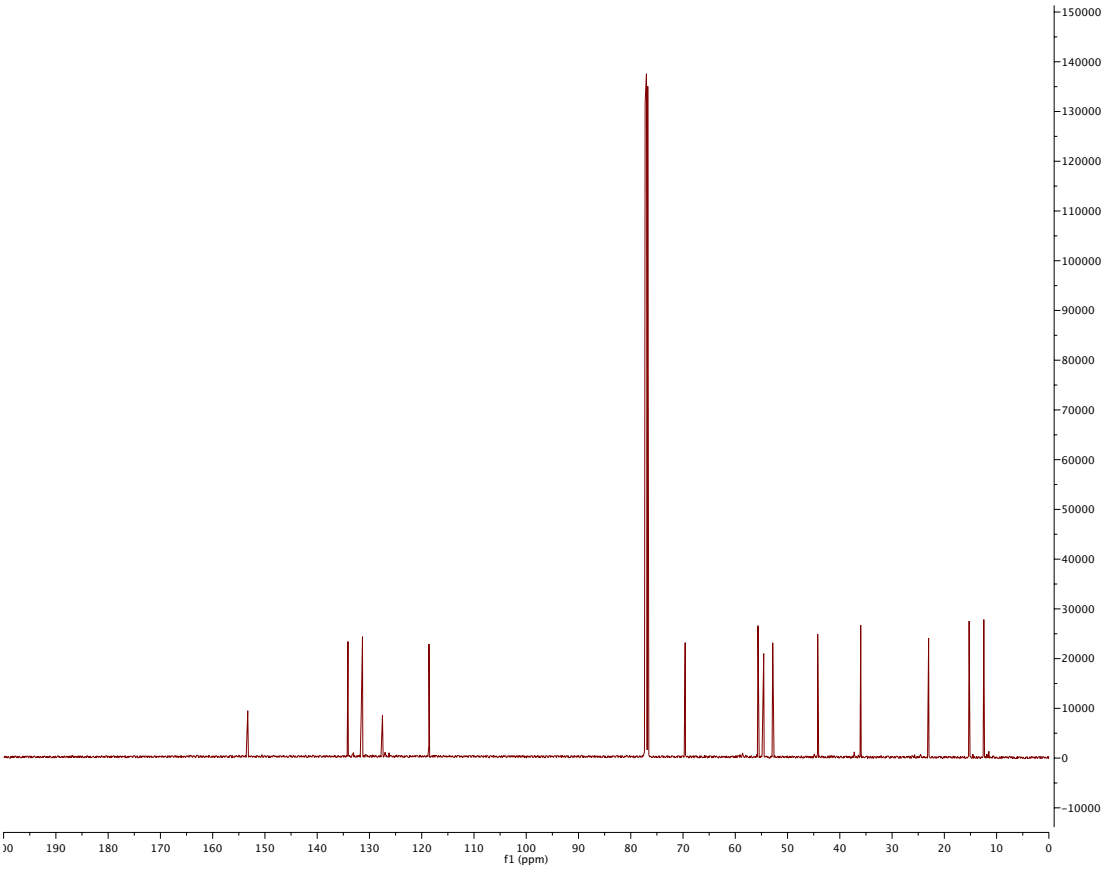
(*S*)-11-chloro-3-isopropyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathiadiazecine 1,1-dioxide (6e)



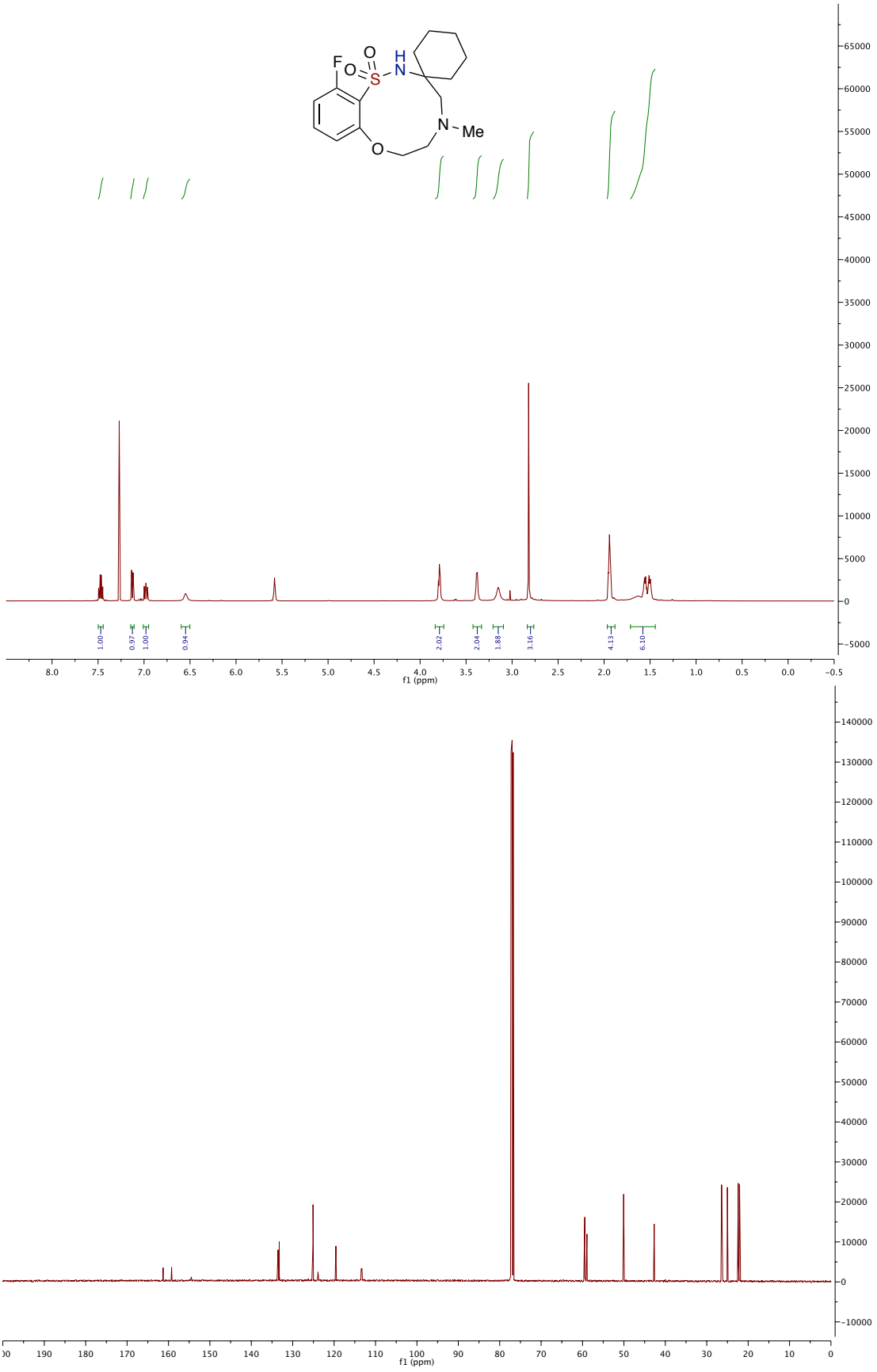


(*S*)-3-((*S*)-*sec*-butyl)-11-chloro-5-methyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathiadiazecine 1,1-dioxide (6f)

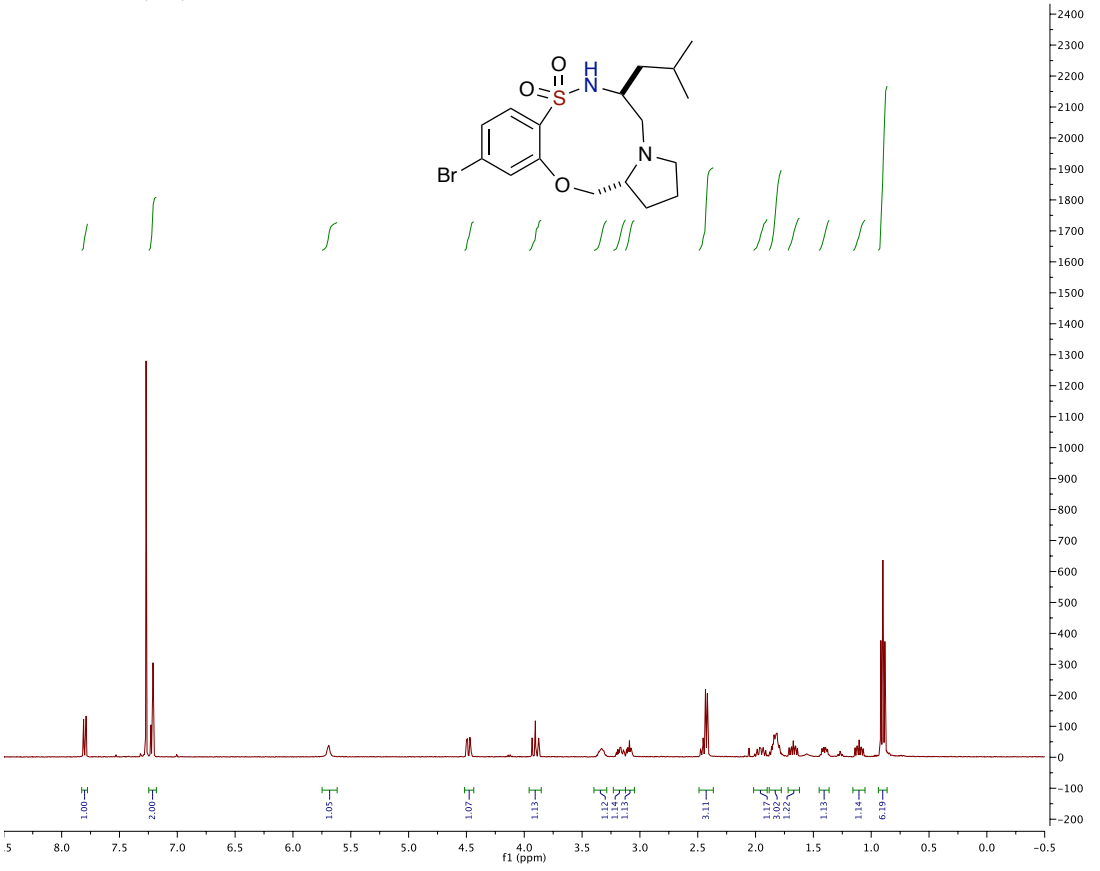


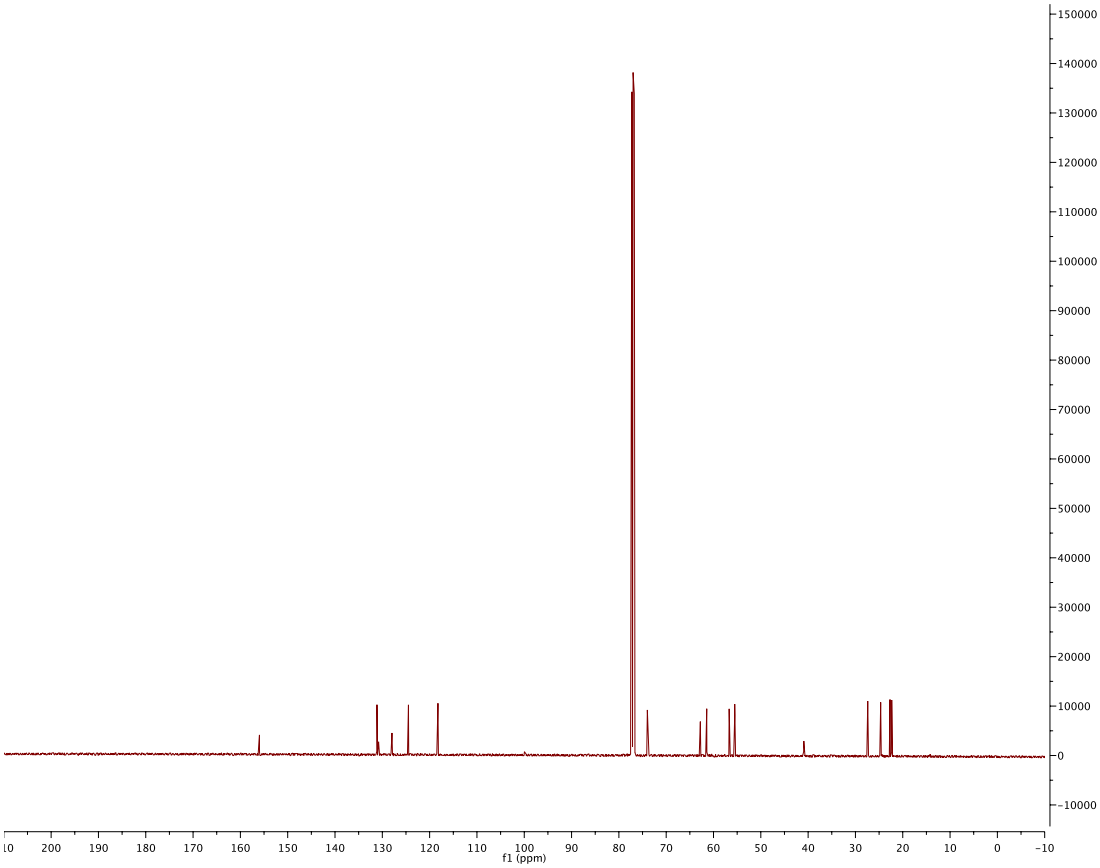


12-fluoro-5-methyl-4,5,6,7-tetrahydro-2*H*-spiro[benzo[*b*][1,4,5,8]oxathiadiazecine-3,1'-cyclohexane] 1,1-dioxide (6g)

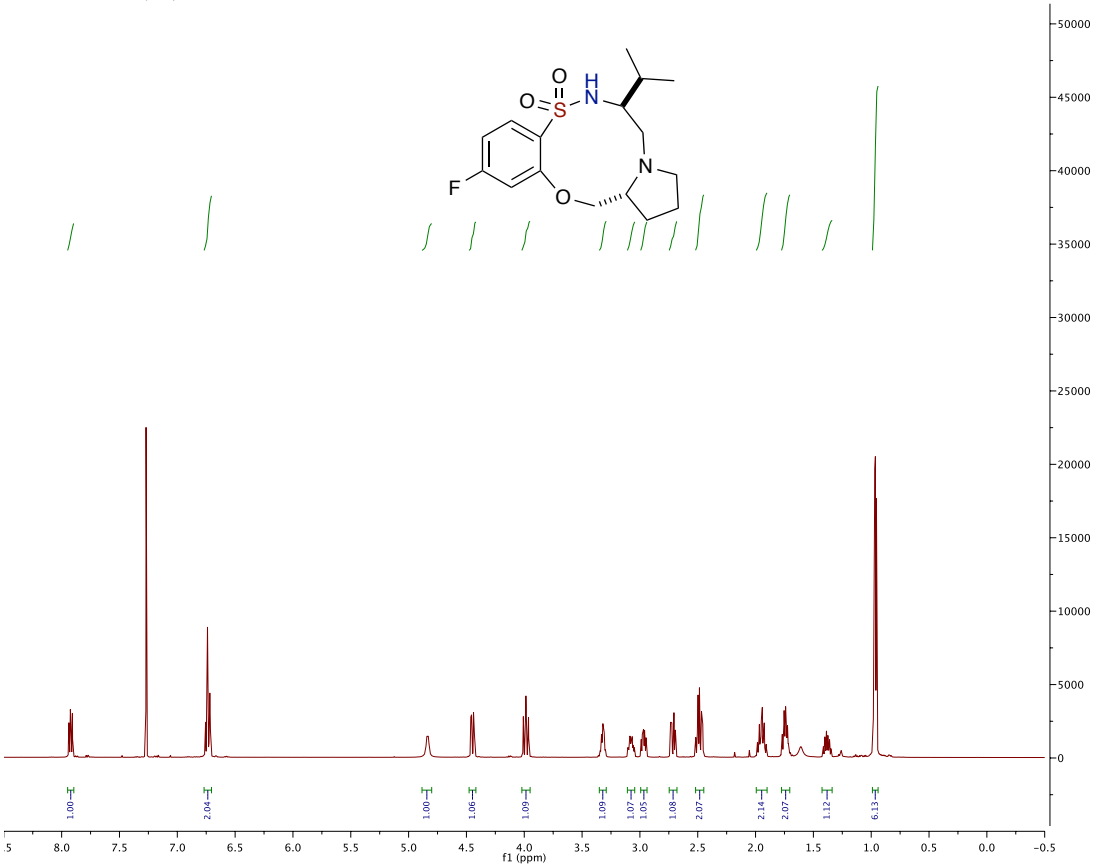


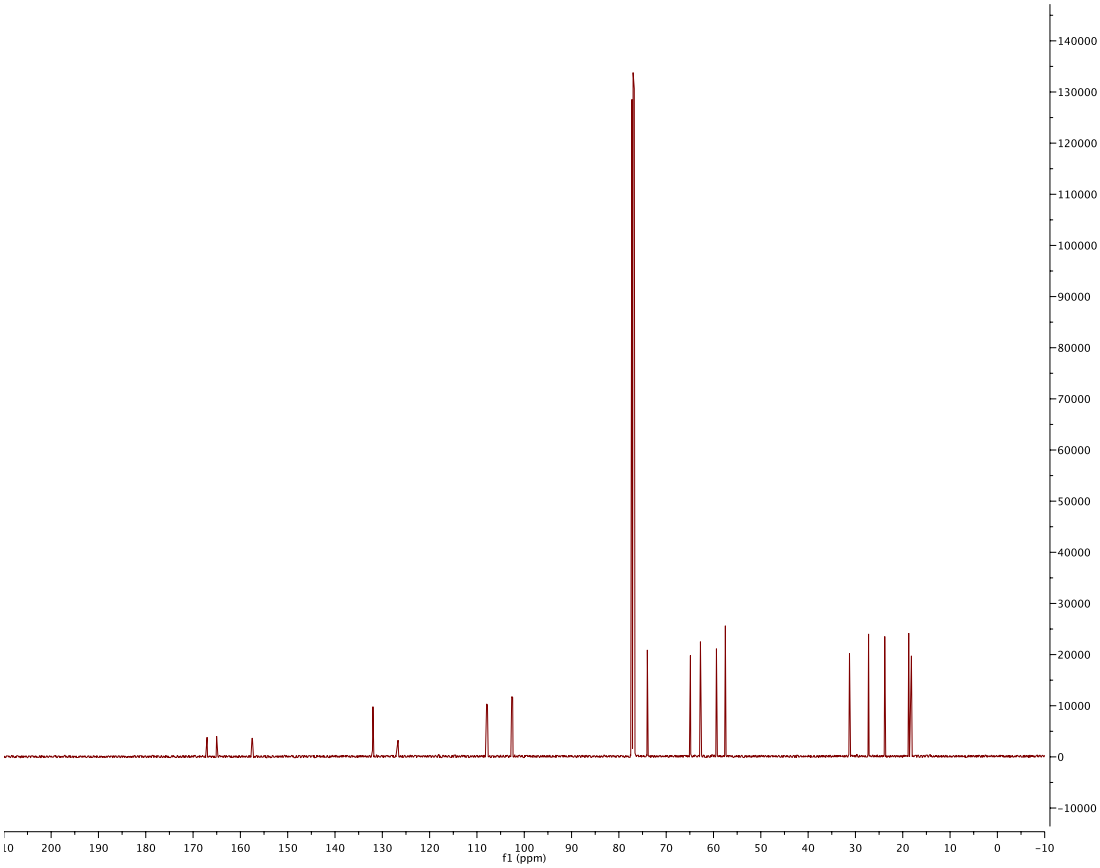
(6*S*,14a*R*)-11-bromo-6-isobutyl-1,2,3,5,6,7,14,14a-octahydrobenzo[*b*]pyrrolo[1,2*h*][1,4,5,8]oxathia-diazecine 8,8-dioxide (6h)





(6*S*,14a*R*)-11-fluoro-6-isopropyl-1,2,3,5,6,7,14,14a-octahydrobenzo[*b*]pyrrolo[1,2*h*][1,4,5,8]oxathiadiazecine 8,8-dioxide (6i)





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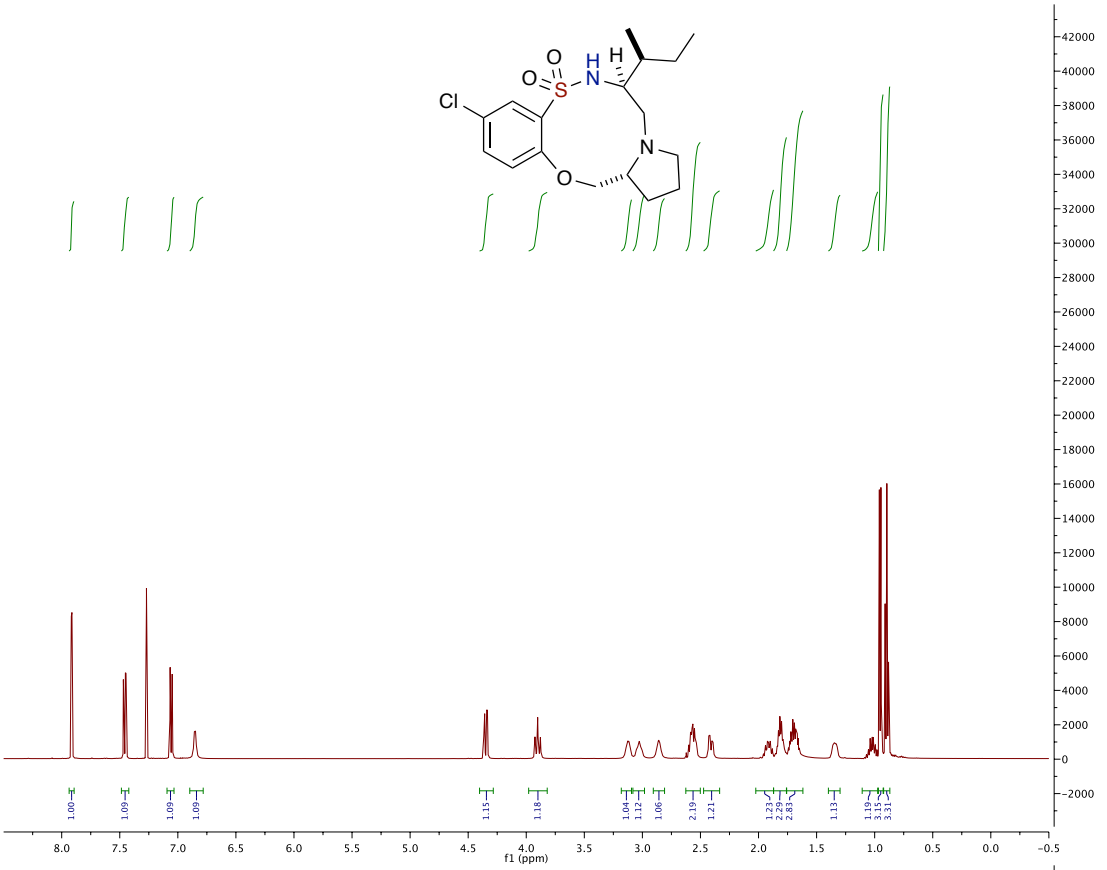
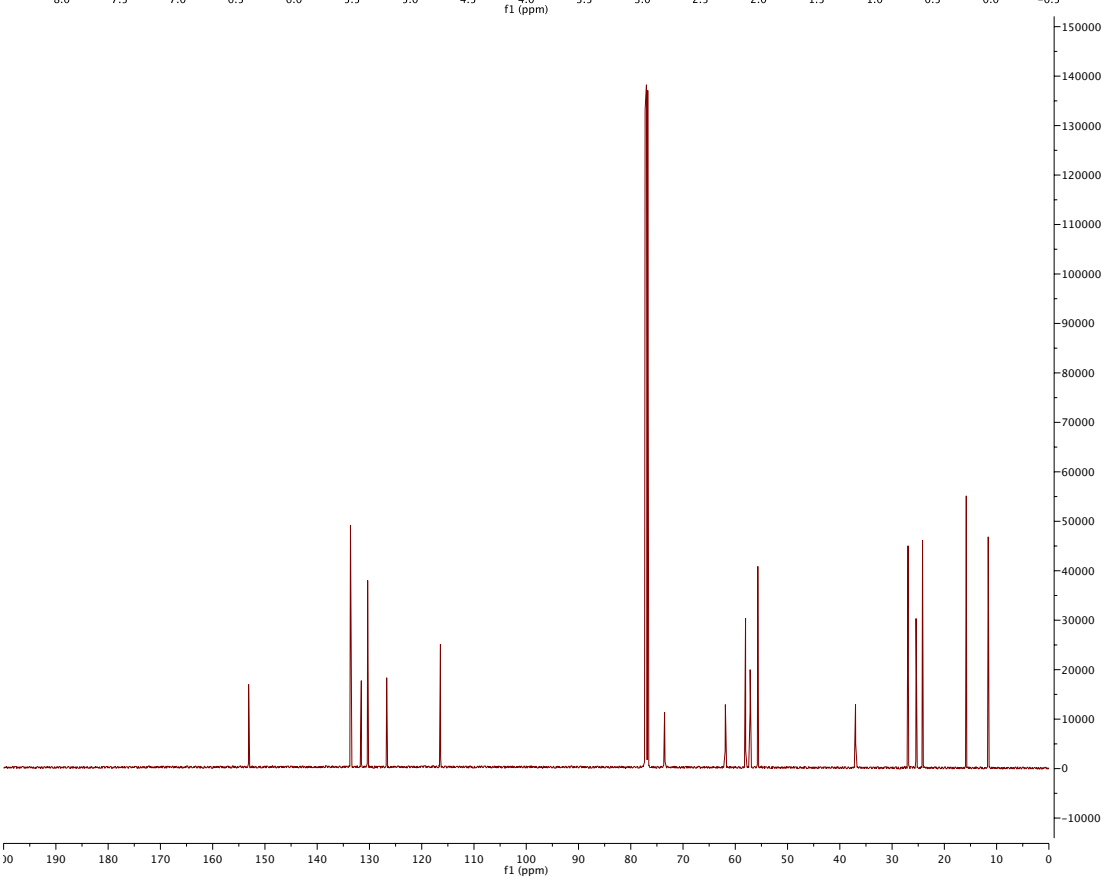
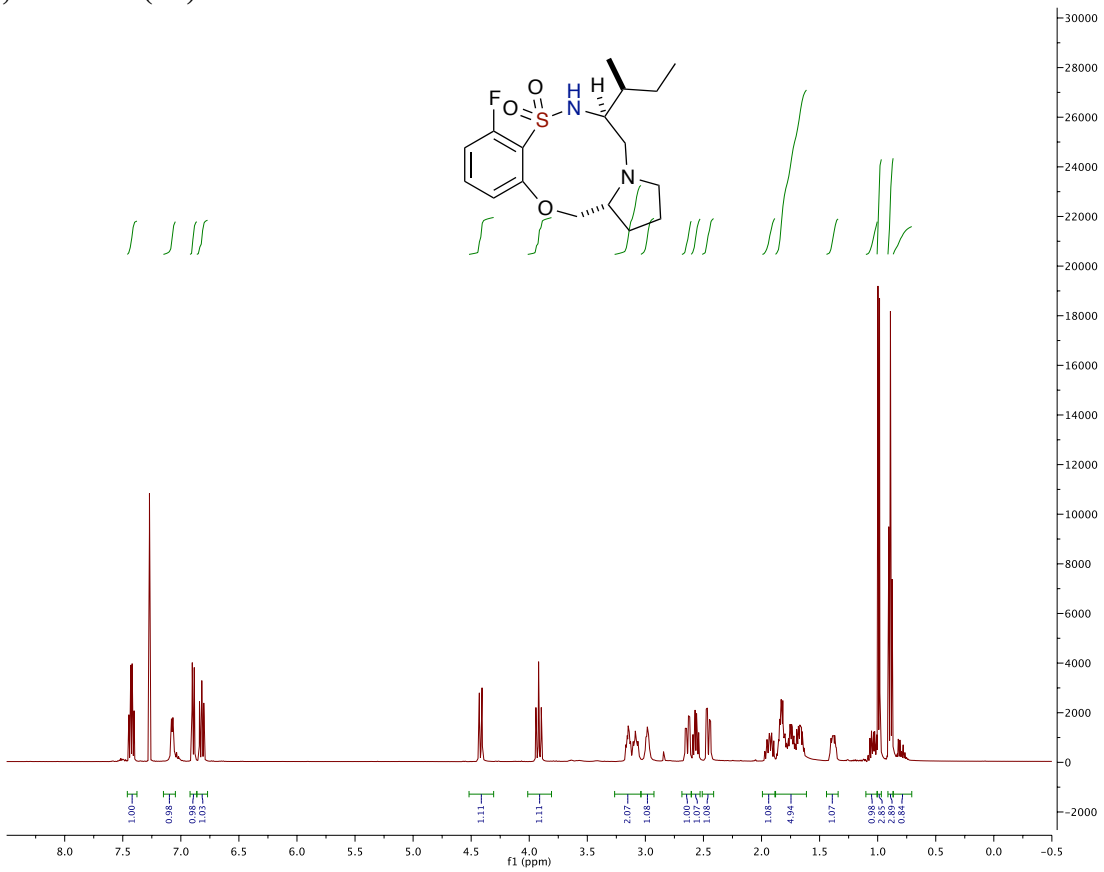
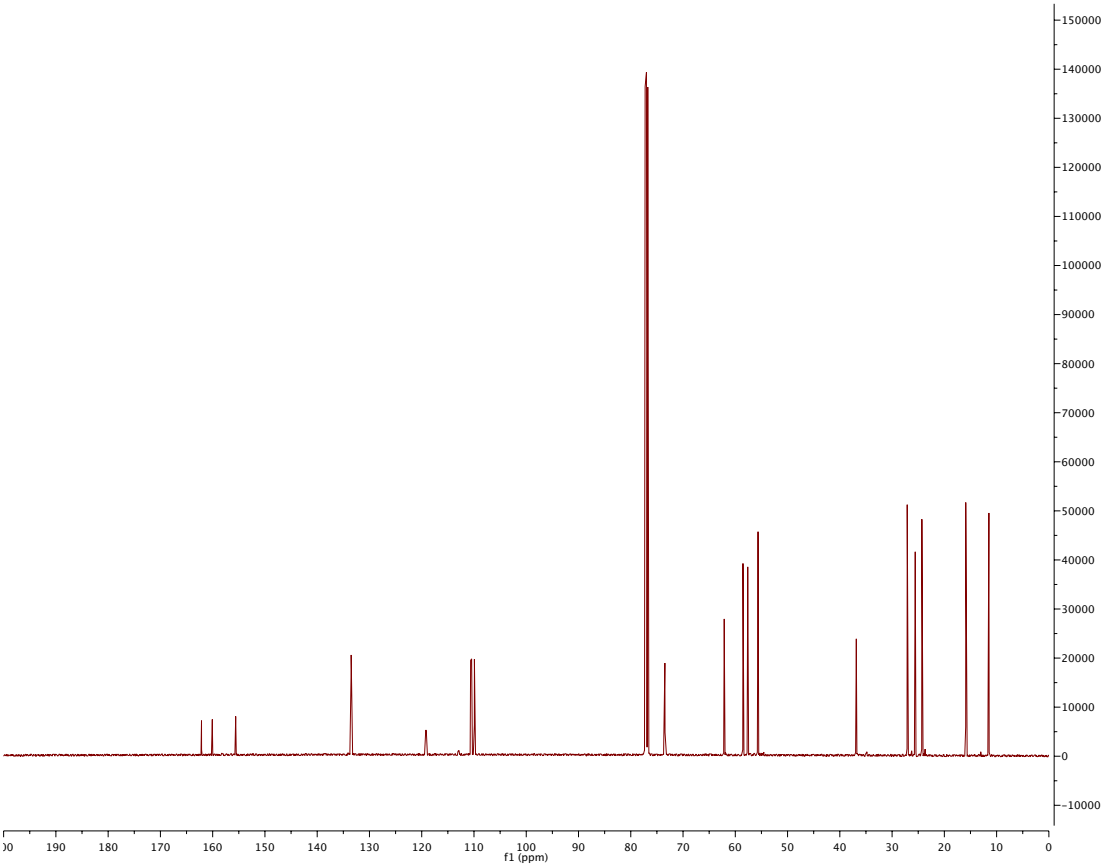




(6*S*,14a*R*)-6-((*S*)-*sec*-butyl)-9-fluoro-1,2,3,5,6,7,14,14a-octahydrobenzo[*b*]pyrrolo[1,2-*h*][1,4,5,8]oxathiadiazecine 8,8-dioxide (6k)





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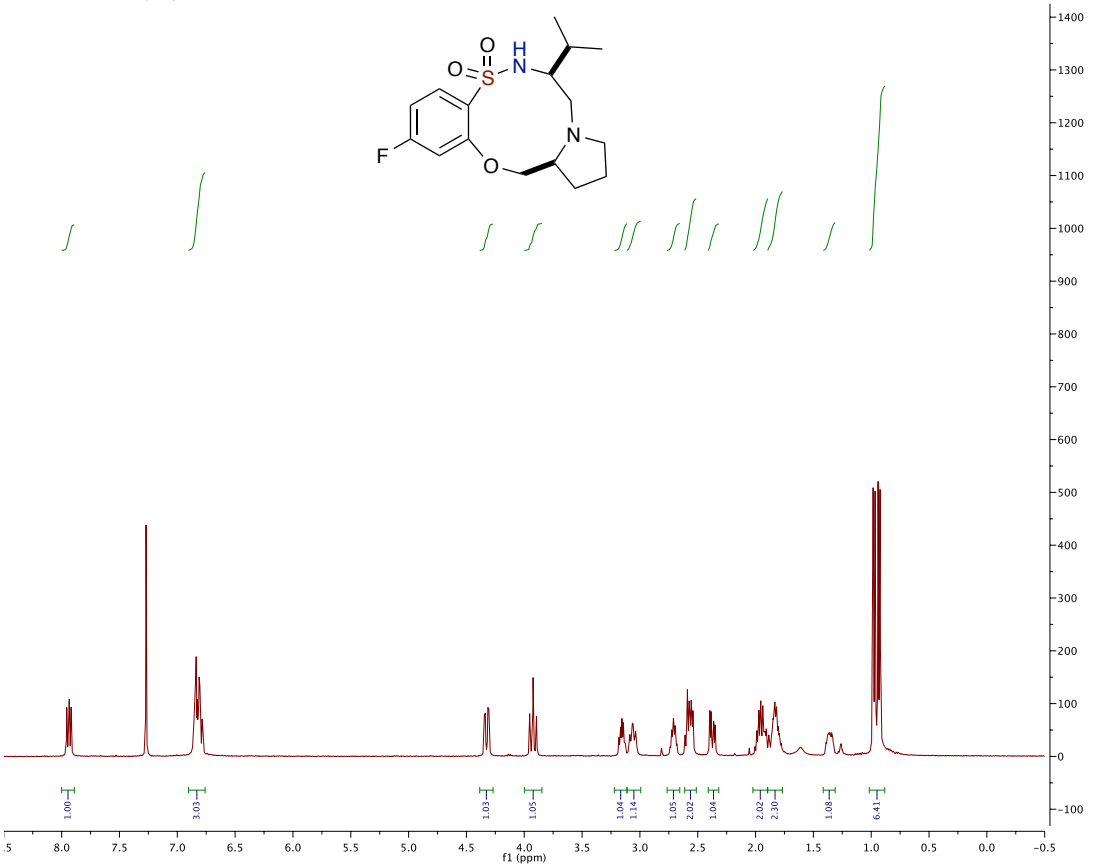
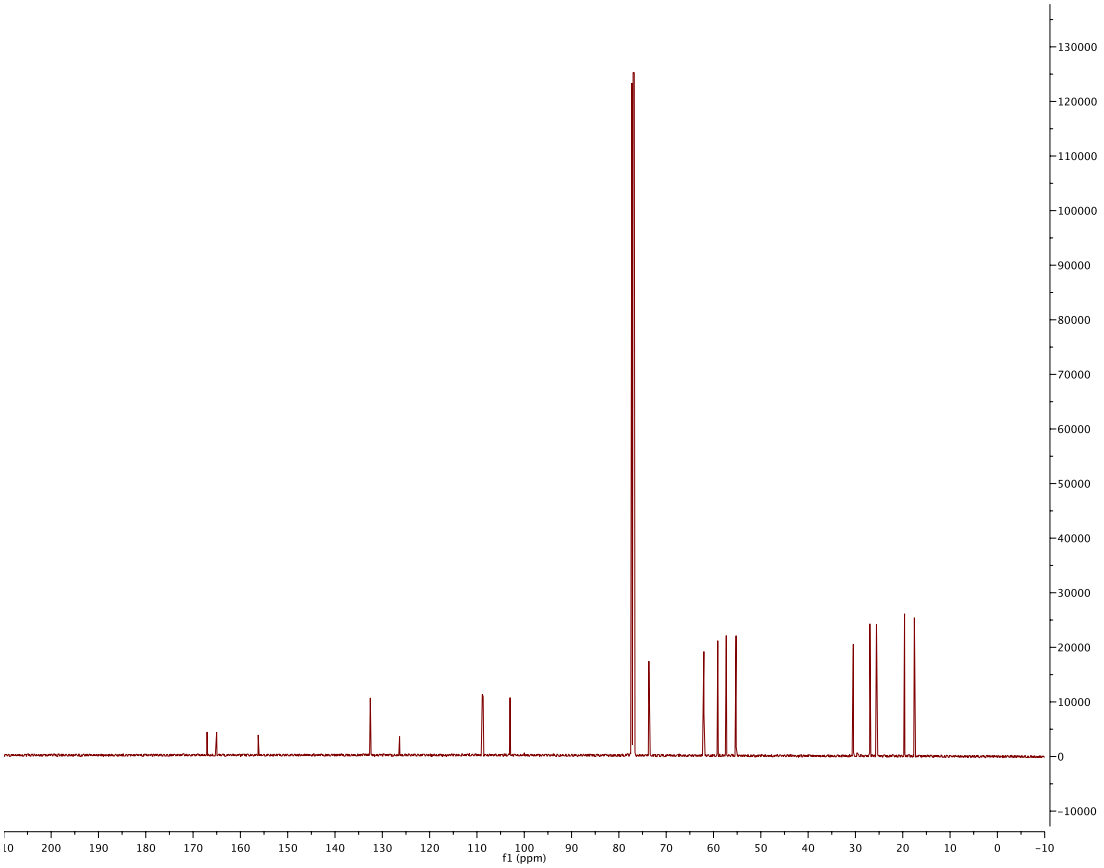
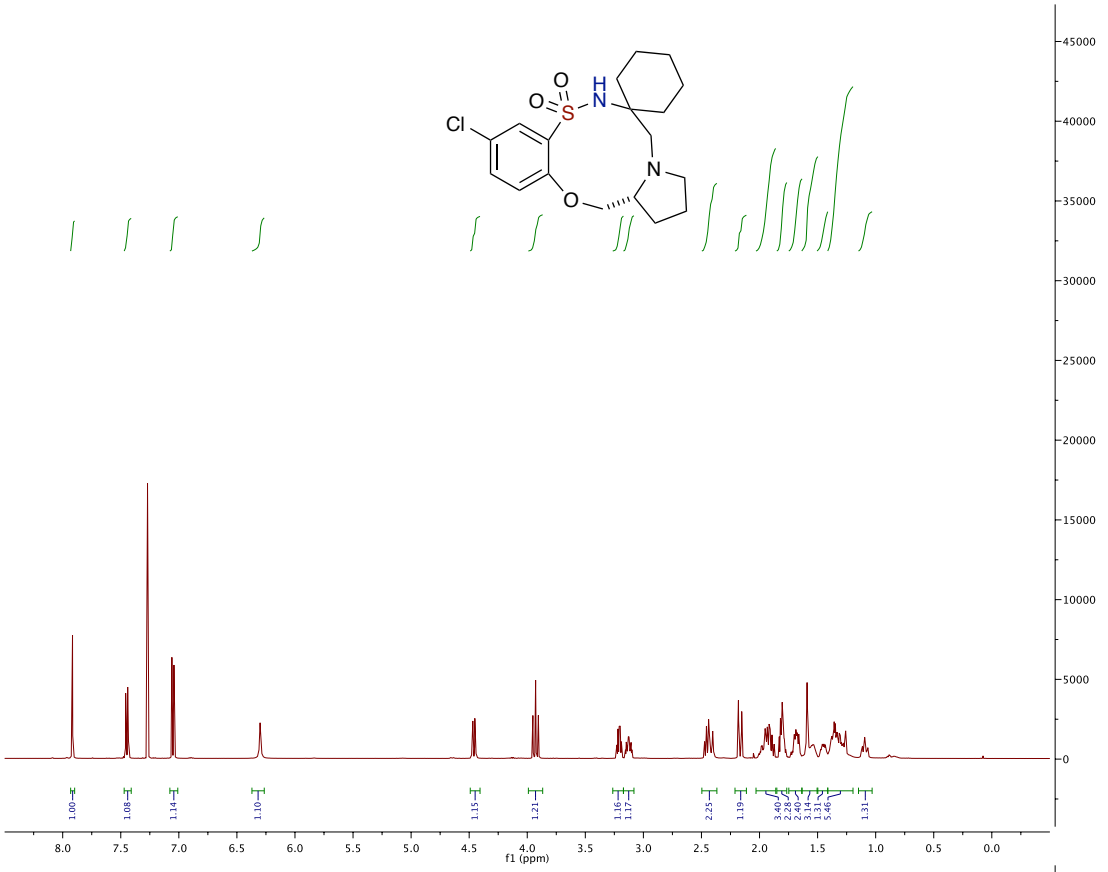
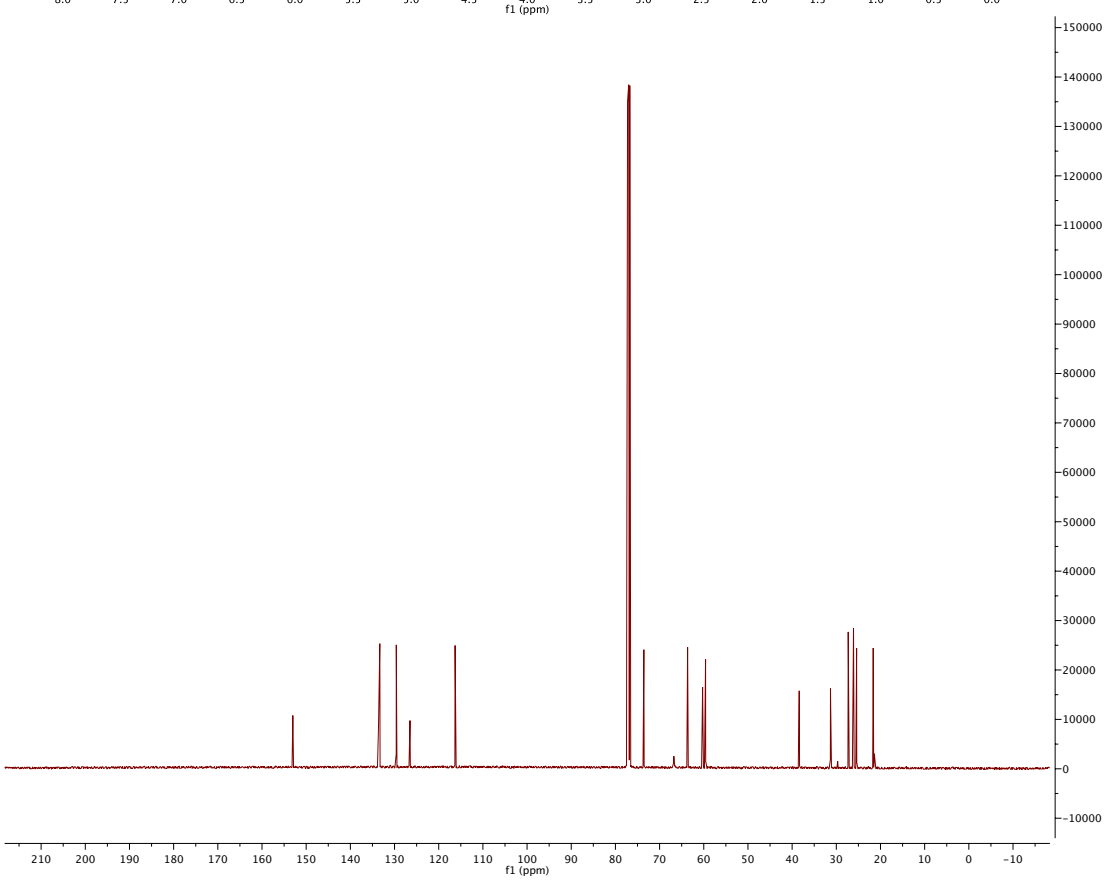


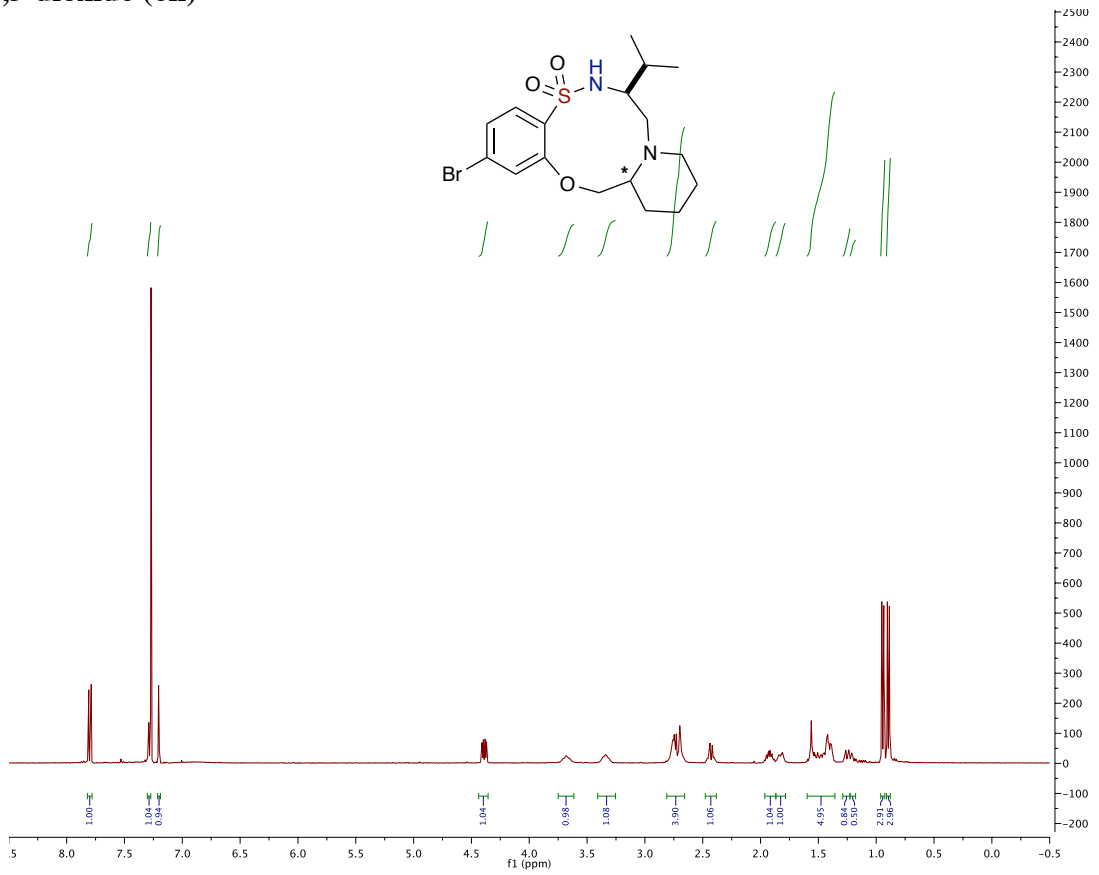


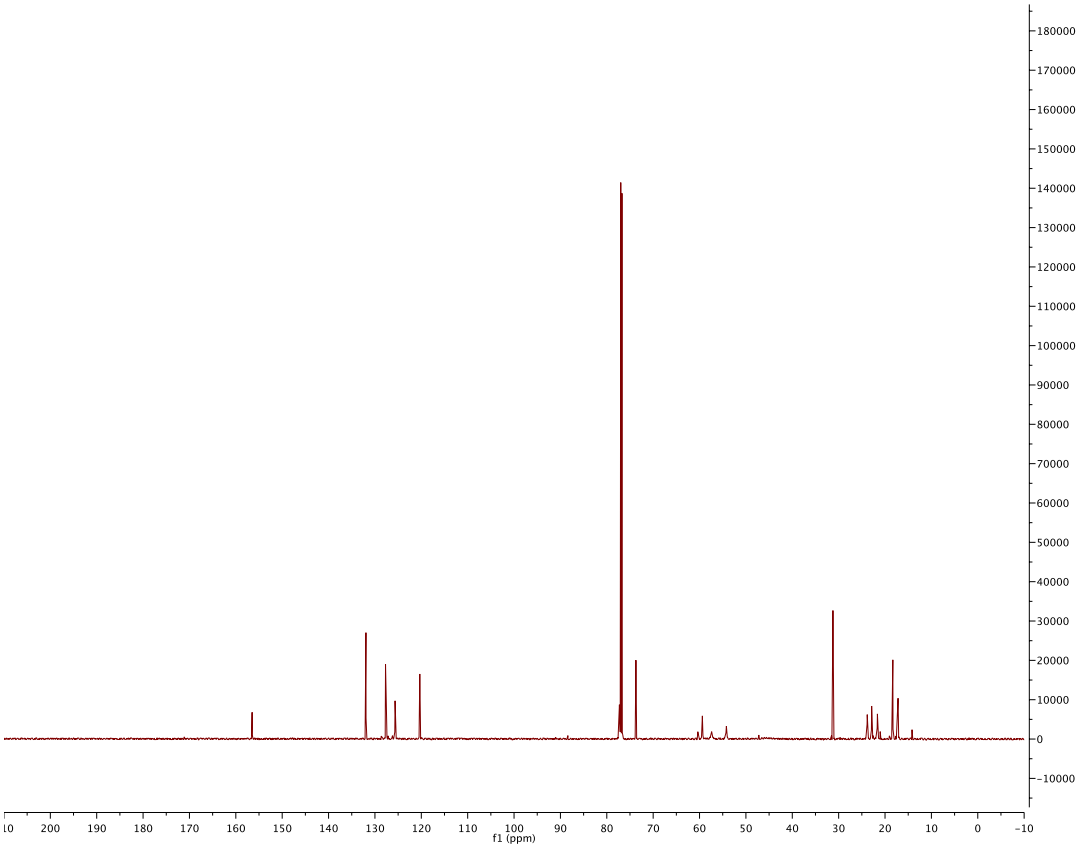
(*R*)-9-fluoro-2,3,5,7,14,14a-hexahydro-1*H*-spiro[benzo[*b*]pyrrolo[1,2-*h*][1,4,5,8]oxathiadiazecine-6,1'-cyclohexane] 8,8-dioxide (6m)



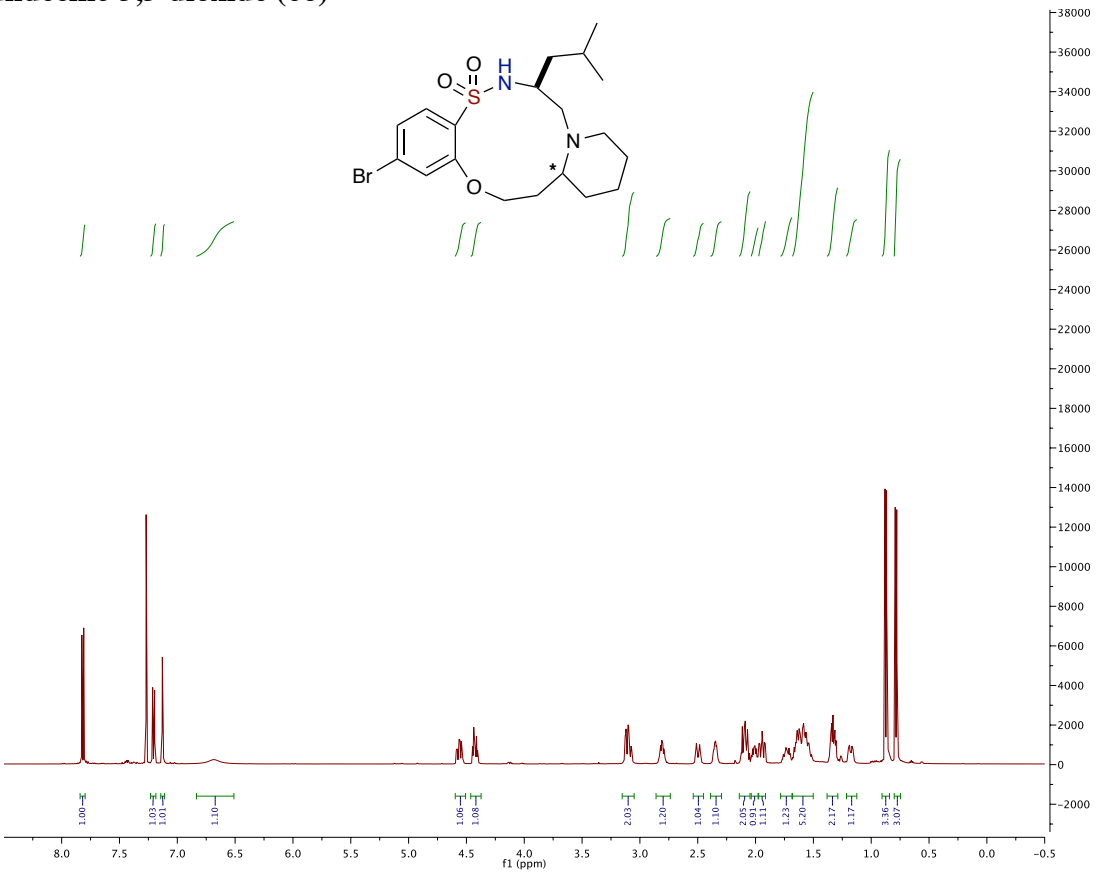


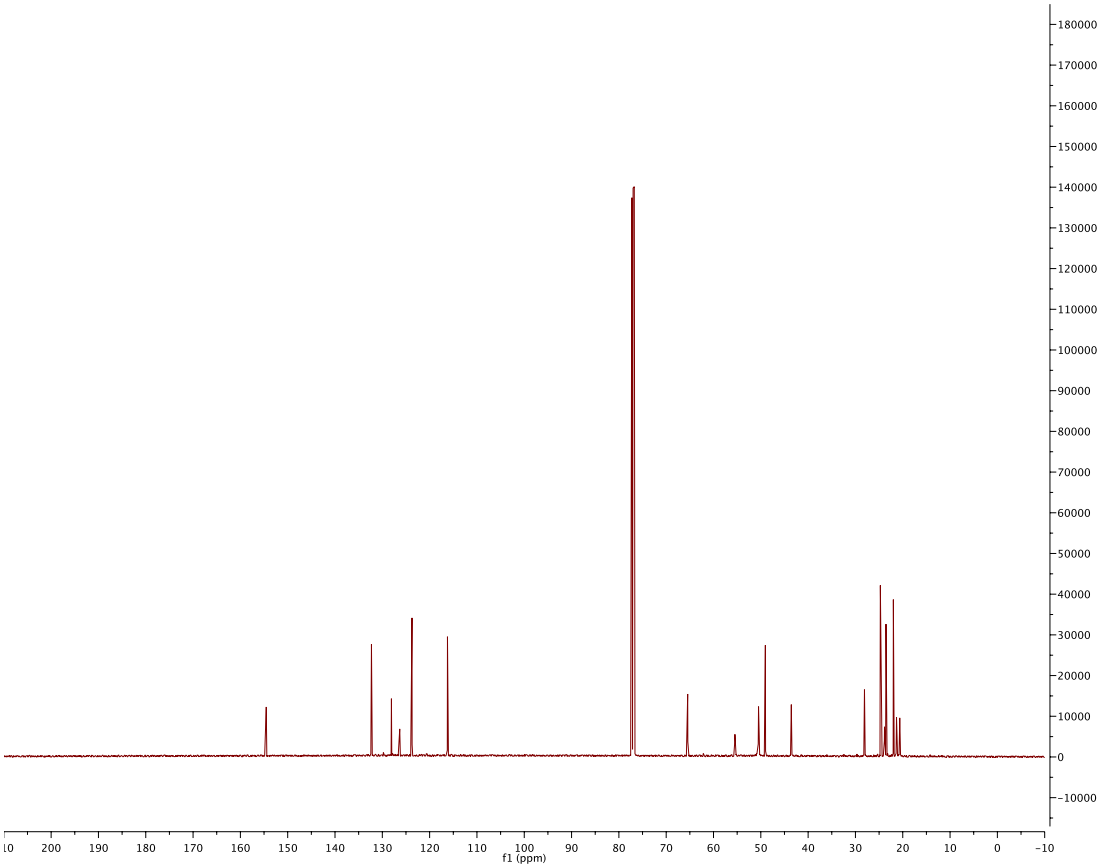
(7*S*)-2-bromo-7-isopropyl-7,8,10,11,12,13,13a,14-octahydro-6*H*-benzo[*b*]pyrido[1,2-*h*][1,4,5,8]oxathiadiazecine 5,5-dioxide (6n)



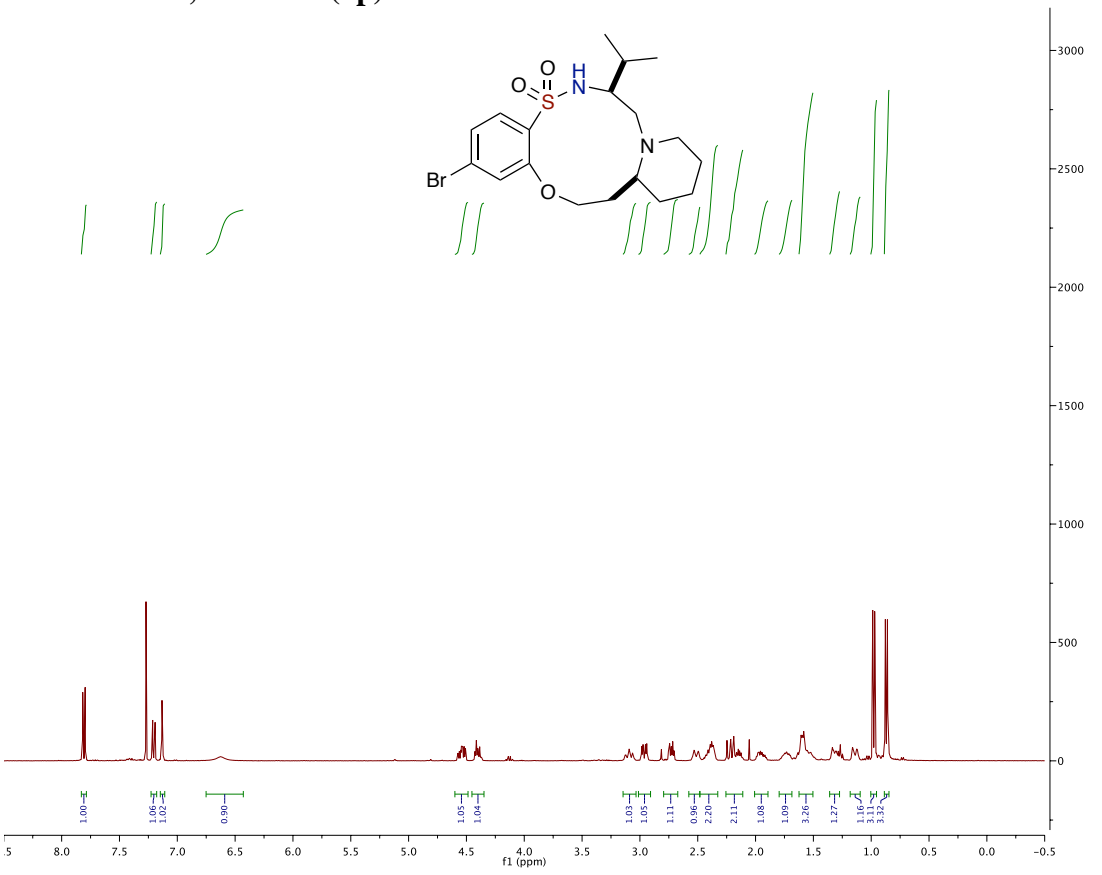


(7*S*)-2-bromo-7-isobutyl-6,7,8,10,11,12,13,13a,14,15-decahydrobenzo[*b*]pyrido[1,2-*h*][1,4,5,8]oxathia-diazacycloundecine 5,5-dioxide (6o)





(7*S*,13a*S*)-2-bromo-7-isopropyl-6,7,8,10,11,12,13,13a,14,15-decahydrobenzo[*b*]pyrido[1,2-*h*][1,4,5,8]oxathiadiazacycloundecine 5,5-dioxide (6p)



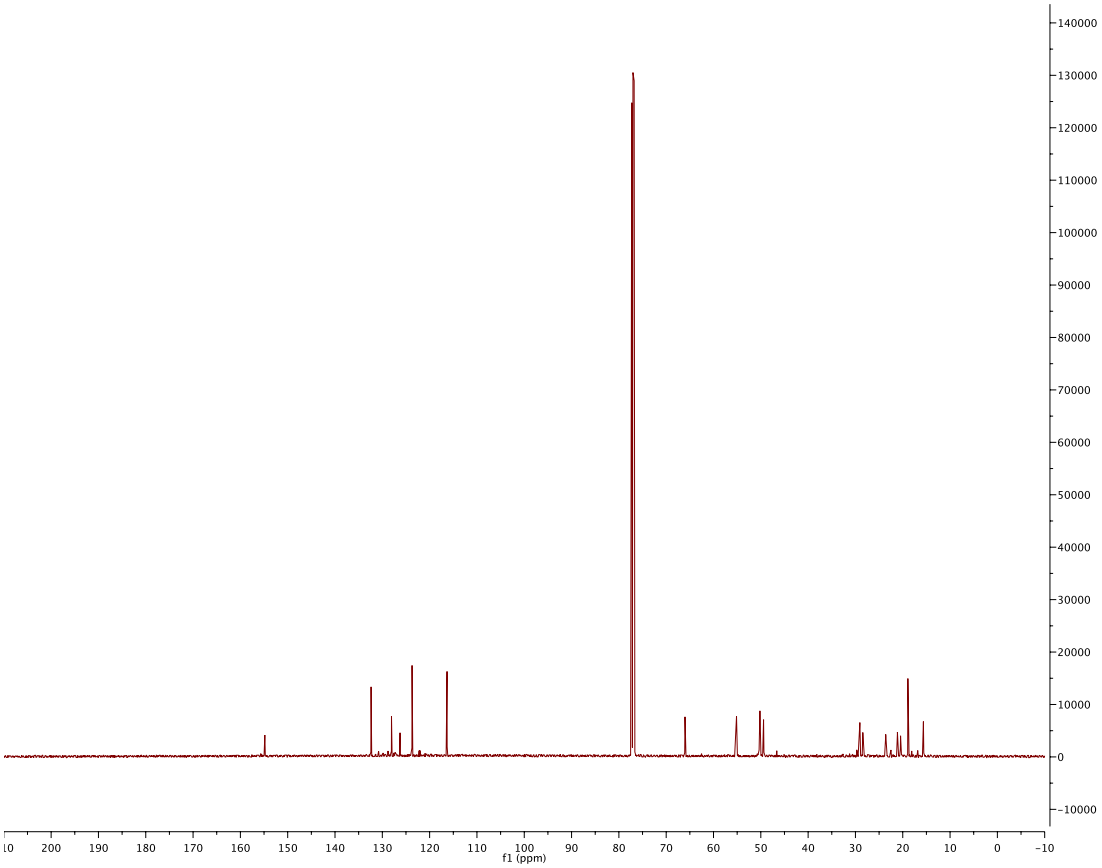
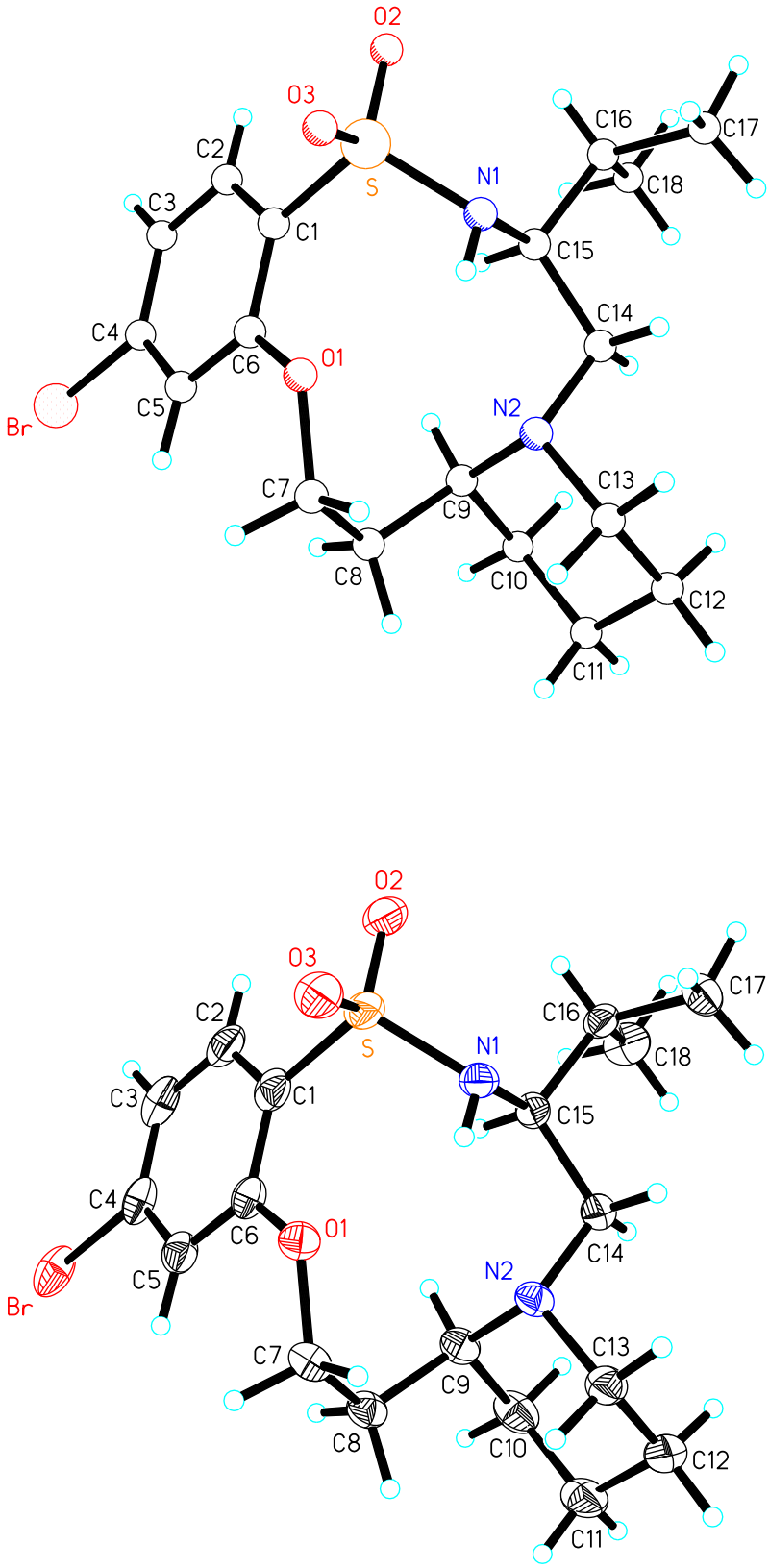
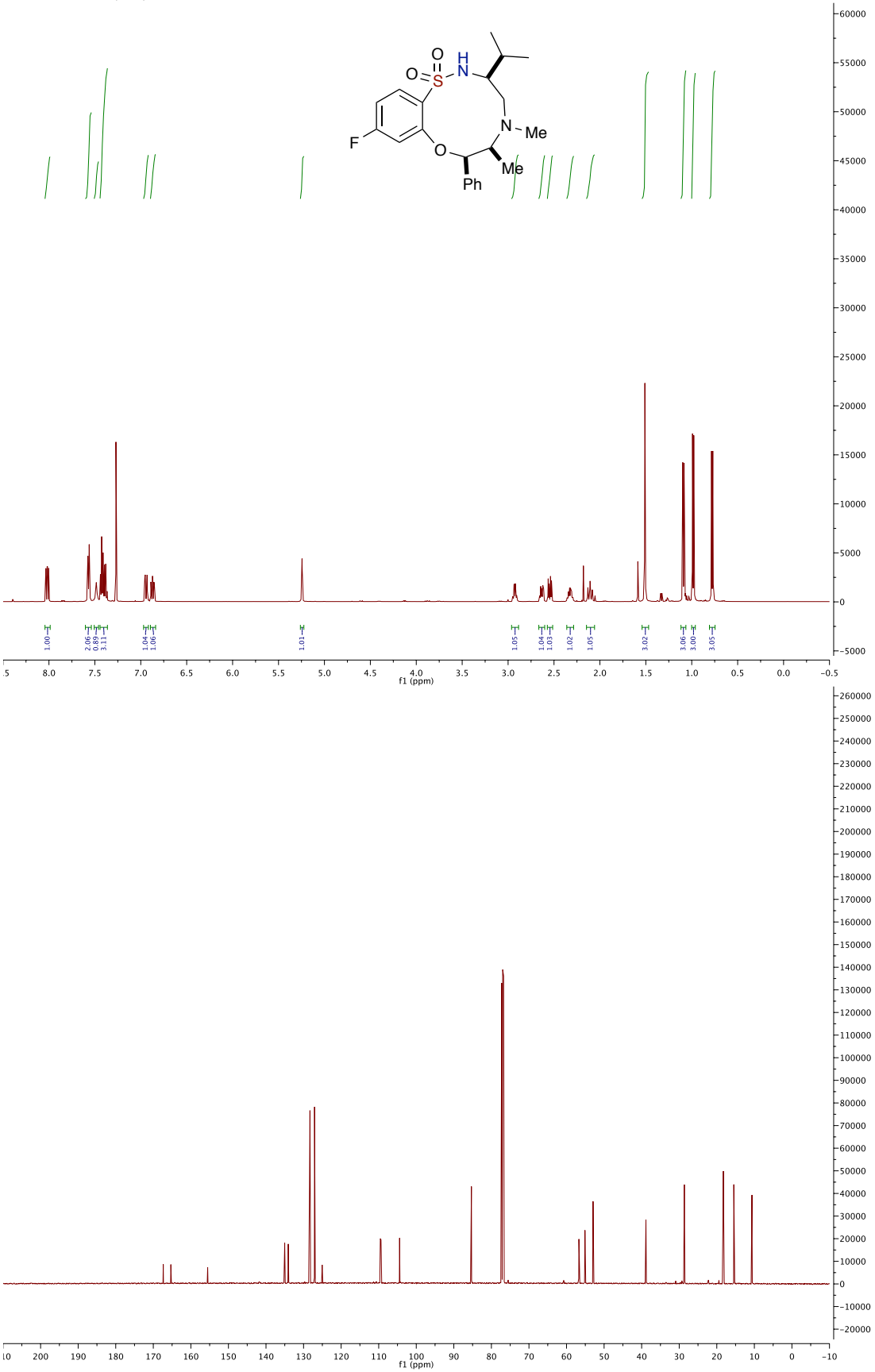


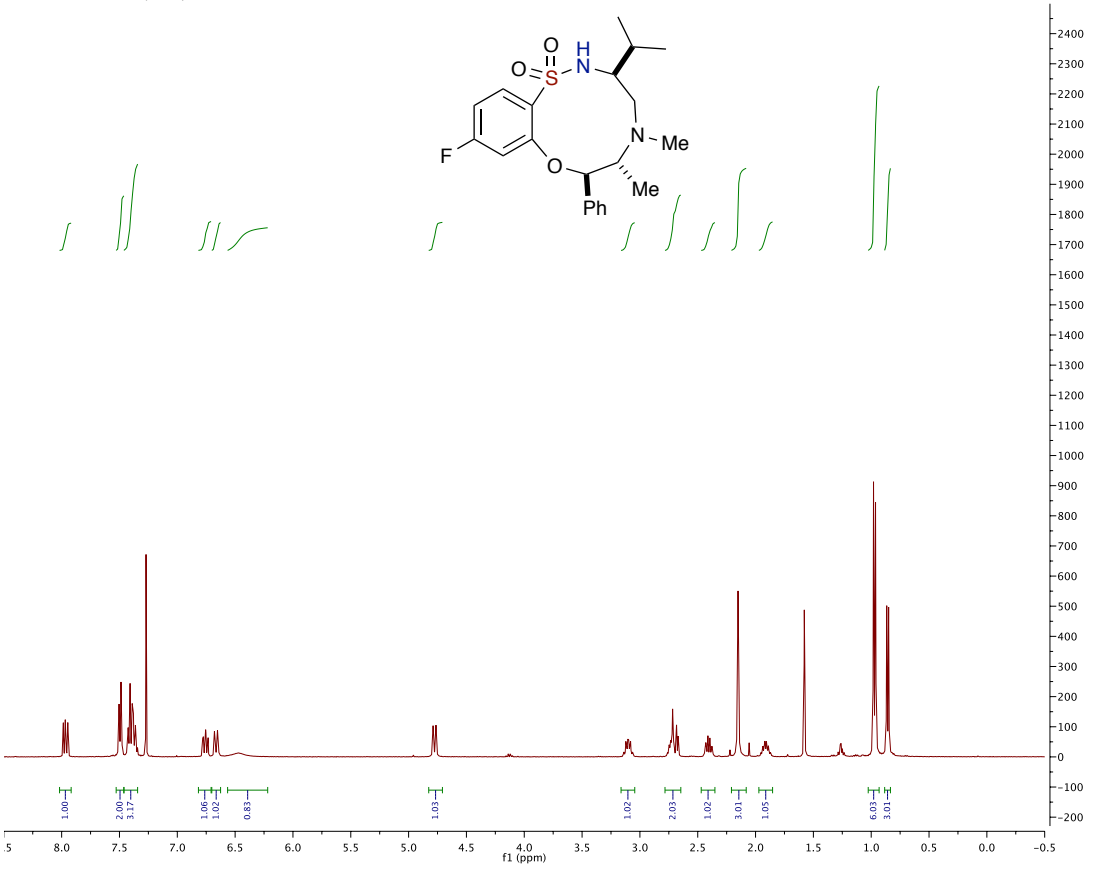
Figure 2. X-ray crystal structure of sultam **6p** where the thermal ellipsoids are set at a 50% probability level.



3*S*,6*S*,7*R*)-10-fluoro-3-isopropyl-5,6-dimethyl-7-phenyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathia-diazecine 1,1-dioxide (8a)



(3*S*,6*R*,7*R*)-10-fluoro-3-isopropyl-5,6-dimethyl-7-phenyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathiadiazecine 1,1-dioxide (8b)



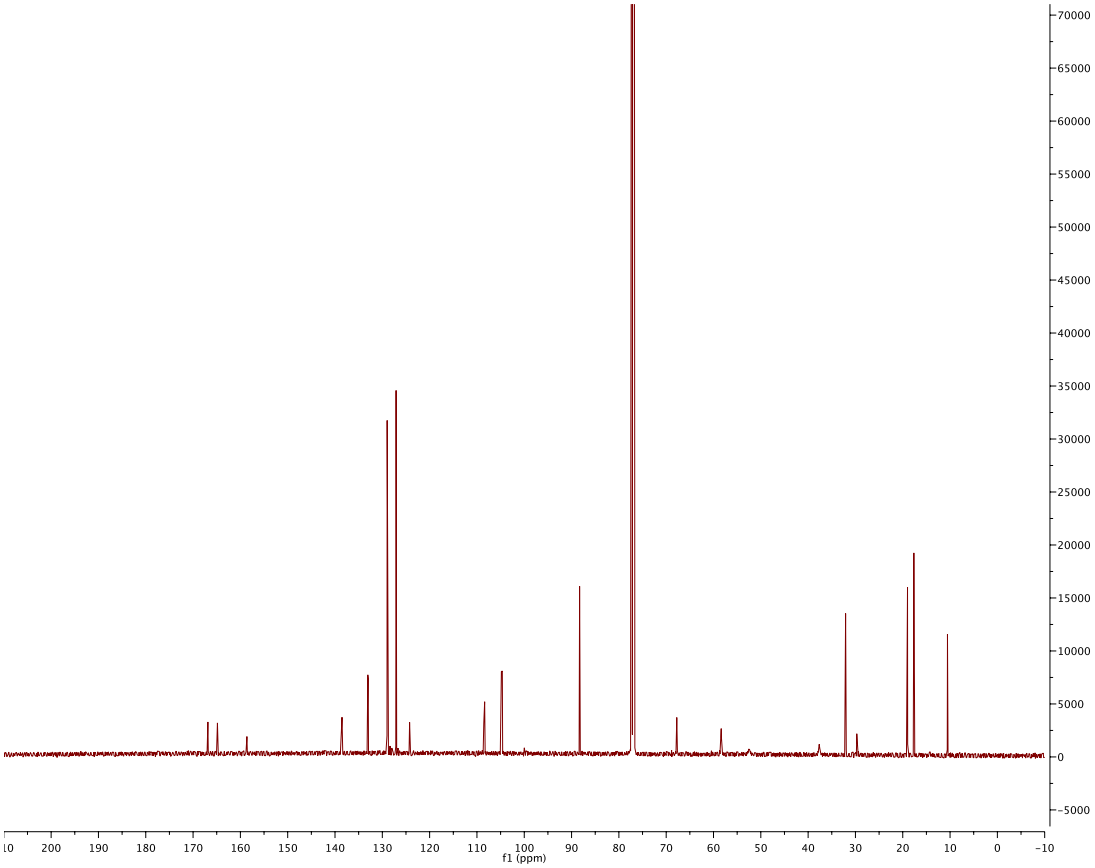
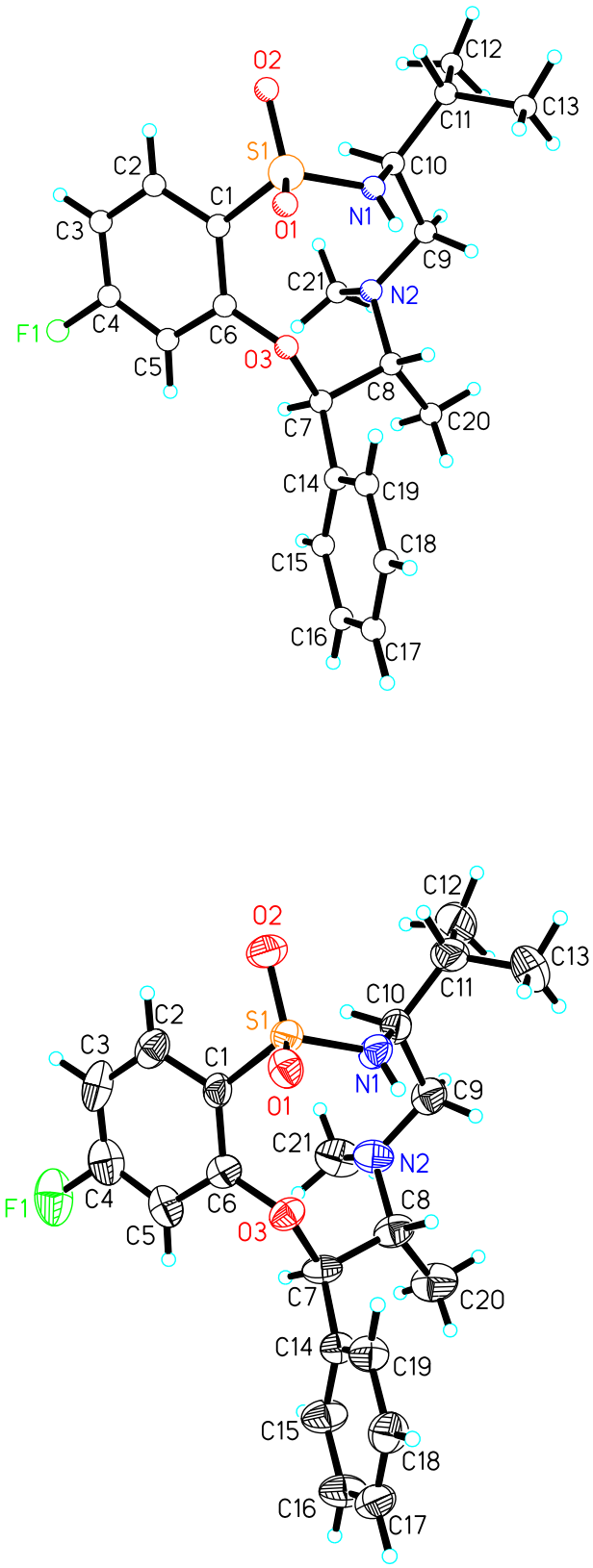
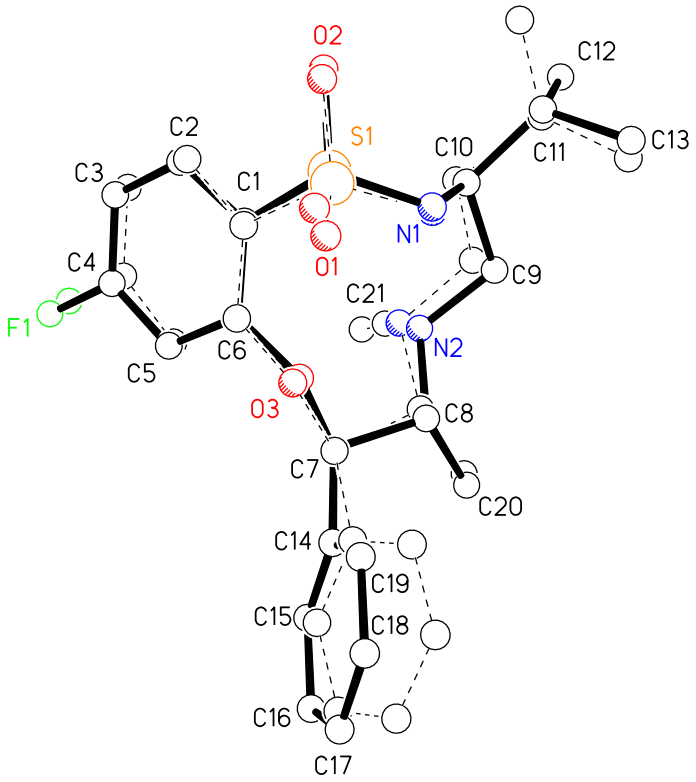
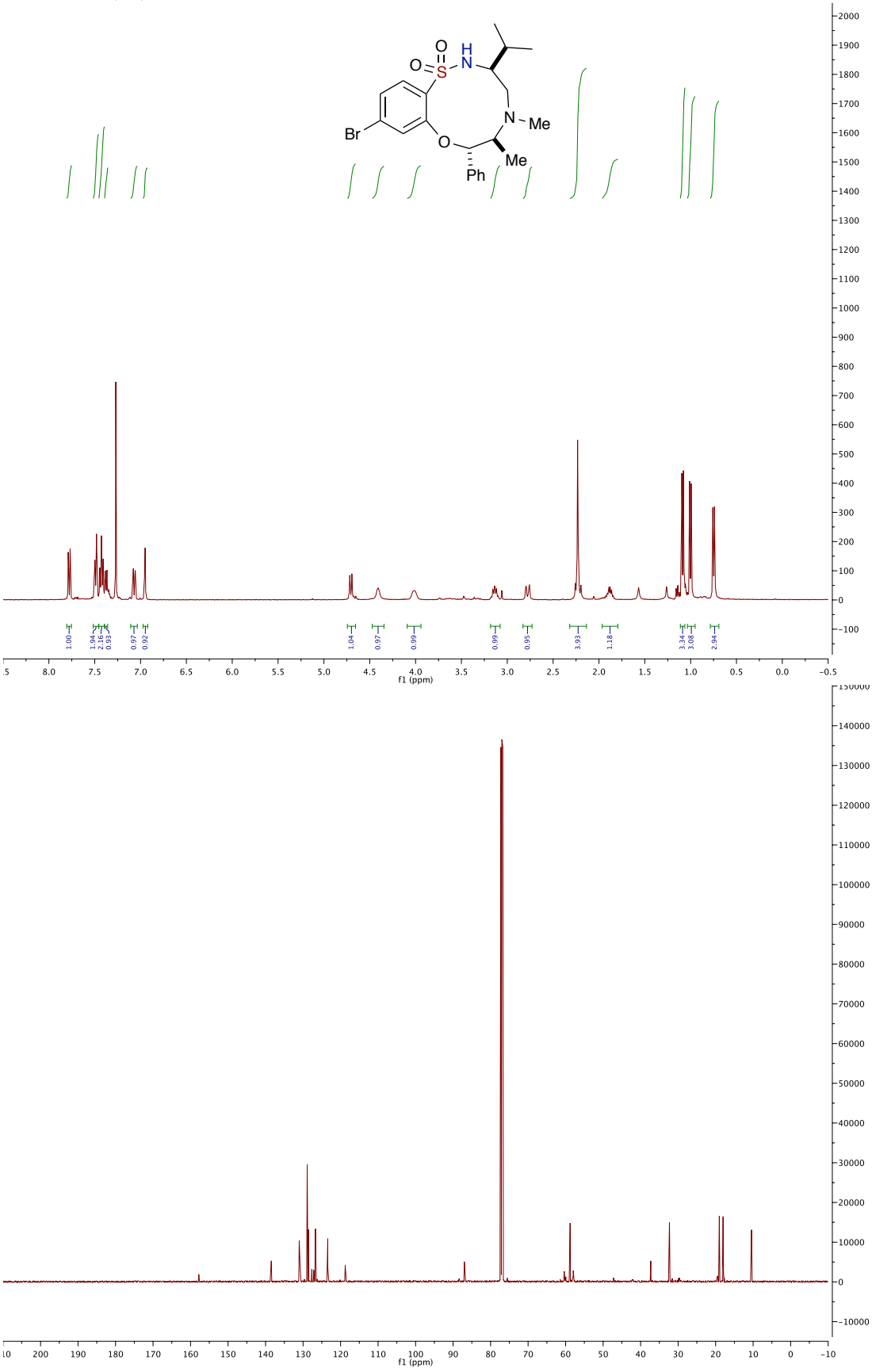


Figure 3. X-ray crystal structure of sultam **8b** where the thermal ellipsoids are set at a 50% probability level.

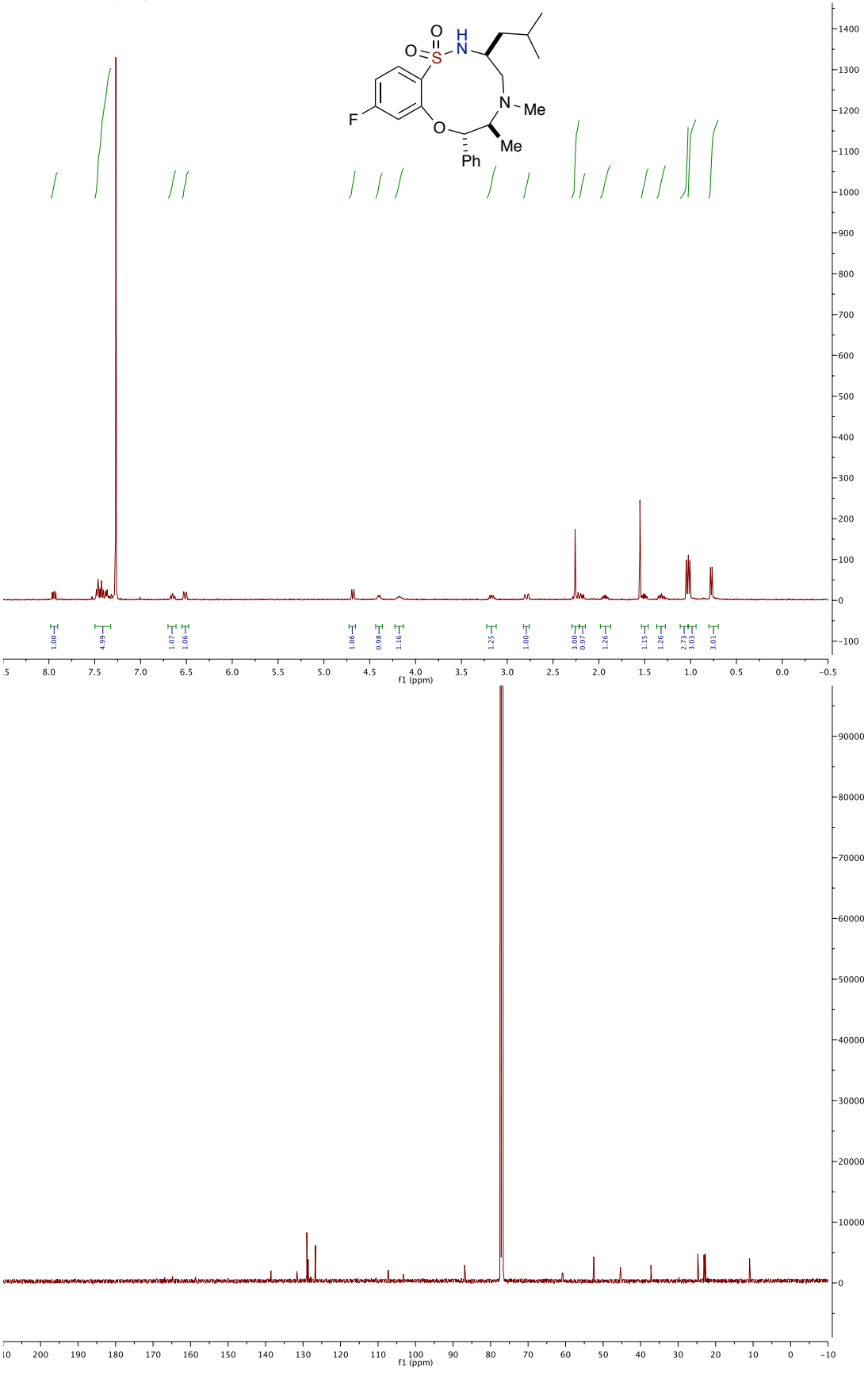



O2
C12
S1
C2
C10
C11
C13
C3
C1
N1
O1
C4
C9
C21
F1
N2
C6
C5
O3
C8
C7
C20
C14
C19
C15
C18
C16
C17

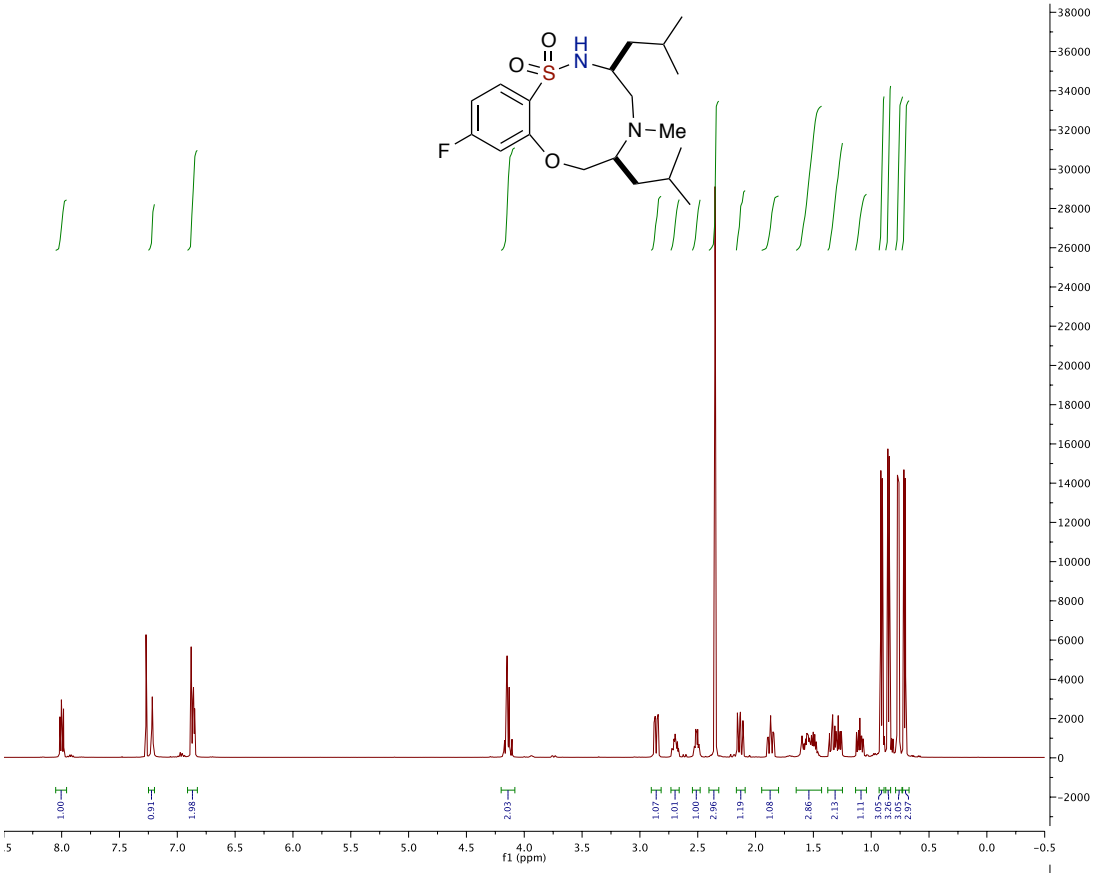
(3*S*,6*S*,7*S*)-10-bromo-3-isopropyl-5,6-dimethyl-7-phenyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathiadiazecine 1,1-dioxide (8c)

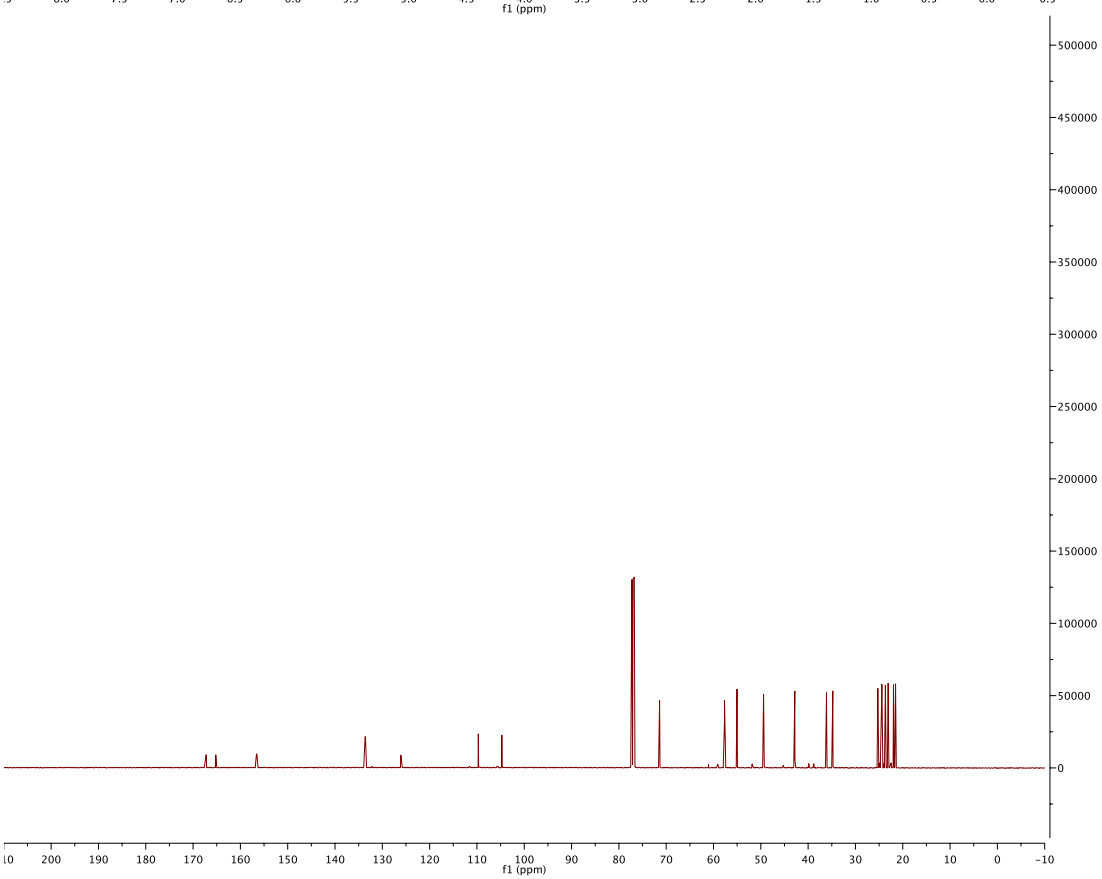


(3*S*,6*S*,7*S*)-10-fluoro-3-isobutyl-5,6-dimethyl-7-phenyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathiadiazecine 1,1-dioxide (8d)

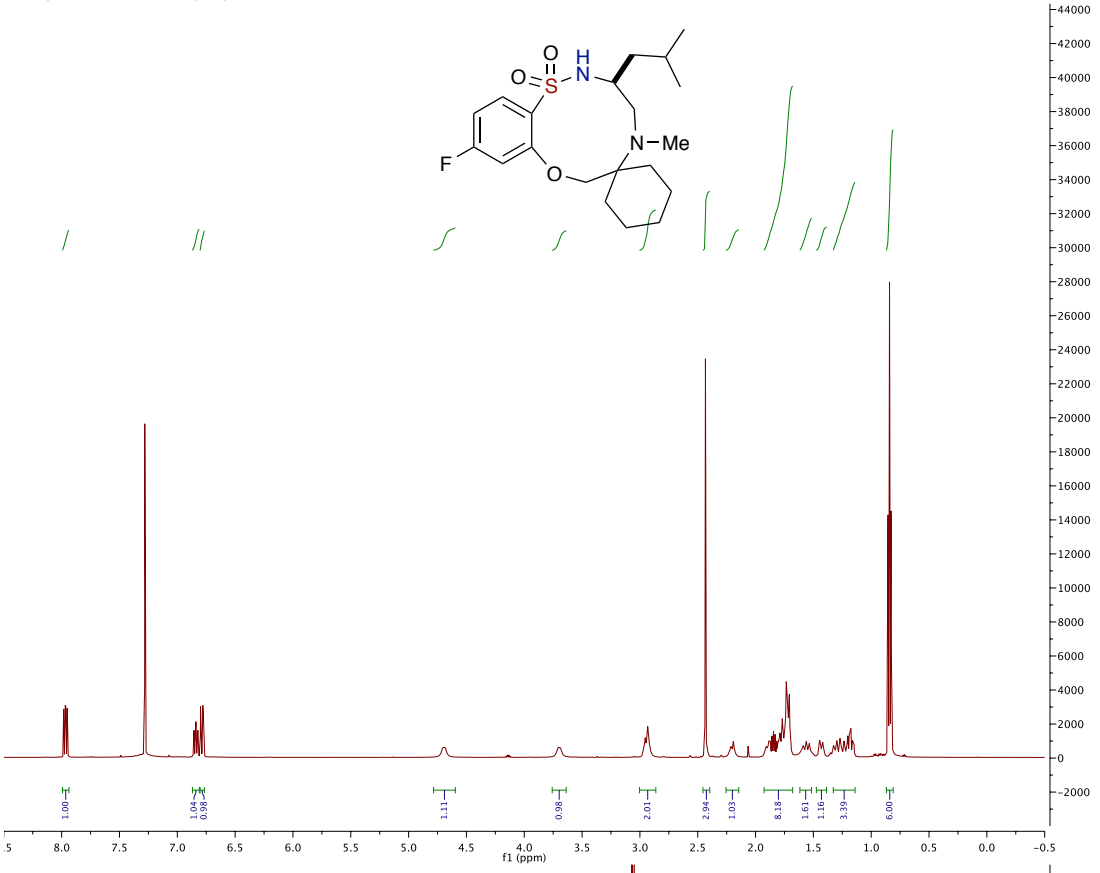


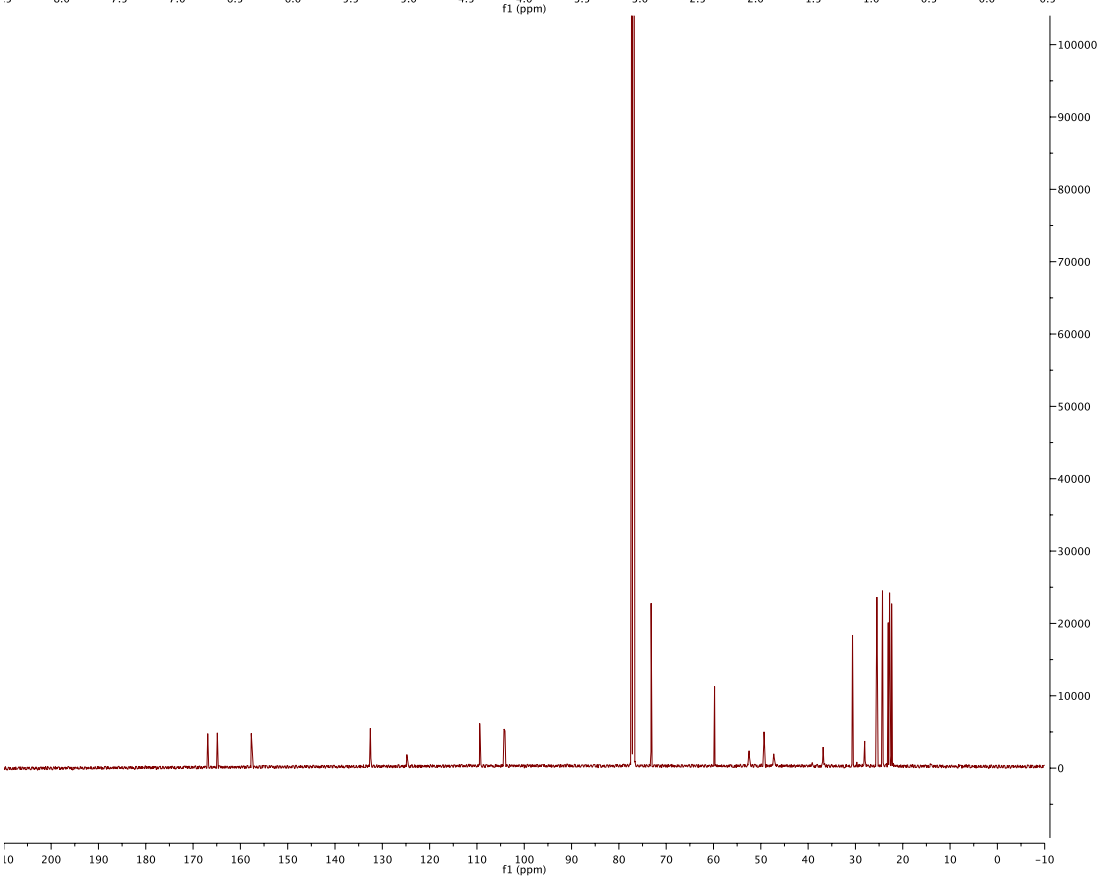
(3*S*,6*S*)-10-fluoro-3,6-diisobutyl-5-methyl-2,3,4,5,6,7-hexahydrobenzo[*b*][1,4,5,8]oxathiadiazecine-1,1-dioxide (8e)



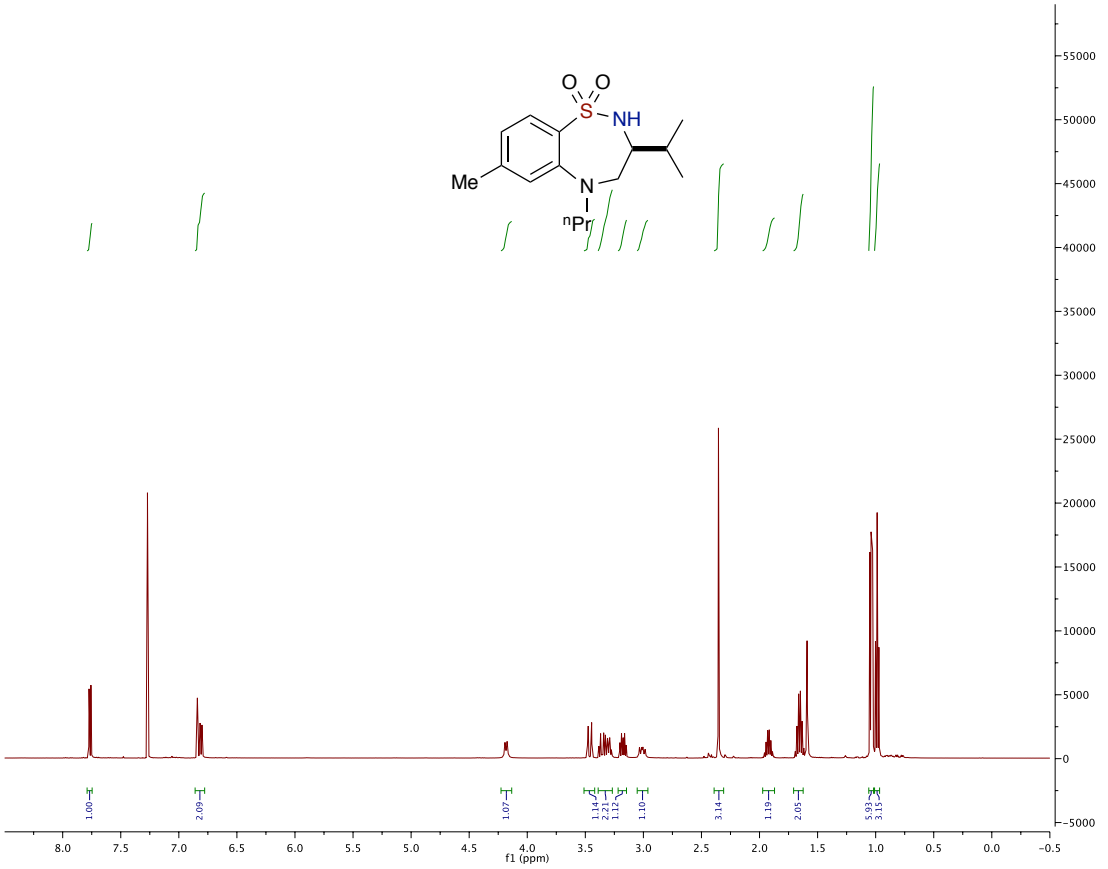


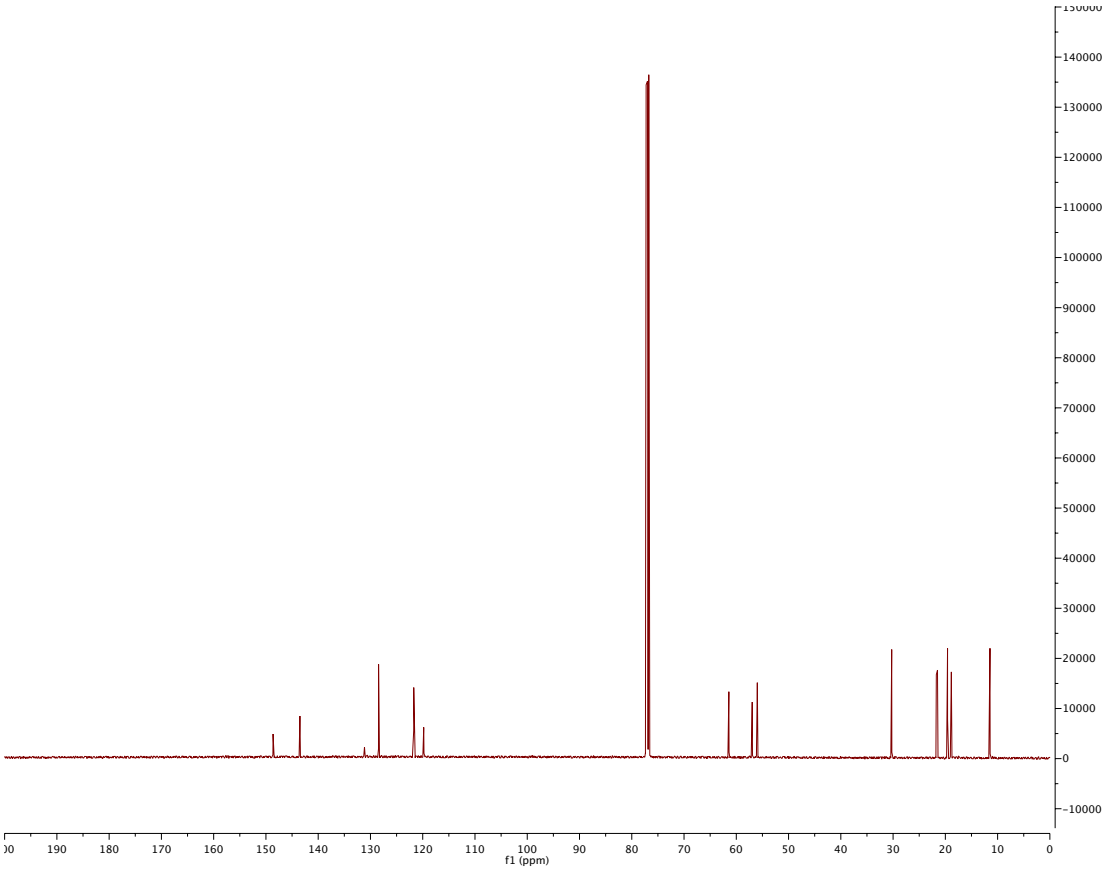
(*S*)-10-fluoro-3-isobutyl-5-methyl-3,4,5,7-tetrahydro-2*H*-spiro[benzo[*b*][1,4,5,8]oxathiadiazecine-6,1'-cyclohexane] 1,1-dioxide (8f)



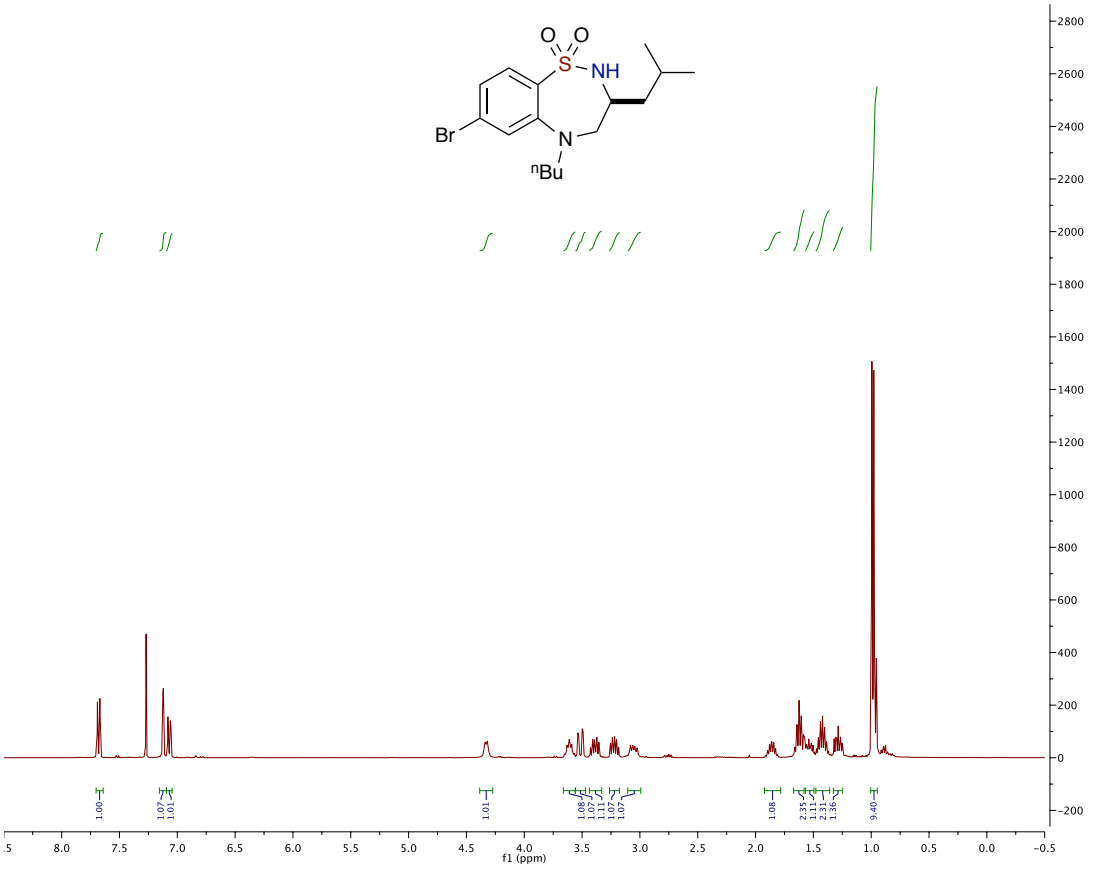


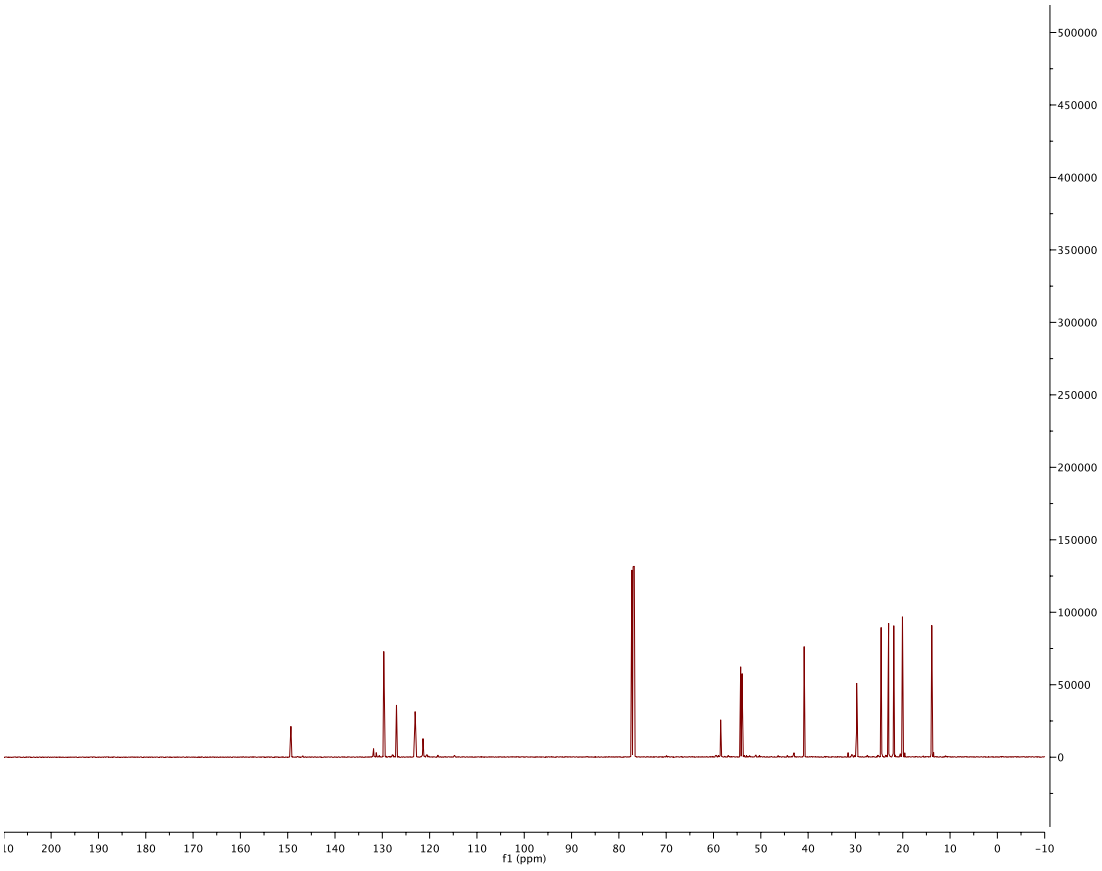
(*S*)-3-isopropyl-7-methyl-5-propyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10a)



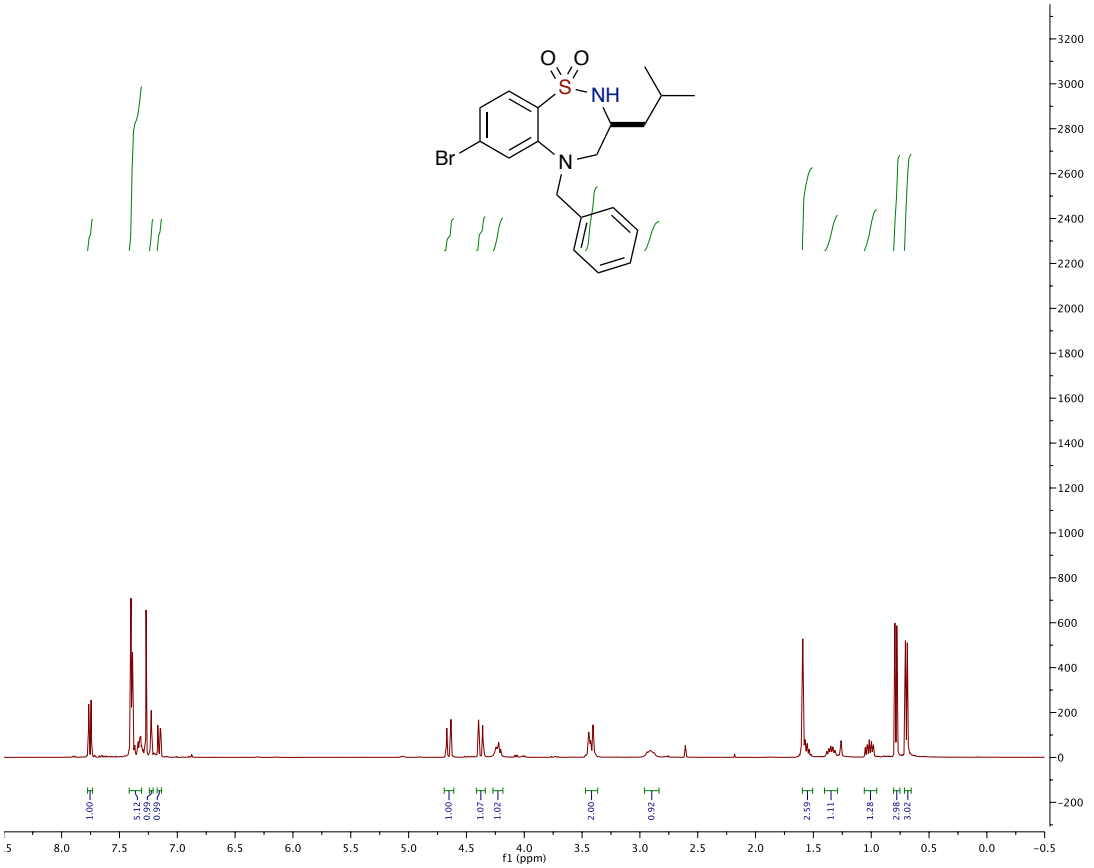


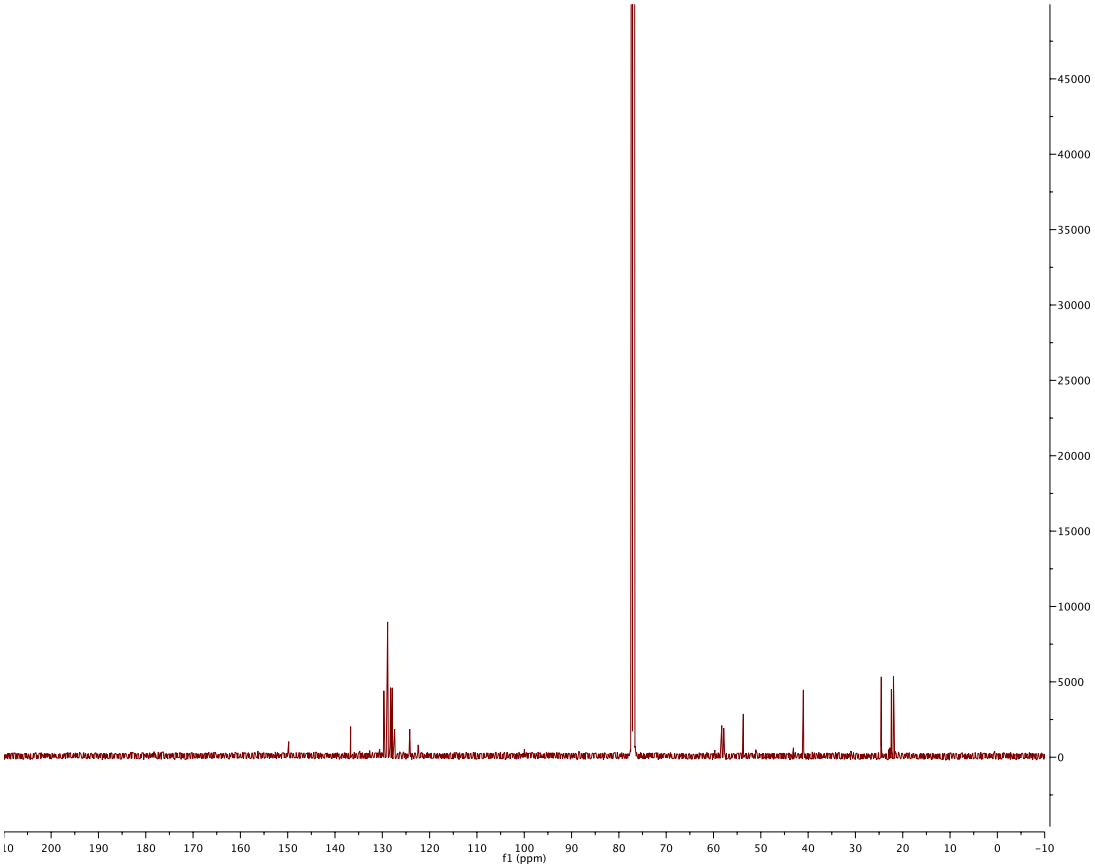
(*S*)-7-bromo-5-butyl-3-isobutyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10b)



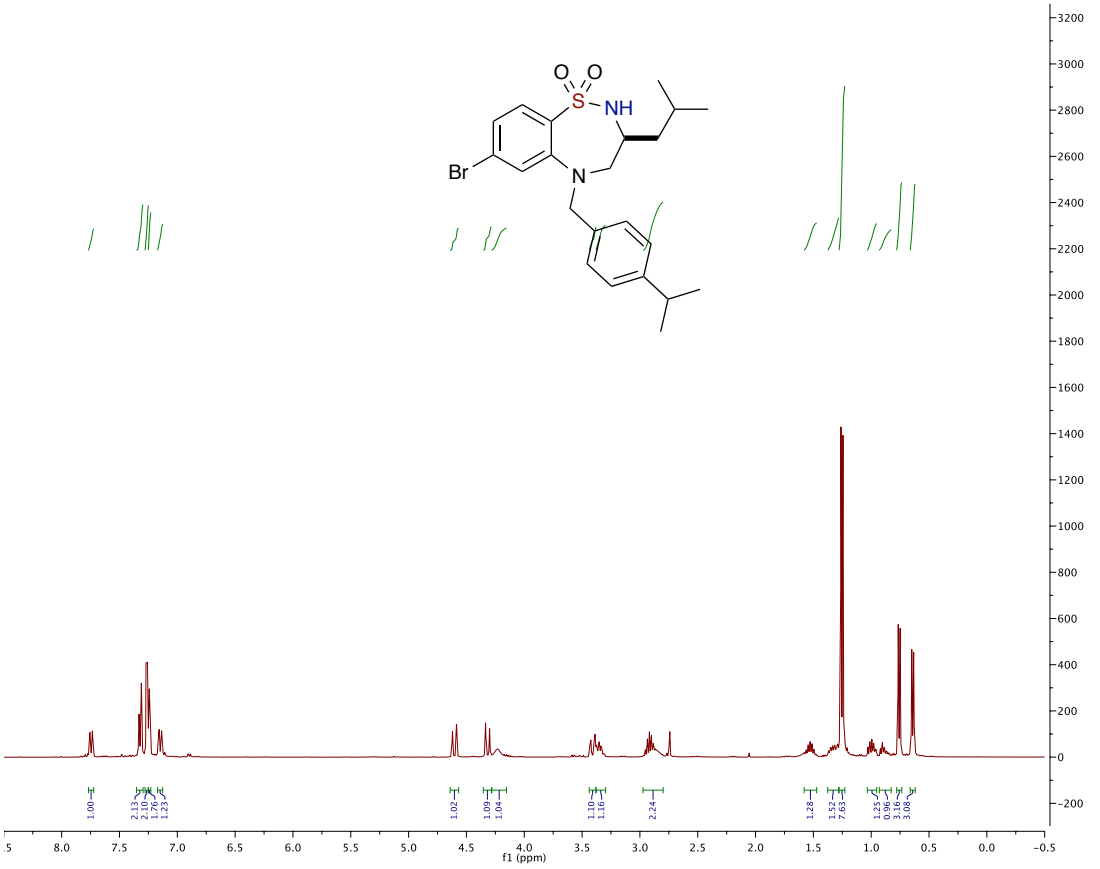


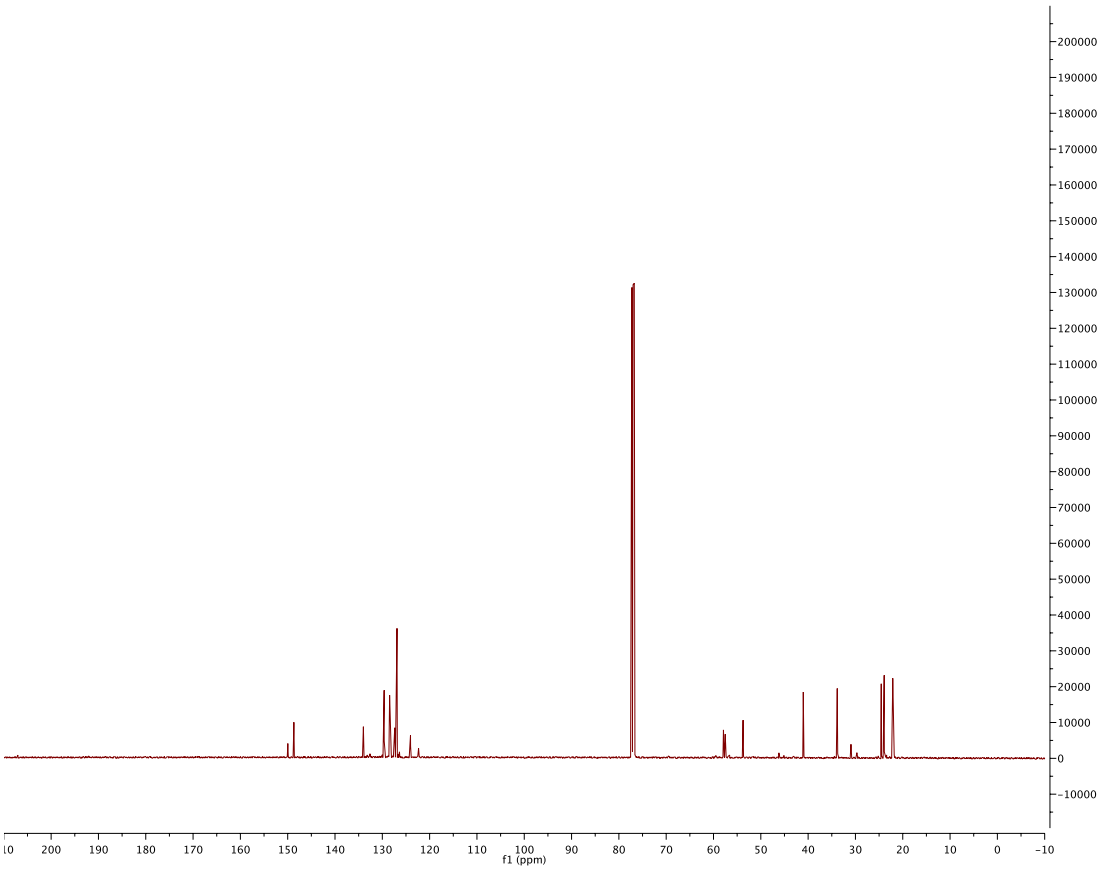
(*S*)-5-benzyl-7-bromo-3-isobutyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10c)



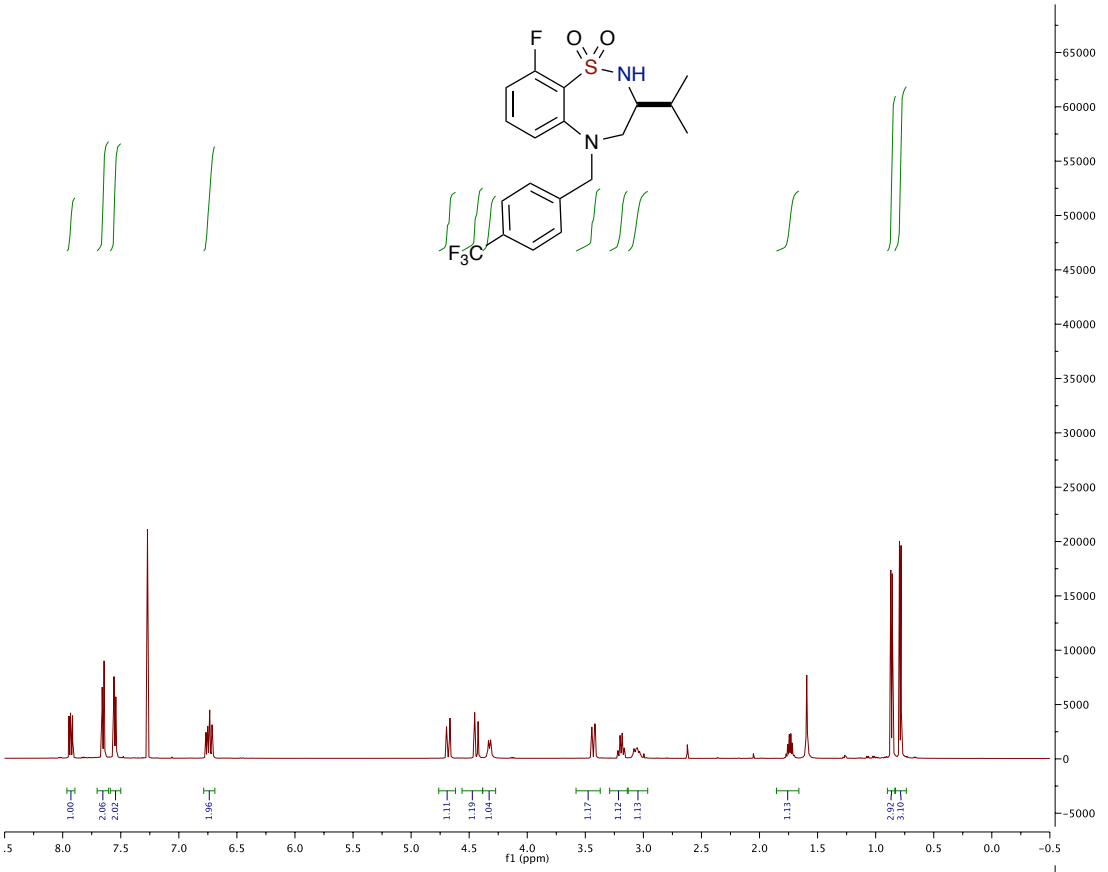


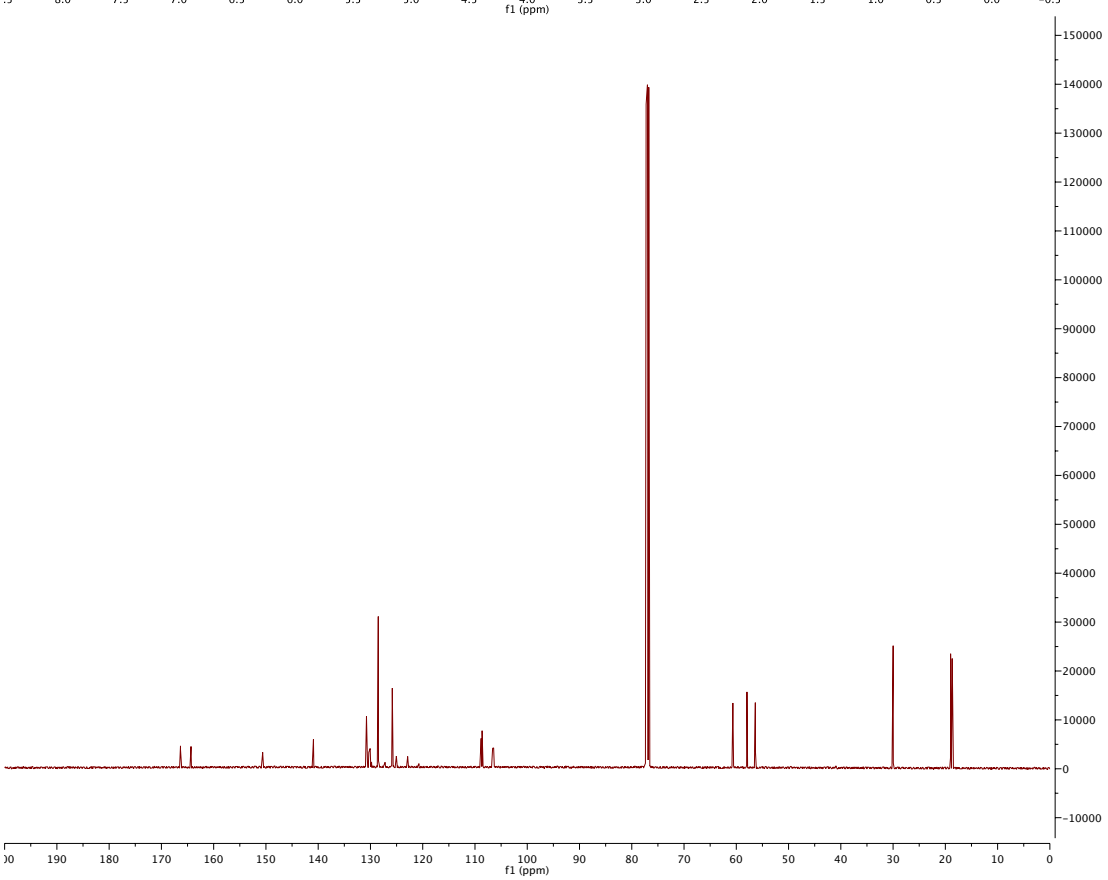
(*S*)-7-bromo-3-isobutyl-5-(4-isopropylbenzyl)-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10d)



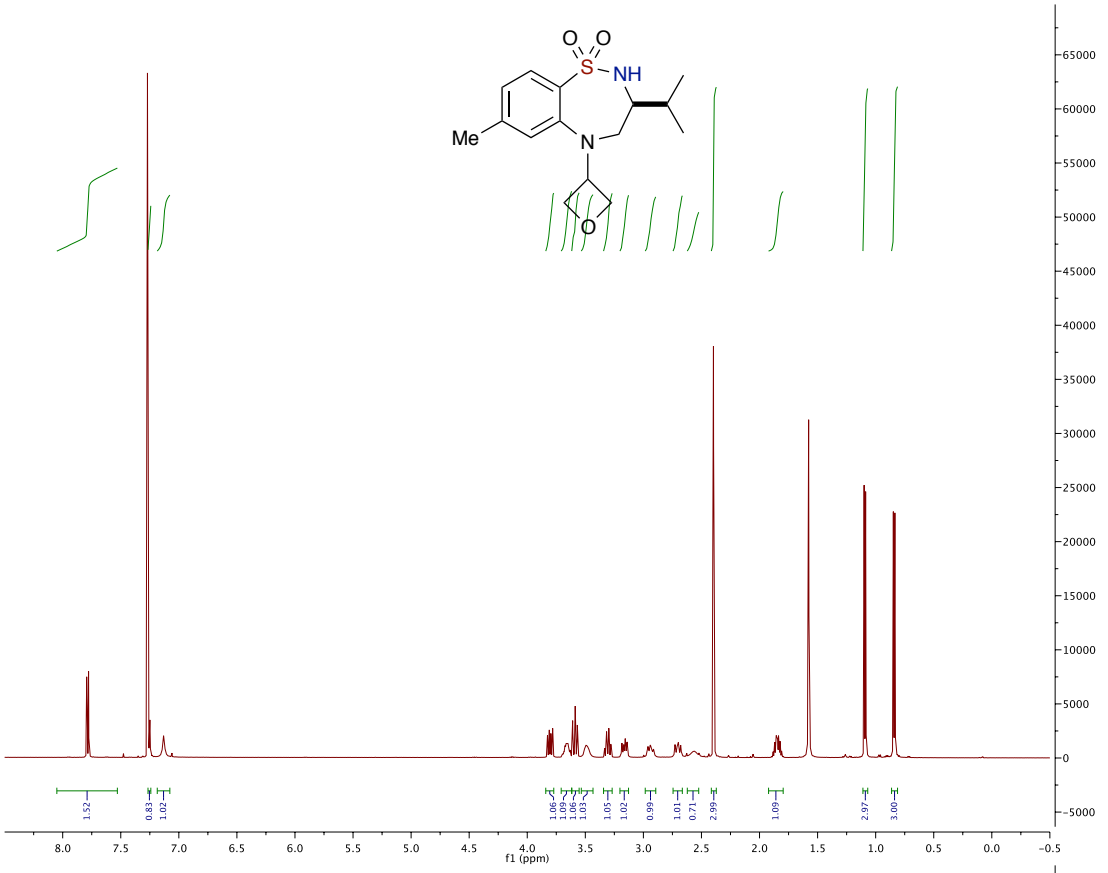


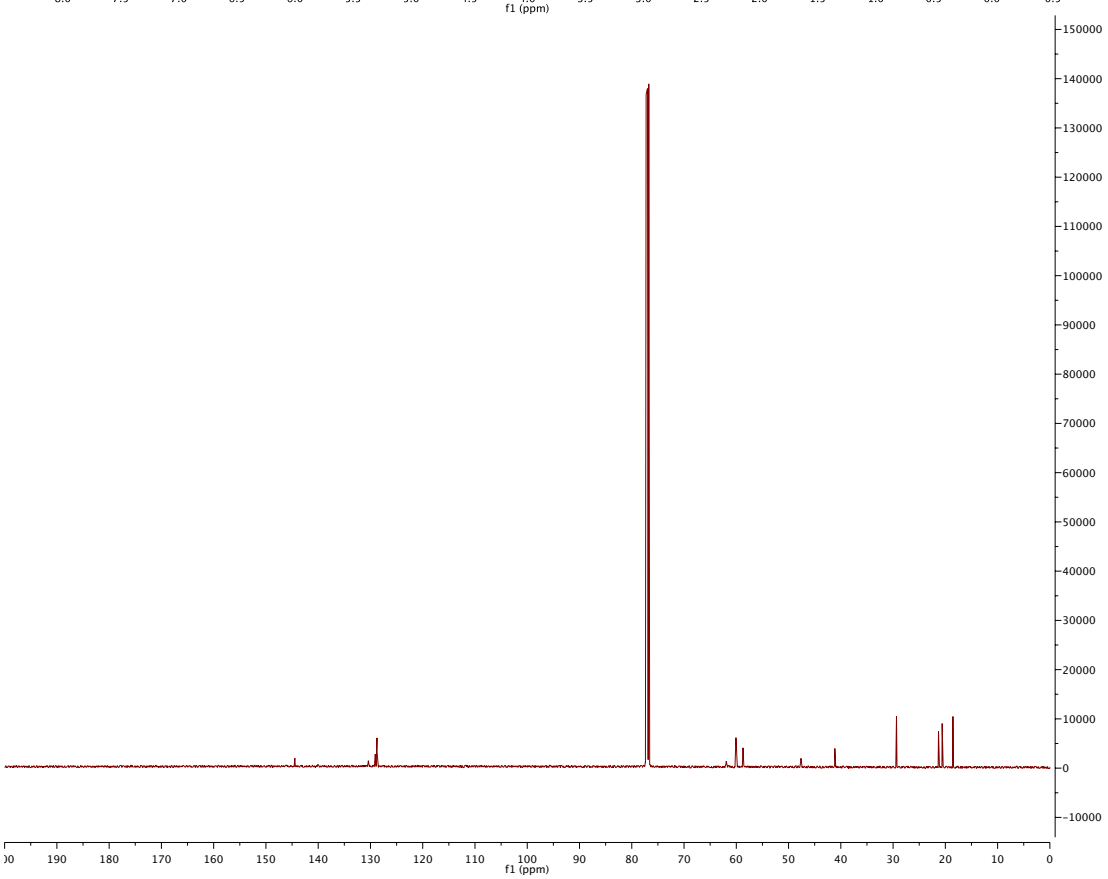
(*S*)-9-fluoro-3-isopropyl-5-(4-(trifluoromethyl)benzyl)-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10e)



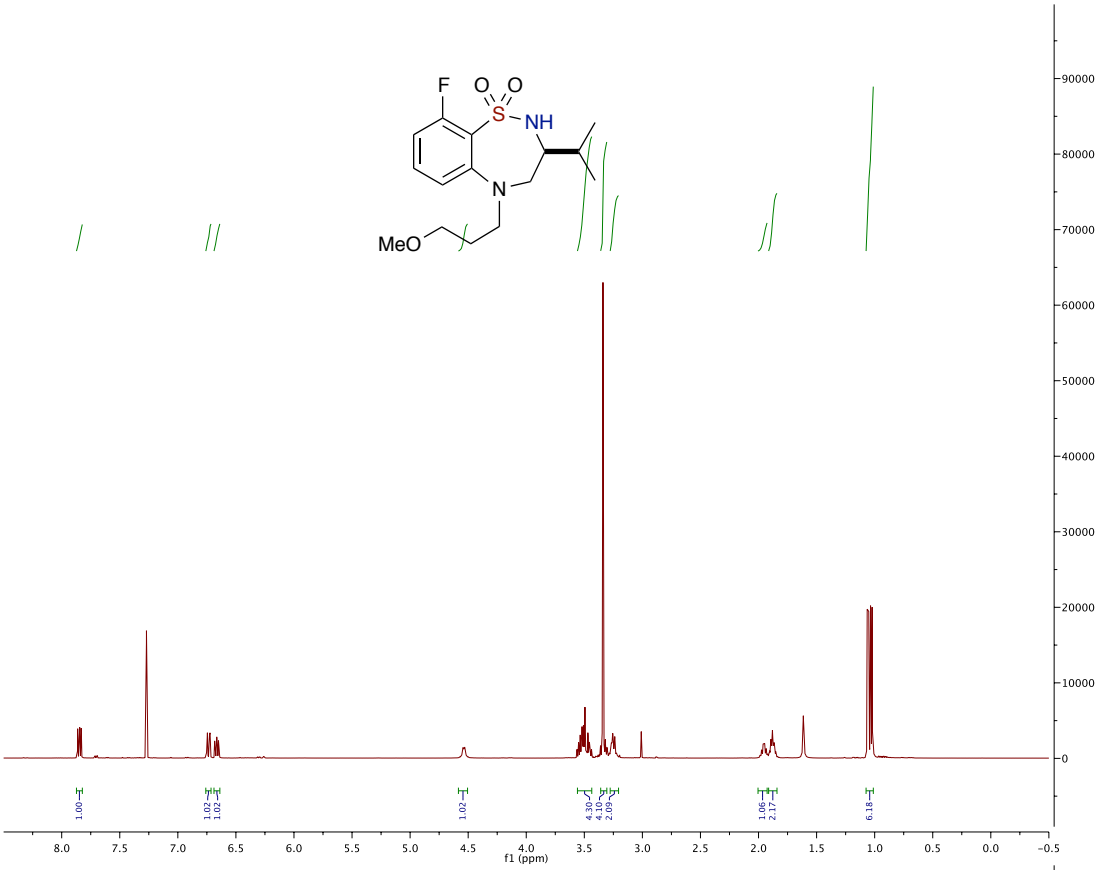


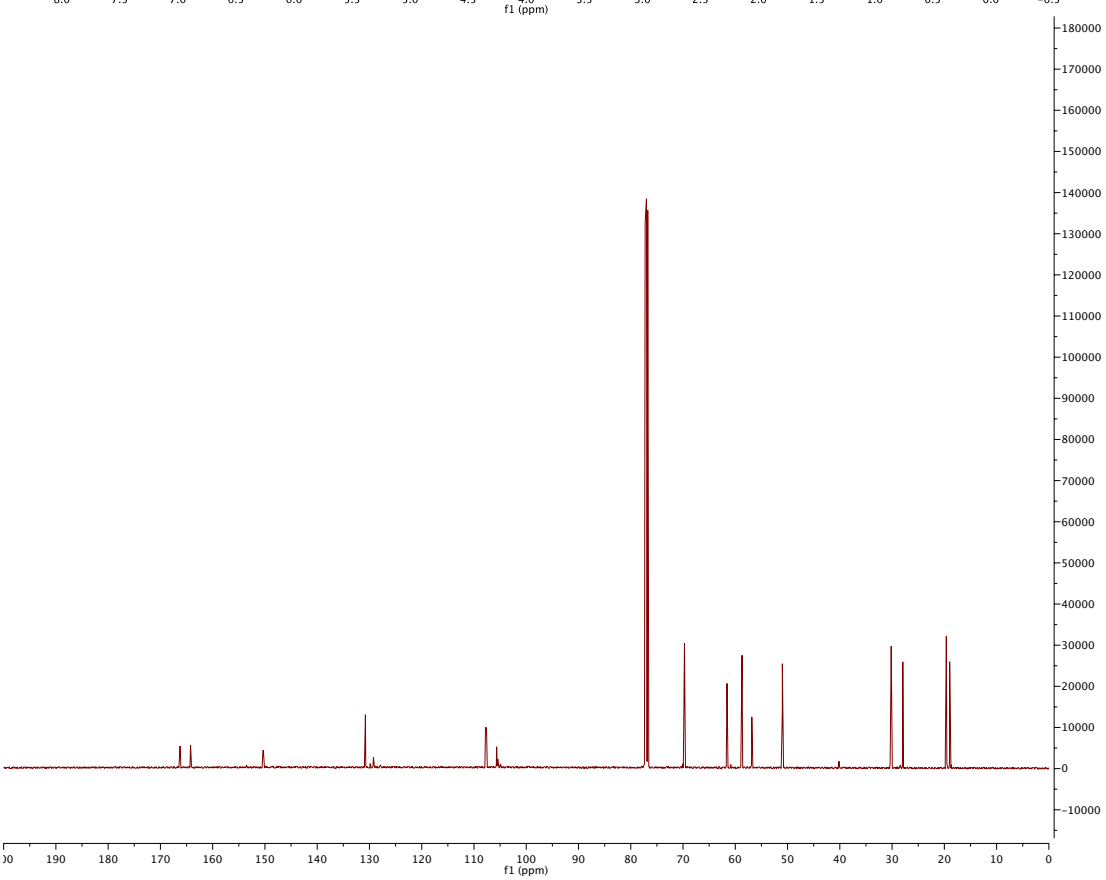
(*S*)-3-isopropyl-7-methyl-5-(oxetan-3-yl)-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10f)



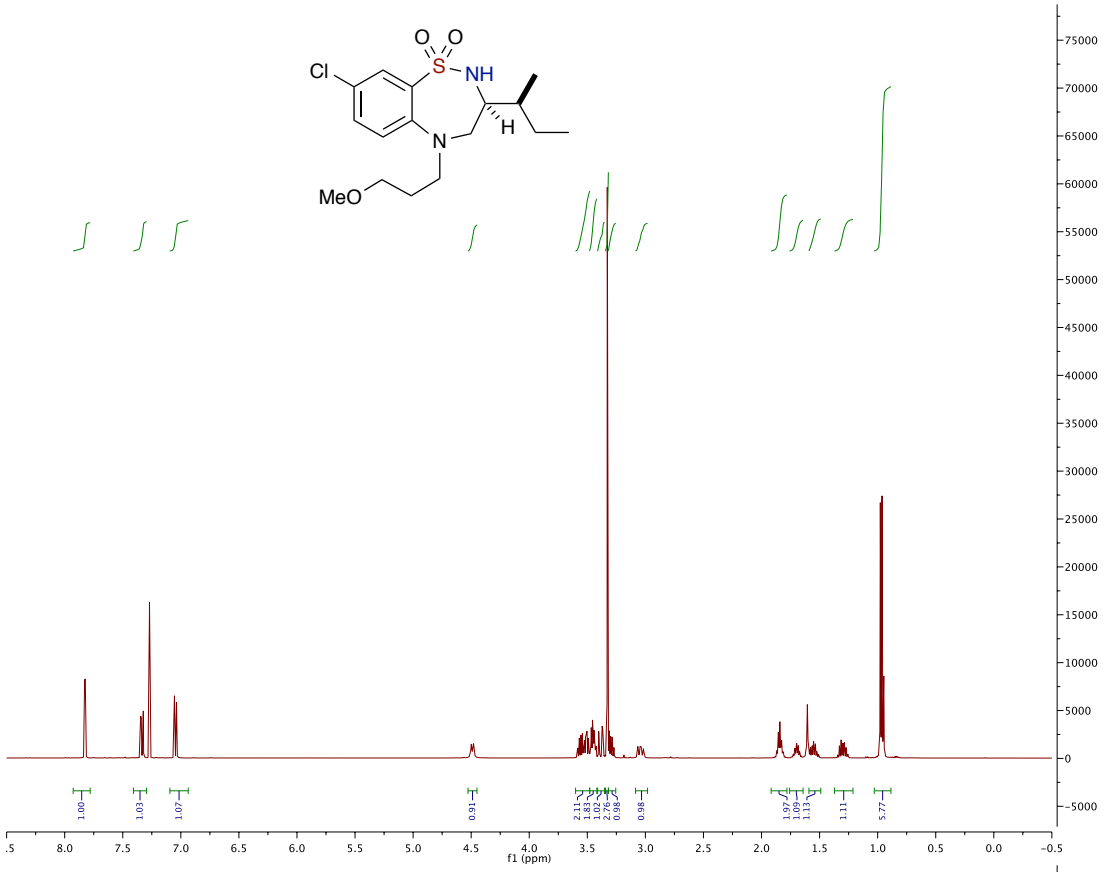


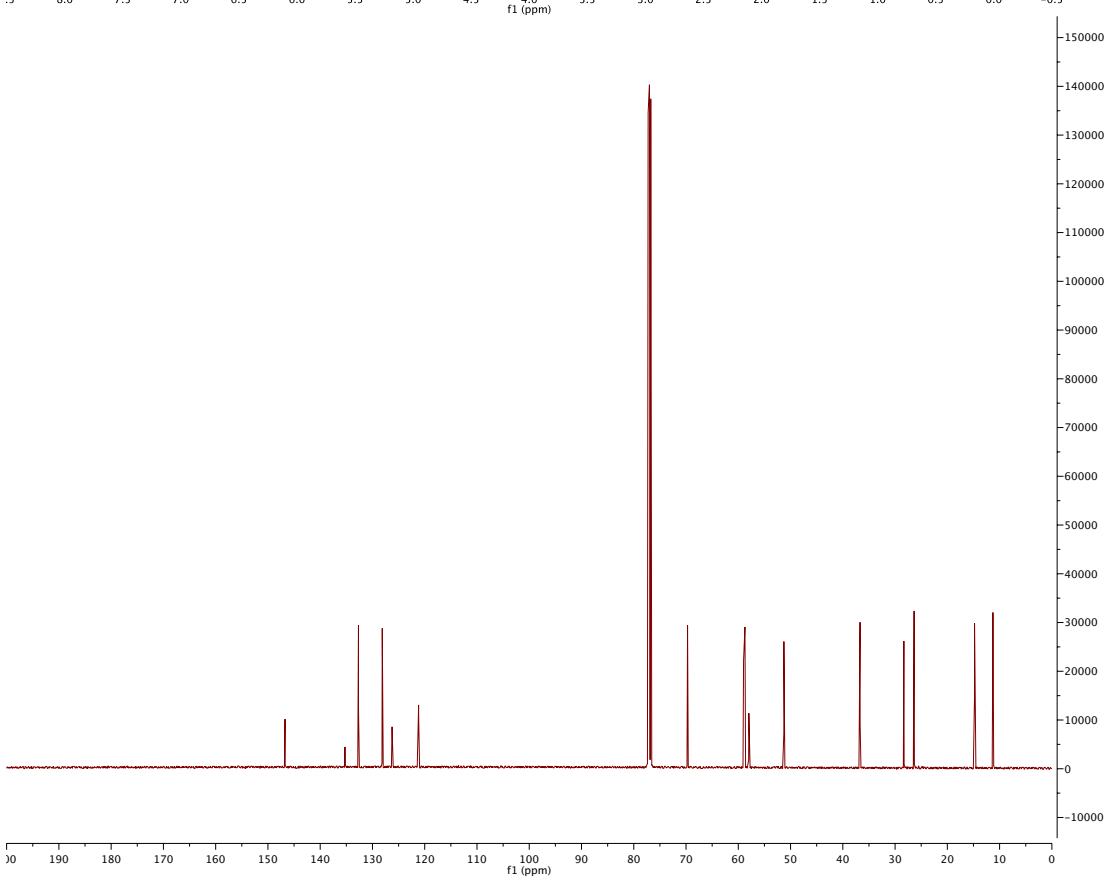
(*S*)-9-fluoro-3-isopropyl-5-(3-methoxypropyl)-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10g)



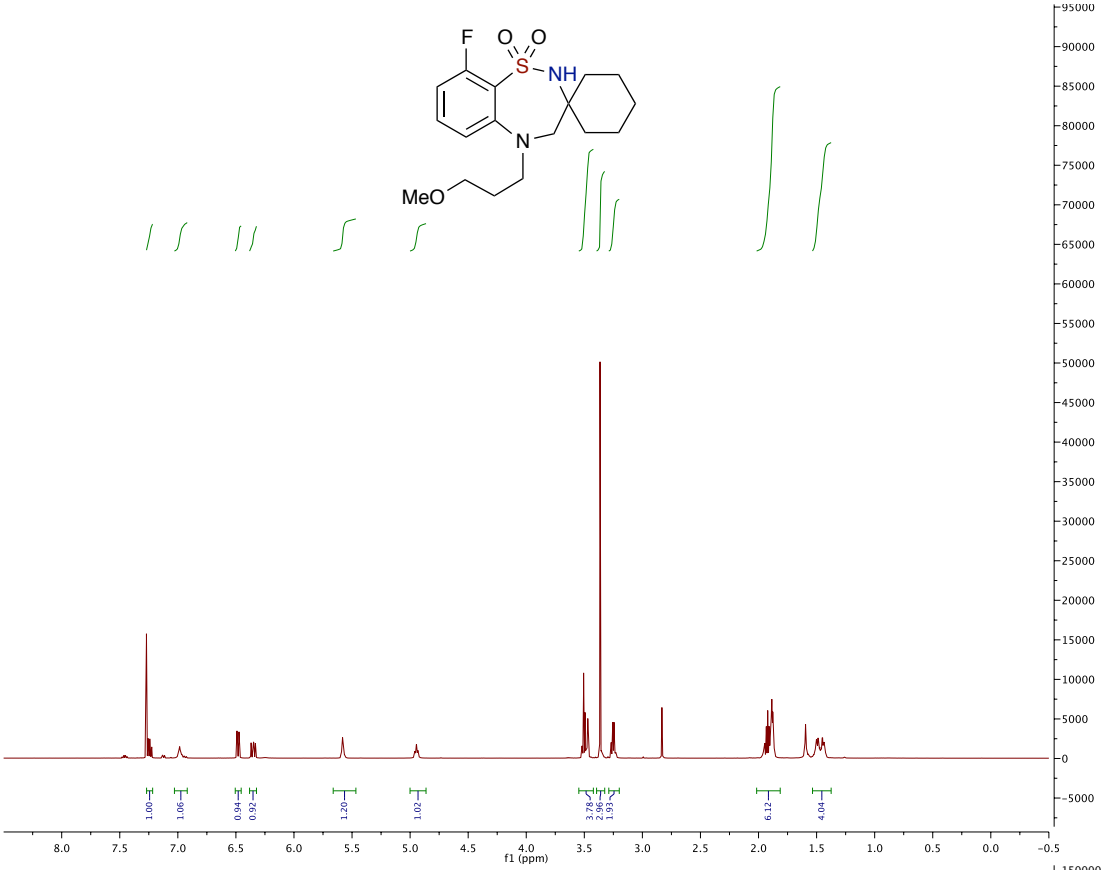


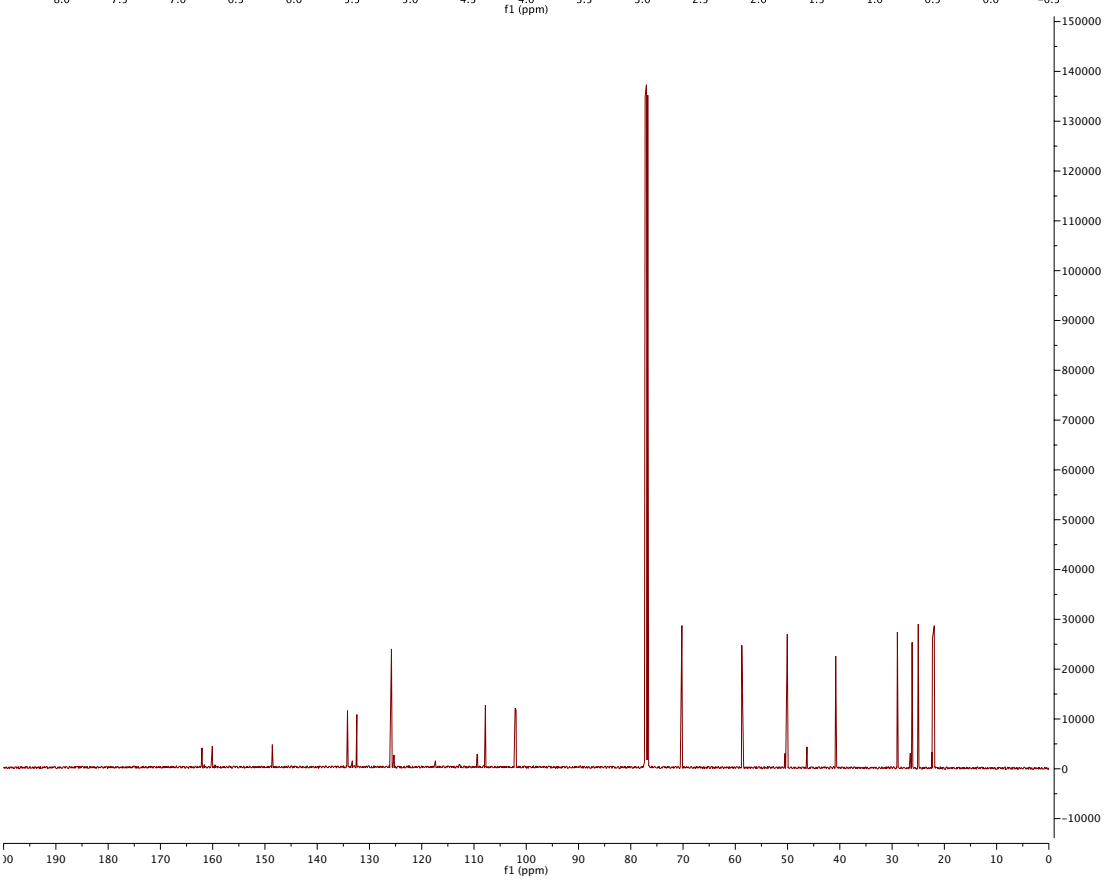
(*S*)-3-((*S*)-*sec*-butyl)-8-chloro-5-(3-methoxypropyl)-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10h)



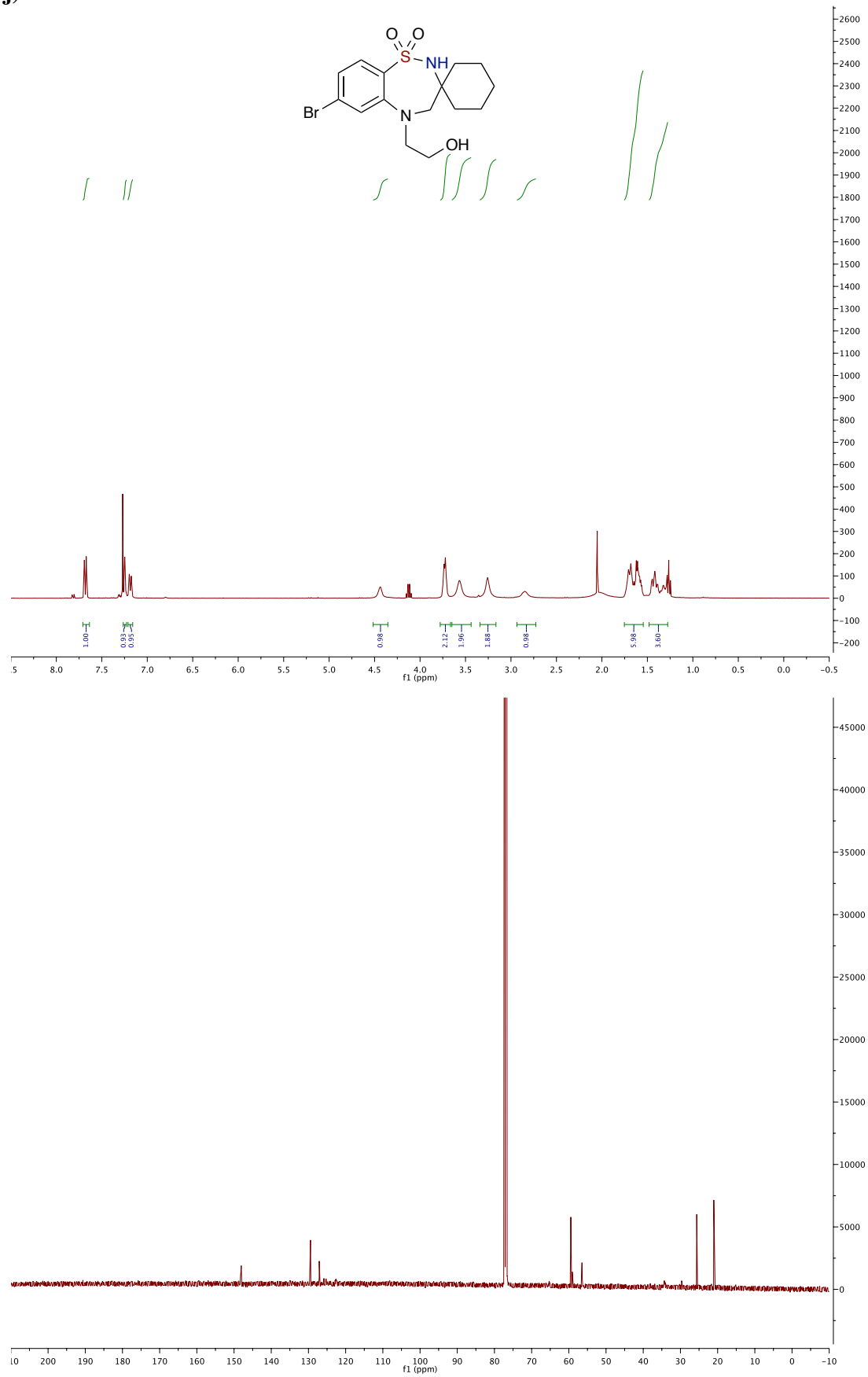


9-fluoro-5-(3-methoxypropyl)-4,5-dihydro-2*H*-spiro[benzo[*f*][1,2,5]thiadiazepine-3,1'-cyclohexane] 1,1-dioxide (10i)

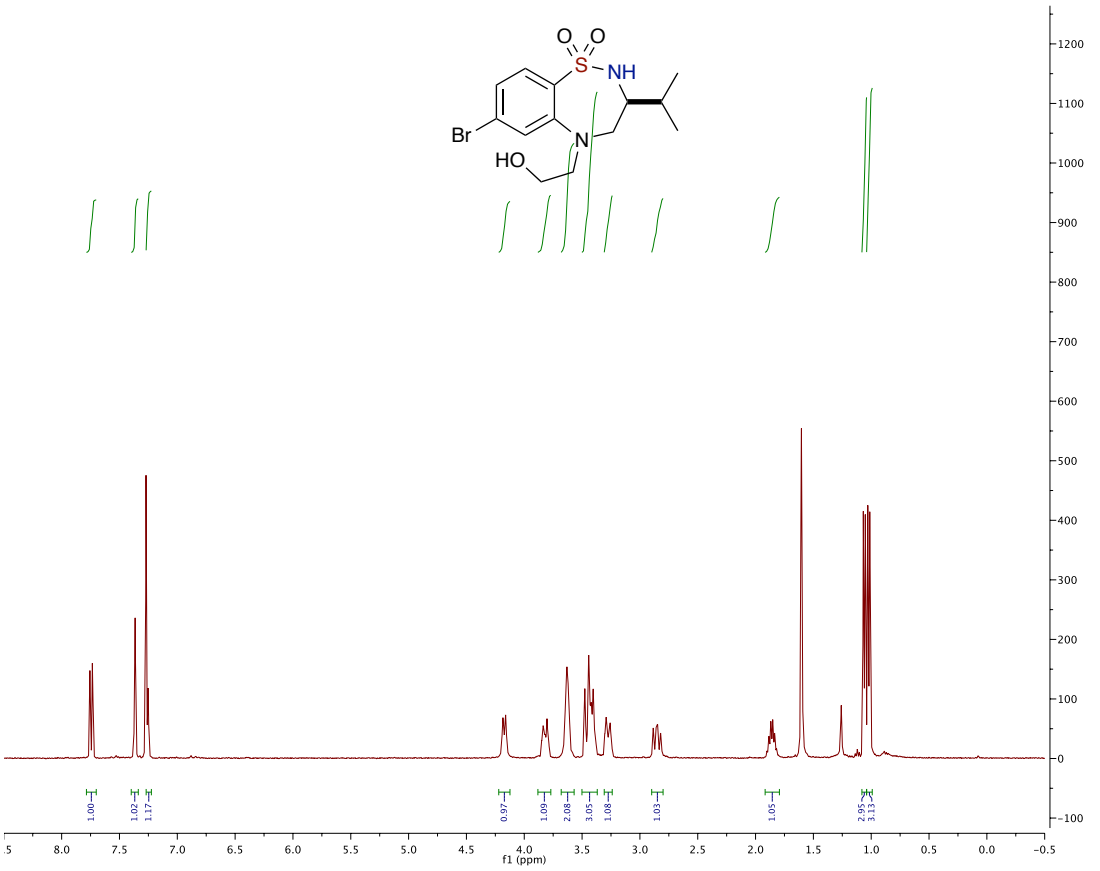


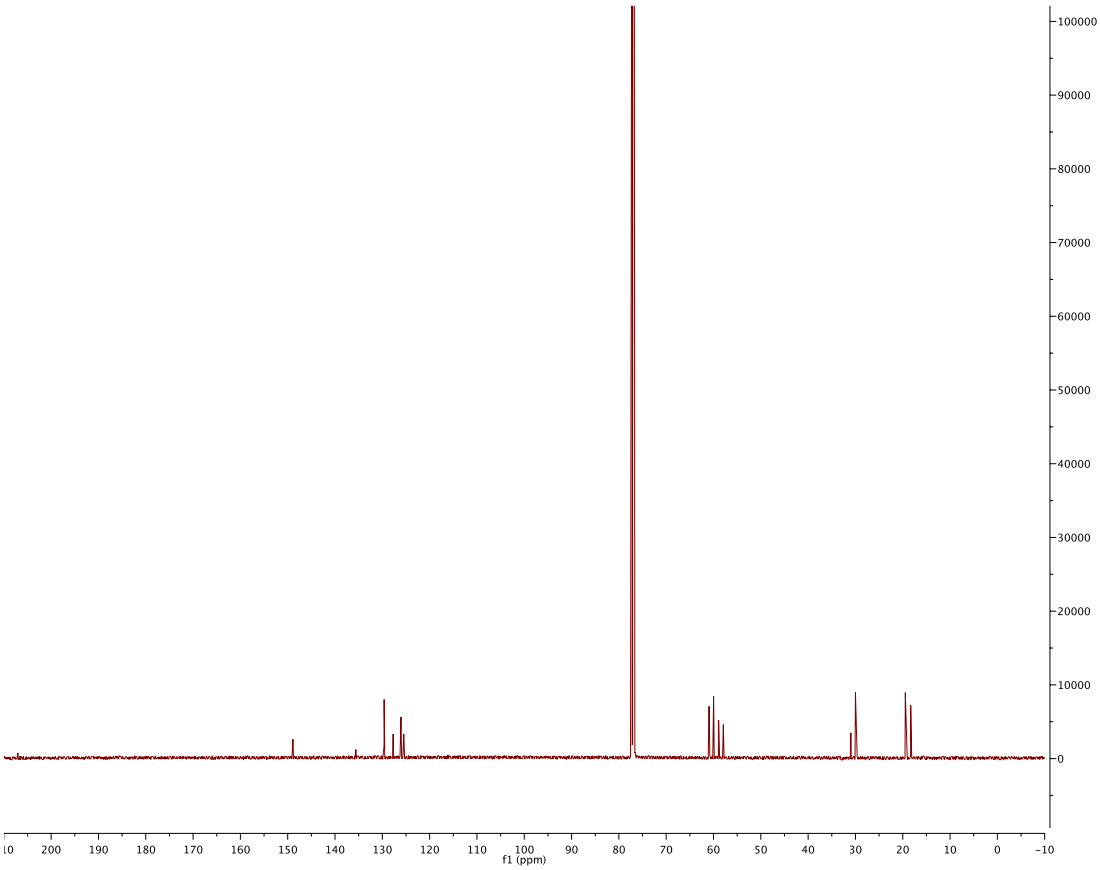


7-bromo-5-(2-hydroxyethyl)-4,5-dihydro-2*H*-spiro[benzo[*f*][1,2,5]thiadiazepine-3,1'-cyclohexane] 1,1-dioxide (10j)

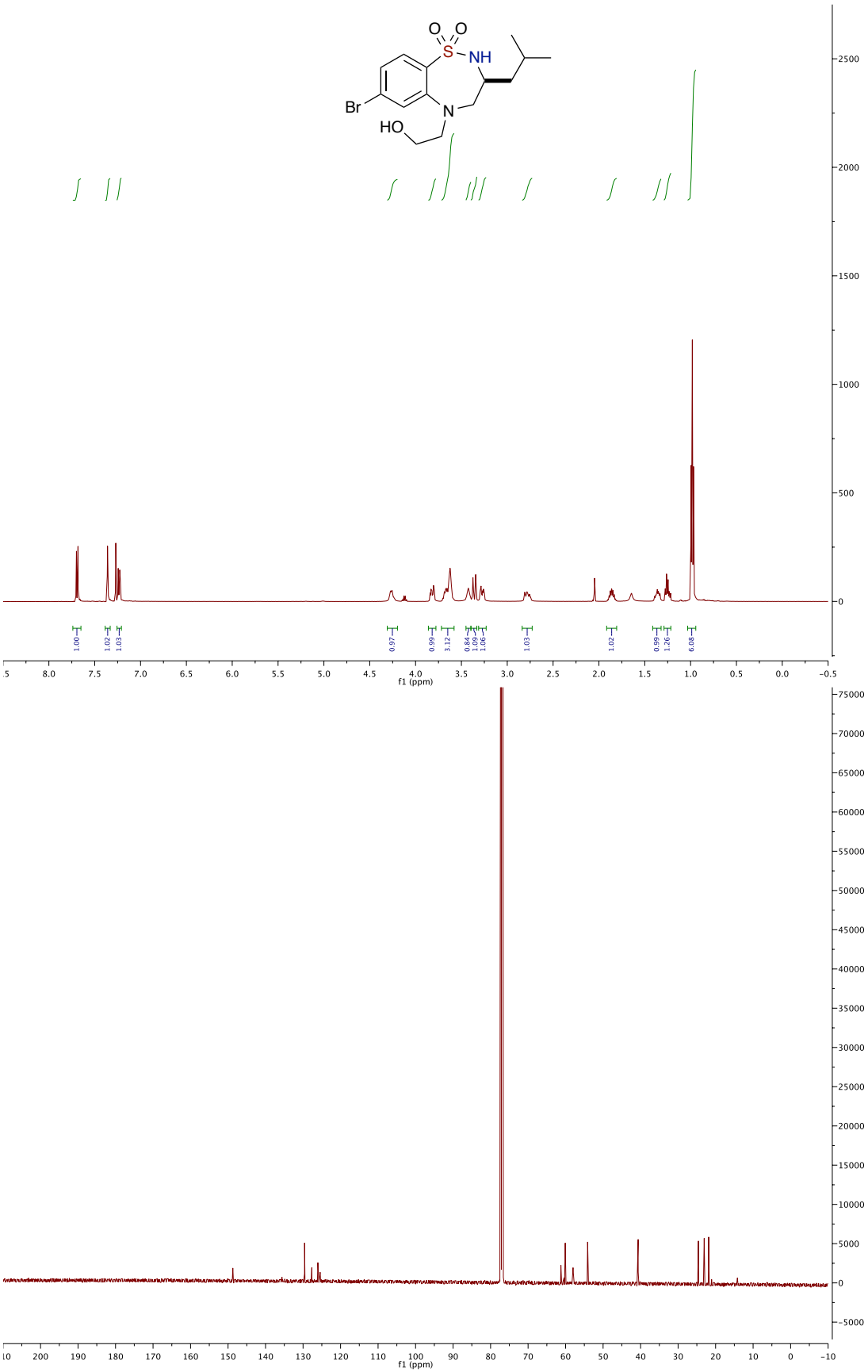


(*S*)-7-bromo-5-(2-hydroxyethyl)-3-isopropyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10k)





(*S*)-7-bromo-5-(2-hydroxyethyl)-3-isobutyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10l)



(*S*)-7-bromo-5-((*R*)-1-hydroxypropan-2-yl)-3-isobutyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10m)

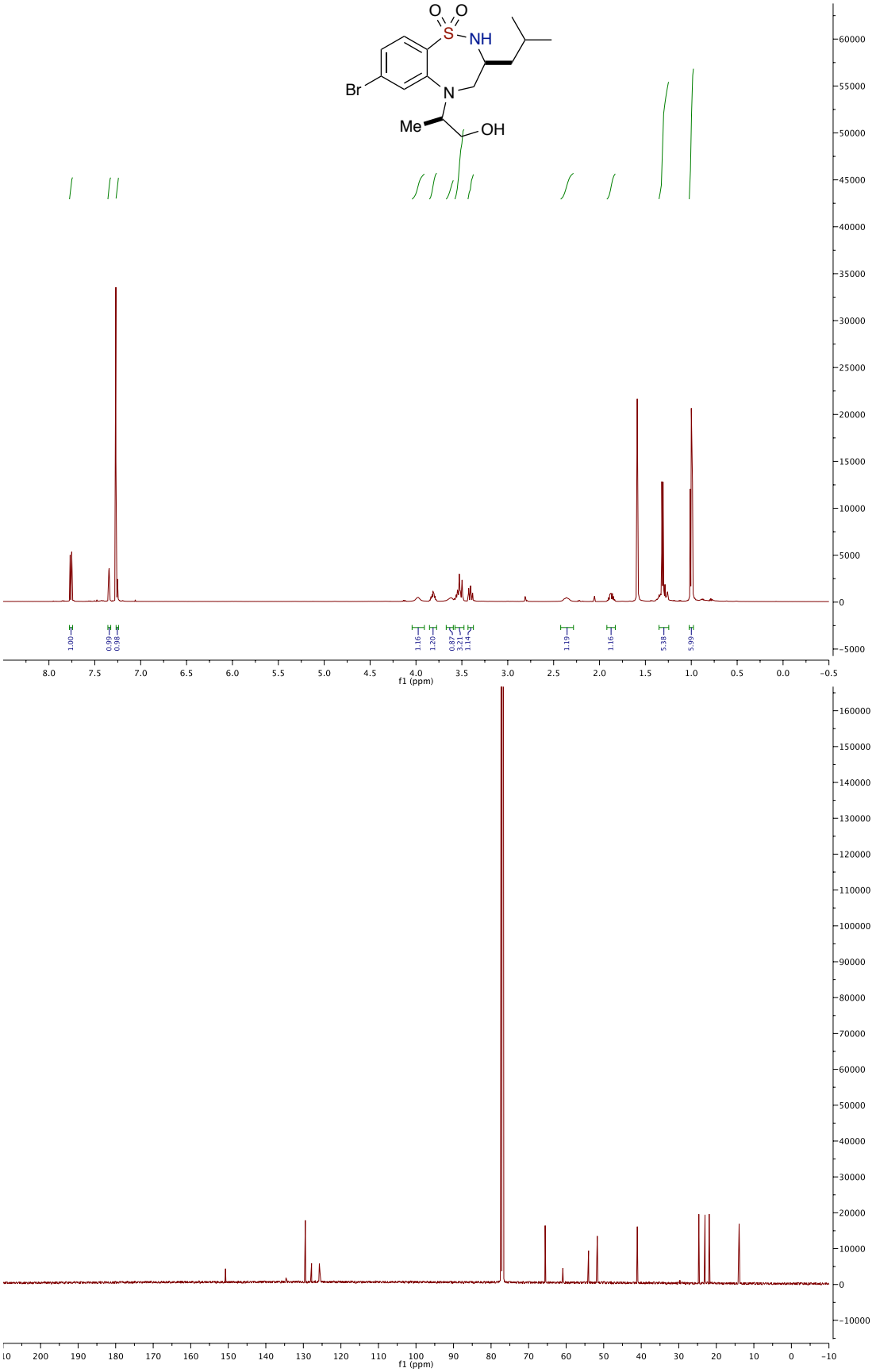
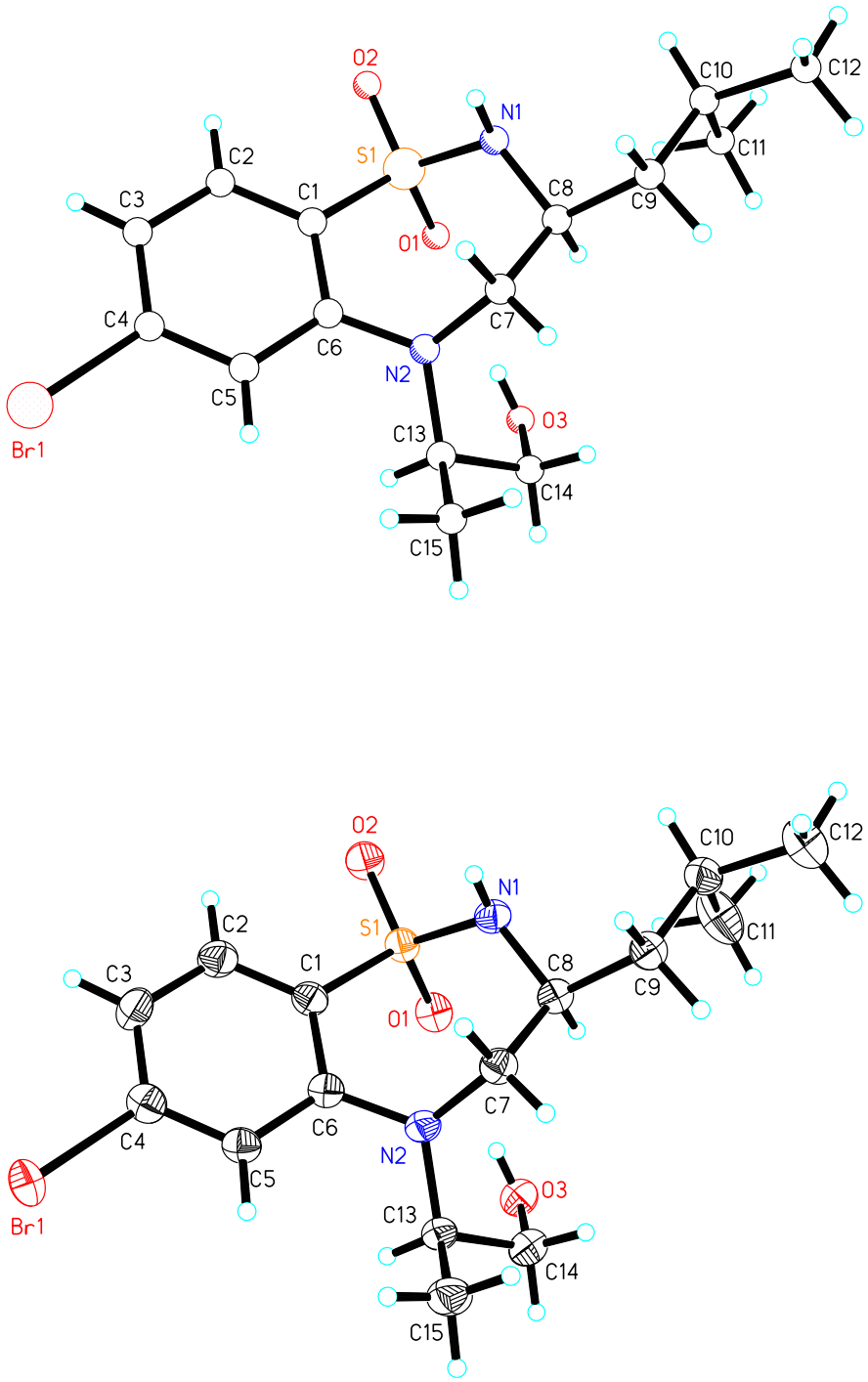
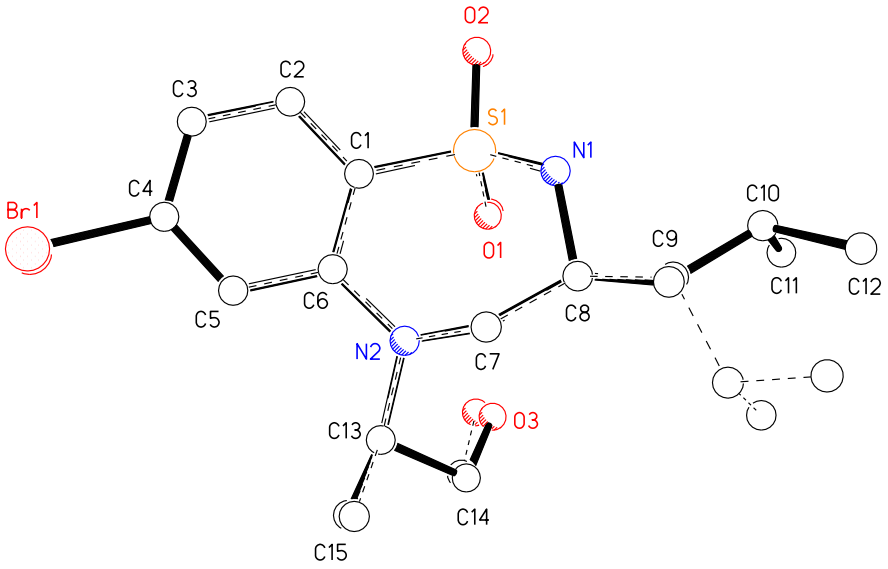
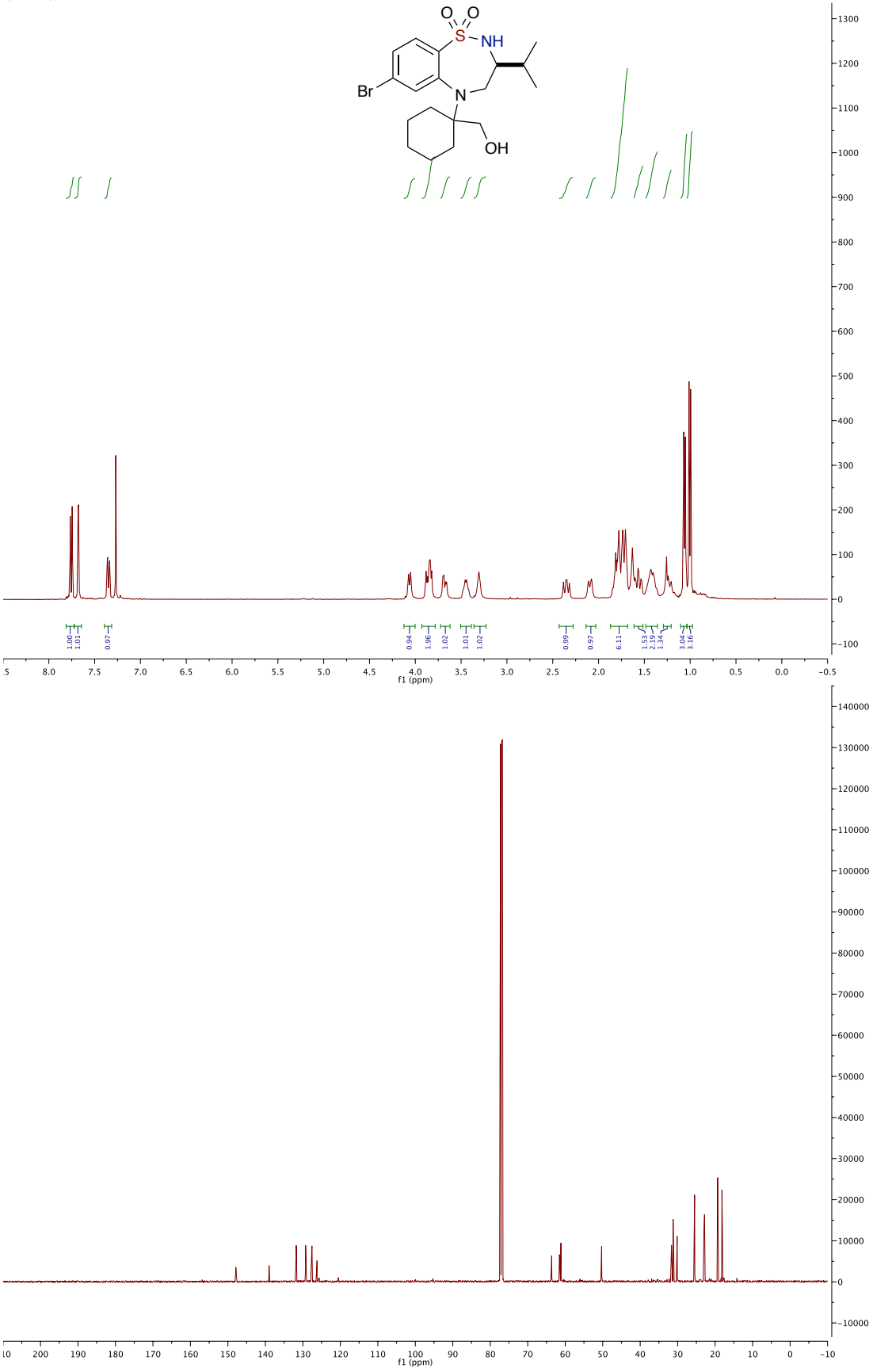


Figure 4. X-ray crystal structure of sultam **10m** where the thermal ellipsoids are set at a 50% probability level.

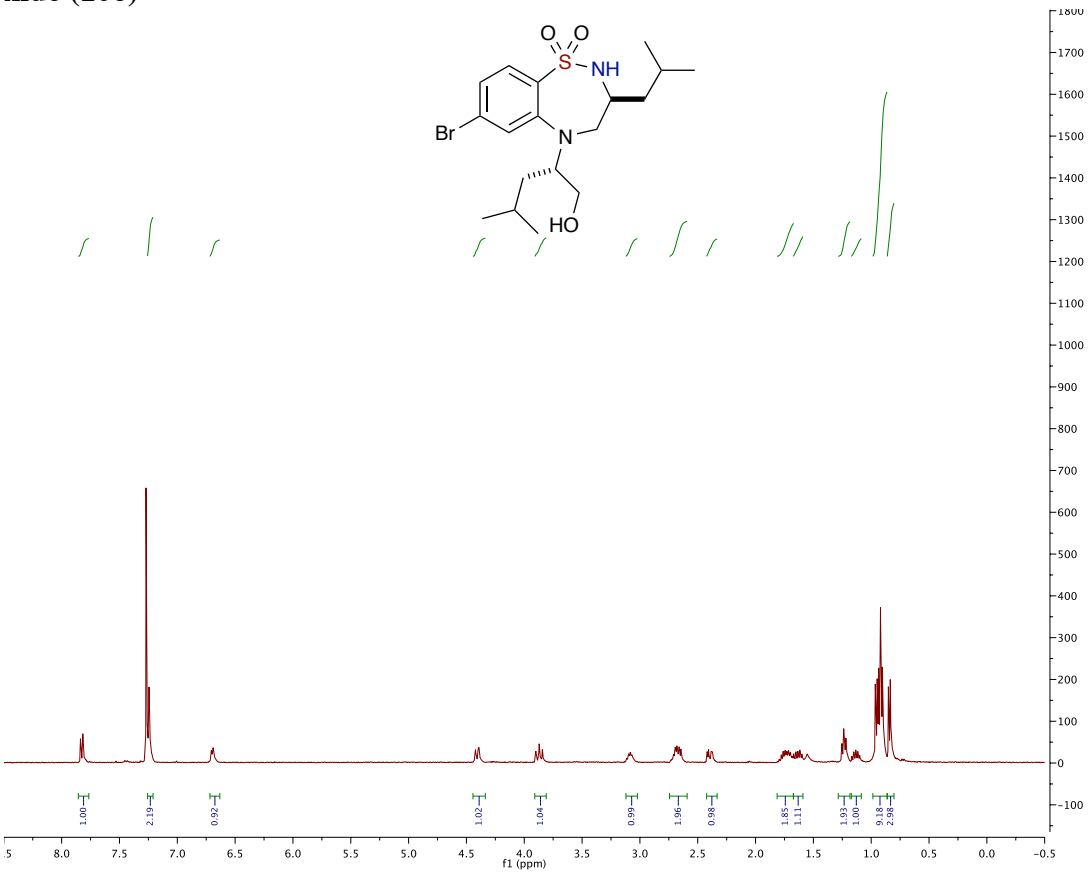


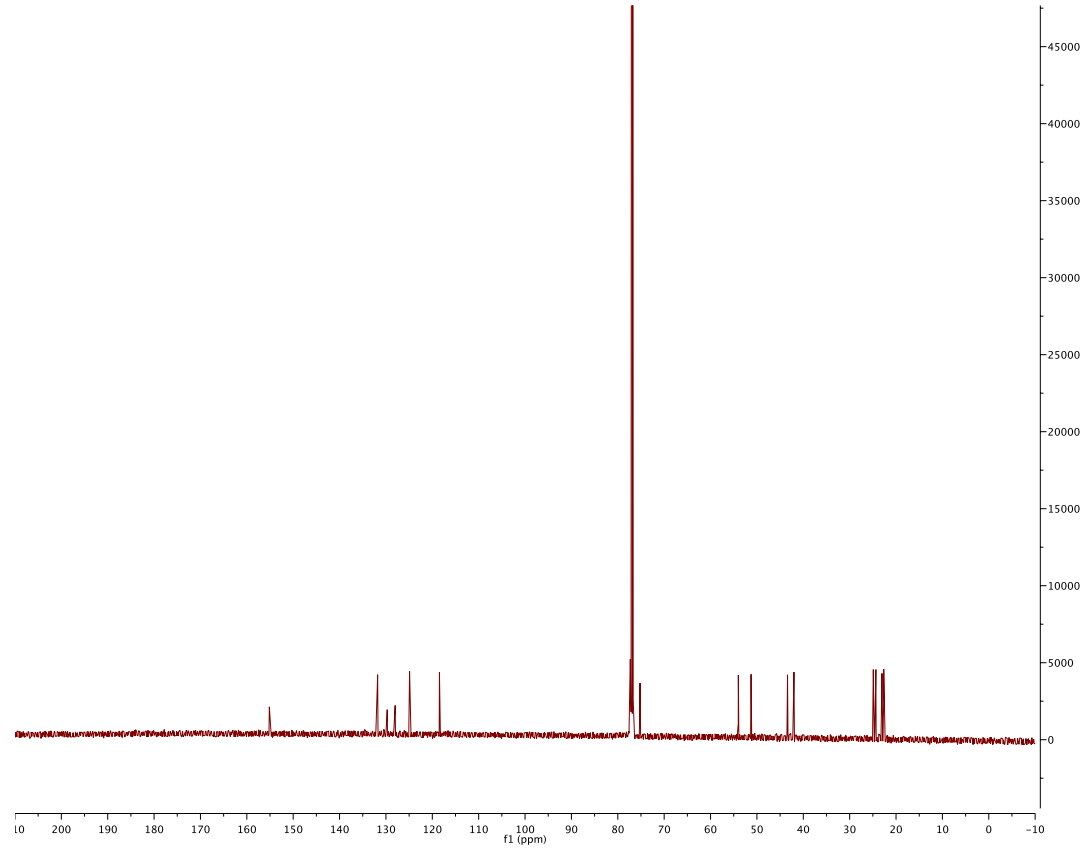

O2
C2
C3
S1
C1
N1
C4
C10
Br1
O1
C9
C11
C12
C5
C6
C8
N2
C7
O3
C13
C14
C15

(*S*)-7-bromo-5-(1-(hydroxymethyl)cyclohexyl)-3-isopropyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10n)

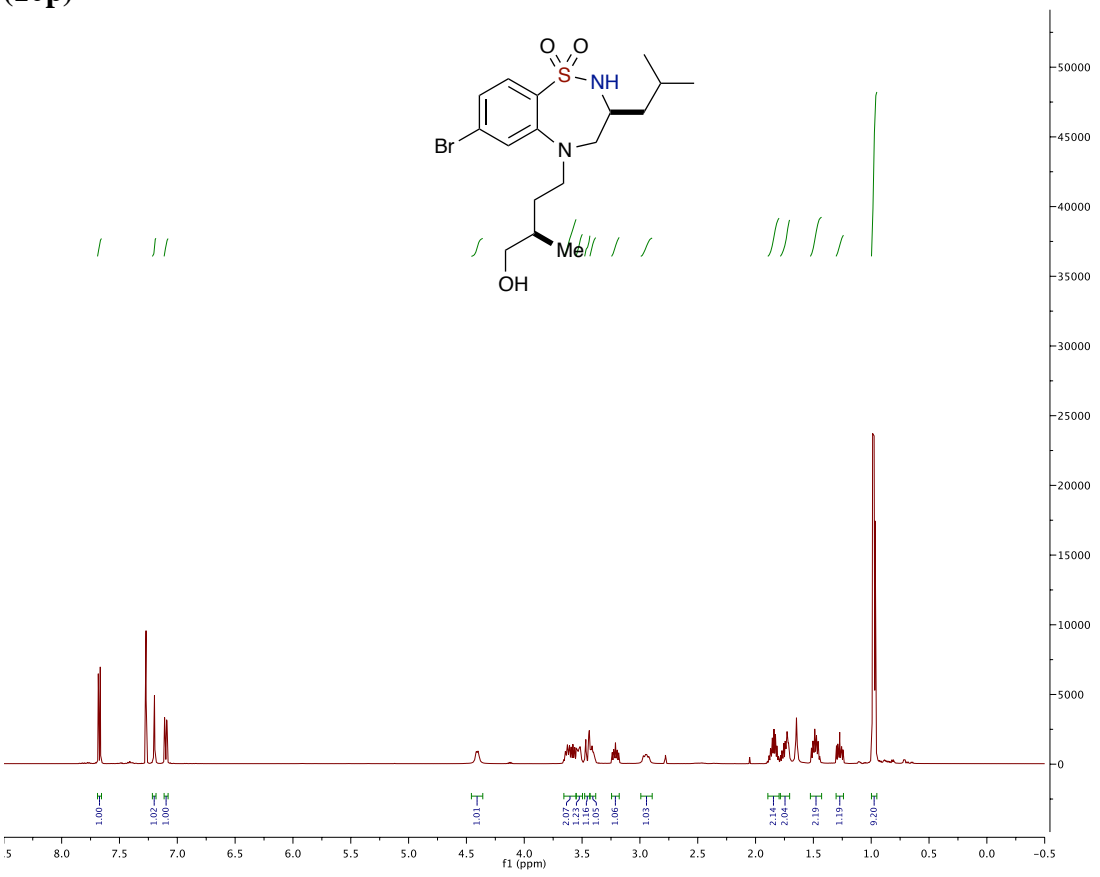


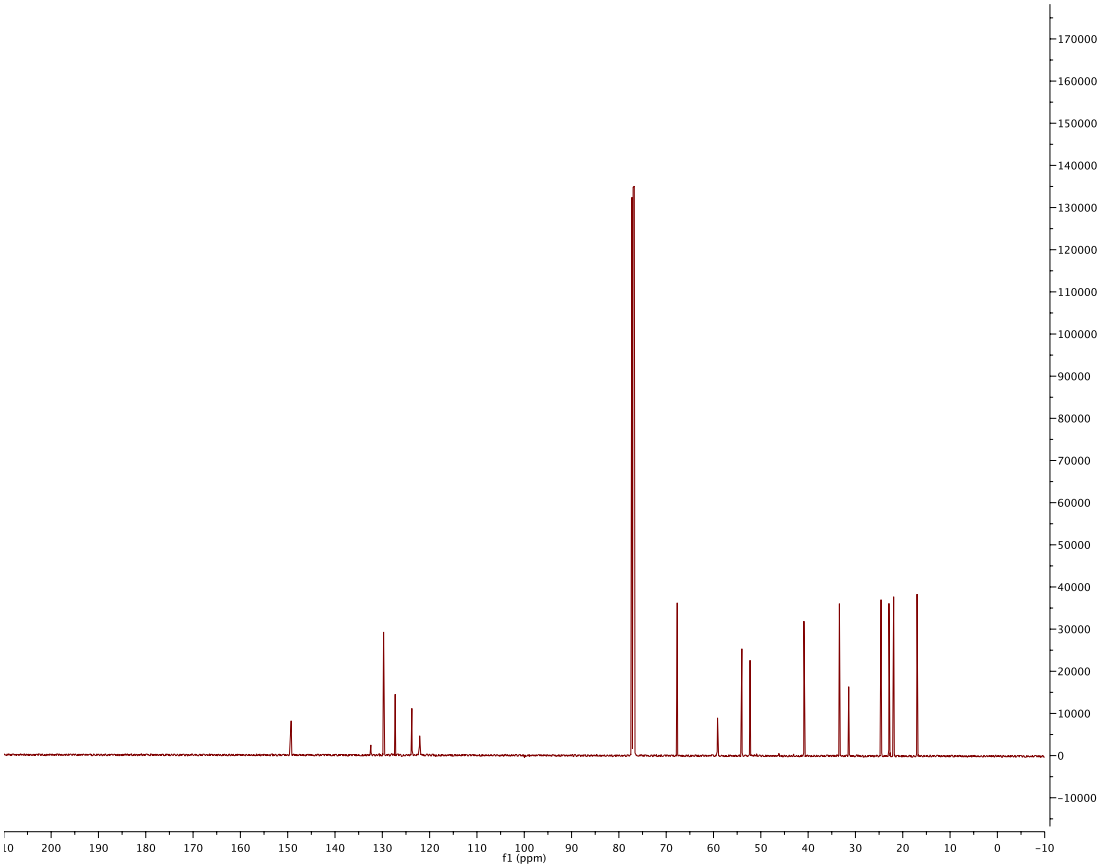
(*S*)-7-bromo-5-((*S*)-1-hydroxy-4-methylpentan-2-yl)-3-isobutyl-2,3,4,5 tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10o)



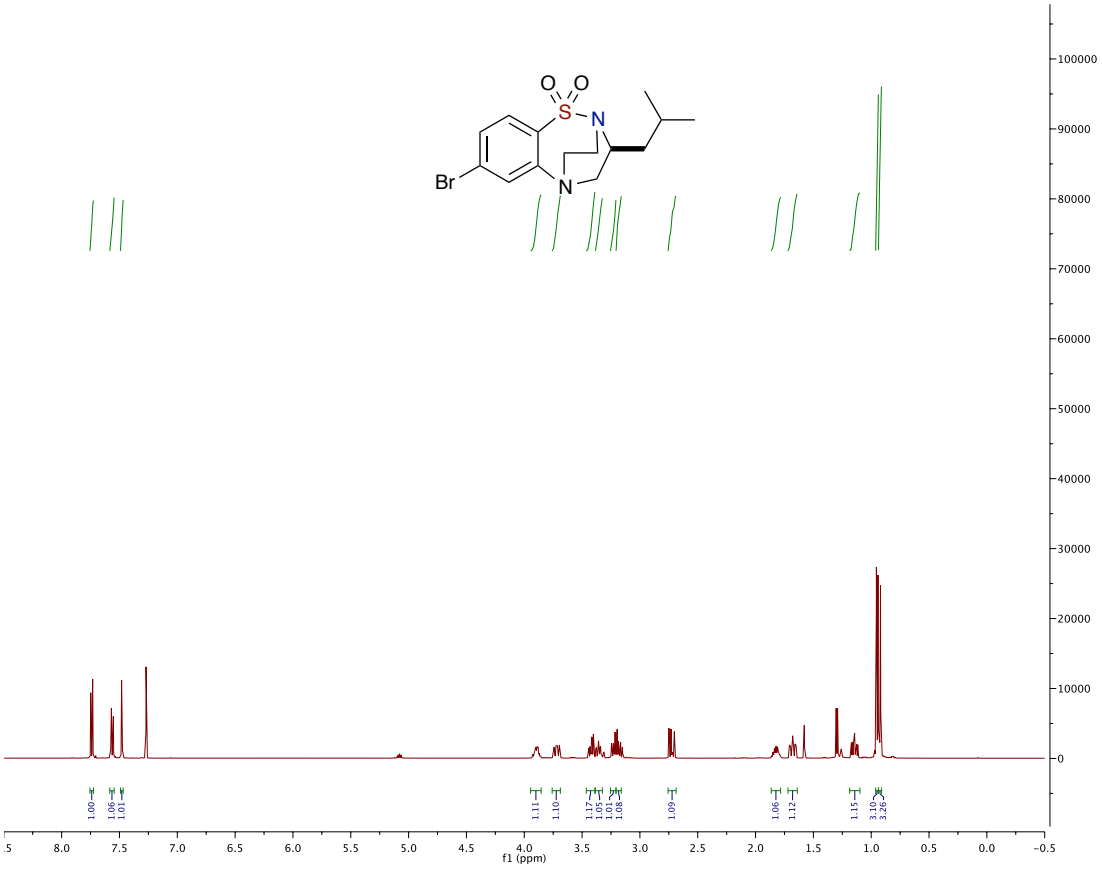


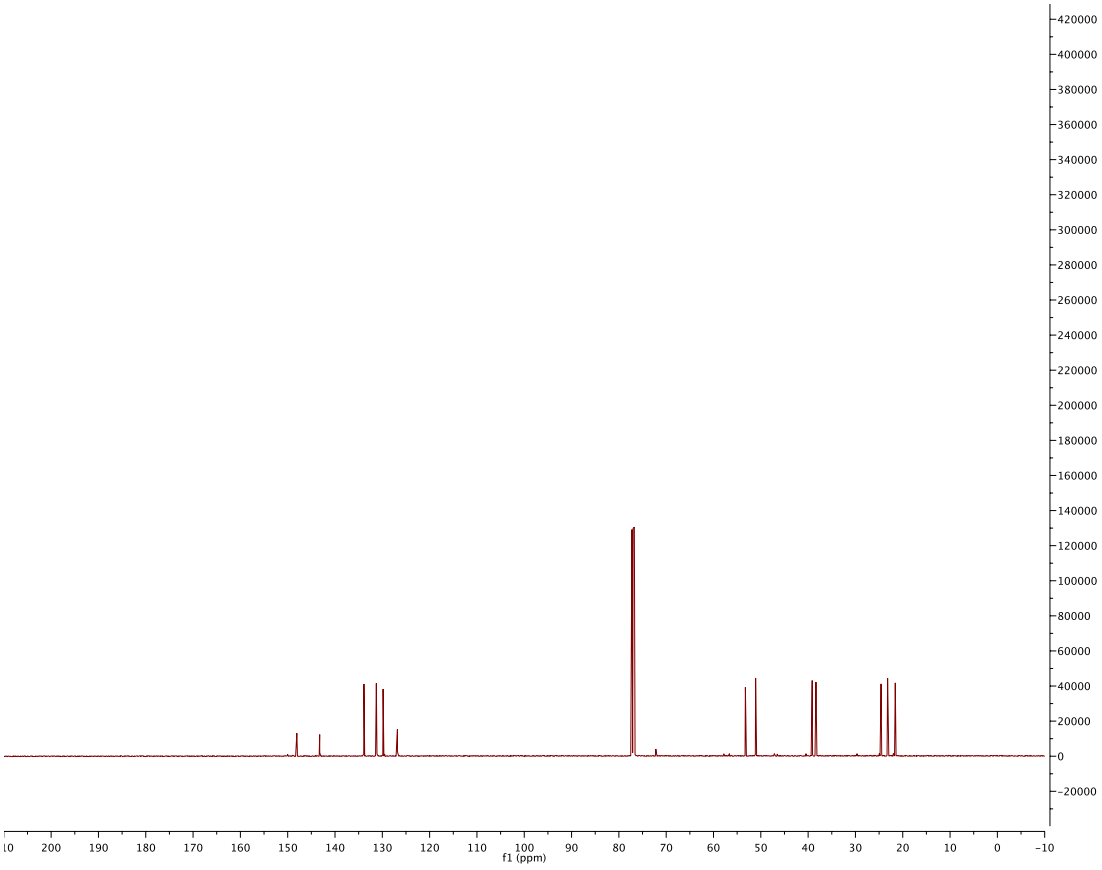
(*S*)-7-bromo-5-((*R*)-4-hydroxy-3-methylbutyl)-3-isobutyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (10p)



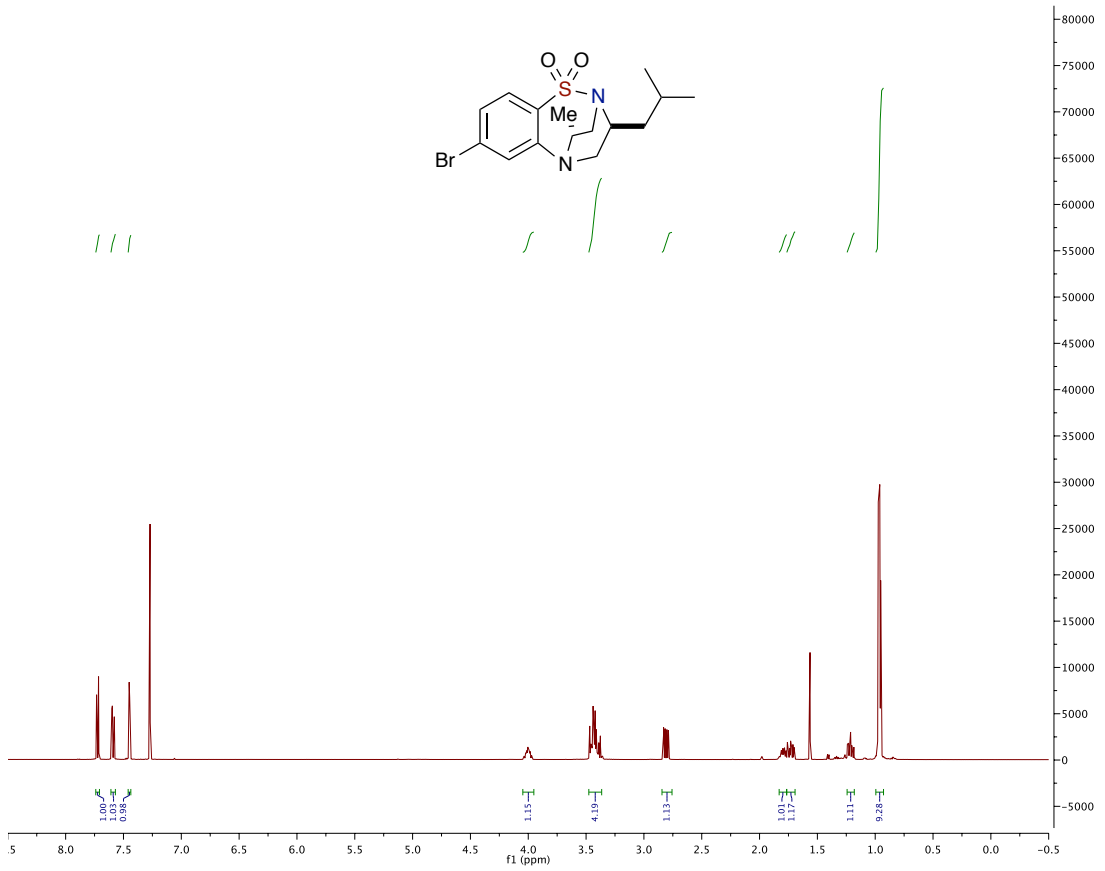


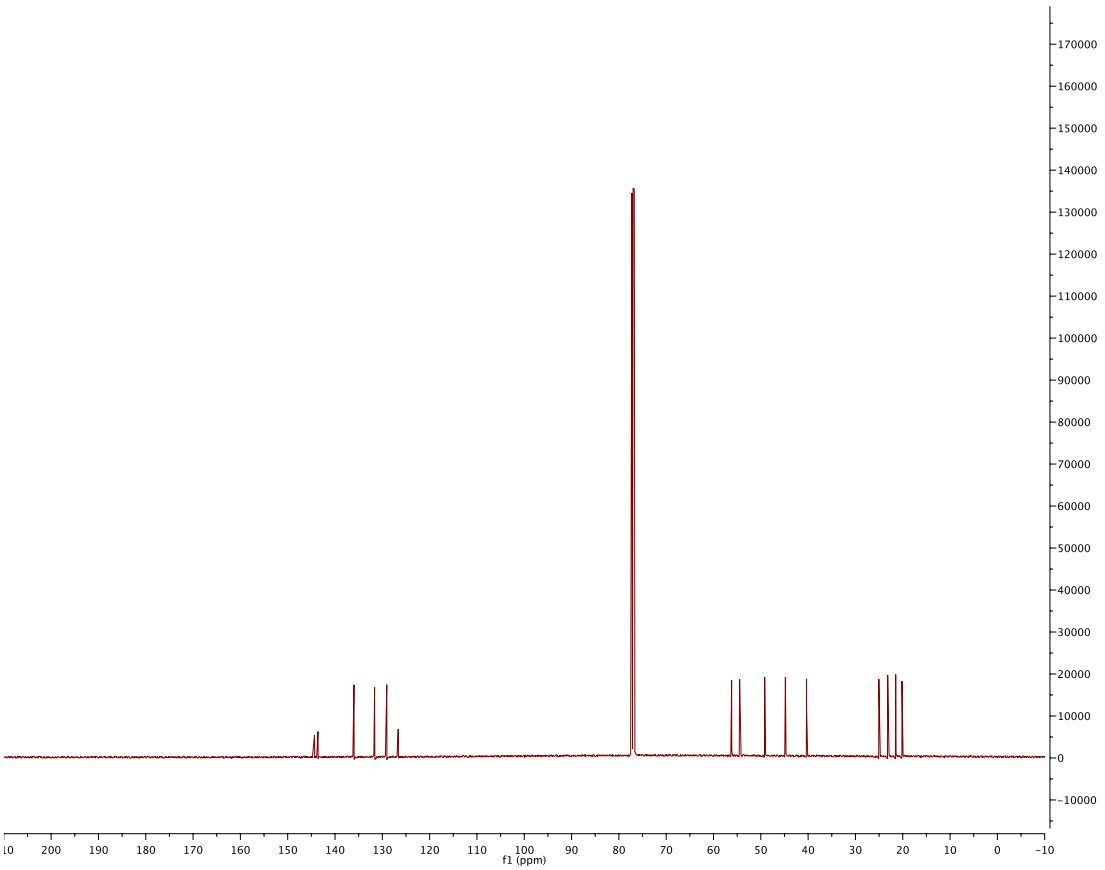
(3*S*)-7-bromo-3-isobutyl-3,4-dihydro-2,5-ethanobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (11a)



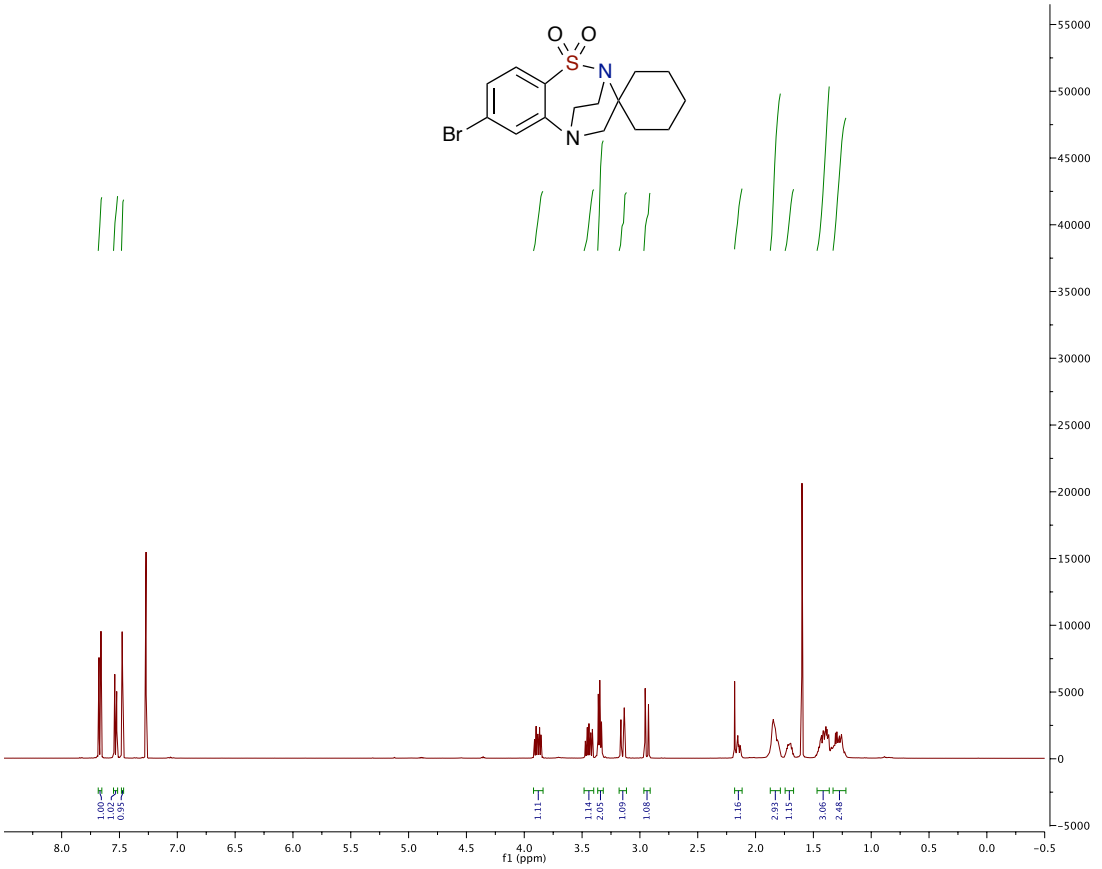


(4*R*,11*S*)-7-bromo-11-isobutyl-4-methyl-3,4-dihydro-2,5-ethanobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (11b)





7-bromo-4*H*-spiro[2,5-ethanobenzo[*f*][1,2,5]thiadiazepine-3,1'-cyclohexane] 1,1-dioxide (11c)



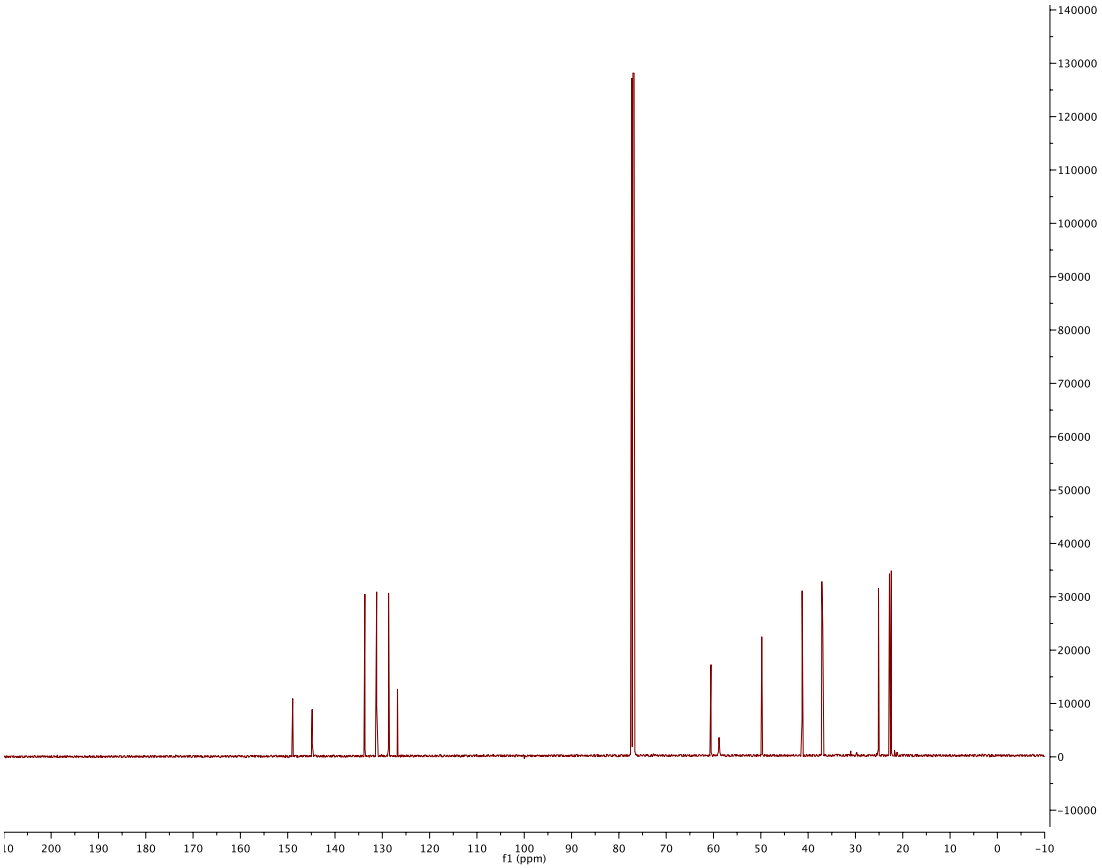
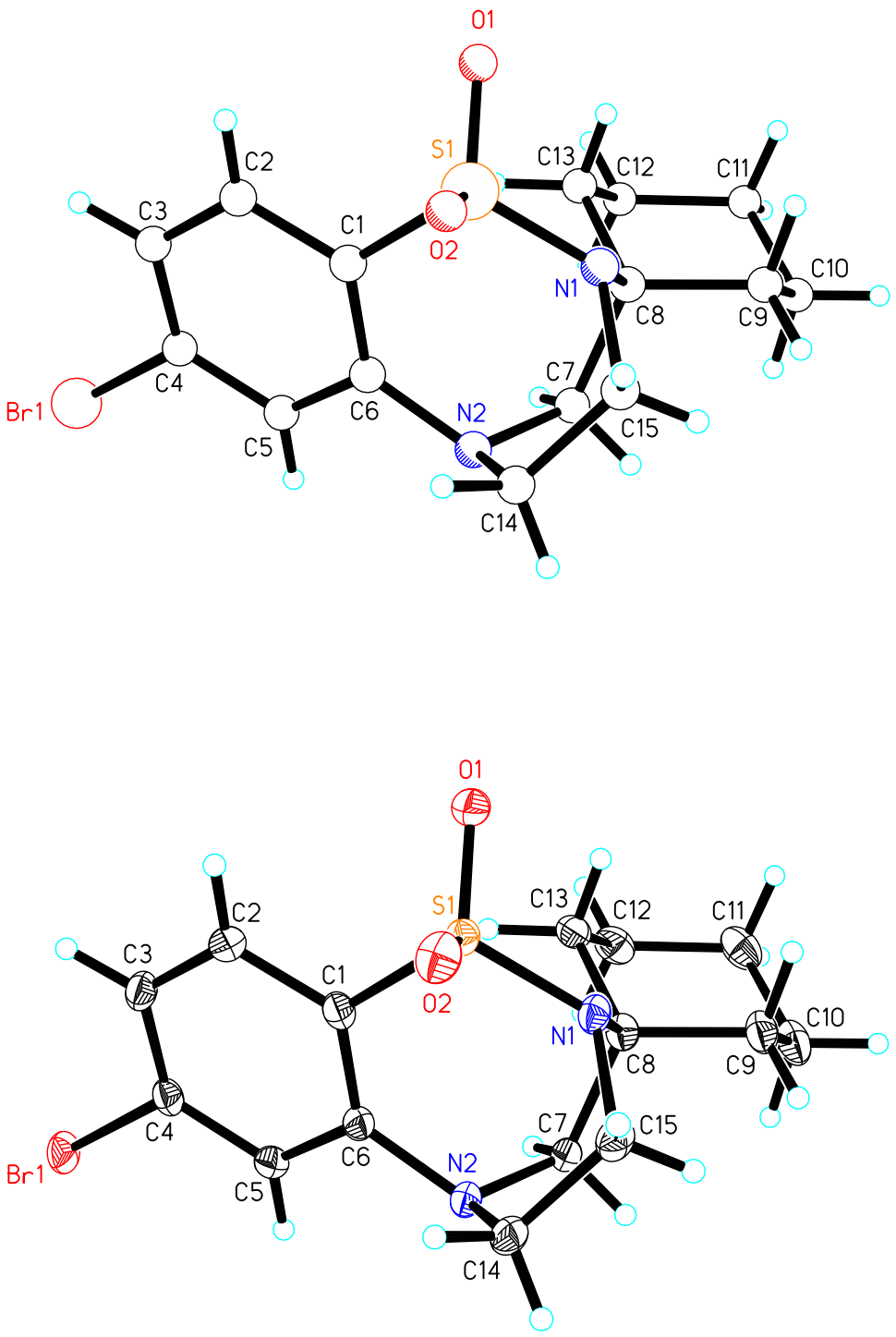
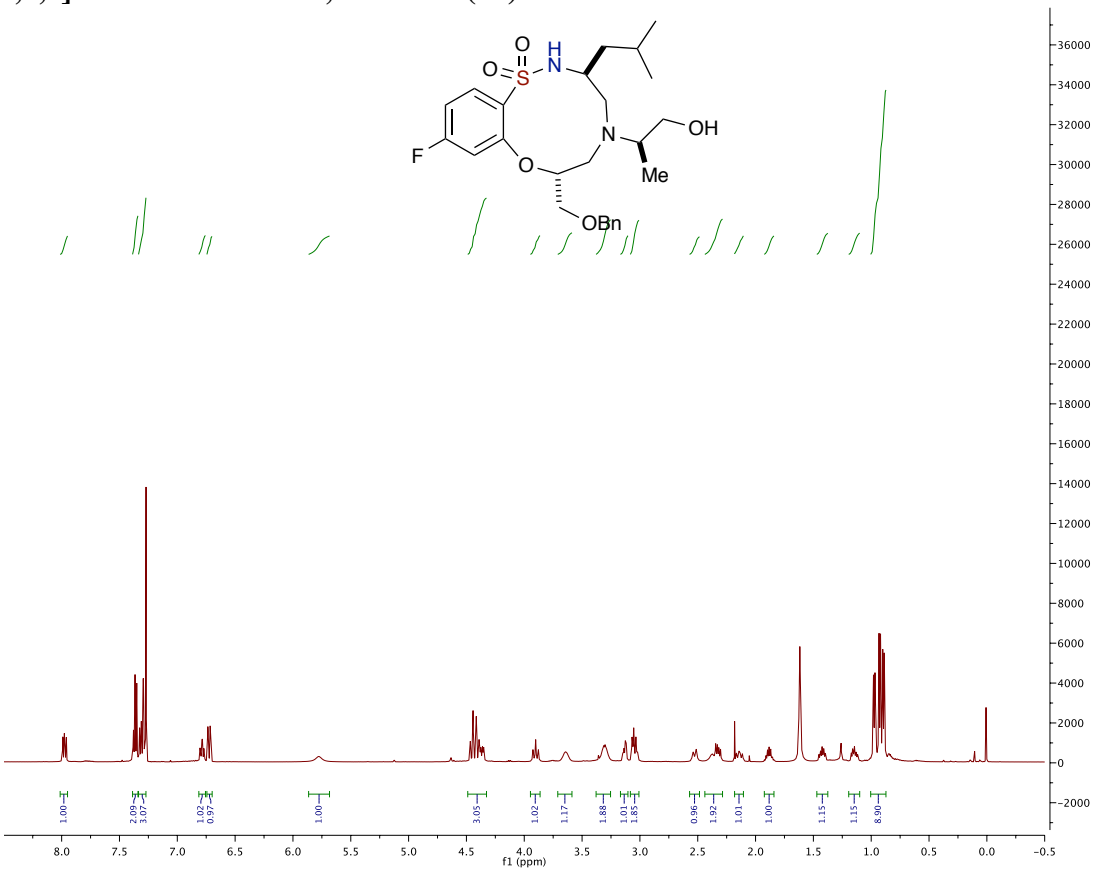
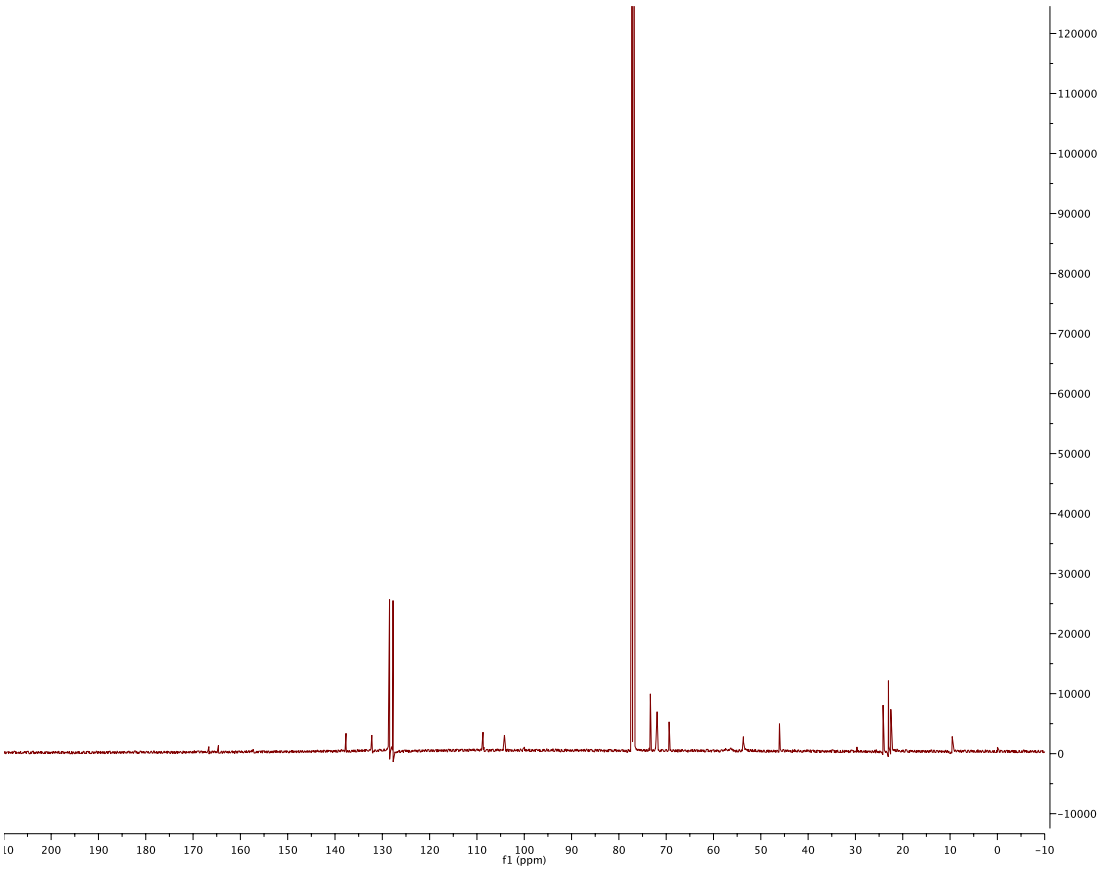


Figure 5. X-ray crystal structure of sultam **11c** where the thermal ellipsoids are set at a 50% probability level.



(3*S*,7*R*)-7-((benzyloxy)methyl)-10-fluoro-5-((*R*)-1-hydroxypropan-2-yl)-3-isobutyl-2,3,4,5,6,7hexahydro-benzo[*b*][1,4,5,8]oxathiadiazecine 1,1-dioxide (18)





(3*S*,7*S*)-7-((benzyloxy)methyl)-10-fluoro-5-((*R*)-1-hydroxypropan-2-yl)-3-isobutyl-2,3,4,5,6,7hexahydro-benzo[*b*][1,4,5,8]oxathiadiazecine 1,1-dioxide (19)