Tacrine-sugar mimetic conjugates as enhanced cholinesterase inhibitors

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Docking and Molecular dynamics simulation studies

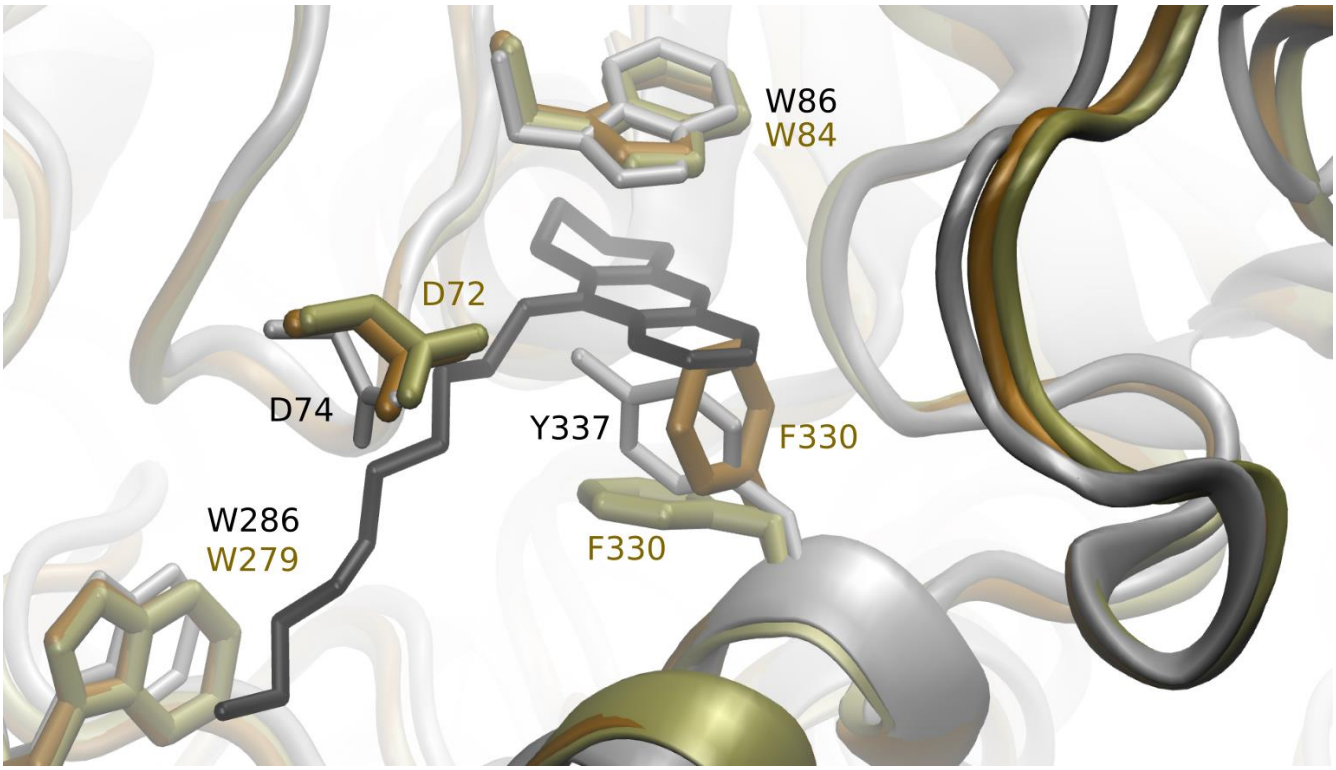

Figure S1: Superposition of Ache from *Torpedo californica* in ligand -bound (pdb ID 1ut6, gold) and apo-(pdb ID 1qt1, brown) form with Ache from *Electrophorous Electricus* (pdb ID 1c2b, silver). The ligand N-9-(1',2',3' Tetrahydroacridinyl)-1,8- diaminooctane of the 1ut6 structure is shown in black. Important active site residues are labelled.

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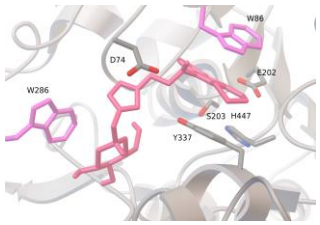
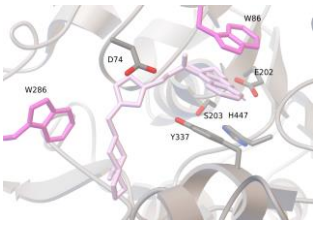
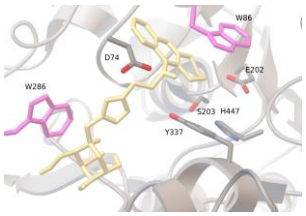
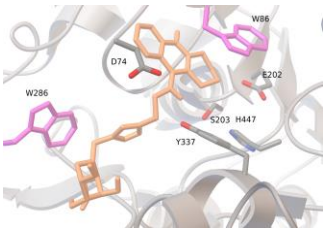
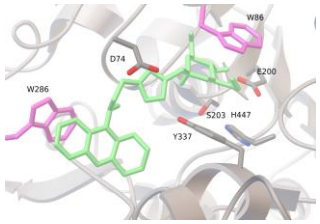
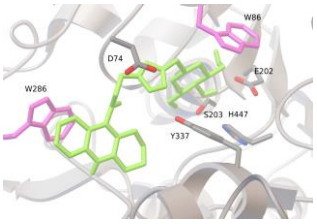
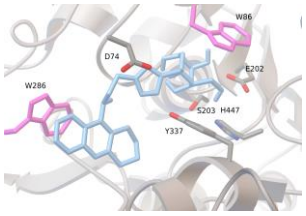
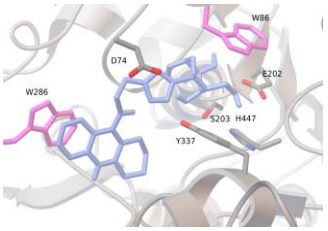
	sugNH	tacNH	sugNH	tacNH
Pose 1				
Pose 2				

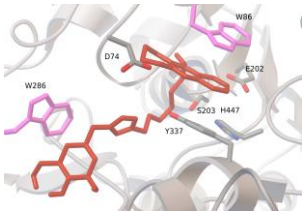
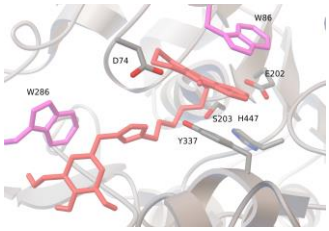
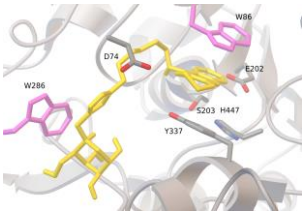
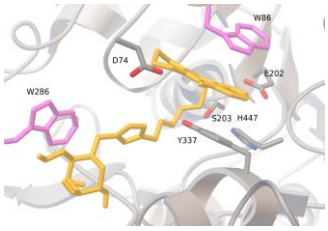
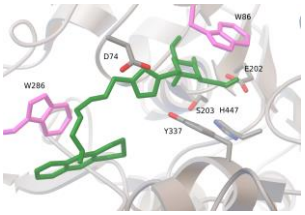
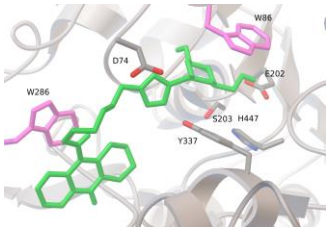
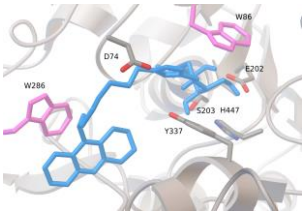
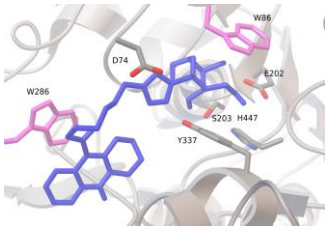
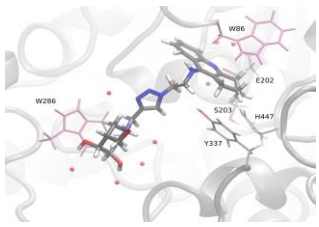
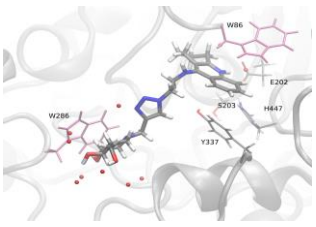
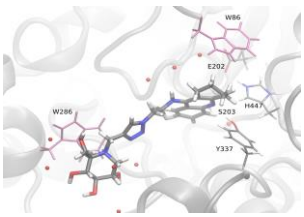
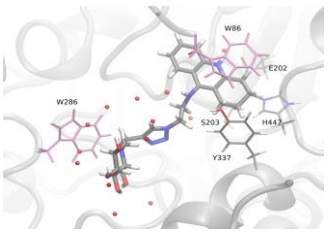
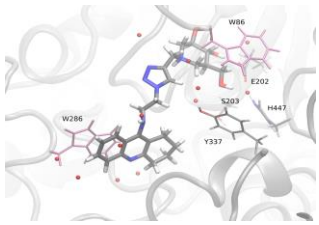
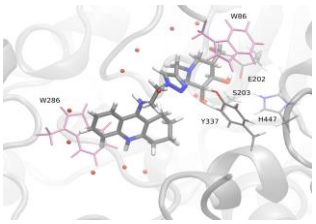
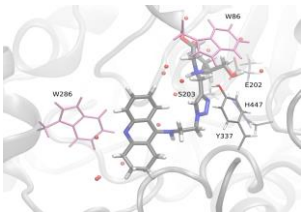
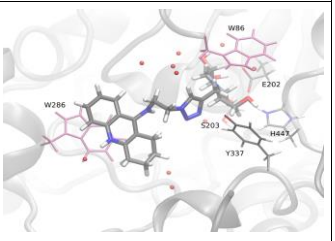
	12c		13c	
	sugNH	tacNH	sugNH	tacNH
Pose 1				
Pose 2				

Figure S2: Binding poses for the different ligand models. For each model, one docking pose with the tacrine moiety at the CAS (Pose 1) and one with the iminosugar at the CAS (Pose 2) are shown. The estimated binding affinities of the respective two poses differ by only 0.4 - 1.0 kcal/mol.

	12a		13a	
	sugNH	tacNH	sugNH	tacNH
Pose 1				
Pose 2				

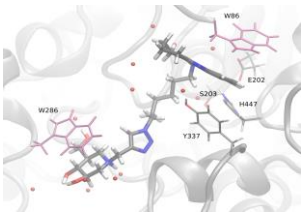
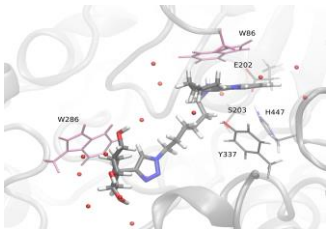
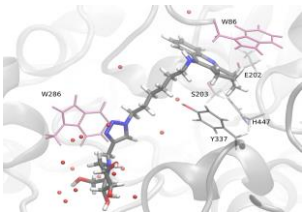
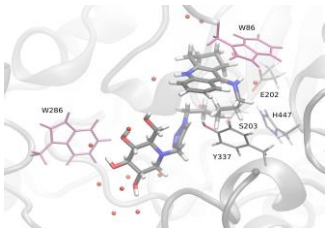
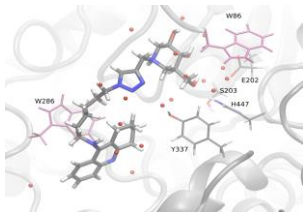
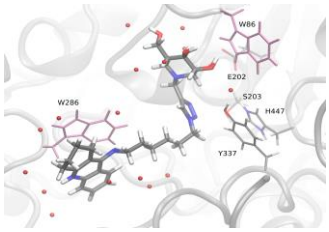
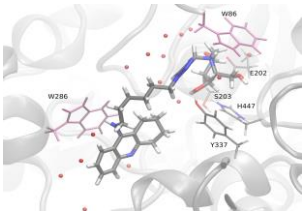
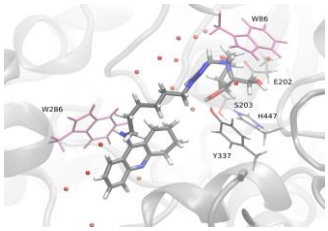
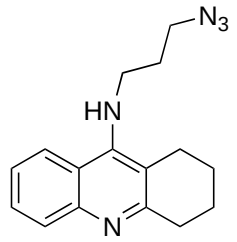
	12c		13c	
	sugNH	tacNH	sugNH	tacNH
Pose 1				
Pose 2				

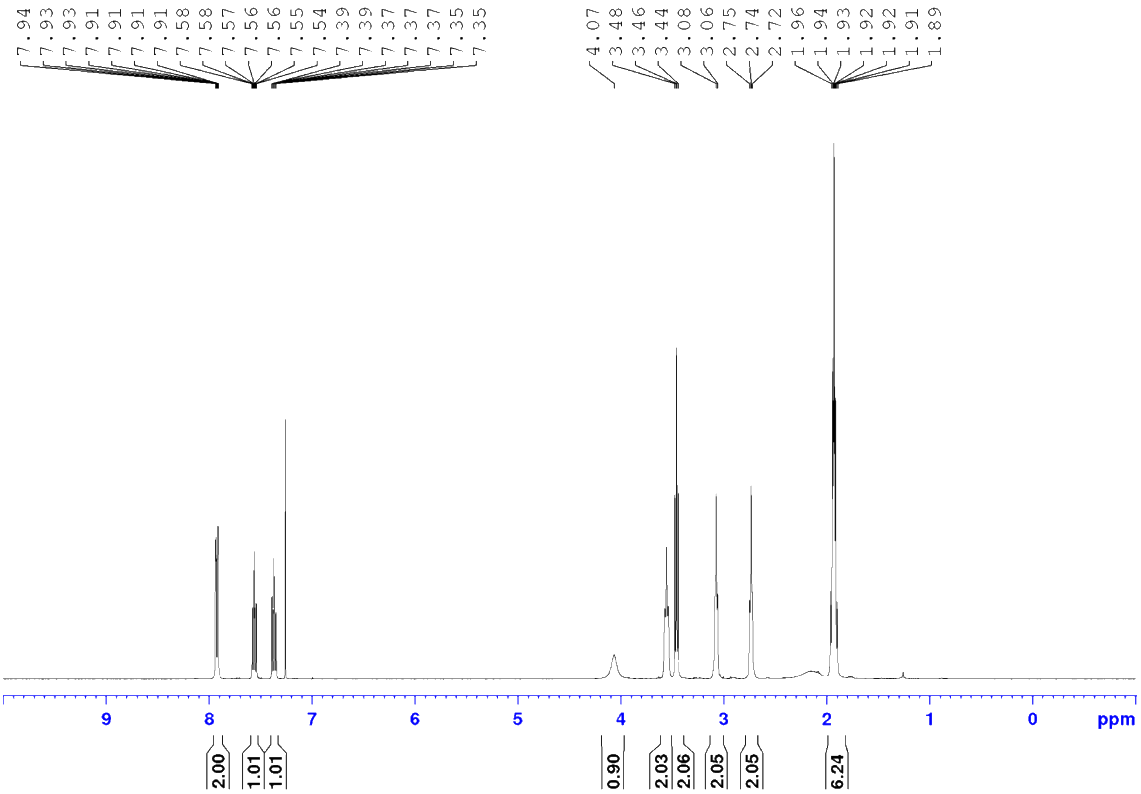
Figure S3: Median structures as most representative snapshots of the protein-ligand complexes. Residues Trp86 and Trp286 (*el. ectricus* numbering) of the CAS and PAS, respectively, are highlighted in magenta. Oxygen atoms of water molecules around the ligands are shown as red spheres.

The snapshots from the MD simulations (see Figure S3) show the ligands accommodated in the protein such that with one end (sugar or tacrine) is bound at the CAS, i.e. close to Trp 86, and the other (tacrine or sugar) in the PAS, close to Trp 286. The two poses can clearly be distinguished from which part is

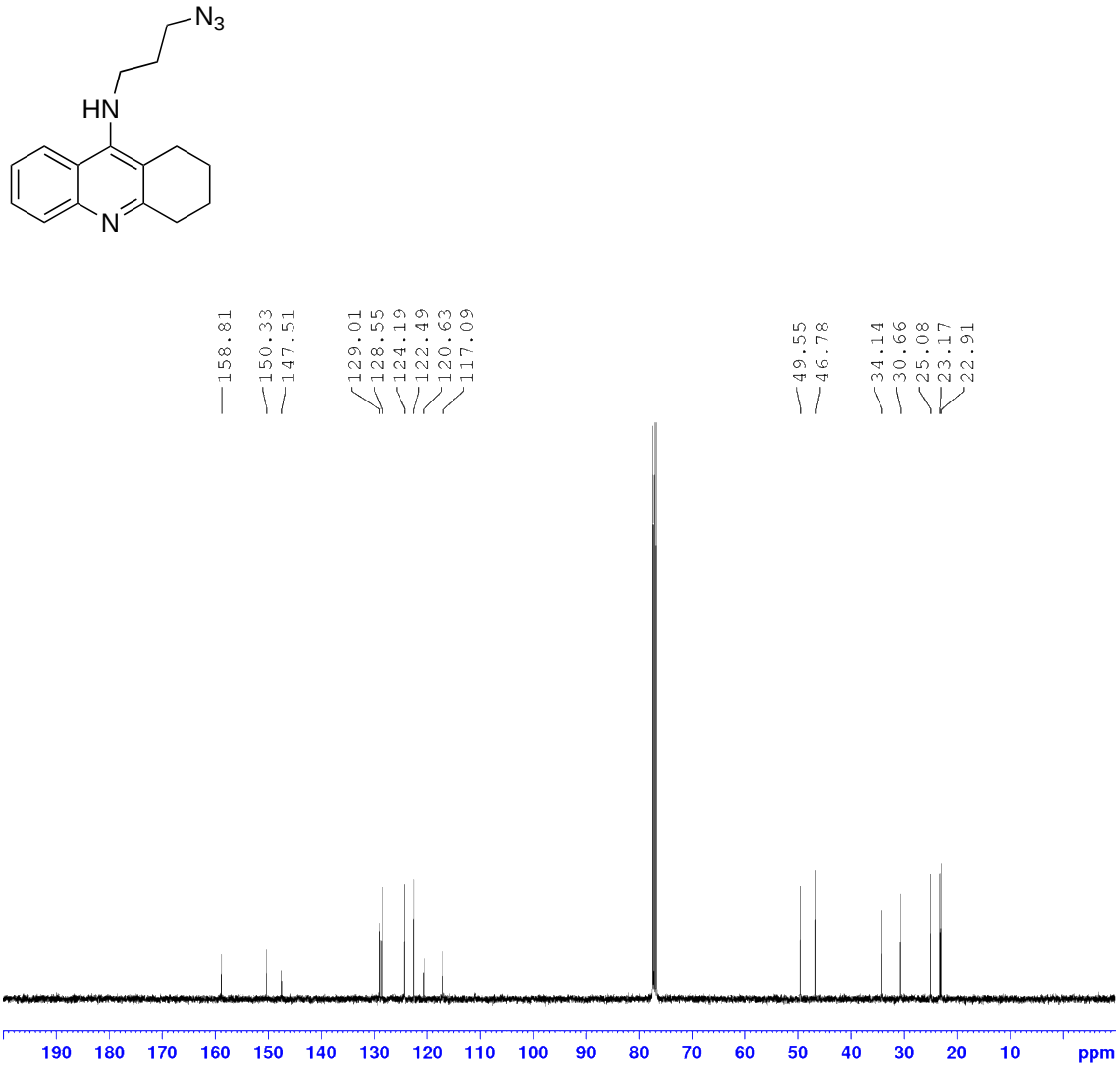
bound to which site, that is Pose 1 has the tacrine moiety at the CAS and in Pose 2 it is the iminosugar that is placed at the CAS.

^{1}H-NMR of compound **17** ($CDCl_3$, 400.13 MHz)

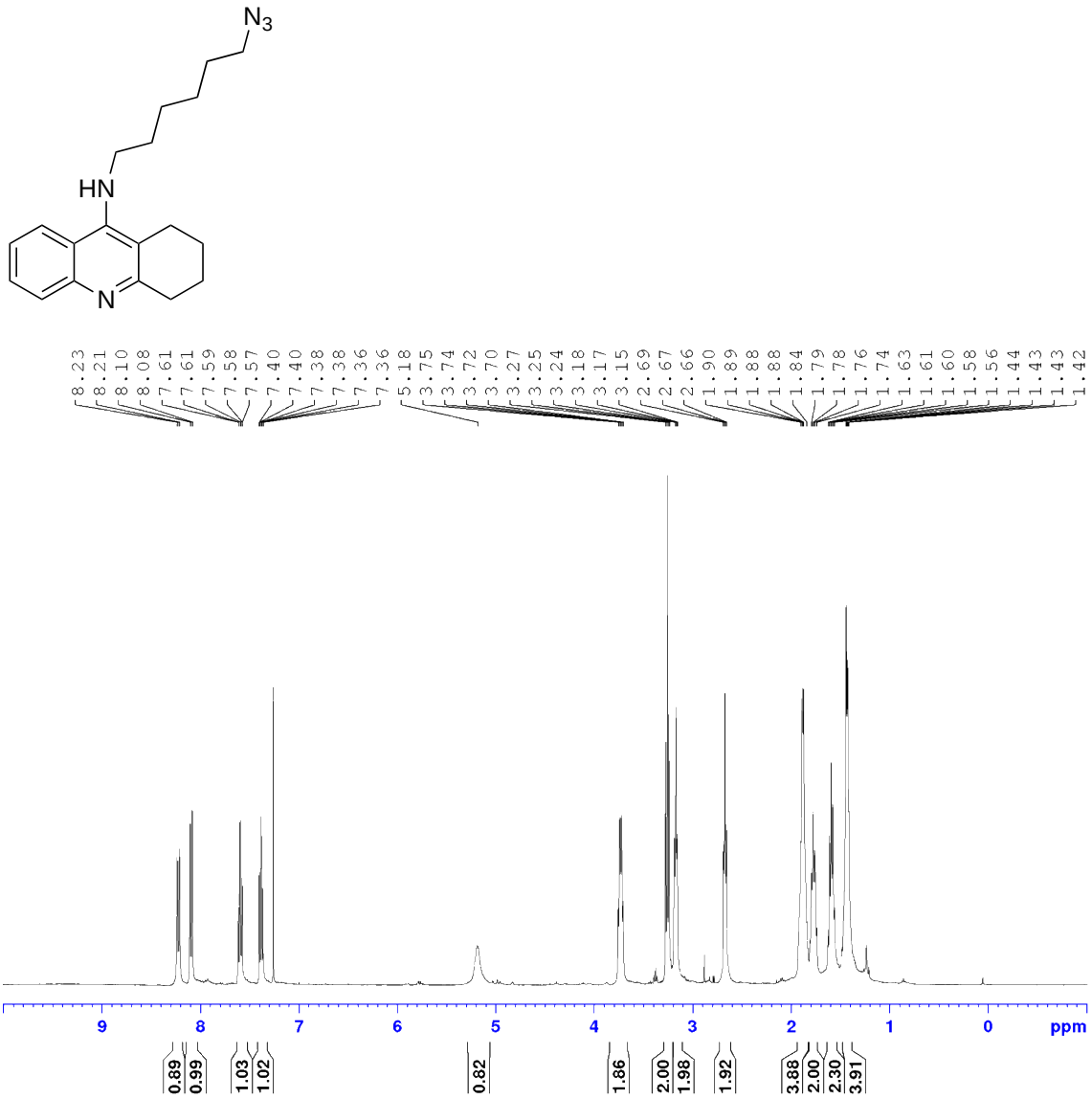




^{13}C-NMR of compound **17** ($CDCl_3$, 100.61 MHz)



^{1}H-NMR of compound **18** ($CDCl_3$, 400.13 MHz)



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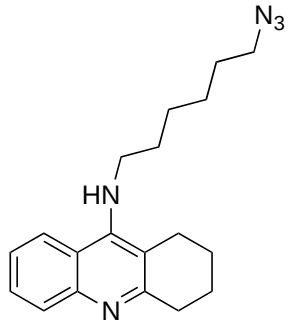

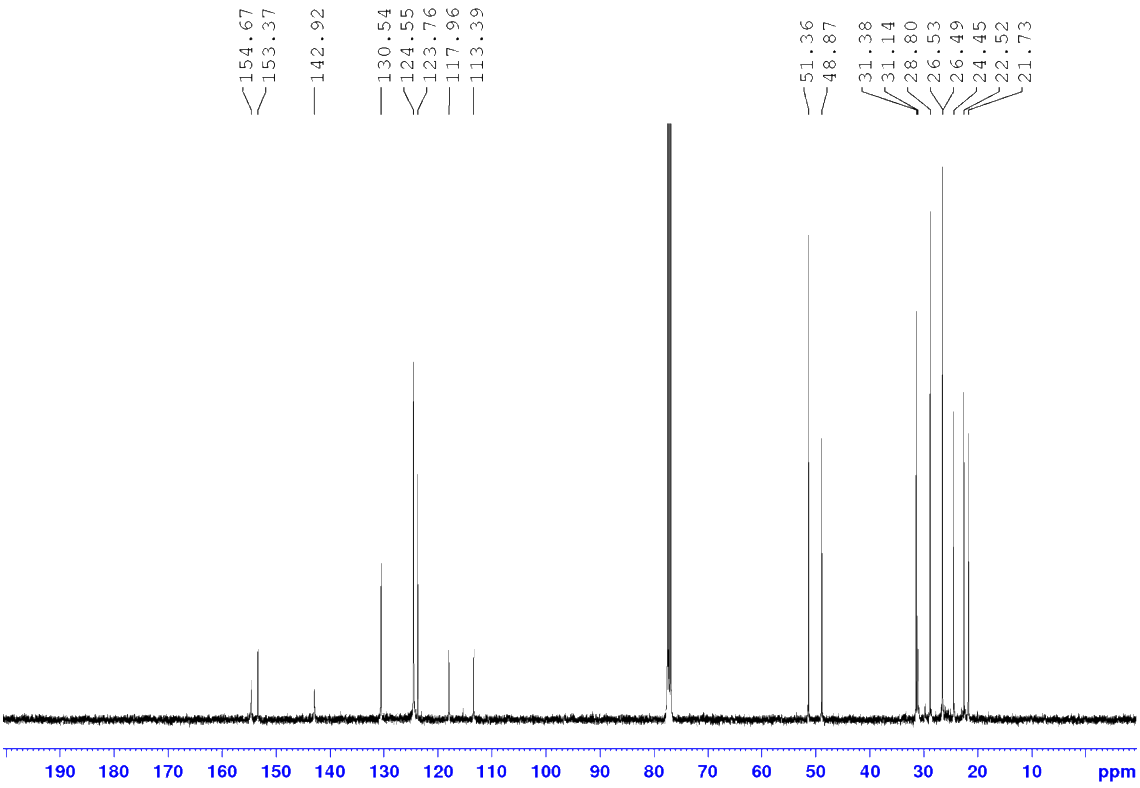

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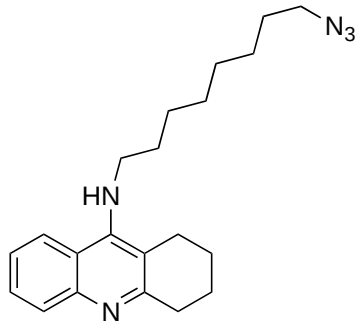

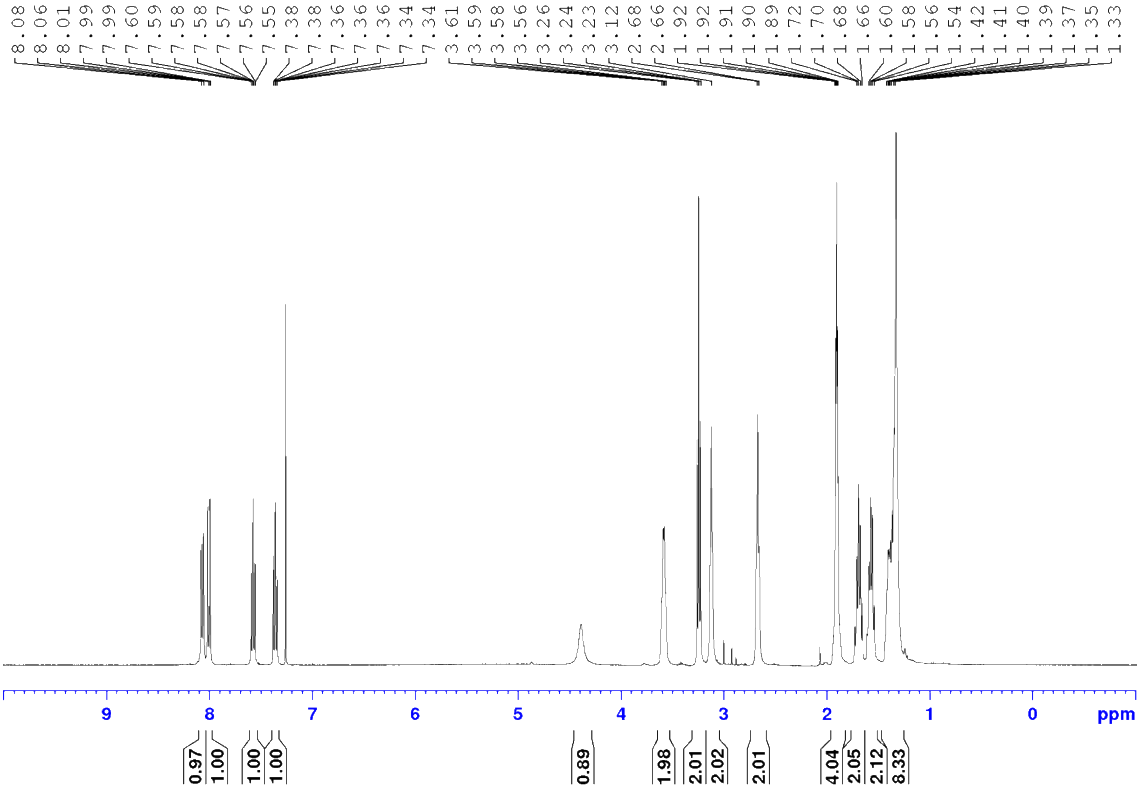

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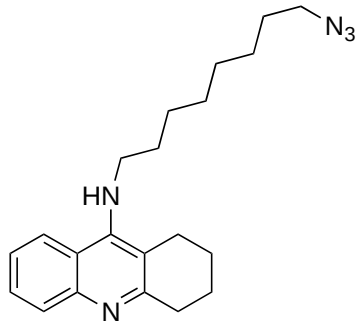

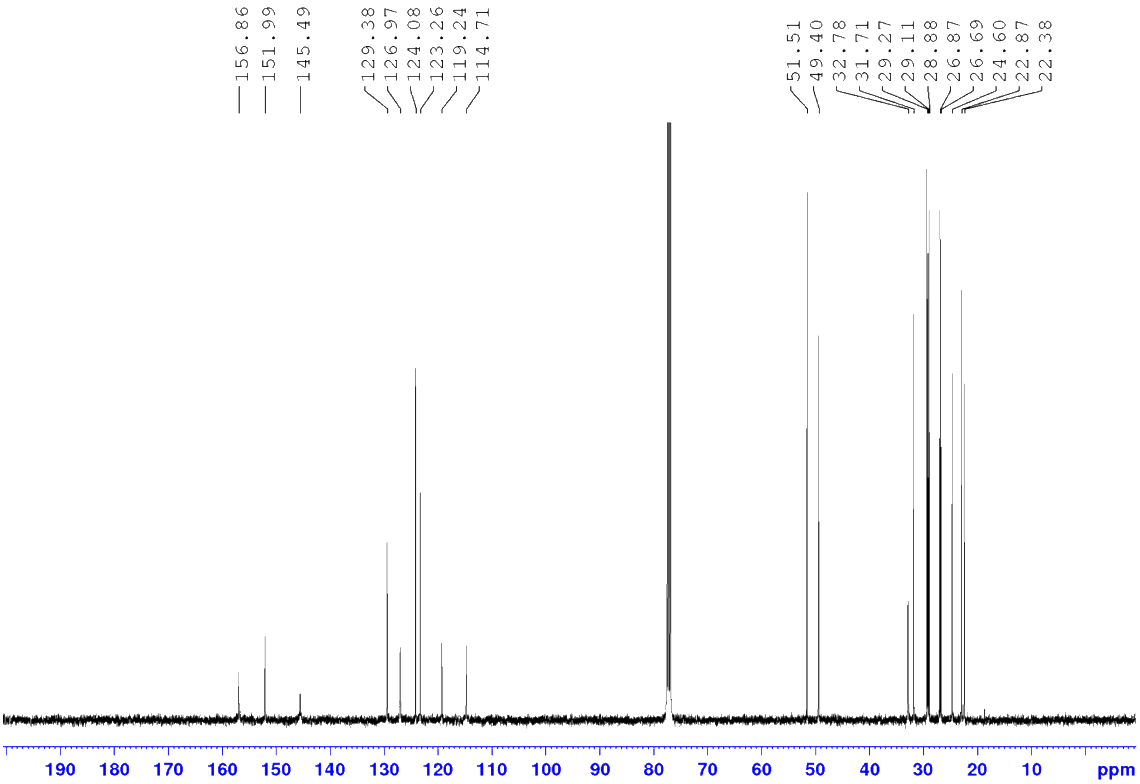

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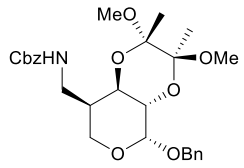
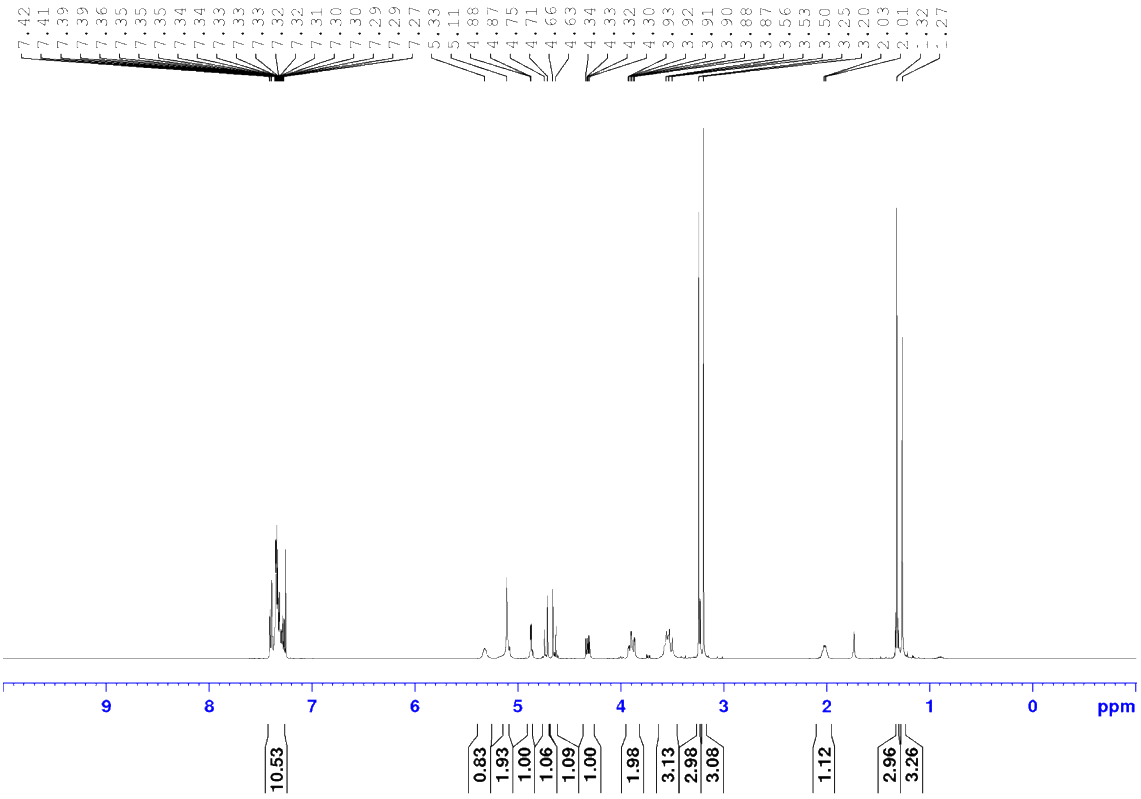
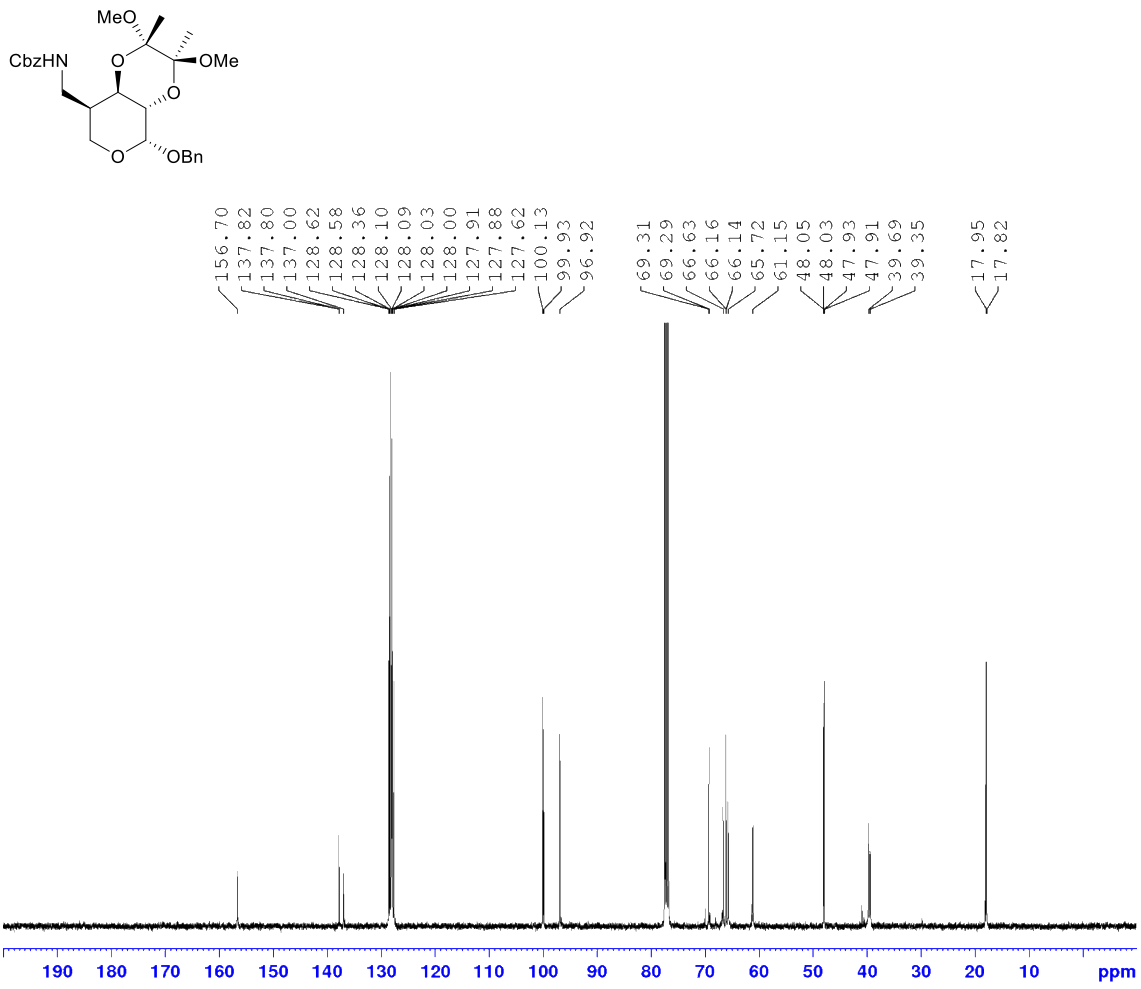




^{13}C-NMR of compound **21** ($CDCl_3$, 100.61 MHz)



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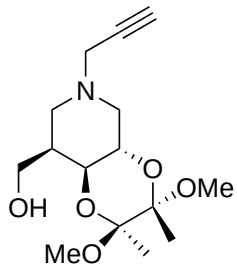
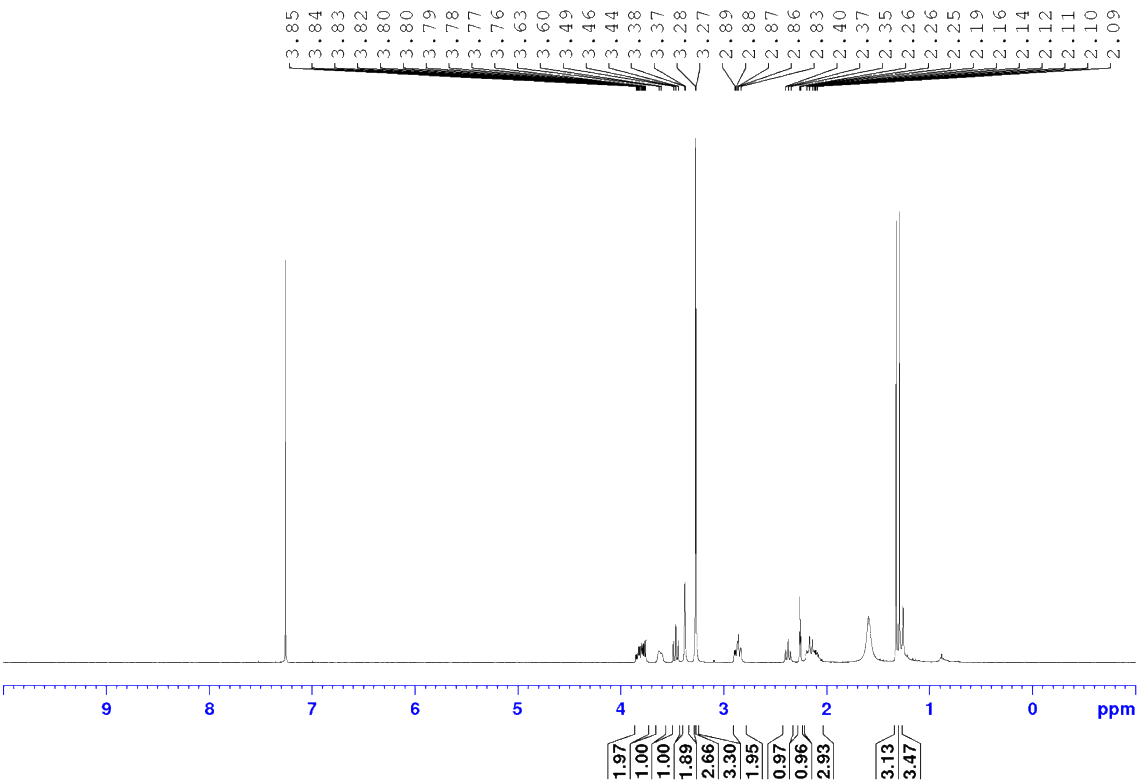
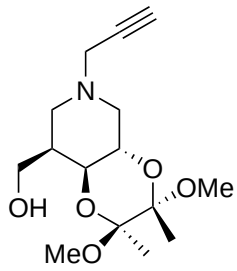
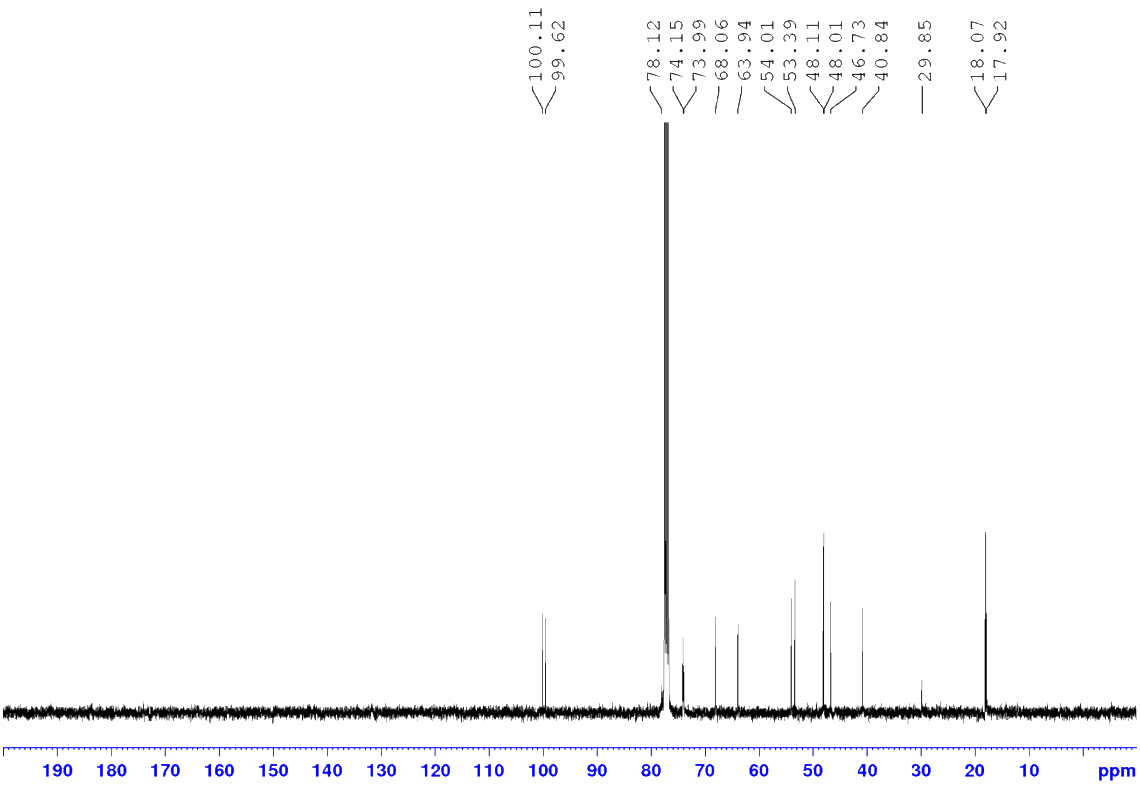




^{13}C-NMR of compound **22** ($CDCl_3$, 100.61 MHz)





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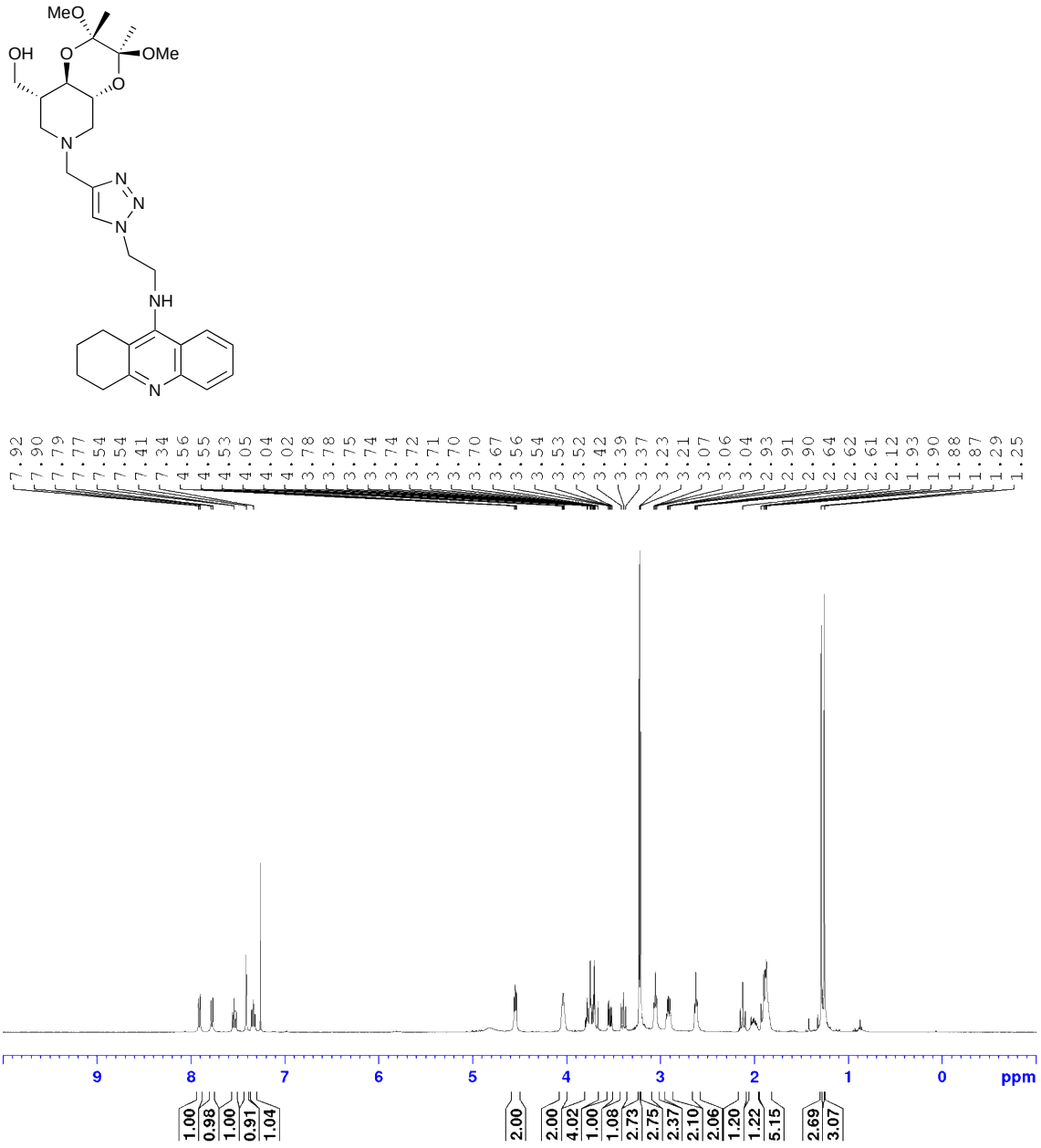
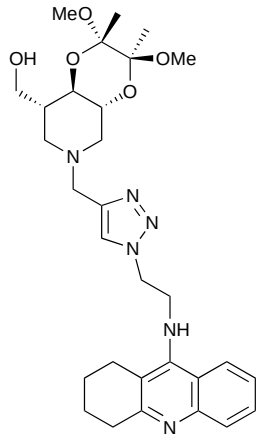
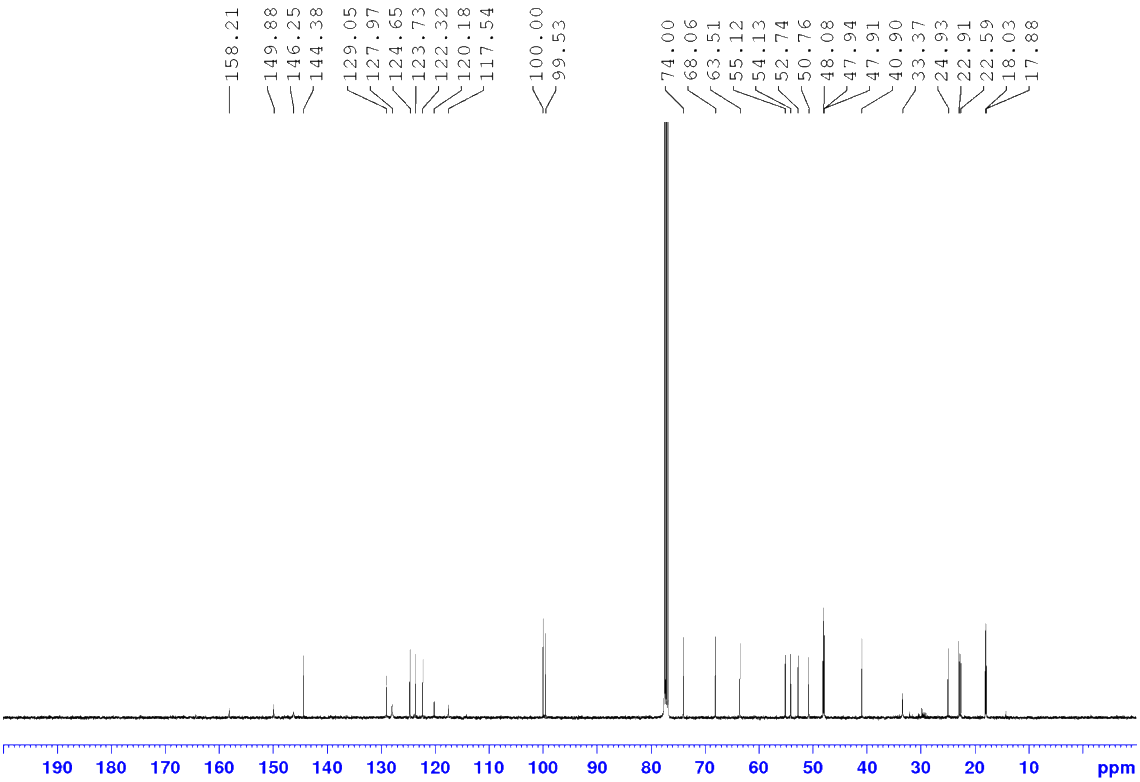
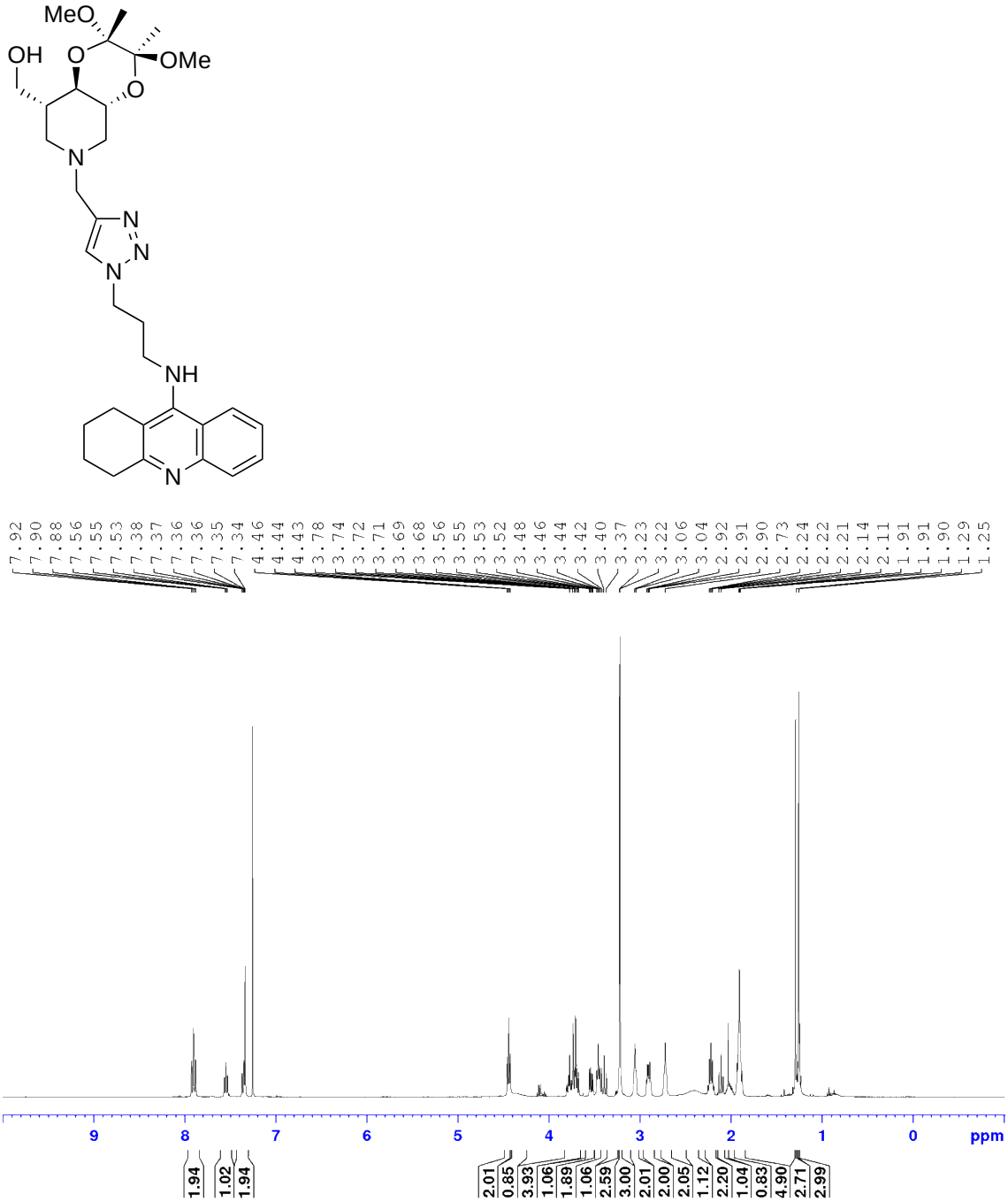


^{13}C-NMR of compound **24a** ($CDCl_3$, 100.61 MHz)

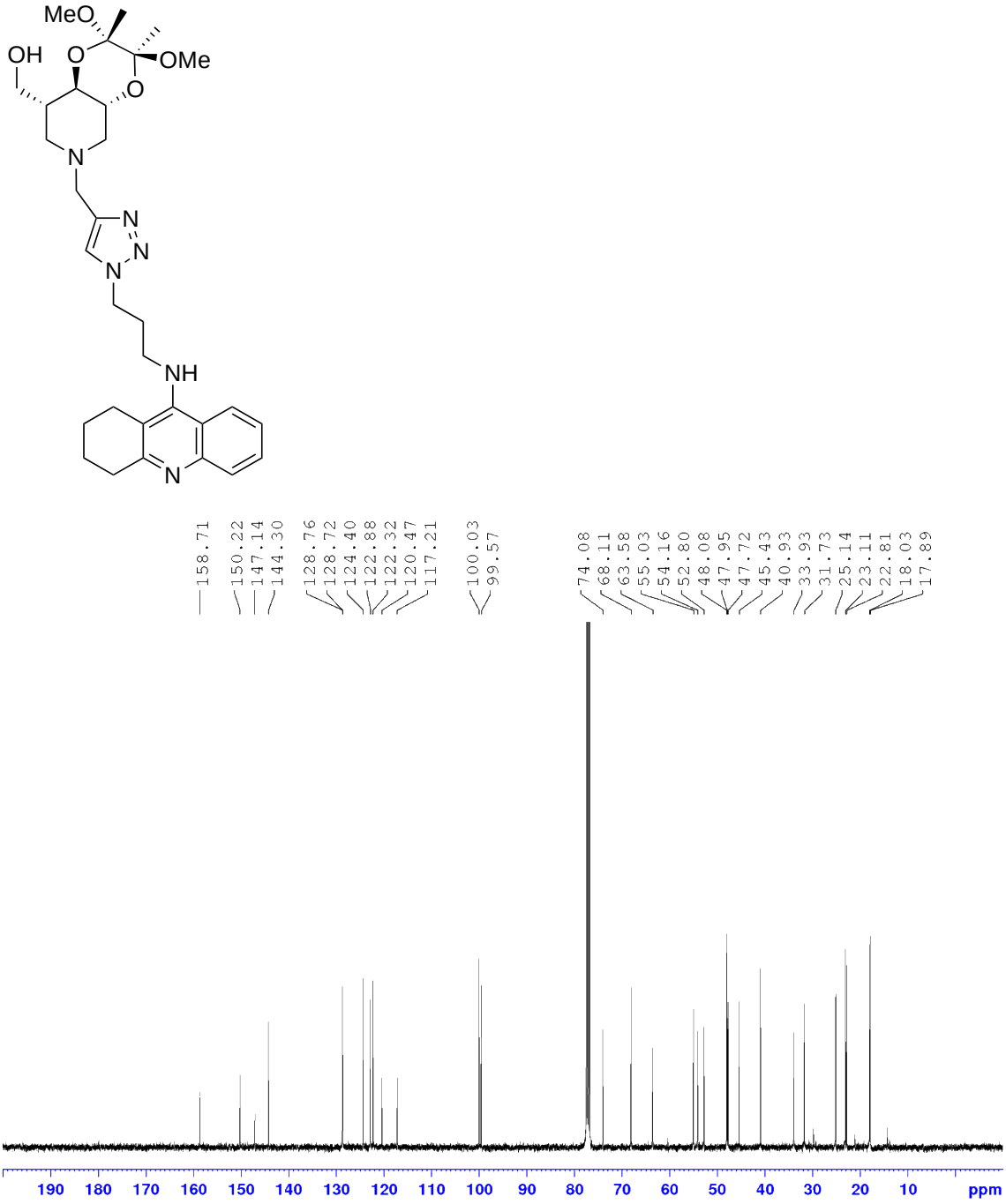




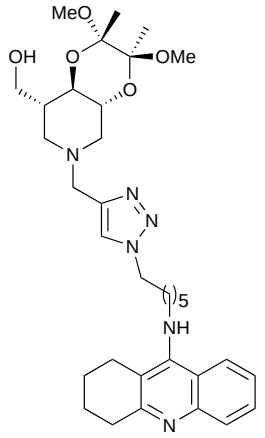
^{1}H-NMR of compound **24b** ($CDCl_3$, 400.13 MHz)

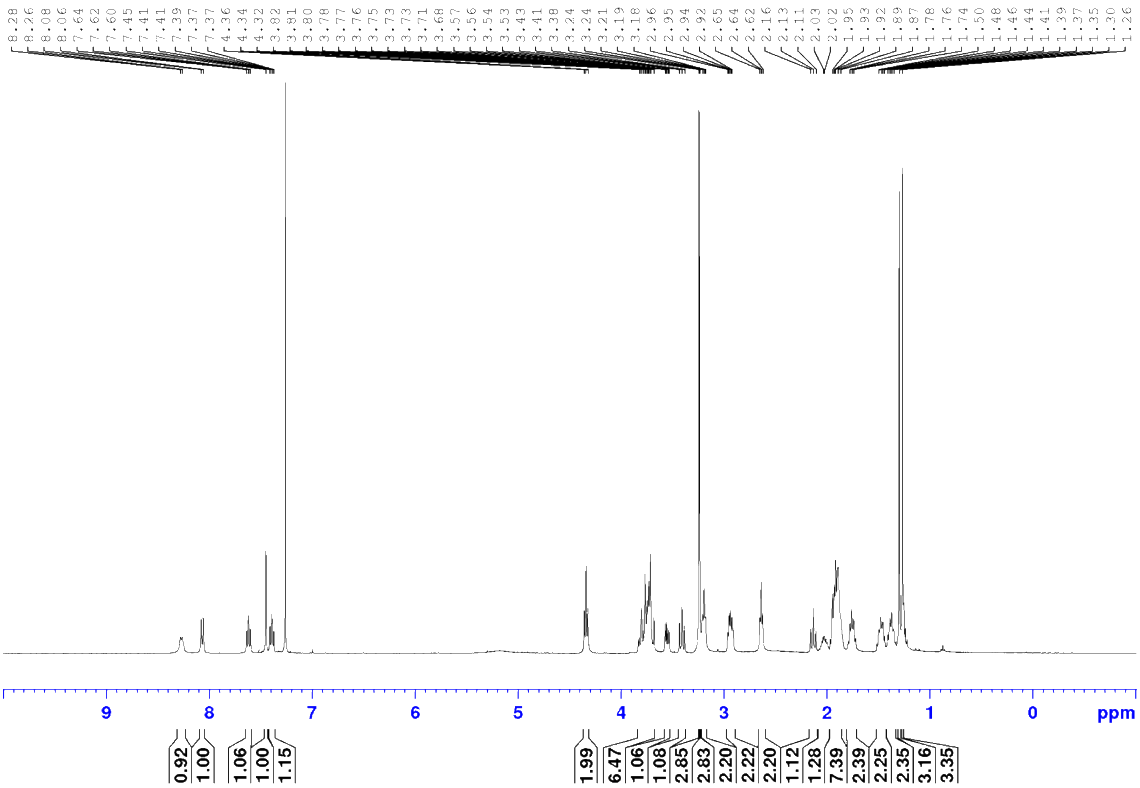


^{13}C-NMR of compound **24b** ($CDCl_3$, 100.61 MHz)

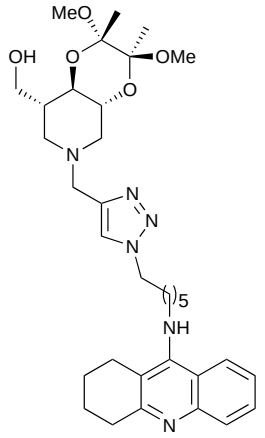


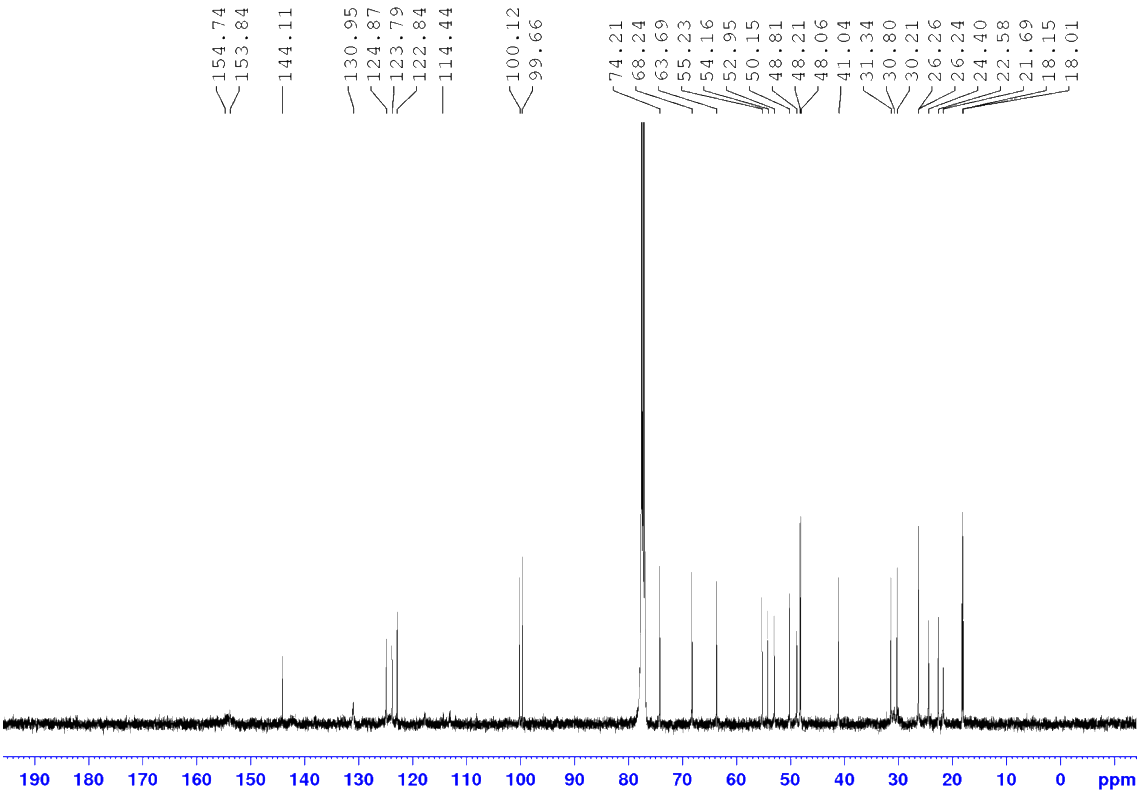
^{1}H-NMR of compound **24c** ($CDCl_3$, 400.13 MHz)



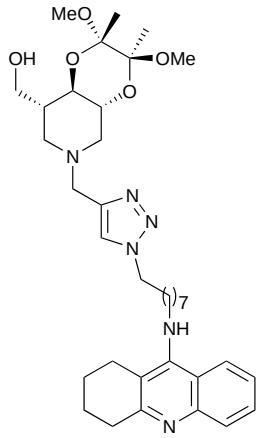


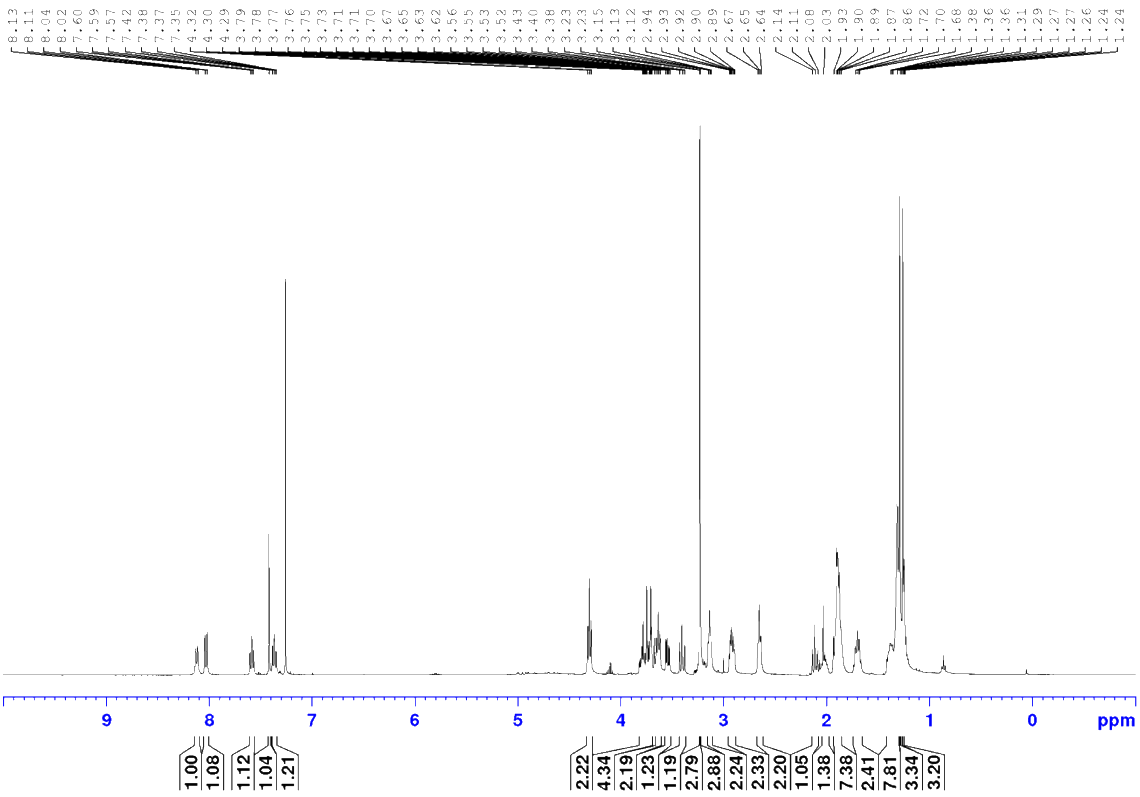
^{13}C-NMR of compound **24c** ($CDCl_3$, 100.61 MHz)



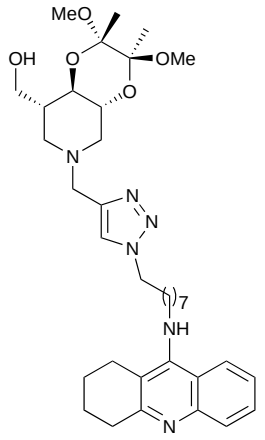


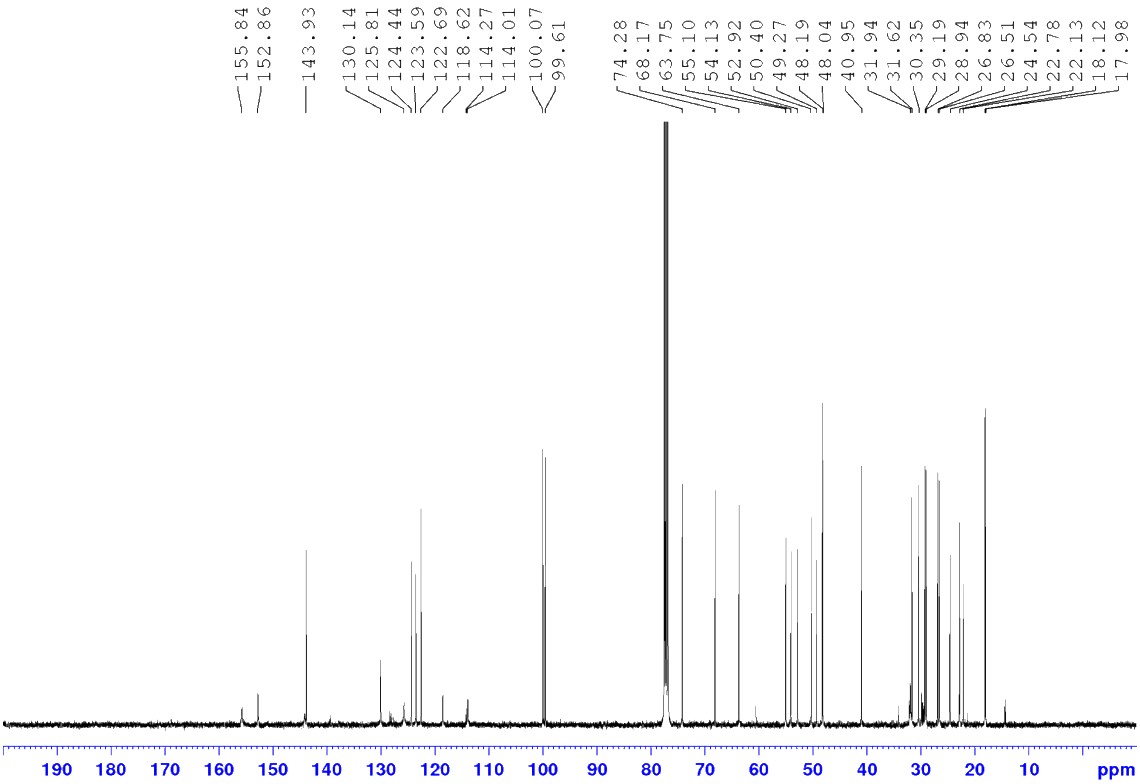
^{1}H-NMR of compound **24d** ($CDCl_3$, 400.13 MHz)



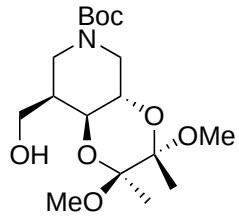


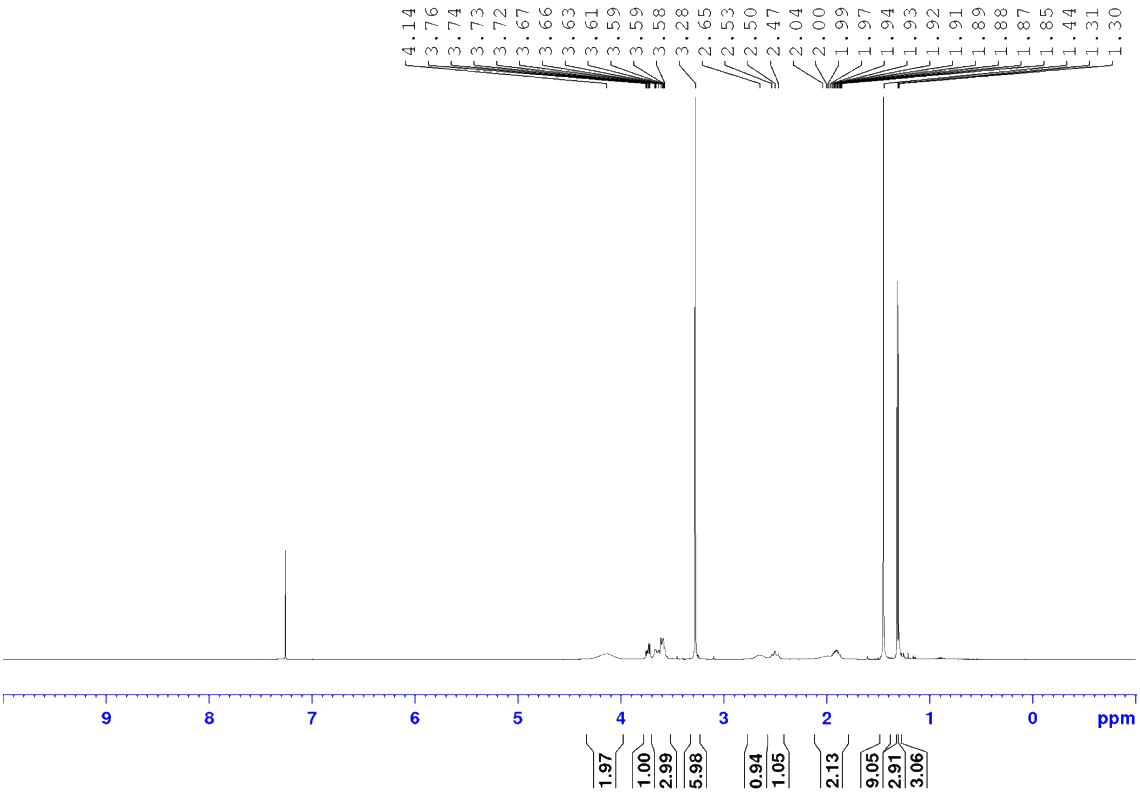
^{13}C-NMR of compound **24d** ($CDCl_3$, 100.61 MHz)



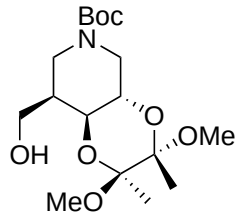


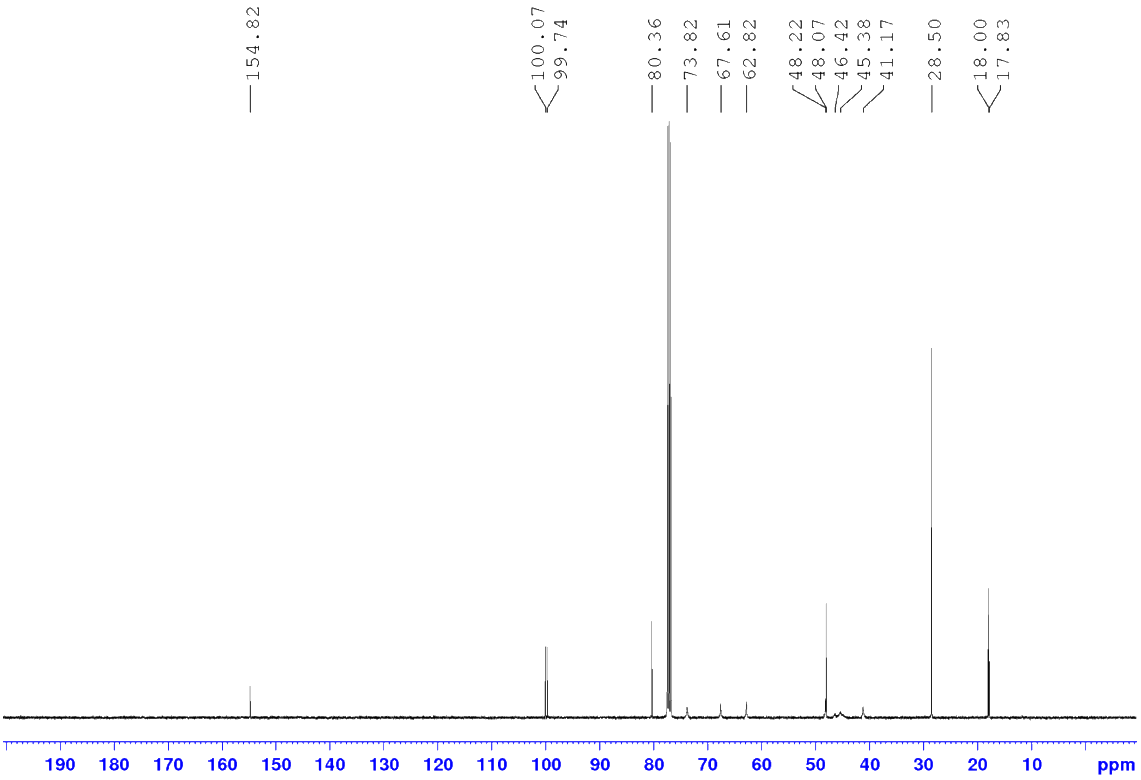
^{1}H-NMR of compound **25** ($CDCl_3$, 400.13 MHz)



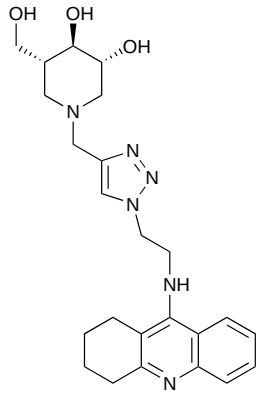


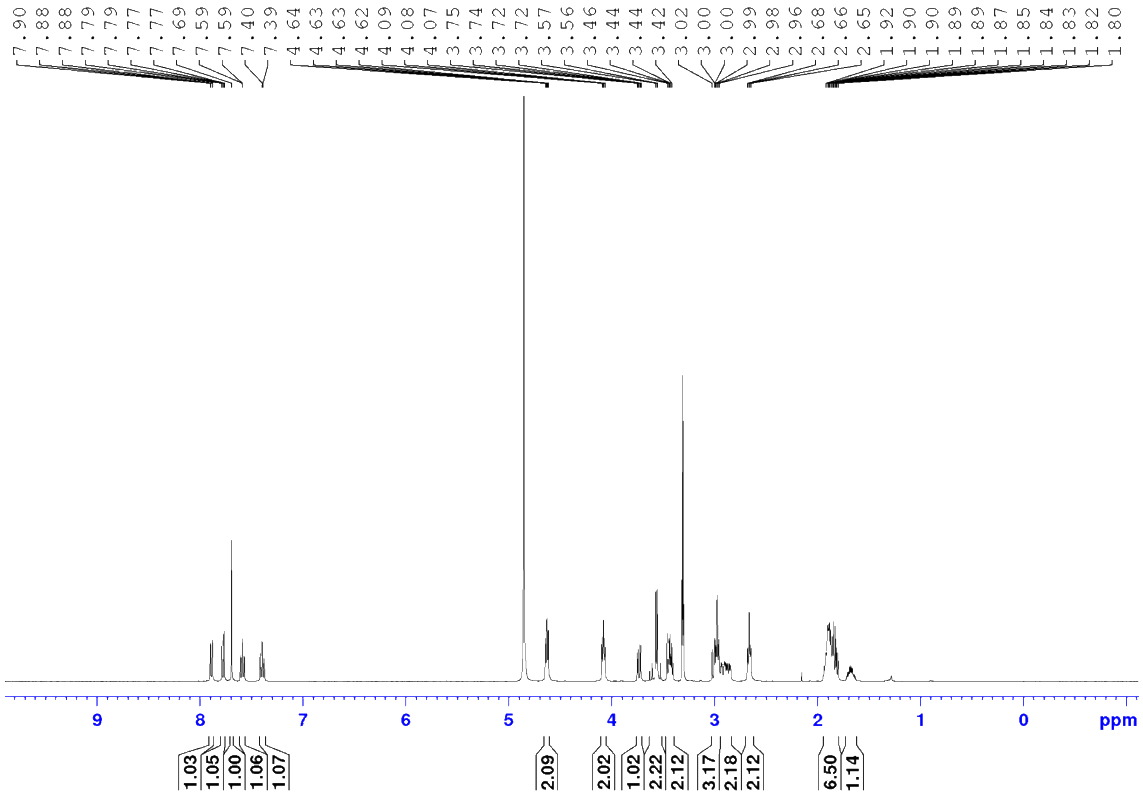
^{13}C-NMR of compound **25** ($CDCl_3$, 100.61 MHz)



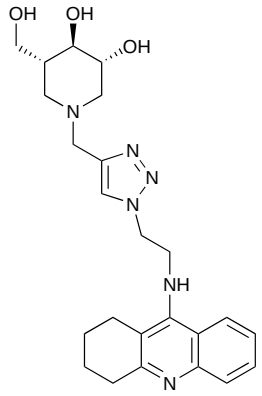


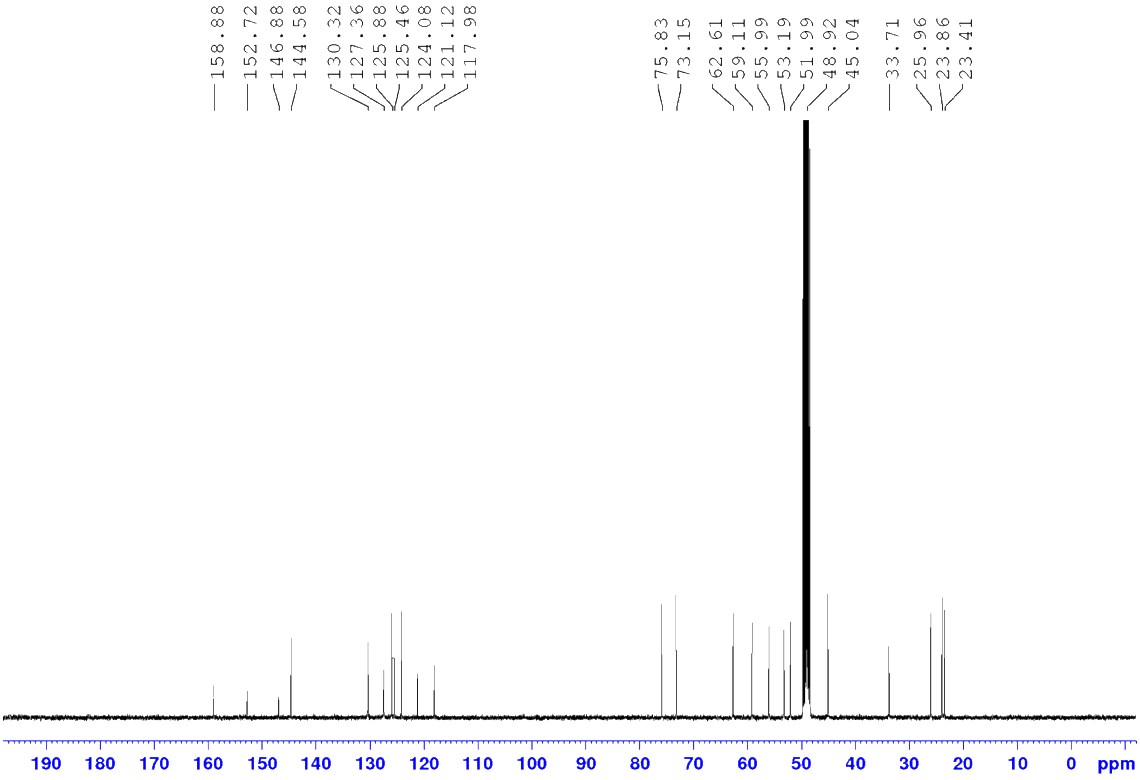
^{1}H-NMR of compound **12a** (CD_3OD, 400.13 MHz)



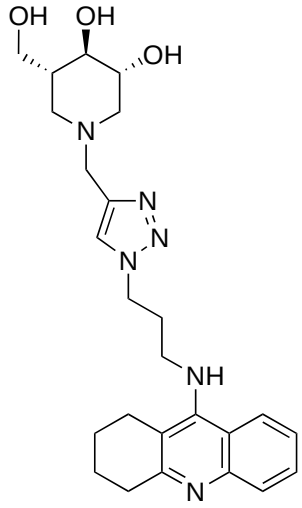


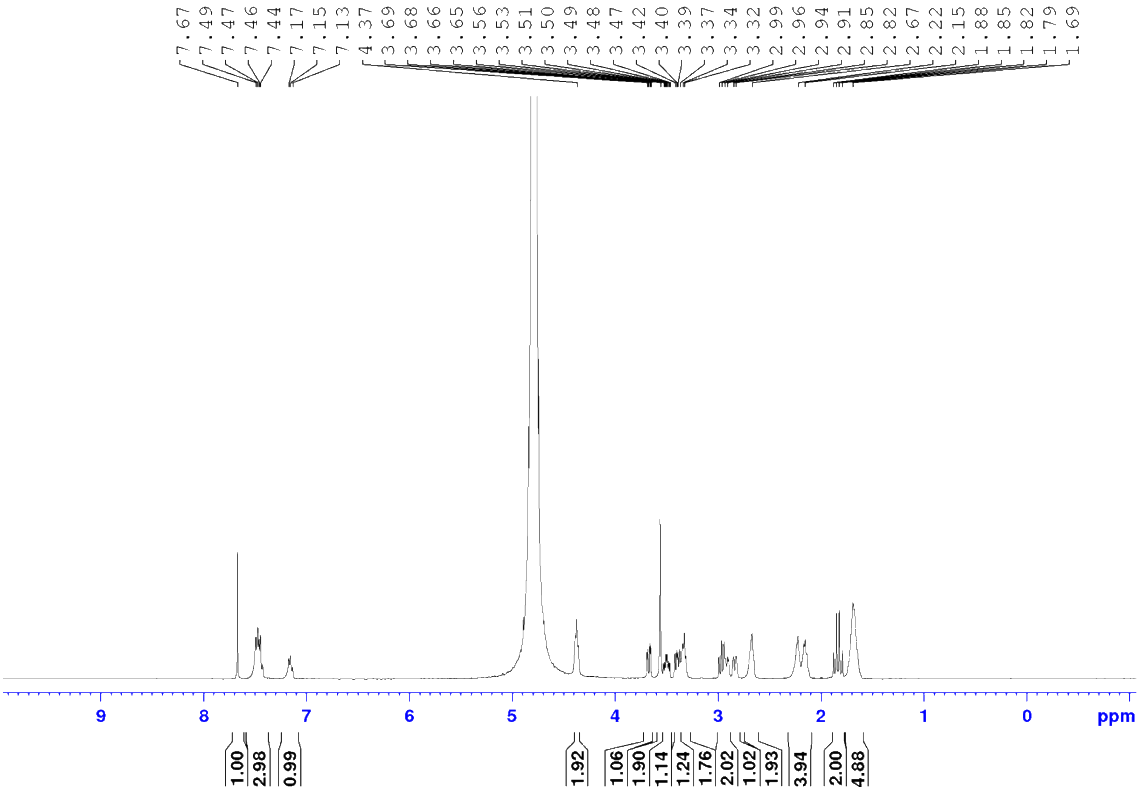
^{13}C-NMR of compound **12a** (CD_3OD, 100.61 MHz)



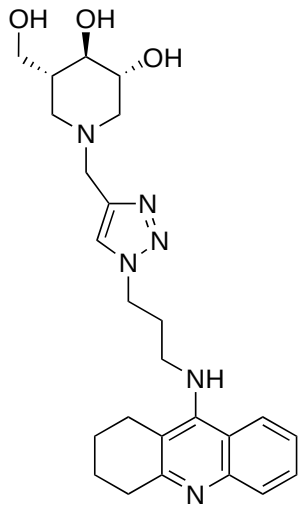


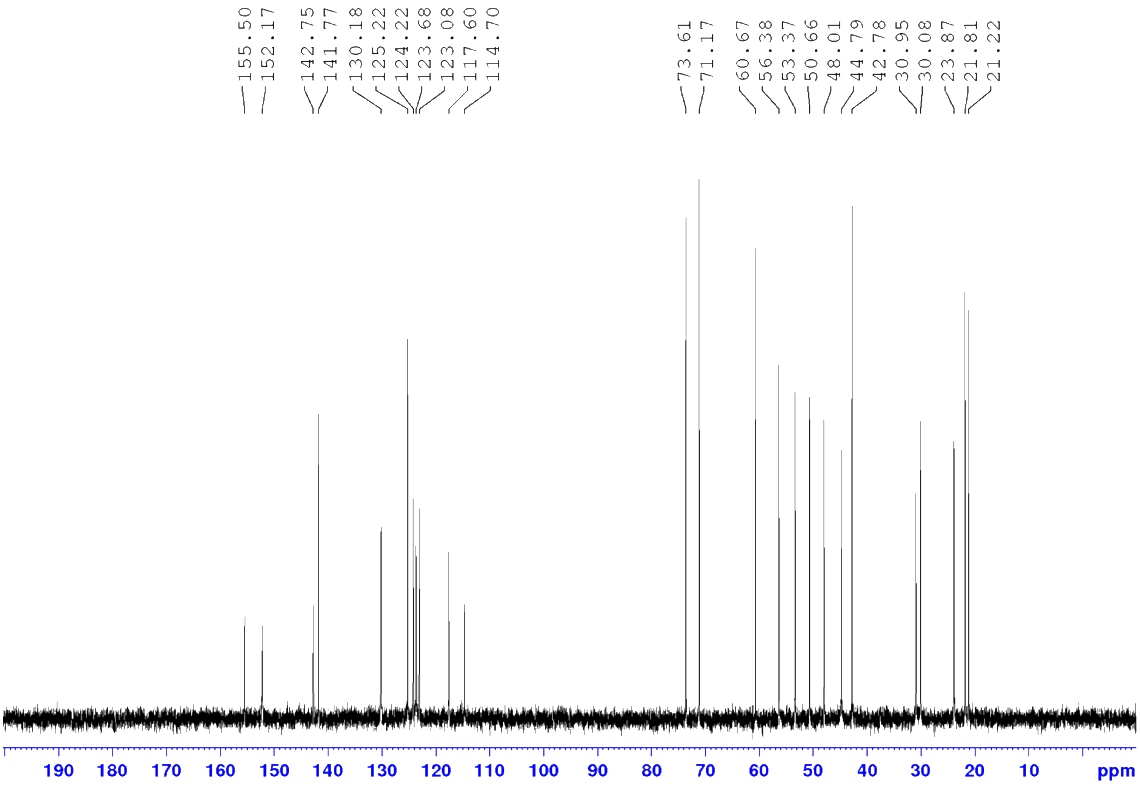
^{1}H-NMR of compound **12b** (D_2O, 400.13 MHz)



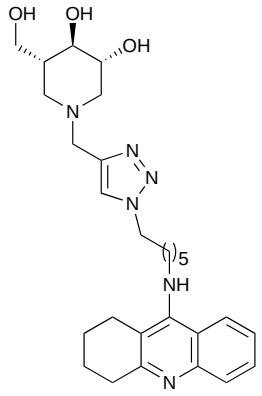


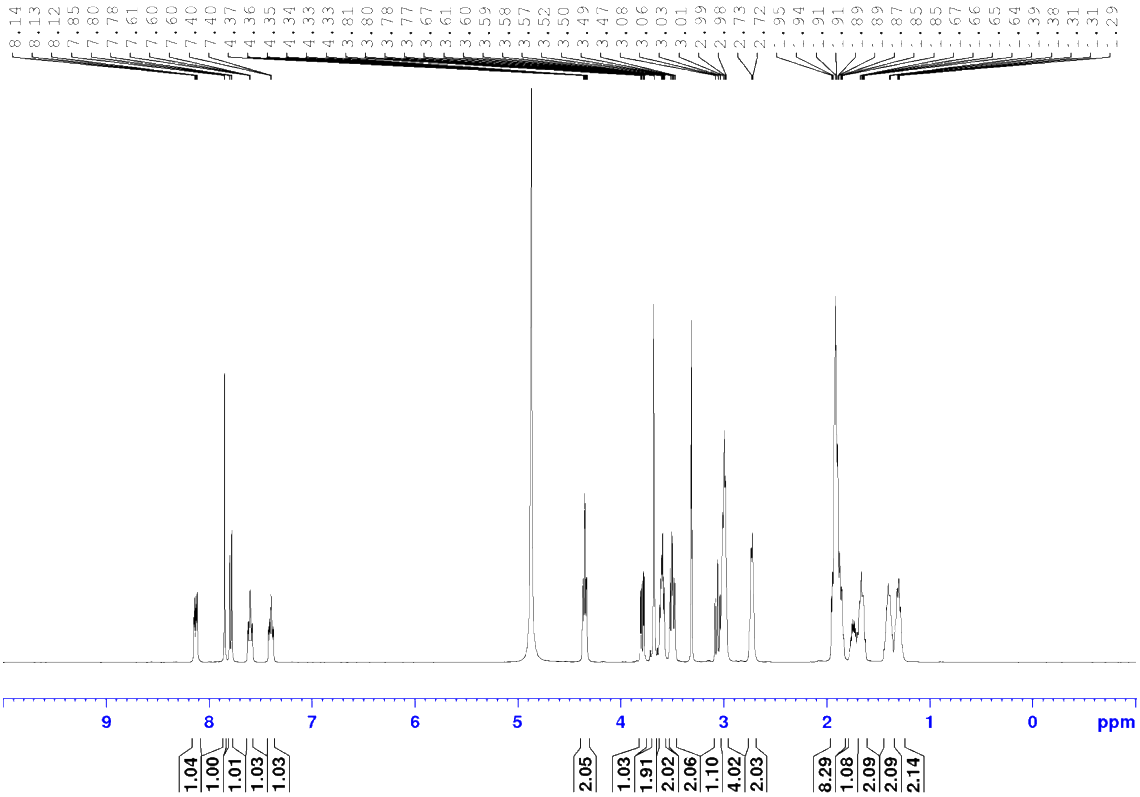
^{13}C-NMR of compound **12b** (D_2O, 100.61 MHz)



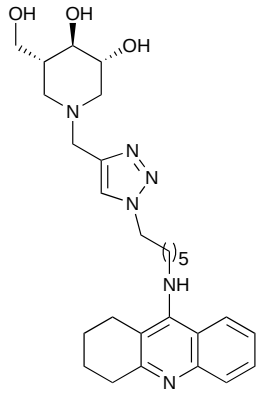


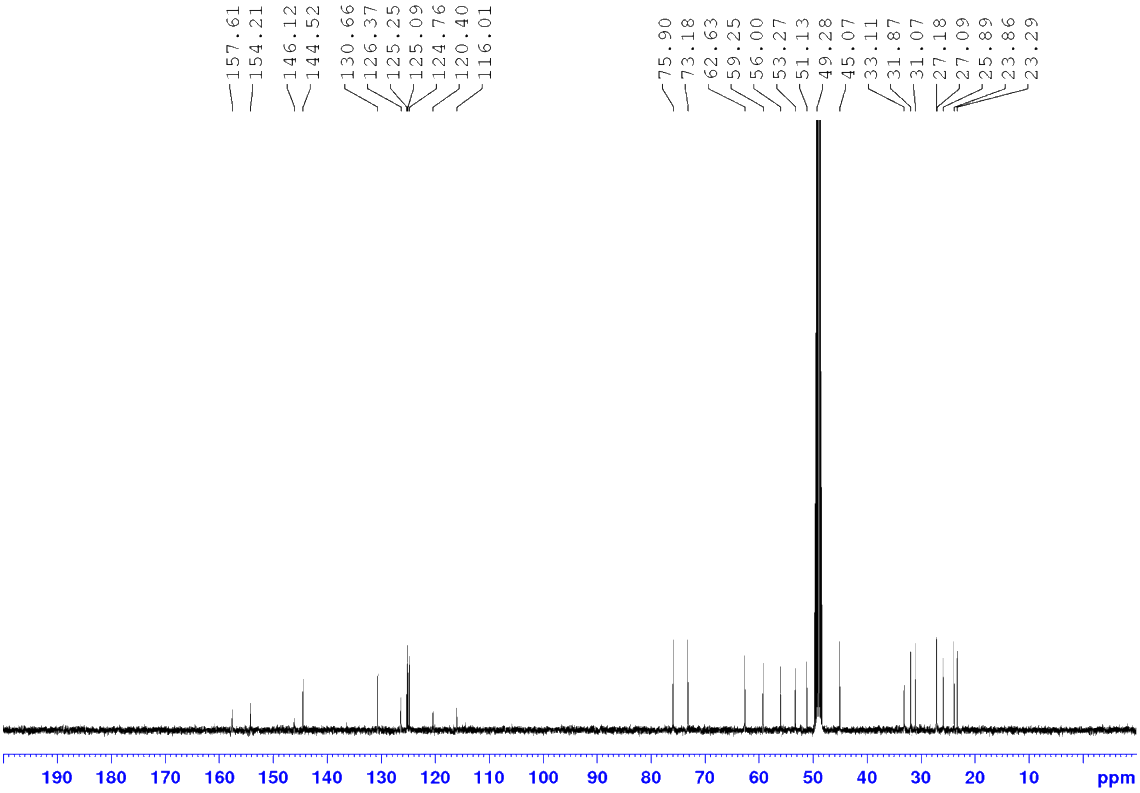
^{1}H-NMR of compound **12c** (CD_3OD, 400.13 MHz)



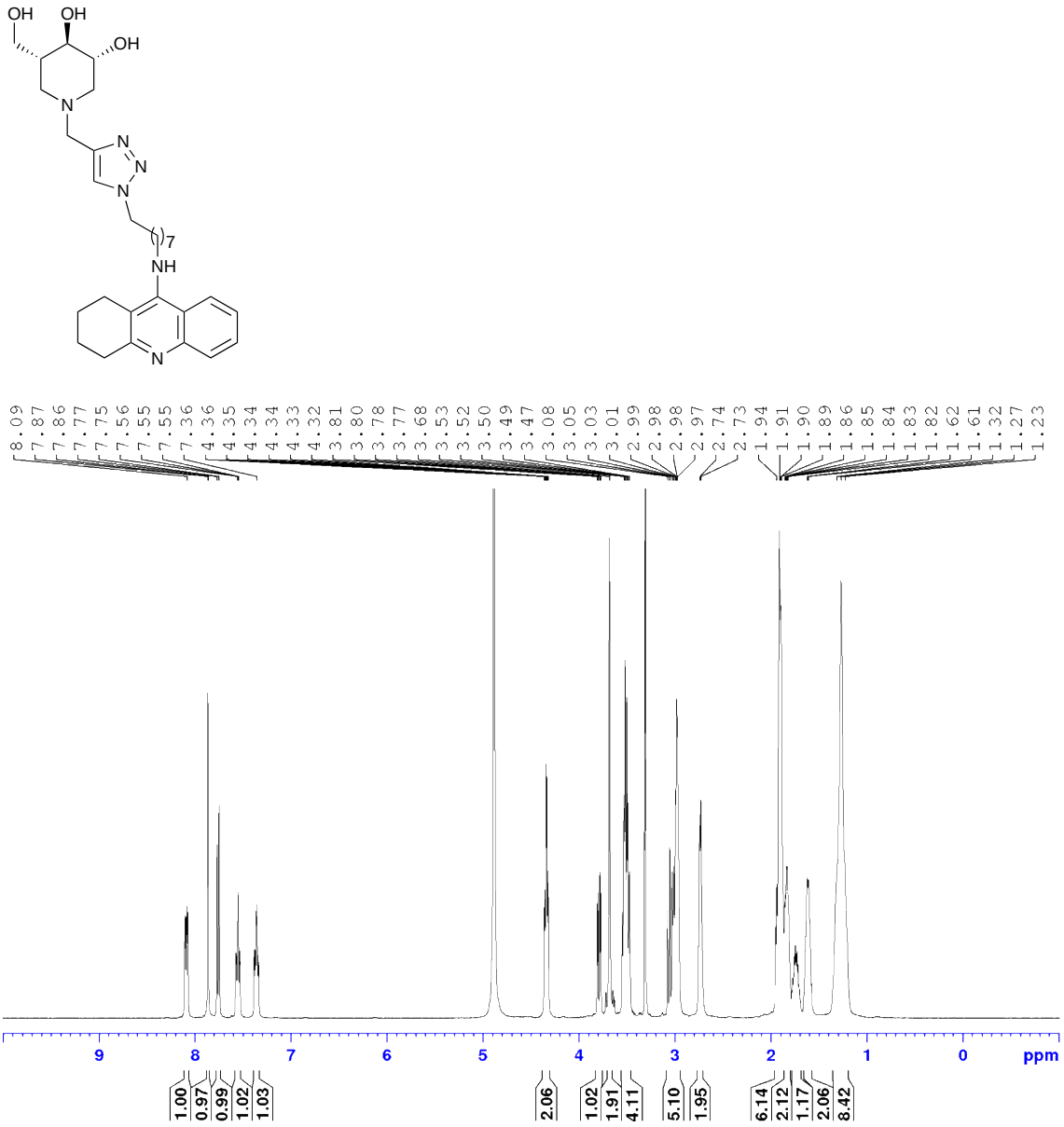


^{13}C-NMR of compound **12c** (CD_3OD, 100.61 MHz)

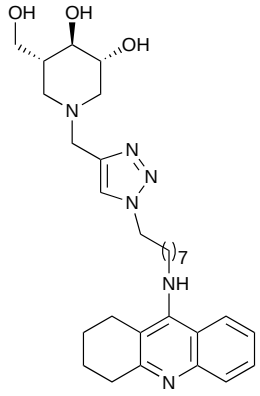


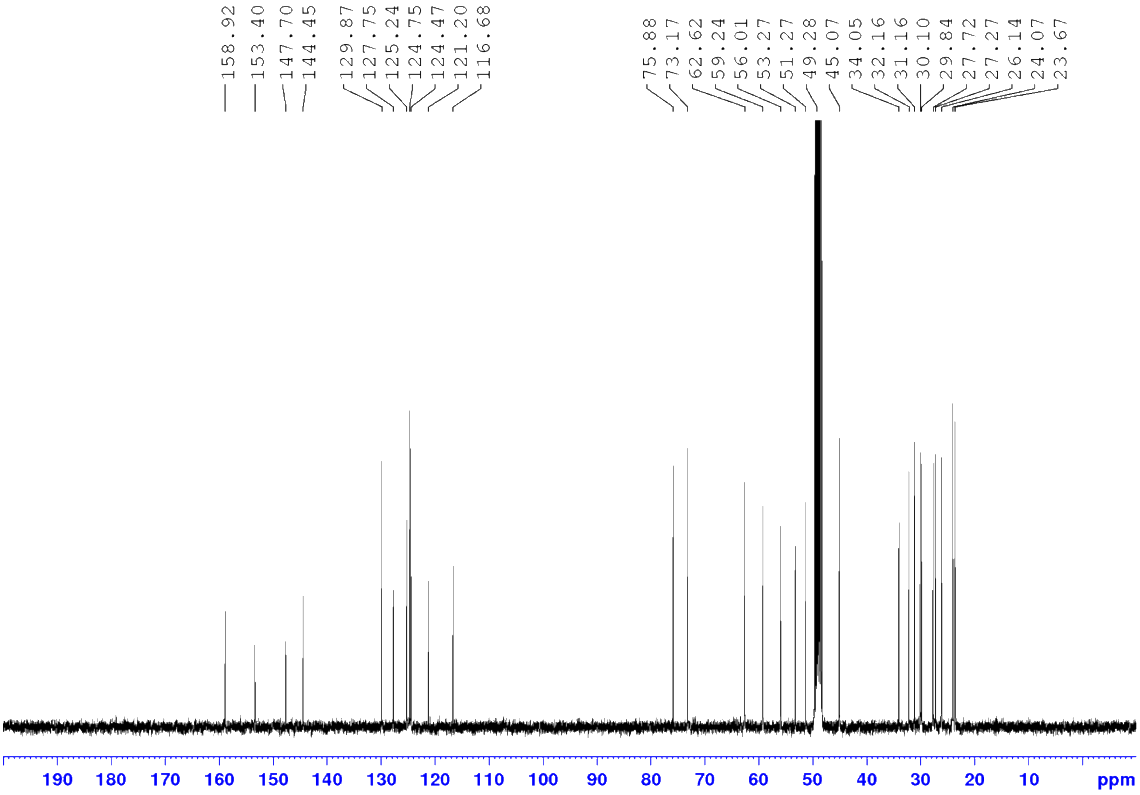


^{1}H-NMR of compound **12d** (CD_3OD, 400.13 MHz)

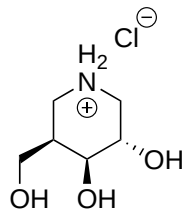


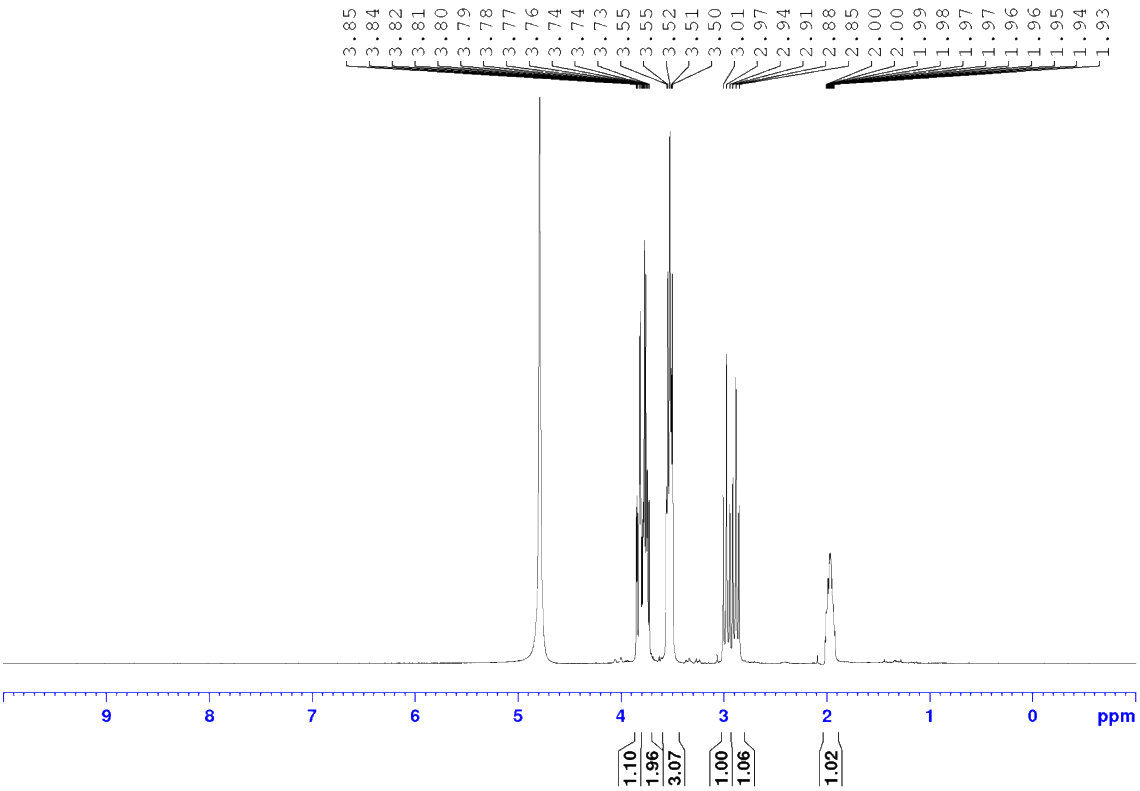
^{13}C-NMR of compound **12d** (CD_3OD, 100.61 MHz)



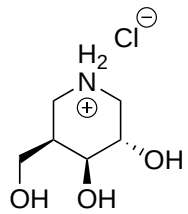


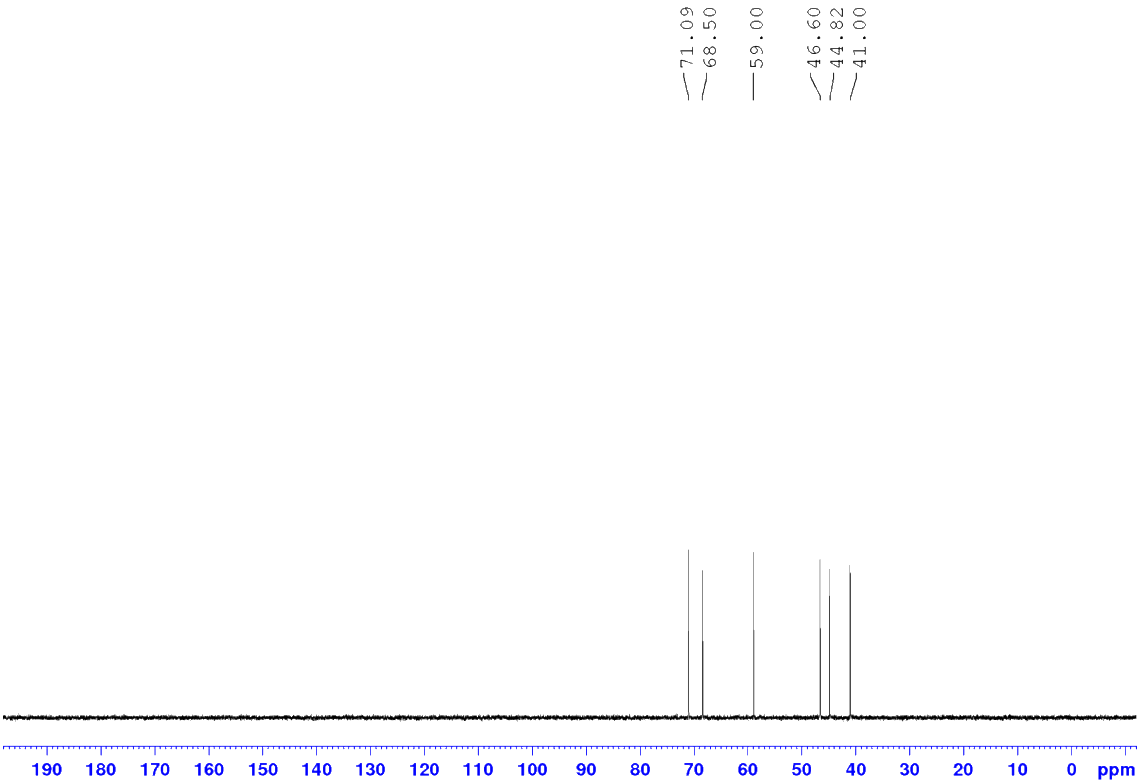
^{1}H-NMR of compound **6HCl** (D_2O, 400.13 MHz)



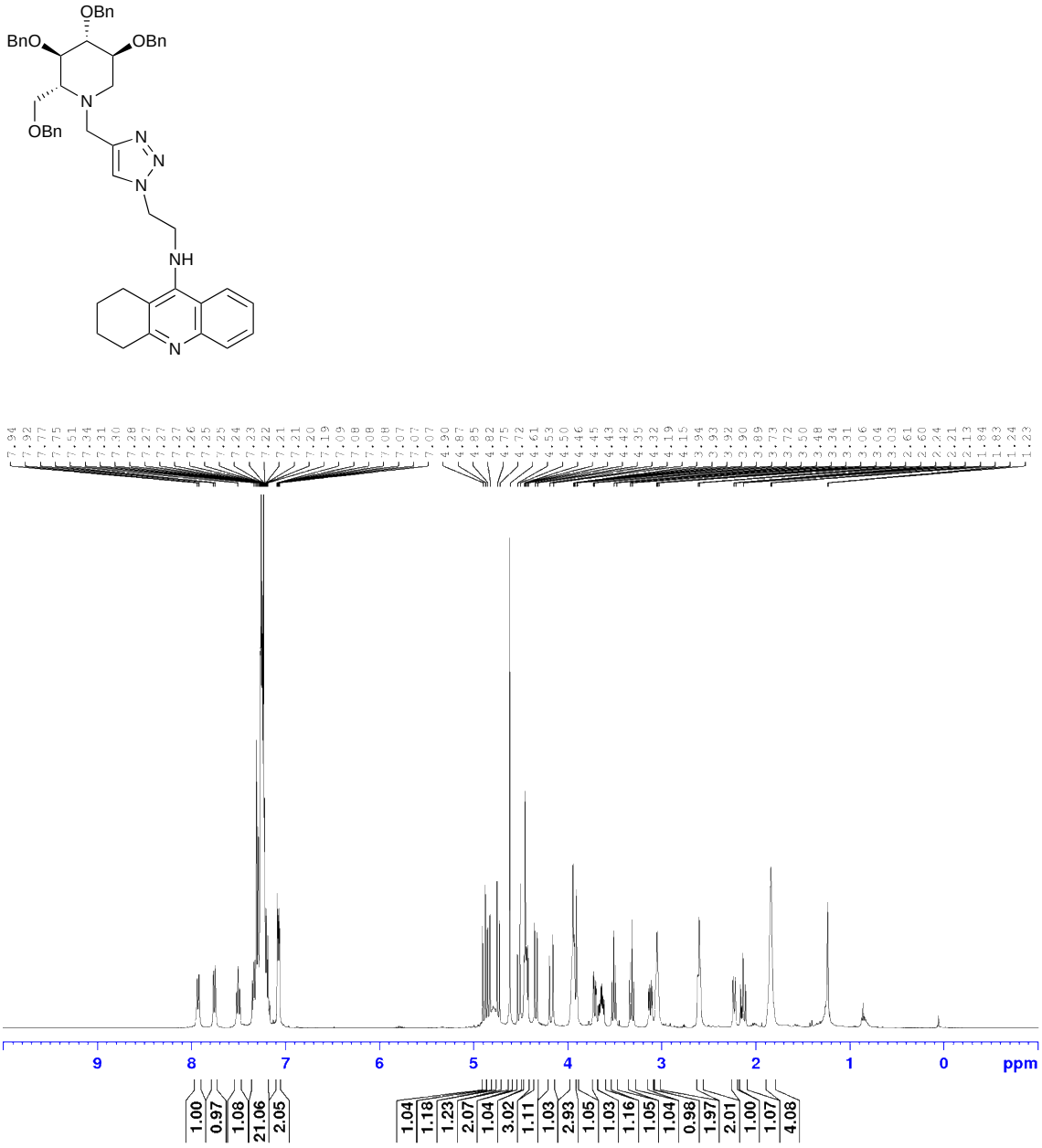


^{13}C-NMR of compound **6HCl** (D_2O, 100.61 MHz)

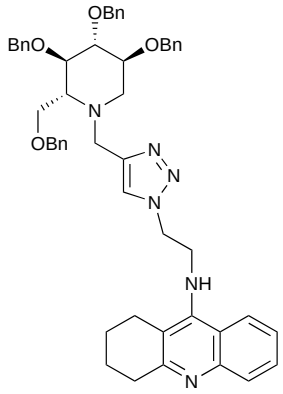


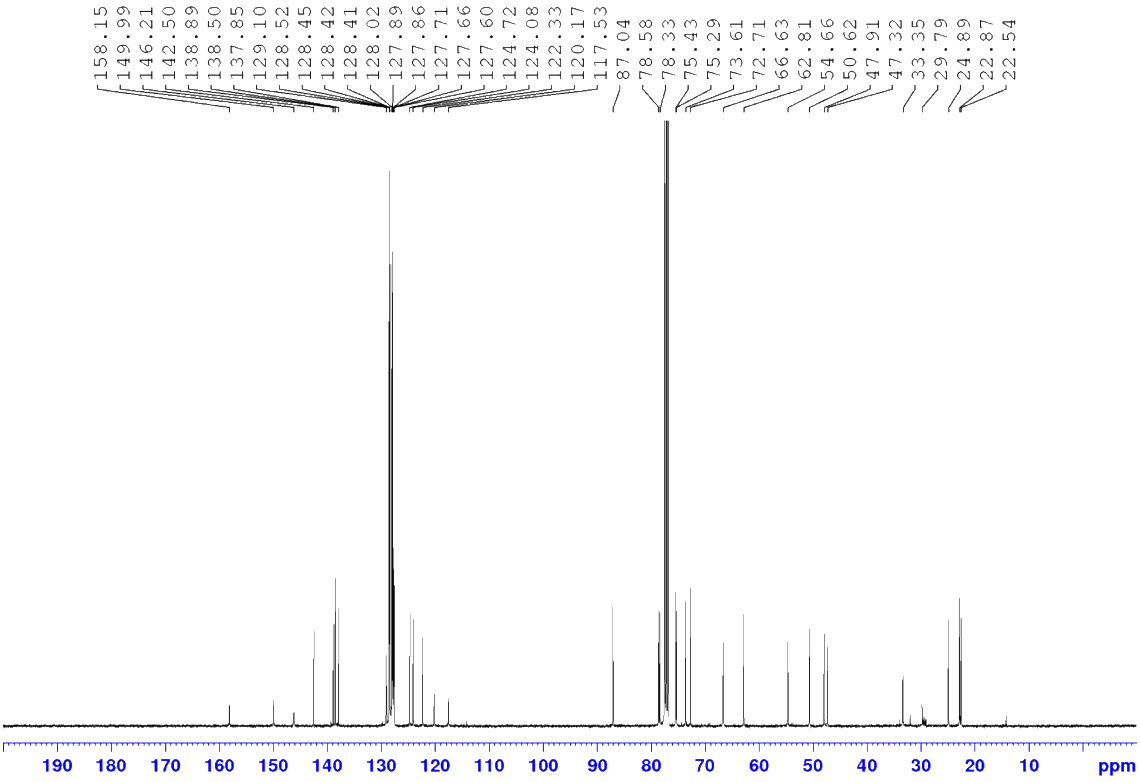


^{1}H-NMR of compound **27a** ($CDCl_3$, 400.13 MHz)

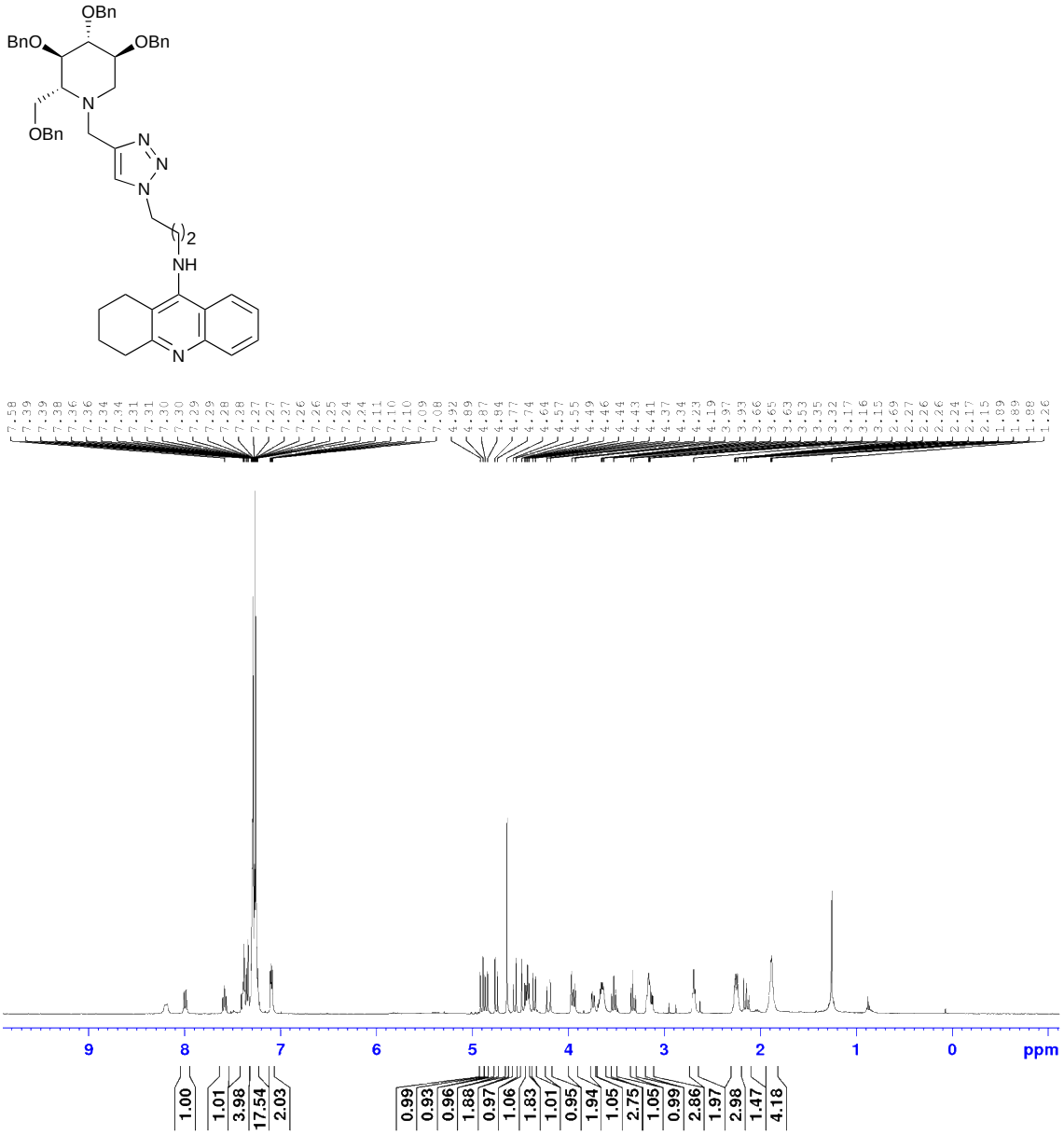


^{13}C-NMR of compound **27a** ($CDCl_3$, 100.61 MHz)

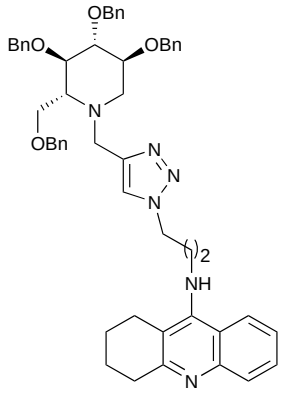


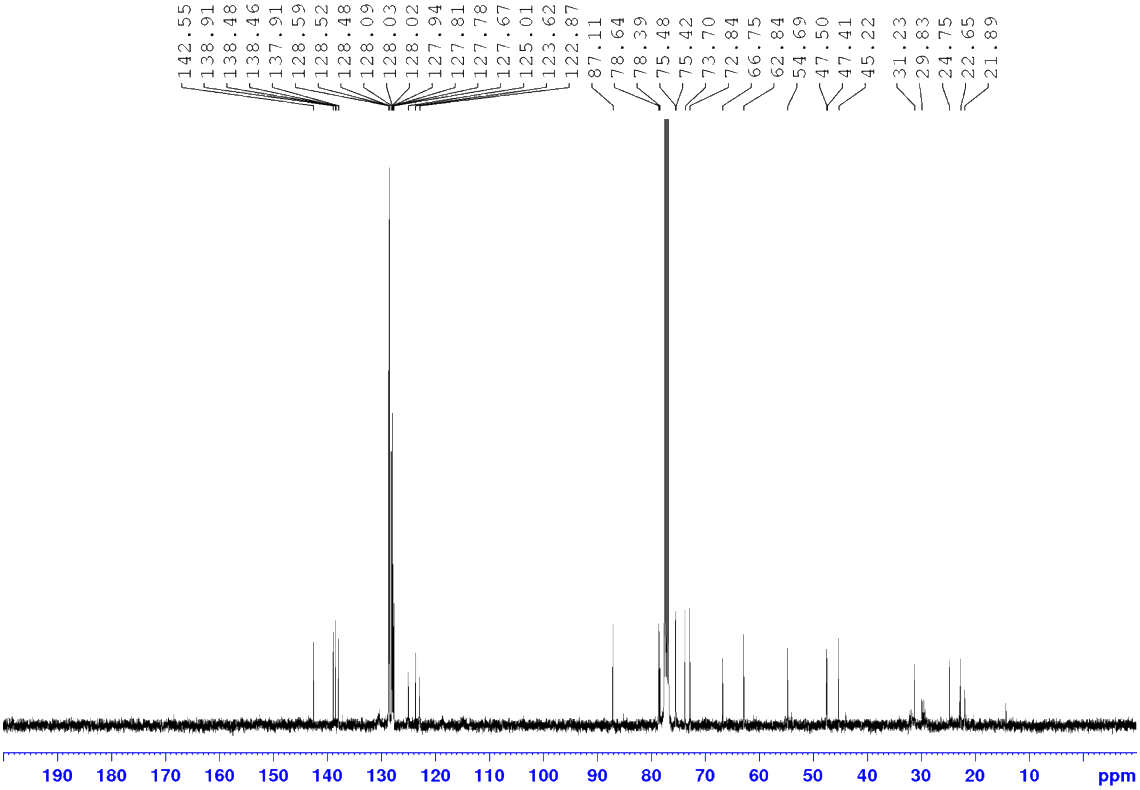


^{1}H-NMR of compound **27b** ($CDCl_3$, 400.13 MHz)

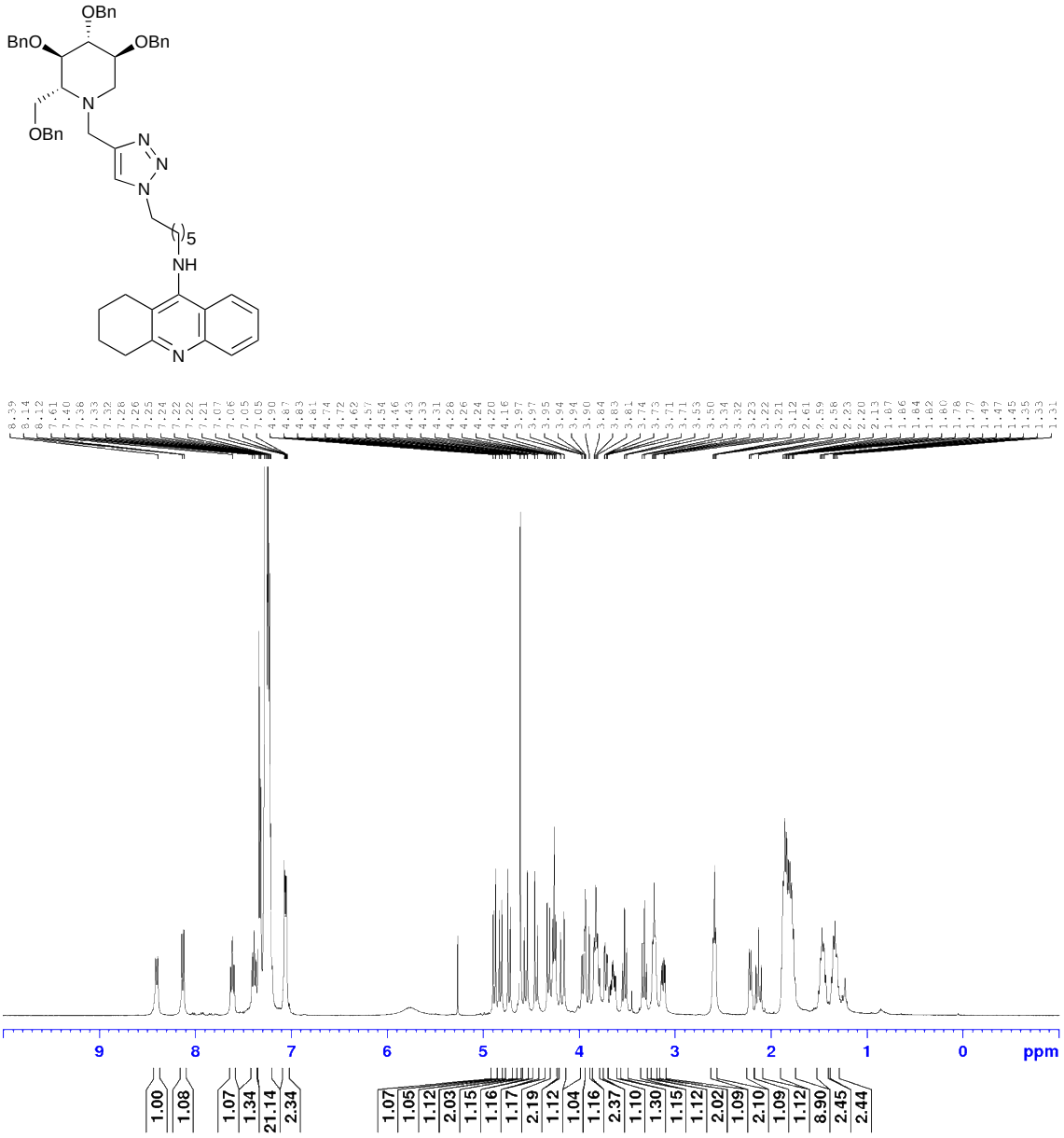


^{13}C-NMR of compound **27b** ($CDCl_3$, 100.61 MHz)

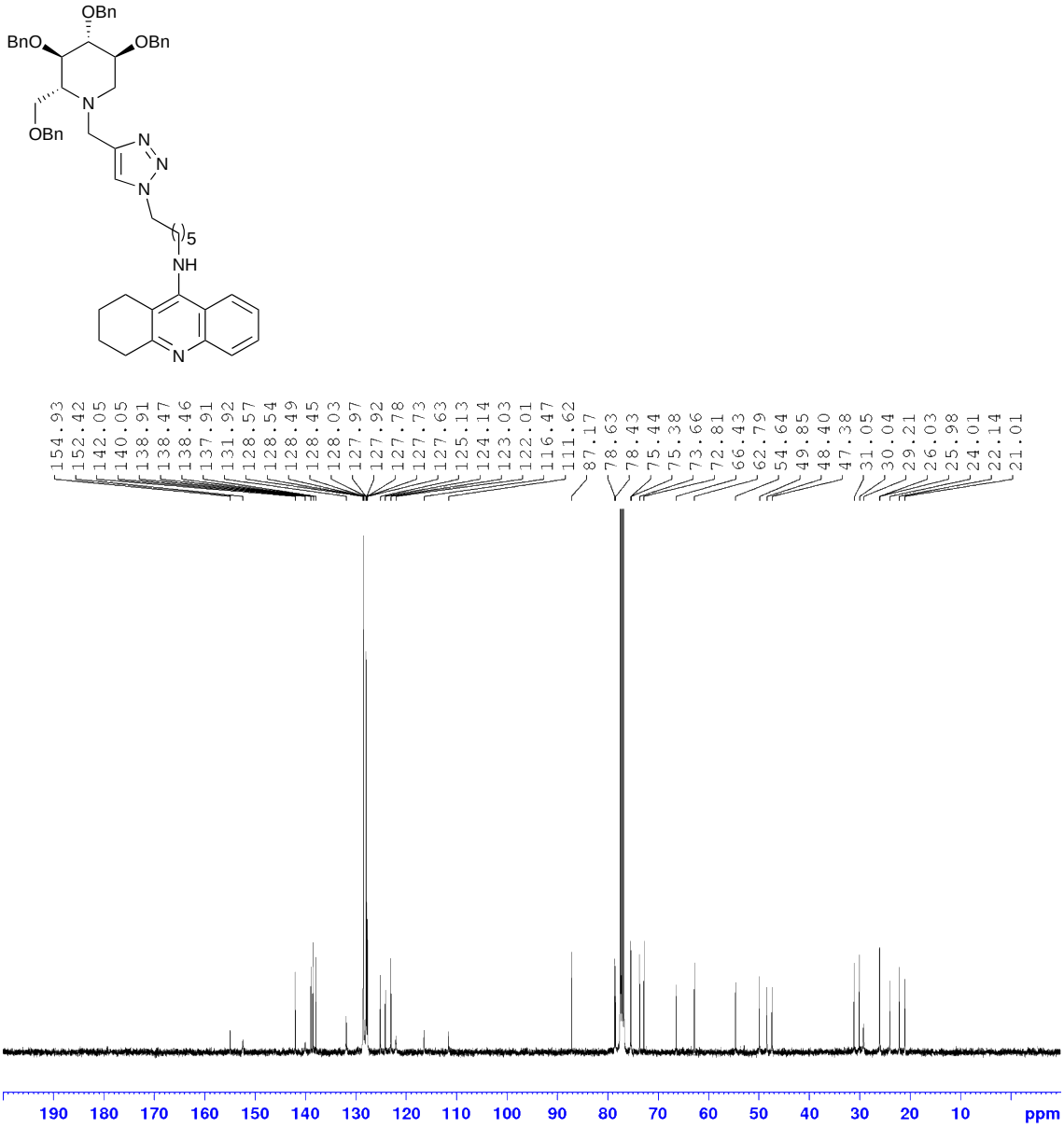




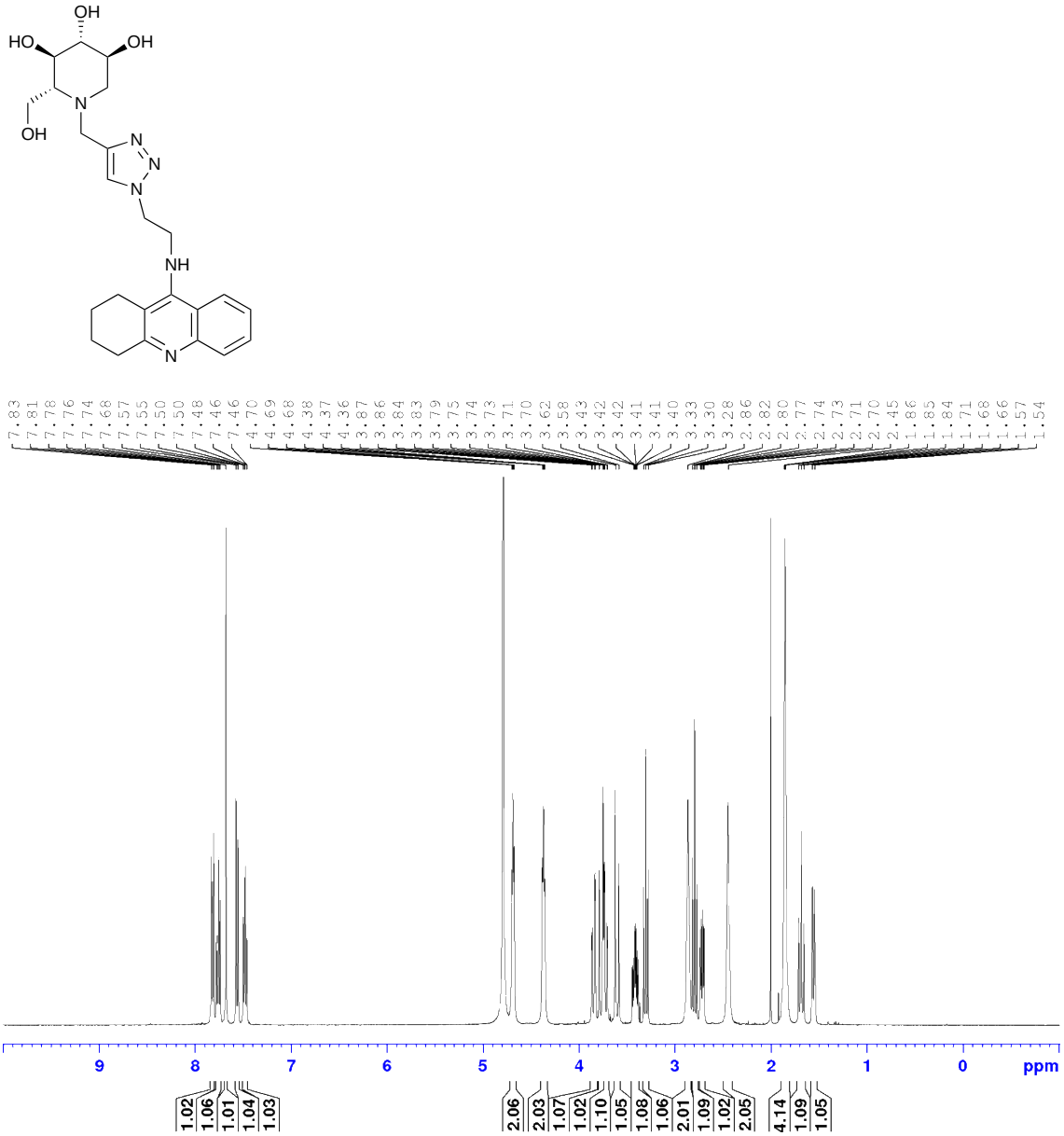
^{1}H-NMR of compound **27c** ($CDCl_3$, 400.13 MHz)



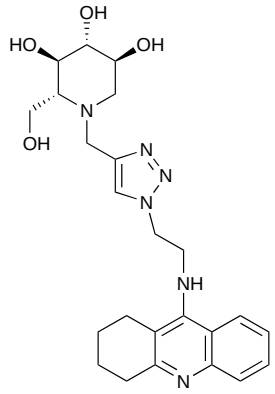
^{13}C-NMR of compound **27c** ($CDCl_3$, 100.61 MHz)

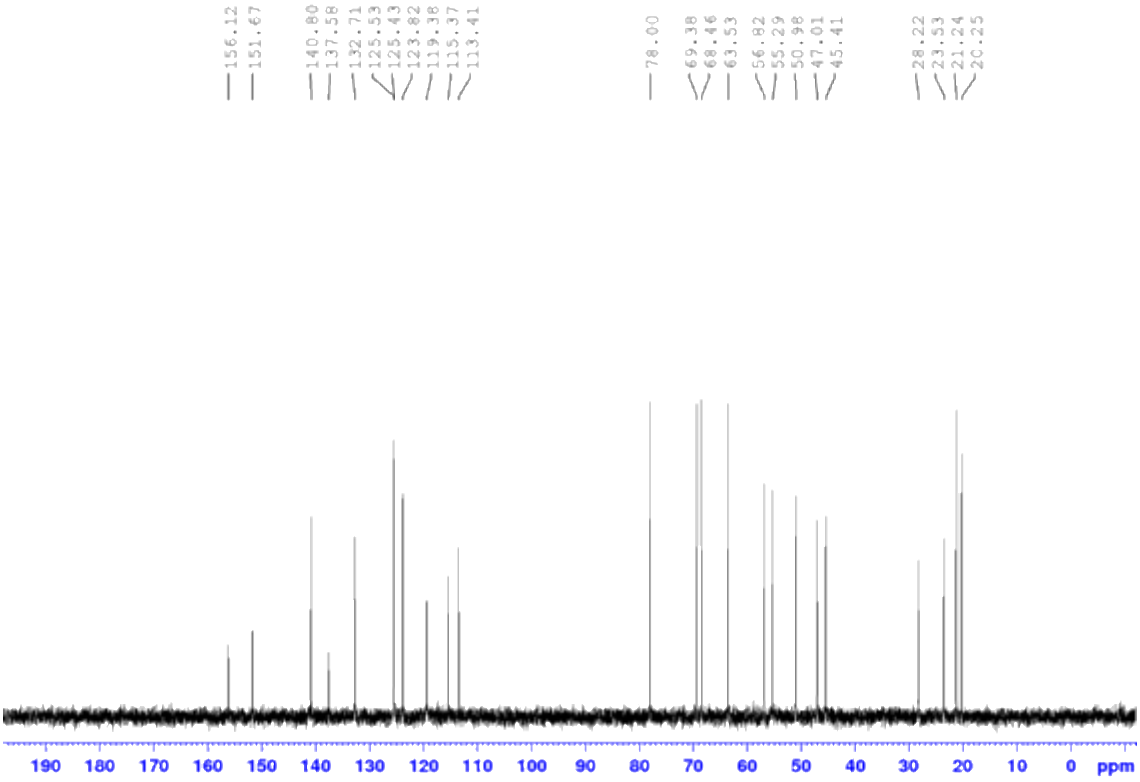


^{1}H-NMR of compound **13a** (D_2O, 400.13 MHz)

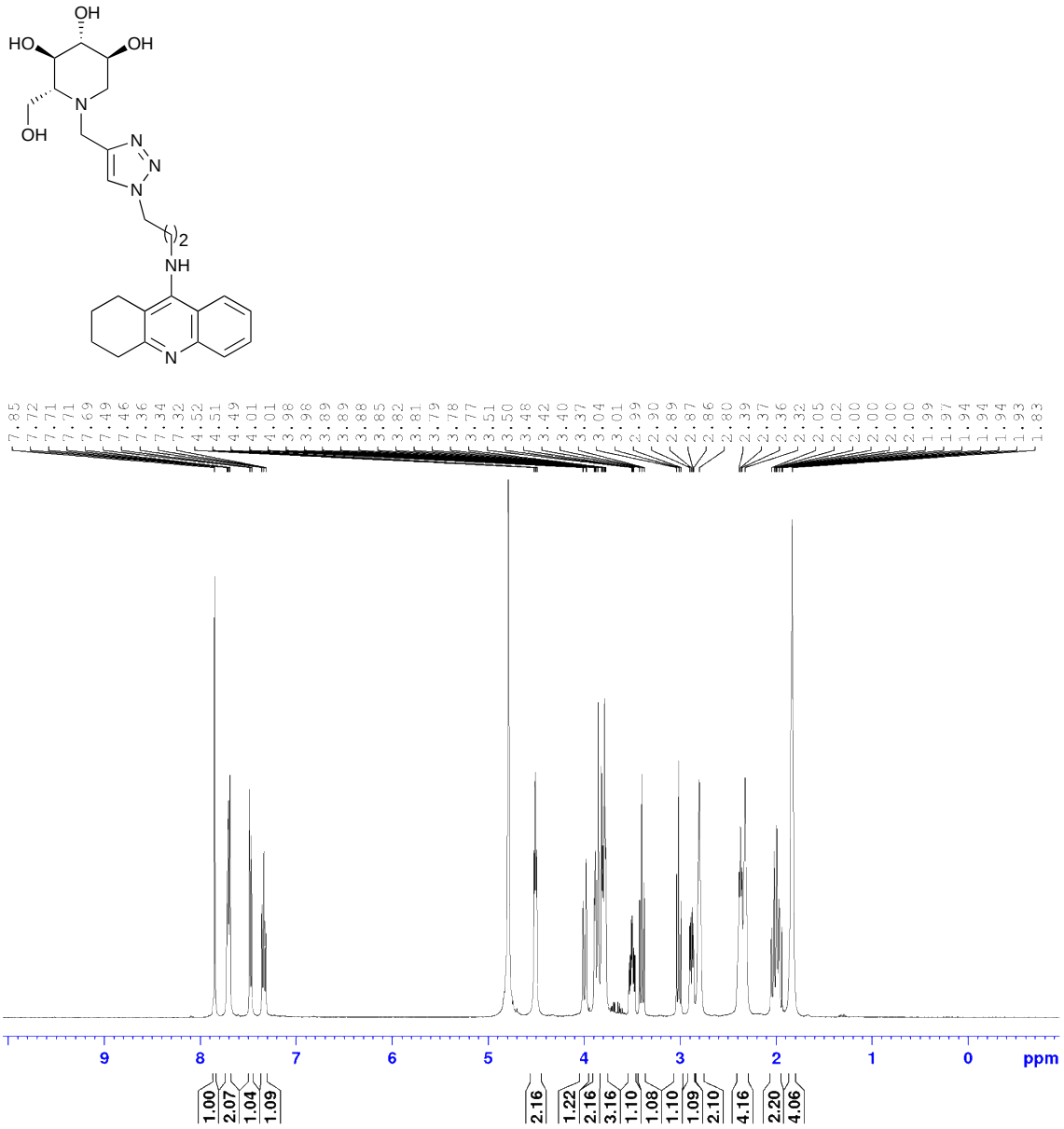


^{13}C-NMR of compound **13a** (D_2O, 100.61 MHz)

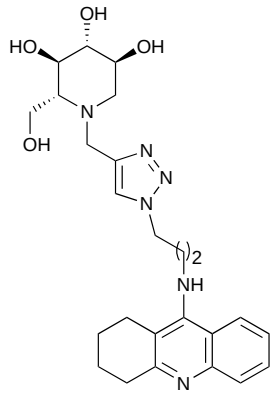


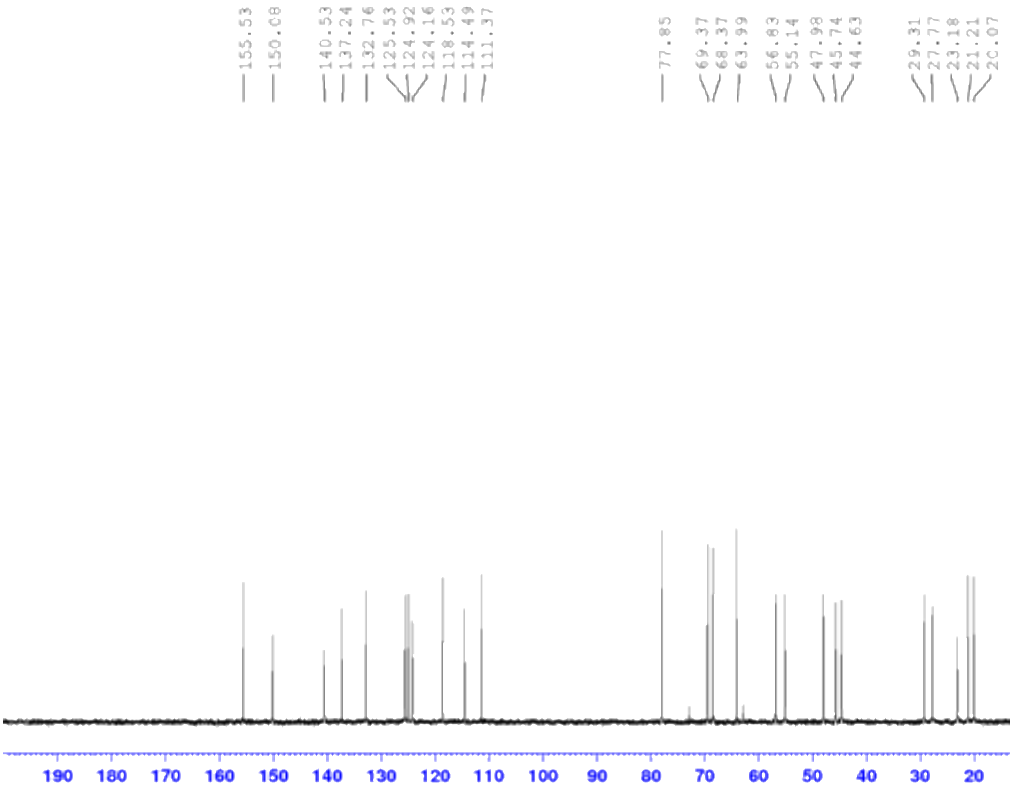


^{1}H-NMR of compound **13b** (D_2O, 400.13 MHz)

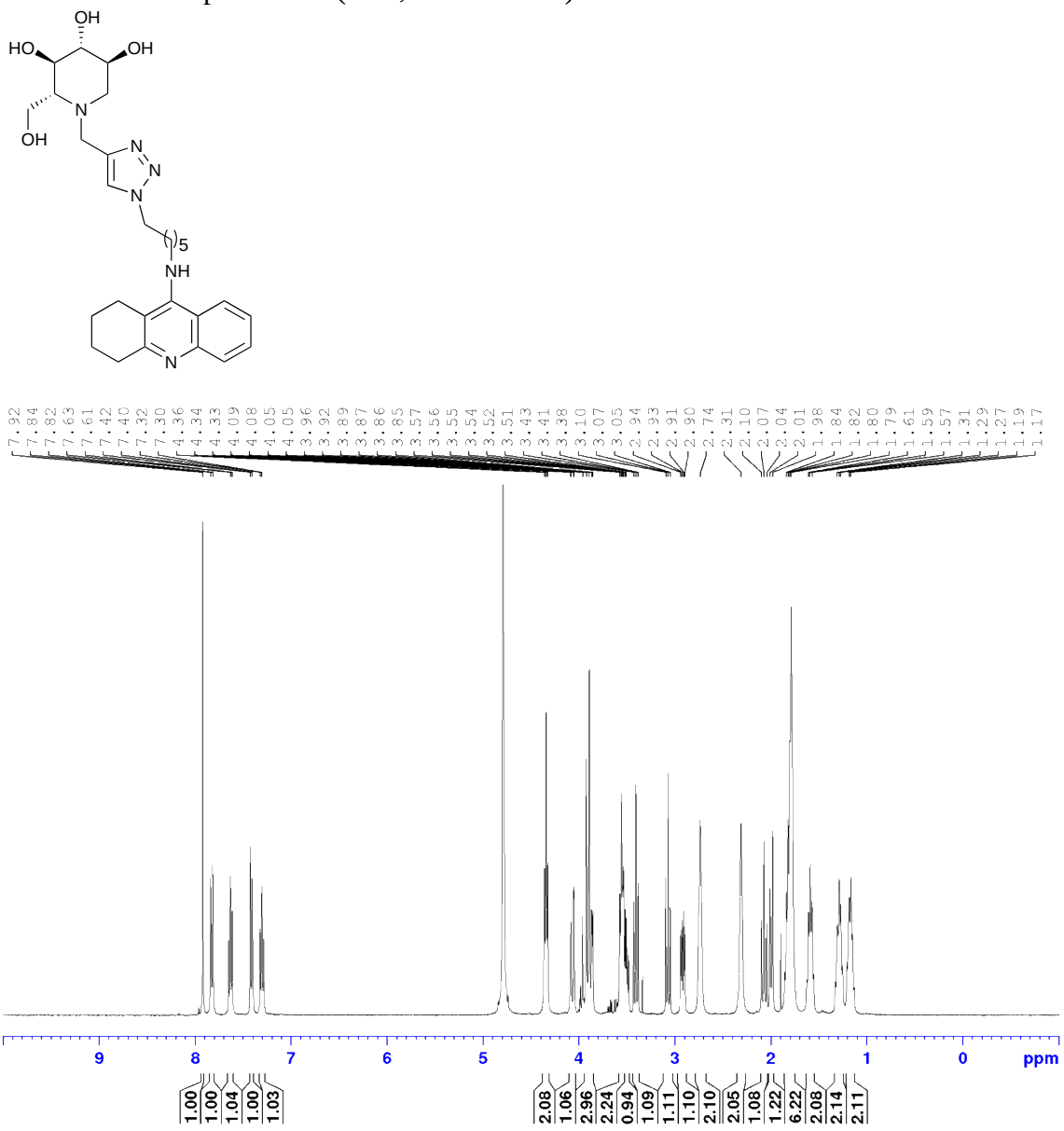


^{13}C-NMR of compound **13b** (D_2O, 100.61 MHz)





^{1}H-NMR of compound **13c** (D_2O, 400.13 MHz)



^{13}C-NMR of compound **13c** (D_2O, 100.61 MHz)