Electronic Supplementary Material (ESI) for Metallomics.

Supplementary Information

Tacrine-deferiprone hybrids as multi-target-directed metal chelators against Alzheimer's disease: two in one drug

Karam Chand[‡,a], Rajeshwari[‡ a], Emanuel Candeias[b], Sandra M Cardoso[b,c], Sílvia Chaves[a], M. Amélia Santos[a]*

[a]Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal

[b]CNC–Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal. [c]Institute of Molecular and Cell Biology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[‡] Authors contributed equally

* Corresponding author: M.A. Santos, E-mail address: masantos@ist.utl.pt

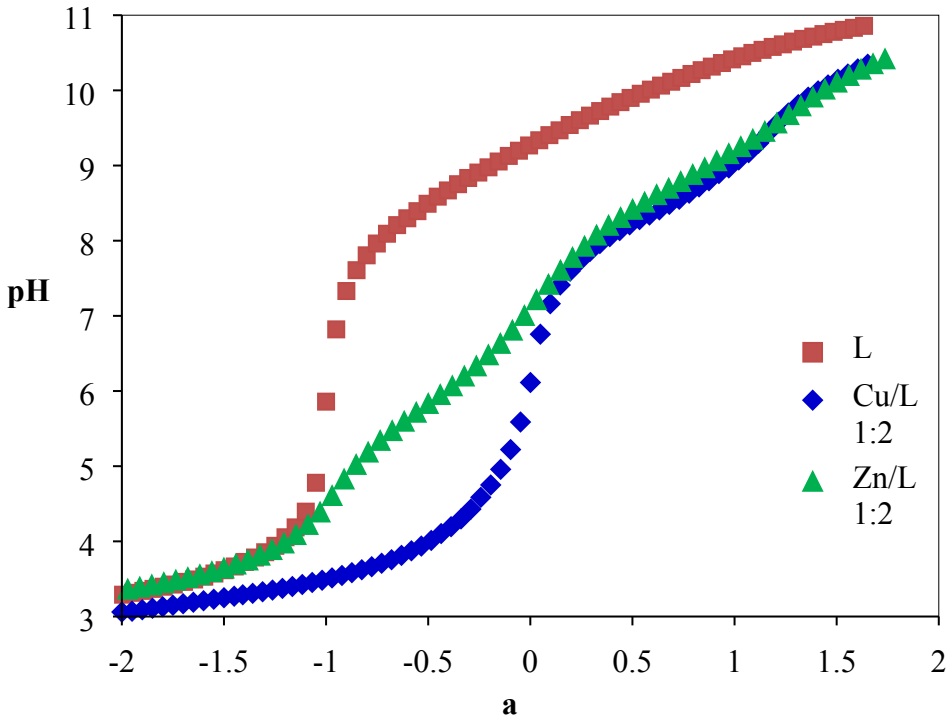


Fig. S1. Potentiometric titration curves of **32** (20% w/w DMSO/H_2O, I = 0.1 M KCl, T = 25.0 ± 0.1 °C, $C_L = 2 \times 10^{-4}$ M); **a** represents moles of base per mole of ligand

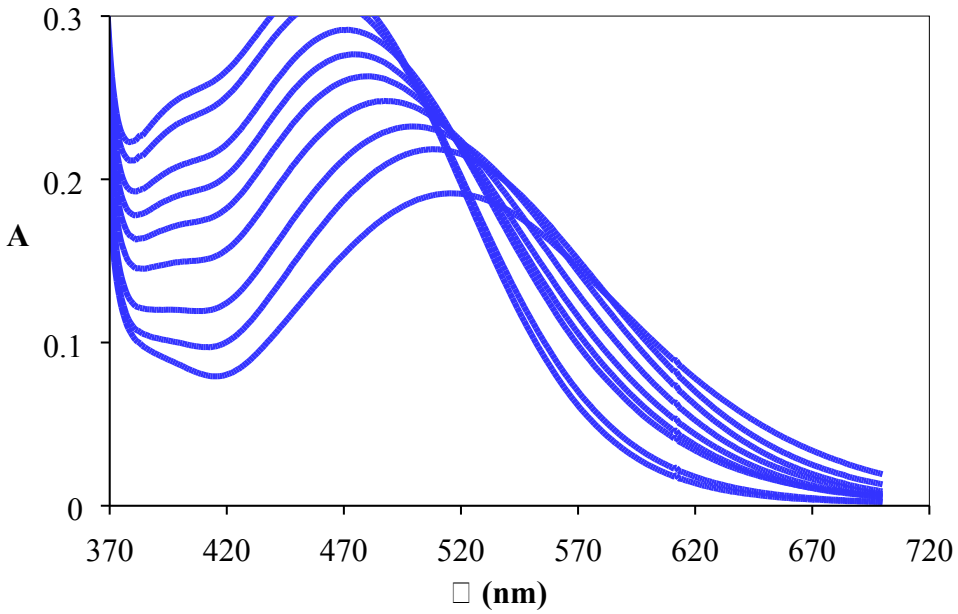


Fig. S2 Electronic spectra for the 1:3 Fe(III)/**32** system (pH 2.42-7.43, C_L = 2.0 $\times 10^{-4}$ M).

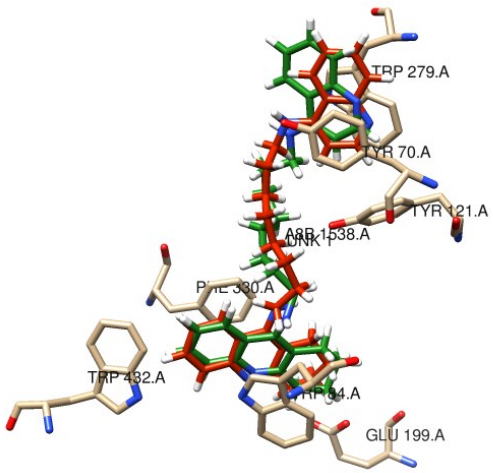
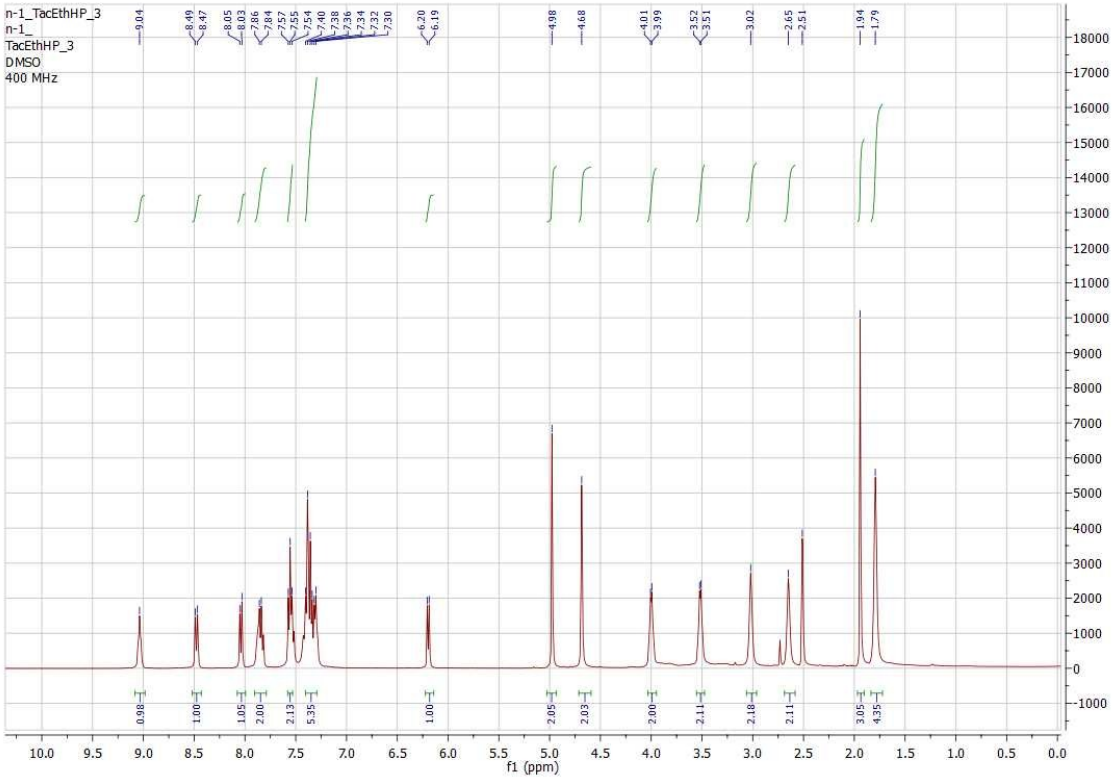
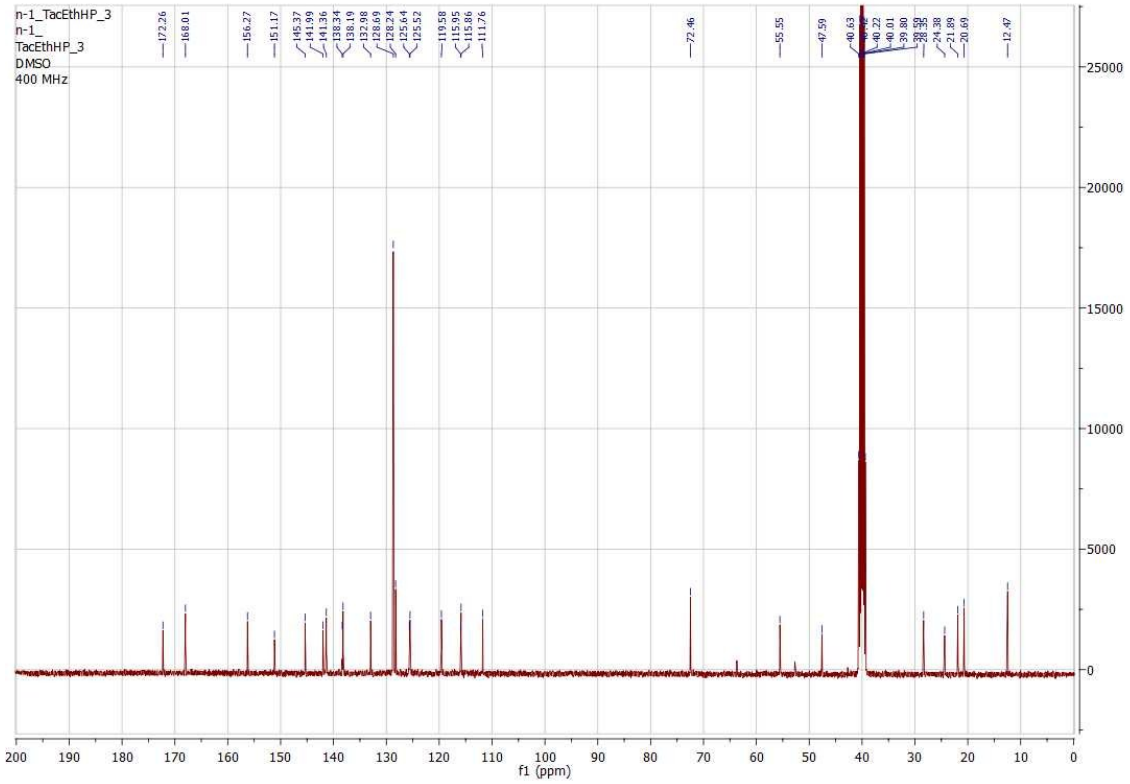


Fig. S3: Redocking results of the original ligand (red) and its superimposition with the original X-ray structure (green) of the corresponding reported complex with AChE (PDB entry 1ODC) (RMSD = 5.2 Å).

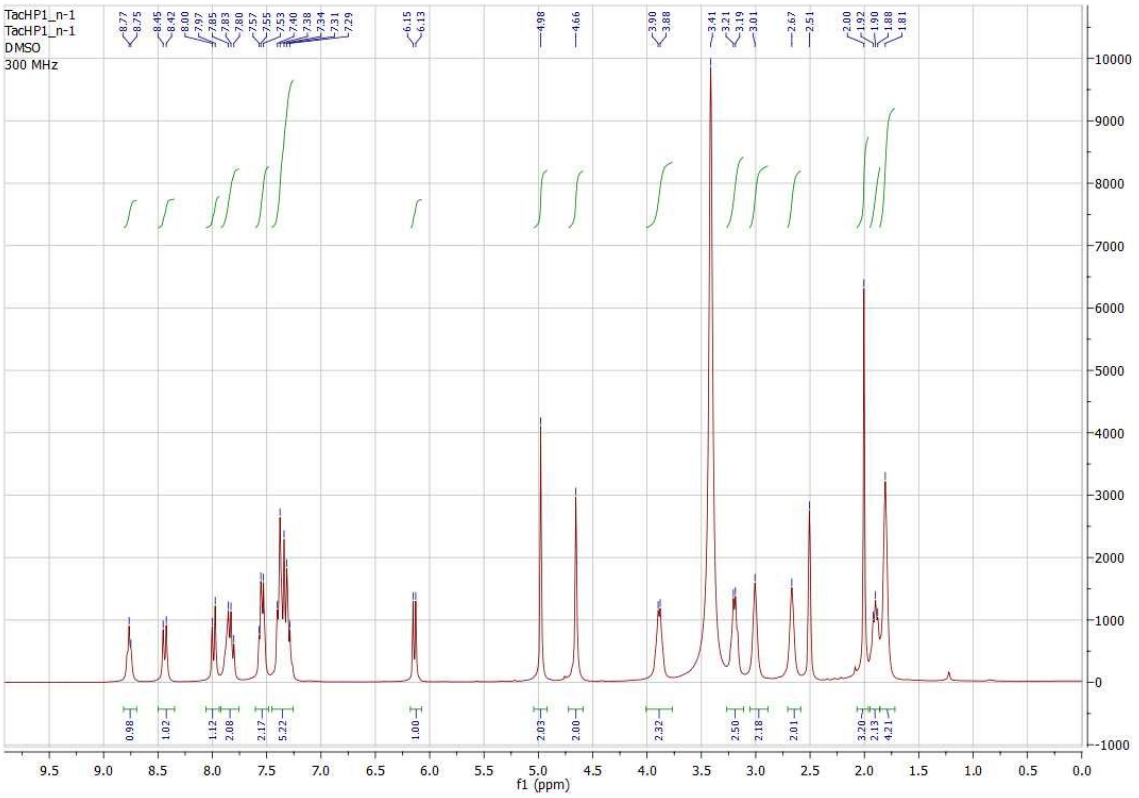
List of NMR spectra (Sp1-Sp16)

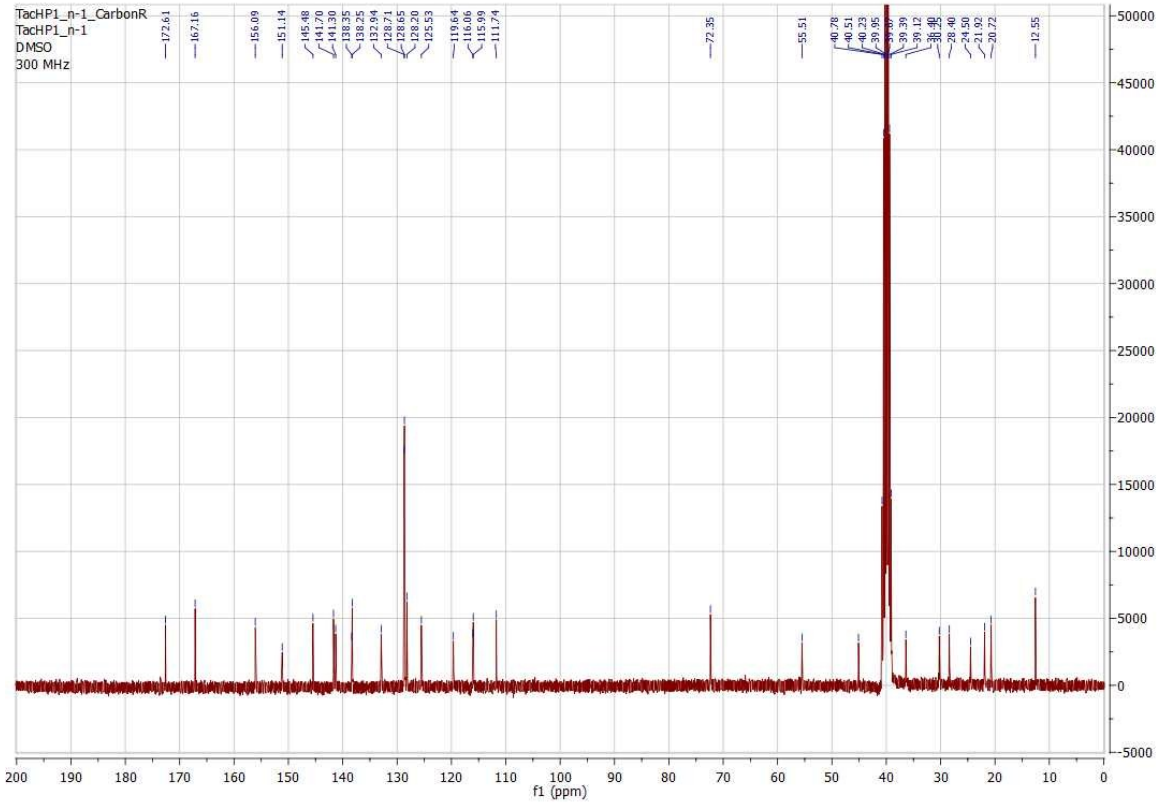
16. ^{1}H & ^{13}C NMR of *N*-(3-((6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)-2-hydroxypropyl)-2-(3-hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)acetamide (**33**)**.**



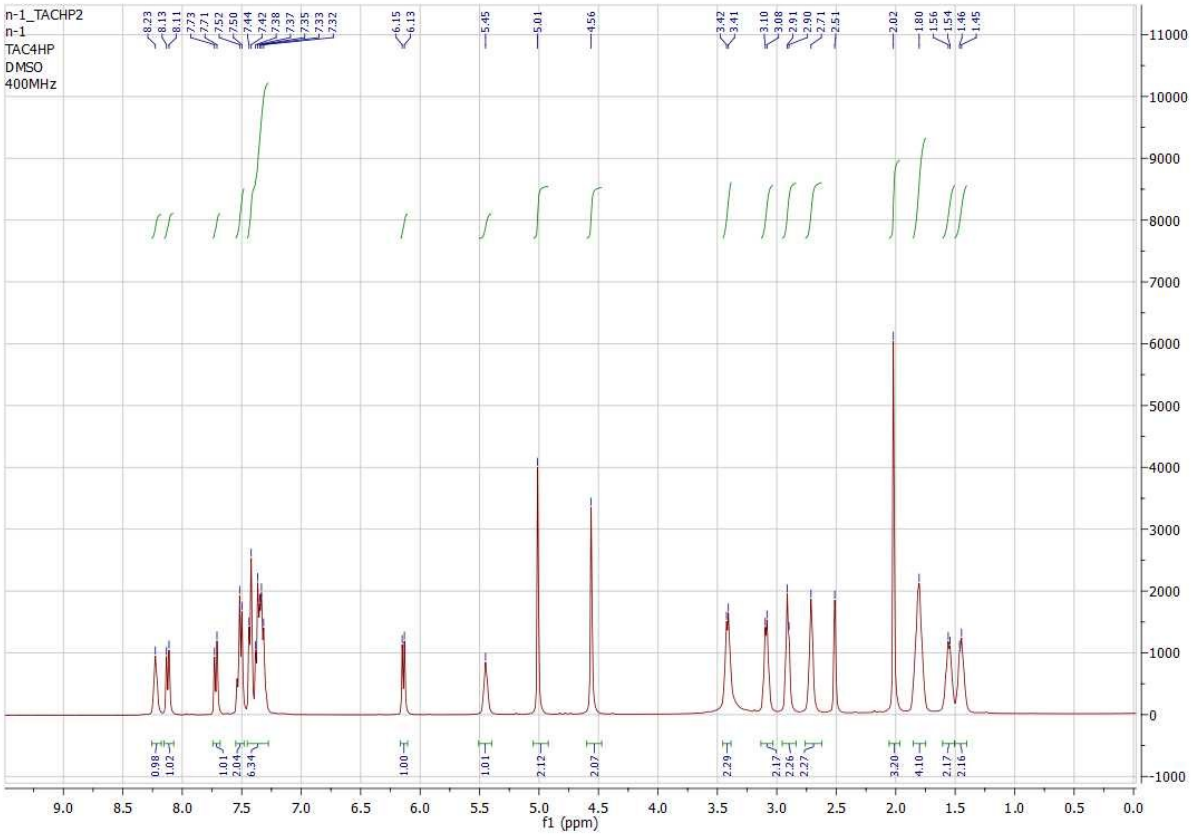


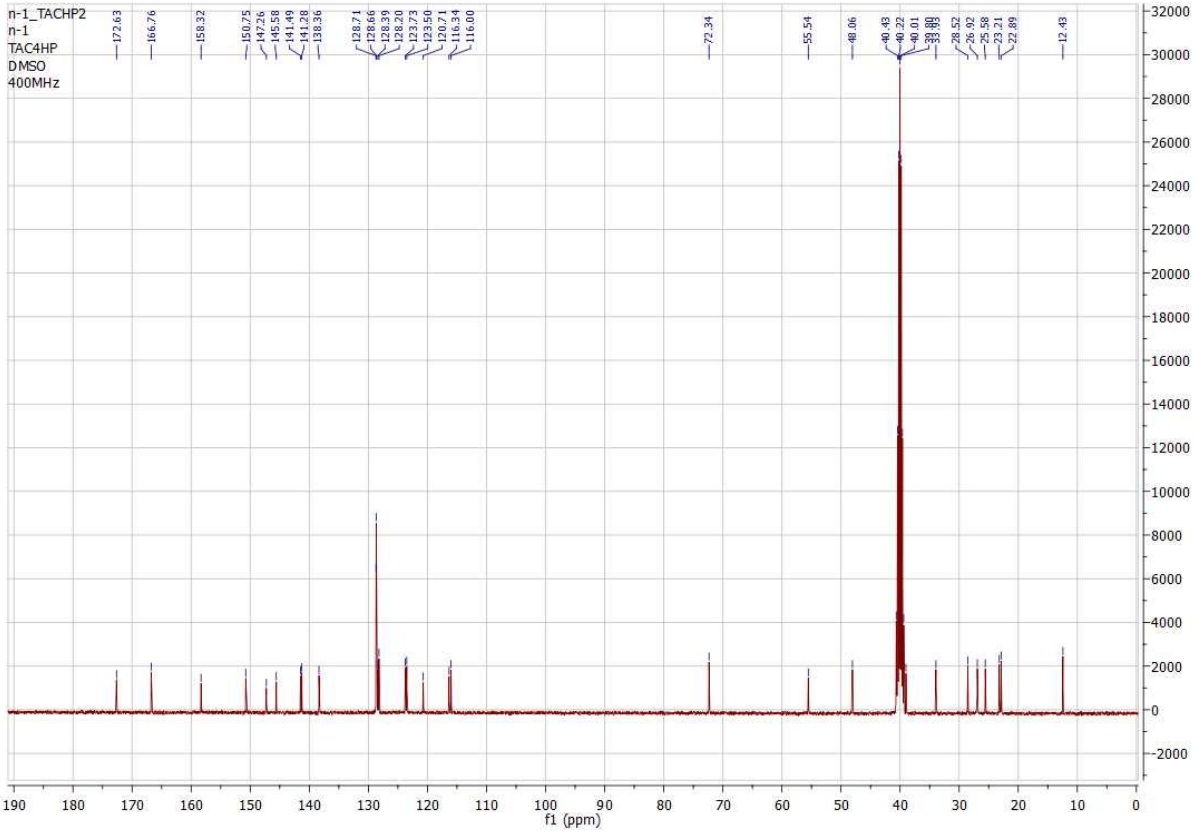
Sp1 - ^{1}H & ^{13}C NMR of 2-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(4H)-yl)-N-(2-((1,2,3,4-tetrahydroacridin-9-yl)amino)ethyl)acetamide (**18).**



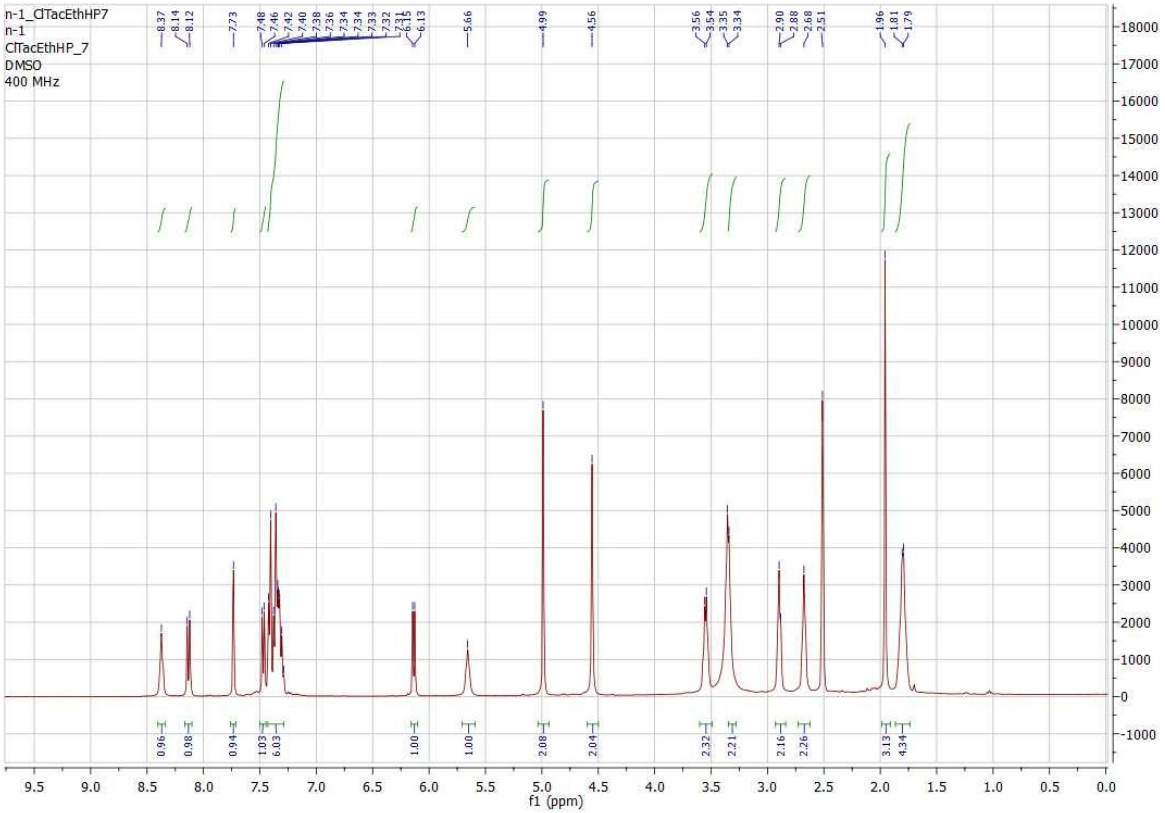


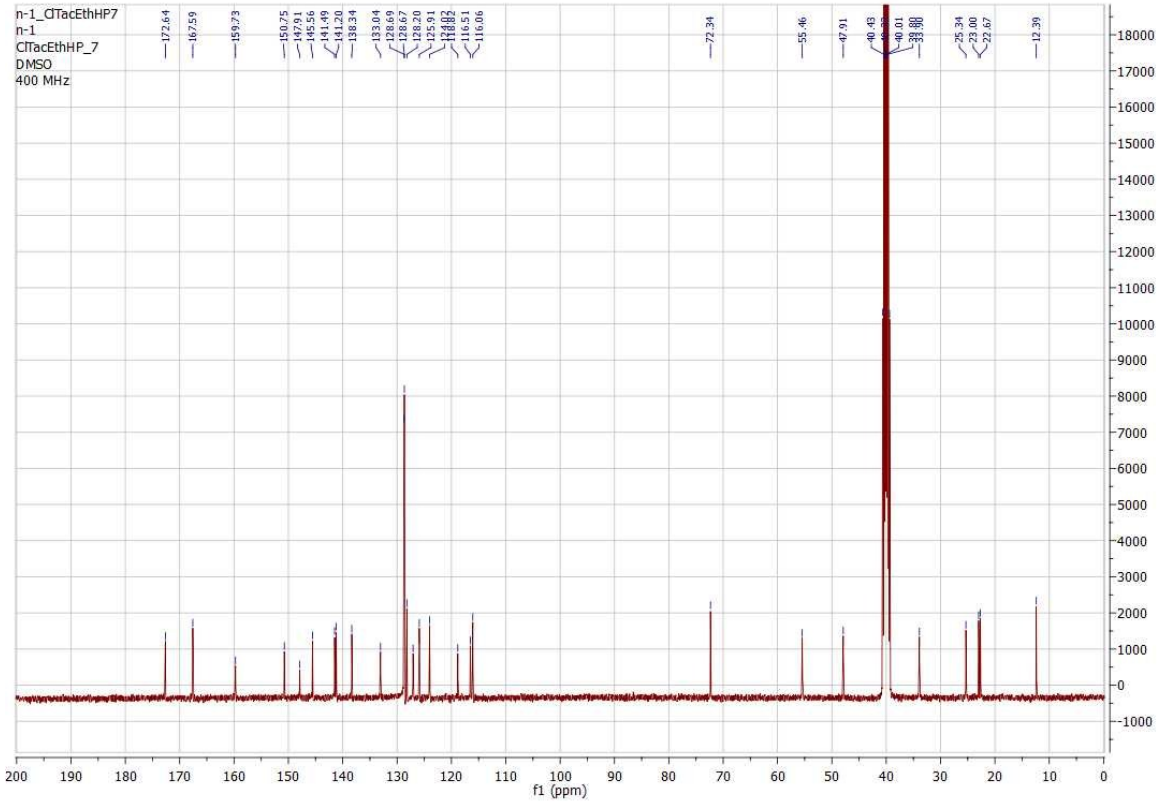
Sp2 - ^{1}H & ^{13}C NMR of *2-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(4H)-yl)-N-(3-((1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)acetamide (**19**).*



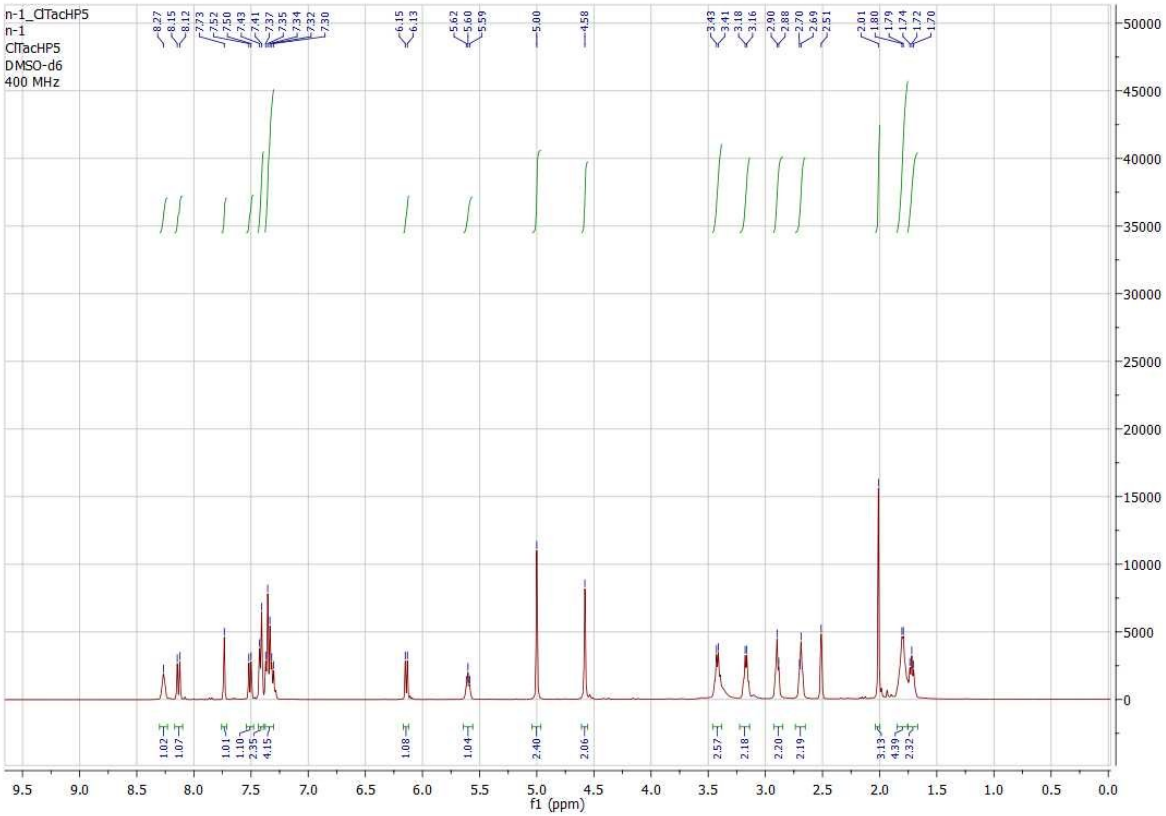


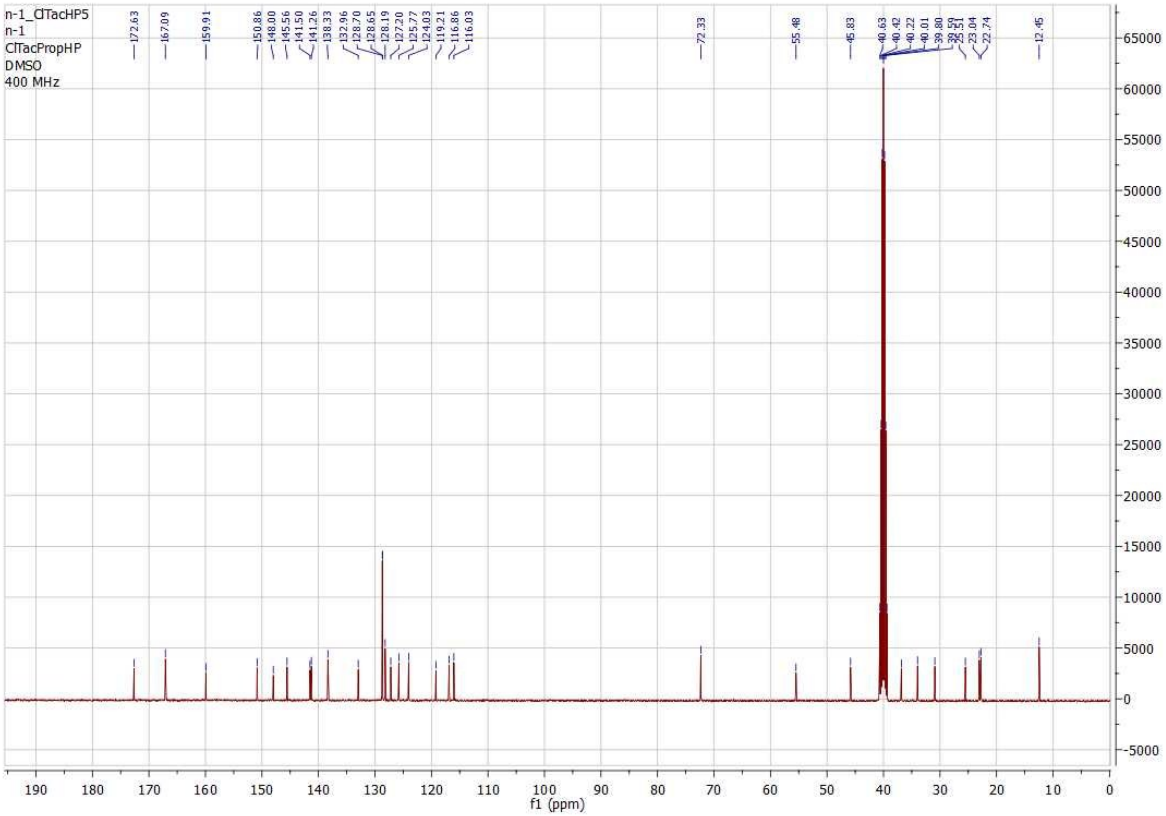
Sp3 - ^{1}H & ^{13}C NMR of *2-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(4H)-yl)-N-(4-((1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)acetamide (***20***).*



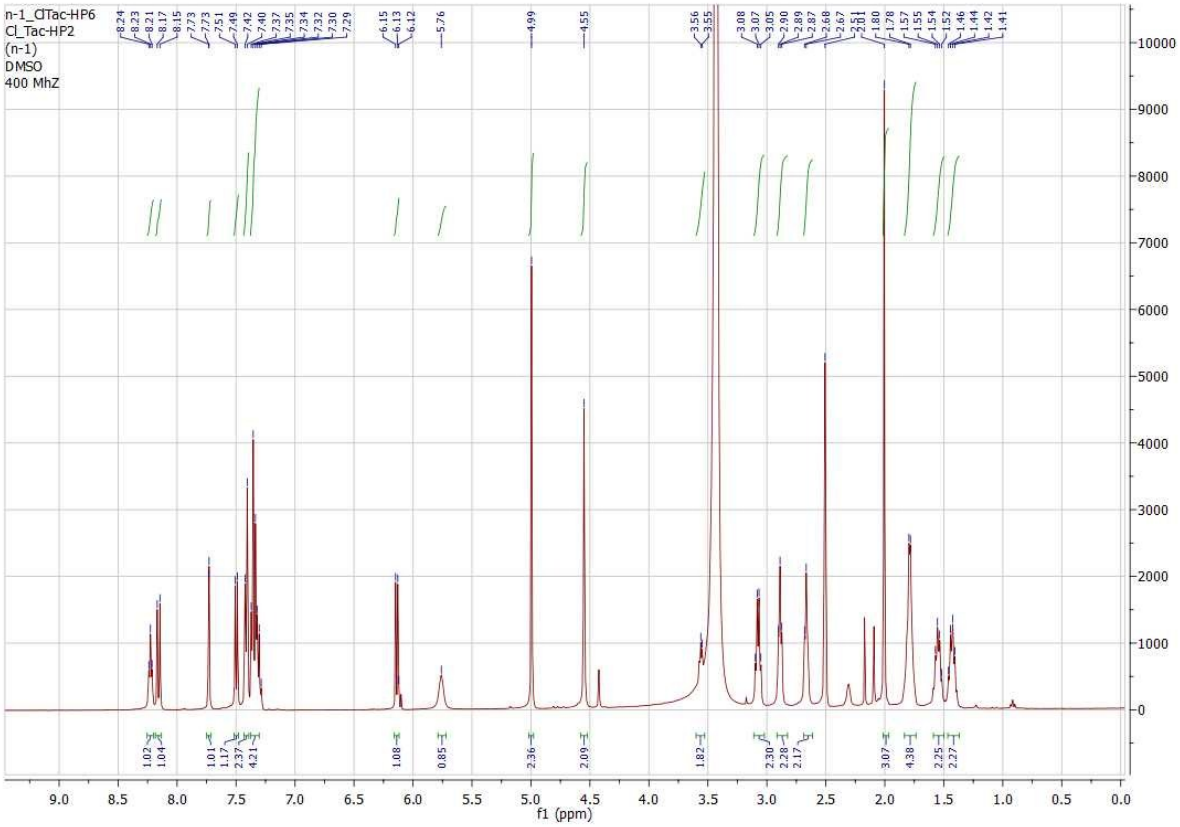


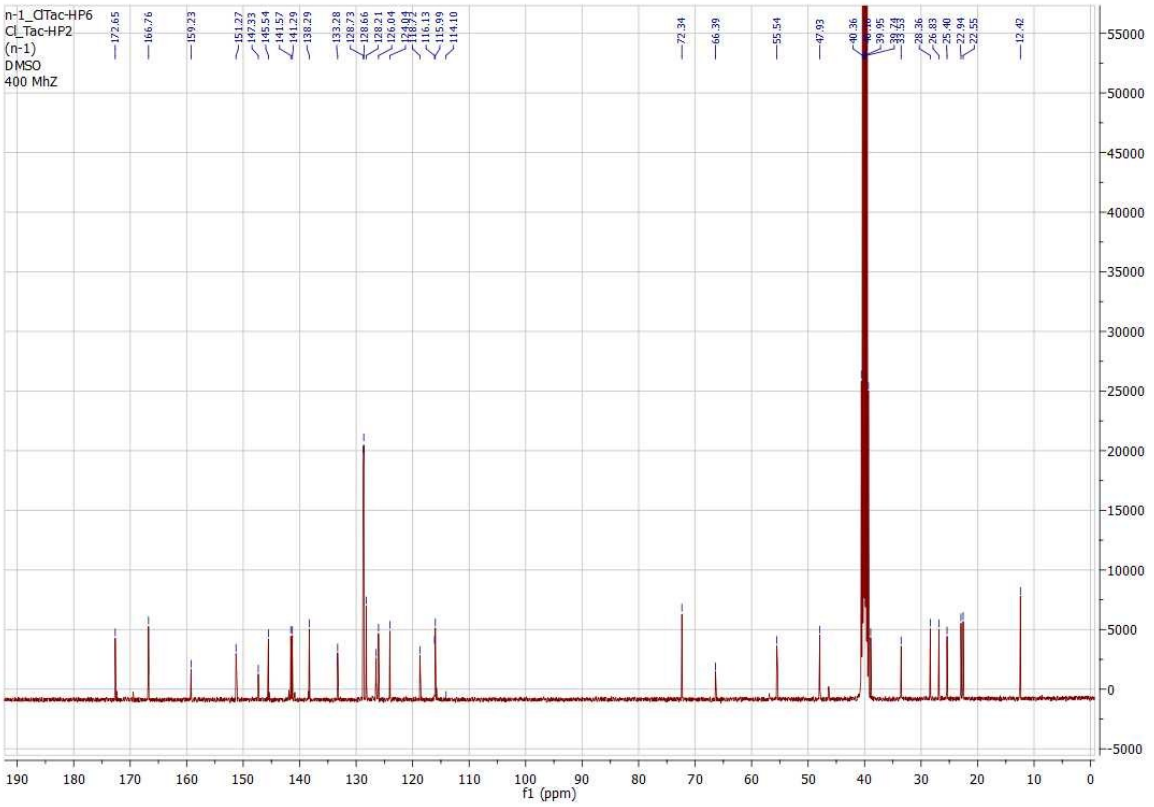
Sp4 - ^{1}H & ^{13}C NMR of *2-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(4H)-yl)-N-(2-((6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)ethyl)acetamide (**21**).*



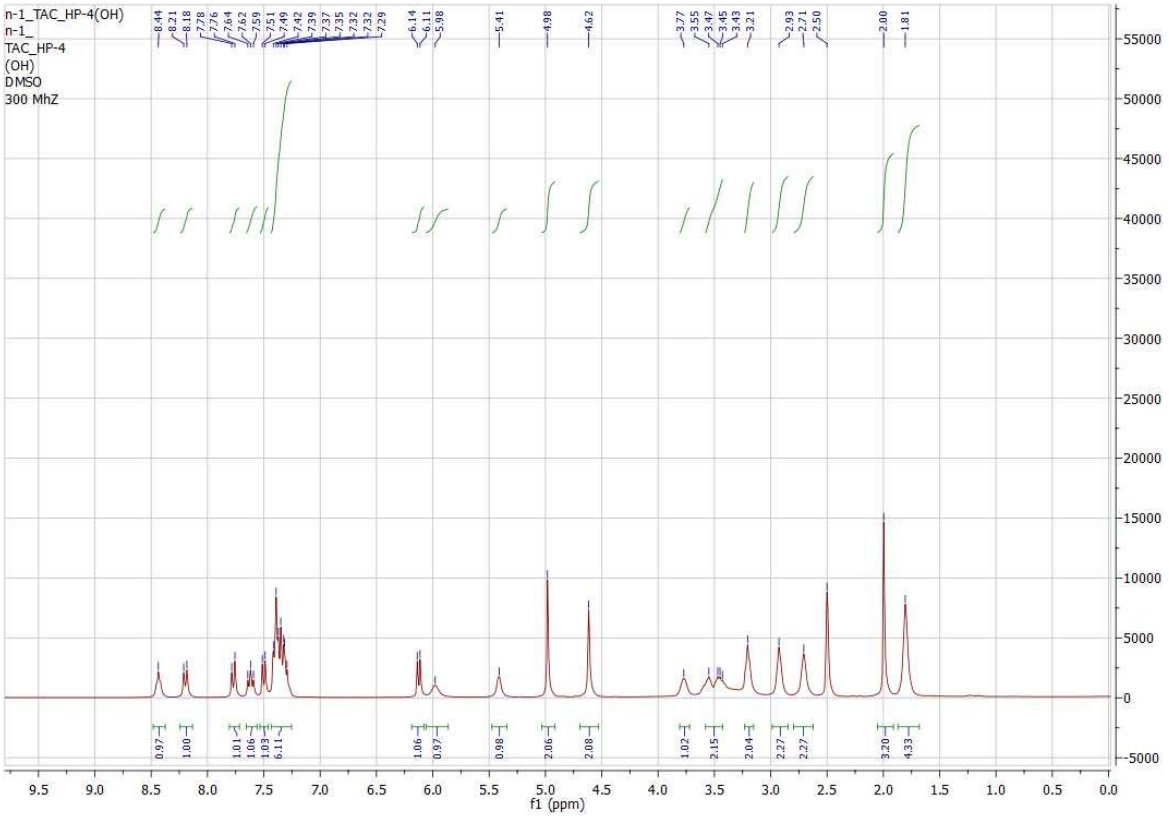


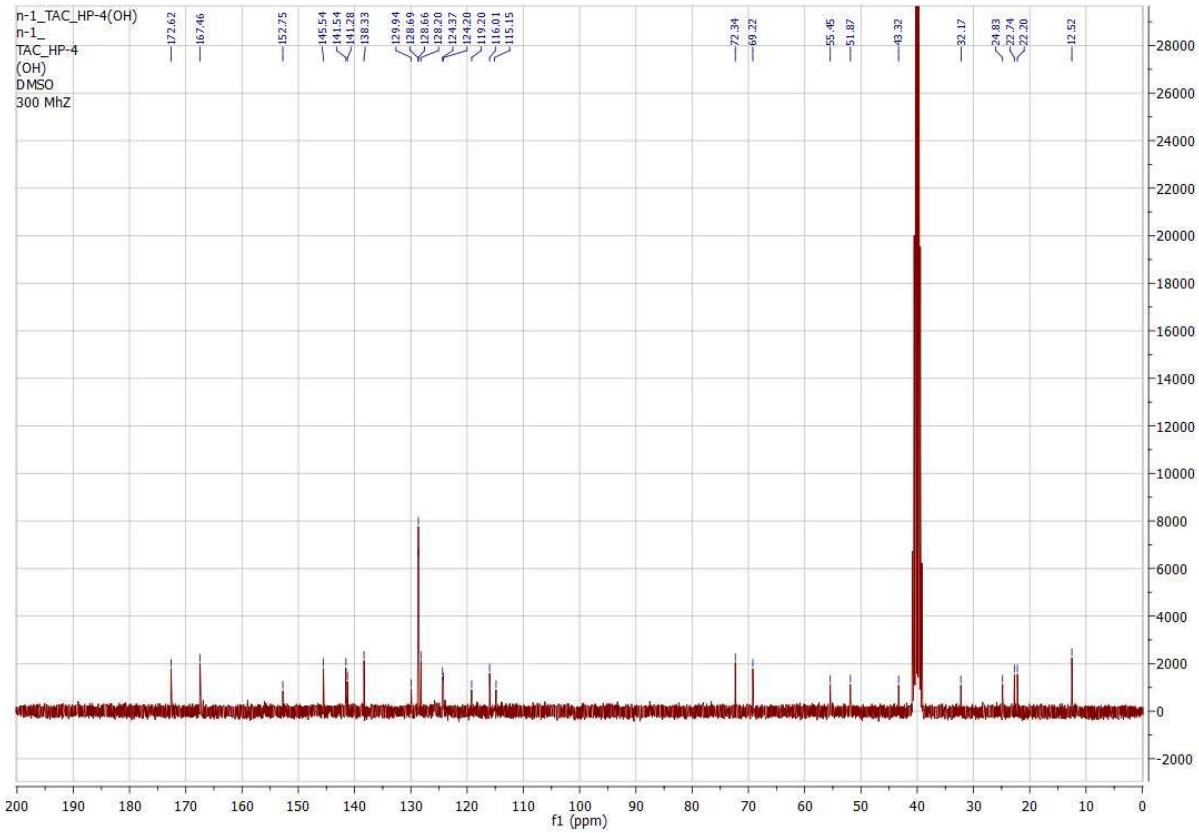
Sp5 - ^{1}H & ^{13}C NMR of 2-(3-(benzyloxy)-2-methyl-4-oxopyridin-1(4H)-yl)-N-(3-((6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)acetamide (**22**).



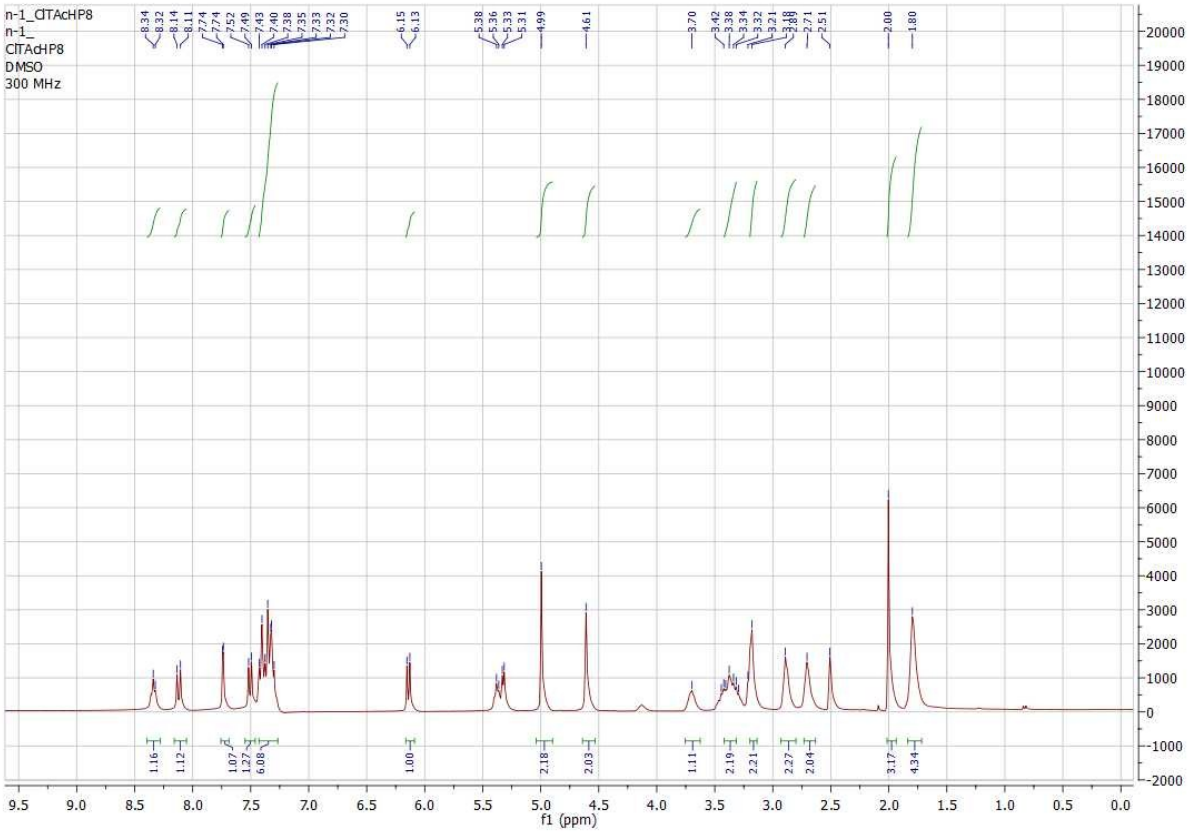


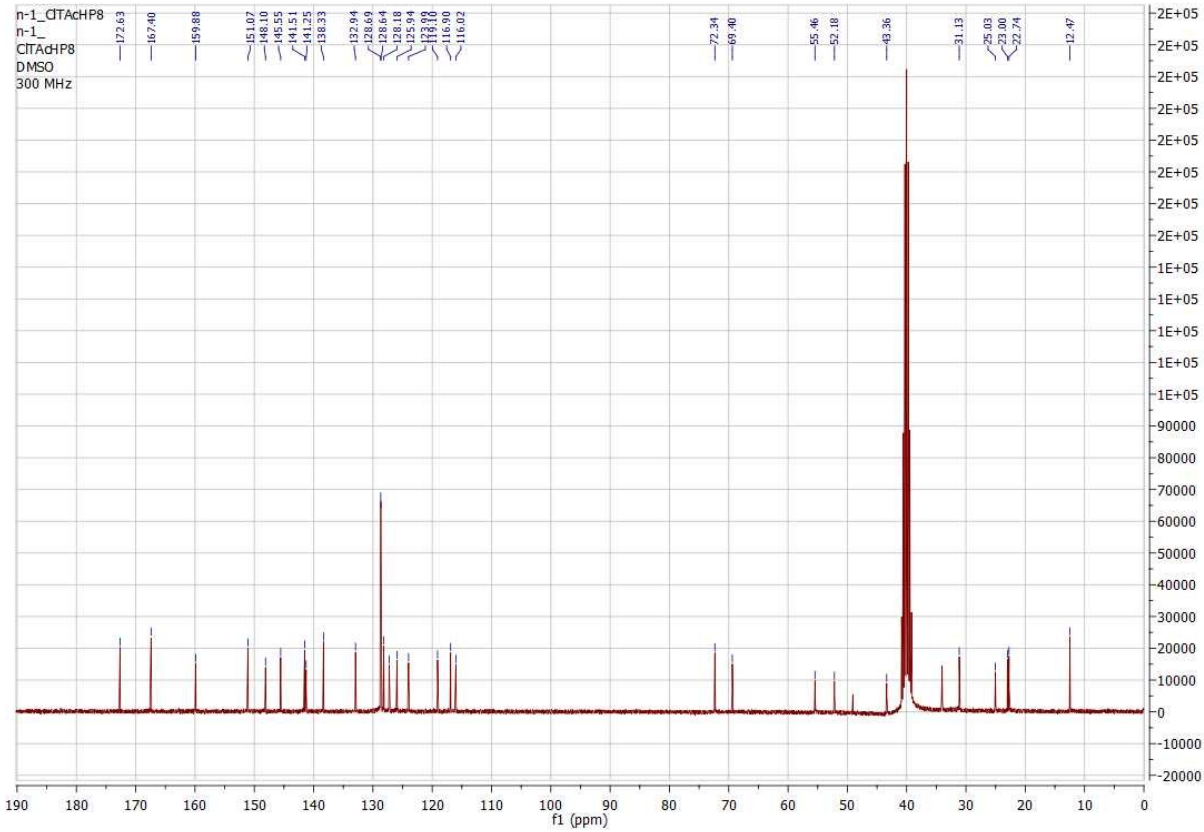
Sp6 - ^{1}H & ^{13}C NMR of *2-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(4H)-yl)-N-(4-((6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)acetamide (**23**).*



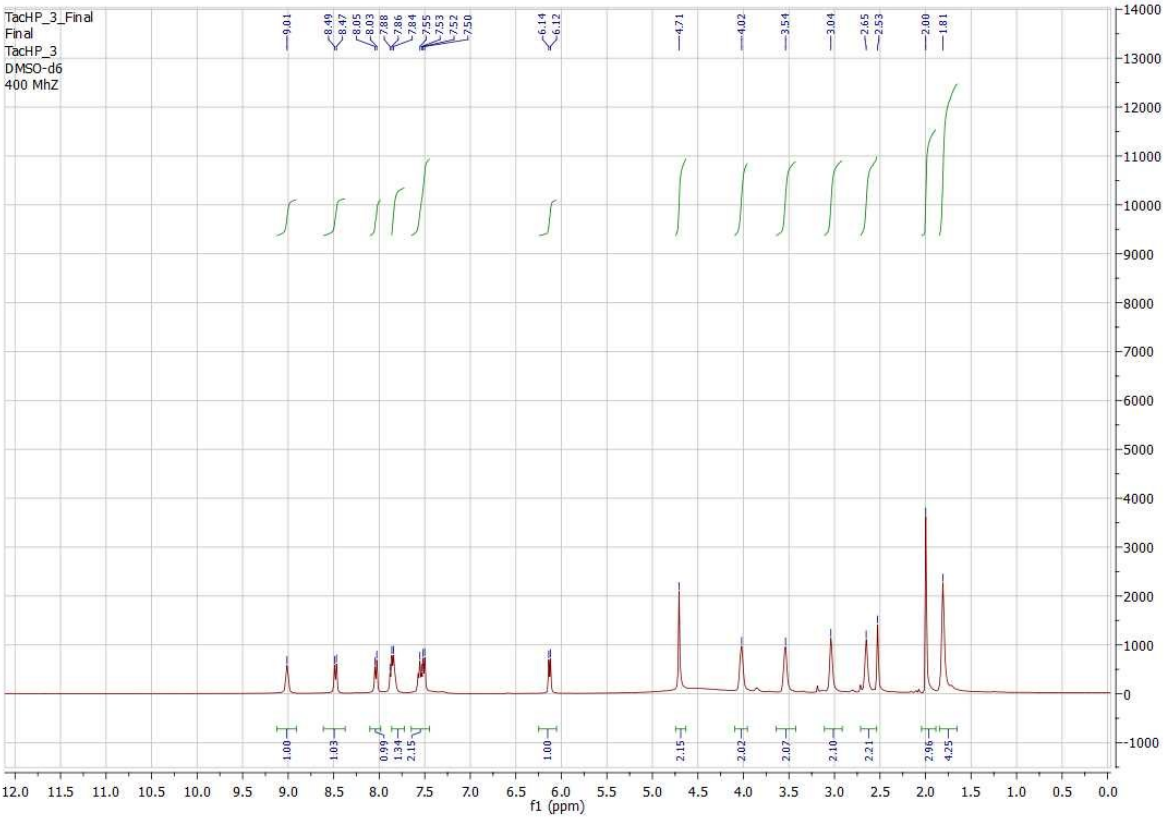


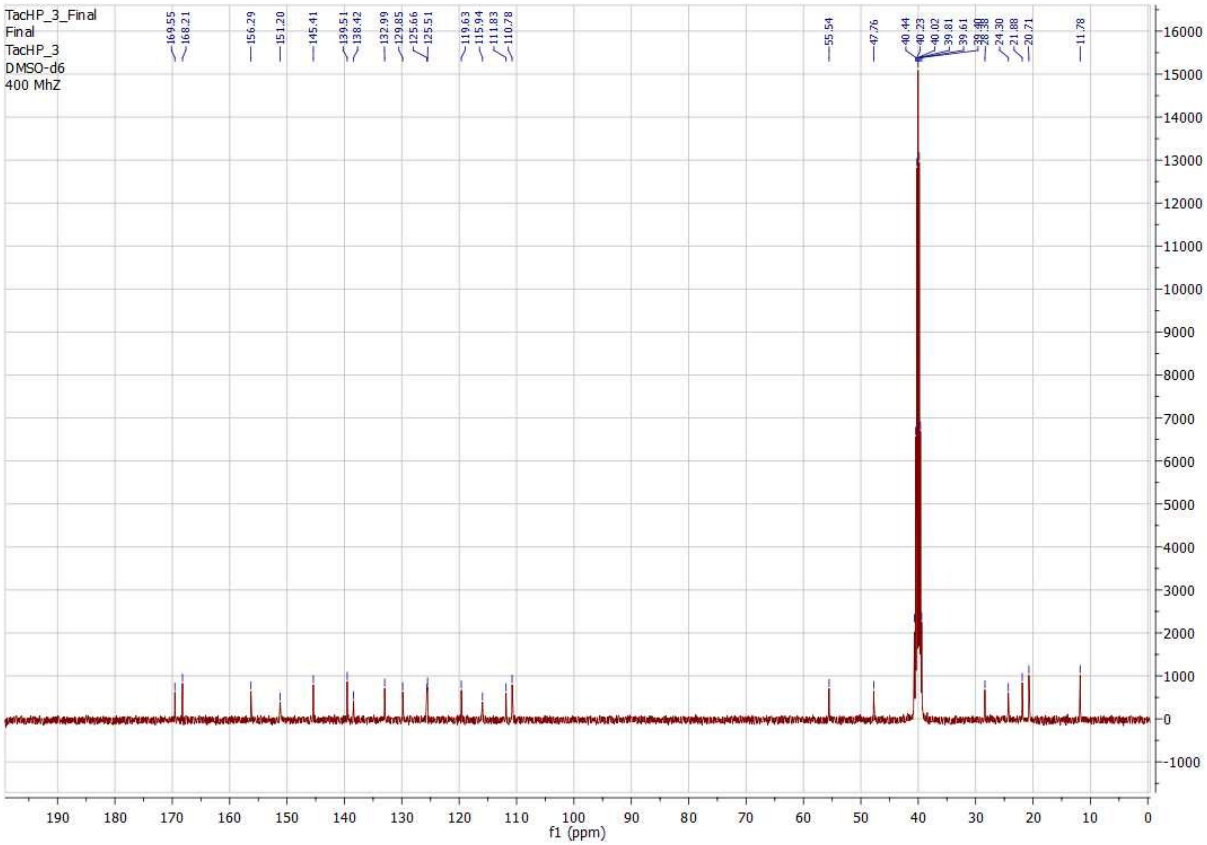
Sp7 - ^{1}H & ^{13}C NMR of 2-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(4*H*)-yl)-*N*-(2-hydroxy-3-((1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)acetamide **(24).**



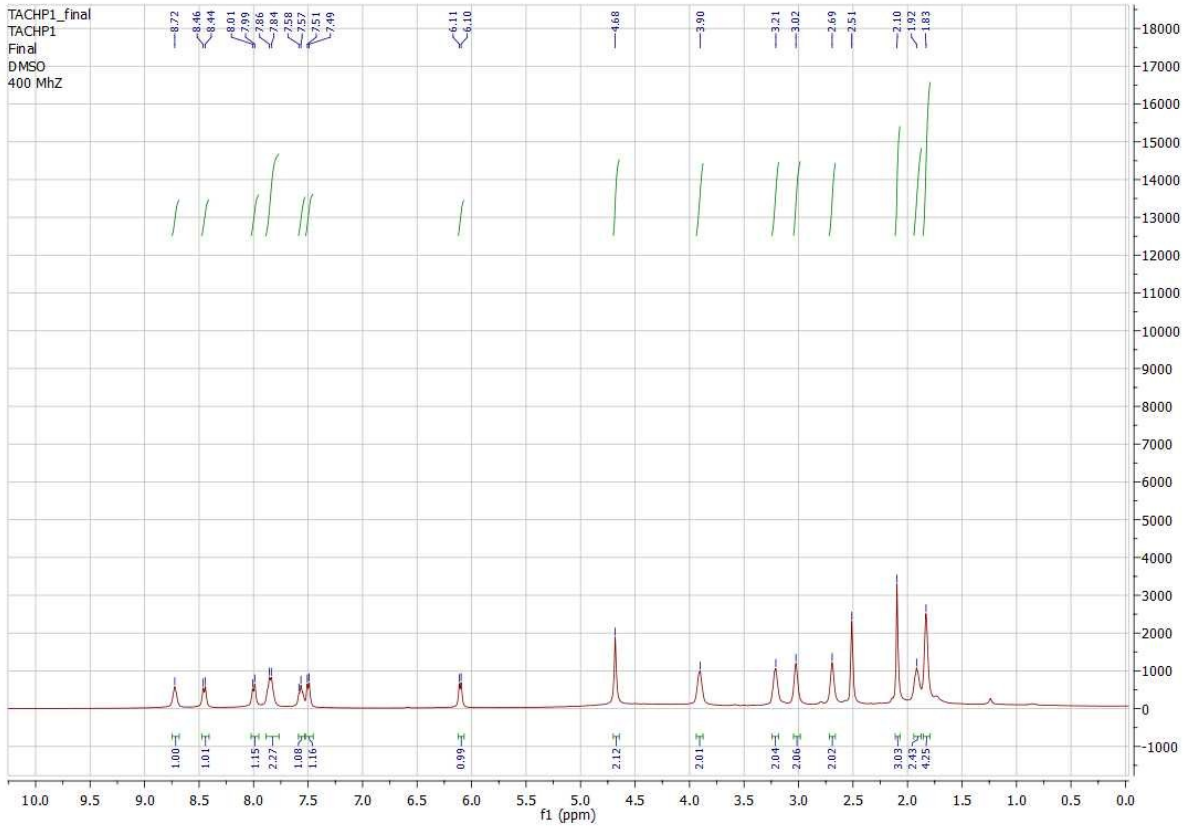


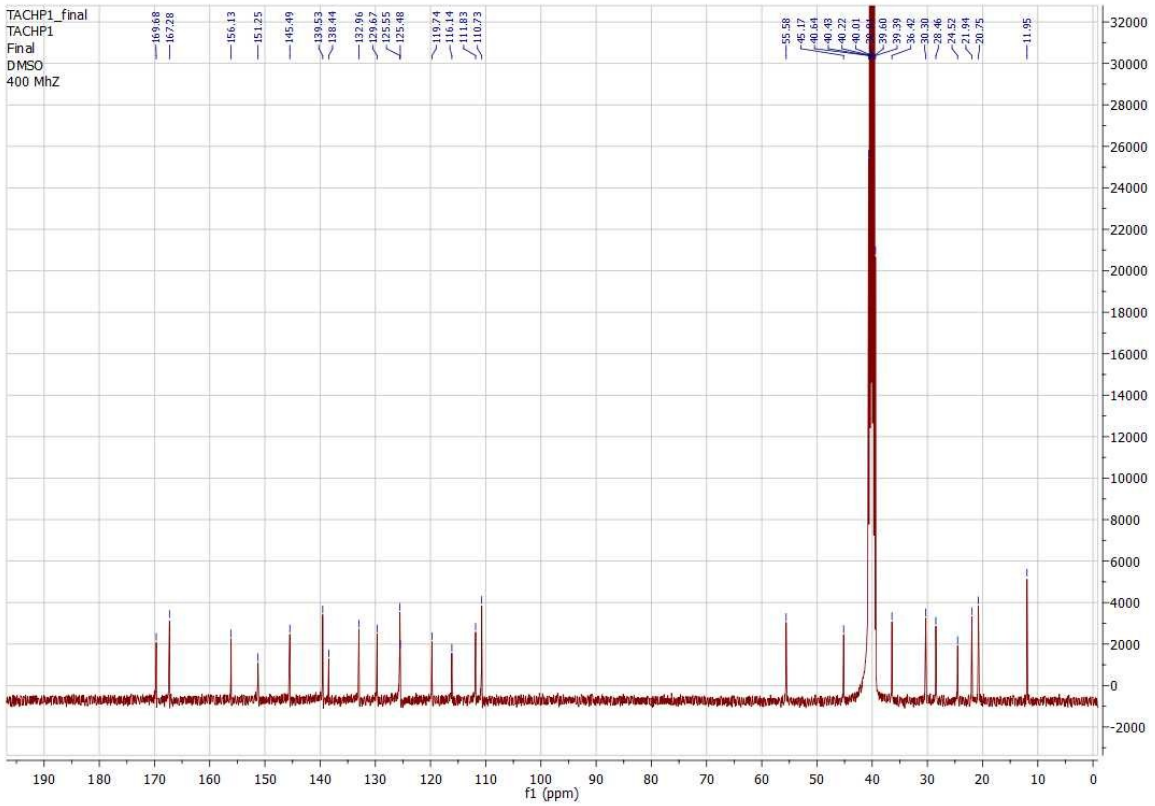
Sp8 - ^{1}H & ^{13}C NMR of 2-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(4*H*)-yl)-*N*-(3-((6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)-2-hydroxypropyl) acetamide (**25**).



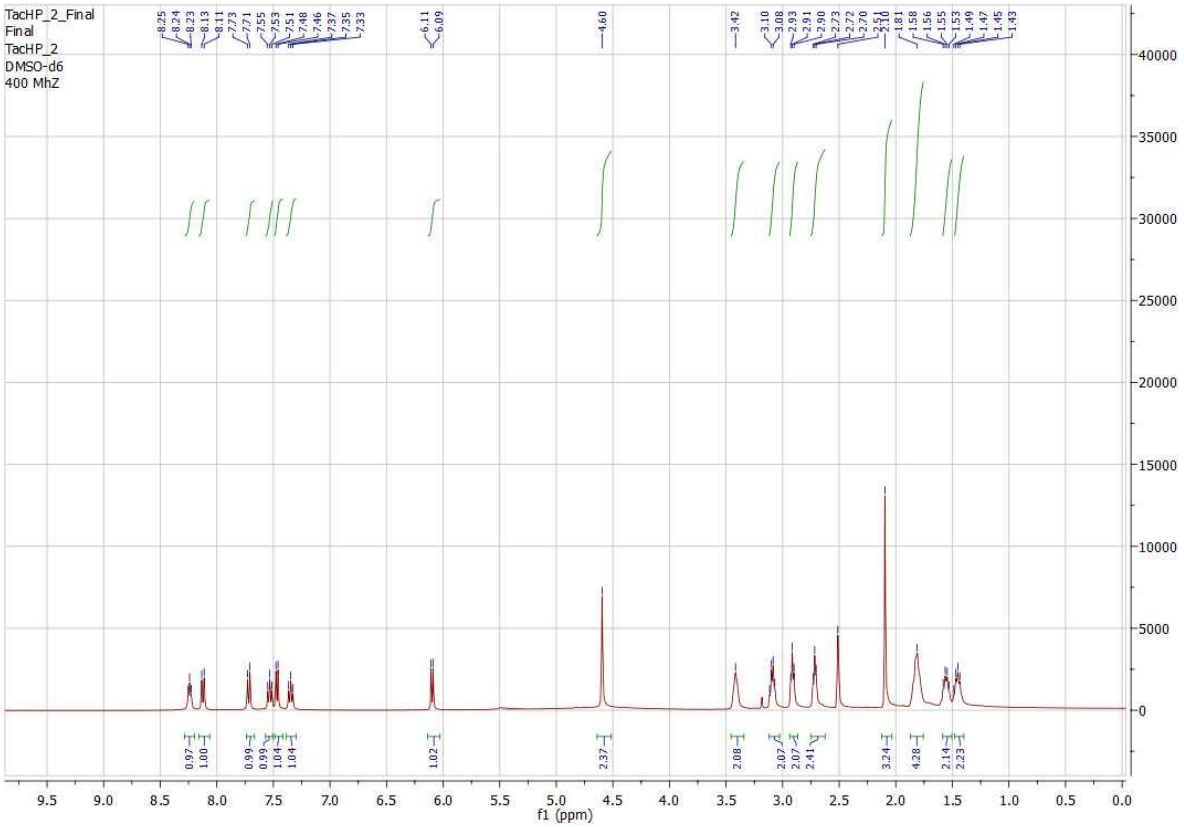


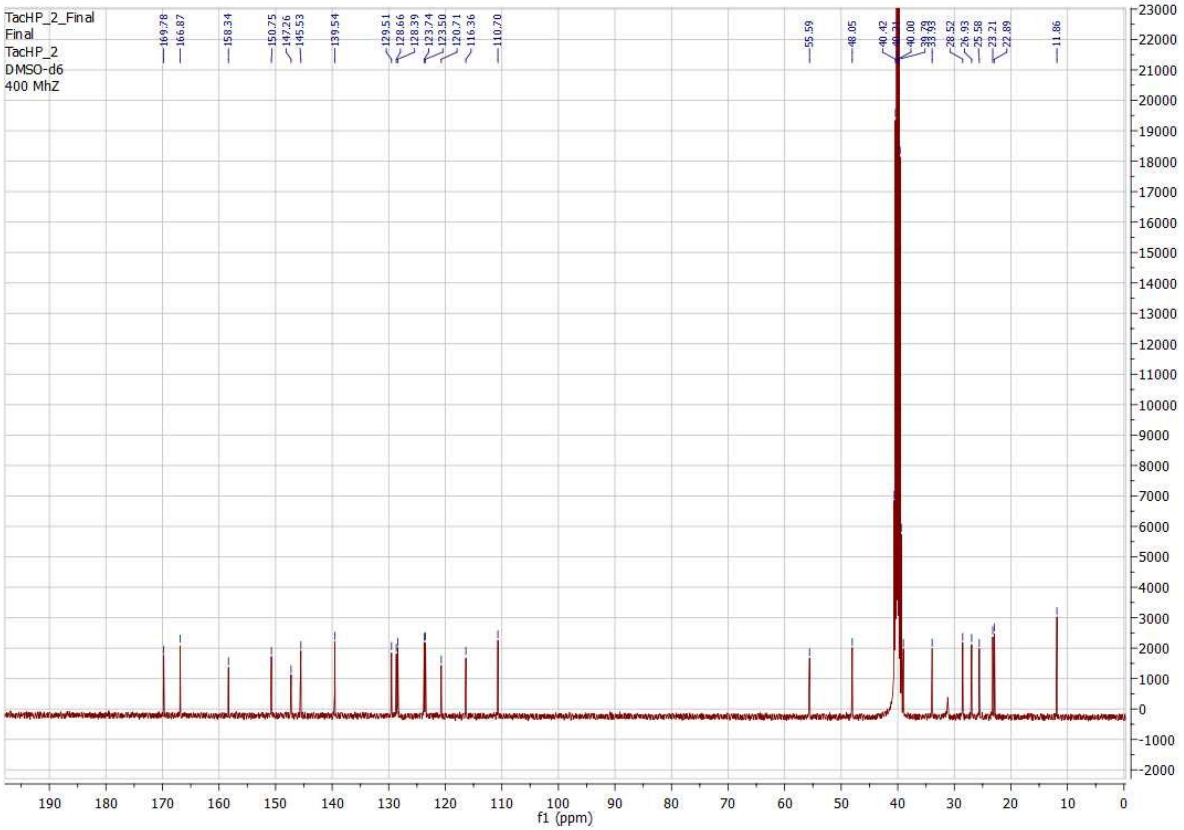
Sp9 - ^{1}H & ^{13}C NMR of 2-(3-hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)-*N*-(2-((1,2,3,4-tetrahydroacridin-9-yl)amino)ethyl)acetamide (**26**).



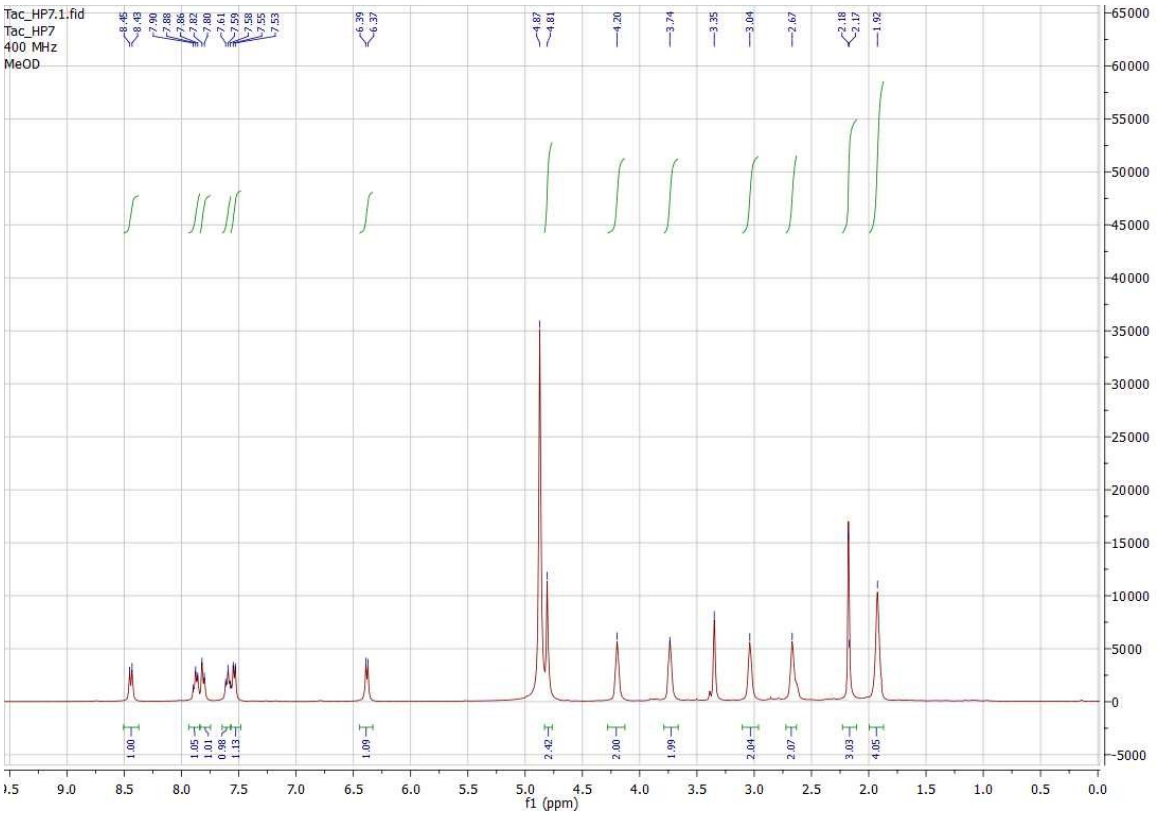


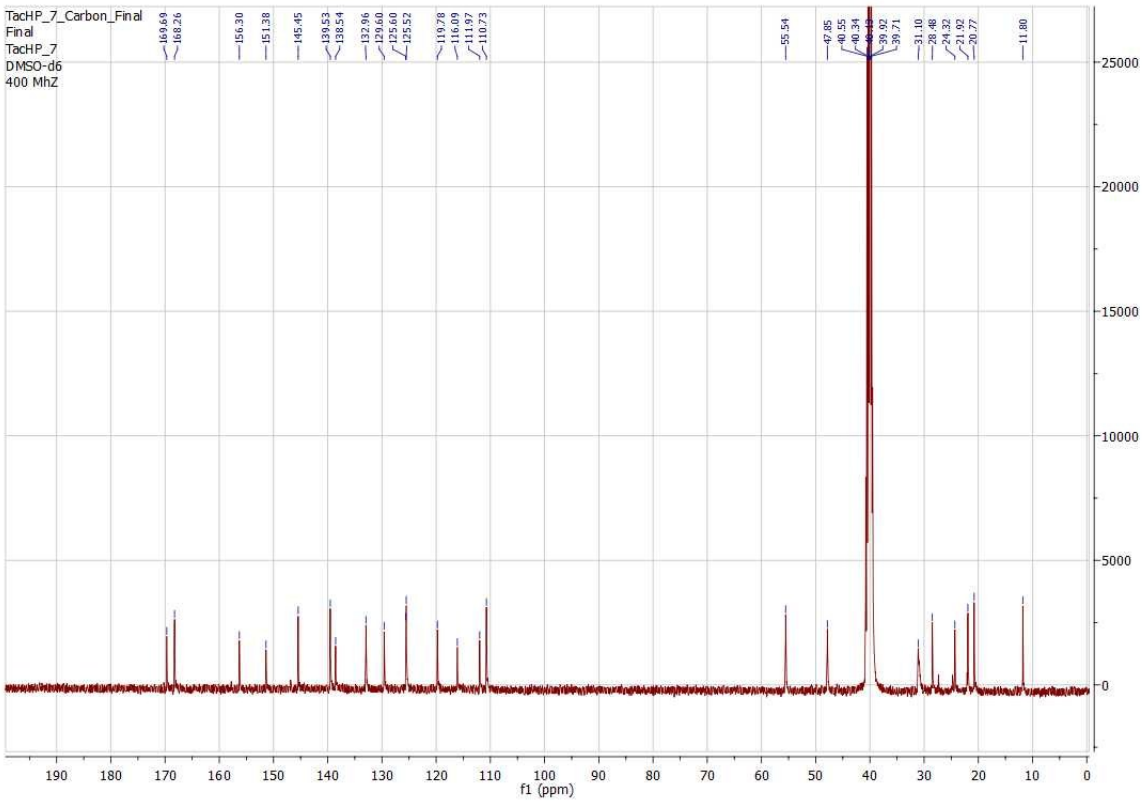
Sp10 - ^{1}H & ^{13}C NMR of 2-(3-Hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)-*N*-(3-((1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)acetamide (**27**).



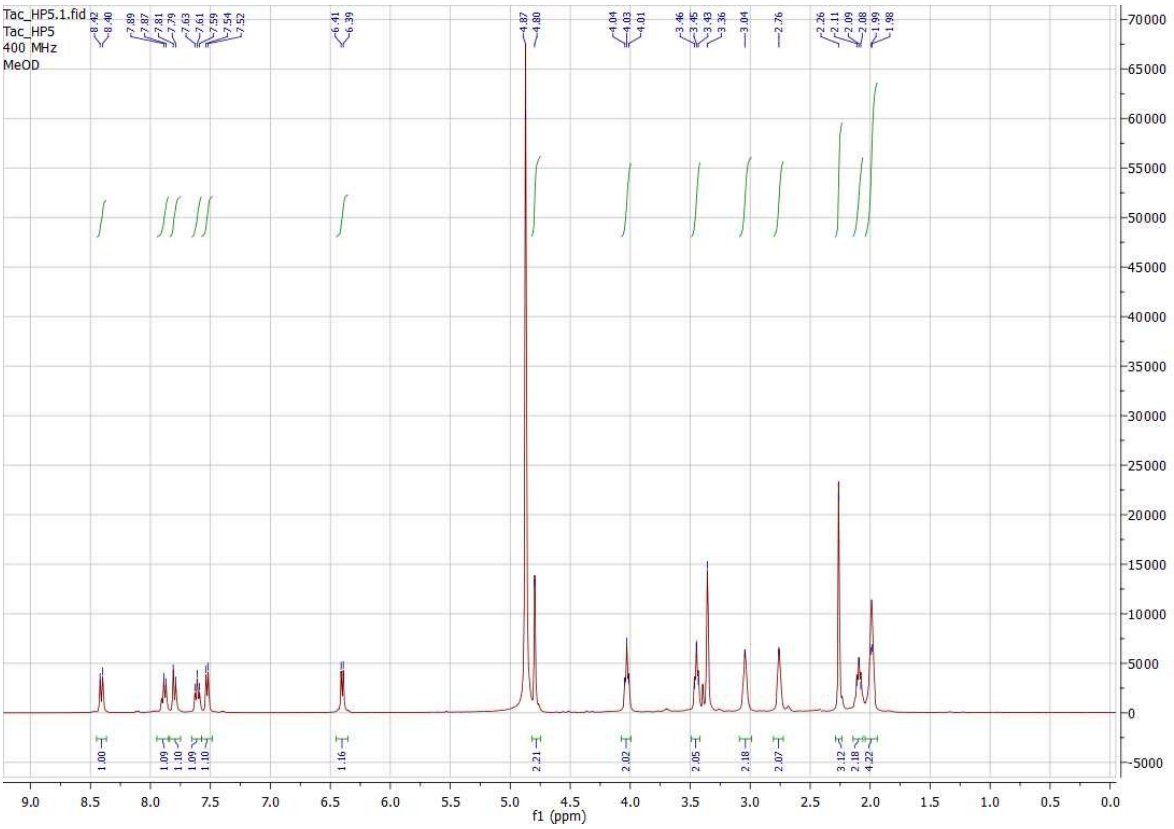


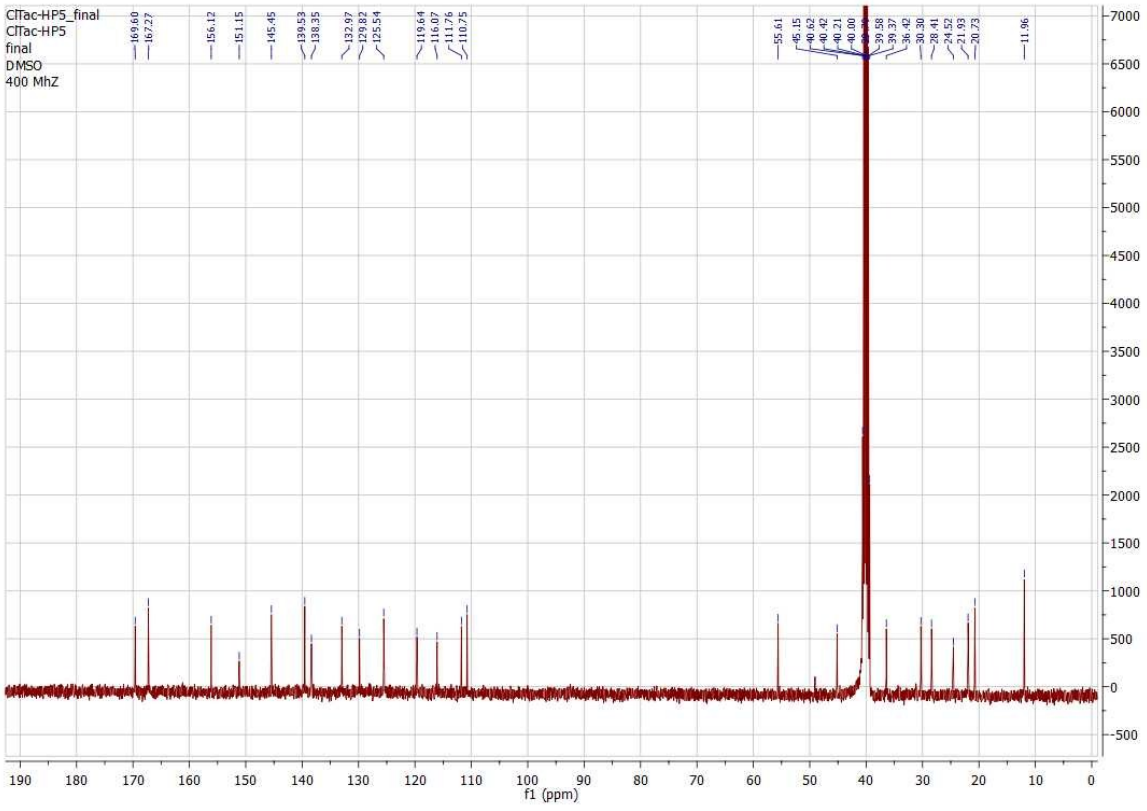
Sp11 - ^{1}H & ^{13}C NMR of 2-(3-hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)-N-(4-((1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)acetamide (**28**).



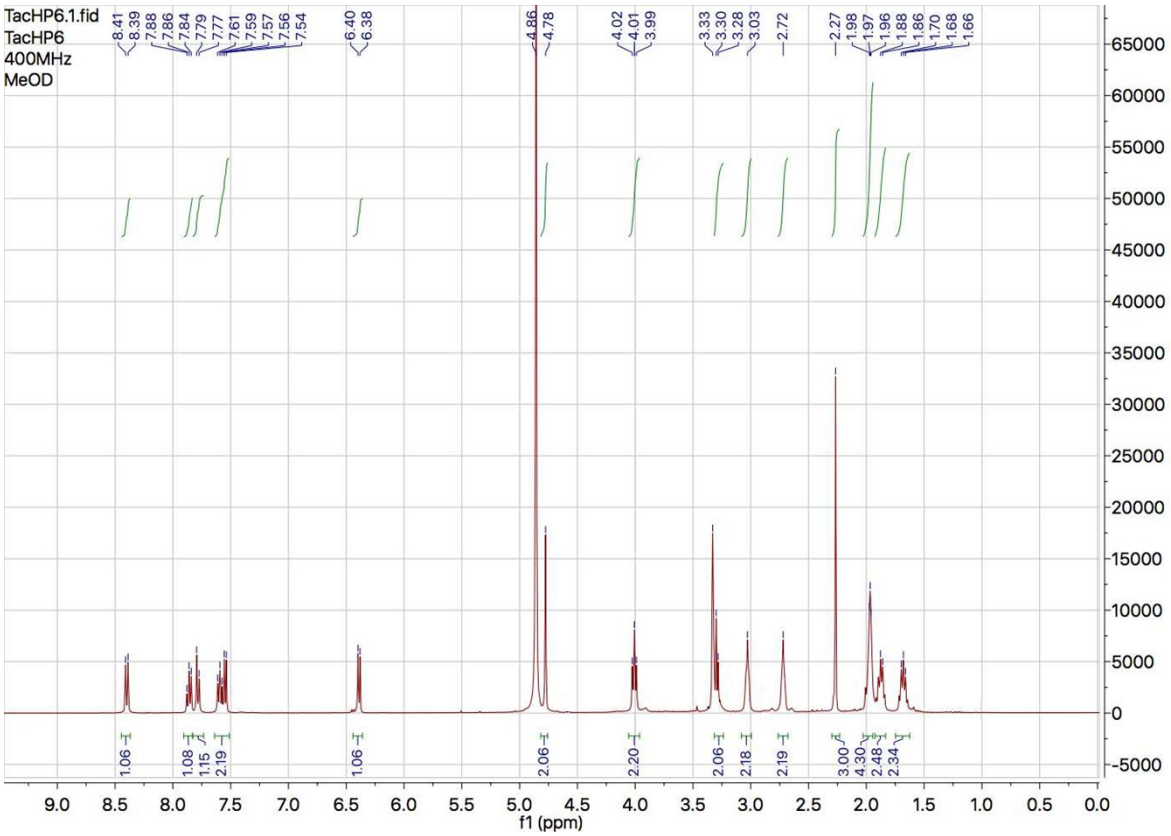


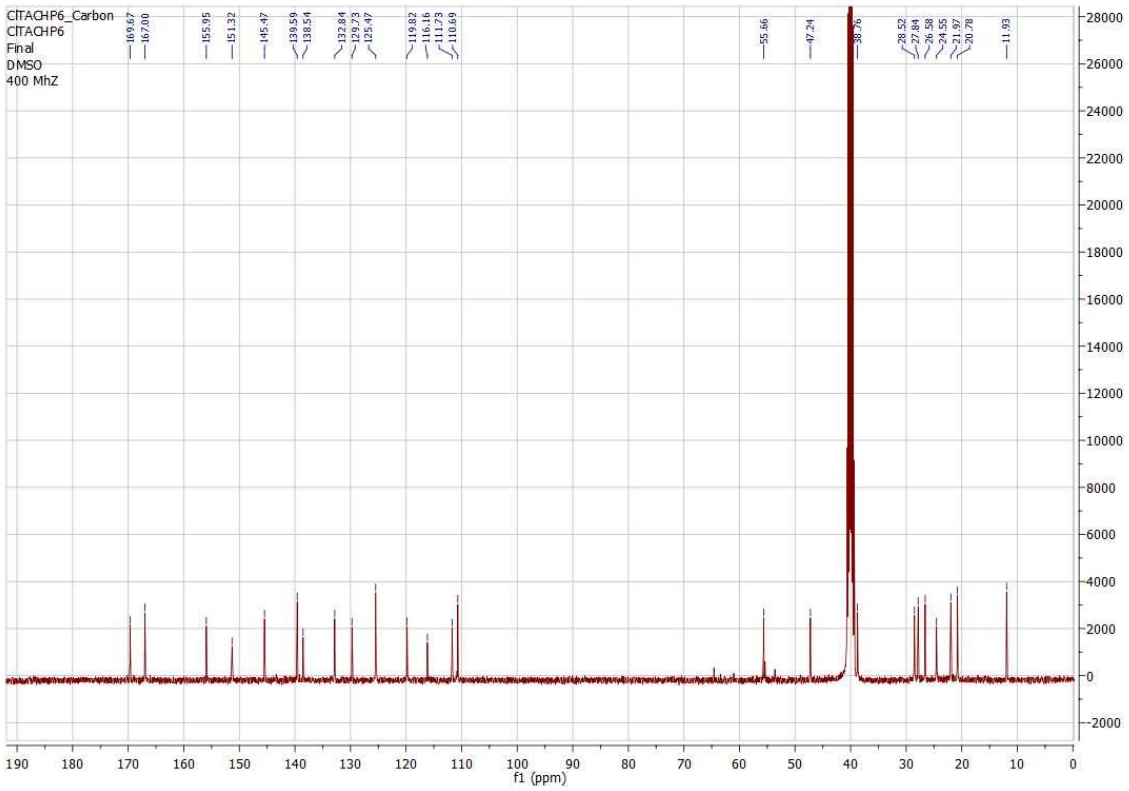
Sp12 - ^{1}H & ^{13}C NMR of *N*-(2-((6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)ethyl)-2-(3-hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)acetamide (**29**).



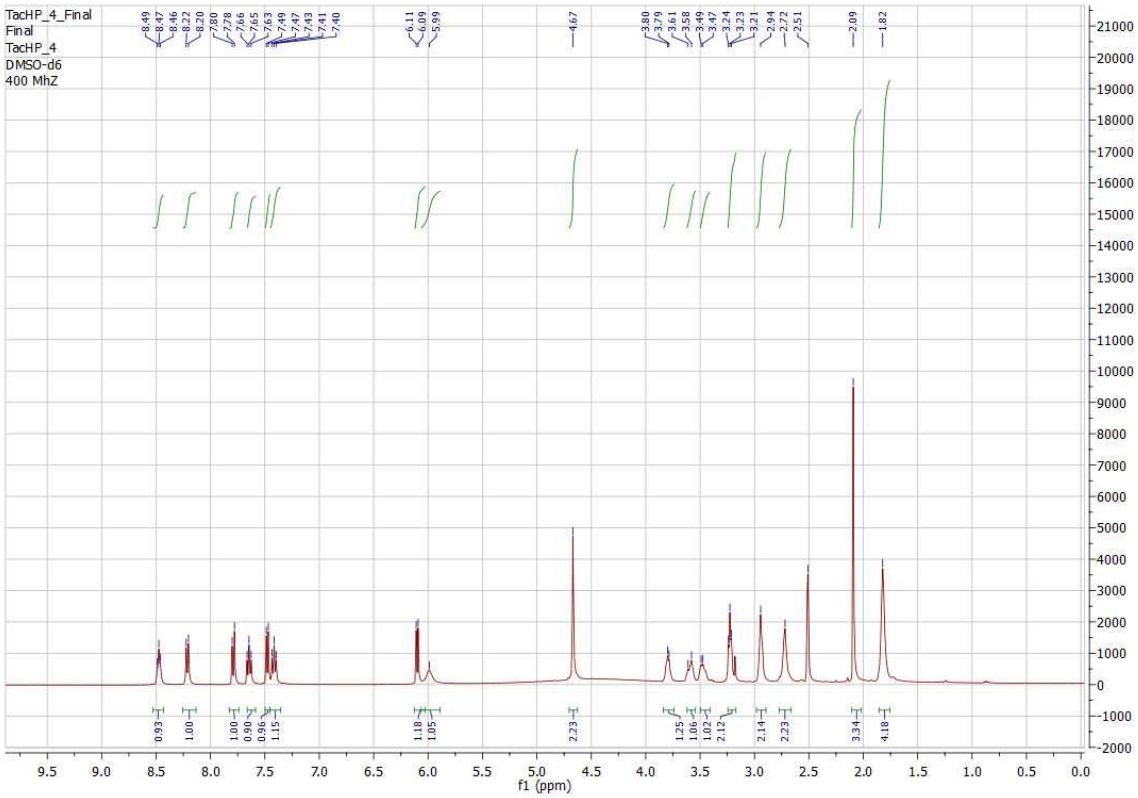


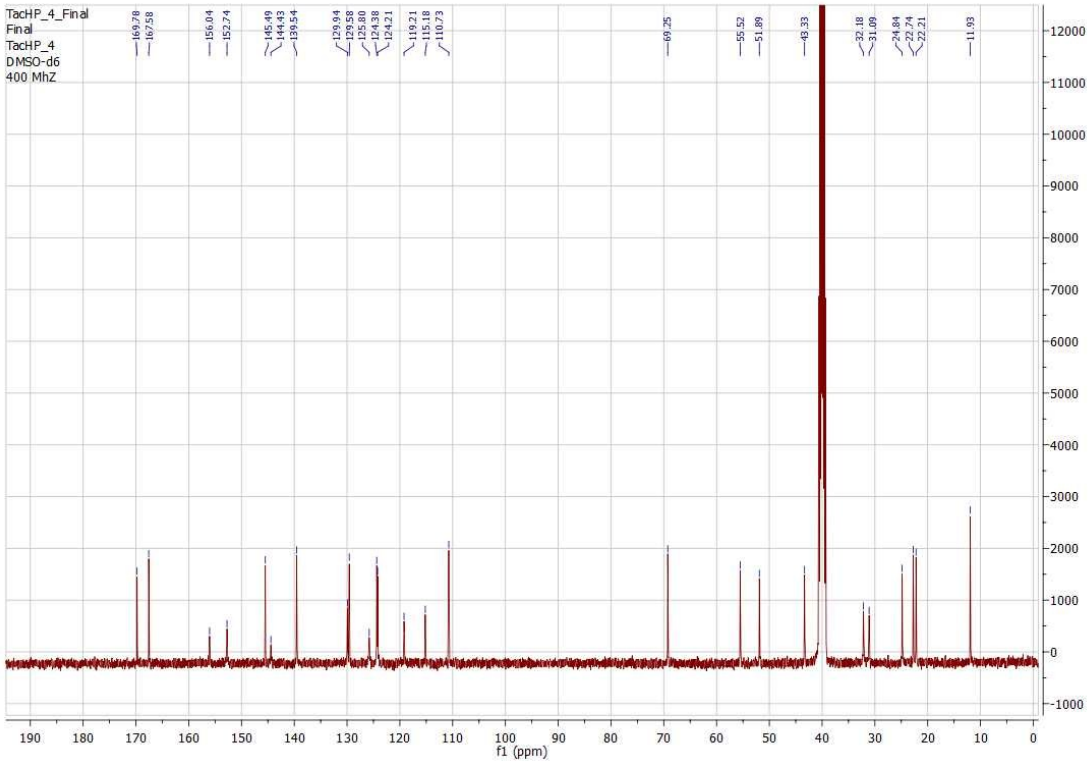
Sp13 - ^{1}H & ^{13}C NMR of *N*-(3-((6-Chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)-2-(3-hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)acetamide (**30**).



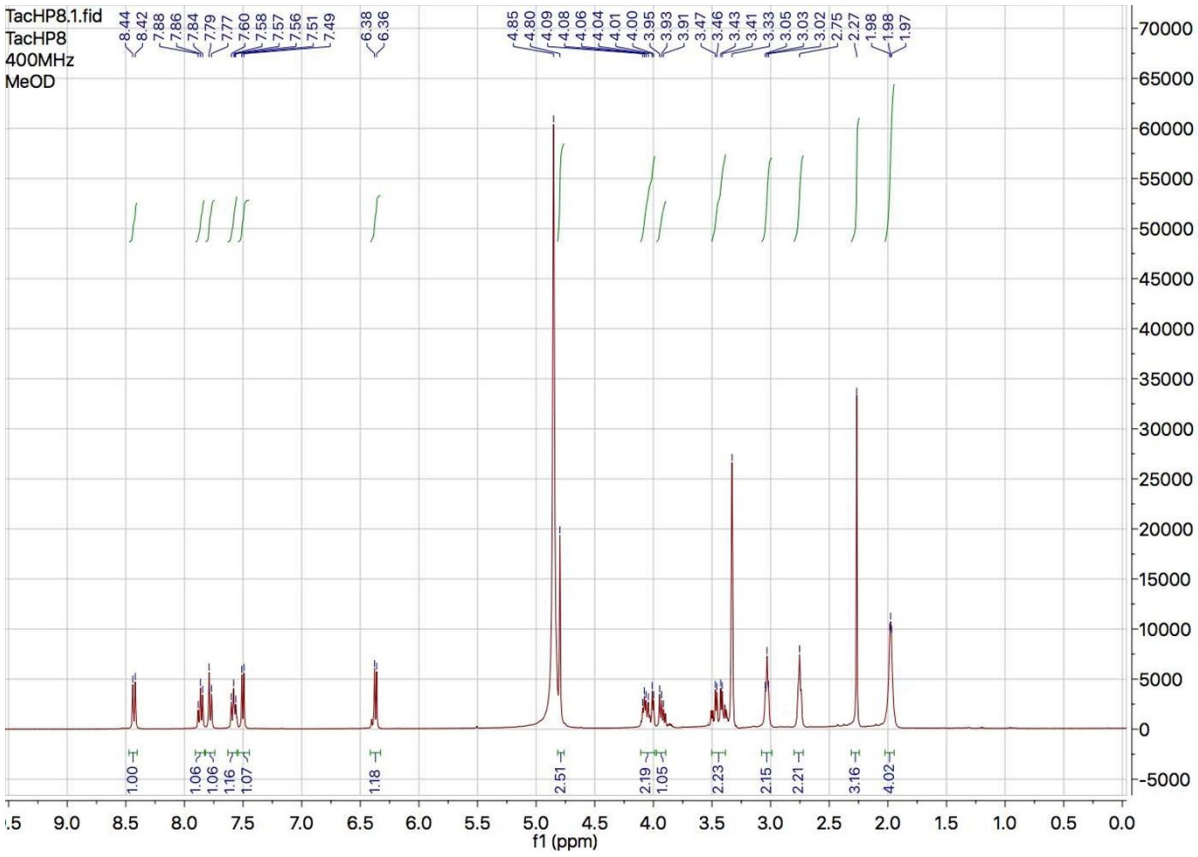


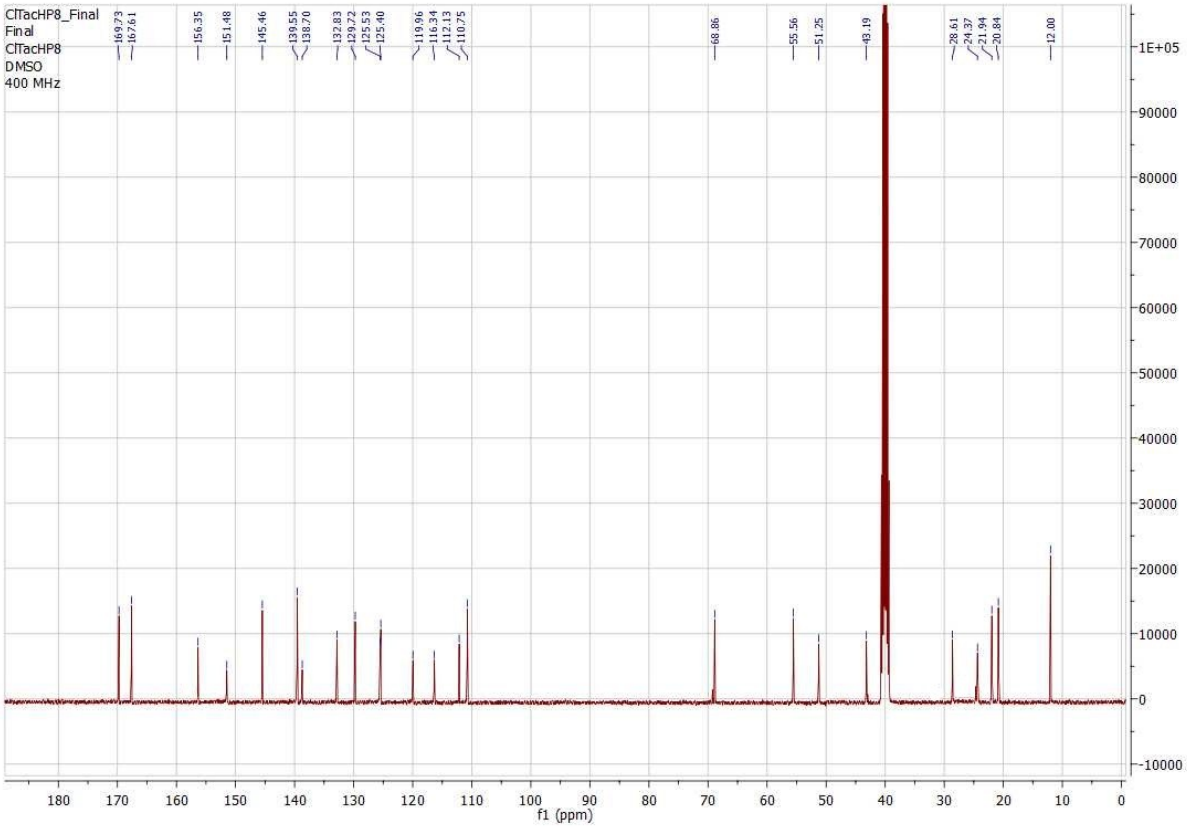
Sp14 - ^{1}H & ^{13}C NMR of *N*-(4-((6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)butyl)-2-(3-hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)acetamide (**31**).





Sp15 - ^{1}H & ^{13}C NMR of 2-(3-hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)-*N*-(2-hydroxy-3-((1,2,3,4-tetrahydroacridin-9-yl)amino)propyl)acetamide (**32**).





Sp16 - ^{1}H & ^{13}C NMR of *N*-(3-((6-chloro-1,2,3,4-tetrahydroacridin-9-yl)amino)-2-hydroxypropyl)-2-(3-hydroxy-2-methyl-4-oxopyridin-1(4*H*)-yl)acetamide (**33**).