Modular Synthesis and Biological Activity of Pyridyl-based Analogs of the Potent Class I Histone Deacetylase Inhibitor Largazole

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SUPPORTING INFORMATION

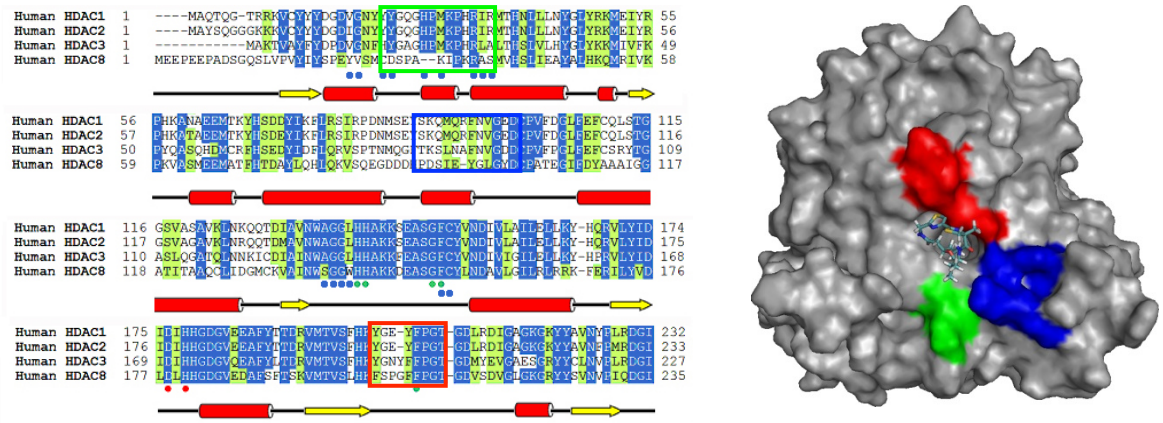

Figure S1: left: sequence alignment of human class I HDACs with residues in the non-conserved surface areas around the binding side highlights. Right: structure of HDAC1 homology model in surface representation with non-conserved residues color-coded

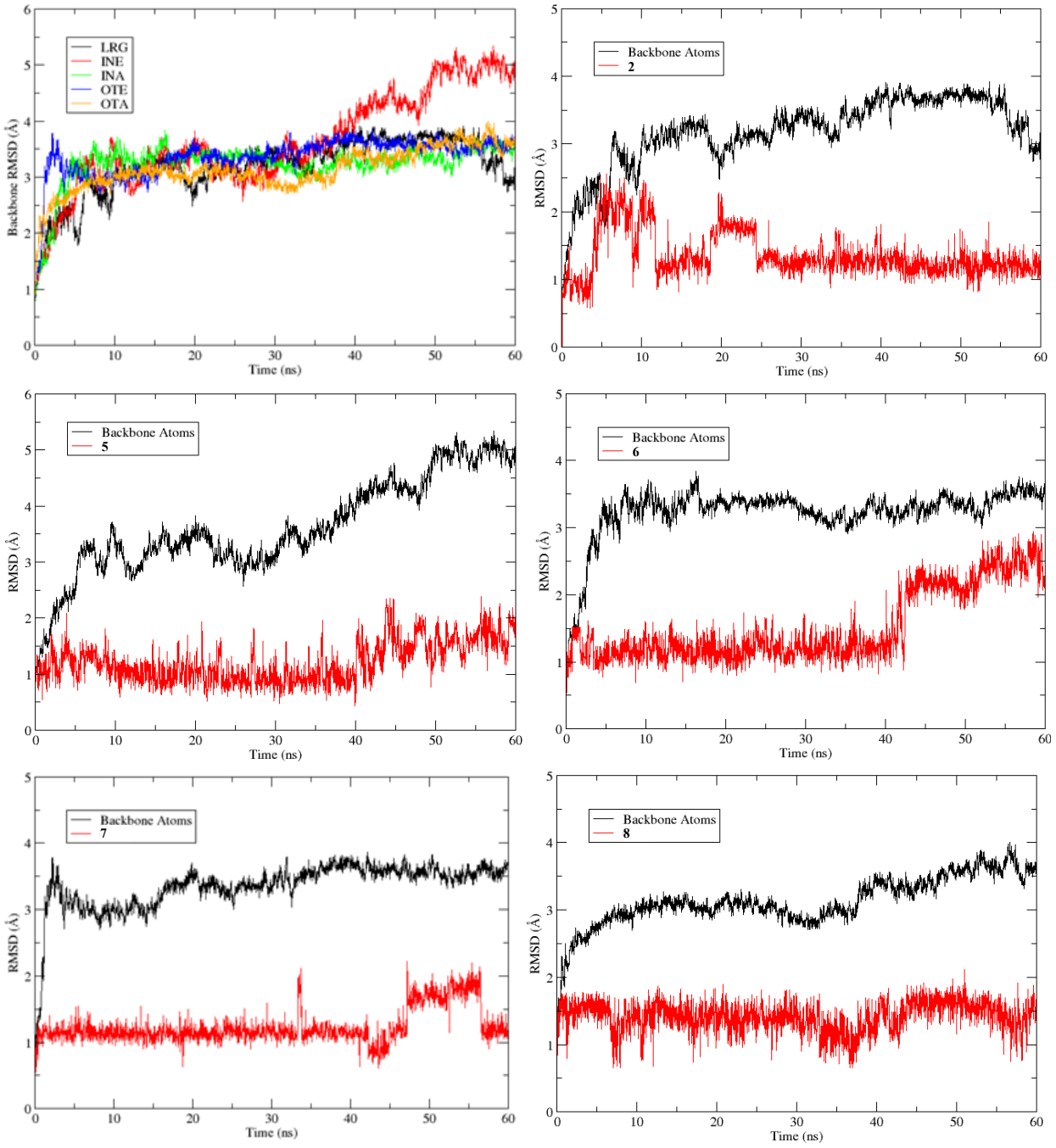

Figure S2: RMSD plots for 60 ns MD simulations of HDAC1: top left: overall backbone RMS and backbone RMDS for protein (black) and all atoms in ligands for complexes of HDAC1 with **2** (top right), **6** (middle left), **8** (middle right), **10** (bottom left) and **12** (bottom right)

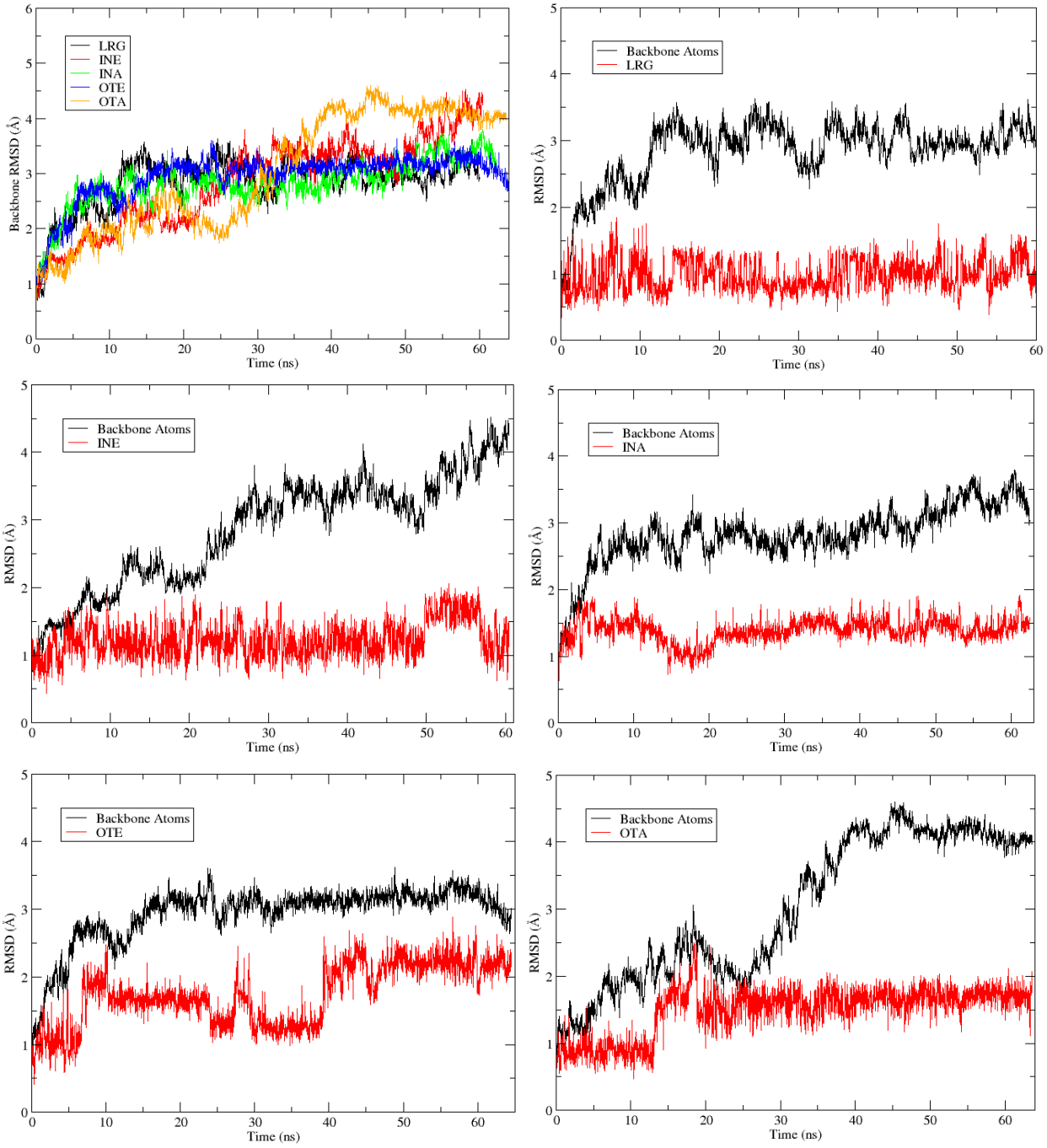

Figure S3: RMSD plots for 60 ns MD simulations of HDAC6: top left: overall backbone RMS and backbone RMDS for protein (black) and all atoms in ligands for complexes of HDAC6 with **2** (top right), **6** (middle left), **8** (middle right), **10** (bottom left) and **12** (bottom right)

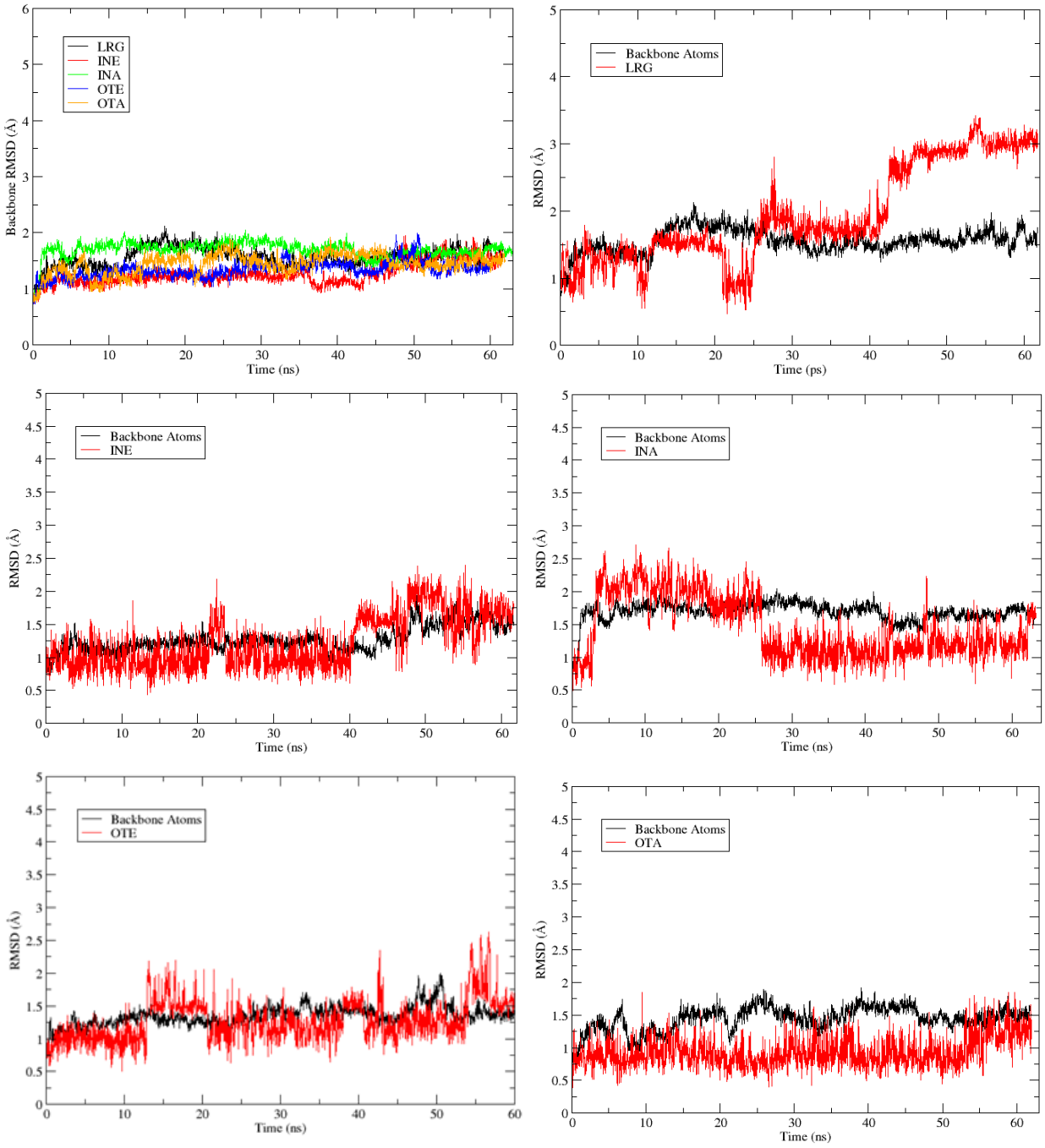

Figure S4: RMSD plots for 60 ns MD simulations of HDAC8: top left: overall backbone RMS and backbone RMDS for protein (black) and all atoms in ligands for complexes of HDAC8 with **2** (top right), **6** (middle left), **8** (middle right), **10** (bottom left) and **12** (bottom right)

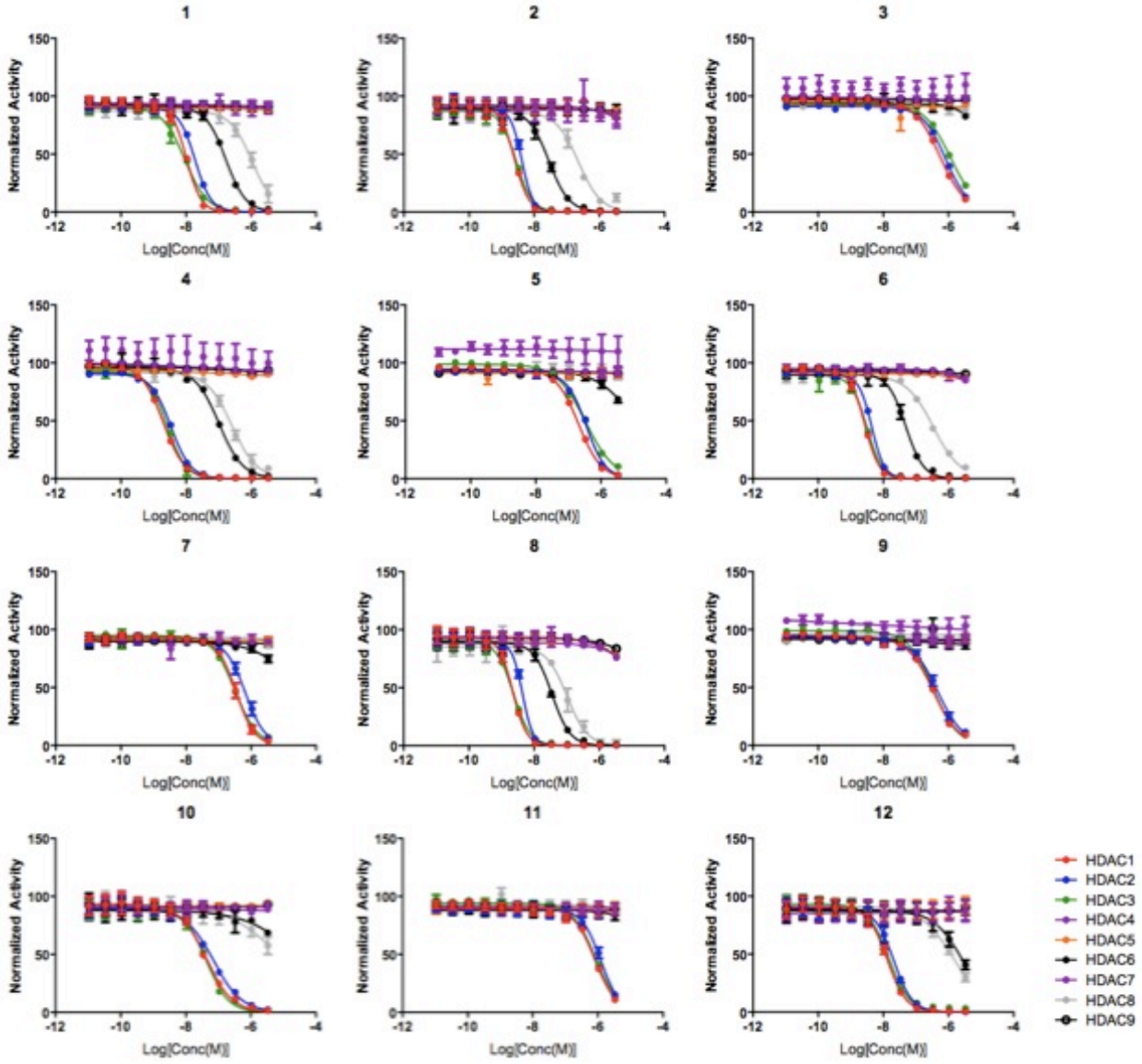

Figure S5. HDAC activity of largazole analogs

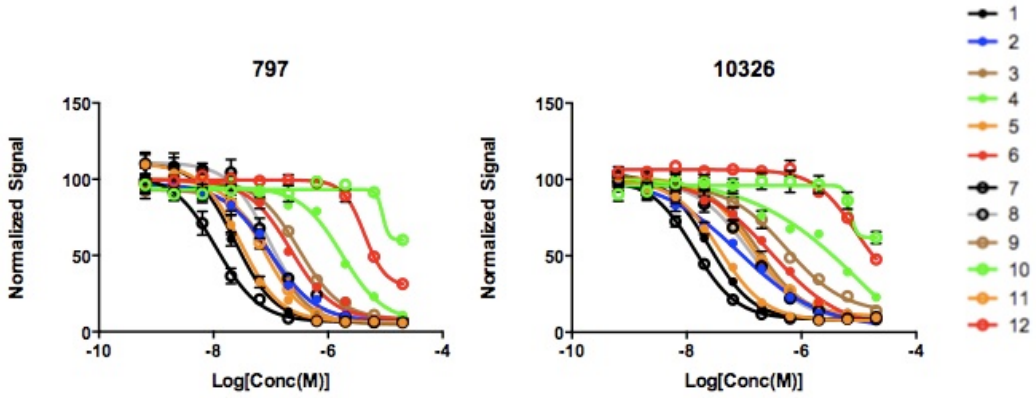

Figure S6. Activity of largazole analogs in 797 and 10326 cell lines

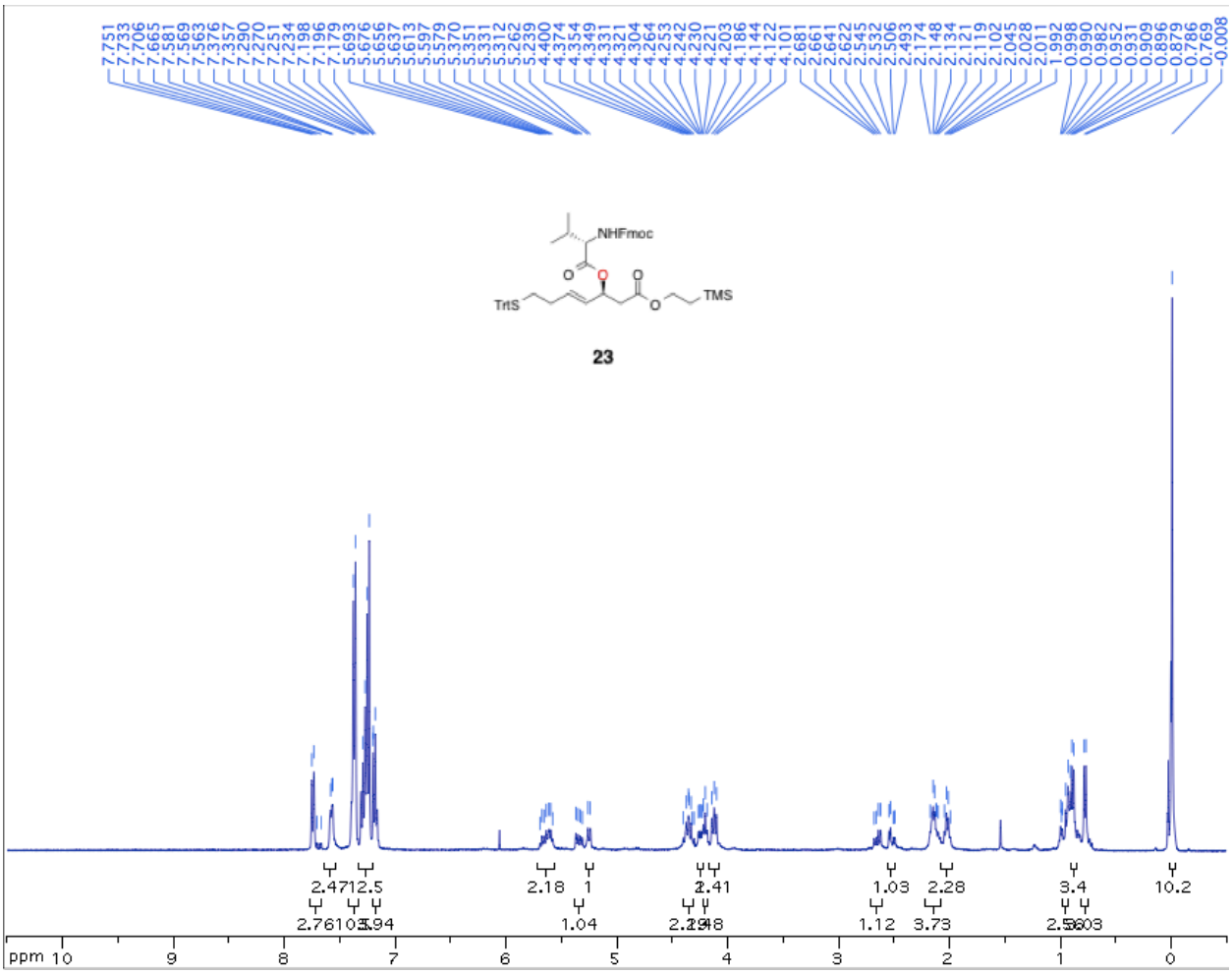

Figure S7. ^{1}H-NMR spectrum of (*S*,*E*)-2-(Trimethylsilyl)ethyl 3-(((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanoyl)oxy)-7-(tritylthio)hept-4-enoate (**23**).

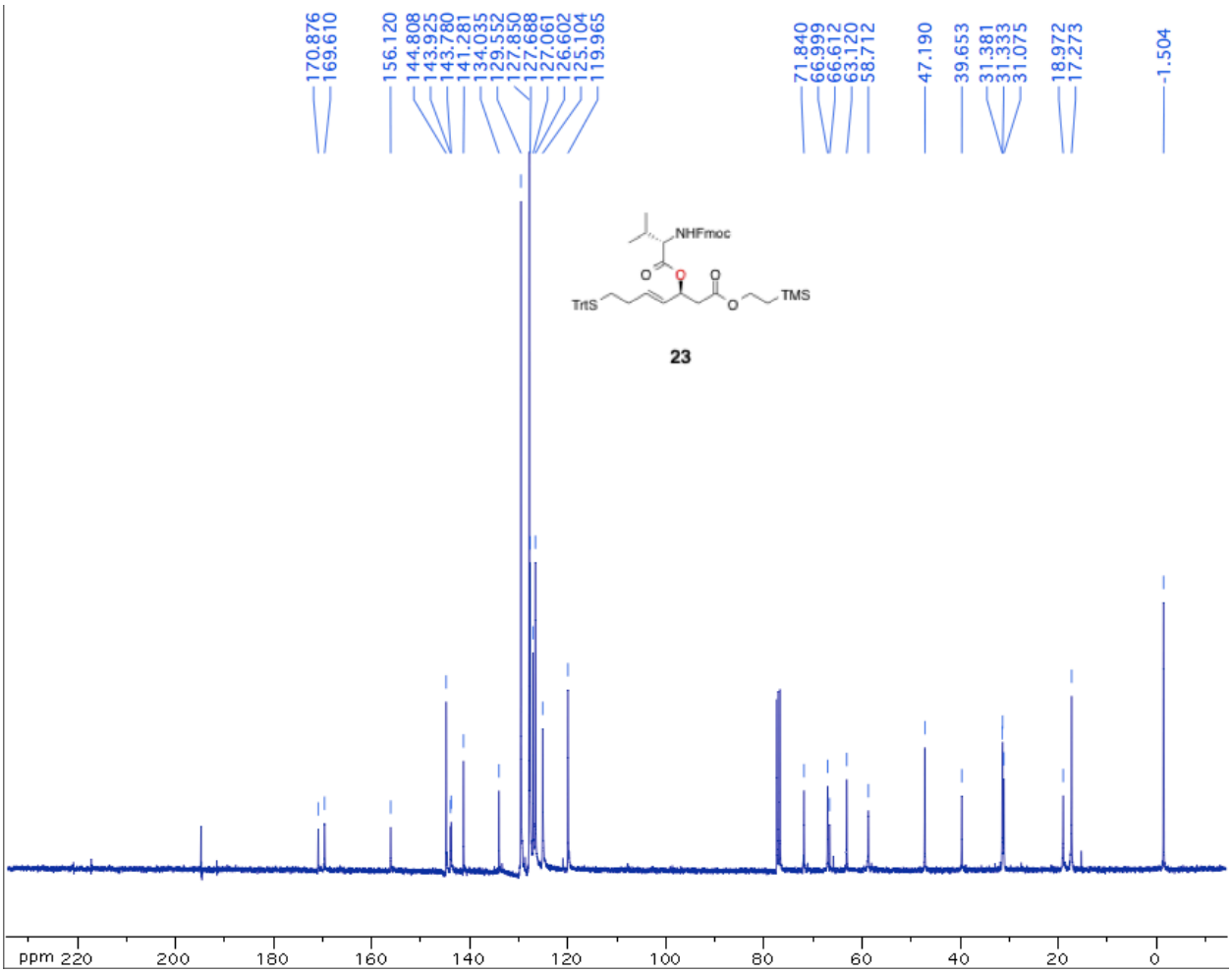

Figure S8. ^{13}C-NMR spectrum of (*S*,*E*)-2-(Trimethylsilyl)ethyl 3-(((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanoyl)oxy)-7-(tritylthio)hept-4-enoate (**23**).

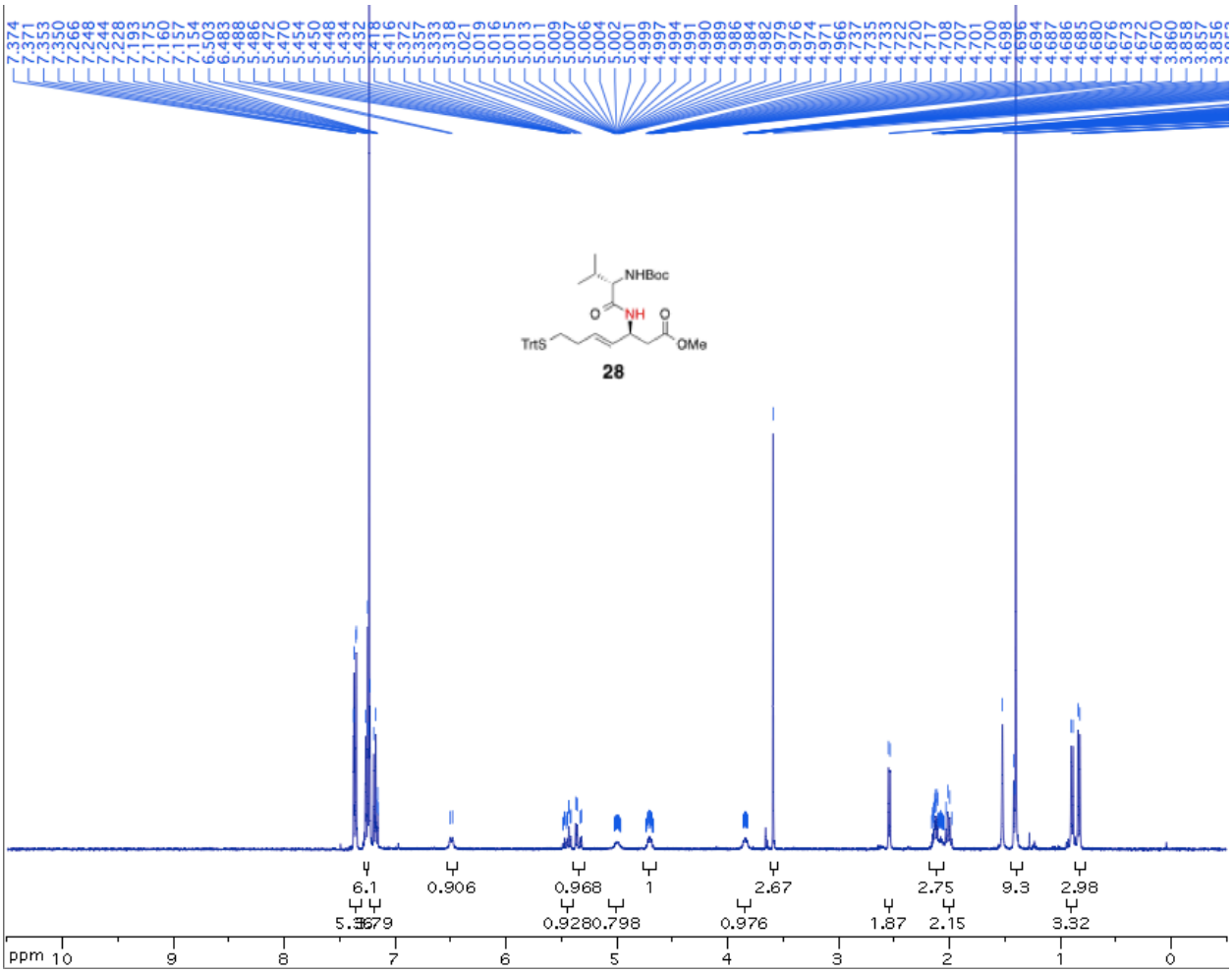

Figure S9. ^{1}H-NMR spectrum of (*S*,*E*)-Methyl 3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-7-(tritylthio)hept-4-enoate (**28**).

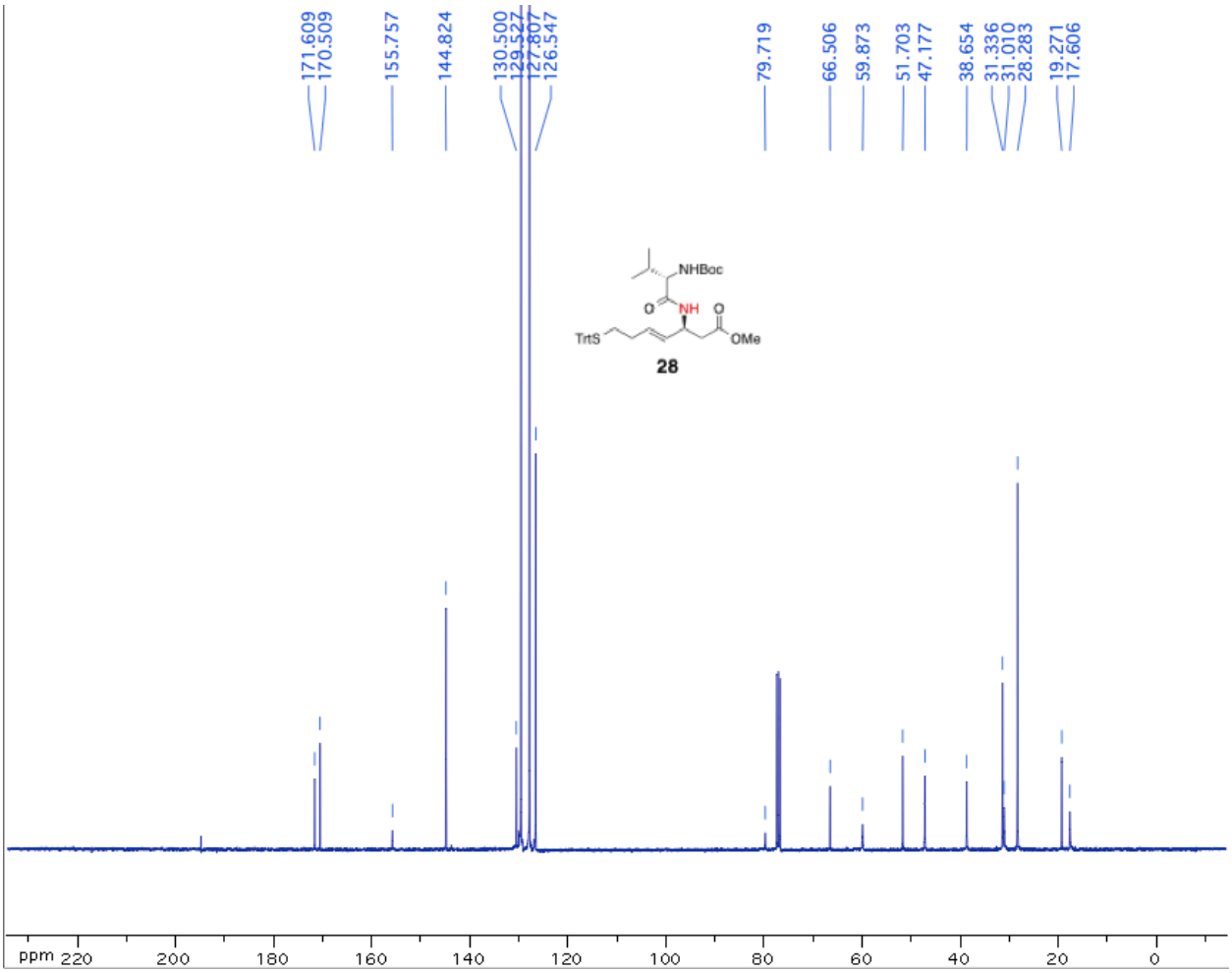

Figure S10. ^{13}C-NMR spectrum of (*S*,*E*)-Methyl 3-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-7-(tritylthio)hept-4-enoate (**28**).

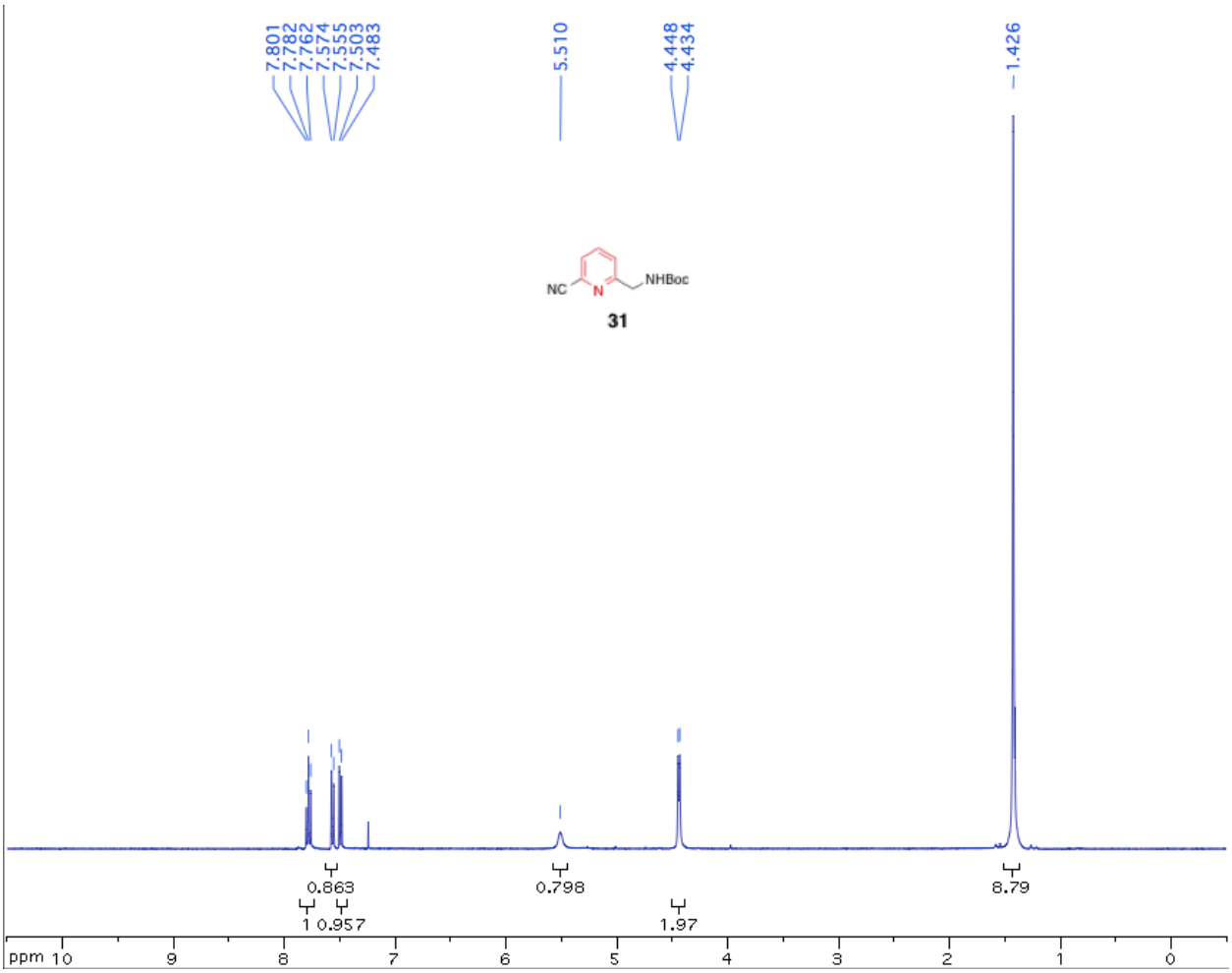

Figure S11. ^{1}H-NMR spectrum of 6-((((*tert*-Butoxy)carbonyl)amino)methyl) picolinonitrile (**31**).

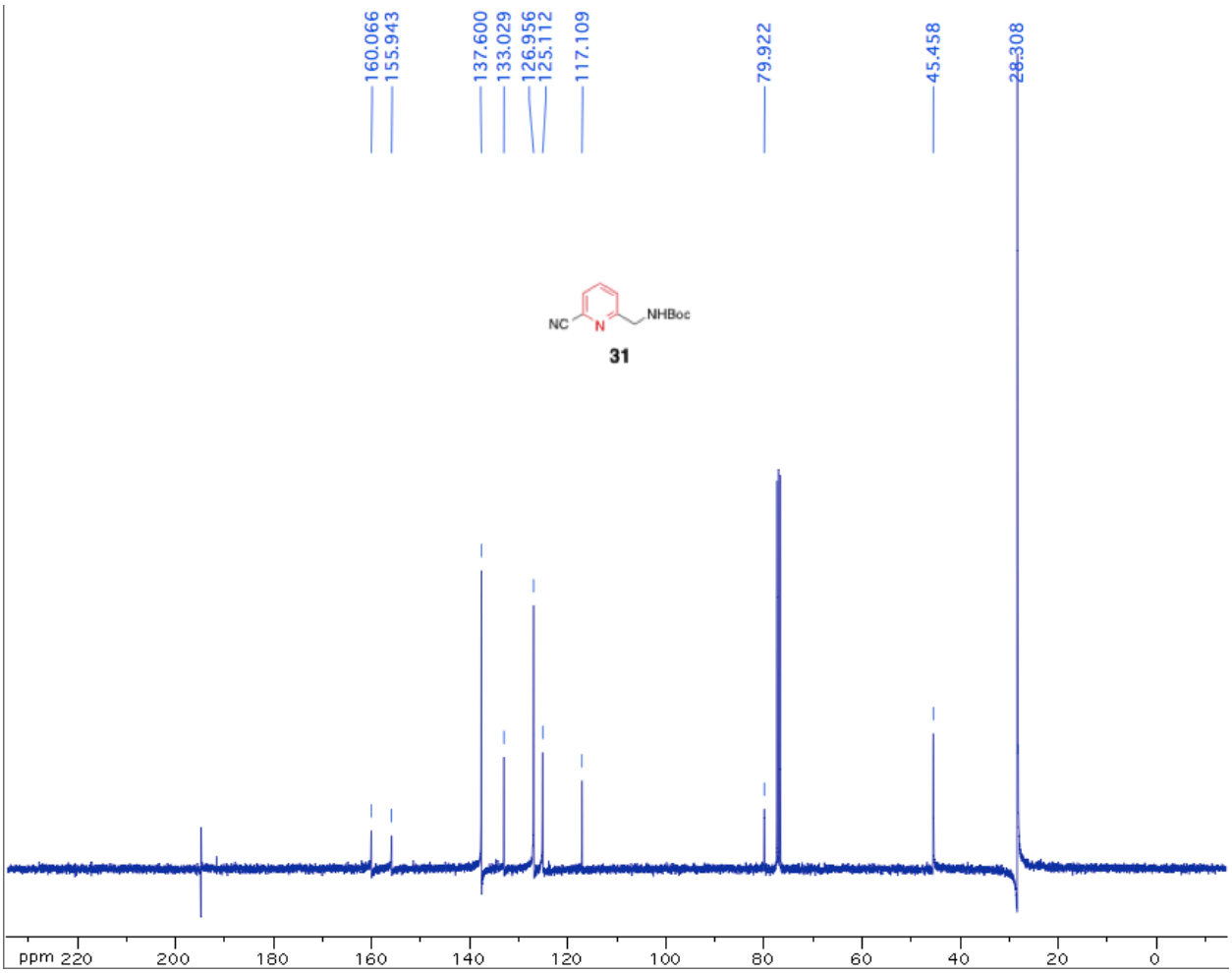

Figure S12. ^{13}C-NMR spectrum of 6-((((*tert*-Butoxy)carbonyl)amino)methyl) picolinonitrile (**31**).

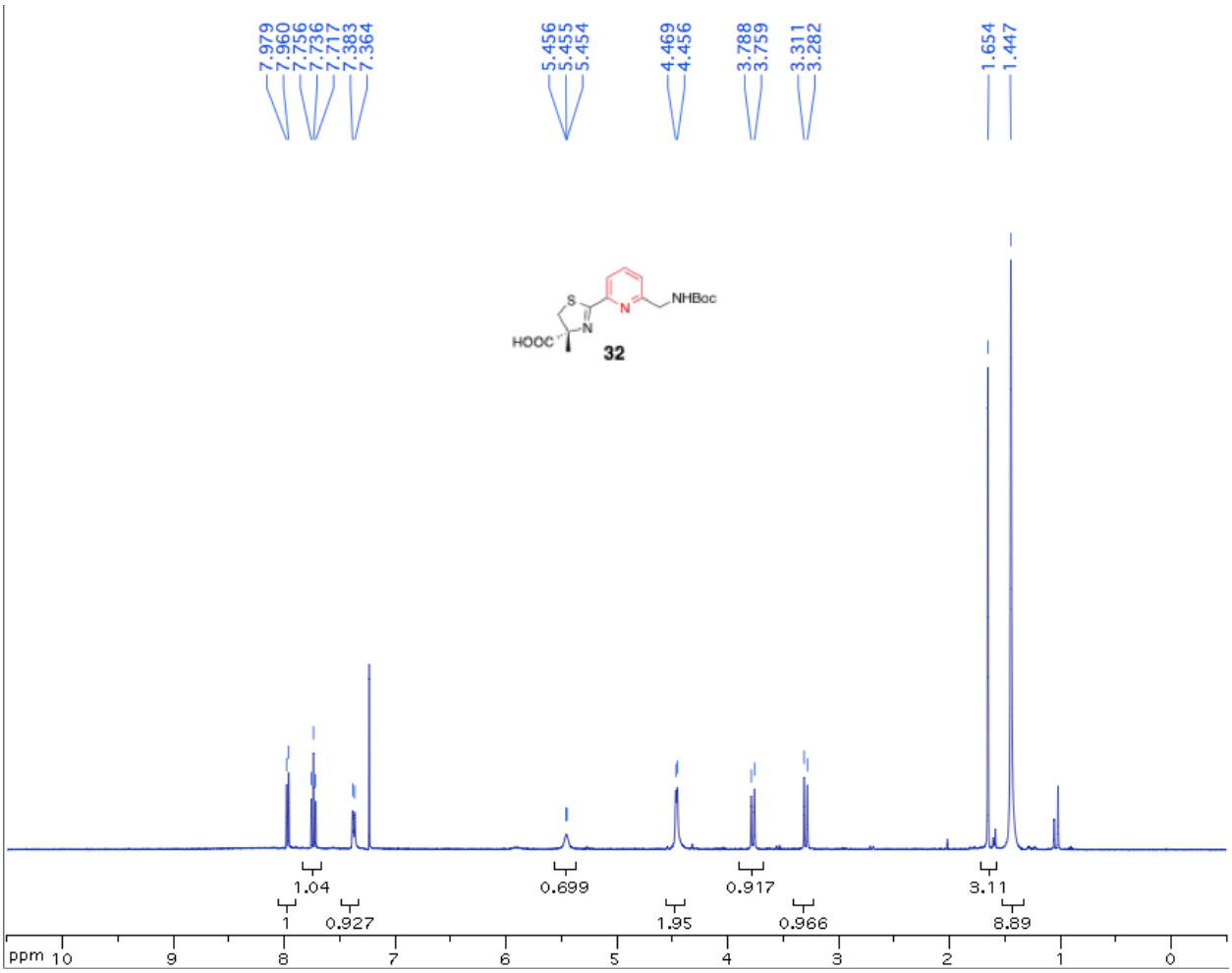

Figure S13. ^{1}H-NMR spectrum of (*R*)-2-(6-(((*tert*-Butoxycarbonyl)amino)methyl) pyridin-2-yl)-4-methyl-4,5-dihydrothiazole-4-carboxylic acid (**32**).

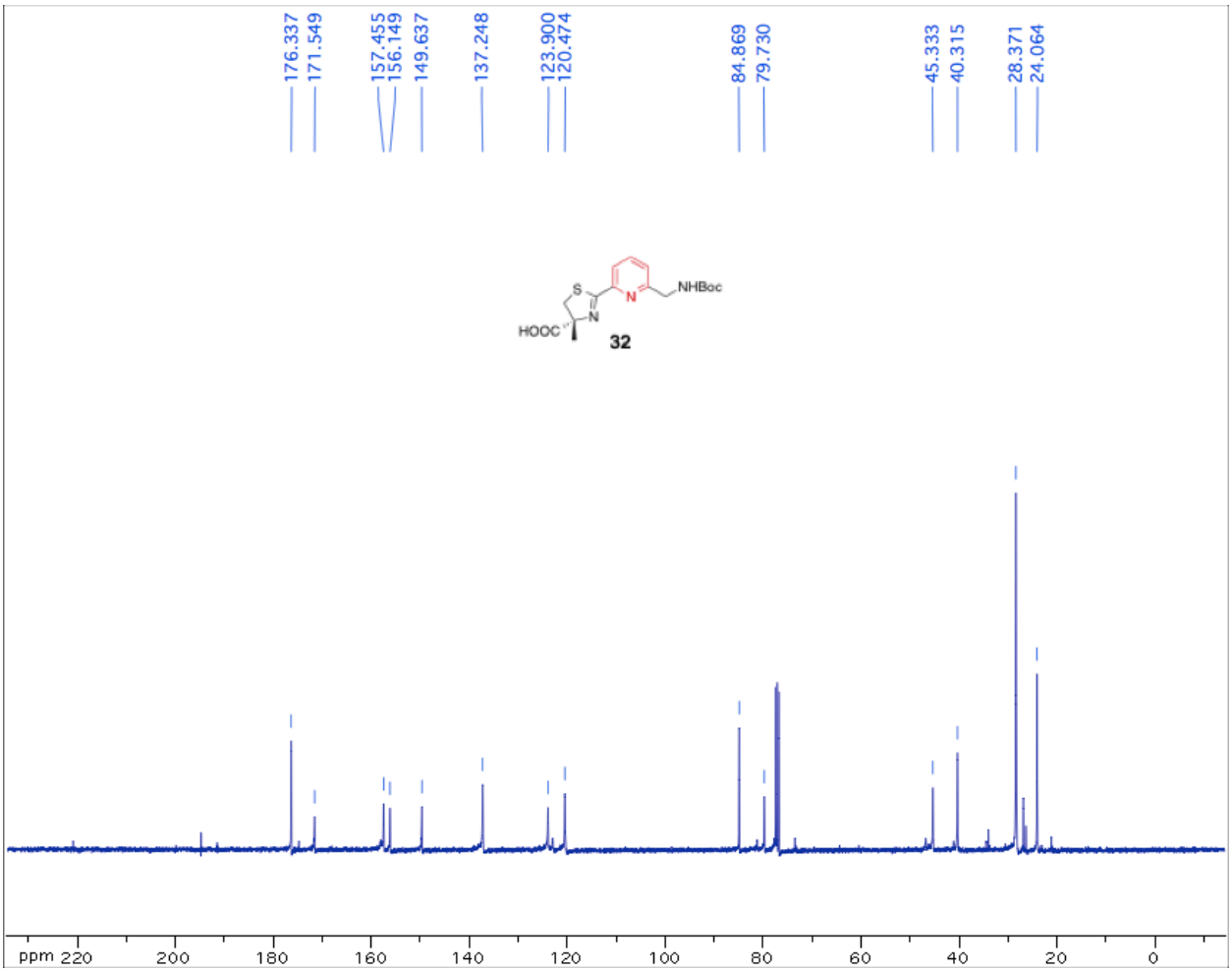

Figure S14. ^{13}C-NMR spectrum of (*R*)-2-(6-(((*tert*-Butoxycarbonyl)amino)methyl) pyridin-2-yl)-4-methyl-4,5-dihydrothiazole-4-carboxylic acid (**32**).

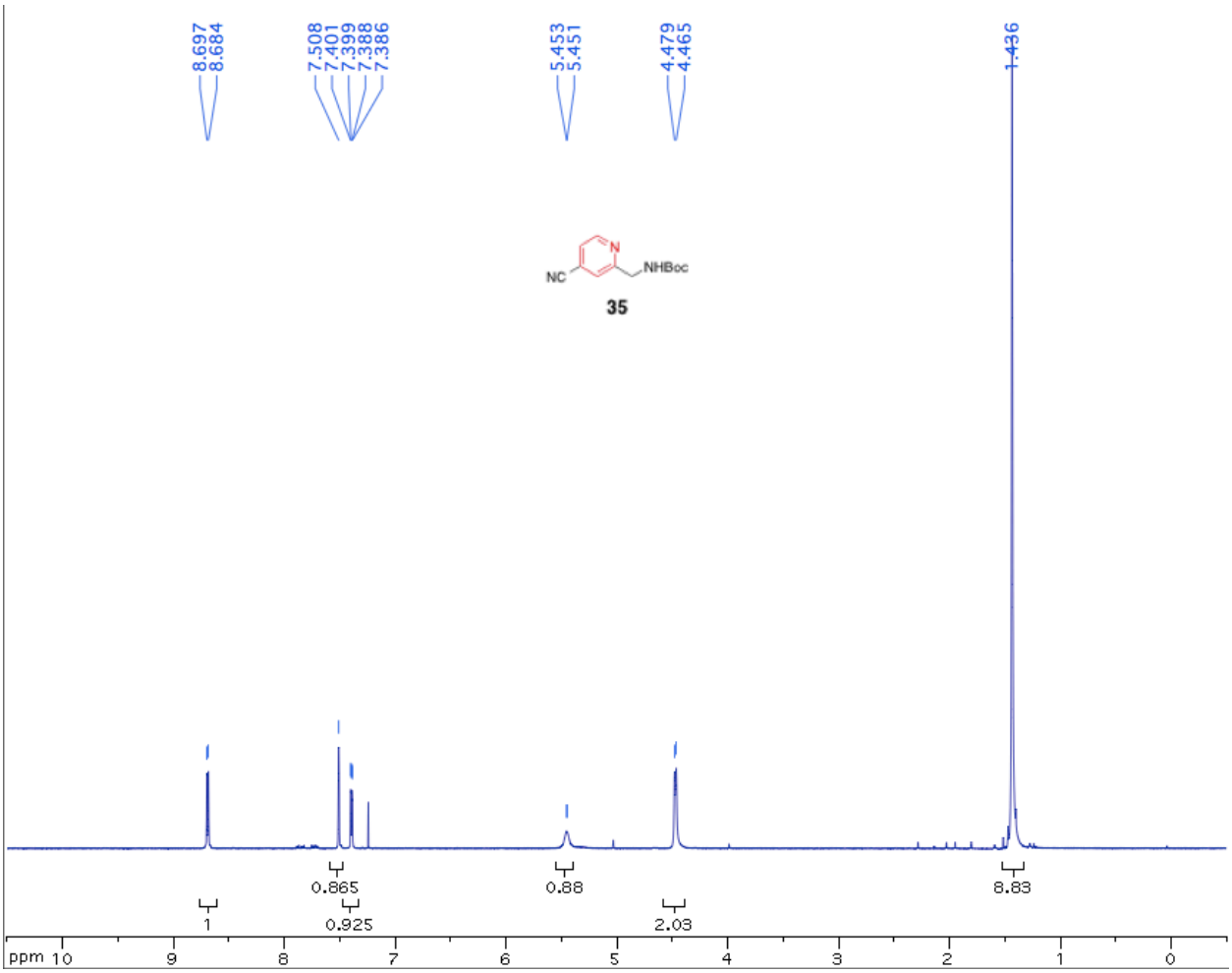

Figure S15. ^{1}H-NMR spectrum of 2-((((*tert*-Butoxy)carbonyl)amino)methyl) isonicotinonitrile (**35**).

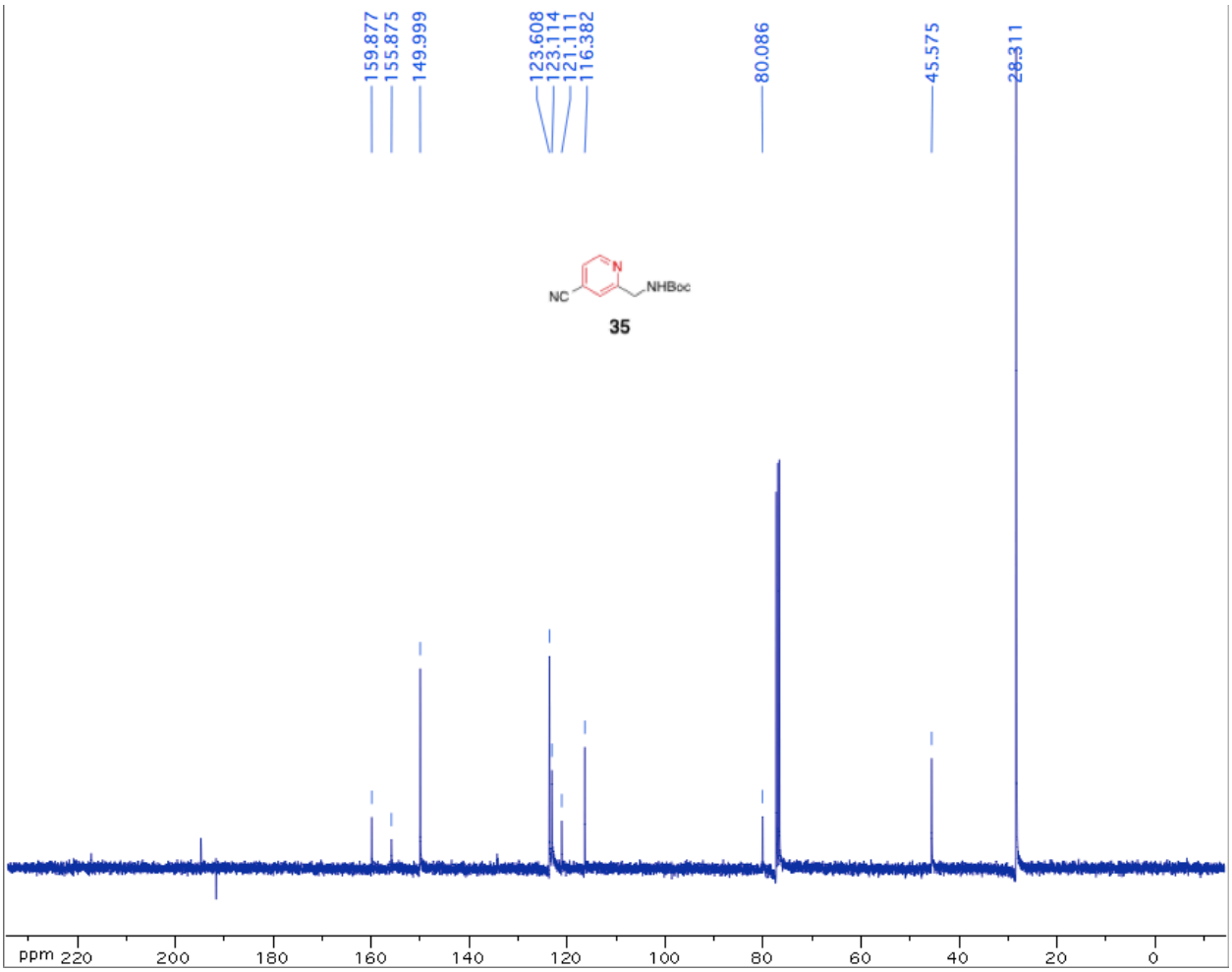

Figure S16. ^{13}C-NMR spectrum of 2-((((*tert*-Butoxy)carbonyl)amino)methyl) isonicotinonitrile (**35**).

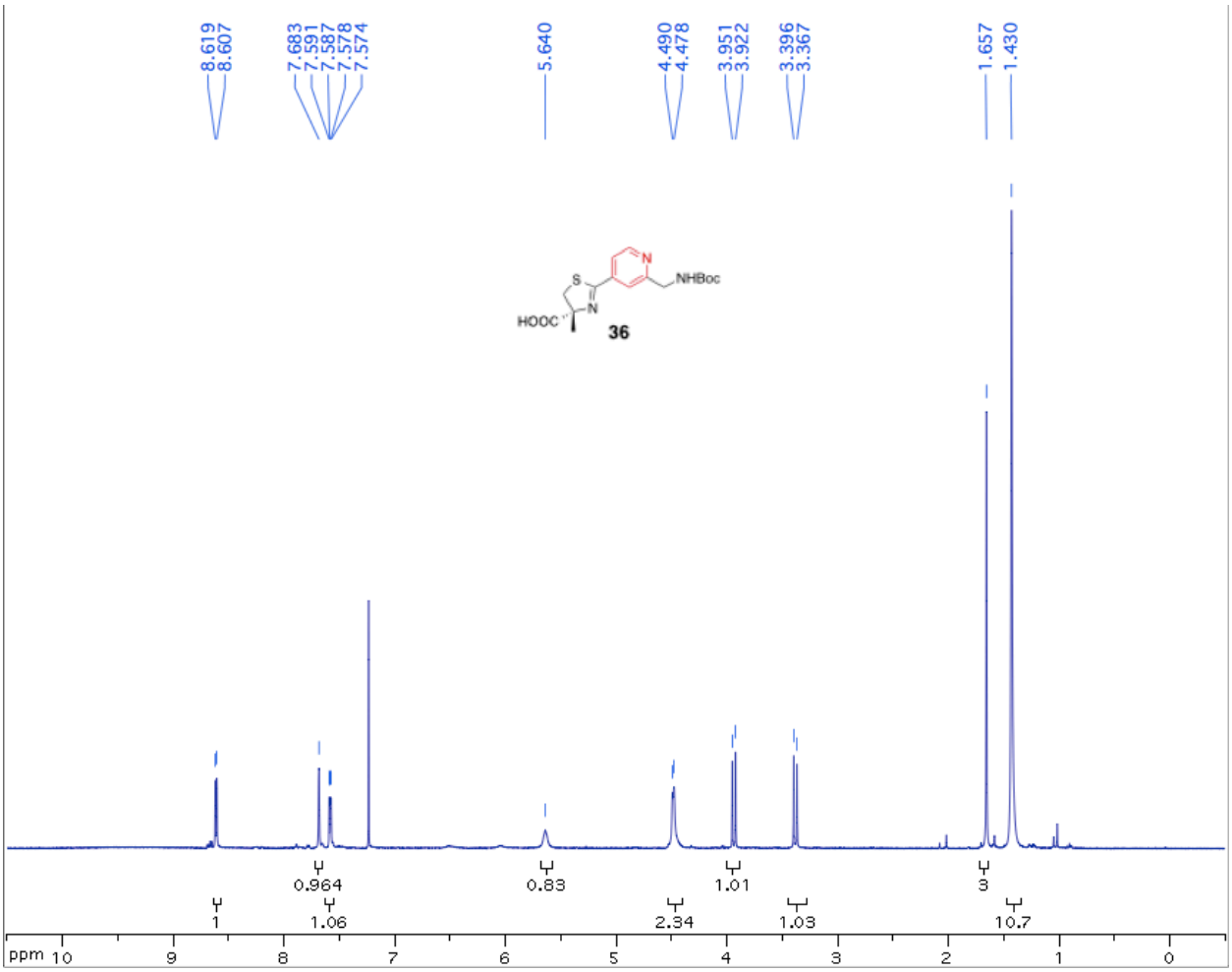

Figure S17. ^{1}H-NMR spectrum of (*R*)-2-(2-(((*tert*-Butoxycarbonyl)amino)methyl) pyridin-4-yl)-4-methyl-4,5-dihydrothiazole-4-carboxylic acid (**36**).

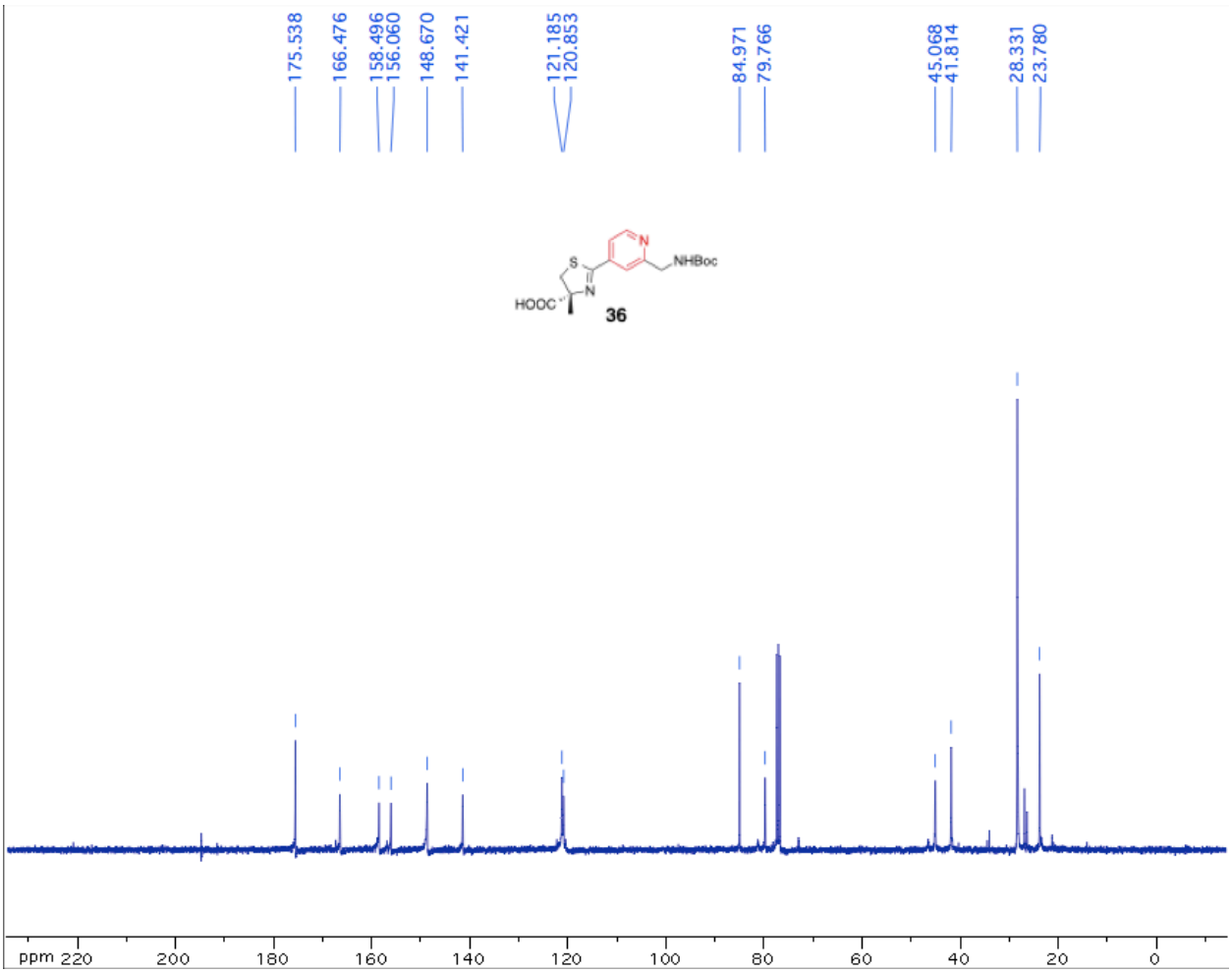

Figure S18. ^{13}C-NMR spectrum of (*R*)-2-(2-(((*tert*-Butoxycarbonyl)amino)methyl) pyridin-4-yl)-4-methyl-4,5-dihydrothiazole-4-carboxylic acid (**36**).

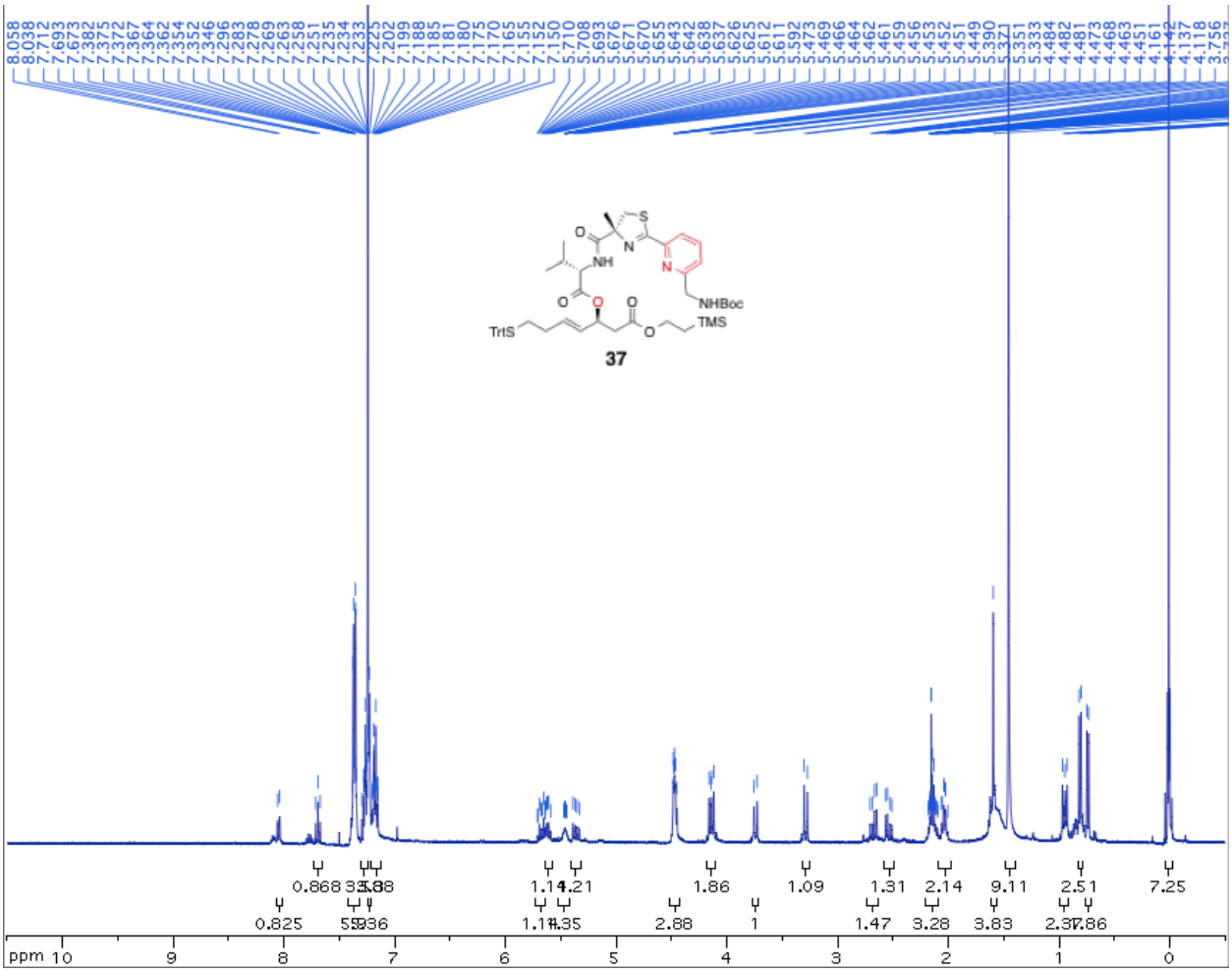

Figure S19. ^{1}H-NMR spectrum of (*S*,*E*)-2-(Trimethylsilyl)ethyl 3-(((*S*)-2-((*R*)-2-(6-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-2-yl)-4-methyl-4,5-dihydrothiazole-4-carboxamido)-3-methylbutanoyl)oxy)-7-(tritylthio)hept-4-enoate (**37**).

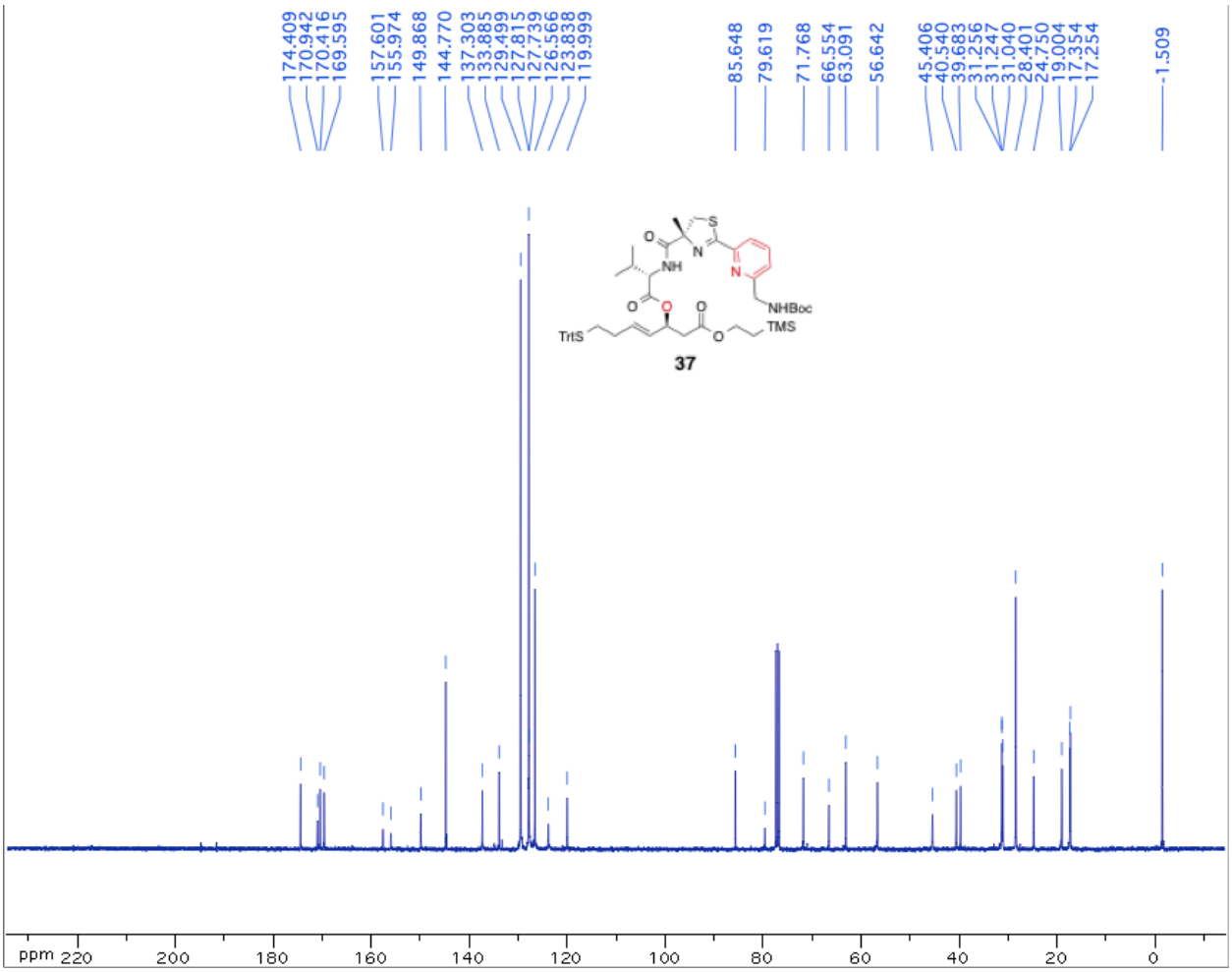

Figure S20. ^{13}C-NMR spectrum of (*S*,*E*)-2-(Trimethylsilyl)ethyl 3-(((*S*)-2-((*R*)-2-(6-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-2-yl)-4-methyl-4,5-dihydrothiazole-4-carboxamido)-3-methylbutanoyl)oxy)-7-(tritylthio)hept-4-enoate (**37**).

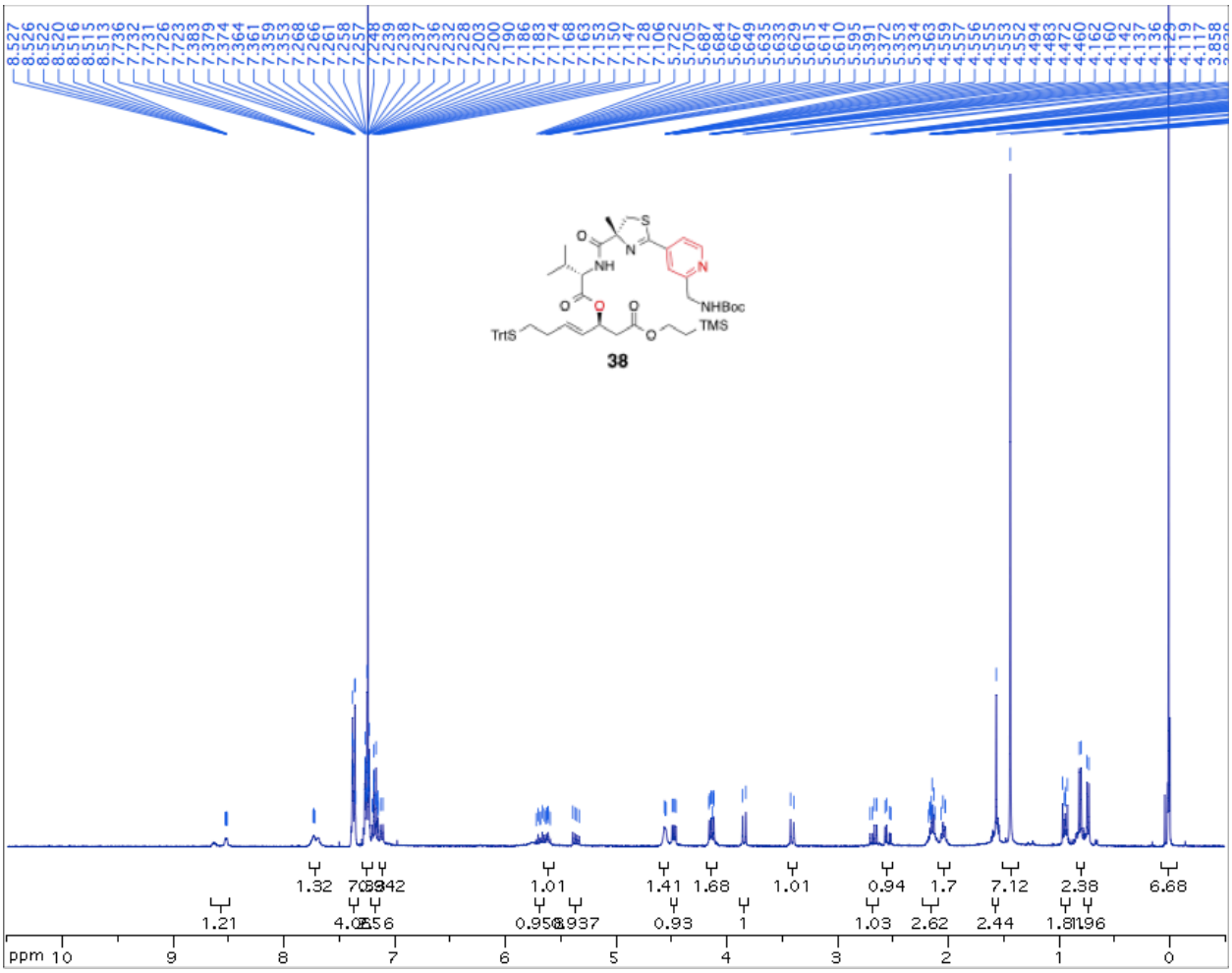

Figure S21. ^{1}H-NMR spectrum of (*S*,*E*)-2-(Trimethylsilyl)ethyl 3-(((*S*)-2-((*R*)-2-(2-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-4-yl)-4-methyl-4,5-dihydrothiazole-4-carboxamido)-3-methylbutanoyl)oxy)-7-(tritylthio)hept-4-enoate (**38**).

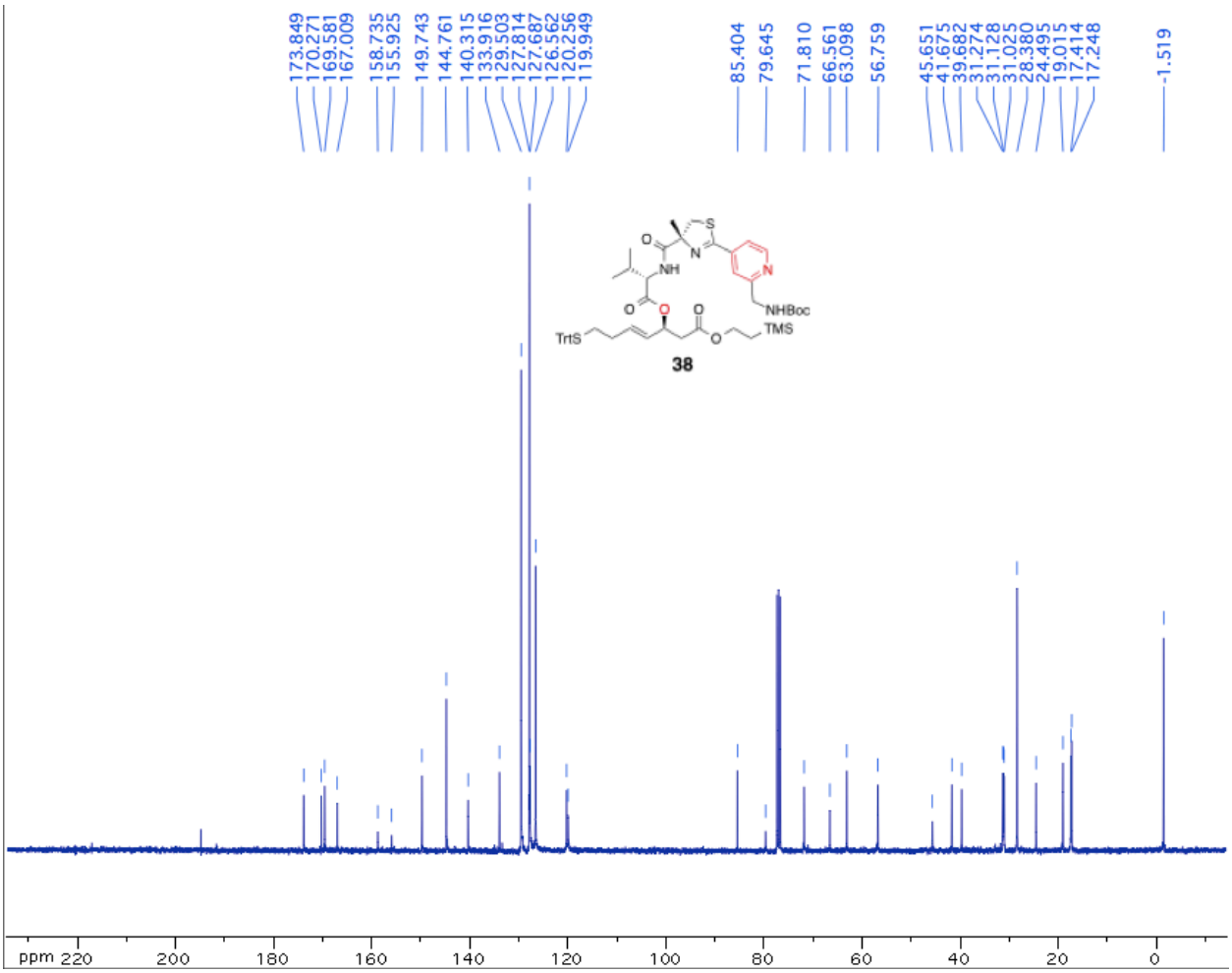

Figure S22. ^{13}C-NMR spectrum of (*S*,*E*)-2-(Trimethylsilyl)ethyl 3-(((*S*)-2-((*R*)-2-(2-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-4-yl)-4-methyl-4,5-dihydrothiazole-4-carboxamido)-3-methylbutanoyl)oxy)-7-(tritylthio)hept-4-enoate (**38**).

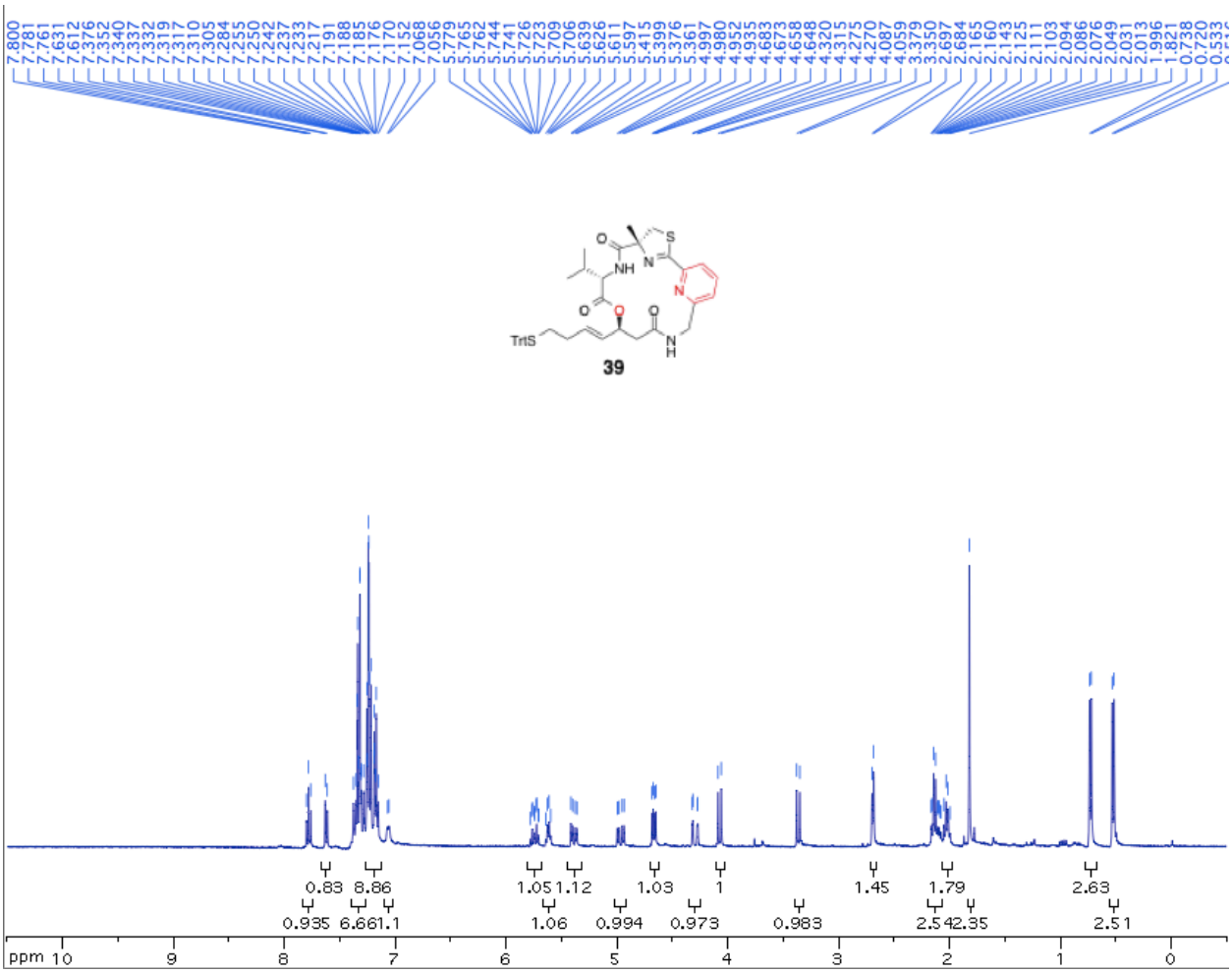

Figure S23. ^{1}H-NMR spectrum of trityl protected depsipeptide pyridyl "IN" macrocycle (**39**).

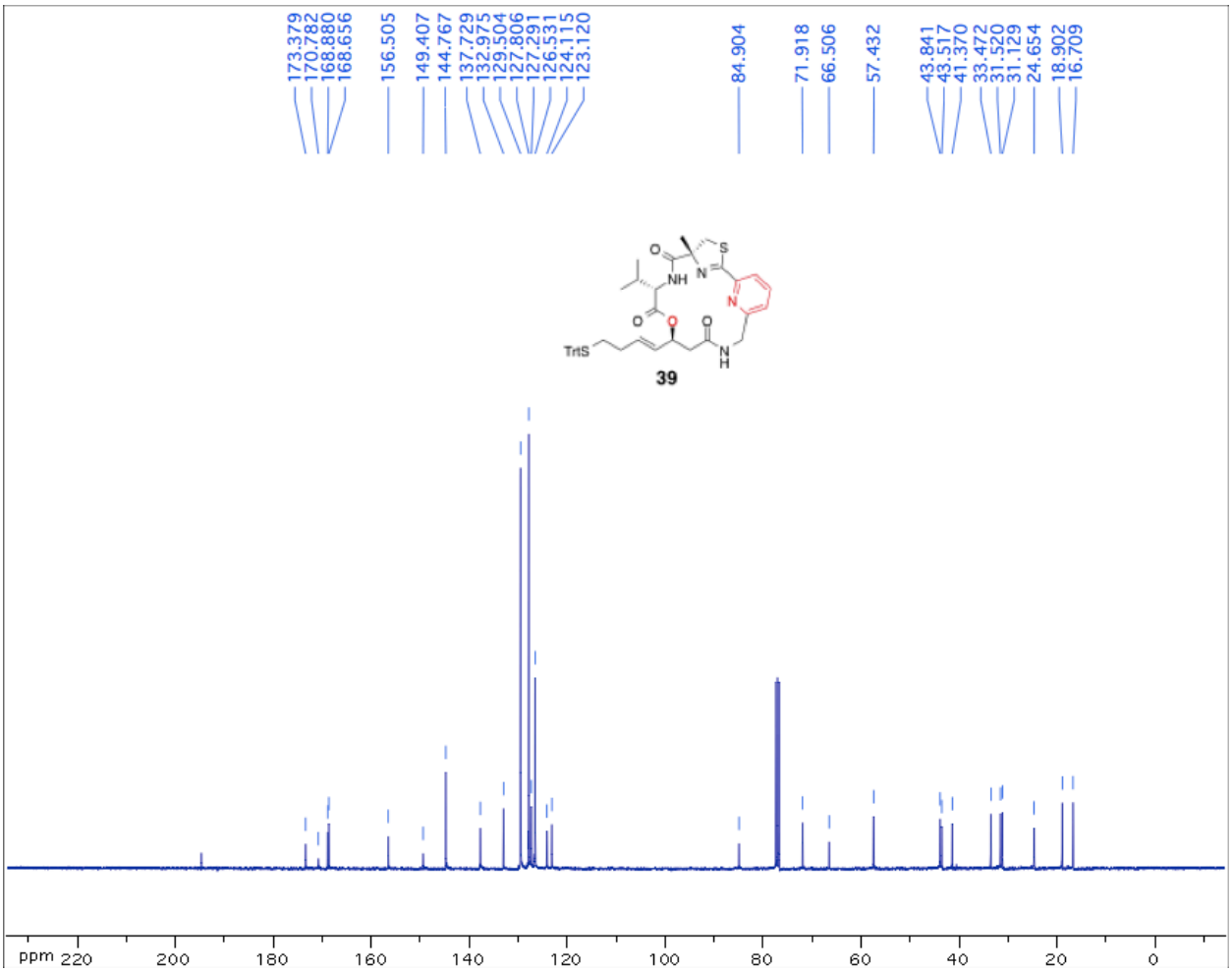

Figure S24. ^{13}C-NMR spectrum of trityl protected depsipeptide pyridyl "IN" macrocycle (**39**).

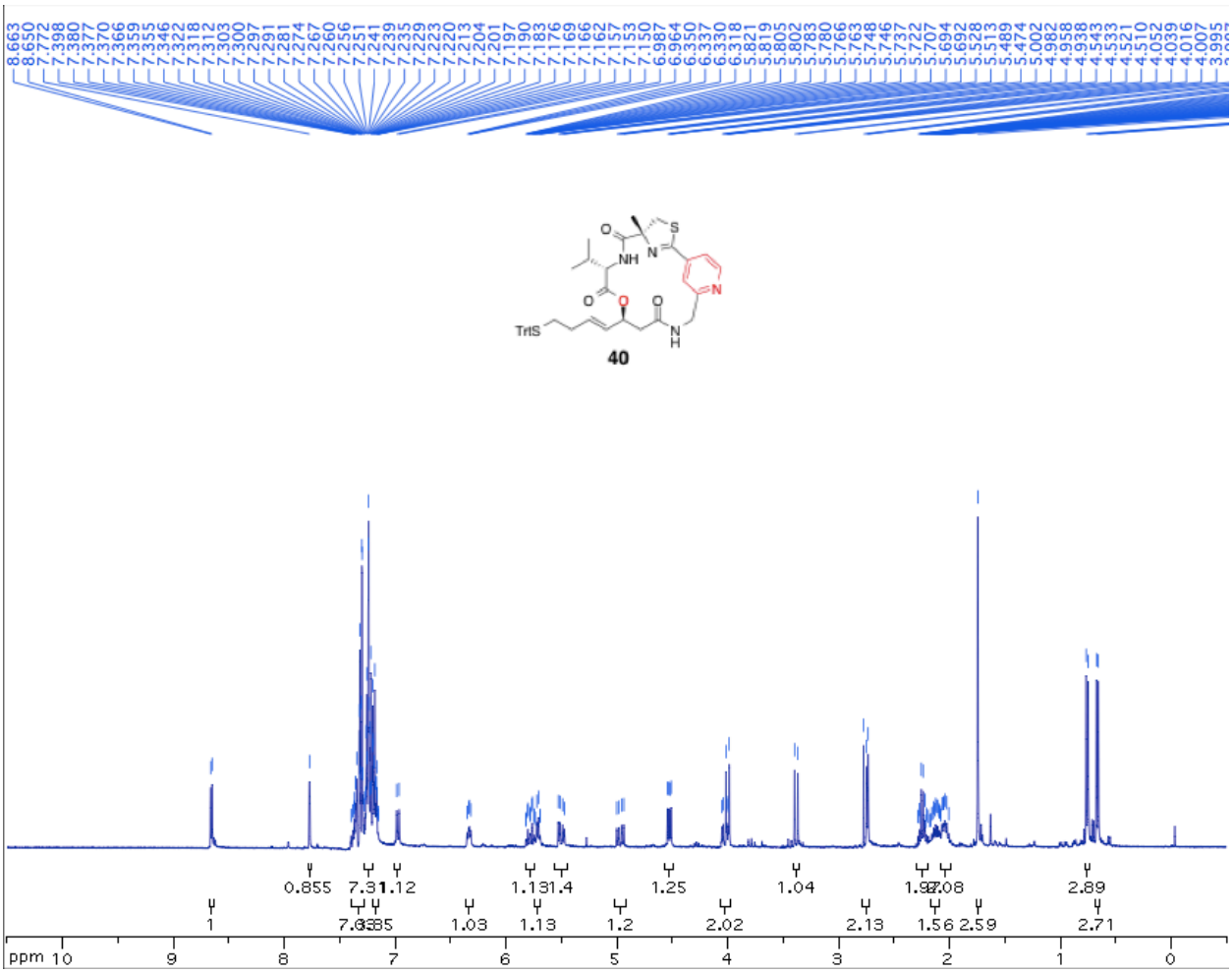

Figure S25. ^{1}H-NMR spectrum of trityl protected depsipeptide pyridyl "OUT" macrocycle (**40**).

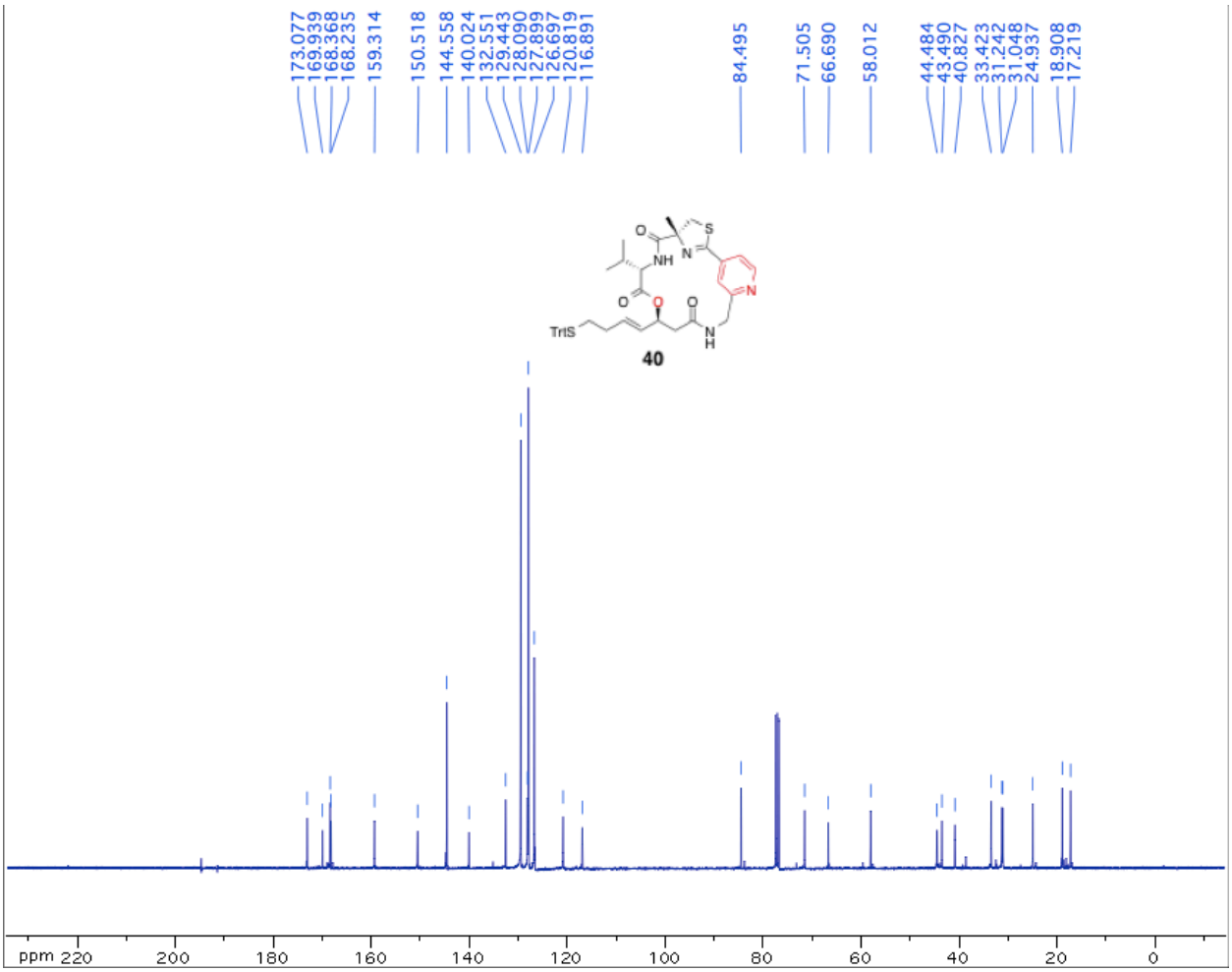

Figure S26. ^{13}C-NMR spectrum of of trityl protected depsipeptide pyridyl "OUT" macrocycle (**40**).

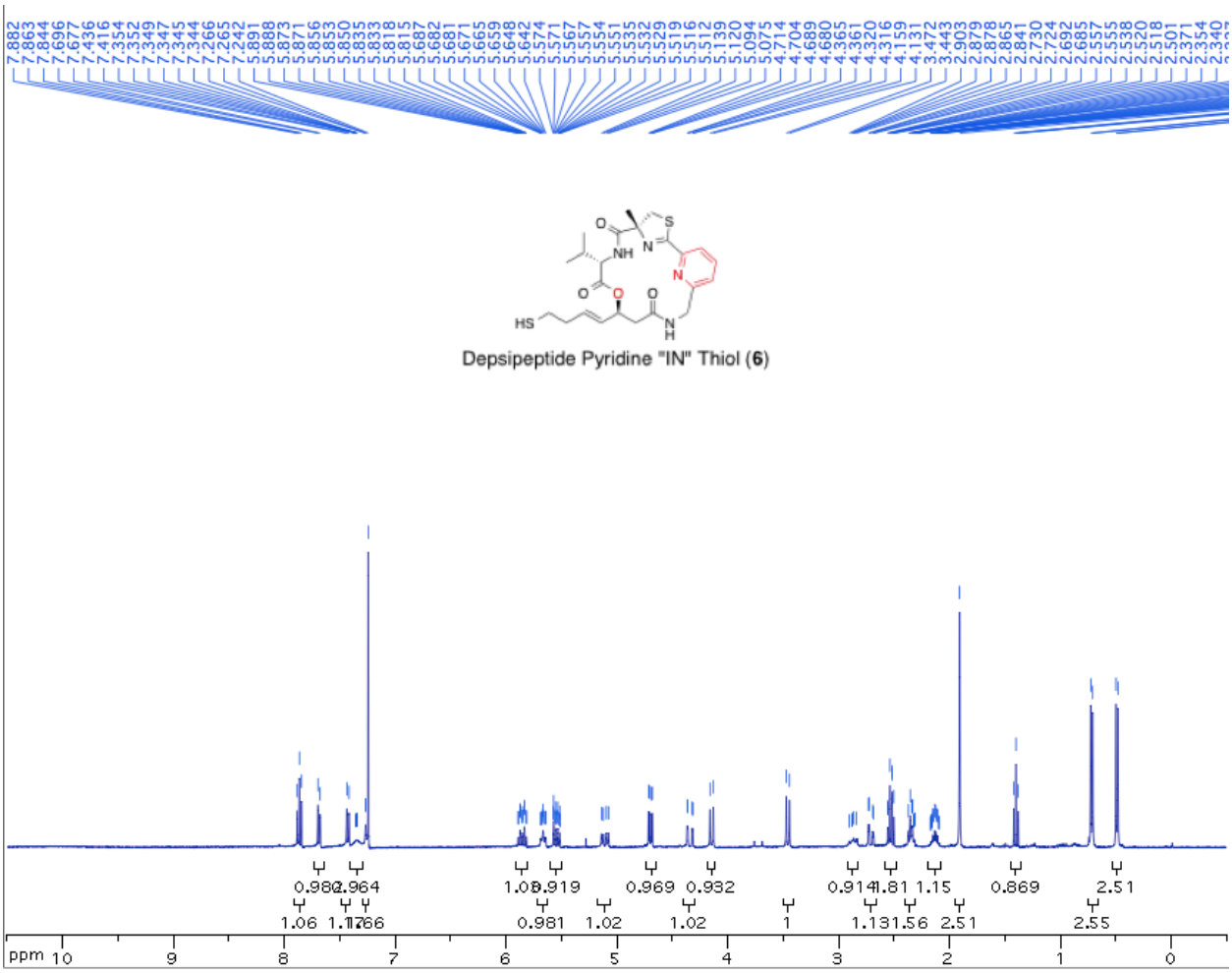

Figure S27. ^{1}H-NMR spectrum of depsipeptide pyridyl “IN” thiol (**6**).

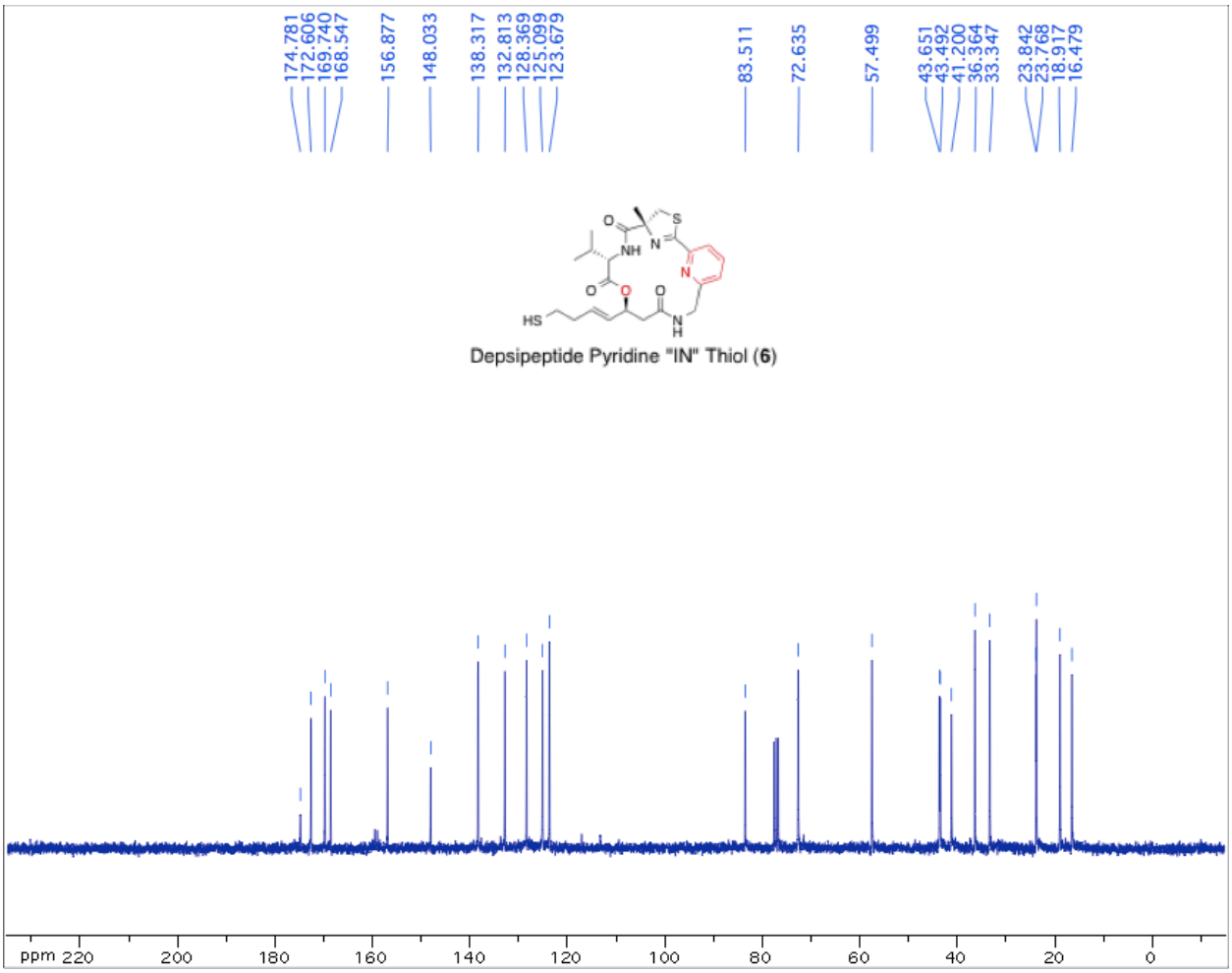

Figure S28. ^{13}C-NMR spectrum of depsipeptide pyridyl “IN” thiol (**6**).

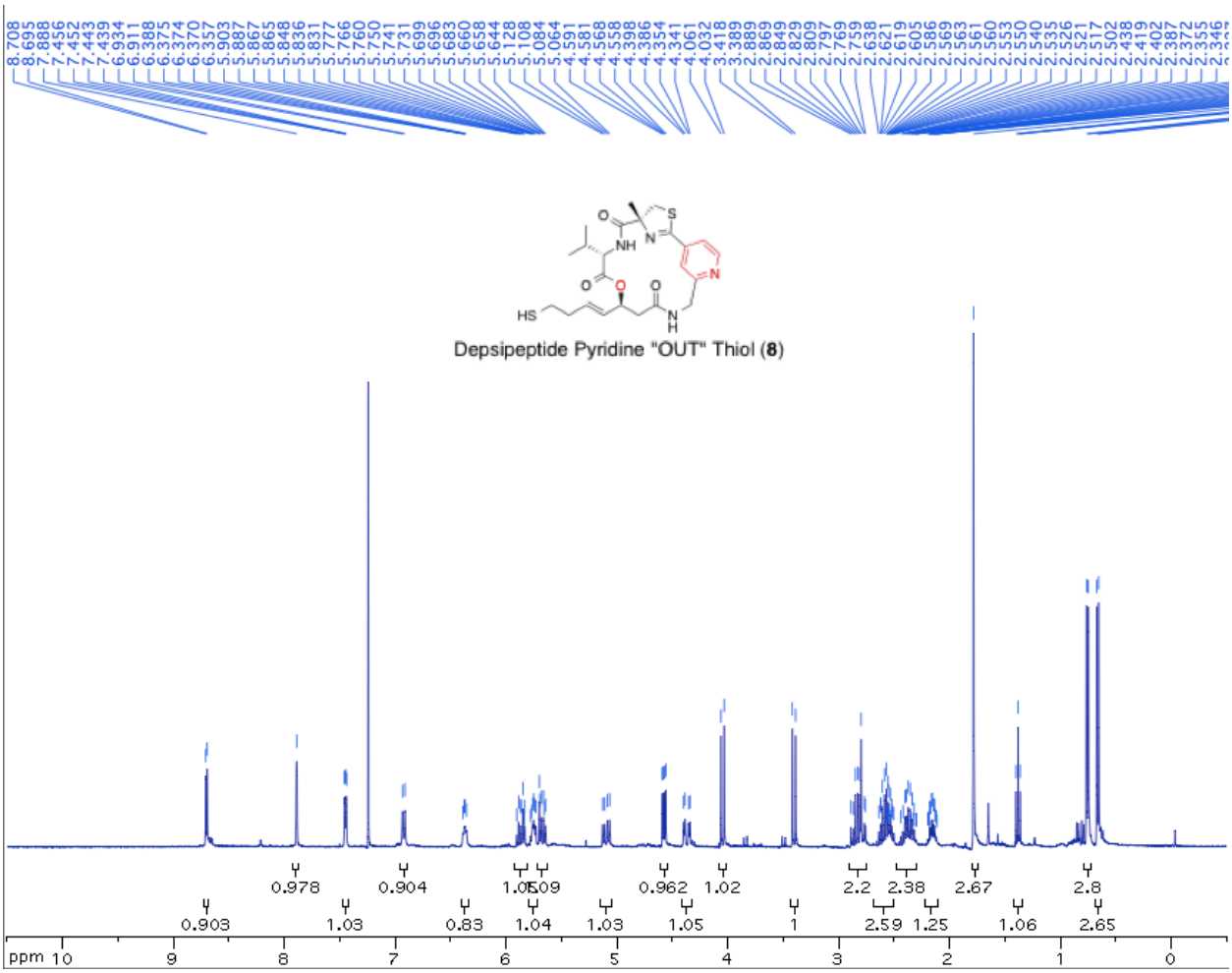

Figure S29. ^{1}H-NMR spectrum of depsipeptide pyridyl “OUT” thiol (**8**).

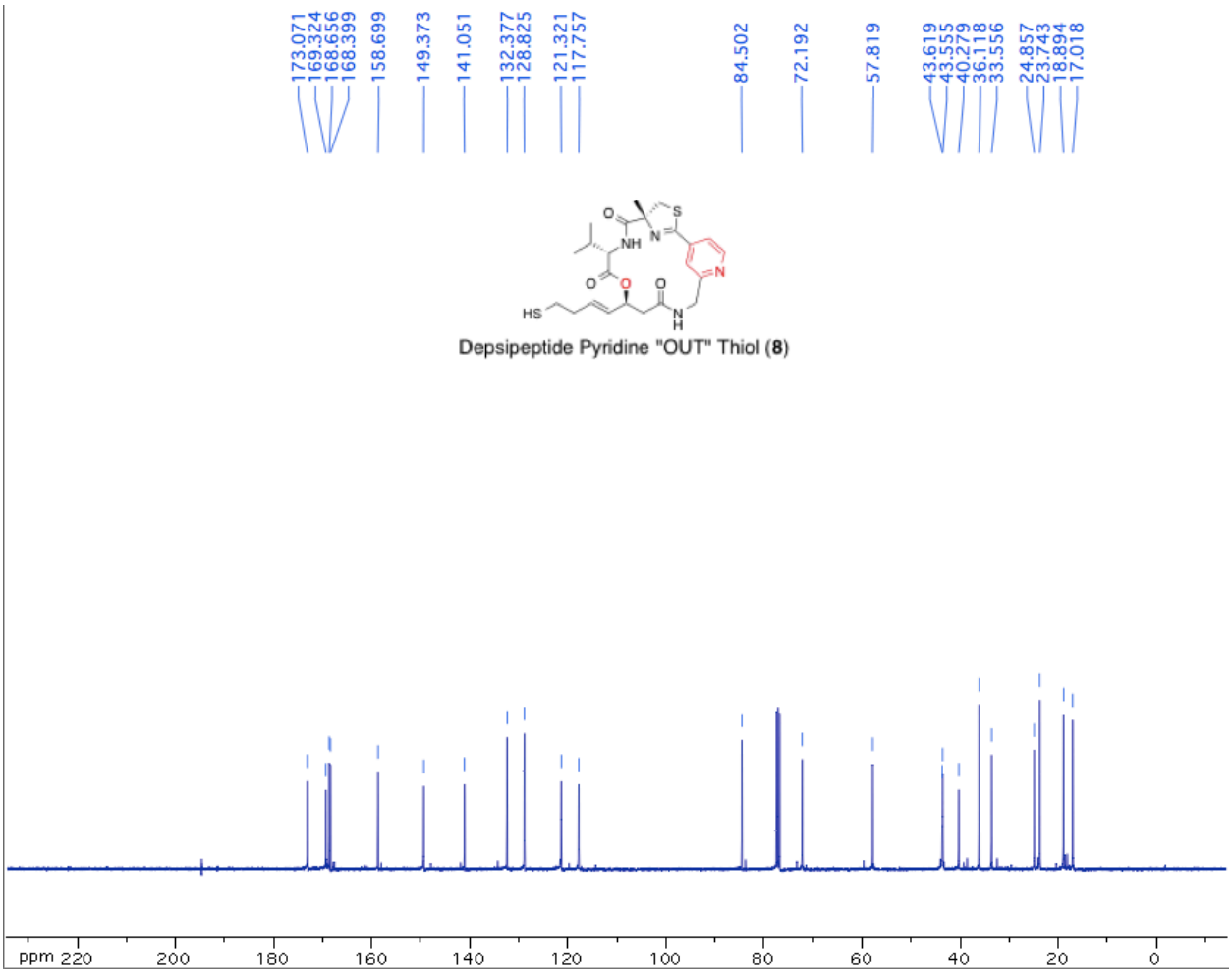

Figure S30. ^{13}C-NMR spectrum of depsipeptide pyridyl "OUT" thiol (**8**).

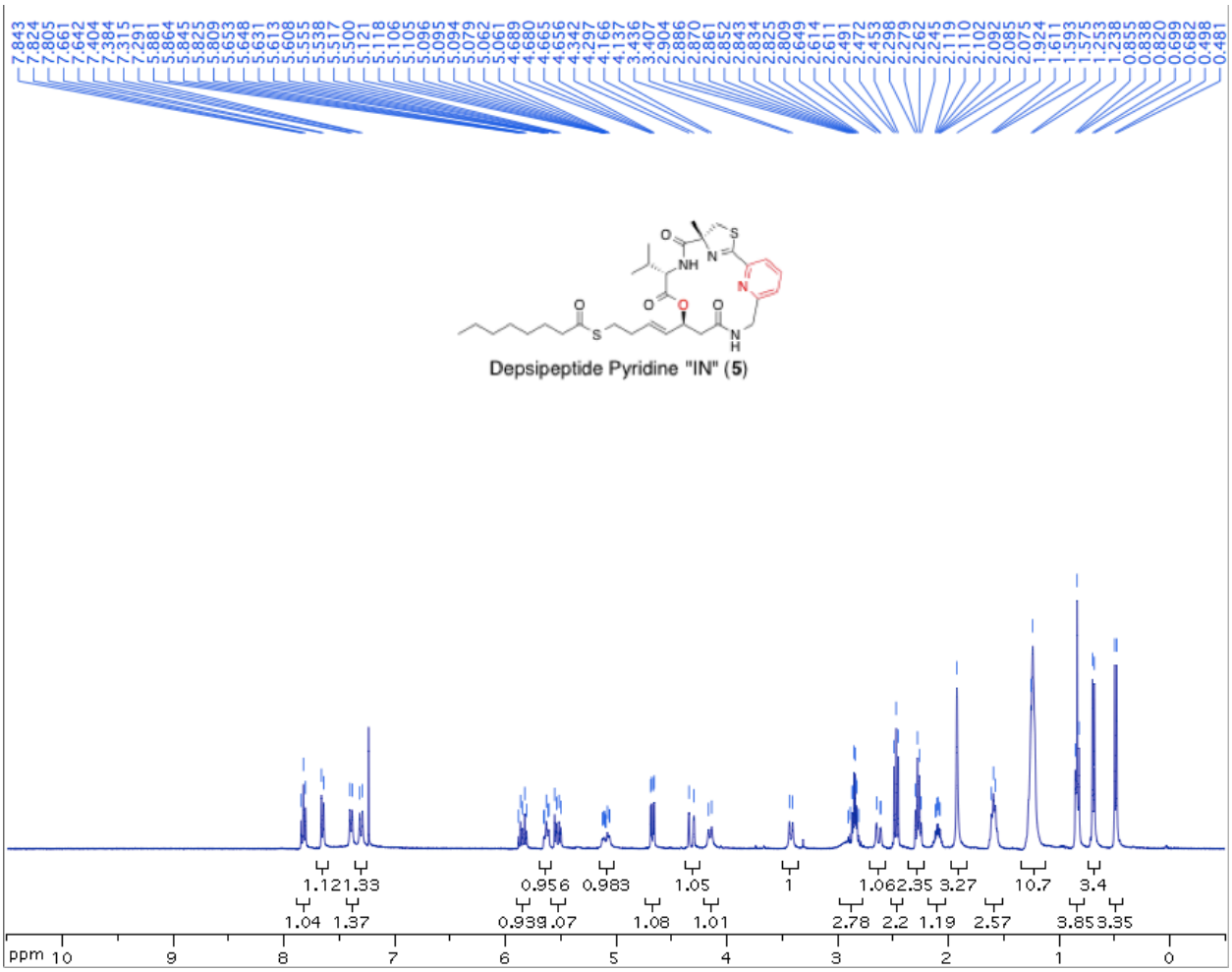

Figure S31. ^{1}H-NMR spectrum of depsipeptide pyridyl "IN" (**5**).

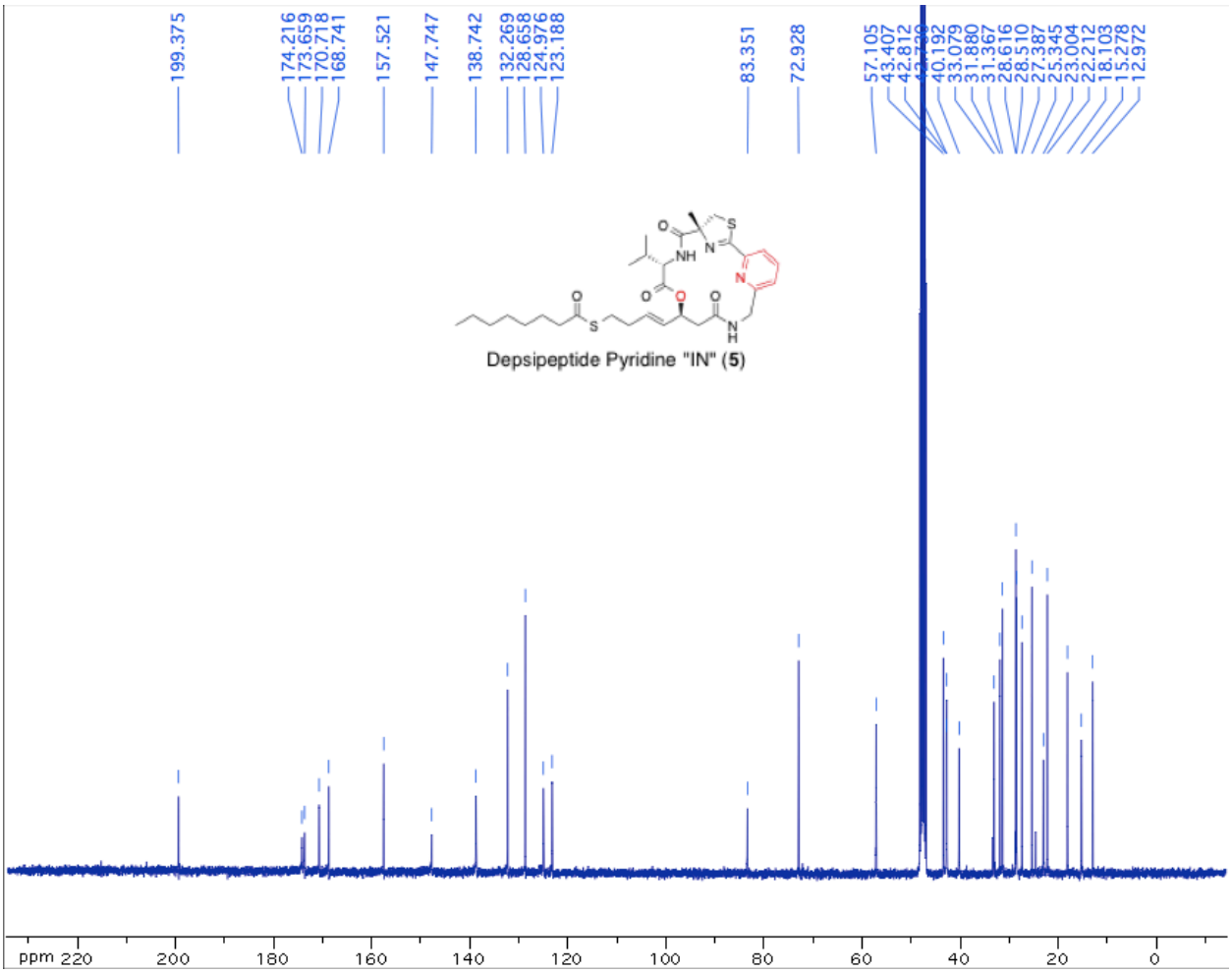

Figure S32. ^{13}C-NMR spectrum of depsipeptide pyridyl “IN” (**5**).

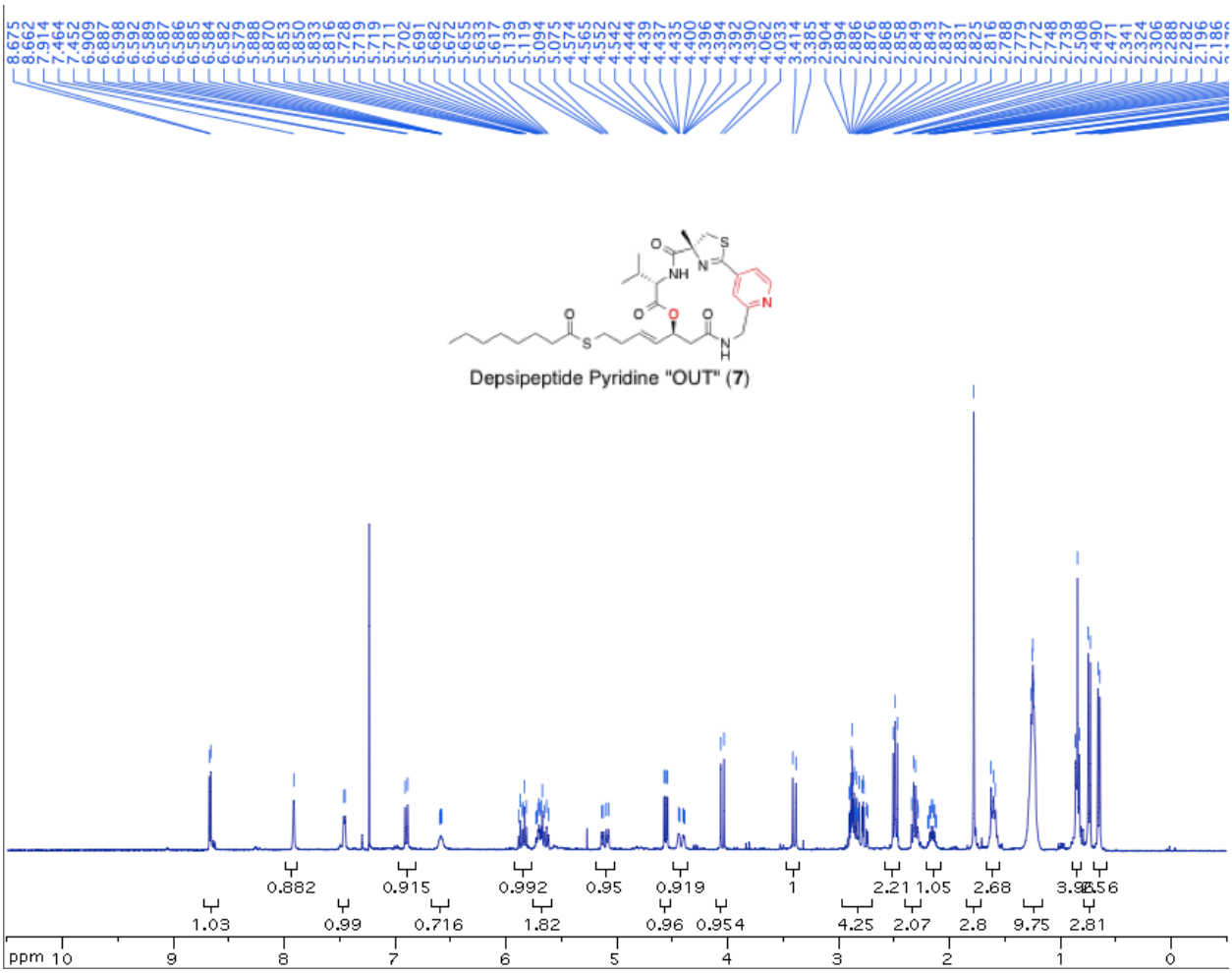

Figure S33. ^{1}H-NMR spectrum of depsipeptide pyridyl "OUT" (**7**).

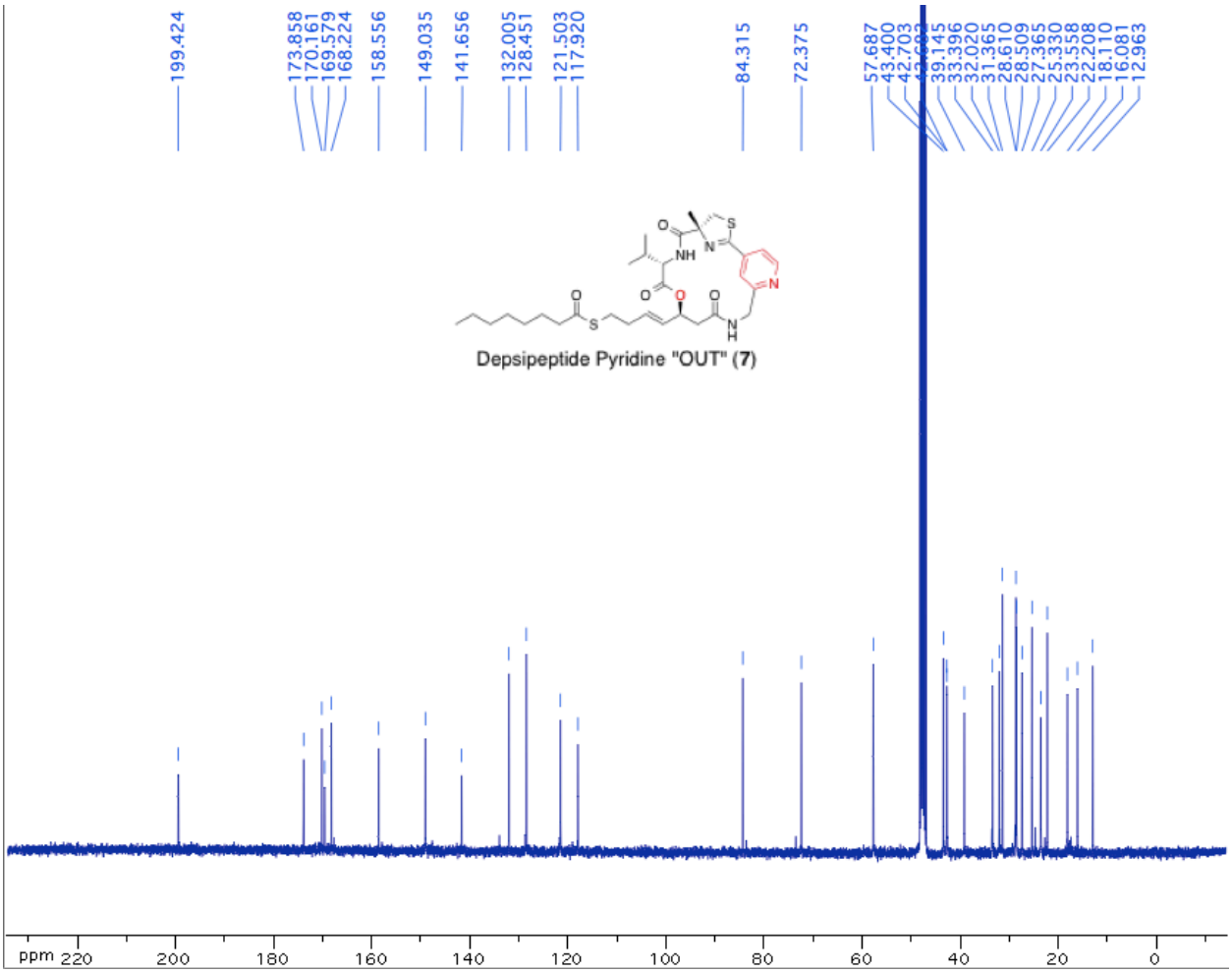

Figure S34. ^{13}C-NMR spectrum of depsipeptide pyridyl "OUT" (**7**).

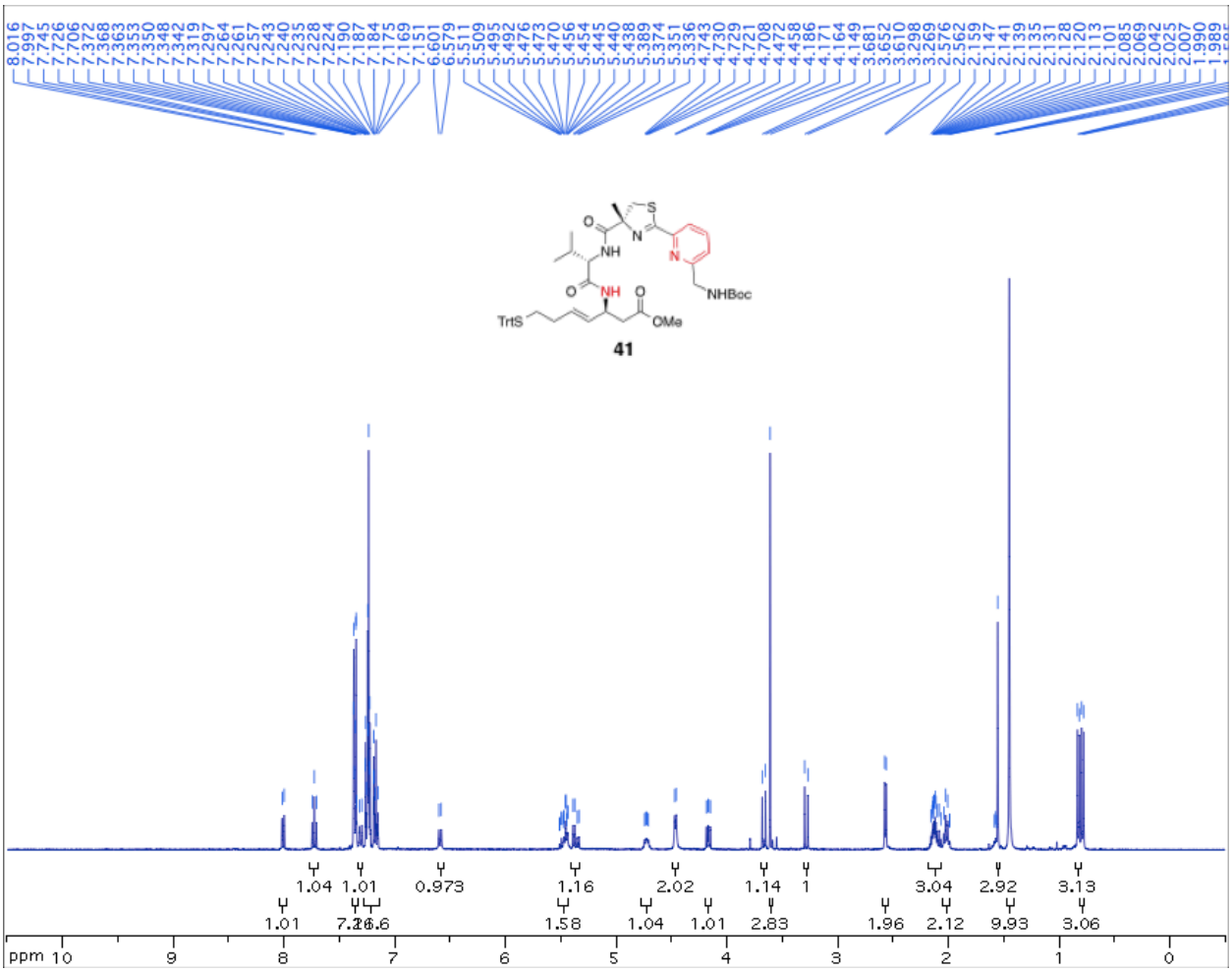

Figure S35. ^{1}H-NMR spectrum of (*S*,*E*)-Methyl 3-((*S*)-2-((*R*)-2-(6-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-2-yl)-4-methyl-4,5-dihydrothiazole-4-carboxamido)-3-methylbutanamido)-7-(tritylthio)hept-4-enoate (**41**).

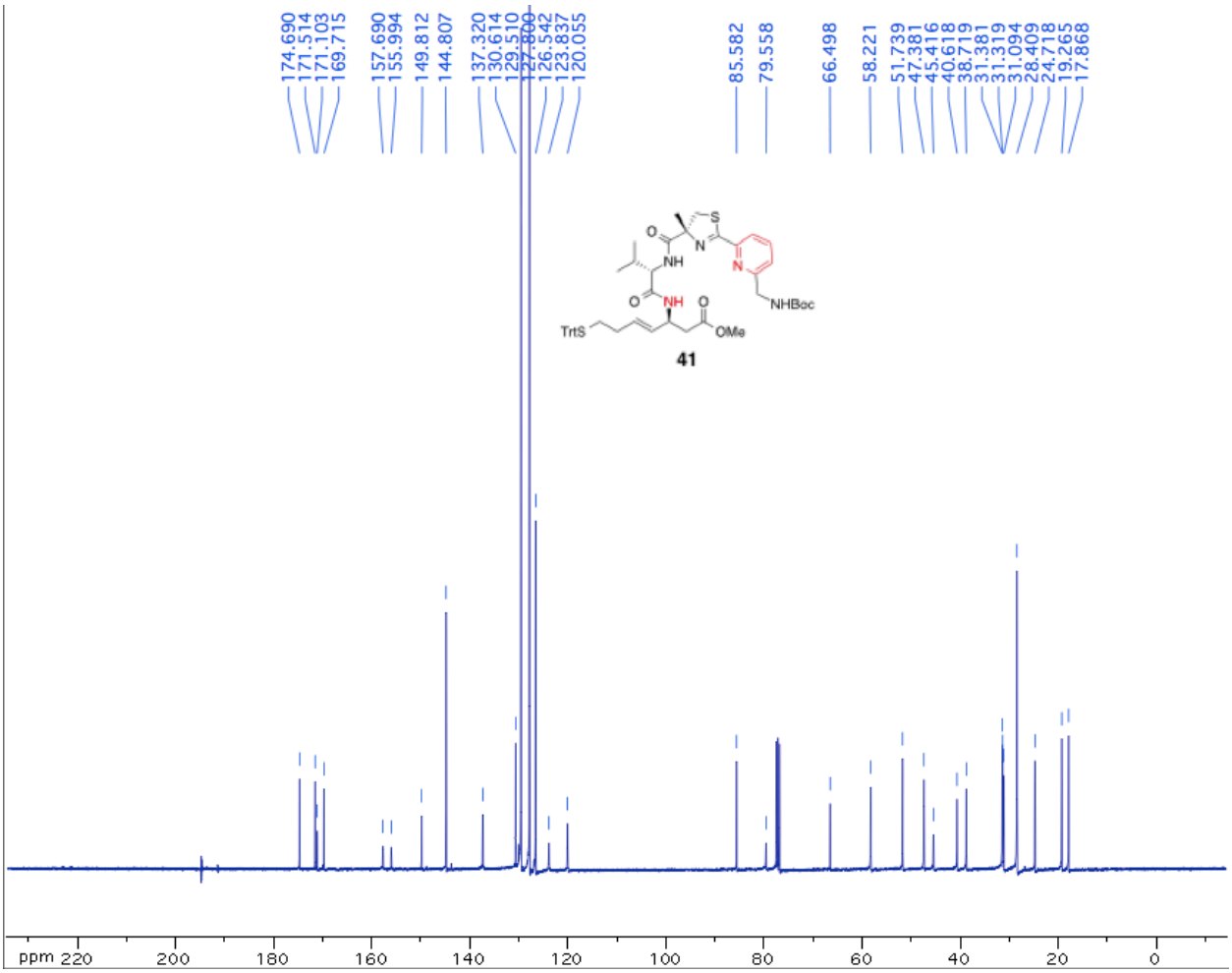

Figure S36. ^{13}C-NMR spectrum of (*S*,*E*)-Methyl 3-((*S*)-2-((*R*)-2-(6-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-2-yl)-4-methyl-4,5-dihydrothiazole-4-carboxamido)-3-methylbutanamido)-7-(tritylthio)hept-4-enoate (**41**).

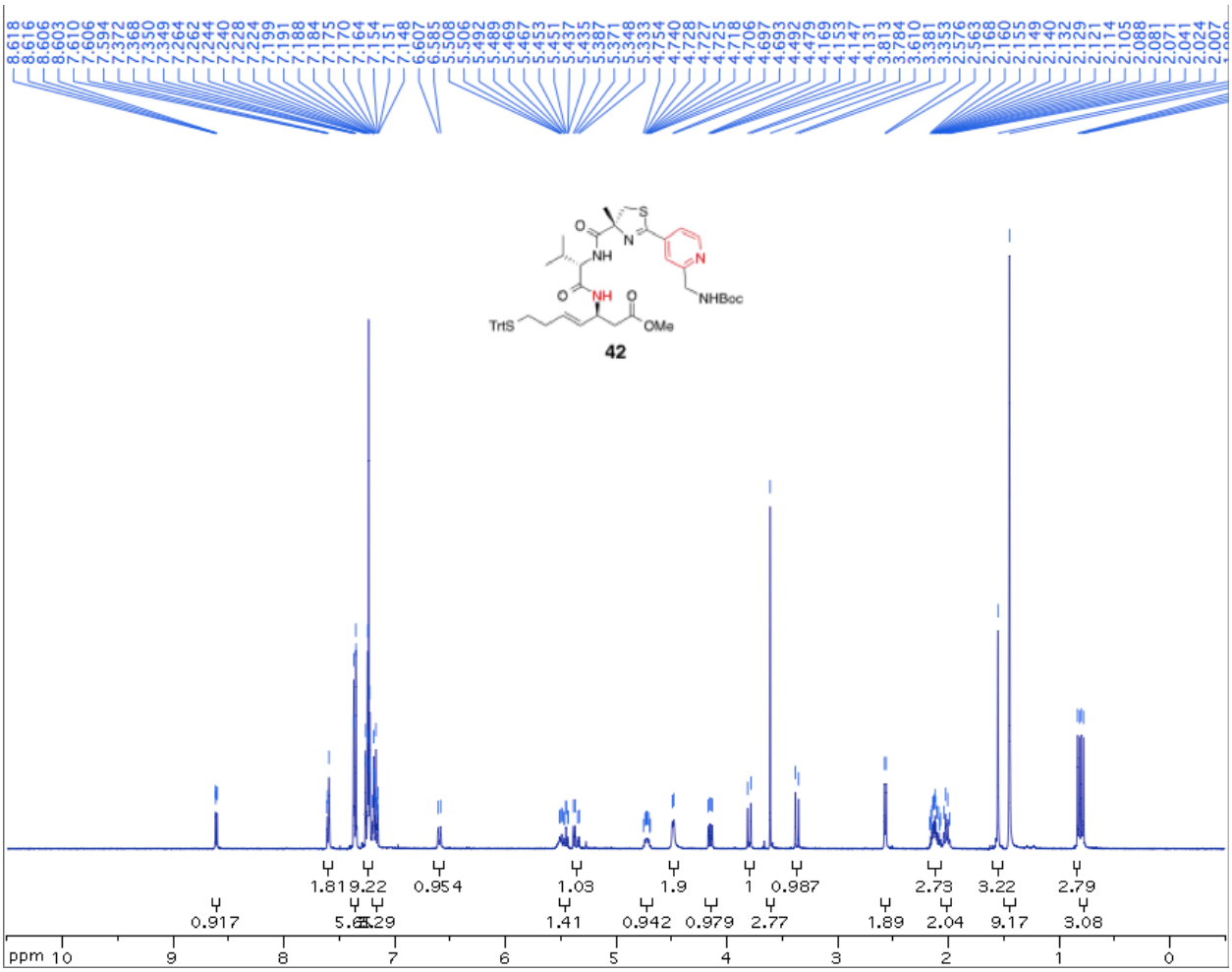

Figure S37. ^{1}H-NMR spectrum of (*S*,*E*)-Methyl 3-((*S*)-2-((*R*)-2-(2-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-4-yl)-4-methyl-4,5-dihydrothiazole-4-carboxamido)-3-methylbutanamido)-7-(tritylthio)hept-4-enoate (**42**).

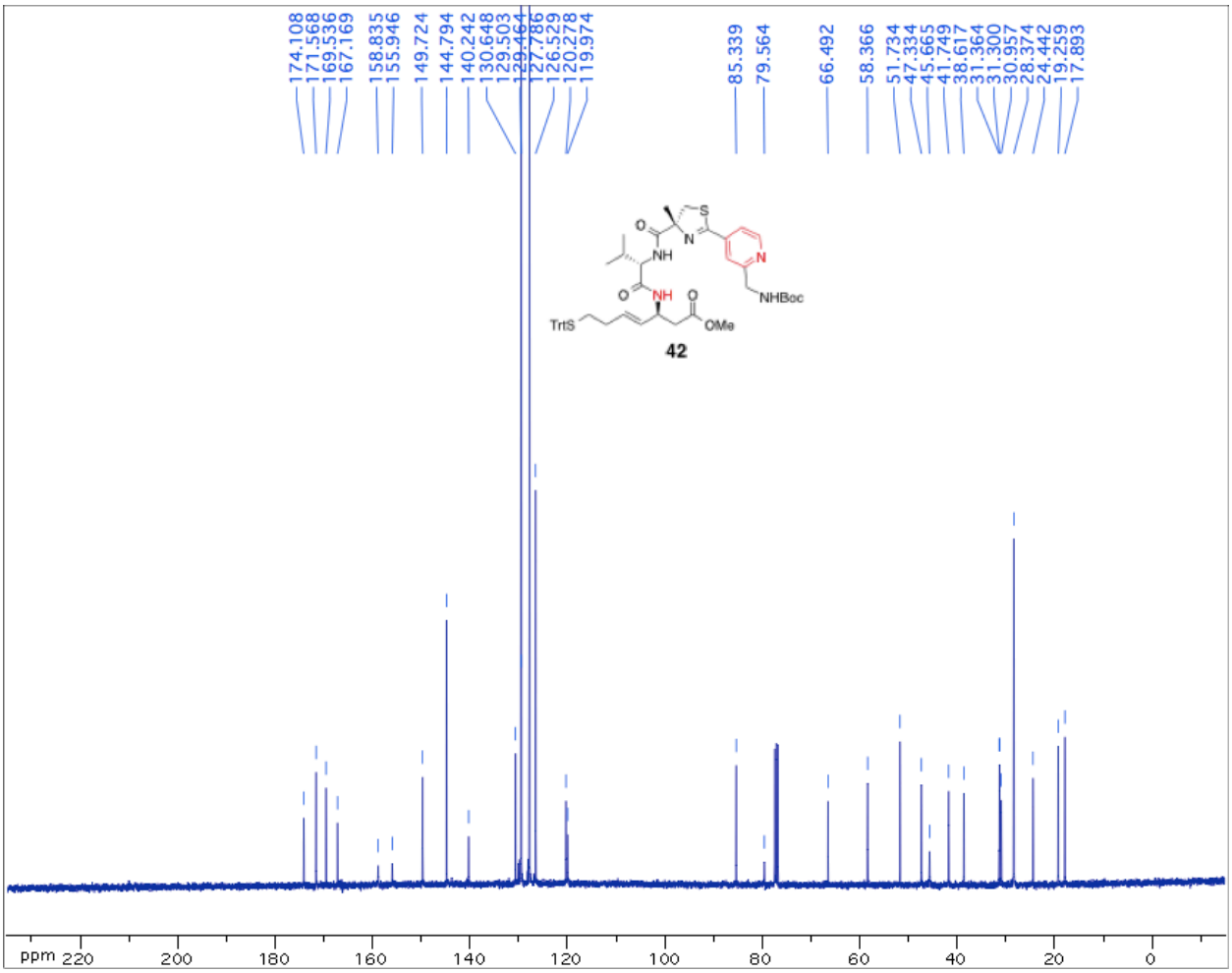

Figure S38. ^{13}C-NMR spectrum of (*S*,*E*)-Methyl 3-((*S*)-2-((*R*)-2-(2-(((*tert*-butoxycarbonyl)amino)methyl)pyridin-4-yl)-4-methyl-4,5-dihydrothiazole-4-carboxamido)-3-methylbutanamido)-7-(tritylthio)hept-4-enoate (**42**).

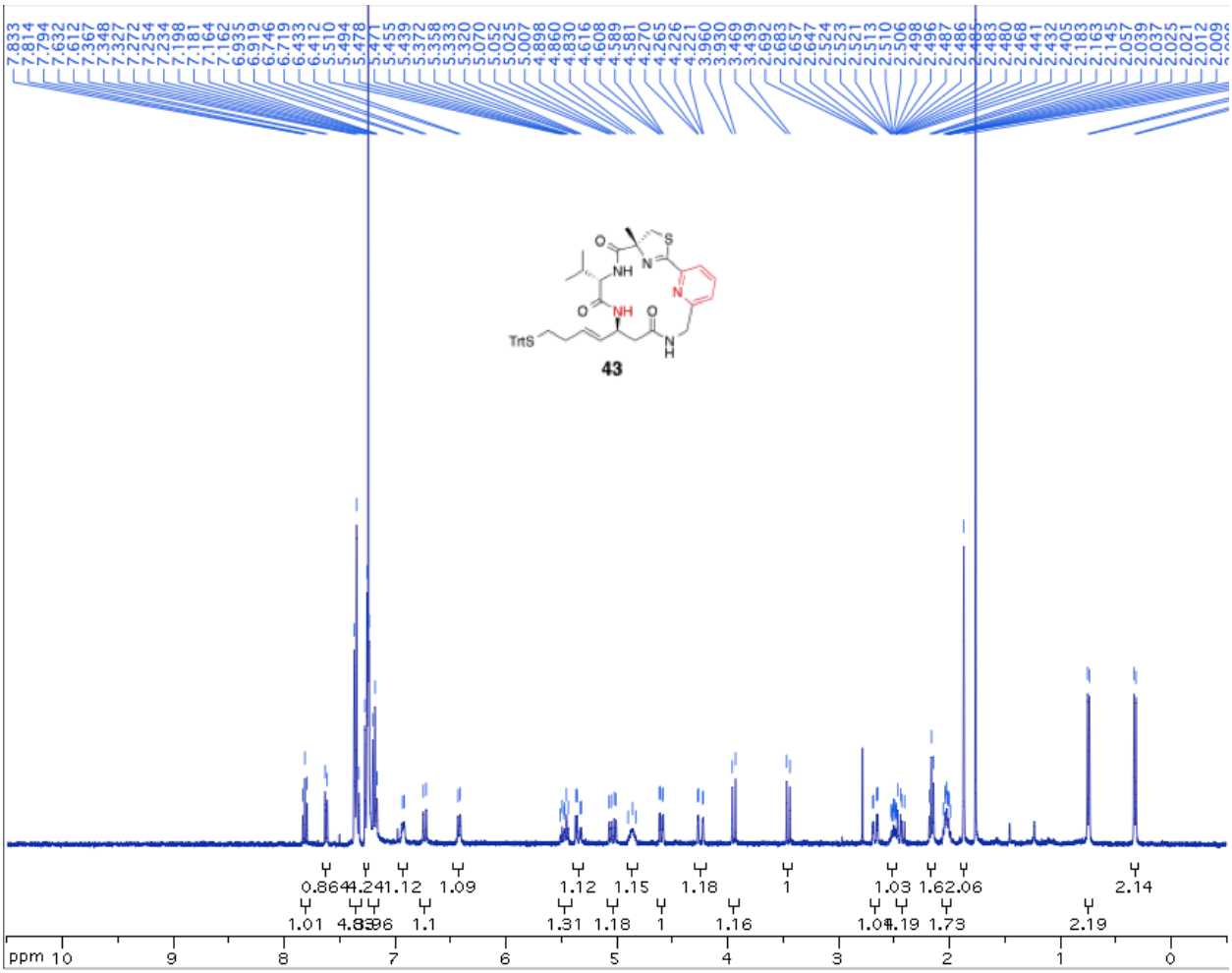

Figure S39. ^{1}H-NMR spectrum of trityl protected peptide isostere pyridyl “IN” macrocycle (**43**).

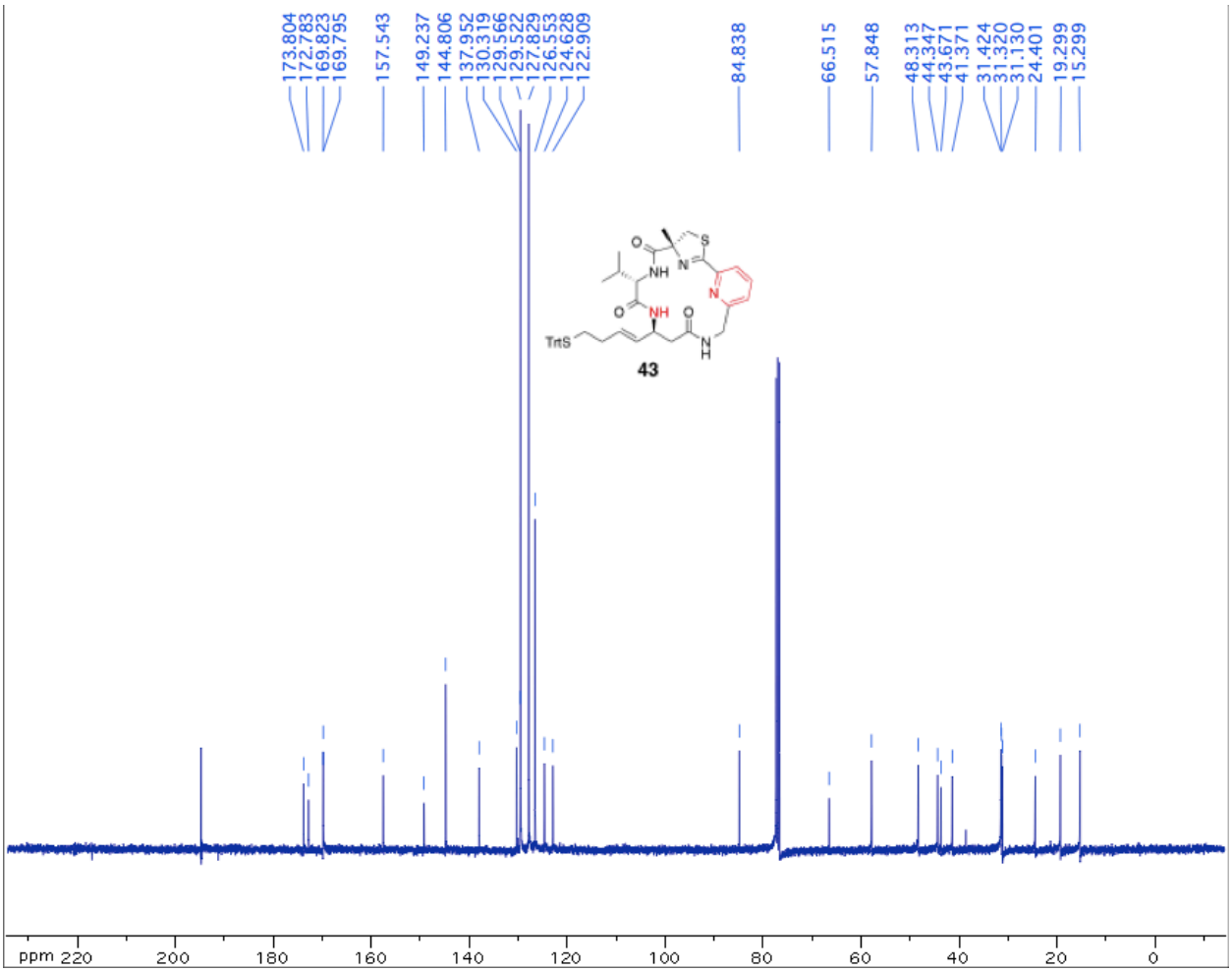

Figure S40. ^{13}C-NMR spectrum of trityl protected peptide isostere pyridyl "IN" macrocycle (**43**).

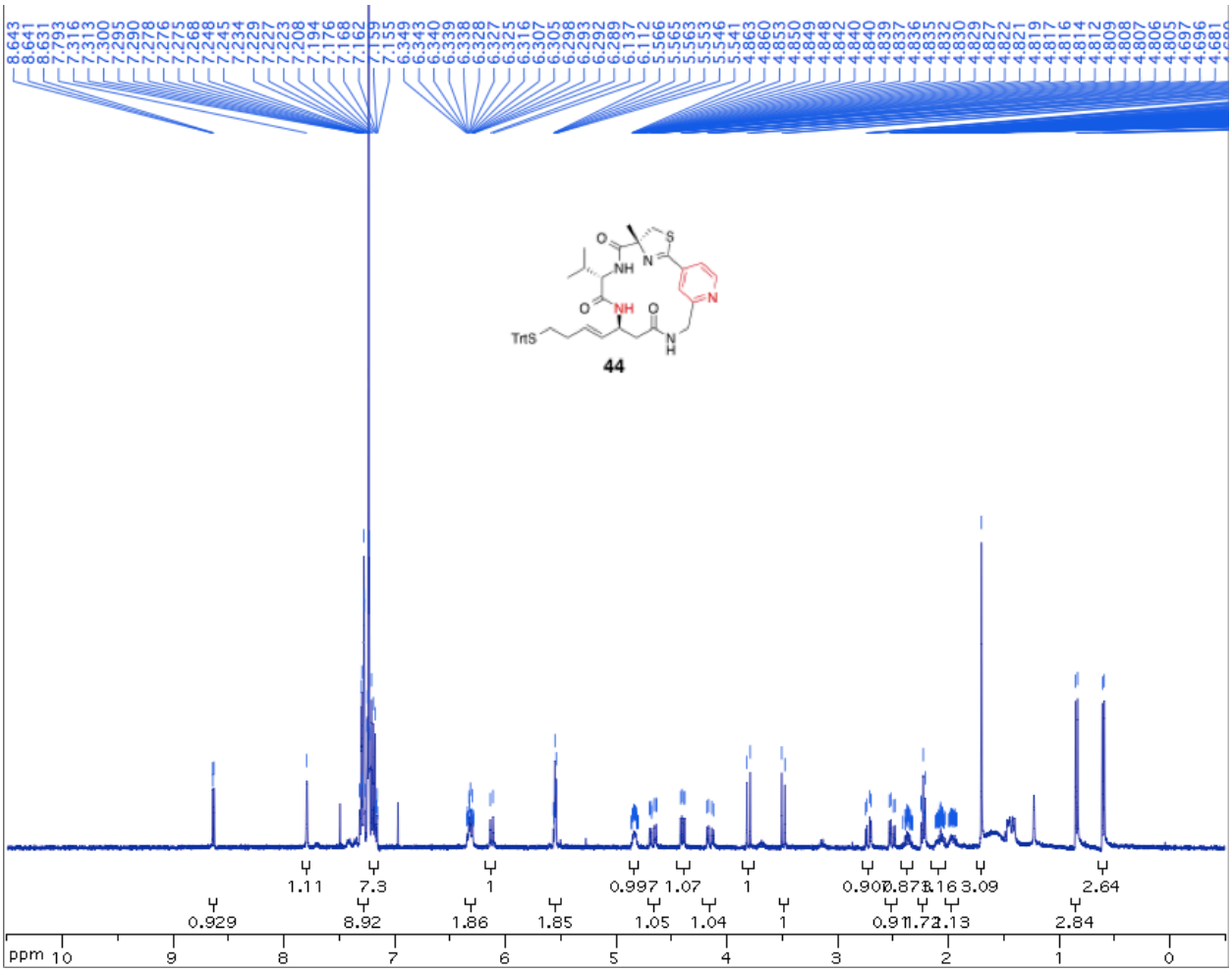

Figure S41. ^{1}H-NMR spectrum of trityl protected peptide isostere pyridyl “OUT” macrocycle (**44**).

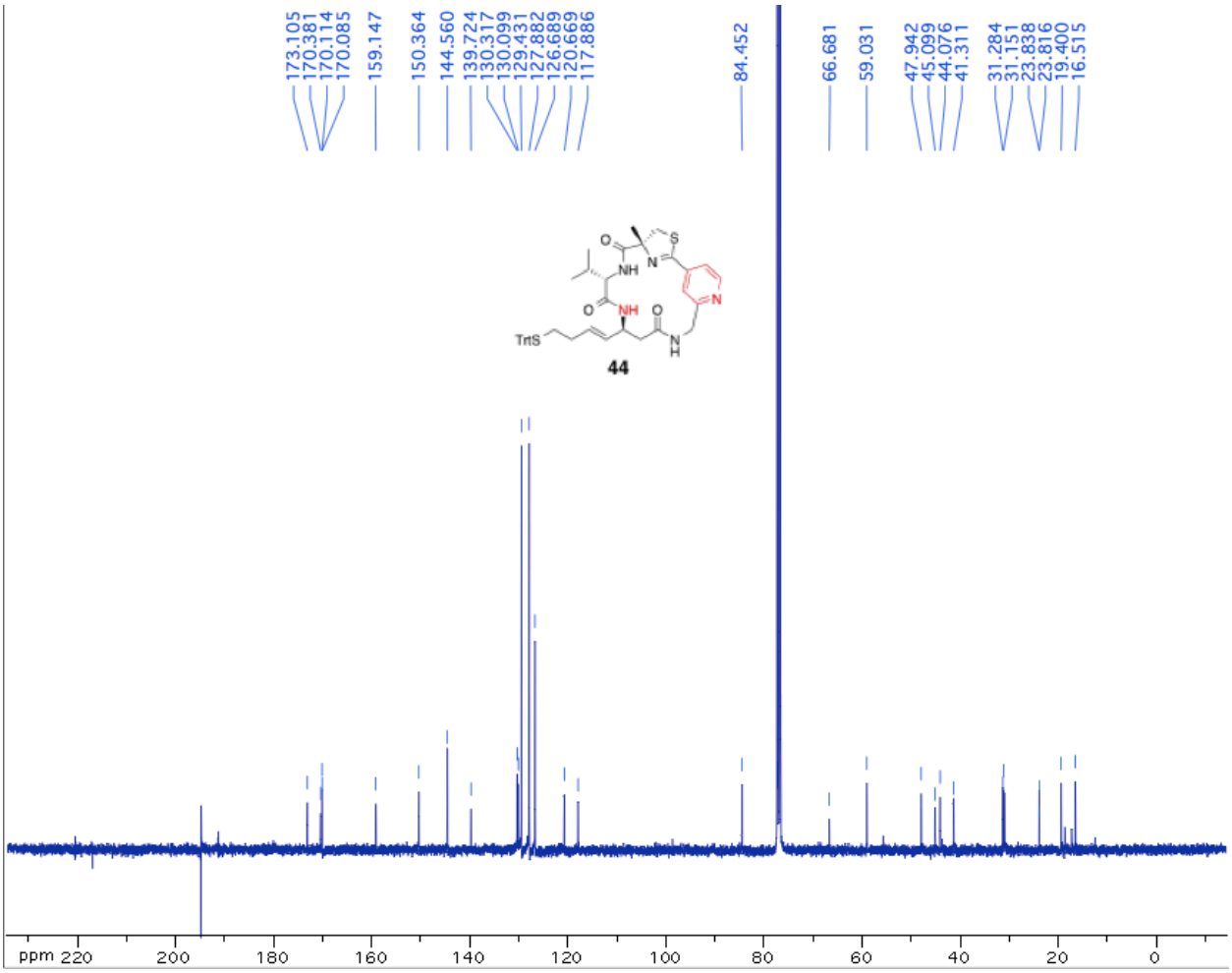

Figure S42. ^{13}C-NMR spectrum of trityl protected peptide isostere pyridyl "OUT" macrocycle (**44**).

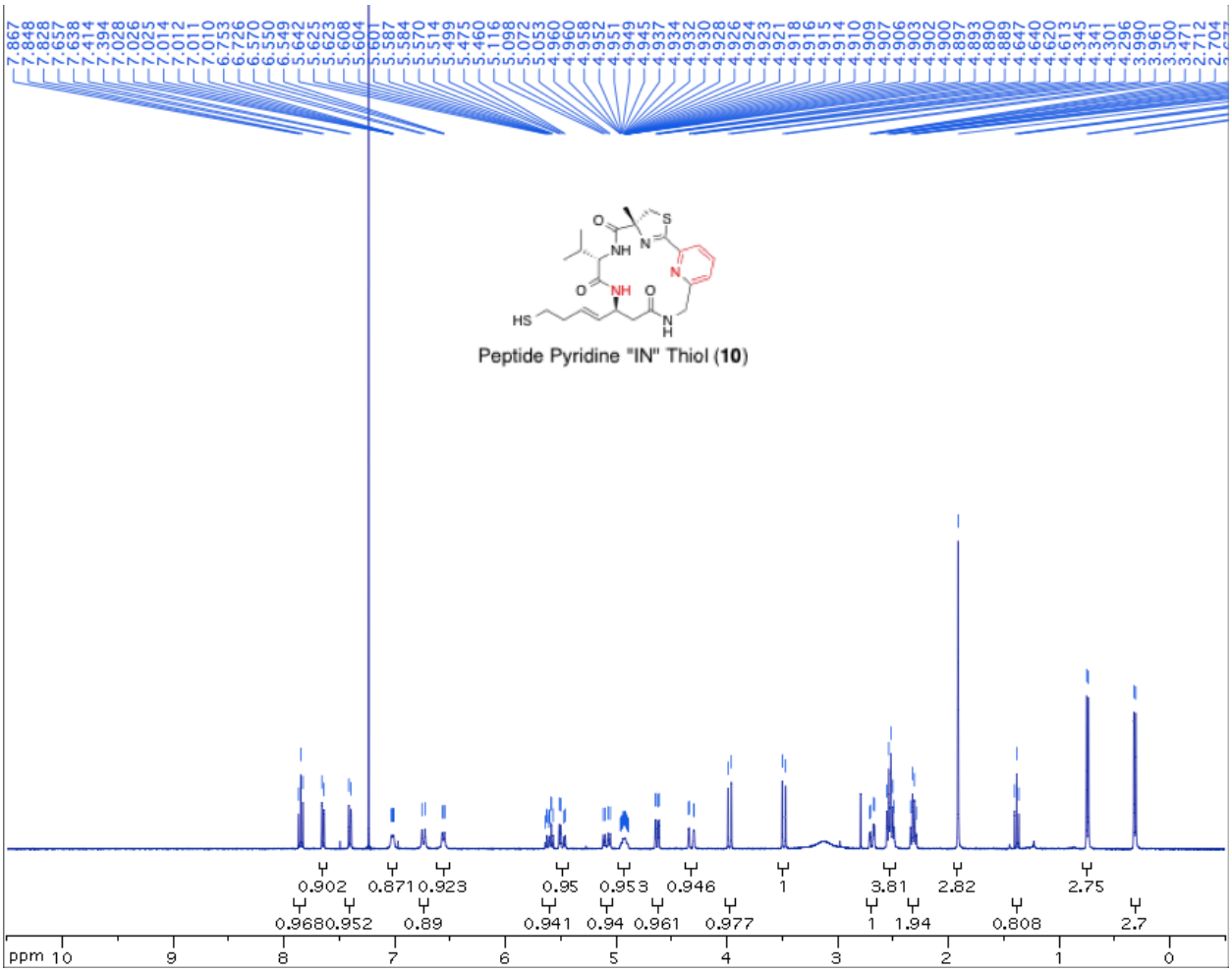

Figure S43. ^{1}H-NMR spectrum of peptide isostere pyridyl “IN” thiol (**10**).

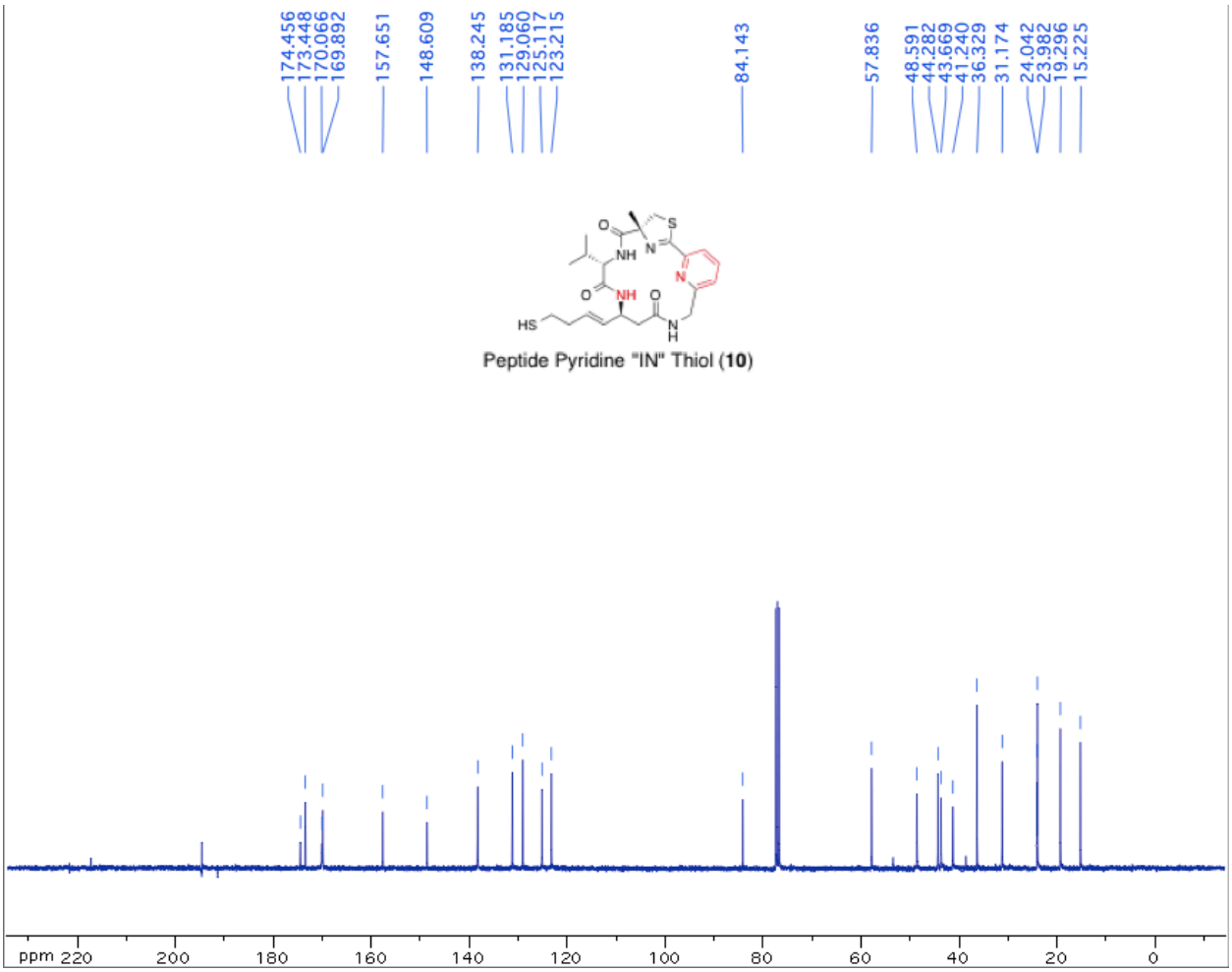

Figure S44. ^{13}C-NMR spectrum of peptide isostere pyridyl “IN” thiol (**10**).

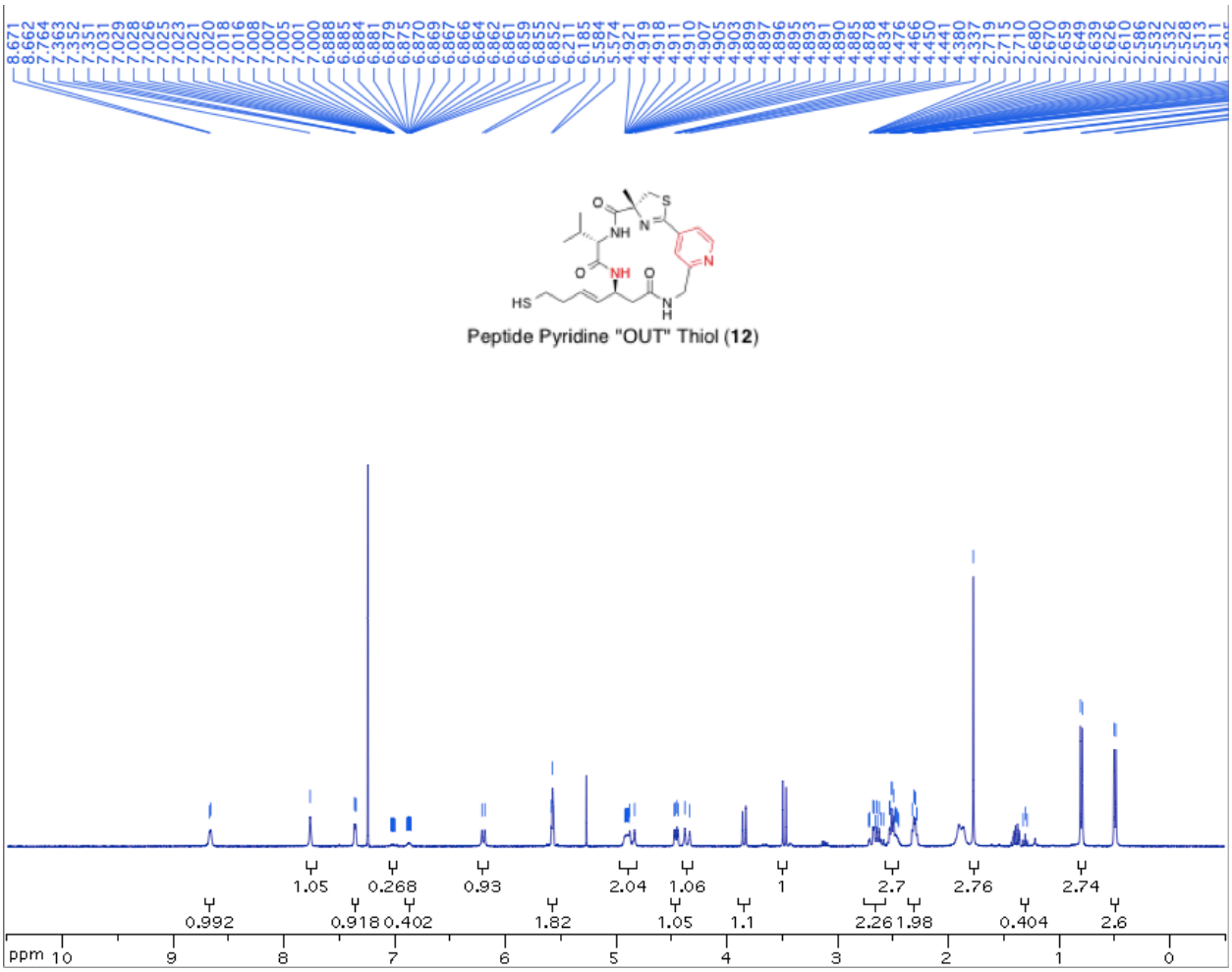

Figure S45. ^{1}H-NMR spectrum of peptide isostere pyridyl “OUT” thiol (**12**).

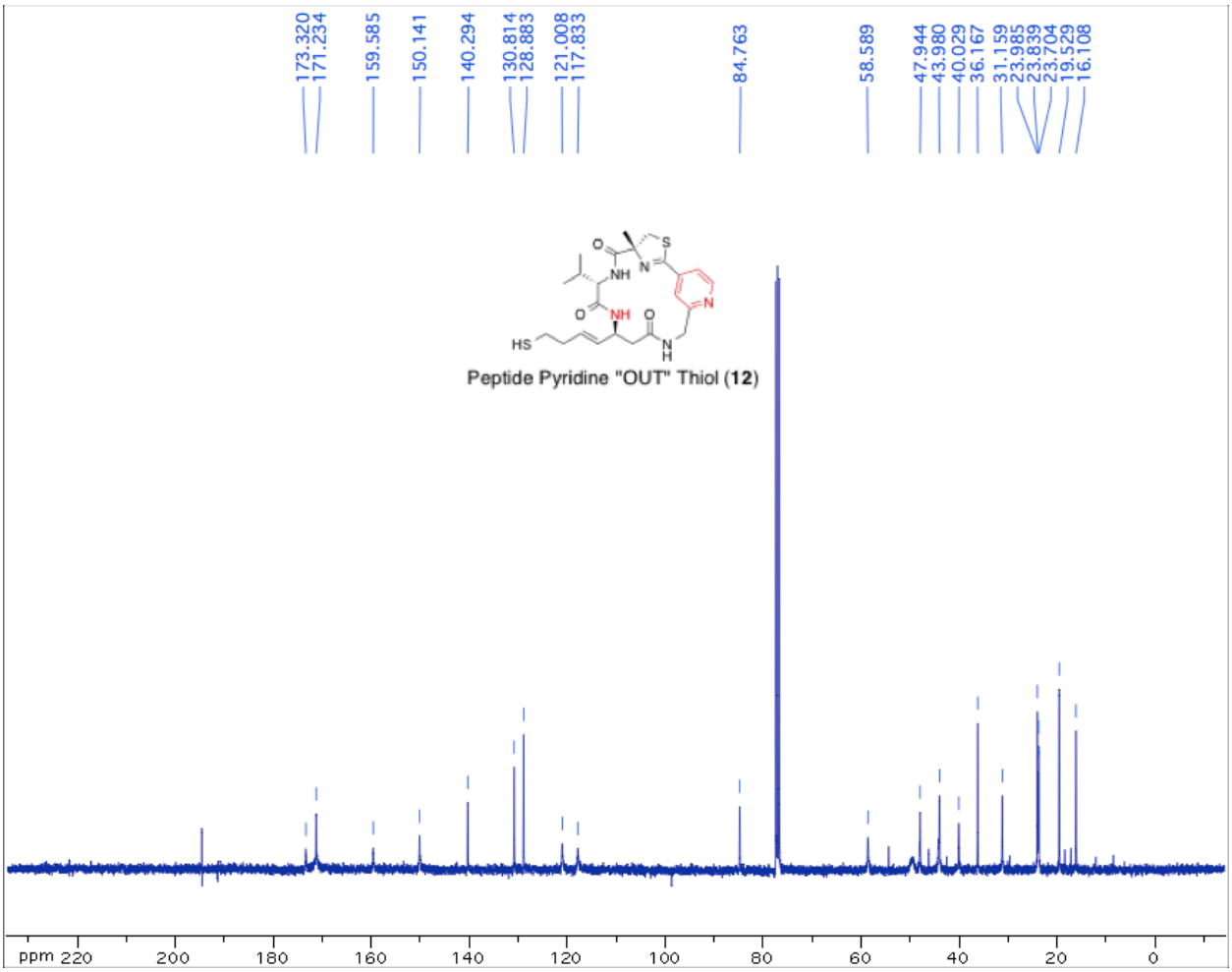

Figure S46. ^{13}C-NMR spectrum of peptide isostere pyridyl “OUT” thiol (**12**).

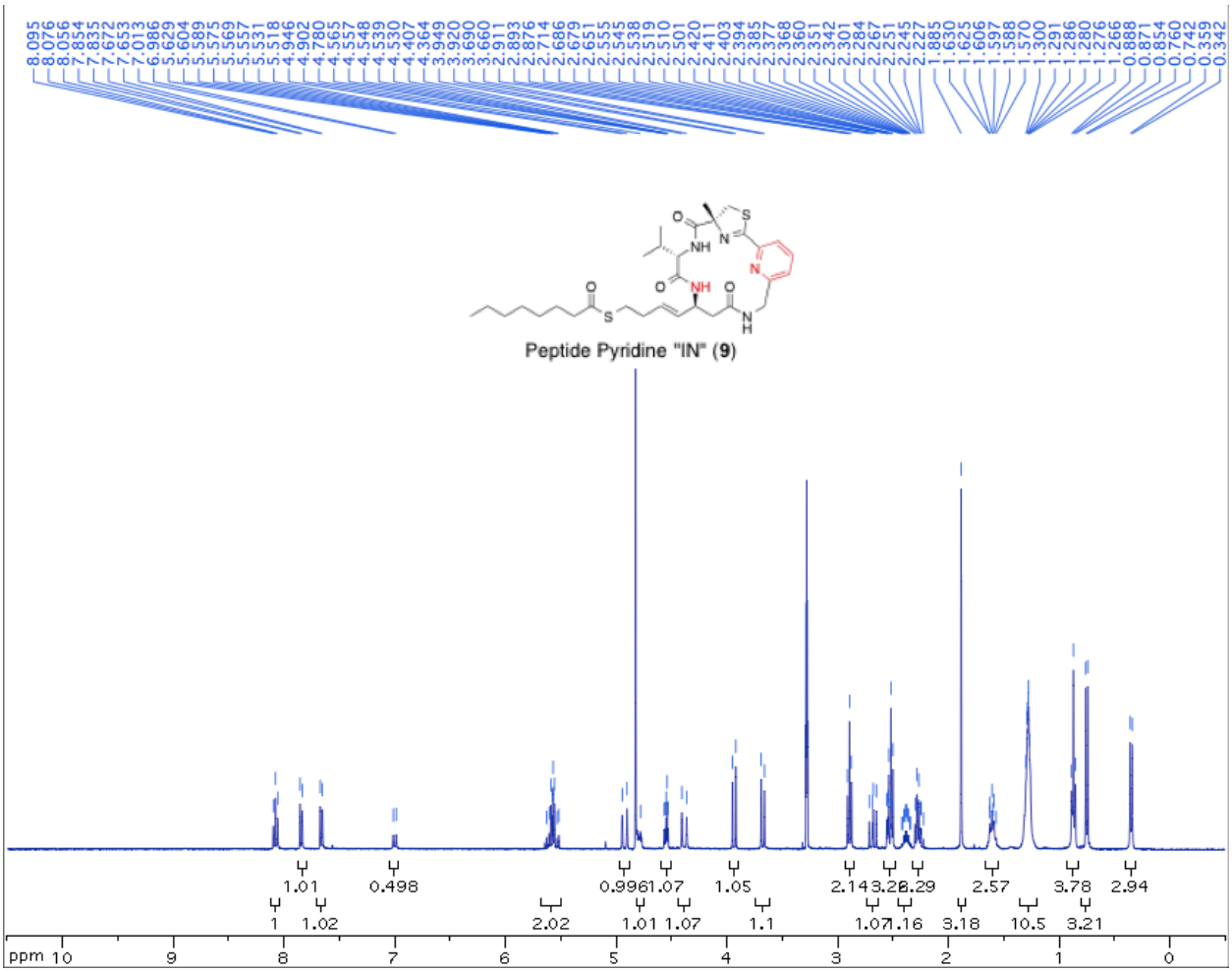

Figure S47. ^{1}H-NMR spectrum of peptide isostere pyridyl “IN” (**9**).

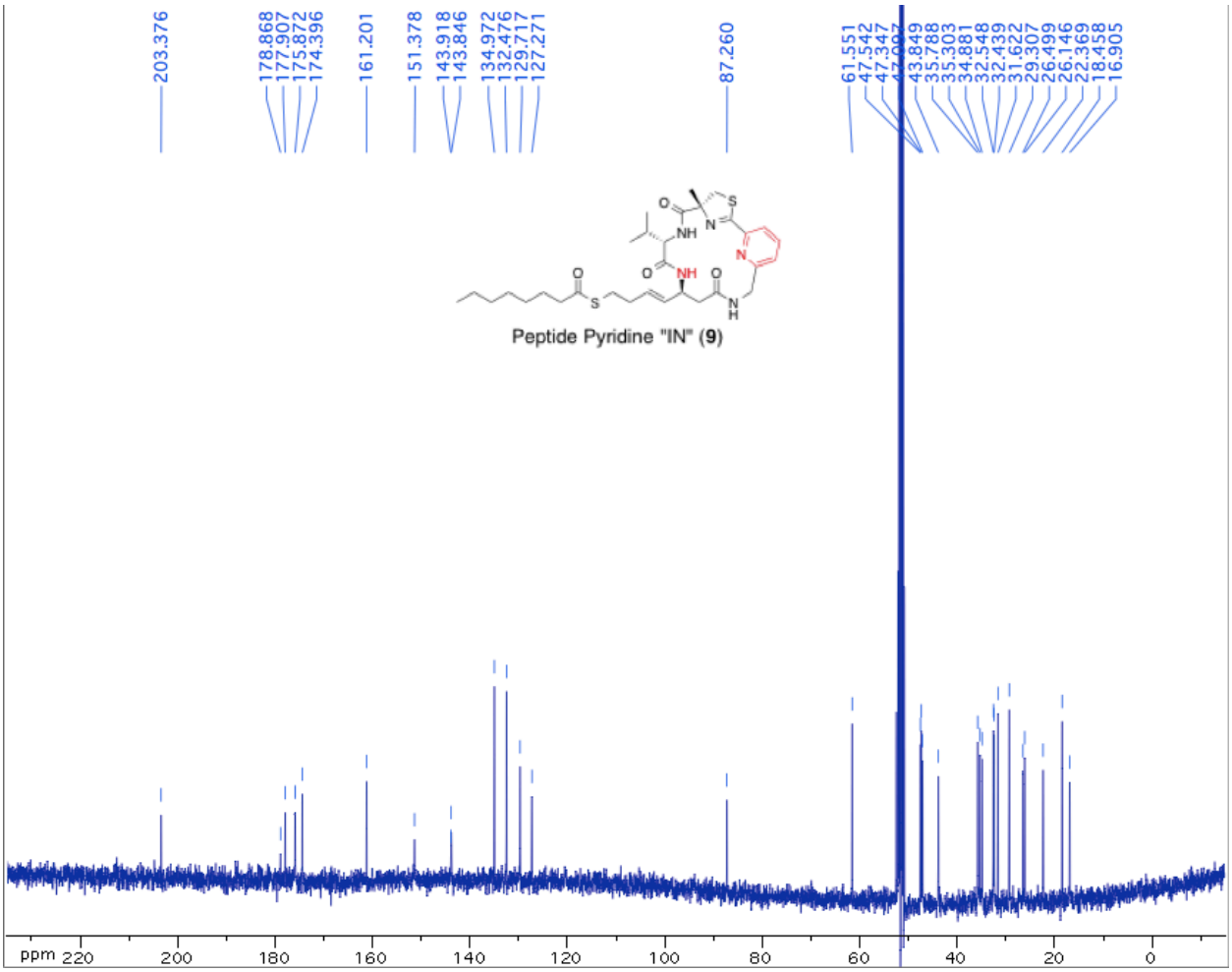

Figure S48. ^{13}C-NMR spectrum of peptide isostere pyridyl "IN" (**9**).

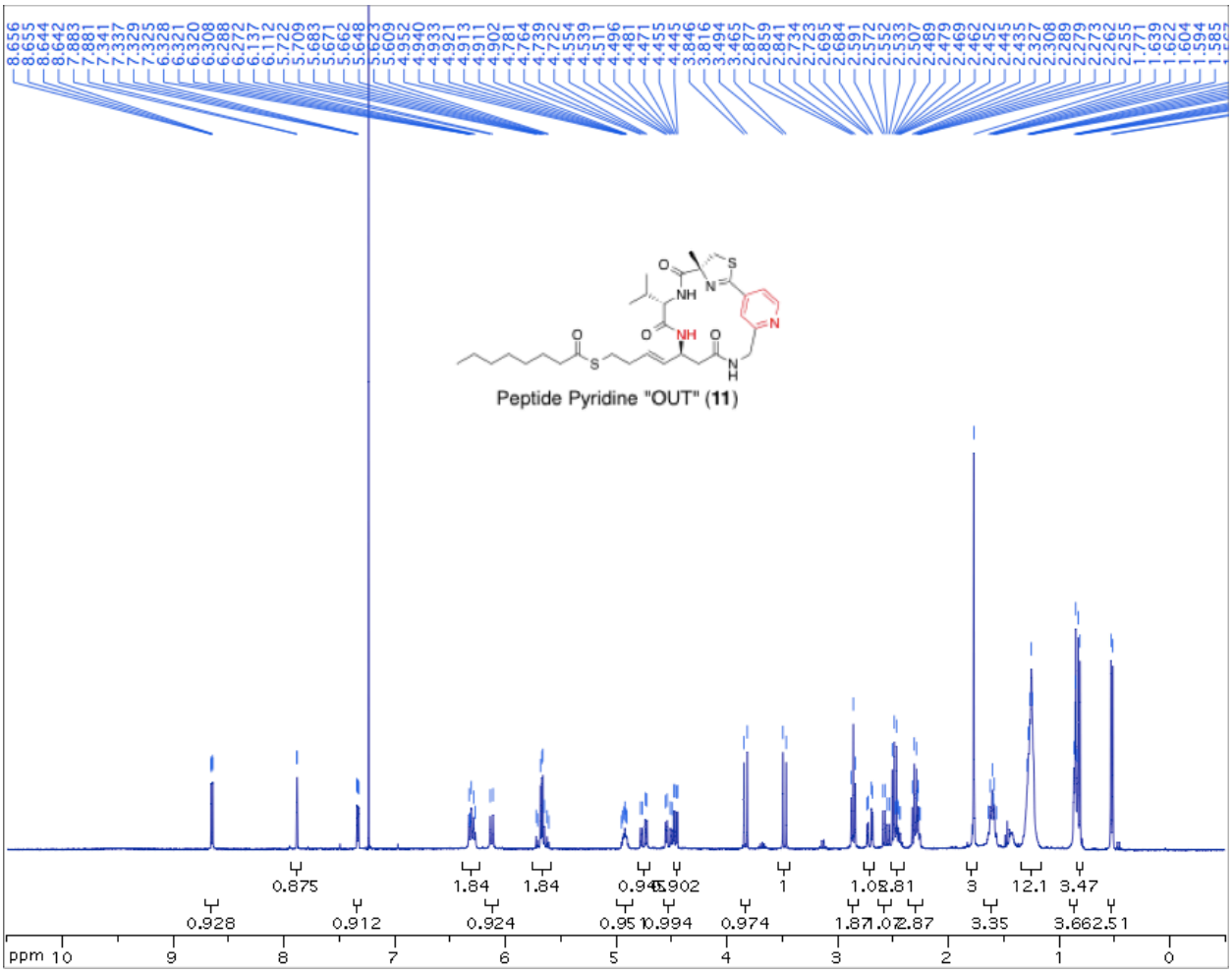

Figure S49. ^{1}H-NMR spectrum of peptide isostere pyridyl "OUT" (**11**).

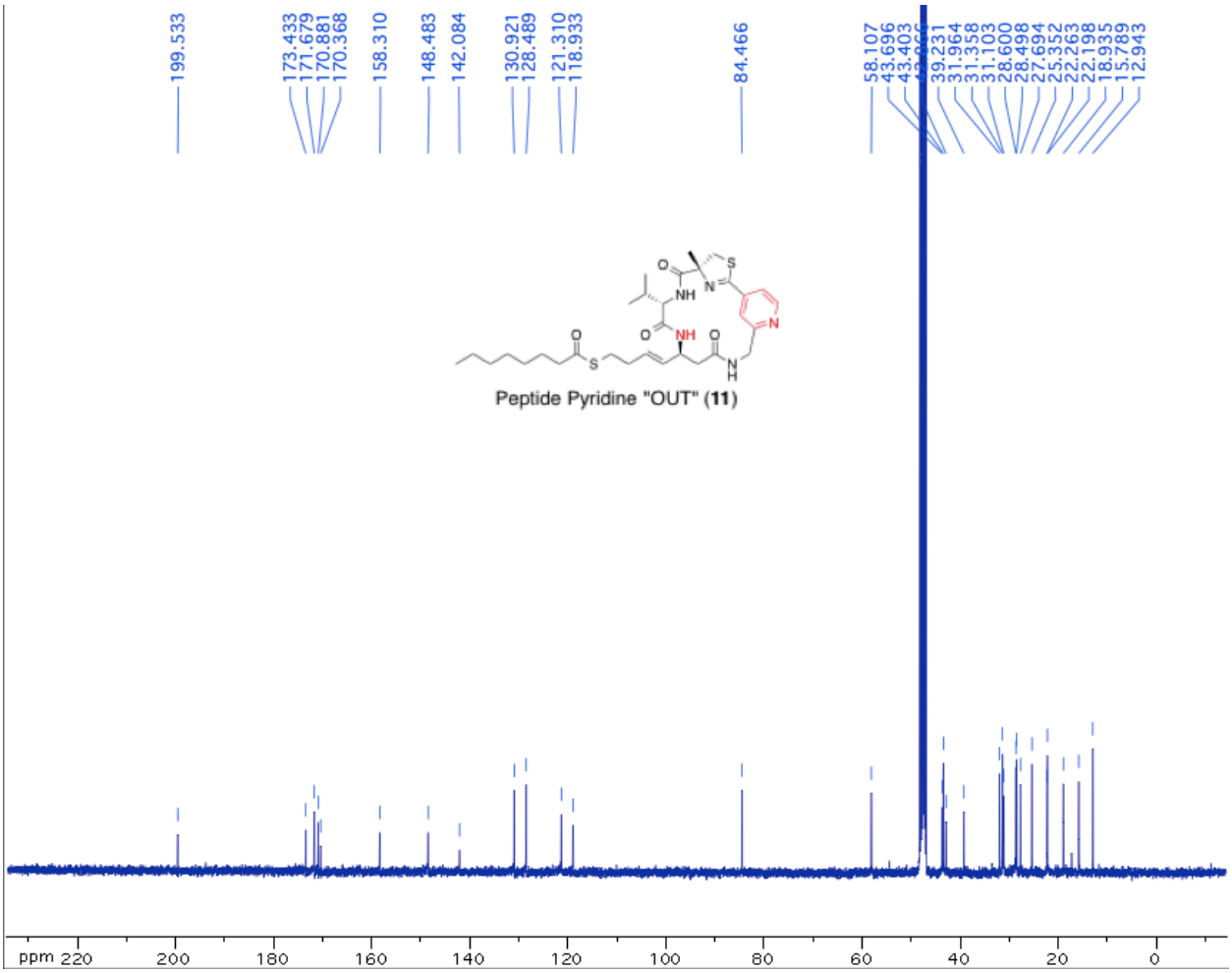

Figure S50. ^{13}C-NMR spectrum of peptide isostere pyridyl "OUT" (**11**).