Design, Synthesis, Biological Evaluation, and Molecular Dynamics Study of Asymmetric N-Isopropyl-4-piperidone Diarylpentanoids as Potential Anticancer and Anti-Inflammatory Agents

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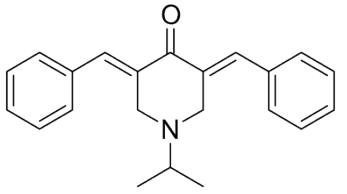
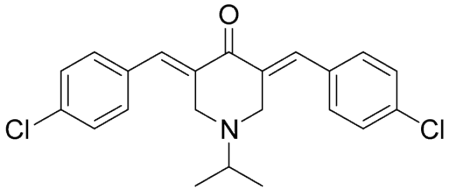
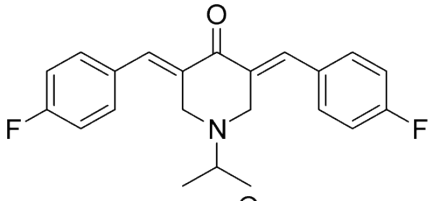
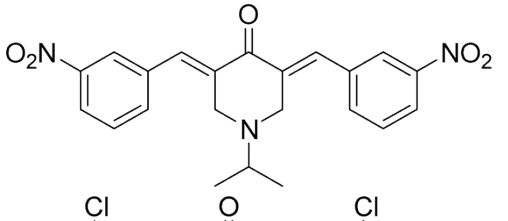
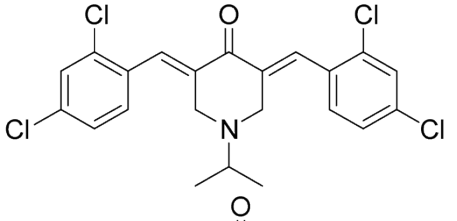
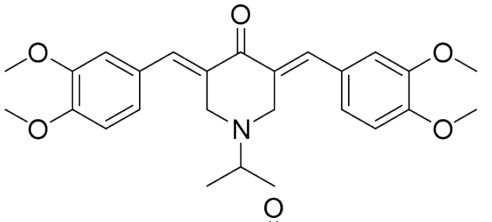
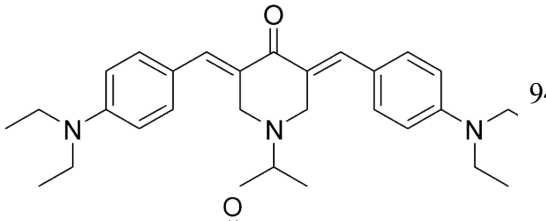
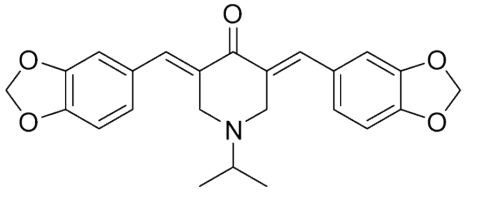
Supplementary Data

Table S1. Structure, synthetic yield of MACs

Comp.	Structures	Yield (%)	Color
KD2a		95.6	Yellow powder
KD2b		94.2	Yellow powder
KD2c		94.1	Yellow powder
KD2d		92.8	Yellow powder
KD2e		92.7	Yellow powder
KD2f		93.4	Yellow powder
KD2g		94.3	Red powder **(New compound)**
KD2h		95.1	Yellow powder

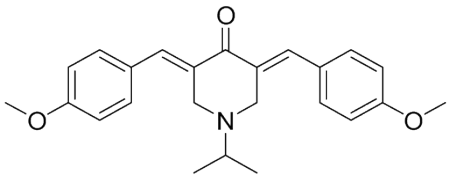
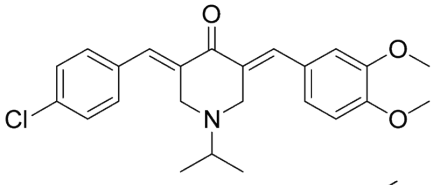
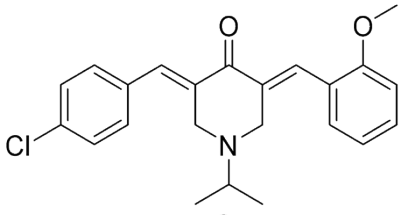
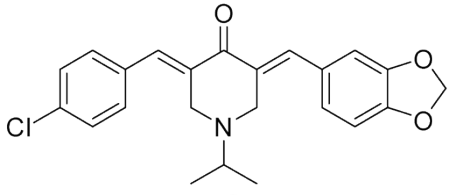
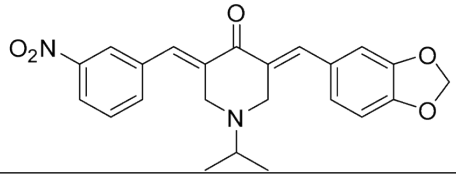
KD2i		94.8 %	Yellow powder
KB2a		54.3%	Yellow powder **(New compound)**
KB2b		54.6%	Yellow powder **(New compound)**
KB2c		56.3%	Yellow powder **(New compound)**
KB2d		56.7%	Yellow powder **(New compound)**

Table S2. Comprehensive comparison of molecular docking, 200 ns molecular dynamics (MD) simulation, and pharmacokinetic properties of the lead compounds.

Property / Evaluation parameter	**KB2c**	**KB2d**
1. Molecular Docking (static state)		
Binding energy ΔG (kcal mol^{-1})	-10.78	-10.96
Inhibition constant Ki	12.49 nM	9.18 nM
2. Molecular Dynamics simulation (200 ns)		
Average ligand RMSD (RMSD_lig)	~0.65 nm (pose drifting)	~0.20 nm (highly stable)
Hydrogen-bond network (H-bonds)	Unstable and intermittent	Continuously maintained
MM-PBSA total binding energy ΔG_bind (kcal mol^{-1})	-29.53	-33.53
van der Waals energy (VDWAALS)	-45.51	-52.17
Electrostatic energy (EEL)	9.53	-25.02
3. Pharmacochemical properties and ADMET		
GI absorption	High	High
Blood–brain barrier permeation (BBB permeant)	Yes	No
Lipinski rule violations	0	0
Water solubility (ESOL LogS)	Moderately soluble (-5.48)	Moderately soluble (-4.96)
4. Overall evaluation		
Practical development conclusion	Low potential (loose binding)	Optimal lead compound

Table S3. Binding free energy of ligand–receptor complexes calculated using the MM/GBSA method

Comp.	**Target**	**VDWAALS**	**EEL**	**EGB**	**ESURF**	**GGAS**	**GSOLV**	**TOTAL**
KB2d	MCF-7	-52.17	-25.02	50.22	-6.55	-77.2	43.67	-33.53
KB2c	NO inhibition	-45.51	9.53	12.42	-5.97	-35.98	6.46	-29.53

Fig S1. ^{1}H NMR Spectrum of compound KD2a

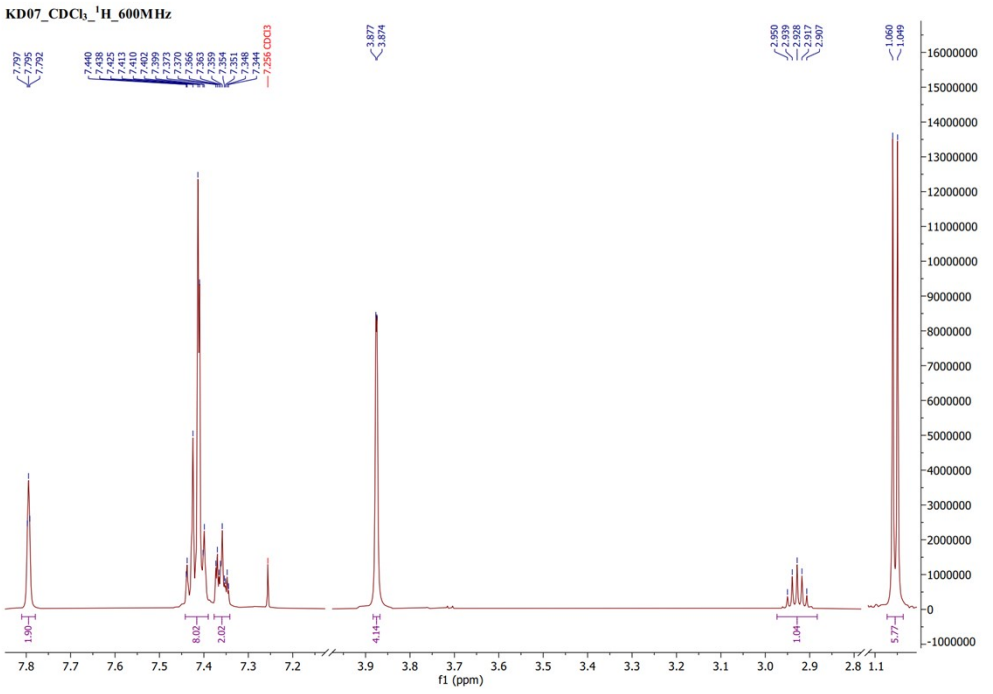


Fig S2. ^{13}C NMR Spectrum of compound KD2a

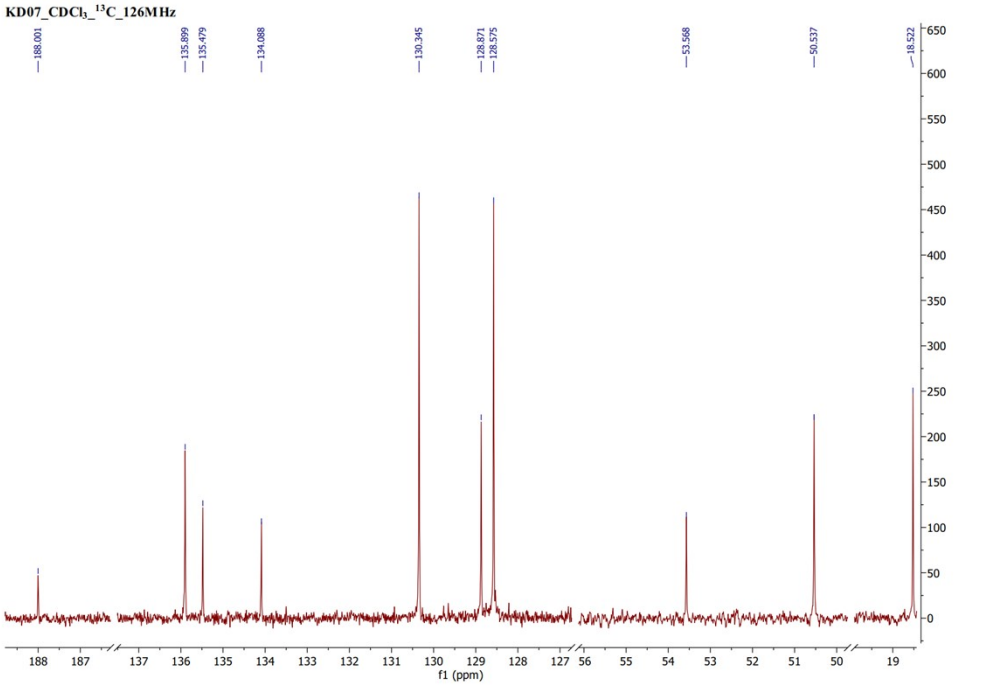


Fig S3. HR-MS spectrum of compound KD2a

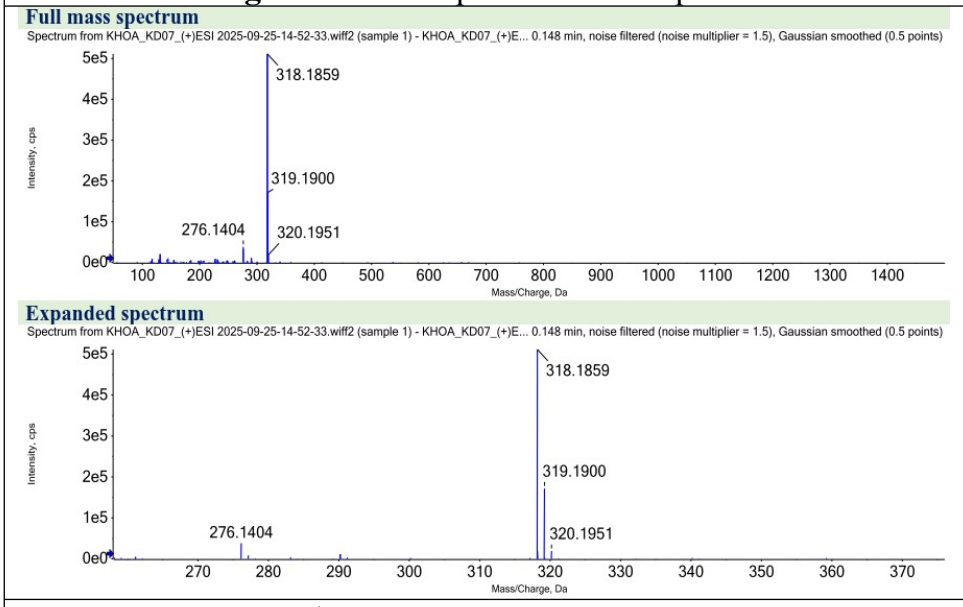


Fig S4. ^{1}H NMR Spectrum of compound KD2b

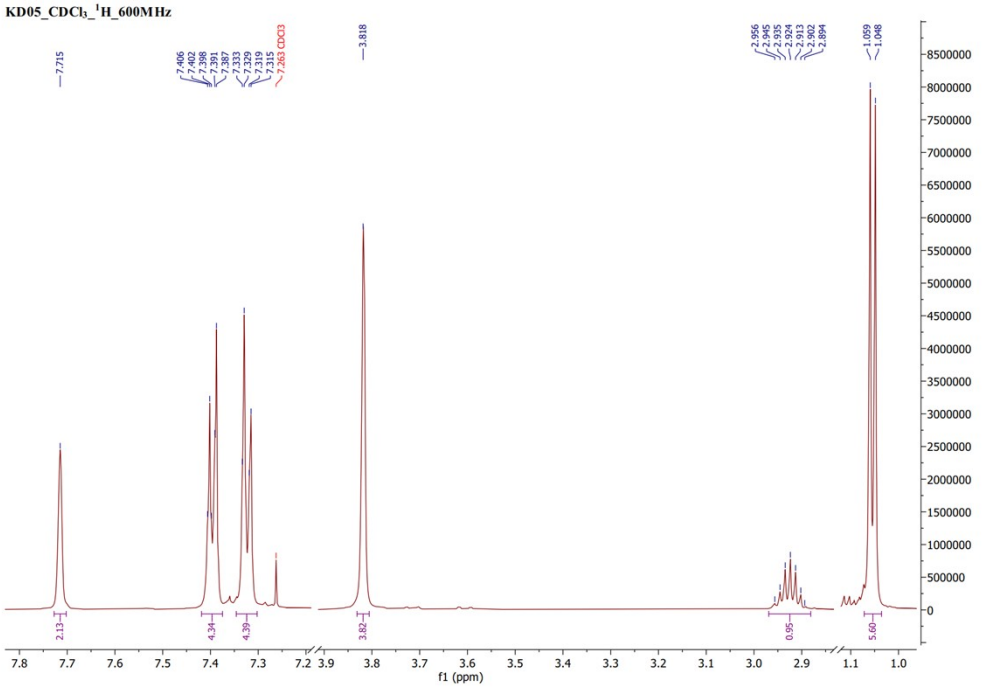


Fig S5. ^{13}C NMR Spectrum of compound KD2b

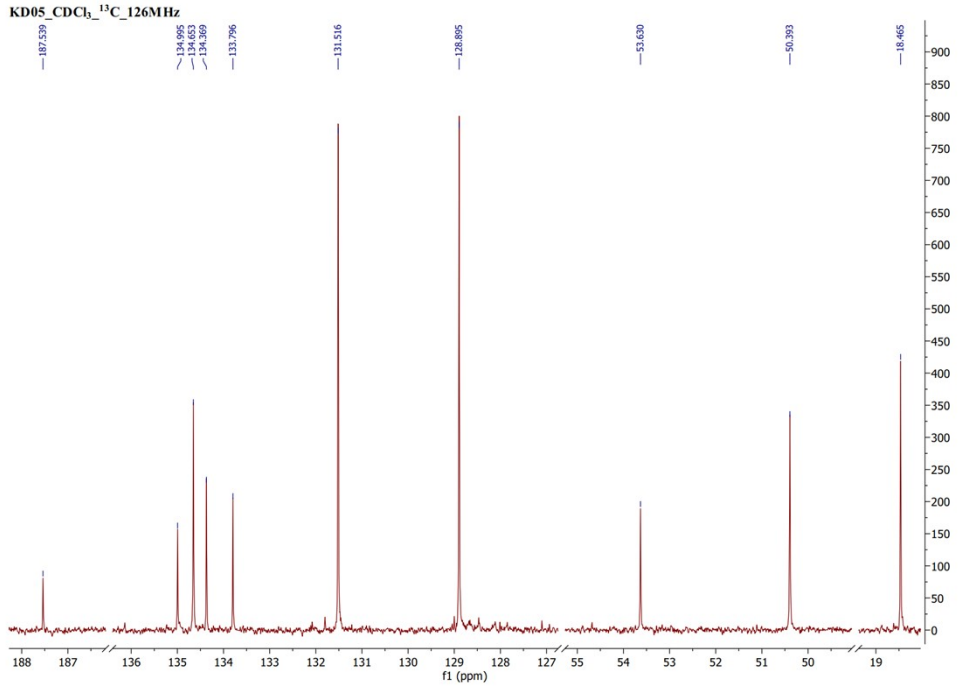


Fig S6. HR-MS Spectrum of compound KD2b

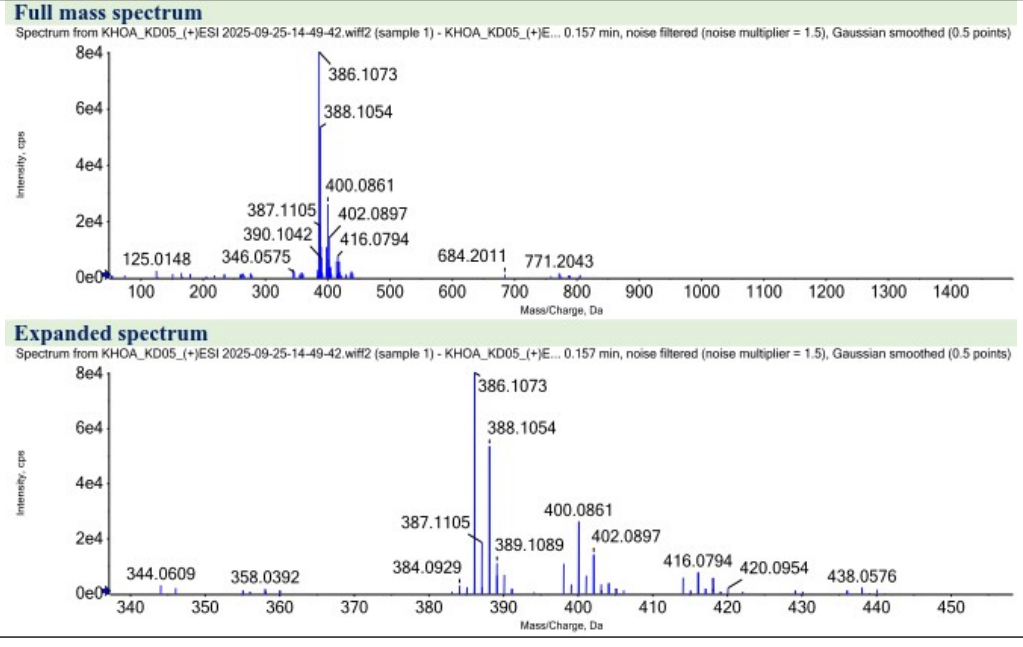


Fig S7. ^{1}H NMR Spectrum of compound KD2c

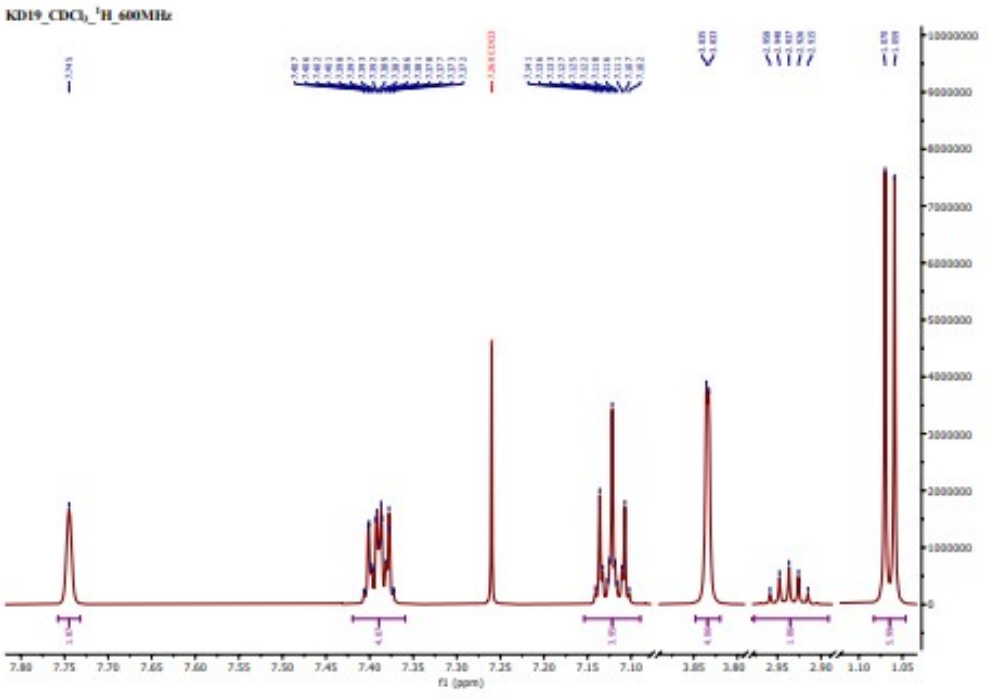


Fig S8. ^{13}C NMR Spectrum of compound KD2c

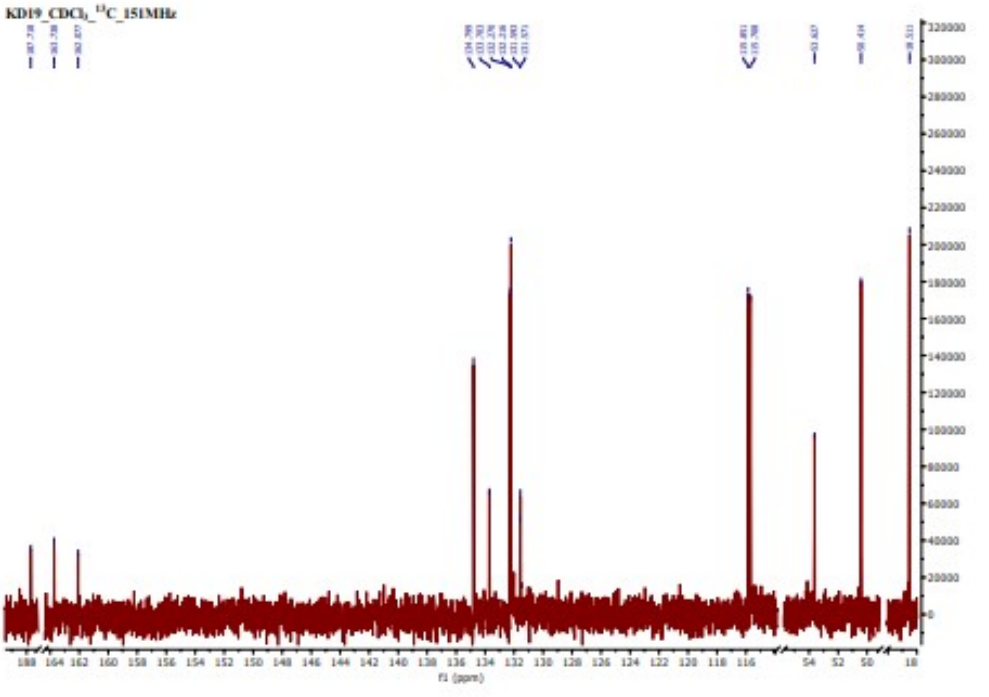


Fig S9. HR-MS spectrum of compound KD2c

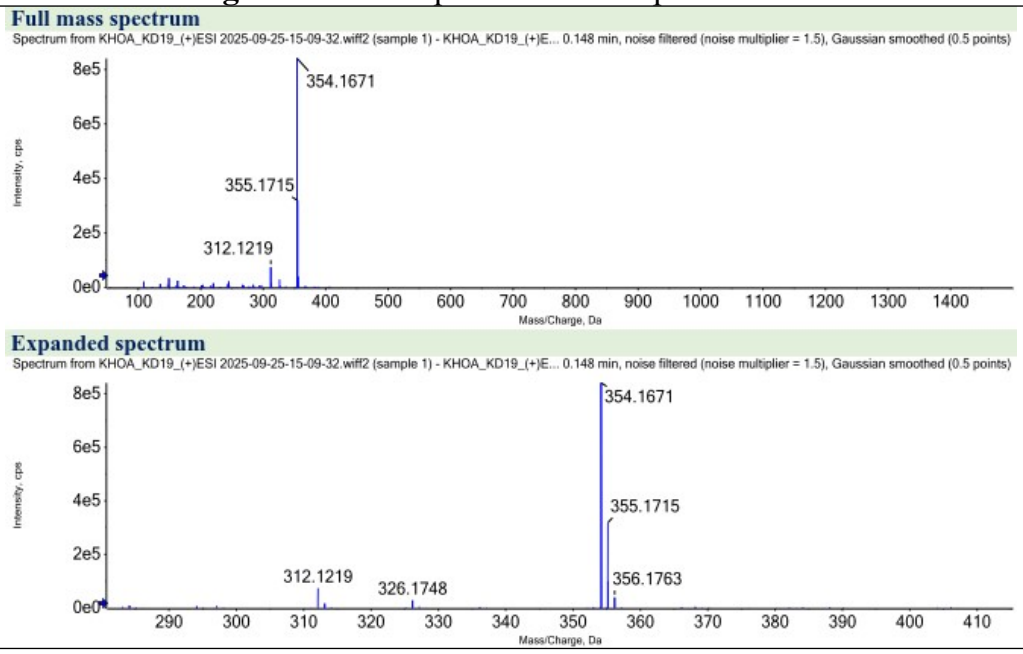


Fig S10. ^{1}H NMR Spectrum of compound KD2d

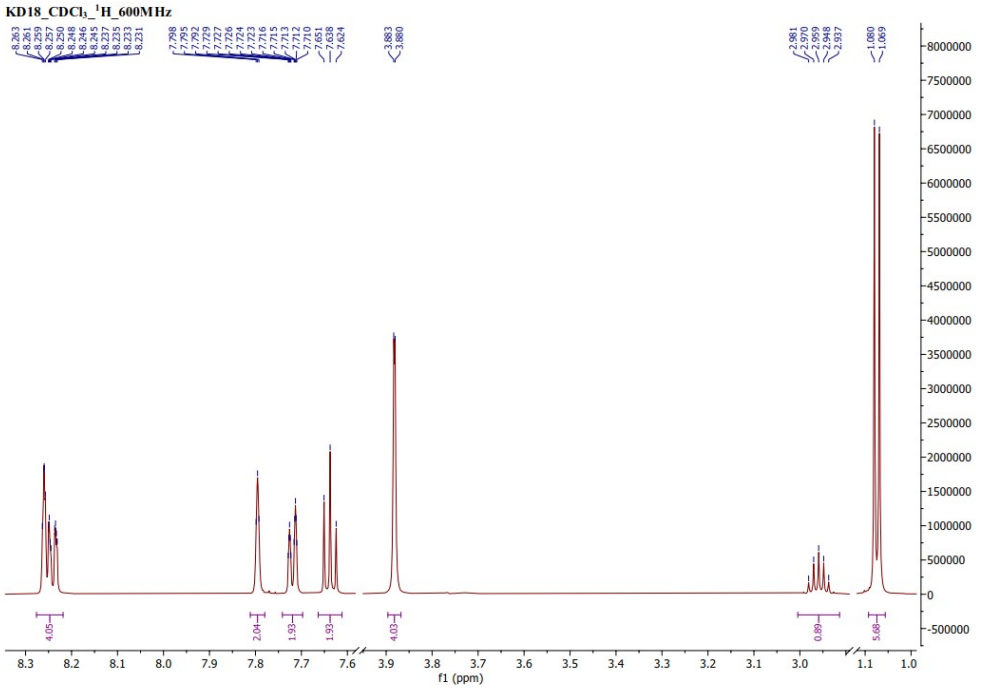


Fig S11. ^{13}C NMR Spectrum of compound KD2d

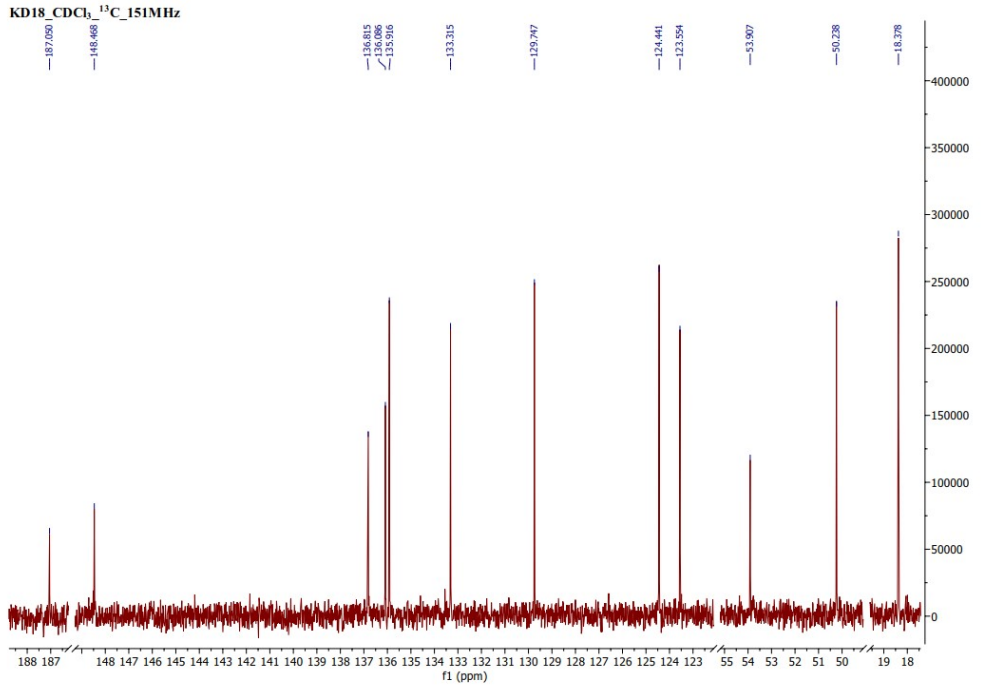


Fig S12. HR-MS spectrum of compound KD2d

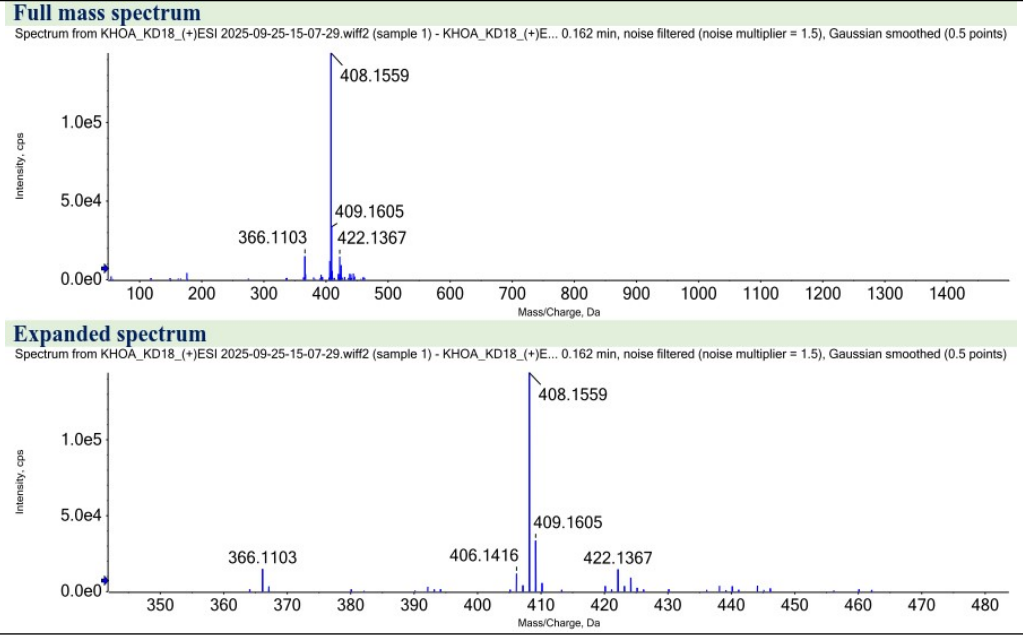


Fig S13. ^{1}H NMR Spectrum of compound KD2e

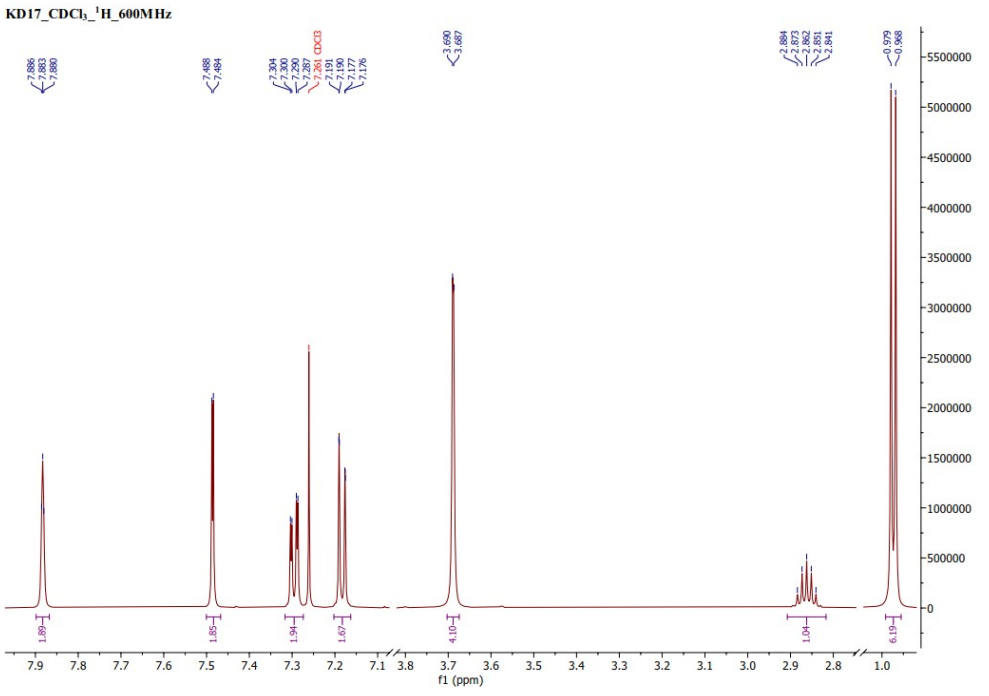


Fig S14. ^{13}C NMR Spectrum of compound KD2e

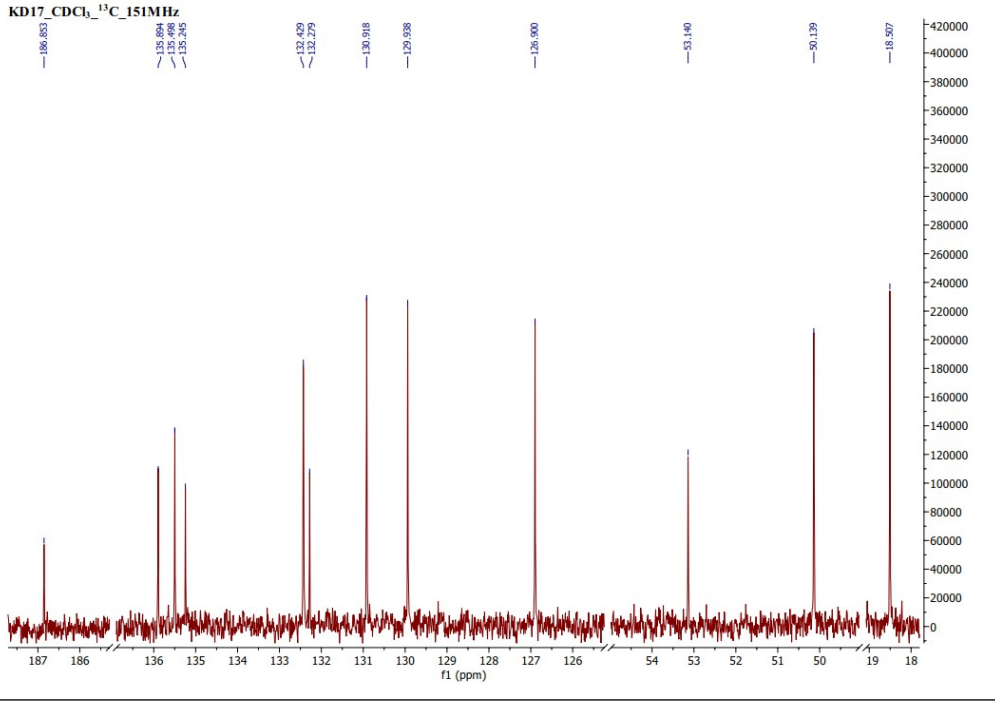


Fig S15. HR-MS Spectrum of compound KD2e

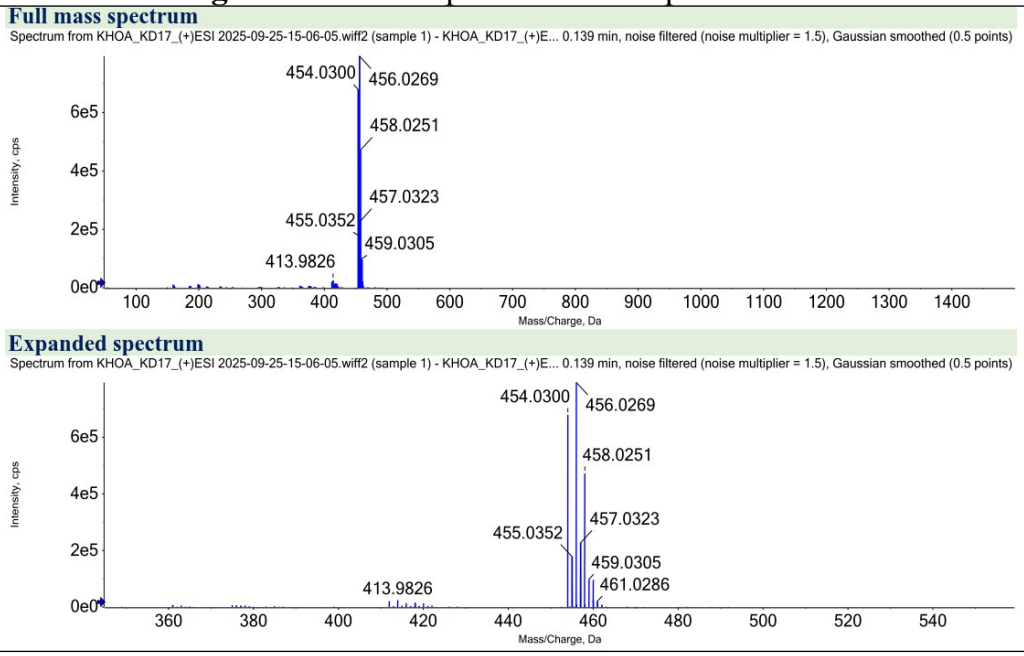


Fig S16. ^{1}H NMR Spectrum of compound KD2f

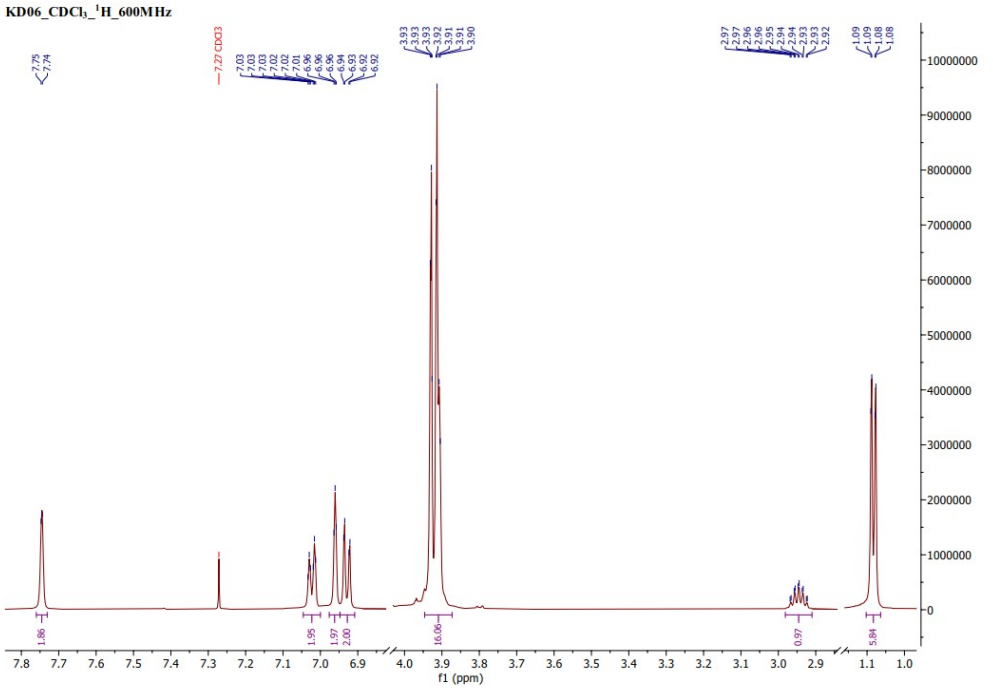


Fig S17. ^{13}C NMR Spectrum of compound KD2f

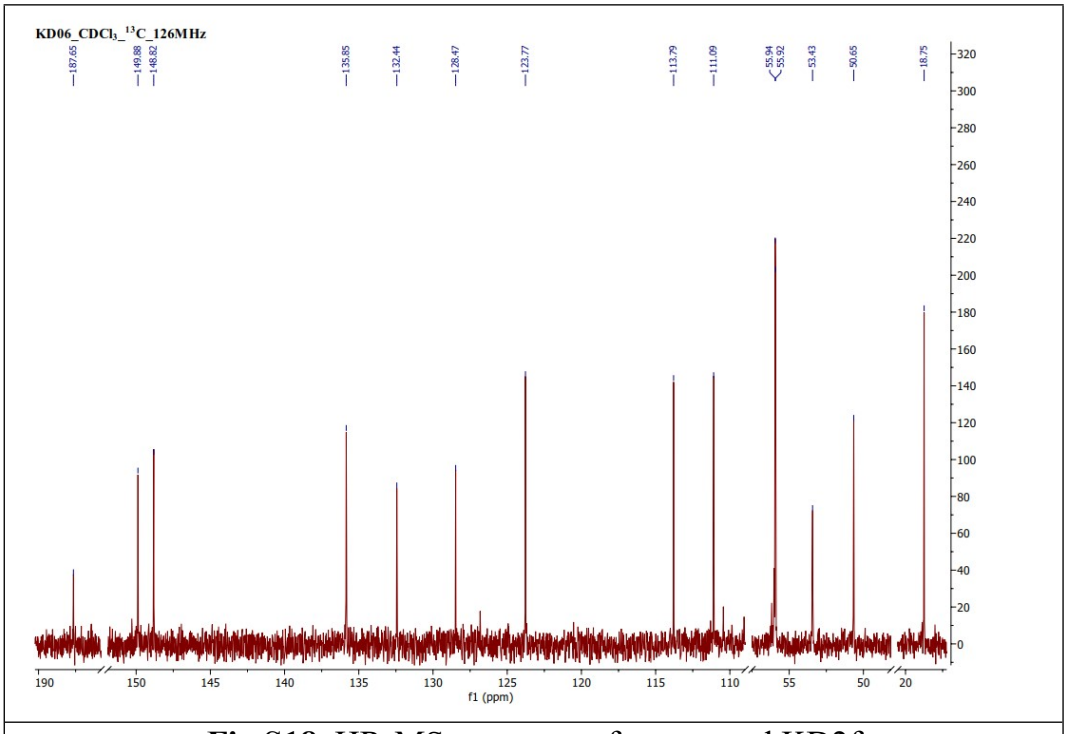


Fig S18. HR-MS spectrum of compound KD2f

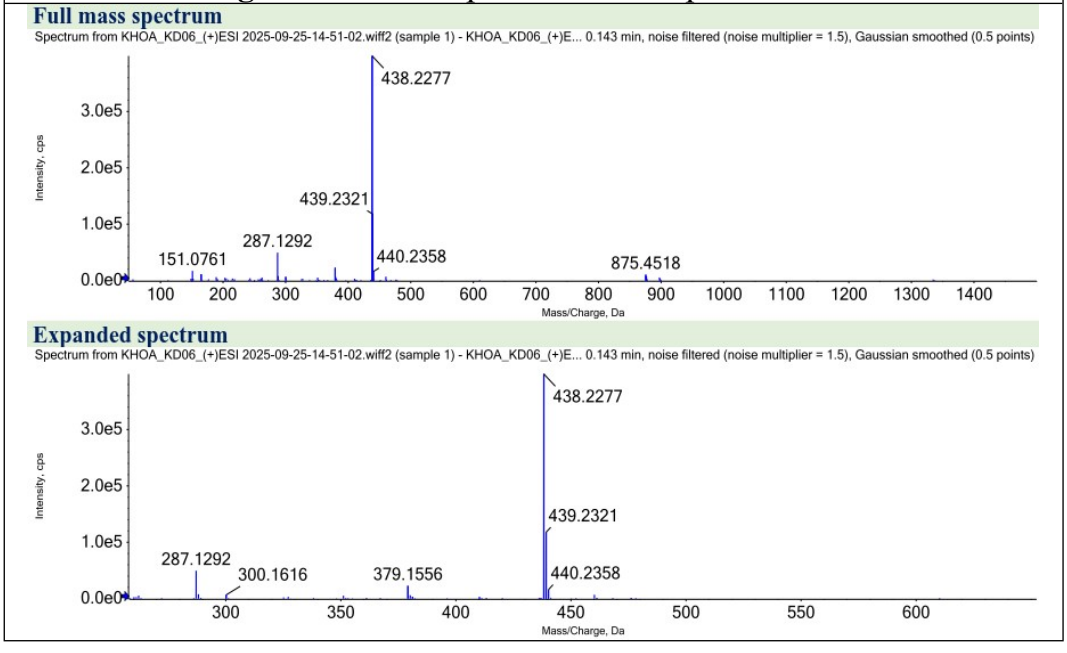


Fig S19. ^{1}H NMR Spectrum of compound KD2g

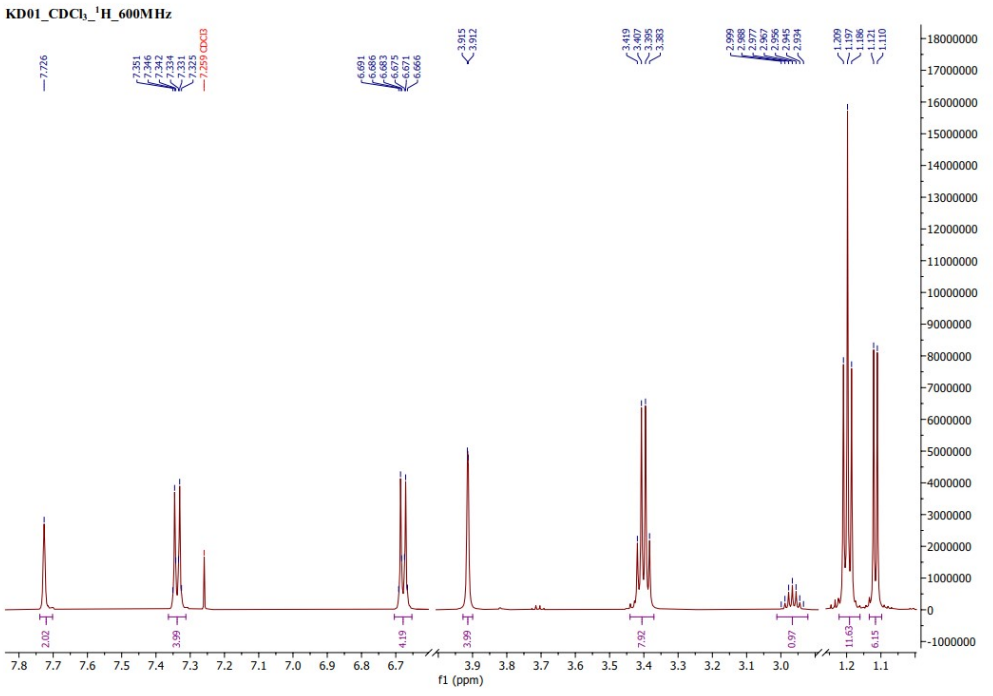


Fig S20. ^{13}C NMR Spectrum of compound KD2g

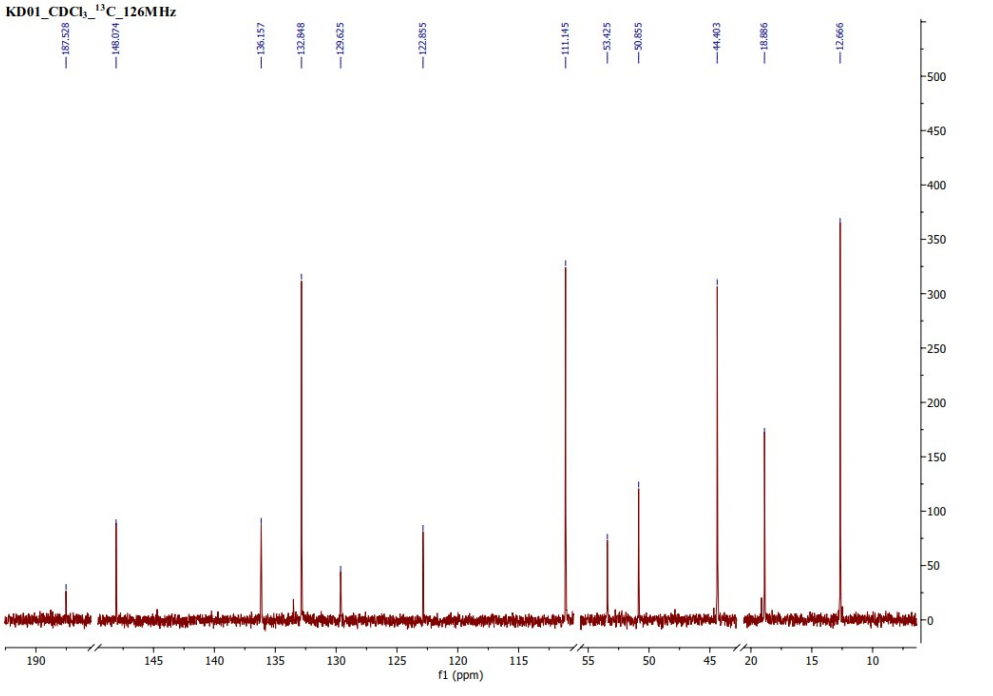


Fig S21. HR-MS spectrum of compound KD2g

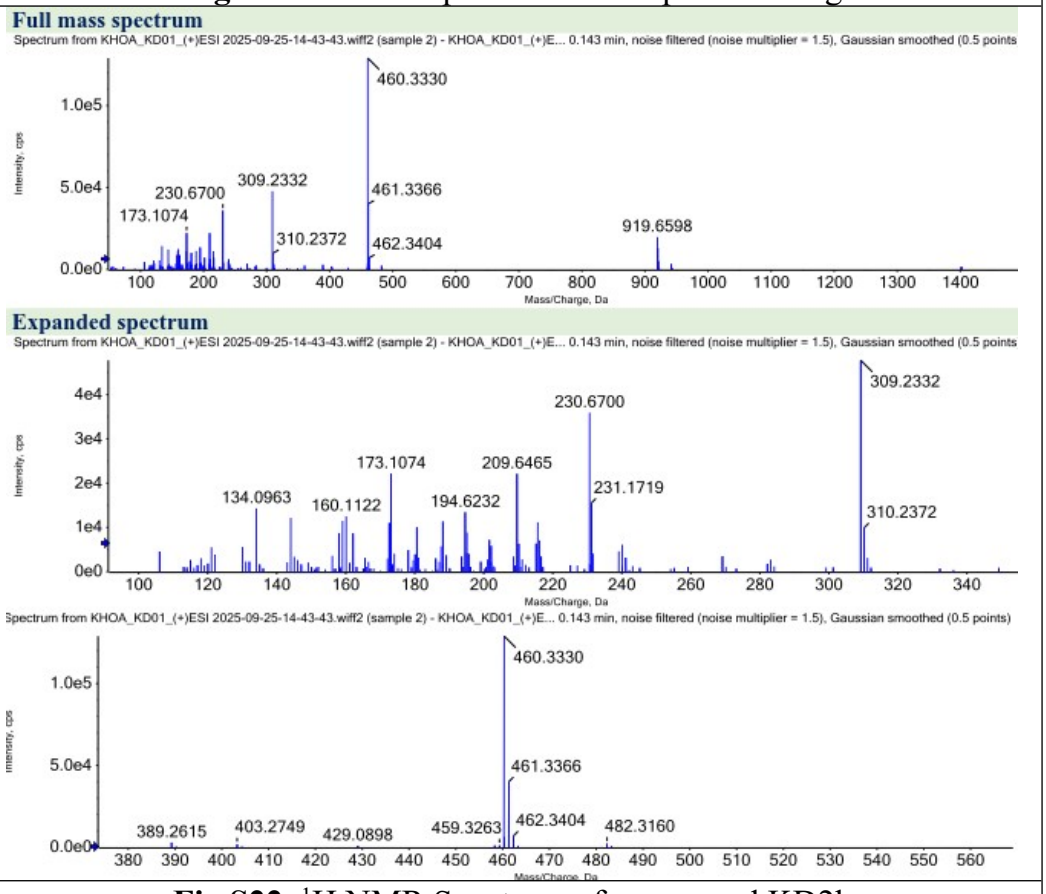


Fig S22. ^{1}H NMR Spectrum of compound KD2h

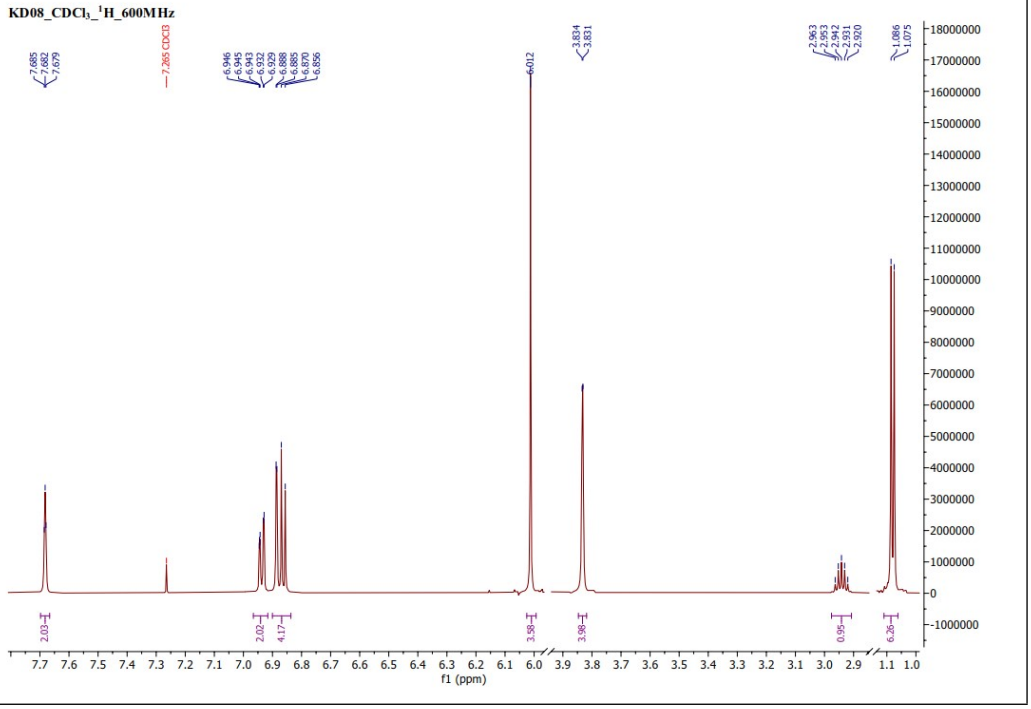


Fig S23. ^{13}C NMR Spectrum of compound KD2h

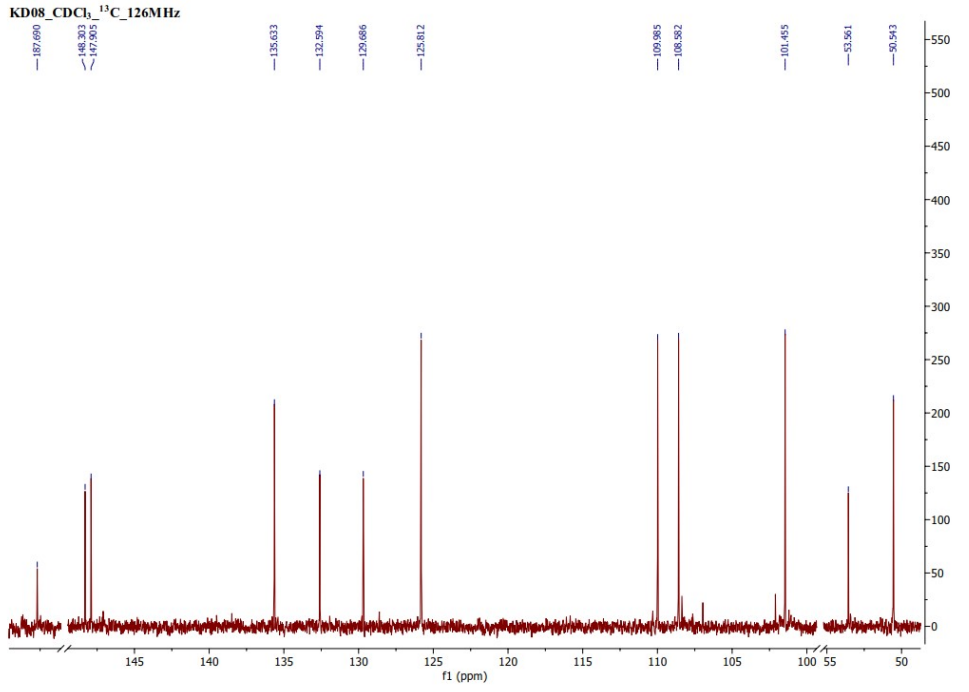


Fig S24. HR-MS spectrum of compound KD2h

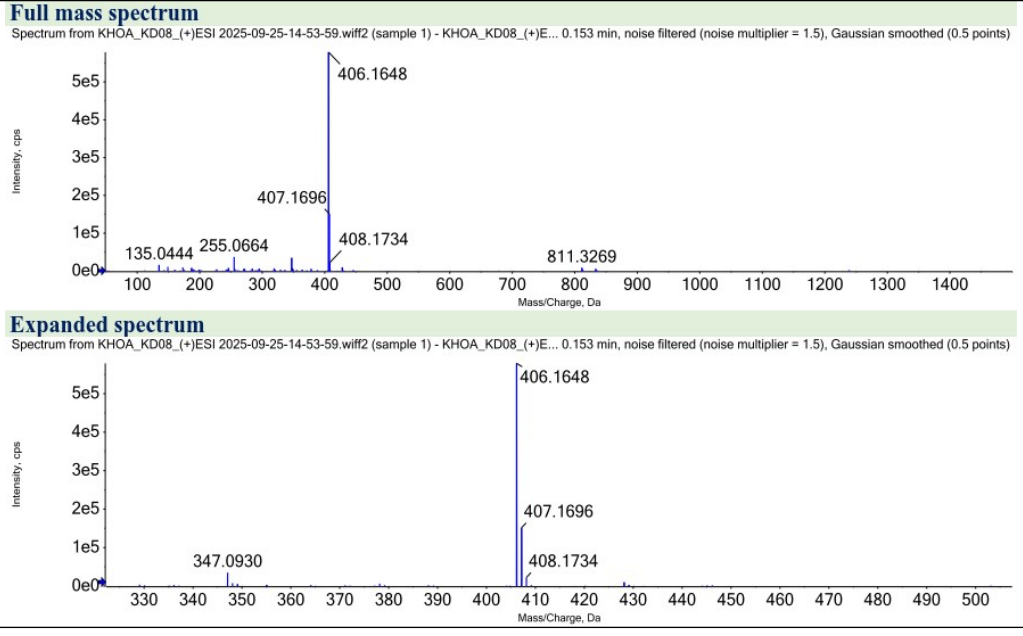


Fig S25. ^{1}H NMR Spectrum of compound KD2i

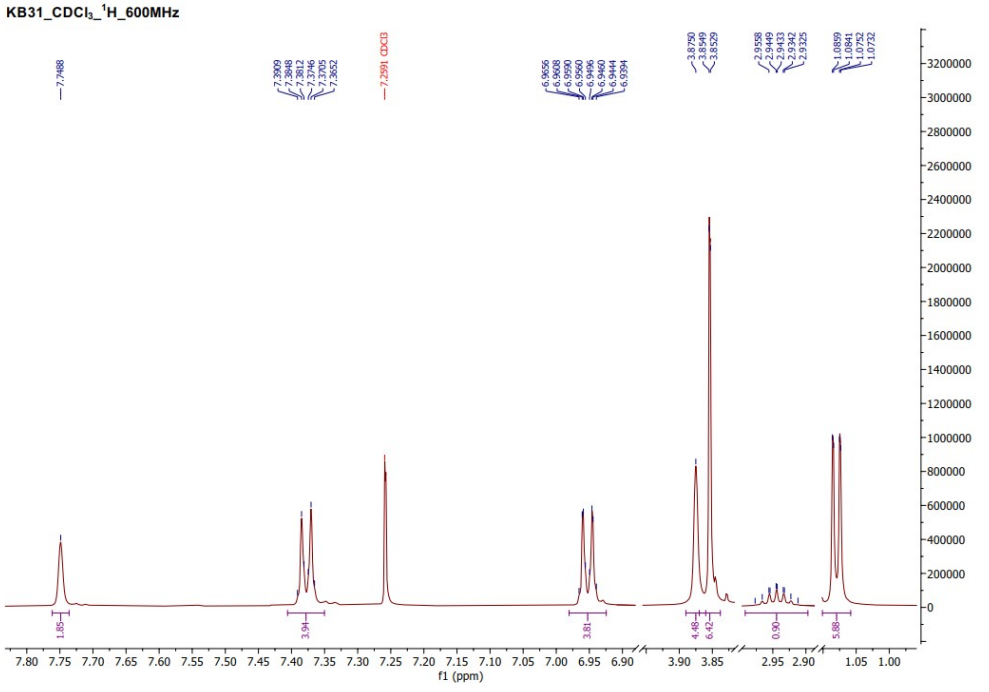


Fig S26. ^{13}C NMR Spectrum of compound KD2i

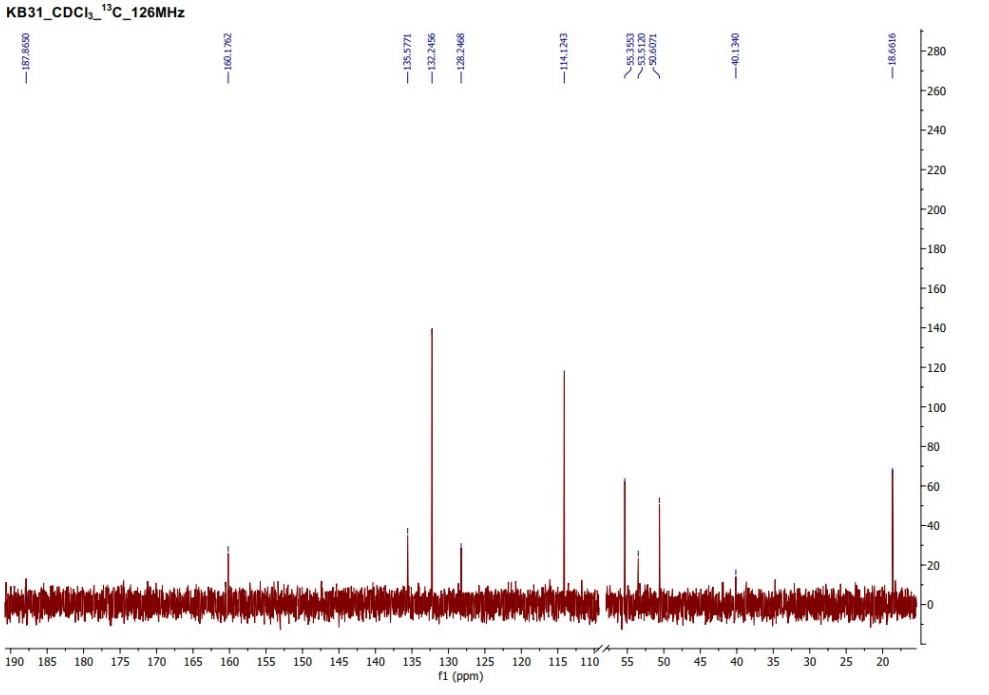


Fig S27. HR-MS spectrum of compound KD2i

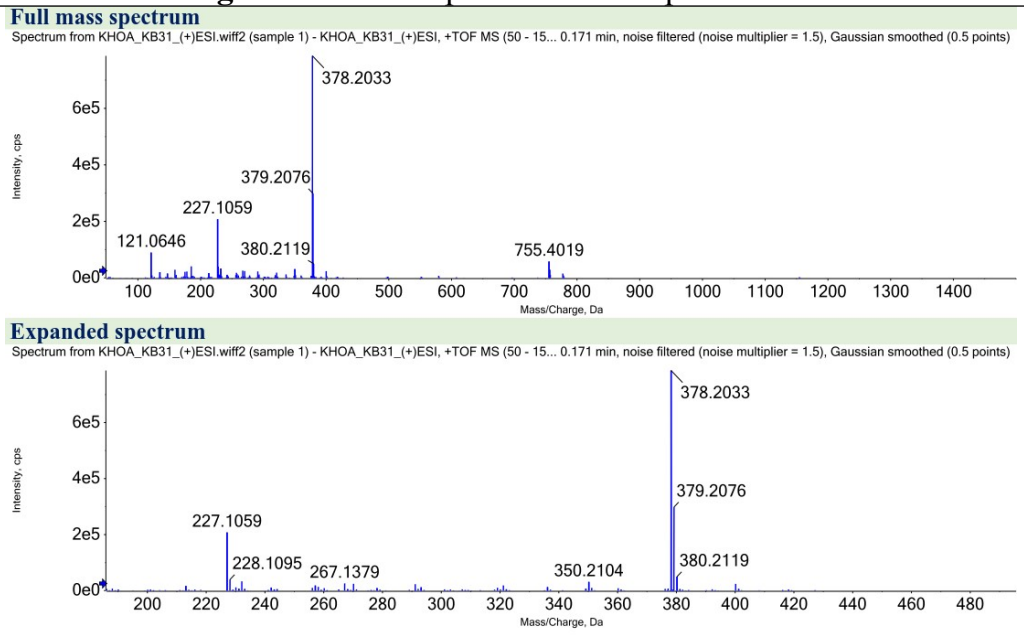


Fig S28. ^{1}H NMR Spectrum of compound KB2a

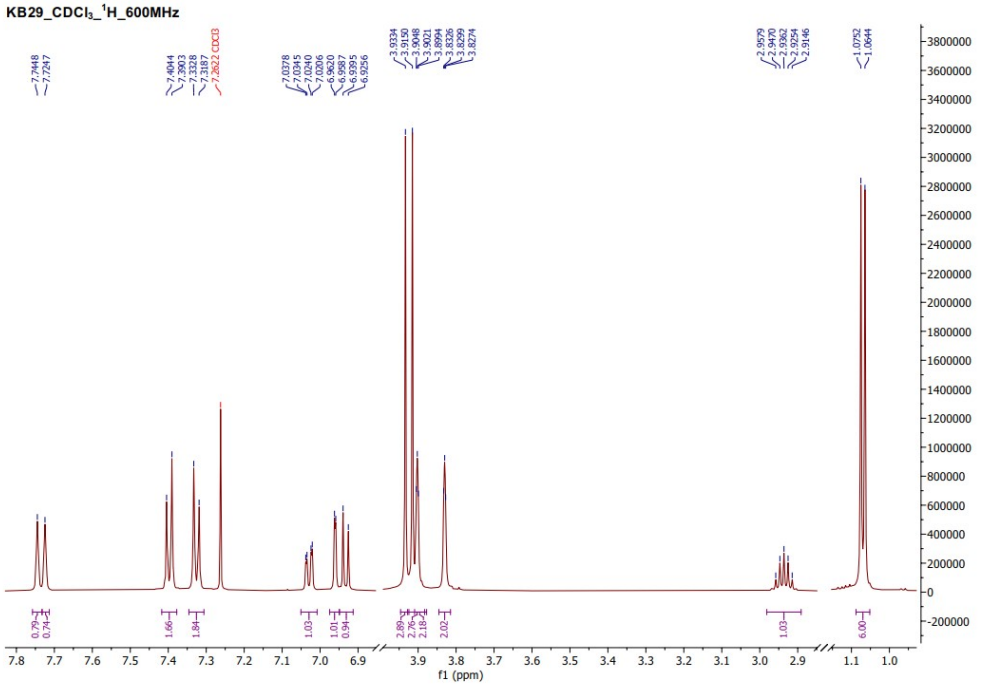


Fig S29. ^{13}C NMR Spectrum of compound KB2a

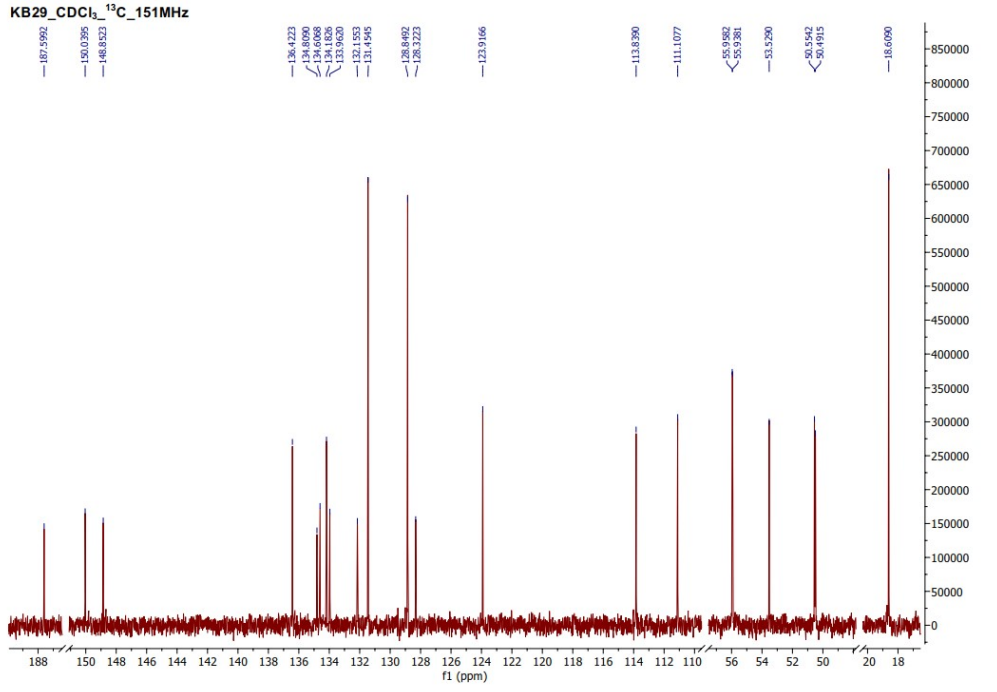


Fig S30. HR-MS spectrum of compound KB2a

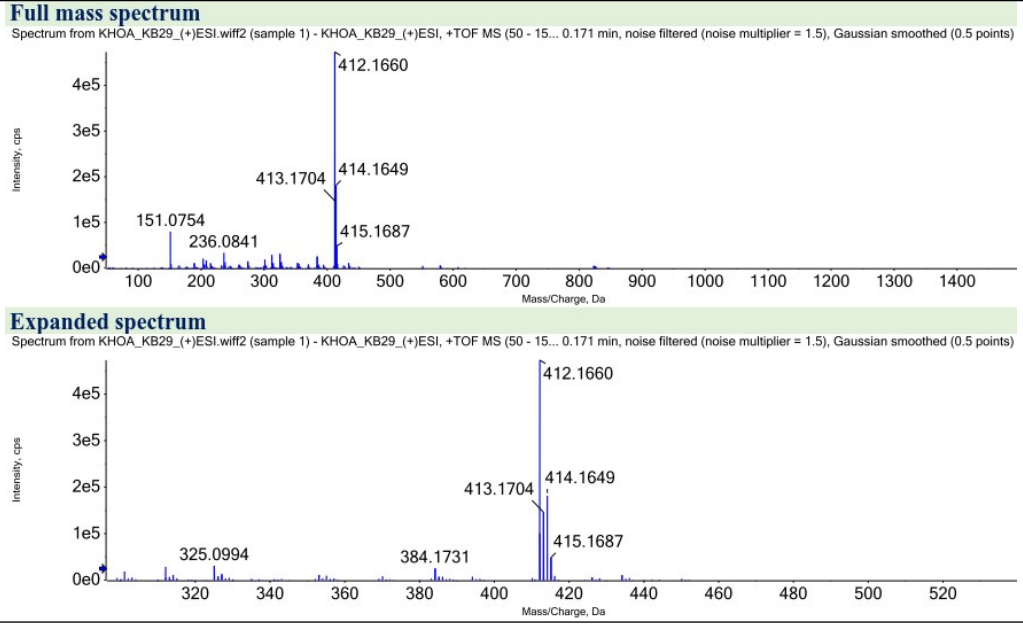


Fig S31. ^{1}H NMR Spectrum of compound KB2b

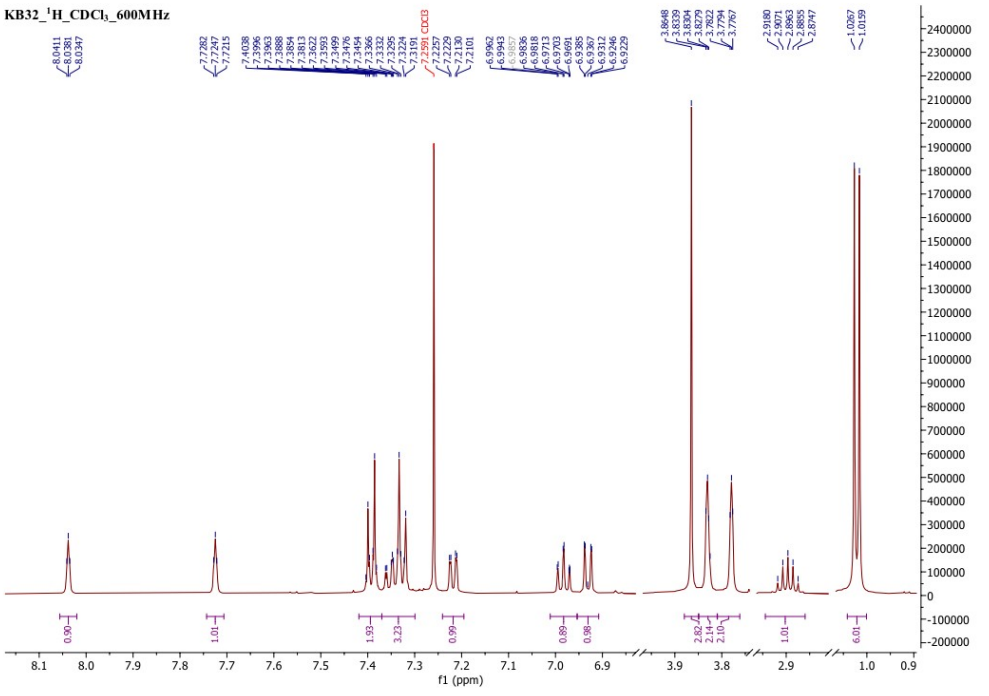


Fig S32. ^{13}C NMR Spectrum of compound KB2b

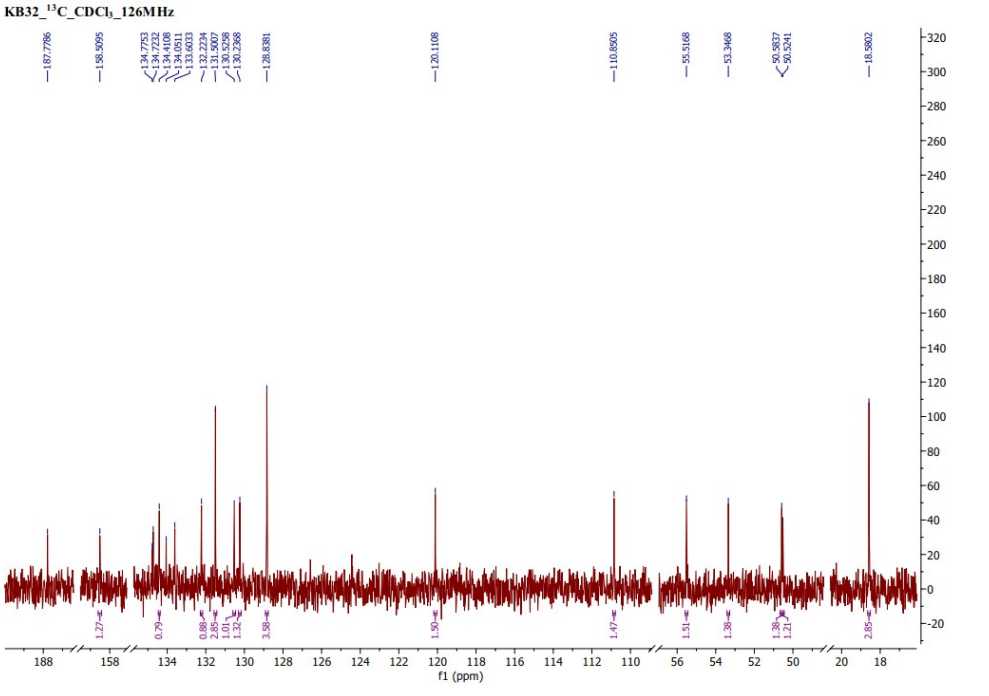


Fig S33. HR-MS spectrum of compound KB2b

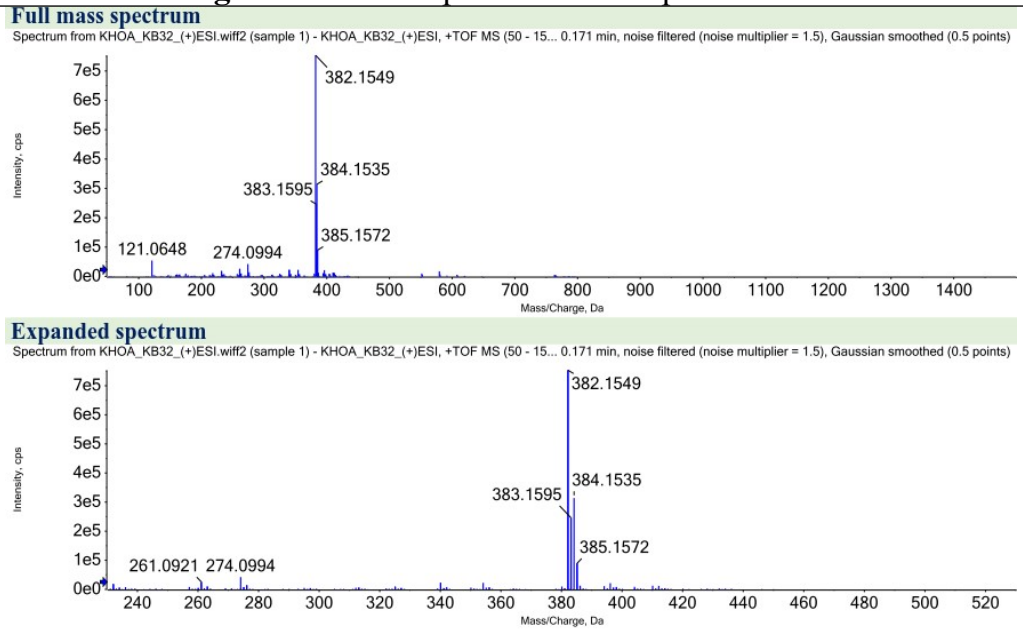


Fig S34. ^{1}H NMR Spectrum of compound KB2c

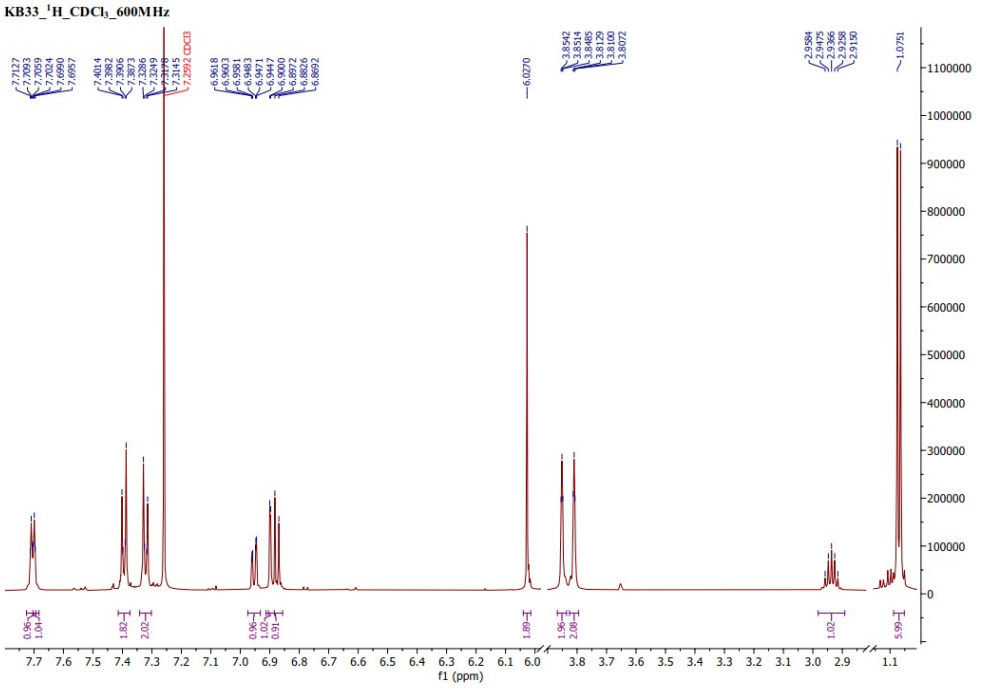


Fig S35. ^{13}C NMR Spectrum of compound KB2c

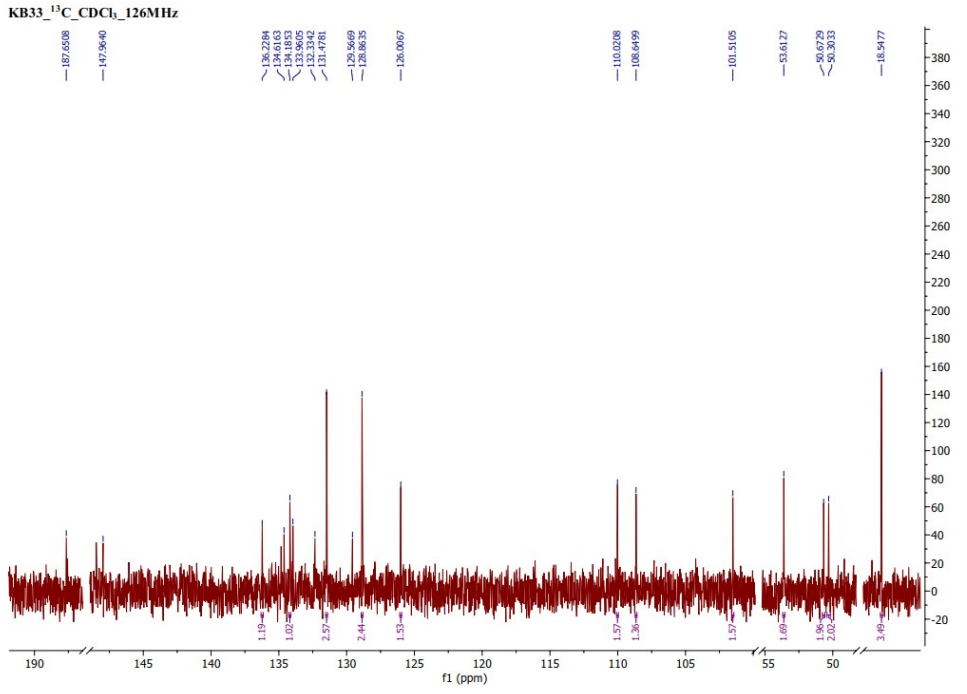


Fig S36. HR-MS spectrum of compound KB2c

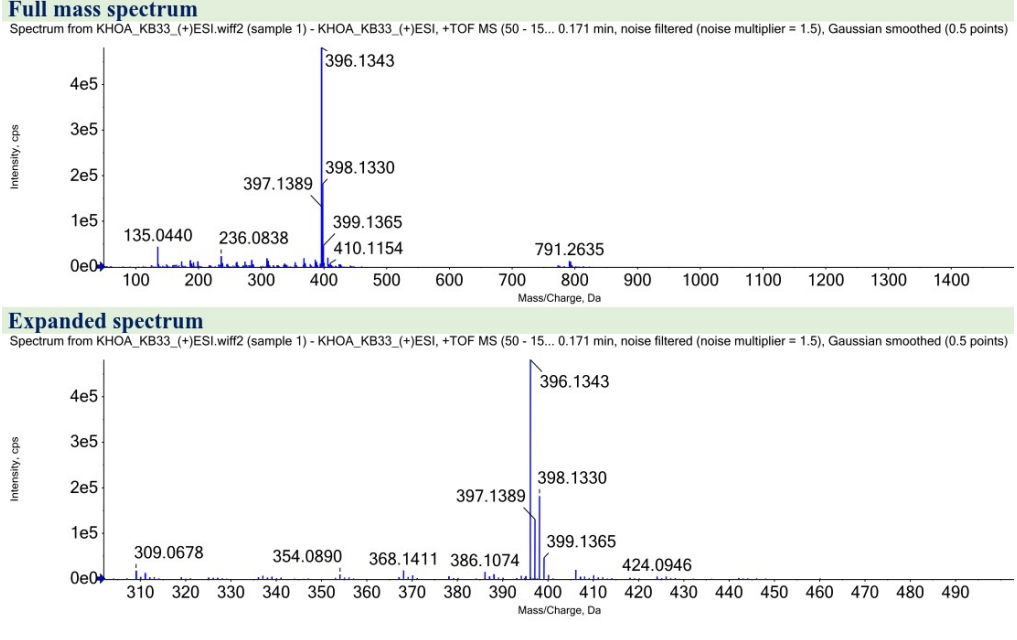


Fig S37. ^{1}H NMR Spectrum of compound KB2d

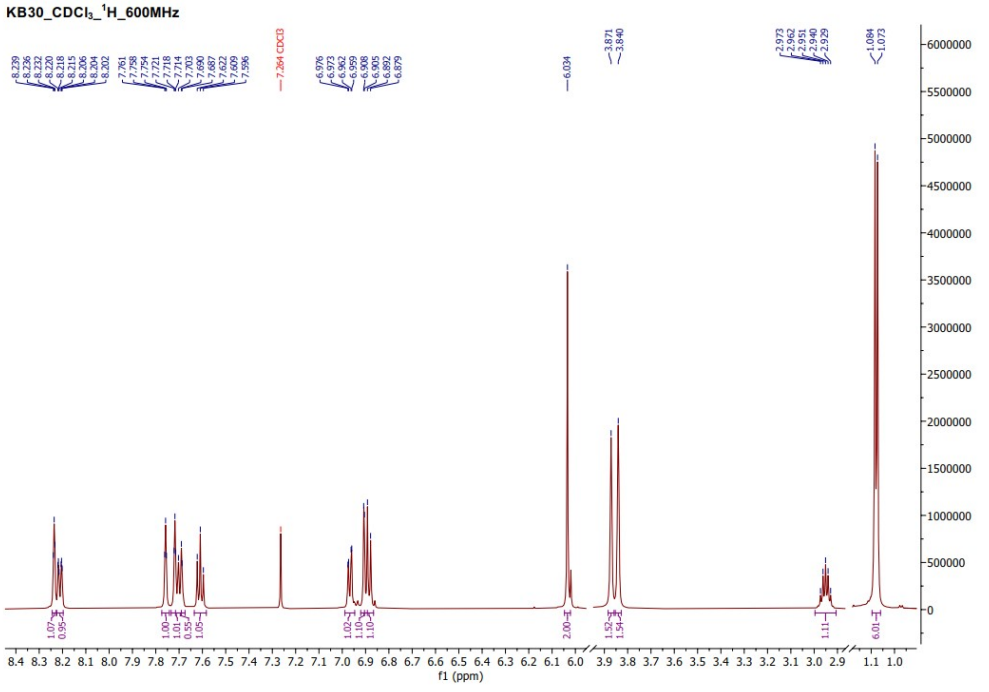


Fig S38. ^{13}C Spectrum of compound KB2d

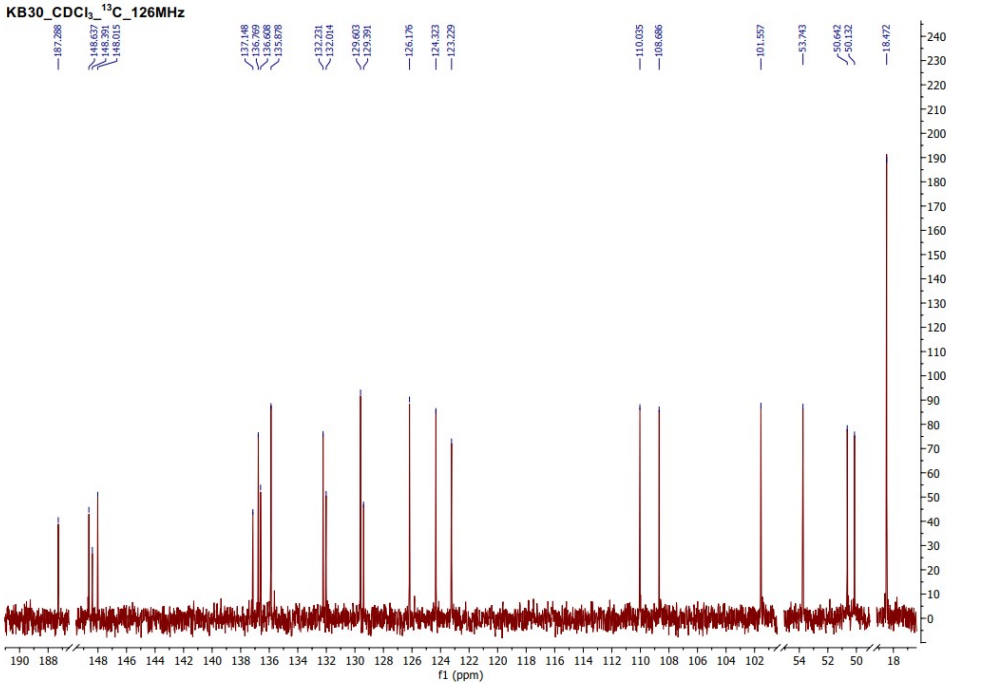


Fig S39. HR-MS spectrum of compound KB2d