

# **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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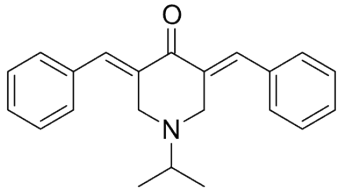
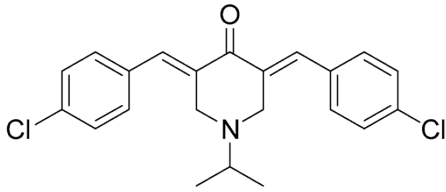
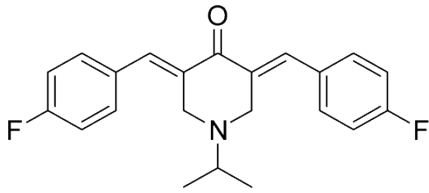
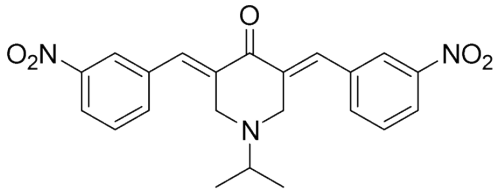
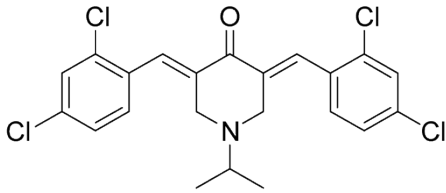
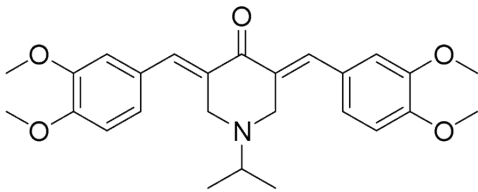
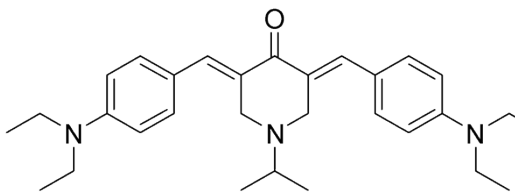
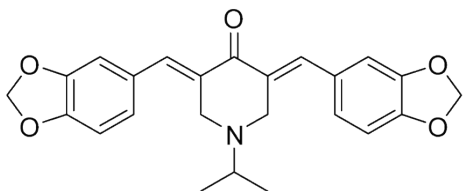
\*Corresponding author: [dangchihien@gmail.com](mailto:dangchihien@gmail.com)

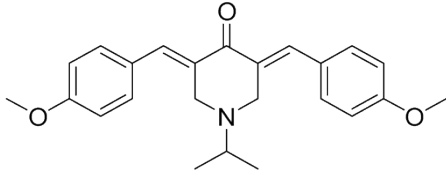
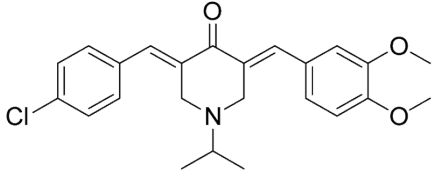
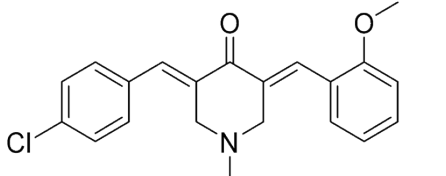
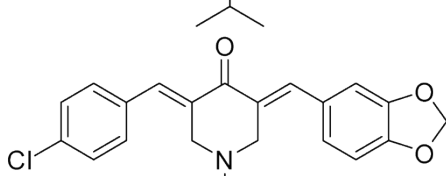
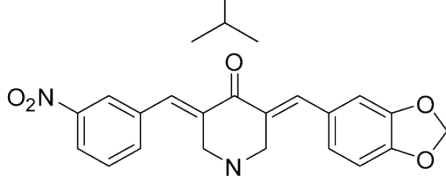
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**Table S1.** Structure, synthetic yield of MACs

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

<b>KD2i</b>		94.8 %	Yellow powder
<b>KB2a</b>		54.3%	Yellow powder <b>(New compound)</b>
<b>KB2b</b>		54.6%	Yellow powder <b>(New compound)</b>
<b>KB2c</b>		56.3%	Yellow powder <b>(New compound)</b>
<b>KB2d</b>		56.7%	Yellow powder <b>(New compound)</b>

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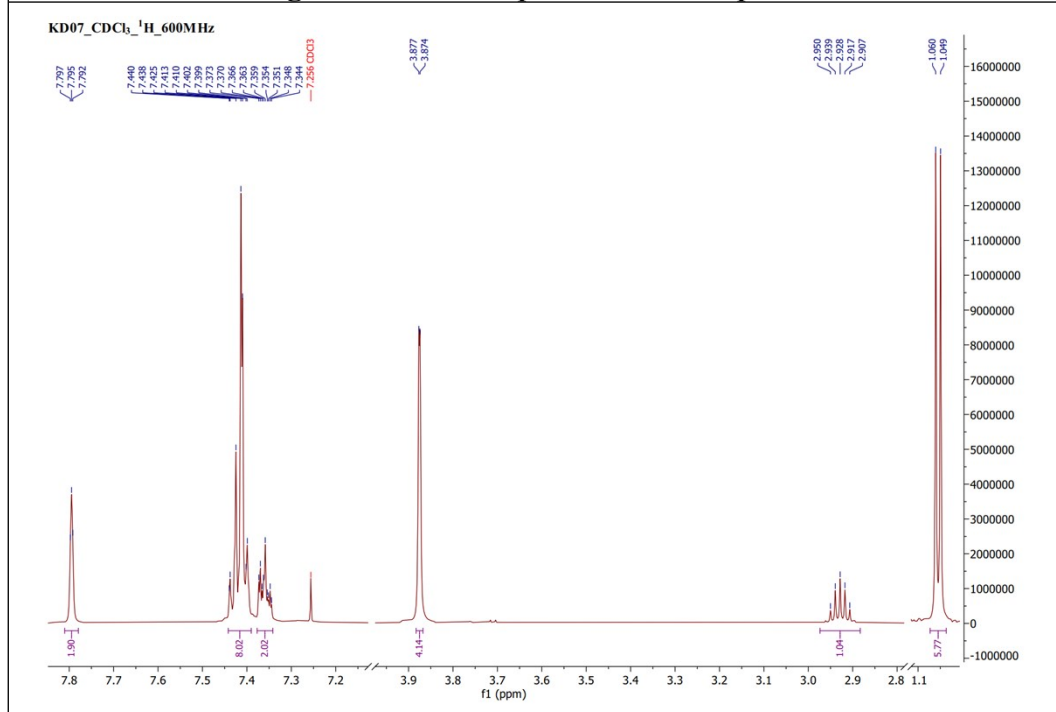
**Table S2.** Comprehensive comparison of molecular docking, 200 ns molecular dynamics (MD) simulation, and pharmacokinetic properties of the lead compounds.

Property / Evaluation parameter	KB2c	KB2d
<b>1. Molecular Docking (static state)</b>		
Binding energy $\Delta G$ (kcal mol <sup>-1</sup> )	-10.78	-10.96
Inhibition constant Ki	12.49 nM	9.18 nM
<b>2. Molecular Dynamics simulation (200 ns)</b>		
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 $\Delta G_{\text{bind}}$ (kcal mol <sup>-1</sup> )	-29.53	-33.53
van der Waals energy (VDWAALS)	-45.51	-52.17
Electrostatic energy (EEL)	9.53	-25.02
<b>3. Pharmacochemical properties and ADMET</b>		
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)
<b>4. Overall evaluation</b>		
Practical development conclusion	Low potential (loose binding)	Optimal lead compound

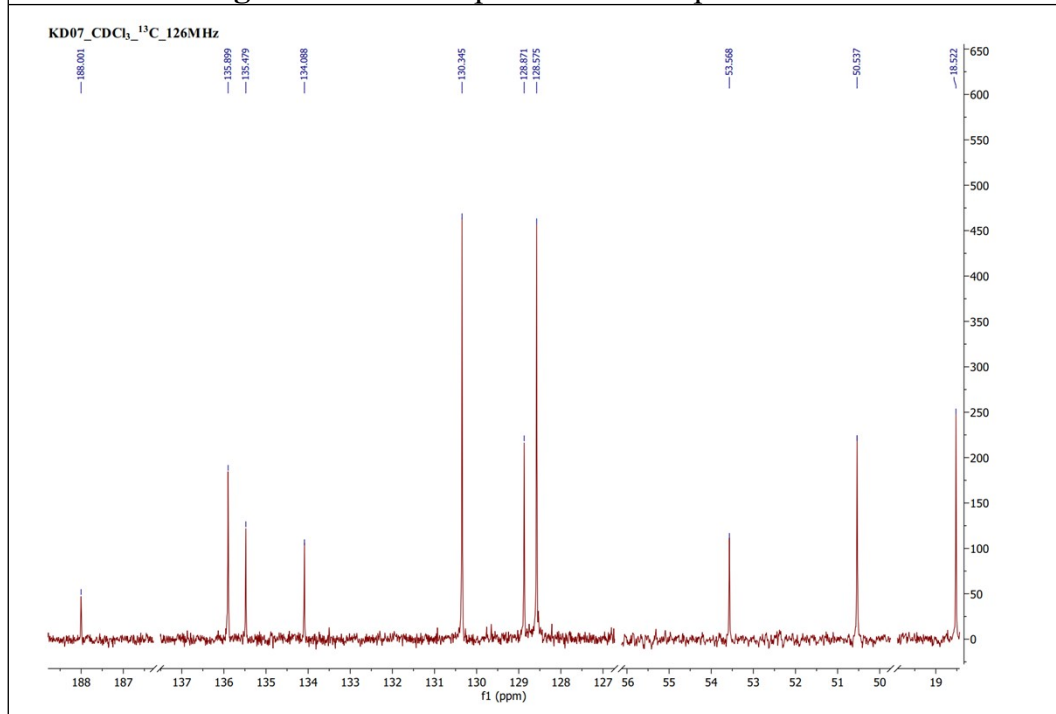
**Table S3.** Binding free energy of ligand–receptor complexes calculated using the MM/GBSA method

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.**  $^1\text{H}$  NMR Spectrum of compound KD2a



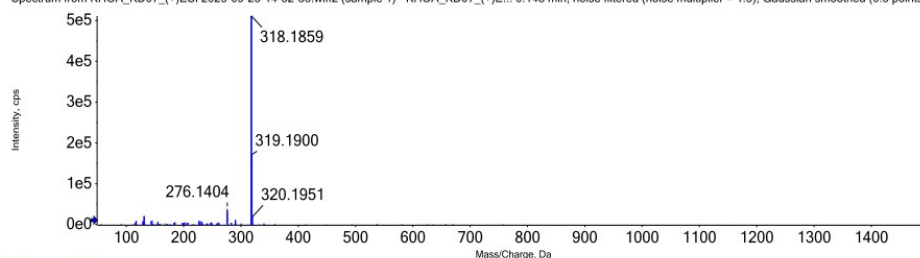
**Fig S2.**  $^{13}\text{C}$  NMR Spectrum of compound KD2a



### Fig S3. HR-MS spectrum of compound KD2a

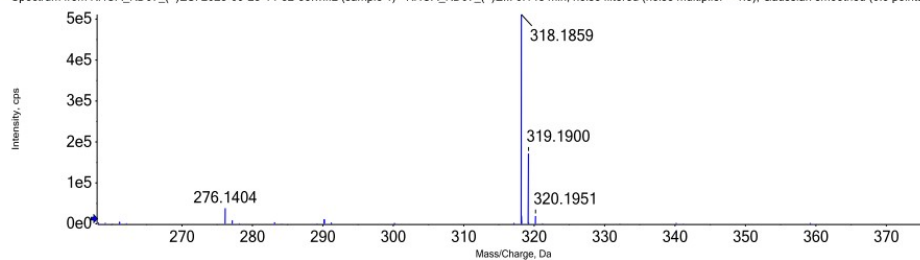
#### Full mass spectrum

Spectrum from KH0A\_KD07\_(+)ESI 2025-09-25-14-52-33.wiff2 (sample 1) - KH0A\_KD07\_(+)E... 0.148 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points)



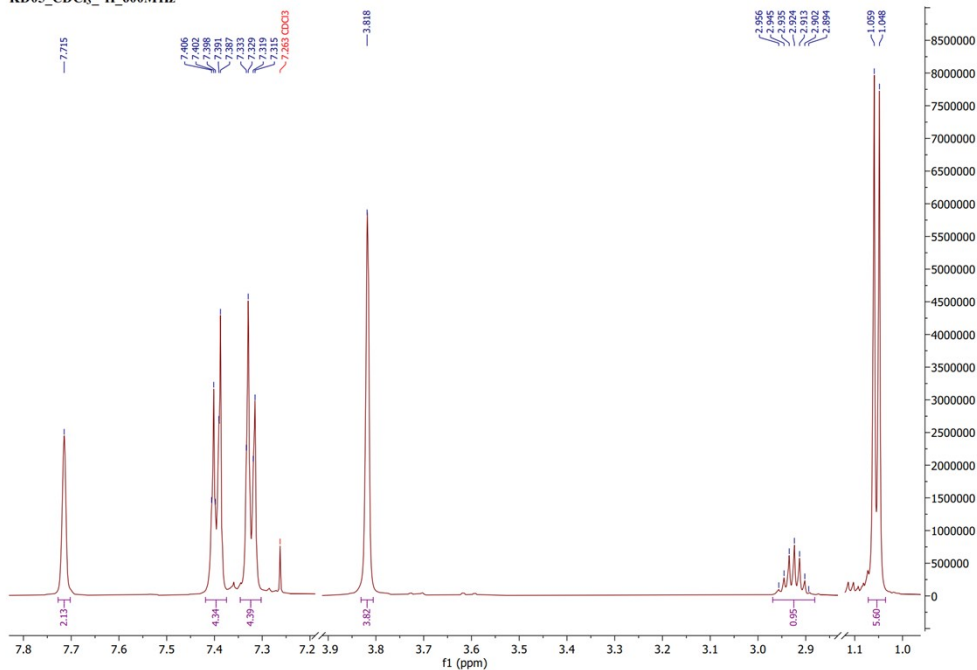
#### Expanded spectrum

Spectrum from KH0A\_KD07\_(+)ESI 2025-09-25-14-52-33.wiff2 (sample 1) - KH0A\_KD07\_(+)E... 0.148 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points)

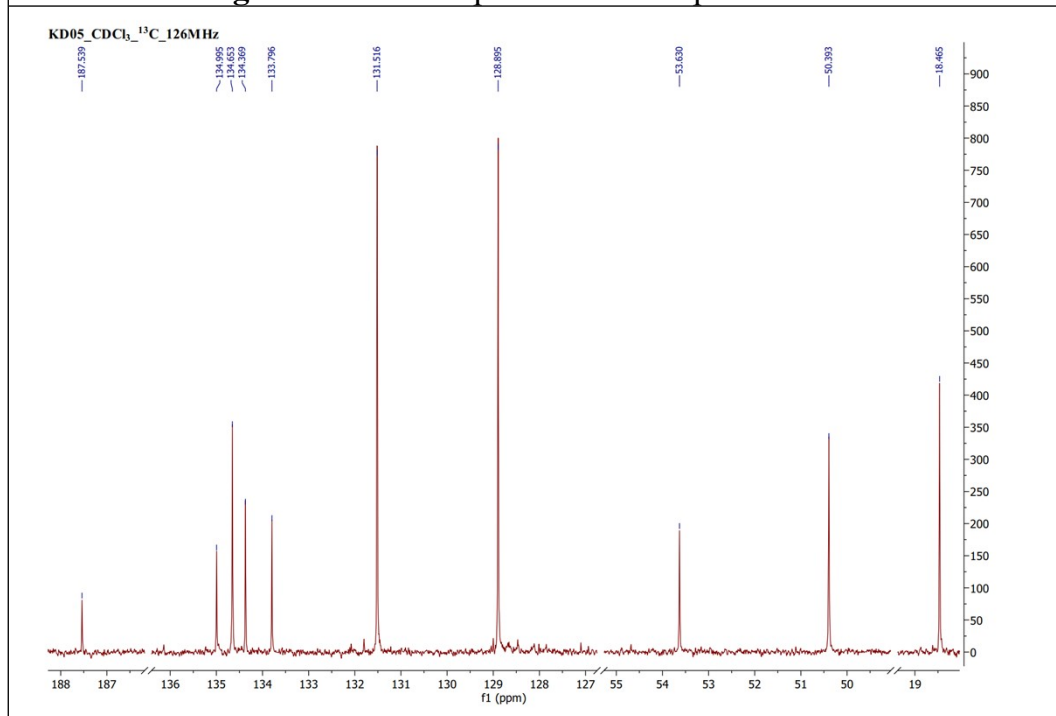


### Fig S4. <sup>1</sup>H NMR Spectrum of compound KD2b

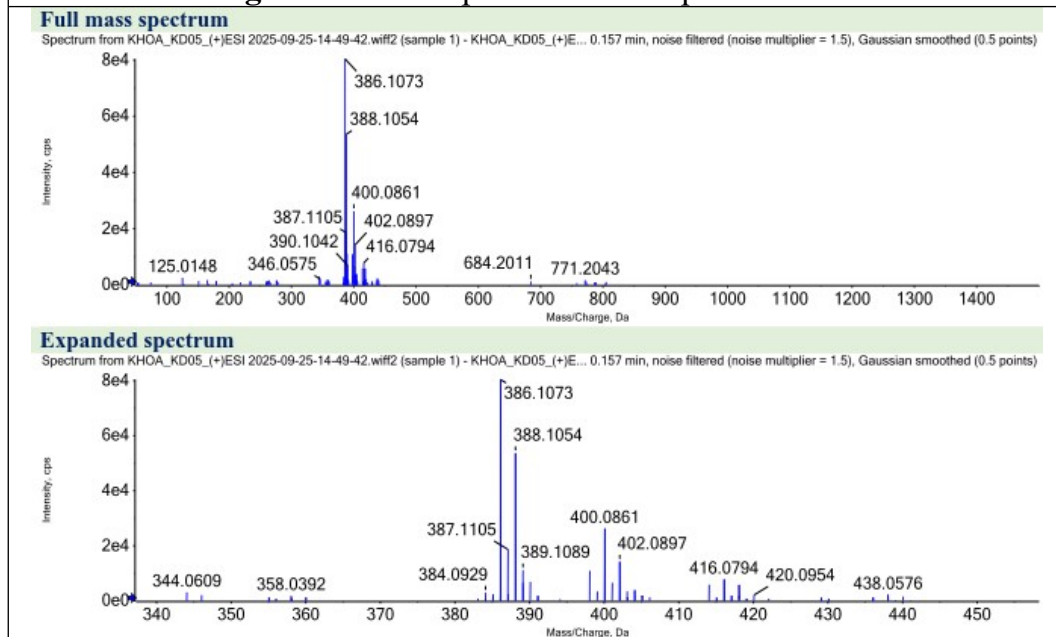
KD05\_CDCl<sub>3</sub>-<sup>1</sup>H\_600MHz



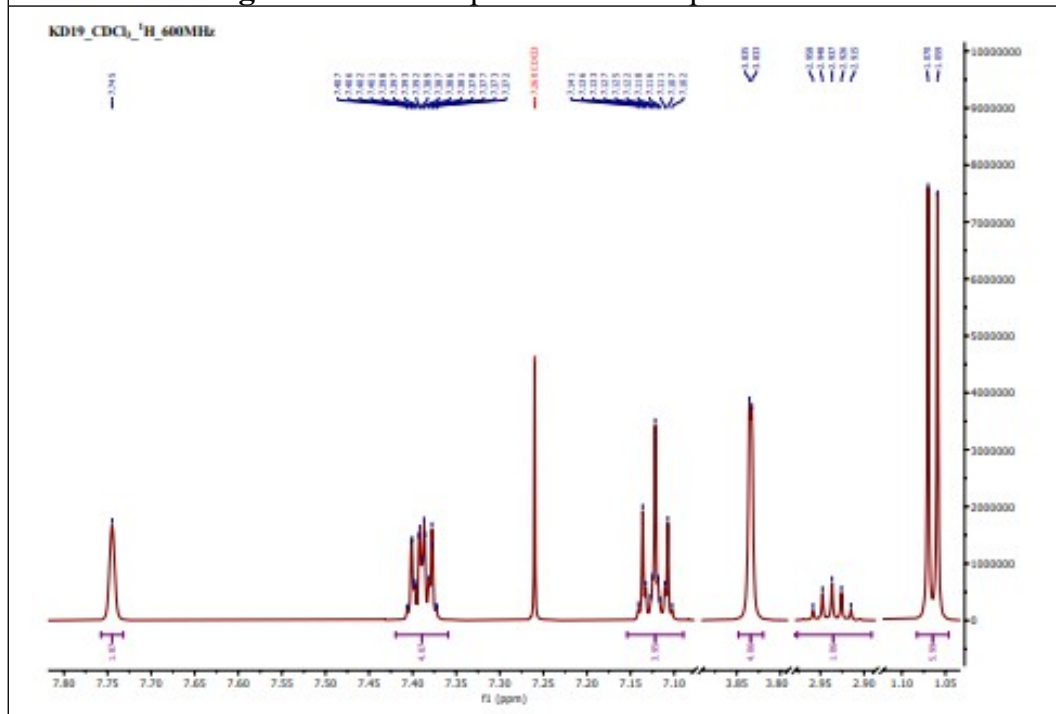
**Fig S5.**  $^{13}\text{C}$  NMR Spectrum of compound KD2b



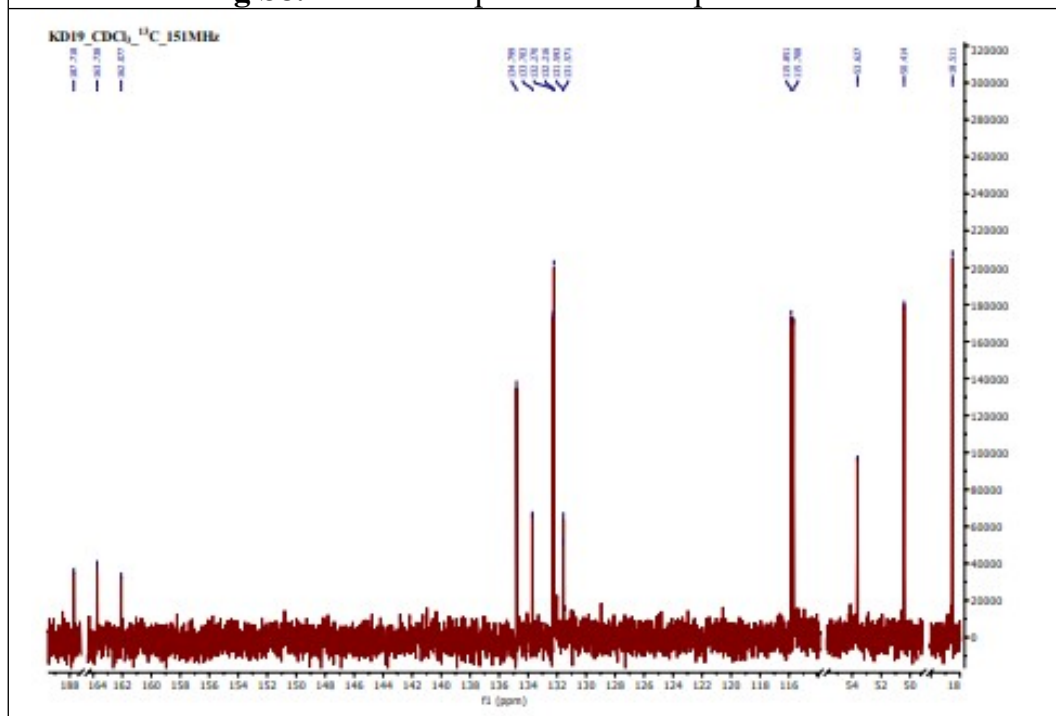
**Fig S6.** HR-MS Spectrum of compound KD2b



**Fig S7.**  $^1\text{H}$  NMR Spectrum of compound KD2c



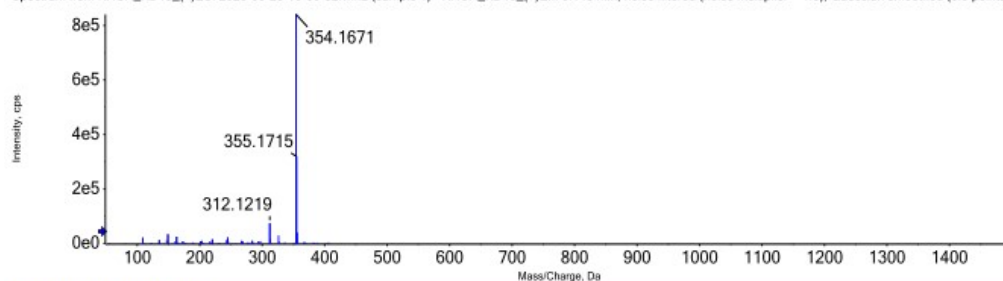
**Fig S8.**  $^{13}\text{C}$  NMR Spectrum of compound KD2c



**Fig S9. HR-MS spectrum of compound KD2c**

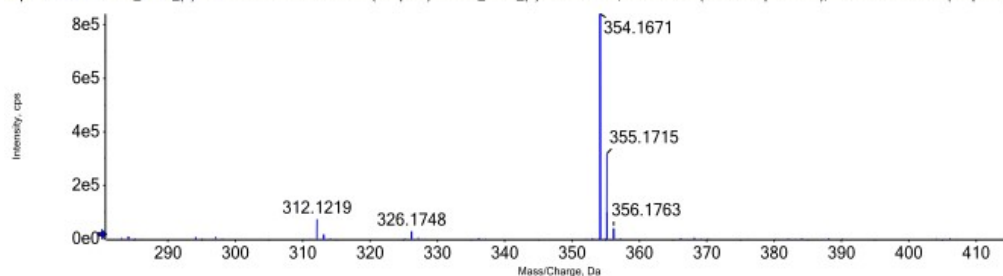
**Full mass spectrum**

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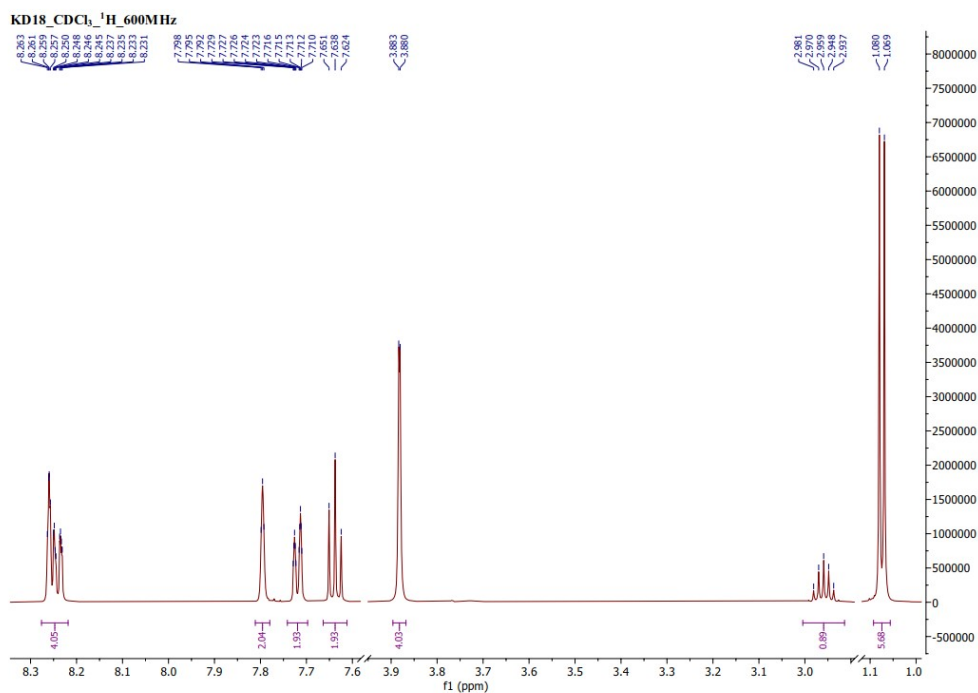


**Expanded spectrum**

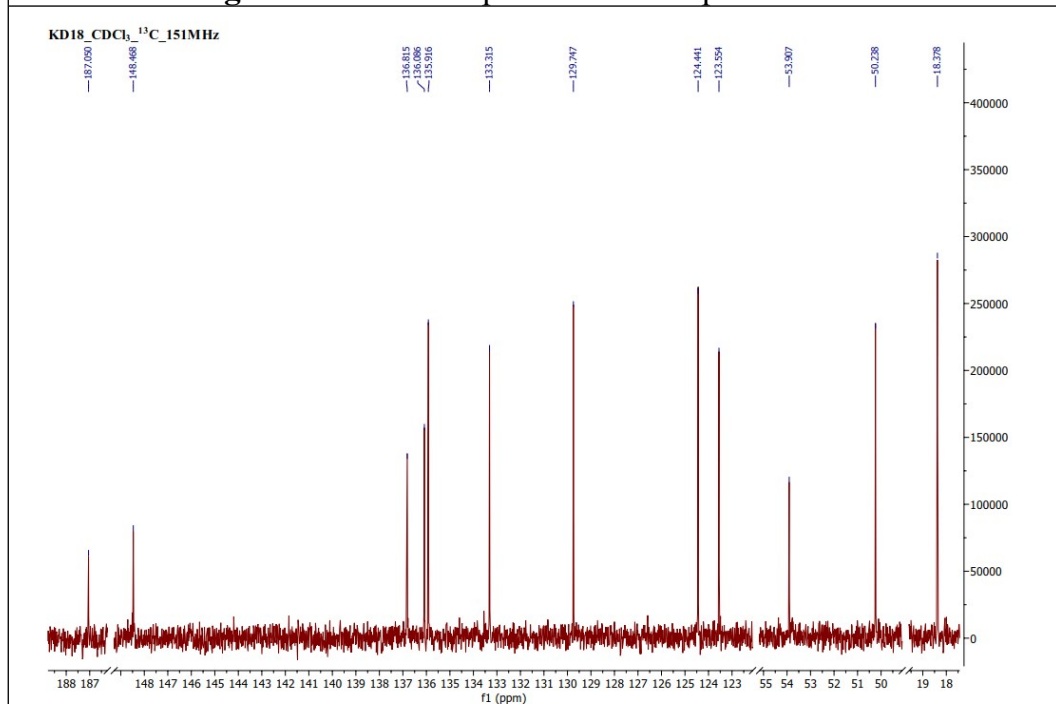
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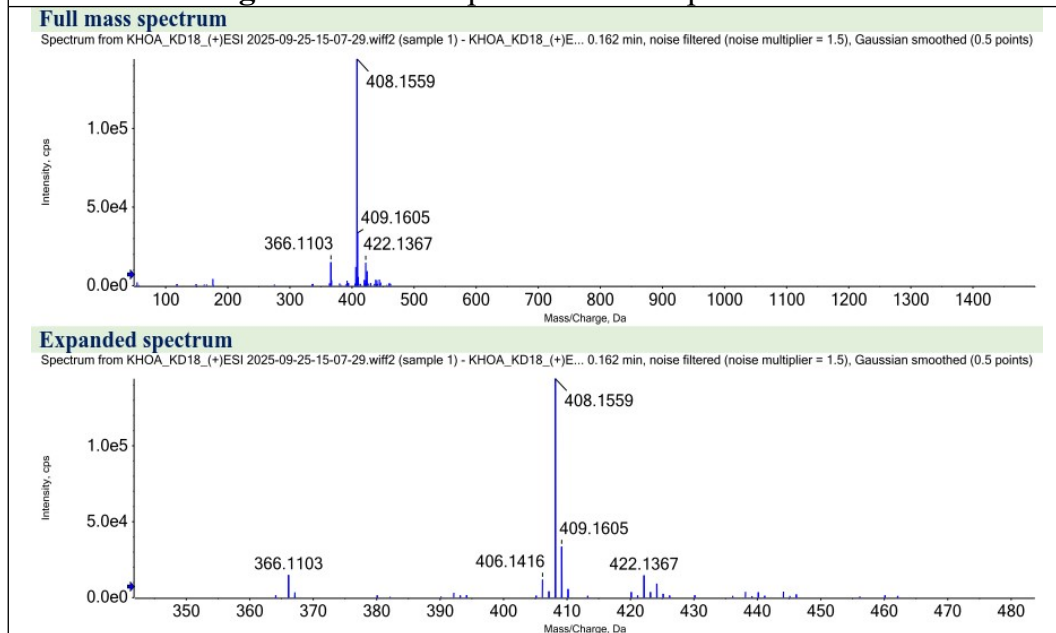
**Fig S10. <sup>1</sup>H NMR Spectrum of compound KD2d**



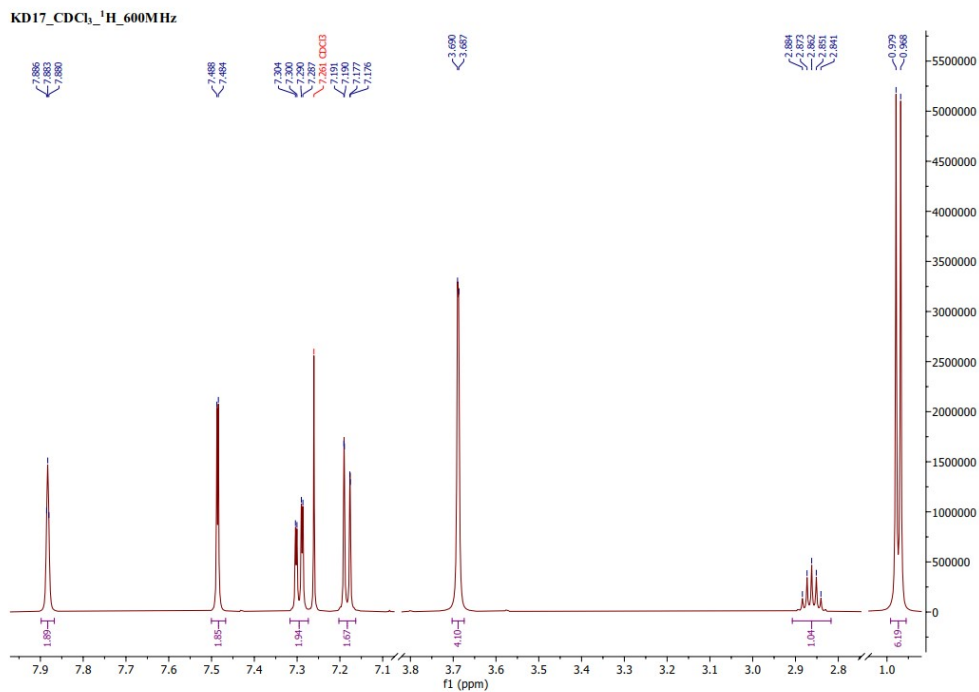
**Fig S11.**  $^{13}\text{C}$  NMR Spectrum of compound KD2d



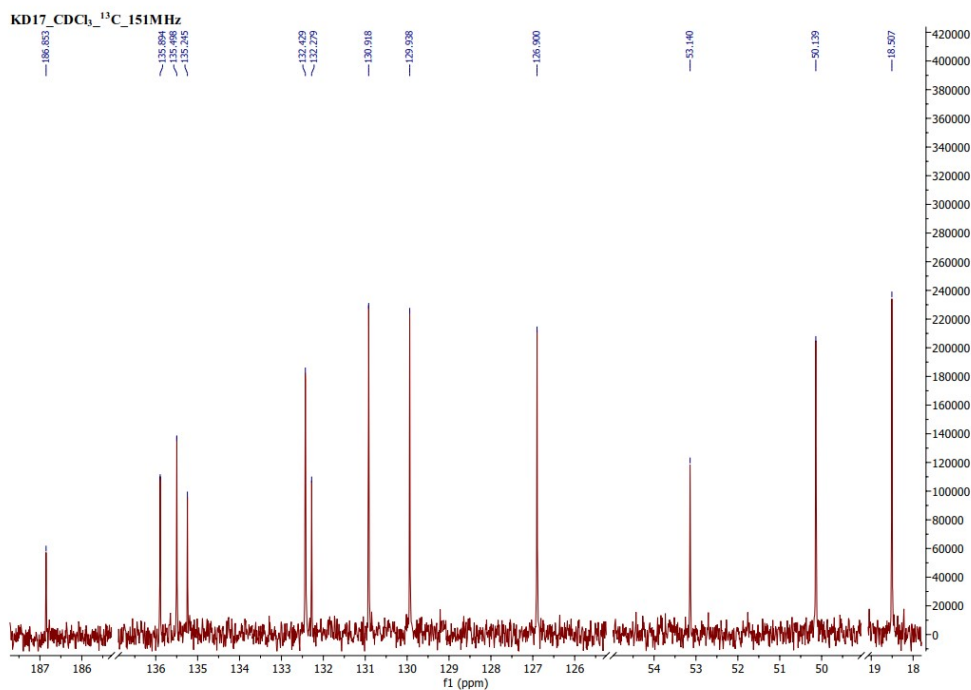
**Fig S12.** HR-MS spectrum of compound KD2d



**Fig S13.**  $^1\text{H}$  NMR Spectrum of compound KD2e



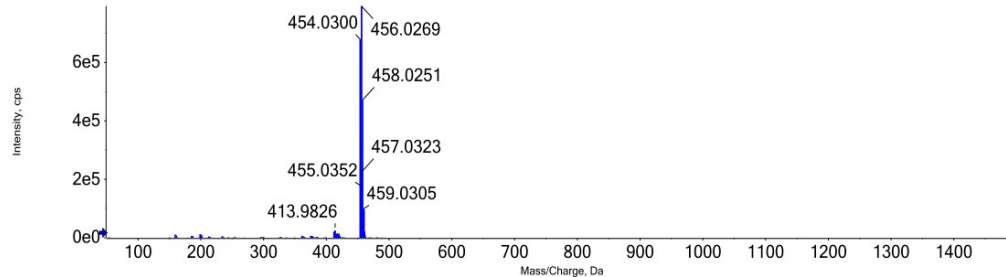
**Fig S14.**  $^{13}\text{C}$  NMR Spectrum of compound KD2e



### Fig S15. HR-MS Spectrum of compound KD2e

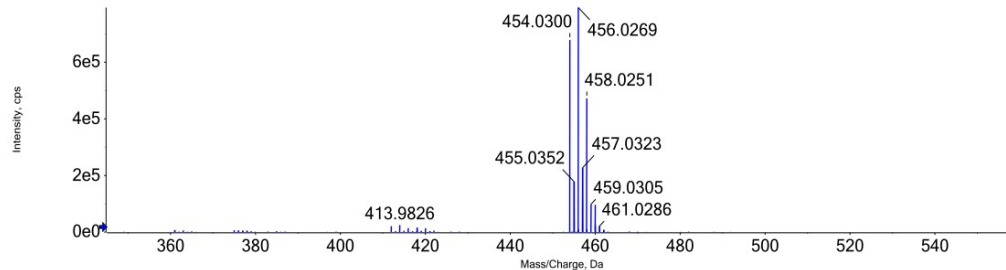
#### Full mass spectrum

Spectrum from KHOA\_KD17\_(+)ESI 2025-09-25-15-06-05.wiff2 (sample 1) - KHOA\_KD17\_(+)E... 0.139 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points)



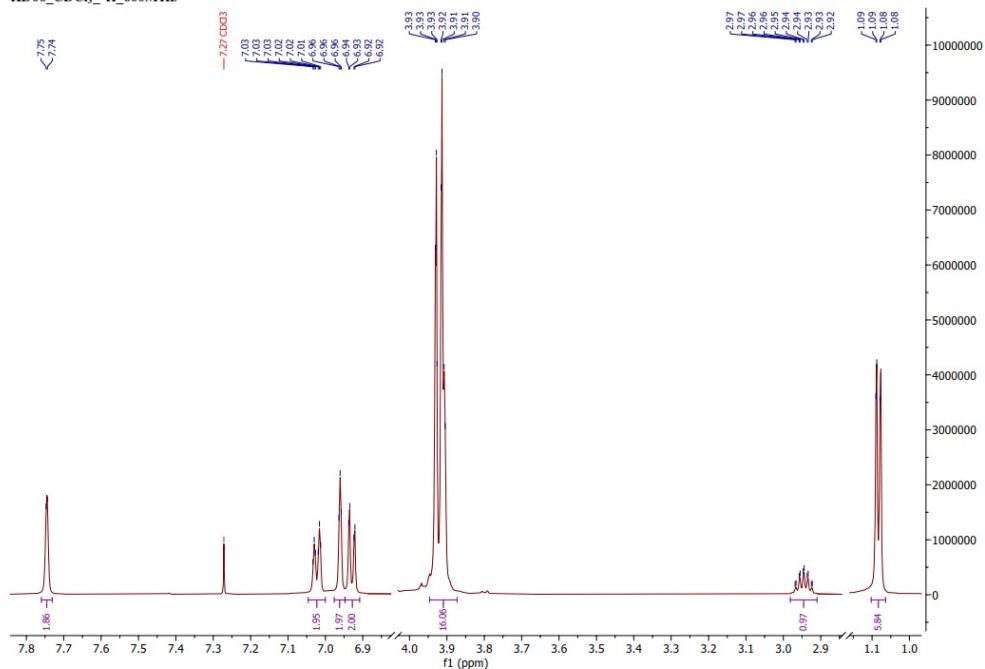
#### Expanded spectrum

Spectrum from KHOA\_KD17\_(+)ESI 2025-09-25-15-06-05.wiff2 (sample 1) - KHOA\_KD17\_(+)E... 0.139 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points)

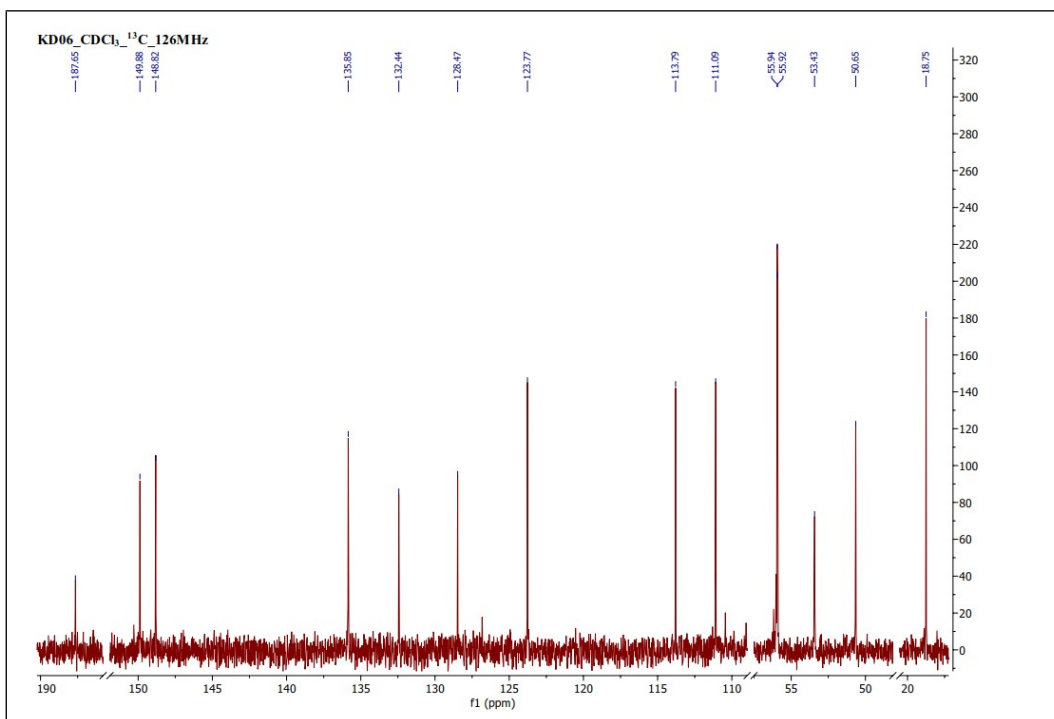


### Fig S16. <sup>1</sup>H NMR Spectrum of compound KD2f

KD06\_CDCl<sub>3</sub>\_1H\_600MHz



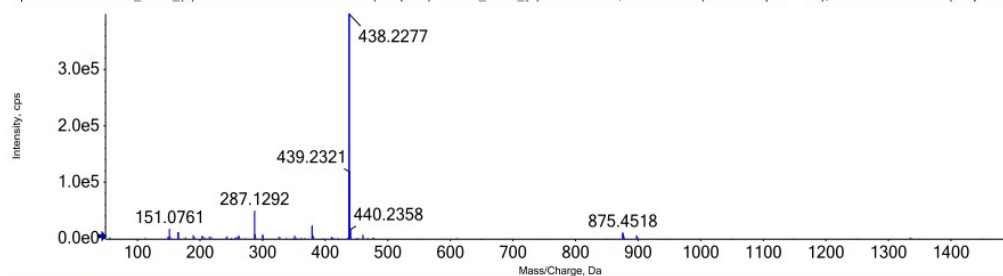
### Fig S17. <sup>13</sup>C NMR Spectrum of compound KD2f



**Fig S18. HR-MS spectrum of compound KD2f**

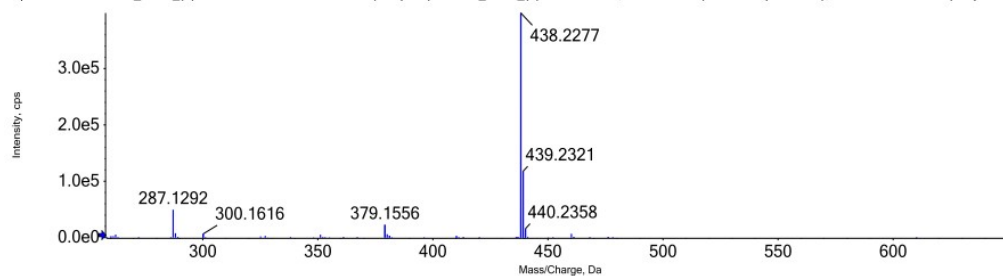
**Full mass spectrum**

Spectrum from KHOA\_KD06\_(+)ESI 2025-09-25-14-51-02.wiff2 (sample 1) - KHOA\_KD06\_(+)E... 0.143 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points)

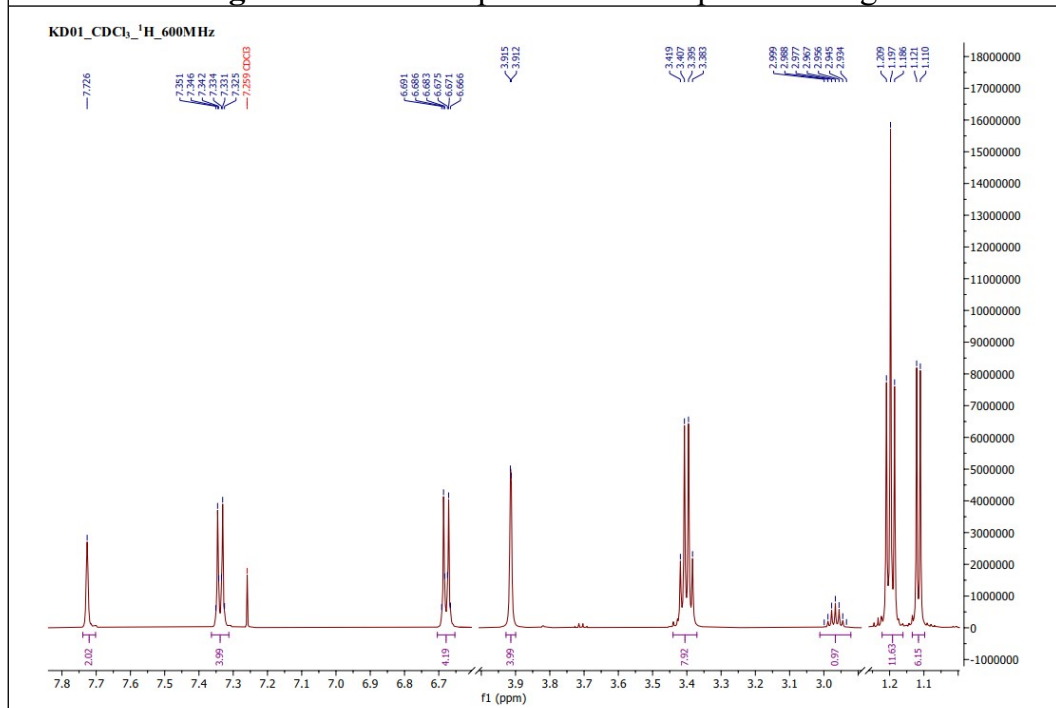


**Expanded spectrum**

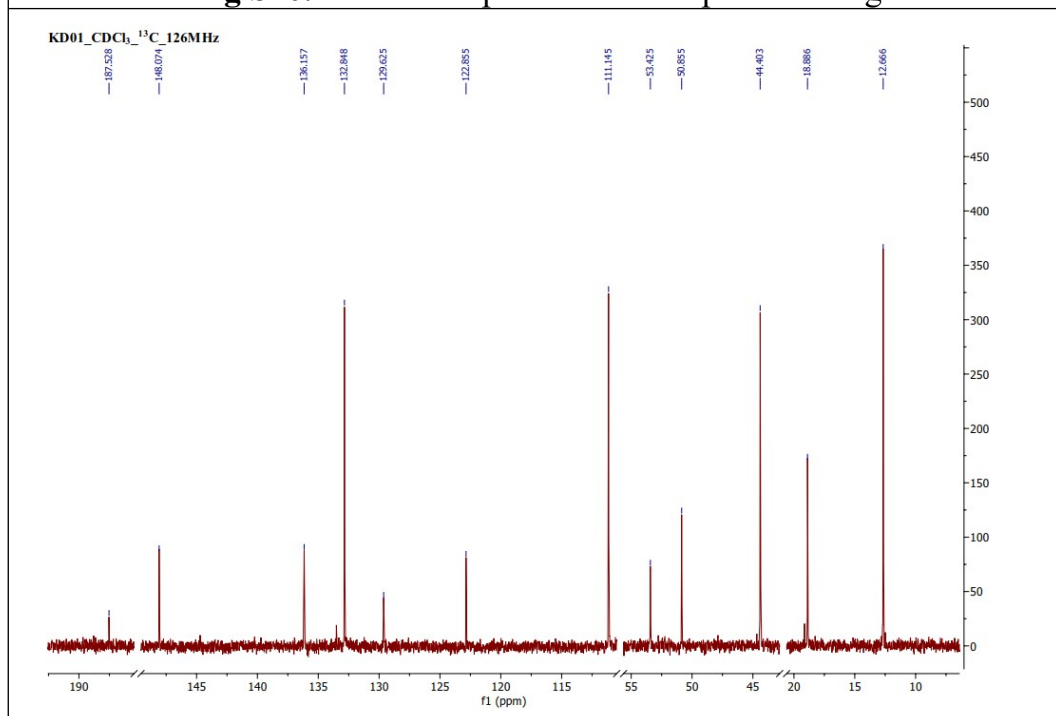
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**Fig S19.**  $^1\text{H}$  NMR Spectrum of compound KD2g



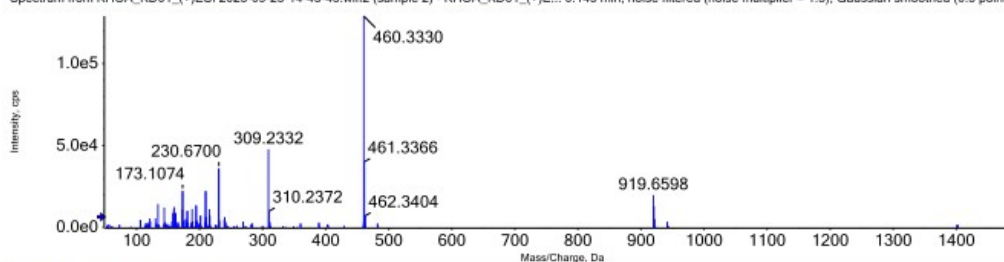
**Fig S20.**  $^{13}\text{C}$  NMR Spectrum of compound KD2g



**Fig S21. HR-MS spectrum of compound KD2g**

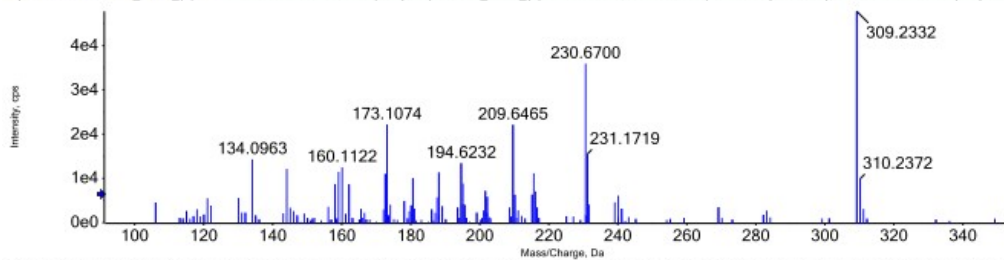
**Full mass spectrum**

Spectrum from KHOA\_KD01\_(+)ESI 2025-09-25-14-43-43.wiff2 (sample 2) - KHOA\_KD01\_(+)E... 0.143 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points)

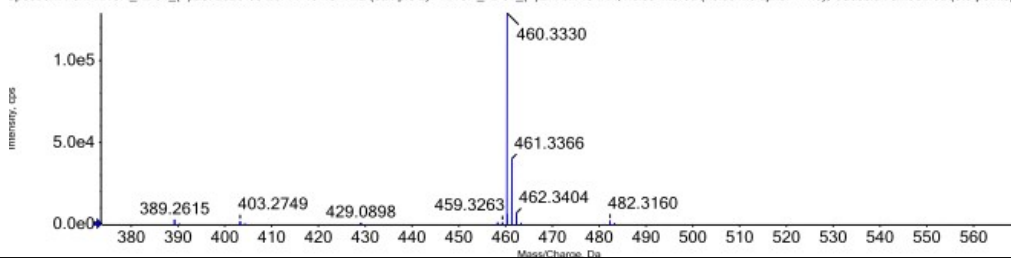


**Expanded spectrum**

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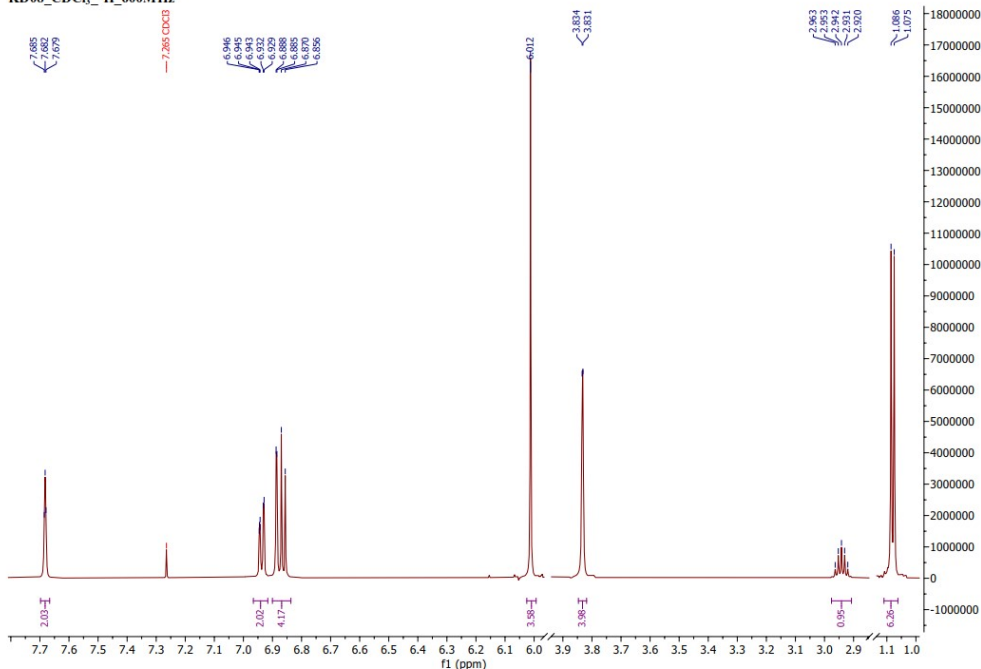


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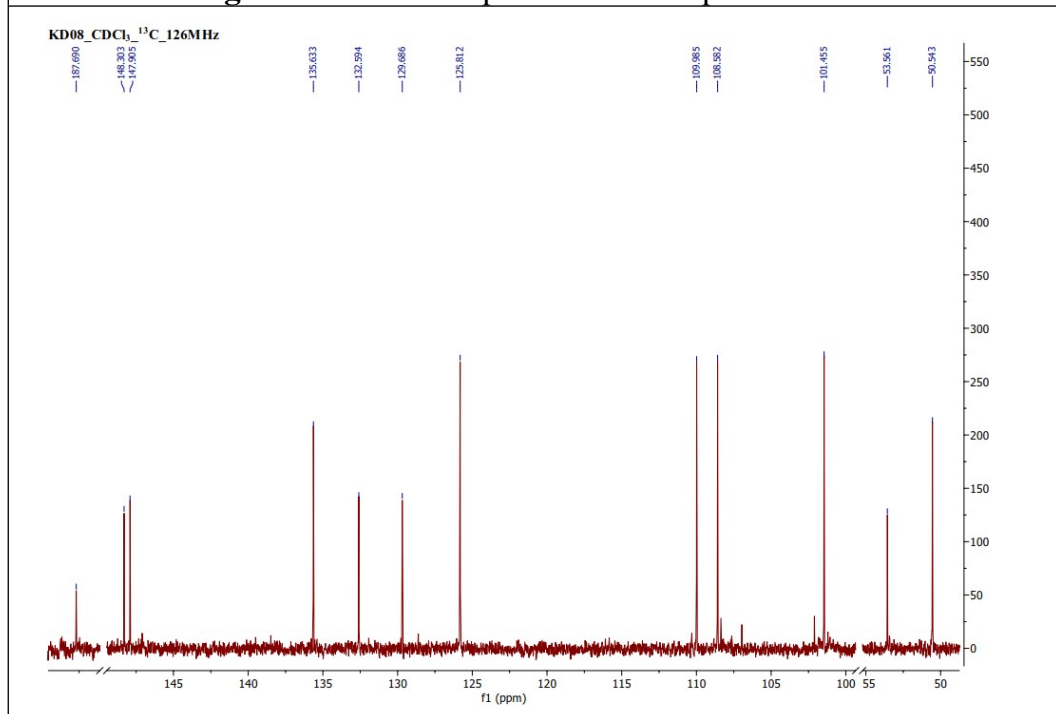


**Fig S22. <sup>1</sup>H NMR Spectrum of compound KD2h**

KD08\_CDCl<sub>3</sub>\_1H\_600MHz



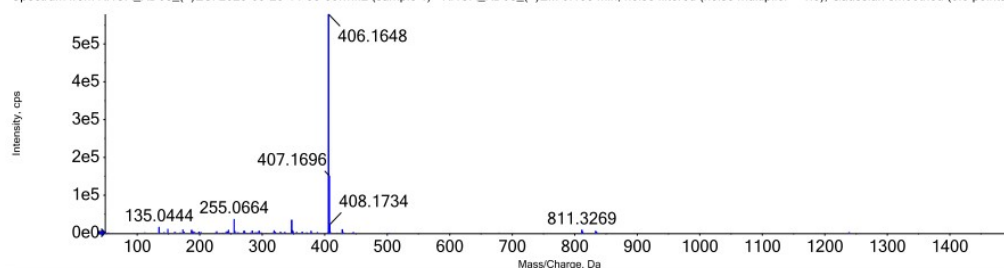
**Fig S23.**  $^{13}\text{C}$  NMR Spectrum of compound KD2h



**Fig S24.** HR-MS spectrum of compound KD2h

**Full mass spectrum**

Spectrum from KHOA\_KD08\_(+)ESI 2025-09-25-14-53-59.wiff2 (sample 1) - KHOA\_KD08\_(+)E... 0.153 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points)



**Expanded spectrum**

Spectrum from KHOA\_KD08\_(+)ESI 2025-09-25-14-53-59.wiff2 (sample 1) - KHOA\_KD08\_(+)E... 0.153 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points)

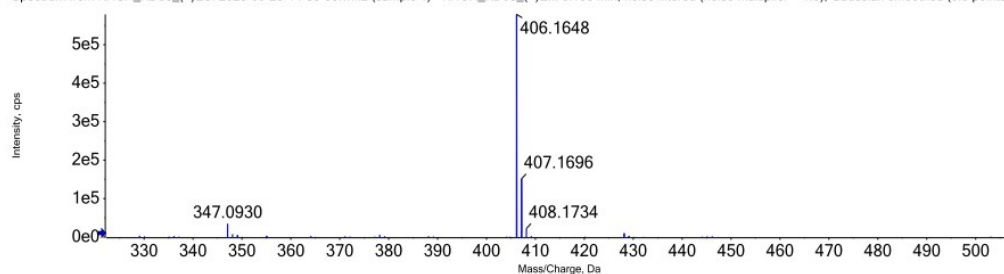


Fig S25. <sup>1</sup>H NMR Spectrum of compound KD2i

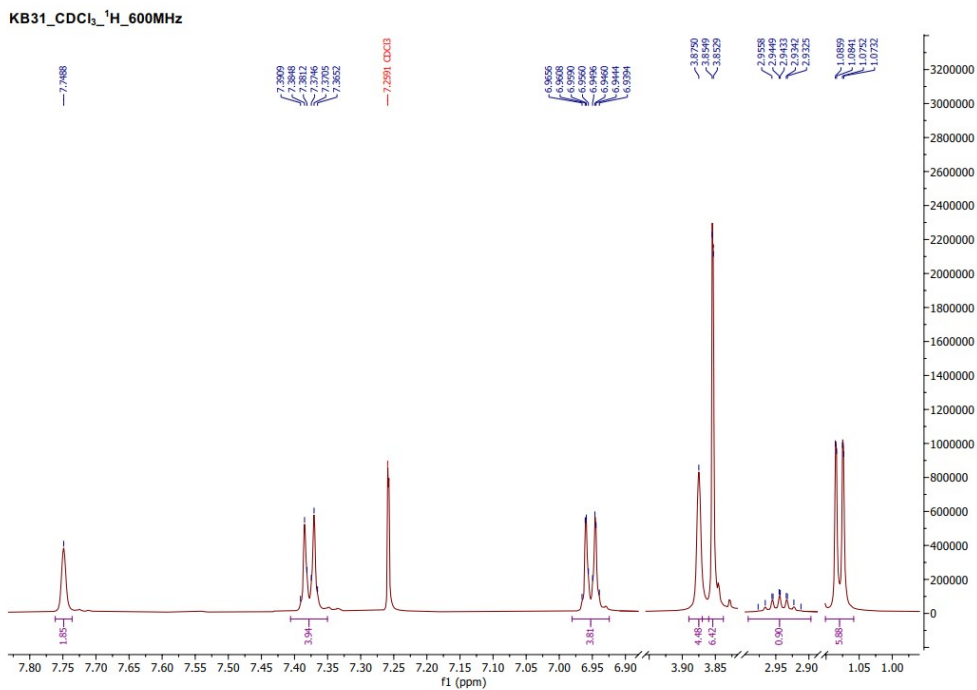
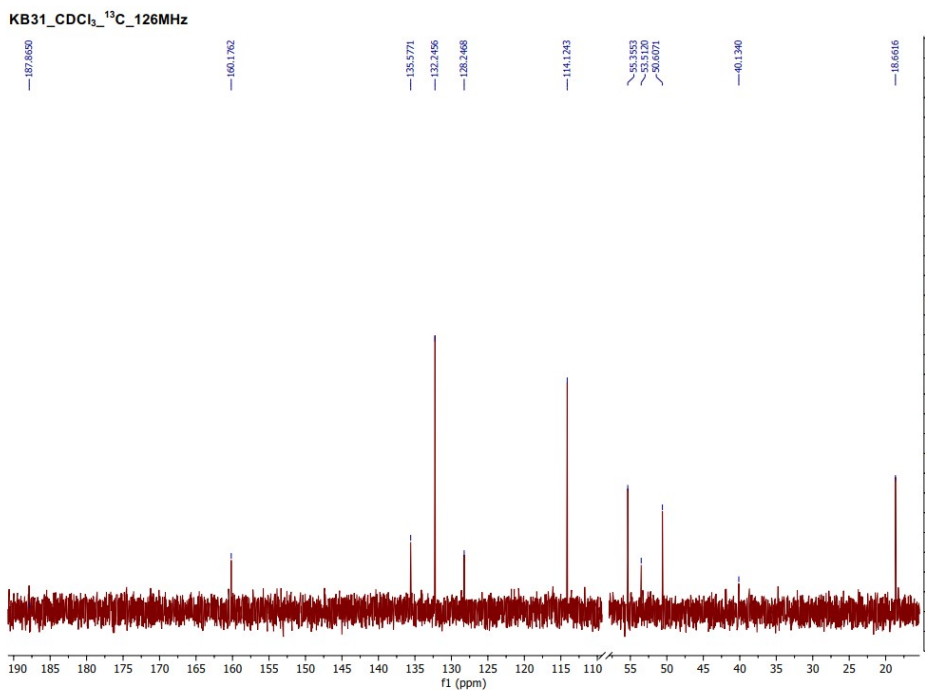


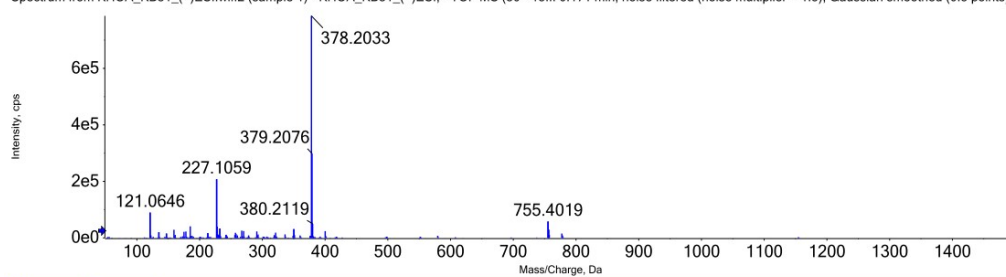
Fig S26. <sup>13</sup>C NMR Spectrum of compound KD2i



### Fig S27. HR-MS spectrum of compound KD2i

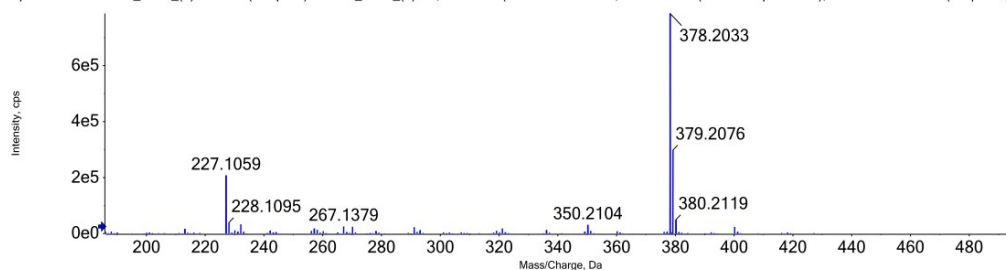
#### Full mass spectrum

Spectrum from KHOA\_KB31\_(+)ESI.wiff2 (sample 1) - KHOA\_KB31\_(+)ESI, +TOF MS (50 - 15... 0.171 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points))



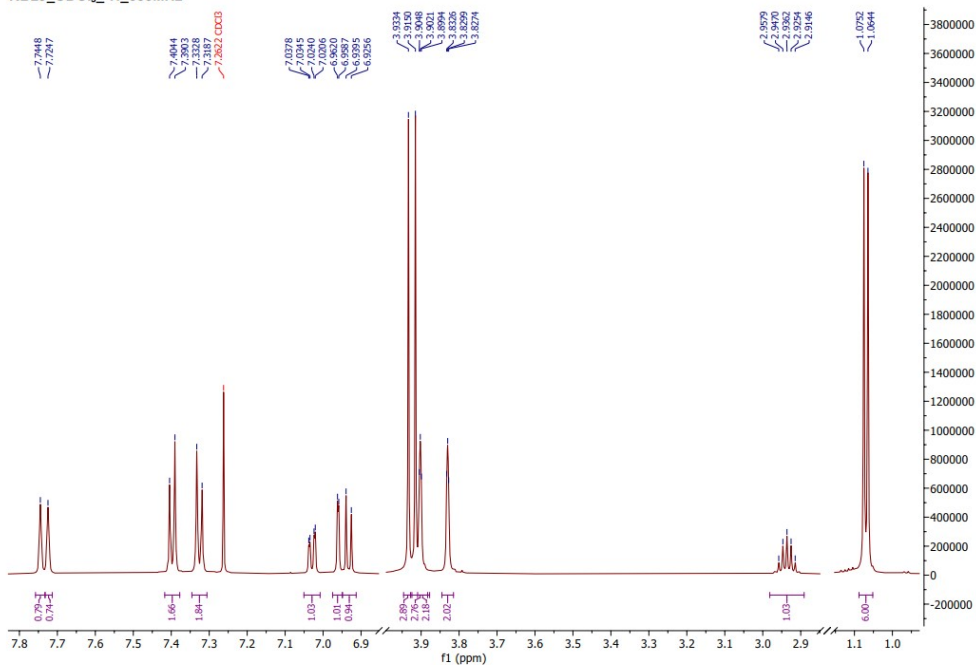
#### Expanded spectrum

Spectrum from KHOA\_KB31\_(+)ESI.wiff2 (sample 1) - KHOA\_KB31\_(+)ESI, +TOF MS (50 - 15... 0.171 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points))

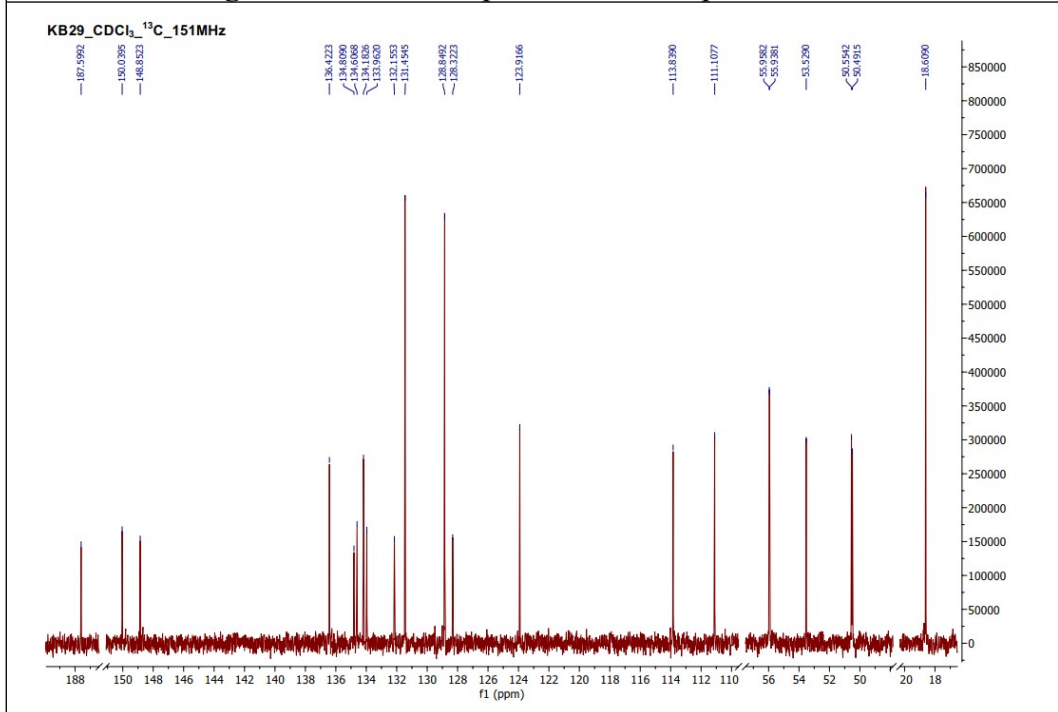


### Fig S28. <sup>1</sup>H NMR Spectrum of compound KB2a

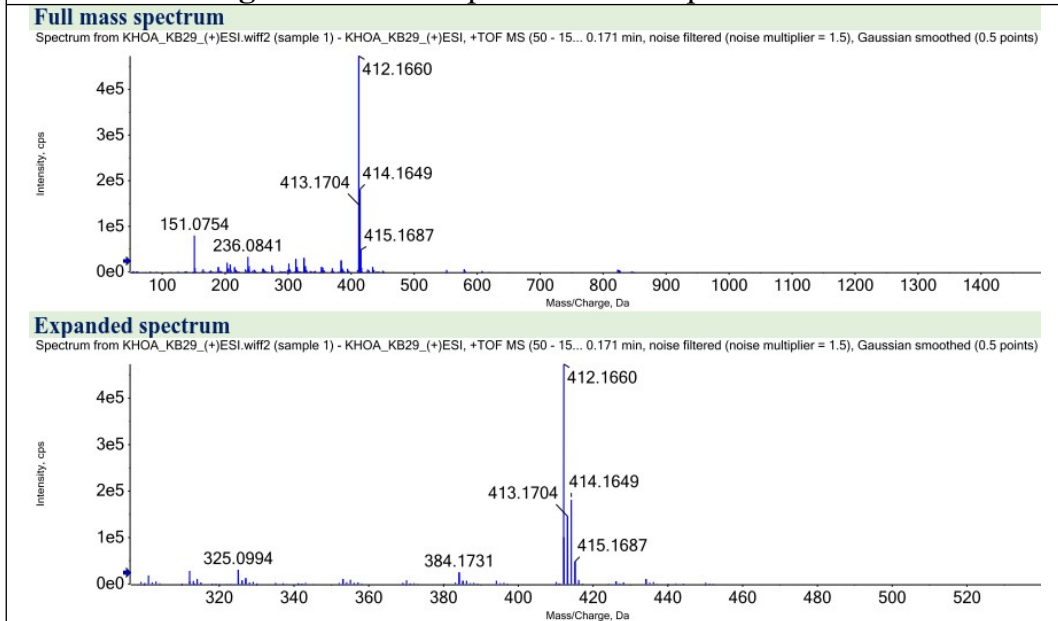
KB29\_CDCl<sub>3</sub>\_1H\_600MHz



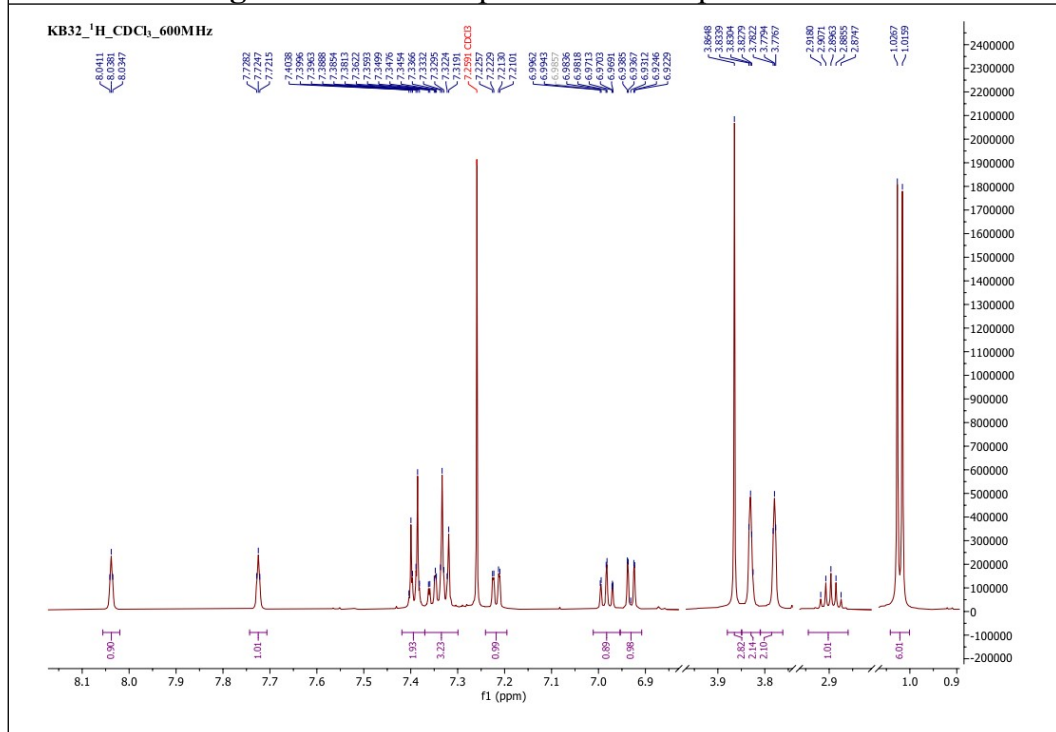
**Fig S29.**  $^{13}\text{C}$  NMR Spectrum of compound KB2a



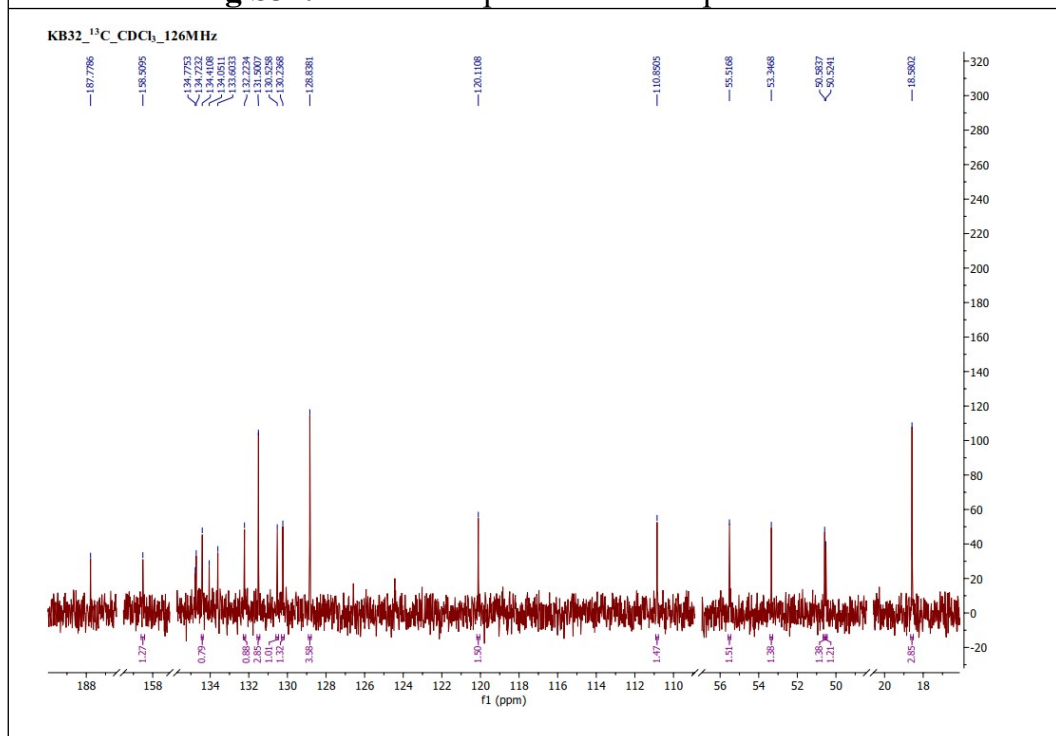
**Fig S30.** HR-MS spectrum of compound KB2a



**Fig S31.**  $^1\text{H}$  NMR Spectrum of compound KB2b



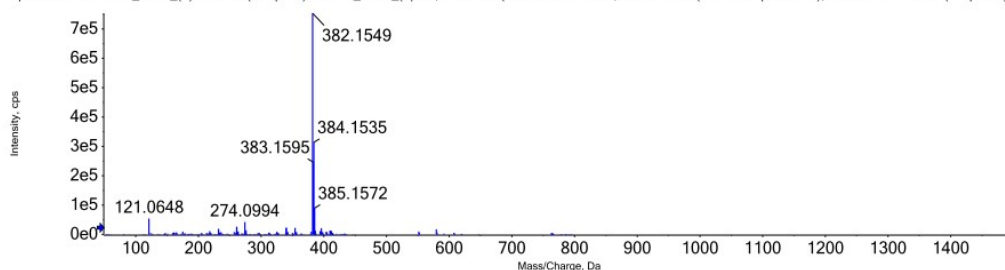
**Fig S32.**  $^{13}\text{C}$  NMR Spectrum of compound KB2b



**Fig S33. HR-MS spectrum of compound KB2b**

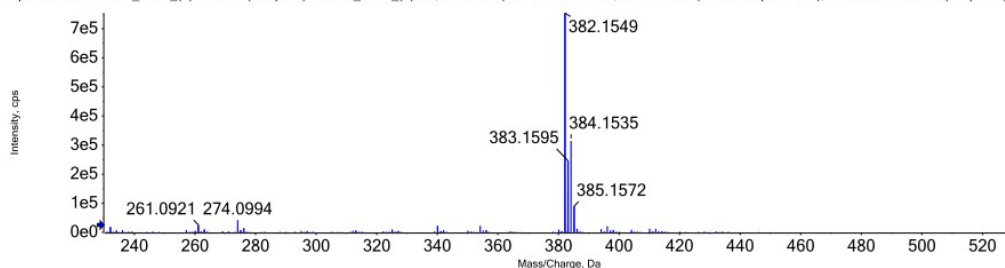
**Full mass spectrum**

Spectrum from KHOA\_KB32\_(+)ESI.wiff2 (sample 1) - KHOA\_KB32\_(+)ESI, +TOF MS (50 - 15... 0.171 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points))



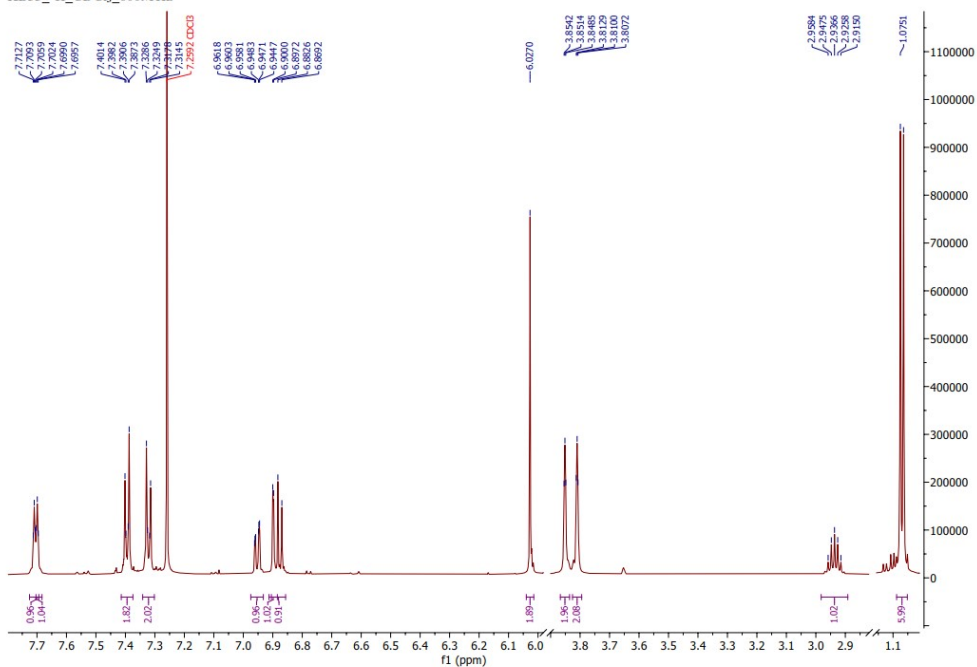
**Expanded spectrum**

Spectrum from KHOA\_KB32\_(+)ESI.wiff2 (sample 1) - KHOA\_KB32\_(+)ESI, +TOF MS (50 - 15... 0.171 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points))

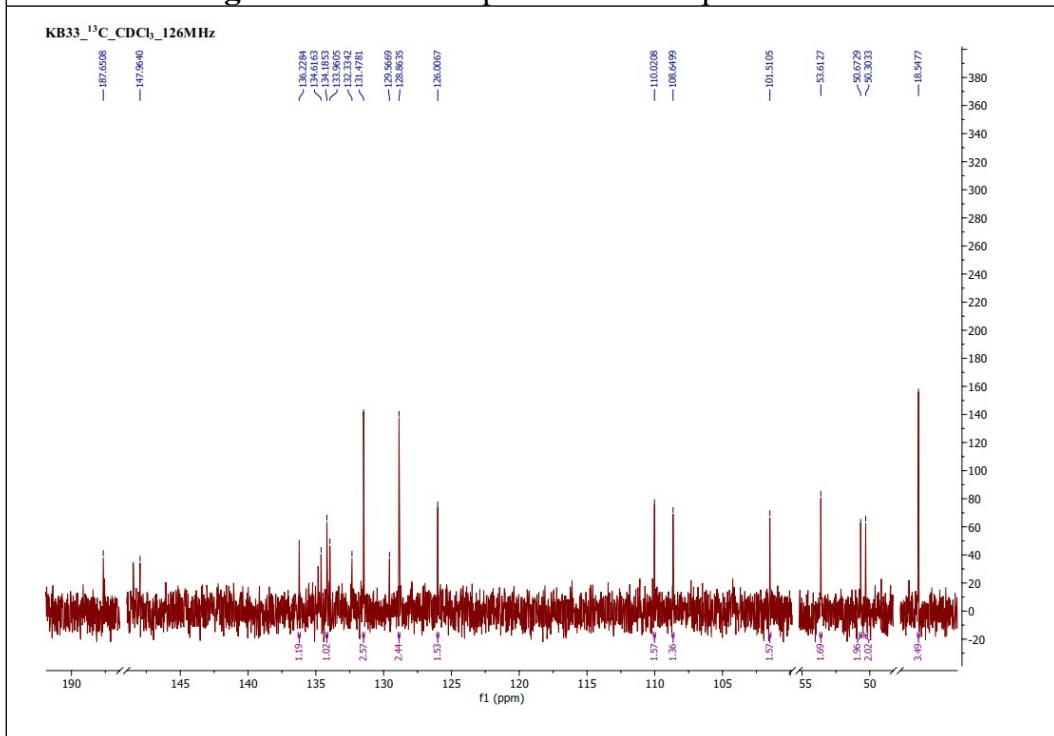


**Fig S34. <sup>1</sup>H NMR Spectrum of compound KB2c**

KB33\_1H\_CDCl3\_600MHz



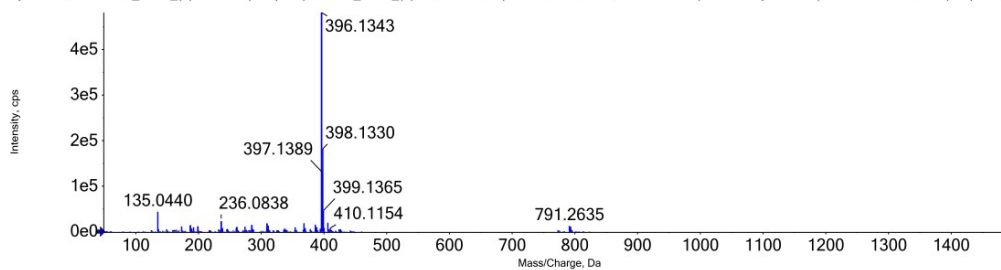
**Fig S35.**  $^{13}\text{C}$  NMR Spectrum of compound KB2c



**Fig S36.** HR-MS spectrum of compound KB2c

**Full mass spectrum**

Spectrum from KHOA\_KB33\_(+)ESI.wiff2 (sample 1) - KHOA\_KB33\_(+)ESI, +TOF MS (50 - 15... 0.171 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points))



**Expanded spectrum**

Spectrum from KHOA\_KB33\_(+)ESI.wiff2 (sample 1) - KHOA\_KB33\_(+)ESI, +TOF MS (50 - 15... 0.171 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points))

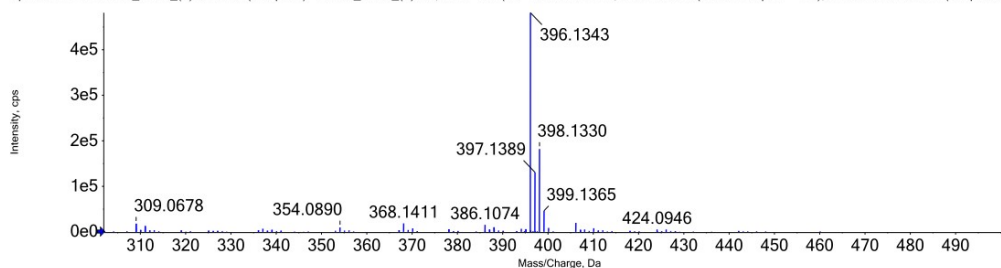


Fig S37. <sup>1</sup>H NMR Spectrum of compound KB2d

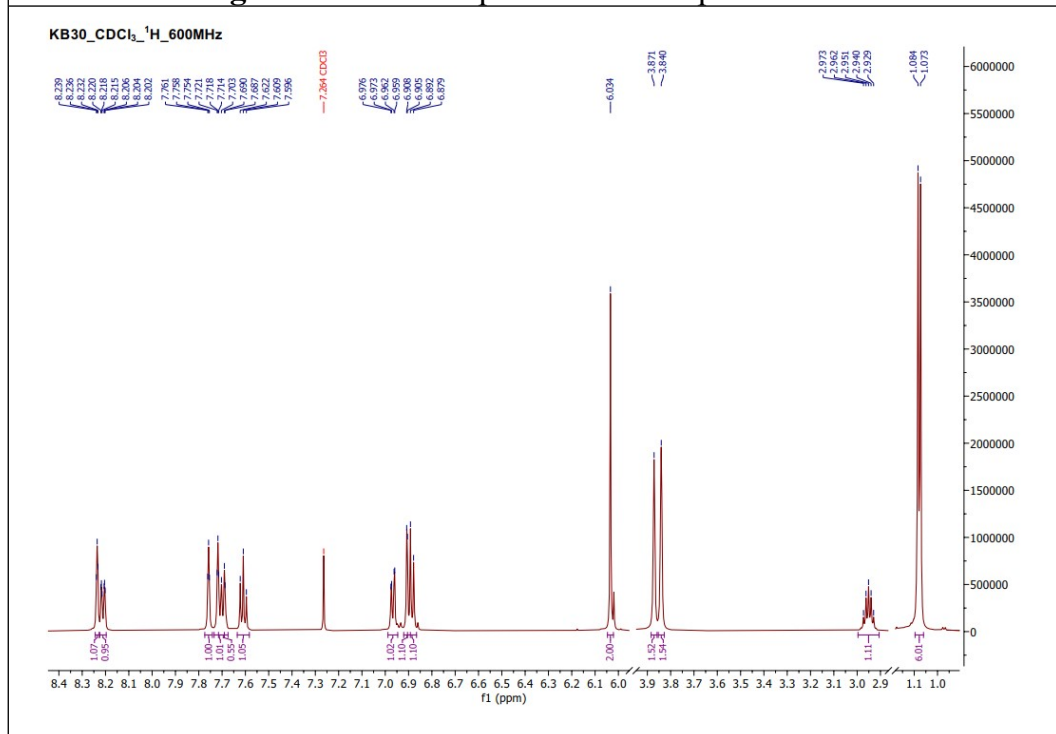
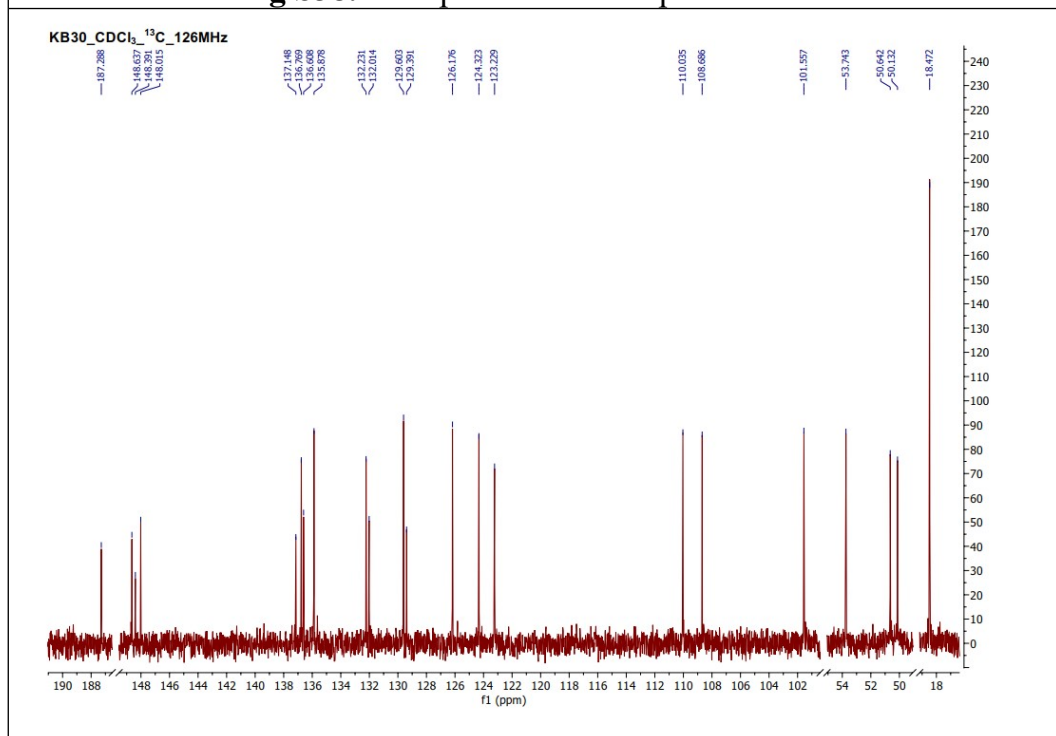


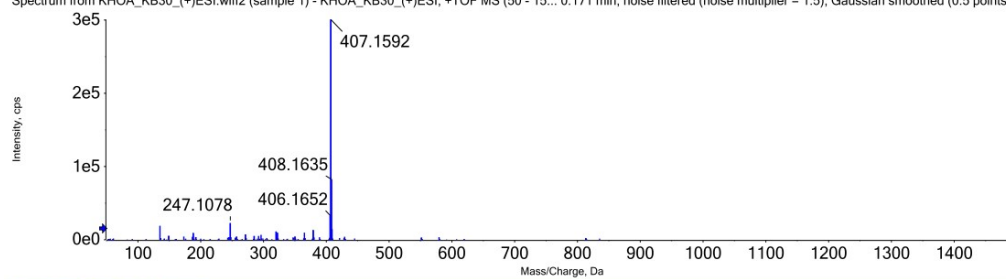
Fig S38. <sup>13</sup>C Spectrum of compound KB2d



## Fig S39. HR-MS spectrum of compound KB2d

### Full mass spectrum

Spectrum from KHOA\_KB30\_(+)ESI.wiff2 (sample 1) - KHOA\_KB30\_(+)ESI, +TOF MS (50 - 15... 0.171 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points))



### Expanded spectrum

Spectrum from KHOA\_KB30\_(+)ESI.wiff2 (sample 1) - KHOA\_KB30\_(+)ESI, +TOF MS (50 - 15... 0.171 min, noise filtered (noise multiplier = 1.5), Gaussian smoothed (0.5 points))

