

Supporting Information

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Synthesis of new analogs of morpholine and their antiplasmodial evaluation against human malaria parasite *Plasmodium falciparum*

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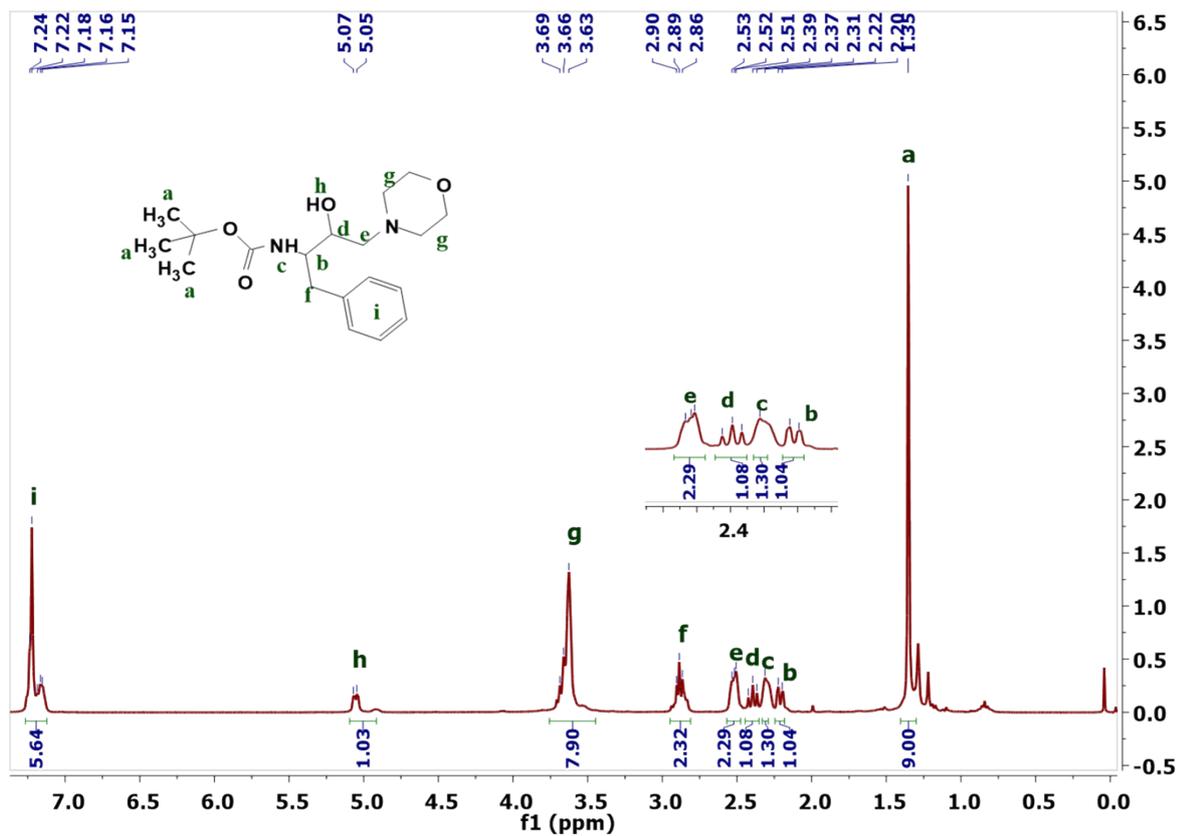


Figure S1. ^1H NMR spectrum of 3.

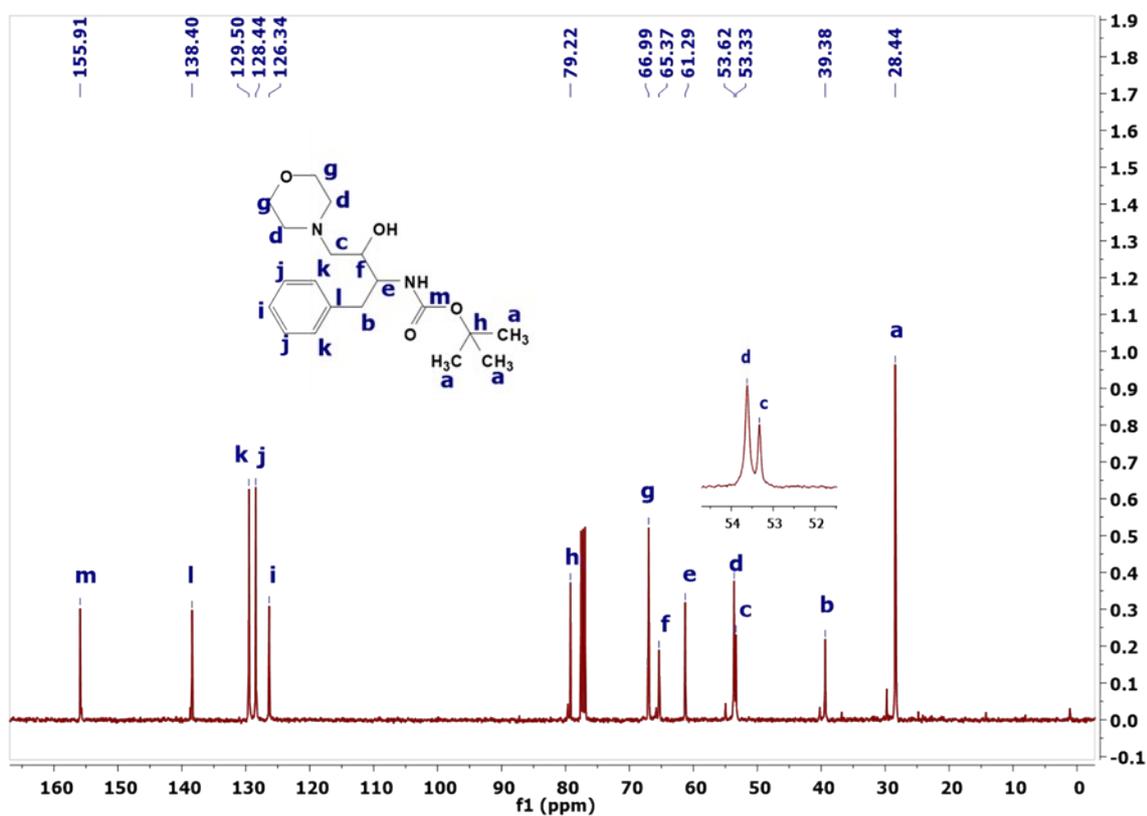
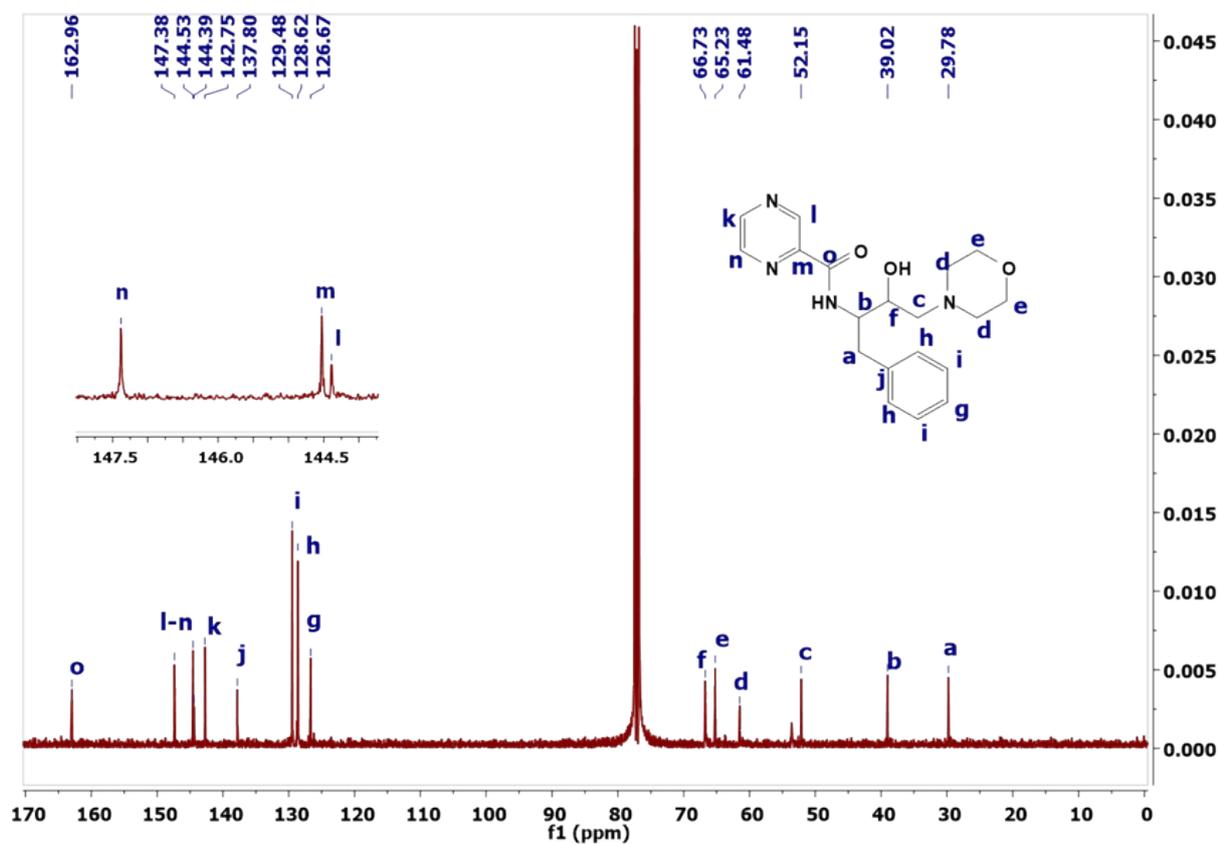
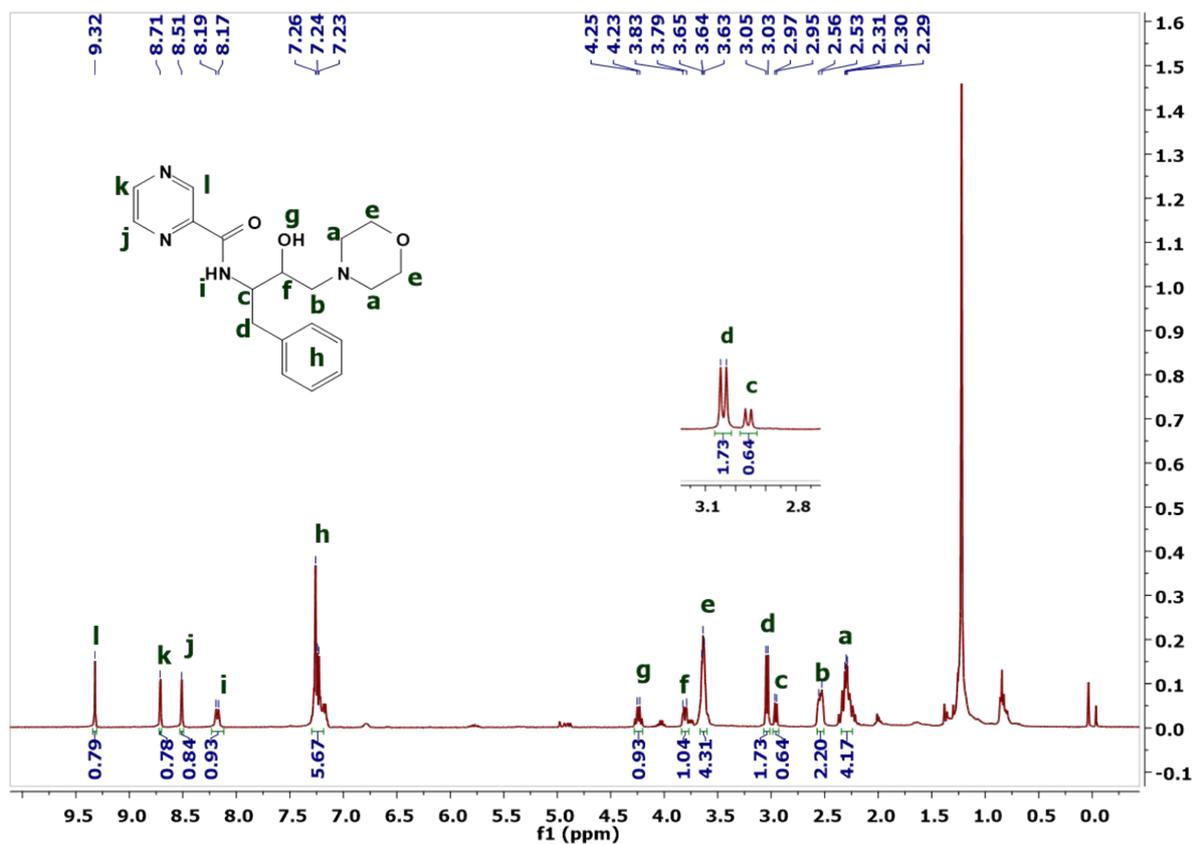


Figure S2. ^{13}C NMR spectrum of 3.



Supporting Information

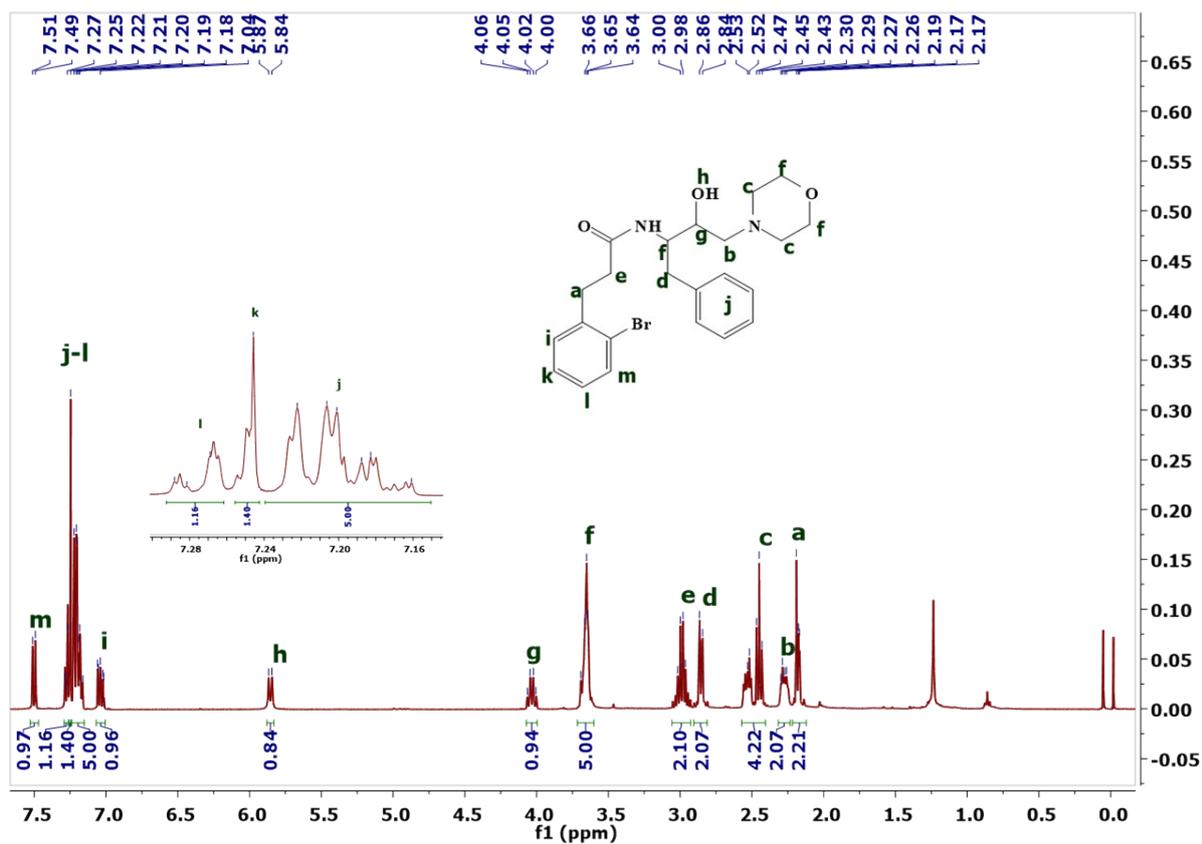


Figure S5. ^1H NMR spectrum of 6b.

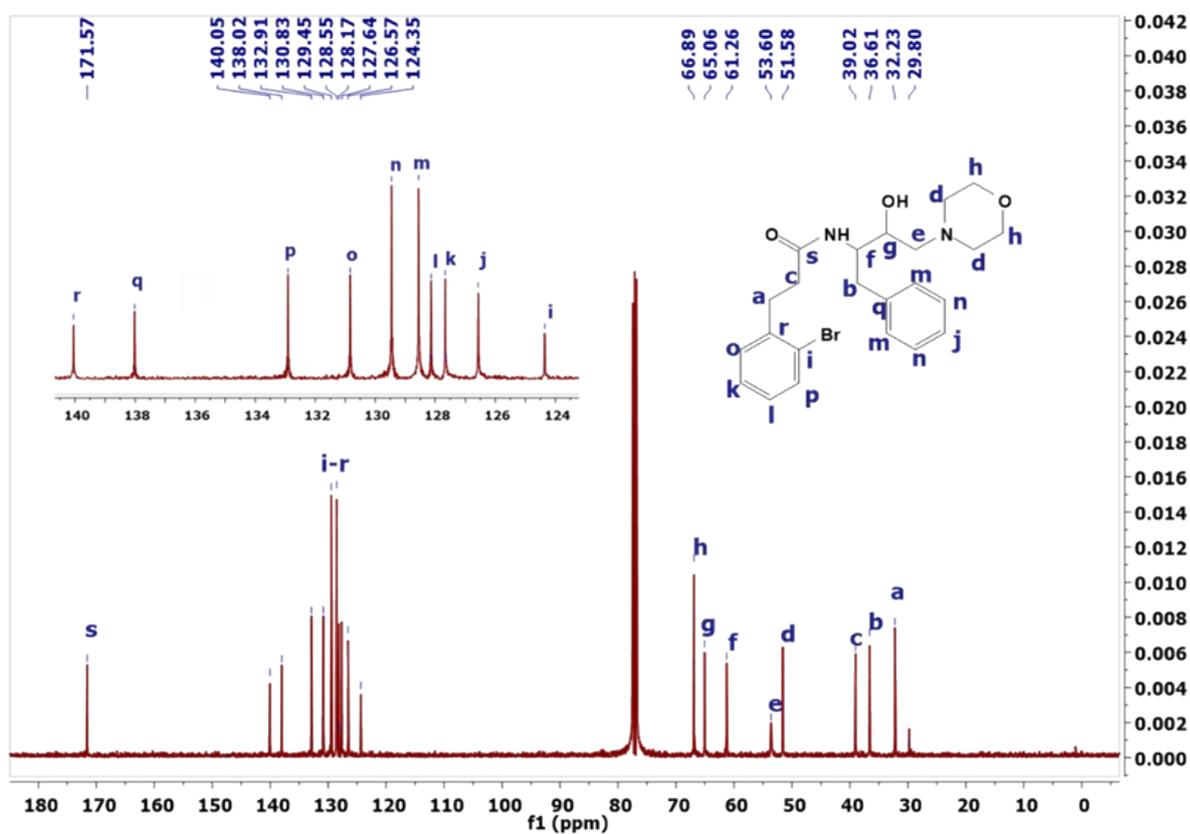


Figure S6. ^{13}C NMR spectrum of 6b.

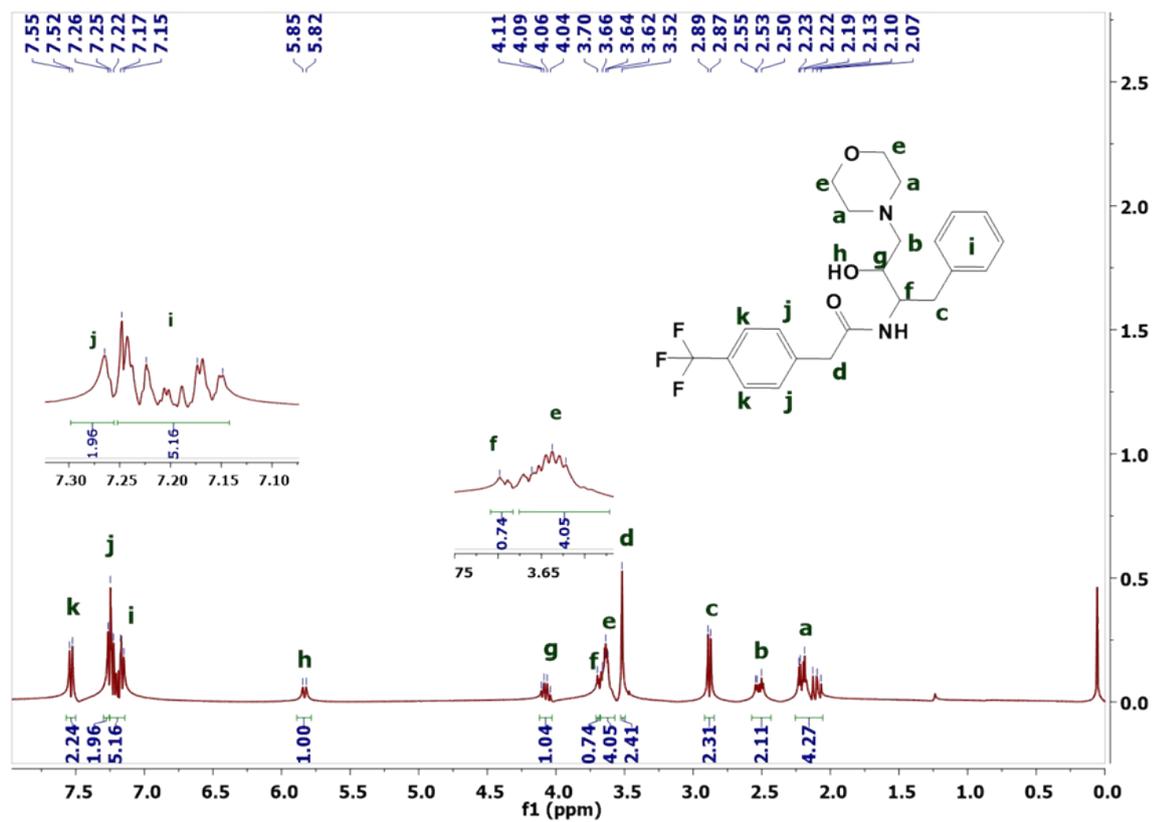


Figure S7. ^1H NMR spectrum of **6c**.

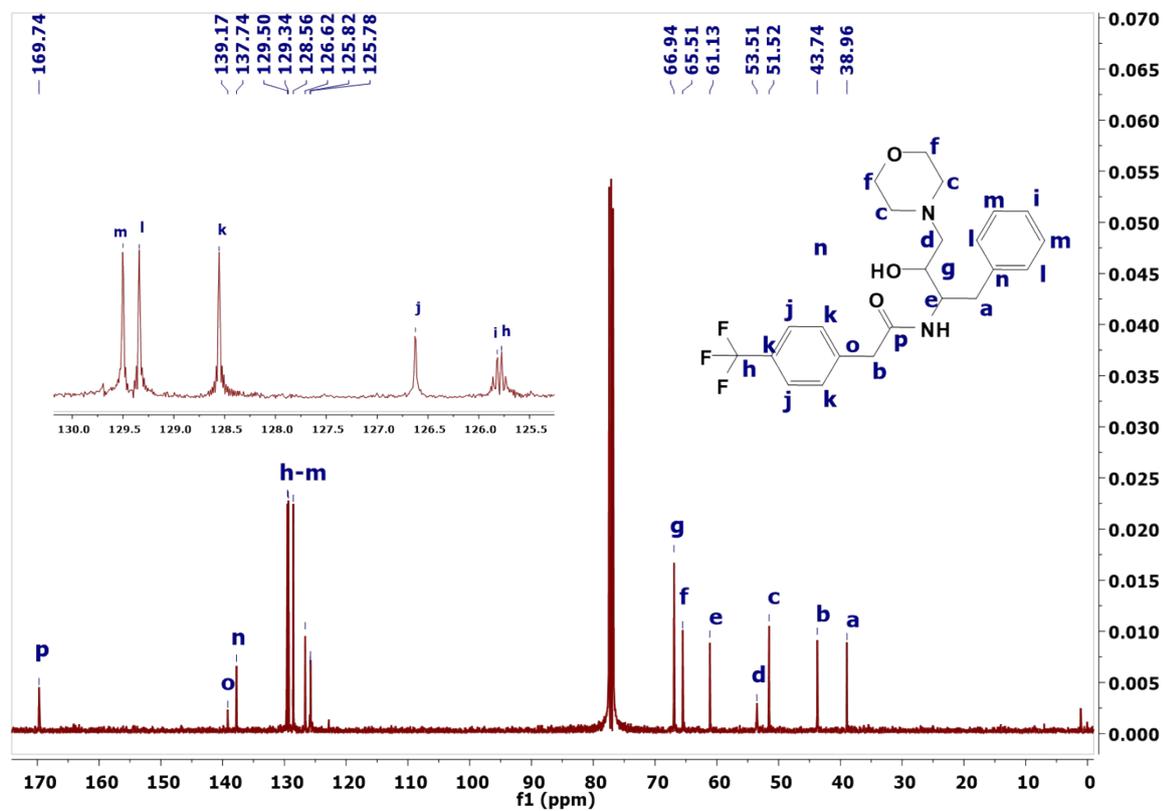
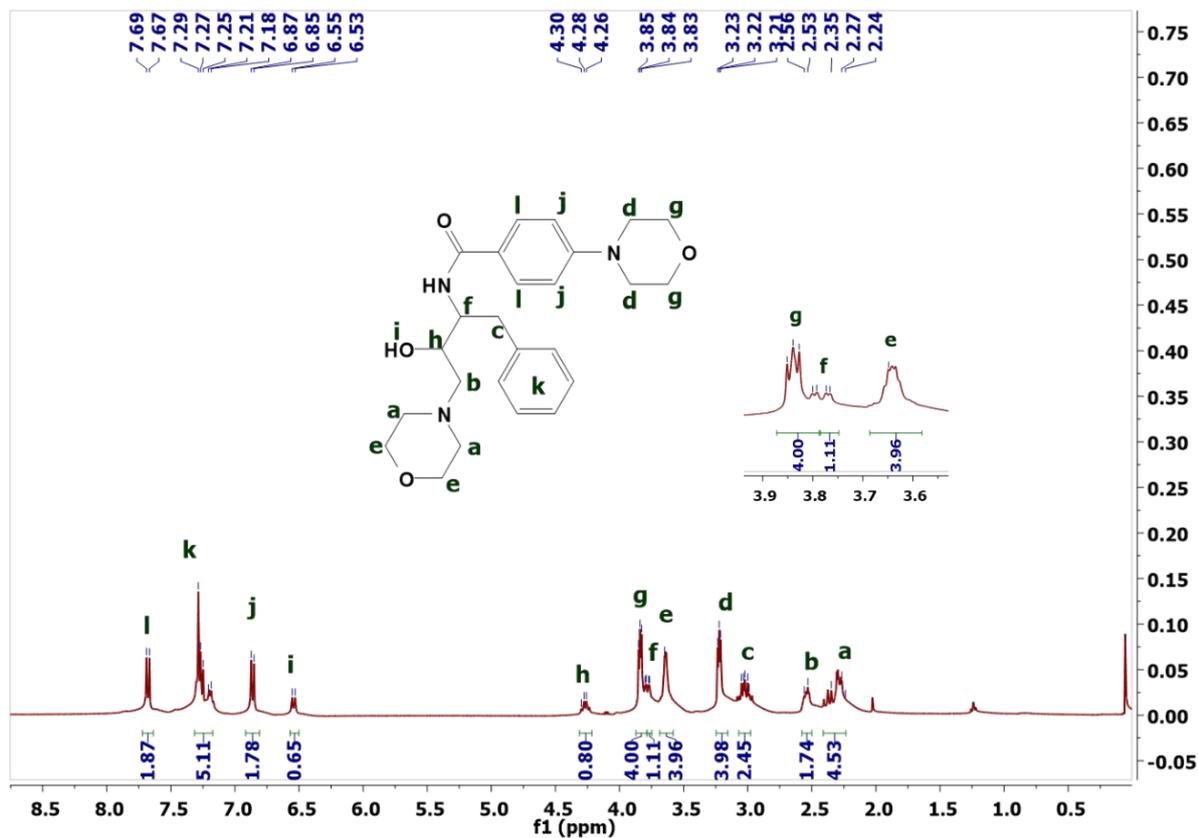
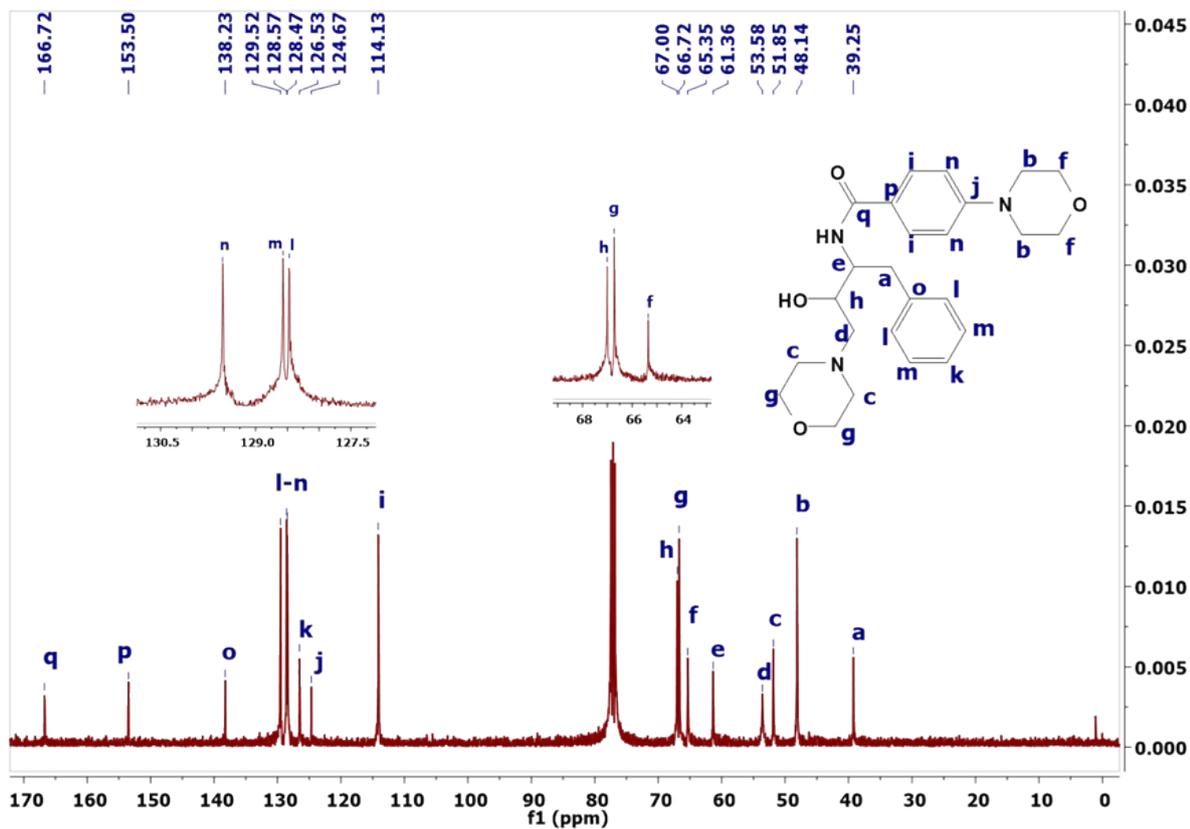
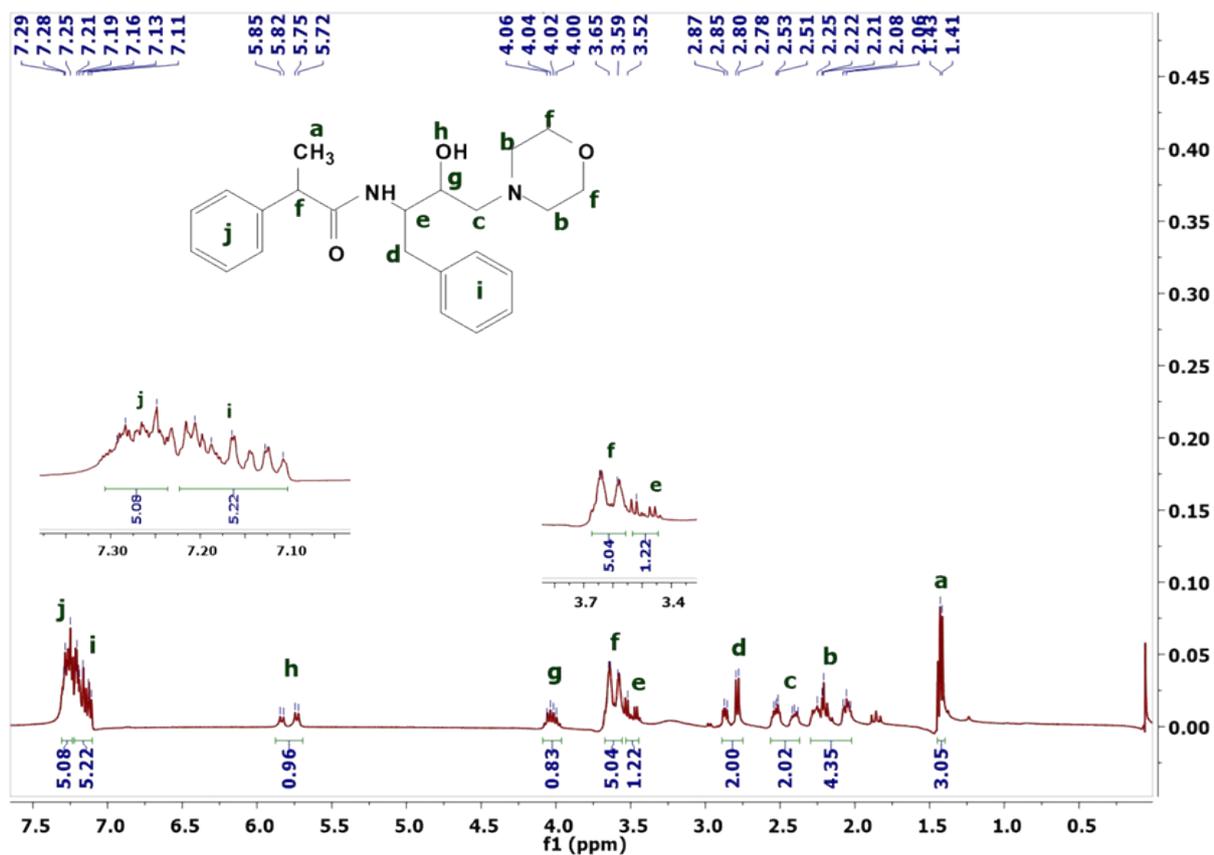
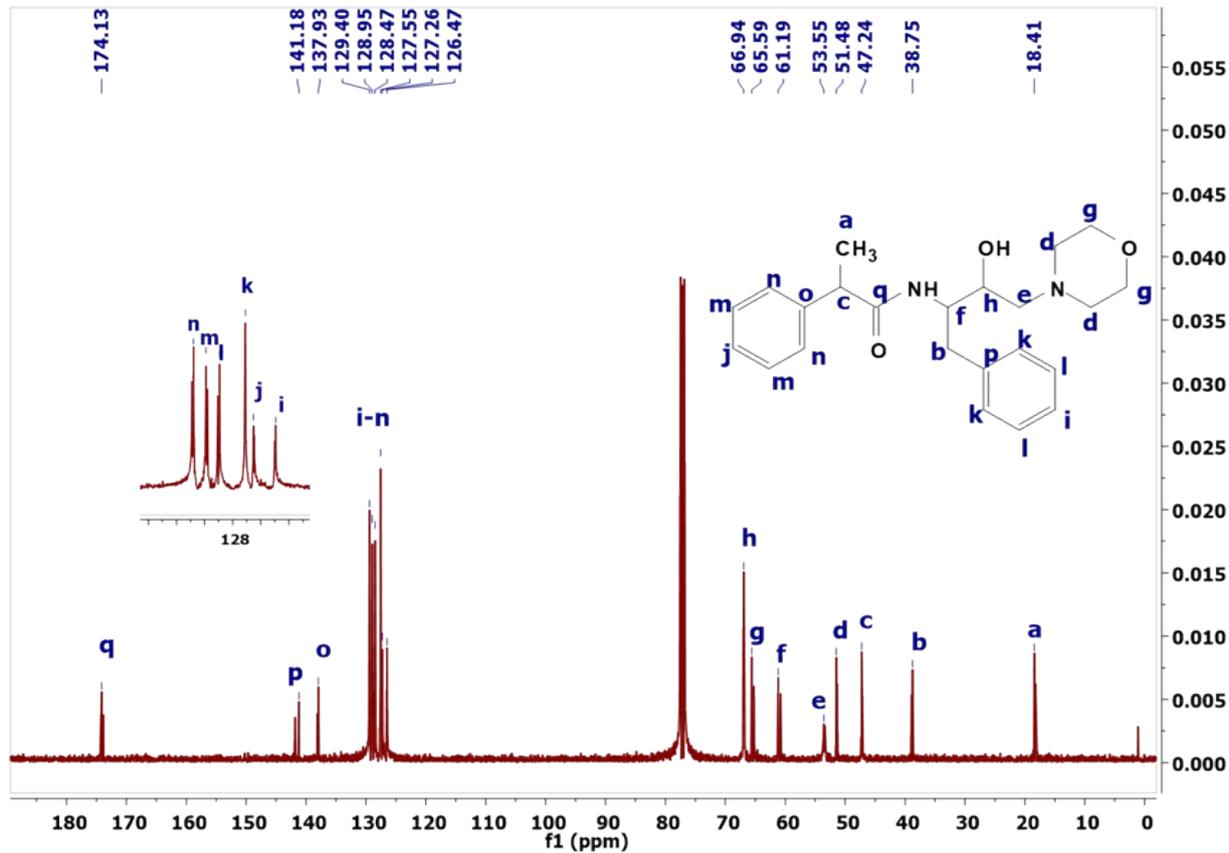


Figure S8. ^{13}C NMR spectrum of **6c**.

Figure S9. ¹H NMR spectrum of 6d.Figure S10. ¹³C NMR spectrum of 6d.

Figure S11. ¹H NMR spectrum of 6e.Figure S12. ¹³C NMR spectrum of 6e.

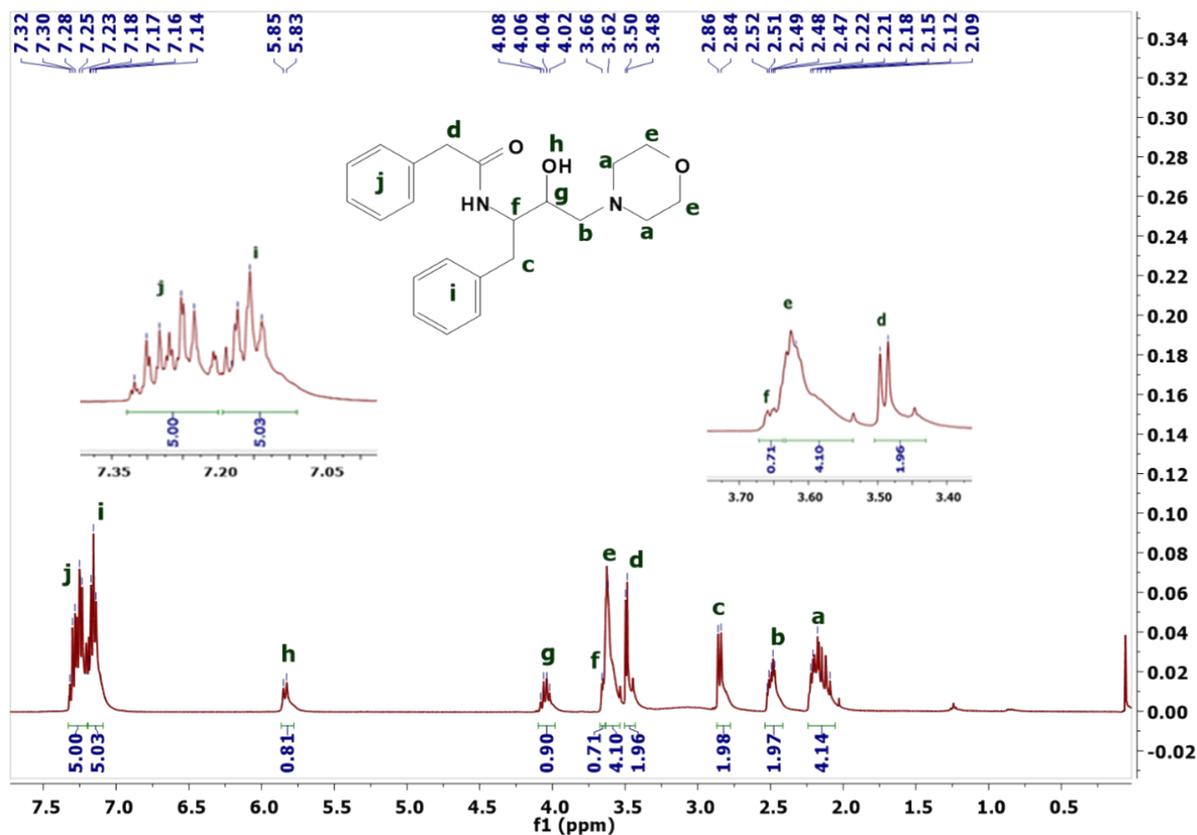


Figure S13. ^1H NMR spectrum of 6f.

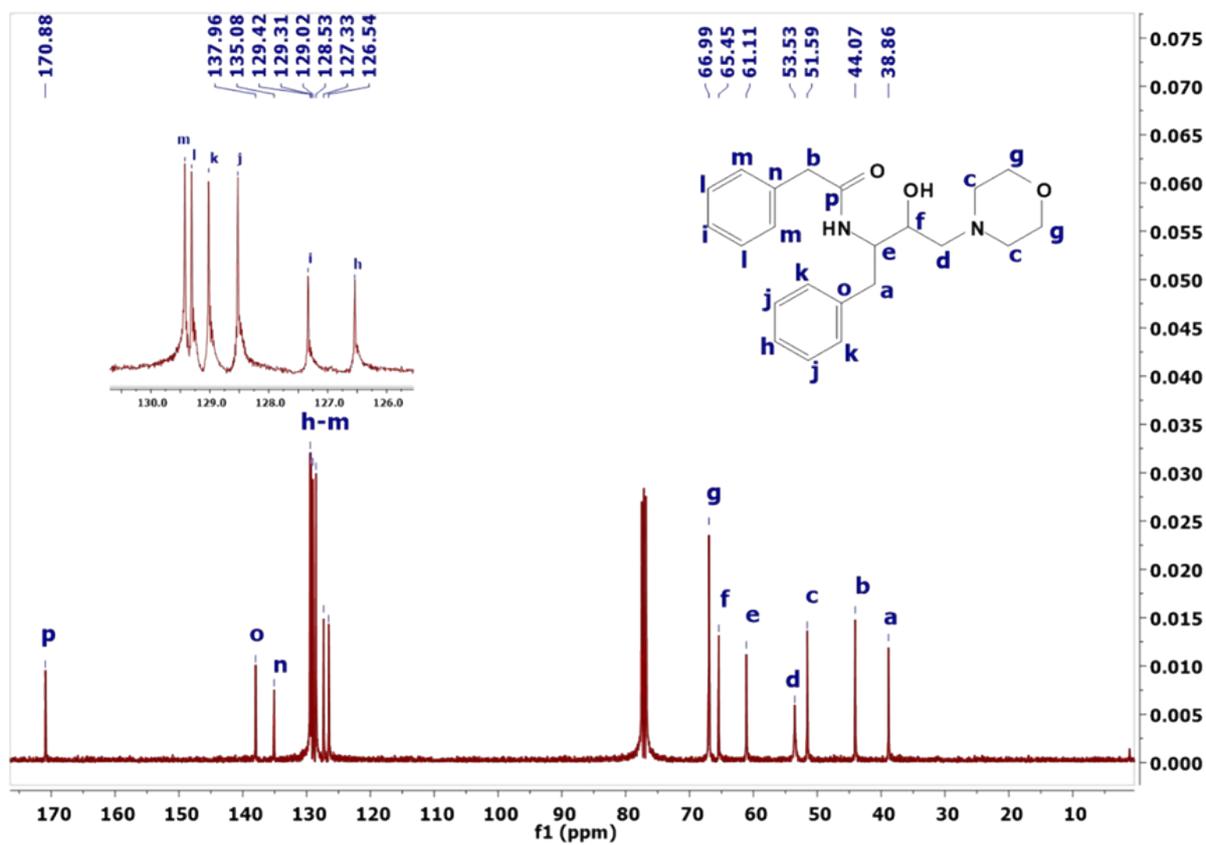
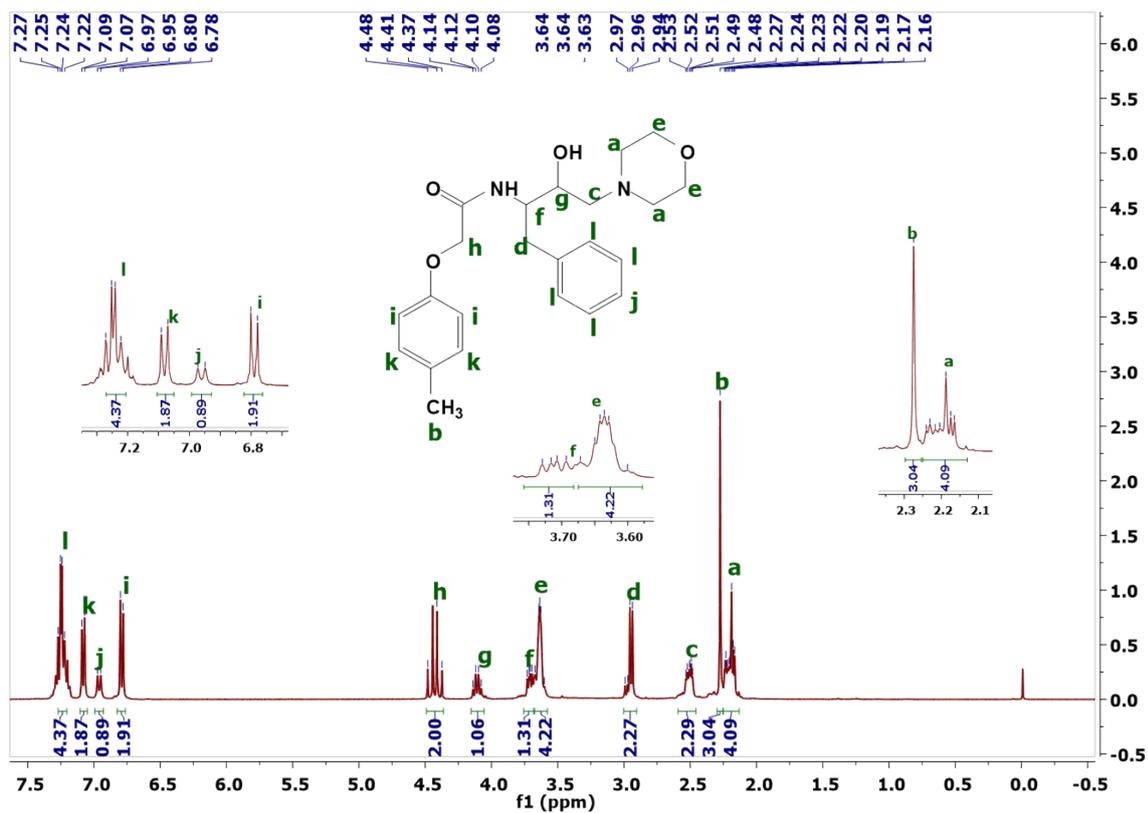
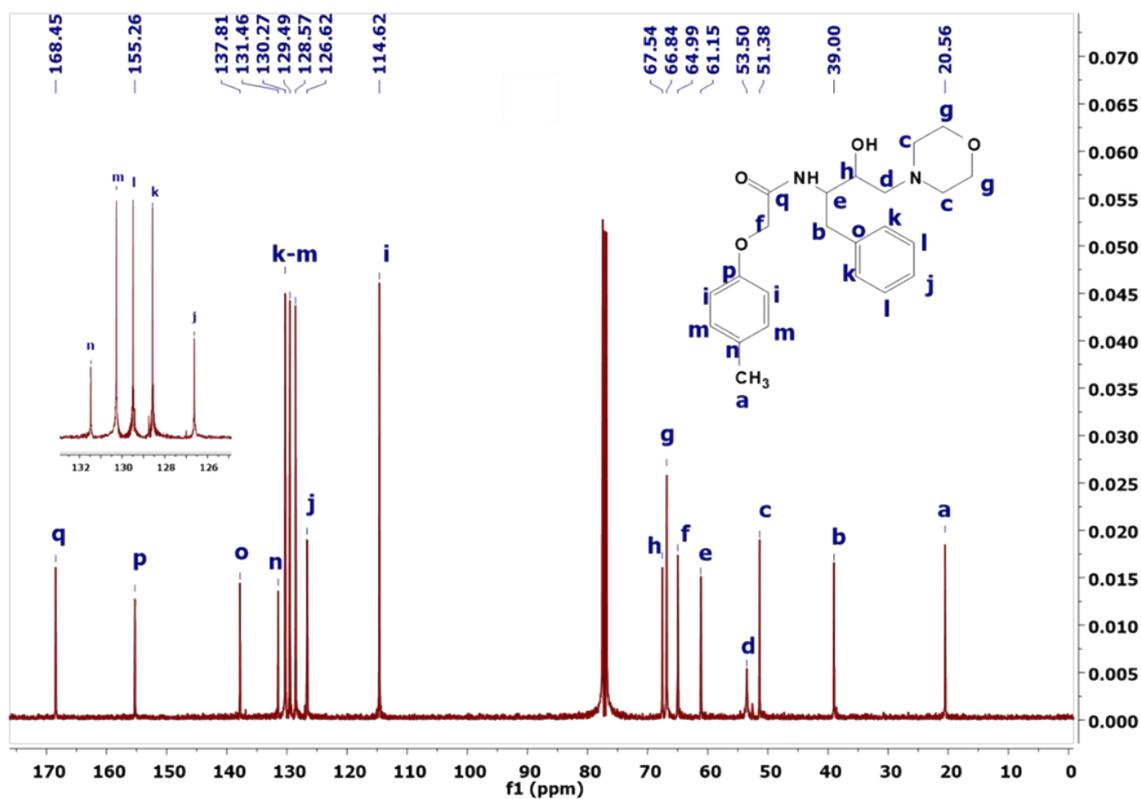


Figure S14. ^{13}C NMR spectrum of 6f.

Figure S15. ^1H NMR spectrum of **6g**.Figure S16. ^{13}C NMR spectrum of **6g**.

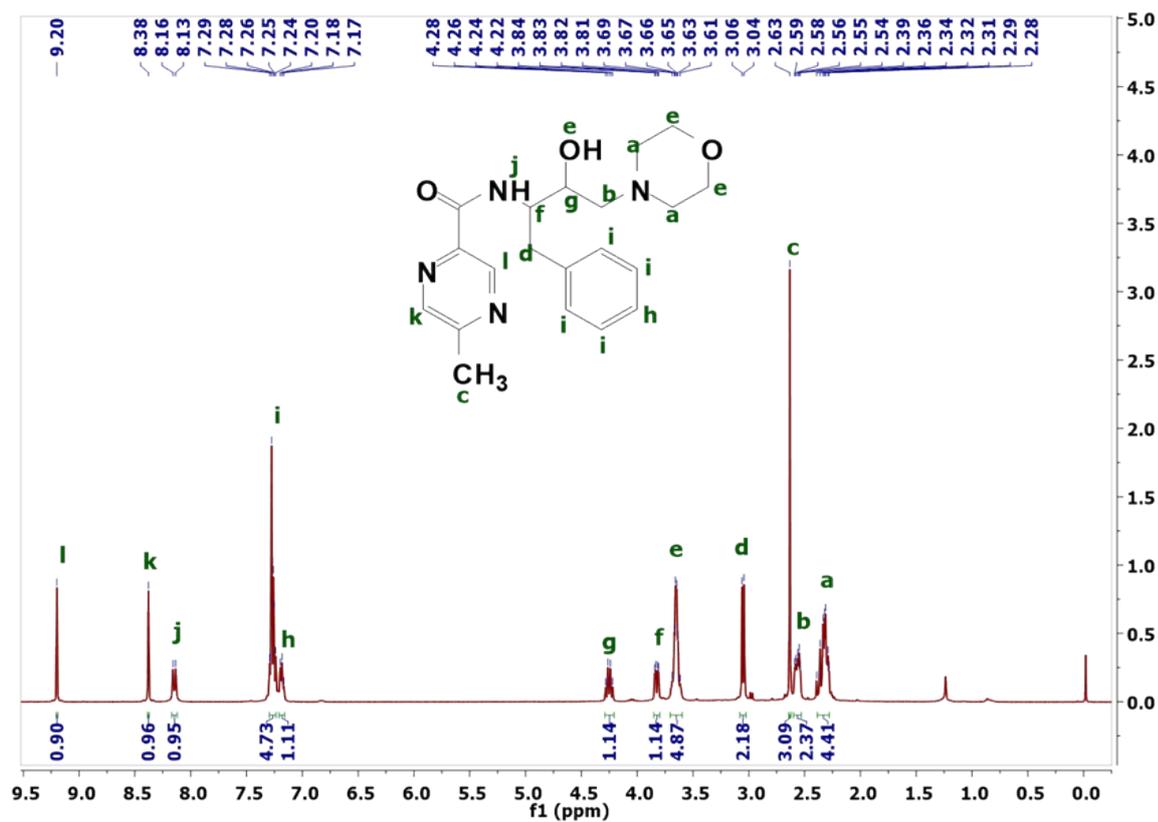


Figure S17. ¹H NMR spectrum of 6h.

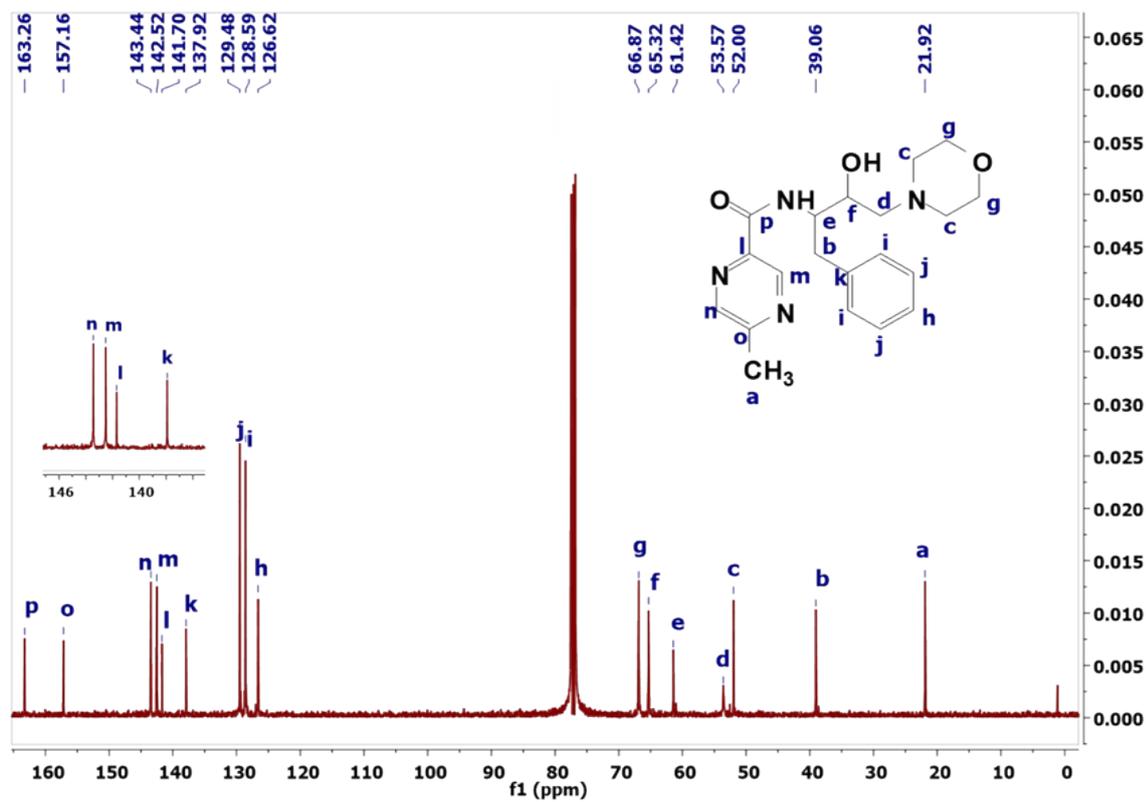


Figure S18. ¹³C NMR spectrum of 6h.

Figure

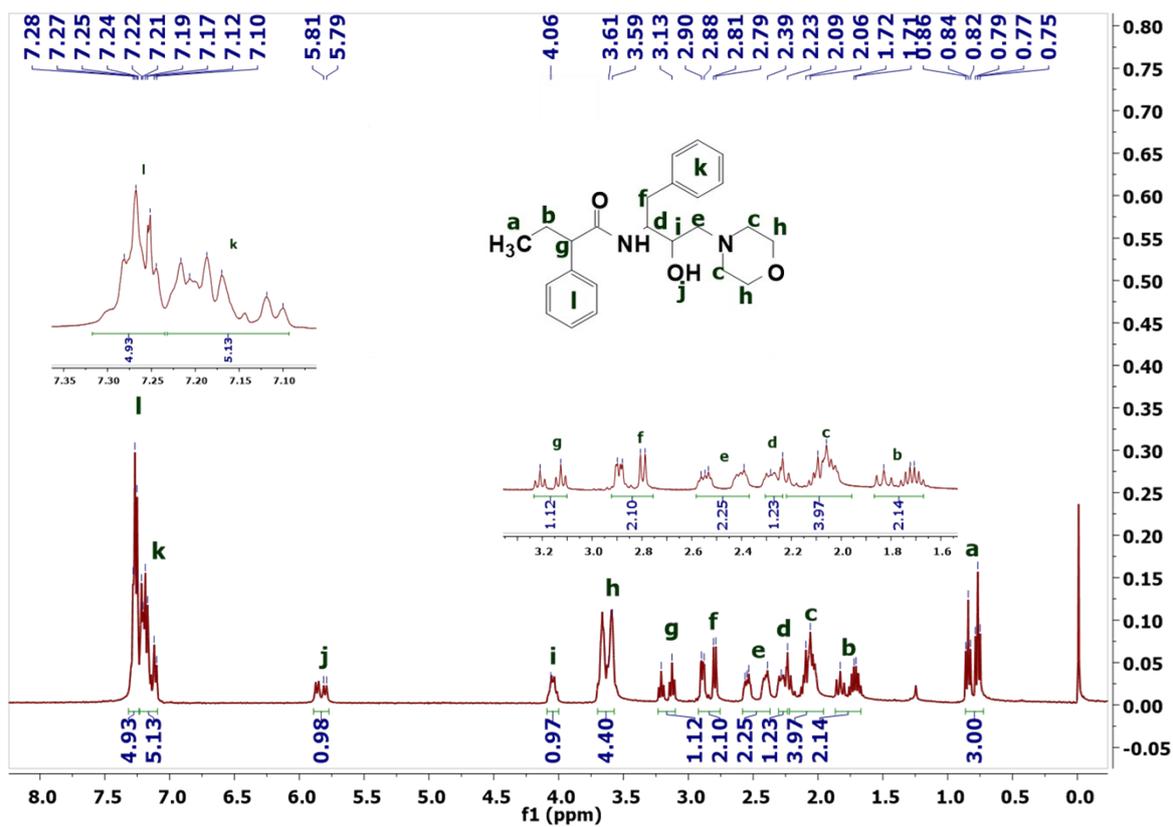


Figure S19. ^1H NMR spectrum of 6i.

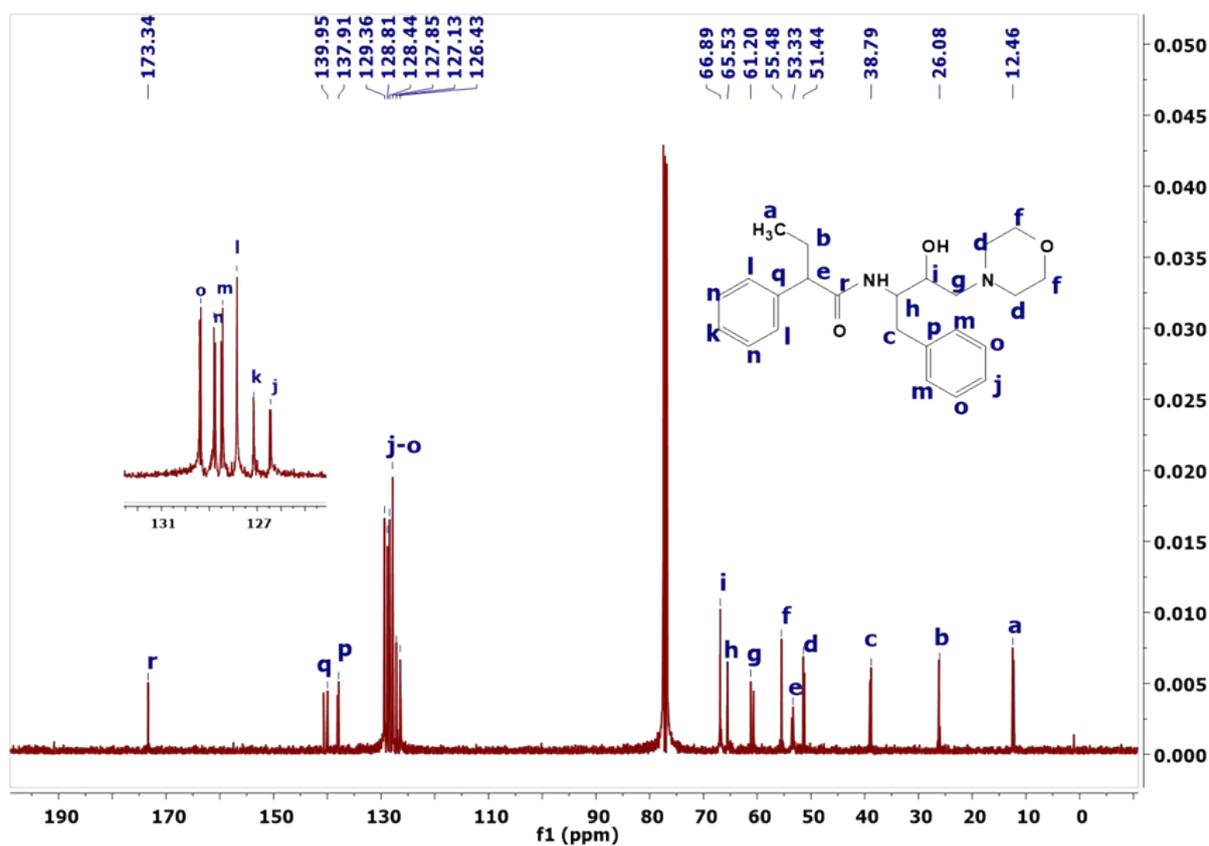
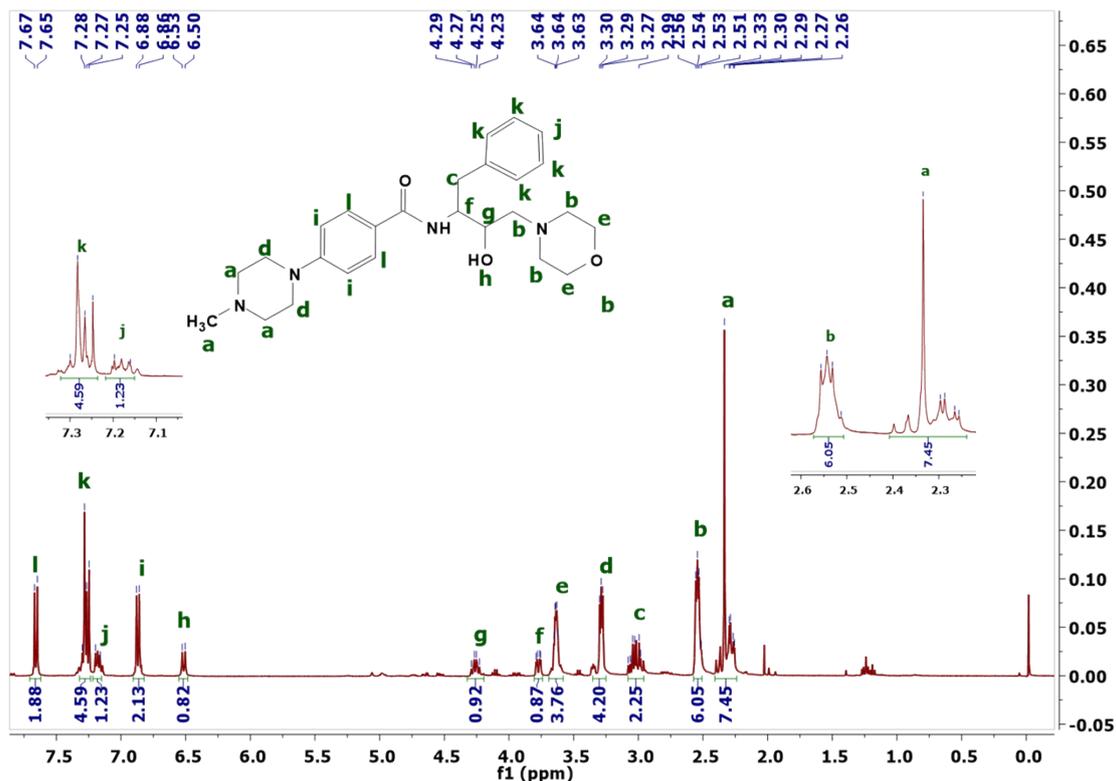
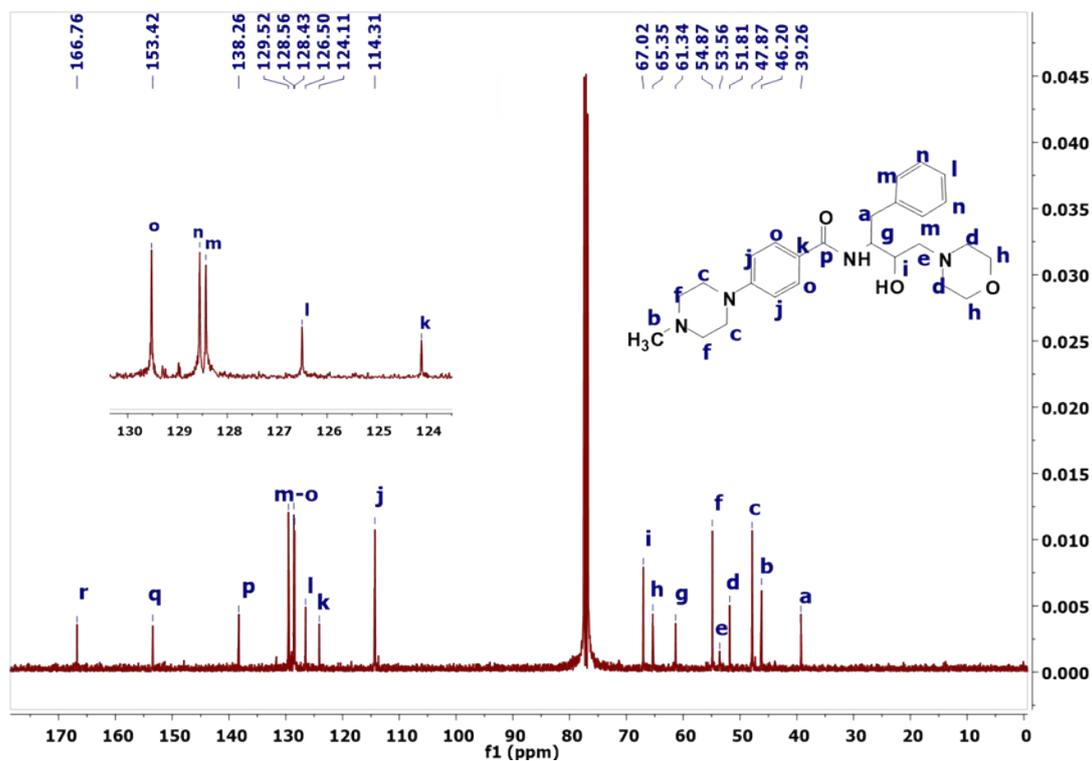
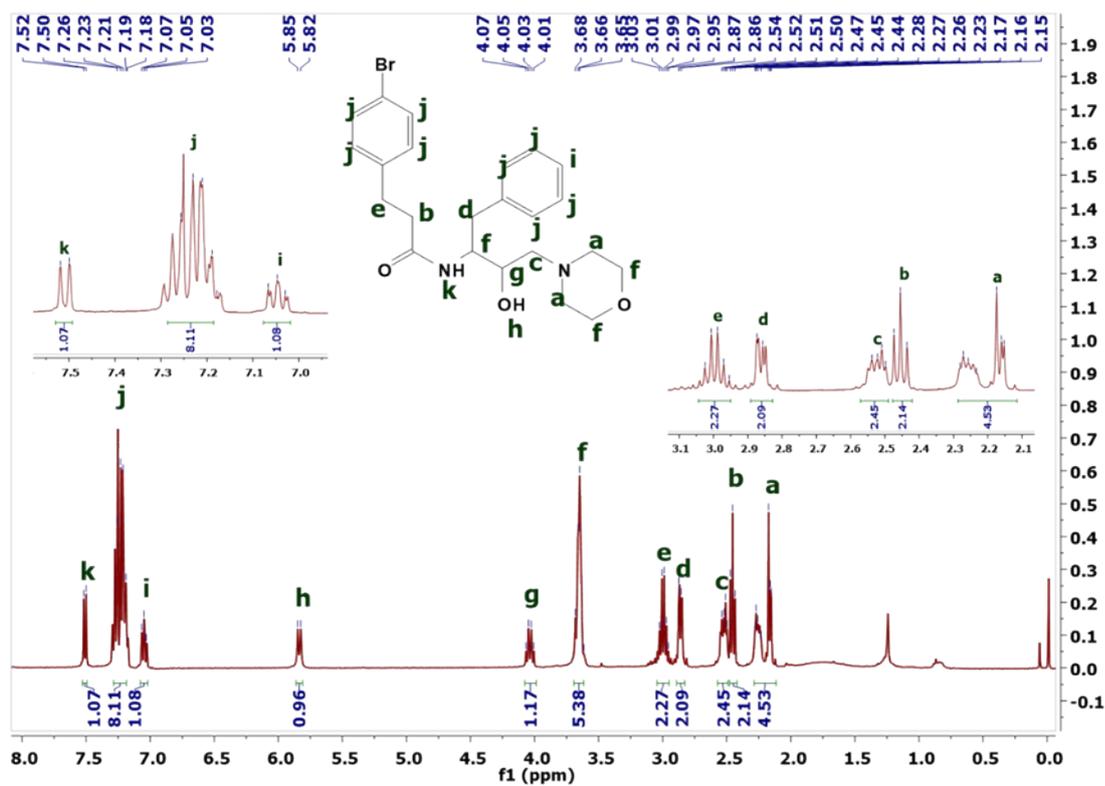
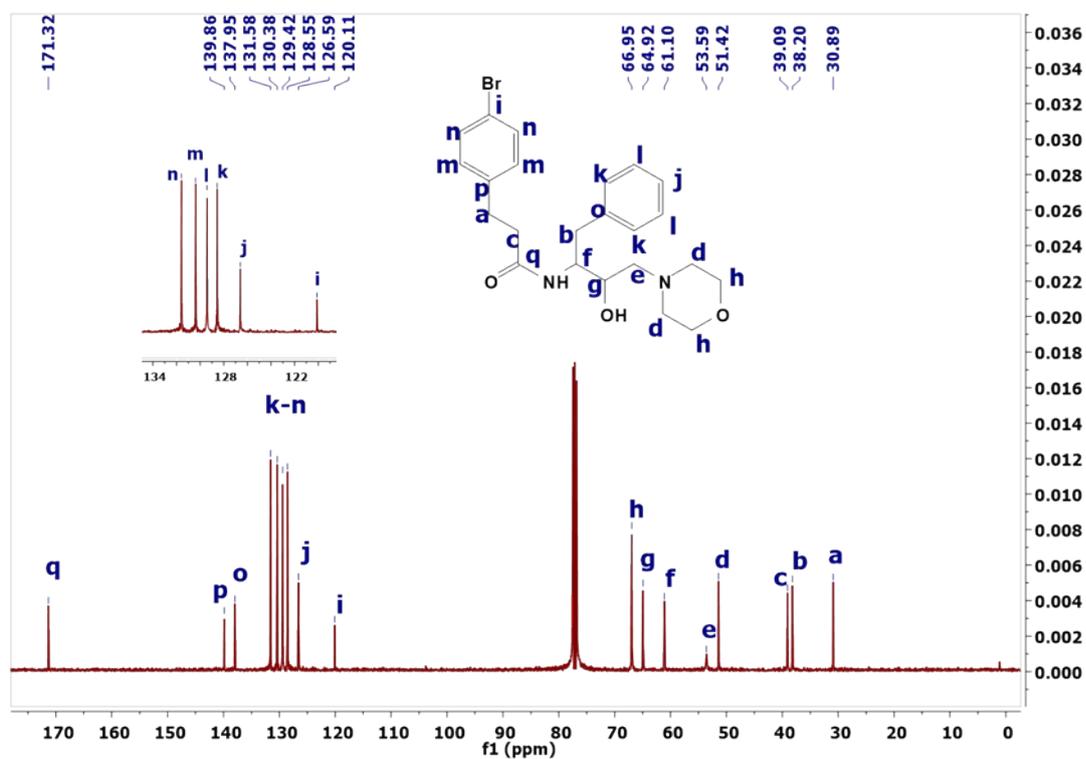
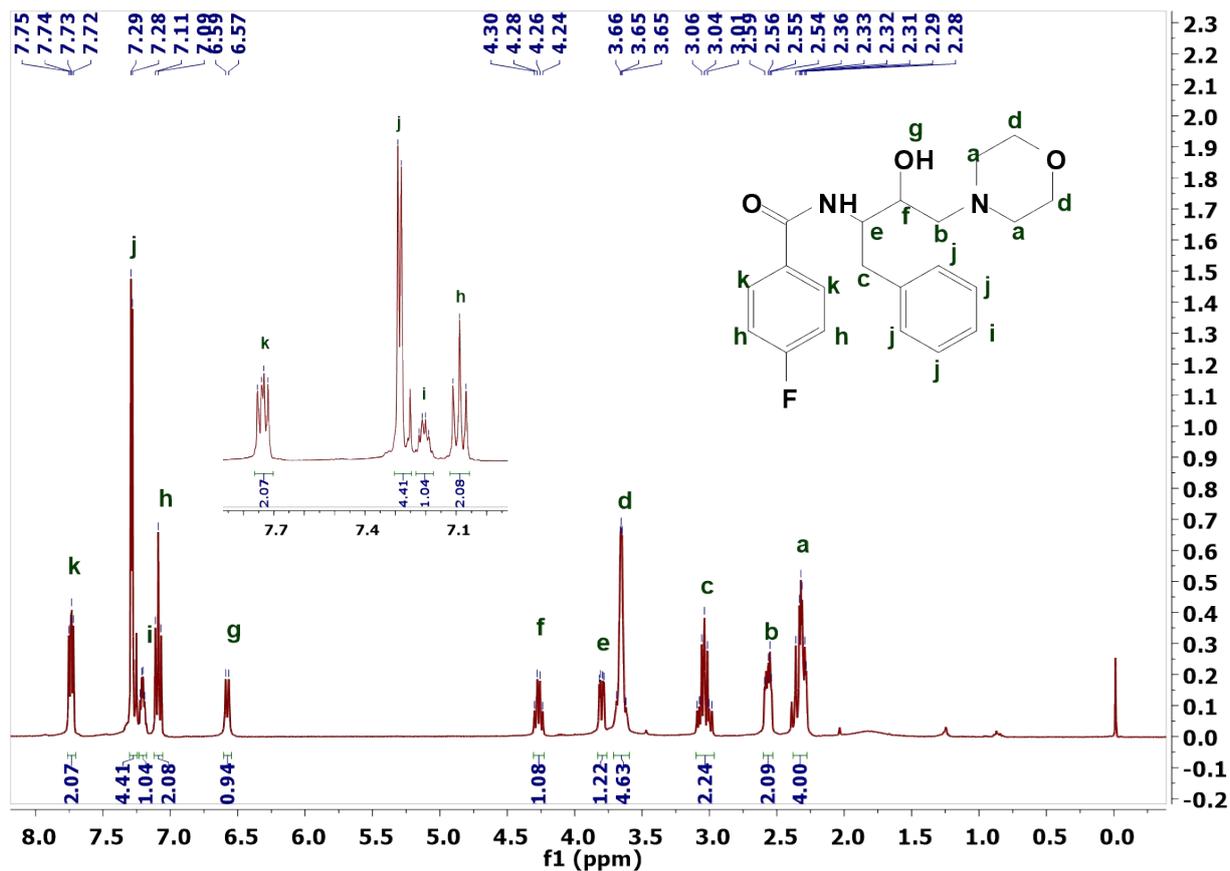
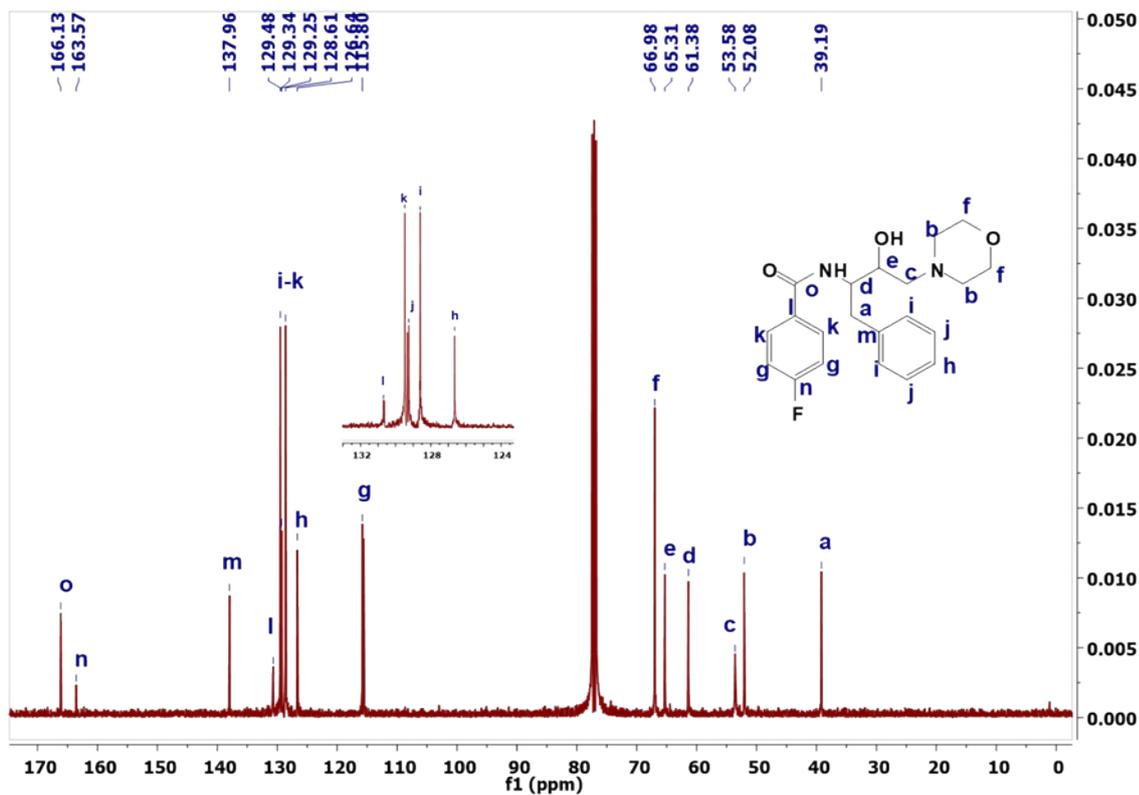


Figure S20. ^{13}C NMR spectrum of 6i.

Figure S21. ^1H NMR spectrum of **6j**.Figure S22. ^{13}C NMR spectrum of **6j**.

Figure S23. ¹H NMR spectrum of 6k.Figure S24. ¹³C NMR spectrum of 6k.

Figure S25. ^1H NMR spectrum of **6l**.Figure S26. ^{13}C NMR spectrum of **6l**.

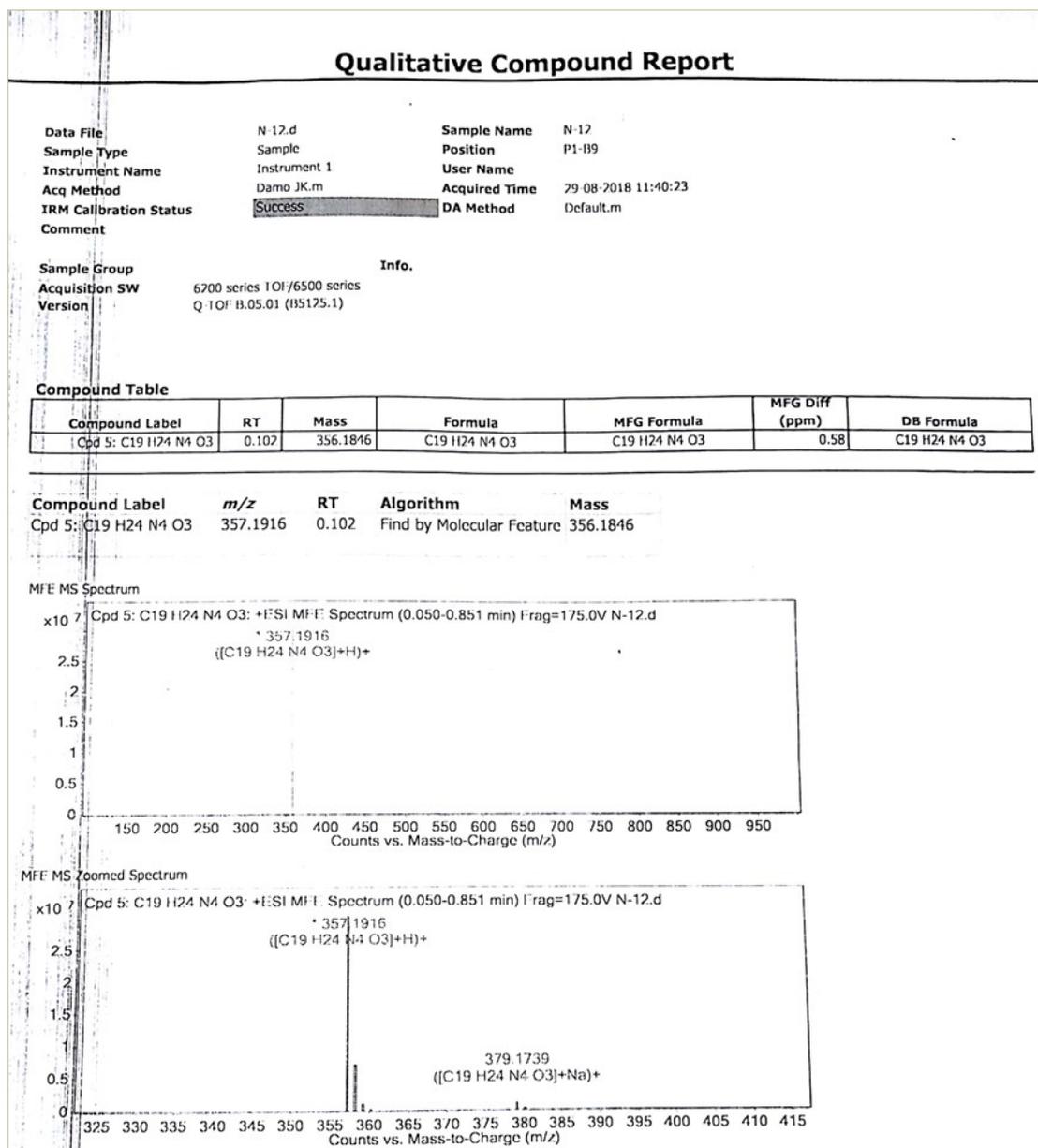
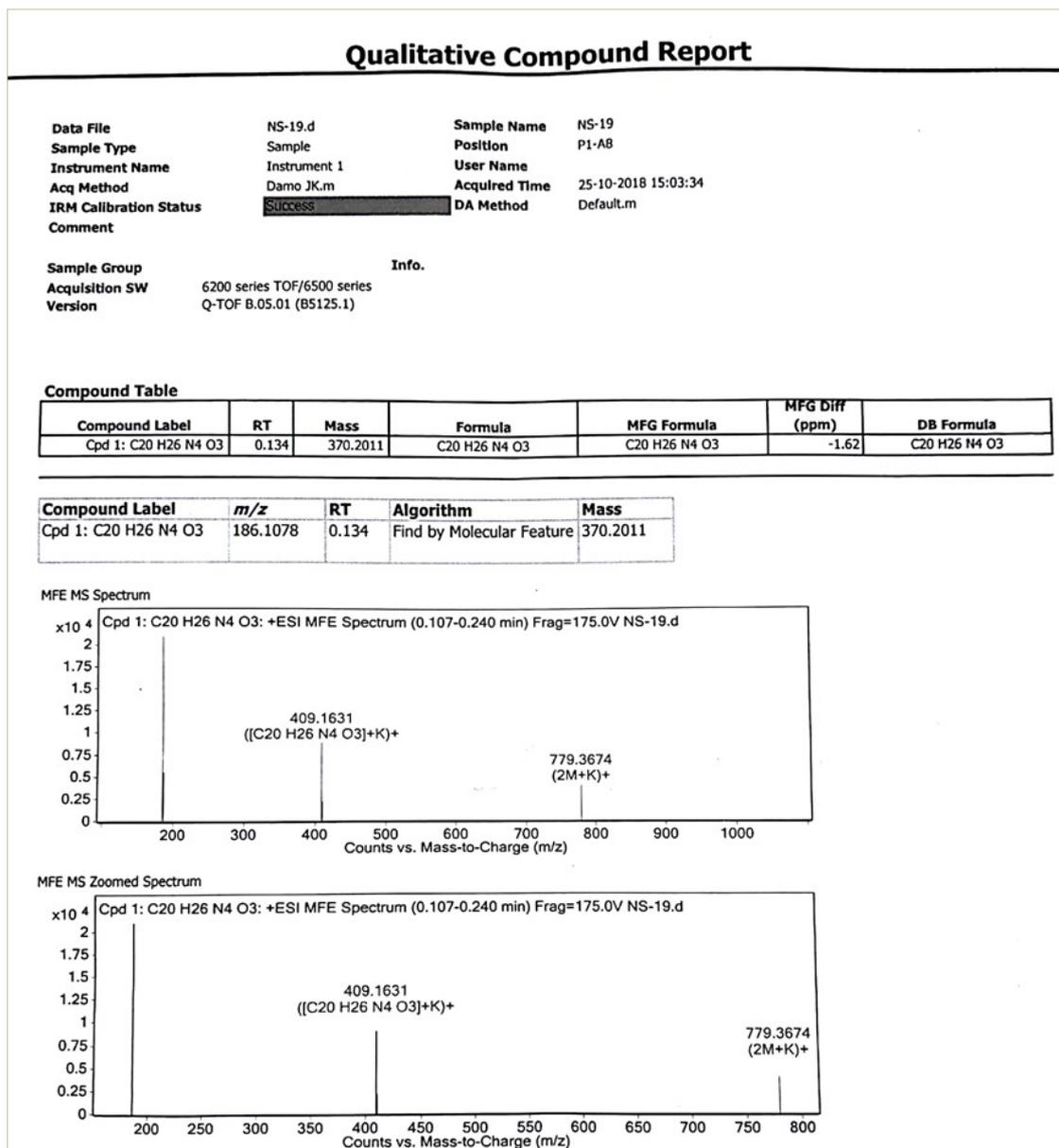


Figure S29. ESI (HR-MS) spectrum of 6a.

Figure S30. ESI (HR-MS) spectrum of **6h**.

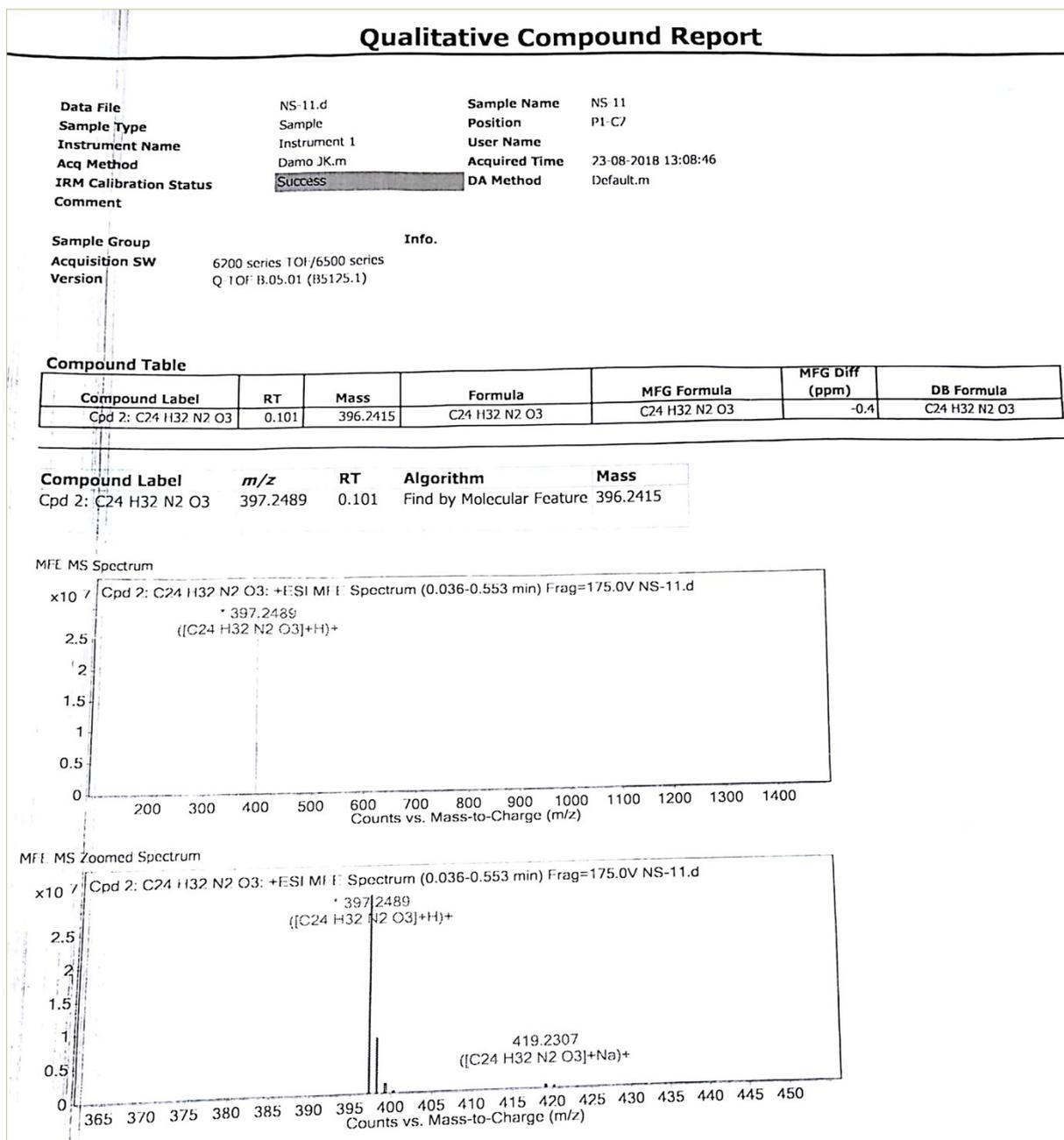
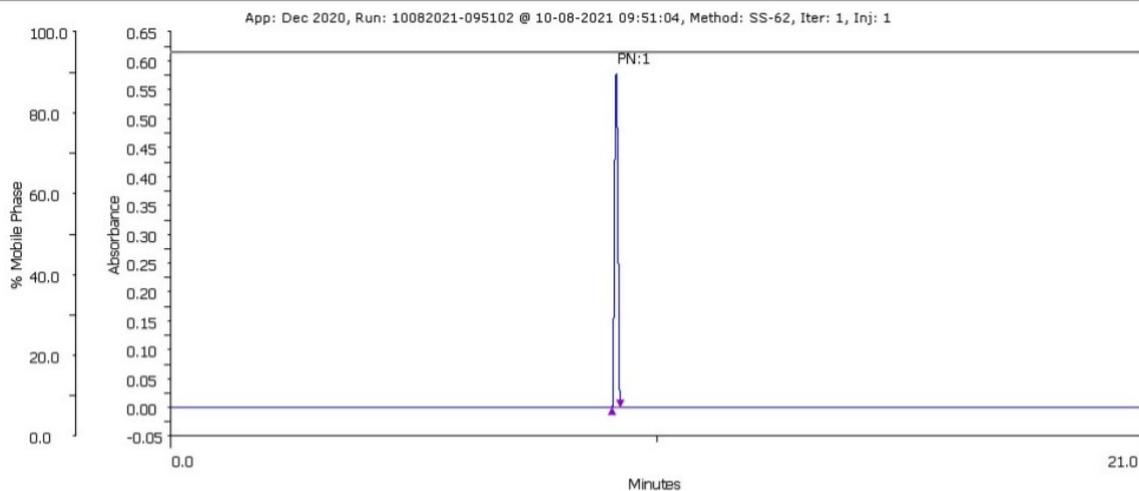


Figure S31. ESI (HR-MS) spectrum of **6i**.

Graph

Sample Name NS-13
Application Name Dec 2020 (Administrator)
Method Name SS-62
Configuration Name Configuration 2
Version 20
Data Instrument Name Detector
Data Channel Name 171 Channel 1
Notes
Injection Number 1

**Sample Table**

Injection Number	Peak Name	Retention Time (min)	Area (mAUmin x100)	Height (Absorbance)	Sample Name	Sample Location	Peak Purity	Amount (mg)
1	1	9.632	4945.005	0.578	NS-13	Sample Zone 1->1	976.006	0

Figure S32. HPLC purity analysis of hit compound **6k**.

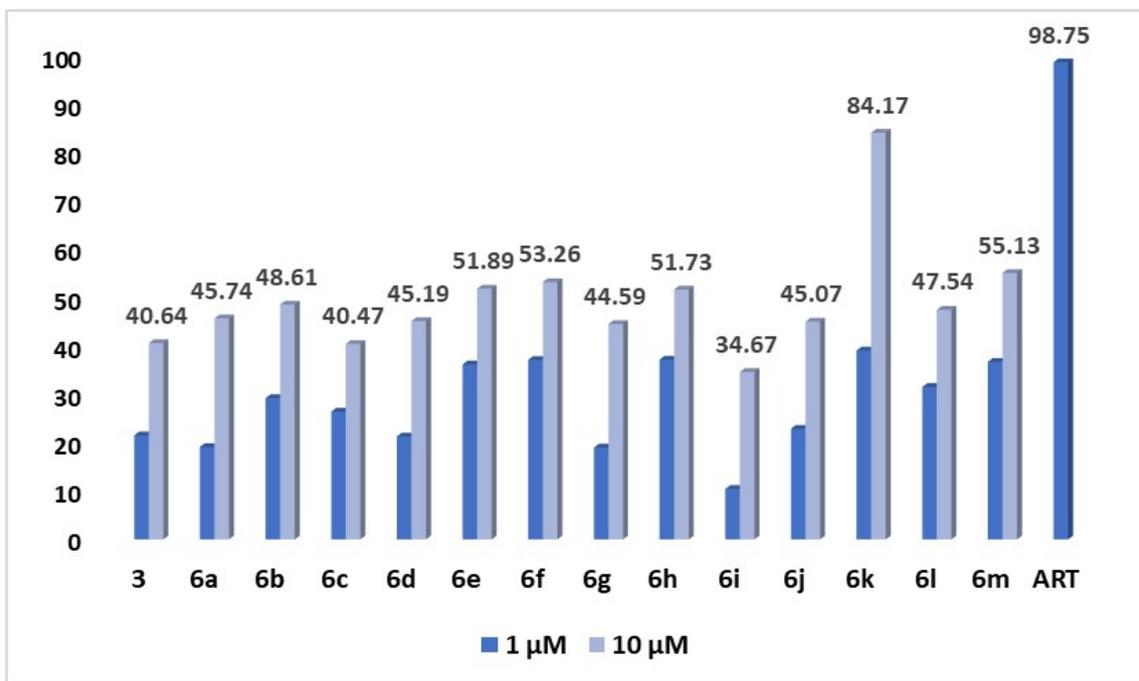


Figure S33: Initial Growth inhibition assay of all fourteen compounds at 1 μ M and 10 μ M with ART as positive control.

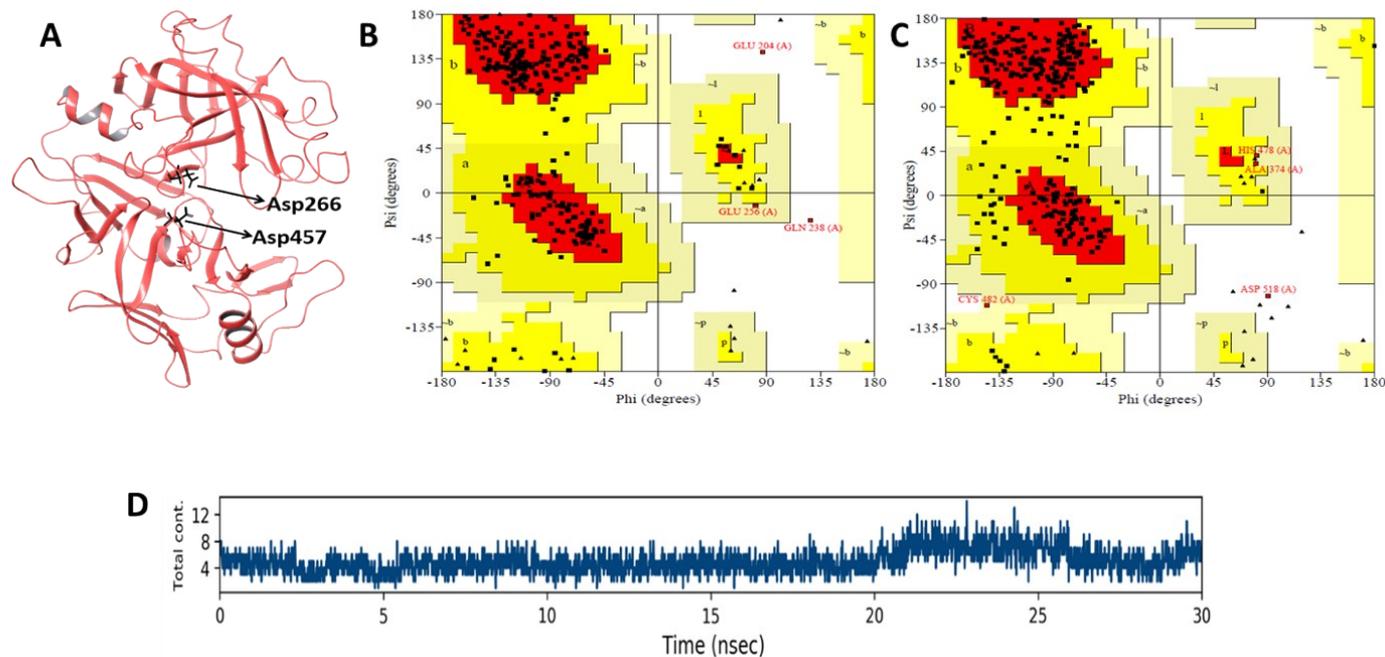


Figure S34: A) 3D modelled structure of PlmX. B) Ramachandran Plot, 3D modelled structure. C) Ramachandran Plot, **6k**-PlmX complex after MD. D) A timeline representation of the interactions and total contacts (H-bonds, hydrophobic interactions, ionic interactions, and water bridges) obtained during the molecular dynamics simulations. The panels show the total number of specific contacts the PlmX protein made with the **6k** over the course of the simulation.

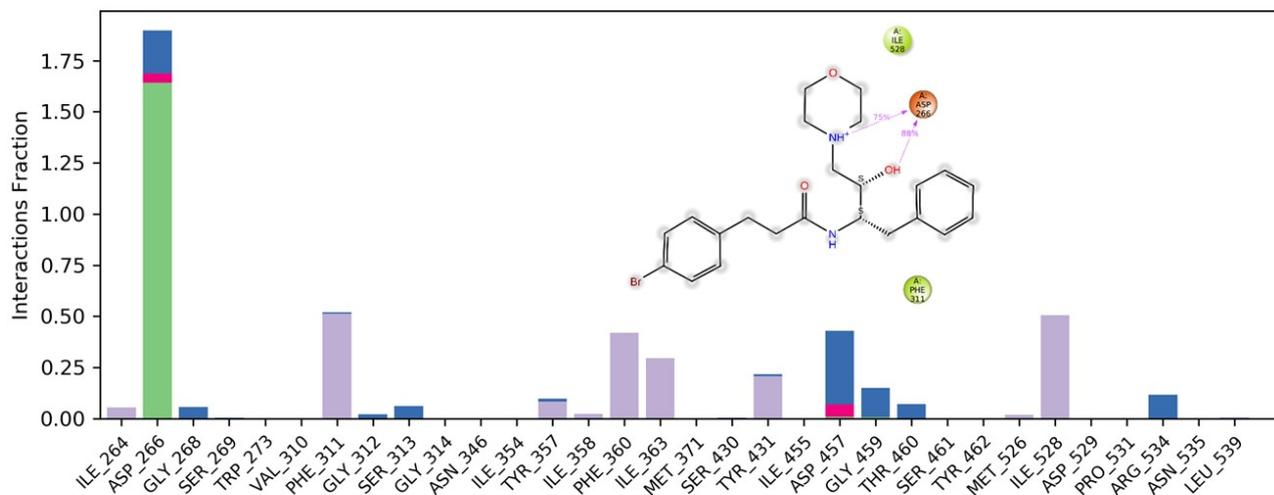


Figure S35. Histogram (stacked bar chart) showing compound **6k-PlmX** forming H-bonds interactions (green color), hydrophobic interaction (grey violet color), and water bridges (blue color) during 30 ns simulation.

Table S1. ADME profile of all the synthesized analogs (**3**, **6a-6m**).

Molecule	#H-bond acceptors	#H-bond donors	TPSA	XLOGP3	ESOL Log S	ESOL Class	GI absorption	BBB permeant	Lipinski #violations
3	5	2	71.03	2	-2.86	Soluble	High	Yes	0
6a	6	2	87.58	0.46	-2.15	Soluble	High	No	0
6b	4	2	61.8	3.19	-4.36	Moderately soluble	High	Yes	0
6c	7	2	61.8	3.09	-4.12	Moderately soluble	High	Yes	0
6d	5	2	74.27	2.02	-3.52	Soluble	High	No	0
6e	4	2	61.8	2.78	-3.69	Soluble	High	Yes	0
6f	4	2	61.8	2.2	-3.25	Soluble	High	Yes	0
6g	5	2	71.03	2.67	-3.64	Soluble	High	No	0
6h	6	2	87.58	0.86	-2.48	Soluble	High	No	0
6i	4	2	61.8	3.13	-3.92	Soluble	High	Yes	0
6j	5	2	68.28	2.2	-3.71	Soluble	High	No	0
6k	4	2	61.8	3.19	-4.36	Moderately soluble	High	Yes	0
6l	5	2	61.8	2.37	-3.44	Soluble	High	Yes	0
6m	7	2	61.8	3.15	-4.15	Moderately soluble	High	Yes	0