Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Biscoumarin scaffold as an efficient anti-Zika virus lead with NS3-Helicase inhibitory potential: Detailed *in-vitro* and *in-silico* Investigation

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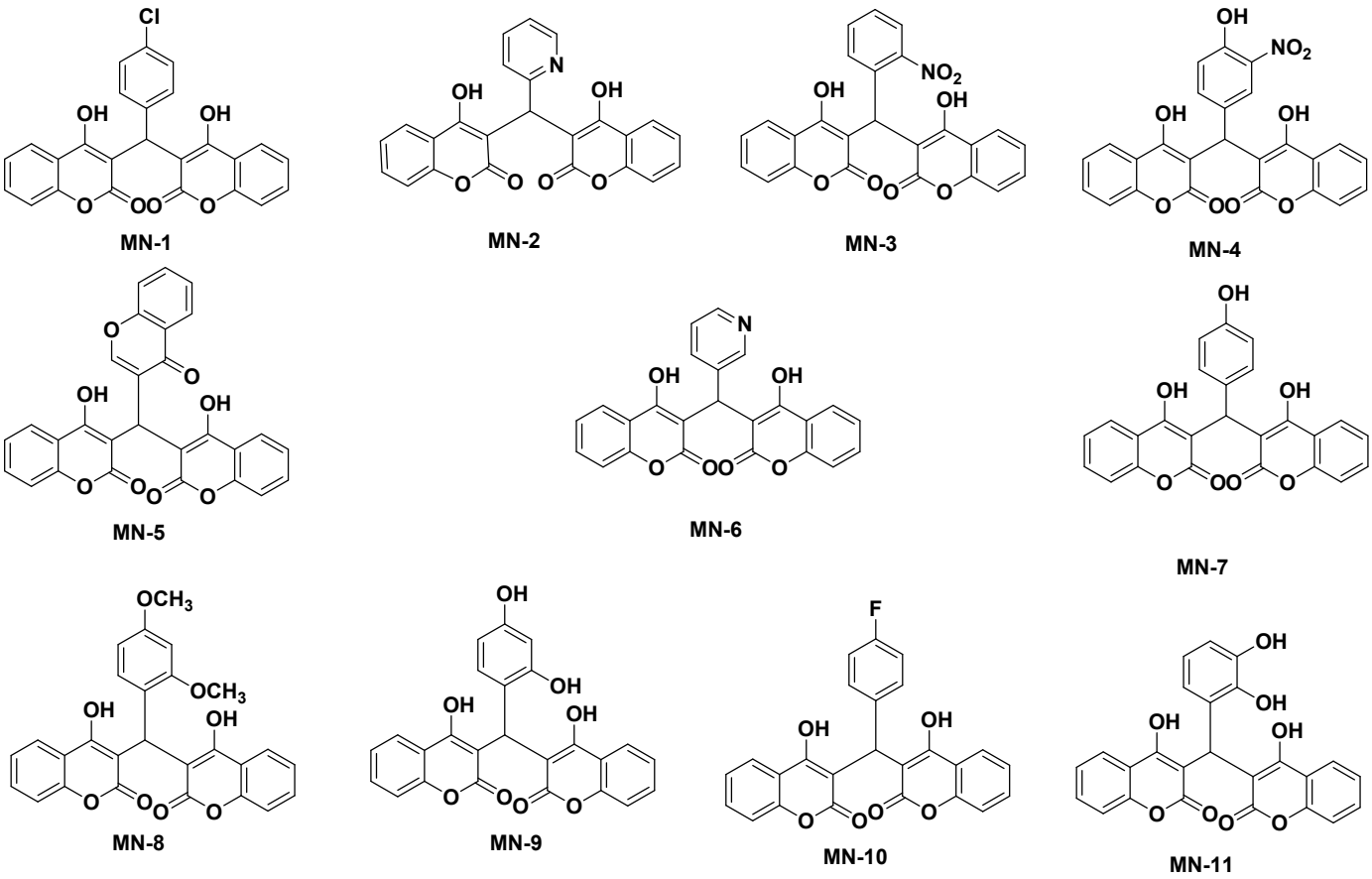
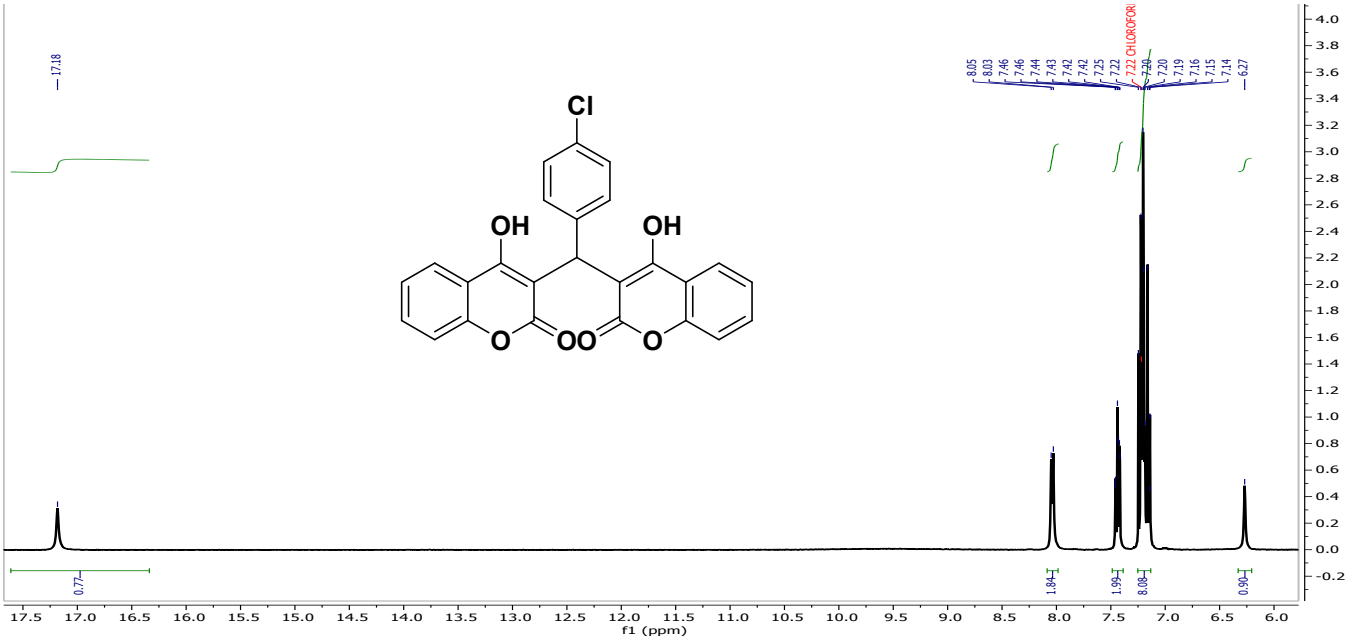
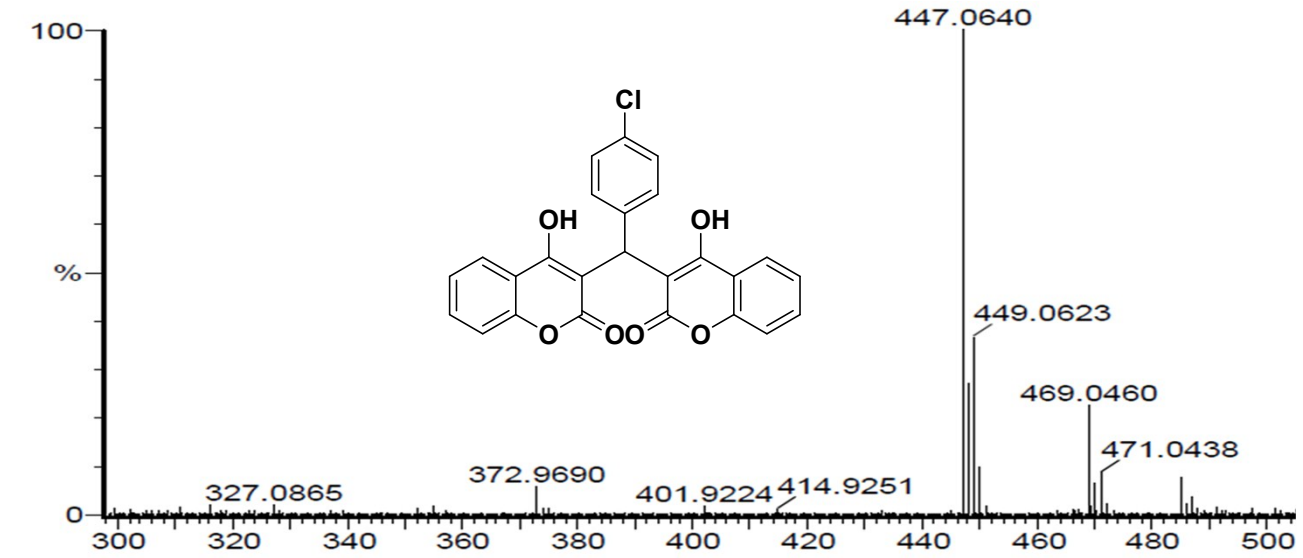


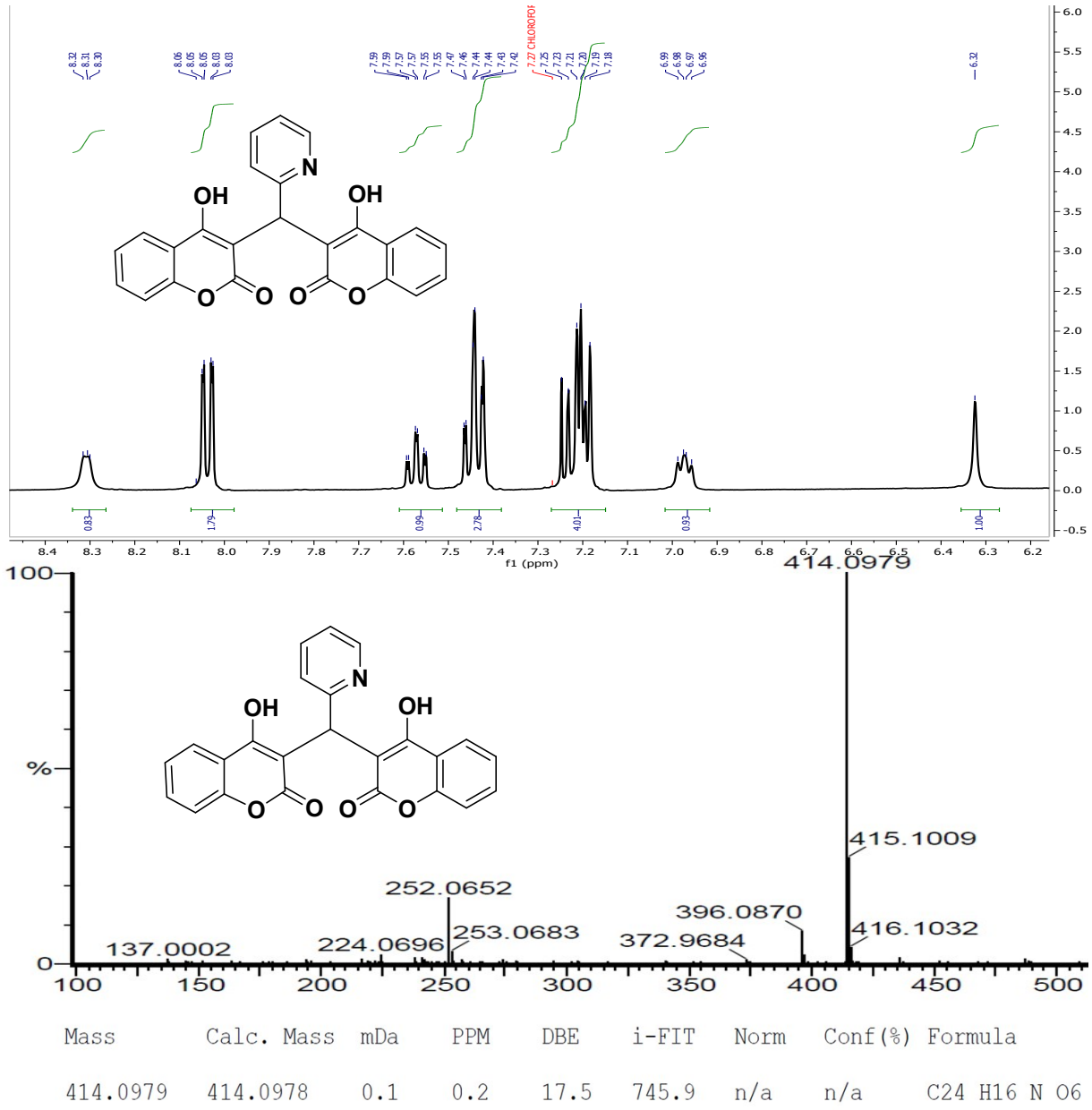
Figure SF-1 Structure of the biscoumarin derivatives used for the study.





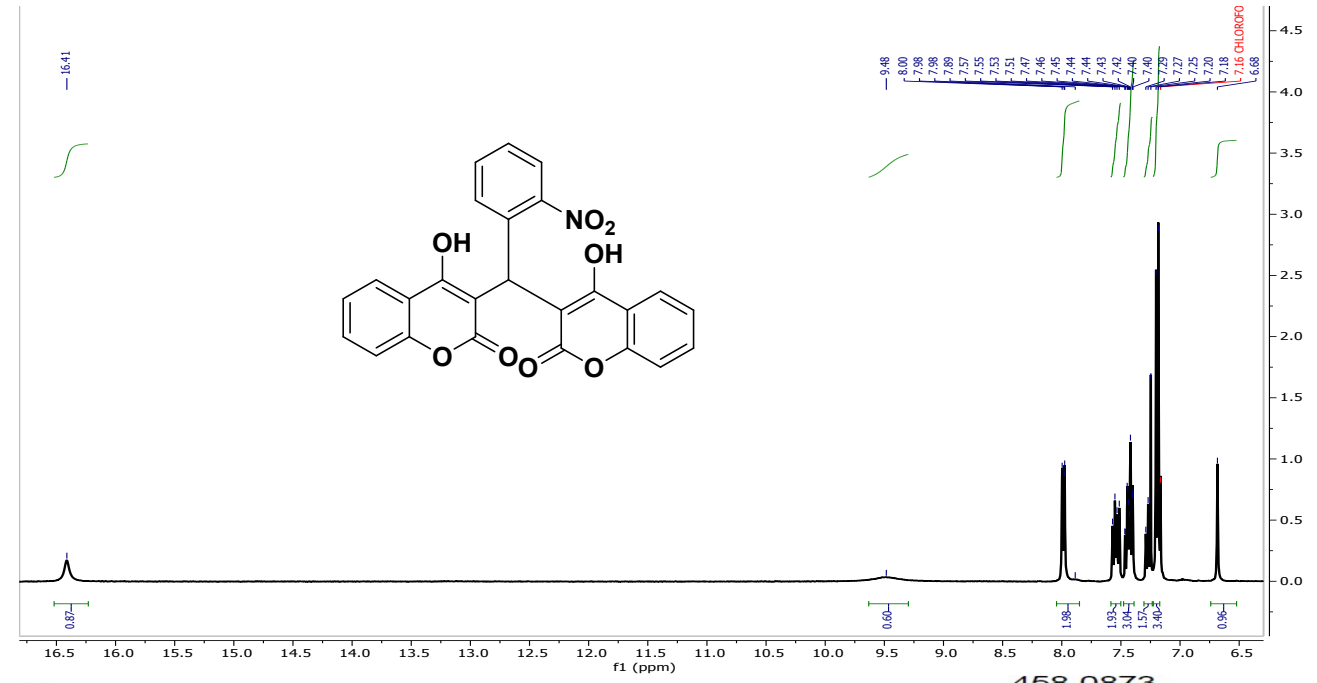
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
447.0640	447.0635	0.5	1.1	17.5	1112.6	n/a	n/a	C25 H16 O6 Cl

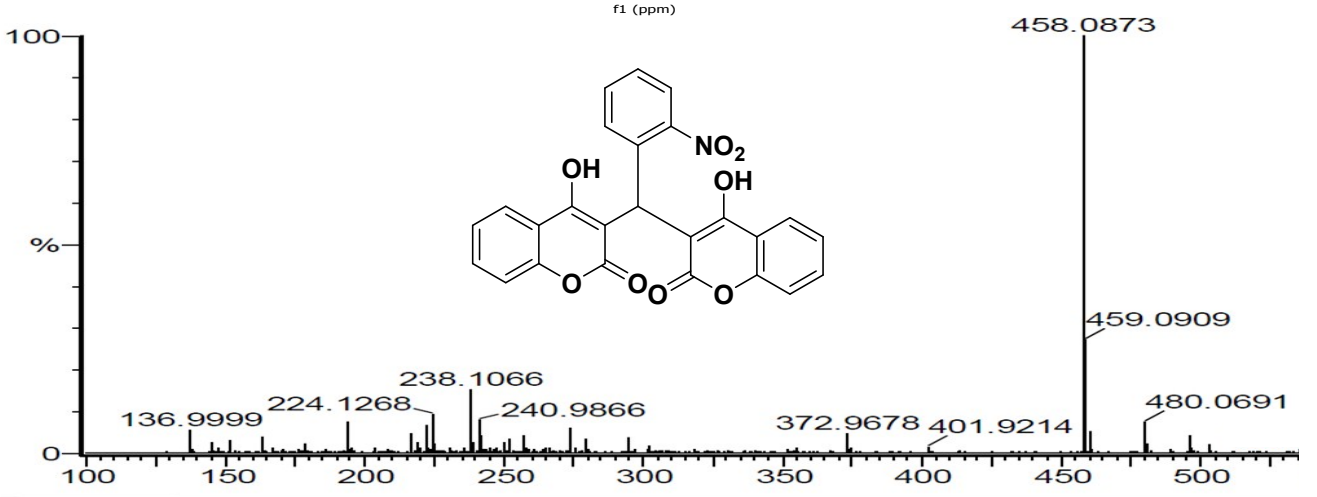
Figure SF-2: NMR and HRMS of **MN-1** used for the study.



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
414.0979	414.0978	0.1	0.2	17.5	745.9	n/a	n/a	C24 H16 N O6

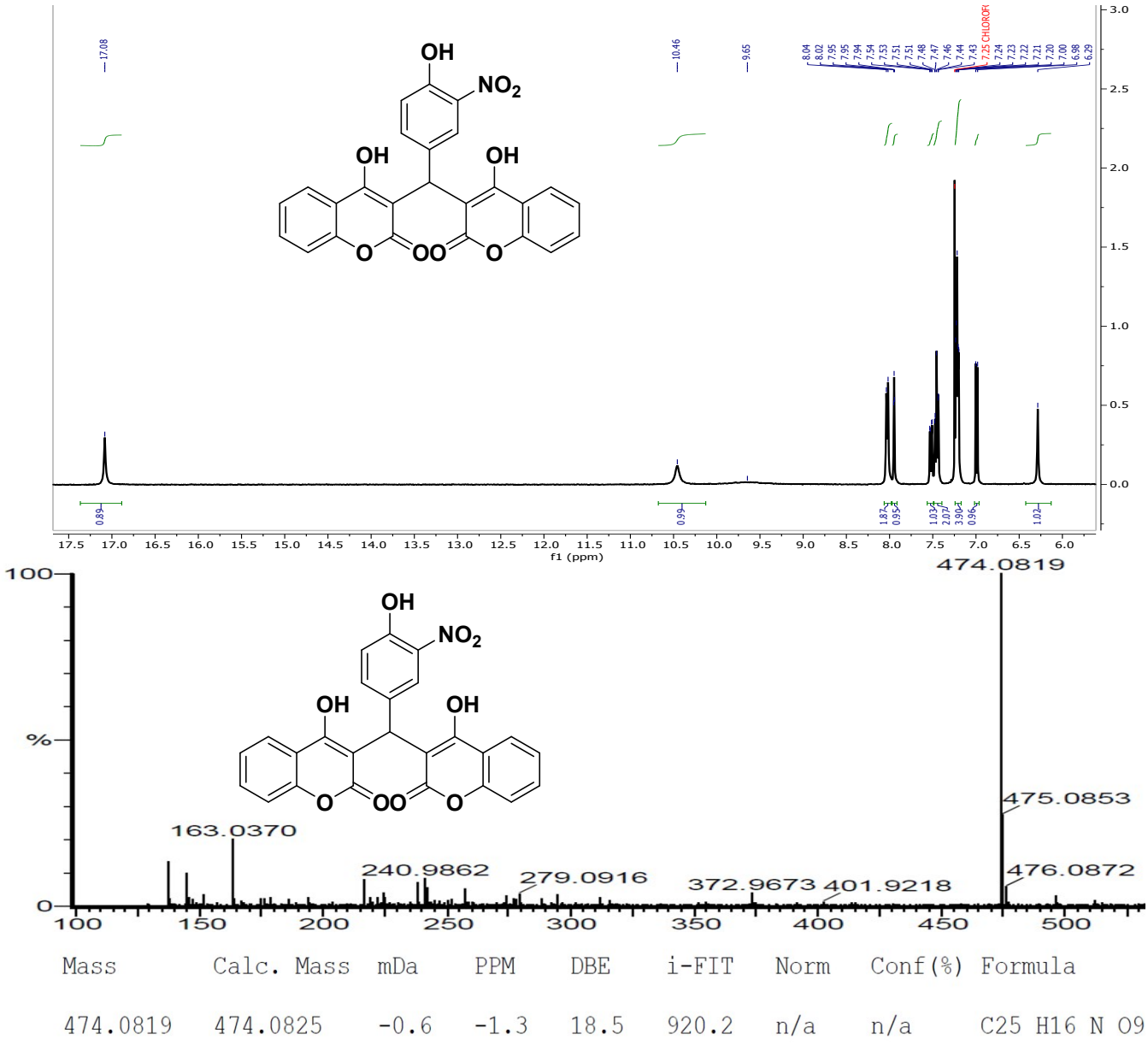
Figure SF-3: NMR and HRMS of **MN-2** used for the study.





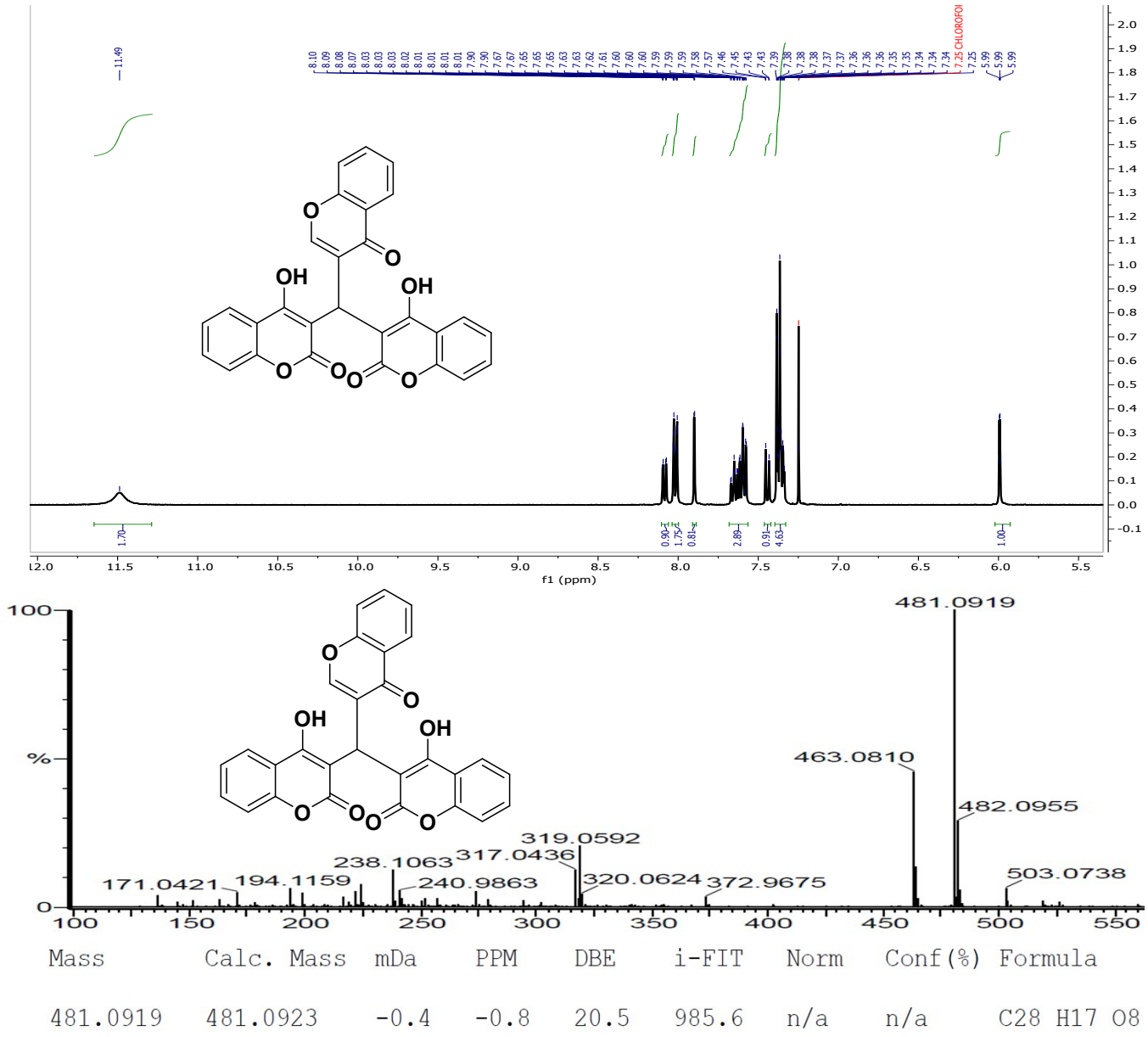
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
458.0873	458.0876	-0.3	-0.7	18.5	885.0	n/a	n/a	C25 H16 N O8

Figure SF-4: NMR and HRMS of **MN-3** used for the study.



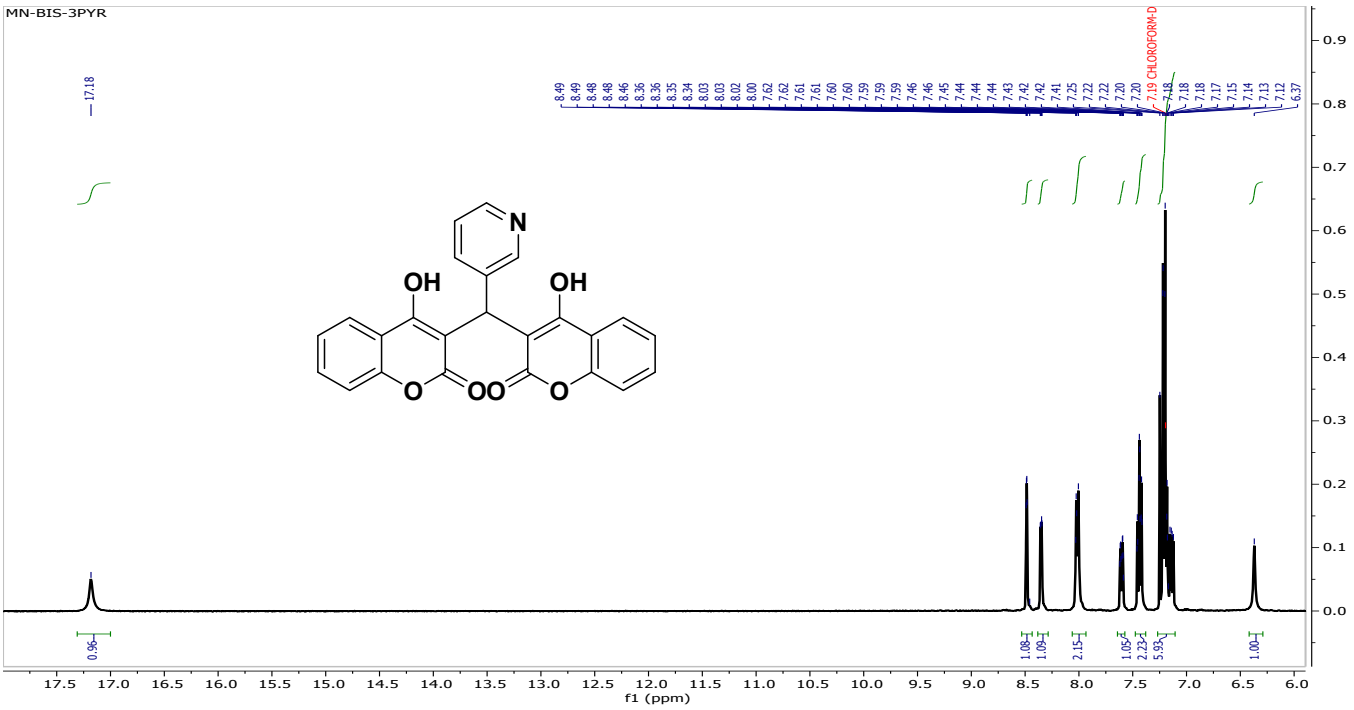
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
474.0819	474.0825	-0.6	-1.3	18.5	920.2	n/a	n/a	C25 H16 N O9

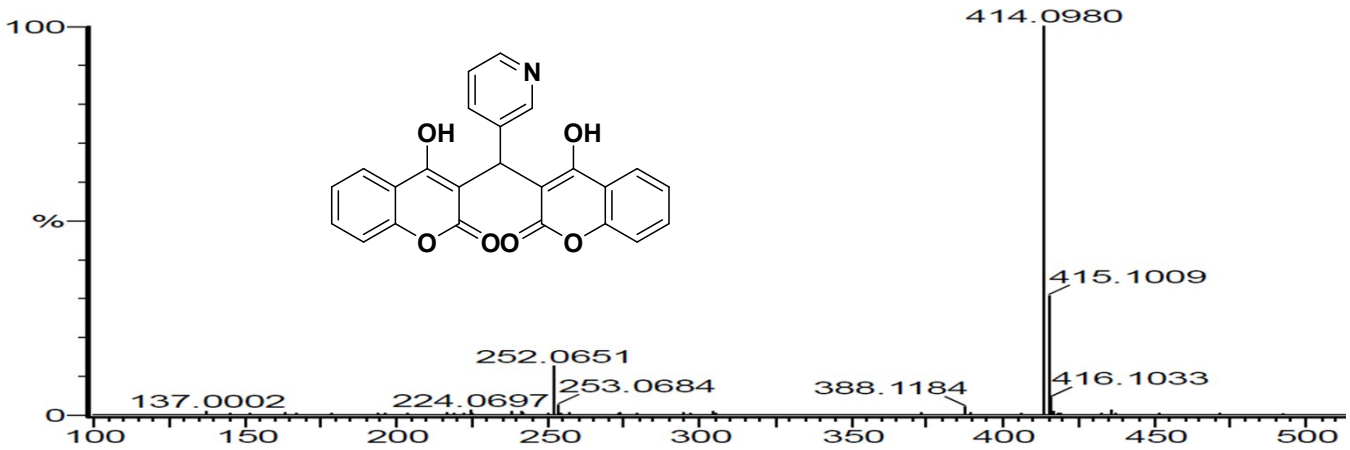
Figure SF-5: NMR and HRMS of **MN-4** used for the study.



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
481.0919	481.0923	-0.4	-0.8	20.5	985.6	n/a	n/a	C28 H17 O8

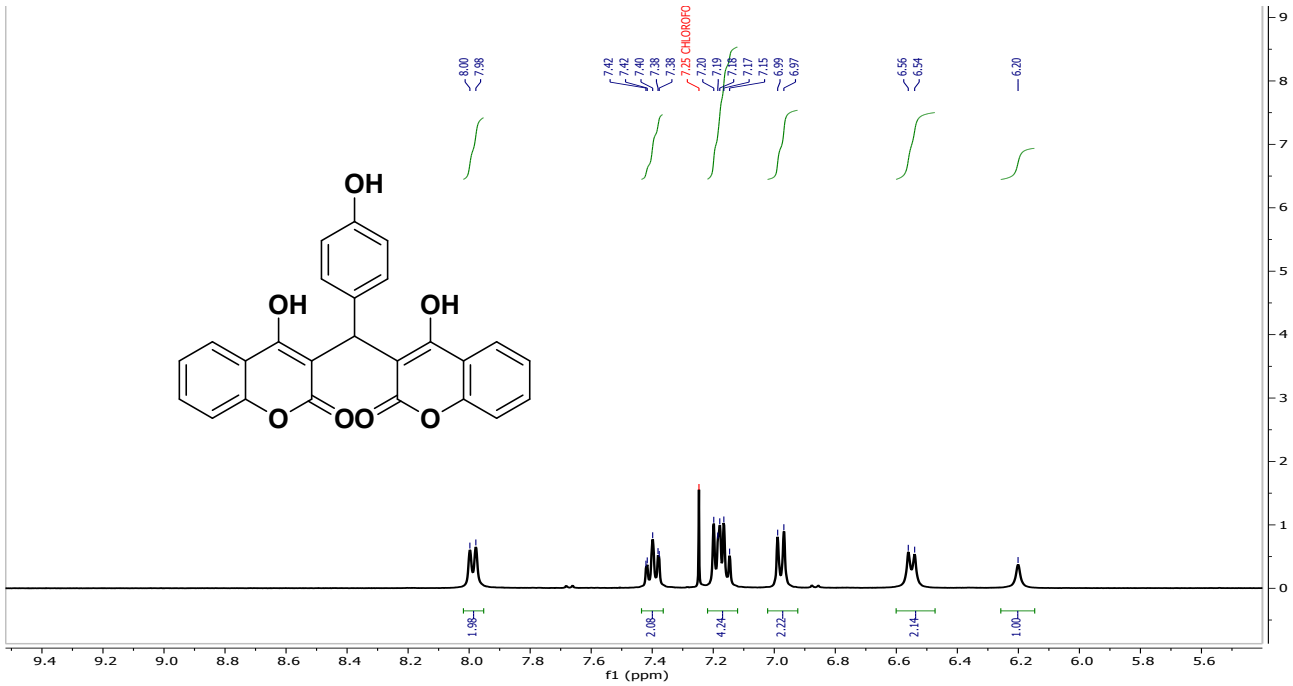
Figure SF-6: NMR and HRMS of **MN-5** used for the study.

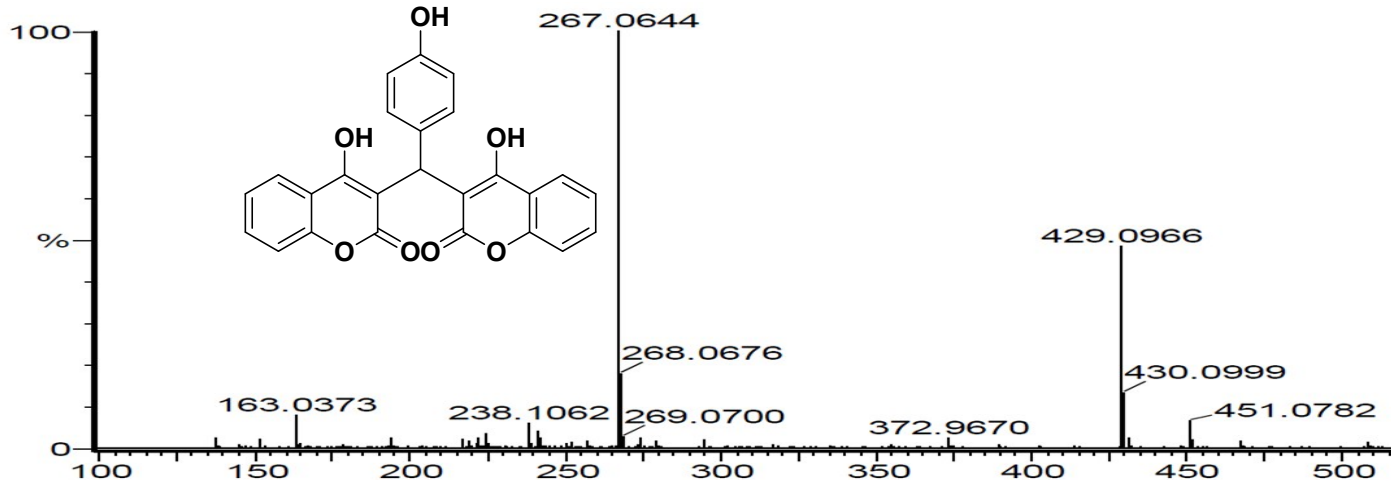




Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
414.0980	414.0978	0.2	0.5	17.5	784.1	n/a	n/a	C24 H16 N O6

Figure SF-7: NMR and HRMS of **MN-6** used for the study.





Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
429.0966	429.0974	-0.8	-1.9	17.5	1047.2	n/a	n/a	C25 H17 O7

Figure SF-8: NMR and HRMS of **MN-7** used for the study.

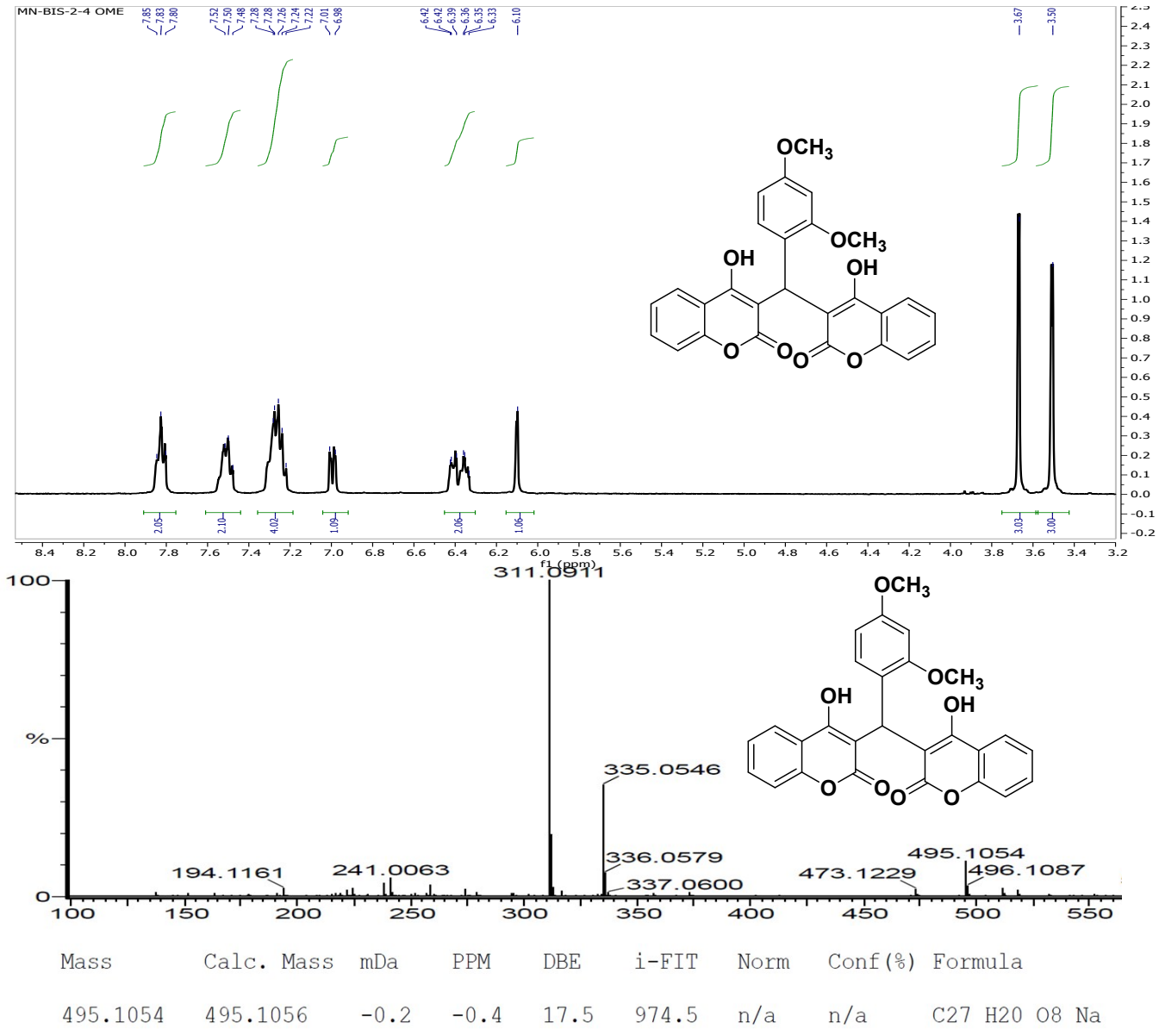
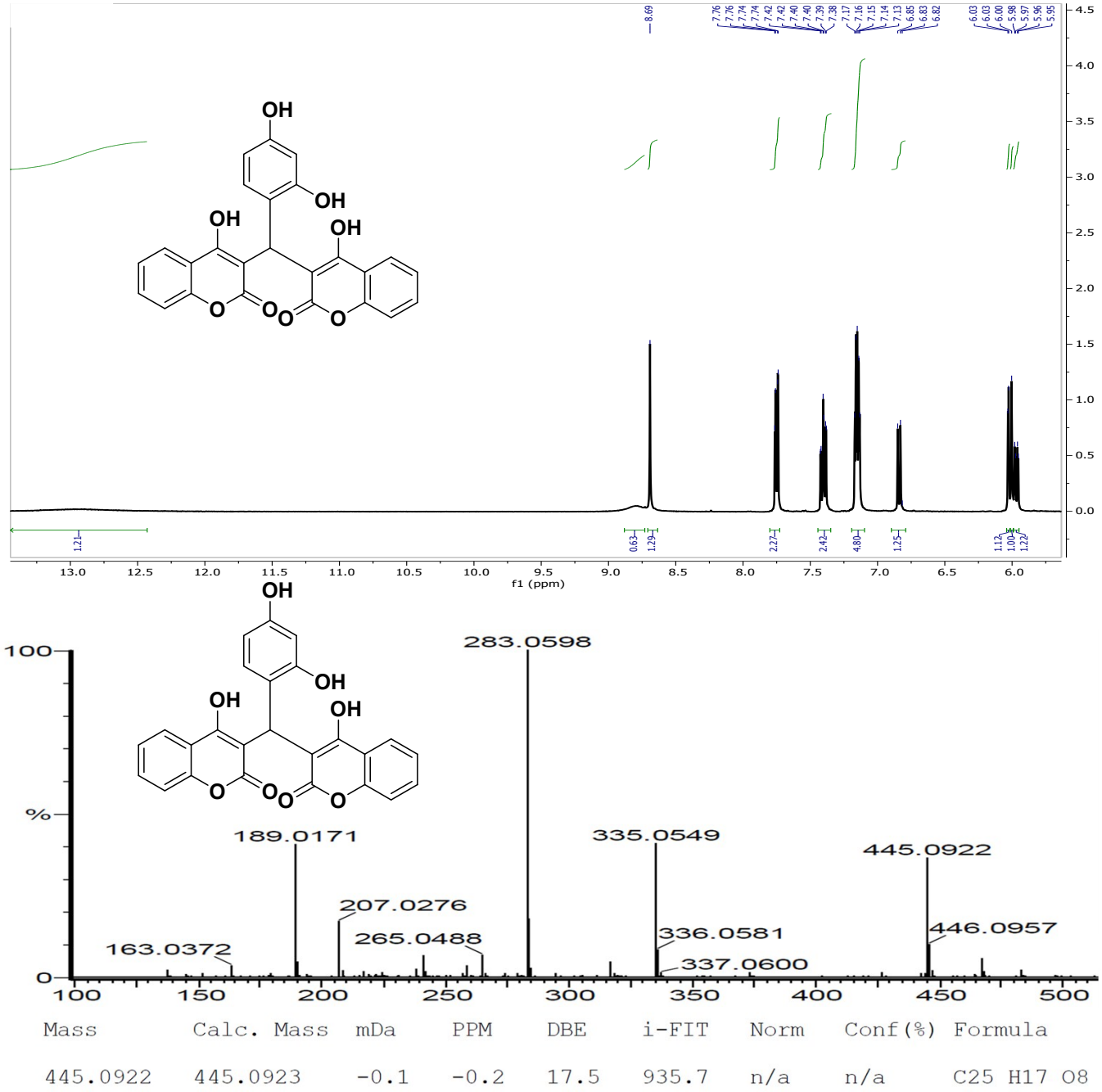


Figure SF-9: NMR and HRMS of **MN-8** used for the study.



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
445.0922	445.0923	-0.1	-0.2	17.5	935.7	n/a	n/a	C25 H17 O8

Figure SF-10: NMR and HRMS of **MN-9** used for the study.

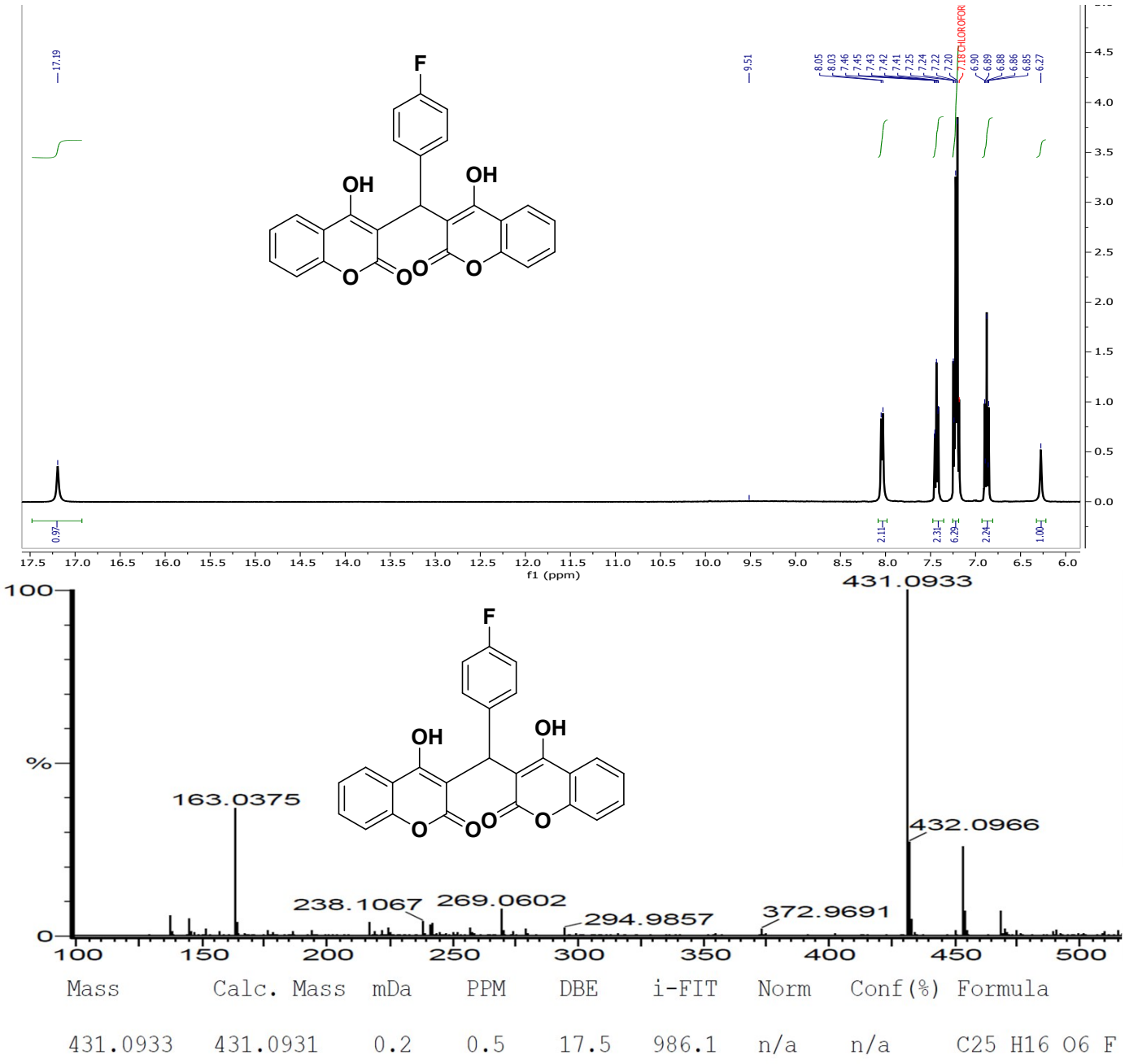
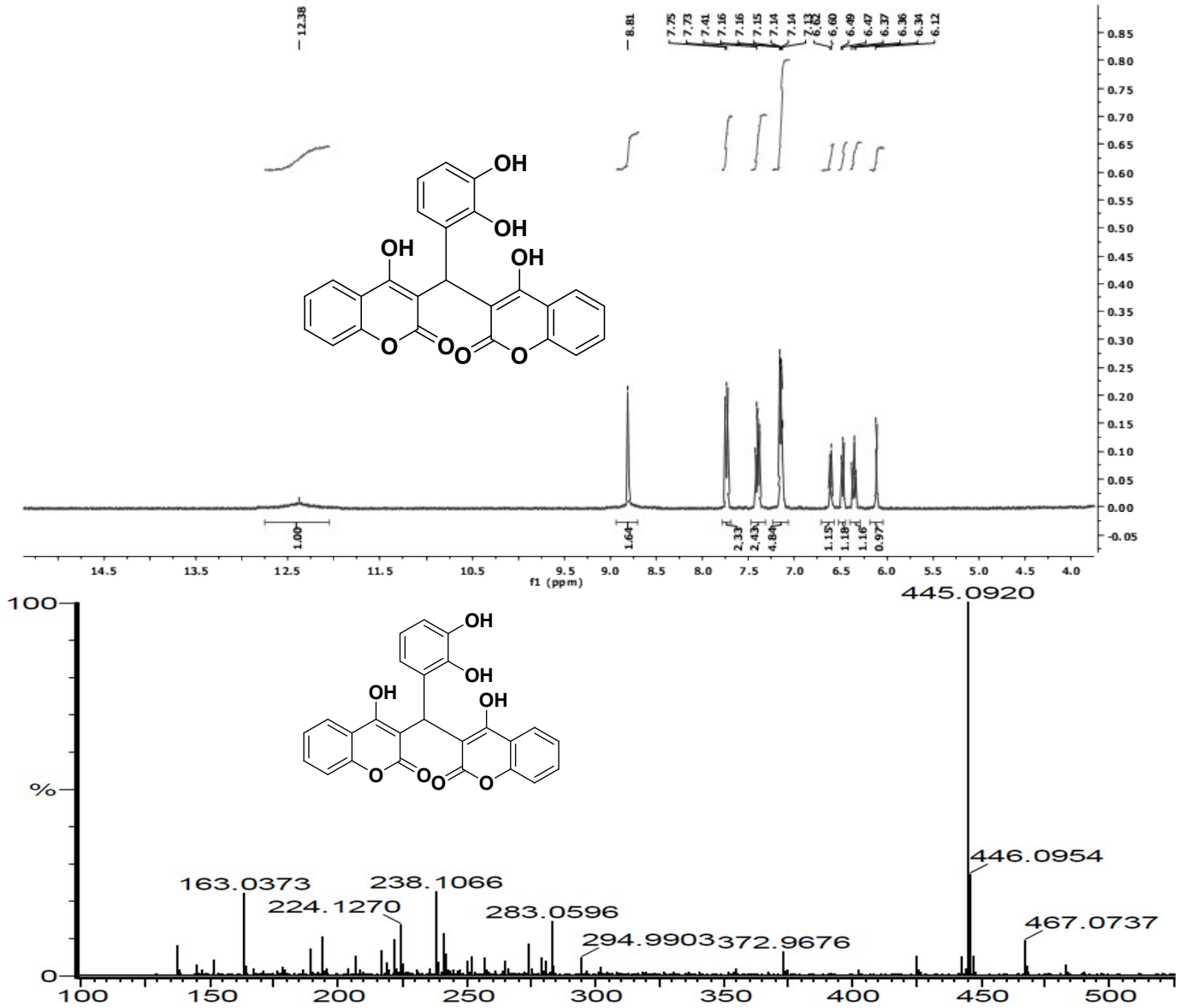


Figure SF-11: NMR and HRMS of **MN-10** used for the study.



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
445.0920	445.0923	-0.3	-0.7	17.5	812.6	n/a	n/a	C25 H17 O8

Figure SF-12: NMR and HRMS of **MN-11** used for the study.

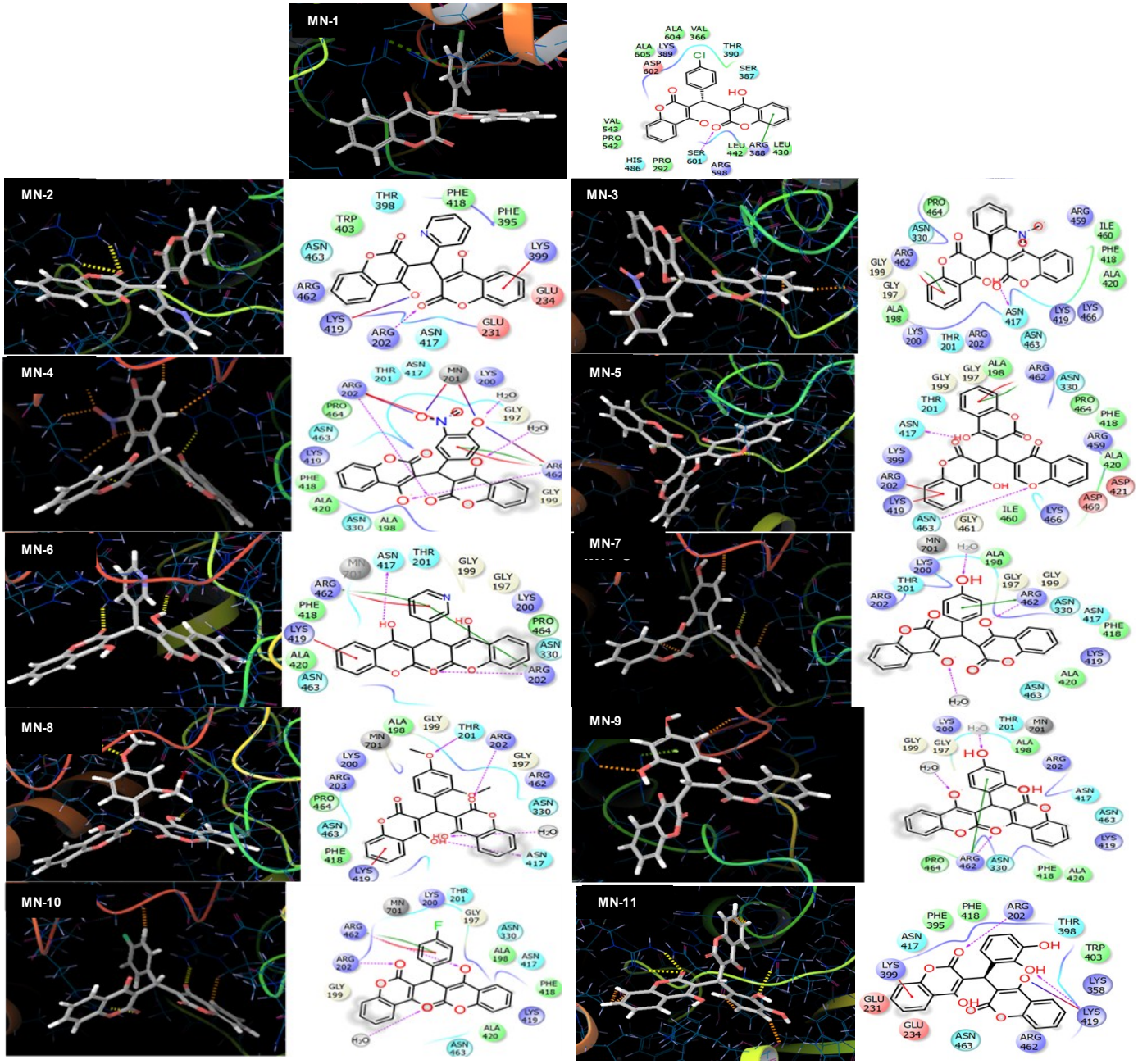


Figure SF-13. 3D and 2D docked poses of all the biscoumarin derivatives against ATP binding cavity of NS3H protein.

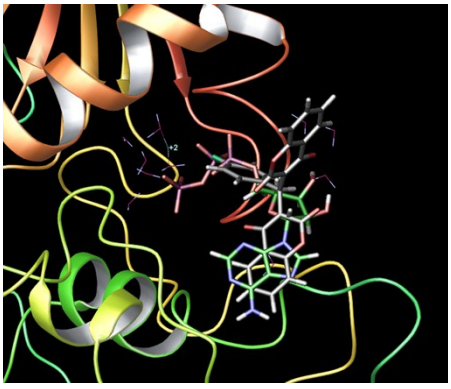


Figure SF-14. Docked pose overlay of best lead MN-9 (grey), simultaneously docked along with ATP (green) inside the ATP binding cavity of NS3H protein.

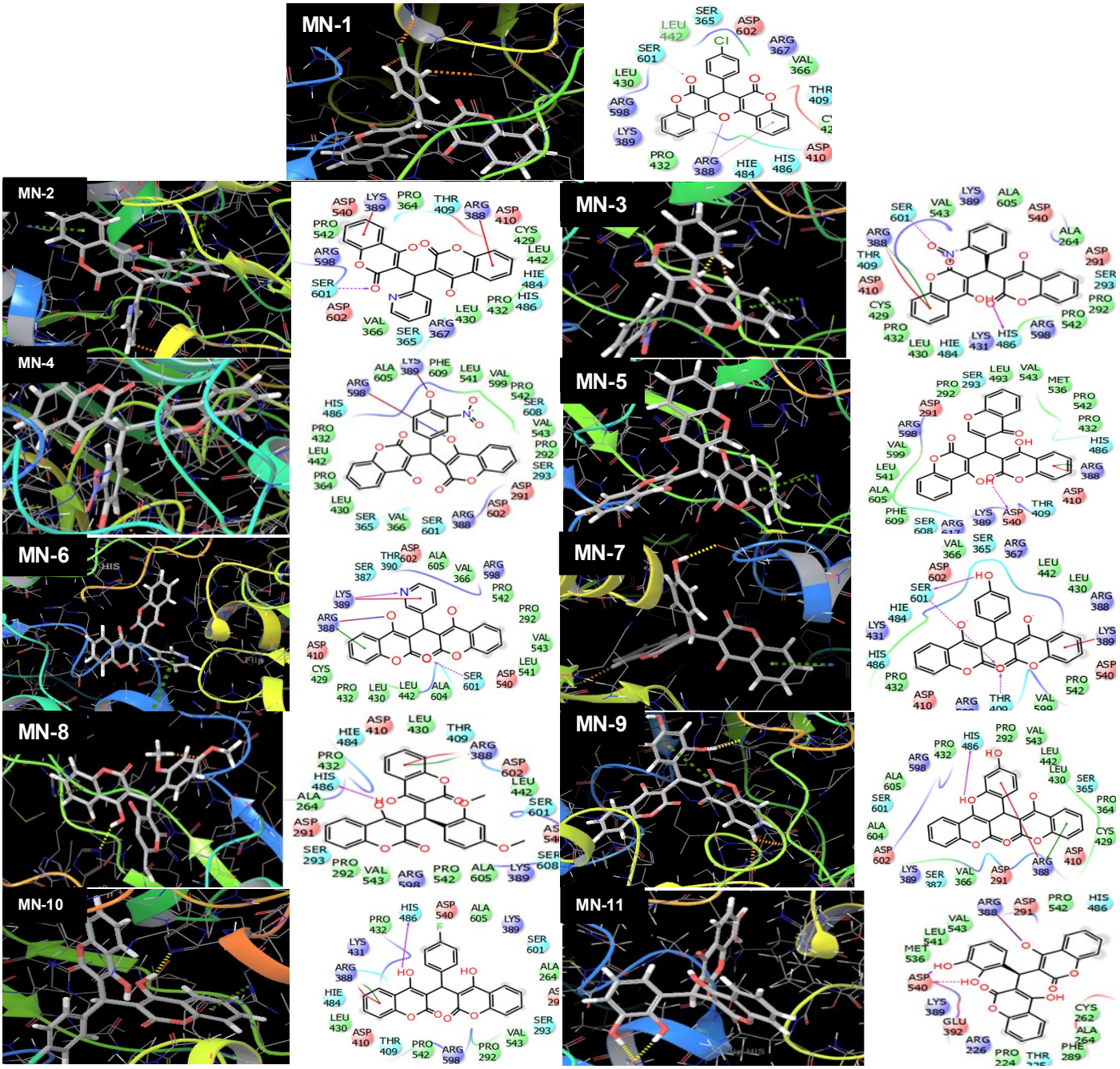


Figure SF-15. 3D and 2D docked poses of all the biscoumarin derivatives against RNA binding cavity of NS3H protein.

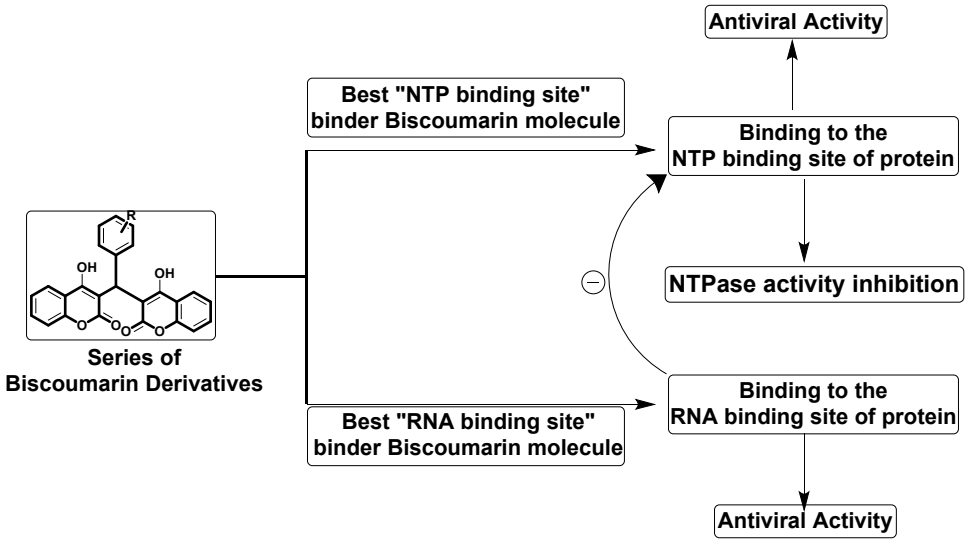


Figure SF-16. Proposed NS3H NTPase modulatory mechanism of biscoumarin derivatives. The biscoumarin derivatives with the best binding ability for the NTP binding cavity of NS3H binds directly to the NTP binding site and causes NTPase inhibitory activity. However, the biscoumarin derivatives having the best binding affinity against the RNA binding cavity binds to the RNA binding site and causes structural modification to the ATP binding site, and imparts a negative impact on the biscoumarin's binding against NTP binding site of the protein. However, we propose that either biscoumarin binds to NTP binding cavity or biscoumarin binds to the RNA binding cavity; the modulation in the NS3H protein occurs in both the case and antiviral activity is also expected in both the case.