Supporting Information

Synthesis and evaluation of novel 12-aryl berberine analogues with hypoxia-inducible factor-1 inhibitory activity

Xiaobo Zhou[#], Ming Chen[#], Zhiyuan Zheng, Guo-Yuan Zhu, Zhi-Hong Jiang[*], Li-Ping Bai[*]

State Key Laboratory of Quality Research in Chinese Medicine, and Macau Institute for Applied Research in Medicine and Health, Macau University of Science and Technology, Taipa, Macau
*Email: lpbai@must.edu.mo ; zhjiang@must.edu.mo

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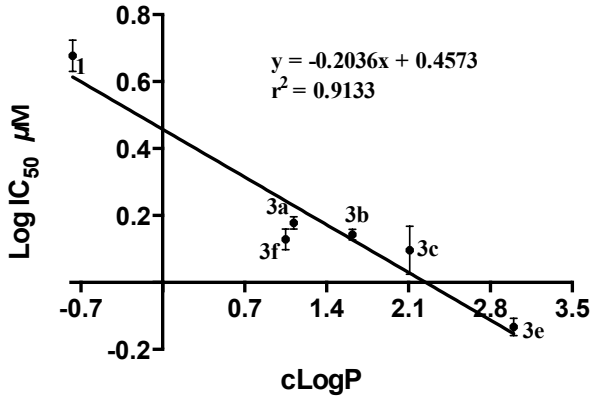
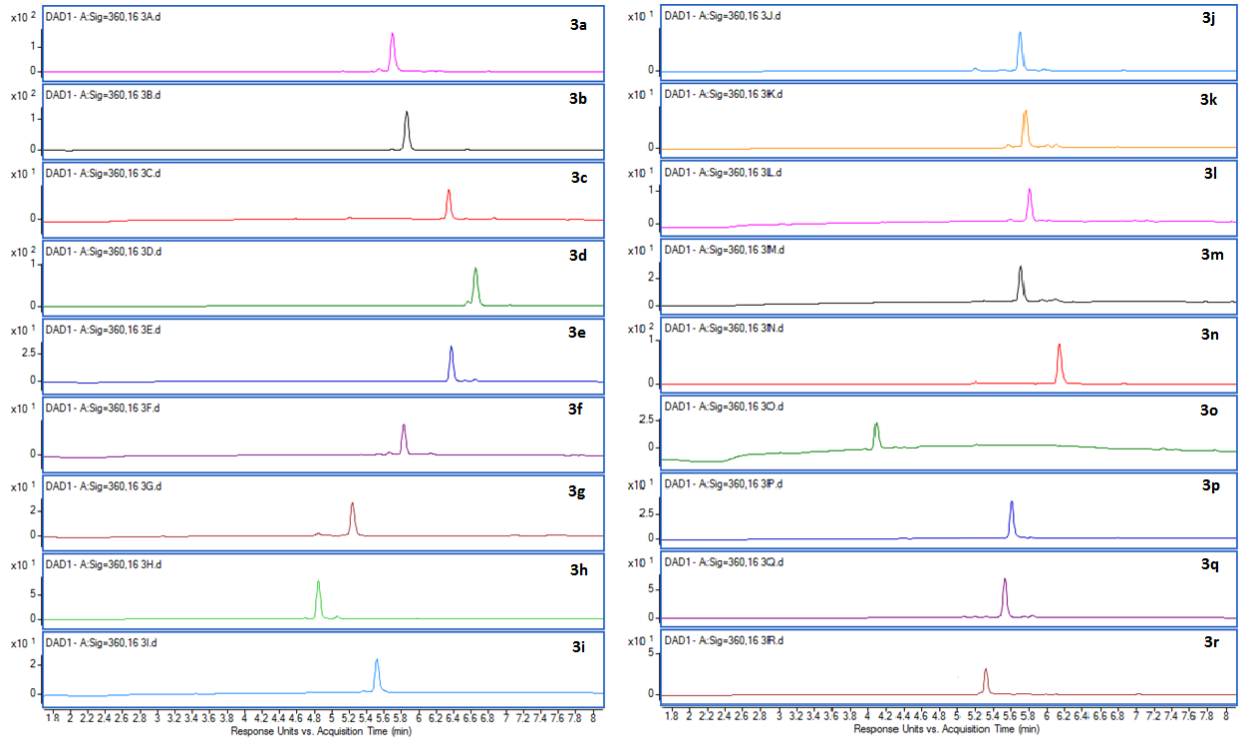


Compd.	HIF-1 inhibitory activity (IC_{50}, μM)	cLogP
1	4.78 ± 0.73	-0.77
3a	1.51 ± 0.09	1.12
3b	1.39 ± 0.07	1.62
3c	1.26 ± 0.29	2.11
3e	0.74 ± 0.06	3.00
3f	1.35 ± 0.14	1.05

Fig. S1 Correlation between Log IC_{50} and cLogP for berberine and its analogues. Partition coefficients (cLogP) were calculated using ChemDraw Ultra, version 12.0.



Compounds	Purity (%)	Compounds	Purity (%)	Compounds	Purity (%)	Compounds	Purity (%)	Compounds	Purity (%)	Compounds	Purity (%)
3a	95.1	**3d**	95.6	**3g**	95.5	**3j**	97.6	**3m**	95.4	**3p**	96.8
3b	95.2	**3e**	95.3	**3h**	95.3	**3k**	94.9	**3n**	96.9	**3q**	95.1
3c	97.5	**3f**	96.1	**3i**	97.4	**3l**	97.3	**3o**	97.3	**3r**	96.2

Fig. S2 UHPLC chromatographs of compounds **3a – 3r**. The purity of compounds **3a – 3r** was determined by the proportion of peak area of **3a-3r** under the wavelength of 360 nm.

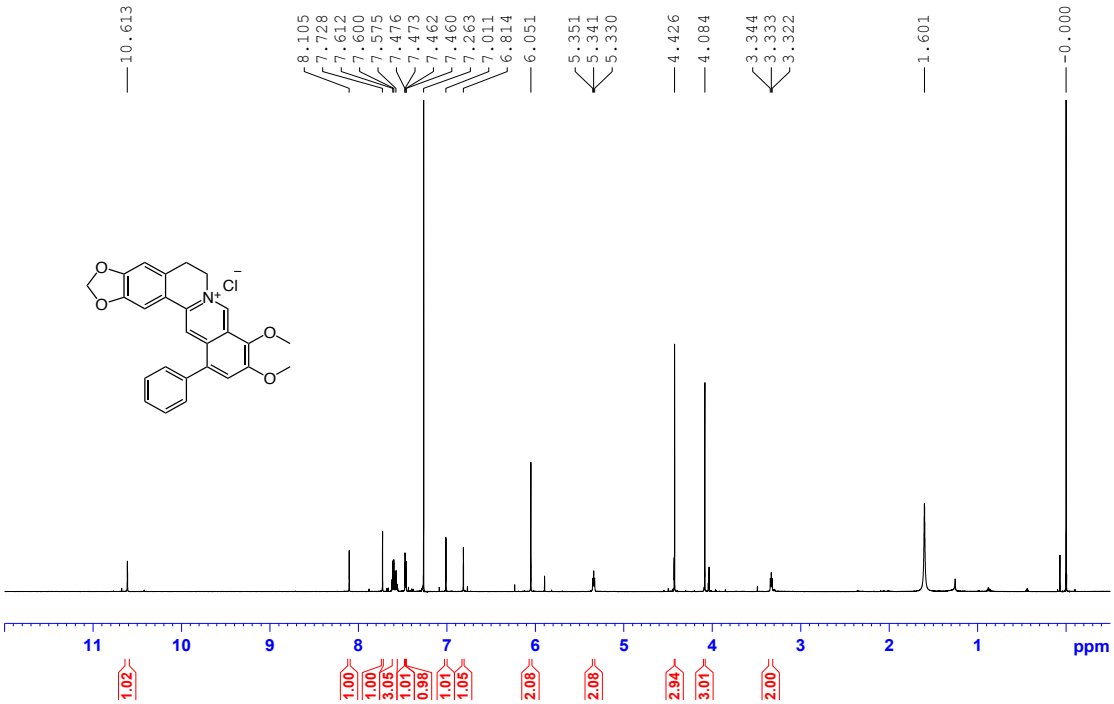


Fig. S3 ^{1}H NMR spectrum of compound **3a**.

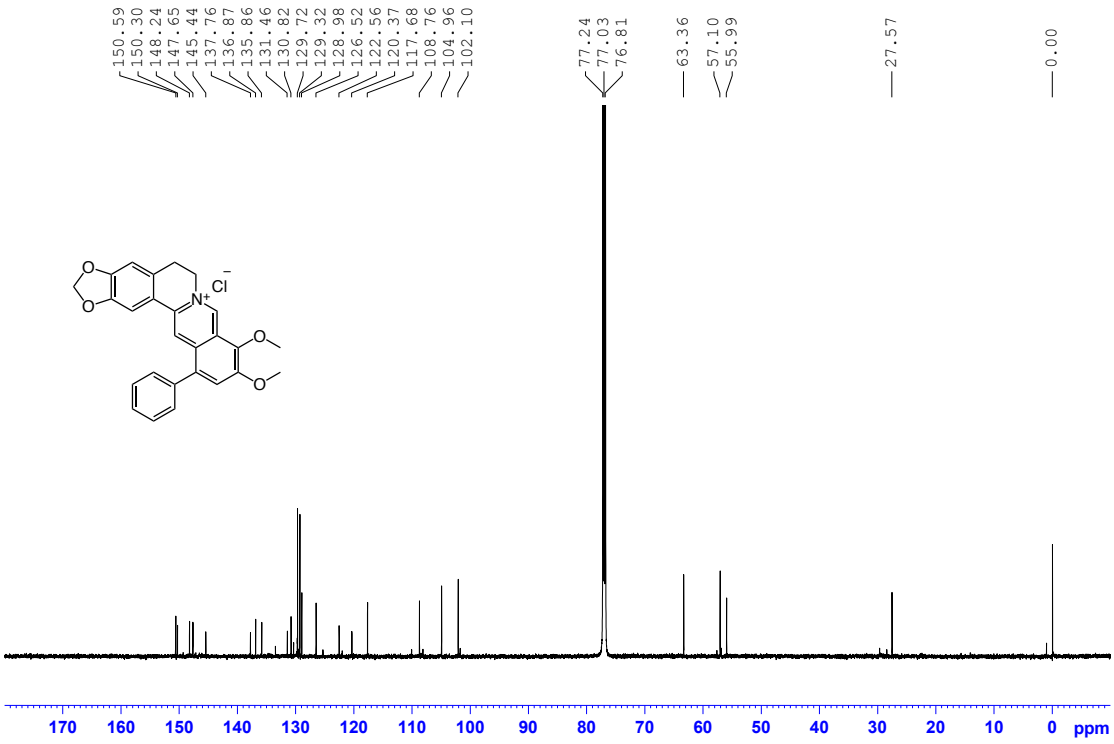


Fig. S4 ^{13}C NMR spectrum of compound **3a**.

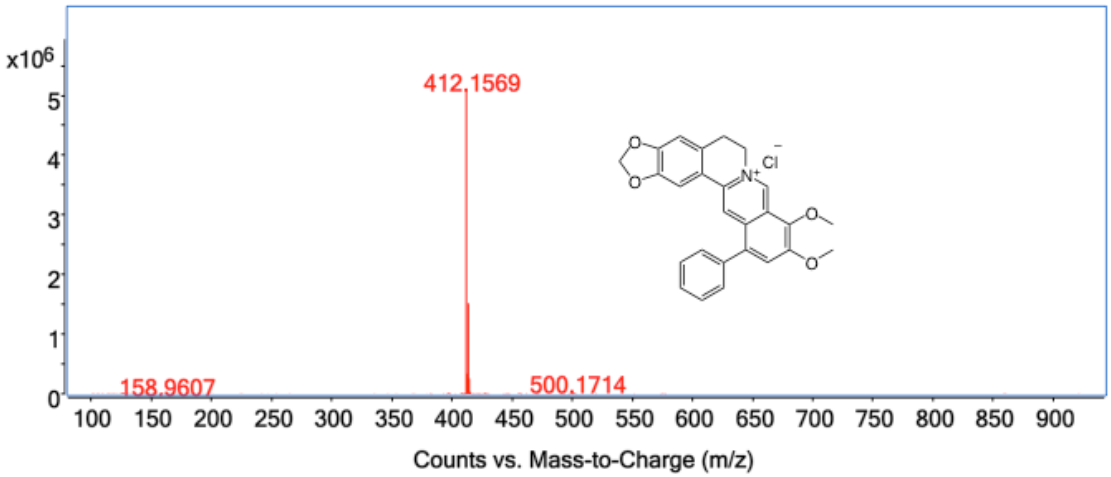


Fig. S5 HR-ESI/TOF-MS spectrum of compound **3a**.

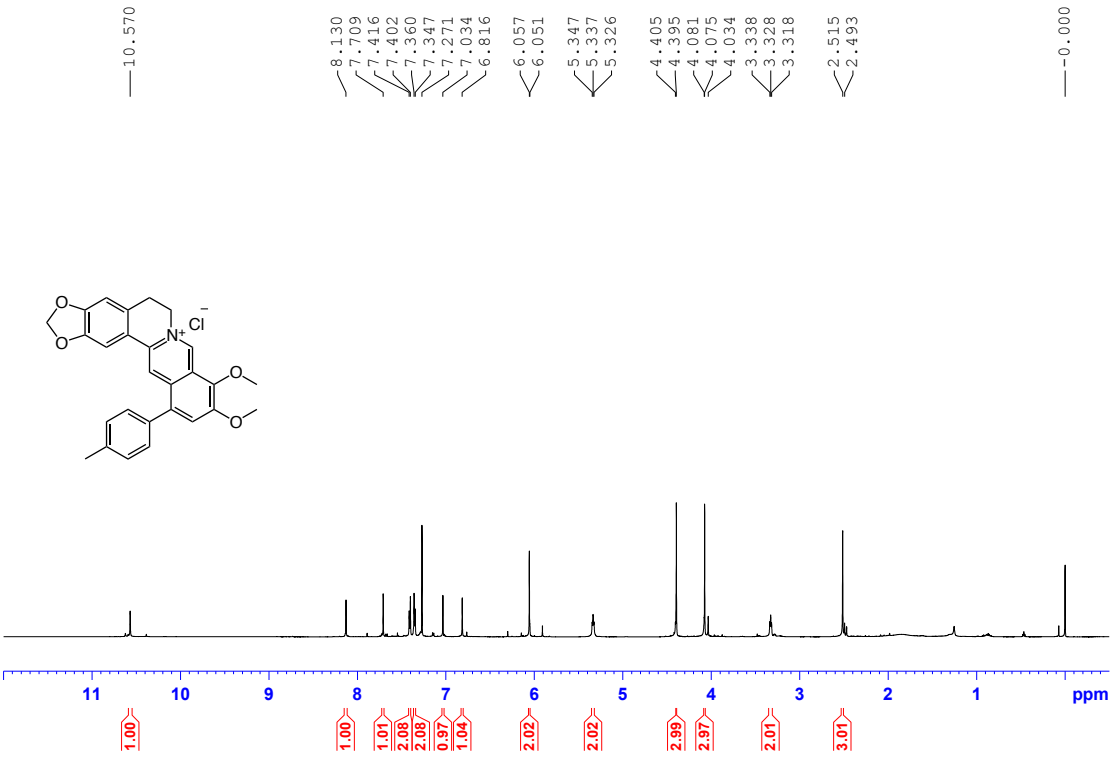


Fig. S6 ^{1}H NMR spectrum of compound **3b**.

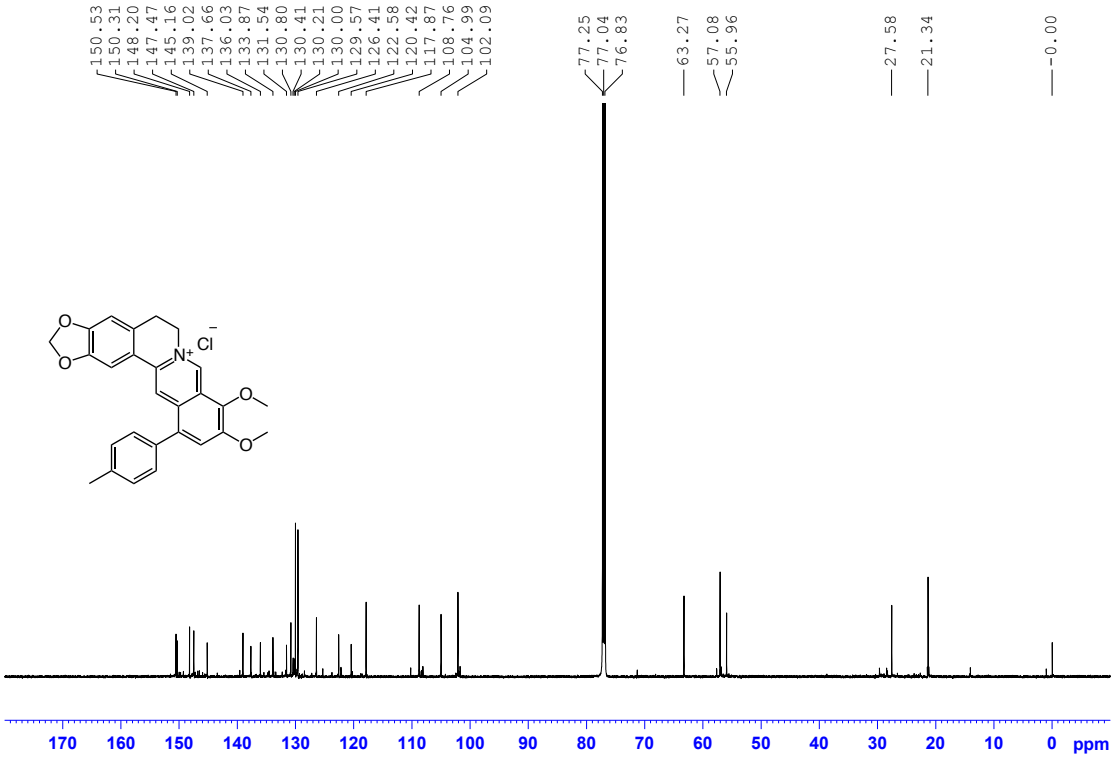


Fig. S7 ^{13}C NMR spectrum of compound **3b**.

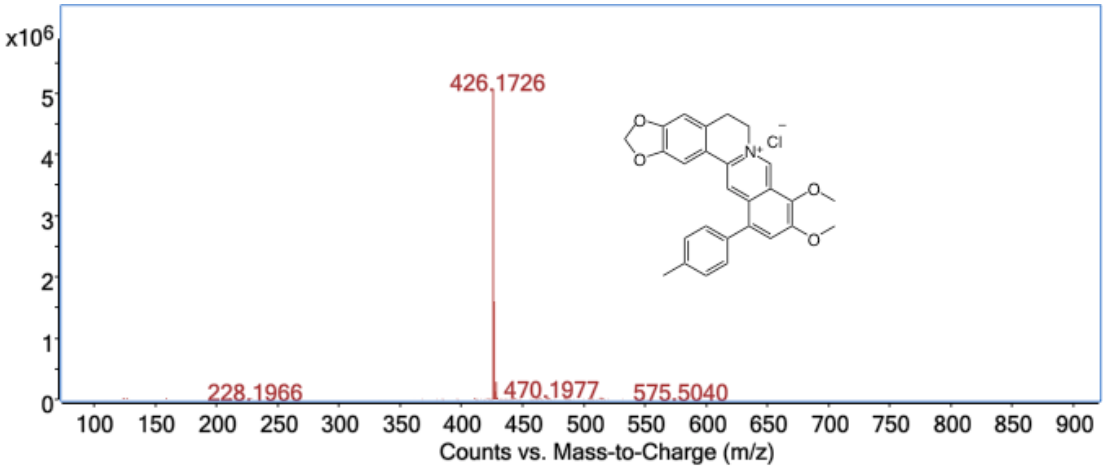


Fig. S8 HR-ESI/TOF-MS spectrum of compound **3b**.

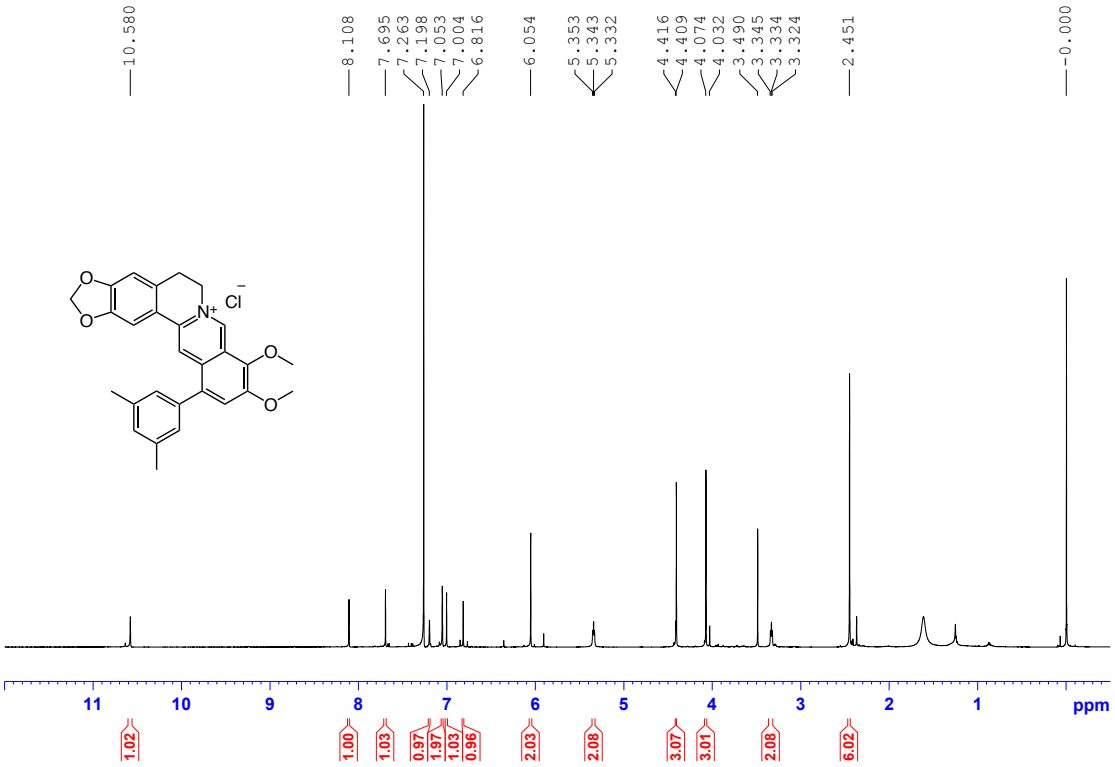


Fig. S9 ^{1}H NMR spectrum of compound **3c**.

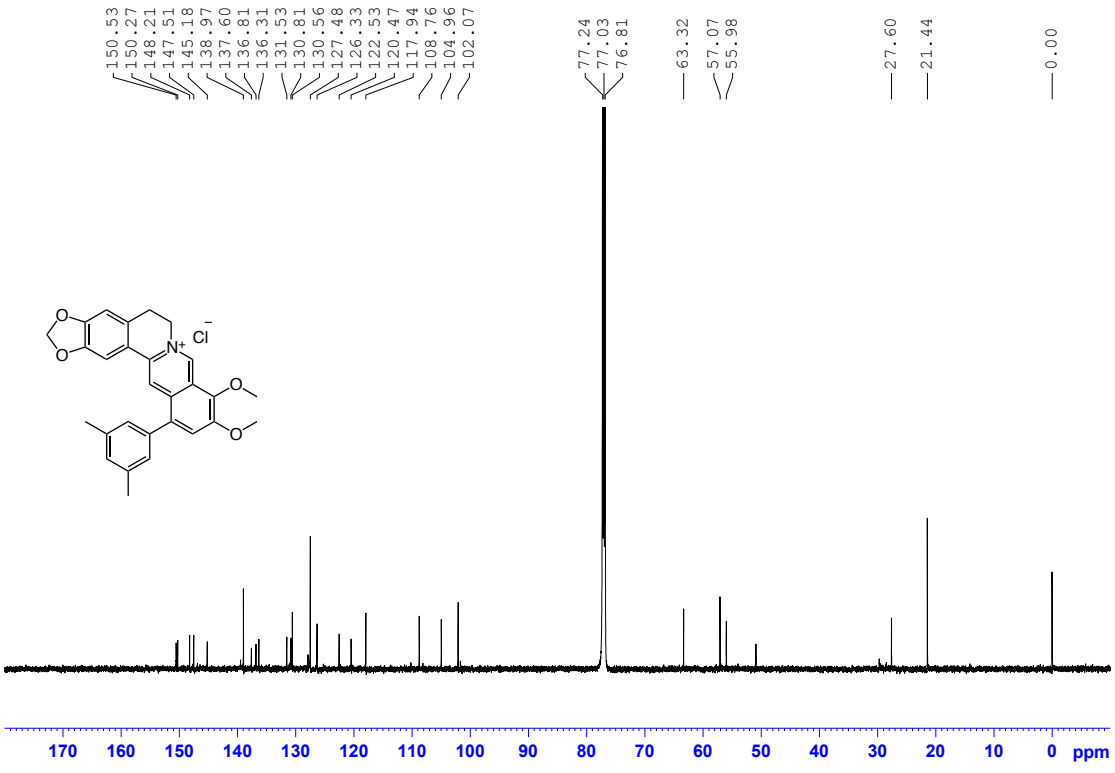


Fig. S10 ^{13}C NMR spectrum of compound **3c.**

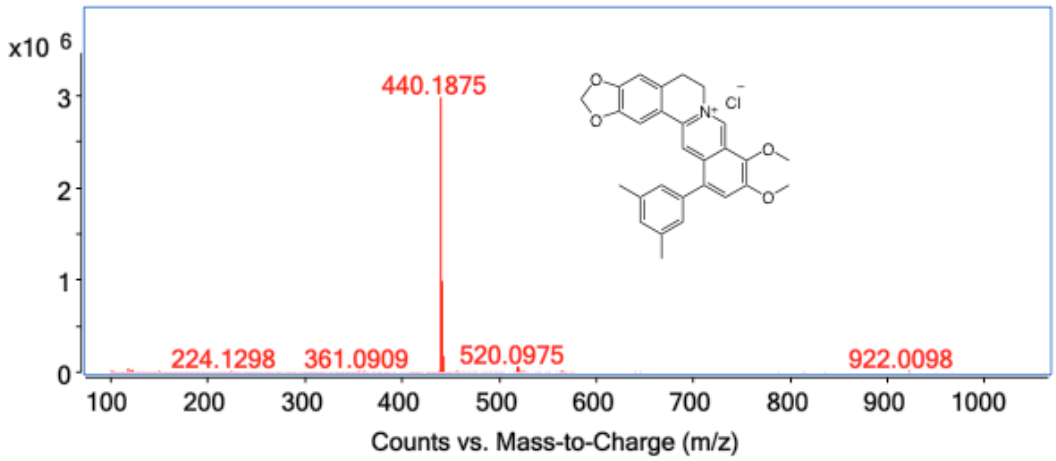


Fig. S11 HR-ESI/TOF-MS spectrum of compound **3c.**

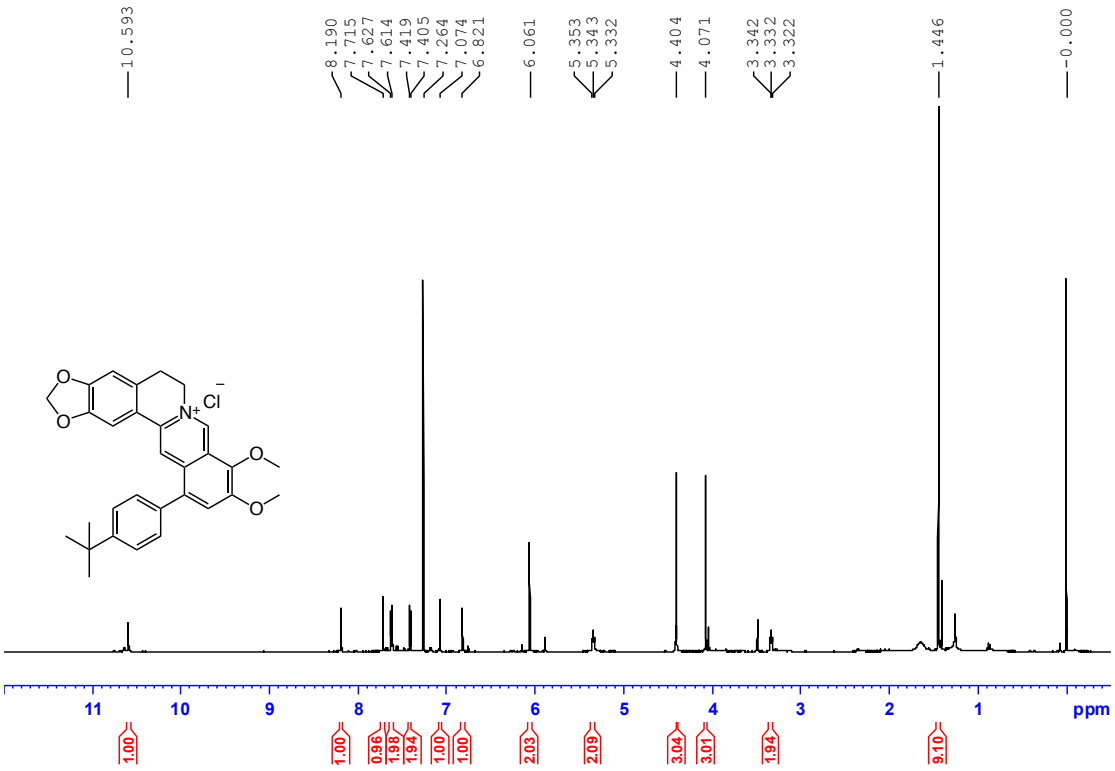


Fig. S12 ^{1}H NMR spectrum of compound **3d**.

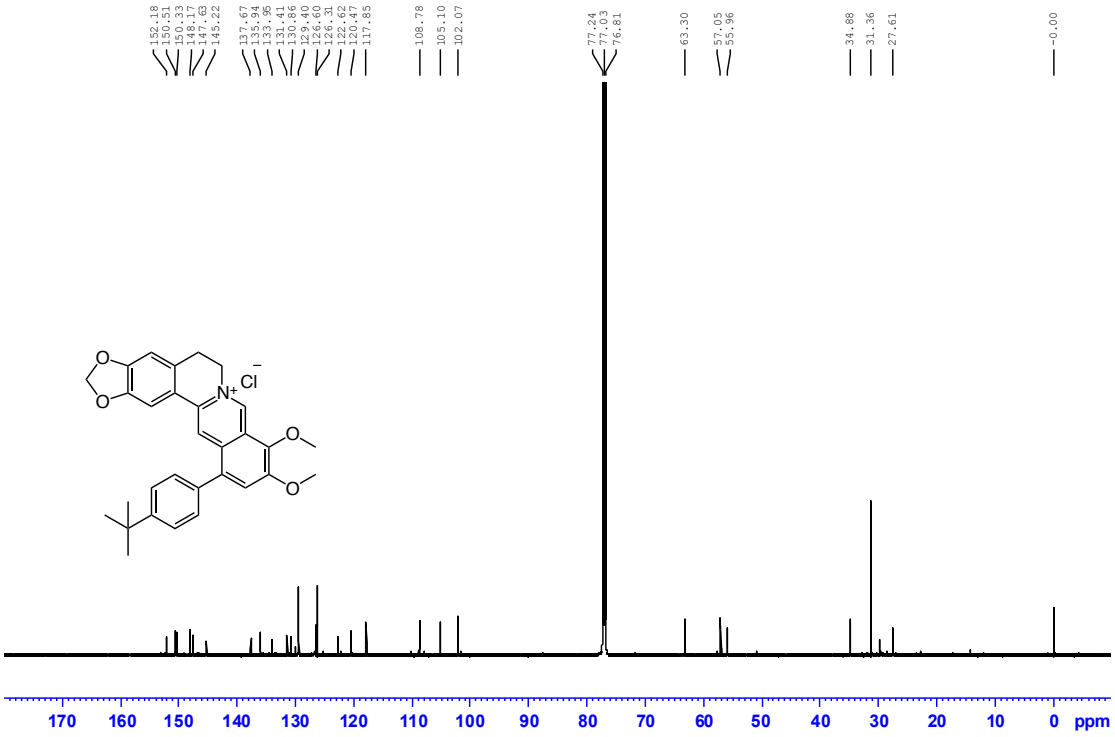


Fig. S13 ^{13}C NMR spectrum of compound **3d.**

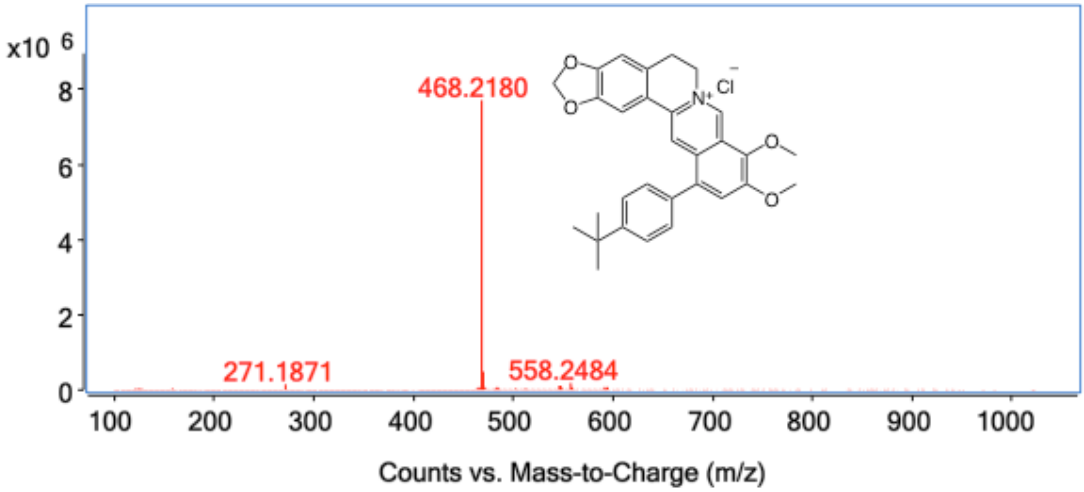


Fig. S14 HR-ESI/TOF-MS spectrum of compound **3d**.

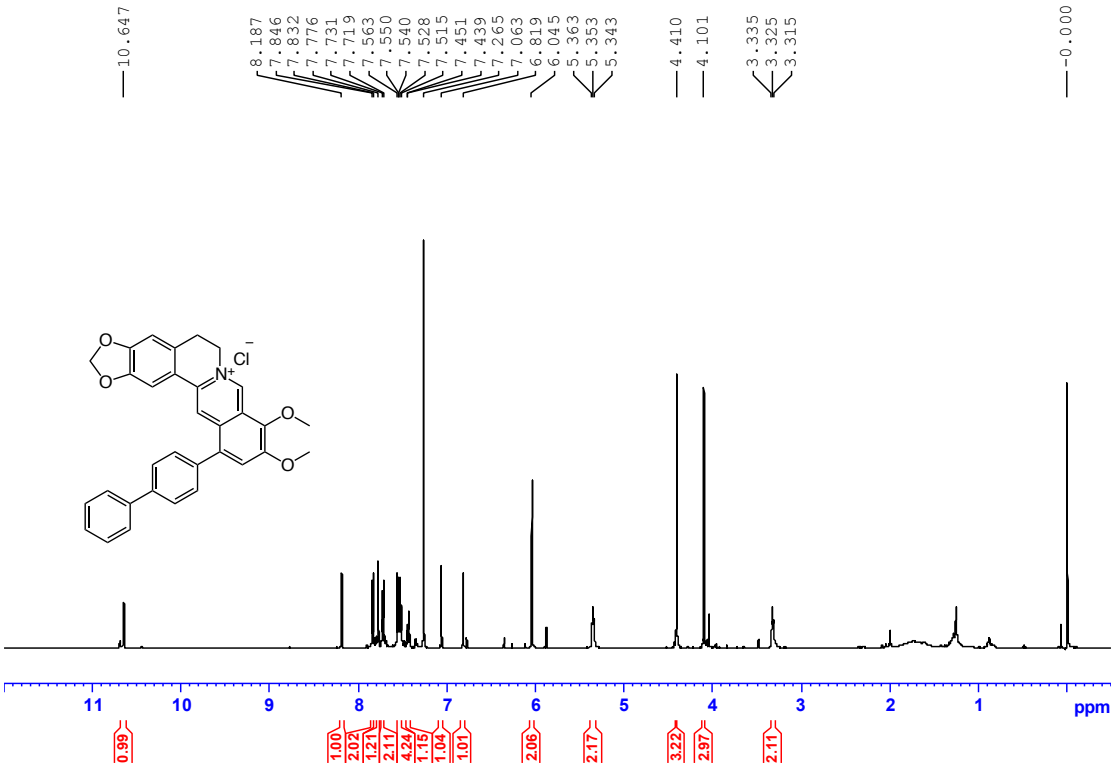


Fig. S15 ^{1}H NMR spectrum of compound **3e**.

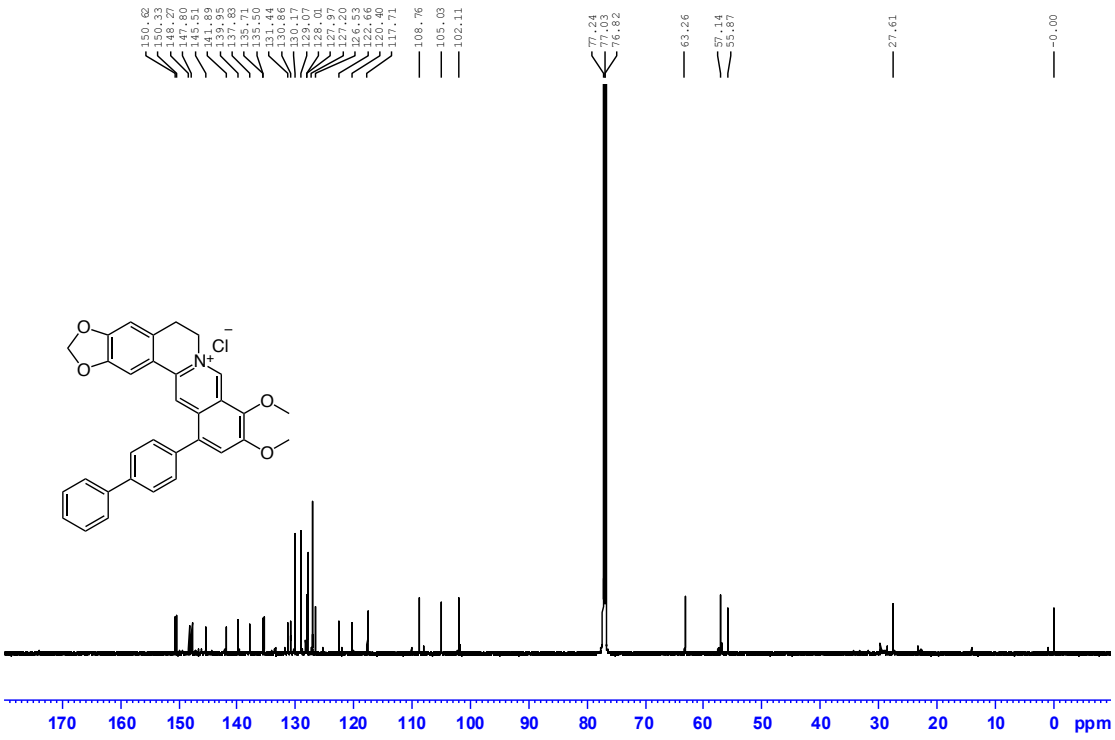


Fig. S16 ^{13}C NMR spectrum of compound **3e**.

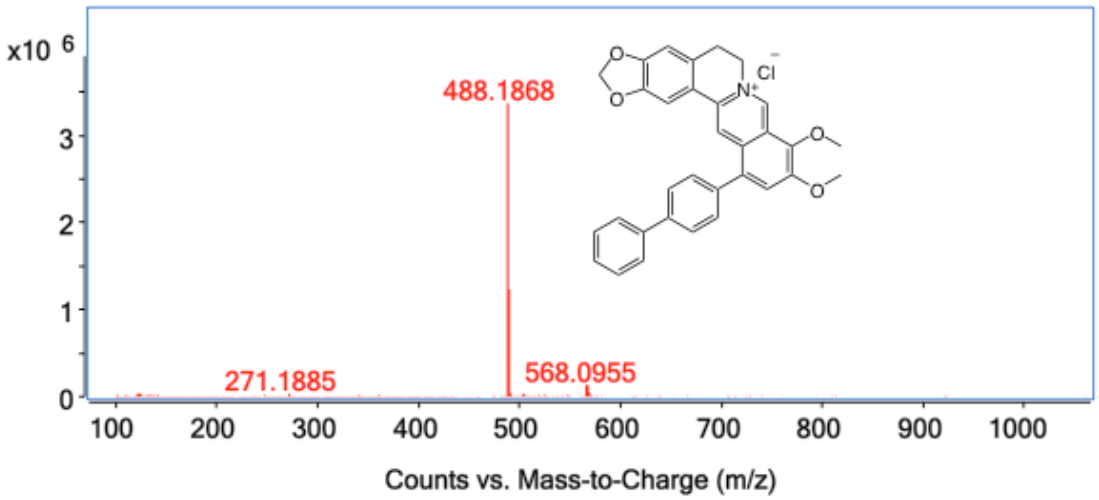


Fig. S17 HR-ESI/TOF-MS spectrum of compound **3e**.

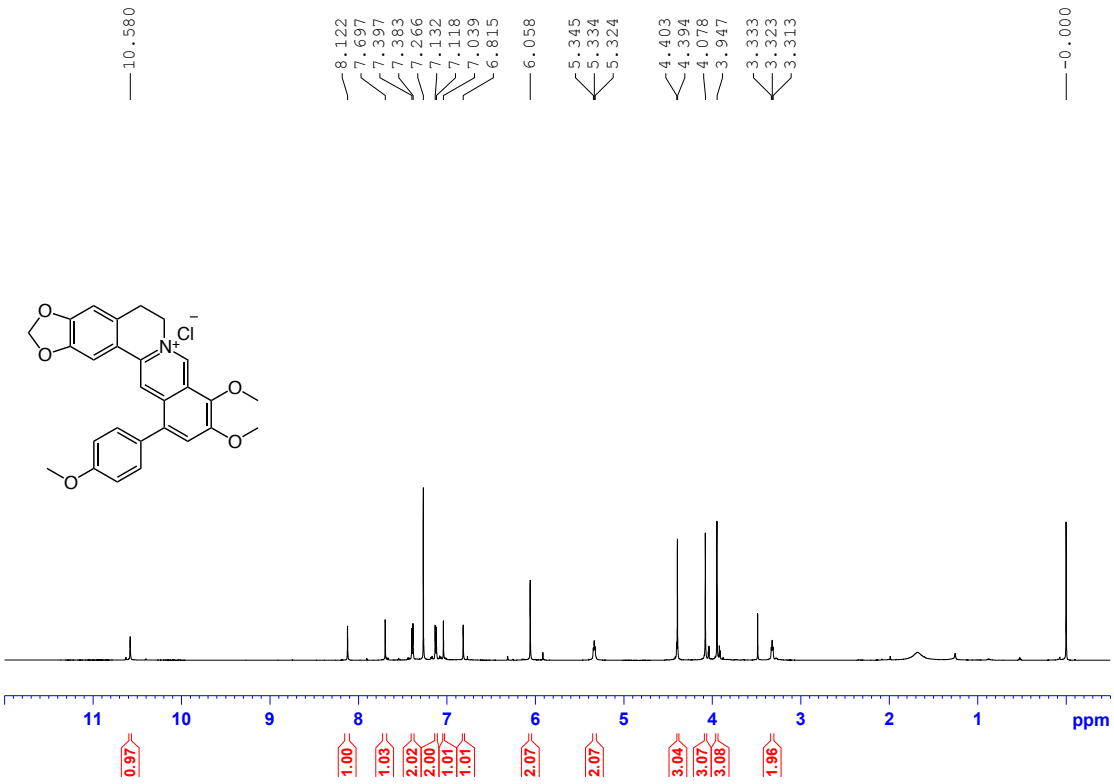


Fig. S18 ^{1}H NMR spectrum of compound **3f**.

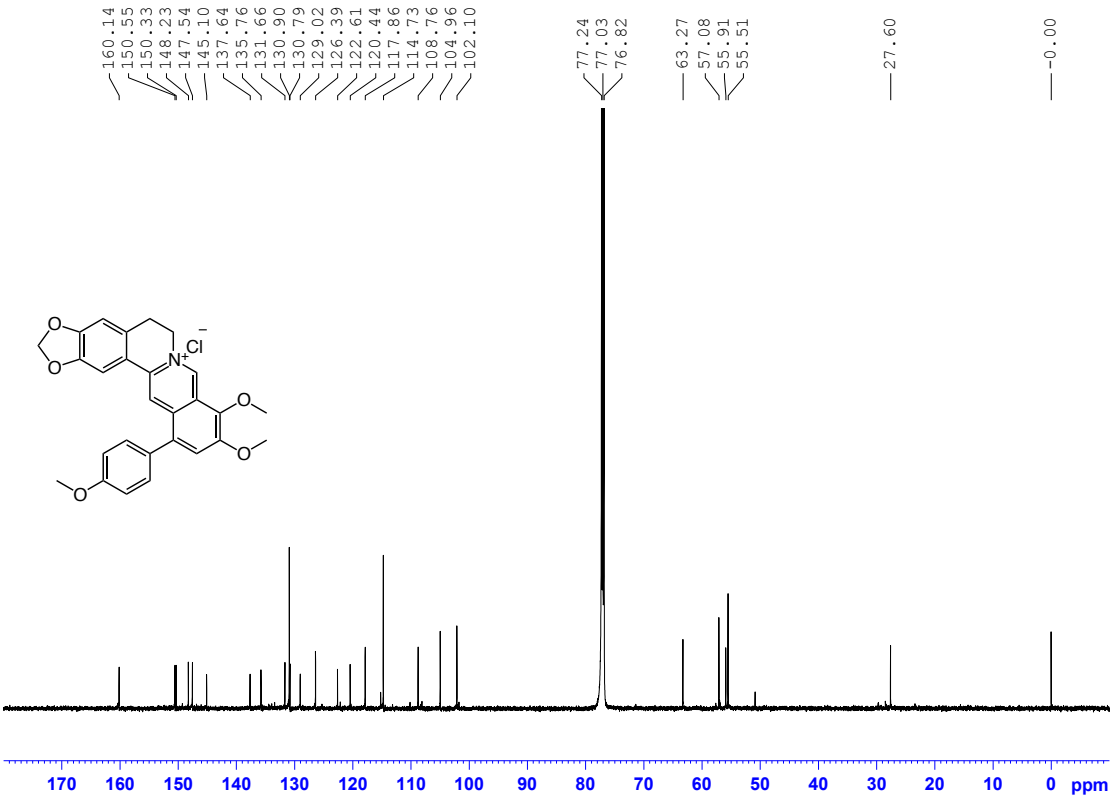


Fig. S19 ^{13}C NMR spectrum of compound **3f.**

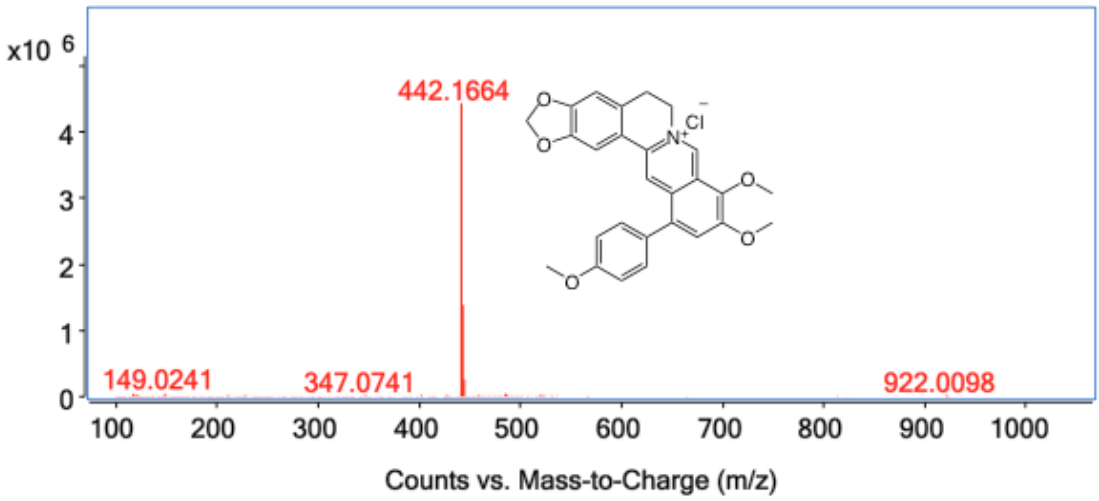


Fig. S20 HR-ESI/TOF-MS spectrum of compound **3f.**

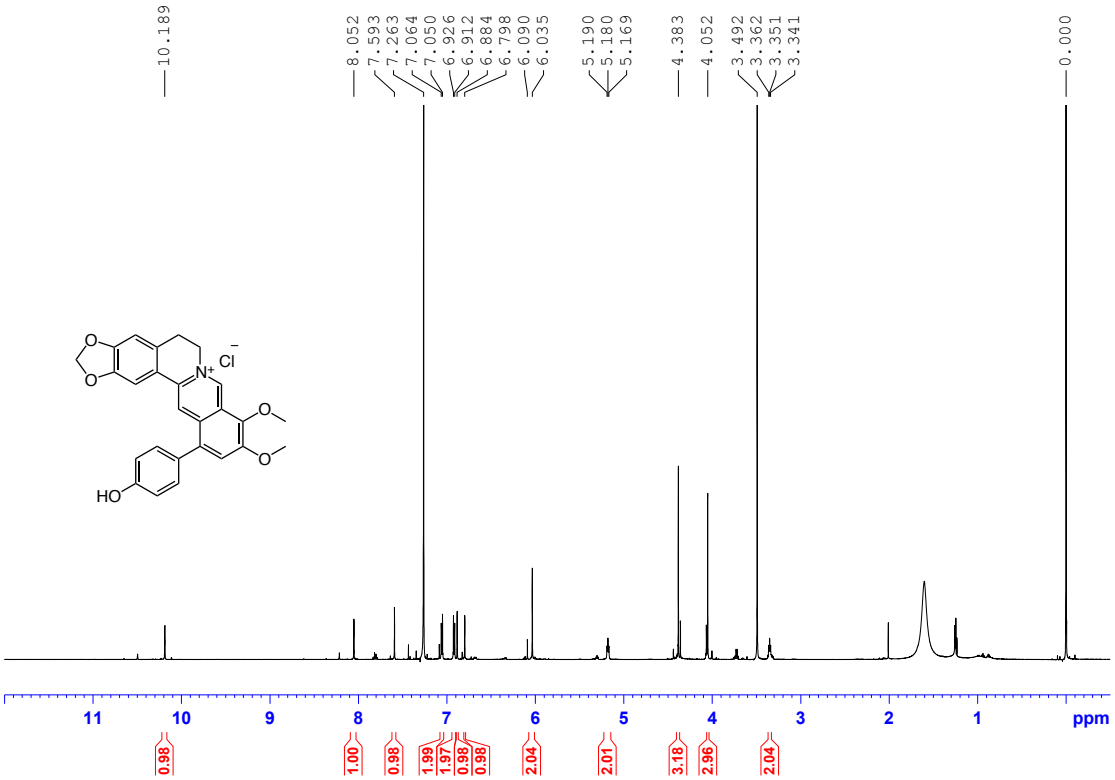


Fig. S21 ^{1}H NMR spectrum of compound **3g**.

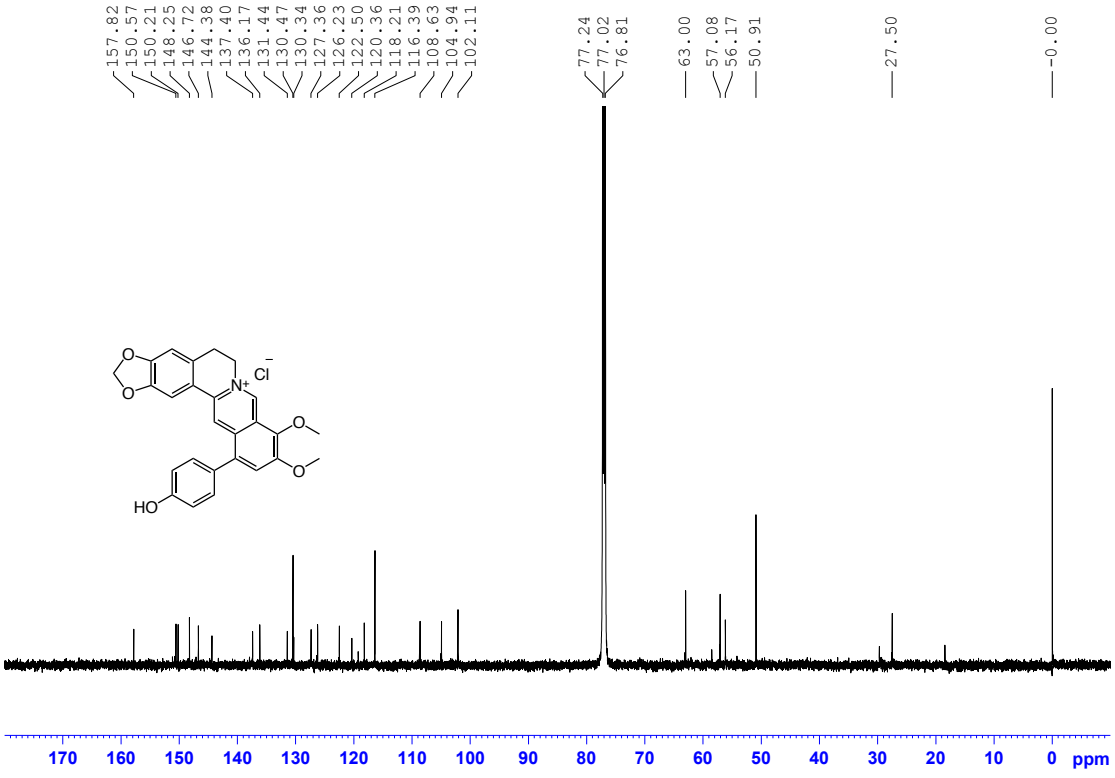


Fig. S22 ^{13}C NMR spectrum of compound **3g**.

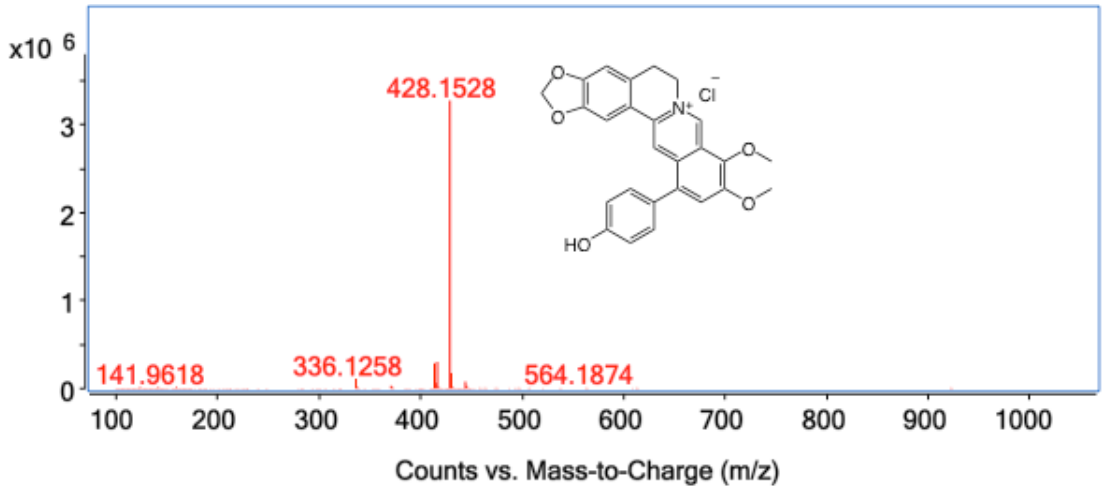


Fig. S23 HR-ESI/TOF-MS spectrum of compound **3g**.

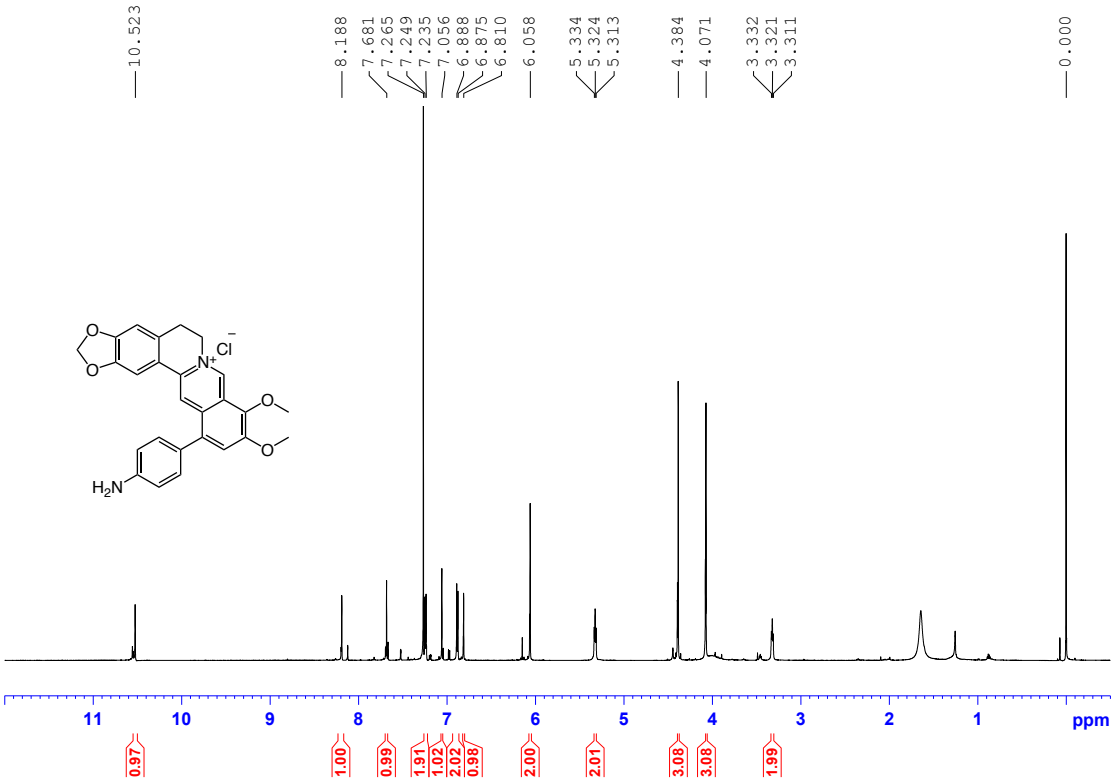


Fig. S24 ^{1}H NMR spectrum of compound **3h**.

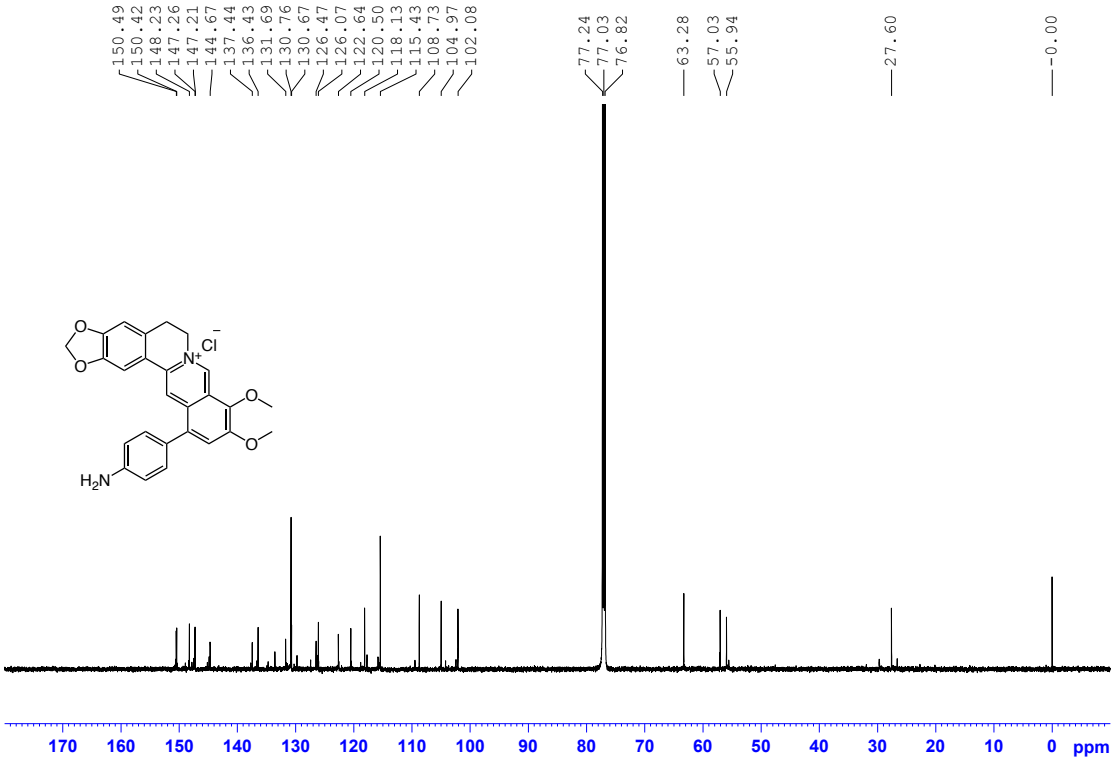


Fig. S25 ^{13}C NMR spectrum of compound **3h**.

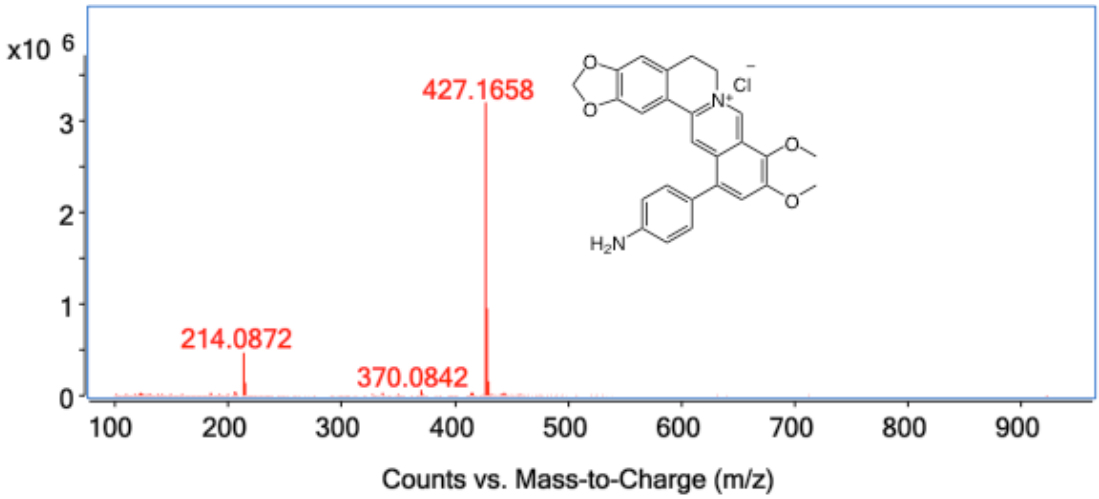


Fig. S26 HR-ESI/TOF-MS spectrum of compound **3h**.

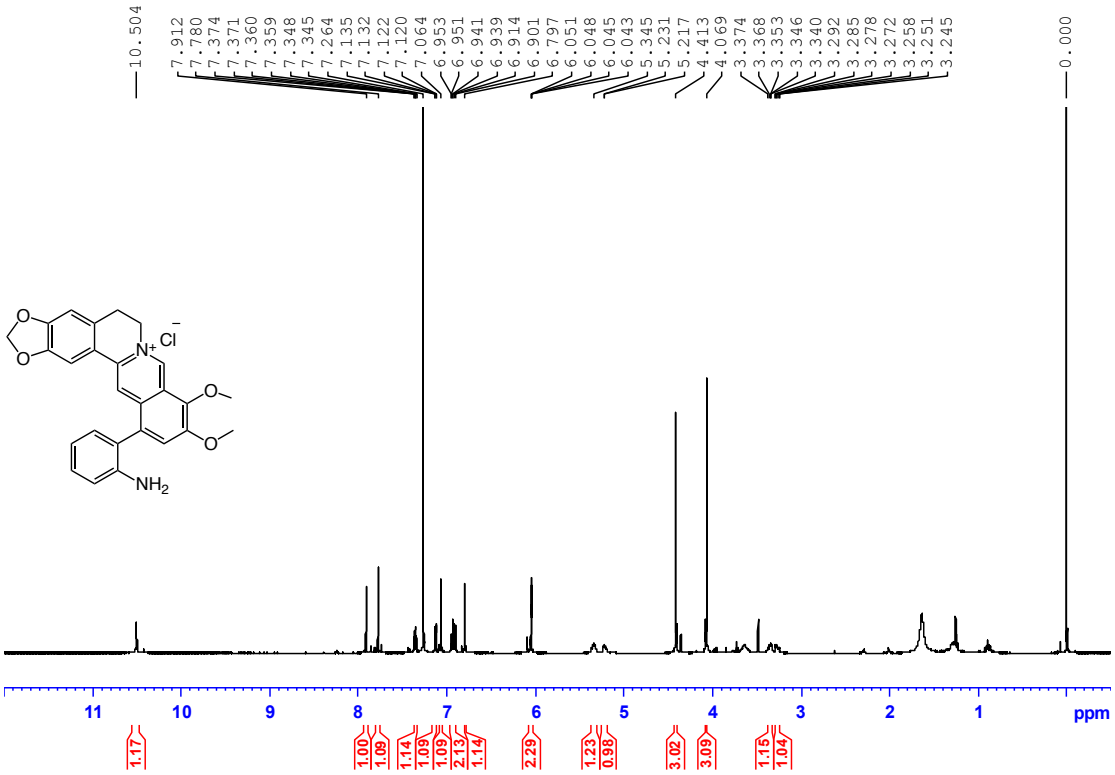


Fig. S27 ^{1}H NMR spectrum of compound **3i**.

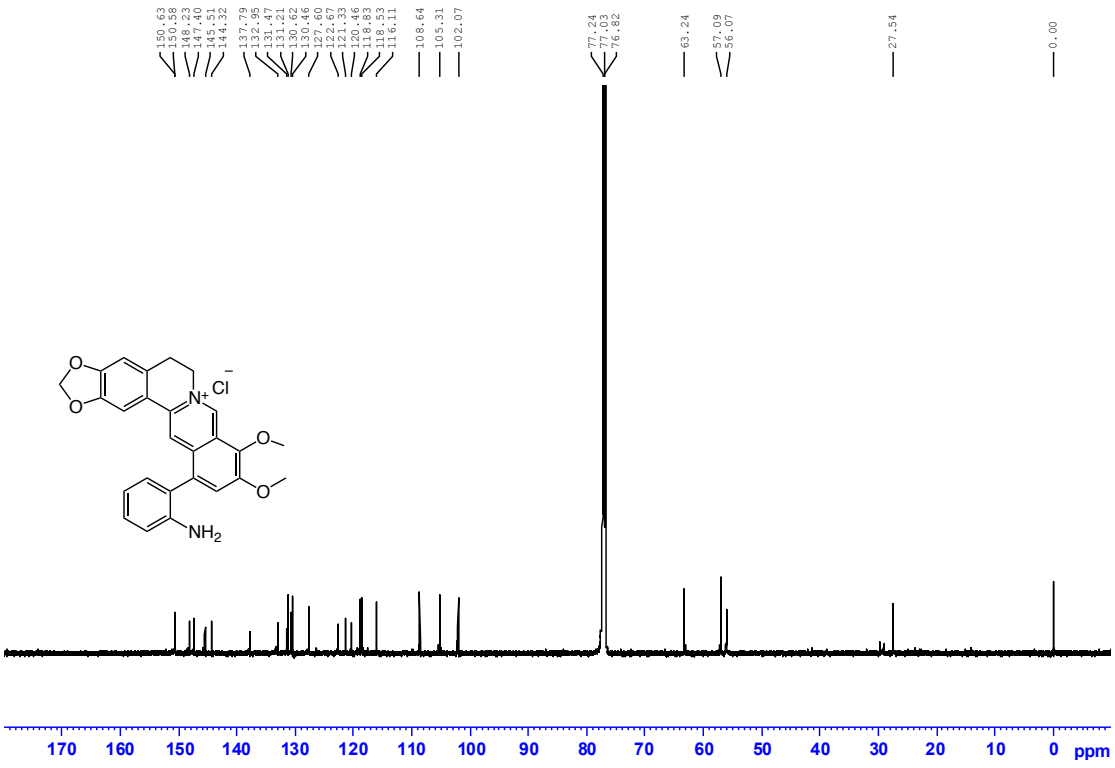


Fig. S28 ^{13}C NMR spectrum of compound **3i**.

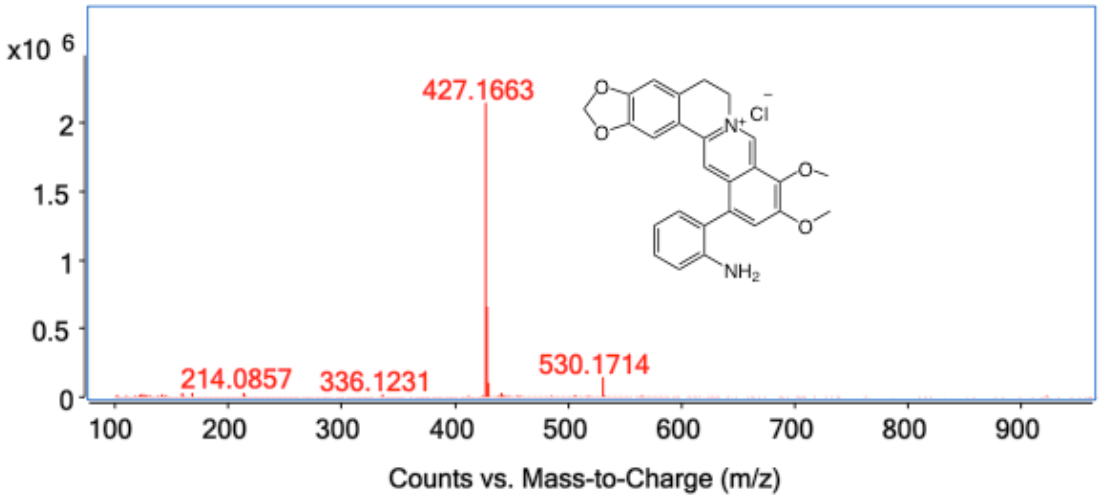


Fig. S29 HR-ESI/TOF-MS spectrum of compound **3i**.

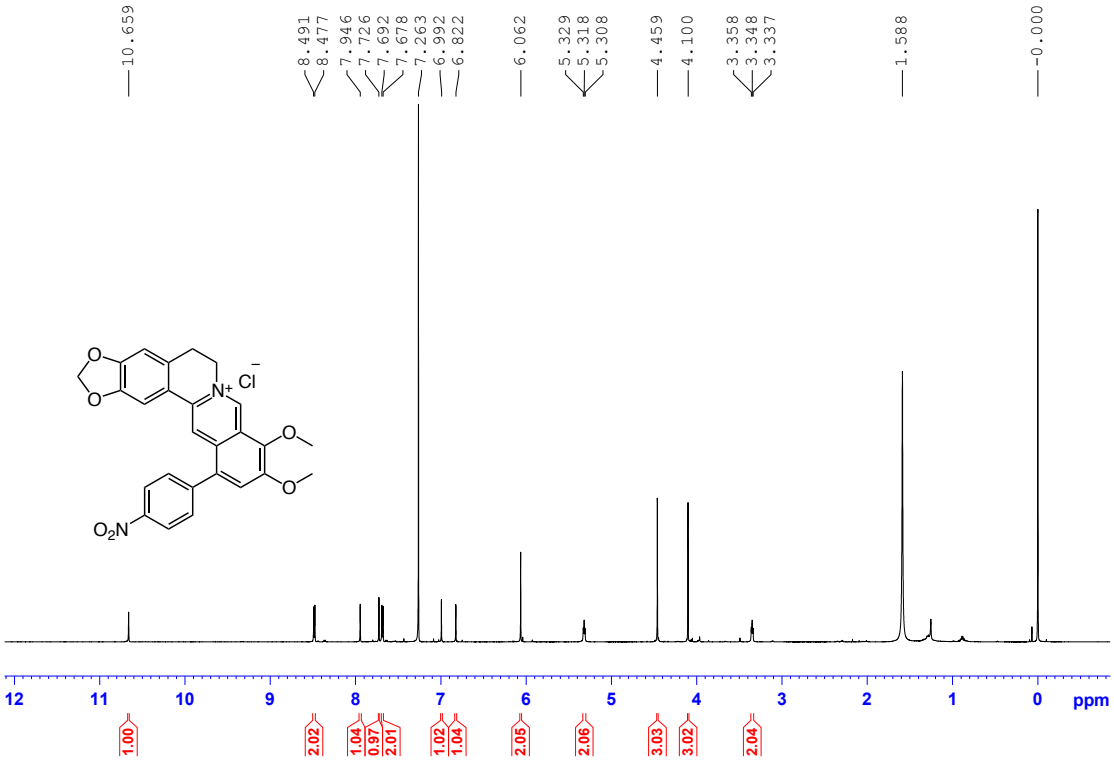


Fig. S30 ^{1}H NMR spectrum of compound **3j**.

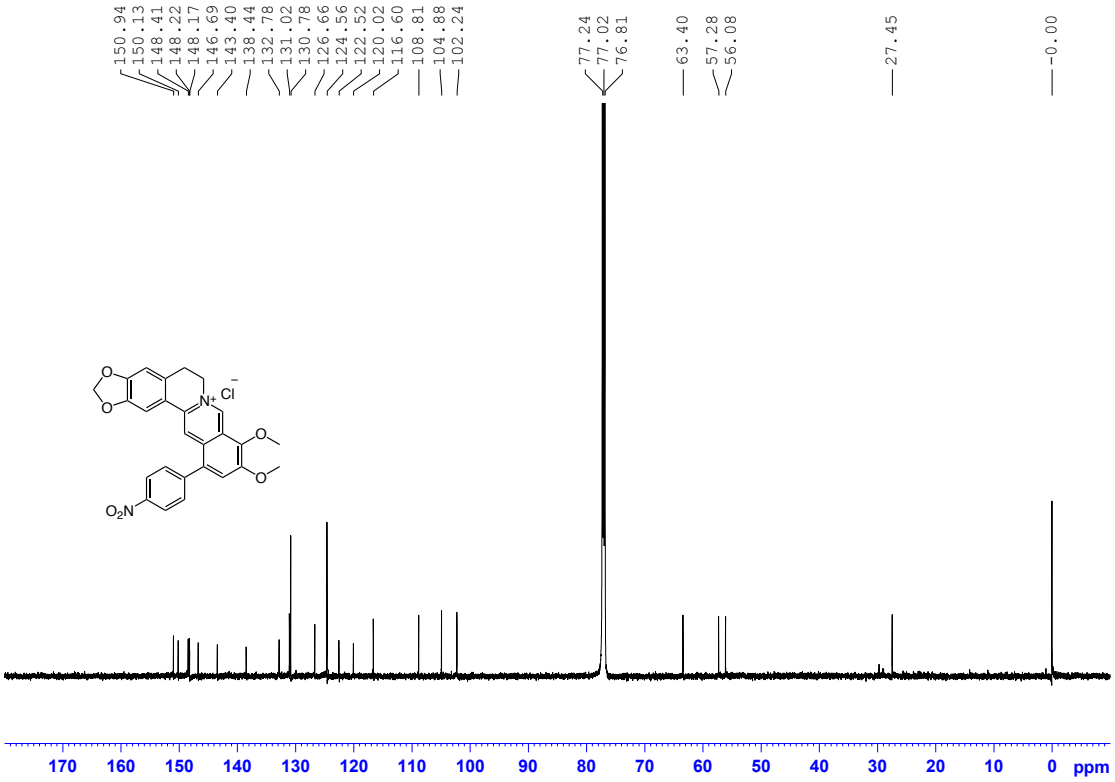


Fig. S31 ^{13}C NMR spectrum of compound **3j**.

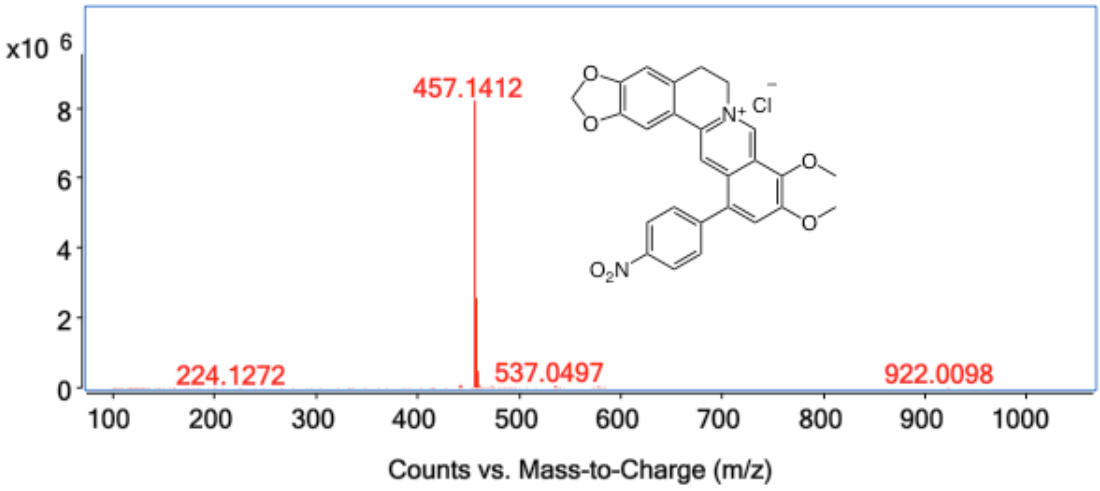


Fig. S32 HR-ESI/TOF-MS spectrum of compound **3j**.

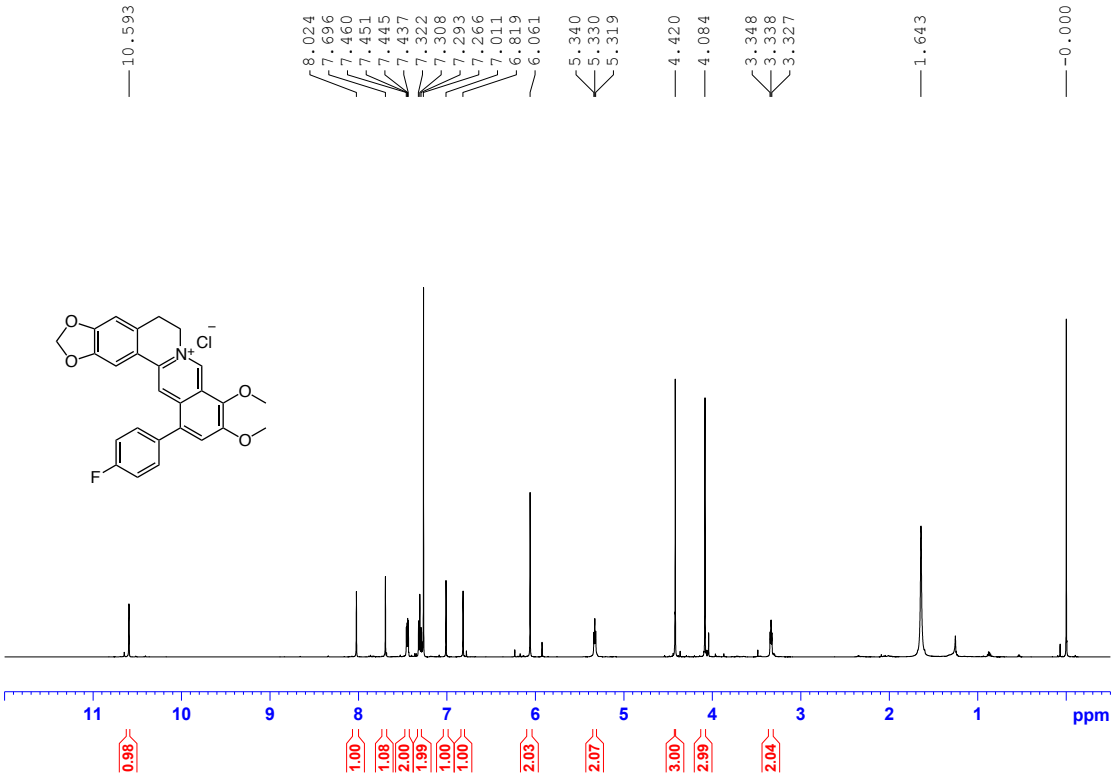


Fig. S33 ^{1}H NMR spectrum of compound **3k**.

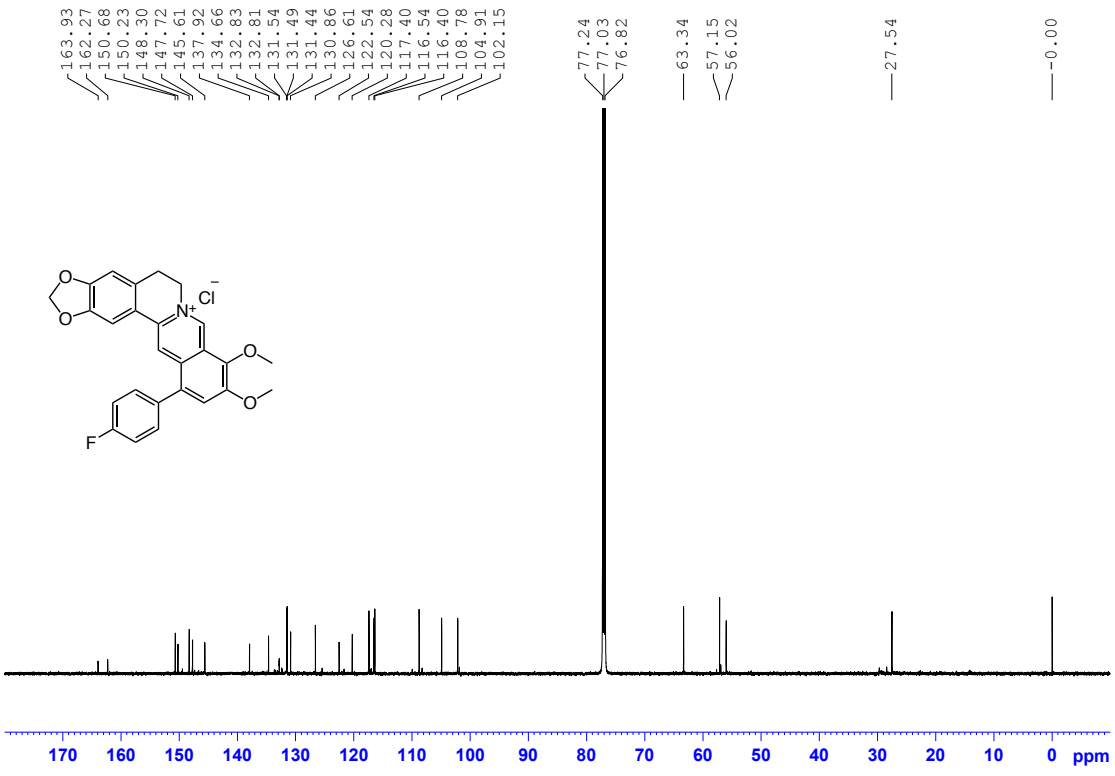


Fig. S34 ^{13}C NMR spectrum of compound **3k.**

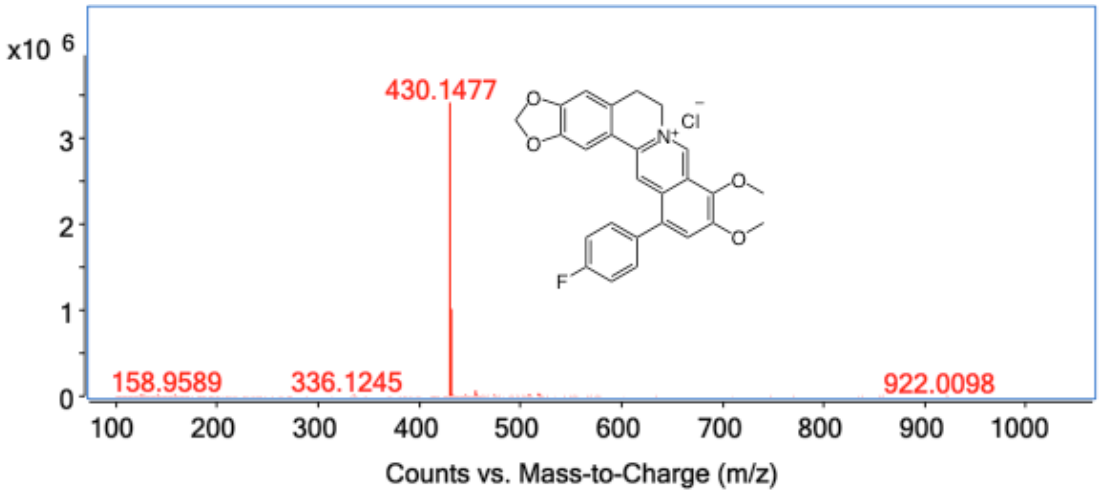


Fig. S35 HR-ESI/TOF-MS spectrum of compound **3k.**

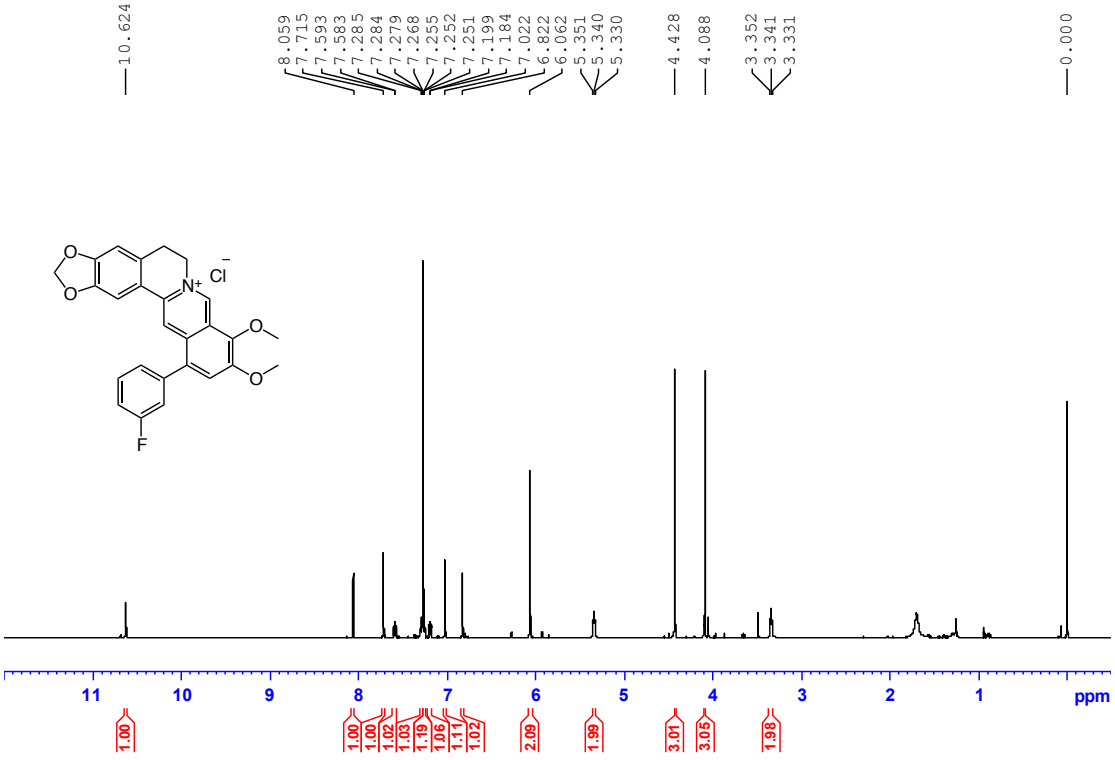


Fig. S36 ^{1}H NMR spectrum of compound **3l**.

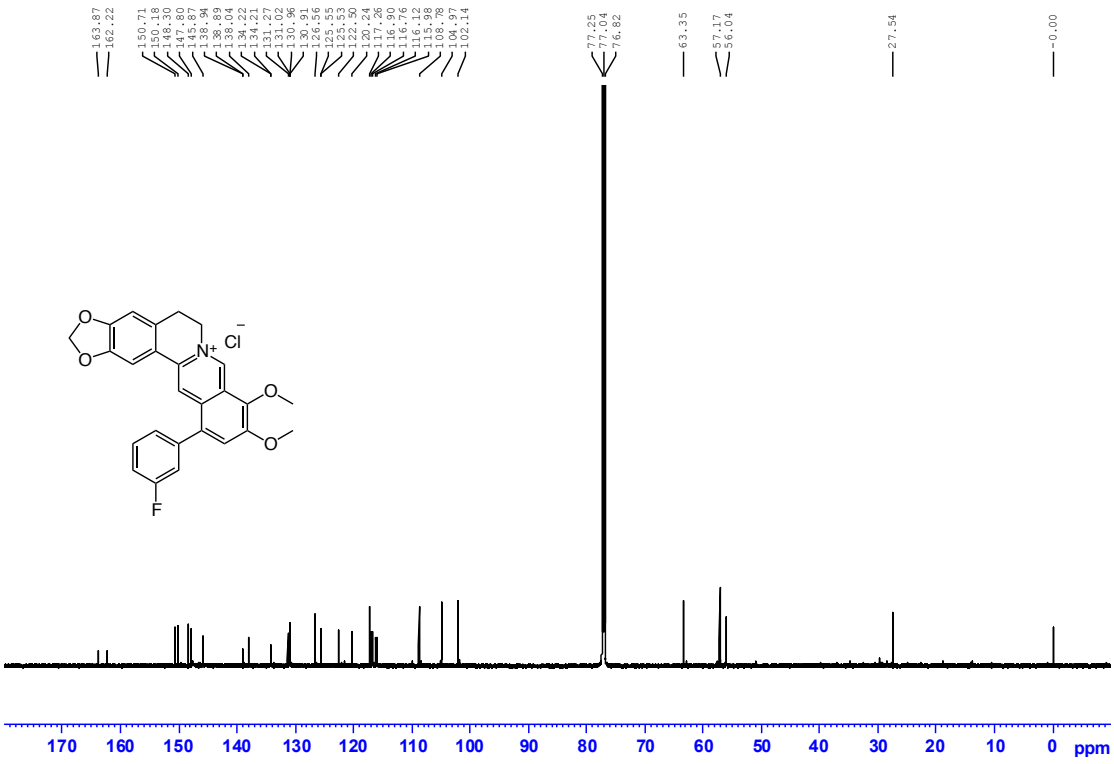


Fig. S37 ^{13}C NMR of compound **3l.**

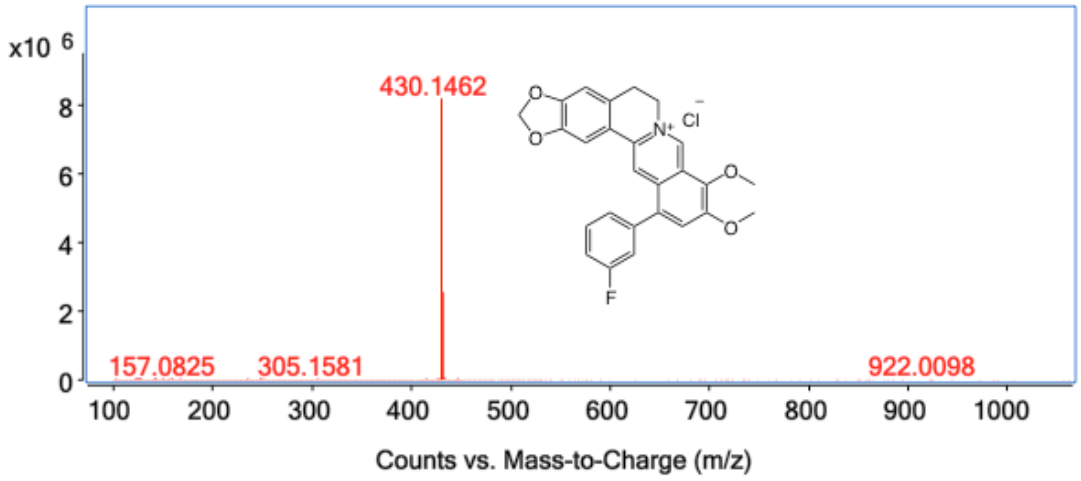


Fig. S38 HR-ESI/TOF-MS of compound **3l.**

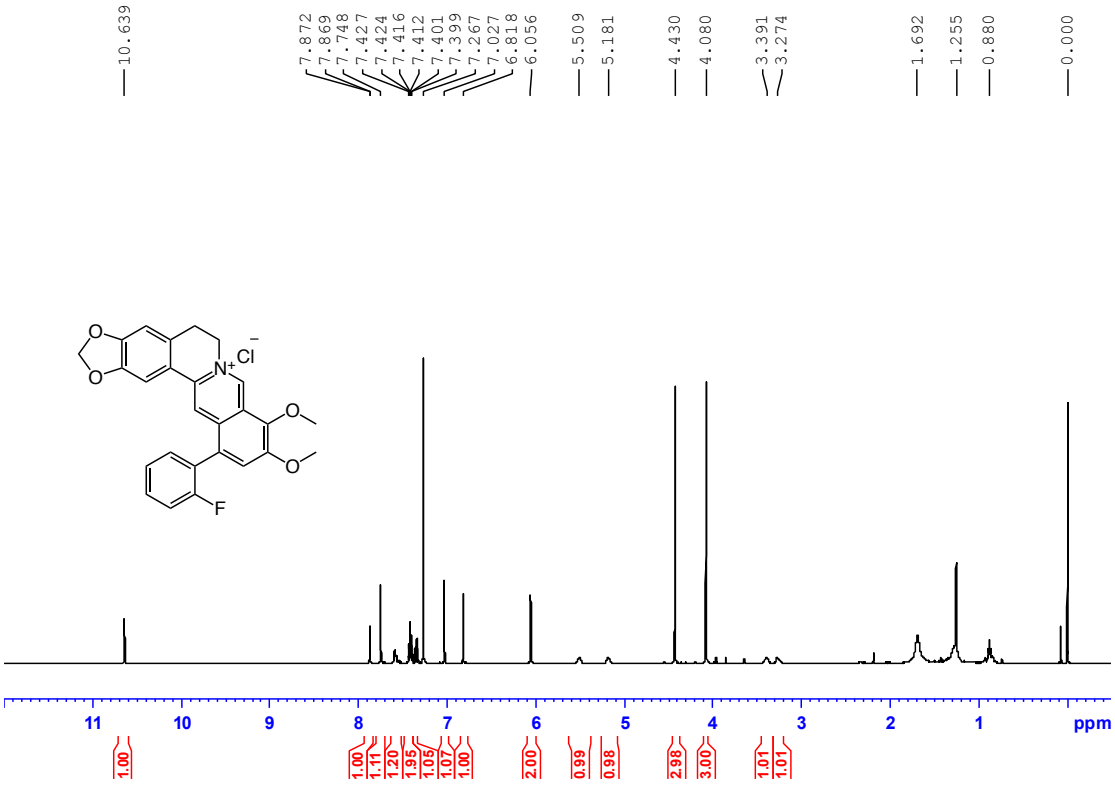


Fig. S39 ^{1}H NMR spectrum of compound **3m**.

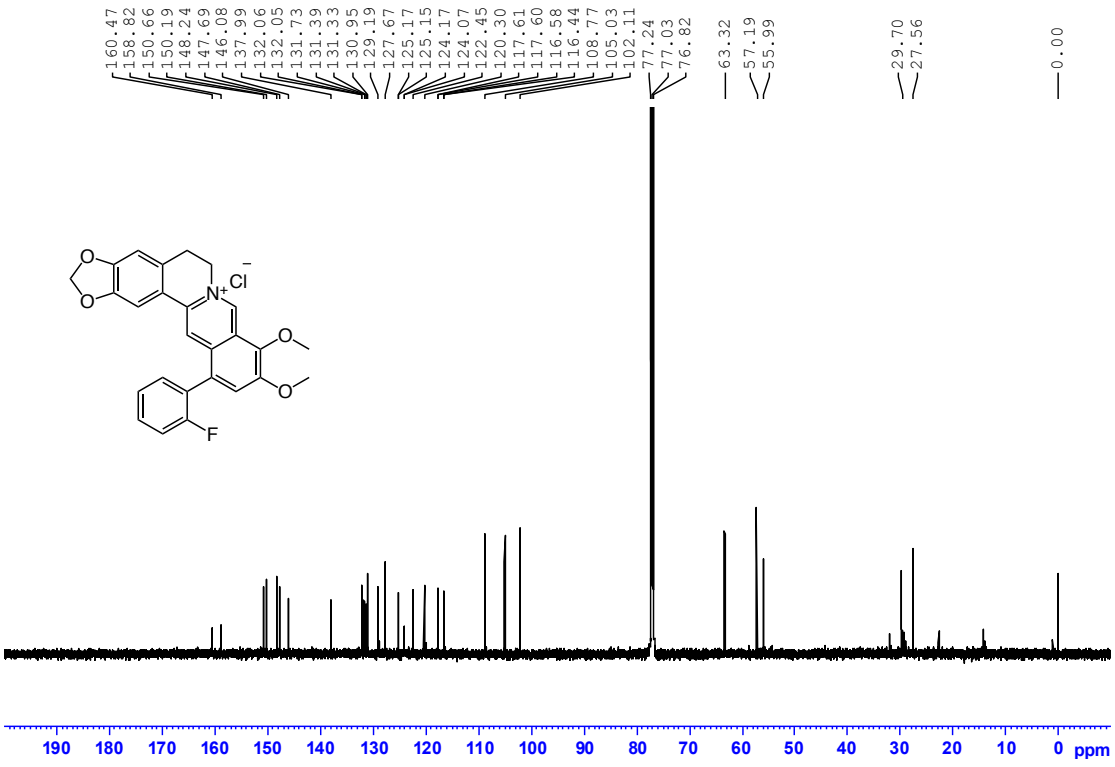


Fig. S40 ^{13}C NMR spectrum of compound **3m.**

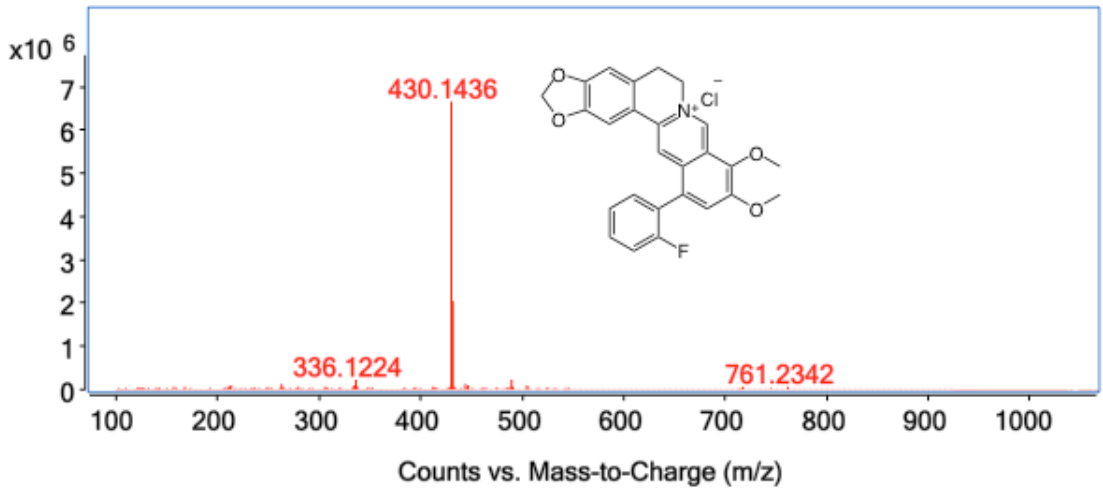


Fig. S41 HR-ESI/TOF-MS spectrum of compound **3m.**

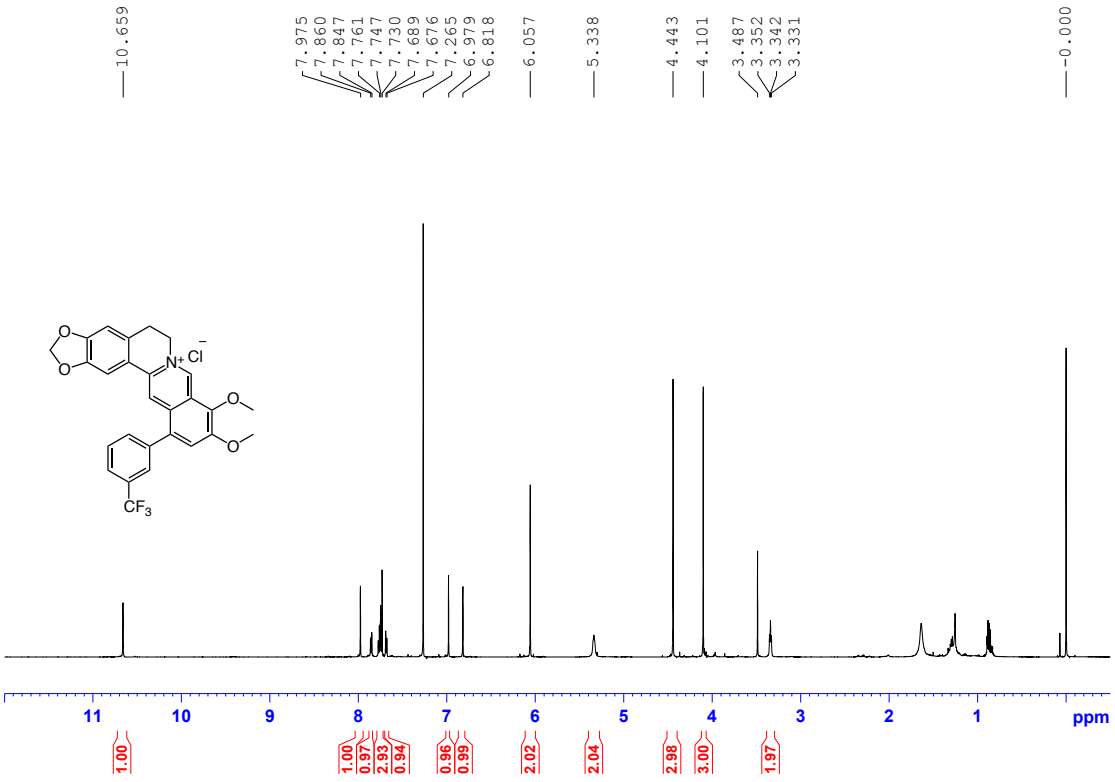


Fig. S42 ^{1}H NMR spectrum of compound **3n**.

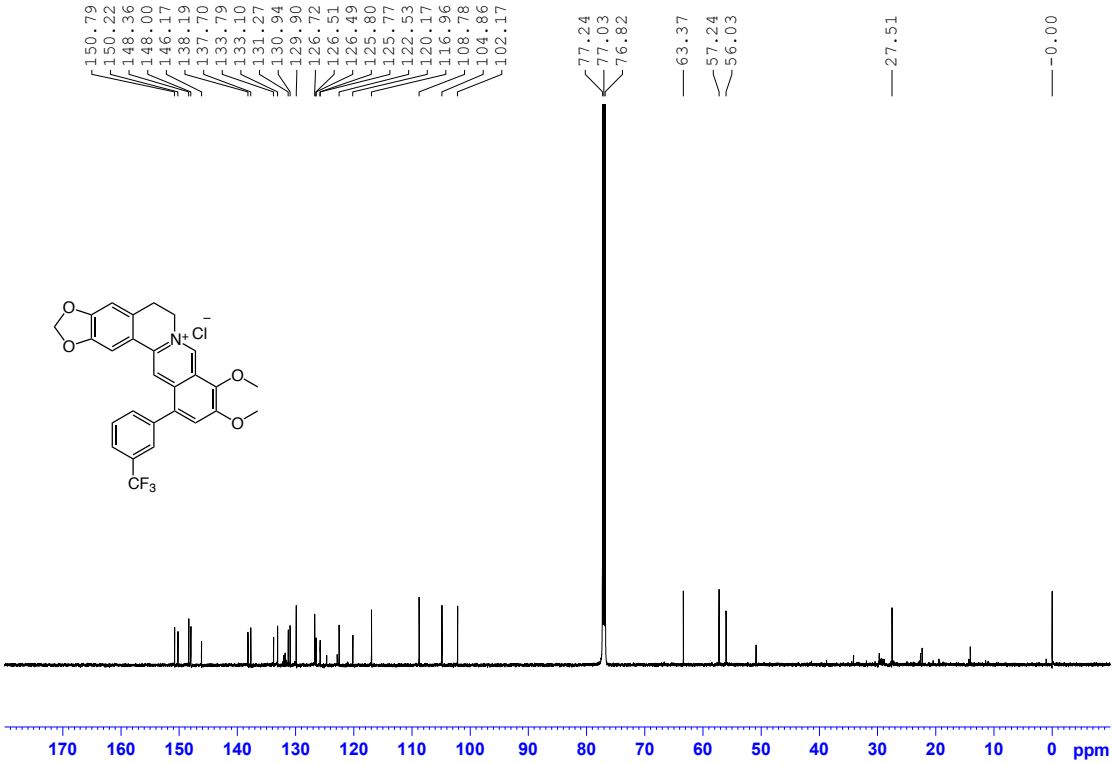


Fig. S43 ^{13}C NMR spectrum of compound **3n**.

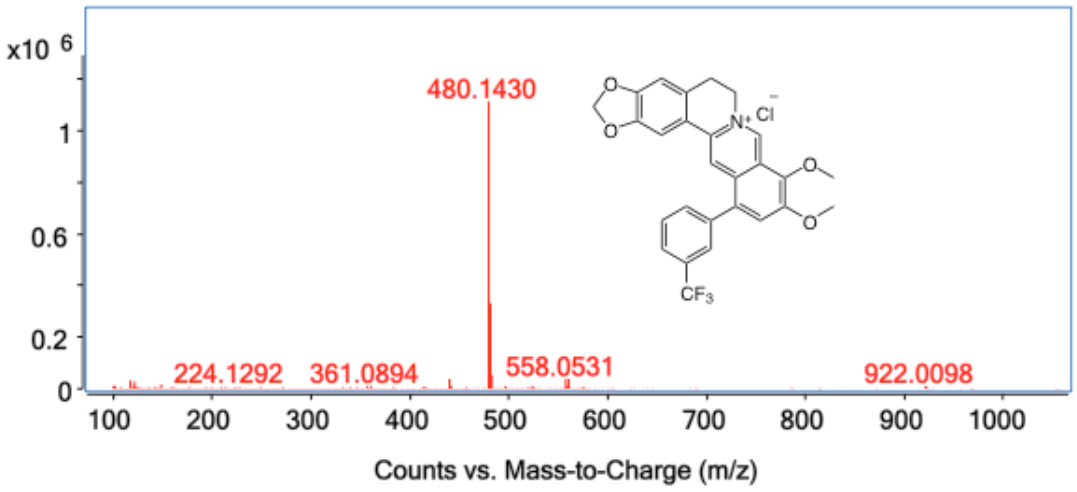


Fig. S44 HR-ESI/TOF-MS spectrum of compound **3n**.

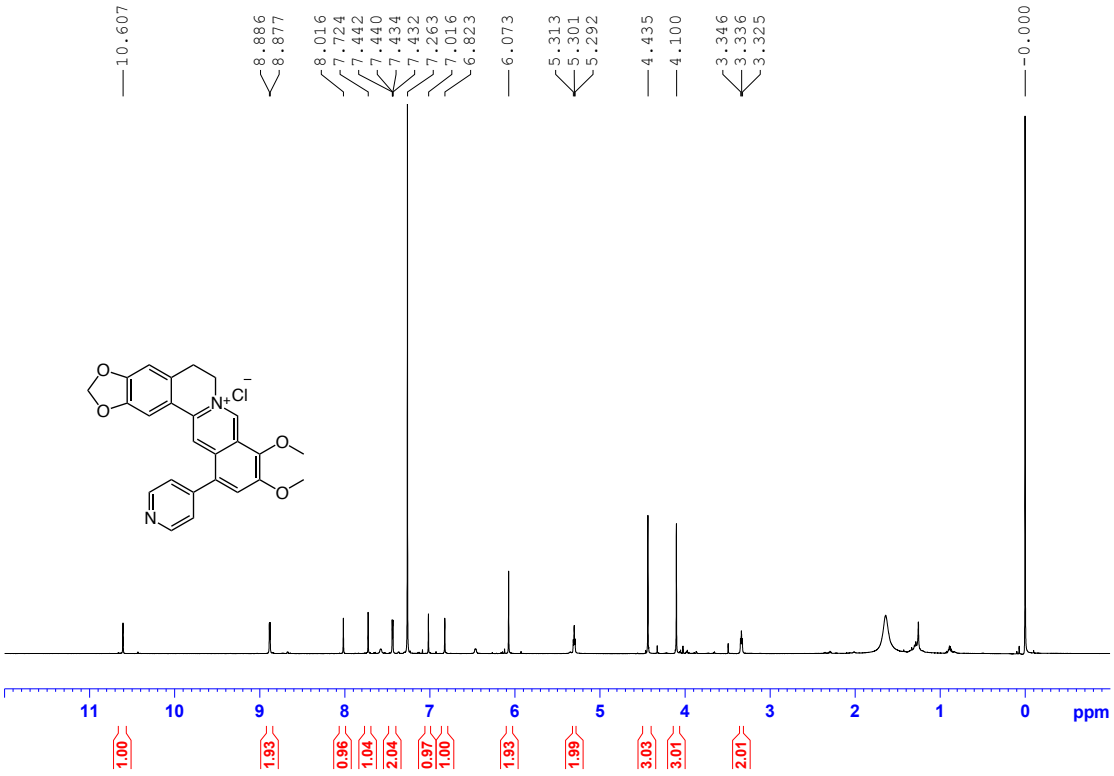


Fig. S45 ^{1}H NMR spectrum of compound **3o**.

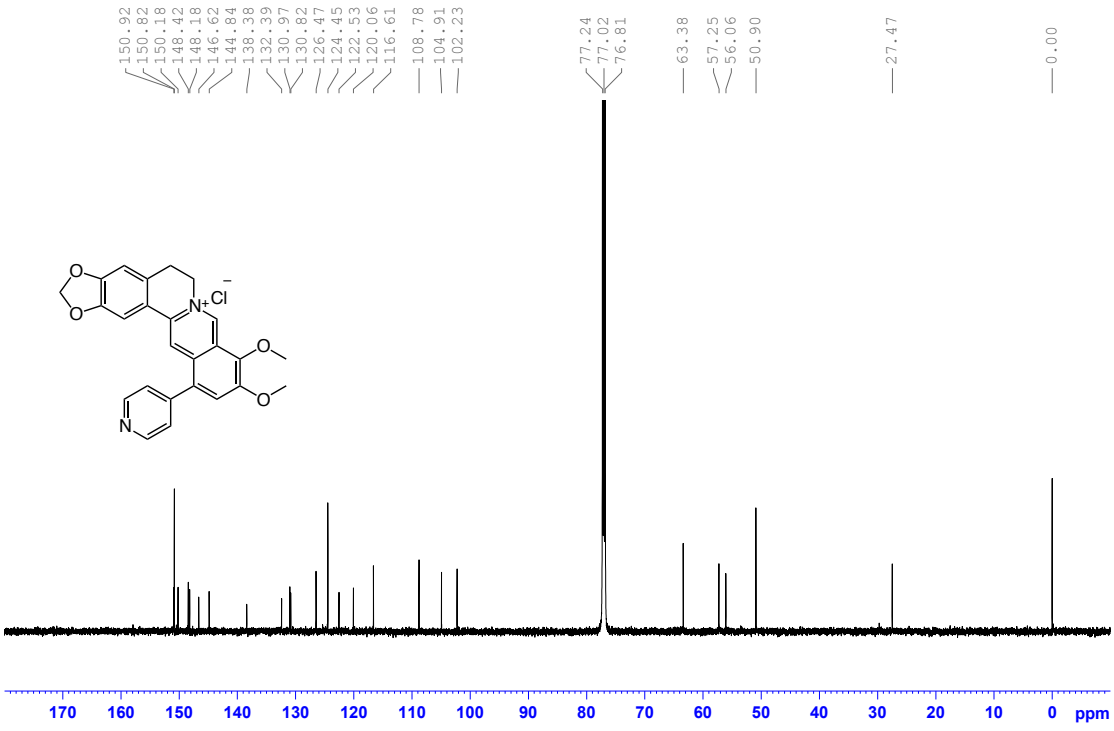


Fig. S46 ^{13}C NMR spectrum of compound **3o**.

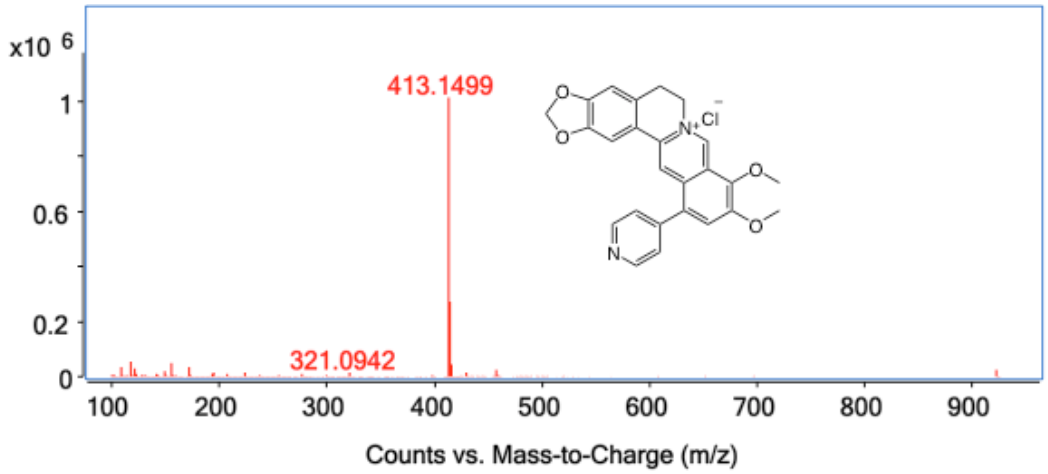


Fig. S47 HR-ESI/TOF-MS spectrum of compound **3o**.

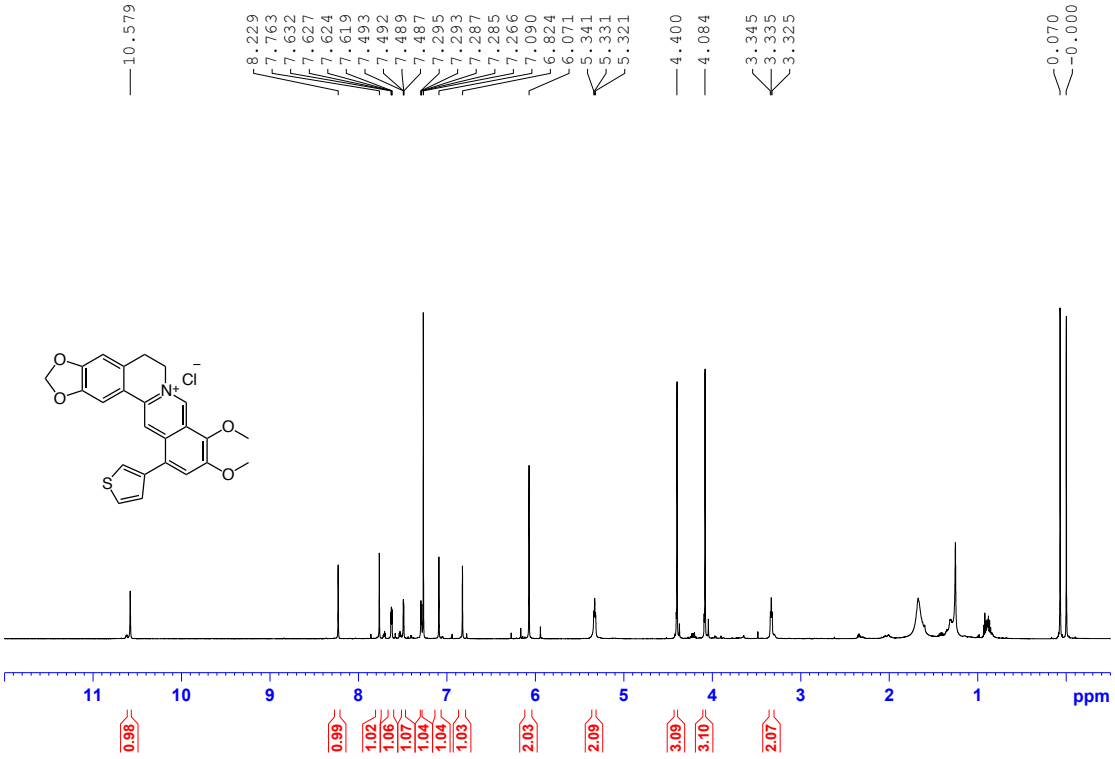


Fig. S48 ^{1}H NMR spectrum of compound **3p**.

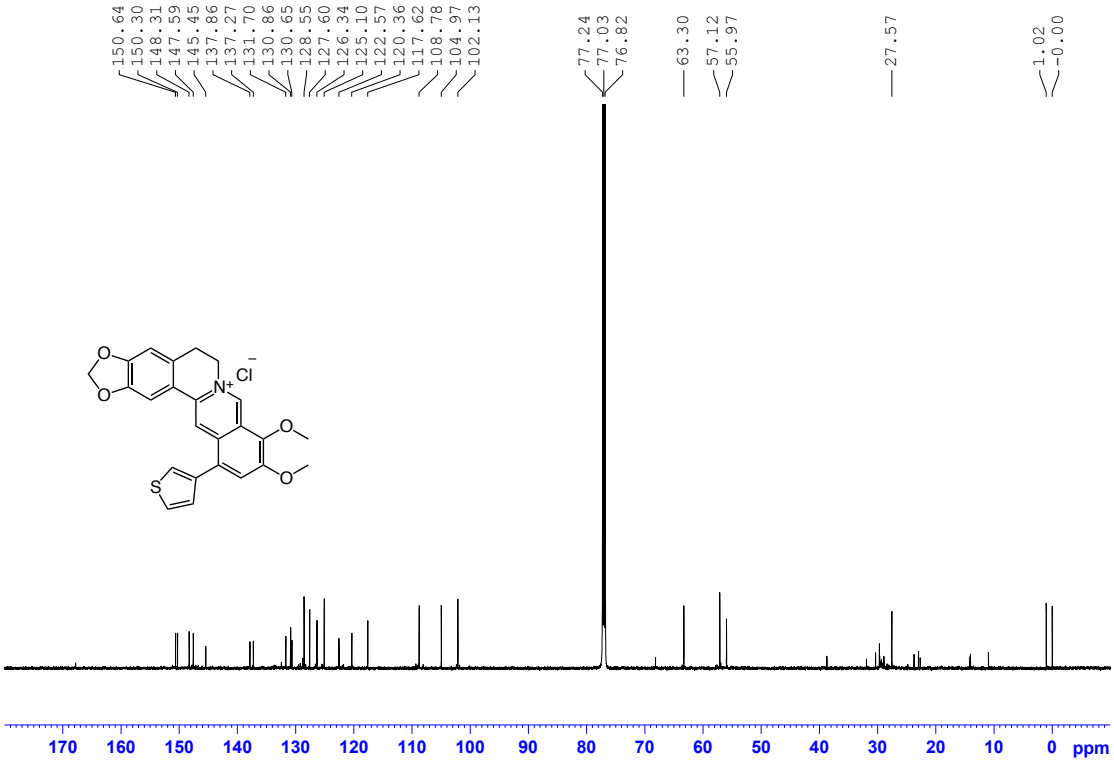


Fig. S49 ^{13}C NMR spectrum of compound **3p**.

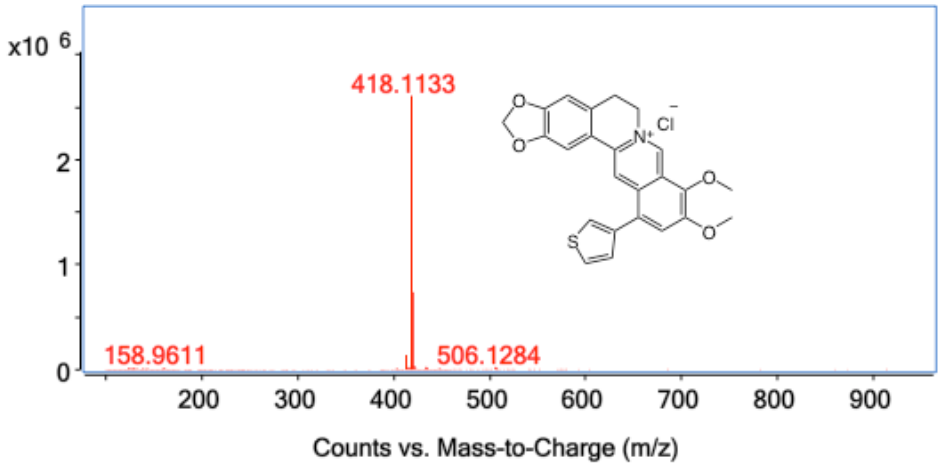


Fig. 50 HR-ESI/TOF-MS spectrum of compound **3p**.

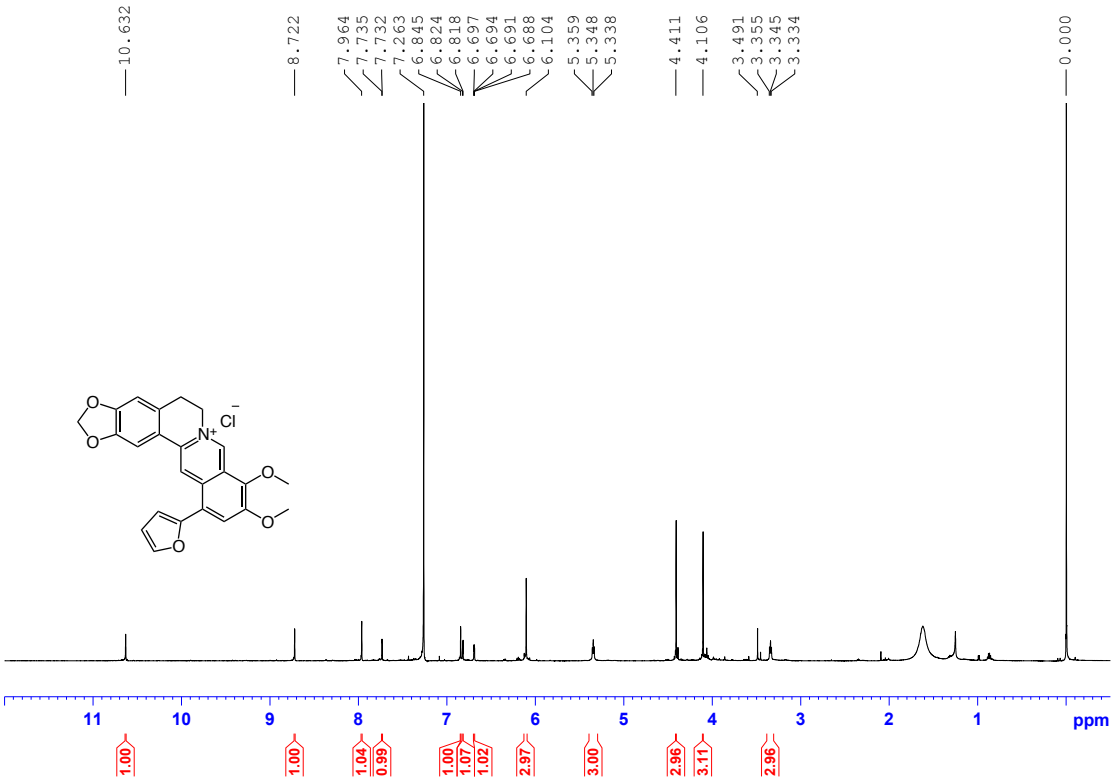


Fig. S51 ^{1}H NMR spectrum of compound **3q**.

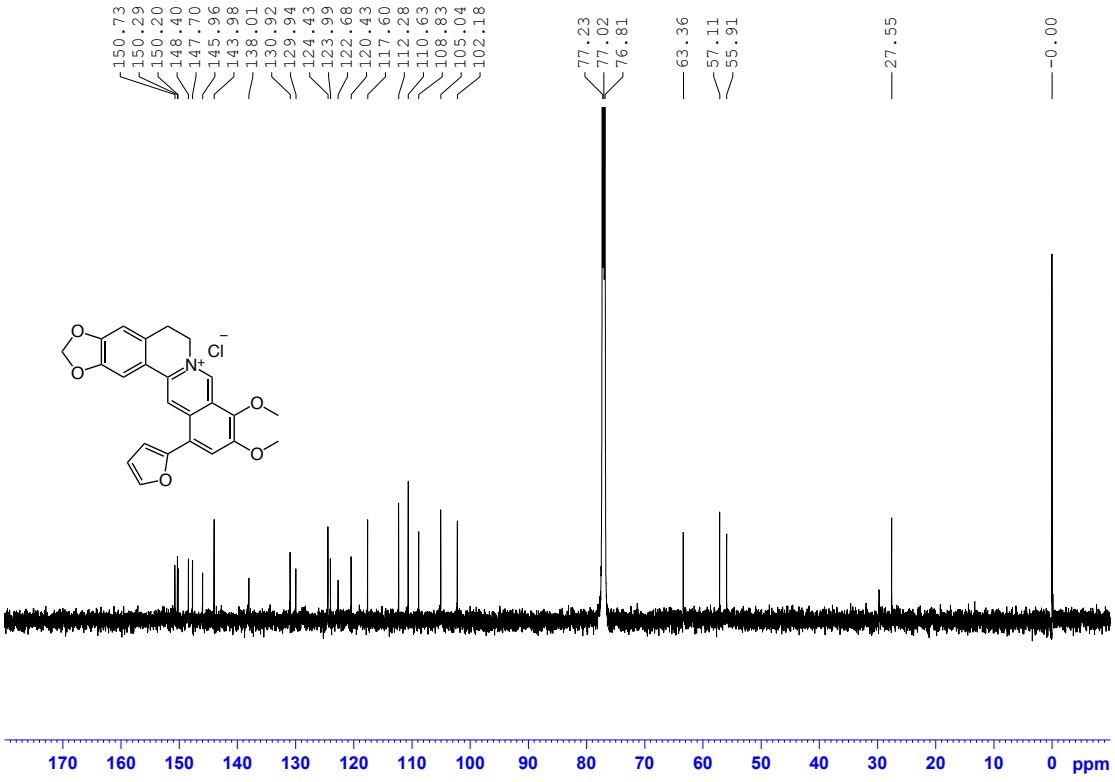


Fig. S52 ^{13}C NMR spectrum of compound **3q**.

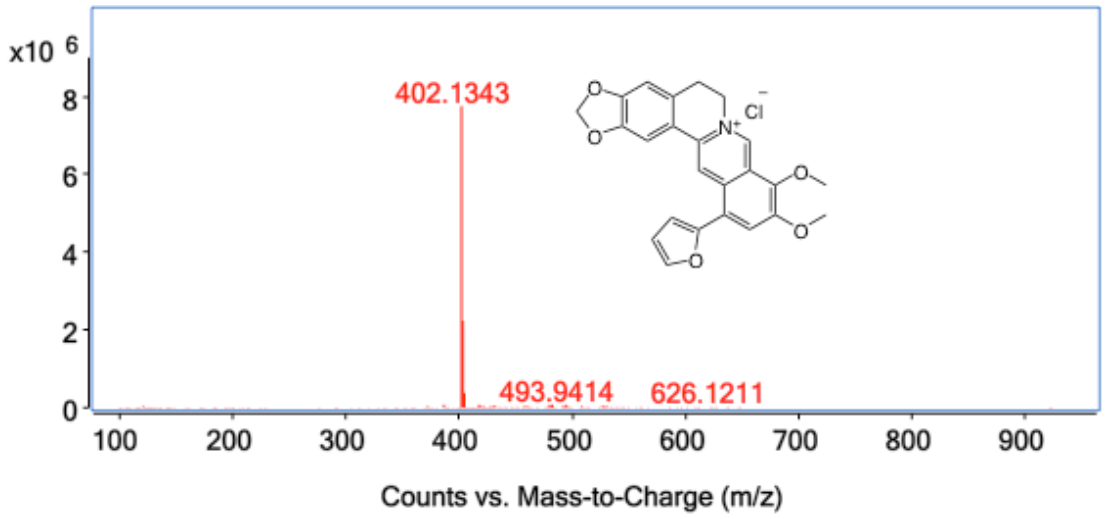


Fig. S53 HR-ESI/TOF-MS spectrum of compound **3q**.

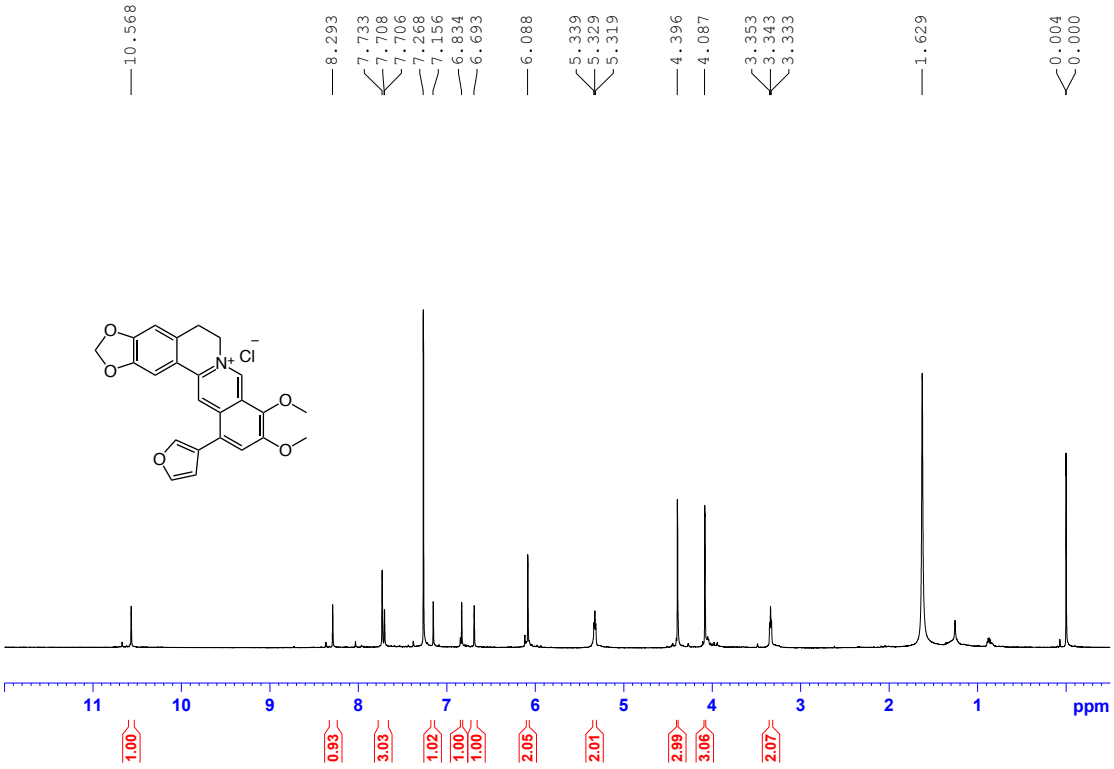


Fig. S54 ^{1}H NMR spectrum of compound **3r**.

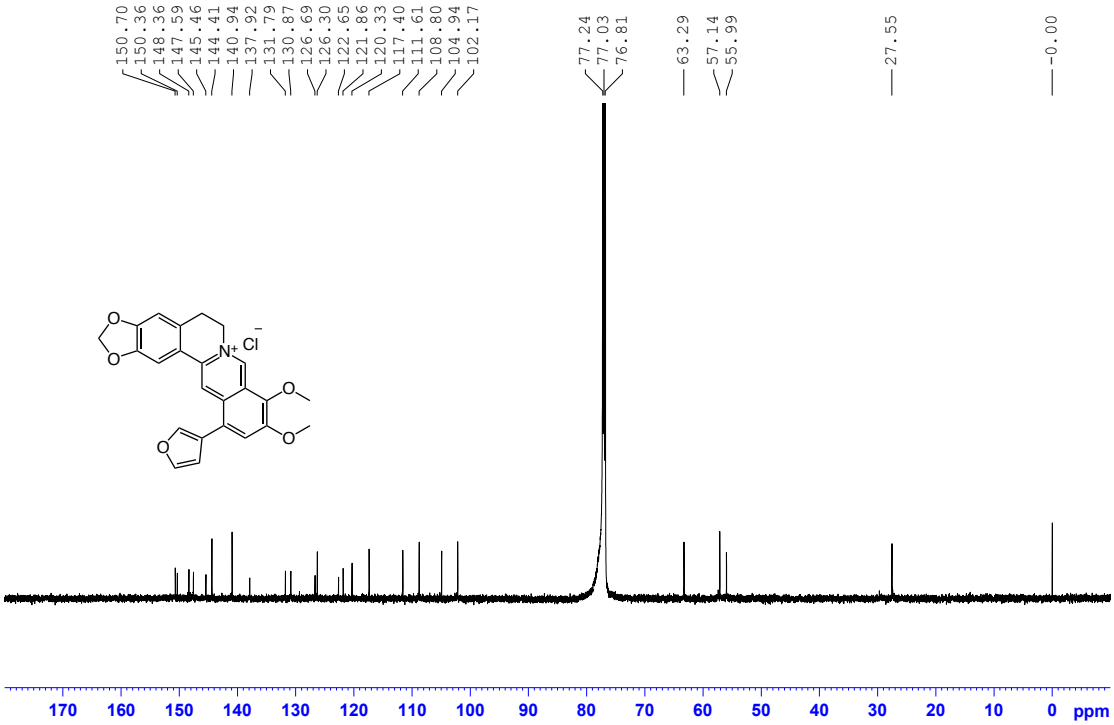


Fig. S55 ^{13}C NMR spectrum of compound **3r.**

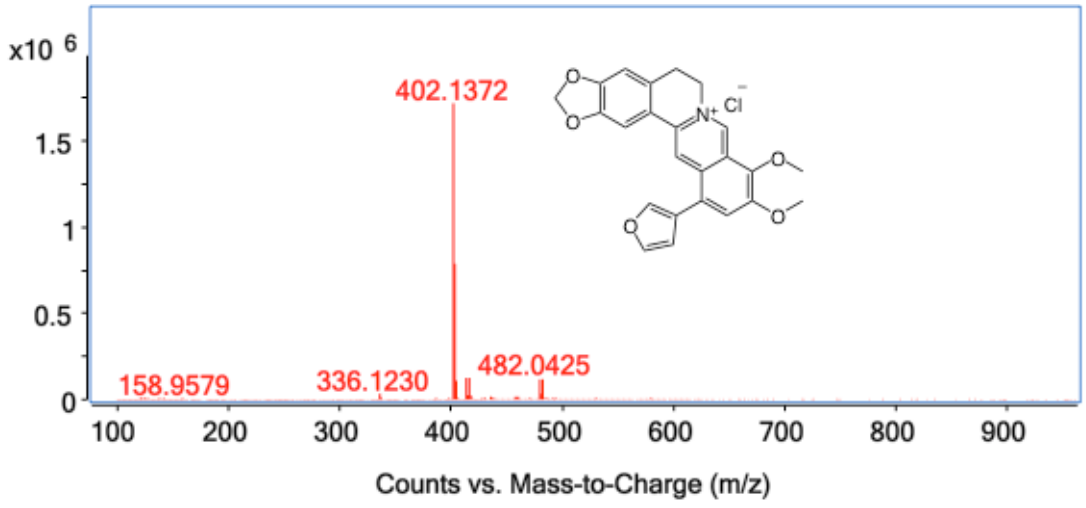


Fig. S56 HR-ESI/TOF-MS spectrum of compound **3r**.

Table S1 Viability (%) of T47D cell treated by berberine and its active derivatives with several concentrations

Compounds/ concentration	Cell viability (% blank control), Mean (SD)			HIF-1 inhibitory activity
	10 μM	5 μM	2.5 μM	IC_{50} (μM), Mean (SD)
berberine	92.5 (9.3)	**98.5 (4.8)**	108.3 (13.6)	4.78 (0.73)
3a	65.6 (5.4)	77.4 (1.0)	**86.5 (2.8)**	1.51 (0.09)
3b	68.8 (3.7)	80.8 (1.5)	**98.1 (2.0)**	1.39 (0.07)
3c	65.9 (6.4)	67.6 (6.6)	**84.7 (8.2)**	1.26 (0.29)
3d	64.3(7.2)	91.9(6.3)	**102.9 (3.0)**	2.12 (0.36)
3e	84.5 (10.3)	96.8 (8.8)	**116.9 (11.4)**	0.74 (0.06)
3f	71.1 (1.4)	70.1 (9.3)	**92.0 (6.4)**	1.35 (0.14)
3k	91.4 (4.9)	94.7 (14.3)	**105.0 (10.9)**	2.07 (0.17)
3l	**88.5 (10.1)**	98.5 (9.6)	98.9 (12.2.2)	11.82 (1.65)
3m	92.9 (5.0)	**96.8 (6.5)**	106.3 (8.6)	5.40 (1.36)

The cell viability was reflected by the control *Renilla* luciferase activity. The data in bold mean the viability of T47D cell treated by berberine derivatives at the concentration around their IC_{50} values.