SUPPORTING INFORMATION

A NEW GUANYLHYDRAZONE DERIVATIVE AS A POTENTIAL ACETYLCHOLINESTERASE INHIBITOR FOR ALZHEIMEIR'S DISEASE: SYNTHESIS, MOLECULAR DOCKING, BIOLOGICAL EVALUATION AND KINETIC STUDIES BY NUCLEAR MAGNETIC RESONANCE

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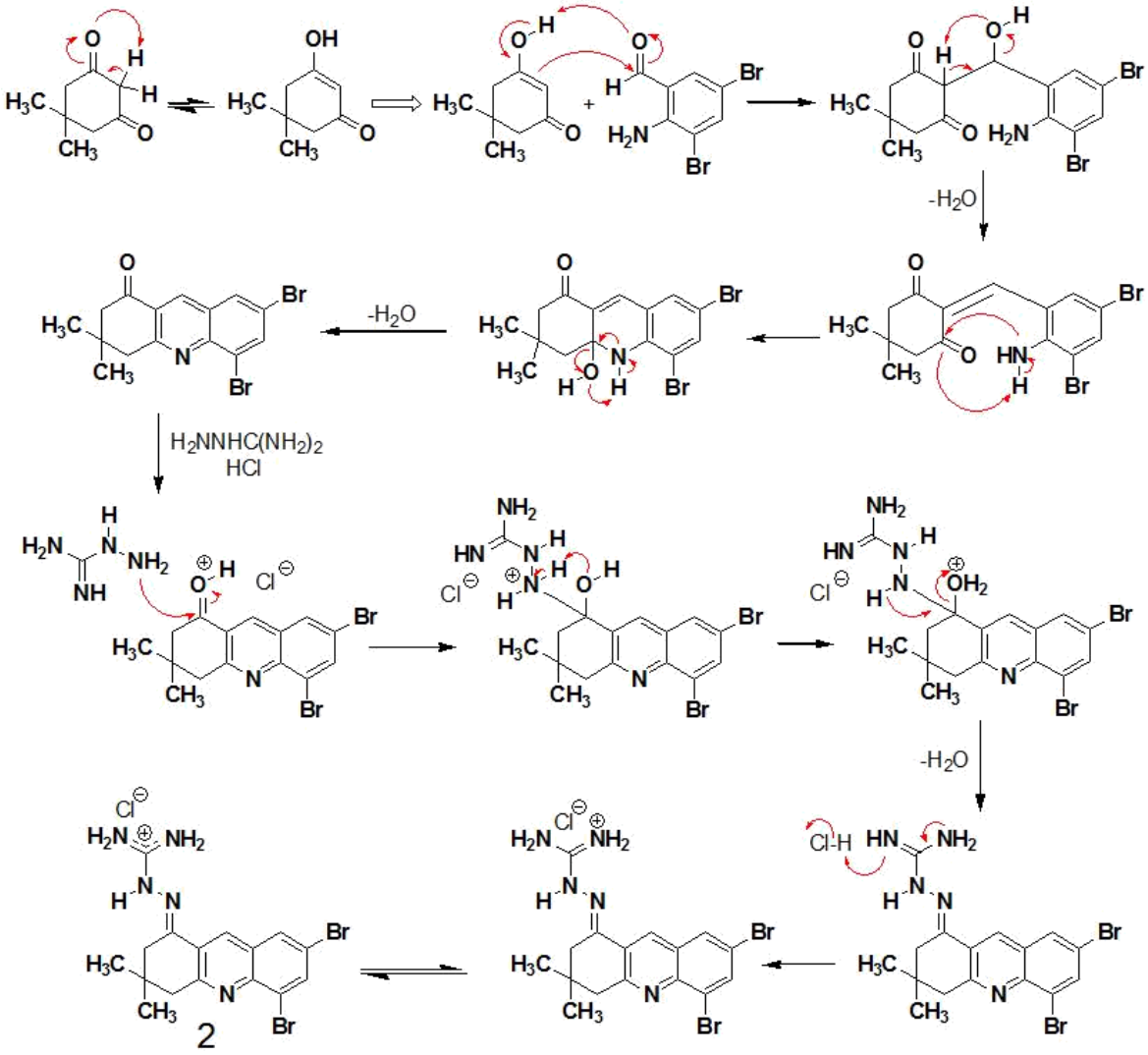
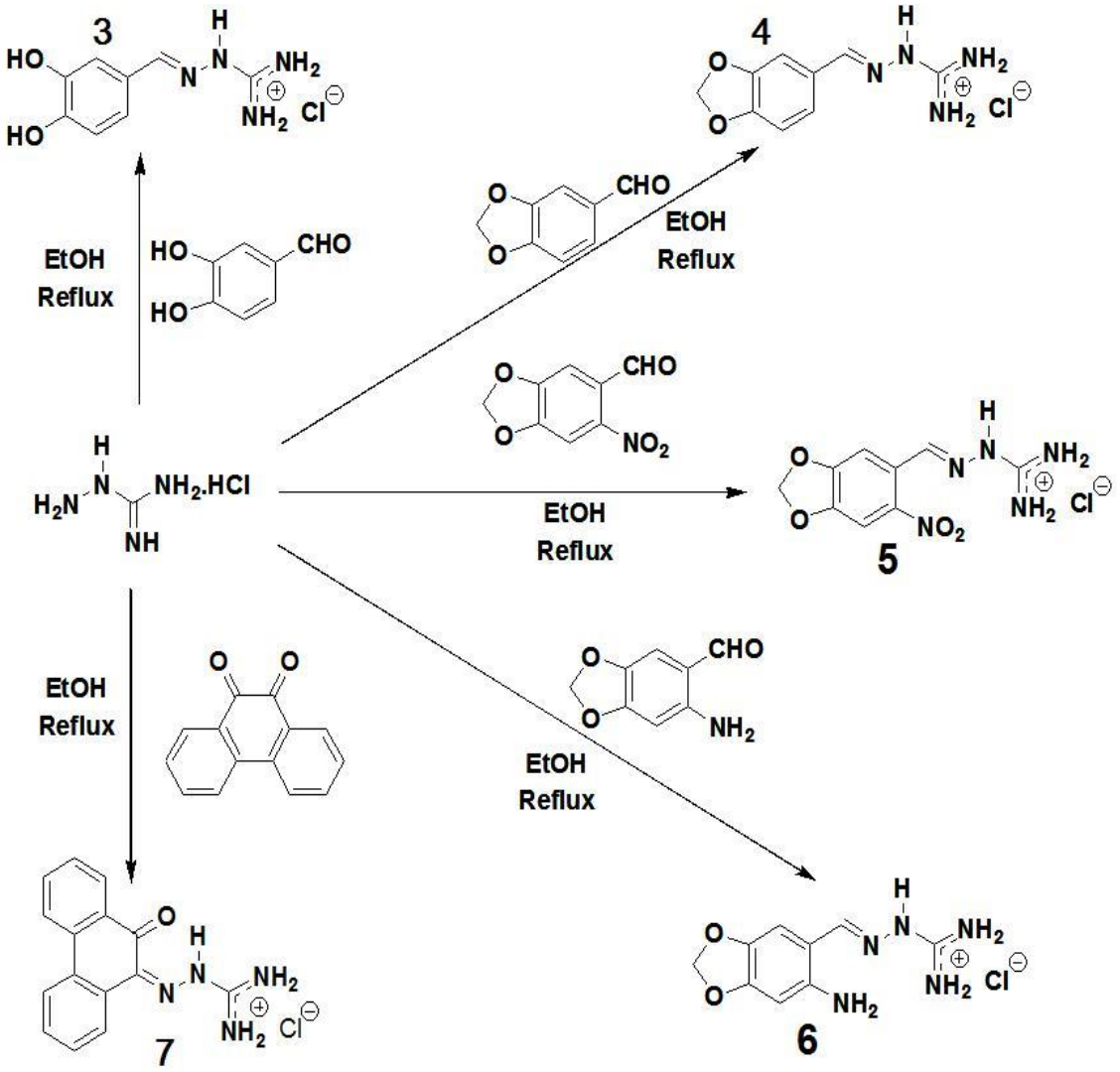


Scheme S.1. Proposed mechanism for the synthesis of compound **2**.



Scheme S.2. Synthesis of guanylhydrazones **3**, **4**, **5**, **6** and **7**.[28-30]

Table S.1. In silico physicochemical properties for oral bioavailability and bioactivity of compounds **2-7** and tacrine (**TAC**).

Comp	MW (amu)	TPSA (Å^2)	Area (Å^2)	Vol. (Å^3)	cLogP	cLogS	drug-likeness	drug Score	Toxicity
2	440.16	74.86	357.68	332.72	3.83	-5.68	-0.12	0.36	NM, NC, NI, NR
3	195.20	107.27	223.22	189.09	0.04	-1.40	4.66	0.97	NM, NC, NI, NR
4	207.21	85.22	230.96	200.04	0.85	-2.70	3.79	0.92	NM, NC, NI, NR
5	252.21	121.89	255.14	221.61	NP	NP	NP	NP	NP
6	222.22	108.45	242.83	210.06	-0.82	-2.65	-1.86	0.22	NM, NC, NI, NR
7	265.29	77.21	278.8	263.47	1.83	-4.67	-1.42	0.36	NM, NC, NI, R(medium) M(high), C(high), NI, NR
TAC	180.00	22.73	313.90	284.22	2.51	-3.51	-7.18	0.16	

Comp, compound; MW, molecular weight; TPSA, topological polar surface area; Area, surface area; Vol, molecule volume; cLogP, lipophilicity; cLogS, water solubility; TAC, tacrine; NP = no prediction - result due to the limitations of Molinspiration and Osiris; NM = non-mutagenic; NC = non-carcinogenic; NI = non-irritable; NR = doesn'taffect the reproductive system; M = mutagenic; C = carcinogenic; R = affects reproductive system

Table S.2: Results of the molecular anchorages for compounds **2-7** and tacrine,showing the hydrogen bonds, their respective distances and possible amino acids involved in van der Walls interactions. In bold one of the amino acids of the catalytic triad (Ser200-His440-Glu327).

Compoud	Hydrogen bond	H-bond distances	Docking Interaction
2	GLY80	2,163	TYR70; SP72; GLY80; TRP84; ASN85; ER122; LY123;GLU199; PHE330, TRP432; ILE439; **HIS440**; TYR442.
3	SER81 (O) TRP84 (O) GLY117 (O) TYR130 (HH) TYR334 (OH)	2,227 1,775 1,987 2,049 2,073	ASP72; SER81; TRP84; GLY117; GLY123; YR130; PHE330;TYR334.
4	GLU199 (OE1) TYR130 (OH) GLU (OE1)	-1,469 -0,057 -1,383	TRP84; GLY117; TYR130; GLU199; PHE330;TRP432; **HIS440**; TYR442.
5	TYR130 (OH) GLU199 (OE1) GLU199 (OE1)	2,146 1,927 1,837	TRP84; GLY117; TYR130; GLU199; PHE330;TRP432; ILE439; **HIS440**; GLY441; TYR442.
6	TYR130 (OH) TYR130 (OH) GLU199 (OE1) GLU199 (OE1)	2,140 1,894 1,614 2,092	ASP72; TRP84; GLY117; TYR130; GLU199;PHE330; **HIS440**;GLY441; TYR442.
7	ASN85 (OD1) ASN85 (OD1)	2,159 1,764	ASP72; SER81; ASN85; TRP84; PHE330; TRP432; **HIS440**;GLY441; TYR442.
TAC	-	-	TYP81; GLU199; PHE330; TRP432; ILE439; **HIS440;** GLY441; TYR442.

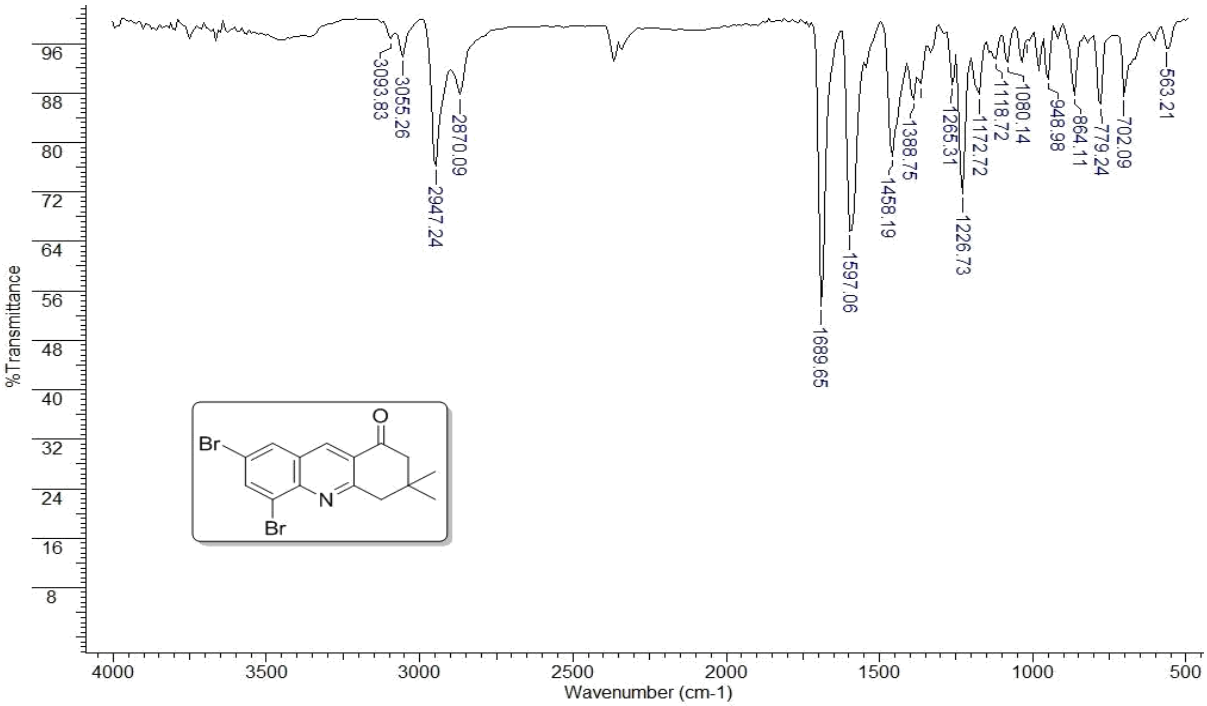


Fig. S.1: IR spectrum of compound **1**.

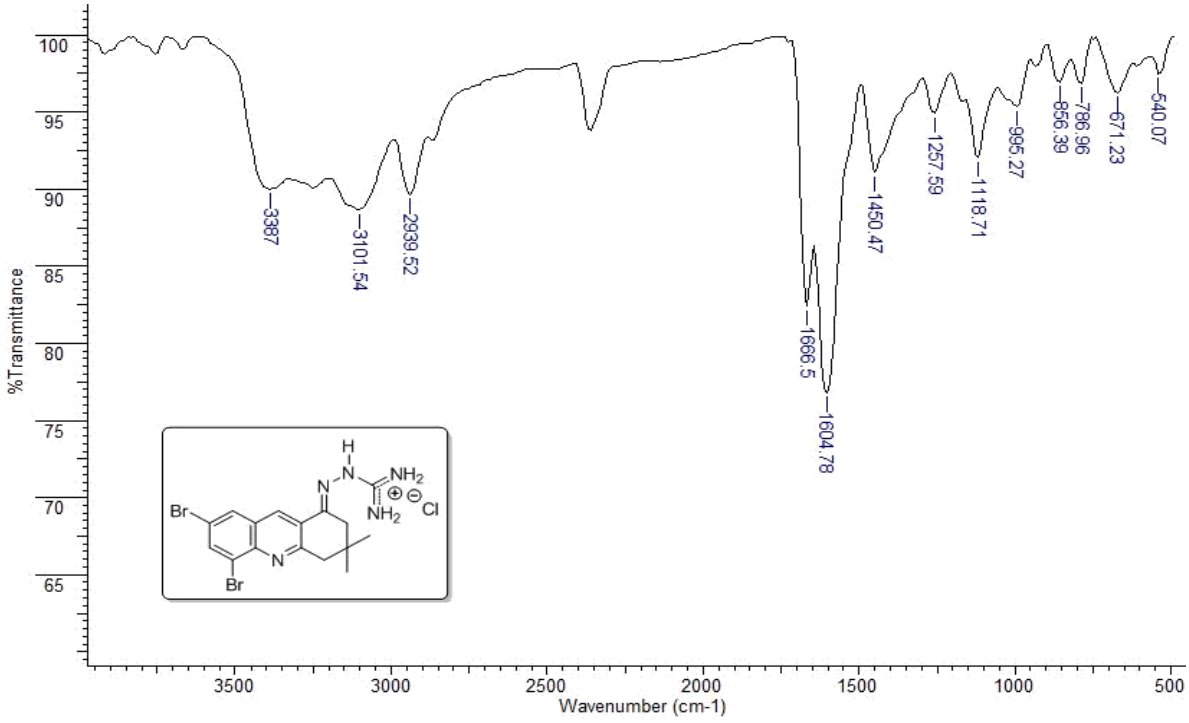


Fig. S.2: IR spectrum of compound **2**.

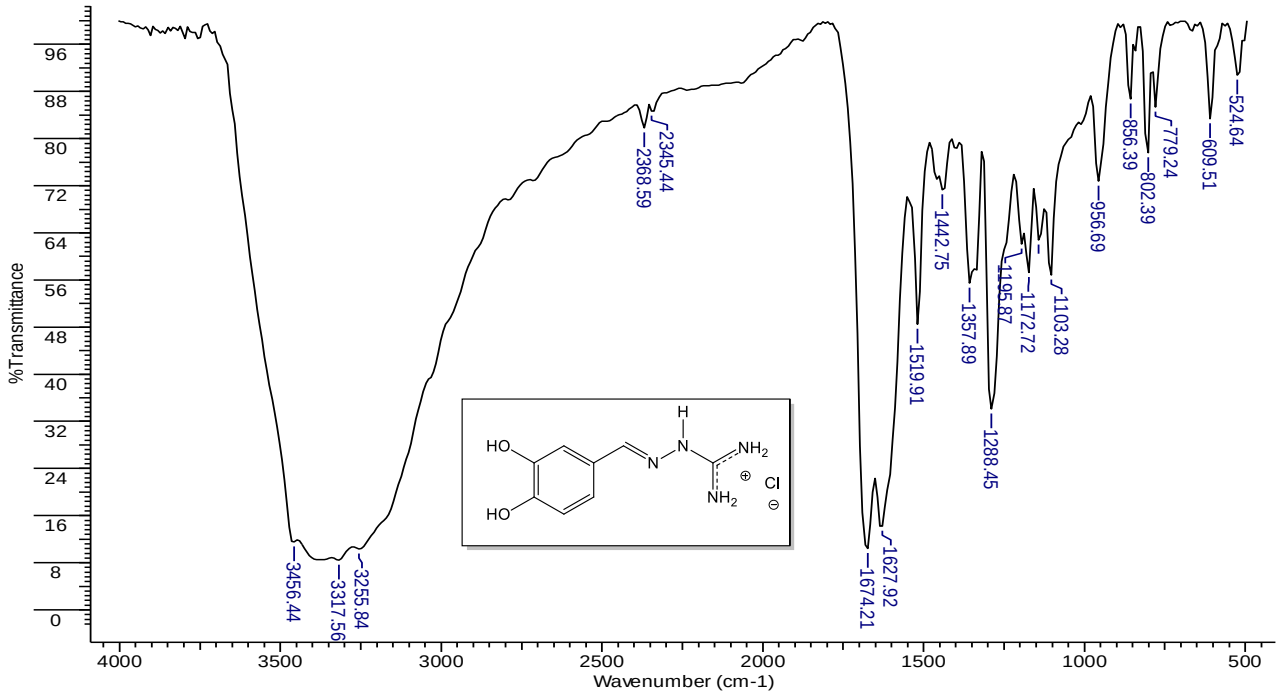


Fig. S.3: IR spectrum of compound **3.**

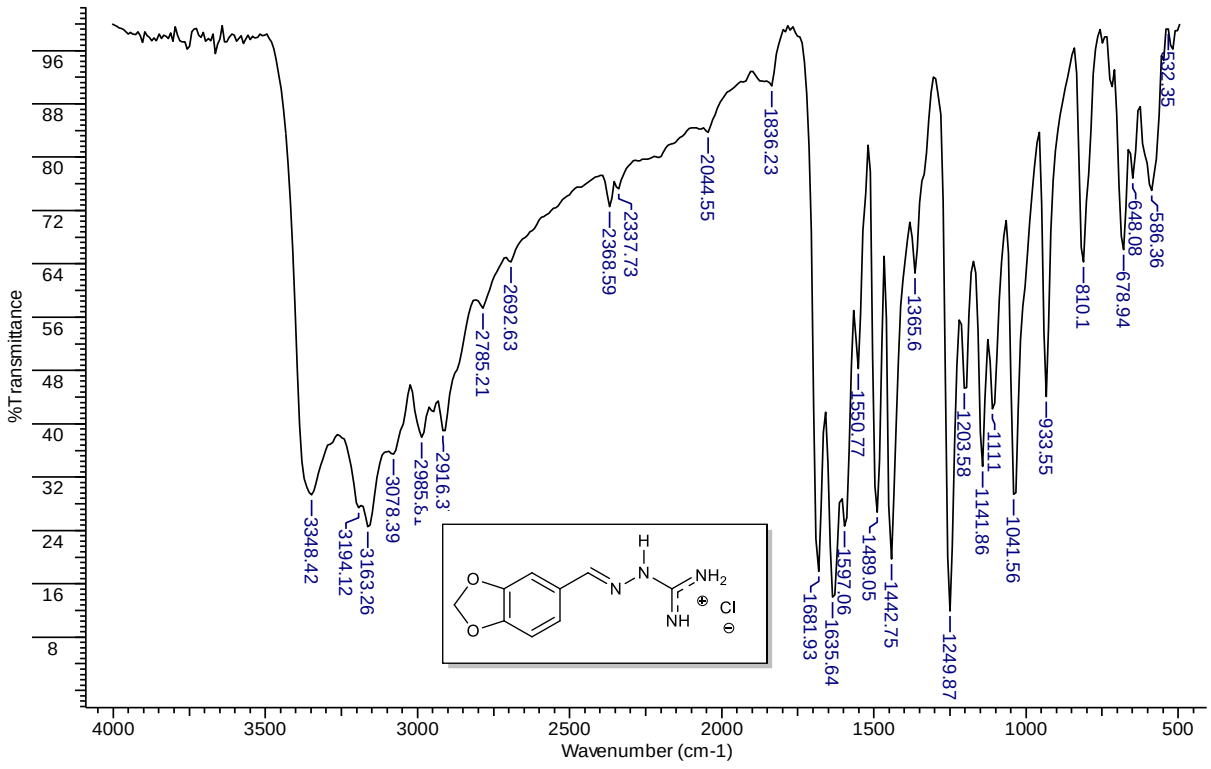


Fig. S.4:IR spectrum of compound **4**.

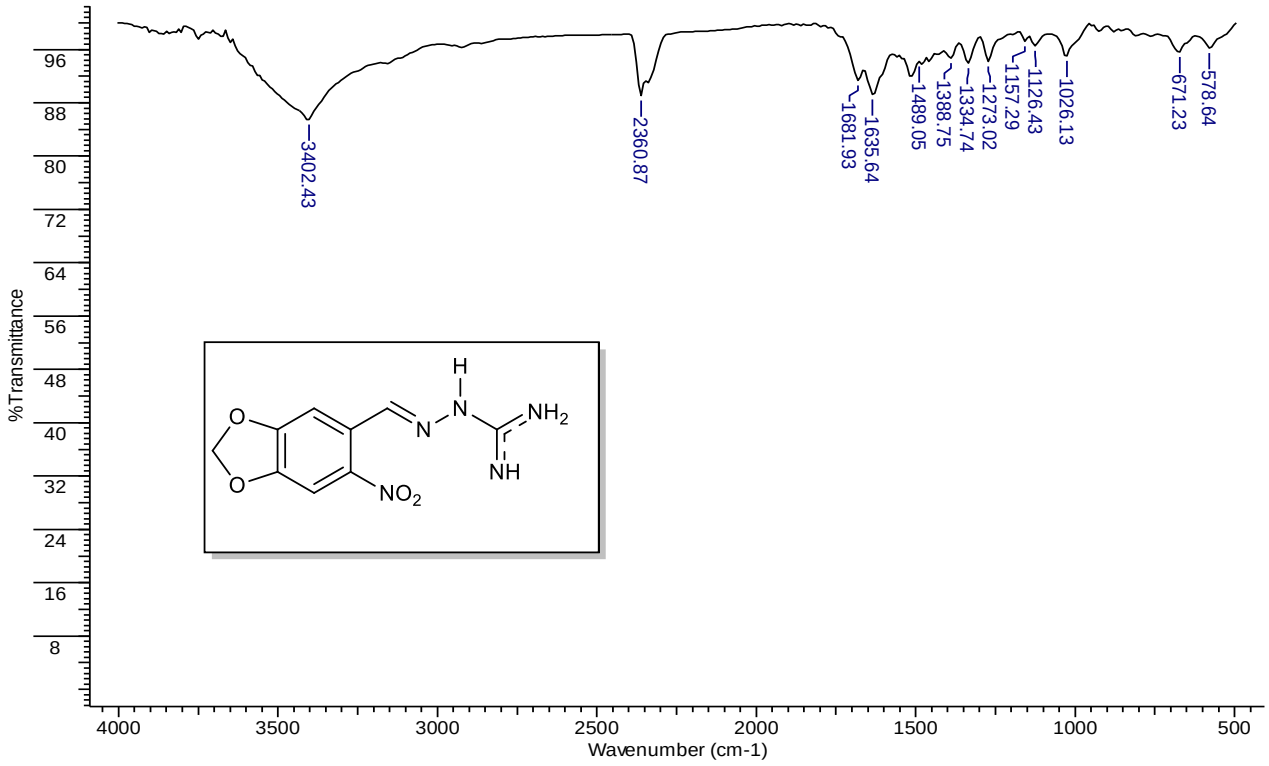


Fig. S.5:IR spectrum of compound **5**.

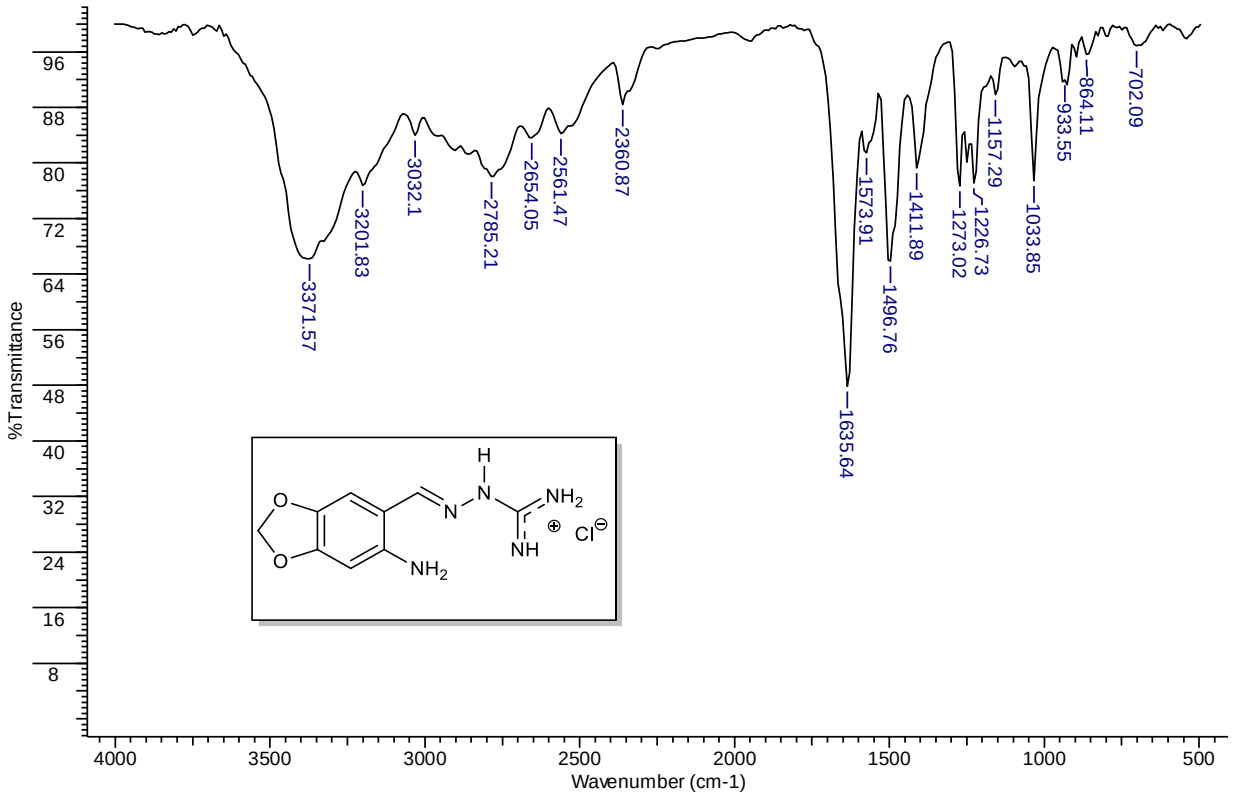


Fig. S.6:IR spectrum of compound **6**.

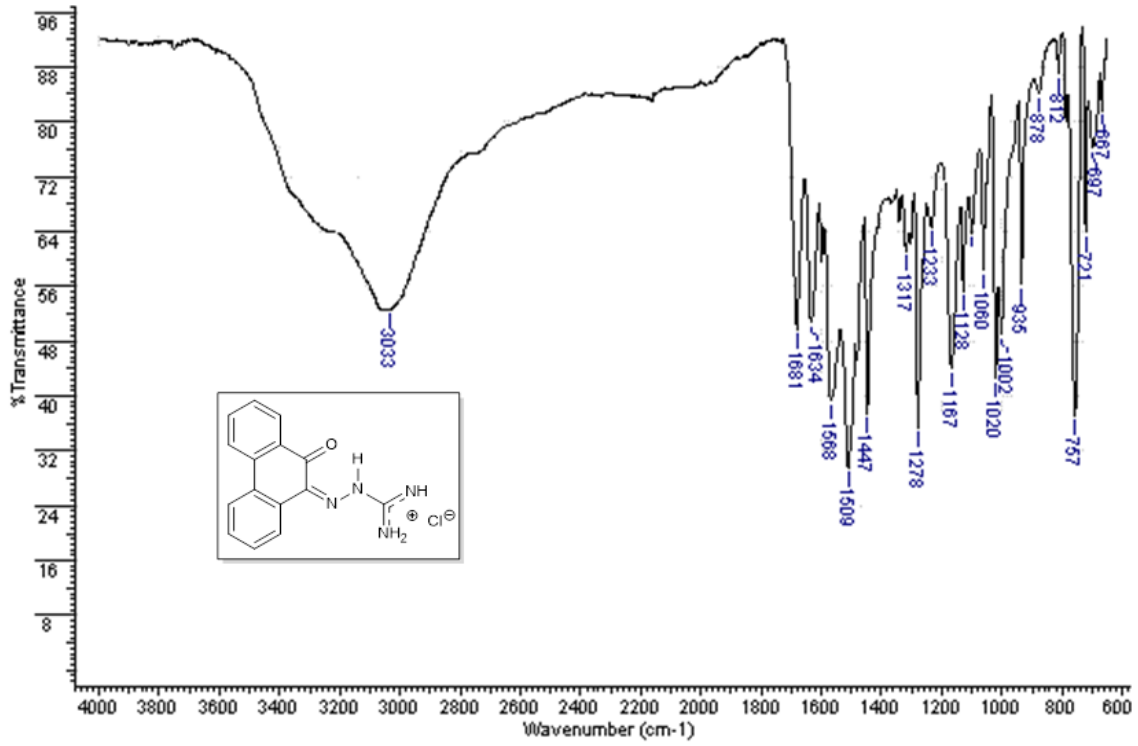


Fig. S.7:IR spectrum of compound **7**.

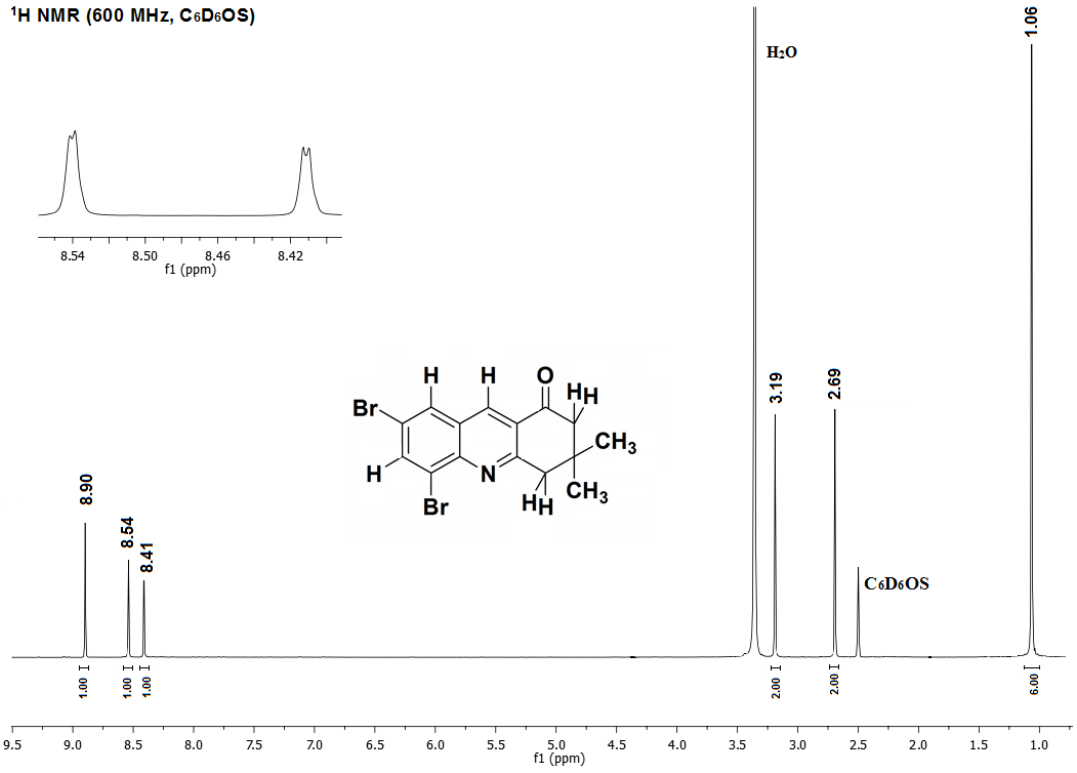


Fig. S.8:[1]H NMR spectrum of compound **1.**

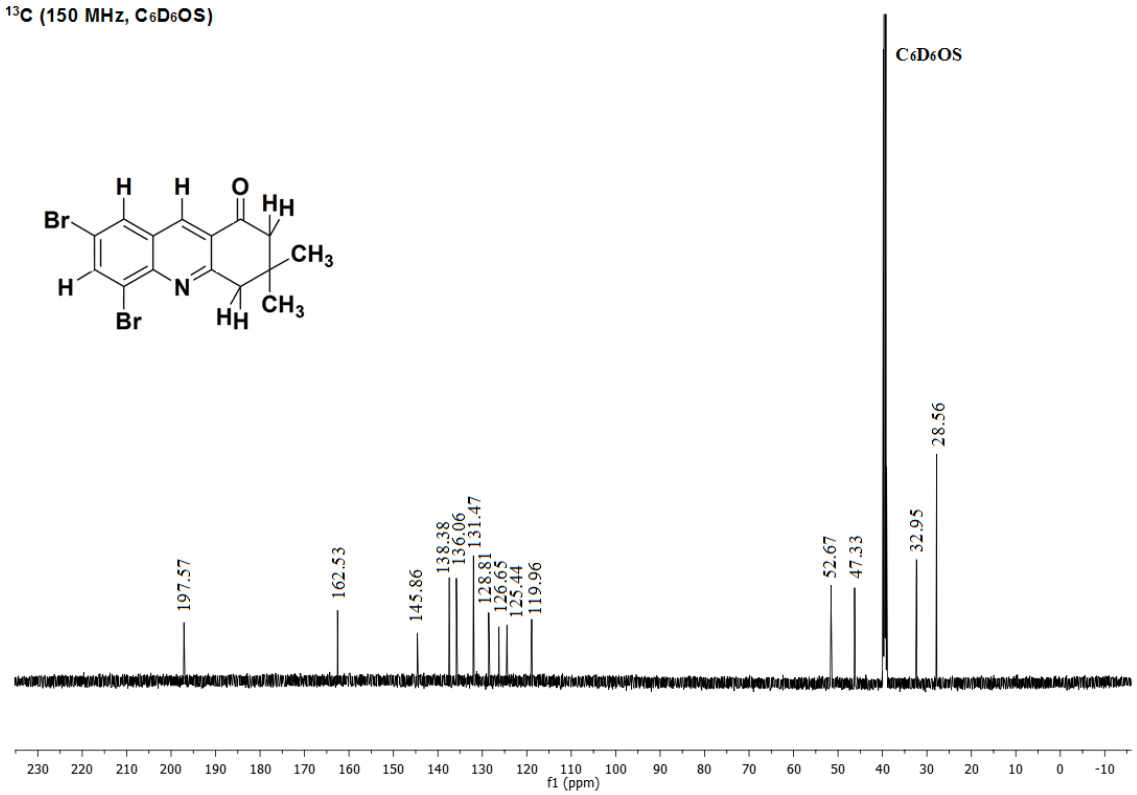


Fig. S.9: ^{13}C NMR spectrum of compound **1.**

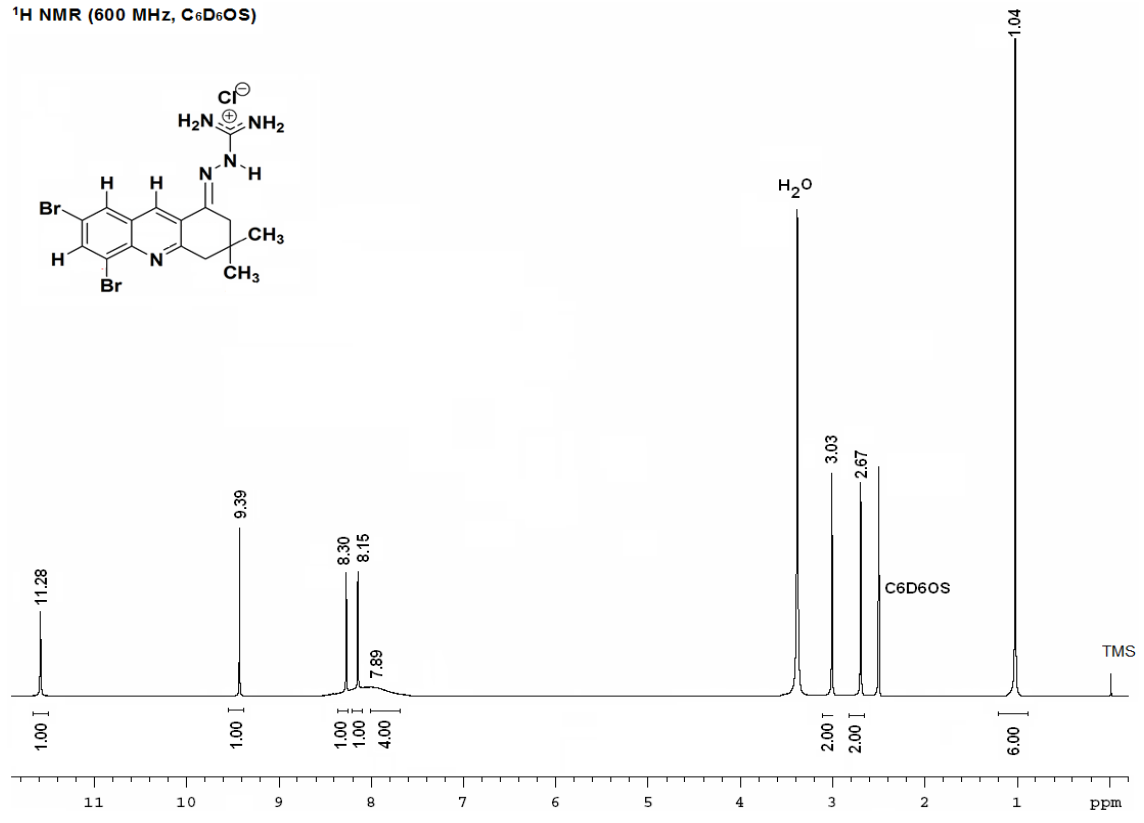


Fig. S.10: ^{1}H NMR spectrum of compound **2.**

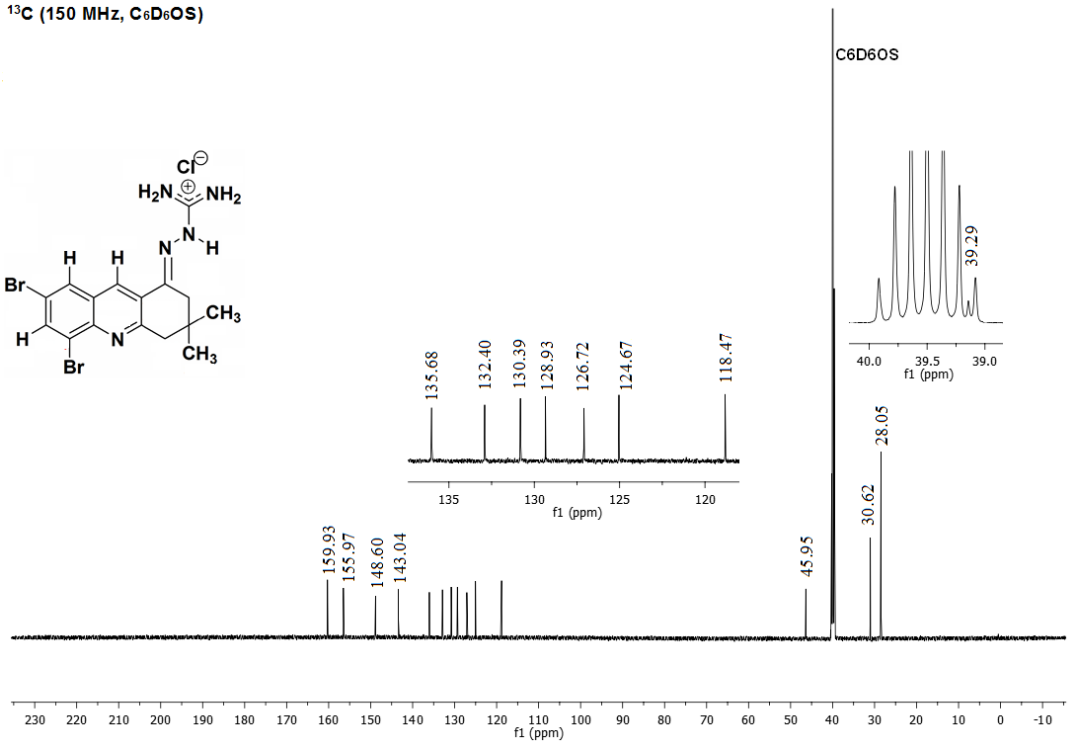


Fig. S.11: ^{13}C NMR spectrum of compound **2.**

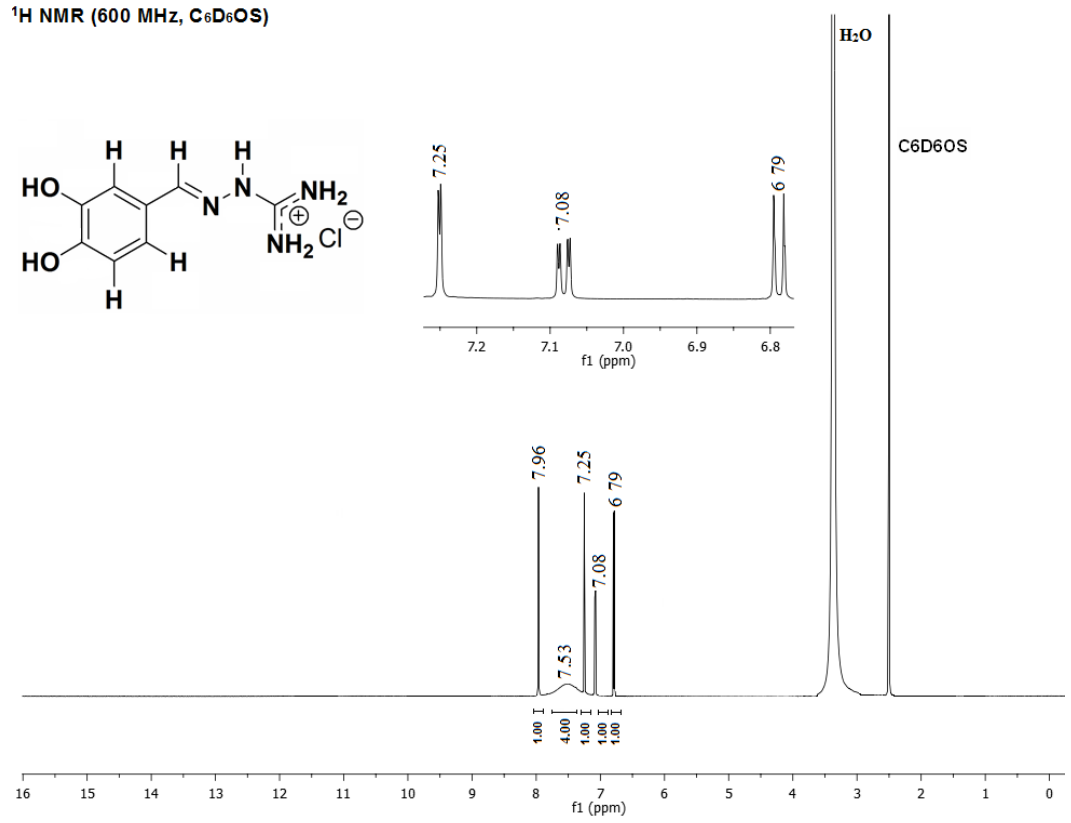


Fig. S.12: ^{1}H NMR spectrum of compound **3.**

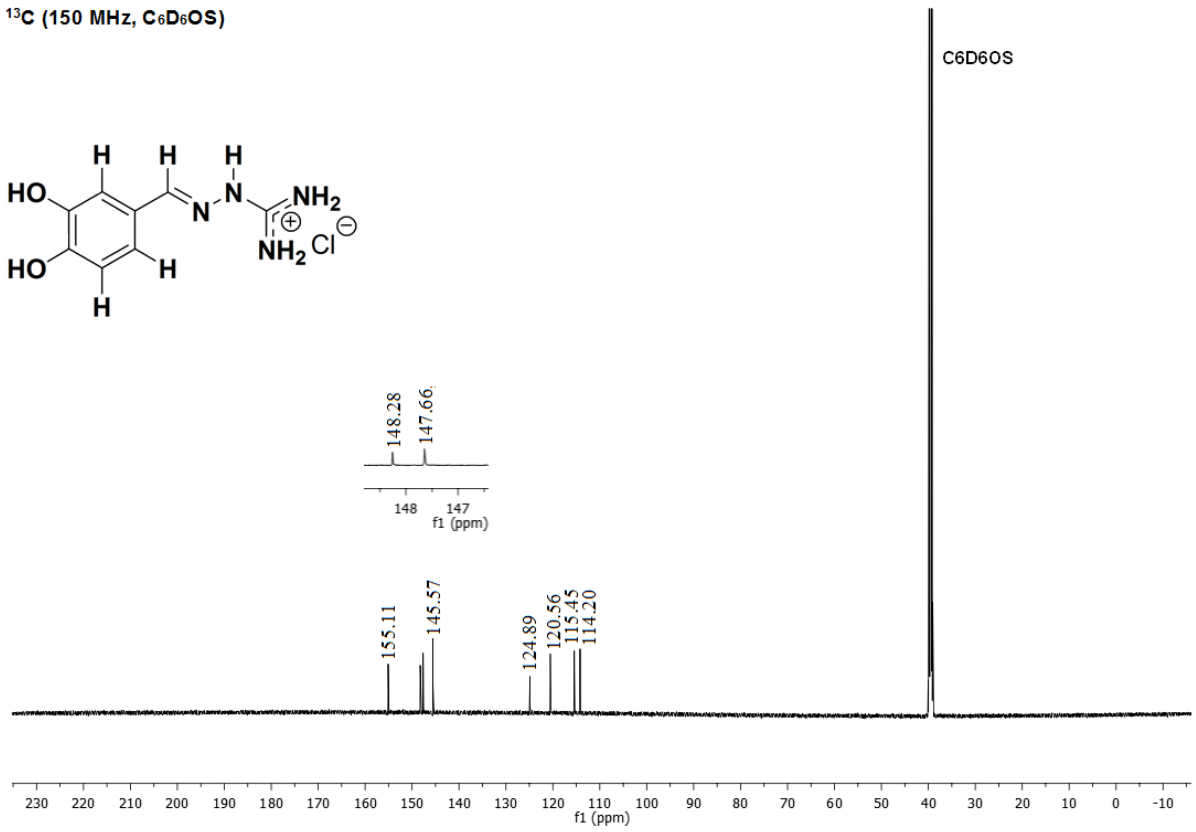


Fig. S.13: ^{13}C NMR spectrum of compound **3.**

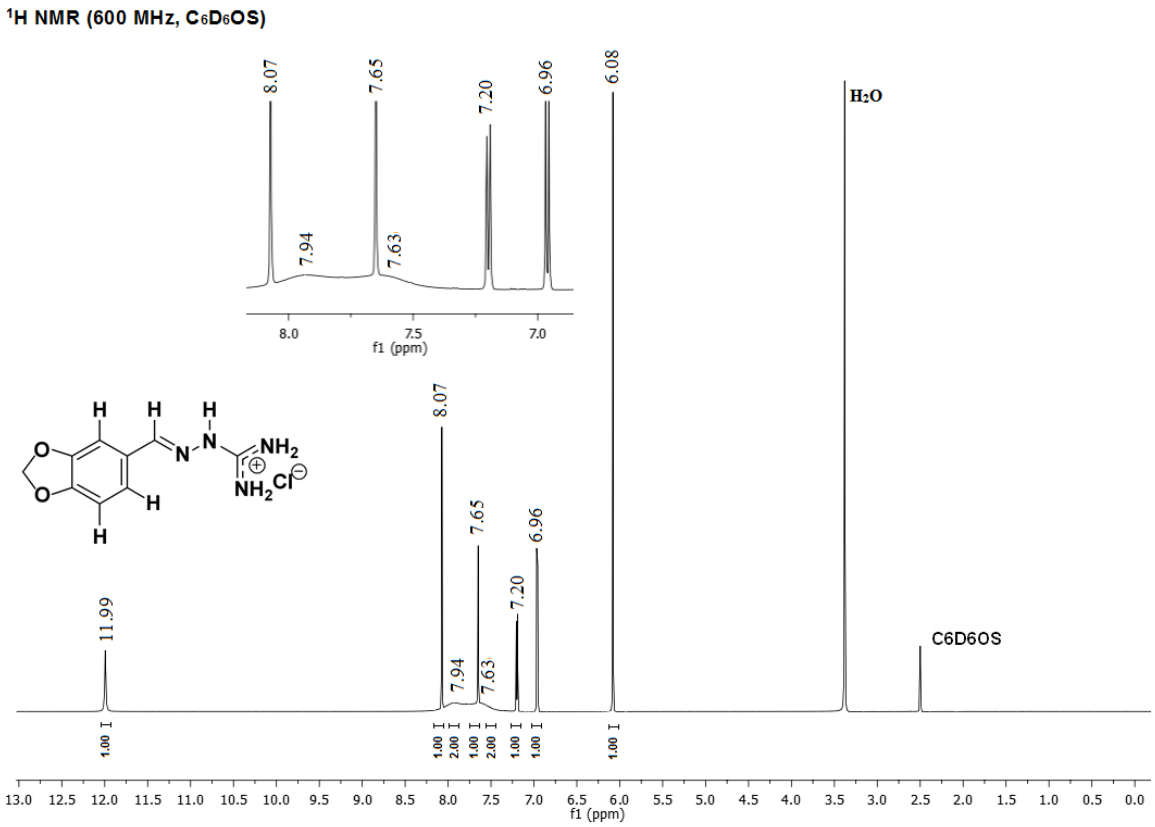


Fig. S.14: ^{1}H NMR spectrum of compound **4.**

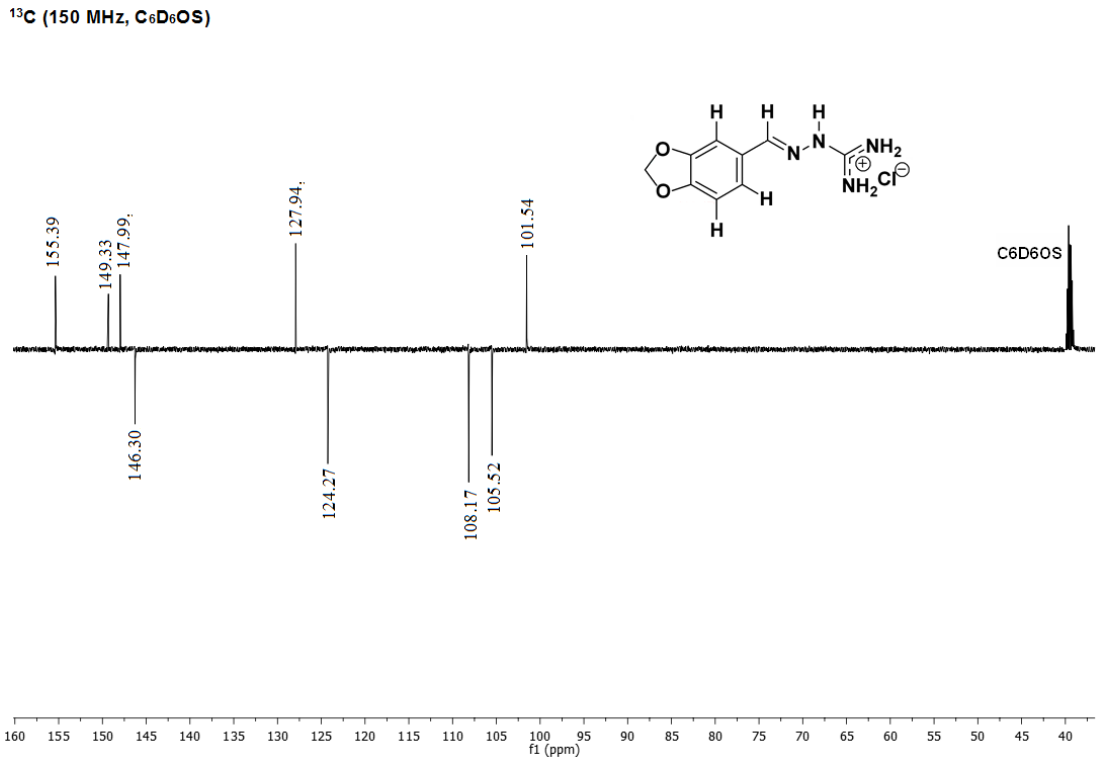


Fig. S.15: ^{13}C APT NMR spectrum of compound **4.**

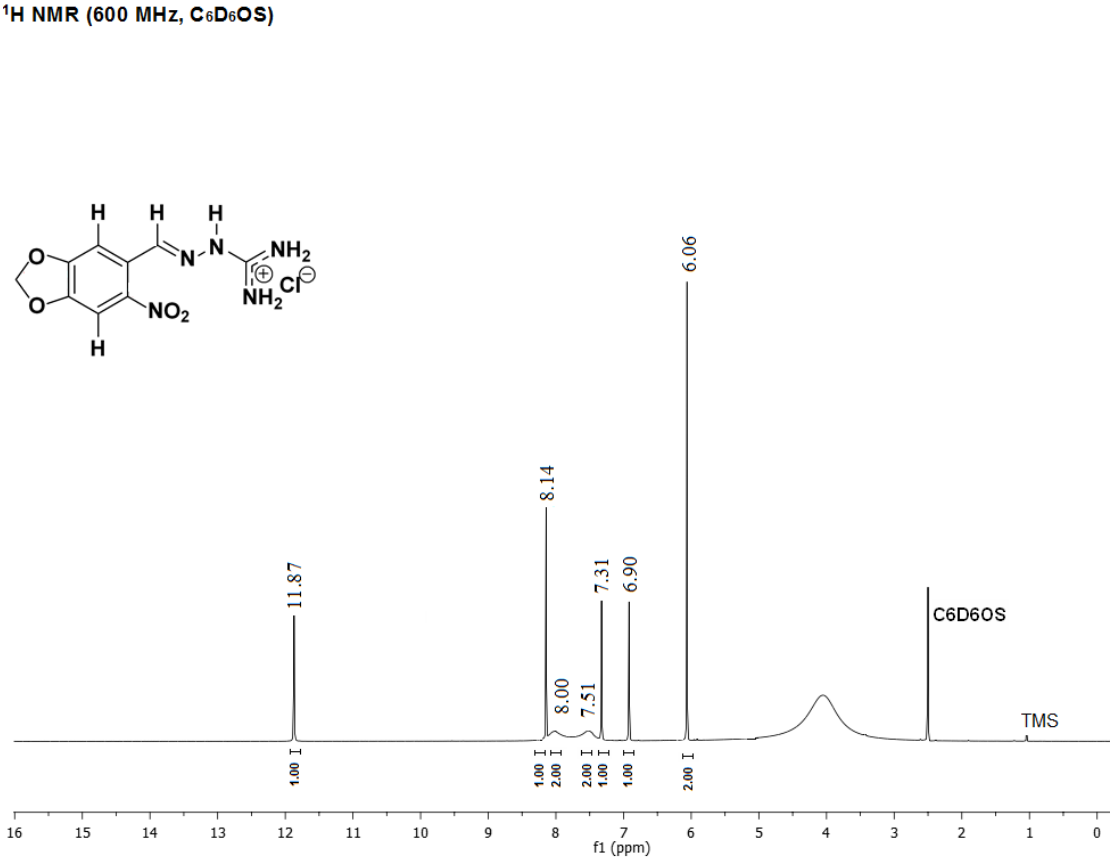


Fig. S.16: ^{1}H NMR spectrum of compound **5.**

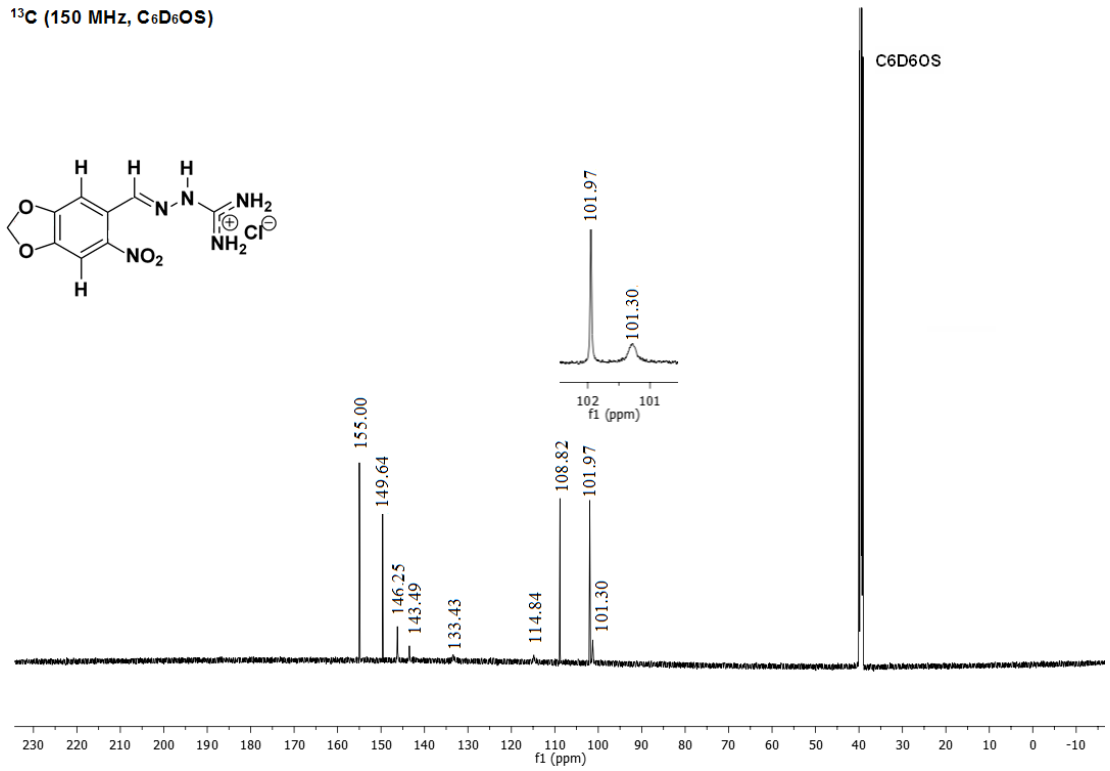


Fig. S.17: ^{13}C NMR spectrum of compound **5.**

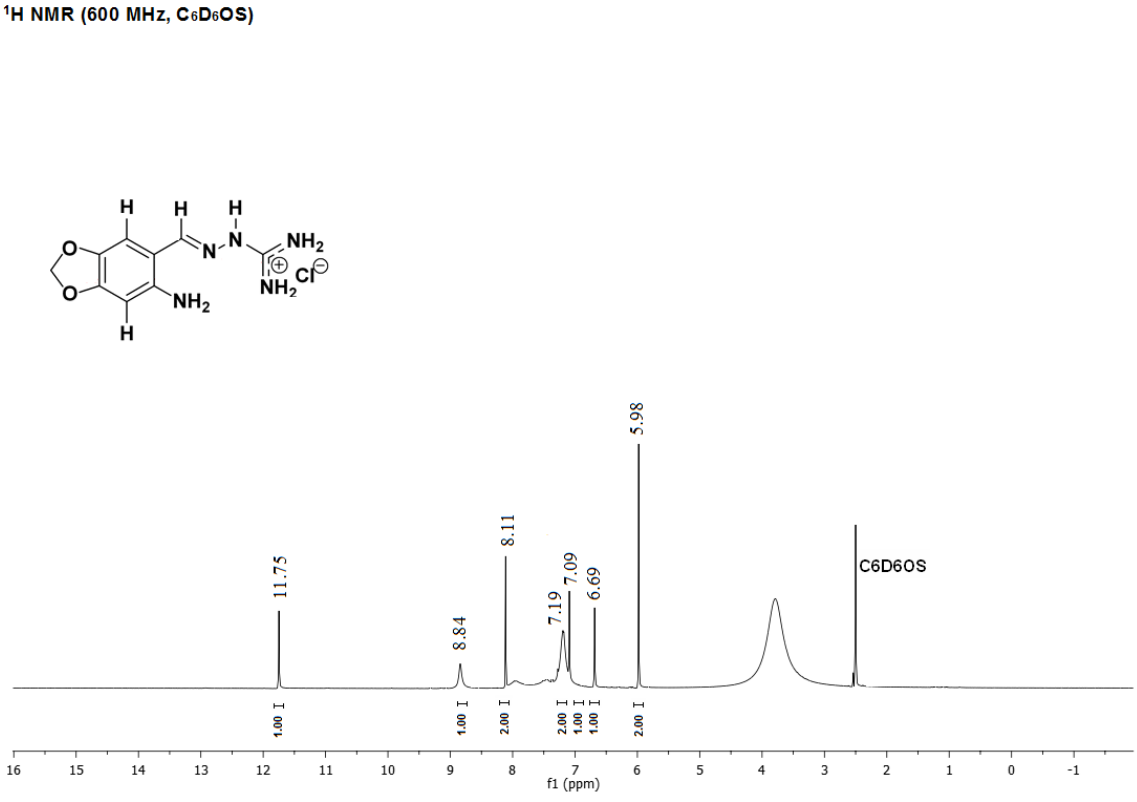


Fig. S.18: ^{1}H NMR spectrum of compound **6.**

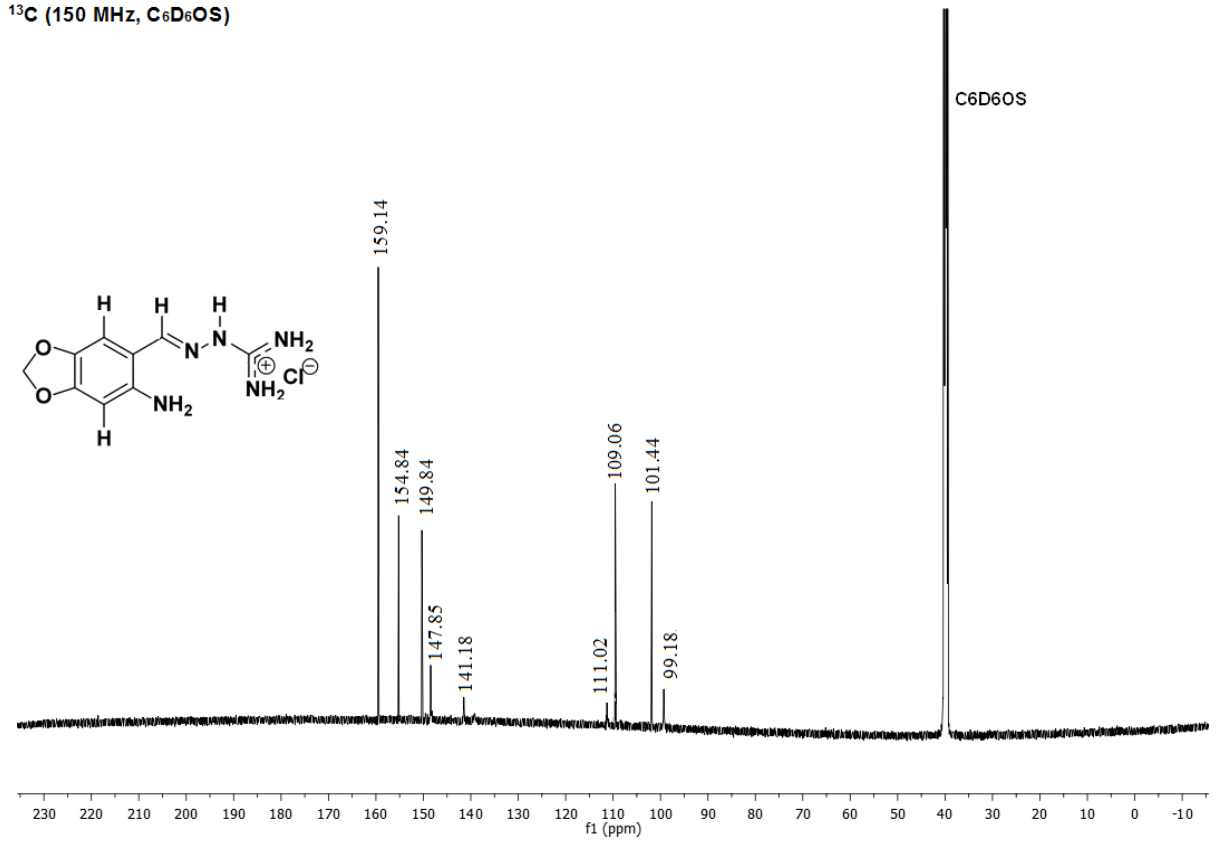


Fig. S.19: ^{13}C NMR spectrum of compound **6.**

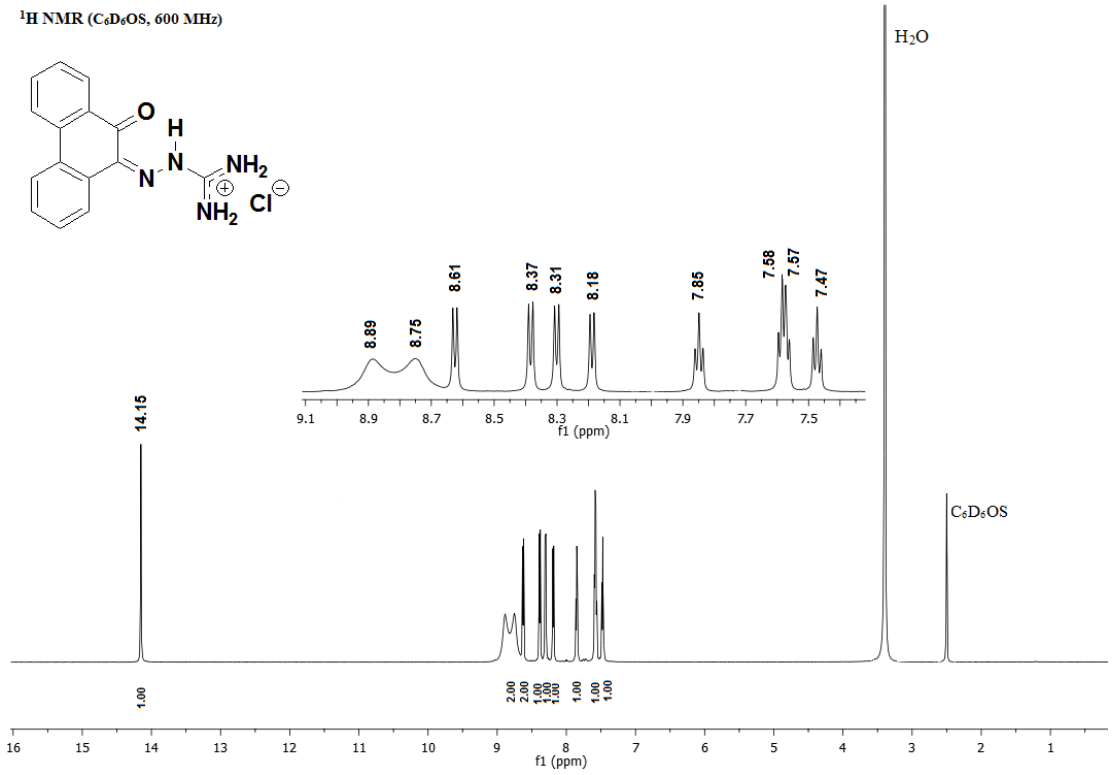


Fig. S.20: ^{1}H NMR spectrum of compound **7.**

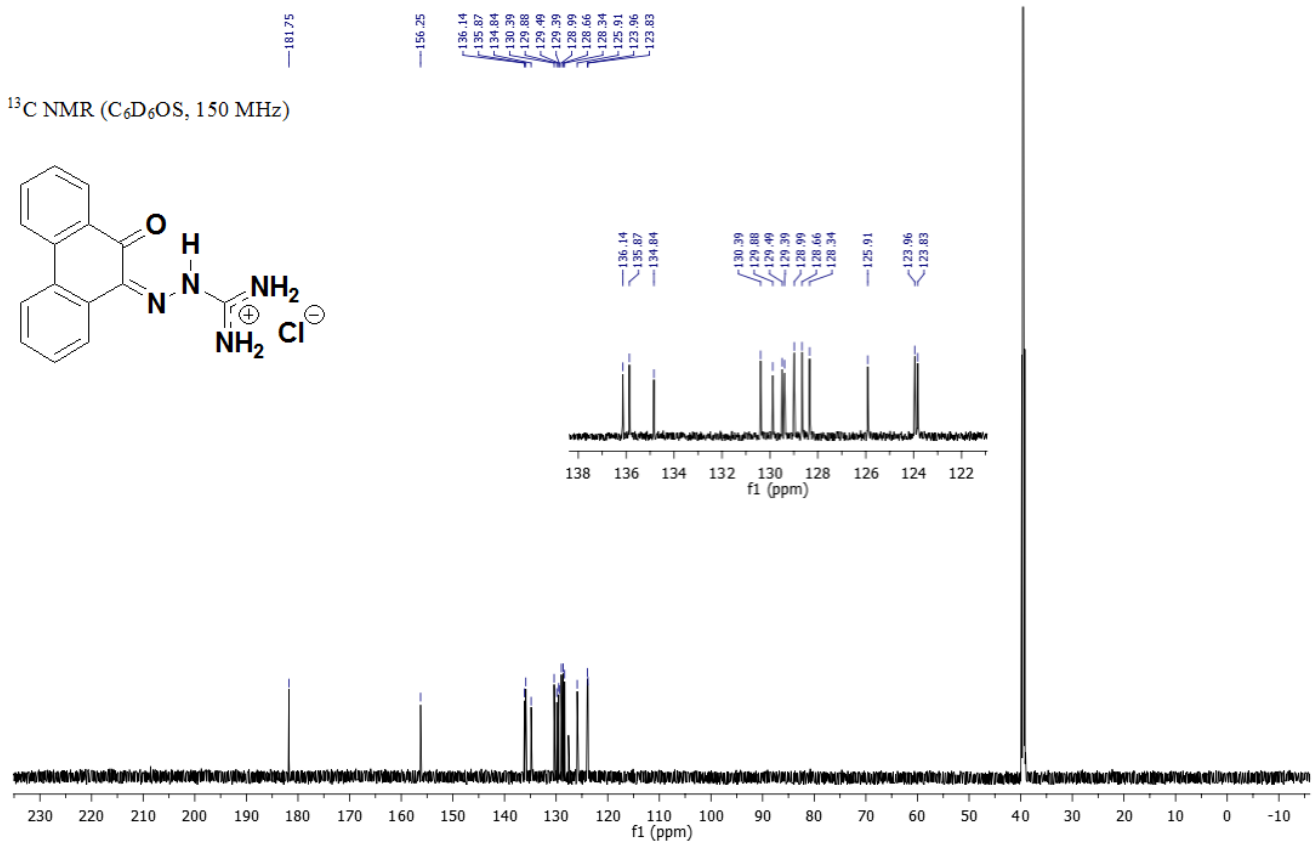


Fig. S.21: ^{13}C NMR spectrum of compound **7.**

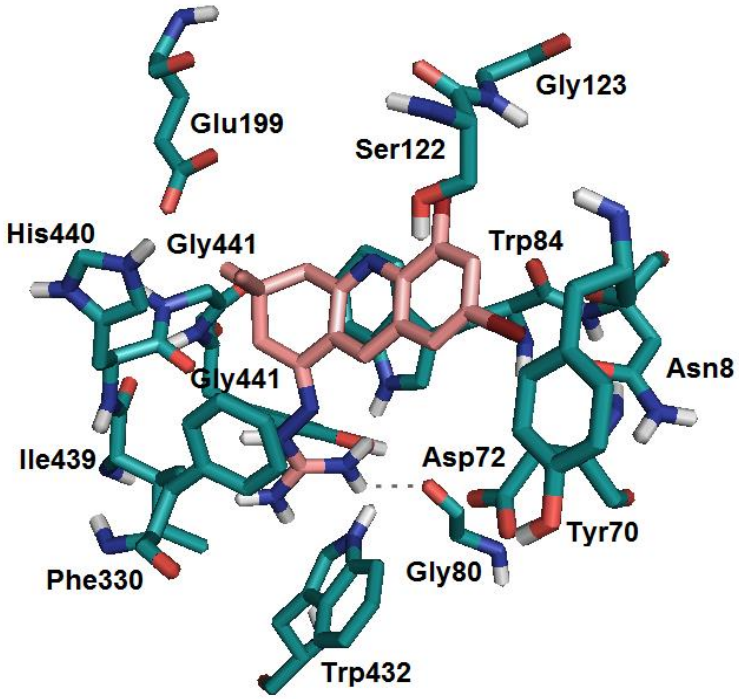


Fig. S.22: Docking interaction of compound **2**.

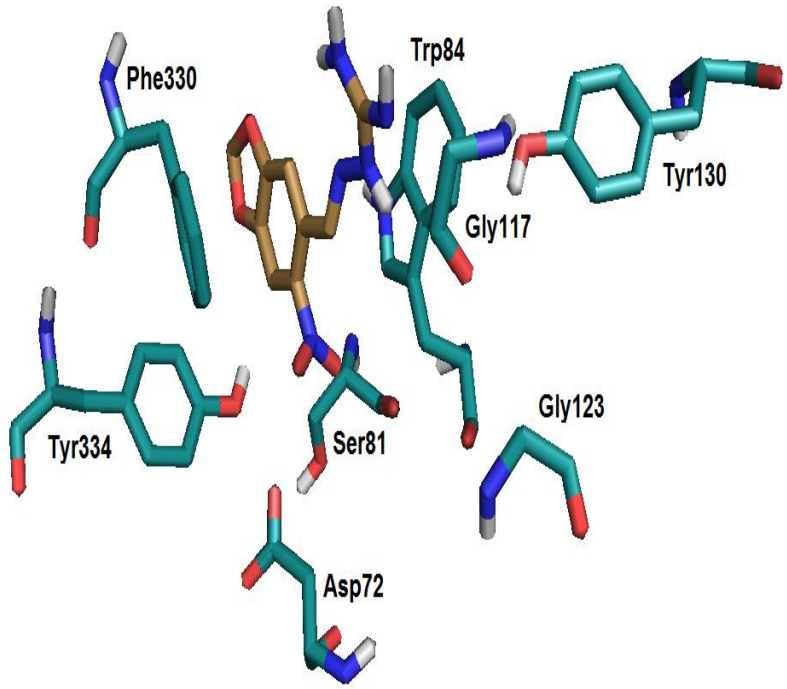


Fig. S.23: Docking interaction of compound **3**.

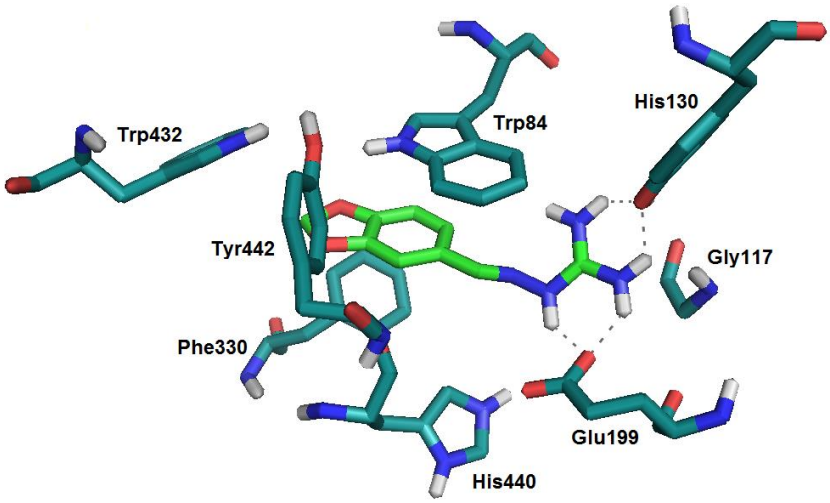


Fig. S.24: Docking interaction of compound **4**.

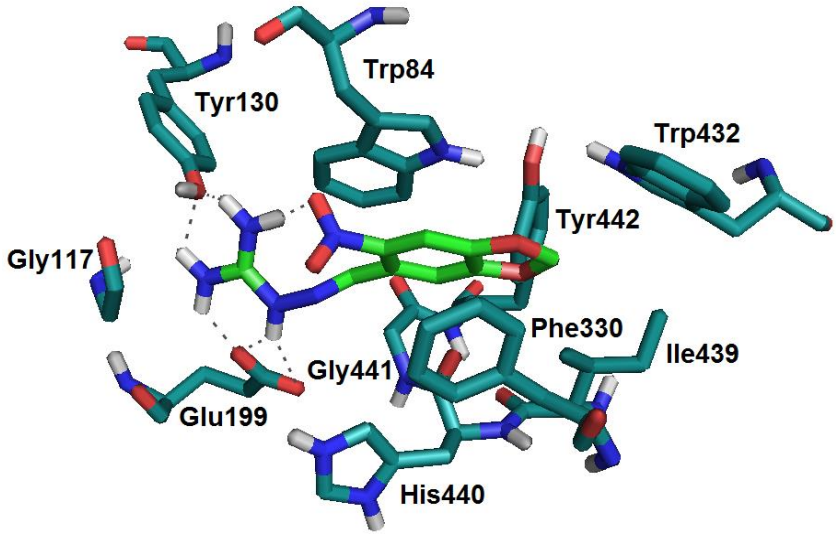


Fig. S.25: Docking interaction of compound **5.**

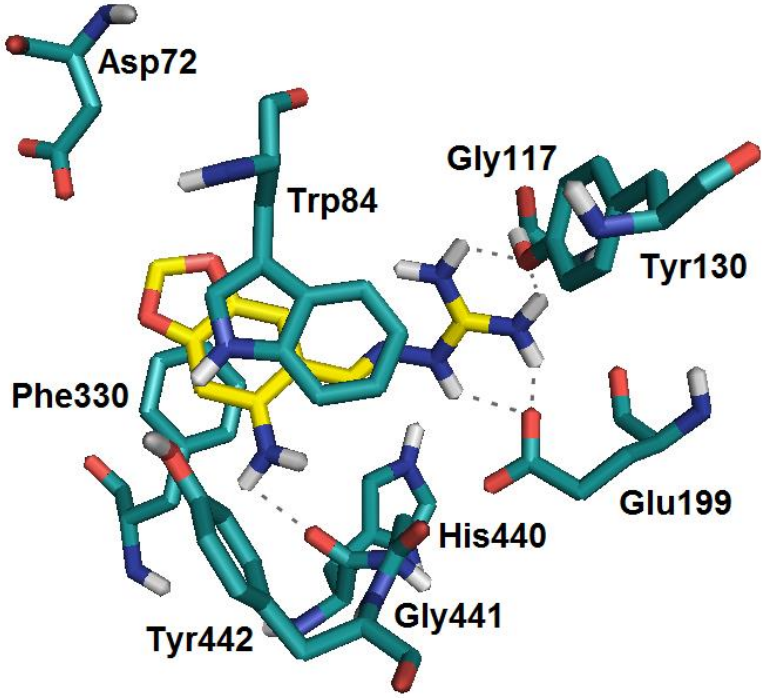


Fig. S.26: Docking interaction of compound **6**.

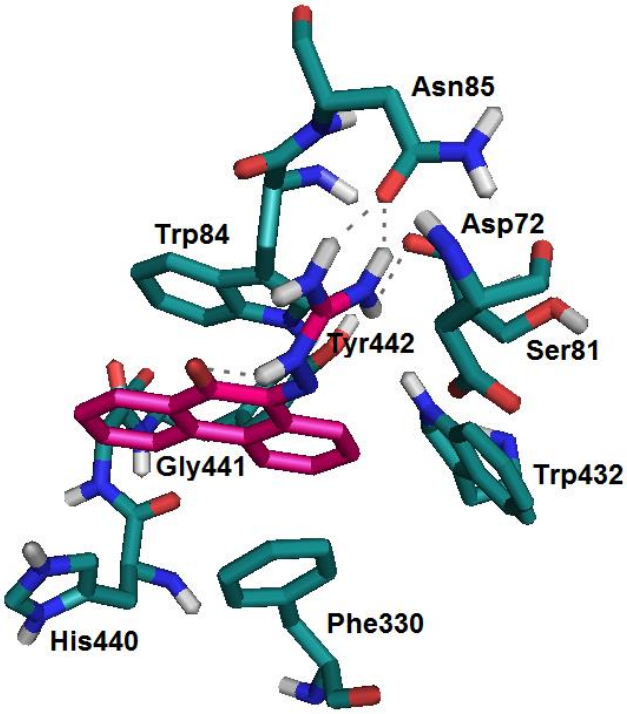


Fig. S.27: Docking interaction of compound **7**.

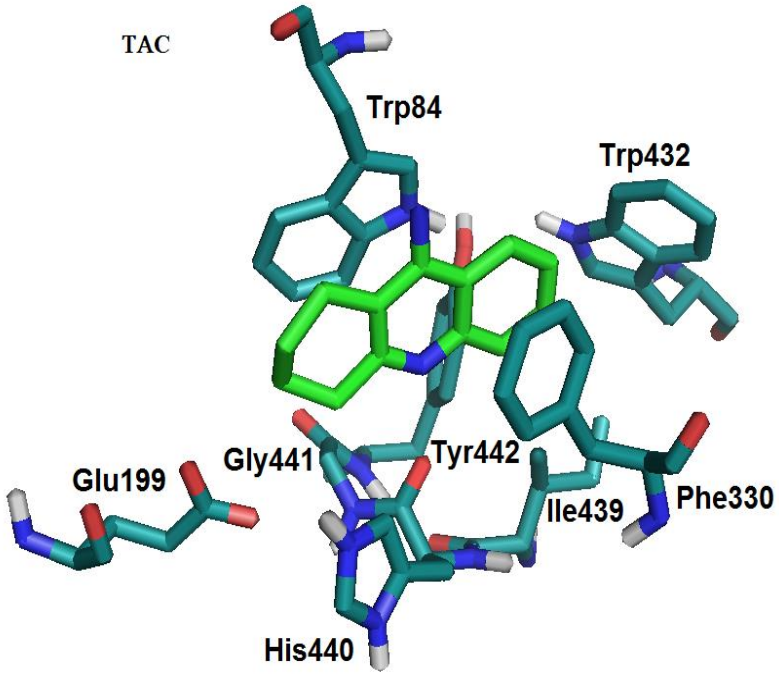


Fig. S.28: Docking interaction of Tacrine (TAC).

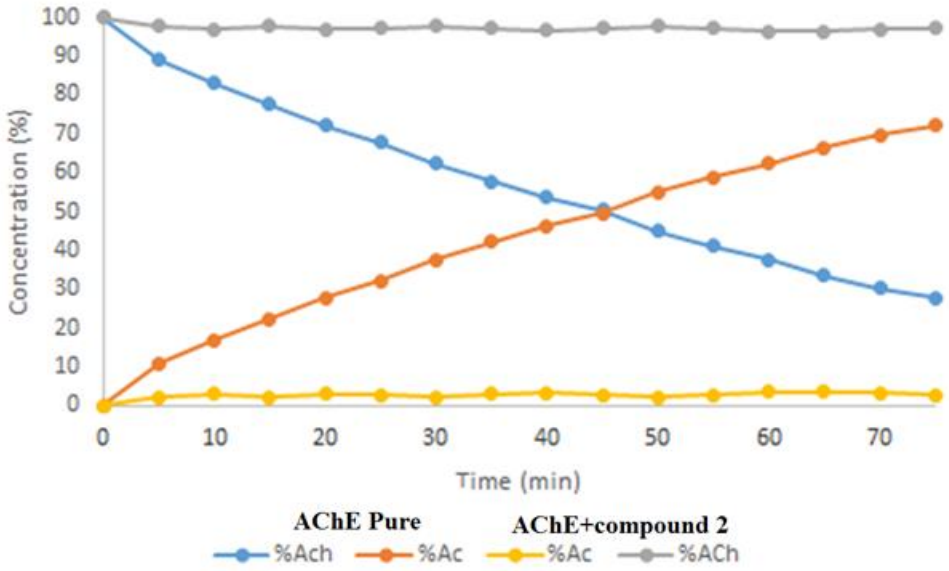


Fig.S.29: Variation of ACh concentration versus time for compound **2**.

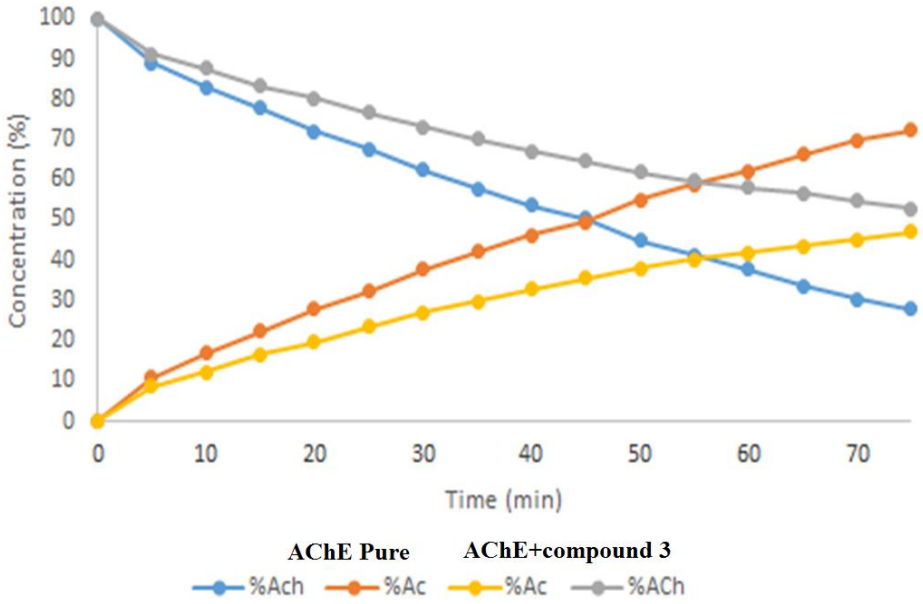


Fig.S.30: Variation of ACh concentration versus time for compound **3**.

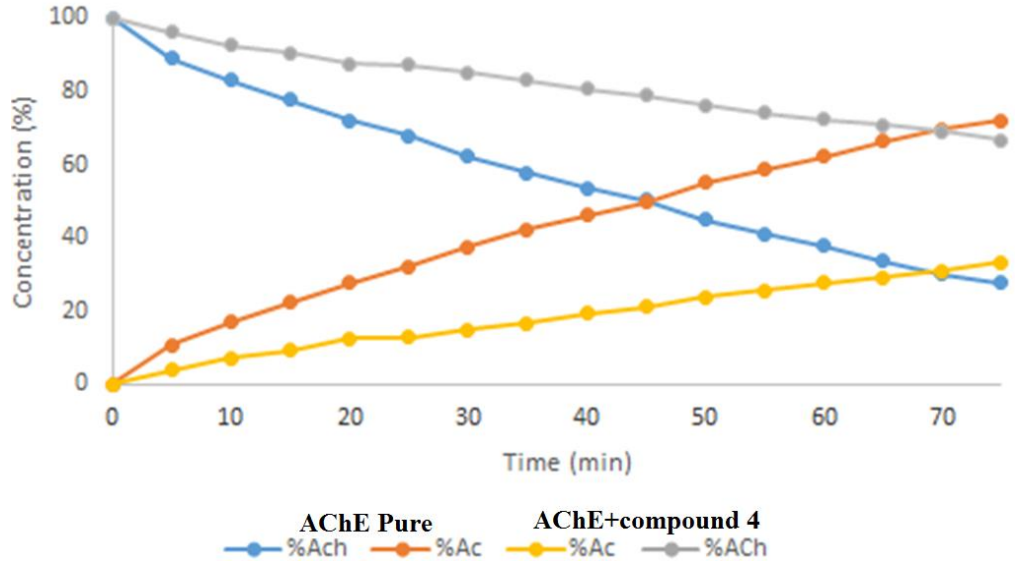


Fig.S.31: Variation of ACh concentration versus time for compound **4**.

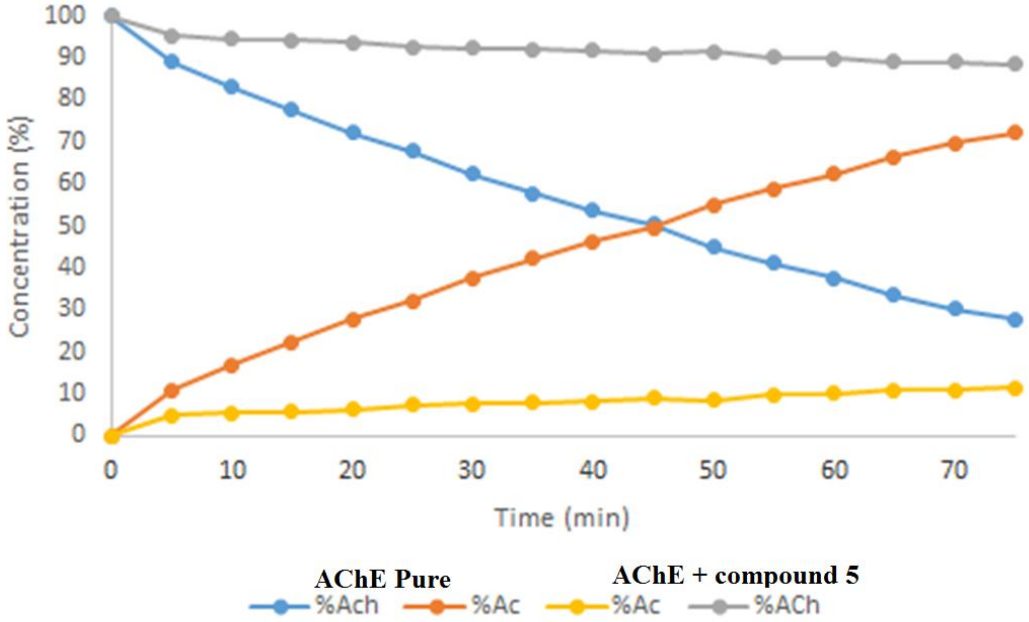


Fig.S.32: Variation of ACh concentration versus time for compound **5**.

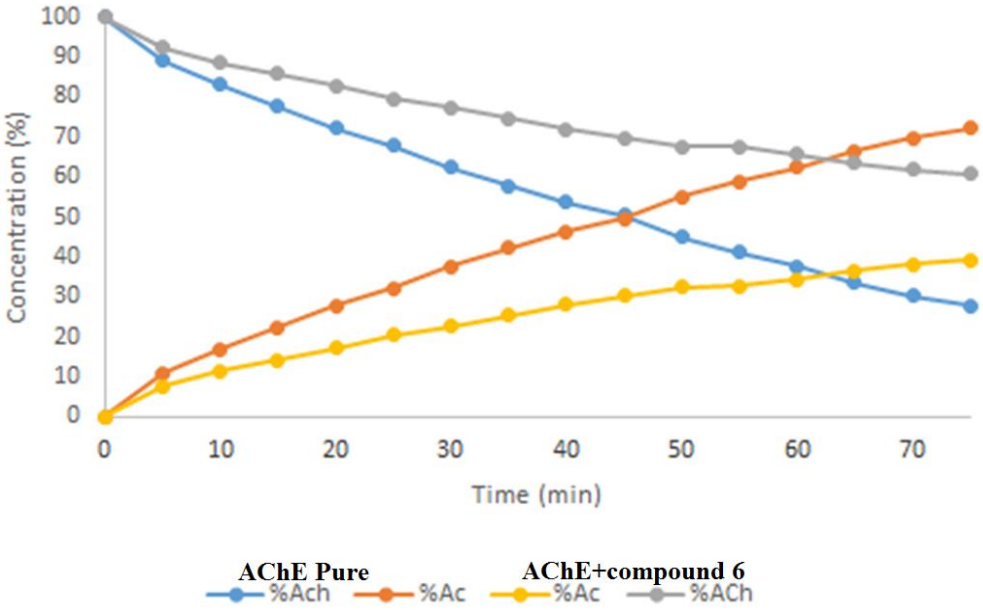


Fig.S.33: Variation of ACh concentration versus time for compound **6**.

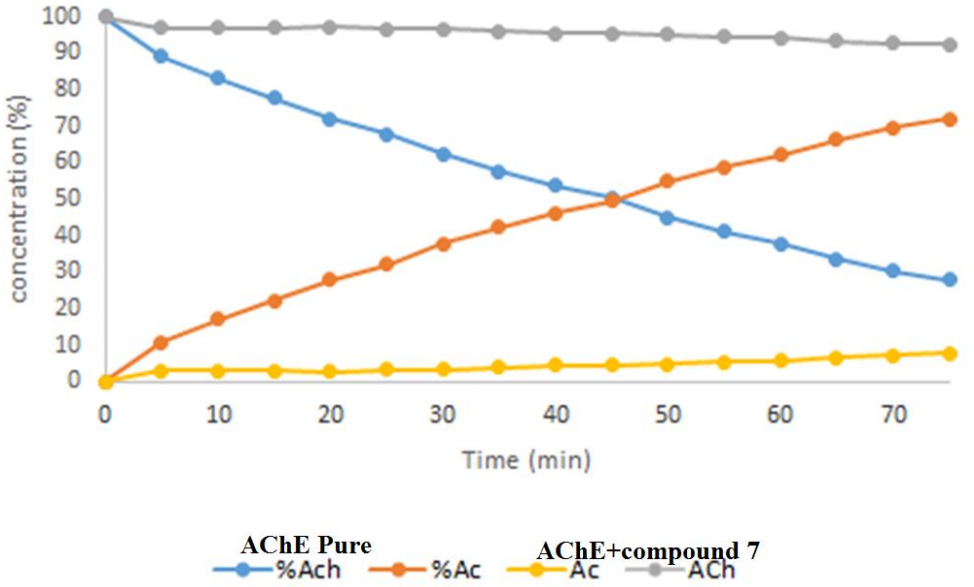


Fig.S.34: Variation of ACh concentration versus time for compound **7**.

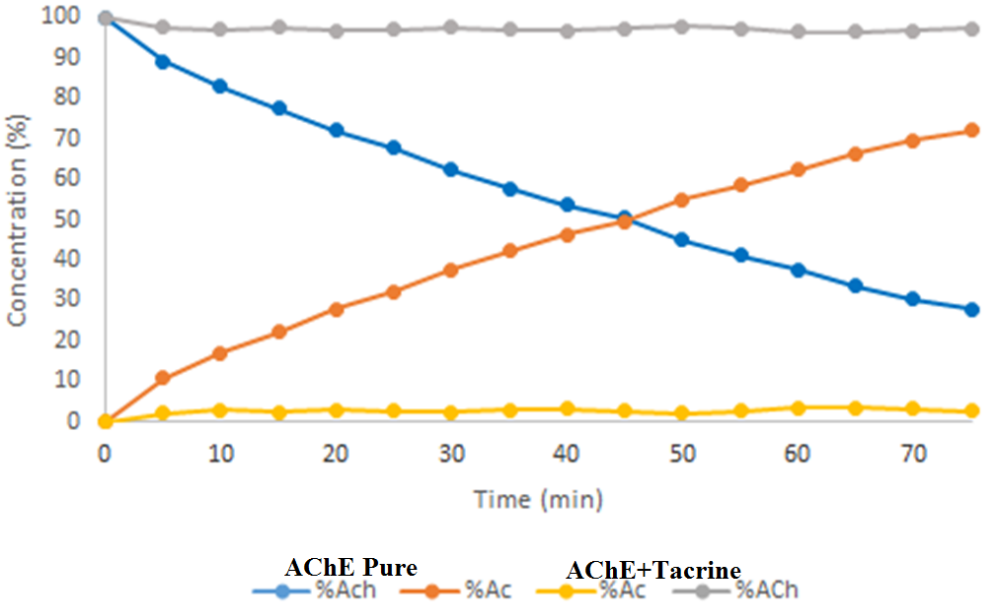


Fig.S.35: Variation of ACh concentration versus time for Tacrine (**TAC**).

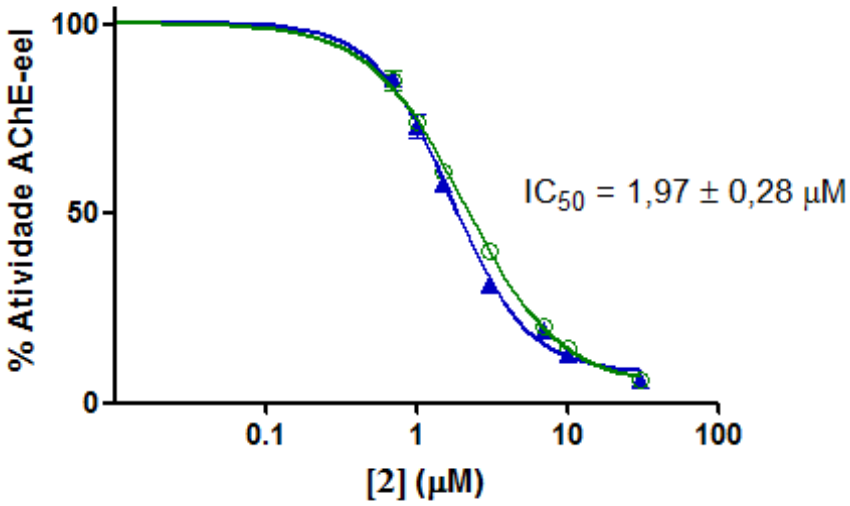


Fig.S.36: Inhibition curve (IC_{50}) of compound **2.**

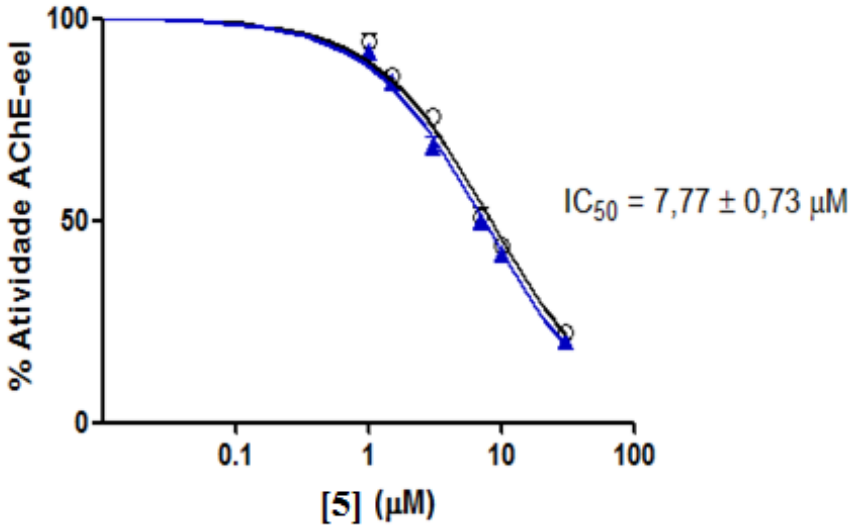


Fig.S.37: Inhibition curve (IC_{50}) of compound **5.**

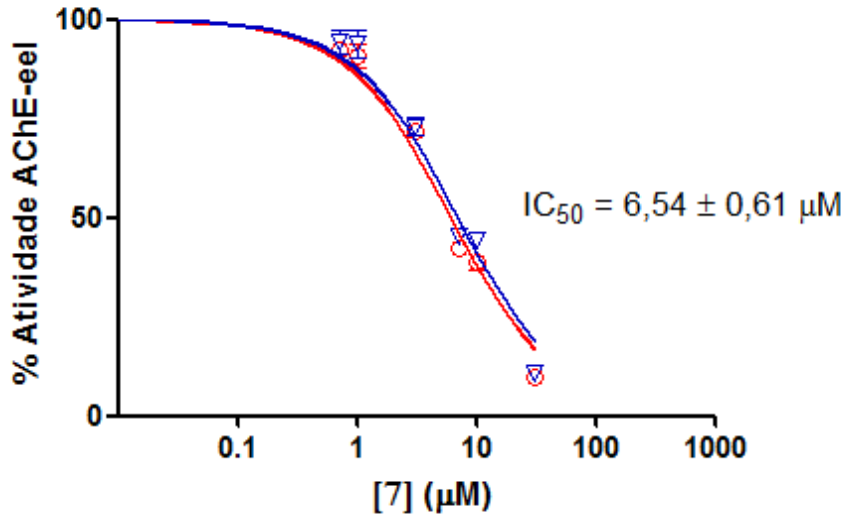


Fig.S.38: Inhibition curve (IC_{50}) of compound **7.**

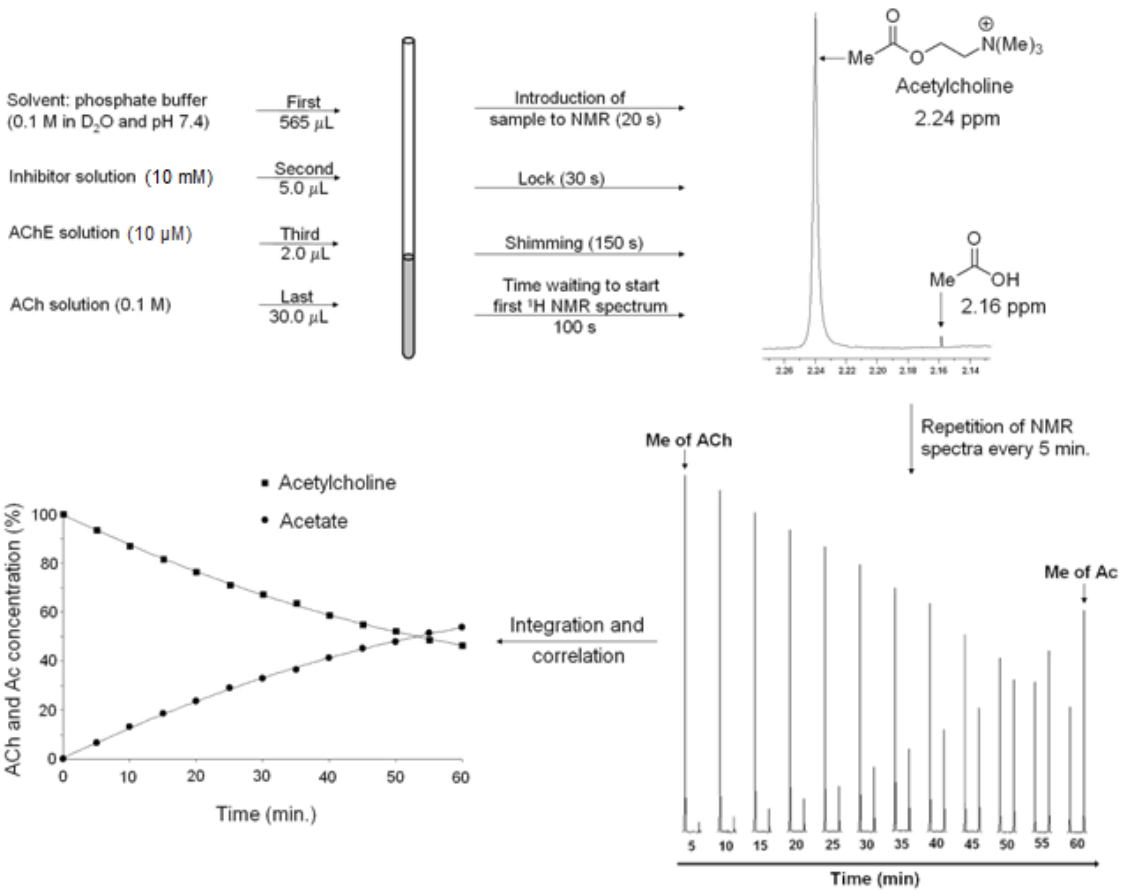


Fig. S.39: Test by NMR for evaluation of AChE inhibition.[37]