Electronic Supplementary Material (ESI) for RSC Advances.

Biomimetic synthesis of galantamine via laccase/TEMPO mediated oxidative coupling

Claudio Zippilli,[a] Lorenzo Botta,[a] Bruno Mattia Bizzarri,[a] Maria Camilla Baratto,[b] Rebecca Pogni,[b] Raffaele Saladino[a*]

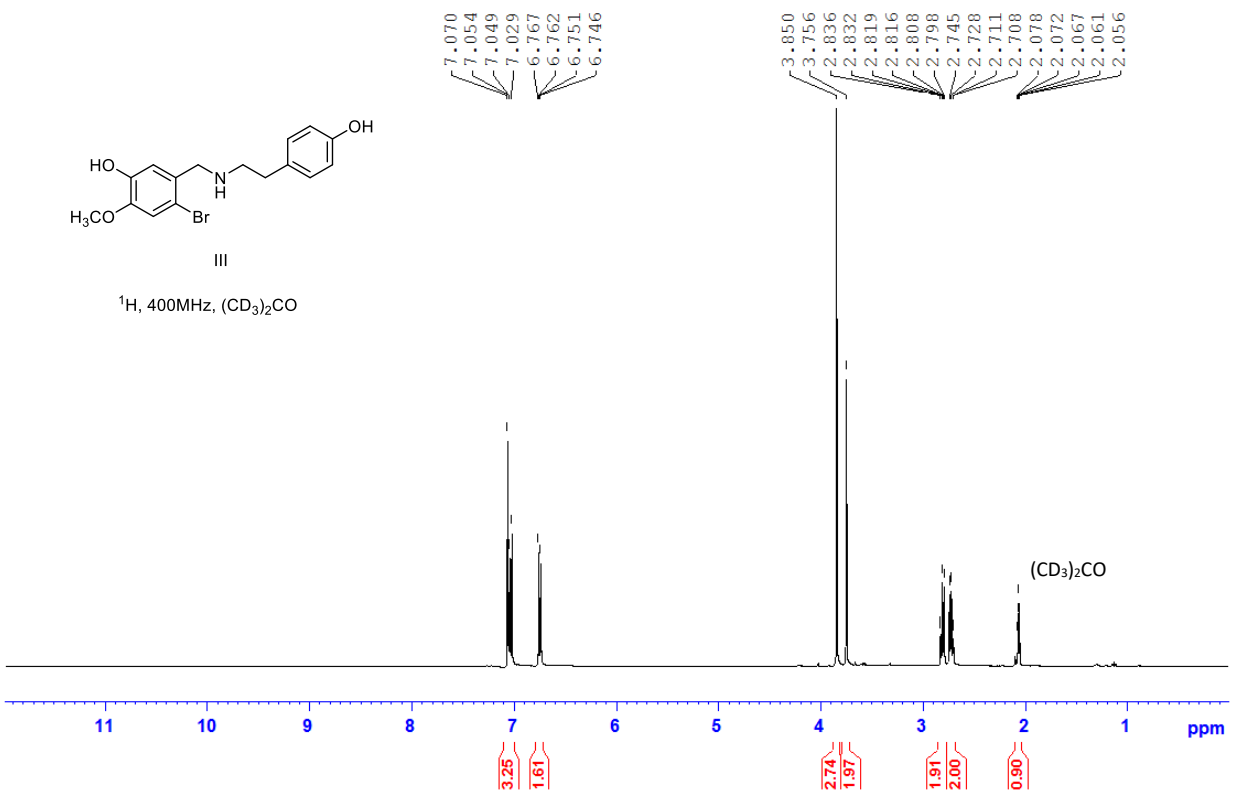
[a]Department of Ecological and Biological Sciences, University of Tuscia, via S. C. De Lellis 44, 01100, Viterbo, Italy

[b]Department of Biotechnology, Chemistry and Pharmacy, University of Siena, via Aldo Moro 2, 53100 Siena, Italy

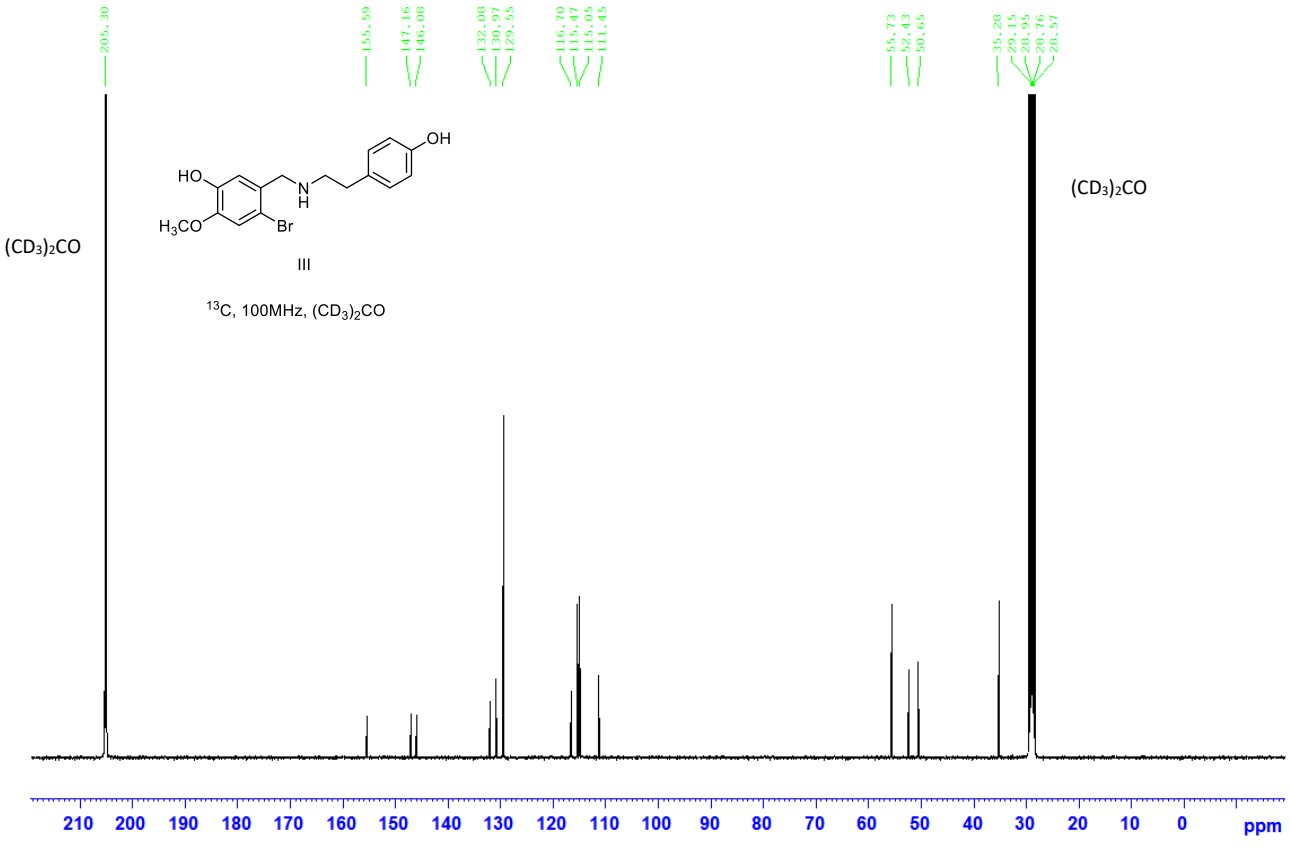
Supplementary Information

1D and 2D NMR spectra

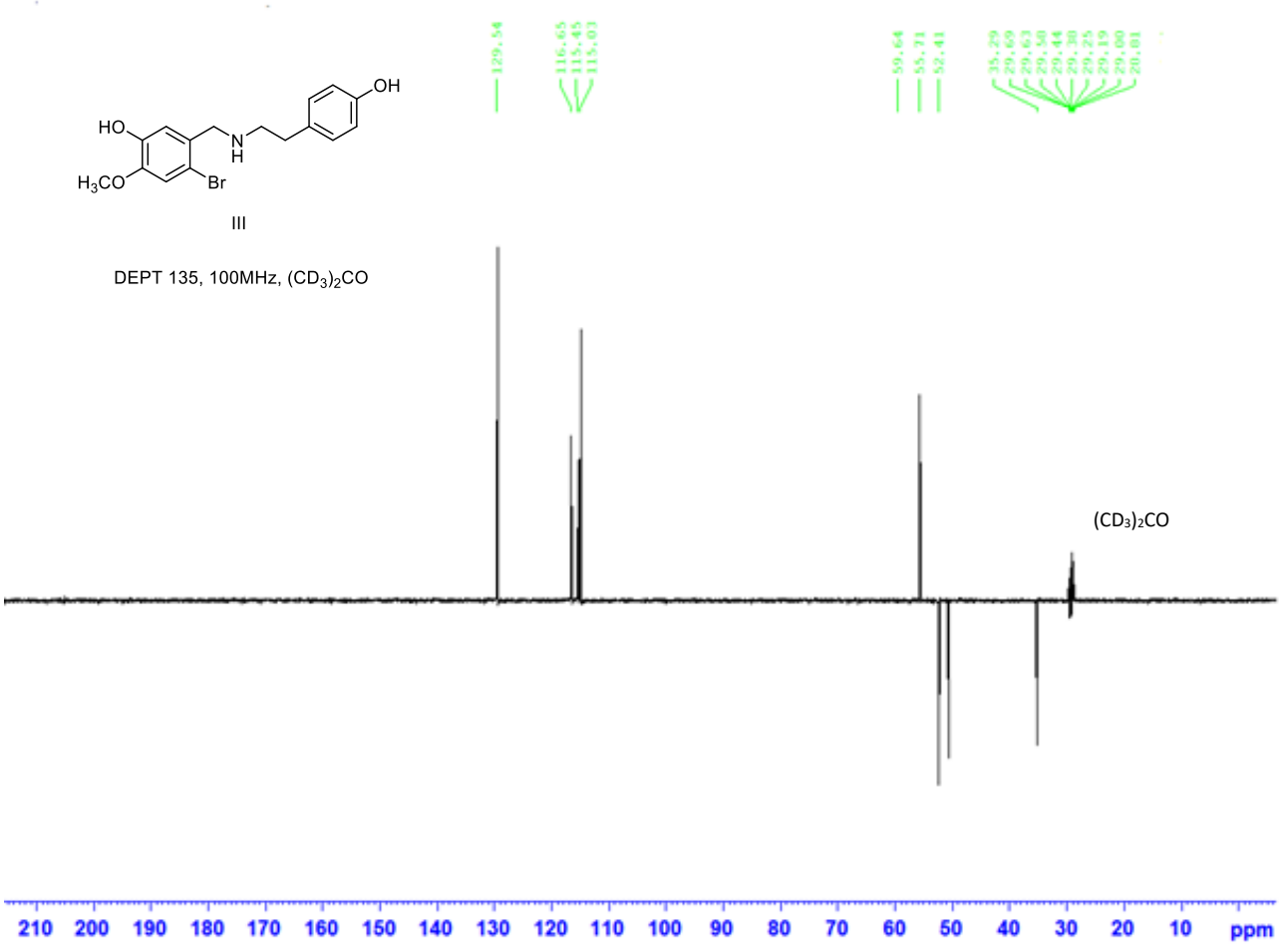
^{1}H-NMR of 4-bromo-5-({[2-(4-hydroxyphenyl)ethyl]amino}methyl)-2-methoxyphenol (III)



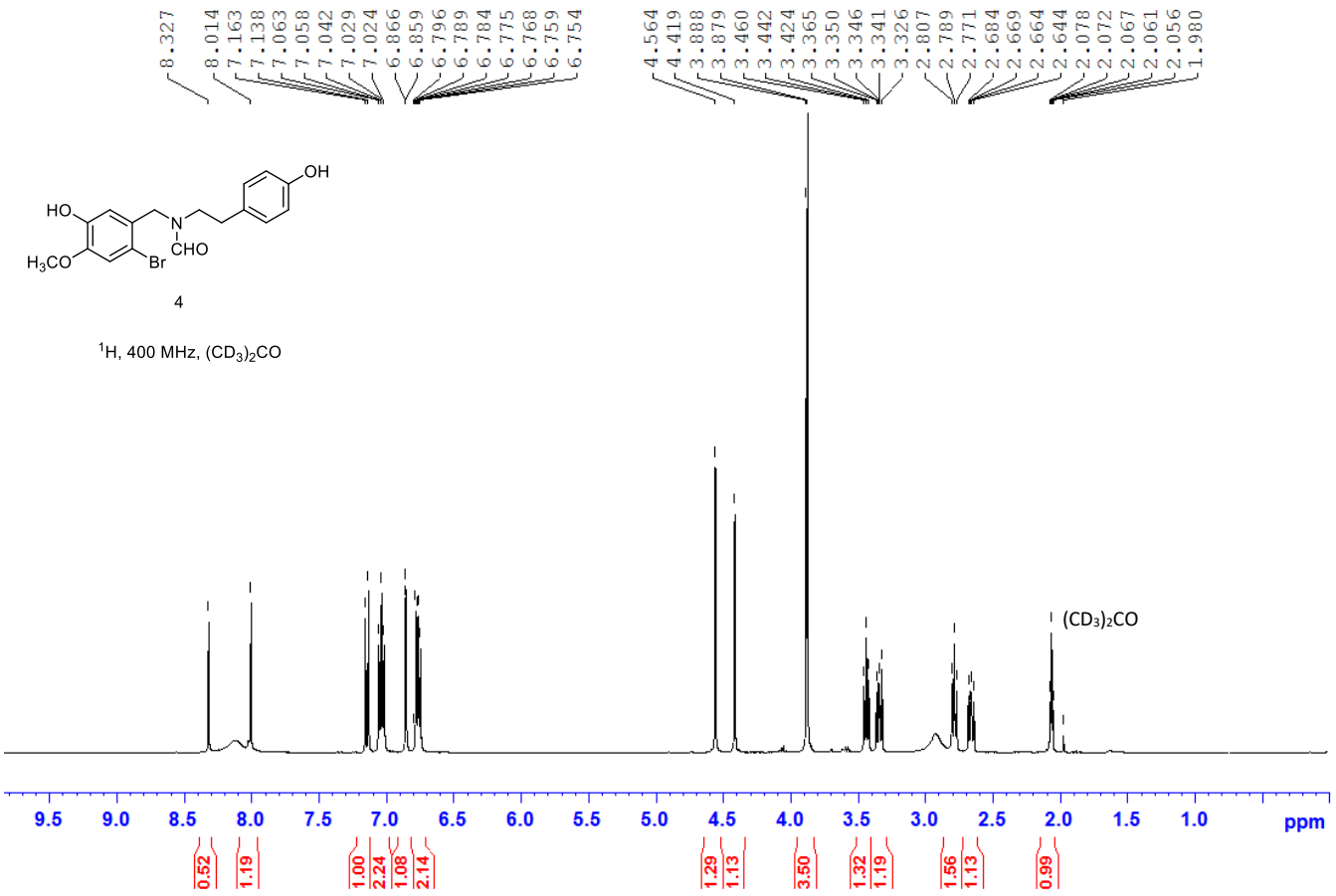
^{13}C -NMR of 4-bromo-5-({[2-(4-hydroxyphenyl)ethyl]amino}methyl)-2-methoxyphenol (III)



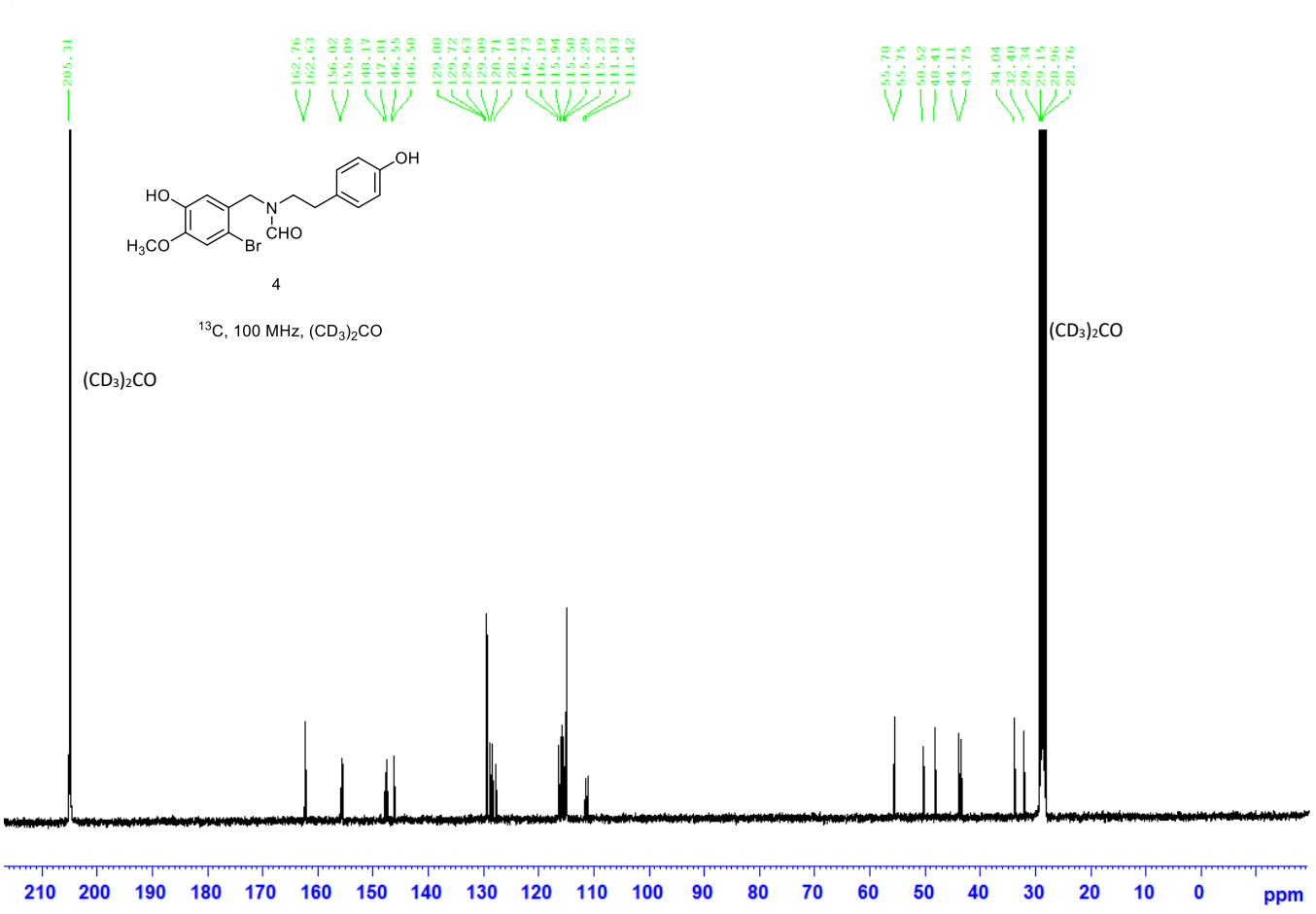
DEPT-135 of 4-bromo-5-({[2-(4-hydroxyphenyl)ethyl]amino}methyl)-2-methoxyphenol (III)



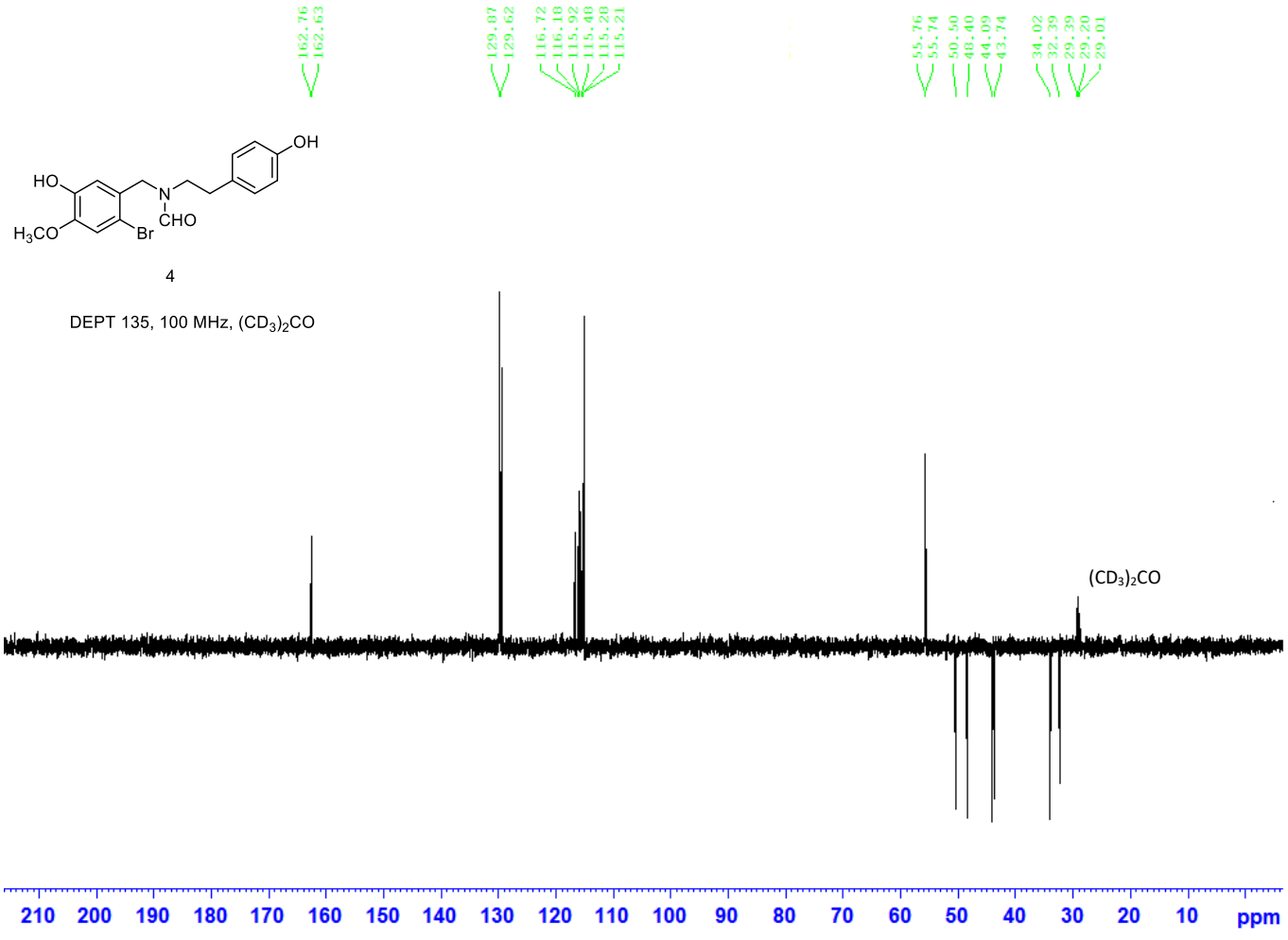
^{1}H-NMR of 4-bromo-5-({[2-(4-hydroxyphenyl)ethyl]amino}methyl)-2-methoxyphenol (4)



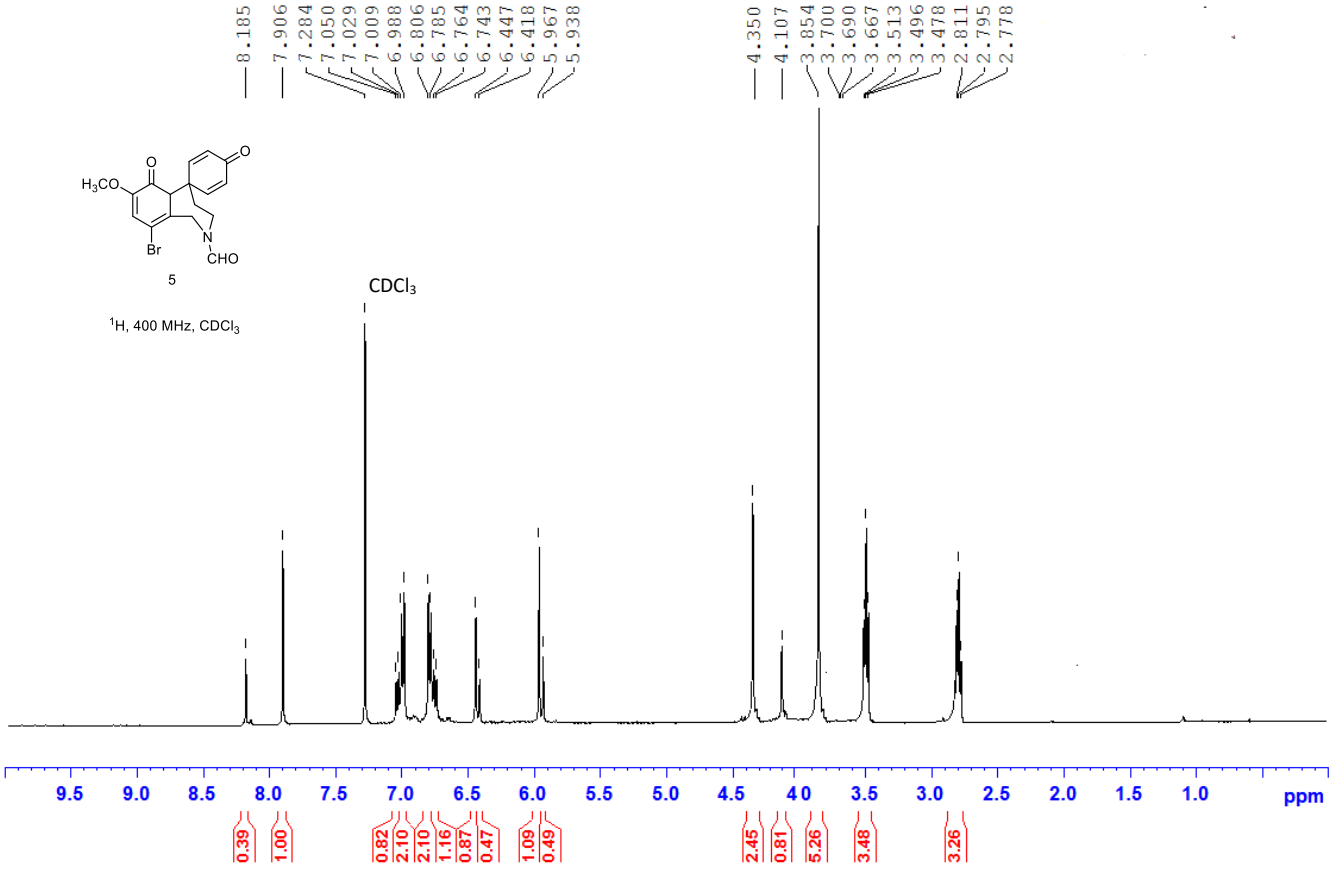
^{13}C-NMR of 4-bromo-5-({[2-(4-hydroxyphenyl)ethyl]amino}methyl)-2-methoxyphenol (4)



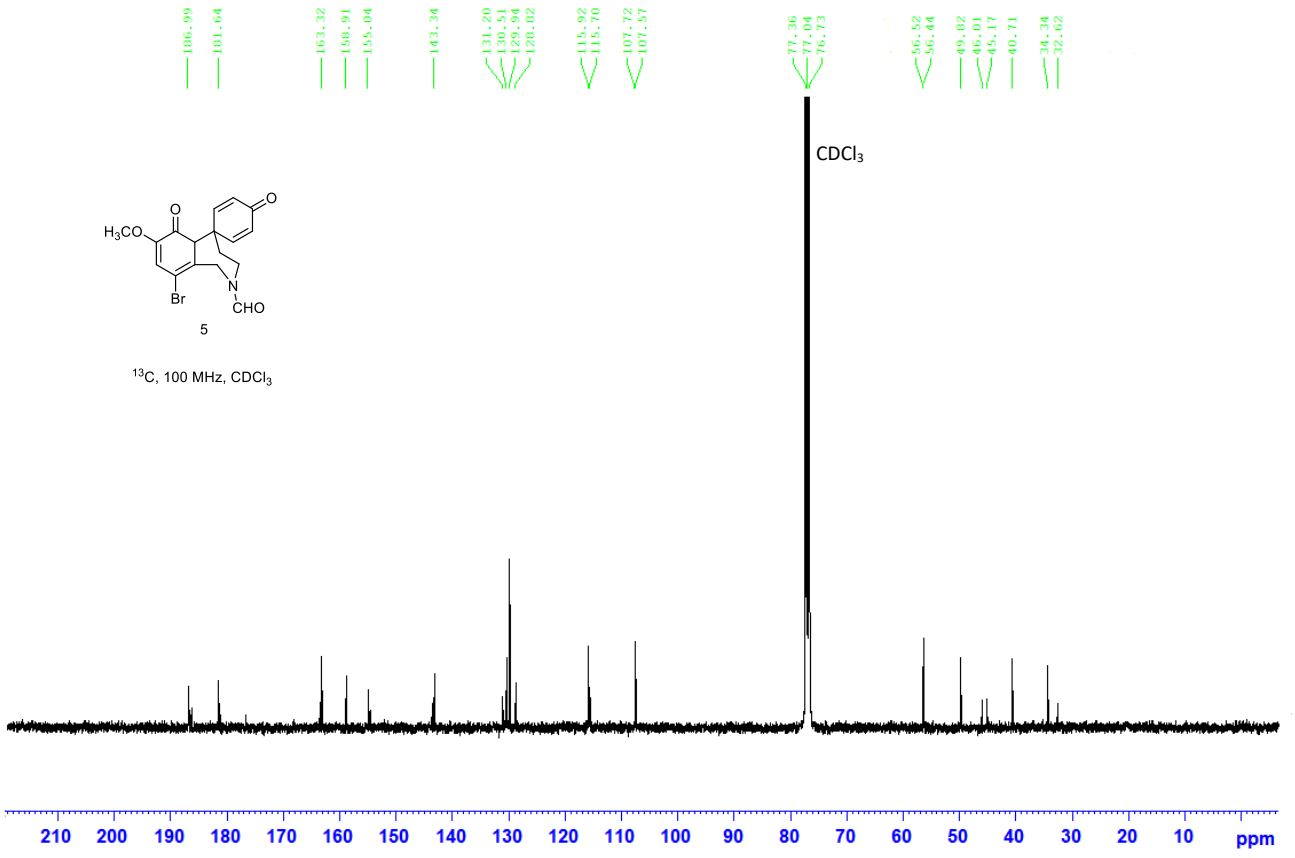
DEPT-135 of 4-bromo-5-({[2-(4-hydroxyphenyl)ethyl]amino}methyl)-2-methoxyphenol (4)



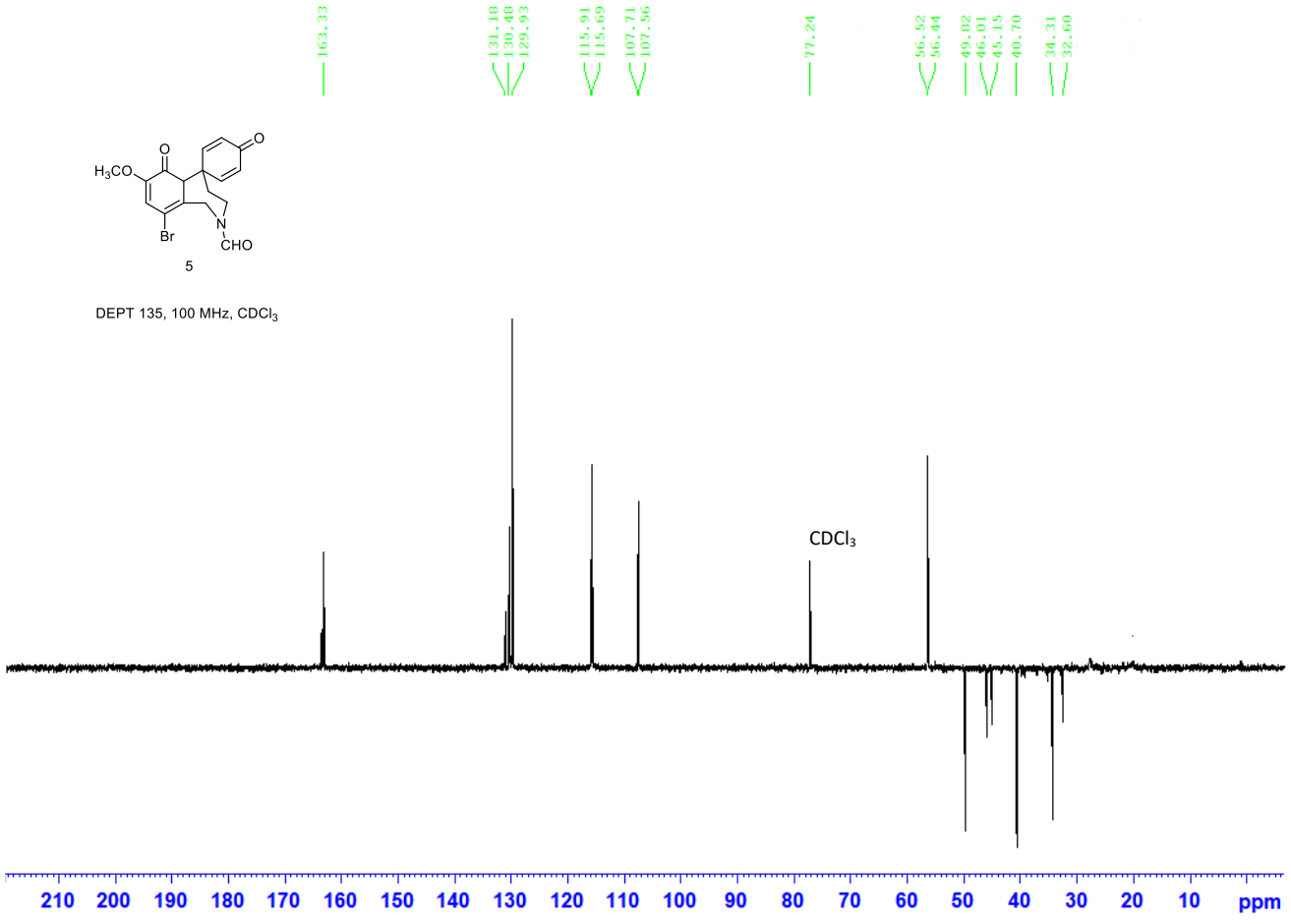
^{1}H-NMR of 2-acetyl-9-bromo-7-methoxy-1,2,3,4-tetrahydro-4'H-spiro[2-benzazepine-5,1'-cyclohexa[2,5]diene]-4',6(5aH)-dione (5)



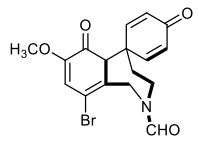
^{13}C-NMR of 2-acetyl-9-bromo-7-methoxy-1,2,3,4-tetrahydro-4'H-spiro[2-benzazepine-5,1'-cyclohexa[2,5]diene]-4',6(5aH)-dione (5)



DEPT-135 of 2-acetyl-9-bromo-7-methoxy-1,2,3,4-tetrahydro-4'H-spiro[2-benzazepine-5,1'-cyclohexa[2,5]diene]-4',6(5aH)-dione (5)

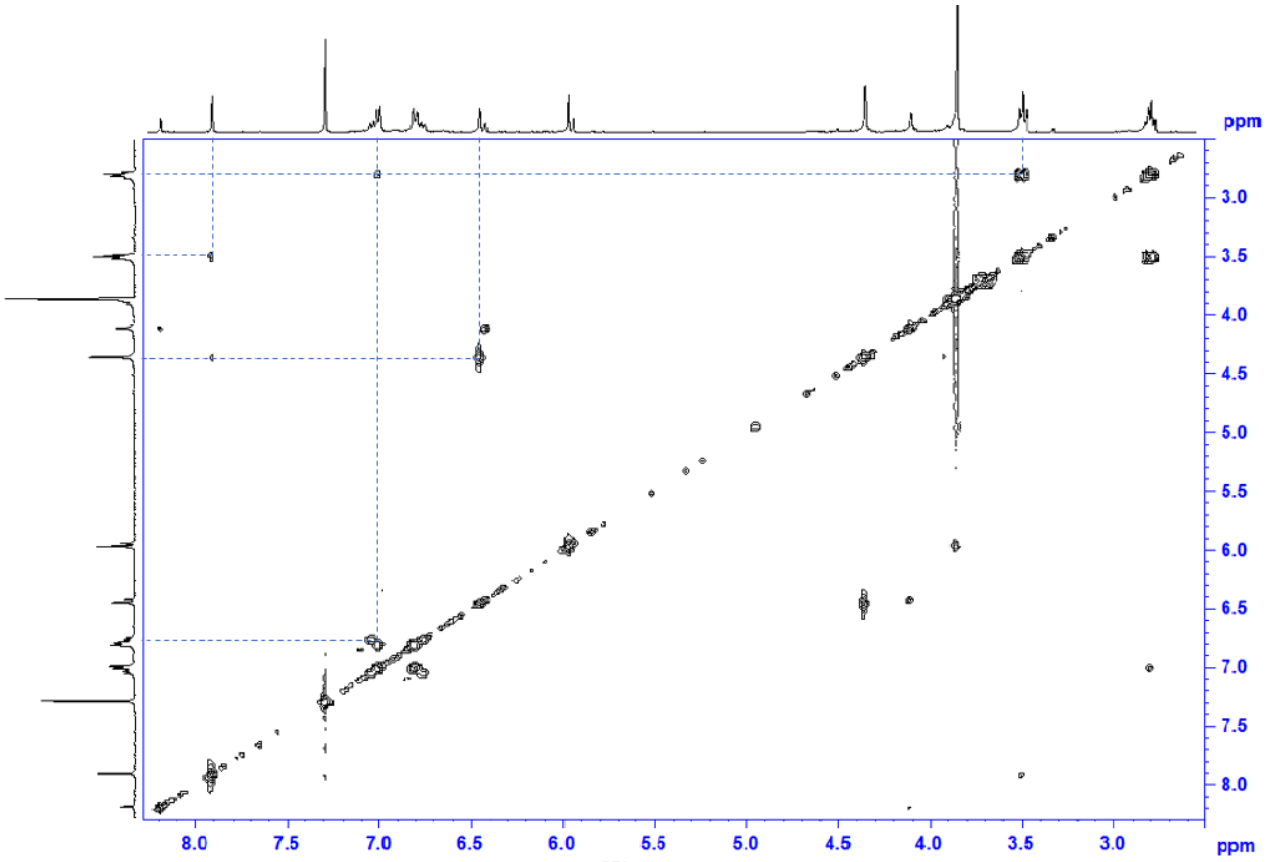


2D-COSY of 2-acetyl-9-bromo-7-methoxy-1,2,3,4-tetrahydro-4'H-spiro[2-benzazepine-5,1'-cyclohexa[2,5]diene]-4',6(5aH)-dione (5)

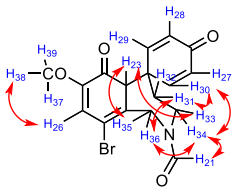


5

2D-COSY, 400 MHz, $CDCl_3$

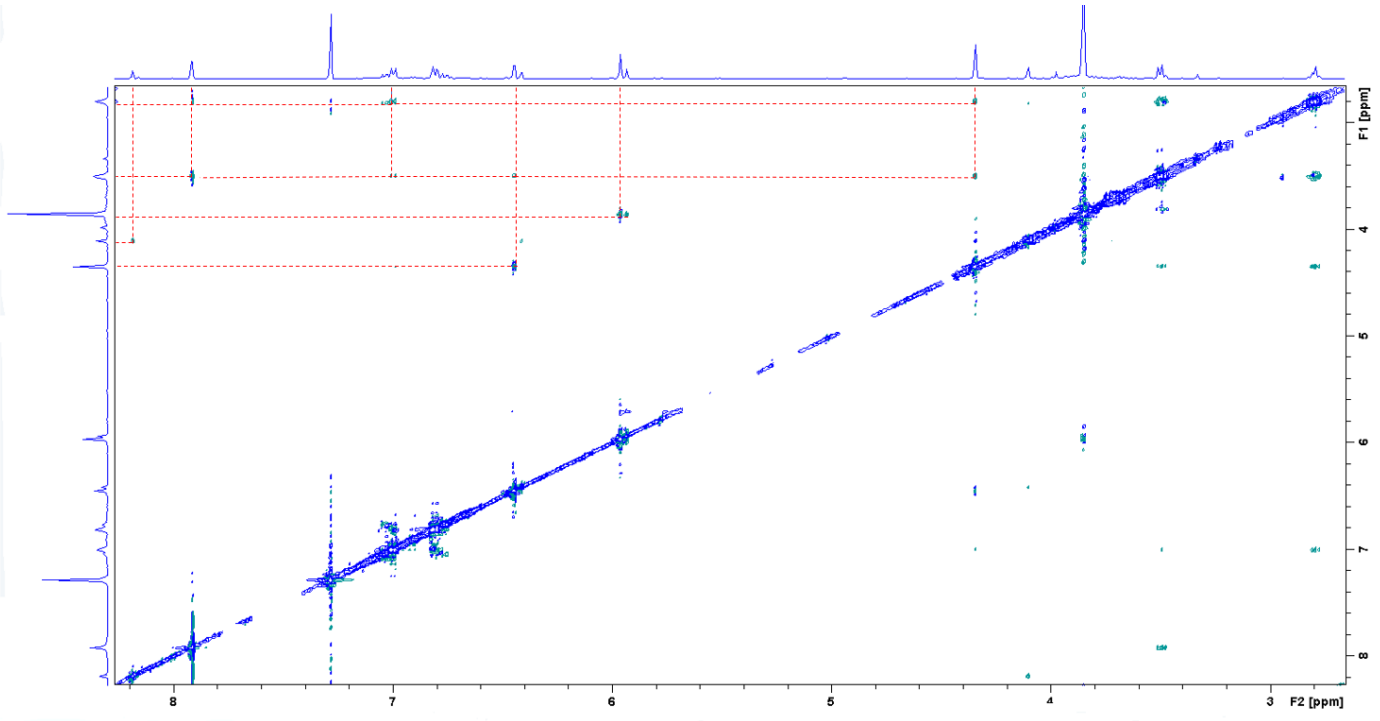


2D-NOESY of 2-acetyl-9-bromo-7-methoxy-1,2,3,4-tetrahydro-4'H-spiro[2-benzazepine-5,1'-cyclohexa[2,5]diene]-4',6(5aH)-dione (5)

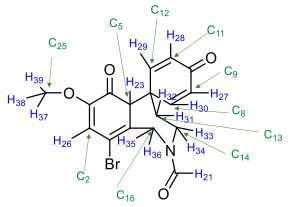


5

2D-NOESY, 400 MHz, $CDCl_3$



2D-HSQC of 2-acetyl-9-bromo-7-methoxy-1,2,3,4-tetrahydro-4'H-spiro[2-benzazepine-5,1'-cyclohexa[2,5]diene]-4',6(5aH)-dione (5)



5

2D-HSQC, 400 MHz, $CDCl_3$

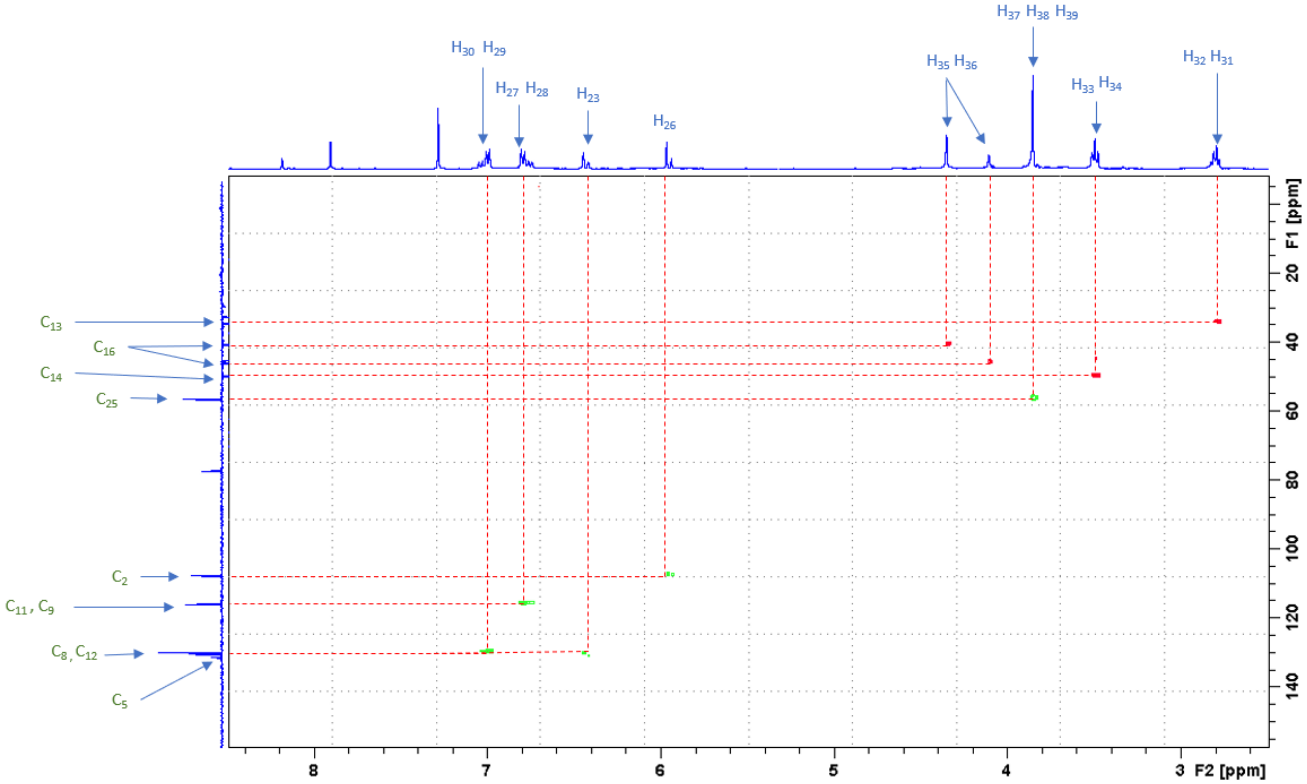
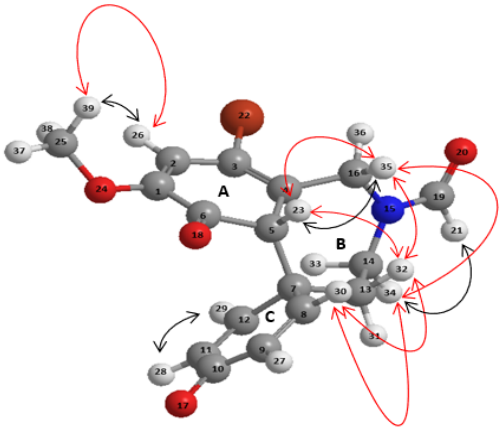


Table S1: representative ^{1}H-NMR, ^{13}C-NMR (HSQC), DEPT-135, ^{1}H-^{1}H COSY and ^{1}H-^{1}H NOESY data for compound **5.**

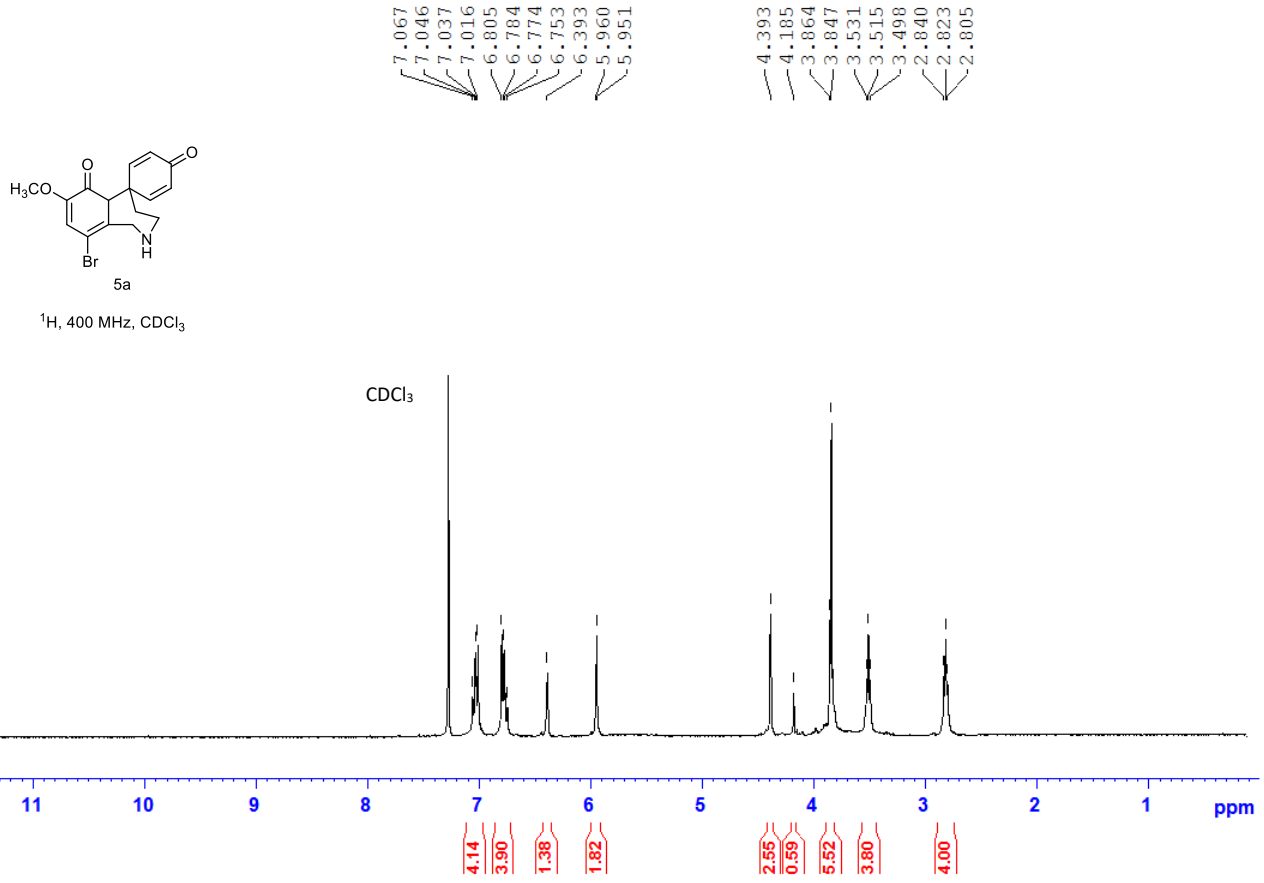


5

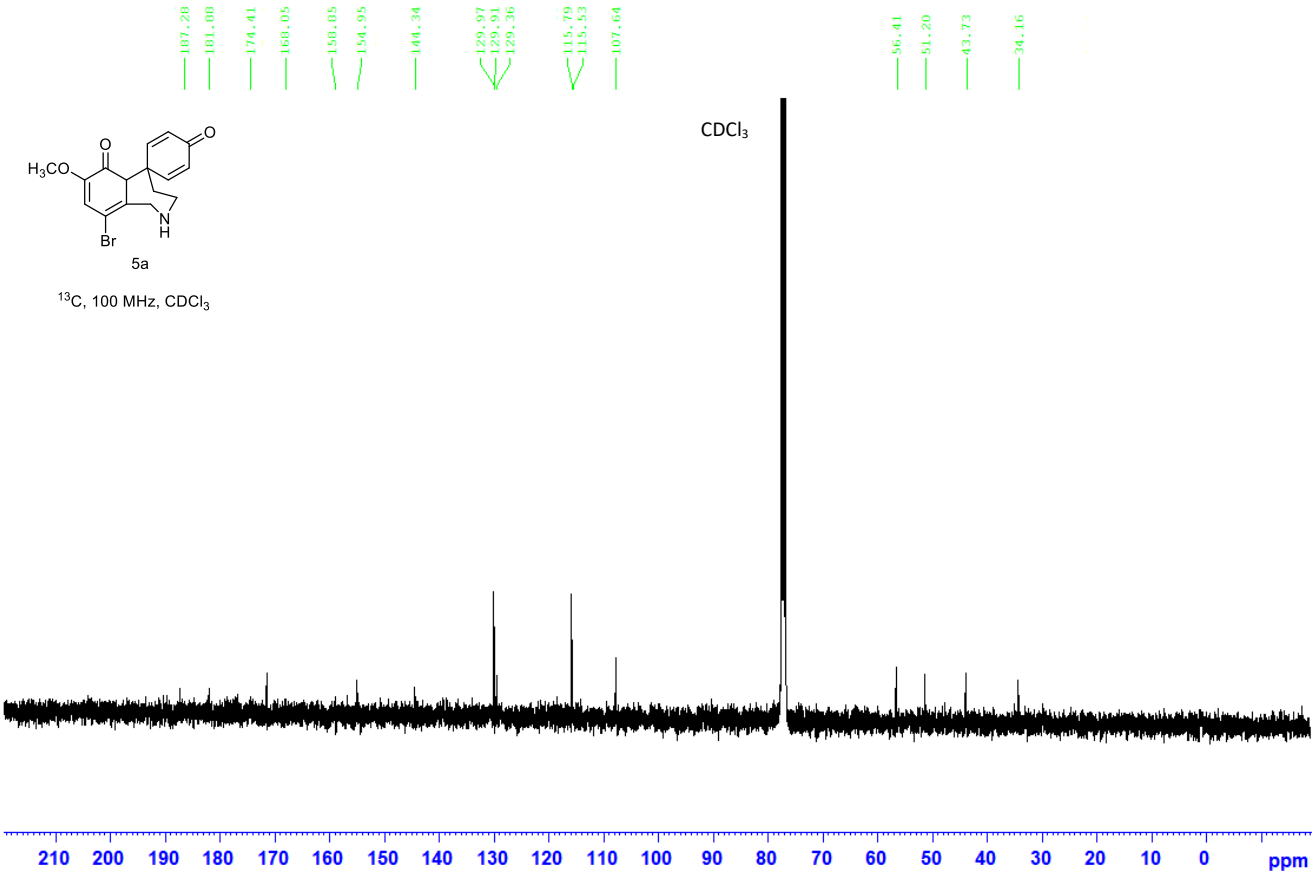
POSITION[a]	N°[b] ^{1}H δ (J in Hz)[c]	^{13}C δ[d;e]	COSY[f]	NOESY[g]	POSITION[a]	N°[b] ^{1}H δ (J in Hz)[c]	^{13}C δ[d;e]	COSY[f]	NOESY[g]
C1	-	158.9 C	-	-	C10	-	181.6 C	-	-
C2	H-26 δ = 5.96 (1H, s)	107.7 CH	-	H-39	C11	H-28 δ = 6.81 (1H, d, J = 8.0)	115.9 CH	H-29	-
C3	-	155.0 C	-	-	C12	H-29 δ = 7.00 (1H, d, J = 7.6)	130.5 CH	H-28	-
C4	-	143.3 C	-	-	C13	H-31,32 δ = 2.79 (J = 12.8, 6.4)	49.8 CH_2	H-33,34; H-30	H-21; H-23; H-30; H-35
C5	H-23 δ =6.44 (1H, s)	131.2 CH	H-35	H-32; H-35	C14	H-33,34 δ = 3.49 (J = 13.6, 6.8)	34.13 CH_2	H-31,32; H-21	H-21; H-30; H-35
C6	-	186.9 C	-	-	C16	H-35,36 δ = 4.34	40.7 CH_2	H-23; H21	H-23; H-32; H-34
C7	-	128.8 C	-	-	C19	H-21 δ = 7.90	163.3 CH	H-35,36; H-33,34	H-34; H-35
C8	H-30 δ = 7.00 (1H, d, J = 7.6)	130.5 CH	H-27	H-32; H-34	C25	H-37,38,39 δ = 3.85	56.5 CH_3	H-26	H-26
C9	H-27 δ = 6.81 (1H, d, J = 8.0)	115.8 CH	H-30	-					

[a] The Numbering of carbon atoms is reported in Figure 2. [b] Numbering for the hydrogen atoms bonded to relative carbon position. [c] δ and J constant values are reported in ppm and Hz, respectively. [d] Carbon atoms assignment based on 2D-NMR and ^{1}H-DEPT-135/HSQC analysis. [e]Multiplicity of carbon atoms as determined by using DEPT-135 data. [f]Numbering of hydrogen atoms that are correlated by ^{1}H-^{1}H COSY. [g]Numbering of hydrogen atoms that are correlated by ^{1}H-^{1}H NOESY.

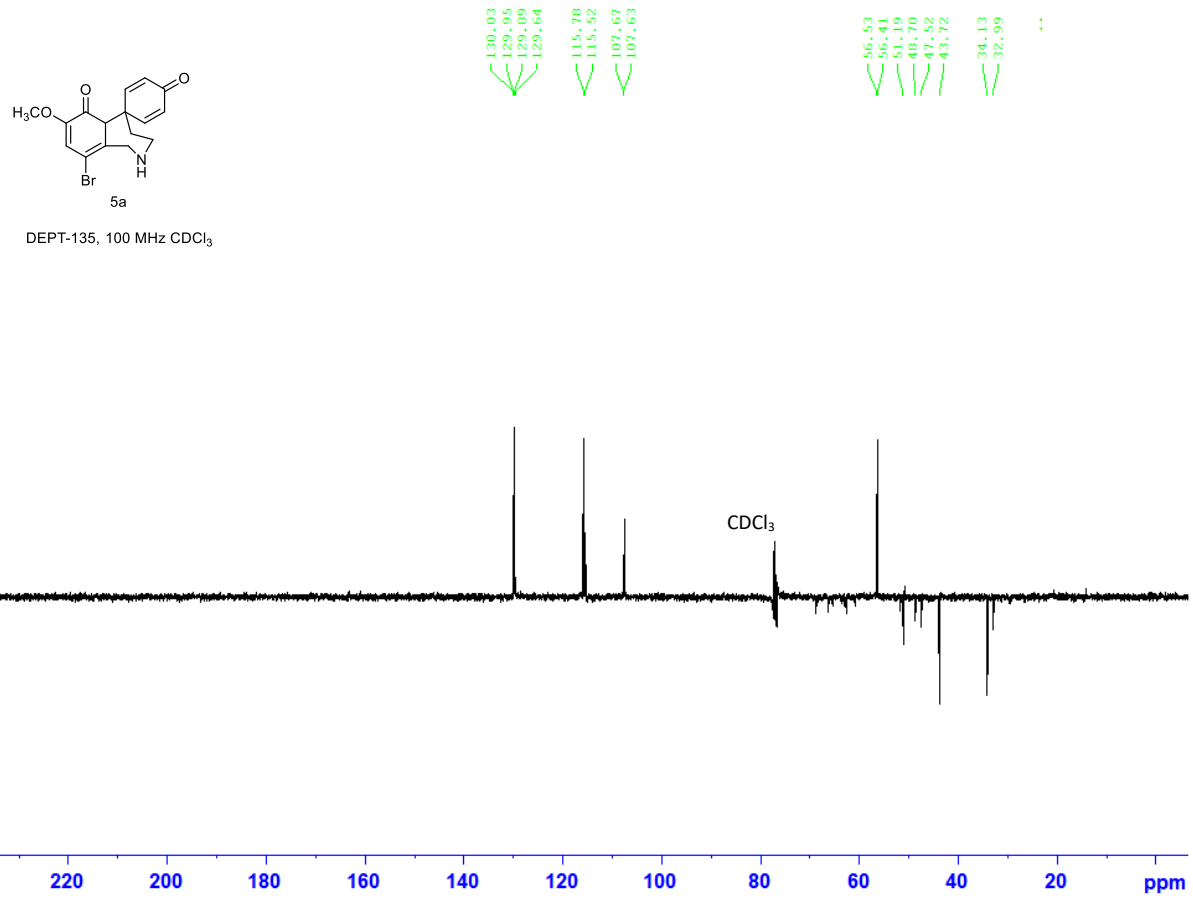
^{1}H-NMR of 9-bromo-7-methoxy-1,2,3,4-tetrahydro-4'H-spiro[2-benzazepine-5,1'-cyclohexa[2,5]diene]-4',6(5aH)-dione (5a)



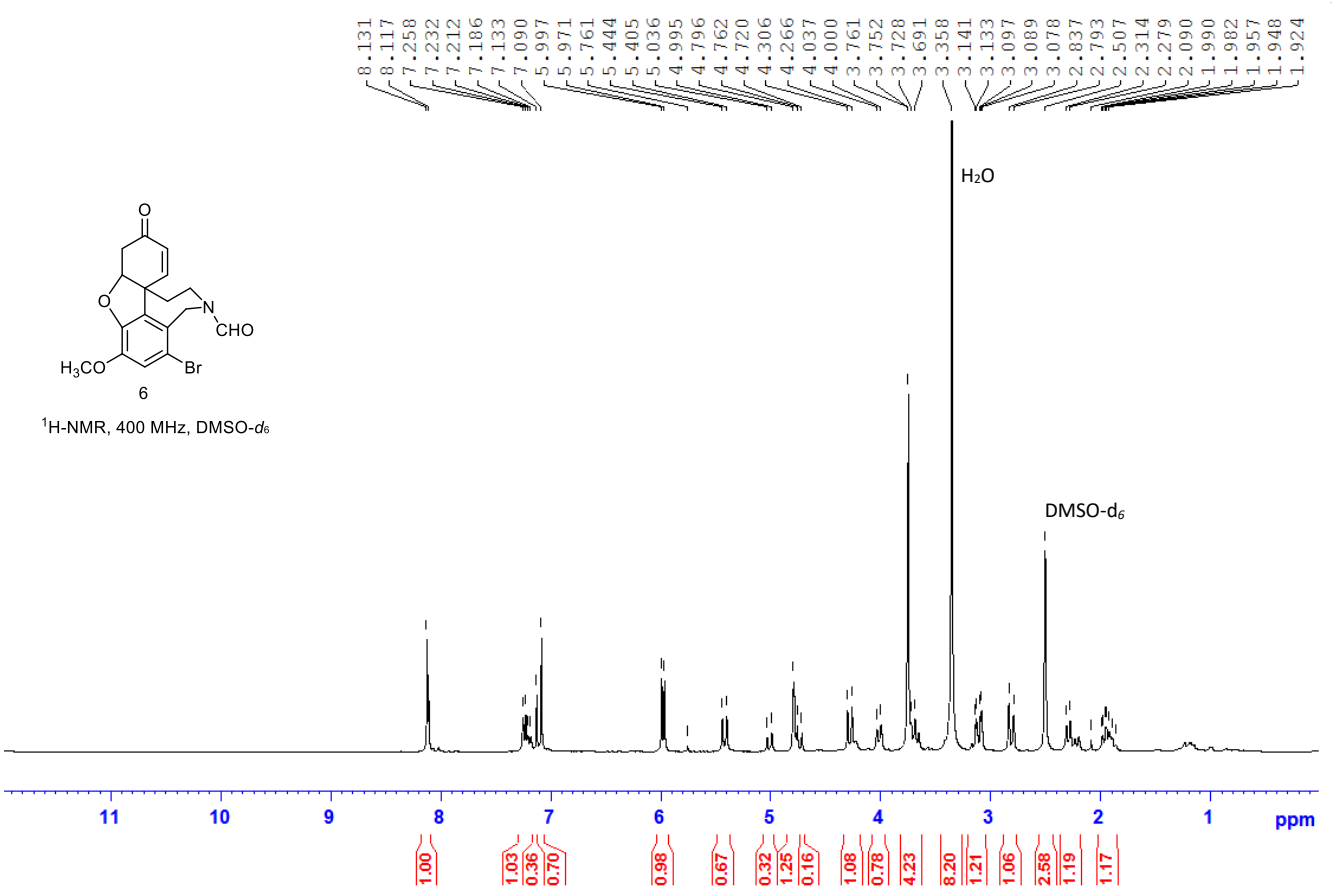
^{13}C-NMR of 9-bromo-7-methoxy-1,2,3,4-tetrahydro-4'H-spiro[2-benzazepine-5,1'-cyclohexa[2,5]diene]-4',6(5aH)-dione (5a)



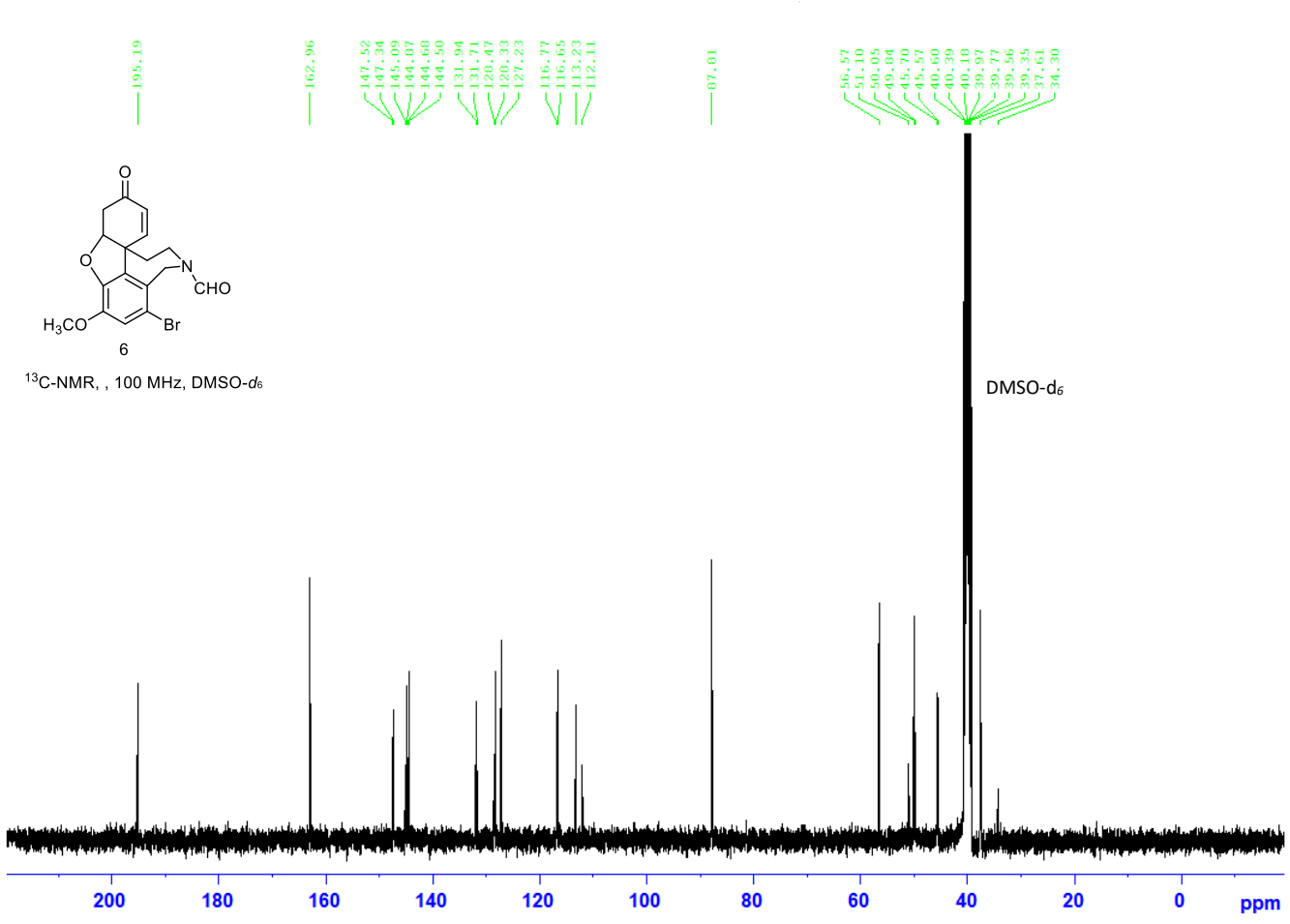
DEPT-135 of 9-bromo-7-methoxy-1,2,3,4-tetrahydro-4'H-spiro[2-benzazepine-5,1'-cyclohexa[2,5]diene]-4',6(5aH)-dione (5a)



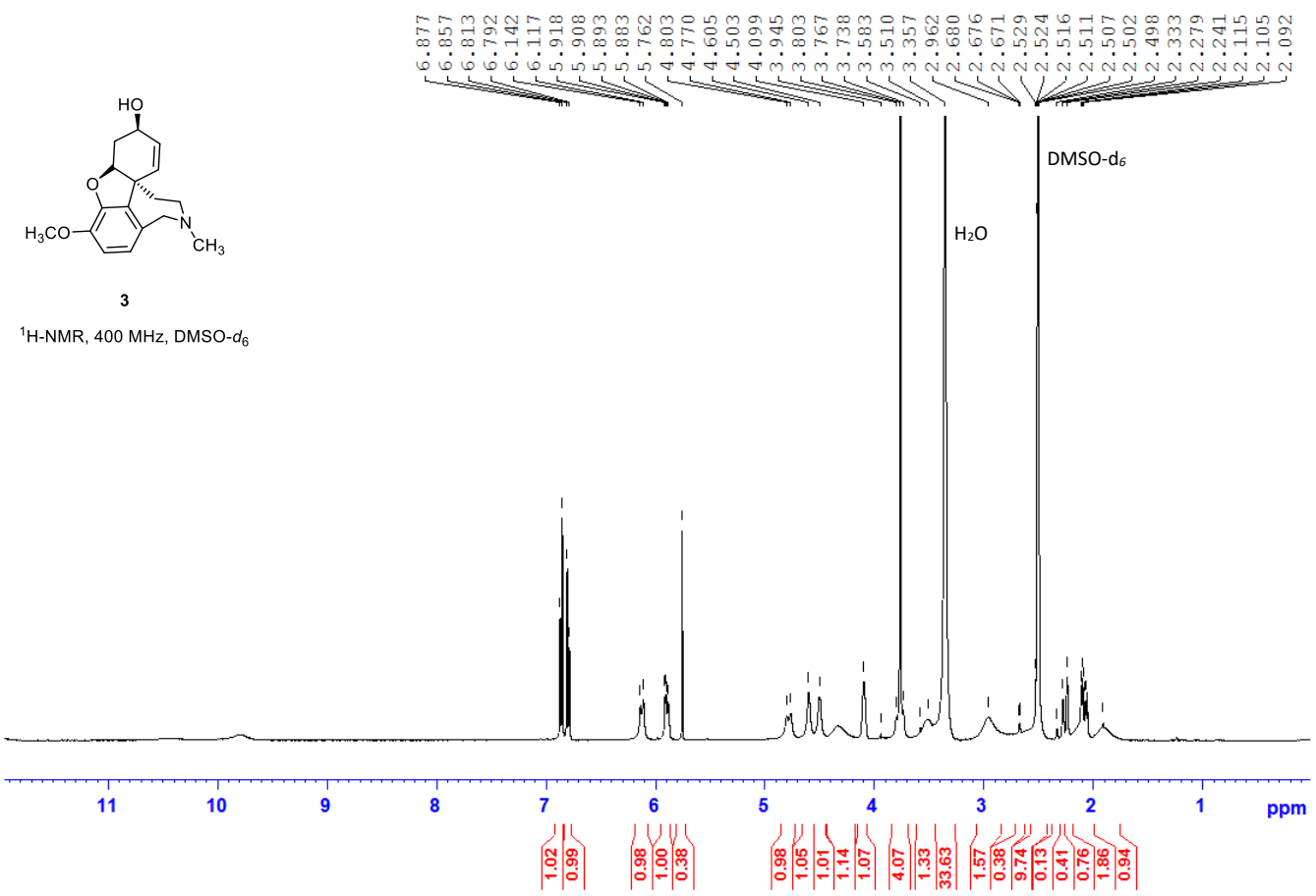
^{1}H-NMR of 1-bromo-N-formyl-narwedine (6)



^{13}C-NMR of 1-bromo-N-methyl-narwedine (6)



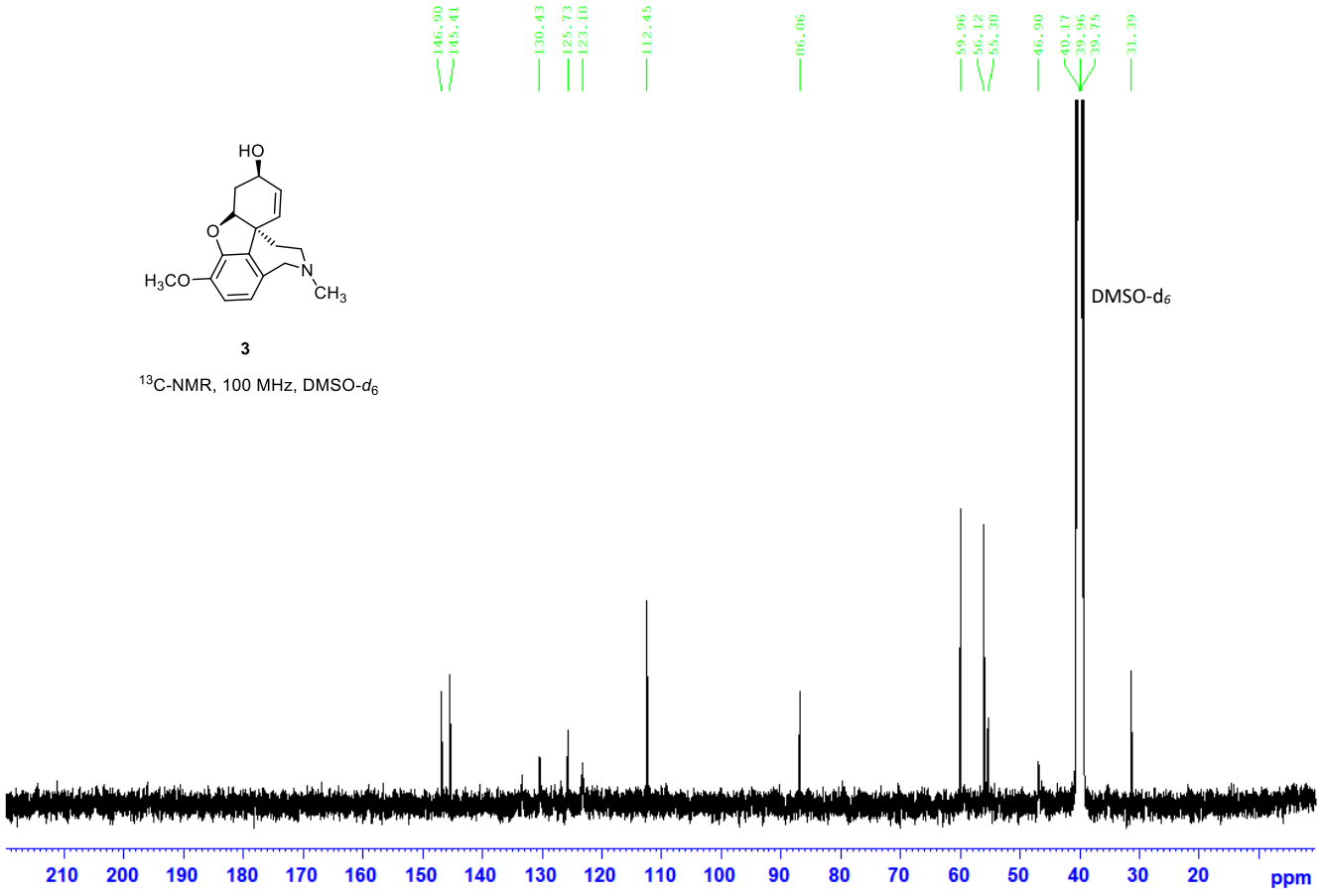
^{1}H-NMR of galantamine (3)



3

^{1}H-NMR, 400 MHz, DMSO-d_6

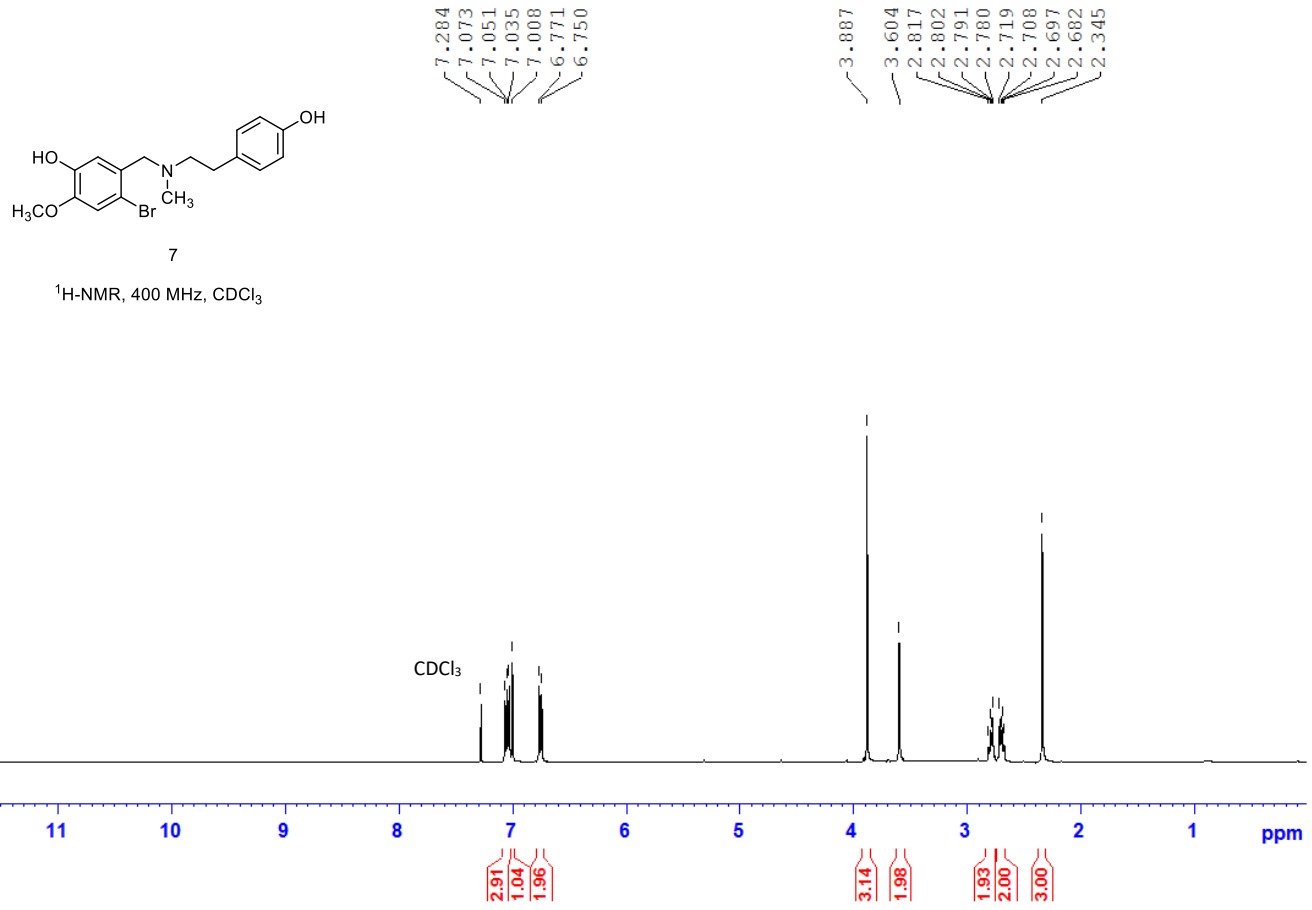
^{13}C-NMR of galantamine (3)



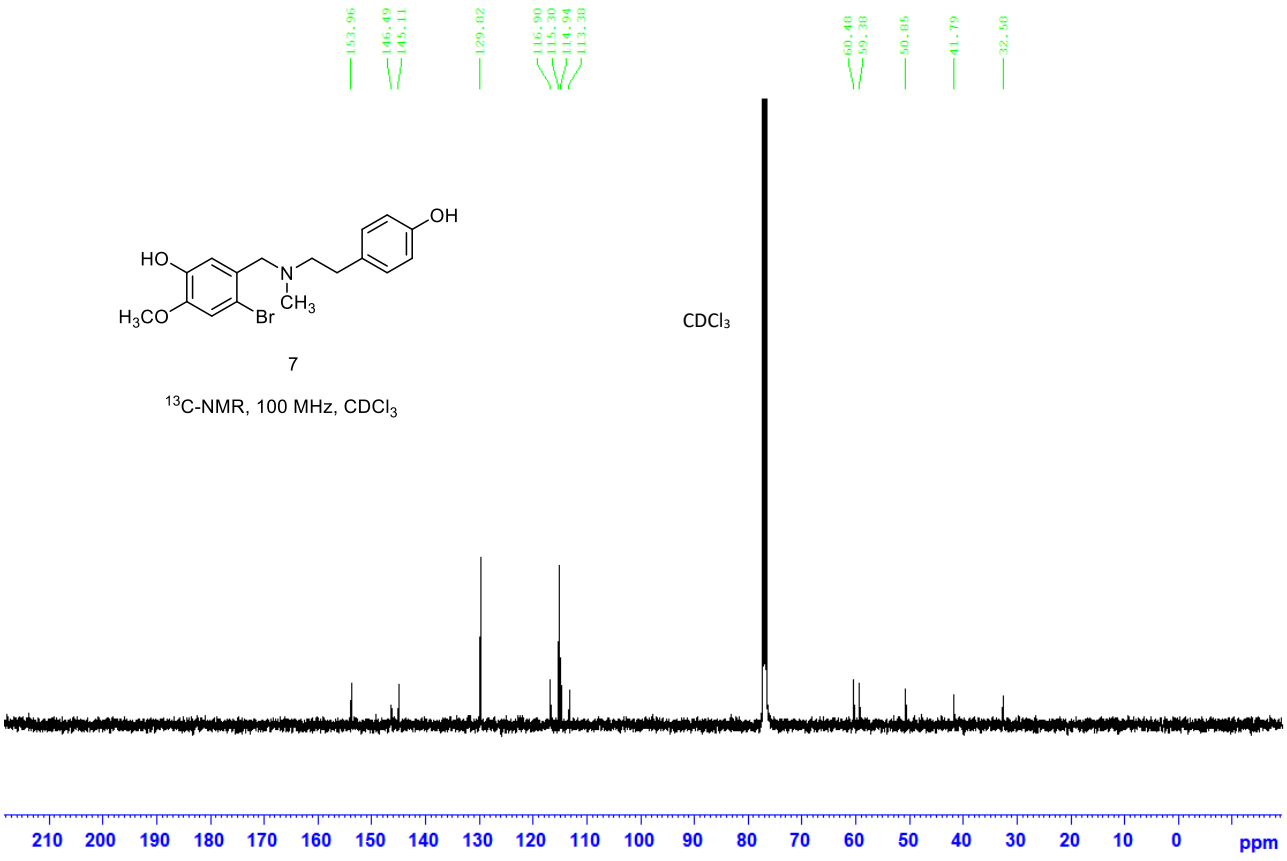
3

^{13}C-NMR, 100 MHz, DMSO-d_6

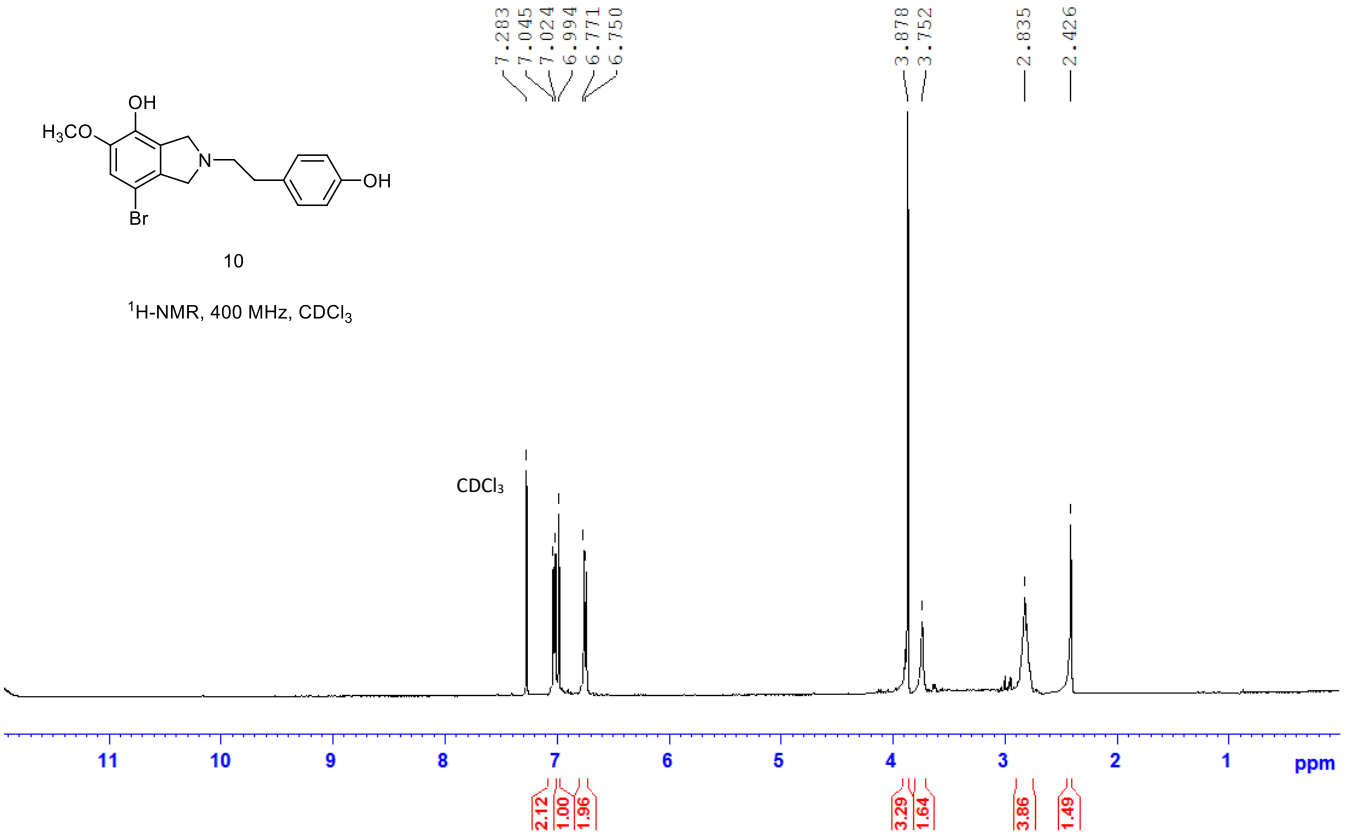
^{1}H-NMR of 4-bromo-5-{[[2-(4-hydroxyphenyl)ethyl](methyl)amino]methyl}-2-methoxyphenol (7)



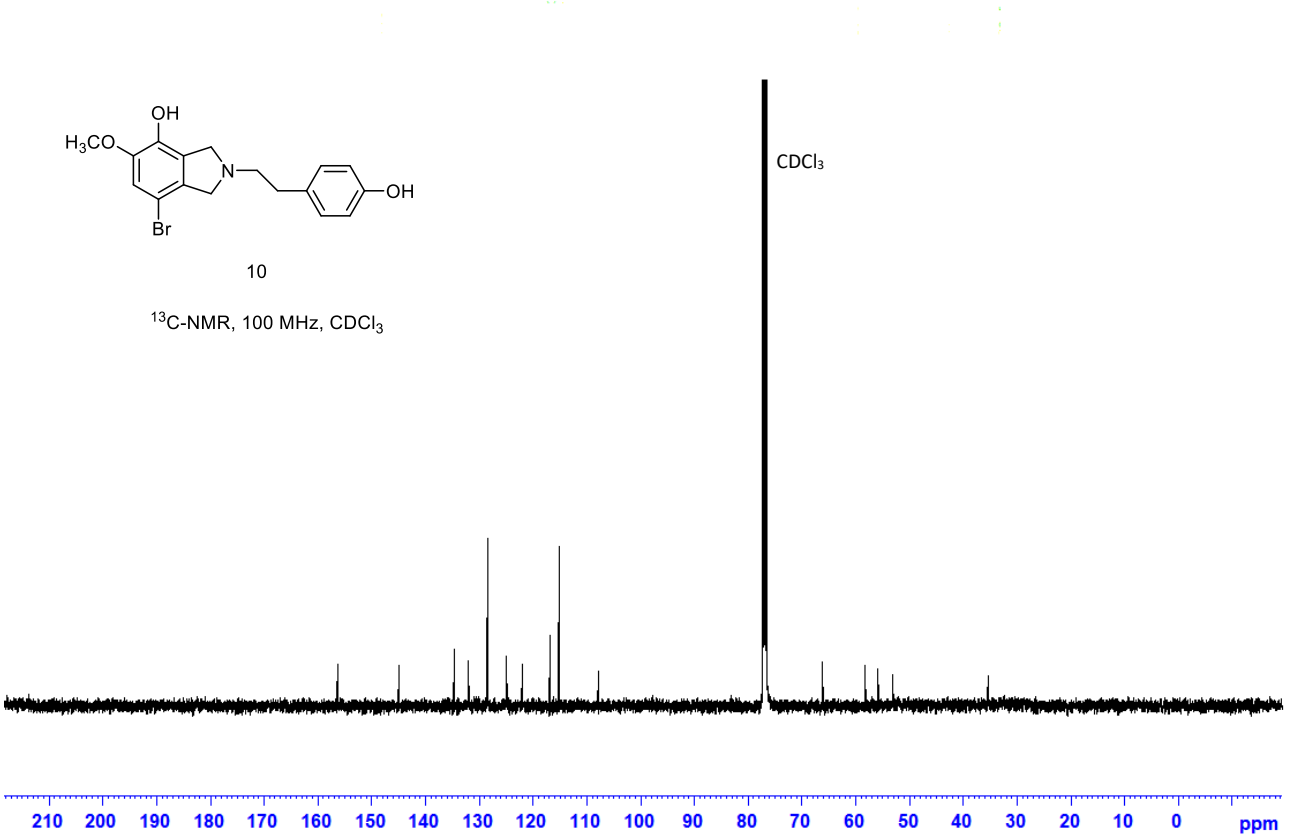
^{13}C-NMR of 4-bromo-5-{[[2-(4-hydroxyphenyl)ethyl](methyl)amino]methyl}-2-methoxyphenol (7)



^{1}H-NMR of 7-bromo-2-[2-(4-hydroxyphenyl)ethyl]-5-methoxyisoindolin-4-ol (10)

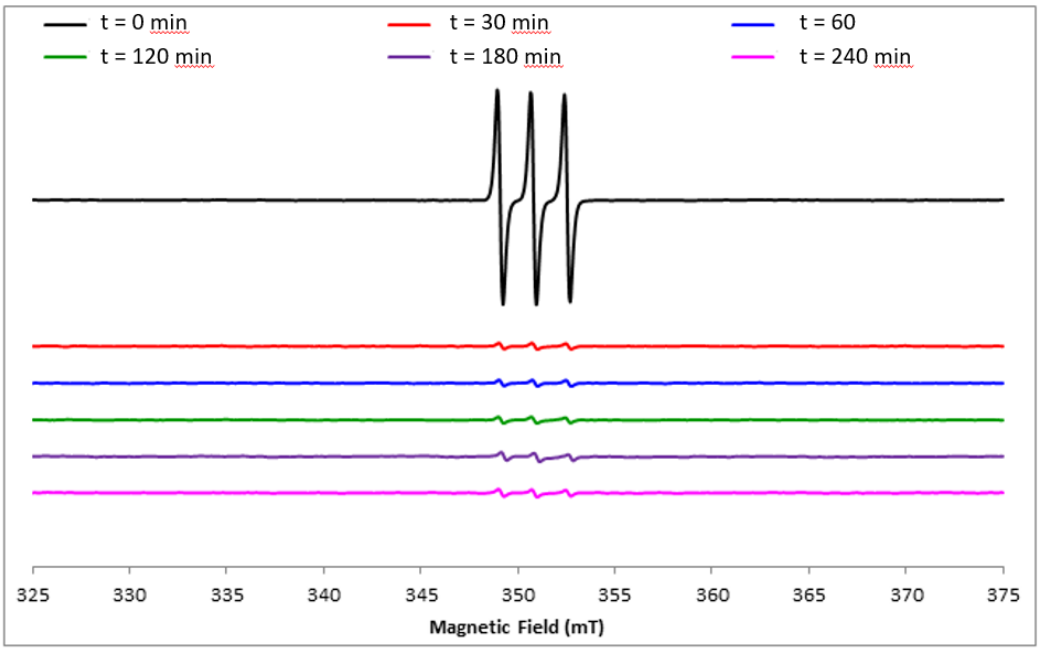


^{13}C-NMR of 7-bromo-2-[2-(4-hydroxyphenyl)ethyl]-5-methoxyisoindolin-4-ol (10)

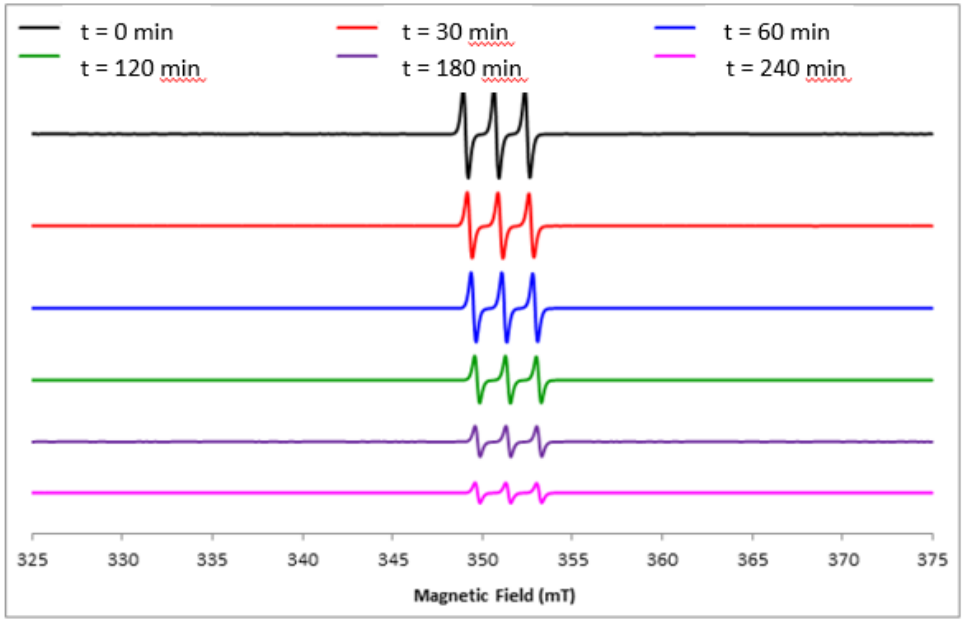


EPR spectra

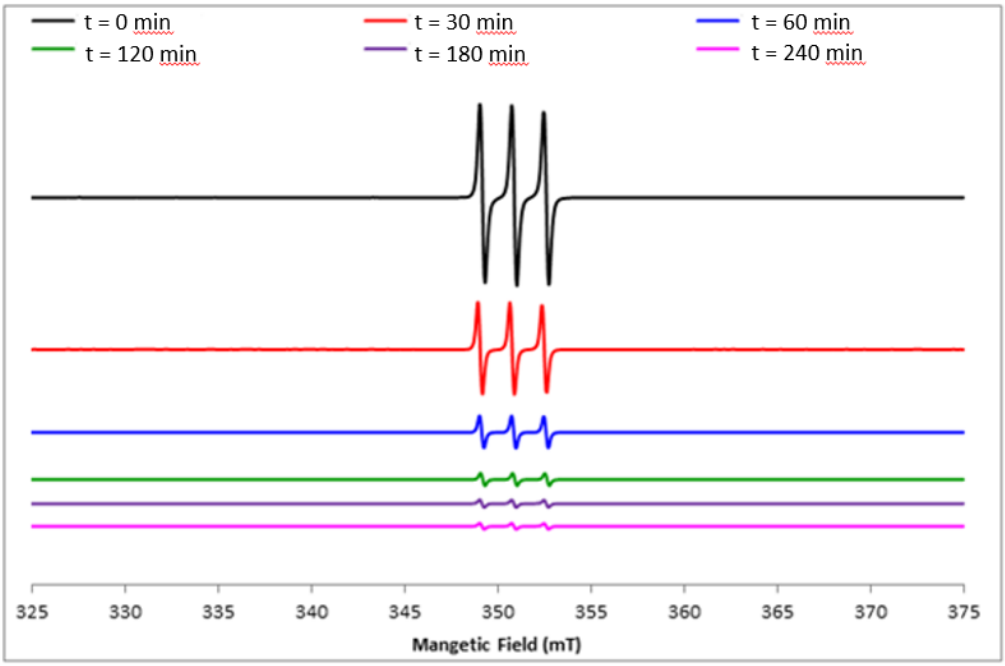
EPR spectrum recorded in the presence of laccase (0.14 mM) and TEMPO (6 µM)



EPR spectrum recorded in the presence of laccase (0.14 mM), TEMPO (6 µM) and compound 5



EPR spectrum recorded in the presence of laccase (0.14 mM) and TEMPO (0.6 mM)



EPR spectrum recorded in the presence of laccase (0.14 mM), TEMPO (0.6 mM) and compound 5