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PII: S0040-4020(13)01648-7

DOI: 10.1016/j.tet.2013.10.087

Reference: TET 24963

To appear in: *Tetrahedron*

Received Date: 12 July 2013

Revised Date: 17 October 2013

Accepted Date: 28 October 2013

Please cite this article as: Rouleau J, Korovitch A, Lion C, Hémadi M, Ha-Duong N-T, El Hage Chahine JM, Le Gall T, Synthesis and evaluation of 3-acyltetronic acid-containing metal complexing agents, *Tetrahedron* (2013), doi: 10.1016/j.tet.2013.10.087.

Synthesis and evaluation of 3-acyltetronic acid-containing metal complexing agents

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Abstract:

Potential metal chelators containing one or several acyltetronic acid moieties were prepared from cyclic or acyclic amines and polyamines, and from bis(phenols) by reaction with 1-4 equivalents of 3-bromoacetyltetronic acid in the presence of potassium carbonate. The affinity constants of the chelating agents for toxic metallic cations Cd^{2+}, Cs^{+} and Pb^{2+} and for dimethylarsinic acid were measured, at pH 7.5 and 9.3. Compound **4**, an acyclic triamine containing four acyltetronic moieties, was found to complex efficiently all the tested species.

Keywords:

Tetronic acid; Alkylation; Metal complexation; Affinity constant

1. Introduction

Organic compounds able to complex efficiently heavy metal cations can find application in the sensing of these cations or for their removal from contaminated waste.[1] It is thus of great value to identify new compounds having such properties. Several natural compounds containing a 3-acyltetronic acid moiety have been found to complex metal cations. Examples include the ionophore tetronasin[2] and the tyrosine phosphatase inhibitor RK-682[3] (Figure 1). Copper complexes of 3-acyltetronic acids have been described,[4] as well as complexes of 3-alkoxycarbonyltetronic acids with salts of copper(II), cobalt(II) and zinc(II).[5]

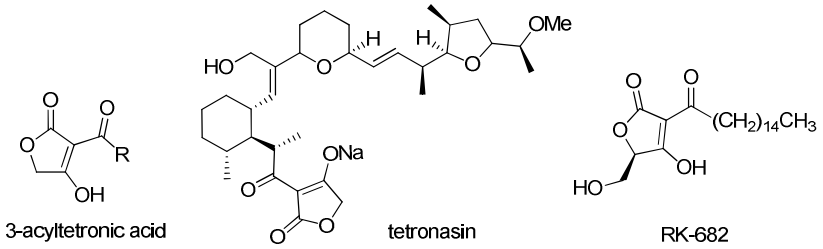


Fig. 1. Structures of 3-acyl tetronic acids

In this paper, we will describe the synthesis of a series of new chelating agents derived from amines or polyamines, containing one or several 3-acyltetronic acid moieties.[6,7] These compounds will then be evaluated as complexing agents for selected, highly toxic species, Pb^{2+}, Cd^{2+}, Cs^{+} and dimethylarsinic acid. Pb^{2+} is well known to cause health problems, such as kidney and neurological diseases.[8] Cadmium toxicity involves oxidative-stress and the alteration of the homeostasis of essential metals such as copper and zinc. Water contamination by arsenic is one of the biggest health threats in several countries.[9] In humans and other mammals inorganic arsenic is converted to trivalent and pentavalent methylated metabolites, including dimethylarsinic acid. This compound has been largely employed as herbicide in agriculture. It has been reported to induce urinary bladder tumors in rats.[10] Moreover, it is genotoxic in human cells, causing decreased DNA production and shorter DNA strands.[11] Cesium is not required for biological processes and few is known about its toxicity.[12] Interest in finding agents able to complex the cesium cation stems largely from the wish to separate radioactive cesium generated in nuclear plants.[13] Such agents might also be employed for the decorporation of radioactive cesium. Radioactive cesium was dispersed in the environment following atmospheric nuclear explosions and also following the accidents of Chernobyl and Fukushima. Norbadione A (Figure 2), a pigment isolated from the mushroom bay boletus (*Xerocomus badius*),[14] was shown to form a strong 1:1 complex with cesium chloride, owing to two chelating moieties that both participate to the complexation.[15] Likewise, we expected that by arranging one or several 3-acyltetronic acid moieties on a template constituted by an amine or a polyamine, would allow to obtain chelating agents able to complex the toxic cations Pb^{2+}, Cd^{2+}, Cs^{+}, as well as dimethylarsinic acid, depending on their structures.

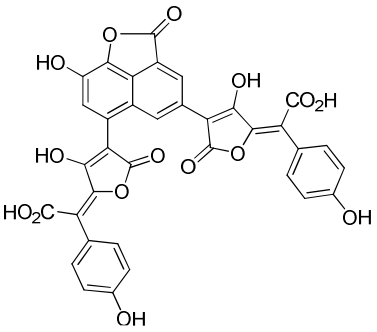


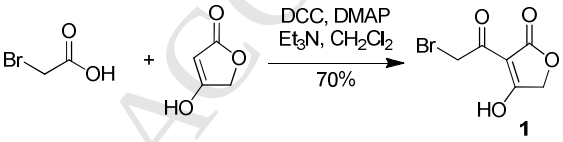
Fig. 2. Norbadione A

2. Results and discussion

2.1. Synthesis of 3-acyltetronic acid-containing compounds

A synthesis of bis(acyltetronic acid) derived from dodecanedioic acid was recently reported,[16] according to the conditions described by Yoshii,[17] using DCC, DMAP and triethylamine as reagents. Hence, this was a potentially attracting method for the preparation of the desired complexing agents. However, several attempts to obtain the acylation of ethylenediaminetetraacetic acid (EDTA) with four equivalents of tetronic acid were unsuccessful.

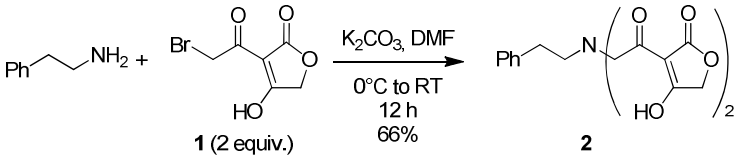
Another possibility to access such compounds was then envisaged, starting from amines or polyamines and an electrophile containing already a 3-acyltetronic acid motif. For this purpose, 3-bromoacetyltetronic acid **1** was then prepared from tetronic acid and bromoacetic acid using the DCC/DMAP coupling (Scheme 1).



Scheme 1

Several amines or polyamines were then efficiently converted to the corresponding adducts by reaction with 3-bromoacetyltetronic acid under mild conditions. For example, the dipodal adduct **2** was prepared as shown in Scheme 2, by treatment of phenethylamine with **1** (two

equivalents) in the presence of K_2CO_3 (two equivalents) in DMF (0°C to RT). Adduct **2** was obtained in 66% yield after purification by reverse phase chromatography (0.01M HCO_2NH_4, pH 9 / MeOH).

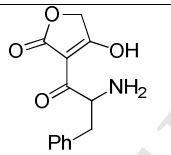
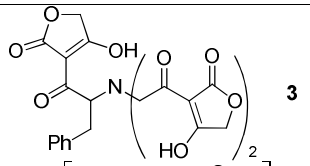
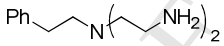
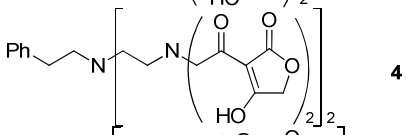
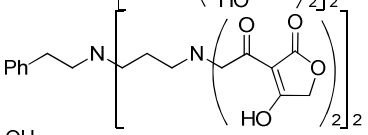
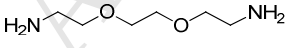
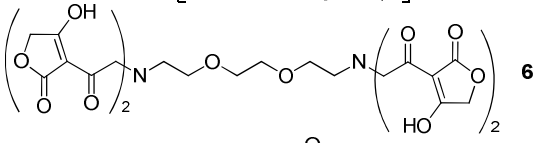
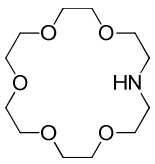
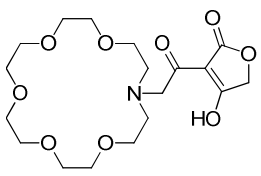


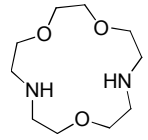
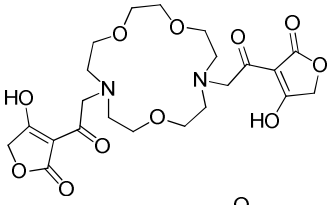
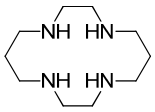
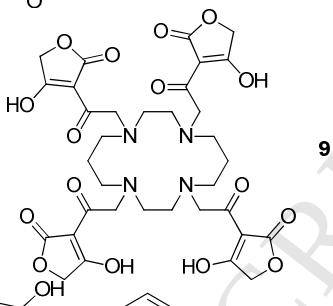
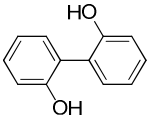
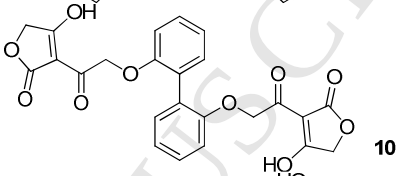
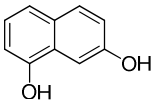
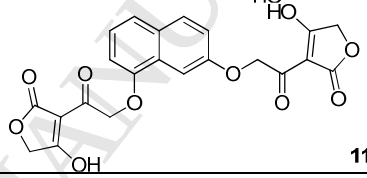
Scheme 2

Using a similar protocol, with varying equivalents of **1** and K_2CO_3, depending on the number of possible alkylations, several adducts, tripodands **3**, acyclic tetrapodands **4**, **5**, **6**, aza-crown ethers derivatives **7**, **8**, **9**, were prepared from the corresponding amines and polyamines (Table 1). Two compounds derived from bis(phenols) were also prepared similarly, using three equivalents of bromide **1** (entries 8,9).

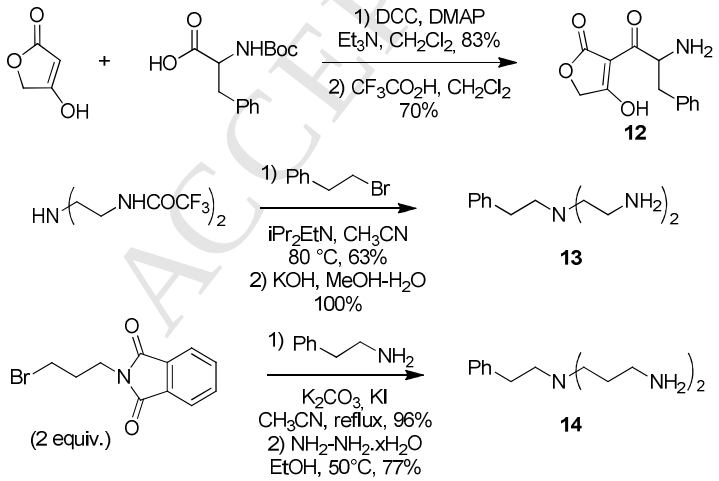
Table 1

Synthesis of 3-acyltetronic acids

Entry	Starting material	Equiv **1**	product	Yield (%)
1		2	 **3**	53
2		4	 **4**	66
3		4	 **5**	37
4		4	 **6**	79
5		1	 **7**	96

6		2	 **8**	91
7		4	 **9**	61
8		3	 **10**	87
9		3	 **11**	79

The preparation of the precursors of compounds **3**-**5** is described in the scheme 3. Amine **12**, precursor of **3,** was obtained by reaction of *N*-Boc-phenylalanine with tetronic acid in the presence of DCC/DMAP, followed by cleavage of the Boc (*tert*-butoxycarbonyl) group using trifluoroacetic acid. The known compounds **13** and **14**[18] were prepared as described. Compounds **6**-**11** were obtained from commercially available products.



Scheme 3

2.2. Complexation studies

The absorption spectra of the chelators were recorded in the presence of varying concentrations of the following species: cadmium nitrate, cesium chloride, dimethylarsinic acid (DMA), lead(II) acetate. They were performed in two aqueous buffers, at pH = 7.5 and 9.3, except for the cadmium species which was insoluble at pH = 9.3. Compound **11** was not evaluated, because of its low solubility in an aqueous medium. The spectra and the measured affinity constants were similar in the two buffers, which is in agreement with the fact that the enol functions of tetronic acids are not protonated in both neutral and basic media. In our experiments, the lower limit of the spectrophotometric detection was of about 0.1 µM of chelator, therefore this approach did not permit the measurements of affinities higher than 10^7.

The absorption spectra obtained with compound **4**, upon addition of Cd^{2+}, Cs^{+}, Pb^{2+} or dimethylarsinic acid, are indicated in Figure 3. The analysis of the data by the SPECFIT32 program showed that for all the ligands, only monocomplexes were formed.[19]

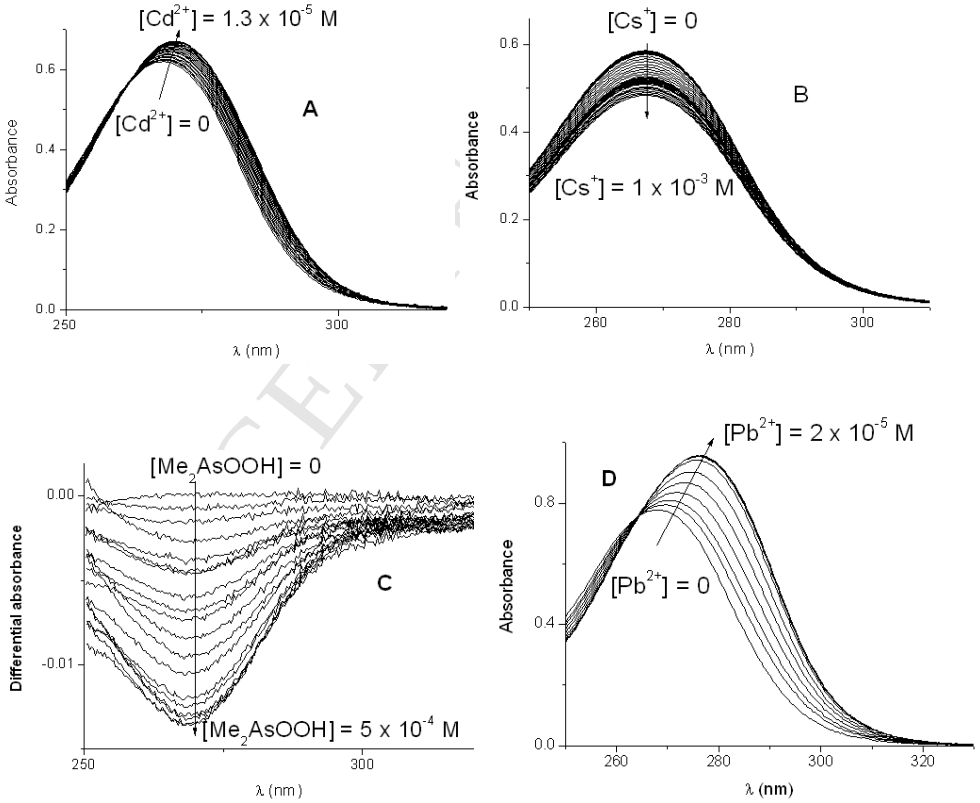


Fig. 3. Variation in the absorption spectra of **4** upon addition of Cd^{2+} (A), Cs^{+} (B) and Pb^{2+} (D); variation of the differential absorption of **4** upon addition of Me_2AsOOH, when **4** is taken as a reference (C); spectra acquired at 25 ± 0.1 °C, pH 7.5.

Table 2

Complexation results[a]

	pH	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	EDTA
Cd^{2+}	7.5	< 2	< 2	6.8 ± 0.2	> 7	4.0 ± 0.1	3.4 ± 0.1	3.1 ± 0.2	5.6 ± 0.3	3.2 ± 0.1	13-14
Cs^{+}	7.5	< 2	< 2	4.3 ± 0.1	3.0 ± 0.3	3.3 ± 0.2	3.9 ± 0.1	2.5 ± 0.3	< 2	4.5 ± 0.1	-
	9.3	< 2	< 2	4.5 ± 0.1	3.1 ± 0.3	4.1 ± 0.2	3.5 ± 0.1	3.6 ± 0.1	< 2	3.5 ± 0.2	-
DMA	7.5	< 2	< 2	5.4 ± 0.1	3.5 ± 0.2	3.0 ± 0.3	4.6 ± 0.1	3.0 ± 0.2	< 2	2.6 ± 0.4	-
	9.3	< 2	< 2	5.0 ± 0.1	3.0 ± 0.1	3.1 ± 0.2	3.8 ± 0.1	2.9 ± 0.1	< 2	2.9 ± 0.1	-
Pb^{2+}	7.5	< 2	< 2	5.7 ± 0.2	> 7	4.2 ± 0.1	4.3 ± 0.1	4.4 ± 0.1	< 2	4.1 ± 0.1	13-14
	9.3	< 2	< 2	6.0 ± 0.2	> 7	4.6 ± 0.1	4.2 ± 0.1	4.1 ± 0.1	< 2	4.0 ± 0.1	17-18

[a] log of the affinity constants (log K) of compounds **2-11** and EDTA for Cd^{2+}, Cs^{+}, dimethylarsinic acid (DMA), and Pb^{2+}, reported for two pH values at 25 ± 0.1 °C.

Affinity constants (as log K) of the synthetic chelators for three metallic cations, Cd^{+}, Cs^{+} and Pb^{2+} and organic dimethylarsinate are reported in the Table 2. These values are also compared to those involving EDTA, which is considered as a universal chelator, since it forms very strong complexes with most metals.[20] EDTA seems also to form strong complexes with inorganic As(III) and to a lesser extent with inorganic As(V).[21] However, to the best of our knowledge, EDTA does not complex Cs^{+} or organic arsinates.

Compounds **2** and **3** have low affinities for the four species. This may be due to the lack of flexibility of the ligands in both chelators. Compound **9**, a tetra(acyltetronic acid) derived from cyclam (1,4,8,11-tetraazacyclotetradecane), seems to be a good chelator for Cd^{2+}. However, despite the fact that it is a tetrapod, it does not complex the other species. Its affinity for Cd^{2+} may be related to the presence of the four nitrogen atoms and the possible occurrence of a cage-like structure. Indeed, nitrogen is considered as a soft base and Cd^{2+} as a soft acid.[22] Compound **5**, which is an acyclic tetra(acyltetronic acid), is a very good chelator for Pb^{2+} and Cd^{2+}, with affinities higher than 10^{7}, and can also slightly complex Cs^{+} and dimethylarsinic acid. This can be due to the higher flexibility of the complexing tetronic ligands in comparison with **9**. Finally, compound **4**, which differs from **5** by the presence of two shorter spacers between nitrogen atoms, is capable of forming stable complexes with the four tested species. As with norbadione A and its derivatives, complex formation probably occurs by inclusion in a pseudo-cavity in which the chelating acyltetronic ligands surround the metallic species. This cavity can be compared to that of some calixarenes, which display similar affinities for Cs^{+}.[15d] The proposed chelators are less efficient than EDTA for the complexation of Cd^{2+} and Pb^{2+}. Therefore, the most interesting chelator seems to be **4**, which has a good affinity for Cs^{+}, and which is, to the best of our knowledge, the only organic molecule known to form a stable complex with an organic arsinate.

3. Conclusion

We have synthesized various compounds containing one or several 3-acyltetronic acid complexing moieties. They were obtained from a new precursor, 3-bromoacetyltetronic acid. Affinity constants of these chelators for three metallic species, Cd^{2+}, Cs^{+}, Pb^{2+} and for dimethylarsinic acid were measured. The best chelating agents were tetra(tetronic acids) **4** and **5** in which the tetronic acid moieties are connected to an acyclic framework. Compound **5** was shown to efficiently complex the cesium cation as well as dimethylarsinic acid, while compound **4** gave stable complexes with all the tested species. We envision preparing

polymers that will incorporate such chelating agents and that will be used for the decontamination of surfaces or water contaminated by toxic metals.

4. Experimental section

4.1. Synthesis

4.1.1. General. Dichloromethane was distilled over P_2O_5; commercially available anhydrous DMF was employed. Non aqueous reactions were performed under an argon atmosphere. TLC: Silica Gel $60F_{254}$ plates with detection by UV light and by an ethanol solution of phosphomolybdic acid. Column chromatographies were carried out with Combiflash Serlabo Rf75 (silica gel columns RediSep® Rf, 35-60 µm; or reversed phase columns packed with Merck LiChroprep® RP-18, 15-25 µm). Melting points were uncorrected. NMR: 400.133 and 100.624 MHz for ^1H and ^{13}C, respectively. Chemical shifts (δ) are in ppm (s = singlet, d = doublet, t = triplet, m = multiplet, b = broad), and are referenced to residual H in the deuterated solvent as the internal standard; coupling constants (J) are in Hz.

*4.1.2. 3-(2-Bromoacetyl)-4-hydroxyfuran-2(5H)-one (**1**).* A solution of tetronic acid (4 g, 39.72 mmol, 1 equiv), triethylamine (6.625 mL, 47.67 mmol, 1.2 equiv), DMAP (465 mg, 3.9 mmol, 0.1 equiv) and bromoacetic acid (6.623 g, 47.67 mmol, 1.2 equiv) in CH_2Cl_2 (100 mL) was cooled to 0 °C. DCC (9.835 g, 47.67 mmol, 1.2 equiv) was added in one portion and the mixture was stirred 30 min at 0 °C and 12 h at room temperature. The mixture was filtered and the filtrate was recovered and then the solvents were removed under vacuum. MeOH (300 mL) was added to the residue and the solution obtained was passed through Dowex H^+ ion exchange resin (eluent: MeOH). The solvent was removed under vacuum and the residue was triturated with MeOH. The precipitate was filtered and dried under vacuum to give the title compound **1** (6,172 g, 70%) as a beige powder; mp 143 °C; ν_{max} (KBr pellet) 3191, 2993, 2970, 2942, 1753, 1661, 1460, 1349, 1224, 1106, 1046, 1014, 959, 879, 845, 759, 671 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 4.37 (2H, s, OC<u>H</u>$_2$), 4.27 (2H, s, C<u>H</u>$_2$Br); δ_C (100 MHz, DMSO-d_6) 190.5, 183.8, 172.1, 96.6, 68.3, 35.5; HRMS (ESI^-): $M-H^-$, found 218.9303. $C_6H_4O_4Br$ requires 218.9293.

4.1.3. General procedure for the alkylation of an amine by 3-bromoacetyltetronic acid. To a solution of amine (0.45 mmol, 1 equiv) in DMF (3 mL) was added K_2CO_3 (188 mg, 1.36 mmol, 4 equiv). After cooling at 0 °C, a solution of 3-bromoacetyltetronic acid **1** (221 mg, 1 mmol, 2.2 equiv) in DMF (2 mL) was added dropwise. The reaction mixture was

stirred at 0 °C for 1 h and at room temperature for 15 h. Solvent was removed under vacuum and the residue was purified by reversed phase chromatography (aqueous 0.01 N HCO_2NH_4 buffer, pH9/MeOH 100/0 to 80/20) to afford the desired product.

*4.1.4. 3,3'-[2,2'-(Phenethylazanediyl)bis(acetyl)]bis[4-hydroxyfuran-2(5H)-one] (**2**).* Phenethylamine (57 μL, 4.53 mmol, 1 equiv), K_2CO_3 (188 mg, 1.36 mmol, 3 equiv) and 3-bromoacetyltetronic acid **1** (221 mg, 1 mmol, 2.2 equiv) were used following the general procedure to afford the title compound (120 mg, 66%) as a white powder; mp 177 °C; ν_{max} (KBr pellet) 3445, 3194, 3030, 1732, 1651, 1463, 1353, 1262, 1146, 1044, 906, 769, 702 cm^{-1}; δ_H (400 MHz, CD_3OD) 7.24 (5H, m, H−Ar), 4.52 (4H, s, C$\underline{H}_2$O), 4.27 (4H, s, C$\underline{H}_2$CO), 3.50 (2H, m, $CH_2C\underline{H}_2N$), 3.04 (2H, m, C$\underline{H}_2CH_2N$); δ_C (100 MHz, CD_3OD) 195.7 (2C), 182.0 (2C), 176.1 (2C), 136.0, 128.4 (2C), 128.5 (2C), 126.7, 94.4 (2C), 70.3 (2C), 61.3 (2C), 57.2, 30.4; HRMS (ESI^-): $M-H^-$, found 400.1032. $C_{20}H_{18}NO_8$ requires 400.1032.

*4.1.5. 3,3'-(2,2'-{[1-(4-Hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-1-oxo-3-phenylpropan-2-yl]azanediyl}bis[acetyl])bis[4-hydroxyfuran-2(5H)-one] (**3**).* Amine **12** (97 mg, 0.39 mmol, 1 equiv), K_2CO_3 (119 mg, 0.86 mmol, 2.2 equiv), 3-bromoacetyltetronic acid **1** (191 mg, 0.86 mmol, 2.2 equiv) and DMF (2 mL) were used following the general procedure to afford the title compound (109 mg, 53%) as a white powder; mp 197 °C; ν_{max} (KBr pellet) 3449, 3186, 1731, 1651, 1463, 1357, 1262, 1146, 1045, 905, 771, 704 cm^{-1}; δ_H (400 MHz, D_2O) 7.71 (5H, m, H−Ar), 5.53 (1H, dd, *J* = 8.8, 5.9 Hz, C$\underline{H}$Bn), 4.52 (1H, d, *J* = 17.8 Hz, C$\underline{H}$HO), 4.45 (1H, d, *J* = 17.8 Hz, CH$\underline{H}$O), 4.26 (2H, s, C$\underline{H}_2$O), 4.21 (2H, s, C$\underline{H}_2$O), 4.17 (3H, m, C$\underline{H}_2$N), 4.02 (1H, d, *J* = 17.6 Hz, C$\underline{H}_2$N), 3.09 (1H, dd, *J* = 14.8, 5.9 Hz, C$\underline{H}$HPh), 2.93 (1H, dd, *J* = 14.8, 8.8 Hz, CH$\underline{H}$Ph); δ_C (100 MHz, D_2O) 197.1, 197.0, 196.8, 187.0, 182.9, 182.8, 176.9 (2C), 176.6, 134.1, 129.0 (2C), 128.7 (2C), 127.4, 96.2, 95.1 (2C), 70.7, 70.6, 70.5, 68.2, 61.1, 59.3, 34.5; HRMS (ESI): MH^+, found 528.1133. $C_{25}H_{22}NO_{12}$ requires 528.1142.

*4.1.6. 3,3',3'',3'''-(2,2',2'',2'''-{[(Phenethylazanediyl)bis(ethane-2,1-diyl)]bis(azanetriyl)}tetrakis[acetyl])tetrakis[4-hydroxyfuran-2(5H)-one] (**4**).* Triamine **13** (146 mg, 0.70 mmol, 1 equiv), K_2CO_3 (437 mg, 3.17 mmol, 4.5 equiv), 3-bromoacetyltetronic acid **1** (655 mg, 2.96 mmol, 4.2 equiv) and DMF (10 mL) were used following the general procedure to afford the title compound (359 mg, 66%) as a light pink powder; mp 195 °C (decomposition); ν_{max} (KBr pellet) 3448, 3191, 1729, 1648, 1464, 1261, 1045, 913, 770, 703

cm^{-1}; δ_H (400 MHz, D_2O) 7.22 (4H, m, H−Ar), 7.15 (1H, m, H−Ar), 4.38 (8H, s, C<u>H</u>$_2$O), 4.32 (8H, s, C<u>H</u>$_2$CO), 3.35 (4H, m, NC<u>H</u>$_2$), 2.98 (4H, m, NC<u>H</u>$_2$), 2.85 (2H, m, C<u>H</u>$_2$Bn), 2.75 (2H, m, C<u>H</u>$_2$Ph); δ_C (100 MHz, D_2O) 196.9 (4C), 183.0 (4C), 176.7 (4C), 139.5, 128.6 (2C), 128.5 (2C), 126.3, 95.2 (4C), 70.7 (4C), 61.1 (4C), 54.2, 53.0 (2C), 47.9 (2C), 31.7; HRMS (ESI): MH^+, found 768.2252. $C_{36}H_{38}N_3O_{16}$ requires 768.2289.

*4.1.7. 3,3',3'',3'''-(2,2',2'',2'''-{[(Phenethylazanediyl)bis(propane-3,1-diyl)]bis(azanetriyl)}tetrakis[acetyl])tetrakis[4-hydroxyfuran-2(5H)-one] (**5**).*

Triamine **14** (35 mg, 0.15 mmol, 1 equiv), K_2CO_3 (82 mg, 0.595 mmol, 4 equiv), 3-bromoacetyltetronic acid **1** (132 mg, 0.595 mmol, 4 equiv) and DMF (2 mL) were used following the general procedure to afford the title compound (44 mg, 37%) as a light pink powder; mp 220 °C (decomposition); ν_{max} (KBr pellet) 3442, 1729, 1648, 1464, 1357, 1262, 916, 769, 702 cm^{-1}; δ_H (400 MHz, D_2O) 7.40-7.20 (5H, m, H−Ar), 4.36 (16H, s, C<u>H</u>$_2$O, C<u>H</u>$_2$CO), 3.38 (6H, m), 3.26 (4H, m), 2.97 (2H, m), 2.13 (4H, m, $CH_2C\underline{H}_2CH_2$); δ_C (100 MHz, D_2O) 196.8 (4C), 189.4 (4C), 177.4 (4C), 137.4, 128.7 (2C) 128.5 (2C), 126.8, 95.8 (4C), 70.4 (4C), 61.3 (4C), 60.9 (2C), 53.7, 51.6 (2C), 28.7, 19.9 (2C); HRMS (ESI): MH^+, found 796.2555. $C_{38}H_{42}N_3O_{16}$ requires 796.2565.

*4.1.8. 1,14-Bis(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-3,12-bis[2-(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-2-oxoethyl]-6,9-dioxa-3,12-diazatetradecane-1,14-dione (**6**).* 2,2'-[Ethane-1,2-diylbis(oxy)]diethanamine (45 µL, 0.31 mmol, 1 equiv), K_2CO_3 (187 mg, 1.35 mmol, 4.4 equiv), 3-bromoacetyltetronic acid **1** (300 mg, 1.35 mmol, 4.4 equiv) and DMF (2 mL) were used following the general procedure to afford the title compound (173 mg, 79%) as a light pink powder; mp 255 °C (decomposition); ν_{max} (KBr pellet) 3449, 2933, 1725, 1648, 1449, 1362, 1248, 1089, 1059, 918, 832, 771, 705 cm^{-1}; δ_H (400 MHz, D_2O) 4.26 (8H, s, C<u>H</u>$_2$O), 4.01 (8H, s, C<u>H</u>$_2$CO), 3.57 (4H, m, OC<u>H</u>$_2$CH$_2$N), 3.45 (4H, s, OCH_2CH_2O), 2.97 (4H, m, $OCH_2C\underline{H}_2N$); δ_C (100 MHz, D_2O) 196.8 (4C), 177.8 (C4), 160.9 (4C), 96.0 (4C), 70.4 (4C), 69.4 (4C), 67.3 (2C), 61.7 (2C), 54.4 (2C); HRMS (ESI): MH^+, found 709.1729. $C_{30}H_{33}N_2O_{18}$ requires 709.1728.

*4.1.9. 3-[2-(1,4,7,10,13-Pentaoxa-16-azacyclooctadecan-16-yl)acetyl]-4-hydroxyfuran-2(5H)-one (**7**).* 1,4,7,10,13-Pentaoxa-16-azacyclooctadecane (108 mg, 0.41 mmol, 1 equiv),

K_2CO_3 (62 mg, 0.45 mmol, 1.1 equiv), 3-bromoacetyltetronic acid **1** (100 mg, 0.45 mmol, 1.1 equiv) and DMF (2 mL) were used following the general procedure to afford the title compound (158 mg, 96%) as a white powder; mp 130-132 °C; ν_{max} (KBr pellet) 3495, 2895, 1718, 1654, 1584, 1436, 1352, 1248, 1106, 958, 836, 767, 698 cm^{-1}; δ_H (400 MHz, D_2O) 4.37 (2H, s, C$\underline{H}_2$O), 4.15 (2H, s, C$\underline{H}_2$CO), 3.67 (16H, s, OCH_2CH_2O), 3.63 (4H, s, $NCH_2C\underline{H}_2O$), 3.22 (4H, s, $NC\underline{H}_2CH_2O$); δ_C (100 MHz, D_2O) 197.1, 184.6, 177.3, 95.5, 70.7, 69.7 (2C), 69.6 (2C), 69.4 (2C), 69.3 (2C), 64.2 (2C), 55.6, 55.4 (2C); HRMS (ESI): MNa^+, found 426.1750. $C_{18}H_{29}NO_9Na$ requires 426.1740.

*4.1.10. 3,3'-[2,2'-(1,4,10-Trioxa-7,13-diazacyclopentadecane-7,13-diyl)bis(acetyl)]bis[4-hydroxyfuran-2(5H)-one] (**8**).* 1,4,10-Trioxa-7,13-diazacyclopentadecane (100 mg, 0.46 mmol, 1 equiv), K_2CO_3 (133 mg, 0.96 mmol, 2.1 equiv), 3-bromoacetyltetronic acid **1** (213 mg, 0.96 mmol, 2.1 equiv) and DMF (3 mL) were used following the general procedure to afford the title compound (208 mg, 91%) as a white powder; mp 230 °C (decomposition); ν_{max} (KBr pellet) 3440, 3235, 2875, 1717, 1633, 1463, 1354, 1251, 1115, 1096, 1045, 938, 774, 704 cm^{-1}; δ_H (400 MHz, D_2O) 4.37 (4H, s, C$\underline{H}_2$O), 4.09 (4H, s, C$\underline{H}_2$CO), 3.73 (4H, t, *J* = 4.6 Hz), 3.70 (4H, s, OCH_2CH_2O), 3.67 (4H, t, *J* = 4.8 Hz), 3.12 (8H, bs, $NC\underline{H}_2CH_2O$); δ_C (100 MHz, D_2O) 197.3 (2C), 183.3 (2C), 177.0 (2C), 95.3 (2C), 70.9 (2C), 69.9 (2C), 63.6 (2C), 63.5 (2C), 60.3 (2C), 55.6 (2C), 54.0 (2C); HRMS (ESI): MNa^+, found 521.1764. $C_{22}H_{30}N_2O_{11}Na$ requires 521.1747.

*4.1.11. 3,3',3'',3'''-[2,2',2'',2'''-(1,4,8,11-Tetraazacyclotetradecane-1,4,8,11-tetrayl)tetrakis(acetyl)]tetrakis[4-hydroxyfuran-2(5H)-one] (**9**).* 1,4,8,11-Tetraazacyclotetradecane (22 mg, 0.11 mmol, 1 equiv), K_2CO_3 (62 mg, 0.45 mmol, 4.1 equiv), 3-bromoacetyltetronic acid **1** (100 mg, 0.45 mmol, 4.1 equiv) and DMF (2 mL) were used following the general procedure to afford the title compound (51 mg, 61%) as a white powder; mp 225-230 °C (decomposition); ν_{max} (KBr pellet) 3444, 2848, 1731, 1644, 1471, 1362, 1253, 1046, 923, 770, 705 cm^{-1}; δ_H (400 MHz, D_2O) 4.19 (8H, br s, C$\underline{H}_2$O), 3.94 (8H, br s, C$\underline{H}_2$CO), 3.60-2.70 (16H, m, NCH_2CH_2N,$NC\underline{H}_2CH_2C\underline{H}_2N$), 1.83 (4H, m, $NCH_2C\underline{H}_2CH_2N$); δ_C (100 MHz, D_2O) 196.8 (4C), 193.3 (4C), 178.2 (4C), 96.6 (4C), 70.3 (4C), 61.0 (4C), 50.9 (4C), 47.2 (4C), 20.1 (2C); HRMS (ESI): MH^+, found 761.2529. $C_{34}H_{41}N_4O_{16}$ requires 761.2518.

*4.1.12. 3,3'-(2,2'-{[1,1'-Biphenyl]-2,2'-diylbis(oxy)}bis[acetyl]}bis[4-hydroxyfuran-2(5H)-one] (**10**).* 2,2'-Biphenol (19 mg, 0.102 mmol, 1 equiv), K_2CO_3 (31mg, 0.226 mmol, 2.2 equiv), 3-bromoacetyltetronic acid **1** (50 mg, 0.226 mmol, 2.2 equiv) and DMF (1 mL) were used following the general procedure to afford the title compound (42mg, 87%) as a white powder; mp 178-180 °C; ν_{max} (KBr pellet) 3247, 3050, 1720, 1606, 1458, 1410, 1370, 1237, 1147, 1121, 1050, 931, 859, 758, 707 cm^{-1}; δ_H (400 MHz, CD_3OD) 7.30-7.20 (4H, m, H−Ar), 6.99 (2H, t, *J* = 7.6 Hz, H−Ar), 6.87 (2H, d, *J* = 8.4 Hz, H−Ar), 5.07 (4H, s, C$\underline{H}_2$OAr), 4.28 (4H, s, C$\underline{H}_2$OCO); δ_C (100 MHz, DMSO-d_6) 193.4 (2C), 186.9 (2C), 174.6 (2C), 155.9 (2C), 131.9 (2C), 128.0 (2C), 126.7 (2C), 119.5 (2C), 112.3 (2C), 93.8 (2C), 71.1 (2C), 69.5 (2C); HRMS (ESI): MNa^+, found 489.0802. $C_{24}H_{18}NaO_{10}$ requires 489.0798.

*4.1.13. 3,3'-{2,2'-[Naphthalene-1,7-diylbis(oxy)]bis(acetyl)}bis[4-hydroxyfuran-2(5H)-one] (**11**).* 1,7-naphthalenediol (241 mg, 1.5 mmol, 1 equiv), K_2CO_3 (1.245 g, 9.0 mmol, 6 equiv), 3-bromoacetyltetronic acid **1** (1.0 g, 4.51 mmol, 3 equiv) and DMF (10 mL) were used following the general procedure to afford the title compound (524 mg, 79%) as a white powder; mp 238-240 °C; ν_{max} (KBr pellet) 3181, 1729, 1629, 1512, 1466, 1364, 1247, 1220, 1046, 939, 826, 779, 742, 693, 638 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.75 (1H, d, *J* = 9.2 Hz, H−Ar), 7.43 (1H, d, *J* = 2.4 Hz, H−Ar), 7.34 (1H, d, *J* = 8.0 Hz, H−Ar), 7.10-7.25 (4H, m, H−Ar, OH), 6.58 (1H, d, *J* = 7.6 Hz, H−Ar), 5.20 (2H, s, C$\underline{H}_2$OAr), 5.11 (2H, s, C$\underline{H}_2$OAr), 4.16 (2H, s, C$\underline{H}_2$OCO), 4.15 (2H, s, C$\underline{H}_2$OCO); δ_C (100 MHz, DMSO-d_6) 193.6 (2C), 186.4, 186.0, 174.7, 174.6, 156.2, 153.2, 129.3, 128.9, 125.9, 123.4, 119.4, 118.8, 105.6, 101.5, 93.9, 93.8, 70.9 (2C), 69.63, 69.58; HRMS (ESI): MNa^+, found 463.0636. $C_{22}H_{16}NaO_{10}$ requires 463.0641.

*4.1.14. 3-(2-Amino-3-phenylpropanoyl)-4-hydroxyfuran-2(5H)-one (**12**).* To a solution of tetronic acid (94 mg, 0.94 mmol, 1 equiv) in CH_2Cl_2 cooled at 0 °C were added triethylamine (157 µL, 1.13 mmol, 1.2 equiv), DMAP (11 mg, 0.094 mmol, 0.1 equiv), *N*-Boc-phenylalanine (299 mg, 1.13 mmol, 1.2 equiv) and DCC (232 mg, 1.13 mmol, 1.2 equiv). The mixture was stirred for 30 min at 0 °C and for 15 h at room temperature. The mixture was filtered and the solvent was removed under vacuum. Then, CH_2Cl_2 (2 mL) and trifluoroacetic acid (2 mL) were added to the residue and the mixture was stirred at room temperature for 1.5 h. After concentration under vacuum, the obtained residue was purified by reversed phase chromatography (aqueous 0.01 N HCO_2NH_4 buffer, pH9/MeOH 100/0 to 90/10) to afford the

title compound (161 mg, 70%) as a white powder; mp 225-230 °C (decomposition); ν_{max} (KBr pellet) 3030, 1715, 1645, 1363, 1247, 1140, 1048, 1030, 963, 917, 787, 746, 699 cm^{-1}; δ_H (400 MHz, CD_3OD) 7.40 (2H, d, *J* = 7.0 Hz, H−Ar), 7.30 (2H, m, H−Ar), 7.24 (1H, m, H−Ar), 4.99 (1H, dd, *J* = 9.7, 3.7 Hz, C<u>H</u>CO), 4.31 (2H, s, C<u>H</u>$_2$O), 3.29 (1H, dd, *J* = 14.3 Hz, 3.7 Hz, C<u>H</u>HPh), 2.78 (1H, dd, *J* = 14.3 Hz, 9.7 Hz, CH<u>H</u>Ph); δ_C (100 MHz, CD_3OD) 195.6, 187.0, 176.6, 135.5, 129.2 (2C), 128.6 (2C), 127.1, 93.8, 70.3, 65.6, 57.4, 36.9; HRMS (ESI): MNa^+, found 270.0738. $C_{13}H_{13}NO_4Na$ requires 270.0742.

4.2. Complexation studies

Absorption measurements were performed at 25 ± 0.1 °C on a Cary 4000 spectrophotometer equipped with Peltier thermostated cell-carriers. The pH of solutions was measured at 25 ± 0.5 °C with a Jenco pH-meter. Affinity constants were determined spectrophotometrically by the use of the Global Analysis program SPECFIT32. SPECFIT32 is a multivariate data analysis program for data sets that are obtained from multiwavelength spectrophotometric measurements. The program utilizes a specially adapted version of the Levenberg-Marquardt method. This procedure returns optimized model parameters, their standard errors, and the predicted spectra of the unknown colored species.[19] The affinity constants were checked when possible by a variant of the Benesi and Hildebrand method.

Acknowledgments

Financial support by the Agence Nationale de la Recherche (ANR-08-SECU-002) is gratefully acknowledged.

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Synthesis and evaluation of new 3-acyltetronic acid-containing metal complexing agents

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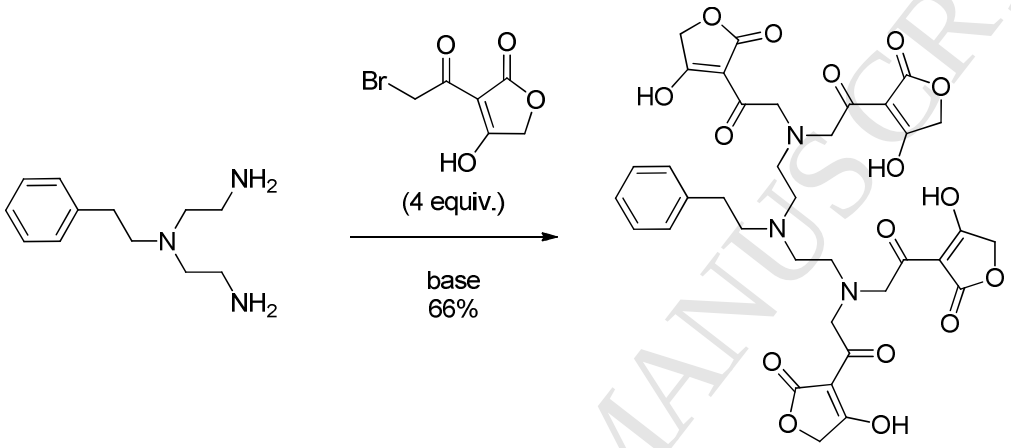

Synthesis and evaluation of new 3-acyltetronic acid-containing metal complexing agents

Julien Rouleau,[a] Alexandre Korovitch,[b] Claude Lion,[b] Miryana Hémadi,[b] Nguyêt-Thanh Ha-Duong,[b] Jean Michel El Hage Chahine,[b] Thierry Le Gall[a,*]

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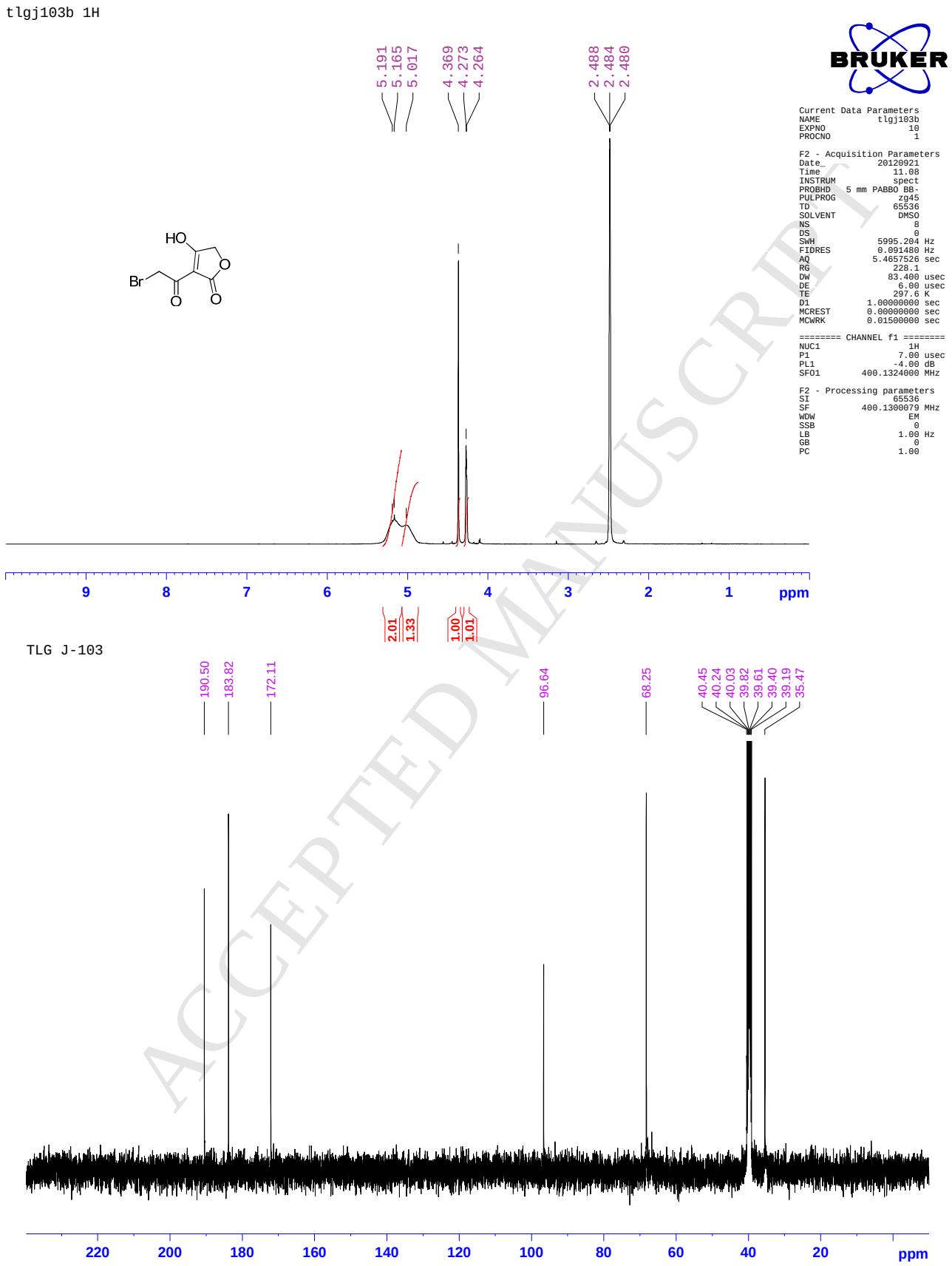
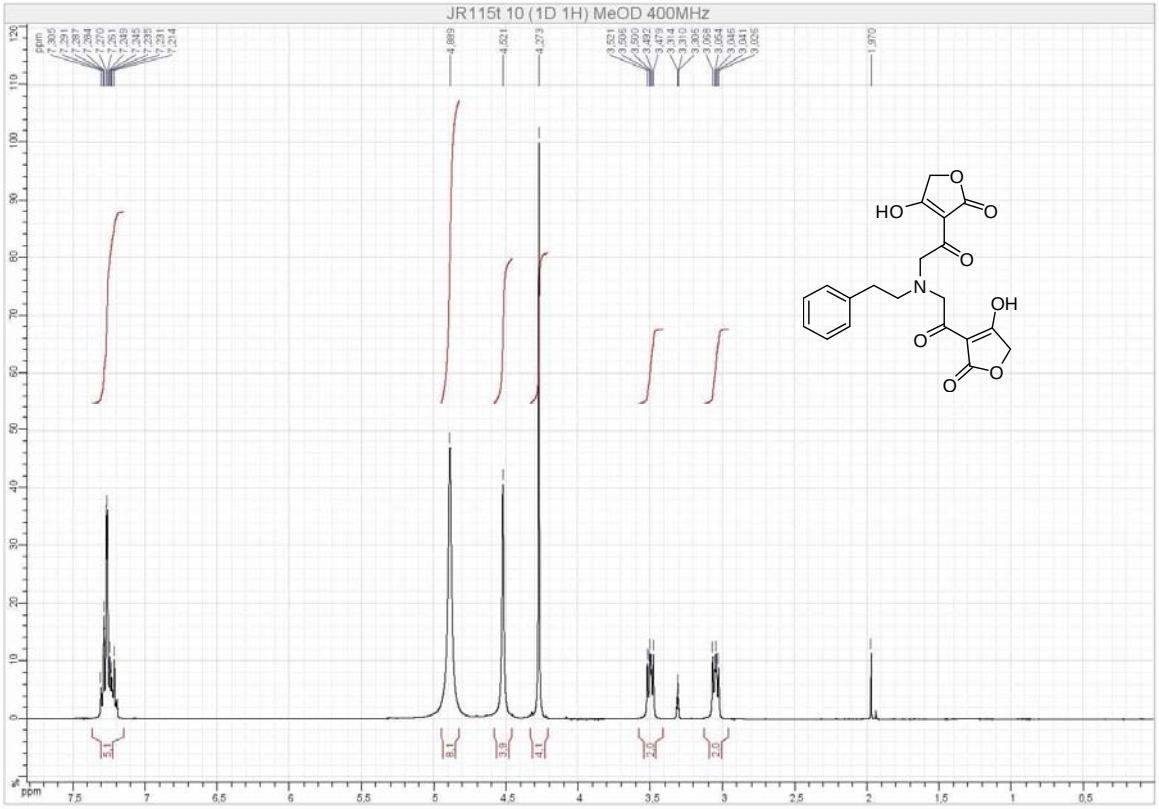
Supporting information

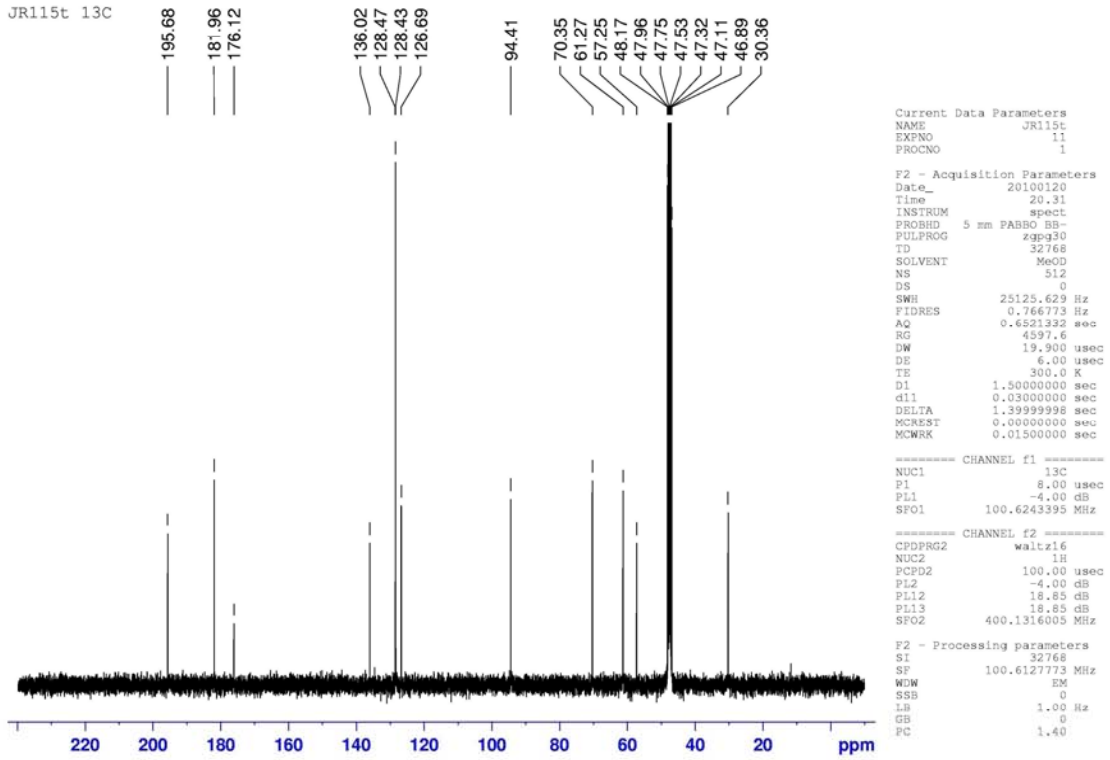
Contents:

^{1}H and ^{13}C NMR spectra of compound **1** (DMSO-d_6)



^{1}H and ^{13}C NMR spectra of compound **2** (CD_3OD)





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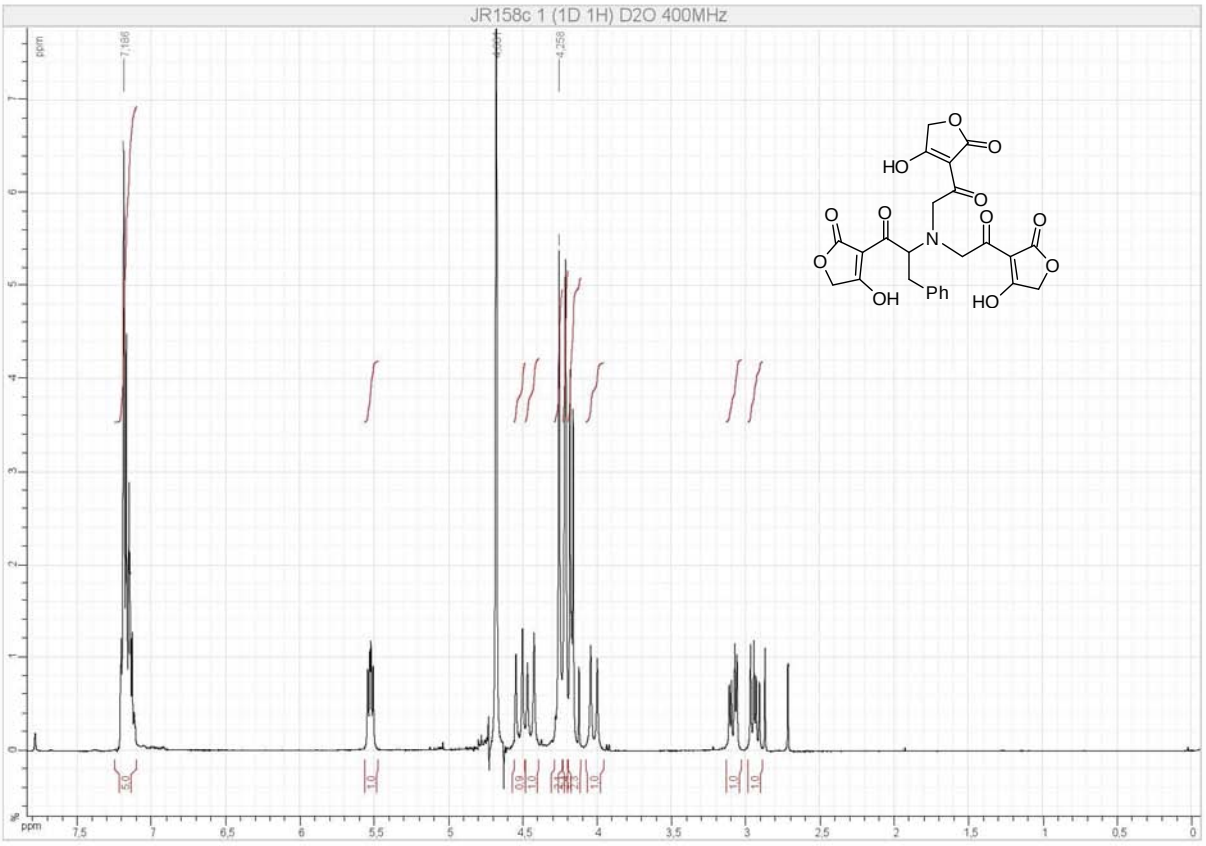

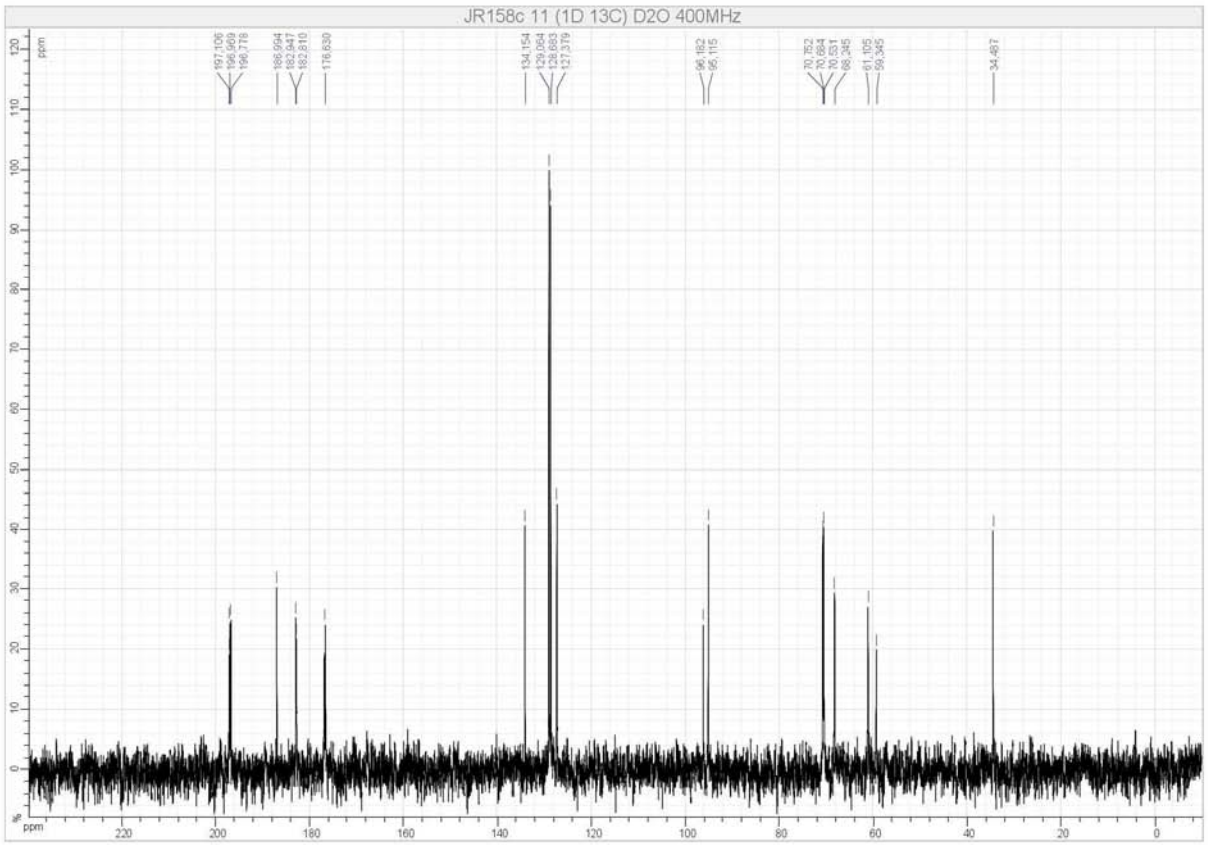

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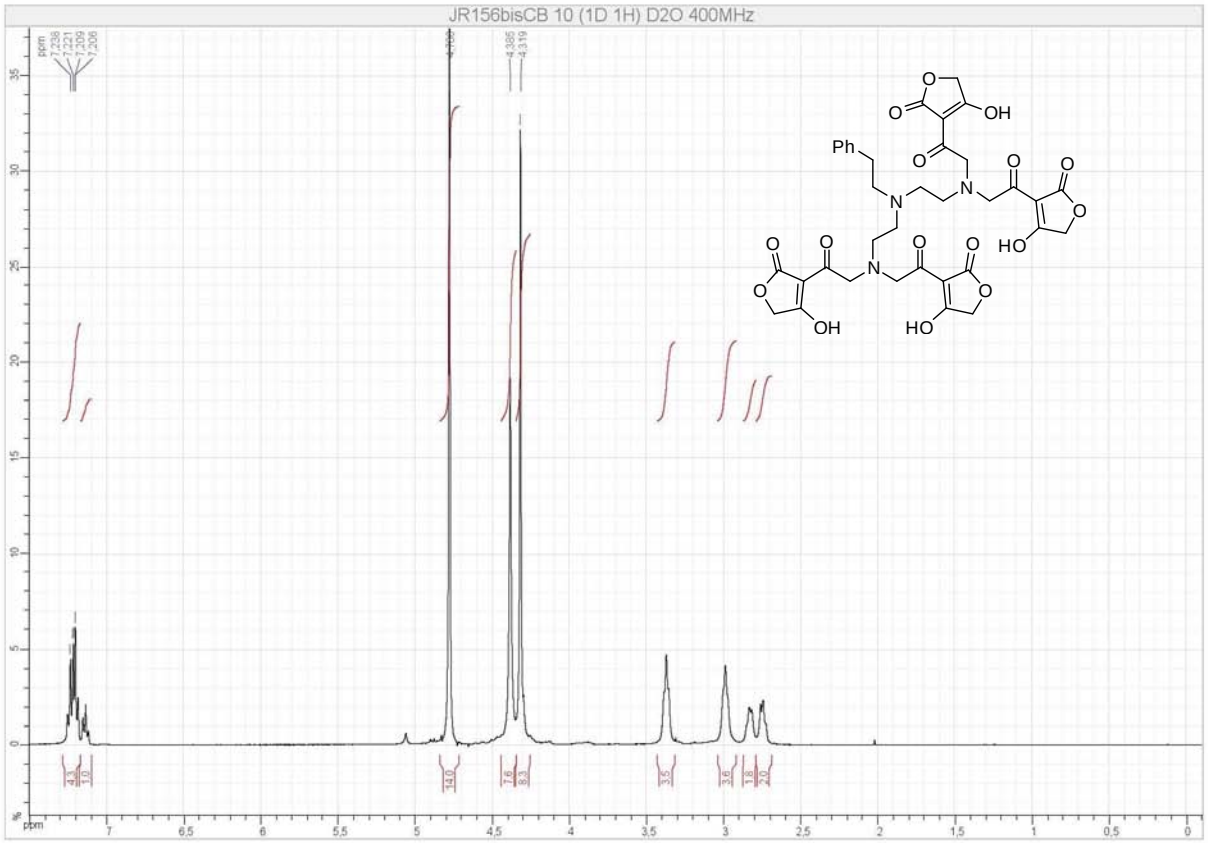

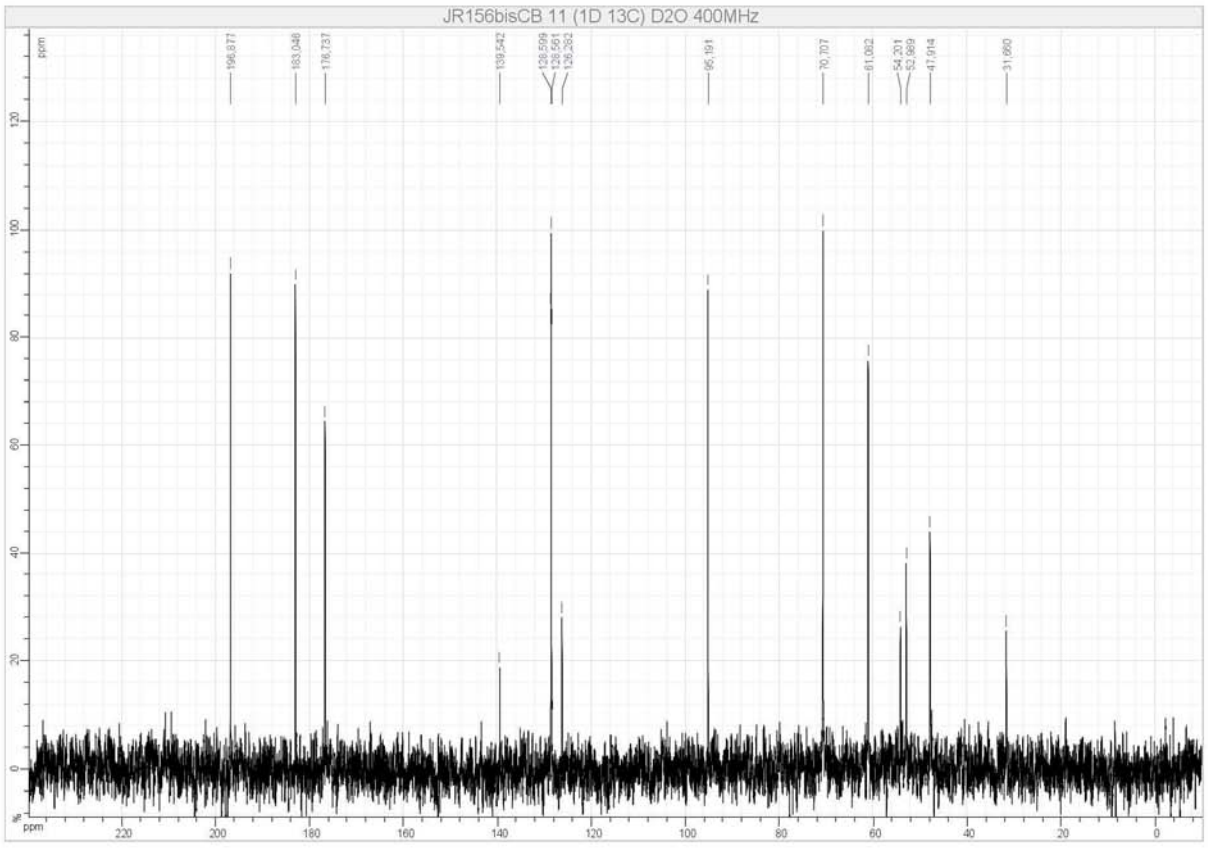

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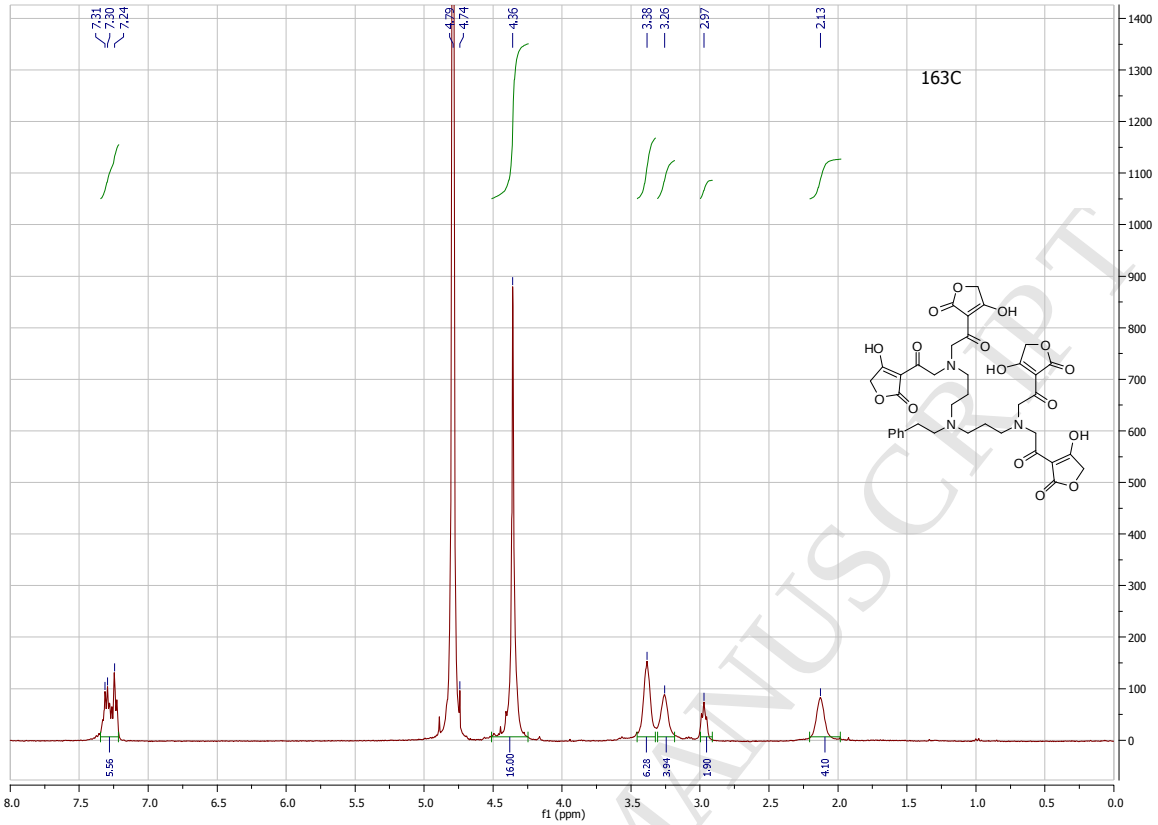

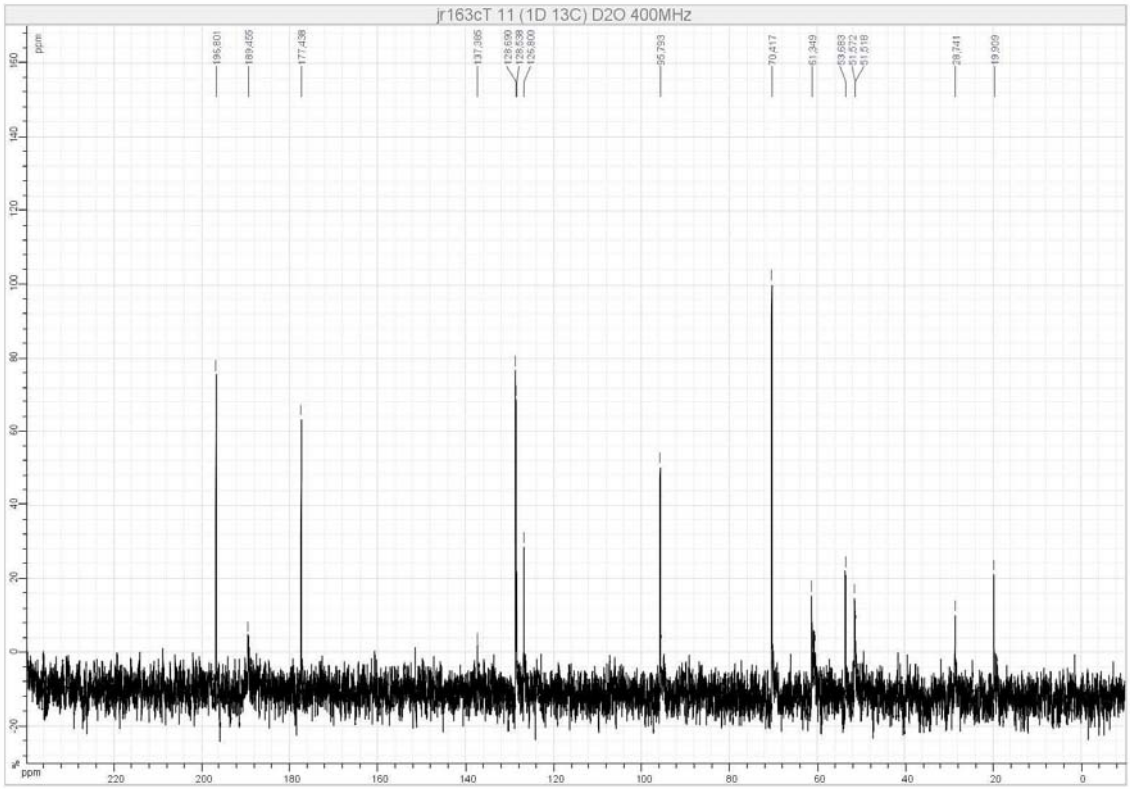

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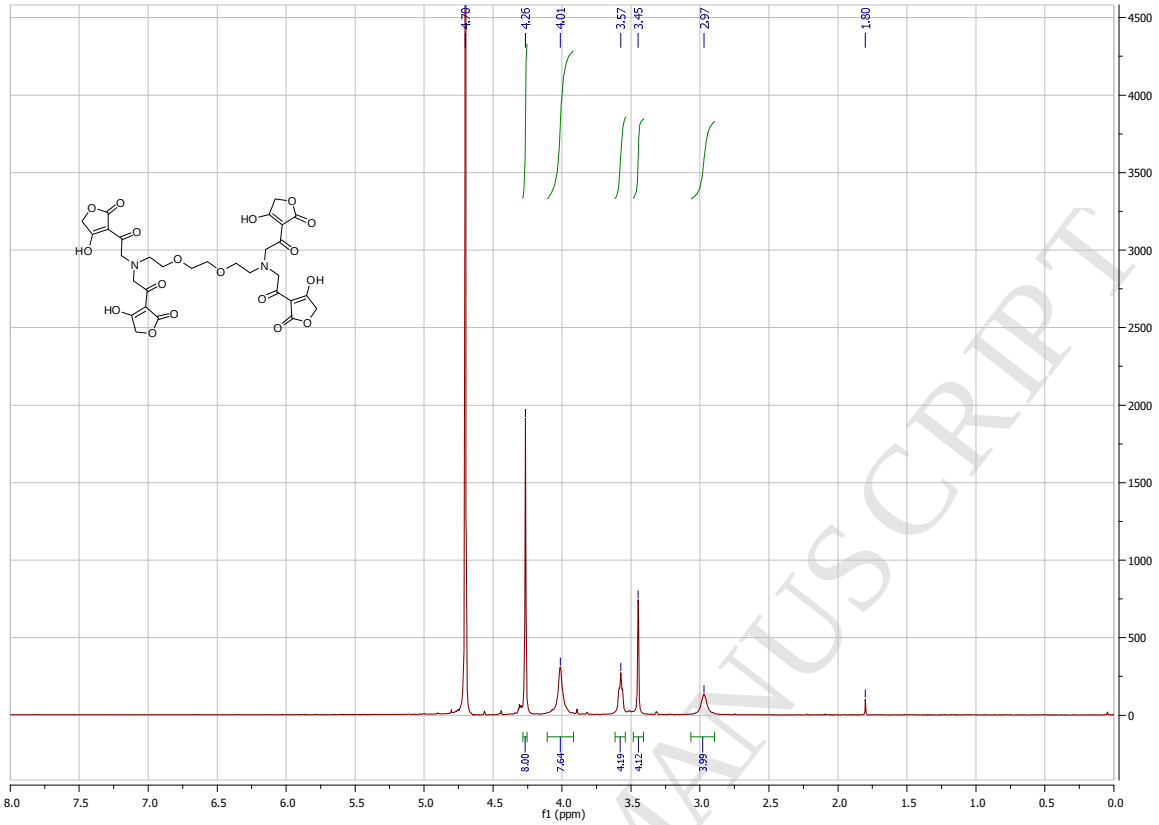
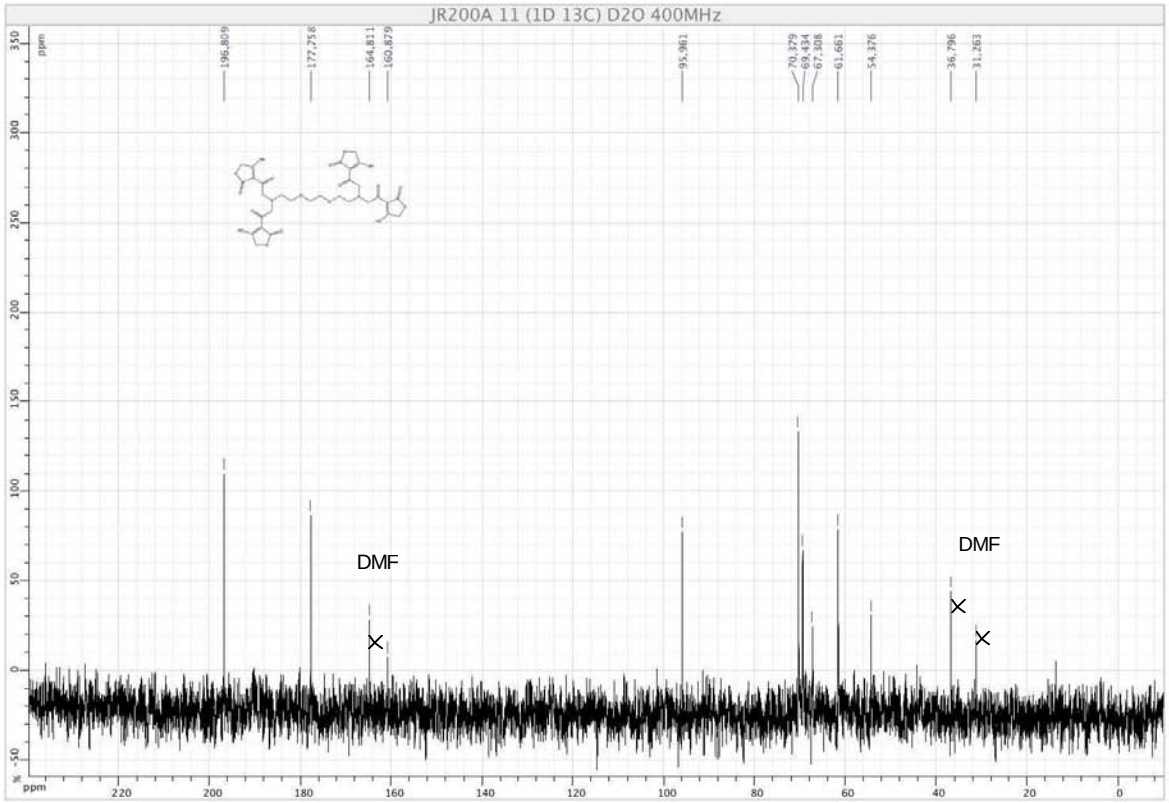
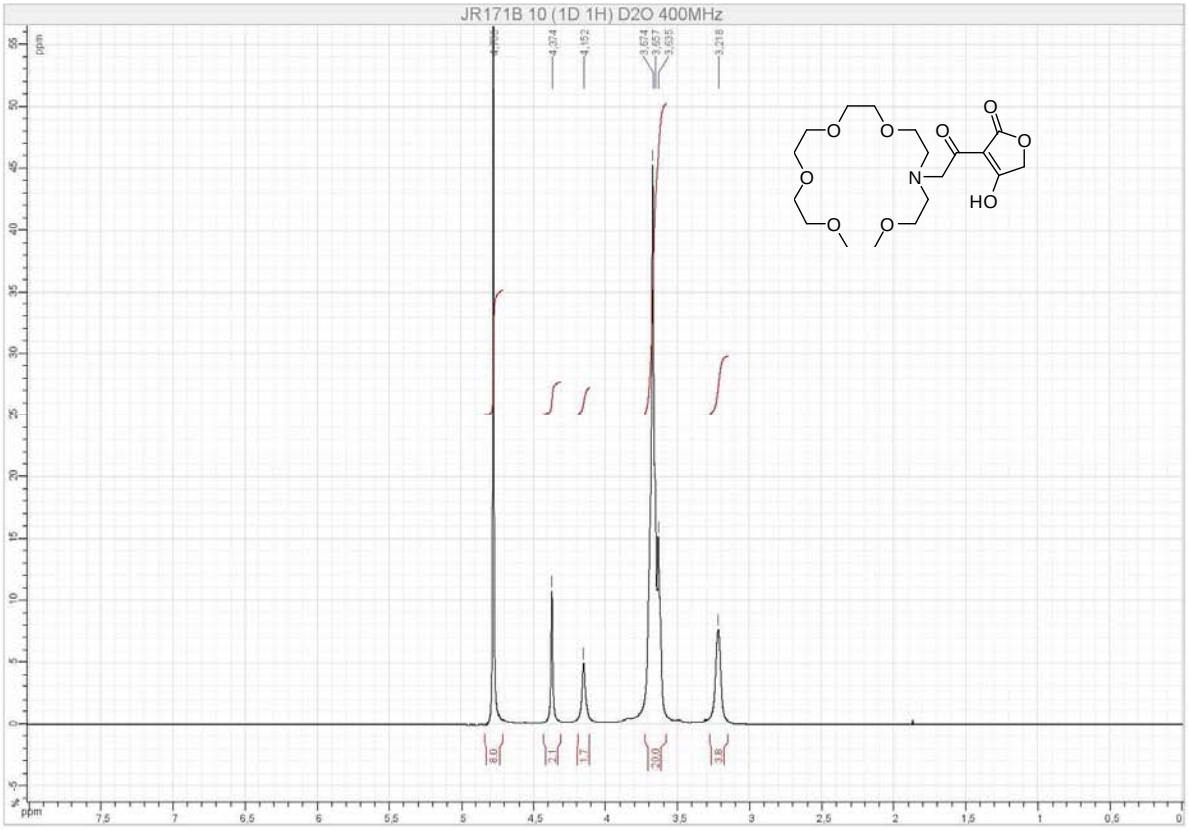
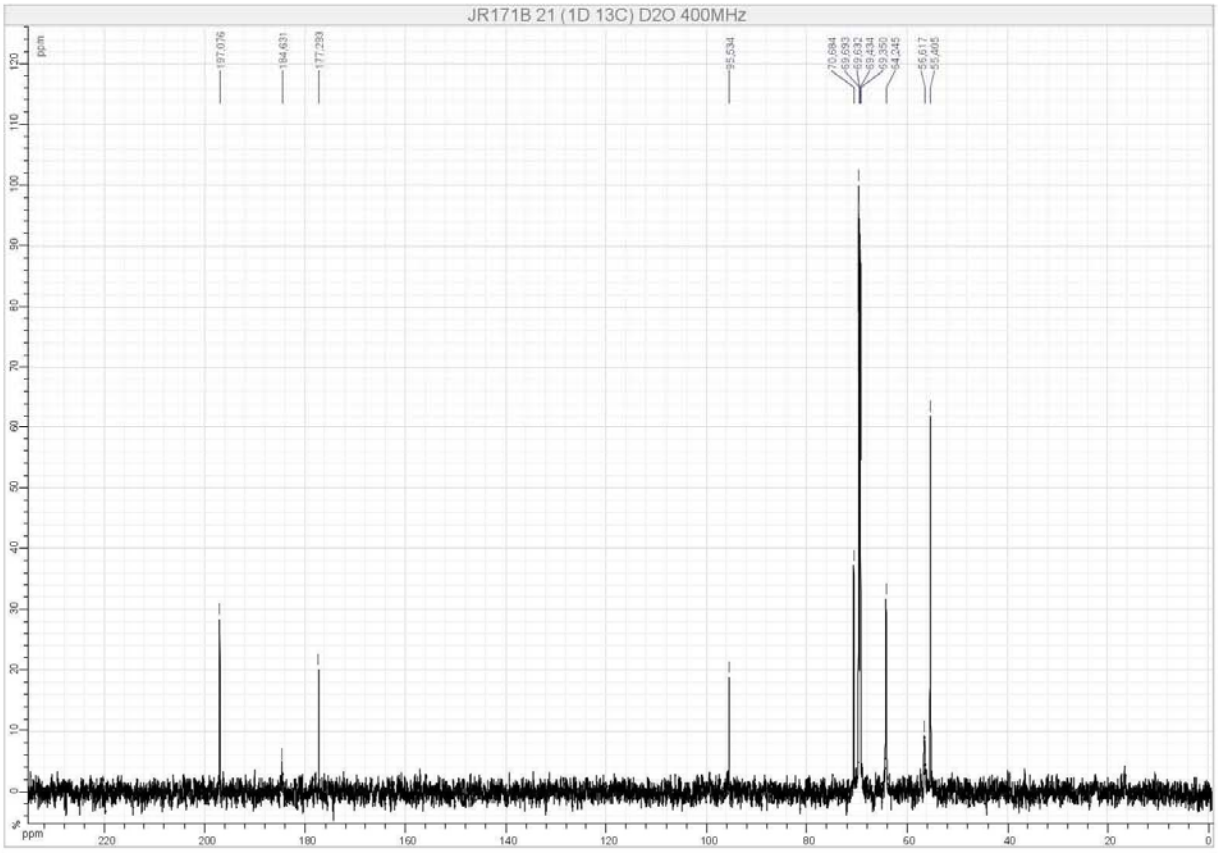


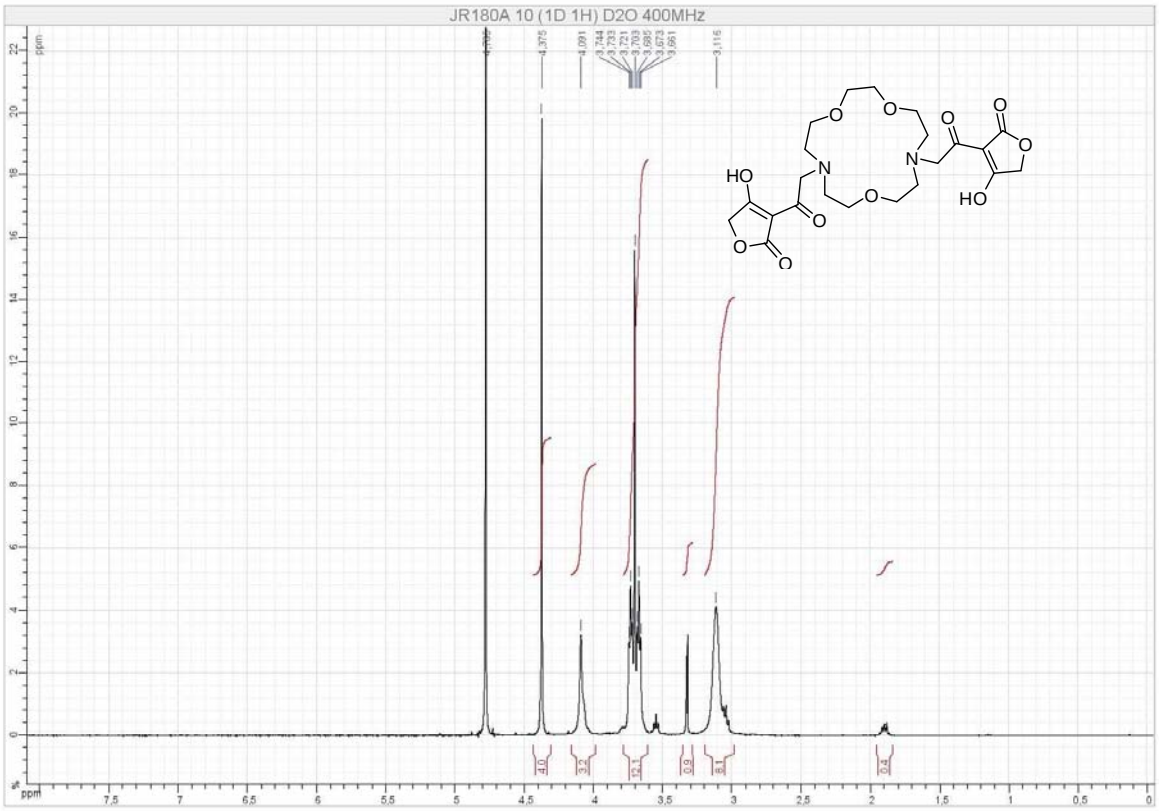


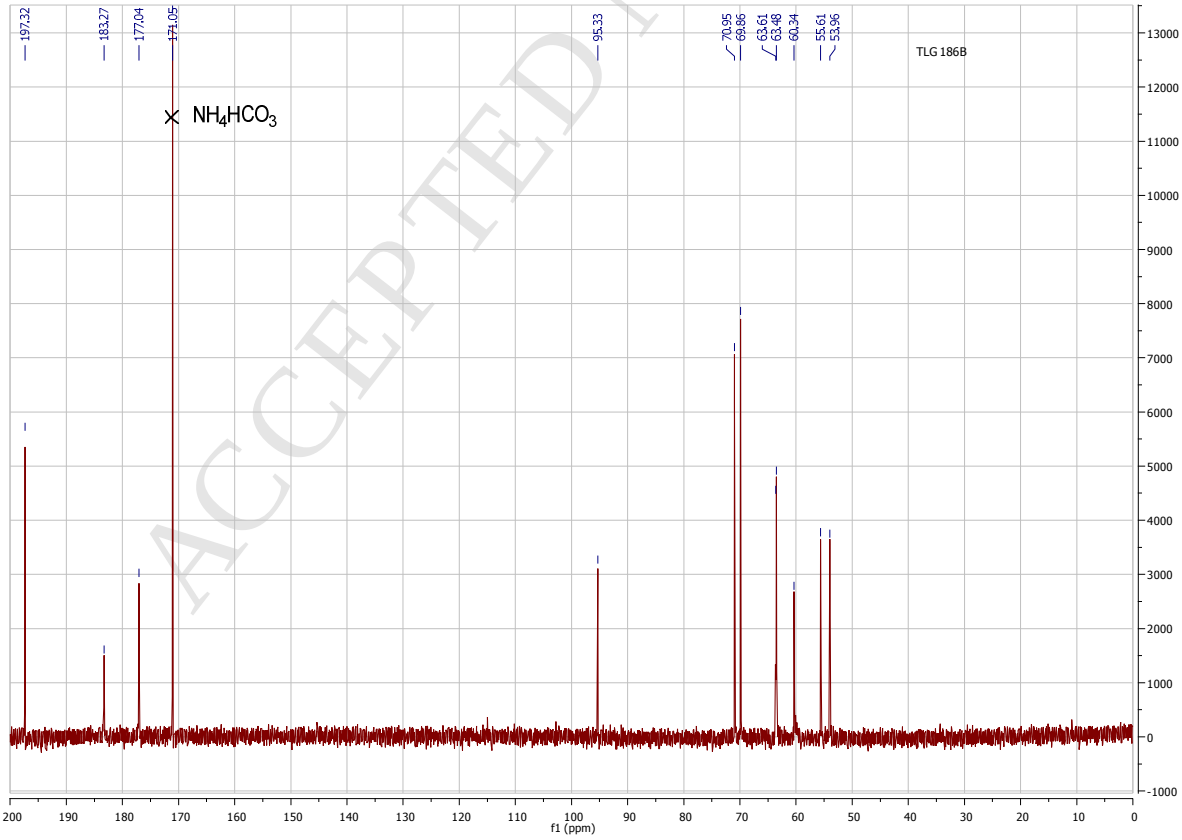
^{1}H and ^{13}C NMR spectra of compound **7** (D_2O)



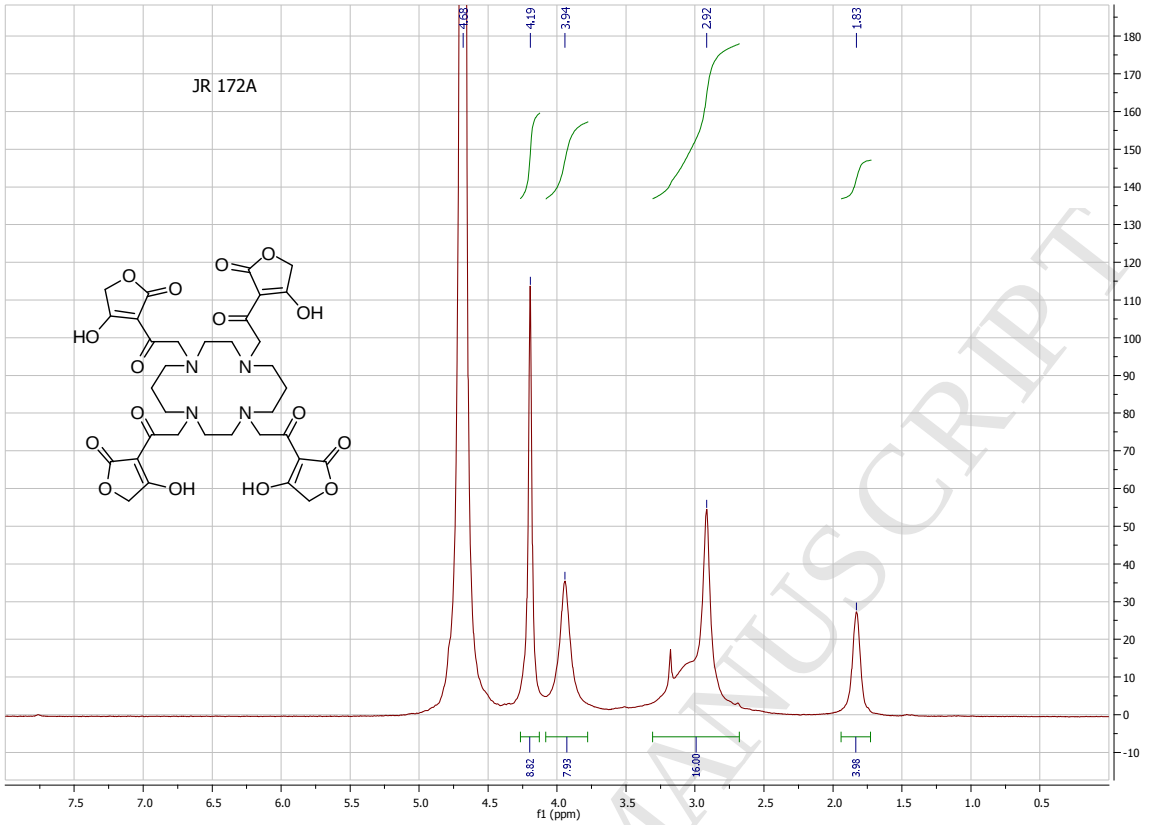


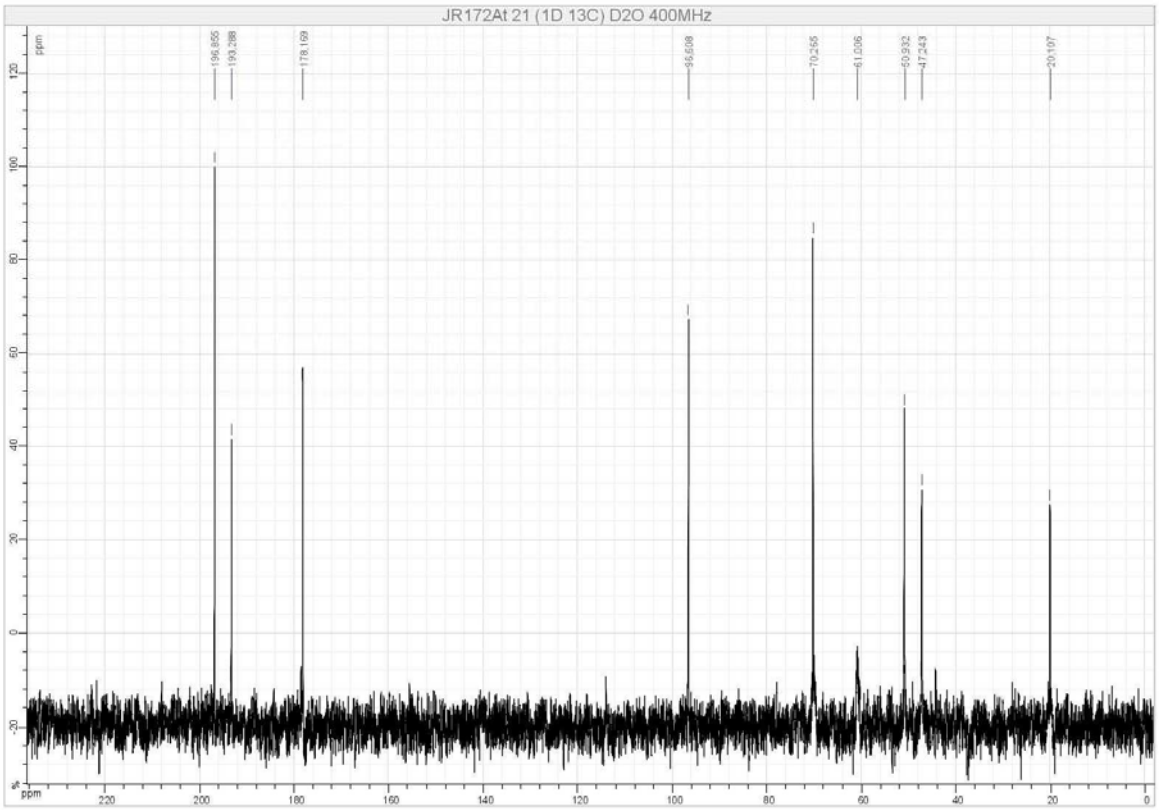
^{1}H and ^{13}C NMR spectra of compound **8** (D_2O)



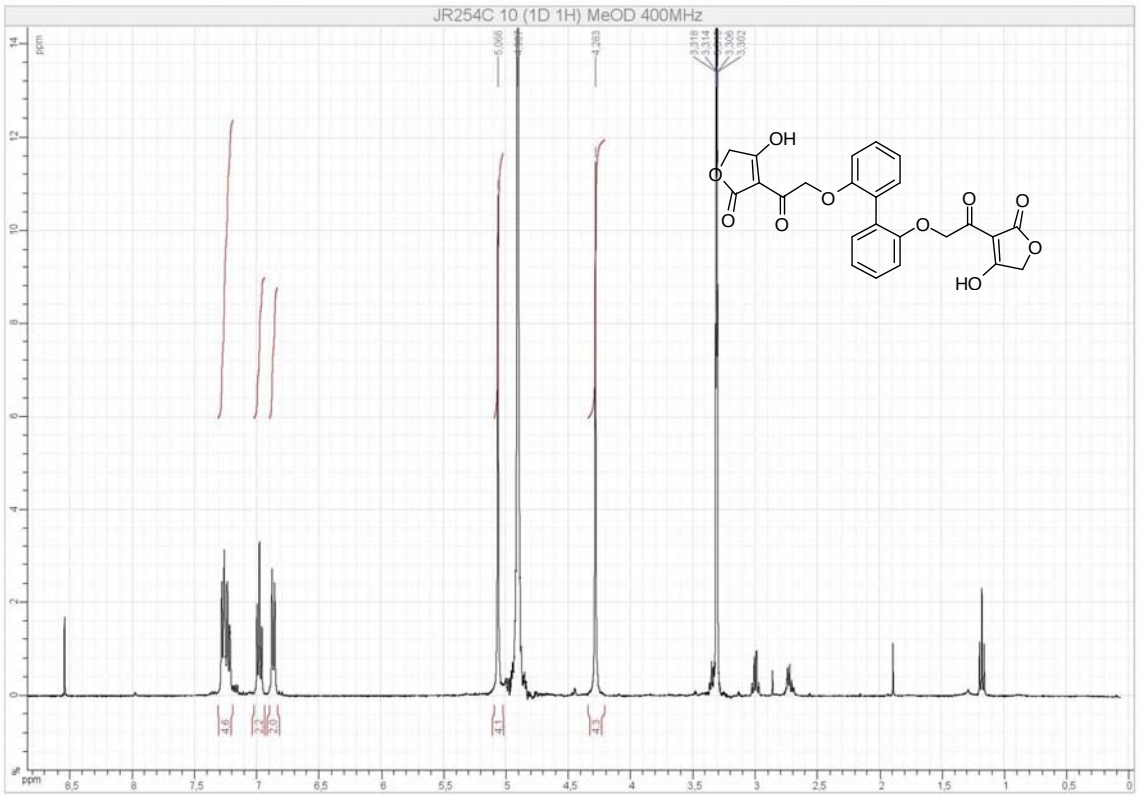


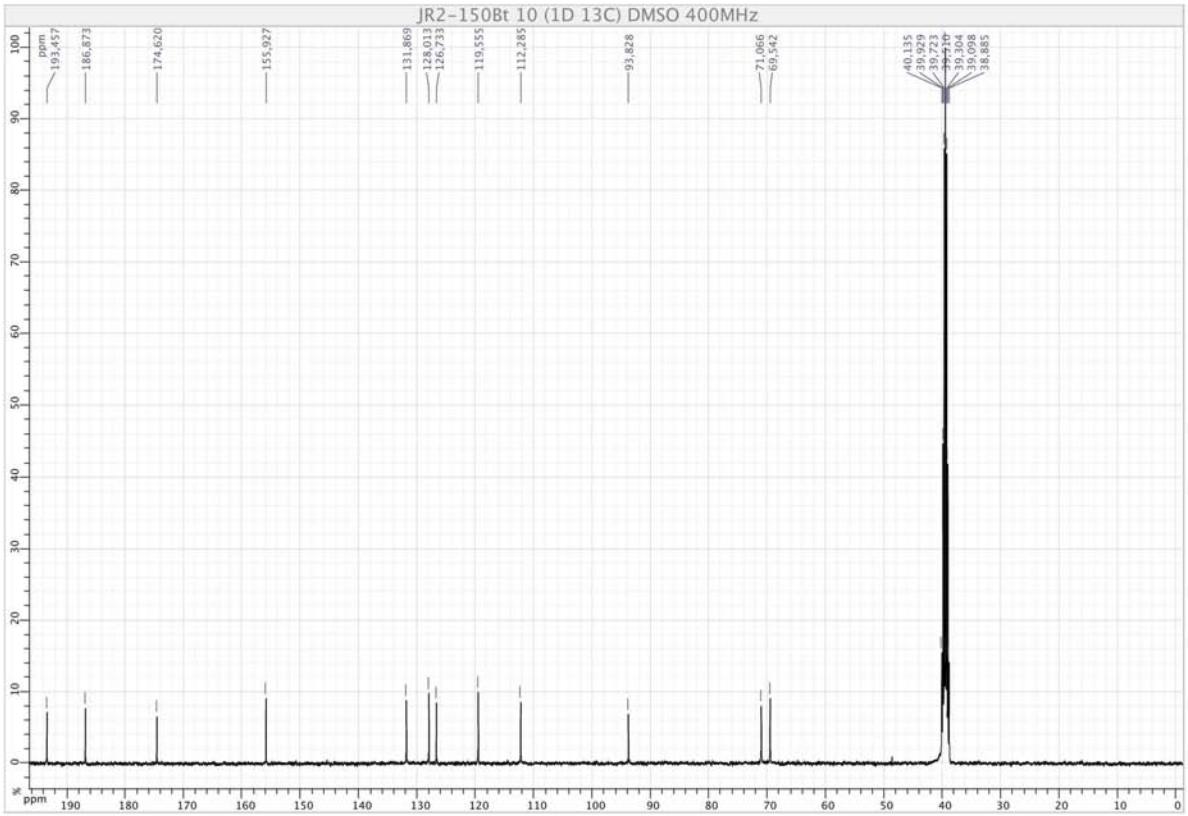
^{1}H and ^{13}C NMR spectra of compound **9** (D_2O)



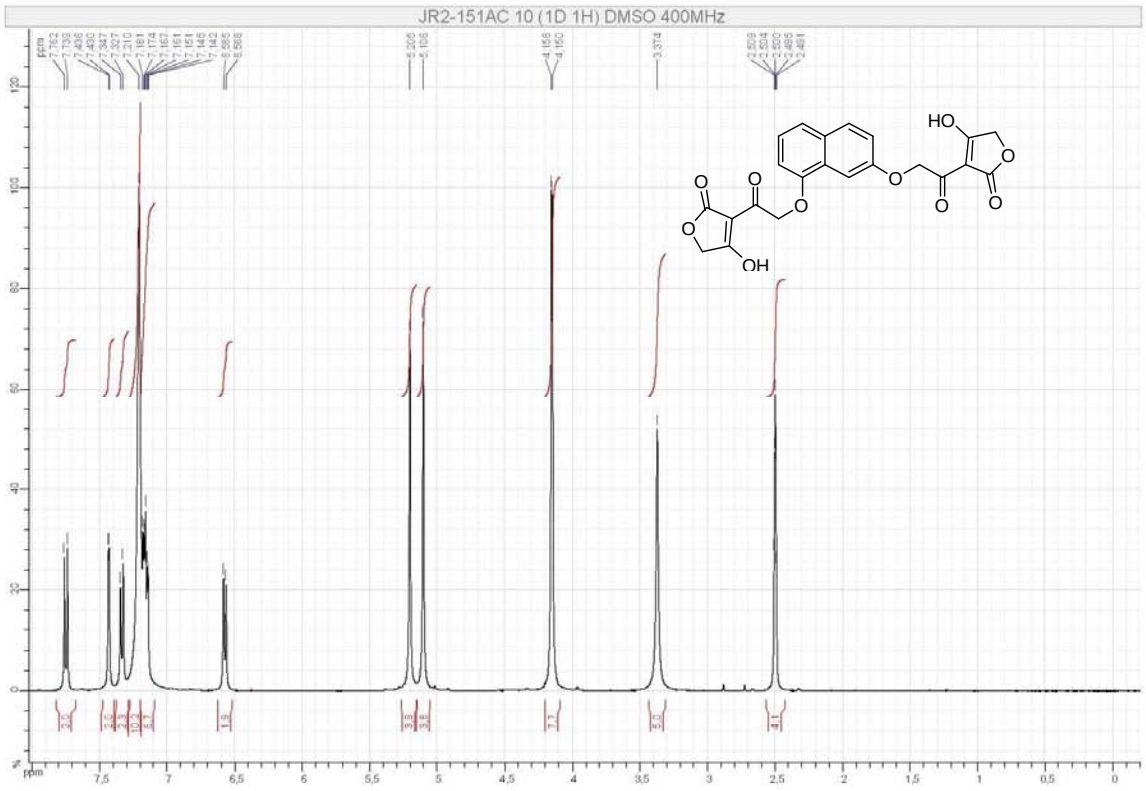


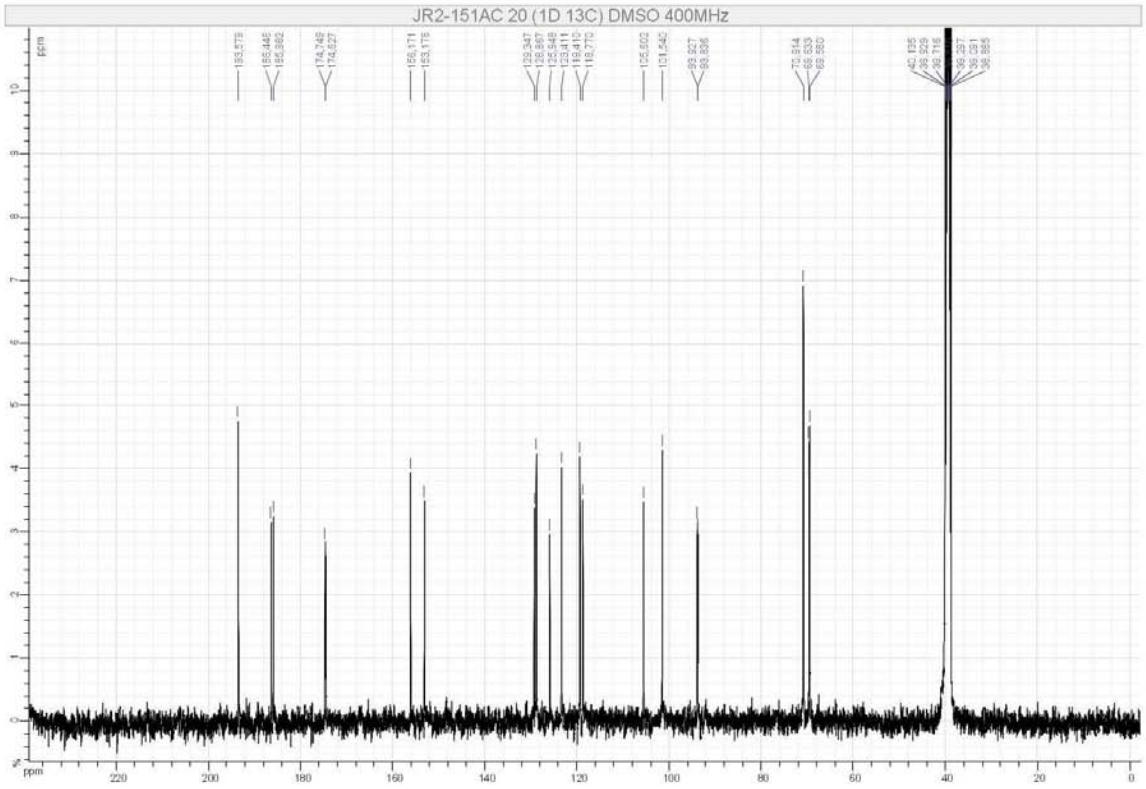
^{1}H NMR spectrum (CD_3OD) and ^{13}C NMR spectrum (DMSO-d_6) of compound **10**





^{1}H and ^{13}C NMR spectra of compound **11** (DMSO-d_6)





^{1}H and ^{13}C NMR spectra of compound **12** (CD_3OD)