Supplementary information

1. Analysis of 5.10^{-3} mol.L^{-1} La and Tb-Macropa samples.

a. Complexation 1:1 of Ln-Macropa complexes

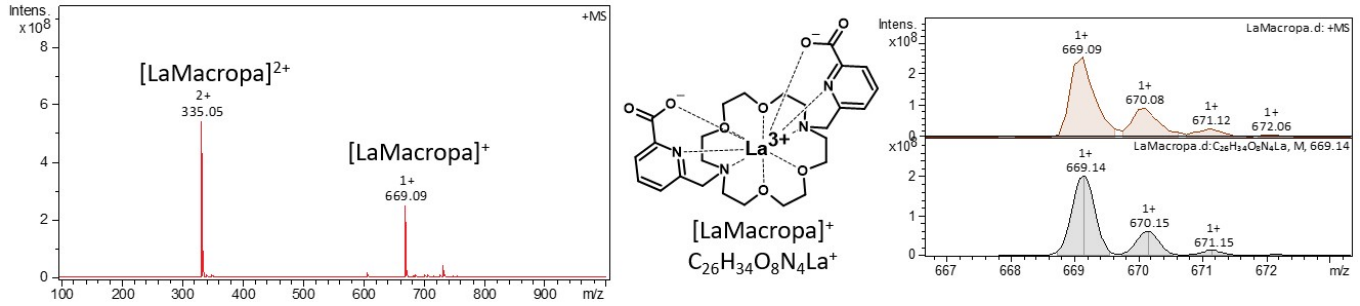


Figure S1. Left: ESI-MS spectra of 1:1 La-Macropa complex. Right: Associated simulated isotopic pattern of $C_{26}H_{34}O_8N_4La^+$.

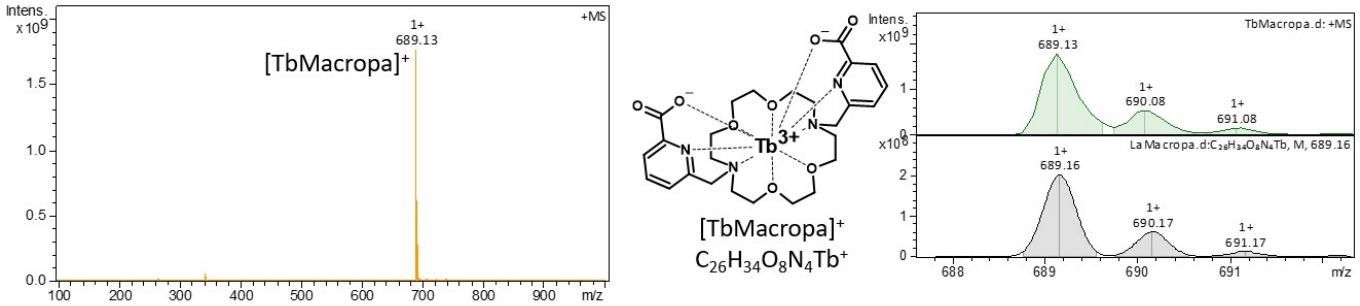


Figure S2. Left: ESI-MS spectra of 1:1 Tb-Macropa complex. Right: Associated simulated isotopic pattern of $C_{26}H_{34}O_8N_4Tb^+$.

b. Attribution of La-Macropa complex hydrogens

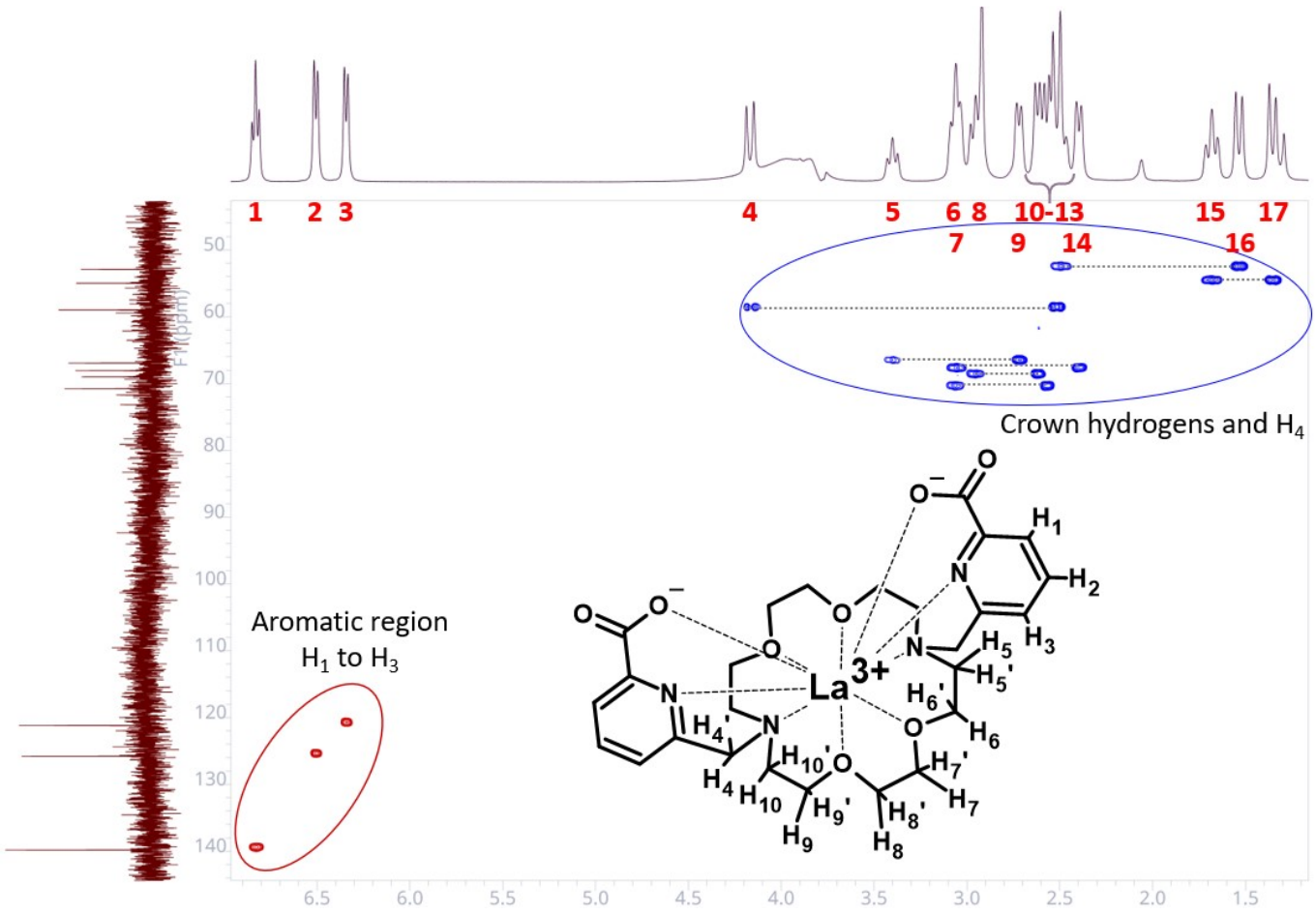


Figure S3. gHSQC of La-Macropa complex.

HSQC is used to determine proton-carbon single bond correlations. 17 signals corresponding to protons of the La-Macropa complex were identified. Signals above 6ppm correspond to aromatic protons.

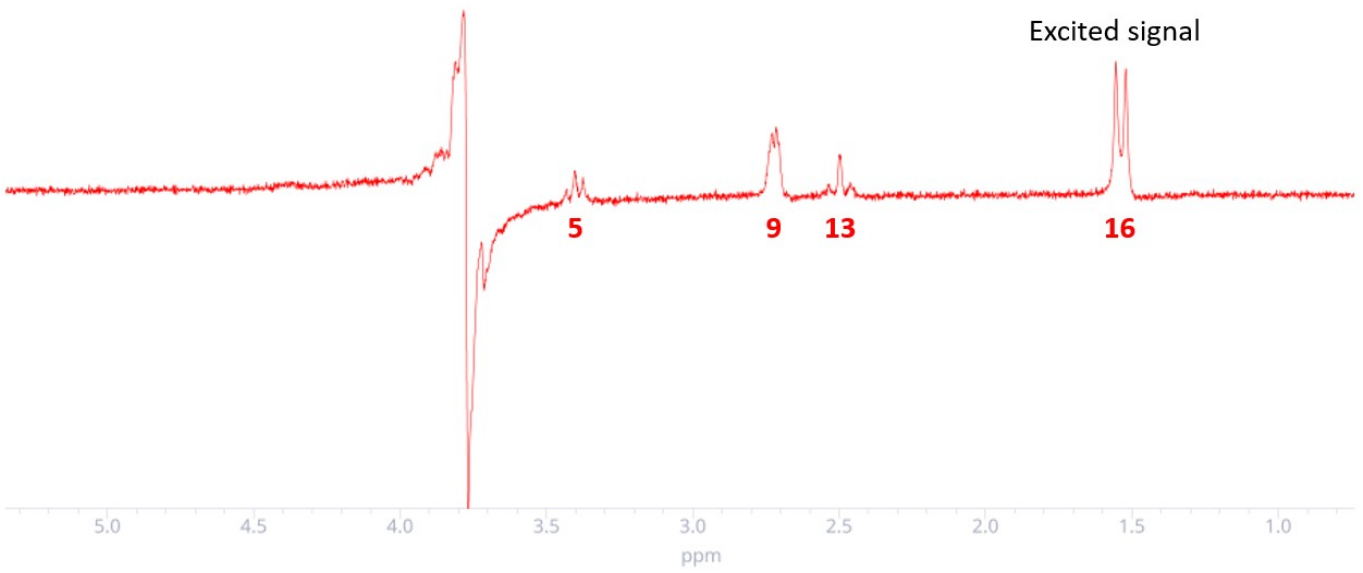


Figure S4. TOCSY1D of signal 16 at 1.54ppm of La-Macropa complex.

In 1D TOCSY, a single resonance is selectively excited, and the magnetization is transferred from that signal to all protons that are coupled. Signal 16 is associated to signals 5, 9 and 13 (See Figure S3).

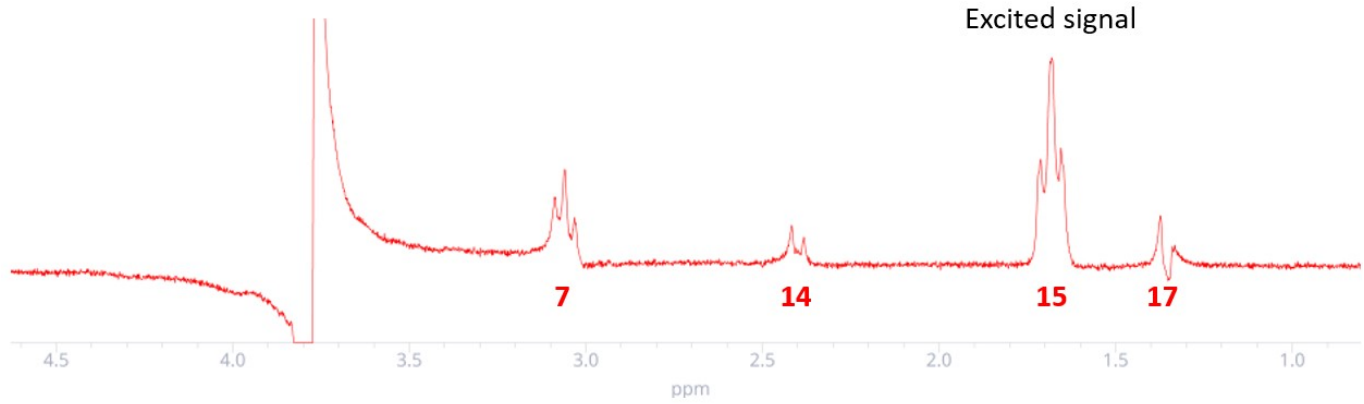


Figure S5. TOCSY1D of signal 15 at 1.68ppm of La-Macropa complex.

Signal 15 is associated to signals 7, 14 and 17 (See Figure S3).

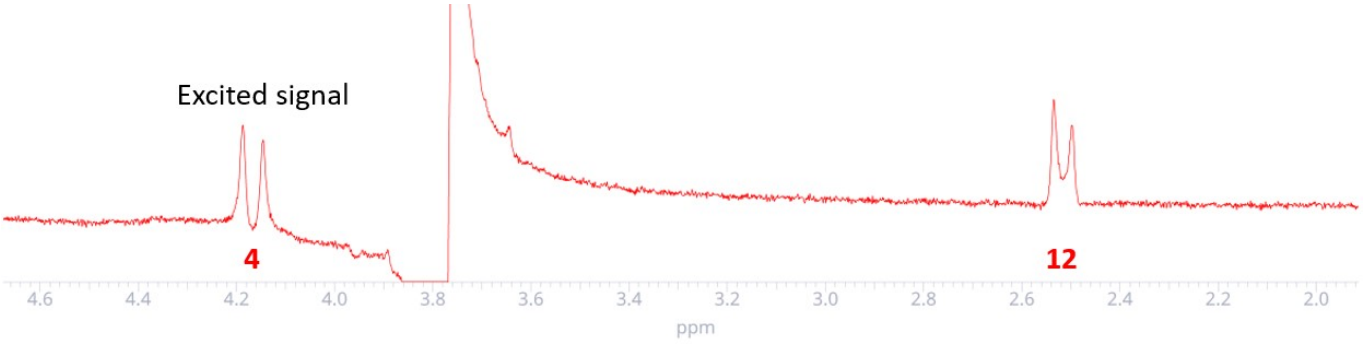


Figure S6. TOCSY1D of signal 4 at 4.2 ppm of La-Macropa complex.

Signal 4 is only associated to signal 12 (See Figure S3). Therefore, they correspond to H_4 and H_4'.

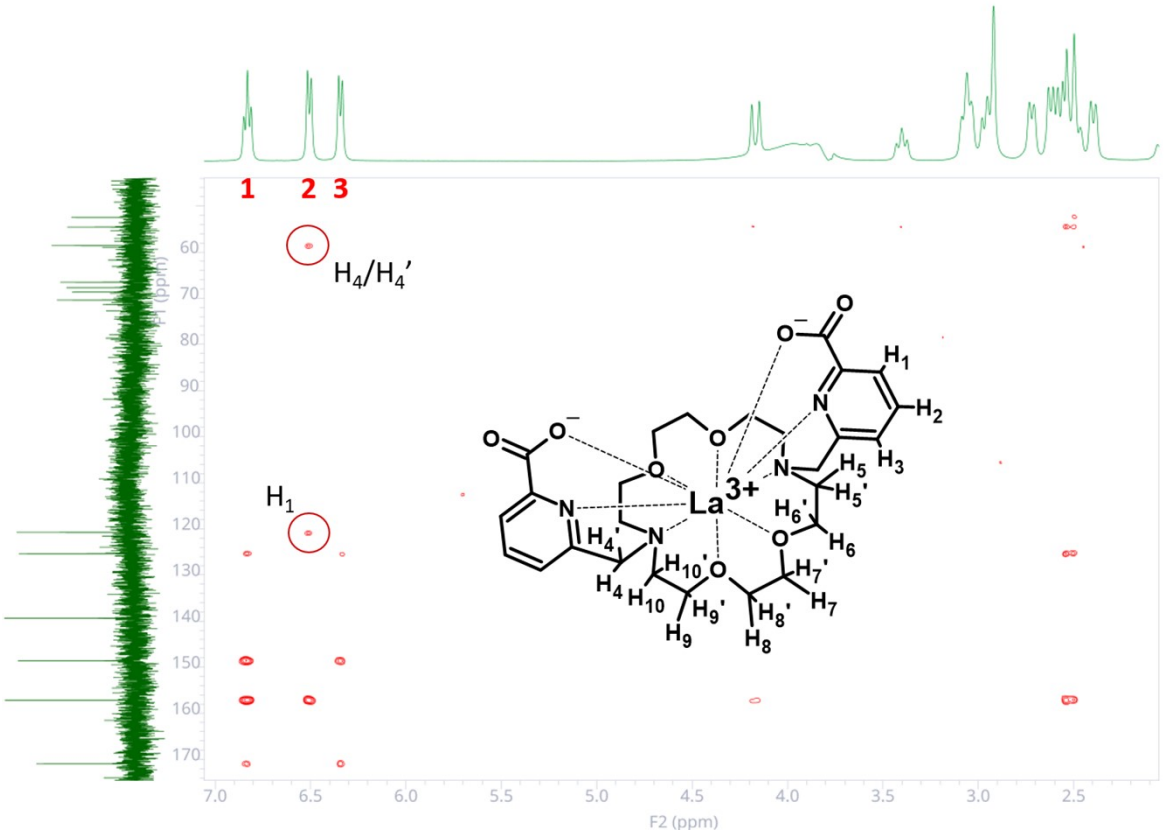


Figure S7. gHMBC ^{13}C of La-Macropa complex.

HMBC gives correlations between carbons and protons that are separated by three bonds. Signal 3 is only correlated to H_3 and therefore attributed to H_1. Signal 2 is correlated to what we assign to H_1 and H_4/H_4' and therefore assigned to H_3. Accordingly, the triplet corresponding to signal 1 was assigned to H_2.

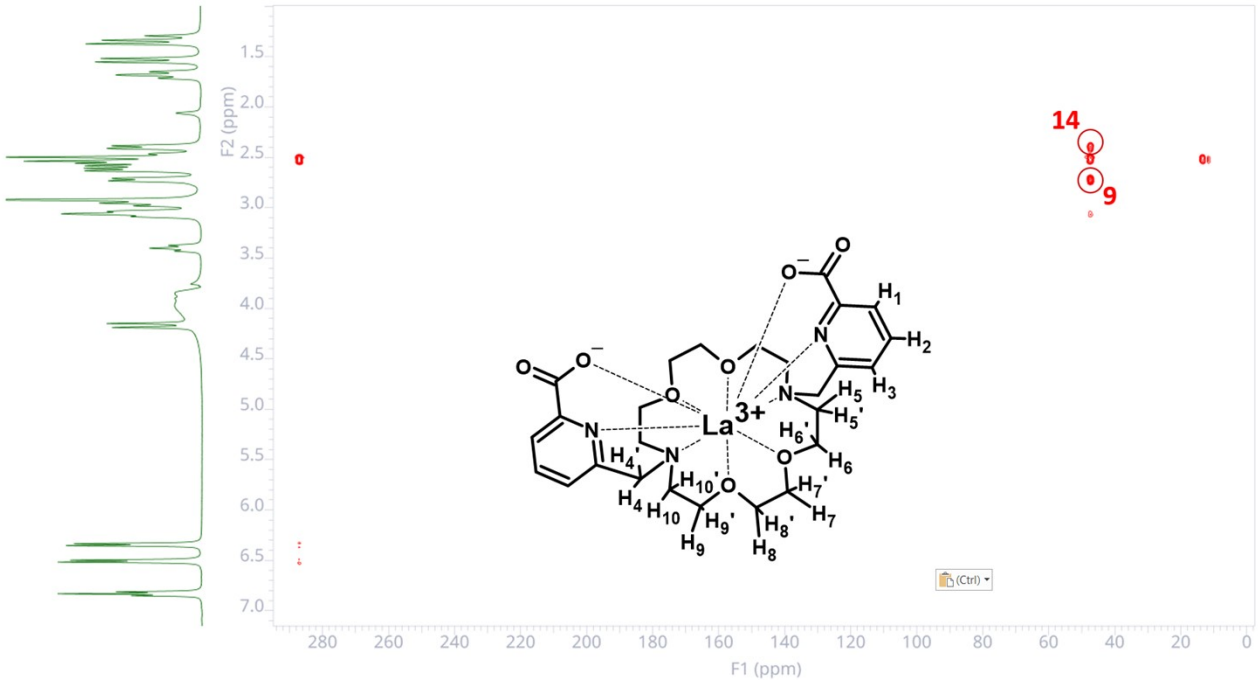
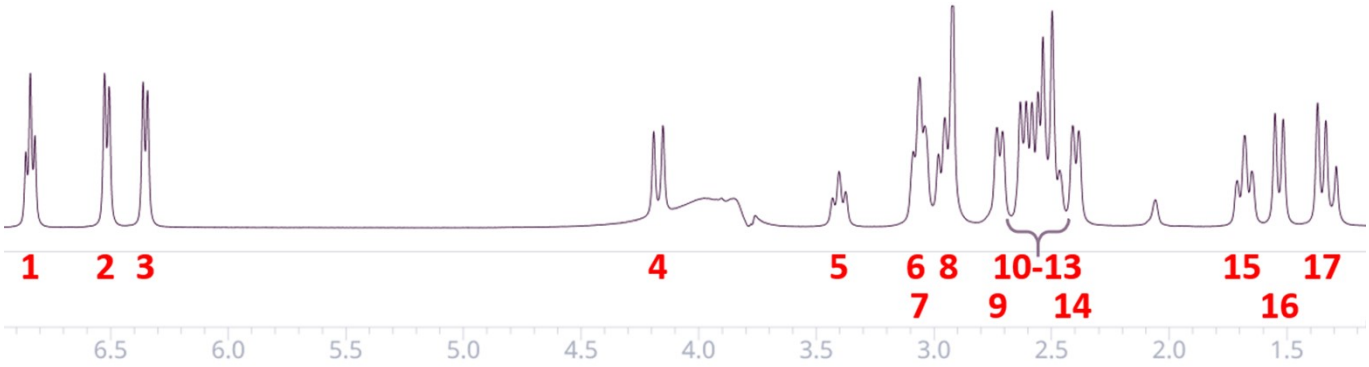
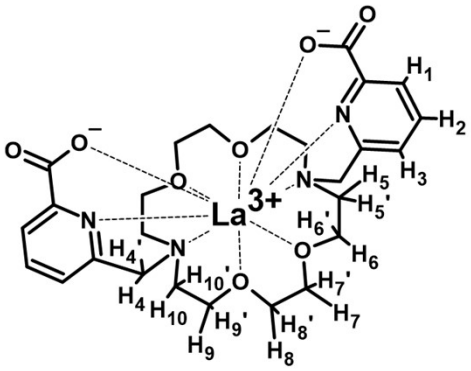


Figure S8. gHMBC ^{15}N of La-Macropa complex.

Signals 9 and 14 are separated from a N-atom by 3 bonds. Therefore, they're associated to H_9/H_9' and H_6/H_6'. Based on previous TOCSY1D studies, we can assume that signals 7, 15, 17 and 5, 13 ,16 are H_{10}/H_{10}', H_9/H_9' and H_6/H_6', H_5/H_5'. The remaining signals 6, 8, 10, and 11 were therefore assigned to H_7/H_7', H_8/H_8'.





H	H_1	H_2	H_3	H_4/H_4'	H_6/H_6' and H_9/H_9'	H_5/H_5' and H_6/H_6'
Signal	3	1	2	4, 12	9, 14	7, 15, 17

H	H_9/H_9' and H_{10}/H_{10}'	H_7/H_7' and H_8/H_8'
Signal	5, 13, 16	6, 8, 10, 11

Figure S9. Attribution of H-atom signals of La-Macropa complex.

2. HPLC-ESI-MS analysis of 5 mM Macropa and La(III)-Macropa samples irradiated from 0 to 30 kGy

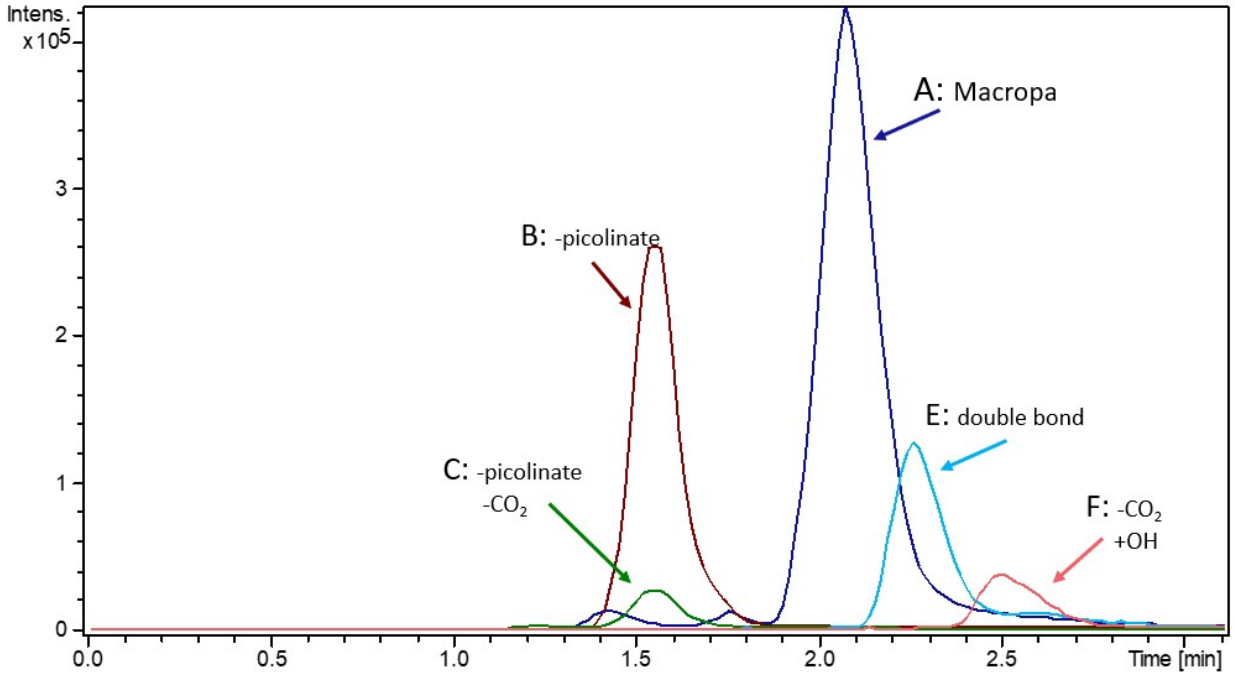


Figure S10. Extracted Ion Chromatogram of a Macropa sample irradiated at 10 kGy. Diluted 10-fold in 90/10 ACN/H2O. Mobile phase: (Milli-Q water + 0.1% formic acid)/ACN 8:92 v/v at 200 µL/min. HILIC mode with a mixed Poroshell 120 column (amphoteric properties), 2.1 × 150 mm in length and 2.7 µm pore size.

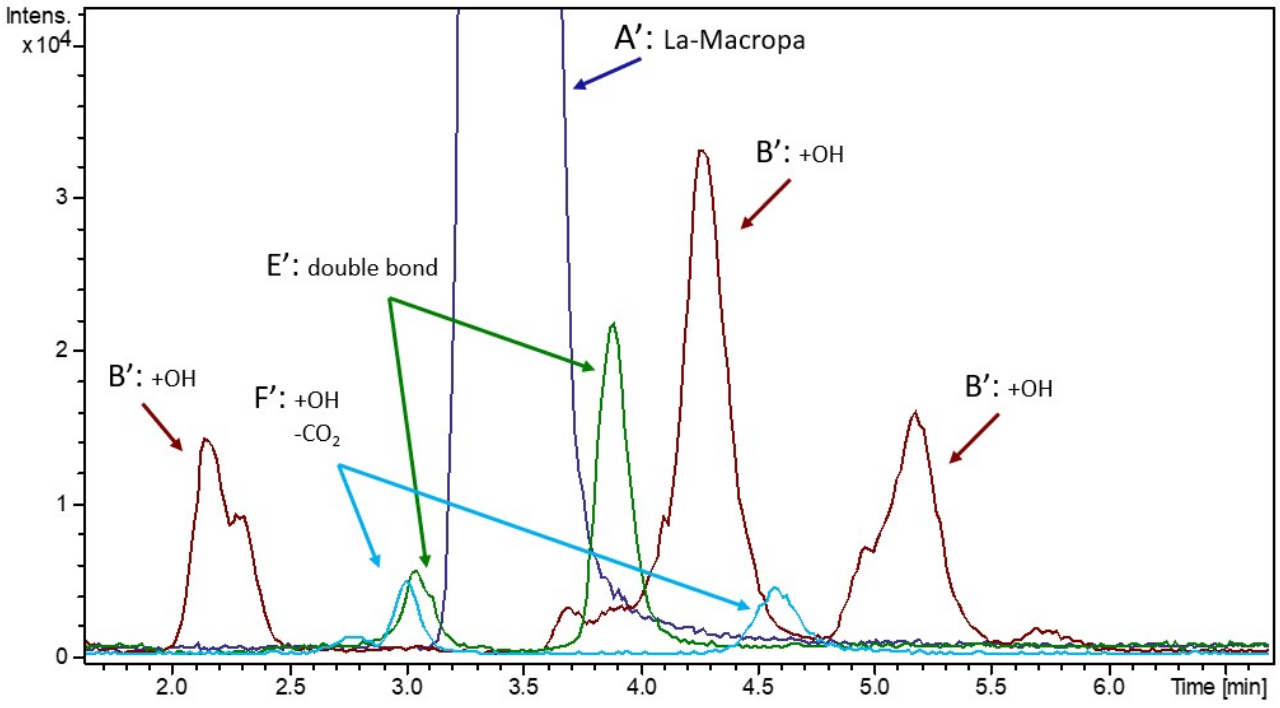


Figure S11. Extracted Ion Chromatogram of a La-Macropa sample irradiated at 10 kGy. Diluted 10-fold in 90/10 ACN/H_2O. Mobile phase: (Milli-Q water + 0.1% formic acid)/ACN 30:70 v/v at 200 µL/min. HILIC mode with a mixed Poroshell 120 column (amphoteric properties), 2.1 × 150 mm in length and 2.7 µm pore size.

3. ESI-MS analysis of Macropa and Ln-Macropa system by ESI-MS

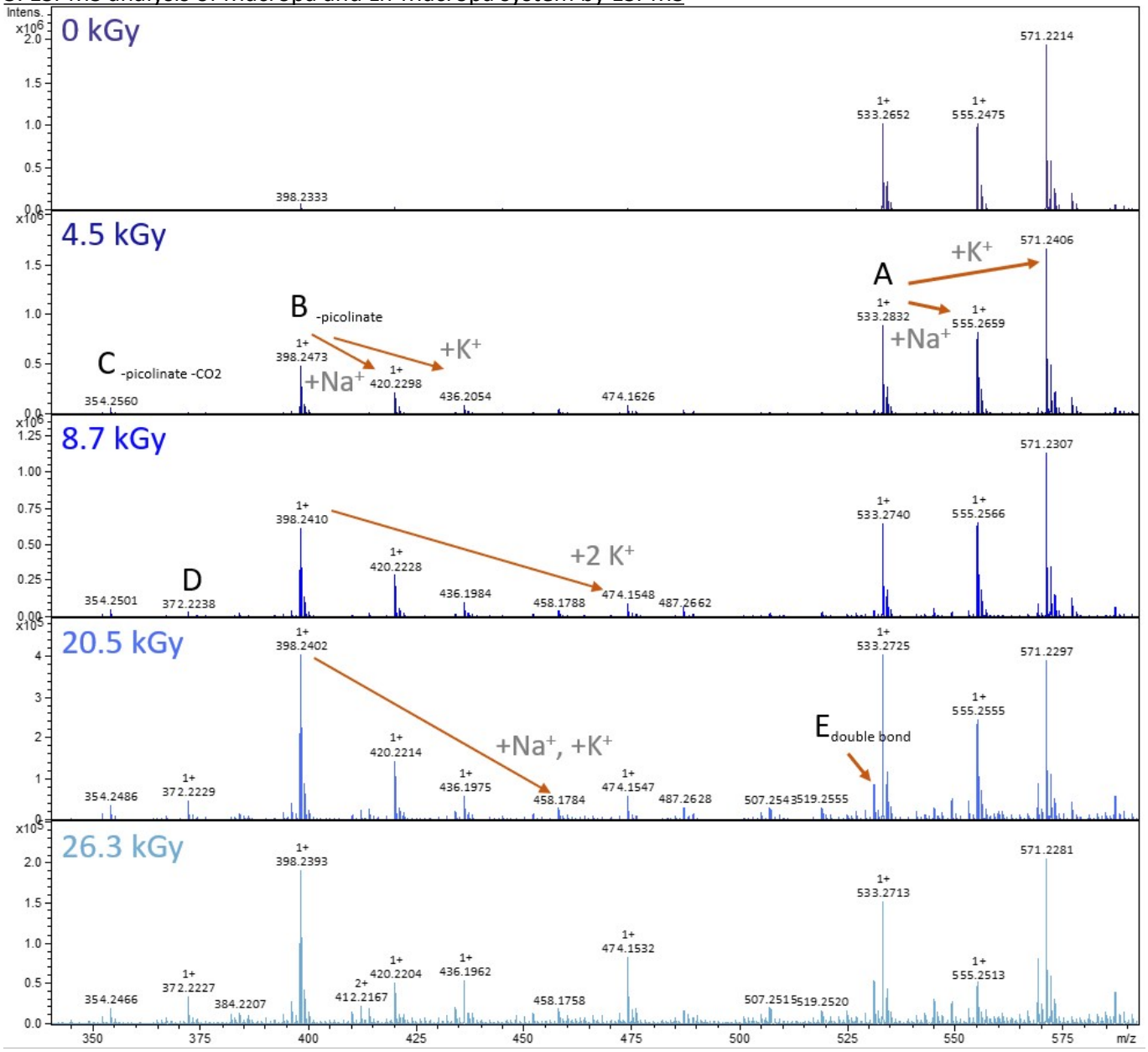


Figure S12. ESI-MS spectra of 5mM γ-irradiated Macropa samples from 0 to 26.3 kGy diluted 20 times in water.

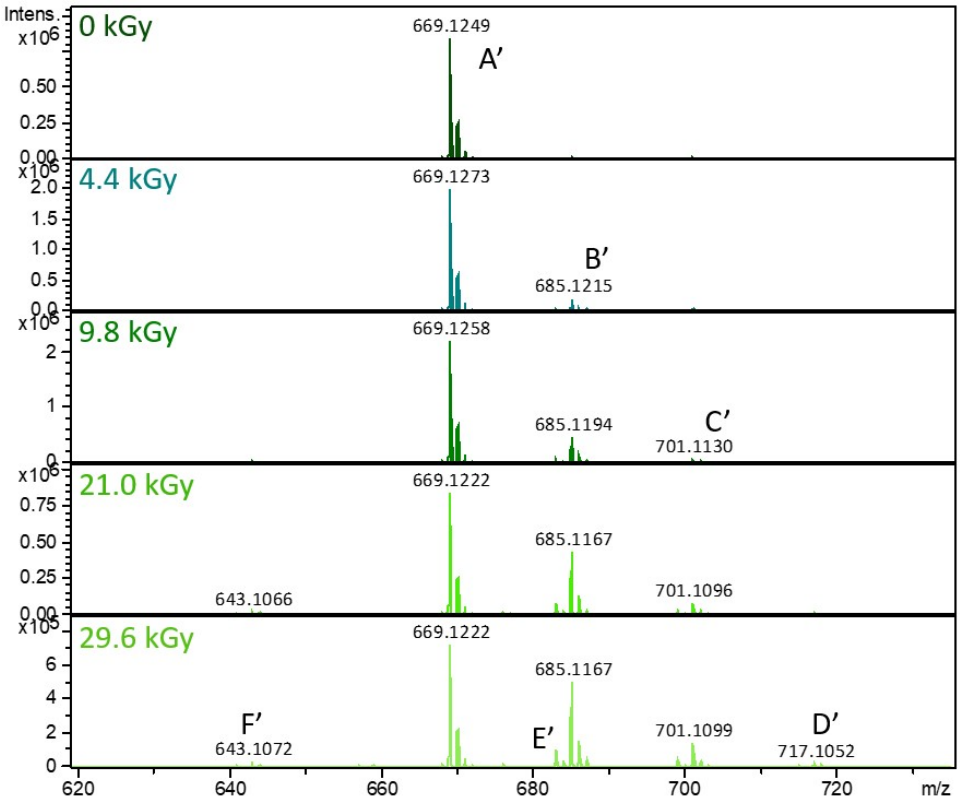


Figure S13. ESI-MS spectra of 5mM γ-irradiated La-Macropa samples from 0 to 29.6 kGy diluted 20 times in water.

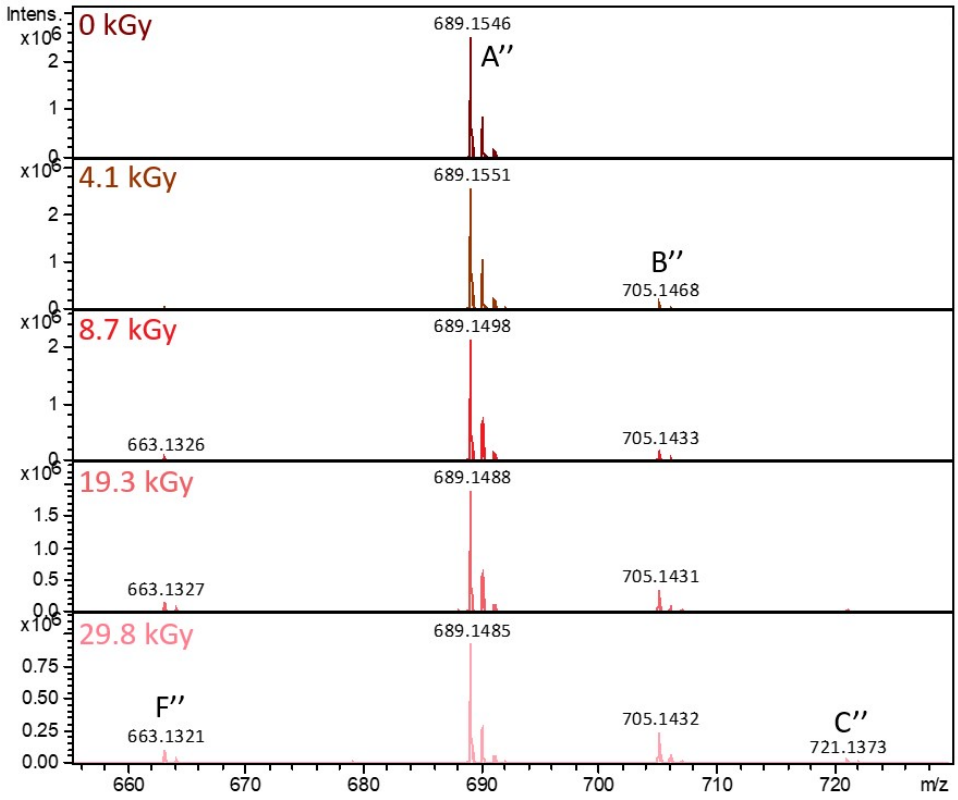


Figure S14. ESI-MS spectra of 5mM γ-irradiated Tb-Macropa samples from 0 to 29.8 kGy diluted 20 times in water.

4. Quantification of Macropa system by ^{1}H NMR

Based on integration on the NMR signals, we quantified the degradation of Macropa system. NMR signal n°4 overlaps with water signal and couldn't be integrated.

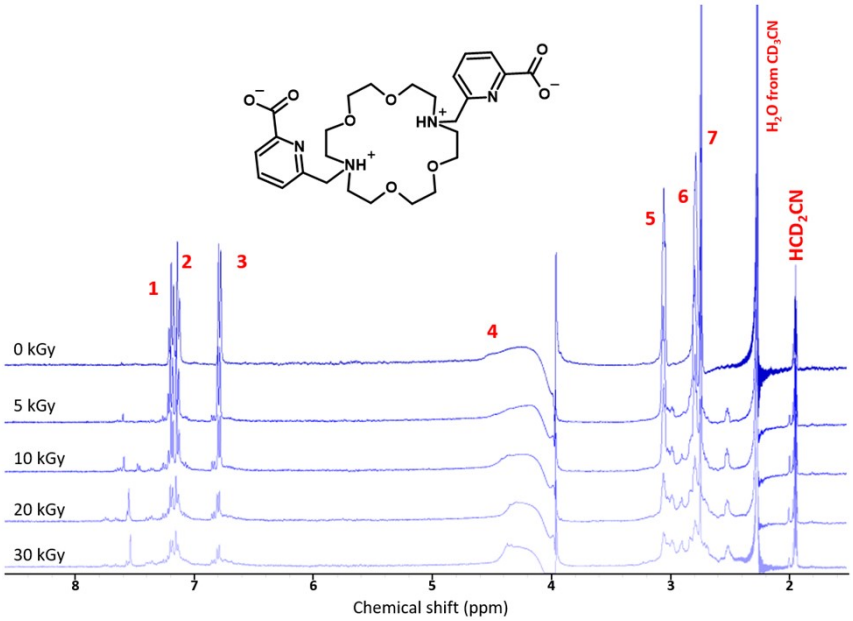


Figure S15. ^{1}H NMR spectra of non-irradiated and irradiated Macropa solutions. Conditions: 5 mM in pure water (pH = 5.2), 25°C. CD_3CN is used as external lock solvent and residual undeuterated signal to normalize spectra. From top to bottom: 0 kGy, 4.5 kGy, 8.7 kGy, 20.5 kGy, 26.7 kGy.

Signals	*% 0kGy*	*% 4.5kGy*	*% 8.7kGy*	*% 20.5kGy*	*% 26.3kGy*
1	100	78.5	65.8	47.0	37.3
2	100	68.1	60.2	37.2	28.8
3	100	67.0	50.4	25.3	17.5
5	100	71.6	56.4	35.2	25.6
6/7	100	74.1	59.4	36.1	26.1
Average	100	71.9	58.5	36.2	27.1
Standard deviation	-	4.2	5.0	6.9	6.4
uncertainty	-	8.3	10.1	13.8	12.8
Concentration (mM)	5.69	4.09	3.33	2.06	1.54
Ln(C/C$_o$)	0	-0.14	-0.23	-0.44	-0.57

Figure S16. Integration values for Macropa pH 5.2 quantification by NMR.

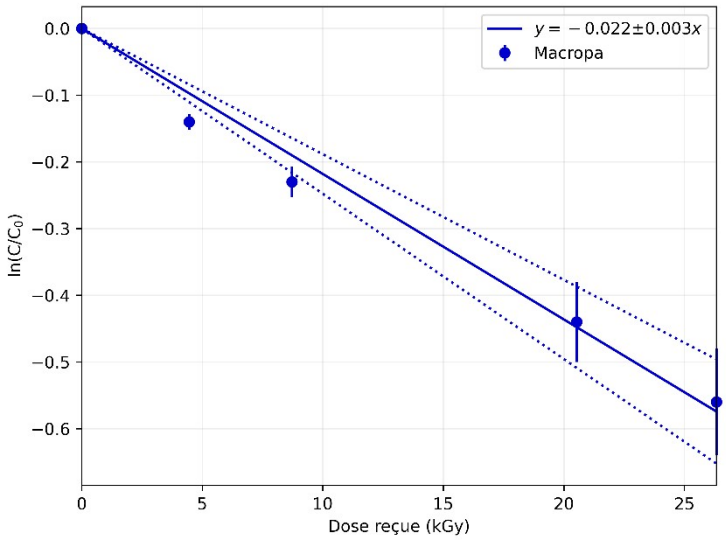


Figure S17. Determination of the dose constant for Macropa pH 5.2 by plotting ln(C/C0) as a function of dose.

Based on the dose constant *d* with a value of (-0.022 ± 0.003) kGy^{-1}, the G_0 of degradation of Macropa was determinated at (1.25 ± 0.15).10^{-7} $mol.J^{-1}$.

5. Quantification of Tb-Macropa system by ^{1}H NMR

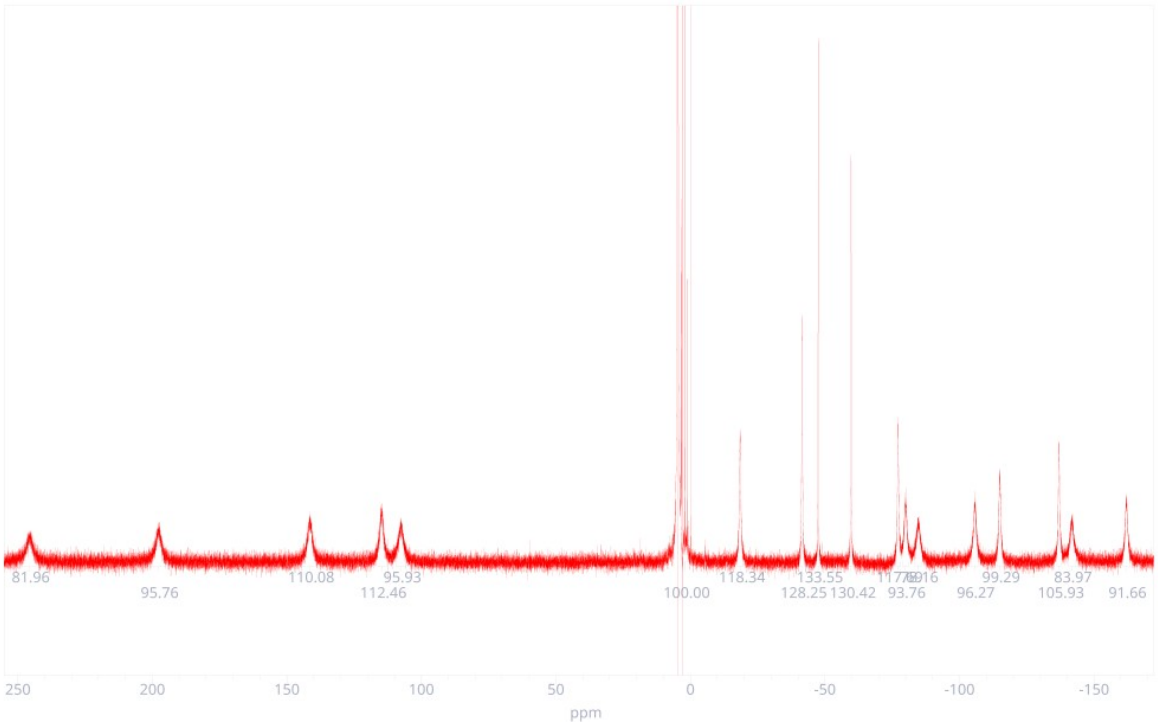


Figure S18. ^{1}H NMR spectra of non-irradiated Tb-Macropa solution. Conditions: 5 mM in pure water (pH = 6.2), 25°C. AcetoneD6 is used as external lock solvent and residual undeuterated signal to normalize spectra.

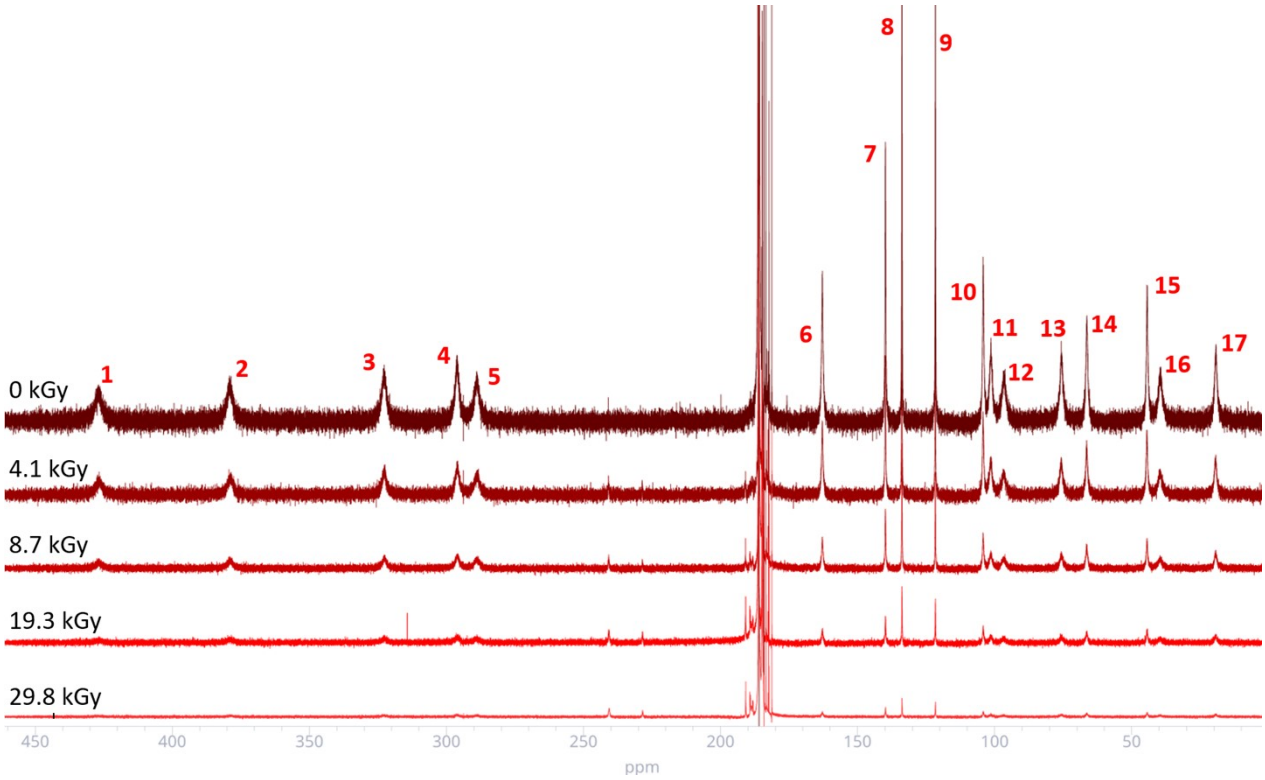


Figure S19. ^{1}H NMR spectra of non-irradiated and irradiated Tb-Macropa solutions. Conditions: 5 mM in pure water (pH = 6.2), 25°C. AcetoneD6 is used as external lock solvent and residual undeuterated signal to normalize spectra. From top to bottom: 0 kGy, 4 kGy, 9 kGy, 19 kGy, 30 kGy.

The main issue for Tb-Macropa quantification is the position of the reference signal. The AcetoneD6 signal appears around 2 ppm. In Tb-Macropa spectra, due to the presence of an apical H_2O molecule in the complex, the water signal around 4.5 ppm is broadened, which slightly elevates the baseline under the acetone reference. In addition, during irradiation, a progressive broadening of the water signal is observed. This effect may be attributed to the increasing number of water molecules able to coordinate to Tb as the complex undergoes degradation. Both of these factors could influence the integration value obtained at each dose, thereby altering the final G_0 value. Therefore, this value should be considered an estimate of the degradation rather than a reference value.

Signals	*% 0kGy*	*% 4.1kGy*	*% 8.7kGy*	*% 19.3kGy*	*% 29.8kGy*
1	100	67.3	47.9	11.3	-0.2
2	100	65.9	51.8	5.4	2.2
3	100	69.7	48.5	1.8	7.5
4	100	71.7	54.9	9.8	11.1
5	100	70.1	53.2	9.5	8.8
6	100	70.4	50.8	14.8	3.9
7	100	70.8	51.9	18.2	9.0
8	100	73.5	53.8	23.7	13.4
9	100	72.0	52.1	19.2	10.9
10	100	72.8	52.0	18.3	8.1
11	100	71.7	52.7	11.4	6.3
12	100	71.1	53.6	10.5	5.1
13	100	71.4	51.0	12.4	7.8
14	100	71.7	53.1	13.8	9.9
15	100	70.4	51.1	15.9	9.9
16	100	67.0	49.3	2.8	4.3
17	100	72.5	52.8	9.1	8.2
Average	100	70.6	51.8	12.2	7.4
Standard deviation	-	2.0	1.8	5.7	5.0
uncertainty	-	4.07	3.67	11.3	10.0
Concentration (mM)	4.94	3.49	2.56	0.60	0.37
Ln(C/C$_o$)	-	-0.15	-0.29	-0.91	-1.13

Figure S20. Integration values for Tb-Macropa quantification by NMR.

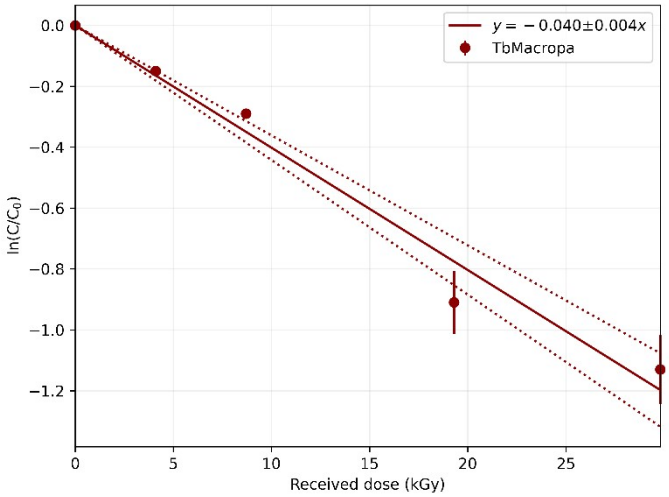


Figure S21. Quantification of Tb Macropa radiolysis by ^{1}H NMR.

Based on the dose constant *d* with a value of (-0.040 ± 0.004) kGy^{-1}, the G_0 of degradation of Tb-Macropa was determinated at (1.98 ± 0.20).10^{-7} mol.J^{-1}.

6. Quantification of La-Macropa system by ^{1}H NMR

LaMacropa pH 6.0:

Only NMR signals n°1,2,3,15,16 and 17 were integrated. Others were too close to water signals or superimposed with degradation products that form with received dose.

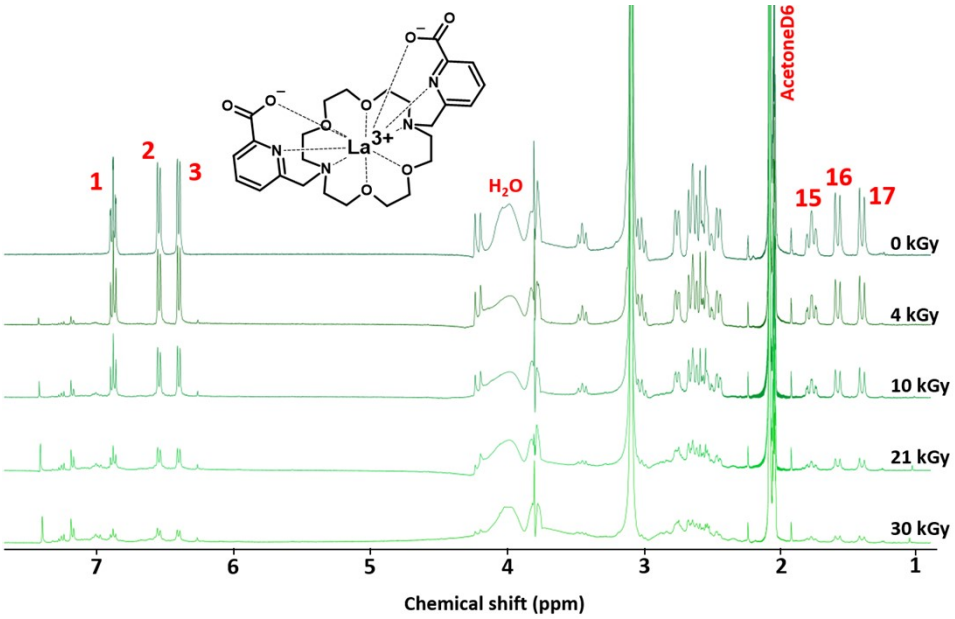


Figure S22. ^{1}H NMR spectra of non-irradiated and irradiated La-Macropa solutions. Conditions: 5 mM in pure water (pH = 6.0), 25°C. AcetoneD6 is used as external lock solvent and residual undeuterated signal to normalize spectra. From top to bottom: 0 kGy, 4.4 kGy, 9.8 kGy, 21.0 kGy, 29.6 kGy.

Signals	*% 0kGy*	*% 4.4kGy*	*% 9.8kGy*	*% 21.0kGy*	*% 29.6kGy*
1	100	96.3	77.5	45.9	30.9
2	100	95.1	77.3	47.6	34.4
3	100	91.3	72.2	39.9	26.2
15	100	96.9	74.5	59.2	48.8
16	100	92.3	70.2	47.2	35.8
17	100	92.1	69.6	43.1	30.7
Average	100	94.0	73.6	47.2	34.5
Standard deviation	-	2.2	3.1	6.0	7.1
uncertainty	-	4.36	6.29	12.01	14.21
Concentration (mM)	5.06	4.76	3.72	2.39	1.74
Ln(C/C$_o$)	-	-0.03	-0.13	-0.33	-0.46

Figure S23. Integration values for La-Macropa pH 6.0 quantification by NMR.

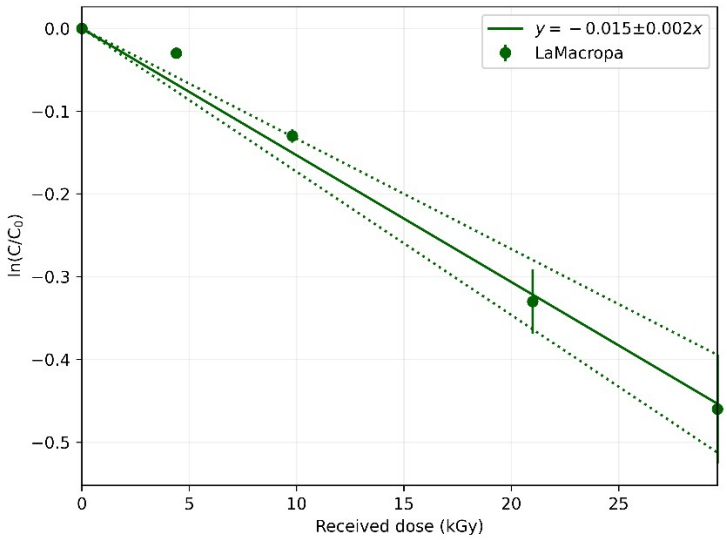


Figure S24. Determination of the dose constant for La-Macropa pH 6.0 by plotting ln(C/C0) as a function of dose.

Based on the dose constant *d* with a value of (-0.015 ± 0.002) kGy^{-1}, the G_0 of degradation of La-Macropa was determinated at (0.76 ± 0.10).10^{-7} $mol.J^{-1}$.

7. Fukui indices f^0 for atoms of Macropa and La-Macropa

Atom	f^0	*position*
C_1	0.057	*Crown*
C_9	0.029	*Picolinate arm*
C_8	0.028	
C_2	0.028	*Crown*
N_a	0.014	*Picolinate arm*
N_b	0.006	*Crown*
C_{11}	0.006	
C_{10}	0.006	*Picolinate arm*
C_7	0.005	
C_5	0.003	*Crown*
C_{12}	0.003	*Picolinate arm*
C_{13}	0.001	
C_6	-0.001	
C_3	-0.002	*Crown*
C_4	-0.004	

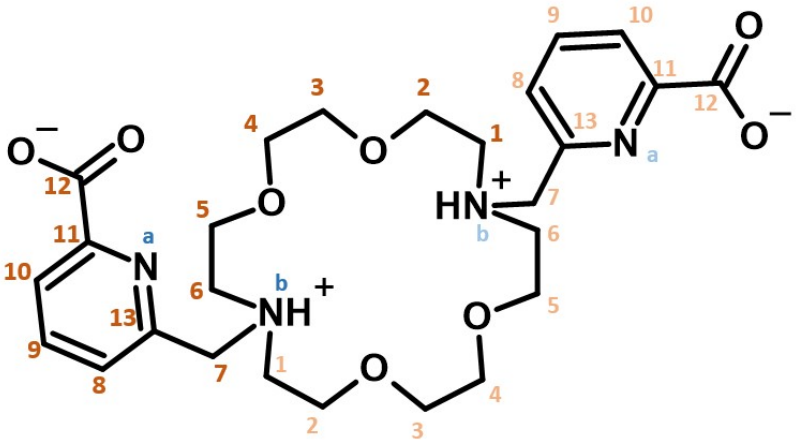


Figure S25. Fukui indices f^0 for C atoms of Macropa.

Atom	f^0	*position*
N_b	0.133	*Crown*
C_{15}	0.110	*Picolinate arm*
N_a	0.079	
C_{18}	0.047	
C_{16}	0.037	
C_{17}	0.034	
C_{14}	0.010	
N_c	0.010	*Crown*
C_{11}	0.003	*Crown*
C_1	0.003	
C_{13}	$1.5e^{-5}$	*Picolinate arm*
C_3	-0.004	*Crown*
C_{10}	-0.005	
C_2	-0.006	
C_{12}	-0.006	
C_5	-0.007	
C_4	-0.007	
C_8	-0.008	
C_9	-0.009	
C_7	-0.021	
C_6	-0.022	

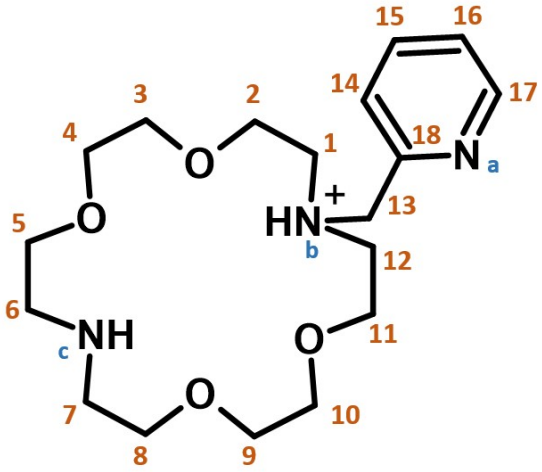


Figure S26. Fukui indices f^0 for C atoms of Species C.

Atom	f^0	*position*
C_9	0.051	*Picolinate arm*
N_a	0.041	
C_8	0.028	
C_{11}	0.022	
N_b	0.020	
C_{13}	0.013	
C_{12}	0.007	
C_{10}	0.005	
C_5	-0.001	*Crown*
C_3	-0.002	
C_1	-0.004	
C_4	-0.005	
C_2	-0.005	
C_7	-0.006	*Picolinate arm*
C_6	-0.009	*Crown*

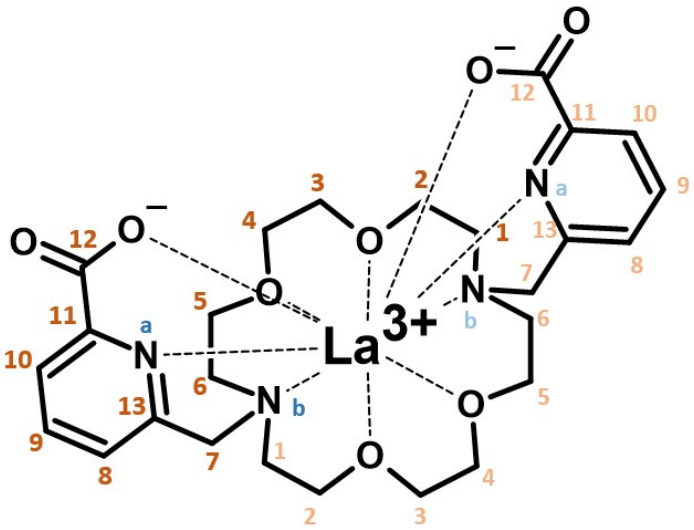


Figure S27. Fukui indices f^0 for C atoms of La-Macropa complex.

Atom	f^0	*position*
N_b	0.023	*Crown*
C_9	0.021	*Picolinate arm*
N_c	0.021	*Crown*
C_{22}	0.010	*Picolinate arm*
C_{23}	0.008	
C_{24}	0.007	
N_d	0.006	
C_{12}	0.005	
C_{10}	0.004	
C_{13}	0.004	
C_{26}	0.004	
C_{21}	0.001	

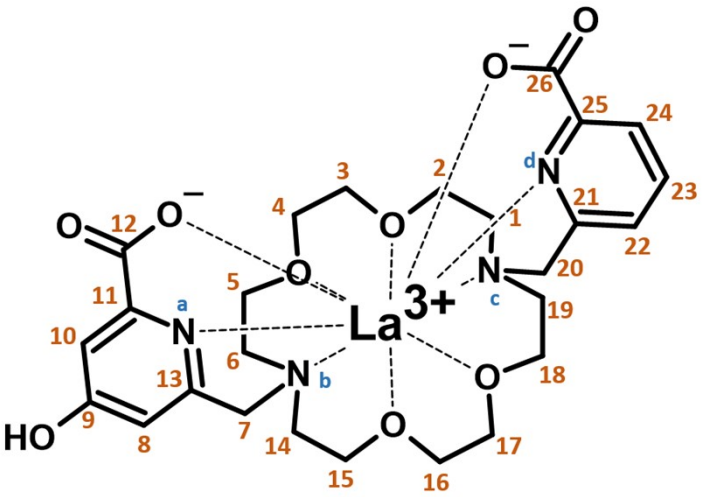


Figure S28. Fukui indices (f^0>0.001) for C atoms of La-Macropa+OH complex.

Atom	f^0	*position*
C_{23}	0.057	
C_{21}	0.053	
N_d	0.048	
C_{25}	0.046	
C_9	0.034	
C_8	0.029	
N_a	0.028	*Picolinate arm*
C_{22}	0.027	
C_{11}	0.018	
C_{24}	0.013	
C_{12}	0.009	
C_{13}	0.008	
C_{10}	0.007	
N_b	0.006	*Crown*

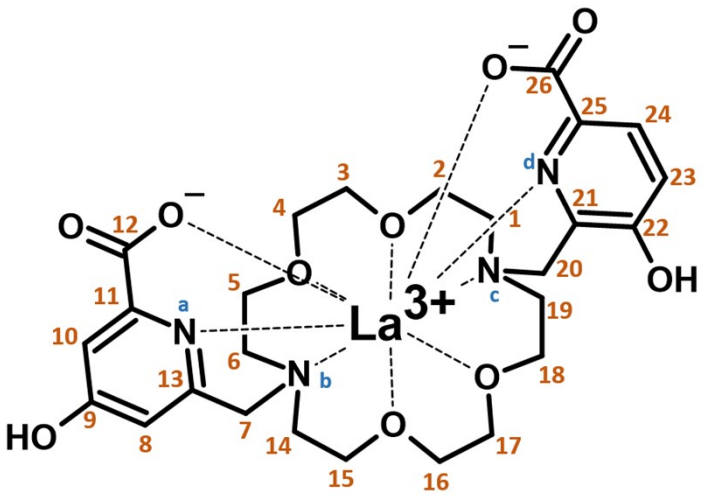


Figure S29. Fukui indices (f^0>0.001) for C atoms of La-Macropa+2 OH complex.

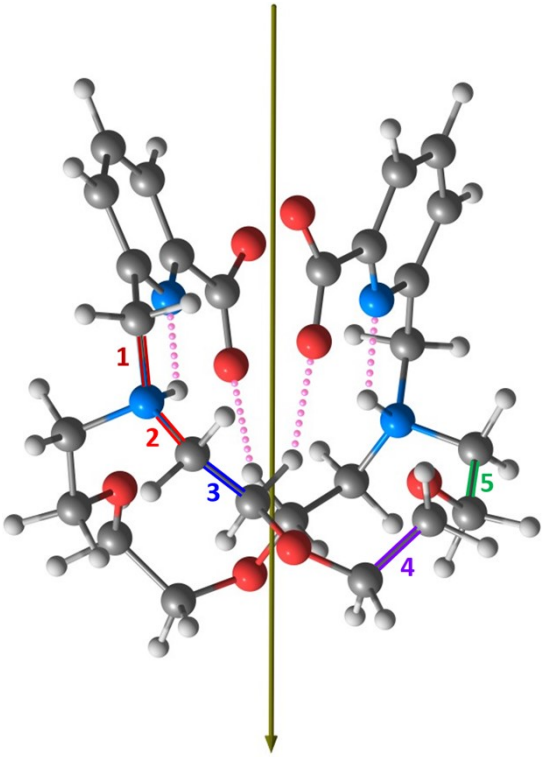


Figure S30. Optimized structure of Macropa. Bonds 3 and 5 are not equivalent because of the C_2 symmetry of the system.