

Supporting Information

Table of contents

Figure S1. Al- ¹⁸ F-NODA-MP-C4 radiochemical conversion as function of reaction time	2
Figure S2. Al- ¹⁸ F-NODA-MP-C4 radiochemical conversion as percentage of ethanol	2
Table S1. Estimated coefficients for the mathematical model and corresponding statistical values	3
Figure S3. ¹ H and ¹³ C{ ¹ H} NMR of NODA-MP-C4 (di-Na form) in D ₂ O	4
Figure S4. ¹ H and ¹³ C{ ¹ H} NMR of NODA-MP-C4 (di-Na form) in DMSO- <i>d</i> ₆	5
Figure S5. ¹⁹ F{ ¹ H} NMR of Al-F-NODA-MP-C4 in D ₂ O and in DMSO- <i>d</i> ₆	6
Figure S6. ¹ H and ¹³ C{ ¹ H} NMR of Al-OH-NODA-MP-C4 in DMSO- <i>d</i> ₆	7
Figure S7. ¹⁹ F{ ¹ H} NMR of Al-F-NODA-MP(O)-C4 in D ₂ O and in DMSO- <i>d</i> ₆	8
Figure S8. RP-HPLC chromatograms of the free chelators NODA-MP(O)-C4 and NODA-MP(O)-C4 and of their Al(III) complexes	9
Experimental section	10
Syntheses of NODA chelating agent and of Al-F-NODA complex.....	11
Syntheses of NODA-MP-NH₂ chelating agent and of Al-OH-NODA complex.....	12
Syntheses of NODA-MP-NHCSNH₂ chelating agent and of the corresponding Al(III) complexes.....	13
Figure S9. ¹ H NMR of NODA-MP-NH₂ in D ₂ O	14
Figure S10. ¹ H and ¹³ C{ ¹ H} NMR of NODA-MP-NHCSNH₂ in D ₂ O	15
Figure S11. ¹⁹ F{ ¹ H} NMR of Al-F-NODA in D ₂ O.....	16
References	16

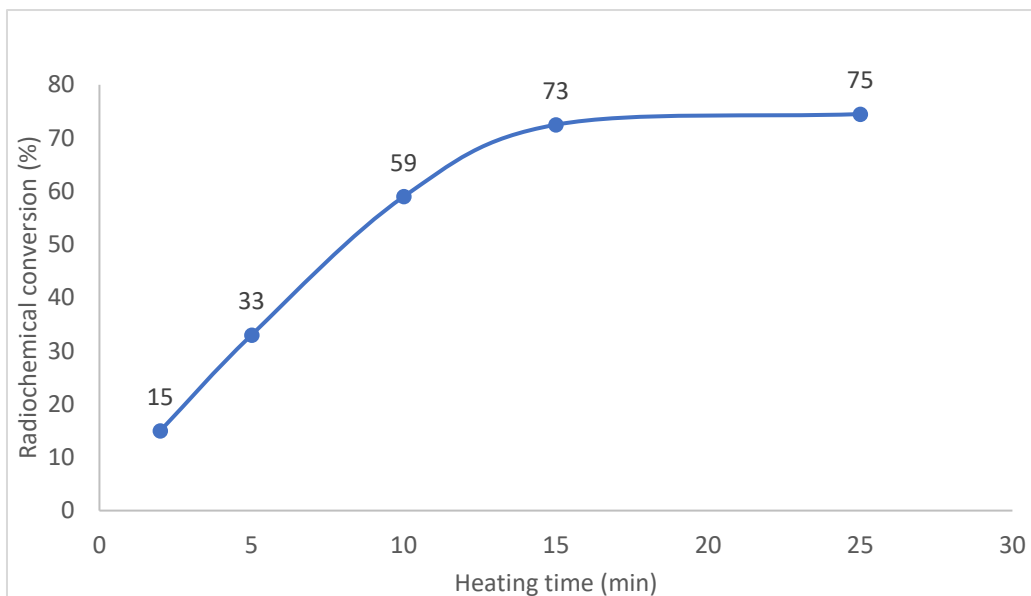


Figure S1. Al-¹⁸F-NODA-MP-C4 radiochemical conversion as function of reaction time. Radiolabeling conditions: 0.1M AcOH/Na buffer pH 4.0, [NODA-MP-C4] = 550 μM, NODA-MP-C4/Al ratio = 1/1, reflux, reaction time = 2, 5, 10, 15 and 25 min.

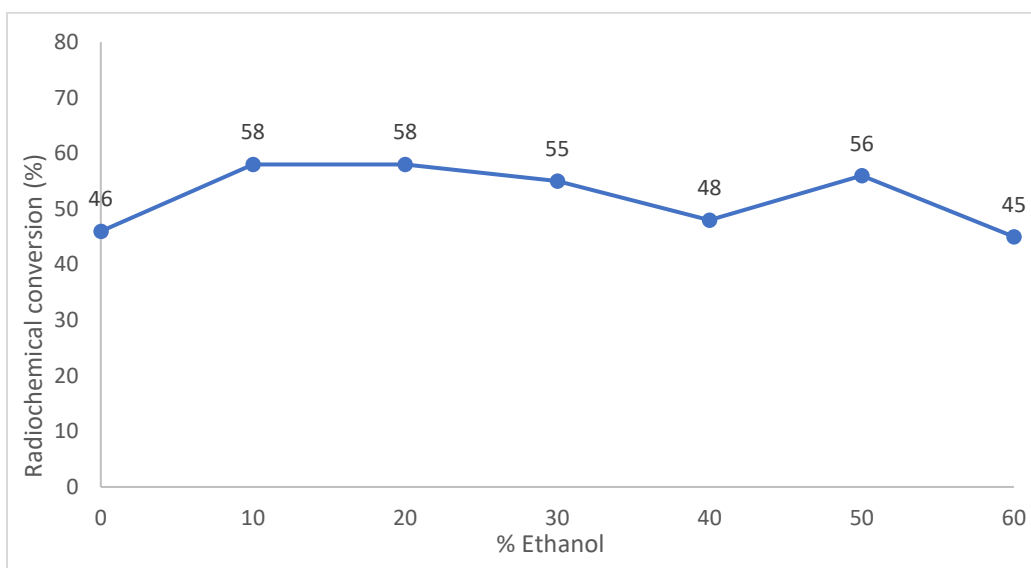


Figure S2. Al-¹⁸F-NODA-MP-C4 radiochemical conversion as percentage of ethanol. Radiolabeling conditions: 0.1M AcOH/Na buffer pH 4.0, [NODA-MP-C4] = 215 μM, NODA-MP-C4/Al ratio = 1/1, reflux, reaction time = 25 min, ethanol rate = 10, 20, 30, 40, 50 and 60 %.

Table S1. Estimated coefficients for the mathematical model and corresponding statistical values like square error, t-statistic and p-value.

	Estimated Coefficient	Square Error	t-statistic	p-value
Intercept	-3233.84	410.2	-7.883568991	3.51832E-09
NODA-MP-C4/Al ratio	-14.9918	3.1	-4.836064516	2.79932E-05
[NODA-MP-C4]	0.331589	0.0517	6.413713733	2.51241E-07
<i>pH</i>	1446.88	182.2	7.941163557	2.9899E-09
[NODA-MP-C4] ²	-0.00036138	8.29E-05	-4.360769881	0.000113853
<i>pH</i> ²	-160.413	20.24	-7.925543478	3.1247E-09

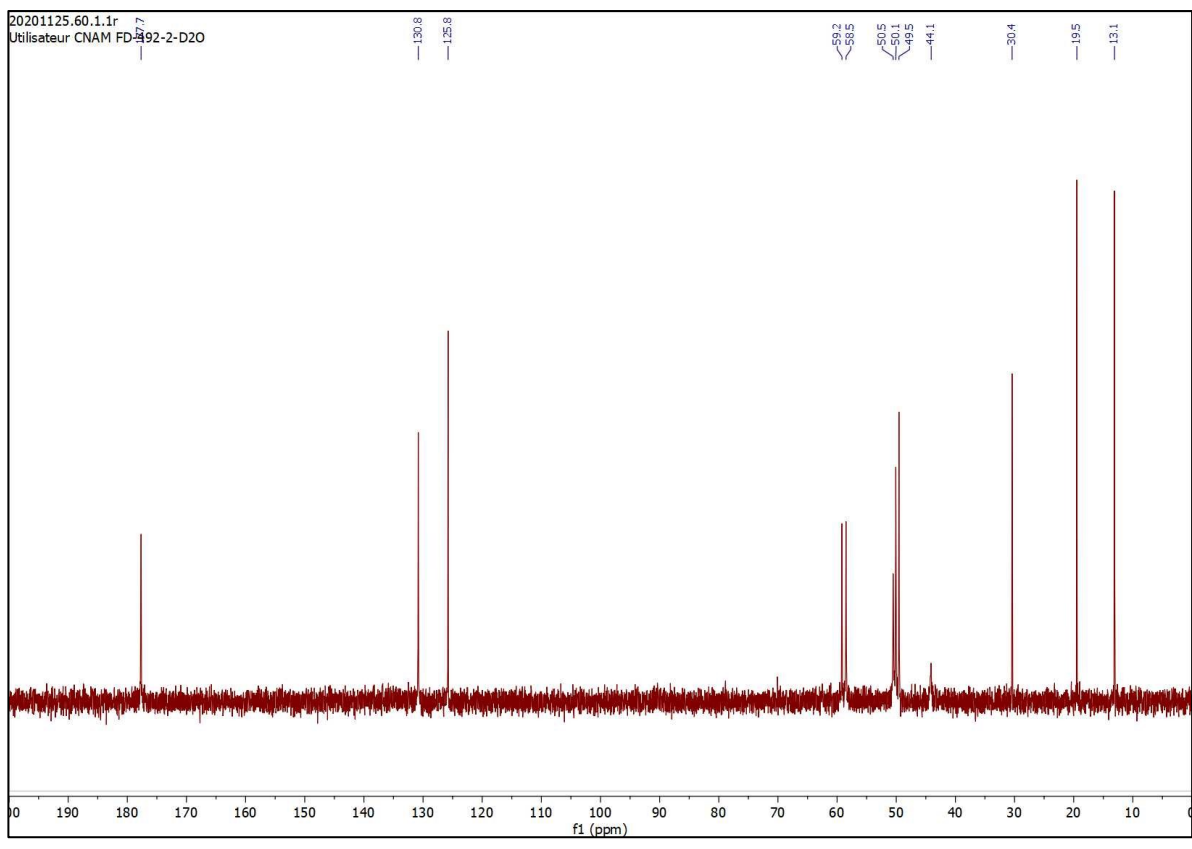
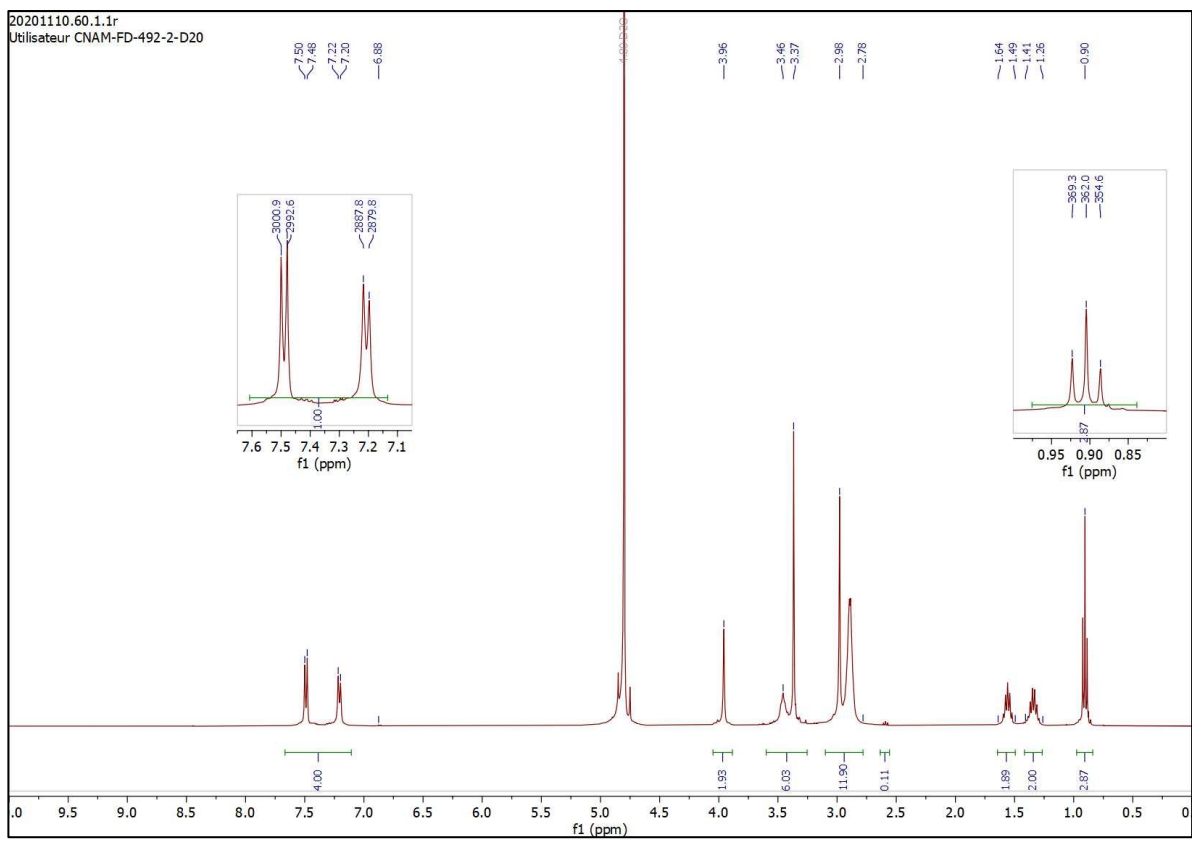


Figure S3. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR of **NODA-MP-C4 (di-Na form)** in D_2O (pH 12); for ^1H : $c \approx 26$ mM; for $^{13}\text{C}\{^1\text{H}\}$: $c \approx 79$ mM.

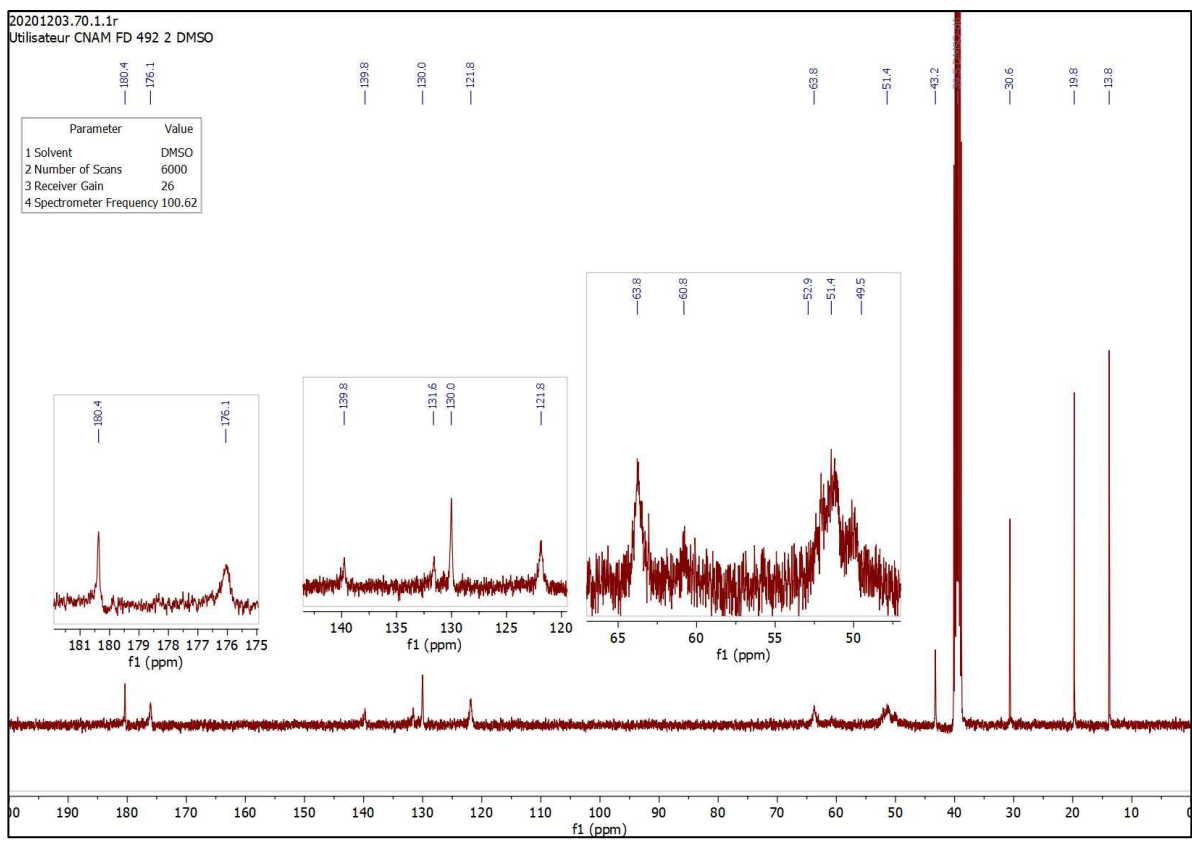
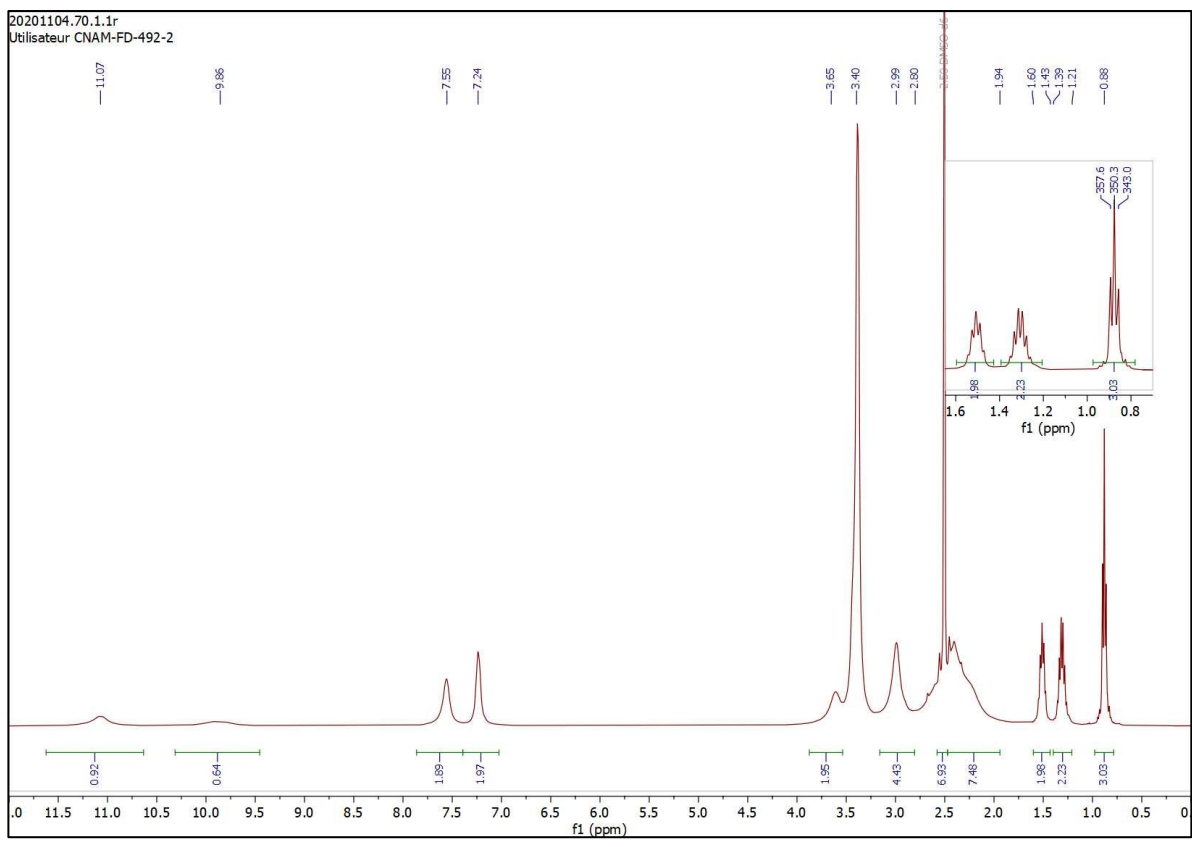


Figure S4. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR of NODA-MP-C4 (di-Na form) in DMSO- d_6 ; for ^1H : $c \approx 54$ mM; for $^{13}\text{C}\{^1\text{H}\}$: $c \approx 75$ mM, 6000 scans.

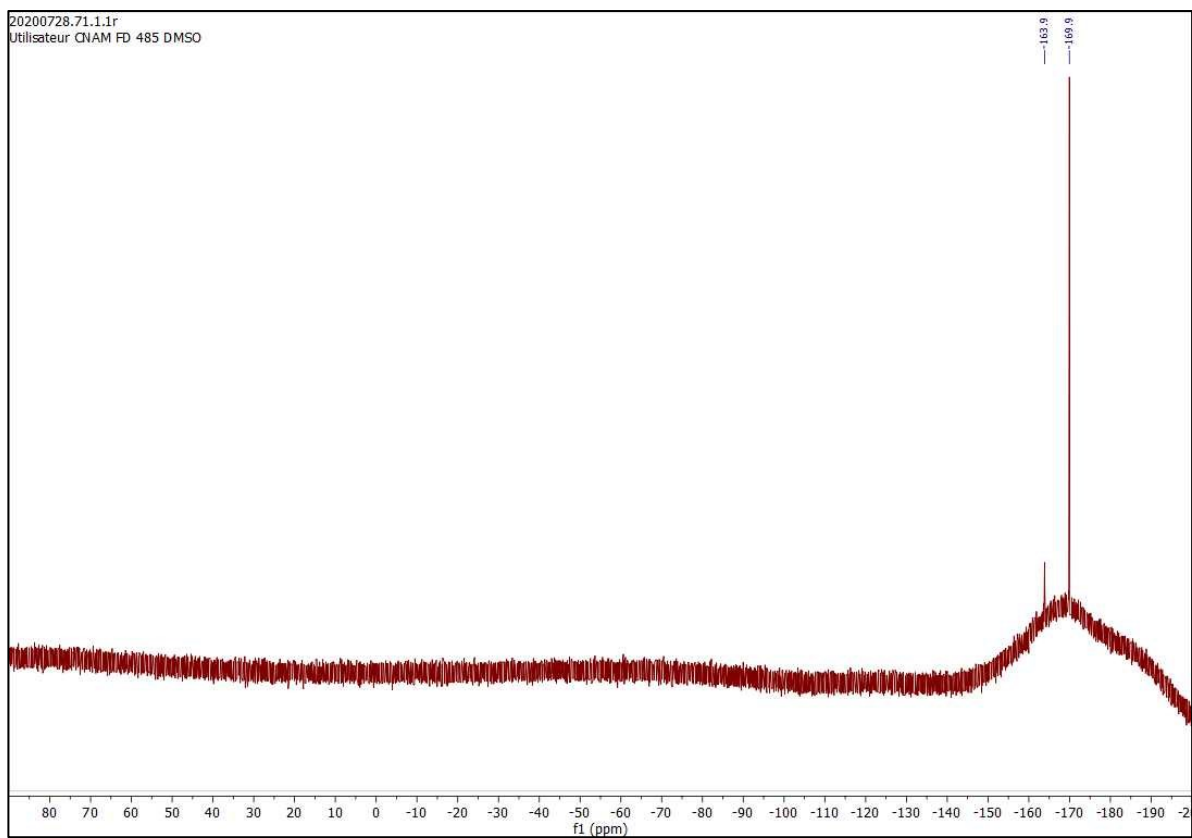
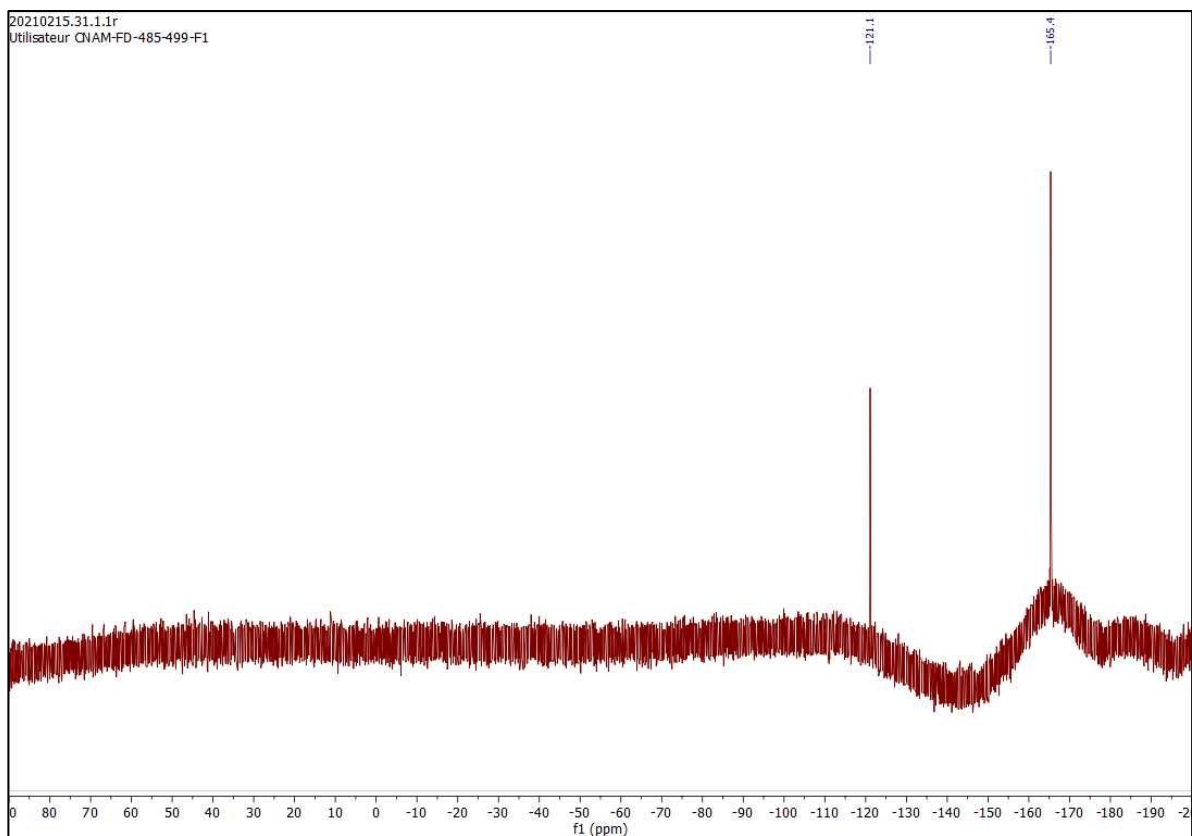


Figure S5. $^{19}\text{F}\{^1\text{H}\}$ NMR of **Al-F-NODA-MP-C4**, $c \approx 40$ mM: (*up*): in D_2O ($\text{pH } 4$, saturated solution: at such concentration, material not completely soluble in D_2O); (*down*): in $\text{DMSO-}d_6$.

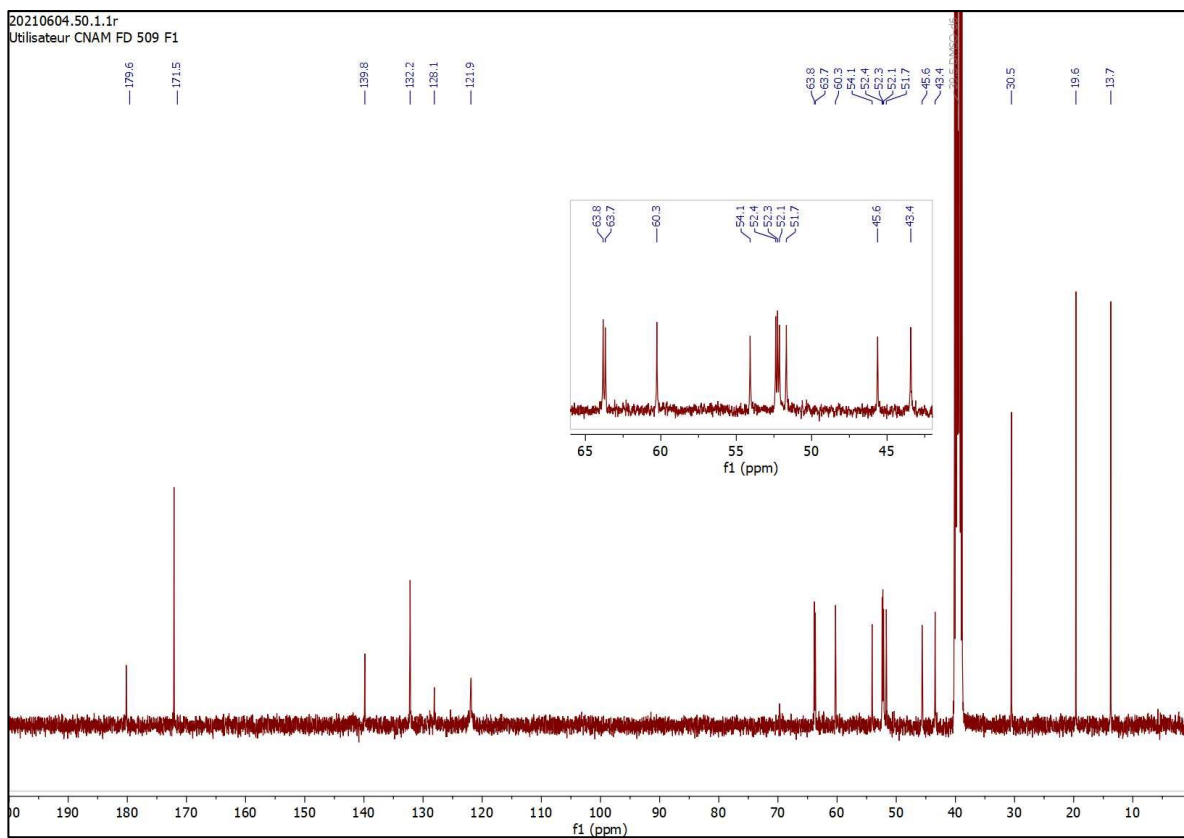
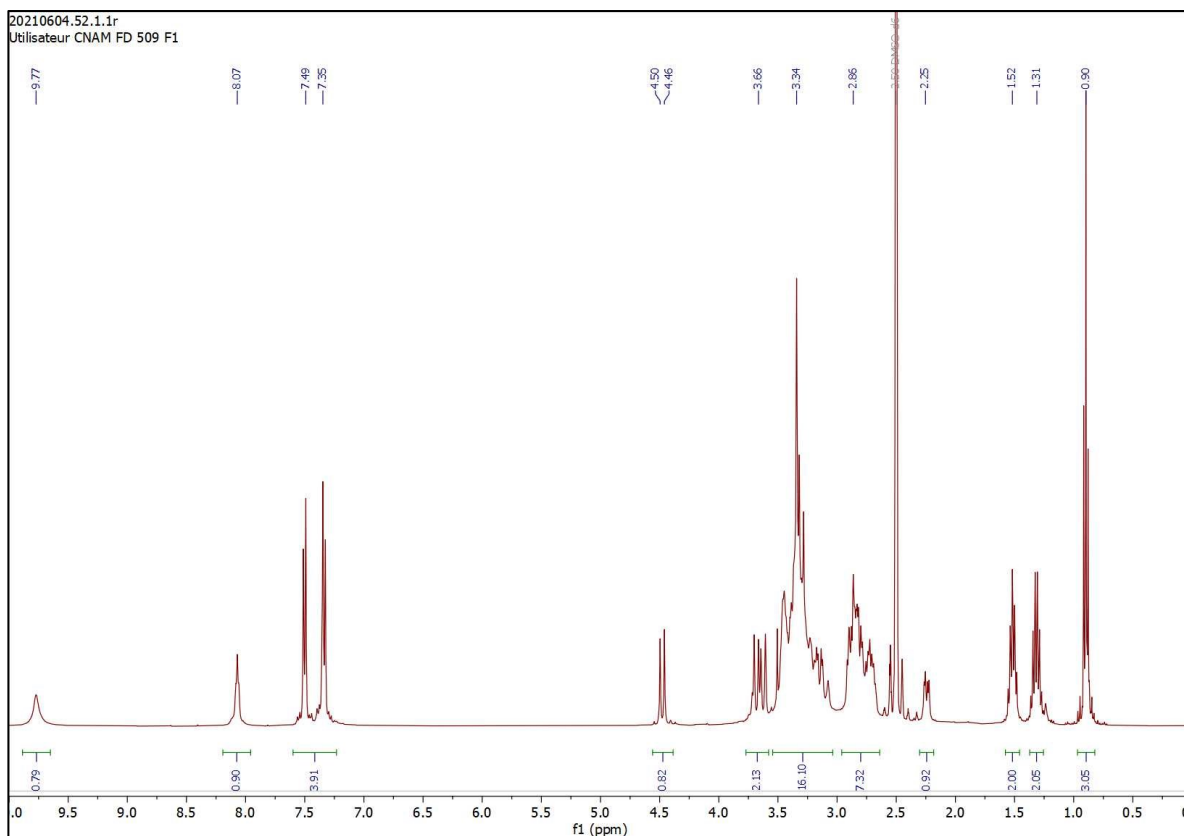


Figure S6. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR of Al-OH-NODA-MP-C4 in DMSO- d_6 , $c \approx 40$ mM. Note: at such concentration, material not completely soluble in D_2O .

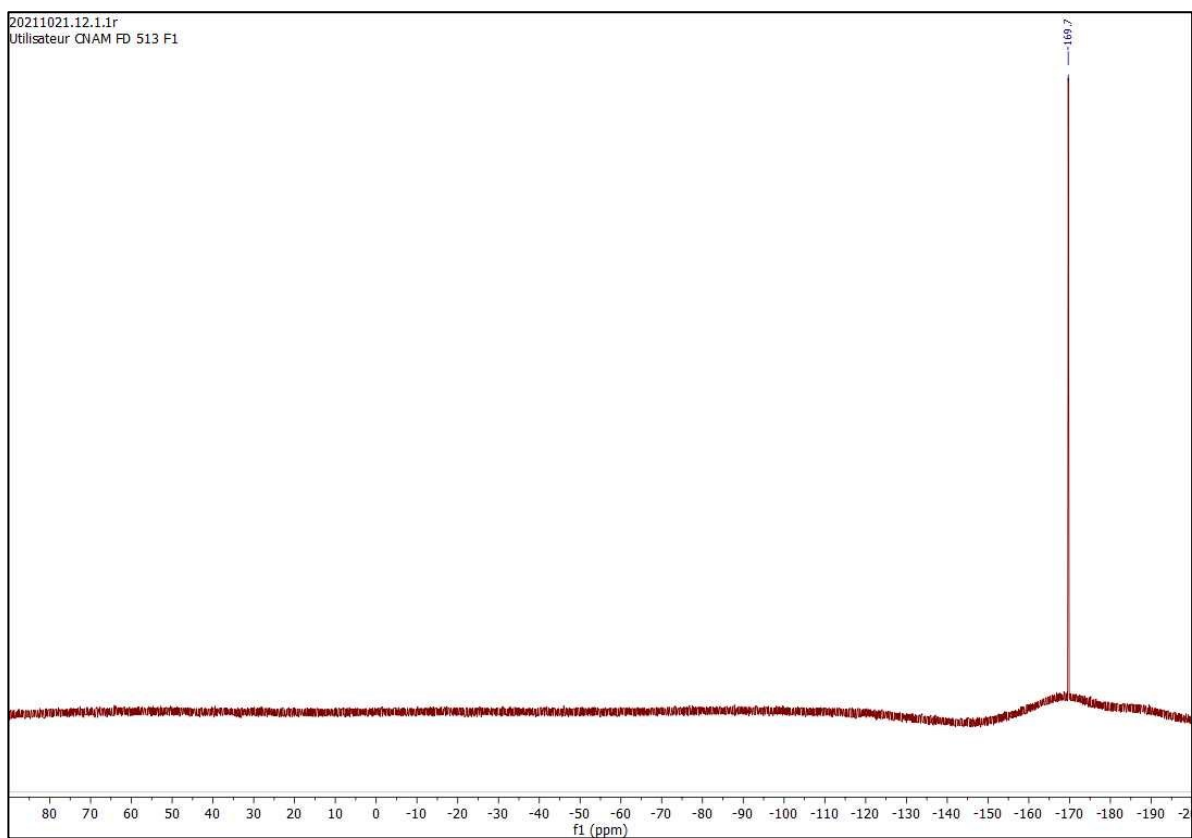
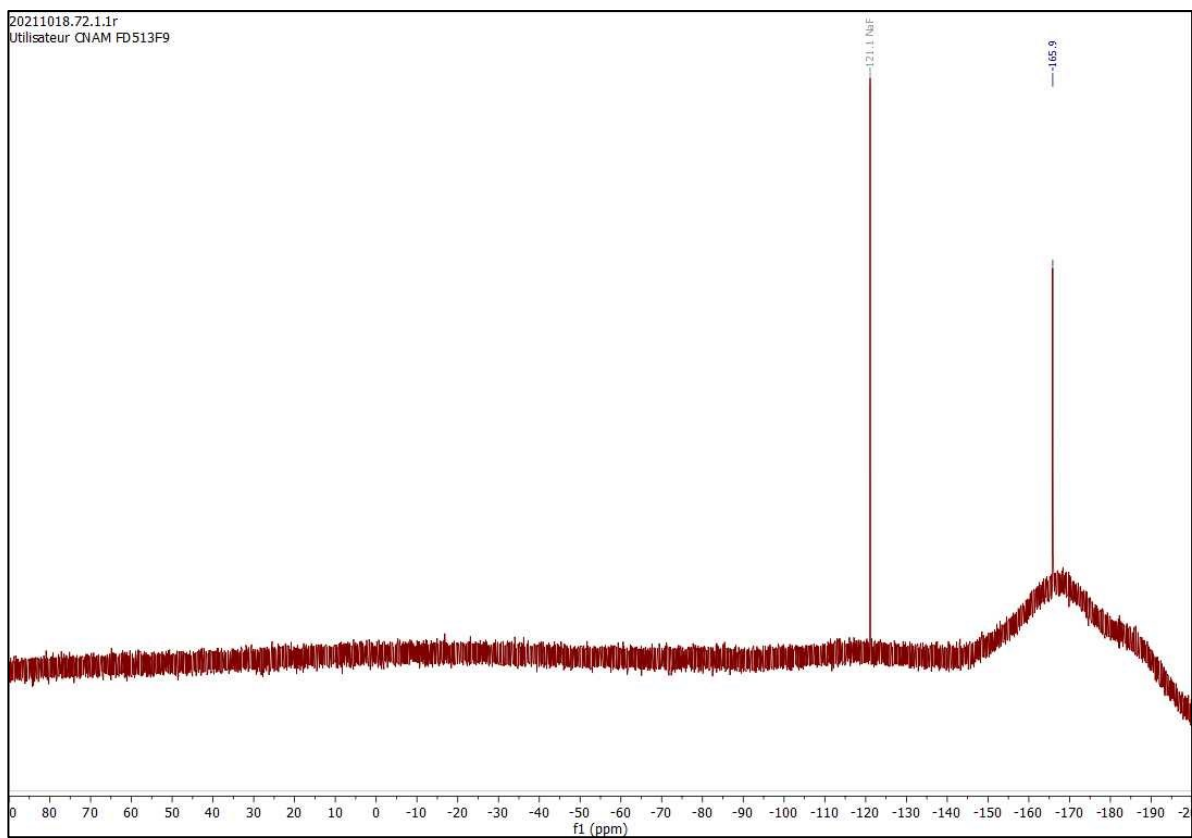


Figure S7. $^{19}\text{F}\{^1\text{H}\}$ NMR of Al-F-NODA-MP(O)-C4, $c \approx 25$ mM: (*up*) in D_2O (pH 6-7); (*down*) in DMSO-d_6 .

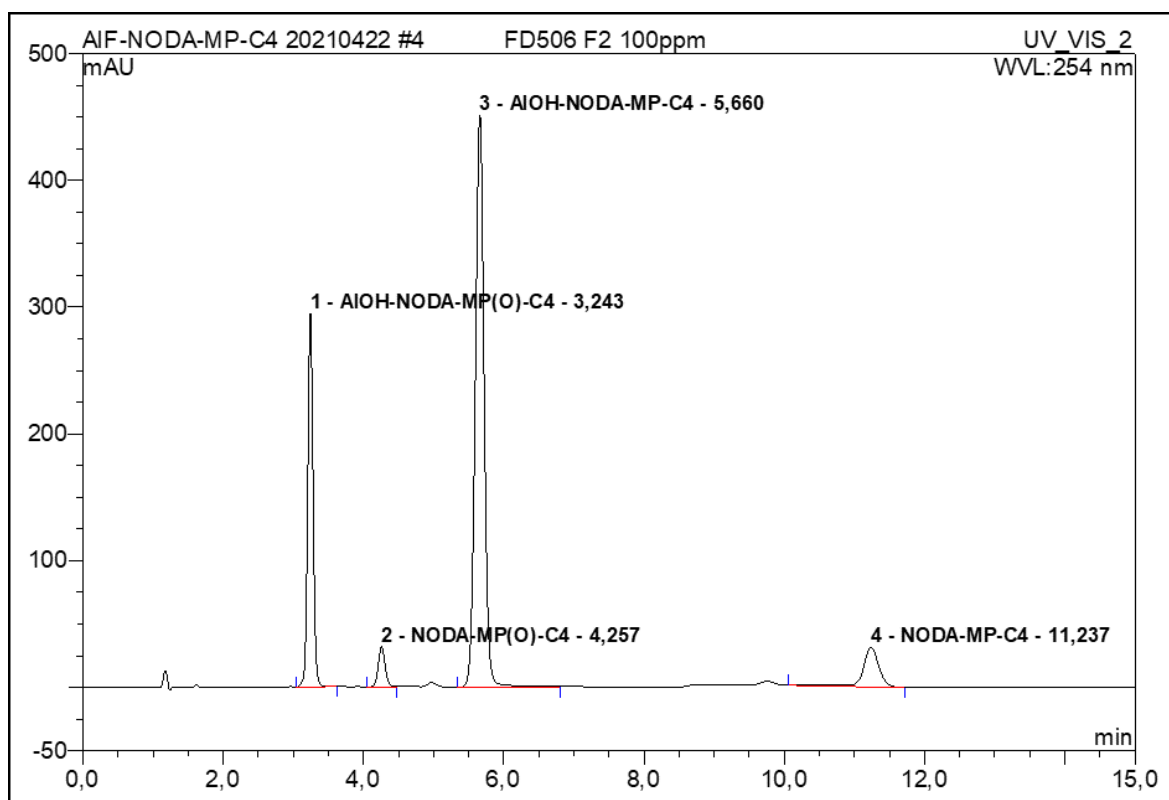
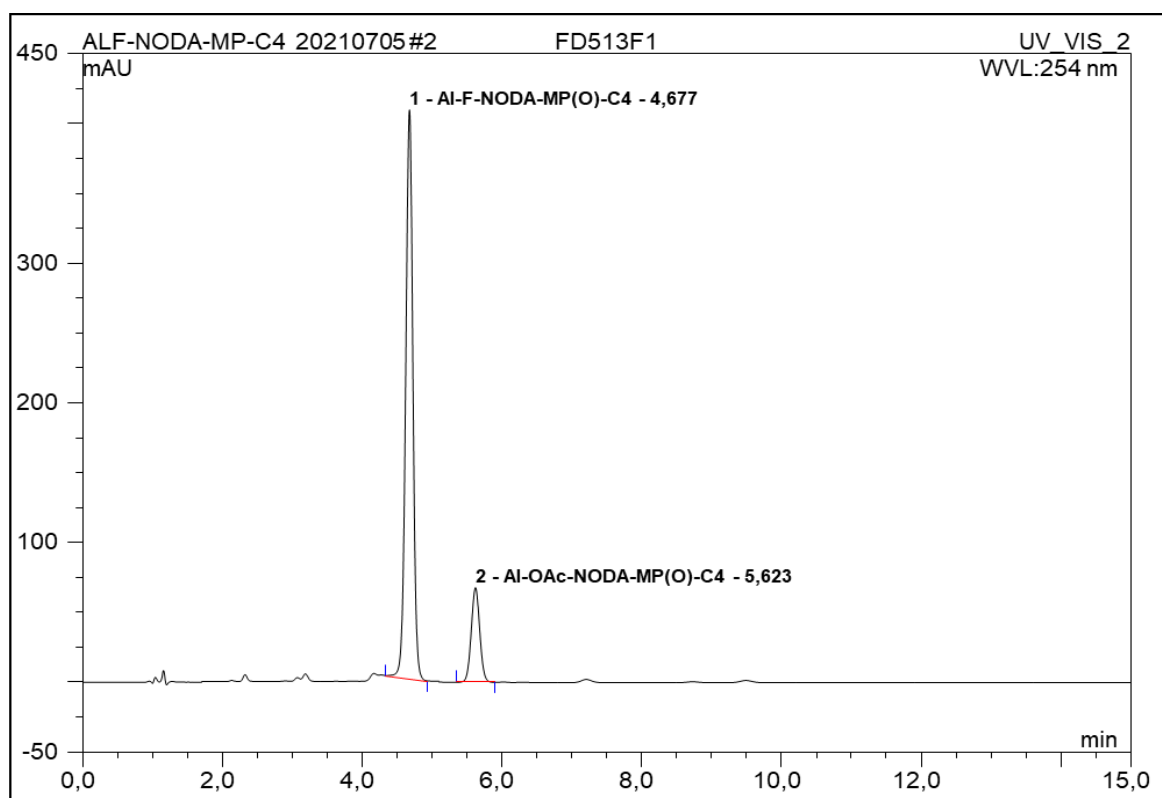


Figure S8. RP-HPLC chromatograms: (*up*): mixture of **Al-F-NODA-MP(O)-C4** and **Al-OAc-NODA-MP(O)-C4**; (*down*): mixture of **Al-OH-NODA-MP-C4** and **Al-OH-NODA-MP(O)-C4** together with the respective residual free chelators **NODA-MP-C4** and **NODA-MP(O)-C4**. Analytical conditions: column: Phenomenex Kinetex Evo C18 100 mm x 4.6 mm – 5 μ m; mobile phase: acetate buffer pH 4.5 / MeCN 85/15, isocratic mode, flow rate: 1 mL/min; detector: PDA (254 nm).

Experimental section

NCS-MP-NODA (CAS RN 1374994-81-6) and NO₂AtBu (CAS RN 174137-97-4) were purchased from Chematech (ref C110 and C065 respectively; formula C₁₈H₂₄N₄O₄S.H₂O and C₁₈H₃₅N₃O₄ respectively). Aluminum chloride hexahydrate (AlCl₃.6H₂O), sodium acetate and acetic acid were purchased from Sigma Aldrich. Free metals trace products were purchased, and synthesis were prepared in metal free containers to avoid metal contamination. Ultrapure H₂O (resistivity 18.2 MΩ.cm at 25 °C) was obtained from a water purification system.

Thin-layer chromatography (TLC) were performed on pre-coated aluminum sheets RP-18W / UV₂₅₄ (Macherey-Nagel, ref. 818146), and visualized under an UV lamp at 254 nm and/or developed with phosphomolybdic acid stain in ethanol.

Purifications on preparative RP-TLC glass plates were conducted on 20x20 cm RP-18 W UV254 glass plates coated with C18-modified silica layer purchased from Macherey-Nagel, (ref 811074). Desorption of the eluted compounds was obtained by washing the recovered silica band with a solution of H₂O/MeCN 1/1 v/v, concentration to dryness; the matter obtained was then taken up in pure water and the solution filtered through a PolyEtherSulfone (PES) membrane 0.22 μm (33 mm syringe filter unit, Millex[®]-GP, Merck, ref SLGP033RS).

Proton (¹H), carbon (¹³C) and fluorine (¹⁹F) NMR spectra were recorded at 400 MHz (¹H) on a Bruker spectrometer Avance 400. Carbon NMR (¹³C{¹H}) spectra were recorded using a broadband decoupled mode with the multiplicities obtained from a DEPT sequence. Chemical shifts (δ) are reported in parts per million (ppm) using the deuterated solvent signals as an internal reference: for D₂O: ¹H: 4.80 ppm. For ¹⁹F{¹H} NMR, NaF was used as internal reference: D₂O: -121.1 ppm.^[1] All spectra were recorded at 298 K. The following abbreviations are used for the proton spectra: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad. For some aromatic protons, second order systems can be observed. The ratio Δδ/J has been used to distinguish between systems AB or AX: if the ratio is less than 10, the spin system is designed « system AB », otherwise the spin system is designed « system AX ». Coupling constants (J) are reported in Hertz (Hz).

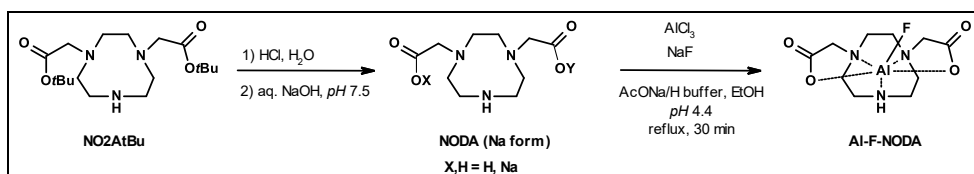
Mass spectroscopy analyses were performed using ElectroSpray Ionization in positive mode (ESI+).

Low-resolution mass spectroscopy analyses (LRMS) were done on an analytic system composed of an LC2030 injection system (Shimadzu) coupled to a Micromass ZQ2000 detector (Waters[®]). Injections were operated by flow injection mode (FIA) with mobile phase being a mixture of MeCN and water at a flow rate of 0.5 mL/min. Data were collected in the full scan mode at m/z 200–1500. Detection was done at a cone voltage (CV) giving the least amount of fragmentations (5 to 40 V); mobile phase and CV value are given for each compound.

High-resolution mass spectroscopy analyses (HRMS) were performed by direct sample introduction on a LTQ Orbitrap[®] XL High Definition mass spectrometer (Thermo Scientific[®]). Data were collected in the full scan mode at m/z 150–1000. The source parameters were as follows: ion spray voltage 4000 V, capillary voltage -35 V, capillary temperature 275 °C, sheath gas flow 10 (a.u.). Data were acquired in high-resolution mode (100,000 FWHM a m/z 500). Data acquisition was managed using Xcalibur™ software (version 2.1.0; Thermo Scientific[®]).

HPLC analyses were carried out on a ThermoFisher[®] Dionex Ultimate 3000 HPLC system equipped with LPG-3400SD pump, WPS-3000SL/TSL autosampler, TCC-3000SD column oven, DAD-3000 detector. Separations were obtained using a Kinetex 5 μm EVO C18 100 mm x 4.6 mm LC column purchased from Phenomenex[®] (ref 00D-4633-E0).

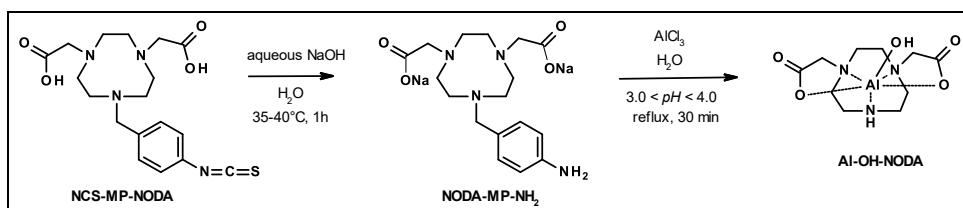
Method: Phase A: AcONa/H buffer, pH 4.5 (5 mM). Phase B: MeCN. Mobile Phase: isocratic; Phase A/Phase B: 85/15; flow: 1 mL/min. Sample: solution in water, ca 0.1-0.5 mg/mL. In such conditions, the dead volume of the system was evaluate by injection of AcONa/H buffer: R_t 0.95 min.



Scheme S1. Syntheses of **NODA** chelating agent and of **Al-F-NODA** complex.

NODA (Na form). Prepared according to reported procedure from commercially available NO2AtBu (78 mg, 0.218 mmol).^[2] The crude material was alkalinized up to *pH* 7.5 by addition of an aqueous solution of NaOH then purified by flash chromatography on RP C18 silica gel (H₂O/MeCN 9/1 *v/v*). The title compound was obtained as a whitish solid (58 mg, 0.218 mmol, 100%). ¹H NMR (D₂O, *pH* 5): Conform to reported data.^[3]

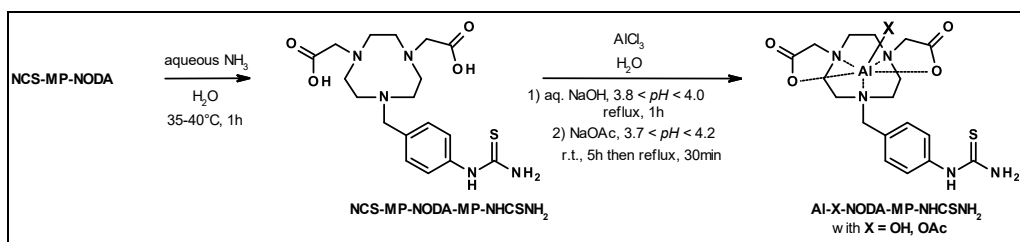
Al-F-NODA. Two stock solutions were prepared in advance, both of them diluted in a 0.5 M AcONa/H buffer solution at *pH* 4.45: *i*) a 0.100 M solution of AlCl₃ (resulting *pH* 3.6); *ii*) a 0.100 M solution of NaF (resulting *pH* 4.45). The previously prepared chelating agent NODA (19.5 mg, *ca* 70 μmol) was solubilized in a 0.5 M AcONa/H buffer solution at *pH* 4.45 (3.1 mL). AlCl₃ (0.100 M stock solution previously prepared, 2.1 mL, 210 μmol; 3 equiv) followed by NaF (0.100 M stock solution previously prepared, 1.1 mL, 110 μmol; 1.5 equiv) were added. Ethanol was then added in order to represent 10% *v/v* of the reactional volume (700 μL). The resulting reaction mixture (*pH* 4.4) was warmed at reflux for 30 min, cooled, and freeze-dried. The crude material was purified on preparative RP-TLC glass plate (H₂O/MeCN 95/5 *v/v*); the title compound was recovered from a silica strip corresponding to *R_f* 0.4–0.6 ranges (20 mg, 100%). ¹⁹F{¹H} NMR (D₂O, *pH* 7, *c* ≈ 0.10 M, *Figure S11*): δ -161.2. LRMS (MeCN/H₂O 5/5 *v/v*, 20 V): *m/z* 312 [M + Na]⁺, 353 [M + Na + MeCN]⁺, 601 [2M + Na]⁺. HRMS: calculated for [C₁₀H₁₇AlFN₃O₄ + Na]⁺, *m/z*: 312.091618, found, *m/z*: 312.09096 with *z* = 1; error: 0.11 ppm. HPLC: *R_t* 0.9 min (dead volume).



Scheme S2. Syntheses of **NODA-MP-NH₂** chelating agent and of **Al-OH-NODA** complex.

NODA-MP-NH₂ (di-Na form). NCS-MP-NODA (21.0 mg, 51.2 μmol) was suspended in ultrapure H₂O (800 μL). An aqueous solution of NaOH (1 M, 160 μL , 160 μmol , *ca* 3 equiv) was then added that gave a clear solution that was gently heated (oil bath temperature 50°C) for 1 hour. The mixture was concentrated to dryness by freeze-drying to give the title compound as a very pale yellow solid (25 mg, 100%). TLC (H₂O/MeCN 8/2 v/v): *R_f* 0.55. ¹H NMR (D₂O, *pH* > 12, *c* \approx 0.13 M, *Figure S9*):^[4] δ (ppm) 7.46-7.30 (3H, m, CH_{ar}), 7.25 (0.5H, part A of AX system, ³*J* = 8.4 Hz, CH_{ar}), 6.84 (0.5H, part X of AX syst, ³*J* = 8.4 Hz, CH_{ar}), 3.92-3.80 (2H, m, CH₂-Ar), 3.34-3.19 (2H, m, CH₂-CO₂), 2.93-2.66 (12H, m, N-CH₂). LRMS (MeCN/H₂O 8/2 v/v, 20 V): *m/z* 293 [M-CH₂CO₂ + H]⁺, 351 [M + H]⁺, 373 [M + Na]⁺, 395 [M - H + 2Na]⁺. HPLC: *R_t* 1.0-1.2 min.

Al-OH-NODA. The previously prepared chelating agent NODA-MP-NH₂, di-Na-form (31 mg, *ca* 78 μmol) was solubilized in ultrapure H₂O (1.5 mL), giving a light yellow solution. AlCl₃·6H₂O (20 mg, 83 μmol , 1.3 equiv) was added as a single solid portion, dropping the *pH* from >12 to 4.7 and giving a cloudy solution. The *pH* was adjusted to *pH* 4.0 by the careful addition of a 1 M aqueous solution of HCl (100 μL , 100 μmol , *ca* 1.2 equiv) leading to a clear solution. The resulting reaction mixture was first left to react at room temperature for 6 hours, after which MS monitoring revealed traces of Al(III) complexation as well as traces of derivated chelator NODA (resulting from methylphenyl acid-assisted hydrolysis). The reaction medium was then refluxed for 30 min. The light yellow solution turned into a heterogeneous medium with non-soluble suspended matter and an orange liquid phase. Heating was stopped. The final *pH* had dropped to *pH* 3.0. The precipitate formed was filtered, and the orange aqueous filtrate was lyophilized. MS analysis of the lyophilisate revealed total conversion to **Al-OH-NODA** resulting from cleavage of the methylphenyl moiety (acid-assisted hydrolysis). The methylphenyl part was recovered in the filtered solid (¹H NMR in DMSO-*d*₆). LRMS (MeCN/H₂O 5/5 v/v, 20 V): *m/z* 270 [Al-L]⁺, 288 [Al-OH-L + H]⁺, 310 [Al-OH-L + Na]⁺, 311 [Al-L + ACN]⁺. HPLC: *R_t* 1.1-1.3 min.



Scheme S3. Syntheses of **NODA-MP-NHCSNH₂** chelating agent and of the corresponding Al(III) complexes.

NODA-MP-NHCSNH₂. NCS-MP-NODA (20.5 mg, 49.9 μ mol) was suspended in ultrapure H₂O (800 μ L). An aqueous solution of NH₃ (20% min, 16 μ L, *ca* 176 μ mol, *ca* 3.5 equiv) was then added that gave a clear solution that was gently heated (oil bath temperature 50°C) for 1 hour. The mixture was concentrated to dryness by freeze-drying to give the title compound as a white solid (21 mg, 100%). TLC (H₂O/MeCN 8/2 *v/v*): *R_f* 0.60. ¹H NMR (D₂O, *pH* 5.4, *c* \approx 0.13 M, *Figure S10*): δ (ppm) 7.55 (2H, part A of AX system, ³*J* = 8.4 Hz, CH_{ar}), 7.32 (2H, part X of AX syst, ³*J* = 8.4 Hz, CH_{ar}), 4,12 (2H, *s*, CH₂-Ar), 3.48 (4H, *s*, CH₂-CO₂), 3.35-2.71 (12H, *m*, N-CH₂). ¹³C{¹H} NMR (D₂O, *pH* 5.4, *c* \approx 0.13 M, *Figure S10*): δ (ppm) 179.6 (CS), 175.7 (CO), 137.2 (C_{quat}-NH), 133.3 (C_{quat}-CH₂), 131.4 (CH_{ar}-C_{quat}-CH₂), 125.5 (CH_{ar}-C_{quat}-NH), 59.2 (CH₂-Ar), 57.7 (CH₂-CO₂), 50.1 (N-CH₂), 49.7 (N-CH₂), 49.0 (N-CH₂). LRMS (MeCN/H₂O 8/2 *v/v*, 20 V): *m/z* 410 [M + H]⁺, 432 [M + Na]⁺, 454 [M - H + 2Na]⁺. HPLC: *R_t* 1.2-1.3 min.

Al-X-NODA-MP-NHCSNH₂ (X = OH, OAc). The previously prepared chelating agent NODA-MP-NHCSNH₂ (32 mg, *ca* 78 μ mol) was solubilized in ultrapure H₂O (1.5 mL), giving a slightly cloudy solution. AlCl₃·6H₂O (20 mg, 83 μ mol, 1.0-1.1 equiv) was added as a single solid portion, dropping the *pH* from 5.1 to 3.5. The *pH* was adjusted to *pH* 4.0 by the careful addition of a 1 M aqueous solution of NaOH (95 μ L, 95 μ mol, *ca* 1.2 equiv). The resulting reaction mixture was first left to react at room temperature for 5 hours, after which MS monitoring revealed trace of Al(III) complexation. The reaction medium was then refluxed for 30 min, resulting in a clear transparent solution and a drop in *pH* from 4.0 to 3.8. MS monitoring revealed incomplete conversion: presence of the desired Al-OH-NODA-MP-NHCSNH₂ complex together with starting chelator. The *pH* was adjusted from 3.80 to 4.06 with careful addition of a 1 M aqueous solution of NaOAc (50 μ L, 50 μ mol, *ca* 0.65 equiv). The reaction medium was refluxed for a further 30 min; *pH* and MS monitoring revealed *i)* a drop in *pH* from 4.06 to 3.67, and *ii)* the persistence of incomplete conversion, with the presence of starting chelator together with a mixture of the desired complexes Al-OH-NODA-MP-NHCSNH₂ and Al-OAc-NODA-MP-NHCSNH₂. A second portion of a 1 M aqueous solution of NaOAc (50 μ L, 50 μ mol, *ca* 0.65 equiv) was added to adjust the *pH* from 3.67 to 4.22. After a further 30 min reflux, the solution changed from transparent to slightly yellow. Heating was stopped. The final *pH* had dropped to *pH* 4.0 and the medium had become slightly cloudy. The aqueous mixture was filtered through a 0.22 μ m PES membrane (syringe filter unit) and then lyophilized (93 mg of solid material recovered). MS analysis revealed a mixture of residual NODA-MP-NHCSNH₂ (LH₂) and of the corresponding desired Al(III) complexes. LRMS (MeCN/H₂O 5/5 *v/v*, 20 V): *m/z* 410 [LH₂ + H]⁺, 432 [LH₂ + Na]⁺, 474 [Al-OH-L + Na]⁺, 490 [Al-OH-L + K]⁺, 516 [Al-OAc-L + Na]⁺, 532 [Al-OAc-L + K]⁺. HPLC: *R_t* 1.0-1.3 min.

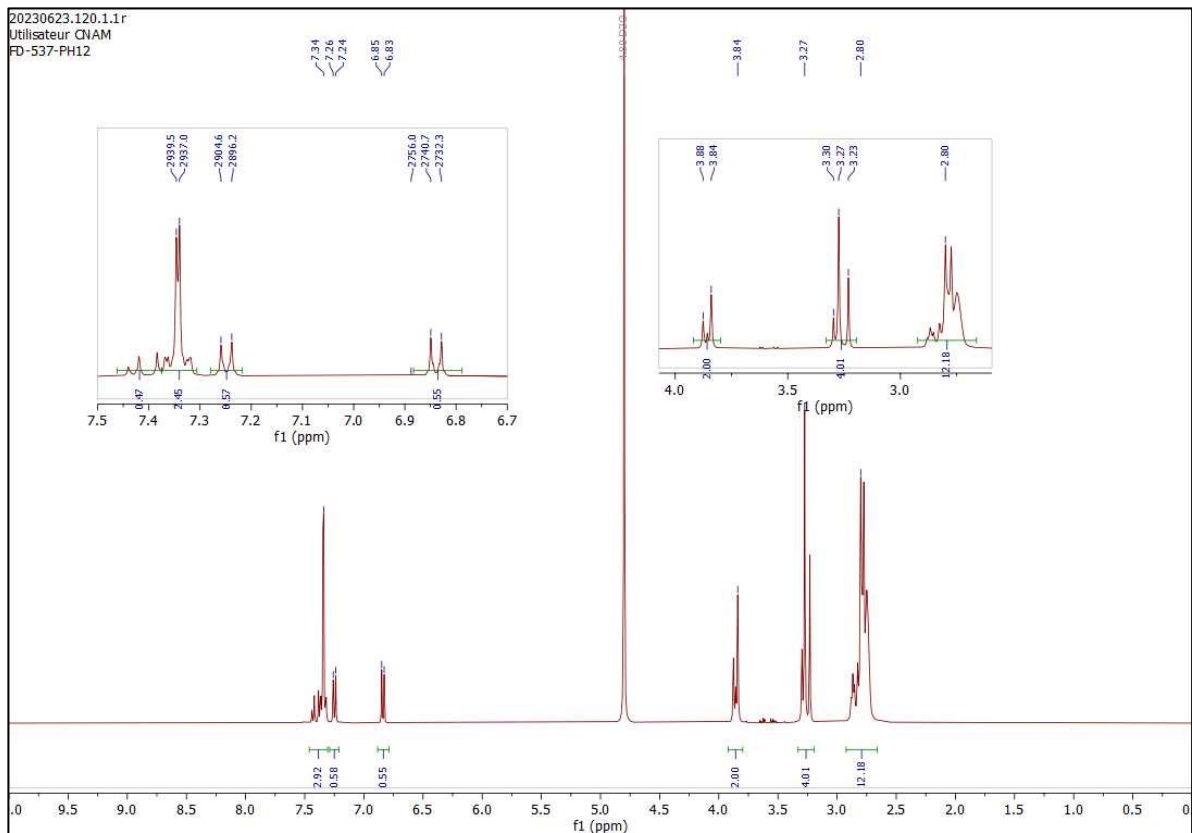


Figure S9. ¹H NMR of NODA-MP-NH₂ in D₂O (*c* ≈ 0.13 M, *pH* > 12).

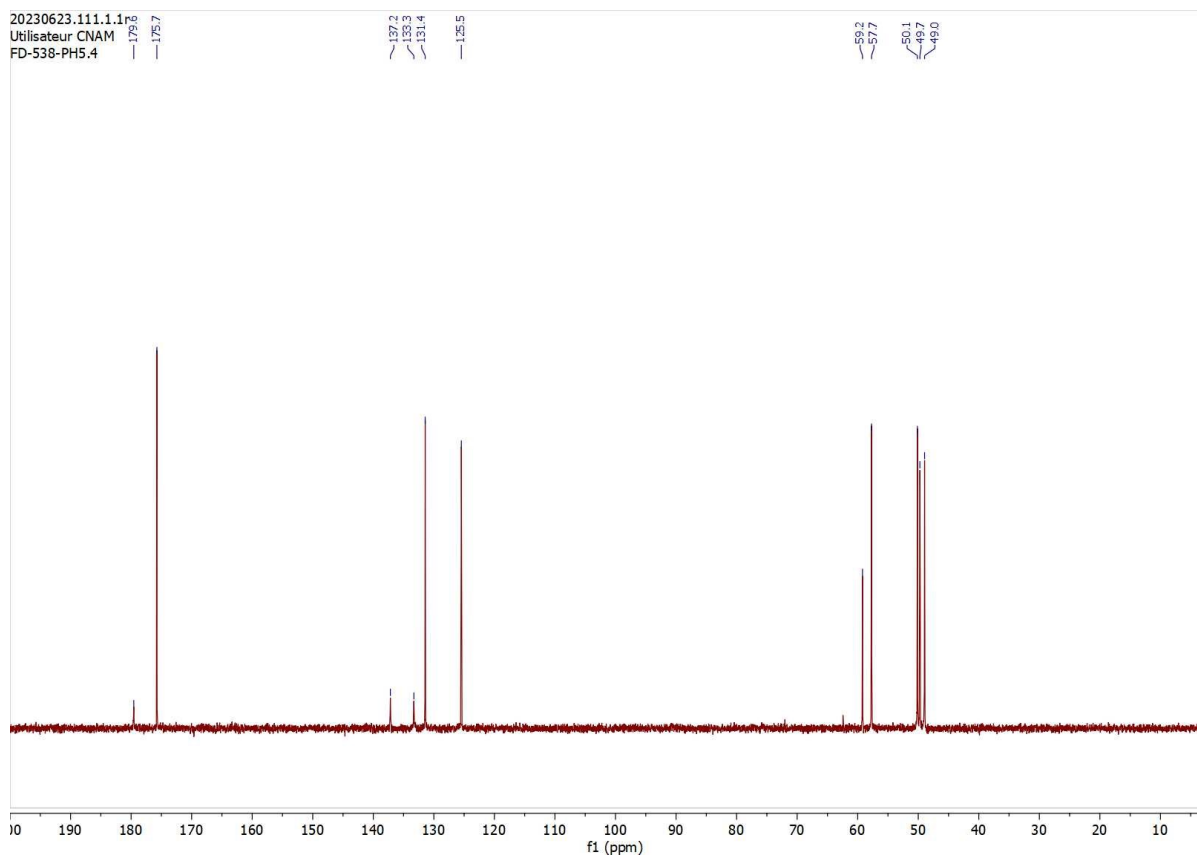
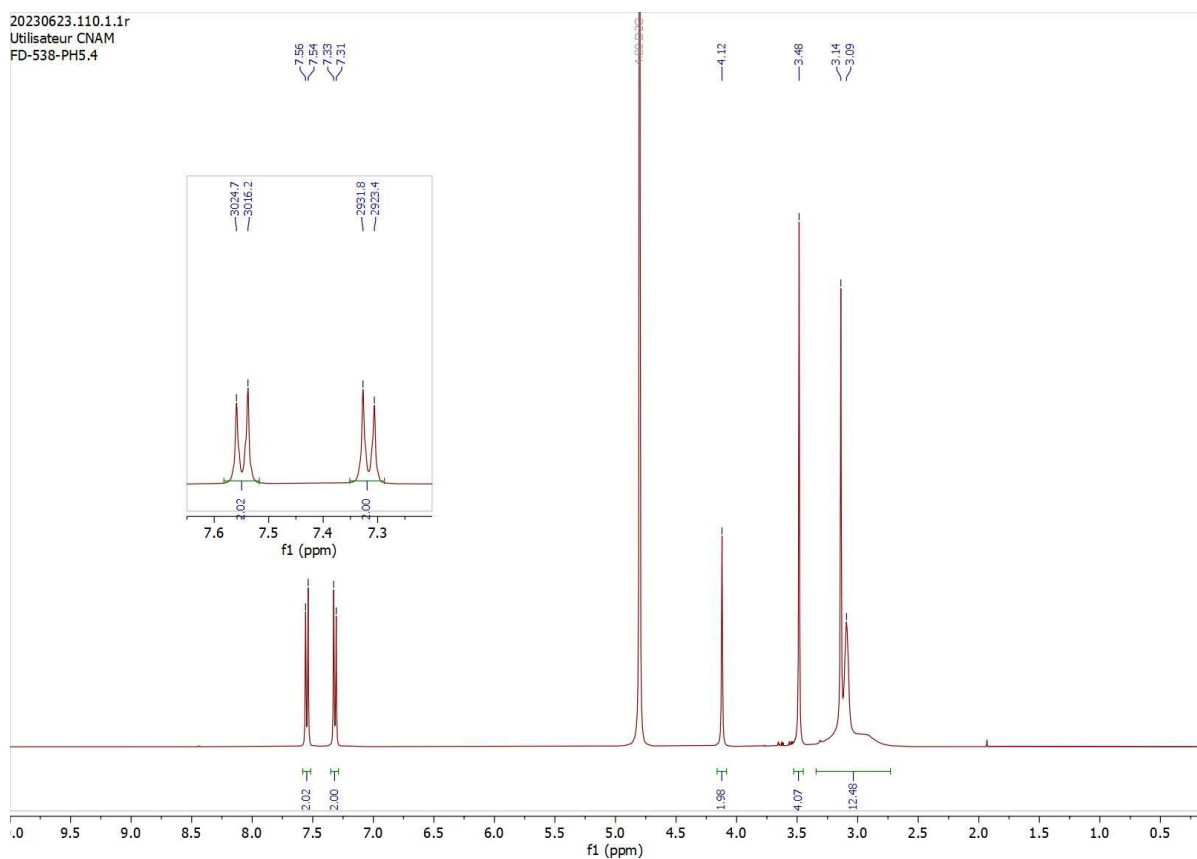


Figure S10. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR of NODA-MP-NHCSNH₂ in D₂O ($c \approx 0.13$ M, $\text{pH } 5.4$).

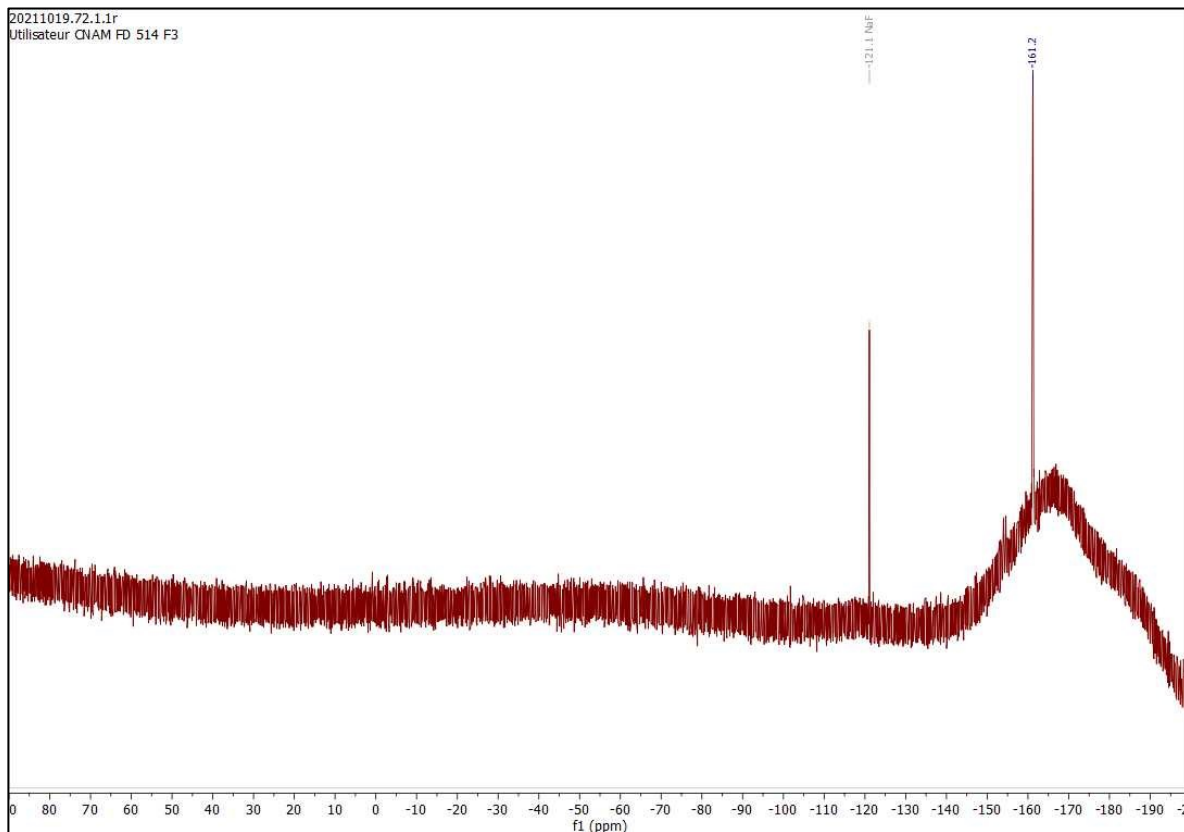


Figure S11. $^{19}\text{F}\{^1\text{H}\}$ NMR of Al-F-NODA in D_2O ($c \approx 0.10$ M, pH 7).

References

- [1] A. Bodor, I. Tóth, I. Bánai, Z. Szabó, G. T. Hefter, *Inorg. Chem.* **2000**, *39*, 2530–2537.
- [2] D. Shetty, S. Y. Choi, J. M. Jeong, J. Y. Lee, L. Hoigebazar, Y.-S. Lee, D. S. Lee, J.-K. Chung, M. C. Lee, Y. K. Chung, *Chem. Commun.* **2011**, *47*, 9732–9734.
- [3] U. Kreher, M. T. W. Hearn, B. Moubaraki, K. S. Murray, L. Spiccia, *Polyhedron* **2007**, *26*, 3205–3216.
- [4] D. Shetty, J. M. Jeong, Y. J. Kim, J. Y. Lee, L. Hoigebazar, Y.-S. Lee, D. S. Lee, J.-K. Chung, *Bioorg. Med. Chem.* **2012**, *20*, 5941–5947.