Supporting information *for*

Effective Mitigation of Gadolinium Deposition Using the Bidentate Hydroxypyridinone Ligand Me-3,2-HOPO†

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S1. Potentiometric titration

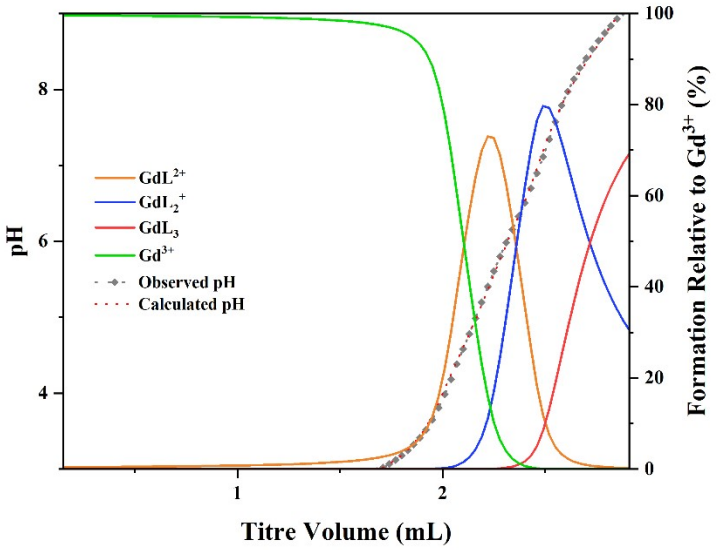

Figure S1. Potentiometric data of titre volume and pH are superimposed on speciation (gray circles and red dots are observed and calculated pH, respectively). Me-3,2-HOPO is denoted as HL**.**

S2. Structure characterization of Gd-Me-3,2-HOPO

The X-ray diffraction data of a Gd-Me-3,2-HOPO single crystal were collected on a Bruker D8-Venture single-crystal X-ray diffractometer with a digital camera, and the crystal was mounted on a cryoloop with paratone oil. The data were collected with a Turbo X-ray Source (Mo Kα radiation, λ = 0.71073Å) at room temperature, which adopted the direct-drive rotating anode technique and a CMOS detector. For the Gd-Me-3,2-HOPO compound, a total of 4836 reflections were collected within the range $2.490 < 2\theta < 27.509$, $-12 < h < 12$, $-13 < k < 13$, $-14 < l < 14$, and 4265 reflections were used for refinement. The final R1 is 0.0257. The structure of Gd-Me-3,2-HOPO was refined using SHELXTL-2017 based on the full-matrix least-squares method, and the nonhydrogen atoms were refined with anisotropic displacement parameters.[1]The detailed crystallographic data are listed in **Table S1, S2**.

Table S1. Crystallographic data and refinement details for the compound of Gd-Me-3,2-HOPO (CCDC : 2110132).

Gd-Me-3,2-HOPO	
Formula	$Gd(H_2O)_3[(C_6H_6NO_2)(C_6H_7NO_2)]\cdot 2Cl\cdot 3H_2O$
F. W.	1168.96
Crystal system	triclinic
Space group	$P\bar{1}$
a /Å	9.9405(4)
b /Å	10.7661(4)
c /Å	11.2466(4)
α /deg	102.2250(10)
β /deg	90.6250(10)
γ /deg	115.2960(10)
V/ Å^3	1056.50(7)
Z	1
ρ_{calcd}/g cm^{-3}	1.837
μ(Mo Kα)/mm^{-1}	3.440
R1, $wR_2[I > 2\sigma(I)]^a$	0.0257, 0.0594
R1, wR_2(all data)^a	0.0353, 0.0679

[a]· $R_1 = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$, $wR_2 = [\Sigma w(Fo^2 - F_c^2)^2/\Sigma w(Fo^2)^2]^{1/2}$

Table S2. Selected bond distances (Å) and Bond Valence (v.u. valence unit) for Gd-Me-3,2-HOPO.

Bond Distances (Å)		BV (v. u.)	Bond Distances (Å)	
Gd1-O1	2.417(3)	0.386		
Gd1-O2	2.397(3)	0.408		
Gd1-O3	2.399(3)	0.405		
Gd1-O4	2.333(2)	0.486	O4-C10	1.271(4)
Gd1-O5	2.542(2)	0.275	O5-C9	1.363(4)
Gd1-O6	2.359(2)	0.452	O6-C11	1.268(4)
Gd1-O7	2.379(2)	0.428	O7-C12	1.343(4)
Gd1-O7	2.379(2)	0.428		

BV= $v_{ij} = \exp[(R_{ij} - d_{ij})/b]$, vij is the valence of the bond between two atoms i and j, d_{ij} is the bond length between the two atoms, R_{ij} is the bond valence parameter, and b is a constant of 0.37 Å.[2]

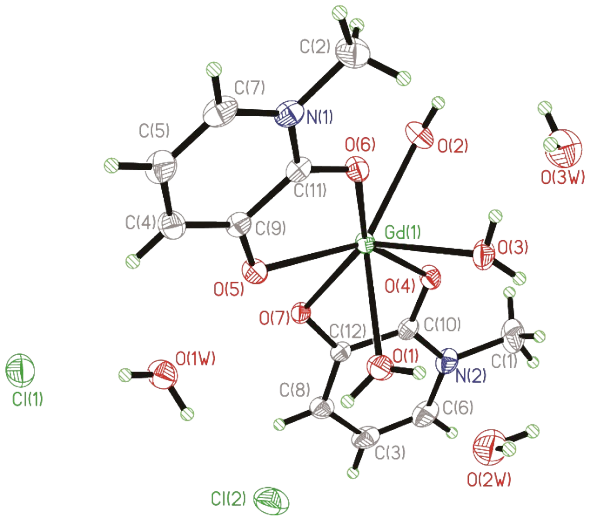

Figure S2. Perspective view of the crystal structure of Gd-Me-3,2-HOPO, illustrating the atom-numbering scheme. Atoms are drawn as ellipsoids of 30 % probability and hydrogen atoms as spheres of radius 0.2 **Å**.

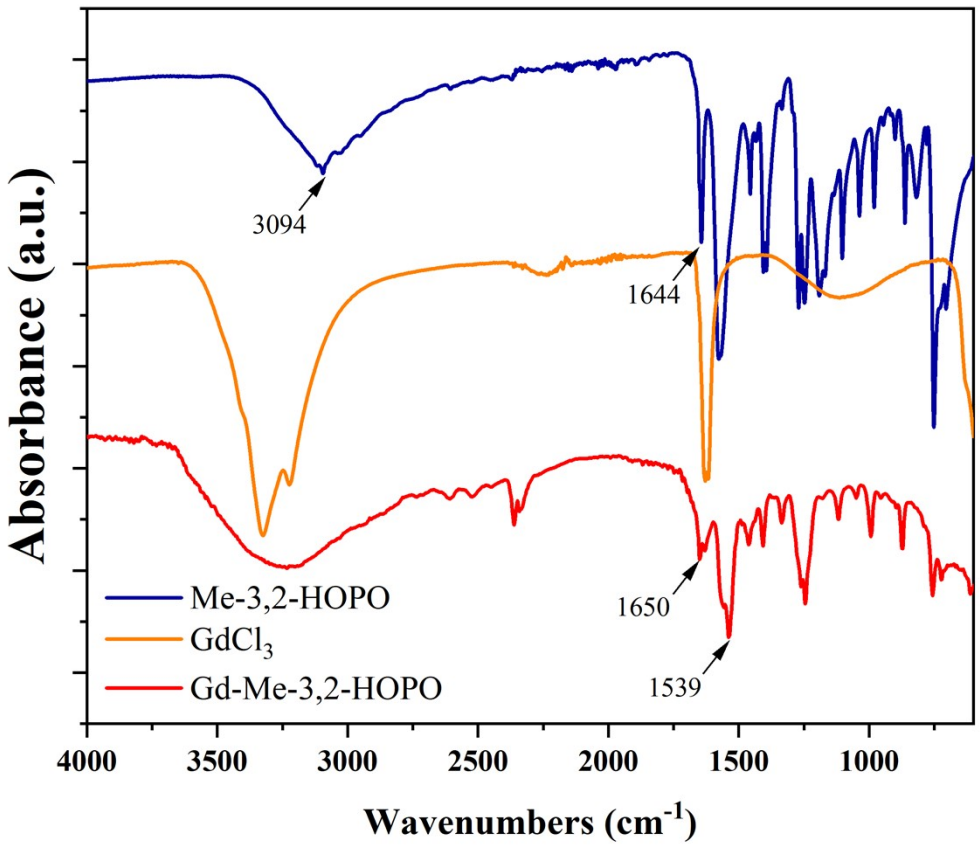

Figure S3. ATR-FT-IR absorption spectra of $GdCl_3$, Me-3,2-HOPO, and Gd-Me-3,2-HOPO.

S3. Cytotoxicity of Gd(III)

Table S3. Dosage-dependent cell growth rate of NRK-52E and AML-12 cells treated with different concentrations of Gd(III), n = 6, *p < 0.05, **p < 0.01, ***p < 0.001 vs control.

Concentration (μM)	NRK-52E cells Survival Rate (%)	AML-12 cells Survival Rate (%)
10	102.87 ± 10.21	94.17 ± 8.99
25	89.11 ± 9.27*	95.46 ± 7.58
50	76.57 ± 5.82***	97.37 ± 10.23
75	65.00 ± 4.26***	83.41 ± 8.06**
100	63.40 ± 4.48***	93.72 ± 4.74

S4. Cytotoxicity of Gd(III) and chelating agents

Table S4. Dosage-dependent cell growth rate of NRK-52E cells treated with 25 μM Gd(III) and different concentrations of ligand (DTPA-$ZnNa_3$ or Me-3,2-HOPO), n = 6, *p < 0.05, **p < 0.01, ***p < 0.001 vs control.

Concentration (μM)	Gd(III)+ DTPA-$ZnNa_3$ Survival Rate (%)	Gd(III) + Me-3,2-HOPO Survival Rate (%)
50	91.78 ± 3.05**	98.50 ± 2.11
100	92.56 ± 4.46**	100.09 ± 4.09
150	92.15 ± 3.31**	97.51 ± 3.62
300	95.69 ± 4.31	90.17 ± 2.77***
450	97.11 ± 4.06	69.69 ± 3.04***
600	101.46 ± 6.13	32.09 ± 1.54***

Table S5. Dosage-dependent cell growth rate of AML-12 cells treated with 25 μM Gd(III) and different concentrations of ligand (DTPA-$ZnNa_3$ or Me-3,2-HOPO), n = 6, *p < 0.05, **p < 0.01, ***p < 0.001 vs control.

Concentration (μM)	Gd(III) + DTPA-$ZnNa_3$ Survival Rate (%)	Gd(III) + Me-3,2-HOPO Survival Rate (%)
50	99.08 ± 2.33	103.52 ± 4.98
100	95.60 ± 3.33**	104.27 ± 2.84
150	92.35 ± 3.51***	101.78 ± 7.07
300	94.37 ± 2.01***	81.58 ± 7.07***
450	99.38 ± 2.57	40.30 ± 3.48***
600	96.16 ± 2.82*	16.42 ± 0.86***

S5. Gd(III) removal

Table S6. Gd(III) removal efficacy of NRK-52E cells exposed to gadolinium that were treated with DTPA-$ZnNa_3$ or Me-3,2-HOPO, n = 4, *p < 0.05, **p < 0.01, ***p < 0.001 vs gadolinium-exposed control.

Group	Gd(III) (ng/10^6 Cells)
Control	231.19 ± 23.05
Gd(III) + DTPA-$ZnNa_3$	212.43 ± 23.24
Gd(III) + Me-3,2-HOPO	51.91 ± 4.74***

Table S7. Gd(III) removal efficacy of AML-12 cells exposed to gadolinium that were treated with DTPA-$ZnNa_3$ or Me-3,2-HOPO, n = 4, *p < 0.05, **p < 0.01, ***p < 0.001 vs gadolinium-exposed control.

Group	Gd(III) (ng/10^6 Cells)
Control	467.17 ± 49.45
Gd(III) + DTPA-$ZnNa_3$	337.75 ± 50.33**
Gd(III) + Me-3,2-HOPO	158.24 ± 17.43***

Reference:

1. G. M. Sheldrick, SHELXTL; Siemens Analytical X-ray Instruments Inc: Madison. WI, 2001.
2. N. E. Brese and M. O'Keeffe, *Acta. Cryst. B.*, 1991, **47**, 192-197.