Supporting Information

Metal complexation for the rational design of gemcitabine formulations in cancer therapy

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Table S1. Hydrolysis constants of Ca^{2+} at different temperatures and ionic strength values.

Species	***t*** **/°C**	***I*** **/ mol L^{-1}**	**logβ** [1]
$Ca^{2+} + H_2O \rightleftharpoons [CaOH]^+ + H^+$	15	0.15	-13.14
	25	0.15	-12.87
	25	0.5	-12.88
	25	1	-12.81
	37	0.15	-12.56
	45	0.15	-12.6(5)[2]

[1] Crea, F.; De Stefano, C., Milea, D., Pettignano, A., Sammartano, S. (2015). SALMO and S3M: A Saliva Model and a Single Saliva Salt Model for Equilibrium Studies, Bioinorg. Chem. Appl. 2015.
[2] Unplubished data.

Table S2. Hydrolysis constants of Zn^{2+} at different temperatures and ionic strength values.

Reaction	*t* /°C	*I* / mol L^{-1}	logβ^1
$Zn^{2+} + H_2O \rightleftharpoons [ZnOH]^+ + H^+$	15	0.15	-9.5
	25	0.15	-9.14
	25	0.5	-9.15
	25	1	-9.16
	37	0.15	-8.78
	45	0.15	-10.02[2]
$Zn^{2+} + 2H_2O \rightleftharpoons [Zn(OH)_2]^0 + 2H^+$	15	0.15	-17.64
	25	0.15	-17.10
	25	0.5	-17.1
	25	1	-17.22
	37	0.15	-16.52
	45	0.15	-16.52[2]
$Zn^{2+} + 3H_2O \rightleftharpoons [Zn(OH)_3]^- + 3H^+$	15	0.15	-29.12
	25	0.15	-28.4
	25	0.5	-28.4
	25	1	-28.47
	37	0.15	-27.54
	45	0.15	-27.54[2]
$Zn^{2+} + 4H_2O \rightleftharpoons [Zn(OH)_4]^{2-} + 4H^+$	15	0.15	-41.67
	25	0.15	-40.40
	25	0.5	-40.85
	25	1	-40.38
	37	0.15	-39.47
	45	0.15	-39.47[2]
$2Zn^{2+} + H_2O \rightleftharpoons [Zn_2(OH)]^{3+} + H^+$	15	0.15	-9.27
	25	0.15	-8.70
	25	0.5	-8.89
	25	1	-8.89
	37	0.15	-8.54
	45	0.15	-8.54[2]
$2Zn^{2+} + 6\ H_2O \rightleftharpoons [Zn_2(OH)_6]^{2-} + 6H^+$	15	0.15	-58.91
	25	0.15	-57.50
	25	0.5	-57.53
	25	1	-57.32
	37	0.15	-55.9
	45	0.15	-55.9[2]

[1] F. Crea, G. Falcone, C. Foti, O. Giuffrè, S. Materazzi. Thermodynamic data for Pb^{2+} and Zn^{2+} sequestration by biologically important S-donor ligands, at different temperatures and ionic strengths, New J. Chem., 2014, 38, 3973.

[2] K. J. Powell, P. L. Brown, R. H. Byrne, T. Gajda, G. Hefter, A. Leuz, S. Sjöberg, H. Wanner, Chemical speciation of environmentally significant metals with inorganic ligands. Part 5: The Zn^{2+} + OH^-, Cl^-, CO_3^{2-}, SO_4^{2-}, and PO_4^{3-} systems (IUPAC Technical Report), Pure Appl. Chem., 2013, 85, 2249–2311.

Table S3. Hydrolysis constants of Mn^{2+} at different temperatures and ionic strength values.

Reaction	***t*** **/°C**	***I* / mol L^{-1}**	**logβ[1]**
$Mn^{2+} + H_2O \rightleftharpoons [MnOH]^+ + H^+$	15	0.15	-10.6
	25	0.15	-10.46
	25	0.5	-10.70
	25	1	-10.95
	37	0.15	-9.20
	45	0.1	-9.66[2]
$2Mn^{2+} + 3H_2O \rightleftharpoons [Mn_2(OH)_3]^- + 3H^+$	15	0.15	-26.35
	25	0.15	-24.47
	25	0.5	-24.69
	25	1	-24.92
	37	0.15	-23.51
	45	0.15	-24.84[2]

[1] C. Foti, O. Giuffrè. Interaction of Ampicillin and Amoxicillin with Mn^{2+}: A Speciation Study in Aqueous Solution. *Molecules*, 2020, *25*, 3110.

[2] Unpublished data.

Table S4. Cartesian components of the atomic species composing the gemcitabine molecular structures shown in Fig. 7 of the main text optimized at the at the B3LYP/6-311++G(d,p) level of theory under CPCM water implicit solvation.

GMT

	X	Y	Z
N	-1.135780	-0.149828	0.483570
C	-2.040774	-0.203497	1.509387
C	-3.371839	-0.229248	1.275122
C	-3.785999	-0.205182	-0.097117
N	-2.918044	-0.164466	-1.103343
H	-1.630814	-0.223674	2.510701
H	-4.081883	-0.271130	2.088047
O	-0.736501	-0.100685	-1.763530
C	-1.582652	-0.137207	-0.869090
N	-5.096252	-0.227095	-0.400066
H	-5.802926	-0.255189	0.316358
H	-5.384191	-0.211832	-1.366152
C	1.940284	-0.955954	-0.734941
C	1.954479	0.586184	-0.878996
C	1.101855	1.072022	0.310024
C	0.293326	-0.154015	0.804332
H	1.582037	-1.397436	-1.666622
H	0.347672	-0.171846	1.893034
O	0.970346	-1.277706	0.301313
F	0.307402	2.140486	-0.005740
F	1.896779	1.497206	1.345396
O	3.264360	1.110392	-0.902210
H	3.259642	1.929936	-1.408394
C	3.256966	-1.625569	-0.358123
H	4.030807	-1.314861	-1.060127
H	3.124573	-2.709827	-0.450350
O	3.716015	-1.290171	0.947452
H	3.054362	-1.601631	1.576419
H	1.405997	0.858143	-1.778739

GMT+MnOH@site1

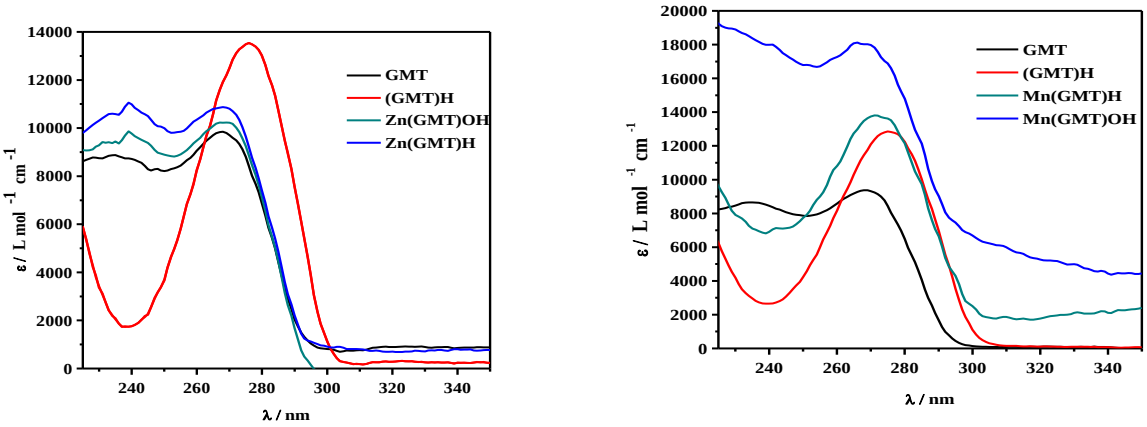
	X	Y	Z
N	2.199392	-0.011148	0.524085
C	3.093037	-0.179605	1.549463
C	4.425221	-0.186029	1.324765
C	4.854228	-0.002821	-0.031621
N	3.996725	0.169055	-1.034208
H	2.672578	-0.306819	2.538252
H	5.127223	-0.320610	2.134532

O	1.820411	0.339686	-1.695271
C	2.662544	0.178130	-0.808936
N	6.165826	0.000113	-0.322991
H	6.865893	-0.122005	0.390258
H	6.463284	0.133518	-1.277193
C	-0.642433	1.311646	-0.596645
C	-0.909341	-0.162174	-0.988625
C	-0.119178	-0.978449	0.064735
C	0.772007	0.032888	0.831762
H	-0.070813	1.786960	-1.393879
H	0.689044	-0.187045	1.895213
O	0.173017	1.285642	0.601353
F	0.578283	-2.012381	-0.479039
F	-0.980507	-1.542942	0.972007
O	-2.304591	-0.476425	-1.004139
H	-2.479123	-1.248953	-1.557645
C	-1.850012	2.180306	-0.306091
H	-2.486138	2.255957	-1.186328
H	-1.516138	3.180862	-0.028432
O	-2.679777	1.657482	0.756992
H	-2.231760	1.745287	1.608405
H	-0.485848	-0.369869	-1.966879
Mn	-3.961057	0.033511	0.318252
O	-5.058273	-1.305149	-0.419477
H	-5.758089	-1.666532	0.133971

GMT+MnOH@site2

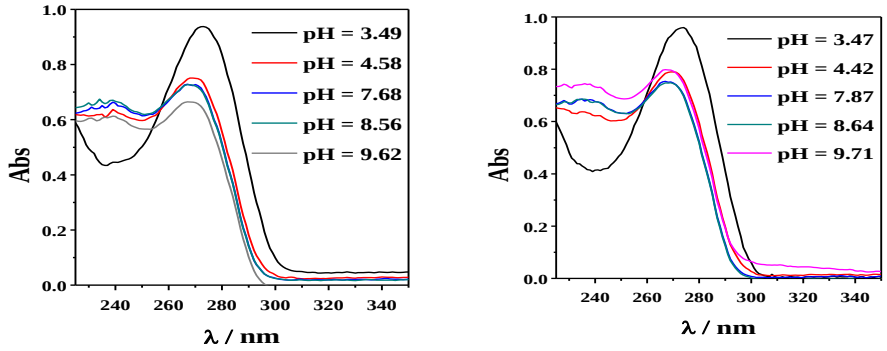
	X	**Y**	**Z**
N	-0.260203	-0.318647	0.532309
C	0.559206	-0.696567	1.551577
C	1.884891	-0.917024	1.346856
C	2.345799	-0.724745	0.021101
N	1.587210	-0.348703	-0.976085
H	0.099622	-0.809572	2.524408
H	2.536300	-1.211803	2.155791
O	-0.513046	0.203992	-1.680094
C	0.248214	-0.129909	-0.781632
N	3.721626	-0.906259	-0.269847
H	4.116735	-1.707402	0.220402
H	3.855562	-1.024888	-1.272451
C	-3.068986	1.278023	-0.564938
C	-3.351271	-0.177831	-1.011562
C	-2.666936	-1.035743	0.072324
C	-1.689252	-0.093853	0.821147

H	-2.591649	1.817562	-1.384452
H	-1.798911	-0.271407	1.891160
O	-2.104404	1.207708	0.525666
F	-2.044167	-2.140166	-0.442781
F	-3.576159	-1.510314	0.979926
O	-4.729312	-0.432930	-1.162065
H	-4.846459	-1.131632	-1.815013
C	-4.261487	2.093716	-0.079030
H	-5.039895	2.073323	-0.841872
H	-3.933597	3.131492	0.049212
O	-4.840831	1.601288	1.124620
H	-4.184614	1.694348	1.825093
H	-2.811714	-0.370236	-1.937718
Mn	5.105583	0.756972	0.307625
O	6.598384	0.602033	-0.826014
H	6.914154	-0.277628	-1.056073



(a) **(b)**

Figure S1. ε vs. λ of **a)** and Zn^{2+}-GMT **b)** Mn^{2+}-GMT species at t = 45°C, I = 0.1 mol L^{-1}.



(**a**) (**b**)

Figure S2. UV spectra at selected pH of a) Mn^{2+}-GMT and b) Zn^{2+}-GMT at t = 45°C, I = 0.1 mol L^{-1}, C_{GMT} = 0.04 mmol L^{-1}, C_M = 0.04 mmol L^{-1}.

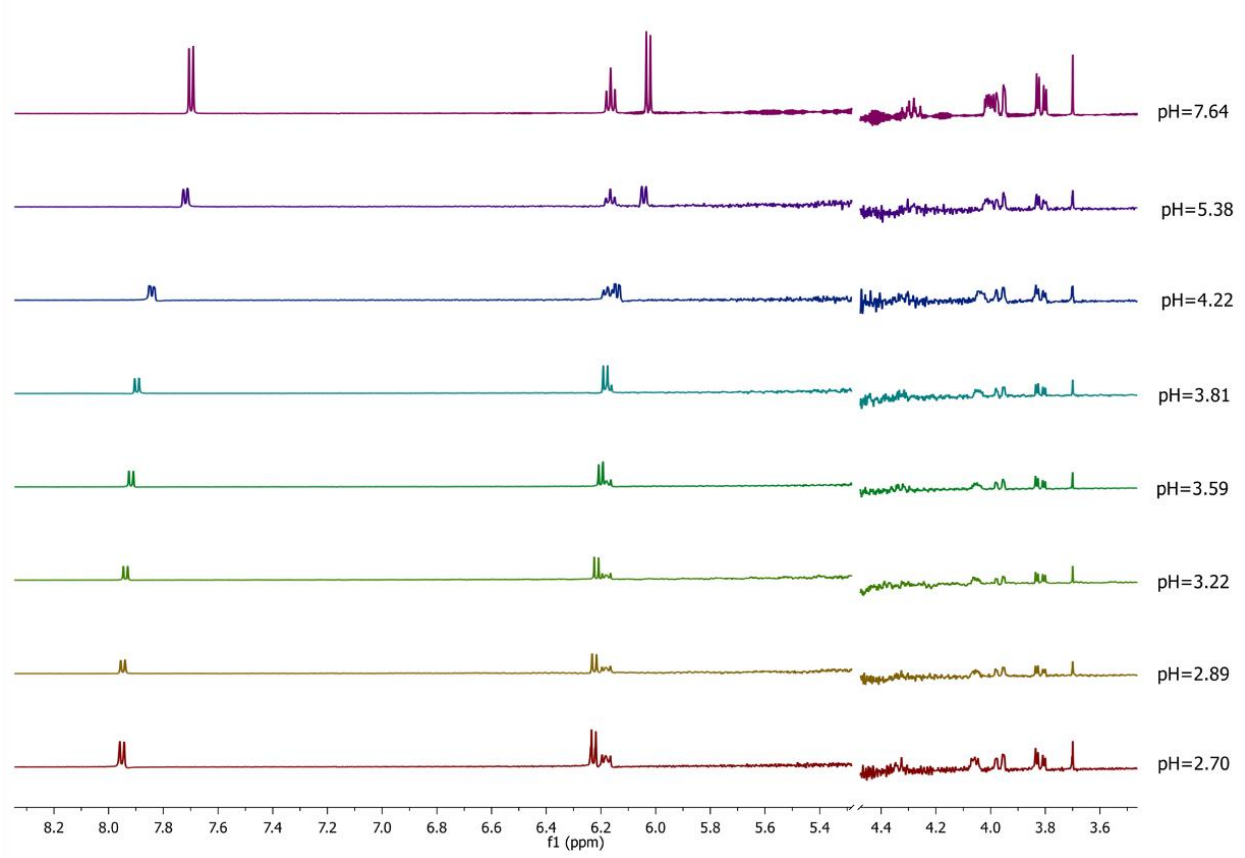


Figure S3. ^{1}H NMR spectra on solutions containing Zn^{2+}-GMT at C_{GMT} = 5 mmol L^{-1} and C_{Zn} = 6 mmol L^{-1}, t = 25°C, I = 0.1 mol L^{-1} in NaCl, 2.70 ≤ pH ≤ 7.64.

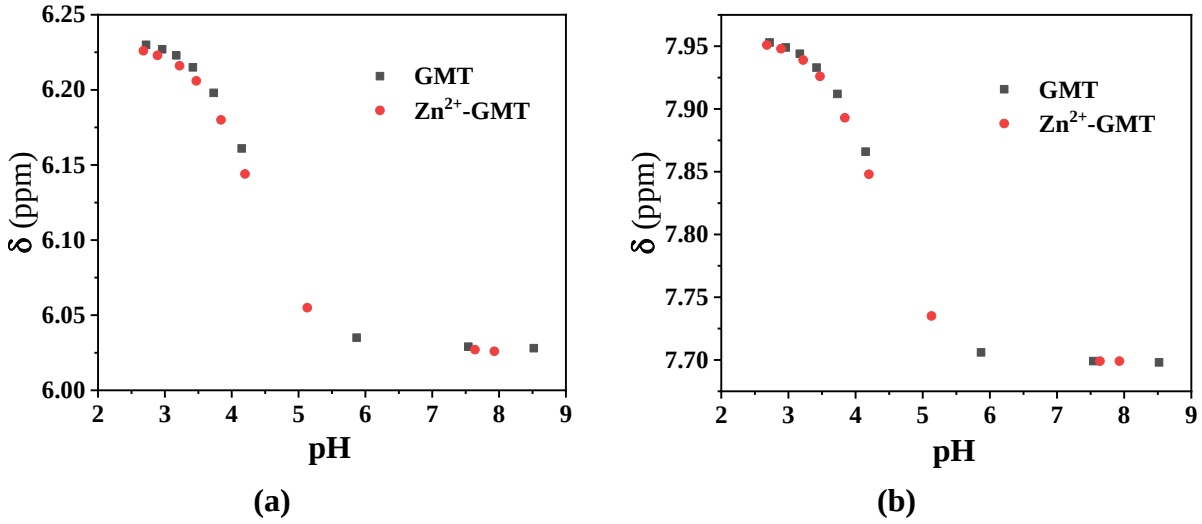


Figure S4. Comparison between chemical shift (δ) of a) CH-5' and b) CH-6' measured on ^{1}H NMR spectra on solutions containing GMT and Zn^{2+}-GMT at C_{GMT} = 5 mmol L^{-1} and C_{Zn} = 6 mmol L^{-1}, *t* = 25°C, *I* = 0.1 mol L^{-1} in NaCl, 2.72 ≤ pH ≤ 8.52.