Polyaminoquinoline Iron Chelators for Vectorization of Antiproliferative Agents: Design, Synthesis and Validation

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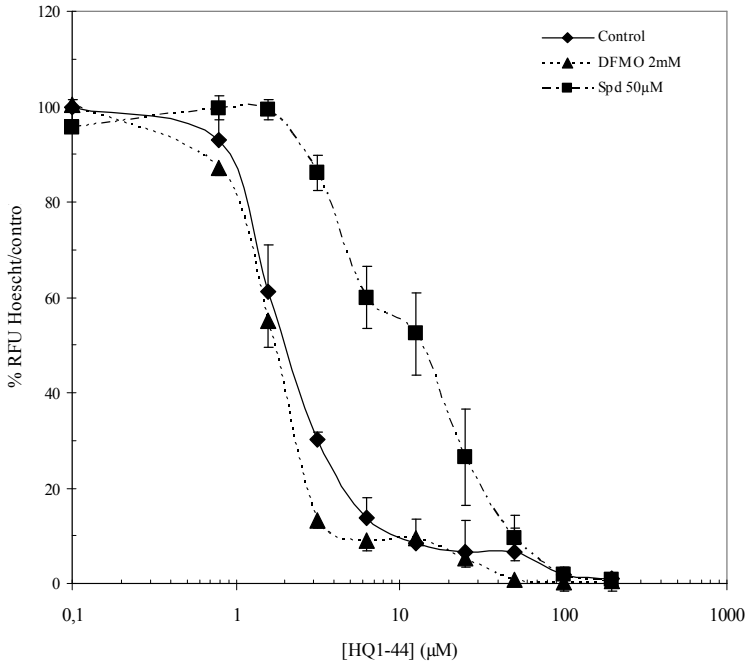

Figure S1. Influence of the PTS on the antiproliferative effect of **HQ1-44** in CHO cell line, determined by measuring DNA content after Hoescht staining. PTS was activated by polyamine depletion induced by DFMO (2mM) pre-treatment or competively inhibited by 50µM exogenous Spermidine.

Table S1 – Overall and stepwise stability constants for the iron(III) complexes of **HQ1-44** (25.0 ºC, I = 0.10 M in KNO_3)

Species[a]	**log β**[b]	**log K**[b]
FeL	25.62	25.62
FeHL	32.13	6.51
FeH_2L	34.94	2.81
FeL(OH)	18.35	7.27
FeL_2	(33.0)	(7.4)
$FeHL_2$	(42.2)	(9.2)
FeH_2L_2	(51.0)	(8.8)
FeH_3L_2	59.1	(8.1)
$FeL_2(OH)$	(23.4)	(9.6)
$FeL_2(OH)_2$	(13.5)	(9.9)
$FeL_2(OH)_3$	(2.9)	(10.6)
$FeL_2(OH)_4$	(-8.0)	(10.9)

[a]HL = **HQ1-44**, and charges are omitted for the sake of clarity. [b]Values in brackets are approximate

Table S2 – Overall and stepwise stability constants of the complexes of **HQ1-44** with selected divalent cations (25.0 ºC, I = 0.1 M in KNO_3).

Species [a]	log β [b]	log K (pK) [b]
CuL	16.87	16.87
CuHL	26.23	9.36
CuH_2L	33.33	7.10
CuH_3L	35.99	2.66

$CuL(OH)$	6.53	10.34
$CuL(OH)_2$	-5.96	12.49
CuL_2	23.17	6.30
$CuHL_2$	33.13	9.96
CuH_2L_2	43.06	9.93
CuH_3L_2	52.18	9.12
CuH_4L_2	61.00	8.82
CuH_5L_2	67.70	6.7
$CuL_2(OH)$	(11.3)	(11.9)
$CuL_2(OH)_2$	(1.4)	(9.9)
ZnL	11.73	11.73
ZnHL	20.01	8.28
ZnH_2L	28.49	8.48
ZnL_2	19.11	7.38
ZnH_2L_2	38.48	–
ZnH_4L_2	56.59	–
$ZnL2(OH)_2$	-2.52	–
MgL	4.1	4.1
MgHL	13.8	9.7
MgH_2L	23.1	9.3
MgL(OH)	(-6.8)	(10.9)
$MgL(OH)_2$	(-17.5)	(10.7)

[a]HL = HQ1-44, and charges are omitted for the sake of clarity. [b] Values in brackets are approximate

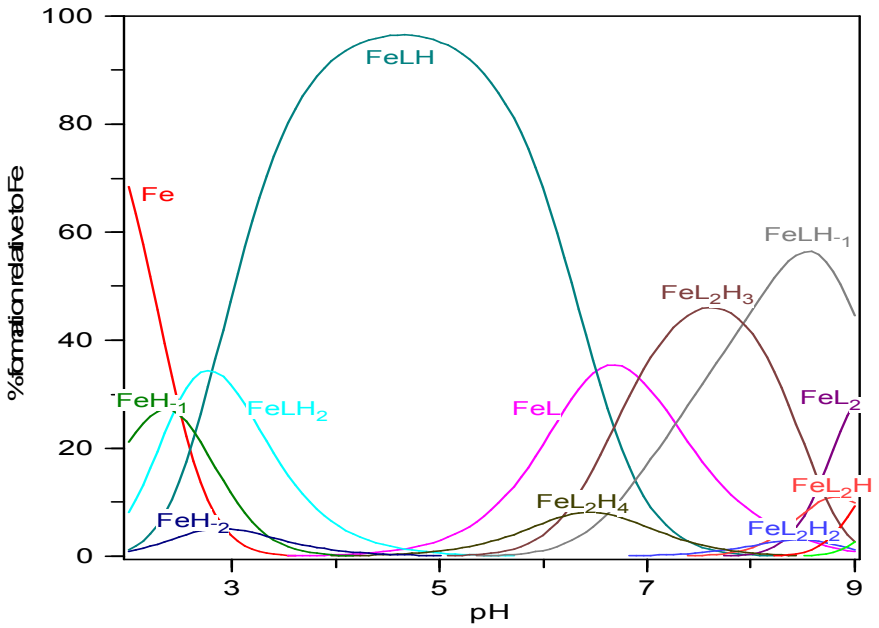

Figure. S2 – Speciation diagram for the iron(III) complexes of **HQ1-44** at 0.5 eq. of metal and $c_L = 2\times10^{-3}$ M.

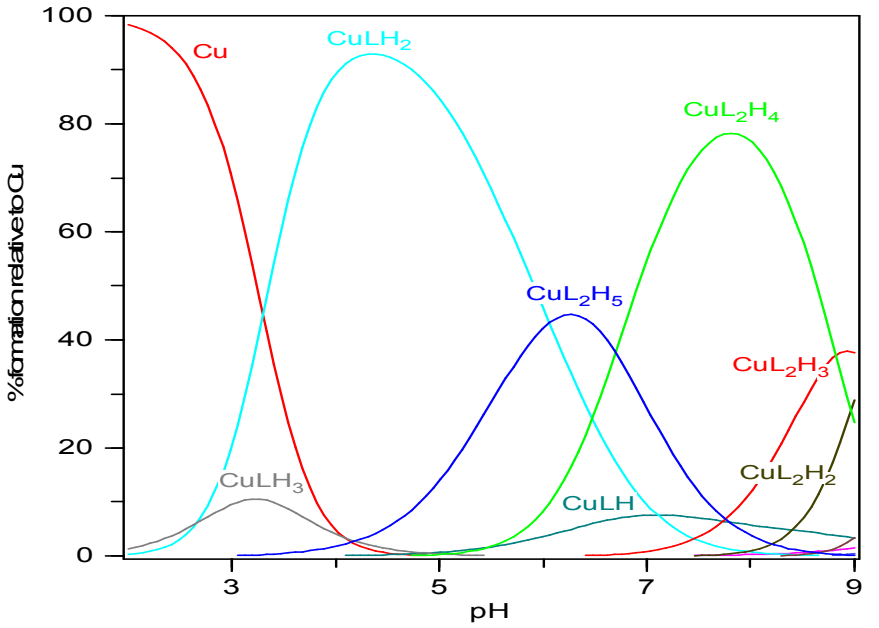

Figure. S3 – Speciation diagram for the copper(II) complexes of **HQ1-44** at 0.5 eq. of metal and $c_L = 2\times10^{-3}$ M.

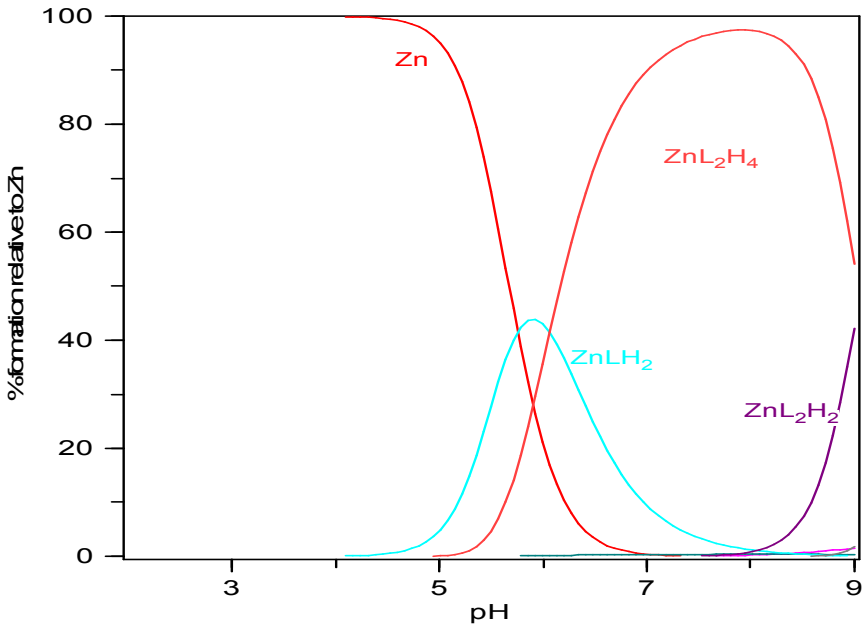

Figure. S4 – Speciation diagram for the zinc(II) complexes of **HQ1-44** at 0.5 eq. of metal and $c_L = 2\times10^{-3}$ M.

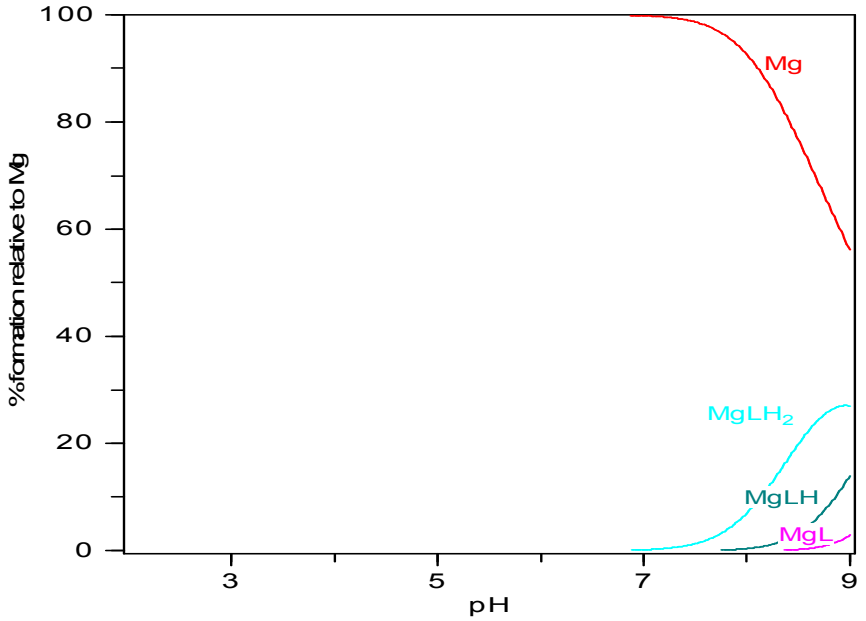

Figure. S5 – Speciation diagram for the magnesium(II) complexes of **HQ1-44** at 0.5 eq. of metal and $c_L = 2\times10^{-3}$ M.

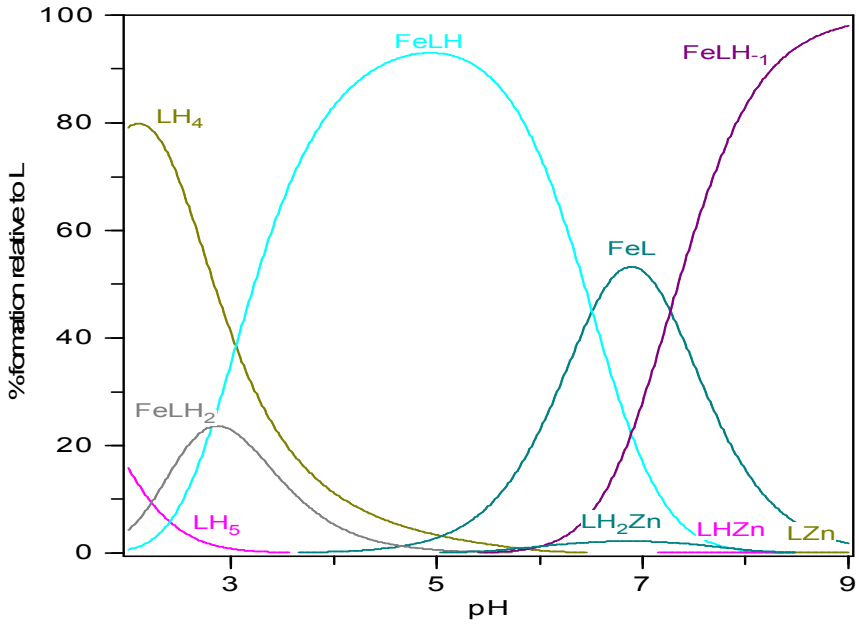

Figure. S6 – Speciation diagram for an equimolar mixture of **HQ1-44**, iron(III) and zinc(II) at 2×10^{-3} M.

Cartesian coordinates of optimized structures

Coordinates are in unit of Å

$[Fe(H_2O)_6]^{3+}$

O	0.0000000	0.0000000	-2.1016910
Fe	0.0000000	0.0000000	0.0000000
O	0.0000000	2.1016910	0.0000000
O	0.0000000	-2.1016910	0.0000000
O	-2.1016910	0.0000000	0.0000000
O	2.1016910	0.0000000	0.0000000
O	0.0000000	0.0000000	2.1016910
H	0.7814900	0.0000000	-2.6858790
H	-0.7814900	0.0000000	-2.6858790
H	-2.6858790	-0.7814900	0.0000000
H	-2.6858790	0.7814900	0.0000000
H	2.6858790	0.7814900	0.0000000
H	2.6858790	-0.7814900	0.0000000
H	0.7814900	0.0000000	2.6858790
H	-0.7814900	0.0000000	2.6858790
H	0.0000000	2.6858790	0.7814900
H	0.0000000	2.6858790	-0.7814900
H	0.0000000	-2.6858790	-0.7814900
H	0.0000000	-2.6858790	0.7814900

8-HQ

N	0.804533	1.492976	0
C	0	0.400421	0
C	0.473075	-0.948231	0
C	1.883264	-1.109219	0
C	2.700989	0.004959	0
C	2.112815	1.292283	0
C	-1.40799	0.671773	0
C	-2.306606	-0.385396	0
C	-1.823713	-1.712936	0
C	-0.470531	-2.007564	0
O	-1.804187	1.954039	0
H	2.310261	-2.112946	0
H	3.785812	-0.094275	0
H	2.742968	2.185307	0
H	-0.956464	2.450616	0
H	-3.375565	-0.180244	0
H	-2.548492	-2.527554	0
H	-0.124586	-3.040583	0

$[Fe(8\text{-}HQ)_1(H_2O)_4]^{3+}$

N	0.29753	0.798543	-0.000002

C	1.432346	0.041516	-0.000002
C	2.738966	0.61177	0
C	2.847331	2.021395	0.000001
C	1.681887	2.78798	0.000001
C	0.438487	2.142468	0
C	1.317115	-1.389646	-0.000003
C	2.453213	-2.224748	-0.000003
C	3.724022	-1.652042	-0.000002
C	3.877551	-0.251998	0
O	0.056035	-1.844592	-0.000004
H	-0.478462	2.730032	-0.000001
Fe	-1.696292	-0.063765	0.000001
O	-1.85041	-0.082499	-2.170867
O	-2.998432	-1.767763	0.000006
O	-1.850393	-0.082505	2.170869
H	1.72175	3.877174	0.000001
H	3.827772	2.500672	0.000002
H	4.87856	0.182723	0.000001
H	4.605304	-2.2944	-0.000002
H	2.342112	-3.311048	-0.000005
H	0.007976	-2.817641	-0.000007
H	-2.650802	-0.075985	-2.716992
H	-3.420424	-2.17013	0.773554
H	-2.650781	-0.075967	2.717002
H	-1.112667	-0.061509	2.797342
H	-1.112689	-0.061495	-2.797345
H	-3.420442	-2.170122	-0.773538
O	-2.95878	1.671274	0
H	-3.383003	2.072137	-0.773753
H	-3.382999	2.072145	0.773752

$[Fe(8\text{-}HQ)_2(H_2O)_2]^{3+}$

C	4.829114	-1.54955	0.579587
C	4.095828	-0.635513	-0.229938
C	2.741334	-0.334218	0.108383
C	2.167888	-0.972118	1.243475
C	2.900065	-1.863608	2.027828
C	4.2317 -2.15042	1.686609	
C	4.64422	0.006864	-1.364983
C	3.856696	0.888092	-2.098725
C	2.534943	1.12112	-1.696956
N	1.977136	0.542693	-0.614738
Fe	0.000005	0.985638	-0.00007
O	0.504706	2.563667	1.448106
O	0.866732	-0.642025	1.473221
N	-1.97714	0.542797	0.614647
C	-2.741332	-0.334249	-0.108317
C	-4.095833	-0.635473	0.230041

C	-4.644239	0.007123	1.364954
C	-3.856723	0.888488	2.09854
C	-2.534963	1.121433	1.696746
C	-2.167874	-0.972368	-1.243282
C	-2.900049	-1.863997	-2.027479
C	-4.231691	-2.150735	-1.686226
C	-4.829114	-1.549657	-0.579322
O	-0.866712	-0.642335	-1.473069
O	-0.50471	2.563347	-1.448612
H	1.902638	1.799066	-2.268058
H	4.247976	1.399164	-2.977246
H	5.674948	-0.192666	-1.660913
H	5.866992	-1.770057	0.33042
H	4.798919	-2.849749	2.300021
H	2.447884	-2.342104	2.898192
H	0.506671	-1.113078	2.242031
H	-0.506648	-1.113531	-2.241789
H	-2.44786	-2.34266	-2.897748
H	-4.798907	-2.850172	-2.299518
H	-5.866996	-1.770113	-0.330126
H	-5.674972	-0.192348	1.660908
H	-4.248013	1.399731	2.976956
H	-1.902664	1.799485	2.26773
H	-1.288744	2.553948	-2.015392
H	-0.164966	3.468429	-1.487403
H	1.288751	2.554388	2.014872
H	0.164934	3.468745	1.48675

HQ1-1

C	2.778452	1.195614	0.318857
C	1.379502	1.126034	0.095457
C	0.773072	-0.145579	-0.133995
C	1.576556	-1.332566	-0.137294
C	2.943046	-1.234941	0.082619
C	3.527433	0.031087	0.308472
C	0.496712	2.236817	0.081123
C	-0.85059	2.042044	-0.146265
C	-1.352171	0.730312	-0.368912
N	-0.552254	-0.328534	-0.361447
C	-2.827915	0.490542	-0.681101
N	-3.423134	-0.741711	-0.21072
C	-3.550112	-0.834185	1.235301
O	0.966528	-2.509368	-0.358133
H	-4.246306	-0.060199	1.588387
H	-1.537418	2.888431	-0.153416
H	0.890154	3.23916	0.256888
H	3.250509	2.161474	0.495318
H	4.603031	0.083215	0.479036

H	3.551149	-2.137765	0.078274
H	0.02728	-2.251464	-0.477862
H	-2.85108	-1.513794	-0.543884
H	-3.41763	1.335601	-0.297194
H	-2.937278	0.523939	-1.778893
H	-3.991508	-1.806152	1.491207
H	-2.609308	-0.726868	1.806799

$[Fe(HQ1\text{-}1)_1(H_2O)_3]^{3+}$

C	4.076048	0.308374	-0.014963
C	2.778511	0.900962	-0.019791
C	1.630782	0.058971	0.00516
C	1.819735	-1.360838	0.050937
C	3.107831	-1.926092	0.059948
C	4.225281	-1.088961	0.025121
C	2.557647	2.298337	-0.045594
C	1.254403	2.7887	-0.036381
C	0.172613	1.890045	-0.006191
N	0.361086	0.550507	0.00241
Fe	-1.406543	-0.613768	0.013071
N	-2.200458	1.349354	-0.419935
C	-3.611321	1.61941	-0.039254
C	-1.252951	2.368149	0.080784
O	0.679605	-2.073255	0.092926
O	-2.622998	-2.355715	0.173513
O	-1.655895	-0.505311	2.196127
O	-1.484996	-1.066257	-2.182743
H	-3.931768	2.606953	-0.400521
H	1.070396	3.862711	-0.054217
H	3.402438	2.988503	-0.071762
H	4.959309	0.948149	-0.04115
H	5.223756	-1.52694	0.031769
H	3.238562	-3.009426	0.097555
H	0.847945	-3.031524	0.135398
H	-2.151551	1.367797	-1.443508
H	-1.485092	2.574358	1.137289
H	-1.381404	3.319313	-0.456869
H	-4.265177	0.865059	-0.490132
H	-3.71908	1.597479	1.049615
H	-2.261134	-1.20935	-2.744439
H	-2.926181	-2.769965	0.994707
H	-2.480155	-0.480276	2.704126
H	-0.946597	-0.471233	2.853735
H	-0.724803	-1.166113	-2.772946
H	-2.900935	-2.94459	-0.543053

$[Fe(HQ1\text{-}1)_2]^{3+}$

Fe	-0.000003	0.569952	-0.000007

N	2.019225	0.265276	-0.414951
N	-2.019222	0.265275	0.414951
C	2.583264	1.079958	-1.329627
C	-2.583251	1.079942	1.329647
C	3.944097	0.983163	-1.672778
C	-3.944083	0.983154	1.672801
C	4.737021	0.020441	-1.062697
C	-4.737018	0.020448	1.062708
C	4.175866	-0.85389	-0.100857
C	-4.175873	-0.853874	0.100853
C	4.914853	-1.865102	0.572308
C	-4.91487	-1.86507	-0.572322
C	4.289178	-2.682348	1.509071
C	-4.289205	-2.682307	-1.5091
C	2.925325	-2.521419	1.812069
C	-2.925352	-2.521382	-1.812102
C	2.186411	-1.535571	1.161261
C	-2.186429	-1.535548	-1.161285
C	2.789454	-0.687165	0.194882
C	-2.789461	-0.687152	-0.194891
O	0.862461	-1.291452	1.382685
O	-0.86248	-1.29143	-1.382711
H	0.486652	-1.947751	1.990562
H	-0.486689	-1.947705	-1.990627
H	2.458143	-3.166756	2.557841
H	-2.458177	-3.166711	-2.557886
H	4.857893	-3.456035	2.023604
H	-4.857927	-3.455984	-2.023641
H	5.97479	-1.991154	0.353608
H	-5.974807	-1.991119	-0.353619
H	5.791475	-0.066932	-1.327294
H	-5.791471	-0.066921	1.327309
H	4.367008	1.658145	-2.415635
H	-4.366985	1.658126	2.415672
C	1.690653	2.135169	-1.92891
C	-1.690624	2.135127	1.928953
N	0.266271	1.756083	-1.821915
N	-0.266247	1.756036	1.82193
C	-0.655434	2.885951	-2.094599
C	0.655466	2.885891	2.094638
H	1.971272	2.335917	-2.973516
H	-1.971231	2.33584	2.973569
H	1.844003	3.079204	-1.383617
H	-1.843974	3.079182	1.383696
H	0.088584	1.053127	-2.544294
H	-0.088553	1.053057	2.544286
H	-0.454491	3.335	-3.077088
H	0.45453	3.334916	3.07714

H	-1.687852	2.523052	-2.086946
H	1.687882	2.522987	2.086969
H	-0.536036	3.661835	-1.331846
H	0.536067	3.661796	1.331906