

SUPPLEMENTARY MATERIALS

Bifunctional 3-hydroxy-4-pyridinones as potential selective iron(III) chelators: solution studies and comparison with other metals of biological and environmental relevance

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Tables

Table S1. Overall and stepwise protonation constants¹ of the 3-hydroxy-4-pyridinones under study reported in the literature at $I = 0.15 \text{ mol L}^{-1}$ in $\text{NaCl}_{(\text{aq})}$ and different temperatures [13].

Ligand	$I/\text{mol L}^{-1}$	T/K	$\log K_1^{\text{H}}$	$\log \beta_2^{\text{H}} (\log K_2^{\text{H}})$	$\log \beta_3^{\text{H}} (\log K_3^{\text{H}})$	$\log \beta_4^{\text{H}} (\log K_4^{\text{H}})$
$\text{H}_2(\text{L1})$	0.15	298.15	9.947	14.36 (4.41)	17.74 (3.38)	-
$\text{H}_2(\text{L2})$	0.15	298.15	10.73	19.52 (8.79)	24.17 (4.65)	27.43 (3.26)
	0.15	310.15	10.99	17.05 (6.06)	21.02 (3.97)	24.08 (3.06)
$\text{H}_2(\text{L3})$	0.15	298.15	10.93	20.70 (9.77)	25.60 (4.90)	29.02 (3.42)
$\text{H}_2(\text{L4})$	0.15	298.15	11.10	20.44 (9.34)	24.60 (4.16)	27.87 (3.27)
$\text{H}(\text{L5})$	0.15	298.15	11.08	20.468(9.388)	23.68 (3.21)	-
	0.15	310.15	10.57	16.53 (5.96)	19.53 (3.00)	-

¹ $\log \beta_r^{\text{H}}$ and $\log K_r^{\text{H}}$ refer to the equilibria: $r\text{H}^+ + \text{L}^{z-} = \text{H}_r\text{L}^{-(z-r)}$ and $\text{H}^+ + \text{H}_{(r-1)}\text{L}^{-(z-(r-1))} = \text{H}_r\text{L}^{-(z-r)}$, respectively.

Table S2. Literature stability constants of Cu²⁺ and Fe³⁺/ligands species reported at different temperatures, ionic strengths and ionic media in molar concentration scale

M ⁿ⁺	Ligand	logβ _{MH₂L}	logβ _{MHL}	logβ _{ML}	logβ _{ML₂}	logβ _{MHL₂}	logβ _{MH₂L₂}	logβ _{MOHL₂}	logβ _{ML₃}	logβ _{MHL₃}	logβ _{MH₂L₃}	logβ _{MH₃L₃}	logβ _{M₂L}	logβ _{M₂L₂}	logβ _{M₂L₃}	Ref.
Cu ²⁺	<i>DFP</i> ¹	-	-	10.62	19.68	-	-	-	-	-	-	-	-	-	-	[33]
Cu ²⁺	<i>DFP</i> ¹	-	-	10.42	19.09	21.98	-	8.49	-	-	-	-	-	-	-	[34]
Cu ²⁺	<i>Asp</i> ²	-	12.84	9.04	15.86	-	-	-	-	-	-	-	-	-	-	[22]
Cu ²⁺	<i>AcNPrHP</i> ¹	-	-	10.29	18.99	-	-	-	-	-	-	-	-	-	-	[35]
Fe ³⁺	H₂(L1) ³	-	19.62	-	28.79	33.12	36.45	-	37.01	-	-	-	-	-	-	[32]
Fe ³⁺	H₂(L4) ³	-	25.01	-	-	-	46.20	-	-	48.43	57.52	65.68	-	-	-	[31]
Fe ³⁺	<i>DFP</i> ¹	-	-	15.10	26.61	-	-	-	35.88	-	-	-	-	-	-	[33]
Fe ³⁺	<i>DFP</i> ¹	-	-	15.14	26.68	-	-	-	35.92	-	-	-	-	-	-	[36]
Fe ³⁺	<i>DFP</i> ¹	-	-	15.01	27.30	-	-	-	37.43	-	-	-	-	-	-	[34]
Fe ³⁺	<i>DFP</i> ¹	-	-	14.80	26.70	-	-	-	36.56	-	-	-	-	-	-	[34]
Fe ³⁺	H₂(S1) ⁴	-	-	14.26	25.73	34.91	-	-	-	-	-	-	-	-	-	[38]
Fe ³⁺	H₂(S2) ⁵	-	-	15.70	27.30	36.70	-	-	-	-	-	-	-	-	-	[39]
Fe ³⁺	H₂(S3) ⁵	-	-	16.60	28.00	35.90	-	-	-	-	-	-	-	-	-	[39]
Fe ³⁺	<i>Asp</i> ⁶	-	-	11.40	-	-	-	-	-	-	-	-	-	-	-	[22]
Fe ³⁺	<i>Orn</i> ⁷	-	-	8.70	-	-	-	-	-	-	-	-	-	-	-	[37]

¹ *I* = 0.10 mol L⁻¹ in KCl_(aq), *T* = 298.15 K; ² *I* = 0.15 mol L⁻¹ in NaCl_(aq), *T* = 298.15 K; ³ *I* = 0.10 mol L⁻¹ in KNO_{3(aq)}, *T* = 298.15 K; ⁴ *I* = 0.10 mol L⁻¹ in KCl_(aq), *T* = 310.15 K; ⁵ *I* = 0.10 mol L⁻¹ in MOPS (3-(*N*-morpholino)propanesulphonic acid) buffer at pH = 7.4, *T* = 298.15 K; ⁶ *I* = 0.10 mol L⁻¹ in Na⁺ background electrolyte, *T* = 293.15 K; ⁷ *I* = 0.10 mol L⁻¹ in NaClO_{4(aq)}, *T* = 293.15 K.

Ligands abbreviations: *DFP* = Deferiprone; *Asp* = *L*-Aspartic acid; *Orn* = *L*-Ornithine; *AcNPrHP* = 1-(3'-methylcarboxyaminopropyl)-3-hydroxy-2-methyl-4-pyridinone; **H₂(L1)** = 4-(3-hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)butanoic acid; **H₂(L4)** = (S)-2-amino-5-(3-hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)pentanoic acid; **H₂(S1)** = 3-hydroxy-2-methylpyridin-4(1H)-one; **H₂(S2)** = 3-hydroxy-1-(2-hydroxyethyl)-2-methylpyridin-4(1H)-one; **H₂(S3)** = 3-(3-hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)propanoic acid.

Table S3. $pL_{0.5}^1$ values of $\text{Fe}^{3+}/\text{H}_2(\text{L2})$ and $\text{Fe}^{3+}/\text{H}(\text{L5})$ systems at different pHs and temperature, from UV-Vis data at $I = 0.15 \text{ mol L}^{-1}$ in $\text{NaCl}_{(\text{aq})}$

Ligand	T/K	pH	$pL_{0.5}$	Ligand	T/K	pH	$pL_{0.5}$
$\text{H}_2(\text{L2})$	298.15	2.0	4.45	$\text{H}_2(\text{L2})$	310.15	5.0	11.37
$\text{H}_2(\text{L2})$	298.15	3.0	6.88	$\text{H}_2(\text{L2})$	310.15	6.0	11.42
$\text{H}_2(\text{L2})$	298.15	4.0	8.12	$\text{H}_2(\text{L2})$	310.15	7.4	11.35
$\text{H}_2(\text{L2})$	298.15	5.0	8.60	$\text{H}(\text{L5})$	310.15	2.0	10.41
$\text{H}_2(\text{L2})$	298.15	6.0	8.77	$\text{H}(\text{L5})$	310.15	3.0	10.83
$\text{H}_2(\text{L2})$	298.15	7.4	9.45	$\text{H}(\text{L5})$	310.15	4.0	10.92
$\text{H}_2(\text{L2})$	298.15	8.1	9.83	$\text{H}(\text{L5})$	310.15	5.0	11.37
$\text{H}_2(\text{L2})$	310.15	2.0	8.04	$\text{H}(\text{L5})$	310.15	6.0	11.52
$\text{H}_2(\text{L2})$	310.15	3.0	10.36	$\text{H}(\text{L5})$	310.15	7.4	11.51
$\text{H}_2(\text{L2})$	310.15	4.0	11.26				

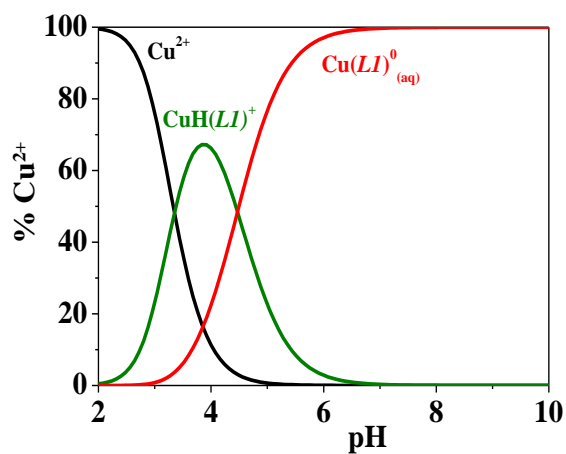
¹ values calculated by eq. (3).

Table S4. Literature stability constants of $\text{ZnL}^{(2-z)}$ [19] and $\text{AlL}^{(3-z)}$ [13] species at $I = 0.15 \text{ mol L}^{-1}$ in $\text{NaCl}_{(\text{aq})}$, $T = 298.15 \text{ K}$.

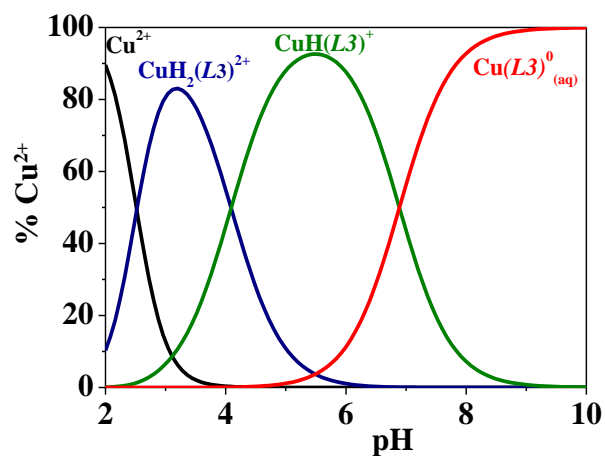
Ligand	$\log K_{110}^1$	
	$\text{ZnL}^{(2-z)}$	$\text{AlL}^{(3-z)}$
$\text{H}_2(\text{L1})$	7.27	12.57
$\text{H}_2(\text{L2})$	8.20	17.90
$\text{H}_2(\text{L3})$	9.52	17.57
$\text{H}_2(\text{L4})$	9.68	18.60
$\text{H}(\text{L5})$	9.22	15.08

¹ $\log K_{110}$ values refer to equilibrium: $\text{M}^{n+} + \text{L}^{z-} = \text{ML}^{(n-z)}$, where $\text{M}^{n+} = \text{Zn}^{2+}$ and Al^{3+}

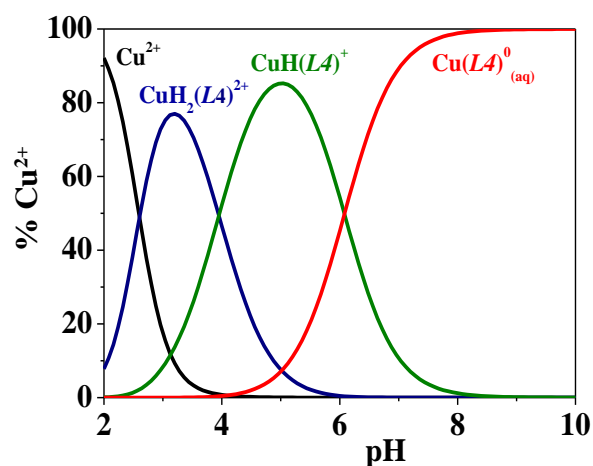
Figures



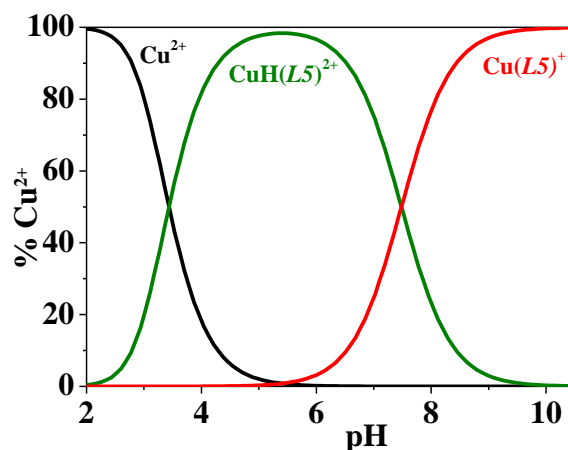
(a)



(b)

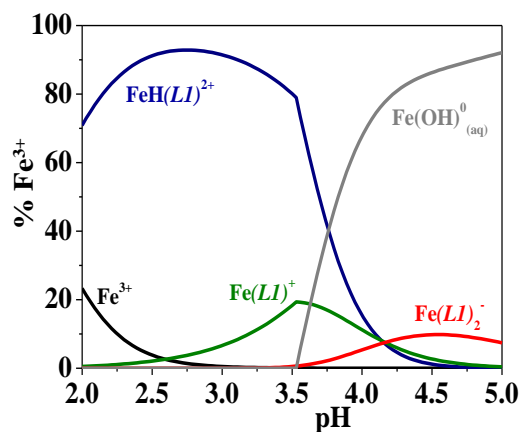


(c)

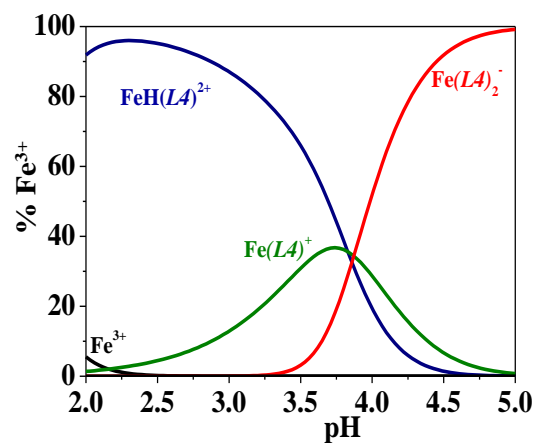


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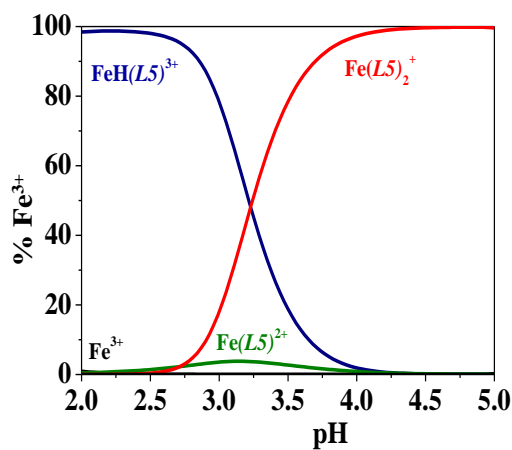
Figure S1. Distribution diagram of $\text{Cu}^{2+}/(3,4\text{-HPs})$ systems at $T = 298.15\text{ K}$, $I = 0.15\text{ mol L}^{-1}$ in $\text{NaCl}_{(\text{aq})}$, $c_{\text{Cu}^{2+}} = 5.0 \cdot 10^{-4}\text{ mol L}^{-1}$ and $c_{\text{ligand}} = 1.5 \cdot 10^{-3}\text{ mol L}^{-1}$. Ligands = $\text{H}_2(\text{L1})$ (a), $\text{H}_2(\text{L3})$ (b), $\text{H}_2(\text{L4})$ (c), $\text{H}(\text{L5})$ (d).



(a)



(b)



(c)

Figure S2. Distribution diagram of Fe³⁺/(3,4-HPs) systems at $T = 298.15$ K, $I = 0.15$ mol L⁻¹ in NaCl_(aq), $c_{\text{Fe}^{3+}} = 5.0 \cdot 10^{-4}$ mol L⁻¹ and $c_{\text{ligand}} = 1.1 \cdot 10^{-3}$ mol L⁻¹. Ligands = H₂(L1) (a), H₂(L4) (b), H(L5) (c).

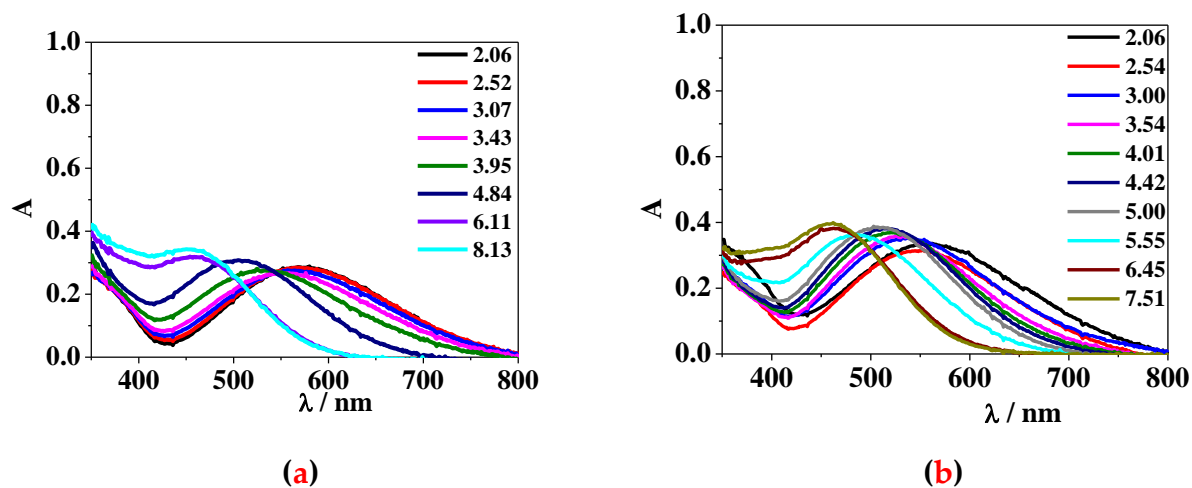
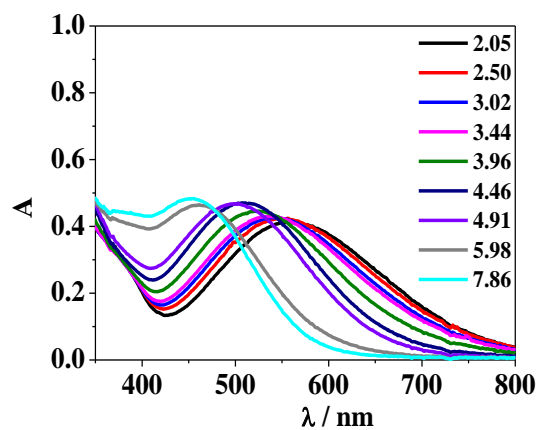


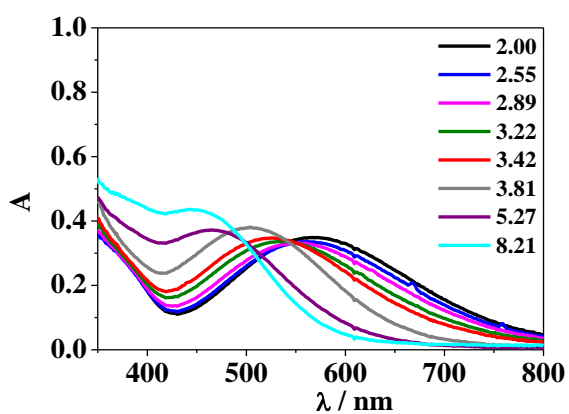
Figure S3. UV-Vis absorption profile of $\text{Fe}^{3+}/\text{H}_2(\text{L}2)$ system at $I = 0.15 \text{ mol L}^{-1}$ in $\text{NaCl}_{(\text{aq})}$, $T = 310.15 \text{ K}$ and at different pH values.

(a) $c_{\text{Fe}^{3+}} = 2.3 \cdot 10^{-4} \text{ mol L}^{-1}$, $c_{\text{ligand}} = 2.2 \cdot 10^{-4} \text{ mol L}^{-1}$;

(b) $c_{\text{Fe}^{3+}} = 2.0 \cdot 10^{-4} \text{ mol L}^{-1}$, $c_{\text{ligand}} = 4.0 \cdot 10^{-4} \text{ mol L}^{-1}$.



(a)

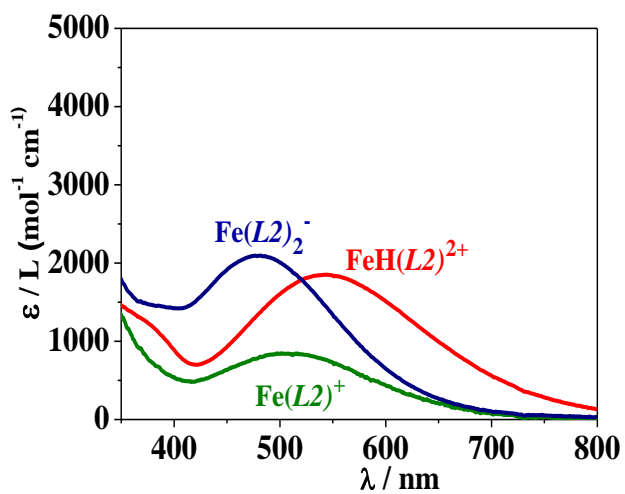


(b)

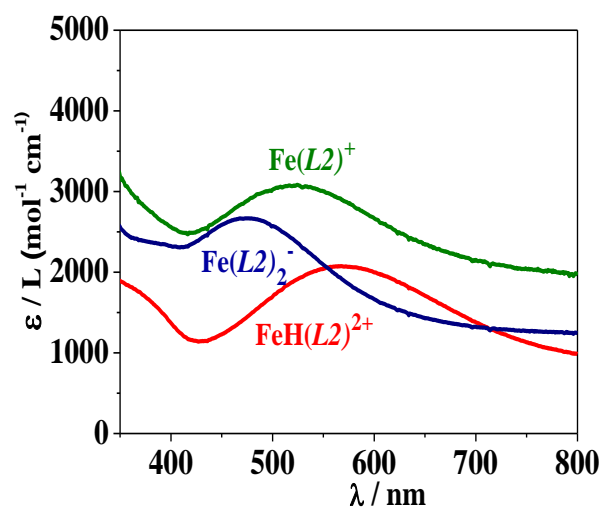
Figure S4. UV-Vis absorption profile of $\text{Fe}^{3+}/\text{H}(\text{L5})$ system at $I = 0.15 \text{ mol L}^{-1}$ in $\text{NaCl}_{(\text{aq})}$, different temperatures and pH values.

(a) $T = 298.15 \text{ K}$, $c_{\text{Fe}^{3+}} = 2.4 \cdot 10^{-4} \text{ mol L}^{-1}$, $c_{\text{ligand}} = 2.6 \cdot 10^{-4} \text{ mol L}^{-1}$;

(b) $T = 310.15 \text{ K}$, $c_{\text{Fe}^{3+}} = 2.5 \cdot 10^{-4} \text{ mol L}^{-1}$, $c_{\text{ligand}} = 2.4 \cdot 10^{-4} \text{ mol L}^{-1}$.



(a)



(b)

Figure S5. Graphical representation of calculated molar absorptivity of $\text{Fe}^{3+}/\text{H}_2(\text{L2})$ species at $T = 298.15 \text{ K}$ (a) and 310.15 K (b), $I = 0.15 \text{ mol L}^{-1}$ in $\text{NaCl}_{(\text{aq})}$.

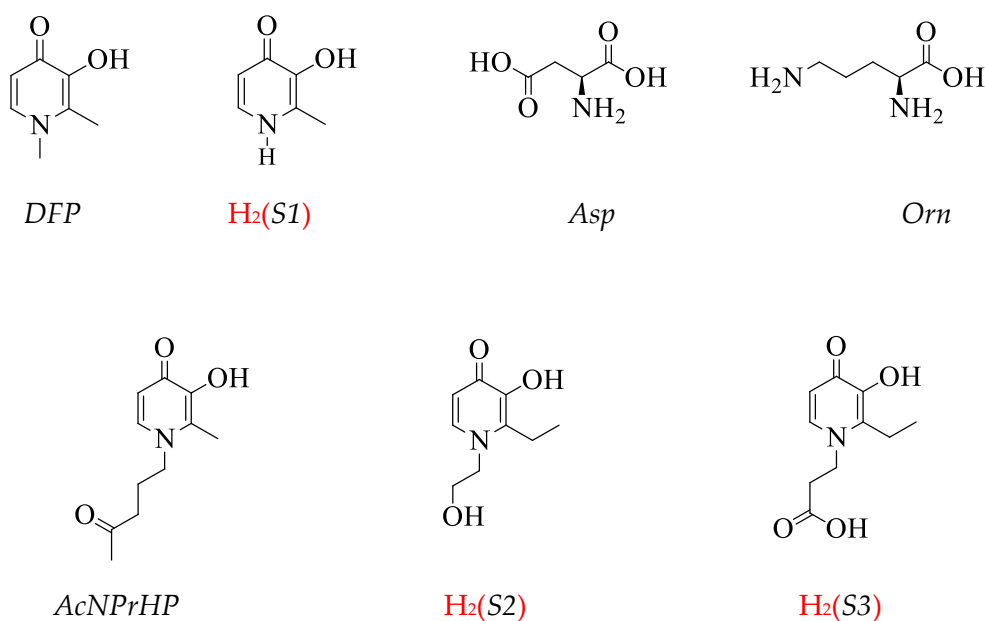
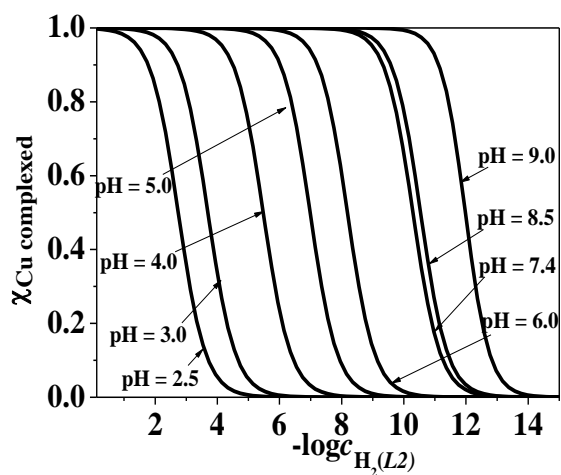
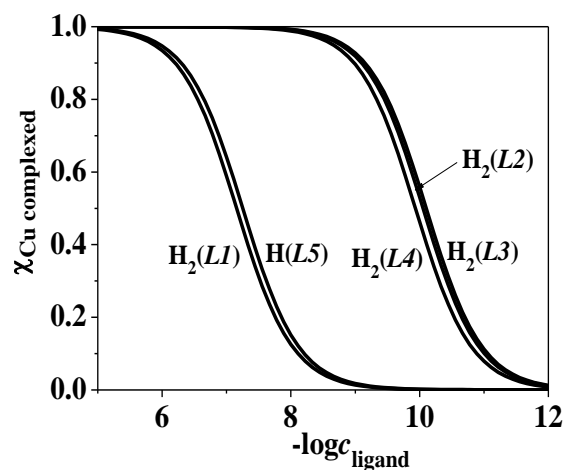


Figure S6. Molecular structures of compounds with similar structures and functional groups with respect to 3-hydroxy-4-pyridinones.

Abbreviations: *DFP* = Deferiprone; *Asp* = L-Aspartic acid; *Orn* = L-Ornithine; *AcNPrHP* = 1-(3'-methylcarboxyaminopropyl)-3-hydroxy-2-methyl-4-pyridinone; **H₂(S1)** = 3-hydroxy-2-methylpyridin-4(1H)-one; **H₂(S2)** = 3-hydroxy-1-(2-hydroxyethyl)-2-methylpyridin-4(1H)-one; **H₂(S3)** = 3-(3-hydroxy-2-methyl-4-oxopyridin-1(4H)-yl)propanoic acid.



(a)



(b)

Figure S7. Sequestration diagrams of: **(a)** $\text{Cu}^{2+}/\text{H}_2(\text{L2})$ species at $I = 0.15 \text{ mol L}^{-1}$ in $\text{NaCl}_{(\text{aq})}$ and $T = 298.15 \text{ K}$ and different pHs, $pL_{0.5}$ values: 2.74 (pH = 2.5), 3.70 (pH = 3.0), 5.48 (pH = 4.0), 6.99 (pH = 5.0), 8.18 (pH = 6.0), 10.29 (pH = 7.4), 10.54 (pH = 8.1), 11.98 (pH = 9.0); **(b)** $\text{Cu}^{2+}/(3,4\text{-HPs})$ systems at the same ionic strengths and temperature, pH = 7.4. $pL_{0.5}$ values: 7.09 ($\text{H}_2(\text{L1})$), 10.29 ($\text{H}_2(\text{L2})$), 10.30 ($\text{H}_2(\text{L3})$), 9.90 ($\text{H}_2(\text{L4})$), 7.25 ($\text{H}(\text{L5})$).

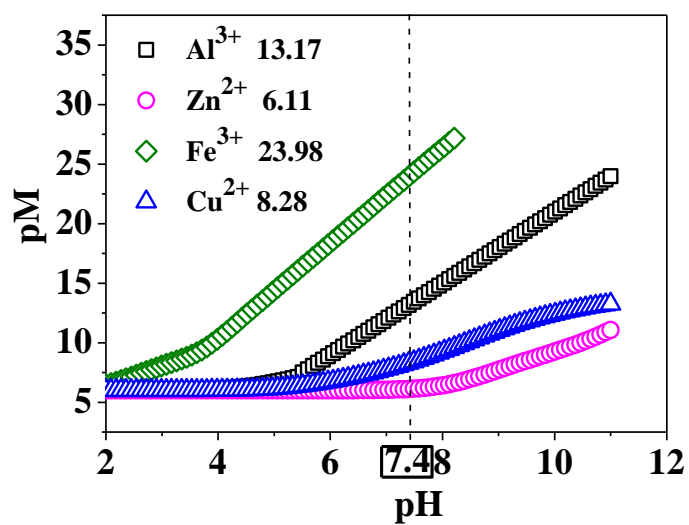


Figure S8. Calculated pM values *vs.* pH for the different $M^{n+}/H(L5)$ systems at $T = 298.15$ K, $I = 0.15 \text{ mol L}^{-1}$ in $\text{NaCl}_{(\text{aq})}$, $c_{M^{n+}} = 1.0 \cdot 10^{-6} \text{ mol L}^{-1}$ and $c_{\text{ligand}} = 1.0 \cdot 10^{-5} \text{ mol L}^{-1}$.