Supplementary material

How copper(II) and zinc(II) bind to tau protein and how might this promote aggregation?

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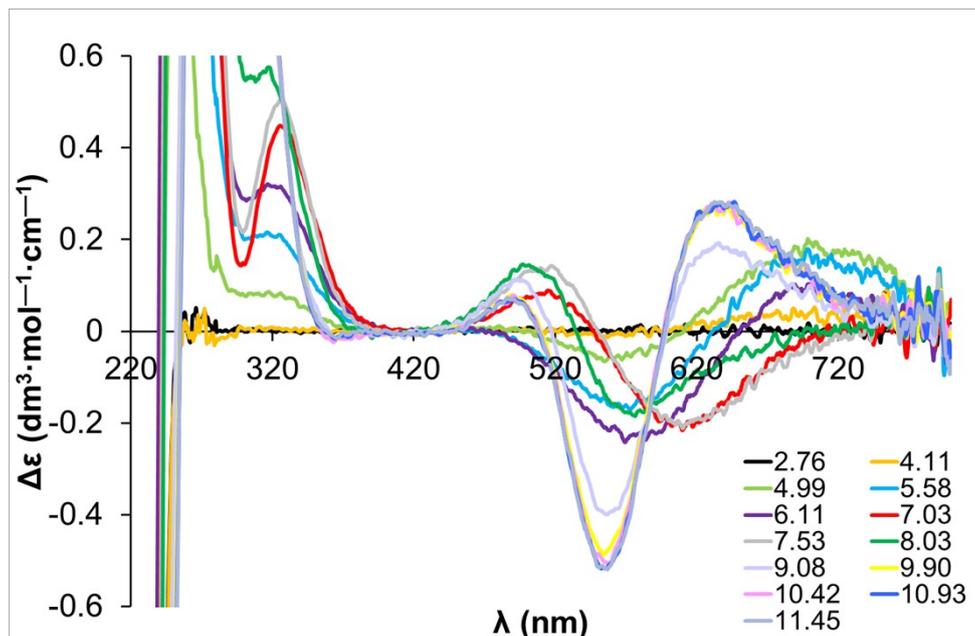
Figure S1. pH-dependent CD spectra of the Cu(II)–tau(30-34)(327-332) system at 1:1 metal to ligand ratio (c(L) = 1.27 mM)
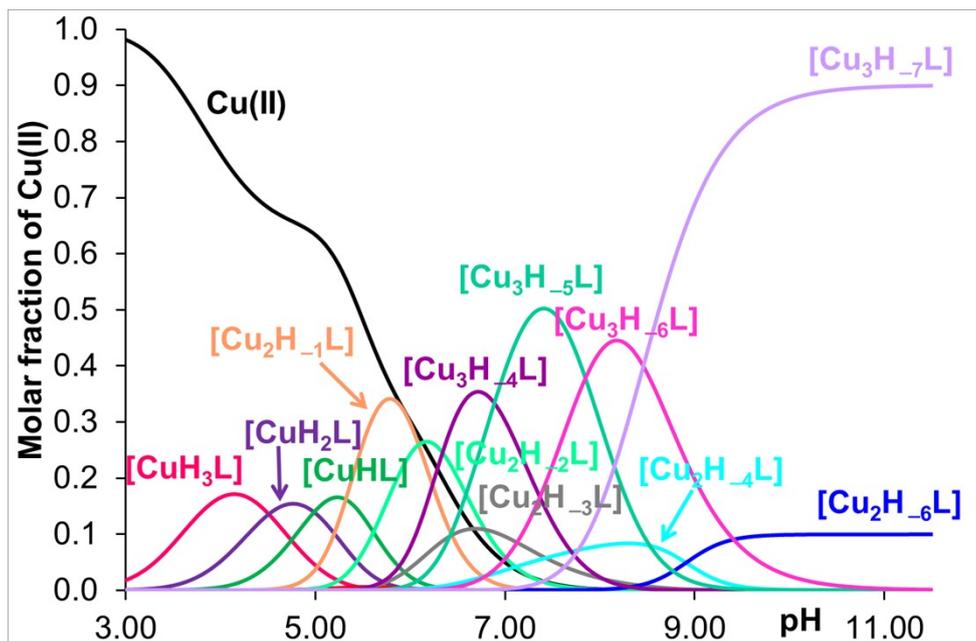

Figure S2. Species distribution diagram of the Cu(II)–tau(30-34)(327-332) system at 3:1 metal to ligand ratio (c(L) = 1.05 mM)
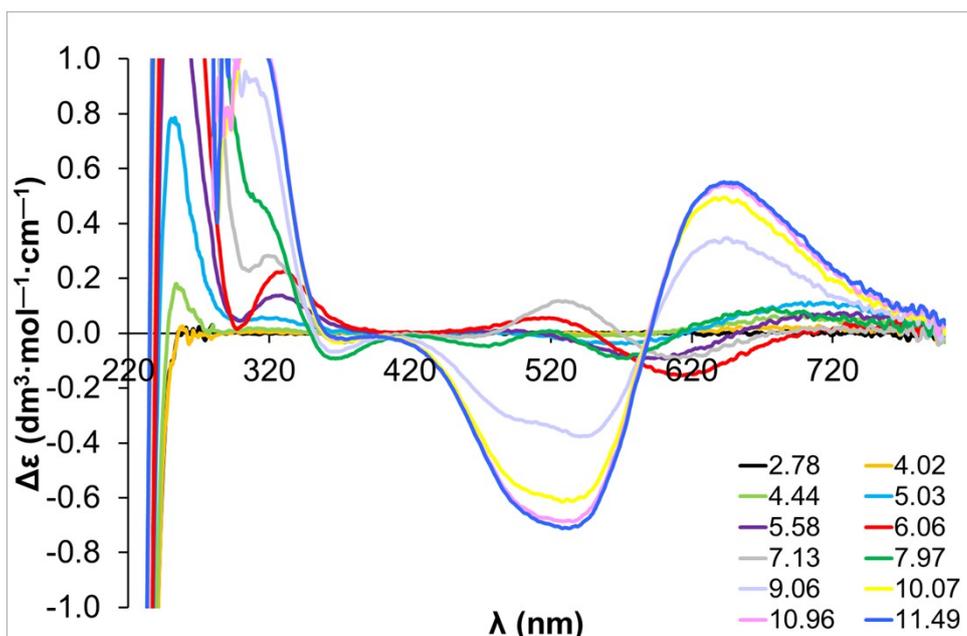
Figure S3. pH-dependent CD spectra of the Cu(II)–tau(30-34)(327-332) system at 2:1 metal to ligand ratio (c(L) = 1.27 mM)
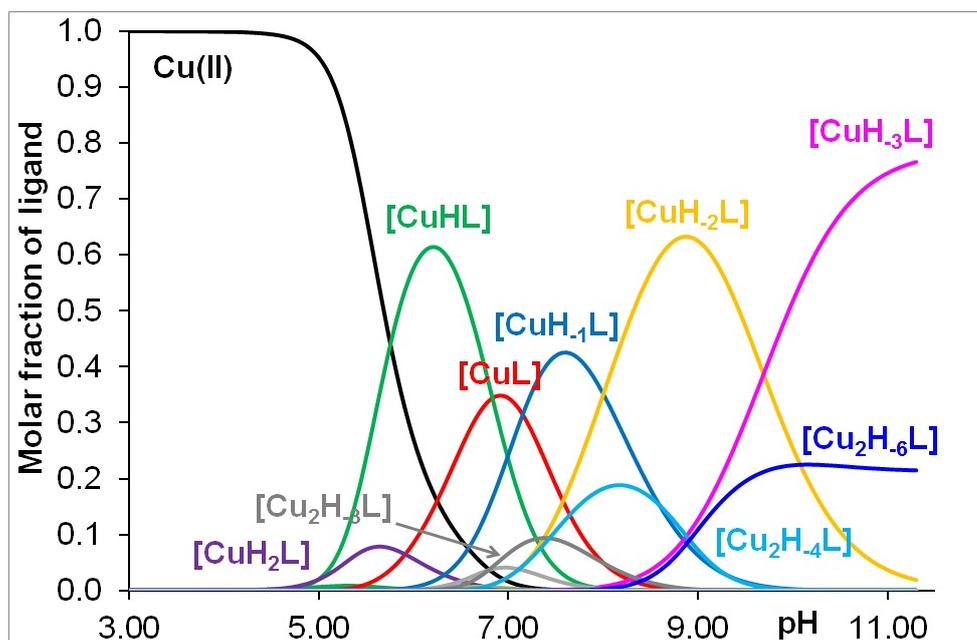

Figure S4. Species distribution diagram of the Cu(II)–tau(30-34)(327-332) system at 1:1 metal to ligand ratio. The distribution curves are plotted together with the change of absorption maxima (c(L) = 1.00 μM) (For simplicity the charges have been omitted.)

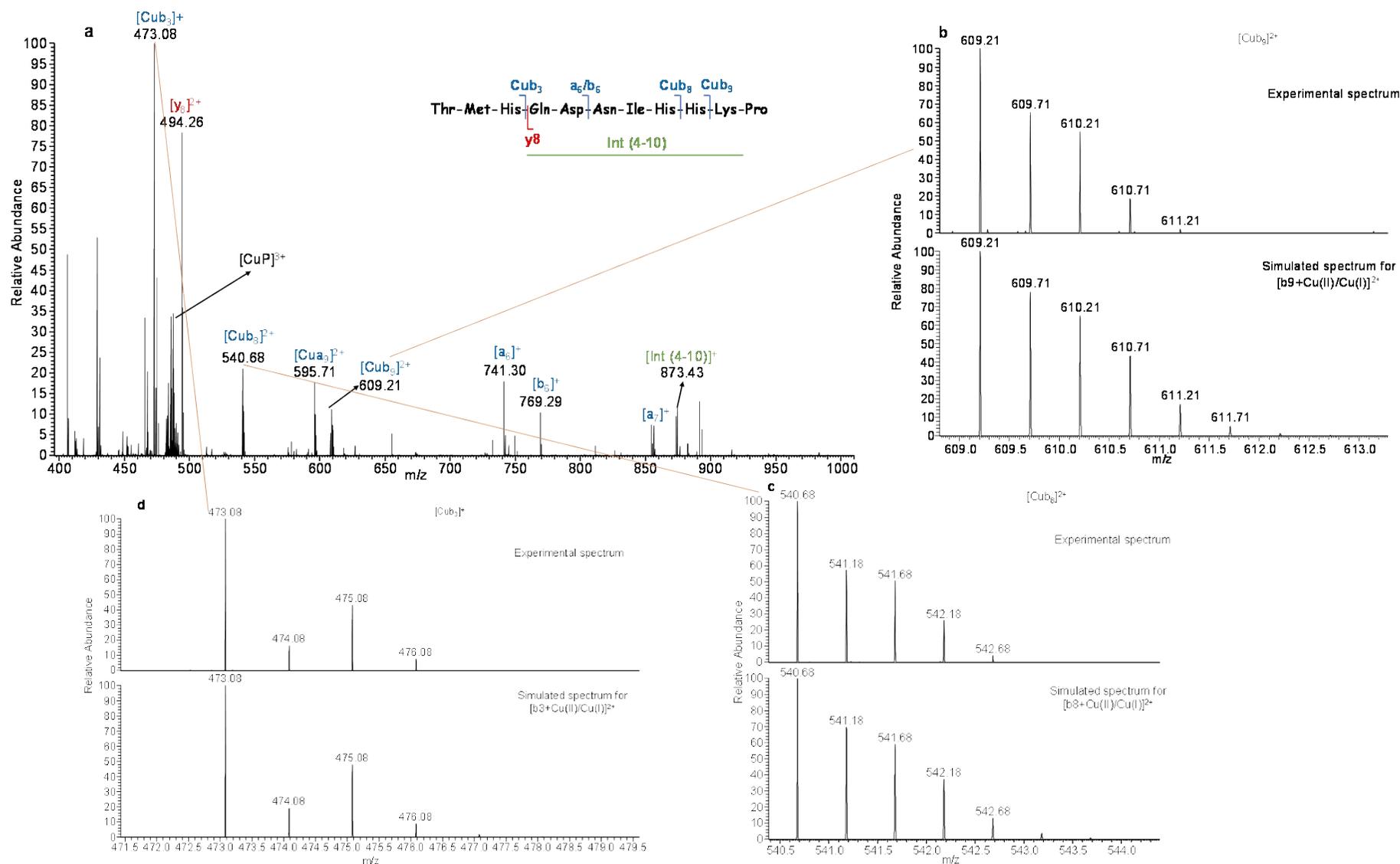**Figure S5**. **a)** HCD spectra of [Cu(II)–tau(30-34)(327-332)]$^{3+}$ (m/z =487.53) at CE 25. b_n/a_n type fragments (blue color), y_n type fragments (red color) and internal fragments (green color), were indicated. **b)** isotopic distribution of the peak corresponding to [Cu–b_9]$^{2+}$ (m/z 609.21), the theoretical isotopic distribution of [b_9+Cu(II)/Cu(I)]$^{2+}$ was calculated considering the molecular formula 0.8 × $C_{48}H_{67}N_{17}O_{15}SCu$ + 0.2 × $C_{48}H_{68}N_{17}O_{15}SCu$; **c)** isotopic distribution of peak corresponding to the Cu–b_8 fragment, the theoretical isotopic distribution of [b_8+Cu(II)/Cu(I)]$^{2+}$ was calculated considering the molecular formula 0.8 × $C_{42}H_{60}N_{14}O_{14}SCu$ + 0.2 × $C_{42}H_{61}N_{14}O_{14}SCu$; **d)** isotopic distribution of peak corresponding to the Cu–b_3 fragment, the theoretical isotopic distribution of [b_3+Cu(II)/Cu(I)]$^{+}$ was calculated considering the molecular formula $C_{17}H_{23}N_5O_5SCu$
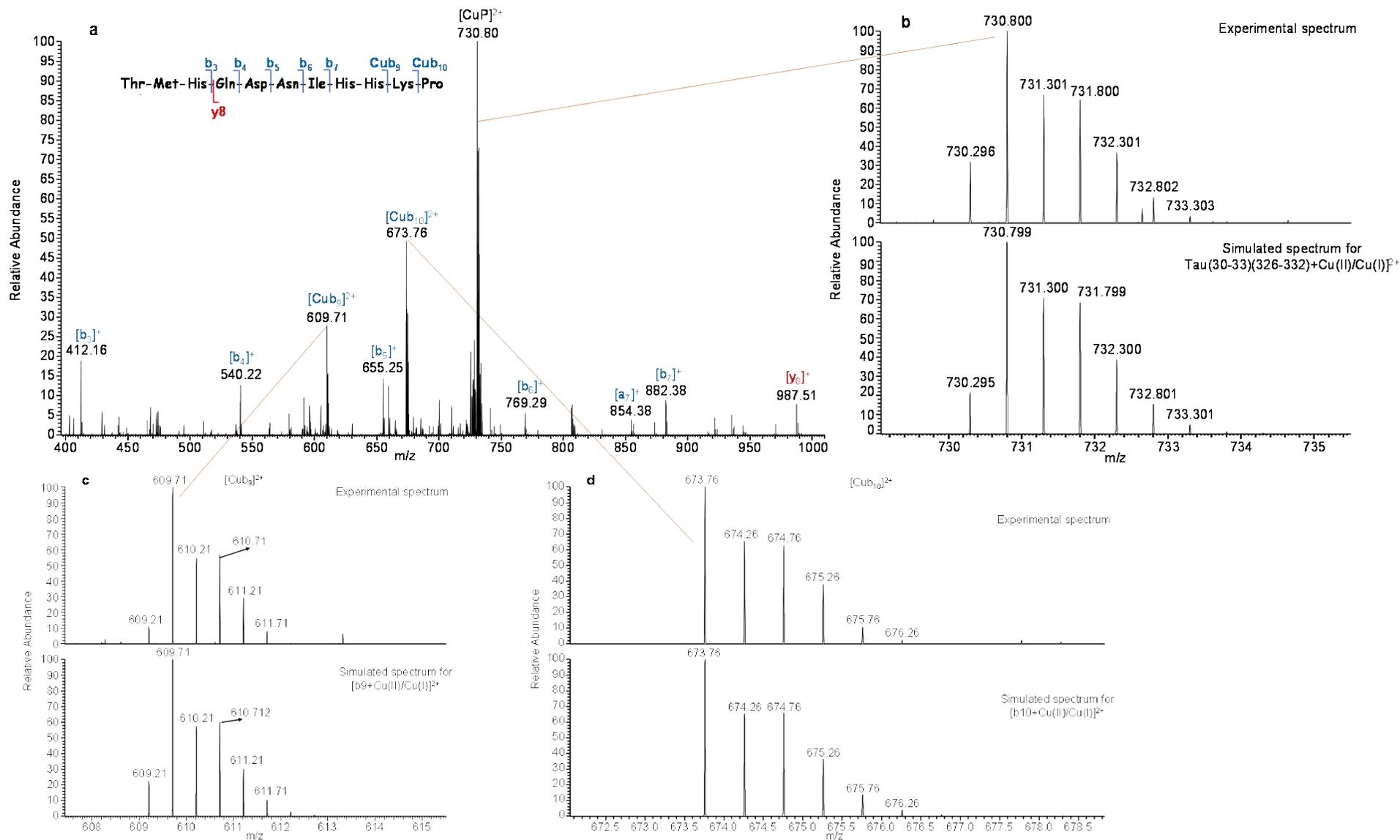
Figure S6. a) HCD spectra of [Cu(II)–tau(30-34)(327-332)]$^{2+}$ (m/z =730.80) at CE 25. b_n/a_n type fragments (blue color) and y_n type fragments (red color), were indicated. **b)** isotopic distribution of the peak corresponding to [Cu–tau(30-34)(327-332)]$^{2+}$ (m/z 730.80), the theoretical isotopic distribution of [tau(30-34)(327-332))+Cu(II)/Cu(I)]$^{2+}$ was calculated considering the molecular formula 0.2 × $C_{59}H_{89}N_{21}O_{17}SCu + 0.8 × C_{59}H_{90}N_{21}O_{17}SCu$; **c)** isotopic distribution of peak corresponding to the Cu–b_9 fragment, the theoretical isotopic distribution of [b_9+Cu(II)/Cu(I)]$^{2+}$ was calculated considering the molecular formula 0.2 × $C_{48}H_{67}N_{17}O_{15}SCu + 0.8 × C_{48}H_{68}N_{17}O_{15}SCu$; **d)** isotopic distribution of peak corresponding to the Cu–b_{10} fragment, the theoretical isotopic distribution of [b_{10}+Cu(II)/Cu(I)]$^{2+}$ was calculated considering the molecular formula 0.2 × $C_{54}H_{79}N_{19}O_{16}SCu + 0.8 × C_{54}H_{80}N_{19}O_{16}SCu$

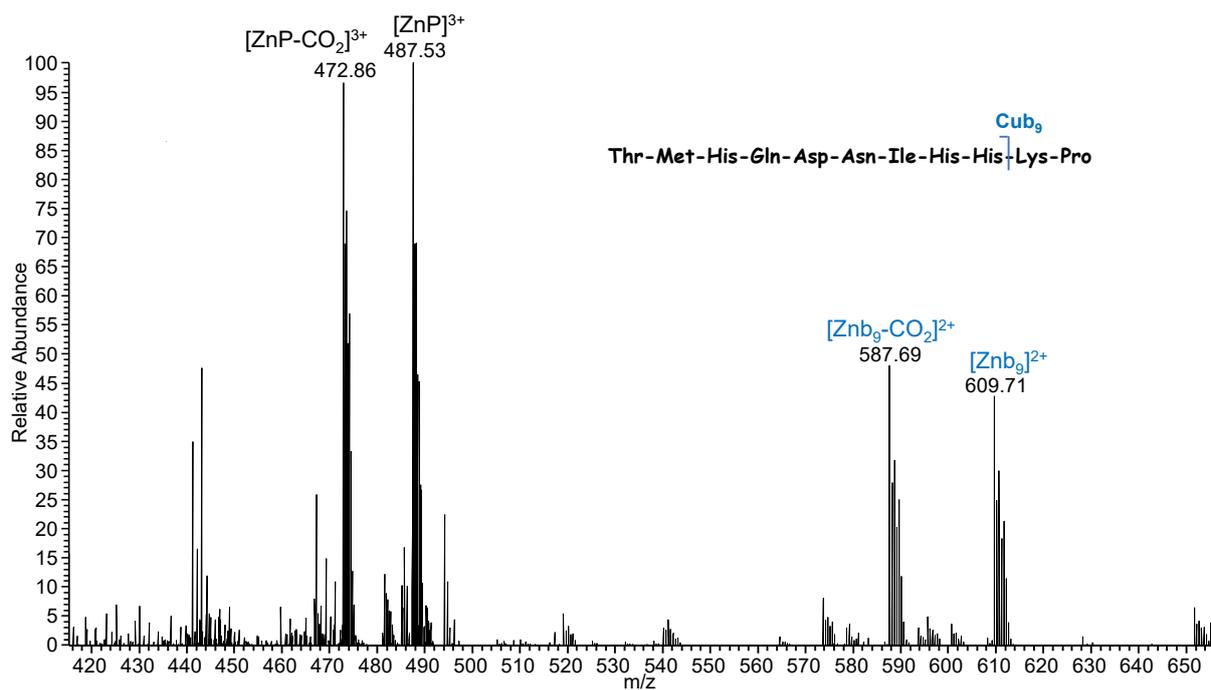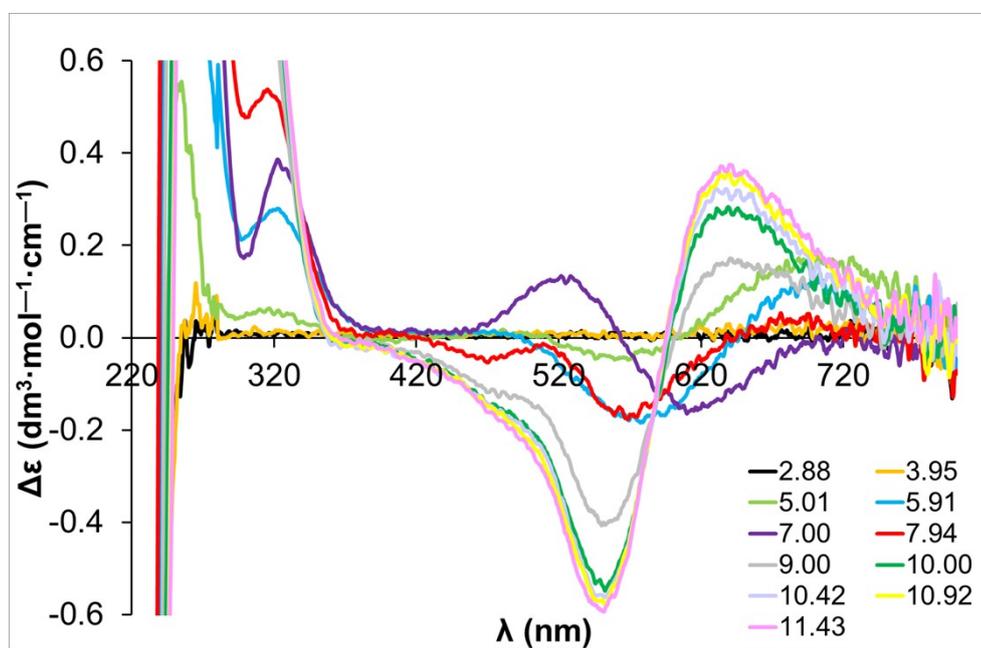**Figure S7**. HCD spectra of [Zn(II)–tau(30-34)(327-332)]$^{3+}$ (m/z =487.53) at CE 10. b_n type fragments were indicated with blue color

Figure S8. pH-dependent CD spectra of the Cu(II)-Zn(II) –tau(30-34)(327-332) system at 1:1 metal to ligand ratio (c(L) = 1.05 mM)

Table S1: UV-Vis spectral parameters of the 4N-coordinated species formed in Cu(II)-tau(30-34)(327-332) system completed with those of copper(II) complexes of other one-histidine containing peptides.

Coordination mode [N⁻;N⁻; N⁻;N(Im)]	λmax/ε
tau(30-34)(327-332)	557/70
tau(26-33)[51]	551/87
Ac-KGGYTMHK-NH$_2$[51]	560/97
Ac-KGGATMHK-NH$_2$[51]	563/90
Ac-KTDHGA-NH$_2$[60]	561/81
Ac-TYTEHA-NH$_2$[61]	556/142
Ac-ATMHQD-NH$_2$[59]	561/52
Ac-ATAHQD-NH$_2$[59]	561/91
Ac-AAMHQD-NH$_2$[59]	520/103

Table S2: Comparison of the UV-Vis spectral parameters of the species formed in the Cu(II) –tau(30-34)(327-332) systems at 2:1 and 3:1 metal to ligand ratios

	λ_{max} (nm) / ε (dm^3·mol^{-1}cm^{-1})	
pH	Cu(II):L = 2:1	Cu(II):L = 3:1
∼ 3	787 / 15	827 / 12
∼ 4	761 / 18	787 / 15
∼ 5	725 / 31	761 / 17
∼ 6	623 / 44	627 / 24
∼ 7	594 / 62	617 / 48
∼ 8	577 / 69	608 / 55
∼ 9	558 / 76	587 / 59
∼ 10	548 / 82	575 / 63
∼ 11	548 / 83	574 / 72