Casiopeinas® with Indomethacin: Synthesis, characterization, DFT studies, antiproliferative activity, and nanoencapsulation

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Supporting Information

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S1. Synthesis and physicochemical characterization of [Cu(N-N)(Indo)(H_2O)]NO_3

All coordination compounds were synthesized as described in Scheme 1(a), starting from $Cu(NO_3)_2$•$2.5H_2O$, with a ratio 1:1:1 Cu-HIndo-diimine in a MeOH/H_2O at 3:1 ratio solution in the presence of a base .Green powders were obtained after 2 hours of reaction, solvent partial evaporation, and recrystallization with a mix EtOH/diethyl ether.

*Aqua(1,10-phenanthroline)(Indo)copper(II) nitrate (1a)***.** Elemental analysis for $[C_{31}H_{23}N_4O_7CuCl(C_4H_{10})_{2.5}]$ (MW = 847.58 g/mol); calculated: %C 56.86, %N 8.03, %H 3.90; founded: %C 56.49, %N 8.45, %H 3.49. Yield 0.78 g (78 %). APSI-MS in methanol: 620.1013, found X 620.925 [M^+]. FTIR ν/cm^{-1}: 2928 ν(CH_3), 1429 δ(CH_3), 1673 ν_{asym}(C=O), 1589 y 1520 ν(C=N/C=C), 1217 ν(C-O), 849 and 721 δ(C-H out of the plane), 1385 ν(NO_3) and 3392 ν(O-H). μ_{eff} = 1.66 MB. $Л_M$= 91.3 Ohm^{-1} cm^2 mol^{-1}. UV-Vis(MeOH): λ_{max} nm (ε M^{-1} cm^{-1}): 222 (9035), 272 (6404), 298 (3010), 653 (22), 758 (15).

Aqua(4,7-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1b). Elemental analysis for the green powder $[C_{33}H_{29}N_4O_8ClCu(H_2O)_{0.5}]$ (717.60 g/mol); calculated: %C 55.23, %N 7.80, %H 4.21; found: %C 55.23, %N 8.07, %H 3.92. Yield 0.74 g (76 %). APSI-MS in methanol: 669.1068, found 669.1045, [M^+]. FTIR ν/cm^{-1}: 2926 ν(CH_3), 1425 δ(CH_3), 1622 ν_{asym}(C=O), 1564 and 1524 ν(C=N/C=C), 1215 ν(C-O), 868 and 723 δ(C-H out of the plane), 1383 ν(NO_3) and 3400 ν(O-H). μ_{eff} = 2.21 MB. $Л_M$= 105.9 Ohm^{-1} cm^2 mol^{-1}. UV-Vis(MeOH): λ_{max} nm (ε M^{-1} cm^{-1}): 234 (9837), 272 (12364), 295 (4209), 633 (28) and 754 (14).

Aqua(5,6-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1c). Elemental analysis for the green powder $[C_{33}H_{27}N_4O_7ClCu(H_2O)_{0.5}]$ (699.58 g/mol); calculated: %C 56.65, %N 8.00, %H 4.03; found: %C 56.49, %N 8.40, %H 3.97. Yield 0.65 g (67 %). APSI-MS in methanol: 647.124824, found 647.1244 [M^+]. FTIR ν/cm^{-1}: 2943 ν(CH_3), 1433 δ(CH_3), 1606 ν_{asym}(C=O), 1587 and 1524 ν(C=N/C=C), 1215 ν(C-O), 812 and 727 δ(C-H out of the plane), 1385 ν(NO_3) and 3394 ν(O-H). μ_{eff}= 1.98 MB. $Л_M$= 93.1 Ohm^{-1} cm^2 mol^{-1}. UV-Vis(MeOH): λ_{max} nm (ε M^{-1} cm^{-1}): 235 (9439), 280 (11285), 301 (4545), 643 (36) and 763 (29).

Aqua(3,4,7,8-tetramethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1d). Elemental analysis for the green powder [$C_{35}H_{37}N_4O_{10}ClCu(H_2O)_2$] (772.68 g/mol); calculated: %C 54.40, %N 7.55, %H 4.82; found: %C 54.38, %N 7.55, %H 4.54. Yield 0.48 g (49 %). APSI-MS in methanol: 657.1456 , found 657.1431, [M^+]. FTIR ν/cm^{-1}: 2926 ν(CH_3), 1431 δ(CH_3), 1618 ν(C=O), 1593 and 1531 ν(C=N/C=C), 1217 ν(C-O), 835 and 721 δ(C-H out of the plane), 1385 ν(NO_3) and 3417 ν(O-H). μ_{eff} = 1.96 MB. $Л_M$= 89.5 Ohm^{-1} cm^2 mol^{-1}. UV-Vis(MeOH): λ_{max} nm (ε M^{-1} cm^{-1}): 234 (9924), 278 (11420), 302 (4446), 632 (51) and 756 (25).

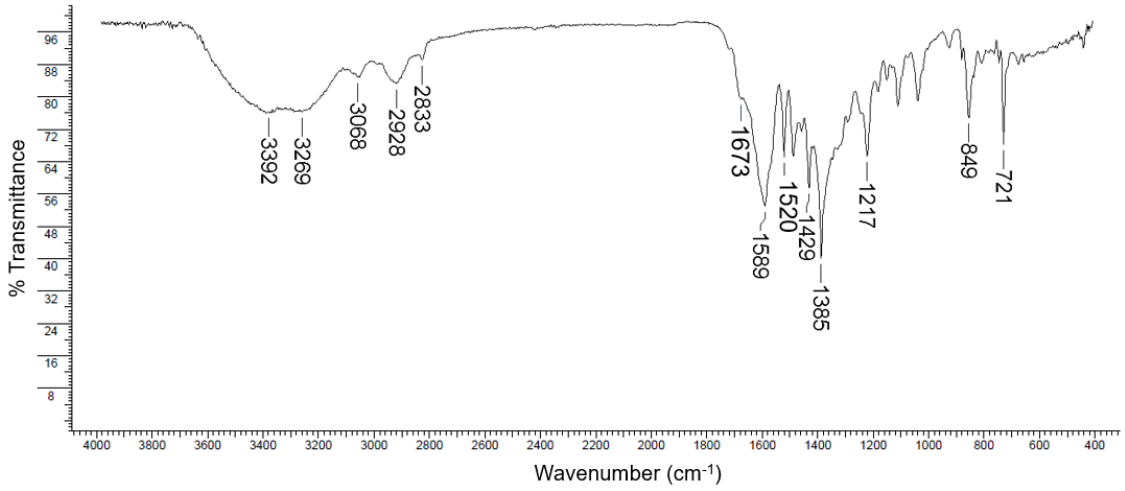
Aqua(2,2'-bipyridine)(Indo)copper(II) nitrate (2a). A green solid was obtained after solvent evaporation and recrystallization on EtOH/diethyl ether. Elemental analysis for [$C_{29}H_{25}N_4O_8ClCu(H_2O)_{1.5}$] (683.54 g/mol); calculated: %C 50.95, %N 8.19, %H 4.12; found: %C 50.48, %N 8.36, %H 4.00. Yield 0.89 g (88 %). APSI-MS in methanol: 579.0986, found 579.0235X [M^+]. FTIR ν/cm^{-1}: 2939 ν(CH_3), 1446 δ(CH_3), 1603 ν_{asym}(C=O), 1579 and 1564 ν(C=N/C=C), 1215 ν(C-O), 769 cm^{-1} δ(C-H out of the plane), 1385 ν(NO_3) and 3406 ν(O-H). μ_{eff}= 2.20 MB. $Л_M$= 102.9 Ohm^{-1} cm^2 mol^{-1}. UV-Vis(MeOH): λ_{max} nm (ε M^{-1} cm^{-1}): 236 (7787), 297 (7233), 308 (5882), 638 (33) and 768 (ε 17).

Aqua(4,4'-dimethyl-2,2'-bipyridine)(Indo)copper(II) nitrate (2b). Elemental analysis for green powder [$C_{31}H_{27}N_4O_7CuCl(0.5C_4H_{10}O)$] (709.63 g/mol), calculated: %C 56.32, %N 7.96, %H 4.58; found: %C 56.51, %N 7.96, %H 4.31. Yield 0.72 g (72 %). APSI-MS in methanol: 607.1299, found 607.1290X, [M^+]. FTIR ν/cm^{-1}: 2928 ν(CH_3), 1477 δ(CH_3), 1616 ν_{asym}(C=O), 1597 and 1570 ν(C=N/C=C), 1225 ν(C-O), 754 δ(C-H out of the plane), 1385 ν(NO_3) and 3431 ν(O-H). μ_{eff}= 1.78 MB. $Л_M$= 90.5 Ohm^{-1} cm^2 mol^{-1}. UV-Vis(MeOH): λ_{max} nm (ε M^{-1} cm^{-1}): 236 (9924), 294 (6289), 305 (5872), 633 (35) and 763 (18).

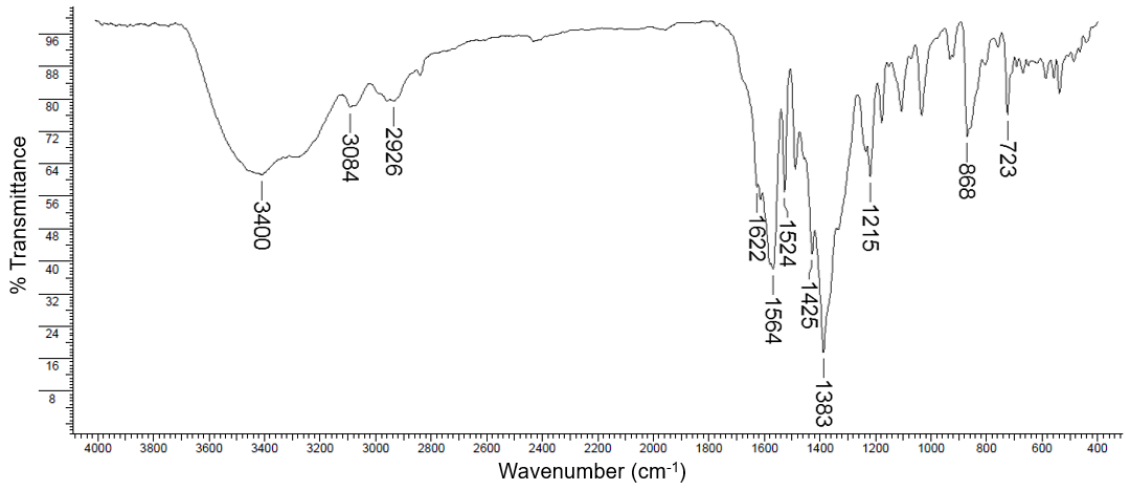
Aqua(5,5'-dimethyl-2,2'-bipyridine)(Indo)copper(II) nitrate (2c). Elemental analysis for green powder [$C_{31}H_{29}N_4O_8CuCl(H_2O)_2$] (720.61 g/mol); calculated: %C 51.66, %N 7.77, %H 4.54; found: %C 51.61, %N 8.07, %H 4.54. Yield 0.76 g (75 %). APSI-MS in methanol: 607.1299, found 607.1230 [M^+]. FTIR ν/cm^{-1}: 2924 ν(CH_3), 1481 δ(CH_3), 16160 ν_{asym}(C=O),

1591and 1568 ν(C=N/C=C), 1217 ν(C-O), 727 δ(C-H out of the plane), 1385 ν(NO_3) and 3396 ν(O-H). μ_{eff} = 1.92 MB. $Л_M$= 90.5 Ohm^{-1} cm^2 mol^{-1}. UV-Vis(MeOH): λ_{max} nm (ε M^{-1} cm^{-1}): 235 (9931), 307 (8377), 319 (6586), 656 (45) and 788 (24).

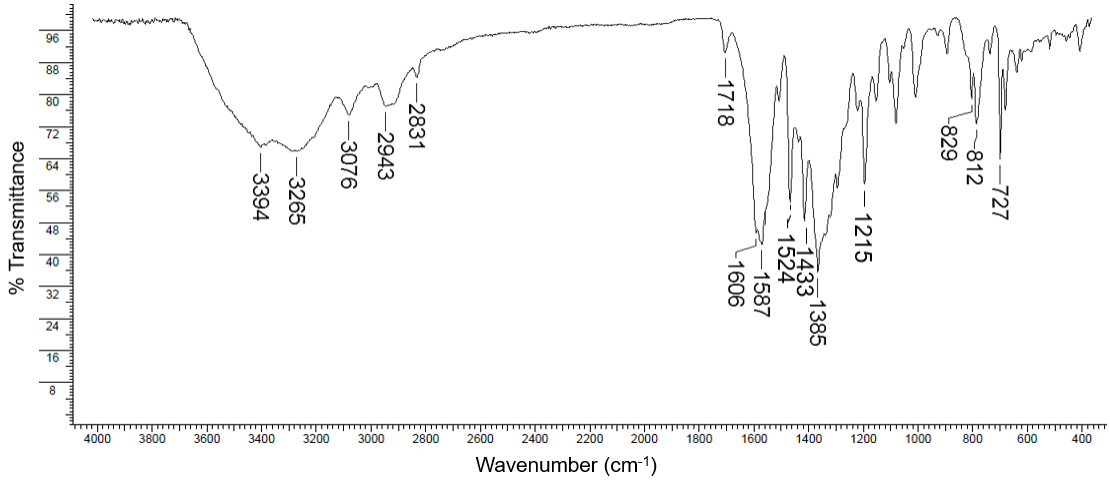
*Aqua(1,10-phenanthroline)(Indo)copper(II)nitrate (1a)***.**



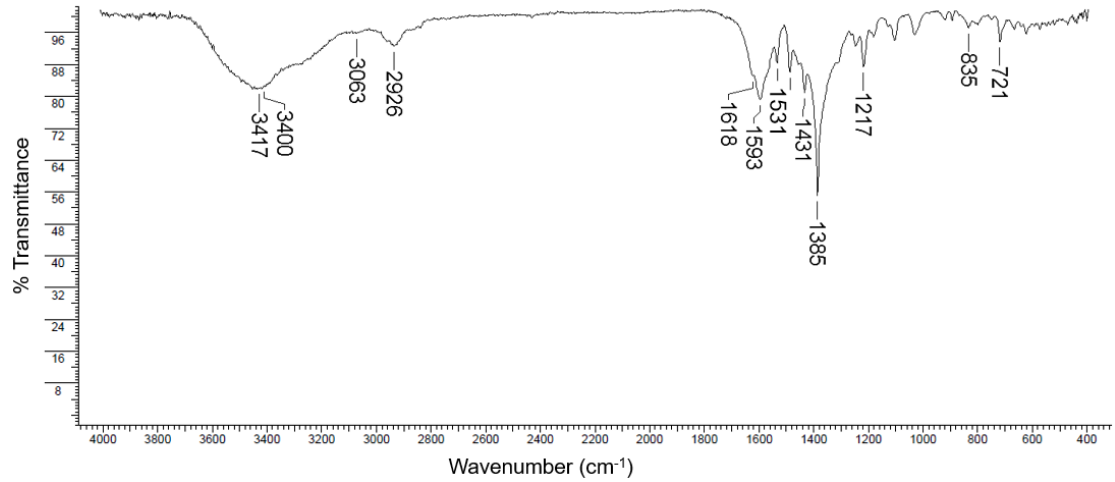
Aqua(4,7-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1b).



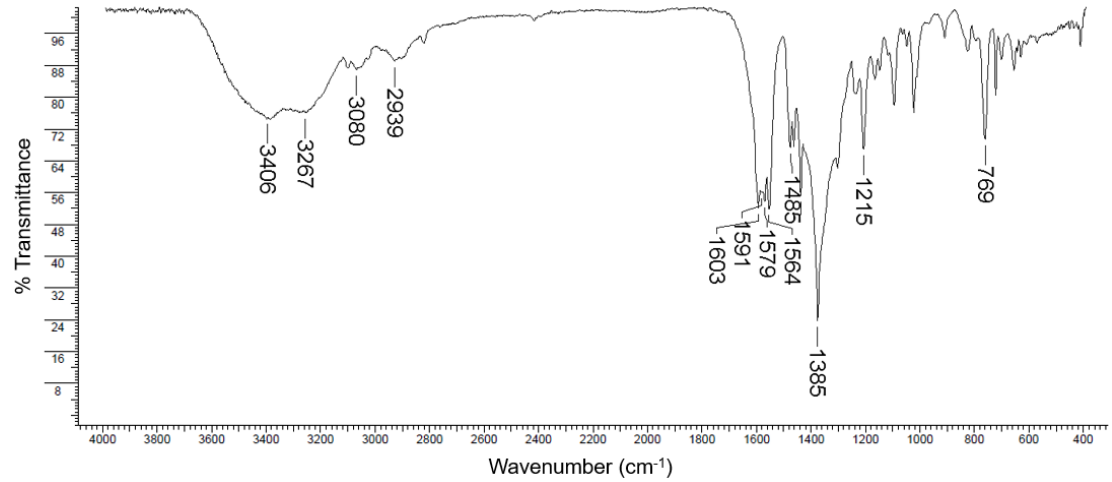
Aqua(5,6-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1c).



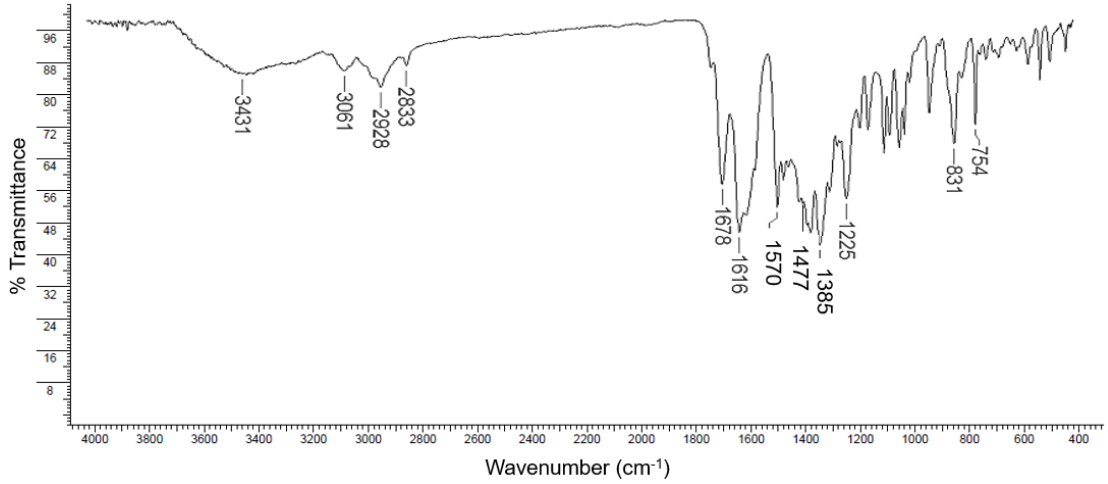
Aqua(3,4,7,8-tetramethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1d).



Aqua(2,2'-bipyridine)(Indo)copper(II) nitrate (2a).



Aqua(4,4'-dimethyl-2,2'-bipyridine)(Indo)copper(II) nitrate (2b).



Aqua(5,5'-dimethyl-2,2'-bipyridine)(Indo)copper(II) nitrate (2c).

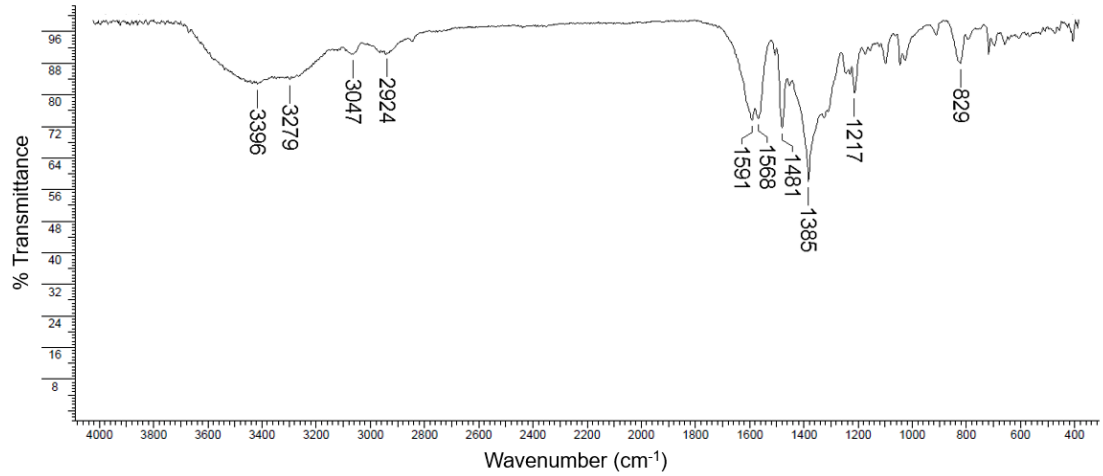
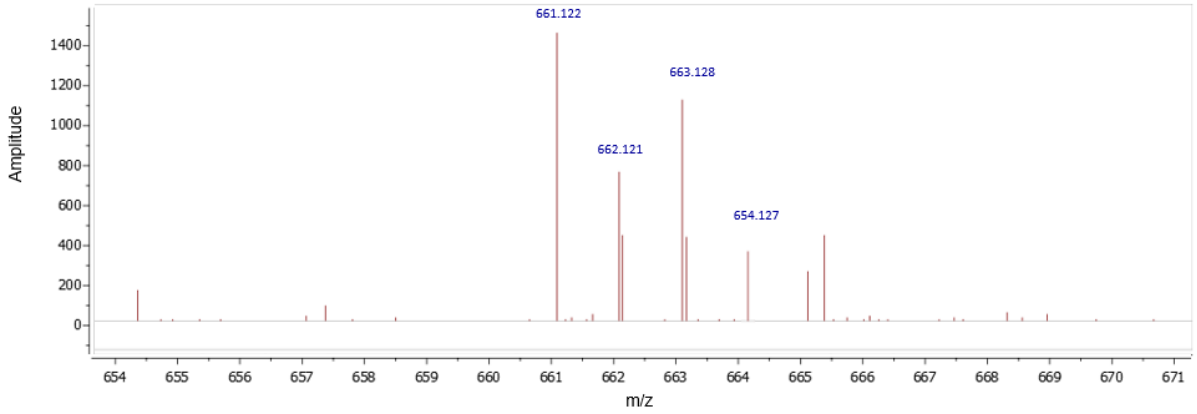
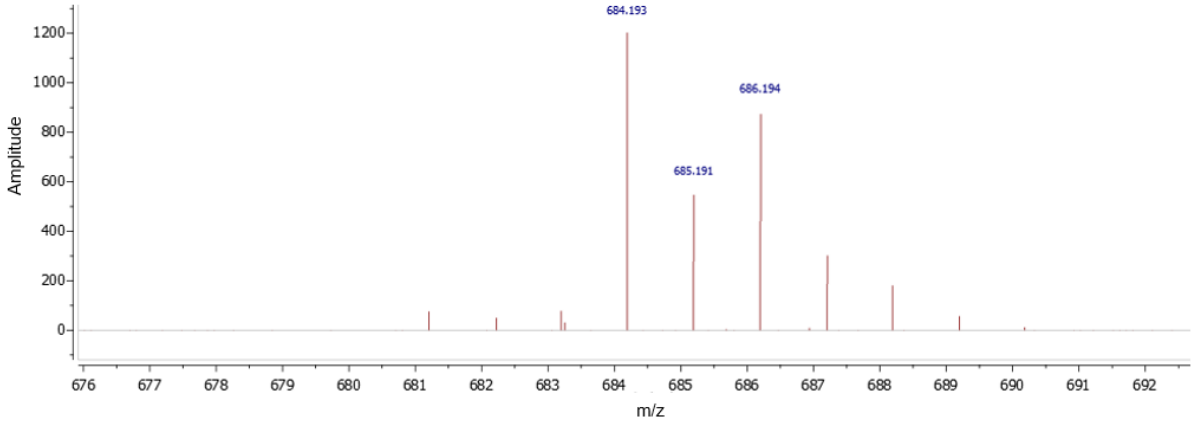


Figure S1. FT-IR spectra of the coordination compounds. All spectra were recorded on KBr disks in a Nexus Thermo Nicolet spectrophotometer in the range 4000 - 400 cm^{-1}.

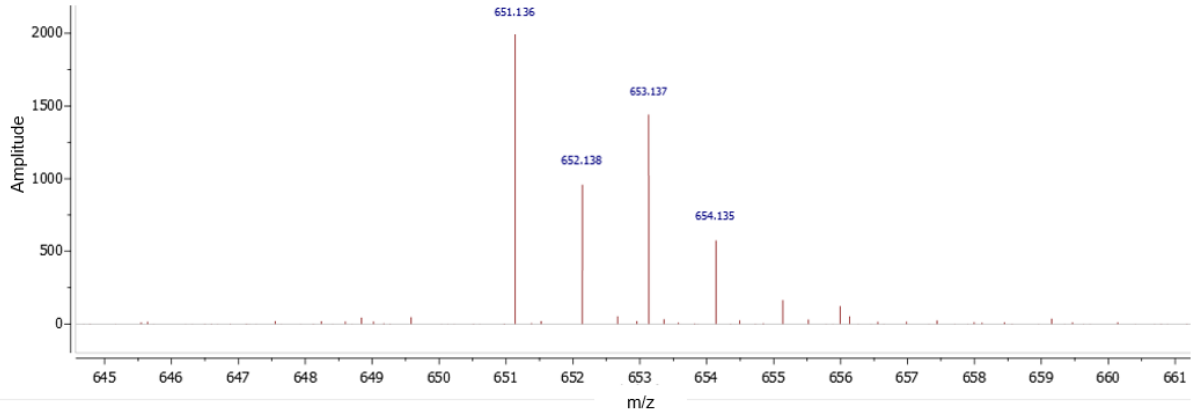
Aqua(1,10-phenanthroline)(Indo)copper(II)nitrate (1a). $C_{31}H_{23}N_4O_7Cu$: 661.055, found 661.122 [M^+].



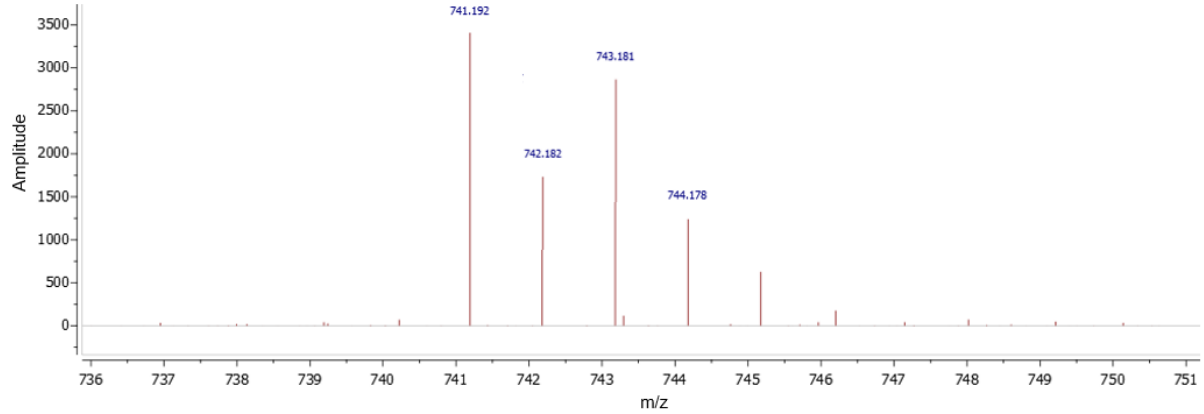
Aqua(4,7-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1b). $C_{33}H_{27}N_3O_4CuCl(H_2O)$: 684.073, found 684.193 [M^+].



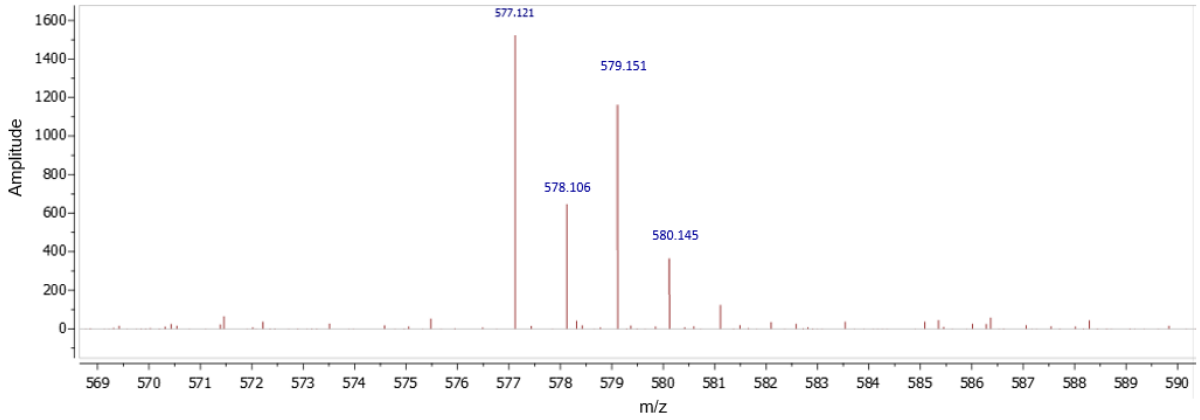
Aqua(5,6-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1c). $C_{33}H_{28}N_3O_4Cu$: 651.096, found 651.136 [M^+].



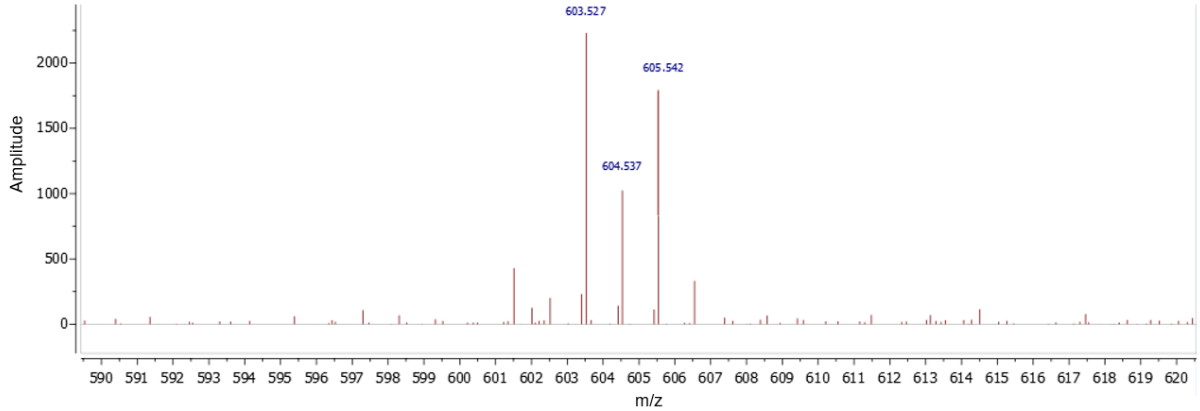
Aqua(3,4,7,8-tetramethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1d). $C_{35}H_{32}N_4O_7Cu$: 741.115, found 741.192 [M^+].



Aqua(2,2'-bipyridine)(Indo)copper(II) nitrate (2a). $C_{29}H_{25}N_3O_4Cu$: 577.083, found 577.121 [M^+].



Aqua(4,4'-dimethyl-2,2'-bipyridine)(Indo)copper(II) nitrate (2b). APSI-MS in methanol, $C_{31}H_{27}N_3O_4Cu$: 603.099, found 603.521 [M^+].



Aqua(5,5'-dimethyl-2,2'-bipyridine)(Indo)copper(II) nitrate (2c). $C_{31}H_{29}N_4O_7CuCl$: 667.102, found 607.149[M^+].

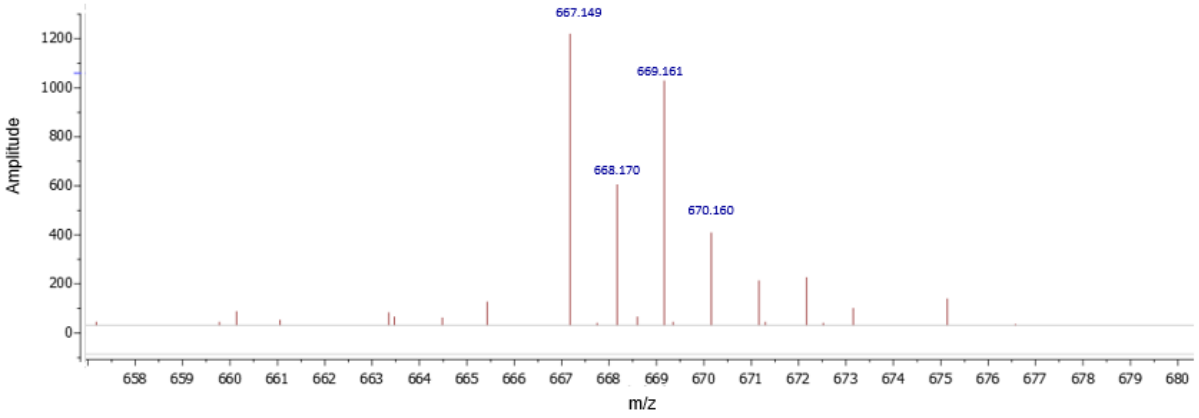
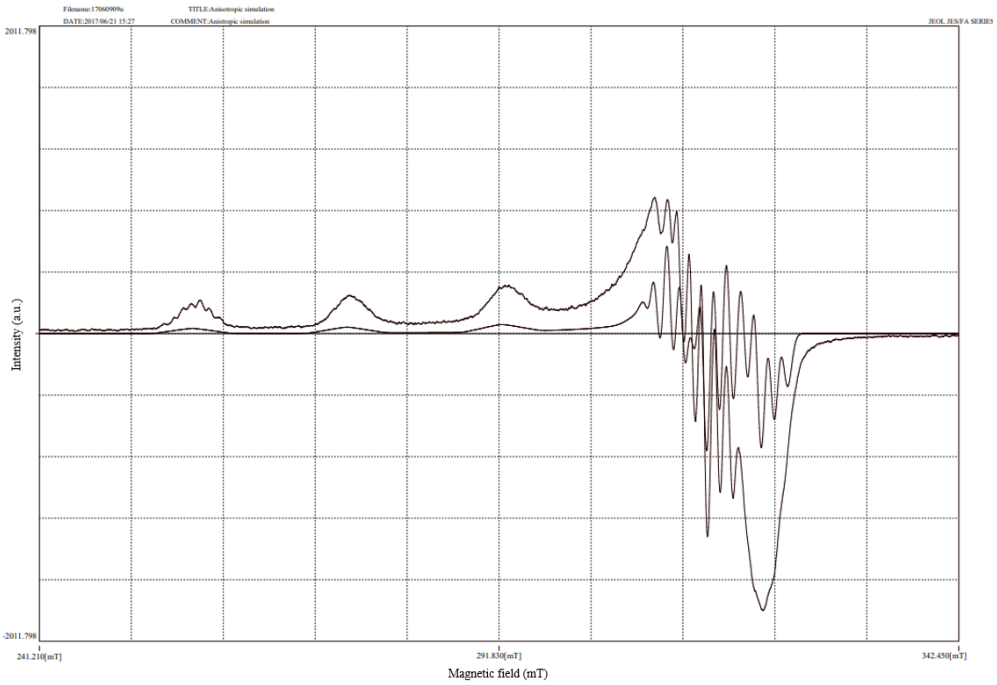


Figure S2. APSI(Appearance Potential Soft Ionization) Mass Spectra in methanol

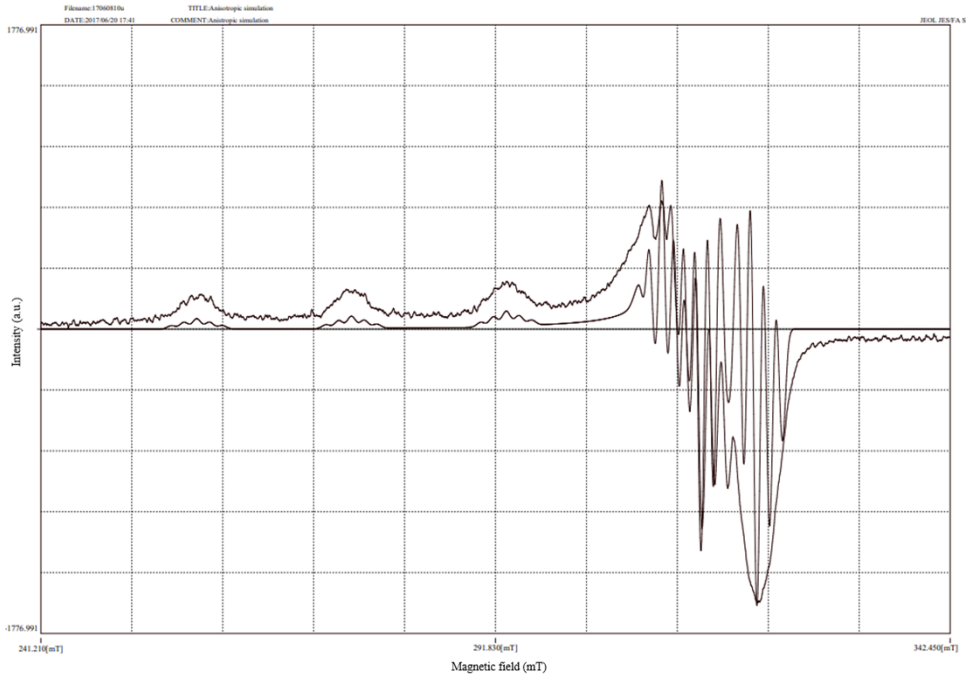
Table S1. g factor values (isotropic, parallel and perpendicular components), A constant coupling (isotropic, parallel and perpendicular components for Cu interactions and nitrogen interaction (A_N).

Compound	$g_{//}$	$g_{\perp}$	$A_{//}$ (a)	$A_{\perp}$ (a)	g_{iso}	A_{iso}(a)	A_N (a)	f(b)
1a	2.276	2.057	180.852	14.405	2.130	66.361	0.0014	126
1b	2.270	2.057	182.558	13.757	2.128	66.534	0.0014	124
1c	2.270	2.057	180.428	14.232	2.128	66.196	0.0013	126
1d	2.258	2.054	189.689	15.957	2.122	70.411	0.0013	119
2a	2.265	2.056	185.593	15.896	2.126	69.015	0.0013	122
2b	2.274	2.056	181.808	14.916	2.129	67.025	0.0007	125
2c	2.262	2.055	188.970	16.310	2.124	70.386	0.0013	120

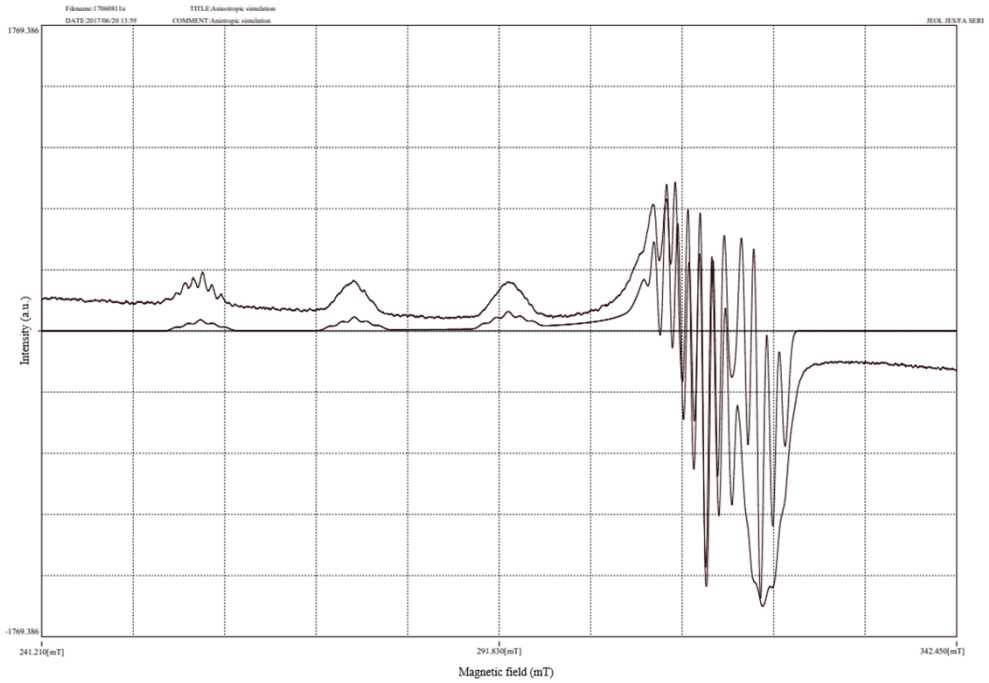
Aqua(1,10-phenanthroline)(Indo)copper(II)nitrate (1a).



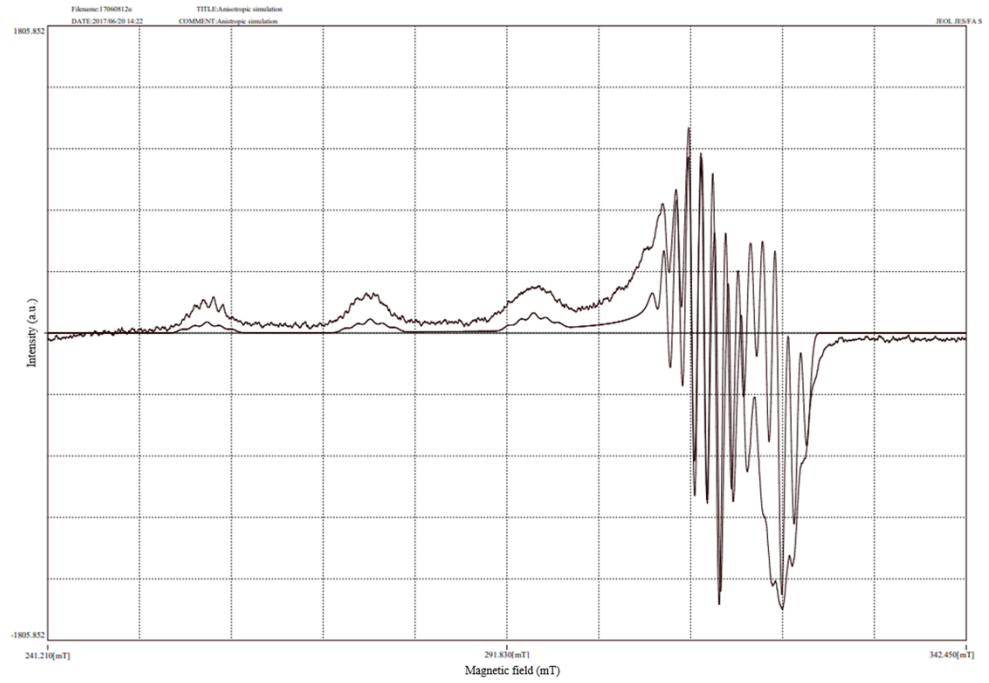
Aqua(4,7-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1b).



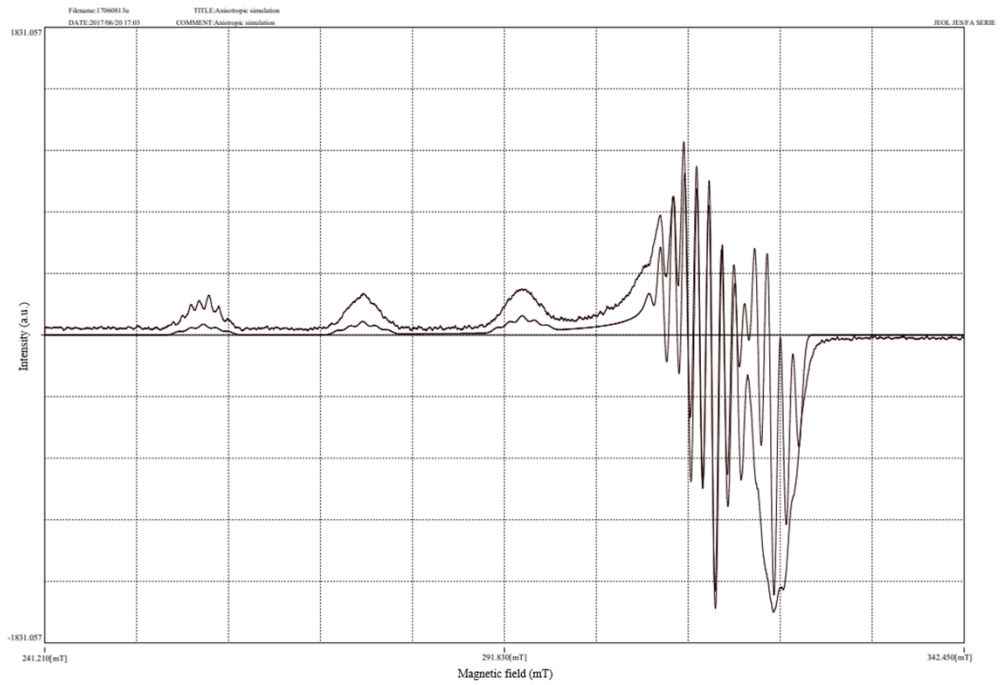
Aqua(5,6-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1c).



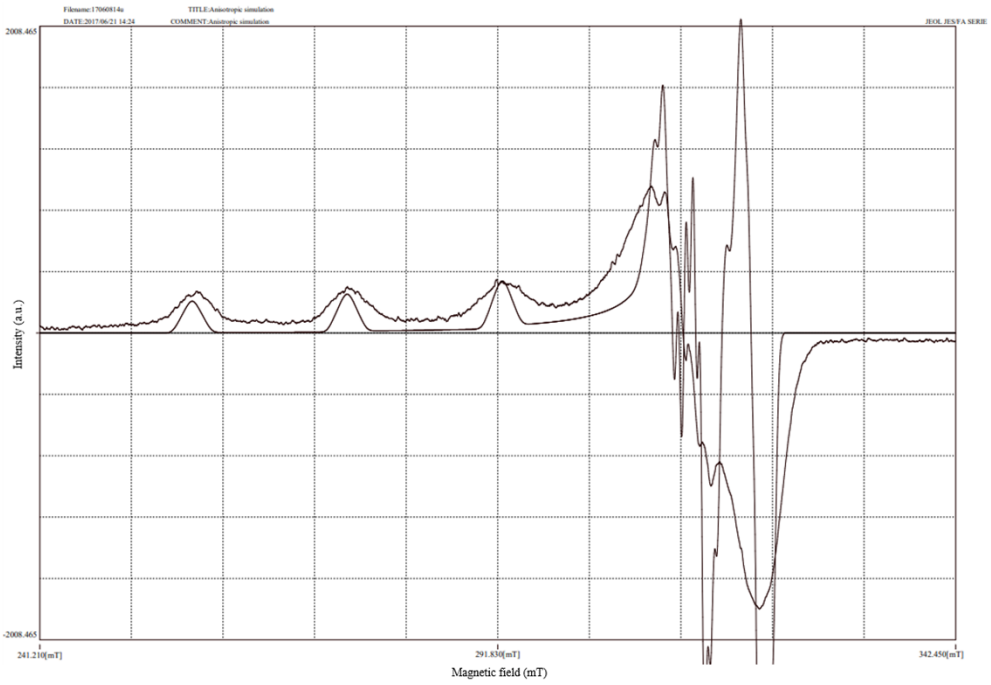
Aqua(3,4,7,8-tetramethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1d).



Aqua(2,2'-bipyridine)(Indo)copper(II) nitrate (2a).



Aqua(4,4'-dimethyl-2,2'-bipyridine)(Indo)copper(II) nitrate (2b).



Aqua(5,5'-dimethyl-2,2'-bipyridine)(Indo)copper(II) nitrate (2c).

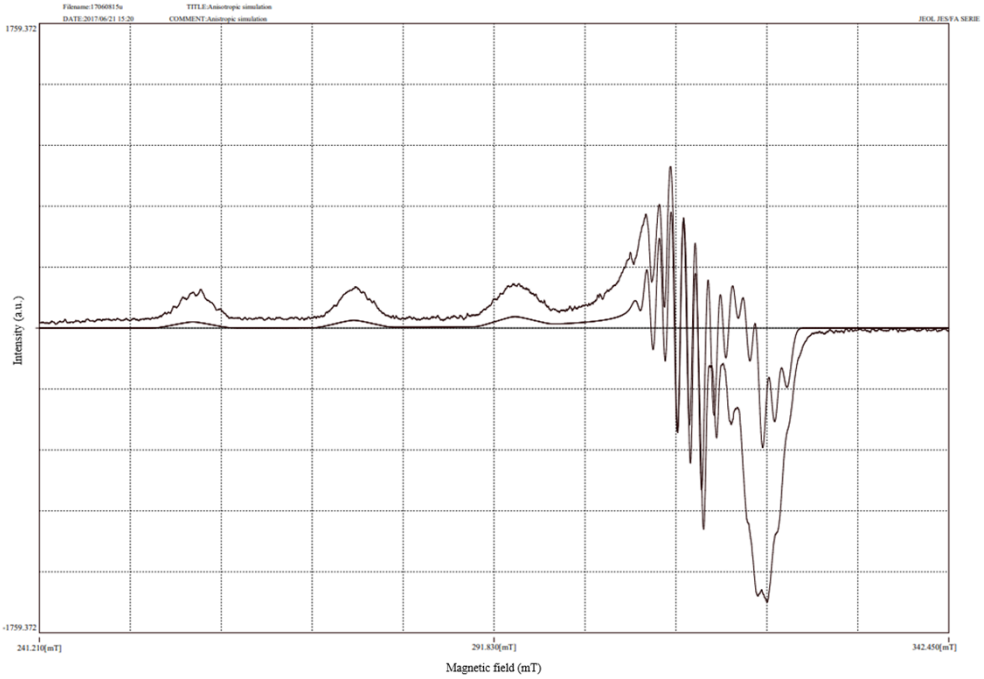


Figure S3. Experimental and simulated EPR spectra. 3 mmol/L MeOH solutions at 77 K.

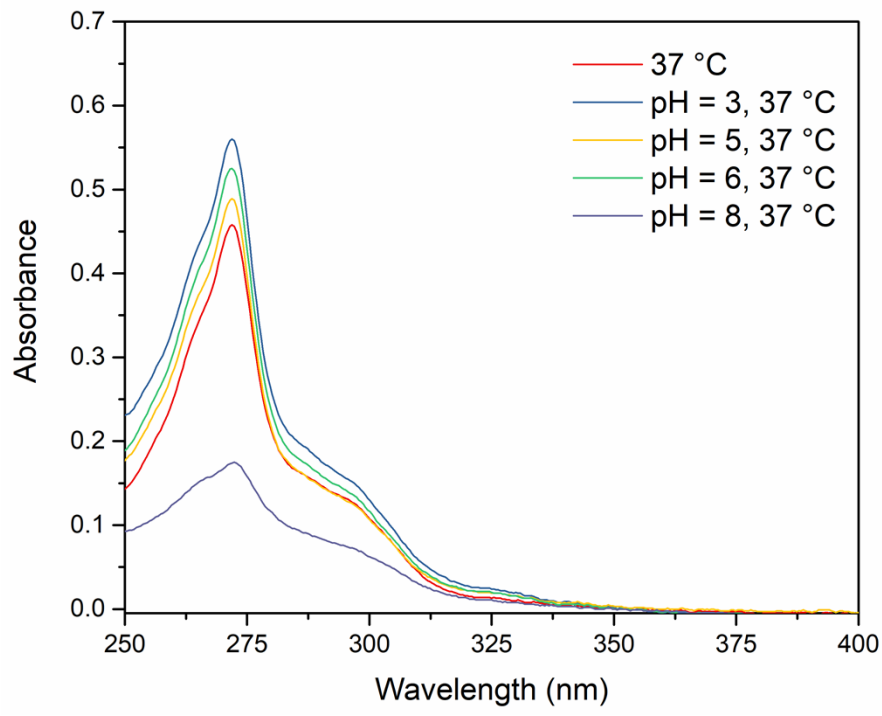


Figure S4. Electronic spectra at different pHs aqua(4,7-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1b) at 37 °C using methanol solutions at 0.001 M.

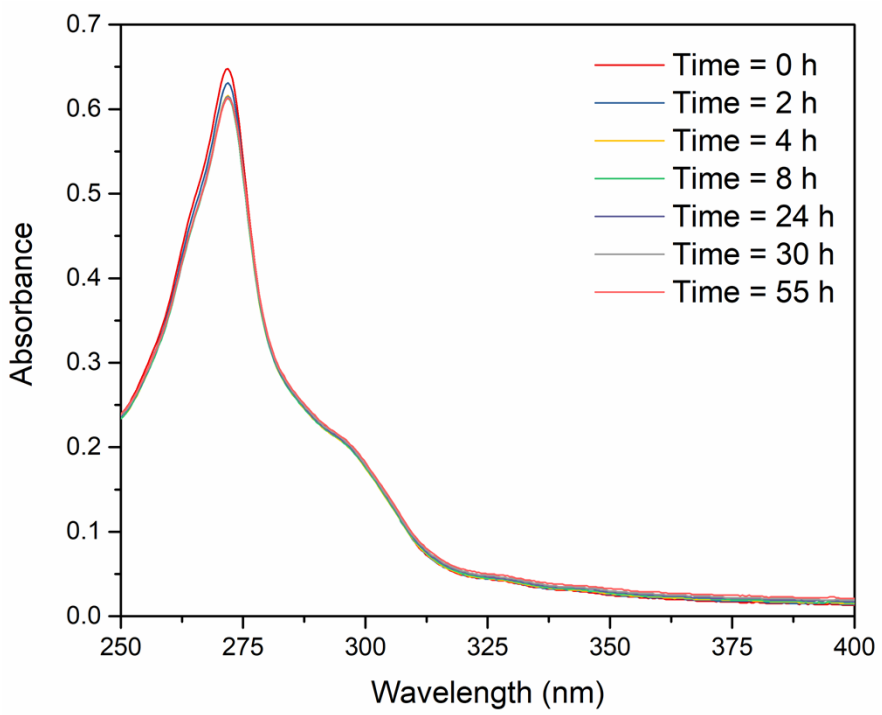


Figure S5. Electronic spectra at different times of aqua(4,7-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1b) using methanol solutions at 0.001 M.

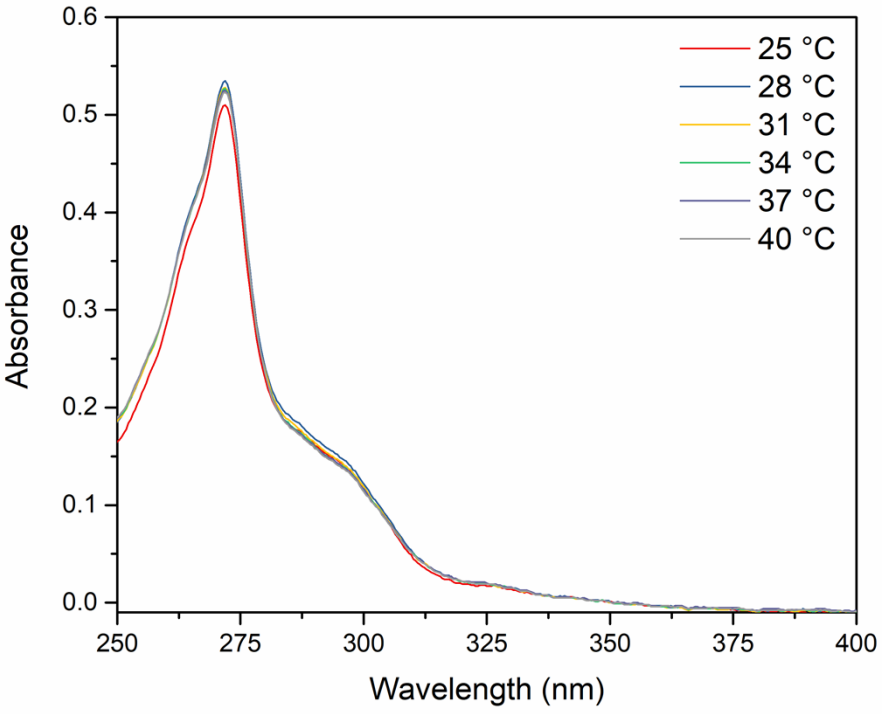
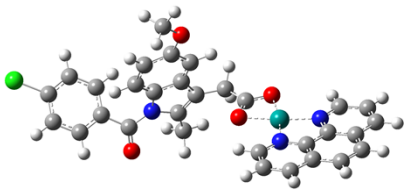


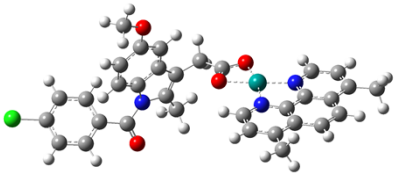
Figure S6. Electronic spectra at different temperatures of the compound aqua(4,7-dimethyl-1,10-phenanthroline)(Indo)copper(II) nitrate (1b) using methanol solutions at 0.001 M.

Figure S7. Optimized (M06/LanL2DZ) geometries, calculated V_M and E^0 for [Cu(Indo)(N-N)] complexes.



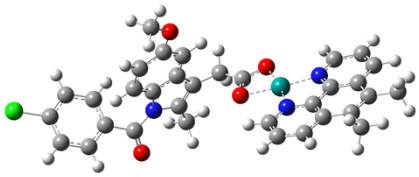
E^0= -0.65 V V_M= 361.6 cm^3/mol

[Cu(Indo)(1,10-phenanthroline)]$^+$



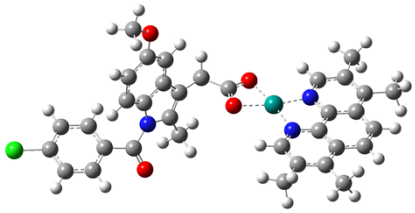
E^0_{calc}= -0.82 V V_M= 372.2 cm^3/mol

[Cu(Indo)(4,7-dimethyl-1,10-phenanthroline)]$^+$



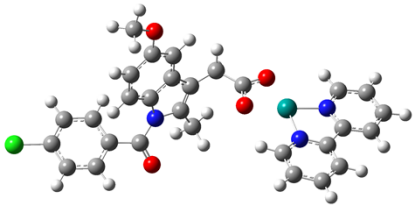
E^0_{calc}= -0.62 V V_M= 377.3 cm^3/mol

[Cu(Indo)(5,6-dimethyl-1,10-phenanthroline)]$^+$



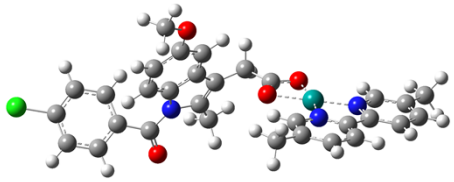
E^0_{calc}= -0.66 V V_M= 385.95 cm^3/mol

[Cu(Indo)(4,3,7,8-tetramethyl-1,10-phenanthroline)]$^+$



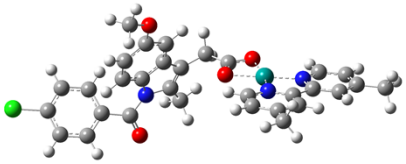
E^0_{calc}= -0.64V V_M= 334.3 cm^3/mol

[Cu(Indo)(2,2'-bipyridine)]$^+$



E^0_{calc}= -0.73 V V_M= 345.2 cm^3/mol

[Cu(Indo)(4,4'-dimethyl-2,2'-bipyridine)]$^+$



E^0_{calc}= -0.76 V V_M= 354.4 cm^3/mol

[Cu(Indo)(5,5'-dimethyl-2,2'-bipyridine)]$^+$

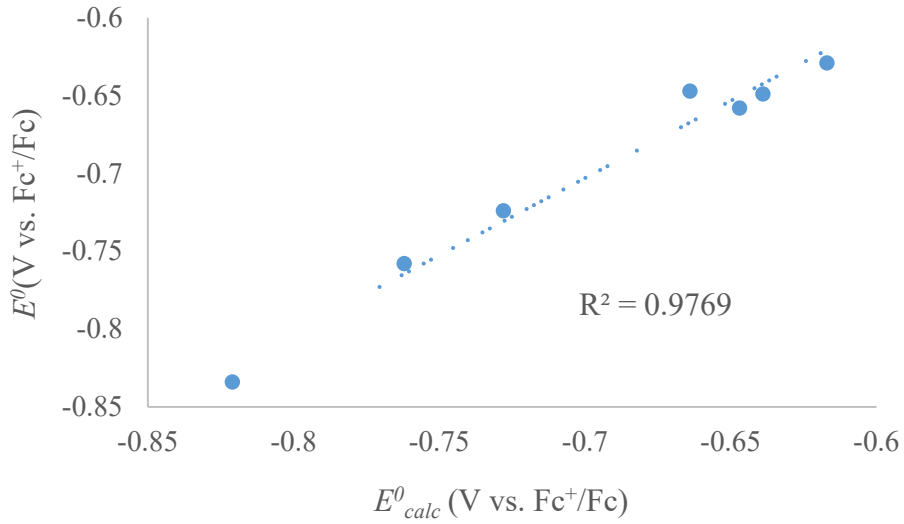


Figure S8. Plot of estimated and calculated redox potential

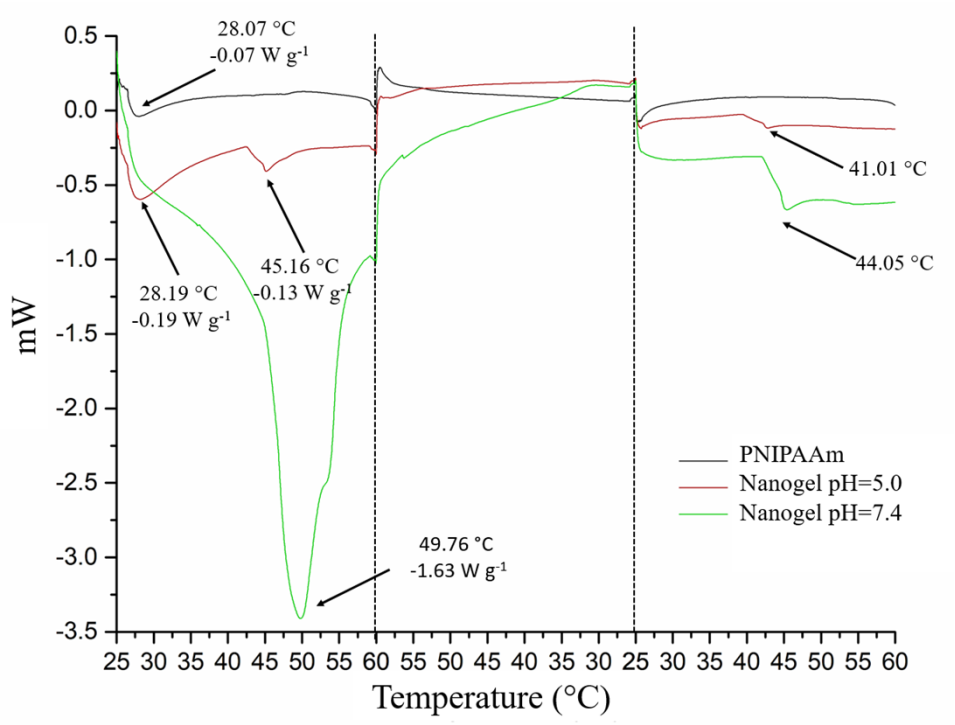


Figure S9. Differential calorimetry screening plot for PNIPAAm and nanogel (pH= 5.0 and 7.4)

Table S2. Encapsulation experiments data

Test	Nanogel mass (mg)	Initial concentration (mg/mL)	Free concentration (mg/mL)	% Encapsulation	Mass complex/nanogel ratio
A	20.2	1.425	0.4437	68.87	0.0486
B	19.9	1.425	0.4537	68.18	0.0488
C	19.9	1.425	0.4143	70.92	0.0508
D	20.0	1.425	0.4150	70.87	0.0505
E	19.8	1.425	0.4601	67.71	0.0487
F	19.8	1.425	0.4236	70.72	0.503

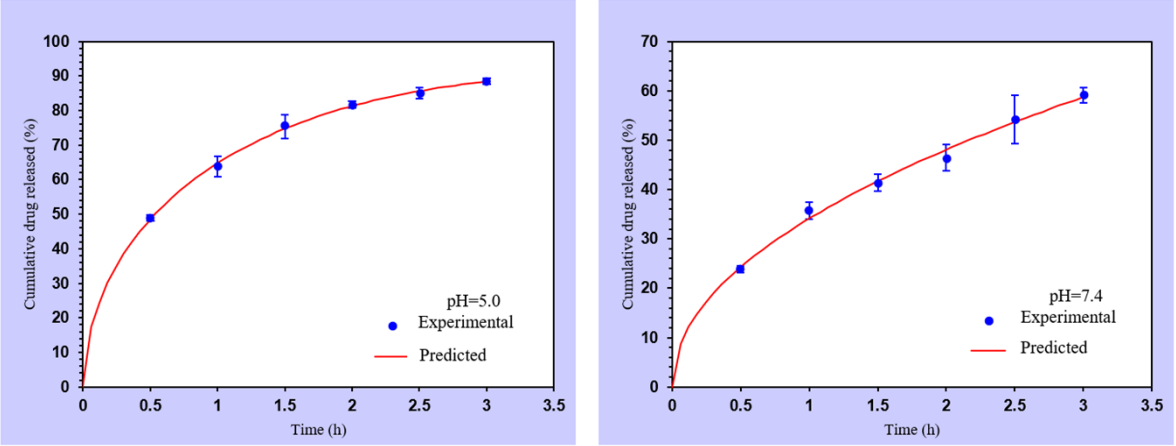


Figure S10. Release compound percentage and Peppas-Sahlin model adjustment