Supporting Information

Title: Investigation of Cobalt(III)-Phenylalanine Complexes for Hypoxia-activated Drug Delivery

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Syntheses of the Precursor Complexes

$[CoCl_2(py_2en)]ClO_4$:[1,2] To a 30 mL of aqueous solution of $Na_3[Co(NO_2)_6]$ (4.0 mmol) was added the py_2en (4.0 mmol) dissolved in 10 mL of water. The reaction mixture was kept at 80°C under magnetic stirring for 1 hour. The $LiClO_4$ (16.0 mmol) was added and the yellow precipitate of $[Co(NO_2)_2(py_2en)]ClO_4$ was isolated by filtration, washed with diethyl ether and dried under vacuum (yield: 40 %). IR (ATR, 4000 – 600 cm^{-1}): 3192 (N-H); 1613 - 1449 (C=C, C=N); 1412, 1341 (O-N=O); 1091 (Cl-O); 820 – 692 (aromatic C-H). ESI-MS (MeOH): m/z^+= 393.11 for $[Co(NO_2)_2(py_2en)]^+$ (calculated 393.07). The complex $[Co(NO_2)_2(py_2en)]ClO_4$ (2.8 mmol) was dissolved in 58 mL of HCl 37% and heated up to 80° C for 3 hours. Then, 12 mL of $HClO_4$ 70% was added. The mixture was stirred for 30 minutes and cooled in an ice bath. The purple precipitate of $[CoCl_2(py_2en)]ClO_4$ was isolated by filtration, washed with diethyl ether and dried under vacuum (yield: 63 %). IR (ATR, 4000 – 600 cm^{-1}): 3211 (N-H); 1610 - 1418 (C=C, C=N); 1085 (Cl-O); 812 – 690 (aromatic C-H). ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 9.34 (d, *J* = 5.7 Hz, 1H, H_1), 8.27 (td, *J* = 7.7, 1.3 Hz, 1H, H_3), 8.02 (td, *J* = 7.7, 1.3 Hz, 1H, $H_{2'}$), 7.98 (b, NH), 7.85 (m, 2H, H_2 and H_4), 7.69 (d, *J* = 7.7 Hz, 1H, $H_{1'}$), 7.59 (b, NH'), 7.36 (t, *J* = 5.7 Hz, 1H, $H_{3'}$), 6.86 (d, *J* = 5.7 Hz, 1H, $H_{4'}$), 5.00 (dd, *J* = 17.5, 7.7 Hz, 1H, H_5), 4.36 (d, *J* = 17.5 Hz, 1H, H_5), 4.04 (d, *J* = 16.4, 7.7 Hz, 1H, $H_{5'}$), 3.81 (dd, *J* = 16.4, 7.7 Hz, 1H, $H_{5'}$), 3.66 (m,

[1] M. V. P. de Mello, G. Cebrián-Torrejón, J. R. Pereira, C. S. Moreira, C. B. S. M. R. Gomes, D. R. da Rocha, E. M. S. Fagundes, G. B. Ferreira and M. Lanznaster, *J. Inorg. Biochem*. 2019, **199**, 110756.
[2] R. C. Batista, F. S. Miranda, C. B. Pinheiro and M. Lanznaster, *Eur. J. Inorg. Chem*., 2018, 612-616.

1H, H_7), 3.13 (dd, *J* = 13.0, 4.1 Hz, 1H, H_7), 2.60 (m, 1H, $H_{7'}$), 2.20-2.27 (m, 1H, $H_{7'}$). ESI-MS (MeOH): m/z$^+$= 371.11 for $[CoCl_2(py_2en)]^+$ (calculated 371.02).

$[CoCl_2(tpa)]ClO_4$:[3] To a solution of $[Co(H_2O)_6]Cl_2$ (4.2 mmol) in 20 mL of methanol, was added a methanol solution (10 mL) of TPA (4.2 mmol) and solid $LiClO_4$ (6.3 mmol) in inert atmosphere. Gaseous chlorine was slowly introduced into this solution under cooling for 15 min. The purple precipitate of $[CoCl_2(TPA)]ClO_4$ was isolated by filtration, washed with diethyl ether and dried under vacuum (yield: 63 %). IR (ATR, 4000 – 600 cm^{-1}): 1609 - 1417 (C=C, C=N); 1083 (Cl-O); 819 – 716 (aromatic C-H). ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 9.44 (d, *J* = 6.0 Hz, 1H, H_{10}), 9.01 (dd, *J* = 6.0, 0.7 Hz, 2H, H_1 and $H_{1'}$), 8.07 (td, *J* = 7.7, 1.4 Hz, 2H, H_3 and $H_{3'}$), 7.88 (td, *J* = 7.7, 1.4 Hz, 1H, H_8), 7.69 (d, *J* = 7.7 Hz, 2H, H_4 and $H_{4'}$), 7.62-7.57 (m, 3H, H_2, $H_{2'}$ and H_9), 7.31 (dd, *J* = 7.7, 0.7 Hz, 1H, H_7), 5.60 (d, *J* = 15.8 Hz, 2H, H_5 and $H_{5'}$), 5.17 (s, 2H, H_6), 4.82 (d, *J* = 15.8 Hz, 2H, H_5 and $H_{5'}$). ESI-MS (MeOH): m/z$^+$= 419.03 for $[CoCl_2(tpa)]^+$ (calculated 419.02).

$[CoCl_2(py_2enMe_2)]ClO_4$: To a solution of $[Co(H_2O)_6]Cl_2$ (3.3 mmol) in 20 mL of methanol, was added a methanol solution (10 mL) of py_2enMe_2 (3.3 mmol) and solid $LiClO_4$ (5.0 mmol) in inert atmosphere. Gaseous chlorine was slowly introduced into this solution under cooling for 15 min. The green precipitate of $[CoCl_2(py_2enMe_2)]ClO_4$ was isolated by filtration, washed with diethyl ether and dried under vacuum (yield: 67 %). IR (ATR, 4000 – 600 cm^{-1}): 1615 - 1418 (C=C, C=N); 1081 (Cl-O); 817 – 722 (aromatic C-H). ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 9.32 (d, *J* = 5.8 Hz, 2H, H_1 and $H_{1'}$), 8,19 (td, *J* = 7.6, 1.3 Hz, 2H, H_3 and $H_{3'}$), 7.75 (m, 4H, H_2, $H_{2'}$, H_4 and $H_{4'}$), 4.82 (d, *J* = 16.0 Hz, 2H, H_5 and $H_{5'}$), 4.02 (d, *J* = 16.0 Hz, 2H, H_5 and $H_{5'}$), 2.89 (d, *J* = 9.6 Hz, 2H, H_7 and $H_{7'}$), 2.56 (d, *J* = 9.6 Hz, 2H, H_7 and $H_{7'}$), 2.25 (s, 6H, CH_3 and $CH_{3'}$). ESI-MS (MeOH): m/z$^+$= 399.14 for $[CoCl_2(py_2enMe_2)]^+$ (calculated 399.06).

$[Co(bipy)_2Cl_2]Cl$: To a solution of $[Co(H_2O)_6]Cl_2$ (4.2 mmol) in 30 mL of methanol, was added solid 2,2´-bipyridine (8.4 mmol) and solid LiCl (23.6 mmol) in inert atmosphere. Gaseous chlorine was slowly introduced into this solution under cooling for 15 min. The resulting precipitate was filtered off and redissolved in methanol on a water

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bath and the methanol was slowly evaporated to half of the solution. The slow evaporation of the solution at room temperature resulted in the formation of violet crystals of $[Co(bipy)_2Cl_2]Cl$ that were isolated by filtration, washed with diethyl ether and dried under vacuum (yield: 60 %). IR (ATR, 4000 – 600 cm^{-1}): 1603, 1424 (C=C, C=N); 803 - 726 (aromatic C-H). ^1H NMR (500 MHz, DMSO-d_6) δ/ppm: 9.84 (dd, *J* = 5.8, 0.8 Hz, 2H, H_1 and $H_{1'}$), 8.95 (d, *J* = 7.7 Hz, 2H, H_4 and $H_{4'}$), 8.79 (d, *J* = 7.7 Hz, 2H, H_8 and $H_{8'}$), 8.64 (td, *J* = 7.7, 1.3 Hz, 2H, H_3 and $H_{3'}$), 8.26 (td, *J* = 7.7, 1.3 Hz, 2H, H_7 and $H_{7'}$), 8.20 (td, *J* = 7.7, 1.3, 2H, H_2 and $H_{2'}$), 7,51 (td, *J* = 7.7, 1.3 Hz, 2H, H_6 and $H_{6'}$), 7,34 (d, *J* = 5.8, 0.8 Hz, 2H, H_5 and $H_{5'}$). ESI-MS (MeOH): m/z^+= 441.12 for $[Co(bipy)_2Cl_2]^+$ (calculated 441.01).

Table S1. Crystallographic data of cobalt(III)-phenylalanine complexes.

Complexes	**1**	**2**	**3**	**4**
Empirical formula	$C_{23}H_{28}CoN_5O_2 \cdot 2(ClO_4)$	$C_{27}H_{28}CoN_5O_2 \cdot 2(ClO_4)$	$C_{25}H_{32}CoN_5O_2 \cdot 2(ClO_4)$	$C_{29}H_{26}CoN_5O_2 \cdot 2(ClO_4) \cdot C_2H_3N$
Formula weight	664.33	712.37	692.38	775.43
Crystal system	Triclinic	Orthorhombic	Orthorhombic	Monoclinic
Space group	P1	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
Temperature (K)	273	290	298	273
Unit cell dimensions (Å,°)	a = 6.5320 (11) b = 9.9881 (18) c = 11.068 (2) α = 71.076 (6) β = 86.884 (5) γ = 89.537 (5)	a = 12.5779 (3) b = 15.3268 (4) c = 16.0033 (5) α = 90 β = 90 γ = 90	a = 10.4694 (3) b = 12.8698 (5) c = 22.5611 (8) α = 90 β = 90 γ = 90	a = 12.5559 (6) b = 9.9926 (4) c = 14.5754 (7) β = 113.235 (2)
Volume ($Å^3$)	682.0 (2)	3085.10 (15)	3039.86 (18)	1680.40 (13)
Z	1	4	4	2
Θ max	26.4°	26.2°	26.5°	25.5°
Absorption coefficient (mm^{-1})	0.89	0.79	0.80	0.74
Reflections collected	46056	37755	20827	61651
Independent reflections	5340	6303	6235	5921
Reflections observed [I>2σ(I)]	5303	5292	5029	5337
R_{int}	0.023	0.070	0.045	0.040
$R[F^2>2\sigma F^2]$	0.025	0.057	0.051	0.040
$wR(F^2)$	0.066	0.164	0.145	0.108
S	1.04	1.07	1.04	1.09
Parameters	370	406	390	452

Table S2. Conformers ensemble energy of two most stable isomers of complexes **1** – **4** and differential stabilization in competing isomers (E_{NCI}) of cation-anion interactions in simulated solution.

Complex	**Condition**	**Isomer 1 Candidate**		**Isomer 2 Candidate**		**E_{NCI} surplus stabilization**	
			Energy (Eh)		Energy (Eh)	kJ/mol	Assigned isomer
$[Co(Phe)(py_2en)](ClO_4)_2$ (**1**)	NAWS WAWS	Λ-cisα-*exo,exo*	-88.98947 -130.85765	Δ-cisβ$_1$-*exo,exo*	-88.98412 -130.86113	23.6	Δ-cisβ$_1$
$[Co(Phe)(tpa)](ClO_4)_2$ (**2**)	NAWS WAWS	β$_1$	-97.54474 -139.41860	β$_2$	-97.54182 -139.41122	11.7	β$_1$
$[Co(Phe)(py_2enMe_2)](ClO_4)_2$ (**3**)	NAWS WAWS	Λ-cisα-*exo,exo*	-95.27150 -137.14090	Δ-cisα-*exo,exo*	-95.26814 -137.14090	8.8	Δ-cisα
$[Co(Phe)(bipy)_2)](ClO_4)_2$ (**4**)	NAWS WAWS	Λ	-100.81285 -142.68309	Δ	-100.81009 -142.68229	5.1	Δ

† At 298.15 K, 1 bar and 1 mol/dm^3 with water as implicit solvent (SMD).

Table S3 – ^{1}H and ^{13}C Chemical shielding and chemical Shift (ppm) for the TMS reference and Internal Calibrators Na(Phe) and py_2enMe_2 in DMSO (SMD) at B97-3c (D4) // RI-B972-D3/pcSseg-1

TMS: Chemical Shielding (ppm) - C – 187,341; H – 31,668

Py_2enMe_2

	Chem shielding (ppm)	**δ (ppm)**
$C_{1/1'}$ (py)	31.492	155.8
$C_{2/2'}$ (py)	60.798	126.5
$C_{3/3'}$ (py)	44.490	142.9
$C_{4/4'}$ (py)	59.857	127.5
$C_{4a/4a'}$ (py)	19.345	168.0
$C_{5/5'}$ (CH2)	121.998	65.3
$C_{6/6'}$ (Me)	140.566	46.8
$C_{7/7'}$ (en)	136.324	51.0

	Chem shielding (ppm)	**δ (ppm)**		
		Calc.	*Corr.*	*Exp.*
$H_{1/1'}$ (py)	22.875	8.79	8.39	8.46
$H_{2/2'}$ (py)	24.173	7.50	7.15	7.21
$H_{3/3'}$ (py)	23.565	8.10	7.73	7.71
$H_{4/4'}$ (py)	23.798	7.87	7.51	7.40
$H_{5/5'}$ (CH_2)	27.964	3.70	3.71	3.62
$H_{6/6'}$ (NCH_3)	29.563	2.10	2.11	2.19
$H_{7/7'}$ (en)	29.068	2.60	2.60	2.56

Scale factors – aromatic (0.954), aliphatic (1.001)

NaPhe

	Chem shielding (ppm)	**δ (ppm)**		
		Calc (DMSO)	Corr. (DMSO)	Exp (D_2O)
H_c (CH-phe)	28.315	3.35	3.42	3.56
H_d (CH_2-phe)	28.818	2.85	2.90	2.90
$H_{d'}$ (CH_2-phe)	28.548	3.12	3.18	3.05
$H_{e/i}$ (Ph)	24.126	7.69	7.33	7.33
$H_{f/h}$ (Ph)	23.959	7.76	7.40	7.42
H_g (Ph)	23.941	7.73	7.36	7.34

Scale factors – aromatic (0.953), aliphatic (1.019)

Table S4 - Complex $[Co(Phe)(py_2en)](ClO_4)_2$, **1**, ^{1}H-NMR chemical shift in DMSO-d_6: calculated and experimental (for assigned structures).

	Calc. (ppm)	Exp. (ppm)	Δ_δ (ppm)	Calc. (ppm)	Exp. (ppm)	Δ_δ (ppm)	Calc. (ppm)	Calc. (ppm)
	Λ-cisα-*exo,exo*	Λ-cisα-*exo,exo*		Δ-cisβ$_1$-*exo,exo*	Δ-cisβ$_1$-*exo,exo*		Λ-cisβ$_1$-*exo,exo*	Λ-cisβ$_1$-*endo,exo*
H1 (py)	7.55	7.87-7.78	≈ -0.28	8.29	7.87-7.79	≈ +0.46	7.06	7.58
H2 (py)	7.22	8.19-8.16	≈ -0.96	7.83	8.19-8.16	≈ -0.34	7.11	7.32
H3 (py)	8.04	7.54	+0.50	8.33	7.48	+0.85	8.10	8.14
H4 (py)	7.61	7.01	+0.60	7.80	6.67	+1.13	7.66	7.66
H5 (CH_2)	4.47, 4.90	4.19, 4.63	+0.28, +0.27	3.75, 4.73	4.03, 4.37-4.30	-0.28, ≈ +0.39	3.71, 4.74	4.14, 4.83
H6 (NH)	– §	7.59	– §	– §	7.16	– §	– §	– §
H7 (en)	2.41, 3.01	2.56, 3.56	-0.15, -0.55	1.81, 3.21	2.12, 3.87	-0.31, -0.66	2.14, 3.44	3.16, 3.53
H7' (en)	2.34, 3.07	2.12, 2.85	+0.22, +0.22	2.75, 2.89	n.i., 3.12	–, -0.23	3.61, 3.78	2.66, 3.99
H6' (NH)	– §	7.59	– §	– §	7.44	– §	– §	– §
H5' (CH_2)	4.58, 5.21	4.01, 4.31	+0.57, +0.90	3.86, 4.21	4.37-4.30, 4.77	≈ -0.48, -0.56	4.69, 4.93	4.59, 4.77
H4' (py)	7.78	7.90	-0.12	7.65	7.87-7.79	≈ -0.18	7.75	7.75
H3' (py)	8.24	8.28	-0.04	8.11	8.19-8.16	≈ -0.06	8.13	8.14
H2' (py)	7.80	8.33	-0.53	7.41	7.87-7.79	≈ -0.42	7.37	7.42
H1' (py)	8.46	7.87-7.78	≈ +0.64	6.94	8.31	-1.37	6.65	6.86
NH_2-phe	– §	5.20, 5.42	– §	– §	4.60, 5.88	– §	– §	– §
Hα (CH-phe)	3.94	2.77	+1.17	4.06	3.40	+0.66	3.96	3.95
Hβ (CH_2-phe)	2.90, 3.54	2.98, 3.24	-0.08, +0.30	3.09, 3.79	n.i.	-	2.94, 3.65	2.82, 3.51
H2/H6 (Ph)	7.05	7.29-7.18	-0.19	7.51	7.36-7.32	+0.17	7.17	6.99
H3/H5 (Ph)	7.06	7.29-7.18	-0.18	7.73	7.36-7.32	+0.39	7.30	7.04
H4 (Ph)	7.11	7.29-7.18	-0.13	7.70	7.36-7.32	+0.36	7.44	7.09

§ - NMR calculations do not correctly determine exchangeable protons.

Table S5 - Complex [Co(Phe)(tpa)]$(ClO_4)_2$, **2**, ^{1}H-NMR chemical shift in DMSO-d_6: calculated and experimental (for assigned structure).

	Calc. (ppm)	Exp. (ppm)	Δ_δ (ppm)	Calc. (ppm)
	β_1	β_1		β_2
H1 (py)	8.32	8.26	+0.06	8.37
H2 (py)	7.55	7.66	-0.11	7.61
H3 (py)	8.09	8.16	-0.07	8.13
H4 (py)	7.68	7.80	-0.12	7.72
H5 (CH_2)	5.13, 5.01	5.43, 5.10-5.00	-0.30, ≈ -0.04	5.53, 5.03
H1' (py)	7.74	8.10	-0.36	6.58
H2' (py)	7.19	7.57	-0.38	6.98
H3' (py)	7.97	8.14	-0.17	7.85
H4' (py)	7.58	7.80	-0.22	7.54
H5' (CH_2)	4.96, 4.63	5.33, 5.10-5.00	-0.37; ≈ -0.42	5.52, 4.92
H6 (CH_2)	5.02, 4.76	5.10-5.00	≈ -0.03, ≈ -0.29	5.08, 5.02
H7 (py)	7.20	7.34	-0.14	7.19
H8 (py)	7.86	7.97	-0.11	7.86
H9 (py)	7.57	7.70	-0.13	7.57
H10 (py)	9.10	9.06	+0.04	8.36
NH_2-phe	– [§]	6.23, 4.86	– [§]	– [§]
Hα (CH-phe)	3.58	3.35	+0.23	3.91
Hβ (CH_2-phe)	3.53, 2.75	3.00-2.85	+0.61, -0.10	3.80, 3.23
H2/H6 (Ph)	7.07	7.16	+0.09	7.68
H3/H5 (Ph)	7.06	7.16	+0.10	7.71
H4 (Ph)	7.05	7.16	-0.11	7.42

[§] - NMR calculations do not correctly determine exchangeable protons.

Table S6 - Complex $[Co(Phe)(py_2enMe_2)](ClO_4)_2$, **3**, ^{1}H-NMR chemical shift in DMSO-d_6: calculated and experimental (for assigned structures).

	Calc. (ppm)	Exp. (ppm)		Calc. (ppm)	Exp. (ppm)	
	Λ-cisα-*exo,exo*	Λ-cisα-*exo,exo*	Δ_δ (ppm)	Δ-cisα-*exo,exo*	Δ-cisα-*exo,exo*	Δ_δ (ppm)
H1 (py)	7.72	8.13	-0.41	7.10	8.56	-1.46
H2 (py)	7.18	7.66	-0.48	7.14	7.52	-0.38
H3 (py)	8.09	8.25	-0.16	8.02	8.20	-0.18
H4 (py)	7.67	7.92-7.85	≈ -0.22	7.66	7.83	-0.17
H5 (CH_2)	4.24, 4.46	4.46-4.36	-0.17, +0.05	4.44, 4.93	n.i.	-
H6 (NMe)	2.58	2.56	+0.02	2.55	2.53	+0.02
H7 (en)	2.55, 2.76	2.64, 2.85	-0.09, -0.09	2.54, 2.78	2.64, 2.87	-0.10, -0.09
H7' (en)	2.67, 2.83	2.85 (both)	-0.18, -0.02	2.68, 2.77	2.64, 2.87	+0.04, -0.10
H6' (NMe)	2.36	2.33	+0.03	2.39	2.38	+0.01
H5' (CH_2)	4.51, 4.84	4.46-4.36, 4.74	≈ +0.10, +0.10	4.54, 4.58	4.38, 4.83	+0.16, -0.26
H4' (py)	7.81	7.92-7.85	≈ -0.07	7.84	n.i.	-
H3' (py)	8.30	8.32	-0.02	8.31	n.i.	-
H2' (py)	7.86	7.92-7.85	≈ -0.02	7.85	n.i.	-
H1' (py)	8.52	9.02	-0.50	8.49	8.31	+0.18
NH_2-phe	– [§]	4.06, 6.93	– [§]	– [§]	4.72, 6.03	– [§]
Hα (CH-phe)	3.63	3.45	+0.18	2.91	3.14	-0.23
Hβ (CH_2-phe)	2.76, 3.39	2.90 (both)	-0.14, +0.49	2.74, 3.50	2.82	-0.08, +0.68
H2/H6 (Ph)	6.94	7.24-7.12	≈ -0.01	7.18	7.24-7.12	≈ -0.00
H3/H6 (Ph)	7.06	7.24-7.12	≈ -0.12	7.34	7.24-7.12	≈ +0.16
H4 (Ph)	7.17	7.24-7.12	≈ -0.01	7.53	7.24-7.12	≈ +0.35

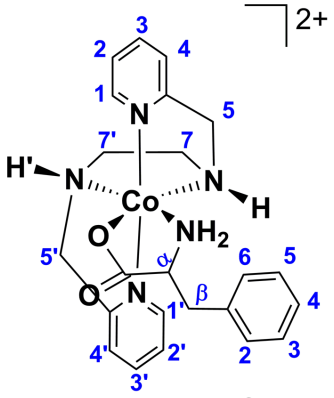
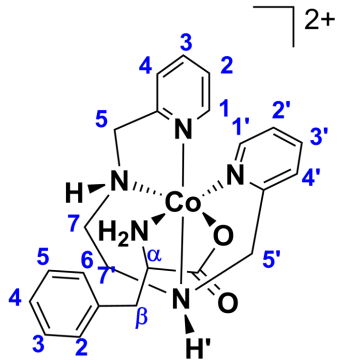
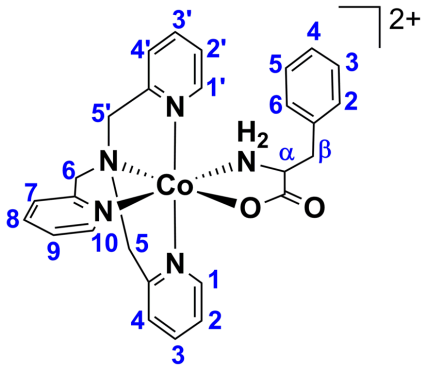
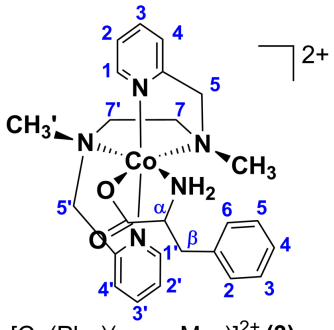
[§] - NMR calculations do not correctly determine exchangeable protons.

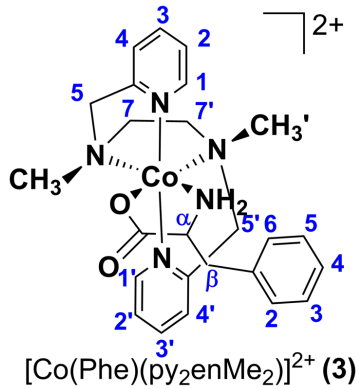
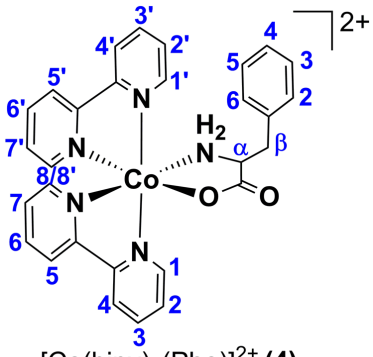
Table S7 - Complex $[Co(bipy)_2(Phe)](ClO_4)_2$, **4**, ^{1}H-NMR chemical shift in DMSO-d_6: calculated and experimental (for assigned structure).

	Calc. (ppm)	Exp. (ppm)	Δ_δ (ppm)	Calc. (ppm)
	Λ	Λ		Δ
H1 (py)	8.72	9.28	-0.56	8.59
H2 (py)	8.10	8.21	-0.11	8.07
H3 (py)	8.61	8.68	-0.07	8.64
H4 (py)	8.69	8.97	-0.28	8.77
H5 (py)	8.54	6.98	+1.56	8.63
H6 (py)	8.27	7.59	+0.68	8.34
H7 (py)	7.35	8.38-8.35	≈ -1.02	7.44
H8 (py)	6.69	8.84	-2.15	7.28
H1' (py)	7.72	8.38-8.35	≈ -0.64	6.77
H2' (py)	7.32	8.09	-0.77	7.33
H3' (py)	8.40	8.68	-0.28	8.35
H4' (py)	8.57	8.97	-0.40	8.55
H5' (py)	8.56	7.65	+0.91	8.49
H6' (py)	8.33	7.65	+0.68	8.28
H7' (py)	7.52	8.38-8.35	≈ -0.85	7.43
H8' (py)	7.54	8.84	-1.30	7.04
NH_2-phe	– [§]	7.15, 5.34	– [§]	– [§]
Hα (CH-phe)	3.97	4.13	-0.16	3.27
Hβ (CH_2-phe)	3.44, 2.80	3.12, 2.81	+0.32, -0.01	3.56, 2.73
H2/H6 (Ph)	6.94	7.30-7.25	≈ -0.34	7.68
H3/H5 (Ph)	7.13	7.30-7.25	≈ -0.14	7.71
H4 (Ph)	7.30	7.30-7.25	≈ +0.02	7.42

[§] - NMR calculations do not correctly determine exchangeable protons

Table S8 - ^{1}H NMR (500 MHz, δ/ppm) assignments for complexes **1**-**4** in DMSO-d_6.

 [Co(Phe)(py$_2$en)]$^{2+}$ **(1)** Isomer Λ-*cis*α-exo-exo	8.33 (td, 7.8 Hz, 1.4 Hz, 1H, *H$_{2'}$*), 8.28 (m, 1H, *H$_{3'}$*), 8.19-8.16 (m, 1H, *H$_2$*), 7.90 (d, 7.8 Hz, 1H, *H$_{4'}$*), 7.87-7.78 (m, 2H, H$_1$, *H$_{1'}$*), 7.59 (b, 1H, NH), 7.54 (t, 6.4 Hz, 1H, *H$_3$*), 7.29-7.18 (m, 5H, *H$_2$-H$_6$-Phen*), 7.59 (overlap, NH'), 7.01 (d, 5.4 Hz, 1H, *H$_4$*), 5.42 (t, 9.0 Hz, 1H, *NH$_2$*), 5.20 (t, 10.2 Hz, 1H, *NH$_2$*), 4.63 (dd, 16.6, 6.3 Hz, 1H, *H$_5$*), 4.31 (m, 1H, *H$_{5'}$*), 4.19 (d, 16.6 Hz, 1H, *H$_5$*), 4.01 (m, 1H, H$_{5'}$), 3.56 (m, 1H, *H$_7$*), 3.24 (overlap, H$_β$), 2.98 (m, 1H, H$_β$), 2.85 (m, 1H, *H$_{7'}$*), 2.77 (m, 1H, *H$_α$*), 2.56 (m, 1H, *H$_7$*), 2.12 (m, 1H, *H$_{7'}$*).
 [Co(Phe)(py$_2$en)]$^{2+}$ **(1)** Isomer Δ-*cis*β1-exo-exo	8.31 (m, 1H, *H$_{1'}$*), 8.19-8.16 (m, 2H, H$_2$, *H$_{3'}$*), 7.87-7.79 (m, 3H, H$_1$, *H$_{2'}$* and *H$_{4'}$*), 7.48 (t, 6.5 Hz, 1H, *H$_3$*), 7.44 (br, 1H, NH'), 7.36-7.32 (m, 5H, *H$_2$-H$_6$-Phen*), 7.16 (br, NH), 6.67 (d, 5.5 Hz, 1H, *H$_4$*), 5.88 (t, 9.0 Hz, 1H, *NH$_2$*), 4.77 (dd, 17.6, 6.2 Hz, 1H, H5'), 4.60 (m, 1H, N*H$_2$*), 4.37-4,30 (m, H5, H5'), 4.03 (dd, 17.4, 9.4 Hz, H5), 3.87 (m, 1H, H7), (3.40 (m, 1H, *H$_α$*), 3.12 (m, 1H, H$_{7'}$), 2.12 (m, 1H, H$_7$). *H$_{8s}$ and H$_{7'}$ could not be identified.*
 [Co(Phe)(TPA)]$^{2+}$ **(2)**	9.06 (d, 5.4 Hz, 1H, *H$_{10}$*), 8.26 (d, 5.4 Hz, 1H, *H$_1$*), 8.16 (td, 7.7, 1.4 Hz, 1H, *H$_3$*), 8.14 (td, 7.7, 1.4 Hz, 1H, *H$_{3'}$*), 8.10 (d, 5.4 Hz, 1H, *H$_{1'}$*), 7.97 (td, 7.7, 1.4 Hz, 1H, *H$_8$*), 7.80 (t, 7.7 Hz, 2H, *H$_4$* and *H$_{4'}$*), 7.70 (t, 7.7 Hz, 1H, *H$_9$*), 7.66 (t, 7.7 Hz, 1H, *H$_2$*), 7.57 (t, 7.7 Hz, 1H, *H$_{2'}$*), 7.34 (d, 7.7 Hz, 1H, *H$_7$*), 7.16 (m, 5H, *H$_2$-H$_6$-Phen*), 6.23 (t, 8.8 Hz, 1H, *NH$_2$*), 5.43 (d, 16.6 Hz, 1H, *H$_5$*), 5.33 (d, 16.6 Hz, 1H, *H$_{5'}$*), 5.10-5.00 (m, 4H, *H$_6$*, H$_5$ and *H$_{5'}$*), 4.86 (t, 8.8 Hz, 1H, *NH$_2$*), 3.35 (t, 5.5 Hz, 1H, *H$_α$*), 3,00-2,85 (qd, 15.0, 5.5 Hz, 2H, *H$_8$*).
 [Co(Phe)(py$_2$enMe$_2$)]$^{2+}$ **(3)** Isomer Λ-*cis*α-exo-exo	9.02 (d, 5.8 Hz, 1H, *H$_{1'}$*), 8.32 (td, 7,7, 1,0 Hz, 1H, *H$_{3'}$*), 8.25 (m, 1H, *H$_3$*), 8.13 (d, 5.4 Hz, 1H, *H$_1$*), 7.92 -7.85 (m, 3H, *H$_{2'}$*, *H$_4$* and *H$_{4'}$*), 7.66 (ddd, 7.7, 6.2, 1.0 Hz, 1H, *H$_2$*), 7.24-7.12 (m, 5H, *H$_2$-H$_6$-Phen*), 6.93 (t, 10.4 Hz, 1H, N*H$_2$*), 4.74 (d, 16.3 Hz, 1H, *H$_{5'}$*), 4.46-4.36 (m, 3H, *H$_{5'}$*, *2H$_5$*), 4.06 (t, 10.4 Hz, 1H, N*H$_2$*), 3.45 (m, 1H, *H$_α$*), 2.90 (m, 2H, *H$_8$*), 2.85 (m, 3H, *H$_7$*, *2H$_{7'}$*), 2.64 (m, 1H, *H$_7$*), 2.56 (s, 3H, C*H$_3$*), 2.33 (s, 3H, C*H$_{3'}$*).

 [Co(Phe)(py$_2$enMe$_2$)]$^{2+}$ **(3)** Isomer Δ-*cis*α-exo-exo	8.56 (d, 5.8 Hz, 1H, H_1), 8,31 (m, $H_{1'}$), 8.20 (dd, 5.8 Hz, 1H, H_3), 7.83 (m, 1H, H_4), 7.52 (t, 7.7, Hz, 1H, H_2), 7.24-7.12 (m, 5H, H_2-H_6-*Phen*), 6.03 (t, 11.0 Hz, 1H, NH_2), 4.83 (d, 16.3 Hz, 1H, $H_{5'}$), 4.72 (overlap NH_2), 4.38 (m, 1H, $H_{5'}$), 3.14 (overlap, H_α), 2.87 (m, $H_{7 \text{ or } 7'}$), 2.82 (m, H_β), 2.64 (overlap, $H_{7 \text{ or } 7'}$), 2.53 (s, 3H, CH_3), 2.38 (s, 3H, C$H_{3'}$). *Some hydrogen atoms could not be identified unequivocally due to overlapping.*
 [Co(bipy)$_2$(Phe)]$^{2+}$ **(4)**	9.28 (d, J = 6.0 Hz, 1H, H_1), 8.97 (t, 7.9 Hz, 2H, H_4 and $H_{4'}$), 8.84 (d, 7.9 Hz, 2H, H_8 and $H_{8'}$), 8.68 (t, 7.9 Hz, 2H, H_3 and $H_{3'}$), 8.38-8,35 (m, 3H, $H_{1'}$, H_7 and $H_{7'}$), 8.21 (ddd, 7.9, 6.0, 1.3 Hz 1H, H_2), 8.09 (ddd, 7.9, 6.0, 1.3 Hz, 1H, $H_{2'}$), 7.65 (m, 2H, $H_{5'}$ and $H_{6'}$), 7.59 (ddd, 7.9, 6.0, 1.3 Hz, 1H, H_6), 7.30-7.25 (m, 5H, H_2-H_6-*Phen*), 7.15 (t, 10.4 Hz, 1H, NH_2), 6.98 (d, 6.0 Hz, 1H, H_5), 5.34 (t, 10.4 Hz, 1H, NH_2), 4.13 (m, 1H, H_α), 3.12 (dd, 15.5, 3.7 Hz, 1H, H_β), 2.81 (dd, 15.5, 8.5 Hz, 1H, H_β).

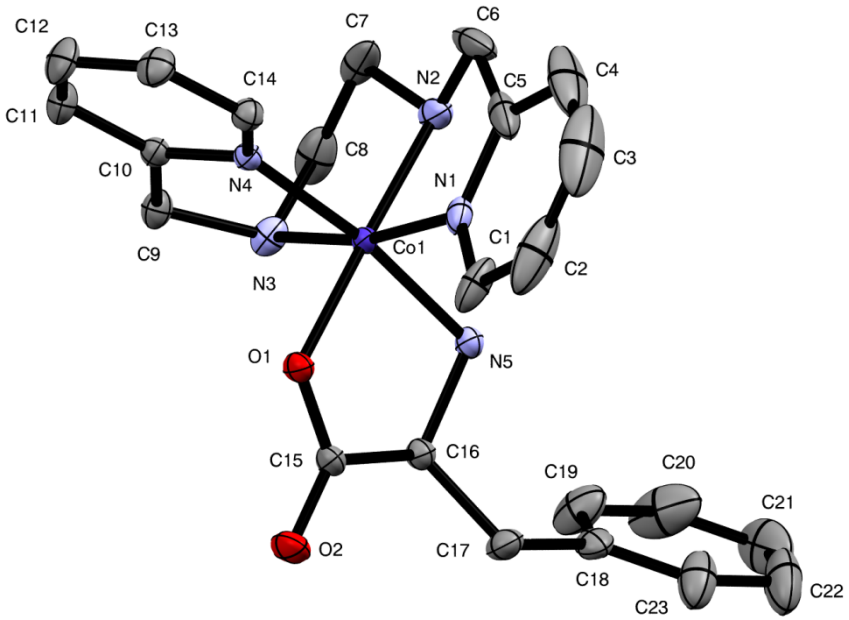


Fig. S1. Representation of $[Co(phenylalanine)(py_2en)]^{2+}$ **(1)**.

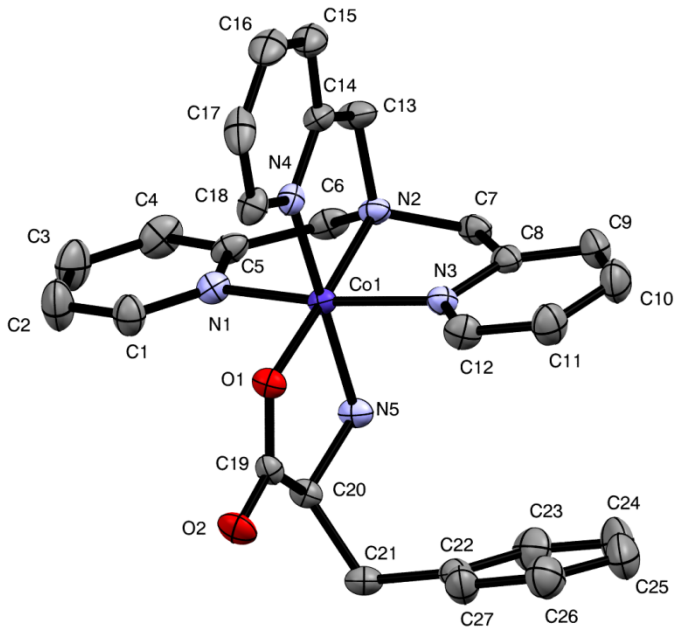


Fig. S2. Representation of $[Co(phenylalanine)(tpa)]^{2+}$ **(2)**.

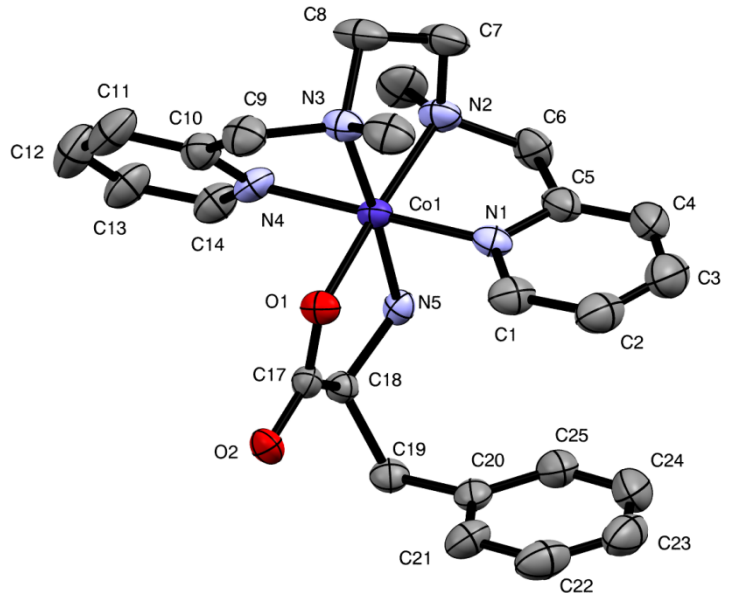


Fig. S3. Representation of $[Co(phenylalanine)(py_2enMe_2)]^{2+}$ **(3)**.

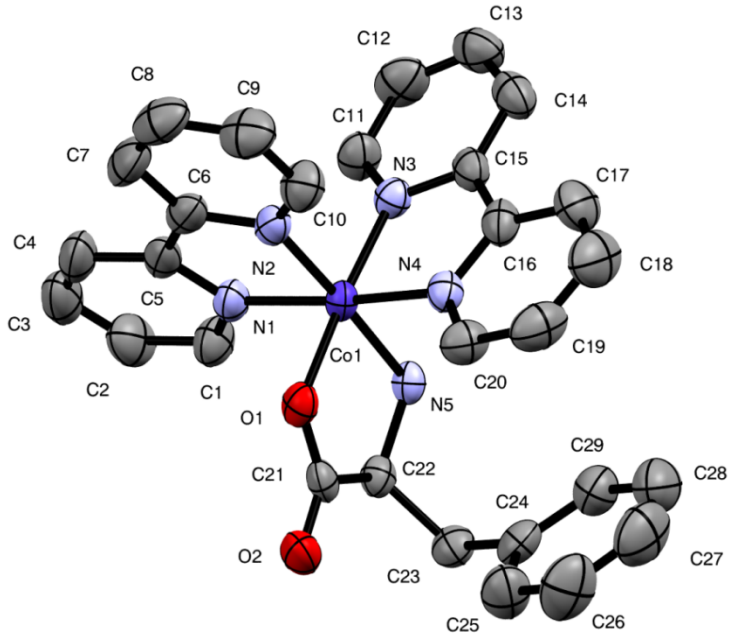


Fig. S4. Representation of $[Co(bipy)_2(phenylalanine)]^{2+}$ **(4)**.

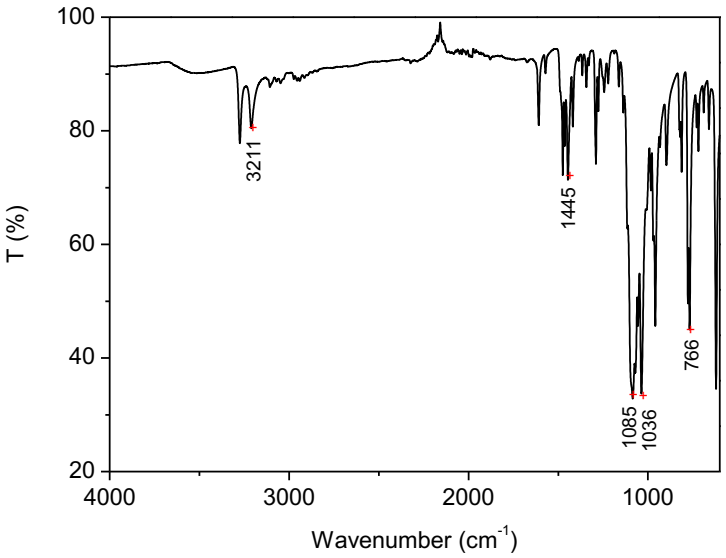


Fig. S5. Infrared spectrum (ZnSe/diamond ATR) of complex $[CoCl_2(py_2en)]ClO_4$.

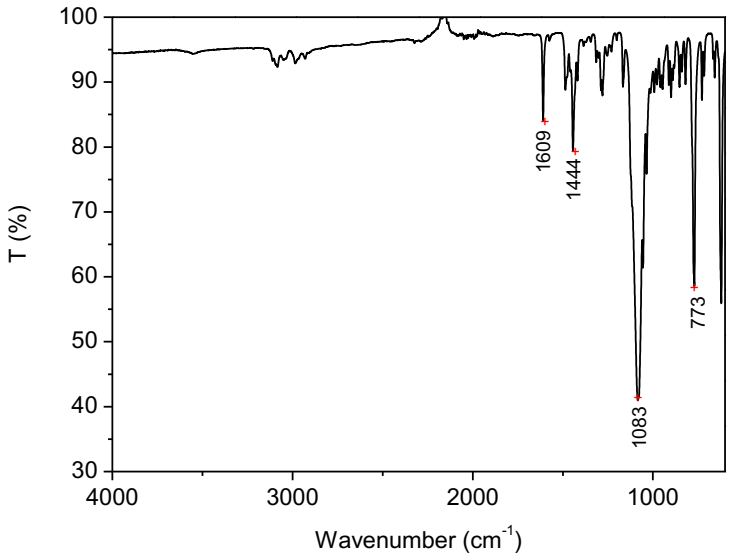


Fig. S6. Infrared spectrum (ZnSe/diamond ATR) of complex $[CoCl_2(tpa)]ClO_4$.

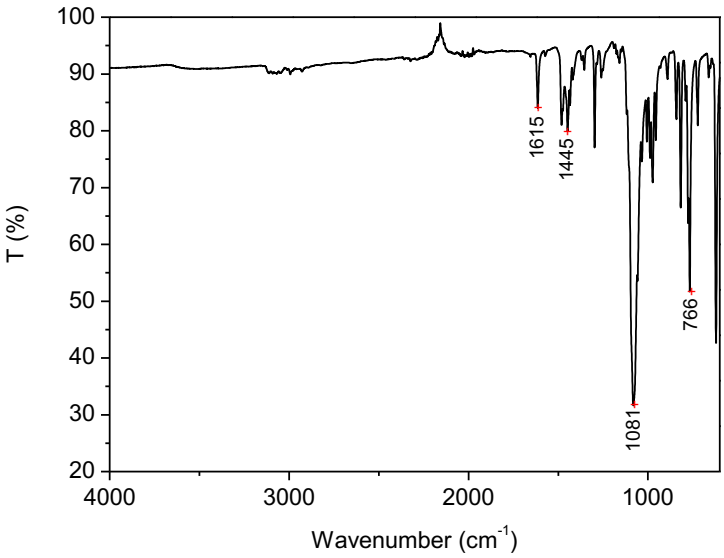


Fig. S7. Infrared spectrum (ZnSe/diamond ATR) of complex $[CoCl_2(py_2enMe_2)]ClO_4$.

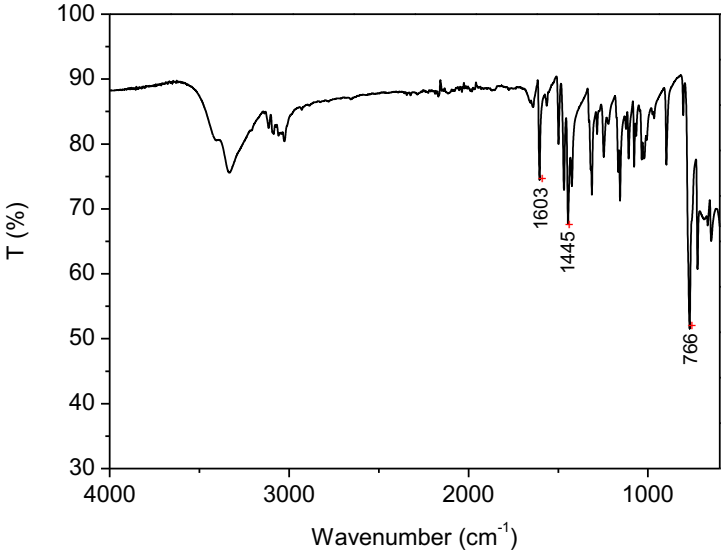


Fig. S8. Infrared spectrum (ZnSe/diamond ATR) of complex $[Co(bipy)_2Cl_2]Cl$.

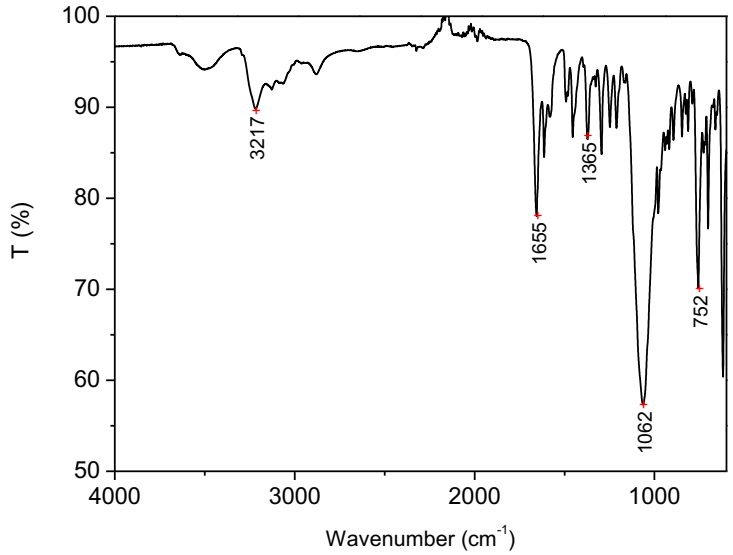


Fig. S9. Infrared spectrum (ZnSe/diamond ATR) of complex **1**.

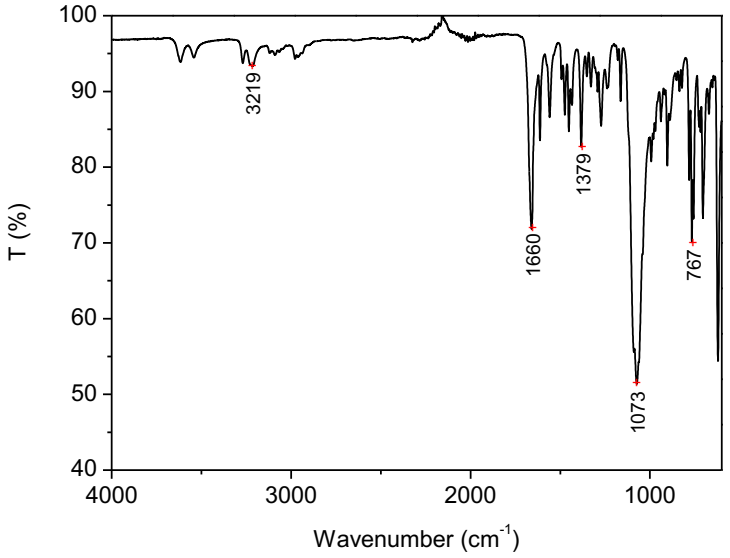


Fig. S10. Infrared spectrum (ZnSe/diamond ATR) of complex **2**.

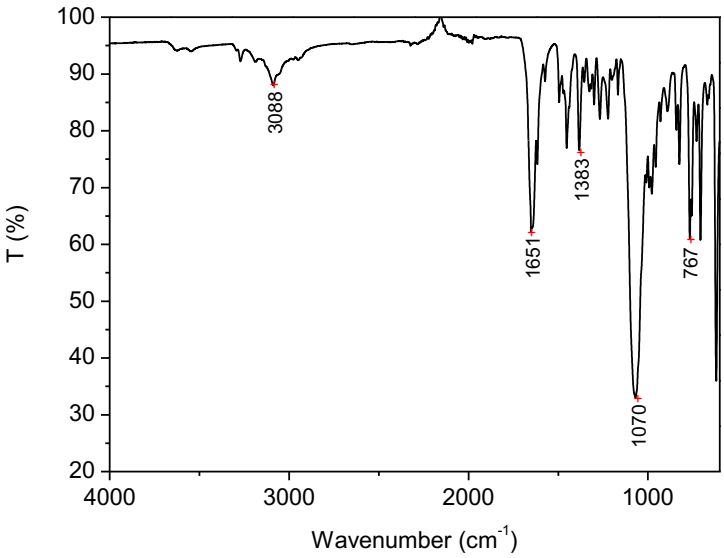


Fig. S11. Infrared spectrum (ZnSe/diamond ATR) of complex **3**.

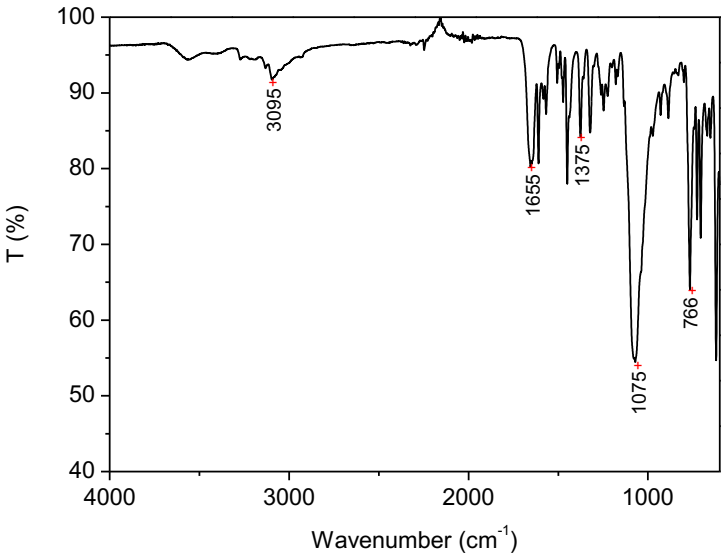


Fig. S12. Infrared spectrum (ZnSe/diamond ATR) of complex **4**.

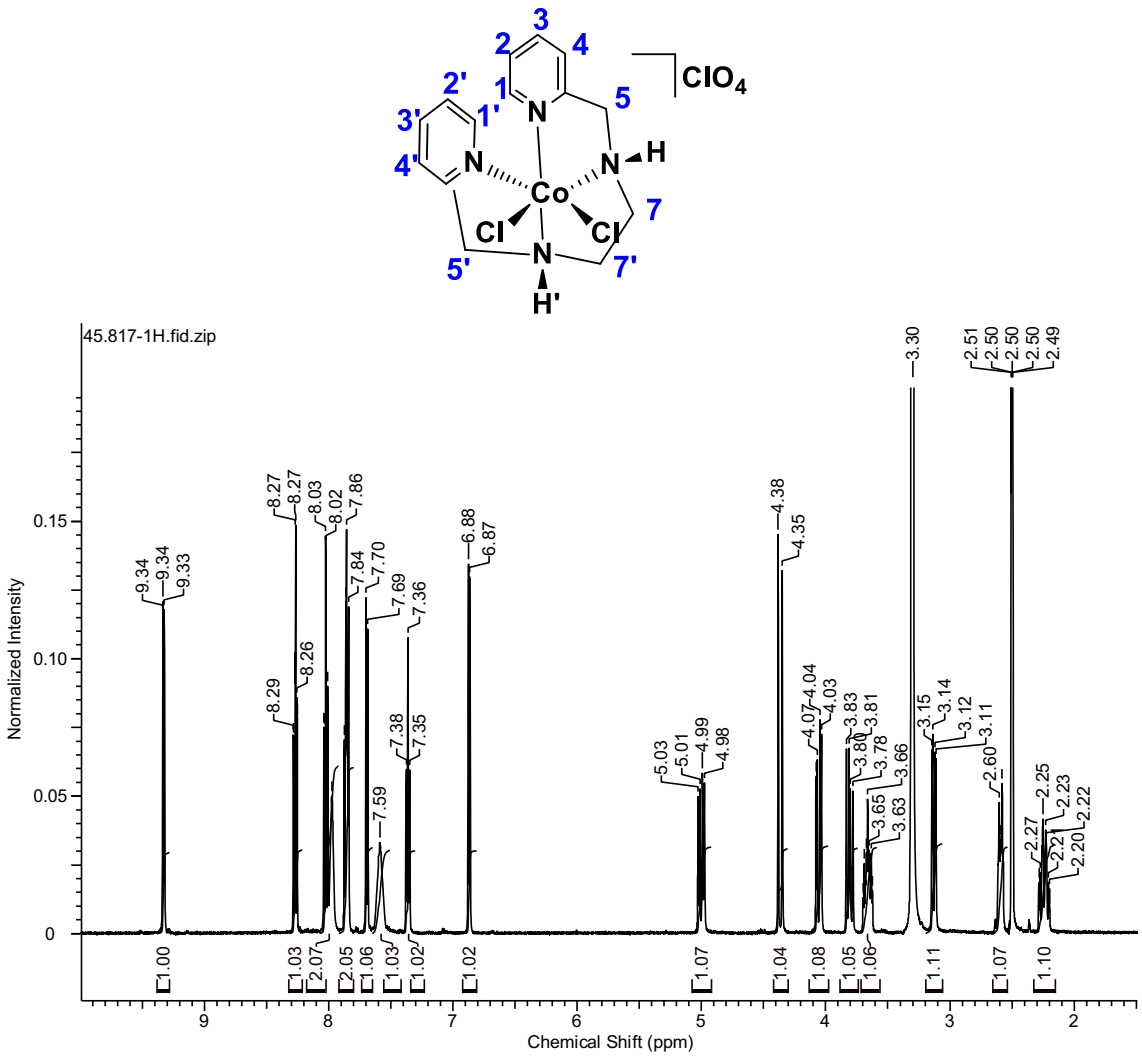


Fig. S13. ^{1}H NMR spectrum of complex $[CoCl_2(py_2en)]ClO_4$ in DMSO-d_6.

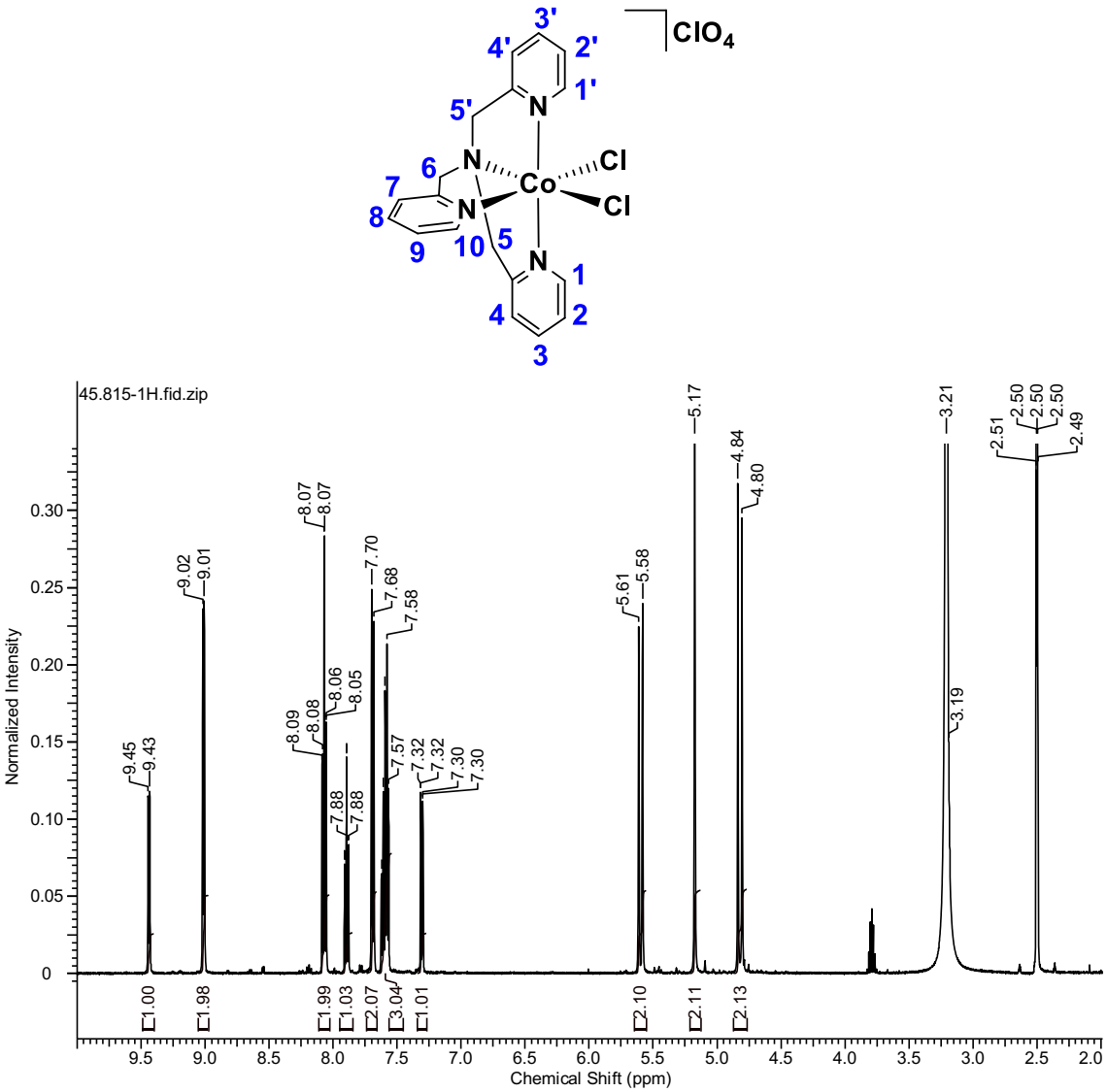


Fig. S14. ^{1}H NMR spectrum of complex $[CoCl_2(tpa)]ClO_4$ in DMSO-d_6.

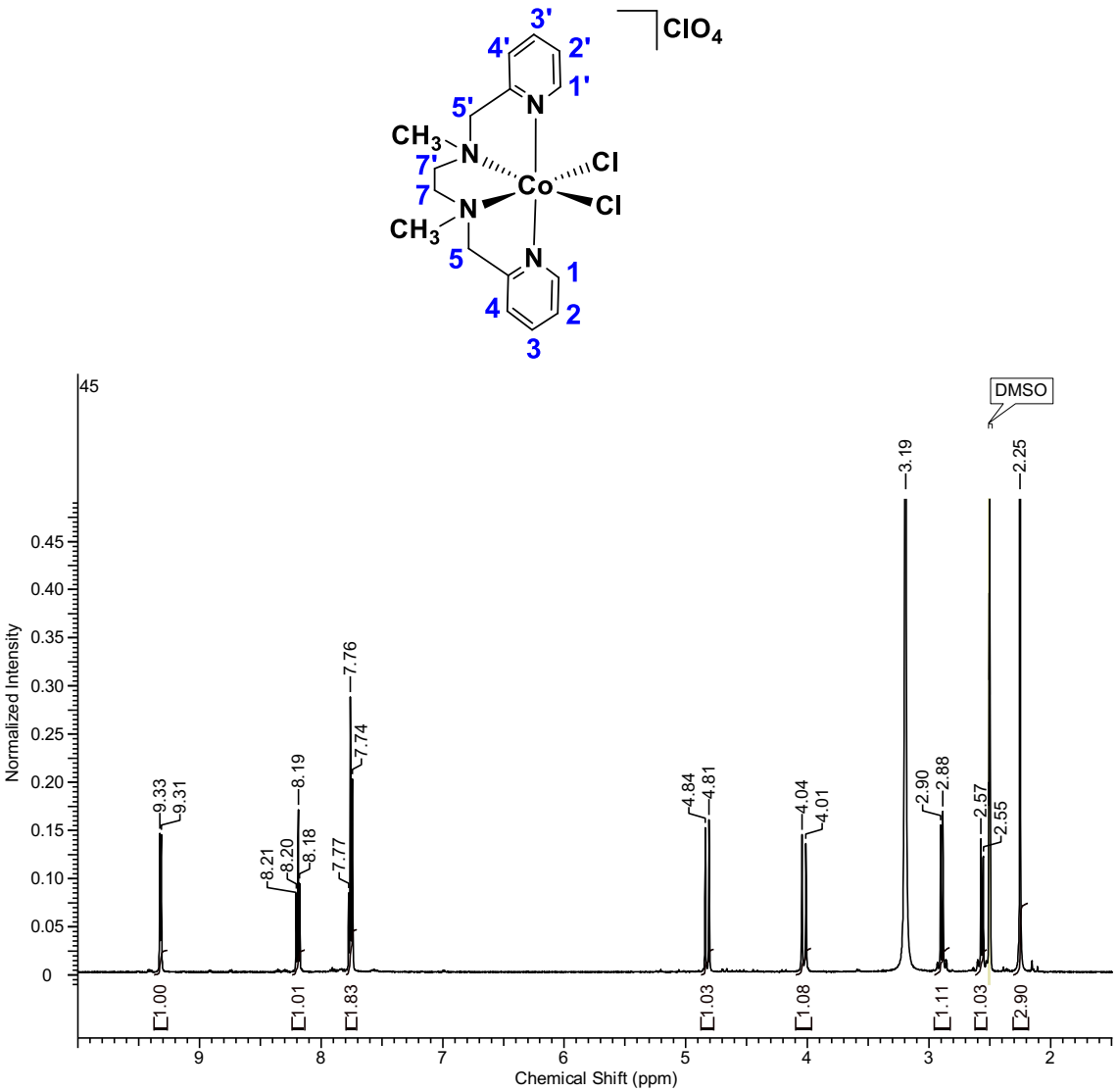


Fig. S15. ^{1}H NMR spectrum of complex $[CoCl_2(py_2enMe_2)]ClO_4$in DMSO-$d_6$.

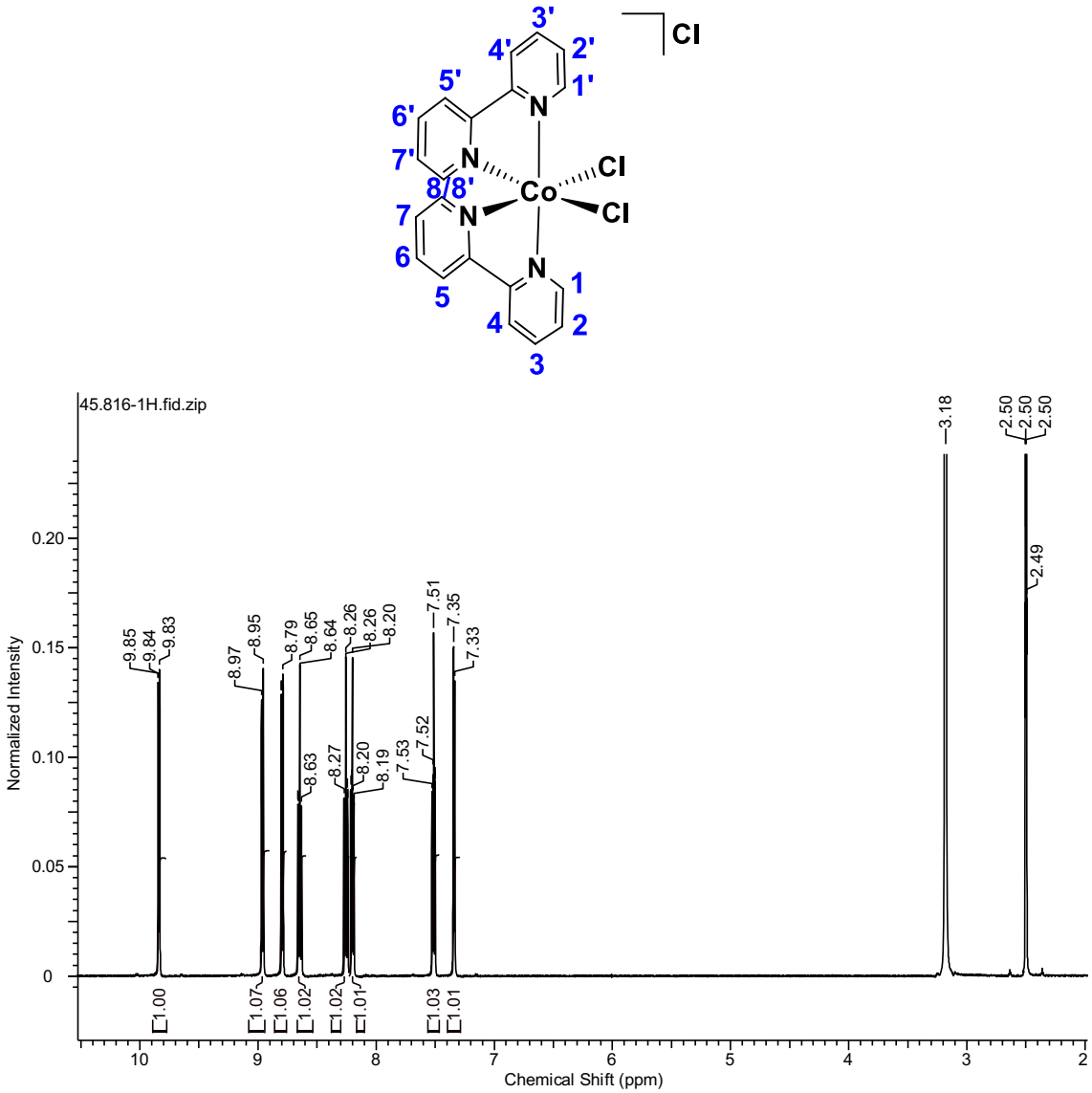


Fig. S16. ^{1}H NMR spectrum of complex $[Co(bipy)_2Cl_2]Cl$ in DMSO-d_6.

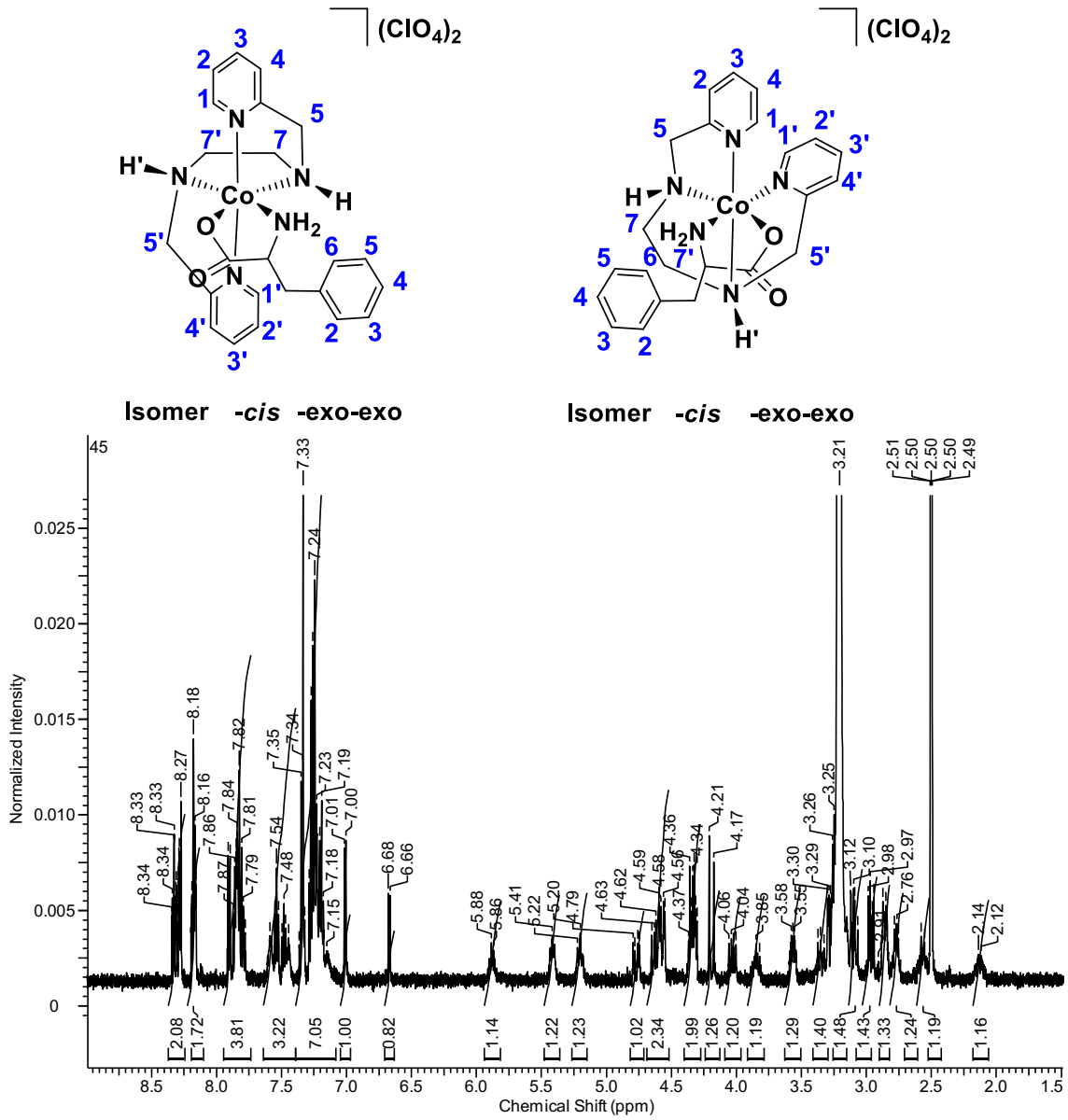


Fig. S17. ^{1}H NMR spectrum of complex **1** in DMSO-d_6. Ratio Λ-cisα-exo-exo: Δ-cisβ1-exo-exo 3:2.

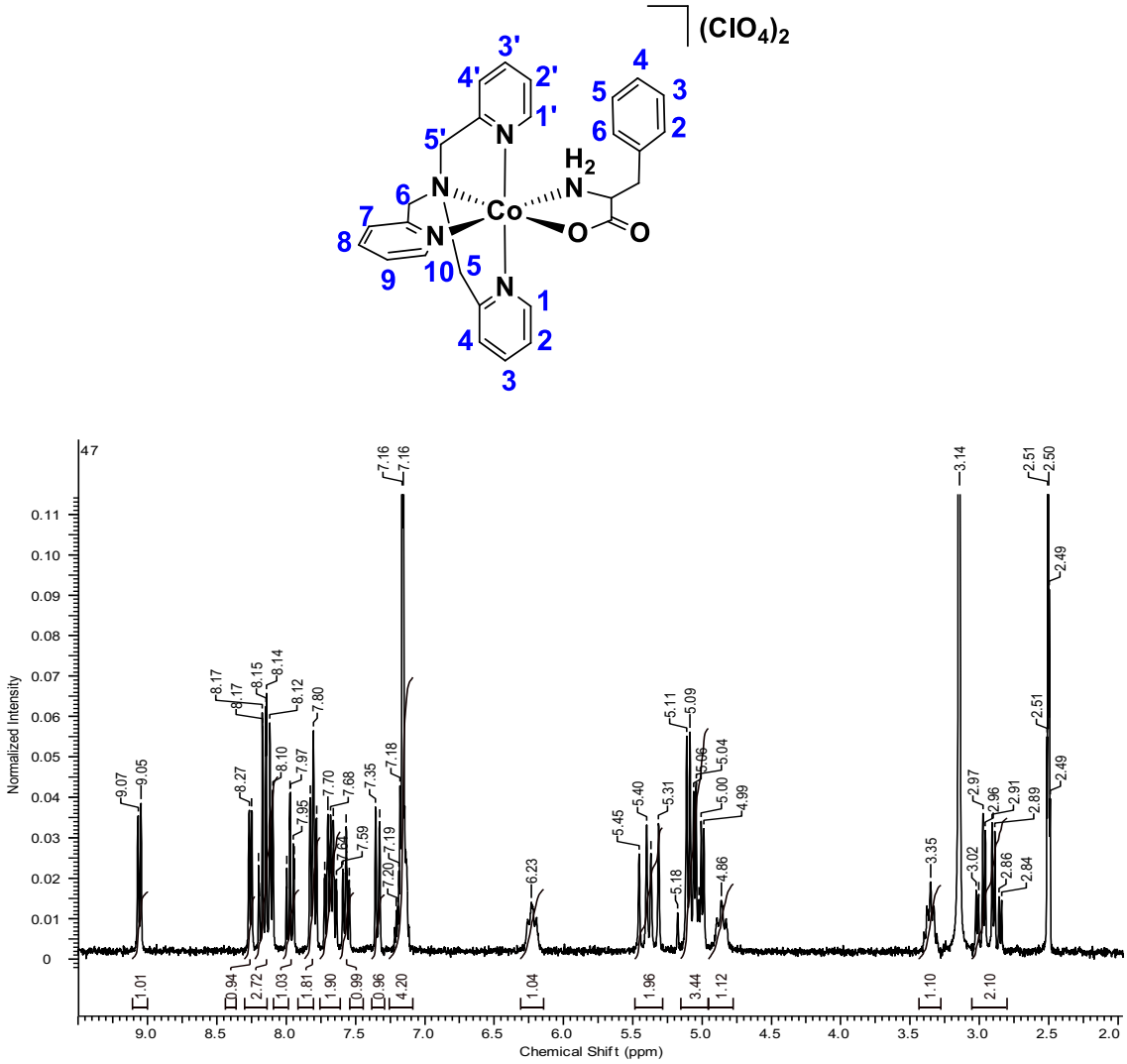


Fig. S18. ^{1}H NMR spectrum of complex **2** in DMSO-d_6.

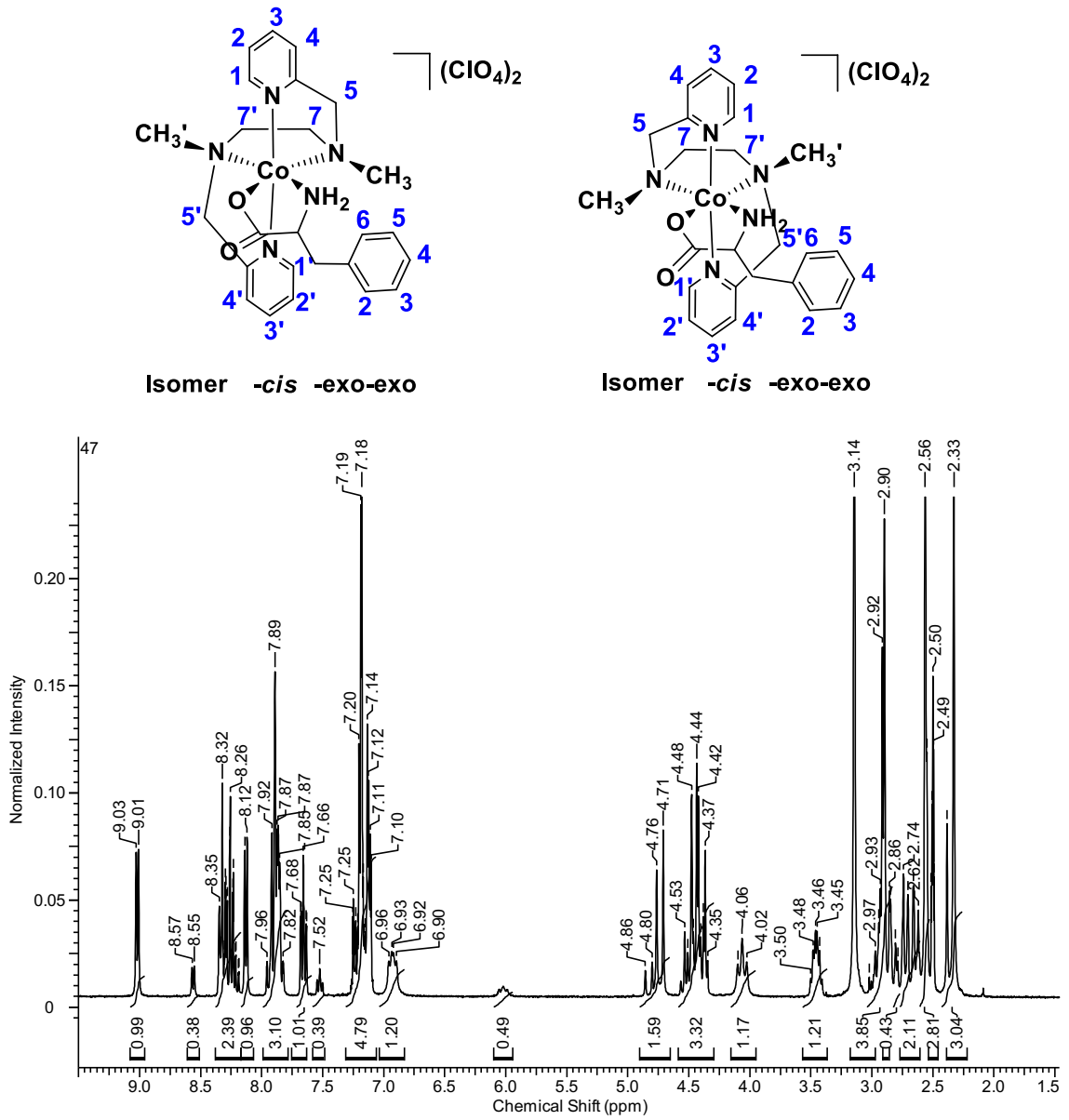


Fig. S19. ^{1}H NMR spectrum of complex **3** in DMSO-d$_6$. Ratio Λ-cisα-exo-exo: Δ-cisα-exo-exo 5:2.

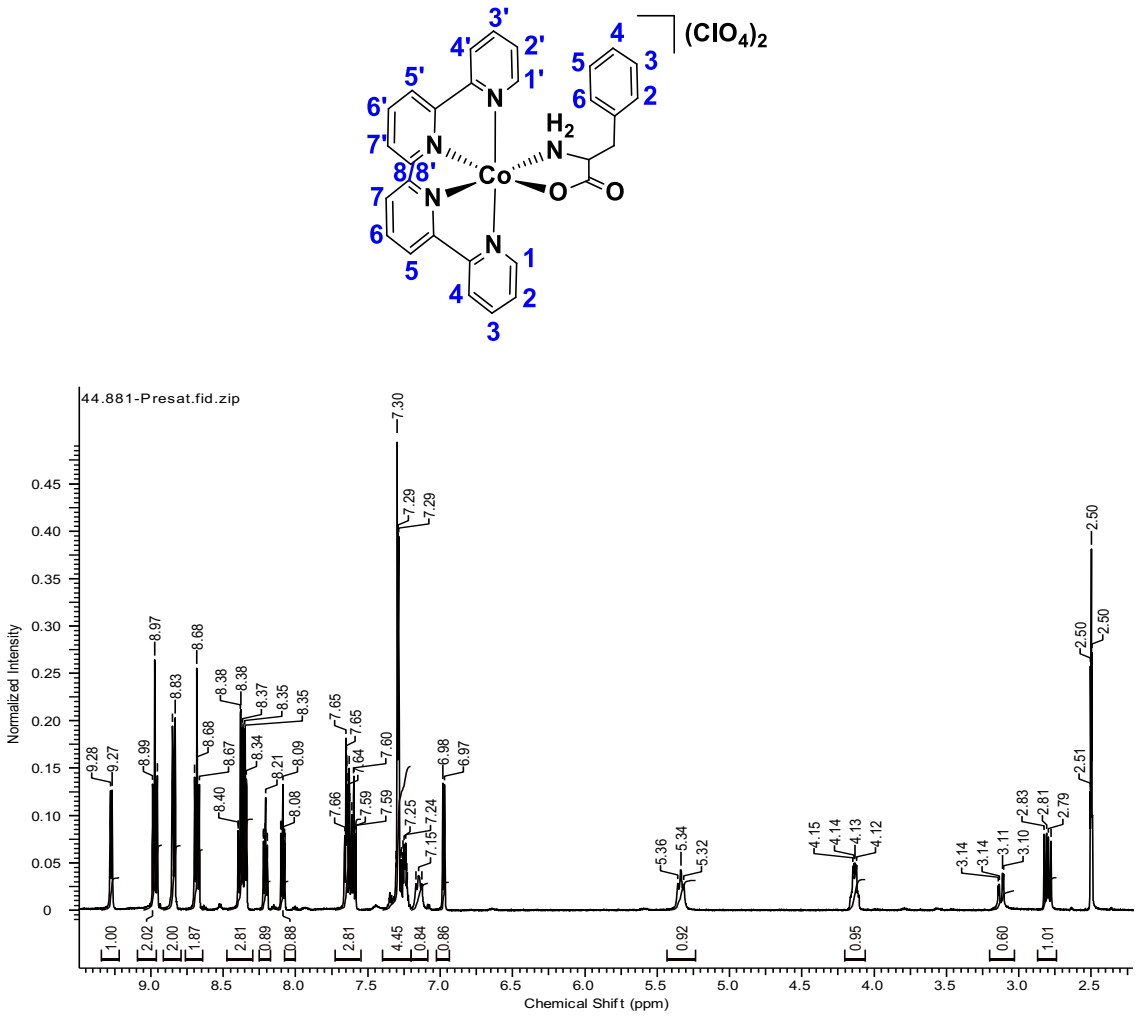


Fig. S20. ^{1}H NMR spectrum of complex **4** in DMSO-d$_6$.

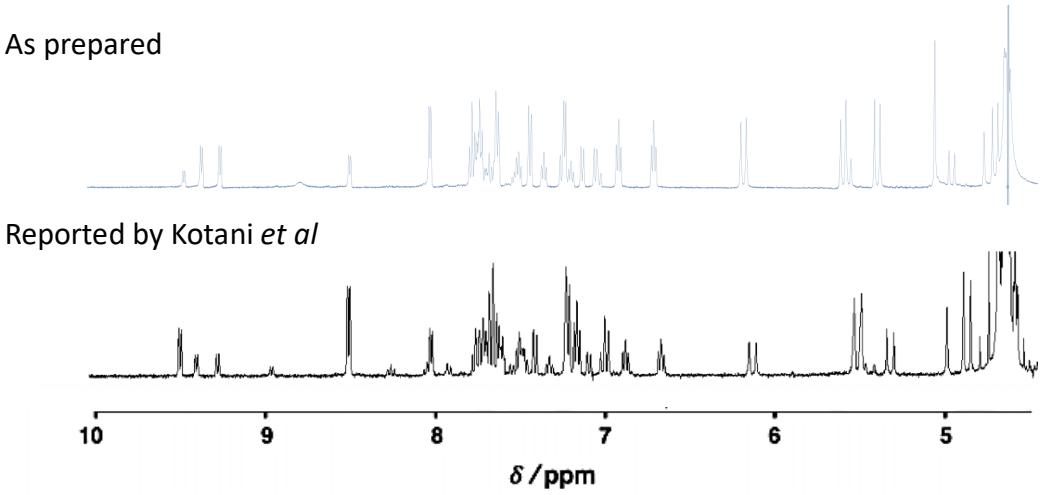


Fig. S21. ^{1}H NMR spectrum of complex [Co$^{III}_2$(μ-OH)(μ-O$_2$)(TPA)$_2$](ClO$_4$)$_3$ obtained in this work (top) and the one reported by Kotani *et al* (bottom).

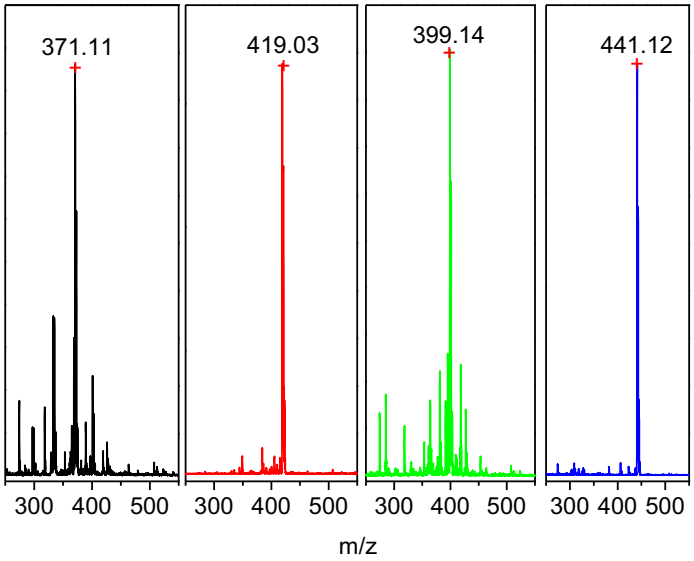


Fig. S22. ESI-MS spectrum (in MeOH) of $[CoCl_2(py_2en)]ClO_4$ **(black)**, $[CoCl_2(tpa)]ClO_4$ **(red)**, $[CoCl_2(py_2enMe_2)]ClO_4$ **(green)** and $[Co(bipy)_2Cl_2]Cl$ **(blue)**.

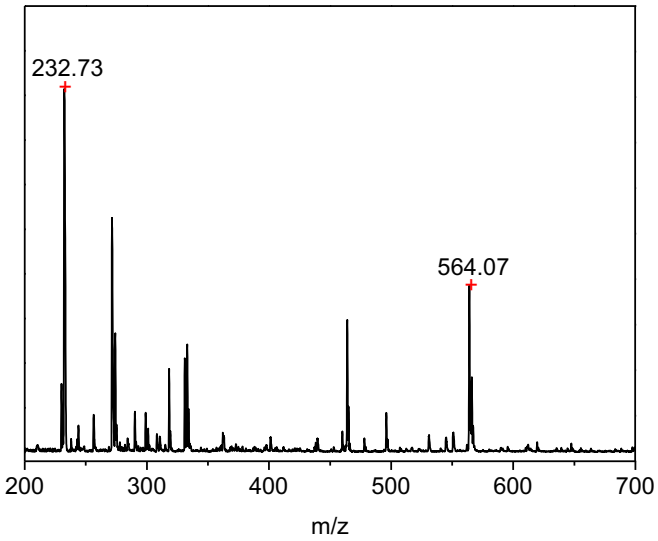


Fig. S23. ESI-MS spectrum of complex **1** in MeCN.

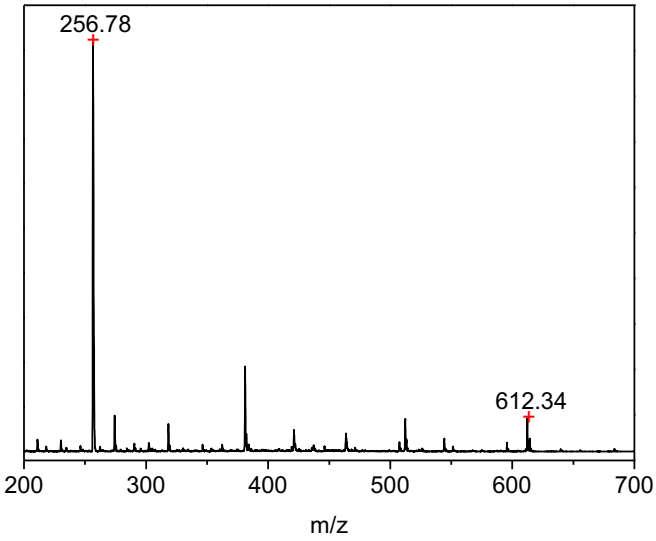


Fig. S24. ESI-MS spectrum of complex **2** in MeCN.

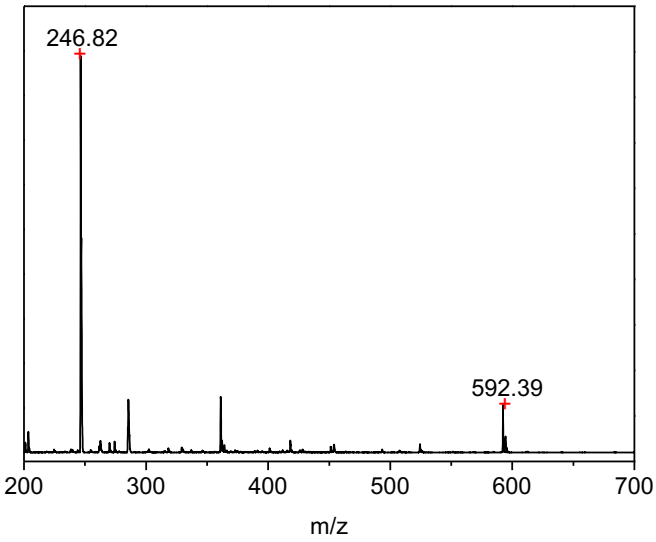


Fig. S25 ESI-MS spectrum of complex **3** in MeCN.

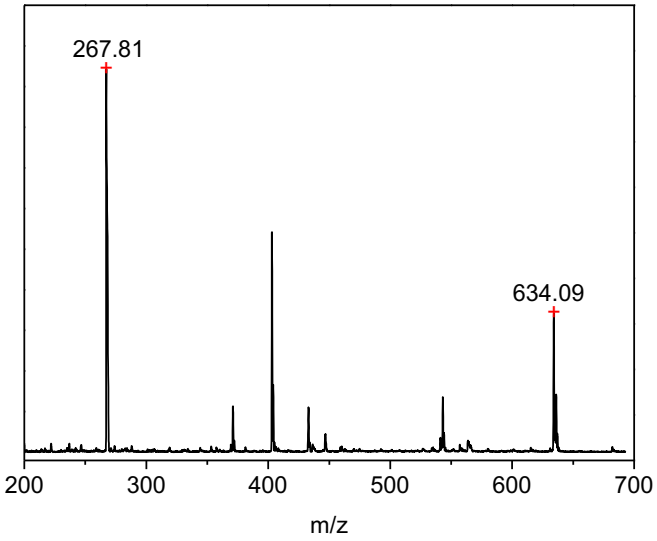


Fig. S26. ESI-MS spectrum of complex **4** in MeCN.

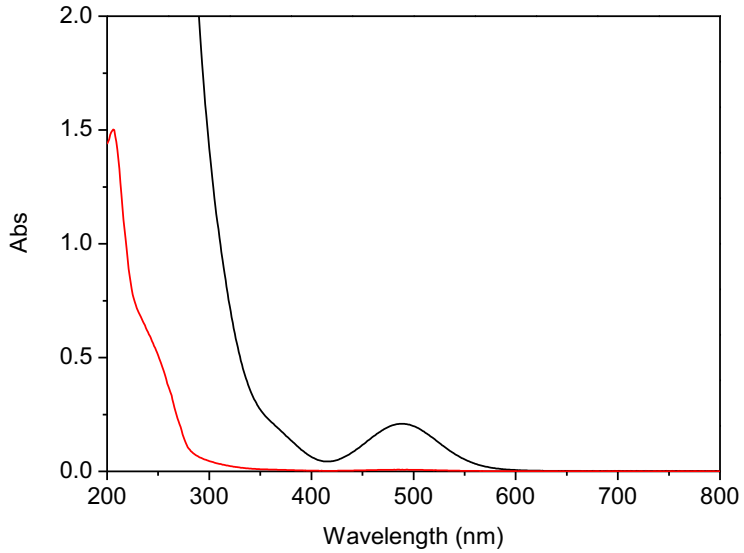


Fig. S27. UV-visible spectra of **1** in MeCN at 1.0×10^{-3} mol L^{-1} and 3.0×10^{-5} mol L^{-1}.

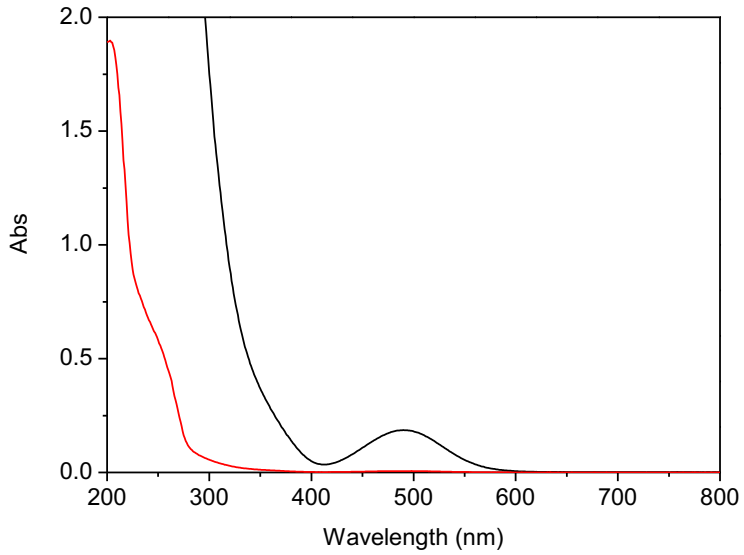


Fig. S28. UV-visible spectra of **2** in MeCN at 1.0×10^{-3} mol L^{-1} and 3.0×10^{-5} mol L^{-1}.

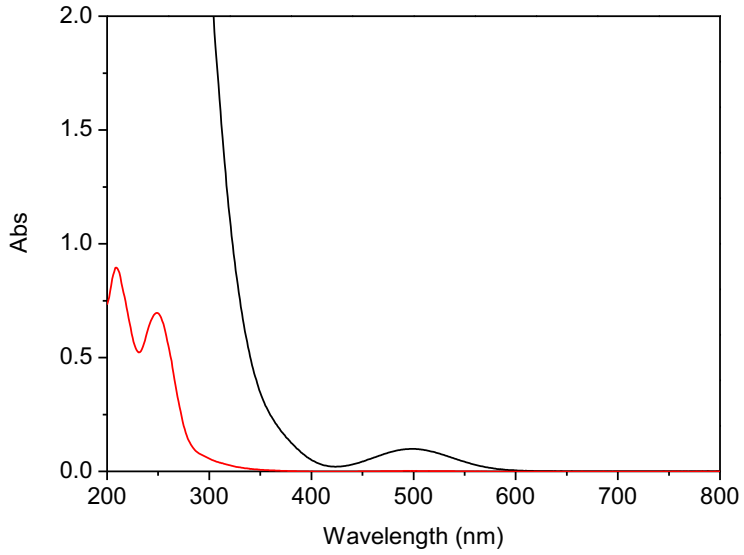


Fig.S29. UV-visible spectra of **3** in MeCN at 1.0×10^{-3} mol L^{-1} and 3.0×10^{-5} mol L^{-1}.

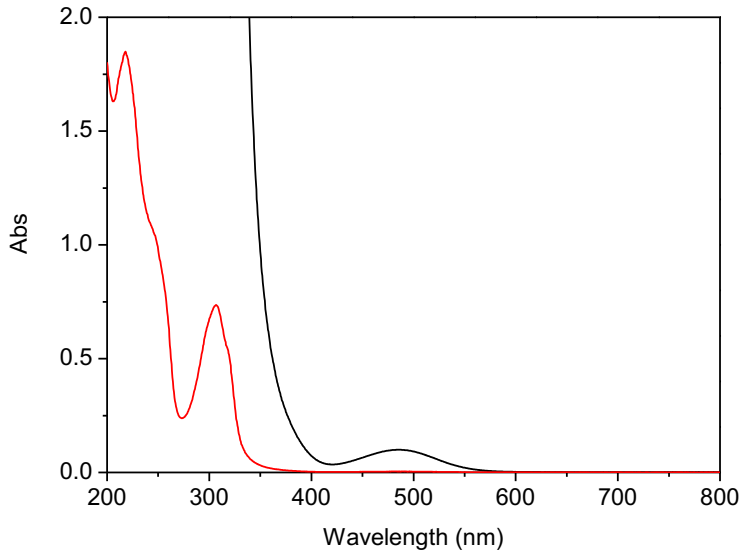


Fig. S30. UV-visible spectra of **4** in MeCN at 1.0×10^{-3} mol L^{-1} and 3.0×10^{-5} mol L^{-1}.

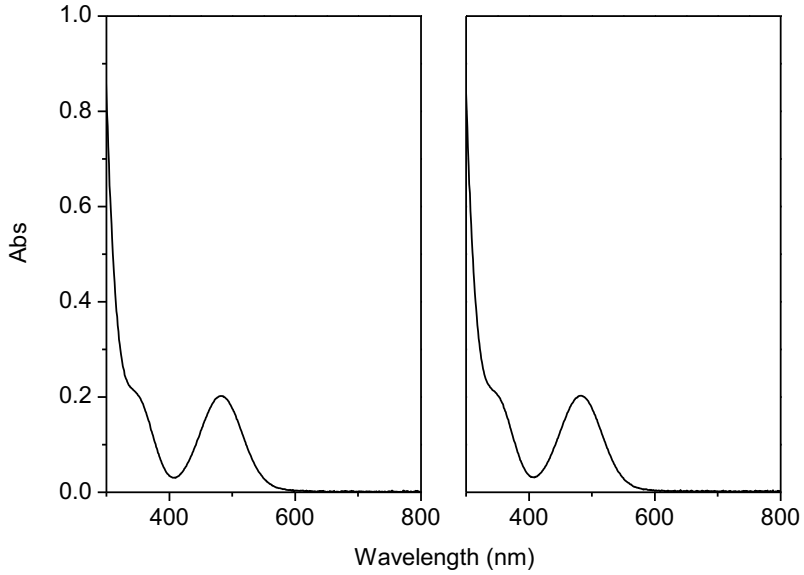


Fig. S31. UV-visible spectra of **1** in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right) at 1.0×10^{-3} mol L^{-1}.

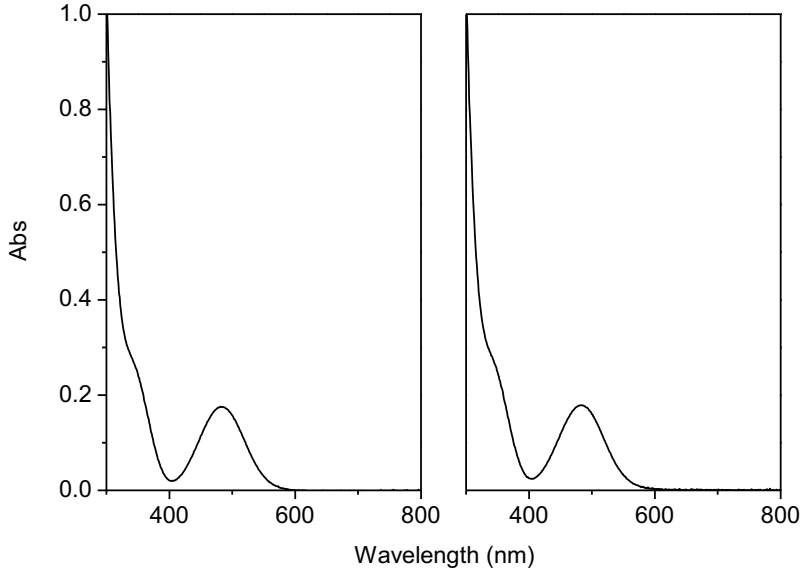


Fig. S32. UV-visible spectra of **2** in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right) at 1.0×10^{-3} mol L^{-1}.

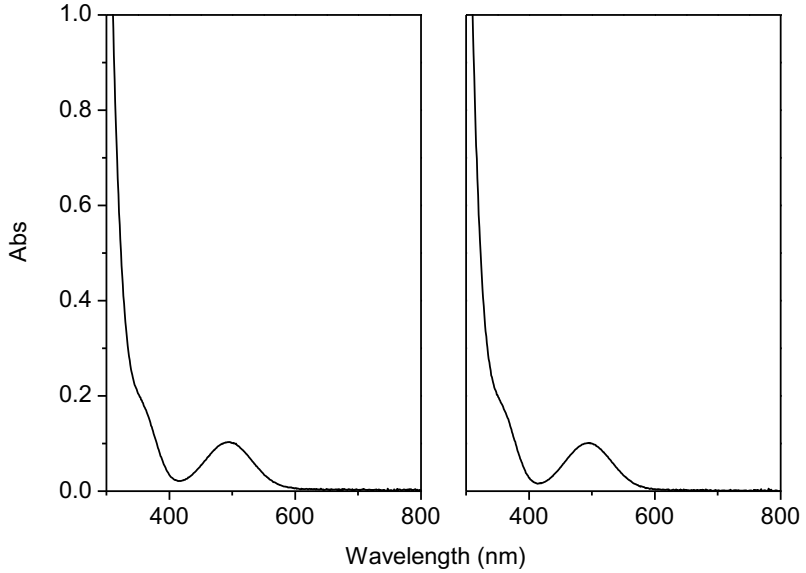


Fig. S33. UV-visible spectra of **3** in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right) at 1.0×10^{-3} mol L^{-1}.

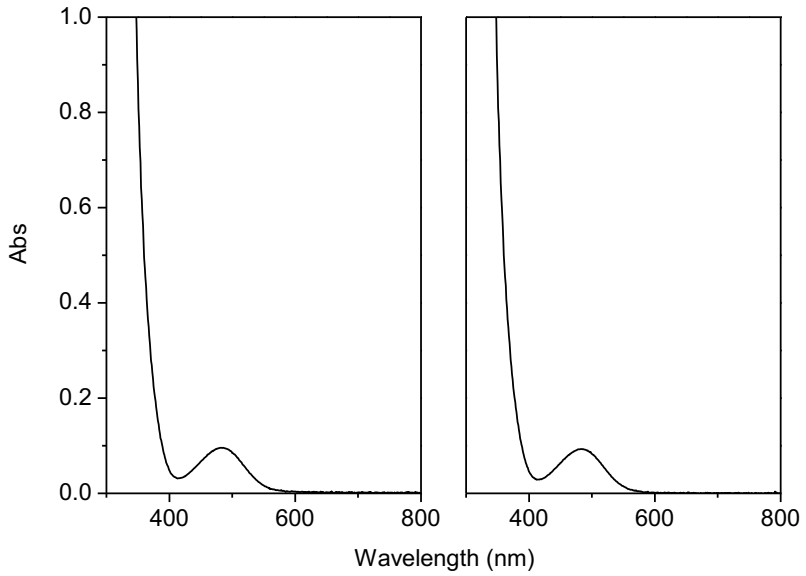


Fig. S34. UV-visible spectra of **4** in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right) at 1.0×10^{-3} mol L^{-1}.

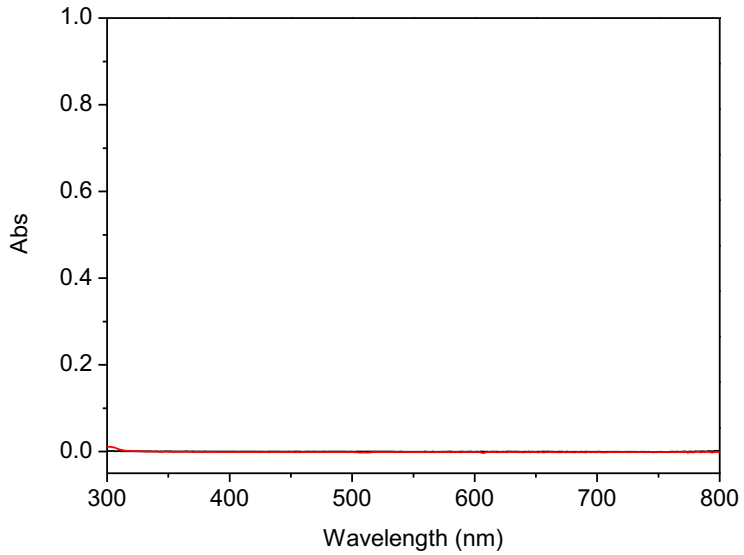


Fig. S35. UV-visible spectra of L-phenylalanine in pH 5.5 MES/DMSO (5%) **(black)** and pH 7.4 HEPES/DMSO (5%) **(red)** at 1.0×10^{-3} mol L^{-1}.

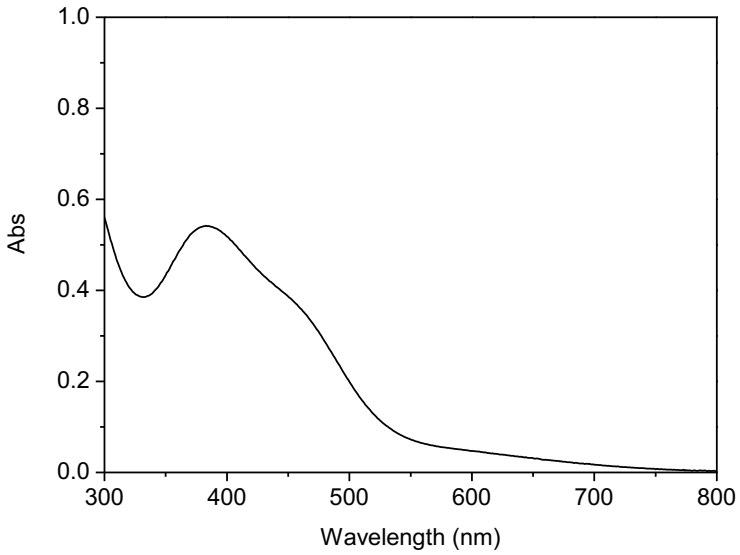


Fig. S36. UV-visible spectra of the complex in $[Co^{III}_2(\mu\text{-}OH)(\mu\text{-}O_2)(TPA)_2](ClO_4)_3$ in pH 7.4 HEPES/DMSO (5%) at 1.0×10^{-4} mol L^{-1}.

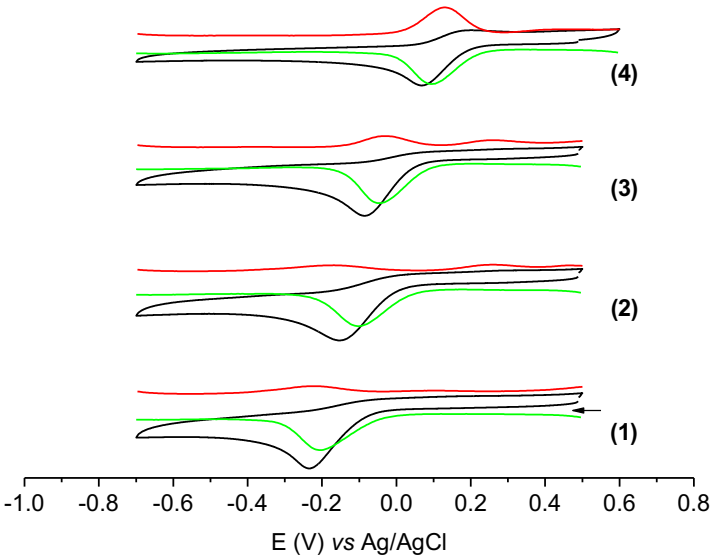


Fig. S37. Cyclic and square wave voltammograms of complexes **1**-**4** (1 x 10^{-4}mol L^{-1}) in MES buffer (pH 5.5), using a three electrode arrange (working: carbon; ref.: Ag/AgCl(NaCl 3 mol L^{-1}); aux.: Pt wire). CV: 0.1 V s^{-1}; SWV: pulse = 25 mV, step size = 4 mV and freq. = 15 Hz.

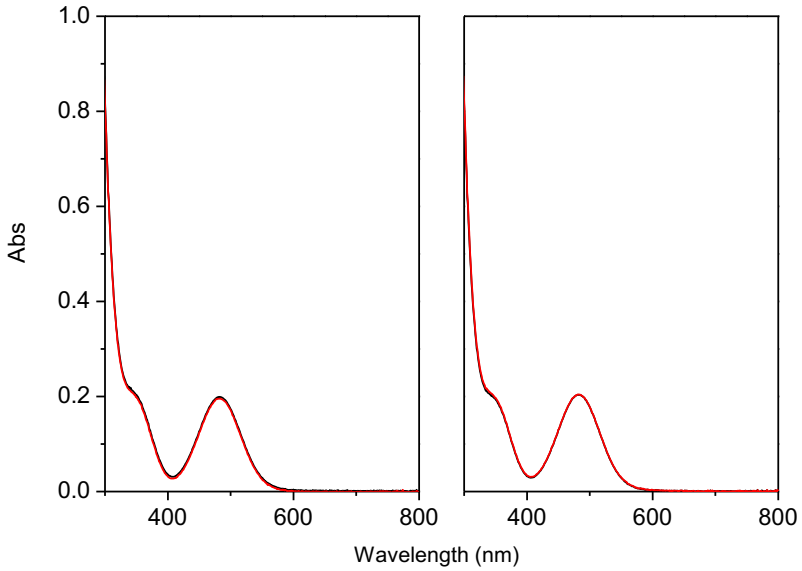


Fig. S38. UV–Visible spectra of complex **1** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES buffer/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right), from freshly prepared solution and after 24 h at 25°C.

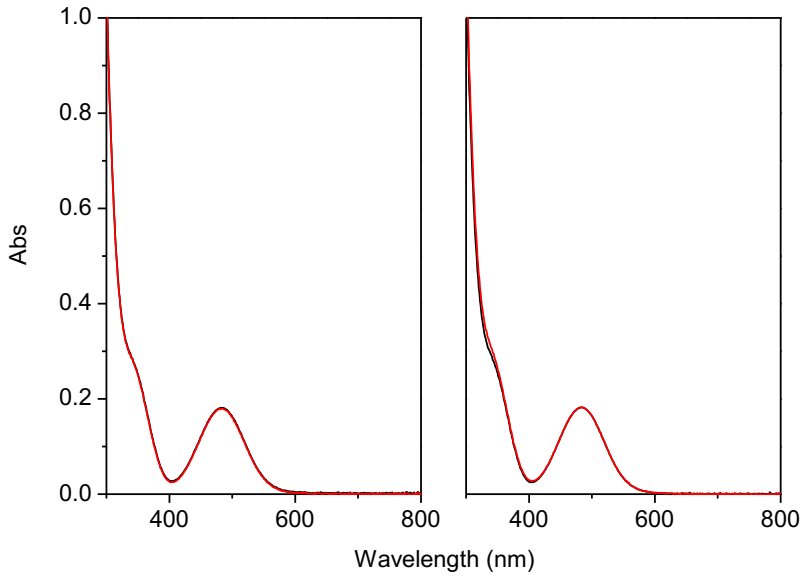


Fig. S39. UV–Visible spectra of complex **2** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right), from freshly prepared solution and after 24 h at 25°C.

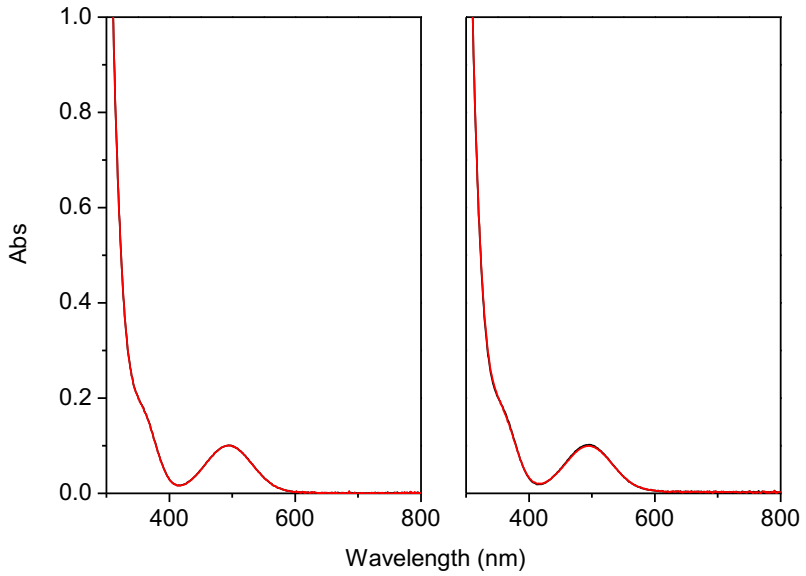


Fig. S40. UV–Visible spectra of complex **3** (1.0×10^{-3} mol L^{-1}) in MES buffer/DMSO (5%) pH 5.5 (left) and HEPES buffer/DMSO (5%) pH 7.4 (right), from freshly prepared solution and after 24 h at 25°C.

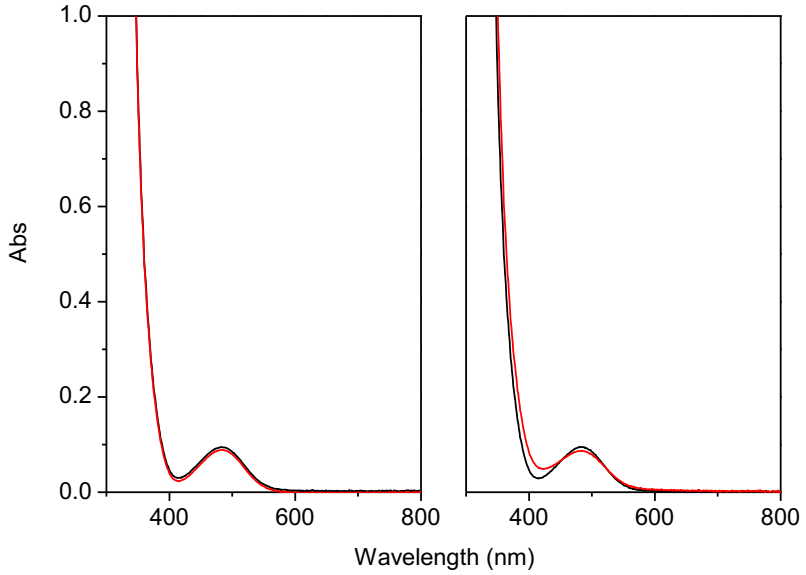


Fig. S41. UV–Visible spectra of complex **4** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right), from freshly prepared solution and after 24 h at 25°C.

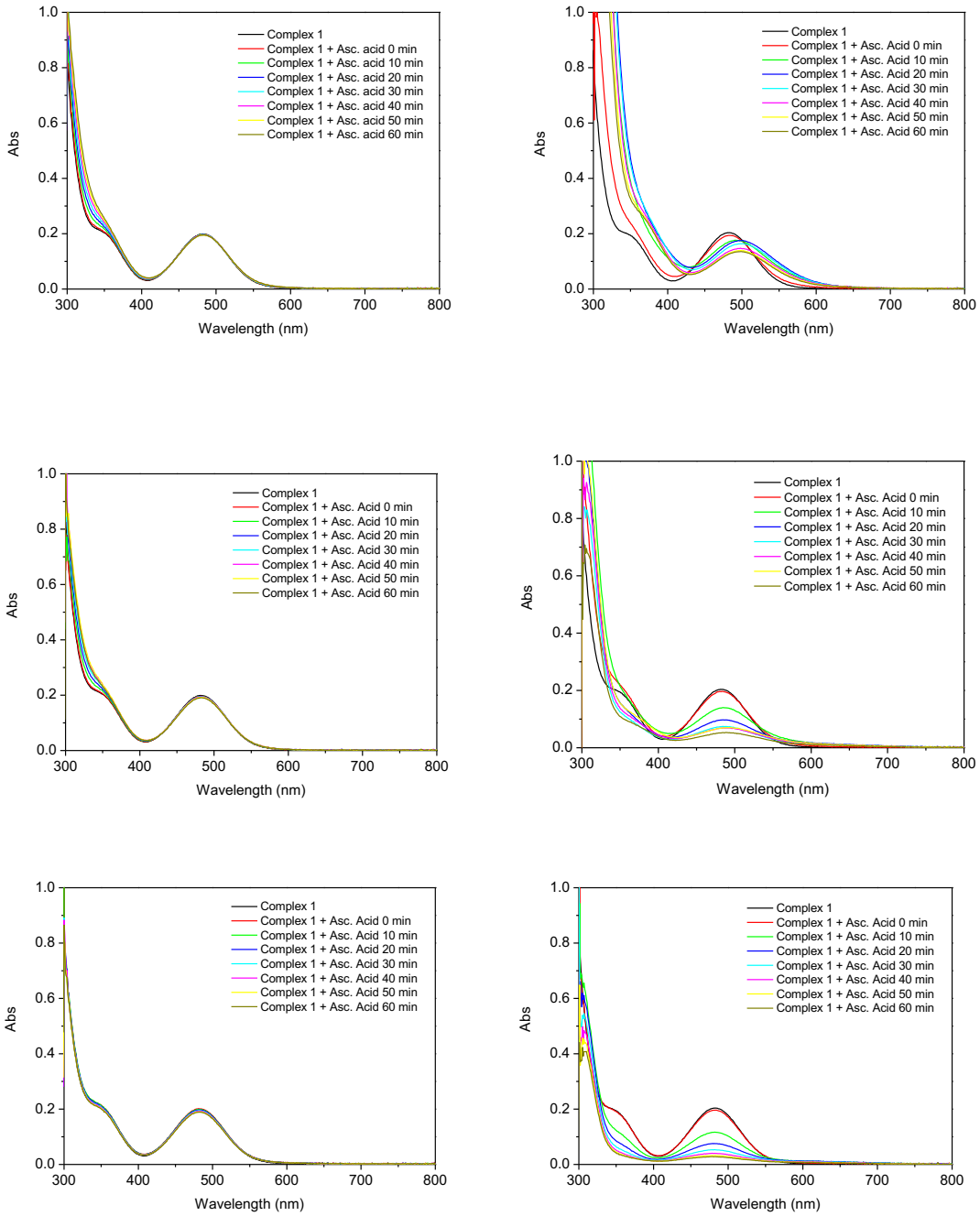


Fig. S42. UV-Visible spectra of complex **1** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right), before and after reaction with ascorbic acid (5:1), saturated with O_2 (top), air (middle) and argon (bottom), at 25°C during 1 hour.

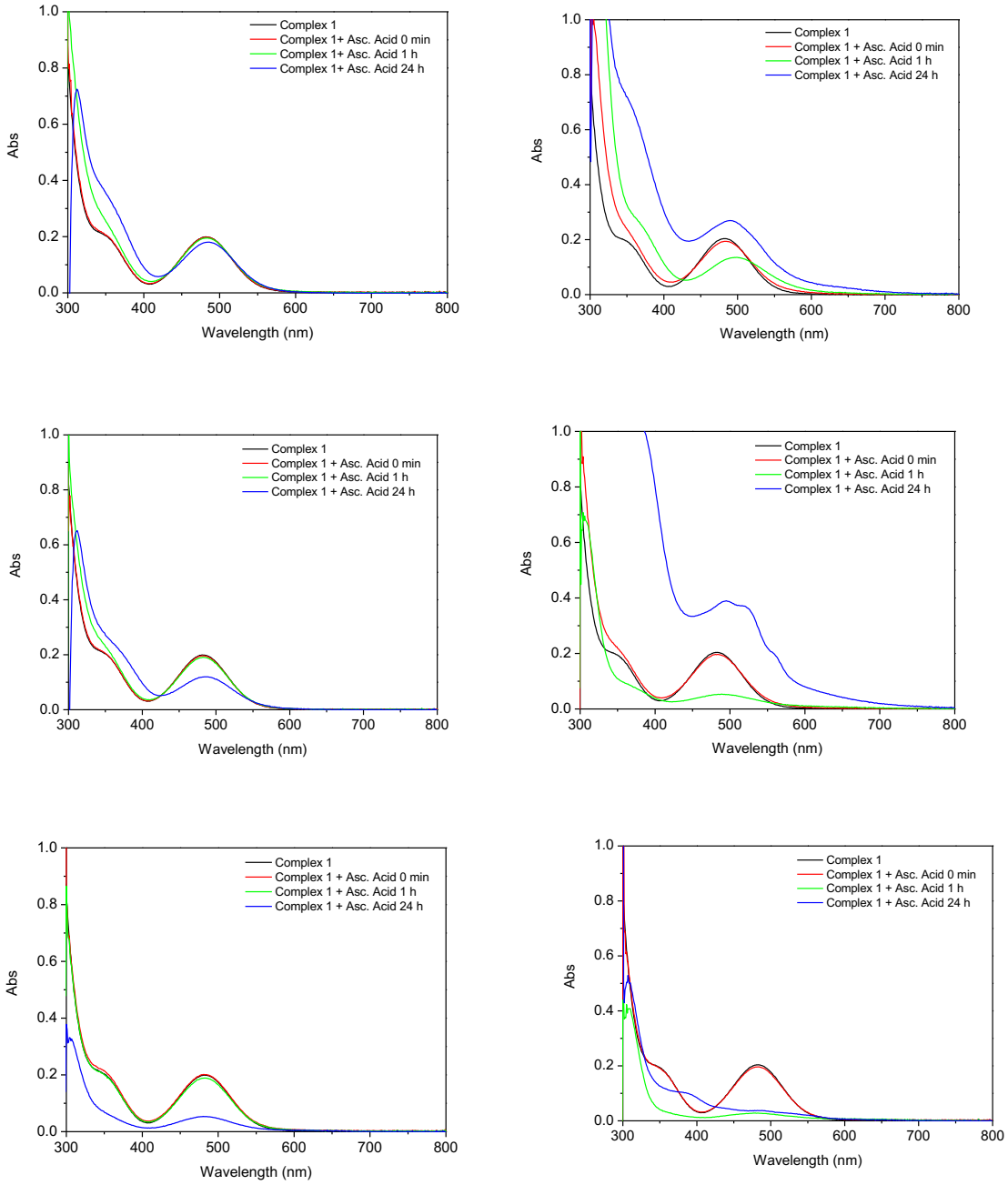


Fig. S43. UV-Visible spectra of complex **1** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right), before and after reaction with ascorbic acid (5:1), saturated with O_2 (top), air (middle) and argon (bottom), at 25°C during 24 hours.

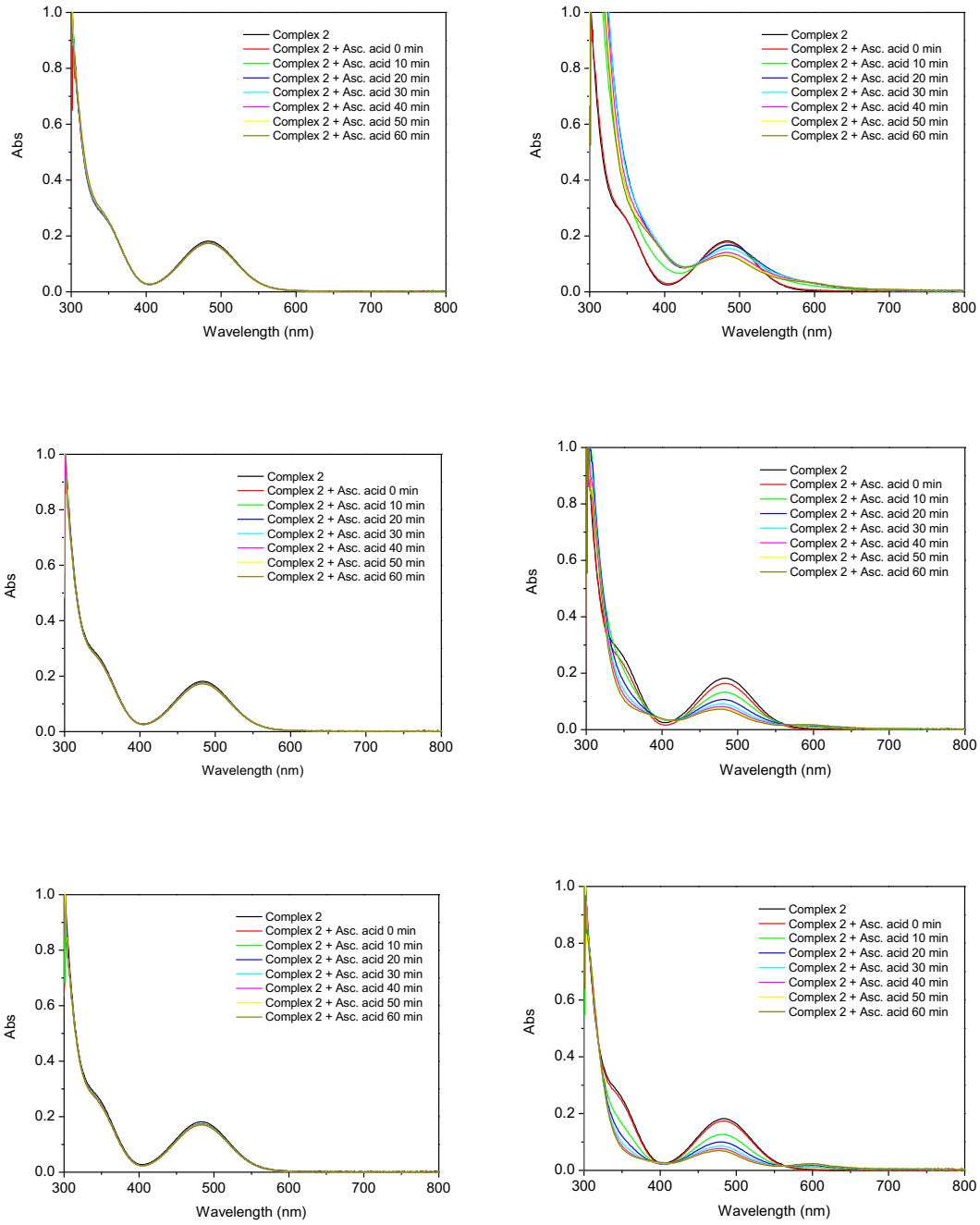


Fig. S44. UV-Visible spectra of complex **2** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right), before and after reaction with ascorbic acid (5:1), saturated with O_2 (top), air (middle) and argon (bottom), at 25°C during 1 hour.

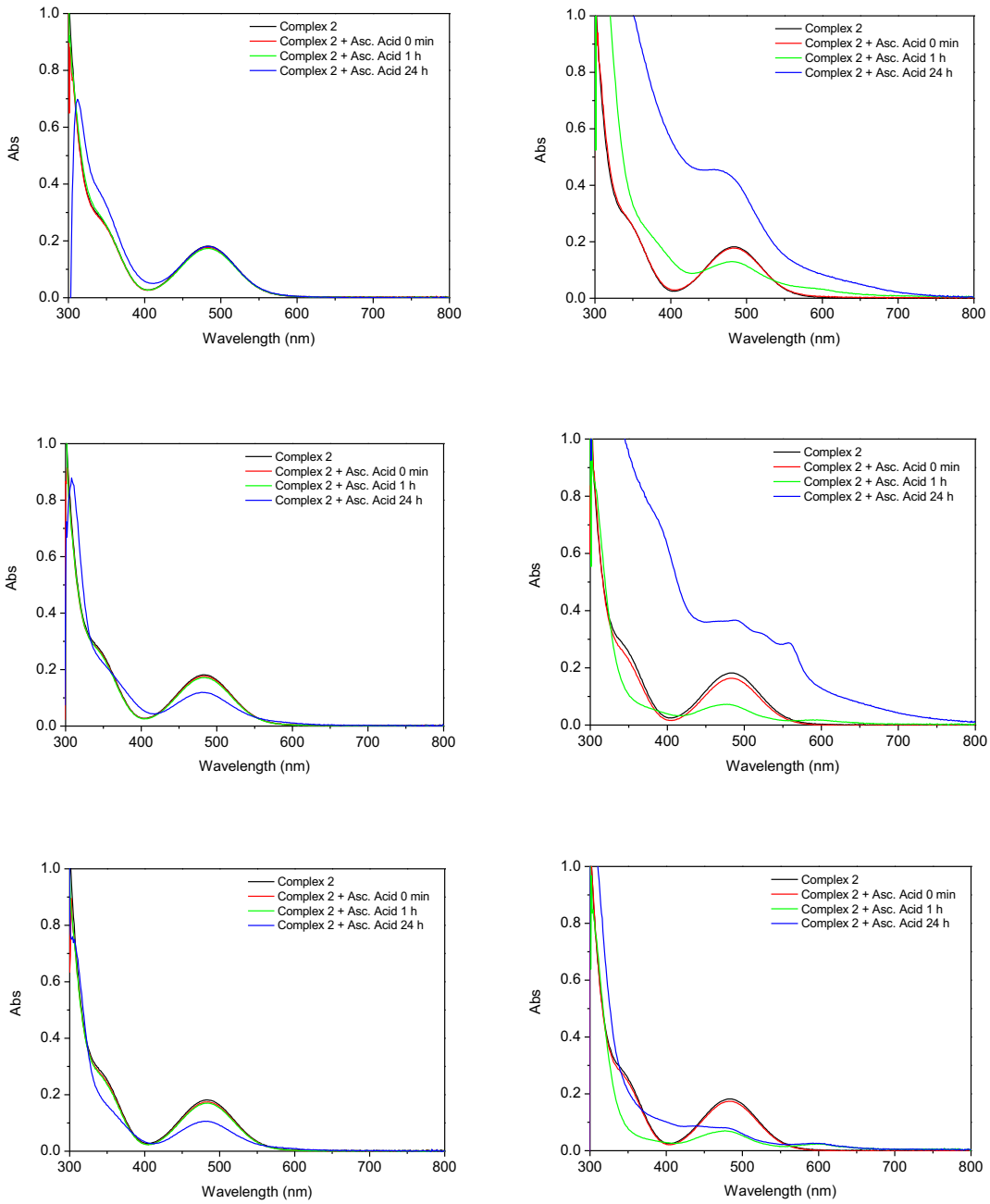


Fig. S45. UV-Visible spectra of complex **2** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES buffer/DMSO (5%) (right), before and after reaction with ascorbic acid (5:1), saturated with O_2 (top), air (middle) and argon (bottom), at 25°C during 24 hours.

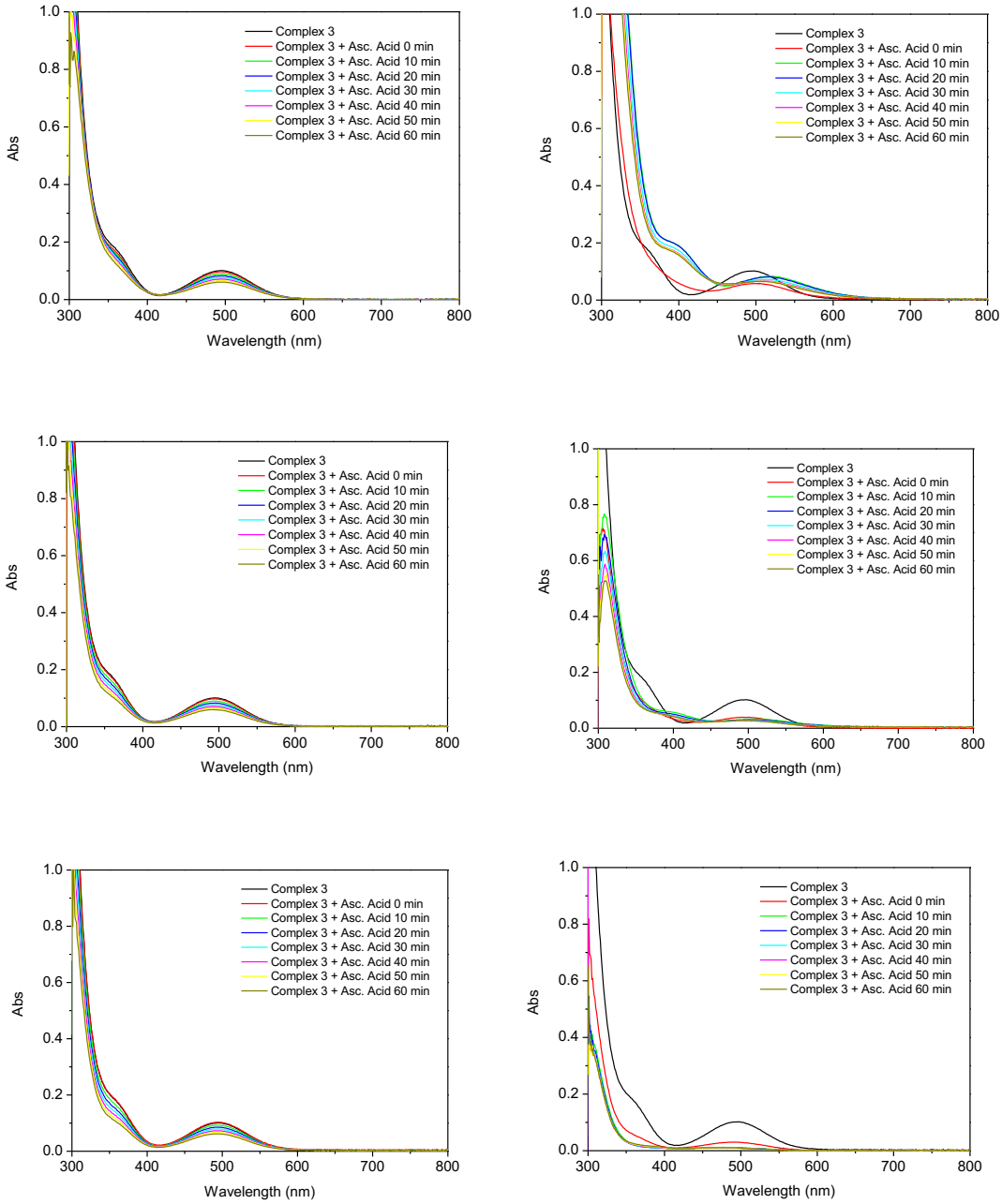


Fig. S46. UV-Visible spectra of complex **3** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right), before and after reaction with ascorbic acid (5:1), saturated with O_2 (top), air (middle) and argon (bottom), at 25°C during 1 hour.

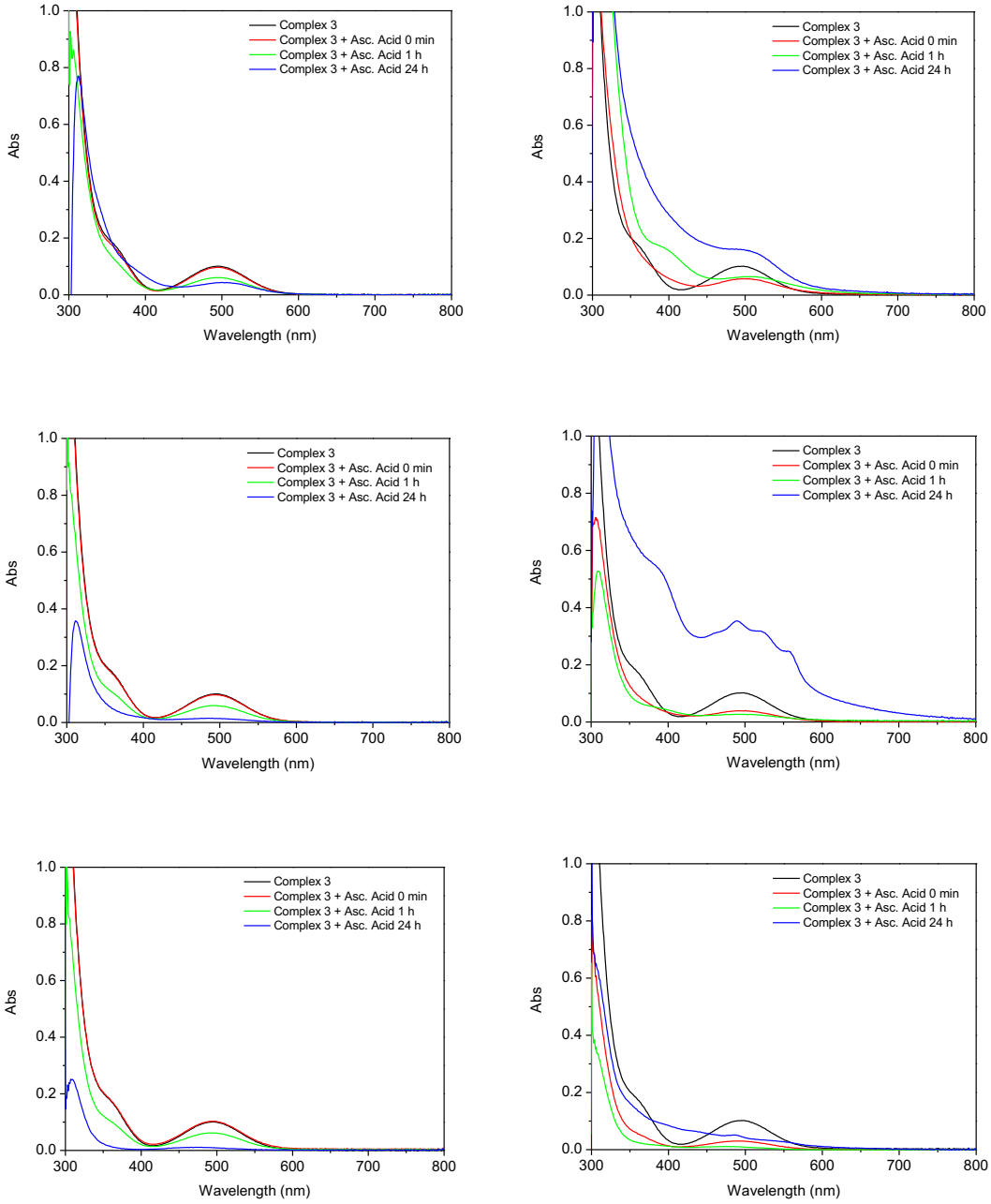


Fig. S47. UV-Visible spectra of complex **3** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right), before and after reaction with ascorbic acid (5:1), saturated with O_2 (top), air (middle) and argon (bottom), at 25°C during 24 hours.

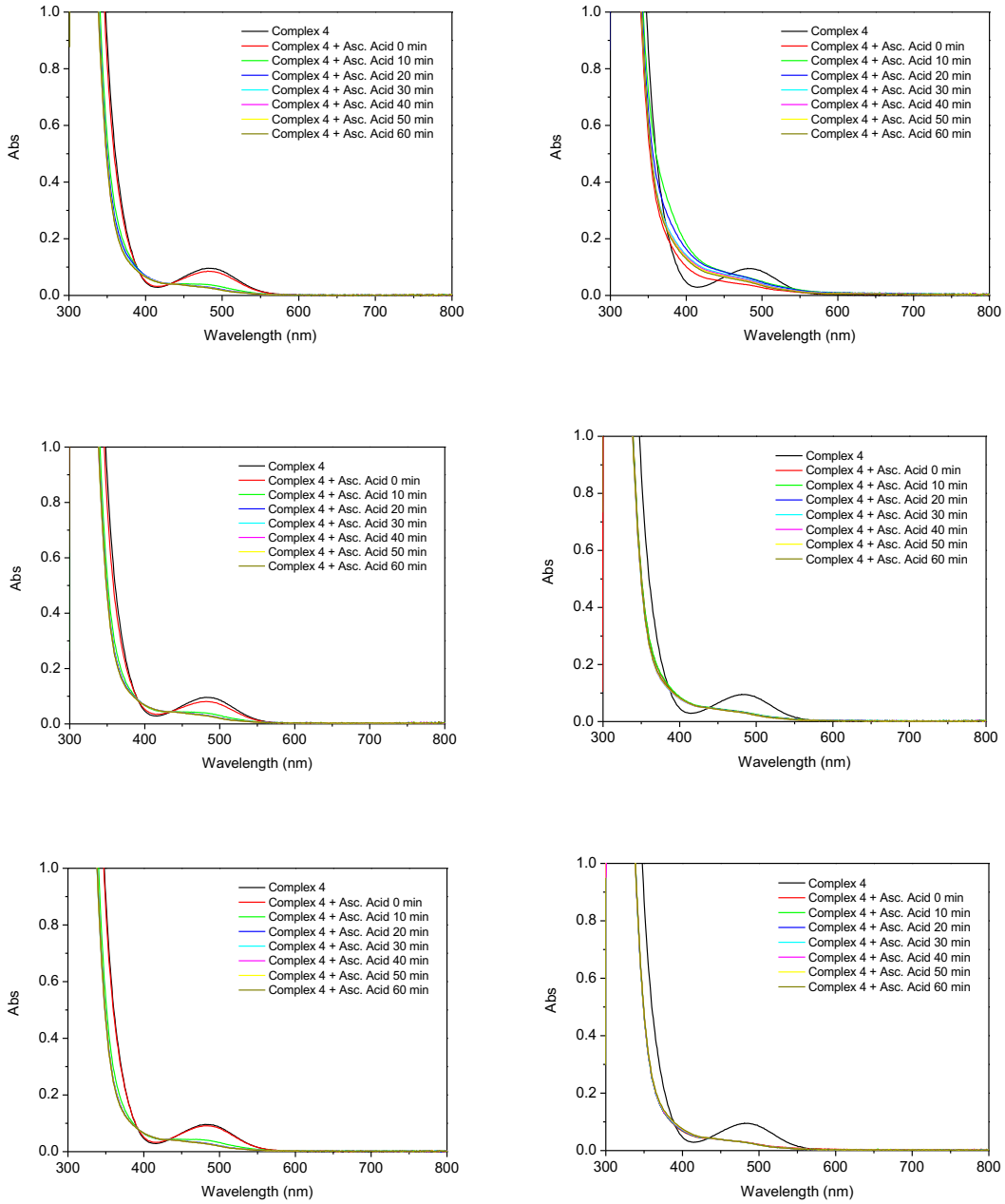


Fig. S48. UV-Visible spectra of complex **4** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right), before and after reaction with ascorbic acid (5:1), saturated with O_2 (top), air (middle) and argon (bottom) at 25°C during 1 hour.

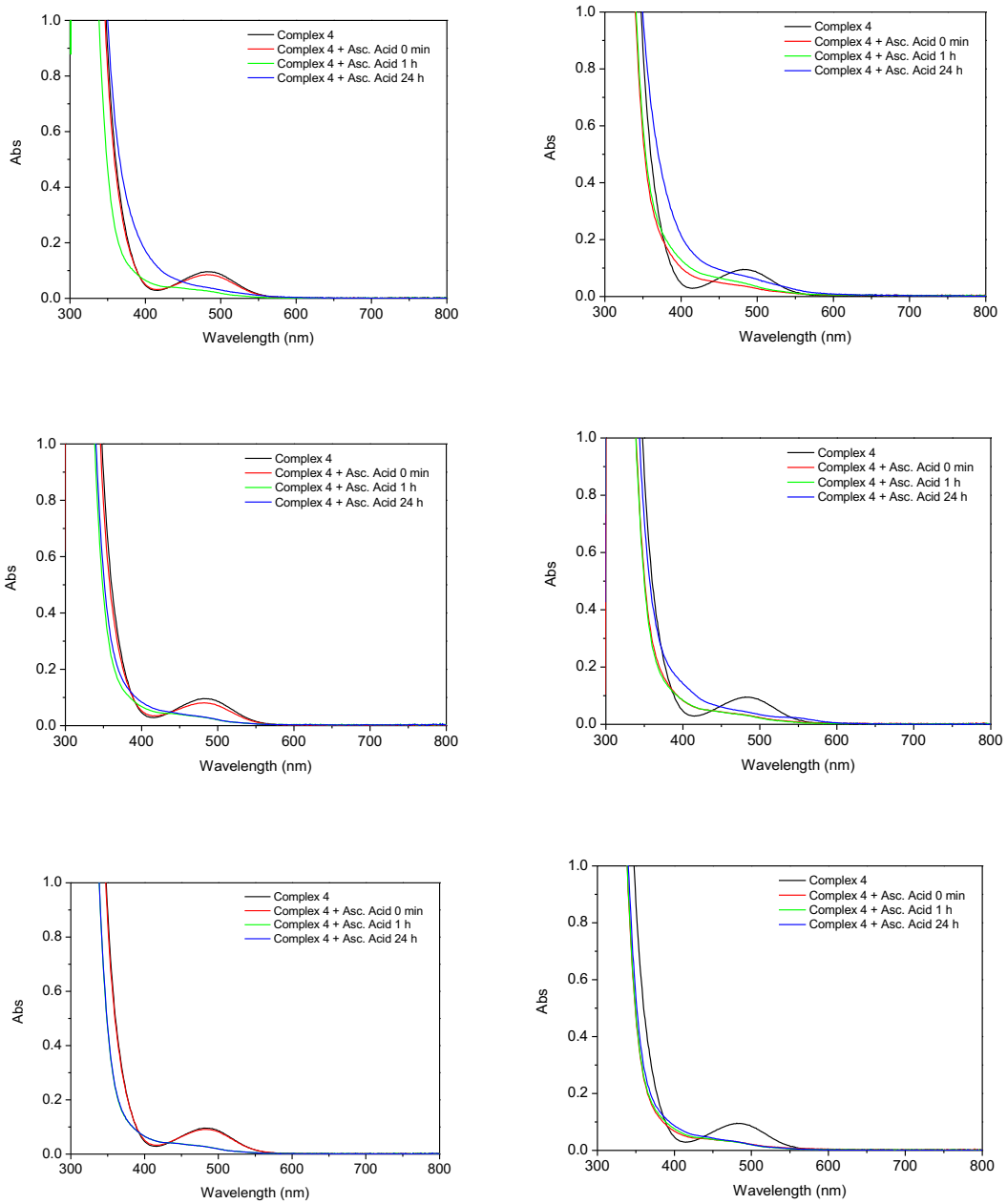


Fig. S49. UV-Visible spectra of complex **4** (1.0×10^{-3} mol L^{-1}) in pH 5.5 MES/DMSO (5%) (left) and pH 7.4 HEPES/DMSO (5%) (right), before and after reaction with ascorbic acid (5:1), saturated with O_2 (top), air (middle) and argon (bottom) at 25°C during 24 hours.

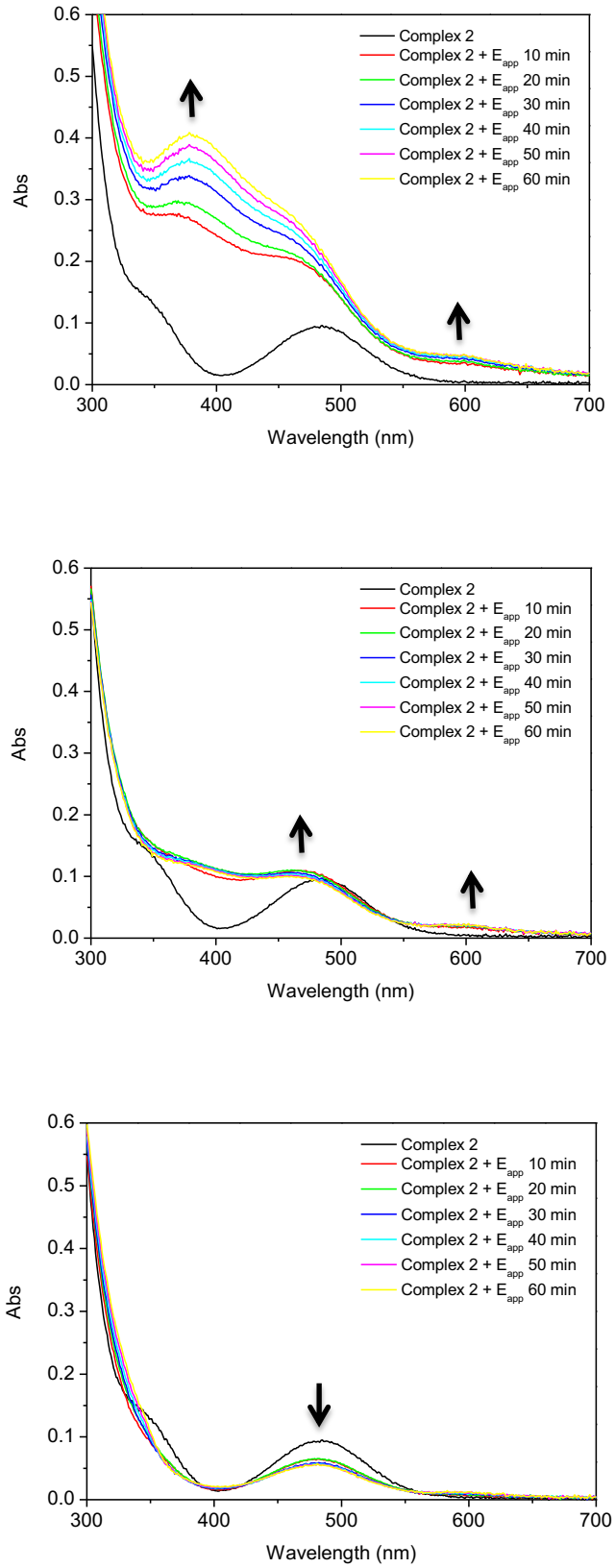


Fig. S50. Spectral changes for complex **2** (5.0×10^{-3} mol L^{-1}) during electrochemical reduction at E_{cpe} = -325 mV vs Ag/AgCl in pH 7.4 HEPES/DMSO (10 %), saturated with O_2 (top), air (middle) and argon (bottom) at 25°C during 1 hour.

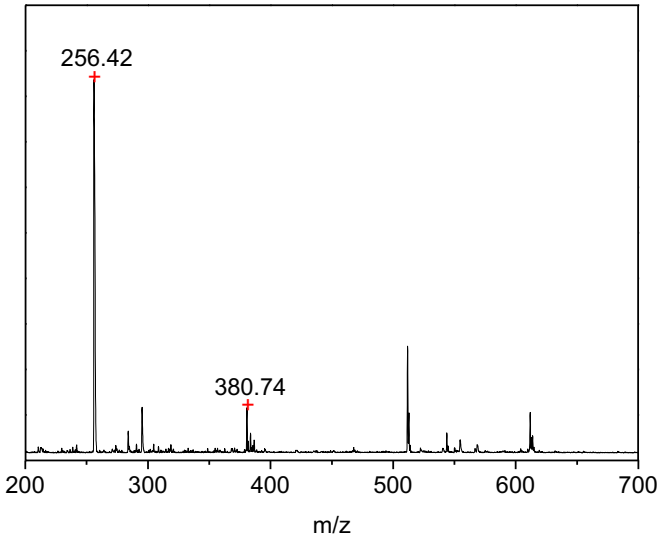


Fig. S51. ESI-MS (m/z^{2+}) in water of complex **2**.

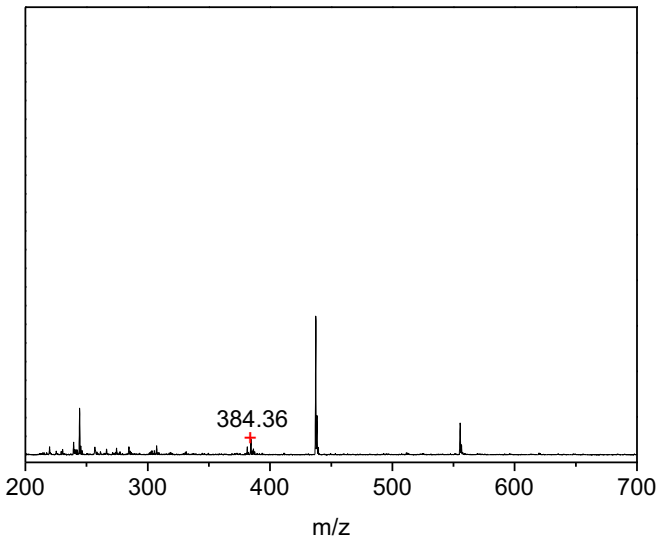


Fig. S52. ESI-MS (m/z^{2+}) in water for reaction of complex **2** after with ascorbic acid (1:5), under air, after 24 h.