Electronic Supplementary Information

Benzimidazole based Pt(II) complexes with better normal cell viability than *cis*platin: Synthesis, substitution behavior, cytotoxicity, DNA binding and DFT study

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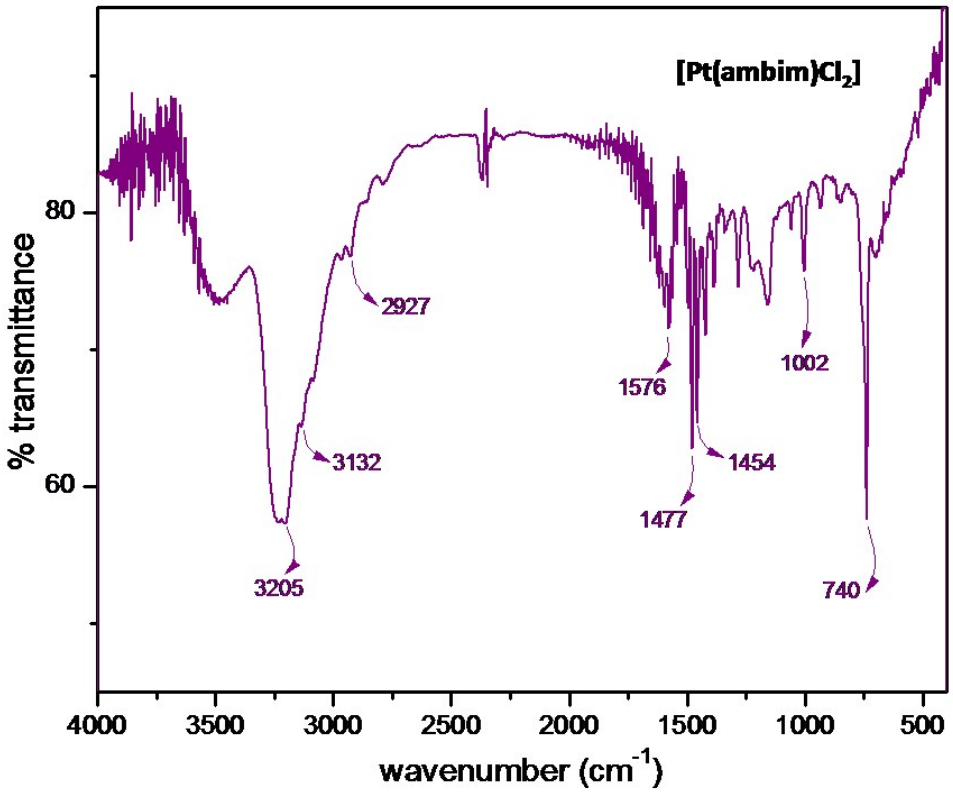
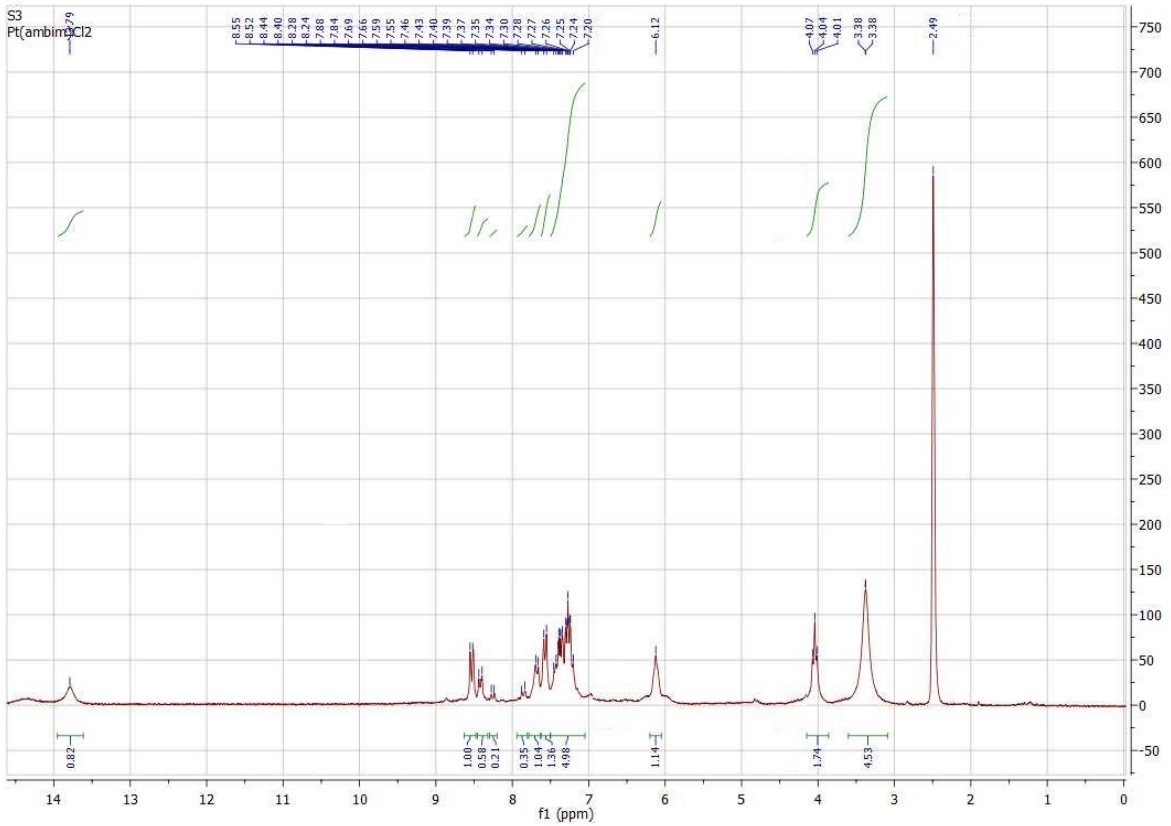
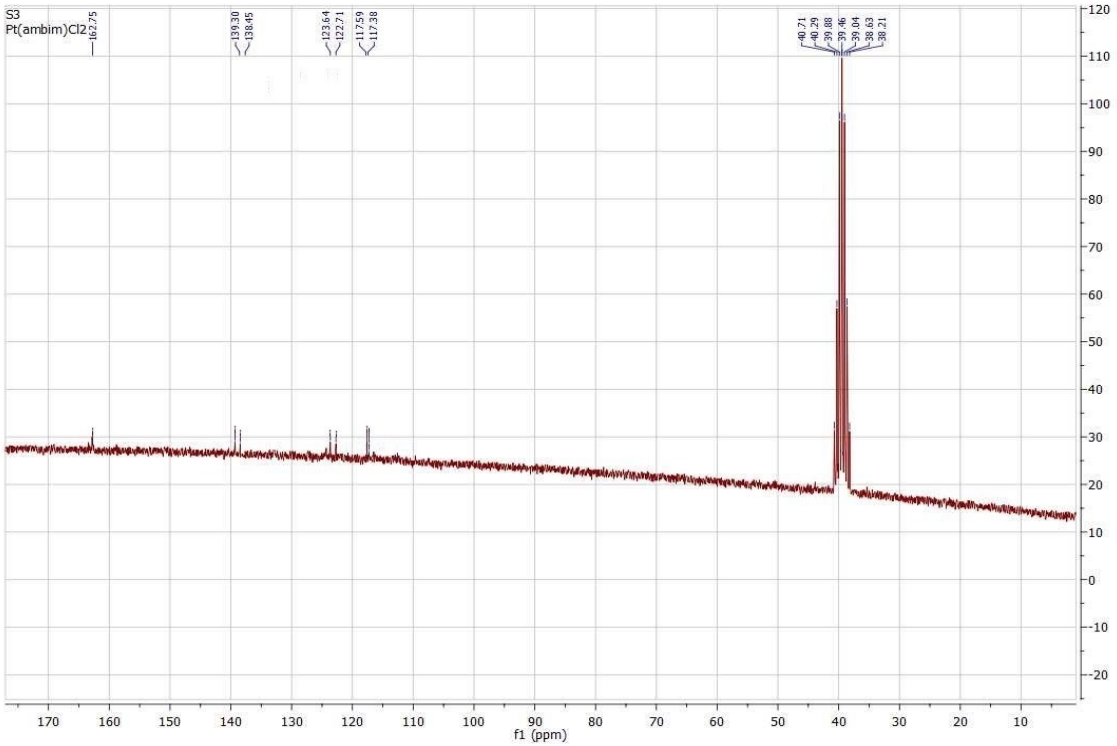


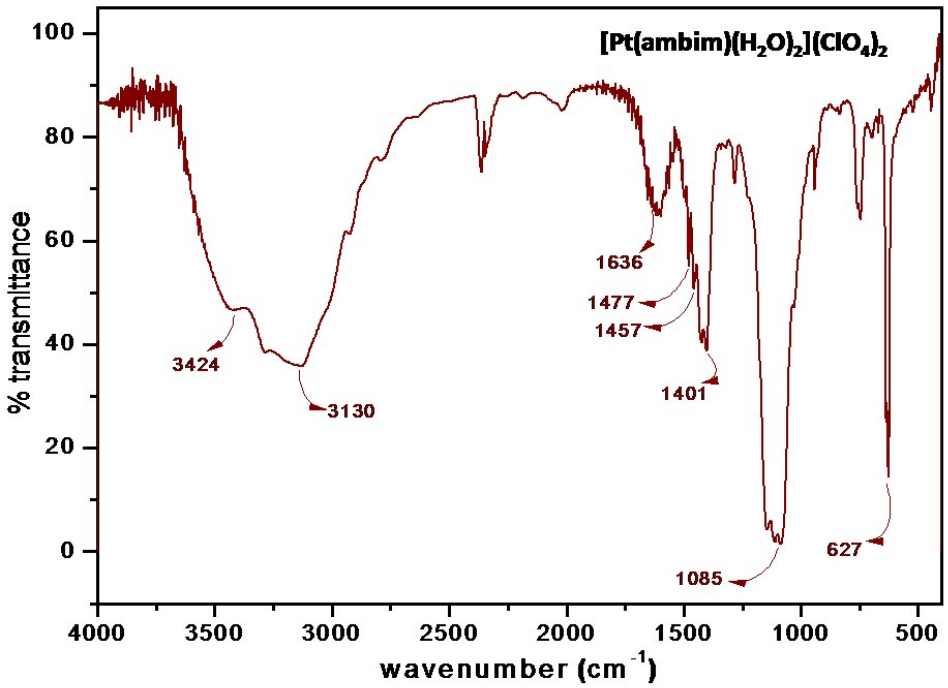
ESI Fig. S1 IR spectra of complex **1**



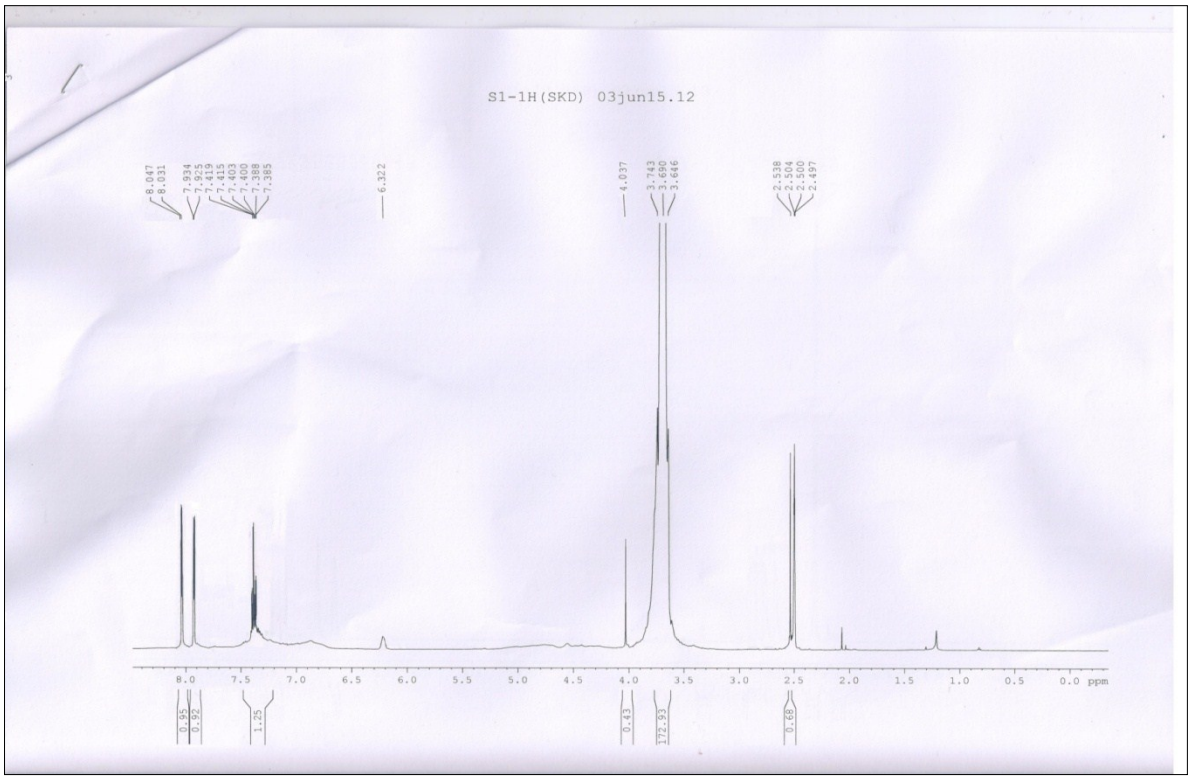
ESI Fig. S2 ^{1}H NMR spectra of complex **1** in DMSO-D_6 as solvent



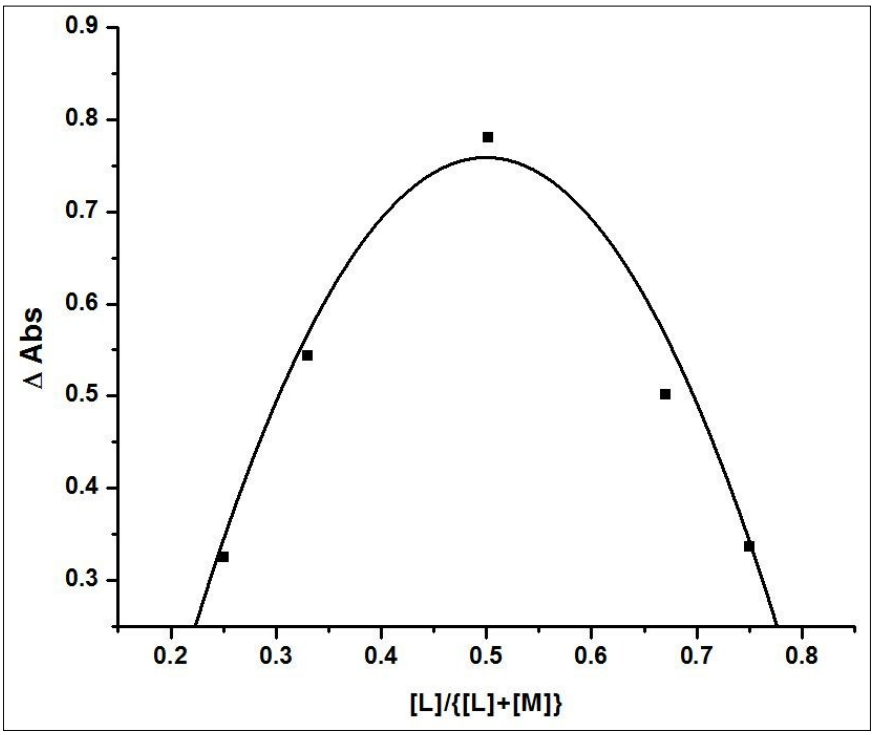
ESI Fig. S3 ^{13}C NMR spectra of complex **1** in DMSO-D_6



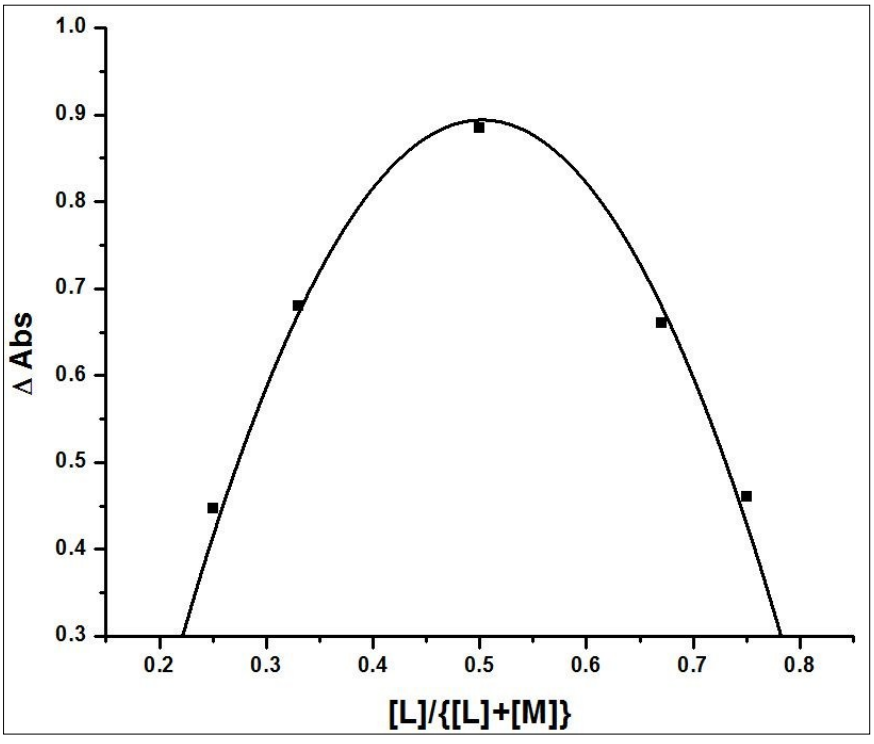
ESI Fig. S4 IR spectra of complex **2**



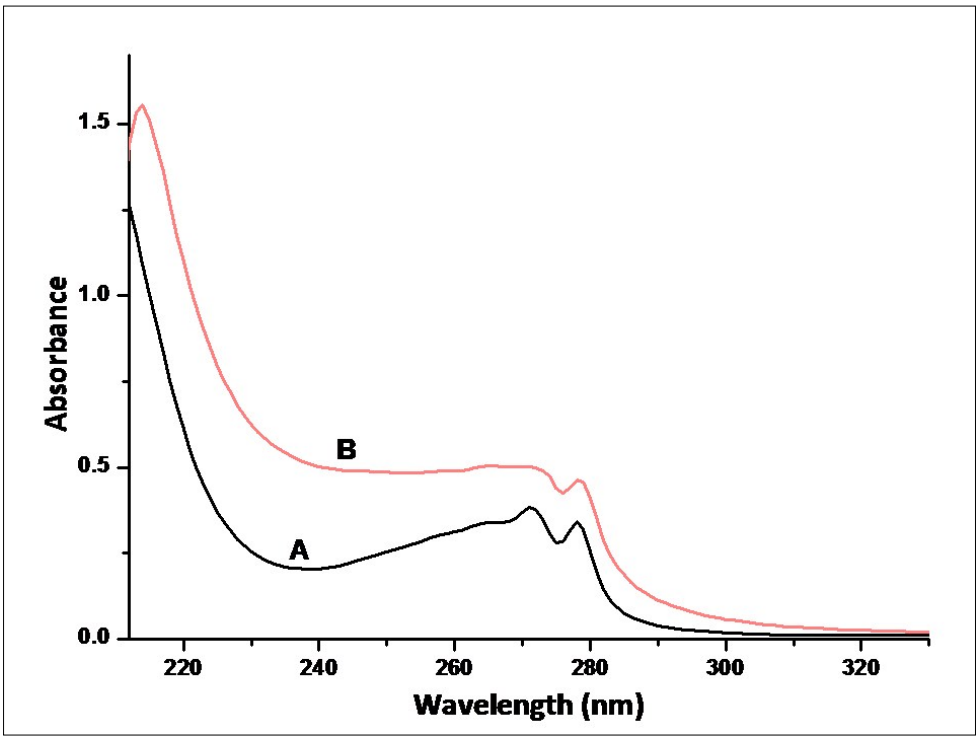
ESI Fig. S5 ^{1}H NMR spectra of complex **2** in DMSO-D_6 as solvent



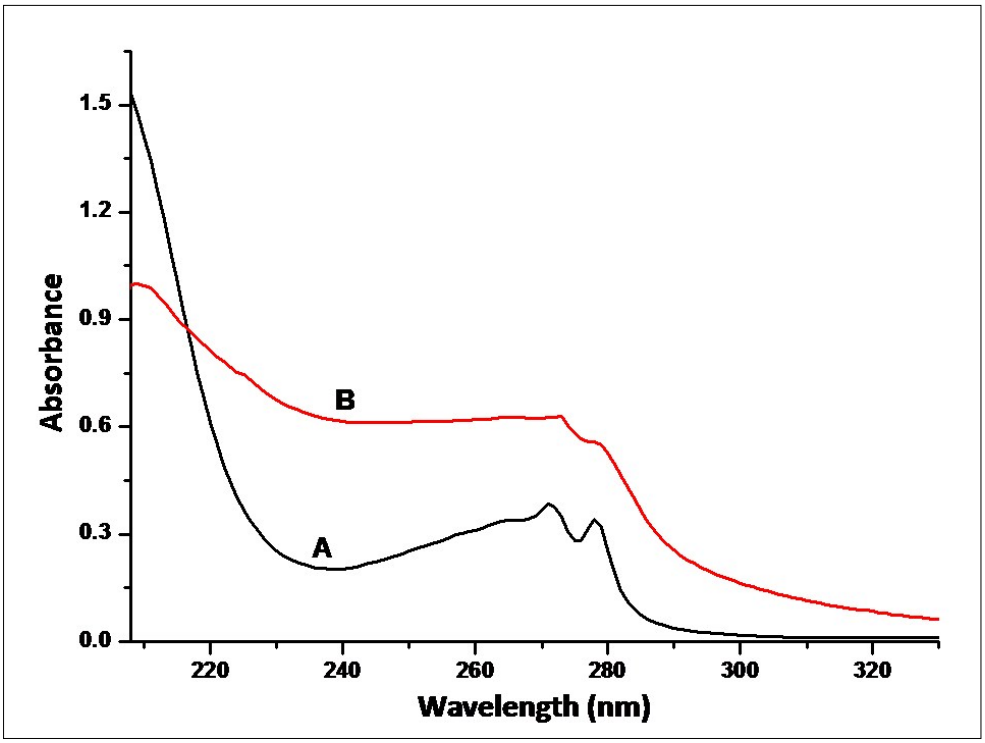
ESI Fig. S6 Job's plot for the formation of complex **3**



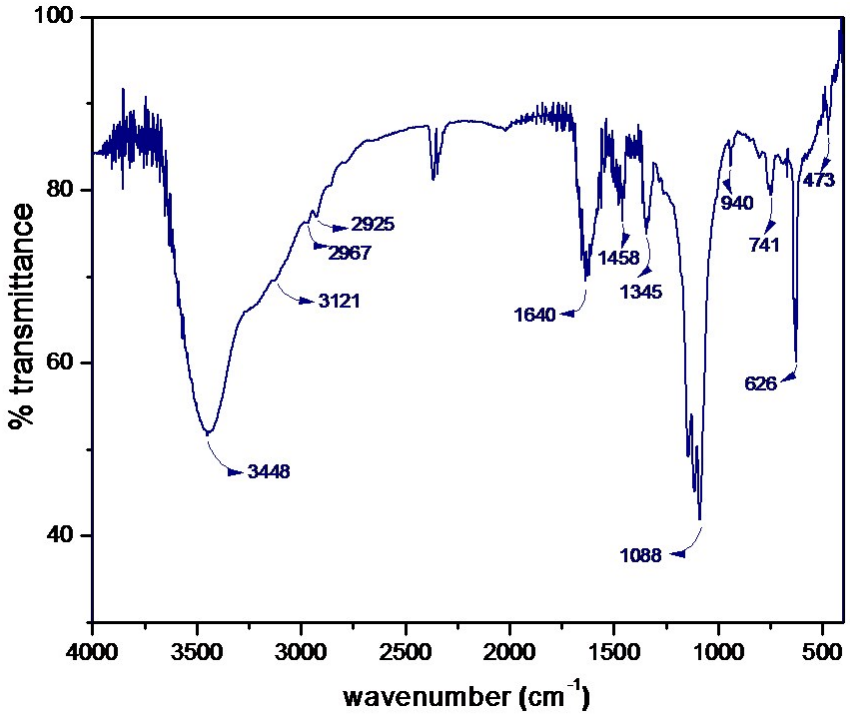
ESI Fig. S7 Job's plot for the formation of complex **4**



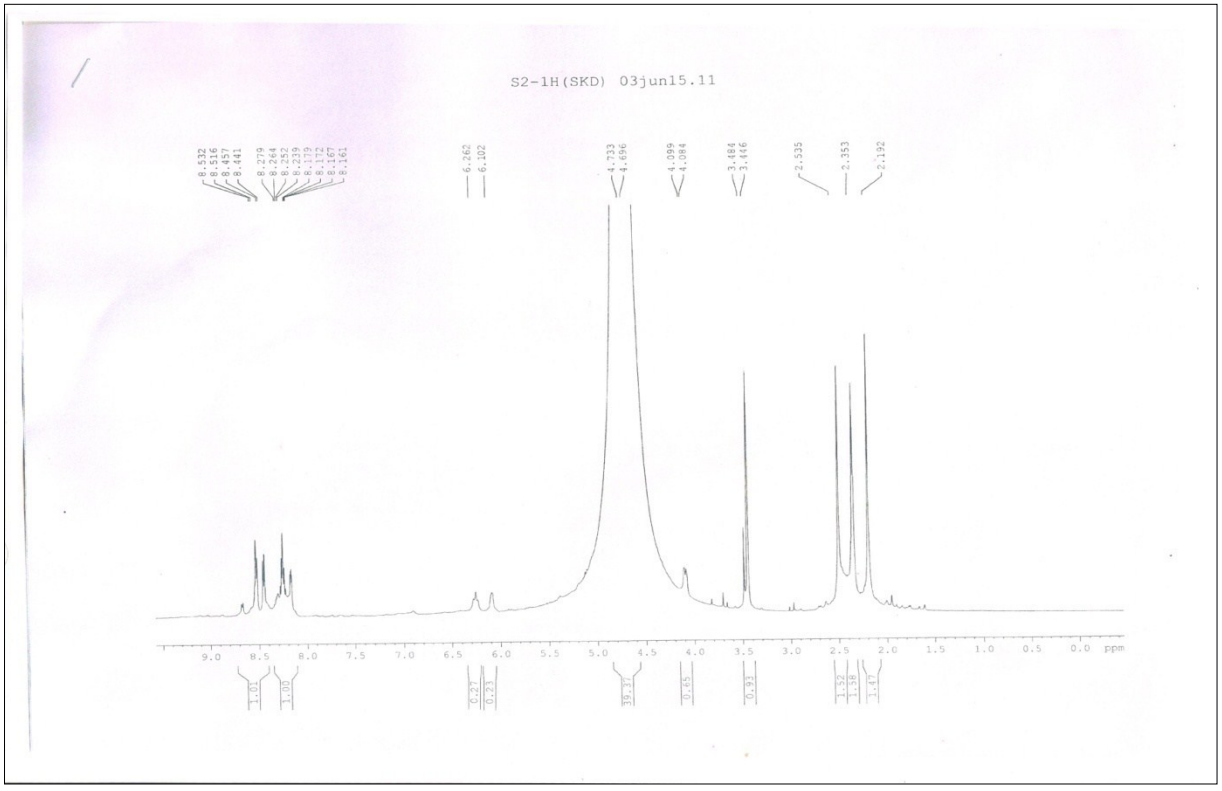
ESI Fig. S8 Spectral difference between the reactant and product - **A**: $[Pt(ambim)(H_2O)_2]^{2+}$ = 1.50×10^{-4} mol.dm^{-3}, **B**: $[Pt(ambim)(H_2O)_2]^{2+}$ = 1.50 × 10^{-4} mol.dm^{-3}, [DL-penicillamine] = 1.50 × 10^{-3} mol.dm^{-3}, pH = 4.0



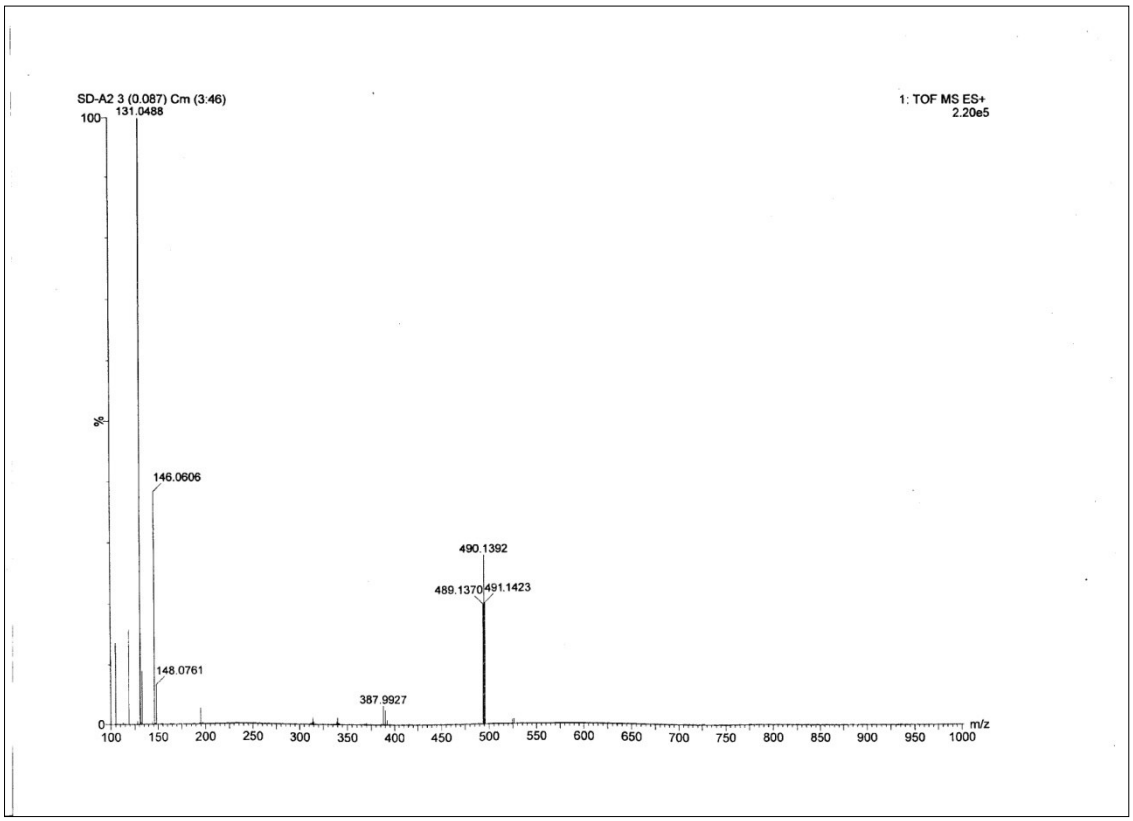
ESI Fig. S9 Spectral difference between the reactant and product - **A**: $[Pt(ambim)(H_2O)_2]^{2+}$ = 1.50×10^{-4} mol.dm^{-3}, **B**: $[Pt(ambim)(H_2O)_2]^{2+}$ = 1.50 × 10^{-4} mol.dm^{-3}, [Glutathione] = 1.50 × 10^{-3} mol.dm^{-3}, pH = 4.0



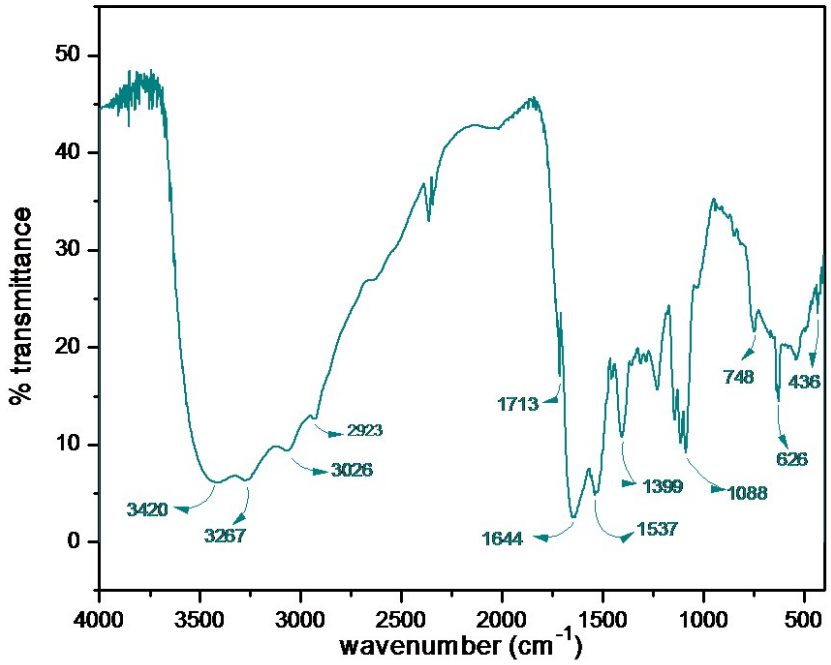
ESI Fig. S10 IR spectra of complex **3**



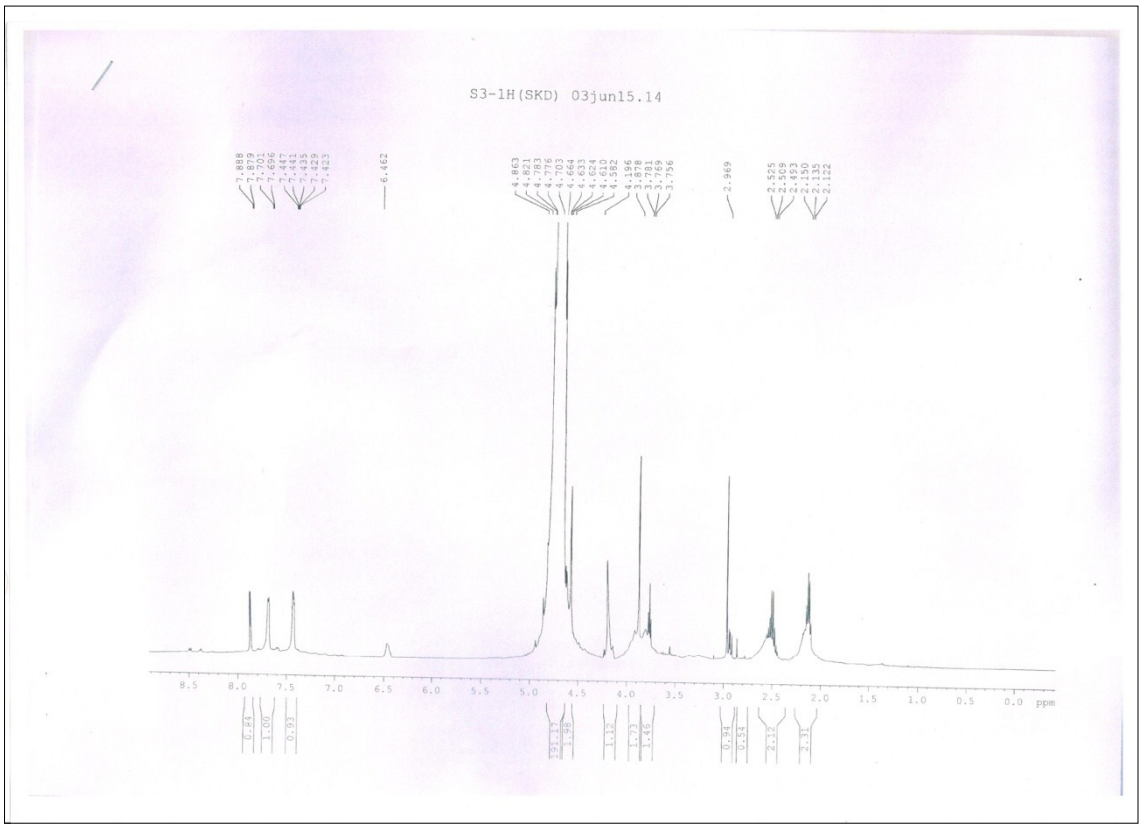
ESI Fig. S11 ^{1}H NMR spectra of complex **3** in DMSO-D_6 as solvent



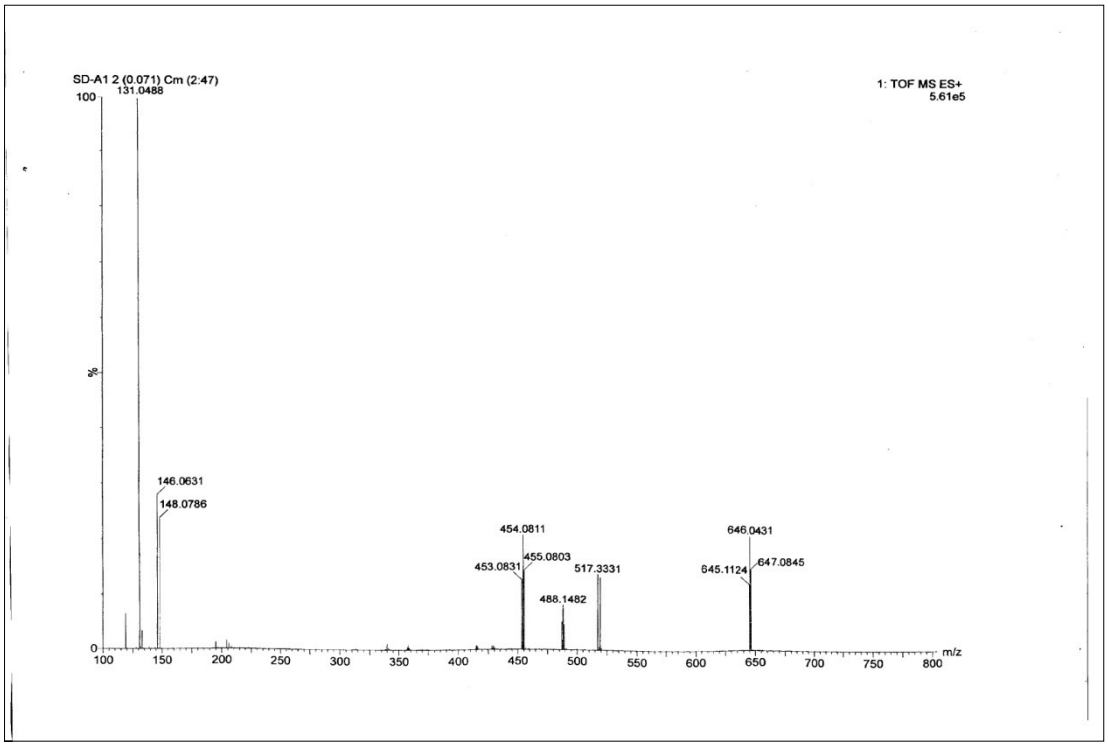
ESI Fig. S12 ESI Mass spectra of complex **3** in water



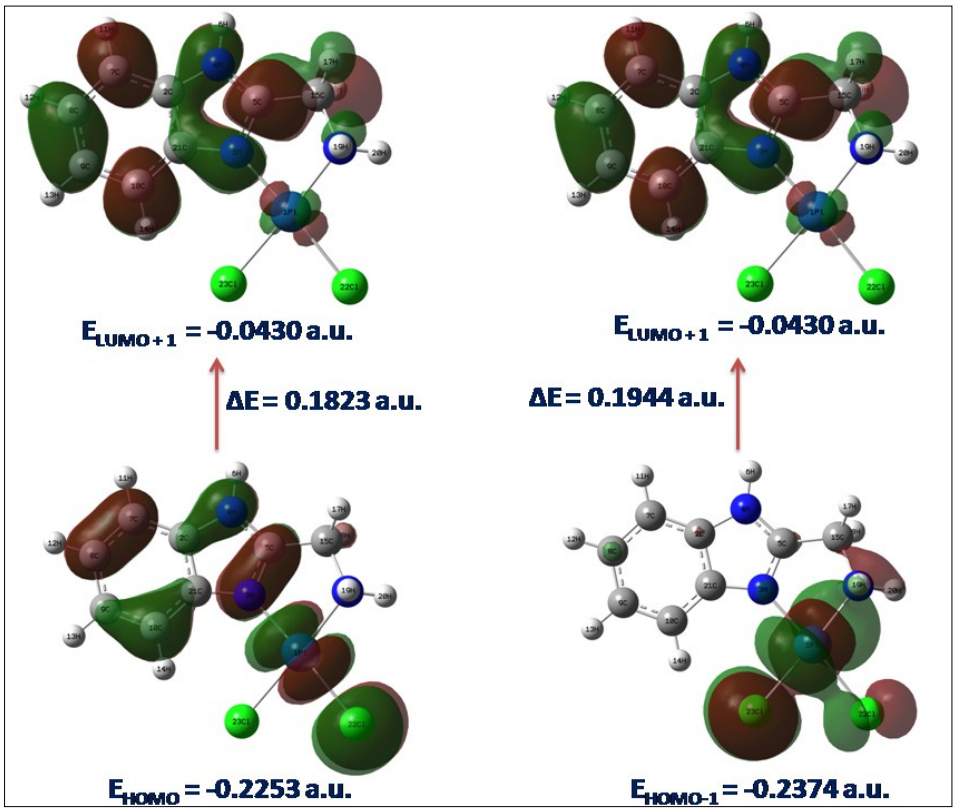
ESI Fig. S13 IR spectra of complex **4**



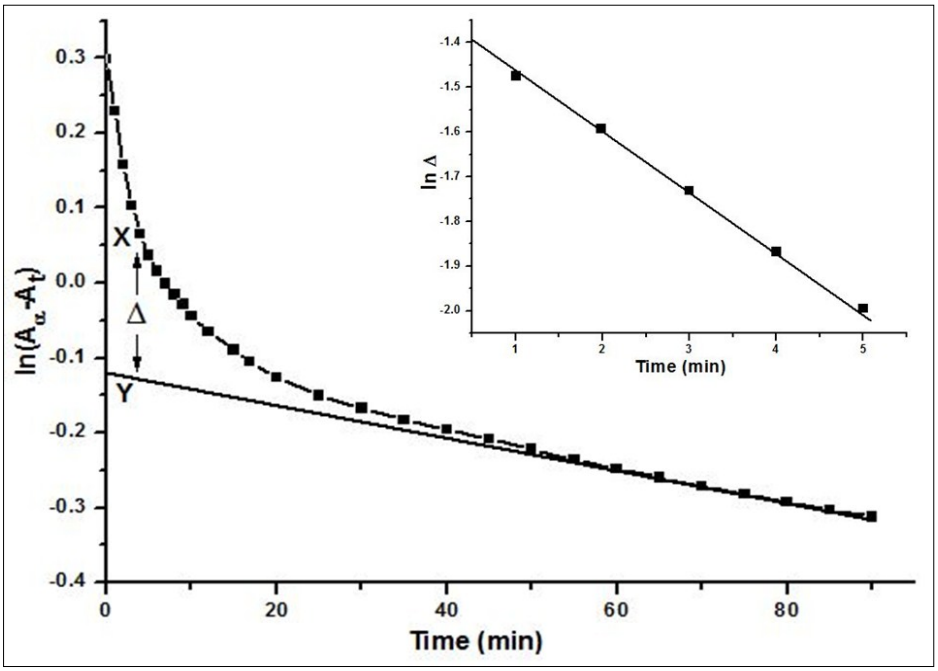
ESI Fig. S14 ^{1}H NMR spectra of complex **4** in DMSO-D_6 as solvent



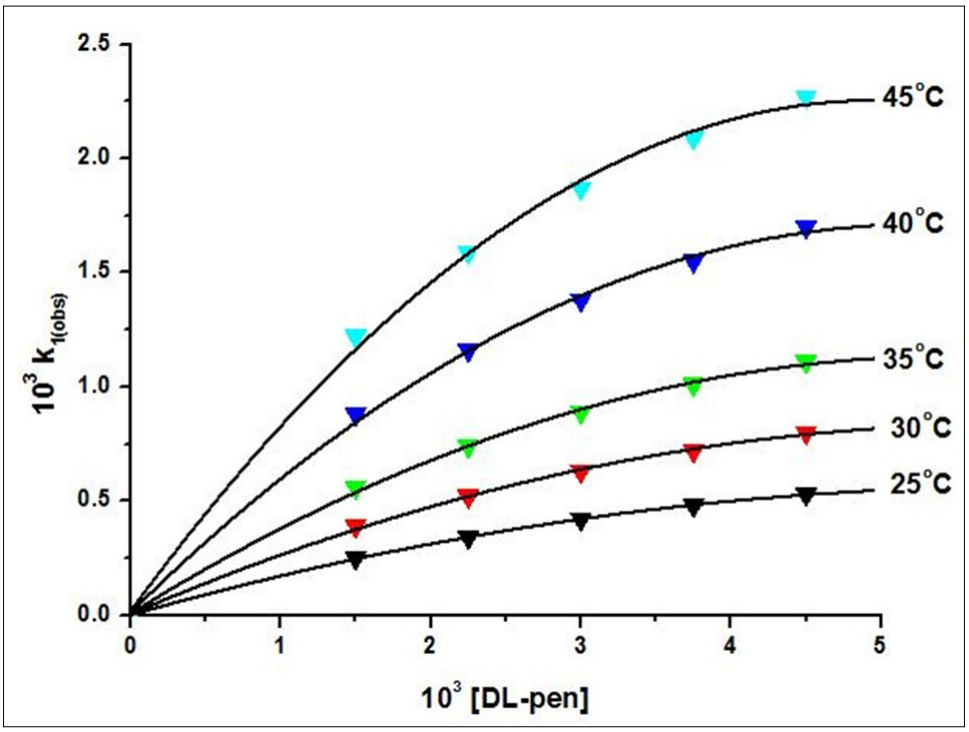
ESI Fig. S15 ESI Mass spectra of complex **4** in water



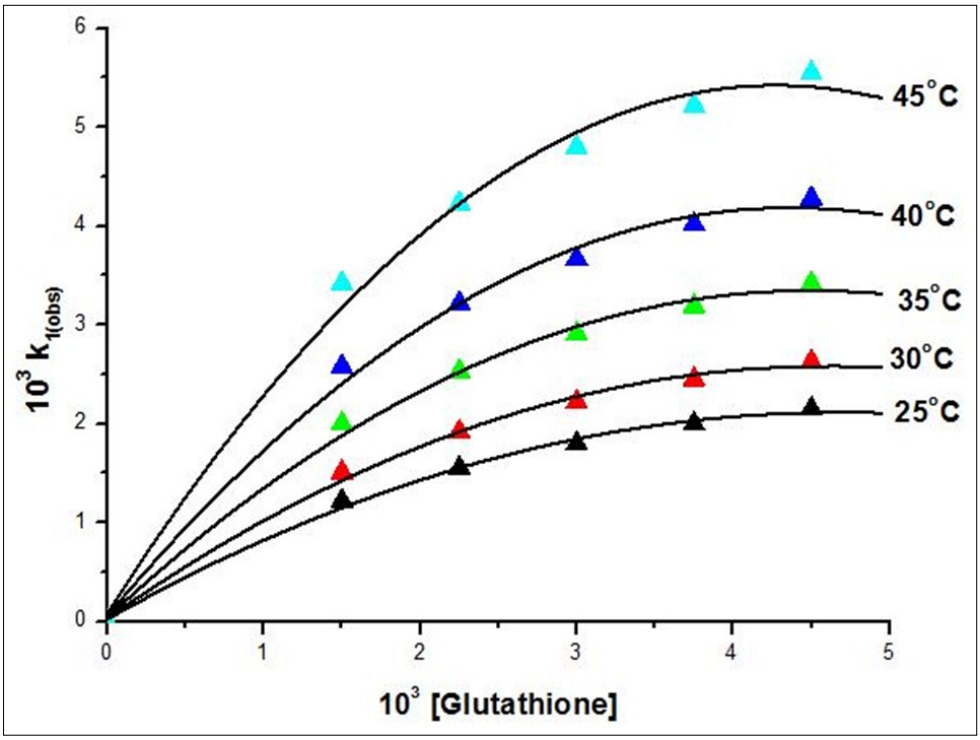
ESI Fig. S16 Major contribution of molecular orbitals involved in electronic transitions in complex **1**



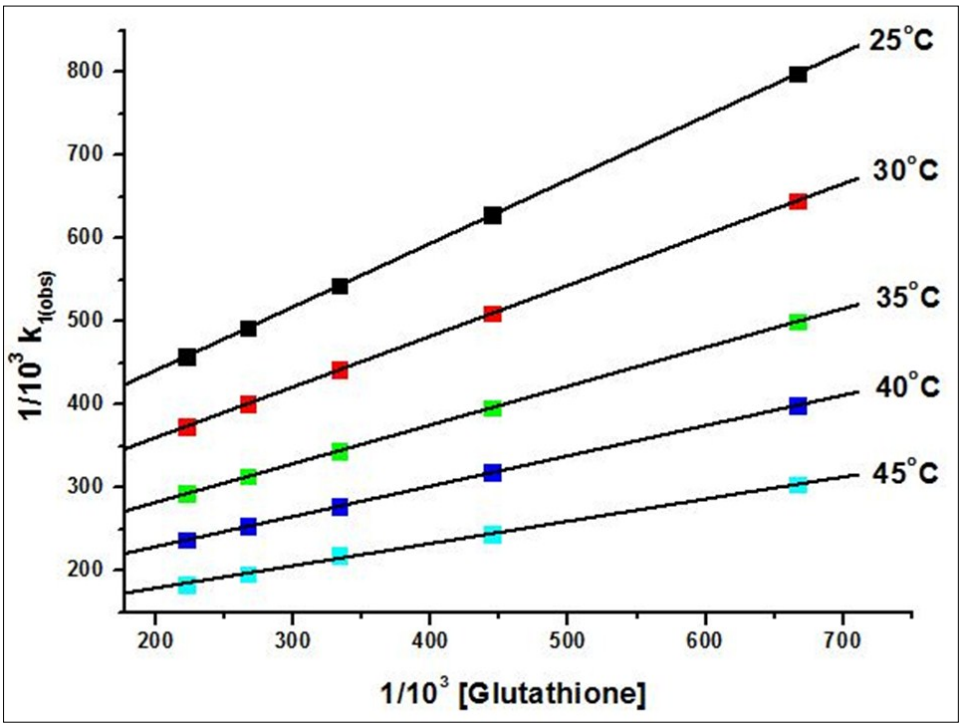
ESI Fig. S17 A typical plot of $\ln(A_\alpha - A_t)$ versus time (min): [complex **2**] = 1.50×10^{-4} M; [GSH] = 1.50×10^{-3} M; temperature = 25 ^{o}C, inset: typical plot of ln Δ vs time (min)



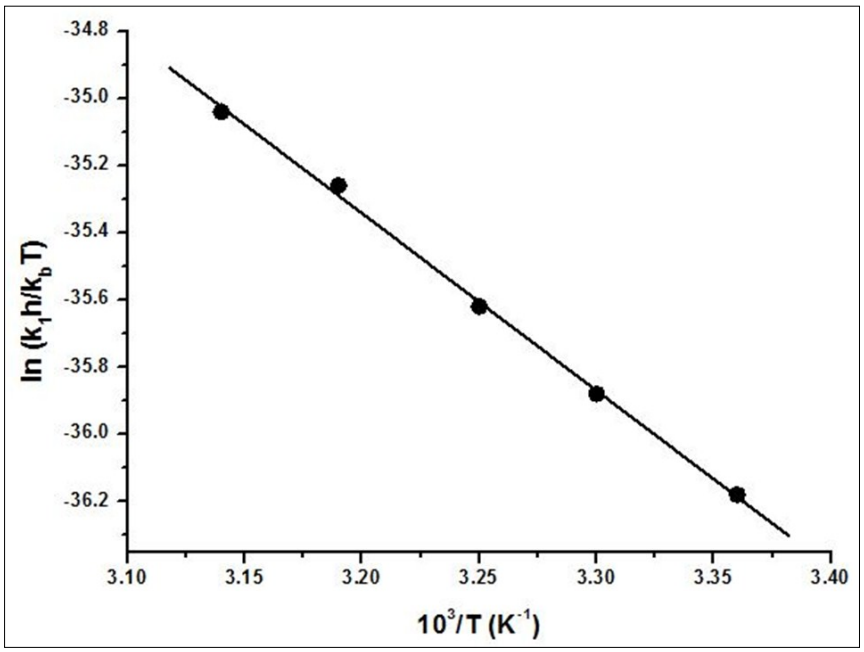
ESI Fig. S18 Plot of $10^3k_{1(obs)}$ versus 10^3[DL-pen] from temperature 25 to 45 °C



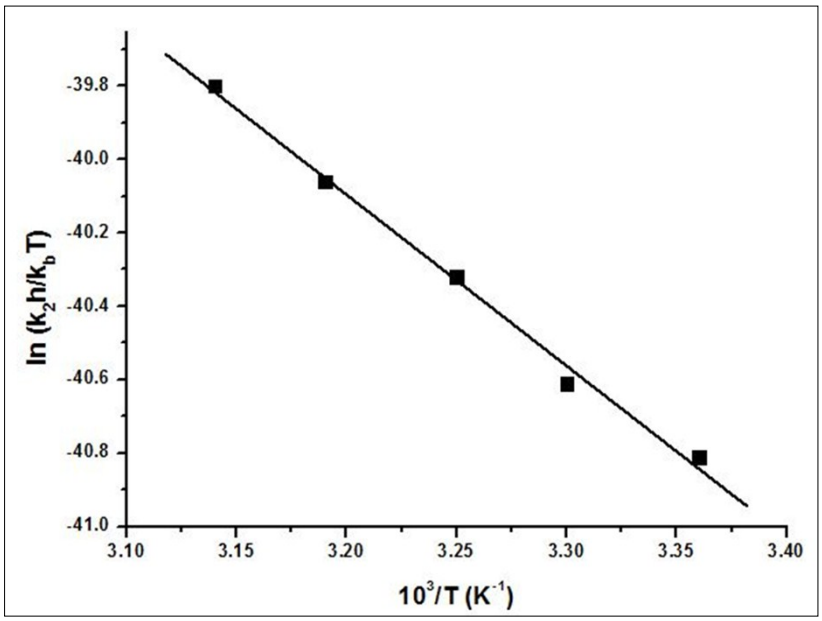
ESI Fig. S19 Plot of $10^3k_{1(obs)}$ versus 10^3[GSH] from temperature 25 to 45 °C



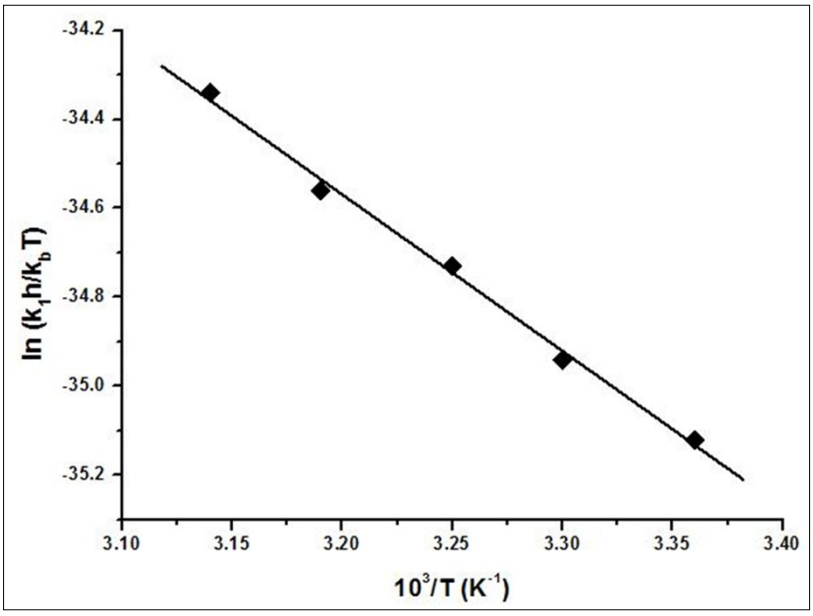
ESI Fig. S20 Plot of $1/10^3 \times k_{1(obs)}$ versus $1/10^3$[GSH] at different temperatures



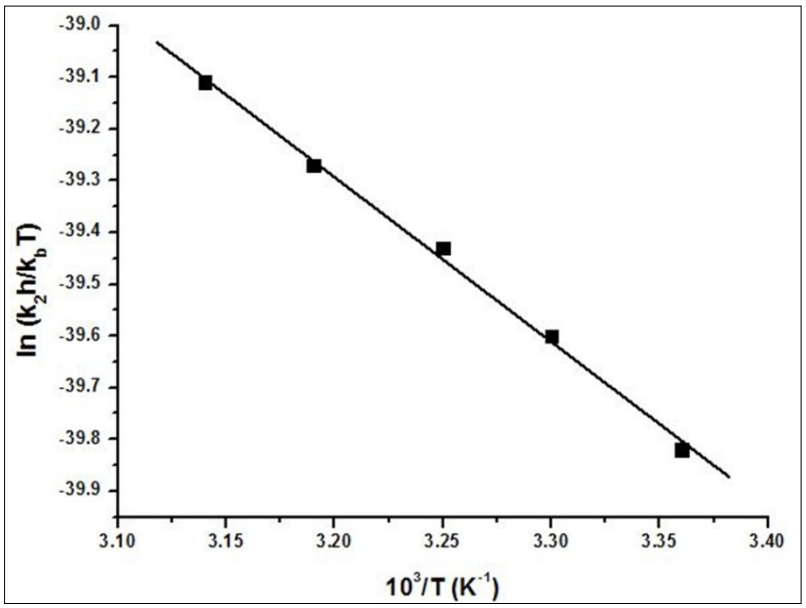
ESI Fig. S21 Eyring plot (ln k_1h/k_BT vs. $10^31/T$) for the reaction of complex **2** with DL-pen



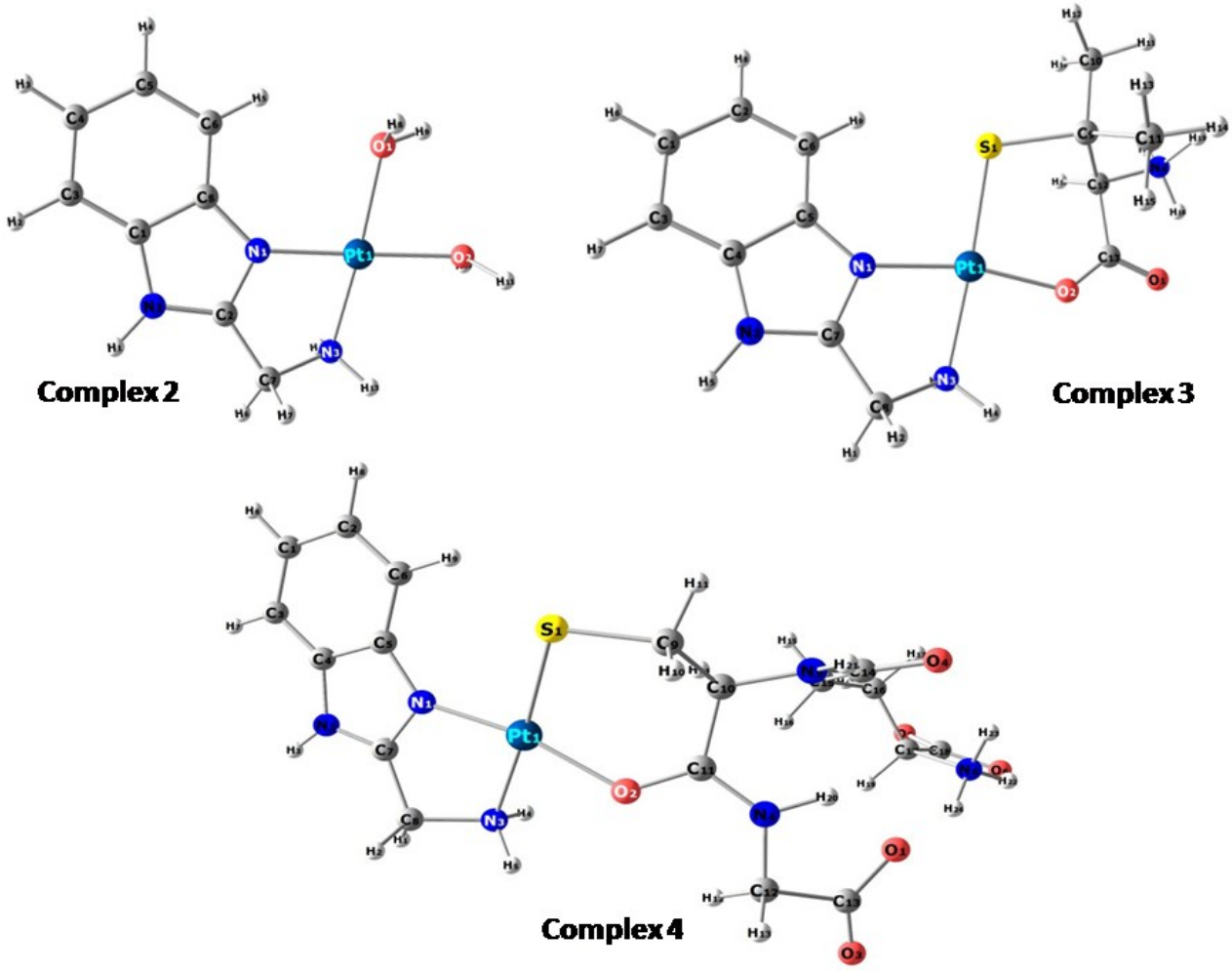
ESI Fig. S22 Eyring plot (ln k_2h/k_BT vs. $10^31/T$) for the reaction of complex **2** with DL-pen



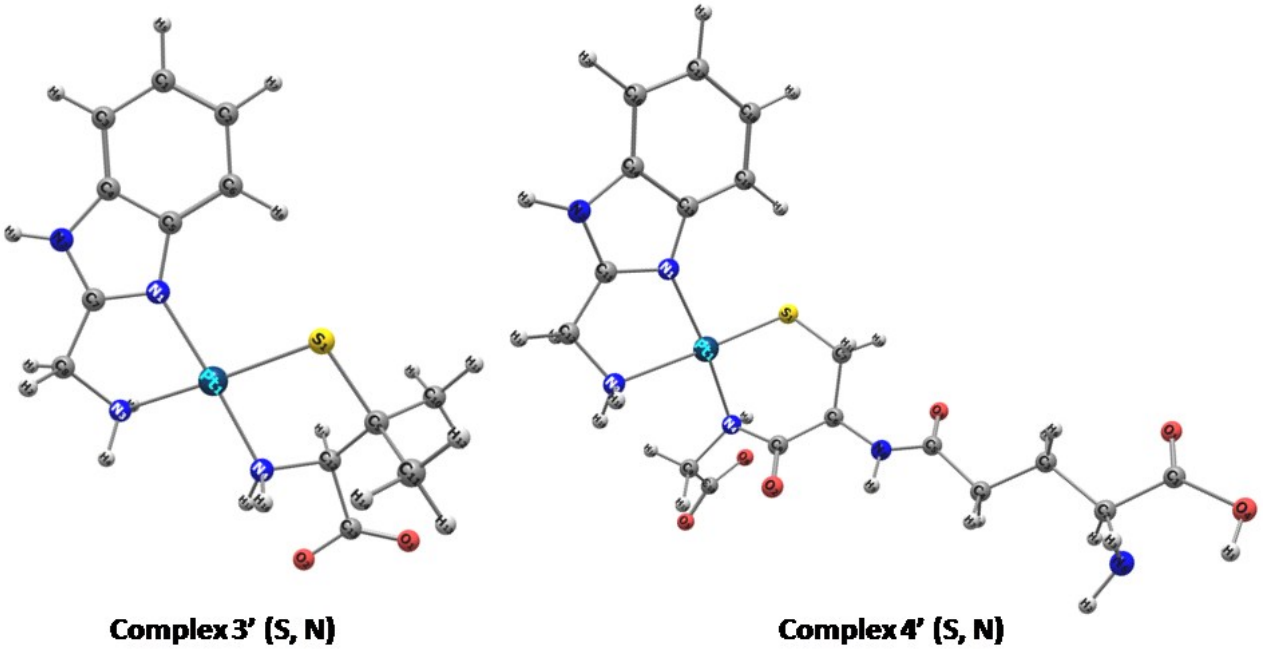
ESI Fig. S23 Eyring plot (ln k_1h/k_BT vs. $10^31/T$) for the reaction of complex **2** with GSH



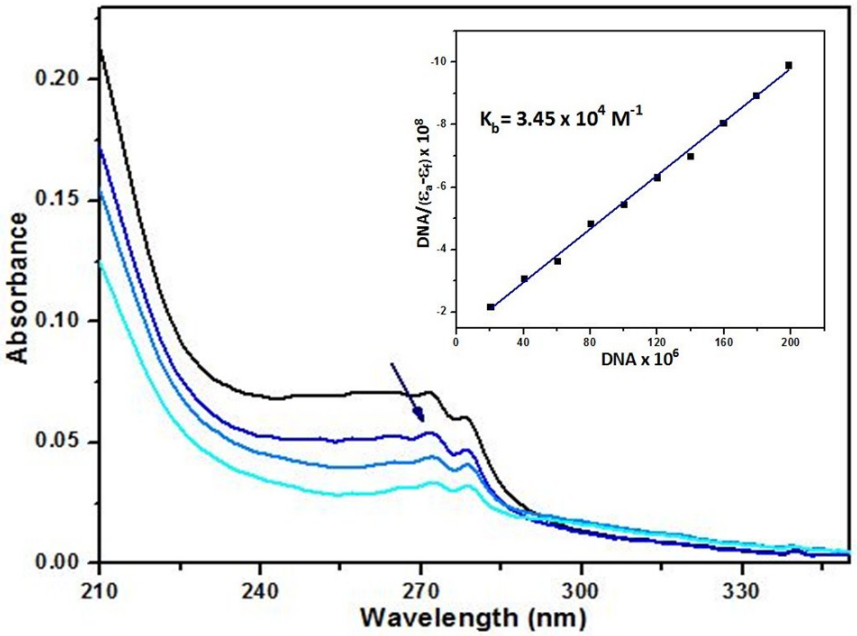
ESI Fig. S24 Eyring plot (ln k_2h/k_BT vs. $10^31/T$) for the reaction of complex **2** with GSH



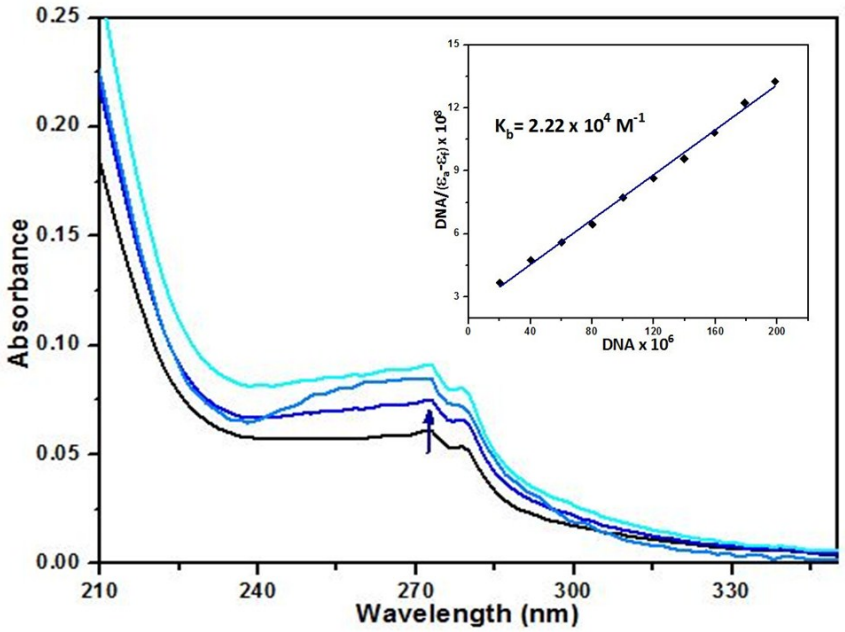
ESI Fig. S25 Optimised structures of complex **2**, **3** and **4**



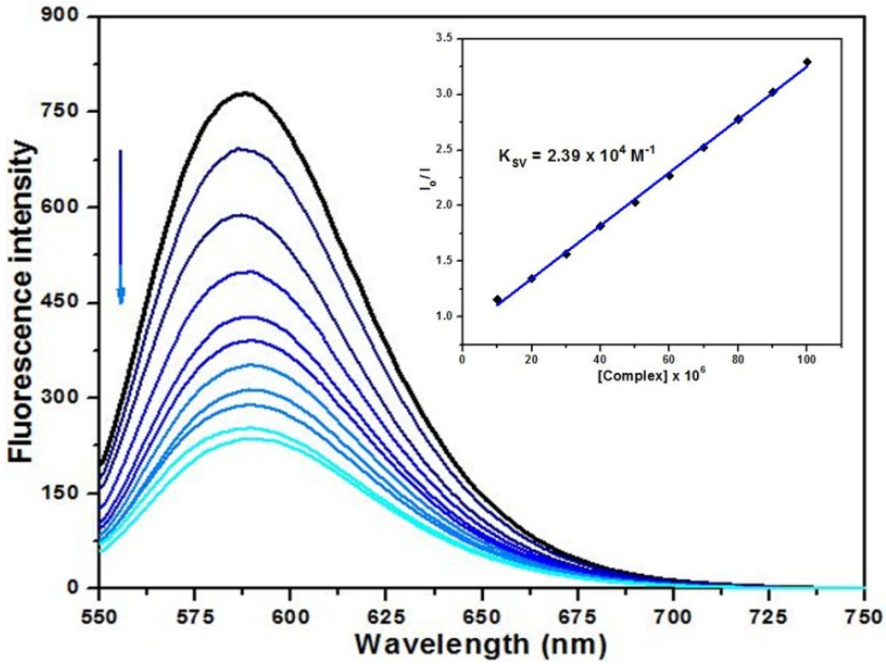
ESI Fig. S26 Optimised structures of probable complex **3'**(S, N) and probable complex **4'**(S, N)



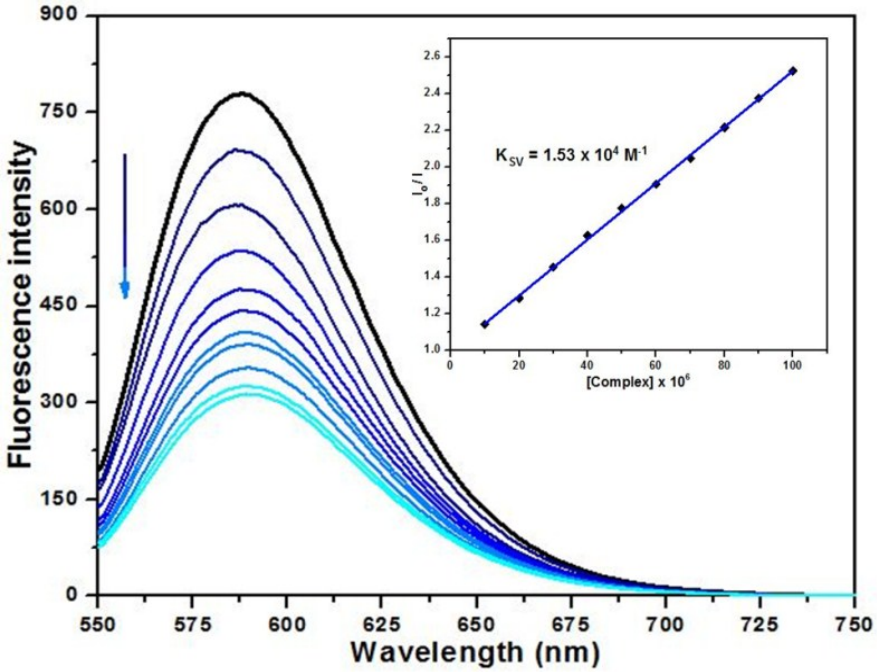
ESI Fig. S27 UV spectra of solutions containing complex **3** (20 µM) upon addition of CT-DNA (0–200 µM) in Tris–HCl buffer. The arrow shows the changes in absorbance on increasing DNA concentration. Inset: Plots of [DNA]/[ε_a-ε_f] vs. [DNA] for the titration of the complex **3** with DNA



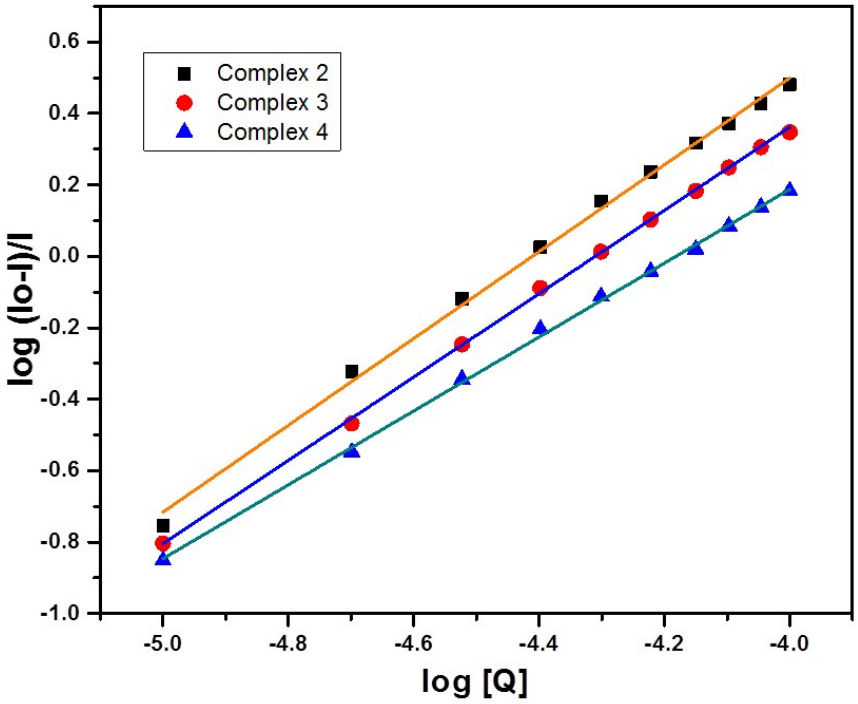
ESI Fig. S28 UV spectra of solutions containing complex **4** (20 µM) upon addition of CT-DNA (0–200 µM) in Tris–HCl buffer. The arrow shows the changes in absorbance on increasing DNA concentration. Inset: Plots of [DNA]/[ε_a-ε_f] vs. [DNA] for the titration of the complex **4** with DNA



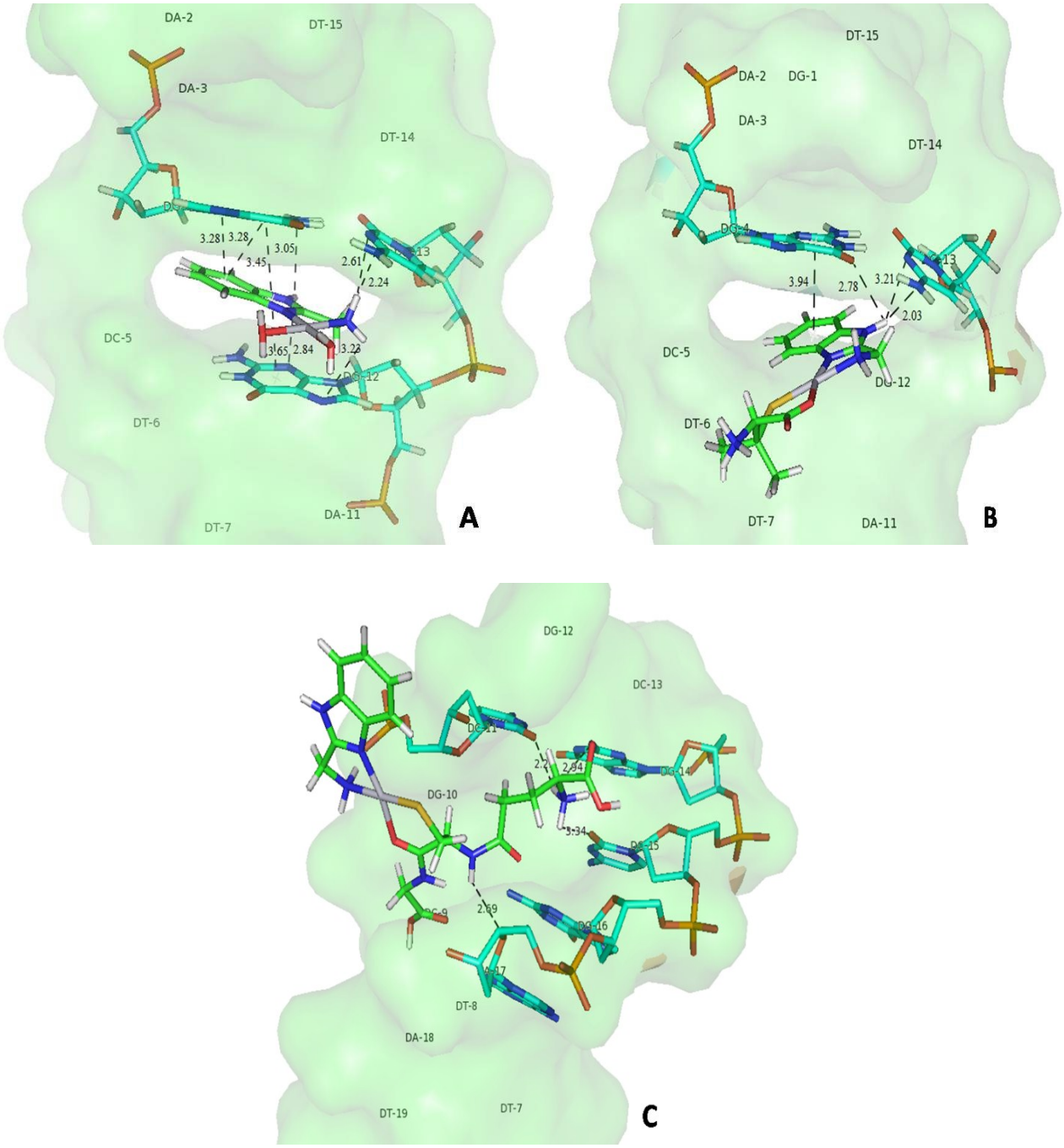
ESI Fig. S29 Emission spectra of EtBr-bound DNA solutions in the absence and presence of increasing concentrations of **3**(10–100 µM) in Tris–HCl. [EtBr]= 20.0 µM, [DNA] = 20.0 µM. The arrow show the change in intensity upon increasing amounts of the complex. Inset: Stern–Volmer plot of the fluorescence data.



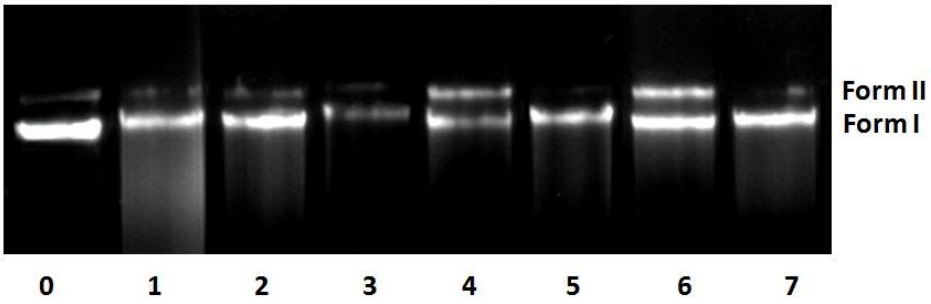
ESI Fig. S30 Emission spectra of EtBr-bound DNA solutions in the absence and presence of increasing concentrations of **4**(10–100 µM) in Tris–HCl. [EtBr]= 20.0 µM, [DNA] = 20.0 µM. The arrow show the change in intensity upon increasing amounts of the complex. Inset: Stern–Volmer plot of the fluorescence data.



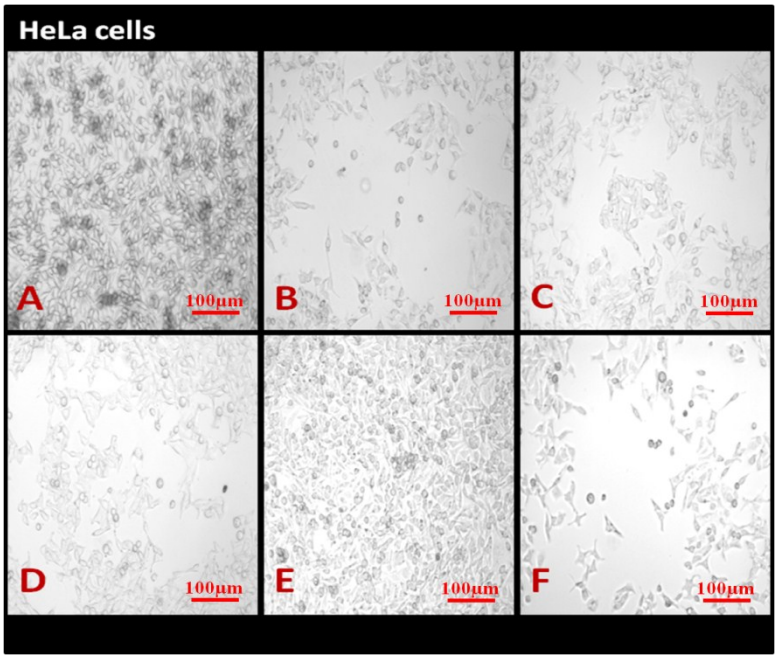
ESI Fig. S31 Scatchard plots for complexes **2**-**4**



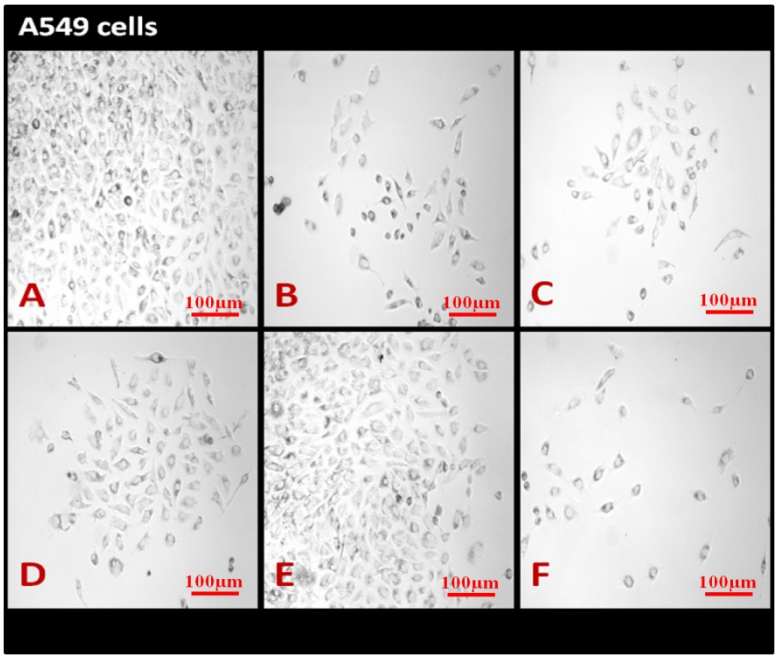
ESI Fig. S32 Magnified view of docked model showing the interaction of DNA bases with **(A)** complex **2**, **(B)** complex **3** and **(C)** complex **4**



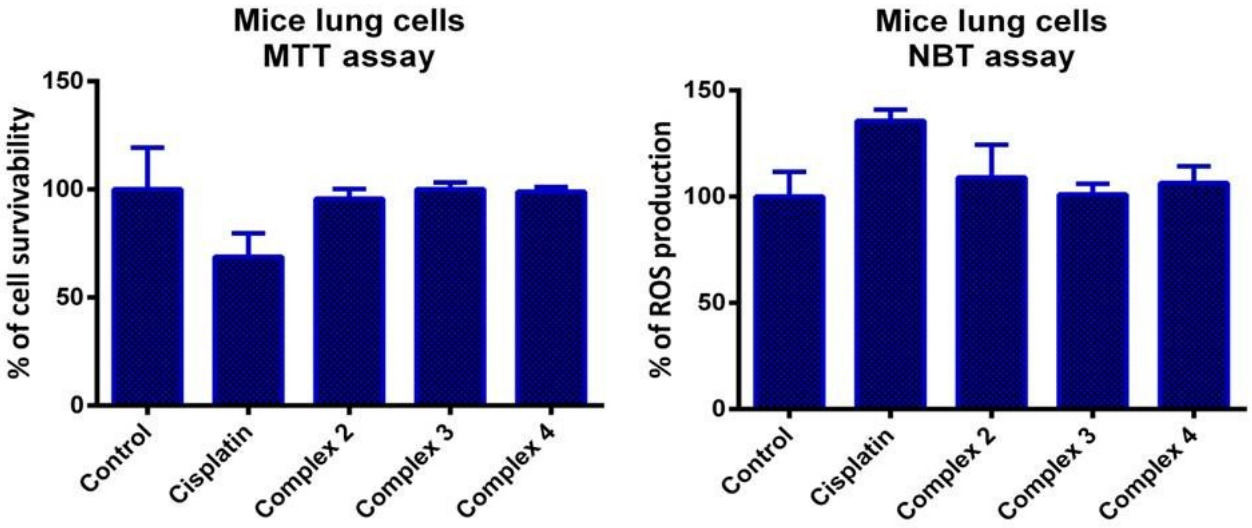
ESI Fig. S33 Gel electrophoresis



ESI Fig. S34 Microscopic images (A) untreated HeLa cells, (B) treated with 10µM of complex **2**, (C) complex **3**, (D) complex **4**, (E) ambim and (F) *cis*platin.



ESI Fig. S35 Microscopic images (A) untreated A549 cells, (B) treated with 10µM of complex **2**, (C) complex **3**, (D) complex **4**, (E) ambim and (F) *cis*platin.



ESI Fig. S36 Percentage of cell survivability and ROS production in mice lung cells after 4h incubation with 50 µM of cisplatin and complexes **2**-**4**.

ESI Table S1 $10^3 \times k_{1(obs)}$ (s^{-1}) values at different [DL-pen] and [GSH] at different temperatures. [Complex **2**] = 2.54×10^{-4} M, pH = 4.0, ionic strength = 0.1 M $NaClO_4$

$10^3 \times$ [L] mol.dm^{-3}	Temp (^{0}C)									
	DL-pen					GSH				
	25 °C	30 °C	35 °C	40 °C	45 °C	25 °C	30 °C	35 °C	40 °C	45 °C
1.50	0.25 ± 0.06	0.39 ± 0.07	0.56 ± 0.04	0.88 ± 0.02	1.22 ± 0.04	1.22 ± 0.06	1.51 ± 0.08	2.00 ± 0.07	2.58 ± 0.04	3.42 ± 0.13
2.25	0.34 ± .10	0.52 ± 0.06	0.74 ± 0.13	1.16 ± 0.08	1.59 ± 0.05	1.55 ± 0.04	1.92 ± 0.05	2.53 ± 0.08	3.22 ± 0.14	4.23 ± 0.06
3.00	0.42 ± 0.12	0.63 ± 0.05	0.89 ± 0.09	1.38 ± 0.06	1.87 ± 0.12	1.80 ± 0.10	2.22 ± 0.12	2.91 ± 0.11	3.67 ± 0.07	4.80 ± 0.09
3.75	0.48 ± 0.09	0.72 ± 0.14	1.01 ± 0.11	1.55 ± 0.09	2.09 ± 0.03	2.00 ± 0.11	2.45 ± 0.07	3.19 ± 0.04	4.02 ± 0.06	5.22 ± 0.10
4.50	0.53 ± 0.02	0.80 ± 0.03	1.11 ± 0.04	1.70 ± 0.04	2.27 ± 0.06	2.15 ± 0.02	2.63 ± 0.05	3.42 ± 0.09	4.28 ± 0.03	5.55 ± 0.15

ESI Table S2 10^5 x $k_{2(obs)}$ (s^{-1}) values at different [DL-pen] and [GSH] at different temperatures;[Complex **2**] = 1.50×10^{-4} mol.dm^{-3}, pH = 4.0, ionic strength = 0.1 mol·dm^{-3} $NaClO_4$

$10^5 \times$ [L] mol.dm^{-3}	Temp(°C)									
	DL-pen					GSH				
	25 °C	30 °C	35 °C	40 °C	45 °C	25 °C	30 °C	35 °C	40 °C	45 °C
1.50	1.03 ± 0.06	1.56 ± 0.10	2.00 ± 0.05	2.49 ± 0.13	3.41 ± 0.04	3.18 ± 0.08	3.92 ± 0.05	4.95 ± 0.12	5.56 ± 0.15	6.94 ± 0.10
2.25	1.18 ± 0.14	1.42 ± 0.04	1.89 ± 0.09	2.68 ± 0.03	3.62 ± 0.05	3.22 ± 0.10	4.07 ± 0.09	4.87 ± 0.06	5.71 ± 0.08	6.85 ± 0.05
3.00	1.25 ± 0.03	1.37 ± 0.07	1.92 ± 0.02	2.56 ± 0.14	3.38 ± 0.08	3.03 ± 0.05	4.15 ± 0.06	4.71 ± 0.08	5.90 ± 0.07	6.69 ± 0.03
3.75	1.11 ± 0.11	1.50 ± 0.03	2.11 ± 0.08	2.73 ± 0.05	3.29 ± 0.06	3.09 ± 0.06	3.97 ± 0.11	4.69 ± 0.07	5.83 ± 0.11	6.97 ± 0.13
4.50	1.28 ± 0.04	1.45 ± 0.05	1.98 ± 0.03	2.59 ± 0.08	3.50 ± 0.10	3.23 ± 0.04	3.89 ± 0.09	4.88 ± 0.10	5.80 ± 0.08	6.90 ± 0.06

ESI Table S3 Activation parameters for analogous systems

Systems	$\Delta H_1^{\ddagger}$ (kJ mol^{-1})	$\Delta S_1^{\ddagger}$ (JK mol^{-1})	$\Delta H_2^{\ddagger}$ (kJ mol^{-1})	$\Delta S_2^{\ddagger}$ (JK mol^{-1})	Ref.
$[Pt(ambim)(H_2O)_2]^{2+}$ / DL-penicillamine	43.79 ±1.31	-149.00 ±1.20	38.7 ±1.16	-205.12 ±1.78	This work
$[Pt(ambim)(H_2O)_2]^{2+}$/ Glutathione	31.04 ±1.44	-184.65 ±1.17	26.46 ±1.19	-239.16 ±1.61	
$[Pt(pic)(H_2O)_2]^{2+}$/ L-cysteine	34.91±0.97	-174.68±2.18	29.11±0.72	-233.74±2.4	1
$[Pt(pic)(H_2O)_2]^{2+}$/ N-acetyl-L- cysteine	21.12±0.35	-294.25±1.05	19.45±0.47	-267.68±1.6	
$[Pt(en)(H_2O)_2]^{2+}$/ Thiourea	57.0 ± 3.0	-24.0 ± 1.1	36.0 ± 2.0	-69.0 ± 6.0	2
$[Pt(terpy)(H_2O)]^{2+}$/ Glutathione	23 ± 1	-116 ± 3	----	----	3
cis-$[Pt(pic)(H_2O)_2]^{2+}$ /Glutathione	52.37±2.10	-112.35±2.98	37.29±1.84	-130.12±3.16	4
[*cis*-$Pt(en)(H_2O)_2]^{2+}$/ thiourea	61.90±1.6	-71±6	26.70±0.8	-186.80±2.7	5
[*cis*-$Pt(dach)(H_2O)_2]^{2+}$ /Glutathione	32.9±1.3	-187.20±4.2	30.50±0.1	-223.1±4.3	6
[*cis*-$Pt(dach)(H_2O)_2]^{2+}$ /DL-penicillamine	36.10±4.1	-175±12	44.4±1.1	-189±3.0	7

ESI Table S4 Charges (a.u.) and electron configurations for the complexes **3**(S, O) and **3'**(S, N)

	Zero point corrected energy (hatree)	Atom	Charge	Natural Electron Configuration
Complex 3 (S, O)	-1393.51581	Pt1	0.36019	[core]6S(0.57) 5d(8.75)6p(0.31) 6d(0.01)
		S1	-0.09227	[core]3S(1.72) 3p(4.34)3d(0.01) 4p(0.01)
		O2	-0.63601	[core]2S(1.65) 2p(4.98)3p(0.01)
		N4	-0.81224	[core]2S(1.39) 2p(4.41)3p(0.01)
		O1	-0.65427	[core]2S(1.71) 2p(4.93)3d(0.01)
Complex 3' (S, N)	-1393.08842	Pt1	0.24480	[core]6S(0.60) 5d(8.84)6p(0.31) 6d(0.01)
		S1	-0.11505	[core]3S(1.73) 3p(4.36)3d(0.01) 4p(0.01)
		N4	-0.81353	[core]2S(1.40) 2p(4.40)3p(0.01)
		O1	-0.71065	[core]2S(1.71) 2p(4.98)3d(0.01)
		O2	-0.76542	[core]2S(1.72) 2p(5.03)3d(0.01)

ESI Table S5 Charges (a.u.) and electron configurations for the complexes **4**(S, O) and **4'**(S, N)

	Zero point corrected energy (hatree)	Atom	Charge	Natural Electron Configuration		Zero point corrected energy (hatree)	Atom	Charge	Natural Electron Configuration
Complex 4 (S, O)	-1997.64846	Pt1	0.33887	[core]6S(0.57) 5d(8.76)6p(0.32) 6d(0.01)	Complex 4' (S, N)	-1997.635519	Pt1	0.30495	[core]6S(0.58) 5d(8.84)6p(0.26) 6d(0.02)
		S1	-0.09714	[core]3S(1.72) 3p(4.34)3d(0.01) 4p(0.01)			S1	-0.06732	[core]3S(1.73) 3p(4.31)3d(0.01) 4p(0.01)
		O2	-0.63051	[core]2S(1.64) 2p(4.98)3p(0.01)			N4	-0.71611	[core]2S(1.36) 2p(4.34)3p(0.01)
		N4	-0.59370	[core]2S(1.26) 2p(4.32)3p(0.01)			O2	-0.57169	[core]2S(1.69) 2p(4.86)3d(0.02)

ESI Table S6 Hydrogen bonding interactions and the binding free energy of the most stable docking conformations for complexes **2**–**4** docked into DNA

Complex	H-bonding			ΔG (kJ mol^{-1})
	Donor (D–H)	Acceptor (H···A)	H···A (Å)	
2	N2-H1(ambim)	DG-4(O)	3.05	-30.25
	N2-H1(ambim)	DG-12(N)	2.84	
	N3-H12(ambim)	DG-12(N)	3.23	
	N3-H13(ambim)	DC-13(N)	2.24	
	N3-H13(ambim)	DC-13(N)	2.61	
3	N2-H5(ambim)	DG-4(O)	2.78	-30.12
	N2-H5(ambim)	DC-13(N)	2.03	
	N2-H5(ambim)	DC-13(N)	3.21	
4	N5-H21(GSH)	DA-17(O)	2.69	-28.45
	N6-H24(GSH)	DC-11(O)	2.20	
	N6-H24(GSH)	DG-14(O)	2.94	
	N6-H22(GSH)	DC-15(O)	3.34	

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