Electronic Supplementary Material (ESI) for Dalton Transactions.

Photocytotoxic cancer cell-targeting platinum(II) complexes of glucose-appended curcumin and biotinylated 1,10-phenanthroline

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SUPPORTING INFORMATION

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Table S3. MTT Assay data (IC_{50}/μM) of free ligands: Hcur and HScur

Table S4. MTT Assay data (IC_{50}/μM) of **2** and **4** in DMEM with and without glucose in HeLa cells

Materials and methods

Supercoiled (SC) pUC19 DNA (cesium chloride purified) was purchased from Bangalore Genie (India). ESI-mass spectral measurements were made using Esquire 3000 plus ESI (Bruker Daltonics) and Q-TOF Mass Spectrometers. ^{1}H NMR spectral measurements were made using a Bruker 400 MHz NMR spectrometer. The FT-infrared, UV-visible and emission spectral measurements were carried out with Bruker Alpha, PerkinElmer Spectrum 650 and PerkinElmer LS55 spectrophotometer, respectively. Flow cytometric experiments were done using Becton Dickinson fluorescent activated cell sorting (BD-FACS) Verse instrument (BD Biosciences) configured with a MoFLo XDP cell sorter and analyzer with three lasers (λ = 488, 365, and 640 nm) and 10-color parameters. FACS data were acquired and analysed with BD-FACS suite software in Windows 7. Elemental analysis was done with a Thermo Finnigan Flash EA 1112 CHNS analyzer. Leica TCS SP_5 confocal microscope was utilized to obtain confocal microscopy images using an oil immersion lens and LAS X software was used for processing of images.

DNA Photocleavage and mechanistic experiments

DNA photocleavage studies were performed by using standard protocols of gel electrophoresis method.[S1] Each sample was incubated for 1.0 h at 37 °C before exposing to light. The samples were analyzed for the photocleaved products by gel electrophoresis. The samples after incubation in a dark chamber were added to the loading buffer containing 0.25% bromophenol blue, 0.25% xylene cyanol, 30% glycerol (3 μL) and the solution was finally loaded on 1% agarose gel containing 1.0 μg/mL ethidium bromide (EB). The mechanistic investigations were done by adding different additives (NaN_3, 4mM; DMSO, 8 μL; KI, 4.0 mM; catalase, 4 units; SOD, 4 units). The gel-electrophoresis completed in about 2 h at 60 V in TAE (Tris-acetate EDTA) buffer. Bands were visualized by UV light and photographed. The extent of DNA cleavage was measured from the intensities of the bands using UVITEC Gel Documentation System. Due corrections were made for the low level of nicked circular (NC) form present in the original supercoiled (SC) DNA sample and for the low affinity of EB binding to SC compared to NC and linear forms of DNA.[S1] The concentrations of the complexes and additives corresponded to that in the 20 μL final volume of the sample using Tris buffer.

Photocytotoxicity studies in presence and absence of glucose in cellular media

MTT assay was performed in HeLa cells treated with complexes **2** and **4** in two sets of cellular media, with (4500mg/L) and without glucose in Dulbecco's modified Eagle's medium (DMEM). Approximately, 8000 cells of HeLa (human cervical cancer) were plated separately in two different 96 wells culture plate and incubated with various concentrations of **2** and **4** from 0.195 to 100 μM in 1% DMSO/Dulbecco's modified Eagle's medium (DMEM) for 4 h in the dark. DMEM with 4500 mg/L of D-glucose was used for one set of the assay while DMEM without D-glucose was used for the other one. After 4 h of incubation, the media containing compounds was removed and replaced with DPBS buffer for one set of the cells which were exposed to visible light for 1 h (400-700 nm, 10 J cm^{-2}), using Luzchem visible light photoreactor (model LZC-1, 10 J cm^{-2}), whereas the other set was kept in the dark for same time period using standard protocols. After exposure to light, DPBS was removed and replaced with fresh medium (glucose containing medium in both sets) and incubation was continued for a further period of 16 h in dark for the plate thus making the total incubation time of ~21 h. After the incubation period, 5 mg/mL of MTT (20 μL) was added to each well and incubated for an additional 3 h. The media was removed entirely from the wells and then DMSO (200 μL) was added and spectral measurement was taken at 570 nm using TECAN microplate reader. Cytotoxicity of the complexes was measured as the percentage ratio of the absorbance of the treated cells to the untreated controls. The IC_{50} values were determined by nonlinear regression analysis (Graph Pad Prism 6). Data were obtained by using three independent sets of experiments done in triplicate for each concentration.

DCFDA and annexin V-FITC/PI assay

Cellular ROS generation was detected by 2′,7′-dichlorofluorescein diacetate (DCFDA) assay using fluorescent oxidized DCF with an emission at 528 nm. The %cell population for ROS generation was obtained from FACS analysis. On incubation of HeLa cells with **2-4** (15 μM) for 4 h, they were photo-irradiated (400–700 nm) for 1 h in DPBS. The cells were gathered by trypsinization and a single cell suspension of 1×10^6 cells per ml was prepared after photo-irradiation. Treatment of DCFDA solution (1 μM) in DMSO was done on these cells in dark for 15 min at 25 °C. The analysis and quantification of DCFDA stained HeLa cells was discovered in the FL-1 channel by flow cytometry. For Annexin V-FTIC/PI assay, HeLa cells (3×10^5) were

plated and grown in 6 wells plate for 24 h. They were treated with **1-4** and incubated for 4 h. The medium first replaced by DPBS followed by sample irradiation for 1 h (400-700 nm, 10 J cm^{-2}). After irradiation, cells were left to grow for 24 h. The cells were washed in DPBS, trypsinized and subjected to re-suspension in 400 μL of 1X binding buffer. For each cell suspension, a 1 μL of annexin V-FITC and 0.5 μL of PI were added. The cells were incubated at 25 °C for 10 min in dark. The resulting fluorescence of the cells under study was recorded with a flow cytometer.

Cellular uptake experiments and platinum estimation

To measure the total platinum uptake using standard protocols[S2], about 10^6 HeLa cells were seeded in 60 mm tissue culture dishes, allowed to attach for 24 h, treated with the complexes **1-4** (5 μM) for 4h. After incubation, medium was aspirated, and the dishes were washed with sterile DPBS. Cells were lysed using 300 μL of 70% HNO_3. Cells were scraped from the dishes and the lysate was transferred to 15 mL tubes. The tubes were allowed to stand at room temperature for 15 min. The lysate was then treated with 100 μL H_2O_2 and incubated for ~3 h at 55 °C. After incubation, lysates were diluted to 10 mL (2% HNO_3) and used for ICP analysis. The samples were run using ICP-MS for platinum content along with the standards (0.01-1.0 ppm), and a blank sample fitted in a linear plot with a correlation of 0.99. Platinum content obtained in ppb units was then expressed as ng of Pt/ 10^6 cells. All the experiments were performed in triplicates and with untreated controls.

Cellular localization experiments and Pt estimation

Localization of the complexes was studied by quantifying platinum content in cellular organelles by ICP-MS technique using reported procedures.[S3,S4]

Nuclear and cytosol fractionation

About 10^6 HeLa cells were seeded in 90 mm tissue culture dishes to measure cellular distribution of platinum in cells and pre-treated with complexes **1-4** (5 μM) for 4 h in the dark. After incubation, medium was aspirated and washed with DPBS. One set was used for platinum estimation in whole cell and cellular fractions, while its similar treatment counterpart was trypsinized and live cells were counted by using trypan blue method. For nuclear and cytosolic

fractions, cells were lysed by using 0.5% of NP40 detergent. Cell lysate was then centrifuged at 12000 g at 4°C for 10 min. Supernatant was collected as the cytoplasmic fraction and nuclear pellet was washed with sterile DPBS to remove traces of cytosolic extract. The cytoplasmic fraction and nuclear pellet were then re-suspended in 70% HNO_3 and H_2O_2. These lysates were incubated at 55°C for ~3 h. After incubation, lysates were diluted to 2% HNO_3 solutions and used for ICP analysis. The samples were run using ICP-MS for platinum content along with the standards (0.01-1 ppm, and a blank sample fitted in a linear plot with a correlation of 0.99). Platinum content obtained in ppb units was then expressed as ng/10^6 cells. All the experiments were performed in duplicates along with untreated controls.

Mitochondrial isolation

Approximately 10^6 HeLa cells were plated in 90 mm tissue culture plates and grown for three days at 37 °C at 5% CO_2 level until it reached 100% confluence. The cells were then incubated with complexes **1**-**4** (5 μM) for 4 h in dark. The DMEM was removed and cells were washed with DPBS. The cells were then detached using a cell scraper and the cell suspensions were transferred to 50 ml Falcon tubes. The plates were thoroughly scraped to get maximum yield of mitochondria. The cells were centrifuged at 600 g at 4 °C for 10 min. The supernatant was discarded, and cells were re-suspended in mitochondrial isolation buffer IB (10 ml of 0.1M tris(hydroxymethyl)aminomethane (Tris)/3-(N-morpholine)propanesulfonic acid and 1 ml of ethylene glycol-bis(b-aminoethyl ether)-*N,N,N',N'*-tetraacetic acid/Tris to 20 ml of 1 M sucrose and volume made up to 100 ml (pH 7.4) and 1 ml EGTA/Tris to 20 ml of 1 M sucrose and volume made up to 100 ml (pH = 7.4). Cells were then homogenized at 4°C using a Teflon pestle (1600 r.p.m.) and the cell suspensions were stroked gently in a glass potter (initially cooled in ice-bath to maintain the mitochondrial integrity). The homogenate was then centrifuged at 600g at 4 °C for 10 min. The supernatant was collected and centrifuged at 7000g at 4 °C for 10 min. The supernatant was discarded, and the pellets were washed with 200 μl of ice-cold isolation buffer IB. The homogenate was centrifuged again at 7000g at 4 °C for 10 min and the pellet containing mitochondria was collected. One such set was used for measuring the concentration by Biuret methods and examining the separation of mitochondria by gel electrophoresis. Another identical set was used for Pt estimation by diluting in 2% HNO_3-DPBS solutions by ICP-MS method.

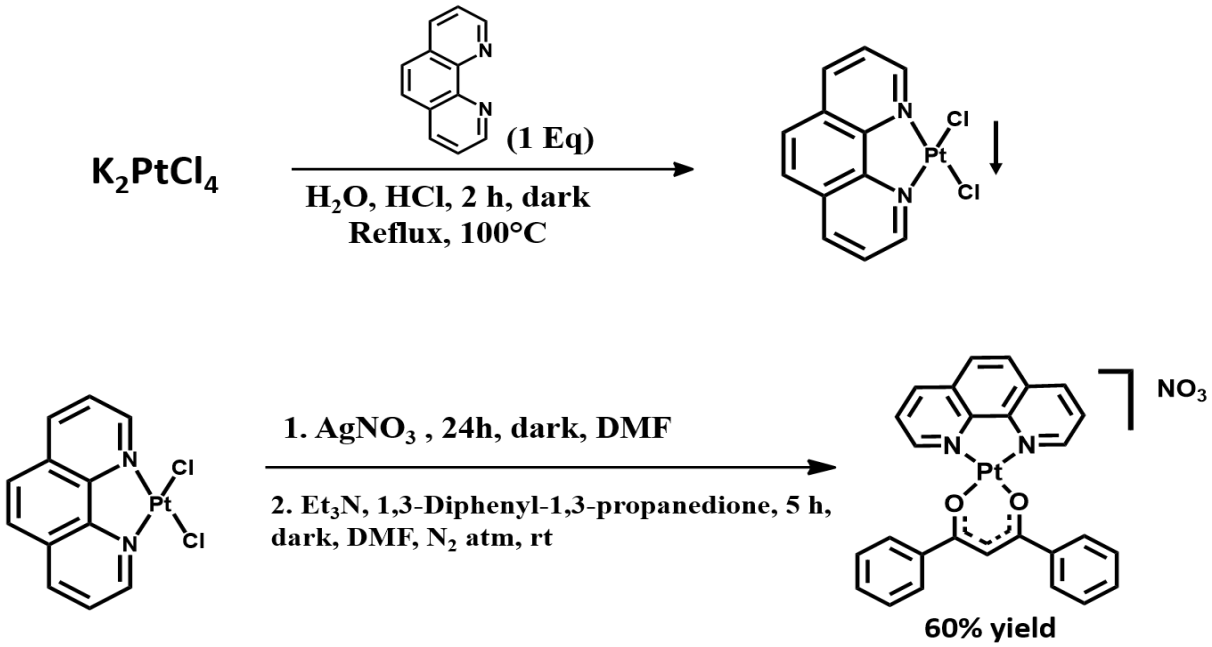
UV-visible absorption-based DNA binding methods

UV-visible absorption-based DNA binding of complexes was studied using standard protocols.[S5] The calf thymus ct-DNA was first tested for purity. The ratio of absorbance at 260 and 280 nm was approximately 1.9:1 confirming that the DNA was apparently free from protein. The concentration of DNA was determined by from the ratio of its absorption intensity at 260 nm and its known molar absorption coefficient value of 6600 dm^3 mol^{-1} cm^{-1}. Absorption titration experiments were performed in DPBS (5 mM, pH 7.2) by varying the concentration of the ct-DNA while keeping the complex concentration as constant (**1**-**4**, 20 μM in 5% DMF- DPBS). The spectra were recorded with increasing concentration of ct-DNA and after equilibration for 5 min with due correction made for the absorbance of only DNA. The regression analysis equation used is (1).

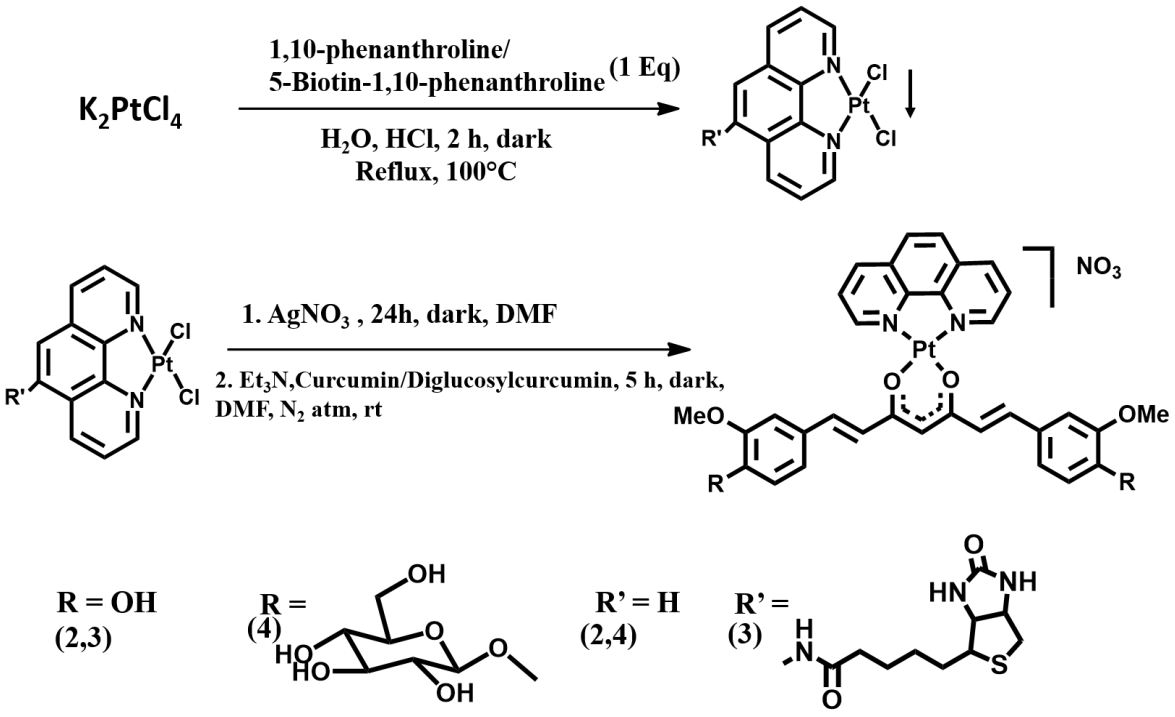
$$(\varepsilon_a - \varepsilon_f)/(\varepsilon_b - \varepsilon_f) = (b - (b^2 - 2K_b^2 C_t[DNA]_t/s)^{1/2})/2K_bC_t, \quad (1)$$

$$b = 1 + K_bC_t + K_b[DNA]_t/2s,$$

where C_t is the total metal complex concentration, ε_a is the extinction coefficient observed for the charge transfer absorption band at a given DNA concentration, ε_f is the extinction coefficient of the DNA unbound complex, ε_b is the extinction coefficient of the complex when fully bound to DNA, $[DNA]_t$ is the DNA concentration, K_b is the equilibrium binding constant, and s is the MvH fitting parameter in base pairs. The graphs were plotted, and non-linear least-squares analysis was done using Origin Lab, version 9.



Scheme **S1**: Synthetic scheme for complex **1**.



Scheme **S2**: Synthetic scheme for complexes **2**-**4**.

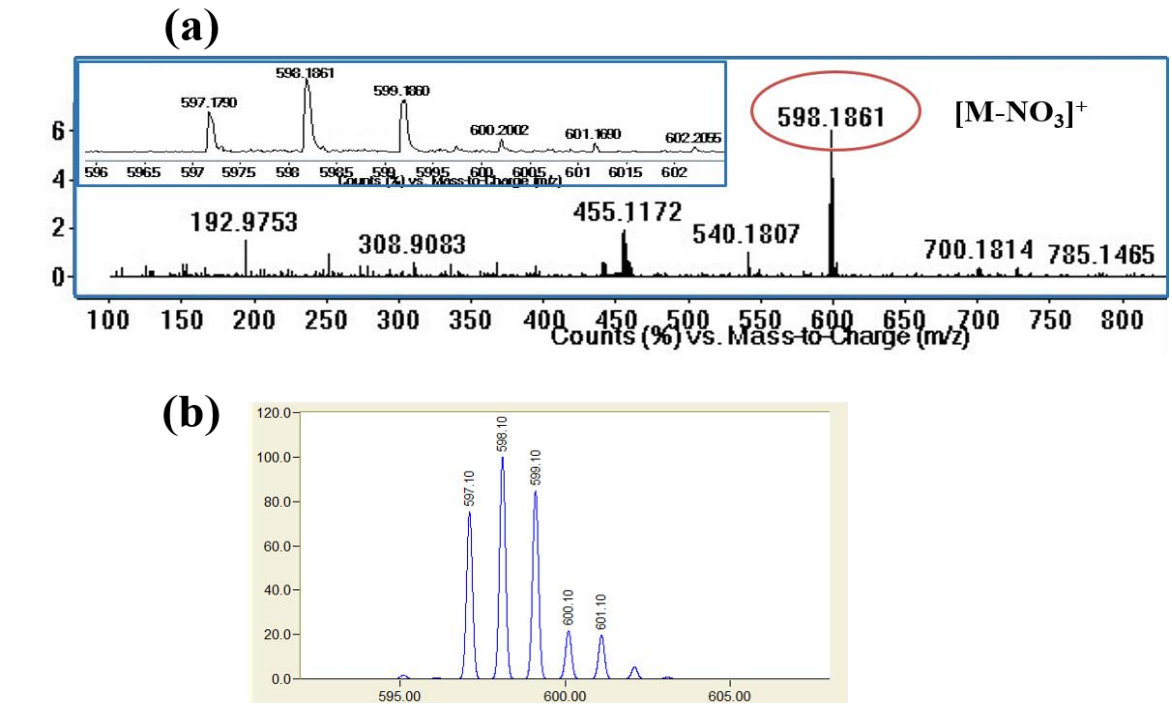


Fig. **S1**: (a) Mass spectrum of complex **1** in MeOH showing prominent parent ion peak at 598.1861 (m/z) which corresponds to $[M\text{-}NO_3]^+$. The peak at 455.1172 (m/z) is assignable to $[M\text{-}pacac+NO_3+H_2O]^+$. Inset shows the isotopic distribution pattern for platinum of the molecular ion peak. (b) Calculated isotopic distribution for complex **1**.

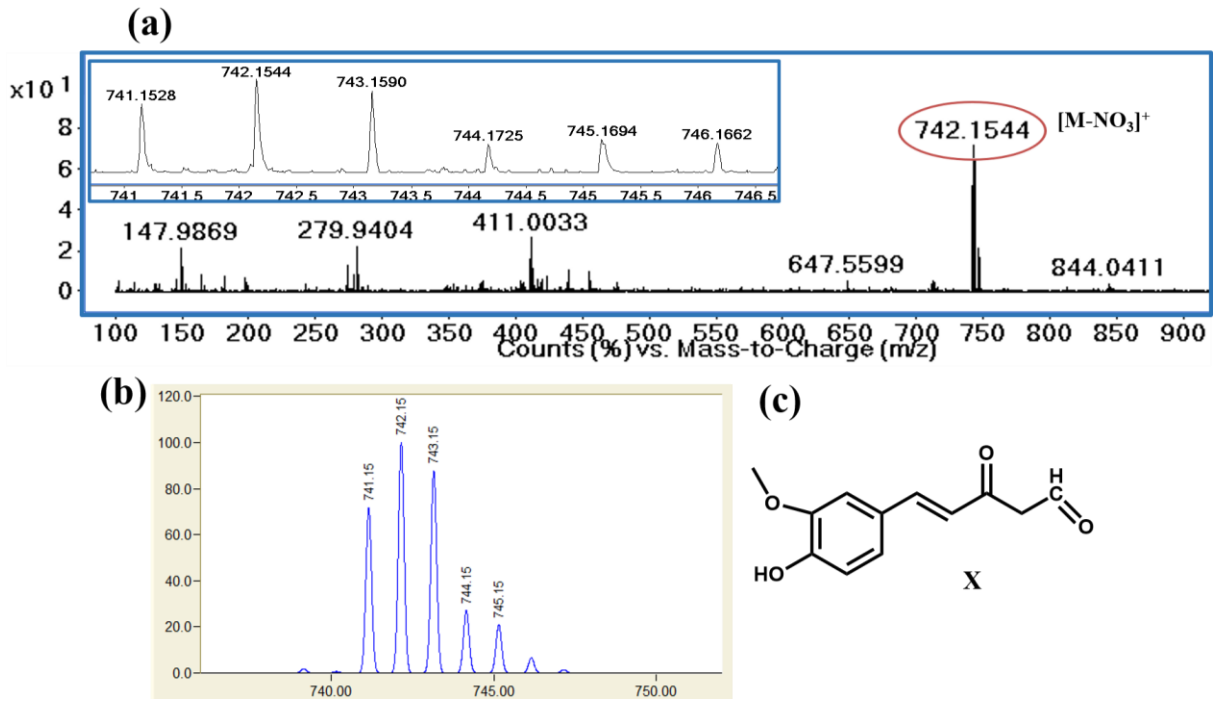


Fig. **S2**: (a) Mass spectrum of complex **2** in MeOH showing prominent parent ion peak at 742.1544 which corresponds to $[M\text{-}NO_3]^+$. The peak at 411.0033 (m/z) is assignable to $[M\text{-}cur+H+Cl]^+$ and 279.9404 corresponds to $[X+Na+H_2O+H_2O]^+$. Inset shows the isotopic distribution pattern for platinum of the molecular ion peak. (b) Calculated isotopic distribution for complex **2**.

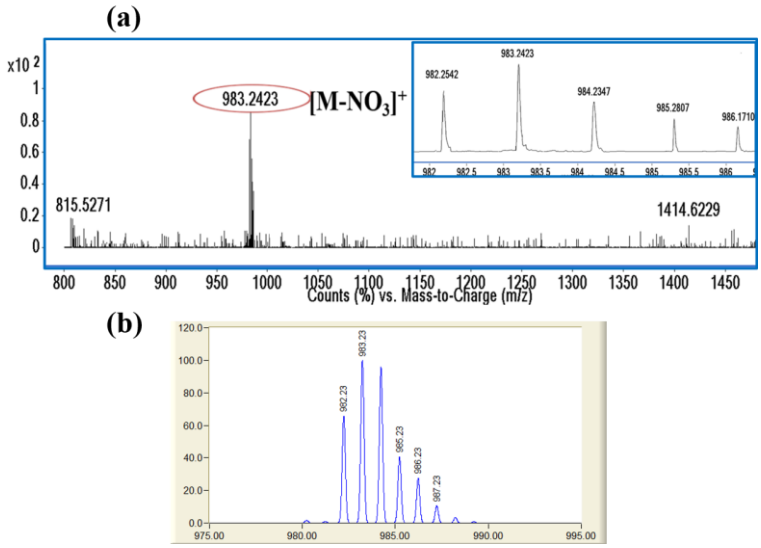


Fig. **S3**: (a) Mass spectrum of complex **3** in MeOH showing prominent parent ion peak at 983.2423 (m/z) which corresponds to $[M\text{-}NO_3]^+$. Inset shows the isotopic distribution pattern for platinum of the molecular ion peak. (b) Calculated isotopic distribution for complex **3**.

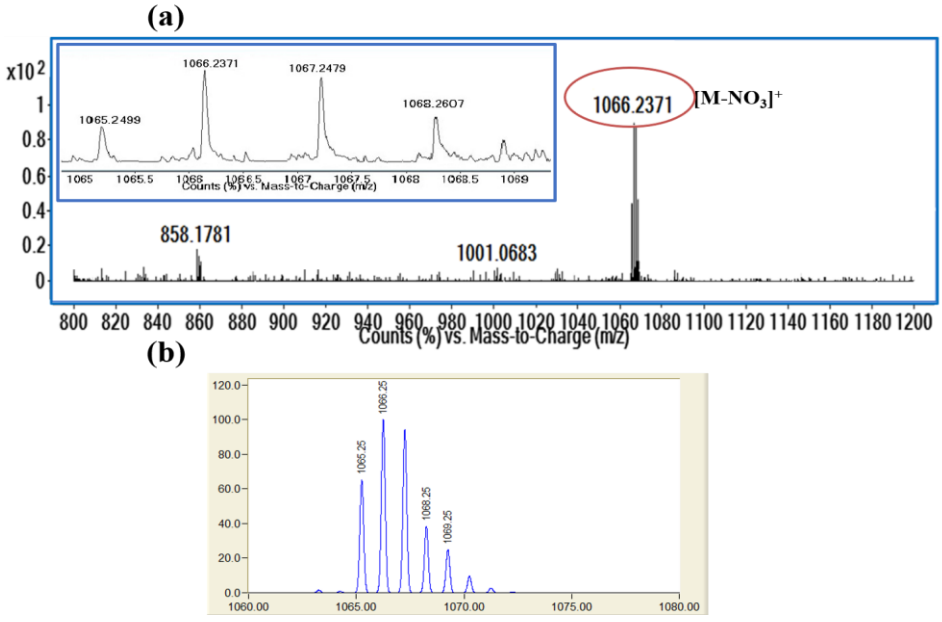


Fig. **S4**: Mass spectrum of complex **4** in MeOH showing prominent parent ion peak at 1066.2371 (m/z) which corresponds to $[M\text{-}NO_3]^+$. Inset shows the isotopic distribution pattern for platinum of the molecular ion peak. (b) Calculated isotopic distribution for complex **4**.

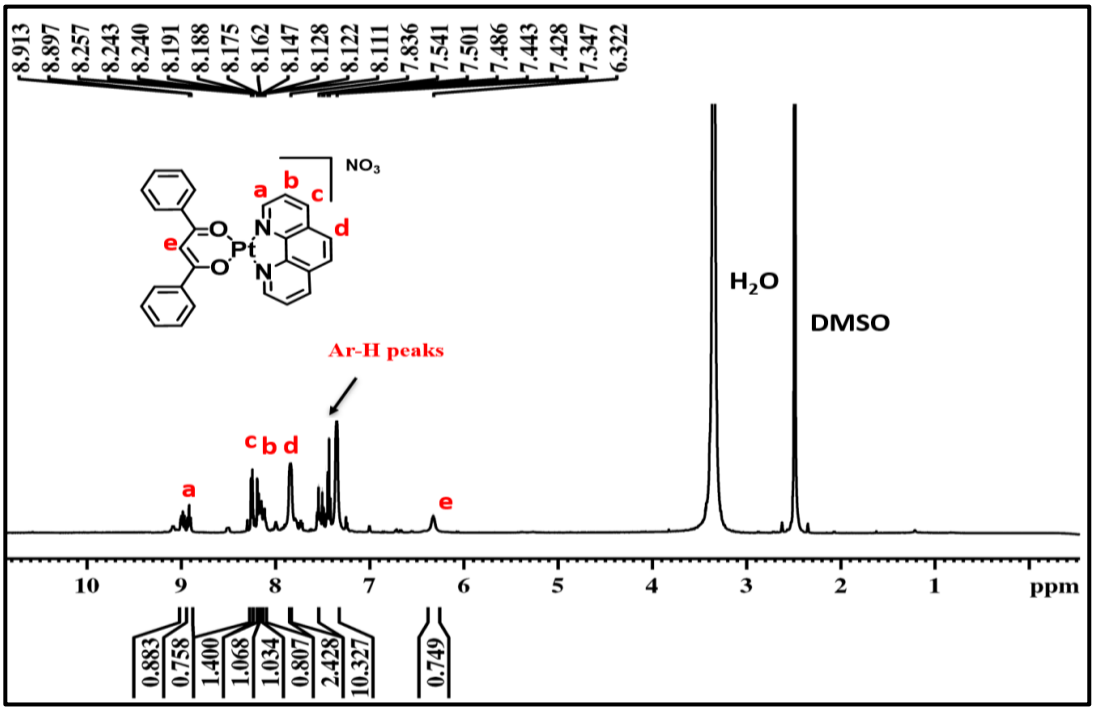


Fig. **S5** : ^{1}H NMR of **1** in DMSO-D_6.

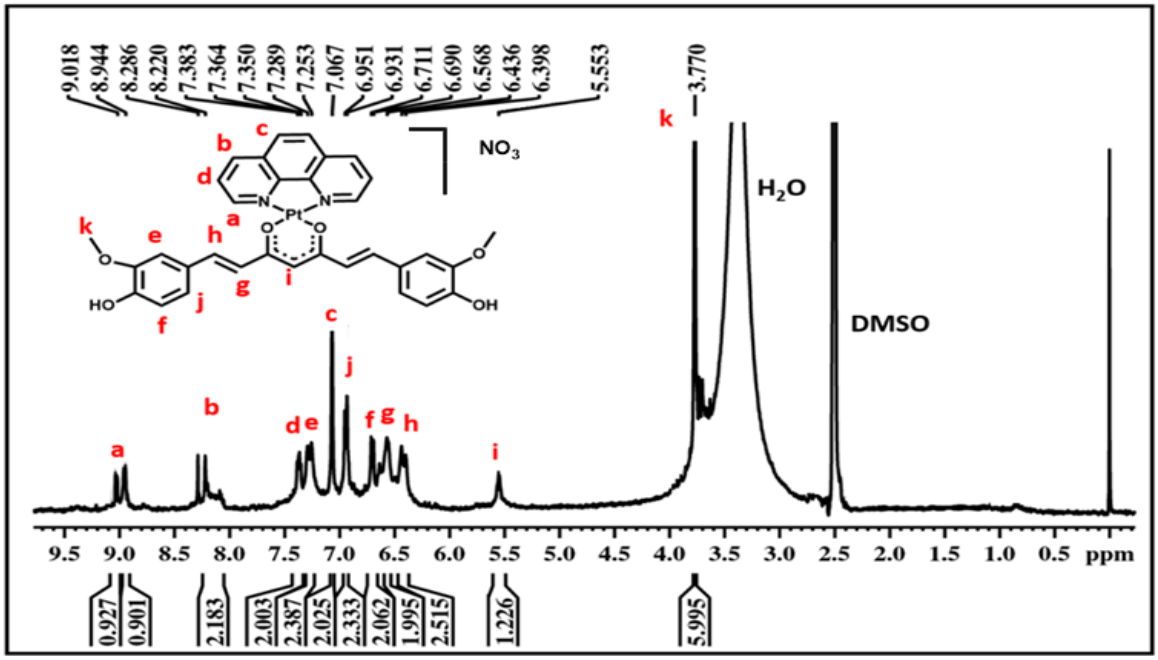


Fig. **S6** : ^{1}H NMR of **2** in DMSO-D_6.

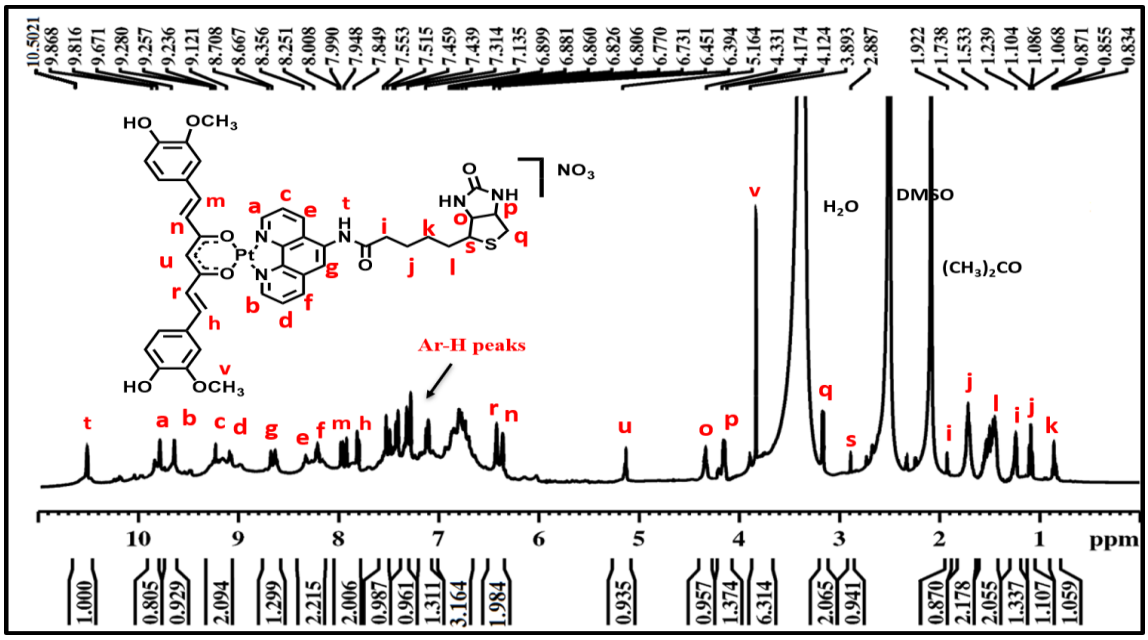


Fig. **S7** : ^{1}H NMR of **3** in DMSO-D$_6$.

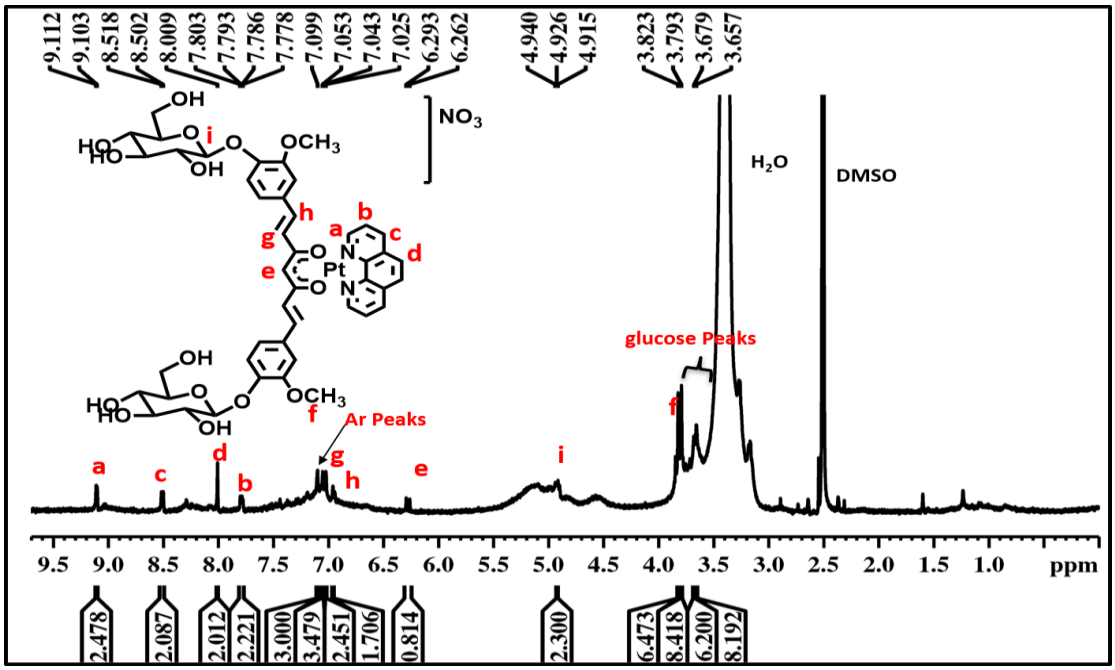


Fig. **S8** : ^{1}H NMR of **4** in DMSO-D$_6$.

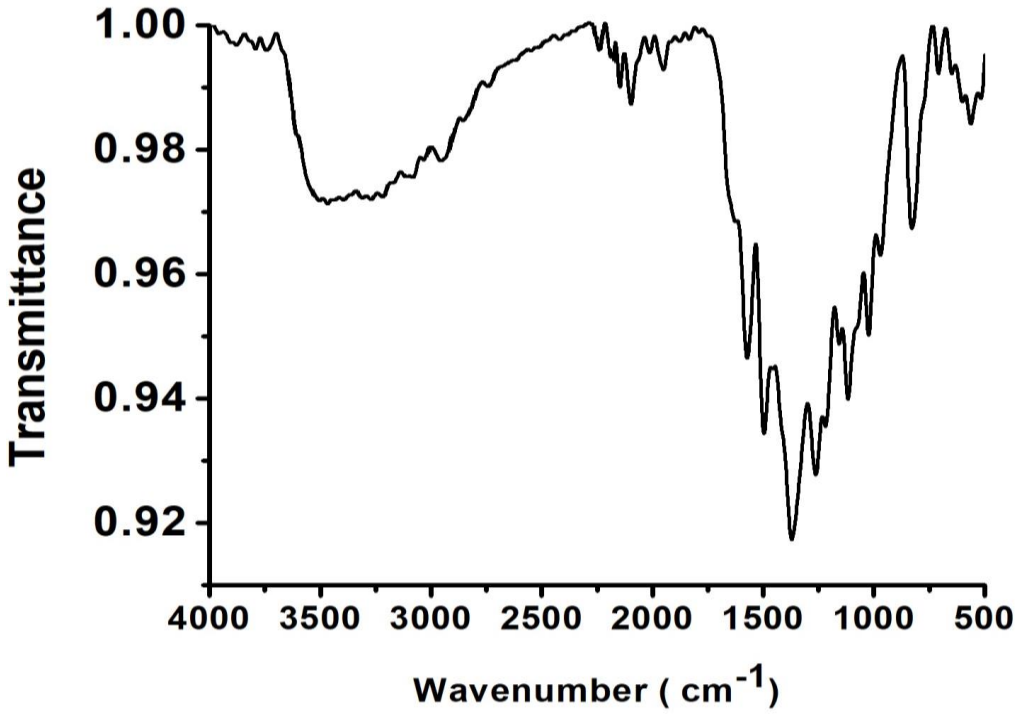


Figure **S9.** IR spectrum of complex **1** in solid phase

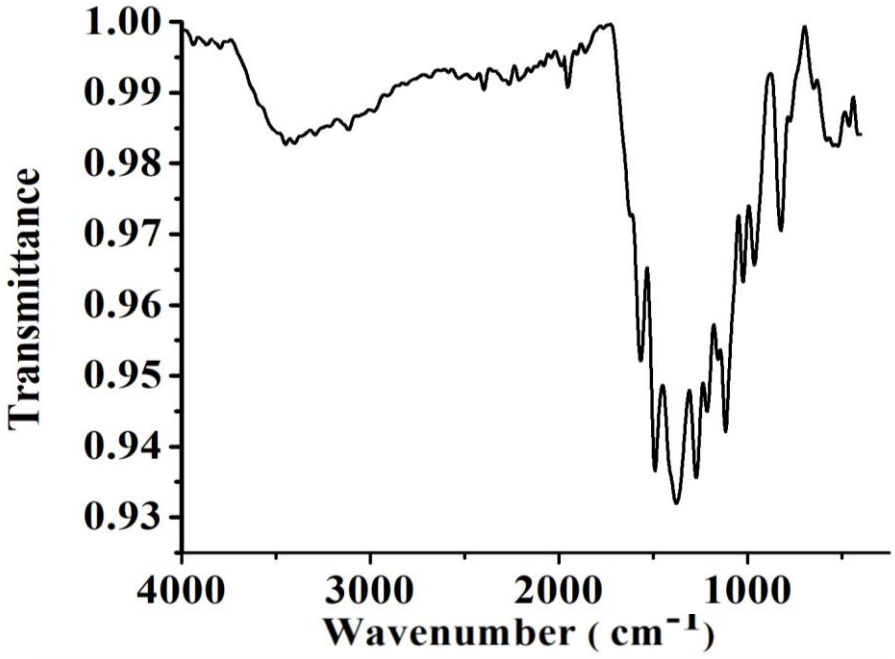


Figure **S10**. IR spectrum of complex **2** in solid phase

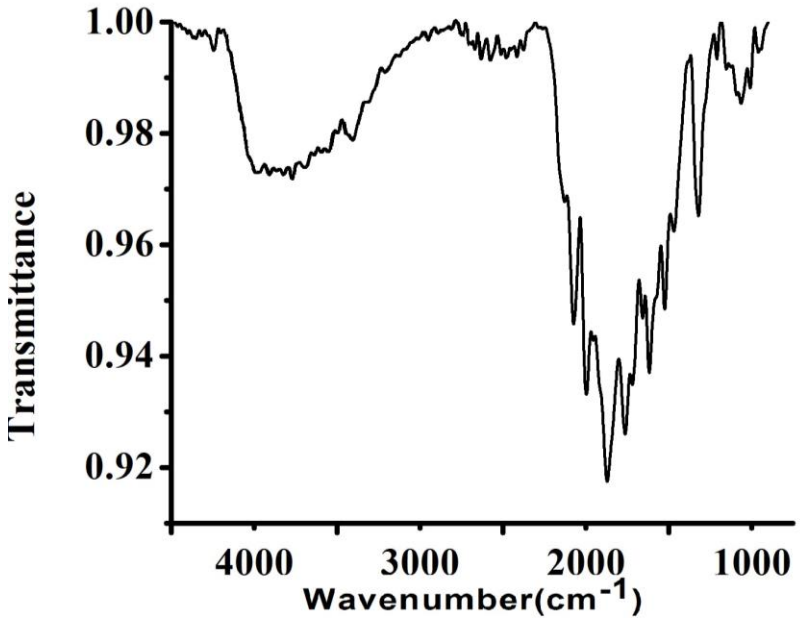


Figure **S11**. IR spectrum of complex **3** in solid phase

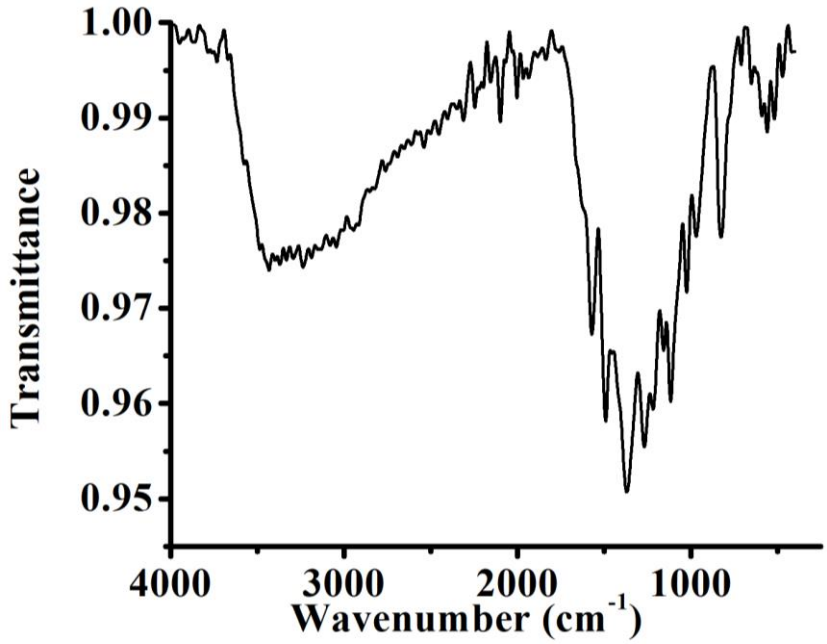


Figure **S12**. IR spectrum of complex **4** in solid phase.

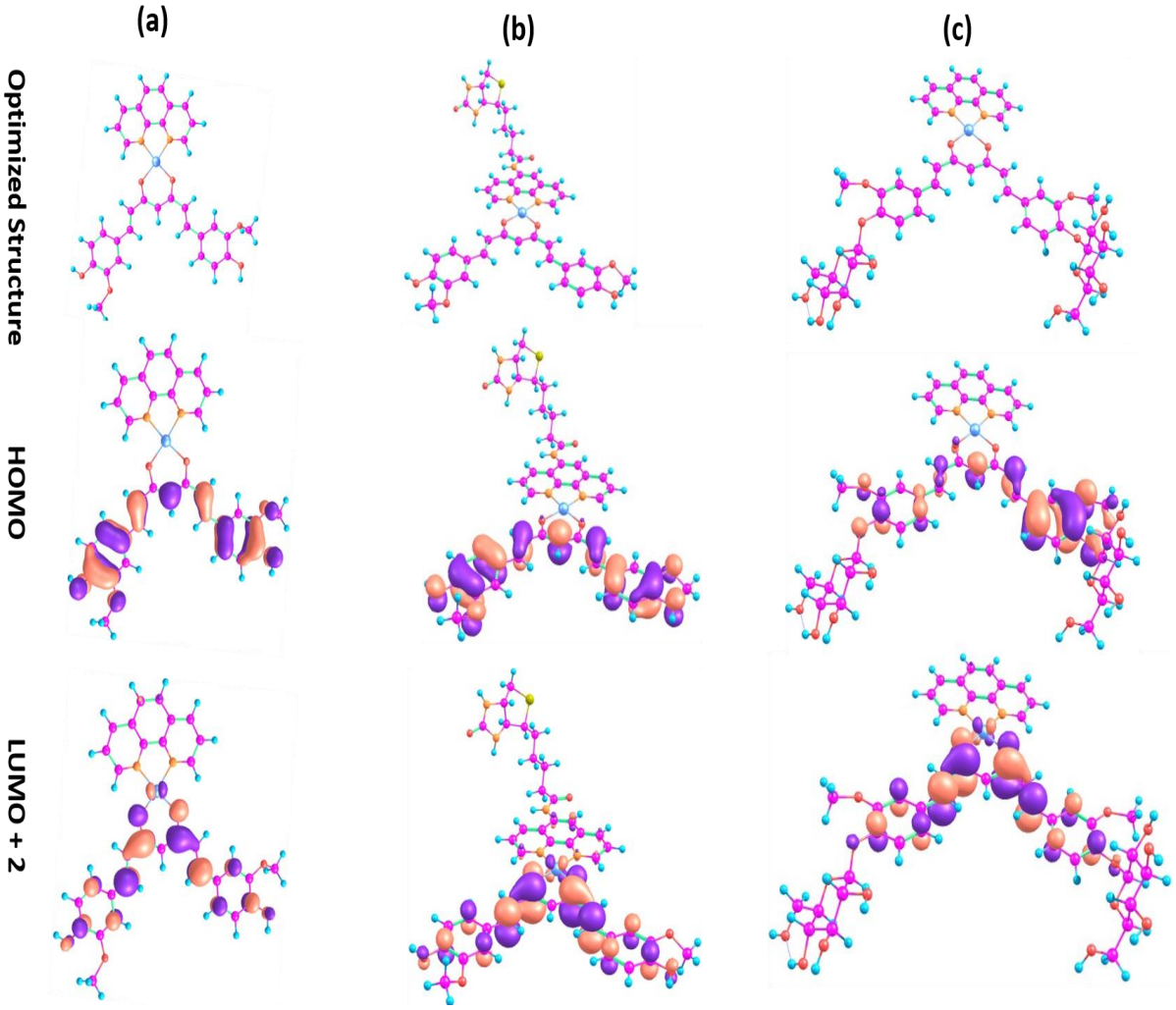


Figure **S13.** Energy minimized structures and frontier molecular orbitals of complexes as obtained from theoretical studies: optimized structure, HOMO and LUMO+2 of **2** (a), **3** (b) and **4** (c). Color codes: Pt, dark blue; O, red; N, orange; C, pink; S, yellow; H, light blue.

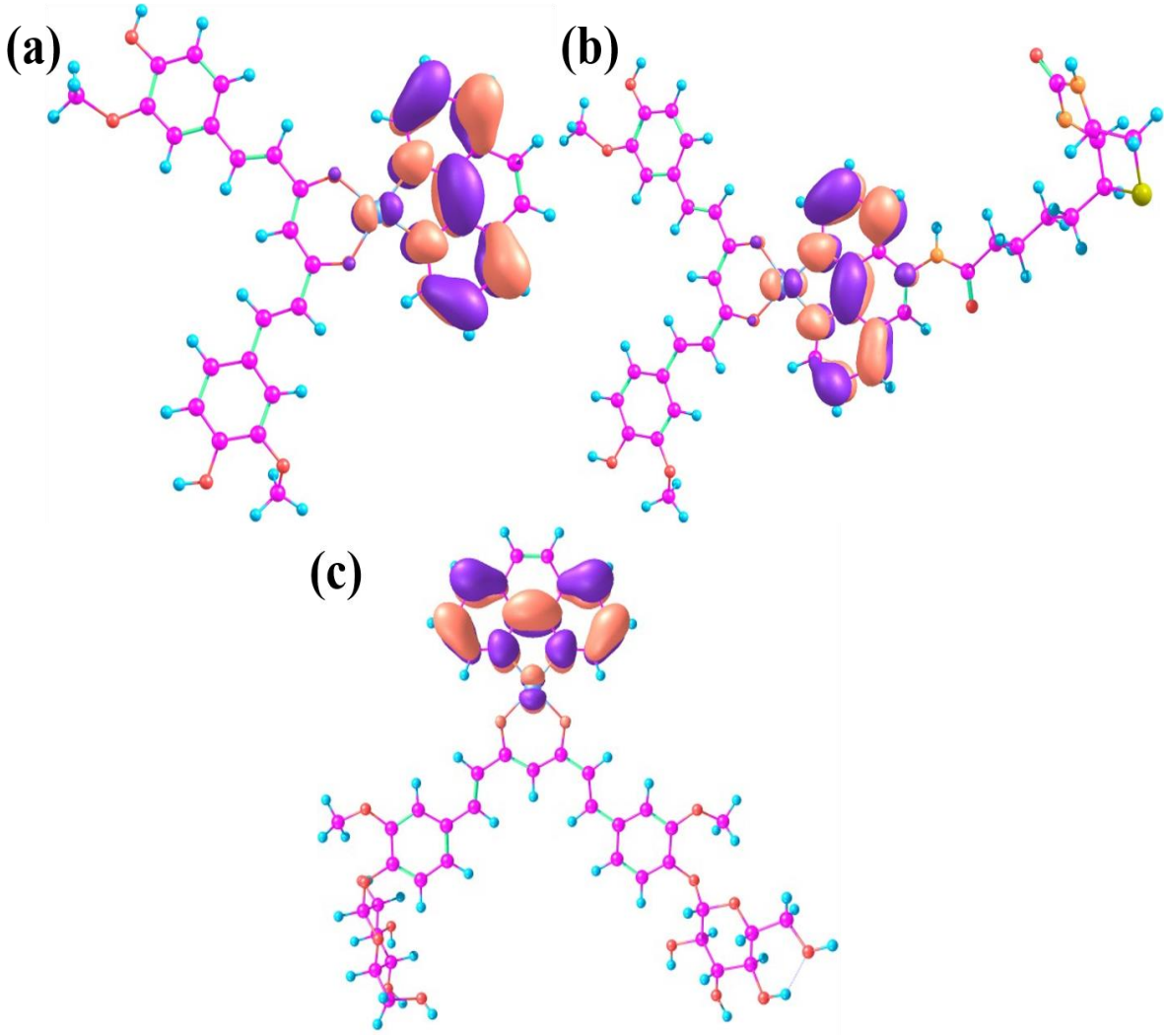


Figure **S14**. Lowest Unoccupied Molecular Orbitals (LUMO) of **2** (a), **3** (b) and **4** (c) as

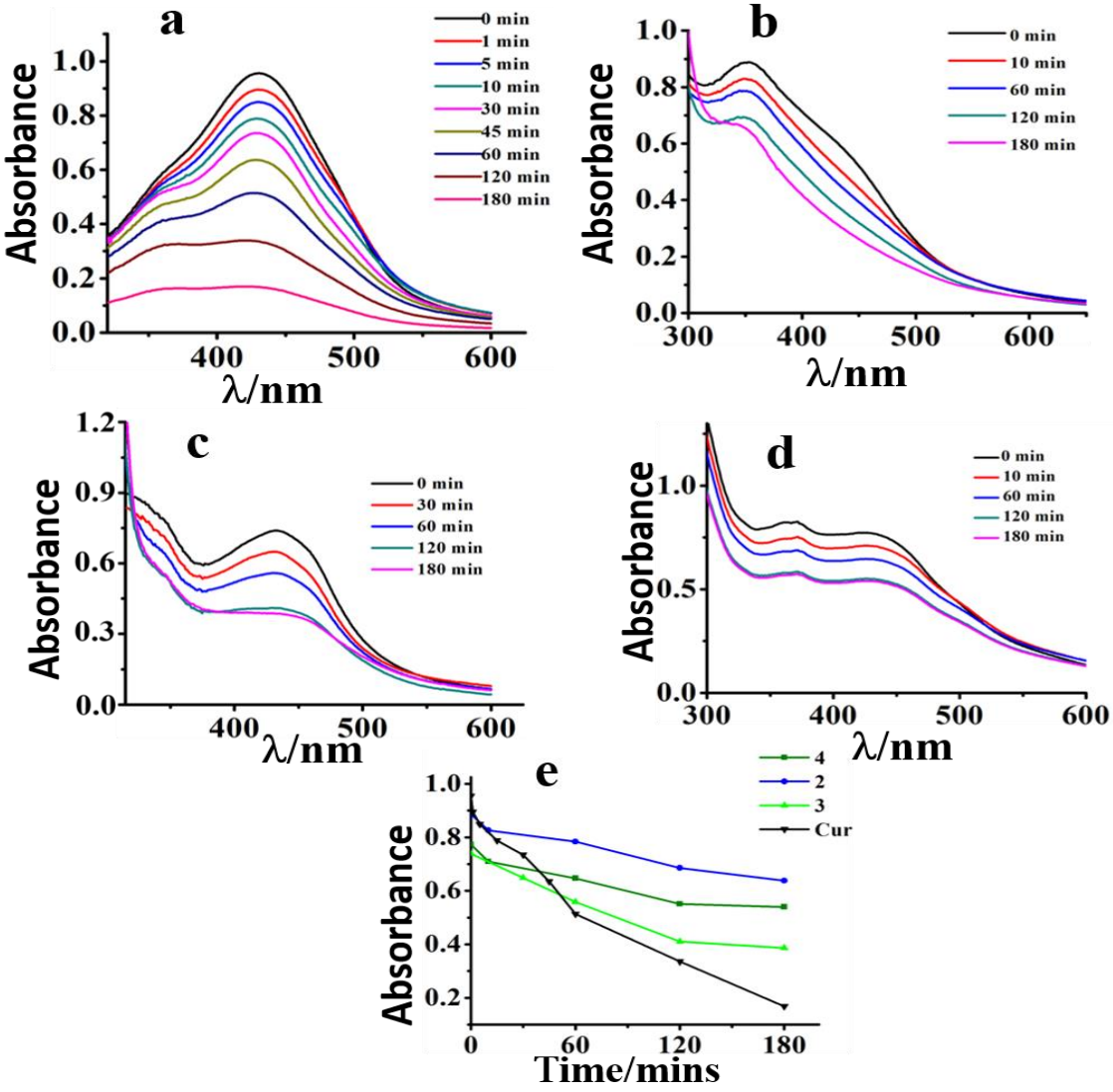


Figure **S15.** Time dependent UV-Vis spectra of complexes HCur (a) , **2** (b), **3** (c), **4** (d) in light (λ = 400-700 nm) in 10% DMSO/DPBS solution. (e) Linear plot of absorbance vs time of irradiation of samples in light. Curcumin is more stable in its complex than in the free form.

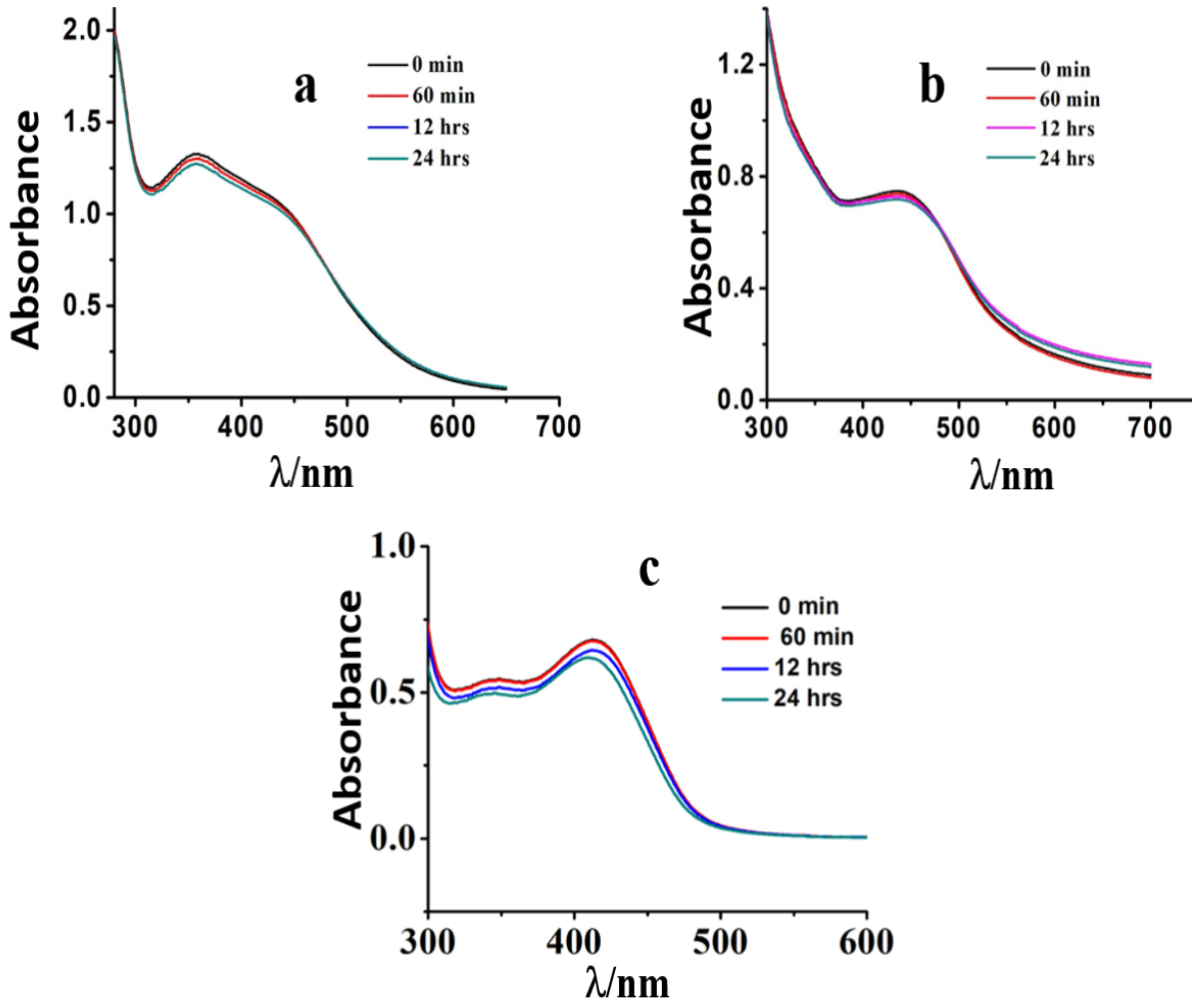


Figure **S16.** Time dependent UV-Vis spectra of complexes **2-4** (a, b, c respectively) in dark in 10% DMSO/DPBS solution.

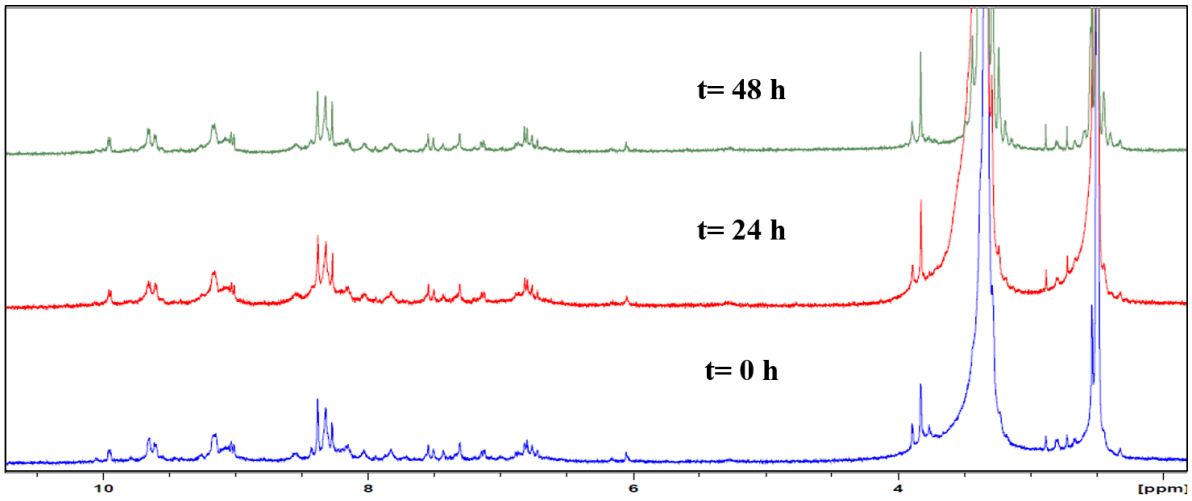


Figure S17. Stability studies on complex **2** at 37 °C in DMSO D_6 in dark as monitored by time dependent ^{1}H NMR spectra. The complexes retain the spectral features over 48 h.

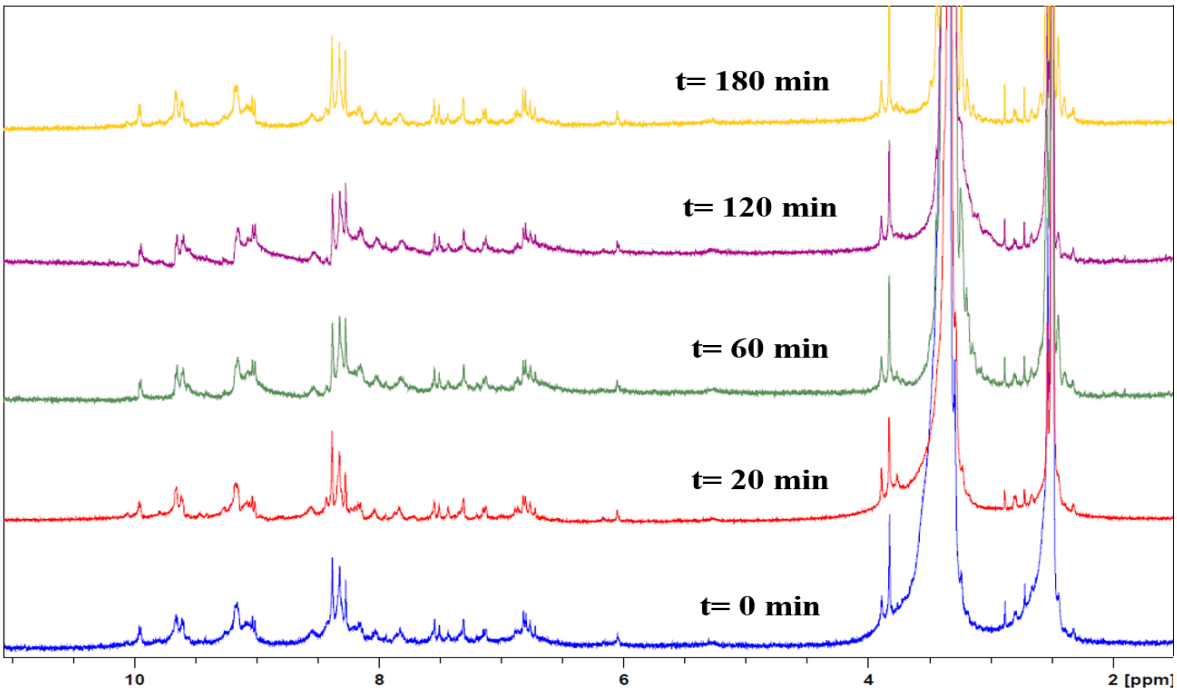
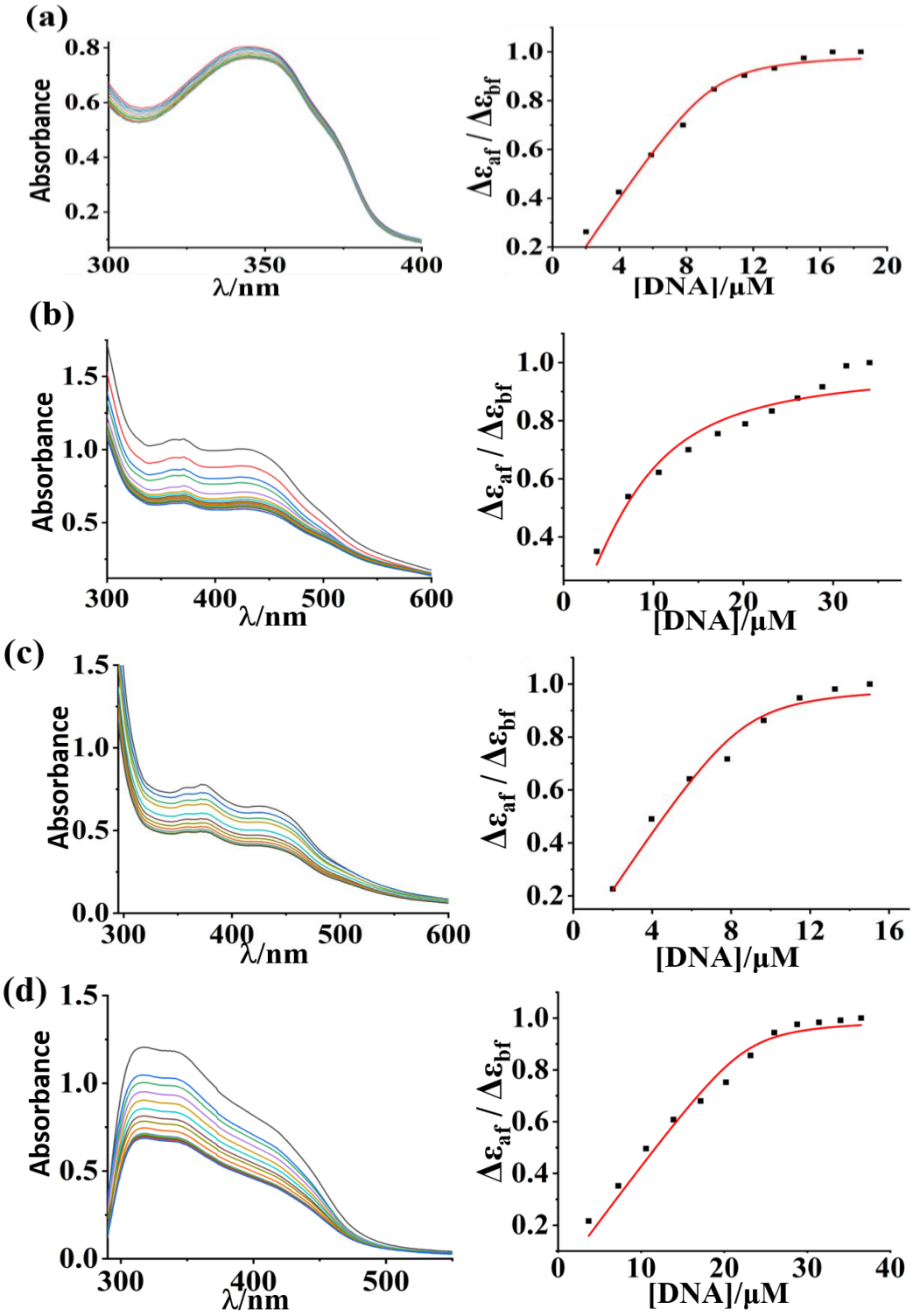


Figure S18. Stability studies of complex **2** at 37 °C in light (400-700 nm) as monitored by time dependent ^{1}H NMR spectra. The complexes retain the spectral features over 3 h.


(a)
Absorbance
λ/nm
$\Delta\varepsilon_{af} / \Delta\varepsilon_{bf}$
[DNA]/μM
(b)
Absorbance
λ/nm
$\Delta\varepsilon_{af} / \Delta\varepsilon_{bf}$
[DNA]/μM
(c)
Absorbance
λ/nm
$\Delta\varepsilon_{af} / \Delta\varepsilon_{bf}$
[DNA]/μM
(d)
Absorbance
λ/nm
$\Delta\varepsilon_{af} / \Delta\varepsilon_{bf}$
[DNA]/μM

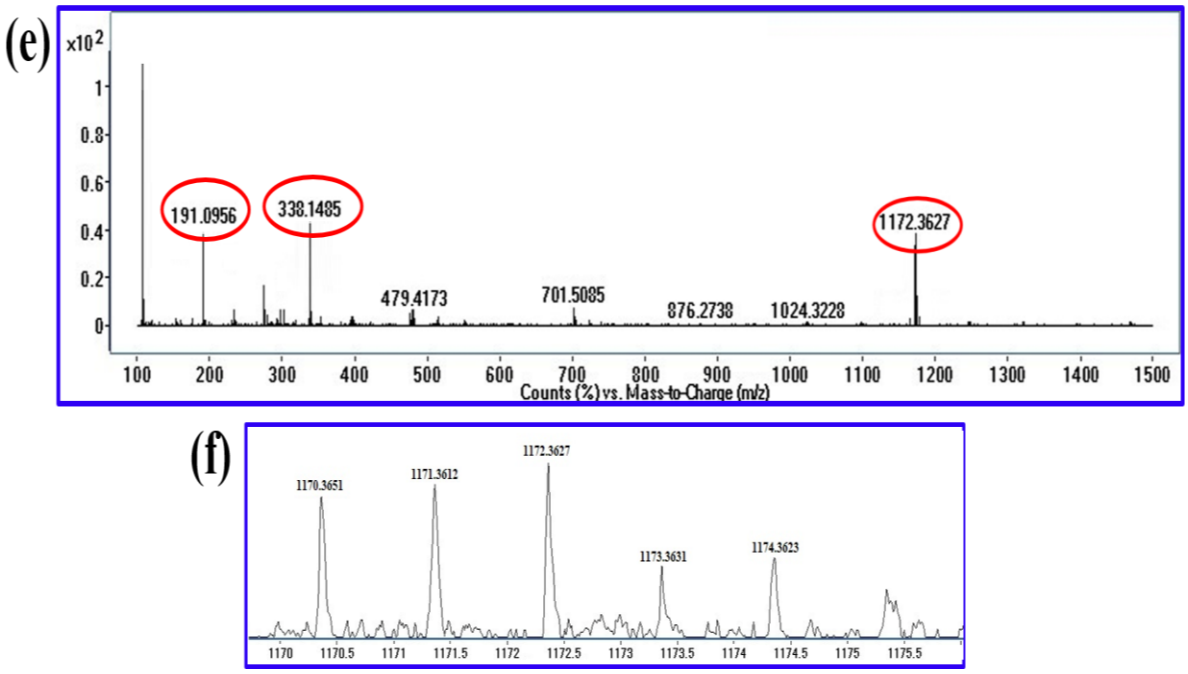


Figure **S19 : (a-d)** UV- visible spectral changes observed for **1** (a), **2** (b), **3** (c) and **4** (d) on gradual addition of ct-DNA (200 μM) to the complexes (20 μM) in 10% DMF-DPBS and their McGhee-von Hippel plot.

(e) Possibility of DNA crosslinking is evidenced from the mass spectrum of a mixture of complex **2** and 2′-deoxyguanosine 5′-monophosphate (in 1:4 concentration in 1:1 H_2O: DMSO) kept in dark for 24 h. The fragment of curcumin as $[C_{20}H_{17}O_5^{\bullet}+H]^+$ is observed at peak 338.1485 (m/z), a fragment of 2′-deoxyguanosine 5′-monophosphate as $[C_5H_4N_5O^{\bullet}+H_2O+Na]^+$ is observed at peak 191.0956 (m/z). The peak 1172.3627 only showed the isotopic distribution indicating presence of platinum. A formulation of $[C_{43}H_{38}KN_7Na_2O_{13}PPt]^+$ with mass of 1171.1345 is close to the observed peak at 1172.3627 (m/z) seems to be based on a mixed ligand complex having Pt(II) bound to chelating phen, neutral monodentate deoxy-GMP and monodentate and monoanionic curcumin. (f) Isotopic distribution of the platinum adduct.

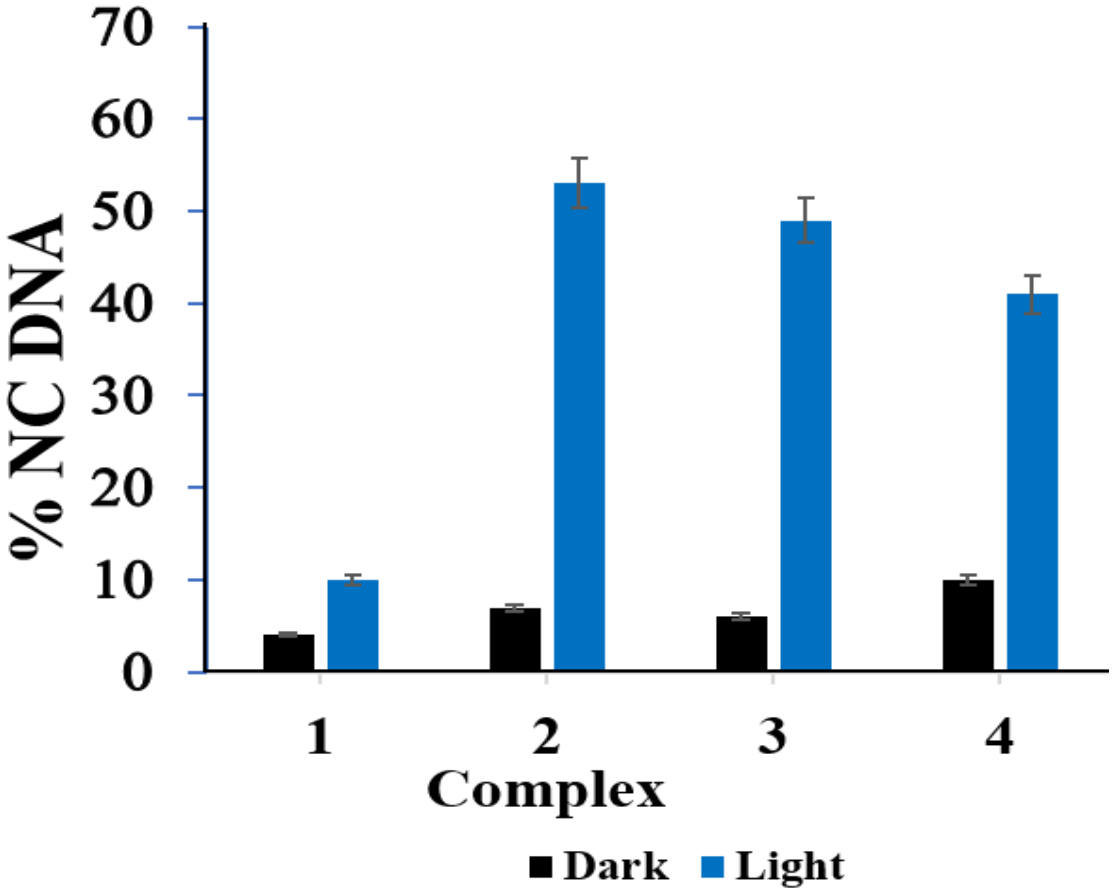


Figure. **S20:** Bar diagram showing photo-induced pUC19 DNA (0.2 μg, 30 μM b.p.) cleavage in Tris-HCl buffer by **1**–**4** (30 μM) in blue light of 446 nm (blue bars) and in the dark (black bars) (NC is nicked circular).

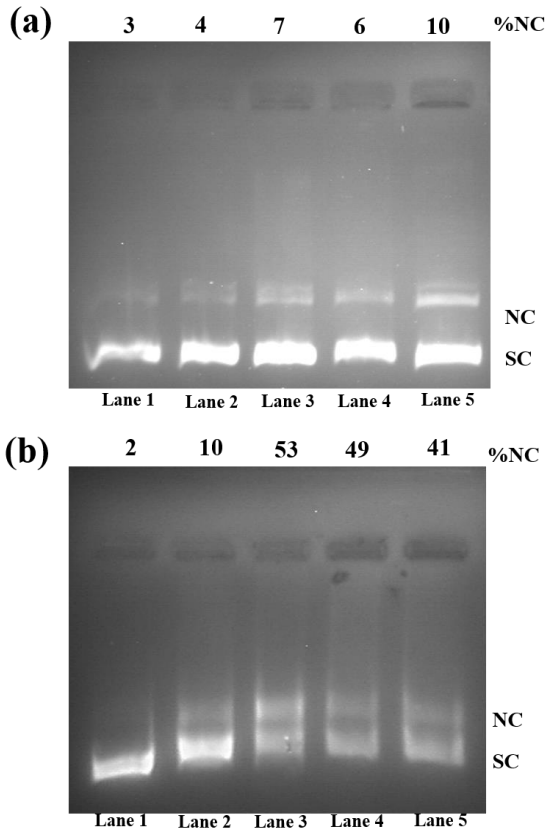


Figure **S21**: (a) Gel diagram showing DNA cleavage upon treatment with complexes **1**-**4** (30 μM) in dark: lane 1, DNA control (dark); lanes 2-5, DNA + complexes **1**-**4** (in dark). (b) Gel diagram showing DNA cleavage upon treatment with complexes **1**-**4** (30 μM) in light (446 nm, 1 h): lane 1, DNA control (light); lanes 2-5, DNA + complexes **1**-**4** (light). NC is Nicked Circular DNA.

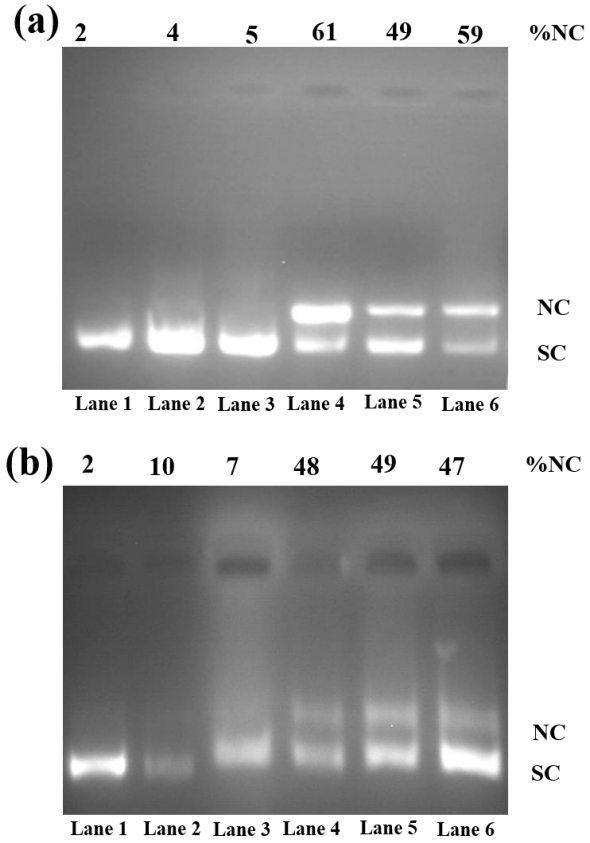


Figure **S22** : (a) Gel diagram showing mechanistic data on DNA cleavage upon treatment with complex **3** (30 μM) in light (446 nm, 1 h): lane 1, DNA control ; lanes 2-5 are for the complex in the presence of various additives: lane 2, KI (8 μL, 4 mM); lane 3, DMSO (8 μL); lane 4, TEMP (8 μL, 4 mM); lane 5, NaN_3 (8 μL, 4mM); lane 6, SOD (8 units) (b) Gel diagram showing mechanistic data for complex **4** (30 μM) in light (446 nm, 1 h): lane 1, DNA control ; lanes 2-5, are for the complex in the presence of various additives: lane 2, KI (8 μL, 4mM); lane 3, DMSO (8 μL); lane 4, TEMP(8 μL, 4mM); lane 5, NaN_3 (8 μL, 4mM); lane 6, SOD (8 units)

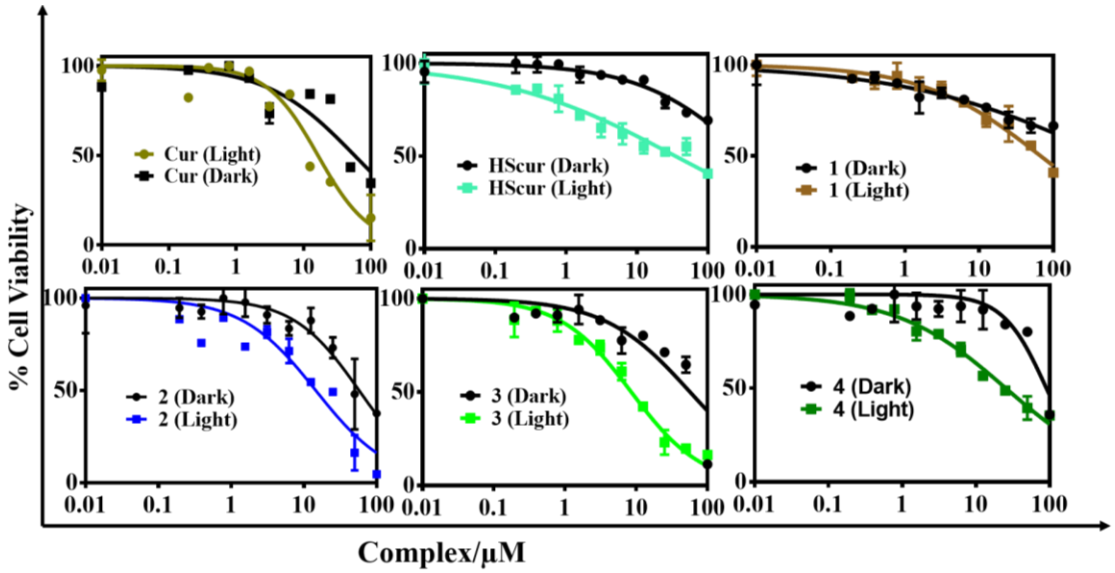


Figure S23. Cell viability plots as obtained from the MTT assay in HeLa cells treated with free ligands HCur, HScur and complexes **1-4** for 4 h initial incubation period in dark. Cells were exposed to visible light (60 min, λ = 400-700 nm, light dose = 10 J cm^{-2}) (black symbols in the dark; colored symbols in visible light).

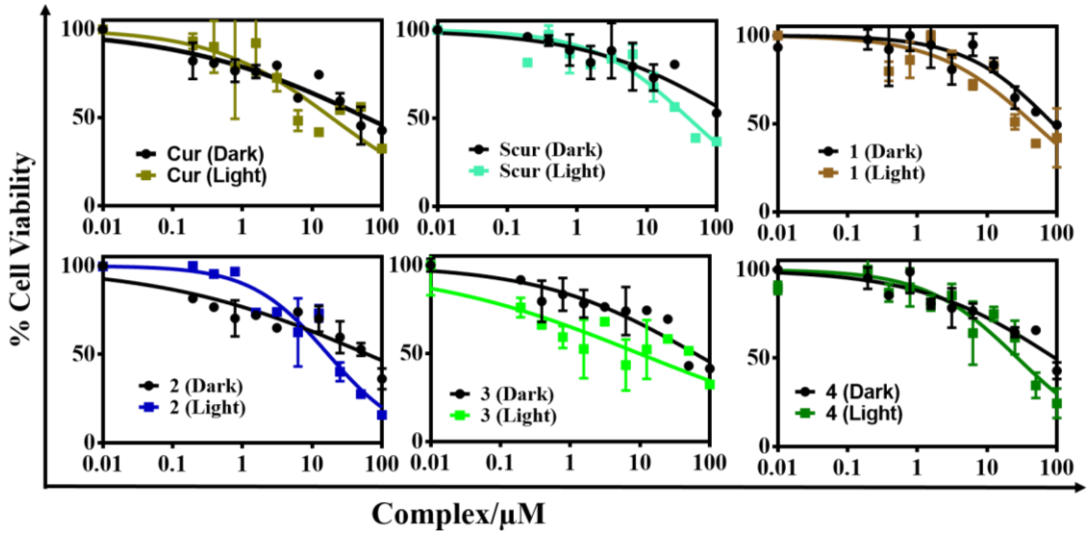


Figure S24. Cell viability plots as obtained from the MTT assay in A549 cells treated with free ligands HCur, HScur and complexes **1-4** for 4 h initial incubation period in dark. Cells were exposed to visible light (60 min, λ = 400-700 nm, light dose = 10 J cm^{-2}) (black symbols in the dark; colored symbols in visible light).

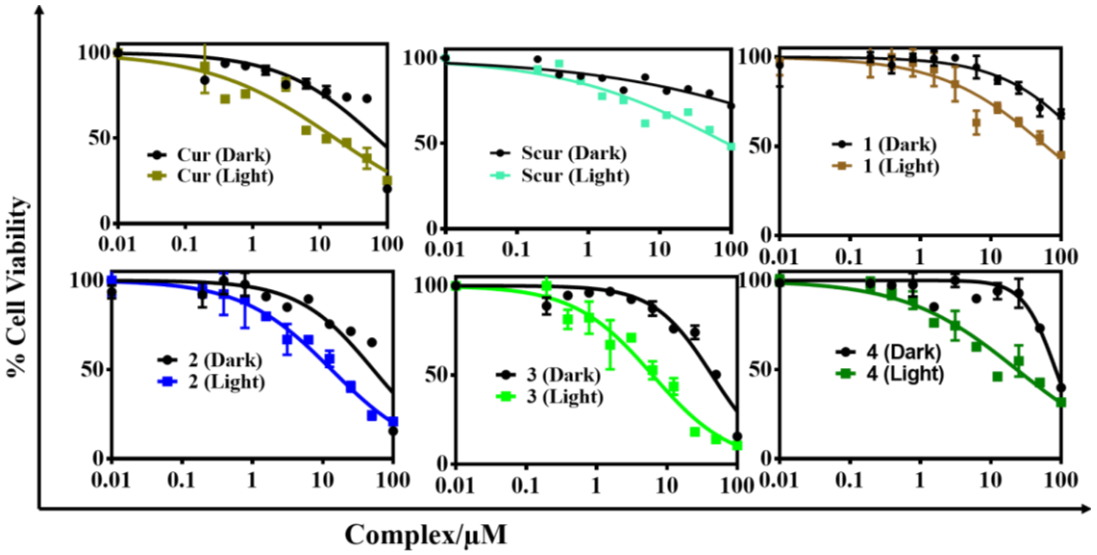


Figure S25. Cell viability plots as obtained from the MTT assay in HepG2 cells treated with free ligands HCur, HScur and complexes **1-4** for 4 h initial incubation period in dark. Cells were exposed to visible light (60 min, λ = 400-700 nm, light dose = 10 J cm^{-2}) (black symbols in the dark; colored symbols in visible light).

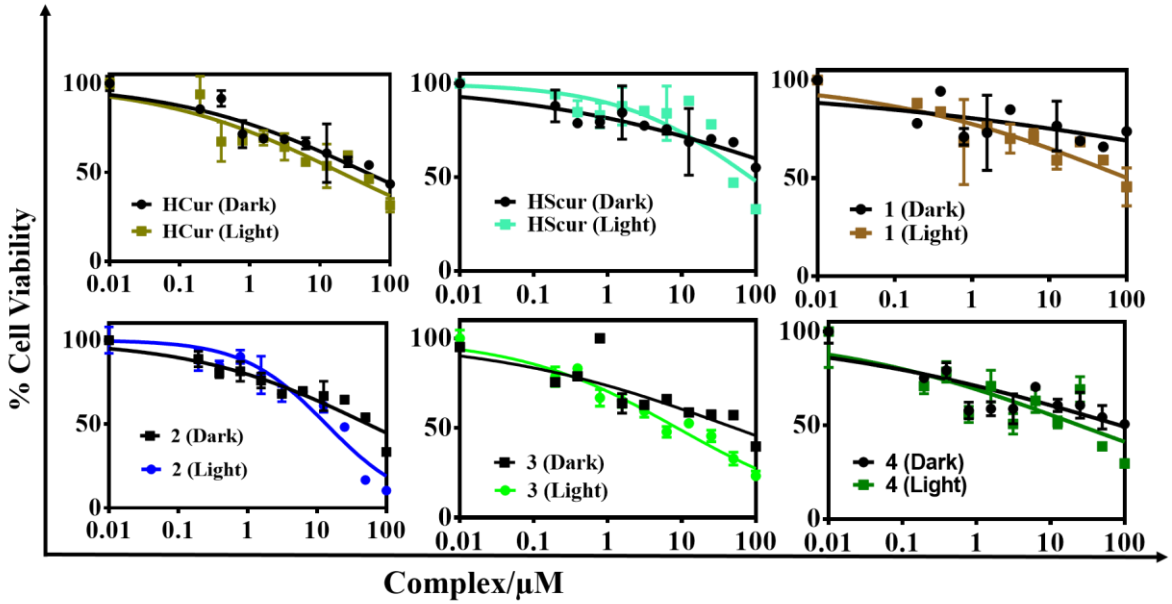


Figure S26. Cell viability plots as obtained from the MTT assay in MDA-MB231 cells treated with free ligands HCur, HScur and complexes **1-4** for 4 h initial incubation period in dark. Cells were exposed to visible light (60 min, λ = 400-700 nm, light dose = 10 J cm^{-2}) (black symbols in the dark; colored symbols in visible light).

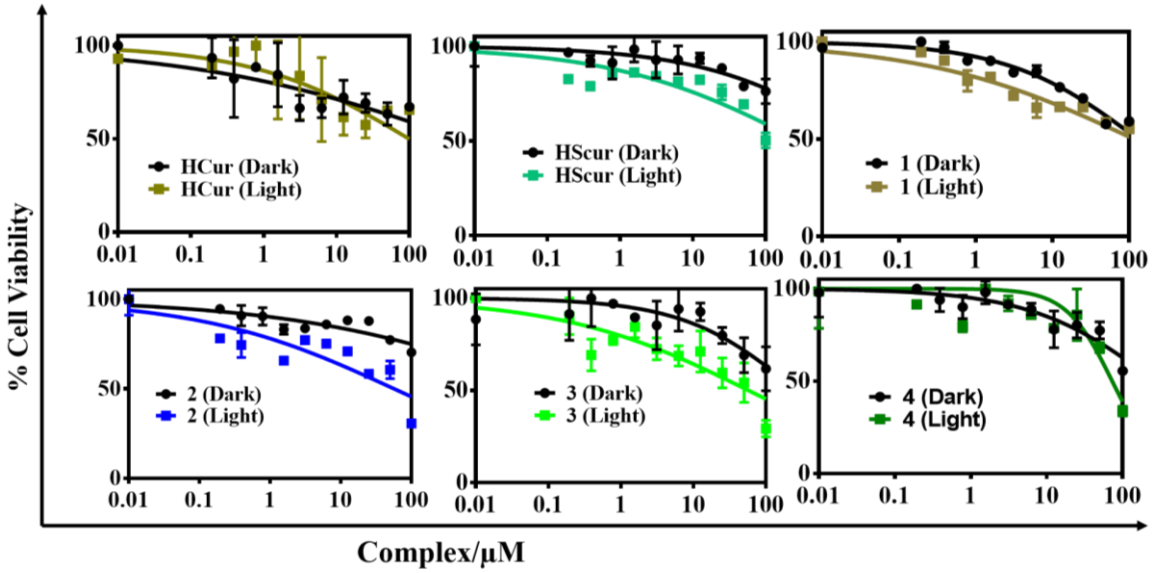


Figure S27. Cell viability plots as obtained from the MTT assay in HPL1D cells treated with free ligands HCur, HScur and complexes **1-4** for 4 h initial incubation period in dark. Cells were exposed to visible light (60 min, λ = 400-700 nm, light dose = 10 J cm^{-2}) (black symbols in the dark; colored symbols in visible light).

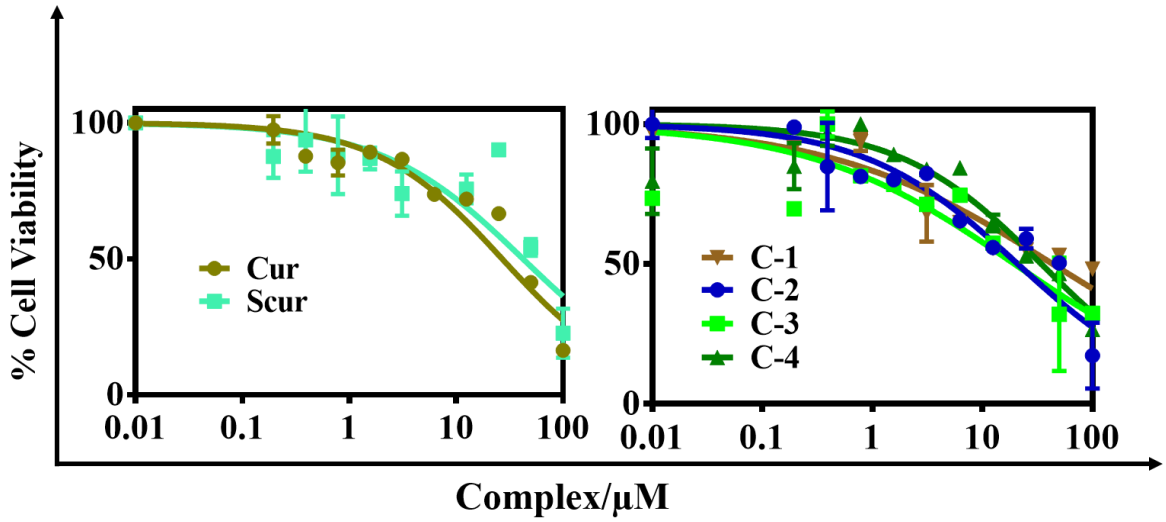


Figure S28. Cell viability plots as obtained from the MTT assay in HeLa cells treated with free ligands HCur, HScur and complexes **1-4** for 24 h incubation period in dark.

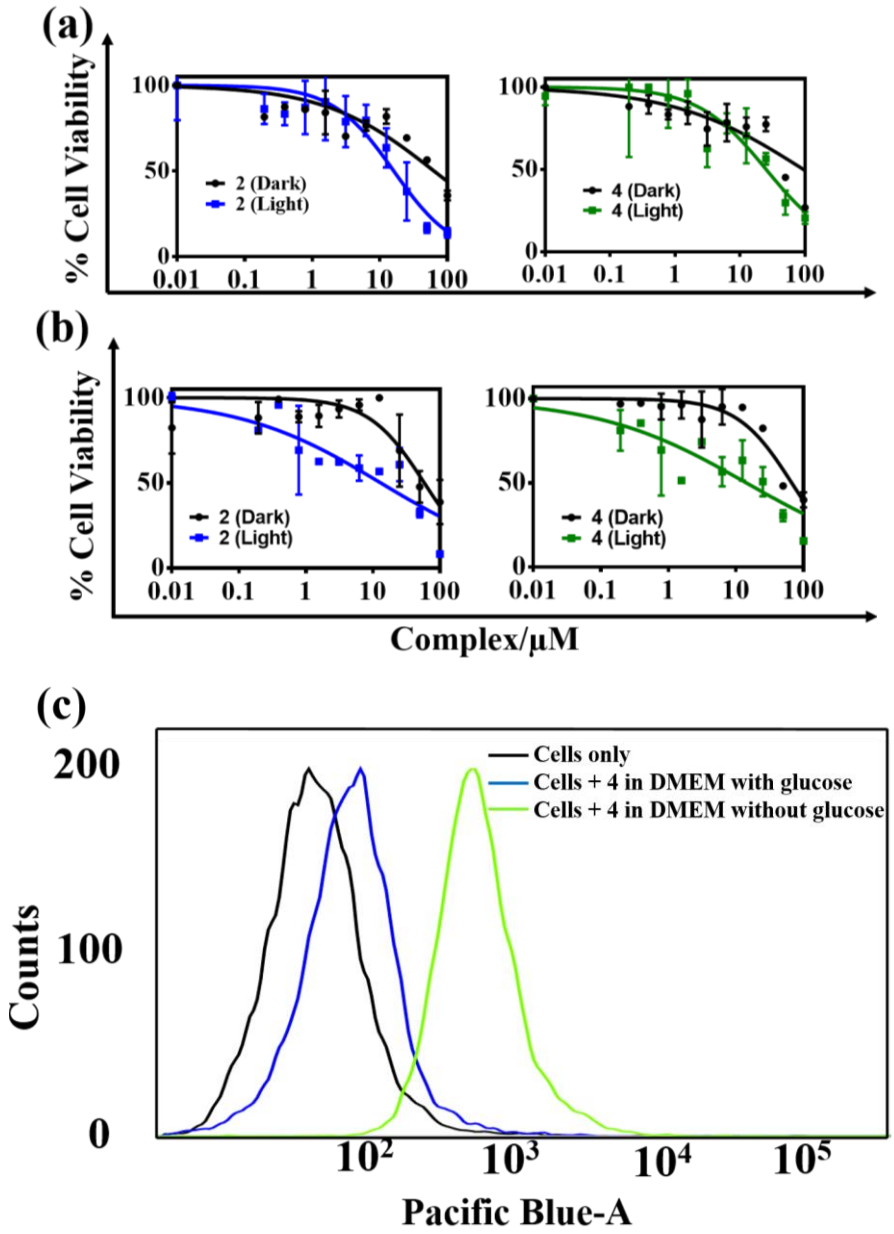


Figure. **S29**: (a) Cell viability plots obtained by MTT assay of complexes **2** and **4** treated in HeLa cells for 4 h initial incubation period in DMEM containing glucose (4500mg/L) in dark. Cells were exposed to visible light (60 min, λ = 400-700 nm, light dose = 10 J cm^{-2}). (b) Cell viability plots obtained by MTT assay of complexes **2** and **4** treated in HeLa cells for 4 h initial incubation period in DMEM without glucose in dark. Cells were exposed to visible light (60 min, λ = 400-700 nm, light dose = 10 J cm^{-2}) (black symbols in the dark; colored symbols in visible light). (c) The data from cellular uptake study on complex **4** (10 μM) in HeLa cells in high glucose (blue) and low glucose DMEM (green). The reduced uptake of complex **4** in high glucose medium (blue) is due to the presence of glucose moieties in the complex.

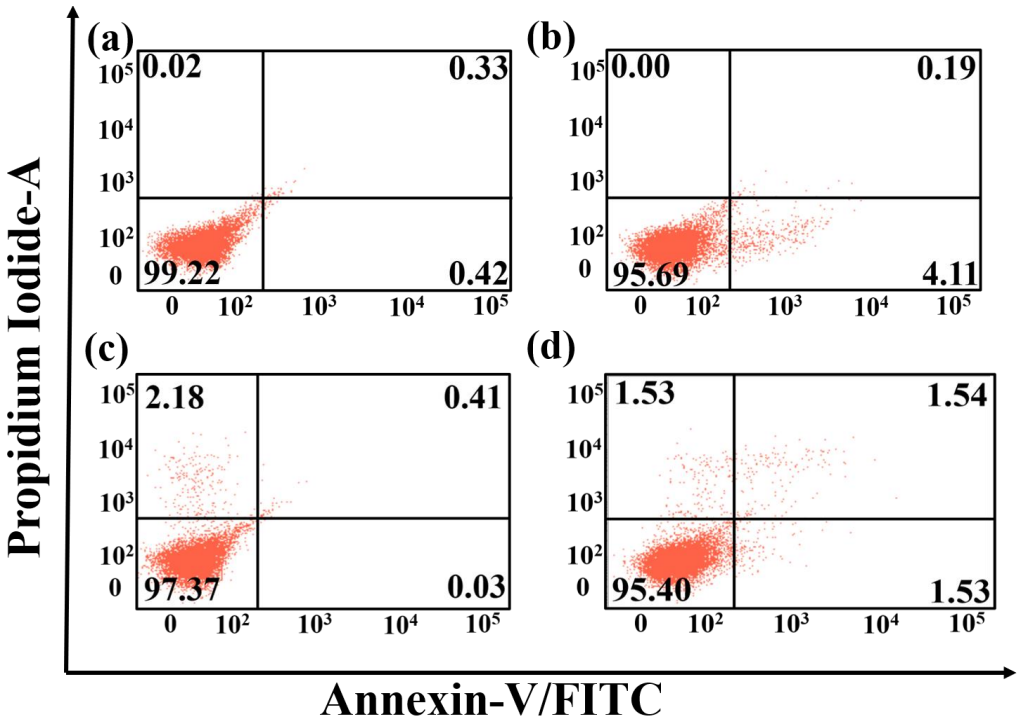


Figure **S30**: AnnexinV-FITC/PI assay in HeLa cells (a) cells alone; (b) cells + annexinV-FITC; (c) cells + PI and (d) cells + PI + annexinV. The % cell population is shown in respective quadrants. [lower left: live cells, lower right: early apoptotic cells, upper right: late apoptotic cells, upper left, dead cells].

Table S1. **Coordinates for Optimized Geometry of Complexes 2-4 obtained from DFT Calculations using B3LYP/LANL2DZ Level of Theory for All Atoms.**

Complex **2**

Pt	-2.09667200	-0.59405300	0.00908400
O	-0.43308500	-1.73017300	-0.01526200
O	-1.04991600	1.12520800	0.01503000
C	0.81557500	-1.25594300	-0.02488800
C	0.28293000	1.20962000	0.00828000
C	1.14487700	0.10535300	-0.01405300
H	2.19787500	0.33366100	-0.03037600
C	1.80884600	-2.32013500	-0.05071400
H	1.36801900	-3.30786600	-0.06447100
C	0.74662800	2.58861900	0.02221500
H	-0.06279800	3.30570000	-0.00302000
C	3.15486100	-2.16937600	-0.05931000
H	3.56763900	-1.16610500	-0.04279700
C	2.03244600	3.01173300	0.07713100
H	2.82609800	2.27283500	0.12051300
C	2.50236300	4.38882100	0.09792900
C	1.63855600	5.49970800	-0.00204800
C	3.88524600	4.63566300	0.21714700
H	0.57055600	5.37952900	-0.10557700
H	4.57606700	3.80585400	0.28543500
C	2.11396400	6.80352700	0.03387600
C	4.37374500	5.93730100	0.25794100
H	5.43692800	6.11481000	0.36424500
C	3.50110600	7.02496100	0.18269200
C	4.16123500	-3.22094800	-0.09134900
C	5.52115800	-2.84974800	-0.08447300

C	3.85253300	-4.59733300	-0.12359400
H	5.81048400	-1.80830600	-0.05741700
H	2.82543100	-4.93237200	-0.12208800
C	6.54804300	-3.78795500	-0.12387300
C	4.86836100	-5.54274100	-0.16469300
H	4.62394800	-6.59760500	-0.20164900
C	6.21372700	-5.15449300	-0.17972400
O	7.24997800	-6.07297700	-0.26313700
H	6.93085000	-6.98871900	-0.32805000
O	3.93818500	8.33823500	0.26090500
H	4.89922900	8.40295100	0.39163100
O	7.84084200	-3.29198100	-0.18963800
O	1.16461800	7.81477300	0.00416900
C	8.91261300	-3.89282500	0.61997400
H	9.74465500	-3.20404300	0.51922100
H	8.60611900	-3.95701400	1.66533600
H	9.17642500	-4.87545200	0.24439000
C	1.36284500	8.99463400	-0.85282500
H	0.41009500	9.51274200	-0.82360000
H	2.15690900	9.62405800	-0.46626000
H	1.58794500	8.68582500	-1.87505500
C	-5.39579400	2.22613600	0.06899000
C	-6.49270500	1.37864800	0.06883200
C	-6.29396500	-0.02345300	0.05166700
C	-4.96106600	-0.47915700	0.03518500
C	-4.09093400	1.70206700	0.05162700
C	-7.34026800	-1.01282500	0.05035400
C	-4.66504300	-1.86746600	0.01913800
C	-5.69654700	-2.82710900	0.01879300
C	-7.05520100	-2.35053600	0.03464000
C	-5.30680100	-4.18832300	0.00327600

H	-6.05983900	-4.96399600	0.00237700
C	-3.95974000	-4.51499300	-0.01038200
C	-2.98182500	-3.50466700	-0.00920300
H	-8.36779200	-0.67671600	0.06243900
H	-5.52654700	3.29725600	0.08262600
H	-7.49644700	1.77994700	0.08208700
H	-3.20420400	2.31661000	0.05119600
H	-7.85633700	-3.07653800	0.03418800
H	-3.64313600	-5.54660800	-0.02215600
H	-1.92168900	-3.70422300	-0.01961400
N	-3.88535200	0.37734500	0.03481600
N	-3.33345800	-2.21096300	0.00518400

Complex **3**

Pt	-1.54865700	-0.53435700	-0.31699800
O	-2.45347600	1.26793200	-0.25673700
O	-3.27949200	-1.52310600	-0.03195100
C	-3.76459500	1.46014400	-0.09132400
C	-4.47653100	-0.95041000	0.11187400
C	-4.69979500	0.43236000	0.08281900
H	-5.72163500	0.74535700	0.22107400
C	-4.12187200	2.87206800	-0.10395700
H	-3.26265100	3.52416000	-0.18698000
C	-5.53384600	-1.93060300	0.30792600
H	-5.16740400	-2.94817000	0.31870500
C	-5.37230200	3.38829400	-0.04171700
H	-6.21476900	2.70724700	0.01857700
C	-6.85521700	-1.67969200	0.46897200
H	-7.19961000	-0.65059800	0.45567900
C	-7.91392300	-2.65821200	0.66925600
C	-7.68385600	-4.04998500	0.68185500

C	-9.23591000	-2.20527600	0.85449200
H	-6.69619500	-4.46224400	0.53935700
H	-9.44812800	-1.14450300	0.84135600
C	-8.71101100	-4.96135900	0.88610800
C	-10.27328200	-3.10805100	1.06325400
H	-11.28303800	-2.74790700	1.21788100
C	-10.02286300	-4.48152400	1.09574200
C	-5.75039700	4.79439300	-0.05697200
C	-7.12103500	5.12155600	-0.01891700
C	-4.81930800	5.85350600	-0.09912200
H	-7.87411900	4.34658900	0.01698700
H	-3.75771400	5.65385000	-0.11628400
C	-7.57195300	6.43783800	-0.03990400
C	-5.25704700	7.17088900	-0.12001900
H	-4.53696000	7.97933700	-0.16199800
C	-6.62363900	7.47631800	-0.10514100
O	-7.09254000	8.78069600	-0.16621100
H	-6.37358900	9.43112100	-0.23442500
O	-11.01818000	-5.41500200	1.34158100
H	-11.88301400	-5.00176500	1.50318200
O	-8.94534000	6.62343800	-0.07897400
O	-8.35178400	-6.29960800	0.95429800
C	-9.58341000	7.65737300	0.75091700
H	-10.64574500	7.45640500	0.66173600
H	-9.27058600	7.55383300	1.79128200
H	-9.34537000	8.64962900	0.38357500
C	-9.15037100	-7.32077900	0.25803500
H	-8.54992700	-8.22219400	0.32112400
H	-10.10901300	-7.46013200	0.74554100
H	-9.29396500	-7.04089700	-0.78697100
C	-0.01894900	-4.59220000	-0.37548100

C	1.33363900	-4.38125000	-0.58418900
C	1.82573600	-3.05633700	-0.71194000
C	0.88112600	-2.01917200	-0.61524300
C	-0.90750100	-3.50408600	-0.28971100
C	3.19814100	-2.71977100	-0.93297100
C	1.29102900	-0.66654600	-0.72818500
C	2.64331600	-0.31986700	-0.94081700
C	3.61202100	-1.40746300	-1.05089400
C	2.92868600	1.06502800	-1.02198600
H	3.93612400	1.42629400	-1.17058200
C	1.90999100	1.99810100	-0.90364700
C	0.58682500	1.58041200	-0.70047000
H	3.93175900	-3.50445000	-1.00877100
H	-0.41115000	-5.59269400	-0.27544200
H	2.01836400	-5.21486800	-0.65062200
H	-1.96827800	-3.61407000	-0.12864000
H	2.12449700	3.05385600	-0.96461900
H	-0.24610800	2.25888600	-0.60297700
N	-0.45811500	-2.24726000	-0.40818500
N	0.29407300	0.27594900	-0.61393600
N	4.95245500	-1.05489400	-1.27903800
C	6.06026100	-1.89955700	-1.37799600
C	7.38000200	-1.20341000	-1.62915700
H	7.24875300	-0.12158000	-1.72294800
H	7.76141800	-1.56333100	-2.58845800
C	8.41610400	-1.50951200	-0.52487100
H	8.02951000	-1.16034700	0.43803900
H	8.53047200	-2.59233400	-0.44471700
C	9.77363000	-0.84281600	-0.80096500
H	10.18084400	-1.22586100	-1.74378700
H	9.62660100	0.23240100	-0.92754300

C	10.78565700	-1.08582200	0.33582600
H	10.37020300	-0.72370400	1.27908700
H	10.93247300	-2.16168600	0.46284500
C	12.15450700	-0.43671600	0.08628100
C	12.27298600	1.07855300	0.28947300
S	13.47050100	-1.03858800	1.32544000
C	12.36006200	1.31190000	1.80934100
C	13.63169500	0.60098700	2.23857600
H	13.68170500	0.39248000	3.30443800
N	11.24195700	2.05973300	-0.07160600
N	12.16953600	2.76292500	1.85952900
H	11.00881500	2.26421900	-1.03004500
H	12.19118200	3.31082300	2.70238300
C	11.34655200	3.16279000	0.80463900
O	10.80269500	4.26614100	0.65577000
H	11.51328800	0.81226100	2.29395200
H	13.23532900	1.38406200	-0.14144400
H	5.15374600	-0.07715000	-1.39696900
O	5.97064400	-3.13425200	-1.25757900
H	12.52559900	-0.72293700	-0.89851600
H	14.52588800	1.13024800	1.91708400

Complex **4**

Pt	-1.43504800	-4.50812000	-0.00160400
O	-2.50147500	-2.80999500	-0.17505500
O	0.31039600	-3.51839200	0.17306000
C	-1.98688300	-1.57754300	-0.16763500
C	0.43903000	-2.18859600	0.15483800
C	-0.62394000	-1.29227700	-0.00961500
H	-0.36013900	-0.24742400	-0.01830800
C	-3.00689700	-0.55634700	-0.34319200
H	-4.00446800	-0.96608500	-0.42396200

C	1.82349300	-1.76841200	0.32062900
H	2.51275100	-2.59966900	0.38430700
C	-2.81348600	0.78217600	-0.42322800
H	-1.80353300	1.17309500	-0.35188600
C	2.27720800	-0.49615700	0.40999000
H	1.56307900	0.31939600	0.36126800
C	3.65867400	-0.06266600	0.57898600
C	4.73982400	-0.95917600	0.65292900
C	3.92564600	1.31904300	0.68862600
H	4.59839900	-2.02696700	0.57699300
H	3.10980600	2.02891900	0.65365800
C	6.05338800	-0.51710200	0.81286200
C	5.22763100	1.77544900	0.85709300
H	5.45131200	2.82651400	0.97610400
C	6.29057100	0.87047000	0.90055900
C	-3.83551400	1.80251000	-0.61063500
C	-3.44137200	3.15356500	-0.70990900
C	-5.20637800	1.50320900	-0.70241700
H	-2.39306100	3.41477600	-0.64931600
H	-5.57336500	0.49074700	-0.62545500
C	-4.38586000	4.15431300	-0.90749800
C	-6.17006000	2.49390100	-0.88826000
C	-5.74584800	3.83868800	-0.99490300
O	-6.72244500	4.80349700	-1.28054300
O	7.60324300	1.32886500	1.08483100
O	7.00708600	-1.51837400	0.82400300
C	8.34296500	-1.34190800	1.41216300
H	8.73749200	-2.35194500	1.46647000
H	8.96428400	-0.71258200	0.78432900
H	8.27084300	-0.91012300	2.40885000
C	1.23883800	-7.90511400	0.38663800

C	0.35535800	-8.97065900	0.31168900
C	-1.02932400	-8.72200900	0.14956700
C	-1.43098100	-7.37386900	0.07216300
C	0.76835300	-6.58266000	0.30216700
C	-2.05205800	-9.73167000	0.05885100
C	-2.79832200	-7.02832300	-0.09006300
C	-3.79121600	-8.02402000	-0.17596200
C	-3.36972300	-9.39865500	-0.09586700
C	-5.12814600	-7.58491400	-0.33496500
H	-5.92778400	-8.30906300	-0.40543900
C	-5.40059900	-6.22728500	-0.39885000
C	-4.35914700	-5.28681600	-0.30750000
H	-1.75772900	-10.77044300	0.11642000
H	2.29744400	-8.07425800	0.51051100
H	0.71561200	-9.98794200	0.37609400
H	1.41211600	-5.71851800	0.35485000
H	-6.41275900	-5.87305800	-0.51982200
H	-4.51596100	-4.22036100	-0.35290900
N	-0.53922300	-6.32981600	0.14794100
N	-3.08809100	-5.68571200	-0.15635700
H	-4.12143300	-10.17304200	-0.16103200
O	-7.46206400	2.02112400	-0.99739800
C	-8.65721100	2.85795100	-0.79672300
H	-8.55743500	3.47690400	0.09084000
H	-8.83264600	3.48074800	-1.66886900
H	-9.45897200	2.13530800	-0.67892500
H	-4.09025600	5.18494600	-1.02381300
C	8.15041200	2.29371300	0.17546100
C	8.52254200	3.56934300	0.91728300
H	7.44125600	2.50085000	-0.63130400
C	9.35244600	4.47847000	0.02435700

H	9.09571800	3.29977900	1.80679500
C	10.16011500	2.49050400	-1.25064700
C	10.58302300	3.77564800	-0.52372700
H	8.74163200	4.80038100	-0.82682700
H	9.58065000	2.76248500	-2.13853200
O	7.28730100	4.23469700	1.28515100
H	7.51091700	5.10669600	1.65911500
O	9.34734000	1.65586100	-0.35329100
O	9.70210300	5.62966500	0.83350900
H	10.27922300	6.21635800	0.31190200
O	11.20646600	4.72499500	-1.42332200
H	11.90553700	4.25800600	-1.92659100
C	-6.74810300	6.07934200	-0.63605600
C	-6.65703900	6.01966300	0.88837800
H	-7.70118000	6.51032100	-0.94432800
C	-6.59544600	7.42860700	1.46831100
H	-5.75128000	5.48527500	1.18440600
C	-5.64431800	8.27193500	-0.66799400
C	-5.45844800	8.22531600	0.85301700
H	-7.54136000	7.94484800	1.26796500
H	-6.61193700	8.72839800	-0.90593200
O	-7.83223800	5.32781100	1.37707600
H	-7.84971200	5.40960400	2.34895900
O	-5.64486400	6.88183500	-1.15948800
O	-6.43012100	7.25584800	2.89893100
H	-6.35563000	8.13310400	3.31553700
O	-5.50999500	9.55474700	1.44230600
H	-4.63085500	9.96752600	1.38367000
H	11.25792900	3.52016700	0.30045300
H	-4.50407200	7.75033700	1.07348500
C	-4.55468600	9.02928700	-1.40118600

H	-4.50060400	8.65207700	-2.42360700
H	-4.80636700	10.09260500	-1.42025400
C	11.32959600	1.59759100	-1.63988700
H	10.97494900	0.76292300	-2.24588000
H	11.80160100	1.21352900	-0.73280800
O	-3.29630600	8.82791700	-0.68761600
H	-2.54306900	9.12756700	-1.22238300
O	12.26017200	2.43629400	-2.39594800
H	13.02257700	1.93114000	-2.71948200

Table S2. Selected TD-DFT singlet transitions for complexes **2-4**.

Complex	Energy/eV	λnm	Oscillator strength (f)	Contribution
2	2.6407	469.52	0.7014	HOMO ⟶ LUMO + 2 (70%)
	2.7927	443.96	0.0181	HOMO - 3 ⟶ LUMO (67%)
	2.8804	430.44	0.2318	HOMO - 1 ⟶ LUMO + 2 (65%)
	3.1976	387.75	0.1043	HOMO - 4 ⟶ LUMO + 1 (64%)
	3.3886	365.88	0.0031	HOMO - 6 ⟶ LUMO (65%)
	3.4433	360.07	0.0952	HOMO - 3 ⟶ LUMO + 2 (57%)
3	2.3107	536.57	0.0416	HOMO ⟶ LUMO + 1 (70%)
	2.5388	488.35	0.0259	HOMO - 1 ⟶ LUMO (69%)
	2.6540	467.16	0.1781	HOMO - 3 ⟶ LUMO (62%)
	2.6559	466.83	0.6112	HOMO ⟶ LUMO + 2 (65%)
	2.8056	441.92	0.0208	HOMO - 6 ⟶ LUMO (67%)
	2.8777	430.84	0.3206	HOMO - 2 ⟶ LUMO + 2 (51%)
4	2.0877	593.6	0.0234	HOMO ⟶ LUMO + 1 (69%)
	2.5312	489.83	0.4114	HOMO ⟶ LUMO + 2 (65%)
	2.5455	487.06	0.0266	HOMO - 3 ⟶ LUMO (61%)
	2.5910	478.53	0.0981	HOMO - 2 ⟶ LUMO + 1 (63%)
	2.9159	425.21	0.2451	HOMO - 4 ⟶ LUMO (62%)
	2.9931	414.23	0.3547	HOMO - 2 ⟶ LUMO + 2 (68%)
	3.3170	373.78	0.1376	HOMO - 3 ⟶ LUMO + 2 (57%)

Table S3. MTT Data (IC_{50}/μM) of free ligands, Hcur and HScur

Cells	Hcur	Hscur
HeLa L[a]	16.4 ± 0.2	34.7 ± 1.1
HeLa D[a]	57.1 ± 1.2	>100
A549 L[a]	19.0 ± 0.1	39.7 ± 0.2
A549 D[b]	61.4 ± 0.4	>100
HepG2 L[a]	16.8 ± 0.4	40.2 ± 0.8
HepG2 D[b]	70.2 ± 1.3	>100
MDA-MB-231 L[a]	19.0 ± 0.6	39.7 ± 0.8
MDA-MB-231 D[b]	61.4 ± 0.8	>100
HPL1D La	98.8 ± 0.7	>100
HPL1D D[b]	>100	>100
HeLa D[c]	27.0 ± 0.4	42.29 ± 1.4

[a] IC_{50} values (μM) were for 1 h light (λ= 400-700 nm) irradiated cells after 4 h incubation in dark and post incubation of 19 h in dark. [b] In dark (D) with 4 h of preincubation of treated cells followed by replacement of culture media and further post incubation of 20 h. [c] In dark (D) with 24 h of preincubation of treated cells (chemotherapeutic activity) [d] platinum content (ng per 1 x 10^6 cells) estimated by ICP-MS in HeLa cells, treated with **1**-4 followed by incubation of 4 h.

Table S4. MTT Data (IC_{50}/μM) of 2 and 4 in DMEM with and without glucose in HeLa cells

Complexes	D/L	With Glucose [c]	Without Glucose [d]
2	L[a]	16.1 ± 0.2	13.1 ± 0.6
	D[b]	63.6 ± 0.5	58.6 ± 0.4
4	L[a]	25.3 ± 0.3	14.3 ± 1.2
	D[b]	95.1 ± 1.3	67.0 ± 0.8

[a] IC_{50} values (μM) were for 1 h light (λ= 400-700 nm) irradiated cells after 4 h incubation in dark and post incubation of 19 h in dark. [b] In dark (D) with 4 h of preincubation of treated cells followed by replacement of culture media and further post incubation of 20 h. [c] 4 h of preincubation of treated cells in DMEM (Dulbecco's Modified Eagle Medium) with glucose (4500 mg/L). [d] 4 h of preincubation of treated cells in DMEM (Dulbecco's Modified Eagle Medium) without glucose followed by replacement of the media with glucose (4500 mg/L) containing DMEM.

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