Electronic supplementary information for publication

# Potent and selective PTP1B inhibition by a platinum(II) complex: Possible implications for a new antitumor strategy †

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**Fig. S12** Effects of different concentration of cisplatin on phosphorylation levels of several PTPs substrates. From left to right, lane 1: control; lane 2-5: complex 1(1, 10, 50 and 100 μM)

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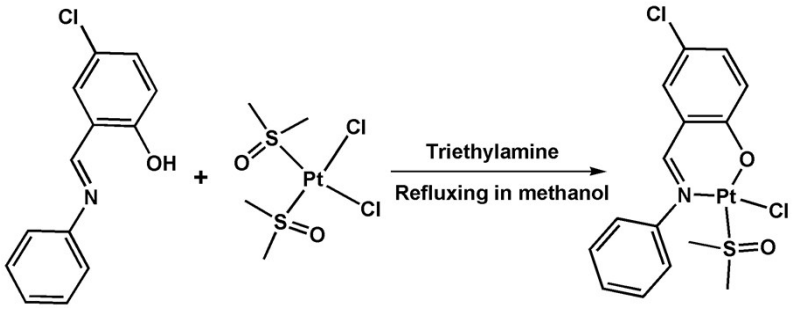
**S1. Materials and measurements**

All chemicals used in the experiments were purchased commercially and used without further purification. Double distilled water was used to prepare all aqueous solutions. Elemental analyses for C, H, and N were carried out with a VARI-EL elemental analyzer. IR spectra were obtained on a BRUKER TENSOR27 spectrometer with KBr disks. Electrospray ionization mass spectrum (ESI-MS) was recorded on a Quattro Micro API in DMSO/methanol/aqueous solution. The electronic spectra were recorded on a Hewlett-Packard HP-8453 Chemstation. Fluorescence emission spectra were recorded using VARIAN-CRAY Eclipse fluorescence spectrophotometer and HORIBA fluoromax-4 spectrofluorometer. Bioactivity assays of the complexes were carried out on a Bio-RAD model 550 microplate reader for $IC_{50}$. Apoptosis of MCF7 cells were determined on FC 500 flow cytometer.

**S2. Synthesis and characterization of [PtL(DMSO)Cl] (1)**

The precursor complex $[Pt(DMSO)_2Cl_2]$ (DMSO = dimethyl sulfoxide) and ligand HL were prepared as described in the literature. [S1] 75 μL triethylamine (0.5 mmol) was added dropwise to a stirring solution of HL (0.5mmol) in 20 mL of methanol and the ligand was dissolved completely after several minutes. Then, 10mL methanol solution of $Pt(DMSO)_2Cl_2$ (0.5 mmol) was added dropwise to this mixture. The reaction mixture was refluxed at 338 K for 2.5 h under a nitrogen atmosphere and then cooled slowly. Filtration was kept at room temperature in two weeks. The yellow crystals were obtained, filtered off and then dried in vacuum desiccator. (Yield 59%). Anal. Calcd for $C_{15}H_{15}Cl_2NO_2PtS$ (%): C, 33.40; H, 2.80; N, 2.60; Found：C, 33.58; H, 2.85; N, 2.56。IR($cm^{-1}$): 3433, 1608, 1458,1305, 1126, 712; UV-vis in DMSO-MOPS (λ/nm): 409, 370, 287。ESI-MS: m/z, 540.0; calcd. $[\mathbf{1}+H]^+$ 540.3.




**Scheme S1** The synthesis diagrams of complex [PtL(DMSO)Cl] **1**

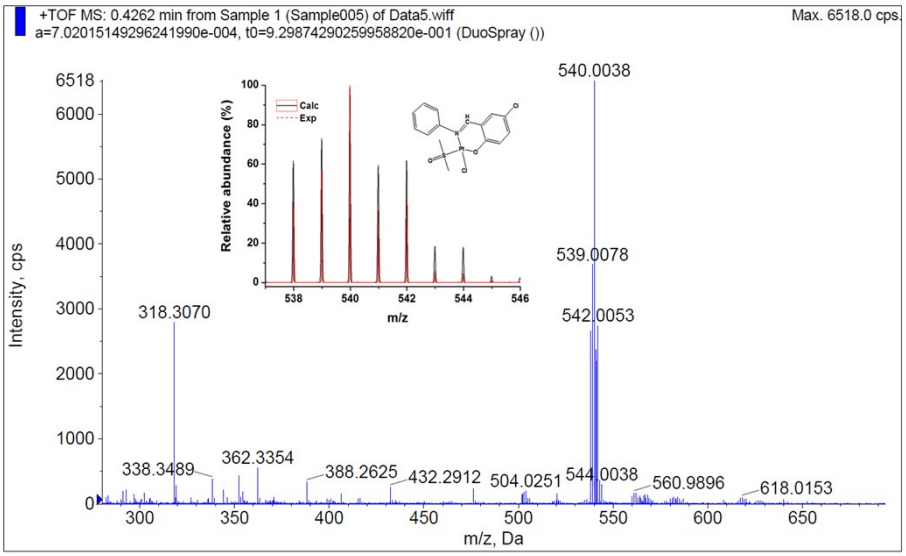
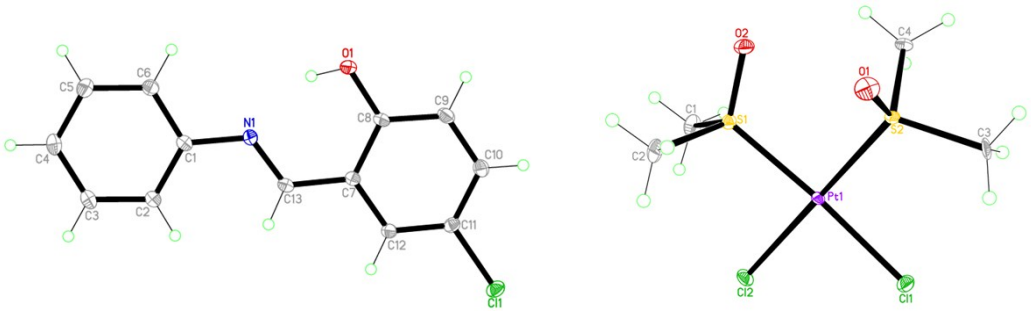



**Fig. S1** The ESI-MS spectrum of **1** in DMSO-acetonitrile solution, inset for experimental and simulation isotopic distribution patterns at the observed peaks (m/z: 539.0078, 540.0038, 542.0053 and 544.0038)

Single-crystal X-ray diffraction data of **1**, $[Pt(DMSO)_2Cl_2]$ and HL were collected in Beijing Synchrotron Radiation Facility (BSRF) beamline 1W2B which mounted with a MARCCD-165 detector with storage ring working at 2.2 GeV. Proper single crystal size was selected for the data collection. In the process, the crystal was protected by liquid nitrogen at 100 K. The data were collected by the program marccd and processed using HKL 2000. The crystal structures for the ligand and the precursor complex were showed in Figure S2 and detailed crystallographic data and structure refinement parameters are summarized in Table S1. The Selected bond lengths (Å) and angles(°) for complex **1** was listed in table S2.[S2]




(a) (b)

**Fig. S2** ORTEP view with 30% probability level of ligand HL (a) and $Pt(DMSO)_2Cl_2$ (b)

**Table S1** Crystallographic data and structure refinement for **1**, ligand HL, and $Pt(DMSO)_2Cl_2$

| | **1** | HL | $Pt(DMSO)_2Cl_2$ |
|---|---|---|---|
| Chemical formula | $C_{15}H_{15}Cl_2NO_2PtS$ | $C_{13}H_{10}ClNO$ | $C_4H_9Cl_2O_2PtS_2$ |
| CCDC | 1580462 | 1580460 | 1580461 |
| Crystal system | Orthorhombic | Orthorhombic | Monoclinic |
| *Mr*/g mol$^{-1}$ | 539.33 | 231.67 | 291.62 |
| Wavelength (Å) | 0.720 Å | 0.720 Å | 0.720 Å |

| | | | |
|---|---|---|---|
| Temp (K) | 100(2) K | 100(2) K | 100(2) K |
| Space group | $P2_12_12_1$ | $Pca2_1$ | $P2_1/c$ |
| *a*/Å | 8.8670(18) | 12.202(2) | 8.6060(17) |
| *b*/Å | 12.232(2) | *4.4920(9)* | 13.546(3) |
| *c*/Å | 15.032(3) | 19.311(4) | 9.3530(19) |
| β/º | 90 | 90 | 105.44(3) |
| *V*/Å$^3$ | 1630.4(5) | *1058.5(4)* | 1051.0(4) |
| *Z* | 4 | *4* | 8 |
| $D_x$(g cm$^{-3}$) | 2.197 | 1.454 | 3.686 |
| F(000) | 1024 | 480 | 1008 |
| *h* | −10→0 | −17→17 | −12→0 |
| *k* | −14→14 | 0→6 | −19→19 |
| *l* | 0→17 | −27→27 | −12→13 |
| *θ* Range/° | 2.175-25.049 | 5.278-30.774 | 2.71-30.67 |
| *μ*/mm$^{-1}$ | 9.319 | 0.342 | 14.606 |
| Total refl./ unique refl. | 2907/2906 | 3200/3194 | 3159/3106 |
| $R_1$ [$I>2\sigma(I)$] | 0.0521 | 0. 0316 | 0.0425 |
| GOF | 1.113 | 1.052 | 1.060 |

**Table S2** Selected bond lengths (Å)and angles(º) for complex **1**

| Parameter | Exp. | parameter | Exp. |
|---|---|---|---|
| Pt1–O1 | 1.991(14) | Pt1–S1 | 2.223(7) |
| Pt1–N1 | 2.053(18) | Pt1–Cl2 | 2.321(4) |
| O1–Pt1–N1 | 90.0(6) | C12–Pt1–S1 | 90.45(16) |
| O1–Pt1–Cl2 | 93.9(4) | N1–Pt1–S1 | 95.9(5) |
| N1–Pt1–S1 | 92.3(3) | C8–N1–Pt1 | 120.4(12) |
| C7–N1–C8 | 118.3(17) | O2–S1–Pt1 | 109.2(8) |

## S3. Cell biological assay

### S3.1 Cell cultures

The human breast adencarcinoma cell lines (MCF-7) were supplied by Dr. Yuying Li, Shanxi University (China). The cells were cultured in DMEM (Dulbecco's Modified Eagle Medium) supplemented the streptomycin/penicillin (100unit/mL) and 10% heat inactivated FBS (Fetal Bovine Serum) and grown in humidified incubator at 310K in an atmosphere of 5% $CO_2$.

### S3.2 Cell viability analysis

Cell proliferation was evaluated using the colorimetric MTT (3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide) assay. Briefly, exponentially proliferating cells were seeded at a density of approximately $2\times10^4$ cells/well in 96-well plates and incubated for 24 h at 310K in an incubator. Thereafter the cells were treated with different

concentrations of the tested compounds (**1**, ligand or cisplatin) under investigations and kept in the incubator for additional 24 or 48 h. For each concentration a set of at least 6 wells were used. The stock solutions of platinum complexes were always freshly prepared before use. To avoid DMSO toxicity, the final concentration of DMSO in cell culture medium was less than 0.1% (V/V) in MTT assays, which was shown not to affect cell growth. Subsequently, 20 µl of MTT solution (at a concentration of 20 mg/ml in 0.85% NaCl solution) was added to each well and microplates were incubated for 4 h at 310K. At the end of the incubation time, the medium was removed and formazan crystals formed were dissolved by addition of 150µl/well DMSO. The formazan absorption was measured using a multimode microplate reader at 490 nm. $IC_{50}$ values were calculated from curves constructed by plotting cell survival versus drug concentration. All tests were run in triplicate.

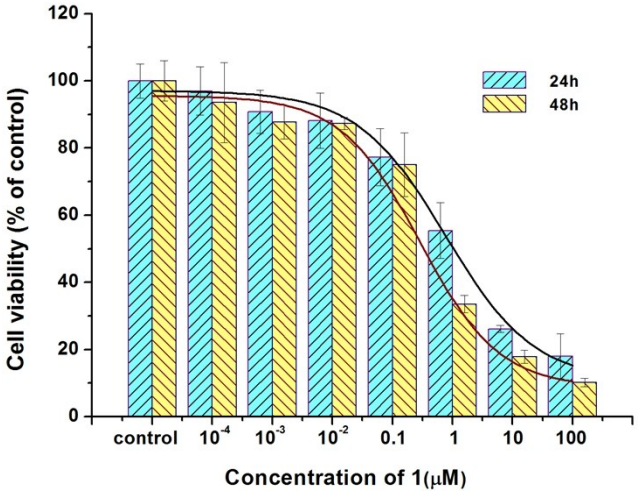



**Fig. S3** Cell viability after incubation with varying concentrations of **1** for 24 h (blue) and 48 h (yellow)

**Table S3** $IC_{50}$ (µM) values for **1** and reported platinum complexes toward MCF7 cell lines and the binding constants ($K_b$) between **1** or the reported platinum complexes and CT-DNA, respectively

| Complex | $IC_{50}$ (µM) | $K_b$($\times 10^5$ $M^{-1}$) | ref |
|---|---|---|---|
| **1** | 0.32 ± 0.10 | 0.2 | This work |
| Cisplatin | 9.56 ± 0.34 | -- | This work |
| *trans*-[Pt(salicylaldimine)(DMSO)Cl] | 6.1 ± 0.9 | -- | S3 |
| $[Pt(CHA)_2I_2]$[a] | 1.70 ± 0.21 | -- | S4 |
| $[Pt(2,4\text{-}di\text{OMeL})_2(ox)]\cdot n H_2O$ [b] | 3.6± 2.1 | -- | S5 |
| $[Pt(cbdc)(L_1)_2]$ [c] | 15.1±6.8 | -- | S6 |
| *cis*-$[PtCl_2(Haza)_2]$ [d] | 3.4 ± 0.3 | -- | S7 |
| *trans*-$[PtCl_2(2\text{-hepy})_2]$ [e] | 8.08 ± 0.21 | -- | S8 |
| $[Pt_2(2\text{-picoline})_4(berenil)_2]$ | 21 ± 2 | 7.0 | S9 |
| $[Pt(bhq)(dppe)]CF_3CO_2$ [f] | 12.20 ±0.20 | 1.3 | S10 |

[a]CHA=Cyclohexylamine; [b]L= 2-chloro-N6-(benzyl)-9-isopropyladenine;
[c]cbdc = cyclobutane-1,1'-dicarboxylate, $L_1$ = 2-chloro-6-(2-fluoro-5-bromobenzyl)- amino-9-isopropylpurine; [d]Haza = 7-azaindole; [e]hepy = (2-hydroxyethyl) pyridine;
[f]bhq = deprotonated benzo, dppe = bis(diphenylphosphino)ethane

### S3.3 Annexin V PI/FITC apoptosis assay

Quantitative assessment of apoptosis was made by an annexin V-FITC assay kit. In brief, MCF-7 cells were treated with **1,** ligand or cisplatin for 24 h. Then they were harvested and washed twice with ice-cold PBS and resuspended in a binding buffer and stained with annexin V-FITC and propidium iodide (PI). After 15min incubation in the dark at room temperature, cells were analyzed for annexin V binding within 1 h with a flow cytometer. Finally, the stained cells were analyzed using FACS Calibur and Cell Quest software.

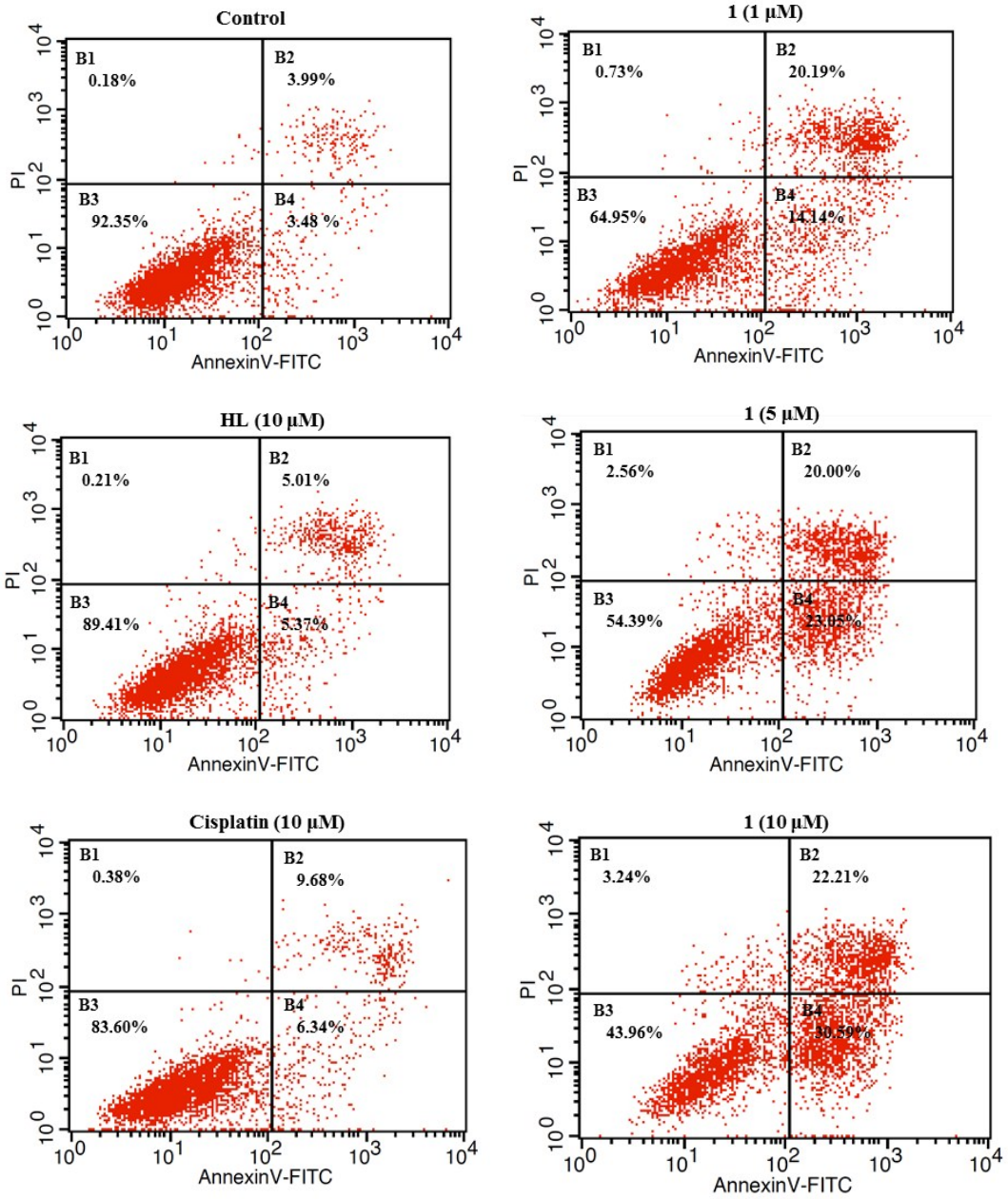



**Fig. S4** Apoptosis induction detected by annexin V-FITC and PI staining and flow cytometric analysis in MCF7 cell lines untreated and treated with complex **1** (1, 5, and 10 µM), HL (10 µM) and cisplatin (10 µM) for 24h. Upper left quadrant (B1) contains necrotic, lower right (B4) early apoptotic, upper right (B2) late apoptotic, and lower left (B3) viable cell population

**S4. DNA/mononucleotides binding assay**

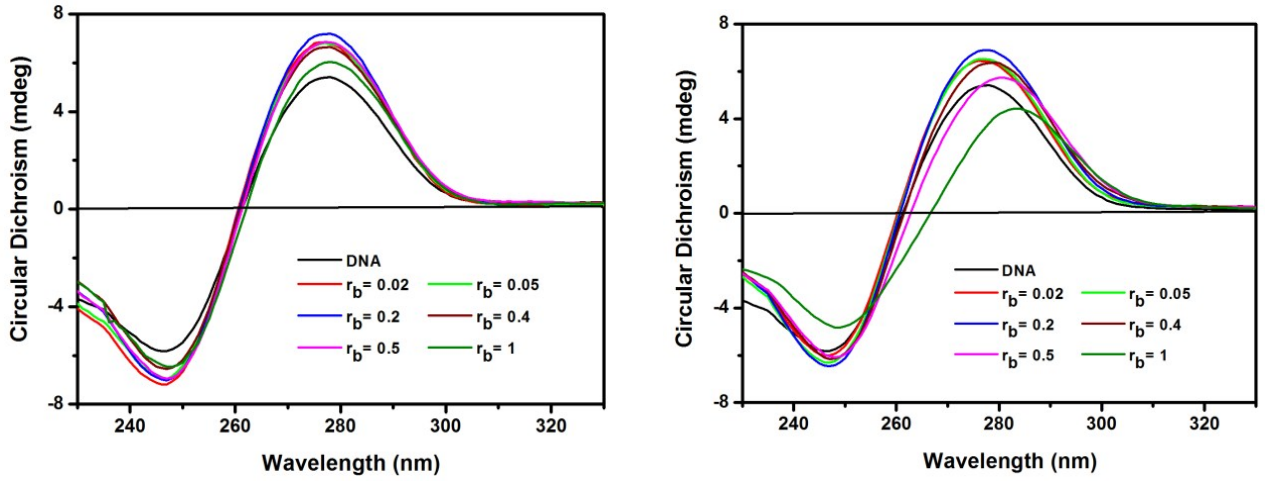
All DNA-binding experiments for compounds were carried out in 5 mM Tris-HCl-50 mM NaCl buffer (pH 7.2).

Calf thymus DNA (CT-DNA) (42% G-C and 58%A-T, mean molecular mass ca 20000 kDa) was purchased from Beijing solarbio science & technology co., ltd and used as received. A solution of CT-DNA in the buffer gave a ration of the absorbance at 260 and 280 nm ≥ 1.8, indicating that DNA was sufficiently free of protein. Concentrated stock solution of DNA ($1\times10^{-4}$ M in terms of monomeric nucleotide content) were prepared in Tris-HCl buffer. The DNA concentration per nucleotide phosphate was determined by absorption spectroscopy using the molar absorption coefficient (ε = 6600 $M^{-1}$ $cm^{-1}$ at 260 nm) [S11]. Relative binding of **1** to CT-DNA has been investigated by the absorption spectra titration in Tris-HCl buffer. Absorption spectral titration experiment was carried out by maintaining a constant concentration of **1** (20 μM) and varying the CT-DNA concentration (0-140 μM). Their UV-vis spectra were recorded in the wavelength range from 200 to 600 nm. From the observed spectral data, the intrinsic binding constants for **1** was calculated by monitoring the changes in absorbance at 290nm with increasing concentrations of CT-DNA, using the following Eq. (1) [S12]

$$\frac{c_{\mathrm{DNA}}}{\left|\varepsilon_a - \varepsilon_f\right|} = \frac{c_{\mathrm{DNA}}}{\left|\varepsilon_b - \varepsilon_f\right|} + \frac{1}{K_b\left|\varepsilon_{\mathrm{b}} - \varepsilon_f\right|} \qquad (1)$$

where $c_{\mathrm{DNA}}$ is the concentration of DNA in base pairs, $\varepsilon_{\mathrm{a}}$, $\varepsilon_{\mathrm{f}}$, and $\varepsilon_{\mathrm{b}}$ are the apparent-, free- and bound-metal complex extinction coefficients respectively. $K_{\mathrm{b}}$ is the equilibrium binding constant of complex binding to DNA. According to the above equation, gave a straight line with a slope of $1/(\varepsilon_{\mathrm{b}}-\varepsilon_{\mathrm{f}})$ and a y-intercept of $1/K_{\mathrm{b}}(\varepsilon_{\mathrm{b}}-\varepsilon_{\mathrm{f}})$ and $K_{\mathrm{b}}$ was determined from the ratio of the slope to intercept. Of them,the binding ratio of Pt-complex and DNA is 1:1, where the concentration of DNA is in terms of monomeric nucleotide content.

Circular dichroci (CD) spectra of CT-DNA were obtained by using the Applied Photophysics Chirascan CD spectrophotometer. The region between 230 and 330nm was scanned for each sample. The CD spectral titration analyses were performed through adding different molar ratios ($r_{\mathrm{b}}$, which indicates mol of compound present per mol of nucleotide) of **1** or cisplatin to DNA, respectively. DNA concentration for CD measurements was fixed at 0.1 mmol of nucleotide. All solutions were incubated for 36 h at 310K before CD measurements. The CD absorption of CT-DNA shows a positive absorbance peak at ~270 nm and a negative absorbance peak at ca. 245 nm, due to the π-π base stacking of DNA and the right-hand helicity of B-form DNA, respectively. [S13-16]




(a) (b)

**Fig. S5** (a) The CD spectra of CT-DNA ($10^{-4}$ M) in the presence of the different ratios ($r_b$) of **1** in Tris-HCl buffer (pH 7.2) at incubating time of 36 h at 310K; (b) The CD spectra of CT-DNA ($10^{-4}$ M) in the presence of the different ratios ($r_b$) of cisplatin in Tris-HCl buffer (pH 7.2) at incubating time of 36 h at 310K.

The binding properties of **1** with the guanosine-5′-monophosphate (5′-GMP) were also assessed by UV-Vis spectrophotometry. **1** was reacted with two molar equivalents of mononucleotides (50 μM) in Tris-HCl buffer at 310K for 10 min. Under the same condition, the binding of cisplatin with the mononucleotide was compared with that of **1**.

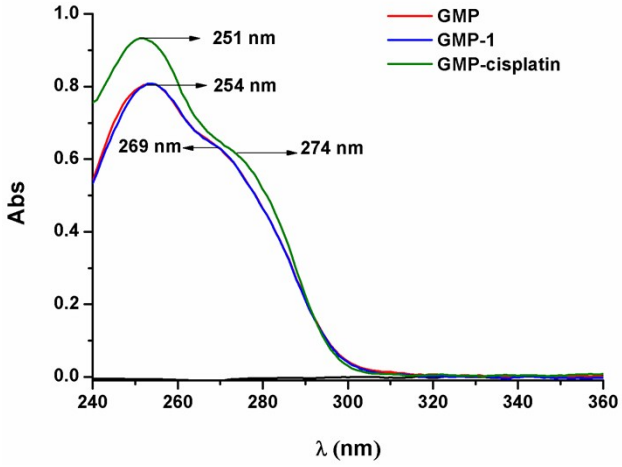



**Fig. S6** The absorbance spectra of GMP (50 μM) in the absence and presence of **1** or cisplatin (25 μM) in Tris-HCl buffer (pH 7.2) after incubating 10 min at 310K

In addition, $^1$HNMR spectra of 5′-GMP in the presence of **1** or cisplatin were also were determined according to references [S17,18]. $D_2O$ including 20% DMSO-$d^6$ was used as a solvent. All chemical shifts were referenced to DMSO-$d^6$ at 2.50ppm. 600 μl of Tris-HCl buffer (pH 7.2) containing NaCl first were freezed-dried, and then the powder of Tris-HCl were redissolved in 80% $D_2O$/20% DMSO-$d^6$. The mixture solutions of **1** (1.5 mM) or cisplatin (1.5 mM) with GMP (1.5 mM) in Tris-HCl buffer were incubated 4 h and 48 h at 298 K, respectively. $^1$HNMR spectra of the mixtures were recorded on a Bruker/Avance III 600 MHz spectrometer. Under the same condition, $^1$HNMR spectra of free GMP

and **1** were recorded as comparison spectra. In addition, $^1$HNMR spectra of **1** in different solvents (such as $CD_3OD$, $(CD_3)_2SO$, and $D_2O$-$(CD_3)_2SO$ (4:1)) also were determined.

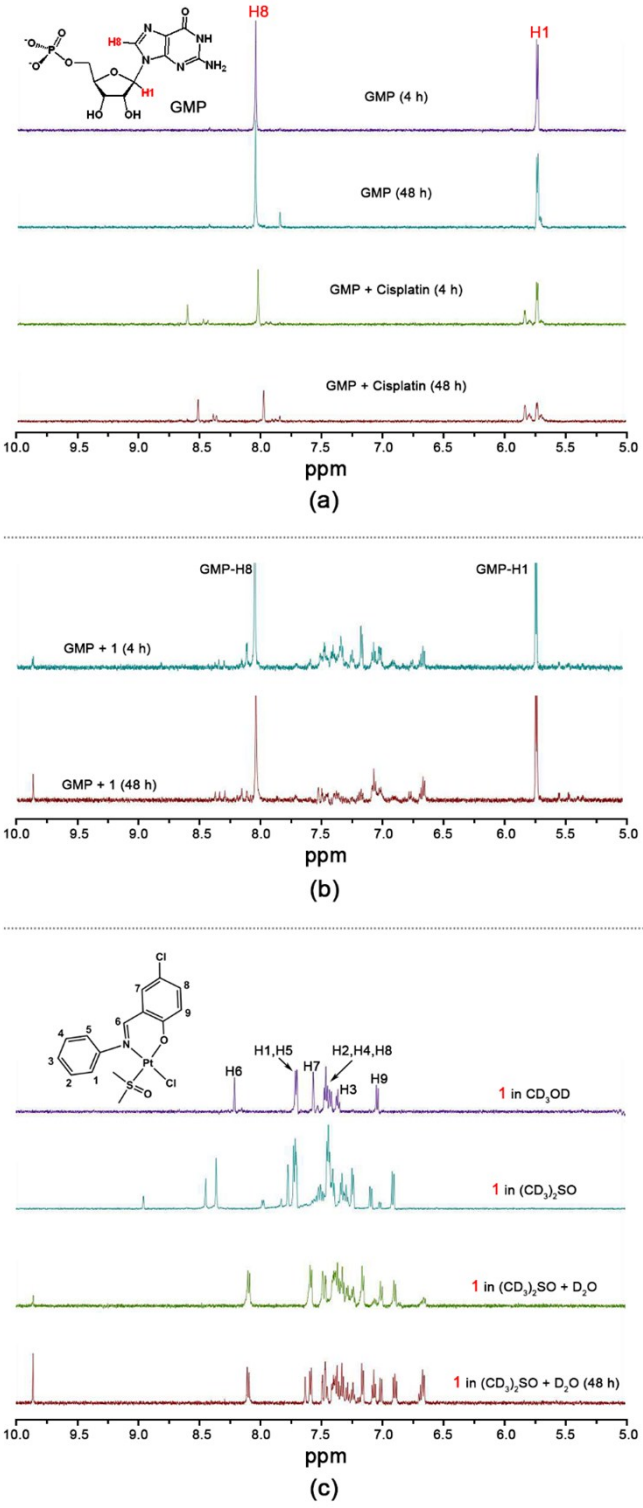



**Fig. S7** (**a**) Selected regions of 600 MHz $^1$HNMR spectra of free GMP, **1**, the mixtures of GMP and cisplatin in Tris-HCl buffer (pH 7.2) containing 20% $(CD_3)_2SO$ and 80% $D_2O$ after incubating for 4 h and 48 h at 298K, respectively. $c_{GMP}$ = 1.5 mM, $c_{cisplatin}$ = 1.5 mM; (**b**) Selected regions of $^1$HNMR spectra of the mixtures of GMP and **1** in Tris-HCl buffer (pH 7.2) containing 20% $(CD_3)_2SO$ and 80% $D_2O$ after incubating for 4 h and 48 h at 298K, respectively. $c_{GMP}$ = 1.5 mM, $c_1$ = 1.5 mM; (**c**) Aromatic regions of $^1$HNMR spectra of **1** in different solvents $CD_3OD$, $(CD_3)_2SO$, and $D_2O$-$(CD_3)_2SO$ (4:1), respectively.

As shown in Fig. S6, the UV-vis absorption band of GMP is almost identical to that of GMP-**1** mixture (incubated for 10 min at 310 K) and both of them are less intense than that of GMP-cisplatin mixture (incubated likewise), suggesting that interaction of **1** with GMP is weaker than that of cisplatin. Their interaction with GMP was also studied using $^1$HNMR spectra in Tris-HCl buffer (pH 7.2) containing 20% $(CD_3)_2SO$ and 80% $D_2O$ after incubating for 4 h and 48 h at 298K. As shown in Fig. S7-a, the intensity of signals for free 5'-GMP at 8.04 and 5.73 ppm decreases in the presence of cisplatin, whereas the same time the signals for coordinated 5'-GMP appears around 8.60 and 5.84 ppm and shift upfield with time, indicative the obvious binding of cisplatin to 5'-GMP. The $^1$HNMR spectra of the mixture of 5'-GMP and **1**, determined in the same condition, are showed in Fig. S7-b. The peaks at 8.04 and 5.73 ppm found for free 5'-GMP (Fig. S7-a) do not shift visibly and their intensities do not decrease dramatically, suggesting that the reaction between **1** and 5'-GMP is weaker than that between cisplatin and 5'-GMP. Simultaneously, the intensity of peaks originated from **1** at 6.6–7.6 ppm is relatively low, possibly due to the low solubility of **1** in aqueous solution.

To confirm the purity of **1**, $^1$HNMR spectra of **1** in the different solvents were determined and compared. As shown in Fig. S7-c, all signals of aromatic regions in the $^1$HNMR spectrum of **1** in $CD_3OD$ can be entirely assigned to $^1$H chemical shifts of **1**, indicating that the complex is pure. However, when **1** is dissolved in $(CD_3)_2SO$ or $(CD_3)_2SO$-$D_2O$ (1:4), the number of peak in the $^1$HNMR spectra of **1** is more than it should be, which may be caused by the ligand exchange process between the solvent molecules ($(CD_3)_2SO$ or $D_2O$) and coordinated Cl atom in **1**.

## S5 PTPs inhibition assays

### S5.1 Inhibition of the platinum(II) complexes on PTPs

Recombinant human Protein tyrosine phosphatases (PTP1B, TCPTP, SHP-1 and HePTP) were expressed and purified as described previously [S19]. PTP activities were measured using p-nitrophenol phosphate (pNPP) as the substrate. Inhibition assays were performed in 20 mM 3-morpholinopropane- sulfonic acid (MOPS) buffer containing 50 mM NaCl (pH 7.2) on a 96-well plate in 100 μL volumes following our previous reported method. $IC_{50}$ values were obtained by fitting the concentration-dependent inhibition curves by use of the origin program. All data points were carried out in triplicate. Solutions of the complexes were all freshly prepared before each experiment.

Enzyme kinetic experiment was determined *via* the Lineweaver-Burk plot method at increasing concentration of substrate (0.2, 0.3, 0.5, 1.0, 2.0, and 4.0 mM) and the inhibitor (0, 0.25, 0.5, 1, and 2 μM).

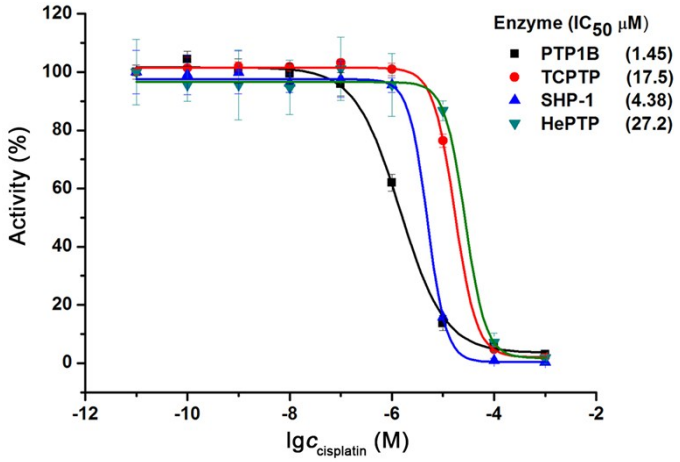



**Fig. S8** Concentration-dependent inhibition of four tyrosine phosphatases by cisplatin, the inset shows $IC_{50}$ values

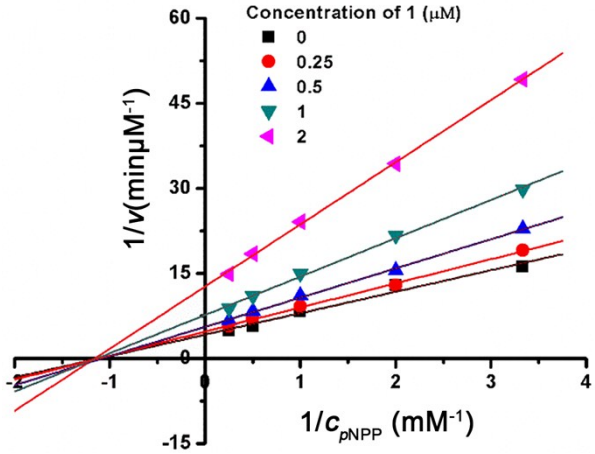



**Fig. S9** Lineweaver–Burk plot of $1/v$ versus $1/c_{pNPP}$ at five concentrations of **1**

**S5.2 Fluorescence spectroscopic studies on the interaction between PTP1B and the platinum(II) complexes**

Usually, proteins containing Trp, Tyr and Phe emit fluorescence around 310–350 nm, when excited at 280–300 nm. As the fluorescence of Trp is sensitive to the conformation change of a protein, fluorescence spectroscopy is used to study the interaction of proteins with small molecules. The fluorescence experiments were recorded in the range of 300-500 nm upon excitation at 280 nm with slit widths of 5 nm in MOPS buffer (pH=7.2) at 298 K. The PTP1B solution was diluted using MOPS buffer and left for half an hour at 298K before addition of **1**. After addition of **1**, the fluorescence emission spectra of PTP1B were recorded at interval of 10 min. Maximum fluorescence intensities of PTP1B without and with **1** as the quencher ($F_0$ and $F$, respectively) were determined and $F_0/F$ values were plotted against **1**. The experimental data were fitted with the Stern–Volmer equation (2): [S20]

$$\frac{F_0}{F} = 1 + k_q \tau_0 c_Q = 1 + k_{sv} c_Q \qquad (2)$$

where $F_0$ and F are the fluorescence intensities before and after the addition of the quencher, respectively. $K_{SV}$ is the Stern–Volmer quenching constant and $c_Q$ is the concentration of quencher. $k_q$ is the quenching rate constant of the

PTP1B and $k_q = K_{SV}/\tau_0$. $\tau_0$ is the average lifetime of the protein without any quencher. The fluorescence lifetime for proteins is ~ $10^{-8}$ s.[S9] The binding constants and the stoichiometry between PTP1B and quencher (**1**) were calculated from the static quenching equation (3) by plotting lg $((F_0-F)/F)$ vs lg $c_Q$:[S21]

$$\lg\frac{F_0-F}{F} = \lg K + n\lg c_Q \qquad (3)$$

Where $K$ is the binding constant and $n$ is the number of binding sites (stoichiometry).

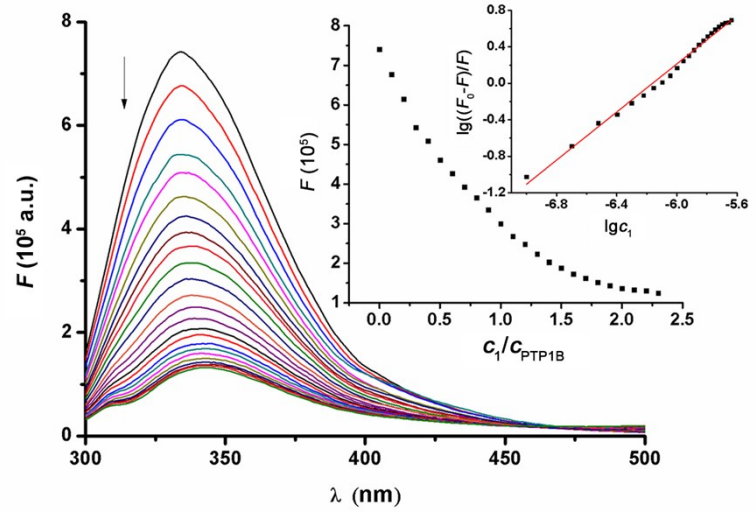



**Fig.S10** The fluorescence spectra of PTP1B in MOPS buffer (pH7.2) at 298K upon addition of **1** at interval of 10 min. Conditions: $\lambda_{ex}$ = 280 nm. Ex = Em = 5 nm, $c_{PTP1B}$ = 1.0 ×$10^{-6}$ M, $c_1$: 0.1 ~ 2.3 ($10^{-6}$ M); Insets: the titration curve of PTP1B upon addition of **1** at 335nm ($F$ vs $c_1/c_{PTP1B}$) and the plot for the binding constant

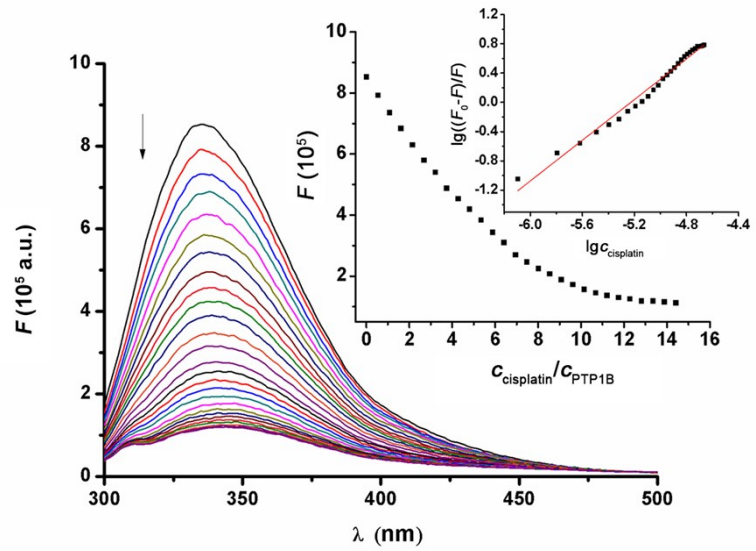



**Fig. S11** The fluorescence spectra of PTP1B in MOPS buffer at 298K upon addition of cisplatin at interval of 10 min. Conditions: $\lambda_{ex}$ = 280 nm. Ex = Em = 5 nm, $c_{PTP1B}$ = 1.5 ×$10^{-6}$ M, $c_{cisplatin}$: 0.8 ~ 21.6 ($10^{-6}$ M); Insets: the titration curves of PTP1B upon addition of cisplatin at 335nm ($F$ vs $c_{cisplatin}/c_{PTP1B}$) and the plot for the binding constant

**S5.3 Western blotting analysis**

In Western blotting analysis, MCF7, HepG2, and A549 cells were cultured in DMEM until mid-log phase and then incubated with ***1*** (1, 10 or 50 μM), ligands (50 μM) or cisplatin (1,10,50 or 100 μM) for 24 h, respectively. All samples and control contain 0.1% DMSO. After exposure, cells were harvested, washed with ice-cold 0.85% NaCl twice, and suspended in 80 μl ice-cold RIPA lysis buffer (Beyotime Institute of Biotechnology). After being incubated on ice for 20min, the cell lysates were centrifuged at 13000 rpm at 4 ºC for 15min and supernantants were collected and protein concentration was measured using a BCA Protein Assay Kit (Beyotime Institute of Biotechnology). Equal amounts of protein (80 μg) were separated by 10% SDS-polyacrylamide gels (SDS-PAGE) and transferred onto PVDF membranes (Millipore, USA). The membranes were blocked with 5% w/v non-fat dry milk for 30 min at room temperature, and incubated with primary antibody (1:500) at 4ºC overnight. After washing and incubation with secondary antibodies at room temperature for 1 h, protein signals were developed and visualized using a chemiluminescence system. Primary antibodies against p-Src (Y529), p-EGFR (Y1092), p-IRS-1 (Y896), GAPDH and Goat anti-Rabbit IgG (H&L)-HRP secondary antibody were the products of Bioworld Technology (China). The (IR/IGF1R) [pYpYpY$^{1158/1162/1163}$] antibody was obtained from Invitrogen Life Technologies. PTP1B antibody was bought from Boster Biological Technology (USA).

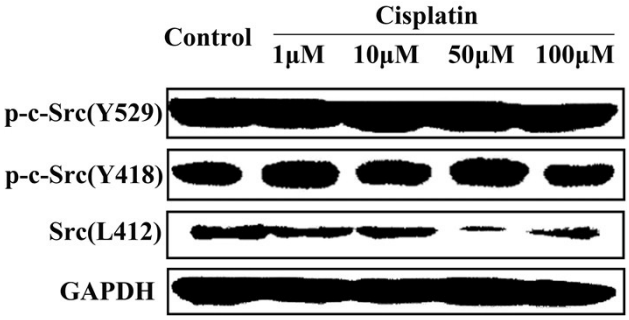



**Fig. S12** Effects of different concentration of cisplatin on phosphorylation levels of several PTPs substrates. From left to right, lane 1: control; lane 2-5: cisplatin (1, 10, 50 and 100 μM)

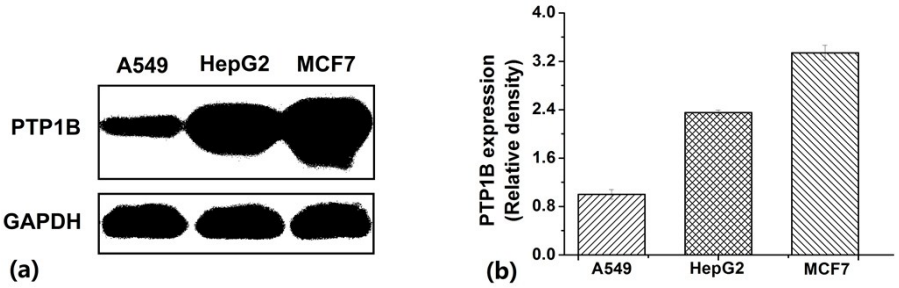



**Fig. S13** Comparison of PTP1B expression among A549, HepG2, and MCF7 cells .(a) Western blot analysis showing specific bands for PTP1B. (b) Densitometry of Western blot to analyze the relative protein expression

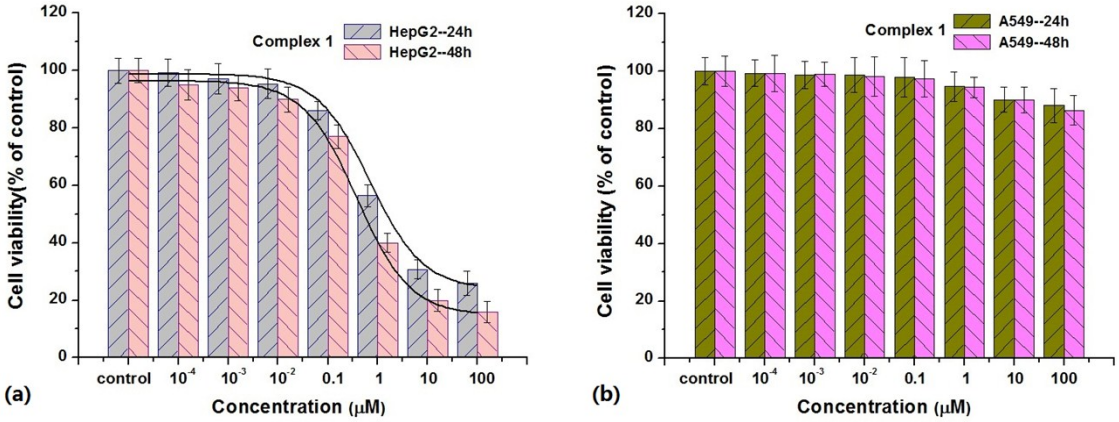



**Fig. S14** HepG2 (a) and A549 (b) cell viability after incubation with varying concentrations of **1** for 24 h and 48 h

## S6 Cellular uptake of 1 from ICP-MS

Uptake of **1** was determined by measuring the cellular platinum content using ICP-MS. MCF7, HepG2, and A549 cells were treated with **1** or ciplatin for 24h at 310K, respectively. Then complex solution were removed and the cells were washed three times with 0.85% NaCl solution and harvested by centirfugation. The cells desity was determined with cell counter. The cellular pellet were digested in 1mL of 65% $HNO_3$. The platinum contents were determined using ICP-MS as an aqueous solution in 1% v/w $HNO_3$ in Mili-Q water. The DMSO (1% in DMEM media) treated cells were used as a control.

**Table S4** The cellular content of Pt in $10^6$ different cancer cells

| Treatment | The content of Pt (ng/$10^6$ cells) | | |
|---|---|---|---|
| | MCF7 | HepG2 | A549 |
| Control | 0.11±0.05 | 0.16 ± 0.08 | 0.18 ± 0.11 |
| **1** | 26.23±0.07 | 18.30 ± 3.60 | 19.18 ± 5.63 |
| Cisplatin | 1.56±0.13 | 2.50 ± 0.79 | 1.71 ± 0.20 |

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