Medicinal Chemistry Research
https://doi.org/10.1007/s00044-023-03175-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH ARTICLE

Self-assembled amphiphilic bipyridine and bisquinoline cisplatin analogues: synthesis and anticancer properties

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Received: 7 September 2023 / Accepted: 26 November 2023
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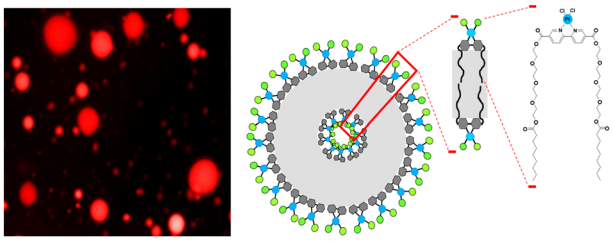
Abstract

We report the synthesis and characterisation of two amphiphilic cisplatin analogues derived from bipyridine and bisquinoline modified with two 3-oxo-3,6,9,12-tetraoxadocosyl groups. The amphiphilic cisplatin analogues readily form vesicles in water such as 200 to 400 nm in diameter for the bipyridine Pt complex and 1000 to 1300 nm in diameter for the bisquinoline Pt complex. The bisquinoline Pt complex exhibited a LD_{50} of ~24 μM for HeLa and HEK cells. On the other hand, the Pt-bipyridine complex exhibited no notable toxicity against HeLa and HEK cells under 121 μM. Amphiphilic cisplatin analogues of this type are paving the way for a new generation of active anticancer compounds that can be carried by lipoproteins for targeted anticancer therapies in clinical applications.



Keywords Bipyridine cisplatin · Bisquinoline cisplatin · Molecular self-assembly · HeLa cells toxicity · Sub-micron liposome

Introduction

Since the 1970's, cis-diamminedichloroplatinum (II) (cisplatin) has been used as an effective antitumor agent in chemotherapy [1]. Cisplatin is widely used as in the treatment of brain, lung, ovarian, testicular, and cervical cancers [2]. However, cisplatin has serious side effects such as nephrotoxicity, nausea, vomiting, myelosuppression, ototoxicity, neurotoxicity, and gastrointestinal toxicity caused by its particular systemic biodistribution in the body [2–5]. It is effective only in a limited number of tumour types also because of its systemic distribution. There are over 300 cisplatin analogues that have been reported, and about 30 have been studied with clinical trials, where more than half of them have failed to advance further [6]. Currently, four platinum compounds similar to cisplatin such as carboplatin, oxaliplatin, nedaplatin, and lobaplatin are currently used to treat cancer [7, 8]. Moreover, many tumours have developed resistance to cisplatin [9–11]. This has led to explore new strategies to overcome the mechanisms of resistance or to approaches to hyperconcentrate cisplatin or its analogues on to the tumour site. One promising strategy

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Published online: 23 December 2023

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is the use of lipid coatings for cisplatin and their analogues [12–14]. In some cases, this approach has lowered the antitumor effectiveness of the cisplatin analogues. However, in other cases, lipophilic derivatives of cisplatin have been reported with increased potency [15–19]. Other analogues of cisplatin featuring aromatic nitrogen-containing ligands have anticancer properties [19–23]. Similarly, cisplatin analogues with heterocyclic compounds that can intercalate to DNA are also promising anticancer compounds [24–27].

Herein, we combine cisplatin features with N-containing heterocycles with amphiphilic properties that emulsify in water and exhibit lipophilic properties that may be able to be transported by lipoproteins. These compounds feature hydrophobic alkyl chains linked with tetraethylene groups that give the cisplatin analogues enhanced amphiphilic properties. We report the synthesis, characterisation, and anticancer properties in vitro of platinum bis(13-oxo-3,6,9,12-tetraoxadocosyl)2,2'-bipyridine-5,5'-dicarboxylate (hereafter referred to as Pt-bipyridine) and platinum bis(13-oxo-3,6,9,12-tetraoxadocosyl)2,2'-bisquinoline -4,4'-dicarboxylate (hereafter referred to as Pt-bisquinoline) (Fig. 1).

Results and discussion

The Pt-bipyridine and Pt-bisquinoline amphiphilic compounds comprised cis-platin-like head groups connected with two tetraethylene glycol decanoate esters that facilitated water dispersion.

The synthesis of the lipophilic Pt-bipyridine cisplatin analogues is shown in Fig. 2. The first step of chemical reaction involved the synthesis of 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl-decanoate (HEED) by mixing 2 equivalents of tetraethylene glycol and one equivalent of decanoyl chloride. In a parallel chemical reaction, the compound 2,2'-bipyridine-5,5'-dicarboxylic dichloride (BpDD) was prepared by mixing

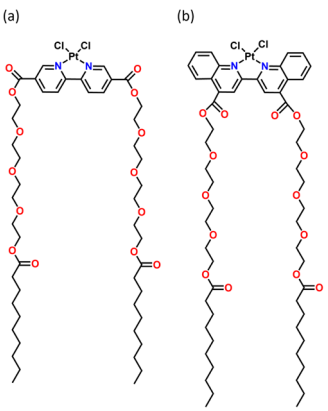

Fig. 1 Chemical structures of amphiphilic cisplatin analogues (**a**) Pt-bipyridine, (**b**) Pt-bisquinoline

2,2'-bipyridine-5,5'dicarboxylic acid (BDA) with thionyl chloride and allowed to react under reflux. Next, one equivalent of HEED and two equivalents of BpDD were allowed to react in chloroform under reflux to produce the compound bis(13-oxo-3,6,9,12-tetraoxadocosyl)2,2'-bipyridine-5,5' dicarboxylate (bis-BpD). Cis(benzonitrile)dichloroplatinum (II) compound (hereafter referred to as cis-b-Cl-Pt) was prepared from potassium tetrachloroplatinate (II) and benzonitrile in water at 60 °C for 6 h. In the final step, the compounds cis-b-Cl-Pt and bis-BpD, one equivalent of each, were dissolved in toluene and refluxed at 40 °C for 24 h giving the final product in quantitative yield. A similar synthesis route was designed for the compound Pt-bisquinoline. The products were characterised with proton ^{1}H-NMR and carbon ^{13}C-NMR, as well as with mass spectrometry.

Figure 3 shows the mass spectra of the Pt-bipyridine and Pt-bisquinoline compounds. The isotope distribution of the compounds confirmed the bond formation of the complexes. The molecular mass of Pt-bipyridine was observed with an average at 1173.48 *m/z* with an isotopic distribution consistent with the presence of Pt. The theoretical mass was simulated to have an average mass of 1165.06 *m/z*. The difference can be attributed to the formation of a Li^{+} (6.94 amu) adduct formed with the polyethylene moieties in the mass spectrometer. Similarly, for the Pt-bisquinoline the observed mass had an average of 1268.90 *m/z*, with the expected theoretical mass to have an average of 1269.20 *m/z*.

The Pt-bipyridine was characterised by fluorescence optical microscopy, dynamic light scattering (DLS), and transmission electron microscopy (TEM) (Figs. 4a, b and 5). The fluorescence image using Nile red is shown in Fig. 4a and suggests that Pt-bipyridine readily forms vesicle emulsions in water. About 0.1% of chloroform/methanol was used to enhance the emulsion of micelles to avoid factors of emulsion failure such as coalescence, flocculation, creaming and breaking [28–33]. DSL analysis of the emulsion revealed three populations of particles with average diameters of 30 nm, 300 nm, and 3 µm. TEM analysis of the Pt-bipyridine emulsion revealed the morphology of the particles, which exhibited structures with micelle- and liposome-type of aggregation (Fig. 5).

The bis-quinoline was studied with fluorescent optical microscopy and DSL (Fig. 4c, d). Nile red stained emulsions observed with fluorescent optical microscopy were like the Pt-pyridine compound, forming stable vesicle emulsions in water. DSL analysis of the emulsion revealed similar particle aggregations to the Pt-pyridine compound with three populations with average diameters of 20 nm, 300 nm, and 2.5 µm.

To test the anticancer effect of Pt-bipyridine and Pt-bisquinoline compounds we performed in vitro experiments with HeLa cancer cells stem from cervical cancer and Human Embryonic Kidney cells (HEK) stem from a normal human

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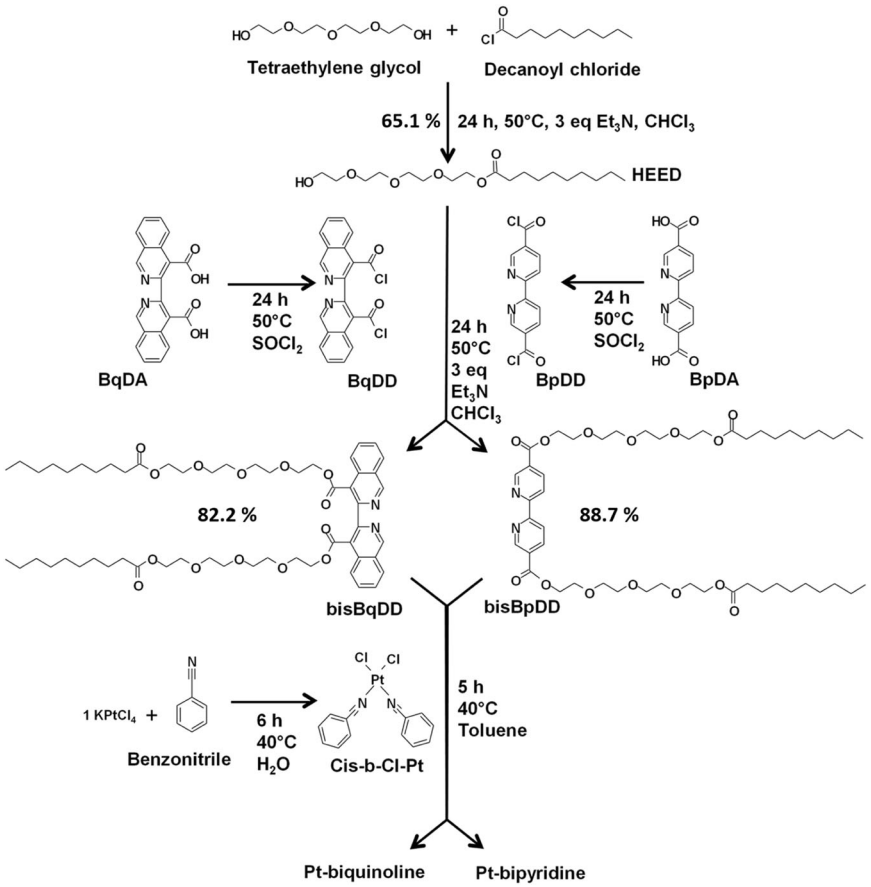

Fig. 2 Total synthesis scheme of Pt-bisquinoline and Pt-bipyridine cisplatin analogues

embryo. HEK cells are considered healthy non-malignant cells that are suitable to serve as controls to be compared to cells of cancer origin. The MTT assay (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide) was used to measure cytotoxicity and surviving cells. Figure 6 shows the cytotoxicity expressed as percentage of cell viability.

For Pt-bipyridine, the cell viability effect against HeLa and HEK cells was 82% ± 0.1% and 94% ± 1.08, respectively. A highly statistically significant p value ($p < 0.01$) points out that low doses of Pt-bipyridine (8 µM) reach the maximum toxicity for HeLa cancerous cells (85% ± 0.6% viability). However, there were no significantly changes up to 121 µM (last point of Fig. 6a). As it can be noticed, Pt-bipyridine did not even reach the 50% of killed cancer cells (LD_{50}) at the highest concentration tested (121.34 µM). When analysed by a fitted test, a tau τ value of 1.1 µM was reached. This value means that for each micro molar unit of Pt-bipyridine complex there is only a 1.1 loss in cell viability. This value indicates that the bipyridine complex is not a good option for cancer therapy, when compared with the LD_{50} of 13 µM of cisplatin for HeLa cells.

For the Pt-bisquinoline complex, the viability trend analysis suggests that the LD_{50} for HeLa cancer cells is reached at 24 µM. The viability of HeLa cancer cells decreases with the increasing concentration of Pt-bisquinoline leaving only 15% ± 0.6% of surviving cells after the maximum dose tested (88.7 uM). For the HEK cells, only 50% of cells were killed at the maximum dose tested (101 µM). Surprisingly, the HEK cells were little affected by increasing Pt-bisquinoline concentration, while the cancerous HeLa cells show sensitivity to increasing Pt-bisquinoline concentration. In addition, the LD_{50} value of this new platinum drug is close to the LD_{50} value of cisplatin (24 µM and 13 µM respectively). Thus, the Pt-bisquinoline promises to be a new chemotherapeutic drug with the advantage of having higher potency against cancer cells than non-cancerous cells. We speculate that this may be due to the presence of more esterases at the cancerous cells relative to non-cancerous cells that may be hydrolysing the ester groups of Pt-bisquinoline releasing the cisplatin analogue head group at a rate that impacts the cytotoxicity profile. Overall, differences in reactivity with esterases may be responsible for the observed variations in anticancer activity in the two Pt complexes.

Conclusion

In conclusion, we report the synthesis of two amphiphilic cisplatin analogues that use the aromatic N-donor

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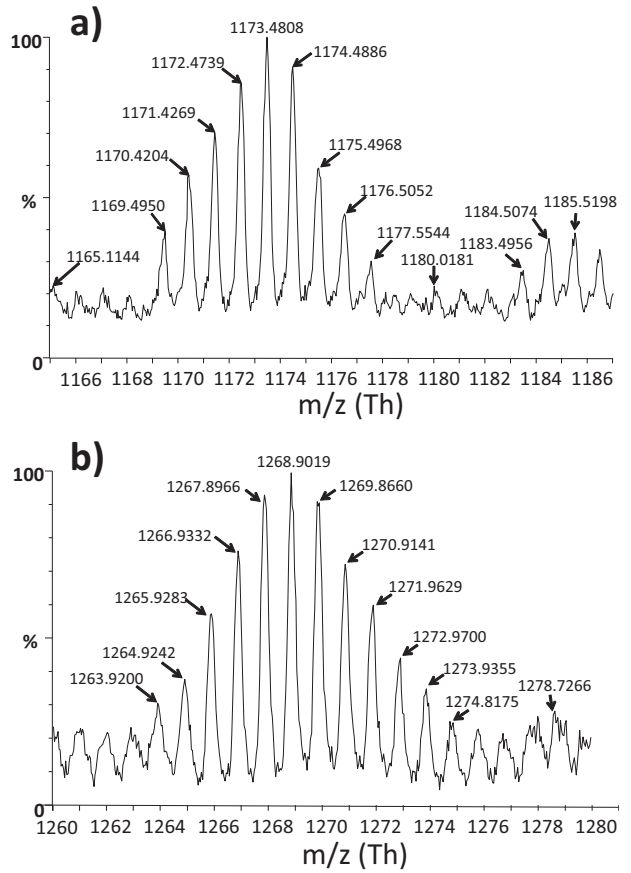

Fig. 3 Mass spectra of (**a**) Pt-bipyridine and (**b**) Pt-bisquinoline cisplatin analogues

heterocycles bipyridine and bisquinoline groups and are functionalized with a combined chain of tetraethylene glycol and alkane groups connected via carboxylic acid esters. The amphiphilic cisplatin analogues readily emulsify in water to form small vesicles. The LD_{50} value against HeLa and HEK cells of the Pt-bisquinoline vesicles is ~24 μM and for Pt-bipyridine vesicles is non-toxic under 121 μM. In addition, the Pt-bisquinoline is more cytotoxic against HeLa cells than HEK cells. The lipophilicity character of the compounds makes them good candidates to investigate the use of lipoproteins carriers for the localised treatment of cancer in clinical settings.

Experimental section

Materials

The synthesis of platinum bis(13-oxo-3,6,9,12-tetraoxadocosyl)2,2'-bipyridine-5,5'-dicarboxylate (hereafter referred to as Pt-bipyridine) and platinum bis(13-oxo-3,6,9,12-tetraoxadocosyl)2,2'-bisquinoline-4,4'-dicarboxylate (hereafter referred to as Pt-bisquinoline) required the same starting compounds. Triethylene Glycol was purchased from TCI Tokyo Kasei. The 2,2'-bipyridine-5,5'-dicarboxylic acid and 2,2'- bisquinoline-4,4'-dicarboxylic acid, decanoyl chloride and benzonitrile were purchased from Sigma Aldrich. The thionyl chloride was purchased from Alfa Aesar. The potassium chloroplatinate crystal was purchased from Johnson Matthey Co. The solvents used were obtained from Sigma-Aldrich.

Instrumental methods

NMR spectra was recorded on a JOEL 600 MHz spectrometer at room temperature, the solvent used was chloroform-d. Mass Spectrometry data were obtained from JOEL USA AccuTOFTM DART at 200 °C and 1500 volts. Fluorescence microscopy was performed from a Nikon AZ100 with confocal C1 at a magnification 5X objective, 8X zoom and 0.6 dimagnifier and a Carl Zeiss axioskop microscope at 20X objective. The hydrodynamic diameter of the micelles was determined by dynamic light scattering using PDDLS/CoolBatch 90T and PD2000DLSPlus Dynamic Light Scattering (Precision Detectors). Infrared spectroscopy information was obtained from an IR Bruker Tensor 27. The TEM images were captured from a Carl Zeiss EM-10 instrument.

Synthesis

Synthesis of 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl-decanoate (HEED)

The 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl-decanoate (HEED) was prepared by adding 2 equivalents of tetraethylene glycol 10 g (51.5 mmol) in anhydrous chloroform and 1 equivalent of decanoyl chloride 4.90 g (25.7 mmol) in chloroform mixed in a round flask at room temperature, the mixture was left stirring for 2 h. The crude was purified by preparative plate using 9:1 v/v chloroform/methanol. Yield 65.1%. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 4.05, 3.88, 3.50, 3.49, 3.37, 1.98, 1.30, 1.2837, 0.99. ^{13}C-NMR (150 MHz, $CDCl_3$): δ 172.7, 71.4, 70.7, 70.4, 68.7, 63.1, 61.4, 33.6, 31.7, 29.3, 29.2, 22.5, 13.8.

Synthesis of 2,2′-bisquinoline-4,4′dicarboxylic dichloride (BpDD)

A treatment of 2,2'-bipyridine-5,5'dicarboxylic acid 0.58 g (2.4 mmol) with thionyl chloride 10 ml was refluxed for 24 h at 50 °C to obtain the compound 2, 2'-bisquinoline-4,4'dicarboxylic dichloride 0.68 g (2.3 mmol). The thionyl chloride excess was removed by vacuum obtaining a white powder. Due to the high instability of this product, it was used directly in the next reaction.

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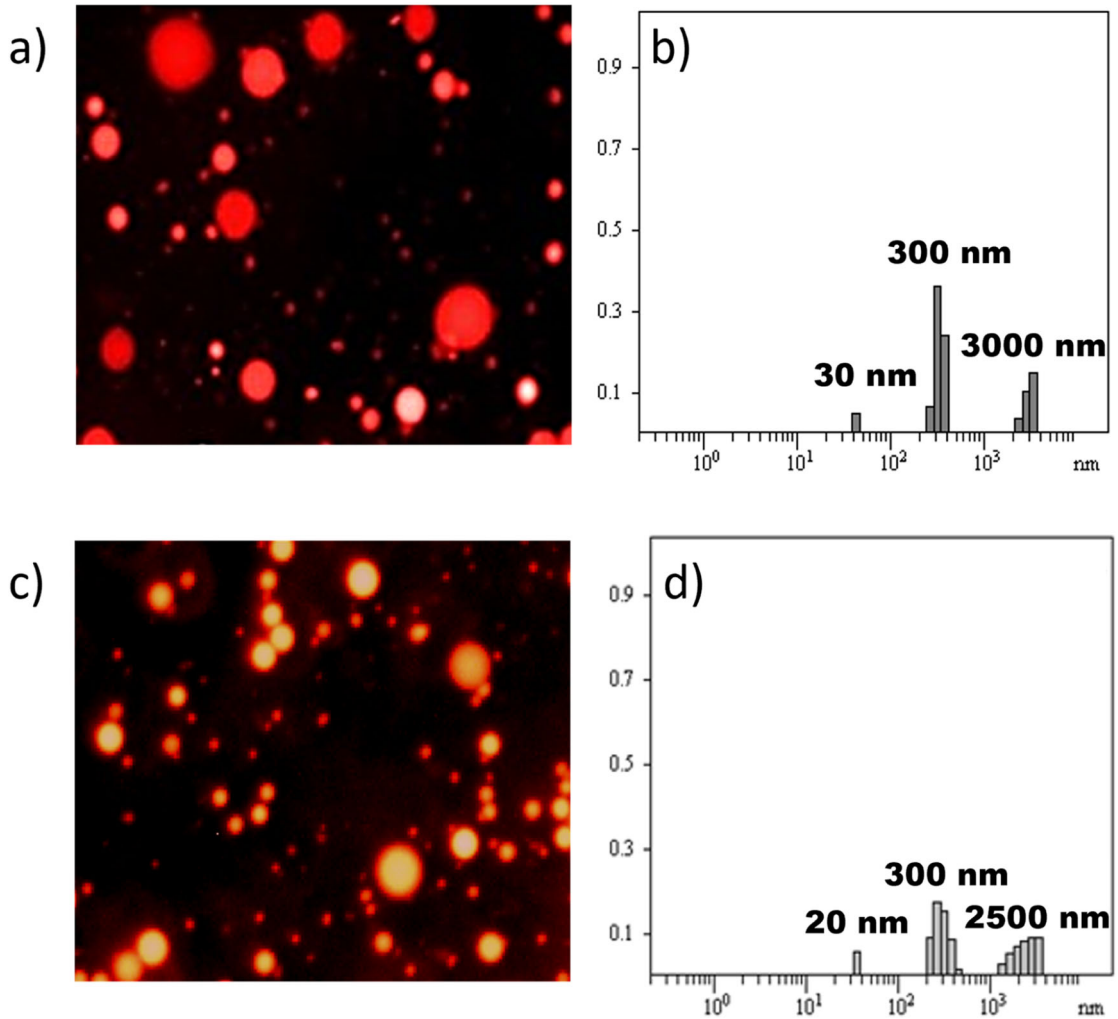

Fig. 4 **a** Fluorescence optical image of Nile red stained Pt-bipyridine in water (1000x), **b** DSL of Pt-bipyridine, **c** fluorescence optical image of Nile red stained Pt-bisquinoline in water (1000x), **d** DSL of Pt-bisquinoline

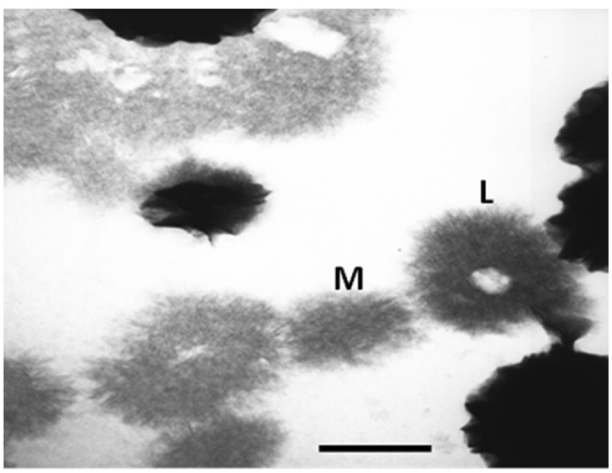

Fig. 5 Transmission electron microscopy of Pt-bipyridine with micelles (M) and liposome (L). Scale bar = 300 nm

Synthesis of Bis (13-oxo-3,6,9,12-tetraoxadocosyl)2,2′-bipyridine-5,5′-dicarboxylate (bisBpDD)

A mass of 0.68 g for 2, 2'-bisquinoline-4,4'dicarboxylic dichloride (2.3 mmol) was dissolved in chloroform and two equivalents of 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy) ethyl-decanoate 1.6 g (4.6 mmol) compound were added as well as 2 equivalents of trimethylamine 0.47 g (4.67 mmol). The mixture was left refluxing for 24 h at 50 °C to obtain 1.80 g (1.5 mmol) of bis(13-oxo-3,6,9,12-tetraoxadocosyl) 2,2'-bipyridine-5,5'-dicarboxylate. Yield 82.2%. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 9.18, 8.48, 8.47, 4.44, 4.13, 3.89, 3.61, 3.55, 2.22, 1.50, 1.15, 0.77. ^{13}C-NMR (150 MHz, $CDCl_3$): δ 174.1, 165.1, 158.2, 150.3, 137.9, 126.3, 122.0, 70.4, 70.3, 69.0, 64.2, 63.3, 34.1, 31.8, 30.2, 29.4, 29.2, 24.8, 22.6, 14.2.

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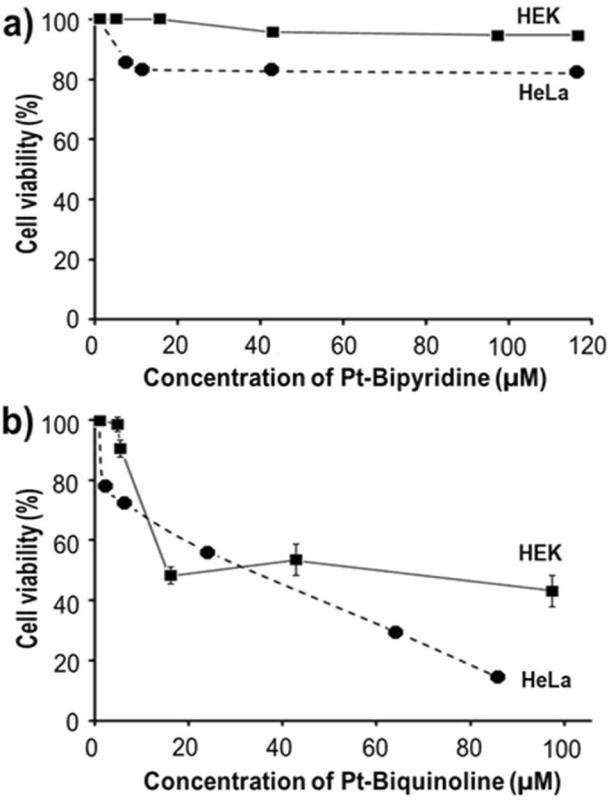

Fig. 6 **a** Percent viability for HeLa cells and normal HEK cells treated with Pt-bipyridine cisplatin analogue, and **b** Percent viability for HeLa cells and normal HEK cells treated with Pt-bisquinoline cisplatin analogue

Synthesis of Cis (benzonitrile) dichloroplatinum (II) (Cis-b-Cl-Pt)

The synthesis of the cis (benzonitrile) dichloroplatinum (II) was carried out by adding 1 equivalent of potassium tetrachloroplatinate (II), 3.35 g (8 mmol), and 1 equivalent of benzonitrile 1.66 g (16.1 mmol) in 50 ml of water mixed in a round flask at 60 °C for 6 h. Cis(benzonitrile) dichloroplatinum (II) green compound 1.9 g (3.8 mmol) was obtained then filtered and dried at vacuum for 3 h. The dried compound was washed 3 times with diethyl ether and 1.9 g (3.8 mmol) were obtained. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.80, 7.79, 7.42. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 135.3, 133.9, 133.6, 116.9, 109.5. Mass spectrum cis (benzonitrile) dichloroplatinum (II), M.W. = 472.2326

Synthesis of platinum bis (13-oxo-3,6,9,12-tetraoxadocosyl) 2,2′-bipyridine-5,5′-dicarboxylate (Pt-bipyridine)

An equivalent of bis(13-oxo-3,6,9,12-tetraoxadocosyl) 2,2'-bipyridine-5,5'-dicarboxylate, 1.80 g (1.53 mmol), was added to an equivalent of cis(benzonitrile)dichloroplatinum(II), 0.76 g (1.53 mmol) in 30 ml of toluene and refluxed at 40 °C for 24 h. The solvent was removed at vacuum and the solid obtained was dissolved in chloroform and removed with the rotovap then the solid was washed with diethyl ether and centrifuged to obtain a platinum bis(13-oxo-3,6,9,12-tetraoxadocosyl) 2,2'-bipyridine-5,5'-dicarboxylate compound 2.2 g (1.86 mmol). Yield quantitative. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 10.25, 9.49, 8.84, 4.57, 4.19, 3.89, 3.61, 3.47, 3.30, 2.34, 1.56, 1.24, 0.85. ^{13}C-NMR (150 MHz, $CDCl_3$): δ 173.9, 165.1, 159.7, 138.2, 127.6, 121.2, 72.1, 70.8, 70.5, 66.8, 65.5, 65.0, 34.0, 31.0, 31.0, 29.7, 22.7, and 15.3.

Synthesis of 2,2′-bisquinoline -4,4′dicarboxylic dichloride (BqDD)

A treatment of 2, 2'-bisquinoline-4,4'dicarboxylic acid, 1 g (2.9 mmol) in 15 ml of thionyl chloride was refluxed for 24 h at 50 °C obtaining the compound 2, 2'-bisquinoline-4,4'dicarboxylic dichloride 1.2 g (3.15 mmol). The thionyl chloride excess was removed by vacuum. Due to the high instability of the product, it was used directly in the next reaction.

Synthesis of bis (13-oxo-3, 6, 9, 12-tetraoxadocosyl) 2, 2′-bisquinoline-4, 4′-dicarboxylate (bisBqDD)

The 2,2'-bisquinoline -4,4'dicarboxylic-dichlorid 0.45 g (1.2 mmol) was dissolved in chloroform and 2 equivalents of 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl decanoate 0.82 (2.4 mmol) was added as well as 2 equivalents of triethylamine 0.24 g (2.4 mmol). The mixture was left refluxing for 24 h at 50 °C temperature to obtain bis(13-oxo-3,6,9,12-tetraoxadocosyl)2,2'-bisquinoline -4,4'-dicarboxylate 1.2 g (0.78 mmol). Yield 88.7%. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.93, 8.42, 8.24, 7.91, 4.36, 4.27, 3.89, 3.64, 3.50, 2.01, 1.83, 1.28, 0.96. ^{13}C-NMR (150 MHz, $CDCl_3$): δ 173.7, 166.4, 155.6, 148.6, 136.0, 130.5, 130.2, 129.4, 128.4, 127.9, 127.5, 126.8, 120.3, 70.4, 70.3, 70.2, 68.0, 64.2, 63.2, 32.0, 31.7, 29.5, 29.3, 22.5, 14.1.

Synthesis of platinum bis (13-oxo-3, 6, 9, 12-tetraoxadocosyl) 2, 2′-bisquinoline-4, 4′-dicarboxylate (Pt-bisquinoline)

One equivalent of bis(13-oxo-3,6,9,12-tetraoxadocosy) 2,2'-bisquinoline -4,4'dicarboxylate (Ligand 2) was added to one equivalent of cis(benzonitrile)dichloroplatinum(II) compound in toluene and refluxed for 24 h the solvent was removed at vacuum and solid obtained was dissolved in chloroform and removed with the rotovap the solid was washed with diethyl ether and centrifuged to obtain a platinum bis (13-oxo-3, 6, 9, 12-tetraoxadocosyl) 2, 2'-bisquinoline-4, 4' dicarboxylate. Yield quantitative. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.83, 8.76, 8.49, 8.27, 4.21, 4.11,

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3.64, 3.59, 2.33, 2.32, 2.31, 1.58, 1.27, 0.85. ^{13}C-NMR (150 MHz, $CDCl_3$) δ 174.0, 166.6, 148.8, 148.7, 136.3, 132.2, 130.5, 120.6, 70.4, 70.1, 68.8, 64.1, 63.4, 34.3, 31.9, 29.3, 29.2, 22.7, 14.3.

Biological assay

Harvested, cells were counted using Neubauer chamber as described above seeded 10,000 cells per well in 96 well plate (BD Falcon) incubated overnight to allow cell attachment. In this study, the bio-imager system (BD Pathway 855; BD Biosciences, Rockville, MD) was utilised to ascertain cell death after the use of a differential nuclear staining (DNS) assay. Cells were stained with a mixture fluorescent dyes Hoechst 33342 (Hoechst; Invitrogen, Eugene, OR), and Propidium iodide (PI; MP Biomedicals, Solon, OH), 1 h prior to image recording. To determine the percentage of cytotoxicity from each individual well, the captured image data was analysed with AttoVision v 1.6.2 software (BD Biosciences), especially designed to assist the Bio-imager system.

Acknowledgements Financial support from NSF grants CHE 0748913, NIH BBRC 5G12MD007592, NIFA 2019-38422-30214 and the Ralph & Kathleen Ponce de Leon Endowment are gratefully acknowledged. We thank Dr. Raymundo Rivas Caceres (Universidad Autonoma de Ciudad Juarez) for useful assistance in this study.

Author contributions GAG: investigation, writing original draft; SK: investigation; JHO: investigation; BAT, AMM, AGDS: characterization and investigation; JCN: conceptualization, project administration, and final draft.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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