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Synthesis of aspirin-ligated cisplatin derivatives and its slow release study over MIL-101(Fe)

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Abstract

An aspirin-ligated cisplatin derivative, biasplatin, was prepared from acetylsalicylic anhydride and oxoplatin in DMF. Biasplatin was synthesized from oxoplatin and aspirin anhydride as starting materials by a substitution reaction of hydroxo leaving groups in its axial position. The obtained biasplatin was fully characterized by FTIR, ^{1}HNMR, ^{13}CNMR, and ESI mass spectroscopy. Biasplatin entrapped into MIL-101(Fe) by suspended in DMF and stirring for 72 h at ambient temperature, known as biasplatin@MIL-101(Fe). The slow release of biasplatin and biasplatin@MIL-101(Fe) was conducted in PBS solution pH 7.20, 37 °C as media and measured by UV–Vis spectrophotometer. The release of biasplatin without loaded into MIL-101(Fe) is persistent for 3%, and biasplatin@MIL-101(Fe) is 0.05% over 72 h. A significant slow release of biasplatin@MIL-101(Fe) only 1% compared with time release of biasplatin without loaded into MIL-101(Fe).

Keywords Cisplatin derivatives · Biasplatin · Aspirin · MIL-101(Fe) · Time release

Introduction

One of the most known cancer treatments is chemotherapy, based on drugs which suppress the cell proliferation. Platinum derivatives are well-known as effective cancer medication, and cisplatin is one of the most commonly used platinum derivative drugs. Despite the fact that cisplatin possesses anticancer activity because of its inhibitor activity to cancer cells (Theiner et al. 2015), it also has some limitations due to toxicities and resistances (Amable 2016; Juhász et al. 2011). To overcome these problems, cisplatin which contains platinum(II) as metal center needs to be modified in a complex containing platinum(IV), in order to achieve products which are less toxic and more stable (Shi et al. 2012). Conjugation of cisplatin(IV) with other organic prodrugs such as nab-Paclitaxel and 5-fluorouracil drugs demonstrated a low relapse rate of human papillomavirus (Adkins et al. 2016). Pt(IV)–polymer conjugations such as Pt(IV)/MPEG-b-PCL-b-PLL conjugation into micelles (Xiao et al. 2011), MPEG-P(LA-co-MCC)/Pt(IV)/DRB and MPEG-P(LA-co-MCC-NHS)/Pt(IV)/DRB micelles (Xiao et al. 2012), and Pt(IV)/PCL-b-PABPA-POEGMEA/curcumin micelles (Scarano et al. 2015) have lower IC50 value and suppress cancer cells growth compared with Pt(II) and Pt(IV) complexes.

The axial ligand substitution on cisplatin derivatives could modify the pharmacokinetic effects of prodrugs, including lipophilicity, toxicity, and solubility (Escola et al. 2016; Arafath et al. 2017; Wexselblatt et al. 2015). Aspirin, one of the most widely used medicines, has anti-inflammatory activity (Clissold 1986), and its ligation with oxoplatin has allowed the achievement of asplatin, a novel platinum prodrugs for cancer treatment (Pathak et al. 2014). Asplatin has lower toxicity than cisplatin. It is proven by less reduction in body weight in asplatin, and in small dose (0.5 mg/kg), there is no influence in the reduction of body weight

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(Cheng et al. 2014). In addition to possessing good activity against cancer cells proliferation, asplatin enhanced apoptosis cancer cells by increasing mitochondrial outer membrane permeability. This causes cytochrome c release from mitochondria into the cytosol and enhances cancer cell apoptosis (Cheng et al. 2016). Cisplatin has fast release properties (Catanzaro et al. 2018). On the other hand, aspirin has slow release properties (Budd et al. 1993), and therefore we could suppress cisplatin fast release by ligated aspirin into cisplatin. However, two-side aspirin-modified cisplatin has not been further investigated. This respective compound hypothetically is also active as an anticancer agent.

Recently, metal–organic frameworks (MOFs) have revealed to be useful for applications in various fields including biosensor (Wang et al. 2015; Jing et al. 2016), catalyst (Xu et al. 2015), imaging and drug delivery (Taylor-Pashow et al. 2009; Liu et al. 2014). Thus, it has been reported several examples about good efficiency of MOFs in drug release, as well as studies proving enhancement of drugs efficiency thanks to encapsulation and conjugation of drugs into MOFs (Mocniak et al. 2015). Aspirin is generally used in host–guest encapsulation in MOFs not only because of the high selectivity to MOFs, but also because molecular size of aspirin (0.41 nm) fits easily in the cavity of MOFs (1.8 and 2.3 nm) (Singco et al. 2016). This drug design has shown good capability for controlled release of aspirin by the intermolecular non-covalent interaction, such as hydrogen bonding, van der Waals, ion–dipol, and dipol–dipol interaction between MOFs and the drug (Xu et al. 2015). On the other side, cisplatin derivatives have also shown efficiency as anticancer drugs (He et al. 2014; Taylor-Pashow et al. 2009). Another interesting alternative has been investigated by introducing a cisplatin derivative-based biphosponate as linker in a coordination polymer for treatment of ovarian cancer (He et al. 2015).

In this study, biasplatin was synthesized by substituting the two hydroxyl axial ligand. Singco et al. (2016) reported aspirin release from MIL-101(Fe) matrix was slower in acidic medium and faster in basic medium. NSAID drug loaded into MIL-101(Fe) also has slower release than loaded into MIL-100(Fe) (Horcajada et al. 2006). Commonly cisplatin derivatives were modified with adding organic complexes, copolymer linker or loaded into nanoparticles and liposomes, encapsulation in UiO-66-NH_2, has shown slower its release. From fact that MIL-101(Fe) can slow down drug release, herein we tried to study how far MIL-101(Fe) could suppress biasplatin release to reduce its toxicity. Due to the large pore volume of MIL-101(Fe) which reach up to 0.75 $cm^3\ g^{-1}$ (Tang et al. 2015), incorporation biasplatin, aspirin-ligated cisplatin derivatives on its two axial sides, would fit the pore size of MIL-101(Fe). Neutral to base buffer solution is used to mimicking the human cell environment. Neutral to base pH is used due to monohydrate form of cisplatin on pH 6.0–7.2 is rapidly converted to cisplatin; meanwhile, monohydrate form of cisplatin on pH higher than 7.2 is more stable (Yachnin et al. 1998).

Experimental

Materials

Chemicals

All chemicals used in the synthesis were of commercial grade and used without further purification. Potassium tetrachloroplatinate(IV) (K_2PtCl_4) was purchased from Carbolution Chemical Gmbh. Potassium iodide (KI), silver nitrate ($AgNO_3$), potassium chloride (KCl), 1,4-benzenedicarboxylic acid (H_2BDC), and $FeCl_3{\cdot}6H_2O$ were purchased from Sigma-Aldrich. Hydrogen peroxide (H_2O_2), ammonia (NH_3), and ethyl acetate (EtOAc) were purchased from VitLab. *o*-acetylsalicylic acid (aspirin) was purchased from Alfa Aesar. *N,N′*-dicyclohexylcarbodiimide (DCC) and sodium chloride (NaCl) were purchased from Across Organic. All solvent, ethanol, diethyl ether, dichloromethane (DCM), dimethylformamide (DMF), and acetonitrile were purchased from VWR Chemical Prolab. FTIR spectra were recorded as KBr disks in the range of 4000–400 cm^{-1} with a Perkin Elmer System 2000 FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Bruker AVANCE III HD 400 MHz NMR spectrometer at room temperature. Mass spectrometry measurements were carried out as ESI–MS with a Bruker Daltonics FT-ICR-MS spectrometer and UV–Vis spectrophotometer by PerkinElmer UV/VIS/NIR Lambda 900. Elemental analysis (C, H, and N) were performed with a Heraeus VARIO EL oven. X-ray diffractogram was recorded by Bruker tipe D8, Cu Kα anode $\lambda = 1.54060$ Å, range $2\theta = 10–50$.

Synthesis of cisplatin

Cisplatin was prepared from K_2PtCl_4 according to the procedure suggested by Alderden et al. (2006).

Synthesis of oxoplatin

H_2O_2 (60 mL, 30% w/v) was added to *cis*-diamminedichloroplatinum(II) (1 g, 3.3 mmol). The mixture was stirred for 5 h at 75 °C. The resulting yellow solution was kept overnight to crystallize. The precipitate was filtered and washed with cold water, ethanol, and diethyl ether, then dried in vacuum.

Synthesis of aspirin anhydride

Aspirin anhydride was synthesized according to Pathak et al. (2014) and Liu et al. (2013).

Synthesis of biasplatin

The reaction was carried out under different solvent without lyophilization and using different purification method. Oxoplatin (50 mg, 0.15 mmol) was suspended in DMF (10 mL). A solid aspirin anhydride (378 mg, 1.1 mmol) was added to oxoplatin suspension. The mixture was stirred at 65 °C for 48 h then the solvent was removed. The product was purified by resuspended in acetonitrile and precipitated in diethyl ether. This step was repeated until the product completely soluble in acetonitrile then washed with diethyl ether. The remaining solvent was then evaporated and dried in vacuum.

Synthesis of MIL-101(Fe)

MIL-101(Fe) was synthesized according to modified literature procedure Santiago-Portillo et al. (2015).

Dilution of phosphate buffer saline (PBS) solution

PBS was prepared following *promega protocol* (Anon n.d.). Salts NaCl (8 g), KCl (0.2 g), Na_2HPO_4 (1.44 g), and $KH_2PO_4$0.24 g were dissolved in 750 mL of warm water (37 °C). The pH was controlled by adding HCl (1 M) drop wise until the pH becomes 7.20, and water was added until the volume become 1 L. The rest of the procedures were done referring to Lestari et al. (2018) with some modifications on pH.

Calibration plot of standard two-side-modified aspirin-ligated cisplatin derivate

Biasplatin (10 mg) was dissolved in PBS (50 mL), and this solution, 0.20 mg/mL concentration, is called mother liquor. The mother liquor was diluted into various concentration 0.02 mg/mL, 0.04 mg/mL, 0.06 mg/mL, 0.08 mg/mL, 0.10 mg/mL, 0.12 mg/mL, 0.14 mg/mL, 0.16 mg/mL, and 0.18 mg/mL. All these solutions were measured the absorbance using UV–Vis spectrophotometer. The absorbance data at maximum wavelength was plotted into graph.

Incorporation of two-side-modified aspirin-ligated cisplatin derivate into MIL-101(Fe)

Biasplatin was entrapped into the porous solids MIL-101(Fe) by 3:1 ratio of biasplatin/MIL-101(Fe). Biasplatin (30 mg) was dissolved in DMF (10 mL), and then 10 mg of MIL-101(Fe) was added. The suspension was stirred for 72 h at ambient temperature. The biasplatin-containing solids, biasplatin@MIL-101(Fe), were recovered by filtration, washed with DMF and dried for 24 h at ambient temperature. The remaining filtrate was collected and then measured its absorbance by UV–Vis spectrophotometer. Loading of biasplatin into the porous solids amount was calculated using the equation from the calibration plot.

Time release of two-side-modified aspirin-ligated to cisplatin derivate

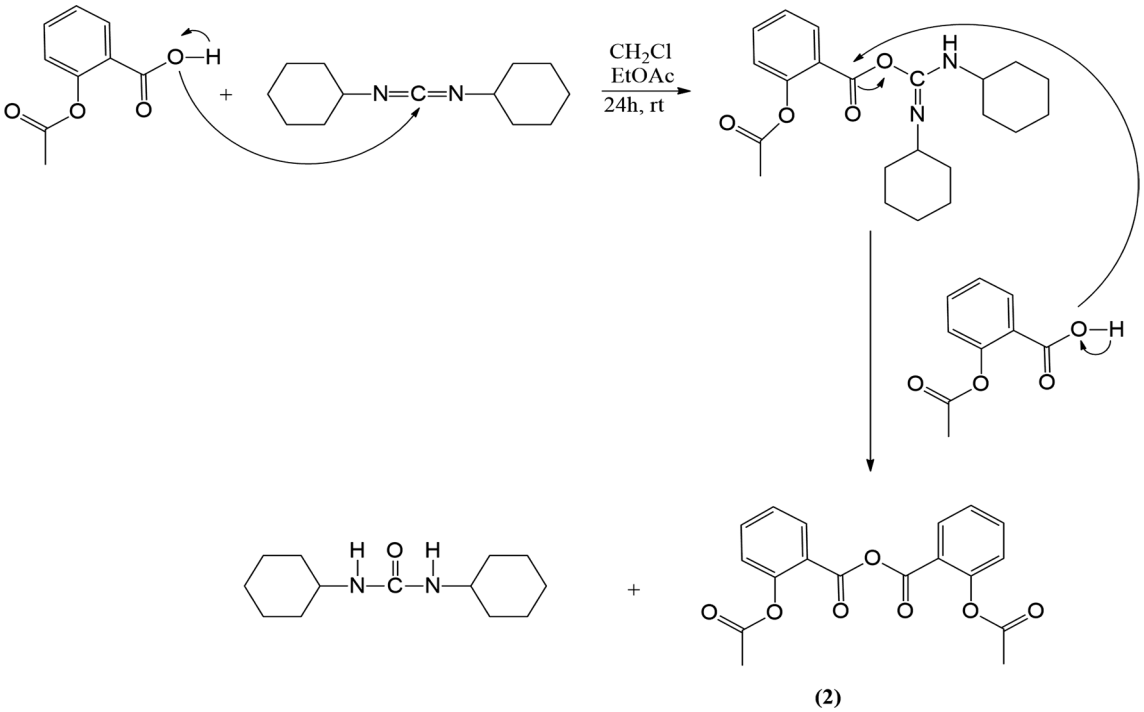
Biasplatin@MIL-101(Fe) (10 mg) was dispersed in 250 mL of PBS, pH = 7.20, stirred at 37 °C for 72 h. At predetermined intervals, 5 mL samples were collected (every 2 min at first 10 min, every 5 min at first 30 min, every 10 min at first 60 min, 30 min in 2 h, 1 h in the next 3 h, 6 h (day) or 12 h (night) in the rest time) and analyzed the content of released biasplatin by UV–Vis spectroscopy. The same amount of fresh PBS solution was added to keep the volume constant.

Results and discussion

Successively, *cis*-$[Pt(NH_3)_2Cl_2]$ was oxidized with H_2O_2 in water, two hydroxyl groups coordinated Pt(IV) in axial position forming oxoplatin (**1**). The achievement of the desired product was confirmed by FTIR spectroscopy (Fig. 2), observing the presence of not only amine groups and chloride ions, but also hydroxyl groups due to oxidation with H_2O_2. Sharp peak at 3515 cm^{-1} indicated O–H stretching. Peaks assigned to Pt–O stretching at 1039 cm^{-1} and to Pt–N stretching at 554 cm^{-1} confirm the presence of hydroxyl and ammonia ligands coordinating Pt(IV). The FTIR result is in full accordance with those reported by Wang et al. (2015) and Pathak et al. (2014).

The preparation of the target anhydride was performed in the presence of *N,N′*-dicyclohexylcarbodiimide (DCC) as condensing agent. The reaction might occur between the aspirin molecule through the carboxylic group, and the central carbon in DCC allows the formation of the *o*-acylurea intermediate, and then the synthesis proceeds with a nucleophilic attack by another aspirin molecule on the highly electrophilic carboxylate, affording the desired product aspirin anhydride (**2**) as shown in Scheme 1 (Otera 2003).

The formation of product (**2**) has been confirmed by infrared spectroscopy, where the expected band due to the anhydride C–O–C stretching at 1043, 1009, and 977 cm^{-1} are observed, and also peak 1130 cm^{-1} of C–O stretching acetic anhydride (Fig. 2). No O–H bond in the spectra indicates that aspirin has lost its hydrogen ion from hydroxyl group. Another strong evidence proving the success of the reaction can be found in ^1H NMR spectrum (Fig. 1), in which



Scheme 1 Synthesis step of aspirin anhydride (**2**)

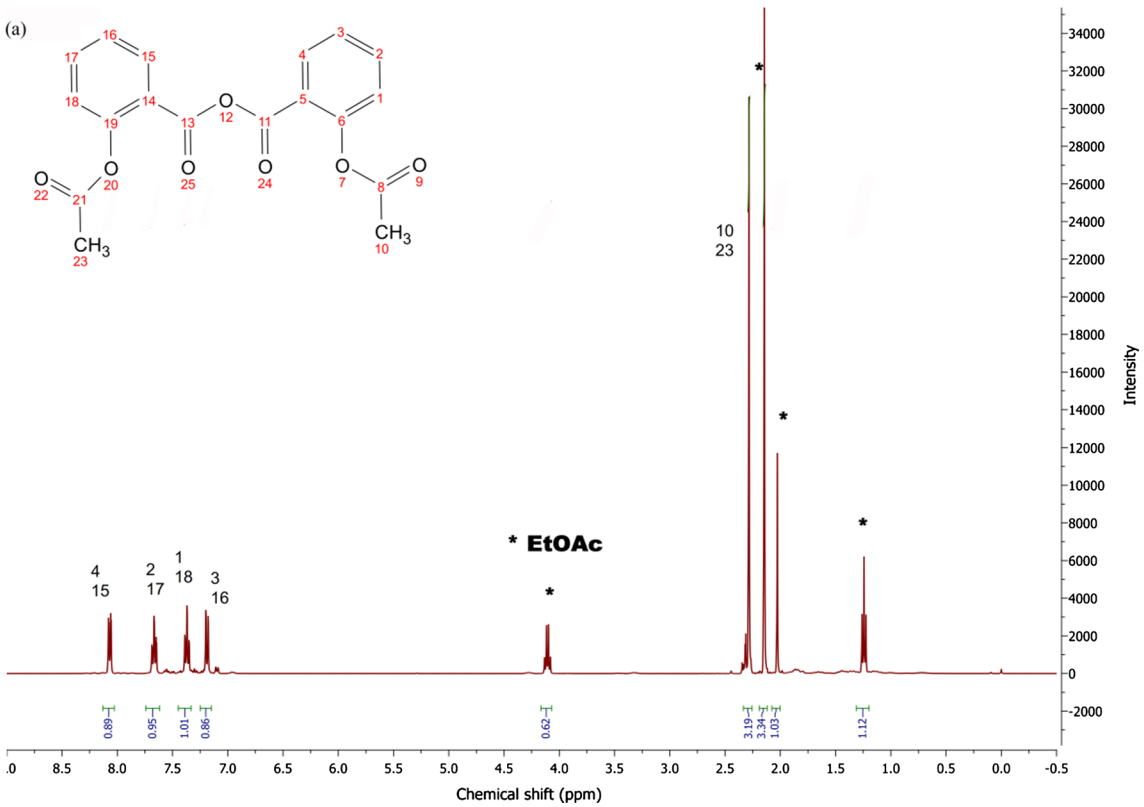


Fig. 1 ^{1}H NMR spectra of aspirin anhydride in $CDCl_3$

the absence of the signal attributable to OH group in aspirin molecule confirms that the starting material has totally reacted.

The reaction of anhydride (**2**) with oxoplatin (**1**) leads to the formation of biasplatin (**3**) by substitution of hydroxyl groups in axial position (Scheme 2). Reaction mechanism is analogue to Pathak et al. (2014). Aspirin anhydride substitute the hydroxo groups of oxoplatin and coordinate with Pt(IV) in the axial position forming biasplatin. Aspirin anhydride becomes carbocation and carbanion. OH as leaving group is substituted by carbanion, while carbocation attach to another hydroxo group (Otera 2003). Evidence of the displacement of the hydroxyl groups with acetyl salicylate can be confirmed by FTIR spectrum (Fig. 2); in fact, the bands due to the C–O–C stretching in anhydride (**2**) and to O–H in oxoplatin (**1**) cannot be observed. The ^{1}H NMR spectrum (Fig. 3) exhibits a multiplet peak at 6.19–5.84 ppm attributable to the proton in NH_3 group. The ^{13}C NMR spectrum (Fig. S2) shows the signals that can be assigned to COO–$C_{aromatic}$ shifted if compared with compound **2** as prove of anhydride cleavage. Finally, the ESI mass spectrum (Fig. S3) confirms the achievement of the new compound (**3**), exhibiting the $[M+H]^+$ peak with the highest intensity and m/z value in accordance with predicted chemical structure of biasplatin.

Scheme 2 Synthesis step of biasplatin (**3**)

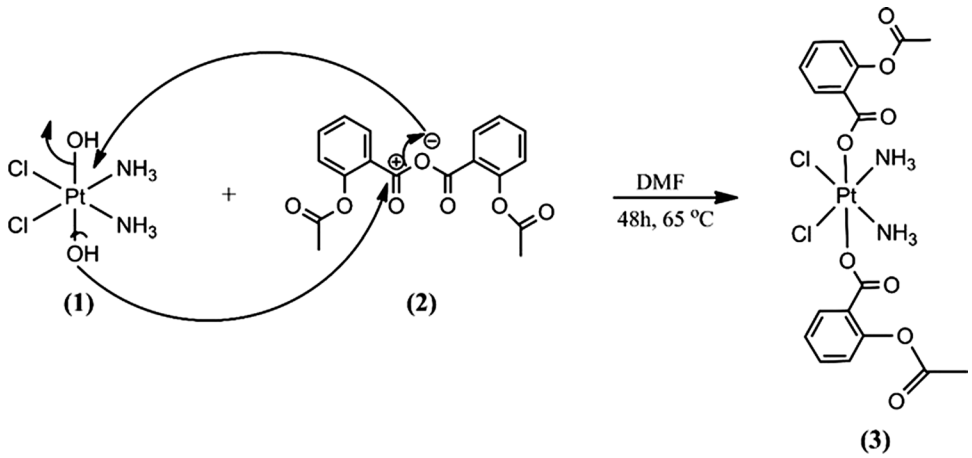
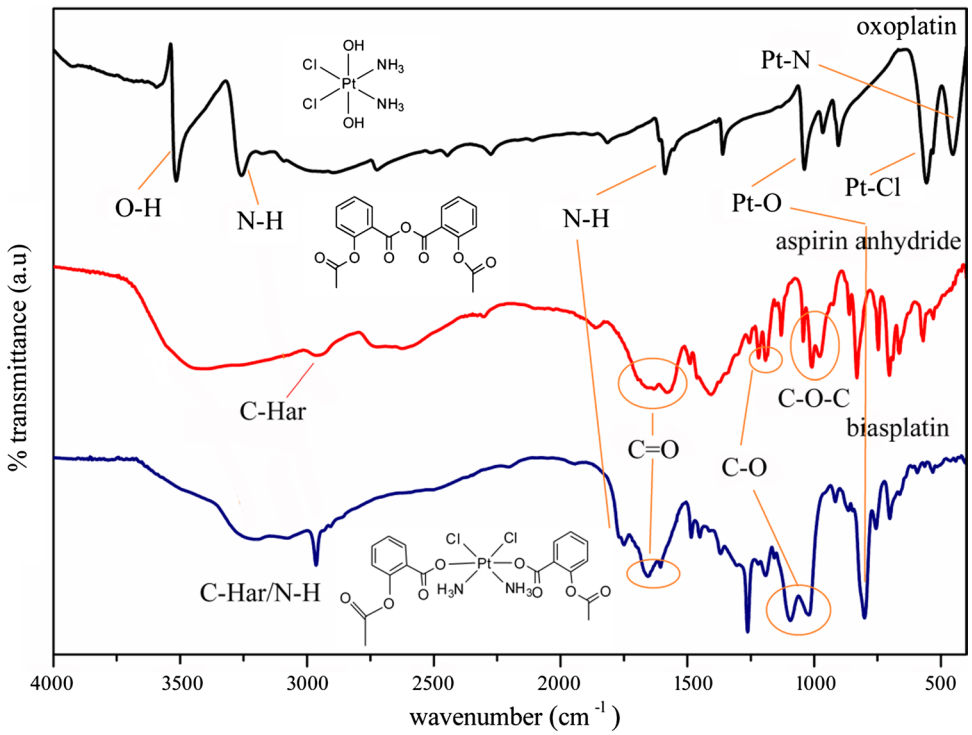


Fig. 2 FTIR spectra of biasplatin



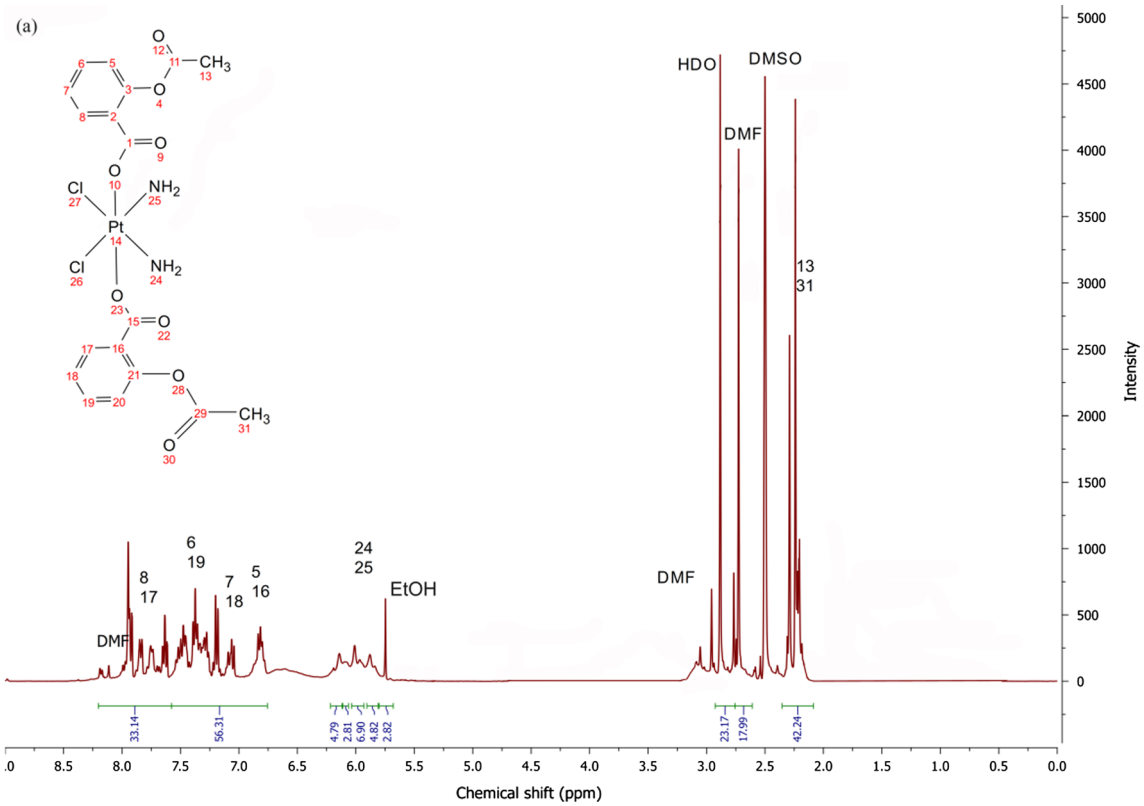


Fig. 3 ^{1}H NMR spectra of biasplatin in DMSO

Biasplatin stability was studied by TG/DTA. TG/DTA graph in Figure S4 shows biasplatin start to decompose at 180 °C by elimination of aspirin ligand.

Biasplatin loading and release over MIL-101 (Fe)

The typical characteristic FTIR absorption peaks of the MIL-101(Fe) are observed at around 1600–1400 cm^{-1} (Fig. S5). Those peaks are from carboxylic group of the linker dicarboxylic ligand. Sharp peaks at 1671–1281 cm^{-1} correspond to C–O stretching of carboxyl groups. The peak at 740 cm^{-1} assigned to C–H vibration of the benzene in the linker. The MOF structure is cubic with characteristic peaks observed at 2θ: 5.9; 6.3; 10.3; and 11.2° in accordance with CCDC No 605510 (Fig. S6).

The UV–Vis spectra of biasplatin in DMF show maximum absorbance at 300 nm (Fig. 4). This absorbance has related to Tao et al. (2010) that cisplatin has intense absorbance in several bands including 300–330 nm. The highest absorbance happened in this range because of d–d transitions of Pt^{4+} ion. Calibration curve is used to calculate the amount of biasplatin incorporated into MIL-101(Fe). The amount of biasplatin loaded into MIL-101(Fe) was calculated based on the unloaded biasplatin to MIL-101(Fe). The entrapped biasplatin into MIL-101(Fe) matrix is 93%.

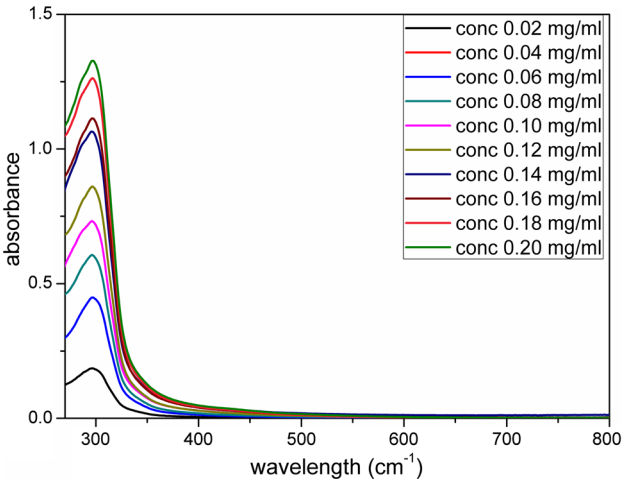


Fig. 4 Calibration curve of biasplatin in DMF

Biasplatin incorporation into MIL-101(Fe) was high. This might because the large pore size of MIL-101(Fe) (according to pore volume analysis, Figure S7) could easily captivate molecule of biasplatin.

The release of biasplatin was carried out in vitro in phosphate buffer saline (PBS). The PBS solution pH 7.20 at 37 °C was used to mimicking intercellular human body environment.

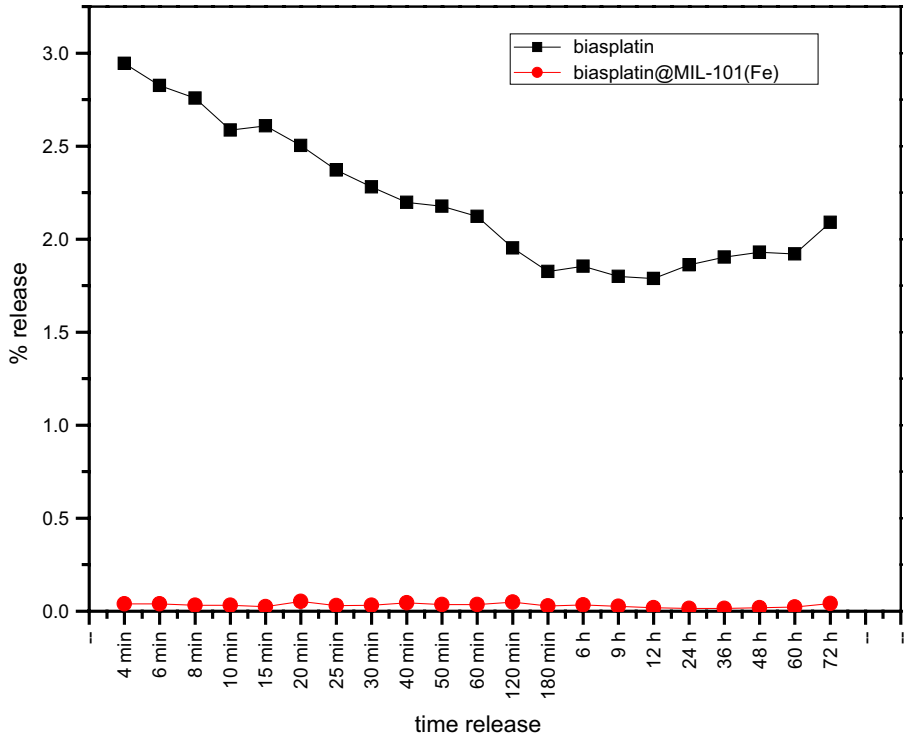


Fig. 5 Biasplatin release in PBS pH 7.20 at 37 °C

Figure 5 shows biasplatin, and biasplatin@MIL-101(Fe) had very slow release compared with other cisplatin modification drugs and other drugs contained in MIL-101(Fe). Cisplatin loaded in polymeric nanoparticles release was almost 100% before 120 h in acidic but lower in basic (Ahmad et al. 2018). The release time of cisplatin cross-linked polymer in base was 50% after 120 h (Fu et al. 2015). Time release of cisplatin encapsulated copolymer and was loaded into UiO-66 achieved 25% and UiO-67 achieved 35% at first 50 h and fully release after 400 h; otherwise, cisplatin only in UiO-66 achieved 70% and UiO-67 achieved 90% at first 50 h (Filippousi et al. 2016). Horcajada et al. (2006) reported ibuprofen in MIL-101(Fe) dissolved 40% in 24 h and fully dissolved in 144 h. Aspirin ligand increases the stability of Pt^{4+} so that biasplatin could interact with MIL-101(Fe) better than cisplatin. The stability of biasplatin also affected the diffusion process from biasplatin inside MIL-101(Fe) matrix into PBS solution. The release of biasplatin without loaded into MIL-101(Fe) is constant for about 3%, and biasplatin@MIL-101(Fe) is 0.05% over 72 h. Slow release of biasplatin@MIL-101(Fe) only 1% compared with time release of bisplatin only. These significant results show the slow diffusion rate of biasplatin release from MIL-101(Fe) into buffer solution due to low solubility of biasplatin in the water.

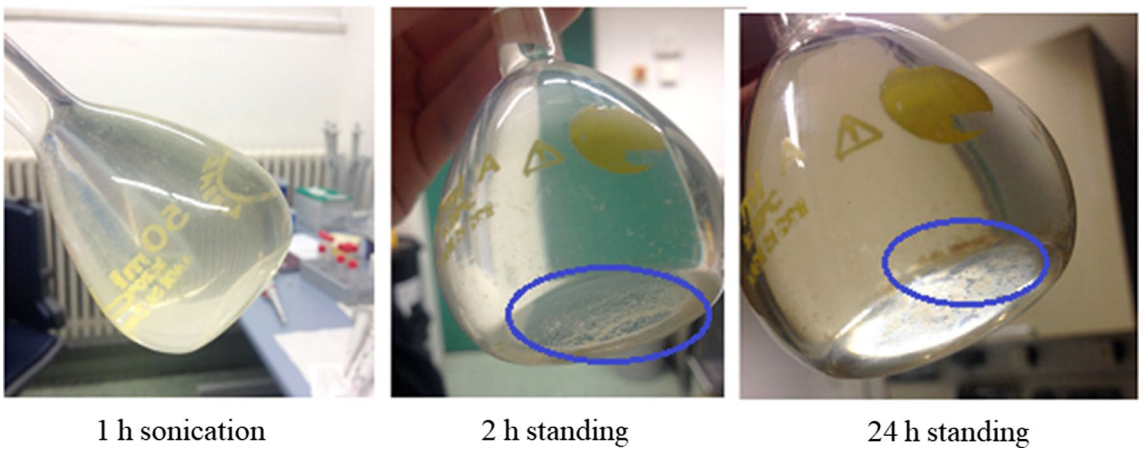


Fig. 6 Nanotracking analysis of biasplatin solubility

Nanoparticle tracking analysis was performed to investigate the low-solubility phenomenon of biasplatin. From nanoparticle tracking analysis result (Fig. 6), biasplatin only partially dissolves in PBS even after 1 h sonication, and pale yellow solution with some particles are floating. After 2 h standing, the particles are almost entirely deposited on the bottom of the flask (shown in blue circle), so that the solution itself looks mostly clear. After 24 h the solution becomes clear, and there is precipitate at the bottom (shown in blue circle). There are aggregates in the solution of different sizes from 120 to 560 nm. The concentration of particles per millilitre is also relatively high (2.25×10^6 particle/mL). The particle size average is 238 nm with a standard deviation of 141.2 nm as shown in the nanotracking curve (Fig. S10).

Biasplatin low-solubility phenomenon has advantages such as makes drug release time slower, while high-solubility cisplatin is very toxic, and one way to reduce its toxicity is by reducing its solubility. On the other hand, slow release of drug enhances drug effectiveness. Biasplatin has higher dosage than maximum dosage cisplatin, so it can be said that biasplatin is less toxic than cispatin. Besides that, the pH 7.2 used also affects slow release of biasplatin. The result shows that biasplatin, cisplatin-ligated aspirin derivative, can be an alternative solution for toxicity limitation of cisplatin.

Conclusions

Biasplatin was successfully synthesized from oxoplatin and aspirin anhydride as starting materials by substitution reaction of hydroxyl leaving groups in axial position. The release of biasplatin without loading into MIL-101(Fe) is persistent 3% and biasplatin@MIL-101(Fe) is 0.05% over 72 h. The significant slow release of biasplatin@MIL-101(Fe) only 1% compared with time release of biasplatin without loading into MIL-101(Fe).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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