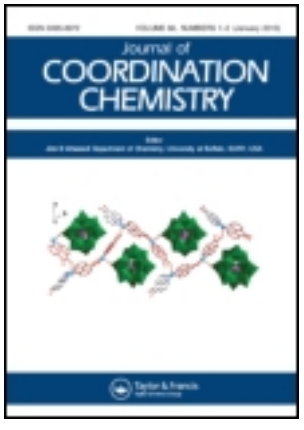

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Synthesis and in vitro cytotoxicity of platinum(II) complexes with chiral N-monosubstituted 1,2-cyclohexyldiamine derivatives as the carrier groups

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Synthesis and *in vitro* cytotoxicity of platinum(II) complexes with chiral N-monosubstituted 1,2-cyclohexyldiamine derivatives as the carrier groups

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Eight platinum(II) complexes with the new chiral ligands, (1*R*,2*R*)-N^1-(pyridine-2-ylmethyl) cyclohexane-1,2-diamine(**R**) or (1*S*,2*S*)-N^1-(pyridine-2-ylmethyl) cyclohexane-1,2-diamine(**S**) as the carrier groups were designed, synthesized, and spectrally characterized. All platinum(II) complexes showed much better aqueous solubility than cisplatin and oxaliplatin. *In vitro* cytotoxicity of the compounds against human HepG-2, MCF-7, A549, and HCT-116 cell lines was evaluated. Results indicate that all compounds with **R** as the carrier group showed cytotoxicity against HCT-116, A549, and MCF-7 cell lines; however, all compounds with **S** as carrier group exhibited disappointing cytotoxicity against tested cell lines. Compound **R2**, bearing $ClCH_2COO^-$ as leaving group, exhibited better cytotoxicity than that of carboplatin against A549 and MCF-7 cell lines and also showed close activity to oxaliplatin against HCT-116 cell line.

Keywords: Chiral 1*R*,2*R*-diaminocyclohexane derivatives; Platinum(II) complexes; *In vitro* cytotoxicity

1. Introduction

Cisplatin is one of the most successful and frequently used anticancer drugs in chemotherapy, especially for testicular cancer, for which the overall cure rate exceeds 90%, and is nearly 100% for early-stage disease [1, 2]. Nevertheless, clinical application is limited by two factors: intolerable side effects and intrinsic/acquired resistance [3, 4]. Tremendous efforts have been devoted to developing cisplatin analogs with improved pharmacological properties and broader range of antitumor activities [5–11], resulting in successful developments of new anticancer platinum drugs, such as world-wide use of carboplatin and oxaliplatin [12, 13].

Oxaliplatin is the first platinum-based drug with chiral 1*R*,2*R*-diaminocyclohexane as a carrier ligand (abbreviated as DACH) and has become the first choice in treating advanced colorectal carcinoma (ACRC) and supplanted cisplatin as the largest selling platinum

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therapeutic. But, the dose-limiting toxicity of oxaliplatin in clinical practice is still insufferable. It has been reported that approximately 90% of patients treated with oxaliplatin suffered from acute neurotoxicity, while 10–15% of patients suffered from cumulative sensory [14]. Like other clinically available platinum anticancer drugs, such as carboplatin and lobaplatin, oxaliplatin cannot offer any substantial clinical advantages over cisplatin, either [15, 16].

Violating the set of classical structure–activity relationships (SAR) summarized by Cleare and Hoeschele [17], recently much effort has been focused on design of non-classical platinum complexes, such as orally active platinum(IV) complexes, sterically hindered platinum(II) complexes, trans-platinum complexes, multinuclear platinum(II) complexes, *etc.* [18–22]. Among non-classical anticancer platinum complexes, sterically hindered platinum(II) complexes have attracted much attention. For instance, ZD0473 (formerly JM-473 and AMD-473), shown in figure 1, is a sterically hindered platinum(II) complex owning a bulky methylpyridine ligand to connect metal ions, which is responsible for its ability to overcome platinum resistance, under development as a potential treatment for cisplatin-resistant cancer and is in phase (III) clinical trial at present [23, 24].

Inspired by the favorable steric effect of methylpyridine in ZD0473 and in order to overcome the drawbacks of oxaliplatin, pyridine-2-ylmethyl has been introduced into DACH to obtain a new tridentate chiral ligand, (1*R*,2*R*)-N^1-(pyridine-2-ylmethyl) cyclohexane-1,2-diamine(**R**), and with I^-, CH_3COO^-, $ClCH_2COO^-$, $CF_3SO_3^-$ as leaving groups, respectively [25–31], we have prepared platinum(II) complexes ([Pt**R**I], **R1**–**R3**). Some research exhibiting platinum complexes with (1*S*,2*S*)-cyclohexane-1,2-diamine also showed a certain cytotoxicity [32]. So, to compare the effect of two different stereoisomers, we also prepared (1*S*,2*S*)-N^1-(pyridine-2-ylmethyl) cyclohexane-1,2-diamine(**S**) and its corresponding platinum complexes [Pt**S**I], **S1**–**S3**.

Herein reported are the platinum complexes and their *in vitro* cytotoxicity against four human cancer cell lines.

2. Experimental

2.1. *Materials*

K_2PtCl_4 was purchased from a local chemical company, mono-Boc protecting DACH (hereinafter **1**), used as starting material and prepared according to the procedure reported [33]. All reagents were of high purity and used without further purification. RPMI-1640 medium, trypsin, and fetal bovine serum were purchased from Gibco. 3-(4,5-Dimethylthiazol-2-yl)2,5-diphenyltetrazoliumbromide (MTT), benzylpenicillin, and streptomycin were

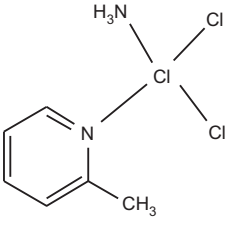

Figure 1. Structure of ZD0473.

from Sigma. Four different human carcinomacelllines, HepG-2 (human hepatocellular carcinoma cell), MCF-7 (human breast cancer cell), A549 (human lung cancer cell), and HCT-116 (human colorectal cancer cell), were obtained from American Type Culture Collection.

2.2. *Instrumentation and measurement*

Elemental analyses for C, H, and N were performed with a Perkin-Elmer 1400C instrument, while Pt was determined according to the method in EP5. ESI-MS spectra were carried out in a Finnigan MAT SSQ 710 (120–1000 amu) apparatus and IR spectra were scanned by a Nicolet IR200 spectrophotometer from 4000 to 400 cm^{-1} in KBr pellets. ^1H NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at 500 MHz in D_2O using TMS as an internal reference. Specific rotations were tested on a Shenguang WZZ-2B instrument.

2.3. *Synthesis of compounds*

2.3.1. Ligand R: (1*R*,2*R*)-*N*^{1}-(pyridine-2-ylmethyl) cyclohexane-1,2-diamine. Mono-Boc protecting DACH (**1**) (21.4 g, 100 mmol), and 2-pyridinecarboxaldehyde (12.8 g, 120 mmol) were dissolved in 300 mL of toluene and refluxed for 4 h. After concentrating the solution, white solids of mono-Schiff base **2** were obtained. Compound **2** was dissolved in 600 mL of methanol and 7.0 g (184 mmol) $NaBH_4$ was added in portions. The mixture was mixed for 5 h and EtO_2 was used to extract the product into the organic phase which was washed with water three times. The organic solution was mixed with excess HCl/EtO_2 (5 mol/L), leading to formation of HR hydrochloride **3**, which was finally neutralized by aqueous $NaHCO_3$ solution (2 mol/L) to give free **R** 6.8 g (33.2 mmol). Yield, 33.2%. Anal. Calcd for $C_{12}H_{19}N_3$ (%): C, 70.24; H, 9.27; N, 20.49. Found (%): C, 70.08; H, 9.36; N, 20.39. IR(KBr, cm^{-1}): 3401–3285 (m, ν_{N-H}), 2928, 2856 (s, ν_{C-H}), 1593 (m, ν_{Py}), 760 (m, γ_{PyH}). ESI-MS *m/z:* $[M+H]^+ = 206$(100%). ^1H NMR (DMSO, ppm) δ: 1.12–2.85(m, 10H, 4CH_2 and 2*CH* of DACH), 4.47–4.50 (d, 2H, NH-CH_2), 5.56–5.73 (m, 3H, NH and NH_2), 7.31–8.46 (m, 4H, C_5H_4N).

2.3.2. Ligand S: (1*S*,2*S*)-*N*^{1}-(pyridine-2-ylmethyl) cyclohexane-1,2-diamine. The procedures for preparing ligand **S** were similar to **R**. Yield, 28.1%. Anal. Calcd for $C_{12}H_{19}N_3$ (%): C, 70.24; H, 9.27; N, 20.49. Found (%): C, 70.11; H, 9.33; N, 20.41. IR (KBr, cm^{-1}): 3389–3270 (m, ν_{N-H}), 2926, 2860 (s, ν_{C-H}), 1590 (m, ν_{Py}), 758 (m, γ_{PyH}). ESI-MS *m/z:* $[M+H]^+ = 206$ (100%). ^1H NMR (DMSO, ppm) δ: 1.09–2.83(m, 10H, 4CH_2 and 2*CH* of DACH), 4.43–4.49 (d, 2H, NH-CH_2), 5.51–5.78(m, 3H, NH and NH_2), 7.329–8.44(m, 4H, C_5H_4N).

2.3.3. [PtRI]. To a stirring aqueous solution of KI (160 mmol), K_2PtCl_4 (24 mmol) in water (80 mL) was added. The solution was stirred at 25 °C for 30 min under nitrogen to get a black solution of K_2PtI_4. Then, an aqueous solution (40 mL) of **R** (24 mmol) was added dropwise under stirring in the dark at 25 °C. After 24 h, the yellow precipitate was

filtered, washed sequentially with water, ethanol, and ether, and then dried in vacuum. Data for [**PtR**I]: 15.0 g, Yield: 95.8%, yellow solid. Anal. Calcd for $C_{12}H_{19}I_2N_3Pt$ (%): C, 22.01; H, 2.91; N, 6.42; Pt, 29.81. Found (%): C, 22.16; H, 2.95; N, 6.44; Pt, 29.68. IR (KBr, cm^{-1}): 3204–3103 (m, ν_{N-H}), 2930, 2856 (s, ν_{C-H}), 1590 (m, ν_{Py}), 760(m, γ_{PyH}). ESI-MS *m/z:* $[M-I]^+ = 527$(80%). ^{1}H NMR (D_2O, ppm) δ: 1.21–3.09 (10H, 4CH_2 and 2*CH* of DACH), 4.40–4.51 (d, 2H, NHCH_2), 7.41–8.60 (m, 4H, C_5H_4N).

2.3.4. [PtSI]. The procedure for preparing [Pt**S**I] was similar to [Pt**R**I]. Anal. Calcd for $C_{12}H_{19}I_2N_3Pt$ (%): C, 22.01; H, 2.91; N, 6.42; Pt, 29.81. Found (%): C, 22.11; H, 2.98; N, 6.40; Pt, 29.71. IR(KBr, cm^{-1}): 3198–3131 (m, ν_{N-H}), 2928, 2858 (s, ν_{C-H}), 1596 (m, ν_{Py}), 758 (m, γ_{PyH}). ESI-MS *m/z:* $[M-I]^+ = 527$ (60%). ^{1}H NMR (D_2O, ppm) δ: 1.18–3.12 (10H, 4CH_2 and 2*CH* of DACH), 4.36–4.48 (d, 2H, NHCH_2), 7.36–8.56 (m, 4H, C_5H_4N).

2.3.5. R1. [Pt**R**I] (4 mmol) was suspended in 250 mL pure water and a solution of 8 mmol $AgNO_3$ in 80 mL pure water was added. After stirring under nitrogen in the dark for 24 h at 40 °C, the precipitate was filtered off. Filtrate was blended with 12 mmol CH_3COONa and stirred at 55 °C for 24 h. The solution was concentrated to 5 mL and then cooled to 0 °C. Pale yellow powder was collected, washed with a small amount of chilled water and ethanol, and then dried at 60 °C in vacuum. Yield 43.6%. Anal. Calcd for $C_{16}H_{25}N_3O_4Pt$ (%): C, 37.06; H, 4.83; N, 8.11; Pt, 37.64. Found (%): C, 37.11; H, 4.86; N, 8.10; Pt, 37.51. IR (KBr, cm^{-1}): 3231–3109 (s, ν_{N-H}), 2932, 2858 (s, ν_{C-H}), 1592 (s, $\nu_{C=O}$), 751 (m, γ_{PyH}). ESI-MS *m/z:* $[M-H]^- = 517$(100%). ^{1}H NMR (D_2O, ppm) δ: 1.01–2.98 (m, 10H of DACH and 6H of 2CH_3COO), 4.33–4.44 (d, 2H, NHCH_2), 7.38–8.58 (m, 4H, C_5H_4N). The procedures for preparing **R2**, **R3**, **S1**, **S2**, and **S3** were similar to **R1**.

2.3.6. R2. The leaving group of **R2** is $ClCH_2COO^-$, so the starting material is $ClCH_2COONa$. Yield 44.0%. Anal. Calcd for $C_{16}H_{23}Cl_2N_3O_4Pt$ (%): C, 32.71; H, 3.92; N, 7.16; Pt, 33.22. Found (%): C, 32.68; H, 3.97; N, 7.09; Pt, 33.06. IR(KBr, cm^{-1}): 3208–3136 (s, ν_{N-H}), 2933, 2852 (s, ν_{C-H}), 1596 (s, $\nu_{C=O}$), 750 (m, γ_{PyH}). ESI-MS *m/z:* $[M-H]^- = 586$ (80%). ^{1}H NMR (D_2O, ppm) δ: 1.06–3.13 (m, 10H of DACH and 4H of 2$ClCH_2$COO), 4.36–4.50 (d, 2H, NHCH_2), 7.38–8.56 (m, 4H, C_5H_4N).

2.3.7. R3. The leaving group of **R3** is $CF_3SO_3^-$, so the starting material is CF_3SO_3Na. Yield 46.1%. Anal. Calcd for $C_{14}H_{19}F_6N_3O_6S_2Pt$ (%): C, 26.21; H, 2.96; N, 6.55; Pt, 30.42. Found (%): C, 26.12; H, 2.99; N, 6.46; Pt, 30.18. IR(KBr, cm^{-1}): 3298–3106 (s, ν_{N-H}), 2938, 2856 (s, ν_{C-H}), 1590 (s, $\nu_{C=O}$), 750 (m, γ_{PyH}). ESI-MS$^-$ *m/z:* $[M-CF_3SO_3]^+ = 492$ (100%). ^{1}H NMR (D_2O, ppm) δ: 1.16–3.08 (m, 10H of DACH), 4.31–4.49 (d, 2H, NHCH_2), 7.36–8.52 (m, 4H, C_5H_4N).

2.3.8. S1. The leaving group of **S1** is the same as for **R1**. Yield 36.8%. Anal. Calcd for $C_{16}H_{25}N_3O_4Pt$ (%): C, 37.06; H, 4.83; N, 8.11; Pt, 37.64. Found (%): C, 37.08; H, 4.81; N, 8.16; Pt, 37.58. IR(KBr, cm^{-1}): 3233–3111 (s, ν_{N-H}), 2936, 2856 (s, ν_{C-H}), 1598 (s, $\nu_{C=O}$), 750 (m, γ_{PyH}). ESI-MS *m/z:* $[M-H]^- = 517$ (75%). ^{1}H NMR (D_2O, ppm) δ:

1.03–3.08 (m, 10H of DACH and 6H of 2CH_3COO), 4.31–4.40 (d, 2H, NHCH_2), 7.36–8.51 (m, 4H, C_5H_4N).

2.3.9. S2. The leaving group of **S2** is $ClCH_2COO^-$, so the starting material is $ClCH_2COONa$. Yield 39.3%. Anal. Calcd for $C_{16}H_{23}Cl_2N_3O_4Pt$ (%): C, 32.71; H, 3.92; N, 7.16; Pt, 33.22. Found (%): C, 32.59; H, 3.93; N, 7.11; Pt, 33.01. IR(KBr, cm^{-1}): 3303–3123 (s, ν_{N-H}), 2936, 2856 (s, ν_{C-H}), 1598 (s, $\nu_{C=O}$), 756 (m, γ_{PyH}). ESI-MS *m/z:* $[M-H]^- = 586$ (100%). ^{1}H NMR (D_2O, ppm) δ: 1.06–3.13 (m, 10H of DACH and 4H of 2$ClCH_2$COO), 4.36–4.50 (d, 2H, NHCH_2), 7.38–8.56 (m, 4H, C_5H_4N).

2.3.10. S3. The leaving group of **S3** is $CF_3SO_3^-$, so the starting material is CF_3SO_3Na. Yield 37.3%. Anal. Calcd for $C_{14}H_{19}F_6N_3O_6S_2Pt$ (%): C, 26.21; H, 2.96; N, 6.55; Pt, 30.42. Found (%): C, 26.08; H, 3.02; N, 6.51; Pt, 30.20. IR(KBr, cm^{-1}): 3266–3116 (s, ν_{N-H}), 2936, 2858 (s, ν_{C-H}), 1596 (s, $\nu_{C=O}$), 760 (m, γ_{PyH}). ESI-MS$^-$ *m/z:* $[M-CF_3SO_3]^+ = 492$ (70%). ^{1}H NMR (D_2O, ppm) δ: 1.10–3.06 (m, 10H of DACH), 4.30–4.44 (d, 2H, NHCH_2), 7.38–8.56 (m, 4H, C_5H_4N).

2.4. *Cell culture*

Four different human carcinoma cell lines, HepG-2, MCF-7, A549, and HCT-116, were cultured in an RPMI-1640 medium supplemented with 10% fetal bovine serum, 100 unit mL^{-1} of penicillin, and 100 μg mL^{-1} of streptomycin. Cells were maintained at 37 °C in a humidified atmosphere of 5% CO_2 in air.

2.5. *Solutions*

The platinum complexes were dissolved in DMSO at 5 mM as stock solution and diluted in culture medium at concentrations of 0, 10, 20, 50, and 100 μM as working-solutions. To avoid dimethylsulfoxide (DMSO) toxicity, the concentration of DMSO was less than 0.1% (v/v) in all experiments.

2.6. *Cytotoxicity analysis*

MTT assay was carried out to evaluate the *in vitro* cytotoxicity of the resulting platinum complexes as described by Mosmann [34]. Tumor cells were plated onto 96-well sterile plates in 100 mL of medium at a density of 4×10^3 to 8×10^3 cells per well and incubated for 24 h at 37 °C in a 5% CO_2 containing incubator. The prepared compounds [Pt**R**I], [Pt**S**I], **R1**–**R3**, and **S1**–**S3** were added in final concentrations ranging from 0 to 100 μM. After 48 h, 50 μl MTT in PBS (5 mg/mL) was added to each well and the plates were incubated for 3 h at 37 °C. The liquid was removed and DMSO (100 mL) added to dissolve the MTT formazan. The OD for each well was measured on a microplate reader at 490 nm. All cytotoxicity tests were carried out three times parallelly; IC_{50} values were from curves constructed by plotting cell survival (%) versus compound concentration (in μM).

3. Results and discussion

3.1. *Preparation of chiral ligands and platinum complexes*

Mono-Boc protecting DACH was used as starting material to prepare the ligands **R**/**S** as before, since it is difficult to directly get the monsubstituted derivatives due to equivalent reactivity of the two amino groups in DACH, and the ligand was obtained via four steps (figure 2).

Before preparing the targeted platinum complexes, important intermediates [Pt**R**I]/[Pt**S**I] were first prepared by similar method described [35]. Then, $AgNO_3$ was used to remove the iodide of [Pt**R**I]/[Pt**S**I] to form *in situ* [Pt**R**(H_2O)]NO_3, which was used to react with sodium salts of the corresponding acetates, respectively, to afford **R1**/**S1** to **R3**/**S3** (figure 3).

3.2. *Characterization of the complexes*

Intermediates [Pt**R**I]/[Pt**S**I] and targeted platinum complexes were characterized by IR, ^{1}H NMR, ESI-MS spectra, and microananlysis. Elemental analyses for each compound were in good agreement with calculated values. IR spectra of these complexes are similar, and Pt-N coordinations were confirmed by $\nu NH_2/\nu NH$ shifting to lower frequencies compared with free amino groups. Carboxylate binding with Pt(II) was confirmed by the C=O absorptions shifting from free carboxylic acids near 1700 cm^{-1} to bands near 1590 cm^{-1} in **R2**/**S2**–**R3**/**S3**. The ^{1}H NMR spectra of the complexes are consistent both in chemical shifts and number of hydrogens. All prepared complexes showed a peak of $[M-Z]^+$ or $[M-H]^-$ in their ESI mass spectra, consistent with expected molecular formula weights. Typical isotopes of Pt element: ^{194}Pt (33%), ^{195}Pt (34%), and ^{196}Pt (25%), were found with three protonated ion isotopic peaks.

3.3. *Aqueous solubility and optical rotation of complexes*

Poor aqueous solubility is a severe problem for some platinum anticancer drugs in clinical use, such as cisplatin. Hence, the aqueous solubility of our Pt compounds was tested at 25 °C (table 1). Compared with cisplatin (1 mg/mL) and oxaliplatin (8 mg/mL), all

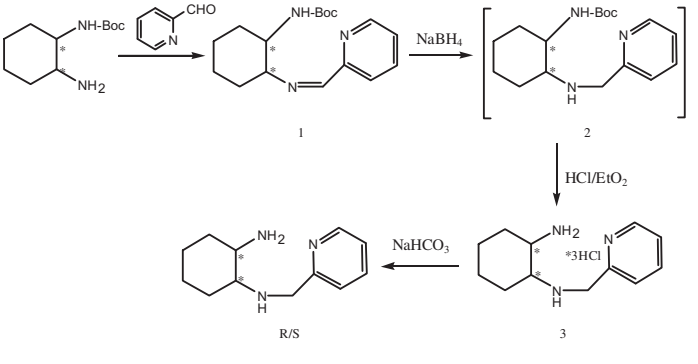

Figure 2. Synthetic scheme for ligands **R**/**S**.

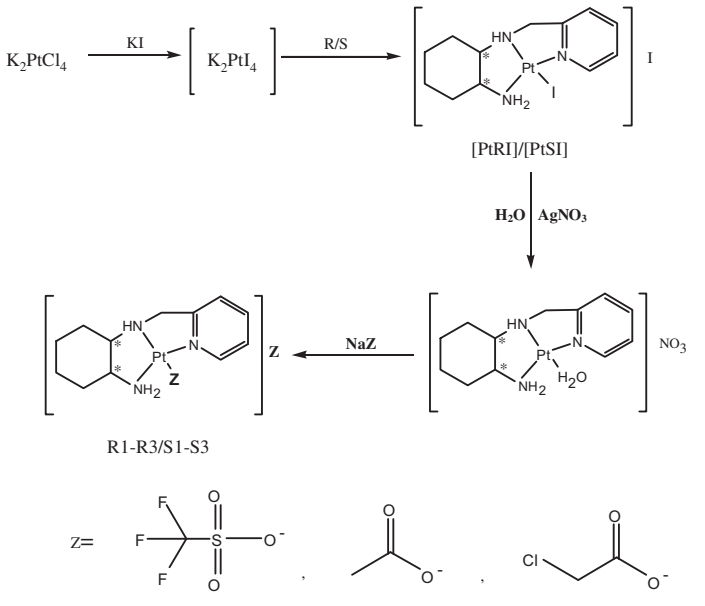

Figure 3. Synthetic scheme for targeted platinum(II) compounds.

prepared platinum compounds are greatly improved ranging from 22.3 to 46.8 mg/mL. Optical rotations of all complexes were tested (table 1).

3.4. *Cytotoxic studies*

In vitro cytotoxicities of platinum compounds were tested by MTT colorimetric assay against HepG-2 human hepatocellular carcinoma cell, MCF-7 human breast cancer cell, A549 human lung cancer cell, and HCT-116 human colorectal cancer cell, with carboplatin and oxaliplatin as positive controls. All platinum compounds with **R** as the carrier group showed activity against MCF-7, HCT-116, and A549 cell lines (table 2). Among them, **R2** gave lower IC_{50} values than carboplatin against MCF-7 and A549 cell lines and also exhibited close activity to oxaliplatin against HCT-116 cell line. Compound **R1** showed better antitumor activity than carboplatin against HCT-116. However, compounds with **S** as the carrier group showed very low or no cytotoxicity against the four tested cell lines.

Table 1. Aqueous solubility and optical rotation of complexes.

Complex	Aqueous solubility (mg/mL, 25 °C)	$\alpha_D^{15\,°C}$ ($C = 1.0$, H_2O)
[Pt**R**I]	22.3	46.9°
R1	39.8	35.1°
R2	44.0	29.8°
R3	30.1	31.3°
[Pt**S**I]	23.6	−43.2°
S1	40.4	−33.6°
S2	46.8	−31.1°
S3	28.6	−29.0°

Table 2. Cytotoxicity of the targeted compounds against four tumor cell lines.

	IC_{50} ($\mu mol \cdot L^{-1}$)			
Compd.	HepG-2	MCF-7	A549	HCT-116
[Pt**RI**]	>100	58.1	63.2	81.6
R1	>100	11.6	26.8	21.3
R2	>100	9.5	7.9	7.6
R3	>100	22.6	30.1	48.3
[Pt**SI**]	>100	>100	>100	>100
S1	>100	>100	>100	86.3
S2	>100	68.1	>100	58.5
S3	>100	>100	>100	>100
Carboplatin	9.7	15.3	11.2	Not tested
Oxaliplatin	Not tested	Not tested	Not tested	4.3

Based on the above results, platinum complexes with values of specific rotations from +29.8° to +46.9° ($\alpha_D^{15^\circ C}$ ($C = 1$, H_2O)), similar to those of oxaliplatin (+76.1°), show cytotoxicity, exhibiting similar SARS to oxaliplatin bearing the *trans*-(1*R*,2*R*)-cyclohexane-1,2-diamine as the carrier group [36,37]. Results also indicated that when CH_3COO^- or $ClCH_2COO^-$ was leaving groups, **R1** and **R2** showed much better antitumor activity than compounds bearing I^- or $CF_3SO_3^-$ as the leaving groups.

4. Conclusions

N-monosubstituted chiral DACH derivatives, **R** and **S**, were synthesized and spectrally characterized to prepare eight Pt(II) complexes. All compounds showed much better aqueous solubility than cisplatin and oxaliplatin. *In vitro* cytotoxicity tests showed that compounds bearing **R** as the carrier group had antitumor activity against MCF-7, A549, and HCT-116 cell lines, with **R2** showing better antitumor activity than carboplatin against MCF-7 and A549 cell lines and also showed close cytotoxicity to oxaliplatin against HCT-116. Compound **R1** also exhibited better activity than carboplatin against MCF-7. Consequently, the prepared platinum compounds, especially **R2**, deserve further investigation.

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