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NOTE

Synthesis and *in vitro* Cytotoxicity of Novel Platinum(II) Complexes

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Four novel multinuclear platinum(II) complexes with 1R,2R-diaminocyclohexane, Pt-S coordination bond and dicarboxylic acid ion chains as bridges, were designed, prepared and spectrally characterized. The *in vitro* cytotoxicities of the new compounds were evaluated against HL-60, SMMC-7721, A-549, MCF-7 and SW480 human tumor cell lines by MTT assay. The results indicated that all compounds showed cytotoxicity, particularly, complex **1a**, which has oxalic acid ion as a bridge, showed comparable anticancer activity to oxaliplatin against HL-60 and SMMC-7721.

Keywords: Multinuclear platinum(II), Synthesis, Antitumor activity.

Multinuclear platinum complexes, which could probably overcome the drug resistance/cross resistance arising from cisplatin and its analogs, have attracted much attention[1]. Recently, a number of multinuclear platinum(II) complexes have been designed and some of the compounds exhibited good antitumor activity[2-4]. The corresponding studies indicate that multinuclear platinum complexes, could not only deliver more platinum containing drugs to the tumor, but also form mutable-binding with tumor cell DNA and increase the activity to block DNA replication[5-7].

In this work, we report a novel set of multinuclear platinum complexes with 1R,2R-diaminocyclohexane (DACH), Pt-S bond formed by the coordination reaction of DMSO with Pt ion and dicarboxylic acid ion chains as bridges, four novel multinuclear platinum(II) complexes have been designed and synthesized and anticancer activity was measured by MTT assay[8].

Chemicals used were AR grade. Elemental analysis for C,H and N was performed with a JY/T 017-1996 elemental analyzer. ESI-MS spectra were carried out in a API QSTAR time-of-flight Spectrometer and a VG Autospec-3000 speitrometer. IR spectra were scanned by a TJ270-30 infrared spectrometer. ^{1}H NMR spectra were recorded on a 400 MHz Bruker DMX spectrometer. Specific rotatory power was performed on JASCO P-1020 spectropolarimeter.

Synthesis of complex 2: To a stirring aqueous solution (20 mL) of DMSO (40 mmol), $K_2[PtCl_4]$ (40 mmol) in water (100 mL) was added. The blending solution was stirred at 25 °C for 24 h. Then an aqueous solution (20 mL) of DACH (40 mmol) was added dropwise at 25 °C. After 4 h the mixture was evaporated, the pale yellow precipitate was collected and dried. Yield: 82 %.

Synthesis of complexes 1a-d: To a stirring aqueous solution (50 mL) of $AgNO_3$ (20 mmol), complex 2(20 mmol) in water (50 mL) was added, then the mixture solution was stirred at 25 °C for 0.5 h. A suspension of the corresponding silver dicarboxylate(10 mmol) was added and was stirred at 25 °C for 2 h, the resulting AgCl deposit was filtered off, the filtrate was evaporated to nearly dryness and some white solids precipitated, which were washed with water and ethanol for several times and dried in vacuum. Yield: Compound **1a**: 87 %, **1b**: Yield 80 %, **1c**: Yield 85 %, **1d**: Yield 78 %. The synthetic scheme is shown in Fig. 1.

Elemental analysis: Compound **1a:** Anal. Calced for $C_{18}H_{40}N_6O_{12}S_2Pt_2$: C 21.91 %, N8.52 %, H4.06 %, found: C 21.61 %, N 8.09 %, H 4.41 %. Compound **1b:** Anal. Calced for $C_{19}H_{42}N_6O_{12}S_2Pt_2$: C 22.80 %, N 8.40 %, H 4.20 %, found: C22.43 %, N 8.09 %, H 4.49 %. Compound **1c:** Anal. calced for $C_{20}H_{44}N_6O_{12}S_2Pt_2$: C23.67 %, N 8.28 %, H4.34 %, found: C 23.56 %, N 7.96 %, H 4.02 %. Compound **1d:** Anal. Calced for $C_{22}H_{46}N_6O_{12}S_2Pt_2$:C 25.38 %, N 8.08 %, H 4.42 %, found, C 25.01 %, N8.29 %, 4.21 %. Elemental analysis for each compound was in good agreement with the empirical formula proposed.

ESI-MS: Compound **1a:** *m/z* 846, $[M\text{-}DMSO\text{-}NO_3]^+$. Compound **1b**: *m/z* 938, $[M\text{-}NO_3]^+$. Compound **1c**: *m/z* 1037, $[M + Na]^+$. Compound **1d**: *m/z* 885, $[M\text{-}2xDMSO + H]^+$. All the complexes showed the positive peaks in their mass spectra, which are in agreement with their molecular formula weights.

TABLE-1
in vitro CYTOTOXICITY AGAINST SELECTED HUMAN TUMOR CELL LINES OF COMPLEXES **1a-1d**

Complex	HL-60	SMMC-7721	A-549	MCF-7	SW480
	IC_{50} (μM)				
Oxaliplatin	1.16	6.72	7.25	15.06	15.11
1a	2.87	7.49	19.21	29.78	39.87
1b	11.83	24.32	37.46	27.65	34.12
1c	10.86	29.81	33.49	37.82	36.54
1d	11.93	22.36	30.46	39.46	31.08

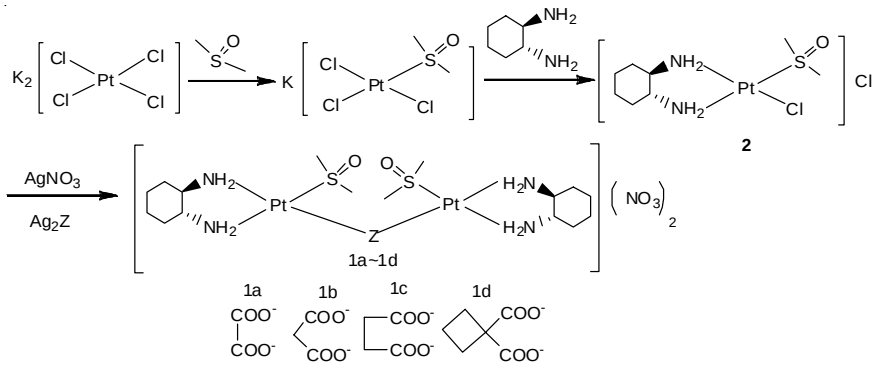

Fig. 1. Synthetic scheme for multinuclear platinum(II) complexes **1a-1d**

IR spectroscopy: IR (KBr, ν_{max}, cm^{-1}) compound **1a:** 3412s, 3170(br), 2934m, 2858m, 1640vs, 1483s, 1387m, 1302vs, 1150m, 877m, 516m, 462m. Compound **1b:** 3429s, 3156(br), 2936m, 2855m, 1620vs, 1456s, 1362m, 1295vs, 1142m, 857m, 523m, 450m. Compound **1c:** 3401s, 3168(br), 2930m, 864m, 1626vs, 1491s, 1380m, 1311vs, 1148m, 870m, 525m, 452m. Compound **1d:** 3412s, 3170(br), 2930m, 2860m, 1622vs, 1485s, 1389m, 1315vs, 1152m, 877m, 510m, 442m. In the IR spectra, the amino group participation in binding with Pt(II) was confirmed by the examination of νNH_2 and δNH_2 frequencies, which were shifted to lower frequencies comparing with the free amino group, due to Pt(II)-NH_2 coordinations. The shifts of the C=O absorption from free carboxylic acids near 1700 cm^{-1} to a band near 1640-1620 cm^{-1} proved that the carboxylate anion was coordinated to Pt^{2+} in each case.

^{1}H NMR (D_2O, 400MHz): Compound **1a:** 0.95-1.02 (m, 4H, 2 × CH_2CH*H*$CH\underline{H}CH_2$ of DACH), 1.49-1.58 (m, 8H, 2 × $C\underline{H}HC\underline{H}HC\underline{H}HC\underline{H}H$ of DACH), 1.93-1.21 (m, 4H, 2 × $CH\underline{H}C$-$H_2CH_2CH\underline{H}$ of DACH), 2.40-2.69 (m, 12H, 2 × $C\underline{H}_3(SO)C\underline{H}_3$), 3.37-3.46 (d, 4H, 2 × $CH_2C\underline{H}C\underline{H}CH_2$ of DACH). Compound **1b:** 0.96-1.02(m, 4H, 2× $CH_2CH\underline{H}CH\underline{H}CH_2$ of DACH), 1.50-1.57 (m, 8H, 2 × $C\underline{H}HC\underline{H}HC\underline{H}HC\underline{H}H$ of DACH), 1.93-1.21 (m, 4H, 2 × $CH\underline{H}CH_2CH_2CH\underline{H}$ of DACH), 2.42-2.70 (m, 12H, 2 × $C\underline{H}_3(SO)C\underline{H}_3$), 3.18-3.20 (m, 2H, $OOCC\underline{H}_2COO$) 3.37-3.46 (d, 4H, 2 × $CH_2C\underline{H}C\underline{H}CH_2$ of DACH). Compound **1c:** 0.96-1.02 (m, 4H, 2 × $CH_2CH\underline{H}CH\underline{H}CH_2$ of DACH), 1.52-1.58 (m, 8H, 2 × $C\underline{H}HC\underline{H}HC\underline{H}HC\underline{H}H$ of DACH), 1.93-1.21 (m, 4H, 2 × $CH\underline{H}CH_2CH_2CH\underline{H}$ of DACH), 2.42-2.70 (m, 12H, 2 × $C\underline{H}_3(SO)C\underline{H}_3$), 2.79-2.84 (m, 4H, $OOCC\underline{H}_2C\underline{H}_2COO$) 3.37-3.46 (d, 4H, 2 × $CH_2C\underline{H}C\underline{H}CH_2$ of DACH). Compound **1d:** 0.97-1.03 (m, 4H, 2 × $CH_2CH\underline{H}CH\underline{H}CH_2$ of DACH), 1.54-1.60 (m, 8H, 2 × $C\underline{H}HC\underline{H}HC\underline{H}HC\underline{H}H$ of DACH), 1.93-1.21 (m, 4H, 2 × $CH\underline{H}CH_2CH_2CH\underline{H}$ of DACH), 2.01-2.21 (m, 6H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.42-2.70 (m, 12H, 2 × $C\underline{H}_3(SO)C\underline{H}_3$), 3.37-3.46 (d, 4H, 2 × $CH_2C\underline{H}C\underline{H}CH_2$ of DACH). ^{1}H NMR spectral data of complexes were compatible with the related molecular structure.

Specific rotatory power: Compound **1a:** $[\alpha]_D^{25}$ (1c, H_2O) = + 70.2°. Compound**1b:** $[\alpha]_D^{25}$ (1c, H_2O) = + 82.7°. Compound **1c:** $[\alpha]_D^{25}$ (1c, H_2O) = + 48.6°. Compound **1d:** $[\alpha]_D^{25}$ (1c, H_2O) = + 40.2°.

***in vitro* Cytotoxicity:** *in vitro* Cytotoxicity was evaluated against five different human carcinoma cell lines: HL-60, SMMC-7721, A-549, MCF-7 and SW480 by MTT assay. The IC50 values of these complexes as well as positive controls, oxaliplatin, are given in Table-1. As we can see, the new complexes showed positive cytotoxicity against selected cell line. Complex **1a** comparable anticancer activity to oxaliplatin against HL-60 and SMMC-7721.

Conclusion

A novel set of multinuclear platinum complexes has been synthesized and the anticancer activity was measured by MTT assay. The novel complexes showed positive cytotoxicity against selected cell line.

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