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

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The novel dinuclear platinum(II) complexes, with 1R,2R-diaminocyclohexane, Pt-S coordination bond and 1,4-diaminobutane, 1,5-diaminopentane, 1,6-diaminohexane, 1,7-diaminoheptane chains as bridges respectively. Elemental analysis, ESI-MS, ^{1}H-NMR, specific rotatory power and IR spectral data were used to characterize the novel complexes. The anticancer activity was measured by MTT assay using HL-60, SMMC-7721, A-549, MCF-7 and SW480 human tumor cell lines. Moreover, the novel complexes showed comparable anticancer activity to oxaliplatin.

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

INTRODUCTION

Platinum-based anticancer drugs are widely used for the treatment of various types of solid tumor. However, their application is severely limited by their cumulative toxicities such as nephrotoxicity, ototoxicity and peripheral neuropathy[1]. These drawbacks have stimulated the search for other platinum-based anticancer agents not obeying the classical structure-activity relationship.

Dinuclear platinum complexes have been reported increasingly as an important type of non-classical anticancer platinum complexes. Recently, a number of novel complexes have been synthesize and some of them showed positive biological activity[2-6].

In this work, we report a novel set of dinuclear platinum complexes with 1R,2R-diaminocyclohexane(DACH), Pt-S bond formed by the coordination reaction of dimethyl sulfoxide with Pt ion and 1,4-diaminobutane, 1,5-diaminopentane, 1,6-diaminohexane, 1,7-diaminoheptane chains as bridges respectively. Anticancer activity was measured by MTT assay[7].

EXPERIMENTAL

Chemicals used were AR grade. Elemental analysis was performed on a JY/T 017-1996 elemental analyzer (C, H, N). Mass spectra was performed on a API QSTAR time-of-flight Spectrometer and a VG Autospec-3000 speitrometer. Infrared spectrum was performed on a TJ270-30 infrared spectrometer. The ^{1}H NMR data was obtained with a 400 MHz Bruker DMX spectrometer. Specific rotatory power was performed on JASCO P-1020 spectropolarimeter.

Synthesis of [(DACH)Pt(DMSO)Cl]Cl (2): K_2PtCl_4 (8.30 g, 20 mmol) dissolved in a 100 mL H_2O, DMSO (1.42 mL, 20 mmol) was added to the K_2PtCl_4 solution and the mixture was stirred 24 h at room temperature, the K[Pt(DMSO)Cl_3] solution was formed. 1R,2R-diaminocyclohexane (DACH) (2.28 g, 20 mmol), dissolved in 20 mL H_2O and added to K[Pt(DMSO)Cl_3] solution and the mixture was stirred for 4 h at room temperature. Finally, the solution was evaporated, the pale yellow precipitate was collected and dried. Yield of [(DACH)Pt(DMSO)Cl]Cl 7.12 g, 85 %.

Synthesis of [{(DACH)Pt(DMSO)}$_2$(μ-1,4-diaminobutane)](NO$_3$)$_4$ (1a): The mixture solution [(DACH)Pt-(DMSO)Cl]Cl (4.58 g, 10 mmol) and $AgNO_3$ (3.40 g, 20 mmol) in 100 mL H_2O was stirred 5 h at 60 °C. After removal of the precipitate of AgCl, 1,4-diaminobutane (0.44 g, 5 mmol) dissolved in a minimum amount of H_2O. The solution was stirred for 3 h at room temperature and evaporated. The white precipitate was collected and dried. Yield 4.33 g, 78 %.

Synthesis of [{(DACH)Pt(DMSO)}2(μ-1,5-diaminopentane)](NO$_3$)$_4$(1b): The solution [(DACH)Pt(DM-SO)Cl]Cl (4.58 g, 10 mmol) and $AgNO_3$ (3.40 g, 20 mmol) in 100 mL H_2O was stirred for 5 h at 60 °C. After removal of the precipitate of AgCl, 1,5-diaminopentane (0.51 g, 5 mmol) dissolved in a minimum amout of H_2O. The solution was stirred for 3 h at room temperature and evaporated, the white precipitate was collected and dried. Yield 3.93 g, 70 %.

Synthesis of [{(DACH)Pt(DMSO)}$_2$(μ-1,6-diaminohexane)](NO$_3$)$_4$ (1c): The mixture solution [(DACH)Pt-(DMSO)Cl]Cl (4.58 g, 10 mmol) and $AgNO_3$ (3.40 g, 20 mmol)

in 100 mL H_2O was stirred for 5 h at 60 °C. After removal of AgCl precipitate, 1,6-diaminohexane (0.58 g, 5 mmol) dissolved in a minimum amout of H_2O, the solution was again stirred for 3 h at room temperature and evaporated. The white precipitate was collected and dried. Yield 3.70 g, 65 %.

Synthesis of [{(DACH)Pt(DMSO)}$_2$(μ-1,7-diaminoheptane)](NO$_3$)$_4$ (1d): The solution [(DACH)Pt(DMSO)Cl]Cl (4.58 g, 10 mmol) and $AgNO_3$ (3.40 g, 20 mmol) in 100 mL H_2O was stirred for 5 h at 60 °C. After removal of the AgCl precipitate, 1,7-diaminoheptane (0.65 g, 5 mmol) dissolved in a minimum amout of H_2O, the solution was stirred again for 3 h at room temperature and evaporated, the white precipitate was collected and dried. Yield 4.78 g, 83 %. The synthetic scheme was shown in Fig. 1.

RESULTS AND DISCUSSION

Elemental analysis: 1a: Anal. calcd (%) for $C_{20}H_{52}N_{10}O_{14}S_2Pt_2$: C 21.62, N12.61, H 4.68, found (%) C 21.37, N 12.48, H 4.8 2. **1b:** Anal. Calcd (%) for $C_{21}H_{54}N_{10}O_{14}S_2Pt_2$: C 22.42, N 12.46, H 4.80, found (%) C 22.21, N 12.19, H 4.67. **1c:** Anal. Calcd (%) for $C_{22}H_{56}N_{10}O_{14}S_2Pt_2$: C23.20, N 12.30, H 4.92, found (%) C 23.01, N 12.19, H 4.71. **1d:** Anal. Calcd (%) for $C_{23}H_{58}N_{10}O_{14}S_2Pt_2$:C 24.00, N 12.15, H 5.03, found (%), C 23.81, N 12.01, 4.82. Elemental analysis for each compound was in good agreement with the empirical formula proposed.

IR: IR (KBr, ν, cm^{-1}) **1a:** 3442s, 3201(br), 2934 m, 2858 m, 1600 m, 1384s, 1126 m, 1025 m, 825 m, 444 m. **1b**: 3434s, 3185 (br), 2936 m, 2851 m, 1610 m, 1387s, 1130 m, 1025 m, 827 m, 456 m. **1c**: 34422, 3204 (br), 2933 m, 2854 m, 1600 m, 1384s, 1128 m, 1027 m, 830 m, 439 m. **1d**: 3442s, 3201 (br), 2934 m, 2858 m, 1602 m, 1385s, 1126 m, 1025 m, 834 m, 445 m. In 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 coordination.

ESI-MS. 1a: *m/z* 1033, [M-DMSO + H]$^+$. **1b:** *m/z* 1062, [M-NO_3]$^+$. **1c:** *m/z* 1076, [M-NO_3]$^+$. **1d:** *m/z* 1035, [M-2 × DMSO + K]$^+$. All the complexes showed the positive peaks in their mass spectra, which are in agreement with their molecular formula weights.

^{1}H-NMR (H_2O, 400 MHz): 1a: 0.97-1.04 (m, 4H, 2 × CH_2CH-HCHHCH_2 of DACH), 1.14-1.24 (m, 4H, NH_2CH_2-(CH_2)$_2$ CH_2NH_2), 1.47-1.56 (m, 8H, 2 × CHHCHHCHHHCHH of DACH), 1.90-1.99 (m, 4H, 2 × CHHCH$_2$CH$_2$CHH of DACH), 2.41-2.85 (m, 12H, 2 × CH_3(SO)CH_3), 3.20-3.23 (d, 4H, NH_2CH_2(CH$_2$)$_2$CH_2 NH_2), 3.38-3.47 (d, 4H, 2 × CH_2CHCHCH$_2$ of DACH). **1b:** 0.97-1.02(m, 4H, 2 × CH_2CHHCHHCH_2 of DACH), 1.17-1.21 (m, 6H, NH_2CH_2(CH$_2$)$_3$CH_2NH_2), 1.44-1.47 (m, 8H, 2 × CHHCHH -CHHCHH of DACH), 1.88-1.97 (m, 4H, 2 × CHHCH$_2$CH$_2$CHH of DACH), 2.36-2.62 (m, 12H, 2×CH_3(SO)CH_3), 3.19-3.21 (d, 4H, NH_2CH_2(CH$_2$)$_3$CH_2NH_2), 3.36-3.45 (d, 4H, 2 × CH_2CH-CHCH_2 of DACH). **1c:** 1.02-1.21 (m, 4H, 2 × CH_2CHHCHHCH_2 of DACH), 1.21-1.27 (m, 8H, NH_2CH_2(CH_2)$_4$CH_2NH_2), 1.49-1.50 (d, 8H, 2 × CHHCHHCHHHCHH of DACH), 1.90-2.02 (m, 4H, 2 × CHHCH$_2$CH$_2$CHH of DACH), 2.42-2.68 (m, 12H, 2xCH_3(SO)CH_3), 3.25 (s, 4H, NH_2CH_2(CH$_2$)$_4$CH_2NH_2), 3.41-3.50 (d, 4H, 2×CH_2CHCHCH_2 of DACH). **1d:** 1.02-1.08 (m, 4H, 2 × CH_2CHHCHHCH_2 of DACH), 1.19-1.29 (m,10H, NH_2CH_2 (CH_2)$_5$CH_2NH_2), 1.49-1.50 (m, 8H, 2×CHHCHHC-HHCHH of DACH), 1.93-2.01 (m, 4H, 2×CHHCH$_2$CH$_2$CHH of DACH), 2.42-2.82 (m, 12H, 2×CH_3(SO)CH_3), 3.23-3.36 (m, 4H, NH_2CH_2 (CH$_2$)$_5$CH_2NH_2), 3.37-3.49 (m, 4H, 2×CH_2-CHCHCH_2 of DACH). ^{1}H NMR spectral data of complexes were compatible with the related molecular structure.

Specific rotatory power: 1a:$[\alpha]_D^{20}$ (1c, H_2O) = + 74.2°. **1b:**$[\alpha]_D^{20}$ (1c, H_2O) = + 86.5°. **1c:**$[\alpha]_D^{20}$ (1c, H_2O) = + 85.4°. **1d:**$[\alpha]_D^{20}$ (1c, H_2O) = + 79.5°.

***in vitro* Cytotoxicity:** *in vitro* Cytotoxicity of the dinuclear platinum complexes was tested by MTT assay using HL-60, SMMC-7721, A-549, MCF-7 and SW480 human tumor cell lines. The IC_{50} values of these complexes as well as positive controls, oxaliplatin, are given in Table-1. As we can see, the complexes showed positive cytotoxicity against selected cell lines and comparable anticancer activity to oxaliplatin.

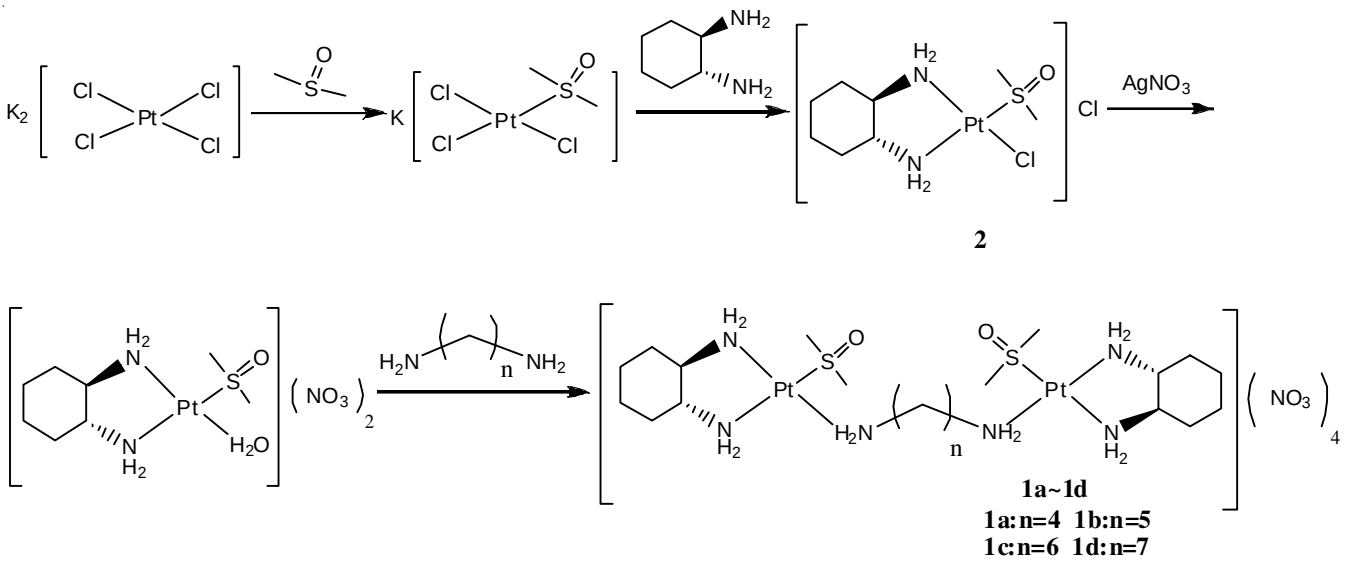

Fig. 1. Synthetic scheme for dinuclear platinum(II) complexes 1a-1d

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	1.16	6.72	7.25	15.06	15.11
1b	1.11	9.66	5.90	17.89	19.58
1c	1.09	9.19	4.20	13.31	14.06
1d	1.42	9.00	4.33	19.60	11.26

Conclusion

A novel set of dinuclear platinum complexes has been synthesized and the anticancer activity was measured by MTT assay. Elemental analysis, ESI-MS, ^{1}H-NMR, specific rotatory power and IR spectral data were used to characterize the novel complexes and the novel complexes showed comparable anticancer activity to oxaliplatin.

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