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Synthesis and cytotoxicity of dinuclear platinum(II) complexes of (1*S*, 3*S*)-1,2,3,4-tetrahydroisoquinolines

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ABSTRACT

A series of novel dinuclear platinum(II) complexes with (1*S*, 3*S*)-1,2,3,4-tetrahydroisoquinolines as the ligands were synthesized as potential anticancer agents in several steps starting from commercially available L-DOPA. The cytotoxicities of the series of dinuclear platinum(II) complexes of tetrahydroisoquinoline were tested against HCT-8, BEL-7402, A2780, MCF-7, Hela, A549 and BGC-823 cell lines by the MTT test. These complexes showed selective inhibition activity against cisplatin-insensitive cell line Skov3.

1. Introduction

Platinum(II) complexes [1–3] are widely used in cancer chemotherapy. Cisplatin [2] is one of the most potent antitumor drugs available for the therapeutic management of solid tumors, such as germ cell tumors, ovarian, lung, head and neck, and bladder cancers. Despite its wide application as a chemotherapeutic agent, cisplatin exhibits two main disadvantages: intrinsic or acquired resistance and toxicity. These side effects limit the use of cisplatin in some cancers. So far, tremendous efforts have been devoted to developing cisplatin analogs with broader spectra of activity, improved clinical efficacy, and reduced toxicity [3].

More recently, to overcome the side effects of cisplatin, there have been efforts directed at the design of non-classical Pt complexes [3–8]. Multinuclear platinum complexes containing two, three or four platinum centers with both *cis* and/or *trans* configurations have been designed and polyamines are generally utilized as linkers to connect the platinum centers. A representative trinuclear complex, BBR3464, has entered a phase II clinical trial and exhibits activity against pancreatic, lung and melanoma cancers [3a].

1,2,3,4-Tetrahydroisosoquinoline alkaloids are widespread occurring natural products possessing various bioactivities [9]. A series of cisplatinum complexes with 1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinolines have been reported [8b,10]. Several of these new complexes showed better *in vitro* cytotoxicity against several human tumor cell lines than cisplatin. In our previous report, we designed and synthesized a novel series of *cis*-dichloroplatinum(II) complexes of (1*S*, 3*S*)-1,2,3,4-tetrahydroisoquinolines [11]. In the present work, we report the design and synthesis of a series of novel dinuclear (1*S*, 3*S*)-1,2,3,4-tetrahydroisoquinolines platinum complex **8a**–**e**. All complexes were evaluated for their *in vitro* cytotoxicity against a panel of human tumor cell lines.

2. Experimental

Synthesis of the new derivatives (**8a**–**e**) was realized by a stereoselective route starting from L-DOPA (Scheme 1). L-DOPA was esterified by $SOCl_2$ and CH_3OH to the corresponding ester **1**. The synthesis of **2** was accomplished *via* an asymmetric Pictet-Spengler reaction from L-DOPA methyl ester and aromatic aldehydes under acidic conditions. The major product with *cis* configuration was obtained *via* 1,3-asymmetric induction [12]. Treatment of compound **2** with HCOOH/Ac_2O/HCOONa at ambient temperature afforded the *N*-protected product. Methylation of the *N*-protected product with Me_2SO_4/K_2CO_3 in acetone under refluxing yielded the corresponding *O*-methylated product. Then

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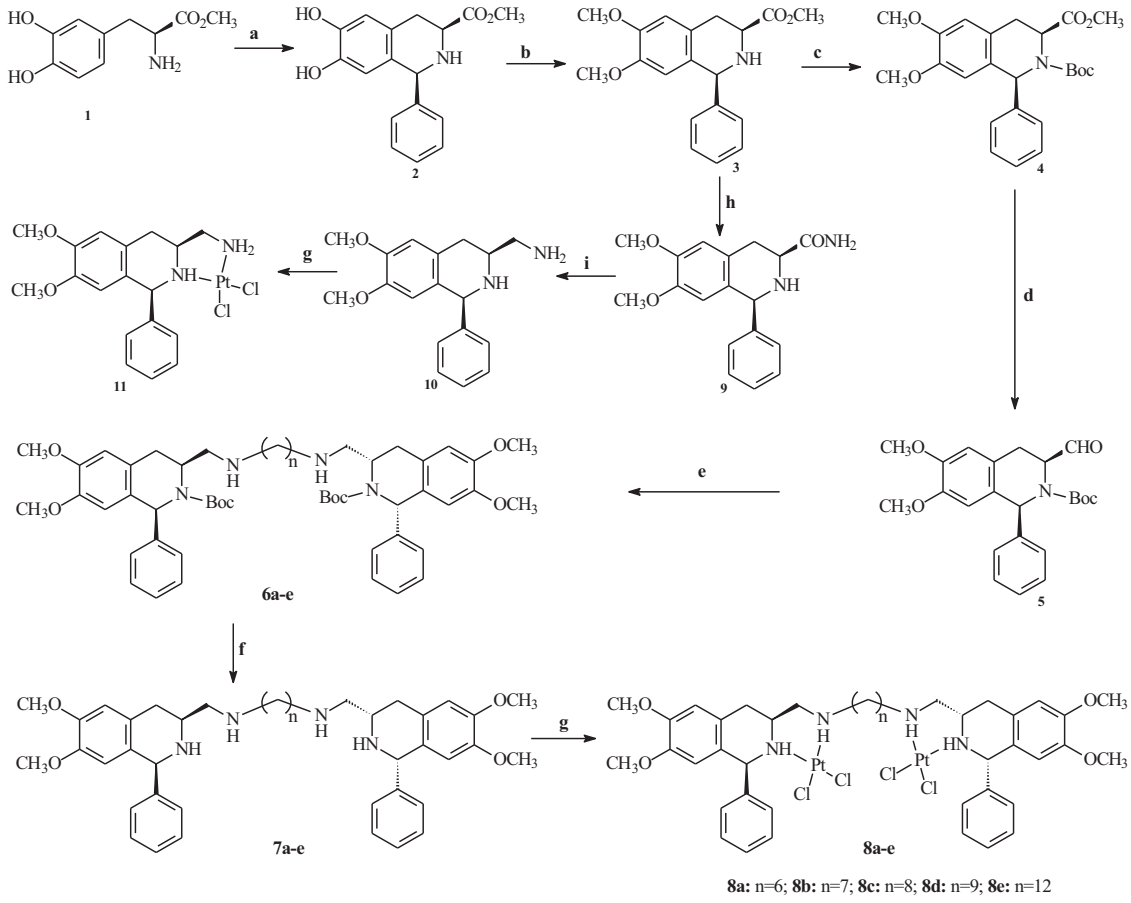

Scheme 1. Reagents and conditions: (a) (1) $SOCl_2$, CH_3OH, rt, 72 h. (2) Benzaldehyde, CH_3COOH, CH_3COONa, rt, 20 h. (b) (1) HCOOH, HCOONa $(CH_3CO)_2O$, rt, 4 h, then 1 mol/L HCl, CH_3OH, rt, 24 h. (2) K_2CO_3, Me_2SO_4, acetone, reflux 10 h. (3) HCl–CH_3OH, reflux 3 h. (c) Boc_2O, TEA, CH_2Cl_2, rt, 16 h. (d) DIBAL-H, toluene, −78 °C, 1.5 h. (e) Aliphatic diamines, CH_3OH, rt, 30 min, then $NaBH_3CN$, rt, 5 h. (f) Me_2S, TFA, CH_2Cl_2, rt, 30 min. (g) K_2PtCl_4, H_2O, 1 M NaOH, 60 °C, 24 h. (h) NH_3-CH_3OH, rt, 16 h. (i) $LiAlH_4$, THF, rt, 13 h.

the *O*-methylated product was refluxed in HCl/CH_3OH to cleave the formyl group and product **3** was afforded [13]. Compound **3** was converted to the *N*-Boc amino ester **4** in almost quantitative yield by treatment with Boc_2O in the presence of triethylamine. The *N*-Boc esters **4** were reduced with DIBAL-H in dichloromethane at −78 °C to give the amino aldehyde **5**, which was then coupled with various aliphatic diamines through reductive amination. Subsequently, removal of Boc in the presence of trifluoroacetic acid and dimethyl sulfide led to compound **7**. The structures of ligands **7a**–**e** were characterized through analysis of their respective data [14]. The platinum(II) complexes (**8a**–**e**) were then prepared by treatment of the ditetrahydroisoquinoline ligands **7** with potassium tetrachloroplatinate(II) under controlled-pH conditions in water at 60 °C [15]. In order to study the difference of standard platinum agents and dinuclear platinum complexes, mononuclear platinum complex **11** was synthesized *via* three steps from intermediate **3**. These complexes were characterized by NMR techniques, mass spectra and elemental analysis. However, due to slow chloro-ligand-DMSO exchange, all ^1H NMR spectra of the platinum complexes **8a**–**e** showed multiple sets of signals which are difficult to assign. This phenomenon was also reported in the literature [16].

3. Results and discussion

The cytotoxicities of the platinum complexes were tested against HCT-8, BEL-7402, A2780, MCF-7, Hela, A549, BGC-823 and Skov3 cell lines by the MTT method. The results are summarized in Table 1. Cisplatin and compound **11** was used as control compounds. From the screening results, it is evident that all of these dinuclear compounds exhibited good activity against these cell lines, and the mononuclear compound **11** was found only

Table 1
Cytotoxicity of compounds **8a**–**e** against human tumor cells (IC_{50}, μmol/L).[a]

Compound	Compound descriptors	Human tumor cells							
		HCT-8	BEL-7402	A2780	MCF-7	Hela	A549	BGC-823	Skov3
8a	*n* = 6	9.4	17.2	12.5	24.9	40.2	35.3	10.7	9.33
8b	*n* = 7	16.7	8.9	10.6	14.4	24.0	39.0	14.5	24.02
8c	*n* = 8	21.5	42.6	12.3	12.1	20.7	37.2	20.2	32.68
8d	*n* = 9	25.3	20.7	6.0	11.2	20.7	11.2	17.4	21.9
8e	*n* = 12	20.9	33.4	18.3	13.8	42.8	17.8	30.2	20.75
11	Mononuclear	>100	>100	73.0	>100	>100	94.5	>100	>100
Control	Cisplatin	2.9	2.5	2.7	5.3	1.4	1.4	0.8	>100

[a] Inhibitory concentration (IC_{50}, μmol/L) as obtained by the MTT assay.

marginally cytotoxic and almost showed no inhibition activity at drug concentrations of >100 μmol/L. MCF-7 and A2780 were more sensitive than Hela and A549 to the dinuclear platinum complexes. It is noteworthy that these complexes showed better selectivity against Skov3 cell than cisplatin, which did not show any dose response at concentrations as high as 100 μmol/L.

4. Conclusion

In conclusion, we have synthesized a series of novel dinuclear platinum(II) complexes with (1*S*, 3*S*)-1,2,3,4-tetrahydroisoquinolines as the ligands. The cytotoxicities of this series of complexes were screened against HCT-8, BEL-7402, A2780, MCF-7, Hela, A549, BGC-823 and Skov3 cell lines by the MTT test. These complexes showed good selective inhibition activity against cisplatin-insensitive cell line Skov3. This result is helpful in designing new platinum anticancer drugs to circumvent acquired resistance to cisplatin.

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[14] Data of ligands **7a**–**e**. **7a**: White solid, mp > 250 °C, $[\alpha]_D^{24}$ −33.3 (*c* 0.81 CH_3OH) ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (s, 4H, C–C_2H_4–C), 1.71 (s, 4H, C–CH_2–C×2), 2.90-3.10 (m, 6H, CH_2–Ar×2), 3.20–3.30 (m, 2H, CH_2–N×2), 3.44 (s, 6H, –OCH_3×2), 3.78 (s, 6H, –OCH_3×2), 4.10 (m, 2H, CH–Ar×2), 5.74 (d, 2H, *J* = 6.6, Ar–CH–Ar×2), 6.07 (s, 2H, Ar–H×2), 6.85 (s, 2H, Ar–H×2), 7.50 (s, 10H, Ar–H×2), 9.58 (br, 4H, –NH×2), 10.07 (br, 2H, –NH×2), 10.27 (br, 2H, –NH×2). ESI-MS: 679 (*m*/*z* + 1); HRMS (ESI) Calcd. for $C_{42}H_{55}N_4O_4$: 679.4217, found: 679.4224. **7b**: White solid, mp 190–192 °C, $[\alpha]_D^{24}$ −35.2 (*c* 0.31 CH_3OH) ^{1}H NMR (300 M Hz, DMSO-d_6): δ 1.35 (s, 6H, C–C_3H_6–C), 1.70 (s, 4H, C–CH_2–C×2), 2.90-3.10 (m, 6H, CH_2–Ar×2), 3.20–3.30 (m, 2H, CH_2–N×2), 3.44 (s, 6H, –OCH_3×2), 3.78 (s, 6H, –OCH_3×2), 4.10 (m, 2H, CH–Ar×2), 5.72 (m, 2H, Ar–CH–Ar×2), 6.07 (s, 2H, Ar–H×2), 6.85 (s, 2H, Ar–H×2), 7.49 (m, 10H, Ar–H×2), 9.65 (br, 4H, –NH×2), 10.17 (br, 2H, –NH×2), 10.33 (br, 2H, –NH×2). ESI-MS: 693 (*m*/*z* + 1); HRMS (ESI) Calcd. for $C_{43}H_{57}N_4O_4$: 693.4374, found: 693.4365. **7c**: White solid, mp 237–239 °C, $[\alpha]_D{}^{24}$ −34.7 (*c* 0.39 CH_3OH) ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.32 (s, 8H, C–C_4H_8–C), 1.68 (m, 4H, C–CH_2–C×2), 2.90–3.10 (m, 4H, CH_2–Ar×2), 3.20–3.30 (m, 8H, CH_2–N–CH_2×2), 3.44 (s, 6H, –OCH_3×2), 3.78 (s, 6H, –OCH_3×2), 4.09 (m, 2H, N–CH–C×2), 5.72 (m, 2H, Ar–CH–Ar×2), 6.07 (s, 2H, Ar–H×2), 6.85 (s, 2H, Ar–H×2), 7.49 (m, 10H, Ar–H×2), 9.62 (br, 4H, –NH×2), 10.10 (br, 2H, –NH×2), 10.33 (br, 2H, –NH×2). ^{13}C NMR (75 MHz, DMSO-d_6): δ 148.64, 147.52, 136.17, 130.19, 129.47, 128.65, 124.13, 123.51, 111.41, 110.54, 60.63, 55.57, 55.46, 51.54, 48.09, 47.16, 29.19, 28.04, 25.66, 25.26. ESI-MS: 707 (*m*/*z* + 1); HRMS (ESI) Calcd. for $C_{44}H_{59}N_4O_4$: 707.4536, found: 707.4553. **7d**: Yellowish solid, mp 185–187 °C, $[\alpha]_D^{24}$ −27.9 (*c* 0.57 CH_3OH) ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.28 (s, 10H, C–C_5H_{10}–C), 1.65 (m, 4H, C–CH_2–C×2), 2.90–3.10 (m, 6H, CH_2–Ar×2), 3.20–3.30 (m, 2H, CH_2–N×2), 3.35 (s, 6H, –OCH_3×2), 3.77 (s, 6H, –OCH_3×2), 4.09 (m, 2H, CH–Ar×2), 5.71 (m, 2H, Ar–CH–Ar×2), 6.06 (s, 2H, Ar–H×2), 6.83 (s, 2H, Ar–H×2), 7.48 (m, 10H, Ar–H×2), 9.63 (br, 4H, –NH×2), 10.15 (br, 2H, –NH×2), 10.32 (br, 2H, –NH×2). ESI-MS: 721 (*m*/*z* + 1); HRMS (ESI) Calcd. for $C_{45}H_{61}N_4O_4$: 721.4687, found: 721.4692. **7e**: Yellowish solid, mp 209–211 °C, $[\alpha]_D^{24}$ −30.9 (*c* 0.58 CH_3OH) ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.27 (s, 16H, C–C_8H_{16}–C), 1.66 (m, 4H, C–CH_2–C×2), 2.90-3.10 (m, 6H, CH_2–Ar×2), 3.20–3.30 (m, 2H, CH_2–N×2), 3.44 (s, 6H, –OCH_3×2), 3.78 (s, 6H, –OCH_3×2), 4.09 (m, 2H, CH–Ar×2), 5.73 (m, 2H, Ar–CH–Ar×2), 6.07 (s, 2H, Ar–H×2), 6.85 (s, 2H, Ar–H×2), 7.49 (m, 10H, Ar–H×2), 9.61 (br, 4H, –NH×2), 10.14 (br, 2H, –NH×2), 10.32 (br, 2H, –NH×2). ESI-MS: 764 (*m*/*z* + 1); HRMS (ESI) Calcd. for $C_{48}H_{67}N_4O_4$: 763.5156, found: 763.5155.

[15] General procedure for the preparation of compound **8a**–**e**: A solution of **7c** (1.0 mmol) and K_2PtC1_4 (2.0 mmol) in distilled water (12 mL) was heated to 65–70 °C with stirring. The pH of the reaction solution was checked continuously and 1 mol/L NaOH was added to keep the pH in the range 3–4. Toward the end of the reaction, pH was adjusted to 6 with 0.1 mol/L NaOH. After the mixture was cooled to ambient temperature, the precipitate was filtered, washed three times with cold water, twice with ethanol, and once with diethyl ether, and dried in vacuo (87% yield) to afford compound **8c**: yellow solid, mp: 237–239 °C, Elemental analysis: Calcd. for $C_{44}H_{58}O_4N_4Cl_4Pt_2$ (%): C 42.66, H 4.72, N 4.52; Found: C 42.59, H 4.92, N 4.36. **8a**: Offwhite solid, mp: 237–239 °C, Elemental analysis: Calcd. for $C_{42}H_{54}O_4N_4Cl_4Pt_2$ (%): C 41.65, H 4.49, N 4.63; Found: C 41.79, H 4.52, N 4.61. **8b**: Offwhite solid, mp: 234–236 °C, Elemental analysis: Calcd. for $C_{43}H_{56}O_4N_4Cl_4Pt_2$ (%): C 42.16, H 4.61, N 4.57; Found: C 42.57, H 4.81, N 4.40. **8d**: Offwhite solid, mp: 238–240 °C, Elemental analysis: Calcd. for $C_{45}H_{60}O_4N_4Cl_4Pt_2$ (%): C 43.14, H 4.83, N 4.47; Found: C 43.30, H 4.68, N 4.64. **8e**: Offwhite solid, mp: 228–230 °C, Elemental analysis: Calcd. for $C_{48}H_{66}O_4N_4Cl_4Pt_2$ (%): C 44.52, H 5.14, N 4.33; Found: C 44.30, H 5.27, N 4.16.

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