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Synthesis, structures, antiproliferative activity of a series of ruthenium(II) arene derivatives of thiosemicarbazones ligands

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ABSTRACT

A series of [(*p*-cymene)Ru(TSC)Cl]Cl compounds ([**1**]Cl, [**2**]Cl and [**3**]Cl) and their corresponding [(*p*-cymene)Ru(TSC)Cl][(*p*-cymene)$RuCl_3$] derivatives ([**1**][(*p*-cymene)$RuCl_3$], [**2**][(*p*-cymene)$RuCl_3$] and [**3**][(*p*-cymene)$RuCl_3$]) have been synthesized and characterized by H^1 NMR, elemental analysis and HR-ESI-mass spectrometry. The molecular structures of [**2**]Cl, [**3**]Cl, [**1**][(*p*-cymene)$RuCl_3$], [**2**][(*p*-cymene)$RuCl_3$] and [**3**][(*p*-cymene)$RuCl_3$] have been characterized by single-crystal X-ray diffraction analysis. The complexes have been further evaluated for their *in vitro* antiproliferative activities against the SGC-7901 human gastric cancer, BEL-7404 human liver cancer and HEK-293T noncancerous cell lines. Furthermore, the interactions of the complexes [**1**]Cl and [**1**][(*p*-cymene)$RuCl_3$] with HSA have been followed by fluorescence spectrometry studies.

Introduction

The synthesis of half-sandwich ruthenium complexes containing η^6-arene ligands has attracted increasing attention [1] for their potential applications as catalysts in synthetic organic chemistry [2] as well as metallopharmaceuticals in cancer therapy [3]. The hydrophobicity of arene ligand is deeming to facilitate the diffusion of the complexes through the lipophilic cell membrane when these complexes are employed as anticancer drug [4]. Meanwhile, the three remaining Ru coordination sites can be filled with various ligands, which offer possibilities to modulate biological and pharmacological properties by selecting proper ligand [5]. For instance, Ru arene complexes containing ethylenediamine (en) ligand have showed cytotoxicity toward cancer cells for their binding ability to DNA [3a], [6]. In addition, related complexes with 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]-decane (PTA) as the ligand, e.g. [(*p*-cymene)Ru(PTA)Cl_2] (RAPTA-C), have exhibited activity against metastases [3b], [7]. Besides en and PTA ligand, some other systems have been investigated in ruthenium-based complexes, including moieties incorporating N,N- [8], N,O- [9], O,O- [10], and O,S- [11] chelating ligands and several monodentate biologically active ligands [12]. It is shown that the nature of the ligands, which can adjust the hydrophobicity of the compounds to penetrate the cell [13] or afford stability of the complexes in aqueous solution [11a], influences the *in vitro* anticancer activity significantly.

Thiosemicarbazones (TSCs), considered as one kind of the most important scaffolds, have been found to be incorporated in many biologically active compounds [14]. TSCs are capable of chelating with a broad range of metal ions to form stable organometallics, which have exhibited such pharmacological properties as antibacterial, antifungal, and antitumor activities and so on [15]. Particularly, the Ru-arene complexes with TSCs ligands have emerged as an approach to develop promising lead TSC-based therapeutic agents [16]. More recently, we have demonstrated the antiproliferative activity of TSCs and the corresponding Ru-anere (arene = η^6-*p*-cymene) complexes [17], and the results have shown that the structures of the compounds have great effects on their antiproliferative activity.

Our motivation for improving the antiproliferative activity of the Ru-arene compounds is based on the adjustment of the structures of the compounds. Here, we report the controlled synthesis of a series of Ru-arene compounds, employing N^4-phenyl-TSC as the ligands. Moreover, the relationships between the structures and antiproliferative activities are investigated. Specially, information are provided on the anticancer activity of the compounds [(arene)

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Ru(TSC)Cl]$^+$[(arene)$RuCl_3$]$^-$ systems that possess an unusual organometallic counterion.

Experimental section

Materials

Ruthenium(III) chloride hydrate, TSC and other reagents were purchased from J&K chemical Co (China). All reagents and solvents were of high purity and used without further purification. The starting materials [(*p*-cymene)$RuCl_2$]$_2$ were prepared according to literature methods [17]. All of the TSC ligands (L′ = L^1, L^2 and L^3) were prepared by previously reported procedures [17].

Synthesis

[(*p*-cymene)Ru(L^1)Cl]Cl ([1]Cl). Compound [**1**]Cl was reported previously by us [17].

[(*p*-cymene)Ru(L^2)Cl]Cl ([2]Cl). Compound [**2**]Cl was synthesized as for [**1**]Cl. [(*p*-cymene)RuCl(μ-Cl)]$_2$ (0.05 mmol, 31.5 mg) and 4-fluoro-benzaldehyde-N^4- phenylthiosemicarbazone (L^2) (0.1 mmol, 25.5 mg) were dissolved in 5 mL of dichloromethane and stirred for 3 h. The clear orange solution was evaporated to dryness and afforded a dark red powder, which was subsequently washed with n-hexane and dried under reduced pressure. Yield 58.2%. HR-ESI-MS (MeOH) *m*/*z* [Found (Calcd)]: 508.2532 (508.6169) {[(*p*-cymene)Ru(L^2)Cl] − HCl}$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.903 (1H, s, CH═N), 8.429–8.382 (2H, m, phenyl-*H*), 7.505–7.424 (7H, m, phenyl-*H*), 5.765 (1H, d, J = 6.0 Hz, *p*-cym phenyl-*H*), 5.202 (1H, d, J = 5.9 Hz, p-cym phenyl-*H*), 5.092 (1H, d, J = 6.0 Hz, *p*-cym phenyl-*H*), 5.046 (1H, d, J = 6.0 Hz, *p*-cym phenyl-*H*), 2.713–2.621 (1H, m, *p*-cym C*H*$(CH_3)_2$), 2.117 (3H, s, *p*-cym CC*H*$_3$), 1.224 (3H, d, J = 6.9 Hz, *p*-cym CH(C*H*$_3)_2$), 1.165 (3H, d, J = 6.9 Hz, *p*-cym CH(C*H*$_3)_2$) ppm. Single crystals suitable for X-ray diffraction were obtained by recrystallization in ethanol and hexane (30/70) solution.

[(*p*-cymene)Ru(L^3)Cl]Cl ([3]Cl). Compound [**3**]Cl was synthesized as for [**1**]Cl. Yield 47.4%. HR-ESI-MS (MeOH) *m*/*z* [Found (Calcd)]: 496.2913 (496.6541) {[(*p*-cymene)Ru(L^3)Cl] − HCl}$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.747 (1H, s, NHCS), 9.009 (1H, s, N*H*Ph), 8.386 (1H, s, CH═N), 7.823 (1H, d, J = 4.9 Hz, thiophene-*H*), 7.598–7.572 (3H, m, thiophene-*H* and phenyl-*H*), 7.459–7.408 (2H, m, phenyl-*H*), 7.346–7.295(2H, m, thiophene-*H* and phenyl-*H*), 5.580 (1H, d, J = 5.9 Hz, *p*-cym phenyl-*H*), 5.272 (1H, d, J = 5.0 Hz, *p*-cym phenyl-*H*), 5.177 (1H, d, J = 5.4 Hz, *p*-cym phenyl-*H*), 5.139 (1H, d, J = 6.0 Hz, *p*-cym phenyl-*H*), 2.771–2.724 (1H, m, *p*-cym C*H*$(CH_3)_2$), 2.178 (3H, s, *p*-cym CC*H*$_3$), 1.238 (3H, d, J = 6.9 Hz, *p*-cym CH(C*H*$_3)_2$), 1.189 (3H, d, J = 6.7 Hz, *p*-cym CH(C*H*$_3)_2$) ppm. Anal. Calcd for $C_{20}H_{27}Cl_2N_3RuS{\cdot}0.5H_2O$: C, 45.97; H, 5.40; N, 8.04; Found: C, 46.24; H, 5.24; N, 8.09. Single crystals suitable for X-ray diffraction were obtained by recrystallization in ethanol and hexane (30/70) solution.

[(*p*-cymene)Ru(L^1)Cl][(*p*-cymene)$RuCl_3$] ([1][(*p*-cymene)$RuCl_3$]). [(*p*-cymene)RuCl(μ-Cl)]$_2$ (0.1 mmol, 63 mg) and benzaldehyde-N^4-phenylthiosemicarbazone (L^1) (0.1 mmol, 25.5 mg) were dissolved in 5 mL of dichloromethane and stirred for 3 h. The clear orange solution was evaporated to dryness and afforded a dark red powder, which was then washed with n-hexane and dried under reduced pressure. Yield 59%. HR-ESI-MS (MeOH, 6 eV, 120 °C) (+) *m*/*z* [Found (calcd)]: 490.0909 (490.0897) {[(*p*-cymene)Ru(L^1)Cl] − HCl}$^+$. HR-ESI-MS (MeOH, 6 eV, 120 °C) (−) *m*/*z* [Found (calcd)]: 340.8477 (340.9199) [(*p*-cymene)$RuCl_3$]$^-$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.394 (1H, s, N*H*Ph), 9.493 (1H, s, CH═N), 8.309–8.284 (2H, m, phenyl-*H*), 7.625–7.551 (5H, m, phenyl-*H*), 7.424–7.373 (2H, m, phenyl-*H*), 7.312 (1H, s, phenyl-*H*), 5.553, 5.336 {4H, 2 × d, $^3J_{AB}$ = 5.9 Hz, [(p-cymene)$RuCl_3$]$^-$ AA′BB′ spin system}, 5.493, 4.937, 4.748, 4.693 {4H, 4 × d, $^3J_{AB}$ = 5.7 Hz, [(p-cymene)Ru(L1)Cl]$^+$ AA′BB′ spin system}, 3.172, 2.685 (2H, 2 × m, 2 × C*H*$(CH_3)_2$), 2.327, 2.071 (6H, 2 × s, 2 × CH_3), 1.390, 1.296 (6H, 2 × d, J = 6.9 Hz, anion-CH(C*H*$_3)_2$), 1.142 (6H, dd, J = 6.9 Hz and 12.5 Hz, cation-CH(C*H*$_3)_2$) ppm. Anal. Calcd for $C_{34}H_{41}Cl_4N_3Ru_2S{\cdot}CH_3CN$: C, 47.57; H, 4.88; N, 6.16; Found: C, 47.92; H, 4.57; N, 5.76. Single crystals suitable for X-ray diffraction were obtained by recrystallization in acetonitrile and hexane (30/70) solution.

[(*p*-cymene)Ru(L^2)Cl][(*p*-cymene)$RuCl_3$] ([2][(*p*-cymene)$RuCl_3$]). Compound [**2**][(*p*-cymene)$RuCl_3$] was synthesized as for [**1**][(*p*-cymene)$RuCl_3$]. Yield 60.8%. HR-ESI-MS (MeOH, 6 eV, 120 °C) (+) *m*/*z* [Found (calcd)]: 508.0794 (508.0802) {[(*p*-cymene)Ru(L^2)Cl] − HCl}$^+$. HR-ESI-MS (MeOH, 6 eV, 120 °C) (−) *m*/*z* [Found (calcd)]: 340.9344 (340.9199) [(η^6-*p*-cymene)$RuCl_3$]$^-$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.358 (1H, s, N*H*Ph), 9.523 (1H, s, CH═N), 8.435–8.389 (2H, m, phenyl-*H*), 7.606 (2H, d, J = 7.9 Hz, phenyl-*H*), 7.426–7.375 (2H, m, phenyl-*H*), 7.315–7.291 (2H, m, phenyl-*H*), 7.249 (1H, s, phenyl-*H*), 5.551, 5.343 {4H, 2 × d, $^3J_{AB}$ = 5.9 Hz, [(p-cymene)$RuCl_3$]$^-$ AA′BB′ spin system}, 5.492, 4.999, 4.863, 4.745 {4H, 4 × d, $^3J_{AB}$ = 5.7 Hz, [(p-cymene)Ru(bzsc)Cl]$^+$ AA′BB′ spin system}, 3.163, 2.696 (2H, 2 × m, 2 × C*H*$(CH_3)_2$), 2.325, 2.078 (6H, 2 × s, 2 × CH_3), 1.388, 1.295 (6H, 2 × d, J = 6.9 Hz, anion-CH(C*H*$_3)_2$), 1.155 (6H, dd, J = 6.9 Hz and 14.0 Hz, cation-CH(C*H*$_3)_2$) ppm. Single crystals suitable for X-ray diffraction were obtained by recrystallization in acetonitrile and hexane (30/70) solution.

[(*p*-cymene)Ru(L^3)Cl][(*p*-cymene)$RuCl_3$] ([3][(*p*-cymene)$RuCl_3$]). Compound [**3**][(*p*-cymene)$RuCl_3$] was synthesized as for [**1**][(*p*-cymene)$RuCl_3$]. Yield 66.7%. HR-ESI-MS (MeOH, 6 eV, 120 °C) (+) *m*/*z* [Found (calcd)]: 496.0459 (496.0460) {[(η^6-*p*-cymene)Ru(L^3)Cl] − HCl}$^+$. HR-ESI-MS (MeOH, 6 eV, 120 °C) (−) *m*/*z* [Found (calcd)]: 340.9230 (340.9199) [(*p*-cymene)$RuCl_3$]$^-$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.419 (1H, s, N*H*Ph), 9.446 (1H, s, CH═N), 8.357 (1H, d, J = 3.1 Hz, thiophene-*H*), 7.774 (1H, d, J = 4.7 Hz, thiophene-*H*), 7.606 (2H, d, J = 7.8 Hz, phenyl-*H*), 7.420-7.369(2H, m, thiophene-*H* and phenyl-*H*), 7.306 (1H, s, phenyl-*H*), 7.258-7.232 (1H, m, phenyl-*H*), 5.555, 5.309 {4H, 2 × d, $^3J_{AB}$ = 5.9 Hz, [(p-cymene)$RuCl_3$]$^-$ AA′BB′ spin system}, 5.492, 5.356, 5.142, 5.115 {4H, 4 × d, $^3J_{AB}$ = 6.0 Hz, [(p-cymene)Ru(bzsc)Cl]$^+$ AA′BB′ spin system}, 3.172, 2.791 (2H, 2 × m, 2 × C*H*$(CH_3)_2$), 2.324, 2.145 (6H, 2 × s, 2 × CH_3), 1.403, 1.293 (6H, 2 × d, J = 6.9 Hz, anion-CH(C*H*$_3)_2$), 1.198 (6H, dd, J = 6.8 Hz and 13.8 Hz, cation-CH(C*H*$_3)_2$) ppm. Anal. Calcd for $C_{32}H_{39}Cl_4N_3Ru_2S_2{\cdot}CH_3CN$: C, 44.64; H, 4.62; N, 6.12; Found: C, 44.52; H, 4.28; N, 5.96. Single crystals suitable for X-ray diffraction were obtained by recrystallization in acetonitrile and hexane (30/70) solution.

Methods and instrumentantion

NMR spectra were recorded on a Bruker AV-300 spectrometer at working frequencies 300. Chemical shifts were expressed in parts per million (δ) values and coupling constants (*J*) in Hertz. Mass spectra for the complexes were recorded on a Waters UPLC XEVO G2 TOF mass spectrometer using electrospray ionization probe. Elemental analyses were carried out using an Elementar Vario EL Cube.

X-ray crystallographic determination

All reflection data were collected on a Bruker SMART CCD instrument by using graphite monochromatic Mo Kα radiation (λ = 0.71073 Å) at room temperature. A semiempirical absorption correction by using the SADABS program was applied, and the raw data frame integration was performed with SAINT [18]. The crystal