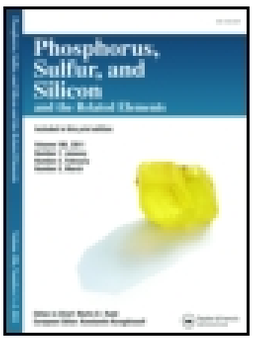

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Synthesis, Characterization, and Anticancer Activity of Dithiocarbamate Ruthenium(II) complexes

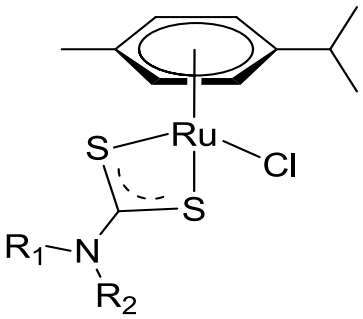
Ye-Hong Dou, Shou-De Xu, Yi Chen, Xiang-Hua Wu*

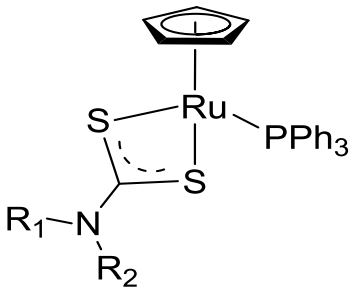
College of Chemistry and Chemical Enginering, Yunnan Normal University, Kunming 650500, P.R. China

*Corresponding Author, Email: chxhwu@sina.com

Abstract

Twelve arene and cyclopentadienyl ruthenium(II) dithiocarbamate complexes have been prepared and characterized by spectroscopic methods. The structures of **3a** and **3c** have been determined by X-ray crystallography. Their in vitro antitumor activities were evaluated by MTT method against four tumor cells (SKOV-3, HepG-2, A549, as well as PC12) and two murine cells (RAW246.7 and L6). Notably, the results in vitro indicated that the arene ruthenium(II) complex **3e** (N-methyl piperazine) displayed the highest activity and selectivity towards cancer HepG-2 cells.





NR_1R_2 = diethylamino, pyrrolidinyl, morpholinyl, piperidinyl, 4-methylpiperazin-1-yl, 4-phenylpiperazin-1-yl

Keywords

p-arene; Cyclopentadienyl; Ruthenium(II) complexes; Dithiocarbamates; Cytotoxic activity

Introduction

Following the major clinical successes achieved with cisplatin toward a variety of cancers, the search for other metal compounds with improved therapeutic properties has been extremely active because some major drawbacks exist in the application of this drug.[1,2] Therefore, a large number of new and alternative metal complexes with considerable cytotoxic properties were disclosed.[3-8] In particular, ruthenium complexes have received increased attention in recent years as potential anticancer agents, such as KP46, KP1019, NAMI-A which entered clinical trials with promising results.[9-12]

In recent years, applications of ruthenium(II)-arene complexes in biology have received increasing attention because of the lower toxicity, high selectivity and the potential synergism that could be achieved by combining a metal ion and a bioactive ligand.[13--20] Dithiocarbamates are highly versatile ligands toward main group metals and their strong metal binding properties are directly related to the possession of two donor sulfur atoms. Their derivatives are used extensively as active antitumor, antibacterial and antifungal agents.[21-33]

It has been noted that tethering of biologically active ligands to the metal ion increases the biological potency of the complexes, through a combination of increased solubility, altered mechanisms of action, increased uptake, and improved cancer targeting properties.[19,31-33] In this paper, the biologically active groups dithiocarbamate are tethered to the arene and

cyclopentadienyl ruthenium(II) units. *In vitro* anticancer activity of these complexes against human cancer cell lines was described.

Results and discussion

The synthesis of ruthenium(II) complexes with dithiocarbamate was shown in Figure 1. The formation of the target arene ruthenium(II) dithiocarbamate complexes **3a**-**3d** was achieved by reacting salts **2a**-**2d** and arene ruthenium(II) **1** in acetone in good yields. The cyclopentadienyl ruthenium(II) dithiocarbamate complexes were prepared according to literature methods. [34] The structures of all the target compounds were characterized by NMR and EI-MS spectroscopy, which are given in Supporting information. The multiplet observed in the region around δ 5.22--5.50 ppm in all the listed complexes have been assigned to the aromatic protons of the phenyl group of *p*-cymene. The two isopropyl methyl protons of the *p*-cymene appeared as doublet in the region of δ 1.23--1.30 ppm and the methine protons comes in the region of δ 2.85--2.87 ppm as a multiplet. Further, the methyl group of the *p*-cymene comes as singlet around the region of δ 2.20--2.28 ppm. The five protons of the *Cp*-ring appeared as singlet in the region of δ4.35--4.39 ppm. In addition, the crystal structures of **3a** and **3c** were determined by X-ray diffraction analyses.

X-Ray Diffraction Studies

Single crystals of complexes **3a** and **3c** suitable for X-ray analysis were obtained by slow diffusion of hexane into solutions in CH_2Cl_2. The single-crystal X-ray structures of complexes **3a** and **3c** are shown in Figures 2 and 3, respectively. The crystallographic details and selected bond distances and angles are presented in Tables S 1 and S 2, respectively, which are given in Supplemental Materials. The Ru-Cl bond distances are within the range of those reported for other *p*-cymene Ru(II) complexes.[34-40] The S1-Ru-S2 bond angles are 72.09(6) (3a) and 71.92(7)° (3c), which are smaller than those of N-Ru-S,[39] N-Ru-C,[40] and N-Ru-N.[36]

Biological evaluations

The in vitro anti-proliferative activity of complexes **3a**-**3d** and **5a**-**5d** was evaluated against four human cancers (human ovarian cancer SKOV-3 cell line, human hepatoma carcinoma HepG-2 cell line, the rat pheochromocytoma PC12 cell line, and human lung cancer A549 cell line) and two murine cell lines (RAW246.7 and L6) by using the classical MTT assay. Cisplatin (CDDP) was used as the reference drug. IC_{50} values of complexes **3a**-**3d** and **5a**-**5d** are listed in Table S 3 (Supplemental Materials). Among the arene ruthenium(II) series, the complexes were markedly less effective in SKOV-3, P12 and A549 cells in comparison to cisplatin, as shown in Table S 3. However, only the complex **3e** (N-methyl piperazine) is strongly cytotoxic against HepG-2 cell line with the lowest IC_{50} of 7.7 μM, which is more cytotoxic than cisplatin (9.83 μM). Moreover, the IC_{50} values of **3e** in the murine RAW246.7 and L6 cell lines are about 6 and

8.3-fold higher than those of cisplatin, respectively. Importantly, it is found that the selectivity of complex **3e** is superior to that of cisplatin.

Compared to the arene ruthenium(II) series, when the dithiocarbamate moiety was introduced into cyclopentadienyl ruthenium(II), the antitumor activities of the resulted complexes **5a**-**5f** were reduced significantly. Only complexes **5a** (*N*,*N*-diethyl amine) and **5b** (pyrrolidine) showed high cytotoxic activity against SKOV-3 cells as compared to other cell lines, with IC_{50} values of 6.8 and 8.7 μM, respectively. In addition, the selectivity of complexes **5a** and **5b** is inferior to that of **3e**. Overall, complex **3e** (N-methyl piperazine) is the most cytotoxic towards four tested cancer cell lines and is also the most selective compound towards cancer cells.

Conclusions

In conclusion, twelve arene and cyclopentadienyl ruthenium(II) complexes bearing the dithiocarbamate unit were synthesized and characterized. Based on the result of MTT assay, the arene ruthenium(II) complex **3e** substituted by N-methyl piperazine displayed the highest activity and selectivity towards cancer HepG-2 cells. Notably, this study was initiated in the frame of ongoing studies aimed at developing new organometallic ruthenium compounds as potential anticancer agents.

Experimental

General Procedures

All manipulations were carried out at room temperature under a nitrogen atmosphere using standard Schlenk techniques, unless otherwise stated. All reagents were purchased from commercial sources and were used without further purification. ^{1}H, ^{13}C, and ^{31}P NMR spectra were collected on a Bruker 500 MHz magnetic resonance spectrometer. ^{1}H and ^{13}C NMR chemical shifts are relative to TMS, and ^{31}P NMR chemical shifts are relative to 85% H_3PO_4. Mass spectrometry was recorded with a Bruker (micrOTOF II). [Ru(η^6-*p*-cymene)Cl_2]$_2$ was purchased from Alfa Aesar. Others reagents were commercially sourced and used as received unless mentioned otherwise. The starting materials dithiocarbamates and Ru(η-C_5H_5)Cl(PPh_3)$_2$ were prepared by the reported in literature method.[41,42]

General synthesis of complexes 3a-3f

[Ru(η^6-*p*-cymene)-Cl_2]$_2$ (0.18 g, 0.3 mmol) and sodium dithiocarbamates (**2a-2f**) (0.6 mmol) were dissolved in acetone (30 mL). Then the resulting solution was refluxed for 6 h and the progress of the reaction was monitored by TLC. The solid product was filtered, and the filtrate was removed under reduced pressure. The residues were purified by neutral alumina column chromatography (eluent: CH_2Cl_2/CH_3OH, 50:1, V/V) to offer complexes **3a-3f**.

3a: orange red solid, 0.103 g (Yield: 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (d, *J* = 5.9 Hz, 2H, -Ph*H*), 5.27 (d, *J* = 5.9 Hz, 2H, -Ph*H*), 3.68 (dq, *J* = 14.3, 7.2 Hz, 2H, -N*C*H_2-), 3.51 (dq, *J* = 14.3, 7.2 Hz, 2H, -N*C*H_2-), 2.85 (m, 1H, -*C*HCH_3CH_3), 2.26 (s, 3H, -PhCH_3), 1.28 (d, *J* = 6.9

Hz, 6H, -CH*CH*$_3$*CH*$_3$), 1.21 (t, *J* = 7.2 Hz, 6H, -CH$_2$*CH*$_3$, -CH$_2$*CH*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.9 (NCS), 126.2, 102.5, 99.2, 83.5, 82.6, 77.2, 76.7, 43.7, 31.6, 24.0, 22.6, 19.0, 12.3. ESI-MS(+): m/z found 384.0369 $[M-Cl]^+$, calcd for $C_{15}H_{24}ClNRuS_2$ 419.0082.

3b: red solid, 0.109 g (Yield: 87%).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (d, *J* = 5.8 Hz, 2H, -Ph*H*), 5.28 (t, *J* = 11.6 Hz, 2H, -Ph*H*), 3.58 (dd, *J* = 10.4, 6.4 Hz, 4H, -N*CH*$_2$-, -N*CH*$_2$-), 2.87 (m, 1H, -*CH*CH$_3$CH$_3$), 2.28 (s, 3H, -PhC*H*$_3$), 2.02--1.89 (m, 4H, -CH$_2$*CH*$_2$-, -CH$_2$*CH*$_2$-), 1.28 (t, *J* = 11.8 Hz, 6H, -CH*CH*$_3$*CH*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.0 (NCS), 126.3, 103.1, 98.4, 83.5, 82.2, 77.2, 76.7, 48.8, 31.5, 24.6, 22.7, 19.1. ESI-MS(+): m/z found 382.0220 $[M-Cl]^+$, calcd for $C_{15}H_{22}ClNRuS_2$ 416.9926.

3c: orange red solid, 0.099 g (Yield: 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (d, *J* = 5.9 Hz, 2H, -Ph*H*), 5.22 (t, *J* = 4.8 Hz, 2H, -Ph*H*), 3.75 (ddd, *J* = 14.4, 7.4, 3.2 Hz, 2H, -O*CH*$_2$-), 3.66 (td, *J* = 7.7, 2.9 Hz, 4H, -N*CH*$_2$-), 3.62-3.56 (m, 2H, -O*CH*$_2$-), 2.78 (m, 1H, -*CH*CH$_3$CH$_3$), 2.20 (s, 3H, -PhC*H*$_3$), 1.23 (d, *J* = 6.9 Hz, 6H, -CH*CH*$_3$*CH*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.0 (NCS), 126.3, 103.4, 99.0, 83.8, 82.6, 77.3, 76.8, 65.8, 46.3, 31.7, 24.1, 22.8, 21.0, 19.2. ESI-MS(+): m/z found 398.0175 $[M-Cl]^+$, calcd for $C_{15}H_{22}ClNRuS_2$ 432.9875.

3d: red solid, 0.100 g (Yield: 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (d, *J* = 5.9 Hz, 2H, -Ph*H*), 5.27 (d, *J* = 5.9 Hz, 2H, -Ph*H*), 3.94--3.86 (m, 2H, -N*CH*$_2$-), 3.52--3.44 (m, 2H, -N*CH*$_2$-), 2.85 (m, 1H, -*CH*CH$_3$CH$_3$), 2.26 (s, 3H, -PhC*H*$_3$), 1.64 (dd, *J* = 18.4, 15.2 Hz, 4H, -CH$_2$*CH*$_2$-,

-CH_2CH_2-), 1.54 (d, *J* = 4.6 Hz, 2H, -CH_2CH_2-), 1.29 (d, *J* = 6.9 Hz, 6H, -$CHCH_3CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.0 (NCS), 126.3, 103.0, 99.02, 83.7, 82.6, 77.3, 76.8, 47.3, 31.6, 25.2, 24.1, 24.0, 22.8, 20.9, 19.1. ESI-MS(+): m/z found 396.0374 $[M-Cl]^+$, calcd for $C_{15}H_{22}ClNRuS_2$ 431.0082.

3e: red solid, 0.114 g (Yield: 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (d, *J* = 5.8 Hz, 2H, -Ph*H*), 5.27 (d, *J* = 5.8 Hz, 2H, -Ph*H*), 3.87--3.79 (m, 2H, -NCH_2-), 3.72 (s, 2H, -NCH_2-), 2.85 (m, 1H, -$CHCH_3CH_3$), 2.47 (d, *J* = 3.8 Hz, 2H, -NCH_2-), 2.37 (s, 2H, -NCH_2-), 2.32--2.24 (m, 6H, -PhCH_3, -NCH_3), 1.29 (d, *J* = 6.9 Hz, 6H,-CHCH_3CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.0 (NCS), 126.3, 103.2, 90.0, 83.8, 82.5, 77.3, 76.8, 53.7, 45.8, 31.6, 24.1, 22.8, 19.2. ESI-MS(+): m/z found 411.0477 $[M-Cl]^+$, calcd for $C_{16}H_{25}ClN_2RuS_2$ 446.0191.

3f: red solid, 0.122 g (Yield: 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 7.0, 1.6 Hz, 2H, -Ph*H*), 6.99--6.86 (m, 3H, -Ph*H*), 5.50 (d, *J* = 5.9 Hz, 2H, -Ph*H*), 5.30 (d, *J* = 5.8 Hz, 2H, -Ph*H*), 4.03 (ddd, *J* = 13.1, 6.2, 3.4 Hz, 2H, -NCH_2-), 3.81 (ddd, *J* = 13.0, 7.8, 3.4 Hz, 2H, -NCH_2-), 3.37-3.24 (m, 2H, -NCH_2-), 3.18--3.07 (m, 2H, -NCH_2-), 2.86 (m, 1H, -$CHCH_3CH_3$), 2.27 (s, 3H, -PhCH_3), 1.30 (d, *J* = 6.9 Hz, 6H, -CHCH_3CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.25 (NCS), 120.8, 116.7, 103.2, 98.9, 83.7, 82.5, 77.2, 76.7, 48.6, 45.8, 31.6, 22.7, 19.1. ESI-MS(+): m/z found 473.0647 $[M-Cl]^+$, calcd for $C_{21}H_{27}ClNRuS_2$ 508.0348.

General synthesis of complexes 5a-5f

Ru(η-C_5H_5)Cl(PPh_3)$_2$ (0.36 g, 0.5 mmol) and sodium dithiocarbamates (**2a-2f**) (0.65 mmol) were dissolved in methanol 30 mL. Then the resulting solution was refluxed for about 16 h and the progress of the reaction was monitored by TLC. The solid product was filtered, and washed with methanol. The residues were purified by column chromatography on silica gel (eluent: CH_2Cl_2/CH_3OH, 100:1, V/V) to offer complexes **5a-5f**.

5a: yellow solid, 0.190 g (Yield: 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (m, 6H, -Ph*H*), 7.32--7.26 (m, 7H, -Ph*H*), 7.26--7.24 (m, 2H, -Ph*H*), 4.35 (d, *J* = 4.5 Hz, 5H, -Cp*H*), 3.34 (m, 4H, -N*CH*$_2$-, -N*CH*$_2$-), 0.97 (t, *J* = 7.2 Hz, 6H, -CH_2*CH*$_3$, -CH_2*CH*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.12 (NCS), 137.8, 133.9, 133.8, 132.9, 132.1, 132.1, 131.9, 131.9, 128.5, 128.5, 128.4, 127.2, 127.1, 77.3, 76.8, 76.2, 76.2, 42.9, 29.7, 12.5. ^{31}P NMR (200 MHz, $CDCl_3$) δ 53.79. ESI-MS(+): m/z found 577.0603 [M], calcd for $C_{28}H_{30}NPRuS_2$ 577.0601.

5b: yellow solid, 0.193 g (Yield: 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (m, 6H, -Ph*H*), 7.34--7.26 (m, 9H, -Ph*H*), 4.37 (s, 5H, -Cp*H*), 3.31 (dd, *J* = 10.9, 5.8 Hz, 2H, -N*CH*$_2$-), 2.96 (dd, *J* = 11.3, 6.0 Hz, 2H, -N*CH*$_2$-), 1.79--1.69 (m, 4H, -CH_2*CH*$_2$-, -CH_2*CH*$_2$-). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5 (NCS), 137.2, 134.2, 134.1, 132.15, 132.1, 131.9, 131.9, 128.5, 128.4, 126.9, 126.8, 77.2, 76.7, 75.5, 75.5, 47.8, 24.8. ^{31}P NMR (200 MHz, $CDCl_3$) δ 54.92. ESI-MS(+): m/z found 575.0456 [M], calcd for $C_{28}H_{28}NPRuS_2$ 575.0444.

5c: yellow solid, 0.163 g (Yield: 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 6H, -Ph*H*), 7.33--7.28 (m, 9H, -Ph*H*), 4.38 (s, 5H, -Cp*H*), 3.50 (s, 4H, -O*CH*$_2$-, -O*CH*$_2$-), 3.49--3.44 (m, 2H, -N*CH*$_2$-), 3.29 (s, 2H, -N*CH*$_2$-). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6 (NCS), 137.4, 134.0, 128.7, 127.1, 77.2, 76.7, 76.0, 65.7, 44.7, 38.1, 31.9, 31.2, 29.7, 29.4, 22.7, 14.1. ^{31}P NMR (200 MHz, $CDCl_3$) δ 54.16. ESI-MS(+): m/z found 591.0412 [M], calcd for $C_{28}H_{28}NOPRuS_2$ 591.0393.

5d: yellow solid, 0.156 g (Yield: 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 -- 7.53 (m, 6H, -Ph*H*), 7.35--7.30 (m, 9H, -Ph*H*), 4.39 (s, 5H, -Cp*H*), 3.43 (d, *J* = 24.1 Hz, 4H, -N*CH*$_2$-, -N*CH*$_2$-), 1.57 (s, 4H, -CH$_2$*CH*$_2$-, -CH$_2$*CH*$_2$-), 1.54 (s, 2H, -CH$_2$*CH*$_2$-). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6 (NCS), 137.3, 134.1, 134.0, 128.7, 128.7, 127.1, 127.1, 77.3, 76.8, 76.1, 76.0, 65.7, 59.5, 44.7, 38.1, 31.9, 31.2, 29.7, 29.7, 29.4, 22.7, 14.1. ^{31}P NMR (200 MHz, $CDCl_3$) δ 54.13. ESI-MS(+): m/z found 589.0628 [M], calcd for $C_{29}H_{30}NPRuS_2$ 589.0601.

5e: yellow solid, 0.216 g (Yield: 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 8H, -Ph*H*), 7.30--7.28 (m, 7H, -Ph*H*), 4.38 (s, 5H, -Cp*H*), 3.61 (s, 2H, -N*CH*$_2$-), 3.29 (s, 2H, -N*CH*$_2$-), 2.25 (d, *J* = 4.9 Hz, 4H, -N*CH*$_2$-, -N*CH*$_2$-), 2.24 (s, 3H, -N*CH*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8 (NCS), 137.5, 134.0, 133.0, 132.2, 132.1, 132.1, 131.9, 131.9, 128.6, 127.1, 77.2, 76.8, 76.1, 53.7, 44.3. ^{31}P NMR (200 MHz, $CDCl_3$) δ 53.90. ESI-MS(+): m/z found 605.0800 $[M+H]^+$, calcd for $C_{29}H_{31}N_2PRuS_2$ 604.0710.

5f: yellow solid, 0.218 g (Yield: 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 6H, -Ph*H*), 7.32-7.26 (m, 11H, -Ph*H*), 6.88 (dd, *J* = 16.3, 8.0 Hz, 3H, -Ph*H*), 4.39 (s, 5H, -Cp*H*), 3.67 (s, 2H, -N*CH*$_2$-), 3.51 (s, 2H, -N*CH*$_2$-), 3.02 (d, *J* = 20.5 Hz, 4H, -N*CH*$_2$-, -N*CH*$_2$-). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7 (NCS), 137.4, 134.1, 133.9, 132.1, 132.1, 129.3, 128.7, 128.5, 128.4, 127.2, 127.1, 120.4, 116.5, 77.3, 76.7, 76.1, 76.1, 48.32, 44.30, 29.71, 14.13. ^{31}P NMR (200 MHz, $CDCl_3$) δ 54.06. ESI-MS(+): m/z found 667.0924 $[M+H]^+$, calcd for $C_{34}H_{33}N_2PRuS_2$ 666.0866.

Crystal structures determination for 3a and **3c**

Single crystals of complexes **3a** and **3c** suitable for X-ray analysis were obtained by slow diffusion of hexane into solutions in dichloromethane. Diffraction intensity data were collected on a Nonius Kappa CCD diffractometer with Mo Kα radiation (0.71073 Å) at room temperature (292 K). The structure was solved by direct methods (SHELXS-97) and refined by full matrix least squares on F^2 (SHELXL-97).[43,44] All non-H atoms were refined anisotropically. The hydrogen atoms were placed in geometric positions and refined using a riding model (then list X-H distances and Uiso relative to parent atom).

Cytotoxicity assay *in vitro*

Cytotoxic activities were evaluated by the MTT [3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide] method in the SKOV-3, HepG-2, PC12, A549, RAW246.7, and L6 cell

lines. Briefly, the cell suspensions (198 μL) were plated in 96 well microtiter plates at a density of 5×10^4 cells/mL and incubated for 12 h at 37 °C in a humidified incubator with 5% CO_2. The test compounds with different concentrations were added to each well and further incubated for 24 h under the same conditions. Then, 20 μL of the MTT solution was added to each well and incubated for 4 h. The old medium (200 μL) containing MTT was then gently replaced by DMSO and pipetted to dissolve any formazan crystals formed. Absorbance was then determined on a Spectra Max Plus plate reader at 570 nm. Dose--response curves were generated and the IC_{50} values were determined. Cisplatin (CDDP), a commonly approved agent for the treatment of many tumors, was used as the positive control.

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References

1. Sava, G.; Jaouen, G.; Hillard, E. A.; Bergamo, A. *Dalton Trans.* **2012**, *41*, 8226-8234.

2. Varbanov, H. P.; Jakupec, M. A.; Roller, A.; Jensen, F.; Galanski, M.; Keppler, B. K. *J. Med. Chem.* **2013**, *56*, 330-344.

3. Sun, R. W. Y.; Ma, D. L.; Wong, E. L. M.; Che, C. M. *Dalton Trans.* **2007**, 4884-4892.

4. Bruijnincx, P. C. A.; Sadler, P. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 197-206.

5. Hartinger, C. G.; Dyson, P. J. *Chem. Soc. Rev.* **2009**, *38*, 391-401.

6. Guo, Z.; Sadler, P. J. *Adv. Inorg. Chem.* **1999**, *49*, 183-306.

7. Guo, Z.; Sadler, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1512-1531.

8. Wang, X.; Guo, Z. *Dalton Trans.* **2008**, 1521-1532.

9. Groessl, M.; Hartinger, C. G. *Anal. Bioanal. Chem.* 2013, 405, 1791-1808.

10. Giannini, F.; Furrer, J.; Süss-Fink, G.; Clavel, C. M.; Dyson, P. J. *J. Organomet. Chem.***2013**, *744*, 41-48.

11. Ang, W. H.; Casini, A.; Sava, G.; Dyson, P. J. *J. Organomet. Chem.* **2011**, *696*, 989-998.

12. Gogna, R.; Madan, E.; Keppler, B. K.; Pati, U. *Br. J. Pharmacol.* **2012**, 166, 617-636.

13. Agonigi, G.; Riedel, T.; Zacchini, S.; Păunescu, E.; Pampaloni, G.; Bartalucci, N.; Dyson, P. J.; Marchetti, F. *Inorg. Chem.* **2015**, *54*, 6504-6512.

14. Singh, A. K.; Pandey, D. S.; Xu, Q.; Braunstein, P. *Coord. Chem. Rev.* **2014**, *270-271*, 31-56.

15. Clavel, C. M.; Păunescu, E.; Nowak-Sliwinska, P.; Griffioen, A. W.; Scopelliti, R.; Dyson, P. J. *J. Med. Chem.* **2015**, *58*, 3356-3365.

16. Pettinari, R.; Marchetti, F.; Pettinari, C.; Petrini, A.; Scopelliti, R.; Clavel, C. M.; Dyson, P. J. *Inorg. Chem.* **2014**, *53*, 13105-13111.

17. Garci, A.; Dobrov, A. A.; Riedel, T.; Orhan, E.; Dyson, P. J.; Arion, V. B.; Therrien, B. *Organometallics* **2014**, *33*, 3813-3822.

18. Clavel, C. M.; Păunescu, E.; Nowak-Sliwinska, P.; Griffioen, A.W.; Scopelliti, R.; Dyson, P. J. *J. Med. Chem.* **2014**, *57*, 3546-3558.

19. Kilpin, K. J.; Clavel, C. M.; Edafe, F.; Dyson, P. J. *Organometallics* **2012**, *31*, 7031-7039.

20. Nowak-Sliwinska, P.; van Beijnum, J. R.; Casini, A.; Nazarov, A. A.; Wagnières, G.; van den Bergh, H.; Dyson, P. J.; Griffioen, A. W. *J. Med. Chem.* **2011**, *54*, 3895-3902.

21. Ronconi, L.; Giovagnini, L.; Marzano, C.; Bettìo, F.; Graziani, R.; Pilloni, G.; Fregona, D. *Inorg. Chem.* **2005**, *44*, 1867-1881.

22. Ronconi, L.; Marzano, C.; Zanello, P.; Corsini, M.; Miolo, G.; Maccà, C.; Trevisan, A.; Fregona, D. *J. Med. Chem.* **2006**, *49*, 1648-1657.

23. Shaik, N.; Martínez, A.; Augustin, I.; Giovinazzo, H.; Varela-Ramírez, A.; Sanaú, M.; Aguilera, R. J.; Contel, M. *Inorg. Chem.* **2009**, *48*, 1577-1587.

24. Zhang, J. J.; Ng, K. M.; Lok, C. N.; Wai-Yin Sun, R.; Che, C. M. *Chem. Commun.* **2013**, *49*, 5153-5155.

25. Altaf, M.; Isab, A. A.; Vaňco, J.; Dvŏřak, Z.; Tŕavńĭcek, Z.; Stoeckli-Evansd, H. *RSC Adv.* **2015**, *5*, 81599-81607.

26. Jamaludin, N. S.; Goh, Z. J.; Cheah, Y. K.; Ang, K. P.; Sim, J. H.; Khoo, C. H.; Fairuz, Z. A.; Halim, S. N. B. A.; Ng, S. W.; Seng, H. L.; Tiekink, E. R. T. *Eur. J. Med. Chem.* **2013**, *67*, 127-141.

27. Keter, F. K.; Guzei, I. A.; Nell, M.; van Zyl, W. E.; Darkwa, J. *Inorg. Chem.* **2014**, *53*, 2058-2067.

28. Khan, H.; Badshah, A.; Said, M.; Murtaza, G.; Sirajuddin, M.; Ahmad, J.; Butle, I. S. *Inorg. Chim. Acta* **2016**, *447*, 176-182.

29. D. C. Onwudiwe, A. C. Ekennia, B. M. S. Mogwase, O. O. Olubiyi, E. Hosten, *Inorg. Chim. Acta* **2016**, *450*, 69-80.

30. Monti, S. M.; Maresca, A.; Viparelli, F.; Carta, F.; Simone, G. D.; Mühlschlegel, F. A.; Scozzafava, A.; Supuran, C. T. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 859-862.

31. Al-Jaroudi, S. S; Altaf, M.; Seliman, A. A.; Yadav, S.; Arjmand, F.; Alhoshani, A.; Korashy, H. M.; Ahmad, S.; Isab, A. A. *Inorg. Chim. Acta* **2017**, *464*, 37-48.

32. Altaf, M.; Monim-ul-Mehboob, M.; Kawde, A.-N.; Corona, G.; Larcher, R.; Ogasawara, M.; Casagrande, N.; Celegato, M.; Borghese, C.; Siddik, Z. H.; Aldinucci, D.; Isab, A. A. *Oncotarget*, **2017**, *8*, 490-505.

33. Altaf, M.; Monim-ul-Mehboob, M.; Seliman, A. A. A.; Sohail, M.; Wazeer, M. I. M.; Isab, A. A.; Li, L.; Dhuna, V.; Bhatia, G.; Dhuna, K. *Eur. J. Med. Chem.* **2015**, *95*, 464-472.

34. Hogarth, G.; Faulkner, S. *Inorg. Chim. Acta* **2006**, *359*, 1018-1022.

35. Bugarcic, T.; Habtemariam, A.; Deeth, R. J.; Fabbiani, F. P. A.; Parsons, S.; Sadler, P. J. *Inorg. Chem.* **2009**, *48*, 9444-9453.

36. Dougan, S. J.; Melchart, M.; Habtemariam, A.; Parsons, S.; Sadler, P. J. *Inorg. Chem.* **2006**, *45*, 10882-10894.

37. Clavel, C. M.; Păunescu, E.; Nowak-Sliwinska, P.; Griffioen, A. W.; Scopelliti, R.; Dyson, P. J. *J. Med. Chem.* **2014**, *57*, 3546-3558.

38. Pettinari, R.; Pettinari, C.; Marchetti, F.; Clavel, C. M.; Scopelliti, R.; Dyson, P. J. *Organometallics* **2013**, *32*, 309-316.

39. Beckford, F.; Dourth, D.; Shaloski Jr., M.; Didion, J.; Thessing, J.; Woods, J.; Crowell, V.; Gerasimchuk, N.; Gonzalez-Sarrías, A.; Seeram, N. P. *J. Inorg. Biochem.* **2011**, *105*, 1019-1029.

40. Li, B.; Roisnel, T.; Darcel, C.; Dixneuf, P. H. *Dalton Trans.* **2012**, *41*, 10934-10937.

41. Anastasiadis, C.; Hogarth, G.; Wilton-Ely J. D. E. T. *Inorg. Chim. Acta* **2010**, *363*, 3222-3228.

42 38. Bruce, M. I.; Windsor, N. J. *Aust. J. Chem.* **1977**, *30*, 1601-1604.

43 39. Sheldrick G. M. (1997) SHELXS-97, a Program for Crystal Structure Solution; University of Göttingen: Göttingen, Germany.

44. Sheldrick G. M. (1997) SHELXL-97, a Program for Crystal Structure Refinement; University of Göttingen, Göttingen, Germany.

ACCEPTED MANUSCRIPT

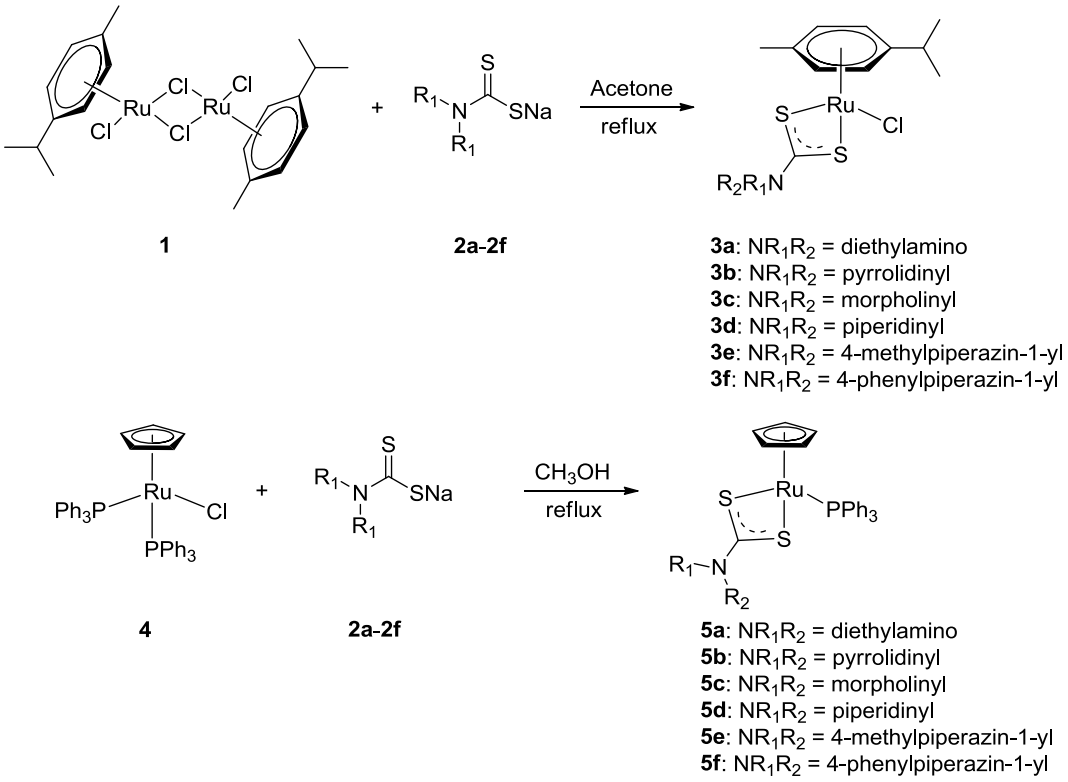

Figure 1. Synthesis of ruthenium(II) dithiocarbamate complexes **3a**-**3f** and **5a**-**5f**

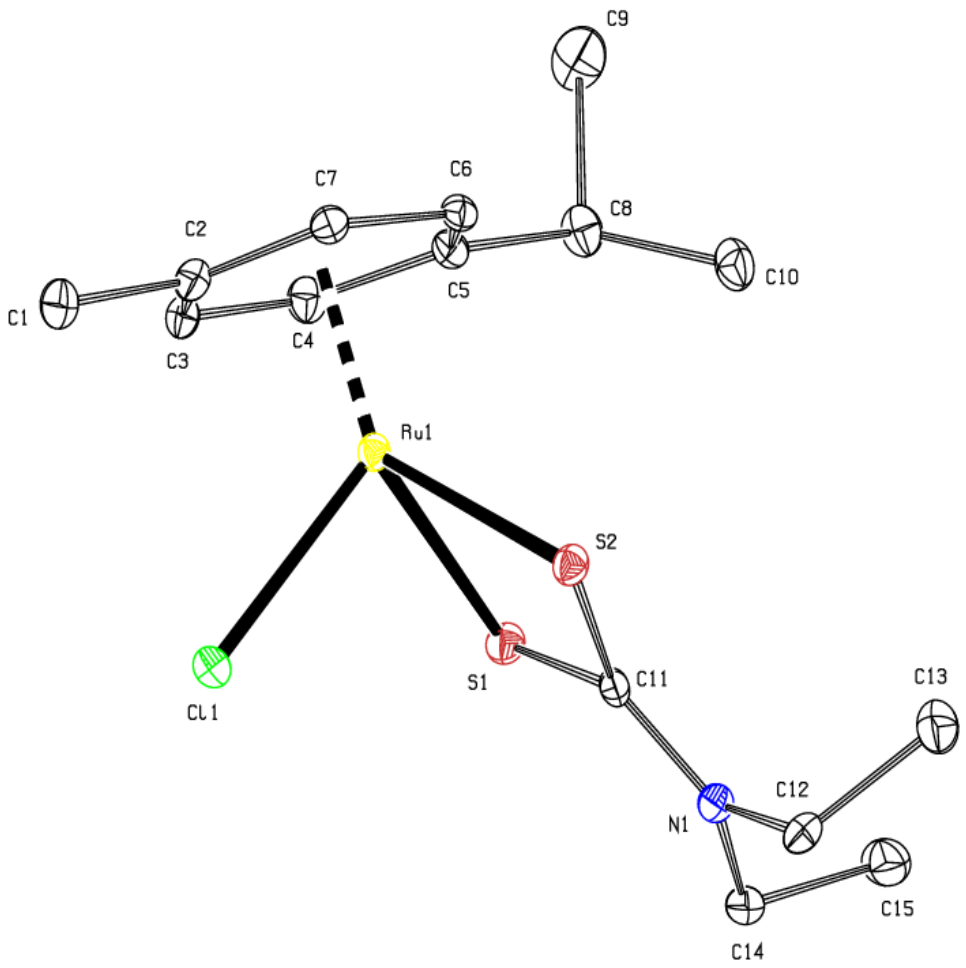

Figure 2. Molecular structure of **3a** with displacement ellipsoids drawn at the 30% probability level.

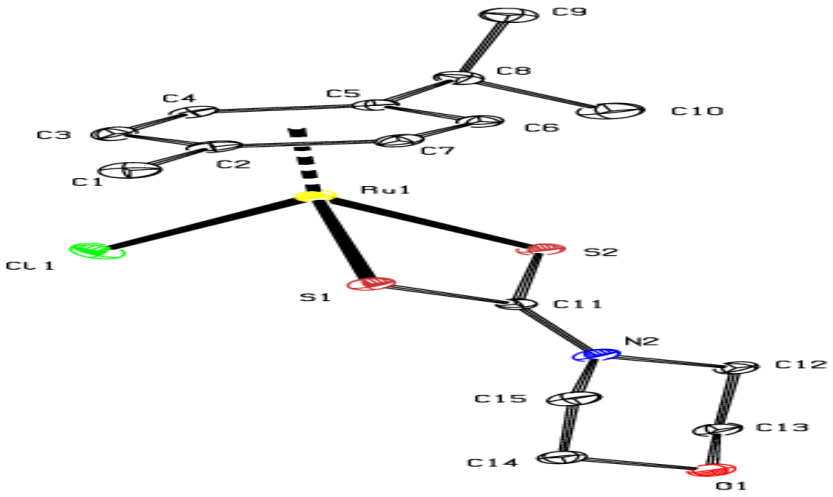

Figure 3. Molecular structure of **3c** with displacement ellipsoids drawn at the 30% probability level.