Synthesis, structural and chemosensitivity studies of arene d^6 metal complexes having N-phenyl-N´-(pyridyl/pyrimidyl)thiourea derivatives

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Abstract

The d^6 metal complexes of thiourea derivatives were synthesized to investigate its cytotoxicity. Treatment of various N-phenyl-N´ pyridyl/pyrimidyl thiourea ligands with half-sandwich d^6 metal precursors yielded a series of cationic complexes. Reactions of ligand (L1-L3) with $[(p\text{-cymene})RuCl_2]_2$ and $[Cp^*MCl_2]_2$ (M = Rh/Ir) led to the formation of a series of cationic complexes bearing general formula $[(arene)M(L1)\kappa^2_{(N,S)}Cl]^+$, $[(arene)M(L2)\kappa^2_{(N,S)}Cl]^+$ and $[(arene)M(L3)\kappa^2_{(N,S)}Cl]^+$ [arene = *p*-cymene, M = Ru (**1**, **4**, **7**); Cp*, M = Rh (**2**, **5**, **8**); Cp*, Ir (**3**, **6**, **9**)]. These compounds were isolated as their chloride salts. X-ray crystallographic studies of the complexes revealed the coordination of the ligands to the metal in a bidentate chelating N,S-manner. Further the cytotoxicity studies of the thiourea derivatives and its complexes evaluated against HCT-116 (human colorectal cancer), MIA-PaCa-2 (human pancreatic cancer) and ARPE-19 (non-cancer retinal epithelium) cancer cell lines showed that the thiourea ligands displayed no activity. Upon complexation however, the metal compounds possesses cytotoxicity and whilst potency is less than cisplatin, several complexes exhibited greater selectivity for HCT-116 or MIA-PaCa-2 cells compared to ARPE-19 cells than cisplatin *in vitro*. Rhodium complexes of thiourea derivatives were found to be more potent as compared to ruthenium and iridium complexes.

Keywords: Ruthenium, rhodium, iridium, thiourea, chemosensitivity.

Introduction

Half-sandwich arene d^6 metal complexes (arene = *p*-cymene and its derivatives) have been given much importance owing to their clinical and industrial applications.[1] These organometallic compounds have been widely exploited for their medicinal applications and it has been proved that these complexes bear the potential to act as metal based anti-cancer drugs.[2,3] In particular, two half-sandwich ruthenium complexes namely $[Ru(\eta^6\text{-arene})Cl(en)]^+$ (en = ethylenediamine) developed by *Chen et.al* and [Ru(*p*-cymene)Cl_2(PTA)], developed by *Allardyce et.al* termed RAPTA-C (PTA = 1,3,5-triaza-7-phosphaadamantane) have been found to exhibit excellent cytotoxic activity *in vitro* and anticancer activity *in vivo*.[4,5] The cyclic arene ligands in these complexes are relatively inert towards substitution, it protects the metal's oxidation state and it also influences hydrophobicity and interaction with biomolecules.[6,7] It has been observed that the mode of action of these compounds depends strongly on the nature of the chelating ligand.[8] In this regard it is important to choose a particular chelating ligand system with known bioactive properties.[9] Nevertheless pentamethylcyclopentadienyl rhodium and iridium complexes have also been explored and studied for their antitumor activities due to the inert facial co-ligand Cp* which offers several advantages.[10]

Much interest has been paid towards the synthesis and development of transition metal complexes containing thiourea ligands because of their interesting binding modes.[11] These ligands can coordinate metal ion in a variety of coordination modes because of the presence of various donor atoms such as N´, O, N´ and S.[12] Thiourea ligands can coordinate transition metal in either neutral bidentate (O, N), monobasic bidentate (O, S), and neutral monodentate (S) modes.[12-14] Numerous thiourea derivatives and its metal complexes are known to exhibit a wide range of biological activities such as antifungal, antibacterial, antimalarial and antitumor,

activities.[15-18] Introduction of various substituents into the thiourea ligand can definitely increase the selectivity towards the metal ion and is also expected to alter the coordination modes of these ligands. Since the choice of ligands plays a crucial role in determining the biological properties of the complexes we decided to substitute aryl group with pyridyl group and determine the coordination properties of pyridyl thiourea derivatives. Previous studies in this laboratory have reported some half-sandwich arene ruthenium, rhodium and iridium complexes with pyridyl thiourea ligands[19,20] and in this study, we report the synthesis, structural and cytotoxic activity against cancer and non-cancer cell lines *in vitro* of *p*-cymene ruthenium, Cp* rhodium and Cp* iridium complexes containing thiourea derivatives. Ligands used in the present study are shown in Chart 1.

Experimental

Materials and Methods

The reagents were of commercial quality and used without further purification. Metal salts $RuCl_3.nH_2O$, $RhCl_3.nH_2O$ and $IrCl_3.nH_2O$ were purchased from Arora Matthey Limited. α-phellandrene, pentamethylcyclopentadiene, 2-aminopyridine, 2-aminopyrimidine and 2-amino-4-methyl-pyridine were purchased from Sigma Aldrich. Phenyl isothiocyanate was obtained from Spectrochem. The solvents were dried and distilled prior to use according to standard procedures.[21] Precursor metal complexes $[(p\text{-cymene})RuCl_2]_2$ and $[Cp^*MCl_2]_2$ (M = Rh/Ir) were prepared according to the published procedures.[22,23] The thiourea ligands 1-phenyl-3-(pyridine-2-yl)thiourea (L1), 1-phenyl-3-(pyrimidin-2-yl)thiourea (L2) and 1-(4-methylpyridin-2-yl)-3-phenylthiourea (L3) were prepared according to reported procedures.[24] ^1H NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer using $CDCl_3$ as solvent; chemical shifts were referenced to TMS. Infrared spectra (KBr pellets; 400-4000 cm^{-1}) were recorded on a

Perkin-Elmer 983 spectrophotometer. Mass spectra were recorded with Q-Tof APCI-MS instrument (model HAB 273) using acetonitrile as solvent. Elemental analyses of the complexes were carried out on a Perkin-Elmer 2400 CHN/S analyzer.

Structure determination by X-ray crystallography

Suitable single crystals of complexes were obtained by slow diffusion of hexane into dichloromethane solution. Single crystal data for the complexes were collected with an Oxford Diffraction Xcalibur Eos Gemini diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The strategy for the data collection was evaluated using the CrysAlisPro CCD software. Crystal data were collected by standard ‘‘phi–omega scan’’ techniques and were scaled and reduced using CrysAlisPro RED software. The structures were solved by direct methods using SHELXS-97 and refined by full-matrix least squares with SHELXL-97 refining on F^2. [25, 26] The positions of all the atoms were obtained by direct methods. Metal atoms in the complex were located from the E-maps and all non-hydrogen atoms were refined anisotropically by full-matrix least-squares. Hydrogen atoms were placed in geometrically idealised positions and constrained to ride on their parent atoms with C-H distances in the range 0.95-1.00 Angstrom. Isotropic thermal parameters U_{eq} were fixed such that they were $1.2U_{eq}$ of their parent atom Ueq for CH's and $1.5U_{eq}$ of their parent atom U_{eq} in case of methyl groups. Crystallographic and structure refinement parameters for the complexes are summarized in Table 1 and selected bond lengths and bond angles are presented in Table 2. Figures 2-4 were drawn with ORTEP3 program whereas Figures 5 and 6 was drawn using MERCURY 3.6 program.[27]

Because of poor crystal quality the crystal structure of complex (**1**) has low theta value, we have presented the data here only to establish the structure. Crystal structure of complex (**5**)

contains solvent molecule ($CHCl_3$) in the solved structure. The crystal structure of complex (**6**) contains DCM and pentane molecules, which has been removed by SQUEEZE method.[28]

Cell lines testing, culture conditions and cytotoxicity against cell lines

The cytotoxic activity of the thiourea derivatives and its corresponding ruthenium, rhodium and iridium complexes were evaluated against HCT-116 colorectal carcinoma and MIA-PaCa-2 pancreatic carcinoma cell lines and the non-cancer ARPE-19 (human epithelial cell line derived from the retina) cell line. These cell lines were purchased from the American Type Culture Collection (ATCC) and the reagents used were purchased from Sigma Aldrich Co. Ltd (Dorset, UK) unless otherwise stated. Cytotoxicity of thiourea ligands and compounds were evaluated using the standard MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) cellular viability assay as follows. Cells were inoculated into 96 well plates at 1.5 x 10^3 cells per well and incubated for 24 hours at 37 $^{\circ}$C in an atmosphere of 5% CO_2 prior to drug exposure. The thiourea ligands and complexes (**1**-**9**) were all dissolved in DMSO at a concentration of 100 mM and diluted further with medium to obtain drug solutions ranging from 0.5 to 100 μM. The final DMSO concentration was 0.1% (v/v), which is nontoxic to cells. Cisplatin was dissolved in phosphate buffered saline at a stock concentration of 25 mM. Cells were exposed to drug for 96 hours and cell survival was determined using the MTT assay.[29,30] Briefly, 20 μL of MTT (0.5 mg/ml) in phosphate buffered saline was added to each well and it was further incubated at 37 $^{\circ}$C for 4 hours in an atmosphere containing 5% CO_2. The solution was then removed and the formazan crystals formed were dissolved in 150 μM DMSO. The absorbance of the solution was recorded at 550 nm using an ELISA spectrophotometer. Percentage cell survival was calculated by dividing the true absorbance of treated cell by the true absorbance for controls (exposed to 0.1% DMSO). The IC_{50} values were determined from plots

of % survival against drug concentration. Each experiment was repeated three times and a mean value obtained and stated as IC_{50} (μM) ± SD. To compare the response of non-cancer cells to cancer cells, the selectivity index (SI) was calculated as the IC_{50} for ARPE-19 cells divided by the IC_{50} for either HCT-116 or MIA-PaCa-2 cells. Values >1 indicate that complexes have selective activity against cancer compared to non-cancer cells *in vitro*.

General procedure for synthesis of metal complexes (1-9)

A mixture of metal precursor $[(p\text{-cymeme})RuCl_2]_2$ or $[Cp^*MCl_2]_2$ (M = Rh/Ir) (0.1 mmol) and thiourea derivatives (L1-L3) (0.2 mmol) were dissolved in dry acetone (10 mL) and stirred at room temperature for 8 hours (Scheme 1). A yellow colored compound precipitated out from the reaction mixture. The precipitate was filtered, washed with cold acetone (2 x 5 ml) and diethyl ether (3 x 10 ml) and air dried.

[(*p*-cymene)Ru(L1)κ$^2_{(N,S)}$Cl]Cl (1)

Yield: 80 mg (74%); **Anal. Calc** for $C_{22}H_{25}N_3Cl_2SRu$ (535.49); C, 49.34; H, 4.71; N, 7.85. Found: C, 49.43; H, 4.84; N, 7.96 %; **FT-IR** (KBr, cm^{-1}): 3337(m), 2203(m), 1620(m), 1545(m), 1443(m), 1484(m), 1231(m), 1122(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.23 (s, 1H, NH), 12.01 (s, 1H, NH), 8.84 (dd, *J* = 4 and 4 Hz, 1H), 7.75 (t, *J* = 4 Hz, 1H), 7.55-7.61 (m, 3H), 7.39 (t, *J* = 8 Hz, 2H), 7.30 (t, *J* = 8 Hz, 1H), 7.15 (t, *J* = 4 Hz, 1H), 5.47 (d, *J* = 8 Hz, 1H), 5.39 (d, *J* = 4 Hz, 1H, $CH_{(p\text{-cym})}$), 5.23 (t, *J* = 8 Hz, 2H, $CH_{(p\text{-cym})}$), 2.74 (sept, 1H, $CH_{(p\text{-cym})}$), 1.89 (s, 3H, $CH_{(p\text{-cym})}$), 1.18 (dd, 6H, *J* = 4 and 4 Hz, $CH_{(p\text{-cym})}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.94, 164.59, 153.65, 151.93, 139.26, 135.40, 128.12, 126.87, 124.26, 120.37, 116.24 (C-L1), 106.01, 99.18, 85.71, 84.42, 84.11, 83.27, 29.69, 21.42, 21.24, 17.18 (C-*p*-cym); **HRMS-APCI** (m/z) [Found (Calcd)]: [464.0753 (464.0734)] $[M\text{-}2H\text{-}2Cl+H]^+$.

[Cp*Rh(L1)κ$^2_{(N,S)}$Cl]Cl (2)

Yield: 79 mg (73%); **Anal. Calc** for $C_{22}H_{26}Cl_2N_3SRh$ (538.33); C, 49.08; H, 4.87; N, 7.81. Found: C, 49.17; H, 4.95; N, 7.93 %; **FT-IR** (KBr, cm^{-1}): 3370(w), 3151(m), 1611(m), 1603(m), 1568(m), 1536(m), 1228(m), 1135(m), 1122(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.41 (s, 1H, NH), 12.07 (s, 1H, NH), 8.74 (d, *J* = 8 Hz, 1H), 7.85 (t, *J* = 8 Hz, 1H), 7.73 (d, *J* = 8 Hz, 2H), 7.60 (d, *J* = 8 Hz, 2H), 7.45 (t, *J* = 8 Hz, 2H), 7.37 (t, *J* = 8 Hz, 1H), 1.54 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.66, 152.33, 151.74, 140.56, 136.38, 129.10, 127.93, 125.70, 122.18, 117.17, (C-L2), 97.07 (Cp^*_{ipso}), 8.78 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [466.0820 (466.0824)] $[M-2H-2Cl+H]^+$.

[Cp*Ir(L1)κ$^2_{(N,S)}$Cl]Cl (3)

Yield: 96 mg (76%); **Anal. Calc** for $C_{22}H_{26}Cl_2N_3SIr$ (627.64); C, 42.10; H, 4.18; N, 6.69. Found: C, 42.25; H, 4.27; N, 6.79 %; **FT-IR** (KBr, cm^{-1}): 3338(w), 3186(m), 1617(m), 1591(w), 1544(m), 1484(m), 1233(m), 1159(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.25 (s, 1H, NH), 12.03 (s, 1H, NH), 8.68 (d, *J* = 4 Hz, 1H), 7.70-7.80 (m, 2H), 7.58 (d, *J* = 8 Hz, 2H), 7.45 (t, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H), 7.19 (t, *J* = 8 Hz, 1H), 1.54 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.32, 153.61, 151.94, 140.21, 135.91, 129.07, 126.42, 124.12, 122.12, 117.17, (C-L1), 97.07 (Cp^*_{ipso}), 8.55 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [556.1381 (556.1398)] $[M-2H-2Cl+H]^+$.

[(*p*-cymene)Ru(L2)κ$^2_{(N,S)}$Cl]Cl (4)

Yield: 84 mg (78%); **Anal. Calc** for $C_{21}H_{24}Cl_2N_4SRu$ (536.48); C, 47.01; H, 4.51; N, 10.44. Found: C, 47.10; H, 4.62; N, 10.56 %; **FT-IR** (KBr, cm^{-1}): 3370(w), 3298(m), 3176(m), 2965(m), 1618(m), 1583(m), 1561(m), 1474(m), 1202(m), 1161(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.11 (s, 1H, NH), 9.14 (dd, *J* = 4 and 4 Hz, 1H), 8.78 (d, *J* = 4 Hz, 1H), 7.66 (d, *J* = 8 Hz, 2H), 7.47 (d, *J* = 8 Hz, 2H), 7.38 (t, *J* = 8 Hz, 1H), 7.27 (t, *J* = 4 Hz, 1H), 5.56 (d, *J*

= 4 Hz, 1H, $CH_{(p\text{-cym})}$), 5.50 (d, *J* = 4 Hz, 1H, $CH_{(p\text{-cym})}$), 5.38 (d, *J* = 4 Hz, 2H, $CH_{(p\text{-cym})}$), 281 (sept, 1H, $CH_{(p\text{-cym})}$), 2.00 (s, 3H, $CH_{(p\text{-cym})}$), 1.25 (d, *J* = 4 Hz, 6H, $CH_{(p\text{-cym})}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 177.08, 163.39, 160.45, 157.56, 136.28, 129.14, 128.05, 125.42, 118.18, (C-L2), 107.60, 100.45, 86.73, 85.60, 85.13, 84.74, 30.70, 22.41, 22.19, 18.20 (C-*p*-cym); **HRMS-APCI** (m/z) [Found (Calcd)]: [465.0685 (465.0687)] $[M\text{-}2H\text{-}2Cl+H]^+$.

[Cp*Rh(L2)κ$^2_{(N,S)}$Cl]Cl (5)

Yield: 78 mg (73%); **Anal. Calc** for $C_{21}H_{25}Cl_2N_4SRh$ (539.32); C, 46.77; H, 4.67; N, 10.39. Found: C, 46.87; H, 4.75; N, 10.48 %; **FT-IR** (KBr, cm^{-1}): 3358(w), 3262(m), 3174(m), 1618(m), 1575(m), 1475(m), 1441(m), 1206(m), 1159(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.09 (dd, *J* = 4 and 4 Hz, 1H), 8.93 (s, 1H, NH), 7.73 (d, *J* = 8 Hz, 2H), 7.56 (t, *J* = 8 Hz, 2H), 7.50 (d, *J* = 8 Hz, 1H), 7.38-7.42 (m, 2H), 1.66 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.23, 161.15, 161.03, 156.27, 136.15, 129.17, 128.14, 125.64, 118.75, (C-L2), 89.91 (Cp^*_{ipso}), 8.51 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [467.0784 (467.0777)] $[M\text{-}2H\text{-}2Cl+H]^+$.

[Cp*Ir(L2)κ$^2_{(N,S)}$Cl]Cl (6)

Yield: 104 mg (83%); **Anal. Calc** for $C_{21}H_{25}Cl_2N_4SIr$ (628.63); C, 40.12; H, 4.01; N, 8.91. Found: C, 40.23; H, 4.11; N, 9.03 %; **FT-IR** (KBr, cm^{-1}): 3374(w), 3252(m), 3171(m), 1616(m), 1585(m), 1463(m), 1204(m), 1162(m), 843(s); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.03 (dd, *J* = 4 and 4 Hz, 1H), 8.87 (s, 1H, NH), 7.70 (d, *J* = 8 Hz, 2H), 7.55 (t, *J* = 8 Hz, 2H), 7.50 (d, *J* = 8 Hz, 1H), 7.35-7.38 (m, 2H), 1.65 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.67, 161.55, 161.06, 156.71, 136.26, 129.12, 128.11, 125.75, 119.01, (C-L2), 97.40 (Cp^*_{ipso}), 8.84 (Cp^*_{Me}); **HRMS-APCI (m/z)** [Found (Calcd)]: [557.1355 (557.1351)] $[M\text{-}2H\text{-}2Cl+H]^+$.

[(*p*-cymene)Ru(L3)κ$^2_{(N,S)}$)Cl]Cl (7)

Yield: 78 mg (71%); **Anal. Calc** for $C_{23}H_{27}Cl_2N_3SRu$ (549.52); C, 50.27; H, 4.95; N, 7.65. Found: C, 50.38; H, 5.06; N, 7.73 %; **FT-IR** (KBr, cm^{-1}): 3356(m), 3160(m), 1618(m), 1594(m), 1547(m), 1487(m), 1224(m), 1125(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.12 (s, 1H, NH), 12.12 (s, 1H, NH), 8.72 (d, *J* = 4 Hz, 1H), 7.64 (d, *J* = 8 Hz, 2H), 7.46 (t, *J* = 8 Hz, 3H), 7.37 (t, *J* = 8 Hz, 1H), 7.04 (d, *J* = 4 Hz, 1H), 2.45 (s, 3H, $CH_{3(py)}$) 5.51 (d, *J* = 4 Hz, 1H, $CH_{(p\text{-}cym)}$), 5.43 (d, *J* = 4 Hz, 1H, $CH_{(p\text{-}cym)}$), 5.27 (t, *J* = 8 Hz, 1H, $CH_{(p\text{-}cym)}$), 2.80 (sept, 1H, $CH_{(p\text{-}cym)}$), 1.96 (s, 3H, $CH_{(p\text{-}cym)}$), 1.24 (dd, *J* = 4 and 4 Hz, 6H, $CH_{(p\text{-}cym)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 178.07, 153.75, 152.97, 152.34, 136.46, 129.07, 127.78, 125.23, 122.92, 117.42, 20.93 (C-L3), 106.97, 100.02, 86.57, 85.30, 85.02, 84.15, 30.68, 22.42, 22.24, 18.21 (C-*p*-cym); **HRMS-APCI** (m/z) [Found (Calcd)]: [478.0902 (478.0891)] $[M\text{-}2H\text{-}2Cl+H]^+$.

[Cp*Rh(L3)κ$^2_{(N,S)}$Cl]Cl (8)

Yield: 86 mg (78%); **Anal. Calc** for $C_{23}H_{28}Cl_2N_3SRh$ (552.36); C, 50.01; H, 5.11; N, 7.61. Found: C, 50.13; H, 5.27; N, 7.75 %; **FT-IR** (KBr, cm^{-1}): 3371(s), 3120(m), 1619(m), 1602(w), 1585(s), 1523(s), 1223(m), 1140(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.20 (s, 1H, NH), 12.10 (s, 1H, NH), 8.55 (d, *J* = 4 Hz, 1H), 7.60 (d, *J* = 8 Hz, 2H), 7.47 (t, *J* = 8 Hz, 2H), 7.43 (t, *J* = 4 Hz, 2H), 7.09 (d, *J* = 4 Hz, 1H), 2.45 (s, 3H, $CH_{3(py)}$), 1.53 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.78, 153.30, 151.55, 151.20, 136.47, 129.08, 127.86, 125.70, 123.77, 117.86, 21.03, (C-L3), 96.89 (Cp^*_{ipso}), 8.80 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [480.0980 (480.0981)] $[M\text{-}2H\text{-}2Cl+H]^+$.

[Cp*Ir(L3)κ$^2_{(N,S)}$Cl]Cl (9)

Yield: 94 mg (73%); **Anal. Calc** for $C_{23}H_{28}Cl_2N_3SIr$ (641.67); C, 43.05; H, 4.40; N, 6.55. Found: C, 43.16; H, 4.47; N, 6.64 %; **FT-IR** (KBr, cm^{-1}): 3340(w), 2922(m), 1618(m), 1593(w), 1541(m), 1489(m), 1232(m), 1189(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.07 (s, 1H,

NH), 12.04 (s, 1H, NH), 8.49 (d, *J* = 8 Hz, 1H), 7.55 (t, *J* = 8 Hz, 3H), 7.44 (t, *J* = 8 Hz, 2H), 7.36 (t, *J* = 4 Hz, 1H), 7.01 (d, *J* = 4 Hz, 1H), 2.49 (s, 3H, $CH_{3(py)}$), 1.52 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 176.44, 153.54, 152.39, 150.85, 136.32, 129.12, 127.91, 125.64, 123.77, 117.53, 20.94, (C-L3), 89.32 (Cp^*_{ipso}), 8.51 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [570.1572 (570.1555)] $[M-2H-2Cl+H]^+$.

Results and discussion

Synthesis of complexes

The present work deals with the synthesis, characterization and chemosensitivity studies of arene d^6 metal complexes containing thiourea derivatives. The metal complexes (**1**-**9**) were synthesized by the reaction of precursor complexes and thiourea derivatives (L1-L3) in acetone. Scheme 1 depicts the synthesis of the metal complexes containing thiourea derivatives. These complexes were isolated as ionic salts with chloride counter ion. The complexes were isolated as dark to light yellow solids in moderate yields and are non-hygroscopic. They are soluble in common organic solvents like acetonitrile, dichloromethane, chloroform, methanol and DMSO but insoluble in petroleum ether, hexane and diethyl ether. Single crystal X-ray diffraction analysis confirmed the coordination of the thiourea derivatives to the metal ion in bidentate chelating N,S- manner. Further the anti-cancer activity of the thiourea derivatives and its metal complexes were evaluated against two cancer cell lines and one non cancer cell line.

Spectral studies of the complexes

IR studies of metal complexes

The preliminary confirmation of the formation of complexes was justified from their IR spectra. The appearance of the N-H stretching frequencies in the complexes around 3100-3370 cm^{-1} indicates that the N-H group is not involved in coordination. The coordination of the thione

sulfur to the metal would result in the displacement of electrons towards the metal ion which will weaken the C=S bonds hence on complexation the C=S stretching vibrations is expected to decrease. Therefore on complexation the C=S stretching frequencies appeared in the lower frequency region around 1202-1233 cm^{-1} as compared to the free ligand suggesting the coordination of thione sulfur. The C=N stretching vibration decreases slightly and was observed in the range of 1598-1620 cm^{-1} which indicates involvement of pyridyl/pyrimidyl nitrogen in coordination.

^{1}H NMR studies of metal complexes

The ^{1}H NMR spectra of the complexes are provided in the supplementary information (Figures S1-S9). The formation of the complexes was supported by the ^{1}H NMR studies. The appearance of the ligand proton signals in addition to the *p*-cymene and Cp* ring protons clearly indicates the formation of the compounds. In the ^{1}H NMR spectra of the complexes the N-H proton signals were observed as a singlet around 9.83-13.12 ppm. For complexes (**5** and **6**) the N-H proton resonance was observed at 8.93 and 8.87 ppm. The appearance of the N-H proton signals in the complexes indicates that the N-H group is not involved in bonding. The aromatic proton signals associated with the thiourea ligands were observed in the downfield region around 7.00-9.14 ppm indicating the coordination of the thiourea ligand to the metal ion. Besides these resonance signals for the aromatic part of the ligand complexes (**1**, **4** and **7**) displayed an unusual pattern of signal for the *p*-cymene moiety. The aromatic proton signal for the *p*-cymene ligand consisted of three doublets for complex (**4**) around 5.38-5.56 ppm whereas for complexes (**1** and **7**) it showed two doublets and one triplet around 5.23-5.51 ppm instead of two doublets in the starting metal precursor. Also the methyl protons of isopropyl group displayed one doublet for complex (**4**) and two doublet of doublet for complexes (**1** and **7**) around 1.18-1.25 ppm as shown

in (Figure 1). This splitting of the aromatic and isopropyl protons of the *p*-cymene ligand is due to the desymmetrization of the *p*-cymene ligand upon coordination of the thiourea derived ligand. Complexes (**1**, **4** and **7**) displayed septet around 2.74-2.81 ppm for the methine protons of the isopropyl group and singlet around 1.89-2.00 ppm for the methyl protons of the *p*-cymene ligand. In complexes (**7**-**9**) a singlet around 2.45-2.49 ppm was observed corresponding to the methyl protons of the pyridine ring of ligand L3. In rhodium and iridium complexes in addition, to the signals for the protons of the ligand a sharp singlet was observed around 1.52-1.66 ppm for the methyl protons of the pentamethylcyclopentadienyl ligand. Overall the ^{1}H NMR spectra of the complexes exhibited the expected resonances and integration which is consistent with the formulation of the compounds.

^{13}C {^{1}H} NMR studies of metal complexes

The ^{13}C NMR spectra of the complexes further justify the coordination of the ligands and formation of complexes. The ^{13}C NMR spectra of the complexes are provided in the supplementary information (Figures S10-S18). The ^{13}C NMR spectra of the complexes displayed signals associated with the ligand carbons, *p*-cymene ligand carbons, methyl carbon of Cp* and ring carbon of Cp*. The carbon resonance of the thiocarbonyl (C=S) group appeared in the lower frequency region around 175.6-178.0 ppm. This shifting of carbon resonances of the thiourea derivatives clearly suggests its involvement in coordination to the metal ion. The aromatic carbons signals for the ligands were observed in the range of 116.2-163.3 ppm. In complexes (**7**-**9**), the methyl carbon resonances of the pyridine ring were observed around 20.9-21.0 ppm. The ring carbon resonances of the *p*-cymene ligand were observed around 84.1-106.9 ppm. The methyl, methine and isopropyl carbon resonances of the *p*-cymene ligand were observed in the region around 17.1-30.7 ppm. The signals associated with the ring carbons of the Cp* ligand was

observed in the region around 89.3-97.4 ppm in contrast the methyl carbon resonances was observed as a sharp peak around 8.51-8.84 ppm. Overall results from the NMR spectral studies strongly support the formation of the metal complexes.

Mass spectral studies of metal complexes

The mass spectra of the thiourea complexes are presented in the supplementary information (Figures S19-S27) and the values are listed in the experimental section (2.4). The mass spectra of the complexes are consistent with the formulation and composition of the complexes. All these complexes displayed their molecular ion peaks at m/z: 464.0753, m/z: 466.0820, m/z: 556.1381, m/z: 465.0685, m/z: 467.0784, m/z: 557.1355, m/z: 478.0902, m/z: 480.0980 and m/z: 570.1572 which corresponds to $[M\text{-}2H\text{-}2Cl+H]^+$ ion peak. The peak corresponding to the loss of the arene ring (arene = *p*-cymene/Cp*) was not observed in its mass spectrum which indicates the stronger metal to arene bond.

Description of the crystal structures of complexes

In addition to the spectroscopic analysis we were also able to confirm the coordination of the thiourea derivatives to the metal by carrying out the single crystal X-ray analysis. Our attempt to isolate the single crystal for all the complexes was unsuccessful; however we obtained single crystals for complexes (**1**, **5**, **6**, **7** and **8**) respectively. Suitable single crystals were attached to a glass fiber and transferred into the Oxford Diffraction Xcalibur Eos Gemini diffractometer. The data and molecular structure of complex **1** presented here is to only confirm the structure and composition of the molecule. The ORTEP plot of complexes along with atom numbering scheme are shown in (Figures 2-4) respectively. The methyl groups of Cp* in complex (**5**) are disordered due to which the methyl groups in Cp* has large thermal ellipsoids The details regarding data collection and structure refinement parameters are summarized in

Table 1 and geometrical parameters including bond lengths, bond angles and metal atom involving ring centroid values are listed in Table 2. Complexes (**1**, **5** and **8**) crystallized in monoclinic crystal system with space group $P2_1/c$ whereas complex (**6**) crystallized with *C2/c* space group in monoclinic crystal system. Complex (**7**) crystallized in triclinic system with space group *P T*. X-ray crystallographic studies showed that these complexes contained the cationic species of general formula [(arene)M(L)Cl] [(arene) = *p*-cymene, Cp*; M = Ru, Rh and Ir; (L) = (L1-L3)] and counter anion chloride. These complexes featured a regular three legged "piano-stool" geometry in which the coordination sites around the metal is occupied by the arene ligand (arene = *p*-cymene/Cp*) in a η^6/η^5 manner, terminal chloride and a chelating N,S- ligand. The metal atom shows pseudo-octahedral coordination geometry wherein the arene ligand occupies the three facial coordination sites acting as seat of "piano-stool" and nitrogen and sulfur donor atoms from thiourea derivatives (L1-L3) and terminal chloride acting as legs. The molecular structures of these complexes revealed that the ligands (L1-L3) coordinated metal in a neutral bidentate chelating N,S- manner through pyridyl nitrogen N(1) in complexes (**1**, **7** and **8**), pyrimidyl nitrogen N(1) in complexes (**5** and **6**) and thione sulfur S(1). This coordination of the ligands in a bidentate manner led to the formation of a six-membered chelated ring with the metal center. The arene ring is essentially planar and the metal to centroid of the arene ring distances are {1.696 (**1**), 1.789 (**5**), 1.794 (**6**), 1.689 (**7**) and 1.789 (**8**) Å}. The iridium to centroid distance is slightly larger than the ruthenium/rhodium centroid distances (Table 2). Further as per the literature survey of these ligands these are known to exhibit several coordination modes but in these half-sandwich d^6 metal complexes reported here the preferable mode of coordination of these ligands is only in a bidentate $\kappa^2_{(N,S)}$ fashion. The deprotonation of the amido hydrogen which was expected to alter the coordination behavior of these ligands was also not observed as

evidenced by ^{1}H NMR and molecular structures. There is significant delocalization of π-electron density in the six-membered chelate ring as evidenced from the bond distances of the complexes which was found to be in the range of 1.33-1.69 Å.[31] The phenyl ring is effectively planar to that of the chelate ring. Further the C-S bond distances in these complexes was found to be in the range of 1.686-1.700 Å suggesting that it is intermediate between single C-S (1.82 Å) and double C=S (1.56 Å) bond distances.[32] The bond lengths in these complexes are normal and consistent with the κ^2-N,S- coordination of the thiourea derivatives which correlates well with reported values for similar complexes.[19,33-35] The metal to nitrogen bond distances is comparatively shorter than the metal to sulfur bond distances (Table 2). The M-Cl bond lengths in these complexes shows no significant differences and was found to be in the range of 2.39-2.40 Å which is comparable to reported literature values.[33,34] With respect to the bond angle values N(1)-M(1)-S(1), N(1)-M(1)-Cl(1), S(1)-M(1)-Cl(1) these are close to 90° suggesting pseudo-octahedral geometry around the metal center (Table 2). Overall all the geometrical parameters are as anticipated.

Non-covalent interactions

Further the crystal packing diagrams of these complexes revealed several weak intermolecular interactions. For instance the crystal structure of complex (**5**) crystallized with solvent molecule ($CHCl_3$) which showed intermolecular hydrogen bonding. The chloride counterion in complex (**5**) displayed three different types of intermolecular hydrogen bonding, C-H···Cl (2.510 Å), N-H(4)···Cl (2.246 Å), N-H(3)···Cl (2.420 Å) and C-H···Cl (2.909 Å) as shown in (Figure 5). Also it possessed C-H···Cl (2.921 Å) interaction between the chloride attached to rhodium and hydrogen atom of phenyl ring and C-H···S (2.788 Å) interaction between thione sulfur and hydrogen atom of phenyl ring (Figure 5). The crystal structure of

complex (**7**) exhibits two different types of C-H···Cl (2.848 and 2.869 Å) interactions between the chloride counterion and H-atom of phenyl ring and methyl hydrogen of *p*-cymene ring. It also showed N-H(2)···Cl (2.291 Å), N-H(3)···Cl (2.425 Å) interactions between the amide hydrogen and chloride counter ion [Figure 6 (a]. Further the crystal structure of complex (**8**) is stabilized by C-H···Cl (2.704 and 2.863 Å) interaction between the methyl-H atom of Cp*, and N-H(3)···Cl (2.320 Å), N-H(4)···Cl (2.277 Å) interaction between chloride counter ion and amide hydrogen [Figure 6 (b)]. These weak intermolecular interactions play a crucial role in the formation of supramolecular architectures.

Table 1 Crystal data and structure refinement parameters of complexes.

Compounds	[**1**]Cl	[**5**]Cl $CHCl_3$	[**6**]Cl	[**7**]Cl	[**8**]Cl
Empirical formula	$C_{22}H_{25}N_3Cl_3SRu$	$C_{22}H_{26}Cl_5N_4SRh$	$C_{21}H_{25}N_4Cl_2SIr$	$C_{23}H_{27}Cl_2N_3SRu$	$C_{23}H_{28}Cl_2N_3SRh$
Formula weight	570.93	658.69	628.61	549.03	552.35
Temperature (K)	293(2)	295(2)	295(2)	296.5(4)	295.88(18)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal system	monoclinic	monoclinic	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$C2/c$	$P\,\bar{1}$	$P2_1/c$
a (Å)/α (°)	13.3257(10)/90	8.0190(7)/90	18.3824(11)/90	10.2397(8)/91.759(5)	13.8075(8)/90
b (Å)/β (°)	13.8131(10)/90.279(8)	13.1219(8)/96.088(7)	16.4907(8)/116.016(8)	10.2855(6)/104.690(6)	7.8091(4)/105.402(6)
c (Å)/γ (°)	13.0173(12)/90	26.9485(16)/90	18.7528(12)/90	11.9684(7)/102.167(6)	23.1017(12)/90
Volume ($Å^3$)	2396.1(3)	2819.7(3)	5108.7(6)	1187.20(14)	2401.5(2)
Z	4	4	8	2	4
Density (calc) (Mg/m^{-3})	1.583	1.552	1.635	1.534	1.528
Absorption coefficient (μ) (mm^{-1})	1.091	1.172	5.532	0.988	1.036
F(000)	1156	1328	2448	558	1128
Crystal size (mm^3)	0.29 x 0.21 x 0.15	0.25 x 0.23 x 0.21	0.49 x 0.36 x 0.25	0.25 x 0.23 x 0.21	0.25 x 0.23 x 0.21
Theta range for data collection	3.130 to 29.069°	3.197 to 28.974°	3.491 to 28.858°	3.246 to 29.110°	3.318 to 29.044°
Index ranges	-14<=h<=18, -12<=k<=18, -17<=l<=9	-10<=h<9, -10<=k<=17, -27<=l<=36	-24<=h<=23, -21<=k<=18, -13<=l<=25	-13<=h<10, -13<=k<=14, -15<=l<=16	-18<=h<=9, -10<=k<=5, -31<=l<27
Reflections collected	7081	10440	10138	8283	9741
Independent reflections	4978 [R(int) = 0.0353]	6211 [R(int) = 0.0257]	5726 [R(int) = 0.0556]	5355 [R(int) = 0.0559]	5504 [R(int) = 0.0276]
Completeness to theta = 25.00°	99.9 %	97.6 %	99.2 %	99.4 %	99.6 %
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	4978/0/271	6211/157/405	5726/0/267	5355/0/271	5504/0/271
Goodness-of-fit on F^2	1.063	1.086	1.063	1.059	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0721, wR2 = 0.1868	R1 = 0.0600, wR2 = 0.1419	R1 = 0.0562, wR2 = 0.1121	R1 = 0.0553, wR2 = 0.1298	R1 = 0.0427, wR2 = 0.0913
R indices (all data)	R1 = 0.0985, wR2 = 0.2130	R1 = 0.0791, wR2 = 0.1551	R1 = 0.0723, wR2 = 0.1195	R1 = 0.0699, wR2 = 0.1430	R1 = 0.0567, wR2 = 0.0974
Largest diff. peak and hole ($e.Å^{-3}$)	2.529 and -0.955	0.932 and -0.625	3.511 and -3.039	0.949 and -0.802	0.434 and -0.452
CCDC No.		1581360	1581361	1581362	1581363

Structures were refined on F_0^2: $wR_2 = [\Sigma[w(F_0^2 - F_c^2)^2] / \Sigma w(F_0^2)^2]^{1/2}$, where $w^{-1} = [\Sigma(F_0^2)+(aP)^2+bP]$ and $P = [\max(F_0^2, 0)+2F_c^2]/3$

Table 2 Selected bond lengths (Å) and bond angles (°) of complexes.

Complex	**1**	**5**	**6**	**7**	**8**
M(1)-CNT	1.696	1.789	1.794	1.689	1.789
M(1)-N(1)	2.122(6)	2.101(3)	2.110(5)	2.109(4)	2.101(3)
M(1)-S(1)	2.3740(18)	2.3411(9)	2.3616(16)	2.3768(12)	2.3411(9)
M(1)-Cl(1)	2.4097(18)	2.3992(10)	2.3962(16)	2.4009(12)	2.3992(10)
C=S(1)	1.699(7)	1.694(3)	1.700(6)	1.686(4)	1.694(3)
N(1)-M(1)-S(1)	85.99(15)	85.08(8)	86.15(13)	84.18(10)	85.08(8)
N(1)-M(1)-Cl(1)	86.14(16)	88.56(8)	88.14(13)	86.88(9)	88.56(8)
S(1)-M(1)-Cl(1)	85.74(7)	90.11(44)	87.34(6)	86.16(4)	90.11(4)

CNT represents the centroid of the arene ring and (M = Ru, Rh and Ir)

Chemosensitivity studies

The response of HCT-116, MIA PaCa-2 and ARPE-19 cells to the thiourea ligands (L1-L3) and its metal complexes (**1**-**9**) are provided in Table 3. The thiourea ligands (L1-L3) were found to be inactive against both the cell line with IC_{50} value > 100. Upon complexation of thiourea ligands all the complexes displayed cytotoxicity against both cancer cell lines. Complexes (**4**-**6**) with ligand L2 were found to exhibit moderate activity against both the cell lines with IC_{50} value in the range of 33.1 ± 0.39 to 77.4 ± 2.71 μM. Complexes (**1**-**3**) with ligand L1 and (**7**-**9**) with ligand L3 possessed similar cytotoxicity against both HCT-116 and Mia-PaCa-2 cell line with IC_{50} value in the range of 9.10 ± 0.09 to 18.2 ± 3.25 μM. These complexes were found to be more active as compared to complexes (**4**-**6**). However, all these thiourea compounds were found to be less cytotoxic as compared to cisplatin whose IC_{50} value is 2.78 μM against HCT-116 and 3.15 μM against MIA-PaCa2 cell lines. Complex (**8**) was found to possess the highest cytotoxicity among all other complexes against HCT-116 cell line with IC_{50} value of 9.16 ± 0.84 μM whereas complex (**9**) was the most potent against Mia-PaCa-2 cell line with IC_{50} value of 9.10 ± 0.09 μM. The response of ARPE-19 non-cancer cell lines is presented in Table 3

and corresponding selectivity indices are presented in Figure 7. With regards to potency, statistically significant differences between the response of cancer cells lines and ARPE-19 cells were observed for all complexes with the exception of complex (**4**). In the case of complexes (**1**, **3**, **7** and **9**) statistically significant differences between the response of MIA-PaCa-2 (but not HCT-116) and ARPE-19 cells was observed suggesting that some selectivity for MIA-PaCa-2 cells exists *in vitro* (Table 3). The selectivity index (SI) is shown in Table 4 which is defined as the ratio of IC_{50} values in ARPE19 cells divided by the IC_{50} for either HCT-116 or MIA-PaCa-2 cells. With regards to selectivity, Figure 7 demonstrates that complexes (**5**, **6** and **8**) have greater selectivity for HCT-116 cells than cisplatin under identical experimental conditions. In some cases (complexes **1**, **3** and **9**) enhanced selectivity towards the MIA-PaCa-2 as opposed to the HCT-116 cell line is obtained. The IC_{50} and selectivity index values of these compounds provide an ideal platform for the design of thiourea complexes possessing high cytotoxicity.

Table 3 IC_{50} values of thiourea ligands (L1-L3) and complexes (**1-9**) along with cisplatin against HCT-116 and MIA-PaCa-2 cancer cell line. Each value represents the mean ± standard deviation from three independent experiments. Statistical analysis comparing the response of cancer cell lines (HCT-116 or MIA-PaCa-2) to non-cancer ARPE-19 cells was performed by a two tailed students t-test with * and ** representing P values of < 0.05 and < 0.01 respectively.

Compounds	IC_{50} (μM)		
	HCT-116	MIA-PaCa-2	ARPE-19
L1	IC_{50}>100	IC_{50}>100	IC_{50}>100
L2	IC_{50}>100	IC_{50}>100	IC_{50}>100
L3	IC_{50}>100	IC_{50}>100	IC_{50}>100
Complex **1**	17.52 ± 2.95	10.05 ± 0.17**	21.31 ± 3.53
Complex **2**	9.69 ± 0.97**	10.17 ± 0.37**	19.46 ± 2.57
Complex **3**	15.38 ± 3.21	9.96 ± 0.11*	24.14 ± 8.33
Complex **4**	68.44 ± 5.82	77.44 ± 2.71	67.52 ± 16.98
Complex **5**	44.82 ± 11.70*	33.66 ± 3.96**	84.41 ± 16.51
Complex **6**	35.59 ± 7.35**	33.17 ± 0.39**	66.28 ± 3.97
Complex **7**	18.23 ± 3.25	16.75 ± 0.42**	20.82 ± 0.57
Complex **8**	9.16 ± 0.84*	9.48 ± 0.32*	15.75 ± 2.87
Complex **9**	16.02 ± 2.13	9.10 ± 0.09**	19.78 ± 1.80
Cisplatin	2.78 ± 1.40	3.15 ± 0.10	3.43±0.48

IC_{50} = concentration of the drug required to inhibit the growth of 50% of the cancer cells (μM).

Table 4 Selectivity index of complexes (**1-9**) and cisplatin in HCT-116 and MIA-PaCa-2 cancer cell lines. The selectivity index (SI) was calculated as the IC_{50} for ARPE-19 cells divided by the IC_{50} for either HCT-116 or MIA-PaCa-2 cells.

Compounds	HCT-116	MIA-PaCa-2
Complex **1**	1.21	2.12
Complex **2**	2	1.91
Complex **3**	1.56	2.42
Complex **4**	0.98	0.87
Complex **5**	1.88	2.5
Complex **6**	1.86	1.99
Complex **7**	1.14	1.242
Complex **8**	1.71	1.66
Complex **9**	1.234	2.173
Cisplatin	1.23	1.08

Conclusion

In summary, we have successfully synthesized ruthenium, rhodium and iridium half-sandwich complexes containing thiourea derivatives. These complexes were fully characterized by various spectroscopic studies and molecular structures were established by single crystal X-ray analysis. X-ray crystallographic studies of the complexes revealed that the thiourea derivatives coordinated metal in a neutral bidentate chelating manner coordinating metal through nitrogen atom from pyridine or pyrimidine and thione sulfur. The chemosensitivity studies of the thiourea derivatives and complexes carried out against HCT-116, MIA-PaCa-2 and ARPE-19 cell lines showed that the thiourea ligands are not cytotoxic but after complexation however, the complexes possessed cytotoxicity. Whilst the potency of these complexes is generally less than cisplatin, this study demonstrates that several complexes have greater selectivity for cancer cell lines (with some showing specific selectivity for MIA-PaCa-2 pancreatic cancer cells) than cisplatin under identical experimental conditions *in vitro*. Further development of these complexes is required to enhance selectivity further and explore mechanism of action responsible for the differential cytotoxic effects observed.

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Supplementary material

CCDC **1581360** (**5**), **1581361** (**6**), **1581362** (**7**) and **1581363** (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by

contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

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