Neutral and cationic half-sandwich arene d^6 metal complexes containing pyridyl and pyrimidyl thiourea ligands with interesting bonding modes: Synthesis, structural and anti-cancer studies

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Abstract

The reaction of [(*p*-cymene)$RuCl_2]_2$ and $[Cp^*MCl_2]_2$ (M = Rh/Ir) with benzoyl(2-pyrimidyl)thiourea (L1) and benzoyl(4-picolyl)thiourea (L2) led to the formation of cationic complexes bearing formula $[(arene)M(L1)\kappa^2_{(N,S)}Cl]^+$ and $[(arene)M(L2)\kappa^2_{(N,S)}Cl]^+$ [(arene) = *p*-cymene, M = Ru, (**1**, **4**); Cp*, M = Rh (**2**, **5**) and Ir (**3**, **6**)]. Precursor compounds reacted with benzoyl(6-picolyl)thiourea (L3) affording neutral complexes having formula $[(arene)M(L3)\kappa^1_{(S)}Cl_2]$ [arene = *p*-cymene, M = Ru, (**7**); Cp*, M = Rh (**8**), Ir (**9**)]. X-ray studies revealed that the methyl substituent attached to the pyridine ring in ligands L2 and L3 affects its coordination mode. When methyl group is at the *para* position of the pyridine ring (L2), the ligand coordinated metal in a bidentate chelating N, S- mode whereas methyl group at *ortho* position (L3), it coordinated in a monodentate mode. Further the anti-cancer studies of the thiourea derivatives and its complexes carried out against HCT-116, HT-29 (human colorectal cancer), Mia-PaCa-2 (human pancreatic cancer) and ARPE-19 (non-cancer retinal epithelium) cell lines showed that the thiourea ligands are inactive but upon complexation, the metal compounds displayed potent and selective activity against cancer cells *in vitro*. Iridium complexes were found to be more potent as compared to ruthenium and rhodium complexes.

Keywords: Ruthenium, rhodium, iridium, thiourea, cytotoxicity

Introduction

Ruthenium based organometallic complexes have evolved as a promising candidates as anti-cancer agents having potential clinical applications in particularly against cisplatin resistant tumors.[1] Half-sandwich arene ruthenium(II) complexes are currently the subject of versatile research which have the capability to act as metal-based anti-cancer drugs.[2,3] In particularly two such complexes developed by Sadler's group $[Ru(\eta^6\text{-arene})Cl(en)]^+$ (en = ethylenediamine) and Dyson's group $[Ru(\eta^6\text{-toluene})Cl_2(pta)]$ (pta = 1,3,5-triaza-7-phosphaadamantane) have been extensively studied and found to have excellent anti-tumor properties.[4-6] The organometallic scaffold present in the ruthenium arene complexes presents an ideal platform for the design of these half-sandwich complexes. The basic building blocks in these complexes include the arene ligand which controls the hydrophobicity and interactions with biomolecules, labile chloride ligand which enables coordination of the metal with protein and nucleic acids.[7,8] Rhodium and iridium pentamethylcyclopentadienyl complexes have also been studied by various research groups for their anti-proliferative activities.[9,10] These complexes have also displayed their remarkable activity as catalyst for various organic transformation reactions.[11-13]

Much interest has been paid towards the coordination chemistry of benzoylthiourea ligands because of their interesting and versatile coordination behavior towards various transition metals. These ligands possesses various hetero donor atoms which can coordinate metal in several coordination modes such as monobasic bidentate (O, S), neutral monodentate (S), and neutral bidentate (O, N) coordination modes.[14,15] Rhodium complex of N-benzoyl-N´-phenylthiourea ligand has been reported wherein the ligand acted as bridging ligand coordinating one rhodium center in a bidentate fashion through (O, S) mode and the other through deprotonated nitrogen.[16] Substitution of alkyl or aryl group with various other substituents is

expected to alter the coordination modes of these ligands. When the alkyl or aryl group is replaced by a pyridyl group the ligand acted as neutral bidentate ligand coordinating metal in a (N, S) mode.[17,18] Transition metal complexes of various thiourea derived ligands have been evaluated for their anti-bacterial, anti-cancer and anti-microbial activities.[19-21] In our present work we report the synthesis spectral and molecular structures of ruthenium, rhodium and iridium half-sandwich complexes containing pyridyl and pyrimidyl thiourea derivatives. Ligands used in the present study are shown in Chart 1.

Experimental

Materials and Methods

The reagents used 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-amino pyrimidine, 2-amino-4-methyl pyridine and 2-amino-6-methyl pyridine were purchased from Sigma-Aldrich and benoylisothiocyanate was purchased from Alfa-Aesar. The solvents were dried and distilled prior to use according to standard procedures.[22] The thiourea derivatives (L1-L3) were prepared according to published procedures.[23,24] Precursor metal complexes $[(p\text{-cymene})RuCl_2]_2$ and $[Cp^*MCl_2]_2$ (M = Rh/Ir) were prepared according to the published procedures.[25,26] ^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 in positive mode 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

Solvent diffusion method was used for growing single crystals of compounds. Suitable single crystals for X-ray structure analysis have been obtained for [**2**]PF_6 and [**3**]PF_6, available from [**2**]Cl and [**3**]Cl and (**4**, **5**, **6**, **7**, **8** and **9**) in a dichloromethane-hexane mixture. The PF_6 salts for complexes (**2** and **3**) were obtained by dissolving quantitative amount of chloride salts *i.e.* [**2**]Cl and [**3**]Cl in acetonitrile and adding excess amounts of ammonium hexafluorophosphate whereupon ammonium chloride precipitated out immediately. This solution was then filtered over celite and the solvent was evaporated under reduced pressure to afford yellow solid which was washed with diethyl ether (2x 5 mL) and air dried. This compound was utilized for growing single crystals for complexes (**2** and **3**). 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.[27,28]. 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 S1 & S2) and selected bond lengths and bond angles are presented in

(Table S3). Figures 1-3 were drawn with ORTEP3 program whereas Figures 4-6 was drawn using MERCURY 3.6 program.[29]

The crystal structure of complex (**4**) contains disordered $CHCl_3$ and H_2O molecule. The asymmetric unit in complex (**5**) contains two molecules along with a H_2O molecule. Crystal structure of complex (**6**) contains H_2O molecule in its solved structure. Asymmetric unit in complex (**7**) contains two molecules.

Cell lines testing, culture conditions and cytotoxicity against cell lines

The *in vitro* cytotoxicity of the thiourea derivatives (L1-L3) and its corresponding arene d^6 metal complexes were performed at the University of Huddersfield against Mia-PaCa-2 human pancreatic cancer cell line, HT-29 and HCT-116 human colorectal carcinoma cell lines and the non-cancer ARPE-19 human epithelial cell line. The cell lines were originally purchased from ATCC and the reagents used were purchased from Sigma Aldrich Co. Ltd (Dorset, UK) unless otherwise stated. Antiproliferative activity of the compounds was evaluated using the standard MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) cellular viability assay as described elsewhere.[30] Briefly cells were seeded into 96 well plates at 1.5 x 10^3 cells per well and incubated for 24 hours at 37˚C in an atmosphere of 5% CO_2 prior to drug exposure. Generally, a stock solution was freshly prepared by dissolving each of the compounds in dimethylsulphoxide at a concentration of 100 mM which was subsequently diluted with medium to obtain drug solutions ranging from 0.5 to 100 µM. The final dimethylsulphoxide 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. The cells were exposed to a range of drug concentrations for 96 hours and cell survival was determined using the MTT assay.[29,30] Following drug exposure 20 µL of MTT (0.5 mg/ mL) in phosphate buffered saline was added to each well and it was

125 further incubated at 37 °C for 4 hours in an atmosphere containing 5% CO_2. The solution was
126 then removed and the formed formazan crystals were dissolved in 150 µM dimethylsulphoxide.
127 The absorbance of the resulting solution was recorded at 550 nm using an ELISA
128 spectrophotometer. The percentage of cell survival was calculated by dividing the true
129 absorbance of treated cell by the true absorbance for controls (exposed to 0.1%
130 dimethylsulphoxide). The IC_{50} values were determined from plots of % survival against drug
131 concentration. Each experiment was performed in triplicate and a mean value obtained and stated
132 as IC_{50} (µM) ± SD. To compare the response of non-cancer cells to cancer cells, the selectivity
133 index (SI) was also calculated which is defined as the IC_{50} for ARPE-19 cells divided by the IC_{50}
134 for each cancer cell line. Values >1 indicate that complexes have selective activity against cancer
135 compared to non-cancer cells *in vitro*.

136 ***General procedure for preparation of thiourea metal complexes (1-9)***

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

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

143 Yield 90 mg (79%); **Anal. Calc.** for $C_{22}H_{24}Cl_2N_4OSRu$ (564.49): C, 46.81; H, 4.29; N, 9.93.
144 Found: C, 46.93; H, 4.38; N, 9.88 %; **FT-IR** (KBr, cm^{-1}): 3430(b), 3045(w), 1710(s), 1585(m),
145 1559(m), 1257(m), 1175(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 14.33 (s, 1H, NH), 9.13 (d, *J* = 4
146 Hz, 1H), 8.76 (s, 1H, NH), 8.59 (d, *J* = 4 Hz, 1H), 8.39 (d, *J* = 8 Hz, 2H), 7.44-7.59 (m, 4H),
147 5.47 (d, *J* = 4 Hz, 2H, $CH_{(p\text{-cym})}$), 5.31 (d, *J* = 8 Hz, 2H, $CH_{(p\text{-cym})}$), 2.85 (sept, 1H, $CH_{(p\text{-cym})}$), 2.11

(s, 3H, $CH_{(p\text{-cym})}$), 1.27 (d, *J* = 8 and 8 Hz, 6H, $CH_{(p\text{-cym})}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 180.05, 166.20, 160.67, 156.28, 134.06, 131.14, 129.46, 128.96, 119.05, (C-L1), 107.33, 101.48, 88.35, 86.63, 85.99, 85.46, 30.72, 22.32, 18.35 (C-*p*-cym); **HRMS-APCI** (m/z) [Found (Calcd)]: [492.0578 (492.0558)] $[M\text{-}2H\text{-}2Cl+H]^+$.

[Cp*Rh(L1)κ$^2_{(N,S)}$Cl]Cl (2)

Yield 87 mg (76%); **Anal. Calc.** for $C_{22}H_{25}Cl_2N_4OSRh$ (556.01): C, 46.57; H, 4.44; N, 9.88. Found: C, 46.68; H, 4.56; N, 9.95 %; **FT-IR** (KBr, cm^{-1}): 3424(b), 3076(w), 1712(s), 1599(m), 1580(w), 1257(m), 1177(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 14.42 (s, 1H, NH), 9.02 (dd, *J* = 4 and 4 Hz, 1H), 8.81 (s, 1H, NH), 8.62 (d, *J* = 4 Hz, 1H), 8.38 (d, *J* = 8 Hz, 2H), 7.51-7.63 (m, 4H), 1.64 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 178.63, 161.42, 161.13, 133.78, 129.48, 128.83, 127.68, 119.58 (C-L1), 96.13 (Cp^*_{ipso}), 8.89 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [494.0672 (494.0648)] $[M\text{-}2H\text{-}2Cl+H]^+$.

[Cp*Ir(L1)κ$^2_{(N,S)}$Cl]Cl (3)

Yield 93 mg (70%); **Anal. Calc.** for $C_{22}H_{25}Cl_2N_4OSRh$ (656.64): C, 40.24; H, 3.84; N, 8.53. Found: C, 40.32; H, 3.93; N, 8.64 %, **FT-IR** (KBr, cm^{-1}): 3431(b), 3120(m), 1714(s), 1596(m), 1588(w), 1258(m), 1176(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 14.31 (s, 1H, NH), 8.91 (dd, *J* = 4 and 4 Hz, 1H), 8.75 (s, 1H, NH), 8.61 (d, *J* = 4 Hz, 1H), 8.37 (d, *J* = 4 Hz, 1H), 7.60 (t, *J* = 8 Hz, 2H), 7.52 (t, *J* = 8 Hz, 2H), 7.23 (m, 1H), 1.84 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 178.31, 162.13, 161.22, 155.25, 134.02, 131.24, 129.46, 128.94, 119.88, 111.67, (C-L1), 90.80 (Cp^*_{ipso}), 8.62 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [584.1256 (584.1222)] $[M\text{-}2H\text{-}2Cl+H]^+$.

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

Yield 98 mg (85%); **Anal. Calc.** for $C_{24}H_{27}Cl_2N_3OSRh$ (577.02): C, 49.91; H, 4.71; N, 7.28. Found: C, 50.02; H, 4.87; N, 7.37 %; **FT-IR** (KBr, cm^{-1}): 3434(b), 3064(w), 1707(m), 1606(m), 1571(m), 1482(m), 1241(m) 1222(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 14.14 (s, 1H, NH), 12.84 (s, 1H, NH), 8.77 (d, *J* = 4 Hz, 1H), 8.41 (d, *J* = 8 Hz, 2H), 7.56-7.67 (m, 4H), 7.11 (d, *J* = 8 Hz, 1H), 5.67 (d, *J* = 4 Hz, 1H, $CH_{(p\text{-cym})}$), 5.59 (d, *J* = 4 Hz, 1H, $CH_{(p\text{-cym})}$), 5.40 (d, *J* = 4 Hz, 2H, $CH_{(p\text{-cym})}$), 2.93 (sept, 1H, $CH_{(p\text{-cym})}$), 2.48 (s, 3H, $CH_{3(py)}$), 2.00 (s, 3H, $CH_{(p\text{-cym})}$), 1.30 (d, *J* = 8 and 8 Hz, 6H, $CH_{(p\text{-cym})}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 178.66, 164.70, 153.53, 152.26, 149.89, 132.89, 130.38, 128.01, 122.81, 116.59, 21.42 (C-L2), 105.75, 99.93, 86.97, 85.26, 84.90, 83.54, 29.69, 20.02, 17.29 (C-*p*-cym); **HRMS-APCI** (m/z) [Found (Calcd)]: [507.0883 (507.0852)] $[M\text{-}2H\text{-}2Cl+H]^+$.

[Cp*Rh(L2)κ^2$_{(N,S)}$Cl]Cl (5)

Yield 103 mg (88%); **Anal. Calc.** for $C_{24}H_{28}Cl_2N_3OSRh$ (580.35): C, 49.67; H, 4.86; N, 7.24. Found: C, 49.76; H, 4.83; N, 7.38 %; **FT-IR** (KBr, cm^{-1}): 3440(b), 3067(w), 1709(m), 1607(m), 1583(m), 1489(m), 1245(m) 1228(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 14.09 (s, 1H, NH), 12.72 (s, 1H, NH), 8.49 (d, *J* = 4 Hz, 1H), 8.31 (d, *J* = 8 Hz, 2H), 7.61 (s, 1H, $CH_{(py)}$), 7.47-7.56 (m, 4H), 7.08 (d, *J* = 4 Hz, 1H), 2.39 (s, 3H, $CH_{3(py)}$), 1.54 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 178.32, 165.68, 153.61, 151.94, 150.0, 139.91, 131.47, 129.07, 129.00, 124.84, 118.19, 21.12 (C-L2), 97.50 (Cp^*_{ipso}), 8.85 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [508.0924 (508.0934)] $[M\text{-}2H\text{-}2Cl+H]^+$.

[Cp*Ir(L2)κ^2$_{(N,S)}$Cl]Cl (6)

Yield 103 mg (77%); **Anal. Calc.** for $C_{24}H_{28}Cl_2N_3OSIr$ (669.68): C, 43.04; H, 4.21; N, 6.27. Found: C, 43.13; H, 4.28; N, 6.41 %; **FT-IR** (KBr, cm^{-1}): 3441(b), 3083(w), 1703(m), 1606(m), 1586(m), 1475(m), 1243(m) 1217(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 13.95 (s, 1H, NH),

12.79 (s, 1H, NH), 8.49 (d, *J* = 8 Hz, 1H), 8.40 (d, *J* = 8 Hz, 2H), 7.74 (s, 1H, $CH_{(py)}$), 7.64 (t, *J* = 8 Hz, 1H), 7.57 (t, *J* = 8 Hz, 2H), 7.07 (d, *J* = 4 Hz, 1H), 2.50 (s, 3H, $CH_{3(py)}$), 1.61 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 177.72, 164.18, 153.70, 152.89, 151.02, 138.41, 133.82, 129.06, 128.97, 124.72, 117.87, 21.03 (C-L2), 90.05 (Cp^*_{ipso}), 8.54 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [598.1529 (598.1504)] $[M-2H-2Cl+H]^+$.

[(*p*-cymene)Ru(L3)κ^1$_{(S)}$Cl$_2$] (7)

Yield 103 mg (89%); **Anal. Calc.** for $C_{24}H_{27}Cl_2N_3OSRh$ (577.02): C, 49.91; H, 4.71; N, 7.28. Found: C, 50.02; H, 4.87; N, 7.37 %; **FT-IR** (KBr, cm^{-1}): 3447(b), 3038(w), 1715(m), 1620(m), 1552(m), 1446(m), 1384(m), 1250(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 15.36 (s, 1H, NH), 10.92 (s, 1H, NH), 8.07 (d, *J* = 8 Hz, 2H), 7.60-7.66 (m, 2H), 7.54 (t, *J* = 8 Hz, 2H), 7.03 (d, *J* = 8 Hz, 1H), 6.95 (d, *J* = 8 Hz, 1H), 5.54 (d, *J* = 8 Hz, 2H, $CH_{(p\text{-cym})}$), 5.37 (d, *J* = 8 Hz, 2H, $CH_{(p\text{-cym})}$), 3.12 (sept, 1H, $CH_{(p\text{-cym})}$), 2.48 (s, 3H, $CH_{3(py)}$), 2.33 (s, 3H, $CH_{(p\text{-cym})}$), 1.36 (d, *J* = 4 Hz, 6H, $CH_{(p\text{-cym})}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.86, 164.59, 154.33, 151.08, 139.32, 132.94, 132.86, 128.39, 127.75, 119.8, 112.35, 21.76 (C-L3), 103.51, 99.61, 84.02, 82.98, 29.88, 23.26, 17.89 (C-*p*-cym); **HRMS-APCI** (m/z) [Found (Calcd)]: [505.0734 (505.0762)] $[M-2H-2Cl+H]^+$.

[Cp*Rh(L3)κ^1$_{(S)}$Cl$_2$] (8)

Yield 92 mg (79%); **Anal. Calc.** for $C_{24}H_{28}Cl_2N_3OSRh$ (580.35): C, 49.67; H, 4.86; N, 7.24. Found: C, 49.76; H, 4.83; N, 7.38 %; **FT-IR** (KBr, cm^{-1}): 3443(b), 3031(w), 1715(m), 1623(m), 1554(m), 1452(m), 1394(m), 1253(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 15.47 (s, 1H, NH), 11.14 (s, 1H, NH), 8.08 (d, *J* = 8 Hz, 1H), 7.61-7.66 (m, 2H), 7.54 (t, *J* = 8 Hz, 2H), 7.20 (d, *J* = 12 Hz, 1H), 6.96 (d, *J* = 8 Hz, 1H), 2.49 (s, 3H, $CH_{3(py)}$), 1.74 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.24, 165.16, 153.14, 151.63, 142.88, 139.25, 133.36, 129.12, 128.02,

126.23, 119.92, 115.18, 23.43 (C-L3), 88.54 (Cp^*_{ipso}), 8.41 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [542.0646 (542.0540)] $[M-2H-Cl]^+$, [506.0881 (507.0852)] $[M-2H-2Cl-1]^+$.

[Cp*Ir(L3)κ$^1_{(S)}$Cl$_2$] (9)

Yield 97 mg (73%); **Anal. Calc.** for $C_{24}H_{28}Cl_2N_3OSIr$ (669.68): C, 43.04; H, 4.21; N, 6.27. Found: C, 43.13; H, 4.28; N, 6.41 %; **FT-IR** (KBr, cm^{-1}): 3436(b), 3038(w), 1704(m), 1620(m), 1550(m), 1446(m), 1384(m), 1248(m); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 15.40 (s, 1H, NH), 11.45 (s, 1H, NH), 8.0 (d, *J* = 8 Hz, 2H), 7.57 (t, *J* = 8 Hz, 2H), 7.46 (t, *J* = 8 Hz, 2H), 7.12 (d, *J* = 8 Hz, 1H), 6.91 (d, *J* = 8 Hz, 1H), 2.42 (s, 3H, $CH_{3(py)}$), 1.63 (s, 15H, $CH_{(Cp^*)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.33, 165.11, 154.91, 151.77, 139.88, 133.50, 133.36, 128.92, 128.20, 127.78, 119.92, 113.34. 23.83 (C-L3), 88.98 (Cp^*_{ipso}), 8.42 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [598.1507 (598.1504)] $[M-2H-2Cl+H]^+$.

Results and discussion

Synthesis of complexes

The work presented herein describes the synthesis of arene metal complexes containing benzoyl thiourea derivatives. The complexes (**1**-**9**) were synthesized by the reaction between precursor complexes and thiourea derivatives (L1-L3) in acetone. Scheme **1** depicts the synthesis of the metal complexes. Reaction of ligands (L1 and L2) with precursors afforded ionic complexes (**1**-**6**) which were isolated as chloride counter ion whereas reaction of (L3) afforded neutral complexes (**7**-**9**). Further X-ray analysis of these complexes revealed that the methyl substituent present at the pyridine ring in ligands (L2 and L3) affects its coordination behavior towards metal ion. Depending on the position of the methyl group attached to the pyridine ring the complexes can be isolated as neutral or ionic. In the present case when methyl group is at the *para* position of the pyridine ring such as in (L2) it acted as bidentate chelating ligand yielding

ionic complexes, whereas methyl group at the *ortho* position of the pyridine ring as in (L3) yielded neutral complexes with monodentate coordination of the ligand. All these complexes were isolated as light to dark yellow solids in moderate yields and characterized by spectroscopic and analytical techniques. Complexes (**1** and **4**) are not very stable in solid state and turned oily liquid which enabled us to evaluate its cytotoxicity analysis. They are soluble in common organic solvents like acetonitrile, dichloromethane, chloroform, methanol and dimethylsulphoxide but insoluble in petroleum ether, hexane and diethyl ether. Single crystal X-ray diffraction analysis confirmed the different coordinating modes of the thiourea derivatives observed in this work *i.e.* a bidentate chelating N, S- mode and a monodentate S- mode. Further the anti-cancer activity of the ligands and its metal complexes were evaluated against cancer cell line and non-cancer cell line.

Spectral studies of the complexes

IR studies of metal complexes

The IR spectra of the metal complexes showed stretching frequencies in the region around 3035-3450, 1770-1720, 1580-1625, and 1240-1260 cm^{-1} corresponding to ν(N-H), ν(C=O), ν(C=N) and ν(C=S). The N-H and C=O stretching frequencies did not show any change upon coordination of the ligands and were almost unaltered which indicates it is not involved in bonding to the metal atom. Whereas the C=S stretching frequencies appeared in the lower frequency region around 1240-1260 cm^{-1} as compared to the free ligand which strongly suggest the coordination of the sulfur atom of the thiocarbonyl group. In cationic complexes (**1**-**6**) the C=N stretching frequency decreases slightly as compared to free ligand and was observed in the region around 1585-1610 cm^{-1} which indicates involvement of pyridyl/pyrimidyl nitrogen in coordination. In contrast the C=N stretching frequencies in neutral complexes (**7**-**9**) remains

unaltered and was observed in the region around 1620-1623 cm^{-1}. The difference in C=N stretching frequencies in neutral and cationic complexes is an indication of coordination of pyridyl/pyrimidyl nitrogen.

^{1}H NMR studies of metal complexes

The ^{1}H NMR spectra of the metal complexes confirms the coordination of the ligands to the metal center. The pyridyl and thiocarbonyl attached N-H and carbonyl and thiocarbonyl attached N-H proton signals were observed as a singlet around 10.92-15.36 ppm. For complexes (**4**, **5** and **6**) the N-H proton resonance was observed around 8.75-8.81 ppm. The appearance of the N-H proton signals indicates that it is not involved in coordination and also suggests the neutral chelating mode of the ligands. The signals due to the aromatic protons of the ligands appeared in the downfield region around 6.44-9.13 ppm following coordination to the metal atom. In complexes (**4**-**9**), the methyl proton of the pyridine ring was observed as a singlet around 2.39-2.50 ppm respectively. The appearance of the *p*-cymene and Cp* ring proton signals in addition to the protons of the ligand confirms the binding of the ligand to the metal atom. The methyl proton signal of the *p*-cymene ligand was observed as a singlet around 2.00-2.33 ppm. The methyl protons of isopropyl group was observed as closely spaced doublet for complexes (**1** and **4**) whereas for complex (**7**) it was observed as doublet around 1.27-1.36 ppm and the methine protons of the isopropyl group was observed as a septet around 2.85-3.12 ppm. The aromatic protons of *p*-cymene moiety displayed two doublets for complexes (**1** and **7**) whereas three doublets for complex (**4**). The methyl protons of the pentamethylcyclopentadienyl (Cp*) ligand displayed a sharp singlet around 1.54-1.84 ppm. 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 ligand. The ^{13}C NMR spectra of the complexes displayed signals associated with the ligand carbons, *p*-cymene moiety carbons, methyl carbon of Cp* and ring carbon of Cp*. The ^{13}C NMR spectra of the complexes showed signal in the range 111.6-153.4 ppm for the aromatic carbons of the thiourea derivatives. The carbon resonance of the thiocarbonyl (C=S) group appeared in the lower frequency region around 175.2-180.0 ppm whereas the carbon peak for carbonyl (C=O) group appeared in the region around 161.4-166.2 ppm. In complexes (**4**-**9**), the methyl carbon resonances of the pyridine ring were observed around 21.0-23.8 ppm. The methyl, methine and isopropyl carbon resonances of the *p*-cymene ligand were observed in the region around 17.1-30.6 ppm whereas the aromatic carbon resonance were observed around 82.9-107.3 ppm. In addition to these carbon resonances the ring carbons of the Cp* ligand displayed signal around 88.5-97.5 ppm whereas the methyl carbon resonances was observed as a sharp peak around 8.07-8.89 ppm. Overall results from NMR spectral studies strongly support the formation of the metal complexes.

Mass spectral studies of metal complexes

The mass spectra of the complexes further confirmed the formation of the metal complexes. The mass spectra of all these complexes except complex (**8**) exhibited their predominant molecular ion peaks at m/z value which corresponds to $[M\text{-}2H\text{-}2Cl+H]^+$ ion peak. For instance the mass spectrum of complex (**6**) displayed its molecular ion peak at m/z: 508.0924 and the mass spectrum of complex (**9**) showed its molecular ion peak at m/z: 598.1507 (Figure S18 & S20). Both these peaks corresponds to $[M\text{-}2H\text{-}2Cl+H]^+$ ion. In complex (**8**) peaks were observed at m/z: 542.0646 which is due to $[M\text{-}2H\text{-}Cl]^+$ ion, and at m/z: 506.0881 which is due to

[M-2H-2Cl-1]$^{+}$ ion (Figure S19). The mass ion peaks observed in these complexes are in accordance with similar reported complexes.[37] The mass spectral values strongly justify the composition and formulation of these complexes.

Description of the crystal structures of complexes

In addition to the spectroscopic analysis the coordination of the thiourea derived ligands to the metal ion was confirmed by carrying out the single crystal X-ray analysis. The detail regarding data collection and structure refinement parameters are summarized in (Table S1 & S2) and geometrical parameters including bond lengths, bond angles and metal atom involving ring centroid values are listed in (Table S3). The molecular structures of some of these complexes were established by carrying out the single crystal analysis which revealed the different coordination mode of the ligands to the metal and the geometry of the complexes. Crystal structures of complexes (**4** and **7**) contain two molecules in its asymmetric unit. X-ray analysis of these complexes featured a regular three legged piano-stool geometry with metal coordinated by π-bonded arene ring /Cp* ring (arene = *p*-cymene and Cp*) in a η^6/η^5 manner, nitrogen and sulfur donor atoms from thiourea derived ligands and terminal chloride. The geometry around the metal center can be regarded as pseudo-octahedral wherein the arene ligand forms the seat; thiourea derivatives and terminal chloride form the legs. The molecular structures of complexes (**2** and **3**) were established with PF_6 counter ion. In cationic complexes (**1**-**6**) the preferable mode of coordination of the thiourea derived ligand to the metal is through the pyridyl and pyrimidyl nitrogen's and thione sulfur probably due to increased stability of the metal sulfur bond as suggested by HSAB principle.

Complexes (**2** and **3**) have the cationic species [Cp*M(L1)$\kappa^2_{(N,S)}$Cl] {M = Rh and Ir} and counter anion PF_6. In complexes (**2** and **3**) the metal center is coordinated through Cp* ring,

ligand (L1) in a bidentate fashion and terminal chloride thus possessing a three-legged piano-stool structure. Ligand L1 acted as a neutral bidentate chelating ligand coordinating metal through pyrimidine nitrogen N(1) and thione sulfur S(1) thus forming a six membered metallacycle (Figure 1).

Methyl substituted pyridyl thiourea derivatives coordinated metal in a different manner depending upon the position of the methyl group present at the pyridine ring. When methyl group is at the *para* position of the pyridine ring such as in benzoyl(4-picolyl)thiourea (L2) it acted as bidentate chelating ligand whereas when methyl group is at the *ortho* position of the pyridine ring as in benzoyl(6-picolyl)thiourea (L3) it behaved as neutral monodentate ligand. Previously we have shown that when methyl group is at the *meta* position of the pyridine ring such as in benzoyl(3-picolyl)thiourea it coordinated metal in a bidentate chelating manner.[17] Complexes (**4**, **5** and **6**) also have the cationic species [(arene)M(L2)$\kappa^2_{(N,S)}$Cl] [(arene) = *p*-cymene, M = Ru and Cp*, M = Rh and Ir] and counter anion chloride. In these complexes the metal atom is coordinated through arene/Cp* ring (arene = *p*-cymene and Cp*) in a η^6/η^5 manner, ligand L2 in a bidentate manner through pyridine nitrogen N(1) and thione sulfur atom S(1) forming a six membered chelate ring and terminal chloride thus featuring a three-legged piano-stool structure (Figure 2).

In contrast complexes (**7** and **8**) have the neutral species having general formula [(arene)M(L3)$\kappa^1_{(S)}Cl_2$] [(arene) = *p*-cymene, M = Ru (**7**) and Cp*, M = Rh (**8**)]. In complexes (**7** and **8**) the metal is coordinated through arene moiety, two chloride's, and ligand L3 wherein it acted as a neutral monodentate ligand coordinating metal through thione sulfur (S1) (Figure 3). The probable reason for ligand L3 to act as monodentate ligand is due to the presence of methyl group at the *ortho* position of the pyridyl ring which is very close to pyridine nitrogen.

The distance between the metal (M) to centroid of the arene/Cp* ring are {1.795 (**2**), 1.794 (**3**), 1.688 (**4**), 1.795 (**5**), 1.800 (**6**), 1.687 (**7**), 1.782 (**8**) and 1.801 (**9**) Å}. In cationic complexes (**2**-**6**) the metal to nitrogen bond distances were found to be in the range of 2.093-2.131 Å while the metal to sulfur bond lengths was in the range of 2.321-2.412 Å. These bond lengths are consistent with the k^2-N,S coordination of the thiourea derivatives which are found to be in close agreement with reported values.[32,33] The bite angle values in these cationic complexes were observed in the range of 84.7-91.3°. The metal to sulfur bond lengths in neutral complexes (**7**-**9**) is 2.410(2), 2.378(1) and 2.362(3) Å respectively. The M-S bond lengths in neutral complexes are slightly longer than that of cationic complexes (Table S3). The M-Cl bond lengths in these complexes shows no significant differences and was found to be in the range of 2.399-2.438 Å which are comparable with earlier reported complexes.[17,18,34,35] The bond angle values S-M-Cl and Cl-M-Cl in neutral complexes (**7**-**9**) lay in the range of 87.7-95.5° (Table S3). The C-S bond length in these complexes lies in the range of 1.671-1.689 Å agrees well with those in other related compounds for a C=S double bond coordinated to a metal atom.[36-38] The C=O bond length lies in the range of 1.199-1.222 Å which purely indicates a double bond and which is not involved in coordination. The oxygen atom of carbonyl group is not involved in bonding to the metal also the deprotonation of amido hydrogen which was expected to alter the bonding modes of these ligands was also not observed as confirmed by ^{1}H NMR and single crystal structures. Despite having a rich variety of bonding modes of these ligands it is interesting to note that these ligands preferably coordinated d^6 metal (Ru, Rh and Ir) half-sandwich complexes in a bidentate $\kappa^2_{(N,S)}$ and monodentate $\kappa^1_{(S)}$ manner.

Non-covalent interactions

The crystal packing of these complexes showed the presence of several intermolecular and intramolecular hydrogen bonding. For instance in complex (**5**) the chloride counterion and H_2O molecule interlinks the two asymmetric units through intermolecular hydrogen bonding. Also N-H···Cl and C-H···Cl intermolecular interactions are also observed (Figure 4). Complex (**6**) is stabilized by intermolecular N-H···Cl, C-H···Cl and O-H···Cl interactions between the chloride counterion and hydrogen atoms from amido, H_2O and aromatic ring. Also C-H···O and C-H···S interactions are observed and the chloride attached to iridium is involved in C-H···Cl and O-H···Cl intermolecular interactions (Figure 5). In complex (**7**) the two asymmetric units possessed intramolecular hydrogen bonding between the two chlorides attached to ruthenium and amido hydrogen. The pyridyl nitrogen is involved in N-H···N interaction (Figure 6). Also the two asymmetric units are stabilized through a dimeric unit formed *via* intermolecular C-H···Cl interaction between the two chlorides and aromatic hydrogen of *p*-cymene moiety (Figure 6). The non-covalent interactions present in these complexes provide an ideal platform for formation of complexes with interesting supramolecular features.

Cytotoxicity studies against cancer cell line

The cytotoxicity of the thiourea derivatives and its d^6 metal complexes was evaluated by determining the IC_{50} values (the concentration of the drug required to inhibit the growth of 50 % of the cancer cells) against human colorectal (HCT-116 and HT-29) and pancreatic cancer (Mia-PaCa-2) cells as well as against the non-cancerous human epithelial cell line (ARPE-19). Following a standard MTT protocol, cells were incubated with the compounds for 92 hours at 37 $^{\circ}$C over a range of different drug concentrations. The IC_{50} values of the compounds against HCT-116, HT-29, Mi-PaCa-2 and ARPE-19 cells are presented in (Table 1). Because of the

hygroscopic nature of complexes (**1** and **4**) the cytotoxicity analysis could not be carried out. The thiourea ligands (L1-L3) were found to be inactive against both the cell lines with IC_{50} value > 100 μM (the highest drug concentration tested) whereas upon coordination of the ligands all the complexes possessed cytotoxicity. The enhanced cytotoxicity in complexes clearly indicates that the chelation of the thiourea derivatives with metal ion is responsible for the observed cytotoxicity. In the case of HCT-116 cells, complexes (**2**, **7** and **8**) were found to possess moderate activity with IC_{50} value in the range of 11.42 ± 1.86 to 24.92 ± 1.91 μM, in contrast complexes (**5**, **6** and **9**) were found to be more active exhibiting IC_{50} value in the low micromolar range of 5.18 ± 0.12 to 6.98 ± 0.50 μM. Iridium complex (**3**) with ligand (L1) was found to be highly cytotoxic with IC_{50} value of 1.37 ± 0.09 μM. This complex was found to be more active with low IC_{50} value of 1.37 ± 0.09 μM as compared to cisplatin whose IC_{50} value is 2.78 ± 1.40 μM. In general the IC_{50} results shows the iridium compounds are more active as compared to ruthenium and rhodium. The higher cytotoxicity of the iridium compounds suggests that the presence of merely arene/Cp* ring or ligand is not only responsible for higher activity; the type of metal also plays a crucial role.

Similar responses were observed with the other cancer cell lines with the exception of complex (**3**) where a broad range of potencies was observed (Table 1). This is also reflected in the selectivity indices where values ranging from 1.27 to 13.33 were observed (Table 2, Figure 7). All the complexes showed less toxicity towards the normal cell line which is evident from its higher IC_{50} values. With regards to potency, statistically significant differences between the response of cancer cells line and ARPE-19 cells were observed for all the compounds. The cytotoxicity of these complexes was compared to that of other reported thiourea ruthenium complexes by Karvembu *et.al.*[34,37] Comparing these results, we found that our complexes

showed promising activity similar to related compounds. With regards to selectivity, all the complexes have selectivity for cancer cells. Complex (**3**) showed enhanced selectivity for HCT-116 cells (13.33) as compared to cisplatin whose selectivity is (1.23). This suggests that complex (**3**) has more selectivity for cancer cells *in vitro* as compared to cisplatin. In addition, complex (**3**) has differential activity against different cancer cell lines suggesting that this complex is exploiting a specific target within this cell line. Further studies on structure–activity relationship will be carried out in future, which is expected to provide us a more insight into the specific activity of the complexes against various cancer cell lines.

Table 1 IC_{50} values of thiourea ligands (L1-L3) and complexes along with cisplatin against HCT-116, HT-29, Mi-PaCa-2 cancer cell line and non-cancer cell line ARPE-19. Each value represents the mean ± standard deviation from three independent experiments.

Compounds	IC_{50} (µM)			
	HCT-116	Mia-PaCa-2	HT-29	ARPE-19
L1	>100	>100	>100	>100
L2	>100	>100	>100	>100
L3	>100	>100	>100	>100
Complex **1**	Data not available	Data not available	Data not available	Data not available
Complex **2**	24.92 ± 1.91	11.23 ± 0.49	23.27 ± 3.57	47.23 ± 0.63
Complex **3**	1.37 ± 0.09	14.33 ± 0.79	4.89 ± 0.56	18.26 ± 0.58
Complex **4**	Data not available	Data not available	Data not available	Data not available
Complex **5**	6.98 ± 0.50	4.01 ± 0.12	4.9 ± 0.09	11.72 ± 0.30
Complex **6**	5.18 ± 0.12	4.48 ± 0.18	6.99 ± 0.51	9.79 ± 0.05
Complex **7**	11.42 ± 1.86	9.02 ± 0.13	13.47 ± 1.66	15.72 ± 0.83
Complex **8**	11.96 ± 2.19	6.21 ± 0.57	10.37 ± 0.17	16.24 ± 1.16
Complex **9**	5.50 ± 1.86	6.22 ± 0.07	8.09 ± 1.06	18.25 ± 0.48
Cisplatin	2.78 ± 1.40	3.15 ± 0.09	2.58 ± 0.72	3.43 ± 0.48

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

Table 2 Selectivity indices of complexes and cisplatin in HCT-116, HT-29 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	Selectivity index (HCT-116)	Selectivity index (Mia-PaCa-2)	Selectivity index (HT-29)
Complex **2**	1.89	4.21	2.02
Complex **3**	13.33	1.27	3.73
Complex **5**	1.67	2.92	2.39
Complex **6**	1.89	2.18	1.40
Complex **7**	1.37	1.74	1.17
Complex **8**	1.36	2.62	1.56
Complex **9**	3.32	2.93	2.25
Cisplatin	1.23	1.09	1.32

Conclusion

In this work, we report a series of cationic and neutral half-sandwich *p*-cymene ruthenium, Cp*rhodium and Cp*iridium complexes containing pyridyl and pyrimidyl thiourea derived ligands. Complexes containing ligands L1 and L2 were isolated as cationic complexes whereas complexes with ligand L3 was isolated as neutral complexes. The position of the methyl group in pyridyl thiourea ligands played a crucial role in determining whether the ligand would act as chelating or monodentate. X-ray crystallographic studies revealed that ligands L1 and L2 acted as chelating bidentate ligand whereas L3 functioned as neutral monodentate ligand. In cationic complexes (**2** and **3**) ligand L1 coordinated metal through pyrimidyl nitrogen (N1) and sulfur atom S(1) whereas in complexes (**4**, **5** and **6**) ligand L2 coordinated metal through pyridyl nitrogen N(1) and thione sulfur S(1). The coordination of the thione sulfur and nitrogen atoms to metal center allowed the formation of a six-membered chelate ring. In neutral complexes (**7** and **8**) L3 acted as neutral monodentate ligand coordinating metal through thione sulfur (S1). The work presented here displays interesting coordination modes of the methyl substituted pyridyl

thiourea ligands depending upon the position of methyl substituent attached to the pyridine moiety. Pharmacologically, certain complexes are potent and selective activity against a panel of cancer cells was observed as compared to non-cancer cells. Whilst further studies are required to identify mechanisms of action, these compounds are promising leads for further development as potential anti-cancer agents.

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Supplementary material

CCDC 1837046 (**2**), 1837047 (**3**), 1837048 (**4**), 1837049 (**5**), 1837050 (**6**), 1837051 (**7**), 1837052 (**8**) and 1837053 (**9**) 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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