

1 Synthesis, structural and chemosensitivity studies of arene d^6 metal complexes
2 having N-phenyl-N'-(pyridyl/pyrimidyl)thiourea derivatives
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15 **Abstract**

16 The d⁶ metal complexes of thiourea derivatives were synthesized to investigate its
17 cytotoxicity. Treatment of various N-phenyl-N' pyridyl/pyrimidyl thiourea ligands with half-
18 sandwich d⁶ metal precursors yielded a series of cationic complexes. Reactions of ligand (L1-L3)
19 with [(*p*-cymene)RuCl₂]₂ and [Cp*MCl₂]₂ (M = Rh/Ir) led to the formation of a series of cationic
20 complexes bearing general formula [(arene)M(L1)κ²_(N,S)Cl]⁺, [(arene)M(L2)κ²_(N,S)Cl]⁺ and
21 [(arene)M(L3)κ²_(N,S)Cl]⁺ [arene = *p*-cymene, M = Ru (**1**, **4**, **7**); Cp*, M = Rh (**2**, **5**, **8**); Cp*, Ir (**3**,
22 **6**, **9**)]. These compounds were isolated as their chloride salts. X-ray crystallographic studies of
23 the complexes revealed the coordination of the ligands to the metal in a bidentate chelating N,S-
24 manner. Further the cytotoxicity studies of the thiourea derivatives and its complexes evaluated
25 against HCT-116 (human colorectal cancer), MIA-PaCa-2 (human pancreatic cancer) and
26 ARPE-19 (non-cancer retinal epithelium) cancer cell lines showed that the thiourea ligands
27 displayed no activity. Upon complexation however, the metal compounds possesses cytotoxicity
28 and whilst potency is less than cisplatin, several complexes exhibited greater selectivity for
29 HCT-116 or MIA-PaCa-2 cells compared to ARPE-19 cells than cisplatin *in vitro*. Rhodium
30 complexes of thiourea derivatives were found to be more potent as compared to ruthenium and
31 iridium complexes.

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

33 **Introduction**

34 Half-sandwich arene d⁶ metal complexes (arene = *p*-cymene and its derivatives) have
35 been given much importance owing to their clinical and industrial applications.^[1] These
36 organometallic compounds have been widely exploited for their medicinal applications and it has
37 been proved that these complexes bear the potential to act as metal based anti-cancer drugs.^[2,3] In
38 particular, two half-sandwich ruthenium complexes namely [Ru(η⁶-arene)Cl(en)]⁺ (en =
39 ethylenediamine) developed by *Chen et.al* and [Ru(*p*-cymene)Cl₂(PTA)], developed by
40 *Allardyce et.al* termed RAPTA-C (PTA = 1,3,5-triaza-7-phosphaadamantane) have been found
41 to exhibit excellent cytotoxic activity *in vitro* and anticancer activity *in vivo*.^[4,5] The cyclic arene
42 ligands in these complexes are relatively inert towards substitution, it protects the metal's
43 oxidation state and it also influences hydrophobicity and interaction with biomolecules.^[6,7] It has
44 been observed that the mode of action of these compounds depends strongly on the nature of the
45 chelating ligand.^[8] In this regard it is important to choose a particular chelating ligand system
46 with known bioactive properties.^[9] Nevertheless pentamethylcyclopentadienyl rhodium and
47 iridium complexes have also been explored and studied for their antitumor activities due to the
48 inert facial co-ligand Cp* which offers several advantages.^[10]

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

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

66 **Experimental**

67 *Materials and Methods*

68 The reagents were of commercial quality and used without further purification. Metal
69 salts RuCl₃.nH₂O, RhCl₃.nH₂O and IrCl₃.nH₂O were purchased from Arora Matthey Limited. α -
70 phellandrene, pentamethylcyclopentadiene, 2-aminopyridine, 2-aminopyrimidine and 2-amino-4-
71 methyl-pyridine were purchased from Sigma Aldrich. Phenyl isothiocyanate was obtained from
72 Spectrochem. The solvents were dried and distilled prior to use according to standard
73 procedures.^[21] Precursor metal complexes [(*p*-cymene)RuCl₂]₂ and [Cp*MCl₂]₂ (M = Rh/Ir)
74 were prepared according to the published procedures.^[22,23] The thiourea ligands 1-phenyl-3-
75 (pyridine-2-yl)thiourea (L1), 1-phenyl-3-(pyrimidin-2-yl)thiourea (L2) and 1-(4-methylpyridin-
76 2-yl)-3-phenylthiourea (L3) were prepared according to reported procedures.^[24] ¹H NMR spectra
77 were recorded on a Bruker Avance II 400 MHz spectrometer using CDCl₃ as solvent; chemical
78 shifts were referenced to TMS. Infrared spectra (KBr pellets; 400-4000 cm⁻¹) were recorded on a

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

82 *Structure determination by X-ray crystallography*

83 Suitable single crystals of complexes were obtained by slow diffusion of hexane into
84 dichloromethane solution. Single crystal data for the complexes were collected with an Oxford
85 Diffraction Xcalibur Eos Gemini diffractometer using graphite monochromated Mo-K α radiation
86 ($\lambda = 0.71073 \text{ \AA}$). The strategy for the data collection was evaluated using the CrysAlisPro CCD
87 software. Crystal data were collected by standard ‘‘phi–omega scan’’ techniques and were scaled
88 and reduced using CrysAlisPro RED software. The structures were solved by direct methods
89 using SHELXS-97 and refined by full-matrix least squares with SHELXL-97 refining on F^2 .^{[25,}
90 ^{26]} The positions of all the atoms were obtained by direct methods. Metal atoms in the complex
91 were located from the E-maps and all non-hydrogen atoms were refined anisotropically by full-
92 matrix least-squares. Hydrogen atoms were placed in geometrically idealised positions and
93 constrained to ride on their parent atoms with C-H distances in the range 0.95-1.00 Angstrom.
94 Isotropic thermal parameters U_{eq} were fixed such that they were $1.2U_{eq}$ of their parent atom U_{eq}
95 for CH's and $1.5U_{eq}$ of their parent atom U_{eq} in case of methyl groups. Crystallographic and
96 structure refinement parameters for the complexes are summarized in Table 1 and selected bond
97 lengths and bond angles are presented in Table 2. Figures 2-4 were drawn with ORTEP3
98 program whereas Figures 5 and 6 was drawn using MERCURY 3.6 program.^[27]

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

101 contains solvent molecule (CHCl₃) in the solved structure. The crystal structure of complex (6)
102 contains DCM and pentane molecules, which has been removed by SQUEEZE method.^[28]

103 *Cell lines testing, culture conditions and cytotoxicity against cell lines*

104 The cytotoxic activity of the thiourea derivatives and its corresponding ruthenium,
105 rhodium and iridium complexes were evaluated against HCT-116 colorectal carcinoma and
106 MIA-PaCa-2 pancreatic carcinoma cell lines and the non-cancer ARPE-19 (human epithelial cell
107 line derived from the retina) cell line. These cell lines were purchased from the American Type
108 Culture Collection (ATCC) and the reagents used were purchased from Sigma Aldrich Co. Ltd
109 (Dorset, UK) unless otherwise stated. Cytotoxicity of thiourea ligands and compounds were
110 evaluated using the standard MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium
111 bromide) cellular viability assay as follows. Cells were inoculated into 96 well plates at 1.5×10^3
112 cells per well and incubated for 24 hours at 37 °C in an atmosphere of 5% CO₂ prior to drug
113 exposure. The thiourea ligands and complexes (1-9) were all dissolved in DMSO at a
114 concentration of 100 mM and diluted further with medium to obtain drug solutions ranging from
115 0.5 to 100 μM. The final DMSO concentration was 0.1% (v/v), which is nontoxic to cells.
116 Cisplatin was dissolved in phosphate buffered saline at a stock concentration of 25 mM. Cells
117 were exposed to drug for 96 hours and cell survival was determined using the MTT assay.^[29,30]
118 Briefly, 20 μL of MTT (0.5 mg/ml) in phosphate buffered saline was added to each well and it
119 was further incubated at 37 °C for 4 hours in an atmosphere containing 5% CO₂. The solution
120 was then removed and the formazan crystals formed were dissolved in 150 μM DMSO. The
121 absorbance of the solution was recorded at 550 nm using an ELISA spectrophotometer.
122 Percentage cell survival was calculated by dividing the true absorbance of treated cell by the true
123 absorbance for controls (exposed to 0.1% DMSO). The IC₅₀ values were determined from plots

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

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

130 A mixture of metal precursor [(*p*-cymene)RuCl₂]₂ or [Cp*RhCl₂]₂ (M = Rh/Ir) (0.1
131 mmol) and thiourea derivatives (L1-L3) (0.2 mmol) were dissolved in dry acetone (10 mL) and
132 stirred at room temperature for 8 hours (Scheme 1). A yellow colored compound precipitated out
133 from the reaction mixture. The precipitate was filtered, washed with cold acetone (2 x 5 ml) and
134 diethyl ether (3 x 10 ml) and air dried.

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

136 Yield: 80 mg (74%); **Anal. Calc** for C₂₂H₂₅N₃Cl₂SRu (535.49); C, 49.34; H, 4.71; N, 7.85.
137 Found: C, 49.43; H, 4.84; N, 7.96 %; **FT-IR** (KBr, cm⁻¹): 3337(m), 2203(m), 1620(m), 1545(m),
138 1443(m), 1484(m), 1231(m), 1122(m); **¹H NMR** (400 MHz, CDCl₃): δ (ppm) = 13.23 (s, 1H,
139 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),
140 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
141 (d, $J = 4$ Hz, 1H, CH(*p*-cym)), 5.23 (t, $J = 8$ Hz, 2H, CH(*p*-cym)), 2.74 (sept, 1H, CH(*p*-cym)), 1.89 (s,
142 3H, CH(*p*-cym)), 1.18 (dd, 6H, $J = 4$ and 4 Hz, CH(*p*-cym)); **¹³C NMR** (100 MHz, CDCl₃): $\delta =$
143 176.94, 164.59, 153.65, 151.93, 139.26, 135.40, 128.12, 126.87, 124.26, 120.37, 116.24 (C-L1),
144 106.01, 99.18, 85.71, 84.42, 84.11, 83.27, 29.69, 21.42, 21.24, 17.18 (C-*p*-cym); **HRMS-APCI**
145 (m/z) [Found (Calcd)]: [464.0753 (464.0734)] [M-2H-2Cl+H]⁺.

146 **[Cp*Rh(L1) $\kappa^2_{(N,S)}$ Cl]Cl (2)**

147 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.
148 Found: C, 49.17; H, 4.95; N, 7.93 %; **FT-IR** (KBr, cm^{-1}): 3370(w), 3151(m), 1611(m), 1603(m),
149 1568(m), 1536(m), 1228(m), 1135(m), 1122(m); **1H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.41
150 (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,
151 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, $CH_{(Cp^*)}$);
152 **^{13}C NMR** (100 MHz, $CDCl_3$): $\delta = 176.66, 152.33, 151.74, 140.56, 136.38, 129.10, 127.93,$
153 $125.70, 122.18, 117.17, (C-L2), 97.07 (Cp^*_{ipso}), 8.78 (Cp^*_{Me})$; **HRMS-APCI** (m/z) [Found
154 (Calcd)]: [466.0820 (466.0824)] [M-2H-2Cl+H]⁺.

155 **$[Cp^*Ir(L1)\kappa^2_{(N,S)}Cl]Cl$ (3)**

156 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:
157 C, 42.25; H, 4.27; N, 6.79 %; **FT-IR** (KBr, cm^{-1}): 3338(w), 3186(m), 1617(m), 1591(w),
158 1544(m), 1484(m), 1233(m), 1159(m); **1H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.25 (s, 1H,
159 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
160 (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**
161 (100 MHz, $CDCl_3$): $\delta = 176.32, 153.61, 151.94, 140.21, 135.91, 129.07, 126.42, 124.12, 122.12,$
162 $117.17, (C-L1), 97.07 (Cp^*_{ipso}), 8.55 (Cp^*_{Me})$; **HRMS-APCI** (m/z) [Found (Calcd)]: [556.1381
163 (556.1398)] [M-2H-2Cl+H]⁺.

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

165 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.
166 Found: C, 47.10; H, 4.62; N, 10.56 %; **FT-IR** (KBr, cm^{-1}): 3370(w), 3298(m), 3176(m),
167 2965(m), 1618(m), 1583(m), 1561(m), 1474(m), 1202(m), 1161(m); **1H NMR** (400 MHz,
168 $CDCl_3$): 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
169 (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

170 = 4 Hz, 1H, CH_(p-cym)), 5.50 (d, *J* = 4 Hz, 1H, CH_(p-cym)), 5.38 (d, *J* = 4 Hz, 2H, CH_(p-cym)), 281
171 (sept, 1H, CH_(p-cym)), 2.00 (s, 3H, CH_(p-cym)), 1.25 (d, *J* = 4 Hz, 6H, CH_(p-cym)); ¹³C NMR (100
172 MHz, CDCl₃): δ = 177.08, 163.39, 160.45, 157.56, 136.28, 129.14, 128.05, 125.42, 118.18, (C-
173 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-**
174 **APCI** (m/z) [Found (Calcd)]: [465.0685 (465.0687)] [M-2H-2Cl+H]⁺.

175 **[Cp**Rh*(L2)κ²_(N,S)Cl]Cl (5)**

176 Yield: 78 mg (73%); **Anal. Calc** for C₂₁H₂₅Cl₂N₄SRh (539.32); C, 46.77; H, 4.67; N, 10.39.
177 Found: C, 46.87; H, 4.75; N, 10.48 %; **FT-IR** (KBr, cm⁻¹): 3358(w), 3262(m), 3174(m),
178 1618(m), 1575(m), 1475(m), 1441(m), 1206(m), 1159(m); ¹H NMR (400 MHz, CDCl₃): δ
179 (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
180 Hz, 2H), 7.50 (d, *J* = 8 Hz, 1H), 7.38-7.42 (m, 2H), 1.66 (s, 15H, CH_(Cp*)); ¹³C NMR (100 MHz,
181 CDCl₃): δ = 176.23, 161.15, 161.03, 156.27, 136.15, 129.17, 128.14, 125.64, 118.75, (C-L2),
182 89.91 (Cp*_{ipso}), 8.51 (Cp*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [467.0784 (467.0777)] [M-
183 2H-2Cl+H]⁺.

184 **[Cp**Ir*(L2)κ²_(N,S)Cl]Cl (6)**

185 Yield: 104 mg (83%); **Anal. Calc** for C₂₁H₂₅Cl₂N₄SIr (628.63); C, 40.12; H, 4.01; N, 8.91.
186 Found: C, 40.23; H, 4.11; N, 9.03 %; **FT-IR** (KBr, cm⁻¹): 3374(w), 3252(m), 3171(m), 1616(m),
187 1585(m), 1463(m), 1204(m), 1162(m), 843(s); ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 9.03 (dd,
188 *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* =
189 8 Hz, 1H), 7.35-7.38 (m, 2H), 1.65 (s, 15H, CH_(Cp*)); ¹³C NMR (100 MHz, CDCl₃): δ = 175.67,
190 161.55, 161.06, 156.71, 136.26, 129.12, 128.11, 125.75, 119.01, (C-L2), 97.40 (Cp*_{ipso}), 8.84
191 (Cp*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]: [557.1355 (557.1351)] [M-2H-2Cl+H]⁺.

192 **[(*p*-cymene)Ru(L3)κ²_(N,S)Cl]Cl (7)**

193 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.
194 Found: C, 50.38; H, 5.06; N, 7.73 %; **FT-IR** (KBr, cm^{-1}): 3356(m), 3160(m), 1618(m), 1594(m),
195 1547(m), 1487(m), 1224(m), 1125(m); **1H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.12 (s, 1H,
196 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),
197 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, $CH_{(p-}$
198 $cym)$), 5.43 (d, $J = 4$ Hz, 1H, $CH_{(p-cym)}$), 5.27 (t, $J = 8$ Hz, 1H, $CH_{(p-cym)}$), 2.80 (sept, 1H, $CH_{(p-cym)}$),
199 1.96 (s, 3H, $CH_{(p-cym)}$), 1.24 (dd, $J = 4$ and 4 Hz, 6H, $CH_{(p-cym)}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ
200 = 178.07, 153.75, 152.97, 152.34, 136.46, 129.07, 127.78, 125.23, 122.92, 117.42, 20.93 (C-L3),
201 106.97, 100.02, 86.57, 85.30, 85.02, 84.15, 30.68, 22.42, 22.24, 18.21 (C- $p-cym$); **HRMS-APCI**
202 (m/z) [Found (Calcd)]: [478.0902 (478.0891)] [M-2H-2Cl+H]⁺.

203 **[Cp*Rh(L3) $\kappa^2_{(N,S)}Cl$]Cl (8)**

204 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.
205 Found: C, 50.13; H, 5.27; N, 7.75 %; **FT-IR** (KBr, cm^{-1}): 3371(s), 3120(m), 1619(m), 1602(w),
206 1585(s), 1523(s), 1223(m), 1140(m); **1H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.20 (s, 1H, NH),
207 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
208 = 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
209 MHz, $CDCl_3$): δ = 176.78, 153.30, 151.55, 151.20, 136.47, 129.08, 127.86, 125.70, 123.77,
210 117.86, 21.03, (C-L3), 96.89 (Cp^*_{ipso}), 8.80 (Cp^*_{Me}); **HRMS-APCI** (m/z) [Found (Calcd)]:
211 [480.0980 (480.0981)] [M-2H-2Cl+H]⁺.

212 **[Cp*Ir(L3) $\kappa^2_{(N,S)}Cl$]Cl (9)**

213 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:
214 C, 43.16; H, 4.47; N, 6.64 %; **FT-IR** (KBr, cm^{-1}): 3340(w), 2922(m), 1618(m), 1593(w),
215 1541(m), 1489(m), 1232(m), 1189(m); **1H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 13.07 (s, 1H,

216 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),
217 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*)); ¹³C
218 NMR (100 MHz, CDCl₃): $\delta = 176.44, 153.54, 152.39, 150.85, 136.32, 129.12, 127.91, 125.64,$
219 $123.77, 117.53, 20.94, (C-L3), 89.32 (Cp^*_{ipso}), 8.51 (Cp^*_{Me});$ HRMS-APCI (m/z) [Found
220 (Calcd)]: [570.1572 (570.1555)] [M-2H-2Cl+H]⁺.

221 Results and discussion

222 *Synthesis of complexes*

223 The present work deals with the synthesis, characterization and chemosensitivity studies
224 of arene d⁶ metal complexes containing thiourea derivatives. The metal complexes (**1-9**) were
225 synthesized by the reaction of precursor complexes and thiourea derivatives (L1-L3) in acetone.
226 Scheme 1 depicts the synthesis of the metal complexes containing thiourea derivatives. These
227 complexes were isolated as ionic salts with chloride counter ion. The complexes were isolated as
228 dark to light yellow solids in moderate yields and are non-hygroscopic. They are soluble in
229 common organic solvents like acetonitrile, dichloromethane, chloroform, methanol and DMSO
230 but insoluble in petroleum ether, hexane and diethyl ether. Single crystal X-ray diffraction
231 analysis confirmed the coordination of the thiourea derivatives to the metal ion in bidentate
232 chelating N,S- manner. Further the anti-cancer activity of the thiourea derivatives and its metal
233 complexes were evaluated against two cancer cell lines and one non cancer cell line.

234 *Spectral studies of the complexes*

235 *IR studies of metal complexes*

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

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

246 *¹H NMR studies of metal complexes*

247 The ¹H NMR spectra of the complexes are provided in the supplementary information
248 (Figures S1-S9). The formation of the complexes was supported by the ¹H NMR studies. The
249 appearance of the ligand proton signals in addition to the *p*-cymene and Cp* ring protons clearly
250 indicates the formation of the compounds. In the ¹H NMR spectra of the complexes the N-H
251 proton signals were observed as a singlet around 9.83-13.12 ppm. For complexes (**5** and **6**) the
252 N-H proton resonance was observed at 8.93 and 8.87 ppm. The appearance of the N-H proton
253 signals in the complexes indicates that the N-H group is not involved in bonding. The aromatic
254 proton signals associated with the thiourea ligands were observed in the downfield region around
255 7.00-9.14 ppm indicating the coordination of the thiourea ligand to the metal ion. Besides these
256 resonance signals for the aromatic part of the ligand complexes (**1**, **4** and **7**) displayed an unusual
257 pattern of signal for the *p*-cymene moiety. The aromatic proton signal for the *p*-cymene ligand
258 consisted of three doublets for complex (**4**) around 5.38-5.56 ppm whereas for complexes (**1** and
259 **7**) it showed two doublets and one triplet around 5.23-5.51 ppm instead of two doublets in the
260 starting metal precursor. Also the methyl protons of isopropyl group displayed one doublet for
261 complex (**4**) and two doublet of doublet for complexes (**1** and **7**) around 1.18-1.25 ppm as shown

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

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

273 The ¹³C NMR spectra of the complexes further justify the coordination of the ligands and
274 formation of complexes. The ¹³C NMR spectra of the complexes are provided in the
275 supplementary information (Figures S10-S18). The ¹³C NMR spectra of the complexes displayed
276 signals associated with the ligand carbons, *p*-cymene ligand carbons, methyl carbon of Cp* and
277 ring carbon of Cp*. The carbon resonance of the thiocarbonyl (C=S) group appeared in the lower
278 frequency region around 175.6-178.0 ppm. This shifting of carbon resonances of the thiourea
279 derivatives clearly suggests its involvement in coordination to the metal ion. The aromatic
280 carbons signals for the ligands were observed in the range of 116.2-163.3 ppm. In complexes (**7-**
281 **9**), the methyl carbon resonances of the pyridine ring were observed around 20.9-21.0 ppm. The
282 ring carbon resonances of the *p*-cymene ligand were observed around 84.1-106.9 ppm. The
283 methyl, methine and isopropyl carbon resonances of the *p*-cymene ligand were observed in the
284 region around 17.1-30.7 ppm. The signals associated with the ring carbons of the Cp* ligand was

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

288 *Mass spectral studies of metal complexes*

289 The mass spectra of the thiourea complexes are presented in the supplementary
290 information (Figures S19-S27) and the values are listed in the experimental section (2.4). The
291 mass spectra of the complexes are consistent with the formulation and composition of the
292 complexes. All these complexes displayed their molecular ion peaks at m/z: 464.0753, m/z:
293 466.0820, m/z: 556.1381, m/z: 465.0685, m/z: 467.0784, m/z: 557.1355, m/z: 478.0902, m/z:
294 480.0980 and m/z: 570.1572 which corresponds to $[M-2H-2Cl+H]^+$ ion peak. The peak
295 corresponding to the loss of the arene ring (arene = *p*-cymene/Cp*) was not observed in its mass
296 spectrum which indicates the stronger metal to arene bond.

297 *Description of the crystal structures of complexes*

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

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

331 evidenced by ^1H NMR and molecular structures. There is significant delocalization of π -electron
332 density in the six-membered chelate ring as evidenced from the bond distances of the complexes
333 which was found to be in the range of 1.33-1.69 Å.^[31] The phenyl ring is effectively planar to
334 that of the chelate ring. Further the C-S bond distances in these complexes was found to be in the
335 range of 1.686-1.700 Å suggesting that it is intermediate between single C-S (1.82 Å) and double
336 C=S (1.56 Å) bond distances.^[32] The bond lengths in these complexes are normal and consistent
337 with the κ^2 -N,S- coordination of the thiourea derivatives which correlates well with reported
338 values for similar complexes.^[19,33-35] The metal to nitrogen bond distances is comparatively
339 shorter than the metal to sulfur bond distances (Table 2). The M-Cl bond lengths in these
340 complexes shows no significant differences and was found to be in the range of 2.39-2.40 Å
341 which is comparable to reported literature values.^[33,34] With respect to the bond angle values
342 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-
343 octahedral geometry around the metal center (Table 2). Overall all the geometrical parameters
344 are as anticipated.

345 *Non-covalent interactions*

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

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

362 **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 ₃ Cl ₃ SRu	C ₂₂ H ₂₆ Cl ₅ N ₄ SRh	C ₂₁ H ₂₅ N ₄ Cl ₂ SiR	C ₂₃ H ₂₇ Cl ₂ N ₃ SRu	C ₂₃ H ₂₈ Cl ₂ N ₃ SRh
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	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>C</i> 2/ <i>c</i>	<i>P</i> <i>T</i>	<i>P</i> 2 ₁ / <i>c</i>
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>2σ(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

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

364 **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)

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

366 *Chemosensitivity studies*

367 The response of HCT-116, MIA PaCa-2 and ARPE-19 cells to the thiourea ligands (L1-
 368 L3) and its metal complexes (**1-9**) are provided in Table 3. The thiourea ligands (L1-L3) were
 369 found to be inactive against both the cell line with IC₅₀ value > 100. Upon complexation of
 370 thiourea ligands all the complexes displayed cytotoxicity against both cancer cell lines.
 371 Complexes (**4-6**) with ligand L2 were found to exhibit moderate activity against both the cell
 372 lines with IC₅₀ value in the range of 33.1 ± 0.39 to 77.4 ± 2.71 μM. Complexes (**1-3**) with ligand
 373 L1 and (**7-9**) with ligand L3 possessed similar cytotoxicity against both HCT-116 and Mia-PaCa-
 374 2 cell line with IC₅₀ value in the range of 9.10 ± 0.09 to 18.2 ± 3.25 μM. These complexes were
 375 found to be more active as compared to complexes (**4-6**). However, all these thiourea compounds
 376 were found to be less cytotoxic as compared to cisplatin whose IC₅₀ value is 2.78 μM against
 377 HCT-116 and 3.15 μM against MIA-PaCa2 cell lines. Complex (**8**) was found to possess the
 378 highest cytotoxicity among all other complexes against HCT-116 cell line with IC₅₀ value of
 379 9.16 ± 0.84 μM whereas complex (**9**) was the most potent against Mia-PaCa-2 cell line with IC₅₀
 380 value of 9.10 ± 0.09 μM. The response of ARPE-19 non-cancer cell lines is presented in Table 3

381 and corresponding selectivity indices are presented in Figure 7. With regards to potency,
382 statistically significant differences between the response of cancer cells lines and ARPE-19 cells
383 were observed for all complexes with the exception of complex (4). In the case of complexes (1,
384 3, 7 and 9) statistically significant differences between the response of MIA-PaCa-2 (but not
385 HCT-116) and ARPE-19 cells was observed suggesting that some selectivity for MIA-PaCa-2
386 cells exists *in vitro* (Table 3). The selectivity index (SI) is shown in Table 4 which is defined as
387 the ratio of IC₅₀ values in ARPE19 cells divided by the IC₅₀ for either HCT-116 or MIA-PaCa-2
388 cells. With regards to selectivity, Figure 7 demonstrates that complexes (5, 6 and 8) have greater
389 selectivity for HCT-116 cells than cisplatin under identical experimental conditions. In some
390 cases (complexes 1, 3 and 9) enhanced selectivity towards the MIA-PaCa-2 as opposed to the
391 HCT-116 cell line is obtained. The IC₅₀ and selectivity index values of these compounds provide
392 an ideal platform for the design of thiourea complexes possessing high cytotoxicity.
393

394 **Table 3** IC₅₀ values of thiourea ligands (L1-L3) and complexes (**1-9**) along with cisplatin against
 395 HCT-116 and MIA-PaCa-2 cancer cell line. Each value represents the mean ± standard deviation
 396 from three independent experiments. Statistical analysis comparing the response of cancer cell
 397 lines (HCT-116 or MIA-PaCa-2) to non-cancer ARPE-19 cells was performed by a two tailed
 398 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

399 IC₅₀ = concentration of the drug required to inhibit the growth of 50% of the cancer cells (μM).

400 **Table 4** Selectivity index of complexes (**1-9**) and cisplatin in HCT-116 and MIA-PaCa-2 cancer
 401 cell lines. The selectivity index (SI) was calculated as the IC₅₀ for ARPE-19 cells divided by the
 402 IC₅₀ 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

403
 404

405 **Conclusion**

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

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424 **Supplementary material**

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

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

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