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**Article:**
Lord, RM, Holmes, J, Singer, FN orcid.org/0000-0002-4345-3187 et al. (2 more authors) (2020) Precious metal N-heterocyclic carbene-carbaboranyl complexes: Cytotoxic and selective compounds for the treatment of cancer. Journal of Organometallic Chemistry, 907. 121062. ISSN 0022-328X

https://doi.org/10.1016/j.jorganchem.2019.121062

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# Precious metal N-heterocyclic carbene-carbaboranyl complexes: cytotoxic and selective compounds for the treatment of cancer

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**Abstract:** A range of precious metal complexes incorporating either benzyl or carbaboranyl functionalised tethered N-heterocyclic carbenes have been prepared, including single X-ray crystallography for one new complex. The library has been screened for their anti-cancer potential against colorectal, ovarian, cisplatin-resistant ovarian and breast cancer cell lines and their selectivity determined by comparing the cytotoxicity towards normal cells. Overall, these complexes show significant selectivity for ovarian carcinoma, and are up to 3-fold more cytotoxic than cisplatin against cisplatin-resistant human ovarian carcinoma. Upon replacing the benzyl moiety of the NHC ligand with a carbaboranyl there is a general increase observed in the potency of the complexes, with the cytotoxicity of the ruthenium complex increasing by >16-fold against human ovarian carcinoma. Generally, the rhodium complex with the benzyl tethered NHC shows the greatest selectivity for cancer, with a selectivity index of 15, which is >2x, >9x and >6x higher than that of cisplatin, carboplatin and oxaliplatin, respectively.

**Keywords: bioinorganic chemistry; cancer; carbaboranyls; N-heterocyclic carbenes; precious metal complexes**

## Introduction

To date, platinum-based therapeutics still dominate as clinical drugs for the treatment of cancer. Although these complexes, especially cisplatin, have been crucial in the fight against cancer, there are major drawbacks associated with their use.[1,2] These include severe patient side effects due to the lack of cancer cell selectivity and only a small range of tumours are treatable due to increases in cancer cell resistance. Such drawbacks have lead researchers to design and test new transition metal complexes with potentially different modes of action, in order to combat the issues of normal cell toxicity and cancer resistance. To date, organometallic complexes of ruthenium (Ru), iridium (Ir) and rhodium (Rh) have shown to be promising candidates.[3]

Since their discovery, N-heterocyclic carbenes (NHCs) have emerged as a versatile class of ligands which can be easily modified.[4] Such modifications have included the addition of sterically demanding functional groups for the stabilisation of a range of metal-NHCs, which have been reported for their use as catalysts, antimicrobial agents and anticancer agents.[4–7] Silver-NHCs once dominated the field of metal-NHCs in the treatment of cancer,[8–11] however, in recent years the use of precious metal complexes incorporating NHCs have shown significance and this is a growing research field.[12–16] In particular, the work by Metzler-Nolte et al.[17–20] and Meggers et al.[21,22] on COD (cyclooctadiene) iridium(I)-NHC complexes has been fundamental in understanding how the complexes charge and functionality of the NHC ligand can affect *in vitro* activities. These complexes incorporate simple NHC ligands and can exhibit up to nanomolar activity, however, they slowly oxidise to Ir(III). More recently, arene Ru(II)-NHC[23] and arene Ir(III)-NHC[24] complexes have emerged as new classes of anticancer metal-NHC compounds, showing increased activity against tumours and were report to cause cell death through apoptosis related pathways. Although rhodium has been reported to have potential as an alternative metal for platinum,[25] to date the anticancer potential of arene rhodium(I)/(III)-NHC complexes is a new research field, with the major of work published on their activity as catalysts.[26]

Carbaboranyl moieties have been used to functionalize phosphonates and their abilities to inhibit acetylcholinestrerase[27] and treat E. Coli[28] have been assessed. Although it was proposed such compounds could treat bone tumours, the biological tests were not conducted.[29] In 1993, the first oligonucleotide was functionalized with carbaboranyls and these were further modified, yet again, no biological data was presented.[30,31] Dicarbaboranyl compounds have also been designed, and show an increase in cytotoxicity on addition of the second carbaboranyl, however, the compounds' activities are only in the millimolar range.[32] The use of metallacarboranes is a growing area of research,[33] and several reports have highlighted their nanomolar potency towards human ovarian carcinoma (A2780).[34,35] Compounds such as these are high in $^{10}B$ content, and have the potential to be used in

boron neutron capture therapy (BNCT).[36] Willans and co-workers have synthesised new NHC ligands with a tethered carbaboranyl arms, and reported the complexation reactions with Ru, Ir, Rh and Ag.[37–39] In 2019, the group reported the Ag-NHC tethered carbaboranyl complexes to have *in vitro* activities which are one order of magnitude more cytotoxic than the Ag-NHC benzyl derivatives, when tested against the isogenic human colorectal cancer HCT116 $p53^{+/+}$ (*p53*-wildtype) and HCT116 $p53^{-/-}$ (*p53*-null).[39]

In this study, we have prepared a range of precious metal complexes incorporating a tethered benzyl or carbaboranyl pendant arm on the NHC. We report the synthesis of a new benzyl tether NHC ligand (ligand **1**), and the synthesis of two new precious metal complexes by complexation of ligand **1** to either *p*-cymene Ru(II) (**1**) or Cp* Rh(III) (**6**). An additional complex was synthesised by complexation of a known carbaboranyl tethered NHC ligand and COD Ir(III) (**5**). All other ligands and complexes have been published by Willans and co-workers,[37–39] and herein we report their stability in dimethyl sulfoxide (DMSO) over a period of 72 h at room temperature. The *p*-cymene Ru(II) complexes (**1**-**2**), Cp* Ir (III)/Rh(III) complexes (**3**, **4**, **6** and **7**) and COD Ir(I)/Rh(I) complexes (**5** and **8**) were screened for their potency against human colorectal carcinoma *p53*-wildtype (HCT116 $p53^{+/+}$), human ovarian carcinomas: cisplatin-sensitive (A2780) and cisplatin-resistant (A2780cisR), and human breast adenocarcinoma (MCF-7). In order to assess the complexes' selectivity towards cancerous cells, the complexes were screened against human prostate cells (PNT2). The results highlight a general increase in potency when the benzyl moiety is replaced with a carbaboranyl group, with >16-fold increase observed for the ruthenium complexes.

## Material and methods

### 1.1 General

Anhydrous solvents were prepared by passing over activated alumina to remove water, copper catalyst to remove oxygen and molecular sieves to remove any remaining water, via the Dow-Grubbs solvent system, and then freeze-pump-thaw degassed prior to use. Decaborane was purchased from KatChem and all other chemicals used in this work were bought from either Sigma Aldrich or Alfa and used without further purification.

### 1.2 X-ray crystallography

X-ray diffraction data was collected on an Agilent SuperNova diffractometer fitted with an Atlas CCD detector with Mo- Kα radiation (λ = 0.71073 Å). The crystal was mounted under oil on nylon fibres and data collected at 120 K. An empirical absorption correction using spherical harmonics was used, the structures were solved by direct methods using SHELXT[40] and refined by full-matrix least squares on $F^2$ using SHELXL[41] interfaced through the program Olex2.[42] Molecular graphics for all structures were generated using Mercury.[43]

### 1.3 Synthesis

Complexes **2**, **3**, **4**, **7**[37] and **8**[38] were prepared by published literature methods.

**Ligand 1**. 2-Phenylethylbromide (500 mg, 2.70 mmol), 1-methylimidazole (219 mg, 2.67 mmol) and MeCN (5 mL) were added to a Schlenk flask and heated at reflux for 18 hours. The reaction was cooled to room temperature and the solvent removed *in vacuo*. The residue was recrystallized from DCM (5 mL)/$Et_2O$ (30 mL) to yield a pale yellow oil. This was cooled to 4°C to afford the product as an off-white solid (620 mg, 2.32 mmol, 86 %). **$^1$H NMR** (300 MHz, $CDCl_3$, δ): 10.08 (s, imidazolium NC**H**N), 7.47 (t, 1H, $^3J(^1H\text{-}^1H)$ = 3 Hz, NC**H**), 7.34 (t, 1H, $^3J(^1H\text{-}^1H)$ = 3 Hz, NC**H**), 7.22-7.11 (m, 5H, ArC**H**), 4.55 (t, 2H, $^3J(^1H\text{-}^1H)$ = 6 Hz, C**H$_2$**), 3.94 (s, 3H, C**H$_3$**), 3.18 (t, 2H, $^3J(^1H\text{-}^1H)$ = 6 Hz, C**H$_2$**). **$^{13}$C{$^1$H} NMR** (75 MHz, $CDCl_3$, δ): 137.1 (Q, N**C**N), 135.8 (Q, Ar**C**), 128.9 (N**C**H), 128.8 (N**C**H), 127.4 (Ar**C**H), 123.4 (Ar**C**H), 122.5 (Ar**C**H), 51.0 (N**C**H$_2$), 36.6 (**C**H$_2$), 36.5 (N**C**H$_3$). **HRMS (ESI$^+$):** *m/z* $[C_{12}H_{15}N_2]^+$ 187.1235, calcd for $[M - Br]^+$ 187.1249.

**Complex 1**: To a Schlenk flask was added the ligand **1** (50 mg, 0.19 mmol), $Ag_2O$ (22 mg, 0.095 mmol), [Ru(*p*-cymene)$Cl_2$]$_2$ (58 mg, 0.095 mmol), anhydrous DCM (5 mL) and anhydrous MeOH (0.1 mL) along with a small number of 4 Å molecular sieves. The reaction was heated at 40 °C for 3 hours. The reaction was cooled to room temperature, filtered over Celite and further washed with DCM (3 × 5 mL). The solvent was removed *in vacuo* and the residue subjected to column chromatography on silica, using a gradient elution with DCM/MeOH (2%) to afford an orange solid. Recrystallization from acetone (5 mL)/ pentane (30 mL) afforded the product as an orange powder (69 mg, 0.14 mmol, 74 %). **$^1$H NMR** (500 MHz, $CDCl_3$, δ): Major isomer; 7.38-7.22 (m, 5H, benzyl), 7.08 (d, 1H, $^3J(^1H\text{-}^1H)$ = 2 Hz, NC**H**), 7.02 (d, 1H, $^3J(^1H\text{-}^1H)$ = 2 Hz, NC**H**), 5.29 (m, 2H, *p*-cymene Ar**H**), 5.05 (d, 1H, $^3J(^1H\text{-}^1H)$ = 5 Hz, *p*-cymene Ar**H**), 4.92 (m, 1H, NC**H$_2$**), 4.84 (d, 1H, $^3J(^1H\text{-}^1H)$ = 5 Hz, *p*-cymene Ar**H**), 4.08 (m, 1H, NC**H$_2$**), 3.97 (s, 3H, C**H$_3$**), 3.34 (m, 1H, C**H$_2$**), 2.97 (m, 1H, C**H$_2$**), 2.88 (septet, 1H, $^3J(^1H\text{-}^1H)$ = 10 Hz, *p*-cymene C**H**$(CH_3)_2$), 1.95 (s, 3H, *p*-cymene C**H$_3$**), 1.20 (d, 6H, $^3J(^1H\text{-}^1H)$ = 5 Hz, *p*-cymene CH(C**H$_3$**)$_2$). **$^{13}$C{$^1$H} NMR** (125 MHz, $CDCl_3$, δ): 174.0 (Q, **C**$_{carbene}$), 138.6 (Q, Ar**C**), 129.3 (N**C**H), 128.8 (N**C**H), 126.8 29 (Ar**C**H), 124.1 (Ar**C**H), 121.8 (Ar**C**H), 109.0 (Q, *p*-cymene), 99.2 (Q, *p*-cymene), 85.1-84.8 (p-cymene Ar**C**H), 82.7/82.4 (p-cymene Ar**C**H), 53.1 (N**C**H$_2$), 39.7

(N**C**$H_3$), 37.9 (**C**$H_2$), 30.7 (**C**H$(CH_3)_2$), 22.7-22.5 (CH(**C**$H_3)_2$), 18.7 (*p*-cymene **C**$H_3$). **HRMS (ESI$^+$):** *m/z* $[C_{22}H_{28}N_2RuCl]^+$ 457.0995, calcd for $[M - Cl]^+$ 457.0982.

**Complex 5**: Ligand **5**[37] (29.6 mg, 0.0894 mmol), $Ag_2O$ (10.6 mg, 0.0457 mmol), $[Ir(COD)Cl]_2$ (30.1 mg, 0.0448 mmol), activated 4 Å molecular sieves and DCM (5 mL) were combined in an ampoule and heated to 45 °C for 19 hours under nitrogen. The reaction mixture was filtered through cotton wool and twice through celite, and the filtrate reduced *in vacuo*. The residue was recrystallized from acetone and cold pentane to yield the produce as a yellow solid (26.9 mg, 0.046 mmol, 51%). **$^1$H NMR** (400 MHz, $CDCl_3$, δ): 6.82-6.78 (m, 2H, NC**H**), 5.01 (td, 1H, $^3J(^1H\text{-}^1H)$ = 12.7 and $^4J(^1H\text{-}^1H)$ = 3.9 Hz, NC**H$_2$**), 4.69-4.54 (m, 2H, COD-C**H**), 4.02 (s, 1H, carbaboranyl-C**H**), 3.97 (ddd, 1H $^3J(^1H\text{-}^1H)$ = 13.1 and 11.7, and $^4J(^1H\text{-}^1H)$ = 6.2 Hz, NC**H$_2$**), 3.92 (s, 3H, NC**H$_3$**), 3.27-3.15 (m, 1H, C**H$_2$**), 3.02 – 2.93 (m, 1H, COD-C**H**), 2.82 – 2.76 (m, 1H, COD-C**H**), 2.59 (ddd, 1H, $^3J(^1H\text{-}^1H)$ = 14.7 and 12.5, and $^4J(^1H\text{-}^1H)$ = 6.2 Hz, C**H$_2$**), 2.35 – 2.19 (m, 5H, COD-C**H$_2$**), 1.89 – 1.81 (m, 1H, COD-C**H$_2$**), 1.76 – 1.60 (m, 4H, COD-C**H$_2$**). **$^{11}$B NMR** (96 MHz, $CDCl_3$, δ): -2.39 (1B), -5.13 (1B), -9.00 (2B), -11.27 (2B), -12.79 4B). **$^{13}$C{$^1$H} NMR** (101 MHz, $CDCl_3$, δ): 181.5 (Q, **C**$_{carbene}$), 122.2 (N**C**H), 120.4 (N**C**H), 86.3 (COD-**C**H), 85.6 (COD-**C**H), 72.2 (Q, carbaboranyl), 63.4 (carbaboranyl-**C**H), 52.7 (COD-**C**H), 52.2 (COD-**C**H), 49.2 (N**C**$H_2$), 38.2 (**C**$H_2$), 37.6 (N**C**$H_3$), 34.0 (COD-**C**$H_2$), 33.4 (COD-**C**$H_2$), 30.0 (COD-**C**$H_2$), 29.2 (COD-**C**$H_2$). **HRMS (ESI$^+$):** *m/z* $[C_{16}H_{32}B_{10}IrN_2]^+$ 553.3309, calcd for $[M\text{-}Cl]^+$ 553.3198.

**Complex 6**: To a Schlenk flask was added the ligand **1** (50 mg, 0.19 mmol), $Ag_2O$ (22 mg, 0.095 mmol), $[Rh(Cp^*)Cl_2]_2$ (59 mg, 0.095 mmol) and anhydrous DCM (5 mL), along with some 4 Å molecular sieves. The reaction was heated at 40 °C for 16 hours, filtered through Celite and washed with DCM (3 × 5 mL). The solvent was removed from the filtrate *in vacuo* and the residue was recrystallised from acetone (5 mL)/ pentane (30 mL), filtered and dried *in vacuo* to yield the product as an orange solid (86 mg, 0.17 mmol, 92 %). **$^1$H NMR** (300 MHz, $CDCl_3$, δ): 7.50-7.15 (m, 5H, benzyl), 7.02-6.97 (m, 2H, NC**H**), 5.20 (m, 1H, NC**H$_2$**), 4.06-4.04 (s, 3H, NC**H$_3$**) 3.92 (m, 1H, NC**H$_2$**), 3.51 (m, 1H, C**H$_2$**) 2.96 (m, 1H, C**H$_2$**), 1.62-1.58 (br. s, 15H, Cp* C**H$_3$**). **$^{13}$C{$^1$H} NMR** (75 MHz, $CDCl_3$, δ): 138.7 (Q, Ar**C**), 129.4 (Ar**C**H), 128.7 (Ar**C**H), 126.7 (Ar**C**H), 124.5 (N**C**H), 122.5 (N**C**H), 96.3 (Q, d, $^1J$(Rh-C) = 15 Hz, Cp*), 52.5 (N**C**$H_2$), 39.3 (N**C**$H_3$), 38.2 (N**C**$H_2$), 9.8-9.6 (Cp* **C**$H_3$). **HRMS (ESI$^+$):** *m/z* $[C_{22}H_{29}N_2RhCl]^+$ 459.1074, calcd for $[M - Cl]^+$ 459.1069.

#### 1.4 DMSO stability studies

10 mg of all complexes were dissolved in 0.6 mL of $d_6$-DMSO and $^1$H NMR and $^{11}$B NMR spectra recorded after 0, 1, 2, 4, 6, 24 and 72 hours. All measurements were recorded either a Bruker AV4 NEO 500 or Bruker AV4 NEO 500-CP NMR spectrometer at 25 °C.

#### 1.5 Chemosensitivity

Chemosensitivity studies were performed against human colorectal adenocarcinoma *p53*-wildtype (HCT116 *p53$^{+/+}$*), cisplatin-sensitive human ovarian carcinoma (A2780), cisplatin-resistant human ovarian carcinoma (A2780cisR) and human breast adenocarcinoma (MCF-7). Additionally, growth inhibitory effects were also tested against normal prostate cell line, PNT2. All cell lines were provided by the Institute of Cancer Therapeutics, University of Bradford and were routinely maintained as monolayer cultures in RPMI 1640 media supplemented with 10% foetal calf serum, sodium pyruvate (1 mM) and L-glutamine (2 mM). All assays were conducted in 96-well round bottom plates, with control lanes for media and 100% cell growth. Cell concentrations of 1 x $10^4$ cells/mL were used, and 100 μL (or 100 μL media in control lane 1) of cell suspension were incubated for 24 h at 37 °C and 5% $CO_2$ prior to drug exposure. Cisplatin (**CDDP**), carboplatin (**CARB**), oxaliplatin (**OXA**) and complexes **1**-**8** were all dissolved in dimethylsulfoxide (DMSO) to provide fresh stock solutions for each run (100 mM). These were further diluted with complete media to provide a range of concentrations (final concentration DMSO <0.1% v/v). After 24 h incubation, 100 μL of the drug/media solutions were added to the plates in columns 3-12 (100 μL media in lanes 1 and 2 for controls), and then the plates incubated for 96 h at 37°C and 5% $CO_2$. After 96 h, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (20 μL, 5 mg/mL) was added to each well and incubated for 3 h at 37 °C and 5% $CO_2$. All solutions were removed via pipette and 150 μL DMSO added to each well in order to dissolve the purple formazan crystals. A Thermo Scientific Multiskan EX microplate photometer was used to measure the absorbance of each well at 540 nm. Percentage cell viabilities were determined on a logarithmic scale, and the half-maximal inhibitory concentration ($IC_{50}$) was determined from a plot of % cell survival versus concentration (μM). Each of the experiments were performed as duplicate technical repeats and triplicate experimental repeats, with mean values stated as $IC_{50}$ ± Standard Deviation (SD).

#### 1.6 Statistical analysis

GraphPad was used to perform a Student T-test and determine the significance of the results, whereby probability values less than 0.05 ($p < 0.05$) are significantly statistically different.

## Results and Discussion

#### Synthesis and Characterisation

A range of precious metal complexes have been synthesised, where complexes **2**-**4** and **7**-**8** have been previously reported by Willans and co-workers (**Figure 1**).[37–39] Using similar reactions, we report herein the synthesis of a new benzyl tethered ligand (ligand **1**), a *p*-cymene Ru(II) complex (**1**) and a Cp* Rh(III) complex (**6**) incorporating ligand **1**, and a COD Ir(III) complex (**5**) with a previously published carbaboranyl tethered NHC ligand (**Scheme 1**).[37] All compounds were characterised by NMR spectroscopy, high-resolution mass spectrometry and where possible single X-ray crystallography. Single crystals of complex **6** were obtained from vapour diffusion of acetone/ pentane, to yield red crystals (**Figure 2**). The complex crystallises in a monoclinic crystal system and solution refinement was performed in the space group *C*2/c. The average Rh1-Cl1 bond lengths are 2.46-2.48 Å and are significantly longer than the previously reported carbaboranyl complex **8**,[38] where the Rh-Cl bond length is reported as 2.156(3) Å. However, the metal carbene (Rh-C1) bond length of 2.048(6) Å is similar to complex **8**, which was reported as 2.036(3) Å. The angles of 86.73(5)-94.91(18)° suggests a *pseudo* octahedral geometry, which is common for these "piano-stool" complexes.

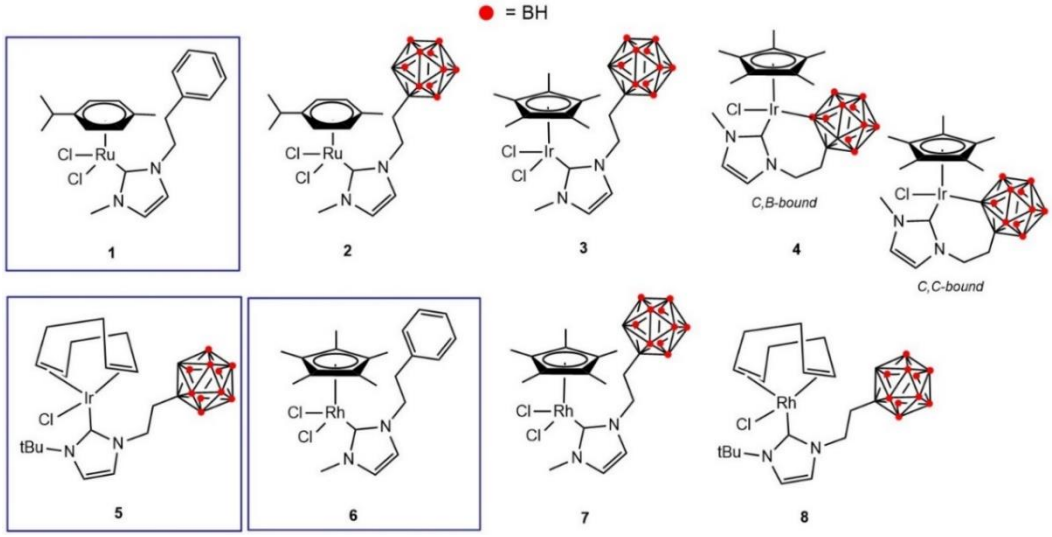
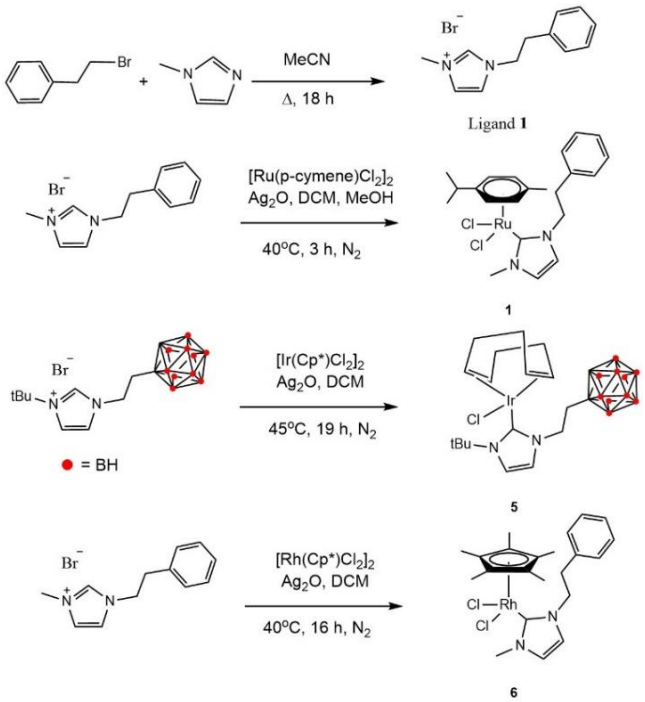
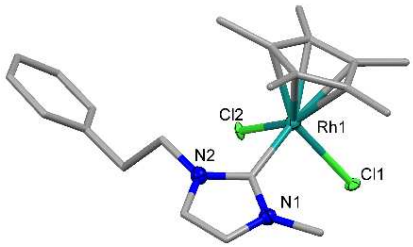



**Figure 1** Structures of ruthenium complexes **1**-**2**, iridium complexes **3**-**5** and rhodium complexes **6**-**8**, incorporating a benzyl or carboranyl tethered N-heterocyclic ligand. The new complexes reported in this work are highlighted in dark blue.




**Scheme 1** Synthesis of the benzyl tether NCH ligand (ligand **1**), *p*-cymene Ru(II) complex **2**, COD Ir(I) complex **5** and Cp* Rh(III) complex **6**.




6

**Figure 2** Molecular structures of complex **6**. Hydrogen atoms have been omitted for clarity and displacement ellipsoids are at the 50% probability level.

### Stability in DMSO

As the chemosensitivity studies were conducted in dimethylsulfoxide (DMSO), the stability of the complexes has been measured in $d_6$-DMSO over 72 h at room temperature. All complexes remain stable in DMSO over this time period with no changes observed for the complexes' resonances. However, for all of the carbaboranyl tethered complexes (**2**, **4**, **7** and **8**), a resonance is observed at ~6.5 ppm which increases over time (**Figure 3A**).

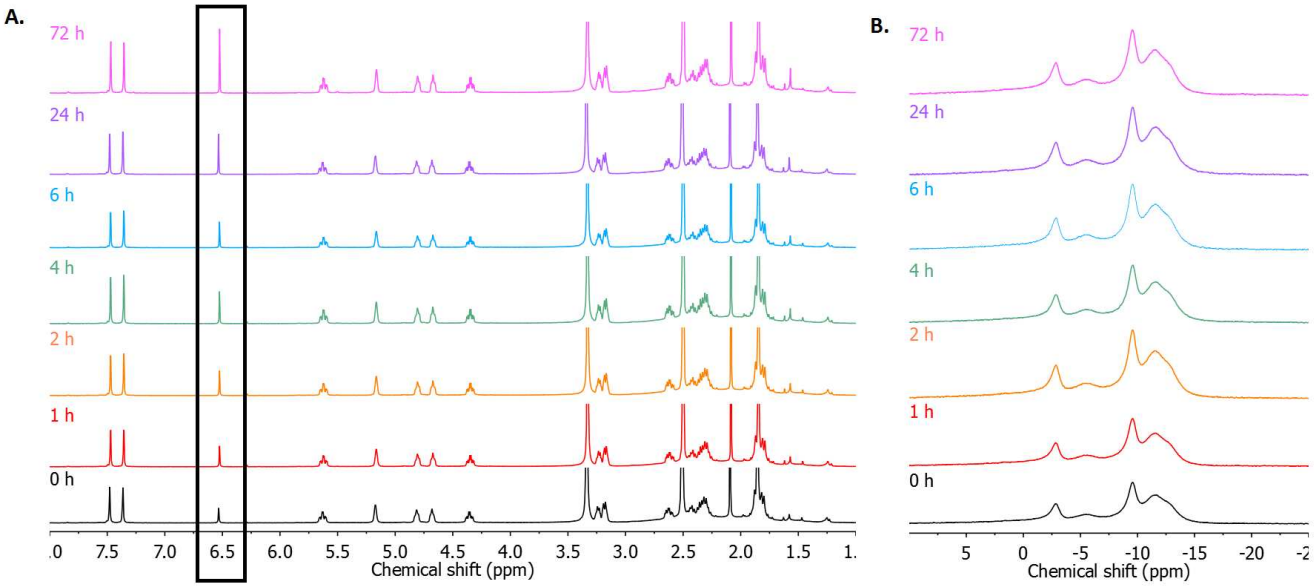



**Figure 3** Stability studies of complex **8** measured by NMR spectroscopy over 72 h; **A)** $^{1}$H NMR spectroscopy and **B)** $^{11}$B NMR spectroscopy

This resonance is broad in complexes **2** and **4** and relatively sharp in complexes **7** and **8**, yet we have not been able to assign this resonance. The $^{11}$B NMR spectra was also recorded over 72 h and shows no changes or additional resonances within the range of -100 to +100 ppm for all of the carbaboranyl tethered complexes (**Figure 3B**).

**Chemosensitivity studies after 96 hours**

Cell viability studies were conducted using the MTT assay, to assess the cytotoxicity of the Ru (**1**-**2**), Ir (**3**-**5**) and Rh complexes (**6**-**8**) (**Figure 1**). The clinically approved platinum complexes cisplatin (**CDDP**), carboplatin (**CARB**) and oxaliplatin (**OXA**) were screened for comparison. All compounds were screened against HCT116 *p53*$^{+/+}$, A2780, A2780cisR and MCF-7 after a 96 hour incubation period. The values are averages from two technical repeats and three experimental repeats, and stated in **Table 1** (**Figure S8**).

On comparison of the ruthenium complexes (**1** and **2**), there are significant increases in the cytotoxicity when replacing the benzyl group (**1**) for the carbaboranyl group (**2**). The benzyl *p*-cymene Ru(II) complex **1** has low to no toxicity against the range of cell lines ($IC_{50}$ values 71 ± 3 to >100 µM), whilst the addition of carbaboranyl (**2**) increases the cytotoxicity by up to >18-fold against A2780cisR ($p < 0.05$). However, it can be noted that though complex **2** has increased cytotoxicity against most cell lines (9.1-18.3x, $p < 0.05$), it remains non-toxic towards MCF-7 ($IC_{50}$ >100 µM), which may be a helpful feature towards future investigations on structure-activity relationships and cancer cell selectivity. Comparing the same functionalised NHCs on Cp* Rh(III) complexes shows a similar effect, whereby the carbaboranyl Cp* Rh(III) complex **7** has >8.8-fold increase in cytotoxicity when compared to the benzyl Cp* Rh(III) complex **6**. However, the effects are only moderate in comparison to the Ru analogues **2** and **1**, with values increasing by 1.1-8.9x ($p < 0.05$). It has been previously noted that Cp* Rh(III)-NHC complexes outperform the analogues *p*-cymene Ru(II)-NHC complexes ($IC_{50}$ > 100 µM), with up to an 11-fold increase in cytotoxicity.[44] However, the reverse trends have been observed with coordinating ligands other than the NHCs.[45] We are currently unable to comment on the effects for the analogues Cp* Ir(III)-NHC complexes, and reports suggests the ligand will play a large role in the observed cytotoxicity values.[46,47]

Complexes **3** and **4** are Cp* Ir(III) complexes incorporating a carbaboranyl tethered NHC and are moderately to highly cytotoxic against all cell lines. Complex **4** has a cyclometallated carbaboranyl moiety and is a mixture of $C_{carbaboranyl}$-$B_{carbaboranyl}$ and $C_{carbaboranyl}$-$C_{carbaboranyl}$, (**Figure 1**), which could not be synthetically separated. On analysis of the results, the cycometallation of the carbaboranyl increases the cytotoxicity of the complex by >3.9x against A2780, and between 1.3-3.0x for other cell lines. The non cyclometallated complex **3** was further modified by synthesising the COD Ir(I)-NHC complex **5**, which again increased the cytotoxicity values. The most promising result was observed against A2780cisR, where complex **5** exhibited >4.6-fold increase in cytotoxicity when compared to the Cp* Ir(III) complex **3**.

**Table 1** $IC_{50}$ values for cisplatin (**CDDP**), carboplatin (**CARB**), oxaliplatin (**OXA**) and complexes **1**-**8** against cancer cell lines HCT116 *p53*$^{+/+}$, A2780, A2780cisR, MCF-7 and normal cell line PNT2. All values are stated as mean values from duplicate technical repeats and triplicate experimental repeats, with selectivity indices (SI) for cancerous cells in parentheses.

| | $IC_{50}$ values (μM) ± SD | | | | |
|---|---|---|---|---|---|
| | **HCT116 *p53*$^{+/+}$** | **A2780** | **A2780cisR** | **MCF-7** | **PNT2** |
| **CDDP** | 1.5 ± 0.1 (5.7) | 1.3 ± 0.1 (6.4) | 14 ± 1 (0.6) | 1.5 ± 0.2 (5.6) | 8.5 ± 0.4 |
| **CARB** | 6.0 ± 0.2 (4.4) | 17 ± 1 (1.6) | >100 (0.3*) | >100 (0.3*) | 27 ± 2 |
| **OXA** | 0.445 ± 0.002 (2.9) | 0.505 ± 0.002 (2.6) | 2.09 ± 0.03 (0.6 | 2.6 ± 0.2 (0.5) | 1.3 ± 0.2 |
| **1** | >100 (n.d.) | 71 ± 3 (1.4*) | 74 ± 1 (1.4) | >100 (n.d.) | >100 |
| **2** | 11.0 ± 0.7 (0.7) | 4.4 ± 0.3 (1.9) | 4.0 ± 0.2 (2.0) | >100 (0.08*) | 8.2 ± 0.4 |
| **3** | 24 ± 2 (1.4) | 6.4 ± 0.2 (5.2) | 14.9 ± 0.8 (2.2) | 66 ± 1 (0.5) | 33.23 ± 0.06 |
| **4** | 7.9 ± 0.4 (1.5) | 1.6 ± 0.2 (7.1) | 6.9 ± 0.2 (1.7) | 49 ± 1 (0.2) | 12 ± 1 |
| **5** | 8.2 ± 0.2 (1.3) | 2.15 ± 0.09 (5.1) | 3.2 ± 0.3 (3.5) | 31 ± 1 (0.4) | 11 ± 1 |
| **6** | >100 (0.9*) | 5.6 ± 0.5 (15.4) | 19.1 ± 0.3 (4.5) | 65 ± 2 (1.3) | 87 ± 2 |
| **7** | 11.3 ± 0.3 (1.5) | 5.2 ± 0.4 (3.3) | 9.5 ± 0.3 (1.8) | 47 ± 3 (0.4) | 17.2 ± 0.7 |
| **8** | 9.0 ± 0.3 (1.4) | 3.3 ± 0.3 (3.7) | 10.2 ± 0.4 (1.2) | 14.1 ± 0.3 (0.9) | 12.8 ± 0.8 |

* denotes minimum SI values, as at least one $IC_{50}$ value is greater than the tested threshold of 100 μM

n.d. denotes SI values which could not be determined, as both $IC_{50}$ values are greater than the tested threshold of 100 μM

Complexes **7** and **8** are the rhodium analogues of the iridium complexes **3** and **5**, where **7** is the Cp* Rh(III)-carbaboranyl-NHC complex and **8** is the COD Rh(I)-carbaboranyl-NHC complex. As with the iridium analogues, there is a general increase in the cytotoxicity when changing from Cp* Rh(III) to COD Rh(I), with values increasing between 1.1-3.2-fold. However, the same trend is not observed against A2780cisR, and complexes **7** and **8** exhibit the similar cytotoxicity values ($p > 0.05$).

### Sensitivity Factor

The $IC_{50}$ values for **CDDP**, **CARB**, **OXA** and complexes **1**-**8** were compared for the human ovarian carcinoma cell lines A2780 and A2780cisR. In order to address the possibility of these complexes to circumvent the issues of cisplatin-resistance in cells, the $IC_{50}$ values are presented as sensitivity ratios (SRs). These values were calculated by dividing the $IC_{50}$ value in A2780 by the $IC_{50}$ value in A2780cisR, where SR values >1 indicate a sensitivity for the cisplatin-resistant cell line A2780cisR (**Figure 4**). Ruthenium complexes **1** and **2** have SR values of ~1, and have the potential to treat tumours which are resistant to cisplatin. As expected, the platinum complexes are not sensitive to this resistant cell line (SR < 0.3) and **CDDP** has a 10-fold decrease in cytotoxicity.

### Selectivity Index

One of the drawbacks with platinum-based drugs is the lack of selectivity towards cancerous cells, where most platinum complexes have high cytotoxicity towards normal cell types as well as cancerous cells. This not only causes side effects in patients, but this dose-limiting toxicity can have significant impact on the drug's effectiveness. The clinical drugs **CDDP**, **CARB** and **OXA** and complexes **1**-**8** have been screened against normal prostate cells (PNT2), in order to provide an indication of their selectivity (**Table 1**). The complexes all show moderate to high selectivity against this normal cell line, though to a lesser degree than towards the cancerous cell lines. It should be noted that the benzyl Cp* Rh(III) complex **6**, has the lowest cytotoxicity of the library, with an $IC_{50}$ value of 87 ± 2. Importantly, this complex is >10x, >3x and >67x less cytotoxic than **CDDP**, **CARB** and **OXA**, respectively ($p < 0.05$).

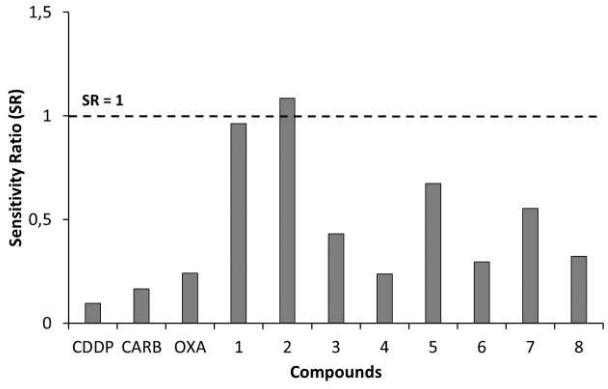



**Figure 4** Sensitivity Ratio (SR) for **CDDP**, **CARB**, **OXA** and complexes **1**-**8** when comparing the potency against A2780 and A2780cisR. SR > 1 shows sensitivity for A2780cisR, SR = 1 shows equitoxicity and SR < 1 shows sensitivity for A2780

The results are presented as a selectivity index (SI) and are shown in **Figure 5** and in the parenthesis of **Table 1**. These values are calculated by dividing the $IC_{50}$ value in the normal cell type by the $IC_{50}$ value in the cancerous cell type. Some of the values are stated as minimum values (*, see **Table 1** footnote), as at least one $IC_{50}$ was >100 μM. Some values could not be determine (n.d., see **Table 1** footnote) as both $IC_{50}$ values were >100 μM. The SI values which are >1 indicate a selectivity towards the cancerous cell line.

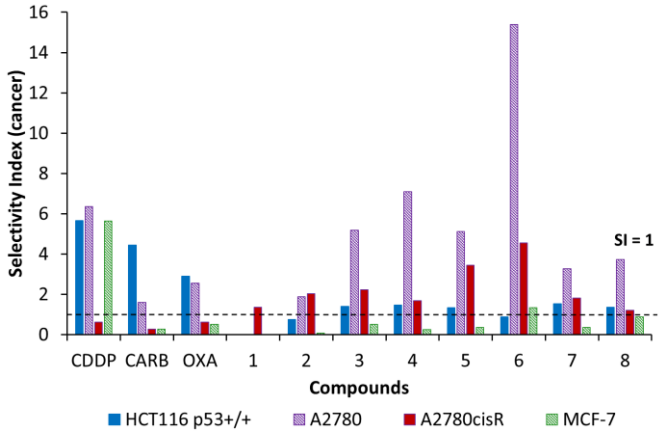



**Figure 5** Selectivity Index (SI) for **CDDP**, **CARB**, **OXA**, complexes **1**-**8** when comparing the normal cell line PNT2. SI > 1 shows selectivity for the cancer cell lines, SI = 1 show equitoxicity for cancerous and normal cell lines, and SI < 1 shows selectivity for the normal cell line PNT2

The platinum complexes have varying selectivity, with **CDDP** having the most promising SI values, ranging from 0.6 (A2780cisR) to 6.4 (A2780). Complexes **1**-**8** have no selectivity for the cell lines HCT116 *p53*$^{+/+}$ or MCF-7, with SI values approximately 1. The complexes are moderately selective for the cisplatin-resistant ovarian carcinoma cell line, A2780cisR, with SI values ranging from 1.2-4.5 ($p$ < 0.05). Importantly, these selectivity values are up to 7.5x, 17x and 7.4x greater than **CDDP**, **CARB** and **OXA**, respectively. The highest degree of selectivity is observed against the cisplatin-sensitive ovarian carcinoma cell line, A2780, where the SI values range between 1.9-15.4. Generally, the complexes reported herein are up to 2.4x, 9.6x and 6.0x more selective than **CDDP**, **CARB** and **OXA**, respectively.

The SI values were calculated for complexes **1**-**8** in comparison with **CDDP**, **CARB** and **OXA**. The results for **CDDP** and **CARB** are shown in **Figure 6A** and **Figure 6B**, respectively, however, the complexes were completely non-selective over **OXA** (all SI <0.6, **Figure S9**) and so this data is not presented. When comparing the $IC_{50}$ values with **CDDP**, there is no selectivity (SI <1) for any of complexes **1**-**8** against HCT116 *p53*$^{+/+}$, A2780, MCF-7 or PNT2, showing **CDDP** still outperforms these complexes. However, there is a general trend whereby the A2780cisR cell line is more sensitive to the metal-carbaboranyl complexes **2**-**5** and **7**-**8**, and are up to 4.4x more selective than this leading clinical drug (**Figure 6A**). The results were compared to **CARB**, and generally HCT116 *p53*$^{+/+}$ and PNT2 are less sensitive to complexes **1**-**8**. However, significant increases in sensitivity were observed against A2780, A2780cisR and MCF-7. In particular, complexes have SI values up to 7.9, 31.2 and 7.1 against these respective cell lines. The most significant result was observed for complex **5**, the carbaboranyl COD Ir(I) complex, which is highly selective against the A2780cisR cell line, with an SI value >31.2 (**Figure 6B**).

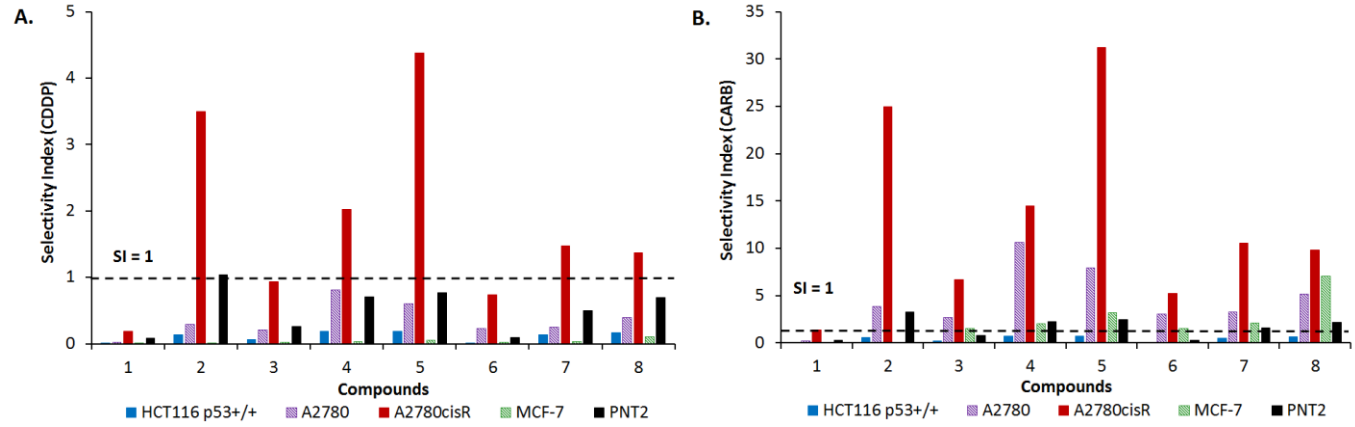



**Figure 6** Selectivity Index (SI) for complexes **1**-**8** when the $IC_{50}$ values of each are compared to **A.** cisplatin (**CDDP**) and **B.** carboplatin (**CARB**). SI > 1 shows selectivity for complexes **1**-**8**, SI = 1 shows equitoxicity, and SI < 1 shows selectivity for the platinum compounds **CDDP** or **CARB**.

## Conclusions

We have presented the synthesis of a new benzyl tethered NHC ligand (ligand **1**) and three new precious metal complexes incorporating either a benzyl tethered NHC ligand (**1**, Ru; **6**, Rh) or a carbaboranyl tethered NHC ligand (**5**, Ir). Additionally, we report the single crystal X-ray structure for the benzyl tether NHC rhodium complex **6**, and show the bond lengths and angles are similar to those previously reported by Willans and co-workers. A library of eight precious metal complexes (**1**-**2**, Ru; **3**-**5**, Ir; **6**-**8**, Rh) has been synthesised and NMR spectroscopy

studies show they all remain stable in DMSO at room temperature over 72 h. *In vitro* chemosensitivity assays were conducted against HCT116 $p53^{+/+}$, A2780, A2780cisR, MCF-7 and PNT2, and show a general trend whereby changing the tethered NHC ligand from benzyl to carbaboranyl increases the complexes potency. The most significant results was observed for the ruthenium p-cymene complex, whereby the addition of the carbaboranyl moiety (**2**) increases the potency by >18-fold against A2780cisR (compared to **1**). It was also noted that changing from Cp*M(III) to COD M(I) also increases the potency of the complexes, and against A2780cisR, the COD Ir(I) complex (**5**) is >4.6-fold more cytotoxic than the Cp* Ir(III) (**3**). The complexes are moderately cytotoxic towards normal cells (PNT2), however, it should be highlighted that the benzyl tethered NHC Cp* Rh(III) complex (**6**), has the lowest cytotoxicity of the library ($IC_{50}$ = 87 ± 2 μM) towards normal cells and is >10x, >3x and >67x less cytotoxic than **CDDP**, **CARB** and **OXA**, respectively. Some of our complexes are more cytotoxic than either **CDDP** or **CARB**, with significantly increased sensitivity against A2780, A2780cisR and MCF-7. Complexes have selectivity indices (SI) up to 7.9, 31.2 and 7.1 against these cell lines. The most significant result was observed for complex **5**, the carbaboranyl tethered COD Ir(I)-NHC complex, which is >31x more potent than **CARB** against A2780cisR. Conclusively, this highlights a potentially different *in vitro* mode of action when compared to the clinical platinum drugs, which could be important in overcoming the current toxicity issues.

## Declaration of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

We would like to thank the following funding for PhD studentships: School of Chemistry, University of Leeds (JH), EPSRC DTA awards (FNS) and the Mary and Alice Smith Memorial Scholarship (AF). Additionally, we would thank the Institute of Cancer Therapeutics (University of Bradford) for providing Cat. II facilities and the University of Bradford's RDF grant awarded to RML.

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