

A General Strategy to Add Diversity to Ruthenium Arene Complexes with Bioactive Organic Compounds via a Coordinated (4-Hydroxyphenyl)diphenylphosphine Ligand

Lorenzo Biancalana,^a Lucinda K. Batchelor,^b Alice De Palo,^a Stefano Zacchini,^c Guido Pampaloni,^a
 Paul J. Dyson,^{b,*} Fabio Marchetti^{a,*}

Receipt/Acceptance Data [DO NOT ALTER/DELETE THIS TEXT]

Publication data [DO NOT ALTER/DELETE THIS TEXT]

DOI: 10.1039/b000000x [DO NOT ALTER/DELETE THIS TEXT]

Abstract. Esterification of (4-hydroxyphenyl)diphenylphosphine, coordinated to the $[\text{Ru}(\eta^6\text{-}p\text{-cymene})\text{Cl}_2]$ fragment, allows a series of bioactive carboxylic acids to be introduced directly into the organometallic molecule. Evaluation of the compounds on human ovarian cancer cells reveals synergistic enhancements in their antiproliferative activity relative to their bioactive organic and organometallic precursors.

Ruthenium compounds are promising candidates as anticancer drugs that potentially overcome the limitations exhibited by the platinum-based chemotherapies currently used in the clinic.¹ For example, [imidazolium][*trans*-Ru(*N*-imidazole)(*S*-dmso)Cl₄], NAMI-A, and [indazolium]*trans*-[tetrachlorobis(1*H*-indazole)ruthenate(III)], KP1019, have undergone clinical evaluation.² In addition to these Ru(III) coordination complexes, organometallic Ru(II) complexes based on the Ru(η^6 -arene) scaffold have attracted considerable interest.³ In this context, ruthenium arene complexes comprising 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane (PTA, affording RAPTA complexes)⁴ or ethylene-1,2-diamine⁵ as ligands have emerged as among the most interesting species with relevant antitumor properties.⁶ It should be noted that several RAPTA analogues in which the PTA is replaced with triphenylphosphine-derived ligands have been studied.^{7,8} Although the lipophilicity of these phosphines result in a decrease in water solubility of the complex, the more hydrophobic phosphines enhance cellular uptake and cytotoxicity.^{7a,b}

With the aim of modulating the biological activity of Ru(η^6 -arene)-type complexes, a number of molecules with a known biological/pharmacological function have been tethered to this unit.⁹ Such compounds have been usually realized by inclusion of prior-functionalized arene species,¹⁰ or by binding appropriately modified *O*,*O*,¹¹ *N*,*O*(*S*)¹² and *N*,*N*¹³ chelate, or monodentate P⁸ and N ligands^{8,14} to the ruthenium(II). Direct modification of a coordinated arene ligand has also been realized using suitable

^a Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Moruzzi 13, I-56124 Pisa (Italy).

e-mail: fabio.marchetti1974@unipi.it.

^b Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland.

e-mail: paul.dyson@epfl.ch.

^c Dipartimento di Chimica Industriale "Toso Montanari", Università di Bologna, Viale Risorgimento 4, I-40136 Bologna (Italy).

† Supporting Information include experimental details, X-ray crystallography, characterization of the products. CCDC 1546169 and 1546170 contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.

protecting groups in order to suppress undesired reactions at the ruthenium centre during the coupling process.¹⁵

Herein we describe an alternative strategy,¹⁶ in which a generic Ru(η^6 -arene)Cl₂ compound with a reactive phosphine ligand can be modified, to introduce diverse bioactive organic components (Chart 1). The selected carboxylic acids are known to exert a biological function and some of them were previously incorporated within anticancer metal compounds.^{17,18,19,20,21,22}

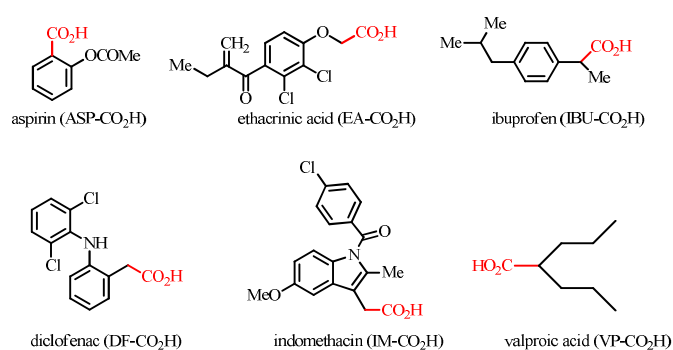
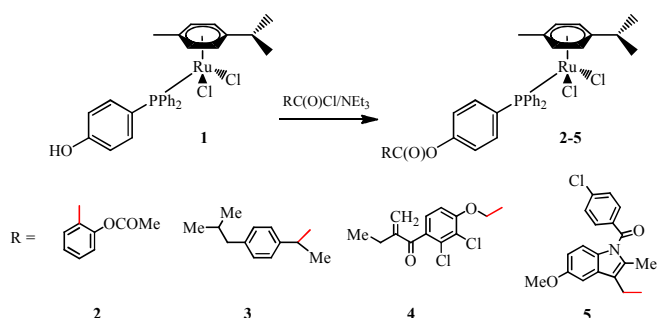
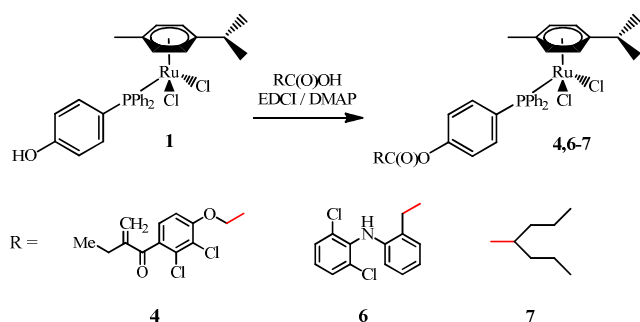


Chart 1. Bioactive carboxylic acids used in this work.

The esterification reactions were conveniently carried out directly on complex **1**, which includes a (4-hydroxyphenyl)diphenylphosphine ligand,²³ with the complex tolerating the reaction conditions negating the need of protecting strategies (Scheme 1).





Scheme 1. Preparation of ruthenium compounds with bioactive organic fragments **2-7** from the starting complex **1**.

The synthetic approach (Scheme 1) avoids manipulation and purification procedures of non coordinated (4-hydroxyphenyl)diphenylphosphine and of its ester derivatives, which are air sensitive (see ESI for details).

Complexes **2-7** were isolated in ca. 60-80% yield after purification using either chromatographic separation or extraction from $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$. Complexes **2** and **3** are functionalized with aspirin and ibuprofen, respectively, which have been conjugated to cisplatin analogues^{17b,19a} and other metals,^{17a,19b} leading to more efficient anticancer behaviour.

Complexes **2-7** were characterized by analytical and spectroscopic techniques (see ESI for full details). They all exhibit an IR absorption in the region $1740\text{-}1780\text{ cm}^{-1}$ due to the ester group. The ^{31}P NMR spectra contain a unique resonance around 24 ppm. The salient feature in the ^{13}C NMR spectra corresponds to the resonance emanating from the ester carbon, being at ca. 9 ppm higher frequency with respect to that observed for the uncoordinated carboxylic acids. The molecular structures of **1** and **2** were determined by single crystal X-ray diffraction and are shown in Figures 1 and 2, together with relevant bonding parameters.

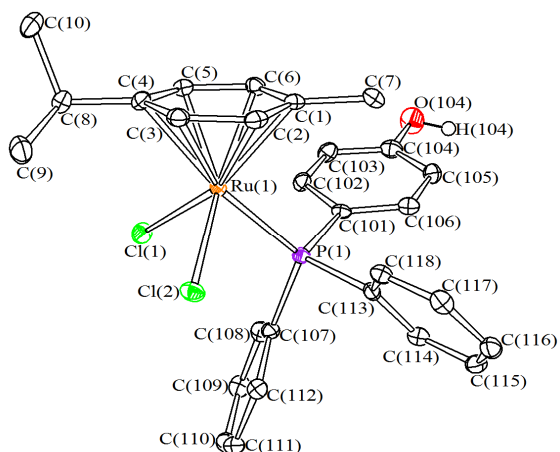


Figure 1. Structure of **1** with key atoms labelled. Displacement ellipsoids are at the 50% probability level. C-H hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Ru(1)-(η⁶-p-cymene)_{av} 2.217(10), Ru(1)-Cl(1) 2.4193(9), Ru(1)-Cl(2) 2.4106(9), Ru(1)-P(1) 2.3584(9), C(104)-O(104) 1.349(5), Cl(1)-Ru(1)-Cl(2) 87.69(3).

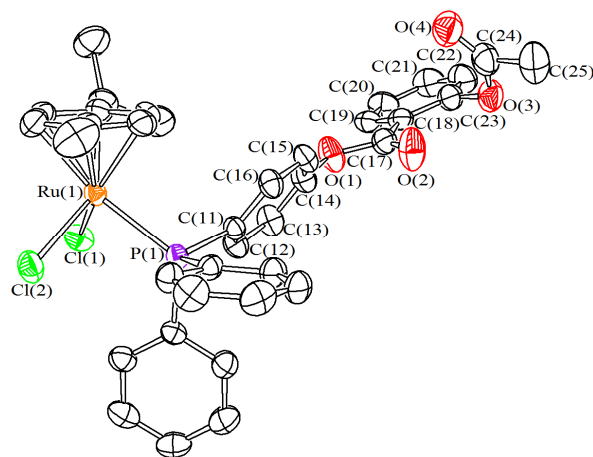


Figure 2. Structure of **2** with key atoms labelled. Hydrogen atoms are omitted for clarity. Displacement ellipsoids are at the 50% probability level. Selected bond lengths (Å) and angles (°): Ru(1)-(η⁶-p-cymene)_{av} 2.215(10), Ru(1)-Cl(1) 2.4038(11), Ru(1)-Cl(2) 2.4223(11), Ru(1)-P(1) 2.3741(11), C(14)-O(1) 1.391(5), O(1)-C(17) 1.359(5), C(17)-O(2) 1.179(5), C(23)-O(3) 1.399(6), O(3)-C(24) 1.354(6), C(24)-O(4) 1.189(6), C(24)-C(25) 1.496(8), Cl(1)-Ru(1)-Cl(2) 89.33(4), C(14)-O(1)-C(17) 121.3(4), sum at C(17) 360.0(7), C(23)-O(3)-C(24) 117.6(4), sum at C(24) 360.0(9).

Compounds **1** and **2** comprise the expected three-leg piano-stool geometry typical of other ruthenium(II)-arene compounds.²⁴ The bonding parameters around the Ru(II) centres are similar to those reported for $[\text{RuCl}_2(\text{p-cymene})(\text{PAR}_3)]$ structures.^{8,25} The bonding parameters of the acetylsalicylic acid ester in **2** are not significantly different to those in other reported structures.²⁶

The cytotoxicity of **1-7** and the bioactive precursors was assessed in human ovarian A2780 and A2780CisR cancer cells, the latter having acquired resistance to cisplatin, and human embryonic kidney HEK-298 cells using the MTT assay (Table 1).

Table 1. IC₅₀ values (μM) determined for **1-7** and other relevant control compounds on human ovarian carcinoma (A2780), human ovarian carcinoma cisplatin resistant (A2780cisR) and human embryonic kidney (HEK-293) cell lines after 72 h exposure. Values are given as the mean ± SD.

| Compound | A2780 | A2780CisR | HEK-293 |
|---|------------|------------|-----------|
| 1 | 50 ± 2 | 67.9 ± 0.2 | 69 ± 1 |
| 2 | 21 ± 1 | 32 ± 2 | 24 ± 1 |
| 3 | 11.6 ± 0.3 | 14 ± 2 | 7.9 ± 1.1 |
| 4 | 19.1 ± 0.1 | 38 ± 1 | 3.8 ± 0.4 |
| 5 | 173 ± 2 | > 200 | > 200 |
| 6 | 41 ± 3 | 74 ± 8 | 61 ± 5 |
| 7 | 9 ± 1 | 10.4 ± 1.3 | 7.4 ± 1.2 |
| L2=O | > 200 | > 200 | > 200 |
| ASP-CO₂H | > 200 | > 200 | > 200 |
| IBU-CO₂H | > 200 | > 200 | > 200 |
| EA-CO₂H ^{8b} | 40 ± 3 | 53 ± 5 | ---- |
| IM-CO₂H ^{8a} | 27 ± 2 | 112 ± 1 | 67 ± 1 |
| DF-CO₂H ^{8a} | 202 ± 16 | 84 ± 3 | 186 ± 14 |
| VP-CO₂H ²⁷ | > 100 | > 100 | 63 ± 38 |
| RAPTA-C ²⁸ | 230 | 270 | > 1000 |

cisplatin 1.9 ± 0.7 23 ± 3 9 ± 1

Compounds **2-4** and **6-7** are more cytotoxic to the A2780 cell line relative to the parent ruthenium compound **1** and the corresponding bioactive carboxylic acids. In particular, **3** and **7**, derivatised with ibuprofen or valproic acid, show cytotoxicity in the low micromolar range against the A2780 cell line, with approximately 5 fold lower IC₅₀ values compared to **1**. Compounds **2**, **3** and **7** show a marked increase in activity compared to ASP-CO₂H, IBU-CO₂H and VP-CO₂H, respectively. Compound **4** is 2-fold more cytotoxic than EA-CO₂H, and **6** is 5-fold more active than DF-CO₂H against the A2780 cell line. In contrast, a ca. 6-fold loss in activity is observed for **5** compared to IM-CO₂H against the A2780 cell line. Complexes **1-7** are all less cytotoxic to the cisplatin resistant A2780CisR cells, and do not display appreciable cancer cell selectivity, i.e. the IC₅₀ values in the tumorigenic and non-tumorigenic HEK-293 cell lines are similar.

Spectroscopic and conductivity measurements (see SI) indicated rapid chloride/solvent exchange when **1-7** were maintained in dmsd/water solutions at 37 °C, similar to that established for other ruthenium(II) arene complexes.³⁻⁵ In addition, slow, partial release of the phosphine ligand was observed over 72 hours. Thus, the antiproliferative activity of the complexes is mainly due to phosphine-bound Ru species (note that **L2=O** was inactive against the cell lines). The cleavage of the ester bond linking the bioactive group to the phosphine moiety was not observed in all the compounds, however, once inside a cell esterases could cleave the ester bond to separate the bioactive fragment from the ligand/complex.²⁹ In summary, a versatile method that allows bioactive organic compounds to be directly incorporated into a ruthenium(II)-arene structure has been developed. Remarkably, the chloride ligands in the complex are not affected by the reaction facilitating the direct transformation and negating the need of protecting groups employed elsewhere.¹⁵ The complexes are more cytotoxic than the ruthenium(II)-arene precursor and the bioactive organic compounds. It seems likely that the present approach could be extended to many other metal-based systems, allowing the rapid synthesis of bioactive organometallic and metal-organic compounds with structural diversity.

Notes and reference

- (a) N. P. E. Barry and P. J. Sadler, *Chem Commun*, 2013, **49**, 5106-5131. (b) G. Gasser, I. Ott and N. Metzler-Nolte, *J. Med. Chem.*, 2011, **54**, 3-25. (c) L. Ronconi and P. J. Sadler, *Coord. Chem. Rev.*, 2007, **251**, 1633-1648.
- (a) E. Alessio, *Eur. J. Inorg. Chem.*, 2017, 1549-1560; (b) R. Trondl, P. Heffeter, C. R. Kowol, M. A. Jakupec, W. Berger and B. K. Keppler, *Chem. Sci.*, 2014, **5**, 2925-2932. (c) A. Bergamo and G. Sava, *Dalton Trans.*, 2007, 1267-1272. (d) C. G. Hartinger, S. Zorbas-Seifried, M. A. Jakupec, B. Kynast, H. Zorbas and B. K. Keppler, *J. Inorg. Biochem.*, 2006, **100**, 891-904.
- (a) C. S. Allardyce and P. J. Dyson, *Dalton Trans.*, 2016, **45**, 3201-320; (b) A. K. Singh, D. S. Pandey, Q. Xu and P. Braunstein, *Coord. Chem. Rev.*, 2014, **270-271**, 31-56; (c) A. A. Nazarov, C. G. Hartinger and P. J. Dyson, *J. Organomet. Chem.*, 2014, **751**, 251-260; (d) A. L. Noffke, A. Habtemariam, A. M. Pizarro and P. J. Sadler, *Chem. Commun.*, 2012, **48**, 5219-5246; (e) C. G. Hartinger and P. J. Dyson, *Chem. Soc. Rev.*, 2009, **38**, 391-401.
- (a) B. S. Murray, M. V. Babak, C. G. Hartinger and P. J. Dyson, *Coord. Chem. Rev.*, 2016, **306**, 86-114; (b) A. Weiss, R. H. Berndsen, M. Dubois, C. Müller, R. Schibli, A. W. Griffioen, P. J. Dyson and P. Nowak-Sliwinska, *Chem. Sci.*, 2014, **5**, 4742-4748.

- (a) J. J. Soldevila-Barreda, I. Romero-Canelón, A. Habtemariam and P. J. Sadler, *Nature Commun.*, 2015, **6**, 6582-6590; (b) A. Habtemariam, M. Melchart, R. Fernández, S. Parsons, I. D. H. Oswald, A. Parkin, F. P. A. Fabbiani, J. E. Davidson, A. Dawson, R. E. Aird, D. I. Jodrell and P. J. Sadler, *J. Med. Chem.*, 2006, **49**, 6858-6868.
- Z. Adhireksan, G. E. Davey, P. Campomanes, M. Groessl, C. M. Clavel, H. Yu, A. A. Nazarov, C. H. Fang Yeo, W. H. Ang, P. Dröge, U. Rothlisberger, P. J. Dyson and C. A. Davey, *Nature Commun.*, 2014, **5**, 3462-3274.
- (a) S. Parveen, M. Hanif, S. Movassaghi, M. Sullivan, M. Kubanik, M. A. Shaheen, T. Söhnle, S. M. F. Jamieson and C. G. Hartinger, *Eur. J. Inorg. Chem.*, 2017, 1721-1727. (b) R. Sáez, J. Lorenzo, M. J. Prieto, M. Font-Bardia, T. Calvet, N. Omeñaca, M. Vilaseca and V. Moreno, *J. Inorg. Biochem.*, 2014, **136**, 1-12. (c) A. Castonguay, C. Doucet, M. Juhás and D. J. Maysinger, *J. Med. Chem.*, 2012, **55**, 8799-8806. (d) A. K. Renfrew, R. Scopelliti and P. J. Dyson, *Inorg. Chem.*, 2010, **49**, 2239-2246.
- (a) E. Păunescu, S. McArthur, M. Soudani, R. Scopelliti, and Paul J. Dyson, *Inorg. Chem.*, 2016, **55**, 1788-1808; (b) G. Agonigi, T. Riedel, S. Zacchini, E. Păunescu, G. Pampaloni, N. Bartalucci, P. J. Dyson and F. Marchetti, *Inorg. Chem.*, 2015, **54**, 6504-6512.
- (a) A. A. Nazarov, C. G. Hartinger and P. J. Dyson, *J. Organomet. Chem.*, 2014, **751**, 251-260; (b) K. J. Kilpin and P. J. Dyson, *Chem. Sci.*, 2013, **4**, 1410-1419.
- (a) A. A. Nazarov, S. M. Meier, O. Zava, Y. N. Nosova, E. R. Milaeva, C. G. Hartinger and P. J. Dyson, *Dalton Trans.*, 2015, **44**, 3614-3623; (b) W. H. Ang, L. J. Parker, A. De Luca, L. Juillerat-Jeanneret, C. J. Morton, M. Lo Bello, M. W. Parker and P. J. Dyson, *Angew. Chem. Int. Ed.*, 2009, **48**, 3854-3857.
- (a) A. Kurzwehnhart, W. Kandoller, C. Bartel, S. Bächler, R. Trondl, G. Mühlgassner, M. A. Jakupec, V. B. Arion, D. Marko and B. K. Keppler, *Chem. Commun.*, 2012, **48**, 4839-4841; (b) W. Kandoller, E. Balsano, S. M. Meier, U. Jungwirth, S. Goschl, A. Roller, M. A. Jakupec, W. Berger, B. K. Keppler and C. G. Hartinger, *Chem. Commun.*, 2013, **49**, 3348-3350; (c) J. Kljun, A. K. Bytzeck, W. Kandoller, C. Bartel, M. A. Jakupec, C. G. Hartinger, B. K. Keppler and I. Turel, *Organometallics*, 2011, **30**, 2506-2512.
- (a) S. Nikolić, D. M. Opsenica, V. Filipović, B. Dojčinović, S. Arandelović, S. Radulović and S. Grgurić-Šipka, *Organometallics*, 2015, **34**, 3464-3473; (b) M. Kubanik, H. Holtkamp, T. Söhnle, S. M. F. Jamieson and C. G. Hartinger, *Organometallics* 2015, **34**, 5658-5668.
- V. B. Arion, A. Dobrov, S. Goschl, M. A. Jakupec and B. K. Keppler, *Chem. Commun.*, 2012, **48**, 8559-8561.
- (a) M. V. Babak, D. Plažuk, S. M. Meier, H. J. Arabshahi, J. Reynisson, B. Rychlik, A. Blauz, K. Szulc, M. Hanif, S. Strobl, A. Roller, B. K. Keppler and C. G. Hartinger, *Chem. Eur. J.*, 2015, **21**, 5110-5117; (b) P. Chellan, K. M. Land, A. Shokar, A. Au, S. Hwan An, D. Taylor, P. J. Smith, T. Riedel, P. J. Dyson, K. Chibale and G. S. Smith, *Dalton Trans.*, 2014, **43**, 513-526; (c) W. H. Ang, A. De Luca, C. Chapuis-Bernasconi, L. Juillerat-Jeanneret, M. Lo Bello and P. J. Dyson, *ChemMedChem*, 2007, **2**, 1799-1806.
- B. S. Murray, L. Menin, R. Scopelliti and P. J. Dyson, *Chem. Sci.*, 2014, **5**, 2536-2545.
- D. Stibal, B. Therrien, G. Süß-Fink, P. Nowak-Sliwinska, P. J. Dyson, E. Čermáková, M. Režáčková and P. Tomšík, *J. Biol. Inorg. Chem.* 2016, **21**, 443-452.
- Aspirin**: (a) G. Rubner, K. Bendorf, A. Wellner, B. Kircher, S. Bergemann, I. Ott and R. Gust, *J. Med. Chem.* 2010, **53**, 6889-6898. (b) Q. Cheng, H. Shi, H. Wang, Y. Min, J. Wang and Y. Liu, *Chem. Commun.*, 2014, **50**, 7427-7430.
- Ethacrynic acid**: G. Agonigi, T. Riedel, M. P. Gay, L. Biancalana, E. Oñate, P. J. Dyson, G. Pampaloni, E. Păunescu, M. A.

- Esteruelas and F. Marchetti, *Organometallics*, 2016, **35**, 1046-1056, and ref. 8b, 10b, 14c.
- 19 **Ibuprofen**: (a) H. Endo, M. Yano, Y. Okumura and H. Kido, *Cell Death and Disease*, 2014, **5**, e1027-e1036. (b) H.-U.-Rehman, T. E. Freitas, R. N. Gomes, A. Colquhoun and D. de Oliveira Silva, *J. Inorg. Biochem.* 2016, **165**, 181–191.
- 20 **Indomethacin**: W. Neumann, B. C. Crews, M. B. Sárosi, C. M. Daniel, K. Ghebreselasie, M. S. Scholz, L. J. Marnett and E. Hey-Hawkins, *ChemMedChem*, 2015, **10**, 183-192, and ref. 8a.
- 21 **Diclofenac**: F. P. Intini, J. Zajac, V. Novohradsky, T. Saltarella, C. Pacifico, V. Brabec, G. Natile and J. Kasparkova, *Inorg. Chem.* 2017, **56**, 1483–1497; see also ref. 8a and references therein.
- 22 **Valproic acid**: a) R. Raveendran, J. P. Braude, E. Wexselblatt, V. Novohradsky, O. Stuchlikova, V. Brabec, V. Gandin and D. Gibson, *Chem. Sci.*, 2016, **7**, 2381-2391. b) W.-h. Feng and S. C. Kenney, *Cancer Res.*, 2006, **66**, 8762-8769. (c) M. Ravera, E. Gabano, I. Zanellato, A. Gallina, E. Perin, A. Arrais, S. Cantamessa and D. Osella, *Dalton Trans.*, 2017, **46**, 1559–1566.
- 23 I. Angurell, C.-O. Turrin, R. Laurent, V. Maraval, P. Servin, O. Rossell, M. Seco, A.-M. Caminade and J.-P. Majoral, *J. Organomet. Chem.*, 2007, **692**, 1928–1939.
- 24 Selected recent references are: (a) J. Palmucci, F. Marchetti, R. Pettinari, C. Pettinari, R. Scopelliti, T. Riedel, B. Therrien, A. Galindo and P. J. Dyson, *Inorg. Chem.*, 2016, **55**, 11770–11781; (b) M. Kubanik, H. Holtkamp, T. Söhnel, S. M. F. Jamieson and C. G. Hartinger, *Organometallics*, 2015, **34**, 5658–5668; (c) C. M. Clavel, E. Păunescu, P. Nowak-Sliwinska, A. W. Griffioen, R. Scopelliti and P. J. Dyson, *J. Med. Chem.*, 2015, **58**, 3356–3365 (d) F. Hackenberg, H. Müller-Bunz, R. Smith, W. Streciwilk, X. Zhu and M. Tacke, *Organometallics*, 2013, **32**, 5551-5560; (e) Grgurić-Sipka, S.; Ivanović, I.; Rakić, G.; Todorović, N.; Gligorijević, N.; Radulović, S.; Arion, V. B.; Keppler, B. K.; Tešić and Z. Lj., *Eur. J. Med. Chem.*, 2010, **45**, 1051-1058.
- 25 (a) R. Garcia-Álvarez, J. Díez, P. Crochet and V. Cadierno, *Organometallics*, 2010, **29**, 3955–3965; (b) L. J. Hounjet, M. Bierenstiel, M. J. Ferguson, R. McDonald and M. Cowie, *Inorg. Chem.*, 2010, **49**, 4288–4300; (c) A. Bacchi, M. Balordi, R. Cammi, L. Elviri, C. Pelizzi, F. Picchioni, V. Verdolino, K. Goubitz, R. Peschar and P. Pelagatti, *Eur. J. Inorg. Chem.*, 2008, 4462–4473 (d) P. Pelagatti, A. Bacchi, M. Balordi, S. Bolaño, F. Calbiani, L. Elviri, L. Gonsalvi, C. Pelizzi, M. Peruzzini and D. Rogolino, *Eur. J. Inorg. Chem.*, 2006, 2422–2436; (e) M. R. J. Elsegood, M. B. Smith and N. M. Sanchez-Ballester, *Acta Crystallogr Sect E Struct Rep Online*, 2006, **62**, m2838-m2840; (f) A. Hafner, A. Mühlebach and P. A. van der Schaaf, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 2121–2124.
- 26 (a) K. A. Solanko and A. D. Bond, *Acta Crystallogr Sect E Struct Rep Online*, 2012, **68**, o2108; (b) X.-W. Liu, J.-Y. Li, Y.-J. Yang and J.-Y. Zhang, *Acta Crystallogr Sect E Struct Rep Online*, 2011, **67**, o1621; (c) A. Foppoli, M. E. Sangalli, A. Maroni, A. Gazzaniga, M. R. Caira and F. Giordano, *J. Pharmaceut. Sci.*, 2004, **93**, 521–531.
- 27 a) A. El-Faham, M. Farooq, S. N. Khatta, N. Abutaha, M. A. Wadaan, H. A. Ghabbour and H.-K. Fun, *Molecules*, 2015, **20**, 14638-14655. b) D. M. Griffith, B. Duff, K. Y. Suponitsky, K. Kavanagh, M. P. Morgan, D. Egan and C. J. Marmion, *J. Inorg. Biochem.*, 2011, **105**, 793–799.
- 28 K. J. Kilpin, C. M. Clavel, F. Edefe and P. J. Dyson, *Organometallics*, 2012, **31**, 7031-7039.
- 29 a) K. Johansson, M. Ito, C. M. S. Schopphuizen, S. M. Thengumtharayil, V. D. Heuser, J. Zhang, M. Shimoji, M. Vahter, W. H. Ang, P. J. Dyson, A. Shibata, S. Shuto, Y. Ito, H. Abe and R. Morgenstern, *Mol. Pharmaceutics* 2011, **8**, 1698-1708. (b) G. Cynkowska, T. Cynkowski, A. A. Al-Ghananeem, H. Guo, P. Ashton and P. A. Crooks, *Bioorg. Med. Chem. Lett.* 2005, **15**, 3524–3527.

