Potent Tethered Osmium(II) Half-Sandwich Anticancer Agents Bearing Phenylpyridine

S. Infante-Tadeo,[a] V. Rodríguez-Fanjul,[a] A.M. Pizarro,[a,b*]
[a] IMDEA Nanociencia, Faraday 9, 28049 Madrid, Spain
[b] Unidad Asociada de Nanobiotecnología CNB-CSIC-IMDEA, 28049 Madrid, Spain
ana.pizarro@imdea.org

Half-sandwich complexes of Ru(II), Os(II), and Ir(III) have recently received much attention due to their potency against cancer cells.[1] These complexes often bear a labile chlorido ligand, which upon substitution in water, renders the metal active towards biomolecule interaction. However, for osmium(II) half-sandwich complexes of formula $[Os(\eta^6\text{-arene})(XY\text{-bidentate})Z]^{n+}$, aquation of the Z monodentate ligand often inhibits Os-reactivity by affording inert Os–hydroxido dimeric species.[2]

We have overcome this activity-loss by introducing a hemilabile arene/alcohol ligand –whereby the pendant alcohol occupies the Z position–, which protects the metal centre against hydroxido-mediated inactivation by forming a tether ring.[3] In addition, we have carefully fine-tuned the design, including XY negatively charged chelating ligands (C,N- or N,O-) that lead to faster hydrolysing compounds and enhanced anticancer activity. Additional proof that Os-reactivity is maintained in cells has been demonstrated by the Os-mediated transformation of pyruvate to lactate in breast cancer cell lines.[3]

In order to comprehensibly understand Os-Cl/Z(tether) hydrolysis, and in the context of the complexes' high anticancer potency, we looked into the correlation between hydrolysis and pH-dependent reactivity of highly potent Os-arenes, tethered and non-tethered, bearing phenylpyridine as XY-bidentate ligand. The Os–Cl bond is stable in pure DMSO yet readily hydrolyses in DMSO:aqueous solution leading to rapid formation of Os–DMSO adduct (following aquation). DMF:aqueous solutions enables titration of the aqua adduct and allows for pK_a* determination, which is above 9.6 in all cases. These values are some of the most basic Os-arene aqua-adducts reported to date.[4] The data are discussed in the context of hydrolysis readiness, low acidity of $Os\text{-}OH_2$, and cytotoxic potency of the Os-phenylpyridine-arene core.

The protection of the tether ring, together with the increase in the effective charge on the metal centre –to which the C,N-ligand greatly contributes– may be the basis for the next generation of highly potent osmium metallodrugs.

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