THE ANTICANCER POTENTIAL OF 4-PHENYLTHIAZOLE DERIVED Ru(II)- AND Os(II) METALACYCLES

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BOLD-100 (Figure 1) represents the first-in-class, antitumor Ru(III) complex,[1] which recently showed promising interim results in a clinical phase II trial.[2] The activation by reduction of the Ru(III) center to the corresponding Ru(II) species is assumed to be the essential step in the mechanism of action.[3] Ru(II) arene compounds offer a versatile scaffold for the development of new anticancer agents whose properties can be easily modified by ligand variation.[4] Sadler´s and Dyson´s group investigated Ru(II) arene-based compounds extensively, which resulted in the development of the two most prominent representatives of this compound class, namely, Sadler´s RAEN organometallics and Dyson´s RAPTA complexes (e.g. RM175 and RAPTA-T, Figure 1).[5]

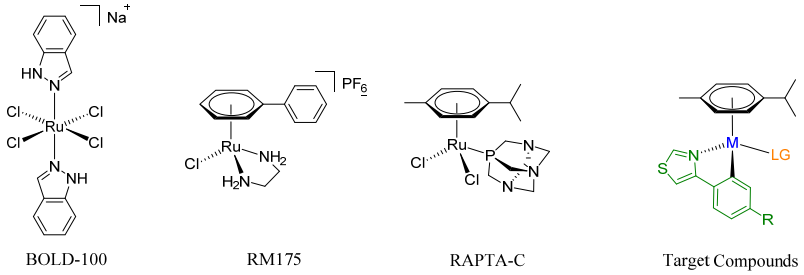

Figure 1: Left: Promising Ru-based coordination compounds for tumor therapy (BOLD-100, RM175 and RAPTA-C). Right: General structure of the target complexes. (LG = leaving group)

Due to limited stability of conventional bidentate motifs (*O,O*, *N,O*, …) the application of the respective organometallics as anticancer therapeutics is oftentimes hampered.[6] Consequently, stable alternatives were emphasized, prompting the Kandioller group to explore *C,N* coordination motifs. This work is based on a series of preliminary research projects regarding *C,N* bidentate coordination.[4][7][8] In this contribution, we examine how cyclometalated derivatives of 4-phenylthiazole impact the anticancer potential of Ru(II)- and Os(II) complexes. Additionally, we delve into the influence of altering the leaving group (shown in Figure 1 as LG) to achieve precise adjustments in the antitumor properties.

[1] R. Trondl *et al.*, "NKP-1339, the first ruthenium-based anticancer drug on the edge to clinical application" *Chem. Sci.*, 2014

[2] https://www.bold-therapeutics.com/

[3] M. A. Jakupec *et al.*, "Redox-active antineoplastic ruthenium complexes with indazole: Correlation of in vitro potency and reduction potential", *J. Med. Chem.*, 2005

[4] C. A. Riedl *et al.*, "Introducing the 4-Phenyl-1,2,3-Triazole Moiety as a Versatile Scaffold for the Development of Cytotoxic Ruthenium(II) and Osmium(II) Arene Cyclometalates", *Inorg. Chem*, 2017

[5] A. Bergamo *et al.*, "Approaching tumour therapy beyond platinum drugs: Status of the art and perspectives of ruthenium drug candidates", *J. Inorg. Biochem.*, 2012

[6] M. Schmidlehner *et al.*, "Organometallic complexes of (thio)allomaltol-based Mannich-products: Synthesis, stability and preliminary biological investigations", *J. Organomet. Chem.*, 2015

[7] C. A. Riedl *et al.*, "N - And S -donor leaving groups in triazole-based ruthena(II)cycles: Potent anticancer activity, selective activation, and mode of action studies", *Dalt. Trans.*, 2018

[8] S. Mokesch *et al.*, "Investigations on the Anticancer Potential of Benzothiazole-Based Metallacycles", *Front. Chem.*, 2020