HIGHLY STABLE *N,O,O*-TRIDENTATE ORGANOMETALLICS AS POTENTIAL NOVEL ANTICANCER AGENTS

Alexander Rosner[a, b], Wolfgang Kandioller[a], and Bernhard Keppler[a]

[a] University of Vienna, Faculty of Chemistry, Institute of Inorganic Chemistry.
[b] University of Vienna, Vienna Doctoral School in Chemistry (DoSChem)

Recently, an *in situ* formed tridentate ligand architecture of piano-stool ruthenium and osmium complexes has been established. The one-pot reaction to a *N,O,O*-tridentate coordination motif takes place *via* base initiated formation of a hemiaminal structure (Figure 1). This novel compound class differs from most literature known organometallic anticancer agents [1]. Highly stable complex formation in biologically relevant solution alongside outstanding cytotoxic impact are promising characteristics for drug administration. Unexpected *in vitro* selectivity for cisplatin resistant cell lines (SW480, CT-26) was observed [2], whereas preliminary *in vivo* results show antiproliferative activity in absence of adverse effects at minor doses. Still, the mode of action needs elucidation.

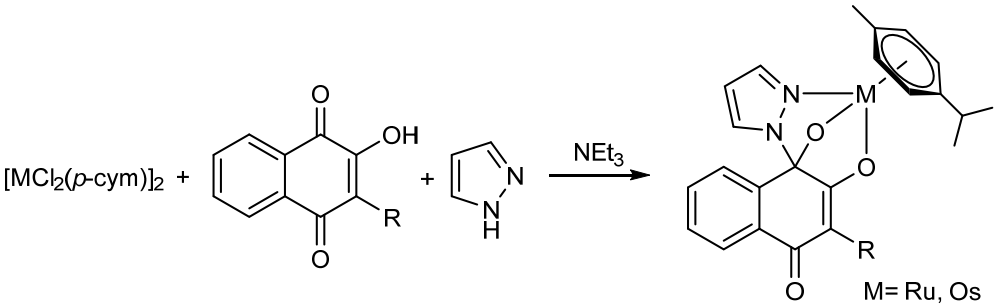

Figure 1: Three component reaction of metal precursor, bioactive naphthoquinones and pyrazole to tridentate complexes [1].

Resolving biological behavior alongside fine-tuning of pharmacokinetic properties are main tasks of this work. For most promising derivatives, drug impact on cellular metabolism is being elucidated, whereas *in vivo* studies have been conducted. Recent *in vitro* and *in vivo* results of this highly promising compound class will be presented.

---

[1] Geisler, H.; Wernitznig, D.; Hejl, M.; Gajic, N.; Jakupec, M. A.; Kandioller, W.; Keppler, B. K. Novel Phthiocol-Based Organometallics with Tridentate Coordination Motif and Their Unexpected Cytotoxic Behaviour. Dalton Trans. 2020, 49 (5), 1393–1397. https://doi.org/10.1039/C9DT04462K.

[2] Geisler, H.; Westermayr, J.; Cseh, K.; Wenisch, D.; Fuchs, V.; Harringer, S.; Plutzar, S.; Gajic, N.; Hejl, M.; Jakupec, M. A.; Marquetand, P.; Kandioller, W. Tridentate 3-Substituted Naphthoquinone Ruthenium Arene Complexes: Synthesis, Characterization, Aqueous Behavior, and Theoretical and Biological Studies. Inorg. Chem. 2021, acs.inorgchem.1c01083. https://doi.org/10.1021/acs.inorgchem.1c01083.