TOWARDS SUPRAMOLECULAR PLATINUM(II) METALLODRUGS

Shib Shankar PAUL,[1,2] Pia JURČEK,[1,2] Jan NOVOTNÝ[1,2], Kateřina PETRLÁKOVÁ,[3] Michal MASAŘIK,[3] Radek MAREK[1,2]

[1] *Department of Chemistry, Faculty of Science, Masaryk University, Kamenice 5, CZ-62500 Brno, Czechia*

[2] *CEITEC – Central European Institute of Technology, Masaryk University, Kamenice 5, CZ-62500 Brno, Czechia*

[3]*Department of Physiology, Faculty of Medicine, Masaryk University, Kamenice 5, CZ-62500 Brno, Czechia*

Platinum(II) based anticancer metallodrugs are one of the most studied drugs in medicinal inorganic chemistry. Three FDA-approved Pt(II) drugs cisplatin, oxaliplatin, and carboplatin are used worldwide[1]. All these Pt(II)-compounds hydrolyze upon cellular entry, this generates the active drug which binds with DNA, blocks transcription, and kills the tumor cell[2]. Despite the worldwide usage of this type of compounds, their toxicity is not controlled towards tumor cells which often leads to numerous side effects[3]. To control the toxicity of the metallodrug and reduce the interaction of biological nucleophiles, it can be temporarily deactivated by encapsulating it in some carrier molecule and slowly releasing the drug for a longer period.

In this work, we synthesized a series of cationic, anionic, and neutral Pt(II) complexes with various anchor ligands which can bind to macrocycles (carrier) like cucurbit[7]uril (CB7) and β-cyclodextrin (βCD). We found neutral and anionic Pt(II) complexes are poorly water-soluble making them ineligible for biological screening. Host-guest (HG) complex with the macrocycles was also not helpful for modulating their solubility. Cationic complexes were nicely water soluble and so were their HG assemblies. We found that CB7 can enhance the rate of hydrolysis in some systems leading to stronger binding making the drug unavailable to the tumor cell[4]. To overcome this effect, we modified the anchor ligands to improve the supramolecular prodrug-active drug equilibrium (**Fig:1**). In this oral contribution I will demonstrate the synthesis, structural analysis, hydrolysis profile, biological response against A2780 and cisplatin-resistant A2780 cell line and future outlook of these type of supramolecular metallodrug systems.

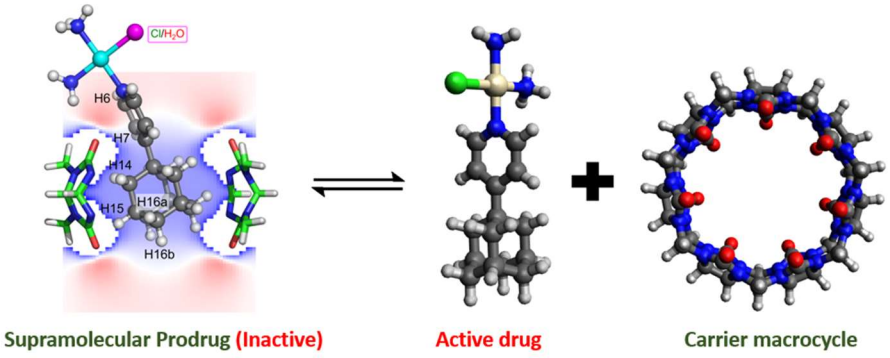

Fig 1: Prodrug-drug equilibrium

References:

1. Johnstone T. C. *et. al.*, *Chem. Rev.,* **2016**, 116, 3436-3486
2. Dasasri S. *et. al.*, *Eur. J. Pharmacol.*, **2014**, 740, 364-378
3. Astolfi L. *et.al.*, *Oncology Reports*, **2013**, 29, 1285-1292
4. Sojka M. *et. al.*, *Inorg. Chem.*, **2021**, 17911-17925