SUPRAMOLECULAR PROPERTIES OF PYRIPLATIN-BASED COMPOUNDS

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Platinum(II)-based drugs such as cisplatin are still frequently used as antineoplastic agents.[1] Their cellular entry represents a first step of the biological mechanism of action. The uptake and release of the drug from cells play a key role in the efficacy as well as in the drug resistance of various cancer cell lines.[2] Organic Cation Transporters (OCTs) were indicated as critical mediators for oxaliplatin transport.[3] This initiated search for cationic Pt-based substrates for OCTs. Pyriplatin (**Fig 1**), a derivative of cisplatin where one of the two chlorides is replaced by pyridine, showed interesting properties compared to cisplatin. It was shown to bind monofunctionally to N(7) position of guanine base in DNA. This monofunctional binding gives several advantages over bifunctional binding of cisplatin. Bifunctional binding bends and structurally damages the DNA which is repaired quickly by nucleotide excision repair. In contrast, monofunctional binding does not damage the DNA structurally so the sensing proteins cannot detect the damage easily.[4,5]

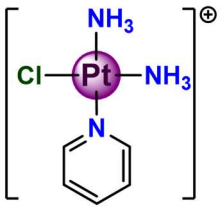

Fig 1

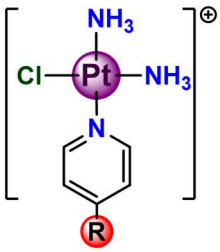

Fig 2

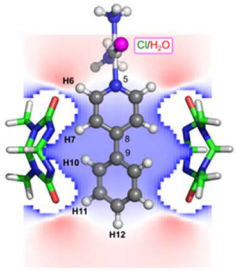

Fig 3

In this work we focus on synthesizing derivatives of pyriplatin (**Fig 2**) and modulating their activity by forming host-guest complexes (**Fig 3**) with cucurbit[7]uril (CB7). We introduced aliphatic and aromatic anchors R to the pyridine which can improve the lipophilicity of the compound and increase the cellular uptake of the drug. Compared to our previous work[6] we were able to improve the biological activity and have a better understanding of the host-guest chemistry of the Pt-compounds with CB7 host. Synthesis, characterization, and biological profile of the pyriplatin derivatives and their host-guest assemblies with CB7 will be discussed in this contribution.

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References

[1] Wang D.; Lippard S.J., *Nat. Rev. Drug Discov.*, **2005**, 4, 307–320

[2] Gately DP., *Br. J. Cancer*, **1993**, 67, 1171–1176.

[3] Zhang S, *et. al.*, *Cancer Res*, **2006**, 66, 8847– 8857

[4] Lovejoy K. S. *et. al.*, *Proc. Natl. Acad. Sci. USA.*, **2008**, 105, 8902-8907

[5] Zhou W. *et. al.*, *J. Am. Chem. Soc.*, **2019**, 141, 4, 1537-1545.

[6] Sojka M. *et. al.*, *Inorg. Chem.*, **2021**, 60, 23, 17911-17925.