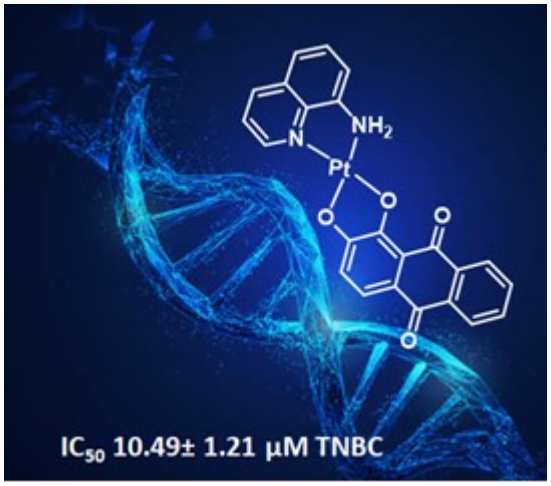
O4.311

Alizarin as a selective carrier in cytotoxic Pt(II) complexes toward Triple Negative Breast Cancer (TNBC)

Giorgio Facchetti[1], Iolinda Aiello[2], Gloria Mazzone[3], Luigi Messori[4], Isabella Rimoldi[1]
[1]Department of Pharmaceutical Sciences, University of Milan, Milano, Italy. [2]Unità INSTM della Calabria, Dipartimento di Chimica e Tecnologie ChimicheDipartimento di Chimica e Tecnologie Chimiche, Università della Calabria, Arcavacata di Rende, Italy. [3]Dipartimento di Chimica e Tecnologie Chimiche, Università della Calabria, Arcavacata di Rende, Italy. [4]Department of Chemistry, University of Florence, Firenze, Italy

Abstract

The lack of tumor selectivity, the associated side effects and acquired drug resistance have greatly limited the therapeutic application of platinum-based drugs. With the aim to improve cancer therapy, a wide range of functional Pt(II)-based drugs have been studied by applying different synthetic strategies. [1] Among them, a rational choice of the leaving group has also been proven to deeply influence the cytotoxicity of the platinum-based chemotherapeutics.[2] The use of *O*,*O* leaving groups different from the popular dicarboxylates for the synthesis of platinum complexes and endowed with a new biological profile, remains largely unexplored. Here, the catechol moiety in alizarin as a dichelating *O*,*O* leaving ligand was exploited as selective carrier for the synthesis of Pt(II) complexes toward TNBC able to exert a cytotoxic DNA metalation. To complete the coordination sphere of the platinum centre, a series of (*N*^*N*) spectator ligands was selected with to probe the influence of the structural and electronic features of the ligands on the cytotoxic activity. Within the series, 8-aminoquinoline-based Pt(II) complex proved the most cytotoxic toward TNBC cell line with an IC_{50} of 10.49 ± 1.21 μM, thus attesting that the cytotoxicity effect is strictly correlated to the proper choice of the diamine ligand whereas replacement of the two chloride ligands with alizarin makes these compounds far more selective for DNA than for proteins, as demonstrated by ICP. These results were further confirmed by computational and ESI-MS interaction studies with model proteins and DNA fragments, mimicking potential biological targets. [3]



References

agents. *Coordination Chemistry Reviews* **2024**, *501*, 215379. DOI: https://doi.org/10.1016/j.ccr.2023.215379.

(2) Mazzone, G.; Scoditti, S.; Caligiuri, R.; Ricciardi, L.; Sicilia, E.; Lupo, M. G.; Rimoldi, I.; Godbert, N.; La Deda, M.; Ionescu, A.; et al. Cytotoxicity of Alizarine versus Tetrabromocathecol Cyclometalated Pt(II) Theranostic Agents: A Combined Experimental and Computational Investigation. *Inorganic Chemistry* **2022**, *61* (18), 7188-7200. DOI: 10.1021/acs.inorgchem.2c00842.

(3) Caligiuri, R.; Massai, L.; Geri, A.; Ricciardi, L.; Godbert, N.; Facchetti, G.; Lupo, M. G.; Rossi, I.; Coffetti, G.; Moraschi, M.; et al. Cytotoxic Pt(ii) complexes containing alizarin: a selective carrier for DNA metalation. *Dalton Transactions* **2024**, 10.1039/D3DT03889K. DOI: 10.1039/D3DT03889K.