

UNRAVELLING THE MODULATION OF THE INTERACTION BETWEEN DRUGS BASED ON METAL COMPLEXES CONTAINING PHENANTHROLINE AND DNA

Gil A.,^{a,b} Ortiz de Luzuriaga I.,^{b,c} Elleuchi S.,^d Jarraya, K.,^d Lopez, X.^{c,e} Calhorda, M.J.^a

^a*Centro de Química e Bioquímica and BioISI – Biosystems and Integrative Sciences Institute, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, Lisboa, 1749-016, Portugal,*

e-mail: agmestres@fc.ul.pt

^b*CIC-nanoGUNE, Tolosa Hiribidea 76, Donostia – San Sebastián, 20018, Euskadi, Spain,*

e-mail: a.gil@nanogune.eu

^c*Kimika Fakultatea, Euskal Herriko Unibertsitatea UPV/EHU, Donostia – San Sebastián, 20080, Euskadi, Spain*

^d*University of Sfax, Laboratory of Inorganic Chemistry, Sfax, Tunisia*

^e*Donostia International Physics Center (DIPC), P. K. 1072, Donostia – San Sebastián, 20080, Euskadi, Spain*

[Mo(η^3 C₃H₅)Br(CO)₂(phen)] metal complex was found to be cytotoxic in several tumor cell lines and its activity is explained by means of the intercalation in DNA duplex chains. On the other hand, it is known that the intercalation active mode of interaction in DNA duplex chains competes with a non-active mode of interaction which is the minor groove binding. Moreover, there are other cytotoxic mechanisms involving the interaction of small molecules such as [Mo(η^3 C₃H₅)Br(CO)₂(phen)] in which the substrate is another motif of DNA called G-quadruplex. In this work, we aim at the comprehension and rationalization of the interaction of [Mo(η^3 C₃H₅)Br(CO)₂(phen)] considering different modes of interaction not only in regular duplex but also in G-quadruplexes. Optimizations without constraints were carried out at DFT level including van der Waals corrections for the whole studied systems of 500-1000 atoms by means of SIESTA software at reasonable core-times. We also performed the Energy Decomposition Analysis (EDA) to evaluate the nature of the interactions in terms of dispersion, electrostatic contributions and in terms of charge transfer and polarization. Finally, we used the Quantum Theory of Atoms in Molecules (QTAIM) to obtain topological pictures of the weak interactions that rule such kind of processes. Our results confirm the importance of the role of weak interactions and the cytotoxicity could be explained by means of a subtle balance between the stabilizing weak interactions and the destabilizing steric contribution. The role of the entropic factor results also crucial when looking at the stability of the investigated systems.