Electrochemical and biological studies on bis tetrahydrocridine derivatives

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In order to modulate their biological activity, new species of bis tetrahydroacridines were synthesized and characterized by chemical analysis, ESI-MS, IR, UV-Vis-NIR, EPR spectroscopy.

In this research electrochemical, antimicrobial activity, quantum computed investigations (DFT) and molecular docking studies were conducted in order to highlight the correlation between electrochemical parameters (redox potentials) and the predicted quantum reactivity parameters derived from energetical levels of frontier molecular orbitals; also, correlations between antimicrobial analyses results and the biomolecular interactions of the complexes with some enzymes responsible for the survival of these microbes were obtained using molecular docking.

The electrochemical study was performed by cyclic voltammetry, differential pulse voltammetry and rotating disk electrode voltammetry in acetonitrile/ dimethylformamide in presence of tetrabutylammonium perchlorate for different concentrations of each target, at different scan rates and electrode rotation rates. Combination of electrochemical analysis and DFT simulations allowed investigating systematically the effect of different substitution on the tetrahydroacridine skeleton, which affects the electrochemical behaviour.

Previous works confirmed the possibility to assess electrochemical properties with good accuracy by quantum mechanical calculations using hybrid density functionals [1,2]. B3LYP/DFT/6-311 (d,p) method [3] was used to predict quantum chemical reactivity parameters for tetrahydroacridines derivatives and to correlate the calculated energies of HOMO and LUMO orbitals with the oxidation and the reduction potentials, respectively.

The antimicrobial activity tested of the newly synthesized derivatives (i) allowed qualitative and quantitative evaluation of the influence of these derivatives on microbial growth and (ii) and highlighted the influence of 1,2-di(quinolinyl)ethane derivatives on microbial adhesion to inert substrate. The in vitro screening of the antimicrobial activity was performed against Gram positive *(S. aureus*, *E. faecalis*), Gram negative (*E. coli*, *P. aeruginosa*), and one fungal strain (*C. albicans*). The derivatives showed high CMI values compared to the tested bacterial strains, while the qualitative tests showed reduced antimicrobial activity. Zones of inhibition of growth were observed for some derivatives. All compounds have the ability to inhibit the biofilm adhesion on inert substratum, and they may be the basis for the development of new anti-biofilm agents.

The molecular docking study was conducted to predict the probable binding site and mode of binding of the tested compounds with *S. Aureus* DNA gyrase, retrieved from the Protein Data Bank (PDB ID: 2XCT) [4]. The docking simulations have been performed using CLC Drug Discovery Workbench Software using the docking protocol established in our previous studies [5], and Molegro Virtual Docker Software with the docking protocol referred in [6]. Molecular docking allowed us to establish an accurate prediction of the optimized conformation of tested ligands and their target receptor protein to achieve a stable complex. The analysis of the data obtained by *in silico* simulation shows that all compounds reveal docking scores higher than those of the natural ligand (ciprofloxacin), thus suggesting a good affinity to the chosen target.

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