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### **ABSTRACT**

The habilitation thesis "Complexes of Cu(II) with ligands bearing pharmacophore groups developed as biologically active species" presents the candidate's main relevant scientific and professional results after obtaining the PhD degree in Chemistry at the University of Bucharest in 1999, providing thus an overview concerning the academic and scientific developments according to the current standards.

Having in view the serious side effects associated with the organic and inorganic drugs that generate resistance in both cancer and microbial infections treatment as well as the complications generated by microbial biofilms in infection developed on prosthetic devices or injured tissues, in last years becomes imperative the finding new approaches for solving these problems. One of the strategies is based on complexes developed on essential metal ions and ligands bearing pharmacophore moieties. Taking into account these aspects, the research activity has been directed to development of new complexes with essential ion Cu(II) and as ligands with biguanide or triazolopyrimidine pharmacophore groups. The thesis purpose is to provide some insights concerning the design, synthesis and characterisation of this kind of species that proved valuable antitumor and antimicrobial properties.

The thesis is divided into three sections: (A) Scientific, academic and professional achievements, (B) Career development plans, and (C) References. Section A comprises two chapters that discuss the main scientific results as well as the main academic and professional achievements. The scientific activity is divided into two parts as follows: Main scientific achievements - general aspects (1.1) including that obtained during doctoral thesis and Scientific achievements presented in habilitation thesis (1.2). In this last part are developed aspects concerning two types of species: Complexes of Cu(II) with biguanides exhibiting biological activity (1.2.1) and Complexes of Cu(II) with 1,2,4-triazolo[1,5-*a*]pyrimidines exhibiting biological activity (1.2.2), and starts with the emphasis of the current scientific context concerning the importance of the addressed research areas.

The first research direction is focused on the design and characterisation of two series of Cu(II) complexes, with bidentate and tetradentate ligands, respectively having a biguanide scaffold in structure. The selections of these ligands is based on the presence of such moieties in the composition of some drugs, the varied biological activities highlighted in such species, as well as the possibility of

modulating this activity through coordination to Cu(II). These compounds were synthesised either by direct reaction of some Cu(II) salts with biguanide derivatives or by one pot method based on biguanide condensation with formaldehyde and ammonia or hydrazine. Complexes were characterised by a plethora of proper methods, including single crystal X-ray diffraction. In absence of structural data provided by this method, some complementary ones such as IR, UV-Vis, and EPR spectroscopy, cyclic voltammetry, thermal analysis as well as molecular modelling studies were used in order to obtain information concerning the complexes formulation and properties. These species were assayed on both planktonic and biofilm embedded microbial strains (Gram-positive, Gram-negative bacteria and fungi), as well as on some tumour cells (cervical (HeLa), and human colon carcinoma (HCT8) cell lines) and results indicated a good activity, especially for perchlorate derivatives. For these, the biological assays were accompanied by experimental or computational studies concerning the interaction with bio-species such as ROS or enzymes in order to gate insights concerning the potential mechanism of action or their drug-like bioavailability.

The purpose of the second research direction was the design and developing complexes with mixed ligands, a 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives and an auxiliary ligand (chloride, water, acetate, 2,2'-bipyridine or 1,10-phenanthroline). Two of these derivatives were also included in  $\beta$ -cyclodextrin in order to improve their bioavailability. The structural characterisation evidenced for compounds with N-based heterocycles an interesting supramolecular networks based on both hydrogen and  $\pi$ - $\pi$  stacking or CH- $\pi$  interactions. Another useful information were obtained through IR, UV-Vis (solid state and solution), and EPR spectroscopy, cyclic voltammetry, thermal analysis as well as by molecular modelling studies. This kind of species proved a good to very good antimicrobial activity, both against planktonic and biofilm embedded strains, including resistant ones. Moreover, the good anti-melanoma activity was achieved for majority of these species with the values of half maximal inhibitory concentration falling in micromolar range, and a favourable therapeutic index. This activity was related to their ability to generate ROS, to intercalate into DNA strands or to exhibit a metalonuclease-like activity. Furthermore, the most active compounds exhibit a low cytotoxicity on normal tissue.

In addition to very good activity evidenced for some species described in thesis, it is worth to mention that some of compounds where for the first time reported in the literature, related to the 16-membered octaaza macrocyclic ligand with biguanide units, cis configuration, two coordinated tautomers, species with 5-phenyl-7-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine, Cu(II) species as cocrystal with 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine and inclusion in  $\beta$ -cyclodextrin.

Section B of the habilitation thesis contains the development plan for the academic, professional and research career, while section C is represented by the list of references.