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A New Age for Iron: Antitumoral Ferrocenes

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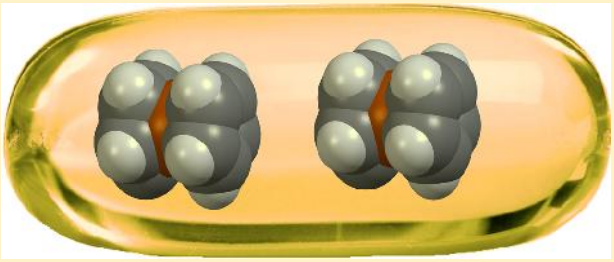
ABSTRACT: From the core of the earth to the core of the archetypal organometallic compound ferrocene, iron and its compounds contribute to create many aspects of our reality: the earth's magnetism, hemoglobin's respiratory function, and a myriad of life-essential biochemical reactions. This review deals with synthetic iron compounds from the literature, in particular ferrocene and derivatives, which are potential new anticancer agents. Cytotoxic ferrocenes are among the most promising metal-based drugs for cancer chemotherapy. There is a vast range of reported compounds, herein classified into three categories, according to their chemical nature and supramolecular organization. The first comprises ferrocenium salts and ferrocene derivatives, from simple functionalized ferrocenes to elaborate iron-based mimics of organic drugs, the second includes heterometallic complexes (with two or more metal centers), in which ferrocene has the role of an ancillary ligand, and the third comprises cytotoxic ferrocenes associated with carrier systems, namely aqueous-soluble polymers, multilayer micelles, and cyclodextrins.



INTRODUCTION

Iron has been an important element for mankind since the dawn of time. In the Iron Age, the dominion of iron shaping and smelting marked a strong technological advance in the society. Agriculture became faster and more advanced due to the higher resistance and stability of iron-made tools in comparison to the preceding copper tools, bringing economic growth and extra free time for developing and disseminating alphabetic writing,[1] for the arts, and for science.

Iron is regarded as the most stable element in the periodic table from a nuclear physics perspective, and it may very well be the last element to survive when our known universe collapses: the decay of all matter into iron by a process of cold fusion (in ca. 10^{1500} years) is postulated as a plausible path to the end of the universe. Still, one needs to look no further than the present moment to realize how versatile and essential to life iron is. From the ruling of the earth's magnetic poles to a myriad of biochemical reactions,[2,3] the ubiquitous iron shapes our inner and outer realities.

The sandwich compound formed by an iron center and two cyclopentadienyl ligands—ferrocene—is considered by many to be the archetypal organometallic compound. Its discovery[4] and structural characterization[5] in the early 1950s opened ground for the fast-blossoming chemistry of sandwich and half-sandwich metal complexes, marking an era that was called the renaissance of inorganic chemistry.[6] The high stability of the organometallic bonds in the ferrocene core (in nonoxidant media) make it an excellent building block, suitable for modifications using most of the procedures known for organic synthesis. Such ease and flexibility of chemical modifications afforded a rapid expansion of ferrocene chemistry, with over 3000 publications in the first 20 years after its discovery.[7] These have reported on new derivatives and their applications, first in catalysis and later on in materials science.[8]

The discovery of the cytotoxic properties of the ferrocenium cation,[9] the oxidized form of ferrocene which occurs in strongly oxidizing environments such as some intracellular media or by action of peroxidases,[10] in combination with the aforementioned versatility of ferrocene functionalization, have opened the way to the preparation and biological testing of a large variety of derivatives. Many of these ferrocene compounds are designed for antitumoral activity; others have found applications in varied medicinal areas or in diagnostics. The cytotoxicity of ferrocenium has also inspired the preparation of other cytotoxic iron compounds. Iron(III) semicarbazone complexes were demonstrated to inhibit the growth of cancer cells from the human esophagus,[11] and even iron oxide, in the form of superparamagnetic nanoparticles, has been proposed as a carrier in chemotherapy, helping to deliver antitumoral drugs by the use of magnetism.[12] Biomolecules containing iron are also under scrutiny as potential antitumorals. A good example is lactoferrin, a human protein of the transferrin family involved in a plethora of biological functions which include mucosal defense by antimicrobial activity. Its known range of action was recently expanded to include tumor growth inhibition. The mechanisms involve increased NK immune response, tumor angiogenesis blockage, and apoptosis.[13] All in all, iron compounds are, once again, at the spotlight of development of the society, this time bringing solutions for health care—it is a new Iron Age.

Special Issue: Ferrocene - Beauty and Function

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