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CHAPTER 33

Recent Synthetic and Biological Advances in Anti-cancer Ferrocene-Analogues and Hybrids

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Abstract: Cancer is among the most severe risks to the global human population. The enduring crisis of drug-resistant cancer and the limited selectivity of anticancer drugs are significant roadblocks to its control and eradication, requiring the identification of new anticancer entities. The stable aromatic nature, reversible redox properties, and low toxicity of ferrocene revolutionized medicinal organometallic chemistry, providing us with bioferrocene compounds with excellent antiproliferative potential, which has been the focus of persistent efforts in recent years. Substituting the aryl/heteroaryl core for ferrocene in an organic molecule alters its molecular characteristics, including solubility, hydro-/lipophilicity, as well as bioactivities. Ferrocifen (ferrocene analogues of hydroxytamoxifen) has shown antiproliferative potential in both hormone-dependent (MCF-7) and hormone-independent (MDA-MB-231) breast cancer cells. It is now in pre-clinical trials against malignancies. These entities operate through various targets, some of which have been revealed and activated in response to product concentrations. They also react to the cancer cells by diverse mechanisms that can work in concert or in isolation, depending on signaling pathways that promote senescence or death. The behavior of ferrocene-containing hybrids with a range of anticancer targets is explained in this chapter.

Keywords: Anti-proliferative Potential, Azide-alkyne Cycloaddition, Biological activities, Bio-organometallic, Bioferrocene compounds, Cancer, Cytotoxicity, Ferrocene compounds, Ferrocifen, Ferrociphenols.

1. INTRODUCTION

Organometallic chemistry and biochemistry have recently been combined to form a new subject known as bioorganometallic chemistry. This new research topic has piqued scientists' interest because of the unusual chemical structure and biological activity of organometallic compounds. These carbon-metal linkage compounds

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offer a potentially rich sector for the discovery of new pharmacological medicines with novel mechanisms of action, and the field is rapidly increasing. In recent years, there has been an increased interest in developing organometallic compounds as structural variants of existing drugs for treating drug resistance cancer [1]. Among the various organometallics, ferrocene [2], the archetypal organometallic compound, serves as a useful platform in bio-organometallic chemistry because of its important role in various fields, including stereoselective, stereospecific, and asymmetric transformations, electrochemistry, polymer chemistry, material science, biochemistry, crystal engineering, and drug design and development [3]. Ferrocene compounds are particularly appealing candidates for biological applications because of their durability in aqueous and aerobic settings, as well as the availability of a wide range of derivatives and outstanding electrochemical characteristics [4]. Ferrocene [5, 6] is a compelling target in fields like drug design mediators of protein redox processes, internal standards in electrochemistry, and organic synthesis, such as functionalization of cyclopentadienyl ligands, due to its sandwich-like structure and chemical representation $(\eta^5\text{-}C_5H_5)_2Fe$. In many ways, ferrocene is similar to benzene in that it behaves like an aromatic ring and conducts electrophilic reactions, including Friedel-alkylation, Craft's acylation, Vilsmeyer formulation, and mercuration reactions, which are all phenyl ring properties. Ferrocene derivatives with asymmetric substituents are extensively used as asymmetric hydrogenation catalysts [7]. Among organometallic compounds, ferrocene has a remarkable range of chemistry. Numerous studies have demonstrated ferrocene's efficacy *in vivo* and *in vitro*, as well as its potential as an anticancer, antimalarial, and antifungal agent [8 - 11]. The anticancer action of ferrocene-based compounds is linked to the oxidation state of the central iron atom. Only the ferrocenium salts with the central iron atom in the oxidation state of +3 have been found to exhibit anticancer activity. Incorporating ferrocene into bioactive compounds is a common technique in this field, with the most successful example being its incorporation into tamoxifen, resulting in the potential therapeutic candidate ferrocifen, which has the unique property of being antiproliferative against both the MCF-7 (hormone-dependent) and MDA-MB-231 (hormone-independent) breast cancer cell lines [12]. Many studies have also shown that ferrocene analogues have the potential to treat a wide range of illnesses, including fungal/bacterial infections, malaria, HIV, and cancer. This chapter aims to keep researchers informed about recent advances in the synthesis and evaluation of ferrocene-containing bioactive pharmacophores, focusing on the structure-activity relationship (2015-2020).