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Ferrocene-appended pharmacophores: an exciting approach for modulating the biological potential of organic scaffolds

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Two exemplary contributions of organometallics in medicinal chemistry, ferroquine and ferrocifen, which exhibit excellent anti-plasmodial and anti-cancer activities, respectively, have opened a new field called medicinal organometallic chemistry. This field has been gaining significant interest due to the recent upsurge in ferrocene-linked organic frameworks with promising biological potential. The success of ferrocene is due to the sustained efforts by organic medicinal chemists and its inherent stability in air, heat and light, low toxicity, low cost and reversible redox properties. The replacement of the aryl/heteroaryl core with a ferrocene nucleus in organic molecules imparts a significant change not only in their molecular properties, such as solubility and hydro-/lipophilicity, but also improves the activities of bioactive compounds. Ferrocifen (ferrocene analogue of hydroxytamoxifen) possesses the remarkable feature of being anti-proliferative against both the MCF-7 (hormone dependent) and MDA-MB-231 (hormone independent) breast cancer cell lines. Accordingly, this review article is aimed at updating researchers on the recent developments (2014–18) on the synthesis and evaluation of ferrocene-containing bio-active pharmacophores with emphasis on their structure–activity relationship and mechanism of action.

Introduction

In recent years, organometallic compounds, which have at least one metal–carbon atom bond, have attracted extensive attention from scientists owing to their peculiar chemical structure and biological activities.[1] Among them, ferrocene,[2] which has a sandwich-like molecular structure and chemical formula (η^5-$(C_5H_5)_2Fe$), has been found to be valuable in many areas, including catalytic stereoselective and asymmetric transformations, materials science, crystal engineering, bio-organometallic chemistry, electrochemistry especially in electron-transfer processes, biochemistry, organic synthesis, polymer chemistry, and drug design and development.[3] Ferrocene is also the safest fuel additive to date since it does not cause any environmental pollution and health-related hazards. It is has been reported that if it is used as a fuel catalyst for rocket propellant, it can improve the combustion speed, lower the temperature of exhaust pipes and avoid infrared chase. When used in diesel oil, heavy oil and light oil, it can eliminate smoke, save energy and reduce air pollution. The use of ferrocene has also been reported for the organometallic derivatization of biologically relevant molecules such as drugs and natural products.[4] For organic and medicinal chemists, natural products are a vast source for the discovery of new drugs *via* structural modifications, for which ferrocene has provided great opportunity. Owing to the favorable electronic properties of ferrocene and its easy functionalization, its applications have been explored in a wide range of scientific areas ranging from catalysis and the design of new nonlinear optic materials to new biologically active compounds.[5] Since its discovery in 1951, ferrocene has received continuous interest, partially due to the rich chemistry of its iron(II) centre, which can undergo facile oxidation, together with its stability in aqueous and aerobic media coupled with aromaticity.[6] The discovery of ferrocene has opened new avenues in chemistry, deepened our understanding of structure, bonding, and reactivity, and hence paved the way for the burgeoning field of organometallic chemistry.[6] Ferrocene, an orange crystalline solid, is diamagnetic in nature. Its high stability at room temperature, insensitivity towards air and water, and reversible redox characteristics make it the foremost choice as a starting material in the synthesis of various ferrocenyl derivatives. Furthermore, the access to a great variety of derivatives and its ability to undergo facile iron oxidation makes it a fascinating target in multiple fields such as electrochemistry, biochemistry, drug design

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