Schiff Bases: A Short Survey on a Promising Scaffold in Drug Discovery

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Hugo Schiff (1834–1915) was born in the vibrant Jewish community in Frankfurt/Main, Germany. He was a prominent chemist a century ago and he prepared a new class of organic compounds, which now have very wide applications, namely Schiff bases (SBs, imines or azomethines, Fig. 1, where R^1, R^2, R^3 = alkyl and/or aryl) [1]. Since then, SBs have attracted attention of inorganic, organic and medicinal chemists for a number of chemical and biological activities [2]. Their importance is underlined by the large number of scientific articles and reviews regarding these interesting compounds [3,4]. However, there is still some confusion with nomenclature in this research area, specifically in the structure of SBs. Compounds bearing R^3 as a substituted nitrogen atom are azo-SBs [5], but they are often named SBs [6,7].

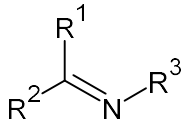

Figure 1. General structure of Schiff bases (SBs)

SBs are versatile pharmacophores showing different activities [8], such as anticancer [9,10], antimicrobial [11], analgesic, anti-inflammatory [12], antitubercular [13], anticonvulsant [14], antioxidant [15], anthelmintic [16], antiamoebic [17], antiparasitic [18], antimalarial [19], antidiabetic [20] and antiviral [21]. Recently, some SBs have also demonstrated activity against SARS-CoV-2 virus [22,23], the etiologic agent of COVID-19, the pandemic of worldwide proportion that has impacted our lives for the past three years [24]. Moreover, some SBs deriving from 4-aminoantipyrine and pyrazolone, have been suggested as potentially anti-Alzheimer drug candidates behaving as inhibitors of acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and tyrosinase

enzymes [25,26]. Recently, two SBs derivatives of silibinin have demonstrated higher solubility than the parent compound and improved hepatoprotective activity (anti-inflammatory and anti-apoptotic) compared to silibinin in CCl_4-induced acute liver injury experiments [27].

An important advance in medicinal chemistry has been obtained with coordination complexes of SBs with metals. Coordination complexes of SBs with metals generally exhibit much higher activity than the corresponding ligands, thus representing promising agents in several biological applications. Complexes of SBs with Mo, Cu, Zr, Pd, Pt, Ni, Ru, Mn, Zn, Nd, Ln and W have been widely studied for antimicrobial, antioxidant, antidiabetic, anticolitic and antiviral activities [28-30]. Doxovir (CTC-96; $[Co(acacen)(2\text{-methylimidazole})_2]^+Br^-$), Fig. 2), a SB-containing complex, has entered phase II antiviral clinical trial showing effectiveness against drug-resistant herpes simplex virus type I through the inhibition of membrane fusion events [31].

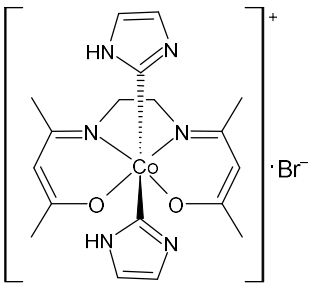

Figure 2. Structure of doxovir

The antiproliferative properties of complexes with SBs have been recently reviewed by our research group [32]. The antiproliferative activity is often related to DNA binding and cleavage [33]. The interaction with DNA involves the formation of hydroxyl free radicals in presence of oxidant H_2O_2 that participate in the oxidation of the deoxyribose moiety leading to hydrolytic cleavage of the sugar phosphate backbone. Xiong *et al.* (2020) [34] reported that complexes of SBs with metals exhibit higher nuclease activity than free base SBs. Moreover, complexation hinders the classical rapid hydrolysis and degradation to which SBs easily undergo in their aqueous solutions, involving the lone pair of electrons on the nitrogen atom [35,36]. Among the diverse complexes with SBs, promising results as anticancer agents were obtained for Co(II) and Co(III) SB complexes, as recently reviewed

by Kar et al. [37]. Recent important advancement deals with SB complexes with biologically compatible metal ions, Co(II), Cu(II), Zn(II), Pd(II), Ag(I), Pt(II), Ir(III) in photodynamic therapy to treat a number of tumors with fewer side effects [38,39].

Finally, and most importantly, the group of Aroua *et al.* [40] is focusing the attention on new studies based on the design of complexes as hybrids of SBs bridged with diarylureas for their antitumor activity obtaining interesting compounds also endowed with low *in vivo* acute oral toxicity. The anticancer activity exerted by the diarylurea sorafenib and its congeners is well-known [41]. The group of Aroua *et al.* [42] recently described the *in vitro* studies of some diarylurea bridged with SBs hybrids complexed with metals (Fig. 3). Copper complexes displayed excellent activity with IC_{50} values in the sub-micromolar range against prostate, ovarian, and cervical cancer cell lines, also showing good safety in *in vivo* toxicity tests. These studies may represent a very interesting starting point for the design of new hybrids of diarylureas and SBs as anticancer agents.

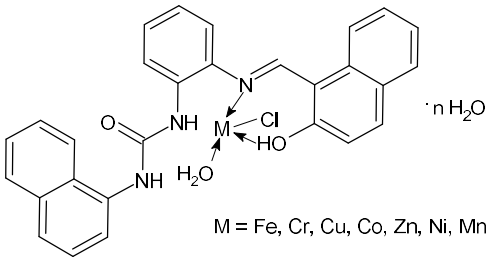

Figure 3. General structure of metal complexes of SBs described by Aroua *et al.* [42]

Moreover, being the diarylurea a versatile scaffold endowed with various biological activities [43-45], the design of such hybrids may be an intriguing idea to be suggested for obtaining new compounds with various activities including antibacterial, antiviral, antithrombotic, antimalarial, antioxidant, and anti-inflammatory, to fight against antimicrobial resistance and to curb new pandemics, that may arise in the near future.

In conclusion, SB represents a very intriguing scaffold, as free base or complexed with metals for numerous biological activities. However, despite the diverse preclinical studies described in the literature for this class of compounds, only few drugs have entered clinical studies. More in depth

studies on these interesting tools are required, in the search for new therapies for cancers and several other diseases.

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