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Ferrocenes in medicinal chemistry; a personal perspective

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ABSTRACT

We present a short review of some of our recent work mainly targeting cancer-related oncoproteins through the development of primarily novel air- and water- stable iron-based organometallic agents. This work was presented at the recent ISBOMC19 conference at York as an invited lecture.

Keywords:
Iron.
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Enzyme Inhibitors.

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1. Introduction.

The chemistry and history of ferrocene is well understood, spanning about 70 years and, recently, medicinal applications have come to the fore[1][2]. The aim of this mini-review is to highlight our work on the development of mostly ferrocene-based agents based on work covered over a period of approximately 10 years.

Air- and water-stable, metal-based complexes allow us to probe biological targets in ways we cannot achieve with carbon-based molecules. Metal incorporation can also alter the pharmacokinetics of a drug, benefiting from ligand-metal exchange reactions and enable unique modes of action, such as reactive oxygen species generation or photorelease, which can add to further DNA damage for example[3,4][5]. Much of this is covered in many excellent treatises[6–9][10]. Pioneering work by the Meggers group described the generation of highly selective kinase inhibitors with sub-nanomolar potency[11] by making use of the “hypervalent carbon” effect. In these examples, improved selectivity and potency were achieved by taking advantage of metal-based octahedral complexes, whereas similar carbon-based compounds, constrained by sp³ tetrahedral geometry, gave inferior biological activities. The literature abounds with examples of ferrocene-based bioactive molecules, including the following representative examples: Taxol analogue 1[12], a redox-active ferrocifen 2[13], carbonic anhydrase inhibitors, which were employed in cocrystal protein studies, e.g. 3,[14] and the antimalarial, ferroquine 4[15], which acts on chloroquine-resistant malaria (Figure 1). Compound 4 has advanced to Phase II clinical trials for malaria in combination therapy[16–18] whereas the ferrocifens are progressing towards clinical trials evidenced by the start-up compare Feroscan (https://www.feroscan.fr/team).
Finally, many ligands, such as the \( \eta^5 \)-bound cyclopentadienyl series, are rather large and the resulting steric clashes may drive selectivity and favour interactions in hydrophobic areas[19][20]. In this regard, we recently continued a very fruitful collaboration with colleagues at Lille-2 University, France, which focussed on the design of inverse agonists of the cannabinoid CB\(_2\) receptor, a well-studied G-protein coupled receptor (GPCR), as well as of ligands acting on fatty acid amide hydrolase (FAAH). [21–23][24] Our efforts culminated in a suitable illustration of aminoferrocene as a 3D-bioisostere of adamantylamine in CB2.
Fig. 2. Similar activity of bulky amide substituents vs a GPCR target.

Our ferrocene-based research efforts mostly concentrate on targeting cancer drivers through replacement of aromatic or heteroaromatic groups in small-molecule drugs or lead compounds by an “escape from flatland”[25] ferrocene group. Our initial studies involved generating analogues based around sunitinib[26], a marketed anti-angiogenesis inhibitor, which acts on a number of kinase targets (Fig. 3). We replaced the pyrrole side group in an oxindole derivative scaffold with a ferrocene moiety (Scheme 1).[27][28]

Scheme 1. Knoevenagel condensations on oxindoles.
During these early studies, we were effectively conducting “fishing” exercises with little structural or mechanistic know-how and conducting random kinase assay screens. Some of the compounds had submicromolar potency and the commercial assays were quite expensive, limiting our scope. Moreover, cell-based data such as GI\textsubscript{50} values, although useful, give little information on actual kinase inhibition as they might be due to non-specific action or toxicity. Nevertheless, the synthetic endeavours led to a number of new air- and water-stable organometallic complexes, many characterised in the solid state and synthesised by microwave-mediated chemistry.\cite{29,30,31}

Since this initial work, we have made a number of ferrocene-based molecules (Fig. 4). Many are oxindole derivatives, including the pentasulfanyl analogue, 8\cite{32}. Such SF\textsubscript{5} bioisosteres are becoming more prevalent in materials and medicinal chemistry\cite{33,34} and we expect them to be exploited more in bioorganometallic chemistry since they form an octahedral complex at sulphur, which is very amenable to X-ray crystallography and are useful as \textsuperscript{19}F NMR probes, and starting materials containing a SF\textsubscript{5} group are now more commonly available. Moreover, to test the steric limits of this inhibitor scaffold, we synthesised compounds 9\cite{35} and 10\cite{36}. Indeed, the mixed sandwich cobalt analogue 10 was too big to fit in even some of the largest kinase ATP pockets, a result that validated our predictive space filling model. In fact, in many
cases, similar docking studies utilising published kinase crystal structures were used to guide our design process. Compounds 11[37] and 12[38] were vaguely linked to Iressa[39] (Fig. 3) and a MnK12 inhibitor[40], respectively, and showed reasonable activities, although the desired ferrocene-based Mnk inhibitor failed to inhibit Mnk. It exhibited reasonable inhibitory activity in cells; however, this emphasises that caution must be made to avoid over-reliance on indirect cellular assays reporting phenotypic data such as GI50 (concentration needed to inhibit growth by 50%) values.
Fig. 4. Other kinase inhibitors made in our laboratory.

We were probably the first group to rationally design a metal-based analogue of SAHA, 13, a histone deacetylase inhibitor (HDACi), by using ferrocene as the aryl cap (Scheme 2, Fig. 5). We called the analogue JAHA and this was followed by a click-JAHA[41,42,43][44]. HDACis tend to comprise such a cap, a linker and a zinc binding group (ZBG)[45]. Reports of a gold-based HDAC inhibitor[46] and a dual action SAHA-cis platin-like hybrid[47] preceded our study. All JAHAs showed good HDAC inhibition, cellular activity and we were able to rationalise binding by docking studies. However, like many HDACis, they inhibited several HDACs and the quest for isoform-selective[48], even specific, inhibitors is desirable in terms of reducing off-target effects and in the development of chemical probe (or tool) compounds[49,50] for elucidating the role of each isoform in disease.

Scheme 2. Synthesis of JAHA.

The HDAC3 selective Pojamide 16[51] was synthesized in our laboratory. Related HDAC3 isoform-selective inhibitors have many uses in cancer and in the CNS[52][53][54]. The presence of the ferrocene moiety in 16 also affords us with the unique ability to generate a Fe(III) species in cells, adding ROS damage to HDAC3 inhibition.
Fig. 5. HDAC3 Selective Inhibitors compared with JAHA and SAHA.

Conclusions. We have had an interest in metal-containing analogues of bioactive molecules for over a decade. The area has significantly evolved since we started our work, with more rational design of complexes, greater synthetic scope and improvements in enzyme docking and X-ray crystallography techniques. With these advancements in the field also comes a better understanding of the pharmacokinetic parameters of these interesting bioactive molecules[55][56].

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