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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.
Ferrocene.
Antitumor activity.
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 sp^3 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).

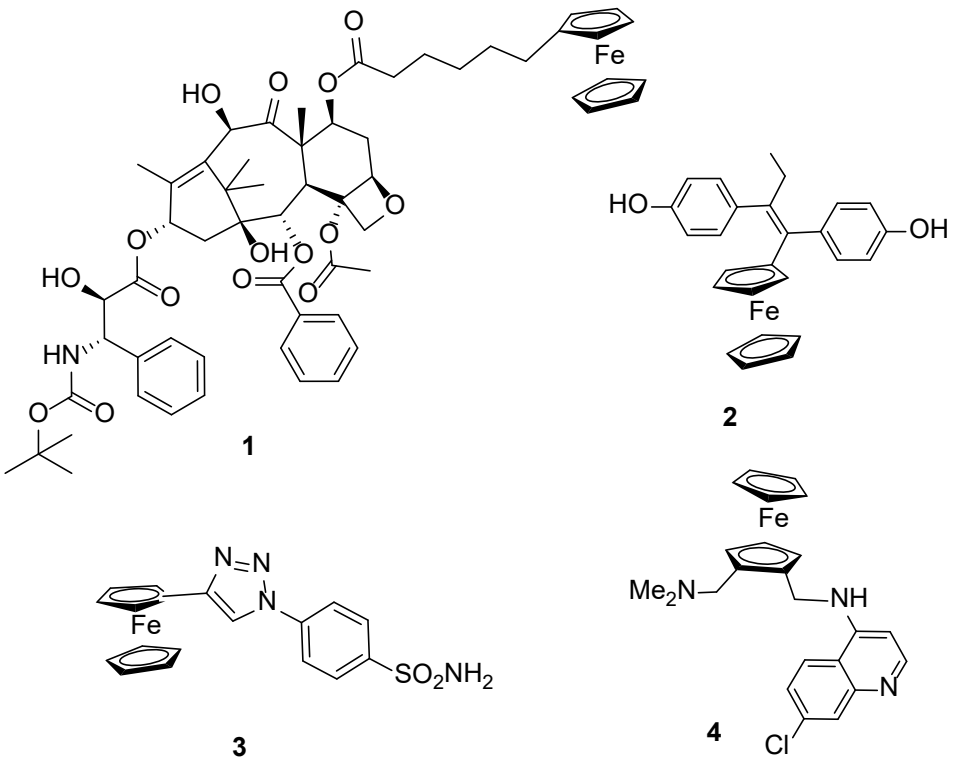


Fig. 1. Representative examples of ferrocenes in medicinal chemistry.

Finally, many ligands, such as the η^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 canabinnoid 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 adamantlyamine in CB2.

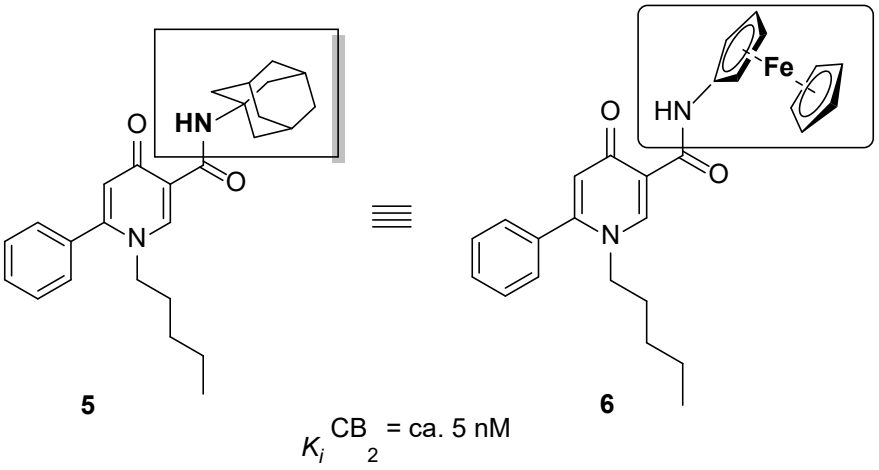
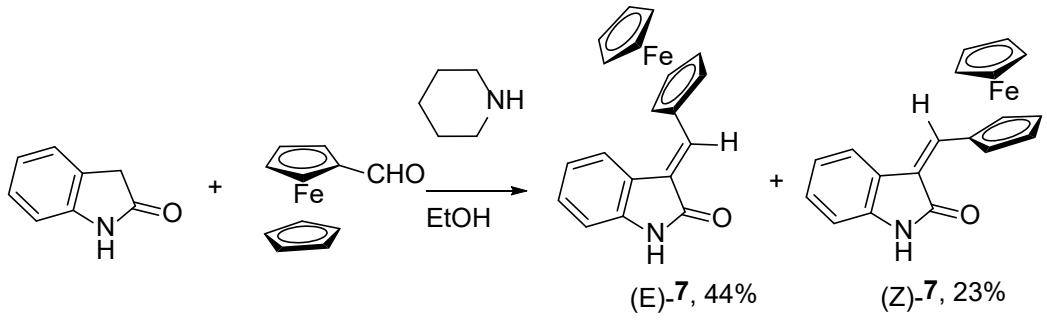


Fig. 2. Similar activity of bulky amide substituents vs a GPCR target.

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.

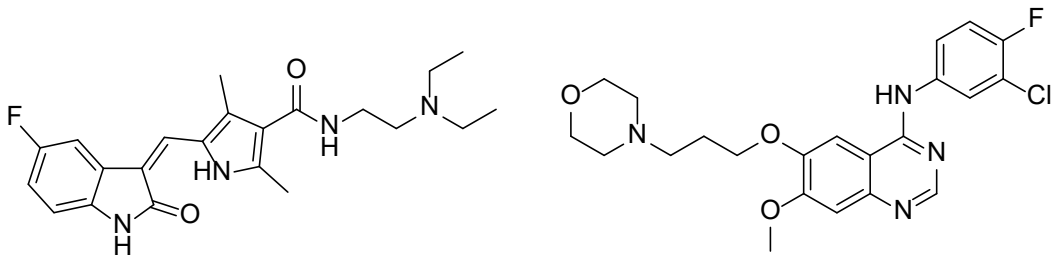
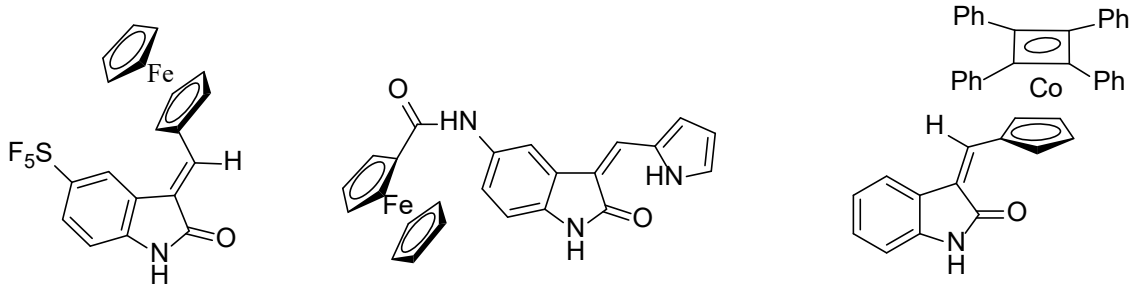


Fig. 3. Marketed kinase inhibitors.

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_{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.[29,30],[31]

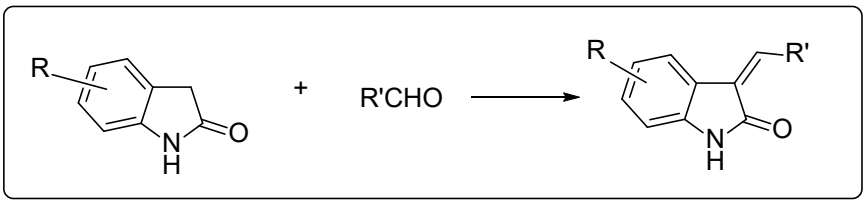
Since this initial work, we have made a number of ferrocene-based molecules (Fig. 4). Many are oxindole derivatives, including the pentasulfanyl analogue, **8**[32]. Such SF_5 bioisosteres are becoming more prevalent in materials and medicinal chemistry[33,34] and we expect them to be exploited more in bioorganometallic chemistry since they form an octahedral complex at sulphur, which is very amenable to X-ray crystallography and are useful as ^{19}F NMR probes, and starting materials containing a SF_5 group are now more commonly available. Moreover, to test the steric limits of this inhibitor scaffold, we synthesised compounds **9**[35] and **10**[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

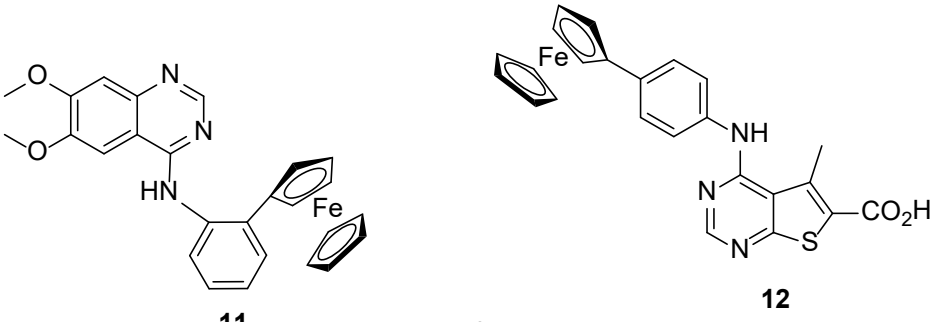
cases, similar docking studies utilising published kinase crystal structures were used to guide our design process. Compounds **11**[37] and **12**[38] were vaguely linked to Iressa[39] (Fig. 3) and a MnK12 inhibitor[40], respectively, and showed reasonable activities, although the desired ferrocene-based 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 GI_{50} (concentration needed to inhibit growth by 50%) values.



8 **9** **10**

via:





11 **12**

via:

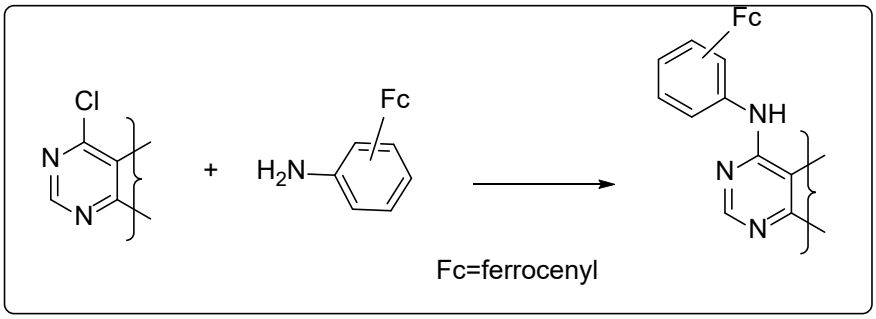
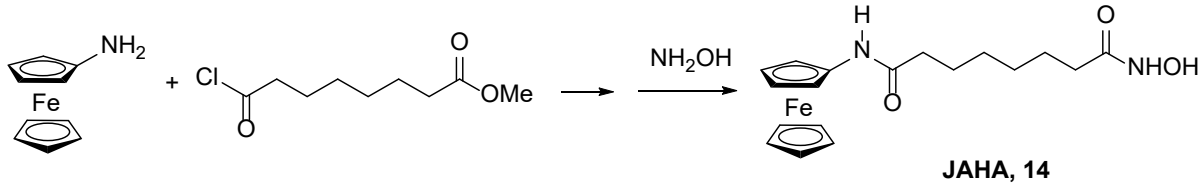


Fig. 4. Other kinase inhibitors made in our laboratory.

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**[41,42,42,43],[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.



JAHA, 14

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.

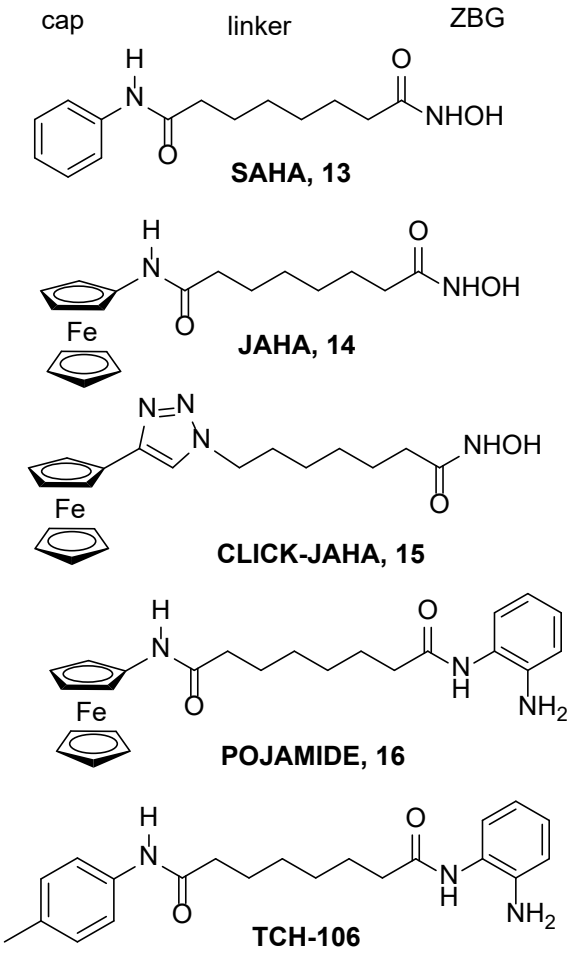


Fig. 5. HDAC3 Selective Inhibitors compared with **JAHA** and **SAHA**.

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].

Acknowledgements

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