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Metal complexes as structural templates for targeting proteins

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This article reviews recent advances in the design and discovery of inert metal complexes as protein binders. In these metal-based probes or drug candidates, the metal is supposed to exert a purely structural role by organizing the coordinating ligands in the three dimensional space to achieve a shape and functional group complementarity with the targeted protein pockets. Presented examples of sandwich, half-sandwich and octahedral d^6-metal complexes reinforce previous perceptions that metal complexes are highly promising scaffolds for the design of small-molecule protein binders and complement the molecular diversity of organic chemistry by opening untapped chemical space.

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Introduction

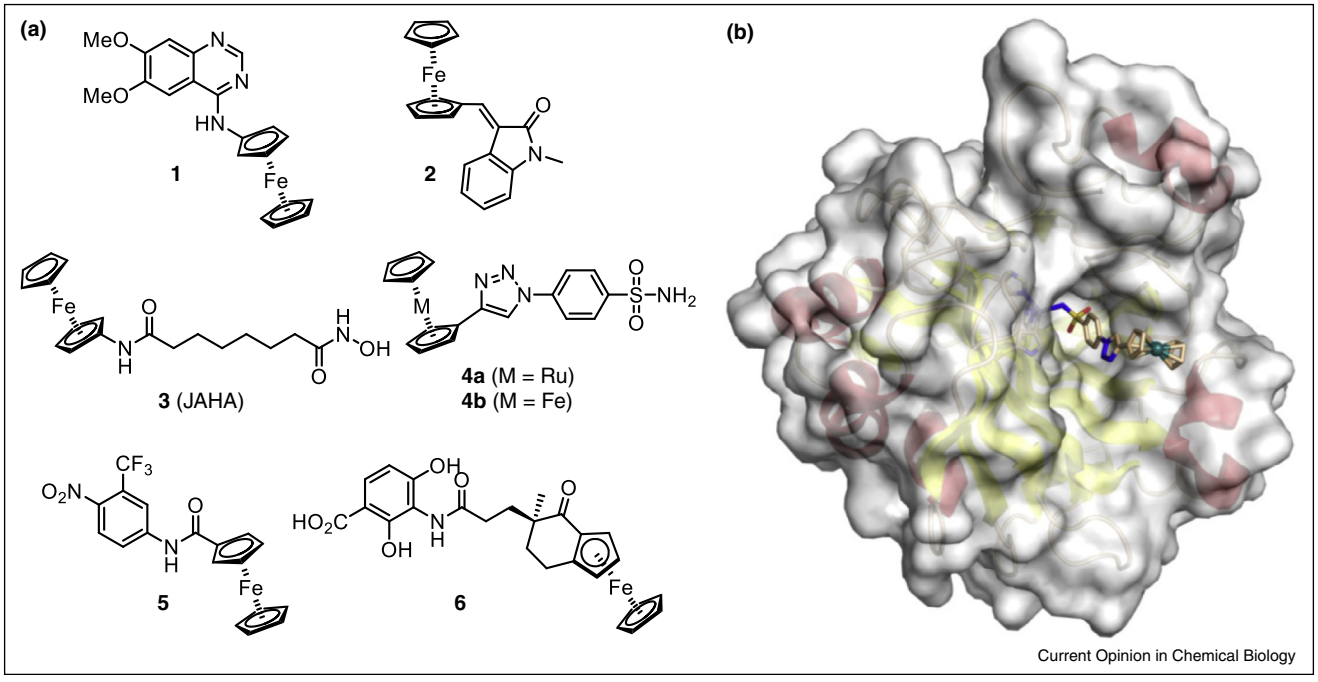
More than half a century after the pioneering work of Dwyer on the investigation of biological activities — including enzyme inhibition properties — of substitutionally inert transition metal polypyridyl complexes, the utilization of metal complexes as inert templates for the design of protein binders has blossomed over the last several years [1]. Traditionally, the design of protein binders (e.g. enzyme inhibitors) for applications in drug design and as molecular probes in chemical biology has focused on purely organic scaffolds, whereas metal-containing compounds predominately found applications for their nucleic acid binding properties (e.g. metal complexes as DNA intercalators), their reactivities (e.g. DNA-reactive Pt-drugs) and physicochemical properties (e.g. Gd-based MRI contrast agents). However, it has been increasingly recognized over the last decade that metal complexes offer untapped opportunities for building structures with unique three-dimensional shapes, thus complementing molecular diversity created by purely organic scaffolds [2–5]. Since in the absence of any reactivity it is the shape and functional group arrangement of a compound that determines its biological properties through the molecular recognition of biological macromolecules, the population of unexplored and unique chemical space with the help of a structural metal promises to promote the discovery of compounds with unprecedented biological properties.

This short review summarizes recent developments in the design of metal-templated protein binders in which the metal is supposed to exert a purely structural function. Although reactive, catalytic and photoactive features of metal complexes offer additional opportunities for achieving desired biological activities [6–8], such (photo)-reactive metal complexes are beyond the scope of this review. Because of space limitations we will focus on inert d^6-metal complexes with sandwich, half-sandwich and octahedral coordination geometries, whereas square-planar systems will not be covered here [9,10].

Protein-binding sandwich complexes

The last few years have witnessed many interesting studies revolving around the design of ferrocene-based enzyme inhibitors by using organic inhibitor scaffolds or drugs as a starting point and inspiration for the design of bioactive organometallics. Correspondingly, the Spencer group reported a number of studies in which ferrocene was used as bioisostere for aryl groups. For example, the ferrocenyl quinazoline compounds (e.g. **1** in Figure 1a), derived from the clinically applied organic quinazoline anticancer drugs erlotinib and geftinib, inhibit the epidermal growth factor receptor (EGFR) kinase with low micromolar IC_{50} values [11], whereas oxindole containing ferrocenes such as **2** were inspired by organic oxindole kinase inhibitor drugs, serve as inhibitors of the protein kinases DYRK3-4 and VEGFR2, and reveal antiangiogenic properties in *Xenopus* embryos [12]. On the other hand, some oxindoles bearing very bulky metallocenes exhibit very poor kinase inhibition properties, most likely due to their inability to fit into the ATP-binding pocket of protein kinases [13]. In a related strategy, Spencer designed a ferrocene-based histone deacetylase (HDAC) inhibitor, so called JAHA (**3**), by replacing the phenyl group of the clinically used HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) with a ferrocenyl group [14•]. According to docking experiments with histone deacetylase 8 (HDAC8), the organometallic JAHA — in analogy to SAHA — coordinates with its hydroxamic acid moiety in a bidentate fashion to a catalytic zinc ion at the bottom of the active site, whereas the ferrocene moiety is located at the entrance area of the pocket where

Figure 1



Recently developed metallocene complexes as enzyme inhibitors.

sufficient space is available to accommodate the bulky metallocene moiety. A small library of ferrocenyl derivatives of SAHA was tested against class I and II HDACs and revealed potent IC_{50} values down to 90 pM, thereby demonstrating the excellent potential of JAHAs as bioorganometallic probes for HDACs. Spencer recently also reported conformationally more restricted ferrocene-containing hydroxamic acids synthesized through Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition (''Click-JAHAs'') [15]. Click chemistry, among other synthetic methods, was also used by the Poulsen group to access a large number of sulfonamides functionalized by ferrocene, ruthenocene, and ruthenium(II) pentamethylcyclopentadienyl benzene sandwich complexes as potent carbonic anhydrase inhibitors [16–18]. Interestingly, the nature of the metal was demonstrated to significantly impact the binding affinity as revealed for the ruthenocene complex **4a** which, with a K_i value of 9.7 nM for human carbonic anhydrase II (hCA II), is by almost one order of magnitude more potent than the analogous ferrocene derivative **4b** (K_i = 80 nM). A co-crystal structure of hCA II in complex with the metallocene inhibitors **4a**,**b** reveals a coordination of the deprotonated sulfonamide to the catalytic zinc ion in the active site with the ruthenocene moiety undergoing a number of van der Waals interactions with residues of a hydrophobic area of the upper active site region (Figure 1b) [19•]. The Jaouen group designed organometallic derivatives of non-steroidal antiandrogen drugs by replacing aliphatic moieties of the drugs flutamide and bicalutamide against the significantly more space-demanding ferrocene (e.g. **5**) [20], thereby significantly diminishing the affinity for the androgen receptor, which is most likely a result of the high steric demand of the ferrocenyl moiety. Metzler-Nolte and coworkers used the antibiotic platensimycin as an inspiration for the design of a planar chiral ferrocene-containing bioorganometallic **6** [21]. Although the compound failed to show antibacterial activity up to 200 μg/mL, which might be due to a poor cellular uptake, modeling suggests that the bioorganometallic **6** fits nicely into the active site of the platensimycin target enzyme FabF with the fused ferrocenyl moiety occupying an area similar to the fused tetracyclic cage of platensimycin.

Ferrocene and other metallocenes adopt sandwich structures that are absent from the organic structural repertoire and therefore expand upon the chemical space that is spanned by purely organic compounds. However, it is important to emphasize that redox chemistry must always be taken into account when evaluating the biological mode of action of ferrocene-based compounds. In a particularly instructive example with the family of ferrocifen organometallics, which are ferrocenyl derivatives of a hydroxylated metabolite of the anticancer drug tamoxifen, the group of Jaouen developed one of the most prominent ferrocene-based anticancer complexes. Interestingly, in contrast to hydroxytamoxifen which binds with high affinity to the estrogen receptor on tumor cells,