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Cobalt derivatives as promising therapeutic agents

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Inorganic complexes are versatile platforms for the development of potent and selective pharmaceutical agents. Cobalt possesses a diverse array of properties that can be manipulated to yield promising drug candidates. Investigations into the mechanism of cobalt therapeutic agents can provide valuable insight into the physicochemical properties that can be harnessed for drug development. This review presents examples of bioactive cobalt complexes with special attention to their mechanisms of action. Specifically, cobalt complexes that elicit biological effects through protein inhibition, modification of drug activity, and bioreductive activation are discussed. Insights gained from these examples reveal features of cobalt that can be rationally tuned to produce therapeutics with high specificity and improved efficacy for the biomolecule or pathway of interest.

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Introduction

The clinical success of inorganic drugs, such as platinum(II) chemotherapeutics and gold-containing antiarthritic agents, has significantly advanced the use of transition metals in medicine in recent years [1,2]. Numerous transition metals (including cobalt) can adopt a wide variety of coordination numbers, geometries, oxidation states, and ligand binding affinities that can be exploited in the development of innovative therapeutic drugs [2,3,4••]. Despite their well-known versatility, cobalt derivatives have not been studied extensively as inorganic pharmaceuticals as compared to other metals. To date, the only cobalt-based therapeutic that has reached clinical trials is Doxovir, a Co(III) Schiff base complex effective against drug-resistant herpes simplex virus 1 [5]. The mechanism of action of Doxovir, however, is not fully understood.

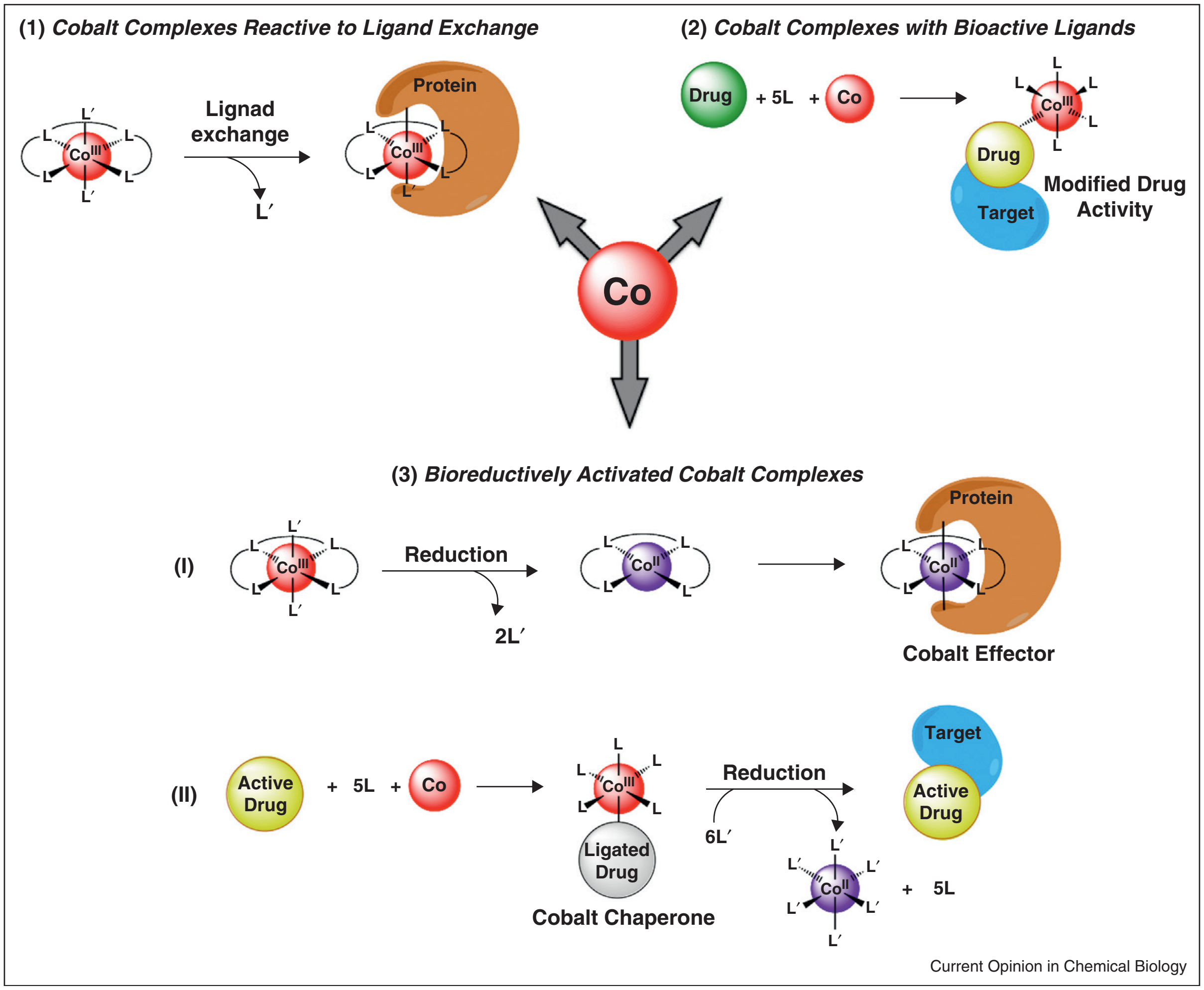
A substantial amount of literature on bioactive cobalt derivatives has been published in the last decade, demonstrating its rich potential in medicinal applications [6,7••]. However, the rationale behind the design and mechanisms of many of these agents has not been clearly elucidated. An understanding of how the unique properties of cobalt complexes interplay with biology to elicit therapeutic effects is clearly necessary for the development of cobalt-based drugs. To this end, we highlight recent articles that address the mechanisms of action of specific cobalt coordination complexes rather than surveying all the bioactive cobalt agents reported. Particular attention has been given to published examples wherein the effects of the physicochemical properties of cobalt are investigated to emphasize and understand the advantages of its use in therapeutic applications (Figure 1).

Cobalt complexes reactive to ligand exchange

The promising antiviral activity of Doxovir is attributed to the direct interaction of the Co(III) Schiff base complex with proteins involved in viral penetration [5]. While the exact mechanism of action of Doxovir is unknown, studies have suggested that this class of Co(III) complexes, $[Co(acacen)(L)_2]^+$, interacts with proteins by coordinating histidine (His) residues through a dissociative exchange of the labile axial ligands, L (e.g. L = 2-methylimidazole [2MeIm] in Doxovir) (Figure 2) [8,9].

Our lab has been investigating the application and mechanism of $[Co(acacen)(L)_2]^+$ as selective inhibitors of His-containing proteins wherein the axial ligands are labile ammines ($L = NH_3$) [8–12]. Conjugation of targeting molecules such as peptides or oligonucleotides to the ancillary acacen chelate improves the specificity of the cobalt complexes for His residues in the proteins of interest. Such conjugates have been recently shown to inhibit Cys_2His_2 zinc finger transcription factors with remarkable specificity, namely the Snail and Gli family of transcription factors associated with embryonic development and cancer progression [10–12]. Aberrant signaling by transcription factors has been implicated in the pathogenesis of diseases including cancer and inflammation and thus, such proteins are attractive drug targets [13,14]. In these examples, DNA sequences mimicking the native binding partners of the respective transcription factors were tethered to $[Co(acacen)(NH_3)_2]^+$ for target

Figure 1



Schematic representation of the different modes of action of bioactive cobalt complexes. Three classes of cobalt complexes are discussed: (1) complexes that directly act on biomolecules through ligand exchange, (2) complexes that modify the activity of ligated drugs and (3) complexes that are activated by bioreduction to either (I) yield a cobalt effector species or (II) release a small molecule drug.

selectivity. The conjugates were found to inhibit relevant pathways in *in vivo* embryo models and cancer cell lines [11•,12].

The mechanism of protein inhibition by [Co(acacen)$(NH_3)_2$]$^+$ has been investigated spectroscopically by employing model peptides of the zinc finger proteins (MC Heffern *et al.*, unpublished data and [8]). Significant changes in NMR ^{1}H resonances (>1 ppm) of His residues in the peptides were observed upon addition of [Co(acacen)$(NH_3)_2$]$^+$. Furthermore, CD, NMR and electronic absorption studies correlated axial Co(III)-His coordination to structural perturbation of the zinc finger motif, likely due to displacement of zinc in the tetrahedral binding site by the octahedral Co(III) complex. These results demonstrated that His is preferentially coordinated to [Co(acacen)$(NH_3)_2$]$^+$ and consequent perturbation of protein structure is likely to be responsible for the loss of activity.

In addition to zinc finger transcription factors, His-containing enzymes including thermolysin, α-thrombin and MMP-2 can be inhibited by [Co(acacen)$(L)_2$]$^+$ complexes [9,15,16]. Enzyme inhibition studies revealed that complexes with the most labile axial ligands (L = NH_3 or 2MeIm) exhibited the highest degree of inhibition [9]. Interestingly, analogous complexes with His mimics (such as imidazole and N-methylimidazole) as the axial ligands showed significantly lower inhibition [9]. We have recently correlated these observations with ligand exchange dynamics through spectroscopic and computational methods (LM Manus *et al.*, unpublished data; LM Matosziuk *et al.*, unpublished data). The lability of NH_3 and 2MeIm was attributed to a combination of pK_a