

Development of Hydroxypyridinones as Fe(II)/ α -Ketoglutarate-Dependent Dioxygenase Inhibitors

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Compounds featuring planar structures based on hydroxypyridinones (HPOs) are found to be efficient biological iron chelators and are effective in the treatment of iron overload resulting from frequent blood transfusions. In addition to allowing for oral bioavailability, the small size of HPOs facilitates enhanced interactions with the active sites of metalloenzymes.

The Fe(II)/ α -ketoglutarate (α -KG)-dependent dioxygenases constitute a family of proteins that are susceptible to inhibition by HPOs and other iron chelators. These non-heme iron enzymes catalyze the oxidation of C-H bonds in a variety of processes, including protein side-chain modification, DNA/RNA repair, biosynthesis of antibiotics, and the biodegradation of a variety of compounds. Two α -KG dioxygenases of considerable medical importance are prolyl 4-hydroxylase (P4H) and deoxyhypusine hydroxylase (DOHH). P4H catalyzes proline hydroxylation during collagen biosynthesis, while DOHH catalyzes the post-translational hydroxylation of a specific lysine residue in eukaryotic initiation factor-5a (eIF-5a), a protein translation initiation factor that is essential for sustained cell proliferation and is implicated in viral replication. P4H and DOHH represent attractive therapeutic targets in the development of antifibrotic and antiproliferative agents, respectively.

The studies presented herein examine the potential of HPOs as α -ketoglutarate (α KG)-dependent dioxygenase inhibitors on three levels: (i.) Small-molecule studies with iron coordination complexes as metalloprotein models are described that aim to answer questions about the inhibition mechanism of HPOs. (ii.) Activity studies of taurine dioxygenase (TauD), a well-characterized α -KG dioxygenase, are presented in which structure-activity relationships are analyzed based upon inhibitor structure and iron chelating ability. (iii.) Cellular studies are described in which HPOs are assayed for both antiretroviral and antiproliferative effects. Taken together, the experiments described herein will substantially expand the detailed understanding of HPO interactions with α -KG-dependent dioxygenases and will aid in the pursuit of novel therapeutics that target this class of proteins.