PROLYL HYDROXYLASE DOMAIN INHIBITOR STUDIES WITH SCORPIONATE COMPLEXES

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The availability of oxygen in mammalian cells is directly linked to an important transcriptional cascade that induces many responses to hypoxic conditions. These effects are caused by the hypoxia-induced transcription factor (HIF), which is responsible for the expression of hundreds of genes, including erythropoietin (EPO). The design of prolyl hydroxylase domain (PHD) inhibitors to activate the HIF signaling pathway has been a hot topic in medicine for the last two decades in order to exploit the beneficial aspects of the HIF system. The mechanism for inhibiting the catalysis of HIF-prolyl hydroxylation is based on its dependence on Fe^{2+} and 2-oxoglutarate. Knowing that N-oxalylglycine inhibits effectively by chelating the Fe^{2+} centre, further inhibitors with an isoquinoline lead structure such as FG-2216 (ICA) or BCA were designed and tested for their activity in cell experiments.[1-5] The mimicking of the active binding pocket of PHD2 by bis(pyrazo-1-yl)acetic acids and the binding of novel lead structures as possible inhibitors candidates plays a major role in our research. To discuss the coordination of PHD2 inhibitors in model complexes, the inhibitors FG-2216 and respective derivatives were coordinated to Fe^{2+}(**a**) and Ru^{2+}(**b**) complexes bearing bis(pyrazo-1-yl)acetic acids.

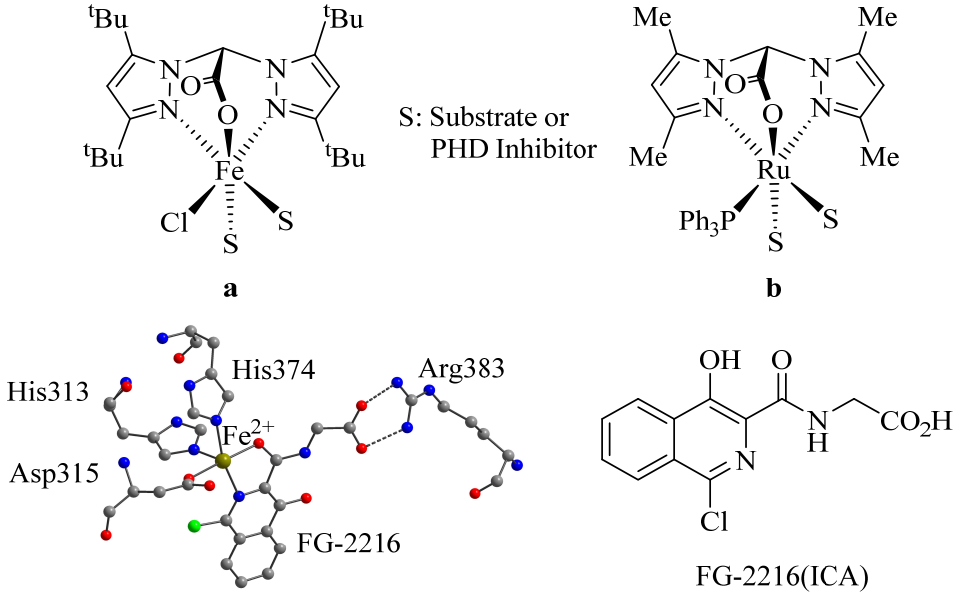

Figure 1: Active side of PHD2 binding site.

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