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Design of 3-hydroxypyridin-4-one chelators with high pFe^{3+} values

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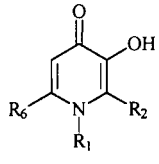
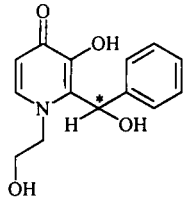
Regular blood transfusion can lead to iron overload and associated toxicity. Desferrioxamine (DFO) has been used to scavenge excess iron, however because of the inconvenient administration, we have attempted to identify an orally active, non-toxic and selective iron chelator. 3-Hydroxy-pyridin-4-one (HPO) chelators have currently been developed as an alternative to DFO (Tilbrook and Hider, 1998). CP20 (1,2-dimethyl-3-hydroxy-pyridin-4-one), is currently in clinical trials but has been found to be toxic to the bone marrow (Brittenham, 1992). Clearly there is potential for improvement.



HPO-Chelator



Novartis-compound

Recently, Novartis has produced a range of bidentate HPO ligands, which possess an aromatic ring at the 2-position. This aromatic substituent is reported to enhance the efficiency of these chelators (Ciba Geigy AG, 1996). We have also designed novel HPO compounds by introducing substituents on the HPO ring in order to stabilise the ionized species. Such substitutions influence the pK_a and pFe^{3+} values by decreasing the former and therefore increasing the latter, as shown in table 1.

Table 1. pFe^{3+}= -log[Fe^{3+}] when $[Fe^{3+}]_{total}=10^{-6}$ M and $[ligand]_{total}=10^{-5}$ M

Code	pK_{a1}	pK_{a2}	$\log\beta_3$ (Fe^{3+})	pFe^{3+} at pH 7.45
Novartis-compound	2.59	8.38	35.57	23.15
CP20	3.68	9.77	36.30	19.40
CP361	3.54	8.99	35.52	21.47
CP365	3.03	8.77	35.08	21.30
CP502	2.83	8.38	35.78	23.42
CP511	2.26	6.58	34.41	24.84

Thus at pH 7.4, CP511 binds to iron(III) over 10^5 times more tightly than CP20, the compound in current clinical use. Another advantage of increasing the pFe^{3+} value is that the 3:1 iron(III) complex is more resistant to partial dissociation under mild acidic conditions, such as those found in the lysosomes. These trends are made clear in figure 1. Under the conditions of the speciation study ($[Fe^{3+}]_{total} = 10^{-6}$ M and $[ligand]_{total}= 10^{-5}$ M), the 3:1 iron(III) complex of CP511 does not begin to dissociate until pH 4.5, in contrast CP20 begins to dissociate at pH 7.0 and at pH 4.5 the plot is dominated by the 2:1 iron(III) species. There is anxiety concerning the partial dissociation of iron complex of bi and tridentate ligands, as the non coordinated iron surface may interact with oxygen and hydrogen peroxide thereby generating hydroxyl radicals (Hider et al, 1996). Thus CP511 is predicted to be highly resistant to such prooxidant activity.

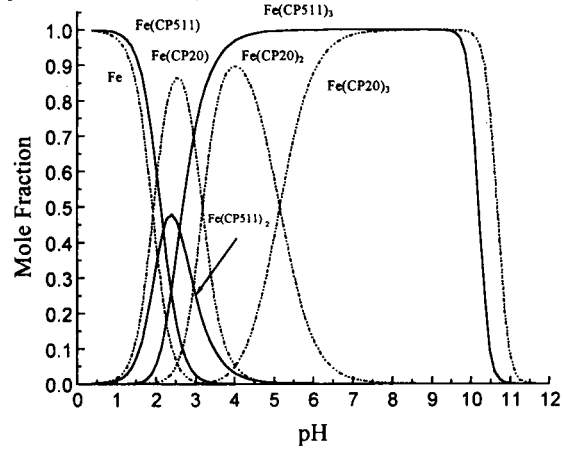


Figure 1. Comparison of the iron complex speciation plots with CP511 (————) and CP20 (—·—·—·—·); [Fe(III)]=10^{-6} M and [Ligand]=10^{-5} M.

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