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The design of low toxicity 3-hydroxy-pyridin-4-one iron chelators

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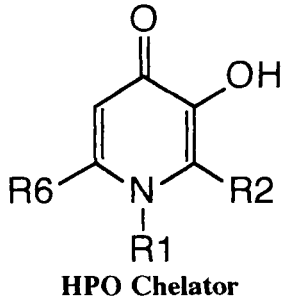
3-Hydroxypyridin-4-one (HPO) chelators form a class of orally active iron chelator which display high specificity and selectivity for iron(III) under physiological conditions. This class of chelators was developed as an alternative to desferrioxamine, the parenterally administered clinically available agent, for the treatment of transfusion-induced iron overload associated with thalassaemia. A ligand designed for this purpose should possess no inhibitory effect on the host iron-containing metalloenzymes such as 5-lipoxygenase (5-LO) and ribonucleotide reductase (RR). CP20 (1,2-dimethyl-3-hydroxypyridin-4-one), the HPO currently in clinical trials, inhibits both 5-LO and RR at a much faster rate than DFO [Abeysinghe et al (1996), Cooper et al (1996)]. Agranulocytosis which is observed in some patients treated with CP20 may be associated with the inhibition of these critically important iron metalloenzymes. Thus the design of a chelator which lacks such inhibitory properties is highly desirable.



HPO Chelator

This study is a structure / activity study in which we have attempted to identify an HPO chelator with minimal inhibitory properties towards the enzymes 5-LO and RR. To achieve this aim, a set of HPO chelators with different substituents were synthesised and their inhibitory influence towards the metalloenzymes, 5-LO and RR, was studied. The inhibition of RR was monitored using an indirect method based on the measurement of [^{3}H]-thymidine incorporation into DNA and a direct method involving the quantification of the ESR (electron spin resonance spectroscopy) signal of the enzyme tyrosyl radical. The inhibition of 5-LO was monitored by a direct spectrophotometric method which measures the rate of linoleic hydroperoxide formation by soybean lipoxygenase.

We have identified particular substituents which, when introduced on the HPO ring, introduce a steric factor which interferes with the accessibility of the chelator to the iron centre in the enzyme active site thereby abrogating the inhibition of 5-LO and decreasing the rate of RR and DNA synthesis inhibition (Figure 1). These findings lead to the identification of a chelator, CP358, which possesses minimal inhibitory properties towards both the iron containing metallo-enzymes, RR and 5-LO. This chelator was found to be more efficient than CP20 in mobilising iron from hepatocyte monolayer cultures. Furthermore, CP358 was found to induce apoptosis in both thymocytes and K562 cells at a much slower rate than CP20. Thus it is anticipated that this chelator will possess lower *in vivo* toxicity than the simple dimethyl chelator, CP20 while maintaining the ability to mobilise excess body iron.

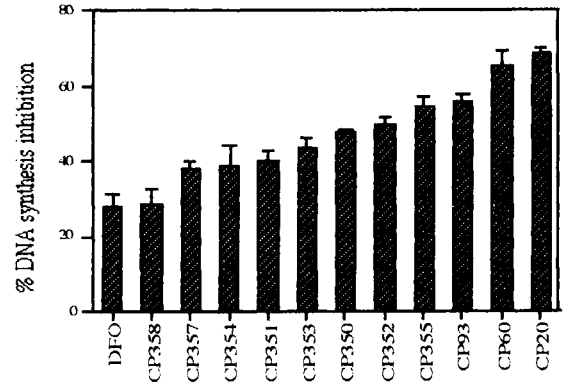


Figure 1: DNA synthesis inhibition by iron chelators at 330μM IBE (iron binding equivalents).

Abeysinghe, R.D., Roberts, P.M., Cooper, C.E., Maclean, K.H., Hider, R.C. and Porter, J.B. (1996) J.Biol.Chem. 271: 4965-4972.

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