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REPORT

Iron(III) Chelators and Thalassemia

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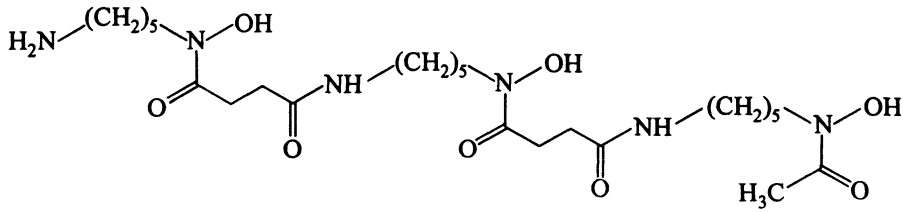
Despite the known fact that iron is necessary for life, it has its limitations too. The lower or higher concentrations of this metal in the body can be fatal if timely precautions are not undertaken. Transfusional iron-overload is one such type of problem which has affected tens of thousands of patients all over the world. Indians are also not untouched from this deadly disease. Around 10,000 thalassemics are born in the country every year. In this perspective, the present report deals with the introductory information regarding the role of iron chelators in the treatment of thalassemia which is also an iron-overload disease.

Key Words: Iron chelators, Anemia, Thalassemia, Desferrioxamine-B, Defeiprone.

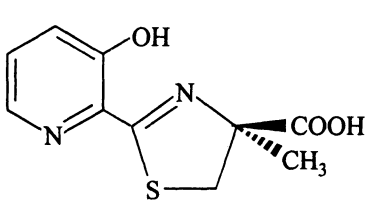
INTRODUCTION

Many microorganisms possess high affinity iron uptake systems mediated by the action of low molecular weight iron chelators termed siderophores (microbial iron transport compounds). Siderophores are produced by microorganisms in response to iron deprivation and are able to convert insoluble ferric hydroxide polymers into soluble chelates. Siderophores are generally classified as either phenolates or hydroxamates, although other siderophores not belonging to these classes have been isolated.

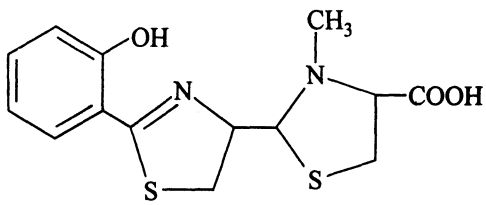
Desferrioxamine-B, a microbial iron chelator was isolated from *Streptomyces pilosus* and characterized by Bickel[1] in 1960. The chelator is currently used therapeutically in the treatment of thalassemia. It was first synthesized in 1962 by Prelog[2]. However, because of the number of steps in the synthesis and the low yield of the sequence, the method does not allow for the production of large quantities of the chelator or its analogues. Later, an efficient total synthesis of desferrioxamine-B has been reported by Bergeron and his co-workers[3] in 1988.



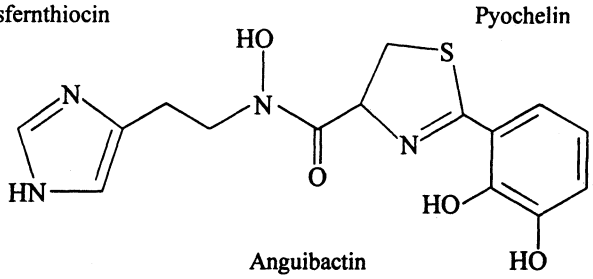
Desferrioxamine-B



Desfernthiocin



Pyochelin



Anguibactin

Desferrithiocin is a unique and unusual naturally occurring ferric ion chelator and was first isolated in 1980 from *Streptomyces antibioticus*[4]. Desferrithiocin has a similar affinity for iron as desferrioxamine-B. It has therefore been suggested that desferrithiocin and its analogues could have a potential in iron-chelation therapy[6,7].

Pyochelin, one of the smallest known phenolic siderophores, was isolated from *Pseudomonas aeruginosa*[8]. Its synthesis and biological activities are also reported in the literature[9].

Anguibactin, a novel siderophore, has been isolated from the iron-deficient cultures of a fish pathogenic bacterium, *Vibrio anguillarum* 775[10]. Anguibactin possesses an unusual molecular composition, $C_{15}H_{16}NaO_4S$, and shows significant structural differences with all known classes of siderophores. The structure of anguibactin has been well established in literature[11].

Iron Related Diseases

(i) Anemia is one of the most common known diseases, which is caused by the deficiency of iron in the body. Its treatment, however, by iron supplements is relatively simpler.

(ii) Iron-overload disease resulting from increased gastrointestinal absorption, *e.g.*, idiopathic heochromatosis, could also be easily treated by phlebotomy.

(iii) In contrast, transfusional iron-overload[12], which affects tens of thousands of patients with thalassemia, myelodysplasia/myelofibrosis, sideroplastic and aplastic anemia, etc., resulting in excessive deposition of iron in the tissues in the form of hemosiderin and, subsequently, damage to organs and eventually death unless iron is removed by a chelator.

Therapeutic Iron Chelators

At present, the treatment of transfusional iron-overload is carried out by desferrioxamine-B (Desferral, Ciba-Geigy), a linear trihydroxamate ligand, which forms a very stable hexacoordinate, octahedral[13] complex with Fe(III). The ligand

employs its three bidentate hydroxamate units in chelating the metal. Although desferrioxamine-B will bind a number of different trivalent metals, *e.g.*, Al(III), Ga(III), Cr(III), it exhibits a high specificity for Fe(III), and is utilized by *Streptomyces pilosus* for the acquisition of iron from the environment.

Because of the ligand's metal selectivity and low toxicity, it has been employed in the treatment of several iron-overload diseases, *e.g.*, thalassemia[14]. However, desferrioxamine-B does not offer a completely satisfactory solution to the iron-overload problem. The reasons are: (i) the drug is a very expensive one, (ii) it is not orally effective at all, (iii) the drug is cleared by the kidneys and has a very short half life in the body, and thus the patient must be maintained on constant infusion therapy, *i.e.*, administration of the drug by 8–10 h subcutaneous infusion daily with the aid of a pump, which is found to be a difficult and painful therapy.

Alternative Potential Ligands

To overcome the negative aspects associated with the only drug desferrioxamine-B, the investigators have explored the potential of other ligands as therapeutic iron chelators[12]. Iron-chelation therapy with DTPA (diethylene triamine pentaacetic acid) is also effective, but suffers from the depletion of other essential metals such as Mn and Zn. Hundreds of other iron chelators have been screened in animals for replacing desferrioxamine-B with a cheap oral drug, but very few have reached the stage of clinical trials, *e.g.*, 2,3-dihydroxybenzoic acid, rhodotorulic and cholyhydroxamic acids, and with disappointing results. The most promising iron chelators which are both orally active and cheap to synthesize are the α-ketohydroxypyridines.

Latest Development

Defeiprone or Kelfer, the first oral drug for patients suffering from thalassemia was launched[15] by its inventor Dr. George J. Kontoghiorghese at the All India Institute of Medical Sciences (AIIMS), New Delhi. This is the first drug which can be given orally and reduces the cost and pain associated with the treatment by 90 per cent. Dr. Kontoghiorghese is a medical scientist at London's Royal Free Hospital.

Despite desferrioxamine-B (Desferral) and defeiprone (Kelfer), the only drugs available for the treatment of iron-overload patients, it has remained an important research field to explore the potential of other ligands as therapeutic iron chelators.

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