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Synthesis, iron binding and antimicrobial properties of hexadentate 3-hydroxypyridinones-terminated dendrimers

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ABSTRACT

Macromolecular chelators have potential applications in the medical area, for instance, in treatment of iron overload-related disorders and in the treatment of external infections. In this investigation, several novel iron (III)-selective hydroxypyridinone hexadentate-terminated first and second generation dendrimeric chelators were synthesized using a convergent strategy. Their iron chelating ability was demonstrated by UV/Visible spectrometry and high resolution mass spectrometry (HRMS). The iron binding affinities were also investigated by the competition with a fluorescent iron chelator CP691. The result indicated that these dendrimers possesses a high affinity for iron with a very high pFe^{3+} value, which is close to that of an isolated hexadentate unit. These dendrimeric chelators were found to exhibit inhibitory effect on the growth of both Gram-positive and Gram-negative bacteria.

Although iron is an essential element for all living system, it is toxic when present in excess, as redox cycling between the two states of iron (bi- and tri-valent) in the presence of oxygen generates reactive oxygen species (ROS). ROS reacts with biological molecules such as nucleic acids, proteins, sugars and phospholipids, leading to tissue damage, organ failure, and eventual death.[1] This situation occurs in patents with iron overload diseases, such as β-thalassaemia, haemochromatosis and sickle cell anemia. The excess iron in principle can be largely eliminated by the use of iron-specific chelators. Indeed, to date three iron chelators, desferrioxamine B (DFO), deferiprone (DFP), and deferasirox (DFX) have been used in the treatment of chronic iron overload in patients.[2] Macromolecular iron chelators, such as dendrimers and polymers, have considerable potential as a supplement in this therapeutic approach.[3] They can effectively bind iron irreversibly to form nontoxic, kinetically inert complexes which are not absorbed by the mammalian gastrointestinal tract due to their large sizes, thereby reducing the absorption of iron from the intestine.[4] Iron is essential for the growth of almost all microorganism. Many microorganisms scavenge iron by secreting siderophores, which are strong iron chelators,[5] thus chelators with high iron affinities can in principle inhibit iron absorption of bacteria by the competition with siderophores for iron. A series of iron chelators have been demonstrated to markedly inhibit the bacterial growth.[6–13] Furthermore, combination treatment of an iron chelator with antibiotics, such as norfloxacin against *Staphylococcus aureus* and *Escherichia coli.*, was found to exhibit a dramatic synergistic bactericidal effect.[14] Thus, in principle, iron chelators, especially macromolecular iron chelators, could find promising application in wound healing and the treatment of other external sites exposed to infections associated with bacteria or fungi.[4]

As the result of our interest in the design and synthesis of clinically useful iron(III)-selective chelators based on hexadentate hydroxypyridinones, we previously reported the synthesis of a range of hexadentate hydroxypyridinone-based dendrimeric and polymeric chelators.[15–18] The particular attraction of dendrimers is that, unlike polymers, they have a unique molecular structure and are therefore amenable to precise quality control. To this end, herein we report the convergent synthesis, characterization and iron-chelating properties of a range of novel hexadentate 3-hydroxypyridinone-terminated dendrimers, and their inhibitory effect on the bacterial growth.

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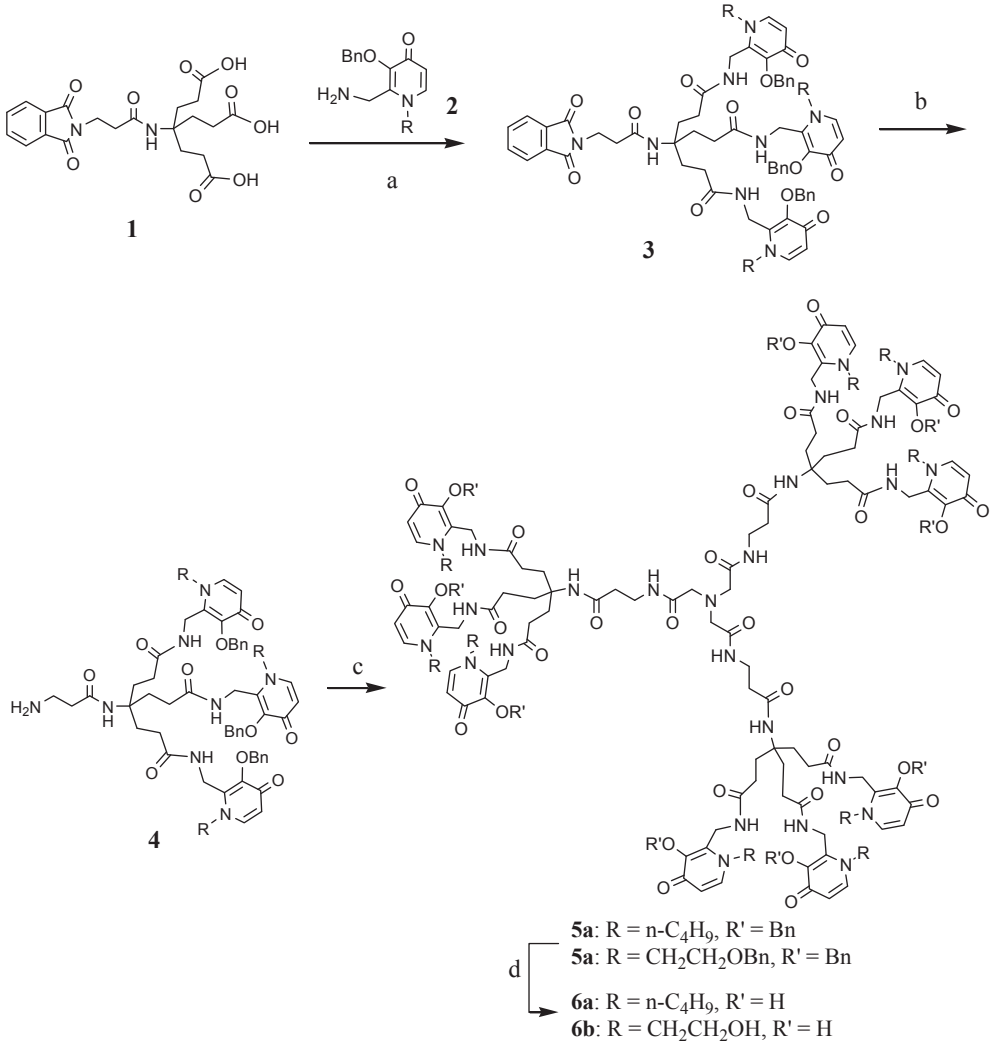

Scheme 1. Reagents and conditions: (a) DCC, HOBt, DMF, rt, 2d, yield: 78% for **3a** (R = *n*-Bu) and 64% for **3b** (R = CH_2CH_2OBn); (b) NH_2NH_2, reflux, 3 h, yield 95% for **4a** and **4b**; (c) NTA, DCC, HOBt, DMF, rt, 3d, yield 87% for **5a** and 90% for **5b**; (d) BCl_3, yield 95% for **6a** (HPLC purity 96.1%) and 96% for **6b** (HPLC purity 98.6%).

Divergent and convergent approaches are widely adopted strategies for the construction of dendrimers.[19] In this investigation, the convergent approach was employed to synthesize both the first and second generation dendrimeric chelators. The synthetic route of the first generation dendrimeric chelators (**6**) is presented in Scheme 1. Firstly, the benzyl protected hexadentate chelators containing the free amino group (**4**) were prepared by conjugating bidentate HPO with an aminomethyl group at position-2[12] with triacid **1**[18], followed by hydrazinolysis. Dendron **4** was then coupled to nitrilotriacetic acid via amide bonds in the presence of 1-hydroxybenzotriazole (HOBt) and 1,3-dicyclohexylcarbodiimide (DCC) in *N*,*N*-dimethylformamide (DMF) at room temperature, providing the protected dendrimer **5**. Deprotection of the benzyl groups on **5** was achieved by hydrogenation in the presence of palladium/charcoal, generating the first generation dendrimeric chelators **6**, which contain three hexadentate moieties. For the second generation dendrimeric chelators, the dendron **7** was firstly synthesized by the conjugation of **4** to triacid **1** using HOBt and DCC as the coupling agents (Scheme 2). Dendron **7** was respectively conjugated to di-acid **8** and tri-acid **11** in the presence of HOBt and DCC, providing protected second generation dendrimers **9** and **12**, which were treated with boron trichloride to generate second generation dendrimeric chelator **10** and **13** (Schemes 3 and 4). The final compounds were identified by NMR and HRMS, their purities were determined by HPLC.

The three 3-hydroxypyridin-4-one ligands with the 2-position groups attached to the same building block could effectively constitute one hexadentate ligand.[20] Thus, the dendrimeric chelators **6a** and **6b** effectively contain three such hexadentate moieties, whereas chelators **10** and **13** contain six and nine hexadentate centres, respectively. Their iron chelating ability was configured with UV/Visible spectrometry and HRMS.

Formation of 3-hydroxypyridinone-iron complexes can be monitored at the absorbance of 460 nm.[16] Thus, iron-binding capacity of the dendrimeric chelators was measured by the titration of these compounds with iron.[21] Titration solutions of the samples with iron (III) were maintained at room temperature for 2 h prior to the measurement of the absorbance at 460 nm in order to ensure the completion of binding process. In fact, kinetic studies indicated that these

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