



A new bis-3-hydroxy-4-pyrone as a potential therapeutic iron chelating agent. Effect of connecting and side chains on the complex structures and metal ion selectivity



Valeria M. Nurchi^{a,*}, Guido Crisponi^a, Massimiliano Arca^a, Miriam Crespo-Alonso^a, Joanna I. Lachowicz^a, Delara Mansoori^a, Leonardo Toso^a, Giuseppina Pichiri^a, M. Amelia Santos^b, Sergio M. Marques^b, Juan Niclós-Gutiérrez^c, Josefa M. González-Pérez^c, Alicia Domínguez-Martín^c, Duane Choquesillo-Lazarte^d, Zbigniew Szewczuk^e, M. Antonietta Zoroddu^f, Massimiliano Peana^f

^a Dipartimento di Scienze Chimiche e Geologiche, Università di Cagliari, Cittadella Universitaria, 09042 Monserrato-Cagliari, Italy

^b Centro Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal

^c Department of Inorganic Chemistry, Faculty of Pharmacy, Campus Cartuja, University of Granada, E-18071, Granada, Spain

^d Laboratorio de Estudios Cristalográficos, IACT, CSIC-Universidad de Granada, Av. de las Palmeras 4, E-18100 Armilla, Granada, Spain

^e Faculty of Chemistry, University of Wrocław, F. Joliot-Curie 14, 50-383 Wrocław, Poland

^f Dipartimento di Chimica e Farmacia, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy

ARTICLE INFO

Article history:

Received 2 June 2014

Received in revised form 3 September 2014

Accepted 3 September 2014

Available online 16 September 2014

Keywords:

X-ray structures

Iron chelators

Complex formation equilibria

Speciation

NMR

ABSTRACT

This work reports the synthesis, characterization and study of complex formation equilibria of the new ligand 6,6'-(2-(diethylamino)ethylazanediy)bis(methylene)bis(5-hydroxy-2-hydroxymethyl-4H-pyran-4-one) with Fe^{III}, Al^{III}, Cu^{II} and Zn^{II}. On the basis of previous encouraging results with tetradentate bis-kojic acid chelators, this ligand was designed to improve the pharmacokinetic properties: increase the solubility, neutral at physiological pH 7.4, and enhancement of membrane crossing ability. Fe^{III} and Al^{III} complexation gave evidence of high metal-sequestering capacity of L9. Cellular assays showed that the ligand is capable of crossing cellular membranes and it does not present toxic effects. Complex formation equilibria with the essential metal ions Cu^{II} and Zn^{II} have been furthermore studied to evaluate disturbances of this chelator on the homeostatic equilibria of these essential metal ions. A variety of techniques (potentiometry, UV–visible spectrophotometry, 1D and 2D NMR spectroscopy, ESI–MS (electrospray ionization–mass spectrometry), quantum mechanical calculations and X-ray diffraction) have facilitated the characterization of the ligand, and the corresponding iron and zinc complexes, together with an exhaustive analysis of the protonation and complex equilibria.

© 2014 Elsevier Inc. All rights reserved.

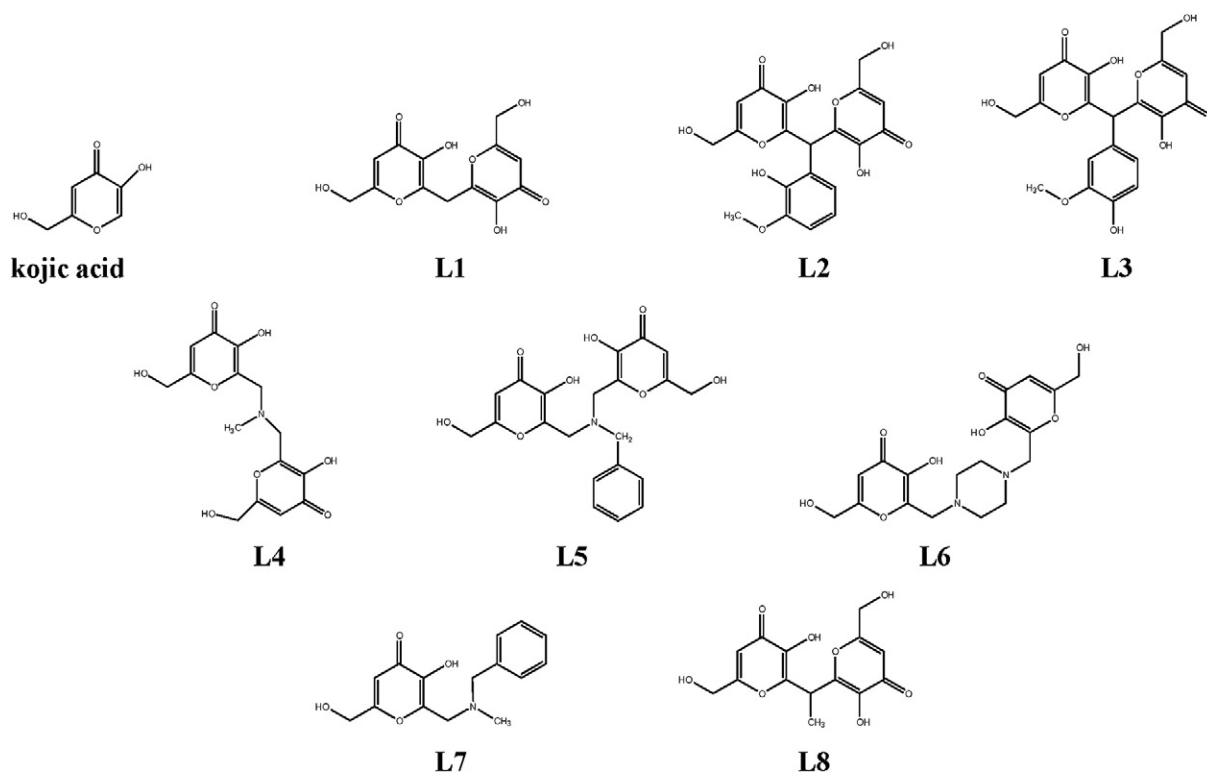
1. Introduction

In the frame of our research on chelating agents for iron and aluminium [1–6], a set of kojic acid (KA) derivatives were synthesized and the complex formation equilibria with these two trivalent metal ions were fully characterized [7–10]. The principal features of these ligands (Scheme 1) are i) the presence of two coordinating groups associated with two kojic units, heterocycles containing a pair of O-donor atoms due to a carbonyl and a vicinal hydroxyl group, which allow the ligands acting as tetradentate chelators (except KA and L7); ii) the formation of binuclear Fe₂L₂ and Fe₂L₃ complexes of high stability; and iii) the remarkable increase of iron binding affinity compared with the parent KA.

Literature search on iron chelating agents shows a preponderant interest, on one side, towards bidentate and tridentate chelators,

apparently due to the better adequacy of their characteristics to the requirements of an oral drug (permeability, molecular mass, etc.); on the other side, towards the not orally active hexadentate chelators, which form the most stable complexes. Archetypes of these ligands are those in clinical use for the treatment of iron overload in thalassemic patients, bidentate Deferiprone, tridentate Deferasirox, and hexadentate Desferal. Minor attention has been devoted towards tetradentate chelators, presumably because denticity two and three allow the formation of octahedral mononuclear complexes FeL₃ and FeL₂. However, by mimicking the natural rhodotorulic acid, a bis-hydroxamate siderophore [11], a number of tetradentate ligands have been proposed to date as potential Fe^{III} chelators, namely bis-hydroxamates [11], bisphosphonates [12], bis(3-hydroxy-4-pyridinone) [13], and a bis-(kojic acid) derivatives, similar to L1 and L8 (Scheme 1), recently proposed by Zhu et al. [14]. The molecular weight of these ligands is generally below the limit of 500 g/mol suggested by Lipinski's rule of five and pFe values are in the range 18–21. In order to completely fulfill the hexacoordination of

* Corresponding author. Tel.: +39 070 675 4476; fax: +39 070 675 4478.
E-mail address: nurchi@unica.it (V.M. Nurchi).



Scheme 1. Chemical structures of ligands KA, L1–L8.

ferric ion, the denticity of these ligands requires formation of polynuclear species, invariably found in these systems. In particular, the most common polynuclear complex is the dimer Fe_2L_3 , with a charge depending on the ligand structure. The tetradentate chelators we proposed display the following features:

- 1 The length of the linker and the molecular conformation do not allow that the ligand acts as a tetradentate ligand toward a single Fe^{III} ion; nevertheless, in all cases the tetradentate nature of the ligand favors the formation of dinuclear complexes Fe_2L_2 or Fe_2L_3 . In particular the complex of stoichiometry FeL_2 found with L1 and L8, of exceptionally higher stability than that of the corresponding FeL_2 complexes with KA and L7, should be better hypothesized as Fe_2L_4 . This complex should be structurally thought as a central Fe_2L_2 , further coordinated by one ligand on each iron through one KA moiety, satisfying its octahedral coordination.
- 2 The formation of Fe_2L_2 or Fe_2L_3 complexes seems dictated by the length of the linker. Linker constituted by a free or substituted methylene group (L1, L2, L3 and L8) allows two ligands bridging the two iron atoms, while a longer chain permits the formation of a helicate, in which three ligands completely satisfy Fe^{III} octahedral coordination. Similar Fe_2L_3 complexes are formed by the natural siderophores rhodotorulic acid and synthetic analogues [11].
- 3 The possible conformations related to the length of the linker are shown in Scheme 2: conformation 1, accessible when the length of the linker allows the tetradentate chelation on the same iron ion by the same ligand (bis(3-hydroxy-4-pyridinone)-IDA derivative) [13]; conformation 2, which is obtained with linkers too short with respect to the above requirements, but long enough to allow the formation of a helicate in which the three ligands completely satisfy the hexacoordination of the two iron atoms (L4, L5, and L6); conformation 3, in which a too short linker does not allow the formation of the above helicate (L1, L8).
- 4 These tetradentate chelators join the advantages of being small enough to allow membrane permeability (molecular weight (MW) < 500) and requiring, for complete iron hexacoordination, an

amount 1.5 times that of chelatable iron, i.e. between the value 1 for hexadentate chelators and 2 and 3 for tridentate and bidentate chelators, respectively.

We have synthesized a new ligand, 6,6'-(2-(diethylamino)ethylazanediyl)bis(methylene)bis(5-hydroxy-2-hydroxymethyl-4H-pyran-4-one), termed L9¹ (Scheme 3), similar to L4 and L5, and bearing a diethylaminoethyl group on the nitrogen atom in the linker, instead of methyl or benzyl groups, with the aim of improving the solubility and having a neutral molecule at pH 7.4. In the present work the characterization of this new ligand and of its Fe^{III} and Al^{III} complexes is presented. The study of the complex formation equilibria with the essential metal ions Cu^{II} and Zn^{II} , whose homeostatic equilibria could be perturbed by iron and aluminium chelation, is furthermore reported.

2. Experimental

2.1. Reagents

Kojic acid, *N,N*-diethyl-ethylenediamine, NaOH, KOH, FeCl_3 , ZnCl_2 , $\text{CuCl}_2\cdot\text{H}_2\text{O}$, AlCl_3 , methyl alcohol, and ethyl alcohol were purchased from Aldrich, formaldehyde from Merck, HCl from Fluka, KCl from Carlo Erba (Milan, Italy), and Desferal from Biofutura Pharma. All the reagents were used without any further purification. Carbonate free 0.1 M KOH solution was prepared as previously described [15]. The metal ion standard solutions were prepared by dissolving the required amount of chloride salts in pure double distilled water to which stoichiometric amounts of HCl were previously added to prevent hydrolysis. All metal solutions were standardized by EDTA titration, except the iron solution, which was standardized by spectrophotometric analysis as Desferal complex.

¹ L9 is a diprotic acid. In the formulae we will represent L9 as LH_2 , and L^{2-} for its completely deprotonated form.

Download English Version:

<https://daneshyari.com/en/article/1317266>

Download Persian Version:

<https://daneshyari.com/article/1317266>

[Daneshyari.com](https://daneshyari.com)