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Biotin-8-hydroxyquinoline conjugates and their metal complexes: Exploring the chemical properties and the antioxidant activity

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ABSTRACT

Metal dyshomeostasis and oxidative stress have been linked to numerous diseases such as Alzheimer's and Parkinson's diseases, cancer and so forth. Herein, we report the synthesis, chelating and antioxidant ability of two novel derivatives of biotin endowed with an 8-hydroxyquinoline moiety.

This family of chelators under study is potentially relevant in the treatment of diseases related to metal dyshomeostasis.

The biotin-8-hydroxyquinoline conjugates and their metal complexes with manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II) were characterized by several techniques such as NMR, ESI-MS and UV–Vis. Moreover, the capacity of these ligands and complexes to act as antioxidants was evaluated. The collected information may provide new insights and suggest further strategies for the development of 8-hydroxyquinoline derivatives for the control of metal dyshomeostasis and oxidative stress.

1. Introduction

8-Hydroxyquinoline (HQ) has attracted considerable interest as a privileged structure, and HQs have been explored for broad-ranging biological applications such as metal-chelators for neuroprotection, chelators of metalloproteins, inhibitors of 2OG-dependent enzymes, *Mycobacterium tuberculosis* inhibitors, botulinum neurotoxin inhibitors and anticancer, anti-HIV, antifungal, antileishmanial, antischistosomal agents [1–3].

The interaction of HQs with metal ions occurs during many important biological processes and therefore the coordination chemistry of these molecules plays a significant role. HQ is a bidentate chelator and binds copper(II) in a square-planar arrangement [4] with moderate affinity [5]. Similar coordination features have been found in the case of other metal ions such as zinc(II), cobalt (II), nickel(II) and manganese(II) [5].

Some of the main drawbacks of HQs as drugs are related to absorption, distribution, metabolism, excretion, and toxicity. For instance, 5-chloro-7-iodo-quinolin-8-ol, known as clioquinol (CQ), was associated with a wave of neurotoxic effects and was withdrawn from the market [6,7]. The explanation for such side effects is not clear, but many of these cases may have been related to the ability of CQ to function as a "carrier of heavy metals" to the central nervous system (CNS) or perturbing the homeostasis of vitamin B12 [8,9].

In order to overcome these disadvantages, HQ scaffold has been conjugated through a number of ways to neuropeptides [10,11], masking the chelation site with boronic ester [12] or sugar [13], or adding monoamine oxidase inhibitor functional groups [14]. Moreover, HQ moiety has also been attached to nanoparticles in order to improve selective permeability [15,16].

We have therefore undertaken a thorough study of HQ bioconjugates. In particular, we have designed and studied HQ glucosides and galactosides with significant antiproliferative activity in the presence of copper, and we have elucidated their mechanism of action [17,18] whereas trehalose and cyclodextrin conjugates have shown interesting antiaggregant and antioxidant properties [19–21].

This context has inspired us to synthesize new conjugates of HQ with biotin. The last one is a vitamin, also known as vitamin H, essential for metabolism, and it is widely distributed in the body [22]. Because of the extraordinarily high affinity of avidin or streptavidin for biotin [23], a host of biomolecules have been biotinylated, usually without significant loss of their biological properties and have been investigated for biomedical applications

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ranging from molecular biology, cell biology, biochemistry, analytical chemistry assays to clinical diagnosis and *in vitro* therapy [24–27]. More recently, attention has been directed to the use of biotin in the targeting of the sodium-dependent multivitamin transporter (SMVT) that is responsible for the transfer of the vitamins H and B5 into many cell types [28,29]. Interestingly, the interaction of biotin conjugates with SMVT improves the intestinal absorption and potentially enhances the bioavailability and therapeutic utility of the conjugating moiety [30].

Herein, we report the synthesis and characterization of two new HQ-biotin conjugates (Fig. 1). These systems were characterized with different techniques such as NMR, ESI-MS and UV–Vis. Moreover, their metal binding and antioxidant activity were also tested. Co^{2+}, Ni^{2+}, Mn^{2+}, Cu^{2+} and Zn^{2+} complexes of the new compounds were also characterized by ESI-MS, UV–Vis as these metals are suspected to be involved in several diseases [31,32].

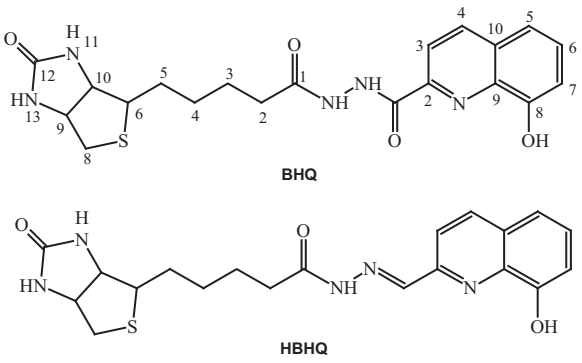

Fig. 1. Biotin-8-hydroxyquinoline conjugates.

2. Results and discussion

2.1. Ligands

BHQ was synthesized by an amide-coupling reaction starting from the biotin hydrazide and 8-hydroxyquinoline-2-carboxylic acid in the presence of typically used activating agents (Fig. S1) [33]. The product was isolated by silica flash chromatography. NMR spectroscopy and MS experiments confirmed the identity of the product. The ESI–MS spectrum of BHQ in methanol is essentially constituted by peaks due to singly charged monomeric (at *m*/*z* 430.0, 452.1 and 468.1 attributable to $[P+H]^+$, $[P+Na]^+$, $[P+K]^+$ ions) and dimeric ions (at *m*/*z* values 880.9 and 896.9 resulting from $[2P+Na]^+$, $[2P+K]^+$ ions). Since the low water solubility of this compound, NMR spectra (Figs. S2–S5) were recorded in DMSO-d_6. The signals of the conjugate in the ^{1}H NMR spectrum were assigned by 2D NMR experiments (COSY, TOCSY, HSQCAD, HMBCAD). ^{1}H NMR spectrum clearly displays the peaks resulting from biotin and quinoline protons (Fig. 2). In particular, aromatic protons of quinoline moiety resonate at lower fields in the aromatic region δ = 7.0–11.3 ppm whereas biotin protons show up in the region δ = 1.0–4.4 ppm except for the ureic protons at 6.3–6.4 ppm.

^{13}C chemical shifts of the carbon atoms of BHQ were unambiguously assigned through heteronuclear correlations (gHSQCAD and gHMBCAD). Carbonyl carbons resonate in the range 162–172 ppm, biotin carbons 25–62 ppm and HQ carbons 112–154 ppm, similarly to other HQ derivatives [34].

Since hydrazones constitute an important class of compounds for new drug development [35], a hydrazone conjugate of biotin with HQ (HBHQ) was designed and synthesized. Furthermore, hydrazones have been demonstrated to possess, among other, antimicrobial, analgesic, anti-inflammatory, antitubercular and antitumoral activities [35].

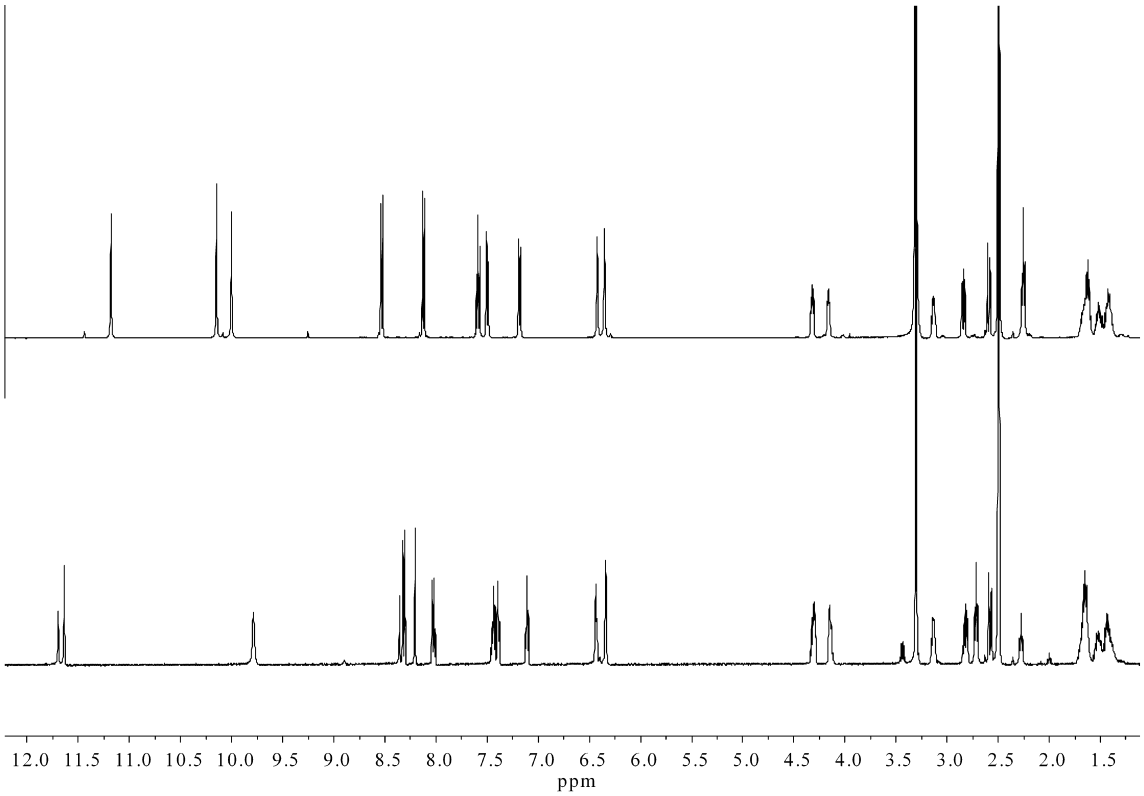

Fig. 2. NMR spectra of BHQ (top) and HBHQ (bottom) in $(CD_3)_2SO$ at 500 MHz.