Chinese Chemical Letters 27 (2016) 283–286

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Assessment of silver(I) complexes of salicylaldehyde derivatives—histidine Schiff base as novel α-glucosidase inhibitors

Jing-Wei Zheng *, Lin Ma

School of Chemistry and Chemical Engineering, Sun Yat-sen University, Guangzhou 510275, China

ARTICLE INFO

Article history:
Received 31 March 2015
Received in revised form 21 August 2015
Accepted 18 November 2015
Available online 13 December 2015

Keywords:
α-Glucosidase
Histidine schiff base silver(I) complexes
Type II diabetes mellitus

ABSTRACT

In this study, a novel class of histidine Schiff base silver (I) complexes derived from salicylaldehyde, **1a–9a**, was found to be an effective inhibitor of α-glucosidase. The results of this study showed that the newly synthesized complexes inhibited α-glucosidase through noncompetitive mechanisms; the IC_{50} values were ranging from 0.00431 μmol L^{-1} to 0.492 μmol L^{-1}. The structure–activity relationship was established as well. These results demonstrated that compound **7a**, 5-nitro salicylaldehyde Schiff base silver complex, is the most promising α-glucosidase inhibitor with the lowest IC_{50} value, which could be exploited as a drug candidate to alleviate postprandial hyperglycemia in the treatment of type II diabetes mellitus. This research provided a catalyst-free, simple, and environmentally benign reaction to synthesize compounds using mechanochemistry.

1. Introduction

Alpha-glucosidase (EC 3.2.1.20, α-D-glucoside glucohydrolase) plays a key role in the synthesis and processing of di-, oligo-, and polysaccharide chains of α-linked glycoproteins in the endoplasmic reticulum and in the metabolism of polysaccharides and glycoconjugates [1]. Thus, α-glucosidase has been considered as a treatment option for the regulation of postprandial hyperglycemia, which is caused by metabolic disorders that occur in type II diabetes mellitus (noninsulin-dependent diabetes mellitus, NIDDM). WHO projects that diabetes will be the seventh leading cause of death worldwide in 2030; type II diabetes comprises 90% of the diabetes population [2]. High blood glucose concentrations, abnormalities in glycoprotein metabolism caused by insulin resistance, impaired hepatic regulatory effects, and a decrease in glucose utilization are common symptoms in type II diabetes patients [3]. However, the postprandial increase in glucose and plasma insulin levels can be reduced by the inhibition of α-glucosidase activity, which is involved in oligosaccharide hydrolysis and intestinal glucose absorption [4]. By retarding the hydrolysis of the complex carbohydrates, postprandial glucose absorption can be subsided by controlling blood-sugar levels [5]. Alpha-glucosidase inhibitors are promising therapeutic agents, acting as mechanistic probes to reduce the rate of carbohydrate digestion, and will eventually alleviate the levels of postprandial blood glucose and insulin [6]. Thus, to date, α-glucosidase inhibitors have gained considerable attention for their implication in the prevention or treatment of type II diabetes mellitus.

Nitrogen-based heterocyclic organic molecules are an important class of inhibitors used in pharmaceutical chemistry because of the electron-donating characteristics of the nitrogen. The pharmacokinetic and bioavailability properties of the imidazole functional group in the protein histidyl residue derivatives have long fascinated researchers; they provide medicinal activities such as HIV-1 protease inhibitors [7], kinase inhibitors [8], cytochrome enzymes inhibitors [9], potent Jak2 inhibitors [10], phosphodiesterase inhibitors [11], diabetes and obesity drugs [12], and others. The imidazole ring was of interest because it contains two nitrogen atoms, one of which protonates at pH range 6–7 [13], providing more binding sites with a variety of enzymes and proteins, in addition to other electron-donor properties. Gluco-configured imidazoles and cellobiose-derived imidazoles have been synthesized as potential glycosidase inhibitors in the past [14]. The biological characteristics of Schiff bases have been well studied, including their antibacterial, antifungal, and anticancer properties. The presence of the *ortho*-hydroxyl group in salicylaldehyde, the

* Corresponding author.
E-mail address: zhengjnw@mail2.sysu.edu.cn (J.-W. Zheng).

http://dx.doi.org/10.1016/j.cclet.2015.11.015

azomethine (C=N) linkage in the Schiff-base, and the carboxylate group (COO^-) in the amino acids provide an electron-rich center to chelate with metal ions. At the same time, the metal ions stabilize the rigid structure of the unstable ligand [15]. Because of their interesting structural features as well as their biological activities, an attempt to research the transition metal complexes derived from amino acids has been reported [16–18]. Structural studies on the Schiff-base ligand metal complexes derived from various amino acids and salicylaldehyde have been well documented. Moreover, metal complexes of Schiff bases derived from salicylaldehydes and amino acids take part in a variety of biological processes and pharmaceutical fields, for example carboxylation, biological racemization [19], antibacterial and antifungal agents [13], and anticancer drugs [20]. Transition metal-based drugs have existed since the 1960s; for instance, platinum-containing drugs, cisplatin, carboplatin, and oxaliplatin, are known as the most widely used anticancer drugs. New metal complexes have been applied in the therapy and diagnosis of diabetes [21]. However, little effort has been expended to silver-based drug development. Silver(I) ions are known to have antimicrobial properties; normally, other biological activities are ignored. Silver(I) complexes derived from amino acid ligands are considered model complexes used to gain insight into the silver(I)–protein interactions [22].

In summary, silver(I) complexes of salicylaldehyde derived from histidine Schiff bases are worth researching as a novel class of α-glucosidase inhibitors; they demonstrate their potential usage in treating PPHG (postprandial hyperglycemia), which can provide a promising avenue for controlling or regulating α-glucosidase activity in order to treat or prevent diseases caused by metabolic disorders such as type II diabetes mellitus. In this study, in order to generate a novel, easily accessible, and high-affinity α-glucosidase inhibitor, we investigated the inhibition properties of complexes with the Schiff bases derived from salicylaldehyde for the first time and explored the inhibition mechanism further.

2. Experimental

2.1. Synthesis of silver(I) complexes (**1a–9a**)

The preparations of the histidine Schiff bases were carried out in the following general solid-state grinding procedure: 1 mmol amino acid, aldehydes and KOH were ground until finely blended in an agate mortar. Deprotonation of ligands becomes easier for the addition of KOH. The reactants were then placed in a microwave oven (500–800 W) for 5 min (grind 15 s min^{-1}). The reaction products were obtained, recrystallized, filtered under reduced pressure, washed with ethanol, and finally dried by the infrared light, with 70%–90% yield. All the amino acid Schiff bases are coloured solids and air stable for an extended period of time. They are soluble in water and DMSO at room temperature. All of them had melting points above 280 °C.

The newly synthesized Schiff base (0.1mmol) and silver acetate (0.1 mmol) were mixed also in an agate mortar. 2–3 drops of ethyl alcohol were added during the grinding. The reactants were then placed in a microwave oven (800 W) for 3 min (grind 30 s min^{-1}). The target complexes were obtained, recrystallized, filtered under reduced pressure, washed with 30%–50% aqueous ethanolic solution and finally dried over by the infrared light, with 70%–90% yield. The complexes are insoluble in water, sparingly soluble in ethyl alcohol and DMSO at room temperature, with solubility increasing with temperature. These compounds are also stable for a fairly long time at room temperature in the solid state. All of them the melting point are above 280 °C.

Referring to the coordination mode of azo-linked Schiff base Cu(II) [23], we hypothesized the common structure of complexes is **1a–9a**. Terdentate complexes were obtained upon reaction between metal ions and ligands at 1:1 molar ratio. The determined structural information needed further confirmation.

2.2. Bioassay procedures

2.2.1. Assay for α-glucosidase inhibitory activity [24] and [25]

The enzyme and the substrate solution was prepared by dissolving *Saccharomyces cerevisiae* α-glucosidase in 0.01 mol L^{-1} potassium phosphate buffer (pH 7). Diluted enzyme solution (10 μL), test samples (0.016–2 μL, in DMSO) and buffer solution (90 μL) were mixed in each well of a 96-well microtiter plate. After pre-incubating for 20 min at 37 °C, PNPG (10 μL, 1.5 mg mL^{-1}) was added to start the enzymatic reaction measured by a microtiter plate reader immediately. The increment of absorption at 405 nm is based on the hydrolysis of PNPG. Controls without enzyme or without substrate were included. The resveratrol was used as reference and averages of three replicates were presented. The inhibition percentage (%) was calculated by the equation: $[Abs_{sample}/Abs_{blank}] \times 100(\%)$, where Abs_{blank} represents the absorbance of the blank with the same volume DMSO.

2.2.2. Kinetic assay

The enzyme solution (10 μL), 0.01 mol L^{-1} potassium phosphate buffer, and test samples (2 μL, in DMSO) were mixed in a 96-well microtiter plate. After incubation at 37 °C for 20 min, PNPG (0.45–1.50 mg mL^{-1}) was added and measured by a microtiter plate reader at 405 nm straight away. The *X*-axis of Lineweaver–Burk plot is the reciprocal of the concentration of PNPG; the *Y*-axis is the reciprocal of the rate of enzyme reaction. All the experiments were carried out in triplicate.

3. Results and discussion

3.1. Inhibitory activity of α-glucosidase

In this paper, we disclose a simple, new synthesis of histidine Schiff base complexes; in the absence of an added solvent, two macroscopic solids interact directly (Scheme 1). The condensation of amines and aldehydes to azomethines in the solid state was recently reported to produce high yields at elevated temperatures. Grinding the solid aldehydes and amino acids together without the addition of a catalyst requires a liquid phase before the completion of the reaction, where a liquid melt would be observed [26].

In order to delineate the structure–activity relationship, and to get an optimized α-glucosidase inhibitor, salicylaldehyde was substituted with electron donating groups such as hydroxyl-withdrawing groups; electron withdrawing groups such as chloro and bromine groups were used in the synthesis of the histidine Schiff base complexes. Different numbers and positions of the substituents were also taken into consideration.

The structure–activity relationships of the compounds are shown in Table 1; all of the silver complexes demonstrated high activity with IC_{50} values ranging from 0.00431 μmol L^{-1} to 0.492 μmol L^{-1}. Compound 5-nitrosalicylaldehyde Schiff base silver complex **7a**, bearing a nitro group at the 5-position of the salicylaldehyde, was proved to be the most active with an IC_{50} value of 0.00431 μmol L^{-1}, showing 3000 times higher activity than the reference inhibitor **11**. However, most of the histidine amino acid Schiff bases **1–9** showed little inhibition. The inhibition screening results exhibited marked enhancement in activity with coordination of the silver ions against the α-glucosidase. This enhancement in activity can be rationalized on the basis of the structures of the ligands because it processes an additional azomethine (C=N) linkage that is important in the coordination of the silver ion. The polarity of the metal ion was reduced by