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Synthesis, crystal structures, molecular docking and urease inhibitory activity of nickel(II) complexes with 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole

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ABSTRACT

Three novel complexes, $[Ni^{II}(dpp)_2(L)_2]$ (**1**), $[Ni^{II}(eda)_2(L)_2]$ (**2**) and $[Ni^{II}(deda)_2(L)_2]$ (**3**) (L = 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole, dpp = 1,3-diaminopropane, eda = ethanediamine, deda = N,N-dimethyl ethylenediamine), were synthesized by reacting 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole with diamines and nickel(II) salt. The complexes were structurally determined by single-crystal X-ray diffraction. The inhibitory activity was tested in vitro against jack bean urease. Molecular docking was investigated to insert complexes into the crystal structure of jack bean urease at the active site to determine the probable binding mode. The experimental values and docking simulation exhibited that complexes **1**, **2**, **3** had better inhibitory activity than the positive reference acetohydroxamic acid, showing IC_{50} values of 48.16, 32.35 and 15.22 μM, respectively. These complexes exhibited inhibitory activities as potent urease inhibitor.

1. Introduction

The coordination chemistry of heterocyclic 1,2,4-triazole derivatives [1] has been a very attractive field of study in recent years, not only from an academic angle of vision but also because of some important applications arising from the correlation of these compounds with their wide biological significance and diverse pharmacological activities [2–4]. The cause of this widespread interest derives from several important properties of the triazole ligands. Because of the position of the donor atoms in the five-membered heterocycle, 1,2,4-triazole derivatives appear to possess the possibility of linking transition metal ions together. The triazole ligands thereby form a bridge between metal ions. Owing to this the triazole ligands form a bridge, depending on the donor atoms of the ligand and the properties of the metal [5]. With this bridging capacity, the 1,2,4-triazole ligands also show great coordination diversity, especially when the triazole nucleus is substituted with additional donor groups, which makes them very appealing for the design of new metal complexes with a broad spectrum of biological activities depending on the substitution pattern around the heterocycle.

Recently, some 1,2,4-triazole derivatives have been reported as urease inhibitors. A comprehensive report about the structure-based design and testing of a novel pharmacophore model for the recognition of urease inhibitors was envisaged by Zareen Amtul. Based on their model, 1,2,4-triazole-3-thiones came out to be the good structural requirement, which may behave as important pharmacophore for urease inhibition due to their structural similarity to the natural substrate of urease [6].

Urease (urea amidohydrolase EC 3.5.1.5) is an enzyme widely distributed in nature. It is synthesized by numerous organisms, including plants, animals and bacteria. Functionally, urease is a hyperactive enzyme which catalyzes the hydrolysis of urea to ammonia and carbon dioxide and responsible for providing organisms with urea as a nitrogen source [7]. Urease is the major cause of pathologies induced by *Helicobacter pylori* (*H. pylori*) as it allows the bacteria to survive in the extremely acidic environment of stomach during colonization [8–11]. Comparing the sequences of jack bean urease and bacteria urease suggests that these two different kinds of urease may have a common evolutionary origin [12]. Therefore, the catalytic site displayed highly conserved amino acid residues, jack bean urease and *H. pylori* urease may have the same catalytic mechanism. In addition, urease is known to be one of the

Abbreviations: L, 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole; dpp, 1,3-diaminopropane; eda, ethanediamine; deda, N,N-dimethyl ethylenediamine; DMSO, dimethylsulfoxide; DMF, N,N-dimethyl formamide; ADT, AutoDockTools; AHA, acetohydroxamic acid.

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major causes of pathologies induced by Helicobacter pylori that infects up to 50% of the world's human population [13]. In the infection it allows the bacteria to survive at low pH of the stomach and therefore could cause many gastroduodenal diseases such as gastritis, gastric and duodenal ulcers, and even gastric cancer [14,15].

Furthermore, heavy metal ions inhibit urease that nearly listed as urease inhibitors such as Ag^{+}, Cu^{2+} and Ni^{2+} ions [7,16–18]. This inhibition was described as slow binding [19,20] and has been habitually ascribed to the reaction of the ions with the thiol groups of urease, resulting in the formation of mercaptides [21–27]. Since 1,2,4-triazole derivatives were reported with urease inhibitory activity, many research groups had investigated the coordination chemistry between 1,2,4-triazole derivatives and transition metal [6,28]. Especially, synthesis and reactions of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles and its complexes had been the subject of a chapter in a review by Temple [29]. However, not many complexes in this class had been described with crystal structures and only very few studies on the urease inhibition activities had appeared in the literature.

In this research, 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole was prepared as ligand and then synthesized metal complexes with nickel(II) salts and organic diamines. Importantly, the discovery of our work is to find potential urease enzyme inhibitor [30–33]. Herein we reported three novel complexes crystal structures of $[Ni^{II}(dpp)_2(L)_2]$ (**1**), $[Ni^{II}(eda)_2(L)_2]$ (**2**) and $[Ni^{II}(deda)_2(L)_2]$ (**3**) (L = 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole, dpp = 1,3-diaminopropane, eda = ethanediamine, deda = N,N-dimethyl ethylenediamine), the complexes were structurally determined by single-crystal X-ray diffraction analysis. The inhibitory activity of all the obtained complexes was tested in vitro against jack bean urease. Docking simulation was investigated from the docking analysis using the AUTODOCK 4.2 program, performed to position the new complexes into the active site of urease to determine the probable binding mode. Importantly, we focused on finding more effective and potent urease inhibitors for structure–activity relationship research of the complexes **1, 2**, **3**, detailed investigations are continuing to study the toxicity of these Ni(II) complexes of urease inhibitory activity for the environment and humans. The wide range of biological activities associated with the metal complexes of 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole described by high-resolution X-ray crystal structures makes them an attractive class for the medicinal chemist [11].

2. Experimental

2.1. Materials

Urease (from *jack beans*, type III, activity 31660 units/mg solid), HEPES (Ultra) buffer and urea (Molecular Biology Reagent) were purchased from Sigma–Aldrich Co. (St. Louis, MO, USA). 1,3-diaminopropane, ethanediamine and N,N-dimethyl ethylenediamine were purchased from Aladdin and used without purification. All other chemicals and solvents were purchased from Aldrich and used as received. Distilled water was used for all procedures. IR spectra were recorded on a FT-IR Nicolet 5700 Spectrometer from 4000 to 400 cm^{-1}. The crystal date of trizole ligands and complexes **1, 2**, **3** were collected on a Bruker D8 VENTURE PHOTON diffractometer. UV–Vis spectra were measured on a Shimadzu UV-3600 spectrophotometer using DMSO–H_2O (1:1 v/v) solvents in the 500–200 nm range. The enzyme inhibitory activity was measured on a BioTek Synergy™ HT microplate reader.

2.2. General method for the preparation of the ligand and complexes

The ligand 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole was prepared through multi step reaction with isonicotinohydrazide as raw materials by using the method of Reid and Heindel [34] with suitable modifications [35] (Scheme 1). Isonicotinohydrazide reacted with carbon disulfide and potassium hydroxide in absolute ethyl alcohol yield potassium dithiocarbazinate, which later cyclized to 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole by reacting with hydrazine hydrate and then synthesized metal complexes with nickel(II) salts and organic diamines. The 1,2,4-triazole ligand (1 mmol) was dissolved in the solvent mixture (10 mL) of methanol and N,N-dimethyl formamide (DMF) (1:1 v/v), which was added to $Ni(NO_3)_2{\cdot}6H_2O$ (1 mmol) in methanol (5 mL), adding 1,3-diaminopropane, ethanediamine and N,N-dimethyl ethylenediamine(1 mmol) in methanol (5 mL), respectively. The resulting solution was stirred for 30 min at room temperature and then filtered. The filtrate was kept in air for about 7 days, forming crystals. The crystals were isolated, washed three times with distilled water and dried in a vacuum desiccator containing anhydrous $CaCl_2$.

2.2.1. $[Ni^{II}(dpp)_2(L)_2]$ (**1**)

Pink crystal, yield: 379 mg (68%). *Anal.* Calc. for $C_{20}H_{32}N_{14}NiS_2$: C, 40.62; H, 5.45; N, 33.16. Found: C, 40.74; H, 5.43; N, 33.23%. IR (KBr, cm^{-1}): 3310, 3244, 3112, 2920, 2867, 1602, 1550, 1454, 1349, 1072, 1009, 825, 693. UV–Vis [DMSO–H_2O (1:1 v/v), λ/nm (ε/M^{-1} cm^{-1})]: 224 (8100), 230 (16200), 248 (19167), 314 (10600), 326 (12067).

2.2.2. $[Ni^{II}(eda)_2(L)_2]$ (**2**)

Brownish crystal, yield: 288 mg (53%). *Anal.* Calc. for $C_{18}H_{28}N_{14}NiS_2$: C, 38.38; H, 5.01; N, 34.81. Found: C, 38.31; H, 5.03; N, 34.91%. IR (KBr, cm^{-1}): 3324, 3227, 3147, 2925, 2875, 1603, 1570, 1455, 1340, 1065, 1007, 828, 678. UV–Vis [DMSO–H_2O (1:1 v/v), λ/nm (ε/M^{-1} cm^{-1})]: 224 (10633), 230 (17967), 248 (20100), 314 (9700), 326 (10300).

2.2.3. $[Ni^{II}(deda)_2(L)_2]$ (**3**)

Green crystal, yield: 0.234 mg (41%). *Anal.* Calc. for $C_{22}H_{36}N_{14}NiS_2$: C, 42.66; H, 5.88; N, 31.66. Found: C, 42.49; H, 5.86; N 31.61%. IR (KBr, cm^{-1}): 3300, 3232, 3130, 2973, 2886, 1602, 1563, 1465, 1329, 1061, 1014, 832, 681. UV–Vis [DMSO–H_2O (1:1 v/v), λ/nm (ε/$M^{-1}cm^{-1}$)]: 224 (10033), 230 (11400), 248 (16233), 314 (8033), 326 (8733).

2.3. Crystal structure determinations

X-ray crystallographic data were collected on a Bruker D8 VENTURE PHOTON diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) using the Genenic omega scan technique. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares with Bruker's SHELXL-97 program [36,37]. All of the non-hydrogen atoms were refined anisotropically. All other hydrogen atoms were placed in geometrically ideal positions and constrained to ride on their parent atoms.

2.4. Measurement of jack bean urease inhibitory activity

The measurement of urease activity was carried out according to the literature reported by Tanaka [38]. Generally, the assay mixture, containing 25 μL of jack bean urease (20 kU/L) (dissolved in distilled water) and 25 μL of the tested complexes of different concentrations (dissolved in DMSO/H_2O mixture (1:1 v/v)) was preincubated for 1 h at 37 °C in a 96-well assay plate. After preincubation, 200 μL of 100 mM HEPES (N-[2-hydroxyethyl]piperazine-N′-[2-ethanesulfonic acid]) buffer pH 6.8 containing 500 mM urea and 0.002% phenol red were added and incubated at 37 °C [39]. The reaction was measured by micro plate reader (570 nm), which was required to produce enough ammonium carbonate to