Polyhedron 29 (2010) 813–822

Contents lists available at ScienceDirect

Polyhedron

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

Quinolin-2(1*H*)-one-triazole derived Schiff bases and their Cu(II) and Zn(II) complexes: possible new therapeutic agents

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ARTICLE INFO

Article history:
Received 9 September 2009
Accepted 2 November 2009
Available online 5 November 2009

Keywords:
Quinolin-2(1*H*)-one
4-Amino-1,2,4-triazole
Schiff bases
Metal(II) complexes
Biological activity
X-ray structures

ABSTRACT

The condensation of 4-amino-1,2,4-triazole with *N*-substituted-3-formyl-4-hydroxyquinolin-2-(1*H*)-one derivatives has lead to the synthesis of a new series of quinolin-2(1*H*)-one-triazole derived Schiff base ligands (**1–3**). Cu(II) and Zn(II) complexes (**1a–3a** and **1b–3b**, respectively) of these ligands were also prepared. The complexes were characterised by standard techniques and for two of the complexes X-ray crystallography confirmed that the geometry at the metal centre was octahedral in both cases and that the Schiff base acted as a bidentate ligand coordinating to the metal(II) ion through the deprotonated oxygen and azomethine nitrogen atoms. All of the compounds were investigated for their antimicrobial activities against a fungal strain, *Candida albicans*, and against Gram-positive and Gram-negative bacteria. The compounds were found to be active against *C. albicans* but inactive against *Staphylococcus aureus* and *Escherichia coli*.

1. Introduction

Antimicrobial drug resistance is not a new phenomenon and indeed the prevalence of clinical drug resistance has increased in recent decades as the use and misuse of antimicrobial therapies has expanded. Antimicrobial drug resistance is not restricted to bacteria and the failure to treat *Candida albicans* as a result of this species' resistance to fluconazole was identified in the 1990s [1]. *C. albicans* is the major fungal pathogen in humans that is carried by over 50% of the population. Although in healthy individuals the pathogen may cause relatively minor health problems such as oral thrush, the interactions of a fungus with its host can be disturbed by hormonal or immunological imbalances in the host to the point of provoking serious superficial infections and life-threatening systemic infections. Infections due to *Candida* species account for about 80% of all major systemic fungal infections. Antifungal resistance is exacerbated by the fact that relatively few antifungal treatments are available and diagnosis of fungal infection is often delayed [1]. As both serious systemic infections and drug-resistant strains of *Candida* become more prevalent, there is an urgent need to develop new and more effective antifungal therapies [2–4]. Quinolinones, an important class of heterocyclic compounds are part of the quinoline alkaloid family and are known for their diverse biological activity [5] and are the basis of many medicinal drugs used in the treatment of heart failure, cancer and inflammatory diseases. These heterocycles have emerged as potential therapeutic agents because of their conformational rigidity and improved physical properties, such as charge density or liphophilicity, and pharmacological advantages such as metabolic stability and oral bioavailability [6]. They are also used as antibacterial [7] antiviral, antineoplastic, anti-ischemic, anti-allergic, antihypertensive and anti-ulcerative agents [8]. Recently a novel series of quinolinones have shown potent inhibitory activity against human immunodeficiency virus type-1 (HIV-1) virus and also exhibited promising activity against several non-nucleoside reverse transcriptase inhibitors [9].

Schiff bases of azomethine nitrogen donor heterocyclic ligands are well known due to their wide range of applications in pharmaceutical and industrial fields [10] and have been found to act as antibacterial [11], antifungal [12,13] anticancer [14,15] and herbicidal agents. Transition metal complexes of *N*-donor ligands such as Schiff bases have attracted a lot of interest due to their potent biological activities and also have found application as antifungal, antibacterial, anticancer and herbicidal applications [16–19]. Results from these studies have also shown that complexation of metals to Schiff base ligands serves to improve the antimicrobial

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doi:10.1016/j.poly.2009.11.002

and anticancer activities of the ligands [16]. There has been recent reports on metal complexes of Schiff bases derived from quinolin-2(1*H*)-one [20–24] and antibacterial and antifungal activities of transition metal complexes of Schiff base ligands derived from pyrimidine [25], pyridine (py) [25,26], 2,2′-bipyridine (bipy) and 1,10-phenanthroline (phen) have also been reported [19,27]. Several Schiff base ligands derived from pyridines and their copper(II) complexes have also been shown to inhibit tumour growth [28].

Our previous work has focussed on the synthesis and therapeutic applications of a series of silver and copper complexes of coumarin derived ligands [29–34]. More recently we have focused on the preparation of a series of coumarin-derived Schiff base ligands and their Cu(II) complexes [35]. In this paper, we report a new series of quinolin-2-one derived Schiff base ligands which feature a triazole unit as part of their structural motif. Despite 1,2,4-triazole belonging to the moderately dangerous compounds, according to the parameters of acute intragastric toxicity, nevertheless a number of commercial antifungal agents are based on triazoles including pramiconazole, fluconazole, isavaconazole etc. The ligands and their copper and zinc complexes were assessed for their antimicrobial activity against *C. albicans* and also against Gram-negative and Gram-positive bacterial species.

2. Experimental

2.1. Materials/instrumentation

All chemicals purchased from Sigma–Aldrich were reagent grade and used without further purification. Microanalytical data were provided by the Microanalytical Laboratory, National University of Ireland, Belfield, Dublin 4. Infrared spectra were recorded in the region of 4000–400 cm^{-1}, on a Nicolet Impact 410 Fourier-Transform Infrared (FITR) spectrophotometer using Omnic software. All spectra were run as KBr discs. Melting point values were recorded on a Stuart scientific SMP1 melting point apparatus and are uncorrected. Values were taken up to 300 °C. All NMR spectra were run on a JEOL JNM-LA300 FT-NMR (300 MHz ^{1}H and 75 MHz ^{13}C) in d_6-DMSO with ^{1}H NMR spectra recorded in the region of −5 ppm to 15 ppm from TMS (tetramethylsilane) with a resolution of 0.18 Hz or 0.0006 ppm. All ^{13}C NMR spectra were recorded in the region −33 ppm to 233 ppm from TMS with a resolution of 0.008 ppm. Atomic absorption spectroscopy (AAS) measurements were recorded on a Perkin–Elmer 460 AAS instrument (emission wavelength 324.8 nm). Solid state magnetic susceptibility measurements were carried out at room temperature using a Johnson Matthey Magnetic Susceptibility Balance with $[HgCo(SCN)_4]$ being used as a reference standard. Molar conductivity was measured on a Systronic conductivity bridge with a dip-type cell, using 4×10^{-3} M solution of complexes in DMSO. UV–Visible (UV–Vis) spectra of the compounds in DMSO were recorded on a Shimadzu UV-1601 spectrophotometer.

2.2. Synthesis of quinolin-2(1H)-one-triazole derived Schiff base derivatives (1–3)

The *N*-substituted-3-formyl-4-hydroxyquinolin-2(1*H*)-ones were synthesised by a modified Reimer–Tiemann reaction [36,37]. The quinolin-2(1*H*)-one-triazole derived Schiff bases (**1–3**) were synthesised by the condensation of the appropriate *N*-substituted-3-formyl-4-hydroxyquinolin-2-(1*H*)-one derivative with 4-amino-1,2,4-triazole [20]. A stirred suspension of 4-amino-1,2,4-triazole (1 mmol, 0.084 g) and *N*-substituted-3-formyl-4-hydroxyquinolin-2-(1*H*)-one (1 mmol) in ethanol (30 mL) was refluxed for 3 h. On cooling to room temperature, cream coloured precipitates (**1–3**) formed which were filtered off and washed with cold ethanol and then dried in a vacuum oven to give the desired triazole-quinolin-2(1*H*)-one Schiff base ligands in excellent yields. The general structure of the quinolin-2(1*H*)-one-triazole derived Schiff bases with the numbering system used for NMR spectral assignments is shown in Fig. 1 with the substituents and their positions given in Table 1. The analytical data for the ligands is given in Table 2.

2.3. Synthesis of metal(II) complexes of quinolin-2(1H)-one-triazole Schiff base ligands (1a–3a and 1b–3b)

All of the copper(II) and zinc(II) complexes (**1a–3a** and **1b–3b**) were synthesised by the following general procedure. The appropriate metal(II) salt (0.125 mmol) in methanol (10 mL) was added drop wise with stirring to a hot methanolic solution of the appropriate ligand (**1–3**) (0.25 mmol) to a final volume of 50 mL. The resulting solution was refluxed with stirring for 4 h until a precipitate formed. Workup afforded either green copper(II) (**1a–3a**) or white zinc(II) (**1b–3b**) complexes which were dried in a vacuum oven at 60 °C to a constant weight. All of the prepared complexes were re-crystallised from an appropriate solvent system but suitable crystals were isolated only for complexes **1a** and **1b**. Crystals suitable for X-ray diffraction measurements were obtained by the slow diffusion of methanol into a solution of the complex in a binary solution of DMSO/DMSO–MeOH. Analytical data for the complexes are given in Table 2.

2.4. X-ray crystallography

X-ray crystallographic studies were carried out at Heriot Watt University, Edinburgh, United Kingdom. A single crystal is coated in Paratone-N heavy oil then mounted on a Hampton Research Cryoloop and placed in a cold stream of nitrogen gas (100 K) on a Bruker Nonius X8 Apex2 CCD diffractometer running the APEX2 software [38]. Intensity data were integrated using SAINT then scaled with SADABS (TWINABS for **1a**). The SHELXTL suites of programs were used for structure solution and refinement [39]. Crystal data and structure refinement of copper(II) complexes **1a** and **1b** are given in Table 3. Compound **1a** was refined as a two-component twin.

2.5. Biological testing

2.5.1. Anti Candida susceptibility testing

The metal-free ligands and their Cu(II) and Zn(II) complexes were tested against a clinical isolate of the fungal strain *C. albicans* (ATCC 10231) and a commercially available antifungal drug, Amphotericin B. The screening was carried out according to the broth microdilution susceptibility protocol method (NCCLS) [40].

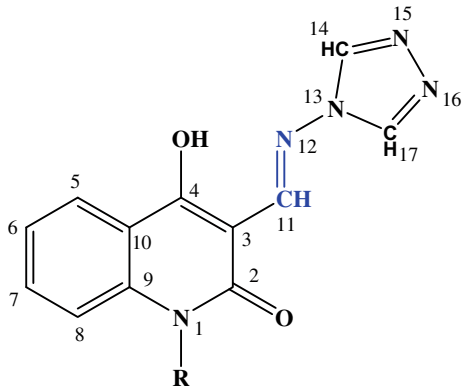

Fig. 1. General structure for quinolin-2(1*H*)-one-triazole Schiff base ligands (**1–3**).