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ORIGINAL ARTICLE

Synthesis, structural studies and antituberculosis evaluation of new hydrazone derivatives of quinoline and their Zn(II) complexes

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Abstract The quinoline hydrazone ligands were synthesized through multi-step reactions. The 2-hydroxy-3-formylquinoline derivatives (**1a–1c)** were prepared from acetanilide derivatives as starting materials using Vilsmeier–Haack reaction. Then the condensation of 2-hydroxy-3-formylquinoline derivatives with hydrazide derivatives (**2a–2c)** yielded quinoline hydrazone ligands (**3a–3i)**. The synthesis of a new series of Zn(II) complexes carried out by refluxing with these quinoline hydrazone ligands (**3a–3i)** is reported. The molecular structures of the ligands (**3a–3i)** and the Zn complexes were characterized by elemental analysis and spectral studies like FT-IR, ^{1}H and ^{13}C NMR, MS, UV–Visible and fluorescence. The preliminary results of antituberculosis study showed that most of the Zn(II) complexes **4a–4i** demonstrated very good antituberculosis activity while the ligands **3a–3i** showed moderate activity. Among the tested compounds **4e** and **4g** were found to be most active with minimum inhibitory concentration (MIC) of 8.00 μM and 7.42 μM respectively against *Mycobacterium tuberculosis* (H37 RV strain) ATCC No-27294 which is comparable to "first and second line" drugs used to treat tuberculosis.

1. Introduction

The extremely drug resistant tuberculosis is a worldwide public health problem in recent years. The wide spread of this disease is primarily due to the development of resistance to the existing drugs that has concerned researchers throughout the world. There is an urgent requirement of improvement in new drug

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molecules with newer targets and with an alternative mechanism of action [1,2]. It is evident from the literature that quinoline-based hydrazone scaffolds are known to exhibit excellent anti-TB properties [3–8]. This broad spectrum of biological and biochemical activities has been further aided by the synthetic flexibility of quinoline hydrazones, which allows the generation of a large number of structurally diverse derivatives and their metal complexes [9,10]. Further, various types of hydrazones have attracted continued interest in the medicinal field due to their broad-spectrum biological activities [11]. Among the ligand systems, quinoline hydrazone derivatives are highly important because, these ligands developed due to their diverse chelating ability, structural flexibility and pharmacological activities like antitumoural, antifungal, antibacterial, antituberculosis, antimalarial, and antiviral [12,13].

Zinc is an important trace element in human beings, and is participating in several biological processes in the form of complexes with proteins and nucleic acids. Moreover, Zn(II) ions are important for the expression of genetic information and structural maintenance of chromatin [14–17]. Numerous examples of Zn(II) complexes have been investigated for their significant antibacterial activity [18].

Recently it is reported that quinoline hydrazones and their Zn(II) complexes showed significant activity against the *Mycobacterium tuberculosis* strain, at low micromolar levels [19,20,10]. Based on these facts, supported by literature and in continuation of our research for new antituberculosis agents [21,22], we have undertaken research studies on synthesis and biological screening of some new quinoline hydrazone derivatives and their Zn(II) complexes shown in Fig. 1.

2. Experimental

The melting points of synthesized compounds were determined in open capillary tubes and are uncorrected. UV–Visible spectra were obtained on Shimadzu UV-1800 spectrophotometer. The fluorescence spectra were recorded on a spectrofluorophotometer Shimadzu RF-5301pc and equipped with quartz cuvette of 1 cm path length. Infrared spectra were measured with KBr disc on a FTIR-7600 Lambda Scientific Pty. Ltd. in the range 4000–400 cm^{-1}. Mass spectra were performed on BRUKER ESQUIRE HCT spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Varian-NMR-Mercury 300 MHz instruments in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard; chemical shifts are reported as δ ppm units. The elemental analyses were done at the SAIF, IIT Mumbai, India. The DSC–TGA analysis was carried out on Universal V4.5A TA instrument. Thin-layer chromatography (TLC) was performed on pre-coated TLC sheets of silica gel 60 F254 (Merck, Darmstadt, Germany), visualized by long- and short-wavelength UV lamps. Chromatographic purifications were performed on Merck silica gel (60−120 mesh).

2.1. General procedure for preparation of hydrazones *3a–3i* and Zn(II) complexes *4a–4i*

A mixture of compound **1a–1c** (0.01 mol) and appropriate hydrazide derivatives **2a–2c** (0.01 mol) in 10 mL of ethanol was stirred for 30 min at 60 °C. Completion of reaction is checked with TLC. The reaction mixture was allowed to cool down to room temperature and the solid formed was filtered, dried and recrystallized from ethanol to afford hydrazones **3a–3i**. Their structures are represented in Table 1 and Fig. 2.

A solution of Zinc chloride dissolved in ethanol was added gradually to a stirred ethanolic solution of the hydrazone ligand **3a–3i** in the molar ratio 1:2. The reaction mixture was further stirred for 2–4 h at 60 °C. The reaction mixture was allowed to cool down to room temperature and the solid formed was filtered, and washed several times with water. Finally, the complexes **4a–4i** were washed with diethyl ether and dried in vacuum desiccators over anhydrous $CaCl_2$. Probable structures are presented in Table 2 and Fig. 2.

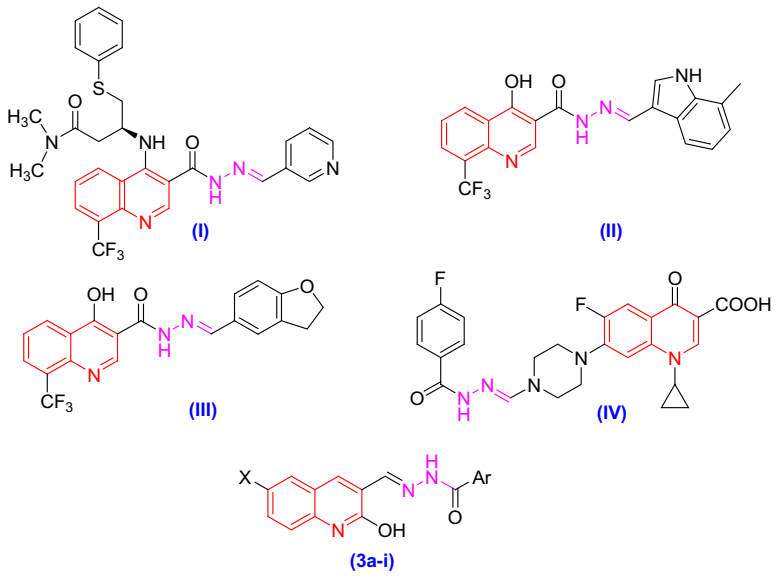

Figure 1 Previously reported quinoline hydrazones as anti-tuberculosis agents and synthesized compounds.