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Bis(4,6-dimethyl-2-pyridylseleno)zinc 3,3'-dicyanide, A Potent Antifungal Agent

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Short Communication

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ABSTRACT

A novel zinc chelate of 3-cyano-4,6-dimethyl-2(1H)-selenone pyridine was synthesized and its structure was confirmed on the basis IR, ^{1}H NMR, ^{13}C NMR spectral analyses and TOF mass spectrometry. Biological screening against *Candida glabrata* reveals a greater antifungal activity of the zinc chelate as compared to the fluconazole reference drug.

Keywords: Synthesis; bis(4,6-dimethyl-2-pyridylseleno)zinc 3,3'-dicyanide; fluconazole; antifungal activity; Candida glabrata.

1. INTRODUCTION

Yeasts are part of the genus Candida which contains more than 150 species [1]. Among them, *C. glabrata* was considered a pathogen that causes infection only when detected with *C. albicans* [2]. More recently, there have been several reports on oropharyngeal Candida (OPC) infections due to *C. glabrata* [3,4] and it is now emerging as an important pathogen in both mucosal and bloodstream infections [5]. In addition, *C. glabrata* is the second-most common

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agent of candidemia in the United States since the early 1990s [6]. *C. glabrata* associated OPC infections in HIV and cancer patients are more severe and difficult to treat [4,5]. This is mainly due to the ability of *C. glabrata* to quickly develop resistance to fluconazole and cross-resistance to the newer azoles has also been found [6]. *C. glabrata* infections are treated with difficulty and are associated with systemic infections having a high mortality rate [7].

It is well known that organoselenium compounds are important from the point of view of medicinal chemistry [8-10]. Likewise, given its therapeutic qualities, the pyridine ring occupies a prominent place in drug design [11,12]. Therefore, when organoselenium and pyridine compounds are coupled, bioactivity might be anticipated. This is the case in 2-selenopyridine-N-oxide derivatives that have been patented as fungicides and bactericides [13].

Based on these findings, a novel selenopyridine zinc chelate with a chemically similar structure to 2-selenopyridine-N-oxide has been synthesized and its biological activity screened against *C. glabrata* and two different Candida species and compared with the reference drug fluconazole.

2. RESULTS AND DISCUSSION

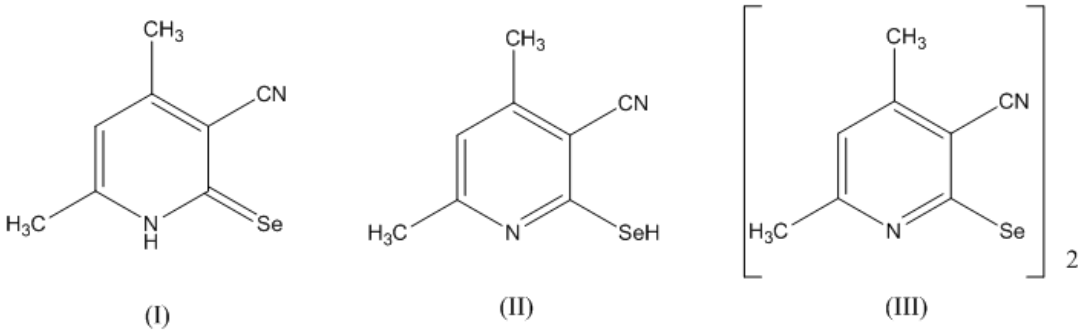
3-cyano-4,6-dimethyl-2(1H)-selenone pyridine was first synthesized by V. P. Litvinov [14]. The product may be in the form (I) or (II) as shown in Scheme 1. Due to the high oxidation properties of the selenium atom a trace of the diselenide (III) is often detected and can be separated by fractional crystallization.

Reacting two moles of 3-cyano-4,6-dimethyl-2(1H)-selenone pyridine with one mole of zinc chloride in ethanol catalyzed by drop of triethylamine on stirring at room temperature led to the target bis(4,6-dimethyl-2-pyridylseleno)zinc-3,3'-dicyanide in 86 % yield.

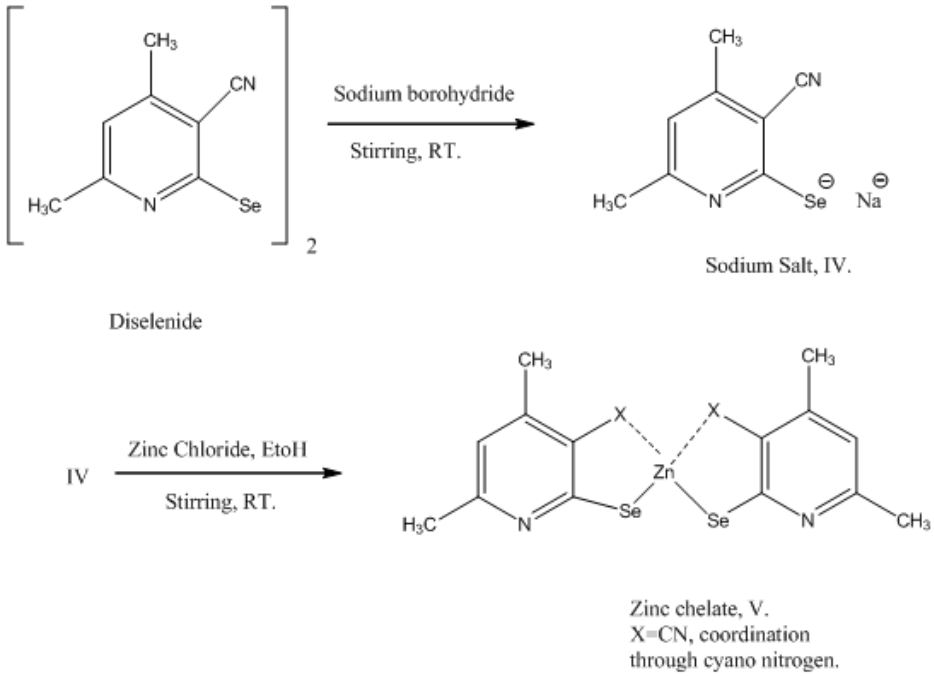
On the other hand, reacting one mole of the diselenide (III) with 2 moles of sodium borohydride in ethanol on stirring at room temperature gave the soluble sodium salt of the Litvinov selenol (IV, Scheme 2) which further reacted in situ with one mole of zinc chloride to afford the same target bis zinc dicyanide product, V, Scheme 2. The structure was confirmed on the basis of spectroscopy, TOF mass spectrometry. The far IR spectrum reveals the formation of a Se-Zn bond and the shift in position of the cyano group absorption band from 2210 cm^{-1} to 2196 cm^{-1} confirms coordination to the zinc atom through the nitrogen of the cyano group. Taken together, the data are consistent with the selenopyridine zinc chelate as structure (V).

The antifungal activity of the synthesized bis(4,6-dimethyl-2-pyridylseleno)zinc 3,3'-dicyanide was determined in vitro using the paper disc method [15] against *Candida glabrata*, Candida Cryptococcus neoformans and Candida albicans in nutrient agar media by measuring the zone of inhibition, Table 1.

The solutions of the zinc chelate compound and fluconazole as a reference drug were prepared in DMF at concentrations 100 µg/ml. The inhibition zones reveal the greater antifungal activity of the selenopyridine zinc chelate than the reference fluconazole drug, Table 1.



Scheme 1. The chemical structures of the selenone and diselenide compounds



Scheme 2. The synthetic route of the zinc chelate

Table 1. Antifungal activity of zinc chelate

Antifungal agent / Candida species	Zinc chelate	Fluconazole, reference drug.
Glabrata	30 mm	19 mm
Cryptococcus neoformans	40 mm	29 mm
Albicans	36 mm	27 mm

3. EXPERIMENTAL

The spectra were recorded on FT-IR spectrophotometer, Shimadzu Affinity 1S. ^{1}H and ^{13}C NMR, Bruker AC 400 MHz, Chemistry Department, Saurashtra University, India. Mass spectrometry was recorded on TOF mass spectrometer, Shimadzu, Central Laboratory, Bhavnagar University.

Bis(4,6-dimethyl-2-pyridylseleno)zinc 3,3'-dicyanide (V): is prepared according to the following synthetic strategy, to a stirred solution of (0.42 gm, 1 mmole) of the diselenide (III) in ethanol at room temperature, (0.08 gm, 2 mmole) of sodium borohydride was added step wise, till dissolution of the diselenide, (0.13 gm, 1 mmole) of zinc chloride is added. The pale yellow precipitate obtained at once is filleted out and washed with boiled ethanol. M.p. >300°C, yield 86%.

Or reacting two moles of 3-cyano-4,6-dimethyl-2(1H)-selenone pyridine (I) [14] with one mole of zinc chloride in stirring ethanol at room temperature catalyzed by one drop triethylamine. IR Spectroscopy, 410 cm^{-1} for Se-Zn bond stretching, 2206 cm^{-1} for CN bond stretching.

^{1}H NMR in DMSO, 2.3(s, CH_3), 2.4(s, CH_3), 6.9(s, CH pyridine).

^{13}C NMR in DMSO, 20(4-CH_3), 24(6-CH_3), 117(CN) and 110-161(Aromatic Pyridine carbons). TOF MS, M^+ 485 (35%), 275 (100 %), M^+- (4,6-dimethyl-3-cyano-2-selena pyridine) radical.

4. CONCLUSION

Bis(4,6-dimethyl-2-pyridylseleno)zinc 3,3'-dicyanide has been synthesized and its structure was confirmed on the basis of spectral and mass analyses. The biological screening against

Candida glabrata reveals a greater antifungal activity of the zinc chelate as compared to the fluconazole reference drug and should undergone further medicinal studies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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