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Study of anti fungal activities of compounds involved in synthetic route of N-(4-Methoxyphenyl)-5-(Pyridin-4-Yl)- 1, 3, 4-oxadiazol-2-amine hemi hydro chloride mono hydrate

Sankatha Prasad Sonkar, Shailendra Yadav
Department of Chemistry, AKS University, Satna, Madhya Pradesh, India

Abstract
The antifungal activities of N-(4-Methoxyphenyl)-5-(Pyridin-4-Yl)-1, 3, 4-oxadiazol-2-amine hemihydrochloride monohydrate and compounds involved in its synthetic route were investigated. Transition metal complexes formed with nitrogen-rich ligands, particularly 1,3,4-oxadiazoles, have garnered significant interest due to their diverse biological activities and applications in various fields. The synthetic pathway involved four compounds, with the final product obtained through cyclization by $CoCl_2$. The antifungal efficacy was assessed against Candida species (Candida glabrata, Candida albicans, Candida kefyr, and Candida krusei) using the Mueller Hinton agar plate method at a concentration of 500 ppm. Results demonstrated that the final compound exhibited substantial antifungal activity, comparable to Clotrimazole, especially against Candida glabrata and Candida krusei, indicating its potential as a promising antifungal agent.

Keywords: Biological activities, candida species, cyclization

Introduction

Metal complexes formed with nitrogen rich ligands are very interesting from the viewpoint of their electrical conductivity, molecular magnetism, electrochemical properties, biological processes, spectral and optoelectronic properties [1]. The above properties have made the coordination chemistry of nitrogen rich chelating ligands an emerging and rapidly developing area of research during the recent years [2]. Furthermore, the multifaceted chemistry of the complexes of this ligand system is reflected in the involvement of these compounds in catalysis of biological and non-biological processes [3]. Transition metal complexes of these ligands are widely studied because of their potential biological properties *viz.* anticancer, antibacterial, antiviral, antifungal, and insecticidal and also for their therapeutic uses. Azoles are an important class of five-membered heterocyclic ligands [4]. They contain a nitrogen atom and at least one other non-carbon atom *(i.e.* nitrogen, sulfur, or oxygen) as part of the ring.1,3,4-Oxadiazoles which belong to an important group of five-membered aromatic heterocyclic compounds, have increased consideration in research owing their diverse biological activities, such as anti-tuberculostatic, anti-inflammatory, antipyretic, analgesic, anti-cancer, antibacterial, antifungal, antimicrobial, antiviral, antidepressant [5, 6]. Because of their electron-accepting properties, highquantum yield, and improved thermal and chemical stabilities, they have also widely used in electroluminescent, optical and electron-transporting materials and chelating agents [7, 8].

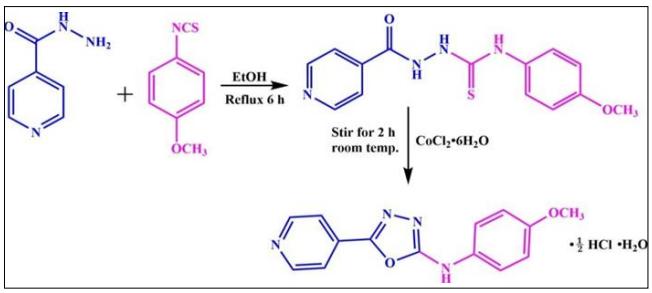
In view of the importance of 1,3,4-oxadiazole we have synthesized *N*-(4-methoxyphenyl)-5-(pyridin-4-yl)-1,3,4-oxa- diazol-2-amine hemihydrochloride monohydrate [9]

Materials and Methods

Anti fungal activities of compounds involved in synthetic routes given in section 2.1 were evaluated for candida species fungus *Candida glabrata, Candida albican, Candida kefyr, Candida krusei* by Mueller Hinton agar plates method [10] at 500 ppm concentration

1. Synthesis of N-(4-Methoxyphenyl)-5-(Pyridin-4-Yl)-1,3,4-oxadiazol-2-amine hemi hydro chloride mono hydrate

2-Isonicotinoyl-N-(4-methoxyphenyl)hydrazine-1-carbothioamide was prepared by adding (1.652 g, 10 mmol) 4-meth- oxy phenyl isothiocyanate in ethanol solution of (1.370 g, 10 mmol) isonicotinohydrazide and the réaction mixture was refluxed for 6 h at 60 °C then white precipitate of 2-isonicotinoyl-N-(4-methoxyphenyl)hydrazine-1-carbothioamide was obtained, upon cooling was filtered off and washed with (50:50 v/v) mixture of water and ether. The 1 mmol isonicotinoyl-N-(4-methoxyphenyl)hydrazine-1-carbothioamide was dissolved in (50:50 v/v) mixture of methanol and chloroform and then added a methanolic solution of 0.5 mmol of CoCl2·6H2O and stir for 2 h. A clédar solution obtained was kept for crystallization. After 15 days, the pink color crystals were grown. Yield: 60.6%; m.p. 222–225°C [9]



Scheme : 1. Synthesis of N-(4-methoxyphenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine hemi hydro-chloride mono hydrate [9]

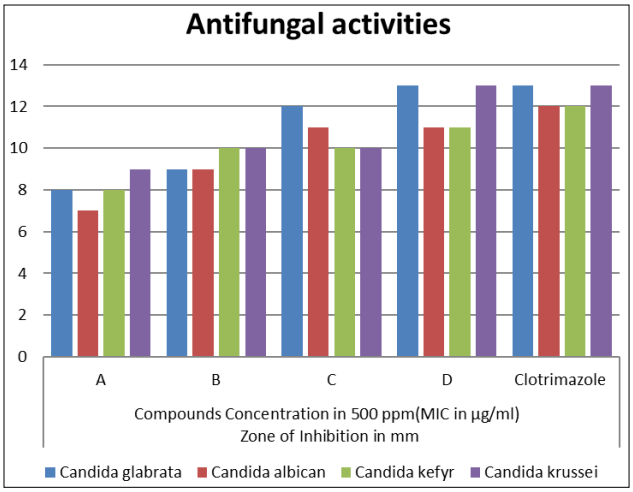
Results and Discussions

In the above given scheme of synthesis of four compounds were involved. In first step two compounds 4-meth- oxy phenyl isothiocyanate(A) and isonicotinohydrazide(B) were reacted and third compound isonicotinoyl-N-(4-methoxyphenyl)hydrazine-1-carbothioamide(C) were obtained. Finally fourth compound N-(4-Methoxyphenyl)-5-(Pyridin-4-Yl)- 1,3,4-oxadiazol-2-amine(D) was obtained

by cyclization by $CoCl_2$. Comparable antifungal activities of all the compounds were evaluated by taking Clotrimazole as reference and results are given in table 1.

Table 1: Antifungal activities of Compounds

Fungal species	Concentration of compounds in 500 ppm (MIC in µg/ml) Zone of Inhibition in mm				
	A	B	C	D	Clotrimazole
Candida glabrata	8(70)	9(60)	12(50)	13(50)	13(50)
Candida albican	7 (70)	9(80)	11(70)	11(60)	12(60)
Candida kefyr	8 (90)	10(80)	10 (80)	11(70)	12(70)
Candida krussei	9 (70)	10(60)	10(90)	13(70)	13 (60)



Across the different Candida species tested, the data indicate that

Compound A: Generally shows the least antifungal activity among the test compounds, with smaller zones of inhibition and higher MICs.

Compound B: Demonstrates moderate antifungal activity but consistently falls short of the efficacy shown by Clotrimazole and Compounds C and D.

Compound C: Exhibits better antifungal activity than A and B but is still less effective than Compound D and Clotrimazole, particularly against Candida albicans and Candida krusei.

Compound D: Emerges as the most promising compound among those tested, showing zones of inhibition and MICs closest to or matching those of Clotrimazole across most species.

Compound D shows significant potential as an alternative antifungal agent to Clotrimazole, particularly against Candida glabrata, Candida krusei, and Candida kefyr. While its efficacy against Candida albicans is slightly lower in terms of the zone of inhibition, its MIC is comparable, suggesting it could still be an effective treatment option. Further research and development could help optimize these compounds, particularly Compound D, for clinical use.

Conclusion

The study successfully investigated antifungal properties of N-(4-Methoxyphenyl)-5-(Pyridin-4-Yl)-1,3,4-oxadiazol-2-amine hemi hydrochloride monohydrate and alongside compound involved in its synthetic route. Among the tested compounds, the final product, Compound (D) N-(4-Methoxyphenyl)-5-(Pyridin-4-Yl)-1,3,4-oxadiazol-2-amine hemi hydrochloride monohydrate, exhibited the most promising antifungal activity, closely matching or surpassing the efficacy of the standard antifungal agent Clotrimazole in several Candida species. This highlights Compound D's potential as an alternative antifungal treatment. The findings suggest that further research and optimization could enhance the clinical applicability of these compounds, particularly Compound D, for antifungal therapies.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Competing Interests: The authors declare that they have no competing interests

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Disclaimer

The authors alone are responsible for the content and writing of the paper.

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