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Anti-microbial of series 3-Hydroxy-Series of -4-(4-((6-methylpyridin-2-yl) oxy) phenethyl) pyridin-2(1H)-ones

Gollamandala Soujanya [1, 2], Sreelatha Beemagani [1•], Radhakrishna Muttineni [2•]

[1] Research Scholar, Chaitanya (Deemed to be University), Himayat Nagar, Hyderabad 500075, Telangana.

[•1] Department of Microbiology, Chaitanya (Deemed to be University), Himayat Nagar, Hyderabad 500075, Telangana.

[•2] Virus Research Laboratory, Department of Zoology, Osmania University, Hyderabad, -500001, Telangana.

[•]**Corresponding authors Email ids:** bslathabathini@gmail.com, muttinenirk@gmail.com

[•]**These authors contributed equally to this work**

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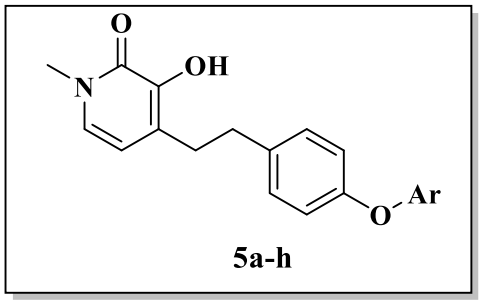
Abstract

A series of structurally diverse compounds 5a–h) (Fig:1, Table:1,2) 3-Hydroxy-Series of -4-(4-((6-methylpyridin-2-yl) oxy) phenethyl) pyridin-2(1*H*)-one derivatives were evaluated for in vitro antibacterial and antifungal activities using the agar well diffusion method. Compounds **5e** and **5g** exhibited excellent antibacterial activity, while **5d**, **5f**, **5g**, and **5h** showed moderate to good antifungal activity. Compound **5g** emerged as the most promising broad-spectrum antimicrobial candidate.

Introduction

The increasing prevalence of multidrug-resistant (MDR) bacterial pathogens has become a major global health concern, necessitating the development of new antibacterial agents with improved therapeutic efficacy.[1,2] Nitrogen-containing heterocycles are widely recognized for their broad spectrum of biological activities, particularly their antibacterial potential.^3 Among these, pyridin-2(1H)-one derivatives have emerged as promising pharmacophores because of their ability to interact with essential bacterial targets.^4 Structural modifications involving substituted aromatic groups, pyridine ether linkages, and hydroxyl functionalities have been reported to enhance antibacterial activity by improving molecular interactions and membrane permeability.[5,6]

In the present study, a series of 3-hydroxy-4-(4-((6-methylpyridin-2-yl)oxy)phenethyl)pyridin-2(1H)-one derivatives were evaluated for their in vitro antibacterial activity against selected Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative (*Escherichia coli* and *Proteus vulgaris*) bacterial strains using the agar well diffusion method. Streptomycin was used as the reference drug, and the results were analyzed to establish preliminary structure–activity relationships (SAR) for the development of potent pyridinone-based antibacterial agents by Agar well diffusion method.[7,8]Herein, we describe the anti-bacterial activity of 3-Hydroxy-Series of -4-(4-((6-methylpyridin-2-yl) oxy) phenethyl) pyridin-2(1H)-ones 5a–5h (Fig:1, Table:1,2)



5a-h

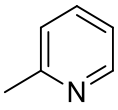
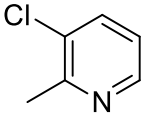
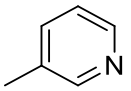
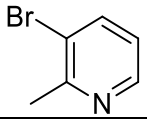
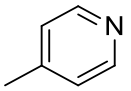
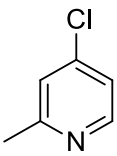
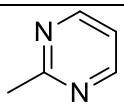
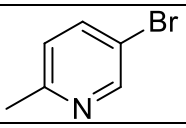
	Ar		Ar
a:		**e:**	
b:		**f:**	
c:		**g:**	
d:		**h:**	

Fig:1

Results and Discussion

All the synthesized compounds were screened for their *in vitro* antibacterial activity against gram positive bacteria *Staphylococcus aureus* and *Bacillus subtilis a*nd gram-negative bacteria *Escherichia coli, and Proteus vulgaris* bacterial strains **(Table 1)** and in vitro antifungal activity against Candida albicans, Sacharromyces cerevisiae, Aspergillus niger and Aspergillus flavus fungal strains **(Table 2)** using agar well diffusion method. Streptomycin for bacteria and Ampothericin-B for fungi are taken as standard drugs.

Table 1: Antibacterial activity data (MIC in μg/mL) values) of 3-Hydroxy-Series of -4-(4-((6-methylpyridin-2-yl) oxy) phenethyl) pyridin-2(1*H*)-ones (**5a-5h**)

	MIC (µg/mL)			
compound	***E.coli***	***S.aureus***	***B.Subtilis***	***P.vulgaris***
5a	>150	**4.250**	>150	**6.745**
5b	>150	>150	**1.546**	>150
5c	>150	>150	>150	>150

5d	>150	>150	>150	>150
5e	**1.268**	**1.546**	**1.420**	**1.450**
5f	>150	>150	>150	>150
5g	**4.251**	**2.650**	**4.532**	**4.253**
5h	>150	>150	>150	**6.745**
Streptomycin	**6.26**	**6.26**	**3.125**	**1.25**

Table 2: Antifungal activity results of 3-Hydroxy-Series of -4-(4-((6-methylpyridin-2-yl) oxy) phenethyl) pyridin-2(1*H*)-ones (**5a-5h**)

Zone of Inhibiton (mm)								
S.No	***Candida albicans***		***Sacharromyces cerevisiae***		***Aspergillus niger***		***Aspergillus flavus***	
	100µg	**150µg**	**100µg**	**150µg**	**100µg**	**150µg**	**100µg**	**150µg**
5a	0	0	0	0	0	0	0	0
5b	0	0	0	0	0	0	0	0
5c	0	0	0	0	0	0	0	0
5d	8mm	11mm	0	0	0	12mm	0	14mm
5e	0	0	0	0	0	0	0	0
5f	12mm	18mm	0	0	0	10mm	0	9mm
5g	16mm	19mm	0	0	0	8mm	0	12mm
5h	11mm	12mm	0	10mm	0	12mm	0	8mm
S	**23.5**		**22**		**25**		**25**	

S-Ampothericin-B

From the antifungal activity results (**Table 2)** we noticed that, the compounds **5d**, **5f**, **5g** and **5h** shown moderate to good activity comparing with the standard drug Ampothericin-B (ZOI ranging from 8 to 20 mm). Antibacterial activity results (**Table 1**) revealed that, the compounds possessing 3,5-dichloro phenyl and napthyl on triazole ring, that is, **5e** and **5g** have shown excellent activity against gram-positive and gram-negative bacterial strains comparing with the standard drug streptomycin. And compounds **5a** against *S.aureus* and *P.vulgaris,* **5b** against *B.Subtilis,* **5h** against *P.vulgaris* have shown good activity.

Experimental Section

All the synthesized compounds were screened for their *in vitro* antibacterial activity against gram-positive bacteria and gram-negative bacterias using broth dilution method.[8] All the bacterial cultures were adjusted to 0.5 McFarland standards, which is visually comparable to a bacterial

suspension of around 1.5×108 CFU/ml. 10 mL of nutrient agar medium was poured into each Petri plate and plates were swabbed with 100 µL inoculum of the test microorganisms and kept for 15 to 30 min for adsorption. Using sterile cork borer of 10 to 12 mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 µL volume with a concentration of 2.0 mg/mL of each compound reconstituted in the dimethylsulphoxide (DMSO). All the plates were incubated at 37 ºC for 24 h. Antimicrobial activity of each complex was evaluated by measuring the zone of growth inhibition against the test organisms with zone reader (Hi Antibiotic zone scale).

The ready-made Potato Dextrose Agar (PDA) medium (Hi-media, 39 g) was suspended in distilled water (1000 ml) and heated to boiling until it dissolved completely, the medium and Petri dishes were autoclaved at a pressure of 15 lb/inc^2 for 20 min. The medium was poured into sterile Petri dishes under aseptic conditions in a laminar air flow chamber. When the medium in the plates was solidified, 0.5 ml of a (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in DMSO and different concentrations (100-150µg) were made. After inoculation, the wells were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. To each well different concentrations of the test solutions were added. Controls were maintained. The treated samples and the controls were kept at 27 ºC for 48 h. Inhibition zones were measured and the diameter was calculated in millimeter. Three to four replicates were maintained for each treatment.

Serial dilutions of the test compounds were performed at concentrations ranging from 150 to 0.58 µg mL^{-1} in a 200 mL culture medium final volume. Afterward, each well was seeded with a 50 µL microbial suspension of 0.5 MacFarland densities. In each test a microbial culture control and a sterility control (negative) were performed. The plates were incubated for 24 h at 37 ºC. The lowest concentration which inhibited the visible microbial growth was considered the MIC.

Conclusion

A series of novel (1-aryl-1H-1, 2, 3-triazol-4-yl) methyl 6-fluoro-4-oxo-4Hchromene- 2-carboxylate derivatives (**5a-5h**) were screened for their antimicobial activity. **5e** and **5g** have shown excellent activity against gram-positive and gram-negative bacterial strains comparing with the standard drug.

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