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ORIGINAL ARTICLE

Biological Screening of Isoxazol-Piperidin-1,2,3-Triazoles

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ABSTRACT
A series of novel hybrid isoxazole–piperidine–1,2,3-triazole derivatives (4a–j) were evaluated for their in vitro antibacterial and antifungal activities to identify promising antimicrobial scaffolds. The synthesized compounds were screened against representative Gram-positive bacteria (Staphylococcus pyogenes and Staphylococcus aureus), Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa), and fungal strains (Candida albicans, Aspergillus niger, and Aspergillus clavatus) using the agar dilution method. Minimum inhibitory concentration (MIC) values were determined and compared with standard drugs ciprofloxacin (antibacterial) and nystatin (antifungal). The antibacterial activity of the tested compounds ranged from 62.5 to 500 µg/mL, indicating moderate efficacy relative to ciprofloxacin. Compounds 4a, 4b, 4g, and 4j, bearing electron-withdrawing substituents on the aryl ring, demonstrated notable activity against S. aureus, while compound 4f exhibited comparatively broader activity against both Gram-positive and Gram-negative bacteria. Antifungal screening revealed moderate activity for derivatives 4b, 4f, 4h, and 4j, though none surpassed nystatin against the tested fungal strains. Structure–activity relationship analysis suggested that the nature and position of aryl substituents significantly influence antimicrobial potency. Overall, the results highlight compound 4f as the most balanced candidate within the series, warranting further structural optimization to enhance antimicrobial efficacy.
Keywords: *Biological Screening, antifungal activities, MIC*

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INTRODUCTION

Coupling reactions are key in organic synthesis, comprising the most widely used reaction in pharmaceuticals [1–4]. The core idea of amide coupling comprises the reaction in which an activated carboxylic acid with an amine [5–9]. The activated carboxylic acid acts as a reactive component, initiating the coupling process with the amine to generate the desired amide product [10].

Because of their attractive structural and chemical characteristics as well as their numerous uses in chemical biology, isoxazole analogues have also attracted a lot of attention in heterocyclic chemistry. A considerable number of isoxazole compounds demonstrated antibacterial activity. In order to synthesize a variety of medicinally noteworthy heterocyclic compounds as practical primary precursors for drug discovery and development, medicinal and organic chemists have thus turned their focus towards isoxazole derivatives. The understanding of molecular hybridization for drug design and development is demonstrated by a current trend in medicinal chemistry [11]. In order to find innovative robust and effective antibacterial medicines, the current study aims to create new molecular hybrids that integrate two active pharmacophores, isoxazole and cinnoline, into a single core structure.

Surfactants are widely studied by researchers due to their promising chemical, industrial and biological applications. Surfactants show a variety of biological properties, notably antimicrobial [11], anti-inflammatory,antiviral [12]. anticancer [13], antioxidant and analgesic [14]. activities.1,2,3-triazoles side

chain in one scaffold may prove to be a breakthrough for chemical and biological activity as continuation of our effort in the designing of novel polyheterocyclic bioactive compounds [15–17]. Herein, we describe the biological evaluation of isoxazol-piperidin-1,2,3-triazoles shown in Figure 1.

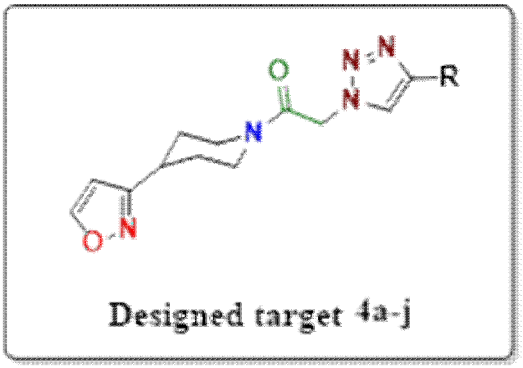
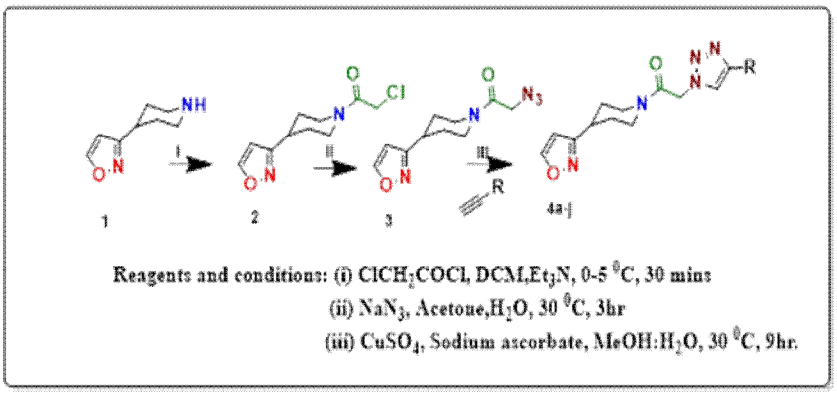


Figure1: isoxazol-piperidin-1,2,3-triazoles

MATERIAL AND METHODS

Antibacterial activity

The antimicrobial properties of novel hybrid isoxazole-piperidine-1,2,3-triazole derivatives were evaluated against several bacterial strains, including *Staphylococcus pyogenes, Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, as well as fungal strains such as *Aspergillus clavatus*, *Aspergillus niger*, and *Candida albicans* (scheme 1). The minimum inhibitory concentration (MIC) of each compound was determined using the agar dilution method. A stock solution of 2000 µg/mL of each of the test samples was prepared in dimethyl sulfoxide and subsequent dilutions were prepared with culture medium i.e., nutrient agar for the evaluation of antibacterial and sabouraud dextrose agar for antifungal activity, respectively. The medium containing the test compound was poured into a petri dish to a depth of 4–5 mm and allowed to solidify under aseptic conditions. A suspension of the respective microorganism, approximately 105 CFU/mL, was prepared and applied to plates with serially diluted compounds at concentrations ranging from 3.12 to 500 µg/mL in dimethyl sulfoxide. These plates were then incubated at (37 ± 1) °C for 24 h. In primary screening, 500 µg/mL, 250 µg/mL, 200 µg/mL, and 125 µg/mL concentrations of the synthesized drugs were taken. The active compounds found in this primary screening were further tested in the second set of dilutions against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100 µg/mL, 62.50 µg/mL 50 µg/mL, 25 µg/mL, 12.50 µg/mL, 6.25 µg/mL, and 3.12 µg/mL concentrations for secondary screening. The minimum inhibitory concentration (MIC) value was defined as the lowest concentration of the substance that prevented visible microbial growth. All the experiments were carried out in triplicate.



Scheme 1. 3 Step Synthesis of isoxazol-piperidin-1,2,3-triazoles 4a-j[18] .

RESULTS

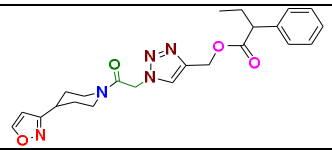
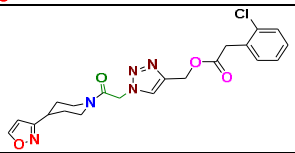
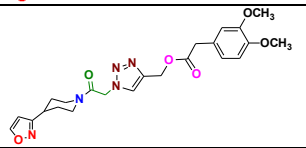
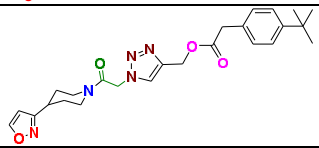
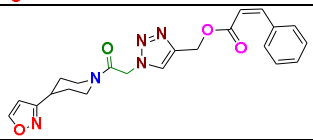
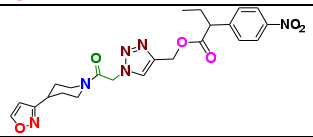
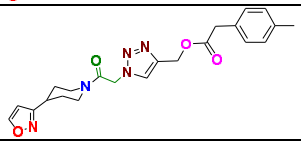
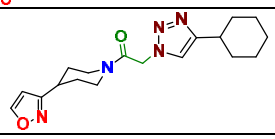
Antimicrobial activity and structure-activity relationship analysis

The antimicrobial efficacy of the synthesized isoxazole-piperidine-1,2,3-triazole derivatives was evaluated against four susceptible bacterial and three fungal strains, i.e., Staphylococcus pyogenes,

Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, Aspergillus clavatus and *Aspergillus niger*. Hence the biological profile of the designed pharmacophore isoxazole, substituted with piperidine along with 1,2,3-triazoles. The results are placed in Table 1 & 2.

The antibacterial activities in terms of MIC (minimum inhibitory concentration) values are in the range from 62.5 µg/mL to 500 µg/mL, exhibit moderate activity compared to the standard drug Ciprofloxacin. Against both gram-positive and gram-negative bacterial strains, compounds with electron-withdrawing groups like -Cl were more active at ortho substitution on the phenyl ring, while compounds with strong electron-withdrawing groups like -NO2 and electron-donating groups like -CH3 were more active at para substitution on the phenyl ring. According to the SAR studies, compounds (4a), (4b), (4j), and (4g) with electron-withdrawing halo and nitro substituents to the aryl nucleus are associated with antibacterial activity against S. aureus. As well as compound (4f) associated with antibacterial activity against almost both gram-positive and gram-negative bacterial strains. One more important aspect observed was that the unsubstituted phenyl ring was responsible for the activities against gram-positive bacterial strains while having the weakest inhibitory capacity against gram-negative bacterial and fungal strains.

Table 1: *In vitro* antibacterial activities of synthesized compounds (4a-m)

Entry	Structure	Antibacterial activities			
		Minimum inhibitory concentration in µg/mL			
		Gram-Positive		Gram-Negative	
		S. pyogenes	*S. aureus*	*E. coli*	*P. aeruginosa*
4a		125	100	500	500
4b		125	100	125	200
4c		500	250	250	250
4d		125	250	250	250
4e		100	200	125	200
4f		125	100	62.50	100
4g		100	200	125	200
4h		500	250	500	250

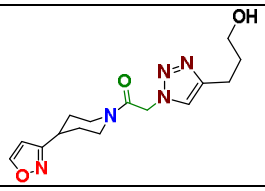
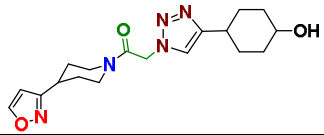
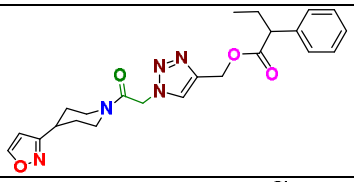
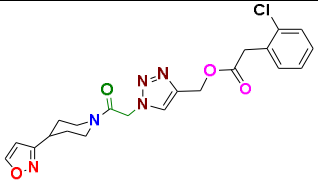
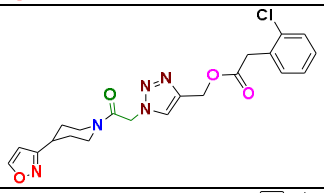
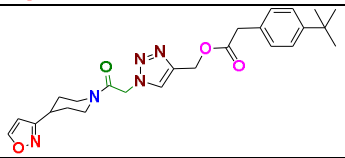
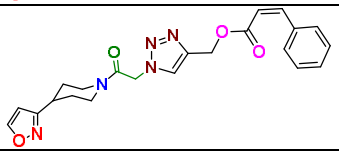
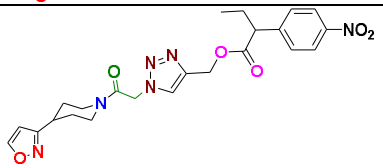
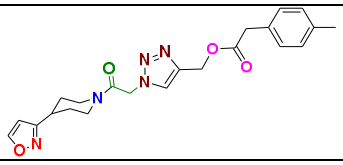
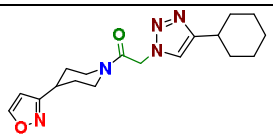
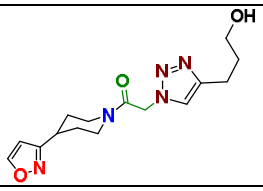
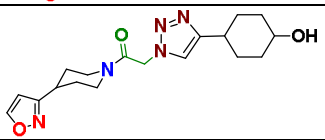
4i		250	500	250	250
4j		500	250	250	250
Stand. drug	Ciprofloxacin	50	50	25	25

Table 2: *In vitro* antifungal activities of synthesized compounds (4a-m)

Entry	Structure	Antifungal activities		
		Minimum inhibitory concentration in µg/mL		
		A. niger	*A. clavatus*	*C. albicans*
4a		1000	1000	500
4b		250	250	500
4c		500	500	250
4d		500	500	1000
4e		1000	>1000	1000
4f		250	500	200
4g		1000	>1000	1000

4h		500	500	250
4i		500	1000	500
4j		500	500	250
Stand. drug	Nystatin	100	100	100

S. pyogenus: *Staphylococcus pyogenes*, *S. aureus*: *Staphylococcus aureus*, *E. coli*: *Escherichia coli*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *A. niger*: *Aspergillus niger*, *A. clavatus*: *Aspergillus clavatus*, *C. albicans*: *Candida albicans*

DISCUSSION

We evaluated for the anti-microbial evaluation of synthesized compounds 4a-j. Among them the compounds (4a), (4b), (4j), and (4g) with electron-withdrawing halo and nitro substituents to the aryl nucleus are associated with antibacterial activity against *S. aureus*. As well as compound (4f) associated with antibacterial activity against almost both gram-positive and gram-negative bacterial strains. Ciprofloxacin is used as standered drug and correlated anti-bacterial activity. While derivatives of (4b, 4f, 4h, 4j) show moderate anti-fungal activity, none exceed the standard drug Nystatin in potency for the tested fungi. Further structural optimization would be needed to improve their MICs to match or beat the standard. Nystatin is used as standard drug and correlated anti-fungal activity.

While some derivatives (4b, 4f, 4h, 4j) show moderate antifungal activity, none exceed the standard drug Nystatin in potency for the tested fungi. Further structural optimization would be needed to improve their MICs to match or beat the standard.

None of the tested compounds (4a-m) are more potent than Nystatin against *A. niger* or *A. clavatus*, as all require higher MICs (≥250 µg/mL vs. 100 µg/mL). Against *C. albicans*, only 4c, 4f, 4h, and 4j show equal or better activity than Nystatin (MIC = 100 µg/mL), with 4f being the most potent at 200 µg/mL. Actually, lower MIC = better potency. *C. albicans*, Nystatin MIC = 100 µg/mL Compounds with MIC ≤ 100 µg/mL would be better; here, none have MIC below 100 (best is 4c, 4h, 4j at 250 µg/mL, which is less potent). Most Active Compounds Relative to Others in the Series 4f is the most well-rounded: MICs = 250 (*A. niger*), 500 (*A. clavatus*), 200 (*C. albicans*) Best against *C. albicans* among all.4b Good against molds (250, 250) but moderate against yeast (500).4c, 4h, 4j moderate against molds (500, 500) and C. albicans (250). 4e and 4g are least potent (MIC ≥ 1000 µg/mL against all).

CONCLUSION

Compounds (4a), (4b), (4j), and (4g) are associated with antibacterial activity against *S. aureus*. As well as compound (4f) associated with antibacterial activity against almost both gram-positive and gram-negative bacterial strains. Ciprofloxacin is used as standered drug and correlated anti-bacterial activity. While derivatives of (4b, 4f, 4h, 4j) show moderate anti-fungal activity, none exceed the standard drug Nystatin in potency for the tested fungi. Further structural optimization would be needed to improve their MICs to match or beat the standard. Nystatin is used as standard drug and correlated anti-fungal activity.4b, 4f, 4h, 4j show moderate anti-fungal activity, none exceed the standard drug Nystatin in potency for the tested fungi. Further structural optimization would be needed to improve their MICs to match or beat the standard.4f is the most well-rounded: MICs = 250 (*A. niger*), 500 (*A. clavatus*), 200 (*C. albicans*) Best against *C. albicans* among all.4b Good against molds (250, 250) but moderate against yeast (500).4c, 4h, 4j moderate against molds (500, 500) and *C. albicans* (250). 4e and 4g are least potent (MIC ≥ 1000 µg/mL against all).

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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