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Triazole Derivatives As New Antimicrobial Agents

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ABSTRACT

The compounds 3-(1*H*-imidazo[4,5-*b*]pyridin-2-ylamino)-*N*'-(5-aryl-1*H*-1,2,3-triazol-1-yl)propanamides (VI) derivatives were evaluated for antimicrobial activity by using cup plate method. The synthesised compounds were characterized and evaluated for antimicrobial activity against *Bacillus subtilis,* and *Staphylococcus aureus* ,*Escherichia coli* and *Staphylococcus typhi* and antifungal activity against *Aspergillus niger* and *Candida albicans* by using Ampicillin sodium and Clotrimoxazole as standards respectively. Among all the compounds Compound VId was most effective against all the testing bacteria. Among this series Compound VIb and Compound VIf were more effective against Gram negative bacteria and Compound VId was also more effective against fungal.

KEY WORDS

Staphylococcus aureus , Escherichia coli, Aspergillus niger , Candida albicans.

INTRODUCTION

The increasing incidences of bacterial and fungal resistance to a large number of antimicrobial agents has prompted studies on the development of new potential antimicrobial agents. Imidazo[4,5-*b*] pyridine nucleus is a very importanct system in the feild of new drug discovery, especially in the area of antimicrobial and antibiotic agents..

The present study has been aimed at evaluation of antibacterial and antifungal activities of newly synthesised triazole derivatives. In view of varied biological and pharmacological importance of different series of triazole derivatives, it has been felt worthwhile to evaluate the present new series of imidazol[4,5-*b*]pyridine derivatives of triazoles for their antimicrobial activity.

SCREENING FOR ANTI-MICROBIAL PROPERTIES

1. Antibacterial activity by cup plate method (Indian Pharmacopoeia, 1996) The antibacterial activity of synthesized compounds was tested against two gram-positive bacteia viz., *Bacillus subtilis* and *Staphylococcus aureus* and two gram-negative bacteia viz., *Escherichia coli* and *Salmonella typhi* by using cup plate method. Ampicillin sodium was employed as standard to compare the results. The test organisms were subcultured using

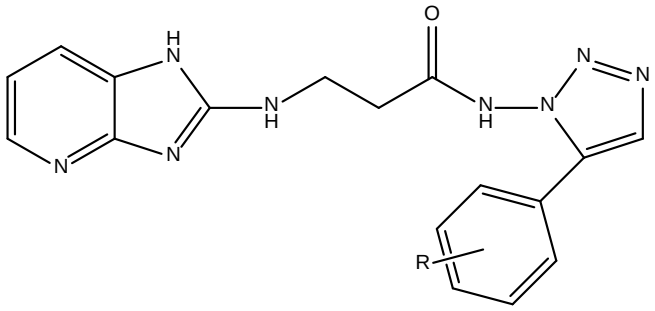
nutrient agar medium. The tubes containing sterilized medium were inoculated with respective bacterial strain. After incubation at 37^0Cfor 24 hours, they were stored in refrigerator. The stock cultures were maintained. Bacteria inoculam was prepared by transferring a loopful of stock culture to nutrient broth (100 ml) in conical flasks (250 ml). The flasks were incubated at 37^0C for 48 hours before the experimentation. Solution of the test compounds were prepared by dissolving 10 mg each in dimethyl formamide(10 ml, AnalaR grade). A reference standard for both gram-positive and gram-negative bacteria was made by dissolving accurately weighed quantity of Ampicillin sodium in sterile distilled water separately. The nutrient agar medium was sterilized by autoclaving at 121^0C (15lb/sq.inch) for 15 minutes. The petriplates, tube and flasks plugged with cotton weresterilized in hot air oven at 160^0 for an hour. Into each sterilized petriplate (10 cm diameter),about 27 ml of molten nutrient agar medium was poured and inoculated with the respective strain of bacteria (6 ml of inoculums to 300 ml of nutrient agar medium) was transferred asceptically. The plates were left at room temperature to allow the solidification. In each plate, three cups of 6 mm diameter were made with sterile borer. Then 0.1 ml of the test solution were added to the respective cups asceptically and labelled, accordingly. The plates were kept undisturbed for atleast 2 hours in the refrigerator to allow diffusion of the solution properly into nutrient agar medium. After incubation of the plates at 37^0C for 24 hours, the diameter of zone of inhibition surrounding each of the cups was measured with the help of an antibiotic zone reader. All the experiments were carried out in triplicate. Simultaneously, controls were maintained employing0.1 ml of dimethyl formamide to observe the solvent effects. The results are presented in Table 1.

2. Antifungal activity (British Pharmacopoeia, 1953)

All those compounds screened for antibacterial activity were also tested for their antifungal activity. The fungi employed for screening were : *Candida albicans* and *Aspergillus niger*. The test organisms were subcultured using potato-dextrose-agar medium. The tubes containing sterilized medium were inoculated with test fungi and after incubation at 25^0C for 48 hours, they were stored at 4^0C in the refrigerator. The inoculam was prepared by transferring a loopful of stock culture to nutrient broth (100 ml) in conical flasks (250 ml). The flasks were incubated at 25^0C for 24 hours before use. Solution of the test compounds were prepared by a similar procedure described under the antibacterial activity. A reference standard (1 mg/ml conc) was prepared by dissolving 10mg of Clotrimazole in 10 ml of dimethylformamide.

Furthur the dilution was made with dimethyformamide itself to obtain a solution of 100µg/ml concentration. The potato-dextrose-agar medium was sterilized by autoclaving at 121^0C (15lb/sq.inch) for 15 minutes. The petriplates, tube and flasks plugged with cotton were sterilized in hot air oven at 150^0 for an hour. Into each sterilized petriplate (10 cm diameter),about 27 ml of molten potato-dextrose- agar medium was poured and inoculated with the respective fungus (6 ml of inoculum in 300 ml of potato-dextrose- agar medium) was transferred asceptically. The plates were left at room temperature to allow the solidification. In each plate, three cups of 6 mm diameter were made with sterile borer. Then 0.1 ml (100 µg/disc) of the test solution were added to the respective cups asceptically and labelled, accordingly. The reference standard 0.1 ml (10 mg/cup) were also added to the discs in each plate.The plates were kept undisturbed at room temperature for 2 hours,atleast to allow the solution to diffuse properly into potato-dextrose-agar medium. After incubation of the plates at 25^0C for 48 hours, the diameter of zone of inhibition surrounding each of the cups was measured with the help of an antibiotic zone reader. All the experiments were carried out in triplicate. The results are presented in **Table- 2**

Table-1. Antibacterial activity of 3-(1*H*-imidazo[4,5-*b*]pyridin-2-ylamino)-*N*'-(5-aryl-1*H*-1,2,3-triazol-1-yl)propanamides (VI)



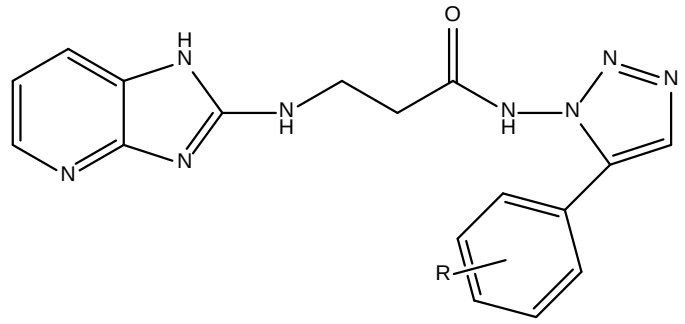
S.No	Compound	Zone of Inhibition (mm)			
		Gram positive bacteria		Gram negative bacteria	
		Bacillus Subtilis	*Staphylococcus aureus*	*Escherichia coli*	*S.typhi*
1	VI a	10	10	22	27

2	VI b	16	11	23	27
3	VI c	19	18	21	28
4	VI d	24	28	28	34
5	VI e	14	17	21	22
6	VI f	12	11	24	25
7	VI g	18	16	20	24
8	VI h	12	14	18	22
9	VI i	19	21	18	24
Standard	**Ampicillin (10µg/ml)**	**22**	**20**	**18**	**22**

Solvent – Dimethylformamide Concentration- 0.1mg/ml

Ar = a) Phenyl b) 2-hydroxy phenyl c) 4-chloro phenyl d) 4-hydroxy phenyl
e) 3,4,5-trimethyl phenyl f) 4-methyl amino g) cinnamyl h) 4-methoxy phenyl
i) 3,4-dimethoxy phenyl

Table-2. Antifungal activity of 3-(1*H*-imidazo[4,5-*b*]pyridin-2-ylamino)-*N*'-(5-aryl-1*H*-1,2,3-triazol-1-yl)propanamides (VI)



S.No	Compound	Zone of Inhibition (mm)	
		A. niger	**C.albicans**
1	VI a	15	16
2	VI b	19	15

3	VI c	-	12
4	VI d	25	20
5	VI e	14	15
6	VI f	16	13
7	VI g	22	17
8	VI h	21	15
9	VI i	21	21
10	**Clotrimazole (10mg/cup)**	**19**	**22**

Concentration of the test compound – 100mg/cup

RESULTS AND DISCUSSION

The reaction of 1*H*-imidazo[4,5-*b*]pyridin-2-amine (I) with ethylacrylate (II) in glacial acetic acid produced the intermediate ethyl3-(1*H*-inidazo[4,5-*b*]pyridin-2-ylamino)propanoate (III). Compound III upon condensation with hydrazine hydrate (99%, 0.01 mol) in alcohol afforded 3-(1*H*-imidazo[4,5-*b*]pyridin-2ylamino)propanehydrazide (IV).

Compound 3-(1*H*-imidazo[4,5-*b*]pyridin-2ylamino)propanehydrazide (IV)

reflux with various aromatic aldehydes in 20ml of absolute alcohol containg few drops of acetic acid, gave the corresponding 3-(1*H*-imidazo[4,5-*b*]pyridin-2ylamino)-*N*’-(3-arylidene)propanehydrazones (V) in good yields. Finally 3-(1*H*-imidazo[4,5-*b*]pyridin-2ylamino)-*N*’-(3-arylidene)propanehydrazones (V) on treatment with diazomethane in benzene, followed by treatment with aq. $KMnO_4$ in presence of tetrabutyl ammonium chloride (TBA) gives the targeted compounds 3-(1*H*-imidazo[4,5-*b*]pyridin-2-ylamino)-*N*'-(5-aryl-1*H*-1,2,3-triazol-1-yl)propanamides (VI) in excellent yields.

The structures of the compounds (III-VI) have been established on the basis of analytical and spectral data.

All the compounds have been evaluated for their antibacterial activity against: *Bacillus subtilis, Staphylococcus aureus* (Gram-positive) and *Escherichila coli, Salmonella typhi*

(Gram-negative). The results of the evaluation have been compared with *Ampicillin* (10µg), a broad spectrum antibiotic as the standard.

Antibacterial activity.

The antibacterial activity results of 3-(1*H*-imidazo[4,5-*b*]pyridin-2-ylamino)-*N*'-(5-aryl-1*H*-1,2,3-triazol-1-yl) propanamides (VI) showed in **Table 1**, only the compound VId (Ar=4-hydroxyphenyl) active against both Gram Positive i.e *B.subtilis and S.aureaus* Gram negative bacteria *E.coli* and *S.typhi* with zone of inhibition of 24mm, 28mm, 28mm and 34 mm respectively. The three compounds i.e Compound VIb (Ar=2-hydroxy pheyl), VIf (Ar=4-dimethylaminophenyl) and compound VIa (Ar=Phenyl) were active only against Gram negative bacteria *E.coli* and *S.typhi* with zone of inhibition of 23mm& 27mm, 24mm & 25mm and 22mm & 27mm respectively. Rest of the compounds showed mild to moderate activity against both Gram positive and Gram negative bacteria.

Antifungal Activity:

The antifungal activity of the six series of compounds has been performed against *Asperilus niger* and *Candida albicans* employing Clotrimazole (10µg) as the standard.

The results revealed that in Type-1 series,3-(1*H*-imidazo[4,5- *b*]pyridin-2-ylamino)-*N*'-(5-aryl-1*H*-1,2,3-triazol-1-yl)propanamides (VI) compound VId (Ar= 4-hydroxyphenyl) and compound VIi (Ar=3,4- dimethoxyphenyl) are more active compared to the standard drug, remaining all compounds showed mild to moderate activity against tested organisms.

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