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Synthesis and antimicrobial evaluation of thiadiazole derivatives

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ABSTRACT

A new series of thiadiazole derivatives were synthesized and screened for their antimicrobial activity. All the newly synthesized compounds were screened for their antibacterial activity against Gram positive species Bacillus subtilis, Staphylococcus aureus and Gram negative species Pseudomonas aeruginosa, E. coli and Candida albicans, A. niger species were used as organism for antifungal activity. Compounds 5c and 5e shows potent activity against the test bacteria and fungi, and emerged as potential molecules for further development. Compounds having substituted phenyl ring were found more biological active and compounds having phenyl ring substituted with electron withdrawing groups gives highest antimicrobial activity.

Keywords: Thiadiazole, antibacterial, antifungal.

INTRODUCTION

Microbial infections caused by various types of bacteria and fungi are one of the leading infections which are responsible for the deaths of the millions of patients worldwide [1]. Treatment of microbial infections including bacterial, fungal and tubercular is becoming difficult because of everlasting problem of microbial resistance towards antibiotics hence the need for new generations of anti-infective agents, and in particular new antimicrobial agents, is constant for effective treatment of microbial infections [2]. The need to design new compounds to deal with this resistance has become one of the most important areas of research today [3].

A heterocyclic compound is a cyclic compound which has atoms of at least two different elements as members of its ring. The counterparts of heterocyclic compounds are homocyclic compounds, the rings of which are made of a single element. Since the beginning of the search of medicinally important synthetic compounds heterocyclic chemistry always remained the point of attraction because of their diverse biological properties. Substitution of heterocyclic compounds on various positions produced medicinally important analogues which are used in the treatment of various diseases [4-5]. In particular, compounds bearing the 1, 3, 4-thiadiazole nucleus is known to have unique antibacterial and anti-inflammatory activities [6-7]. Thiadiazole can act as the bio-isosteric replacement of the thiazole moiety. So it acts like third and fourth generation cephalosporins, hence can be used in antibiotic preparations. There are several isomers of thiadiazole, that is 1,2,3 Thiadiazole (1), 1,2,4 Thiadiazole (2), 1,2,5 Thiadiazole (3) and 1,3,4 Thiadiazole (4) [8-9].

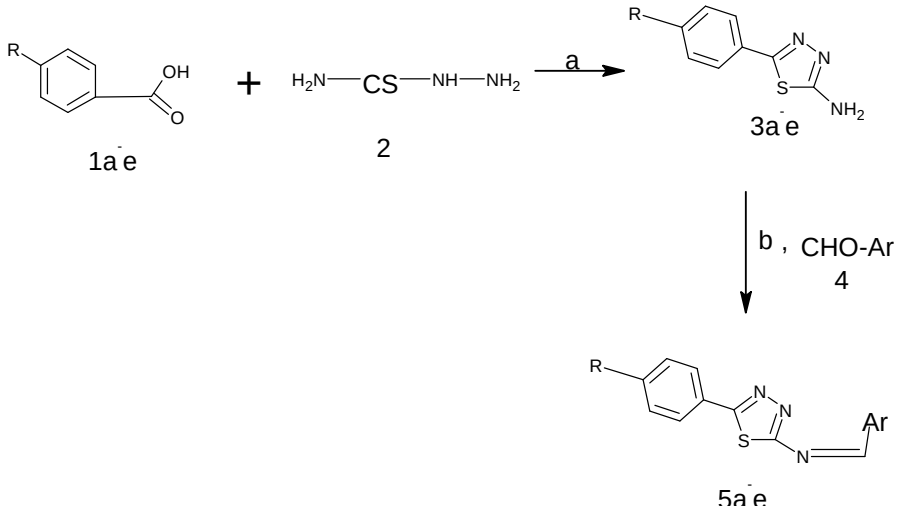
(1) (2) (3) (4)

Thiadiazoles were reported to possess antimicrobial [10], analgesic [11], anti-inflammatory [12], anticancer [13], anti-tubercular [14], anthelmintic [15], diuretic [16], anticonvulsant [17], anti-depressant [18], Anti-Helicobacter pylori [19], anticonvulsant [20] activities. Thiadiazoles are easily metabolized by routine biochemical reactions and are non-carcinogenic in nature [21]. These reports prompted us to synthesize the novel derivatives of Thiadiazoles which would be effective against various strains of microorganisms [22]. All the compounds have been screened for antimicrobial activity against two Gram positive bacteria *S. aureus, B. subtilis* and two Gram negative bacteria *E. coli, P. aeruginosa* and also against two fungal strains *C. albicans, A. niger*. Some of the synthesized compounds showed good antimicrobial activity against these strains even comparable with Ciprofloxacin and Miconazole.

Chemistry

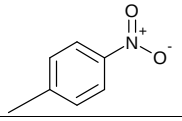
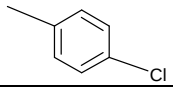
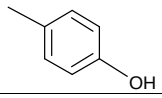
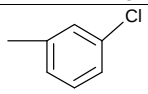
Thiadiazole is a heterocyclic compound featuring both two nitrogen atom and one sulfur atom as part of the aromatic five-membered ring. Thiadiazole and related compounds are called 1, 3, 4-thiadiazole (two nitrogen and one other hetero atom in a five-membered ring). They occur in nature in four isomeric forms as 1,2,3-thiadiazole;1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. 1, 3, 4-thiadiazole are important because of their versatile biological actions.

Substituted thiadiazole derivatives were synthesized by the given synthesis scheme (scheme-I). In starting substituted aromatic acids treated with thiosemicarbazide in the presence of ethanol and H_2SO_4 gives compound (3a-e). Then compound (3a-e) in the presence of methanol and glacial acetic acid reacts with substituted benzaldehyde (4) and gives the final compounds (5a-e).



Scheme 1: Synthesis scheme for the synthesis of compound 5a-e. [(a): ethanol, H_2SO_4, reflux for 3.5 hrs. ; (b): methanol, glacial acetic acid, reflux 4.5 hrs]

Table-I: Physicochemical characteristics of synthesized thiadiazole derivatives

Comp.	-Ar	-R	Mol. Formula	Mol. Wt.	M.P. (°C)	R_f	% yield
5a		-H	$C_{16}H_{13}N_4O_2S$	325.36	134-136	0.69	48.51
5b		-Cl	$C_{16}H_{13}ClN_3S$	314.81	141-143	0.57	34.10
5c		-OH	$C_{16}H_{13}ClN_3OS$	330.81	149-151	0.54	52.09
5d		$-NO_2$	$C_{16}H_{13}N_4O_3S$	341.36	117-119	0.68	38.34
5e		-OH	$C_{16}H_{13}ClN_3OS$	330.81	127-129	0.52	42.80
TLC mobile phase –ethanol : ethyl acetate(7:3)							

Antimicrobial Activity:

For bacterial growth nutrient agar media was used having composition beef extract, 3g; bacteriological peptones, 5g; agar, 20g, the pH was adjusted to 6.2 ± 0.2 at 25 (±2) °C and for fungal growth malt extract agar (MEA) was used composed of malt extract, 20 g; bacteriological peptone, 5g; agar, 20g, the pH was adjusted to 5.4 ± 0.2 at 25 (±2) °C. Media was prepared by dissolving the all ingredients in 1L distilled water and heated upto 60-70°C and was sterilized in an autoclave at 121°C for 15-20 mins. Against the several species the antibacterial and antifungal activity was expressed by the measurement of zone of inhibition by diffusion agar method. At equal distance four holes were made in the sterile agar plates with the help of sterile cork borer in both media i.e. in nutrient agar and in malt extract agar. The synthesized compounds were dissolved in DMSO and 100µg/ml concentration of each compound was filled in the holes. Controlled holes were filled with DMSO solvent. For bacterial isolates plates were placed in a BOD at 37°C ± 2°C and on the other hand fungal isolates were incubated at 28°C ± 2°C for 24-48 hrs. Zone of inhibition created by active compounds were measured after 24-48 hrs. Ciprofloxacin was used as standard antibacterial agent while Miconazole was used as a standard antifungal agent.

RESULTS

The antimicrobial activity of the synthesized compounds were assayed using cup plate technique in the nutrient agar at 100 µg/ml concentration is shown in [Table 2] . Ciprofloxacin standard were active at 50 µg/ml on all the Gram (+ve) bacteria with a zone of inhibition for *Bacillus subtilis*, *Staphylococcus aureus* and Gram (-ve) bacteria *Pseudomonas aeruginosa*, *Escherichia coli*. From the antibacterial screening, it was concluded that compounds 5c and 5e showed larger zone of inhibition as compare to standard drug Ciprofloxacin and Miconazole.

Table II: Antimicrobial results of the synthesized and tested compounds

Compound	Concentration (µg/ml)	Zone of inhibition (in mm)					
		Gram positive		Gram negative		Fungal strain	
		B. subtilis (MTCC 96)	*S.aureus* (MTCC 121)	*P. aeruginosa* (MTCC 2453)	*E.coli* (MTCC 40)	*C. albicans* (MTCC 8184)	*A.niger* (MTCC 8189)
5a	100	22	26	20	26	20	18
5b	100	21	25	19	26	19	18
5c	100	27	28	23	29	22	21
5d	100	21	24	20	24	18	17
5e	100	26	27	22	28	21	20
Ciprofloxacin	50	25	28	22	27	-	-
Miconazole	50	-	-	-	-	20	19

CONCLUSION

All the newly synthesized 1,3,4-thiadiazole derivatives were screened for their antimicrobial activity. For antibacterial studies microorganisms employed were Gram positive species *Bacillus subtilis*, *Staphylococcus aureus* and Gram negative species *Pseudomonas aeruginosa* and for antifungal *Candida albicans*, *A. niger* species were used as organism.

In all above synthesized compounds one side amine chain is present with phenyl ring (-Ar). The compounds with substituted rings have more activity as compared to unsubstituted rings. Compounds 5c, 5e exhibited the maximum activity because in these compounds phenyl ring of side amine chain was substituted by electron withdrawing groups. The second reason for higher activity of 5c, 5e is another substitution by electron donating groups at –R position. While the phenyl ring of compound 5d was substituted by electron donating groups so it exhibited less activity as compared to 5c and 5e. Compounds 5a and 5b exhibited less activity due to no substitution at –R and no substitution on aryl ring respectively. So compounds 5b, 5d have least antimicrobial activity among all synthesized compounds.

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