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Synthesis and Antimicrobial Evaluation of Substituted Thiazole Compounds

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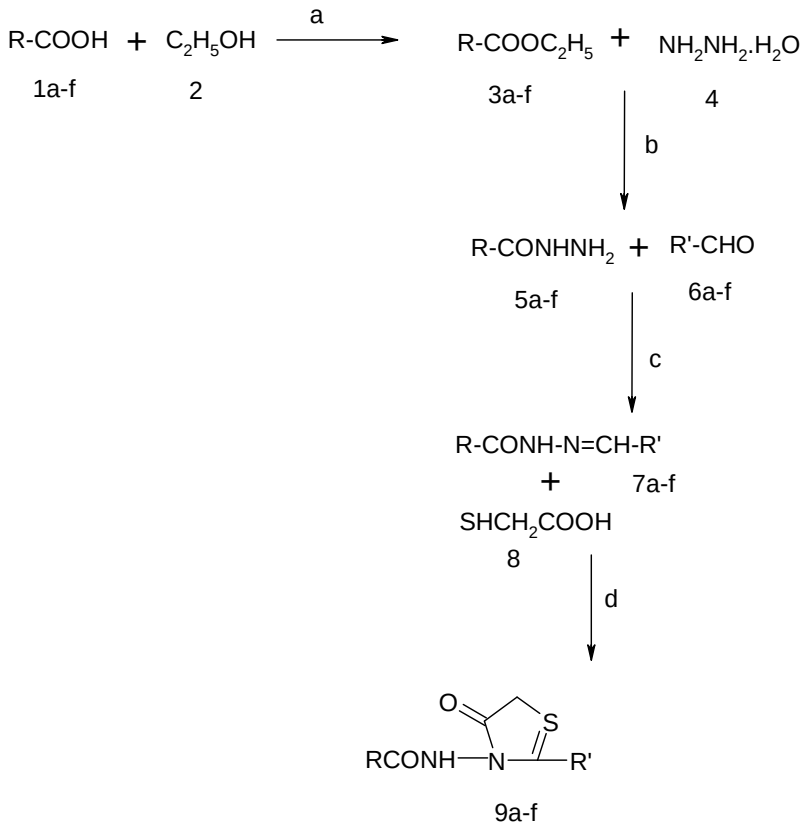
Abstract: A series of N-substituted thiazole derivatives were synthesized for improved antimicrobial activity. The synthesized compounds were evaluated for antimicrobial activity by the means of zone of inhibition by agar cup plate method. The compounds were screened for their antibacterial activity against positive species *Bacillus subtilis, Staphylococcus aureus* and Gram negative species *Pseudomonas aeruginosa, E.coli* and antifungal activity against *Candida albicans, A. niger* species. Ciprofloxacin and Miconazole were used as standard drugs for antibacterial, antifungal activity respectively. Compounds 9a, 9d were found most active due to appropriate position of electron withdrawing and electron donating groups.
Keywords: Thiazole, antimicrobial, Ciprofloxacin, Miconazole.

Introduction:

Thiazole derivatives are considered as one of the most important classes of heterocyclic compounds. Their derivatives are characterized by high biological activity in pharmaceutical fields and have shown antibacterial activity.[1] On the other hand, thiazoles are basic class of heterocyclic moieties which possess a wide range of therapeutic interest and their importance is also very much established in medicine.[2] The development of antibacterial agents has been a very important step for research, most of the research programme efforts are directed toward the design of new drugs, because of the unsatisfactory status of present drugs side effects and the acquisition of resistance by the infecting organism to present drugs.[3]. The massive use of antibacterial drugs by mankind leads to a major problem i.e. drug resistance.[4] A potential approach to overcome the resistance problem may be represented by the design of innovative agents having a different mechanism of action, so that it can't occur any cross-resistance with the therapeutic agents in use.[5] In spite of a large number of antibiotics and chemotherapeutics available today, due to the widespread and excess use of antibiotics, bacterial resistance has become a serious public health problem, always demanding new classes of antibacterial agents. The development of new potential drugs, will be one of the possible solutions to treat various infectious diseases with multi drug treatment and will be devoid of side effect and resistance profile of currently available drugs[6]. Thiazole derivatives have attracted a great deal of interest owing to their antimicrobial[7], anti-inflammatory[8-9], CNS depresent[10], antitubercular[11], antitumor[12], anthelmintic[13], sedative[14], antiretroviral properties[15] and antineoplastic[16] activity.

Chemistry:



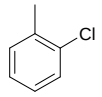
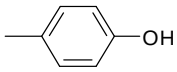
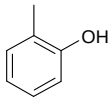
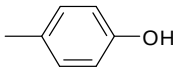
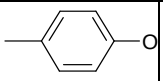
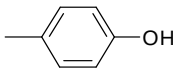
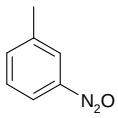
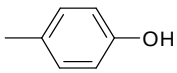
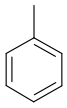
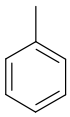
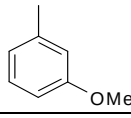
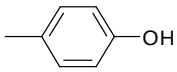
Scheme 1: Synthesis scheme for the synthesis of compound 9a-f (**a:** H_2SO_4, 3hr reflux, **b:** ethanol, 3.5hr, **c:** methanol, glacial acetic acid, 4hr reflux, **d:** DMF, $ZnCl_2$, 6hr reflux.

Esterification of substituted aromatic acid **1** was done with ethanol **2** in the presence of H_2SO_4 acid yield compound **3.** Then compound **3** reacted with hydrazine hydrate **4** in the presence of ethanol to give hydrazone derivatives **5** which react with aromatic substituted benzaldehyde **6** in the presence of methanol forms **7**. Finally by reacting compound **7** with thioglycolic acid **8** in the presence of DMF/ $ZnCl_2$ synthesized substituted thiazole compound **9**.

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 $\pm$ 0.2 at 25 ($\pm$2) $^{\circ}$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 $\pm$ 0.2 at 25 ($\pm$2) $^{\circ}$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 were filled in the holes. Controlled holes were filled with DMSO solvent. For bacterial isolates plates were placed in a BOD at 37°C $\pm$ 2°C and on the other hand fungal isolates were incubated at 28°C $\pm$ 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.

Table-I: Physicochemical characteristics of synthesized thiazole derivatives

compound	-R	-R'	Mol. Formula	Mol. Wt.	M.P. (°C)	Rf	% yield
9a			$C_{16}H_{12}ClN_2O_3S$	347.797	136-138	0.63	53.02
9b			$C_{16}H_{13}N_2O_4S$	329.349	133-135	0.42	39.63
9c			$C_{16}H_{13}N_2O_4S$	329.349	133-135	0.54	42.29
9d			$C_{16}H_{13}N_4O_4S$	356.355	141-143	0.70	35.21
9e			$C_{16}H_{13}N_2O_2S$	297.351	135-137	0.49	65.35
9f			$C_{17}H_{15}N_2O_4S$	343.376	144-146	0.56	47.60
TLC mobile phase- Hexane: ethylacetate (4:6)							

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 9a and 9d 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)
9a	100	27	30	28	31	27	26
9b	100	23	25	21	24	20	18
9c	100	22	24	22	28	19	18
9d	100	26	29	27	28	25	24
9e	100	25	26	25	27	24	22
9f	100	25	26	23	26	22	20
Ciprofloxacin	50	24	27	23	26	-	-
Miconazole	50	-	-	-	-	22	21

Conclusion:

Results obtained from antimicrobial activity showed that compound 9a, 9d were highest active against Gram positive species *Bacillus subtilis, Staphylococcus aeuras* and Gram negative species *Pseudomonas aeruginosa, Escherichia coli.* These both compounds have highest zone of inhibition among all the synthesized compounds due to appropriate presence of electron withdrawing and electron donating groups. Compound 9a, 9d also shows highest antifungal activity against *Candida albicans* and *A. niger* species.

Compound 9b, 9c, 9f were substituted with hydroxyl and methoxy groups at –R position and by hydroxyl at –R' position. This may be the reason for lowest activity of these compounds, i.e. wrong side (-R and –R') substitution by electron withdrawing and electron donating groups. So we can say that at –R position electron withdrawing and at -R' position electron donating groups are good to increase the binding of molecule with the target.

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