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CODEN: IAASCA **ORIGINAL ARTICLE**

Synthesis And Antimicrobial Activity Of Some New Thiadiazole Derivatives

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ABSTRACT
A new series of potential thiadiazole derivatives had been synthesized using 3-(4- substituted benzoyl)propionic acid. The structures of the synthesized compounds were confirmed on the basis of IR and ^1H NMR and elemental analysis data. All the synthesized compounds were screened for their antibacterial and antifungal activities. The antibacterial activity was checked against S. aureus (gram-positive) and E.coli (gram-negative) bacteria and antifungal activity against A. niger fungi. Some of tested compounds exhibited promising antibacterial and antifungal activities.
Keywords: *1,3,4-Thiadiazole, Aroylpropionic acid, Antibacterial, Antifungal.*
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INTRODUCTION

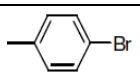
Antibacterial and antifungal diseases are very common all over the world. Currently used antimicrobial agents are not effective due to the resistance developed by the microbes. Further infection caused by various microorganisms pose a serious challenge to the medical community and need for an effective therapy has led to search for novel antimicrobial agents[1]. A diversity of useful biological effects is possessed by heterocyclic compounds containing the five-membered nucleus. Interesting pharmacological properties exhibited by thiadiazole derivatives [2-8] promoted us to synthesize a few nitrogen containing heterocyclic nucleus to evaluate their antimicrobial activities.

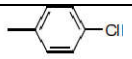
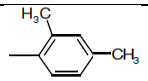
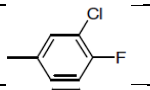
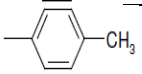
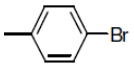
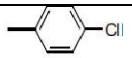
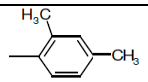
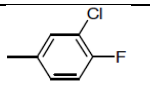
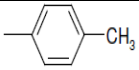
In view of the above mentioned facts and in continuation of our work on the synthesis of biologically important heterocyclic compounds, we describe herein the synthesis of some thiadiazole derivatives and evaluation of their antimicrobial activities. The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in Scheme 1. The structures of the compounds were assigned on the basis of IR, ^1H NMR spectral data

EXPERIMENTAL

The chemicals and solvents used for the experimental work were commercially procured from E. Merck, CDH, S. D. Fine Chem. and Qualigens, all from India. Melting points were determined in open capillary tubes. IR spectra were recorded on a Perkin-Elmer 157 spectrometer and ^1HNMR spectra on a Bucker WM-400 (400 MHZ FT NMR) spectrophotometer using TMS (Tetramethyl Silane) as internal reference (chemical shift in d ppm). Purity of the compounds was checked by TLC (Thin Layer Chromatography) on silica gel plates and spot were visualized by exposure to iodine vapours.

Table 1. Characterization data of the compounds

Compd.	R	Ar	M.P.	Yield%	Mol. Formula
5a	CH_3		264	60	$C_{18}H_{16}BrN_3OS$

5b	**CH_3**		**238**	**62**	**$C_{18}H_{16}ClN_3OS$**
5c	**CH_3**		**278**	**59**	**$C_{20}H_{21}N_3OS$**
5d	**CH_3**		**269**	**63**	**$C_{18}H_{15}FClN_3OS$**
5e	**CH_3**		**240**	**62**	**$C_{19}H_{19}N_3OS$**
5f	**Cl**		**265**	**65**	**$C_{17}H_{15}ClBrN_3OS$**
5g	**Cl**		**258**	**61**	**$C_{17}H_{15}Cl_2N_3OS$**
5h	**Cl**		**280**	**58**	**$C_{19}H_{18}ClN_3OS$**
5i	**Cl**		**281**	**65**	**$C_{17}H_{14}FCl_2N_3OS$**
5j	**Cl**		**244**	**61**	**$C_{18}H_{16}Cl_2N_3OS$**

Preparation of 3-(4-substituted benzoyl)propionic acid (1)

Succinic anhydride (0.1 mole) was reacted with an appropriate aromatic compound (substituted benzene; 50 mL) in presence of anhydrous aluminium chloride (0.1125 moles). The reaction mixture was refluxed under anhydrous conditions for two hours and after completion of the reaction excess solvent was removed by steam distillation. On cooling, a solid mass separated out which was filtered and purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. The solid mass so obtained was filtered, washed with cold water, dried and recrystallized from methanol. Yield 72%; M.p. 124° C. ^{1}H-NMR ($CDCl_3$, δ, ppm): 2.81 & 3.38 (t, e, 2x -CH2-), 7.45 & 7.92 (d, each, A_2B_2, *p*-substituted phenyl).

Synthesis of3-(4- substituted benzoyl)propionate (2)

To a 100 mL RB flask, a mixture of *3*-(4-substituted benzoyl) propionic acid (0.001 mol) and absolute alcohol (50 mL) were taken. Few drop of conc. H_2SO_4 along with a small porcelain chip were added. A condenser was attached to the RB flask fitted with a calcium chloride guard tube to maintain anhydrous condition. The reaction mixture was refluxed for 40 h on water bath, concentrated under reduced pressure to give the ester. ^{1}HNMR($CDCl_3$): δ 1.41 (t, 3H, CH3), δ 4.38 (q, 2H, OCH_2), δ 7.48-7.64 (m, 3H, Ar-H).

Synthesis of3-(4- substituted benzoyl)propiohydrazide (3)

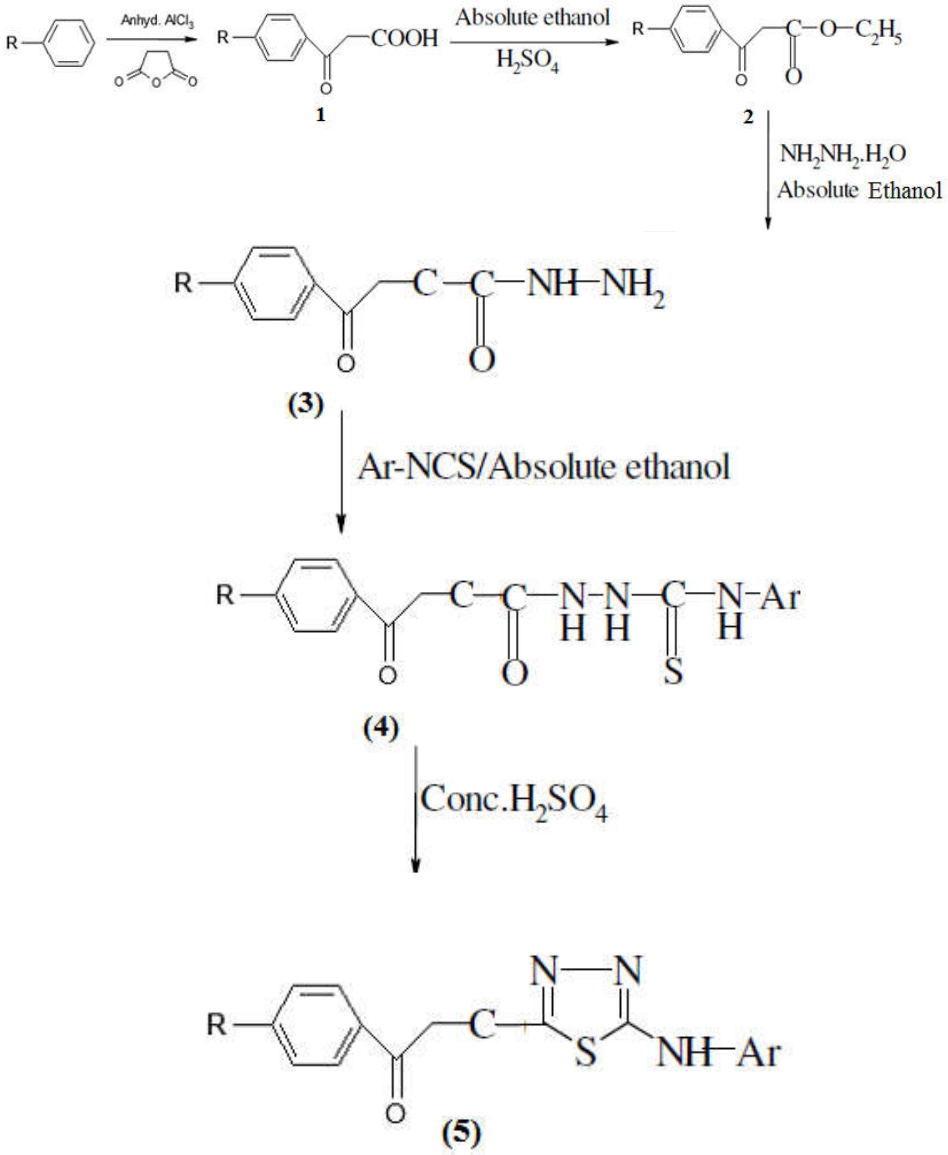
To a RB flask, compound **2** (0.01 mol), hydrazine hydrate (0.2 mol) and absolute alcohol (50 mL) were taken. A condenser with calcium guard tube was attached to the flask and mixture was refluxed for 60h on water bath. The mixture was concentrated, cooled and poured in to crushed ice. It was kept for 3-4 h at room temperature and solid mass separated out was filtered and dried. ^{1}HNMR ($CDCl_3$): δ 7.50-7.78 (m, 3H, Ar-H), δ 7.87-7.97 (m, 3H, $CONHNH_2$)

Synthesis of [4-(4- substituted pheyl)-4-oxo-butanoyl]-N-(substituted phenyl)hydrazine carbothio amide(4)

A mixture of compound 3 (0.001 mol) and substituted phenyl isothiocyanate (0.001 mol) in ethanol (25.0 mL) was refluxed on a water bath for 2 h. The solvent was concentrated and the precipitated product was filtered, dried and recrystalized from methanol. IR (KBr): 3390 (N-H), 1620 (CONH), 600 (ArH), 1040 (C=S). ^{1}HNMR (CDCl3): δ 7.12-7.60 (m, 3H, Ar-H), δ 7.72-7.83 (m, 3H, CONHNHCSNH)

Synthesis of 3-[2-(substituted phenyl)amino-1,3,4-thiadiazole-2-yl]-1-(4- substituted phenyl) propanone(5)

Compound **3a** (0.002 mole) was added portion wise in 5.0 mL conc. H_2SO_4 and stirred with cooling for 2h. The mixture was poured over crushed ice and the precipitated solid was filtered, washed with water, dried and recrystallised from methanol. IR (KBr): 3412 (N-H), 1615 (C=N), 2920 (C-H). **6a** 1HNMR (CDCl3): δ 3.84 (s, 3H, CH3), δ 6.58-7.53 (complex m, 7 Ar-H and 1NH). 6b IR (KBr): 3436 (N-H), 1624 (C=N), 2938 (C-H). **6b** 1HNMR (CDCl3): δ 3.86 (s, 3H, OCH3), 6.59-7.55 (complex m, 7 Ar-H and 1NH).



SCHEME:1

RESULTS AND DISCUSSION

Spectral characterization of the compounds

The IR spectrum of the compounds (**5a-j**) showed peaks at 3436-3410 cm^{-1},N-H stretching; 2938-2920 cm^{-1}, CH stretching; 1624-1609 cm^{-1}, C=N stretching. The NMR spectrum of the compound **5a** showed a singlet at d 3.84 indicating the presence of CH_3 protons. In the aromatic region complex multiplet at d 6.58-7.53 was observed indicating the presence of seven aromatic protons and one NH protons.

Antimicrobial activity

The synthesized compounds were evaluated for their antimicrobial activity against bacterial strain *Staphylococcus aureus* (*S. aureus*) (gram-posative), *Escherchia coli* (*E. coli*) (gramnegative) and fungal strain *A niger* by cup plate method at 200, 100, 50 and 25 µg/mL concentration. Ofloxacin and ketoconazole was used as standard drugs for antibacterial and antifungal activity respectively. The minimal inhibitory concentration (MICs, μgmL^{-1}) of the tested compounds are recorded in Table 2.

Table 2: Antimicrobial activities of the compound

Compound	MIC(μg/ml)		
	S.aureus	*E.Coli.*	*A. niger*
Ofloxacin	10.0	12.5	--
Ketoconazole	----	----	12.5
5a	100	100	50
5b	25	50	25
5c	100	100	200
5d	25	25	25
5e	100	100	100
5f	100	100	50
5g	25	50	25
5h	100	100	100
5i	25	25	25
5j	100	100	50

---- *Not tested*

Out of all the synthesized thiadiazole derivatives of the series, compound 5d,5i having having 3-chloro-4-fluorophenyl amino group at 2nd position of thiadiazole ring was found to have MIC 25 μg/mL against *S. aureus*, *E.coli* and *A. niger* chloro and fluoro group at 3rd and 4th position. 1,3,4-thiadiazole derivatives **5b, 5g** also exhibited promising antibacterial activity (MIC 25 μg/mL) against *S. aureus* and *A. niger*.

CONCLUSION

A total of 10 compounds were synthesized and screened for their antibacterial activity against *S. aureus* (gram positive) and *E. coli* (gram negative) bacteria and antifungal activity against *A. niger*. The minimal inhibitory concentrations (MIC) of all the compounds were determined by observing the zones of inhibition formed around the cup after 24h of incubation for antibacterial and 48h for antifungal activities. Compounds were found to have moderate antimicrobial activity.

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