SYNTHESIS AND EVALUATION OF SOME NEW 1,3,4-THIADIAZOLE DERIVATIVES FOR THEIR ANTIMICROBIAL AND ANTITUBERCULAR ACTIVITY

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ABSTRACT

A new series of 1,3,4-thiadiazole derivatives were synthesized and the structures of the compounds were established by means of IR, ^{1}H-NMR and elemental analysis. All the compounds were evaluated for antibacterial, antifungal and antitubercular activities. Most of the compounds have shown significant antibacterial, antifungal and antitubercular activity when compared with the standard drugs.

Keywords: 1,3,4-thiadiazole, antibacterial, antifungal and antitubercular.

INTRODUCTION

Tuberculosis is currently the leading killer of youths, women and AIDS patients in the world. Although many active antitubercular agents have since been developed, a disturbing co-occurrence with the use of present drugs as single agent has developed drug resistance. The development of this resistance can be forestalled through the use of combination regimens, it is clear that drug resistance will continue to be a problem. Therefore there is a need for the discovery of new derivatives with antitubercular activity for the management of tuberculosis.

1, 3, 4-thiadiazoles are associated with diverse biological activities. A large number of 1, 3, 4-thiadiazoles have been reported to be antifungal, antibacterial and antileukemic agents. These observations promoted us to synthesis the title compound with presumption that incorporation of aromatic amines would produce new compounds with significant antibacterial, antifungal and antitubercular properties.

MATERIALS AND METHODS

Antimicrobial activity

The antimicrobial activity of the synthesized compounds was determined by cup-plate method. The organisms selected for antibacterial activity were *Staphylococcus aureus* and *Escherichia coli.* Similarly the antifungal activity was carried out by using *Aspergillus niger* and *Candida albicans*. The concentration of sample compounds was 100 mcg/mL. Norfloxacin and griseofulvin were used as standard drugs for antibacterial and antifungal activity respectively. Control test with solvents were performed for every assay but showed no inhibition of the microbial growth.

Antitubercular evaluation

The antitubercular screening was carried out by Lowenstein–Jensen egg medium (L J Medium) as described by Watt against $H_{37}Rv$. Strain. L J Medium containing standard drug as well as control. L J Medium was inoculated with mycobacterium tuberculosis of $H_{37}Rv$ Strain. The inoculated medium was incubated for 37°C for 6 weeks. At the end of 6 weeks and the growth of mycobacterium tuberculosis was read.

EXPERIMENTAL

M.P.s was determined in open capillary method and are uncorrected. IR spectra were recorded on Thermo Nicolet IR 200 spectrophotometer using KBr disc method. The ^{1}H-NMR spectra were recorded on sophisticated multinuclear FT-NMR Spectrometer model Avance-II (Bruker) using dimethylsulfoxide-d_6 as solvent and tetramethylsilane as internal standard. The reactions were carried in Microwave oven.

Synthesis of 5-(4-Nitro-phenyl)-[1, 3, 4] thiadiazol-2-ylamine (I).

A mixture of thiosemicarbazide (9.11 g, 0.1 mol), aryl carboxylic acid (8.49 g, 0.1 mol), and conc. sulphuric acid (10 drops) was refluxed for 1 hour and poured onto crushed ice. The solid separated out was filtered, washed with cold water and recrystallized from ethanol to give. Yield 68%, m.p. 135-36 °C.

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Synthesis of N'-2-Nitro-phenyl)-N'-(5-pyridin-3-yl-[1, 3, 4] thiadiazol-2-yl)-methanediamine (C_1)

A mixture of 5-(4-Nitro-phenyl)-[1,3,4]thiadiazol-2-ylamine (2.22 g, 0.01 mol) and 2-nitro aniline (1.38 g, 0.01 mol) and formaldehyde (1-2 drops) were taken in a beaker. The mixture was irradiated in a microwave oven for about 1-2 mins. After that ice cold water was pored and separated solid product was obtained and dried to get N'-2-Nitro-phenyl)-N'-(5-pyridin-3-yl-[1,3,4]thiadiazol-2-yl)-methanediamine. Recrystallized from ethanol. Yield 68%, m.p. 140-42°C. The compounds C_2-C_5 were synthesized following a similar procedure. The yields & m.p. are listed in Table-I.

RESULTS AND DISCUSSION

All the compounds were evaluated for antibacterial and antifungal activity by cup-plate method. Compounds C_2, C_4, and C_5 have shown significant antibacterial activity. Remaining compounds have also shown moderate or weak antibacterial activity. Compounds C_2 and C_4 and have shown significant antifungal activity. Remaining compounds have also shown moderate or weak antifungal activity.

The antitubercular screening was carried out by Lowenstain–Jensen egg medium (L J Medium) as described by Watt against $H_{37}Rv$ Strain. Compounds C_2, C_4 and C_5 have shown significant antitubercular activity. Streptomycin was used as a standard drug. Remaining compounds have also shown moderate or weak antitubercular activity. With the suitable molecular modification of these compounds can prove as potent antibacterial, antifungal and antitubercular agents in future.

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Scheme-1

Table I - Characterization data and results of antimicrobia l activity (C_1-C_5)

Compd.	Yield %	m.p. °C	Elemental Analyses Found (Calcd.)			Zone of Inhibition in mm*			
						Antibacterial		Antifungal	
			C	H	N	S.aureus	E.coli	A.niger	C.albicans
C_1	68	140-42	51.21 (51.56)	3.68 (3.65)	25.59 (25.75)	12	16	15	18
C_2	74	178-80	59.34	4.62	24.72	22	23	17	18
C_3	80	150-51	52.91 (52.86)	3.81 (3.75)	22.04 (22.15)	16	15	19	20
C_4	55	190-91	52.47 (52.67)	3.82 (3.75)	20.40 (20.56)	23	23	24	23
C_5	60	158-61	51.37	4.00	29.95	22	24	22	24
STD.	Norfloxacin					23	24	--	--
	Griseofulvin					--	--	25	26

STD: Standard drugs. *Including diameter of the well 6 mm disk.

Table II- Antitubercular activity of the synthesized compounds (C_1-C_5)

SL. No.	Compounds	50 mcg/mL	100 mcg/mL
1.	C_1	+ -	+ -
2.	C_2	- -	- -
3.	C_3	+ -	+ -
4.	C_4	- -	- -
5.	C_5	- -	- -
STD.	Streptomycin	- -	- -

Table III – Spectral data

Compd.	IR (cm-1)	^{1}H-NMR (δ, ppm)
C1	3471 (N-H str.), 2360 (Ar.–CH str.), 1634 (Ar. C-C str.), 1415 (C-N str.), 1566 (N-O str.), 640 (C-S str.)	6.74-8.1 (8H,Ar-CH), 5.11 (2H, CH_2), 3.9 (1H, NH)
C2	3440 (N-H str.), 2353 (Ar.–CH str.), 1605 (Ar. C-C str.), 1416 (C-N str.), 622 (C-S str.)	--
C3	3443 (N-H str.), 2360 (Ar.–CH str.), 1641 (Ar. C-C str.), 1420 (C-N str.), 620 (C-S str.)	--
C4	3414 (N-H str.), 2282 (Ar.–CH str.), 1624 (Ar. C-C str.), 1433 (C-N str.), 612 (C-S str.)	--
C5	3393 (N-H str.), 2932 (Ar.–CH str.), 1696 (CONH str.), 1498 (C-N str.), 667 (C-S str.)	11.28 (2H, OH, PAS), 7.3-8.09 (8H,Ar-CH), 6.05 (2H, CH_2), 3.23 (1H, NH)

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