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Research Article

SYNTHESIS AND EVALUTION OF ANTIBACTERIAL ACTIVITY OF SOME 2-AMINO/SUBSTITUTED AMINO-4-(PHENYL/p-CHLOROPHENYL) THIAZOLES

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ABSTRACT

One of the first commercial synthetic drugs containing thiazole ring was sulphathiazole, a simple sulfamide antibiotic derived from 2-amino thiazole. Moreover, a large number of thiazole derivatives have been found to exhibit pharmacological activities. More specifically, thiabendazole is widely used as anthelmintic and fungicide. Dcngolinc is used as ingredient of herbicide. 3- substituted-4-amino thiazole-2-thione possesses antifugal activity. Moreover, ever large number of functional derivatives of thiazole exhibit interesting biological properties. These reports substantiated the importance of 2-amino -4- (phenyl/p-chlorophenyl) thaizole moiety. In the view of the above facts and wide spectrum of activity associated with thiosemicarbazide, **thiadiazole**, thiazolidinones, and pyrimidine diones, it was thought worthwhile to synthesize a series of 2-amino/substituted amino-4-(phenyl/p-chlorophenyl) thiazoles and their derivatives (**Scheme-1)** as possible anti bacterial agents. A series of 2-amino/substituted [thiosemicarbazide/2-(N-2'mercapto-1',3',4'-thiadiazol-5'-yl] amino-4- (phenyl/p-chlorophenyl) thaizole moieties were prepared. The structures of compounds have been established on the basis of their IR and ^{1}H NMR spectral data. All the synthesized compounds were evaluated for their antibacterial activity using gram (+) ve and gram (-) ve organisms. The following tests compounds **2a, 2b, 3a, 3b, 4b and 5b** shows moderately active against gram +ve bacteria like SA and LB. Remaining compounds like 1a, 2a and 5b which are highly active against gram (+) ve organisms. The following compounds 1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b, 5a and 5b shows moderately active against gram - ve organisms like EC, ST, PA and PB. Remaining compounds like 1a, 3b, 4a, 4b, 5a and 5b which are highly active gram - ve organisms. In the present study, we concluded that some of the synthesized compounds possessed highly antibacterial activity.

Keywords: 2-amino/substituted amino-4- (phenyl/p-chlorophenyl) thiazole, synthesis, microorganism, antibacterial activity.

1. INTRODUCTION

Thiazole is a weak base having pKa value 2.5 than pyridine pKa value 5.2, but it forms a crystalline hydrochloride and aurichloride. It also forms thiazolium salt with alkali halides, and these like 1-alkylpyridinuim salts of decomposed alkali. One of the first commercial synthetic drugs containing thiazole ring was sulphathiazole, a simple sulfamide antibiotic derived from 2-amino thiazole [1]. Moreover, a large number of thiazole derivatives have been found to exhibit pharmacological activities [2-7]. More specifically, thiabendazole is widely used as anthelmintic and fungicide[1]. Benzoline is used as ingredient of herbicide, 3- substited-4-amino thiazole-2-thione possesses anti-fungal activity.

In view of wide spectrum of activity associated with thiosemicarbazides [8-12], thiadiazoles [13-16], thiazolidinone [17-22] and pyrimidinediones [23], it was planned to synthesize some thiazole derivatives carrying the biodynamic heterocyclic system at position-2. During present investigation required starting materials 2-aminothiazoles (1a-b) were prepared according to the literature method [24]. These compounds underwent reaction with carbon disulphide and hydrazine hydrate in presence of sodium hydroxide to furnish the corresponding N-(4-Phenyl-/p-chlorophenylthiazole-2-yl) thiosemicarbazide (2a-b). Thiosemicarbazide (2a-b) were reacted with carbon disulphide in presence of triethylamine to afford 2-[N-(2-mercapto-1',3',4'-thiadiazole-5-yl)amino]-4-phenyl-/p-chlorophenyl thiazoles (3a-b). Compounds 2a-b were reacted with chloroacetic acid in presence of sodium acetate to get 3-(4'-phenyl-/p-chlorophenylthiazole-2-yl)-2-hydrazino-4 thiazolidinones (4a-b). The thiosemicarbazide were also treated with malonic acid in presence of acetyl chloride to afford 3-amino-1-(4'-phenyl-/p-chlorophenylthiazole-2'-yl)-2-3-dihydro-2-thioxo-4,6(1H,5H) pyrimidindiones (5a-b). These reports substantiated the importance of 2-amino-4- (phenyl/p-chlorophenyl) thiazole moiety. In the view of the above facts and wide spectrum of activity associated with thiosemicarbazide, thiadiazoles, thiazolidinones, and pyrimidindiones, it was thought worthwhile to synthesize a series of 2-amino/substituted

amino-4- (phenyl/p-chlorophenyl) thiazoles and their derivatives (Scheme 1) as possible anti bacterial agents.

2. MATERIAL AND METHODS

Chemistry: 2-aminothaizole (I) were prepared according to the literature method. These compounds underwent reaction with carbon disulphide and hydrazine hydride in presence of sodium hydroxide to furnish the corresponding N- (4-phenyl/p-cholorophenyl thiazole-2-yl) thiosemicarbazide (II).thiosemicarbazide were reacted with carbon disulphide in presence triethylamine to offered 2-(N-2′mercapto-1′,3′,4′-thiadiazol-5′-yl)amino-4-(phenyl/p-chlorophenyl) thiazole (III).

Synthesis

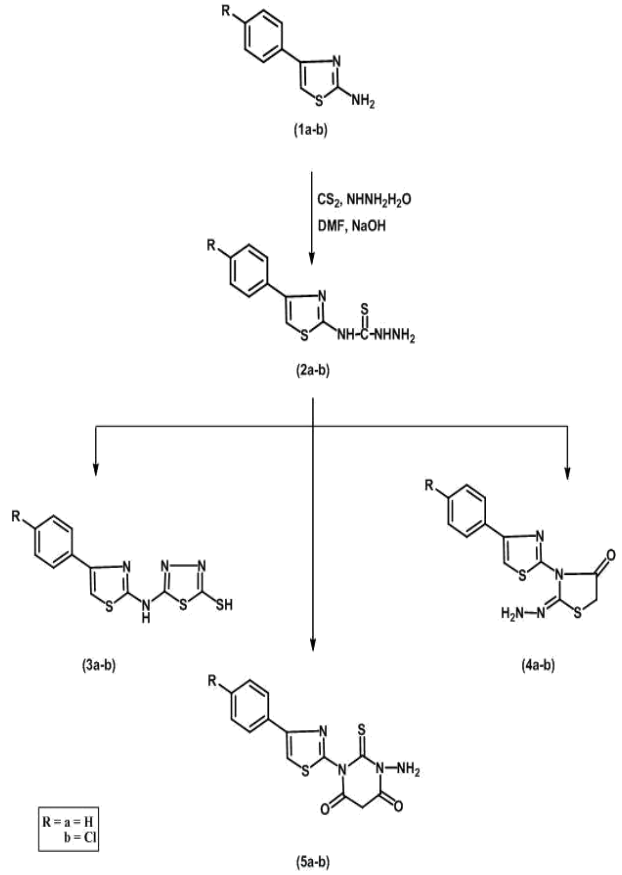
Apparatus: Melting points were determined in open capillary method and are uncorrected. The IR spectra were recorded on Perkin-Elmer 781 spectrometer using KBr/nujal pellet technique. ^{1}H-NMR spectra of the final compounds were recorded on jeol JNM-LA 300 MHz FT-NMR spectrophotometer using TMS as internal standard and Cdcl3 as standard.

General procedure for the synthesis of 2-amino/substitutedamino-4-(phenyl/p-chlorophenyl) thiazoles and their derivatives

Carbon disulfide was distilled off and the solid 2-(N-2'mercapto-1',3',4'-thiadiazol-5'-yl) amino-4-(phenyl/p-chlorophenyl) thiazoles (compound 3a and 3b)obtained on adding to crushed ice and acetic acid, was filtered and washed with water, dried and recrystallized by using benzene. The structure of compound 2a and 3a were confirmed by elemental and spectral data. Their physical data are given in (Table 1).

Synthesis of 3-(4'phenyl/p-chlorophenylthiazole-2-yl)-2-hydrazino-4-thiazolidinone (4a and 4b): To a solution of N-(4'phenyl/p-chlorophenylthiazole-2-yl)-thiosemicarbazide (0.005 mol) in acetic acid (7.5 ml) monochloroacetic acid (0.005 mol) were added. The reaction mixture was refluxed for 8 hrs. Cooled, poured into crushed ice. The separated solid was filtered, washed thoroughly with water dried and crystallized from benzene. Their physical data are given in (Table 1).

Synthesis of 3-amino-1-(4'phenyl/p-chlorophenylthiazole-2-yl)-2,3-dihydro-2-thioxo-4,6 (1H, 5H) pyrimidindiones (5a and 5b): Thiosemicarbazide (0.0015 mol) and malonic acid (3.2 gm : 0.02 mol) in acetyl chloride (7 ml) were refluxed for 4 hrs at 40 ° C. The reaction mixture was cooled and poured into ice cold water. The 3-amino-1-(4'phenyl/p-chlorophenylthiazole-2-yl)-2,3-dihydro-2-thioxo-4,6 (1H, 5H) pyrimidindiones was filtered , dried and recrystallized with ethanol. Their physical data are given in (Table 1).



Scheme 1

Spectral data:

IR: Compound (2a) showed peak at 3420/3240 and 1030 cm^{-1} may be due to NH2/NH and C=S stretching respectively. The compound (3a and 4a) showed peak at 3250, 1530 and 1070 cm^{-1} due to NH, C=N and C=s stretching respectively (Fig 1-3).

^{1}HNMR of the compound (2a and 4a) showed chemical shifted at 5.2 δ representing –NH2 function of thiosemicarbazide group. The aromatic protons were noticed as assigned to 5-H proton of thiazole nucleus and peak at 7.8 δ was accounted for two -NH of thiosemicarbazide group (Fig 4-5).

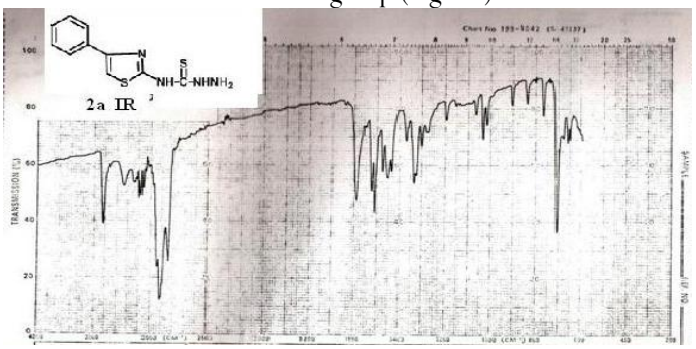
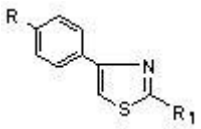
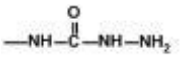
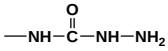
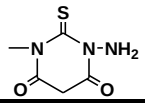


Fig 1: IR spectrum of compound 2a

Table 1: Physical data of 2-amino/substituted amino-4-(phenyl/p-chlorophenyl)-thiazoles and their derivatives



Compound	Substituents		Melting point °C	Yield %	Crystallizing Solvent	Molecular formula
	R_1	R_2				
1a	H	$-NH_2$	158	50	Ethanol	$C_9H_8N_2S$
1b	Cl	$-NH_2$	100	56	Ethanol	$C_9H_7N_2SCl$
2a	H		142	57	Ethanol	$C_{10}H_{10}N_4S_2$
2b	Cl		152	63	Ethanol	$C_{10}H_9N_4S_2Cl$
3a	H		123	75	Benzene	$C_{11}H_8N_4S_3$
3b	Cl		132	55	Benzene	$C_{10}H_7N_4S_3Cl$
4a	H		142	60	Benzene	$C_{12}H_{10}N_4S_2O$
4b	Cl		149	86	Benzene	$C_{12}H_9N_4S_2OCl$
5a	H		168	100	Ethanol	$C_{13}H_{10}N_4S_2O_2$
5b	Cl		172	72	Ethanol	$C_{13}H_9N_4S_2O_2Cl$

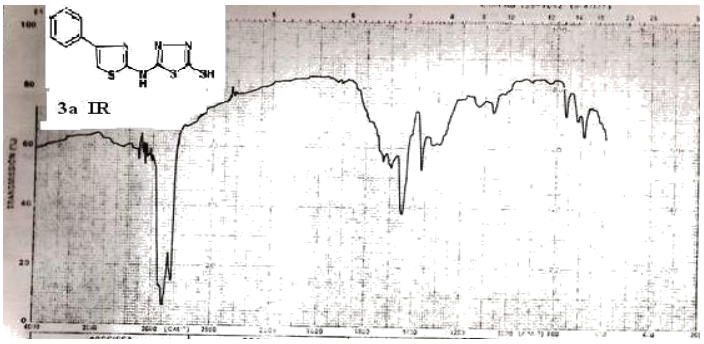


Fig 2: IR spectrum of compound 3a

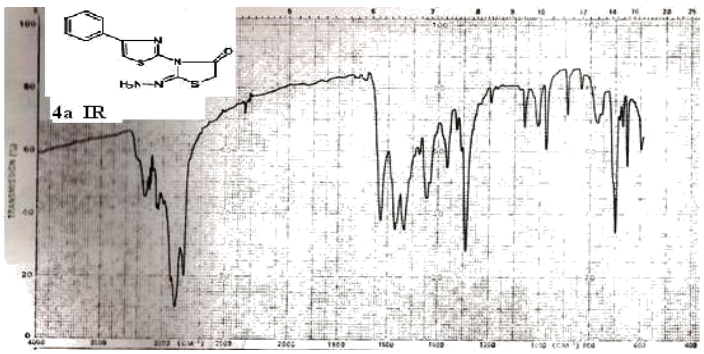


Fig 3: IR spectrum of compound 4a

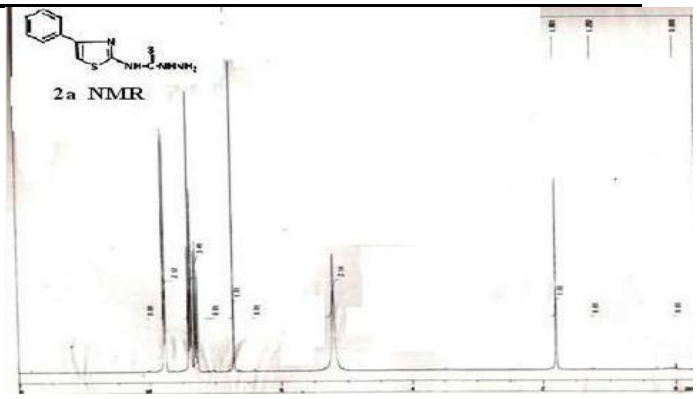


Fig 4: NMR spectrum of compound 2a

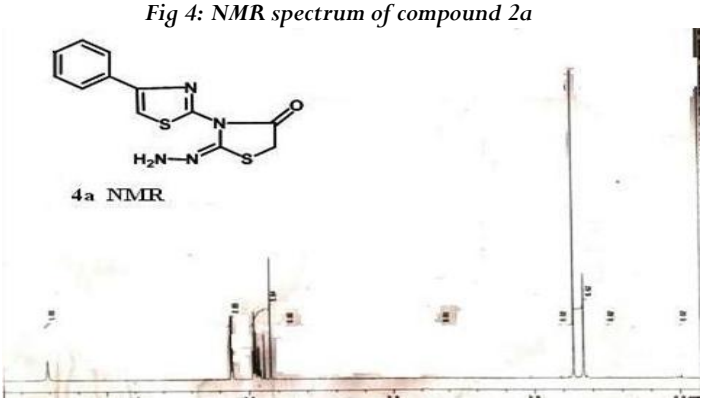


Fig 5: NMR spectrum of compound 4a

Antibacterial activity:

Disc-diffusion method

The newly synthesized derivatives 1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b, 5a and 5b were screened for their antibacterial activity against gram (+) ve (S. aureus and L. bacillus) and gram (-) ve (E. coli, P. vulgaris, S. typhosa and P.aureginosa) organisms using Disc-diffusion method. The media were melted at 100°C and after cooled to 50°C, were poured in to petri plates of 6-7cm in diameter, in quantities of 15-20 ml and flat surfaces to solidify and the Surface of the media was dried at 37°C. Then the inoculum was prepared using nutrient broth culture of each bacterium. The 25µgm /0.1ml and 35µgm /0.1ml (in DMSO) test compounds impregnated disc were applied to the surface of inoculated plates. The nutrient agar plates were incubated at 37°C for 24 hrs .The plates were examined and the inhibition of zone was measured in millimeters.

3. RESULTS AND DISCUSSION

The compounds which were screened for their antibacterial activity showed considerable activities against various pathogenic organisms used in the present investigation. In general all are considerable active some of them are highly active and other compounds are weakly active on the basis of the inhibition obtained (measured) by each series. In general all the tested compounds were considerably active but some compounds were highly active and others are weakly active on the basis of the zone of inhibition obtained by each series of drugs (Table 2).

The standard values of zone of inhibition in mm for 25 and 35 µgm/0.1 ml diameter in mm. The zone of inhibition values for weakly active 10-14 and 16-18 respectively. The zone of inhibition values for moderately active 15-18 and 19-22 respectively. The zone of inhibition values for highly active 19 or above and 23 or above respectively (Table 3).

The following tests compounds 2a, 2b, 3a, 3b, 4b and 5b showed moderately active against gram +ve bacteria like SA and LB. Remaining compounds like 1a, 2a and 5b which are highly active against gram (+) ve organisms. Whereas other compounds do not shows any activity gram + bacterias. The following compounds 1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b, 5a and 5b shows moderately active against gram -ve organisms like EC, ST, PA and PB. Remaining compounds like 1a, 3b, 4a, 4b, 5a and 5b which are highly active gram -ve organisms. Whereas other compounds do not shows any activity gram -ve bacterias. The results were shown in Table 3. In the present study, we concluded that some of the synthesized compounds possessed highly antibacterial activity.

Table 2: Results of Antibacterial activity of 2-amino/substituted amino-4-(phenyl/p-chlorophenyl) thiazole and their derivatives

Compounds	Conc./0.1ml	E. C	S.T	P.A	P.V	S.C	L.B
1a	25 µgm	16	14	36	14	14	20
	35 µgm	30	--	--	26	14	24
1b	25 µgm	16	20	14	16	--	--
	35 µgm	20	20	18	20	14	14
2a	25 µgm	14	16	14	14	16	20
	35 µgm	18	--	18	18	20	22
2b	25 µgm	--	14	16	14	14	16
	35 µgm	20	18	20	14	22	18
3a	25 µgm	16	--	14	--	16	16
	35 µgm	16	20	20	14	20	18
3b	25 µgm	--	16	20	14	16	--
	35 µgm	18	20	24	20	20	--
4a	25 µgm	18	20	26	20	--	--
	35 µgm	24	22	36	22	16	--
4b	25 µgm	--	16	16	18	--	18
	35 µgm	18	24	18	18	14	20
5a	25 µgm	18	14	26	18	22	--
	35 µgm	20	16	28	22	--	--
5b	25 µgm	20	18	14	18	20	16
	35 µgm	24	20	20	24	22	20
SMZ (STD)	25 µgm	18	16	18	20	22	22
	35 µgm	24	20	20	24	26	24
DMSO (Control)	25 µgm	10	14	10	12	14	12
	35 µgm	12	14	14	14	16	14

Note: E.C= E. Coli, S.T= S.Typhosa, P.A= P.Aeraginosa, P.V= P.Valgaris, S.C= S.Coccus, L.B = L.Bacillus.

Table 3: Activity against different types of organisms at 25 µgm and 35 µgm

Organisms	25µgm/0.1ml			35µgm/0.1 ml		
	Weakly active	Moderatly active	Highly Active	Weakly active	Moderatly active	Highly Active
EC	2a	1a, 1b, 3a, 4a, 5a	5b	2a, 3a, 3b, 4b	1b, 2b, 5a	1a, 4a, 5b
ST	1a, 2b, 5a	2a, 3b, 4b, 5b	1b, 4a	2b, 5a	1b, 3a, 3b, 4a, 5b	4b
PA	1b, 2a, 3a, 5b	2b, 4b	1a, 3b, 4a, 5a	1b, 2a, 4b	2b, 3a, 5b	3b, 4a, 5a
PV	1a, 2a, 2b, 3b	1b, 4b, 5a, 5b	4a	2a, 2b, 3a, 4b	1b, 3b, 4a, 5a	1a, 5b
SA	1a, 2b	3a, 3b	5a, 5b	1a, 1b, 4a, 4b	2a, 2b, 3a, 3b, 5b	--
LB	2b	2b, 3a, 4b	1a, 2a, 5b	1b, 2b, 3a	2a, 4b, 5b	1a

4. CONCLUSION

Some tests compound shows moderately active against gram +ve bacteria, few compounds like 1a, 2a and 5b which are highly active against gram (+)ve organisms. The few compounds 1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b, 5a and 5b were shows moderately active against gram -ve organisms like EC, ST, PA and PB. Remaining compounds like 1a, 3b, 4a, 4b, 5a and 5b which are highly active gram -ve organisms. In the present study, we concluded that some of the synthesized compounds possessed highly antibacterial activity.

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