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A Convenient route for the synthesis of antimicrobial 1, 3, 4- thiadiazole derivatives

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Abstract

Thiosemicarbazide of 6-chloro-2- aminobenzothiazole on cyclization with different aromatic carboxylic acids in Phosphorus oxychloride provided the corresponding 2-aryl-5-(6'-chloro-1',3'-benzothiazole-2-yl-amino)-1,3,4-thiadiazoles **4a-j**. The compounds are characterized by elemental analysis, IR and ^{1}H NMR spectral data. All the compounds are evaluated *in vitro* for their antimicrobial activities against several fungal and bacterial strains and showed significant activities.

Keywords: Aminobenzothiazole; 1, 3, 4- thiadiazole; antimicrobial; cyclization

1. Introduction

Benzothiozoles are bicyclic ring systems with diverse chemical reactivity and broad spectrum of biological activities such as antimicrobial[1,2],antitumor[3,4],anti-inflammatory[5,6]and antilieshmanial[7,8], etc. Several 1, 3, 4- thiadiazole derivatives are also known to exhibit diverse biological properties like antimicrobial [9,10] , antitubercular[11,12] , anti-inflammatory[13] and anticonvulsant[14]. The synthesis and biological activities of a few benzothiozole derivatives linked with 1,3,4-thiadiazole systems is reported here owing to their pharmaceutical importance.

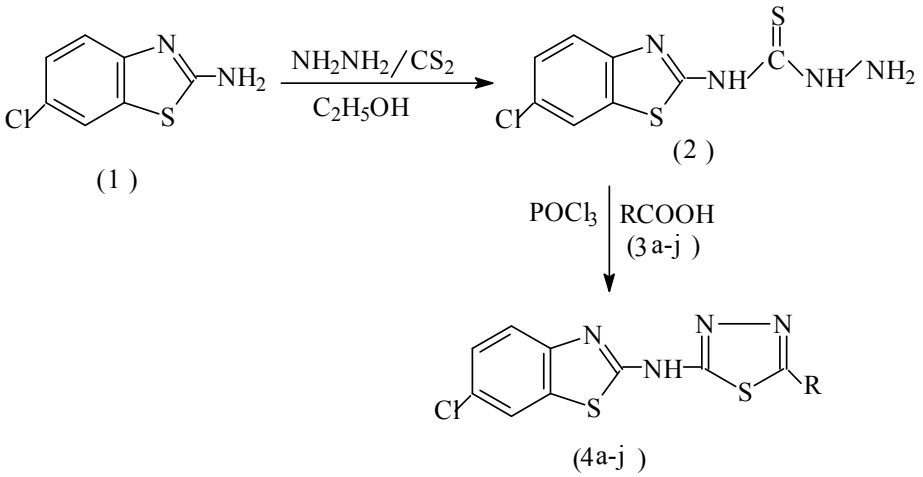
The reaction sequence leading to the formation of the desired heterocyclic compounds are outlined in scheme 1.The 6-chloro-1,3-benzothiazol-2-yl-thiosemicarbazide **2** was prepared by the reaction of 6-chloro-2-aminobenzothiazole **1** with CS_2 and hydrazine in the presence of ethanol. Several 2-aryl-5-(6'-chloro-1,'3'-benzothiazol-2-yl-amino)- 1, 3, 4- thiadiazoles 4a-j were synthesized by the reaction of 6-chloro-1,3-benzothiazol-2-yl-thiosemicarbazide **2** with various substituted aromatic carboxylic acids **3a-j** in the presence of phosphorous oxychloride.

2. Material and Methods

Melting points were measured in open capillary tubes and are uncorrected. IR spectra were recorded on a Nicolet, 5PC FT-IR spectrometer in KBr pelletes and ^{1}H NMR spectra on the bruker DRX-300 FT NMR spectrometer using TMS as internal reference.Chemical shifts are observed with DMSO-d^6 solvent in ppm. The purity of the compounds was checked on silica gel

G plates using iodine vapor as visualizing agents. Ofloxacin was used as standard dug for antibacterial activity ketoconazole as standard drug for antifungal activity [15,16].
The precursor 6-chloro-2- aminobenzothiazole **1** was synthesized by the already reported procedure [17].

Scheme 1



R = a. Phenyl b. 4-Chlorophenyl c. 2,4-Dichlorophenyl
d. 4-Nitrophenyl e. 2-Aminophenyl f. 2,4-Dichlorophenoxymethyl
g. 2-Naphthylmethyl h. 4-methoxyphenyl i. 2-Acetoxyphenyl
j. 3-Pyridyl

2.1 General Procedure for the Synthesis of 6-Chloro-1,3- benzothiazol-2-yl-thiosemicarbazide (2)

The 6-chloro-2- aminobenzothiazole **1** (0.01 mole) was dissolved in ethanol (90%, 50ml) and then CS_2 (20ml) was added slowly within 10 minutes with constant shaking. The resulted solution was then allowed to stand for 1.0 hr. Then 20 ml of 50% hydrazine solution was added to it. The reaction mixture was warmed slowly for 1.30 hr then filtered, washed with cold water and dried. The solid thus obtained was purified by recrystallization from methanol.

2.2 General Procedure for the Synthesis of 2-Aryl-5-(6'-chloro-1', 3'- benzothiazol-2-yl-amino)- 1,3,4-thiadiazoles (4a-j)

A mixture of 6-chloro-1,3- benzothiazol-2-yl- thiosemicarbazide **2** (0.01 mole), an aromatic acid **3a-j** (0.01 mole) and phosphorous oxychloride (25 ml) was refluxed for 3 hr. After cooling to room temperature the reaction mixture was slowly poured over crushed ice and kept for 1 hr. The solid thus separated was filtered, washed with cold water, dried and purified by recrystallization from methanol.

3. Results and Discussion

All the synthesized thiadiazole derivatives **4a-j** are confirmed by different spectral analysis (table 2).These compounds have given similar IR and ^{1}H NMR signals for main moiety with variations for substitutions. The characteristic observations for the substitutions have further supported the formation of mentioned products **4a-j**.The IR spectrum of the typical compound **4i** showed absorption peak at 1710 cm^{-1} due to the stretching of C=0. The N-H stretching vibration appeared at 3436 cm^{-1}. The absorption at 795 cm^{-1} was obtained due to C-Cl stretching vibration. The ^{1}H

NMR spectra of this compound displayed on singlet at δ 2.13 showing the presence of $OCCH_3$ protons of acetyl group. A broad singlet appeared at δ 12.36 showing the presence of NH proton. The seven aromatic protons of benzothiozole and phenyl ring were observed as a multiplet at δ 7.5-8.0.

Table 1: Physical characterization data of compounds (4a-j)

Comp.no	R	Yield (%)	m.p.(˚C)
4a	Phenyl	65	225
4b	4-Chlorophenyl	61	270
4c	2,4-dichlorophenyl	67	283
4d	4-Nitrophenyl	72	285
4e	2-Aminophenyl	66	227
4f	2,4-dichlorophenoxymethyl	58	215
4g	2-Napthylmethyl	73	165
4h	2-Methoxyphenyl	61	201
4i	2-Acetoxyphenyl	60	272
4j	3-Pyridyl	55	242

4. Biological Evaluation

All the compounds have been screened for both antibacterial and antifungal activities using cup-plate agar diffusion method by measuring the inhibition zone in mm. Ofloxacin(50 µg/ml) was used as a standard drug for antibacterial activity and ketoconazole(50 µg/ml) as a standard drug for antifungal activity. The compounds **4a-j** were screened for antibacterial activity against E. coli, S. aureus and P. aerugenosa in nutrient agar medium and for antifungal activity against A. niger and C. albicans in sabouraud's dextrose agar medium. These sterilized agar media were poured into petri-dishes and allowed to solidify. On the surface of media microbial suspensions were spreaded with the help of sterilized triangular loop. A presterilized stainless steel cylinder of 8 mm diameter was used to bore cavities. All synthesized compounds (50 µg/ml) were placed serially in the cavities with the help of micropipette and allowed to diffuse for 1.00 hr. DMF was used as a solvent for all the compounds and as a control. These plates were incubated at 37˚C for 36 hr. and 28˚C for 48 hr, for antibacterial and antifungal activities respectively. The zone of inhibition observed around the cups after respective incubation was measured and percentage inhibition of

the compounds was calculated (tables 3&4).The thiadiazole derivative **4i** having acetoxyphenyl group showed potent activity against S. aureus(92%), wereas compound **4g** having 2-nepthylmethyl group showed maximum inhibition against E. coli(95%), when compared to standard drug ofloxacin. The compound **4c** having 2,4-dichlorophenyl group also showed significant antibacterial activity(85, 87 and 82%) against S. aureus, E. coli, and P. aerugenosa respectively. Rest of the compounds showed moderate to good antibacterial activity.

Table 2: Spectral data of the compounds (4a-j)

Comp.no.	IR, v (cm^{-1})	^1H NMR, δ (ppm)
4a	3360(N-H) 3030(C-H) 750(C-Cl)	7.35-7.8(m,8H,ArH) 8.27(S,1H,NH)
4b	3369(N-H) 3032(C-H) 755(C-Cl)	7.30-7.96(m,7H,ArH) 10.48(S,1H,NH)
4c	3386(N-H) 3060(C-H) 765(C-Cl)	7.34-7.62(m,6H,ArH) 10.50(S,1H,NH)
4d	3366(N-H) 3033(C-H) 752(C-Cl)	7.37-8.38(m,7H,ArH) 13.25(S,1H,NH)
4e	3411(N-H) 3033(C-H) 752(C-Cl)	4.5(S,2H,NH_2) 7.08-7.86(m,7H,ArH) 12.56(S,1H,NH)
4f	3408(N-H) 3028(C-H) 750(C-Cl)	4.97(S,2H,CH_2O) 7.06-7.89(m,6H,ArH) 12.59(S,1H,NH)
4g	3402(N-H) 3021(C-H) 752(C-Cl)	3.27(S,2H,CH_2) 7.50-7.87(m,10H,ArH) 12.34(S,1H,NH)
4h	3399(N-H) 3032(C-H) 752(C-Cl)	3.86(S,3H,OCH_3) 7.05-7.86(m,7H,ArH) 12.56(S,1H,NH)
4i	3436(N-H) 3038(C-H) 1710(C=O) 795(C-Cl)	2.13(S,3H,OCH_3) 7.5-8.0(m,7H,ArH) 12.36(S,1H,NH)
4j	3421(N-H) 3036(C-H) 745(C-Cl)	7.05-7.89(m,7H,ArH) 13.0(S,1H,NH)

Table 3: Antibacterial activity of 1, 3, 4-thiadiazole derivatives (4a-j)

Comp.	Staphylococcus aureus		Escherichia coli		Pseudomonas aerugenosa	
	Zone of inhibition (mm)	% inhibition	Zone of inhibition (mm)	% inhibition	Zone of inhibition (mm)	% inhibition
4a	10	65	9	63	13	77
4b	12	80	10	69	12	70
4c	15	85	16	87	14	82
4d	11	76	14	85	12	71
4e	11	80	13	71	11	74
4f	14	82	12	65	13	76
4g	13	76	16	95	13	81
4h	10	78	12	75	12	70
4i	16	92	13	72	14	83
4j	12	80	11	69	13	79

Table 4: Antifungal activity of 1, 3, 4- thiadiazole derivatives (4a-j)

Comp.	Aspergillus niger		Candida albicans	
	Zone of inhibition (mm)	% inhibition	Zone of inhibition (mm)	% inhibition
4a	20	62	12	66
4b	14	55	11	58
4c	13	47	13	62
4d	11	45	11	61
4e	25	87	15	78
4f	23	82	16	83
4g	16	56	14	67
4h	12	46	13	69
4i	13	48	12	63
4j	15	52	14	71

The results of antifungal activity of the test compounds were quite different from their antibacterial activity. The 1,3,4- thiadiazole derivative **4e** having 2-aminophenyl group showed maximum inhibition(87%) against A. niger whereas **4f** having 2,4-dichlorophenoxymethyl groups showed maximum inhibition (83%) against C. albicans. Furthermore 1, 3, 4- thiadiazole dericatives **4e** showed 78% inhibition against C. albicans. Whereas **4f** showed 82% inhibition against A. niger. Rest of the thiadiazole derivatives showed moderate to good antifungal activity as compared to the reference drug ketoconazole. Thus it is concluded from the screening results that 1,3,4-thiadiazole derivatives **4a-j** have been proved to be more effective against all the tested microorganisms at a concentration of 50 µg/ml.

5. Conclusion

The reaction of 6-Chloro-2- aminobenzothiazole **1** with hydrazine and carbon disulphide in alcoholic medium yielded corresponding thiosemicarbazide **2** in excellent yield of 82% within 1 hr. Thus obtained thiosemicarbazide produced various 1,3,4-thiadiazoles **4a-j**, through cyclization upon reaction with carboxylic acids **3a-j** in presence of phosphorous oxychloride in 75% yield within 3 hr. All the synthesized thiadiazoles **4a-j**, showed excellent to moderate antifungal and antibacterial activities, which has proved the thiadiazoles **4a-j** as pharmaceutically valuable heterocycles. This synthetic method is proved to be simple, easier to workup and environment friendly tool in pharmaceutical chemistry.

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