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Synthesis and Pharmacological Screening of New Benzothiazole Derivatives

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Abstract: A new series of five compounds of benzothiazole were synthesized by ring closure reactions of different 4,6-disubstitued-benzo(d)thiazo with aniline and potassium thiocyanate separately. Further, the 4,6-disubstitued-benzo(d)thiazo were treated with aromatic amines , hydarazine hydrate and Thiosemicarbazide. The structures of the synthesized compounds were consistent with IR, spectroscopy. The synthesized compounds were screened by disc diffusion method for their antibacterial and antifungal activity. Among the compounds synthesized SV-3 and SV-5 shown significant antimicrobial activity against both bacterial and fungal strains.The synthesized compounds (SV-3 and SV-5) were tested for their antiinflammatory activity.

Keywords: Benzothiazole, Antiinflammatory, Antibacterial and Antifungal activity

INTRODUCTION

Benzothiazole derivatives possess multi-range of biological actions such as antibacterial, antifungal , anti-inflammatory, herbicidal, anticonvulsant, ant tubercular and anticancer activity, etc. In the present study newer analogs of the 2,4,-disubstitued aniline were prepared from various 4,6-disubstitued-benzo(d)thiazol react with different aromatic acids using sodium cynate , Hydrazine hydrate and Thiosemicarbazide as agent. The 4,6-disubstitued-benzo(d)thiazol were obtained by reacting respective alcohol, acids with hydrazine hydrate. (SV-1-SV-5). All the synthesized compounds were screened for in vitro antimicrobial activity by disc diffusion method and The synthesized compounds were tested for their antiinflammatory activity by carragenan induced rat paw edema method.

EXPERIMENTAL SECTION

Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on pre-coated silica gel GF 254 plates. IR spectra were recorded through KBr pellet method in Perkin-Elmer FTIR spectrophotometer.

Synthesis of 4,6-disubstitued-benzo(d)thiazol-2-amine (I)

To glacial acetic acid (20ml) precooled to 5Oc Potassium thiocyanate (0.01mol) and substituted aniline(0.01mol) were added. The mixture was placed in a freezing mixture of ice and salt, stirred using mechanical stirrer with addition of bromine(0.01mol) in acetic acid (8ml) from a dropping funnel at such a rate that temperature does not rise above 5Oc . the reaction mixture was stirred for an additional 8 hours and then poured into cold water (100ml) , neutralized with aqueous ammonium hydroxide and extracted with chloroform(3x30ml) .Evaporation of the chloroform gave a residue, which was purified by column

chromatography on silica gel (light petroleum ether/ethyl acetate 8/2(v/v) as eluent) to give 4,6-disubstitued-benzo(d)thiazol-2-amine (I).

Synthesis of 1-(4,6-disubstitutedbenzo(d)thiazol-2yl)urea (II)

To a solution of sodium cyanate (0.5g) in 25ml of water, glacial acetic acid (5ml) was added. This solution was heated on a water bath at 60oC with respective 6-substituted-benzothiazol-2-amine (I), in 95% v/v alcohol, until the contents of the mixture became turbid and volume half of the original volume. The Contents were added in to 100ml of ice cold water. The solid (II) obtained was filtered and dried.

Synthesis of 4-(4,6-disubstitutedbenzo(d)thiazol-2yl)semicarbazide (III)

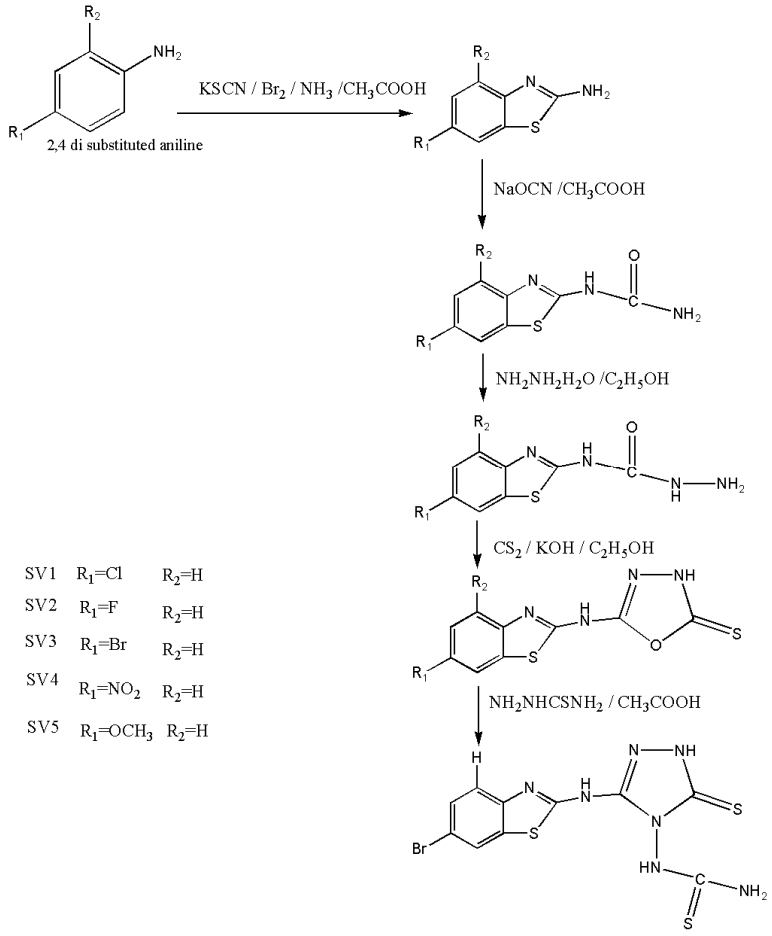
To a solution of compound (II) (0.00ml) in ethanol (25ml) was added to hydrazine hydrate (99%w/w,0.01mol). the reaction mixture was heated under reflux for 6 hours and the solvent was removed under reduced pressure. The separeted solid was recrystallized from ethanol(III).

Synthesis of 5-(4,6-disubstitutedbenzo(d)thiazol-2-ylamino)-1,3,4-oxadiazole-2(3H)-thione (IV)

To a solution containing 95% v/v ethanol and 0.05 mol potassium hydroxide (dissolved in 10ml water) was added to compound III (0.05mol) and 0.8ml of carbon disulfide.The mixture was refluxed for 6 hours, contents were concentrated and the residue obtained was dissolved in water and pour into cold water: acetic acid (1:1). the solidified product thus obtained was filtered, dried and recrystallized from ethanol(IV).

Synthesis of 1-(3-((4,6-disubstitutedbenzo(d)thiazol-2yl)amino)-5-thio-1H-1,2,4-triazol-4(5H)-yl) thiourea (V)

Scheme:



SV1 R_1=Cl R_2=H
SV2 R_1=F R_2=H
SV3 R_1=Br R_2=H
SV4 R_1=NO_2 R_2=H
SV5 R_1=OCH_3 R_2=H

Table 1- *Physical data of the title compounds*

Code	Molecular Formula	Molecular Weight	Yield (%)	Melting Point (□C)	*R_f value
SV-1	$C_{10}H_8N_7S_3Cl$	357.19	91.16	175	0.79
SV-2	$C_{10}H_8N_7S_3F$	340.22	78.45	180	0.58
SV-3	$C_{10}H_8N_7S_3Br$	401.45	92.21	189	0.38
SV-4	$C_{10}H_8N_8S_3O_2$	368.35	86.87	196	0.56
SV-5	$C_{11}H_{11}N_7S_3O$	353.57	88.81	172	0.55

Antimicrobial activity

The synthesized compounds were tested for their in vitro antibacterial activity against Bacillus cereus, Staphylococcus aureus (gram positive) and Pseudomonus aeruginosa, Klebsiella pneumonia (gram negative) and the antifungal activity was screened against Candida albicans and Aspergillus fumigates at the concentrations of 50, 100 and 150 µg/ml by disc diffusion method.

Ciprofloxacin and Ketoconazole were used as standard drugs for antibacterial and antifungal activity respectively. Diethyl sulfoxide was used as a control and the zone of inhibition of the compounds are presented in the table 2 & 3.

Sterile disc of 5 mm in diameter made from Whitman filter paper which is previously sterilized in U.V. lamp was dipped in solution of different concentrations of synthesized compounds, standard and blank and placed the disc on the surface of agar plates.

Allowed the plates to stand for 1hr at room temperature as a period of pre-incubation to minimize the effects of variation in time between the applications of different solutions. Then the plates were incubated for 24 hr at 37º C ± 1º C for bacteria and 72 h at 25ºC± 1ºC for fungi. The diameter of zone of inhibition was measured.

RESULTS AND DISCUSSION

Five derivatives of each of 4,6-disubstitued-benzo(d)thiazol were synthesized by ring closure reactions of different Hydrazine hydrate with ethanol and Thiosemicarbazide separately.

The structures of the synthesized compounds were confirmed on the basis of IR. All the compounds were screened for their in vitro antibacterial and antifungal activities. The compounds

SV-1,SV-3 and SV-4 shown good antibacterial activity against gram positive organisms and the compounds SV-2 and SV-5 could show better action against gram negative organisms. About antifungal screening, the compounds SV-2,SV-3 and SV-5 shown significant activity. To conclude, SV-3 and SV-5 are fruitful compounds among the series synthesized for both bacterial and fungal inhibition.

Table 2-*Antibacterial activity*

COMP Code	Zone of Inhibition (in mm)					
	Bacillus cereus			*Pseudomonas aeruginosa*		
	50 (µg/ml)	100 (µg/ml)	150 (µg/ml)	50 (µg/ml)	100 (µg/ml)	150 (µg/ml)
SV-1	11	13	18	12	14	20
SV-2	12	14	18	12	15	18
SV-3	12	15	19	13	16	20
SV-4	12	13	19	12	14	19
Ciprofloxacin (10µg/m1)	39			38		

Table 3- *Antifungal activity*

Compounds	Zone of Inhibition (in mm)		
	Aspergillus fumigates		
	50 (µg/ml)	100 (µg/ml)	150 (µg/ml)
SV-1	15	18	19
SV-2	15	17	20
SV-3	16	18	20
SV-4	15	19	21
SV-5	16	20	21
Ketoconazole(10µg/ml)	39		

CONCLUSION

The 4,6-disubstitued-benzo(d)thiazo derivatives shown moderate antibacterial and antifungal activities. Among the five compounds synthesized only two were tested for antiinflammatory activity and it could show significant action compared to the standard. Hence less information is obtained in terms of antiinflammatory action for the synthesized compounds. On antimicrobial screening, though the compounds could show activities against bacterial and fungal strains but it is less compared to standard. Further research is needed to correlate the benzothiazole derivatives with its antiinflammatory and antimicrobial activities.

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