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Synthesis and antibacterial activity of some new benzothiazole derivatives

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Abstract

In the present study, seven new derivatives (R1 to R7) of benzothiazoles were synthesized and evaluated their anti-bacterial activity. *p*-toluidine on reacting with ammonium thiocynate formed 2-benzothiazolamines, which on reacted with hydrazine hydrate formed hydrazino derivative. Compounds (R1 to R7) were synthesized by reacting hydrazine derivative with different acetophenones (2'-fluoroacetophenone, 4'-fluoroacetophenone, 2'-Chloroacetophenone, 4'- Chloroacetophenone, p-Hydroxyacetophenone, 2'- Hydroxyacetophenone, 2, 5- Dihydroxyacetophenone). All the synthesized compounds were identified by IR, NMR. The anti-bacterial activity were investigated and appreciate activity were observed.

Keywords: Benzothiazole, substituted acetophenones, anti-bacterial activity.

Introduction

From the literature survey, it has been found that tremendous work has been reported on 2-substituted benzothiazole derivatives in past and evaluated for different activities like anti-inflammatory, anti-bacterial, anti-tumor, anti-viral, anti-microbial, anti-helmintic, anti-convulsant, anti-oxidative, anti-fungal, anti- diabetic, anti-parkinsonian (Yoshihisa Kitamura et al. 1998, Danzeisen et al. 2006, Rana et al. 2007, Pattan et al. 2005, Al-Masoudi et al. 2008, Mantz et al. 1996). Keeping this in view, new derivatives of Benzothiazoles were synthesized.

Materials and Methods

Melting points of all synthesized compounds were determined using open capillary tube and were uncorrected. IR data were recorded in KBr disks on Hitachi 270-30 infrared and Bruker Vector 22 spectrophotometer and H^1 NMR spectra on Bruker AC 30 of NMR spectrometer 400 MHz .

Chemistry

p-tolylthiourea: Dissolve *p*-toluidine (5.35 g) [0.05 mol] in a mixture of conc. HCl (4.3 ml) and water (11.6 ml) by heating on water bath. Cooled the contents

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and added solid ammonium thiocyanate (3.5 g) [0.047 mol], heated the mixture on water bath for 22 h. Cooled the precipitated product and filtered. Washed with water 3-4 times and dried. Recrystallized with aqueous methanol to get cream colored crystals.

2-amino-6-methylbenzothiazole

15 ml of conc. H_2SO_4 was added to 8.3 g [0.05 mol] of p-tolylthiourea and the temperature of mixture was raised to 80 °C on water bath. After 0.5 g of 48 % HBr acid was added slowly and the reaction mixture was stirred for 2 h set at 80 °C and cooled to room temperature and the reaction mixture was slowly introduced to cold water and then adjusted to pH 9 or 10 by adding ammonia water. The whole mixture was stirred for 1 h by heating at 70 °C and then cooled to room temperature. The mixture was extracted 2 times with dichloroethane and the combine extract was dried with anhydrous Na_2 SO_4 and evaporated to obtain the title compound.

2-Hydrazino-6-methylbenzothiazole

2-amino-6-methylbenzothiazole (20 g) [0.82 mmol] and hydrazine hydrate (85 %) [0.11 mmol] in 50 ml of ethylene glycol, refluxed by stirring for 4 h (60 °C). The colour of reaction changed to green and the homogeneous solution appeared. A white solid was precipitated at the end of the reflux period. The mixture was cooled and the product was filtered and then washed with water several times. Air dried and recrystallized from ethanol.

2{2"-fluorophenyl)-1'-ethylhydrazinyl}-6-methyl benzothiazole (R1)

2-Hydrazino-6-methylbenzothiazole (1.5 mmol) and 2'-fluoroacetophenone (2.2 mmol) and glacial acetic acid (2-3 drops) were taken in absolute ethanol (20 ml) and refluxed on water bath for 10 hours till a different spots on TLC may appears. On cooling, solid get separated which was filtered and washed with little water and recrystallized with absolute ethanol.

2{4"-fluorophenyl)-1'-ethylhydrazinyl}-6-methyl benzothiazole (R2)

2-Hydrazino-6-methylbenzothiazole (1.5 mmol) and 4'-fluoroacetophenone (2.2 mmol) and glacial acetic acid (2-3 drops) were taken in absolute ethanol (20 ml) and refluxed on water bath for 15 h till a different spots on TLC may appears. On cooling, solid get separated which was filtered and washed with little water and recrystallized with absolute ethanol.

2{2"-chlorophenyl)-1'-ethylhydrazinyl}-6-methyl benzothiazole (R3)

2-Hydrazino-6-methylbenzothiazole (1.5mmol) and 2'-Chloroacetophenone (2.2 mmol) and glacial acetic acid (2-3 drops) were taken in absolute ethanol (20 ml) and refluxed on water bath for 12 h till a different spots on TLC may appears. On cooling, solid get separated which was filtered and washed with little water and recrystallized with absolute ethanol.

2{4"-chlorophenyl)-1'-ethylhydrazinyl}-6-methyl benzothiazole (R4)

2-Hydrazino-6-methylbenzothiazole (1.5 mmol) and 4'-Chloroacetophenone (2.2 mmol) and glacial acetic acid (2-3 drops) were taken in absolute ethanol (20 ml) and refluxed on water bath for 16 hours till a different spots on TLC may appears. On cooling, solid get separated which was filtered and washed with little water and recrystallized with absolute ethanol.

2{p-hydroxyphenyl)-1'-ethylhydrazinyl}-6-methyl benzothiazole (R5)

2-Hydrazino-6-methylbenzothiazole (1.5 mmol) and p-Hydroxyacetophenone (2.2 mmol) and glacial acetic acid (2-3 drops) were taken in absolute ethanol (20 ml) and refluxed on water bath for 10 h till a different spots on TLC may appears. On cooling, solid get separated which was filtered and washed with little water and recrystallized with absolute ethanol.

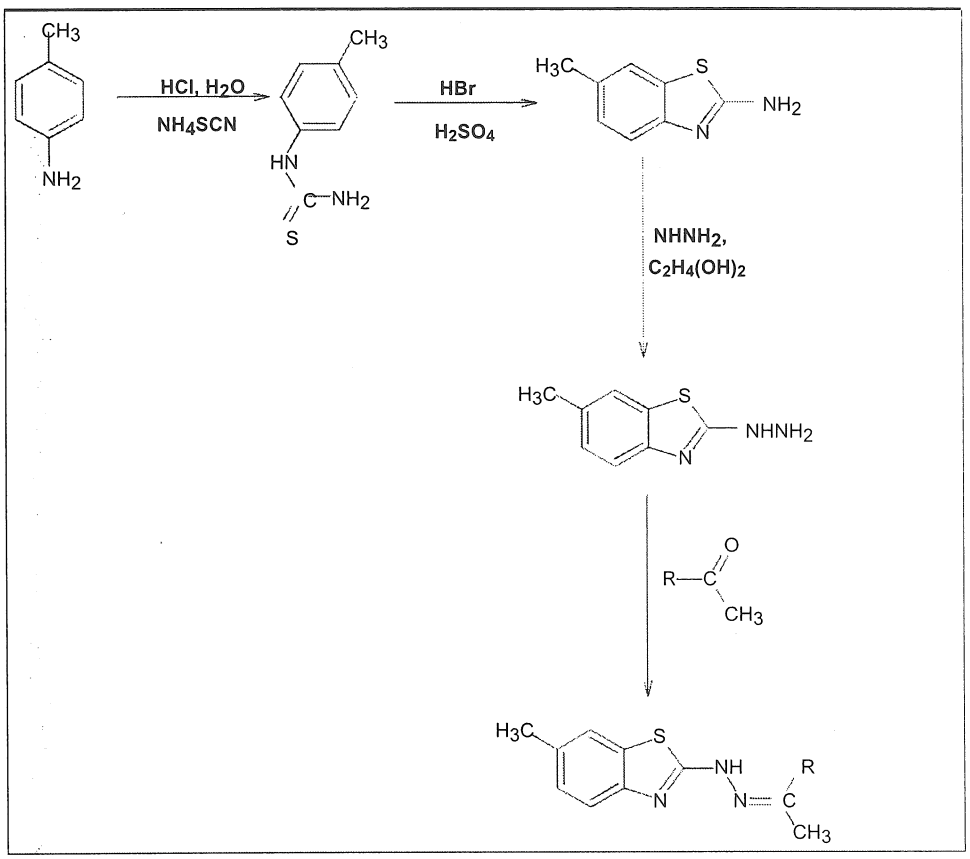
2{2''-hydroxyphenyl)-1'-ethylhydrazinyl}-6-methyl benzothiazole (R6)

2-Hydrazino-6-methylbenzothiazole (1.5 mmol) and 2-Hydroxyacetophenone (2.2 mmol) and glacial acetic acid (2-3 drops) were taken in absolute ethanol (20 ml) and refluxed on water bath for 18 h till a different spots on TLC may appears. On cooling, solid get separated which was filtered and washed with little water and recrystallized with absolute ethanol.

2{2'', 5''-dihydroxyphenyl)-1'-ethylhydrazinyl}-6-methyl benzothiazole (R7)

2-Hydrazino-6-methylbenzothiazole (1.5 mmol) and 2,5-Dihydroxyacetophenone (2.2 mmol) and glacial acetic acid (2-3 drops) were taken in absolute ethanol (20 ml) and refluxed on water bath for 16 h till a different spots on TLC may appears. On cooling, solid get separated which was filtered and washed with little water and recrystallized with absolute ethanol.

Systematic Scheme



R^1 = 2'-fluoroacetophenone, R^2 = 4'-fluoroacetophenone, R^3 = 2'-Chloroacetophenone, R^4 = 4'-Chloroacetophenone, R^5 = p-Hydroxyacetophenone, R^6= 2'-Hydroxyacetophenone, R^7= 2, 5-Dihydroxyacetophenone

Characterisization of the compounds synthesized

IR (KBr ν cm^{-1}) and ^{1}HNMR (DMSO, δ ppm)

1: IR (cm^{-1}) 3739.5*w* (N-H*str*), 2886.0*m* (Aliphatic C-H*str*), 1624.7w (N-H*ben*), 1303.6w (Aromatic C-H*ben*) ^{1}HNMR 9.55 (2H, s) NH_2, 7.19-7.10 (4H, d) Ar-H, 2.24 (3H, s) CH_3

2: IR (cm^{-1}) 3437.1s (N-H$str_{(assym)}$)3273.8*m* (N-H$str_{(sym)}$)1407.8w (Aro-C and Aro-N

Ring*str*)1259,1235w (C-S*str*) ^{1}HNMR 9.33 (1H, s) NH,7.60-7.23 (3H) Ar-H,6.78 (2H, s) NH_2,2.32 (3H, s) CH_3

3: IR (cm^{-1}) 3437.3, 3273.3*s* (NHNH*str*) 3166.4*m* (Aromatic C-H*str*) 3000.9*w* (Aliphatic C-H*str*) 1582.8s (N-H*ben*) ^{1}HNMR 9.23 (1H, s) NH, 7.53-7.22 (5H) Ar-H, 6.71 (2H, s) NH, 2.33 (3H, s) CH_3

4: IR (cm^{-1})3437.2*s* (N-H*str*) 3165.7m (Aromatic C-H*str*) 1631s (C=N*str*) 1016.8m (Aromatic C-F*str*) ^{1}HNMR 9.35 (1H, s) NH, 7.14-7.63 (7H) Ar-H, 6.82 (1H, s) NH, 3.07 (3H, s) CH_3, 2.32 (3H, s) CH_3

5: IR (cm^1)3437.1*s* (NH*str*) 3166.1m (Aromatic C-H*str*) 1631s (C=N*str*) 1582.4w (NH*ben*) 1069.4m (AromaticC-F*str*) ^{1}HNMR 9.31 (1H, s) NH, 7.14-7.60 (7H) Ar-H, 6.82 (1H, s) NH, 3.01 (3H, s) CH_3, 2.32 (3H, s) CH_3

6: IR (cm^{-1}) 3436.6*s* (N-H*str*) 3166.1m (Aromatic C-H*str*) 1612s (C=N*str*) 1582.1w (N-H*ben*) 801.6s (Aromatic C-Cl*str*) ^{1}HNMR 7.26-7.11 (7H) Ar-H, 6.02 (1H, s) NH, 2.36 (3H, s) CH_3, 1.60 (3H, s) CH_3

7: IR (cm^{-1}) 3439*w*(N-H*str*)3165.3*m* (Aromatic C-H*str*)1677.9*s* (C=N*str*)1585.5*s* (N-H*ben*)801.7,734.8*w* (Aromatic C-Cl*str*) ^{1}HNMR 9.31 (1H, s) NH,7.90-7.44 (7H) Ar-H,6.74 (2H, s) NH,3.03 (3H, s) CH_3,2.58 (3H, s) CH_3

8: IR (cm^{-1}) 3437.3*s* (O-H and N-H*str*) 3167.4m (Aromatic C-H*str*) 1631.4s (C=N*str*) 1582.6s (N-H*ben*) 1235.8 (Aromatic O-H*ben*) ^{1}HNMR 9.4 (1H, s) NH, 7.24-7.12 (7H) Ar-H, 6.90 (2H, s) NH, 3.20 (3H, s) CH_3, 2.30 (3H, s) CH_3

9: IR (cm^{-1})3412.7*s* (O-H and N-H*str*)3156.8*m* (Aromatic C-H*str*)1639.5*w* (C=N*str*)1585.6*w* (N-H*ben*)1319.7*w* (Phenolic C-O*str*)1237.6*m*(Aromatic O-H*ben*) ^{1}HNMR 12.2 (1H, s) OH,9.31 (1H, s) NH,7.70-6.90 (7H) Ar-H,6.76 (2H, s) NH,2.65 (3H, s) CH_3,2.16 (3H, s) CH_3

10: IR (cm^{-1})3243.0*s* (O-H and-H*str*) 3057.5*w* (Aromatic C-H*str*) 1616.0w (C=N*str*) ^{1}HNMR 11.66 (1H, s) OH, 9.35 (1H, s) NH, 7.14-7.63 (7H) Ar-H, 6.82 (2H, s) NH, 3.07 (3H, s) CH_3, 2.32 (3H, s) CH_3

Pharmacology

Antibacterial activity

All the compounds synthesized were screened in vitro for anti-bacterial activity against Gram positive bacteria- *Staphylococcus aureus subsp. aureus* (MTCC 737) (*S. aureus*) and *Staphylococcus epidermidis* (MTCC 3615) (*S. epidermidis*) and Gram negative bacteria- *Pseudomonas aeruginosa* (MTCC 424) (*P.aeruginosa)* and *Escherichia coli* (MTCC 1687) (*E.coli*) using disc diffusion method at 1mg/ml disc concentration, Ampicillin (17-22 mm, zone of inhibition) was taken as standard. DMF (Dimethyl formamide) is used as solvent control.

Table 2. Comparison of zone of inhibition of various derivatives synthesized

Compounds	Anti-bacterial activity			
	S.aureus	*S.epidermis*	*P.aeruginosa*	*E.coli*
Ampicillin (std)	22 mm	20 mm	20 mm	21 mm
R1	15 mm (68%)	-	10 mm (50%)	12 mm (57%)
R2	10 mm (45%)	14 mm (70%)	13 mm (65%)	14 mm (67%)
R3	13 mm (59%)	8 mm (40%)	15 mm (75%)	-
R4	14 mm (63%)	10 mm (50%)	-	13 mm (62%)
R5	11 mm (50%)	8 mm (40%)	17 mm (85%)	-
R6	-	17 mm (85%)	10 mm (50%)	14 mm (67%)
R7	13 mm (59%)	-	12 mm (60%)	10 mm (48%)

Table 3. Comparison of anti-bacterial activity with different derivatives synthesized

Compounds	Anti-bacterial activity			
	S.aureus	*S.epidermis*	*P.aeruginosa*	*E.coli*
Ampicillin (std)	+++	+++	+++	+++
R1	++	-	+	++
R2	+	++	++	++
R3	++	+	++	-
R4	++	+	-	++
R5	+	+	+++	-
R6	-	+++	+	++
R7	++	-	++	+

+++ Diameter of zone of inhibition between 17-22 mm, ++ Diameter of zone of inhibition between 12-16 mm, +Diameter of zone of inhibition between 8-11 mm, - No zone of inhibition observed.

Results and Discussion

Because of the biological activities exhibited by benzothiazole, present study was undertaken wherein different compounds based on benzothiazole as a basic moiety have been synthesized with the hope to enhance the biological properties of newly designed compounds.

Review of literature has shown that substituted 2-aminobenzothiazole derivatives possess antimicrobial activity. In the view of this, an effort was made to check some synthesized compounds for their anti-microbial activity. The inhibition of microorganisms under standardized conditions was utilized to demonstrate microbial action of the compounds.

For present work efficacy of seven compounds were detected against *Staphylococcus aureus subsp. aureus* (MTCC 737) (*S.aureus*) and *Staphylococcus epidermidis* (MTCC 3615) (*S.epidermidis*) *Pseudomonas aeruginosa* (MTCC 424) (*P. aeruginosa*) and *Escherichia coli* (MTCC 1687) (*E.Coli*). The concentration of the test compound used was 1mg/ml. and Ampicillin was taken as the standard drug.

Conclusion

From the results of anti-bacterial activity conducted on seven derivatives, it was concluded that compounds R3 and R7 had shown moderate activity against S.aureus and P.aeruginosa while R1 and R4 showed the same activity against E.coli.

Compound R5 showed excellent activity against P.aeruginosa while Compound R6 showed prominent activity against S.epidermidis when tested at 1mg/ml concentration taking Ampicillin as the standard.

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