

Synthesis, Characterization and Biological Evaluation of Some Benzothiazole Derivatives

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Abstract: Some new benzothiazole derivatives were synthesized from 2-(4-aminophenyl)benzothiazol-5-ol as the parent compound. All the synthesized compounds were characterized by IR and NMR spectral data and evaluated for antibacterial activity. The results show that all the compounds have moderate to good antibacterial activity against Gram positive and Gram negative bacteria.

Keywords: Antibacterial activity, benzothiazole, synthesis.

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I. Introduction

Benzothiazole is a privileged bicyclic ring system having diverse chemical and biological activity. A large no. of therapeutic agents have been synthesized with the help of benzothiazole nucleus, and have been evaluated for their pharmacological properties. They show very intensive biological activities like antibacterial, antiviral, antitumour, anticancer etc. Benzothiazole nucleus is present in many natural products such as bleomycin, epothilone A, lyngbyabellin A and dolastatin. Due to their pharmaceutical utilities, the synthesis of these compounds is of considerable interest. It has reactive sites which are used for functionalization. [1-17] Looking into their pharmacological importance, here in we report the synthesis of some new benzothiazole derivatives (2-4) using 2-(4-aminophenyl)benzothiazol-5-ol (1d) as the parent compound and their biological activity.

II. Materials And Methods

2.1 Preparation of [(4-hydroxyphenyl)-4-azaneyl(4-nitrophen)]methanone (1a)[18]

To a solution of p-amino phenol and p-nitrobenzoyl chloride, pyridine (40 ml) was added followed by the addition of toluene (30 ml) then the mixture was refluxed for 5hrs. The product obtained was recrystallized from alcohol. Yield: 60%, m.p-150°C

2.2 Preparation of N-(4-hydroxyphenyl)-4-nitrobenzothioamide (1b)

To an ethanolic solution of compound 1(a), Lawesson's reagent (0.6 molar eq) was added. The mixture was heated for 2hrs after which it was dried and recrystallised from alcohol. Yield: 65%, m.p-160°C

2.3 Preparation of 2-(4-nitrophenyl)benzothiazol-6-ol (1c)

To a benzene solution of compound 1(b), 0.5 ml ethanol and 1ml NaOH was added. The solution was cooled in an ice bath and freshly prepared aqueous potassium ferricyanide (2-3 molar equivalent) was added. The reaction mixture was stirred at room temperature. Then the mixture was neutralized with 1M HCl. The organic layer was removed in vacuum and residue is purified by chromatography and recrystallised from alcohol. Yield: 50%, m.p-190°C

2.4 Preparation of 2-(4-aminophenyl)benzothiazol-5-ol (1d)

To an ethanolic solution of compound 1(c), 10 ml water, 4 g iron powder and 7g ammonium chloride was added. The mixture was stirred at 85°C for one hr. cooled at room temp. then filtered and washed with water and recrystallised from alcohol.

Yield: 65%, m.p-180°C.

IR (cm⁻¹) 3575 (-C-OH), 3279-3638 ((-NH₂)¹H) NMR (DMSO) δ ppm-6.6 (1H, OH) 7.2-8.4 (9H-Ar) ¹³C NMR (DMSO) δ ppm-155.4, 134.6, 129, 127.65, 122, 118.66, 108.6, 79.25, 40.11, 39.90, 39.06

2.5 Preparation of 4-[(4-hydroxyphenyl)diazenyl]phenyl]benzothiazol-6-ol (2a)[19]

1(d) was diazotized followed by coupling with phenol at 0-10°C temp. to give 2(a) The compound thus obtained was recrystallized from alcohol. Yield: 52%, m.p: 260°C.

IR(cm^{-1}) : 3298-33472 (C-OH), 2924(C-aliph),1696(-N=N-).¹HNMR (400 MHz ,DMSO δ ppm): 7.16-7.20(2H,OH), 7.64-7.72(13H-Ar) ¹³CNMR(DMSO) δ ppm-134.61,129.07,127.65,125.86,122.41,118.66,108.65

2.6 Preparation of 4-[(4-(6-hydroxybenzothiazol-2-yl)phenyl)diazinyl]phenyl 4-alkoxybenzoate (2b)

It was prepared by dissolving compound 2(a) in dry pyridine 5ml and 4-n alkoxy benzoyl chloride 0.02 mol and then add in K_2CO_3 2gm and alkyl bromide 2ml. The reaction mixture was refluxed on water bath for 8-10 hrs. The solid obtained was recrystallised from alcohol. Yield:62%, m.p:270⁰C.

IR (cm^{-1}): 3479(-C-OH),1859 (-COO-),1598.50(-N=N-),1219-1597 (Ar-O-CH₃). ¹HNMR (400 MHz, DMSO δ ppm): 7.4-7.5(s,1H,OH) ,6.5-7.7 (17H-Ar),3.48 (s,3H,Ar-O-CH₃) ¹³CNMR(DMSO) δ ppm-155.44,134.61,127.65,125.86,122.41,108.65,79.25,78.60,40.11,39.69,39.27,38.85

2.7 Preparation of 2-[4-((7-hydroxynaphthalen-1-yl)diazenyl)phenyl]benzothiazol-6-ol (3)[20]

It was diazotized in usual manner using sodium nitrite and conc. HCl and then cold solution of 2-naphthol in 10% NaOH was added to it.The resultant mixture was allowed to stand for one hr. to give ppt.of the product which was filtered and recrystallized from alcohol. Yield:45%. m.p:196⁰C.

IR(cm^{-1}): 3379-3387(-C-OH),1435 (-N=N-). ¹HNMR (400 MHz ,DMSO δ ppm): 6.70,6.72(2H,OH), 6.7-7.7(14HAr) ¹³CNMR(DMSO) δ ppm-162.92,154.05,148.78,140.63,130.02,122.2,114.85,79.12,78.47,40.11,39.70,39.07,38.86

2.8 Preparation of 4-(6-propoxybenzothiazol-2-yl)aniline (4a)[21]

It was prepared from (1d) by dissolving anhydrous potassium carbonate 0.80 g in 20 ml acetone,then adding a 2g solution of (1d) in n-alkyl bromide 4 ml. The mixture was refluxed overnight and then was poured into ice water, the ppt.obtained was filtered and washed with water, dried and recrystallized from ethanol. Yield:60% . m.p:220⁰C.

IR(cm^{-1}): 3569 (Ar-O-CH₃),3233-3669((-NH₂),858(C-S-C).¹HNMR (400 MHz, DMSO δ ppm): 6.75(1H,OH) 7.5-8.3(9H-Ar) ¹³CNMR(DMSO) δ ppm-163.01,154.08,148.8,140.130,130.08,128.87,123.30,122.30,115.51,114.9

2.9 Preparation of 1-(4-alkoxyphenyl)-N-(4-(7-propoxybenzothiazol-2-yl)phenyl)methanimine. (4b)

4(b) derivative was prepared by mixing of compound 4(a) and 4-n alkoxybenzaldehyde 10 ml in THF40 ml and the refluxing for 4hrs.in the presence of catalytic quantity of piperidine. The product obtained was filtered and recrystallized from alcohol.

Yield:70%, m.p:250⁰C.

IR(cm^{-1}) 1673.27(-CH=N),3344-3739(Ar-O-CH₃).¹HNMR (400 MHz,DMSO δ ppm): 6.7-7.5(13H-Ar),9.4287(-N=CH),3.4800 (O-CH₃) ¹³CNMR(DMSO) δ ppm-167.57,165.9,160.73,152.48,149.81,140.7,136.90,132,131.09,130,123,122.31,121.69,119,11,

2.10 Antibacterial Activity

The antibacterial activity was studied by agar diffusion technique using *Bacillus*,*Staphylococcus*,*Pseudomonas* and *E.Coli* bacteria.All the compounds were dissolved in DMSO at the concentration of 100 ug/ml for testing antibacterial activity.The compound diffused into the medium and produced a concentration gradient, After the incubation period, the zone of inhibition was measured in mm.

Antibacterial activity of standard drugs(Table-1)

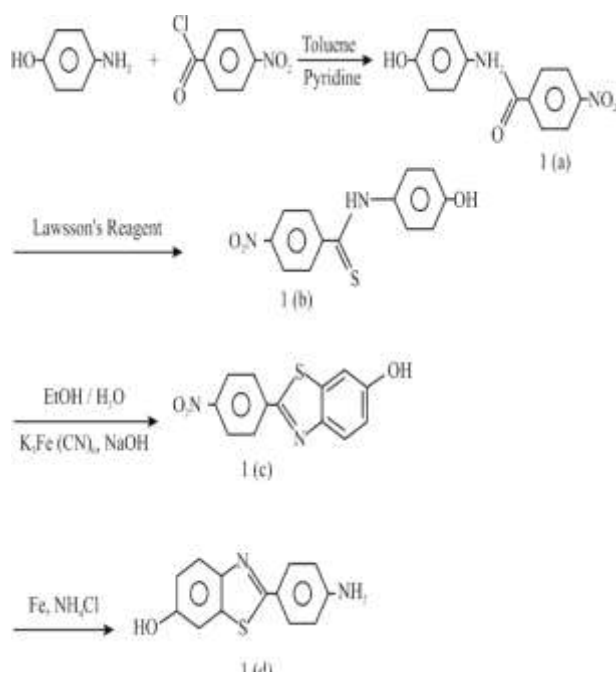
Standard	Gram Positive		Gram Negative	
	<i>Bacillus</i>	<i>Staphylococcus</i>	<i>Pseudomonas</i>	<i>E.Coli</i>
Chloremphenicol	20	20	19	23
Ciprofloxacin	21	22	26	28

Zone of inhibition (mm)

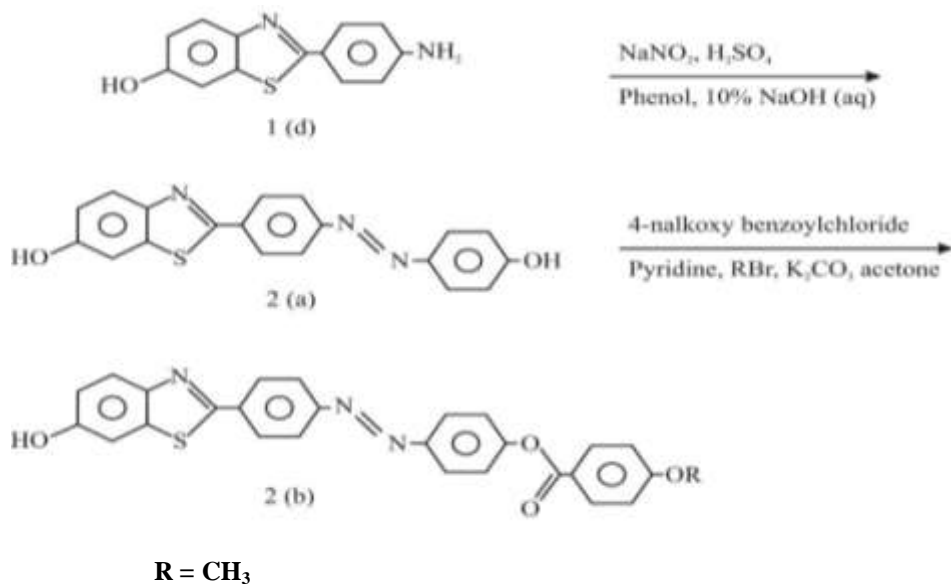
III. Results And Discussions

The parent benzothiazole derivative (1d) was synthesized by Jacobson method using Lawesson’s reagent (scheme 1).The product obtained was used for the synthesis of other benzothiazole derivatives.

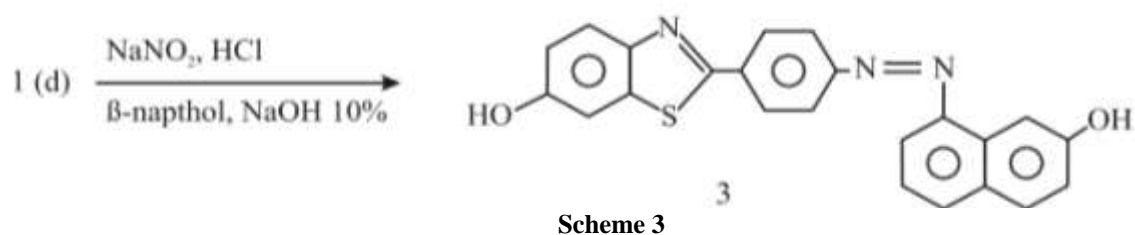
3.1 Synthesis of 2-(4-aminophenyl)benzothiazole-5-ol (1d)



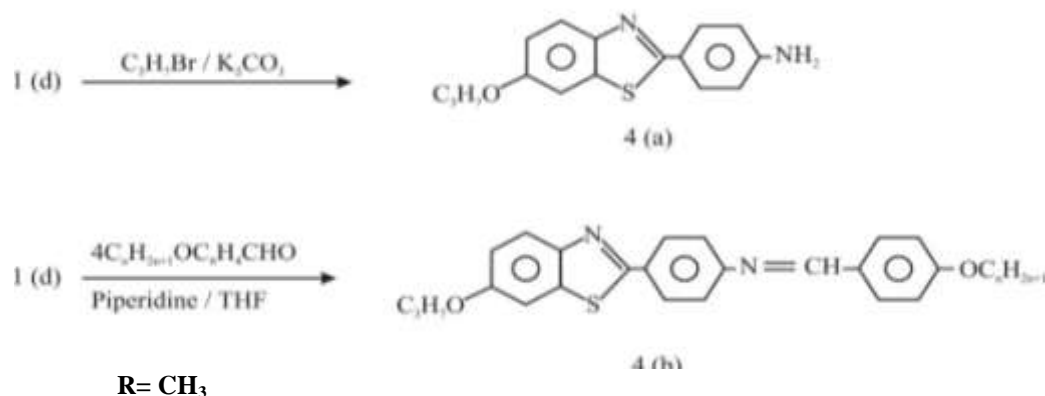
3.2 Synthesis of 4-[(4-(6-hydroxybenzothiazol-2-yl)phenyl)diazenyl]phenyl 4-alkoxybenzoate (2b)



3.3 Synthesis of 2-[4-((7-hydroxynaphthalen-1-yl)diazenyl)phenyl]benzothiazol-6-ol (3)



3.4 Synthesis of 1-(4-alkoxyphenyl)-N-(4-(7-propoxybenzothiazol-2-yl)phenyl)methanimine(4b)



The structures of all the synthesized compounds have been established with the help of their IR and NMR spectral data which correspond well with the predicted structures.

Antibacterial activity of synthesized compounds (Table-2)

Compounds no.	Gram Positive		Gram Negative	
	<i>Bacillus</i>	<i>Staphylococcus</i>	<i>Pseudomonas</i>	<i>E. Coli</i>
2 (a)	11	11	18	10
2 (b)	11	11	14	13
3	13	12	19	11
4 (a)	8	10	18	12
4 (b)	12	13	15	11

All the synthesized compounds are broad spectrum because they are active against both gram positive and gram negative bacteria. The results of antibacterial activity show that the compounds have moderate to good antibacterial activity. However compound 3 was found to be the most potent. (Table-2)

IV. Conclusion

The present paper highlights the use of 2-(4-aminophenyl)benzothiazol-5-ol as a template for development of new benzothiazole derivatives with potent biological activity. The biological profile of this new generation of benzothiazole represents its better use in drug development against bacterial infection in future.

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