

Synthesis and Antimicrobial Activity of Some Benzothiazole Derivatives

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ABSTRACT

Five new diazenyl derivatives were synthesized by reaction of 6-substituted-2-aminobenzothiazole derivatives with 2-naphthol in presence of sodium hydroxide. All the derivatives were screened for antimicrobial activity against *S. aureus*, *S. pyrogens*, *E. coli*, *P. mirabilis*, *C. albicans* and *A. fumigatus* using Ciprofloxacin and Amphotericin B as standard drugs for evaluation of antibacterial and antifungal activity respectively. Some derivatives exhibit mild to moderate activity.

Keywords: 2-aminobenzothiazole, 2-naphthol, antibacterial, antifungal, diazo.

INTRODUCTION¹⁻⁵

Decreased or no antibacterial activity shown by existing antibacterial agents including antibiotics is largely confined to resistance developed by the pathogenic bacteria toward these agents. Production of drug inactivating enzymes such as β -lactamase is the common mechanism of resistance to β -lactam antibiotics. Alteration in a single aminoacid of bacterial enzyme is found to make the bacteria resistant and is observed with quinolone antibiotics. Bacterial species including pseudomonas are developing resistance through changing the cell permeability. Some bacteria are resistant to tetracyclines because they have an active transport pump which removes tetracycline from the cell membrane. Resistance developed by *S. aureus* is mainly confined to alteration in penicillin binding proteins (transpeptidases). Thus increasing bacterial resistance towards the existing antibacterial agent became a major reason for introduction of new and potential drugs to combat various bacterial infections.

Derivatives of benzothiazole used clinically include ethoxazolamide (a good carbonic anhydrase inhibitor), Firefly Luciferin (which is used in assay of ATP), TCMTB (2-benzothiazolythio)methyl thiocyanate

(antimicrobial, marine biocide and fungicidal), tiaramide (an anti asthmatic and anti-inflammatory agent), zopolrestat (which is indicated in treatment of diabetic complications) and fostedil (antianginal and antihypertensive).

Clinically used 2-aminobenzothiazole⁶⁻⁷ derivatives include 2-amino-6-methylbenzothiazole, sabeluzole (a nootropic agent), riluzole (neuroprotective), pramipexole (antiparkinsonian agent) and dianithazole (antifungal).

Naphthalene derivatives are well known for their antimicrobial and insecticide activity. Further the diazenyl and triazenyl systems proved potent antimicrobial activities e.g. Prontosil, Sulphasalazine and dacarbazine.

MATERIAL AND METHODS

All the chemicals used were purified by the established methods. Melting points were determined on open capillary tubes and are uncorrected. The purity and homogeneity of the synthesized compounds was routinely ascertained by TLC using Benzene: Methanol (50:50 v/v). The absorption maxima of the synthesized compounds were carried out in methanol (analytical grade, 1mg/100mL). The methanolic solutions of the synthesized compounds

were scanned on Shimadzu UV 1700 spectrophotometer, Kyoto, Japan in the region 200-400 nm. The infra red absorption spectra of the synthesized compounds were recorded on FTIR (Brucker, Tensor 27) spectrophotometer. The $^1\text{H-NMR}$ spectra of the synthesized compounds were recorded on Brucker Spectrospin DPX 300 spectrophotometer. The solutions of the test compounds were prepared in dimethyl sulfoxide $\text{DMSO-}d_6$. Tetra Methyl Silane (TMS) was used as internal standard. The antimicrobial activity was measured by cup plate method using ciprofloxacin as standard during evolution of antibacterial activity. Amphotericin B was used as standard drug during evolution of antifungal activity.

EXPERIMENTAL WORK AND RESULTS

A. Synthesis⁸⁻¹¹: The 3(a-e) derivatives were synthesized by the reported methods and were obtained as per the reported yields. These derivatives were diazotized in usual manner using sodium nitrite and conc. HCl to yield 4(a-e). The corresponding solutions of 4(a-e) in 10% NaOH were mixed with cold solutions of 2-naphthol in 10% NaOH. The resultant mixtures were withstood for about one hour to give the precipitated products, which were recrystallized from rectified spirit to give 5(a-e).

5a: 1-[2-(benzothiazol-2-yl) diazenyl] naphthalen-2-ol, white crystals, Yield 36%, m.p. 143-5°C, R_f 0.78, λ_{max} 264 nm (methanol), IR (V max, cm^{-1}): 3580 (C-OH), 3030 (CH, Ar), 1428 (N=N stretching), $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, δ ppm): 4.91 (s, 1H, OH), 6.54-6.78 (m, 10H, Ar)

5b: 1-[2-(6-methyl benzothiazol-2-yl) diazenyl] naphthalen-2-ol, white crystals, Yield 39%, m.p. 131-3°C, R_f value 0.79, λ_{max} 275 nm (methanol), IR (V max, cm^{-1}): 3564 (C-OH), 3028 (CH, Ar), 2910 ($-\text{CH}_3$), 1430

(N=N stretching), $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, δ ppm): 0.61 (s, 3H, $-\text{CH}_3$), 4.96 (s, 1H, OH), 6.36-6.58 (m, 9H, Ar)

5c: 1-[2-(6-methoxy benzothiazol-2-yl) diazenyl] naphthalen-2-ol, white crystals, Yield 41%, m.p. 172-4°C, R_f value 0.74, λ_{max} 324 nm (methanol) IR (V max, cm^{-1}): 3493 (C-OH), 3033 (CH, Ar), 1425 (N=N stretching), 1247 (C-O- CH_3 stretching), $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, δ ppm): 0.54 (s, 3H, $-\text{OCH}_3$), 4.98 (s, 1H, OH), 6.56-6.65 (m, 9H, Ar)

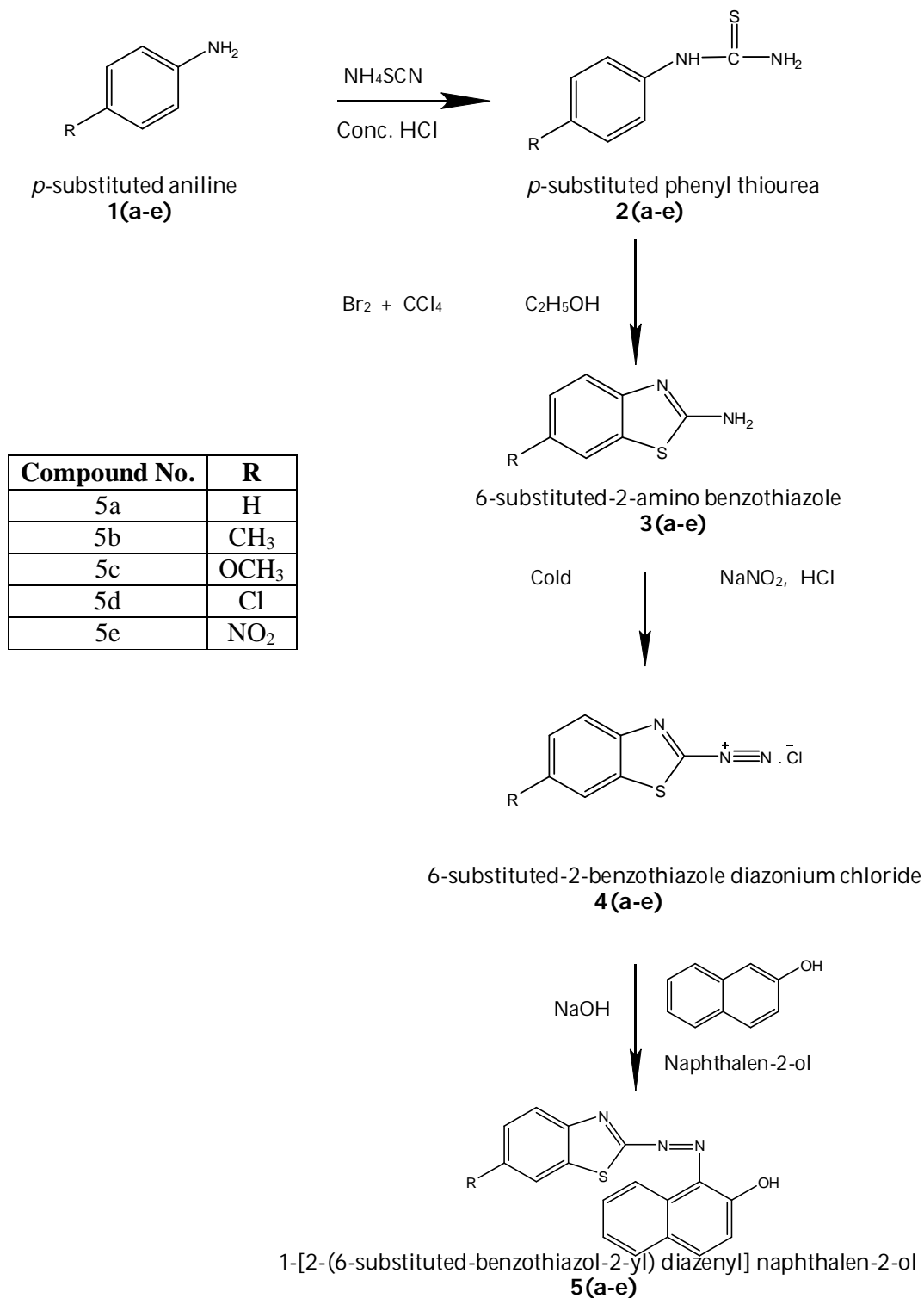
5d: 1-[2-(6-chloro benzothiazol-2-yl) diazenyl] naphthalen-2-ol, white crystals, Yield 38%, m.p. 187-9°C, R_f value 0.69, λ_{max} 320 nm (methanol), IR (V max, cm^{-1}): 3499 (C-OH), 3017 (CH, Ar), 1435 (N=N stretching), 754 (C-Cl), $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, δ ppm): 4.72 (s, 1H, OH), 6.58-6.75 (m, 9H, Ar)

5e: 1-[2-(6-nitro benzothiazol-2-yl) diazenyl] naphthalen-2-ol, yellow crystals, Yield 36%, m.p. 172-4°C, R_f value 0.68, λ_{max} 314 nm (methanol), IR (V max, cm^{-1}): 3462 (C-OH), 3008 (CH, Ar), 1431 (N=N stretching), 1320 (C- NO_2), $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, δ ppm): 4.75 (s, 1H, OH), 6.48-6.62 (m, 9H, Ar)

B. Antimicrobial Activity¹²

All the synthesized compounds i.e. 5(a-e) were screened for *in vitro* antimicrobial activity against four pathogenic bacteria viz. *S. aureus*, *S. pyrogens*, *E. coli* and *P. mirabilis* using Ciprofloxacin as the standard drug. The *in vitro* antifungal activity of the synthesized compounds was screened against the pathogenic fungi *C. albicans* and *A. fumigatus* using Amphotericin B as the standard drug. The solutions of the test and standard compounds were prepared in Dimethyl Formamide (DMF), the concentration of the prepared solutions being 100 $\mu\text{g/ml}$. The results of antimicrobial activity are reported in Table 1 and 2.

SYNTHETIC SCHEME



DISCUSSION

The IR and ¹H-NMR data of the synthesized compounds indicates their successful synthesis. All the synthesized compounds exhibit mild to moderate antibacterial activity as compared to the standard drug ciprofloxacin. Compound **5c** was found to be the most potent antibacterial amongst the synthesized derivatives. Activity of this compound confined to the presence of powerful electron releasing -OCH₃ group. Moderate antifungal activity shown by 5b

and 5d attributed to the presence of electron releasing -CH₃ and -Cl groups.

CONCLUSION

The findings on the current research work are in strong suggestion of need of further extensive exploration of the current topic that may lead to introduction of a novel and potent antimicrobial agent of therapeutic importance. The 6-substituted-2-aminobenzothiazole can be a lead and strong molecule targeted to introduce new antimicrobials.

Table 1: In Vitro Antibacterial Activity of the synthesized compound 5(a-e)

Compound no	<i>S. aureus</i>		<i>S. pyogenes</i>		<i>E. coli</i>		<i>P. mirabilis</i>	
	Z.O.I	% Inhi.	Z.O.I	% Inhi.	Z.O.I	% Inhi.	Z.O.I	% Inhi.
5a	7	35	8	33	11	48	9	34
5b	8	40	11	45	9	39	10	38
5c	11	55	6	25	13	56	12	46
5d	8	40	9	37	7	30	6	23
5e	8	40	7	29	10	43	11	42
Standard *	20	100	24	100	23	100	26	100

*Ciprofloxacin, ZOI= Zone of inhibition

Table 2: In Vitro Antifungal Activity of the synthesized compound 5(a-e)

Compound No.	<i>C. albicans</i>		<i>A. fumigatus</i>	
	Zone of Inhibition	% Inhibition	Zone of Inhibition	% Inhibition
5a	8	40	5	41
5b	10	50	4	33
5c	7	35	4	33
5d	8	40	6	50
5e	7	35	4	33
Standard *	20	100	12	100

* Amphotericin B

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