Synthesis and Antimicrobial Activity of 2-Mercaptobenzothiazole Derivatives

Sanjay Kumar Deivedi [1*], Ashok Kumar Tripathi[1], V.K. Singh[2]

[1]Drug Design and Medicinal Chemistry Laboratory, College of Pharmacy, IFTM, Uttar Pradesh, India.
[2]Institute of Pharmacy, Bundelkhand University, Jhansi, UP, India

Summary

The condensation of 2-mercaptobenzothiazole **(A)** with chloroacetyl chloride in refluxing chloroform in the presence of anhydrous potassium carbonate yielded S-benzo[d]thiazol-2-yl 2-chloroethanethioate **(B).** Compound **(B)** on treatment with different substituted aniline in presence of anhydrous potassium carbonate and in dry acetone yielded a series of derivatives. The synthesized compounds **(Ci-vii)** were characterized on the basis of their m.p., TLC, IR, ^{1}H-NMR and Elemental analysis data, and screened for their antimicrobial activity.

Key words: 2-mercaptobenzothiazole, antimicrobial, substituted aniline.

***Corresponding author:**

College of Pharmacy, IFTM, Lodhipur Rajput, Delhi Road, Moradabad-244001, UP, India; Fax: 0591-2360818; E-mail: **sanjaydeivedi@yahoo.co.in**

Introduction

The compounds containing nitrogen, sulphur and thiazole moieties constitute the core structure of a number biologically interesting compounds **[1]**. Moreover literature survey reveals that 2-mercaptobenzothiazole derivatives possess various pharmacological activities **[2-10]**. On the basis of literature survey, we aimed the synthesis of new 2-mercaptobenzothiazole derivatives by chemical changes at 2nd position in 2-mercaptobenzothiazole and evaluated their antimicrobial activity.

Materials and Methods

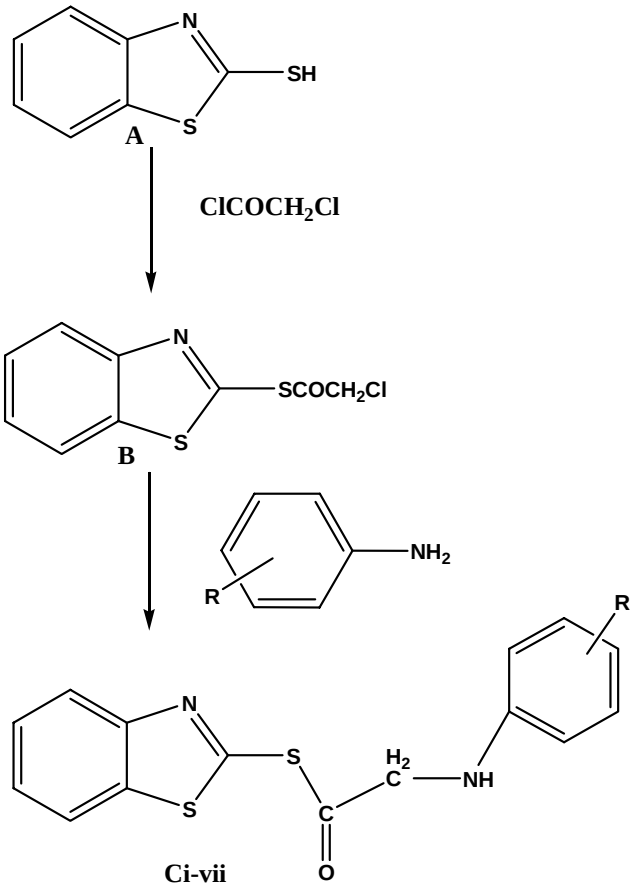
Experimental

All the melting point was determined in open capillaries and are uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer and ^{1}H-NMR spectra were recorded on a Bruker 250 MHz spectrometer instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d6 as a solvent. Chemical shifts are given in parts per million (ppm). Elemental

analyses were recorded on Perkin Elmer EAL 240 spectrometer. Purity of the compounds was checked by TLC (Thin Layer Chromatography) on silica gel plates and spot were visualized by exposure to iodine vapours.

S-benzo[d]thiazol-2-yl 2-chloroethanethioate (B) S-benzo[d]thiazol-2-yl 2-chloroethanethioate is prepared by a reported method **[11]**. Yield: 78.20%, m.p, 99-100$^{\circ C}$, Mol. Formula $C_9H_6ClNOS_2$.

Scheme I



R= 4-CH_3, 2,3- CH_3, 4-OCH_3, 3-Cl4-F, 4-Cl,

General procedure for the synthesis of S-(benzo[d]thiazol-2-yl)-2-(phenyl amino) ethanethioate: Equimolar amounts of S-benzo[d]thiazol-2-yl 2-chloroethanethioate (0.01 mole) with different substituted anilines (0.01 mole) in presence of anhydrous potassium carbonate

(0.01 mole), in dry acetone were refluxed for 11-14 h. The compounds were then filtered and washed thoroughly with water and recrystallized from ethanol.

S-benzo[d]thiazol-2-yl 2-(p-tolylamino)ethanethioate: **(Ci)** Yield: 62.7% m.p., 113-114^{0}C, Mol. Formula - $C_{16}H_{14}N_2OS_2$, IR (KBr, cm^{-1}) 3178 (-NH), 721 (C-S-C), 1670 (-C=O), 3027.18 (Ar-H), 2806.23 (C-H in CH_2), 2930(C-H in CH_3) 1600.00 (C=C in Aromatic ring), ^{1}HNMR δ 3.8 (s, 3H, CH_3), 4.2 (s, 2H,CH_2), 7.9 (s, 1H, NH), 6.28-8.21 (m, 8H, Ar-H). Anal. Cal. for $C_{16}H_{14}N_2OS_2$: C, 61.12; H, 4.49; N, 8.91; Found C, 61.14; H, 4.48; N, 8.92.

S-benzo[d]thiazol-2-yl 2-(2,3-dimethylphenylamino)ethanethioate: **(Cii)** Yield: 60.2%, m.p., 118-119^{0}C, Mol. Formula - $C_{17}H_{16}N_2OS_2$, IR (KBr, cm^{-1}) 3180 (-NH), 725 (C-S-C), 1668 (-C=O), 3032 (Ar-H), 2806.23 (C-H in CH_2), 2933(C-H in CH_3), 1600.00 (C=C in Aromatic ring), ^{1}HNMR δ 2.12 (s, 6H, CH_3), 4.1 (s, 2H,CH_2), 7.8 (s, 1H, NH), 6.00-8.3 (m, 7H, Ar-H). Anal. Cal. for $C_{17}H_{16}N_2OS_2$: C, 62.16; H, 4.91; N, 8.53; Found C, 62.18; H, 4.90; N, 8.54.

S-benzo[d]thiazol-2-yl 2-(4-methoxyphenylamino)ethanethioate: **(Ciii)** Yield: 65.27%, m.p., 98-99^{0}C, Mol. Formula - $C_{16}H_{14}N_2O_2S_2$, IR (KBr, cm^{-1}) 3180 (-NH), 725 (C-S-C), 1668 (-C=O), 3032 (Ar-H), 2806.23 (C-H in CH_2), 2933(C-H in CH_3), 1600.00 (C=C in Aromatic ring), ^{1}HNMR δ 3.64 (s, 3H, OCH_3), 4.14 (s, 2H,CH_2), 8.0 (s, 1H, NH), 6.32-8.10 (m, 8H, Ar-H). Anal. Cal. for $C_{16}H_{14}N_2O_2S_2$: C, 58.16; H, 4.27; N, 8.48; Found C, 58.18; H, 4.28; N, 8.50.

S-benzo[d]thiazol-2-yl 2-(3-chloro-4-fluorophenylamino)ethanethioate: **(Civ)** Yield: 68.20%, m.p., 188-189^{0}C, Mol. Formula - $C_{15}H_{10}ClFN_2OS_2$, IR (KBr, cm^{-1}) 3180 (-NH), 725 (C-S-C), 1668 (-C=O), 3032 (Ar-H), 2806.23 (C-H in CH_2), 2933(C-H in CH_3), 1600.00 (C=C in Aromatic ring), ^{1}HNMR δ 4.2 (s, 2H,CH_2), 7.9 (s, 1H, NH), 6.20-8.10 (m, 7H, Ar-H). Anal. Cal. for $C_{15}H_{10}ClFN_2OS_2$: C, 51, 06; H, 2.86; N, 7.94; Found C, 51.08; H, 2.88; N, 7.96.

S-benzo[d]thiazol-2-yl 2-(4-chlorophenylamino)ethanethioate: **(Cv)** Yield: 63.10%, m.p., 177-178^{0}C, Mol. Formula - $C_{15}H_{11}ClN_2OS_2$, IR (KBr, cm^{-1}) 3180 (-NH), 725 (C-S-C), 1668 (-C=O), 3032 (Ar-H), 2806.23 (C-H in CH_2), 2933(C-H in CH_3), 1600.00 (C=C in Aromatic ring), ^{1}HNMR δ 4.18 (s, 2H,CH_2), 8.0 (s, 1H, NH), 6.30-8.16 (m, 8H, Ar-H).Anal. Cal. for $C_{15}H_{11}ClN_2OS_2$: C, 53.80; H, 3.31; N, 8.37; Found C, 53.82; H, 3.82; N, 8.36.

S-benzo[d]thiazol-2-yl 2-(phenylamino)ethanethioate: **(Cvi)** Yield: 58.10%, m.p., 166-167^{0}C, Mol. Formula - $C_{15}H_{12}N_2OS_2$, IR (KBr, cm^{-1}) 3180 (-NH), 725 (C-S-C), 1668 (-C=O), 3032 (Ar-H), 2806.23 (C-H in CH_2), 2933(C-H in CH_3), 1600.00 (C=C in Aromatic ring), ^{1}HNMR δ 4.24 (s, 2H,CH_2), 8.2 (s, 1H, NH), 6.4-8.26 (m, 9H, Ar-H). Anal. Cal. for $C_{15}H_{12}N_2OS_2$: C, 59.97; H, 4.03; N, 9.33; Found C, 59.98; H, 4.02; N, 9.32.

S-benzo[d]thiazol-2-yl 2-(cyclohexylamino)ethanethioate: **(Cvii)** Yield: 55.20%, m.p., 122-123^{0}C, Mol. Formula - $C_{15}H_{18}N_2OS_2$, IR (KBr, cm^{-1}) 3180 (-NH), 725 (C-S-C), 1668 (-C=O), 3032 (Ar-H), 2806.23 (C-H in CH_2), 2933(C-H in CH_3), 1600.00 (C=C in Aromatic ring), ^{1}HNMR δ 3.5 (s, 2H,CH_2), 8.0 (s, 1H, NH), 7.4-8.18 (m, 8H, Ar-H), 1.2-2.38 (m, 11H, cyclohexane) Anal. Cal. for $C_{15}H_{18}N_2OS_2$: C, 58.79; H, 5.92; N9.14; Found C, 58.81; H, 5.94; N, 9.12.

Antimicrobial activity:

Antibacterial activity of the compounds, **(Ci-vii)** was studied against *Staphylococcus aureus* (NCIM NO. 2654), *Bacillus subtilis* (NCIM NO. 2195), *Escherchia coli* (NCIM NO. 2341) and *Pseudomonas aeruginosa* (NCIM NO. 2914) by disc-diffusion method and Ofloxacin used as the reference antibiotics **[12-13]**. Agar media (Hi-media) was taken in the pre-sterilized petri-dishes and the microorganisms were grown. Each test compounds were dissolved in dimethyl sulphoxide (DMSO) to get a concentration of 10 mg/ml. The disc (6 mm in diameter) was impregnated with 10µl and 5µl of each test solution to get 100 µg/disc and 50 µg/disc respectively, placed on the seeded agar medium and the petri-dishes were incubated at 37^0C for 24 hr. Zone of inhibition of each compound in mm was recorded and the results were furnished in Table 1. The antifungal activity of the compounds, **(Ci-vii)** was also determined against *Aspergillus niger* (NCIM NO. 618*)* and *Aspergillus flavipes* (NCIM NO. 1209) by filter paper disc technique. The antifungal activity was studied using Sabouraud dextrose agar (SDA) medium (Hi-media) by incubating for 48 hr at 22^0C and Fluconazole (10 µg/disc) was used as standard drug **[14].**

Table: 2 *Determination of antibacterial activity of compounds (Ci - Cvii)

Compounds (µg/disc)		**Gram positive bacteria**		**Gram negative bacteria**	
		S. aureus	***B. subtilis***	***E. coli***	***P. aeruginosa***
Ci	50	9.0±0.57	9.67±1.20	14.33±0.88	10.67±0.88
	100	11.33±0.33	13.67±0.33	16.67±0.67	14.67±0.33
Cii	50	11.67±0.33	10.0±1.15	12.33±1.20	13.33±0.88
	100	15.67±0.88	12.67±0.88	14.23±0.33	19.67±0.88
Ciii	50	11.33±1.20	12.0±1.15	11.0±1.0	11.0±0.57
	100	14.33±0.88	15.67±0.33	16.0±1.15	15.67±0.33
Civ	50	13.67±0.33	12.67±0.33	14.67±0.33	13.67±0.88
	100	18.33±0.33	14.0±1.0	18.67±0.88	15.33±.33
Cv	50	14.0±0.57	12.67±1.45	15.33±1.20	12.67±0.33
	100	20.67±0.33	15.0±1.15	22.23±0.33	13.33±0.88
Cvi	50	10.33±0.88	9.0±0.57	13.0±0.67	11.67±0.88
	100	13.67±0.88	12.33±0.33	16.67±0.33	15.0±0.57
Cvii	50	11.33±1.20	12.0±1.15	12.0±1.0	15.33±0.88
	100	14.33±0.88	15.33±0.33	17.0±1.15	19.67±0.88
Ofloxacin	10	25.33±0.33	23.0±0.0	24.33±0.33	26.00±0.0

*Values are mean ± SEM of three readings

Results and Discussion

S-benzo[d]thiazol-2-yl 2-chloroethanethioate on treatment with different substituted Anilines in presence of anhydrous potassium carbonate in dry acetone yielded S-(benzo[d]thiazol-2-yl)-2-(phenyl amino) ethanethioate derivatives. The purity of the compounds was routinely checked by thin layer chromatography (TLC). The synthetic route of compounds is outlined in **Scheme 1**.

The IR spectra of 2-mercaptobenzothiazole derivative (Ci-vii) showed characteristic C=O stretching found in 1700-1660 cm^{-1}, NH stretching band observed at 3444 - 3088 cm^{-1}, aromatic (C=C) stretching observed at 1590-1610 cm^{-1} and all other functional group were observed in the expected stretching regions. In the ^{1}H-NMR spectra of synthesized compounds, NH peaks were observed as singlet at 7.8-8.2 ppm, the signal due to $COCH_2$ methylene proton, presented in all compounds appeared at 4.1- 4.2 ppm as singlet and all other aromatic and aliphatic protons were observed at expected regions. In elemental analyses all values were within ± 0.4 % of the theoretical values.

Antibacterial activity: To determine the antibacterial activity of these agents, the filter paper disc technique was used, with Ofloxacin as the reference antibiotics. The prepared compounds

were examined against two strains each of gram positive and gram negative bacteria. The test results, presented in Table 1, suggest that compounds **Civ** and **Cv** are highly active against *S. aureus* and *E. coli* respectively. Compounds **Cii** and **Cvii** are also highly active against *P. aeruginosa*. The rest of the compounds were found to be moderately active or slightly active against the tested microorganisms.

Antifungal activity: The antifungal activities of the prepared compounds were tested against three different fungi such as, *A. niger* and Aspergillus flavipes by filter paper disc technique. None of the compounds were found to be active against the fungi species tested.

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