

Note

Synthesis and biological evaluation of 2-aminobenzothiazole derivatives

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As a part of systematic investigation of synthesis and biologically active compounds of 2-amino benzothiazoles, several new [(2"-substituted aryl)-4"-oxo-1",3"-thiazolidine-3"-iminoacetyl]-2-aminobenzothiazole **5** and [(5"-arylidene-2"-substituted aryl-4"-oxo-1",3"-thiazolidine)-3"-iminoacetyl]-2-aminobenzothiazole **6** from 2-aminobenzothiazole have been synthesized. All the synthesized products are evaluated for their antibacterial activity against *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporum* and *Trichoderma viride*. The structures of all the synthesized compounds have been determined by spectral and chemical methods.

Keywords: 2-Aminobenzothiazole, thiazolidinone, chloroacetyl chloride, thioglycolic acid, antimicrobial activity

Benzothiazole derivatives play a vital role in biological fields such as antitubercular, antiallergic, antiinflammatory and fungicidal activities¹⁻⁴. 1,3-thiazolidine have been reported to display anti-inflammatory⁵, fungicidal⁶ and antibiotic⁷ activities. 5-Arylidene derivatives showed good pharmacological properties⁸. Heterocycles bearing thiazole, sulphur and nitrogen moieties constitute the core structure of a number of pharmacologically and biologically active interesting compounds. The efficiency of azoles as chemotherapeutic agent is well established^{9,10}. Looking at the importance of these compounds, the present work aims to synthesize and screen the antifungal and antibacterial activities of new thiazolidine and arylidine derivatives of 2-aminobenzothiazole.

Result and Discussion

2-aminobenzothiazole on reaction with chloroacetyl chloride gave (1'-chloroacetyl)-2-aminobenzothiazole **1**, which on amination with hydrazine hydrate yielded (1'-hydrazinoacetyl)-2-aminobenzothiazole **2**.

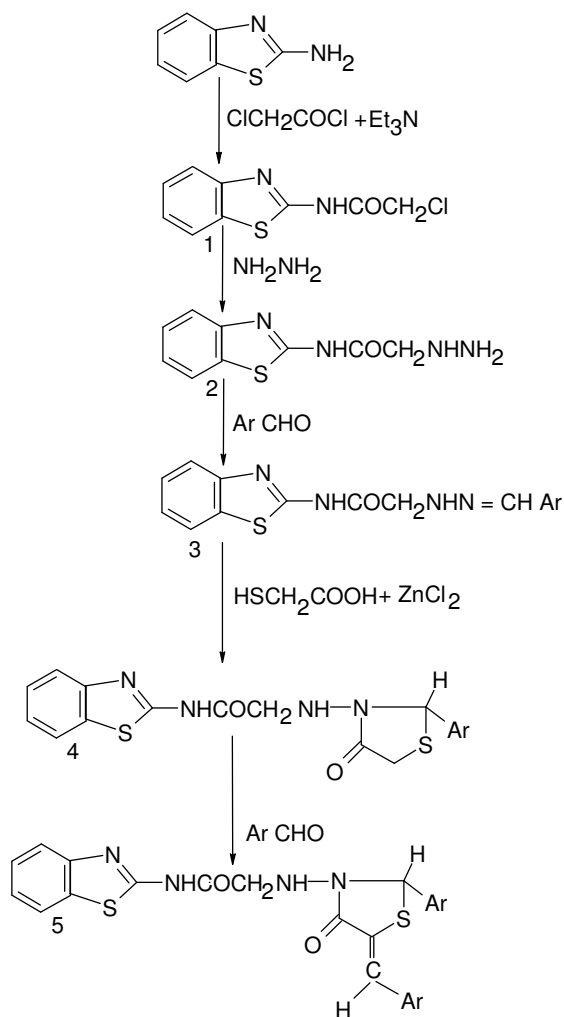
The compound **2** on condensation with various aromatic aldehydes afforded [1'(N-arylidene)-hydrazinoacetyl]-2-aminobenzothiazole **3**. The compound **3** on reaction with thioglycolic acid underwent dehydrative annulation to give [(2"-substituted aryl-4"-oxo-1",3"-thiazolidine)-3"-iminoacetyl]-2-aminobenzothiazole **4**, which on the application of Knoevenagel reaction with various aldehydes yielded [(5"-arylidene-2"-substituted aryl-4"-oxo-1",3"-thiazolidine)-3"-iminoacetyl]-2-aminobenzothiazole **5** (**Scheme I**). The purity of the compounds was monitored by TLC and the structures of the compounds were deduced on the basis of their elemental analysis and spectra data (**Table I**).

Antimicrobial Activity

The synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (*Ec*), *Staphylococcus aureus* (*Sa*), *Klebsiella pneumoniae* (*Kp*) and *Bacillus subtilis* (*Bs*) by filter paper disc technique at two concentrations (50 and 100 ppm) and antifungal activity against *Aspergillus niger* (*An*), *Aspergillus flavus* (*Af*), *Fusarium oxysporum* (*Fo*) and *Trichoderma viride* (*Tv*) by filter paper disc technique^{11,12} at two concentrations (100 and 500 ppm). Standard antibacterial streptomycin and antifungal griseofulvin were also screened under the similar conditions for comparison. The following compounds were found active against the noted bacteria and fungi: **3b** (*Sa*, *Kp*, *Af*, *Tv*), **3c** (*Ec*, *Bs*, *An*), **3d** (*Bs*, *Af*, *Fo*, *Tv*), **4b** (*Bs*, *Af*), **4c** (*Ec*, *Sa*, *Tv*), **4d** (*Bs*, *An*, *Fo*), **5a** (*Ec*, *An*), **5b** (*Ec*, *Bs*, *An*, *Tv*) and **5d** (*Ec*, *Bs*, *An*, *Tv*).

Experimental Section

The melting points were taken in an open capillary tube. IR spectra (KBr) were recorded on a Shimadzu 8201 PC spectrophotometer (ν_{\max} in cm^{-1}) and ^1H NMR spectra in CDCl_3 at 300 MHz on a Bruker DRX 300 spectrometer using TMS as an internal standard (Chemical shifts in δ , ppm). Mass spectra were recorded on a Jeol SX-102 (FAB) spectrometer. Compounds reported gave satisfactory elemental analysis.



Where Ar = - C₆H₅/2,3,4-BrC₆H₄/2,3,4, - ClC₆H₄/2,3,4-NO₂C₆H₄/-N(CH₃)₂C₆H₄

Scheme I

Synthesis of (1'-chloroacetyl)-2-aminobenzothiazole, **1**

To a stirred solution of 2-aminobenzothiazole (8 g, 0.05 mole) and triethyl amine (7.40 mL, 0.05 mole) in dry benzene (50 mL), chloroacetyl chloride (4.24 mL, 0.05 mole) was added dropwise to an ice-cold condition. The reaction-mixture was stirred for about 6 hr and the separated amine hydrochloride was filtered off. The filtrate was refluxed on a water-bath for about 4 hr, concentrated at reduced pressure and the separated solid was purified over the column of silica gel using CHCl₃ as an eluant. The product was crystallized from ethanol to give compound **1**. yield 75%, m.p. 140-43 °C Anal. Calcd for C₉H₇N₂OSCl: C, 47.68; H, 3.09; N, 12.36. Found: C, 47.66; H, 3.07; N, 12.33%. IR: 3027, 1634, 1572, 1523, 1179, 1072,

780, 730 and 691(benzothiazole ring), 3310(C-NH), 1660(>C=O amide), 3420, 3445 and 2880(CH₂), 760Cm⁻¹ (C-Cl); ¹H NMR: 4.41(s, 2H, CH₂), 6.90-7.72(m, 4H, ArH), 8.14(s, 1H,-CONH); MS: 226 (M⁺), 191, 149, 134.

Synthesis of (1'-hydrazinoacetyl)-2-aminobenzothiazole, **2**

Equimolar solution of the compound **1** (5 g, 0.02 mole) and hydrazine hydrate (1.072 mL, 0.02 mole) in methanol (30 mL) was refluxed for about 10 hr on a water-bath. After cooling the solution was filtered, dried and recrystallized from chloroform to give yield 72%, m.p. 148-50°C Anal. Calcd for C₉H₁₀N₄OS: C, 48.64; H, 4.50; N, 25.22. Found: C, 48.62; H, 4.47; N, 25.20%. IR: 3030, 1637,

Table I — Characterization data of the compounds **3b-k**, **4b-k** and **5b-k**

Comp	Ar	Yield (%)	m.p. (°C)	Mol. Formula
3b	2-BrC ₆ H ₄	72	117-19	C ₁₆ H ₁₃ N ₄ OSBr
3c	3-BrC ₆ H ₄	70	127-28	C ₁₆ H ₁₃ N ₄ OSBr
3d	4-BrC ₆ H ₄	71	136-38	C ₁₆ H ₁₃ N ₄ OSBr
3e	2-ClC ₆ H ₄	73	160-62	C ₁₆ H ₁₃ N ₄ OSCl
3f	3-ClC ₆ H ₄	72	165-68	C ₁₆ H ₁₃ N ₄ OSCl
3g	4-ClC ₆ H ₄	70	172-75	C ₁₆ H ₁₃ N ₄ OSCl
3h	2-NO ₂ C ₆ H ₄	68	168-70	C ₁₆ H ₁₃ N ₅ O ₃ S
3i	3-NO ₂ C ₆ H ₄	70	169-71	C ₁₆ H ₁₃ O ₃ N ₅ S
3j	4-NO ₂ C ₆ H ₄	72	176-79	C ₁₆ H ₁₃ O ₃ N ₅ S
3k	4,4'-N(CH ₃) ₂ C ₆ H ₄	75	153-55	C ₁₈ H ₁₉ N ₅ OS
4b	2-BrC ₆ H ₄	70	197-99	C ₁₈ H ₁₅ N ₄ O ₂ S ₂ Br
4c	3-BrC ₆ H ₄	71	192-96	C ₁₈ H ₁₅ N ₄ O ₂ S ₂ Br
4d	4-BrC ₆ H ₄	72	198-200	C ₁₈ H ₁₅ N ₄ O ₂ S ₂ Br
4e	2-ClC ₆ H ₄	75	181-83	C ₁₈ H ₁₅ N ₄ O ₂ S ₂ Cl
4f	3-ClC ₆ H ₄	72	186-88	C ₁₈ H ₁₅ N ₄ O ₂ S ₂ Cl
4g	4-ClC ₆ H ₄	70	190-91	C ₁₈ H ₁₅ N ₄ O ₂ S ₂ Cl
4h	2-NO ₂ C ₆ H ₄	71	203-05	C ₁₈ H ₁₅ N ₅ O ₄ S ₂
4i	3-NO ₂ C ₆ H ₄	74	208-10	C ₁₈ H ₁₅ N ₅ O ₄ S ₂
4j	4-NO ₂ C ₆ H ₄	72	214-16	C ₁₈ H ₁₅ N ₅ O ₄ S ₂
4k	4,4'-N(CH ₃) ₂ C ₆ H ₄	76	220-22	C ₂₀ H ₂₁ N ₅ O ₂ S ₂
5b	2-BrC ₆ H ₄	72	224-27	C ₂₅ H ₁₈ N ₄ O ₂ S ₂ Br ₂
5c	3-BrC ₆ H ₄	73	230-32	C ₂₅ H ₁₈ N ₄ O ₂ S ₂ Br ₂
5d	4-BrC ₆ H ₄	78	236-39	C ₂₅ H ₁₈ N ₄ O ₂ S ₂ Br ₂
5e	2-ClC ₆ H ₄	72	243-46	C ₂₅ H ₁₈ N ₄ O ₂ S ₂ Cl ₂
5f	3-ClC ₆ H ₄	70	249-50	C ₂₅ H ₁₈ N ₄ O ₂ S ₂ Cl ₂
5g	4-ClC ₆ H ₄	71	252-55	C ₂₅ H ₁₈ N ₄ O ₂ S ₂ Cl ₂
5h	2-NO ₂ C ₆ H ₄	73	257-59	C ₂₅ H ₁₈ N ₆ O ₆ S ₂
5i	3-NO ₂ C ₆ H ₄	74	262-64	C ₂₅ H ₁₈ N ₆ O ₆ S ₂
5j	4-NO ₂ C ₆ H ₄	72	266-69	C ₂₅ H ₁₈ N ₆ O ₆ S ₂
5k	4,4'-N(CH ₃) ₂ C ₆ H ₄	75	272-75	C ₂₉ H ₃₀ N ₆ O ₂ S ₂

1570, 1521, 1176, 1074, 779, 734 and 689 (benzothiazole ring), 3312 (C-NH), 1662 (>C=O amide), 3422, 3443 and 2884 (CH₂) and 3352 cm⁻¹ (NHNH₂); ¹H NMR: 4.36 (s, 2H, -CH₂), 4.45 (s, 2H, -NH₂), 8.29 (s, 1H, -NH) 8.18 (s, 1H, -CONH) and 6.88-7.71(m, 4H, Ar-H); MS: 222 (M⁺), 191, 177, 149, 134.

Synthesis of (1'(N-arylidene)-hydrazinoacetyl)-2-aminobenzothiazole, **3a**

A mixture of compound **2** (3.5 g, 0.015 mole) and benzaldehyde (1.593 mL, 0.015 mole) and 2-3 drops of gl acetic acid in methanol (25 mL) was refluxed on a water-bath for about 5 hr. The solvent was removed

under reduced pressure and the residue thus obtained was purified over the column of silica gel using CHCl₃ as an eluant. The product was crystallized from chloroform to give a product **3a**, yield 70%, m.p. 192-95°C, Anal, Calcd for C₁₆H₁₄N₄OS: C, 61.93; H, 4.51; N, 18.06. Found: C, 61.90; H, 4.48; N, 18.04%. IR: 3035, 1632, 1575, 1524, 1179, 1078, 782, 746 and 691 (benzothiazole with aromatic ring), 3313 (C-NH), 1665 (>C=O amide), 3415, 3439 and 2880 (CH₂), 1590 and 1548 cm⁻¹ (-CH=N); ¹H NMR: 4.35 (s, 2H, -CH₂), 8.19 (s, 1H, -CONH), 8.20 (s, 1H, -NHN), 4.90 (s, 1H, -N=CH), 7.11-7.93 (m, 9H, Ar-H); MS: 310 (M⁺), 206, 161, 149, 134, 133, 90.

Synthesis of [(2''-aryl-4''-oxo-1'',3''-thiazolidene)-3''-iminoacetyl]-2-amino benzothiazole, 4a

To a stirred solution of the compound 3a (2.25 g, 0.007 mole) in methanol (30 mL) containing a pinch of anhyd. ZnCl_2 , thioglycolic acid (0.0504 g, 0.007 mole) was added and the mixture was refluxed on a water-bath for about 12 h. The separated solid was purified over the column of silica gel, eluted with CHCl_3 and recrystallized from chloroform to give compound 4a, yield 70%, m.p. 180-82 °C. (Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_2\text{S}_2$: C, 56.25; H, 4.17; N, 14.58%. Found, C, 56.23; H, 4.15; N, 14.55%. IR: 3044, 1644, 1568, 1527, 1180, 1079, 787, 742 and 687(benzothiazole with aromatic ring), 3319(C-NH), 1670(>C=O amide), 3431, 3409 and 2879(CH_2), 1714(>C=O cyclic), 2980(N-CH-S), 2962 cm^{-1} (CH_2 -S cyclic); ^1H NMR: 4.42(s, 2H, $-\text{CH}_2$), 8.17(s, 1H, -CONH), 8.25(s, 1H, -NH-N), 3.57(s, 2H, S- CH_2), 3.23(s, 1H, N-CH-Ar), 7.25-7.52(m, 9H, Ar-H); MS: 384 (M^+), 310, 177, 149, 134, 133, 74.

Other compounds 4b-k were synthesised in the similar way using compounds 3b-k with various aromatic aldehydes. Characterization data are presented in Table I.

Synthesis of [(5''-arylidene-2''-aryl-4''-oxo-1'',3''-thiazolidine)-3''-iminoacetyl]-2-aminobenzothiazole, 5a

Equimolar solution of the compound 4a (1.42 g, 0.003 mole) and benzaldehyde (0.385 mL, 0.003 mole) in dioxane (30 mL) in the presence of sodium ethoxide was refluxed on a water-bath for about 6 h. Solvent was removed *in vacuo*. The separated solid thus obtained was purified over the column of silica gel, eluted with CHCl_3 and recrystallized from chloroform to give compound 5a, yield 70%, m.p. 215-17°C. (Anal. Calcd for $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_2\text{S}_2$: C, 63.55; H, 4.23; N, 11.86. Found, C, 63.54; H, 4.20; N, 11.84%. IR: 3040, 1649, 1569, 1529, 1186, 1088, 789, 730 and 690 (benzothiazole with aromatic ring),

3324(C-NH), 1668(>C=O amide), 3440, 3411 and 2880(CH_2), 1715(>C=O cyclic), 2982(N-CH-S), 1620 cm^{-1} (C=CH-Ar); H NMR: 4.44(s, 2H, $-\text{CH}_2$), 8.18(s, 1H, -CONH), 8.23(s, 1H, -NH-N), 3.21(s, 1H, N-CH-Ar), 5.20(s, 1H, C=CH-Ar), 7.04-7.91(m, 14H, Ar-H); MS: 472 (M^+), 444, 281, 191, 177, 134, 131, 122.

Other compounds 5b-k were prepared the similar way using compounds 4b-k and various aromatic aldehydes. Characterization data are presented in Table I.

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