# SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY SCREENING OF SOME NOVEL SUBSTITUTED BENZOTHIAZOLE DERIVATIVES

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***ABSTRACT: Several new 2-substituted benzothiazole structures were synthesized in an attempt for exploring a new class of antibacterial, andantifungal agents. These derivatives include 2-(5-cyano-1,6-dihydro-6- oxo-4-arylpyrimidin-2-ylthio)-N-(6-substituted benzo [d] thiazol-2-yl)acetamide 4a-n, 2-imino-3-(6-substituted benzo[d]thiazol-2-yl)-5-(4-(un) substituted arylidenyl)thiazolidin-4-one 6a-n and 3-(6-Substitutedbenzo[d]thiazol-2- yl)-2-((N,N-disubstituted amino methyl)imino) thiazolidin-4-one 7a-f. The target compounds were synthesized starting from 6-substitutedbenzo [d]thiazol-2-amine 1a, 1b and their structures were elucidated on the basis of elemental analyses and spectral data. These compounds were screened for their antibacterial activity against grampositive bacteria (B. subtilis, S. lutea and S. aureus), gram-negative bacteria (E. coli ATCC 25922, E. coli ATCC 5087, P. aeruginosa and P. vulgaris) and antifungal activity against C. albicans through the sensitivity test using cup plate method. Minimum inhibitory concentration was measured for the only active compounds using agar dilution method. It was shown that the two classes incorporating the 2-imino-thiazolidin-4-one structure showed more antibacterial and antifungal activities and more pronounced MIC values than the class incorporating the dihydropyrimidinone. Additionally, the antibiofilm activity of the most active compounds 6a, 6b, 6h, 6i, 6k, 6l, 7c, 7d, 7e and 7f as antifungals comparing to fluconazole were screened against 2 pathogenic Candida isolates CA1 and CA2 using the fluconazole as the model system. Biofilm growth was monitored semiquantitatively by colorimetric assay using the crystal violet as indicator.***

***Keywords: 2-aminobenzothiazole, antimicrobial,***

## I.INTRODUCTION

Benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity such as antitumor agents,[1-3] antimicrobial,[4-6] analgesics,[7] anti-inflammatory,[7-9] anti-HIV,[10] antileishmanial,[11] etc. These reports prompted us for synthesis of some new benzimidazole derivatives. 2-substituted benzothiazole was prepared by condensation of Substituted 2- amino thiophenol with aliphatic, aromatic, heteroaromatic aldehydes in the presence samarium triflate. The main advantages of this methodology are simple catalyst system, cleaner reaction, high yields, and ethanol: water (2:2) as a greener solvent media and easy synthetic procedure. The synthesized compounds were characterized by spectral analysis, IR and $^{1}$H NMR spectral studies. Antimicrobial studies have been screened to observe their antibacterial and antifungal activities.

## II.EXPERIMENTAL

**Materials and Methods:**

2-Aminothiophenol and all aldehydes were commercial products and were used without further purification. Yields refer to yield of the isolated products. Melting points were measured on a Raaga, Chennai, Indian make melting point apparatus; GC-Mass spectra were recorded on a Shimadzu GC-MS QP 5050A instrument. Infrared spectra were recorded using Shimadzu FT-IR-8400s Spectrophotometer as KBr pellets

**General procedure for synthesis of substituted benzothiazoles:**

To a mixture of the requisite *2*-aminothiophenol (1 mmol) and aldehydes (1 mmol) in ethanol: water (2:2 mL), 10mol% of samarium triflate catalyst was added and the resulting mixture was stirred at 600C. After completion of the reaction, as monitored by TLC, the mixture was diluted with 1:1 water/ ethyl acetate (10 mL) and catalyst

recovered by filtration. The filtrate was extracted with diethyl ether (2 x 10 mL) and dried with anhydrous sodium sulfate. After filtration and evaporation of solvent, the crude product was recrystallized from ethyl acetate or methanol.

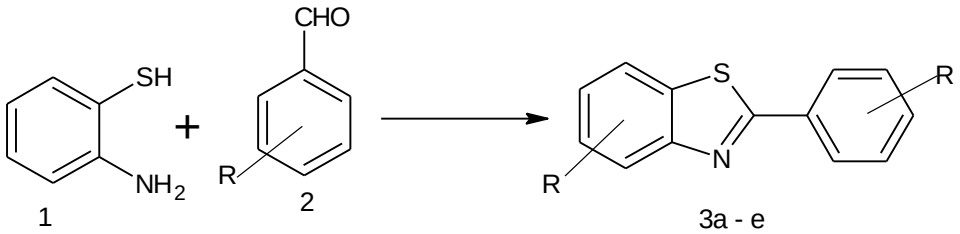


Figure: Reaction scheme for synthesis of benzothiazole

**Antimicrobial Activity**

To determine the biological activity of the compounds, the series of compounds **4a–f** was screened for antimicrobial activity against bacteria (e.g. *Escherichia coli*, *Staphylococcus aureus*,*Bacillus subtilis* and *Salmonella typhimurium*), filamentous fungi (*Helminthosporumoryzae*, *Aspergillus niger*, *Penicillium* sp.) and *Candida albicans* (Table 2).

The disc diffusion method[12] with little modification was used.Briefly 0.1 mL of diluted inoculum (105 CFU mL–1) of testorganism was spread on nutrient agar (NA) and sabourauddextrose (SD) agar plates. Sterile filter paper (Hi-Media Pvt. Ltd., Mumbai, India) disc (8 mm) impregnated with 50 µg of each compound and a disc without compound was used as a negative control. The NA was incubated for 18 h at 37 °C for test bacteria and *Candida albicans.* The SD plates for filamentous fungi were incubated for 5–6 days at 25 °C. The antimicrobial activity was evaluated by measuring the zone of growth inhibition of the test organism. Antibiotics, chloramphenicol and nystatin (Hi-Media Pvt. Ltd., Mumbai, India) were used in the test system as positive controls. The compounds were dissolved in DMF. The results are shown in Table 2, which revealed that the compounds showed good activity against *C. albicans*, *A. niger*, *H. oryzae*and *Penicillium* sp. and moderate activity against *E. coli*, *S. aureus* and *Bacillus subtilis*. However the title compounds showed no activity against *Salmonella typhimurium.*

## III.RESULT AND DISCUSSION

**Table 1: Physical characterization of 2-substituted benzothiazole**

| Compound | Aldehyde | Compound name | Yield (%) | M.P (ºC) |
|---|---|---|---|---|
| **3a** | $C_6H_5CHO$ | 2-phenyl benzothiazole | 90 | 113-115 |
| **3b** | 4-$OCH_3C_6H_4CHO$ | 2-(4'-Methoxyphenyl) benzothiazole | 93 | 122-124 |
| **3c** | 4-$CH_3C_6H_4CHO$ | 2-(4-methylphenyl) benzothiazole | 82 | 86-88 |
| **3d** | 3-$OCH_3C_6H_4CHO$ | 2-(3'-Methoxyphenyl) benzothiazole | 93 | 80-82 |
| **3e** | 3-$NO_2C_6H_4CHO$ | 2-(3'-Nitrophenyl) benzothiazole | 88 | 185-186 |

**Spectral Characterization data**

**2-Phenylbenzothiazole**

$^1$H NMR (DMSO-d6, 400 MHz): 7.48 (t, J = 7.8 Hz, 1H, Ar-H), 7.54-7.60 (m, 4H, Ar- H), 8.07-8.12 (m, 3H, Ar-H), 8.16 (d, J = 7.8 Hz, 1H, Ar-H) ppm; MS: m/e = 211 (M + ).

***2-(4-methylphenyl) benzothiazole***

IR (KBr pallets): *V*max 3026, 2811, 2343, 1606, 1581, 1520, 1361, 1297, 1258, 1152, 1034, 951, 867 and 659 cm-1. $^1$H NMR (CDCl3): δ 8.00-8.06 (m, 3H, Ar-H), 7.96 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.51 (t, 1H, *J* = 8.4 Hz, Ar-H), 7.41 (t, 1H, *J* = 8.4 Hz, Ar-H), 7.36 (d, 2H, *J* = 8.1 Hz, Ar-H) and *δ* 2.45 (s, 3H, -CH3).$^{13}$C NMR (CDCl3): δ 168.0, 154.2, 141.6, 135.0, 131.0, 129.7, 127.3, 126.2, 125.0, 122.9, 121.6 and 21. 2.MS (EI, m/z): 225.40 [M+].

***2-(4-Methoxyphenyl) benzothiazole***

IR (KBr): Vmax cm $^{-1}$ 3379.3, 3283.1, 3090.6, 2936.7, 1636, 1544.6, 1457.9, 1332.9, 1270.3, 1049, $^1$H NMR (CDCl3): δ 8.06 (m, 3H, Ar-H), 7.94 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.51 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.39 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.02 (d, 2H, *J* = 8.4 Hz, Ar-H) and 3.89 (s, 3H, -OCH3) .$^{13}$C NMR (CDCl3): δ 167.7, 162.0, 154.3, 135.0, 129.0, 126.4, 126.2, 124.8, 122.7, 121.6, 114.3 and 55.4. MS: m/e = 241 ($M^+$).

**2-(3'-Methoxyphenyl) benzothiazole**

$^1$H NMR (DMSO-d6, 400 MHz) 3.73 (s, 3H), 6.73-6.79 (m, 1H), 6.99-7.04 (m, 2H), 7.21-7.26 (m, 1H), 7.55-7.60 (m, 1H), 8.12 (t, J = 8 Hz, 1H) 8.23 (t, J = 8 Hz, 1H) ppm; MS: m/e = 241 (M +).

**2-(3'-Nitrophenyl) benzothiazole**

$^1$H NMR (DMSO-d6, 400 MHz) : 7.54 (t, J = 8.0 Hz, 1H, Ar-H), 7.60 (t, J = 8.0 Hz, 1H, ArH), 7.88 (t, J = 8.0 Hz, 1H, Ar-H), 8.16 (d, J = 8.0 Hz, 1H, Ar-H), 8.24 (d, J = 8.0 Hz, 1H, Ar-H), 8.41 (d, J = 8.0 Hz, 1H, Ar-H), 8.44 (d, J = 8.0 Hz, 1H, Ar-H), 8.84 (s, 1H, Ar-H) ppm; MS: m/e = 256 (M + ).

**Table 2**Antimicrobial activity a of compounds (3a-e)

| Compound | Zone of inhibition | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Bacteria | | | | Fungi | | | |
| | *E. coli* | *B. subtilis* | *S. aureus* | *S. typhimurium* | *C. albicans* | *Penicillium* sp. | *A. niger* | *H. oryzae* |
| **3a** | + | + | + | - | + + | + + | + + | + + |
| **3b** | + | + | ++ | - | +++ | + + | + + | + + |
| **3c** | + | + | ++ | - | +++ | + + | + + | + + |
| **3d** | + | + | ++ | - | +++ | + + | +++ | + + |
| **3e** | + | + | ++ | - | + + | + + | ++ | + |
| Control DMF | - | - | - | - | - | - | - | - |
| Chloramphenicol | +++ | +++ | +++ | - | - | - | - | - |
| Nystatin | - | - | - | - | +++ | +++ | +++ | +++ |

Zone of diameter of growth inhibition; <10 mm (-), 10–12 mm (+), 13–15 mm (++), 16–20 mm (+++).

## IV.CONCLUSION

In conclusion, two efficient methods for the synthesis of novel benzothiazole derivatives have been developed. The fact that readily available reagents are used along with short reaction time, no additives, simple work-up and isolation of the product make the current approach a feasible and attractive protocol for the generation of 2-substituted benzothiazoles from 2-aminothiophenol. Most of the compounds exhibited good activity against fungi and moderate activity against bacteria.

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