

Full Paper

## Synthesis and Biological Activity of N-Substituted-3-chloro-2-azetidinones

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**Abstract:** 2-Aminobenzothiazole-6-carboxylic acid (**1**), on condensation with chloroacetyl chloride yielded 2-(2-chloroacetylamino)benzothiazole-6-carboxylic acid (**2**), which on amination with hydrazine hydrate yielded in turn 2-(2-hydrazinoacetylamino)benzothiazole-6-carboxylic acid (**3**). Compound **3**, on condensation with various aromatic aldehydes afforded a series of 2-{2-[N'-(arylidene)hydrazino]acetylamino}benzothiazole-6-carboxylic acids **4a-h**, which upon dehydrative annulation in the presence of chloroacetyl chloride and triethylamine yielded 2-{2-[3-chloro-2-(aryl)-4-oxoazetidin-1-ylamino]-acetylamino}benzothiazole-6-carboxylic acids **5a-h**. The synthesized compounds **4a-h** and **5a-h** were screened for their antibacterial activity against four microorganisms: *Staphylococcus aureus* (Gram positive), *Bacillus subtilis* (Gram positive), *Pseudomonas aeruginosa* (Gram negative) and *Escherichia coli* (Gram negative). They were found to exhibit good to moderate antibacterial activity. The antifungal activity of these compounds were also tested against three different fungal species. None of them were active against the species tested.

**Keywords:** 2-Aminobenzothiazole, azetidinones, antibacterial activity.

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## Introduction

The  $\beta$ -lactam heterocycles are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity [1]. The most widely used antibiotics such as the penicillins, cephalosporins, carumonam, aztreonam, thienamycine and the nocardicins all contain  $\beta$ -lactam rings [2]. The long-term use of  $\beta$ -lactam antibiotics exerts selective pressure on bacteria and permits the proliferation of resistant organisms [3]. A comparative study of current antibiotics with those from previous decades shows an alarming increase in bacterial resistance to  $\beta$ -lactam antibiotics [4]. The development of several synthetic and semi-synthetic  $\beta$ -lactam antibiotics by the pharmaceutical industry was due to the growing resistance of bacteria towards the  $\beta$ -lactam antibiotics and the need for medicines with a more specific antibacterial activity [5]. An interesting group of  $\beta$ -lactams are the monocyclic  $\beta$ -lactams, which are molecules that do not contain another ring fused to the  $\beta$ -lactam one.

Azetidinones, which are part of the antibiotic structure, are known to exhibit interesting biological activities [6]. A large number of 3-chloro monocyclic  $\beta$ -lactams possess powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulsant and antitubercular activity [7-11]. They also function as enzyme inhibitors and are effective on the central nervous system [12]. 2-Aminobenzothiazoles constitute another class of heterocycles that possess antimicrobial and various other pharmacological activities like diuretic, antiulcer, antihistamine and anticancer properties [13-16].

Rey *et al.* have described methods for the preparation of *N*-substituted-2-azetidiones, which are useful in the synthesis of taxol and taxol derivatives [17]. Patel. *et al.* have carried out the synthesis of azetidione and thiazolidinone derivatives from 2-amino-6-(2-naphthalenyl)thiazolo[3,2-d]thiadiazole [18]. Singh and co-workers have prepared some new 2-azetidiones from *N*-(salicylidene)amines and 2-diazo-1,2-diarylethanones [19]. Singh has also reviewed  $\beta$ -lactams in the new millennium, i.e. monobactams and carbapenems [20].

Hence, with a view to further assess the pharmacological profile of this class of compounds, it was thought worthwhile to synthesize some new congeners of  $\beta$ -lactam heterocycles by incorporating the 2-aminobenzothiazole and azetidione moieties in a single molecular framework. The present work deals with the synthesis of the title compounds starting from 2-aminobenzothiazole-6-carboxylic acid, followed by their antimicrobial screening.

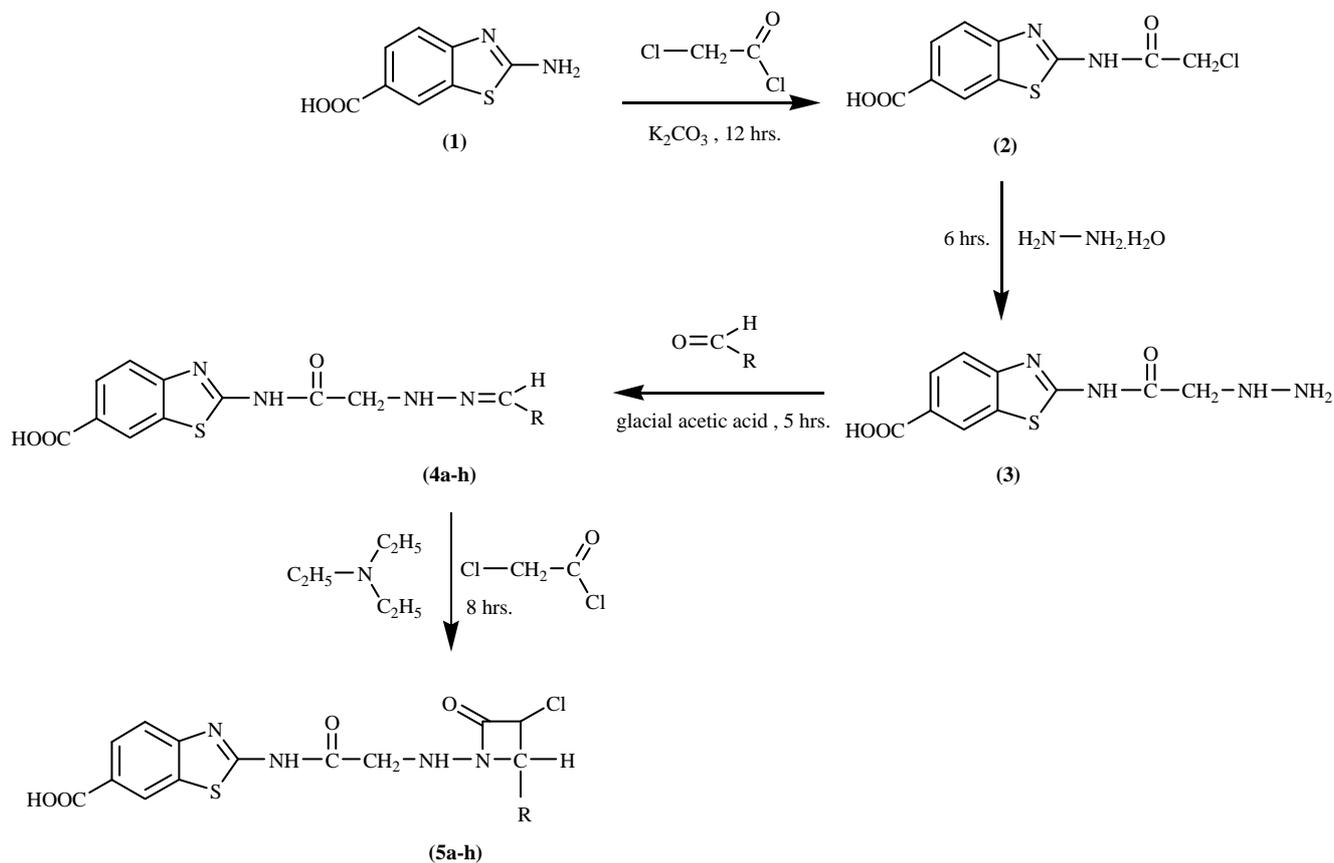
## Results and Discussion

### Synthesis

2-Aminobenzothiazole-6-carboxylic acid (**1**) was prepared in quantitative yield according to a known method [21]. This compound, on condensation with chloroacetyl chloride yielded 2-(2-chloroacetylamino)benzothiazole-6-carboxylic acid (**2**). Compound **2** on amination with hydrazine hydrate afforded 2-(2-hydrazinoacetylamino)benzothiazole-6-carboxylic acid (**3**). The condensation reaction of compound **3** with various aromatic aldehydes yielded 2-{2-[*N'*-(arylidene)hydrazino]acetylamino}-benzothiazole-6-carboxylic acids **4a-h**. Compounds **4a-h**, on reaction with chloroacetyl chloride in the presence of triethylamine underwent dehydrative annulation to afford 2-{2-[3-chloro-2-(aryl)-4-

oxoazetidin-1-ylamino]acetylamino}benzothiazole-6-carboxylic acids **5a-h**. These reactions are summarized in Scheme 1. Yields were moderate to fair (50-77%). The purity of the compounds was monitored by TLC and the structure of the compounds was deduced on the basis of their elemental analysis and spectral data. The substituents of the compounds are given in Table 1.

Scheme 1.

Table 1. Substituents of compounds **4a-h** and **5a-h**.

Compd.	Substituent R
<b>4a, 5a</b>	3-BrC <sub>6</sub> H <sub>4</sub>
<b>4b, 5b</b>	4-OHC <sub>6</sub> H <sub>4</sub>
<b>4c, 5c</b>	C <sub>6</sub> H <sub>5</sub>
<b>4d, 5d</b>	4-OCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
<b>4e, 5e</b>	2-ClC <sub>6</sub> H <sub>4</sub>
<b>4f, 5f</b>	4-ClC <sub>6</sub> H <sub>4</sub>
<b>4g, 5g</b>	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>
<b>4h, 5h</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>

## Antibacterial activity

To determine the antibacterial activity of these agents, the cup plate method was used, with Ampicillin and Streptomycin as the reference antibiotics [22]. The prepared compounds were examined against two strains each of gram positive and gram negative bacteria. The test results, presented in Table 2, suggest that compounds **5e**, **5g**, **5h** and **4e**, **4f**, **4g**, **5f**, **5h** are highly active against *S. aureus* and *E. coli* respectively. Compounds **4g** and **4h** are also highly active against *P. aeruginosa*. The rest of the compounds were found to be either moderately active, slightly active or inactive against the tested microorganisms.

**Table 2.** Antibacterial activity of the compounds **4a-h** and **5a-h**.

Compound	Gram positive bacteria		Gram negative bacteria	
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>P. aeruginosa</i>	<i>E. coli</i>
<b>Ampicillin</b>	+++	++	++	+++
<b>Streptomycin</b>	+++	+++	+++	+++
<b>4a</b>	++	-	+	++
<b>4b</b>	+	-	-	+
<b>4c</b>	-	+	-	+
<b>4d</b>	++	+	+	++
<b>4e</b>	++	+	++	+++
<b>4f</b>	++	++	-	+++
<b>4g</b>	+	-	+++	+++
<b>4h</b>	+	++	+++	++
<b>5a</b>	+	++	++	+
<b>5b</b>	-	+	-	+
<b>5c</b>	+	+	+	++
<b>5d</b>	++	++	-	+
<b>5e</b>	+++	-	+	++
<b>5f</b>	-	+	+	+++
<b>5g</b>	+++	-	++	++
<b>5h</b>	+++	++	++	+++

Key to symbols: Inactive = - (inhibition zone < 6 mm); Slightly active = + (inhibition zone 6-9 mm); Moderately active = ++ (inhibition zone 9-12 mm); Highly active = +++ (inhibition zone > 12 mm).

## Antifungal activity

The antifungal activities of the prepared compounds were tested against three different fungi such as *C. tropicalis*, *A. niger* and *F. heterosporium* by filter paper disc technique [23]. None of the compounds were found to be active against the fungi species tested.

## Experimental

### General

Melting points were determined in open capillaries on Thomas Hoover apparatus and are uncorrected.  $^1\text{H-NMR}$  spectra were recorded on a Bruker AM400 (400 MHz) instrument using tetramethylsilane (TMS) as an internal standard and  $\text{DMSO-d}_6$  as a solvent. Chemical shifts are given in parts per million (ppm). Mass spectra (MS) were recorded on Shimadzu GC-MS. Infrared spectra were recorded on Shimadzu-IR Prestige 21. Elemental analysis (C, H, N) was performed on Perkin Elmer 240 analyzer and all compounds are within  $\pm 0.4\%$  of theory unless otherwise specified. All products were purified by recrystallisation. The reactions were followed up and the purity of products was carried out on pre-coated TLC plates (Silica gel 60 F<sub>254</sub>, Merck), visualizing the spots under ultraviolet light. Column chromatography was performed on Merck silicagel (60-120 mesh). The antimicrobial screening was carried out at Chemo Test Laboratory. 2-Aminobenzothiazole-6-carboxylic acid (**1**): was prepared by a reported method [21].

### Synthesis of 2-(2-chloroacetylamino)benzothiazole-6-carboxylic acid (**2**)

Equimolar amounts of 2-aminobenzothiazole-6-carboxylic acid (**1**, 0.1 mole) and chloroacetyl chloride (0.1 mole) in chloroform (30 mL) was refluxed in the presence of  $\text{K}_2\text{CO}_3$  (0.1 mole) for about 12 h. Excess of solvent was removed in *vacuo* and the residue was stirred with water (50 mL). The residue was washed with 5%  $\text{NaHCO}_3$  (30 mL) and subsequently with water (30 mL). The crude product was dried and crystallized from methanol to furnish a pale yellow solid. Yield 81%; m.p. 162 °C; IR (KBr,  $\text{cm}^{-1}$ ) 3430 (NH), 1710 (C=O), 1635 (CONH);  $^1\text{H-NMR}$   $\delta$  4.29 (s, 2H,  $\text{CH}_2$ ), 8.0 (s, 1H, NH), 8.42-8.99 (m, 3H, benzothiazole), 11.1 (s, 1H, COOH); Anal. calcd. for  $\text{C}_{10}\text{H}_7\text{ClN}_2\text{O}_3\text{S}$ : C 44.36, H 2.59, N 10.35, S 11.83 %. Found: C 44.38, H 2.63, N 10.33, S 11.85 %.

### Synthesis of 2-(2-hydrazinoacetylamino)benzothiazole-6-carboxylic acid (**3**)

A mixture of 2-(2-chloroacetylamino)benzothiazole-6-carboxylic acid (**2**, 0.1 mole) and hydrazine hydrate (0.1 mole) in ethanol (30 mL) was refluxed for about 6 h. After cooling the resulting solid was filtered, dried and crystallized from  $\text{CHCl}_3$ -MeOH mixture to give light brown solid. Yield 75%; m.p. 173 °C; IR (KBr,  $\text{cm}^{-1}$ ) 3455 (NH), 3350 ( $\text{NHNH}_2$ ), 2886 ( $\text{CH}_2\text{NH}$ ), 1705 (C=O), 1650 (CONH);  $^1\text{H-NMR}$   $\delta$  2.0 (s, 2H,  $\text{NH}_2$ ), 2.2 (s, 1H, NH), 3.58 (s, 2H,  $\text{CH}_2$ ), 8.16 (s, 1H, CONH), 8.40-8.96 (m, 3H, benzothiazole), 11.2 (s, 1H, COOH); Anal. calcd. for  $\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}_3\text{S}$ : C 45.11, H 3.76, N 21.05, S 12.03 %. Found: C 45.08, H 3.74, N 21.09, S 12.06 %.

### General procedure for the synthesis of

### 2-{2-[N'-(arylidene)hydrazino]acetylamino}benzothiazole-6-carboxylic acids **4a-h**

A mixture of 2-(2-hydrazinoacetylamino)benzothiazole-6-carboxylic acid (**3**, 0.01 mole), aromatic aldehyde (0.01 mole) and 2-3 drops of glacial acetic acid in ethanol (30 mL) was refluxed for 5 h. The

solvent was removed under reduced pressure. The residue was stirred with ice cold water (50 mL), filtered and dried. The crude product obtained was purified by column chromatography over silica gel (eluent: *n*-hexane/EtOAc 9:1).

2-{2-[*N'*-(3-Bromobenzylidene)hydrazino]acetylamino}benzothiazole-6-carboxylic acid (**4a**). Yield 77%; m.p. 188-190 °C; IR (KBr, cm<sup>-1</sup>) 3472 (NH), 1719 (C=O), 1638 (CONH), 1548 (N=CH); <sup>1</sup>H-NMR δ 2.1 (s, 1H, NH), 3.59 (s, 2H, CH<sub>2</sub>), 7.9 (s, 1H, CONH), 8.1 (s, 1H, N=CH), 7.22-7.84 (m, 4H, ArH), 8.40-8.97 (m, 3H, benzothiazole), 11.12 (s, 1H, COOH); Anal. calcd. for C<sub>17</sub>H<sub>13</sub>BrN<sub>4</sub>O<sub>3</sub>S: C 47.11, H 3.00, N 12.93, S 7.39 %. Found: C 47.14, H 3.04, N 12.89, S 7.37 %.

2-{2-[*N'*-(4-Hydroxybenzylidene)hydrazino]acetylamino}benzothiazole-6-carboxylic acid (**4b**). Yield 72%; m.p. 172 °C; IR (KBr, cm<sup>-1</sup>) 3464 (NH), 3590 (ArOH), 1704 (C=O), 1652 (CONH), 1554 (N=CH); <sup>1</sup>H-NMR δ 2.14 (s, 1H, NH), 3.50 (s, 2H, CH<sub>2</sub>), 5.1 (s, 1H, ArOH), 6.82-7.46 (m, 4H, ArH), 7.94 (s, 1H, CONH), 8.16 (s, 1H, N=CH), 8.38-8.99 (m, 3H, benzothiazole), 11.10 (s, 1H, COOH); Anal. calcd. for C<sub>17</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>S: C 55.13, H 3.78, N 15.14, S 8.65 %. Found: C 55.11, H 3.81, N 15.12, S 8.68 %.

2-[2-(*N'*-Benzylidenehydrazino)acetylamino]benzothiazole-6-carboxylic acid (**4c**). Yield 68%; m.p. 166-168 °C; IR (KBr, cm<sup>-1</sup>) 3477 (NH), 1715 (C=O), 1648 (CONH), 1550 (N=CH); <sup>1</sup>H-NMR δ 2.08 (s, 1H, NH), 3.58 (s, 2H, CH<sub>2</sub>), 7.28-7.64 (m, 5H, ArH), 7.90 (s, 1H, CONH), 8.04 (s, 1H, N=CH), 8.35-8.92 (m, 3H, benzothiazole), 11.02 (s, 1H, COOH); Anal. calcd. for C<sub>17</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub>S: C 57.63, H 3.95, N 15.82, S 9.04 %. Found: C 57.59, H 3.92, N 15.87, S 9.08 %.

2-{2-[*N'*-(4-Methoxybenzylidene)hydrazino]acetylamino}benzothiazole-6-carboxylic acid (**4d**). Yield 64%; m.p. 181-183 °C; IR (KBr, cm<sup>-1</sup>) 3469 (NH), 1700 (C=O), 1641 (CONH), 1545 (N=CH); <sup>1</sup>H-NMR δ 2.05 (s, 1H, NH), 3.54 (s, 2H, CH<sub>2</sub>), 3.75 (s, 3H, Ar-OCH<sub>3</sub>), 6.82-7.54 (m, 4H, ArH), 7.96 (s, 1H, CONH), 8.2 (s, 1H, N=CH), 8.38-9.03 (m, 3H, benzothiazole), 11.08 (s, 1H, COOH); Anal. calcd. for C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>S: C 56.25, H 4.17, N 14.58, S 8.33 %. Found: C 56.31, H 4.13, N 14.55, S 8.32 %.

2-{2-[*N'*-(2-Chlorobenzylidene)hydrazino]acetylamino}benzothiazole-6-carboxylic acid (**4e**). Yield 61%; m.p. 155-157 °C; IR (KBr, cm<sup>-1</sup>) 3460 (NH), 1707 (C=O), 1645 (CONH), 1551 (N=CH); <sup>1</sup>H-NMR δ 2.0 (s, 1H, NH), 3.48 (s, 2H, CH<sub>2</sub>), 7.18-7.58 (m, 4H, ArH), 7.92 (s, 1H, CONH), 8.14 (s, 1H, N=CH), 8.39-8.96 (m, 3H, benzothiazole), 11.0 (s, 1H, COOH); Anal. calcd. for C<sub>17</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>3</sub>S: C 52.51, H 3.35, N 14.41, S 8.24 %. Found: C 52.49, H 3.39, N 14.43, S 8.27 %.

2-{2-[*N'*-(4-Chlorobenzylidene)hydrazino]acetylamino}benzothiazole-6-carboxylic acid (**4f**). Yield 69%; m.p. 165 °C; IR (KBr, cm<sup>-1</sup>) 3462 (NH), 1713 (C=O), 1647 (CONH), 1549 (N=CH); <sup>1</sup>H-NMR δ 2.04 (s, 1H, NH), 3.52 (s, 2H, CH<sub>2</sub>), 7.28-7.64 (m, 4H, ArH), 7.88 (s, 1H, CONH), 8.1 (s, 1H, N=CH), 8.42-8.99 (m, 3H, benzothiazole), 11.04 (s, 1H, COOH); Anal. calcd. for C<sub>17</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>3</sub>S: C 52.51, H 3.35, N 14.41, S 8.24 %. Found: C 52.48, H 3.33, N 14.44, S 8.26 %.

2-{2-[N'-(3-Nitrobenzylidene)hydrazino]acetylamino}benzothiazole-6-carboxylic acid (**4g**). Yield 76%; m.p. 218-220 °C; IR (KBr,  $\text{cm}^{-1}$ ) 3473 (NH), 1720 (C=O), 1666 (CONH), 1559 (N=CH), 1345,1520 ( $\text{NO}_2$ );  $^1\text{H-NMR}$   $\delta$  2.12 (s, 1H, NH), 3.58 (s, 2H,  $\text{CH}_2$ ), 7.62-8.64 (m, 4H, ArH), 7.98 (s, 1H, CONH), 8.18 (s, 1H, N=CH), 8.40-8.97 (m, 3H, benzothiazole), 11.06 (s, 1H, COOH); Anal. calcd. for  $\text{C}_{17}\text{H}_{13}\text{N}_5\text{O}_5\text{S}$ : C 51.13, H 3.26, N 17.54, S 8.02 %. Found: C 51.16, H 3.29, N 17.52, S 8.01 %.

2-{2-[N'-(4-Nitrobenzylidene)hydrazino]acetylamino}benzothiazole-6-carboxylic acid (**4h**). Yield 73%; m.p. 208 °C; IR (KBr,  $\text{cm}^{-1}$ ) 3468 (NH), 1708 (C=O), 1669 (CONH), 1556 (N=CH), 1338,1515 ( $\text{NO}_2$ );  $^1\text{H-NMR}$   $\delta$  2.1 (s, 1H, NH), 3.54 (s, 2H,  $\text{CH}_2$ ), 7.86-8.16 (m, 4H, ArH), 7.94 (s, 1H, CONH), 8.16 (s, 1H, N=CH), 8.36-8.93 (m, 3H, benzothiazole), 11.1 (s, 1H, COOH); Anal. calcd. for  $\text{C}_{17}\text{H}_{13}\text{N}_5\text{O}_5\text{S}$ : C 51.13, H 3.26, N 17.54, S 8.02 %. Found: C 51.15, H 3.29, N 17.55, S 7.98 %.

*General procedure for the synthesis of 2-{2-[3-chloro-2-(aryl)-4-oxoazetididin-1-yl-amino]acetylamino}benzothiazole-6-carboxylic acids **5a-h***

To a stirred solution of Schiff base **4a-h** (0.05 mole) and  $\text{Et}_3\text{N}$  (0.01 mole) in dioxane (50 mL),  $\text{ClCH}_2\text{COCl}$  (0.01 mole) was added dropwise at 0-5 °C. The reaction mixture was stirred for about 5 h and the precipitated amine hydrochloride was filtered off. The filtrate was refluxed for about 3 h and excess of solvent was evaporated under reduced pressure. The solid obtained was washed with water (30 mL), filtered and dried. The crude product obtained was purified by column chromatography technique (eluent: *n*-hexane/EtOAc 8:2).

2-{2-[2-(3-Bromophenyl)-3-chloro-4-oxoazetididin-1-ylamino]acetylamino}benzothiazole-6-carboxylic acid (**5a**). Yield 58%; m.p. 261-264 °C; I.R (KBr,  $\text{cm}^{-1}$ ) 3456 (NH), 1646 (CONH), 1755 (CO,  $\beta$ -lactam);  $^1\text{H-NMR}$   $\delta$  3.1 (s, 1H, NH), 3.57 (s, 2H,  $\text{CH}_2$ ), 5.2 (d, 1H, CH-Ar), 5.52 (d, 1H, CH-Cl), 7.08-7.31 (m, 4H, ArH), 8.0 (s, 1H, CONH), 8.32-8.90 (m, 3H, benzothiazole), 11.06 (s, 1H, COOH);  $^{13}\text{C-NMR}$   $\delta$  52.5 ( $\text{CH}_2$ ), 61.6 (CH), 64.2 (CH-Cl), 122.7-145.9 (6 aromatic carbons), 121.4-174.7 (7 carbons, benzothiazole), 163.7 (CO,  $\beta$ -lactam), 168.3 (CONH), 169.5 (COOH); MS (m/e) 509.91 ( $\text{M}^+$ ); Anal. calcd. for  $\text{C}_{19}\text{H}_{14}\text{BrClN}_4\text{O}_4\text{S}$ : C 44.75, H 2.74, N 10.99, S 6.28 %. Found: C 44.71, H 2.76, N 10.97, S 6.32 %.

2-{2-[3-Chloro-2-(4-hydroxyphenyl)-4-oxoazetididin-1-ylamino]acetylamino}benzothiazole-6-carboxylic acid (**5b**). Yield 50%; m.p. 220-222 °C; IR (KBr,  $\text{cm}^{-1}$ ) 3462 (NH), 1648 (CONH), 1750 (CO,  $\beta$ -lactam), 3585 (Ar-OH);  $^1\text{H-NMR}$   $\delta$  3.05 (s, 1H, NH), 3.56 (s, 2H,  $\text{CH}_2$ ), 5.0 (s, 1H, Ar-OH), 5.24 (d, 1H, CH-Ar), 5.48 (d, 1H, CH-Cl), 6.64-6.99 (m, 4H, ArH), 8.06 (s, 1H, CONH), 8.38-8.95 (m, 3H, benzothiazole), 11.1 (s, 1H, COOH);  $^{13}\text{C-NMR}$   $\delta$  52.2 ( $\text{CH}_2$ ), 62.4 (CH), 64.7 (CH-Cl), 115.4-156.6 (6 aromatic carbons), 121.9-174.2 (7 C, benzothiazole), 163.2 (CO,  $\beta$ -lactam), 168.7 (CONH), 169.1 (COOH); MS (m/e) 446.07 ( $\text{M}^+$ ); Anal. calcd. for  $\text{C}_{19}\text{H}_{15}\text{ClN}_4\text{O}_5\text{S}$ : C 51.06, H 3.36, N 12.54, S 7.17 %. Found: C 51.08, H 3.34, N 12.50, S 7.14 %.

2-[2-(3-Chloro-2-oxo-4-phenylazetididin-1-ylamino)acetylamino]benzothiazole-6-carboxylic acid (**5c**). Yield 53%; m.p. 215 °C; IR (KBr,  $\text{cm}^{-1}$ ) 3452 (NH), 1656 (CONH), 1742 (CO,  $\beta$ -lactam);  $^1\text{H-NMR}$   $\delta$

3.08 (s, 1H, NH), 3.59 (s, 2H, CH<sub>2</sub>), 5.1 (d, 1H, CH-Ar), 5.50 (d, 1H, CH-Cl), 7.06-7.23 (m, 5H, ArH), 8.12 (s, 1H, CONH), 8.44-8.97 (m, 3H, benzothiazole), 11.0 (s, 1H, COOH); <sup>13</sup>C-NMR δ 52.9 (CH<sub>2</sub>), 62.3 (CH), 64.5 (CH-Cl), 126.4-143.7 (6 aromatic carbons), 121.7-174.3 (7 C, benzothiazole), 163.9 (CO, β-lactam), 168.1 (CONH), 169.7 (COOH); MS (m/e) 430.09 (M<sup>+</sup>); Anal. calcd. for C<sub>19</sub>H<sub>15</sub>ClN<sub>4</sub>O<sub>4</sub>S: C 52.96, H 3.48, N 13.01, S 7.43 %. Found: C 52.93, H 3.52, N 13.04, S 7.44 %.

*2-{2-[3-Chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-ylamino]acetylamino}benzothiazole-6-carboxylic acid (5d)*. Yield 59%; m.p. 231-233 °C; IR (KBr, cm<sup>-1</sup>) 3459 (NH), 1650 (CONH), 1745 (CO, β-lactam); <sup>1</sup>H-NMR δ 3.15 (s, 1H, NH), 3.54 (s, 2H, CH<sub>2</sub>), 3.77 (s, 3H, Ar-OCH<sub>3</sub>), 5.16 (d, 1H, CH-Ar), 5.46 (d, 1H, CH-Cl), 6.74-7.03 (m, 4H, ArH), 8.04 (s, 1H, CONH), 8.42-8.96 (m, 3H, benzothiazole), 11.2 (s, 1H, COOH); <sup>13</sup>C-NMR δ 52.6 (CH<sub>2</sub>), 55.7 (OCH<sub>3</sub>), 62.6 (CH), 64.8 (CH-Cl), 114.4-158.5 (6 aromatic carbons), 122.1-173.9 (7 C, benzothiazole), 163.1 (CO, β-lactam), 168.5 (CONH), 169.8 (COOH); MS (m/e) 460.06 (M<sup>+</sup>); Anal. calcd. for C<sub>20</sub>H<sub>17</sub>ClN<sub>4</sub>O<sub>5</sub>S: C 52.12, H 3.69, N 12.16, S 6.95 %. Found: C 52.10, H 3.73, N 12.11, S 6.97 %.

*2-{2-[3-Chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-ylamino]acetylamino}benzothiazole-6-carboxylic acid (5e)*. Yield 52%; m.p. 238 °C; IR (KBr, cm<sup>-1</sup>) 3445 (NH), 1659 (CONH), 1749 (CO, β-lactam); <sup>1</sup>H-NMR δ 3.0 (s, 1H, NH), 3.50 (s, 2H, CH<sub>2</sub>), 5.12 (d, 1H, CH-Ar), 5.48 (d, 1H, CH-Cl), 7.02-7.24 (m, 4H, ArH), 8.08 (s, 1H, CONH), 8.36-8.93 (m, 3H, benzothiazole), 11.16 (s, 1H, COOH); <sup>13</sup>C-NMR δ 52.1 (CH<sub>2</sub>), 61.3 (CH), 63.5 (CH-Cl), 126.1-143.8 (6 aromatic carbons), 121.2-174.4 (7 C, benzothiazole), 163.5 (CO, β-lactam), 168.9 (CONH), 169.1 (COOH); MS (m/e) 464.10 (M<sup>+</sup>); Anal. calcd. for C<sub>19</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S: C 49.03, H 3.01, N 12.04, S 6.88 %. Found: C 49.07, H 3.04, N 12.07, S 6.83 %.

*2-{2-[3-Chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-ylamino]acetylamino}benzothiazole-6-carboxylic acid (5f)*. Yield 55%; m.p. 244-246 °C; IR (KBr, cm<sup>-1</sup>) 3449 (NH), 1657 (CONH), 1752 (CO, β-lactam); <sup>1</sup>H-NMR δ 3.12 (s, 1H, NH), 3.53 (s, 2H, CH<sub>2</sub>), 5.08 (d, 1H, CH-Ar), 5.40 (d, 1H, CH-Cl), 7.08-7.26 (m, 4H, ArH), 8.02 (s, 1H, CONH), 8.38-8.95 (m, 3H, benzothiazole), 11.12 (s, 1H, COOH); <sup>13</sup>C-NMR δ 52.4 (CH<sub>2</sub>), 62.5 (CH), 64.9 (CH-Cl), 128.6-141.8 (6 aromatic carbons), 121.4-174.1 (7 C, benzothiazole), 163.2 (CO, β-lactam), 168.3 (CONH), 169.4 (COOH); MS (m/e) 464.05 (M<sup>+</sup>); Anal. calcd. for C<sub>19</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S: C 49.03, H 3.01, N 12.04, S 6.88 %. Found: C 49.05, H 3.02, N 12.06, S 6.90 %.

*2-{2-[3-Chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-ylamino]acetylamino}benzothiazole-6-carboxylic acid (5g)*. Yield (54%); m.p. 273-277 °C; IR (KBr, cm<sup>-1</sup>) 3460 (NH), 1654 (CONH), 1760 (CO, β-lactam), 1342, 1525 (NO<sub>2</sub>); <sup>1</sup>H-NMR δ 3.09 (s, 1H, NH), 3.60 (s, 2H, CH<sub>2</sub>), 5.04 (d, 1H, CH-Ar), 5.42 (d, 1H, CH-Cl), 7.49-8.07 (m, 4H, ArH), 8.06 (s, 1H, CONH), 8.41-8.98 (m, 3H, benzothiazole), 11.1 (s, 1H, COOH); <sup>13</sup>C-NMR δ 52.7 (CH<sub>2</sub>), 61.5 (CH), 64.8 (CH-Cl), 119.5-148.4 (6 aromatic carbons), 122.3-173.9 (7 C, benzothiazole), 163.9 (CO, β-lactam), 168.9 (CONH), 170.1 (COOH); MS (m/e) 475.03 (M<sup>+</sup>); Anal. calcd. for C<sub>19</sub>H<sub>14</sub>ClN<sub>5</sub>O<sub>6</sub>S: C 47.95, H 2.94, N 14.72, S 6.73 %. Found: C 47.97, H 2.92, N 14.75, S 6.77 %.

2-{2-[3-Chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-ylamino]acetylaminobenzothiazole-6-carboxylic acid (**5h**). Yield 60%; m.p. 276-278 °C; IR (KBr, cm<sup>-1</sup>) 3457 (NH), 1651 (CONH), 1754 (CO, β-lactam), 1333,1523 (NO<sub>2</sub>); <sup>1</sup>H-NMR δ 3.04 (s, 1H, NH), 3.56 (s, 2H, CH<sub>2</sub>), 5.12 (d, 1H, CH-Ar), 5.46 (d, 1H, CH-Cl), 7.36-8.12 (m, 4H, ArH), 8.12 (s, 1H, CONH), 8.38-8.95 (m, 3H, benzothiazole), 11.08 (s, 1H, COOH); <sup>13</sup>C-NMR δ 52.2 (CH<sub>2</sub>), 62.5 (CH), 64.7 (CH-Cl), 120.6-149.2 (6 aromatic carbons), 121.3-174.1 (7 C, benzothiazole), 163.6 (CO, β-lactam), 168.2 (CONH), 169.7 (COOH); MS (m/e) 475.11 (M<sup>+</sup>); Anal. calcd. for C<sub>19</sub>H<sub>14</sub>ClN<sub>5</sub>O<sub>6</sub>S: C 47.95, H 2.94, N 14.72, S 6.73 %. Found: C 47.98, H 2.91, N 14.67, S 6.76 %.

#### Antibacterial activity

The cup plate method using Hi-Media agar medium was employed to study the antibacterial activity of **4a-h** and **5a-h** against *S. aureus* (ATCC6538P), *B. subtilis* (ATCC6633), *P. aeruginosa* (ATCC9027) and *E. coli* (ATCC10536) [22]. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound (50 mg) was dissolved in dimethylformamide (50 mL, 1000 µg/mL), which was used as sample solution. Sample size for all the compounds was fixed at 0.1 mL. Using a sterilized cork borer cups were scooped out of agar medium contained in a petri dish which was previously inoculated with the microorganisms. The test compound solution (0.1 mL) was added in the cups and the petri dishes were subsequently incubated at 37 °C for 48 h. Ampicillin and Streptomycin were used as reference drugs and dimethylformamide as a negative control. Zones of inhibition produced by each compound was measured in mm, and the results are listed in Table 2.

#### Antifungal activity

The antifungal activities of compounds **4a-h** and **5a-h** were tested against three different fungi such as *C. tropicalis* (ATCC9763), *A. niger* (ATCC16404) and *F. heterosporium* by the filter paper disc technique [23].

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*Sample Availability:* Not available.

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