

## Note

### Synthesis and antimicrobial activity of some new 2-substituted aminothiazoles

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Amino group of thiazole (**SMB-1**) have been treated with various aromatic aldehydes to get corresponding Schiff bases (**SMB-2** to **SMB-9**). These Schiff bases have been then reacted with chloroacetyl chloride to get corresponding azetidinones (**SMB-2a** to **SMB-9a**). The structures of all these compounds have been established on the basis of analytical and spectral data. Compounds **SMB-1**, **SMB-2** and **SMB-6** are comparable with standard drug ampicillin against *S. aureus* and *S. epidermidis*. Compounds **SMB-1**, **SMB-2**, **SMB-6** and **SMB-6a** are comparable with ampicillin against *E. coli* and *K. pneumoniae*. Compounds **SMB-1** and **SMB-6** show good activity as compared to standard drug micanazole nitrate against *C. albicans* and **SMB-1** activity is comparable with micanazole nitrate against *A. niger*.

**Keywords:** Aminothiazoles, Schiff base, azetidinones, antibacterial activity, antifungal activity

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Thiazole is the five membered ring system with two hetero atoms (S, N) placed in the heterocyclic ring at 1,3-positions. Thiazoles are useful structural units in the field of medicinal chemistry and have been reported to exhibit a variety of biological activity<sup>1-7</sup>. Various substituted thiazoles have been synthesized and examined for antifungal<sup>8</sup> and antibacterial<sup>9-12</sup> activity.

In the present study, various 2-substituted aminothiazoles were synthesized and screened for their antibacterial and antifungal activity. Starting compound *p*-acetamidoacetophenone was obtained by treating *p*-aminoacetophenone with acetic anhydride. The required substituted 2-aminothiazole was obtained according to the reported method<sup>13</sup>. Substituted 2-aminothiazole was treated with various aromatic aldehydes in alcohol to get 2-[(substituted benzylidene)amino]-4-(4'-acetanilido) thiazoles

(**SMB-2** to **SMB-9**), and these compounds on reaction with chloro acetyl chloride produced N-2-[(2R)-3"-chloro-4"(substituted phenyl)-2"oxoazetidin-1"-yl]-4-(4'-acetanilido)thiazoles (**SMB-2a** to **SMB-9a**, Scheme I).

## Experimental Section

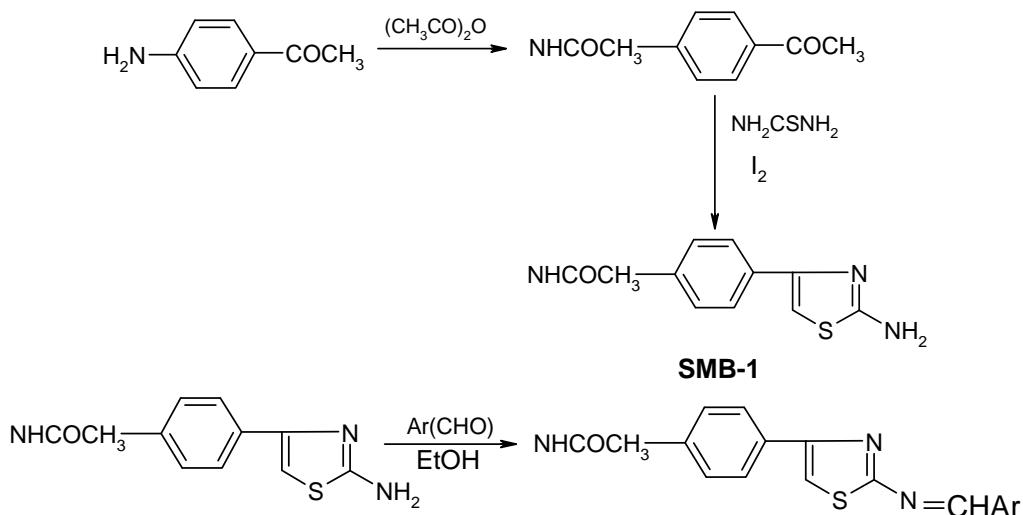
Melting points were determined in open capillaries and are uncorrected. Physical characterization data of all the compounds are given in Table I. The IR spectra were run on a Perkin-Elmer FTIR spectrometer in KBr pellets. <sup>1</sup>H NMR were recorded using AMX-400 NMR spectrometer in CDCl<sub>3</sub>/DMSO-*d*<sub>6</sub> using TMS as internal standard. Mass spectra were recorded on MSN-9629 mass spectrometer. All the chemicals used were of analytical grade.

***p*-Acetamidoacetophenone (SMB).** A mixture of *p*-aminoacetophenone (0.076 mole) and acetic anhydride (30 mL) was taken in a beaker. The reaction mixture was heated on a steam-bath for 45 min and allowed to stand for 2 hr. The solid obtained was filtered, dried and purified by recrystallization from ethanol.

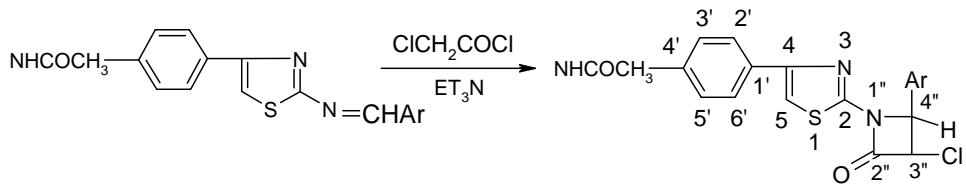
IR (KBr): 1675 (C=O, amide), 1743 (C=O, aromatic), 3296 cm<sup>-1</sup> (NH).

**2-Amino-4-(4'-acetanilido)thiazole (SMB-1).** A mixture of iodine (0.033 mole) and thiourea (0.066 mole) was triturated and the mixture poured into a conical flask containing *p*-acetamidoacetophenone (0.033 mole). The reaction mixture was heated for 8 hr on a water bath with occasional stirring. The solid obtained was washed with diethyl ether to remove any unreacted *p*-acetamidoacetophenone, after which it was washed with sodium thiosulfate to remove unreacted iodine. Finally, it was washed with water and the residue filtered and dried. Purification was done by dissolving in hot water, the mass filtered and dilute ammonia was added to the filtrate to precipitate the starting material. It was purified by recrystallization from distilled water.

IR (KBr): 1671(C=O), 3123(CH<sub>3</sub>), 3302(NH), 3405 cm<sup>-1</sup> (NH<sub>2</sub>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.14(s, 3H, COCH<sub>3</sub>), 7.4-7.7(m, 4H, Ar-H), 7.55(s, 1H, CH at C<sub>5</sub> of thiazole), 9.46(s, 2H, NH<sub>2</sub>); MS: *m/z* 232.9(M<sup>+</sup>), 191, 162 and 80.



**SMB-2**, Ar = 4-hydroxy phenyl, **SMB-3**, Ar = 4-chloro phenyl, **SMB-4**, Ar = 3,4,5-trimethoxy phenyl, **SMB-5**, Ar = N,N-dimethylamino phenyl, **SMB-6**, Ar = 3-methoxy, 4-hydroxy phenyl, **SMB-7**, Ar = 4-methoxy phenyl, **SMB-8**, Ar = 3-nitro phenyl, **SMB-9**, Ar = 2-chloro phenyl



**SMB-2a**, Ar = 4-hydroxy phenyl, **SMB-3a**, Ar = 4-chloro phenyl, **SMB-4a**, Ar = 3,4,5-trimethoxy phenyl, **SMB-5a**, Ar = N,N-dimethylamino phenyl, **SMB-6a**, Ar = 3-methoxy, 4-hydroxy phenyl, **SMB-7a**, Ar = 4-methoxy phenyl, **SMB-8a**, Ar = 3-nitro phenyl, **SMB-9a**, Ar = 2-chloro phenyl

**Scheme I**

**2-[(Substituted benzylidene)amino]-4-(4'-acetanilido)thiazole (SMB-2 to SMB-9).** A mixture containing 2-amino-4-(4'-acetanilido)thiazole (0.01 mole) and substituted aromatic aldehyde (0.01 mole) in 40 mL of ethanol along with glacial-acetic acid (2-3 drops) was refluxed for 2 hr. The reaction mixture was cooled. The solid obtained was filtered, washed with ethanol, dried and purified by recrystallization from DMF:water (1:1) mixture. **SMB-2:** IR (KBr): 1596(N=CH), 1674(C=O), 3181 cm<sup>-1</sup> (NH); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.0 (s, 3H, COCH<sub>3</sub>), 6.7-7.4(m, 8H, Ar-H), 7.3(s, 1H, CH at C<sub>5</sub> of thiazole), 7.35(s, 1H, NH), 9.4(s, 1H, N=CH); MS: *m/z* 337(M<sup>+</sup>), 217, 159, 135. **SMB-3:** IR (KBr): 760(C-Cl), 1595(N=CH), 1673(C=O), 3295 cm<sup>-1</sup> (NH); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.91(s, 3H, COCH<sub>3</sub>), 7.15-7.5 (m, 8H, Ar-H), 7.31(s, 1H, CH at C<sub>5</sub> of thiazole), 7.4 (s, 1H, NH), 8.9(s, 1H, N=CH); MS: *m/z* 335(M<sup>+</sup>), 197, 139,

and 115. **SMB-5:** IR (KBr): 1352(>N-), 1572(N=CH), 2961(CH<sub>3</sub>), 3145 cm<sup>-1</sup> (NH); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.32(s, 3H, CH<sub>3</sub>), 2.5(S, 3H, COCH<sub>3</sub>), 6.6-7.0(m, 8H, Ar-H), 7.12 (s, 1H, CH at C<sub>5</sub> of thiazole), 7.5(s, 1H, NH), 8.7(s, 1H, N=CH); MS: *m/z* 364(M<sup>+</sup>), 320, 216 and 156. **SMB-7:** IR (KBr): 1542(N=CH), 1643(C=O), 3199 cm<sup>-1</sup> (NH); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.7(s, 3H, COCH<sub>3</sub>), 3.2(s, 3H, OCH<sub>3</sub>), 6.5-7.1(m, 8H, Ar-H), 7.41 (s, 1H, CH at C<sub>5</sub> of thiazole), 7.55(s, 1H, NH), 9.3(s, 1H, N=CH); MS: *m/z* 351(M<sup>+</sup>), 320, 205, 147, 123.

**N-2-[(2R)-3''-Chloro-4''-(substitutedphenyl)-2''-oxoazetidin-1''-yl]-4-(4'-acetanilido)thiazole (SMB-2a to SMB-9a).** A mixture of 2-[(substituted-benzylidene)amino]-4-(4'-acetanilido)thiazole (0.01 mole), dry dioxane (10 mL) and triethylamine (0.03 mole) was taken into a conical flask. The reaction was stirred on an ice-bath and when the temperature

**Table I** — Characterization data of new compounds synthesized

Compd	Mol.formula	Mol.wt	m.p. °C	Yield (%)	R <sub>f</sub>
<b>SMB-1</b>	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> OS	233	220	59	0.90
<b>SMB-2</b>	C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	337	198	68	0.40
<b>SMB-3</b>	C <sub>18</sub> H <sub>14</sub> N <sub>3</sub> OSCl	335	187	67	0.40
<b>SMB-4</b>	C <sub>21</sub> H <sub>21</sub> N <sub>3</sub> O <sub>4</sub> S	411	165	72	0.59
<b>SMB-5</b>	C <sub>20</sub> H <sub>20</sub> N <sub>4</sub> OS	364	208	71	0.96
<b>SMB-6</b>	C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> S	367	180	67	0.12
<b>SMB-7</b>	C <sub>19</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S	351	102	68	0.26
<b>SMB-8</b>	C <sub>18</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub> S	366	179	72	0.23
<b>SMB-9</b>	C <sub>18</sub> H <sub>14</sub> N <sub>3</sub> OSCl	355	223	73	0.21
<b>SMB-2a</b>	C <sub>20</sub> H <sub>16</sub> N <sub>3</sub> O <sub>3</sub> SCl	413	251	58	0.20
<b>SMB-3a</b>	C <sub>20</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> SCl <sub>2</sub>	431	276	57	0.18
<b>SMB-4a</b>	C <sub>23</sub> H <sub>22</sub> N <sub>3</sub> O <sub>5</sub> SCl	481	98	72	0.92
<b>SMB-5a</b>	C <sub>22</sub> H <sub>21</sub> N <sub>4</sub> O <sub>2</sub> SCl	440	201	68	0.19
<b>SMB-6a</b>	C <sub>21</sub> H <sub>18</sub> N <sub>3</sub> O <sub>4</sub> SCl	443	248	42	0.78
<b>SMB-7a</b>	C <sub>21</sub> H <sub>18</sub> N <sub>3</sub> O <sub>3</sub> SCl	427	272	52	0.89
<b>SMB-8a</b>	C <sub>20</sub> H <sub>15</sub> N <sub>4</sub> O <sub>4</sub> SCl	442	225	65	0.08
<b>SMB-9a</b>	C <sub>20</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> SCl <sub>2</sub>	431	265	63	0.82

dropped below 10°C chloroacetyl chloride (0.015 mole) was added dropwise with stirring. After completion of addition the stirring was continued for 6 hr at RT. The reaction mixture was then kept aside for 48 hr. Finally, the reaction mass was added to ice cold water to obtain the final product. It was dried and purified by recrystallization from chloroform. **SMB-2a**: IR (KBr): 740(C-Cl), 1371(NC), 1596(C=O, cyclized), 1673(C=O, non-cyclized), 3287 cm<sup>-1</sup> (OH); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.2(s, 3H, COCH<sub>3</sub>), 4.57(s, 1H, CH-Cl), 6.73(d, 2H, Ar-CHCHCl), 6.9-7.2(m, 8H, Ar-H), 7.23(s, 1H, CH at C<sub>5</sub> of thiazole), 8.15(s, 1H, NH); MS: *m/z* 413(M<sup>+</sup>), 310, 207, and 149. **SMB-3a**: IR (KBr): 675(C-Cl, alkyl), 743(C-Cl, aryl), 1317(NC), 1597(C=O, cyclized), 1681(C=O, non-cyclized), 3298cm<sup>-1</sup> (NH); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.0(s, 3H, COCH<sub>3</sub>), 4.7(s, 1H, CH-Cl), 6.87(d, 2H, Ar-CHCHCl), 7.15(m, 8H, Ar-H), 7.2(s, 1H, CH at C<sub>5</sub> of thiazole), 7.61(s, 1H, NH); MS: *m/z* 431(M<sup>+</sup>), 320, 217. **SMB-5a**: IR (KBr): 762(C-Cl), 1345(NC), 1575(C=O, cyclized), 1653(C=O, non-cyclized), 2961(CH<sub>3</sub>), 3203cm<sup>-1</sup> (NH); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.3(s, 3H, CH<sub>3</sub>), 2.46(s, 3H, COCH<sub>3</sub>), 4.23(s, 1H, CH-Cl), 6.62(d, 2H, Ar-CHCHCl), 6.9-7.2(m, 8H, Ar-H), 7.31(s, 1H, CH at C<sub>5</sub> of thiazole), 8.23(s, 1H, NH); MS: *m/z* 440(M<sup>+</sup>), 396, 319, 251 and 193. **SMB-7a**: IR (KBr): 763(C-Cl), 1325(NC), 1591(C=O, cyclized), 1673(C=O, non-cyclized), 2676 cm<sup>-1</sup>

(OCH<sub>3</sub>); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.21(s, 3H, COCH<sub>3</sub>), 3.1(s, 3H, OCH<sub>3</sub>) 4.52(s, 1H, CH-Cl), 6.51(d, 2H, Ar-CHCHCl), 7.1-7.3(m, 8H, Ar-H), 7.35(s, 1H, CH at C<sub>5</sub> of thiazole), 7.65(s, 1H, NH); MS: *m/z* 427(M<sup>+</sup>), 320, 217, 134, 96.

## Results and Discussion

The structures of all the compounds have been established on the basis of spectral data analysis. The appearance of primary amino group band at 3405 cm<sup>-1</sup> in the IR spectrum, the NMR signal for thiazole proton at δ 7.55, the molecular ion peak at *m/z* 232.9 and fragmentation peaks at *m/z* 191, 162, and 80 confirmed the formation of **SMB-1**. Compounds **SMB-2** to **SMB-9** showed -N=CH- band in IR between 1530-1600 cm<sup>-1</sup>. The NMR spectra of the compounds **SMB-2** to **SMB-9** exhibited absence of amino group signal of thiazole at δ 9.46 and appearance of sharp signal of -N=CH- between δ 8.7-9.4 which indicated the formation of Schiff bases. The representative compounds **SMB-2**, **SMB-3**, **SMB-5** and **SMB-7** showed molecular ion peaks at *m/z* 337, 335, 364 and 351 respectively. Compounds **SMB-2a** to **SMB-9a** showed NC group band between 1317-1371 cm<sup>-1</sup> their IR, and their NMR spectrum showed the absence of -N=CH- group signal between δ 8.7-9.4 and appearance of a sharp signal of C-Cl between δ 4.2-4.7. MS of representative compounds **SMB-2a**, **SMB-3a**, **SMB-5a** and **SMB-7a** exhibited molecular ion peaks at *m/z* 413, 431, 440, 427 alongwith their fragmentation peaks which indicated the formation of azetidinone derivatives.

**Antibacterial screening.** All the synthesized compounds were tested for their antibacterial activity against two Gram+ve (*S. aureus* and *S. epidermidis*) and two Gram -ve (*E. coli* and *K. pneumoniae*) bacteria at a concentration of 2 mg/mL using Kirby-Bauer method<sup>14</sup>. Ampicillin was used as a reference standard at a concentration of 2 mg/mL. Compounds **SMB-1**, **SMB-2** and **SMB-6** were comparable in their activity with the activity of the standard drug ampicillin against *S. aureus* and *S. epidermidis*. **SMB-3** to **SMB-5**, **SMB-7**, and **SMB-2a**, **SMB-4a** to **SMB-7a** showed moderate activity as compared to the standard drug. Compounds **SMB-1**, **SMB-6** and **SMB-6a** were comparable in their activity with the activity of ampicillin against *E. coli* and *K. pneumoniae*. Compounds **SMB-3** to **SMB-5**, **SMB-7** to **SMB-2a**, **SMB-4a**, **SMB-5a**, **SMB-8a** and **SMB-9a** exhibited moderate activity against *E. coli*. Compounds **SMB-3** to **SMB-5**, **SMB-7** to **SMB-9**,

**Table II** — Antimicrobial data

Compd	Bacterial Growth Inhibition (Diameter in mm)				Fungal Growth Inhibition (Diameter in mm)	
	<i>S. aureus</i>	<i>S. epidermidis</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>C. albicans</i>	<i>A. niger</i>
<b>SMB-1</b>	14	15.1	7	6.5	7.5	6.3
<b>SMB-2</b>	13	12.4	6.5	5.8	5.5	5.2
<b>SMB-3</b>	8	7.8	4.5	4.2	3.9	3.9
<b>SMB-4</b>	10.5	9.8	6.25	5.1	4.4	4.1
<b>SMB-5</b>	9.5	9.1	5.7	5.2	4.7	4.5
<b>SMB-6</b>	12.6	12.2	7.5	5.7	7.1	5.1
<b>SMB-7</b>	12.4	10.8	5.5	5.2	5.5	4.3
<b>SMB-8</b>	6.5	6.1	4.3	4.1	3.9	2.9
<b>SMB-9</b>	7	6.2	4.7	4.7	3.5	3.1
<b>SMB-2a</b>	8.5	7.8	6	5.4	4.2	4.9
<b>SMB-3a</b>	6	5.9	3.4	3.2	3.2	3.2
<b>SMB-4a</b>	9.2	8.9	5.5	5.1	4.2	4.2
<b>SMB-5a</b>	8	7.1	5.3	5.1	4.7	4.0
<b>SMB-6a</b>	9	8.6	6.3	5.9	4.8	5.1
<b>SMB-7a</b>	8.5	8.1	3.2	4.2	4.2	4.8
<b>SMB-8a</b>	5.5	5.2	4.1	2.9	3.1	3
<b>SMB-9a</b>	5.7	4.9	4.2	2.4	3	3.1
<b>Std.Drug</b>	18	16.8	9	7.7	10	8.2

**SMB-3a** to **SMB-5a** and **SMB-9a** displayed moderate activity against *K. pneumoniae*. Zones of inhibition of all the derivatives are given in **Table II**.

**Antifungal screening.** All the synthesized compounds were tested for antifungal activity against two fungi (*C. albicans* and *A. niger*) at a concentration of 10 mg/mL using Kirby-Bauer method<sup>14</sup>. Miconazole nitrate was used as the standard drug at a concentration of 10 mg/mL. The antifungal activity results revealed that the compounds **SMB-1** and **SMB-6** were comparable in their activity with the activity of miconazole nitrate against *C. albicans*. On the other hand compound **SMB-1** displayed good activity against *A. niger*. On the other hand compounds **SMB-2**, **SMB-4**, **SMB-5**, **SMB-7**, **SMB-2a** and **SMB-4a** to **SMB-7a** showed moderate activity against *C. albicans*. Compounds **SMB-2** to **SMB-7**, **SMB-2a** and **SMB-4a** to **SMB-7a** exhibited moderate activity against *A. niger*. Zones of inhibition of all compounds are given in **Table II**.

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