

## Synthesis of Some Novel 2,4-Disubstituted Thiazoles as Possible Antimicrobial Agents

Shivananda Wagle , Airody Vasudeva Adhikari & Nalilu Suchetha Kumari

To cite this article: Shivananda Wagle , Airody Vasudeva Adhikari & Nalilu Suchetha Kumari (2008) Synthesis of Some Novel 2,4-Disubstituted Thiazoles as Possible Antimicrobial Agents, Phosphorus, Sulfur, and Silicon and the Related Elements, 183:5, 1285-1300, DOI: 10.1080/10426500701641049

To link to this article: <https://doi.org/10.1080/10426500701641049>



Published online: 09 May 2008.



Submit your article to this journal [↗](#)



Article views: 77



View related articles [↗](#)



Citing articles: 1 View citing articles [↗](#)

## Synthesis of Some Novel 2,4-Disubstituted Thiazoles as Possible Antimicrobial Agents

Shivananda Wagle,<sup>1,2</sup> Airody Vasudeva Adhikari,<sup>2</sup>  
and Nalilu Suchetha Kumari<sup>3</sup>

<sup>1</sup>Strides Research and Specialty Chemicals Ltd., New Mangalore  
575011, India

<sup>2</sup>Department of Chemistry, National Institute of Technology Karnataka,  
Surathkal, Mangalore, 575025, India

<sup>3</sup>Department of Biochemistry, Justice K. S. Hegde Medical Academy,  
Deralakatte, Mangalore, India

*A series of 4-aryl-2-(3-methyl-7-substituted quinoxaline-2-one-1-yl)-1,3-thiazoles (6a-l) and 4-substituted alkyl-2-(3-methyl-7-substituted quinoxaline-2-one-1-yl)-1,3-thiazoles (8a-i) were synthesized in good yield by condensing 2-(3-methyl-7-substituted 1,2-oxoquinoxalin-1(2H)-yl)ethanethioamides (5a-c) with substituted phenacyl bromide and dichloroacetone followed by treatment with secondary amines, respectively. The intermediates, 5a-c were conveniently obtained by reacting phosphorus pentasulphide with 2-(3-methyl-7-substituted-2-oxoquinoxalin-1(2H)-yl) acetamides (4a-c) which in turn were synthesized from ethyl (3-methyl-7-substituted-2-oxoquinoxalin-1(2H)-yl) acetates (3a-c) by aqueous ammonia treatment. The newly synthesized compounds were characterized by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and Mass spectral and elemental analyses. These compounds were screened for in vitro antibacterial activity against five pathogenic strains and antifungal activity against four fungi. Preliminary results revealed that some of the synthesized compounds showed promising antimicrobial activity.*

**Keywords** 2,4-Disubstituted thiazoles; 3,7-Dimethyl quinoxalines; antibacterial; anti-fungal activity; phenacyl bromide

Received 18 June 2007; accepted 30 July 2007.

The authors are grateful to the Head, SAI, CDRI, Lucknow and the Head, NMR Research Centre IISc, Bangalore for providing NMR and mass spectral data. They are also thankful to the Heads of Department of Chemistry, NITK, Department of Biochemistry, KSHMA, Strides Research and Specialty Chemicals Ltd, Mangalore for providing necessary laboratory facilities.

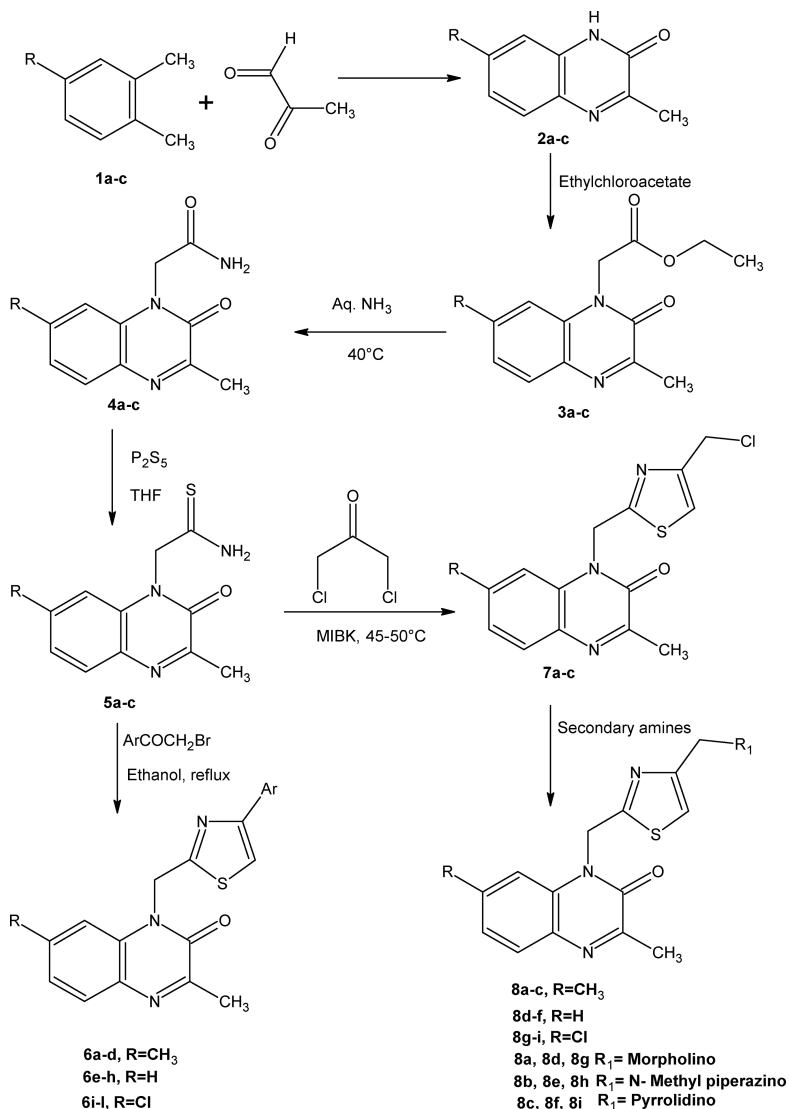
Address correspondence to Airody Vasudeva Adhikari, Department of Chemistry, National Institute of Technology Karnataka, Surathkal, Mangalore 575025, India. E-mail: avadhikari123@yahoo.co.in

## INTRODUCTION

The thiazoles and their derivatives are found in many natural and synthetic products with a wide spectrum of biological activities such as antibacterial,<sup>1</sup> antifungal,<sup>2</sup> anti-inflammatory,<sup>3,4</sup> antiparasitic, and antitumor activity.<sup>5</sup> A survey of literature reveals that a number of 2,4-disubstituted 1,3-thiazoles were reported to exhibit antibacterial, antifungal, antiviral, analgesic, anti-inflammatory, antitumor, and cytotoxic activities.<sup>6-8</sup> On the other hand, many quinoxaline derivatives have been shown to possess a variety of pharmacological properties such as antibacterial, antifungal, antituberculosis, analgesic, and anti-inflammatory activities.<sup>9-14</sup> Encouraged by the above reports, we planned to synthesize a series of new thiazoles containing biologically active 3-methyl-7-substituted quinoxalin-2-one moiety at position 2, and substituted aryl/alkyl group at position 4, with the hope that the resulting molecules would exhibit enhanced biological activity. The present communication reports the multi-step synthesis of the title compounds (**6a-l**) and (**8a-i**) from 3,7-dimethylquinoxalin-2(1H)-ones and investigation of their *in vitro* antibacterial and antifungal activity against pathogenic strains.

## RESULTS AND DISCUSSION

The synthetic route followed for obtaining the title compounds is outlined in the Scheme-1. The intermediates, 3-methyl-7-substituted quinoxalin-2(1H)-ones (**2a-c**), prepared by condensing 4-substituted 1,2-phenylene diamine with pyruvic acid was readily converted to ethyl (3-methyl-7-substituted-2-oxoquinoxalin-1(2H)-yl) acetates (**3a-c**) by reacting with ethyl chloroacetate in presence of dry acetone and potassium carbonate. The compounds **3a-c**, on treatment with aqueous ammonia gave 2-(3-methyl-7-substituted-2-oxoquinoxalin-1(2H)-yl) acetamides (**4a-c**), which on reaction with phosphorous pentasulphide in tetrahydrofuran at 50°C afforded 2-(3-methyl-7-substituted-2-oxoquinoxalin-1(2H)-yl) ethanethioamides (**5a-c**) in good yield. The target molecules 4-aryl-2-(3-methyl-7-substituted quinoxaline-2-one-1-yl)-1,3-thiazoles (**6a-l**) were synthesized by the reaction of **5a-c** with various phenacyl bromides in refluxing ethanol medium. Further, the compounds **5a-c** were readily converted to 4-(chloromethyl)-2-(3-methyl-7-substituted quinoxaline-2-one-1-yl)-1,3-thiazoles (**7a-c**) by refluxing with 1,3-dichloroacetone in methylisobutylketone. The title compounds, 4-substituted-2-(3-methyl-7-substituted quinoxaline-2-one-1-yl)-1,3-thiazoles (**8a-i**) were prepared by the condensation of various secondary amines with **7a-c** in the presence of a base.



SCHEME 1

The structural assignments to the new compounds were based on their elemental analysis and spectral (IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and Mass) data. The formation of 3,7-dimethylquinoxalin-2(1H)-one (**2a**) was confirmed by its  $^1\text{H}$  NMR and IR spectra. FTIR spectrum showed absorption bands at 3224, 1680, 1544  $\text{cm}^{-1}$  owing to  $-\text{NH}$ ,  $>\text{C}=\text{O}$ , and

>C–C< groups respectively. Further,  $^1\text{H}$  NMR spectrum of **2a** showed two sharp singlets at  $\delta$  2.37 and  $\delta$  2.50 indicating the presence of two methyl groups. The appearance of two doublets at  $\delta$  7.15 and  $\delta$  7.27 was due to one aromatic proton and a –NH group respectively and two singlets at  $\delta$  7.48 and 7.55 was due to two aromatic protons of quinoxaline ring. In the mass spectrum, it appeared molecular ion peak at  $m/z$  175 (100%), which matches with its molecular formula  $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$ . The compound **3a**, obtained by condensing **2a** with ethyl chloroacetate, was confirmed by recording its NMR and IR spectra. A quartet at  $\delta$  4.24 and a triplet at 1.30 clearly indicate the formation of ester. The mass spectrum of **3a** showed a molecular ion peak at  $m/z$  261 ( $M+1$ , 100%), which matches with its molecular formula  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$ . The formation of **4a** was confirmed by its IR and  $^1\text{H}$  NMR spectral data. Its FTIR spectrum showed strong peaks at 3340 and 1743  $\text{cm}^{-1}$  indicating the presence of –NH<sub>2</sub> and >C=O groups respectively while its  $^1\text{H}$  NMR spectrum showed a peak at  $\delta$  6.65 confirming the presence of –NH<sub>2</sub> group. The mass spectrum showed a molecular ion peak at  $m/z$  232 ( $M+1$ , 100%) which matches with its molecular formula  $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2$ . The structure of thioamide **5a** was confirmed by recording the FAB mass spectra. It showed the molecular ion peak at  $m/z$  248 ( $M+1$ , 80%), which is consistent with its molecular.

Formations of thiazoles are confirmed by IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and Mass spectral studies. In the IR spectrum of compounds **6a**, the typical absorption bands due to CS and NH<sub>2</sub> groups of thioamide **5a** were absent. The absorption bands corresponding to C=N stretching of thiazole ring appeared at 1611–1602  $\text{cm}^{-1}$ . Further, the mass spectrum of **6a** showed a molecular ion peak at  $m/z$  407 ( $M+1$ , 100%), which is in consistent with its molecular formula  $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$ . Similarly, the formation of chloroalkyl thiazole **7a** was confirmed by its IR spectral results. In the IR spectrum of compound **7a**, the typical absorption bands due to CS and NH<sub>2</sub> groups of thioamide **5a** were absent. Further, in its mass spectrum, a molecular ion peak appeared at  $m/z$  320 ( $M+1$ , 100%), which matches with its molecular formula  $\text{C}_{15}\text{H}_{14}\text{ClN}_3\text{OS}$ . Physical data and results of elemental analysis of **6a–l** and **8a–i** are listed in Table I and Table II, respectively.

All the title compounds were screened for their in vitro activity against bacterial and fungal pathogens. Antibacterial activity was determined against Gram positive and Gram negative bacteria by serial plate dilution method.<sup>15,16</sup> The investigation of antibacterial screening (Table III) revealed that most of the newly synthesized compounds showed moderate to good inhibition at 1.56–25  $\mu\text{g}/\text{ml}$  in DMSO.

The compounds **6a**, **6c**, **6e**, **8a**, **8b**, and **8h** were found to be active against all the microbes studied. They manifested zone of inhibition

**TABLE I Characterization Data of Compounds 6a-1**

Compd	Ar	Molecular formula	Mol. weight	M.P (°C)/ Crystallization solvent	Yield (%)	Analysis % found		
						Found (Calc.)	C	H
<b>6a</b>	4(OH) <sub>3</sub> (CONH <sub>2</sub> )C <sub>6</sub> H <sub>3</sub>	C <sub>21</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub> S	406.45	210-212 / DMF	88	62.24 (62.00)	4.50 (4.42)	13.90 (13.77)
<b>6b</b>	4(Cl) C <sub>6</sub> H <sub>4</sub>	C <sub>20</sub> H <sub>16</sub> ClN <sub>3</sub> OS	381.87	180-182 / CHCl <sub>3</sub>	86	62.80 (62.84)	4.26 (4.18)	11.06 (10.99)
<b>6c</b>	4(CH <sub>3</sub> ) C <sub>6</sub> H <sub>4</sub>	C <sub>21</sub> H <sub>19</sub> N <sub>3</sub> OS	361.46	134-136 / CHCl <sub>3</sub>	85	69.84 (69.71)	5.30 (5.25)	11.66 (11.61)
<b>6d</b>	3(NH <sub>2</sub> ) C <sub>6</sub> H <sub>4</sub>	C <sub>20</sub> H <sub>18</sub> N <sub>4</sub> OS	362.44	160-162 / CHCl <sub>3</sub>	86	66.08 (66.21)	4.90 (4.96)	15.60 (15.45)
<b>6e</b>	4(OH) <sub>3</sub> (CONH <sub>2</sub> )C <sub>6</sub> H <sub>3</sub>	C <sub>20</sub> H <sub>16</sub> N <sub>4</sub> O <sub>3</sub> S	392.43	220-222 / DMF	87	61.20 (61.15)	4.12 (4.07)	14.29 (14.27)
<b>6f</b>	4(Cl) C <sub>6</sub> H <sub>4</sub>	C <sub>19</sub> H <sub>14</sub> ClN <sub>3</sub> OS	367.85	188-190 / CHCl <sub>3</sub>	83	61.90 (61.98)	3.83 (3.80)	11.50 (11.41)
<b>6g</b>	4(CH <sub>3</sub> ) C <sub>6</sub> H <sub>4</sub>	C <sub>20</sub> H <sub>17</sub> N <sub>3</sub> OS	347.43	120-122 / CHCl <sub>3</sub>	85	69.11 (69.07)	4.93 (4.89)	12.10 (12.08)
<b>6h</b>	3(NH <sub>2</sub> ) C <sub>6</sub> H <sub>4</sub>	C <sub>19</sub> H <sub>16</sub> N <sub>4</sub> OS	348.42	180-182 / CHCl <sub>3</sub>	82	65.45 (65.43)	4.45 (4.59)	16.13 (16.07)
<b>6i</b>	4(OH) <sub>3</sub> (CONH <sub>2</sub> )C <sub>6</sub> H <sub>3</sub>	C <sub>20</sub> H <sub>15</sub> ClN <sub>4</sub> O <sub>3</sub> S	426.87	216-218 / DMF	87	56.25 (56.22)	3.53 (3.51)	13.15 (13.11)
<b>6j</b>	4(Cl) C <sub>6</sub> H <sub>4</sub>	C <sub>19</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>3</sub> OS	402.29	198-200 / CHCl <sub>3</sub>	86	56.70 (56.67)	3.18 (3.23)	10.50 (10.44)
<b>6k</b>	4(CH <sub>3</sub> ) C <sub>6</sub> H <sub>4</sub>	C <sub>20</sub> H <sub>16</sub> ClN <sub>3</sub> OS	381.87	150-152 / CHCl <sub>3</sub>	84	62.80 (62.84)	4.16 (4.18)	11.08 (10.99)
<b>6l</b>	3(NH <sub>2</sub> ) C <sub>6</sub> H <sub>4</sub>	C <sub>19</sub> H <sub>15</sub> ClN <sub>4</sub> OS	382.86	174-176 / CHCl <sub>3</sub>	85	59.60 (59.55)	3.94 (3.91)	14.65 (14.62)

TABLE II Characterization Data of Compounds 8a-i

Compd	R1	Molecular formula	Molecular weight	M.P. (°C)/ Crystallization solvent	Yield (%)	Analysis % found		
						C	H	N
8a	Morpholino	C <sub>19</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub>	354.40	118–120 / CHCl <sub>3</sub>	80	64.36 (64.33)	6.28 (6.20)	15.82 (15.80)
8b	N-Methylpi-perazino	C <sub>20</sub> H <sub>25</sub> N <sub>5</sub> O <sub>2</sub>	367.44	280–282 / CHCl <sub>3</sub>	81	65.28 (65.31)	6.76 (6.80)	19.09 (19.05)
8c	Pyrrolidino	C <sub>19</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub>	338.40	218–220 / CHCl <sub>3</sub>	78	67.40 (67.37)	6.42 (6.50)	16.50 (16.54)
8d	Morpholino	C <sub>18</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub>	340.37	102–104 / CHCl <sub>3</sub>	78	63.50 (63.46)	5.80 (5.87)	16.40 (16.45)
8e	N-Methylpi-perazino	C <sub>19</sub> H <sub>23</sub> N <sub>5</sub> O <sub>2</sub>	353.41	278–280 / CHCl <sub>3</sub>	81	64.60 (64.51)	6.52 (6.50)	19.82 (19.80)
8f	Pyrrolidino	C <sub>18</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub>	324.37	202–204 / CHCl <sub>3</sub>	76	66.60 (66.59)	6.20 (6.16)	17.30 (17.26)
8g	Morpholino	C <sub>18</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>3</sub>	374.82	100–102 / CHCl <sub>3</sub>	81	57.65 (57.62)	5.10 (5.06)	14.97 (14.94)
8h	N-Methylpi-perazino	C <sub>19</sub> H <sub>22</sub> ClN <sub>5</sub> O <sub>2</sub>	387.86	268–270 / CHCl <sub>3</sub>	78	58.80 (58.78)	5.70 (5.67)	18.05 (18.04)
8i	Pyrrolidino	C <sub>18</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>2</sub>	358.82	190–192 / CHCl <sub>3</sub>	74	60.23 (60.19)	5.31 (5.29)	15.63 (15.60)

TABLE III Antibacterial Activity of Compounds 6a-l and 8a-i

Compound	<i>Escherichia coli</i>	<i>K.pneumoniae</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>
<b>6a</b>	6.25(16–20)	6.25(16–20)	6.25(16–20)	12.5(16–20)
<b>6b</b>	12.5(16–20)	12.5(16–20)	12.5(16–20)	6.25(16–20)
<b>6c</b>	6.25(16–20)	6.25(11–15)	6.25(16–20)	12.5(16–20)
<b>6d</b>	12.5(16–20)	25(<10)	6.25(16–20)	12.5(16–20)
<b>6e</b>	6.25(16–20)	6.25(16–20)	12.25(16–20)	12.5(16–20)
<b>6f</b>	12.5(11–15)	12.5(16–20)	12.5(16–20)	25(<10)
<b>6g</b>	12.5(11–15)	25(<10)	6.25(16–20)	6.25(16–20)
<b>6h</b>	6.25(16–20)	6.25(16–20)	25(<10)	12.5(16–20)
<b>6i</b>	12.5(16–20)	6.25(16–20)	12.5(11–15)	6.25(16–20)
<b>6j</b>	25(<10)	12.5(11–15)	25(<10)	12.5(16–20)
<b>6k</b>	12.5(16–20)	12.5(16–20)	6.25(16–20)	12.5(11–15)
<b>6l</b>	25(<10)	12.5(16–20)	6.25(16–20)	25(<10)
<b>8a</b>	6.25(16–20)	6.25(16–20)	6.25(16–20)	12.5(11–15)
<b>8b</b>	6.25(16–20)	6.25(16–20)	12.5(16–20)	6.25(16–20)
<b>8c</b>	12.5(11–15)	12.5(16–20)	6.25(16–20)	12.5(11–15)
<b>8d</b>	25(<10)	6.25(16–20)	12.5(16–20)	25(<10)
<b>8e</b>	6.25(16–20)	12.5(16–20)	6.25(16–20)	12.5(16–20)
<b>8f</b>	25(<10)	6.25(16–20)	12.5(16–20)	25(<10)
<b>8g</b>	25(<10)	12.5(16–20)	6.25(16–20)	6.25(16–20)
<b>8h</b>	6.25(16–20)	6.25(16–20)	6.25(16–20)	12.5(16–20)
<b>8i</b>	12.5(16–20)	12.5(11–15)	25(<10)	12.5(16–20)
Standard (Ciprofloxacin)	6.25(30–40)	6.25(23–27)	6.25(25–33)	1.56(22–30)

The MIC values were evaluated at concentration range, 1.56–25  $\mu\text{g/ml}$ . The figures in the table show the MIC values and the corresponding zones of inhibition (in mm).

up to 16–20 mm at concentration of 6.26 mg/ml, which are comparable to standard. Amongst the tested compounds, **6h** and **8h** displayed considerable activity against *E.coli* and *K.pneumoniae* with zone of inhibition 16–20mm at 6.25 mg/ml, whereas compounds **6d**, **6g**, **6k**, **6l**, **8c** and **8e** exhibited good activity against *S. aureus* with zone of inhibition 16–20 mm diameter at 6.25 mg/ml. The compounds **6b**, **6g**, **6i**, and **8g** demonstrated good activity (inhibition zone of 16–20 mm at 6.25 mg/ml) against *P. aeruginosa*.

The test results measured at four different concentrations reveal that presence of halogen and N-methyl piperazino substitutions in the aromatic ring system caused increase in activity mainly because of their structural similarities with the standard drug. As reported in the literature,<sup>17</sup> presence of active groups like  $-\text{NH}_2$ ,  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{CH}_3$ ,  $-\text{CONH}_2$  in a molecule enhances its antimicrobial activity probably due to the enhancement of the rate of electron flow in chloroplasts concomitant with an inhibition of phosphorylation. Thus, it has been concluded



**TABLE IV Antifungal Activity of Compounds 6a-l and 8a-i**

Compound	<i>Trichophyton</i>	<i>Asp. Fumigatus</i>	<i>Can. Albicans</i>	<i>Penicillium</i>
<b>6a</b>	6.25(16–20)	12.5(16–20)	6.25(16–20)	6.25(16–20)
<b>6b</b>	12.5(11–15)	6.25(16–20)	6.25(16–20)	25(<10)
<b>6c</b>	12.5(11–15)	12.5(11–15)	12.5(16–20)	12.5(16–20)
<b>6d</b>	12.5(11–15)	6.25(16–20)	12.5(16–20)	12.5(16–20)
<b>6e</b>	6.25(16–20)	6.25(16–20)	6.25(16–20)	12.5(16–20)
<b>6f</b>	12.5(11–15)	12.5(16–20)	12.5(16–20)	6.25(16–20)
<b>6g</b>	6.25(16–20)	6.25(16–20)	12.5(16–20)	12.5(16–20)
<b>6h</b>	12.5(16–20)	25(<10)	12.5(11–15)	6.25(16–20)
<b>6i</b>	12.5(16–20)	12.5(16–20)	12.5(16–20)	25(<10)
<b>6j</b>	6.25(16–20)	6.25(16–20)	12.5(16–20)	6.25(16–20)
<b>6k</b>	12.5(11–15)	12.5(16–20)	25(<10)	12.5(16–20)
<b>6l</b>	12.5(16–20)	12.5(11–15)	12.5(11–15)	12.5(16–20)
<b>8a</b>	12.5(11–15)	6.25(16–20)	6.25(16–20)	12.5(11–15)
<b>8b</b>	6.25(16–20)	12.5(11–15)	6.25(16–20)	6.25(16–20)
<b>8c</b>	12.5(11–15)	12.5(11–15)	12.5(11–15)	12.5(11–15)
<b>8d</b>	12.5(11–15)	12.5(11–15)	12.5(16–20)	6.25(16–20)
<b>8e</b>	25(<10)	12.5(11–15)	12.5(11–15)	25(<10)
<b>8f</b>	12.5(11–15)	6.25(16–20)	12.5(16–20)	12.5(11–15)
<b>8g</b>	12.5(11–15)	12.5(11–15)	25(<10)	12.5(11–15)
<b>8h</b>	6.25(16–20)	6.25(16–20)	12.5(11–15)	6.25(16–20)
<b>8i</b>	25(<10)	12.5(16–20)	12.5(11–15)	25(<10)
Standard (Cicloprixolamine)	6.25(20–27)	3.125(27–33)	3.125(25–30)	6.25(25–30)

The MIC values were evaluated at concentration range, 1.56–25  $\mu\text{g/ml}$ . The figures in the table show the MIC values and the corresponding zones of inhibition (in mm).

that amongst the various tested thiazoles, compounds containing 4-methyl, 4-chloro, 4-amine, and 3-amide groups on phenyl moiety at position 4 and 7-methyl quinoxaline at position 2 of thiazole ring have demonstrated encouraging results, which are comparable to the standard drug.

Similarly, the investigation of antifungal activity (Table IV) revealed that all the newly synthesized compounds showed moderate to good inhibition at 1.56–25  $\mu\text{g/ml}$  in DMSO. The compounds **6a**, **6e**, **6j**, **8b** and **8h** exhibited good activity against all the four fungal strains, while the compounds **6g**, **6b**, **6d**, **8a** and **8f** were found to be active against *Trichophyton* and *Asp.Fumigatus* (inhibitory zone 16–20 mm at 6.25 mg/ml), whereas the compounds **6b**, **6f**, **8a**, and **8d** displayed good activity against *Can.Albicans* and *Penicillium* (inhibitory zone 16–20 mm at 6.25 mg/ml). Therefore, it can be concluded that presence of 4-hydroxy, 3-amide groups on phenyl ring and 4-N-methyl piperazine through methylene link at position 4, in addition to 7-methyl quinoxaline at

position 2 of thiazole ring enhanced the antifungal activity of the title compounds. Further, it is interesting to note that compounds **6a**, **6e**, **8b**, and **8h** displayed both antibacterial and antifungal activities.

## EXPERIMENTAL

### General

Melting points were determined by open capillary and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer.  $^1\text{H}$  NMR spectra were recorded either on Perkin-Elmer EM-390 (300 MHz) and Bruker WH-200 (400 MHz) spectrometers using TMS as an internal standard.  $^{13}\text{C}$  NMR spectra were obtained on a Perkin-Elmer (Model RB-12, 100 MHz) spectrometer. All chemical shifts are reported in ppm downfield from tetramethylsilane. The mass spectra were recorded on a Jeol JMS-D 300 mass spectrometer (FAB) operating at 70eV. Elemental analysis was performed on Flash E A 1112 Thermo Electron Corporation CHNS analyzer. The purity of the compounds was checked by thin layer chromatography (TLC) on Merck silica gel 60 F<sub>254</sub> precoated sheets using hexane and ethyl acetate 4:1, v/v. Starting materials were purchased from Aldrich Chemical Company or Spectrochem Chemical Company and used without further purification. All solvents were of analytical grade and freshly distilled prior to use.

### Chemistry

#### **2-(3-Methyl-7-substituted-2-oxoquinoxalin-1(2H)-yl)acetamide (4a-c)**

A mixture of ethyl (3-methyl-7-substituted-2-oxoquinoxalin-1(2H)-yl) acetate (**3a-c**) (25 g, 96.15 mmol), and aqueous ammonia (100 ml) was stirred at 40°C for 8–10 h. Progress of the reaction was monitored by TLC (ethyl acetate/hexane, 1:1, v/v). After completion of the reaction, the mixture was cooled to 10°C and filtered. The product was thoroughly washed with cold water to remove trace of ammonia and finally dried at 60–70°C under vacuum.

**4a.** Off-white solid. Yield: 20.5 g (92.7%), M.p., 218–220°C. MS (m/z, %): 232 (M+1, 100), 231(M<sup>+</sup>, 30), 187(40), 173(15), 157(40), 150(40), 147(10), 121(20), 102(40).  $^1\text{H}$ -NMR (DMSO-d<sub>6</sub>)  $\delta$ : 7.25 (s, 1H, CH), 7.12–7.14 (d, 1H, J = 8.8 Hz), 6.65 (s, 2H, NH<sub>2</sub>), 6.50–6.52 (d, 1H, J = 8.8 Hz), 4.71 (s, 2H, CH<sub>2</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 2.46 (s, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (DMSO): 20.60 (CH<sub>3</sub>), 21.85 (CH<sub>3</sub>-), 53.18, 118.88, 123.03, 123.21, 133.45, 135.64, 137.25, 159.93 (C=O), 164.92 (N=C-CH<sub>3</sub>), 171.66 (C=O). Anal. Calcd.

for  $C_{12}H_{13}N_3O_2$ : C, 62.27; H, 5.62; N, 18.16; Found: C, 62.40; H, 5.72; N, 18.54%.

**4b.** Off-white solid. Yield: 16.5 g (74.8%), M.p., 220–222°C. MS (m/z, %): 218 (M+1, 100), 217(M<sup>+</sup>, 30), 187(20), 157(40), 150(10), 147(30), 121(20), 102(40), 79(20). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 8.11–8.13 (d, 1H, CH, J = 7.65 Hz), 7.48–7.52 (t, 1H, J = 7.68 Hz), 7.18–7.14 (t, 1H, CH, J = 7.65 Hz), 6.73–6.70 (d, 1H, CH, J = 7.50 Hz), 6.54 (s, 2H, NH<sub>2</sub>), 4.78 (s, 2H, NH<sub>2</sub>), 2.50 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO): 20.64 (CH<sub>3</sub>), 53.18, 117.19, 122.48, 127.92, 129.36, 135.64, 137.09, 159.93 (C=O), 164.90 (N=C–CH<sub>3</sub>), 171.66 (C=O). Anal. Calcd. for  $C_{11}H_{11}N_3O_2$ : C, 60.76; H, 5.06; N, 19.33; Found: C, 60.48; H, 5.16; N, 19.63%

**4c.** Beige colored solid. Yield: 17.25 g (78%), M.p., 216–218°C. MS (m/z, %): 252(M+1, 80), 251(M<sup>+</sup>, 30), 235(80), 234(20), 207(40), 179(60), 120(20), 105(10), 95(20). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.51–7.49 (d, 1H, CH, J = 8.50 Hz), 7.46 (s, 1H), 6.98–7.00 (d, 1H, CH, J = 8.50 Hz), 6.65 (s, 2H, NH<sub>2</sub>), 4.74 (s, 2H, CH<sub>2</sub>), 2.46(s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO): 20.60 (CH<sub>3</sub>), 53.18, 116.21, 122.68, 125.27, 132.30, 134.81, 135.85, 160.06 (C=O), 164.92 (N=C–CH<sub>3</sub>), 171.61 (C=O). Anal. Calcd. for  $C_{11}H_{10}ClN_3O_2$ : C, 52.45; H, 3.97; N, 16.68; Found: C, 52.60; H, 4.08; N, 16.90%.

### **2-(3-Methyl-7-substituted-2-oxoquinoxalin-1(2H)-yl)ethanethioamide (5a–c)**

To a solution of 2-(3-methyl-7-substituted-2-oxoquinoxalin-1(2H)-yl)acetamide (**4a–c**) (20 g, 86.6 mmol) in tetrahydrofuran (50 ml), phosphorous pentasulphide (38.5 g, 171 mmol) was slowly added at 50°C over a period of 2 h while stirring. The resulting slurry was further stirred at 50–55°C for 2 h, and the reaction mass was poured into ice-cold water. The precipitated solid was filtered, washed with water and dried at 50–60° under vacuum. The product was recrystallized from ethyl acetate.

**5a.** Brown colored solid. Yield: 14.5 g (68%), M.p., 212–214°C. MS (m/z, %): 248 (M+1, 80), 247(M<sup>+</sup>, 50), 187(25), 173(30), 157(40), 147(10), 121(20), 102(40). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.70 (s, 1H, CSNH<sub>2</sub>), 7.25 (s, 1H, CH), 7.12–7.14 (d, 1H, J = 8.8 Hz), 6.96 (s, 1H, CSNH<sub>2</sub>), 6.50–6.52 (d, 1H, J = 8.8), 4.88 (s, 2H, CH<sub>2</sub>), 2.50(s, 3H, CH<sub>3</sub>), 2.42 (s, 3H, CH<sub>3</sub>). Anal. Calcd. for  $C_{12}H_{13}N_3OS$ : C, 58.21; H, 5.25; N, 16.97; Found: C, 58.24; H, 5.20; N, 16.90%.

**5b.** Brown colored solid. Yield: 13.6 g (63.5%), M.p., 210–212°C. MS (m/z, %): 234 (M+1, 100), 235(M<sup>+</sup>, 80), 173(40), 157(40), 121(30),

102(40), 91(20). Anal. Calcd. for  $C_{11}H_{11}N_3OS$ : C, 56.58; H, 4.71; N, 18.00; Found: C, 56.60; H, 4.75; N, 18.08%.

**5c.** Pale yellow colored solid. Yield: 14.2 g (66.6%), M.p., 206–208°C. MS (m/z, %): 268 (M+1, 50), 267(M<sup>+</sup>, 50), 147(40), 121(20), 91(25), 73(15). Anal. Calcd. for  $C_{11}H_{10}ClN_3OS$ : C, 49.30; H, 3.73; N, 15.68; Found: C, 49.26; H, 3.70; N, 15.60%.

#### **4-Aryl-2-(3-methyl-7-substituted quinoxaline-2-one-1-yl)-1,3-thiazoles (6a-l)—General Procedure**

An equimolar mixture of appropriate thioamide **5a–c** (10 mmol) and substituted phenacylbromide (10 mmol) in ethanol (10 ml) was refluxed for 6 h. Then the reaction mixture was cooled to room temperature. The solid separated was filtered and recrystallized from chloroform/dimethyl formamide.

**6a.** MS (m/z, %): 407(M+1, 100), 406(M<sup>+</sup>, 60), 207(40), 179(60), 105(10), 91(20). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 13.21 (s, 1H, OH), 8.15 (s, 2H, NH<sub>2</sub>), 7.96–7.98 (d, 1H, CH, J = 8.50 Hz), 7.88–7.89 (d, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 7.05–7.07 (d, 1H, CH, J = 8.50 Hz), 6.84–6.86 (d, 1H), 6.58–6.60 (d, 1H), 4.31 (s, 2H, CH<sub>2</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 2.46 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO): 21.08 (CH<sub>3</sub>), 21.85 (CH<sub>3</sub>), 40.42, 118.87, 119.61, 122.80, 123.00, 124.02, 128.11, 128.20, 128.88, 133.48, 134.18, 135.58, 137.02, 152.80, 160.25, 163.07, 163.12, 163.74, 165.84.

**6b.** MS (m/z, %): 382(M+1, 80), 381(M<sup>+</sup>, 60), 179(25), 105(10), 91(10). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.83 (d, 2H, p-chlorophenyl, J = 5.20 Hz), 7.50 (s, 1H, thiazole), 7.40 (s, 1H), 7.34 (d, 2H, p-chlorophenyl, J = 5.20 Hz), 6.84–6.86 (d, 1H), 6.60–6.62 (d, 1H), 4.76 (s, 2H, CH<sub>2</sub>), 2.60 (s, 3H, CH<sub>3</sub>), 2.49 (s, 3H, CH<sub>3</sub>).

**6e.** IR (KBr)  $\nu/cm^{-1}$ : 1580 (C=N), 1540 (C=C), 1070 (C=S), 815, 710. MS (m/z, %): 393(M+1, 100), 392(M<sup>+</sup>, 60), 207(50), 179(30), 105(20), 91(20), 73(25).

**6g.** MS (m/z, %): 348(M+1, 70), 347(M<sup>+</sup>, 20), 207(20), 179(30), 105(20), 91(10). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.89 (d, 1H, CH, J = 7.65 Hz), 7.81 (d, 2H, p-methylbenzene, J = 8.30 Hz), 7.43 (d, 2H, p-methylbenzene, J = 8.30 Hz), 7.30 (s, 1H, thiazole), 7.25–7.28 (m, 2H, quinoxaline protons), 6.62 (d, 1H, quinoxaline, J = 7.50 Hz), 4.03 (s, 2H, CH<sub>2</sub>), 2.48 (s, 3H, CH<sub>3</sub>), 2.37 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO): 20.60 (CH<sub>3</sub>), 21.22 (CH<sub>3</sub>), 51.76, 116.31, 117.46, 122.46, 125.26, 127.56, 128.99, 129.41, 130.72, 134.41, 134.76, 136.71, 137.08, 143.54, 162.79, 167.53.

**6j.** IR (KBr)  $\nu/cm^{-1}$ : 1600 (C=N), 1530 (C=C), 1070 (C=S), 820, 707. MS (m/z, %): 403(M+1, 80), 402(M<sup>+</sup>, 30), 395(10), 391(10), 339(15),

273(20), 252(10), 235(30), 207(50), 179(30), 167(20), 120(20), 105(20), 95(20).

6l. IR (KBr)  $\gamma/\text{cm}^{-1}$ : 1598 (C=N), 1529 (C=C), 1078 (C=S), 830, 708. MS (m/z, %): 383(M+1, 50), 382(M<sup>+</sup>, 30), 339(25), 273(20), 235(30), 207(30), 179(20), 167(10), 120(10), 105(5), 95(20). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) $\delta$ : 7.45–7.47 (t, 2H, p-aminiphenyl, J = 9.00 Hz), 7.36 (s, 1H), 7.32 (s, 1H, thiazole), 7.26–7.28 (s, 1H, quinoxaline protons), 7.08–7.10 (d, 1H, quinoxaline, J = 8.50 Hz), 6.64 (t, 2H, p-aminiphenyl, J = 9.00 Hz), 6.18 (s, 2H, NH<sub>2</sub>), 4.01 (s, 2H, CH<sub>2</sub>), 2.48 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO): 20.60 (CH<sub>3</sub>), 51.78, 115.33, 117.46, 118.86, 122.31, 123.62, 125.25, 128.97, 130.56, 131.93, 133.93, 135.47, 143.54, 148.60, 162.79, 167.53.

#### **4-(Chloromethyl)-2-(3-methyl-7-substituted quinoxaline-2-one-1-yl)-1,3-thiazoles (7a–c)**

A mixture of appropriate thioamide (**5a–c**) (**5a**:10 g, 40.48 mmol; **5b**:7.5 g, 32.08 mmol; **5c**:10 g, 37.38 mmol) and 1,3-dichloroacetone (7.7 g, 60.72 mmol) in methylisobutylketone (MIBK) was refluxed for 5 h. After completion of the reaction, the mass was poured into chilled water. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and finally evaporated to dryness under reduced pressure. The product was recrystallized from chloroform.

**7a.** Beige colored solid. Yield: 8.0g (62%), M.p., 180–182°C. MS (m/z, %): 320(M+1, 100), 319(M<sup>+</sup>, 50), 235(40), 234(20), 207(40), 179(60), 120(20), 105(10), 95(20). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$ : 7.74 (s, 1H, thiazole), 7.24 (s, 1H), 6.93–6.95 (d, 1H, CH, J = 8.88 Hz), 6.61–6.64 (d, 1H, CH, J = 8.88 Hz), 5.62 (s, 2H, CH<sub>2</sub>), 4.39 (s, 2H, CH<sub>2</sub>), 2.56 (s, 3H, CH<sub>3</sub>), 2.46 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO): 20.63 (CH<sub>3</sub>), 21.85, 36.88, 44.01, 118.59, 121.21, 123.44, 124.32, 133.15, 136.55, 137.67, 137.82, 145.68, 159.03, 165.60. Anal. Calcd for C<sub>15</sub>H<sub>14</sub>ClN<sub>3</sub>OS : C, 56.28; H, 4.37; N, 13.13; Found: C, 56.32; H, 4.30; N, 13.17%.

**7b.** Off-white solid. Yield: 7.0 g (71.4%), M.p., 190–194°C. MS (m/z, %): 306(M+1, 80), 305(M<sup>+</sup>, 30), 235(20), 207(30), 179(10), 120(20), 105(20), 95(20). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>)  $\delta$ : 7.92 (d, 1H, CH, J = 7.65 Hz), 7.72 (s, 1H, thiazole), 7.24–7.33 (m, 2H, 2-CH), 6.69–6.72 (d, 1H, CH, J = 7.50 Hz), 5.52 (s, 2H, CH<sub>2</sub>), 4.63 (s, 2H, CH<sub>2</sub>), 2.54(s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO): 20.72 (CH<sub>3</sub>), 36.92, 44.01, 116.89, 121.25, 123.64, 128.34, 129.78, 135.36, 137.82, 138.00, 159.09, 165.69. Anal. Calcd for C<sub>14</sub>H<sub>12</sub>ClN<sub>3</sub>OS : C, 54.94; H, 3.92; N, 13.73; Found: C, 54.98; H, 3.96; N, 13.82%.

**7c.** Brown colored powder. Yield: 8.6 g (67.2%), M.p., 178–180°C. MS (m/z, %): 341(M+1, 100), 340(M<sup>+</sup>, 60), 235(80), 234(10), 207(5), 179(40),

120(20), 105(10), 95(20). Anal. Calcd for  $C_{14}H_{11}Cl_2N_3OS$  : C, 49.37; H, 3.23; N, 12.34; Found: C, 49.34; H, 3.20; N, 12.31%.

#### **4-Substituted- 2-(3-methyl-7-substituted quinoxaline-2-one-1-yl)-1,3-thiazoles (8a-i)— General Procedure**

An equimolar mixture of **7a-c** (10 mmol) and amine (10 mmol) was refluxed in methylisobutylketone (MIBK, 20 ml) for 3–4 hours, in the presence of sodium hydroxide. The product was then poured into chilled water. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate and finally evaporated to dryness under reduced pressure and the solid obtained was recrystallized from chloroform.

**8a.** MS (m/z, %): 355(M+1, 40), 354(M<sup>+</sup>, 20), 277(10), 235(10), 207(20), 179(20), 120(20), 105(10), 95(5). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.53 (s, 1H, thiazole), 7.23 (s, 1H, CH), 6.93–6.95 (d, 1H, CH, J = 8.88 Hz), 6.61–6.64 (d, 1H, CH, J = 8.88 Hz), 5.04 (s, 2H, CH<sub>2</sub>), 3.55 (s, 2H, -N-CH<sub>2</sub>), 3.25 (t, 4H, -CH<sub>2</sub>-O-CH<sub>2</sub>-, morpholine protons), 2.82–2.87 (t, 4H, -CH<sub>2</sub>-N-CH<sub>2</sub>-, morpholine protons), 2.55 (s, 3H, CH<sub>3</sub>), 2.48(s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO): 20.71, 21.85, 44.26, 50.80, 53.49, 66.85, 118.64, 123.44, 124.36, 131.80, 133.16, 137.06, 137.67, 139.92, 141.98, 159.00, 166.02.

**8e.** MS (m/z, %): 354(M+1, 100), 353(M<sup>+</sup>, 30), 277(10), 207(30), 120(20), 105(20), 95(15). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.92 (d, 1H, CH, J = 7.67 Hz), 7.55 (s, 1H, thiazole), 7.27–7.33 (m, 2H, 2-CH), 6.69 (d, 1H, CH, J = 7.50 Hz), 4.98 (s, 2H, CH<sub>2</sub>), 3.56 (s, 2H, -N-CH<sub>2</sub>), 2.46–2.49(m, 8H), 2.41(s, 3H, CH<sub>3</sub>), 2.26(s, 3H, N-CH<sub>3</sub>). <sup>13</sup>C NMR (DMSO): 20.72, 44.26, 45.70, 50.19, 52.44, 53.67, 116.89, 123.59, 128.34, 129.77, 133.99, 135.34, 138.51, 139.92, 141.98, 141.98, 159.08, 165.79.

**8i.** MS (m/z, %): 359(M+1, 80), 358(M<sup>+</sup>, 30), 277(10), 235 (20), 207(30), 120(20), 105(20), 95(15). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.50 (s, 1H), 7.45 (s, 1H, thiazole), 7.30–7.32 (d, 1H, CH, J = 8.50 Hz), 7.08–7.11 (d, 1H, CH, J = 8.50 Hz), 5.06 (s, 2H, CH<sub>2</sub>), 3.53 (s, 2H, -N-CH<sub>2</sub>), 2.59–2.67(m, 4H), 2.44(s, 3H, CH<sub>3</sub>), 1.72–1.76 (m, 4H, pyrrolidine protons). <sup>13</sup>C NMR (DMSO): 20.64, 23.65, 44.26, 49.68, 53.96, 115.91, 123.09, 126.37, 126.76, 132.72, 134.51, 137.27, 139.92, 141.98, 159.12, 165.97.

## **BIOLOGICAL ACTIVITY**

### **Antibacterial Studies**

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* [ATTC-25922], *Staphylococcus*

*aureus* [ATTC-25923], *Pseudomonas aeruginosa* [ATTC-27853], and *Klebsiella pneumoniae* [Recultered] bacterial strains by serial plate dilution method. Serial dilutions of the drug in Muller-Hilton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16–18 h at 37°C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth.

A number of antimicrobial discs are placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each petri dish. Excess of suspension was decanted and plates were dried by placing in incubator at 37°C for an hour. Using an agar punch, wells were made on these seeded agar plates and minimum inhibitory concentrations of the test compounds in dimethylsulfoxide (DMSO) were added into each well. A control was also prepared for the plates in the same way using solvent DMSO. The petri dishes were prepared in triplicate and maintained at 37°C for 3–4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with Ciprofloxacin as standard.<sup>18,19</sup> The results of antibacterial activity are summarized in Table III.

### Antifungal Studies

The newly synthesized compounds were screened for their antifungal activity against *Aspergillus flavus* (NICM No.524), *Aspergillus fumigatus* (NICM No.902), *Candida albicans* (NICM No.300), *Penicillium marneferi* (Recultered) and *Trichophyton mentagrophytes* (Recultered) in DMSO by serial plate dilution method.<sup>20,21</sup> Subourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g), and agar (2 g) in distilled water (100 ml) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of corresponding species. Twenty millimeter of agar media was poured into each petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37°C for 1 hour. Using an agar punch, wells were made and each well is labeled, and minimum inhibitory concentrations of the test compounds in DMSO were added into each well. A control was also prepared for the plates in the same way using solvent DMSO. The petri dishes were prepared in triplicate and maintained at 37°C for 3–4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity

of each compound was compared with Ciclopirixolamine as standard. The results of antifungal activity are given in the Table IV.

## CONCLUSIONS

A new series of thiazole derivatives containing 3-methyl-7-substituted quinoxaline-2-one moiety in position 2 and substituted aryl/alkyl groups in position 4 were synthesized and screened for their antimicrobial activities. The testing results indicated that out of thirty compounds tested, six compounds showed good antimicrobial activity, which is almost comparable with the standard. We noticed that, the observed antimicrobial activity is due to the presence of pharmacologically active substituents like salicylamide, p-methyl benzene and N-methyl morpholine substituents in the thiazoles and methyl group in quinoxalines moiety.

## REFERENCES

- [1] N. Hans, Swiss Patent 592103/1977, *Chem. Abstr.*, **88**, 22,886, (1978).
- [2] K. J. Wilson, C. R. Utig, N. Subhasinghe, J. B. Hoffman, N. J. Rudolph, R. Soll, C. J. Molloy, R. Bone, D. Green, and J. Randall, *Bio. Org & Med. Chem. Lett.*, **11**, 915–918 (2001).
- [3] K. D. Berlin and M.D. Herd, *Proc. Okala. Acad. Sci.*, **71**, 29–33 (1991).
- [4] G. Beck and H. Heitzer, U.S. Patent 4,748,243 (1987).
- [5] Y. Kumar, R. Green, D. S. Wise, L. L. Wotring, and L. B. Townsend, *J. Med. Chem.*, **36**(24), 3849–3852 (1993).
- [6] B. Plouvier, R. Houssin, N. Helbecque, P. Colson, C. Houssier, J. P. Henichart, and C. Bailly, *Anticancer Drugs*, **10**, 155 (1995).
- [7] R. Bai, D. G. Covell, G. F. Taylor, J. A. Kepler, T. D. Copeland, N. Y. Nguyen, G. R. Pettit, and E. Hamel, *J. Biol. Chem.*, **279**, 30,731 (2004).
- [8] E. Brantley, V. Patel, S. F. Stinson, V. Trapani, C. D. Hose, H. P. Ciolino, G. C. Yeh, J. S. Gutkind, E. A. Sausville, and A. I. Loaiza, *Anticancer Drugs*, **16**, 137 (2005).
- [9] D. A. Vyas, N. A. Chauhan, and A. R. Parikh, *J. of Ind. Chem. Soc.*, **82**(11), 972–974 (2005).
- [10] Z. Michaus and M. Belen, Universidad de Navarra, Pamplona, Spain. *Diss. / Abstr. Int. C.*, **66**(1), 148 (2005).
- [11] J. Dudash, Y. Zhang, B. J. Moore, R. Look, Y. Liang, M. P. Beavers, R. B. Conway, J. Rybczynski, D. Philip, and T. K. Demarest *Bioorganic & Medicinal Chemistry Letters*, **15**(21), 4790–4793 (2005).
- [12] C. Obafemi and D. A. Craig, *Phosphorus, Sulfur and Silicon and the Related Elements*, **180**(8), 1795–1807 (2005).
- [13] K. Kojima, *Jpn. Kokai Tokkyo Koho*, **39**, (2004).
- [14] Y. Sainz, M. E. Montoya, F. J. Martinez-Crespo, M. A. Ortega, A. Lopez de Cerain, and A. Monge, *Arzneimittel-Forschung* **49**(1), 55–59 (1999).
- [15] A. Barry, Procedures and theoretical considerations for testing antimicrobial agents in agar media. In *Antibiotics in laboratory medicine*, 5th ed. Corian, Ed. (Williams and Wilkins, Baltimore, MD, 1991).



- [16] J. D. MacLowry, M. J. Jaqua, and S. T. Selepak, *Applied Microbiology*, **20**(1), 46–53 (1970).
- [17] J. J. Kabara, A. J. Conley, and J. P. Truant, *Antimicrobial agents and chemotherapy*, **2**(6), 492–498 (1972).
- [18] C. H. Fenlon and M. H. Cynamon, *Antimicrobial Agents and Chemotherapy*, **29**(3), 386–388 (1986).
- [19] R. Davis, A. Markam, and J. A. Balfour, *Drugs*, **51**(6), 1019 (1996).
- [20] B. A. Arthington-Skaggs, M. Motley, D. W. Warnock, and C. J. Morrison. *Journal of Clinical Microbiology*, 2254–2260 (2000).
- [21] R. S. Varma, Ed. Antifungal agents, In *Past, Present and Future Prospects* (National Academy and Biology, Lucknow, India, 1998).