

## DRUG SYNTHESIS

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION  
OF SOME NEW 1, 3-THIAZOLE-2,4-DIAMINE DERIVATIVESNADEEM SIDDIQUI<sup>1\*</sup>, SHAQUIQUZZAMAN<sup>1</sup>, MUJEEB UR RAHMAN<sup>1</sup>, M. FAIZ ARSHAD<sup>1</sup>,  
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**Abstract:** Various *N,N'*-diaryl-1,3-thiazole-2,4-diamines (**3a-w**) were synthesized by a three steps process. The structures of the synthesized compounds were confirmed by spectral data and elemental analyses. All the synthesized compounds were tested against two bacterial strains and two fungal strains. Bacterial strains included Gram positive *Staphylococcus aureus* and Gram negative *Escherichia coli* and fungal strains included *Monascus purpurea* and *Penicillium citrinum*. Most of the compounds showed moderate to good antibacterial as well as antifungal activity.

**Keywords:** diaminethiazole; aryl thioureas; antimicrobial activity

Nitrogen containing heterocycles with sulfur atom are an important class of compounds in medicinal chemistry. Thiazoles being an integral part of many potent biologically active molecules such as sulfathiazole (antimicrobial drug), ritonavir (antiretroviral drug), abafungin (antifungal drug) with trade name Abasol cream and bleomycin and tiazofurin (antineoplastic drugs) have been explored previously. It has been noticed continuously over the years that interesting biological activities (1, 2) were associated with thiazole derivatives. The applications of thiazoles were found in drug development for the treatment of allergies (3), hypertension (4), inflammation (5), schizophrenia (6), bacterial (7) and HIV infections (8), hypnotics (9) and more recently for the treatment of pain (10), as fibrinogen receptor antagonists with antithrombotic activity (11) and as new inhibitors of bacterial DNA gyrase B (12).

In view of the above mentioned findings, to identify new candidates that may be valued in designing new, potent, selective and less toxic antimicrobial agents, we report here the synthesis of some new *N,N'*-diaryl-1,3-thiazole-2,4-diamines (**3a-w**) in order to investigate their antimicrobial activity.

## EXPERIMENTAL

## Chemistry

The chemicals used for experimental work were commercially procured from various chemical units viz. E. Merck Ltd., CDH, s. d. Fine Chem. and Qualigens. The solvents and reagents were of LR grade and used without purification. The purity of compounds was routinely checked by thin layer chromatography (TLC) using silica gel G (Merck). Two solvent systems were used: ethyl acetate : hexane (1:1, v/v) and toluene : ethyl acetate : formic acid (5:4:1, v/v/v). Ashless Whatman (no.1) filter paper was used for vacuum filtration. Melting points were determined in open glass capillaries using Hicon melting point apparatus (Hicon, India) and are uncorrected. The proton magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on Burker 400 MHz instrument in DMSO-*d*<sub>6</sub>/CDCl<sub>3</sub> using tetramethylsilane [(CH<sub>3</sub>)<sub>4</sub>Si] as an internal standard. The infrared spectra of the compounds were recorded in KBr on Bio Rad FT-IR spectrometer, iodine chamber and UV lamp were used for visualization of TLC spots.

Synthesis of the title compounds (**3a-w**)2-Chloro-*N*-arylacetamides (**1a-d**)

The synthesis of 2-chloro-*N*-arylacetamide was carried out according to the procedure reported previ-

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ously (13). Chloroacetyl chloride (0.04 mol) was added to arylamines (0.02 mol) in dry toluene (30 mL) at 0-5°C. The reaction mixture was stirred for 4 h at room temperature and refluxed for 6 h. The solid obtained was washed with petroleum ether (40-60°C) and kept in refrigerator. The solid obtained was recrystallized from alcohol to yield the product (**1a-d**).

#### Preparation of arylthioureas (**2a-f**)

The synthesis of aryl thioureas was carried out according to the procedure reported previously (14). Respective arylamines (0.10 mol) were mixed with conc. HCl (2.4 mL, 0.10 mol) and ammonium thiocyanate (0.10 mol), dissolved in minimal amount of water. The resulting mixture was heated on water bath till the half of the original volume and a semi-solid mass was formed which on pouring into ice cold water gave respective arylthioureas. Recrystallization was made from ethanol. The physico-chemical and spectral data were found to be identical with those reported earlier (14).

#### *N,N'*-diaryl-1,3-thiazole-2,4-diamines (**3a-w**)

A mixture of 2-chloro-*N*-arylacetamide (**1a-d**) (0.02 mol) and substituted aryl thioureas (**2a-f**) (0.01 mol) was refluxed for 12 h in dry acetone (80 mL). An excess of solvent was removed by distillation and a solid obtained was poured into ice cold water, recrystallized from ethanol, washed with 2% sodium bicarbonate and dried to obtain compounds (**3a-w**).

#### *N*<sup>4</sup>-(4-nitrophenyl)-*N*<sup>2</sup>-phenyl-1,3-thiazole-2,4-diamine (**3a**)

IR (KBr, cm<sup>-1</sup>): 3543 (NH), 3250 (CH), 1810 (C=N), 1450 (NO<sub>2</sub>), 760 (C-S-C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ, ppm): 6.37 (s, 1H, CH, thiazole), 7.60-8.07 (m, 9H, Ar-H), 9.21 (s, 1H, NH), 10.94 (s, 1H, NH).

#### *N*<sup>4</sup>-(4-chlorophenyl)-*N*<sup>2</sup>-phenyl-1,3-thiazole-2,4-diamine (**3b**)

IR (KBr, cm<sup>-1</sup>): 3415 (NH), 3245 (CH), 1684 (C=N), 733 (C-S-C), 503(C-Cl). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 6.25 (s, 1H, CH, thiazole), 6.66-8.28 (m, 9H, Ar-H), 8.77 (s, 1H, NH), 10.76 (s, 1H, NH).

#### *N*<sup>4</sup>-(3,4-dichlorophenyl)-*N*<sup>2</sup>-phenyl-1,3-thiazole-2,4-diamine (**3c**)

IR (KBr, cm<sup>-1</sup>): 3250 (NH), 3200 (CH), 1656 (C=N), 746 (C-S-C), 684 (C-Cl). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 6.21 (s, 1H, CH, thiazole), 6.36-8.02 (m, 8H, Ar-H), 9.40 (s, 1H, NH), 10.94 (s, 1H, NH).

#### *N*<sup>4</sup>-(4-methylphenyl)-*N*<sup>2</sup>-phenyl-1,3-thiazole-2,4-diamine (**3d**)

IR (KBr, cm<sup>-1</sup>): 3477 (NH), 3464 (CH), 2850 (CH<sub>3</sub>), 1666 (C=N), 814 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 2.47 (s, 3H, -CH<sub>3</sub>), 6.31 (s, 1H, CH, thiazole), 6.85-8.41 (m, 9H, Ar-H), 8.99 (s, 1H, NH), 10.34 (s, 1H, NH).

#### *N*<sup>2</sup>-(4-fluorophenyl)-*N*<sup>4</sup>-(4-nitrophenyl)-1,3-thiazole-2,4-diamine (**3e**)

IR (KBr, cm<sup>-1</sup>): 3699 (NH), 3593 (CH), 1442 (NO<sub>2</sub>), 845 (C-F), 720 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 7.16 (s, 1H, CH, thiazole), 7.42-7.86 (m, 8H, Ar-H), 9.90 (s, 1H, NH), 10.43 (s, 1H, NH).

#### *N*<sup>4</sup>-(4-chlorophenyl)-*N*<sup>2</sup>-(4-fluorophenyl)-1,3-thiazole-2,4-diamine (**3f**)

IR (KBr, cm<sup>-1</sup>): 3400 (NH), 2842 (CH), 1862 (C=N), 954 (C-S-C), 830 (C-F), 750 (C-Cl). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 6.44 (s, 1H, CH, thiazole), 6.82-7.36 (m, 8H, Ar-H), 8.88 (s, 1H, NH), 10.56 (s, 1H, NH).

#### *N*<sup>4</sup>-(3,4-dichlorophenyl)-*N*<sup>2</sup>-(4-fluorophenyl)-1,3-thiazole-2,4-diamine (**3g**)

IR (KBr, cm<sup>-1</sup>): 3388 (NH), 3177 (CH), 1599 (C=N), 905 (C-F), 805 (C-Cl), 780 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 6.35 (s, 1H, CH, thiazole), 6.68-7.75 (m, 7H, Ar-H), 9.31 (s, 1H, NH), 12.77 (s, 1H, NH).

#### *N*<sup>2</sup>-(4-fluorophenyl)-*N*<sup>4</sup>-(4-methylphenyl)-1,3-thiazole-2,4-diamine (**3h**)

IR (KBr, cm<sup>-1</sup>): 3707 (NH), 3132 (CH), 1681 (C=N), 809 (C-F), 697 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 2.47 (s, 3H, -CH<sub>3</sub>), 6.76 (s, 1H, CH, thiazole), 6.94-7.90 (m, 8H, Ar-H), 8.58 (s, 1H, NH), 11.70 (s, 1H, NH).

#### *N*<sup>2</sup>-(2-methoxyphenyl)-*N*<sup>4</sup>-(4-nitrophenyl)-1,3-thiazole-2,4-diamine (**3i**)

IR (KBr, cm<sup>-1</sup>): 3698 (NH), 3564 (CH), 1605 (C=N), 1490 (NO<sub>2</sub>), 800 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 3.83 (s, 3H, -OCH<sub>3</sub>), 6.86 (s, 1H, CH, thiazole), 7.03-8.95 (m, 8H, Ar-H), 9.05 (s, 1H, NH), 12.00 (s, 1H, NH).

#### *N*<sup>4</sup>-(4-chlorophenyl)-*N*<sup>2</sup>-(2-methoxyphenyl)-1,3-thiazole-2,4-diamine (**3j**)

IR (KBr, cm<sup>-1</sup>): 3484 (NH), 3174 (CH), 1670 (C=N), 733 (C-Cl), 733 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 3.63 (s, 3H, -OCH<sub>3</sub>), 6.53 (s, 1H, CH, thiazole), 7.02-7.92 (m, 8H, Ar-H), 9.19 (s, 1H, NH), 10.17 (s, 1H, NH).

*N*<sup>4</sup>-(3,4-dichlorophenyl)-*N*<sup>2</sup>-(2-methoxyphenyl)-1,3-thiazole-2,4-diamine (**3k**)

IR (KBr, cm<sup>-1</sup>): 3463 (NH), 3190 (CH), 1600 (C=N), 804 (C-S-C), 801 (C-Cl). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 3.61 (s, 3H, -OCH<sub>3</sub>), 6.63 (s, 1H, CH, thiazole), 7.01-8.20 (m, 7H, Ar-H), 9.21 (s, 1H, NH), 10.33 (s, 1H, NH).

*N*<sup>2</sup>-(2-methoxyphenyl)-*N*<sup>4</sup>-(4-methylphenyl)-1,3-thiazole-2,4-diamine (**3l**)

IR (KBr, cm<sup>-1</sup>): 3607 (NH), 2997 (CH), 1872 (C=N), 720 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 2.31 (s, 3H, -CH<sub>3</sub>), 4.16 (s, 3H, -OCH<sub>3</sub>), 6.51 (s, 1H, CH, thiazole), 7.13-7.41 (m, 8H, Ar-H), 8.18 (s, 1H, NH), 9.41 (s, 1H, NH).

*N*<sup>2</sup>-(2-methylphenyl)-*N*<sup>4</sup>-(4-nitrophenyl)-1,3-thiazole-2,4-diamine (**3m**)

IR (KBr, cm<sup>-1</sup>): 3484 (NH), 3250 (CH), 1621 (C=N), 1473 (NO<sub>2</sub>), 742 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 2.46 (s, 3H, -CH<sub>3</sub>), 6.50 (s, 1H, CH, thiazole), 6.69-8.04 (m, 8H, Ar-H), 9.40 (s, 1H, NH), 10.22 (s, 1H, NH).

*N*<sup>4</sup>-(4-chlorophenyl)-*N*<sup>2</sup>-(2-methylphenyl)-1,3-thiazole-2,4-diamine (**3n**)

IR (KBr, cm<sup>-1</sup>): 3379 (NH), 3146 (CH), 823 (C-Cl), 750 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 2.26 (s, 3H, -CH<sub>3</sub>), 6.82 (s, 1H, CH, thiazole), 7.04-7.74 (m, 8H, Ar-H), 9.73 (s, 1H, NH), 10.82 (s, 1H, NH).

*N*<sup>4</sup>-(3,4-dichlorophenyl)-*N*<sup>2</sup>-(2-methylphenyl)-1,3-thiazole-2,4-diamine (**3o**)

IR (KBr, cm<sup>-1</sup>): 3430 (NH), 3171 (CH), 1594 (C=N), 867 (C-Cl), 815 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 2.34 (s, 3H, -CH<sub>3</sub>), 6.64 (s, 1H, CH, thiazole), 6.82-7.76 (m, 7H, Ar-H), 11.05 (s, 1H, NH, D<sub>2</sub>O exchangeable), 14.04 (s, 1H, NH, D<sub>2</sub>O exchangeable).

*N*<sup>2</sup>-(2-methylphenyl)-*N*<sup>4</sup>-(4-methylphenyl)-1,3-thiazole-2,4-diamine (**3p**)

IR (KBr, cm<sup>-1</sup>): 3285 (NH), 3204 (CH), 1672 (C=N), 724 (C-S-C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ, ppm): 2.39 (s, 3H, -CH<sub>3</sub>), 2.43 (s, 3H, -CH<sub>3</sub>), 6.59 (s, 1H, CH, thiazole), 7.02-7.86 (m, 8H, Ar-H), 9.14 (s, 1H, NH), 10.21 (s, 1H, NH).

*N*<sup>2</sup>-(3-methylphenyl)-*N*<sup>4</sup>-(4-nitrophenyl)-1,3-thiazole-2,4-diamine (**3q**)

IR (KBr, cm<sup>-1</sup>): 3250 (NH), 2900 (CH), 1670 (C=N), 1487 (NO<sub>2</sub>), 832 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 2.41 (s, 3H, -CH<sub>3</sub>), 6.53

(s, 1H, CH, thiazole), 6.92-8.09 (m, 8H, Ar-H), 9.16 (s, 1H, NH), 10.23 (s, 1H, NH).

*N*<sup>4</sup>-(4-chlorophenyl)-*N*<sup>2</sup>-(3-methylphenyl)-1,3-thiazole-2,4-diamine (**3r**)

IR (KBr, cm<sup>-1</sup>): 3255 (NH), 2931 (CH), 1688 (C=N), 832 (C-Cl), 832 (C-S-C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ, ppm): 2.69 (s, 3H, -CH<sub>3</sub>), 6.89 (s, 1H, CH, thiazole), 6.91-7.84 (m, 8H, Ar-H), 9.38 (s, 1H, NH), 9.97 (s, 1H, NH).

*N*<sup>4</sup>-(3,4-dichlorophenyl)-*N*<sup>2</sup>-(3-methylphenyl)-1,3-thiazole-2,4-diamine (**3s**)

IR (KBr, cm<sup>-1</sup>): 3649 (NH), 3144 (CH), 1771 (C=N), 689 (C-Cl), 549 (C-S-C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ, ppm): 2.38 (s, 3H, -CH<sub>3</sub>), 6.63 (s, 1H, CH, thiazole), 7.13-8.26 (m, 7H, Ar-H), 9.03 (s, 1H, NH), 10.20 (s, 1H, NH).

*N*<sup>2</sup>-(3-methylphenyl)-*N*<sup>4</sup>-(4-methylphenyl)-1,3-thiazole-2,4-diamine (**3t**)

IR (KBr, in cm<sup>-1</sup>): 3236 (NH), 3182 (CH), 1620 (C=N), 738 (C-S-C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ, ppm): 2.41 (s, 3H, -CH<sub>3</sub>), 2.52 (s, 3H, -CH<sub>3</sub>), 6.65 (s, 1H, CH, thiazole), 7.15-7.81 (m, 8H, Ar-H), 9.04 (s, 1H, NH), 10.35 (s, 1H, NH).

*N*<sup>2</sup>-(4-methoxyphenyl)-*N*<sup>4</sup>-(4-nitrophenyl)-1,3-thiazole-2,4-diamine (**3u**)

IR (KBr, cm<sup>-1</sup>): 3497 (NH), 3210 (CH), 1635 (C=N), 1460 (NO<sub>2</sub>), 760 (C-S-C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ, ppm): 3.59 (s, 3H, -OCH<sub>3</sub>), 6.08 (s, 1H, CH, thiazole), 6.97-8.03 (m, 8H, Ar-H), 9.16 (s, 1H, NH), 10.23 (s, 1H, NH).

*N*<sup>4</sup>-(4-chlorophenyl)-*N*<sup>2</sup>-(4-methoxyphenyl)-1,3-thiazole-2,4-diamine (**3v**)

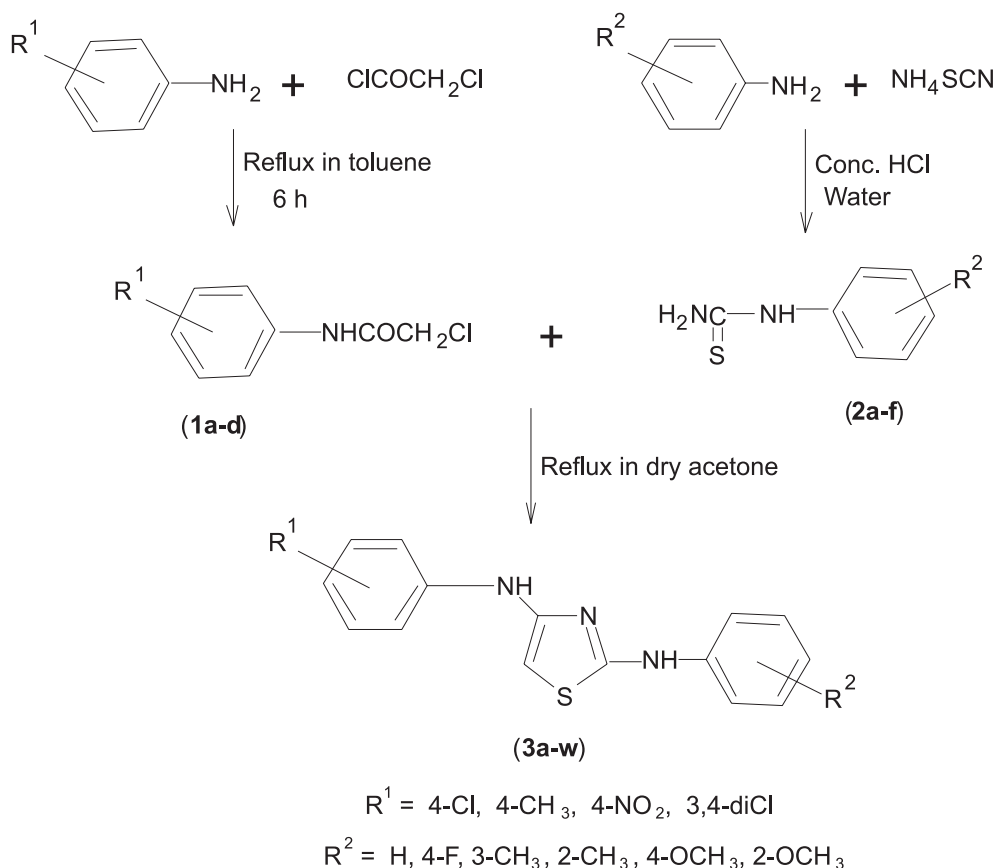
IR (KBr, cm<sup>-1</sup>): 3640 (NH), 3197 (CH), 1835 (C=N), 826 (C-Cl), 710 (C-S-C). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 3.52 (s, 3H, -OCH<sub>3</sub>), 6.61 (s, 1H, CH, thiazole), 7.01-7.85 (m, 8H, Ar-H), 9.27 (s, 1H, NH), 10.32 (s, 1H, NH).

*N*<sup>4</sup>-(3,4-dichlorophenyl)-*N*<sup>2</sup>-(4-methoxyphenyl)-1,3-thiazole-2,4-diamine (**3w**)

IR (KBr, cm<sup>-1</sup>): 3514 (NH), 3137 (CH), 1634 (C=N), 823 (C-S-C), 710 (C-Cl). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 3.55 (s, 3H, -OCH<sub>3</sub>), 6.48 (s, 1H, CH, thiazole), 7.05-8.05 (m, 7H, Ar-H), 9.13 (s, 1H, NH), 10.21 (s, 1H, NH).

#### Antimicrobial activity

The microorganisms were obtained from Majeedia Hospital, Department of Biochemistry,



Scheme 1.

Jamia Hamdard. Three concentrations of test compounds were prepared i.e. 50 µg/mL, 100 µg/mL and 200 µg/mL. Antimicrobial activity of the compounds has been evaluated using standard methods (15, 16).

#### Antibacterial activity

The nutrient agar medium was prepared and autoclaved at 15.1 lbs pressure for 20 min. This medium was poured into Petri plates and allowed to solidify. On the surface of media microbial suspension was spread with the help of sterilized cotton swab. Cups were made by boring into agar surface with a previously sterilized cork borer and scooping out the punched part of agar. Five cups were made in each Petri plate and into these cups was added the concentration (50 µg/mL, 100 µg/mL, 200 µg/mL) of the test compounds, fourth was filled with the standard, amikacin, and fifth was filled with the control (DMSO).

The plates were kept in cold for one hour to allow the diffusion of test compounds and then incubated at  $37 \pm 0.5^\circ\text{C}$  for 24 h for antibacterial activity. The zone of inhibition formed around the cups after respective incubation was measured and percentage inhibition of the compounds were calculated.

#### Antifungal activity

For antifungal screening, spore suspension (5 mL) of each test microorganism (72 h culture) was added to sterilized Sabouraud dextrose agar medium at  $35\text{--}40^\circ\text{C}$  with shaking. The Petri dishes were seeded with the mixture and the filter paper discs of test compounds (concentration 50 µg/mL, 100 µg/mL, 200 µg/mL), reference drug, Griseofulvin and control (DMSO) were placed in the same manner as in antibacterial activity determination. These Petri dishes were incubated at  $30 \pm 1^\circ\text{C}$  for 48 h. The zone of inhibition of growth was considered as an indicator for the antifungal activity.

Table 1. Physicochemical parameters of synthesized compounds (3a-w).

Compd.	Molecular formula	R <sup>1</sup>	R <sup>2</sup>	M.p. (°C)	Yield (%)	R <sub>f</sub>
3a	C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> S	4-NO <sub>2</sub>	H	120-122	64	0.46 <sup>a</sup>
3b	C <sub>15</sub> H <sub>12</sub> ClN <sub>3</sub> S	4-Cl	H	110-112	56	0.55 <sup>a</sup>
3c	C <sub>15</sub> H <sub>11</sub> Cl <sub>2</sub> N <sub>3</sub> S	3,4-diCl	H	68-70	50	0.57 <sup>a</sup>
3d	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> S	4-CH <sub>3</sub>	H	200-202	76	0.50 <sup>a</sup>
3e	C <sub>15</sub> H <sub>11</sub> FN <sub>4</sub> O <sub>2</sub> S	4-NO <sub>2</sub>	4-F	128-130	82	0.64 <sup>b</sup>
3f	C <sub>15</sub> H <sub>11</sub> ClFN <sub>3</sub> S	4-Cl	4-F	178-180	84	0.70 <sup>b</sup>
3g	C <sub>15</sub> H <sub>10</sub> Cl <sub>2</sub> FN <sub>3</sub> S	3,4-diCl	4-F	90-92	62	0.62 <sup>b</sup>
3h	C <sub>16</sub> H <sub>14</sub> FN <sub>3</sub> S	4-CH <sub>3</sub>	4-F	158-160	72	0.66 <sup>a</sup>
3i	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> S	4-NO <sub>2</sub>	2-OCH <sub>3</sub>	118-120	56	0.58 <sup>a</sup>
3j	C <sub>16</sub> H <sub>14</sub> ClN <sub>3</sub> OS	4-Cl	2-OCH <sub>3</sub>	122-124	60	0.72 <sup>b</sup>
3k	C <sub>16</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>3</sub> OS	3,4-diCl	2-OCH <sub>3</sub>	102-104	66	0.60 <sup>b</sup>
3l	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> OS	4-CH <sub>3</sub>	2-OCH <sub>3</sub>	150-152	70	0.44 <sup>a</sup>
3m	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> S	4-NO <sub>2</sub>	2-CH <sub>3</sub>	98-100	93	0.65 <sup>a</sup>
3n	C <sub>16</sub> H <sub>14</sub> ClN <sub>3</sub> S	4-Cl	2-CH <sub>3</sub>	110-112	85	0.77 <sup>a</sup>
3o	C <sub>16</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>3</sub> S	3,4-diCl	2-CH <sub>3</sub>	38-40	75	0.56 <sup>a</sup>
3p	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> S	4-CH <sub>3</sub>	2-CH <sub>3</sub>	118-120	80	0.77 <sup>a</sup>
3q	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> S	4-NO <sub>2</sub>	3-CH <sub>3</sub>	100-102	90	0.52 <sup>b</sup>
3r	C <sub>16</sub> H <sub>14</sub> ClN <sub>3</sub> S	4-Cl	3-CH <sub>3</sub>	138-140	92	0.76 <sup>b</sup>
3s	C <sub>16</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>3</sub> S	3,4-diCl	3-CH <sub>3</sub>	68-70	89	0.72 <sup>a</sup>
3t	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> S	4-CH <sub>3</sub>	3-CH <sub>3</sub>	126-128	85	0.63 <sup>a</sup>
3u	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> S	4-NO <sub>2</sub>	4-OCH <sub>3</sub>	128-130	60	0.43 <sup>a</sup>
3v	C <sub>16</sub> H <sub>14</sub> ClN <sub>3</sub> OS	4-Cl	4-OCH <sub>3</sub>	64-66	50	0.82 <sup>b</sup>
3w	C <sub>16</sub> H <sub>13</sub> Cl <sub>2</sub> N <sub>3</sub> OS	3,4-diCl	4-OCH <sub>3</sub>	40-42	55	0.67 <sup>b</sup>

Elemental analyses for C, H and N were within  $\pm 0.4\%$  of the theoretical values. <sup>a</sup>R<sub>f</sub> in ethyl acetate : hexane (1 : 1, v/v), <sup>b</sup>R<sub>f</sub> in and toluene : ethyl acetate : formic acid (5 : 4 : 1, v/v/v)

## RESULTS AND DISCUSSION

In the present work, the synthesis of titled compounds (3a-w) was carried out according to Scheme 1. Respective aryl amines were refluxed with chloroacetyl chloride in toluene to get 2-chloro-*N*-arylacetamides (1a-d). On the other hand, when respective aryl amines were treated with ammonium thiocyanates under acidic conditions, it led to the formation of substituted arylthioureas (2a-e). Compounds (1a-d) and (2a-e) were refluxed in dry acetone for 12 h to afford *N,N'*-diaryl-1,3-thiazole-2,4-diamines (3a-w). The physical parameters are given in Table 1.

All the synthesized compounds were characterized by IR and <sup>1</sup>H NMR analysis. The IR spectra showed bands at 3707-3240 cm<sup>-1</sup> which was attributed to the NH-stretching. Bands at 3293-2782 cm<sup>-1</sup>

were of aromatic CH-stretching. The bands of (C=N) were observed in the range of 1875-1594 cm<sup>-1</sup> whereas the bands of (C-S-C) were found to be at 954-503 cm<sup>-1</sup> range.

<sup>1</sup>H NMR spectra showed a singlet at  $\delta$  value 2.26-2.69 ppm, which was attributed to -CH<sub>3</sub> protons. A singlet at  $\delta$  value 3.52-4.16 ppm confirmed the presence of -OCH<sub>3</sub> protons. A multiplet at the aromatic region in the range of  $\delta$  value 6.36-8.95 ppm showed the presence of aromatic protons. The proton of thiazole came in the range of 6.08-7.16 ppm. There were two broad singlets present downfield which showed the presence of two -NH protons. These were present in the range of 8.18-11.05 and 9.41-14.04 ppm. The presence of all desired peaks confirmed the structures of the synthesized compounds.

All the compounds (3a-w) were screened for antibacterial activity against *S. aureus* (Gram posi-

Table 2. The antimicrobial activity of compounds (3a-w) against bacterial and fungal strains.

Compd.	% zone of inhibition at the concentration of 50, 100 and 200 µg/mL <sup>a</sup>											
	<i>E. coli</i>			<i>S. aureus</i>			<i>M. purpurea</i>			<i>P. citrinum</i>		
	50	100	200	50	100	200	50	100	200	50	100	200
<b>3a</b>	53	53	66	57	62	65	61	70	75	66	72	66
<b>3b</b>	69	66	72	57	68	65	53	58	70	46	50	61
<b>3c</b>	69	73	72	57	62	75	66	70	70	60	61	66
<b>3d</b>	46	60	72	50	62	60	73	70	65	73	72	71
<b>3e</b>	38	46	61	42	50	55	46	52	60	33	38	47
<b>3f</b>	46	53	55	35	43	50	40	47	50	46	50	57
<b>3g</b>	53	60	72	42	56	60	40	52	55	40	50	66
<b>3h</b>	53	53	66	50	62	60	33	41	45	40	44	47
<b>3i</b>	61	73	77	57	68	65	60	70	75	66	66	66
<b>3j</b>	61	66	66	71	75	75	53	58	65	46	72	66
<b>3k</b>	61	66	72	71	68	70	46	58	75	60	61	71
<b>3l</b>	69	66	72	42	50	50	66	70	65	73	72	71
<b>3m</b>	46	53	55	64	68	70	73	76	75	66	72	76
<b>3n</b>	46	60	66	42	50	50	40	52	65	40	50	52
<b>3o</b>	53	60	72	35	56	60	46	58	70	40	55	52
<b>3p</b>	38	46	55	50	62	60	33	41	50	33	44	57
<b>3q</b>	46	53	61	57	62	65	66	70	75	73	72	71
<b>3r</b>	61	73	72	57	56	60	60	64	65	53	55	66
<b>3s</b>	53	66	72	64	75	70	66	70	70	53	66	71
<b>3t</b>	69	66	66	35	50	60	73	70	75	40	55	61
<b>3u</b>	69	66	77	64	75	75	66	76	75	73	72	76
<b>3v</b>	76	73	77	64	68	70	46	52	60	66	72	76
<b>3w</b>	69	73	72	64	68	75	66	70	65	33	38	47
amikacin	100	100	100	100	100	100	-	-	-	-	-	-
grieseofulvin	-	-	-	-	-	-	100	100	100	100	100	100

<sup>a</sup>The percent zone of inhibition was calculated against the bacterial strains *Staphylococcus aureus* NCTC (10418) and *Escherichia coli* NCTC (6571). The fungal strains used were *Monascus purpurea* NBIMCC 2325 and *Penicillium citrinum* CCRC 93002.

tiveve) and *E. coli* (Gram negativeve) strains and the results are shown in Table 2. Most of the compounds showed moderate to good antibacterial activity against the Gram positive bacteria in the range of 35–71% at the concentration of 50 µg/mL. Compounds that have shown > 50% inhibition include **3a**, **3b**, **3c**, **3i**, **3j**, **3k**, **3m**, **3q**, **3r**, **3s**, **3u**, **3v** and **3w**. These compounds showed even better inhibition when tested at higher concentration (100 µg/mL and 200 µg/mL) comparative to the standard drug, amikacin. Compounds that showed highly significant activity were **3j**, **3k**, **3m**, **3s**, **3u**, **3v** and **3w**. These compounds displayed in the range of 64–71% inhibition at 50 µg/mL concentration. When tested

at a concentration of 100 µg/mL, these compounds showed 68–75% inhibition. When the concentration further increased no significant change in inhibition was observed for the compounds, as it remained in the range of 70–75%.

These compounds also showed moderate to good antibacterial activity against the *E. coli* bacteria in the range of 38–77% at the concentration of 50 µg/mL. Compounds that have shown > 50% inhibition include **3a**, **3b**, **3c**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3o**, **3r**, **3s**, **3t**, **3u**, **3v** and **3w**. These compounds showed even better inhibition when tested at higher concentration (100 µg/mL and 200 µg/mL) comparative to the standard drug, amikacin. Compounds that

showed highly significant activity were found to be **3b**, **3c**, **3l**, **3t**, **3u**, **3v** and **3w**. These compounds displayed the activity in the range of 69–76% at 50 µg/mL concentration. When tested at a concentration of 100 µg/mL, these compounds showed 66–73% inhibition. When the concentration further increased, no significant change in inhibition was observed for the compounds (72–77%).

A majority of the compounds showed moderate to good antifungal activity against *Monascus purpurea* in the range of 33–73% at the concentration of 50 µg/mL. Compounds that have shown > 50% inhibition include **3a**, **3b**, **3c**, **3d**, **3i**, **3j**, **3l**, **3m**, **3q**, **3r**, **3s**, **3t**, **3u** and **3w**. These compounds showed even better inhibition when tested at higher concentration (100 µg/mL and 200 µg/mL) comparative to the standard drug, griseofulvin. Compounds that showed highly significant activity were **3c**, **3d**, **3l**, **3m**, **3q**, **3s**, **3t**, **3u** and **3w**. These compounds displayed inhibition in the range of 66–73% at 50 µg/mL concentration. When tested at a concentration of 100 µg/mL, these compounds showed 70–76% inhibition. When the concentration further increased, no significant change in inhibition was observed for the compounds as it remained in the range of 65–75%.

A number of the compounds showed moderate to good antifungal activity against the *Penicillium citrinum* in the range of 33–73% at the concentration of 50 µg/mL. Compounds that have shown > 50% inhibition include **3a**, **3c**, **3d**, **3i**, **3k**, **3l**, **3m**, **3q**, **3r**, **3s**, **3u** and **3v**. These compounds showed even better inhibition when tested at higher concentration (100 µg/mL and 200 µg/mL) comparative to the standard drug, griseofulvin. Compounds that showed highly significant activity were **3a**, **3d**, **3i**, **3l**, **3m**, **3q**, **3u** and **3v**. These compounds displayed inhibition in the range of 66–73% at 50 µg/mL concentration. When tested at a concentration of 100 µg/mL, these compounds showed 66–72% inhibition. When the concentration further increased, no significant change in inhibition is observed for the compounds as it remained in the range of 66–76%.

Structure activity relationships of the compounds were studied and it was observed that the chloro substituted derivatives were the most active of the series. All the compounds that showed significant activity were either mono or di-chloro substituted derivatives. Introduction of another chloro group tends to increase the activity in some compounds (**3c** and **3w**). Substitutions at the other phenyl ring also changed the activity as the fluoro substituted and methyl substituted derivatives were the least active of the series.

The unsubstituted derivatives and the methoxy-substituted derivatives were more active than the other compounds of the series. This may lead to the conclusion that if one of the phenyl ring is substituted with an electron withdrawing group of optimum size and the other phenyl ring is substituted with an electron releasing group of optimum size, the activity of the compounds is increased significantly.

## CONCLUSIONS

In conclusion, it can be stated that the synthesized thiazole derivatives (**3a-w**) can be regarded as a newer class of antimicrobial agents with broad spectrum of activity against both bacteria and fungi. They need to be explored further to get better agents, which could add to the current antimicrobial therapy.

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