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Synthesis and antimicrobial activity of some thiazole and 1,3,4-oxadiazole hybrid heterocycles

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Among the 5-membered nitrogen heterocycles, the privileged scaffolds thiazole and 1,3,4-oxadiazole have been incorporated in a single molecular framework to explore new potential antimicrobial agents. The newly synthesized compounds **5a-l** have been synthesized and characterized by IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The structures of the synthesized compounds are in full agreement with proposed structures and they have been evaluated for their *in vitro* antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and antifungal activity against *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* using serial broth dilution method.

Keywords: Thiazole, 1,3,4-oxadiazole, hybrid molecules, antibacterial activity, antifungal activity, MIC

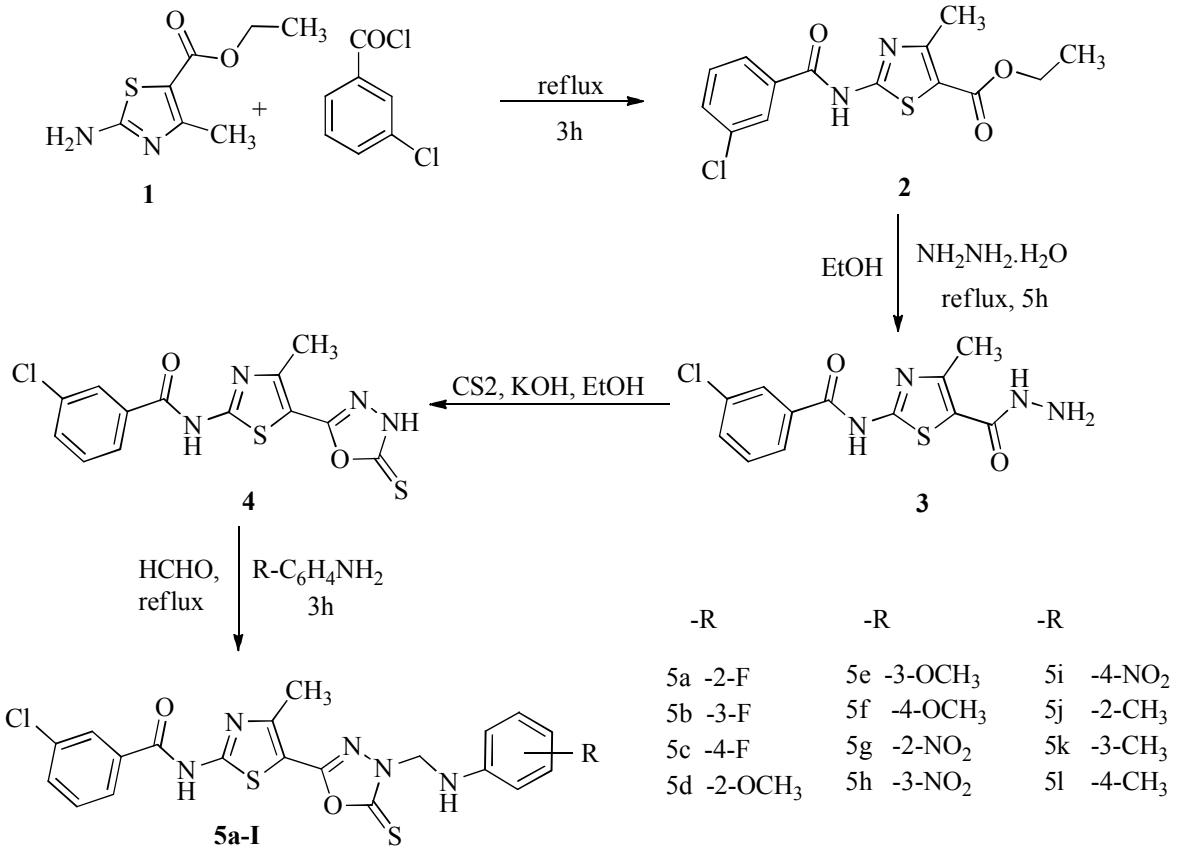
Antimicrobial infections have taken up centre stage as they are among the most common diseases and it is dreaded that they would be most prevalent disease in humans in the future. The rise of "Antimicrobial resistance" (AMR) is complex and a severe health problem. The increasing rate of infection caused by rapid expansion of AMR has reached alarming levels. Ample attention is given by medicinal chemists to thiazole and 1,3,4-oxadiazole motifs for the development of many drugs with diverse biological activities. A potential solution to counteract antibiotic resistance is to design and explore innovative heterocyclic scaffolds with novel modes of action. In this context, thiazole derivatives have played a crucial role in medicinal chemistry. Thiazoles flaunt a wide range of biological activities like antimicrobial[1-5], analgesic[6,7], anticonvulsant[8,9], antioxidant[10], hypolipidemic[11], anti-HIV-1 [12,13], adenosine receptor antagonist[14,15] and osteoporosis inhibitor[16].

On the other hand 1,3,4-oxadiazole is an essential class of heterocyclic motif with a broad spectrum of biological activities. Potent pharmacological activity of 1,3,4-oxadiazoles can be attributed to the presence of toxophoric –N=C-O- linkage which may react with the nucleophilic centers of the microbial cell[17]. Substituted 1,3,4-oxadiazoles possess noteworthy biological properties such as antibacterial[18], antifungal[19], anti-inflammatory[20], analgesic[21] and anticonvulsant[22-27] properties. 1,3,4-Oxadiazole heterocycles are very good bioisosteres of amides and esters, contributing substantially to increase their pharmacological activity by participating in hydrogen bonding interactions with the receptors[28].

Results and Discussion

Synthetic routes of the target compounds are depicted in Scheme I. Ethyl 2-amino-4-methylthiazole-5-carboxylate **1** was taken as a starting material and reacted with 3-chloro benzoyl chloride to afford ethyl 2-(3-chlorobenzamido)-4-methylthiazole-5-carboxylate **2**, which on further reaction with hydrazine hydrate in ethanol (99.9%) yielded intermediate 3-chloro-*N*-(5-(hydrazinecarbonyl)-4-methylthiazol-2-yl)benzamide **3**. The intermediate **3** was refluxed with carbon disulphide in presence of potassium hydroxide in ethanol (99.9%) to yield intermediate 3-chloro-*N*-(4-methyl-5-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) thiazol-2-yl)benzamide **4**. On Mannich condensation, intermediate **4** with 36% formaldehyde and substituted aniline derivatives in ethanol (99.9%) furnished the desired compounds **5a-l**.

The structures of final compounds **5a-l** were established by spectral analysis. Using compound **5a** as a representative compound, IR spectrum of **5a** showed absorption bands at 3322 and 3293 cm^{-1}



Scheme I — Synthetic route for the preparation of title compounds **5a-l**

corresponded to –NH stretching of secondary amine and –NH stretching of amide. A strong absorption band appearing at 1709 cm^{-1} was assigned to >C=O group. Singlets at δ 2.43, 4.02, 4.44 and 9.16 in ^{1}H NMR were due to (i) $–CH_3$ in anilide group, (ii) secondary amine, (iii) $-CH_2-$ and (iv) -NH amide group respectively. Multiplet signals at δ 6.58-7.92 were observed due to aromatic ring protons. Characteristic peaks at δ 134.4, 165.7 and 177.1 in ^{13}C NMR corresponded to the presence of –C-Cl, >C=O in anilide group and >C=S in heterocyclic ring respectively. Molecular ion peak in mass spectrum at *m/z* 475.95 [M+] was in agreement with molecular weight of compound **5a**. All the targeted compounds were screened for their *in vitro* antimicrobial activity against diverse bacterial and fungal strains by the conventional broth-dilution method[29] using Ciprofloxacin and Griseofulvin as standard drugs. The results of antimicrobial studies are presented in Table I.

Intermediates **2**, **3** and **4** exhibited poor antimicrobial activity against all tested strains as compared to the title compounds **5a-l**. Examination of the antimicrobial data in Table I revealed that all the final compounds showed better results against examined bacterial strains than fungal strains. Compounds **5b**, **5c**, **5h** and **5i** showed proficient activity against all the bacterial strains with MIC in the range of 12.5–100 μg/mL. Compounds **5c** and **5i** with MIC value in the range 12.5–50.0 μg/mL showed 2-4 fold higher MIC than standard drug Ciprofloxacin and hence were deemed to be the most potent compounds. Compounds **5c** and **5h** are equipotent to standard Ciprofloxacin against *P. aruginosa*. Compounds **5b** and **5h** showed comparable antibacterial activity with MIC values 50-100 μg/mL. Result of biological activity revealed that substitution pattern on phenyl skeleton plays a major role in case of antibacterial activity *i.e.*, most active compounds have inductively electron withdrawing substituent at *meta* or *para* position of the phenyl ring. In addition to this, the results of the antifungal activity indicated that compound **5f** adorned with methoxy group to be the most potent

Table I—Results of antibacterial and antifungal screening of compounds **5a-l**

Entry	-R	Minimum inhibitory concentration (MIC) µg/mL						
		Gram-negative[a]		Gram-positive[b]		Fungi[c]		
		Ec	Pa	Sa	Sp	Ca	An	Ac
2	-	>1000	1000	>1000	1000	500	>1000	500
3	-	>1000	>1000	1000	>1000	>1000	>1000	1000
4	-	>1000	>1000	>1000	1000	500	>1000	>1000
5a	-2-F	500	500	250	500	500	1000	500
5b	-3-F	100	100	50	100	>1000	1000	500
5c	-4-F	12.5	50	12.5	25	>1000	1000	500
5d	-2-OCH_3	>1000	1000	>1000	1000	500	>1000	500
5e	-3-OCH_3	>1000	>1000	1000	250	>1000	250	1000
5f	-4-OCH_3	>1000	>1000	1000	500	12.5	12.5	50
5g	-2-NO_2	>1000	500	1000	100	>1000	1000	250
5h	-3-NO_2	100	50	100	100	500	1000	>1000
5i	-4-NO_2	25	12.5	12.5	25	>1000	250	500
5j	-2-CH_3	500	500	>1000	>1000	>1000	>1000	>1000
5k	-3-CH_3	500	250	500	500	500	1000	>1000
5l	-4-CH_3	>1000	500	1000	1000	500	250	>1000
Ciprofloxacin		25	25	50	50	--	--	--
Griseofulvin		--	--	--	--	500	100	100

[a]Ec: *Escherichia coli* MTCC 443; Pa: *Pseudomonas aeruginosa* MTCC 1688;
[b]Sa: *Staphylococcus aureus* MTCC 96; Sp: *Staphylococcus pyogenes* MTCC 442;
[c]Ca: *Candida albicans* MTCC 227; An: *Aspergillus niger* MTCC 282; Ac: *Aspergillus clavatus* MTCC 1323.

antifungal agent. It displayed MIC in the range of 12.5-50 µg/mL against three fungal strains keeping Griseofulvin as a positive control.

Structure activity relationship

The outcome of the antimicrobial screening revealed that in case of structural activity relationship (SAR); the substitution pattern of 1,3,4-oxadiazole derivatives is affected by the electronic environment and hence antimicrobial activity was also altered. In general, compounds **5a-l** showed better antibacterial activity than antifungal activity. Compounds **5b**, **5c**, **5f**, **5h** and **5i** emerged as the most promising antimicrobial agents with MIC in the range of 12.5-100 µg/mL as compared to standard drugs. Antimicrobial activity was substantially affected by substitution pattern on the phenyl ring. The activity results revealed that the electron withdrawing groups enhanced antibacterial activity while electron releasing group increased antifungal activity. The highest antibacterial activity was observed when the electron withdrawing substituents were present at *para* position (**5c** and **5i**) rather than the presence of electron withdrawing substituents at *ortho* or *meta* positions (**5a**, **5b**, **5g** and **5h**) of the phenyl ring. In the case of antifungal activity, the trend alters and compound **5f** emerged as the most potent antifungal compound with electron releasing substituent at *para* position of phenyl ring.

Biological evaluation

Antibacterial assay

The newly synthesized compounds were screened for their antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* (MTCC-96), *Streptococcus pyogenes* (MTCC-442)) and Gram-negative bacteria (*Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688)). Antibacterial activity was measured as per National Committee for Clinical Laboratory Standards (NCCLS) protocol by Mueller-Hinton Broth (Becton-Dickinson, USA)[16-18]. Standard strains were procured from the Institute of Microbial Technology, Chandigarh. Compounds were primarily screened for their antibacterial activity in six sets against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes* at different concentrations of 1000, 500 and 250 µg/mL as shown in Table I. The drugs found to be active in primary screening were similarly diluted to obtain 200, 125, 100, 62.5, 50, 25 and 12.5 µg/mL concentrations for secondary screening to test in a second set of dilutions

against all microorganisms. The antibacterial activity is carried out as per the protocol[19]. The standard drug used in the present study was Ciprofloxacin for evaluating antibacterial activity which showed 25, 25, 50 and 50 µg/mL MIC against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* respectively.

Antifungal assay

The same compounds were tested for antifungal activity as primary screening in six sets against *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* at various concentrations of 1000, 500, 200 and 100 µg/mL as shown in Table I. Results were recorded in the form of primary and secondary screening. Synthesized compounds were diluted to 1000 µg/mL concentration, as stock solution. Those synthesized compounds which were found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. *Griseofulvin* was used as a standard drug for antifungal activity, which showed 500, 100 and 100 µg /mL MIC against *C. albicans*, *A. Niger* and *A. Clavatus* respectively. 2% DMSO and sterilized distilled water was used as negative control, while *Griseofulvin* (1 U strength) was used as positive control. Results of antimicrobial evaluation of derivatives **5a-l** are shown in Table I. For fungal growth, in the present protocol, we have used Sabourauds dextrose broth at 28°C in aerobic condition for 48 h.

Experimental Section

All reactions except those in aqueous media were carried out by standard techniques with the exclusion of moisture. Melting points were determined on an electro thermal melting point apparatus and are reported uncorrected. TLC on silica gel plates (Merck, 60, F_{254}) was used for checking homogeneity and reaction monitoring. Column chromatography over silica gel (Merck, 70–230 and 230–400 mesh ASTH for flash chromatography) was applied when necessary to isolate and purify the reaction products. Elemental analysis (% C, H, and N) was carried out using a Perkin-Elmer 2400 CHN analyzer. IR spectra of all compounds have been recorded on a Perkin-Elmer FT-IR spectrophotometer in KBr. ^{1}H NMR spectra were recorded on Varian Gemini 300 MHz and ^{13}C NMR spectra on Varian Mercury-400, 100 MHz in DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Shimadzu LCMS 2010 spectrometer. Anhydrous reactions were carried out in oven dried glassware in nitrogen atmosphere.

Preparation of ethyl 2-(3-chlorobenzamido)-4-methylthiazole-5-carboxylate, 2

In a round bottom flask, a mixture of 2-amino-4-methyl-1,3-thiazole-5-carboxylate (0.01 mol) and pyridine (40 mL) was taken and 3-chloro benzoyl chloride (0.01 mol) was added drop-wise at 0-5°C. The mixture was stirred at a temperature not exceeding 5°C for 3 h. The solution was poured into ice-cold water. The solid product was filtered and washed with cold dilute hydrochloric acid solution to remove excess 2-amino-4-methyl-1,3-thiazole-5-carboxylate. The resulting solid was purified by recrystallization from ethanol (99%). Yield 47%; m.p. 125°C; IR (KBr): 3283 (-NH, -CONH-), 3081 (C-H, aromatic), 2974 (C-H, CH_3), 1711 (C=O), 1301 (C-H bending), 748 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.25 (t, 3H, CH_3, ester group), 2.46 (s, 3H, -N-C(CH_3)-C-), 4.28 (m, 2H, CH_2, ester group), 7.55-8.00 (m, 4H, Ar-H), 9.13 (s, 1H, -CONH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.2, 16.4, 60.7, 116.0, 125.4, 127.6, 130.1, 132.3, 134.5, 135.5, 156.4, 162.5, 163.0, 165.6; LCMS: *m/z* 324.5 (M^+). Anal. Calcd for $C_{14}H_{13}ClN_2O_3S$: C, 51.77; H, 4.03; N, 8.63. Found: C, 51.74; H, 4.06; N, 8.60%.

Preparation of 3-chloro-*N*-(5-(hydrazinecarbonyl)-4-methylthiazol-2-yl)benzamide, 3

Ethyl 2-(3-chlorobenzamido)-4-methylthiazole-5-carboxylate **2** (0.01 mol) and 99% hydrazine hydrate (0.015 mol) were taken in a round bottom flask and the mixture was refluxed for 10 min. Alcohol was added till both the layers were miscible and refluxing was continued for 5 h. Excess of alcohol and unreacted hydrazine hydrate was distilled out and the contents were poured into ice cold water. The solid was purified by recrystallization from ethanol to get pure white crystalline product. Yield 59%. m.p. 145°C. IR (KBr): 3288 (-NH, -CONH-), 3077 (C-H, aromatic), 2970 (C-H, CH_3), 1717 (C=O stretching, -CONH-), 1300 (C-H bending), 743 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.44 (s, 3H, -N-C(CH_3)-C-), 4.61 (s, 2H, NH_2), 7.55-8.00 (m, 4H, Ar-H), 9.15 (s, 1H, -CONH-), 9.79 (s, 1H, -NH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.8, 125.5, 127.4, 130.1, 132.3, 134.5, 135.7, 156.4, 160.5, 162.8, 165.7; LCMS: *m/z* 310.5 (M^+). Anal. Calcd for $C_{12}H_{11}ClN_4O_2S$: C, 46.38; H, 3.57; N, 18.03. Found: C, 46.42; H, 3.59; N, 18.09%.

Preparation of 3-chloro-*N*-(4-methyl-5-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl) benzamide, 4

A mixture of intermediate **3** (0.01 mol), potassium hydroxide (0.01 mol), carbon disulfide (0.02 mol) and ethanol (50 mL, 99.9%) was refluxed for 12 h. The excess solvent was removed by vacuum evaporation, and the residue was dissolved in water and acidified with acetic acid to get solid product. It was filtered, dried and purified by recrystallization from water-ethanol (60-40). Yield 56%. m.p. 161°C. IR (KBr): 3293 (-NH, -CONH-), 3074 (C-H, aromatic), 2972 (C-H, CH_3), 1709 (C=O stretching,-CONH-), 1301 (C-H bending), 744 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.45 (s, 3H, -N-C(CH_3)-C-), 7.55-7.95 (m, 4H, Ar-H), 9.14 (s, 1H,-CONH-), 10.97 (s, 1H, -NH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.1, 125.5, 127.4, 130.3, 132.1, 132.4, 134.5, 135.5, 156.4, 157.0, 162.8, 165.6, 189.8; LCMS: *m/z* 352.5 (M^+). Anal. Calcd for $C_{13}H_9ClN_4O_2S_2$: C, 44.25; H, 2.57; N, 15.88. Found: C, 44.32; H, 2.55; N, 15.82%.

Preparation of 3-chloro-*N*-(5-(4-((arylphenyl-amino) methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)benzamides, 5a-l

Mannich condensation of 3-chloro-N-(4-methyl-5-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)benzamide **4** (0.01 mol) with 36% formaldehyde (0.02 mol) and appropriately substituted aniline (0.01 mol) derivatives in absolute ethanol (99.9%) furnished the desired compounds **5a-l**.

3-Chloro-*N*-(5-(4-((2-fluorophenylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)benzamide, 5a: Yield 56%. m.p. 154°C. IR (KBr): 3397 (N–H stretching, -NH-), 3293 (-NH, -CONH-), 3073 (C-H, aromatic), 2977 (C-H, CH_3), 2856 (C-H, CH_2), 1709 (C=O stretching,-CONH-), 1663, 1541, 1517 (C=C, C=N stretching, aromatic ring), 1300 (C-H bending), 1110 (C-F), 742 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.40 (s, 3H, -N-C(CH_3)-C-), 4.10 (s, 1H, -NH-), 4.60 (s, 2H, CH_2), 6.50-8.40 (m, 8H, Ar-H), 9.15 (s, 1H,-CONH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.1, 165.7, 162.8, 157.7, 156.4, 154.6, 135.7, 134.4, 132.4, 132.2, 130.6, 130.2, 127.3, 125.5, 125.0, 121.9, 116.1, 115.2, 70.7, 17.1; LCMS: *m/z* 475.95 (M^+). Anal. Calcd for $C_{20}H_{15}ClFN_5O_2S_2$: C, 50.47; H, 3.18; N, 14.71. Found: C, 50.43; H, 3.22; N, 14.65%.

3-Chloro-*N*-(5-(4-((3-fluorophenylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)benzamide, 5b: Yield 58%. m.p. 162°C. IR (KBr): 3390 (N–H stretching, -NH-), 3291 (-NH, -CONH-), 3074 (C-H, aromatic), 2975 (C-H, CH_3), 2857 (C-H, CH_2), 1711 (C=O stretching,-CONH-), 1662, 1542, 1518 (C=C, C=N stretching, aromatic ring), 1301 (C-H bending), 1111 (C-F), 745 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.43 (s, 3H, -N-C(CH_3)-C-), 4.05 (s, 1H, -NH-), 4.58 (s, 2H, CH_2), 6.50-8.00 (m, 8H, Ar-H), 9.15 (s, 1H,-CONH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.3, 165.7, 163.6, 162.8, 157.1, 156.5, 149.3, 135.5, 134.3, 132.5, 132.2, 131.2, 130.2, 127.5, 125.5, 109.1, 108.8, 102.0, 70.7, 17.1; LCMS: *m/z* 475.95 (M^+). Anal. Calcd for $C_{20}H_{15}ClFN_5O_2S_2$: C, 50.47; H, 3.18; N, 14.71. Found: C, 50.42; H, 3.14; N, 14.67%.

3-Chloro-*N*-(5-(4-((4-fluorophenylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)benzamide, 5c: Yield 66%. m.p. 169°C. IR (KBr): 3392 (N–H stretching, -NH-), 3290 (-NH, -CONH-), 3073 (C-H, aromatic), 2978 (C-H, CH_3), 2855 (C-H, CH_2), 1713 (C=O stretching, -CONH-), 1661, 1544, 1519 (C=C, C=N stretching, aromatic ring), 1307 (C-H bending), 1114 (C-F), 748 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.44 (s, 3H, -N-C(CH_3)-C-), 4.07 (s, 1H, -NH-), 4.60 (s, 2H, CH_2), 6.50-8.40 (m, 8H, Ar-H), 9.17 (s, 1H, -CONH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.1, 165.7, 162.6, 157.1, 156.4, 143.1, 135.5, 134.3, 132.4, 132.3, 130.1, 127.4, 125.5, 118.9, 116.5, 70.7, 17.1; LCMS: *m/z* 475.95 (M^+). Anal. Calcd for $C_{20}H_{15}ClFN_5O_2S_2$: C, 50.47; H, 3.18; N, 14.71. Found: C, 50.41; H, 3.23; N, 14.66%.

3-Chloro-*N*-(5-(4-((2-methoxyphenyl-amino)methyl) -5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)benzamide, 5d: Yield 64%. m.p. 179°C. IR (KBr): 3391 (N–H stretching, -NH-), 3292 (-NH, -CONH-), 3071 (C-H, aromatic), 2977 (C-H, CH_3), 2853 (C-H, CH_2), 1713 (C=O stretching, -CONH-), 1660, 1542, 1524 (C=C, C=N stretching, aromatic ring), 1302 (C-H bending), 1211-1107 (C-O-CH_3), 743 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.46 (s, 3H, -N-C(CH_3)-C-), 3.82 (s, 3H, Ar-OCH_3), 4.04 (s, 1H, -NH-), 4.59 (s, 2H, CH_2), 6.50-8.40 (m, 8H, Ar-H), 9.17 (s, 1H, -CONH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.1, 165.7, 157.0, 156.4, 144.5, 138.2, 135.5, 134.3, 132.5, 132.1, 130.3, 127.3, 125.5, 121.7, 121.0, 114.5, 113.4, 71.1,

55.7, 17.1; LCMS: *m/z* 488 (M^+). Anal. Calcd for $C_{21}H_{18}ClN_5O_3S_2$: C, 51.69; H, 3.72; N, 14.35. Found: C, 51.63; H, 3.77; N, 14.31%.

3-Chloro-*N*-(5-(4-((3-methoxyphenylamino) methyl) -5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)benzamide, 5e: Yield 61%. m.p. 145°C. IR (KBr): 3394 (N–H stretching, -NH-), 3292 (-NH, -CONH-), 3069 (C-H, aromatic), 2971 (C-H, CH_3), 2852 (C-H, CH_2), 1715 (C=O stretching, -CONH-), 1662, 1545, 1528 (C=C, C=N stretching, aromatic ring), 1305 (C-H bending), 1210-1102 (C-O-CH_3), 742 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.44 (s, 3H, -N-C(CH_3)-C-), 3.83 (s, 3H, Ar-OCH_3), 4.07 (s, 1H, -NH-), 4.58 (s, 2H, CH_2), 6.15-7.95 (m, 8H, Ar-H), 9.14 (s, 1H,-CONH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.0, 165.7, 162.8, 161.5, 157.1, 156.4, 148.5, 135.5, 134.3, 132.5, 132.2, 130.1, 127.6, 125.5, 110.2, 109.3, 105.8, 105.5, 70.9, 55.9, 17.0; LCMS: *m/z* 488 (M^+). Anal. Calcd for $C_{21}H_{18}ClN_5O_3S_2$: C, 51.69; H, 3.72; N, 14.35. Found: C, 51.60; H, 3.66; N, 14.30%.

3-Chloro-*N*-(5-(4-((4-methoxyphenylamino)methyl) -5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)benzamide, 5f: Yield 62%. m.p. 143°C. IR (KBr): 3398 (N–H stretching, -NH-), 3290 (-NH, -CONH-), 3065 (C-H, aromatic), 2974 (C-H, CH_3), 2850 (C-H, CH_2), 1714 (C=O stretching, -CONH-), 1660, 1544, 1529 (C=C, C=N stretching, aromatic ring), 1302 (C-H bending), 1208-1096 (C-O-CH_3), 740 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.43 (s, 3H, -N-C(CH_3)-C-), 3.82 (s, 3H, Ar-OCH_3), 4.04 (s, 1H, -NH-), 4.60 (s, 2H, CH_2), 6.75-7.95 (m, 8H, Ar-H), 9.13 (s, 1H, -CONH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.2, 165.6, 162.8, 157.1, 156.5, 151.5, 139.9, 135.5, 134.6, 132.5, 132.1, 130.1, 127.4, 125.5, 115.8, 115.1, 70.9, 55.9, 17.0; LCMS: *m/z* 488 (M^+). Anal. Calcd for $C_{21}H_{18}ClN_5O_3S_2$: C, 51.69; H, 3.72; N, 14.35. Found: C, 51.63; H, 3.71; N, 14.33%.

3-Chloro-*N*-(4-methyl-5-(4-((2-nitrophenylamino) methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) thiazol-2-yl)benzamide, 5g: Yield 70%. m.p. 153°C. IR (KBr): 3390 (N–H stretching, -NH-), 3293 (-NH,-CONH-), 3067 (C-H, aromatic), 2973 (C-H, CH_3), 2856 (C-H, CH_2), 1711 (C=O stretching, -CONH-), 1662, 1541, 1527 (C=C, C=N stretching, aromatic ring), 1538 (Ar-NO_2), 1304 (C-H bending), 747 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.44 (s, 3H, -N-C(CH_3)-C-), 4.06 (s, 1H, -NH-), 4.61 (s, 2H, CH_2), 7.35-8.05 (m, 8H, Ar-H), 9.14 (s, 1H, -CONH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.1, 165.7, 162.8, 157.2, 156.4, 146.5, 135.6, 135.5, 134.3, 132.3, 132.2, 131.6, 130.1, 127.4, 125.6, 118.1, 114.3, 69.7, 17.0; LCMS: *m/z* 502.5 (M^+). Anal. Calcd for $C_{20}H_{15}ClN_6O_4S_2$: C, 47.76; H, 3.01; N, 16.71. Found: C, 47.72; H, 3.08; N, 16. 75%.

3-Chloro-*N*-(4-methyl-5-(4-((3-nitrophenylamino) methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) thiazol-2-yl)benzamide, 5h: Yield 68%. m.p. 179°C. IR (KBr): 3383 (N–H stretching, -NH-), 3297 (-NH,-CONH-), 3063 (C-H, aromatic), 2971 (C-H, CH_3), 2854 (C-H, CH_2), 1715 (C=O stretching, -CONH-), 1666, 1543, 1524 (C=C, C=N stretching, aromatic ring), 1535 (Ar-NO_2), 1301 (C-H bending), 746 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.43 (s, 3H, -N-C(CH_3)-C-), 4.05 (s, 1H, -NH-), 4.58 (s, 2H, CH_2), 7.20-7.95 (m, 8H, Ar-H), 9.13 (s, 1H, -CONH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.3, 165.6, 162.9, 157.1, 156.4, 148.8, 148.5, 135.5, 134.3, 132.5, 132.2, 130.3, 130.1, 127.6, 125.5, 119.5, 112.4, 106.3, 70.7, 17.0; LCMS: *m/z* 502.5 (M^+). Anal. Calcd for $C_{20}H_{15}ClN_6O_4S_2$: C, 47.76; H, 3.01; N, 16.71. Found: C, 47.70; H, 2.97; N, 16.75%.

3-Chloro-*N*-(4-methyl-5-(4-((4-nitrophenylamino) methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) thiazol-2-yl)benzamide, 5i: Yield 72%. m.p. 183°C. IR (KBr): 3389 (N–H stretching, -NH-), 3295 (-NH,-CONH-), 3062 (C-H, aromatic), 2970 (C-H, CH_3), 2857 (C-H, CH_2), 1714 (C=O stretching, -CONH-), 1665, 1542, 1527 (C=C, C=N stretching, aromatic ring), 1534 (Ar-NO_2), 1300 (C-H bending), 743 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.44 (s, 3H, -N-C(CH_3)-C-), 4.06 (s, 1H, -NH-), 4.54 (s, 2H, CH_2), 6.70-8.05 (m, 8H, Ar-H), 9.14 (s, 1H, -CONH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.1, 165.8, 162.9, 157.1, 156.5, 153.6, 136.2, 135.7, 134.3, 132.5, 132.2, 130.1, 127.6, 127.5, 125.5, 114.4, 70.7, 17.1; LCMS: *m/z* 502.5 (M^+). Anal. Calcd for $C_{20}H_{15}ClN_6O_4S_2$: C, 47.76; H, 3.01; N, 16.71. Found: C, 47.71; H, 3.04; N, 16.65%.

3-Chloro-*N*-(4-methyl-5-(5-thioxo-4-((*o*-tolylamino) methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)benzamide, 5j: Yield 63%. m.p. 126°C. IR (KBr): 3385 (N–H stretching, -NH-), 3295 (-NH, -CONH-),

3062 (C-H, aromatic), 2977 (C-H, CH_3), 2951 (C-H, Ar-CH_3), 2857 (C-H, CH_2), 1714 (C=O stretching,-CONH-), 1665, 1542,1527 (C=C, C=N stretching, aromatic ring), 1300 (C-H bending), 743 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.33 (s, 3H, Ar-CH_3), 2.44 (s, 3H, -N-C(CH_3)-C-), 4.06 (s, 1H, -NH-), 4.58 (s, 2H, CH_2), 6.70-8.00 (m, 8H, Ar-H), 9.14 (s, 1H, -CONH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.0, 165.8, 162.9, 157.1, 156.5, 146.4, 135.5, 134.4, 132.3, 132.2, 130.1, 127.4, 127.0, 126.4, 125.5, 122.1, 121.8, 110.5, 71.2, 17.5, 17.1; LCMS: *m/z* 471.5 (M^+). Anal. Calcd for $C_{21}H_{18}ClN_5O_2S_2$: C, 53.44; H, 3.84; N, 14.84. Found: C, 53.39; H, 3.87; N, 14.81%.

3-Chloro-*N*-(4-methyl-5-(5-thioxo-4-((*m*-tolylamino) methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)benzamide, 5k: Yield 59%. m.p. 137°C. IR (KBr): 3392 (N–H stretching, -NH-), 3297 (-NH, -CONH-), 3060 (C-H, aromatic), 2979 (C-H, CH_3), 2950 (C-H, Ar-CH_3), 2854 (C-H, CH_2), 1711 (C=O stretching,-CONH-), 1668, 1547,1520 (C=C, C=N stretching, aromatic ring), 1301 (C-H bending), 742 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.34 (s, 3H, Ar-CH_3), 2.43 (s, 3H, -N-C(CH_3)-C-), 4.05 (s, 1H, -NH-), 4.51 (s, 2H, CH_2), 6.50-8.05 (m, 8H, Ar-H), 9.15 (s, 1H, -CONH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.1, 165.8, 162.9, 157.1, 156.5, 147.4, 135.5, 134.4, 132.4, 132.2, 130.3, 129.3, 127.4, 125.5, 117.3, 113.3, 110.4, 70.9, 21.3, 17.1; LCMS: *m/z* 471.5 (M^+). Anal. Calcd for $C_{21}H_{18}ClN_5O_2S_2$: C, 53.44; H, 3.84; N, 14.84. Found: C, 53.41; H, 3.78; N, 14.81%.

3-Chloro-*N*-(4-methyl-5-(5-thioxo-4-((*p*-tolylamino) methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)benzamide, 5l: Yield 59%. m.p. 134°C. IR (KBr): 3393 (N–H stretching, -NH-), 3299 (-NH, -CONH-), 3063 (C-H, aromatic), 2977 (C-H, CH_3), 2958 (C-H, Ar-CH_3), 2859 (C-H, CH_2), 1718 (C=O stretching,-CONH-), 1661, 1543,1526 (C=C, C=N stretching, aromatic ring), 1313 (C-H bending), 741 cm^{-1} (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.33 (s, 3H, Ar-CH_3), 2.44 (s, 3H, -N-C(CH_3)-C-), 4.04 (s, 1H, -NH-), 4.54 (s, 2H, CH_2), 6.45-8.00 (m, 8H, Ar-H), 9.14 (s, 1H, -CONH-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.2, 165.8, 162.9, 157.1, 156.5, 144.5, 135.5, 134.3, 132.4, 132.3, 130.2, 129.7, 129.5, 127.4, 113.5, 70.9, 21.3, 17.1; LCMS: *m/z* 471.5 (M^+). Anal. Calcd for $C_{21}H_{18}ClN_5O_2S_2$: C, 53.44; H, 3.84; N, 14.84. Found: C, 53.38; H, 3.78; N, 14.81%.

Conclusion

In conclusion, some new structural hybrids of thiazole and 1,3,4-oxadiazole were synthesized and examined for their antimicrobial property in anticipation of generating new structural leads serving as broad spectrum antimicrobial agents. Compounds **5a-l** have been tested for their antimicrobial activity and most of them showed stimulating results. The activity data of the synthesized compounds showed that electron withdrawing groups such as nitro and flouro at *para* and *meta* positions emerged as the most potent antibacterial agents. Though, it was observed that *para* position was more favorable for enhancing the antibacterial activity. Compound **5f** with electron donating group at *para* position emerged as the most promising antifungal agent. The results obtained here require further investigations in our laboratories using an advanced chemical-genetic approach to find lead molecules as antimicrobial agents.

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