Synthesis and antimicrobial screening of novel 2-(5-{4-[1-aza-2-(4-chlorophenyl) vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-arylacetamides derivatives

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Abstract

A new series of 2-(5-{4-[1-aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-arylacetamides **4a-l** had been synthesized and chemical structures of newly synthesized compounds were elucidated by using IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Newly synthesized compounds screened for their antibacterial and antifungal activities on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus pyogenes*, *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*. The synthesized bio-active compounds exhibited significant antimicrobial action. Compounds **4d**, **4e**, **4h** and **4i** possess significant antibacterial activity. Compounds **4a**, **4e** and **4i** possess significant antifungal activity.

KEYWORDS : 1,3,4-Oxadiazole; antibacterial activity; antifungal activity.

Introduction

Heterocyclic compounds are commonly used scaffolds on which pharmacophores are arranged to provide potent and selective drugs.[1-3] This is especially true for five-membered ring heterocyclic compounds, which serve as the core components of a large number of substances that possess a wide range of interesting biological activities. 1,3,4-Oxadiazole is a versatile lead molecule for designing potential bioactive agents. Moreover 1,3,4-oxadiazoles have been used as " privileged" scaffolds to produce substances of interest in numerous therapeutic areas, such as antimicrobial,[4] anti-inflammatory,[5] analgesic,[6] anti-HIV,[7] antimycobacterial,[8] cathepsin K inhibitors,[9] tyrosinase inhibitors,[10] monoamine oxidase (MAO) inhibitors,[11] anticonvulsant,[12] anticancer,[13] antidiarrheal[14] and other biological properties such as genotoxic studies[15] and lipid peroxidation inhibitor.[16] 1,3,4-Oxadiazole-carboxamides containing different lipophilic moieties (i.e. 4-diphenyl, 1-napthyl, phenyl propyl and *n*-hexyl substituents) and additional basic groups which are mainly alkyl and amino alkyl residues have been recently described as antiplatelet and antithrombotic compounds as well as serotonin antagonist.[17] 2-Amino-1,3,4-oxadiazoles have demonstrated biological activity as muscle relaxants,[18] while biarylpyrazolyl oxadiazole behaves as potent, selective, orally bioavailable cannabinoid-1 receptor antagonists for the treatment of obesity.[19]

The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bio-active class of heterocycles. These molecules are also utilized as pharmacophores due to their favourable metabolic profile and ability to engage

in hydrogen bonding. In particular, marketed antihypertensive agents such as tiodazosin[20] and nesapidil[21] as well as antibiotic such as furamizole[22] contain the oxadiazole nucleus. Although there are a number of antibiotics, which are commercially used in medicine, the synthesis of new compounds is of vital importance due to increasing drug resistance. Moreover it is important to obtain therapeutically active compounds having less toxic effects. A number of syntheses for substituted derivatives of these heterocyclic systems have been developed. 4-Aminobenzohydrazide is versatile intermediate for the synthesis of 1,3,4-oxadiazole.[23, 24] The retrosynthetic analysis lead to the conclusion that 4-aminobenzohydrazide can have ambient site for cyclization, which readily afford this heterocycle carryings various reactions as shown in **Scheme-1**.

Therefore, we wanted to develop an efficient procedure for the synthesis of new heterocyclic systems containing 1,3,4-oxadiazole, Schiff base and amide linkage while attempt to develop a potential bioactive molecules. The structures of synthesized compounds were assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. These compounds were evaluated for their antimicrobial screening on different strains of bacteria and fungi.

Results and discussion

The synthetic strategies adopted to obtain the target compounds are depicted in **Scheme-1**. The present scaffold **4** is the part of the synthesis of new chemical entities in the form of antimicrobial agents. The key intermediate **2** was prepared in an excellent yield in to one consequence step by cyclization of *N*-amino(4-aminophenyl)carboxamide **1** afforded 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol **2**. To investigate the structure activity relationship with respect to antimicrobial properties compound **2** on condensation with 4-chloro bezaldehyde yielded 5-{4-[1-aza-2-(4-chlorophenyl)vinyl]phenyl}-1,3,4-oxadiazole-2-thiol **3**. Finally, compound **3** on treatment with different substituted α-chloro acetanilides in alkaline media furnished 2-(5-{4-[1-aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-aryl-acetamides **4a-l**. The completion of the reaction and the purity of all compounds were checked on aluminium coated TLC plates 60 F_{245} (E. Merck) using hexane-ethyl acetate (7.5: 2.5 V/V) as mobile phase and visualized with ultraviolet (UV) light, or iodine vapour. The title compounds **4a-l** were purified by flash chromatographic method using hexane-ethyl acetate (7.5: 2.5 V/V) step gradient mixtures as an eluent. Their structures were established by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

The IR spectrum of the title compound **4a** (molecular formula $C_{23}H_{17}ClN_4O_2S$, m.w. 448.05) has given stretching vibration at 3235 cm^{-1} over the range, which showed medium intensity absorption peaks corresponding to secondary amine which is present in amide linkage. The vibration at 3070 and 3058 cm^{-1} over the range showed strong intensity absorption peaks corresponding to Ar-H stretching vibrations. The absorption peak at 2914 cm^{-1} is due to the stretching vibration corresponding to methylene group, while the absorption peak at 1450 cm^{-1} is due to the bending vibration corresponding methylene group. The strong intensity absorption at 1715 cm^{-1} is due to the stretching vibration of C=O which is present in amide linkage. The weak intensity absorption at 1620 cm^{-1} corresponds to a C=N stretching vibration, while C=C showed medium intensity absorption stretching vibration at 1594 and 1558 cm^{-1}. The absorption peaks in the range of 1207 cm^{-1} corresponds to C-O-C linkage of oxadiazole nucleus. The

absorption peak at 825 cm^{-1} arises due to the stretching vibration of C-Cl group present in moiety.

It has been observed from the chemical structure of compound **4a** that different pairs of carbons e.g. C-12 and C-14, C-11 and C-15, C-5 and C-7, C-4 and C-8, C-19 and C-23, C-20 and C-22 are attached to chemically equivalent protons, which appeared between δ = 7.20-7.87 ppm respectively. The protons attached at C-16 appeared as a singlet at δ = 4.00 ppm due to one side attachment with sulphur and other side attachment with carbonyl group. The proton attached at C-9 position appeared as a singlet at δ = 8.52 ppm, due to the influence of imine linkage. The proton of the secondary amine appeared as a singlet at δ = 10.3 ppm. The protons attached with C-21 of phenyl ring appeared as a multiplet at δ = 6.90 ppm.

The final compound **4a** has oxadiazole nucleus. The chemical shifts of the final compound carbon vary from δ = 171.5-32.8 ppm. The carbon nucleus under the influence of a strong electronegative environment appeared downfield, e.g. the C-17 carbonyl carbon, which is present in amide linkage, which is directly linked to nitrogen, has a chemical shift value of δ = 165.2 ppm. The carbons which are present in oxadiazole nucleus C-1 and C-2 both are on one side attached with oxygen atom and on other side attached with nitrogen. So, carbon C-1 gave a chemical shift at δ = 162.3 ppm and C-2 gave a chemical shift at δ = 171.5 ppm. Carbon C-2 was more downfield then C-1 because it is directly attached with sulphur. The carbon which is present in imine linkage C-9 gave a chemical shift at δ = 152.8 ppm. The carbon C-6 appeared at δ = 149 ppm because it is attached with nitrogen of imine. The carbon C-16 appeared at δ = 32.8 ppm due to the influence of electronegativity of carbonyl group and sulphur. The carbon C-3 of the phenyl ring which is directly attached to oxadiazole ring appeared at δ = 129.7 ppm. The carbons of the phenyl rings C-12 and C-14, C-11 and C-15, C-5 and C-7, C-4 and C-8, C-19 and C-23, C-22 and C-20 which are equivalent carbons gave a chemical shift between δ = 119.6- 130.4 ppm respectively. The carbon C-18 appeared at δ = 139.6 ppm due to the influence of amide linkage. The carbon of phenyl ring C-21 gave a chemical shift at δ = 122.9 ppm. The carbons of chloro phenyl ring C-13 gave a chemical shift at δ = 137.6 ppm because it is directly attached with chloro group, while carbon C-10 gave a chemical shift at δ = 134.5 ppm because it is attached with carbon of imine. The carbon skeleton of compound **4a** is described in **Figure-1**.

Antimicrobial screening

The results of antimicrobial studies of newly synthesized compounds reveal that the compounds possess significant antibacterial and antifungal activities. The results of these studies are given in **Table-1**. From antibacterial screening results, it has been observed that compounds **4a**, **4f**, **4i** and **4j** (R= -H, -3-OCH_3, -4-Cl and -4-Br) possess good activity against *E. coli*. While compound **4e** (R= -2,4-$(CH_3)_2$) possesses very good activity against *E. coli* and compound **4d** (R= -2-CH_3) possesses excellent activity against *E. coli*. Compounds **4d**, **4e** and **4f** (R= -2-CH_3, -2,4-$(CH_3)_2$ and -3-OCH_3) possess good activity against *P. aeruginosa*. While compounds **4c** and **4i** (R= -2-NO_2 and -4-Cl) possess a very good activity against *P. aeruginosa* Compounds **4c**, **4d** and **4g** (R= -2-NO_2, -2-CH_3 and -3,4-$(Cl)_2$) possess good activity against *S. aureus*. While compounds **4a**, **4b, 4h** and **4i** (R= -H, -2-Cl, -4-F and -4-Cl) possess very good activity against *S.*

aureus and compounds **4e** and **4j** (R= -2,4-$(CH_3)_2$ and -4-Br) possesses excellent activity against *S. aureus*. While Compounds **4d** and **4f** (R= -2-CH_3, and -3-OCH_3) possess good activity against *S. pyogenes* and compound **4h** possesses excellent activity against *S. pyogenes.* Antifungal screening data showed that compounds **4b**, **4c**, **4d**, **4f**, **4g**, **4h**, **4j**, **4k** and **4l** (R= -2-Cl, -2-NO_2, -2-CH_3, -3-OCH_3, -3,4-$(Cl)_2$, -4-F, -4-Br, -4-NO_2 and -4-OCH_3) possess good activity against *C. albicans*. While compounds **4e** and **4i** (R=-2,4-$(CH_3)_2$ and -4-Cl) possess good activity against *C. albicans* and Compound **4a** (R = -H) possesses excellent activity against *C. albicans*. Compound **4a**, **4c** and **4i** (R= -H, 2-NO_2 and -4-Cl) possesses good activity against *A. niger*. The enhancement of the activity of these compounds is due to the presence of methyl, methoxy and halogen groups in the title compounds. The discussion and comparison of antibacterial activity was given with respect to ampicillin antibiotic. In a similar manner, antifungal activity was compared with griseofulvin.

Biological activity

We have synthesized 2-(5-{4-[1-aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-arylacetamides **4a-l** derivatives. Minimum inhibitory concentration (MIC) for bacteria of all the synthesized compounds was determined against four different strains, viz two gram positive bacteria (*S. aureus* & *S. pyogenes)* and two gram negative bacteria *(E. coli* & *P. aeruginosa)* as compared to the standard drug ampicillin by broth dilution method[25-27]. Minimum inhibitory concentration (MIC) for antifungal activity was carried out against *C. albicans*, *A. niger* and *A. clavatus* organisms and results were compared with standard drug griseofulvin by the same method.

Statistical analysis

The standard deviation value is express in terms of ± SD. On the basis of the calculated value by using ANOVA method, it has been observed that differences below 0.0001 level ($p \leq 0.0001$) were considered as statistically significant.

Experimental

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. All reaction courses and product mixtures were routinely monitored by aluminium coated thin-layer chromatography (TLC) plates 60 F_{245} (E. Merck) and visualized with ultraviolet (UV) light, or iodine vapour. Flash chromatography was performed with E. Merck silica gel 60, 230400 mesh. Melting points were determined on an electro thermal melting point apparatus and are reported uncorrected. Elemental analysis (% C, H, N) was carried out by 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 and ^{13}C NMR spectra were recorded on Bruker (400 MH_Z) spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on Schimadzu LCMS 2010 spectrophotometer. Anhydrous reactions were carried out in oven-dried glassware in nitrogen atmosphere. In the conventional method, compounds were synthesized by using Random synthesizer. Bookie Rotavapour is used for distillation.

Preparation of *N*-amino(4-aminophenyl)carboxamide 1.
Compound *N*-amino(4-aminophenyl)carboxamide **1** was prepared according to the literature method.[28]

Preparation of 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol 2.
A mixture of *N*-amino(4-aminophenyl)carboxamide **1** (0.1 mole), potassium hydroxide (0.1 mole), carbon disulphide (0.1 mole) and ethanol (20 mL) was heated under reflux until the evolution of hydrogen sulphide ceased . The reaction mixture was cooled to room temperature and poured into ice cold water (100 mL). It was neutralized with dilute hydrochloric acid. The precipitated solid was filtered, washed with water and the dried product was recsrystallized from ethanol. Yield: 70%; m.p.: 254-256°C; IR (KBr, cm^{-1}): 3416, 3350, 3067, 3052 1620, 1591, 1554, 1204; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.31 (s, 2H, NH_2), 6.45-7.60 (m, 4H, Ar-H), 13.21, (s, 1H, SH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 115.1, 116.1, 128.3, 143.6, 162.2, 171.3; LCMS (m/z): 193 (M^+); Ana Calcd. for $C_8H_7N_3OS$: C-49.73, H-3.65, N-21.75; Found.: C-49.67, H-3.62, N-21.78%.

Synthesis of 5-{4-[1-aza-2-(4-chlorophenyl)vinyl]phenyl}-1,3,4-oxadiazole-2-thiol 3.
Compound **2** (0.1 mole) was dissolved in ethanol (75 mL). Then, 4-chlorobenzaldehyde (0.1 mole) was added drop wise. The reaction mixture was refluxed for 5 h. Excess of solvent was distilled off and the mixture was allowed to cool at room temperature. The separated product was filtered, washed with cold water, dried and recrystallized from ethanol. Yield 80%, m.p.: 114-116°C; IR (KBr, cm^{-1}): 3238, 3073, 3051 1617, 1591, 1552, 1204, 782; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 6.78-7.88 (m, 8H, Ar-H), 8.22 (s, 1H, -CH=N-), 13.20 (s, 1H, SH); ^{13}C NMR 400 MHz, DMSO-d_6, δ, ppm): 122.6, 127.5, 130.2, 131.1, 134.5, 136.6, 149.5, 152.7, 162.3, 171.3; LCMS (m/z): 261 (M^+). Ana. Calcd. for $C_{15}H_{10}ClN_3OS$: C-57.05, H-3.19, N-13.30; Found: C-57.11, H-3.10, N-13.33%.

General Preparation of 2-(5-{4-[1-aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-arylacetamides 4a-l.
In a round bottom flask, compound **3** (0.01 mole) was dissolved in an aqueous solution of potassium hydroxide (25%). The reaction mixture was heated at 80°C and different substituted α-chloro acetanilide (0.015 mole) in ethanol (10 mL) was added with constant stirring followed by refluxing it for 2 h. The contents were left overnight. The crystals were filtered, washed with water, dried and recrystallized from ethanol.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-phenyl-acetamide 4a.
Yield: 73%; m.p.: 199-201°C; IR (KBr, cm^{-1}): 3235, 3070, 3058, 2914, 1715, 1620, 1594, 1558, 1452, 1207, 825; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.01 (s, 2H, -S-CH_2-), 6.78-7.8 (m, 13H, ArH), 8.48 (s, 1H, -CH=N-), 10.31 (s, 1H, -CONH-); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 32.8, 119.6, 122.6, 122.9, 128.7, 128.9, 129.7, 129.8, 130.4, 134.5, 137.6, 139.6, 149, 152.8, 162.3, 165.2, 171.5; LCMS (m/z): 448 (M^+). Anal. Calcd. For $C_{23}H_{17}ClN_4O_2S$: C-61.53, H-3.81, N-12.48; Found: C-61.55, H-3.75, N-12.35 %.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(2-chloro phenyl)acetamide 4b.
Yield: 71%; m.p.: 162-164°C; IR (KBr, cm^{-1}): 3236, 3073, 3054, 2917, 1713, 1613, 1592, 1557, 1455, 1205, 822, 754; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.03 (s, 2H, -S-CH_2-), 8.53 (s, 1H, -CH=N-), 6.92-7.93 (m, 12H, ArH), 10.34 (s, 1H, -CONH-); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 32.6, 121.4, 122.6, 124.2, 125.3, 128.7, 129.7, 129.8, 130.1, 130.4, 131, 133.7, 134.5, 137.6, 149.4, 152.6, 162.3, 165.4, 171.5; LCMS (m/z): 482 (M^+). Anal. Calcd. For $C_{23}H_{16}Cl_2N_4O_2S$: C-57.15, H-3.33, N-11.59; Found: C-57.20, H-3.28, N-11.54%.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(2-nitro-phenyl)acetamide 4c.
Yield: 49%; m.p.: 150-152°C; IR (KBr, cm^{-1}): 3246, 3073, 3053, 2920, 1716, 1615, 1592, 1560, 1483, 1458, 1357, 1209, 828; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.06 (s, 2H, -S-CH_2-), 6.94-7.96 (m, 12H, ArH), 8.57 (s, 1H, -CH=N-), 10.35 (s, 1H, -CONH-); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 32.7, 122.7, 124.8, 125, 125.3, 128.7, 129.8, 129.8, 130.6, 131.3, 133.1, 134.5, 137.6, 142.4, 149.6, 152.8, 162.3, 165.4, 171.6, LCMS (m/z): 493 (M^+). Anal. Calcd. For $C_{23}H_{16}ClN_5O_4S$: C-55.93, H-3.26, N-14.17; Found: C-55.89, H-3.11, N-14.13%.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(2-methyl-phenyl)acetamide 4d.
Yield: 74%; m.p.: 198-200°C; IR (KBr, cm^{-1}): 3235, 3070, 3056, 2915, 2890, 1715, 1620, 1598, 1560, 1452, 1405, 1205, 825; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.12 (s, 3H, -CH_3), 4.02 (s, 2H, -S-CH_2-), 6.94-7.89 (m, 12H, ArH), 8.54 (s, 1H, -CH=N), 10.32 (s, 1H, -CONH-); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 25.4, 32.6, 122.6, 125, 126.1, 126.3, 128.7, 129.5, 129.6, 129.8, 130.3, 130.7, 131.4, 134.5, 136.2, 137.6, 149.2, 152.4, 162.3, 165.2, 171.2; LCMS (m/z): 462 (M^+). Anal. Calcd. For $C_{24}H_{19}ClN_4O_2S$: C-62.26, H-4.13, N-12.10; Found: C-62.33, H-4.12, N-12.18%.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(2,4-dimethyl-phenyl)acetamide 4e.
Yield: 64%; m.p.: 128-130°C; IR (KBr, cm^{-1}): 3234, 3073, 3053, 2918, 2894, 1714, 1619, 1592, 1561, 1450, 1403, 1203, 821; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.08 (s, 6H, -CH_3), 4.03 (s, 2H, -S-CH_2-), 6.89-7.90 (m, 11H, ArH), 8.52 (s, 1H, -CH=N), 10.30 (s, 1H, -CONH-); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 22.8, 24.4, 32.6, 114.7, 122.4, 126.3, 128.7, 129.7, 129.8, 130.4, 131.1, 133.2, 134.3, 134.5, 137.6, 143.3, 149.4, 152.6, 162.3, 165.1, 171.4; LCMS (m/z): 476 (M^+). Anal. Calcd. For $C_{25}H_{21}ClN_4O_2S$: C-62.95, H-4.43, N-11.74; Found: C-62.89, H-4.41, N-11.72%.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(3-methoxy-phenyl)acetamide 4f.
Yield: 62%; m.p.: 185-187°C; IR (KBr, cm^{-1}): 3238, 3073, 3056, 2916, 2902, 1718, 1619, 1595, 1559, 1454, 1418, 1205, 820; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.62 (s, 3H, -OCH_3), 4.05 (s, 2H, -S-CH_2-), 6.92-7.95 (m, 12H, ArH), 8.53 (s, 1H, -CH=N), 10.32 (s, 1H, -CONH-); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 32.8, 53.8, 109.8, 110.3, 116.4, 122.6, 128.7, 129.7, 129.8, 129.9, 130.4, 134.5, 137.6, 138.5, 149, 152.8,

159.4, 162.3, 165.3, 171.4; LCMS (m/z): 478 (M^+). Anal. Calcd. For $C_{24}H_{19}ClN_4O_3S$: C-60.18, H-3.99, N-11.69; Found: C-60.15, H-3.82, N-11.72%.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(3,4-dichloro-phenyl)acetamide 4g.
Yield: 69%; m.p.: 223-225°C; IR (KBr, cm^{-1}): 3240, 3075, 3052, 2918, 1720, 1616, 1598, 1560, 1462, 1208, 822, 763; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.08 (s, 2H, -S-CH_2-), 6.92-7.94 (m, 11H, ArH), 8.56 (s, 1H, -CH=N-), 10.32 (s, 1H, -CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 32.7, 121, 122.5, 124.3, 128.2, 128.7, 129.7, 129.8, 130.4, 130.5, 131.3, 134.5, 137.6, 138.2, 149.2, 152.6, 162.3, 165.4, 171.5. LCMS (m/z): 516 (M^+). Anal. Calcd. For $C_{23}H_{15}Cl_3N_4O_2S$: C-53.34, H-2.92, N-10.82; Found: C-53.31, H-2.79, N-10.90%.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(4-fluoro-phenyl)acetamide 4h.
Yield: 76%; m.p.: 164-166°C; IR (KBr, cm^{-1}): 3238, 3078, 3057, 2920, 1718, 1617, 1596, 1558, 1465, 1210, 822, 1146; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.07 (s, 2H, -S-CH_2-), 6.94-7.95 (m, 12H, ArH), 8.57 (s, 1H, -CH=N-), 10.34 (s, 1H, -CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 32.9, 115.4, 121.6, 122.5, 128.7, 129.7, 129.9, 130.5, 134.1, 134.5, 137.6, 149.6, 152.9, 161.7, 162.5, 165.3, 171.6; LCMS (m/z): 466.07 (M^+). Anal. Calcd. For $C_{23}H_{16}ClFN_4O_2S$: C-59.16, H-3.45, N-11.99; Found: C-59.25, H-3.32, N-11.96%.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(4-chloro-phenyl)acetamide 4i.
Yield: 80%; m.p.: 210-212°C; IR (KBr, cm^{-1}): 3236, 3073, 3055, 2917, 1713, 1613, 1592, 1557, 1455, 1205, 822, 768; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.02 (s, 2H, -S-CH_2-), 6.92-7.88 (m, 12H, ArH), 8.55 (s, 1H, -CH=N-), 10.31 (s, 1H, -CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 32.8, 120.4, 122.6, 128.7, 129, 129.7, 129.8, 130.4, 133.2, 134.5, 136.6, 137.6, 149.4, 152.7, 162.3, 165.2, 171.5; LCMS (m/z): 482.04 (M^+). Anal. Calcd. For $C_{23}H_{16}Cl_2N_4O_2S$: C-57.15, H-3.33, N-11.59; Found: C-57.19, H-3.38, N-11.44%;

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(4-bromo-phenyl)acetamide 4j.
Yield:65%; m.p.: 202-204°C; IR (KBr, cm^{-1}): 3239, 3075, 3054, 2916, 1715, 1617, 1596, 1554, 1454, 1207, 825, 664; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.04 (s, 2H, -S-CH_2-), 6.90-7.88 (m, 12H, ArH), 8.58 (s, 1H, -CH=N-), 10.35 (s, 1H, -CONH); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 32.8, 121.9, 122.4, 122.5, 128.7, 129.7, 129.8, 130.4, 131.7, 134.5, 137.5, 137.6, 149.4, 152.7, 162.4, 165.1, 171.5; LCMS (m/z): 527 (M^+). Anal. Calcd. For $C_{23}H_{16}BrClN_4O_2S$: C-52.33, H-3.05, N-10.61. Found: C-52.26, H-3.16, N-10.77%.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(4-nitro- phenyl)acetamide 4k.
Yield: 59%; m.p.: 152-154°C; IR (KBr, cm^{-1}): 3242, 3077, 3060, 2921, 1718, 1612, 1598, 1552, 1485, 1457, 1352, 1207, 825; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 4.07

(s, 2H, -S-CH_2-), 6.94-7.96 (m, 12H, ArH), 8.55 (s, 1H, -CH=N), 10.34 (s, 1H, -CONH-); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 32.9, 119.8, 122.6, 124.1, 128.7, 129.7, 129.8, 130.6, 134.5, 137.6, 143.5, 145.5, 149.2, 152.8, 162.3, 165.3, 171.4; LCMS (m/z): 493 (M^+). Anal. Calcd. For $C_{23}H_{16}ClN_5O_4S$: C-55.93, H-3.26, N-14.17; Found: C-55.88, H-3.19, N-14.14%.

2-(5-{4-[1-Aza-2-(4-chlorophenyl)vinyl]phenyl}(1,3,4-oxadiazol-2-ylthio))-*N*-(4-methoxy-phenyl)acetamide 4l.

Yield: 71%; m.p.: 194-196°C; IR (KBr, cm^{-1}): 3236, 3071, 3057, 2918, 2895, 1716, 1619, 1593, 1556, 1462, 1416, 1207, 823; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.61 (s, 3H, -OCH_3), 4.06 (s, 2H, -S-CH_2-), 6.92-7.93 (m, 12H, ArH), 10.31 (s, 1H, -CONH-), 8.54 (s, 1H, -CH=N); ^{13}C NMR (400 MHz, DMSO-d_6, δ, ppm): 32.7, 53.5, 114.5, 122.3, 122.7, 128.6, 129.7, 129.8, 130.4, 130.8, 134.5, 137.6, 149.1, 152.8, 158.4, 162.3, 165.5, 171.4, LCMS (m/z): 478 (M^+). Anal. Calcd. For $C_{24}H_{19}ClN_4O_3S$: C-60.18, H-3.99, N-11.69; Found: C-60.20, H-3.80, N-11.64%.

Conclusion

In conclusion, we have synthesized some new derivatives of 1,3,4-oxadiazoles as microorganisams groth inhibitors. Our interest in the synthesis of such compounds was to shed some light on their biological study as antimicrobial agents as a part of our program aimed at the development of new heterocyclic compounds as most potent antimicrobial agents, an more extensive study is also warranted to determine additional physiochemical and biological parameters to have a deeper insight in to its structure activity relationship and to optimize the effectiveness of this series of molecules, which can be used in the bigger scenario such as drug design or development of antimicrobial therapeutics.

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References

[1] Krchnak, V.; Holladay, M. W. Solid phase heterocyclic chemistry. *Chem. Rev.* **2002**, 102, 61-92.

[2] Nefzi, A.; Ostresh, J. M.; Houghten, R. A. The current status of heterocyclic combinatorial libraries. *Chem. Rev.* **1997**, 97, 449-472.

[3] Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele J. Combinatorial synthesis – the design of compound libraries and their application to drug discovery. *Tetrahedron* **1995**, 51, 8135-8173.

[4] Karthikeyan, M. S.; Prasad, D. J.; Mahalinga, M.; Holla, B. S.; Kumari, N. S.; Antimicrobial studies of 2,4-dichloro-5-fluorophenyl containing oxadiazoles. *Eur. J. Med. Chem.* **2008**, 43, 25-31.

[5] Kalsi, R.; Bhalla, T. N.; Parmar, S. S.; Barthwal, J. P. Anti-inflammatory and analgesic activities of 5-{4-[aryl(arylazo)methyleneamino]phenyl}-1,3,4-oxadiazole-2(3*H*)-thiones. *Pharmacology* **1989**, 39, 103-108.

[6] Dewangan, D.; Pandey, A.; Sivakumar, T.; Rajavel, R.; Dubey, R. D. Synthesis of some novel 2,5-disubstituted 1,3,4-oxadiazole and its analgesic, anti-inflammatory, antibacterial and antitubercular activity. *Int. J. Chem. Tech. Res.* **2010**, 2, 1397-1412.

[7] Sriram, D.; Banerjee, D.; Yogeeswari, P. Efavirenz mannich bases: Synthesis, anti-HIV and antitubercular activities. *J. Enzyme Inhib. Med. Chem.* **2009**, 24, 1-5.

[8] Macaev, F.; Rusu, G.; Pogrebnoi, S.; Gudima, A. Synthesis of novel 5-aryl-2-thio-1,3,4-oxadiazoles and the study of their structure-anti-mycobacetrial activities. *Bioorg. Med. Chem.* **2005**, 13, 4842-4850.

[9] Palmer, J. T.; Hirschbein, B. L.; Cheung, H.; McCarter, J. Keto-1,3,4-oxadiazoles as cathepsin K inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, 16, 2909-2914.

[10] Khan, M. T. H.; Choudhary, M. I.; Khan, K. M.; Rani, M. Structure-activity relationships of tyrosinase inhibitory combinatorial library of 2,5-disubstituted-1,3,4-oxadiazole analogues. *Bioorg. Med. Chem.* **2005**, 13, 3385-3395.

[11] Ke, S.; Li, Z.; Qian, X. 1,3,4-Oxadiazole-3(2*H*)-carboxamide derivatives as potential novel class of monoamine oxidase (MAO) inhibitors: Synthesis, evaluation, and role of urea moiety. *Bioorg. Med. Chem.* **2008**, 16, 7565-7572.

[12] Almasirad, A.; Tabatabai, S. A.; Faizi, M.; Kebriaeezadeh, A.; Mehrabi, N.; Dalvandi, A.; Shafiee, A. Synthesis and anticonvulsant activity of new 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxdiazoles and 1,2,4-triazoles. *Bioorg Med Chem lett.* **2004**, 14, 6057-6059.

[13] Aboraia, S. A.; Abdel-Rahman, H. M.; Mahfouz, N. M.; El-Gendy, M. A. Novel 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives: promising anticancer agents. *Bioorg. Med. Chem.* **2006**, 14, 1236-1246.

[14] Adelstein, G. W.; Yen, C. H.; Dajani, E. Z.; Bianchi, R. G. 3,3-Diphenyl-3-(2-alkyl-1,3,4-oxdiazole-5-yl)propylcycloalkylamines, a novel series of antidiarrheal agents. *J. Med. Chem.* **1976**, 19, 1221-1225.

[15] Maslat, A. O.; Abussaud M,; Tashtoush H, Al-Talib M. Synthesis, antibacterial, antifungal and genotoxic activity of bis-1,3,4-oxadiazole derivatives. *Pol. J. Pharmacol.* **2002**, 54, 55-59.

[16] Farghaly A. A.; Bekhit A. A.; Park J. Y. Design and synthesis of some oxadiazolyl, thiadiazolyl, thiazolidinyl, and thiazolyl derivatives of 1-*H*-pyrazole as anti-inflammatory antimicrobial agents. *Arch. Pharm.*(weinheim) **2000**, 333, 53-57.

[17] Bethge, K.; Pertz, H. H.; Rehse, K. New oxadiazole derivatives showing partly antiplatelet, antithrombotic and serotonin antagonistic properties. *Archiv der pharmazie* **2005**, 338, 78-86.

[18] Yale, H. L.; Losee, K. 2-Amino-5-substituted 1,3,4-oxadiazoles and 5-imino-2-sbstitutedΔ^2-1,3,4-oxadiazolines. A group of novel muscle relaxants. *J. med. Chem*. **1966**, 9, 478-483.

[19] Lee, S. H.; Seo H. J.; Jung M. E.; Park J.; Lee S.; Park H.; Yoo J.; Yun H.; Na J.; Kang S. Y.; Song K.; Kim M.; Chang C.; Kim J.; Lee J.; Biarylpyrazolyl oxadiazole as potent, selective, orally bioavailable cannabinoid-1 receptor antagonists for the treatment of obesity. *J. Med. Chem.* **2008**, 51, 7216-7233.

[20] Vardan, S. M. D.; Smulyan, H. M. D.; Mookherjee, S.; Eich, R. Effects of tiodazosin, a new antihypertensive, hemodynamics and clinical variables. *Clin. Pharm. Ther*. **1983**, 34, 290-296.

[21] Schlecker, R.; Thieme, P. C. The synthesis of antihypertensive 3-(1,3,4-oxadiazol-2-yl)phenoxypropanolahines. *Tetrahedron* **1988**, 44, 3289-3294.

[22] Ogata, M.; Atobe, H.; Kushida, H.; Yamamoto, *K. J.* In vitro sensitivity of mycoplasmas isolated from various animals and sewage to antibiotics and nitrofurans. *J. Antibiot.* **1971**, 24, 443-451.

[23] Grekov, A. P.; Malyutenko S. A.; Kornev K. A. Synthesis and study of poly (1,3,4-oxadiazoles). *Chemistry of Heterocyclic Compounds* **1966**, 2, 253-255.

[24] Padmavathi, V.; Reddy, G. S.; Mahesh, K. Synthesis of symmetrical and unsymmetrical 1,3,4-oxadiazoles and their interconversion to 1,3,4-thiadiazole and 1,2,4-triazoles. *Arkivoc* **2008**, xvii, 48-60.

[25] Ghalem, B. R.; Mohamed, B. Antimicrobial activity evaluation of the oleoresin oil of *pistacia vera* L. *African Journal of Pharmacy and pharmacology* **2009**, 3, 92-96.

[26] Desai N. C.; Dodiya A.; Bhatt N.; Kumar M.; Dimeric 2-(2-chlorophenyl)-quinazolin-4-ones as potential antimicrobial agents. *Med Chem. Res.* **2012**, 21, 1127-1135

[27] Al-Bayati, F. A.; Al-Mola, H. F. Antibacterial and antifungal activities of different parts of Tribulus *terrestris* L. growing in Iraq. *Journal of Zhejiang* **2008**, 9, 154-159.

[28] Mathew, V.; Keshavayya, J.; Vaidya, V. P. Heterocyclic system containing bridgehead nitrogen atom: synthesis and pharmacological activities of some substituted 1,2,4-triazolo[3,4-***b***]-1,3,4-thiadiazoles. *Eur. J. Med. Chem.* **2006**, 41, 1048-1058.

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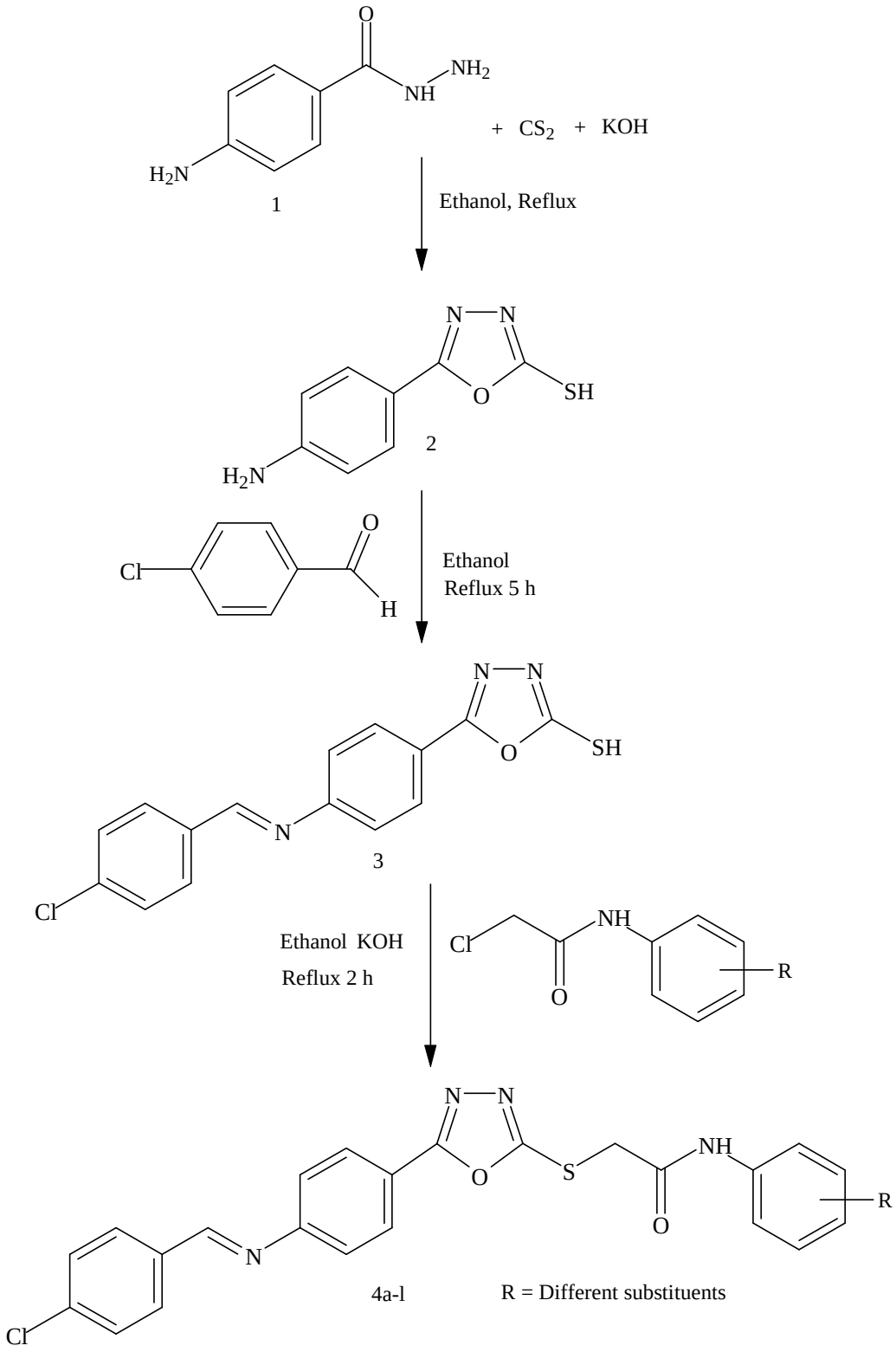
Table – 1 Results of antibacterial and antifungal screening of compounds **4a-l**

Sr. No.	-R	MINIMUM INHIBITORY CONCENTRATION (MIC) ug/ml ±SD				MINIMUM INHIBITORY CONCENTRATION (MIC) in ug/ml ±SD		
		E. coli MTCC 443	*P.* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
4a	H	100±4.04*	500±3.21*	100±4.16*	500±4.04*	50±2.51*	100±3.05*	1000±3.21*
4b	2-Cl	500±4.50*	250±2.08*	100±3.60*	250±2.64*	500±3.05*	500±3.60*	1000±3.51*
4c	2-NO_2	250±2.64*	50±2.64*	250±2.08*	500±2.51*	500±3*	100±4.50*	250±4.35*
4d	2-CH_3	25±1*	100±3.51*	125±2.08*	100±3.51*	250±2.08*	1000±2.64	1000±3.51*
4e	2,4-$(CH_3)_2$	62.5±3.78*	100±1*	50±4.04*	200±4.16*	100±3.21*	250±2.08*	500±3.21*
4f	3-OCH_3	100±3*	100±3.60*	500±3.16*	100±3.78*	500±4.04*	1000±3.0*	1000±2.30*
4g	3,4-$(Cl)_2$	250±3.21*	125±4.72*	250±3.05*	500±3.51*	500±3.05*	500±4.05*	1000±3.51*
4h	4-F	500±3.51*	500±3.05*	100±3.60*	25±1*	500±3.51*	1000±3*	1000±3.05*
4i	4-Cl	100±3.51*	50±2.64*	100±4.04*	500±4.50*	125±4.93*	100±3.60*	500±3.21*
4j	4-Br	100±3.46*	250±2.51*	50±3.05*	1000±3.5*	250±3.05*	1000±3.51	1000±3.21*
4k	4-NO_2	125±3.21*	250±3*	500±3.51*	100±2.08*	200±2.08*	500±3.05*	1000±2.30*
4l	4-OCH_3	250±3.05*	250±3.78*	500±3.05*	500±4.58*	500±3.46*	1000±2.64	1000±4*
	Ampicillin	100±2.05*	100±1.0*	250±1.52*	100±2.06*	-	-	-
	Griseofulvin	-	-	-	-	500±0.58*	100±3*	100±3.46*

SD = Standard deviation *$p \leq 0.0001$



Scheme-1 Synthetic pathway for the synthesis of title compounds **4a-l.**

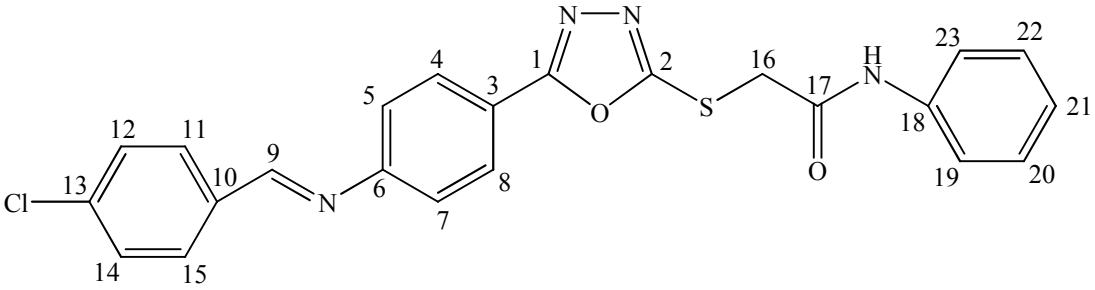


Figure-1 Carbon skeleton of final compound **4a**.

GRAPHICAL ABSTRACT