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Research Paper

Synthesis and *in vitro* antimicrobial studies of 4-thiazolidinone incorporated 1,3,4-oxadiazoles

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Abstract: We have synthesized 4-thiazolidinone incorporated 1,3,4-oxadiazoles. 2-Chloromethyl-5-substituted phenyl-1,3,4-oxadiazoles **1a-o** have been synthesized separately on reaction between chloroacetic acid and acid hydrazide, then coupled with phenolic group of 4-hydroxy aniline, further converted to 2-chloro-*N*-substituted phenyl acetamides **3a-o** on reaction with chloro acetyl chloride and finally cyclised with ammonium thiocyanate to form targeted compounds **4a-o**. All the compounds have been characterized by ^1H NMR, ^{13}C NMR, IR and Mass spectral analysis and also evaluated for antimicrobial activity against two Gram positive, two Gram negative bacteria and three fungal species.

1. Introduction

A bacterial resistance gained by microorganisms to classical antimicrobials is current challenges. Searching of antimicrobial agents with new structure and mode of action is an essential strategy of research. 1,3,4-Oxadiazoles is five member heterocyclic ring with two nitrogen and one oxygen as heteroatoms. 1,3,4-Oxadiazoles have been synthesized by heating of acid hydrazide and carboxylic acid in phosphoryl chloride (POCl_3) [1], also by reaction of Schiff base prepared from hydrazide with chloramines-T [2]. 1,3,4-Oxadiazole have highlighted due to its pharmacological properties such as antimicrobial [3],

anticancer [4], anti-HIV [5], antitumor [6], anti-convulsant [7], antidiabetic [8], anti-inflammatory [9], anti-tubercular [10]. 4-Thiazolidinone is five membered heterocyclic ring with sulfur and nitrogen as heteroatoms with carbonyl group. 4-Thiazolidinones generally synthesized by cyclization of Schiff base with thioglycolic acid [11], mechanism consist nucleophilic attack of mercaptoacetic acid anion upon the carbon atom of Schiff base, followed by protonation of nitrogen, and subsequent cyclization with removal of water molecule [12]. 2-Hydrazono-4-thiazolidinones have been prepared by reaction of acylthiosemicarbazide with ethyl bromoacetate or ethyl chloroacetate [13]. α -Halogenated amides on reaction with ammonium thiocyanate in presence of absolute ethanol furnished 2-imino-4-thiazolidinones [14]. Thiazole ring present

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in therapeutically important drug such as penicillin, sulfathiazole, abafungin, meloxicam etc. Mechanism of action of penicillin and cephalosporin involve the inhibition of peptidoglycan biosynthesis in cell wall of bacteria. 4-Thiazolidinones also inhibit the biosynthesis of the peptidoglycan by interacting with MurB enzyme [15]. Its derivatives have demonstrated significant pharmacological activities like antimicrobial [16], anticancer [17], anti-HIV [18], antitumor [19], anti-convulsant [20], antidiabetic [21], diuretic [22], nimeticidal [23], anti-inflammatory [24], anti-tubercular [25]. We have synthesized and studied antimicrobial activity of quinazolin-4-(3*H*)one based 1,3,4-oxadiazoles [26-27], 4-thiazolidinones [28-31], pyridine based 1,3,4-oxadiazoles [32-34], 1,3-benzothiazole based 4-thiazolidinones [35-36] and fluoroquinolone based 4-thiazolidinones [37-39]. We have studied antimicrobial activity of 1,3,4-oxadiazole and 4-thiazolidinone incorporated in to other moieties and results encouraged us to study their incorporation as single moiety. The synthesis of new derivatives has been outlined in Scheme-I and III

The structures of compounds were established from their elemental analysis and spectral data. The absorption band at 3445, 3344 cm^{-1} was observed for amino group of **2a-o**, when it converted to acetamides absorption band at 3352 cm^{-1} was observed for N-H stretching and additional absorption band at 1680 cm^{-1} was observed for amide-I, on conversion of acetamides to 4-thiazolidinones absorption band for $>\text{C}=\text{O}$ was shifted from 1684 cm^{-1} to 1732 cm^{-1} . Two absorption bands in all the compounds for methylene group were observed at 2990-2820 cm^{-1} . Absorption bands for functional groups like 1552, 1330 cm^{-1} ($-\text{NO}_2$ asym, sym), 1220 cm^{-1} (C-F), 1215, 1028 cm^{-1} (C-O-C), 767 cm^{-1} (C-Cl) were also observed. In ^1H NMR spectra singlet

observed at δ 4.68 for methylene proton of 1,3,4-oxadiazole **1a-o**, which shifted to δ 5.28 on formation of ether linkage. Singlet at δ 5.88 for amino group was observed for compounds **2a-o**, singlet at δ 8.81 was observed for $-\text{NH.CO}-$ and additional singlet at δ 3.84 for chloromethyl proton of acetamides **3a-o**. On formation of 4-thiazolidinones singlet shifted to δ 3.71 for methylene group. Singlet at δ 2.29 for methyl group and 3.80 for methoxy group were also observed. ^{13}C NMR spectra for compounds **4a-o** were recorded, which matched with expected shifts. Mass spectra of compounds **4a-o** was collected and molecular ion found correct according to molecular formula.

2. Material and Methods

Experimental

Melting points were measured by open capillary method and all were uncorrected. IR absorption spectra were recorded on Thermo scientific nicoleet iS10 FT-IR spectrometer using KBr pellet, ^1H -NMR spectra were recorded in $\text{CDCl}_3/\text{DMSO}-d_6$ Bruker Avance II 400 NMR (400 MHz FT NMR) instrument (chemical shifts in δ ppm), ^{13}C -NMR spectra were recorded in Bruker Avance II 400 NMR (100 MHz FT NMR) instrument (chemical shifts in δ ppm) and Mass spectra recorded on micromass Q-T of micro (TOF MS ES^+). Elemental analyses were performed on a Heraeus Carlo Erba 1180 CHN analyzer. The purity of products routinely checked by TLC using silica gel in toluene : ethyl acetate and toluene : methanol solvents. Substituted benzoic acid hydrazides were prepared by reported method [40].

2.1.1 General procedure for the preparation of 2-Chloromethyl-5-(substituted phenyl)-1,3,4-oxadiazoles (**1a-o**)

A mixture of chloro acetic acid (0.005 mol) and substituted benzoic acid hydrazides (0.005 mol) in 5 ml POCl₃ was refluxed on water bath for 7-10 h. Progress of the reaction was checked by TLC using toluene:ethylacetate:methanol (70:20:10) as mobile phase. The reaction mixture was cooled and poured on to crushed ice with continuous stirring. The solid mass separated was neutralized with NaHCO₃ solution (10% w/v). The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from absolute ethanol.

2-Chloromethyl-5-(4-chlorophenyl)-1,3,4-oxadiazole (1a)

Yield 88 %, mp 80-81 °C (Lit. ⁴¹ 80.5-81 °C); IR (KBr $\nu_{\max}$ cm⁻¹): 2954, 2835 (C-H, asym, sym), 1622 (>C=N-), 748 (C-Cl); ¹H NMR (400 MHz, CDCl₃, δ ppm): 7.82-6.85 d,d (4H, Ar-H), 4.62 s (2H, -CH₂Cl).

2-Chloromethyl-5-(4-methoxyphenyl)-1,3,4-oxadiazole (1b)

Yield 82 %, mp 88-90 °C (Lit. ⁴¹ 88.5-90 °C), IR (KBr $\nu_{\max}$ cm⁻¹): 2958, 2842 (C-H, asym, sym), 1630 (>C=N-), 1028, 1220 (C-O-C), 745 (C-Cl); ¹H NMR (400 MHz, CDCl₃, δ ppm): spectrum, δ , ppm: 7.96-6.92 d,d (4H, Ar-H), 4.68 s (2H, -CH₂Cl), 3.80 s (3H, -OCH₃).

2-Chloromethyl-5-(4-nitrophenyl)-1,3,4-oxadiazole (1c)

Yield 83 %, mp 134-135.5 °C (Lit. ⁴² 134-135 °C); IR (KBr $\nu_{\max}$ cm⁻¹): 2963, 2840 (C-H, asym, sym), 1615 (>C=N-), 1556, 1372 (-NO₂ asym, sym), 743 (C-Cl); ¹H NMR (400 MHz, CDCl₃, δ ppm) : 7.82-6.85 d,d (4H, Ar-H), 4.67 s (2H, -CH₂Cl).

2-Chloromethyl-5-(3-nitrophenyl)-1,3,4-oxadiazole (1d)

Yield 86 %, mp 117.5-119 °C (Lit. ⁴² 118-119 °C); IR (KBr $\nu_{\max}$ cm⁻¹): 2957, 2844 (C-H, asym, sym), 1612 (>C=N-), 1548, 1364 (-NO₂ asym, sym), 748 (C-Cl). ¹H

NMR (400 MHz, CDCl₃, δ ppm): 7.76-6.88 m (4H, Ar-H), 4.61 s (2H, -CH₂Cl).

2-Chloromethyl-5-(4-methylphenyl)-1,3,4-oxadiazole (1e)

Yield 89 %, mp 119-121 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 2956, 2832 (C-H, asym, sym), 1624 (>C=N-), 754 (C-Cl); ¹H NMR (400 MHz, CDCl₃, δ ppm): 7.72-6.65 d,d (4H, Ar-H), 4.64 s (2H, -CH₂Cl), 2.28 s (3H, -CH₃).

2-Chloromethyl-5-(3-chlorophenyl)-1,3,4-oxadiazole (1f)

Yield 90 %, mp 97-98 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 2954, 2835 (C-H, asym, sym), 1622 (>C=N-), 748 (C-Cl); ¹H NMR (400 MHz, CDCl₃): 7.70-6.82 m (4H, Ar-H), 4.62 s (2H, -CH₂Cl).

2-Chloromethyl-5-(2-chlorophenyl)-1,3,4-oxadiazole (1g)

Yield 99 %, mp 120-121 °C (Lit. ⁴³ 120-122 °C); IR (KBr $\nu_{\max}$ cm⁻¹): 2953, 2832 (C-H, asym, sym), 1625 (>C=N-), 749 (C-Cl); ¹H NMR (400 MHz, CDCl₃, δ ppm): 7.73-6.85 m (4H, Ar-H), 4.69 s (2H, -CH₂Cl).

2-Chloromethyl-5-(3-methoxyphenyl)-1,3,4-oxadiazole (1h)

Yield 82 %, mp 101-103 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 2955, 2839 (C-H, asym, sym), 1625 (>C=N-), 1023, 1215 (C-O-C), 752 (C-Cl); ¹H NMR (400 MHz, CDCl₃, δ ppm): 7.88-6.85 m (4H, Ar-H), 4.67 s (2H, -CH₂Cl), 3.78 s (3H, -OCH₃).

2-Chloromethyl-5-(2-methoxyphenyl)-1,3,4-oxadiazole (1i)

Yield 85 %, mp 78-79 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 2945, 2837 (C-H, asym, sym), 1627 (>C=N-), 1027, 1212 (C-O-C), 745 (C-Cl); ¹H NMR (400 MHz, CDCl₃, δ ppm): 7.77-6.81 m (4H, Ar-H), 4.61 s (2H, -CH₂Cl), 3.76 s (3H, -OCH₃).

2-Chloromethyl-5-(2-nitrophenyl)-1,3,4-oxadiazole (1j)

Yield 87 %, mp 71-72.5 °C (Lit. ⁴³ 71-72 °C); IR (KBr $\nu_{\max}$ cm⁻¹): 2955, 2843 (C-H,

asym, sym), 1622 ($>C=N-$), 1545, 1363 ($-NO_2$ asym, sym), 742 (C-Cl). ^1H NMR (400 MHz, $CDCl_3$, δ ppm) 7.72-6.83 m (4H, Ar-H), 4.62 s (2H, $-CH_2Cl$).

2-Chloromethyl-5-(3-methylphenyl)-1,3,4-oxadiazole (1k)

Yield 85 %, mp 60.5-62 °C (Lit. ⁴³ 61-62 °C); IR (KBr ν_{max} cm^{-1}): 2952, 2835 (C-H, asym, sym); 1628 ($>C=N-$); 752 (C-Cl); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.72-6.65 m (4H, Ar-H), 4.63 s (2H, $-CH_2Cl$), 2.27 s (3H, $-CH_3$).

2-Chloromethyl-5-(2-methylphenyl)-1,3,4-oxadiazole (1l)

Yield 82 %, mp 68-69 °C; IR (KBr ν_{max} cm^{-1}): 2952, 2835 (C-H, asym, sym), 1628 ($>C=N-$), 755 (C-Cl); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.72-6.65 m (4H, Ar-H), 4.66 s (2H, $-CH_2Cl$), 2.28 s (3H, $-CH_3$).

2-Chloromethyl-5-(3-fluorophenyl)-1,3,4-oxadiazole (1m)

Yield 85 %, mp 71-73 °C; IR (KBr ν_{max} cm^{-1}): 2952, 2835 (C-H, asym, sym), 1628 ($>C=N-$), 1220 (C-F), 755 (C-Cl); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.76-6.68 m (4H, Ar-H), 4.59 s (2H, $-CH_2Cl$).

2-Chloromethyl-5-(4-methoxy-3-nitrophenyl)-1,3,4-oxadiazole (1n)

Yield 84 %, mp 114-116 °C; IR (KBr ν_{max} cm^{-1}): 2945, 2838 (C-H, asym, sym), 1632 ($>C=N-$), 1552, 1345, ($-NO_2$ asym, sym), 1028, 1232 (C-O-C), 755 (C-Cl); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.74-6.69 m (3H, Ar-H), 4.63 s (2H, $-CH_2Cl$), 3.78 s (3H, $-OCH_3$).

2-Chloromethyl-5-(4-nitro-3-chloro)-1,3,4-oxadiazole (1o)

Yield 86 %, mp 105-106 °C; IR (KBr ν_{max} cm^{-1}): 2952, 2842 (C-H, asym, sym), 1635 ($>C=N-$), 1552, 1345, ($-NO_2$ asym, sym), 779 (C-Cl); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.75-6.78 m (3H, Ar-H), 4.67 s (2H, $-CH_2Cl$).

2.1.2 General procedure for the preparation of 4-[5-(Substituted phenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2a-o)

Solution of 2-chloromethyl-5-(4-substituted phenyl)-1,3,4-oxadiazole **1a-o** (0.01 mol) in 15 ml methanol part wise added in 15 ml methanolic solution of 4-hydroxy aniline (0.012 mol) and potassium hydroxide (0.15 mol). After addition reaction mixture was refluxed on water bath for 12-15 h. Progress of the reaction was checked by TLC using toluene:ethylacetate (75:25) as mobile phase. The reaction mixture was cooled and poured on to crushed ice with continuous stirring. The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from absolute ethanol.

4-[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2a)

Yield 88 %, mp 145-147 °C, IR (KBr ν_{max} cm^{-1}): 3445, 3344 (N-H asym, sym), 2919, 2818 (C-H, asym, sym), 1628 ($>C=N-$), 716 (C-Cl); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 5.84 s (2H, $-NH_2$), 8.81-6.86 m (8H, Ar-H), 5.28 s (2H, $-CH_2O-$).

4-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2b)

Yield 82 %, mp 156-157 °C; IR (KBr ν_{max} cm^{-1}): 3442, 3345 (N-H asym, sym), 2950, 2830 (C-H, asym, sym), 1622 ($>C=N-$), 1025, 1222 (C-O-C). ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 5.78 s (2H, $-NH_2$), 8.79-6.92 m (8H, Ar-H), 5.25 s (2H, $-CH_2O-$), 3.75 s (3H, $-OCH_3$).

4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2c)

Yield 83 %, mp 159-160 °C; IR (KBr ν_{max} cm^{-1}): 3432, 3342 (N-H asym, sym), 2945, 2830 (C-H, asym, sym), 1621 ($>C=N-$), 1545, 1366 ($-NO_2$ asym, sym); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 5.81 s (2H, -

NH₂), 8.81-6.78 m (8H, Ar-H), 5.28 s (2H, -CH₂O-).

4-[5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2d)

Yield 86 %, mp 134-136 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 3438, 3335 (N-H asym, sym), 2945, 2843 (C-H, asym, sym), 1624 (>C=N-), 1542, 1354 (-NO₂ asym, sym); ¹H NMR (400 MHz, CDCl₃, δ ppm): 5.87 s (2H, -NH₂), 8.79-6.92 m (8H, Ar-H), 5.23 s (2H, -CH₂O-).

4-[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2e)

Yield 89 %, mp 129-131 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 3434, 3328 (N-H asym, sym), 2946, 2828 (C-H, asym, sym), 1626 (>C=N-); ¹H NMR (400 MHz, CDCl₃, δ ppm): 5.88 s (2H, -NH₂), 8.00-6.93 m (8H, Ar-H), 5.26 s (2H, -CH₂O-), 2.28 s (3H, -CH₃).

4-[5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2f)

Yield 90 %, mp 138-140 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 3434, 3318 (N-H asym, sym), 2951, 2832 (C-H, asym, sym), 1621 (>C=N-); ¹H NMR (400 MHz, CDCl₃): 5.84 s (2H, -NH₂), 8.76-6.86 m (8H, Ar-H), 5.28 s (2H, -CH₂O-).

4-[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2g)

Yield 89 %, mp 149-151 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 3431, 3324 (N-H asym, sym), 2948, 2828 (C-H, asym, sym), 1628 (>C=N-), 765 (C-Cl); ¹H NMR (400 MHz, CDCl₃, δ ppm): 5.85 s (2H, -NH₂), 8.87-6.95 m (8H, Ar-H), 5.38 s (2H, -CH₂O-).

4-[5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2h)

Yield 82 %, mp 162-164 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 3433, 3325 (N-H asym, sym), 2950, 2837 (C-H, asym, sym), 1625 (>C=N-), 1020, 1228 (C-O-C); ¹H NMR (400 MHz, CDCl₃, δ ppm): 5.83 s (2H, -NH₂), 8.82-6.85 m (8H, Ar-H), 5.28 s (2H, -CH₂O-), 3.68 s (3H, -OCH₃).

4-[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2i)

Yield 85 %, mp 167-168 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 3431, 3330 (N-H asym, sym), 2935, 2823 (C-H, asym, sym), 1624 (>C=N-), 1023, 1215 (C-O-C); ¹H NMR (400 MHz, CDCl₃, δ ppm): 5.82 s (2H, -NH₂), 8.74-6.88 m (8H, Ar-H), 5.25 s (2H, -CH₂O-), 3.75 s (3H, -OCH₃).

4-[5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2j)

Yield 87 %, mp 172-174 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 3428, 3322 (N-H asym, sym), 2945, 2842 (C-H, asym, sym), 1627 (>C=N-), 1547, 1362 (-NO₂ asym, sym). ¹H NMR (400 MHz, CDCl₃, δ ppm): 5.86 s (2H, -NH₂), 8.81-6.76 m (8H, Ar-H), 5.28 s (2H, -CH₂O-).

4-[5-(3-methylphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2k)

Yield 85 %, mp 123-125 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 3434, 3322 (N-H asym, sym), 2935, 2845 (C-H, asym, sym), 1622 (>C=N-); ¹H NMR (400 MHz, CDCl₃, δ ppm): 5.86 s (2H, -NH₂), 8.87-6.75 m (8H, Ar-H), 5.28 s (2H, -CH₂O-), 2.32 s (3H, -CH₃).

4-[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2l)

Yield 85 %, mp 131-132 °C; IR (KBr $\nu_{\max}$ cm⁻¹): 3425, 3323 (N-H asym, sym), 2925, 2832 (C-H, asym, sym), 1626 (>C=N-). ¹H NMR (400 MHz, CDCl₃, δ ppm): 5.83 s (2H, -NH₂), 8.74-6.72 m (8H, Ar-H), 5.32 s (2H, -CH₂O-), 2.45 s (3H, -CH₃).

4-[5-(3-fluorophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2m)

Yield 85 %, mp 167-169 °C, IR (KBr $\nu_{\max}$ cm⁻¹): 3434, 3332 (N-H asym, sym), 2950, 2832 (C-H, asym, sym), 1623 (>C=N-), 1221 (C-F); ¹H NMR (400 MHz, CDCl₃, δ ppm): 5.80 s (2H, -NH₂), 8.79-6.78 m (8H, Ar-H), 5.32 s (2H, -CH₂O-).

4-[5-(4-methoxy-3-nitrophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2n)

Yield 84 %, mp 176-178 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3428, 3335 (N-H asym, sym), 2952, 2840 (C-H, asym, sym), 1628 ($>\text{C}=\text{N}-$), 1545, 1338 ($-\text{NO}_2$ asym, sym), 1032, 1232 (C-O-C); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 5.79 s (2H, $-\text{NH}_2$), 8.80-6.79 m (7H, Ar-H), 5.32 s (2H, $-\text{CH}_2\text{O}-$), 3.75 s (3H, $-\text{OCH}_3$).

4-[5-(4-nitro-3-chloro)-1,3,4-oxadiazol-2-yl-methoxy]-phenylamine (2o)

Yield 84 %, mp 152-156 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3430, 3334 (N-H asym, sym), 2954, 2835 (C-H, asym, sym), 1627 ($>\text{C}=\text{N}-$), 1542, 1328 ($-\text{NO}_2$ asym, sym), 754 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 5.81 s (2H, $-\text{NH}_2$), 8.91-6.81 m (7H, Ar-H), 5.28 s (2H, $-\text{CH}_2\text{O}-$).

2.1.3 General procedure for the preparation of 2-Chloro-N-{4-[5-(substituted phenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3a-o)

Solution chloroacetylchloride (0.015 mol) in DMF was added to a solution of 4-[5-(substituted phenyl)-1,3,4-oxadiazol-2-ylmethoxy]-phenylamine **2a-o** (0.01 mol) in DMF and K_2CO_3 (0.02 mol) at 0-5 °C. The reaction mixture was stirred for overnight and reaction solution was poured in ice, the product was filtered and washed water. The solid obtained was recrystallized from alcohol.

2-Chloro-N-{4-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3a)

Yield 88 %, mp 182-184 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3352 (N-H), 2953, 2818 (C-H, asym, sym), 1684 (amide-I), 1617 ($>\text{C}=\text{N}-$), 1502 (amide-II), 1231 (amide-III), 716 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.81 s (1H, $-\text{NH}$), 8.11-6.84 m (8H, Ar-H), 3.84 s (2H, $-\text{CH}_2\text{Cl}$), 5.28 s (2H, $-\text{CH}_2\text{O}-$).

2-Chloro-N-{4-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3b)

Yield 82 %, mp 172-174 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3345 (N-H), 2945, 2832 (C-H, asym, sym), 1685 (amide-I), 1618 ($>\text{C}=\text{N}-$), 1512 (amide-II), 1225 (amide-III), 1022, 1230 (C-O-C), 726 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.78 s (1H, $-\text{NH}$), 8.15-6.82 m (8H, Ar-H), 3.87 s (2H, $-\text{CH}_2\text{Cl}$), 5.32 s (2H, $-\text{CH}_2\text{O}-$), 3.74 s (3H, $-\text{OCH}_3$).

2-Chloro-N-{4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3c)

Yield 83 %, mp 192-194 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3348 (N-H), 2952, 2838 (C-H, asym, sym), 1628 ($>\text{C}=\text{N}-$), 1518 (amide-II), 1232 (amide-III), 1552, 1365 ($-\text{NO}_2$ asym, sym), 726 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.73 s (1H, $-\text{NH}$), 8.12-6.88 m (8H, Ar-H), 3.82 s (2H, $-\text{CH}_2\text{Cl}$), 5.28 s (2H, $-\text{CH}_2\text{O}-$).

2-Chloro-N-{4-[5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3d)

Yield 83 %, mp 199-201 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3356 (N-H), 2945, 2834 (C-H, asym, sym), 1632 ($>\text{C}=\text{N}-$), 1515 (amide-II), 1228 (amide-III), 1546, 1352 ($-\text{NO}_2$ asym, sym), 732 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.78 s (1H, $-\text{NH}$), 8.01-6.78 m (8H, Ar-H), 3.78 s (2H, $-\text{CH}_2\text{Cl}$), 5.32 s (2H, $-\text{CH}_2\text{O}-$).

2-Chloro-N-{4-[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3e)

Yield 83 %, mp 165-167 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3348 (N-H), 2952, 2842 (C-H, asym, sym), 1628 ($>\text{C}=\text{N}-$), 1520 (amide-II), 1232 (amide-III), 732 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.81 s (1H, $-\text{NH}$), 8.06-6.99 m (8H, Ar-H), 3.84 s (2H, $-\text{CH}_2\text{Cl}$), 5.37 s (2H, $-\text{CH}_2\text{O}-$), 2.56 s (3H, $-\text{CH}_3$).

2-Chloro-*N*-{4-[5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3f)

Yield 83 %, mp 205-207 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3352 (N-H), 2948, 2838 (C-H, asym, sym), 1628 ($>\text{C}=\text{N}-$), 1525 (amide-II), 1227 (amide-III), 745 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.78 s (1H, -NH), 8.11-6.79 m (8H, Ar-H), 3.75 s (2H, $-\text{CH}_2\text{Cl}$), 5.28 s (2H, $-\text{CH}_2\text{O}-$).

2-Chloro-*N*-{4-[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3g)

Yield 83 %, mp 177-179 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3345 (N-H), 2952, 2828 (C-H, asym, sym), 1623 ($>\text{C}=\text{N}-$), 1523 (amide-II), 1228 (amide-III), 750 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.79 s (1H, -NH), 8.15-6.82 m (8H, Ar-H), 3.82 s (2H, $-\text{CH}_2\text{Cl}$), 5.32 s (2H, $-\text{CH}_2\text{O}-$).

2-Chloro-*N*-{4-[5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3h)

Yield 82 %, mp 188-186 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3352 (N-H), 2952, 2835 (C-H, asym, sym), 1678 (amide-I), 1622 ($>\text{C}=\text{N}-$), 1518 (amide-II), 1230 (amide-III), 1025, 1245 (C-O-C), 736 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.82 s (1H, -NH), 8.13-6.78 m (8H, Ar-H), 3.86 s (2H, $-\text{CH}_2\text{Cl}$), 5.35 s (2H, $-\text{CH}_2\text{O}-$), 3.77 s (3H, $-\text{OCH}_3$).

2-Chloro-*N*-{4-[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3i)

Yield 82 %, mp 196-198 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3345 (N-H), 2956, 2831 (C-H, asym, sym), 1682 (amide-I), 1623 ($>\text{C}=\text{N}-$), 1521 (amide-II), 1212 (amide-III), 1032, 1228 (C-O-C), 728 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.78 s (1H, -NH), 8.11-6.79 m (8H, Ar-H), 3.87 s (2H, $-\text{CH}_2\text{Cl}$), 5.32 s (2H, $-\text{CH}_2\text{O}-$), 3.77 s (3H, $-\text{OCH}_3$).

2-Chloro-*N*-{4-[5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3j)

Yield 83 %, mp 211-213 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3345 (N-H), 2952, 2832 (C-H, asym, sym), 1628 ($>\text{C}=\text{N}-$), 1512 (amide-II), 1232 (amide-III), 1542, 1345 ($-\text{NO}_2$ asym, sym), 733 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.68 s (1H, -NH), 8.11-6.77 m (8H, Ar-H), 3.76 s (2H, $-\text{CH}_2\text{Cl}$), 5.31 s (2H, $-\text{CH}_2\text{O}-$).

2-Chloro-*N*-{4-[5-(3-methylphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3k)

Yield 83 %, mp 207-209 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3354 (N-H), 2945, 2842 (C-H, asym, sym), 1632 ($>\text{C}=\text{N}-$), 1528 (amide-II), 1223 (amide-III), 728 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.72 s (1H, -NH), 8.16-6.78 m (8H, Ar-H), 3.78 s (2H, $-\text{CH}_2\text{Cl}$), 5.31 s (2H, $-\text{CH}_2\text{O}-$), 2.52 s (3H, $-\text{CH}_3$).

2-Chloro-*N*-{4-[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3l)

Yield 83 %, mp 157-159 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3348 (N-H), 2954, 2845 (C-H, asym, sym), 1628 ($>\text{C}=\text{N}-$), 1530 (amide-II), 1222 (amide-III), 732 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.75 s (1H, -NH), 8.18-6.75 m (8H, Ar-H), 3.82 s (2H, $-\text{CH}_2\text{Cl}$), 5.28 s (2H, $-\text{CH}_2\text{O}-$), 2.45 s (3H, $-\text{CH}_3$).

2-Chloro-*N*-{4-[5-(3-fluorophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3m)

Yield 83 %, mp 161-163 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3352 (N-H), 2945, 2852 (C-H, asym, sym), 1623 ($>\text{C}=\text{N}-$), 1531 (amide-II), 1225 (amide-III), 1213 (C-F), 728 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.78 s (1H, -NH), 8.01-6.88 m (8H, Ar-H), 3.81 s (2H, $-\text{CH}_2\text{Cl}$), 5.23 s (2H, $-\text{CH}_2\text{O}-$).

2-Chloro-*N*-{4-[5-(4-methoxy-3-nitrophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3n)

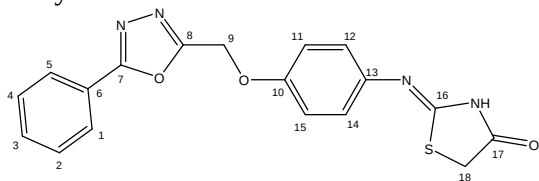
Yield 83 %, mp 209-211 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3345 (N-H), 2945, 2852 (C-H, asym, sym), 1623 ($>\text{C}=\text{N}-$), 1531 (amide-II), 1225 (amide-III), 1538, 1345 ($-\text{NO}_2$ asym, sym), 1032, 1228 (C-O-C), 732 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.82 s (1H, -NH), 8.11-6.89 m (7H, Ar-H), 3.82 s (2H, $-\text{CH}_2\text{Cl}$), 5.27 s (2H, $-\text{CH}_2\text{O}-$), 3.72 s (3H, $-\text{OCH}_3$).

2-Chloro-*N*-{4-[5-(4-nitro-3-chlorophenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide (3o)

Yield 83 %, mp 217-219 °C; IR (KBr $\nu_{\max}$ cm^{-1}): 3352 (N-H), 2937, 2845 (C-H, asym, sym), 1628 ($>\text{C}=\text{N}-$), 1528 (amide-II), 1223 (amide-III), 1528, 1352 ($-\text{NO}_2$ asym, sym), 731 (C-Cl); ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.78 s (1H, -NH), 8.12-6.87 m (7H, Ar-H), 3.85 s (2H, $-\text{CH}_2\text{Cl}$), 5.32 s (2H, $-\text{CH}_2\text{O}-$).

2.1.4 General procedure for the preparation of *N*-(4-Oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(substituted phenyl)-1,3,4-oxadiazol-2-yl-methoxy)-phenyl]amine (4a-o)

Solution of 2-Chloro-*N*-{4-[5-(substituted phenyl)-1,3,4-oxadiazol-2-yl-methoxy]-phenyl}-acetamide **3a-o** (0.01 mol) and ammonium thiocyanate in 30 ml ethanol was refluxed for 15-17 h. Progress of the reaction was checked by TLC using toluene:ethylacetate (75:25) as mobile phase. The reaction mixture was cooled and poured on to crushed ice with continuous stirring. The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from absolute methanol.



N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl-methoxy)-phenyl]amine (4a)

Yield 63 %, mp 135-137 °C; Anal. Calculated % $\text{C}_{18}\text{H}_{13}\text{N}_4\text{O}_3\text{ClS}$: C-53.94, H-03.27, N-13.98. Found C-53.92, H-03.25, N-13.96; IR (KBr $\nu_{\max}$ cm^{-1}): 3404 (N-H), 2957, 2871 (C-H asym, sym), 1732 ($>\text{C}=\text{O}$), 1679 ($>\text{C}=\text{N}-$), 743 (C-Cl); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ ppm): 9.12 s (1H, -NH), 7.94-6.98 m (8H, Ar-H), 3.77 s (2H, $-\text{CH}_2\text{S}-$), 5.32 s (2H, $-\text{CH}_2\text{O}-$); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, δ ppm): 42.44 (C-18), 72.28 (C-9), 115.28 (C-11,15), 122.90 (C-2,4), 124.84 (C-1,5), 127.88 (C-12, 14), 136.45 (C-6), 139.42 (C-3), 143.21 (C-13), 154.67 (C-16), 160.82 (C-8), 162.45 (C-10), 163.12 (C-7), 169.25 (C-17); MS : m/z 400.2 (M^+), 401.1 ($\text{M}^+ + 1$), 402.2 ($\text{M}^+ + 2$), 403.2 ($\text{M}^+ + 3$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4b)

Yield 64 %, mp 167-169 °C; Anal. Calculated % $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_4\text{S}$: C-57.57, H-04.07, N-14.13. Found C-57.59, H-04.07, N-14.15; IR (KBr $\nu_{\max}$ cm^{-1}): 3414 (N-H), 2945, 2872 (C-H asym, sym), 1725 ($>\text{C}=\text{O}$), 1682 ($>\text{C}=\text{N}-$), 1012, 1225 (C-O-C); ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ ppm): 9.06 s (1H, -NH), 7.92-6.92 m (8H, Ar-H), 3.78 s (2H, $-\text{CH}_2\text{S}-$), 5.29 s (2H, $-\text{CH}_2\text{O}-$), 3.62 s (3H, $-\text{OCH}_3$); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$, δ ppm): 42.42 (C-18), 57.55 ($-\text{OCH}_3$), 72.32 (C-9), 115.35 (C-11,15), 121.98 (C-2,4), 123.92 (C-1,5), 128.08 (C-12, 14), 135.98 (C-6), 138.79 (C-3), 143.05 (C-13), 155.15 (C-16), 161.12 (C-8), 161.85 (C-10), 162.88 (C-7), 168.88 (C-17); MS : m/z 396.1 (M^+), 397.2 ($\text{M}^+ + 1$), 398.2 ($\text{M}^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4c)

Yield 65 %, mp 177-179 °C; Anal. Calculated % $\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_5\text{S}$: C-52.55, H-03.19, N-17.02. Found C-52.53, H-03.17,

N-17.04; IR (KBr $\nu_{\max}$ cm^{-1}): 3366 (N-H), 2952, 2859 (C-H asym, sym), 1744 ($>\text{C}=\text{O}$), 1663 ($>\text{C}=\text{N}$ -), 1547, 1336 ($-\text{NO}_2$ asym, sym); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.16 s (1H, -NH), 7.94-6.88 m (8H, Ar-H), 3.81 s (2H, $-\text{CH}_2\text{S}$ -), 5.32 s (2H, $-\text{CH}_2\text{O}$ -); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 42.45 (C-18), 72.32 (C-9), 114.26 (C-11,15), 123.90 (C-2,4), 125.86 (C-1,5), 127.98 (C-12, 14), 136.67 (C-6), 139.75 (C-3), 143.67 (C-13), 154.23 (C-16), 160.74 (C-8), 161.67 (C-10), 163.54 (C-7), 168.63 (C-17); MS : m/z 411.2 (M^+), 412.1 ($\text{M}^+ + 1$), 413.2 ($\text{M}^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(3-nitrophenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4d)
Yield 66 %, mp 181-183 °C; Anal. Calculated % $\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_5\text{S}$: C-52.55, H-03.19, N-17.02. Found C-52.55, H-03.19, N-17.04; IR (KBr $\nu_{\max}$ cm^{-1}): 3412 (N-H), 2942, 2848 (C-H asym, sym), 1725 ($>\text{C}=\text{O}$), 1679 ($>\text{C}=\text{N}$ -), 1532, 1345 ($-\text{NO}_2$ asym, sym); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.13 s (1H, -NH), 7.91-6.93 m (8H, Ar-H), 3.77 s (2H, $-\text{CH}_2\text{S}$ -), 5.37 s (2H, $-\text{CH}_2\text{O}$ -); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 42.45 (C-18), 72.32 (C-9), 115.34-162.63 (C-1-C-6, C-10-C-15), 154.23 (C-16), 160.74 (C-8), 163.54 (C-7), 168.63 (C-17); MS : m/z 411.2 (M^+), 412.2 ($\text{M}^+ + 1$), 413.2 ($\text{M}^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(4-methylphenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4e)
Yield 61 %, mp 152-154 °C; Anal. Calculated % $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$: C-59.99, H-04.24, N-14.73. Found C-59.97, H-04.26, N-14.71; IR (KBr $\nu_{\max}$ cm^{-1}): 3423 (N-H), 2948, 2835 (C-H asym, sym), 1721 ($>\text{C}=\text{O}$), 1680 ($>\text{C}=\text{N}$ -); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.02 s (1H, -NH), 7.96-6.93 m (8H, Ar-H), 3.71 s (2H, $-\text{CH}_2\text{S}$ -), 5.28 s (2H, $-\text{CH}_2\text{O}$ -), 2.29 s (3H, $-\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 21.98 ($-\text{CH}_3$), 42.39 (C-18), 72.36 (C-9), 114.21 (C-11,15), 123.90 (C-2,4),

125.92 (C-1,5), 127.82 (C-12, 14), 136.85 (C-6), 139.92 (C-3), 143.24 (C-13), 153.63 (C-16), 160.88 (C-8), 161.43 (C-10), 163.32 (C-7), 168.65 (C-17); MS : m/z 380.1 (M^+), 381.2 ($\text{M}^+ + 1$), 382.2 ($\text{M}^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(3-chlorophenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4f)

Yield 65 %, mp 187-189 °C; Anal. Calculated % $\text{C}_{18}\text{H}_{13}\text{N}_4\text{O}_3\text{ClS}$: C-53.94, H-03.27, N-13.98. Found C-53.92, H-03.24, N-13.96; IR (KBr $\nu_{\max}$ cm^{-1}): 3404 (N-H), 2957, 2871 (C-H asym, sym), 1732 ($>\text{C}=\text{O}$), 1679 ($>\text{C}=\text{N}$ -), 743 (C-Cl); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.12 s (1H, -NH), 7.96-6.92 m (8H, Ar-H), 3.72 s (2H, $-\text{CH}_2\text{S}$ -), 5.32 s (2H, $-\text{CH}_2\text{O}$ -); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 42.67 (C-18), 72.35 (C-9), 115.58-163.42 (C-1-C-6, C-10-C-15), 154.31 (C-16), 161.05 (C-8), 163.89 (C-7), 168.90 (C-17); MS : m/z 400.1 (M^+), 401.1 ($\text{M}^+ + 1$), 402.2 ($\text{M}^+ + 2$), 403.2 ($\text{M}^+ + 3$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(2-chlorophenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4g)

Yield 69 %, mp 158-160 °C; Anal. Calculated % $\text{C}_{18}\text{H}_{13}\text{N}_4\text{O}_3\text{ClS}$: C-53.94, H-03.27, N-13.98. Found C-53.92, H-03.25, N-13.96; IR (KBr $\nu_{\max}$ cm^{-1}): 3452 (N-H), 2932, 2842 (C-H asym, sym), 1728 ($>\text{C}=\text{O}$), 1677 ($>\text{C}=\text{N}$ -), 756 (C-Cl); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.05 s (1H, -NH), 7.92-6.98 m (8H, Ar-H), 3.77 s (2H, $-\text{CH}_2\text{S}$ -), 5.28 s (2H, $-\text{CH}_2\text{O}$ -); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 42.45 (C-18), 72.57 (C-9), 115.89-163.67 (C-1-C-6, C-10-C-15), 154.28 (C-16), 161.15 (C-8), 163.74 (C-7), 168.86 (C-17); MS : m/z 400.1 (M^+), 401.2 ($\text{M}^+ + 1$), 402.2 ($\text{M}^+ + 2$), 403.2 ($\text{M}^+ + 3$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4h)

Yield 71 %, mp 171-173 °C; Anal. Calculated % $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_4\text{S}$: C-57.57, H-04.07, N-14.13. Found C-57.59, H-04.05,

N-14.15; IR (KBr $\nu_{\max}$ cm^{-1}): 3442 (N-H), 2925, 2843 (C-H asym, sym), 1723 ($>\text{C}=\text{O}$), 1677 ($>\text{C}=\text{N}$ -), 1012, 1220 (C-O-C); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.15 s (1H, -NH), 7.84-6.88 m (8H, Ar-H), 3.75 s (2H, $-\text{CH}_2\text{S}$ -), 5.28 s (2H, $-\text{CH}_2\text{O}$ -), 3.65 s (3H, $-\text{OCH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 42.52 (C-18), 57.78 ($-\text{OCH}_3$), 72.62 (C-9), 115.90-163.52 (C-1-C-6, C-10-C-15), 153.54 (C-16), 161.43 (C-8), 163.28 (C-7), 168.31 (C-17); MS : m/z 396.2 (M^+), 397.2 ($\text{M}^+ + 1$), 398.2 ($\text{M}^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4i)
Yield 73 %, mp 185-186 °C; Anal. Calculated % $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_4\text{S}$: C-57.57, H-04.07, N-14.13. Found C-57.59, H-04.08, N-14.14; IR (KBr $\nu_{\max}$ cm^{-1}): 3442 (N-H), 2941, 2849 (C-H asym, sym), 1731 ($>\text{C}=\text{O}$), 1675 ($>\text{C}=\text{N}$ -), 1014, 1217 (C-O-C); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.15 s (1H, -NH), 7.77-6.92 m (8H, Ar-H); 3.79 s (2H, $-\text{CH}_2\text{S}$ -), 5.31 s (2H, $-\text{CH}_2\text{O}$ -), 3.75 s (3H, $-\text{OCH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 42.57 (C-18), 57.67 ($-\text{OCH}_3$), 72.68 (C-9), 115.85-163.42 (C-1-C-6, C-10-C-15), 153.48 (C-16), 161.58 (C-8), 163.30 (C-7), 168.47 (C-17); MS : m/z 396.1 (M^+), 397.2 ($\text{M}^+ + 1$), 398.2 ($\text{M}^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(2-nitrophenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4j)
Yield 75 %, mp 195-197 °C; Anal. Calculated % $\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_5\text{S}$: C-52.55, H-03.19, N-17.02. Found C-52.55, H-03.17, N-17.04; IR (KBr $\nu_{\max}$ cm^{-1}): 3443 (N-H), 2948, 2839 (C-H asym, sym), 1728 ($>\text{C}=\text{O}$), 1678 ($>\text{C}=\text{N}$ -), 1538, 1348 ($-\text{NO}_2$ asym, sym); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.12 s (1H, -NH), 7.79-6.95 m (8H, Ar-H); 3.75 s (2H, $-\text{CH}_2\text{S}$ -), 5.28 s (2H, $-\text{CH}_2\text{O}$ -); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 42.52 (C-18), 72.64 (C-9), 115.69-163.65 (C-1-C-6, C-10-C-

15), 154.32 (C-16), 161.25 (C-8), 163.64 (C-7), 168.76 (C-17); MS : m/z 411.1 (M^+), 412.2 ($\text{M}^+ + 1$), 413.2 ($\text{M}^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(3-methylphenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4k)
Yield 65 %, mp 141-143 °C; Anal. Calculated % $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$: C-59.59, H-04.24, N-14.73. Found C-59.61, H-04.22, N-14.75; IR (KBr $\nu_{\max}$ cm^{-1}): 3442 (N-H), 2945, 2842 (C-H asym, sym), 1732 ($>\text{C}=\text{O}$), 1665 ($>\text{C}=\text{N}$ -); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.08 s (1H, -NH), 7.82-6.93 m (8H, Ar-H), 3.77 s (2H, $-\text{CH}_2\text{S}$ -), 5.32 s (2H, $-\text{CH}_2\text{O}$ -), 2.32 s (3H, $-\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 21.98 ($-\text{CH}_3$), 42.45 (C-18), 72.78 (C-9), 115.85-163.45 (C-1-C-6, C-10-C-15), 153.64 (C-16), 161.52 (C-8), 163.32 (C-7), 168.25 (C-17); MS : m/z 380.1 (M^+), 381.2 ($\text{M}^+ + 1$), 382.2 ($\text{M}^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(2-methylphenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4l)
Yield 61 %, mp 147-149 °C; Anal. Calculated % $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{S}$: C-59.59, H-04.24, N-14.73. Found C-59.61, H-04.22, N-14.75; IR (KBr $\nu_{\max}$ cm^{-1}): 3435 (N-H), 2932, 2834 (C-H asym, sym), 1728 ($>\text{C}=\text{O}$), 1668 ($>\text{C}=\text{N}$ -); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.08 s (1H, -NH), 7.82-6.93 m (8H, Ar-H), 3.77 s (2H, $-\text{CH}_2\text{S}$ -), 5.32 s (2H, $-\text{CH}_2\text{O}$ -), 2.32 s (3H, $-\text{CH}_3$); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 21.98 ($-\text{CH}_3$), 42.54 (C-18), 72.68 (C-9), 115.67-163.52 (C-1-C-6, C-10-C-15), 153.52 (C-16), 161.45 (C-8), 163.28 (C-7), 168.31 (C-17); MS : m/z 380.1 (M^+), 381.2 ($\text{M}^+ + 1$), 382.2 ($\text{M}^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(3-fluorophenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4m)
Yield 59 %, mp 169-171 °C; Anal. Calculated % $\text{C}_{18}\text{H}_{13}\text{N}_4\text{O}_3\text{FS}$: C-56.25, H-03.41, N-14.58. Found C-56.27, H-03.43, N-14.56; IR (KBr $\nu_{\max}$ cm^{-1}): 3444 (N-H),

2945, 2838 (C-H asym, sym), 1732 ($>C=O$), 1672 ($>C=N-$), 1212 (C-F); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.18 s (1H, -NH), 7.76-6.98 m (8H, Ar-H), 3.76 s (2H, -CH₂S-), 5.28 s (2H, -CH₂O-); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 42.49 (C-18), 72.45 (C-9), 115.12-162.89 (C-1-C-6, C-10-C-15), 154.37 (C-16), 160.87 (C-8), 163.61 (C-7), 168.73 (C-17); MS : m/z 384.1 (M^+), 385.2 ($M^+ + 1$), 386.2 ($M^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(4-methoxy-3-nitrophenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4n)
Yield 71 %, mp 198-200 °C; Anal. Calculated % C₁₉H₁₅N₅O₆S: C-51.07, H-03.43, N-15.87. Found C-51.06, H-03.41, N-15.88; IR (KBr ν_{max} cm⁻¹): 3448 (N-H), 2935, 2842 (C-H asym, sym), 1728 ($>C=O$), 1665 ($>C=N-$), 1542, 1352 (-NO₂ asym, sym), 1020, 1234 (C-O-C); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.06 s (1H, -NH), 7.92-6.91 m (7H, Ar-H); 3.79 s (2H, -CH₂S-), 5.31 s (2H, -CH₂O-), 3.65 s (3H, -OCH₃); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 42.54 (C-18), 57.67 (-OCH₃), 72.72 (C-9), 115.68-163.45 (C-1-C-6, C-10-C-15), 153.45 (C-16), 161.56 (C-8), 163.32 (C-7), 168.28 (C-17); MS : m/z 441.1 (M^+), 442.2 ($M^+ + 1$), 443.2 ($M^+ + 2$).

N-(4-oxo-1,3-thiazolidin-2-ylidene)-[4-(5-(4-nitro-3-chlorophenyl)-1,3,4-oxadiazol-2-ylmethoxy)-phenyl]amine (4o)
Yield 78 %, mp 160-162 °C; Anal. Calculated % C₁₈H₁₂N₅O₅ClS: C- 48.49, H- 2.71, N- 15.71. Found C-48.47, H-02.69, N-15.73; IR (KBr ν_{max} cm⁻¹): 3452 (N-H), 2942, 2848 (C-H asym, sym), 1732 ($>C=O$), 1662 ($>C=N-$), 1545, 1343, (-NO₂ asym, sym), 760 (C-Cl); ^1H NMR (400 MHz, DMSO- d_6 , δ ppm): 9.16 s (1H, -NH), 7.88-6.95 m (7H, Ar-H), 3.79 s (2H, -CH₂S-), 5.31 s (2H, -CH₂O-); ^{13}C NMR (100 MHz, DMSO- d_6 , δ ppm): 42.58 (C-18), 72.68 (C-9), 115.48-163.52 (C-1-C-6, C-10-C-15), 153.69 (C-16), 161.62 (C-8),

163.45 (C-7), 168.31 (C-17); MS : m/z 445.1 (M^+), 446.2 ($M^+ + 1$), 447.2 ($M^+ + 2$), 448.2 ($M^+ + 3$).

Results and Discussion

Antibacterial activity

Antimicrobial activity of synthesized compounds reported in Table 1. Compounds were screened for antibacterial and antifungal *in vitro* activity against *E. coli* (MTCC 443), *P. aeruginosa* (MTCC 2488), *S. aureus* (MTCC 96), *S. pyogenes* (MTCC 442), *C. albicans* (MTCC 227), *A. niger* (MTCC 282), *A. clavatus* (MTCC 1323) respectively using broth microdilution method [44]. Minimum inhibitory concentration was determined and compared with standard drugs ampicillin and greseofulvin.

Results of antimicrobial activity were revealed that 2-chloromethyl-5-substituted-1,3,4-oxadiazoles **1b** (4-OCH₃), **1e** (4-CH₃), **1f** (3-Cl), **1l** (2-CH₃) showed good activity at 100 µg/ml, **1d** (3-NO₂) showed very good activity at 62.5 µg/ml against *E. coli*. **1d** (3-NO₂) showed good activity at 100 µg/ml against *P. aeruginosa*. **1e** (4-CH₃), **1g** (2-Cl), **1i** (2-OCH₃), **1j** (2-NO₂), **1n** (4-OCH₃, 3-NO₂), **1o** (4-NO₂, 3-Cl) demonstrated very good activity at 100-125 µg/ml, compounds **1k** (3-CH₃), **1m** (3-F) demonstrated higher activity at 62.5 µg/ml against *S. aureus*. Compounds **1g** (2-Cl), **1i** (2-OCH₃), **1m** (3-F) showed good activity at 100 µg/ml against *S. pyogenes*. Acetamides **3f** (3-Cl), **3h** (3-OCH₃), **3n** (4-OCH₃, 3-NO₂), **3o** (4-NO₂, 3-Cl) showed good activity at 100 µg/ml, **3b** (4-OCH₃) showed very good activity at 62.5 µg/ml against *E. coli*. Compounds **3i** (2-OCH₃), **3j** (2-NO₂), **3k** (3-CH₃) demonstrated good activity at 100 µg/ml, **3l** (2-CH₃) demonstrated very good activity at 62.5 µg/ml against *P. aeruginosa*. Compounds **3a** (4-Cl), **3b** (4-

OCH₃), **3c** (4-NO₂), **3d** (3-NO₂), **3e** (4-CH₃), **3i** (2-OCH₃), **3l** (2-CH₃) showed very good activity at 100-125 µg/ml against *S. aureus*. Compounds **3a** (4-Cl), **3k** (3-CH₃), **3m** (3-F) showed good activity at 100 µg/ml, **3i** (2-OCH₃), **3l** (2-CH₃) showed very good activity at 62.5 µg/ml against *S. pyogenes*. 4-Thiazolidinones **4b** (4-OCH₃), **4m** (3-F) demonstrated good activity at 100 µg/ml against *E. coli*. Compounds **4a** (4-Cl), **4e** (4-CH₃), **4h** (3-OCH₃), **4i** (2-OCH₃), **4k** (3-CH₃), **4l** (2-CH₃), **4n** (4-OCH₃, 3-NO₂) showed good activity at 100-125 µg/ml against *S. aureus*. Compound **4i** (2-OCH₃) showed very good activity at 62.5 µg/ml against *S. pyogenes*. Other compounds demonstrated good activity at 200-250 µg/ml against *S. aureus* with few exceptions and showed moderate activity against other bacterias.

Antifungal Activity

2-Chloromethyl-5-substituted-1,3,4-oxadiazoles **1c** (4-NO₂), **1e** (4-CH₃), **1i** (2-OCH₃), **1k** (3-CH₃) showed good activity at 500 µg/ml, compound **1j** (2-NO₂) showed very good activity at 250 µg/ml. Acetamides **3b** (4-OCH₃), **3f** (3-Cl), **3j** (2-NO₂), **3m** (3-F), **3o** (4-NO₂, 3-Cl) showed good activity, **3i** (2-OCH₃) showed very good activity at 250 µg/ml. 4-Thiazolidinones **4e** (4-CH₃), **4g** (2-Cl), **4n** (4-OCH₃, 3-NO₂) showed good activity at

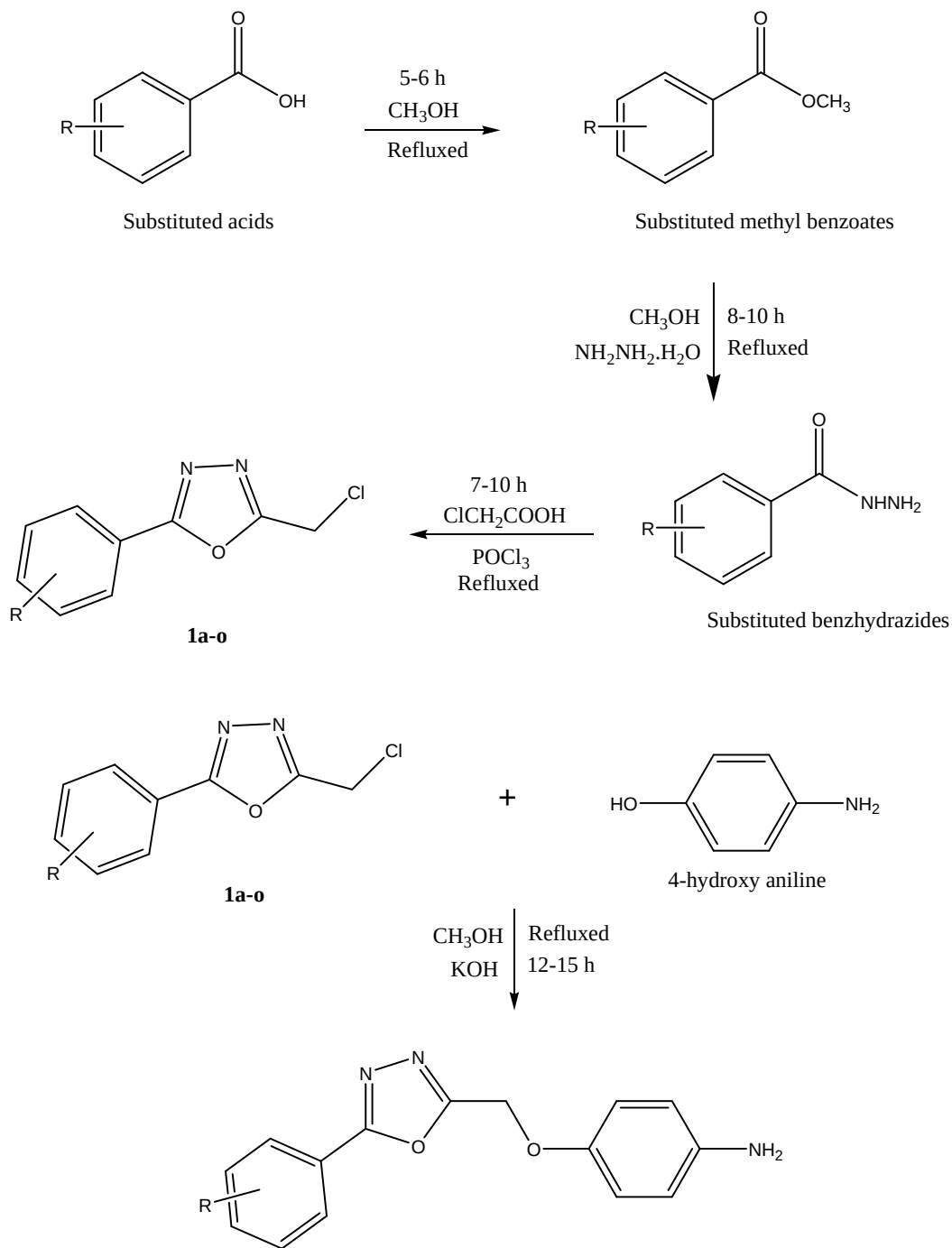
500 µg/ml, **4a** (4-Cl) showed very good activity at 250 µg/ml against *C. albicans*. Other compounds demonstrated moderate activity against other fungal species.

Conclusion

Activity was improved with chloro methyl group either in 1,3,4-oxadiazoles **1a-o** or in acetamides **3a-o**. Activity was decreased on formation of 4-thiazolidinones **4a-o**. Growth of the *S. aureus* was inhibited by most of the compounds with few exceptions in comparison with ampicillin. Antimicrobial activity against *E. coli* and *S. pyogenes* was similar. In comparison with other bacterias *P. aeruginosa* showed bacterial resistance for synthesized compounds except acetamides. 1,3,4-Oxadiazoles **1a-o**, acetamides **3a-o** and 4-thiazolidinones **4a-o** have showed similar antifungal activity. Significant antifungal activity was observed for *C. albicans* than other fungal species.

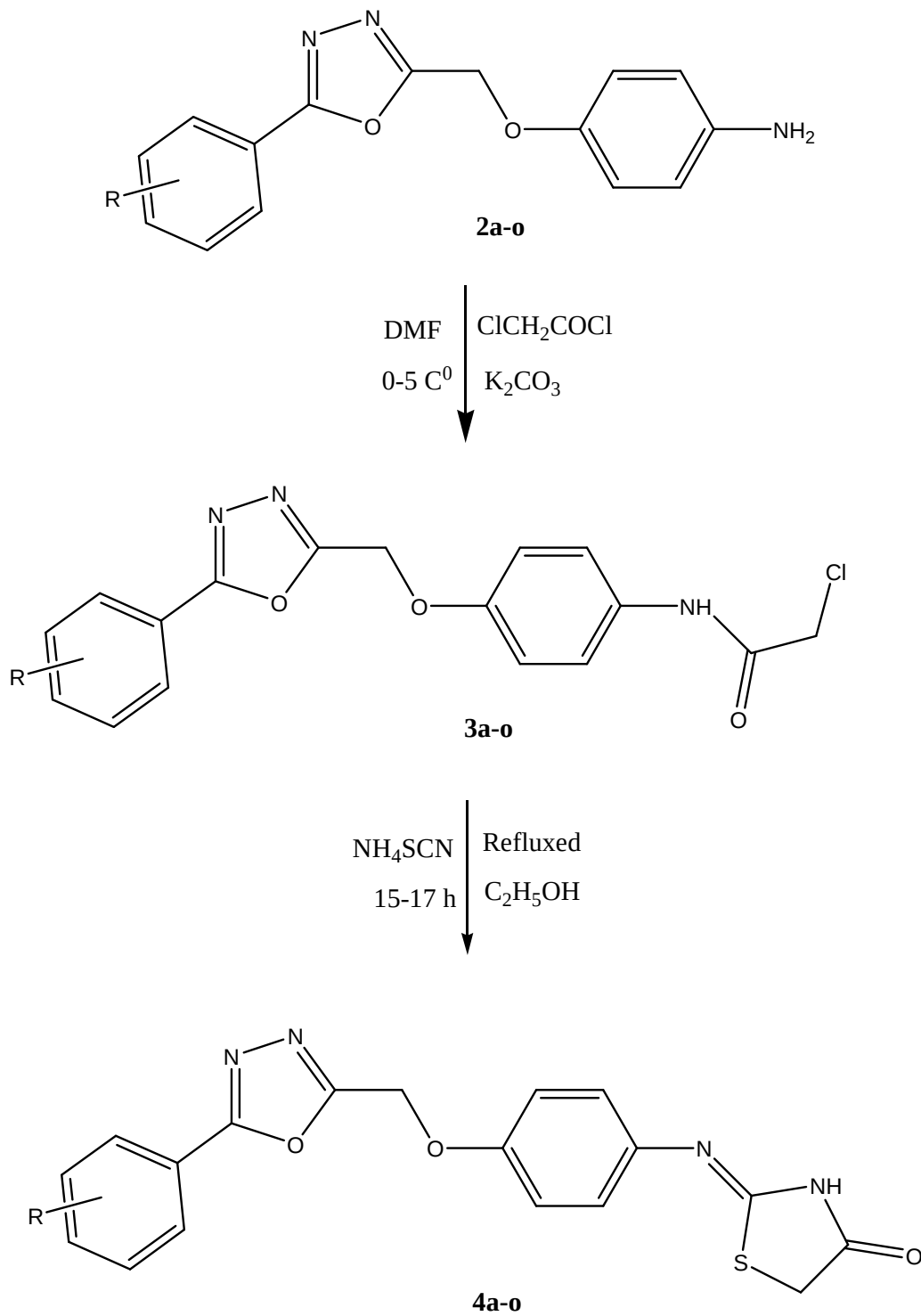
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2a-o
Scheme I

- | | | | | | | | | | |
|----|-------------------|----|--------------------|----|--------------------|----|--|----|--------------------------|
| a. | 4-Cl | b. | 4-OCH ₃ | c. | 4-NO ₂ | d. | 3-NO ₂ | e. | 4-CH ₃ |
| f. | 3-Cl | g. | 2-Cl | h. | 3-OCH ₃ | i. | 2-OCH ₃ | j. | 2-NO ₂ |
| k. | 3-CH ₃ | l. | 2-CH ₃ | m. | 3-F | n. | 4-OCH ₃ , 3-NO ₂ | o. | 2-NO ₂ , 3-Cl |

**Scheme II****R =**

- | | | | | | | | | | |
|----|-------------------|----|--------------------|----|--------------------|----|--|----|--------------------------|
| a. | 4-Cl | b. | 4-OCH ₃ | c. | 4-NO ₂ | d. | 3-NO ₂ | e. | 4-CH ₃ |
| f. | 3-Cl | g. | 2-Cl | h. | 3-OCH ₃ | i. | 2-OCH ₃ | j. | 2-NO ₂ |
| k. | 3-CH ₃ | l. | 2-CH ₃ | m. | 3-F | n. | 4-OCH ₃ , 3-NO ₂ | o. | 2-NO ₂ , 3-Cl |

Table I Antimicrobia l activity of synthesized compounds

Compd · No.	R	Minimum Inhibition Concentration in µg/ml						
		Gram negative		Gram negative		Fungal species		
		<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>S. pyogenes</i>	<i>C. albicans</i>	<i>A. niger</i>	<i>A. clavatus</i>
1a	4-Cl	200	125	200	250	1000	1000	>1000
1b	4-OCH ₃	100	200	250	250	>1000	>1000	>1000
1c	4-NO ₂	200	250	200	200	500	500	500
1d	3-NO ₂	62.5	100	250	250	>1000	250	250
1e	4-CH ₃	100	125	125	200	500	500	500
1f	3-Cl	100	125	250	200	1000	1000	>1000
1g	2-Cl	250	250	125	100	>1000	>1000	>1000
1h	3-OCH ₃	200	200	200	250	>1000	>1000	>1000
1i	2-OCH ₃	125	250	100	100	500	>1000	>1000
1j	2-NO ₂	200	200	125	125	250	500	500
1k	3-CH ₃	250	250	62.5	100	500	>1000	>1000
1l	2-CH ₃	100	200	200	200	1000	>1000	>1000
1m	3-F	250	250	62.5	100	1000	500	250
1n	4-OCH ₃ , 3-NO ₂	200	125	100	250	>1000	1000	1000
1o	4-NO ₂ , 3-Cl	250	125	125	200	>1000	>1000	>1000
3a	4-Cl	250	250	100	100	>1000	1000	1000
3b	4-OCH ₃	62.5	200	125	200	500	>1000	>1000
3c	4-NO ₂	200	200	125	250	>1000	>1000	>1000
3d	3-NO ₂	125	250	100	250	>1000	>1000	>1000
3e	4-CH ₃	125	250	125	250	>1000	250	250
3f	3-Cl	100	200	200	200	500	>1000	>1000
3g	2-Cl	200	250	200	125	1000	1000	1000
3h	3-OCH ₃	100	250	250	200	1000	>1000	>1000
3i	2-OCH ₃	200	100	125	62.5	250	1000	>1000
3j	2-NO ₂	250	100	250	200	500	>1000	1000
3k	3-CH ₃	250	100	200	100	1000	1000	>1000
3l	2-CH ₃	200	62.5	125	62.5	1000	>1000	1000
3m	3-F	250	125	200	100	500	>1000	>1000
3n	4-OCH ₃ , 3-NO ₂	100	125	500	250	>1000	>1000	>1000
3o	4-NO ₂ , 3-Cl	100	250	200	250	500	>1000	>1000
4a	4-Cl	250	200	125	500	250	>1000	>1000
4b	4-OCH ₃	100	200	250	250	>1000	>1000	>1000
4c	4-NO ₂	250	250	250	250	>1000	>1000	>1000
4d	3-NO ₂	250	200	200	200	>1000	>1000	>1000
4e	4-CH ₃	250	200	100	125	500	1000	>1000
4f	3-Cl	200	125	200	200	1000	1000	1000
4g	2-Cl	125	125	250	125	500	500	>1000
4h	3-OCH ₃	200	200	125	200	1000	1000	1000
4i	2-OCH ₃	125	250	125	62.5	>1000	>1000	>1000
4j	2-NO ₂	200	125	250	200	>1000	500	500
4k	3-CH ₃	200	250	100	250	1000	>1000	>1000
4l	2-CH ₃	200	250	100	200	1000	>1000	>1000
4m	3-F	100	200	250	125	>1000	1000	1000
4n	4-OCH ₃ , 3-NO ₂	250	250	125	200	500	>1000	>1000
4o	4-NO ₂ , 3-Cl	200	200	200	125	>1000	>1000	>1000
Ampicillin		100	100	250	100	-	-	-
Chloramphenicol		50	50	50	50	-	-	-
Greseofulvin		-	-	-	-	500	100	100

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