

Synthesis, Characterization and Antimicrobial Screening of Sulphonamide Based 1, 3, 4-Oxadiazoles

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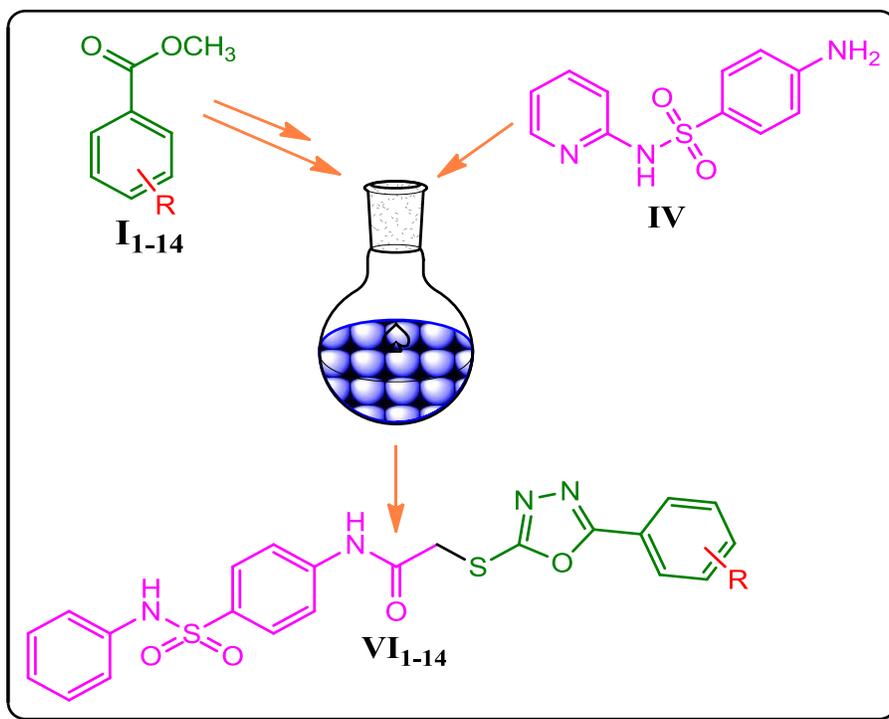
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Abstract

A new series of 2-((5-aryl-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl) acetamide (**VI**₁₋₁₄) was prepared by using an intermediate; Substituted 5-phenyl-1,3,4-oxadiazole-2-thiol derivatives (**III**₁₋₁₄) and 2-chloro-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (**V**). The structures of newly synthesized products were established from their spectral data viz. IR, ¹H NMR, ¹³C NMR, Mass spectra, and Elemental analysis data. All the compounds were screened for their significant antibacterial and antifungal activity against standard drug Ciprofloxacin and Fluconazole respectively. The compounds **VI**₃, **VI**₅, **VI**₆, **VI**₈, **VI**₇ and **VI**₁₃ exhibited significant activity.

Keywords: Sulphapyridine, 1,3,4-oxadiazole, Antimicrobial activity, MIC, SAR



Introduction

There is a fast interest in recent year in the synthesis of sulphonamide based 1,3,4 oxadiazole heterocycles because of the significant role of the sulphonamide unit. The sulphonamide scaffold is a useful structural motif for displaying chemical functionality in biologically active molecules. Several drugs containing sulfonamide functionality are in clinical use which includes antifungal and antibacterial drugs [1], carbonic anhydrase inhibitors [2], anti-inflammatory agents [3], anticonvulsant agents [4], antimalarial agents [5], protease inhibitors [6], hypertension agent [7], and cytotoxic agent [8]. They are also found to have wide applications in anti-cancer agent [9]. Some sulfonamides have verified to be valuable as herbicides [10]. The well-known example of a sulphonamide based drug is Glisoxepide (Fig. 1, Formula 1), which is used to treat diabetic disease [11].

1,3,4-oxadiazoles derivatives have also attracted considerable attention because this type of skeleton is present in many compounds having various biological activities [12]. The development of efficient synthesis of 1,3,4-oxadiazole is an important target in current organic synthesis. Some derivatives containing a 1,3,4-oxadiazole ring system have been shown to possess useful pharmacological activities, such as antiviral [13], CNS depressant [14], genotoxic [15], anticonvulsant [16], antitubercular [17], anti-HIV [18], anti-inflammatory [19]. They have also known to exhibit antitumor and antiviral activity [20], antimicrobial, antimalarial and antitubercular [21], and outstanding anti-inflammatory, analgesic and ulcerogenicity properties [22]. 1,3,4-oxadiazole based are well known as chemotherapy agents. Furamizole (Fig. 1, Formula 2) is an excellent antibiotics drug having 1,3,4-oxadiazole as core moiety [23]. In the present program, our aim is to synthesize new molecules containing multiple heterocyclic systems and to study their characterization as well as their activities. In continuation to our previous work [24] and because of the medicinal importance of sulphonamide and 1,3,4-oxadiazole as a core moiety, we report herein the synthesis of a new class of 2-((5-aryl-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (**VI₁₋₁₄**) and try to develop potential antimicrobials. The structures of newly synthesized compounds were elucidated on the basis of infrared (IR), ¹H NMR, ¹³C NMR, and mass spectral analysis. These compounds were evaluated for their antimicrobial screening on various strains of bacteria and fungi.

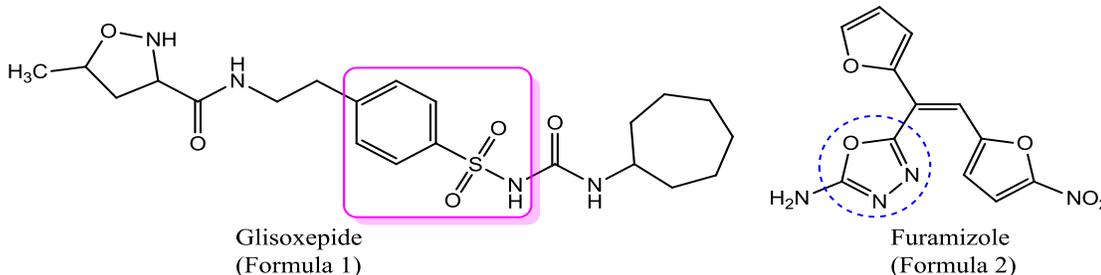


Fig. 1: Sulphonamide and 1,3,4-oxadiazole based drugs.

Experimental

Methods, Materials and Physical Measurements

The required chemicals and solvents for the synthesis were purchased from Merck Ltd., SD fine chemicals, LOBA Chemicals and HIMEDIA. The majority of the reactions were carried out by standard techniques for the exclusion moisture. Open-end capillary method was used to determine the melting points of the synthesized derivatives and the results were reported uncorrected. TLC on silica gel plates

(Merck $^{60}\text{F}_{254}$) was used for purity checking and reaction monitoring, the spots were developed in UV Chamber and appropriate solvents were used as mobile phase. IR spectra of all compounds were recorded on a Bruker FT-IR alpha-t (ATR) model. The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrophotometer-400 MHz, where DMSO-d_6 was used as solvent and TMS as the internal reference. All chemical shifts were expressed in ppm. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. Elemental analysis was carried by a Perkin-Elmer 2400 CHN analyzer.

Synthesis and Physical data

Synthesis of substituted benzohydrazide (II₁₋₁₄)

A substituted methyl benzoate (I₁₋₁₄) (0.01 mol) take in a round bottom flask (moisture free) and made soluble in appropriate quantity of Methanol. This solution was added slowly to the solution of hydrazine hydrate (0.05 mol, 50.06 gm/mol, 2.45 mL). This reaction mixture was allowed to refluxed for 12 -14 hrs. The methanol was distilled off and then cooled to room temperature. The content was poured into crushed ice and stirred well for 15 min. The solid separated out was filtered and washed with cold water. The product obtained was dried and recrystallized from alcohol. The purity of the synthesized compound and the extent of completion of reaction were monitored using TLC with mobile phase *n*-hexane: Ethyl acetate (6:4).

Synthesis of substituted 5-phenyl-1,3,4-oxadiazole-2-thiol (III₁₋₁₄)

Ethanol (40 ml) and potassium hydroxide (0.01 mol, 56.11 gm/mol, 0.56 gm in 2 mL H₂O) taken were occupied in a dry round bottom flask. Substituted benzohydrazide(II₁₋₁₄) (0.01 mol) were added to it and stirred well to get a clear solution. Carbon disulfide (0.02 mol, 76.14 gm/mol, 1.2 mL) was added to the clear solution obtained above and refluxed for 12 -15 hrs. The ethanol was distilled off and then cooled to room temperature. The content was poured into water and acidified with diluted HCl till the precipitates were separated. The separated solid was washed with cold water and dried to get the desired product. The completion of the reaction was monitored on TLC using ethyl acetate: benzene (6:4) as mobile phase. All the derivatives (III₁₋₁₄) were obtained using the same procedure.

Synthesis of 2-chloro-N-(4-(N-(pyridin-2-yl) sulfamoyl) phenyl) acetamide (V)

Sulphapyridine (IV) (0.01 mol, 249.29 gm/mol, 2.49 gm) was made soluble in appropriate quantity of dimethyl formamide containing a few drops of triethyl amine (3-4 drops) and stirred well for 10 minutes. To this well stirred mixture, chloro acetyl chloride (CAC) (0.015 mol, 113 gm/mol, 1.19 mL) was added slowly within 15 minutes maintaining the temperature below 5°C. The mixture thus obtained was stirred for 4hrs at room temperature and then the solution containing precipitates was poured onto crushed ice. The solid separated out was well stirred, kept overnight and filtered. The product was crystallized from acetone. The purity of the synthesized derivative and the extent of completion of reaction was monitored using TLC with mobile phase *n*-hexane: ethyl acetate (6:4).

Synthesis of final compounds (VI₁₋₁₄)

In a round bottom flask (moisture free) containing 2-chloro-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide(V) (0.01 mol, 325.77 gm/mol, 3.25 gm), in acetone, substituted 5-phenyl-1,3,4-oxadiazole-2-thiol(III₁₋₁₄) (0.01 mol) were added. K₂CO₃ (0.02 mol, 138 gm/mol, 2.76 gm) was added to neutralize the liberated hydrochloric acid during the reaction. This mixture was allowed to stir

for 4hrs at room temperature. The resulting material was poured onto crushed ice and stirred well for 30 min. The solid separated out was filtered and washed with cold water. The product obtained was dried and recrystallized from alcohol. All the targeted derivatives were obtained by the above stated procedure. The completion of the reaction was confirmed by using TLC with mobile phase n-hexane: ethyl acetate (8:2) and (7:3) (as per the resolution).

2-((5-phenyl-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₁)

Yield: 76%; M.P.: 216 °C; IR (ATR, cm⁻¹): 3667 (N-H str. sec. amine), 3217 (C-H str. aromatic ring), 2892 (-C-H str. methylene group), 1680 (C=O str. carbonyl group), 1520 (C=C str. aromatic ring), 1352, 1112 (S=O, str. sulphonamide group), 1262 (C-N str. carbon nitrogen linkage), 1273, 1062 (C-O-C str. oxadiazole ring); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.03(2H, s, -CH₂), 6.64-8.86 (13H, m, Ar-H), 10.75 (1H, s, -NH), 11.42 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 39.3(C₁₃), 112.3(C₄), 116.1(C₂), 118.4(C₈, C₁₀), 124.1(C₁₆), 126.3(C₁₇, C₂₁), 129.4(C₁₉), 130.1(C₁₈, C₂₀), 131.3(C₇, C₁₁), 135.1(C₆), 137.4(C₃), 139.1(C₉), 145.8(C₁), 153.7(C₅), 163.1(C₁₅), 164.4(C₁₂), 166.1(C₁₄); MS (m/z): 467(M⁺). For C₂₁H₁₇N₅O₄S₂:C, 53.95; H, 3.67; N, 14.98; S, 13.72. Found: C, 53.90; H, 3.69; N, 14.96; S, 13.73%.

2-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₂)

Yield-59 %; M. P.: 216 °C; IR (ATR, cm⁻¹): 3720 (N-H str. sec. amine), 3309 (C-H str. aromatic ring), 2918 (-C-H str. methylene group), 1692 (C=O str. carbonyl group), 1481, 1328 (NO₂ group), 1534 (C=C str. aromatic ring), 1312, 1183 (S=O, str. sulphonamide group), 1371 (C-N str. carbon nitrogen linkage), 1284, 1078 (C-O-C str. oxadiazole ring); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.12 (2H, s, -CH₂), 6.85-8.64 (12H, m, Ar-H), 10.12 (1H, s, -NH), 11.63 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 39.4 (C₁₃), 110.1 (C₄), 116.6 (C₂), 118.1 (C₈, C₁₀), 127.0 (C₁₈, C₂₀), 130.4 (C₇, C₁₁), 131.3 (C₁₇, C₂₁), 133.1 (C₁₆), 134.6 (C₆), 137.8 (C₃), 143.4 (C₉), 145.3 (C₁₉), 147.8 (C₁), 150.1 (C₅), 163.3 (C₁₅), 164.1 (C₁₂), 166.1 (C₁₄); LCMS (m/z): 512(M⁺). For C₂₁H₁₆N₆O₆S₂:C, 49.21; H, 3.15; N, 16.40; S, 12.51. Found: C, 49.25; H, 3.12; N, 16.36; S, 12.49%.

2-((5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₃)

Yield-60 %; M. P.: 154 °C; IR (ATR, cm⁻¹): 3688 (N-H str. sec. amine), 3362 (C-H str. aromatic ring), 2936 (-C-H str. methylene group), 1673 (C=O str. carbonyl group), 1467, 1381 (NO₂ group), 1490 (C=C str. aromatic ring), 1307, 1093 (S=O, str. sulphonamide group), 1367 (C-N str. carbon nitrogen linkage), 1212, 1087 (C-O-C str. oxadiazole ring); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.38 (2H, s, -CH₂), 6.49-8.11 (12H, m, Ar-H), 10.35 (1H, s, -NH), 11.12 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 38.4 (C₁₃), 107.1 (C₄), 115.3 (C₂), 118.8 (C₈, C₁₀), 121.4 (C₂₁), 124.9 (C₁₉), 126.9 (C₁₆), 130.8 (C₇, C₁₁), 131.4 (C₁₈), 132.3 (C₁₇), 133.3 (C₆), 139.1 (C₃), 142.4 (C₉), 149.4 (C₁), 149.5 (C₂₀), 151.6 (C₅), 163.4 (C₁₅), 164.1 (C₁₂), 165.7 (C₁₄); LCMS (m/z): 512(M⁺). For C₂₁H₁₆N₆O₆S₂:C, 49.21; H, 3.15; N, 16.40; S, 12.54. Found: C, 49.18; H, 3.19; N, 16.41; S, 12.54%.

2-((5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₄)

Yield-54 %; M. P.: 190 °C; IR (ATR, cm⁻¹): 3676 (N-H str. sec. amine), 3312 (C-H str. aromatic ring), 2889 (-C-H str. methylene group), 1670 (C=O str. carbonyl group), 1415, 1387 (NO₂ group), 1417

(C=C str. aromatic ring), 1379, 1109 (S=O, str. sulphonamide group), 1378 (C-N str. carbon nitrogen linkage), 1275, 1013 (C-O-C str. oxadiazole ring); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.67 (2H, s, -CH₂), 6.37-8.89 (12H, m, Ar-H), 10.08 (1H, s, -NH), 11.37 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 39.1 (C₁₃), 110.5 (C₄), 114.1 (C₂), 117.4 (C₈, C₁₀), 123.1 (C₂₀), 127.1 (C₁₇), 128.3 (C₇, C₁₁), 130.6 (C₁₉), 131.1 (C₁₆), 134.3 (C₁₈), 136.7 (C₆), 137.4 (C₃), 140.1 (C₉), 144.6 (C₂₁), 145.2 (C₁), 147.6 (C₅), 163.7 (C₁₅), 164.3 (C₁₂), 165.4 (C₁₄); LCMS (m/z): 512(M⁺). For C₂₁H₁₆N₆O₆S₂:C, 49.21; H, 3.15; N, 16.40; S, 12.51. Found: C, 49.23; H, 3.17; N, 16.43; S, 12.44%.

2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₅)

Yield-68 %; M. P.: 246 °C; IR (ATR, cm⁻¹): 3750 (N-H str. sec. amine), 3317 (C-H str. aromatic ring), 2945 (-C-H str. methylene group), 1631 (C=O str. carbonyl group), 1456 (C=C str. aromatic ring), 1392, 1138 (S=O, str. sulphonamide group), 1359 (C-N str. carbon nitrogen linkage), 1295, 1087 (C-O-C str. oxadiazole ring), 666 (C-Cl group); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.38 (2H, s, -CH₂), 6.82-8.18 (12H, m, Ar-H), 10.76 (1H, s, -NH), 11.78 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 39.3 (C₁₃), 113.4 (C₄), 115.6 (C₂), 118.6 (C₈, C₁₀), 122.1 (C₁₆), 127.7 (C₁₇, C₂₁), 130.8 (C₁₈, C₂₀), 130.9 (C₇, C₁₁), 131.7 (C₁₉), 132.8 (C₆), 135.9 (C₃), 139.6 (C₉), 141.9 (C₁), 152.8 (C₅), 163.2 (C₁₅), 163.8 (C₁₂), 165.2 (C₁₄); LCMS (m/z): 501(M⁺). For C₂₁H₁₆ClN₅O₄S₂:C, 50.25; H, 3.21; N, 13.95; S, 12.78. Found: C, 50.27; H, 3.24; N, 13.97; S, 12.75%.

2-((5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₆)

Yield-73 %; M. P.: 215 °C; IR (ATR, cm⁻¹): 3743 (N-H str. sec. amine), 3365 (C-H str. aromatic ring), 2981 (-C-H str. methylene group), 1648 (C=O str. carbonyl group), 1473 (C=C str. aromatic ring), 1380, 1107 (S=O, str. sulphonamide group), 1363 (C-N str. carbon nitrogen linkage), 1290, 1067 (C-O-C str. oxadiazole ring), 695 (C-Cl group); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.15 (2H, s, -CH₂), 6.58-8.46 (12H, m, Ar-H), 10.11 (1H, s, -NH), 11.48 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 38.8 (C₁₃), 110.1 (C₄), 115.4 (C₂), 117.8 (C₈, C₁₀), 122.2 (C₁₆), 127.6 (C₁₇, C₂₁), 128.1 (C₁₉), 128.7 (C₁₈, C₂₀), 130.4 (C₇, C₁₁), 131.1 (C₆), 135.3 (C₃), 139.9 (C₉), 146.1 (C₁), 151.4 (C₅), 162.3 (C₁₅), 165.6 (C₁₂), 166.3 (C₁₄); LCMS (m/z): 501(M⁺). For C₂₁H₁₆ClN₅O₄S₂:C, 50.25; H, 3.21; N, 13.95; S, 12.78. Found: C, 50.21; H, 3.18; N, 13.90; S, 12.79%.

2-((5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₇)

Yield-68 %; M. P.: 219 °C; IR (ATR, cm⁻¹): 3643 (N-H str. sec. amine), 3267 (C-H str. aromatic ring), 2874 (-C-H str. methylene group), 1671 (C=O str. carbonyl group), 1436 (C=C str. aromatic ring), 1362, 1015 (S=O, str. sulphonamide group), 1297 (C-N str. carbon nitrogen linkage), 1272, 1053 (C-O-C str. oxadiazole ring), 776 (C-Cl group); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.42 (2H, s, -CH₂), 6.38-8.45 (11H, m, Ar-H), 10.41 (1H, s, -NH), 11.08 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 39.0 (C₁₃), 109.3 (C₄), 116.1 (C₂), 117.4 (C₈, C₁₀), 124.7 (C₁₆), 126.4 (C₁₇), 127.1 (C₂₁), 128.8 (C₇, C₁₁), 130.6 (C₁₈), 131.4 (C₂₀), 132.1 (C₁₉), 134.3 (C₆), 135.4 (C₃), 140.6 (C₉), 145.1 (C₁), 150.7 (C₅), 163.4 (C₁₅), 165.6 (C₁₂), 166.8 (C₁₄); LCMS (m/z): 536(M⁺). For C₂₁H₁₅Cl₂N₅O₄S₂:C, 47.02; H, 2.82; N, 13.06; S, 11.96. Found: C, 47.07; H, 2.80; N, 13.04; S, 11.93%.

2-((5-(2-chloro-5-nitrophenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₈)

Yield-77 %; M. P.: 242⁰C; IR (ATR, cm⁻¹): 3767 (N-H str. sec. amine), 3283 (C-H str. aromatic ring), 2839 (-C-H str. methylene group), 1674 (C=O str. carbonyl group), 1548 (C=C str. aromatic ring), 1435, 1321 (NO₂ group), 1315, 1088 (S=O, str. sulphonamide group), 1365 (C-N str. carbon nitrogen linkage), 1293, 1067 (C-O-C str. oxadiazole ring), 721 (C-Cl group); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.17 (2H, s, -CH₂), 6.68-8.12 (11H, m, Ar-H), 10.13 (1H, s, -NH), 11.53 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 39.1 (C₁₃), 108.3 (C₄), 116.6 (C₂), 119.1 (C₈, C₁₀), 123.3 (C₁₇), 126.8 (C₁₉), 130.4 (C₇, C₁₁), 131.6 (C₂₀), 132.1 (C₆), 135.4 (C₁₆), 137.5 (C₂₁), 138.1 (C₃), 140.6 (C₉), 145.8 (C₁₈), 147.3 (C₁), 150.1 (C₅), 161.7 (C₁₅), 162.2 (C₁₂), 166.1 (C₁₄); LCMS (m/z): 546(M⁺). For C₂₁H₁₅ClN₆O₆S₂:C, 46.11; H, 2.76; N, 15.36; S, 11.72. Found: C, 46.13; H, 2.77; N, 15.36; S, 11.70%.

2-((5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₉)

Yield-81 %; M. P.: 164⁰C; IR (ATR, cm⁻¹): 3690 (N-H str. sec. amine), 3312 (C-H str. aromatic ring), 2978 (-C-H str. methylene group), 1710 (C=O str. carbonyl group), 1517 (C=C str. aromatic ring), 1335, 1145 (S=O, str. sulphonamide group), 1325 (C-N str. carbon nitrogen linkage), 1267, 1052 (C-O-C str. oxadiazole ring), 668(C-Br group); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.58 (2H, s, -CH₂), 6.18-8.37 (12H, m, Ar-H), 10.62 (1H, s, -NH), 11.28 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 39.8 (C₁₃), 107.4 (C₄), 116.1 (C₂), 117.6 (C₈, C₁₀), 122.8 (C₁₉), 124.7 (C₁₆), 128.4 (C₇, C₁₁), 130.6 (C₁₇, C₂₁), 131.1 (C₁₈, C₂₀), 133.8 (C₆), 135.9 (C₃), 140.4 (C₉), 148.4 (C₁), 151.1 (C₅), 163.7 (C₁₅), 165.3 (C₁₂), 166.7 (C₁₄); LCMS (m/z): 546(M⁺). For C₂₁H₁₆BrN₅O₄S₂:C, 46.16; H, 2.95; N, 12.82; S, 11.74. Found: C, 46.18; H, 2.93; N, 12.86; S-11.76%.

2-((5-(2-iodophenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₁₀)

Yield-77 %; M. P.: 114⁰C; IR (ATR, cm⁻¹): 3685 (N-H str. sec. amine), 3295 (C-H str. aromatic ring), 2961 (-C-H str. methylene group), 1673 (C=O str. carbonyl group), 1589 (C=C str. aromatic ring), 1310, 1287 (S=O, str. sulphonamide group), 1384 (C-N str. carbon nitrogen linkage), 1296, 1110 (C-O-C str. oxadiazole ring), 712 (C-I group); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.48 (2H, s, -CH₂), 6.89-8.17 (12H, m, Ar-H), 10.18 (1H, s, -NH), 11.49 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 39.4 (C₁₃), 97.1 (C₂₁), 110.8 (C₄), 118.7 (C₂), 119.4 (C₈, C₁₀), 125.3 (C₁₈), 128.2 (C₁₇), 129.3 (C₇, C₁₁), 131.6 (C₁₉), 134.3 (C₆), 137.1 (C₂₀), 139.4 (C₃), 140.6 (C₉), 144.4 (C₁₆), 147.8 (C₁), 153.6 (C₅), 164.3 (C₁₅), 165.4 (C₁₂), 166.6 (C₁₄); LCMS (m/z): 593(M⁺). For C₂₁H₁₆IN₅O₄S₂:C, 42.50; H, 2.72; N, 11.80; S, 10.81. Found: C, 42.46; H, 2.68; N, 11.83; S, 10.80%.

2-((5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₁₁)

Yield-60 %; M. P.: 255⁰C; IR (ATR, cm⁻¹): 3713 (N-H str. sec. amine), 3612 (O-H str.) 3187 (C-H str. aromatic ring), 3010 (-C-H str. methylene group), 1713 (C=O str. carbonyl group), 1467 (C=C str. aromatic ring), 1315, 1142 (S=O, str. sulphonamide group), 1345 (C-N str. carbon nitrogen linkage), 1289, 1077 (C-O-C str. oxadiazole ring); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.38 (2H, s, -CH₂), 5.12 (1H, s, -OH), 6.11-8.38 (12H, m, Ar-H), 10.79 (1H, s, -NH), 11.13 (1H, s, -NH beside pyridine); ¹³C

NMR (400 MHz, DMSO-d₆, δ, ppm): 39.1 (C₁₃), 107.3 (C₄), 115.4 (C₁₇, C₂₁), 116.2 (C₁₈, C₂₀), 118.6 (C₂), 119.9 (C₈, C₁₀), 121.3 (C₁₆), 128.3 (C₇, C₁₁), 134.4 (C₆), 139.6 (C₃), 140.7 (C₉), 147.6 (C₁), 151.1 (C₅), 157.9 (C₁₉), 163.6 (C₁₅), 164.7 (C₁₂), 164.3 (C₁₄); LCMS (m/z): 483(M⁺). For C₂₁H₁₇N₅O₅S₂:C, 52.16; H, 3.54; N, 14.48; S, 13.26. Found: C, 52.19; H, 5.58; N, 14.43; S, 13.24%.

N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)-2-((5-(m-tolyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (VI₁₂)

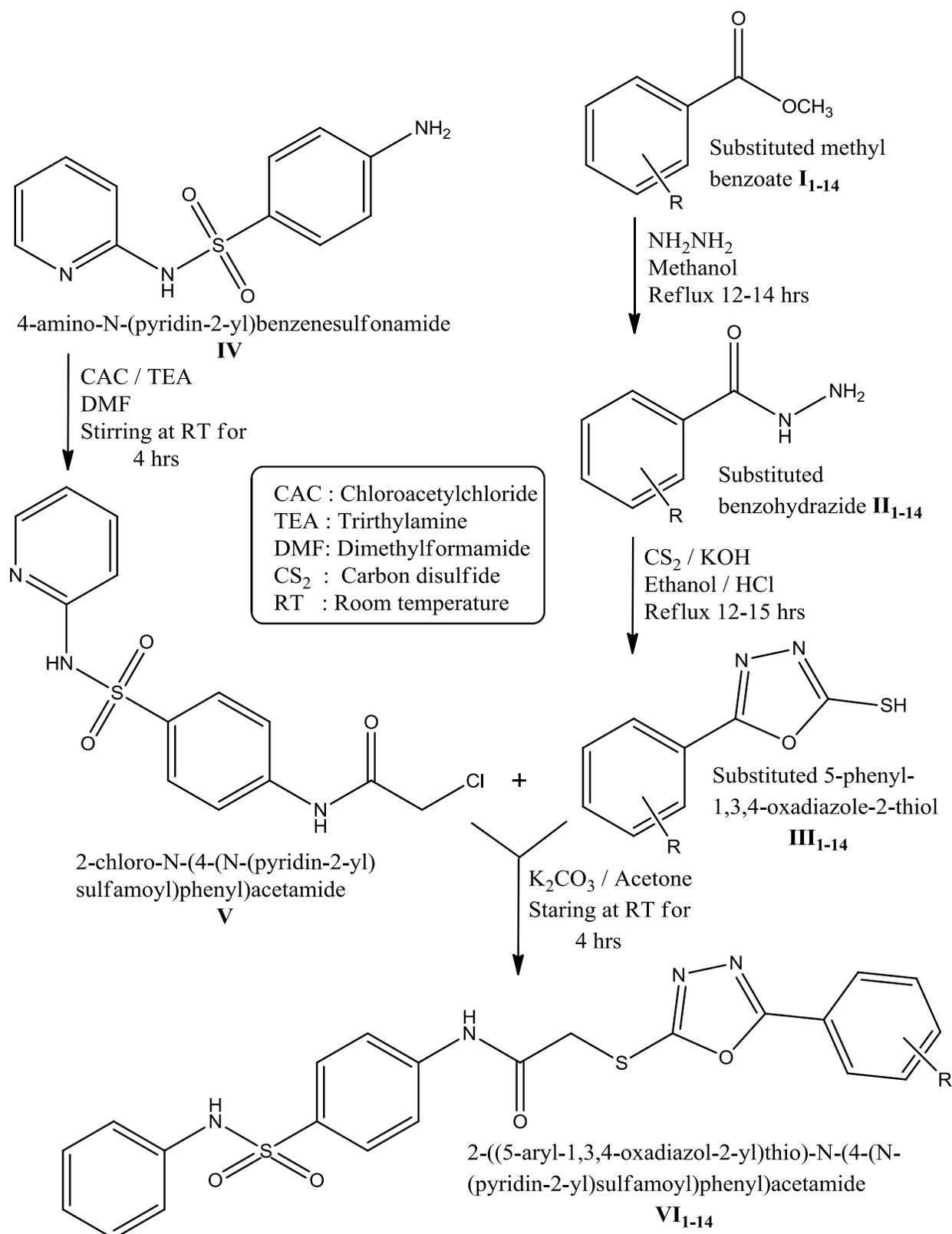
Yield-78 %; M. P.: 230⁰C; IR (ATR, cm⁻¹): 3735 (N-H str. sec. amine), 2945 (C-H str. aromatic ring), 2867 (-C-H str. methylene group), 1650 (C=O str. carbonyl group), 1532 (C=C str. aromatic ring), 1358, 1217 (S=O, str. sulphonamide group), 1315 (C-N str. carbon nitrogen linkage), 1236, 1083 (C-O-C str. oxadiazole ring); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.018 (3H, s, -CH₃), 4.31 (2H, s, -CH₂), 6.19-8.63 (12H, m, Ar-H), 10.38 (1H, s, -NH), 11.39 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 20.7 (-CH₃), 38.1 (C₁₃), 105.4 (C₄), 115.8 (C₂), 117.1 (C₈, C₁₀), 125.0 (C₁₇), 127.4 (C₁₆), 128.8 (C₁₉), 129.2 (C₁₈), 130.3 (C₁₇, C₁₁), 131.6 (C₂₁), 132.7 (C₆), 137.6 (C₃), 139.1 (C₂₀), 140.2 (C₉), 147.4 (C₁), 151.8 (C₅), 165.6 (C₁₅), 166.7 (C₁₂), 167.1 (C₁₄); LCMS (m/z): 481(M⁺). For C₂₂H₁₉N₅O₄S₂:C, 54.87; H, 3.98; N, 14.54; S, 13.32. Found: C, 54.91; H, 3.94; N, 14.57; S, 13.35%.

2-((5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)acetamide (VI₁₃)

Yield-65 %; M. P.: 232⁰C; IR (ATR, cm⁻¹): 3681 (N-H str. sec. amine), 2985 (C-H str. aromatic ring), 2910 (-C-H str. methylene group), 1678 (C=O str. carbonyl group), 1448 (C=C str. aromatic ring), 1317, 1289 (S=O, str. sulphonamide group), 1386 (C-N str. carbon nitrogen linkage), 1287, 1013 (C-O-C str. oxadiazole ring); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 3.08 (3H, s, -OCH₃), 4.74 (2H, s, -CH₂), 6.39-8.88 (12H, m, Ar-H), 10.49 (1H, s, -NH), 11.74 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 39.7 (C₁₃), 56.1 (-OCH₃), 105.3 (C₄), 110.4 (C₂₁), 115.8 (C₁₉), 117.2 (C₂), 119.1 (C₈, C₁₀), 120.6 (C₁₇), 126.4 (C₁₆), 130.1 (C₇, C₁₁), 131.6 (C₁₈), 134.1 (C₆), 137.4 (C₃), 140.5 (C₉), 146.4 (C₁), 151.8 (C₅), 160.2 (C₂₀), 162.7 (C₁₅), 164.4 (C₁₂), 164.5 (C₁₄); LCMS (m/z): 497(M⁺). For C₂₂H₁₉N₅O₅S₂:C, 53.11; H, 3.85; N, 14.08; S, 12.89. Found: C, 53.07; H, 3.89; N, 14.06; S, 12.91%.

N-(4-(N-(pyridin-2-yl)sulfamoyl)phenyl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)acetamide (VI₁₄)

Yield-62 %; M. P.: 180⁰C; IR (ATR, cm⁻¹): 3728 (N-H str. sec. amine), 3313 (C-H str. aromatic ring), 2919 (-C-H str. methylene group), 1698 (C=O str. carbonyl group), 1437 (C=C str. aromatic ring), 1338, 1061 (S=O, str. sulphonamide group), 1343 (C-N str. carbon nitrogen linkage), 1246, 1082 (C-O-C str. oxadiazole ring); ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 4.66 (2H, s, -CH₂), 6.34-8.31 (12H, m, Ar-H), 10.63 (1H, s, -NH), 11.45 (1H, s, -NH beside pyridine); ¹³C NMR (400 MHz, DMSO-d₆, δ, ppm): 39.4 (C₁₃), 107.6 (C₄), 118.1 (C₂), 119.2 (C₈, C₁₀), 120.4 (C₁₇, C₂₁), 130.3 (C₇, C₁₁), 136.7 (C₆), 139.9 (C₃), 140.5 (C₉), 142.6 (C₁₆), 147.8 (C₁), 148.2 (C₁₈, C₂₀), 151.6 (C₅), 163.1 (C₁₅), 165.4 (C₁₂), 166.3 (C₁₄); LCMS (m/z): 468(M⁺). For C₂₀H₁₆N₆O₄S₂:C, 51.27; H, 3.44; N, 17.94; S, 13.69. Found: C, 51.30; H, 3.48; N, 17.90; S, 13.67%.



Scheme 1: Synthesis pathway of Compounds (**VI₁₋₁₄**)

Table 1: In vitro result of antibacterial and antifungal screening of compounds (VI₁₋₁₄)

-R Derivatives	Minimum inhibitory concentration (MIC) in µg/mL					
	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	S. aureus ATCC 25923	E. faecalis ATCC 29212	E. coli ATCC 25922	P. aeruginosa ATCC 27853	C. albicans ATCC 10231	A. niger ATCC 1015
VI ₁ (-H)	125	125	250	250	250	250
VI ₂ (-4-NO ₂)	250	250	250	250	250	250
VI ₃ (-3-NO ₂)	250	250	125	125	250	250
VI ₄ (-2-NO ₂)	250	250	500	500	250	250
VI ₅ (-4-Cl)	250	250	62.5	125	250	250
VI ₆ (-2-Cl)	500	125	62.5	125	500	250
VI ₇ (-3,4-diCl)	500	250	125	125	500	500
VI ₈ (-2-Cl-5--NO ₂)	125	125	62.5	62.5	125	125
VI ₉ (-4-Br)	125	125	250	250	125	125
VI ₁₀ (-2-I)	250	250	250	250	125	250
VI ₁₁ (-4-OH)	250	250	250	250	125	125
VI ₁₂ (-3-CH ₃)	125	125	125	125	125	125
VI ₁₃ (-3-OCH ₃)	125	125	62.5	125	250	250
VI ₁₄ (pyridine)	250	250	250	250	250	250
Fluconazole (Std)	-	-	-	-	125	62.5
Ciprofloxacin (Std)	62.5	125	125	125	-	-

Standard (Std) drugs: fluconazole for antifungal and ciprofloxacin for antibacterial tests.

Results and Discussion

Chemistry

Synthetic approaches adopted to obtain the target compounds are represented in Scheme 1. The series of title compounds (**VI**₁₋₁₄) were synthesized in four steps. Two parallel reactions were undertaken simultaneously. In the first step, substituted methyl benzoate (**I**₁₋₁₄) was refluxed with hydrazine hydrate in the presence of methanol as a solvent to give compound substituted benzohydrazide (**II**₁₋₁₄). In the second step, compound (**II**₁₋₁₄) was refluxed with carbon disulfide (CS₂) in ethanol as a solvent in the presence of potassium hydroxide to achieve substituted 5-phenyl-1,3,4-oxadiazole-2-thiol (**III**₁₋₁₄). Compound (**V**) was prepared by a Sulphapyridine (**IV**) and chloro acetyl chloride stirred at 0-5 °C and a catalytic amount of triethylamine was added. In the final step, compounds (**VI**₁₋₁₄) were generated by condensation of the compound (**III**₁₋₁₄) and intermediate (**V**) stirred were again at room temperature in acetone which is used as solvent. The minimum inhibitory concentration (MIC) value of the synthesized derivatives are specified in Table 1.

Characterization

IR data of compound (**VI**₅)

IR spectrum of compound (**VI**₅) (molecular formula C₂₁H₁₆ClN₅O₄S₂, M. W. 501 gm/mol) has a stretching vibration at 3750 cm⁻¹ indicating the presence of N-H stretching of secondary amine. The absorption band at 3317 cm⁻¹ indicates the presence of Ar-H stretching vibrations. The absorption band at 2945 cm⁻¹ is the proof of -CH₂ group in compound **VI**₅. The presence of C=O group in a locality to -NH linkage can be predicted by the stretching frequency of 1631 cm⁻¹. The presence of C=C bond in the aromatic ring was established due to the visibility of a band at 1456 cm⁻¹ in **VI**₅ respectively. The sulfonamide functional group in the vicinity to -NH linkage was confirmed by two sharp and the intense absorption peak at 1392 and 1138 cm⁻¹ in compound **VI**₅. The carbon-nitrogen (-C-N-) linkage of the secondary amine group was further confirmed by an intensified absorption band at 1359 cm⁻¹. The formation of oxadiazole nucleus was confirmed by the presence of two absorption bands at 1295 and 1087 cm⁻¹ indicating the -C-O-C- linkage in the structure. The stretching vibration at 666 cm⁻¹ in compound **VI**₅ supported the presence of -C-Cl functionality.

¹H NMR data of compound (**VI**₅)

The ¹H-NMR spectrum detected for the compound under examination exhibited several absorption peaks corresponding to desired protons. In the structure there are two -NH (secondary amine) present; the two protons of each secondary amine can be easily separated from the shift observed in the peaks of the corresponding amines. The proton of -NH in the locality between pyridine ring and -SO₂ group was confirmed by its presence by screening a broad singlet at the downfield shift of δ = 11.78 whereas the proton of secondary amine vicinity beside of C=O group was confirmed by δ = 10.76. The proton of aromatic rings corresponded to the δ values between δ = 6.82-8.18. A singlet at δ = 4.38 helped to verify the presence of two protons of the methylene group.

¹³C NMR data of compound (**VI**₅)

The ¹³C NMR spectral data helped to approve the formation of desired structure. The δ of the final compound **VI**₅ varied from δ = 39.34 to 165.22 ppm. The carbon atom C-14 in contact to a strong electronegative elements nitrogen, oxygen and sulfur appeared downfield, nearly at δ = 165.22. The

carbon atom C-12 in the environment of secondary amine and methylene was look to a chemical shift at $\delta = 163.85$. The 1,3,4-oxadiazole ring of carbon C-15 appeared with chemical shifts at $\delta = 163.22$. The carbon (C-1 to C-5) of pyridine ring nearby sulfonamide group has a chemical shift value observed between $\delta = 113.41$ and 152.83 . Aromatic carbons (C-6 to C-11 & C-16 to C-21) displayed a chemical shift value between 118.60 and 132.85 . The chloro group at C-19 in the aromatic ring gave a chemical shift at the $\delta = 131.79$. Methylene carbon C-13, which is attached to both side of electronegative environment, appeared as a chemical shift at $\delta = 39.34$. The carbon numbering to the structure is given in Fig. 2.

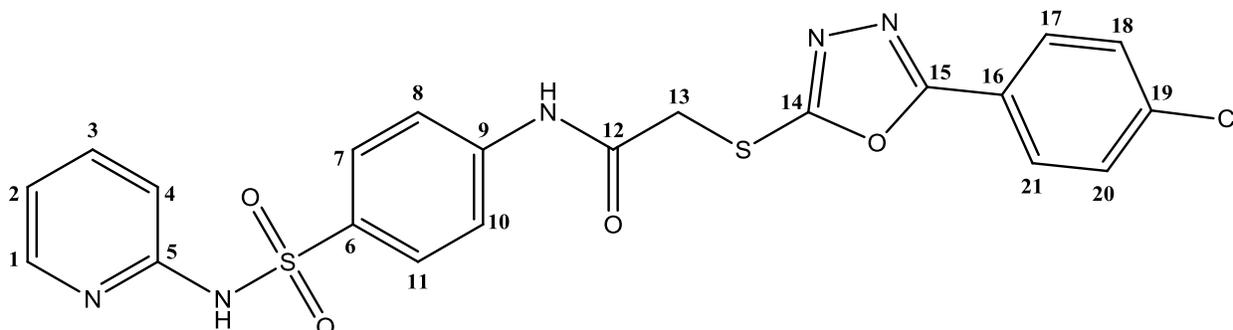


Fig. 2: Carbon enumeration of the final Compound VI₅

Antimicrobial Evolution

All the newly synthesized entities (VI₁₋₁₄) were screened for their in vitro antimicrobial activity against a broad panel of Gram-positive bacteria *S. aureus* and *E. faecalis*, Gram-negative bacteria *E. coli* and *P. aeruginosa* and Fungi *C. albicans* and *A. niger*. The samples for antifungal, as well as antibacterial evaluation, were tested by conventional broth microdilution method [25]. The standards used for antibacterial testing was Ciprofloxacin and Fluconazole was used as standard for antifungal activity at different concentrations of 1000, 500, 250, 125, 62.5, 31.25, 15.62 up to $7.8 \mu\text{g ml}^{-1}$ as shown in Table 1. Many of them had proven their antimicrobial potency varied from moderate to excellent. The MIC value of ciprofloxacin was noted to be $62.5 \mu\text{g/ml}$ against gram-positive bacterial strain *S. aureus*, whereas the same standard responded at $125 \mu\text{g/ml}$; when used against *E. faecalis*, *E. coli*, and *P. aeruginosa*. Fluconazole, when used as a standard drug against fungal strains *C. albicans* and *A. niger*, MIC value was observed at $125 \mu\text{g/ml}$ and $62.5 \mu\text{g/ml}$ respectively. In general, it was observed that most of the compounds have resulted in being potent anti-bacterial, and a very few of them were good anti-fungal and in detail in the argument of antibacterial and antifungal part below.

Antibacterial screening

Gram-positive bacteria *S. aureus* (ATCC No. 25923) and *E. faecalis* (ATCC No. 29212) were presented for testing the antibacterial potential of the synthesized molecules VI₁₋₁₄. When tested against *S. aureus*, it was found that from the complete series synthesized, compounds VI₁ (-H), VI₈(2-Cl-5-NO₂), VI₉ (-Br), VI₁₂(3-CH₃) and VI₁₃ (3-OCH₃) exhibited activity excellent to that of the standard ciprofloxacin ($62.5 \mu\text{g/ml}$). Other derivatives viz. VI₂ (4-NO₂), VI₃ (3-NO₂), VI₄ (2-NO₂), VI₅ (4-Cl), VI₁₀ (2-I), VI₁₁ (4-OH) and VI₁₄ (-Pyridine) were exhibiting good activity (MIC $250 \mu\text{g/ml}$). Only two derivatives VI₆ (2-Cl) and VI₇ (3,4-diCl) exhibiting activity of poor MIC value to that of a standard drug. Similarly, the synthesized series was tested against another gram-positive bacterial strain *E. faecalis*,

where it was observed that the derivatives **VI**₁ (-H), **VI**₆ (2-Cl), **VI**₈ (2-Cl-5-NO₂), **VI**₉ (4-Br), **VI**₁₂ (3-CH₃) and **VI**₁₃ (3-OCH₃) exhibited even equal MIC value than the standard ciprofloxacin. MIC values poor to that of the standard drug was shown by the remaining derivatives **VI**₂ (4-NO₂), **VI**₃ (3-NO₂), **VI**₄ (2-NO₂), **VI**₅ (4-Cl), **VI**₇ (3,4-diCl), **VI**₁₀ (2-I), **VI**₁₁ (4-OH) and **VI**₁₄ (-Pyridine). Overall half of the derivatives showed good activity against gram-positive bacteria *S. aureus* and *E. faecalis* when compared with the standard drug ciprofloxacin. The final derivatives **VI**₁₋₁₄ were also tested against two gram-negative bacteria *E. coli* (ATCC No. 25922) and *P. aeruginosa* (ATCC No. 27853) and compared with the same standard ciprofloxacin. The results of most of the compounds as antibacterial were excellent against both the gram-negative bacterial strains. The compounds **VI**₅ (4-Cl), **VI**₆ (2-Cl), **VI**₈ (2-Cl-5-NO₂) and **VI**₁₃ (3-OCH₃) showed MIC value (62.5 µg/ml) even better than that of the standard drug ciprofloxacin proving excellent potency as antibacterial. The derivatives from the same series which included **VI**₃ (3-NO₂), **VI**₇ (3,4-diCl) and **VI**₁₂ (3-CH₃) exhibited activity equivalent to the standard (125 µg/ml). These derivatives when tested against *P. aeruginosa* also resulted in very good antibacterial activity. Compounds **VI**₈ (2-Cl-5-NO₂) showed excellent activity (62.5 µg/ml), even better than ciprofloxacin. There were other compounds exhibiting good activity (125 µg/ml) as compared to the standard viz. **VI**₃ (3-NO₂), **VI**₅ (4-Cl), **VI**₆ (2-Cl), **VI**₇ (3,4-diCl), **VI**₁₂ (3-CH₃) and **VI**₁₃ (3-OCH₃). The remaining other derivatives from series exhibited poor activity as compared to the standard. Thus from the series of synthesized derivatives **VI**₁₋₁₄, more than half of the compounds showed good activity against gram-positive bacteria and all the compounds were excellent or equivalent when tested against gram-negative bacteria with respect to ciprofloxacin.

Antifungal screening

The antifungal tests were carried against two fungal strains *C. albicans* and *A. niger*, where fluconazole was used as a standard drug for comparison and evaluation of antifungal activity of the synthesized molecules **VI**₁₋₁₄. The derivatives **VI**₈ (2-Cl-5-NO₂), **VI**₉ (4-Br), **VI**₁₀ (2-I), **VI**₁₁ (4-OH) and **VI**₁₂ (3-CH₃) showed equivalent activity (125 µg/ml) to that of the standard drug when tested against fungal strain *C. albicans*. The rest of the compounds exhibited poor activity as compared to the standard drug result. *A. niger* when introduced for antifungal activity test, **VI**₈ (2-Cl-5-NO₂), **VI**₉ (4-Br), **VI**₁₁ (4-OH) and **VI**₁₂ (3-CH₃) compounds exhibited good activity to that of the standard drug. The rest of the compounds were seen to exhibit poor activity. Very few compounds among the synthesized derivatives **VI**₁₋₁₄ were capable of exhibiting antifungal property.

SAR studies

The substitution designs of the derivatives are carefully selected to confer different electronic surroundings of the molecules. The electronic nature of the substituent groups leads to important deviation in antimicrobial activity. Additionally, considering the relationship between the structure of final compounds (**VI**₁₋₁₄) and antimicrobial potency, the identity of different substituents showed to be a substantial restriction for inducing the activity of testified compounds. The presence of chloro and nitro substituents present at *ortho* and *para* position on the aromatic ring has increased the antibacterial activity of compounds compared to those of electron-donating substituents. Combination of electron-donating groups such as methoxy and hydroxy reduced the antibacterial property. The presence of hydrophilic substituents on the phenyl ring affords a positive inspiration on antifungal activity. In agreement with these results, electron-donating group displayed optimal activity. It may be observed that position of

substituent on the phenyl ring clearly affected the activity. Finally, it can be incidental from Table 1 that a compound without any substitution dose not exhibit antimicrobial activity against a panel of microorganisms.

Conclusions

From the antimicrobial results and SAR study supported above, it can be concluded that the derivatives having electron withdrawing substituent were found to exhibit outstanding antimicrobial property in VI₁₋₁₄. On the basis of above results, efforts are made to improve the chief structure to obtain additional potent antimicrobial molecules. The derivatives bearing chloro-substituted presented here; up to a great extent have verified to be potent antibacterial agents. Also from the SAR study, it is much clear that the use of electron-withdrawing functional groups in the final derivatives as substituents has influenced the biological property of the synthesized motifs VI₁₋₁₄. This concept of applying electron-withdrawing substituents will be kept in mind while responsibility other scientific work of the same kind.

References

- [1] Camoutsis C, Geronikaki A, Ciric A, Sokovic M, Zoumpoulakis P & Zervou M, Chem. Pharm. Bull. 58, 2010, 160-167.
- [2] Thomas TH, Jankowska L, Sanyal G & Edelhauser HF, Exp. Eye Res. 36, 1983, 457-479.
- [3] Ottonello L, Dapino P, Scirocco MC, Balbi A, Bevilacqua M & Dallegri Clin. Sci. 88, 1995, 331-336.
- [4] Siddiqui N, Pandeya SN, Khan SA, Stables J, Rana A, Alam M, Arshad MF & Bhat MA, Bioorg. Med. Chem. Lett. 17, 2007, 255-259.
- [5] Dominguez, JN, Leon C, Rodrigues J, Dominguez NG, Gut J & Rosenthal PJ, Il Farmaco 60, 2005, 307-311.
- [6] Supuran, CT, Casini A & Scozzafava A, Med. Res. Rev. 23, 2003, 535-558.
- [7] Lee AG, Anderson R, Kardon RH & Wall M, J. Ophthalmol. 138, 2004, 114-118.
- [8] Ahmed MF, El-Haggag R (2017) Synthesis and evaluation of some dibromoquinazoline-sulphonamide hybrids and some Schiff's base analogs for their cytotoxic activity. Anti-cancer agents Med. chem. (2017).doi: 10.2174/1871520617666170327154409
- [9] Alaoui S, Dufies M, Driowya M, Demange L, Bougrin K, Robert G, Auberger P, Pages G, Benhida R (2017) Synthesis and anti-cancer activities of new sulfonamides 4-substituted-triazolyl nucleosides. Bioorg. Med. Chem. Lett. doi: 10.1016/j.bmcl.2017.03.018
- [10] Percival A, Pest Manag. Sci. 31, 1991, 569-580.
- [11] Haupt E, Beyer J & Schoffling K, Arzneim.-Forsch. 24, 1974, 418.
- [12] Parikh K, Joshi A, Kshatriya R & Joshi D, Pharm. Chem. J. 49, 2015, 523-529.
- [13] El-Sayed, WA, El-Essawy FA, Ali OM, Nasr BS, Abdalla MM & Adel AH, Monatsh. Chem. 141, 2010, 1021-1028.
- [14] Singh P, Sharma PK, Sharma JK, Upadhyay A & Kumar N, Orga. Med. Chem. Lett. 2, 2012, 8.
- [15] Maslat AO, Abussaud M, Tashtoush H & Al-Talib M, Pol. J. Pharmacol. 54, 2002, 55-60.
- [16] Zarghi A, Tabatabai SA, faizi M, Ahadian A, Navabi P, Zanganeh V & Shafiee A, Bioorg. Med. Chem. Lett. 15, 2005, 1863-1865.
- [17] Kumar GV, Rajendraprasad Y, Mallikarjuna BP, Chandrashekar SM & Kistayya C, Eur. J. Med. Chem. 45, 2010, 2063-2074.



- [18] Zareef M, Iqbal R, Al-Masoudi N, Zaidi J, Arfan M & Shahzad SA, Phosphorus, Sulfur, and Silicon Relat. Elem.182, 2007, 281-298.
- [19] Jayashankar B, Rai KM, Baskaran N & Sathish HS, Eur. J. Med. Chem. 44, 2009, 3898-3902.
- [20] Akhtar T, Hameed S & Al-Masoudi NA, (2008), Acta Pharm.58, 2008, 135-149.
- [21] Ladani GG & Patel MP, New J. Chem. 39(12), 2015, 9848-9857.
- [22] Bhandari SV, Bothara KG, Raut MK, Patil AA, Sarkate AP & Mokale VJ, Bioorg Med. chem. 16(4), 2008, 1822-1831.
- [23] Desai NC, Bhatt N, Somani H, Trivedi A, Euro. J. Med. Chem. 67, 2013, 54-59.
- [24] Joshi D & Parikh K, Med. Chem. Res. 23(4), 2014, 1855-1864.
- [25] Zgoda JR & Porter JR, Pharm. Biol. 39, 2011, 221-225.