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CONVENTIONAL SYNTHESIS AND STRUCTURAL ELUCIDATION OF NEWER 1,3,4-OXADIAZOLE DERIVATIVES BIO FUNCTIONING AS ANTI-BACTERIAL AND ANTI-FUNGAL

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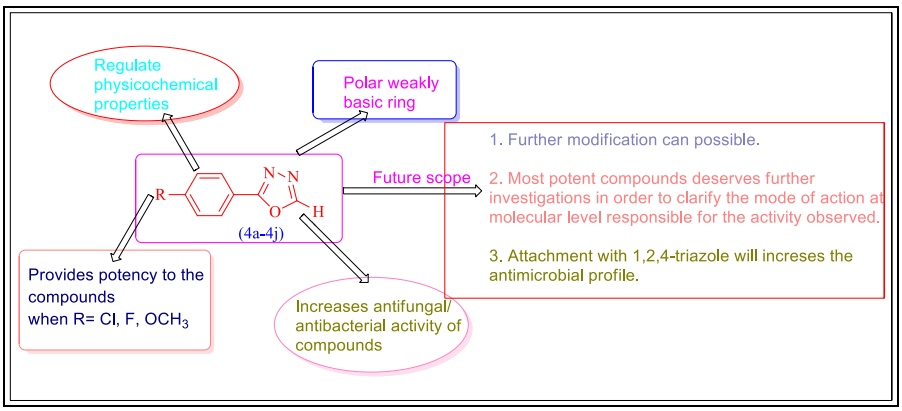
ABSTRACT

A series of newer 1,3,4-oxadiazole derivatives containing R-phenyl moiety were synthesized by reacting R-substituted aromatic acids with hydrazine hydrate in presence of various reagents at different reaction conditions. The structural elucidation of these compounds is based on their spectral data (IR, ^{1}H NMR, MS and elemental analysis). All the newly Synthesized 1,3,4-oxadiazole derivatives have been screened for their antibacterial activity against three different strains, namely *E. coli, S. aureus* and *P. aeruginosa*, while antifungal activity was determined against three different strains such as *C. neoformans, C. albicans* and *C.glabrata*. The investigation of antimicrobial screening revealed that compounds 4a, 4g, and 4h exhibited excellent activity when compared with the standard drugs.

KEYWORDS: 1,3,4-oxadiazole derivatives containing R-phenyl moiety, Antibacterial activity, Antifungal activity, Characterization data, Conventional conditions.

Graphical Abstract



1. INTRODUCTION

1,3,4-Oxadiazole is apparently among the most significant heterocyclic cores. 1,3,4-Oxadiazoles constitute an important family of heterocyclic compounds as they have attracted significant interest in medicinal chemistry, pesticide chemistry and polymer science.[1,2,3] Oxadiazoles have gained great importance in medicinal chemistry owing to their broad spectrum and metabolic profile. The 1,3,4-oxadiazole derivatives may act as ester and amide bioisosteres and hence are of interest in pharmaceutical and agrochemical fields.[4] The wide range of biological activities associated with 1,3,4-oxadiazoles include anti-viral[5], antimicrobial[6], antineoplastic[7], fungicidal[8], inhibition of tyrosinase[9] and cathepsin K.[10] Also, much attention has been focused on the oxadiazole core P-systems as electron-transporting and hole-blocking materials in the area of organic light-emitting diodes (OLEDs) [11]. Further 1,3,4-oxadiazole heterocycles can contribute substantially to increasing the pharmacological activity by participating in hydrogen bonding interactions with the receptors.[12]

Infectious diseases are one of the leading causes of death worldwide. During the past few decades, new infectious diseases have appeared and old ones previously thought to be controlled have reemerged.[13] Despite the critical need for new antimicrobial agents, the development of these agents is declining. Solutions encouraging and facilitating the development of new antimicrobial agents are needed. Since many of 1,3,4-oxadiazoles display a remarkable biological activity[14,15], their synthesis and transformations have been receiving particular interest for a long time.[16]

We report herein, the synthesis of 1,3,4-oxadiazoles derivatives containing R-phenyl moiety with an expectation to find new and more potent antimicrobial agents.

2. EXPERIMENTAL

2.1. Materials and methods

All the laboratory grade reagents were obtained commercially. The reaction was monitored by thin layer chromatography, which was performed on Merck precoated plates (silica gel. 60 F254, 0.25 mm) and was visualized by fluorescence quenching under UV light (254 nm). Melting points were determined by the open capillary method and were uncorrected. The IR spectra were recorded on a Thermo Nicolet avatar 330-FTIR spectrophotometer. 1H-NMR and 13C-NMR spectra were recorded (DMSO-d6) on a Bruker (400 and 100 MHz). Chemical shift values are given in delta scales. The mass spectra were recorded on LC–MS-Agilent 1100 series. Elemental analyses were performed on a Flash EA 1112 series CHNS–O Analyzer.

2.2. General procedures for synthesis of 1,3,4-oxadiazole derivatives containing R-phenyl moiety

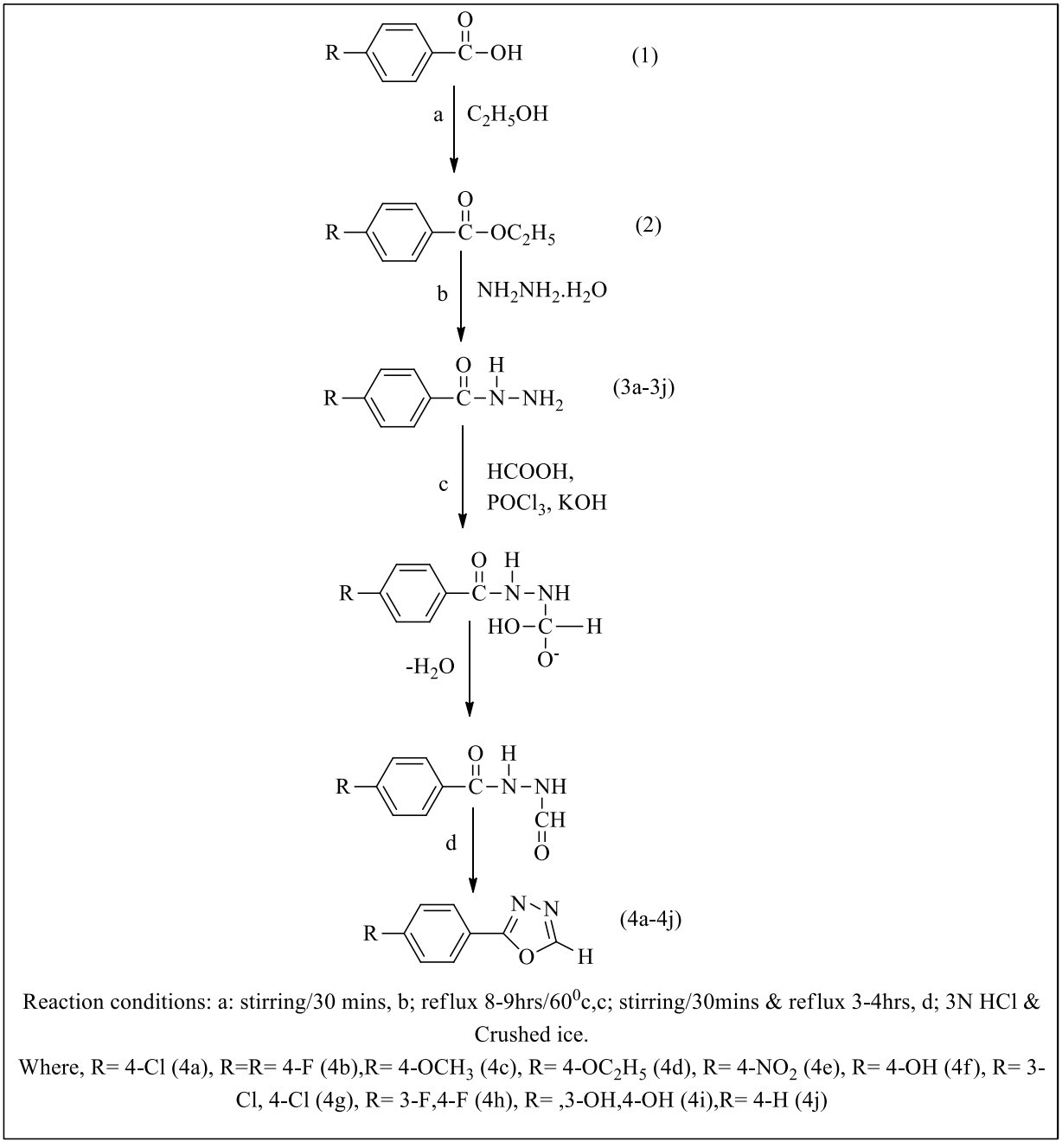
2.2.1. Preparation of acid hydrazide solution

In a single necked flask fitted with a reflux condenser mixture of organic acids [1] (4.0 gm) in ethanol (6 ml) was taken and stirred for a 30 mins, after that hydrazine hydrate (5ml) was added to the above mixture. Reaction mixture stirred for a 30 mins and refluxed for 8-9 hrs at 60^0c. Progress of the reaction was monitored by taking TLC.

2.2.2. Synthesis of 1,3,4-oxadiazole derivatives containing R-phenyl moiety

In a 250 ml three necked flask equipped with a double surface condenser, a mechanical stirrer, a dropping funnel and a heating mantle, a solution of potassium hydroxide (2.8 gm) in water (100 ml) was added drop wise to the previously prepared acid hydrazide solution [3a-3j] with continuous stirring. Along with phosphorous oxychloride (2.4 ml) in toluene (50 ml) was also added drop wise to the acid hydrazide solution with continues stirring. Reaction mixture was

stirred for 30 mins and refluxed for 3-4 hrs. Progress of reaction was monitored by taking TLC. Reaction mixture was cooled to room temperature and added drop wise to the mixture of 3N HCl and crushed ice with stirring. After that solution of reaction mixture was poured into petri dishes and put on water bath to evaporate solvent. Off white coloured solid was crystallized out. [4a-4j]



Reaction conditions: a: stirring/30 mins, b; reflux 8-9hrs/60^{0}c,c; stirring/30mins & reflux 3-4hrs, d; 3N HCl & Crushed ice.

Where, R= 4-Cl (4a), R=R= 4-F (4b),R= 4-OCH_3 (4c), R= 4-OC_2H_5 (4d), R= 4-NO_2 (4e), R= 4-OH (4f), R= 3-Cl, 4-Cl (4g), R= 3-F,4-F (4h), R= ,3-OH,4-OH (4i),R= 4-H (4j)

Scheme 1: Schematic diagram showing the synthesis of 1,3,4-oxadiazole derivatives containing R-phenyl moiety.

2.3. Characterization data of compounds 4a-4j

2.3.1. 2-(4-chlorophenyl)-1,3,4-oxadiazole. (4a)

Color: off white amorphous solid. Yield 66%, m.p. 224–226 ^{0}C, IR (KBr, Vmax cm^{-1}):, 3052 (C–Hstr), 1593 (C-N), 1531 (C-C), 1087 (C–O–C), 762 (C-Cl); H^1-NMR (DMSO-d6): 7.55-7.73 (m), MS: m/z = 180.01 (M-1). Anal. calcd. For : $C_8H_5ClN_2O$;C-53.21, H-2.79, N-15.51,O-8.86, Cl-2,9. Found: C-53.23, H-2.49, N-15.30, O-8.90, Cl-3.0.%

2.3.2. 2-(4-fluorophenyl)-1,3,4-oxadiazole. (4b)

Color: off white amorphous solid. Yield 74%, m.p. 242–246 ^{0}C, IR (KBr, Vmax cm^{-1}):, 3050 (C–Hstr), 1596 (C-N), 1530 (C-C), 1087 (C–O–C),801 (C-F); H^1-NMR (DMSO-d6): 7.45-7.80 (m), MS: m/z = 164.01 (M-1). Anal. calcd. For : $C_8H_5FN_2O$; C-58.54, H-3.07, N-11.57,O-9.75, F-11.57, Found: C-57.53, H-3.09, N-11.37, O-9.80, F-10.55%.

2.3.3. 2-(4-methoxyphenyl)-1,3,4-oxadiazole. (4c)

Color: off white amorphous solid. Yield 54%, m.p. 212–216 ^{0}C, IR (KBr, Vmax cm^{-1}):, 3050 (C–Hstr), 1594 (C-N), 1528 (C-C), 1089 (C–O–C), 2776 (OCH_3); H^1-NMR (DMSO-d6): 7.52- 7.60 (m),3.83 (s), MS: m/z = 176.1 (M-1). Anal. Calcd. For: $C_9H_8N_2O_2$; C-61.49, H-4.53, N-15.49,O-18.99, Found: C-61.02, H-4.58, N-15.97, O-18.90%.

2.3.4. 2-(4-ethoxyphenyl)-1,3,4-oxadiazole. (4d)

Color: off white amorphous solid. Yield 60%, m.p. 232–234 ^{0}C, IR (KBr, Vmax cm^{-1}):, 3048 (C–Hstr), 1585, (C-N), 1542 (C-C), 1089 (C–O–C), 2835, (OC_2H_5); H^1-NMR (DMSO-d6): 7.23-7.48 (m) 1.32 (t), 4.09 (q) MS: m/z = 174.1 (M-1). Anal. Calcd. For: $C_{10}H_{10}N_2O_2$; C-63.95, H-5.39, N-14.73,O-16.82, Found: C-63.54, H-5.80, N-16.07, O-16.19%.

2.3.5. 2-(4-nitrophenyl)-1,3,4-oxadiazole. (4e)

Color: off white amorphous solid. Yield 78%, m.p. 202–204 ^{0}C, IR (KBr, Vmax cm^{-1}):, 3040 (C–Hstr), 1588 (C-N), 1549 (C-C), 1089 (C–O–C),1550 (NO_2); H^1-NMR (DMSO-d6): 7.62-7.26 (m), MS: m/z = 191.1 (M-1). Anal. Calcd. For: $C_8H_5N_3O_3$; C-50.27, H-2.64, N-21.98, O-25.11, Found: C-50.01, H-2.60, N-20.60, O-25.22%.

2.3.6. 4-(1,3,4-oxadiazol-2yl)phenol. (4f)

Color: off white amorphous solid. Yield 65%, m.p. 180–182 ^{0}C, IR (KBr, Vmax cm^{-1}):, 3050 (C–Hstr), 1586 (C-N), 1546 (C-C), 1081 (C–O–C), 3450 (OH); H^1-NMR (DMSO-d6): 7.20-7.42 (m), MS: m/z = 146.1 (M-1). Anal. Calcd. For: $C_8H_6N_2O$; C-65.75, H-4.1 4, N-19.17,O-10.95, Found: C-65.70, H-4.20, N-19.07, O-11.0%.

2.3.7. 2-(3,4-dichlorophenyl)-1,3,4-oxadiazole. (4g)

Color: off white amorphous solid. Yield 68%, m.p. 240–242 ^{0}C, IR (KBr, Vmax cm^{-1}):, 3052 (C–Hstr), 1590 (C-N), 1554 (C-C), 1086 (C–O–C), 754 (C-Cl); H^1-NMR (DMSO-d6): 7.29-7.62(m), MS: m/z = 214 (M-1). Anal. Calcd. For: $C_8H_4Cl_2N_2O$; C-44.86, H-1.87, N-13.03, O-7.44, Cl-32.97, Found: C-44.80, H-1.90, N-13.0, O-7.50, Cl-32.98%.

2.3.8. 2-(3,4-difluorophenyl)-1,3,4-oxadiazole. (4h)

Color: off white amorphous solid. Yield 58%, m.p. 262–264 ^{0}C, IR (KBr, Vmax cm^{-1}):, 3082 (C–Hstr), 1600 (C-N), 1556 (C-C), 1096 (C–O–C), 801 (C-F); H^1-NMR (DMSO-d6): 7.42-7.79 (m), MS: m/z = 182.1 (M-1). Anal. Calcd. For: $C_8H_4F_2N_2O$; C-52.76, H-2.21, N-15.38,O-8.38, F-20.80, Found: C-51.78, H-2.18, N-15.40, O-8.80, F-20.86%.

2.3.9. 4-(1,3,4-oxadiazol-2-yl)benzene-1,2-diol. (4i)

Color: off white amorphous solid. Yield 79%, m.p. 182–144 ^{0}C, IR (KBr, Vmax cm^{-1}):, 3048 (C–Hstr), 1601 (C-N), 1553 (C-C), 1099 (C–O–C), 3490 (OH); H^1-NMR (DMSO-d6): 7.52 (d), 7.78 (d), MS: m/z = 178.1 (M-1). Anal. Calcd. For: $C_8H_6N_2O_3$; C-53.94, H-3.39, N-15.73,O-26.94, Found: C-54.0, H-3.40, N-15.75,O-26.98%.

2.3.10. 2-phenyl-1,3,4-oxadiazole. (4j)

Color: off white amorphous solid. Yield 85%, m.p. 161–163 ^{0}C, IR (KBr, Vmax cm^{-1}):, 3030 (C–Hstr), 1605 (C-N), 1573 (C-C), 1089 (C–O–C), 3355 (OH); H^1-NMR (DMSO-d6): 7.72-4H (d), 7.08 -4H (d), MS: m/z = 146.1 (M-1). Anal. Calcd. For: $C_8H_6N_2O$; C-65.75, H-4.14, N-19.17, O-10.95, Found: C-65.70, H-4.20, N-19.07, O-11.00%.

2.4. Antimicrobial evaluation

2.4.1. Antibacterial activity

The antibacterial activity of the synthesized compounds (4a-4j) was determined using Disc-diffusion method, against panel of pathogenic microorganism including *E. coli, S. aureus and P. aeruginosa.* Etc. Stock solutions of different test compounds (100µg/ml and 50µg/ml) were made in DMSO. Standard inoculums were introduced on to the surface of sterilized agar plates and a sterilized glass spreader was used for even distribution of inoculum. The inoculum was allowed to dry for 5 minutes with lid in placed. Sterile discs of 6 mm diameter (Hi Media Laboratories Ltd., Mumbai, India) were used. Test compounds (100 µg/ml and 50µg/ml) were incorporated in to the sterile disc using micropipette. Precautions were taken to prevent the flow of the solution from the disc to outer surface. The disc was applied under aseptic technique. The plates were inverted and incubated for 24 hours at 37˚C. Streptomycin was used as a standard drug (100 µg per disc). The diameters of the zones were measured to the nearest millimeter using Zone scales PW096. In all the determinations test were performed in triplicate and the results were taken as a mean of at three determinations. The results are presented in Table1.

Table 1: Antibacterial activity of compounds 4a-4j.

Compound codes	Zone of inhibition (mm)					
	Escherichia coli		***Staphylococci aureus***		***Pseudomonas aeruginosa***	
Conc. in µg/ml	100	50	100	50	100	50
4a	18	09	15	07	13	06
4b	17	08	19	09	11	04
4c	15	06	10	04	12	05
4d	16	08	12	06	09	04
4e	05	01	04	00	02	00
4f	11	05	10	05	05	00
4g	24	10	22	11	19	07
4h	23	11	20	10	21	08
4i	19	09	18	08	20	05
4j	08	04	05	02	00	00
Streptomycin (Std.)	50	25	48	20	40	18

2.4.2. Antifungal activity

Antifungal studies of newly synthesized compounds 4a-4j were determined by the well plate method[17,18] against *C. neoformans, C. albicans* and *C. glabrata*. Sabourauds agar media were prepared by dissolving peptone (10 g), D-glucose (40 g) and agar (20 g) in distilled water (1000 ml) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured into each petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at ±37^{0}C for 1 h. Six millimeter diameter well were then punched carefully using a sterile cork borer and 30 µl of test solutions of different concentrations (100 µg/ml and 50 µg/ml) were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at ±25 ^{0}C for 72 h. Antifungal

activity was determined by measuring the diameter of inhibition zone. The activity of each compound was compared with fluconazole as standard. The results are presented in Table 2.

Table 2: Antifungal activity of compounds 4a-4j.

Compound codes	Zone of inhibition (mm)					
	Cryptococcus neoformans		***Candida albicans***		***Candida glabrata***	
Conc. in µg/ml	100	50	100	50	100	50
4a	14	06	18	08	17	08
4b	12	04	20	11	17	07
4c	09	05	12	06	16	08
4d	08	04	12	07	15	06
4e	03	00	04	01	01	00
4f	11	05	13	06	10	04
4g	19	09	24	13	22	10
4h	18	07	19	09	17	09
4i	15	06	16	08	14	05
4j	05	02	06	04	8	03
Fluconazole (Std.)	25	13	30	16	28	14

3. RESULTS AND DISCUSSION

3.1. Chemistry

The synthetic route has been outlined in Scheme 1. In the current work, aromatic esters (2) were synthesized from the appropriate aromatic acids (1) by treating with ethanol in the presence of catalytic amount of sulfuric acid. Reaction of compound (1) with hydrazine hydrate yielded corresponding acid hydrazides (3).[19] Similarly, Phenyl substituted -carboxylic acids were synthesized as per the reported procedure.[20] Subsequently condensation of substituted acid hydrazides (3) with various Phenyl substituted carboxylic acids in the presence of phosphorous oxychloride and formic acid afforded a series of 1,3,4-oxadiazoles derivatives containing R-phenyl moiety. (4a-4j). newly synthesized compounds (4a-4j) were characterized by IR, NMR, and MS spectral and C, H, N, O analyses. Analytical and spectral data of all synthesized compounds were in full agreement with the proposed structures. IR spectrum of compound 4a showed absorption bands at 3052, 1593, 1531, 1087, 762 cm^{-1} which was due to the (C–Hstr), (C-N), (C-C), (C–O–C), (C-Cl) groups, respectively. In H^1NMRspectra, all protons were seen according to the expected chemical shift and integral values. The H^1NMR spectrum of 4a showed a multiplet at 7.55-7.73 corresponds to aromatic Protons. The mass spectrum of 4a showed a molecular ion peak at m/z = 180.01 (M-1), which is in agreement with the molecular formula $C_8H_5ClN_2O$. When the Para position of the phenyl ring attached to 1,3,4-oxadiazole nucleus was substituted by electron donating and electron withdrawing groups, a change in delta values of aromatic protons was observed. In the presence of the electron donating group, delta value shifted to lower wavelength side whereas in the presence of electron withdrawing groups, delta value shifted to higher end. In compound 4d, due to the presence of the $–OCH_3$ group an additional singlet peak was observed at d 3.83. Due to the presence of two chlorine atoms in mass spectrum of compound 4g, M+1, M+2 and M+4 chlorine patterns were clearly observed. Similarly, the presence of one chorine atom in compound 4a showed M+1 and M+2 chlorine pattern which further confirms the structure. Similarly the spectral values for all the compounds and C, H, N, O analyses are given in the experimental part.

3.2. Biology

E. coli is a common micro-organism which causes secondary infection, food poisoning in human. *S. aureus* causes septic arthritis, staphylococcal endocarditis and pneumonia. On the other hand *P. aeruginosa* causes skin and soft tissue

infection, gastrointestinal infection, urinary tract infection and septic shock pneumonia. These pathogens are commonly causing harmful effects on human life. The evaluation of antimicrobial activity of 1,3,4-oxadiazole moiety against *E. coli, S. aurous* and *P. aeruginosa* has been carried out by many researchers and reported good results with respect to the above mentioned microorganisms.[21,22,23] Hence it was thought worthwhile to evaluate antimicrobial activity using these microorganisms. The newly synthesized compounds 4a–j were tested for their antibacterial activity (in vitro) against *E. coli, S. aurous* and *P. aeruginosa* and their activity was compared to a well-known commercial antibiotic, streptomycin. Antibacterial activity was carried out by the Disc-diffusion method by measuring its zone of inhibition. The compounds 4a–4j were screened for their antibacterial activity in triplicate against *E. coli, S. aureus* and *P. aeruginosa* at two different concentrations of 100 µg/ml and 50 µg/ml as shown in Table 1. The investigation of antibacterial screening data revealed that most of the tested compounds showed moderate to good bacterial inhibition. Compound 4g exhibited maximum activity as compared to remaining compounds but less than that of standard against *E. coli* whereas slightly less than that of standard against *S. aureus* and *P. aeruginosa* at 50µg/ml. 4h, 4d, 4a, 4i also inhibited the growth of *S. aureus* similarly as that of standard whereas slightly less than that of standard against E. coli and *P.* aeruginosa at 50 µg/ml. Compounds 4e and 4f were found to be active against all the tested bacterial strains. Compound 4b showed moderate activity against *E. coli* and *S. aureus*. Remaining compounds showed fair or poor activity against tested bacterial strains. All the synthesized compounds were also tested for their antifungal activity (in vitro) against *C. neoformans, C. albicans and C. glabrata* by measuring their average zone of inhibition (Table 2). Fluconazole was used as standard for antifungal activity. Among the tested compounds, 4i and 4j showed a good antifungal profile against *C. neoformans, C. albicans and C. glabrata* at a concentration of 50µg/ml when compared with the standard. 4a, 4g and 4h showed moderate activity against *C. albicans* but showed poor activity against rest of two microorganisms. Remaining compounds showed poor activity against the tested microorganisms. The enhanced activity of 4a and 4g can be attributed to the presence of chloro substituent attached to the 3rd & 4th position of the phenyl moiety attached to the 1,3,4-oxadiazole ring. The presence of chlorophenyl substituent (4th position of 1,3,4-oxadiazole) along with 4-fluorophenyl, 4-methoxyphenyl substituent on the 1,3,4-oxadiazole ring in 4a, 4b and 4c respectively may be the reason for its enhanced activity. Compounds 4g, 4h and 4i contain dichloro, difluoro and diol groups (3rd & 4th position) as phenyl substituents on a 1,3,4-oxadiazole ring which may be the reason for its excellent activity.

It can be concluded that the compounds 4g, 4h and 4i, which contain dichloro, difluoro and diol substituent on the 3rd and 4th position of the phenyl ring attached to the 1,3,4-oxadiazole ring may increase the antimicrobial profile of the compound along with this, compound 4e which contain nitro substituent on 4th position of phenyl ring attached to the 1,3,4-oxadiazole ring may decrease the antimicrobial profile.

4. CONCLUSION

In summary, we have synthesized a new series of 1,3,4-oxadiazole derivatives containing R-phenyl moiety and screened for their antimicrobial activity against few microorganisms. Among the synthesized compounds 4a, 4g and 4h showed excellent antimicrobial activity against various tested microorganisms. Hence it can be concluded that the compounds 4a, 4g and 4h are identified as the most potent antimicrobial agents in the present series and deserve further investigation in order to clarify the mode of action at molecular level responsible for the activity observed.

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