Syntheses, Characterization and Biological Evaluation of a Series of 2-Phenylamino-5-(2-Chlorophenyl)-1,3,4-Oxadiazole Derivatives

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ABSTRACT: Electrochemical synthesis of 2-phenylamino-5-(2-chlorophenyl)-1,3,4-oxadiazoles have been carried out in good yields at platinum electrode through the electrochemical oxidation of acyl thiosemicarbazide at room temperature in acetic acid. Two platinum electrodes in the form of square plates were used as working as well as counter electrode and saturated calomel electrode was used as reference electrode. The structure of the compounds was confirmed by IR, NMR, mass spectral and elemental analyses. The antibacterial activity of the derivatives was also assessed and compared with data against a series of Gram-positive *Klebsiella pneumoniae*, *Escherichia coli* and Gram-negative bacteria *Streptococcus aureus* and *Bascillus subtilis*. The antifungal activity was assessed against the fungal strain *Aspergillus niger*, *Crysosporium pannical*, *Pellicularia solmanicolor* and *Candida albicans* and compared against the standard antifungal drug Griesvofulvin.

Key words*:* 1,3,4-Oxadiazoles, Arylthiosemicarbazide, Controlled potential electrolysis, Platinum electrode, Green chemistry.

INTRODUCTION

Various 1,3,4-oxadiazole derivatives were reported in the literature to have a broad spectrum of biological activities including such as antibacterial[1,2], anti-HIV[1], antifungal[3,6], genotoxic[3,6], antitubercular[6], virucidal[7], antimalarial[8], insecticidal[9], herbicidal[10], analgesic[11], anti-inflammatory[12], muscle relaxants[13,14], anticonvulsant[15], sedative[16], hypnotic[16], anticancer[17] and lipid peroxidation inhibitors. In the present investigation, a series of substituted 1,3,4-oxadiazole derivatives were synthesized as potential antibacterial and antifungal agents by the electrooxidative synthesis.

The oxadiazole ring systems have a long history of application in pharmaceutical and agrochemical industries due to their activity. On the study of literature it have been found that the methods for synthesis of oxadiazoles[19] 2,5-disubstituted or 2-amino-5-substituted-1,3,4-oxadiazoles include bromine oxidation of semicarbazide derivative and the cyclodesulfurisation of acylthiosemicarbazide derivative in the solution using I_2/NaOH or 1,3-dicyclohexylcarbodimide (DCC) as well as mercury (II) acetate [$Hg(OAc)_2$] or yellow mercury (II) oxide HgO.[20-22] All these methods are usually carried out in various different synthetic steps and requires the heating at high temperature. The handling of these reagents is not only difficult but also very hazardous to the environment. The each stage of the reaction including extraction and purification of the products from the mixture required great precautions. Karen Evans[23] have synthesized a similar cyclized product by the chemical method in which 2-amino-5-substituted-1,3,4-oxadiazoles were prepared by rapid parallel synthesis in efficient one-pot preparation using resin-bound reagents.

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The electrochemical oxidation reaction has several merits. These reactions do not require oxidizing reagents and can be performed at room temperature. Application of electricity as a non conventional energy source for activation of reactants in suitable solvents has now gained popularity over the usual homogeneous and heterogeneous reactions. It provides chemical processes with special attributes, such as enhanced reaction rate, higher yield of pure products, better selectivity and several ecofriendly advantages.

During hit to lead efforts following a recent high throughput screening campaign, we initiated the electrolysis of semicarbazone for the synthesis of 2-amino-5-substituted-1,3,4-oxadiazoles at the platinum electrode as a green synthesis. Later on, it have been found out from the literature that the activity of the oxadiazoles can be enhanced if the amino group is also substituted by an alkyl, aryl or acyl group. Keeping this observation in view and in continuation of our research on the synthesis of heterocyclic compounds containing nitrogen and oxygen with expected biological activity, this paper presents the synthesis of several derivatives of 2-phenylamino-5-(2-chlorophenyl)-1,3,4-oxadiazoles which contain phenyl moiety and the study of their antibacterial and antifungal activity.

EXPERIMENTAL

Physical measurements. Melting points were determined using open capillary tubes and were uncorrected. The purity of the synthesized compounds were ascertained by thin layer chromatography on Silica gel G 60 F_{254} plates from Merck and visualized by exposure to iodine vapor. Spectra were obtained as follows: Infra red (IR) spectra were recorded on a Shimadzu 8201 PC IR spectrophotometer (4000-400 cm^{-1}) in KBr pellets and reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were measured at room temperature on Bruker DRX 300 MHz and 75 MHz FT spectrometer instruments, with tetramethylsilane (TMS) and $CDCl_3$ or C_6D_6 and their chemical shifts are reported in δ (parts per million). Carbon multiplities were assigned by DEPT techniques. Microanalysis for C, H, N was performed in the Elementar Vario EL III.

General procedures for the synthesis of acylthiosemicarbazide (4a-4l). Arylisothiocyanate **3** was prepared directly from an arylamine. The sparingly soluble ammonium aryldiathiacarbamate was obtained by the reaction of an arylamine, CS_2, and aqueous ammonia. Then aryldiathiacarbamate is decomposed by lead nitrate to produce arylisothiocyanate. The equimolar amount of arylhydrazine **2** and arylisothiocynate **3** were mixed in a small beaker with continuous stirring. After few minutes of stirring, the mixture was left overnight, which gave a solid compound arylthiosemicarbazide **4**.

(**4a**): IR/cm^{-1}: 1015 (N-N), 1265 (C=S), 1449 (C=N + ArC=C), 1632 (C=O), 3068 (ArC-H); ^1H-NMR: δ 6.88-7.98 (m, 8H, ArH), 10.60-11.96 (s, 3H, NH); ^{13}C-NMR: δ 116.1, 119, 126.4, 127.6, 128.6, 129.8, 133.4, 140.7, 143.06, 148.1, 159.5, 181.6; M/Z=305.5 [M^+]. Calcd. for $C_{14}H_{12}N_3OSCl$: C, 54.98; H, 3.92; N, 13.74; Cl, 11.62; S, 10.47. Found: C, 54.09; H, 3.61; N, 13.46; Cl, 11.22; S, 10.17.

General procedure for the synthesis of 2-N-phenylamino-5-(2-chlorophenyl)-1,3,4-oxadiazol (1a-l). Arylthiosemicarbazide **4**, **4a** (1000 mg, 3.27 mmol) and $LiClO_4$ (106 mg, 0.67 mmol) were dissolved in acetic acid (100 ml) to prepare the reaction mixture for electrolysis.

Electrolysis. Preparative scale controlled potential electrolyses[21-29] were performed at room temperature in 250 ml three-electrode cell assembly with platinum plate (1.0 cm x 1.0 cm) as working as well as counter electrode and saturated calomel electrode (SCE) as reference electrode. Magnetic stirrer was used for the proper mixing of reaction mixture.

All the electrolysis experiments were carried out at their corresponding oxidation potentials and were completed in 3 to 5 hrs. After which no oxidation product was seen to diffuse in the bulk. All the products were solid and colored and entirely different from the starting compound. The current potential data was recorded with the help of a potentiostat at

the interval of 15 min as depicted in table 1. Approximately 4.5-6 $Fmol^{-1}$ quantity of electricity was passed for the electrolysis which is very small in comparison to energy used in other conventional methods.

Extraction. The products were extracted from the acetic acid solution to chloroform layer after diluting reaction solution with double distilled water by the simple solvent extraction technique. Two-immiscible layers of acetic acid containing water and chloroform were shaken in a seperatory funnel and allowed to settle down. After some time the chloroform layer containing the product oxadiazole, was removed. The extracted chloroform layer was evaporated with the help of rotatory evaporator and collected while the product oxadiazole **1** remain in flask, were obtained in the excellent yield. The purity of the compounds oxadiazoles have been checked by the TLC.

2-Phenylamino-5-(2-chlorophenyl)-1,3,4-oxadiazole (1a). Brown crystals; m.p. 152-154 ^{0}C; IR/cm^{-1}: 3230 (NH), 3045 (ArC-H), 1607 (C=N), 1265, 1069 (C-O-C), 910, 860, 735 (benzene), 600-800 (Ar-Cl); ^{1}H NMR (DMSO-d_6, δ ppm): 10.25 (1H, s, NH), 7.29-7.47 (9H, m, ArH); ^{13}C NMR (DMSO-d_6, δ ppm): 176.2, 159.8, 148.1, 140.8, 129.8, 129, 128.6, 127.9, 126.4, 119, 116.1; *m/z* = 272 (M^+ + 1). Calcd. for $C_{14}H_{10}N_3OCl$: C, 61.89; H, 3.70; N, 15.46; Cl, 13.04. Found: C, 61.23; H, 3.54; N, 15.02; Cl, 12.89.

2-Phenylamino-5-(2-hydroxyphenyl)-1,3,4-oxadiazole (1b). Yellow crystals; m.p. 144-146 ^{0}C; IR/cm^{-1}: 3440 (O-H), 3250 (NH), 3045 (ArC-H), 1607 (C=N), 1265, 1069 (C-O-C), 910, 860, 735 (benzene); ^{1}H NMR (DMSO-d_6, δ ppm): 11.69 (1H, s, OH), 10.35 (1H, s, NH), 7.28-7.99 (9H, m, ArH); ^{13}C NMR (DMSO-d_6, δ ppm): 175.2, 159.6, 153.3, 148.4, 128.8, 128.3, 127.90, 121.1, 119.12, 116.2, 115.7; *m/z* = 254 (M^++1). Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 65.85; H, 4.07; N, 16.23.

2-Phenylamino-5-(2-nitrophenyl)-1,3,4-oxadiazole (1c). Brown needles; m.p. 172-174 ^{0}C; IR/cm^{-1}: 3260 (NH), 3055 (ArC-H), 1604 (C=N), 1580 (Ar-NO_2), 1255, 1080 (C-O-C), 950, 860, 740 (benzene); ^{1}H NMR (DMSO-d_6, δ ppm): 10.32 (1H, s, NH), 6.97-7.88 (9H, m, ArH); ^{13}C NMR (DMSO-d_6, δ ppm): 174.4, 157.4, 148.4, 146.3, 135.3, 134.4, 128.8, 127.8, 123.1, 119.12, 116.2; m/z = 283 (M^+ + 1). Calcd. for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.54; N, 19.85. Found: C, 58.92; H, 3.46; N, 18.63.

2-(2-Methoxyphenyl)amino-5-(2-chloro-phenyl) -1,3,4-oxadiazole (1d). Dark brownish needles; m.p. 186-188 ^{0}C; IR/cm^{-1}: 3244 (NH), 2822 (O-CH_3), 2927 (ArC-H), 2853 (alipC-H), 1611 (C=N), 1250, 1062 (C-O-C), 915, 870, 675 (benzene), 600-800 (Ar-Cl); ^{1}H NMR (DMSO-d_6, δ ppm): 10.35 (1H, s, NH), 6.92-7.45 (8H, m, ArH), 3.74 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6, δ ppm): 174.7, 158.4, 147.5, 140.8, 133.5, 128.6, 127.9, 126.4, 122.1, 119.9, 117.1, 115.4, 53.7; *m/z* = 304 (M^+ + 1). Calcd. for $C_{15}H_{13}N_3O_2Cl$: C, 59.60; H, 4.30; N, 13.90; Cl, 11.75. Found: C, 58.26; H, 4.22; N, 13.15; Cl, 11.29.

2-(2-Methoxyphenyl)amino-5-(4-N,N-diethyl-aminophenyl)-1,3,4-oxadiazole (1e). Dark brown crystals; m.p. 191-193 ^{0}C; IR/cm^{-1}: 3261 (NH), 3045 (ArC-H), 2815 (O-CH_3), 2855 (alipC-H), 1609 (C=N), 1270, 1069 (C-O-C), 915, 870, 790 (benzene); ^{1}H NMR (DMSO-d_6, δ ppm): 10.48 (1H, s, NH), 8.03 (2H, d, *J*=8.3 Hz, ArH), 6.93-7.46 (4H, m, ArH), 6.91 (2H, d, *J*=8.3 Hz, ArH), 6.49-7.75 (8H, m, ArH), 4.07 (2H, q, *J*=7.3 Hz, CH_3CH_2N), 3.11 (3H, s, OCH_3), 1.33 (3H, t, *J*=7.3 Hz, CH_3CH_2N); ^{13}C NMR (DMSO-d_6, δ ppm): 175.2, 159.8, 147.5, 142.4, 133.5, 127.7, 122.3, 119.4, 117.6, 115.1, 53.8, 35.5, 17.9; *m/z* =339 (M^+ + 1). Calcd. for $C_{19}H_{22}N_4O_2$: C, 67.43; H, 6.55; N, 16.56. Found: C, 66.87; H, 6.42; N, 16.25.

2-(2-Methoxyphenyl)amino-5-(2-nitrophenyl)-1,3,4-oxadiazole (1f). Dark brown crystals; m.p. 195-197 ^{0}C; IR/cm^{-1}: 3260 (NH), 2860 (alipC-H), 2822 (O-CH_3), 1585 (Ar-NO_2), 1608 (C=N), 1280, 1066 (C-O-C), 925, 890, 785 (benzene); ^{1}H NMR (DMSO-d_6, δ ppm): 10.29 (1H, s, NH), 6.89-7.75 (8H, m, ArH), 3.78 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6, δ ppm): 174.4, 157.4, 147.5, 146.2, 135.3, 134.4, 133.5, 127.8, 123.1, 122.1, 119.9, 117.1, 115.4, 53.8; *m/z* = 313 (M^++1). Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.70;

H, 3.85; N, 17.94. Found: C, 57.16; H, 3.72; N, 17.15.

2-(4-Methoxyphenyl)amino-5-(2-chloro-phenyl)-1,3,4-oxadiazole (1g). Yellow crystals; m.p. 99-101 ^{0}C; IR/ cm^{-1}: 3236 (NH), 3033 (=C-H), 3030 (ArC-H), 2855 (aliphC-H), 2820 (O-CH_3), 1670 (C=C), 1606 (C=N), 1262, 1067 (C-O-C), 920, 860, 790 (benzene), 600-800 (Ar-Cl); ^{1}H NMR (DMSO-d_6, δ ppm): 10.32 (1H, s, NH), 8.03 (2H, d, *J*=8.5 Hz, ArH), 7.35-7.45 (4H, m, ArH), 6.98 (2H, d, *J*=8.3 Hz, ArH), 3.77 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6, δ ppm): 174.4, 157.4, 141.3, 133.5, 132.6, 128.6, 127.8, 126.2, 119.5, 114.1, 55.5; *m/z* =304 (M^++1). Calcd. for $C_{15}H_{13}N_3O_2Cl$: C, 59.47; H, 4.30; N, 13.87; Cl, 11.73. Found: C, 58.89; H, 4.03; N, 13.22; Cl, 11.36.

2-(4-Methoxyphenyl)amino-5-(2-nitrophenyl)-1,3,4-oxadiazole (1h). Brownish needles; m.p. 172-174 ^{0}C; IR/cm^{-1}: 3244 (NH), 2870 (alipC-H), 2822 (O-CH_3), 2927 (ArC-H), 1611 (C=N), 1583 (Ar-NO_2), 1250, 1062 (C-O-C), 915, 870, 675 (benzene); ^{1}H NMR (DMSO-d_6, δ ppm): 10.35 (1H, s, NH), 8.03 (2H, d, *J*=8.5 Hz, ArH), 7.31-7.51 (4H, m, ArH), 6.98 (2H, d, *J*=8.3 Hz, ArH), 3.74 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6, δ ppm): 174.7, 158.4, 146.3, 135.5, 134.8, 132.5, 127.6, 123.2, 114.1, 53.8; *m/z* = 313 (M^++1). Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.84; N, 17.94. Found: C, 57.11; H, 3.76; N, 17.25.

2-(4-Methoxyphenyl)amino-5-(2,4-dinitrophenyl)-1,3,4-oxadiazole (1i). Brownish needles; m.p. 182-184 ^{0}C; IR/cm^{-1}: 3244 (NH), 2870 (alipC-H), 2815 (O-CH_3), 2927 (ArC-H), 1611 (C=N), 1585 (Ar-NO_2), 1250, 1062 (C-O-C), 915, 870, 675 (benzene); ^{1}H NMR (DMSO-d_6, δ ppm): 10.35 (1H, s, NH), 8.78 (1H, s, ArH), 8.52 (1H, d, *J*=8.7 Hz, ArH), 8.03 (1H, d, *J*=8.5 Hz, ArH), 7.69 (1H, d, *J*=8.7 Hz, ArH), 6.98 (2H, d, *J*=8.3 Hz, ArH), 3.14 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6, δ ppm): 174.75, 158.47, 147.2, 141.3, 136.0, 129.4, 128.8, 127.8, 126.8, 125.8, 117.9, 53.8; *m/z* = 268 (M^+ + 1). Calcd. for $C_{15}H_{11}N_5O_6$: C, 67.41; H, 4.12; N, 26.25. Found: C, 66.76; H, 4.01; N, 25.96.

2-(4-Methylphenyl)amino-5-(2-chlorophenyl)-1,3,4-oxadiazole (1j). Brownish needles; m.p 189-191 ^{0}C; IR/: 3244 (NH), 2870 (alipC-H), 2927 (ArC-H), 1611 (C=N), 1250, 1062 (C-O-C), 915, 870, 675 (benzene), 600-800 (ArCl); ^{1}H NMR (DMSO-d_6, δ ppm): 10.36 (1H, s, NH), 8.03 (2H, d, *J*=8.3 Hz, ArH), 7.30-7.45 (4H, m, ArH), 7.01 (2H, d, *J*=8.3 Hz, ArH), 1.12 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, δ ppm): 174.7, 158.4, 141.3, 140.8, 136.1, 133.3, 129.3, 128.6, 127.6, 126.8, 126.4, 125.8, 21.18; *m/z*=343 (M^++1). Calcd. for $C_{15}H_{12}N_3OCl$: C, 63.04; H, 4.20; N, 14.71; Cl 12.43. Found: C, 62.68; H, 4.05; N, 13.92; Cl 12.23.

2-(4-Methylphenyl)amino-5-(4-N,N-diethylaminophenyl)-1,3,4-oxadiazole (1k). Yellow crystals; m.p. 190-192^{0}C; IR/cm^{-1}: 3261 (NH), 3045 (ArC-H), 2855 (alipC-H), 3033 (=C-H), 1609 (C=N), 1270, 1069 (C-O-C), 915, 870, 790 (benzene); ^{1}H NMR (DMSO-d_6, δ ppm): 10.55 (1H, s, NH), 8.03 (2H, d, *J*=8.3 Hz, ArH), 7.25 (2H, d, *J*=8.3 Hz, ArH), 6.93-7.46 (4H, m, ArH), 4.05 (2H, q, *J*=7.3 Hz, CH_3*CH_2*N), 1.12 (3H, s, CH_3), 1.35 (3H, t, *J*=7.3 Hz, *CH_3*CH_2N); ^{13}C NMR (DMSO-d_6, δ ppm): 174.7, 158.4, 142.4, 141.5, 136, 129.3, 127.7, 126.8, 125.8, 119.4, 35.9, 21.18, 17.7; *m/z* = 323 (M^+ + 1). Calcd. for $C_{19}H_{22}N_4O$: C, 78.26; H, 6.83; N, 17.39. Found: C, 77.87; H, 6.42; N, 17.27.

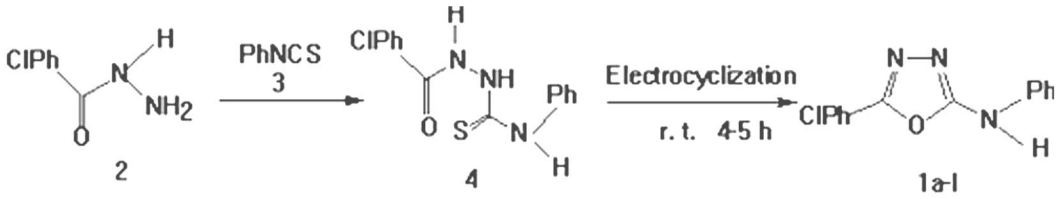
2-(4-Methylphenyl)amino-5-(2,4-dinitrophenyl)-1,3,4-oxadiazole (1l). Brownish needles; m.p. 183-185 ^{0}C; IR/cm^{-1}: 3244 (NH), 2870 (alipC-H), 2927 (ArC-H), 1611 (C=N), 1585 (Ar-NO_2), 1250, 1062 (C-O-C), 915, 870, 675 (benzene); ^{1}H NMR (DMSO-d_6, δ ppm): 10.35 (1H, s, NH), 8.78 (1H, s, ArH), 8.52 (1H, d, *J*=8.7 Hz, ArH), 7.69 (1H, d, *J*=8.5 Hz, ArH), 7.33 (2H, d, *J*=8.3 Hz, ArH), 7.26 (2H, d, *J*=8.3 Hz, ArH), 1.12 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, δ ppm): 174.7, 158.4, 153.3, 141.3, 136.1, 129.3, 128.5, 127.9, 126.8, 125.8, 119.4, 115.7, 21.18; *m/z* = 342 (M^+ + 1). Calcd. for $C_{15}H_{11}N_5O_5$: C, 52.78; H, 3.22; N, 20.53. Found: C, 52.06; H, 3.12; N, 20.25.

Antimicrobial activity. All the title compounds were tested for their antibacterial and antifungal activities by utilizing the disc diffusion method.[30,31] Whatman No.1 filter paper discs of 6 mm diameter, placed in a petri dish, were autoclaved. The test

compounds in measured quantities (1.0 mg, 0.5 mg) were dissolved in 5 ml of dimethylformamide to produce 200 ppm and 100 ppm solutions, respectively. The filter paper discs were allowed to dry and the amount of the substance per disc was taken as 500 and 250 µg. The bacterial (24 hrs) and fungal (48 h) cultures from the slants were diluted with sterile water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were uniformly spread on solidified agar (nutrient and potato dextrose agar) medium. The filter paper discs prepared from dimethylformamide medium were carefully placed over the spreaded cultures and incubated at 37 ^{0}C for 24 h for bacteria and at 28-30^{0}C for 48 h for fungi. Paper discs treated with dimethylformamide alone served as control. After the incubation period the plates were examined for inhibition zones. The diameters of inhibition zones (including the diameter of the disc) were measured. All determinations were made in triplicate for each of the compounds and the average value was taken.

RESULTS AND DISCUSSION

A novel series of 2-phenylamino-5-(2-chlorophenyl)-1,3,4-oxadiazoles **(1a-l)** have been synthesized in good yields using the synthetic route outlined in scheme 1 and scheme 2. IR, ^{1}H NMR, ^{13}C NMR and mass spectral data are in agreement with the proposed structures of all synthesized compounds.



Scheme 1

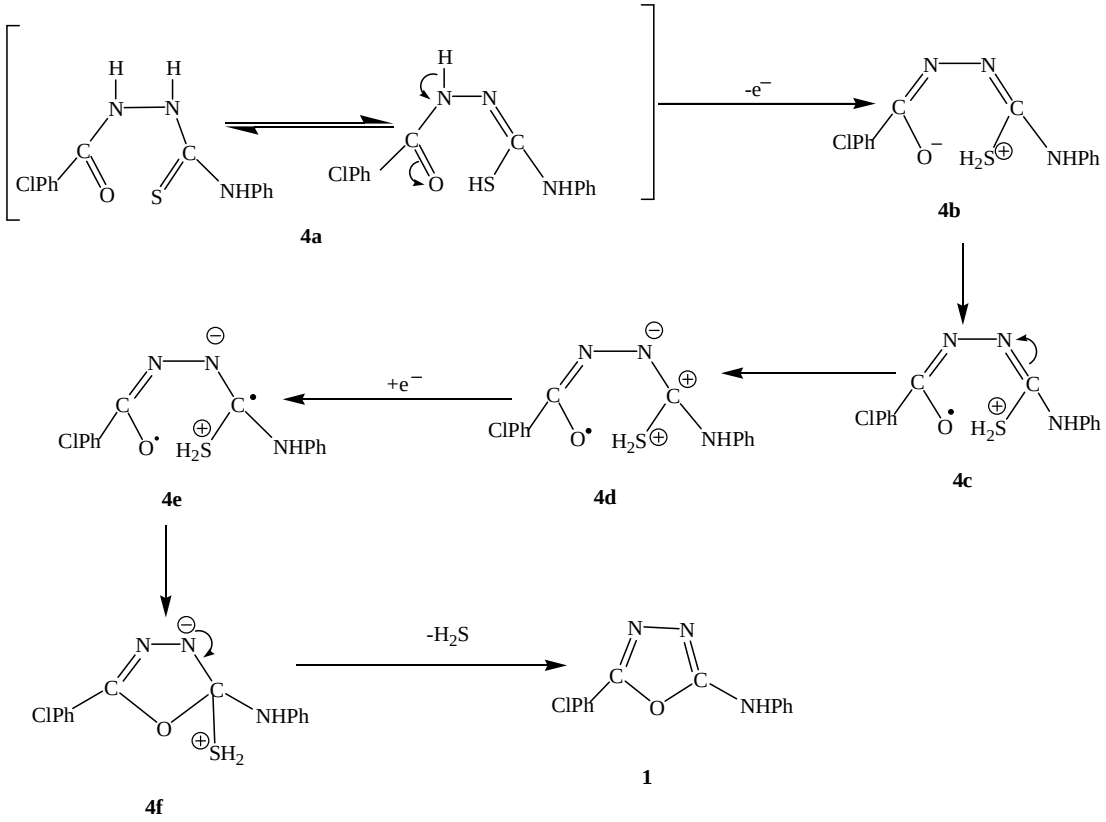
In the IR spectrum of **2** showed broad stretching bands at around 3335 and 3278 cm^{-1} due to amine/amide NH while strong stretching band at 1615 cm^{-1} was attributed to amide carbonyl. ^{1}H NMR spectrum showed a singlet at δ 4.51 and 9.81 which were accounted for NH_2 and NH which disappeared on D_2O exchange. The four protons of phenyl moiety resonated as multiplets at δ 6.68-7.90. The mass spectrum of **2a** showed a molecular ion peak at *m/z* 170.5 which confirmed its molecular weight.

In the IR spectrum of **4** displayed broad stretching bands at around 1632 cm^{-1} for carbonyl and 1265 cm^{-1} for C=S bonding. ^{1}H NMR spectrum showed a singlet at δ 10.60-11.96 which were accounted for NH. The four protons of phenyl moiety resonated as two doublets at δ 7.67 and 7.89 while five aryl protons show the multiplets at δ 6.96-7.25. The mass spectrum of **4** showed a molecular ion peak at *m/z* 305.5 which confirmed its molecular weight.

Lack of ^{1}H NMR resonances observed with NH and NH_2 functions in the ^{1}H NMR spectrum of **1** proved that ring closure starting from **4** resulted in the formation of 1,3,4-oxadiazole ring. This was further substantiated by the ^{13}C NMR data of **1** which showed a peak δ 170-173 and 155-160 due to C_2 and C_5 of oxadiazole. The IR spectrum showed beaks at 1600-1622 cm^{-1} for (C=N-N=C) and 1062-1075 cm^{-1} for (C-O-C) in the compounds **1a-l** which confirmed the synthesis of 1,3,4-oxadiazoles.

The antibacterial activity of compounds **1a-l** was studied against the growth of *Klebsilla penumoniae, Escherichia coli,* (Gram-negative) and *Basillus subtilis, Streptococus aureus* (Gram-positive) organisms at the three concentrations (25, 50 and 100 ppm) taking Penicillin as the standard (Table 2). The majority of the compounds exhibited significant (good) antibacterial activity against *E. coli, K. pneumonia, B. subtilis* and *S. aureus* as compared to penicillin. The screening results of antibacterial activity revealed that compound **1a**, **d**, **g** and **1j**

exhibited greater activity than the standard Penicillin. Compounds **1c**, **f**, **h**, **i**, **l** display approximately similar or slightly less activity than the standard. The remaining compounds exhibited weak to moderate antibacterial activity against all bacterial strains used for our evaluation.



Scheme 2. Mechanistic proposal

Table 1. Current, potential and yield in the synthesis of 1,3,4-oxadiazole derivatives (1a-1l).

Compound	R^1 (5-)	R^2 (2-amino-)	Time [h]	Applied potential [V]	Current [mA]	Yield [%]
1a	2-ClC_6H_4	C_6H_5	3	1.80	1180	83
1b	2-$(OH)C_6H_4$	C_6H_5	3	2.10	1016	76
1c	2-$(NO_2)C_6H_4$	C_6H_5	4	1.95	1213	79
1d	2-ClC_6H_4	2-$OMeC_6H_4$	5	2.00	1350	71
1e	2-$(Et_2N)C_6H_4$	2-$OMeC_6H_4$	4	1.75	1055	81
1f	2-$(NO_2)C_6H_4$	2-$OMeC_6H_4$	3	2.15	1115	84
1g	2-ClC_6H_4	4-$OMeC_6H_4$	4	1.85	1185	78
1h	2-$(NO_2)C_6H_4$	4-$OMeC_6H_4$	5	1.90	1265	73
1i	2,4-$(NO_2)_2C_6H_3$	4-$OMeC_6H_4$	4	2.10	1232	76
1j	2-ClC_6H_4	4-MeC_6H_4	4	1.90	1205	83
1k	2-$(Et_2N)C_6H_4$	4-MeC_6H_4	3	1.95	1015	81
1l	2,4-$(NO_2)_2C_6H_3$	4-MeC_6H_4	4	2.05	1184	74

Table 2. Antibacterial activity of compounds (1a-1l).

Compound	Zone of inhibition (mm)											
	E. coli (μgdisc^{-1})			*K. pneumoniae* (μgdisc^{-1})			*B. subtilis*. (μgdisc^{-1})			*S. aureus* (μgdisc^{-1})		
	25	50	100	25	50	100	25	50	100	25	50	100
1a	2	6	13	2	5	10	2	8	12	2	6	12
1b	0	4	7	0	3	8	0	3	7	0	2	6
1c	0	5	10	2	6	10	2	7	11	0	6	11
1d	0	7	12	2	6	12	0	7	12	2	6	12
1e	0	2	4	0	0	5	0	2	4	0	2	5
1f	0	5	9	0	4	8	2	4	7	1	4	8
1g	2	7	14	0	6	11	0	7	11	0	6	12
1h	0	6	12	2	7	10	0	6	10	0	5	11
1i	0	5	11	0	5	10	0	7	12	0	5	10
1j	2	8	13	0	7	11	2	7	13	0	6	11
1k	0	2	5	0	0	4	0	3	5	0	2	4
1l	0	7	11	0	6	11	0	6	12	0	6	10
Penicillin	0	8	12	2	7	10	2	8	12	2	7	11

Table 3. Antifungal activity of the compounds (1a-1l).

Compound	Zone of inhibition (mm)											
	A. niger (μgdisc^{-1})			*P. solmanicolor* (μgdisc^{-1})			*C. pannical,* (μgdisc^{-1})			*C. albicans* (μgdisc^{-1})		
	25	50	100	25	50	100	25	50	100	25	50	100
1a	2	6	12	0	5	11	2	7	13	2	8	12
1b	0	2	6	0	0	6	0	0	5	0	2	6
1c	0	6	10	0	5	10	0	6	11	2	6	11
1d	0	7	13	0	5	10	0	5	10	2	8	12
1e	0	2	7	0	0	5	0	3	6	0	2	7
1f	2	4	7	0	5	8	1	3	6	2	4	6
1g	0	7	12	0	6	11	2	7	13	0	6	12
1h	0	5	10	0	5	9	0	6	11	0	5	10
1i	0	6	11	0	6	10	0	7	11	0	5	10
1j	2	7	13	0	6	11	2	7	12	0	6	11
1k	0	5	9	0	4	8	0	3	9	0	6	10
1l	0	6	12	0	5	9	0	6	11	0	5	10
Griseofulvins	0	8	12	2	7	10	2	8	12	2	7	11

The compounds (**1a-1l**) were screened for their antifungal activity against *Aspergillus niger*, *Crysosporium pannical*, *Pellicularia solmanicolor* and *Candida albicans* species along with the standard fungicide Griseofulvins **1a-1l** (Table 3). The disc diffusion method was followed for screening the compounds at three concentrations (25, 50 and 100 ppm). The screening results showed that all the compounds displayed good antifungal activity. However, compounds **1a**, **1d**, **1g** and **1j** showed approximately equal or greater antifungal activity for different strains when compared with the griseofulvin.

The antimicrobial activity of the compounds varied upon the type and position of the substituents at 5-substituted-2-amino-1,3,4-oxadiazole moiety. It can be concluded from the antimicrobial screening results that when 5-substituted-2-amino-1,3,4-oxadiazoles were substituted with aryl halide the antimicrobial activity was altered to an appreciable extent.

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