# Studies of Biologically Active Heterocycles: Synthesis, Characterization and Antimicrobial Activity of Some 5-Substitutd-2-Amino-1,3,4-Oxadiazoles

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**ABSTRACT:** In the present study, 5-substituted-2-amino-1,3,4-oxadiazoles (4a-k) have been synthesized by the electrochemical oxidation of semicarbazones (3a-k) using platinum anode at room temperature under controlled potential electrolysis in an undivided cell assembly. The structural assignment of these compounds (4a-k) has been made on the basis of elemental analysis, IR, $^{1}$H NMR and $^{13}$C NMR. The synthesized compounds were screened for their inhibiting activity against *Klebsilla penumoniae*, *Escherichia coli*, *Bassilus subtilis* and *Streptococcus aureus* and antifungal activity against *Aspergillus niger* and *Crysosporium pannical* and results have been compared with the standard antibacterial agents, Streptomycin and antifungal drug, Griseofulvin. The Compounds exhibited significant antibacterial activity and antifungal activity.

**Key words:** Electrochemical oxidation, controlled potential, 5-substituted-2-amino-1,3,4-oxadiazole, semicarbazone, antimicrobial agents

## INTRODUCTION

5-substituted-2-amino-1,3,4-oxadiazoles have been found to exhibit diverse biological activities such as antibacterial[1], anti HIV[1], antifungal[2], genotoxic[2], antitubercular[3], virucidal[4], antimalarial[5], insecticidal[6], herbicidal[7], analgesic[8], antiinflammatory[9], muscle relaxants[10], anticonvulsant[11], sedative, hypnotic[12], anticancer[13] and lipid peroxidation inhibitor.[14]

In context of green chemistry, some 5-substituted-2-amino-1,3,4-oxadiazoles **4** have been synthesized by electrooxidative cyclization of semicarbazone **3** as a new general environmentally benign synthetic method. The development of eco-friendly synthetic methods would be most welcome. In this respect, organic synthesis involving multi-component reactions under reagents free conditions is a basic protocol because multistep conventional synthesis produces considerable amounts of environmentally unfavorable wastes, mainly due to a series of complex isolation procedures often involving expensive, toxic and hazardous solvents and reagents after each step. The application of electricity as a non conventional energy source for activation of reactions in the suitable solvents has now gained popularity over the usual homogeneous and heterogeneous reactions, as it provides chemical processes with special attributes, such as enhanced reaction rates, better selectivity, higher yield of pure products and several eco-friendly advantages. These reactions do not require oxidizing reagents and can be performed at ordinary room temperature.

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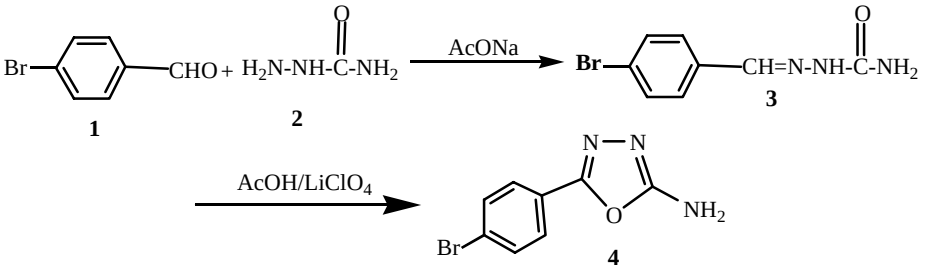
## MATERIALS AND METHODS

**General experimental procedure.** Column chromatography was carried out by using Merck silica gel 60. The purity of the synthesized

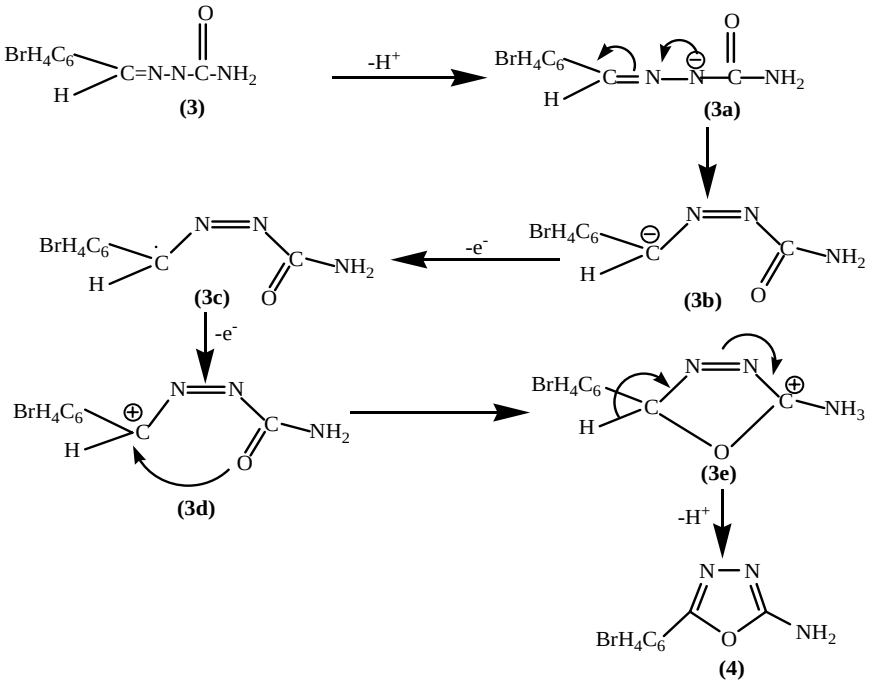
compounds was ascertained by TLC on precoated Silica gel plates in various solvent systems using iodine vapors and UV Flourescence as the detecting agents. The melting points were recorded on an electrothermal apparatus GSI-MP-3 and are uncorrected. Infra red spectra were recorded on a Shimadzu 8201 PC IR spectrophotometer in KBr pellets and reported in $cm^{-1}$. $^{1}H$ NMR and $^{13}C$ NMR spectra were measured on Bruker DRX 300 MHz FT spectrometer instruments using DMSO-$d_6$ as solvent with TMS and $CDCl_3$ as internal standards (chemical shift in δ ppm). Carbon multiplicities were assigned by DEPT techniques. The structures of the newly synthesized compounds were assigned on the basis of elemental analysis and were recorded on a Elementar Vario EL III. Carbon, hydrogen and nitrogen analyses were within ± 0.4% of the theoretical values. All the chemicals used were of synthetic and AR grade and were procured from Acros-Organics, USA, S.D. Fine Chem. Ltd., Mumbai and Merck, Mumbai, India.

**Synthesis of 2-amino-5-(*p*-bromophenyl)-1,3,4-oxadiazoles.** Semicarbazide hydrochloride (1.0 g, 8.96 mmol) **2** and NaOAc were dissolved in (10 mL) water then an aldehyde (0.5 g, 3.04 mmol) **1** was added with continuous stirring. The mixture was left overnight to yield a solid semicarbazone **3** which was used as initial compound for the electrolysis. Semicarbazone (1.0 g, 4.52 mmol) **3** and $LiClO_4$ (0.106 g, 0.67 mmol) were dissolved in (100 mL) acetonitrile.

**Scheme 1. Synthetic route for the preparation of 5-substituted-2-amino-1,3,4-oxadiazoles**

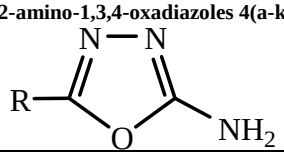



**Scheme 2. Mechanistic proposal for electrooxidation of semicarbazone (3a-k)**



**Electrolysis.** Preparative scale controlled potential electrolysis[15-19] was performed at room temperature in 250 mL three-electrode cell assembly with platinum plate as working as well as counter electrode (both anode and cathode are Pt electrode) and saturated calomel electrode 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 h. 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 potentiostat at the interval of 15 min as depicted in the Table 1. Approximately 4-6.5 $Fmol^{-1}$ of electricity was passed for the electrolysis which is very small in comparison to energy used in other conventional methods.

**Table 1. Electroorganic synthesis of 5-substituted-2-amino-1,3,4-oxadiazoles 4(a-k)**




| Entry | R | Time (Hr) | Applied Potential (mV) | Current (mA) | Yield in AcOH (%) | Yield in $CH_3CN$ (%) |
|---|---|---|---|---|---|---|
| **4a** | *o*-$BrC_6H_4$ | 4 | 1540 | 110 | 88 | 80 |
| **4b** | *m*-$BrC_6H_4$ | 5 | 2100 | 150 | 96 | 92 |
| **4c** | *p*-$BrC_6H_4$ | 5 | 2250 | 120 | 86 | 81 |
| **4d** | *o*-$(NO_2)C_6H_4$ | 3 | 1850 | 90 | 92 | 90 |
| **4e** | 3-Pyridinyl | 4 | 1800 | 70 | 79 | 75 |
| **4f** | $CH_2Cl$ | 5 | 2000 | 120 | 75 | 73 |
| **4g** | $CHCl_2$ | 5 | 1900 | 80 | 81 | 77 |
| **4h** | *p*-$(CH_3)C_6H_4$ | 3 | 1450 | 90 | 85 | 81 |
| **4i** | 3,4,5-$(OCH_3)_3C_6H_2$ | 5 | 1700 | 80 | 92 | 84 |
| **4j** | 1-$C_{10}H_7$ | 4 | 1600 | 100 | 87 | 81 |
| **4k** | 2-$C_{10}H_7$ | 4 | 2200 | 120 | 86 | 78 |

**2-amino-5-(*o*-bromophenyl)-1,3,4-oxadiazole (4a).** Brownish crystal; mp: 68-69$^0$C; IR (KBr, $cm^{-1}$): 3360 (NH), 3045 (ArC-H), 1613 (C=N-N=C), 1265, 1072 (C-O-C), 980, 890, 750, 595 (substituted benzene); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.75 (2H, s, $NH_2$), 6.94-7.14 (4H, dd, Ar-H); $^{13}$C NMR (DMSO-$d_6$,δ ppm): δ 168.9 ($C_{Oxadiazole}$-5), 147.7 ($C_{Oxadiazole}$-2), 144.6 (C-1), 131.9 (C-3), 129.1 (C-4), 128.9 (C-6), 126.4 (C-5), 121.3 (C-2). MS (ESI) m/z Calcd $C_8H_6N_3OBr$ (M+H) 241.01, Found: 240.69. Anal. Calcd. C 40.00, H 2.50, N 17.50, Br 33.33 %, Found: C 39.52, H 2.40, N 17.35, Br 33.12 %.

**2-amino-5-(*m*-bromophenyl)-1,3,4-oxadiazole (4b).** Brownish crystal; mp: 75-76$^0$C; IR (KBr, $cm^{-1}$): 3362 (NH), 3042 (ArC-H), 1620 (C=N-N=C), 1265, 1072 (C-O-C), 980, 890, 7505, 595 (substituted benzene); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.75 (2H, s, $NH_2$), 6.94-7.14 (4H, dd, Ar-H); $^{13}$C NMR (DMSO-$d_6$, ppm): δ 170.9 ($C_{Oxadiazole}$-5), 147.7 ($C_{Oxadiazole}$-2), 132.9 (C-1), 131.9 (C-4), 130.1 (C-2), 128.4 (C-5), 125.1 (C-6), 123.4 (C-3). MS (ESI) m/z Calcd $C_8H_6N_3OBr$ (M+H) 241.01, Found: 240.52. Anal. Calcd. C 40.00, H 2.50, N 17.50, Br 33.33 %, Found: C 39.56, H 2.42, N 17.35, Br 33.22 %.

**2-amino-5-(*p*-bromophenyl)-1,3,4-oxadiazole (4c).** Brownish crystal; mp: 69-70$^0$C; IR (KBr, $cm^{-1}$): 3360 (NH), 3045 (ArC-H), 1615 (C=N-N=C), 1275, 1075 (C-O-C), 985, 890, 755, 597 (substituted benzene); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.75 (2H, s, $NH_2$), 6.94-7.14 (4H, dd, Ar-H); $^{13}$C NMR (DMSO-$d_6$, ppm): δ 171.9 ($C_{Oxadiazole}$-5), 147.7 ($C_{Oxadiazole}$-2), 136.6 (C-1), 132.9 (C-3), 131.9 (C-5), 125.4 (C-2), 125.1 (C-6), 121.5 (C-4). MS (ESI) m/z Calcd $C_8H_6N_3OBr$ (M+H) 241.01, Found: 240.56. Anal. Calcd. C 40.00, H 2.50, N 17.50, Br 33.33 %, Found: C 39.53, H 2.41, N 17.35, Br 33.15 %.

**2-amino-5-(*o*-nitrophenyl)-1,3,4-oxadiazole (4d).** Dark Yellowish needle; mp: 71-73$^0$C; IR (KBr, cm$^{-1}$): 3341 (NH), 3035 (ArC-H), 1607 (C=N-N=C), 1550 (N=O), 1275, 1070 (C-O-C), 985, 865, 810, 730 (substituted benzene); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.75 (2H, s, $NH_2$), 7.25-7.69 (3H, dd, Ar-H); $^{13}$C NMR (DMSO-$d_6$, ppm): δ 171.3 ($C_{Oxadiazole}$-5), 147.1($C_{Oxadiazole}$-2), 146.8 (C-2), 136.8 (C-1), 134.7 (C-5), 130.4 (C-4), 127.2 (C-3), 126.5 (C-6). MS (ESI) m/z Calcd $C_8H_6N_5O_5$ (M+H) 253.12, Found: 252.72. Anal. Calcd. C 38.09, H 2.38, N 27.77 %, Found: C 37.89, H 2.40, N 27.35 %.

**2-amino-5-(3-pyridinyl)-1,3,4-oxadiazole (4e).** Dark yellowish crystal; mp: 67-68$^0$C; IR (KBr, cm$^{-1}$): 3350 (NH), 3037 (PyC-H), 1628 (C=N-N=C), 1430-1600 (C=C and C=N str.), 1070 (C-O-C); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.18-8.56 (4H, dd, Ar-H)), 7.75 (2H, s, $NH_2$); $^{13}$C NMR (DMSO-$d_6$, ppm): δ 171.2 ($C_{Oxadiazole}$-5), 149.8 (C-5), 148.8 (C-2), 147 ($C_{Oxadiazole}$-2), 135.7 (C-4), 135.5 (C-3), 123.6 (C-5). MS (ESI) m/z Calcd $C_7H_6N_4O$ (M+H) 163.15, Found: 162.01. Anal. Calcd. C 51.85, H 3.70, N 34.57 %, Found: C 51.35, H 3.40, N 34.58 %.

**2-amino-5-chloromethyl-1,3,4-oxadiazole (4f).** Brownish crystal; mp: 61-62$^0$C; IR (KBr, cm$^{-1}$): 3360 (NH), 3062 (C-H), 1618 (C=N-N=C), 1280, 1066 cm$^{-1}$ (C-O-C), 680 (C-Cl); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.75 (2H, s, $NH_2$), 3.8 (2H, s, $CH_2$); $^{13}$C NMR (DMSO-$d_6$, ppm): δ 170.6 ($C_{Oxadiazole}$-5), 147.6 ($C_{Oxadiazole}$-2), 24.9 ($CH_2$). MS (ESI) m/z Calcd $C_3H_4N_3OCl$ (M+H) 134.53, Found: 133.56. Anal. Calcd. C 26.96, H 2.69, N 31.46, Cl 26.59 %, Found: C 26.55, H 2.59, N 31.15, Cl 26.60 %.

**2-amino-5-dichloromethyl-1,3,4-oxadiazole (4g).** Brownish crystal; mp: 64-65$^0$C; IR (KBr, cm$^{-1}$): 3360 (NH), 3065 (C-H), 1609 (C=N-N=C), 1280, 1066 (C-O-C), 690 (C-Cl); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.75 (2H, s, $NH_2$), 3.9 (1H, s, CH); $^{13}$C NMR (DMSO-$d_6$, ppm): δ 172.1 ($C_{Oxadiazole}$-5), 148.2 ($C_{Oxadiazole}$-2), 51.2 (CH). MS (ESI) m/z Calcd $C_3H_3N_3OCl_2$ (M+H) 168.9, Found: 168.02. Anal. Calcd. C 21.55, H 1.70, N 25.14, Cl 41.91 %, Found: C 21.35, H 1.68, N 25.14, Br 41.66 %.

**2-amino-5-(*p*-methylphenyl)-1,3,4-oxadiazole (4h).** Light brown needles; mp: 74-75$^0$C; IR (KBr, cm$^{-1}$): 3270 (NH), 3045 (ArC-H), 3010 (C-H), 2927, 1602 (C=N-N=C), 1265, 1069 (C-O-C), 960, 765 (substituted benzene); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.75 (2H, s, $NH_2$), 6.52-7.24 (4H, dd, Ar-H), 1.12 (3H, s, CH); $^{13}$C NMR (DMSO-$d_6$, ppm): δ 178.2 ($C_{Oxadiazole}$-5), 149.9 ($C_{Oxadiazole}$-2), 141.3 (C-1), 138.6 (C-4), 129.3 (C-3), 129.2 (C-5), 127.8 (C-2), 127.5 (C-6), 20.6 ($CH_3$). MS (ESI) m/z Calcd $C_9H_9N_3O$ (M+H) 176.19, Found: 175.42. Anal. Calcd. C 61.71, H 5.14, N 24.00 %, Found: C 61.52, H 5.11, N 23.85 %.

**2-amino-5-(3,4,5-methoxyphenyl)-1,3,4-oxadiazole (4i).** Dark brownish needle; mp: 84-85$^0$C; IR (KBr, cm$^{-1}$): 3261 (NH), 3045 (ArC-H), 2815 ($OCH_3$), 1609 (C=N-N=C), 1270, 1069 (C-O-C), 915, 870, 790 (substituted benzene); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.75 (2H, s, $NH_2$), 6.46-7.70 (2H, dd, Ar-H), 3.11 (9H, s, $OCH_3$); $^{13}$C NMR (DMSO-$d_6$, ppm): δ 172.4 ($C_{Oxadiazole}$-5), 147.5 ($C_{Oxadiazole}$-2), 146.7 (C-3), 146.3 (C-5), 141.9 (C-4), 129.5 (C-1), 106.5 (C-2), 105.7 (C-6), 54.3 and 44.6 ($CH_3$). MS (ESI) m/z Calcd $C_{11}H_{13}N_3O_4$ (M+H) 252.24, Found: 251.56. Anal. Calcd. C 52.59, H 5.17, N 16.73 %, Found: C 52.40, H 5.11, N 16.52 %.

**2-amino-5-(1-naphthyl)-1,3,4-oxadiazole (4j).** Dark brownish needle; mp: 94-95$^0$C; IR (KBr, cm$^{-1}$): 3330 (NH), 3045 (ArC-H), 1612 (C=N-N=C), 1055 (C-O-C), 775 (substituted aromatics); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.75 (2H, s, $NH_2$), 7.25-7.69 (7H, dd, Ar-H); $^{13}$C NMR (DMSO-$d_6$, ppm): δ 171.5 ($C_{Oxadiazole}$-5), 149.5 ($C_{Oxadiazole}$-2), 140.1 (C-1), 133.7 (C), 128.1 (C-5), 128.1 (C-8), 127.7 (C-4), 126.8 (C-9), 126.8 (C-10), 126.3 (C-6), 126.3 (C-7), 125.1 (C-3), 123.6 (C-2). MS (ESI) m/z Calcd $C_{12}H_9N_3O$ (M+H) 228.22, Found: 227.45. Anal. Calcd. C 68.24, H 4.26, N 19.90 %, Found: C 67.92, H 4.26, N 19.85 %.

**2-amino-5-(2-naphthyl)-1,3,4-oxadiazole (4k).** Dark brownish needle; mp: 96-97$^0$C; IR (KBr, cm$^{-1}$): 3335 (NH), 3045 (ArC-H), 1622 (C=N-N=C), 1045 (C-O-C), 775 (substituted aromatics); $^1$H NMR (DMSO-$d_6$, ppm): δ 7.75 (2H, s, $NH_2$), 7.25-7.69

(7H, dd, Ar-H); $^{13}$C NMR (DMSO-$d_6$, ppm): δ 171.6 ($C_{Oxadiazole}$-5), 149.5 ($C_{Oxadiazole}$-2), 137.6 (C-2), 133.7 (C), 128.1 (C-5), 128.1 (C-8), 127.7 (C-4), 126.8 (C-9), 126.8 (C-10), 126.3 (C-6), 126.3 (C-7), 126.3 (C-1), 125.1 (C-3). MS (ESI) m/z Calcd $C_{12}H_9N_3O$ (M+H) 228.22, Found: 227.51. Anal. Calcd. C 68.24, H 4.26, N 19.90 %, Found: C 67.95, H 4.25, N 19.86 %.

**Screening for Antimicrobial activity.** All the synthesized compounds were tested for their antimicrobial activity by adopting the experimental method of Benson[20]. 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 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 h) 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. The antibacterial and antifungal screening results were presented in Table 2 and Table 3.

**Table 2. Antibacterial screening results of 5-substituted-2-amino-1,3,4-oxadiazole (4a-k)**

| Compound | Zone of inhibition (mm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *E. coli* | | *K. pneumonia* | | *B. subtilis* | | *S. aureus* | |
| | 25 ppm | 50 ppm | 25 ppm | 50 ppm | 25 ppm | 50 ppm | 25 ppm | 50 ppm |
| **4a** | 18 | 21 | 17 | 23 | 18 | 24 | 17 | 22 |
| **4b** | 4 | 6 | 4 | 7 | 5 | 7 | 4 | 6 |
| **4c** | 15 | 18 | 3 | 20 | 14 | 19 | 13 | 19 |
| **4d** | 12 | 17 | 9 | 13 | 12 | 15 | 11 | 15 |
| **4f** | 16 | 20 | 17 | 21 | 15 | 20 | 14 | 19 |
| **4g** | 17 | 21 | 14 | 20 | 16 | 20 | 16 | 20 |
| **4i** | 15 | 18 | 14 | 18 | 13 | 17 | 17 | 19 |
| Streptomycin | 20 | 23 | 19 | 24 | 19 | 24 | 19 | 23 |

**Table 3. Antifungal screening results of 5-substituted-2-amino-1,3,4-oxadiazole (4a-k)***

| Compound | *A. niger* | | | *C. pannical* | | |
|---|---|---|---|---|---|---|
| | 10 ppm | 100 ppm | 1000 ppm | 10 ppm | 100 ppm | 1000 ppm |
| **4a** | 18 | 43 | 76 | 19 | 43 | 78 |
| **4b** | 15s | 38 | 65 | 16 | 36 | 67 |
| **4c** | 44 | 58 | 98 | 45 | 57 | 98 |
| **4d** | 21 | 46 | 75 | 24 | 43 | 78 |
| **4f** | 38 | 56 | 97 | 40 | 51 | 96 |
| **4g** | 40 | 53 | 96 | 42 | 53 | 97 |
| **4i** | 21 | 44 | 70 | 20 | 43 | 68 |
| Griseofulvin | 66 | 86 | 100 | 65 | 83 | 100 |

*Average inhibition of fungal growth (%) at stated concentration (mg/liter$^{-1}$)

## RESULTS AND DISCUSSION

The antimicrobial screening indicated that compounds **a, b, c, d, f, g** and **i** were found to be active against *Klebsilla penumoniae, Escherichia coli, Basillus subtilis, Streptococus aureus* at 25 and 50 ppm taking Streptomycin as the standard. The majority of the compounds exhibited significant antibacterial activity against *E. coli, K. pneumonia, B. subtilis* and *S. aureus* when compared to that of Streptomycin. The screening results further revealed

that compound **a** and **g** exhibited approximately similar activity to the standard Streptomycin. Compounds **c, d, i** and **j** exhibited slightly less antibacterial activity. Compound **b** exhibited weak inhibition of growth while other compounds should no or negligible antibacterial activity against all bacterial strains used for our evaluation. The screening results showed that compounds **b, c d, f** and **i** displayed better antifungal activity against *Aspergillus niger* and *C. pannical* along with the standard fungicide Griseofulvins. The results demonstrated that compounds **a** and **g** showed equal antifungal activity when compared with Griseofulvins.

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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