NEW 1,3,4-OXADIAZOLE BASED SCHIFF BASE DERIVATIVES: SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY ALONG WITH IN SILICO STUDIES

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A series of novel 1,3,4-oxadiazole based Schiff base derivatives were designed and synthesized using the efficient strategy with excellent yields. Synthesized molecules evaluated in vitro antibacterial studies in contradiction of microorganisms, namely *Escherichia coli*, *Klebsiella pneumoniae*, *Bacillus subtilis*, and *Bacillus megaterium*. The bioassay result revealed that most of tested compounds good to moderate inhibition against microorganisms. Some among them show excellent inhibitory effects towards the Gram-positive and Gram-negative bacteria. Besides, the drug-likeness, lipophilicity and cytotoxicity.

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INTRODUCTION

Schiff bases are a significant class of organic compounds that show curiosity in industrial and biological and pharmaceutical science. They are one of the widely used moieties in the field of organic chemistry. A Schiff base is a compound that possesses an R'-C=NR'common structure and is obtained by a simple condensation reaction between aldehyde or ketone and primary amines. It is also called imine or azomethine. Common uses of Schiff base are drug-like molecules dyes, intermediates and catalyst.[1] Schiff bases containing an aromatic ring show more biological potency due to their free electron delocalization.[2] Eventually, hetero atom containing Schiff base derivatives shows enormous applicability in field of drug discovery.[3] Schiff bases have also been appeared to show a wide range of biological responses including, antimicrobial, anti-inflammatory, antipyretic, and antimalarial activities.[4-8] Diverse substitution of heterocyclic moiety Schiff base possesses different biological responses like benzimidazole-based Schiff base derivatives potent as antimicrobial agent[9] and cytotoxic effects on colon and cervix cancer cells lines.[10] Cu (II) complexes with Schiff base of benzimidazole shows DNA interaction and antiproliferative activities.[11] 1,3,4-oxadiazole and 1,3,4-thiadiazole based Schiff base moiety parade antitumor activities.[12] 1,2,4-Triazole, 1,3,4-oxadiazole and 1,3,4-thiadiazole based Schiff base potent as antimicrobial and antiproliferative agents[13] and anti-inflammatory activities.[14] Schiff base of coumarin based 1,3,4-oxadiazole derivatives having antimicrobial activity.[15]

Another motif oxadiazole, possesses two nitrogen and one oxygen atom five-membered heterocyclic ring for the synthesis of 1,3,4-oxadiazole numerous method available including the reaction of acid hydrazides with diversity of dehydrating agents such as phosphorous oxychloride,[16-18] triflic anhydride,[19] polyphosphoric acid,[20] phosphorous pentoxide,[21] using (N-isocynimino) triphenylphosphorane,[22-23] by the help of Iminophosphorane,[24] Hypervalent iodine(V) mediated synthesis,[25] from isoselenocyanates via cyclodeselenization.[26] In this paper, we have done the synthesis of some new 1,3,4-oxadiazole based Schiff bases and check their potency toward the antimicrobial activity.

EXPERIMENTAL

All chemicals, solvents and media were purchased from Sigma Aldrich, combi-block, enamine, Himedia, SRL. All purchased chemicals were used without further purification. Reactions were continuous monitored by thin-layer chromatography (TLC) on silica gel-(G60 F254 (Merck)) of 0.5 mm thickness, visualizing with ultraviolet light (254 and 365nm), or with iodine vapor. Melting points were determined using a Buchi B-540 capillary apparatus. NMR spectra were recorded on a Bruker Advance 400 MHz spectrometer (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR) respectively in solvents like $CDCl_3$, DMSO and chemical shifts are referenced to the solvent residual signals with respect to tetramethylsilane. Standard abbreviations are used to represent signal multiplicities for ^{1}H NMR spectrum s - singlet, d - doublet, t - triplet, q - quartet, dd - double doublet, m - multiplet.

Antibacterial assay

The method depends on the rule that includes the compound's ability to inhibit the growth of microorganisms, as exhibited by a clear zone of inhibition.[27-29] The lowest concentration inhibiting the microorganism's growth is recorded as the MIC (Minimum inhibitory concentration). To evaluate the antimicrobial activity, using culture media: nutrient agar plates, nutrient broth. For inoculum preparation, take 50 mL nutrient broth in a flask and inoculate wire loop culture of bacterial strains and for fungi, Bacterial culture incubates at 37 °C for 24 hours. Synthesized compounds

were dissolved in stock solution as a DMSO (2000 µg mL^{-1} concentration). For primary screening, three different dilutions, such as 1000 µg mL^{-1}, 500 µg mL^{-1}, and 250 µg mL^{-1} from stock solution of synthesized compounds, were made. To check MIC prepared nutrient agar plate and allowed to solidify after solidification bacterial strains were spread on plates by spread plate technique and make well on the agar plates by using a 7 mm cupbearer. After preparation of the well, synthesized compounds dilutions (1000 µg mL^{-1}, 500 µg mL^{-1}, and 250 µg mL^{-1}) were added 100 µL into the well of plates. After that, bacterial plates were incubated at 37 ^{o}C for 24 hours. The diameter of the zone of inhibition extending laterally around the wells was measured. A reference to this screening goes for secondary screening. For secondary screening, the synthesized compound found active in primary screening were similarly diluted to obtain 200 µg mL^{-1}, 10 µg mL^{-1}, 25 µg mL^{-1}, and 50 µg mL^{-1} concentrations. The screening was performed in 50 µg mL^{-1} concentration for all synthesized compounds. The diameter of the zone of inhibition was measured in millimeters (mm).

Procedure for the synthesis of 4-nitrobenzohydrazide (1)

To a stirred solution of 4-nitrobenzoic acid 10.00 g (59.84 mmol) in methanol solvent (50 mL) sulphuric acid was added and the reaction mixture to reflux at 60 ^{o}C for 2 hours. The progress of the reaction was monitored by TLC. After completing the reaction, the reaction mixture was concentrated and poured into ice-cold water (200 mL). The solid material was precipitated out, filtered out and dried u/vacuum to get methyl-4-nitrobenzoate (**1a**). Now, to a stir solution of methyl-4-nitrobenzoate (**1a**) 5 g (27.62 mmol) in ethanol (30 mL) was added hydrazine hydrate 3 ml (60 mmol) and the reaction mixture was reflux at 78 ^{o}C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated and poured into ice-cold water (100 mL). The solid material was precipitate out, which was filtered out, washed with water, and dried under vacuum to get 4-nitrobenzo hydrazide (**1**)**.**

Methyl-4-nitrobenzoate (1a)

Yield: 87.14% as an off-white solid material. m.p. 94-96^{0}C. ^{1}H NMR (400 MHz, DMSO) δ 8.36 (d, *J*=8.4 Hz, 2H, Ar-H), 8.20 (d, *J* = 8.8 Hz, 2H, Ar-H), 3.92 (s, 3H, -CH_3), Mass m/z: 181.15.

4-Nitrobenzohydrazide (1)

Yield: 84.61 % as a light-yellow solid material. m.p. 212-214^{0}C. ^{1}H NMR (400 MHz, DMSO) δ: 10.14 (s, 1H, -NH), 8.30 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.04 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.65 (s, 2H, -NH_2), :MS m/z: 181.15.

Procedure for the synthesis of 2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (3)

To a stirred solution of phosphoryl chloride (15 mL), 4-nitrobenzo hydrazide 5 g (27.62 mmol) and chloroacetic acid 4.5 g (48.93 mmol) were added at 0 ^{o}C, then reaction mixture was refluxed at 80 ^{o}C for 4 h. Progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated and poured into ice-cold water (100 mL), the solid material was precipitate out which was filtered out washed with water and dried in vacuum to get 2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (**3**).

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

Yield: 86.71 % as an off-white material, m.p. 134-136^{0}C. ^{1}H NMR (400 MHz, DMSO) δ: 8.45 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.29 (d, *J* = 8.8 Hz, 2H, Ar-H), 5.19 (s, 2H, -CH_2), MS: m/z: 239.62.

Procedure for the synthesis of 4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy)benzaldehyde (4)

To a stirred a solution of 2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (**3**) 0.239 g (1 mmol) and 4-hydroxybenzaldehyde 0.144 g (1.2 mmol) in MeCN solvent (20 mL) and K_2CO_3 (10 mol %) was added as a catalyst, then reaction mixture was refluxed for 5 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated and poured into ice-cold water (30 mL) and filtered out, washed with water and dried u/vacuum to get 4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) benzaldehyde (**4**). The yield obtained 86 %, light brown solid powder.

General procedure for the synthesis of (E)-N-(substituted phenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6a-l)

To a stirred a solution of 4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl) methoxy) benzaldehyde (**4**) 0.325 g (2 mmol) and substituted aromatic amines (**5a-l**) (1 mmol) were added K_2CO_3 (5 mol %) in DMF solvent (10 mL) for 5 h heating. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated and poured into ice-cold water (30 mL) and filtered out, washed with water and dried u/vacuum to get (E)-N-(substituted phenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (**6a-l**). Yield obtained ranging from 80 to 85 %.

(E)-N-(4-Nitrophenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6a)

Yield: 85 %. IR (KBr, ν_{max}, cm^{-1}): 3140 ($\nu_{=C-H}$ aromatic), 2947 & 2831 (ν_{C-H} aliphatic), 1658 ($\nu_{C=C}$ aromatic), 1512 (ν_{NO2} asymmetric), 1473 (ν_{C-H} bending), 1365 (ν_{NO2} symmetric), 1257 ($\nu_{=C-O-C}$ asymmetric), 1165 (ν_{C-N}), 817 (δ_{C-H} p-disubstituted aromatic), 748 & 686 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.98 (s, 1H, N=CH), 8.38 (dd, J = 8.4 Hz, 2H, Ar-H), 8.27 (dd, J = 8.8 Hz, 2H, Ar-H), 7.94-8.05 (m, 4H, Ar-H) 7.58 (dd, J = 7.2 Hz, 2H, Ar-H), 7.12 (dd, J = 7.5 Hz, 2H, Ar-H), 5.46 (s, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 163.06, 162.07, 158.01, 150.45, 147.39, 144.19, 130.36, 132.08, 131.17, 128.79, 127.45, 125.39, 124.68, 121.48, 116.04, 57.05. EA calc.: C, 59.33; H, 3.39; N, 15.72; found: C, 59.29; H, 3.36; N, 15.70. MS: m/z: 445.

(E)-N-(4-Nitrophenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6b)

Yield: 81 %. IR (KBr, ν_{max}, cm^{-1}): 3134 ($\nu_{=C-H}$ aromatic), 2928 & 2871 (ν_{C-H} aliphatic), 1642 ($\nu_{C=C}$ aromatic skeleton), 1521 (ν_{NO2} asymmetric), 1427 (ν_{C-H} bending), 1359 (ν_{NO2} symmetric), 1248 ($\nu_{=C-O-C}$ asymmetric), 1141 (ν_{C-N}), 813 (δ_{C-H} p-disubstituted aromatic), 746 & 676 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.95 (s, 1H, N=CH), 8.34 (dd, J = 8.2 Hz, 2H, Ar-H), 8.20 (dd, J = 8.6 Hz, 2H, Ar-H), 7.89-7.97 (m, 4H, Ar-H) 7.54 (d, J = 7.1 Hz, 2H, Ar-H), 7.14 (m, J = 7.6 Hz, 2H, Ar-H), 5.41 (s, 2H, CH_2) 3.12 (s, 3H, $-OCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 163.10, 161.17, 154.01, 151.44, 147.42, 143.26, 130.75, 132.73, 131.47, 128.74, 127.22, 125.93, 124.62, 121.44, 116.24, 60.89, 57.05. EA calc.: C, 64.18; H, 4.22; N, 13.02; found: C, 64.13, H, 4.19; N, 12.95; MS: m/z: 430.

(E)-N-(2-Methoxyphenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6c)

Yield: 80 %. IR (KBr, ν_{max}, cm^{-1}): 3162 ($\nu_{=C-H}$ aromatic), 2935 & 2890 (ν_{C-H} aliphatic), 1618 ($\nu_{C=C}$ aromatic), 1506 (ν_{NO2} asymmetric), 1467 (ν_{C-H} bending), 1370 (ν_{NO2} symmetric), 1251 ($\nu_{=C-O-C}$ asymmetric), 1142 (ν_{C-N}), 848 (ν_{C-H} o-disubstituted aromatic), 732 & 673 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.92 (s, 1H, -N=CH), 8.33 (d, J = 8.3 Hz, 2H, Ar-H), 8.21 (dt, J = 8.7 Hz, 2H, Ar-H), 7.89-8.02 (m, 4H, Ar-H) 7.52 (d, J = 7.2, 1H, Ar-H) 7.41 (dt, J = 7.0 Hz, 1H, Ar-H), 7.16 (dd, J = 7.7 Hz, 2H, Ar-H), 5.40 (s, 2H, $-CH_2$) 3.15 (s, 3H, $-OCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 162.98, 161.45, 153.12, 151.60, 147.75, 143.35, 130.43, 132.43, 131.11, 128.46, 127.69, 126.01, 124.27, 121.41, 116.20, 60.75, 57.07. EA % calc.: C, 64.18; H, 4.22; N, 13.02. Found: C, 64.12, H, 4.17; N, 12.96. MS: m/z: 430.

(E)-N-(4-Chlorophenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6d)

Yield: 83 %. IR (KBr, ν_{max}, cm^{-1}): 3129 ($\nu_{=C-H}$ aromatic), 2947 & 2831 (ν_{C-H} aliphatic), 1627 ($\nu_{C=C}$ aromatic), 1522 (ν_{NO2} asymmetric), 1469 (ν_{C-H} bending), 1371 (ν_{NO2} symmetric), 1243 ($\nu_{=C-O-C}$ asymmetric), 1158 (ν_{C-N}), 829 (δ_{C-H} p-disubstituted aromatic), 810 (ν_{C-Cl} stretching) 748 & 686 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.96 (s, 1H, -N=CH), 8.35 (d, J = 8.4 Hz, 2H, Ar-H), 8.22 (dd, J = 8.7 Hz, 2H, Ar-H), 7.88 (m, 4H, Ar-H) 7.56 (dd, J = 7.2 Hz, 2H, Ar-H), 7.11 (dd, J = 7.4 Hz, 2H, Ar-H), 5.40 (s, 2H, $-CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 163.72, 161.45, 154.07, 151.79, 147.42, 143.26, 130.75, 132.78, 131.13, 128.69, 127.46, 125.93, 124.62, 121.44, 116.24, 57.99. EA % calc.: C, 60.77; H, 3.48; N, 12.88; Found: C, 60.74; H, 3.44; N, 12.85; MS: m/z: 434 and 436.

(E)-N-(3,5-Dimethoxyphenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6e)

Yield: 80 %. IR (KBr, ν_{max}, cm^{-1}): 3162 ($\nu_{=C-H}$ aromatic), 2937 & 2872 (ν_{C-H} aliphatic), 1647 ($\nu_{C=C}$ aromatic), 1520 (ν_{NO2} asymmetric), 1472 (ν_{C-H} bending), 1360 (ν_{NO2} symmetric), 1243 ($\nu_{=C-O-C}$ asymmetric), 1169 (ν_{C-N}), 755 & 845 (δ_{C-H} m-disubstituted aromatic), 735 & 680 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.91 (s, 1H, -N=CH), 8.32 (d, J = 8.3 Hz, 2H, Ar-H), 8.21 (d, J = 8.5 Hz, 2H, Ar-H), 7.84-7.98 (m, 4H, Ar-H) 7.54 (s, 2H, Ar-H), 7.14 (s, 2H, Ar-H), 5.41 (s, 1H, $-CH_2$) 3.19 (s, 6H, $-OCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 163.45, 161.37, 154.01, 151.78, 147.42, 143.26, 130.49, 132.73, 131.11, 128.74, 127.69, 125.21, 124.62, 121.44, 116.24, 65.32, 60.89, 57.45. EA % calc.: C, 62.61; H, 4.38; N, 12.17; Found: C, 62.58; H, 4.32; N, 12.11; MS: m/z: 460.

(E)-N-(3-Chlorophenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6f)

Yield: 81 %. IR (KBr, ν_{max}, cm^{-1}): 3125 ($\nu_{=C-H}$ aromatic), 2940 & 2827 (ν_{C-H} aliphatic), 1650 ($\nu_{C=C}$ aromatic), 1509 (ν_{NO2} asymmetric), 1468 (ν_{C-H} bending), 1362 (ν_{NO2} symmetric), 1249 ($\nu_{=C-O-C}$ asymmetric), 1158 (ν_{C-N}), 756 & 849 (δ_{C-H} m-substituted aromatic), 748 & 686 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.92 (s, 1H, -N=CH), 8.33 (d, J = 8.3 Hz, 2H, Ar-H), 8.21 (dt, J = 8.7 Hz, 2H, Ar-H), 7.89-8.01 (m, 4H, Ar-H) 7.52 (s, 1H, Ar-H), 7.23-7.39 (m, 3H, Ar-H) 5.40 (s, 2H, $-CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 162.98, 161.45, 153.12, 151.60, 147.75, 145.36, 143.35, 130.43, 132.43, 131.11, 128.46, 127.69, 126.01, 125.74, 124.27, 121.41, 116.20, 57.07. EA % calc.: C, 60.77; H, 3.48; N, 12.88; Found: C, 60.71; H, 3.45; N, 12.83; MS: m/z: 434 and 436.

(E)-N-(4-Bromophenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6g)

Yield: 83 %. IR (KBr, ν_{max}, cm^{-1}): 3136 ($\nu_{=C-H}$ aromatic), 2951 & 2842 (ν_{C-H} aliphatic), 1664 ($\nu_{C=C}$ aromatic), 1519 (ν_{NO2} asymmetric), 1468 (ν_{C-H} bending), 1370 (ν_{NO2} symmetric), 1263 ($\nu_{=C-O-C}$ asymmetric), 1165 (ν_{C-N}), 821 (ν_{C-H} p-disubstituted aromatic), 740 & 673 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.95 (s, 1H, -N=CH), 8.45 (d, J = 8.6 Hz, 2H, Ar-H), 8.32 (dd, J = 8.7 Hz, 2H, Ar-H), 7.84-8.00 (m, 4H, Ar-H) 7.60 (d, J = 7.4 Hz, 2H, Ar-H), 7.23 (d, J = 7.7 Hz, 2H, Ar-H), 5.50 (s, 2H, $-CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 163.10, 162.21, 158.37, 150.47, 146.87, 142.65, 130.74, 132.45, 131.23, 129.69, 127.45, 126.37, 124.46, 121.58, 116.04, 57.65. EA % calc.: C, 55.13; H, 3.15; N, 11.69; Found: C, 55.09; H, 3.11; N, 11.64; MS: m/z: 478 and 480.

(E)-1-(4-((5-(4-Nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)-phenyl)-N-(p-tolyl)methanimine (6h)

Yield: 82 %. IR (KBr, ν_{max}, cm^{-1}): 3153 ($\nu_{=C-H}$ aromatic), 2936 & 2876 (ν_{C-H} aliphatic), 1642 ($\nu_{C=C}$ aromatic), 1526 (ν_{NO2} asymmetric), 1453 (ν_{C-H} bending), 1327 (ν_{NO2} symmetric), 1250 ($\nu_{=C-O-C}$ asymmetric), 1172 (ν_{C-N}), 823 (δ_{C-H} p-disubstituted aromatic), 745 & 677 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.39 (s, 1H, -N=CH), 8.24 (d, J = 8.1 Hz, 2H, Ar-H), 8.19 (dd, J = 8.4 Hz, 2H, Ar-H), 7.81-7.93 (m, 4H, Ar-H) 7.42 (d, J = 7.0 Hz, 2H, Ar-H), 7.01 (m, J = 7.2 Hz, 2H, Ar-H), 5.44 (s, 2H, $-CH_2$), 2.10 (s, 3H, $-CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 163.14, 162.98, 158.40, 150.36, 147.89, 144.19, 130.36, 132.45, 131.17, 128.79, 127.12, 125.28, 124.67, 121.48, 116.24, 57.09 30.15. EA % calc.: C, 66.66; H, 4.38; N, 13.52; Found: C, 66.61; H, 4.35; N, 13.47. MS: m/z: 414.

(E)-N-(4-Fluorophenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6i)

Yield: 80 %. IR (KBr, ν_{max}, cm^{-1}): 3118 ($\nu_{=C-H}$ aromatic), 2928 & 2839 (ν_{C-H} aliphatic), 1663 ($\nu_{C=C}$ aromatic), 1520 (ν_{NO2} asymmetric), 1446 (ν_{C-H} bending), 1356 (ν_{NO2} symmetric), 1227 ($\nu_{=C-O-C}$ asymmetric), 1170 (ν_{C-N}), 821 (δ_{C-H} p-disubstituted aromatic), 745 & 681 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.94 (s, 1H, -N=CH), 8.21 (d, J = 8.1 Hz, 2H, Ar-H), 8.19 (dd, J = 8.2 Hz, 2H, Ar-H), 7.87-8.05 (m, 4H, Ar-H) 7.47 (d, J = 7.1 Hz, 2H, Ar-H), 7.02 (m, J = 7.1 Hz, 2H, Ar-H), 5.34 (s, 2H, -CH_2). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 163.11, 161.35, 159.13, 150.40, 147.27, 144.27, 130.36, 132.47, 131.17, 128.76, 127.91, 125.39, 124.67, 121.41, 116.04, 57.27. EA % calc.: C, 63.16; H, 3.61; N, 13.39; Found: C, 63.12; H, 3.57; N, 13.33; m/z: 418.

(E)-N-(3-Fluorophenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6j)

Yield: 80 %. IR (KBr, ν_{max}, cm^{-1}): 3152 ($\nu_{=C-H}$ aromatic), 2963 & 2848 (ν_{C-H} aliphatic), 1662 ($\nu_{C=C}$ aromatic), 1528 (ν_{NO2} asymmetric), 1484 (ν_{C-H} bending), 1371 (ν_{NO2} symmetric), 1268 ($\nu_{=C-O-C}$ asymmetric), 1179 (ν_{C-N}), 730 & 849 (δ_{C-H} m-substituted aromatic), 753 & 690 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.90 (s, 1H, -N=CH), 8.24 (d, J = 8.1 Hz, 2H, Ar-H), 8.18 (dt, J = 8.3 Hz, 2H, Ar-H), 7.89-8.08 (m, 4H, Ar-H) 7.48 (s, 1H, Ar-H), 7.20-7.36 (m, 3H, Ar-H) 5.37 (s, 2H, -CH_2). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 162.98, 161.45, 153.12, 151.60, 147.75, 145.36, 143.35, 130.43, 132.43, 131.11, 128.46, 127.69, 126.01, 125.74, 124.27, 121.41, 116.20, 57.34. EA % calc.: C, 63.16; H, 3.61; N, 13.39; Found: C, 63.09; H, 3.58; N, 13.31; m/z: 418.

(E)-N-(3-Nitrophenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6k)

Yield: 82 %. IR (KBr, ν_{max}, cm^{-1}): 3142 ($\nu_{=C-H}$ aromatic), 2939 & 2825 (ν_{C-H} aliphatic), 1645 ($\nu_{C=C}$ aromatic), 1509 (ν_{NO2} asymmetric), 1467 (ν_{C-H} bending), 1362 (ν_{NO2} symmetric), 1248 ($\nu_{=C-O-C}$ asymmetric), 1157 (ν_{C-N}), 760 & 835 (δ_{C-H} m-substituted aromatic), 742 & 685 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.95 (s, 1H, -N=CH), 8.36 (d, J = 8.4 Hz, 2H, Ar-H), 8.27 (dt, J = 8.5 Hz, 2H, Ar-H), 7.92-8.11 (m, 4H, Ar-H) 7.51 (s, 1H, Ar-H), 7.28-7.41 (m, 3H, Ar-H) 5.42 (s, 2H, -CH_2). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 163.25, 161.74, 153.27, 151.76, 147.89, 145.36, 143.35, 130.43, 132.82, 131.19, 128.29, 127.61, 126.76, 125.68, 124.27, 121.39, 116.27, 57.46. EA % calc.: C, 59.33; H, 3.39; N, 15.72; Found: C, 59.30; H, 3.36; N, 15.69; m/z: 445.

(E)-N-(2-Nitrophenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (6l)

Yield: 84 %. IR (KBr, ν_{max}, cm^{-1}): 3138 ($\nu_{=C-H}$ aromatic), 294 & 2831 (ν_{C-H} aliphatic), 1655 ($\nu_{C=C}$ aromatic), 1516 (ν_{NO2} asymmetric), 1478 (ν_{C-H} bending), 1345 (ν_{NO2} symmetric), 1257 ($\nu_{=C-O-C}$ asymmetric), 1165 (ν_{C-N}), 815 (δ_{C-H} o-disubstituted aromatic), 748 & 686 ($\nu_{=C-H}$ bending). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.93 (s, 1H, -N=CH), 8.27 (d, J = 8.4 Hz, 2H, Ar-H), 8.26 (dt, J = 8.8 Hz, 2H, Ar-H), 7.91-8.07 (m, 4H, Ar-H) 7.58 (d, J = 7.4, 1H, Ar-H) 7.45 (dt, J = 7.1 Hz, 1H, Ar-H), 7.19 (dd, J = 7.7 Hz, 2H, Ar-H), 5.42 (s, 2H, -CH_2). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 163.27, 161.99, 153.72, 151.69, 147.47, 145.37, 143.83, 130.63, 132.49, 131.18, 130.64, 128.38, 127.27, 126.33, 124.91, 121.41, 116.20, 57.17. EA % calc.: C, 59.33; H, 3.39; N, 15.72; Found: C, 59.31; H, 3.35; N, 15.68; m/z: 445.

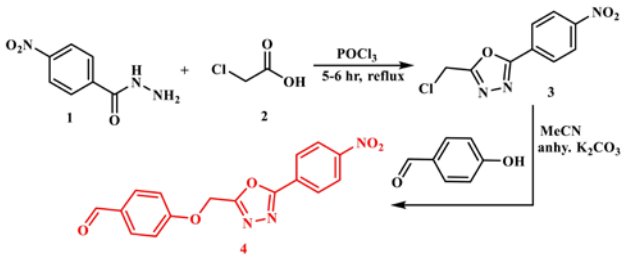
RESULT AND DISCUSSION

In continuation our afford toward the bioactive heterocyclic motif parade 1,3,4-oxadiazole ring. In our previous work we synthesized substituted oxadiazole moiety incorporated with different heterocycles like quinoline,[30] Schiff base,[31] polysubstituted 4*H*- pyran derivatives.[32] Now, we did a synthesis of 4-((5-(4-nitrophenyl)-1,3,4-oxadiazole-2- yl)methoxy) benzaldehyde (**4**) with the help of 4-nitrobenzohydrazide (**1**) react with chloroacetic acid (**2**) in the presence of $POCl_3$ under 5-6 hours reflux condition to cyclization takes place and product obtained as 2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (**3**). It further reacts with 4-hydroxybenzaldehyde in the presence of anhydrous K_2CO_3 in acetonitrile solvent for 5 hr reflux to get the product (**4**). Optimization of the reaction based on the basis of different solvents like polar protic solvents as methanol, ethanol, and isopropyl alcohol didn't get satisfactory response, or no yield increment obtained. Instead of polar protic solvent we used polar aprotic solvent such as THF, dichloromethane, MeCN and DMF to enhance yield as well as to shorten the reaction time (**Table 1).**

Table 1. Reaction optimization condition for preparation of aldehyde **(4)**

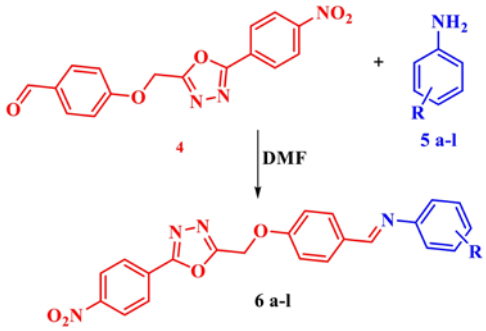
Entry	Catalyst, mol %	Solvent and condition[a]	Time, h	Yield, %[b]
1	NaOH (5 %)	MeOH, reflux	8-9	25
2	K_2CO_3 (5 %)	EtOH, reflux	8-9	40
3	KOH (5 %)	2-propanol, reflux	9-10	23
4	K_2CO_3 (5 %)	THF, reflux	8	42
5	K_2CO_3 (5 %)	DCM, reflux	6	78
6	K_2CO_3 (5 %)	DMF, reflux	8	70
7	K_2CO_3 (5 %)	MeCN, reflux	6	85
8	K_2CO_3 (10 %)	MeCN, reflux	5	86

[a]Reaction conditions: 2-(chloromethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (1 mmol), 4-hydroxybenzaldehyde (1.2 mmol), K_2CO_3 (10 mol %) in MeCN solvent (20 mL) for 5 h reflux condition; [b]Isolated yield



Scheme 1. Preparation of 1,3,4-oxadiazole based aldehyde

Now, move on to final reaction for preparation of Schiff base using condensation of 4-((5-(4-nitrophenyl)-1,3,4-oxadiazole-2-yl)methoxy) benzaldehyde (**4**) and substituted aromatic amines (**5a-l**) in the presence of DMF solvent without any catalyst for 5-6 hours reflux condition to imine formation and the product obtained as N-(substituted phenyl)-1-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)methanimine (**6a-l**) **Scheme 2**. All the substitution mention in **Table 2**.



Scheme 2. Synthesis of substituted Schiff base derivatives

Table 2. Synthesis of 1,3,4-oxadiazole based Schiff base derivatives (**6 a-l**)

Product	R	Time, h	Yield, %
6a	4-nitrophenyl	5	92
6b	4-methoxyphenyl	5	87
6c	2-methoxyphenyl	5.5	83
6d	4-chlorophenyl	5	80
6e	3,5-dimethoxyphenyl	6	78
6f	3-chlorophenyl	6	81
6g	4-bromophenyl	5	91
6h	4-Tolyl	5	89
6i	4-fluorophenyl	5	88
6j	3-fluorophenyl	5.5	69
6k	3-nitrophenyl	5.5	72
6l	2-nitrophenyl	5	70

Biology

Synthesized compounds **6a-j** were tested to determine the minimum inhibitory concentration (MIC) by the agar well diffusion method. All synthesized compounds activity checked against Gram-positive and Gram-negative bacteria like *Bacillus megaterium*, *Bacillus subtilisis*, *E. coli*, and *Klebsiella pneumoniae*. Yield larger inhibition zone in primary screening then secondary screening, the experiment was done with 10 µg mL^{-1}, 25 µg mL^{-1} and 50 µg mL^{-1} concentrations. Amongst them, compound **6a** was extremely active against gram-positive bacteria *Bacillus megaterium*, *Bacillus subtilisis* and growth inhibition value nearer to standard drug erythromycin. Compounds **6b** and **6e** also shows moderate activity compare to erythromycin. Gram-negative bacterial strains in secondary screening are **6a**, **6b** and **6e** show moderate activity compared to standard drug tetracycline (**Table 3**).

Table 3. secondary antibacterial screening of synthesized compounds[a]

Compound	Zones of growth inhibition[b]			
	Gram-positive bacteria		Gram-negative bacteria	
	Bacillus megaterium	***Bacillus subtilisis***	***E. coli***	***Klebsiella pneumoniae***
6a	13	9	10	7
6b	9	7	3	nt
6c	10	7	6	2
6d	16	15	17	10
6e	8	3	1	nt
6f	14	11	13	15
6g	13	15	11	13
6h	7	4	0	nt
6i	15	14	10	9
6j	11	8	9	14
6k	10	9	11	10
6l	9	6	2	nt
T	nt	nt	19	20
E	20	18	nt	Nt

[a]Concentration of each sample is 50 µg mL^{-1}; [b]Zone of growth inhibition value measured in millimeter (mm); E – Erythromycin; T – Tetracycline; nt – Not tested

Drug-likeness

Drug-likeness is an impressive rule for the start phases of medication disclosure. Empowered by our synthesized outcomes this prompted our emphasis on the implementation of drug-likeness etiquette. Thus, our vision to the expedient synthesis of drug substituent molecules as a means to access pharmacologically pertinent with their broad application in the medicinal research area. Given the underlying assumption that 1,3,4-oxadiazole base Schiff base derivatives **6a-6l** would possess excellent properties in drug discovery. All synthesized compounds were evaluated using the online free tool SwissADME, freely accessible at http://www.swissadme.ch. Drug-likeness parameters follow the five diverse protocols and mapping with our targeted compounds.[33]

According to these phenomena, some compounds gained a good score for bioavailability[34] and many of the derivatized compounds show no violation for a drug-likeness rule, which is summarized up in **Table 4**.

Lipophilicity

Lipophilicity is an important parameter for drug discovery and patterned of molecule affinity towards the lipid environment. SwissADME is an online free tool to evaluate that kind of study such as iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT, Consensus Log $P_{o/w}$ values.[35]

The results are given in a boiled egg diagram (**Fig.1**) and in **Table 5**.

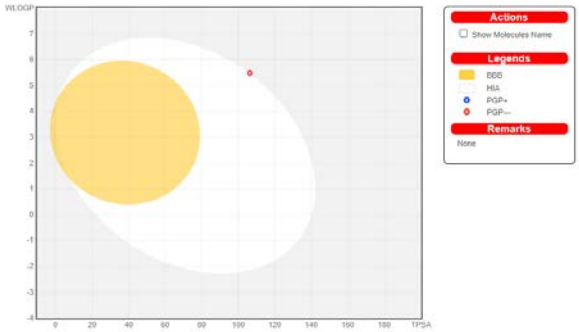


Figure 1. Boiled-Egg diagram for synthesized compound **6f**

Cytotoxicity

Toxicity is one of the parameters which a majorly considerable part of drug discovery. The toxicity of all synthesized compounds has been predicted through the preADMET server. From the toxicity prediction it was found that all the synthesized compounds are non-toxic and checked their different parameter similar to Acute algae toxicity, Acute daphnia toxicity, hERG inhibition, Ames TA100 (-S9). Among them almost are non-carcinogenic to rat and medium risk towards the hERG inhibition. all results mentioned in **Table 6**.

Table 4. Drug-likeness rule violation and bioavailability score of some synthesized compounds by Swiss ADME.

Compound	Lipnki	Ghose	Veber	Egan	Muegge	Bioavailability score
6b	No	No	No	No	No	0.55
6c	No	No	No	No	No	0.55
6d	No	No	No	No	No	0.55
6f	No	No	No	No	No	0.55
6g	No	No	No	No	No	0.55
6i	No	No	No	No	No	0.55

Table 5. Lipophilicity parameter studies for some synthesized compounds by Swiss ADME

Compound	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{o/w}$
6b	3.56	4.01	4.83	2.89	3.06	3.67
6d	3.70	4.67	5.48	2.86	3.63	4.07
6f	3.51	4.67	5.48	2.86	3.63	4.03
6g	3.67	4.73	5.59	2.96	3.67	4.12
6i	3.37	4.14	5.38	2.75	3.42	3.81

Table 6. Cytotoxicity assay for synthesized compounds by preADMET.

Compound	Acute algae toxicity	Carcinogenicity (rat)	Carcinogenicity (mouse)	Acute daphina toxicity	hERG inhibition	Ames TA100(-S9)
6a	0.02311	negative	positive	0.0155	Medium risk	negative
6c	0.02121	negative	positive	0.0136	Medium risk	negative
6d	0.0130	positive	positive	0.0060	Medium risk	negative
6f	0.0138	positive	positive	0.0063	Medium risk	negative
6i	0.019	negative	positive	0.011	Medium risk	negative

CONCLUSION

Herein, we have synthesized 1,3,4-oxadiazole based Schiff base analogous by the efficient protocol. All synthesized compounds were checked for their characterization, antibacterial activity by minimum inhibitory concentration method, and in-silico parameters like drug-likeness, lipophilicity, and cytotoxicity. Among the synthesized compounds, derivatives possess halogen group 6d, 6f, 6g, and 6i exhibits extreme potency towards antibacterial activities and in-silico parameters. These kinds of synthesis work going on in our laboratory.

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