SYNTHESIS OF 5-SUBSTITUTED-1,3,4-OXADIAZOLE CLUBBED PYRAZOLE AND DIHYDROPYRIMIDINE DERIVATIVES AS POTENT BIOACTIVE AGENTS

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A series of 4-fluorophenylpyrazole clubbed 1,3,4-oxadiazole and 3,4-dihydropyrimidin-2(1*H*)-ones were prepared by cyclization of Biginelli-type adducts. Their structures were assigned on the basis of known spectral techniques. All the scaffolds were evaluated for *in vitro* antimicrobial activity by broth microdilution bioassay method and *in vitro* antitubercular property by microplate alamar blue assay method. Compounds **3j** and **3l** containing -OH and -CH_3 groups were found to act as potent antimicrobials and antitubercular candidates with relatively low cytotoxicity on VERO cells.

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INTRODUCTION

Resistance of microbes is a major hurdle for the treatment of several infectious diseases. The WHO has considered antimicrobial drug resistance (AMR) to be one of the utmost threats to human life. The structural modifications in existing drugs have shown astonishing results in the field of drug discovery programs. In view of this, novel scaffold architecture by molecular hybridization approach is considered as the best tool for the development of newer potent agents.[1,2] Nowadays, Biginelli type reaction has captured the attention of numbers of medicinal chemists for dihydropyrimidines (DHPMs) synthesis having varied bioactivity.[3-5] Pyrazoles engage a diverse alcove in synthetic heterocycles as a chief motif in medicinal chemistry because of their wide array of biological effects, including antimicrobial, antidepressant, anticonvulsant, antipyretic, anti-influenza and anticancer activities.[6-8] Various catalysts such as $Sc(OTf)_3$, $Mg(ClO_4)_2$ and H_2SO_4 were used to synthesize pyrazole derivatives in multicomponent reaction.[9-11]

In recent years, oxadiazole is a frequently utilized pharmacophore due to its metabolic profile and capability to engage in hydrogen bonding with the receptor site. The presence of azole group in oxadiazole uplifts lipophilicity and influences the easy ability of the drug to target leads to generate numerous biological activities like hypoglycaemic, anti-HIV, analgesic, anti-inflammatory, antitubercular.[12,13] oxadiazole have displayed remarkable inhibitory potential against important biological targets like tyrosinase, monoamine oxidase (MAO) and cathepsin K.[14-19]

Recognizing these particulars and our continuing endeavours toward the development of bioactive agents,[20-22] emphasis is given to the development of new prototypes as potent antimicrobial as well as antitubercular molecules. These include the lead of the three medicinally important pharmacophores - DHPMs, pyrazole and 1,3,4-oxadiazole in one hybrid molecular framework.

EXPERIMENTAL

The required chemicals were purchased from Aldrich and E. Merck and used without further purification. Buchi Rotavapor was used for distillation. Melting points were determined in the Gallenkamp apparatus and are uncorrected. The completion of the reaction and the purity of all compounds was checked on aluminum-coated TLC plates G60, F_{245} (E. Merck) using hexane and ethyl acetate (7:3) as eluent and visualized under UV light (λ 254 and 365 nm), or iodine vapor. Elemental analysis was carried out by a Perkin-Elmer 2400 CHN analyzer. ^{1}H NMR spectra were recorded on a Bruker Avance II 400 MHz and ^{13}C NMR spectra on Varian Mercury-400, 100 MHz in DMSO-d_6 as a solvent and TMS as a reference standard for chemical shifts. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer, while mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer.

Ethyl-4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1)

Compound **1** was prepared according to the literature method.[23]

4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carbohydrazide (2)

Compound **1** (0.01 mol) was dissolved in 1,4-dioxane (20 mL) and to this, hydrazine hydrate (99 %, 0.01 mol) was added, followed by the addition of a catalytic amount of

conc. H_2SO_4 and allowed to stir for 5 h at 100 °C. After cooling, the reaction mixture was poured into ice-cold water. Product, obtained as off-white precipitate, was filtered, washed with water, dried and recrystallized from ethanol (95 %) to obtain compound **2**.

Yield: 73 %, m.p. 224-225 ºC. IR (KBr): 3454, 3340 (N-H), 3060 (C-H_{arom}), 1689 (C=O), 1582 (C=N), 1512 (C=C), 1124 (C-F) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.95 (s, 2H, NH_2), 2.34 (s, 3H, -CH_3), 5.16 (s, 1H, $CH_{pyrimidine}$), 5.87 (s, 1H, -N**H**NH_2), 6.91 (s, 1H, NH-C-Ph), 7.30-7.89 (m, 10H, Ar-H), 9.03 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 17.9 (-CH_3), 50.6 (-$CH_{pyrimidine}$), 123.3 (-$CH_{pyrazole}$), 118.5-149.1 (Ar-C), 150.3 (C=O, NHCONH), 166.2 (C=O). LCMS (ESI) *m/z*: 406.16 $[M]^+$. Anal. calcd. for $C_{21}H_{19}FN_6O_2$: C, 62.06; H, 4.71; N, 20.68. Found: C, 62.00; H, 4.62; N, 20.73 %.

General procedure of synthesis of 4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyr-azol-4-yl)-6-methyl-5-(5-aryl-1,3,4-oxadiazol-2-yl)-3,4-dihyd-ropyrimidin-2(1*H*)-ones (3a-o)

Compound **2** (0.01 mol) with various derivatives of aromatic acids (0.01 mol) were dissolved and stirred in one pot having phosphoryl chloride ($POCl_3$) (20 mL). The mixture was refluxed at 80 °C for 6 h. After completion of the reaction (TLC), the mixture was slowly quenched on crushed ice. The precipitates were filtered, washed with $NaHCO_3$ to remove excess $POCl_3$ trace followed by water, dried and recrystallized from ethanol (95 %) to furnished final compounds.

4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-5-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (3a)

Yield: 71 %, m.p. 241-242 ºC. IR (KBr): 3223 (NH), 3061 (C-H_{arom}), 2983 (H-C=C<), 2848 (C-H, CH_3), 1685 (C=O), 1598 (C=N), 1527 (C=C), 1281 (C-O-C), 1122 (C-F) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.36 (s, 3H, -CH_3), 5.18 (s, 1H, $CH_{pyrimidine}$), 6.88 (s, 1H, NH-C-Ph), 7.28-8.06 (m, 14H, Ar-H), 8.14 (s, 1H, $CH_{pyrazole}$), 9.10 (s, 1H, NH-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.1 (-CH_3), 53.6 ($C_{pyrimidine}$), 123.2 ($C_{pyrazole}$), 113.5-149.5 (Ar-C), 150.4 (C=O), 160.3, 164.1 ($C_{oxadiazole}$), 161.6 (C-F). LCMS (ESI) *m/z*: 492.17 $[M]^+$. Anal. calcd. for $C_{29}H_{21}FN_6O_2$: C, 68.28; H, 4.30; N, 17.06. Found: C, 68.19; H, 4.41; N, 17.11 %.

5-(5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3b)

Yield: 65 %, m.p. 218-220 ºC. IR (KBr): 3221 (NH), 3062 (C-H_{arom}), 2981 (H-C=C<), 2850 (C-H, CH_3), 1691 (C=O), 1597 (C=N), 1514 (C=C), 1288 (C-O-C), 1107 (C-F), 754 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.28 (s, 3H, -CH_3), 5.18 (s, 1H, $CH_{pyrimidine}$), 6.89 (s, 1H, NH-C-Ph), 7.28-8.20 (m, 13H, Ar-H), 8.28 (s, 1H, $CH_{pyrazole}$), 9.16 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.2 (CH_3), 53.5 ($C_{pyrimidine}$), 123.6 ($C_{pyrazole}$), 135.3 (C-Cl), 113.2-149.7 (Ar-C), 150.6 (C=O), 160.1, 164.4 ($C_{oxadiazole}$), 161.4 (C-F). LCMS (ESI) *m/z*: 526.13 $[M]^+$. Anal. calcd. for $C_{28}H_{20}ClFN_6O_2$: C, 68.82; H, 3.83; N, 15.95. Found: C, 63.79; H, 3.85; N, 15.93 %.

5-(5-(3-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3c)

Yield: 59 %, m.p. 186-188 ºC. IR (KBr): 3222 (NH), 3063 (C-H_{arom}), 2980 (H-C=C<), 2852 (C-H, CH_3), 1691 (C=O), 1599 (C=N), 1517 (C=C), 1280 (C-O-C), 1110 (C-F), 754 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.30 (s, 3H, -CH_3), 5.16 (s, 1H, $CH_{pyrimidine}$), 6.85 (s, 1H, NH-C-Ph), 7.29-8.16 (m, 13H, Ar-H), 8.24 (s, 1H, $CH_{pyrazole}$), 9.15 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.0 (CH_3), 53.3 ($C_{pyrimidine}$), 123.4 ($C_{pyrazole}$), 135.2 (C-Cl), 113.3-149.5 (Ar-C), 150.7 (C=O), 160.3, 164.6 ($C_{oxadiazole}$), 161.2 (C-F). LCMS (ESI) *m/z*: 526.13 $[M]^+$. Anal. calcd. for $C_{28}H_{20}ClFN_6O_2$: C, 68.82; H, 3.83; N, 15.95. Found: C, 63.90; H, 3.80; N, 15.85 %.

5-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3d)

Yield: 63 %, m.p. 225-227 ºC. IR (KBr): 3293 (NH), 3066 (C-H_{arom}), 2978 (H-C=C<), 2929 (C-H, CH_3), 1680 (C=O), 1591 (C=N), 1504 (C=C), 1219 (C-O-C), 1155 (C-F), 752 (C-Cl) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.31 (s, 3H, CH_3), 5.26 (s, 1H, $CH_{pyrimidine}$), 6.82 (s, 1H, NH-C-Ph), 7.20-8.05 (m, 13H, Ar-H), 8.16 (s, 1H, $CH_{pyrazole}$), 9.04 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.3 (CH_3), 53.9 ($C_{pyrimidine}$), 123.8 ($C_{pyrazole}$), 135.6 (C-Cl), 113.0-149.7 (Ar-C), 150.5 (C=O), 160.6, 164.4 ($C_{oxadiazole}$), 161.7 (C-F). LCMS (ESI) *m/z*: 526.13 $[M]^+$. Anal. calcd. for $C_{28}H_{20}ClFN_6O_2$: C, 68.82; H, 3.83; N, 15.95. Found: C, 63.75; H, 3.86; N, 15.89 %.

4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-5-(5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (3e)

Yield: 58 %, m.p. 233-235 ºC. IR (KBr): 3224 (NH), 3063 (C-H_{arom}), 2981 (H-C=C<), 2862 (C-H, CH_3), 1687 (C=O), 1606 (C=N), 1531 (C=C), 1508 (-N=O), 1234 (C-O-C), 1150 (C-F) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.37 (s, 3H, CH_3), 5.20 (s, 1H, $CH_{pyrimidine}$), 6.85 (s, 1H, NH-C-Ph), 7.22-8.15 (m, 13H, Ar-H), 8.20 (s, 1H, $CH_{pyrazole}$), 9.04 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.2 (CH_3), 54.0 ($C_{pyrimidine}$), 122.9 ($C_{pyrazole}$), 113.0-149.7 (Ar-C), 147.3 (C-NO_2), 150.4 (C=O), 160.2, 164.1 ($C_{oxadiazole}$), 161.5 (C-F). LCMS (ESI) *m/z*: 537.16 $[M]^+$. Anal. calcd. for $C_{28}H_{20}FN_7O_4$: C, 62.57; H, 3.75; N, 18.24. Found: C, 62.53; H, 3.69; N, 18.21 %.

4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-5-(5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (3f)

Yield: 60 %, m.p. 250-252 ºC. IR (KBr): 3221 (NH), 3060 (C-H_{arom}), 2985 (H-C=C<), 2854 (C-H, CH_3), 1680 (C=O), 1603 (C=N), 1533 (C=C), 1507 (-N=O), 1231 (C-O-C),

1155 (C-F) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3), 5.23 (s, 1H, $CH_{pyrimidine}$), 6.86 (s, 1H, NH-C-Ph), 7.20-8.21 (m, 13H, Ar-H), 8.29 (s, 1H, $CH_{pyrazole}$), 9.08 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.1 (CH_3), 54.4 ($C_{pyrimidine}$), 123.1 ($C_{pyrazole}$), 113.4-149.9 (Ar-C), 147.6 (C-NO_2), 150.5 (C=O), 160.1, 164.6 ($C_{oxadiazole}$), 161.3 (C-F). LCMS (ESI) *m/z*: 537.10 $[M]^+$. Anal. calcd. for $C_{28}H_{20}FN_7O_4$: C, 62.57; H, 3.75; N, 18.24. Found: C, 62.52; H, 3.61; N, 18.20 %.

4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-5-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (3g)

Yield: 66 %, m.p. 269-271 ºC. IR (KBr): 3211 (NH), 3059 (C-H_{arom}), 2980 (H-C=C<), 2848 (C-H, CH_3), 1693 (C=O), 1598 (C=N), 1527 (C=C), 1504 (N=O), 1284 (C-O-C), 1157 (C-F) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.40 (s, 3H, CH_3), 5.21 (s, 1H, $CH_{pyrimidine}$), 6.80 (s, 1H, NH-C-Ph), 7.29-8.23 (m, 13H, Ar-H), 8.31 (s, 1H, $CH_{pyrazole}$), 9.24 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.7 (CH_3), 54.7 ($C_{pyrimidine}$), 123.4 ($C_{pyrazole}$), 113.2-149.2 (Ar-C), 147.1 (C-NO_2), 150.6 (C=O), 160.4, 164.9 ($C_{oxadiazole}$), 161.6 (C-F). LCMS (ESI) *m/z*: 537.13 $[M]^+$. Anal. calcd. for $C_{28}H_{20}FN_7O_4$: C, 62.57; H, 3.75; N, 18.24. Found: C, 62.62; H, 3.78; N, 18.29 %.

4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3h)

Yield: 68 %, m.p. 179-181 ºC. IR (KBr): 3409 (OH), 3216 (NH), 3062 (C-H_{arom}), 2984 (H-C=C<), 2845 (C-H, CH_3), 1697 (C=O), 1602 (C=N), 1525 (C=C), 1280 (C-O-C), 1151 (C-F) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3), 5.22 (s, 1H, $CH_{pyrimidine}$), 6.82 (s, 1H, NH-C-Ph), 7.02-8.07 (m, 13H, Ar-H), 8.18 (s, 1H, $CH_{pyrazole}$), 9.16 (s, 1H, N**H**-C-CH_3), 9.20 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.0 (CH_3), 53.4 ($C_{pyrimidine}$), 123.2 ($C_{pyrazole}$), 113.2-149.7 (Ar-C), 150.1 (C=O), 157.3 (C-OH), 160.1, 164.4 ($C_{oxadiazole}$), 161.8 (C-F). LCMS (ESI) *m/z*: 508.16 $[M]^+$. Anal. calcd. for $C_{28}H_{21}FN_6O_3$: C, 66.14; H, 4.16; N, 16.53. Found: C, 66.23; H, 4.12; N, 16.58 %.

4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(5-(3-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3i)

Yield: 57 %, m.p. 271-273 ºC. IR (KBr): 3412 (OH), 3217 (NH), 3064 (C-H_{arom}), 2987 (H-C=C<), 2848 (C-H, CH_3), 1698 (C=O), 1609 (C=N), 1528 (C=C), 1252 (C-O-C), 1151 (C-F) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.34 (s, 3H, CH_3), 5.19 (s, 1H, $CH_{pyrimidine}$), 6.80 (s, 1H, NH-C-Ph), 6.99-8.14 (m, 13H, Ar-H), 8.20 (s, 1H, $CH_{pyrazole}$), 9.14 (s, 1H, N**H**-C-CH_3), 9.19 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.3 (CH_3), 53.1 ($C_{pyrimidine}$), 123.4 ($C_{pyrazole}$), 113.0-149.8 (Ar-C), 150.4 (C=O), 157.6 (C-OH), 160.2, 164.3 ($C_{oxadiazole}$), 161.2 (C-F). LCMS (ESI) *m/z*: 508.16 $[M]^+$. Anal. calcd. for $C_{28}H_{21}FN_6O_3$: C, 66.14; H, 4.16; N, 16.53. Found: C, 66.26; H, 4.20; N, 16.61 %.

4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3j)

Yield: 73 %, m.p. 237-239 ºC. IR (KBr): 3418 (OH), 3219 (NH), 3062 (C-H_{arom}), 2981 (H-C=C<), 2853 (C-H, CH_3), 1692 (C=O), 1605 (C=N), 1526 (C=C), 1278 (C-O-C), 1160 (C-F) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.37 (s, 3H, CH_3), 5.22 (s, 1H, $CH_{pyrimidine}$), 6.83 (s, 1H, NH-C-Ph), 6.96-8.17 (m, 13H, Ar-H), 8.21 (s, 1H, $CH_{pyrazole}$), 9.16 (s, 1H, N**H**-C-CH_3), 9.20 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.0 (CH_3), 53.3 ($C_{pyrimidine}$), 123.0 ($C_{pyrazole}$), 113.6-149.9 (Ar-C), 150.6 (C=O), 158.4 (C-OH), 160.6, 164.7 ($C_{oxadiazole}$), 161.8 (C-F). LCMS (ESI) *m/z*: 508.16 $[M]^+$. Anal. calcd. for $C_{28}H_{21}FN_6O_3$: C, 66.14; H, 4.16; N, 16.53. Found: C, 66.19; H, 4.22; N, 16.60 %.

4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3k)

Yield: 64 %, m.p. 184-186 ºC. IR (KBr): 3216 (NH), 3063 (C-H_{arom}), 2985 (H-C=C<), 2944 (OCH_3), 2850 (C-H, CH_3), 1698 (C=O), 1606 (C=N), 1527 (C=C), 1281 (C-O-C), 1163 (C-F) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.39 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 5.19 (s, 1H, $CH_{pyrimidine}$), 6.84 (s, 1H, NH-C-Ph), 7.01-8.14 (m, 13H, Ar-H), 8.20 (s, 1H, $CH_{pyrazole}$), 9.17 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.2 (CH_3), 53.6 ($C_{pyrimidine}$), 55.6 (OCH_3), 123.7 ($C_{pyrazole}$), 113.4-149.8 (Ar-C), 150.1 (C=O), 160.1, 164.5 ($C_{oxadiazole}$), 161.9 (C-F). LCMS (ESI) *m/z*: 522.17 $[M]^+$. Anal. calcd. for $C_{29}H_{23}FN_6O_3$: C, 66.66; H, 4.44; N, 16.08. Found: C, 66.71; H, 4.53; N, 16.17 %.

4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-5-(5-*p*-tolyl-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (3l)

Yield: 74 %, m.p. 213-215 ºC. IR (KBr): 3219 (NH), 3068 (C-H_{arom}), 2986 (H-C=C<), 2856, 2860 (C-H, CH_3), 1701 (C=O), 1602 (C=N), 1531 (C=C), 1284 (C-O-C), 1165 (C-F) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.37 (s, 3H, $CH_{3Pyrimidine}$), 2.44 (s, 3H, CH_{3arom}), 5.21 (s, 1H, $CH_{pyrimidine}$), 6.86 (s, 1H, NH-C-Ph), 7.07-8.18 (m, 13H, Ar-H), 8.22 (s, 1H, $CH_{pyrazole}$), 9.18 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.0 ($CH_{3Pyrimidine}$), 21.2 (CH_{3arom}), 53.2 ($C_{pyrimidine}$), 123.2 ($C_{pyrazole}$), 113.1-149.7 (Ar-C), 150.2 (C=O), 160.2, 164.2 ($C_{oxadiazole}$), 161.4 (C-F). LCMS (ESI) *m/z*: 506.19 $[M]^+$. Anal. calcd. for $C_{29}H_{23}FN_6O_2$: C, 66.76; H, 4.58; N, 16.59. Found: C, 66.77; H, 4.52; N, 16.68 %.

***N*-((5-(4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-oxadiazol-2-yl)methyl)benzamide (3m)**

Yield: 61 %, m.p. 227-229 ºC. IR (KBr): 3221 (NH), 3061 (C-H_{arom}), 2984 (H-C=C<), 2921 (C-H, CH_2), 2852 (C-H, CH_3), 1703 (C=O), 1605 (C=N), 1528 (C=C), 1281 (C-O-C), 1160 (C-F) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 2.36 (s, 3H, CH_3), 4.06 (s, 2H, CH_2), 5.25 (s, 1H, $CH_{pyrimidine}$), 6.87 (s, 1H, NH-C-Ph), 7.10-8.20 (m, 14H, Ar-H), 8.24 (s, 1H, $CH_{pyrazole}$), 8.68 (s, 1H, NHCO), 9.17 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.4

(CH_3), 43.4 (CH_2), 53.5 ($C_{pyrimidine}$), 123.6 ($C_{pyrazole}$), 113.0-149.1 (Ar-C), 150.7 (C=O), 160.4, 164.3 ($C_{oxadiazole}$), 161.5 (C-F), 167.5 (NHCO). LCMS (ESI) *m/z*: 549.19 $[M]^+$. Anal. calcd. for $C_{30}H_{24}FN_7O_3$: C, 66.57; H, 4.40; N, 17.84. Found: C, 66.55; H, 4.46; N, 17.88 %.

5-(5-Benzyl-1,3,4-oxadiazol-2-yl)-4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3n)

Yield: 62 %, m.p. 195-197 ºC. IR (KBr): 3219 (NH), 3066 (C-H_{arom}), 2987 (H-C=C<), 2923 (C-H, CH_2), 2854 (C-H, CH_3), 1705 (C=O), 1604 (C=N), 1531 (C=C), 1284 (C-O-C), 1166 (C-F) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.34 (s, 3H, CH_3), 4.01 (s, 2H, CH_2), 5.22 (s, 1H, $CH_{pyrimidine}$), 6.86 (s, 1H, NH-C-Ph), 7.12-8.19 (m, 14H, Ar-H), 8.22 (s, 1H, $CH_{pyrazole}$), 9.15 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.1 (CH_3), 31.2 (CH_2), 53.7 ($C_{pyrimidine}$), 123.3 ($C_{pyrazole}$), 113.4-149.6 (Ar-C), 150.4 (C=O), 160.1, 164.7 ($C_{oxadiazole}$), 161.7 (C-F). LCMS (ESI) *m/z*: 506.19 $[M]^+$. Anal. calcd. for $C_{29}H_{23}FN_6O_2$: C, 68.76; H, 4.58; N, 16.59. Found: C, 68.85; H, 4.65; N, 16.62 %.

4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-5-(5-styryl-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (3o)

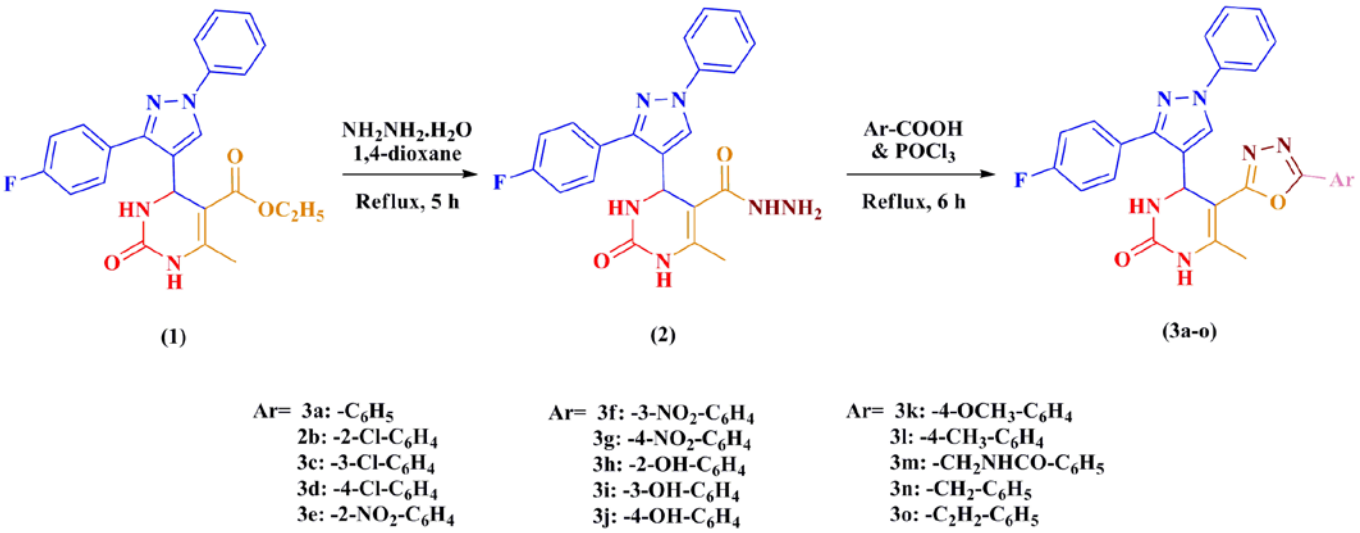
Yield: 72 %, m.p. 275-277 ºC. IR (KBr): 3224 (NH), 3151 (C-H_{arom}), 3024 (H-C=C-H), 2980 (H-C=C<), 2920 (C-H, CH_3), 1708 (C=O), 1597 (C=N), 1500 (C=C), 1217 (C-O-C), 1178 (C-F) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.26 (s, 3H, CH_3), 5.44 (s, 1H, $CH_{pyrimidine}$), 6.42 (d, 1H, CH=C**H**$_{arom}$), 6.46 (d, 1H, CH=C**H**$_{oxadiazole}$), 7.06 (s, 1H, NH-C-Ph), 7.13-7.97 (m, 14H, Ar-H), 8.00 (s, 1H, $CH_{pyrazole}$), 9.21 (s, 1H, N**H**-C-CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 15.1 (CH_3), 53.4 ($C_{pyrimidine}$), 123.1 ($C_{pyrazole}$), 123.1 (CH=$CH_{oxadiazole}$), 133.1 (CH=CH_{arom}), 113.4-149.8 (Ar-C), 150.1 (C=O), 159.9, 164.0 ($C_{oxadiazole}$), 161.2 (C-F). LCMS (ESI) *m/z*: 518.19 $[M]^+$. Anal. calcd. for $C_{30}H_{23}FN_6O_2$: C, 69.49; H, 4.47; N, 16.21. Found: C, 69.45; H, 4.44; N, 16.32 %.

RESULTS AND DISCUSSION

Scheme **1** shows the synthesis of targeted compounds. Compound **2** was synthesized by adopting the well-known approach of Biginelli reaction by means of diaryl-pyrazole-4-carbaldehyde followed by the addition of NH_2-NH_2 (hydrazine hydrate). This adduct was treated with different aryl acid derivatives in one-pot to produce the final compounds 4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-5-(5-aryl-1,3,4-oxadiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-ones **3a-o**.

Synthesized molecules were characterized by well known spectroscopic techniques before evaluating theirs *in vitro* antimicrobial activity. IR spectrum of compound **3a-o** showed characteristic absorption band of the carbonyl group at 1710-1680 cm^{-1}, while absorption band appeared at 3293-3212 cm^{-1} corresponding to a secondary amine. The vibrations appeared at 3151-3058, 2998-2978 and 2929-2845 cm^{-1} corresponding to C-H stretching of the aromatic ring, H-C=C< and -CH_3, respectively. Absorption bands at 1609-1592, 1533-1500 cm^{-1} corresponding to >C=N-, >C=C< stretching of the aromatic ring, while absorption displayed at 1289-1217 cm^{-1} was due to C-O-C stretching in oxadiazole ring.

In ^{1}H NMR, the appearance of three singlet peaks at δ = 2.26-2.40, 5.17-5.45 and 9.04-9.24 ppm were due to three protons of the methyl group, -CH of the pyrimidine ring and proton of -NH of pyrimidine ring (-N<u>H</u>-C-CH_3), respectively. The appearance of singlet peak at δ = 6.80-7.06 ppm was due to one proton of -NH of pyrimidine ring (-N<u>H</u>-C-Ph). ^{13}C NMR of compound **3a-o** showed a characteristic signal at δ = 150.2-151.3 ppm due to carbonyl carbon of pyrimidine scaffold as well as the appearance of a signal around δ = 15.0-15.2 ppm assignable to the carbon of the methyl group. Moreover, the mass spectrum had shown a molecular ion peak corresponding to molecular formula **3a-o** along with other fragment peaks, which were in agreement with the proposed molecular weight and elemental analysis of the anticipated structure of compounds.



Scheme 1. Synthetic pathway of novel compounds **3a-o**

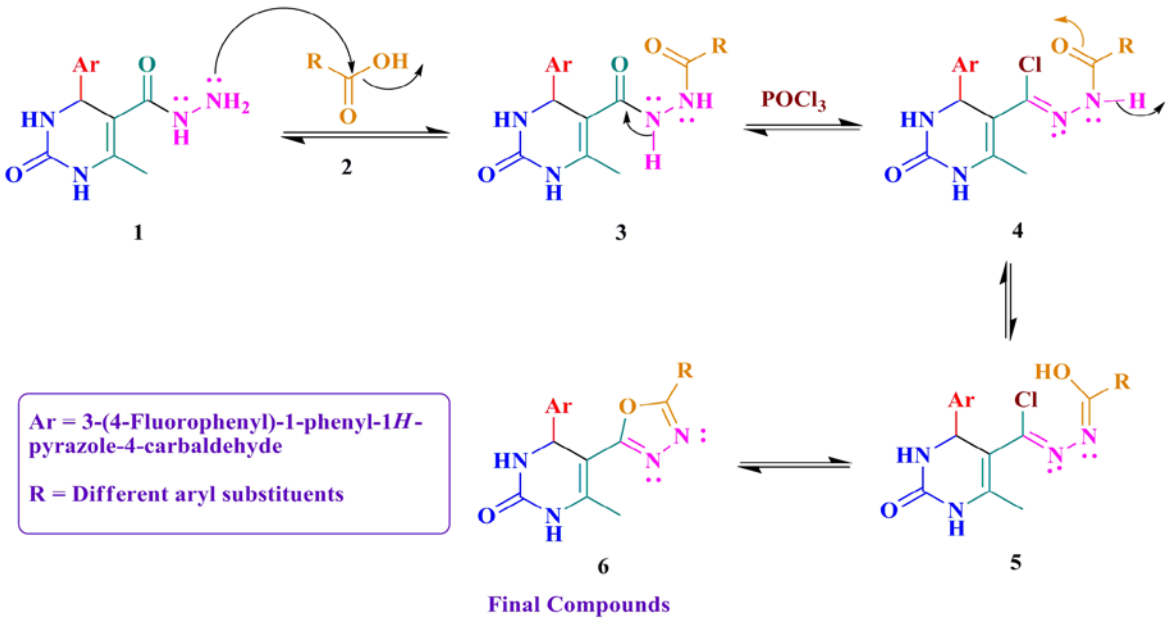


Figure 1. Plausible mechanistic pathway of synthesized analogs

A plausible mechanistic path for compounds **3a-o** is suggested in Figure **1**. Biginelli hydrazide **(1)** was transformed to targeted compounds **(6)** by intermolecular nucleophilic attack on the carbonyl carbon of different aromatic acids **(2)** followed by the cyclocondensation (removal of HCl) **(5)** in the presence of phosphorus oxychloride ($POCl_3$).

Antimicrobial activity

Amongst the synthesized compounds **3a-o**, several compounds revealed the antimicrobial influence that ranged from good to excellent. On the basis of antibacterial screening results given in Table 1, compounds **3j** (-4-OH-C_6H_4), **3k** (-4-OCH_3-C_6H_4) and **3l** (-4-CH_3-C_6H_4) displayed noteworthy antibacterial activities against *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenes* compared to chloramphenicol and Ciprofloxacin used as standard drugs. MIC values of antifungal activity were determined by means of conventional broth microdilution bioassay method using Nystatin and Griseofulvin as a reference standard.[24] Compounds **3h** (-2-OH-C_6H_4) and **3l** (-4-CH_3-C_6H_4) unveiled remarkable inhibitory effect at MIC = 12.5 μg mL^{-1} against selected fungal strains.

Antitubercular and cytotoxic activity

Synthesized oxadiazole hybrid molecules **3a-o** were screened for their *in vitro* antitubercular activity at 6.25 μg mL^{-1} against *Mycobacterium tuberculosis* $H_{37}Rv$ strain in BACTEC 12B medium using the microplate alamar blue assay (MABA).[25] In an initial screen, the compounds which shown more than or equal to 90 % inhibition were retested at and below 6.25 μg mL^{-1} by using 2-fold dilution to determine the definite MIC. In preliminary *in vitro* screening, compounds **3d**, **3h, 3j**, **3k** and **3l** inhibited Mtb in the range of 92-98 %. In secondary level screening, two compounds **3j** (-4-OH-C_6H_4) and **3l** (-4-CH_3-C_6H_4) inhibited Mtb with MIC of 0.03 μg mL^{-1} correspond to the same MIC as the reference standard isoniazid.

Compounds revealing comparatively low MICs were tested for cytotoxicity (IC_{50}) in VERO cell lines. Their selectivity index (SI) was calculated as per the following formula IC_{50}/MIC. The compounds **3h**, **3j** and **3l** were somehow less toxic than **3d** and **3k**. Basically, the compounds with MIC≤6.25 μg mL^{-1} and SI≥10 are remarkable compounds and MIC≤1 μg mL^{-1} in the newly synthesized compound may be considered as excellent leadership, which makes compounds **3j** and **3l** promising bioactive molecules for future research. The results of the antitubercular studies, actual IC_{50} and SI of tested compounds were reported in Table 2.

Determination of 50 % IC_{50} in VERO cells (Cytotoxicity assay)

Compounds were tested for cytotoxicity (IC_{50}) in VERO cells at concentrations less than or equal to 62.5 μg mL^{-1} or 10 times the MIC for *M. tuberculosis* $H_{37}Rv$. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega CellTiter 96 Non-radioactive Cell Proliferation Assay. The Selectivity Index (SI = IC_{50}/MIC) was also determined; it was considered significant when SI >10.

Structure-activity relationship study

In this manuscript, 1,3,4-oxadiazole motifs were used to impart electronic location on the hankering of molecules. It is observed that the electron releasing group on the phenyl nucleus of 1,3,4-oxadiazole enhanced, whereas electron-withdrawing substituent caused a substantial decrease in the biological potency.

Table 1. Antimicrobial screening of the compounds **3a-o**.

No.	-Ar	MINIMUM INHIBITORY CONCENTRATIONS, MIC, in μg mL^{-1}						
		Gram-negative		Gram-positive		Fungi		
		E.C.[a]	*P.A.*[b]	*S.A.*[c]	*S.P.*[d]	*C.A.*[e]	*A.N.*[f]	*A.C.*[g]
3a	-C_6H_5	500	250	500	250	500	N.A.[h]	N.A.
3b	-2-Cl-C_6H_4	125	250	500	100	500	NA.	NA.
3c	-3-Cl-C_6H_4	100	100	100	500	NA.	NA.	500
3d	-4-Cl-C_6H_4	25	62.5	25	100	500	NA.	NA.
3e	-2-NO_2-C_6H_4	1000	500	500	500	NA.	250	NA.
3f	-3-NO_2-C_6H_4	1000	1000	500	500	250	100	250
3g	-4-NO_2-C_6H_4	500	100	1000	1000	500	NA.	NA.
3h	-2-OH-C_6H_4	100	1000	1000	500	NA.	100	12.5
3i	-3-OH-C_6H_4	1000	100	500	50	NA.	1000	NA.
3j	-4-OH-C_6H_4	12.5	25	1000	100	1000	1000	100
3k	-4-OCH_3-C_6H_4	100	250	500	12.5	50	1000	1000
3l	-4-CH_3-C_6H_4	500	500	25	1000	100	12.5	NA.
3m	-$CH_2NHCOC_6H_5$	1000	1000	250	500	1000	NA.	50
3n	-CH_2-C_6H_5	500	1000	100	500	NA.	50	1000
3o	-C_2H_2-C_6H_5	1000	500	250	1000	1000	500	1000
S.d.[i] **1**	Chloramphenicol	50	50	50	50	-	-	-
S.d. 2	Ciprofloxacin	25	25	50	50	-	-	-
S.d. 3	Nystatin	-	-	-	-	100	100	100
S.d. 4	Griseofulvin	-	-	-	-	500	100	100

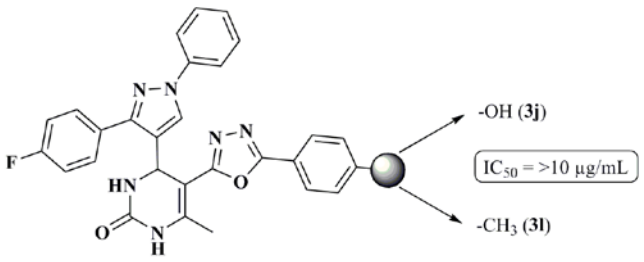
[a]*E.C.: Escherichia coli* MTCC 443; [b]*P.A.:Pseudomonas aeruginosa* MTCC 1688, [c]*S.A.: Staphylococcus aureus* MTCC 96; [d]*S.P.: Staphylococcus pyogenes* MTCC 442; [e]*C.A.: Candida albicans* MTCC 227; [f]*A.N.: Aspergillus niger* MTCC 282; [g]*A.C.: Aspergillus clavatus* MTCC 1323; [h]N.A.: No activity; [i]S.d.: Standard drug.

Table 2. *In vitro* antitubercular screening data of oxadiazole analogs **3a-o**.

No.	-Ar	% Inhibition, at 6.25 μg mL^{-1}	MIC[a], μg mL^{-1}	IC_{50}[b], VERO cells	SI[c]=IC_{50}/MIC
3a	-C_6H_5	65	n.d.[f]	n.d.	n.d.
3b	-2-ClC_6H_4	55	n.d.	n.d.	n.d.
3c	-3-ClC_6H_4	52	n.d.	n.d.	n.d.
3d	-4-ClC_6H_4	92	6.25	7.2	1.15
3e	-2-$NO_2C_6H_4$	48	n.d.	n.d.	n.d.
3f	-3-$NO_2C_6H_4$	71	n.d.	n.d.	n.d.
3g	-4-$NO_2C_6H_4$	62	n.d.	n.d.	n.d.
3h	-2-HOC_6H_4	93	3.13	>10	>3.19
3i	-3-HOC_6H_4	82	n.d.	n.d.	n.d.
3j	-4-HOC_6H_4	98	0.03	>10	333
3k	-4-$MeOC_6H_4$	96	1.56	8.9	5.70
3l	-4-CH_3-C_6H_4	97	0.03	>10	333
3m	-$CH_2NHCOC_6H_5$	81	n.d.	n.d.	n.d.
3n	-$CH_2C_6H_5$	73	n.d.	n.d.	n.d.
3o	-$C_2H_2C_6H_5$	84	n.d	n.d.	n.d.
R.S.[d]	INH[e]	99	0.03	-	-

[a]Minimum inhibitory concentration against $H_{37}Rv$ strain of *M. tuberculosis* (μg mL^{-1}). [b]Measurement of cytotoxicity in VERO cells: 50% inhibitory concentrations (μg mL^{-1}). [c]Selectivity index (*in vitro*): IC_{50} in VERO cells/MIC against *M. tuberculosis*. [d]R.S.: Reference Standard; [e]INH: Isoniazid; [f]n.d.: Not determined.

Compounds **3h**, **3j, 3k** and **3l**, substituted with inductively electron-donating groups like methyl, methoxy (on *para*) and hydroxyl (on *ortho* and *para*), showed the maximum inhibitory antimicrobial as well as antitubercular influence with an IC_{50} of >10 μg mL^{-1}. Looking at the MIC values, it may be concluded that electron-donating groups at *the para* position of the phenyl ring induced a positive effect on bio-activity.



CONCLUSION

The pivotal point of the present work was to focus on the development of novel structural hybrids based on DHPMs and pyrazole clubbed 1,3,4-oxadiazole, which could be useful as effective antimicrobial as well as antitubercular agents. It is concluded from biological activity that the structural and electronic diversity of these compounds influences their activity. Synthesized scaffolds **3h**, **3j, 3k** and **3l** having an electron-donating group such as -OH, -OCH_3, -CH_3 are found as the most potent antimicrobials and antitubercular candidates. Moreover, most active compounds (i.e**., 3j** and **3l**) were conveyed with moderately low cytotoxicity. Consequently, this hybrid nucleus may unlock a moderately simplistic route to new potent antimicrobials and antitubercular scaffolds.

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