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

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Abstract: By cyclizing Biginelli-type adducts, a series of 4, fluorophenylpyrazole clubbed 1,3,4-oxadiazole and 3,4-dihydropyrimidin-2(1H)-ones were produced. The established spectrum approaches were used to assign their structures. The scaffolds were tested for their antitubercular and antibacterial properties in vitro using microplate alamar blue assay and broth microdilution bioassay, respectively. In terms of antibacterial and antitubercular potential, compounds 3j and 3l containing -OH and -CH3 groups exhibited moderate cytotoxicity on VERO cells.

INTRODUCTION

A number of infectious illnesses have significant therapeutic challenges due to microbial resistance. One of the greatest dangers to human life, according to the World Health Organisation (WHO), is antimicrobial drug resistance (AMR). In the realm of drug development programmes, structural alterations to current medications have shown remarkable outcomes. Accordingly, the most effective method for creating new, more powerful drugs is to use a molecular hybridization strategy to create scaffold architecture that is completely unique.1, 2 The synthesis of dihydropyrimidines (DHPMs) with diverse bioactivities has recently attracted the interest of many medicinal chemists, and the Biginelli type reaction in particular.3-5 The varied pharmacological properties of pyrazoles, which include antibacterial, antidepressant, anticonvulsant, antipyretic, anti-influenza, and anticancer actions, have made them a prominent motif in medicinal chemistry and a hub for synthetic heterocycles.6-8 Several catalysts, including Sc(OTf)3, Mg(ClO4)2, and H2SO4, were used in a multicomponent process to produce pyrazole derivatives.9-11 Because of its metabolic profile and capacity to form hydrogen bonds with the receptor site, oxadiazole has been a widely used pharmacophore in recent years. Numerous biological actions, including hypoglycaemic, anti-HIV, analgesic, anti-inflammatory, and antitubercular effects, are generated by the presence of an azole group in oxadiazole, which increases its lipophilicity and impacts its easy ability to target.12,13 Oxadiazole have shown great promise as inhibitors of key biological targets, such as tyrosinase, MAO, and cathepsin K.14–19.

Keywords: 1,3,4-Oxadiazole, 3,4-dihydropyrimidin-2(1H)-one, pyrazole, antimicrobial, antitubercular, minimum inhibitory concentration (MIC).

EXPERIMENTAL

No further purification was performed on the compounds that were acquired from Aldrich and E. Merck. Distillation was carried out using Buchi Rotavapor. The Gallenkamp apparatus was used to determine the melting points, and these values have not been revised. The reaction was seen under ultraviolet light (λ 254 and 365 nm) or iodine vapour to ensure that all compounds were pure and that the reaction had finished on aluminum-coated TLC plates G60, F245 (E. Merck) with an eluent ratio of 7:3. The Perkin-Elmer 2400 CHN analyzer was used for the elemental analysis. The chemical shifts were measured using TMS as a reference standard, and 1H NMR spectra were captured using a Bruker Avance II 400 MHz. The 13C NMR spectra were recorded on a Varian Mercury-400, 100 MHz, using DMSO-d6 as the solvent. A Shimadzu LCMS 2010 spectrometer was used for mass spectra scanning, while a Perkin-Elmer FT-IR spectrophotometer was used for infrared spectra recording.

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}. ^1H NMR (400 MHz, DMSO-*d6*, 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-*d6*, 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-phe- nyl-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}. ^1H NMR (400 MHz, DMSO-*d6*, 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-*d6*, 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-fluorophe- nyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-3,4-dihydropyrimid-in-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}. ^1H NMR (400 MHz, DMSO-*d6*, 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-*d6*, 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-fluorophe- nyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-3,4-dihydropyrimi- din-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-fluorophe- nyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-3,4-dihydropyrimi- din-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}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δ ppm): (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}. ^{1}H 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-hyd- roxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methyl-3,4-dihydropyri- midin-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}. ^{1}H 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), , 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-hyd- roxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methyl-3,4-dihydropyri- midin-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}. ^{1}H 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), , 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-hyd- roxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methyl-3,4-dihydropyri- midin-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}. ^{1}H 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-meth- oxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methyl-3,4-dihydropyrimi- din-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}. ^{1}H 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}. ^{1}H 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-oxa- diazol-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}. ^{1}H NMR (400 MHz, DMSO-*d*$_6$, *δ* ppm): (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}. ^1H 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}. ^1H 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 %.

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RESULTS AND DISCUSSION

Synthesis of compounds of interest is shown in Scheme 1. Second, hydrazine hydrate (NH2-NH2) was added to the mixture after the diaryl-pyrazole-4-carbaldehyde step in the famous Biginelli reaction, which yielded compound 2. The final compounds were produced by treating this adduct with various aryl acid derivatives in a one-pot reaction. The chemical compound 4-(3-(4-fluorophenyl)The compound is named phenyl-1-hydrazolyl.6 -methyl-5-(5-aryl-1,3,4-oxadiazol-2-yl)2, 1-hydropyrimidin-2-one hydrogen bonded to C=Oand ones from 3a to o.

Prior to testing the synthetic compounds for antibacterial activity in vitro, they underwent spectroscopic characterization using established methods. Compound 3a-o's infrared spectra revealed a carbonyl group absorption band at 1710-1680 cm-1 and a secondary amine absorption band at 3293-3212 cm-1. At 3151-3058, 2998-2978, and 2929-2845 cm-1, respectively, vibrations were detected that correspond to the aromatic ring's C-H stretching, H-C=C<, and -CH3. The stretching of the aromatic ring is shown by the absorption bands at 1609–1592, 1533–1500 cm-1, and 1289–1217 cm-1, while the stretching of the oxadiazole ring is indicated by the bands at 1289–1217 cm-1.
The three singlet peaks seen in 1H NMR at δ = 2.26-2.40, 5.17-5.45, and 9.04-9.24 ppm, respectively, were caused by three protons: one from the methyl group, one from the -CH of the pyrimidine ring, and one from the -NH of the pyrimidine ring (-NH-C-CH3). It was one proton of the -NH group in the pyrimidine ring (-NH-C-Ph) that caused the singlet signal at δ = 6.80-7.06 ppm to arise. A distinct signal at δ = 150.2-151.3 ppm, attributed to the carbonyl carbon of the pyrimidine scaffold, and an additional signal at δ = 15.0-15.2 ppm, attributed to the carbon of the methyl group, were seen in the 13C NMR spectrum of compound 3a-o. In addition, the mass spectra confirmed the predicted chemical structure and molecular weight by showing a peak for a molecular ion with the formula 3a-o in addition to other fragment peaks.

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

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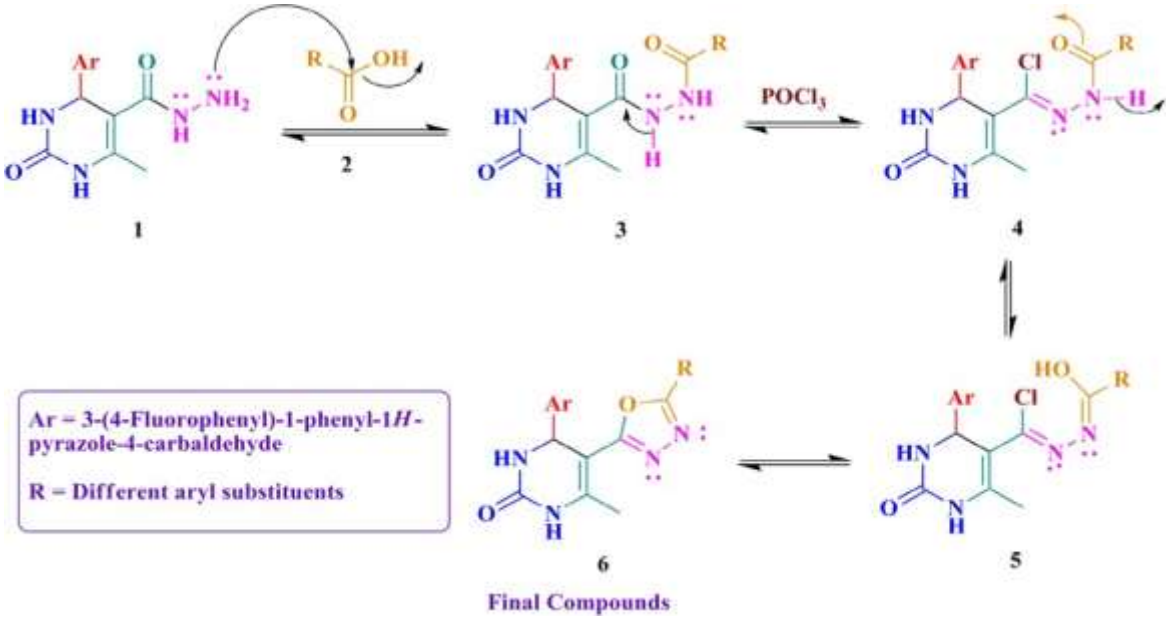

Figure 1. Plausible mechanistic pathway of synthesized analogs

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* H37Rv 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)

At doses below or equivalent to 62.5 µg mL-1, or 10 times the MIC for M. tuberculosis H37Rv, compounds were examined for cytotoxicity (IC50) in VERO cells. The Promega CellTiter 96 Non-radioactive Cell Proliferation Assay was used to measure cellular conversion of MTT into a formazan product after 72 hours of exposure, which is a measure of viability. Additionally, the Selectivity Index (SI) was calculated as IC50 divided by MIC. A SI greater than 10 was deemed statistically significant.

Structure-activity relationship study

Substances were tested for cytotoxicity (IC50) in VERO cells at doses less than or equal to 62.5 µg mL-1, which is 10 times the minimum inhibitory concentration (MIC) for Mycobacterium tuberculosis H37Rv. For the purpose of determining cell viability, the Promega CellTiter 96 Non-radioactive Cell Proliferation Assay was used to assess the amount of MTT converted into a formazan product after 72 hours of exposure. One more thing: we divided the IC50 by the MIC to get the Selectivity Index (SI). Statistical significance was determined by a SI higher than 10.

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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. 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

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

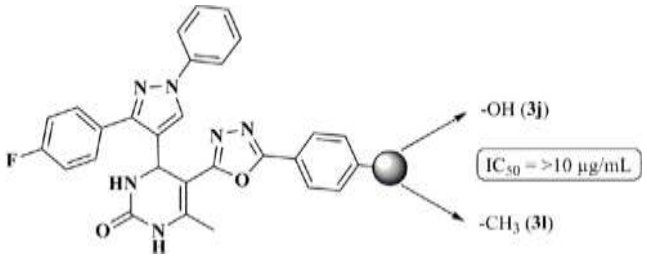
[a]*E.C.: Escherichia coli* MTCC 443; [b]*P.A.:Pseudomonas aeruginosa* MTCC 1688, [c]*S.A.: Staphylococcus aureus* MTCC 96; [d]*S.P.: Staphylococcus pyogenes* MTCC 442; [e]*C.A.: Candida albicans* MTCC 227; [f]*A.N.: Aspergillus niger* MTCC 282; [g]*A.C.: Aspergillus clavatus* MTCC 1323; [h]N.A.: No 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 H37Rv 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*): IC50 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



CONCLUSION

An important goal of this study was to create new structural hybrids of DHPMs and pyrazole called 1,3,4-oxadiazole; these compounds have the potential to be powerful antibacterial and antitubercular medicines. Biological activity leads us to believe that these compounds' structural and electrical diversity impact their activity. The most effective antimicrobials and antitubercular candidates were scaffolds 3h, 3j, 3k, and 3l that included an electron-donating group like -OH, -OCH3, or -CH3. In addition, the compounds with the highest activity, 3j and 3l, were transported with a moderate level of cytotoxicity. So, this hybrid nucleus might provide a relatively easy way to novel antibacterial and antitubercular scaffolds.

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