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Synthesis, antimicrobial and cytotoxic activity of pyrazole derivatives of pyridyloxadiazoles

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In the present communication, a series of novel 1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)-3-(aryl)prop-2-en-1-ones **5a-o** have been efficiently synthesized and evaluated for their *in vitro* antimicrobial and cytotoxic activities. The results of antimicrobial study reveal the compounds **5f**, **5g** and **5k-m** to be among the most potent antimicrobial agents compared to the standard drugs chloramphenicol and griseofulvin. From the standpoint of SAR studies, it is observed that presence of electron donating groups remarkably enhanced the antimicrobial activity of newly synthesized compounds. Further, the results of preliminary MTT cytotoxicity studies on HeLa cells suggest that the potent antimicrobial activity of **5f, 5g** and **5k-m** is accompanied by low cytotoxicity. All the newly synthesized analogues have been characterized by IR, ^{1}H and ^{13}C NMR and mass spectroscopic techniques.

Keywords: Antimicrobial activity, cytotoxicity, pyrazole, 1,3,4-oxadiazole, pyridine

Mortality has been found to be escalating in developing countries which are highly affected by infectious diseases. Resistance to antimicrobial agents in existing use has been mounting for a great multiplicity of microorganisms and the resistance to multiple drugs is commonly found for several microorganisms. The emergence of "Antimicrobial resistance" (AMR) is multifaceted and causes severe health problems. Consequently, the quest for the discovery or optimization of antimicrobial agents active against these resistant strains is of paramount significance. In this context, this research group had reported synthesis of 1-[2-(2-chloro(3-quinolyl))-5-(4-nitrophenyl)(1, 3, 4-oxadiazolin-3-yl)]-3-(aryl)prop-2-en-1-ones[1] containing quinoline and 1,3,4-oxadiazole nucleus and these compounds were screened for antibacterial and antifungal activity. Inspired by this, in the present paper, the synthesis of 1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)- 5- (pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)-3-(aryl)-prop-2-en-1-ones **5a-o** by introducing pyrazol, 1,3,4-oxadiazole and pyridine nucleus has been reported. In this attempt, the antimicrobial activity was enhanced enormously. It is observed that this may be due to the presence of three hybrid motifs *i.e.* pyrazol, 1,3,4-oxadiazoline and pyridine. Structural relevance of title compounds **5a-o** with previously synthesized compounds is shown in **Figure 1**.

Pyrazole framework plays an essential role in biologically active compounds and therefore represents an interesting template for combinatorial[2], as well as medicinal chemistry[3,4]. Numerous representatives of this heterocycle exhibit antibacterial[5,6], analgesic[7], fungistatic[8] and anti-hyperglycemic activity[9]. Also, some arylpyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity[10]. Extensive studies have been devoted to arylpyrazole derivatives such as Celecoxib, a well-known cyclooxygenase-2 inhibitor[11,12]. Moreover, oxadiazoles are important class of compounds which have long attracted attention, owing to their remarkable biological and pharmacological properties, such as antitubercular[13], antimicrobial[14,15], anti HIV[16], anti-inflammatory[17] and insecticidal[18] activities. Also, the azole group of heterocyclic compounds possess significant pharmacokinetic property, lipophilicity that influences the ability of the drug to reach the target by transmembrane diffusion and show promising activity against resistant TB by inhibiting the biosynthesis of lipids[19,20].

Pyridine derivatives occupy a pivotal position in modern heterocyclic chemistry and consequently pyridine substructure is one of the most important heterocycle found in natural products, pharmaceuticals and functional materials[21,22]. Pyridine derivatives

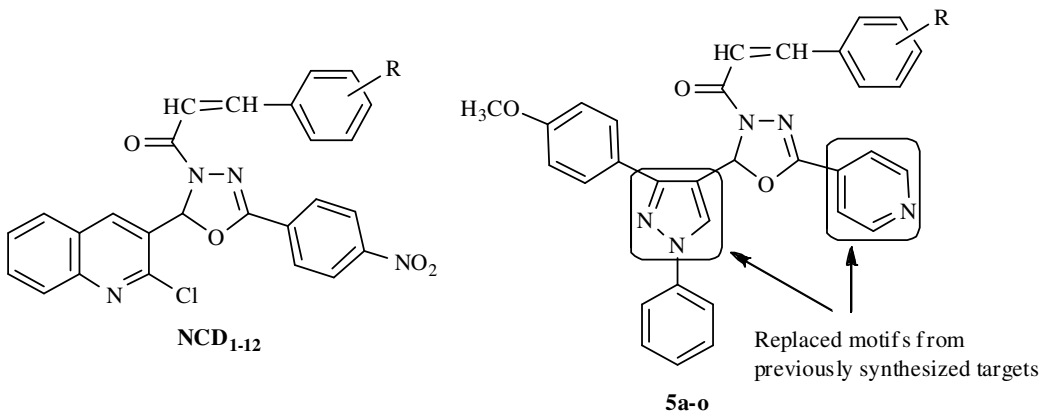


Figure 1 — Structural relevance of title compounds **5a-o** with previously synthesized compounds **NCD_{1-12}**

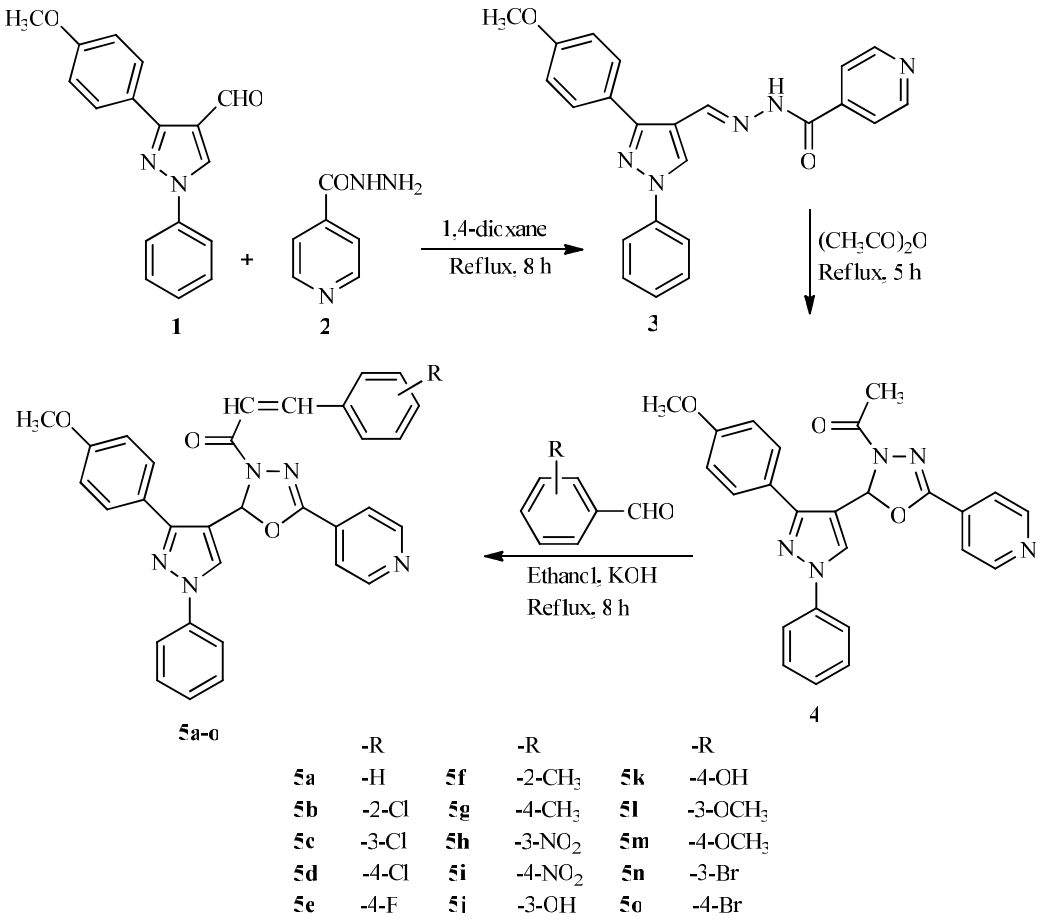
containing multi-functional groups such as streptonigrin, streptonigrone and lavendamycin are reported as anticancer drugs and cerivastatin is reported as the HMGCoA enzyme inhibitors[23]. Moreover, substituted pyridines are reported as leukotriene B-4 antagonists[24].

In view of the high degree of bioactivity shown by the above three heterocyclic systems and continuation of the search for novel antimicrobial agents[25,26], it was envisaged to construct a system in which all these systems are in a single molecular frame for exploring the additive effects towards antimicrobial activity. Hence, a new series of 1-(2-(3-(4-methoxyphenyl)-1-phenyl- 1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)-3-(aryl)-prop-2-en-1-ones **5a-o** have now been synthesized.

Results and Discussion

In the attempt to synthesize cost effective drugs, pyrazole and oxadiazole were identified as better targets, easy and cheaper to synthesize. The synthetic route for the preparation of title compounds was followed as reported in **Scheme I**. 3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** was used as key starting material and was obtained by reported methods[27]. Compound **1** condensed with isoniazide in 1,4-dioxane to afford *N*′-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-methylene) isonicotinohydrazide **3**. Compound **3** showed stretching vibration at 3278 cm^{-1} and 1686 cm^{-1} corresponding to secondary amine as amide linker and carbonyl group respectively. In addition, ^{1}H NMR revealed the appearance of singlet at δ 10.32 due to one proton of the secondary amine group. Resultant compound **3** underwent cyclization with acetic anhydride at 90°C for 5 hr through removal of water and yielded intermediate 1-(2-(3-(4-methoxy-phenyl)-1-phenyl- 1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone **4** which could be proved by the disappearance of imine proton signal in ^{1}H NMR spectroscopy. The intermediate **4** obtained thus, was refluxed with different aromatic aldehydes in the presence of potassium hydroxide in ethanol (99.5%) to obtain the desired compound 1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)-3-(aryl)prop- 2-en-1-ones **5a-o**. Both analytical and spectral data of the synthesized compounds **5a-o** were fully in agreement with proposed structures.

Formation of 1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)-3-(aryl)prop-2-en-1-ones **5a-o** were confirmed on the basis of their spectroscopic data. IR spectrum of compounds **5a-o** showed absorption bands at 2826-2831 cm^{-1} and 1684-1689 cm^{-1} which were due to methoxy (OCH_3) group and carbonyl (>C=O) group stretching vibration respectively. Moreover, compounds **5f** and **5j** having methyl group displayed absorption bands at 2932 cm^{-1} and 2935 cm^{-1} respectively, while compounds **5b-d** encompassing chloro group showed absorption band at 746-751 cm^{-1}. Fluorine present in compound **5e** displayed a stretching frequency at 1142 cm^{-1} and bromine atom present in compounds **5n** and **5o** was confirmed by a peak appearing at 536 cm^{-1} and 538 cm^{-1} respectively. Strong absorption bands appeared at 3442 and 3447 cm^{-1} for hydroxy group present in compounds **5j** and **5k** respectively, while compounds **5h** and **5i** endowed with nitro group displayed vibrational bands at 1511 and 1515 cm^{-1} respectively. In addition, the ^{1}H NMR spectrum of compounds **5a-o** showed two doublets at δ 6.57-6.71 and 7.86-8.02 due to the protons of alkene



	-R		-R		-R
5a	-H	**5f**	-2-CH_3	**5k**	-4-OH
5b	-2-Cl	**5g**	-4-CH_3	**5l**	-3-OCH_3
5c	-3-Cl	**5h**	-3-NO_2	**5m**	-4-OCH_3
5d	-4-Cl	**5i**	-4-NO_2	**5n**	-3-Br
5e	-4-F	**5j**	-3-OH	**5o**	-4-Br

Scheme I — Synthetic route for the preparation of title compounds **5a-o**

carbons attached with carbonyl group and different aryl groups respectively. The singlet signal observed at δ 6.82-6.92 integrating for one proton attached with asymmetric carbon, while singlet for three protons in methoxy group was observed at δ 3.83-3.88. Moreover, in ^{13}C NMR spectra of compounds**5a-o**, carbon atom of carbonyl group and methine carbon (asymmetric carbon) appeared at δ 167.0-167.3 and δ 78.5-78.9 respectively. Two carbons of alkene group displayed chemical shifts at δ 141.7-143.8 and δ 118.6-118.9 due to carbon attached with different aryl ring and carbonyl group respectively whereas carbon of methoxy group showed chemical shift value at δ 55.6-55.9. The detailed spectral values for all the compounds and C, H, N analysis are presented in the experimental part.

The antibacterial screening results (**Table I**) revealed that some of the tested compounds showed excellent inhibition against various tested microbial strains compared to the standard drug. In general, compounds **5a-o** demonstrated better antibacterial activity rather than antifungal activity. From antibacterial activity data **(Table I)**, it was observed that compounds **5f**, **5g** and **5k-m** were the most potent antibacterial agents. Out of them, compounds **5g** (4-CH_3) and **5m** (4-OCH_3) emerged as the most effective antibacterial agents with 2 to 4-fold higher MIC (12.5-25 µg/mL) than the reference drug chloramphenicol. Compounds **5f** (2-CH_3), **5k** (4-OH) and **5l** (3-OCH_3) exhibited comparable antibacterial activity with the standard drug. The highest inhibition of such derivatives may be attributed to the presence of electron donating groups at *para*, *meta* or *ortho* positions of the phenyl ring. Compounds **5g** (4-CH_3) and **5m** (4-OCH_3) emerged as candidates with the highest inhibition against *P. aeruginosa* at MIC = 12.5 µg/mL as compared to standard chloramphenicol. Compounds **5g** (4-CH_3) and **5m** (4-OCH_3) displayed excellent activity with MIC = 25 µg/mL against *E. coli*. In addition, derivative **5m** (4-OCH_3) also exhibited excellent inhibition against *S. pyogenes* with MIC = 25 µg/mL whereas compound **5g** (4-CH_3) also displayed excellent activity against *S. aureus* as compared to standard chloramphenicol (50 µg/mL).

Table I — Results of antibacterial and antifungal screening of compounds **5a-o**

Entry	-R	Minimum inhibitory concentration (MIC) µg/mL						
		Gram-negative[a]		Gram-positive[b]		Fungi[c]		
		Ec	Pa	Sa	Sp	Ca	An	Ac
5a	-H	250	250	250	500	500	250	250
5b	-2-Cl	250	250	500	500	1000	500	500
5c	-3-Cl	200	250	250	250	>1000	500	250
5d	-4-Cl	100	250	250	200	500	250	100
5e	-4-F	250	250	250	500	500	250	250
5f	-2-CH_3	50	50	100	50	100	50	50
5g	-4-CH_3	25	12.5	25	25	25	12.5	25
5h	-3-NO_2	500	250	>1000	500	>1000	1000	500
5i	-4-NO_2	250	250	250	500	500	200	250
5j	-3-OH	100	100	200	100	250	100	100
5k	-4-OH	50	50	100	50	100	50	50
5l	-3-OCH_3	50	25	100	50	50	25	25
5m	-4-OCH_3	25	12.5	25	25	12.5	25	25
5n	-3-Br	250	200	250	500	250	250	200
5o	-4-Br	250	100	200	250	250	250	100
Chloramphenicol		50	50	50	50	--	--	--
Griseofulvin		--	--	--	--	500	100	100

[a]Ec: *Escherichia coli* MTCC 443; Pa: *Pseudomonas aeruginosa* MTCC 1688;
[b]Sa: *Staphylococcus aureus* MTCC 96; Sp: *Staphylococcus pyogenes* MTCC 442;
[c]Ca: *Candida albicans* MTCC 227; An: *Aspergillus niger* MTCC 282;
Ac: *Aspergillus clavatus* MTCC 1323.

The *in vitro* antifungal activity of synthesized compounds **5a-o** were determined against *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323 by conventional broth dilution method. Similar trends were observed for the antifungal activity and compounds **5f**, **5g** and **5k-m** were the most potent antifungal agents. Furthermore, the results indicated that compounds **5g** (4-CH_3) and **5m** (4-OCH_3) substituted with methyl and methoxy group at *para* position of the phenyl ring were found to be the most promising agents against all the fungal strains having 2 to 4-fold higher MIC (12.5-25 µg/mL) in comparison with control drug griseofulvin. The enhanced activity of compounds **5g** (4-CH_3) and **5m** (4-OCH_3) may be attributed to the presence of electron donating group at *para* position. Here also the electron donating groups played a major role for increasing the antifungal activity. Derivatives **5l** (3-OCH_3) and **5m** (4-OCH_3) displayed excellent inhibition against both *A. niger* and *A. clavatus* with MIC = 25 µg/mL whereas compound **5g** (4-CH_3) showed highest inhibition against *A. clavatus* with MIC = 25 µg/mL as compared to standard griseofulvin (100 µg/mL).

Antimicrobial assay

Antibacterial studies of newly synthesized compounds **5a-o** were carried out against the representative panel of Gram-positive (*Staphylococcus aureus* (MTCC-96), *Streptococcus pyogenes* (MTCC-442)) and Gram-negative (*Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688)) bacteria. All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh. The activity of compounds was determined as per National Committee for Clinical Laboratory Standards (NCCLS) protocol using Mueller Hinton Broth (Becton Dickinson, USA)[28]. Primary screening was done first for antibacterial activity in six sets against *E. coli*, *S. aureus*, *P. aeruginosa* and *S. pyogenes* at different concentrations of 1000, 500, 250 µg/mL. The compounds found to be active in primary screening were similarly diluted to obtain 200, 125, 100, 62.5, 50, 25 and 12.5 µg/mL concentrations for secondary screening to test in a second set of dilution against all microorganisms. Inoculum size for test strain was adjusted to 10^6 CFU/mL (Colony Forming Unit per milliliter) by comparing the turbidity (turbidimetric method). Mueller Hinton Broth was used as a nutrient

medium to grow and dilute the compound suspension for test organisms. 2% DMSO was used as a diluent/vehicle to obtain the desired concentration of synthesized compounds and standard drugs to test upon standard microbial strains. Synthesized compounds were diluted to 1000 µg/mL concentration, as stock solution. The control tube containing no antibiotic was immediately subcultured [before inoculation] by spreading a loopful evenly over quarter of a plate of medium suitable for the growth of test organisms. The culture tubes were then incubated for 24 hr at 37°C and the growth was monitored visually and spectrophotometrically. Suspensions of 10 µg/mL were further inoculated on an appropriate media and growth was noted after 24 hr and 48 hr. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC) *i.e.* the amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Solvent had no influence on strain growth. The result of this was greatly affected by the size of inoculum. The test mixture contained 10^6 CFU/mL organisms. DMSO and sterilized distilled water were used as negative control while chloramphenicol antibiotic (1 U strength) was used as positive control. Standard drug used in the present study was 'chloramphenicol' for evaluating antibacterial activity which showed 50 µg/mL MIC against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes*.

The newly prepared compounds **5a-o** were also screened for their antifungal activity as primary screening in six sets against *C. albicans*, *A. niger* and *A. clavatus* at various concentrations of 1000, 500, 250 µg/mL. The primary active compounds were similarly diluted to obtain 200, 125, 100, 62.5, 50, 25 and 12.5 µg/mL concentrations for secondary screening to test in a second set of dilution against all fungi. The antifungal activity of each compound was compared with griseofulvin as a standard drug, which showed 500, 100 and 100 µg/mL MIC against *C. albicans*, *A. niger* and *A. clavatus* respectively. For fungal growth, in the present protocol, Sabourauds dextrose broth has been used at 28°C under aerobic conditions for 48 hr. DMSO and sterilized distilled water were used as negative control while griseofulvin (1 U strength) was used as positive control.

In vitro Cytotoxicity studies (MTT assay)

In vitro cytotoxic activity of newly synthesized compounds **5a-o** was evaluated against human cervical cancer cell line (HeLa) by the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay[29], which measures the reduction of the tetrazolium bromide salt into a formazan dye by mitochondrial dehydrogenases in treated *versus* untreated cells. In brief, exponentially growing cells were plated in 96-well plates (10^4 cells/well in 100 µL of medium) and incubated for 24 hr. All the tested compounds were dissolved in 0.1% DMSO and were diluted with the medium. After 24 hr, the medium was removed and the cell cultures were incubated with 100 µL MTT reagent (1 mg/mL) for 4 hr at 37°C. IC_{50} values were determined at 24, 48 and 72 hr of drug incubation. The IC_{50} values obtained for these compounds are shown in **Table II**. *In vitro* cytotoxic activity results revealed that the derivatives **5f**, **5g**, and **5k**-**m** displayed no toxicity at concentration of 100 µM (IC_{50}> 100 µM), while other derivatives displayed moderate toxicity against HeLa cell lines. It was confirmed that none of the tested compounds exhibited any significant cytotoxic effects on HeLa cell lines, suggesting great potential for their *in vivo* use as antimicrobial agents

Structure Activity Relationship

The results of the antimicrobial screening demonstrated the following assumptions about the structural activity relationship (SAR): the substitution pattern of the three biolabile pyrazole, pyridine and 1,3,4-oxadiazole derivatives were carefully selected to bestow different electronic environment on the molecules. In general, compounds **5a-o** demonstrated

Table II — Levels of cytotoxicity induced by compounds **5a-o** on HeLa cells

Entry	Cytotoxicity (IC_{50})[a]
5a	78.12
5b	67.42
5c	76.24
5d	82.30
5e	54.40
5f	>100
5g	>100
5h	61.32
5i	72.80
5j	91.20
5k	>100
5l	>100
5m	>100
5n	84.44
5o	87.82
Doxorubicin	3.24

[a] IC_{50} is the concentration required to inhibit 50% of cell growth.
[b] HeLa: human cervical cancer cell line.

better antibacterial activity than antifungal activity. In addition, it was ascertained that the compounds were more effective against tested gram negative bacterial strains compared to gram positive bacterial strains. Compounds **5f**, **5g** and **5k-m** emerged as the most effective antimicrobial agents with the MIC in the range of 12.5-100 μg/mL as compared to standard drugs. Antimicrobial activity was considerably affected by substitution pattern on the phenyl ring and the most active compounds contained an electron donating substituent. The highest antimicrobial activity was observed when the electron donating substituents were present at *para* position (**5g** and **5m**) rather than *ortho* or *meta* position (**5f**, **5k** and **5l**) of the phenyl ring. The reason of this result may be due to increase of the electron density which makes compounds active against microorganisms and enhance the antimicrobial potency[30].

Experimental Section

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. Melting points were determined on an electro thermal melting point apparatus by open capillary method and are uncorrected. TLC on silica gel plates (Merck, 60, F_{254}) was used for reaction monitoring. Column chromatography over silica gel (Merck, 70-230 mesh and 230-400 mesh ASTH for flash chromatography) was applied when necessary to isolate and purify the reaction products. Yields refer to purified products and are not optimized. Elemental analysis (% C, H, N) was carried out by a Perkin-Elmer 2400 CHN analyzer. IR spectra of all compounds were recorded on a Perkin-Elmer FT-IR spectrophotometer in KBr, frequencies are reported in cm^{-1}. ^1H NMR spectra were run on Varian Gemini 300 MHz and ^{13}C NMR spectra on Varian Mercury-400, 100 MHz spectrometers in DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in δ (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. Anhydrous reactions were carried out in oven-dried glassware in nitrogen atmosphere.

General procedure for the synthesis of 3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde, 1. Synthesis of 3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** was achieved by reported methods[27].

General procedure for the synthesis of *N′*-((3-(4-methoxyphenyl)- 1 -phenyl-1*H*-pyrazol-4-yl)methylene)-isonicotinohydrazide, 3.

Compound 3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** (0.01 mol) and isoniazide **2** (0.01 mol) were dissolved in 1,4-dioxane (20 mL) and the reaction mixture was refluxed for 8 hr. After cooling, the crystals formed were filtered and purified by recrystallization from absolute alcohol. Yield 78%; m.p. 173°C; IR (KBr): 3278 (-NH,-CONH-), 3058 (C-H, aromatic), 2822 (C-H, OCH_3), 1686 (C=O), 1572 (C=N), 1512 cm^{-1} (C=C); ^1H NMR (DMSO-d_6,): δ 3.84 (s, 3H, OCH_3), 7.11-7.70 (m, 9H, Ar-H), 7.82 (d, 2H, J = 7.9 Hz, C_3-H and C_5-H pyridine ring), 8.42 (s, 1H,-CH=N), 8.64 (s, 1H, pyrazole ring), 8.92 (d, 2H, J = 7.8 Hz, C_2-H and C_6-H pyridine ring), 10.32 (s, 1H,-NH D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.4, 160.7, 150.5, 149.8 (2), 143.4, 140.7, 139.8, 130.4, 129.4 (2), 128.6 (2), 126.3, 125.4, 121.8, 119.8, 114.7 (2), 113.2, 55.9; LCMS: *m/z* 397.14 (M^+). Anal. Calcd for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62. Found: C, 69.42; H, 4.89; N, 17.69%.

General procedure for the synthesis of 1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4 - yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone, 4.

Acetic anhydride (0.03 mol) was added to compound *N′*-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-methylene)isonicotinohydrazide **3** (0.01 mol) and refluxed at 90°C for 5 hr. After cooling, the reaction mixture was poured into ice cold water. The precipitate was filtered, washed with water, dried and purified by recrystallization from ethanol (95%). Yield 71%; m.p. 189°C; IR (KBr): 3058 (C-H, aromatic), 2930 (C-H, CH_3), 2822 (C-H, OCH_3), 1681 (C=O), 1570 (C=N), 1510 (C=C), 1210 cm^{-1} (C-O-C); ^1H NMR (300 MHz, DMSO-d_6): δ 2.07 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.84 (s, 1H, C_2-H oxadiazole ring), 7.14-7.70 (m, 9H, Ar-H), 7.96 (d, 2H, J = 7.6 Hz, C_3-H and C_5-H pyridine), 8.08 (s, 1H, pyrazole ring), 8.82 (d, 2H, J = 7.8 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.9, 160.7, 157.1, 149.9, 149.2 (2), 139.8, 138.5, 129.4 (2), 128.6 (2), 126.3, 125.4, 124.3 (2), 123.1, 119.4 (2), 117.4, 114.9 (2), 78.4, 55.6, 23.6; LCMS: *m/z* 439.12 (M^+). Anal. Calcd for $C_{25}H_{21}N_5O_3$: C, 68.33; H, 4.82; N, 15.94. Found: C, 68.41; H, 4.89; N, 15.85%.

General procedure for the synthesis of 1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)-3-(aryl)prop-2-en-1-ones, 5a-o.

A mixture of intermediate compound 1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-

4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone **4** (0.01 mol) and different aromatic aldehydes (0.01 mol) were stirred in ethanolic potassium hydroxide for 20 min at RT. After stirring, the reaction mixture was refluxed for 8 hr and excess of solvent was distilled out to obtain final compound **5a-o**.

Characterization of Compounds, 5a-o

1-(2-(3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2*H*)-yl)-3-phenyl-prop-2-en-1-one, 5a: Yield 62%; m.p. 211°C; IR (KBr): 3052 (C-H, aromatic), 3012 (C-H,-CH=CH-), 2826 (C-H, OCH_3), 1684 (C=O), 1574 (C=N), 1514 (C=C), 1212 cm^{-1} (C-O-C); ^1H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 6.58 (d, 1H, *J* = 15.8 Hz,-COCH=), 6.88 (s, 1H, C_2-H oxadiazole ring), 7.16-7.66 (m, 14H, Ar-H), 7.84 (d, 1H, *J* = 16.1 Hz, =CH-Ar), 8.06 (d, 2H, *J* = 7.8 Hz, C_3-H and C_5-H pyridine), 8.22 (s, 1H, pyrazole ring), 8.89 (d, 2H, *J* = 8.1 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 160.7, 157.1, 149.9, 149.3 (2), 141.8, 139.8, 138.3, 135.3, 129.4 (2), 128.9 (2), 128.5 (2), 128.1 (2), 127.8, 126.3, 125.4, 124.1 (2), 123.2, 119.8 (2), 118.7, 117.3, 114.8 (2), 78.7, 55.6; LCMS: *m/z* 527.18 (M^+). Anal. Calcd for $C_{32}H_{25}N_5O_3$: C, 72.85; H, 4.78; N, 13.27. Found: C, 72.74; H, 4.71; N, 13.34%.

3-(2-Chlorophenyl)-1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2*H*)-yl)prop-2-en-1-one, 5b: Yield 65%; m.p. 231°C; IR (KBr): 3058 (C-H, aromatic), 3017 (C-H,-CH=CH-), 2830 (C-H, OCH_3), 1688 (C=O), 1575 (C=N), 1515 (C=C), 1211 (C-O-C), 746 cm^{-1} (C-Cl); ^1H NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 6.67 (d, 1H, *J* = 15.4 Hz,-COCH=), 6.86 (s, 1H, C_2-H oxadiazole ring), 7.12-7.62 (m, 13H, Ar-H), 7.94 (d, 1H, *J* = 15.9 Hz, =CH-Ar), 8.08 (d, 2H, *J* = 7.7 Hz, C_3-H and C_5-H pyridine), 8.21 (s, 1H, pyrazole ring), 8.85 (d, 2H, *J* = 8.1 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 160.8, 157.1, 149.8, 149.4 (2), 143.8, 139.6, 138.5, 134.1, 133.1, 129.9, 129.5, 129.1 (2), 128.5 (2), 127.8, 126.9, 126.4, 125.2, 124.2 (2), 123.1, 119.9 (2), 118.9, 117.1, 114.7 (2), 78.5, 55.9; LCMS: *m/z* 561.16 (M^+). Anal. Calcd for $C_{32}H_{24}ClN_5O_3$: C, 68.39; H, 4.30; N, 12.46. Found: C, 68.31; H, 4.38; N, 12.54%.

3-(3-Chlorophenyl)-1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)prop-2-en-1-one,5c: Yield 61%; m.p. 217°C; IR (KBr): 3054 (C-H, aromatic), 3015 (C-H,-CH=CH-), 2829 (C-H, OCH_3), 1687 (C=O), 1573 (C=N), 1512 (C=C), 1214 (C-O-C), 751 cm^{-1} (C-Cl); ^1H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 6.61 (d, 1H, *J* = 15.4 Hz,-COCH=), 6.82 (s, 1H, C_2-H oxadiazole ring), 7.13-7.64 (m, 13H, Ar-H), 7.88 (d, 1H, *J* = 15.8 Hz, =CH-Ar), 8.06 (d, 2H, *J* = 7.8 Hz, C_3-H and C_5-H pyridine), 8.24 (s, 1H, pyrazole ring), 8.84 (d, 2H, *J* = 8.2 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 160.7, 157.0, 149.9, 149.3 (2), 141.8, 139.8, 138.4, 136.7, 134.3, 130.1, 129.4 (2), 128.8 (2), 128.1, 126.9, 126.6, 126.2, 125.3, 124.1 (2), 123.2, 119.7 (2), 118.8, 117.1, 114.9 (2), 78.7, 55.7; LCMS: *m/z* 561.15 (M^+). Anal. Calcd for $C_{32}H_{24}ClN_5O_3$: C, 68.39; H, 4.30; N, 12.46. Found: C, 68.29; H, 4.38; N, 12.54%.

3-(4-Chlorophenyl)-1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)prop-2-en-1-one, 5d: Yield 67%; m.p. 247°C; IR (KBr): 3061 (C-H, aromatic), 3018 (C-H,-CH=CH-), 2831 (C-H, OCH_3), 1689 (C=O), 1571 (C=N), 1514 (C=C), 1214 (C-O-C), 748 cm^{-1} (C-Cl); ^1H NMR (300 MHz, DMSO-d_6): δ 3.86 (s, 3H, OCH_3), 6.58 (d, 1H, *J* = 15.4 Hz,-COCH=), 6.83 (s, 1H, C_2-H oxadiazole ring), 7.13-7.70 (m, 13H, Ar-H), 7.86 (d, 1H, *J* = 15.8 Hz, =CH-Ar), 8.08 (d, 2H, *J* = 7.7 Hz, C_3-H and C_5-H pyridine), 8.21 (s, 1H, pyrazole ring), 8.86 (d, 2H, *J* = 8.2 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 160.8, 157.1, 149.7, 149.4 (2), 141.9, 139.6, 138.6, 133.8, 133.3, 129.7 (2), 129.3 (2), 128.8 (2), 128.2 (2), 125.4, 126.3, 124.2 (2), 123.1, 119.8 (2), 118.7, 117.3, 114.7 (2), 78.7, 55.8; LCMS: *m/z* 561.14 (M^+). Anal. Calcd for $C_{32}H_{24}ClN_5O_3$: C, 68.39; H, 4.30; N, 12.46. Found: C, 68.30; H, 4.37; N, 12.53%.

3-(4-Fluorophenyl)-1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)prop-2-en-1-one, 5e: Yield 62%; m.p. 223°C; IR (KBr): 3056 (C-H, aromatic), 3015 (C-H,-CH=CH-), 2827 (C-H, OCH_3), 1686 (C=O), 1568 (C=N), 1516 (C=C), 1211 (C-O-C), 1142 cm^{-1} (C-F); ^1H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 6.59 (d, 1H, *J* = 15.7 Hz,-COCH=), 6.86 (s, 1H, C_2-H oxadiazole ring), 7.14-7.74 (m, 13H, Ar-H), 7.87 (d, 1H, *J* = 15.8 Hz, =CH-Ar), 8.04 (d, 2H, *J* = 7.9 Hz, C_3-H and C_5-H pyridine), 8.24 (s, 1H, pyrazole ring), 8.85 (d, 2H, *J* = 8.1 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 162.2, 160.7, 157.2, 149.8, 149.3 (2), 141.8, 139.8, 138.5, 130.9, 130.3 (2), 129.4 (2), 128.7 (2), 126.3, 125.4, 124.1 (2), 123.0, 119.7 (2), 118.9,

117.4, 115.6 (2), 114.9 (2), 78.9, 55.8; LCMS: *m/z* 545.17 (M^+). Anal. Calcd for $C_{32}H_{24}FN_5O_3$: C, 70.45; H, 4.43; N, 12.84. Found: C, 70.34; H, 4.49; N, 12.91%.

1-(2-(3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2*H*)-yl)-3-*o*-tolylprop-2-en-1-one, 5f: Yield 64%; m.p. 234°C; IR (KBr): 3052 (C-H, aromatic), 3016 (C-H,-CH=CH-), 2932 (C-H, CH_3), 2827 (C-H, OCH_3), 1687 (C=O), 1568 (C=N), 1518 (C=C), 1214 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.52 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.64 (d, 1H, *J* = 15.8 Hz,-COCH=), 6.89 (s, 1H, C_2-H oxadiazole ring), 7.11-7.64 (m, 13H, Ar-H), 7.89 (d, 1H, *J* = 16.2 Hz, =CH-Ar), 8.08 (d, 2H, *J* = 7.7 Hz, C_3-H and C_5-H pyridine), 8.22 (s, 1H, pyrazole ring), 8.84 (d, 2H, *J* = 8.0 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 160.5, 157.1, 149.9, 149.3 (2), 143.8, 139.7, 138.6, 136.6, 136.1, 129.4 (2), 128.6 (2), 127.9, 127.4, 126.7, 126.1, 125.8, 125.2, 124.2 (2), 123.1, 119.8 (2), 118.7, 117.3, 114.8 (2), 78.6, 55.7, 19.4; LCMS: *m/z* 541.18 (M^+). Anal. Calcd for $C_{33}H_{27}N_5O_3$: C, 73.18; H, 5.02; N, 12.93. Found: C, 73.28; H, 5.10; N, 12.98%.

1-(2-(3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2*H*)-yl)-3-*p*-tolylprop-2-en-1-one, 5g: Yield 61%; m.p. 247°C; IR (KBr): 3054 (C-H, aromatic), 3017 (C-H,-CH=CH-), 2935 (C-H, CH_3), 2828 (C-H, OCH_3), 1684 (C=O), 1570 (C=N), 1516 (C=C), 1215 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.59 (d, 1H, *J* = 15.8 Hz, -COCH=), 6.84 (s, 1H, C_2-H oxadiazole ring), 7.12-7.61 (m, 13H, Ar-H), 7.84 (d, 1H, *J* = 16.1 Hz, =CH-Ar), 8.04 (d, 2H, *J* = 7.9 Hz, C_3-H and C_5-H pyridine), 8.24 (s, 1H, pyrazole ring), 8.82 (d, 2H, *J* = 8.1 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 160.7, 157.2, 149.8, 149.4 (2), 141.8, 139.6, 138.5, 137.7, 132.3, 129.2 (2), 128.9 (2), 128.5 (2), 128.1 (2), 126.3, 125.4, 124.1 (2), 123.0, 119.7 (2), 118.8, 117.4, 114.7 (2), 78.6, 55.9, 21.4; LCMS: *m/z* 541.20 (M^+). Anal. Calcd for $C_{33}H_{27}N_5O_3$: C, 73.18; H, 5.02; N, 12.93. Found: C, 73.28; H, 5.09; N, 12.99%.

1-(2-(3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2*H*)-yl)-3-(3-nitrophenyl)prop-2-en-1-one, 5h: Yield 68%; m.p. 229°C; IR (KBr): 3058 (C-H, aromatic), 3019 (C-H,-CH=CH-), 2830 (C-H, OCH_3), 1689 (C=O), 1572 (C=N), 1518 (C=C), 1511, 1328 (N=O, Ar-NO_2), 1216 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (s, 3H, OCH_3), 6.74 (d, 1H, *J* = 15.6 "Hz,-COCH=), 6.92 (s, 1H, C_2-H oxadiazole ring), 7.16-7.98 (m, 13H, Ar-H), 8.06 (d, 1H, *J* = 15.8 Hz, =CH-Ar), 8.14 (d, 2H, *J* = 7.8 Hz, C_3-H and C_5-H pyridine), 8.28 (s, 1H, pyrazole ring), 8.91 (d, 2H, *J* = 8.2 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 160.8, 157.1, 149.9, 149.5 (2), 147.7, 141.9, 139.8, 138.4, 137.8, 134.7, 129.7, 129.3 (2), 128.6 (2), 126.1, 125.5, 124.2 (2), 123.5, 123.1, 122.8, 119.8 (2), 118.6, 117.3, 114.9 (2), 78.7, 55.7; LCMS: *m/z* 572.16 (M^+). Anal. Calcd for $C_{32}H_{24}N_6O_5$: C, 67.13; H, 4.22; N, 14.68. Found: C, 67.22; H, 4.29; N, 14.75%.

1-(2-(3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2*H*)-yl)-3-(4-nitrophenyl)prop-2-en-1-one, 5i: Yield 66%; m.p. 261°C; IR (KBr): 3059 (C-H, aromatic), 3020 (C-H, -CH=CH-), 2832 (C-H, OCH_3), 1687 (C=O), 1571 (C=N), 1520 (C=C), 1512, 1326 (N=O, Ar-NO_2), 1214 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.88 (s, 3H, OCH_3), 6.72 (d, 1H, *J* = 15.8 Hz, -COCH=), 6.90 (s, 1H, C_2-H oxadiazole ring), 7.18-7.96 (m, 13H, Ar-H), 8.07 (d, 1H, *J* = 16.2 Hz, =CH-Ar), 8.14 (d, 2H, *J* = 7.9 Hz, C_3-H and C_5-H pyridine), 8.26 (s, 1H, pyrazole ring), 8.90 (d, 2H, *J* = 8.2 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 160.7, 157.2, 149.7, 149.3 (2), 147.1, 141.9, 141.2, 139.7, 138.3, 129.8 (2), 129.1 (2), 128.4 (2), 126.2, 125.6, 124.0 (2), 123.9 (2), 123.1, 119.7 (2), 118.7, 117.2, 114.7 (2), 78.6, 55.8; LCMS: *m/z* 572.14 (M^+). Anal. Calcd for $C_{32}H_{24}N_6O_5$: C, 67.13; H, 4.22; N, 14.68. Found: C, 67.22; H, 4.29; N, 14.74%.

3-(3-Hydroxyphenyl)-1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)prop-2-en-1-one, 5j: Yield 64%; m.p. 241°C; IR (KBr): 3442 (OH), 3054 (C-H, aromatic), 3016 (C-H, -CH=CH-), 2830 (C-H, OCH_3), 1685 (C=O), 1569 (C=N), 1516 (C=C), 1214 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 6.57 (d, 1H, *J* = 15.6 Hz,-COCH=), 6.84 (s, 1H, C_2-H oxadiazole ring), 7.14-7.72 (m, 13H, Ar-H), 7.84 (d, 1H, *J* = 15.8 Hz, =CH-Ar), 8.06 (d, 2H, *J* = 7.9 Hz, C_3-H and C_5-H pyridine), 8.22 (s, 1H, pyrazole ring), 8.81 (d, 2H, *J* = 8.0 Hz, C_2-H and C_6-H pyridine), 9.12 (s, 1H, OH D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 160.6, 158.5, 157.1, 149.8, 149.4 (2), 141.8, 139.8, 138.5, 135.5, 130.1, 129.3 (2), 128.6 (2), 126.3, 125.4, 124.2 (2), 123.0, 121.2, 119.8 (2), 118.9, 117.7, 117.1, 114.8 (2), 78.7, 55.9; LCMS: *m/z*

543.16 (M^+). Anal. Calcd for $C_{32}H_{25}N_5O_4$: C, 70.71; H, 4.64; N, 12.88. Found: C, 70.81; H, 4.71; N, 12.95%.

3-(4-Hydroxyphenyl)-1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2*H*)-yl)prop-2-en-1-one, 5k: Yield 67%; m.p. 267°C; IR (KBr): 3447 (OH), 3055 (C-H, aromatic), 3017 (C-H,-CH=CH-), 2829 (C-H, OCH_3), 1687 (C=O), 1567 (C=N), 1517 (C=C), 1212 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 6.56 (d, 1H, *J* = 15.4 Hz,-COCH=), 6.82 (s, 1H, C_2-H oxadiazole ring), 7.06-7.64 (m, 13H, Ar-H), 7.81 (d, 1H, *J* = 15.7 Hz, =CH-Ar), 8.04 (d, 2H, *J* = 7.8 Hz, C_3-H and C_5-H pyridine), 8.21 (s, 1H, pyrazole ring), 8.82 (d, 2H, *J* = 8.1 Hz, C_2-H and C_6-H pyridine), 9.11 (s, 1H, OH D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 160.7, 157.8, 157.1, 149.9, 149.3 (2), 141.7, 139.7, 138.4, 130.7 (2), 129.4 (2), 128.4 (2), 127.7, 126.2, 125.3, 124.2 (2), 123.1, 119.9 (2), 118.7, 117.3, 115.9 (2), 114.7 (2), 78.8, 55.9; LCMS: *m/z* 543.17 (M^+). Anal. Calcd for $C_{32}H_{25}N_5O_4$: C, 70.71; H, 4.64; N, 12.88. Found: C, 70.80; H, 4.70; N, 12.94%.

3-(3-Methoxyphenyl)-1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)prop-2-en-1-one, 5l: Yield 64%; m.p. 237°C; IR (KBr): 3056 (C-H, aromatic), 3018 (C-H,-CH=CH-), 2830 (C-H, OCH_3), 1688 (C=O), 1568 (C=N), 1518 (C=C), 1216 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3 in phenyl attached alkene), 6.54 (d, 1H, *J* = 15.7 Hz,-COCH=), 6.84 (s, 1H, C_2-H oxadiazole ring), 7.02-7.64 (m, 13H, Ar-H), 7.84 (d, 1H, *J* = 16.1 Hz, =CH-Ar), 8.04 (d, 2H, *J* = 7.9 Hz, C_3-H and C_5-H pyridine), 8.20 (s, 1H, pyrazole ring), 8.82 (d, 2H, *J* = 8.0 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 160.7, 160.1, 157.2, 149.7, 149.4 (2), 141.6, 139.6, 138.3, 135.1, 129.8, 129.3 (2), 128.6 (2), 126.1, 125.4, 124.1 (2), 123.0, 120.7, 119.8 (2), 118.7, 117.1, 114.9 (2), 113.8, 113.2, 78.7, 55.7 (2); LCMS: *m/z* 557.16 (M^+). Anal. Calcd for $C_{33}H_{27}N_5O_4$: C, 71.08; H, 4.88; N, 12.56. Found: C, 71.17; H, 4.95; N, 12.47%.

3-(4-Methoxyphenyl)-1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)prop-2-en-1-one, 5m: Yield 67%; m.p. 271°C; IR (KBr): 3054 (C-H, aromatic), 3017 (C-H,-CH=CH-), 2831 (C-H, OCH_3), 1686 (C=O), 1569 (C=N), 1520 (C=C), 1215 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3 in phenyl attached alkene), 6.56 (d, 1H, *J* = 15.7 Hz,-COCH=), 6.82 (s, 1H, C_2-H oxadiazole ring), 7.05-7.66 (m, 13H, Ar-H), 7.86 (d, 1H, *J* = 16.1 Hz, =CH-Ar), 8.06 (d, 2H, *J* = 7.9 Hz, C_3-H and C_5-H pyridine), 8.21 (s, 1H, pyrazole ring), 8.84 (d, 2H, *J* = 8.0 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 160.6, 159.7, 157.1, 149.8, 149.3 (2), 141.7, 139.8, 138.5, 130.3 (2), 129.4 (2), 128.5 (2), 127.6, 126.3, 125.4, 124.2 (2), 123.2, 119.7 (2), 118.8, 117.3, 114.9 (2), 114.2 (2), 78.9, 55.8 (2); LCMS: *m/z* 557.18 (M^+). Anal. Calcd for $C_{33}H_{27}N_5O_4$: C, 71.08; H, 4.88; N, 12.56. Found: C, 71.16; H, 4.94; N, 12.48%.

3-(3-Bromophenyl)-1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)prop-2-en-1-one, 5n: Yield 63%; m.p. 237°C; IR (KBr): 3056 (C-H, aromatic), 3019 (C-H,-CH=CH-), 2830 (C-H, OCH_3), 1688 (C=O), 1570 (C=N), 1521 (C=C), 1214 (C-O-C), 536 cm^{-1} (C-Br); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 6.58 (d, 1H, *J* = 15.8 Hz,-COCH=), 6.84 (s, 1H, C_2-H oxadiazole ring), 7.12-7.68 (m, 13H, Ar-H), 7.84 (d, 1H, *J* = 16.2 Hz, =CH-Ar), 8.08 (d, 2H, *J* = 7.7 Hz, C_3-H and C_5-H pyridine), 8.22 (s, 1H, pyrazole ring), 8.81 (d, 2H, *J* = 8.0 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 160.7, 157.2, 149.9, 149.4 (2), 141.9, 139.6, 138.4, 137.3, 133.1, 130.8, 129.8, 129.2 (2), 128.4 (2), 127.6, 126.3, 125.4, 124.1 (2), 123.5, 123.0, 119.8 (2), 118.9, 117.1, 114.8 (2), 78.7, 55.8; LCMS: *m/z* 605.11 (M^+). Anal. Calcd for $C_{32}H_{24}BrN_5O_3$: C, 63.37; H, 3.99; N, 11.55. Found: C, 63.43; H, 3.92; N, 11.63%.

3-(4-Bromophenyl)-1-(2-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2*H*)-yl)prop-2-en-1-one, 5o: Yield 69%; m.p. 257°C; IR (KBr): 3054 (C-H, aromatic), 3017 (C-H,-CH=CH-), 2830 (C-H, OCH_3), 1688 (C=O), 1571 (C=N), 1520 (C=C), 1215 (C-O-C), 538 cm^{-1} (C-Br); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (s, 3H, OCH_3), 6.59 (d, 1H, *J* = 15.8 Hz,-COCH=), 6.86 (s, 1H, C_2-H oxadiazole ring), 7.14-7.68 (m, 13H, Ar-H), 7.82 (d, 1H, *J* = 16.1 Hz, =CH-Ar), 8.06 (d, 2H, *J* = 7.9 Hz, C_3-H and C_5-H pyridine), 8.24 (s, 1H, pyrazole ring), 8.82 (d, 2H, *J* = 7.9 Hz, C_2-H and C_6-H pyridine); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.1, 160.8, 157.1, 149.8, 149.3 (2), 141.8, 139.8, 138.5, 134.3, 131.6 (2), 129.4 (2), 128.8 (2), 128.3 (2), 126.1, 125.5, 124.2 (2), 123.1, 122.4, 119.7 (2), 118.7, 117.2, 114.7 (2), 78.8, 55.9; LCMS: *m/z*605.12 (M^+). Anal. Calcd for $C_{32}H_{24}BrN_5O_3$: C, 63.37; H, 3.99; N, 11.55. Found: C, 63.44; H, 3.92; N, 11.62%.

Conclusion

In summary, some new structural hybrid pyrazole derivatives of pyridyloxadiazoles were synthesized and investigated for their *in vitro* antimicrobial property. We anticipate generation of new structural leads serving as potent antimicrobial agents. Many of the synthesized motifs (**5f**, **5g** and **5k**-**m**), possessing electron donating groups such as methoxy, methyl and hydroxy at *para*, *meta* or *ortho* positions were identified as the most potent antimicrobial agents. In addition, compounds **5g** (4-CH_3) and **5m** (4-OCH_3) emerged as the most potent antimicrobial agents. The promising activity of these precursors is mainly due to the presence of electron donating functional groups (OCH_3, CH_3, OH) on phenyl ring. Albeit, it was observed that *para* position was more favorable for enhancing the antimicrobial activity. The potent antimicrobial activity of most active compounds **5f**, **5g** and **5k-m** was accompanied with relatively low level of cytotoxicity. The results described here, merit further investigations in our laboratories using a forward chemical genetic approach for finding lead molecules as antimicrobial agents.

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