CHAPTER-4

SYNTHESIS, CHARACTERIZATION OF NEW (1H-PYRAZOL-3-YL)-1, 2, 4-OXADIAZOLE DERIVATIVES
4.1. Introduction

The simple doubly unsaturated compound containing two nitrogen and three carbon atoms in the ring, with the nitrogen atoms neighbouring, is known as pyrazole. Pyrazole is the name given by “LUDWIG KNORR” to this class of compounds in 1883. Pyrazole is a colorless solid, having M.p. 70 °C. This high value (compared with 1-alkyl or aryl substituted pyrazoles) is due to intermolecular hydrogen bonding which results in a dimer. Pyrazole is a tautomeric substance; the existence of tautomerism cannot be demonstrated in pyrazole itself, but it can be inferred by the consideration of pyrazole derivatives.

![Resonance structure of pyrazole](image)

Fig 4.1: Resonance structure of pyrazole

Pyrazole, a five-membered heterocycle motif found in a number of small molecules that possess a wide range of agricultural [1] and pharmaceutical activities [2]. Moreover, some pyrazoles are used in supramolecular and polymer chemistry, in the food industry, and as cosmetic colorings and UV stabilizers, while some have liquid crystal properties [3].

4.1.1. Biological importance of Pyrazoles

The synthesis of pyrazoles remains of great interest due to the wide applications of such heterocycles in the pharmaceutical and agrochemical industry. Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. A systematic investigation of this class of heterocyclic lead revealed that, pyrazole containing pharmaacoactive agents play important role in medicinal chemistry. The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these
heterocyclic lead. Among the family of heterocycles, nitrogen containing heterocycles especially pyrazoles is an important class of heterocyclic compound and its derivatives are reported to have the broad spectrum of biological activities such as anti-inflammatory [4], herbicidal [5], antitumour and antiviral activities [6]. Pyrazole derivatives also act as A3 adenosine receptor antagonists [7], neuropeptide YY5 receptor antagonists [8], hyperlipidemia and thrombopiotinmimetics [9].

Very few pyrazole derivatives are naturally occurring may be due to the difficulty of living organisms to construct the N-N bond. Owing to the widespread applications, synthesis and biological activity evaluation of pyrazoles and their derivatives has been a subject of intensive investigations as revealed by enormous literature covering the subject.

**Table- 4.1:** Some of the drugs which are having pyrazole as core molecule

<table>
<thead>
<tr>
<th>Deracoxib</th>
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<tbody>
<tr>
<td>(Anti-inflamatory )</td>
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</table>

<table>
<thead>
<tr>
<th>Celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Anti-inflamatory)</td>
</tr>
<tr>
<td>Chemical Structure</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td><img src="image" alt="Rimonabant" /></td>
</tr>
<tr>
<td><img src="image" alt="Epirizole" /></td>
</tr>
<tr>
<td><img src="image" alt="Isolan" /></td>
</tr>
<tr>
<td><img src="image" alt="Phenazone" /></td>
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</tbody>
</table>
Burnes et al, (1960) synthesized derivatives of phenyl butazone (219) and studied their pharmacological activities. A metabolite of phenyl butazone, oxyphen butazone is clinically used as analgesic and anti-inflammatory drug [10].

![Fig. 4.2: 4-Butyl-1-(4-hydroxyphenyl)-2-phenylpyrazolidine-3,5-dione](image1)

L-β-Pyrazolylalanine (220) and γ-L-glutamyl-β-pyrazole-L-alanine are found in the seeds of many species of Cucurbitaceae (Dunnill and Fowden, 1965) [11].

![Fig. 4.3: 2-Amino-3-(1H-pyrazol-1-yl)propanoic acid](image2)

A tricyclic pyrazoles (221) have been found to possess antiarrhythmic and anti-inflammatory activities (Hamilton et al, 1976) [12].
Thiele et al., (1981) synthesized pyrazolidine diones (222) as xanthine oxidase inhibitor. In addition, they showed good analgesic and inflammation inhibitory activity [13].

Carl et al., (1991) reported the synthesis of 1-phenylpyrazolyl-4-heteroarylalkanoic acid (223). These compounds were found to possess anti-inflammatory activity [14].
A series of 4-(5-aryl-2-furfurylidine)-1,3-disubstituted-2-pyrazolin-5-ones (224) were prepared by Kalluraya et al., (1995). These compounds were evaluated for their antibacterial activity against Gram +ve and Gram -ve bacteria [15].

![Fig. 4.7: 4-(5-Aryl-2-furfurylidine)-1,3-disubstituted-2-pyrazolin-5-ones](image)

Kudo et al., (1999) synthesized series of 1,5-diaryl pyrazole carboxylates and carboxamides and investigated for their herbicidal activities against various kinds of weeds and found that 4-chloro-1-(2,5-difluorophenyl)-5-(4-fluorophenyl)-pyrazole-3-carboxylate (225) as a potent herbicidal agent [16].

![Fig. 4.8: Methyl 4-chloro-1-(2,5-difluorophenyl)-5-(4-fluorophenyl)-1H-pyrazole-3-carboxylate](image)

Duma et al., (2000) reported the synthesis of some new 1-phenyl-5-pyrazolyl urea derivative (226) and its selective P38 kinase inhibition properties [17].

![Fig. 4.9: 1-(3-Tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,3-dichlorophenyl)urea](image)
Biological activities of new series of 4-arylhydrazono-2-pyrazolin-5-ones (27) by Kucukguzel et al, (2000) revealed that the derivatives (227, 228) are very much active against Staphylococcus aureus [18].

Isloor et al, (2000) reported the synthesis of 3-aryl-4-(substituted pyrazolidine hydrazine-4-thiazolyl) sydnones (229) and its analgesic, anticonvulsant activities [19].

Tewari et al, (2001) reported the synthesis of pyrazolopyridazines from the pyrazolone derivative (Scheme-4.1) (Edaravone) and their anti-inflammatory activity against carragenin induced paw edema in albino rats [20].
Scheme- 4.1: Preparation of pyrazolopyridazines

Synthesis and antitumor activity of novel pyrimidinyl pyrazole derivatives (232) were reported by Naito et al, (2002) [21].

Fig. 4.12: Pyrimidinyl pyrazole derivative

Pyrazole (233) was synthesized by Finn et al, (2003) with significantly improved potency on bacterial methionyl-t-RNA synthetase and selectivity over human methionyl-t-RNA synthetase [22].

Fig. 4.13: Pyrazolo tetrazole derivative

Tanitame et al, (2004) initially reported a new class of pyrazole derivative 4-(5-(4-(benzyloxy)phenyl)-1H-pyrazol-3-yl)piperidine (234) represents a new class of bacterial DNA gyrase
inhibitors have potent antibacterial activity against *Staphylococcus aureus* and *Enterococcus faecalis*. They found that the one of the derivative 1-(3- Chlorophenyl)-5-(4-phenoxyphenyl)-3-(4-piperidyl) pyrazole (235) have the target related antibacterial activity and improved DNA gyrase inhibition [23].

**Fig. 4.14:** 4-(5-(4-(Benzoyloxy)phenyl)-1H-pyrazol-3-yl)piperidine derivative

The synthesis of novel series of structurally related 1*H*-pyrazolyl derivatives (236) described by the Bekhit and Aziem (2004). All the newly synthesized compounds were tested for their anti-inflammatory and antimicrobial activities. COX-1 and COX-2 inhibitory activities, ulcerogenic effects and acute toxicity were also determined [24].

**Fig. 4.15:** Structurally related 1*H*-pyrazolyl derivatives

Tanitame et al, (2005) reported the synthesis, antibacterial activity of 5-[(E)-2-arylvinyl] pyrazoles (237) and are found to be potent antibacterial activity against quinolone resistant clinical isolates of Gram-positive bacteria [25].
Aggarwal et al, (2006) reported the synthesis of new 1-heteroaryl-5-amino-3H-methyl-4-phenyl pyrazoles (238, 239) and screened for their antibacterial activity. These derivatives found to be either equipotent or more potent than the antibacterial agents Linezolid and Cefroxime axetil [26].

A series of pyrazole derivatives (240) via 1,3-dipolar addition of sydnone and nitrofuran acetylenic ketones were reported by Rai et al, (2006) [27].
Synthesis of several 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives (241) were prepared by reacting substituted 3-(2-thienyl)-5-aryl-1-thiocarbamoyl-2-pyrazolines with phenacyl bromides in ethanol is reported by Ozdemir et al, (2007). Newly synthesized compounds were screened for their antimicrobial activity [28].

![Chemical structure](image)

**Fig. 4.19:** 1-(4-Aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives

Kang et al, (2008) synthesized 3-tetrazole-1, 5-diaryl-4-methyl pyrazoles and examined their CB1 receptor binding ability, cannabinoid CB1 receptor antagonists. Few compounds (242, 243, 244) showed good binding affinity and selectivity for CB1 receptor (IC50 =11.6nM and CB2/CB1 = 366) [29].

![Chemical structures](image)

Where R¹ =Me, Et, n-Pr, i-Pr, n-Bu, t-Bu, n-Pentyl, n-Octyl, Ph, Benzyl, 2-Methylpyridine, 3-Methylpyridine, 4-Methylpyridine, 2-Methylfuran, 3-Methylfuran, 3-Methylthiophene, Cyclopropyl, Cyclobutyl, Cyclopentyl,
Fig. 4.20: 3-Tetrazole-1, 5-diaryl-4-methyl pyrazoles derivatives

Silvestri et al, (2008) studied the cannabinoid receptor affinity and molecular modelling studies of substituted 1-aryl-5-(1H-pyrrol-1-yl)-1H-pyrazole-3-carboxamides (245) and found that (246) was most selective ligand to hCB1 receptor [30].

Fig. 4.21: 1-Aryl-5-(1H-pyrrol-1-yl)-1H-pyrazole-3-carboxamides

Dhanya et al, (2009) reported the synthesis and anticancer activity of new 3,6-disubstituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles containing pyrazole moiety(247) [31].

Fig. 4.22: 6-(3-(4-Chlorophenyl)-1H-pyrazol-4-yl)-3-p-tolyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole

Isloor et al, (2009) reported the synthesis of Schiff and Mannich Bases containing pyrazole moiety. The newly synthesized compounds (248) were screened for their antibacterial and antifungal activity. Some of the compounds were found to exhibit significant antimicrobial activity [32].
Fig. 4.23: Oxadiazole-diarylpyrazole 4-carboxamides

Synthesis of pyrazoline derivatives bearing benzimidazoles (249) and its anticancer studies were reported by Shaharyar et al. (2010) [33].

Fig. 4.24: Pyrazoline derivatives bearing benzimidazoles

Sulfonamides are the best-known inhibitors of carbonic anhydrase enzyme, currently used for the treatment of glaucoma in clinical medicine. Kasimogullari et al. (2010) have reported pyrazole derivatives which contain sulfonamide (Scheme 4.2) group have more inhibition effects to CA-I and CA-II isoenzymes [34].
**Scheme 4.2:** Preparation of sulphonamide containing pyrazole derivatives

Singh *et al*, (2011) synthesized a series of 1-[(4, 5-dihydro-5-phenyl-3-(phenylamino) pyrazol-1-yl)] ethanone derivatives and evaluated for their anticonvulsant activity against electric shock induced convulsion method. Molecule (253) found to be the most potent compound among all the synthesized compounds [35].

**Fig. 4.25:** 1-(5-Phenyl-3-(phenylamino)-4,5-dihydropyrazol-1-yl)ethanone

Discovery of novel, potent, selective, and orally active human glucagon receptor antagonists containing a pyrazole core were reported by Shen *et al*, (2011). One of the synthesized compound (254) was selective and orally active in several *in vivo* preclinical models of type II diabetes [36].
Fig. 4.26: 3-(4-((3-(3,5-Dichlorophenyl)-5-(4-(trifluoromethoxy)phenyl)-1H-pyrazol-1-yl)methyl)benzamido)propanoic acid

A series of novel pyrazole pyrimidines (255) structurally related to kinase inhibitor AS703569 were prepared by Curtin et al., (2012). SAR work provided analogs with significant cellular activity, measureable aqueous solubility and moderate antitumor activity in a mouse tumor model after weekly ip dosing. Unfortunately these compounds were pan-kinase inhibitors that suffered from narrow therapeutic indices which prohibited their use as antitumor agents [37].

Fig. 4.27: Pyrazole pyrimidines

The design and synthesis of 4-alkynyl pyrazole derivatives (256) and their *invitro* PDE4B properties and molecular modelling studies of these compounds reported by Dhilli et al (2012) [38].

Fig. 4.28: 4-Alkynyl pyrazole derivatives
Patak et al, (2012) have reported the synthesis of 3-(4-chlorophenyl)-4-sustituted pyrazole derivatives (257) and studied their activity against *Mycobacterium tuberculosis* H37Rv strain. The results suggest that the compounds containing pyrazole moieties would be potential antitubercular agent [39].

![Fig. 4.29: 3-(4-Chlorophenyl)-4-sustituted pyrazole derivatives](image)

Compounds comprising a 1,2,4-oxadiazole backbone have a wide range of biological activities as discussed in detail in Chapter-III. As evident from the above discussions the inclusion of two bioactive motifs like pyrazole and oxadiazole into a single carbon skeleton may further enhance the biological activity. Keeping in view of these observations it was planned to synthesize pyrazoles containing 1,2,4-oxadiazole group and their pharmacological evaluation.

### 4.2. Results and discussions

Semicarbazone intermediate (259) was prepared by the reaction of different substituted acetophenones (258) with semicarbazide in the presence of sodium acetate in ethanol at 0°C [40]. Semicarbazone intermediate (259) was further cyclised and formylated using vilsmeier condition to get substituted pyrazole-3 aldehydes (260) [40]. Amidoxime intermediates (262) were prepared in good yields by treating corresponding nitriles (261) with hydroxylamine in reflux condition using Aqueous methanol as solvent [41]. Microwave irradiation of pyrazole aldehydes with amidoximes using dimethyl sulfoxide as solvent produced 1,2,4-oxadiazoles in 3 min (263 a-l). The synthetic strategy for preparation of the pyrazolo-oxadiazoles is depicted in (Scheme-4.3).
Scheme 4.3: Preparation of (1H-Pyrazol-3-yl)-1,2,4-oxadiazole derivatives 263(a-l)

Proposed mechanism for the synthesis 1H-Pyrazole-3-aldehyde

136
The resulting compounds were confirmed with the NMR, Mass and IR spectroscopy. Formation of aldehydes (260) was confirmed by aldehydes peak at 9.87 in $^1$H NMR and by checking the DNP activity in TLC plate. The characterization data of aldehydes intermediates is mentioned in Table-4.2.

**Table-4.2: Characterization data of Aldehydes (260a, 260c, 260g, 260j)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>M.P (°C)</th>
<th>Molecular formula</th>
<th>Mol wt</th>
<th>M+, m/z</th>
<th>$^1$H NMR(δ, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>260a, R= 4-Methyl</td>
<td>60%</td>
<td>123-125</td>
<td>C$<em>{11}$H$</em>{10}$N$_2$O</td>
<td>186.2</td>
<td>187.2</td>
<td>2.40 (s, 3H, CH$_3$), 7.29 (d, 2H, 2CH), 7.67 (d, 2H, 2CH), 8.00-8.40 (d, 1H, CHN), 9.87 s (1H, CHO), 13.63 (s, 1H, NH)</td>
</tr>
<tr>
<td>260c, R= 3-Methoxy</td>
<td>40</td>
<td>158-160</td>
<td>C$<em>{11}$H$</em>{10}$N$_2$O$_2$</td>
<td>202.2</td>
<td>203</td>
<td>3.77 (s, 3H, OCH$_3$), 7.10 (d, 1H, CH), 7.42 (m, 2H, 2CH), 7.55 (t, 1H, CH), 8.34 (d, 1H, CHN), 9.90 (s, 1H, CHO), 13.81 (s, 1H, NH)</td>
</tr>
<tr>
<td>260g, R= 4-Chloro</td>
<td>34</td>
<td>142-144</td>
<td>C$_{10}$H$_7$ClN$_2$O$_2$</td>
<td>206.6</td>
<td>207.6</td>
<td>7.45 (d, 2H, 2CH), 7.89 (d, 2H, 2CH), 8.12 and 8.40 (s, 1H, CHN), 9.91 (s, 1H, CHO), 13.60 (s, 1H, NH)</td>
</tr>
<tr>
<td>260j, R= 4-Trifluoromethyl</td>
<td>40</td>
<td>172-174</td>
<td>C$_{11}$H$_7$F$_3$N$_2$O$_2$</td>
<td>240.1</td>
<td>241.1</td>
<td>7.30 (d, 2H, 2CH), 7.90 (d, 2H, 2CH), 8.22 and 8.40 (d, 1H, CHN), 9.90 (s, 1H, CHO), 13.60 (s, 1H, NH)</td>
</tr>
</tbody>
</table>
Pyrazolo-oxadiazoles **260 (a-l)** confirmed by $^1$H NMR, $^{13}$C NMR, Mass and IR spectral studies. Presence of pyrazole –CH at δ 7.2-7.6 and appearance of C=N peak at 1599 cm$^{-1}$ in IR spectrum indicates the formation of oxadiazole. For example in case of compound **260h** IR peaks at 1598 (C=N), 1545 (N-O), 1285 (C-O) cm$^{-1}$ confirms the oxadiazole and nitro functional groups. In $^1$H NMR a singlet peak at δ 7.63 indicates the pyrazole –CH, para pattern observed at δ 8.24, 8.40 indicates nitrophenyl group. In $^{13}$C NMR peaks at δ 167.2, 160.0, indicates the oxadiazole carbons. Similarly in LCMS, m/z = 364.1 confirms the molecular weight of the compound.

4.3. Synthesis

4.3.1. General procedures

4.3.1.1. General procedure for preparation of semicarbazones (**259 a-l**)

To a stirred solution of acetophenones (**258**) (1 mmol) in ethanol (5 ml) and water (10 ml) was added sodium acetate (2.5 mmol) at 0°C. Reaction mixture stirred at 0-310°C for 4 hours. Solid separated was filtered off washed with cold water and suck dried.

4.3.1.2. General procedure for preparation of pyrazole-3-aldehydes (**260 a-l**)

Phosporousoxychloride (2 mmol) was added drop-wise to DMF (10 ml) at 0 °C and stirred at same temperature for 30 min. Semicarbazone (**259**) (1 mmol) was added portion wise at 0 °C, the reaction mixture was heated to 60°C for 4 hours, and poured into crushed ice. The reaction mixture was then neutralised with 10 % sodium hydroxide solution, and heated to 60 °C for 5 min, cooled to 0°C and neutralised using 11N hydrochloric acid. Extracted with ethyl acetate, combined organic layer washed with water, brine and concentrated to get crude aldehyde, which was recrystalised using ethyl acetate and hexane to get pure product.

4.3.1.3. General procedure for preparation of Amidoximes (**262 a-l**)
To stirred solution of carbonitrile compound (261) (1 mmol) in methanol (10 ml) was added hydroxylamine hydrochloride (2.0 mmol) and triethylamine (3 mmol) at 0 °C. Reaction mixture was heated to reflux for 8 hours; mass analysis of reaction mixture confirms completion of reaction. Reaction mixture was cooled to room temperature, diluted with water (100 ml), solid separated was filtered, dried to get pure compound as yellow solid.

4.3.1.4. General procedure for preparation of 5-(4-phenyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole derivatives (263 a-l)

To a mixture of Pyrazole aldehydes (260) (1 mmol) and amidoximes (262) (1 mmol) was added DMSO (2 mL) and resulting paste was irradiated in microwave synthesis system at 120W power and 100 °C temperature for 3 minutes. Mass analysis of crude reaction mixture confirms the completion of reaction. Reaction mixture was poured to water extracted with ethylacetate, washed with brine solution and concentrated to get crude product. Crude product was purified by column chromatography using 5-15% of methanol in dichloromethane as eluent.

4.4. Characterization

4.4.1. Experimental data

4.4.1.1. 3-Phenyl-5-(4-p-tolyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (263a)

Yield 75 %, Off white solid, M. p. 128-120 °C, IR (KBr, \( \nu_{\text{max}} \) cm\(^{-1} \)): 3143 (N=H),  3080 (C-H), 1599 (C=N), 1284 (C-O). \(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \( \delta \) (ppm): 2.2 (s, 1H, CH\(_3\)), 7.20 (d, 2H, Ar-H, J = 8 Hz), 7.33 (m, 2H, Ar-H), 7.48 (m, 2H, Ar-H), 8.4 (m, 4H, Ar-H). \(^13\)C NMR (75 MHz, DMSO-d\(_6\)) \( \delta \) (ppm): 166.2, 160.8, 150.9, 140.3, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 126.0, 121.5, 116.2, 98.0, 27.2. MS: m/z = 303.2 (M+1). Anal. calcd. for C\(_{18}\)H\(_{14}\)N\(_4\)O: 71.51; H, 4.67; N, 18.53. Found: 71.41; H, 4.63; N, 18.50.

4.4.1.2. 3-(4-Chlorophenyl)-5-(4-p-tolyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (263b)
Yield 66 %, Off white solid, M. p. 138-140 °C, IR (KBr, ν max cm⁻¹): 3141 (N-H), 3080 (C-H), 1597 (C=N), 1284 (C-O). ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 2.3 (s, 1H, CH₃), 7.20 (d, 2H, Ar-H, J = 8 Hz), 7.33 (m, 2H, Ar-H), 7.48 (m, 2H, Ar-H), 8.58 (m, 4H, Ar-H). ¹³C NMR (75 MHz, DMSO-d₆) δ (ppm): 166.2, 161.8, 150.9, 140.3, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 126.0, 121.5, 116.2, 98.0, 27.2. MS: m/z = 338.7 (M+1). Anal. calcd. for C₁₈H₁₃ClN₄O: C, 64.19; H, 3.89; N, 16.64. Found: C, 64.39; H, 3.89; N, 16.54.

4.4.1.3. 3-(4-Chlorophenyl)-5-(4-(3-methoxyphenyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (263c)

Yield 63 %, Off white solid, M. p. 135-137 °C, IR (KBr, ν max cm⁻¹): 3138 (N-H), 3070 (C-H), 1589 (C=N), 1283 (C-O). ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 3.7 (s, 1H, -OCH₃), 7.10 (d, 2H, Ar-H, J = 8 Hz), 7.23 (m, 2H, Ar-H), 7.38 (m, 2H, Ar-H), 8.18 (m, 4H, Ar-H). ¹³C NMR (75 MHz, DMSO-d₆) δ (ppm): 166.2, 161.8, 150.1, 140.3, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 126.0, 121.5, 116.2, 98.0, 57.2. MS: m/z = 354.0 (M+1). Anal. calcd. for C₁₈H₁₃ClN₄O: C, 64.28; H, 3.90; N, 16.66. Found C, 61.28; H, 3.68; N, 15.86.

4.4.1.4. 3-(4-Fluorophenyl)-5-(4-(3-methoxyphenyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (263d)

Yield 69 %, Off white solid, M. p. 142-144 °C, IR (KBr, ν max cm⁻¹): 3137 (N-H), 3060 (C-H), 1599 (C=N), 1285 (C-O), 1102 (N-H). ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 6.93 (d, 2H, Ar-H, J = 8 Hz), 7.03 (m, 2H, Ar-H), 7.38 (m, 4H, Ar-H), 8.18 (m, 2H, Ar-H). ¹³C NMR (75 MHz, DMSO-d₆) δ (ppm): 166.5, 161.1, 152.0, 151.1, 140.3, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 126.0, 121.5, 116.5, 98.0, 57.0. MS: m/z = 337.32 (M+1). Anal. calcd. for C₁₈H₁₃FN₄O₂: C, 64.28; H, 3.90; N, 16.66. Found C, 64.28; H, 3.94; N, 16.56.

4.4.1.5. 3-(4-Methoxyphenyl)-5-(4-p-tolyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (263e)

Yield 74 %, White solid, M. p. 137-139 °C, IR (KBr, ν max cm⁻¹): 3139 (N-H), 3080 (C-H), 1598 (C=N), 1285 (C-O), 1100 (N-H). ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 2.3 (s, 1H, CH₃), 3.7 (s, 1H,
-OCH₃), 6.93 (d, 2H, Ar-H, J = 8 Hz), 7.13 (d, 2H, Ar-H), 7.38 (m, 4H, Ar-H), 8.18 (m, 2H, Ar-H). ¹³C NMR (75 MHz, DMSO-d₆) δ (ppm): 166.2, 161.8, 150.9, 140.3, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 121.5, 116.2, 98.0, 57.2, 27.1. MS: m/z = 333.36 (M+1). Anal. calcd. for C₁₉H₁₆N₄O₂: C, 68.66; H, 4.85; N, 16.86. Found C, 68.59; H, 4.75; N, 16.56.

4.4.1.6. 3-(2-Bromo-4-chlorophenyl)-5-(4-p-tolyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (263f)
Yield 74 %, White solid, M. p. 141-143 °C, IR (KBr, νmax cm⁻¹): 3140 (N₃H), 3080 (C₃H), 1596 (C=N), 1285 (C=O). ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 2.3 (s, 1H, CH₃), 7.13 (d, 2H, Ar-H), 7.38-7.50 (m, 4H, Ar-H), 8.18 (m, 2H, Ar-H). ¹³C NMR (75 MHz, DMSO-d₆) δ (ppm): 166.5, 161.8, 150.9, 140.3, 134.2, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 126.0, 121.5, 116.2, 98.0, 27.2. MS: m/z = 417.67 (M+2). Anal. calcd. for C₁₈H₁₂BrClN₄O: C, 52.01; H, 2.91, N, 13.48. Found C, 52.23; H, 2.87, N, 13.44.

4.4.1.7. 5-(4-(4-Chlorophenyl)-1H-pyrazol-3-yl)-3-(2,4-dichlorophenyl)-1,2,4-oxadiazole (263g)
Yield 59 %, Off white solid, M. p. 134-136 °C, IR (KBr, νmax cm⁻¹): 3140 (N₃H), 3080 (C₃H), 1596 (C=N), 1285 (C=O). ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 7.13-7.36 (m, 5H, Ar-H), 7.38 (d, 2H, Ar-H), 8.18 (m, 2H, Ar-H). ¹³C NMR (75 MHz, DMSO-d₆) δ (ppm): 166.2, 161.8, 150.9, 140.3, 134.2, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 126.0, 121.5, 116.1. MS: m/z = 392.64 (M+1). Anal. calcd. for C₁₇H₁₂Cl₃N₄O: C, 52.14; H, 2.32; N, 14.31. Found C, 52.17; H, 2.35; N, 14.24.

4.4.1.8. 5-(4-(3-Methoxyphenyl)-1H-pyrazol-3-yl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (263h)
Yield 62 %, Yellow solid, M. p. 151-153 °C, IR (KBr, νmax cm⁻¹): 3141 (N₃H), 3094 (C₃H), 1598 (C=N), 1545 (N-O), 1285 (C=O). ¹H NMR (75 MHz, DMSO-d₆) δ (ppm): 3.9 (s, 1H, -OMe), 7.20 (d, 1H, Ar-H), 7.52 (m, 1H, Ar-H), 7.63 (s, 1H, Py-H), 7.82 (m, 1H, Ar-H), 8.24 (d, 2H, Ar-H), 8.40 (d, 2H, Ar-H). ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 167.2, 160.0, 150.1, 134.6, 131.4, 129.0, 124.9,
124.7, 120.8, 120.2, 113.0, 56.0. MS: m/z = 364.1 (M+1). Anal. calcd. for C_{18}H_{13}N_{5}O_{4}: C, 59.50; H, 3.61; N, 19.28. Found C, 59.53; H, 3.61; N, 19.34.

4.4.1.9. 3-(3-Methoxyphenyl)-5-(4-p-tolyl-1H-pyrazol-3-yl)-1,2,4-oxadiazole (263i)

Yield 69 %, Off white solid, M. p. 135-137 °C, IR (KBr, v_{max} cm^{-1}): 3145 (N-H), 3080 (C-H), 1599 (C=N), 1285 (C-O). $^1$H NMR (300 MHz, DMSO-d$_6$) δ (ppm): 2.3 (s, 1H, CH$_3$), 3.7 (s, 1H, -OCH$_3$), 6.93 (d, 2H, Ar-H, J = 8 Hz), 7.13 (d, 2H, Ar-H), 7.38 (m, 4H, Ar-H), 8.18 (m, 2H, Ar-H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ (ppm): 166.0, 161.8, 150.1, 140.3, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 126.0, 121.5, 116.2, 98.0. MS: m/z = 333.36 (M+1). Anal. calcd. C$_{19}$H$_{16}$N$_4$O$_4$: C, 68.66; H, 4.85; N, 16.86. Found C, 68.69; H, 4.75; N, 15.86.

4.4.1.10. 3-(4-Fluorophenyl)-5-(4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazole (263j)

Yield 55 %, Off white solid, M. p. 128-130 °C, IR (KBr, v_{max} cm^{-1}): 3143 (N-H), 3080 (C-H), 1595 (C=N), 1285 (C-O). $^1$H NMR (300 MHz, DMSO-d$_6$) δ (ppm): 7.03 (d, 2H, Ar-H, J = 8 Hz), 7.43 (d, 2H, Ar-H), 7.48-7.60 (m, 4H, Ar-H), 8.18 (m, 2H, Ar-H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ (ppm): 166.3, 161.2, 150.9, 140.3, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 126.0, 121.5, 116.2, 98.0. MS: m/z = 375.29 (M+1). Anal. calcd. C$_{18}$H$_{10}$F$_4$N$_4$O: C, 57.76; H, 2.69 N, 14.97. Found C, 57.86; H, 2.58, N, 14.99.

4.4.1.11. N,N-Dimethyl-4-(5-(4-(4-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)benzenamine (263k)

Yield 56 %, Off white solid, M. p. 130-135 °C, IR (KBr, v_{max} cm^{-1}): 3140 (N-H), 3080 (C-H), 1596 (C=N), 1282 (C-O). $^1$H NMR (300 MHz, DMSO-d$_6$) δ (ppm): 2.85 (s, 6H), 6.8 (d, 2H, Ar-H, J = 8 Hz), 7.33-7.45 (m, 4H, Ar-H), 7.51-7.60 (m, 2H, Ar-H), 8.18 (m, 2H, Ar-H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ (ppm): 166.3, 161.8, 150.1, 140.3, 132.8, 131.3, 131.0, 130.6, 129.1, 127.1, 126.0, 121.5,
116.2, 98.0, 40.3. MS: m/z = 400.37 (M+1). Anal. calcd. C_{20}H_{16}F_3N_5O: C, 60.15; H, 4.04; 17.54. Found C, 57.86; H, 2.58, N, 14.99.

4.4.1.12. 4-(5-(4-p-Tolyl-1H-pyrazol-3-yl)-1,2,4-oxadiazol-3-yl)morpholine (2631)

Yield 50 %, Gummy liquid, IR (KBr, \(\nu_{\text{max}}\) cm\(^{-1}\)): 3141 (N\(\equiv\)H), 3080 (C-H), 1599 (C=N), 1285 (C-O). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 2.9 (bs, 4H, -NCH\(_2\)), 3.62 (bs, 4H, -OCH\(_2\)), 7.12 (d, 2H, Ar-H), 7.36 (m, 3H, Ar-H), 8.18 (bs, 1H, NH). \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 166.2, 161.1, 150.3, 140.4, 131.8, 131.3, 130.6, 129.51, 127.1, 126.0, 116.2, 67.2, 46.0, 24.3. MS: m/z = 312.34 (M+1). Anal. Calcd C\(_{16}\)H\(_{17}\)N\(_5\)O\(_2\): C, 61.72; H, 5.50; N, 22.49. Found C, 61.66; H, 5.50; N, 22.49.
4.3.2. Spectral data

Fig. 4.30: $^1$H NMR Spectrum of compound 263h
Fig. 4.31: $^{13}$C NMR Spectrum of compound 263h
263h
C_{16}H_{13}N_{5}O_{4}
Mol. Wt.: 363.33

[Chemical structure image]

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Mol. Wt.: 363.33
4.5. Conclusion

A series of novel (1H-pyrazol-3-yl)-1, 2, 4-oxadiazole derivatives were synthesized by microwave irradiation in reasonably good yields. They were characterized by $^1$H NMR, $^{13}$C NMR, mass spectrometry, IR studies and elemental analyses. All the newly synthesized compounds were screened for antibacterial activity by MIC method. The structural activity relationship (SAR) and antimicrobial activity of the entire compound are discussed in CHAPTER 6.
4.6. References


