Synthesis, Evaluation & Pharmacological action of Oxadiazole derivatives

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Abstract
Impacted numerous drug discovery programs including-muscarinic antagonists, benzodiazepine receptor partial agonists, Dopamine transporters, antihivirals, growth hormone secretagogues, 5-HT antagonists, antispasmodics. Heterocyclic compounds possess diverse biological properties that have led to intense study and research of these compounds. One of these compounds is Oxadiazole which has been found to exhibit various pharmacological activities. 1, 3, 4-oxadiazole having heterocyclic nucleus is a novel molecule which attract the chemist to search for a new therapeutic molecule. 1,3,4-oxadiazole exhibited a wide range of biological activities which includes antibacterial, anti-tubercular, anticonvulsant, hypoglycemic, anti-allergic, enzyme inhibitor, vasodialatory, antifungal, cytotoxic, anti-inflammatory, analgesic, hypolipidemic, anticancer, insecticidal, ulcerogenic activities etc. Out of the various derivative 2, 5-Disubstituted-1, 3, 4-oxadiazole is a widely exploited for various application. A large number of drugs used clinically have oxadiazole ring as a structural building block. The capacity of 1,3,4-oxadiazole nucleus to undergo variety of chemical reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical which make it medicinal backbone on which a number of potential molecules can be constructed. This review has basic information about 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives published in various journals for further development in the field. Oxadiazole derivatives are a class of heterocyclic compounds. The titled compounds were synthesized according to the procedures as given in the methodology. The reactions were monitored by TLC. The physical constants like melting point and solubility were determined for all the intermediates and final products. The compounds were further characterized by IR and 1H NMR and mass spectra. All the titled compounds were evaluated for their Anticonvulsant, Anti-inflammatory, Antibacterial, Anti-tubercular and Antioxidant activity.

Keywords: 1, 3, 4-oxadiazoles, antibacterial, antimicrobial, anti-tubercular, anti-inflammatory, antioxidant

1. Introduction
The chemistry of heterocyclic compounds is an interesting field of study since a long time. Oxadiazole is a cyclic compound having one oxygen and two nitrogen atoms in a five member ring [1]. Oxadiazoles have occupied a specific place in the field of medicinal chemistry due to its wide range of activities [2]. From the existing literature we can see that 1, 3, 4-Oxadiazole nucleus has been possessing antimicrobial [3], antifungal [4], anti-inflammatory [5], anticonvulsant [6], antioxidant, analgesic [7], antitubercular [8] and mutagenic activity [9]. One pot synthesis of 1, 3, 4-oxadiazoles has been reported by the reaction of appropriate hydrazide and carboxylic acid [10]. Derivatives of oxadiazole are used in the market such as Tiodazos in, Nosapidil, and Furamizole [11]. The present review attempts to summarize some pharmacological activities of 2, 5-disubstituted 1, 3, 4-oxadiazole.

2. Antimicrobial activity
Ajaykumar TV et al., synthesized some new 3-acetyl-5-(3-chloro-1-benzo[b]thiophen-2-yl)-2-substituted phenyl-2, 3-dihydro-1, 3, 4-oxadiazoles and 2-(3-chloro-1- benzob[b]thiophen-2-yl)-5-substituted phenyl-1,3,4 oxadiazoles derivatives. All the newly synthesized compounds are evaluated for antimicrobial activity against Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa and for antifungal activity against Candida albicans and Aspergillus niger. The compounds showed significant antibacterial and moderate antifungal activities. Compounds 4c and 4e were found to be most potent against Staphylococcus aureus and Bacillus subtilis when compared with standard drug ciprofloxacin [12].
S. Kumar synthesized a new series 1-(2-aryl-5-phenethyl-1, 3, 4-oxadiazole-3(2H)-yl)-ethanones and found to exhibit good antibacterial and antifungal activity. These newly synthesized compounds were shown the maximum activity against the strains of micro-organisms Staphylococcus aureus and Pseudomonas aeruginosa [13].

1, 3, 4-oxadiazole derivatives were obtained from aromatic aldehyde and acetic anhydride and POCl₃ by Glory Mathew et al. All the synthesized compounds showed significant analgesic, anti-inflammatory, anti-bacterial and anti-tubercular activities. But compound 1a and 1b was found to possess better activity then others [14].

Fig 2: 1, 3, 4-oxadiazole (1a and 1b)

A series of 2, 5-disubstituted-1, 3, 4-oxadiazoles were prepared by Hemavathi SN et al., which contain pyridine and piperidine ring. These synthesized compounds have been found to be potent antibacterial [15].

3, 5-bis(5-(furan-2-yl)-1, 3, 4-oxadiazol-2-yl)azodyes were Synthesized by Palak K et al. The newly synthesized azodye fused with (5-(furan-2-yl)-1, 3, 4-oxadiazole) were screened for their in-vitro anti-microbial activity. The antimicrobial activity of the test compounds were screened against bacterial strains belonging of Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis and Escherichia coli and fungal strains Candida albicans and Candida parapsilosis respectively. Synthesized compounds exhibit significant biological activity [16].

Fig 3: 3, 5-bis(5-(furan-2-yl)-1, 3, 4-oxadiazol-2-yl)azo dyes

A series of 2-[5-(substituted sulfanyl)-1, 3, 4-oxadiazol-2-yl]phenol derivatives were prepared by Arun KW by condensation reaction between 2-hydroxybenzohydrazine and carbon disulfide. The in-vitro antibacterial activity of synthesized compound was tested against Gram positive bacteria viz. Staphylococcus aureus ATCC 9144, Bacillus subtilis ATCC 6633 and Pseudomonas aeruginosa MTCC1688, Gram negative bacteria viz., Escherichia coli ATCC 25922 and antifungal activity was tested against Candida albicans. All the compounds showed good activity against all cultures [17].

Shridhar AH et al. Synthesized a new series of 2, 5-disubstituted-1, 3, 4-oxadiazoles by reaction of nicotinic acid hydrizide with various substituted aromatic acids in presence of POCl₃. Some of the synthesized compounds showed very good antifungal activity when compared to standard. Antibacterial activity was carried out against Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli and Bacillus subtilis at a concentration of 100µg/ml. The standard drug used was Ampicillin and DMF was kept as solvent control. The antifungal studies were carried out against fungus Candida albicans and Aspergillusniger using Griseofulvin as standard [18].

Fig 4: 2-[5-(substituted sulfanyl)-1, 3, 4-oxadiazol-2-yl]phenol derivatives

The synthesis of 1-[5-(sustituted-1, 3, 4-oxadiazol-2-yl) methyl]-4-benzylperazines was carried out by Sudhir Bhardwaj et al. All the title compounds were screened for their antibacterial activity against Staphylococcus aureus, Escherichia coli, Bacillus subtilis and Pseudomonas vulgaris. One compound showed highest activity (figure-6) [19].

Fig 5: 2, 5-disubstituted-1, 3, 4-oxadiazoles

Some 2-[5-(aryl)-1, 3, 4-oxadiazole-2-ylsulfanyl]alkanoic acids were synthesized and screened for their antibacterial activity by Mudasir RB et al. All the compounds were studied for their in-vitro antibacterial activity against two Gram negative strains such as Escherichia coli and Pseudomonas aeruginosa and two Gram positive strains like Bacillus subtilis and Staphylococcus aureus and their Minimum Inhibitory Concentration (MIC) were determined. Ciprofloxacin was used as a standard drug [20].

Fig 6: 1-[5-(substituted-1, 3, 4-oxadiazol-2-yl) methyl]-4-benzylperazines

A series of 3-[1(3, 4-oxadiazole-2-yl)-quinazolin-4(3H)-ones were synthesized by Patel NB et al., and screened for their in-vitro antimicrobial activity against Gram positive bacteria Staphylococcus aureus and Gram negative bacteria Escherichia coli. The synthesized compounds are found to be potent antibacterial [21].

Fig 7: 2-[5-(aryl)-1, 3, 4-oxadiazole-2-ylsulfanyl]alkanoic acids

A series of 3-[1(3, 4-oxadiazole-2-yl)-quinazolin-4(3H)-ones

Fig 8: 3-[1(3, 4-oxadiazole-2-yl)-quinazolin-4(3H)-ones
Ravitas Deshmukh et al., synthesized a series of new 1, 3, 4-oxadiazole derivatives having 6-bromonaphthalene moiety. The oxadiazole derivatives as potential antimicrobial agents. The抗菌ulant activity against Staphylococcus aureus using tetracycline as the standard. Some compounds were antibacterial against Staphylococcus aureus, Streptococcus pyogenes, Gram-ve organisms such as Escherichia coli, Klebsiella aerogenes and Candida albicans. Amikacin and ketoconazole (10µg/ml) were used as reference standard for antibacterial and antifungal activity respectively. Three compounds showed moderate antibacterial and antifungal activities at a concentration of 100µg/ml.

Fig 9: 1, 3, 4-oxadiazole derivatives having 6-bromonaphthalene moiety

Anil MM et al., prepared a series of 5-(2-aminophenyl)-1, 3, 4-oxadiazole-2(3H)-thione derivatives by Mannich reaction. In vitro anti-microbial activity of all newly synthesized compounds was evaluated against Gram +ve organisms such as Staphylococcus aureus, Streptococcus pyogenes, Gram –ve organisms such as Escherichia coli, Klebsiella aerogenes and fungus such as Candida albicans. Amikacin and ketoconazole (10µg/ml) were used as reference standard for antibacterial and antifungal activity respectively. Three compounds showed moderate antibacterial and antifungal activities at a concentration of 100µg/ml.

Fig 10: 5-(2-aminophenyl)-1, 3, 4-oxadiazole-2(3H)-thione derivates

New 5-alkyl and 3-(2,4-dimethylphenyl)-substituted-1, 3, 4-oxadiazole-2-thione derivatives were synthesized by Rakesh Chawla et al. Mannich bases for some of these compounds were also synthesized by condensation with benzaldehyde and primary amines. All new compounds were tested for their antibacterial against Staphylococcus aureus using tetracycline as the standard. Some compounds were found to be most effective antibacterial.

Fig 11: 5-alkyl and 3-(2, 4-dimethylphenyl)-substituted-1, 3, 4-oxadiazole-2-thione derivatives

Jha KK et al. synthesized 1, 3, 4-oxadiazole derivatives. The synthesized compounds were evaluated for their antimicrobial activity against Escherichia coli, Staphylococcus aureus and Staphylococcus epidermidis and found to be most potent. Kantham Srinivas et al., investigated four 1, 3, 4-bis-oxadiazole derivatives as potential antimicrobial agents. The compounds are: 5, 5’-dimercapto-bis-[1, 3, 4-oxadiazol-2-yl]propane (2a), 5, 5’-dimercapto-bis-[1, 3, 4-oxadiazol-2-yl]butane (2b), 5, 5’-dimercapto-bis-[1, 3, 4-oxadiazol-2-yl]octane (2c) and 5, 5’-dibenzythio-bis-[1, 3, 4-oxadiazol-2-yl]butane. The newly synthesized compounds were investigated for their antibacterial and antifungal activities. The results revealed that the compounds 2a-c exhibited both antibacterial and antifungal activities against Staphylococcus aureus and Bacillus subtilis. Compound 2a also showed activity against Pseudomonas aeruginosa. All the above compounds and compound 3 exhibited activity against Candida albicans.

Fig 12: 1, 3, 4-bis-oxadiazole derivatives

Various new 2-Amino-5-(substituted)phenyl-1, 3, 4-Oxadiazole derivatives were synthesized by Manish Srivastava et al. The synthesized compounds were evaluated for their antimicrobial properties against Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa, Candida albicans, Norfloxacin was used for comparison with antibacterial activity. Microwave assisted as well as conventional synthesis of 5-substituted-2-(2-methyl-4-nitro-1-imidazomethyl)-1, 3, 4-oxadiazoles containing the nitroimidazole moiety is carried out by Manish KM et al., and tested for their antibacterial and antifungal activity. Studies on the antibacterial activity of synthesized compounds proved it to be more effective against four pathogenic organisms, viz., Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli and Pseudomonasaeruginosa.

Fig 13: 5-substituted-2-(2-methyl-4-nitro-1-imidazomethyl)-1, 3, 4-oxadiazoles containing the nitroimidazole moiety

Disubstituted 1, 3, 4-oxadiazoles, Mannich bases and S-alkylated derivatives have been synthesized from 2-(aryloxy-methyl)-benzoic acids through a multi-step reaction sequence by Channamata SN. All the synthesized compounds were screened for their in-vitro antibacterial and antifungal activity and some of them exhibited good activity. Jumat Salimon et al., synthesized 6-Methyl-4-aryl-5-(5-phenyl-1, 3, 4-oxadiazol-2-yl)-1, 2, 3, 4-tetrahydroxypyrimidine-2(1H)-one derivatives. Compound 3 has significant effect against Streptococcus pneumonia and Escherichia coli. A series of 2, 2’-(5-nitrobenzene-1, 3-diy1)bis(5-alkyl-1, 3, 4-oxadiazole), 5, 5’-(5-nitrobenzene-1, 3-diy1)bis(1, 3, 4-oxadiazole) derivatives have been synthesized and evaluated.
oxadiazole-2-thiol) and 5, 5'-(5-nitrobenzene-1, 3-diyl)bis(4-amino-4H-1, 2, 4-triazole-3-thiol were obtained via reaction of 5-nitroso-phthalic dihydrazide by Kantham Srinivas et al. All these newly synthesized compounds were displayed potent antibacterial activity [31].

A series of 2-(3, 4, 5-trihydroxyphenyl)-5-aryl-1, 3, 4-oxadiazole was synthesized by Jain et al. All the synthesized compounds were subjected to antimicrobial and anti-fungal activity. Antimicrobial activity was carried out against Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae and Staphylococcus aureus at a concentration of 100μg/ml. Streptomycin was used as standard. Anti-fungal activity was performed against Aspergillus niger with test compounds at a concentration of 100μg/ml. Ketaconazole was the standard drug [32].

A series of novel 5-aryl-2-[N, N-di-substituted-thiocarbamoylthio]-calamine]-1, 3, 4-oxadiazole derivatives were synthesized by R. Saini et al., and screened for their antimicrobial activity against various micro-organism such as Staphylococcus aureus, Staphylococcus epidermidis. The synthesized compound possesses high antimicrobial activity [36].

A series of 2-(Phenyl substituted)-5-indole-1, 3, 4-oxadiazole derivatives were prepared by Niti Bhardwaj et al. Three compounds were found effective against bacterial strains at a much higher concentration and none of the synthesized compound was found effective against fungal strain. Norfloxacin and Fluconazole were used as standard drugs for antibacterial and anti-fungal activities respectively [37]. Mojahidul Islam et al., studied anti-bacterial and anti-fungal activity of a series of five new 1-(2-aryl-5-phenethyl-1, 3, 4-oxadiazol-3-(2H)-yl)ethanones. Among the newly synthesized compounds, 1-(2-(4-(dimethylamino)phenyl)-5-phenethyl-1, 3, 4-oxadiazol-3(2H)-yl)ethanone and 1-(2-(4-chlorophenyl)-5-phenethyl-1, 3, 4-oxadiazol-3(2H)-yl)ethanone were found to possess maximum activity against the tested strains of Staphylococcus aureus and Pseudomonas aeruginosa [38].

ZuhairMuhi-eldene et al. synthesized a series of N-substituted-aryl-1, 3, 4-oxadiazole-2(yl) methyl-N-(4H-1,2,4-triazol-4-yl) benzamide derivatives. Antimicrobial and antifungal activities of the final compounds have been evaluated and all the compounds have shown significant inhibition of bacterial and fungal growth [39]. Shahar Yar M et al. Synthesized (ethyl-2-(1H) Benzo[fd][1, 2, 3triazole–1-yl]acetate) and (2H–benzo[d][1, 2, 3] triazole–1–yl-acetohydrazine) derivatives. The antimicrobial activity of the synthesized compounds was evaluated, on Staphylococcus aureus and Escherichia coli. Ofloxacin was used as standard in a concentration of 30μg/disc. One compound (figure) showed maximum activity was found in against Staphylococcus aureus [40].

Alkyl, alklenyl, sulfonl, thiocarbamates and Mannich derivatives were synthesized Priya VF et al. The most
promising compound as antibacterial agent was 5-(pyridyl)-1, 3, 4-oxadiazole-2-benzylthiocarbamates [40].

The series of several new 5-[4’-(5-phenyl-1, 3, 4-oxadiazole-2-yl-sulfonylmethyl)-biphenyl-2-yl]-tetrazole derivatives were synthesized by Chao Jun-Shiu et al., and these compound screened for their antimicrobial activity against Bacillus subtilis and Escherichia coli at the concentration of 100µg/ml. These compounds showed a better inhibitory of this bacterial growth [43].

Feray Aydogan synthesized a series of novel 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives were synthesized and tested for their in vitro antimycobacterial activity. Some compounds showed interesting activity of greater than 90% inhibition against a strain of Mycobacterium tuberculosis H37Rv [43].

Ahmed OM et al., prepared a series of 5-[3’-oxo-6’-(substituted-aryl)-2’, 3’, 4’, 5’-tetrahydropyridazini-2-ylmethyl]-2-substituted-1, 3, 4-oxadiazole. All the final compounds were screened for antibacterial and antifungal activity. All the compounds are evaluated for their antibacterial activity against Escherichia coli, Staphylococcus aureus, Micrococcus luteus and Klebsiella pneumonia and antifungal activity against Candida albicans and C. neoformans at 100µg/ml concentration. The zone of inhibition of each compound was determined and compared with standard drug fluconazole [44].

A novel series of 5-[substituted-(1, 1-biphenyl)-3-yl]-1, 3, 4-oxadiazole-2(3H)-thiones and its 5-alkyl derivatives were synthesized by Aatesh OE et al. All the synthesized compounds were screened for their antimicrobial activity against various bacterial strains namely Staphylococcus aureus and Pseudomonas aeruginosa. The compounds exhibited good antimicrobial activity [45].

3. Anti-inflammatory activity
Singh AK synthesized a new series of 1-(2’, 4’-chloroacridine-9’yl)-3-(5’-pyridine-4-yl)-(1, 3, 4-oxadiazole-2-yl-thiomethyl)-pyrazole-5-one derivatives. The all new synthesized compounds were evaluated for their anti-inflammatory activity. The reference drugs used was phenylbutazone and aspirin. The compounds possess high activity as compared with standard [46].

A novel series of 2-(2-naphthoxy-methyl)-5-substitutedamino-1, 3, 4-oxadiazole derivatives has been synthesized by Chandra T et al., and found to possess considerable anti-inflammatory property as compared with standard [47].

Burbuliene MM prepared a 1, 3, 4-oxadiazole derivatives belonging to a series of 5-[2-disubstituted-amino-6-methylpyrimidine-4-yl]-sulfonylmethyl]-3H-1, 3, 4-oxadiazole-2-thiones.

Another series of 1, 3, 4-oxadiazole derivatives of biphenyl-4-yloxy acetic acid were synthesized by Mymoona et al., and screened for their potent anti-inflammatory activity. The lead compound having much more anti-inflammatory activity (81.81%) than the reference drug flurbiprofen (79.54%) [49].

Kumar H et al., synthesized a new series of 2-[3-(4-bromophenyl)-propane-3-ones]-5-(substituted phenyl)-1, 3, 4-oxadiazoles derivatives. All new synthesized compounds...
were screened for their anti-inflammatory activity. The results were compared with standard drug indomethacin. The compounds showed a potent anti-inflammatory activity [50].

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\text{Fig 28: } 2\{3\{4\{bromophenyl\}\} propane-3-ones\}5- \text{ (substitutedphenyl)}-1, 3, 4-\text{oxadiazoles derivatives}
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A. Mohammad et al. synthesized some new 2-substituted-aryl-5-(2, 4, 6-trichloro-phenoxy-methyl)-1, 3, 4-oxadiazole derivatives and tested for their in-vitro anti-inflammatory activity by using carrageenan induced ratpaw oedema method [51].

Potent anti-inflammatory activity has been reported in 2, 5-disubstituted-1, 3, 4-oxadiazoles derivatives based on aryl propionic acid by Erhan P et al. These synthesized compounds showed anti-inflammatory activity 81.46% and 81.48% respectively against the standard drug ibuprofen [52].

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\text{Fig 29: } 2, 5\text{-disubstituted-1, 3, 4-oxadiazoles derivatives}
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Analgesic Activity: A series of 5-(2-aminophenyl)-1, 3, 4-oxadiazole-2(3H)-thione derivatives have been synthesized by K. Selvakumar et al. Among the newly synthesized 1, 3, 4-oxadiazoles, four compounds showed highly significant (p < 0.001) analgesic activity, Pentazocine (5mg/ml, IP) was used as reference standard [53].

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\text{Fig 30: } 5\{2\{aminophenyl\}\}-1, 3, 4-\text{oxadiazole-2(3H)-thione derivative}
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Jayashankar B et al. synthesized a series of novel ether-linked bis-(heterocycles) via [3+2]-cycloaddition reaction of nitricoxide with allyl alcohol followed by intramolecular 1, 3-dipolar cycloaddition reaction of nitrile imine with carbonyl group. All the newly synthesized compounds were screened for their anti-inflammatory and analgesic activities. Among all synthesized four compounds exhibited excellent activity comparable to ibuprofen and aspirin at the similar dosages [54].

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\text{Fig 31:} \text{ ether-linked bis-(heterocycles) derivatives}
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4. Anticonvulsant activity

Y. Mohammad et al. synthesized some new derivatives of 2-(4-chlorophenyl)-amino-5-(4-pyridyl)-1, 3, 4-oxadiazole. The newly synthesized compounds were tested for their anticonvulsant activity. The range of all compounds showed activity in 33-100%. Compound (a) showed maximal activity and compound (b) showed good activity (Figure) [55].

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\text{Fig 32: } 2\{4\{chlorophenyl\}\} amino-5\{4\{pyridyl\}\}-1, 3, 4-\text{oxadiazole derivatives}
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A. Zarghi et al. synthesized some new series of 2-substituted-5-[2-{(2-halobenzyl)-thio}-phenyl]-1, 3, 4-oxadiazoles derivatives and evaluated for their anticonvulsant activity. The synthesized compounds containing main essentials pharmacophore for binding to the benzodiazepine receptor and possess good anticonvulsant activity [56].

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\text{Fig 33: } 2\text{-substituted-5\{2\{-(2-halobenzyl)-thio\}-phenyl\} -1, 3, 4-\text{oxadiazoles derivatives}
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5. Anti-tubercular activity

F. Macaev et al. synthesized a new series of 5-aryl-2-thio-1, 3, 4-oxadiazole derivatives. All the synthesized compounds were screened for their anti-mycobacterial activities against Mycobacterium tuberculosis H37Rv. The synthesized compounds appeared to be the most active derivatives exhibiting more than 90% inhibition of mycobacterial growth at 12.5μg/ml [57].

Pathan SR et al. prepared some novel 1, 3, 4-oxadiazole derivatives and pyrazole derivatives and evaluated for their antitubercular activity against H37Rv strain as compare to the standard drug streptomycin. One Compound have shown promising activity and two compound have shown moderate activity (Figure) [58].

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\text{Fig 34: } 1, 3, 4-\text{oxadiazole derivatives and pyrazole derivatives}
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Some novel series of 2, 5-di-substituted-1, 3, 4-oxadiazoles were synthesized by Yarshahar M. et al. and the newly synthesized compound have been found to exhibit good anti-tubercular activity when compared with standard drug [59].
6. Conclusion
This review highlights the synthesis and pharmacological properties of the Oxadiazole derivatives. Thus this paper proves to be significant for further research work on the bioactive oxadiazole ring containing compounds.

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8. References


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