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A PANACROMIC REVIEW ON OXADIAZOLE SCAFFOLDS AND THEIR POTENTIAL ANTI-MYCOBACTERIAL ACTIVITY

DAS P*, RAMYA A, NAYAK A, GAZMER A, RAJU R AND TEJASWINI R

Krupanidhi College of Pharmacy, #12/1, Chikkabellandur, Carmelaram Post, Varthur, Banglore-560035, Karnataka, India

***Corresponding Author: Dr. Paramita Das: E Mail: paramitadas04@gmail.com**

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ABSTRACT

Heterocyclic compounds form the main family of organic compounds. These are of enormous importance for a variety of synthetic, pharmaceutical, and industrial applications and are known for their biological activities. Oxadiazole or furadiazole is a five-membered ring containing two carbons, one oxygen atom, two nitrogen atoms, and two double bonds. They are derived from furan by replacing two nitrogen atoms (N =) with two methylene groups (= CH). The particular structural feature of the 1,3,4-oxadiazole ring with pyridine nitrogen atom type is advantageous for binding effectively with various enzymes and receptors in biological systems through numerous weak interactions, thereby exhibiting various pharmacological activities. Compounds containing the 1,3,4-oxadiazole moiety have recently received attention for their antiviral, anti-inflammatory, anti-tuberculous, anti-cancer, anti-parasitic, enzyme-inhibiting, antioxidant, anti-bacterial, and anti-fungal potentials. These are the results of recent developments in the synthesis and anti-tubercular activity of 1,3,4-oxadiazole candidates over the past 15 years. It is believed that this review will be of great help for new ideas in the search for rational designs for the development of more active and less toxic 1,3,4-oxadiazole-based drugs as an anti-tubercular.

Keywords: 1,3,4-Oxadiazole, Anticancer, Anti-microbial. Anti-oxidant, Furadiazole, Anti-tubercular

INTRODUCTION:

About 1 billion people suffer from respiratory disease and 4-5 million people die every year. Over 10 million tuberculosis (TB) cases are being reported every year worldwide and about 1.4 million are fatal to tuberculosis **[1]**. According to WHO, Tuberculosis ranks 12th in overall prevailing disease, but it is the 2nd most infectious killing disease About 26% of cases are reported from India and it ranks 1st globally **[2-4]**. TB is associated with HIV in 11% of people **[4]**. TB was 1st detected in the bones of fossils that were about 4000 years old in Egypt. Tuberculosis (TB) is a generalized contagious disease primarily affected by *Mycobacterium tuberculosis*, where it is airborne that spreads in the form of droplets and primarily affects the lungs, though it has slowly subsided with new cases of TB and TB-related deaths in these years, the number of TB patients and TB-related deaths remains enormously high. The causative agent *Mycobacterium bovis* was primarily found in soil and affected the cattle, later this species infected the humans and evolved into *Mycobacterium tuberculosis* **[5]**. In the 19th century, TB affected 50% of Europeans. This made scientists around the world work on TB **[6]**. The use of first-line drugs is an effective method of treating the disease caused by *Mycobacterium tuberculosis*. This therapy leads to recovery in about 90% of patients but long-term causes multi-drug resistance to *mycobacterium*. In such cases, strains are required to take second and third-line anti-TB drugs **[7]**. Unfortunately, most of these drugs are poorly accepted when used as a part of long-term chemotherapy for tuberculosis. : Only 50% of patients with MDRTB have been successfully treated with the drugs available, which is one of the main problems in current tuberculosis treatments. The global number of deaths officially classified as caused by TB (1.3 million) in 2020 was almost double the number caused by HIV/AIDS (0.68 million), and TB mortality has been more seriously impacted by the COVID-19 pandemic in 2020 than HIV/AIDS **[8]**.

Compounds having different heterocyclic moieties have shown special importance in the drug development process. The design of new biosimilars based on molecular credit has attracted all medicinal chemists. In recent years, azo-based heterocycles have been broadly studied that are responsible for a wide range of pharmacological activities **[9]**. The introduction of heterocyclic moieties helps in modifying physicochemical properties and obtaining the optimal ADMET properties for the drug molecules. Conversely, there is a huge demand for novel anti-tubercular drugs for multidrug-

resistant tuberculosis which is a major challenge for chemists. Specifically, there is an increased interest in developing and designing new anti-tubercular molecules containing the oxadiazole group **[10]**. Hybrid drugs having two or more pharmacophores showed potential to overcome drug resistance and even reduce the risk of side effects by several modes, reported that molecules with heterocyclic compounds **[11]**. Therefore, the hybridization of oxadiazole with various heterocyclic pharmacophores rises the capability of new drug molecules to solve MDRT **[12]**.

In this review, a piece of short information about the chemistry of oxadiazole, then it is followed by the pharmacological activities and various hybrids of oxadiazole that is composed with the scheme, biological evaluations, and SAR studies of the various hybrids are reviewed and reported.

CHEMISTRY OF OXADIAZOLES

Since, the oxadiazole pharmacophore has a low electron density on carbon atom and a high electron density on nitrogen atom, thereby the main reactions shows a nucleophilic attack on carbon, which is then followed by ring beakage and attack of electrophile on nitrogen. The acid-catalyzed reaction causes various difficulties to carry out reactions under alkaline or acidic conditions. The ring gets stabilized when one or more aryl groups are substituted. The low electron density on carbon, when coupled with the attack of proton on nitrogen, makes the electrophilic substitution on carbon more difficult. Other problem is by using acid as a catalyst for ring cleavage, particularly in the case of alkyloxadiazoles **[13]**. Attack by a nucleophile on carbon results in a nucleophilic displacement or ring disruption. Based on of the position of Azo and Oxygen atoms in the oxadiazole ring, there are four positional isomers formed **(Table 1)**. Amongst which 1,3,4-Oxadiazole has showed the attention of medicinal chemists as a unique Pharmacophore. The Azole moiety that is present in 1,3,4-oxadiazole ring increases the lipophilicity of the drug which in turn helps the drug molecule to transfer the drug to its target by transmembrane diffusion. The 1,3,4-Oxadiazoles are presently available commercially in the form of drugs such as Furamizole, Raltegravit, and Nespidil **[14]**.

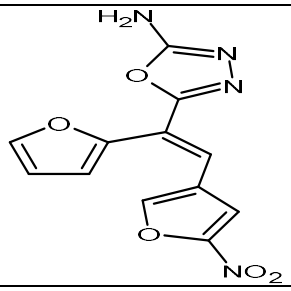
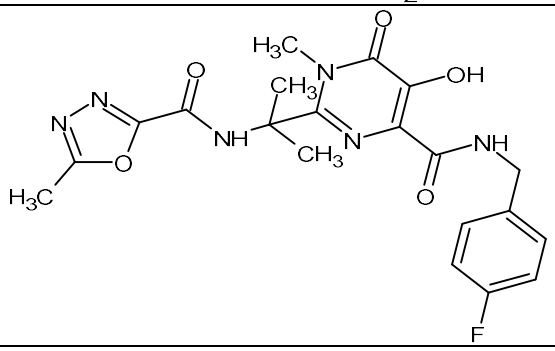
Table 1: Isomers of Oxadiazole

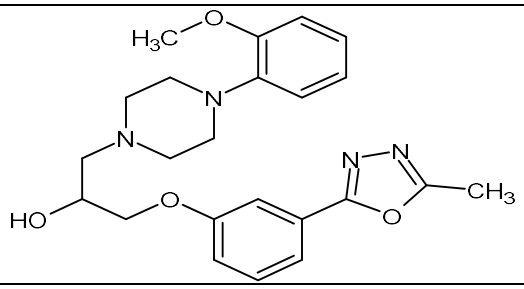
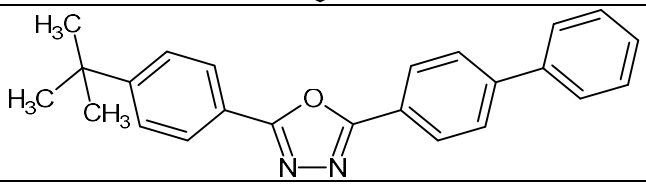
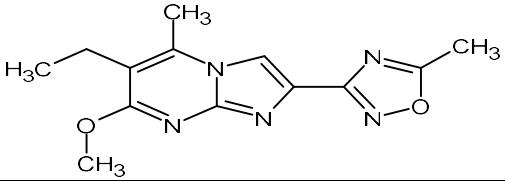
S. No	Isomer	Structure	Properties			
			XLogP3-AA	H-Bond Donor	H-Bond Acceptor	Rotatable Bond
1.	1,2,5-Oxadiazole		-0.4	1	5	1
2.	1,2,3-Oxadiazole		0.1	0	6	0
3.	1,2,4-Oxadiazole		0.1	0	3	0
4.	1,3,4-Oxadiazole		-0.2	0	3	0

OXADIAZOLE- PHARMACOLOGY PROFILE

Among the isomers of oxadiazole, 1,3,4-oxadiazole isomer proved a very important pharmacophore due to its biological activities like antimicrobial, antiepileptic, anticancer, antidiabetic, antipyretic, anti-mycobacterial, anti-viral, immunosuppressive, antioxidant, anti-helimentic, antiemetic, antidepressant, vasodilator activity, antimycotic activity, ulcerogenic and antihypertensive activities, etc. **[15]**. 1,3,4-Oxadiazoles are one of the good bioisosteres of esters, carboxamides and carboxylic acids which are responsible that provide a wide variety of pharmacological activity as it shows H-bonding interactions with a wide range of receptors **[16]**.

Table 2: Commercially available drugs containing 1,3,4-Oxadiazole

S. No.	Name of the Drug	Class of Drug	Structure
1.	Furamizole	Antimicrobial	
2.	Raltegravir	Antiviral	

3.	**Nesapidil**	**Antihypertentive**	
4.	**Butyl PBD**	**Liquid Scintillator Neutrino Detector**	
5.	**Fasiplon**	**Anxiolytic**	

VARIOUS DERIVATIVES OF OXADIAZOLE AS AN ANTI-TUBERCULAR AGENTS

1. OXADIAZOLE CONTAINING COUMARINYL MOIETY

1.1. Ronak *et al*. synthesized novel 3-chloro-4-(2-oxo-4-((5-(pyridin-3-yl) -1,3,4- oxadiazol-2-yl) thio)-2H-chromen-3-yl) -1-Substituted phenylazetidin-2-one and 2-(2-oxo4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-2H-chromen-3-yl)-3-Substituted phenyl thiazolidin4-one. The synthesized analogs were seen for their primary in vitro anti-microbial activity against Gram-positive and Gram-negative bacteria and antifungal activity various strains using broth dilution method. It was noted that an aromatic ring that lacked in the chloro group on ortho, meta & para positions showed antibacterial activity **[17]**.

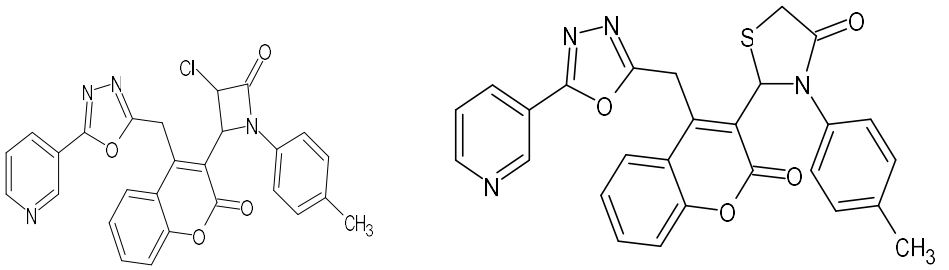


Figure 1: novel 3-chloro-4-(2-oxo-4-((5-(pyridin-3-yl) -1,3,4- oxadiazol-2-yl) thio)-2H-chromen-3-yl) -1-Substituted phenylazetidin-2-one and 2-(2-oxo4-((5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)thio)-2H-chromen-3-yl)-3-Substituted phenyl thiazolidin4-one

1.2. Manoj *et al*. A series of cinnamide derivatives were designed as potential anti-mycobacterial agents using a molecular hybridization approach. The minimum inhibitory concentration (MIC) of all the synthesized compounds was determined against *M. tuberculosis* H37Rv using the Resazurin Microtitre plate Assay (REMA) method. The synthesized molecules showed good to moderate activity with MIC in the range of 5–150 lM and good safety profile. In summary, a small library of cinnamide derivatives has been synthesized using a molecular hybridization approach. Thus this strategy could prove useful in design of antimycobacterial agents with inherent activity as well as synergy with rifampicin **[18]**.

1.3. Abhay *et al*. designed and evaluated oxadiazole bioisters where in which cinnamic acid moiety was used. In the cinnamic acid, the acid moiety was replaced by the oxadiazole ring which gave rise to styryl oxadiazole derivatives whereupon using substituted cinnamic acid derivatives various 3-styryl 1,2,4-oxadiazole hybrids were synthesized. It resulted as that the electron-withdrawing substituents and halogens on the phenyl ring were favored for increased anti-tubercular activity. Bulky groups and electron-donating substituents on the phenyl ring decreased the activity, but an increase in the bulkiness in the oxadiazole ring increases the activity. The *in silico* results were correlated with the theoretical/experimental observations where the thermodynamic interactions governing the binding of the derivatives with InhA, are the preliminary information for the structure-based optimization of this scheme **[19]**.

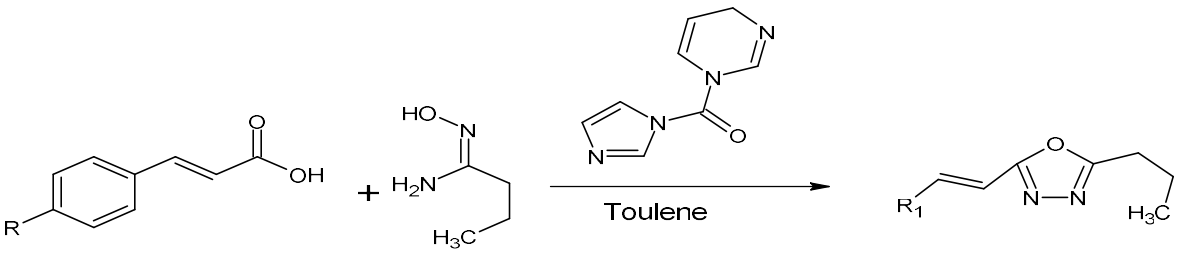


Figure 2: Substituted Cinnamic acid was treated with Amidoxime in the presence of Toulene and CDI which was refluxed for 3-4 hours to form 3,5-disubstituted 1,2,4-oxadiazole

2. OXADIAZOLE CONTAINING BEZOTHIAZINE MOIETY

2.1. Chao *et al*. Decaprenylphosphoryl-β-D-ribose 2′-epimerase (DprE1 enzyme) has been designed to be an attractive therapeutic agent that addresses immediate demand. Here in, it is identified that class of DprE1 inhibitors, benzothiazinethiones as antimycobacterial agents. Benzo-thiazinethione derivative SKLB-TB1001 showed a very good activity against *Mycobacterium* using Microplate Alamar blue assay, and SKLB-TB1001 was also highly active against MDRT. There was no antagonism interaction found with any two-drug combinations tested in this study, and the synergestic action of SKLB-TB1001 with rifampicin (RMP) was proved. Then, benzothiazinethione exhibited in vivo anti-tubercular ability in an acute tubercular infection mouse model, expressively better than BTZ043 **[20]**.

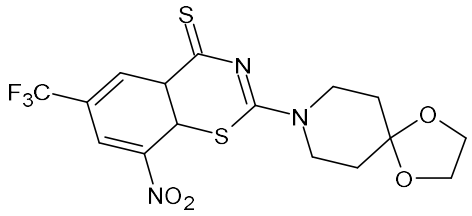


Figure 4: Benzothiazine containing 1,3,4-Oxadiazole

2.2. Benzothiazinone (BTZ) inhibitors have shown nanomolar potency against both drug-susceptible and multidrug-resistant strains of the tubercle bacillus. However, their proposed mode of action is lacking structural evidence. We report here the crystal structure of the BTZ target, FAD-containing oxidoreductase *Mycobacterium tuberculosis* DprE1, which is essential for viability **[21]**. Structures of complexes with the BTZ-derived nitroso derivative CT325 reveal the mode of inhibitor binding, which includes a covalent link to conserved Cys387, and reveal a trifluoromethyl group as a second key determinant of interaction with the enzyme. On the basis of the structural and activity data, we propose that the complex of DrpE1 bound to CT325 is a representative of the BTZ-target complex. These results mark a significant step forward in the characterization of a key TB drug target **[22]**.

3. OXADIAZOLE CONTAINING QUINAZOLINE MOIETY

3.1. Patel *et al*. It is reported that the synthesis and in vitro antimicrobial

activity of various 3-(1,3,4-oxadiazol-2-yl)- quinazolin-4(3H)-ones. The antimicrobial activity of title compounds were examined against two gram positive bacteria (S. aureus, S. pyogenes), two gram negative bacteria (E. coli, P. aeruginosa) and three fungi (C. albicans, A. niger, A. clavatus) using the broth microdilution method. Some derivatives bearing a bromo or iodo group exhibited very good antimicrobial activity **[23]**. Aminosubstituted 1,3,4-oxadiazoles derivatives exhibited very good antimicrobial activity. Antimicrobial results were found uneven but most of the bromo and iodo derivatives of quinazolinone possessed very good antimicrobial activity. Furthermore CH2 link between 3rd position of quinazolinone and 2nd position of oxadiazole were found most active than other two series. So, it seems from the antimicrobial results that halogen atom and CH_2 link played vital role in increasing antimicrobial activity **[24]**.

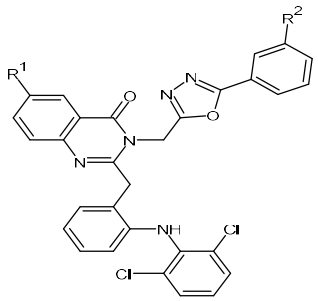


Figure 5: 3-(1,3,4-oxadiazol-2-yl)- quinazolin-4(3H)-ones

4. OXADIAZOLE CONTAINING PYRIDINE MOIETY

4.1. Sunhee *et al*. A critical unmet clinical need to combat the global tuberculosis epidemic is the development of potent agents capable of reducing the time of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis therapy. It was found that the amide linker with IPA core is very important for activity against *Mycobacterium tuberculosis* H37Rv. Linearity and lipophilicity of the amine part in the IPA series play a critical role in improving in vitro and in vivo efficacy and pharmacokinetic profile. The optimized IPAs, showed not only excellent oral bioavailability (80.2 and 90.7%, respectively) with high exposure of the area under the curve (AUC) but also displayed significant colony-forming unit (CFU) reduction (1.52 and 3.13 log10 reduction at 10 mg/kg dosing level, respectively) in the lung of mice **[25]**.

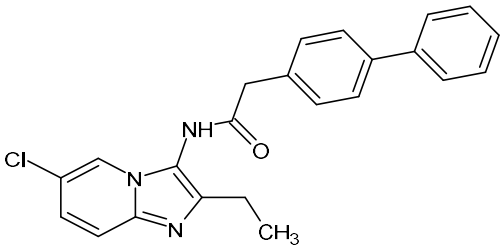


Figure 6: Pyridine containing 1,3,4- Oxadiazole

4.2. Desai *et al*., synthesized, evaluated, and performed molecular docking studies of Pyridine clubbed 1,3,4-Oxadiazole derivatives as anti-tubercular agents; A series of pyridine clubbed 1,3,4oxadiazole derivatives were efficiently synthesized, characterized by standard spectral techniques, and evaluated for their in vitro antitubercular activity against *Mycobacterium tuberculosis* (*Mtb*) H37Ra and *Mycobacterium Bovis* BCG inactive and dormant state which was performed using Rifampicin and Isoniazid as a standard. Molecular Docking was performed against the enzyme *Mtb* EnoylACP (CoA) reductase (FabI/ ENR/InhA) which predicted binding modes and affinity. It was witnessed that the presence of phenoxy ring was favorable for the antitubercular activity compared to the phenyl ring at the R position. The presence of phenyl ring at R position showed a significant diminution in antitubercular potency. In addition, the electronic environment of substituents on either phenoxy or phenyl ring at R position had no substantial effect on the biological activity as the active compounds had both electron-withdrawing as well as donating substituents on them. During these studies, compounds showed very less/nil potent Anti-TB activity up to 100µg/ml **[26]**.

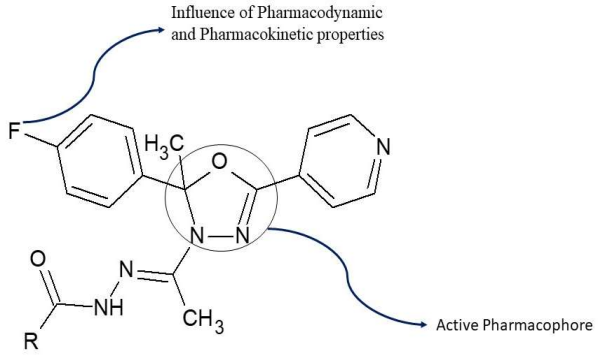


Figure 7: SAR of Pyrindine containing oxadiazole

4.3. Sambaji *et al*. Synthesis and Antitubercular Activity of New 1,3,4-Oxadiazoles Bearing Pyridyl and Thiazolyl Scaffolds; The initial projection of anti-internal activity of all newly synthesized compounds were tested against H37RV using Isoniazid, with a standard drug of the tested compounds being determined by a dilution assay of L.J. agar method. Compared with methoxy replacement in the second position of the phenyl ring and the substitution of composite bearing fluorine into the fourth position of the phenyl ring, which has shown better activity against *M. tuberculosis* H37RV. Furthermore, it could provide quantitative insight into various bonded and nonbonded interactions which can be systematically alerted to arrive at potent candidates. So it can be concluded from the above observations that the 1,3,4-oxadiazoles bearing pyridyl and thiazolyl scaffolds offer an attractive lead series for the discovery of novel antitubercular agents **[27]**.

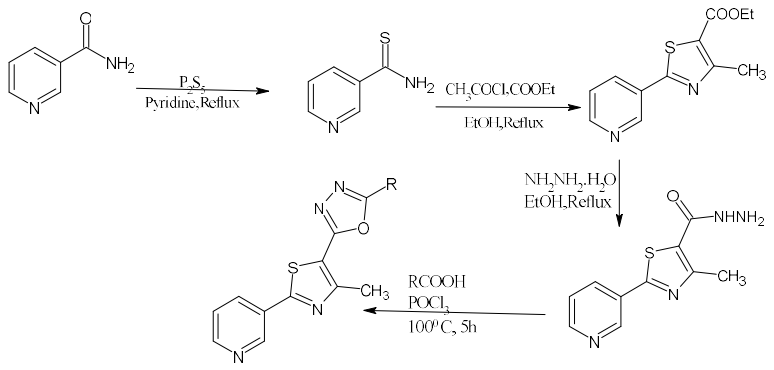


Figure 8: Scheme for of New 1,3,4-Oxadiazoles Bearing Pyridyl and Thiazolyl Scaffolds

5. OXADIAZOLE CONTAINING PYRAZINE MOIETY

5.1. Das *et al*., synthesized and assessed the anti-tubercular activity of triazole and tetrazole fused 1,3,4-Oxadiazole molecules containing Pyrazine moiety; It is based on the summary of the triazoles, tetrazoles, and 1, 3, 4, oxadiazoles are privileged structures that attract considerable attention in the design of pharmacologically dynamic molecules and their combination in a molecular scaffold. The activity of some new triazole-fused 1,3,4-oxadiazole and tetrazole-fused 1,3,4-oxadiazole molecules containing a pyrazine moiety were estimated. The synthesized compounds were evaluated for their in vitro anti-mycobacterial activity

against *Mycobacterium tuberculosis* strain named H37Rv (MTCC200) by the Lowenstein-Jensen (L.J.) Agar (MIC) method using isoniazid and rifampin as the standards. The MIC value of one of the derivatives was found as 6.25 µg/ml. However, although specifically synthesized compound showed potent antituberculous activity, is still less active compared to standard drugs (isoniazid and rifampin) **[28]**.

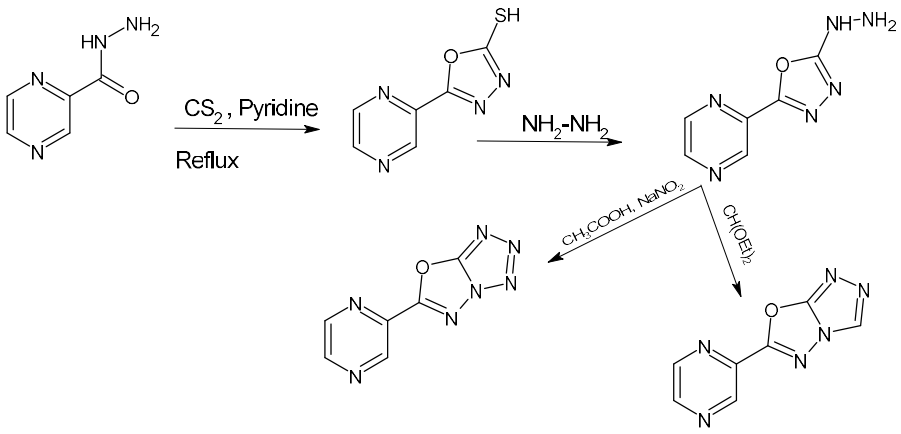


Figure 10: Scheme for triazole and tetrazole fused 1,3,4-Oxadiazole molecules containing Pyrazine moiety

5.2. Rajesh *et al*., synthesized and evaluated novel 4-tetrapyrrole based 1,3,4-oxadiazole derivative as anti-microbial and anti-tubercular activity. In recent days, nitropyrole based natural products and their derivatives were reported for their anti-microbial activity, pyrrolonitrins reported anti-tubercular activity where the scheme proposed is acetylation using trichloroacetic chloride in diethyl ether as an acetylating agent **[29]**.

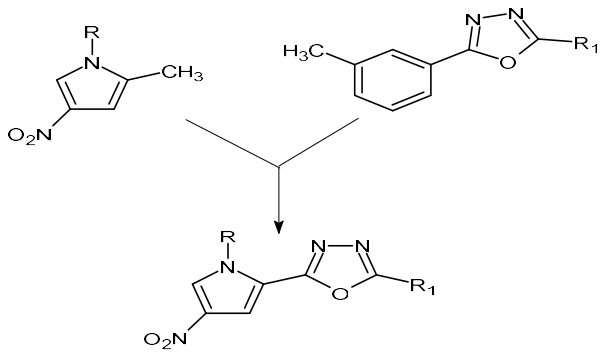


Figure 11: Scheme for novel 4-tetrapyrrole based 1,3,4-oxadiazole derivative

The best derivative was the substitution with a 4-fluorophenyl moiety which showed the activity close to Isoniazid that is 0.46µg/ml and 0.4µg/ml **[30]**.

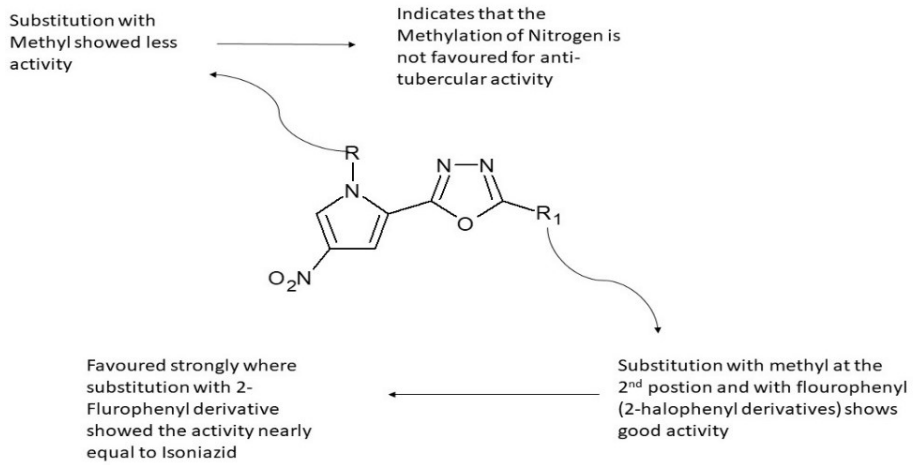


Figure 12: SAR of Oxadiazole containing Pyrole ring

5.3. Das *et al*. Evaluation and Docking study of Pyrazine containing 1,3,4-Oxadiazole clubbed with substituted Azetidine-2-ones; In this, the aim is to synthesize and determine the antituberculosis and antimicrobial potential of some novel 3-chloro-4-aryl-1[4(5pyrazin2yl[1,3,4]oxadiazol-2-ylmethoxy)phenyl]-azetidine-2-one derivatives. Thereby reported the synthesis of a new class of heterocyclic molecules in which pyrazine, 1,3,4-oxadiazole, and azetidine residues are present as a backbone. Docking simulations were performed using the Biopredicta tool in the grip docking mode. Few compounds were found to have the highest negative dock score ranging from − 59.0 to − 54.0 which meant that they the formed most stable drug-receptor complex amongst other compounds **[31]**.

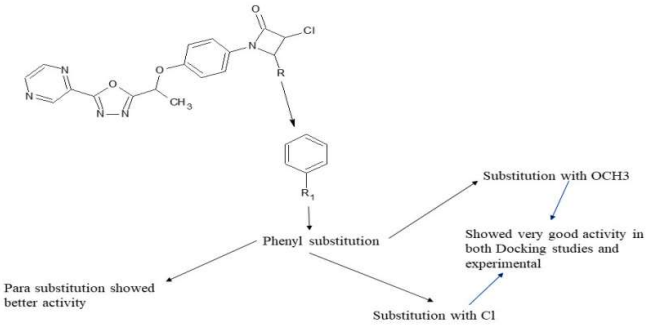


Figure 13: SAR of Oxadiazole containing Pyrazine ring

6. OXADIAZOLE CONTAINING OTHER MOIETIES

6.1. OXADIAZOLE WITH SULFONYL GROUP

Galina *et al*. Development of 3,5-Dinitrobenzyl Sulfonyl-1,3,4-Oxadiazole as a selective anti-tubercular agent; In this, the

majority of the compounds showed outstanding in vitro activity against *Mycobacterium tuberculosis* CNCTC My 331/88 and six multidrug-resistant clinically isolated strains of *M. tuberculosis*, with lower inhibitory concentration values as low as 0.03 µM (0.0110.026 µg/mL). The oxadiazole and thiadiazole derivatives with the most favorable activity/toxicity profiles have also shown the power comparable to that of the rifampicin against the undeveloped strain *Streptomycin*-starved *Mycobacterium tuberculosis* 18b-lux **[32]**.

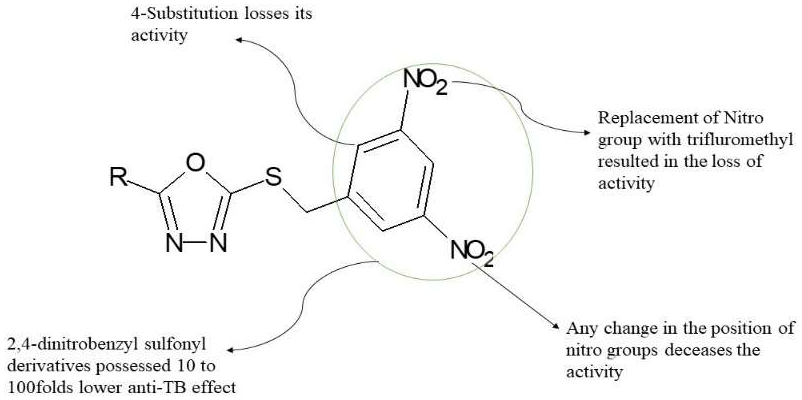


Figure 14: SAR of Oxadiazole containing Sulfonyl group

6.2. OXADIAZOLE CONTAINING ISOXAZOLE RING

Ramesh *et al*. Synthesis, biological evaluation and docking studies of some novel isoxazole clubbed 1,3,4-oxadiazoles derivatives; The initial screening of anti-tuberculosis activity of all synthesized compounds has been tested against *M. tuberculosis* H37RV using isoniazid as standard medicine. The compound with a methoxy substitution in the second position of the phenyl ring and the compound bearing the fluorine substitution in the fourth position of the phenyl ring showed better activity against *M. tuberculosis* H37Rv; Substitution of fluorine-containing the compound in the fourth position of the phenyl ring showed the highest activity against *M. tuberculosis* H37Rv. The majority of the synthesized compounds had shown less activity when compared to the standard drug Isoniazid **[33]**.

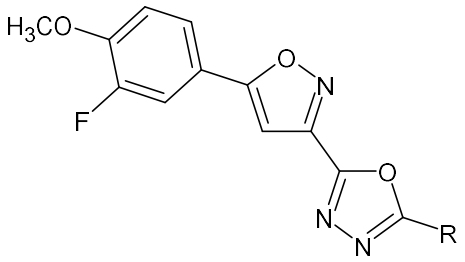


Figure 15: Novel isoxazole clubbed 1,3,4-oxadiazoles derivative

6.3. OXADIAZOLE CONTAINING TRIAZOLE RING

Suresh *et al*. synthesis of some novel 2-substitution-5-(isopropylthiazole) clubbed 1,2,4-triazole and 1,3,4-Oxadiazole as potential anti-tubercular; One of the important strategies for the designing of effective antitubercular agents is to develop inhibitors of mycobacterial cell-wall biosynthesis Earlier, several reports have appeared that the azole class of composed key property (lipophilicity) that influences the ability of the drug to the each target by transmembrane diffusion and show promising activity against resistant tuberculosis by blocking the biosynthesis of lipids **[34]**. The preliminary antitubercular screening for test compounds was obtained for *M. tuberculosis* H37Rv, the MIC of each drug was determined by broth dilution assay and is defined as the lowest concentration of the drug, which inhibits 99% of the bacterial population present at the beginning of the assay. The final concentration of DMSO in the assay medium was 1.3%. The growth in the U-tubes was compared with visibility against positive control (without drug), negative control (without drug and inoculum) and with standard isoniazid **[35]**.

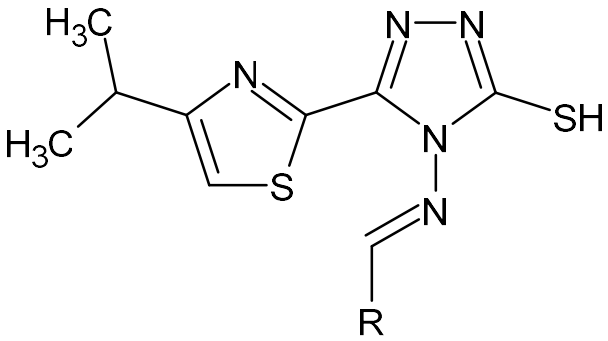


Figure 16: Novel 2-substitution-5-(isopropylthiazole) clubbed 1,2,4-triazole and 1,3,4-Oxadiazole

CONCLUSION:

In this review article, we have summarized various pharmacological activities of oxadiazgol-containing compounds. From this study, we found that oxadiazole-containing compounds can be synthesized through different types of synthetic pathways, and these derivatives exhibit a wide range of biological activities, such as: This review article supports the fact that oxadiazole is a useful template for further modification or derivatization of to design more potent biologically active compounds **[36]**. The methods we present in this review can help researchers design a new bioactive molecule containing the 1,3,4-oxadiazole moiety. Furthermore, we also present the various biological activities of 1,3,4-oxadiazole core, such as anticancer, antimicrobial, analgesic, anti-inflammatory, antifungal, fungicidal, herbicidal, antispasmodic **[37]**. Tuberculosis is one of the dark spots on the face of the global health system **[38]**. Scientists are focused on developing new anti-tuberculosis drugs with high potency and minimal toxicity. Unfortunately, few anti-TB drugs are available for the treatment of drug-resistant TB **[39]**. Heterocyclic oxadiazole hybrids play a crucial role in the treatment of tuberculosis and also as an antibacterial agent **[40]**. Oxadiazole hybridization with other antituberculous pharmacophores shows different mechanisms of action by targeting different enzymes such as Enoly CoA or proteins responsible for the emergence of resistance to *Mycobacterium* **[41]**. The presence of more than one pharmacophore in a hybrid allows for various backbone structural modifications, and the SAR study also contributes to the development of new heterocycles **[42]**. Oxadiazole hybrids with minimal toxicity to healthy cells **[43]**. This reviews the antituberculous potential of oxadiazole-heterocycle hybrids over the past decade. Furthermore, the SAR and mechanisms of action of the hybrids have been summarized to provide a clear insight into the development of non-toxic and effective anti-TB drugs .

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Ramya prepared the rough copy of the article and framed it. Paramita D reviewd the paper and corrected. The other authors helped in research of the various articles required for the reviewing. And the final manuscript was read.

CONFLICTS OF INTEREST:

There is no conflict of interest.

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