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# 3, 5-disubstituted 1,2,4- oxadiazole: A potent inhibitor of Mycolic acid synthesis

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## Abstract

Oxadiazoles are 5-membered, unsaturated, unstable, heteroaromatic ring containing two carbon atom, one oxygen atom and two pyridine type nitrogen atom linked in continuity. They fall under non beta lactam class of antibiotics. Oxadiazoles are potent inhibitors of mycolic acid synthesis. Mycolic acids are long fatty acids important for cell wall formation in class of bacterias called Mycolata taxon. The article focuses on various scaffolds of 1, 2, and 4- oxadiazole having inhibitory action on mycolic acid synthesis and can be applied for anti-tuberculosis treatment.

**Keywords:** Oxadiazole; Non beta Lactam antibiotics; Mycolic acid; Mycobacterium tuberculosis

## 1. Introduction

Mycolic acids are 2-alkyl, 3-hydroxy long chain fatty acids that form the vital participant in the biosynthesis of the cell envelope of mycobacterium class of bacterias. This outer layer is often referred as the mycomembrane. These membranes are often seen in the causatives of tuberculosis and leprosy and inhibition of its biosynthesis may be prominent step that can be taken to prevent the proliferation of such disease. Isoniazid is an anti-tubercular drug that utilizes this mechanism to exhibit its action [1].

1, 2, 4-oxadiazoles will antagonize the polyketide synthase enzyme that plays a crucial role in the biosynthesis of mycolic acid from its precursor mycolate and thereby inhibiting the production of the prominent mycolic acid. This mechanism of oxadiazole enables it to be used as an anti tubercular drug and also a drug against MDR and XDR tuberculosis. The putative target for the drug is polyketide synthase (Pks13) enzyme [2].

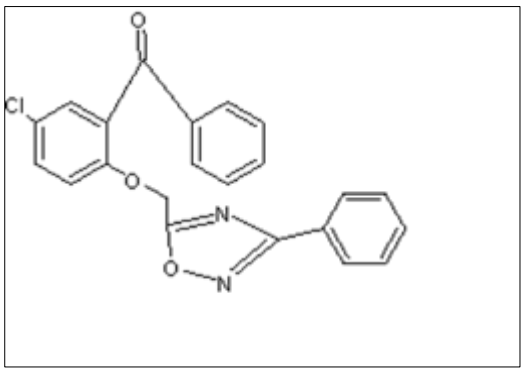


**Figure 1** Structure of Oxadiazole

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## 2. Synthesis

Oxadiazoles are usually synthesized by the reaction of acid hydrazides with acid chlorides or carboxylic acid followed by direct cyclisation of diacylhydrazines with dehydrating agents like phosphorus oxychloride, thionyl chloride or phosphorus pentoxide.

3, 5 disubstituted 1, 2, 4- oxadiazoles are synthesized by a mild and facile reaction of O-acylamidoximes and tetrabutyl ammonium fluoride in the presence of THF at room temperature[26].

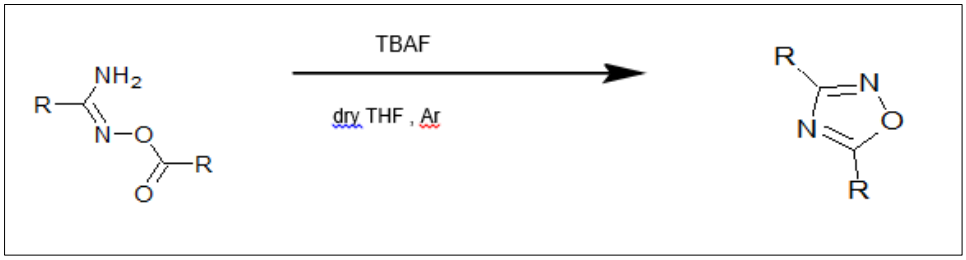


**Figure 2** Synthesis of Oxadiazole

## 3. SAR

The structural activity relationship of oxadiazole is as follows.

A hydrophobic or halogen substitution can be made at ring D of the compound. Substitution with fluorine or chlorine retained the activity of the drug. Replacement with a bromine group also retained the activity of the drug. The antibacterial activity is however retained when substituted with trifluromethoxy or methoxy group. No prominent in increase in activity was observed when substituted with benzylic bromide [5].

Para trifluro substitution shows excellent activity[2].

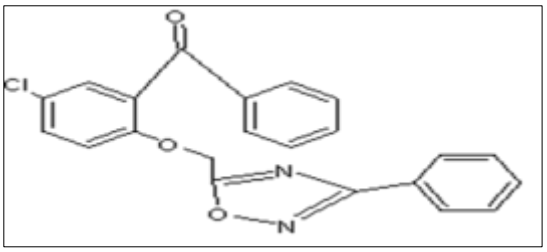


**Figure 3** Oxadiazole

## 4. Findings

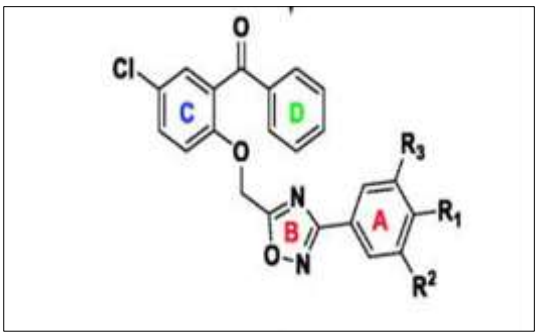


**Figure 4** 3,5-disubstituted 1,2,4-oxadiazole

**Table 1** Substituents at R1,R2 and R3

| Compounds | Substituents at | | |
|---|---|---|---|
| | **R1** | **R2** | **R3** |
| 1. | - | - | - |
| 2. | - | HYDROXYL | CHLORO |
| 3. | FLURO | - | HYDROXYL |
| 4. | FLURO | AMINO | - |
| 5. | PHENYL | - | - |
| 6. | - | METHYL | METHYL |
| 7. | CHLORO | METHYL | METHYL |
| 8. | FLURO | CHLORO | CHLORO |
| 9. | NITRO | - | - |
| 10. | TOLUENE | - | - |
| 11. | - | NITRO | - |
| 12. | NITRO | - | CHLORO |
| 13. | FLURO | METHYL | - |
| 14. | FLURO | FLURO | FLURO |
| 15. | FLURO | - | - |
| 16. | FLURO | CHLORO | - |
| 17. | FLURO | METHOXY | - |
| 18. | FLURO | FLURO | - |
| 19. | METHYL | FLURO | FLURO |
| 20. | FLURO | - | FLURO |

**Table 2** The IUPAC name and SMILES of newly proposed derivatives

| Sl. No | IUPAC name | Smiles |
|---|---|---|
| 1. | 5-chloro-2-[(3-phenyl-1,2,4-oxadiazol-5-yl)methoxy]phenyl}(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2ccccc2)c(c3)C(=O)c4ccccc4 |
| 2. | (5-chloro-2-{[3-(3-chloro-5-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(Cl)cc(O)c2)c(c3)C(=O)c4ccccc4 |
| 3. | (5-chloro-2-{[3-(4-fluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(O)c(F)cc2)c(c3)C(=O)c4ccccc4 |
| 4. | (2-{[3-(3-amino-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]methoxy}-5-chlorophenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(N)c(F)cc2)c(c3)C(=O)c4ccccc4 |

| | | |
|---|---|---|
| 5. | (5-chloro-2-{[3-(3-chloro-5-hydroxyphenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc4ccc(OCc1nc(no1)c2ccc(cc2)c3ccccc3)c(c4)C(=O)c5ccccc5 |
| 6. | 5-chloro-2-{[3-(3,5-dimethylphenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(C)cc(C)c2)c(c3)C(=O)c4ccccc4 |
| 7. | (5-chloro-2-{[3-(4-chloro-3,5-dimethylphenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(C)c(Cl)c(C)c2)c(c3)C(=O)c4ccccc4 |
| 8. | (5-chloro-2-{[3-(3,5-dichloro-4-fluorophenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(Cl)c(F)c(Cl)c2)c(c3)C(=O)c4ccccc4 |
| 9. | (5-chloro-2-{[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | [O][N+](=O)c1ccc(cc1)c4nc(COc3ccc(Cl)cc3C(=O)c2ccccc2)on4 |
| 10. | (5-chloro-2-{[3-(4-chloro-3,5-dimethylphenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Cc1ccc(cc1)c2ccc(cc2)c5nc(COc4ccc (Cl)cc4C(=O)c3ccccc3)on5 |
| 11. | (5-chloro-2-{[3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | [O][N+](=O)c1ccc(cc1)c4nc(COc3ccc (Cl)cc3C(=O)c2ccccc2)on4 |
| 12. | (5-chloro-2-{[3-(4-fluoro-3-methylphenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | [O][N+](=O)c1ccc(cc1Cl)c4nc(COc3ccc(Cl)cc3C(=O)c2ccccc2)on4 |
| 13 | (5-chloro-2-{[3-(4-fluoro-3-methylphenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(C)c(F)cc2)c(c3)C(=O)c4ccccc4 |
| 14. | (5-chloro-2-{[3-(3,4,5-trifluorophenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(F)c(F)c(F)c2)c(c3)C(=O)c4ccccc4 |
| 15. | (5-chloro-2-{[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2ccc(F)cc2)c(c3)C(=O)c4ccccc4 |
| 16. | (5-chloro-2-{[3-(4-fluoro-3-methylphenyl)-1,2,4-oxadiazol-5yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(C)c(F)cc2)c(c3)C(=O)c4ccccc4 |
| 17. | (5-chloro-2-{[3-(4-fluoro-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(OC)c(F)cc2)c(c3)C(=O)c4ccccc4 |
| 18. | (5-chloro-2-{[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(F)c(F)cc2)c(c3)C(=O)c4ccccc4 |
| 19. | (5-chloro-2-{[3-(3,5-difluoro-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(F)c(C)c(F)c2)c(c3)C(=O)c4ccccc4 |
| 20. | (5-chloro-2-{[3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl]methoxy}phenyl)(phenyl)methanone | Clc3ccc(OCc1nc(no1)c2cc(F)c(F)cc2)c(c3)C(=O)c4ccccc4 |

## 5. Conclusion

The study envisions the action of oxadiazole derivatives as a potent mycolic acid synthesis and which can be considered as an anti tubercular drug . Different substituents were opted for the study and their activity was analysed and concluded . The study revealed that the substituents are having a considerable action in MDR tuberculosis and later on can be used in the treatment of most emerging deadly condition of MDR tuberculosis.

## Compliance with ethical standards

*Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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