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SYNTHESIS, CHARACTERIZATION AND ANTI-MYCOBACTERIAL ACTIVITY OF 2, 5 DI-SUBSTITUTED 1, 3, 4 OXADIAZOLES

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ABSTRACT:
Hydrazide and its Hydrazone derivatives are shown biological activities. Hydrazones converted to heterocyclic compounds shows great importance in medicine. Hydrazide–hydrazones are converted into oxadiazoles using oxidative cyclization. Synthesized 1, 3, 4 oxadiazoles compounds were characterized using spectroscopic techniques. Oxadiazoles derivatives have shown good anti-mycobacterial activity. In silico prediction of compounds carried on online tool ADMET-SAR and chemical admet properties were predicted. These compounds may proposed as an efficient anti-tuberculosis agent in the future.

KEYWORDS: Hydrazide, Hydrazone, Oxadiazoles, anti-mycobacterial activity.

INTRODUCTION:

Hydrazide-hydrazone derivatives have demonstrated biological activities including antiviral, antitubercular, antibacterial, antifungal, anticancer and antiprotozoal effects[i-iii] Azomethine, which is present in hydrazide-hydrazones and has many medicinal uses and it is helpful in the synthesis of triazoles, oxadiazoles and other heterocyclic compounds. Different heterocyclic molecules that hydrazones provide have a significant role in medicine.

The five-membered heterocyclic system 1,3,4-oxadiazole is made up of two nitrogen and one oxygen atom. As presented in F**igure 1.1**, there are four known isomers of oxadiazole: 1,3,4-oxadiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, and 1,2,5-oxadiazole. Since 1,2,4-oxadiazole has so many significant chemical and biological properties, it is well-known and extensively researched. The primary biological features of 1,3,4-Oxadiazolines derivatives that have drawn attention are their insecticidal activity. They exhibit a range of biological properties[iv-vi] such as antimicrobial, analgesic, antiviral, anticancer, anti-inflammatory, antifungal, anticonvulsant, antihypertensive and anti-diabetic. Because of its reactivity sites, 1,3,4-oxadiazole undergoes a variety of chemical reactions, including thermal, photochemical, nucleophilic, and electrophilic substitutions. We have investigated the synthesis and anti-mycobacterial properties of 1,3,4-oxadiazole in light of this. A large number of them are made with hydrazides. A study on the one-step synthesis of 1,3,4-oxadiazole using hydrazide and carboxylic acid has been published[vii].

Important aromatic heterocycles with five members, 1,3,4-Oxadiazoles have been shown to have a variety of biological and pharmacological actions, including antibacterial, analgesic, anti-inflammatory, anti-diabetic, anticonvulsant, anticancer, antiviral, and antifungal activities[viii].

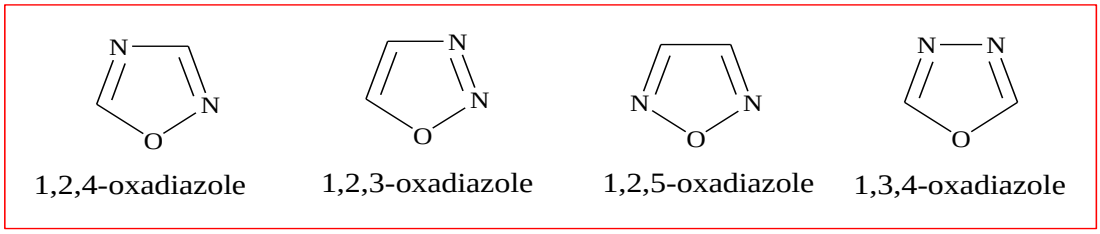


Figure 1.1 Isomers of Oxadiazoles

EXPERIMENITAL:

Mechanism of cyclization is explained In **Figure 1.2**. It is a simple and convenient oxidative C−O bond formation reaction and forms 1,3,4-oxadiazoles. This reaction can be applied to the hydrazide-hydrazones, obtained through the condensation of aldehydes and hydrazides. It gives a series of symmetrical and asymmetrical 2,5-disubstituted 1,3,4-oxadiazoles[ix].

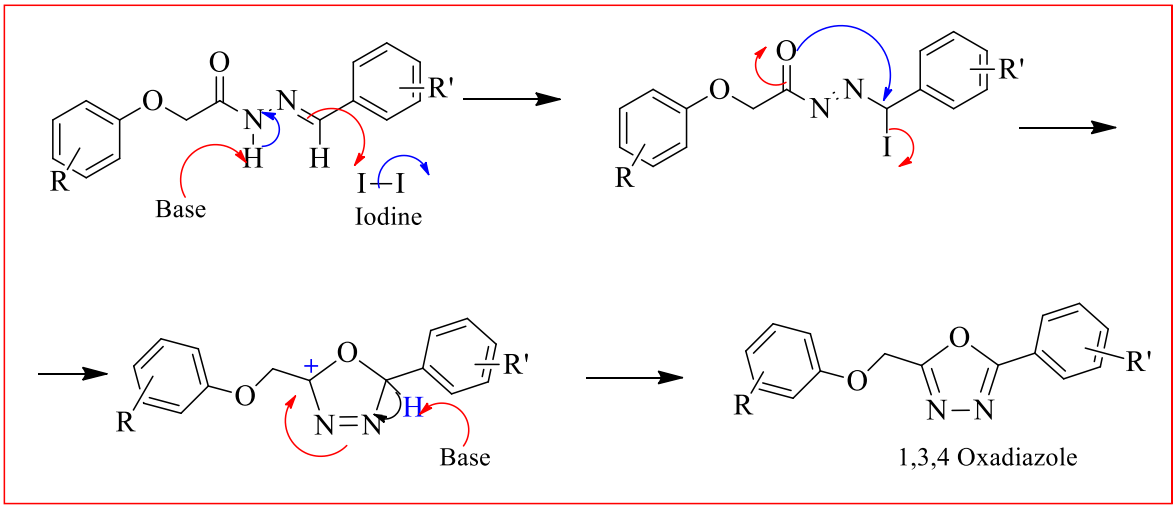


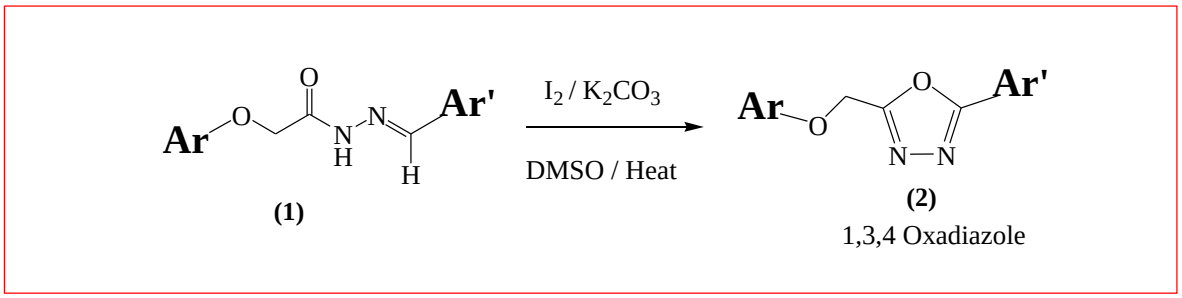
Figure 1.2 Mechanism of Oxidative cyclization of hydrazone

GENERAL PROCEDURE: 1.0 mmol Hydrazone derivative was dissolved in 5 ml dimethyl sulphoxide (DMSO), followed by addition of 3.0 mmol K_2CO_3 and stirred to dissolve[x]. Then 1.2 mmol I_2 was added slowly in small quantities. The reaction mixture was stirred for 4 to 6 hours at 100^0C to 120^0C. Reaction progress was monitored by using TLC. Reaction mixture cooled to RT followed by treatment with 5% sodium thiosulphate solution to neutralize remaining excess of Iodine present in the reaction mixture. Solid product was separated, filtered, dried and purified using SiO_2 column chromatography.

PURIFICATION: Purification of oxadiazoles performed using SiO_2 column chromatography. Silica gel used for the preparation of column was 60-120 mesh size. Solvent system used for elution of column was from 1% ethyl acetate: petroleum ether to 5% ethyl acetate: petroleum ether. All impurities were removed using column chromatography and pure products were isolated on evaporation of solvent. Yield and melting points of oxadiazole products were determined.

Synthesis of Oxadiazoles: Cyclization of aryloxy acetohydrazide hydrazones

Cyclization of *Halo*phenoxy-*N'*-(substituted benzylidene) acetohydrazide[xi] (**Scheme 1.1)**



Scheme 1.1 Reaction of Cyclization of 2-chlorophenoxy acetohydrazide hydrazones

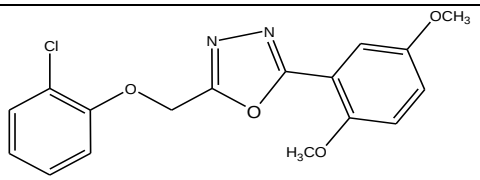
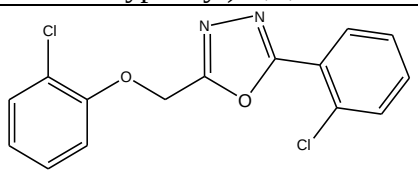
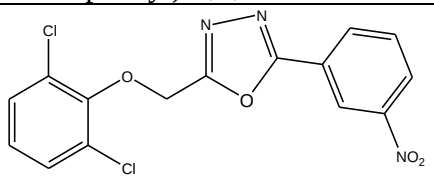
Hydrazones (**1**) were dissolved in DMSO, followed by addition of K_2CO_3 and I_2. Solid products 1,3,4 Oxadiazole (**2**) were isolated, filtered and purified.

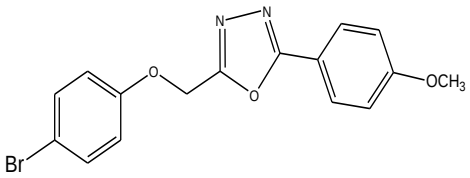
Table 1.1: Synthesis of 1,3,4 Oxadiazole derivatives

Oxadiazole	**-Ar**	**-Ar'**
2a	2-chloro phenyl	2,5 dimethoxy phenyl
2b	2-chloro phenyl	2-chloro phenyl
2c	2,5 dichloro phenyl	4-methoxy phenyl
2d	2,6 dichloro phenyl	2,5 dimethoxy phenyl
2e	2,6 dichloro phenyl	2-chloro phenyl
2f	2,6 dichloro phenyl	4-methoxy phenyl
2g	2,6 dichloro phenyl	3-nitro phenyl
2h	4-bromo phenyl	4-methoxy phenyl

These are the 1,3,4 oxadiazole derivatives were synthesized and some of them are characterized using spectroscopic methods. Characterization details are mentioned below.

Table 1.2: Characterization of Oxadiazoles:

Entry	Cyclized Product	Yield	M.P.^{0}C	^{1}HNMR data
2a	 2-((2-chlorophenoxy)methyl)-5-(2,5-dimethoxyphenyl)-1,3,4-oxadiazole	60%	165-168	3.8 (s, 3H), 3.89 (s, 3H), 5.4 (s, 2H), 6.95 (d,1H), 6.98(d, 1H), 7.05(d,1H), 7.2 (m, 2H), 7.38 (d,1H), 7.48 (d,1H)
2b	 2-((2-chlorophenoxy)methyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole	58%	150-152	5.44 (s, 2H), 6.97 (t,1H), 7.02(m, 2H), 7.23(m,1H), 7.43 (d, 1H), 7.48 (d,1H), 7.53 (t,1H), 8.01(d, 1H)
2g		62%	175-178	4.92 (s,2H), 7.48 (m,1H), 7.60(m, 3H), 8.02(d, 1H), 8.26(d, 1H), 8.37 (s. 1H)

	2-((2,6-dichlorophenoxy)methyl)-5-(3-nitrophenyl)-1,3,4-oxadiazole			Mass:M^+ ion 367.9, 359.9, 340.3, 130.1, 74.1. Due to presence of chlorine, molecular ions are showing isotopic peaks.
2h	 2-((4-bromophenoxy)methyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole	65%	100-102	3.86(s, 3H), 5.26 (s, 2H), 6.92 (d, 2H), 6.98 (d, 2H), 7.40 (d, 2H), 7.98 (d, 2H)
				Mass:m/z: 360.9, 362.9, 364.9, 282.9, 269.1, 74.2

Oxadiazoles were characterized using ^{1}HNMR spectroscopy and Mass spectrometry**.**

ANTI-MYCOBACTERIAL ACTIVITY OXADIAZOLES:

The anti-microbial studies of the compounds were screened against *Mycobacterium tuberculosis* having H37 RV strain and ATCC No- 27294, at the Department of Microbiology, Maratha Mandal's, NGH Institute of Dental Sciences and Research Centre, Belgaum. The method reported by Maria, C. S. et al.[xii]

Oxadiazoles showed very good anti-mycobacterial activity (**Table 1.3**). Minimum Inhibitory concentration values are very less. MIC values are showed in the range of 1.625µg/mL. These are significantly less than standard drugs (**Figure 1.3**) indicating more potency of Oxadiazoles than standard drugs. Results are highly encouraging and shown very good anti-mycobacterial activity.

This increase in the activity due to formation a specific interaction of substituted oxadiazole moieties with cell wall protein and interfering in cell wall formation of *Mycobacterium tuberculosis* during cell mitosis.

Table 1.3 Anti-tuberculosis assessment of Oxadiazoles

Sl. No.	**Sample**	**100 µg/ml**	**50 µg/ml**	**25 µg/ml**	**12.5 µg/ml**	**6.25 µg/ml**	**3.12 µg/ml**	**1.6 µg/ml**	**0.8 µg/ml**
2a	6c	S	S	S	S	S	S	S	R
2b	6d	S	S	S	S	S	S	S	R
2g	7a	S	S	S	S	S	S	S	R
2h	7b	S	S	S	S	S	S	S	R

S: Sensitive and R: Resistant

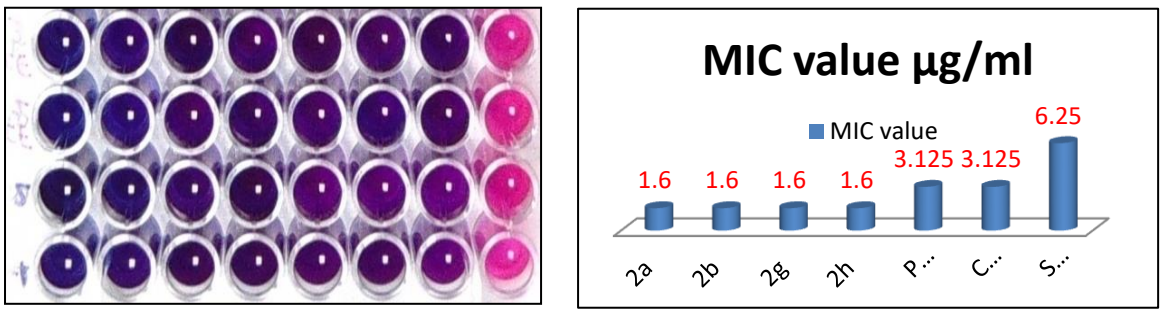


Figure 1.3 Photograph and graph of Anti-tuberculosis assessment

IN SILICO PREDICTION OF CHEMICAL ADMET PROPERTIES:

For in-silico calculations of metabolic profiles and toxicity study, the ADMET-SAR web tool was used[xiii]. It gives in silico prediction of chemical ADMET properties[xiv] such as Absorption,

Distribution, Metabolism, Excretion, and Toxicity profile for compounds (**Table 1.4**). In silico predictions such as Absorption in which Human Intestinal Absorption, Human oral bioavailability have shown good results. In Distribution: Blood Brain Barrier, P-glycoprotein inhibitor shown good results. In Metabolism properties such as CYP1A2 inhibition, CYP2C9 inhibition, CYP2C9 substrate,CYP2C19 inhibition, CYP2D6 inhibition, CYP2D6 substrate, CYP3A4 substrate, CYP inhibitory promiscuity all the compounds show good results. In the Toxicity profile carcinogenicity, Eye corrosion Eye irritation , Fish aquatic toxicity Honey bee toxicity are also showing very less or no toxicity.

CYP3A4 and CYP2D6 enzymes were showed the most significant roles in our bodies. In Ames mutagenesis all the products show nontoxic nature and Blood Brain Barrier property. It has been reported that genetic variability in these enzymes may alter patient's response to medications. From the in-silico results, it was found that all the compounds were non-substrate profile for CYP2D6, CYP2C9 whereas CYP3A4 shown substrate. All the compounds may act as inhibitors for CYP1A2, CYP2C19 and CYP2C9. The compounds showed non-inhibition in CYP3A4, CYP2D6 whereas P-glycoprotein shown inhibition for 2g and 2h. In overall results the compounds are good.

Table 1.4 In-silico calculations of metabolism and toxicity profile of oxadiazoles

Entry/ Properties	**2a**	**2b**	**2g**	**2h**
Ames mutagenesis	Non Toxic	Non Toxic	Non Toxic	Non Toxic
Blood Brain Barrier	Barrier	Barrier	Barrier	Barrier
Carcinogenicity	Non-carcinogenic	Non-carcinogenic	Non-carcinogenic	Non-carcinogenic
CYP1A2 inhibition	Inhibition	Inhibition	Inhibition	Inhibition
CYP2C19 inhibition	Inhibition	Inhibition	Inhibition	Inhibition
CYP2C9 inhibition	Inhibition	Inhibition	Inhibition	Inhibition
CYP2C9 substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
CYP2D6 inhibition	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor
CYP2D6 substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
CYP3A4 inhibition	Non-Inhibitor	Inhibitor	Non-Inhibitor	Non-Inhibitor
CYP3A4 substrate	Substrate	Substrate	Substrate	Substrate
Eye irritation	No	No	No	No
Human Intestinal Absorption	Absorption	Absorption	Absorption	Absorption
Acute Oral Toxicity	1.0931	1.6322	1.744	1.8443
P-glycoprotein inhibitor	Non-Inhibitor	Non-Inhibitor	Inhibitor	Inhibitor

RESULTS AND DISCUSSION: 1,3,4 oxadiazoles products were characterized using ^{1}HNMR spectroscopy. Signals of hydrazones at (δ, ppm; CDCl3, 400 MHz) 11-12 (s, -NH-CO), 8-9 (s, -N=CH-) disappeared or vanished and information of protons present in compound in terms of appropriate signals confirms that the cyclization has completed. (**Table 1.2)**. Oxadiazoles were screened for anti-mycobacterium studies and showed very good anti-mycobacterium activity as compared to hydrazones and assessed as per Almer blue assay method. In silico prediction of chemical ADMET properties such as Absorption, Distribution, Metabolism, Excretion, and Toxicity profile for compounds carried out through admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties.

CONCLUSION:

Compounds were screened for anti-mycobacterium studies and showed very good anti-mycobacterium activity in Almer blue assay method. In silico prediction of chemical ADMET properties such as Absorption, Distribution, Metabolism, Excretion, and Toxicity

profile for compounds were carried out through admetSAR. These results are highly encouraging and compounds may lead as a possible anti-tubercular agents in future.

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