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Synthesis, Characterization, and Anti-Mycobacterial Evaluation of Oxadiazole and Pyrazolone Derivatives

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Abstract: ***Hydrazides and hydrazones are important precursors for synthesizing heterocyclic compounds. This study focuses on the synthesis and characterization of pyrazolone and 1,3,4-oxadiazole derivatives using spectroscopic techniques. These compounds were screened for their anti-mycobacterial activity, showing promising results. Additionally, in silico ADMET predictions were performed to evaluate their chemical properties. The results indicate the potential of these derivatives as effective anti-tuberculosis agents, paving the way for further biological evaluations.***

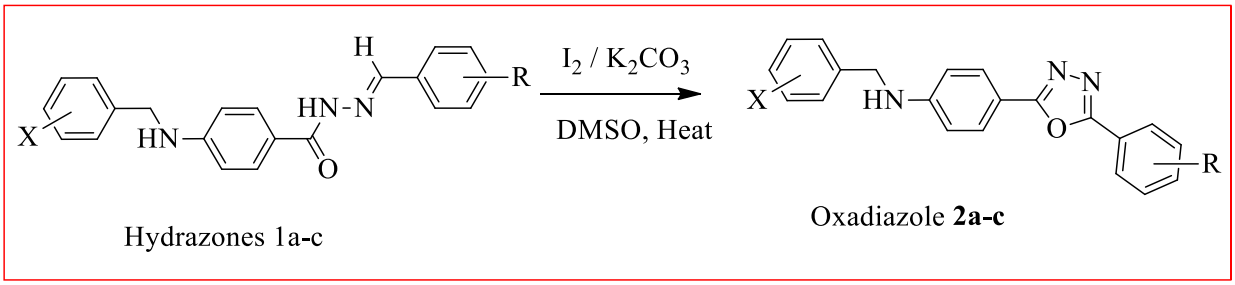
Keywords: Hydrazide, hydrazone, oxadiazole, pyrazolone, anti-tuberculosis

1. Introduction

Oxadiazoles are a class of five-membered heterocyclic compounds that belong to the azole family, with the molecular formula $C_2H_2N_2O$. They contain a nitrogen atom and at least one oxygen atom in the ring, and are available in four isomeric forms: 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole. These compounds have a wide range of pharmaceutical applications, particularly in the development of antimicrobial agents. Researchers have synthesized various oxadiazole derivatives [1] and evaluated their antimicrobial activity against a range of microorganisms, including bacteria and fungi. Patel et al [2] synthesized 1,3,4-oxadiazole derivatives that showed potent antibacterial activity against Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, and Pseudomonas aeruginosa, with a minimum inhibitory concentration (MIC) of 64-256 mg/mL. Mayekar et al. [3] reported the synthesis of 2-(6-bromo-2-naphthyloxy-methyl-5-aryl-oxadiazole and 6-bromo-2-naphthyl) oxy-methyl-5(alkyl or aryl)thio]-1,3,4-oxadiazole, which showed good antibacterial and antifungal activity. This study is significant as it explores novel oxadiazole and pyrazolone derivatives with potential anti-mycobacterial properties, addressing the urgent need for new tuberculosis treatments.

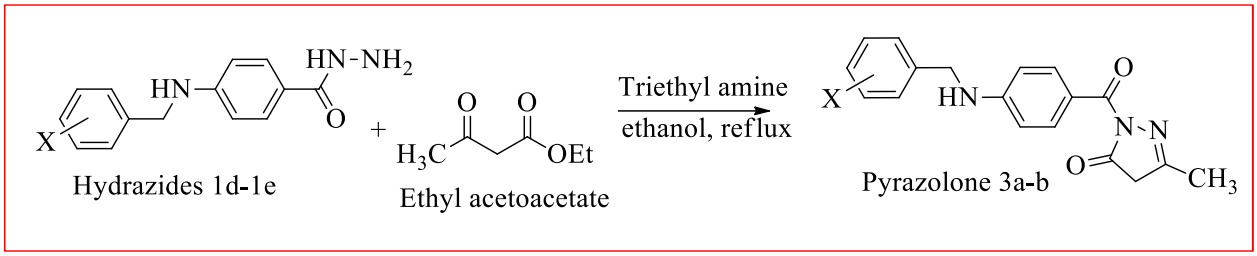
2. Experimental:

Cyclization of Acid hydrazone to Oxadiazoles:
Hydrazone [4, 5] was heated with I_2 and K_2CO_3 in dimethyl sulphoxide at 90-100^{0}C for 4- 6 hours (**Scheme 1**). Reaction progress was monitored on TLC. Reaction mixture was treated with sodium thiosulphate solution to neutralize excess of unreacted I_2. Oxadiazole product was isolated and purified using column chromatography [6].



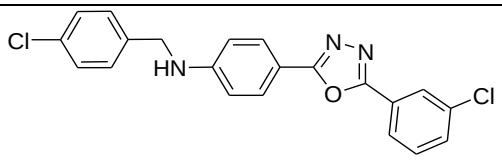
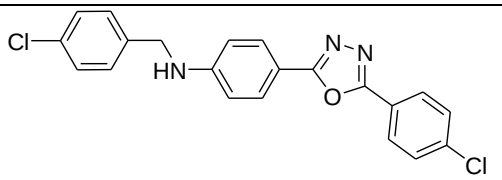
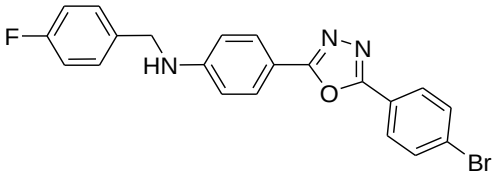
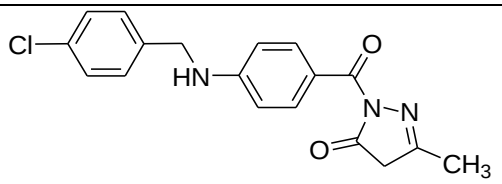
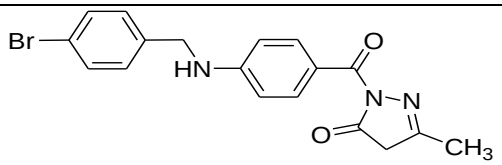
Scheme 1 Oxidative cyclization of hydrazones

Synthesis of Pyrazolones: Reaction of Acid hydrazide with Ethyl acetoacetate: As depicted in **scheme 2**, 1.0 mmol hydrazide [4] taken in 10 mL ethanol in RBF, followed by addition of 1.0 mmol ethyl acetoacetate, 5.0 mL triethyl amine and reaction mixture was refluxed for 10 hours [7]. Reaction mixture was cooled at room temperature. Solid product pyarazolone was precipitated and filtered, dried and purified using recrystallization in hot ethanol.



Scheme 2 Synthesis of pyrazolones

Table 1: Synthesis of oxadiazoles and pyrazolones

Code	Name	Structure	M.P.^{0}C	Yield
2a	N-[(4-chlorophenyl)methyl]-4-[5- (3-chlorophenyl)-1,3,4-oxadiazol- 2-yl]aniline		166-168	58%
2b	N-[(4-chlorophenyl)methyl]-4-[5- (4-chlorophenyl)-1,3,4-oxadiazol- 2-yl]aniline		158-160	62%
2c	N-[(4-Fluorophenyl)methyl]-4-[5- (4-bromophenyl)-1,3,4-oxadiazol- 2-yl]aniline		168-170	56%
3a	2-(4-{[(4-chlorophenyl)methyl]amino}benzoyl)-5-methyl-2,4-dihydro-*3H*-pyrazol-3-one		110-112	61%
3b	2-(4-{[(4-bromophenyl)methyl]amino}benzoyl)-5-methyl-2,4-dihydro-*3H*-pyrazol-3-one		118-120	64%

Characterization of Oxadiazole and Pyrazolone:
Oxadiazoles and pyrazolones are synthesized as shown in **Table 1**. 1,3,4 oxadiazoles and pyrazolones products were characterized using ^{1}HNMR spectroscopy. Signals of hydrazones at 11-12 δ, ppm (s, -NH-CO), 8-9 (s, -N=CH-) are disappeared/ vanished after the oxidative cyclization of hydrazones and information of protons present in compound appropriate in terms of signals confirms the completion of cyclization. In case of pyrazolone derivatives structure confirmed by ^{1}HNMR. Signals of -CH_2-CO-, =C-CH_3 suggest the structure.

2a: N-[(4-chlorophenyl)methyl]-4-[5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl]aniline
^{1}HNMR: 4.4(s, 2H), 6.68(d, 2H), 6.70(s. 1H) (**7**), 7.32 (m, 3H), 7.47(m, 3H), 7.9 (d, 2H), 8.18(d, 2H).

3a: 2-(4-{[(4-chlorophenyl) methyl]amino}benzoyl)-5-methyl-2,4-dihydro-3H-pyrazol-3-one
^{1}HNMR: 1.35 (t, 3H), 5.30(q, 2H), 5.36(d, 2H), 6.56(d, 2H), 6.66 (t, 1H), 7.30(d, 2H), 7.33 (d, 2H), 7.87(d, 2H)**.** In pyarazolone -CH_3 protons couples with methylene (-CH_2**)** protons through long range coupling and giving triplet while methylene protons gives quartet.

Anti-Mycobacterial Activity:
Tuberculosis is caused by Mycobacterium tuberculosis infection and is treated with antibiotics [8]. It is the most enduring infectious diseases and a leading cause of death in the world. In the low income countries due to very poor facilities of diagnosis and treatment it is main healthcare issue because the unavailability of new TB antibiotics to the clinic. Tuberculosis is an infectious disease caused by bacteria *Mycobacterium tuberculosis*.

Table 2: Anti-tuberculosis assessment

Compound	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	S	S	S	S	S	S	S	R
2b	S	S	S	S	S	S	S	R
2c	S	S	S	S	S	S	S	R
3a	S	S	S	S	S	S	R	R
3b	S	S	S	S	S	S	S	R

R: Resistant **S:** Sensitive

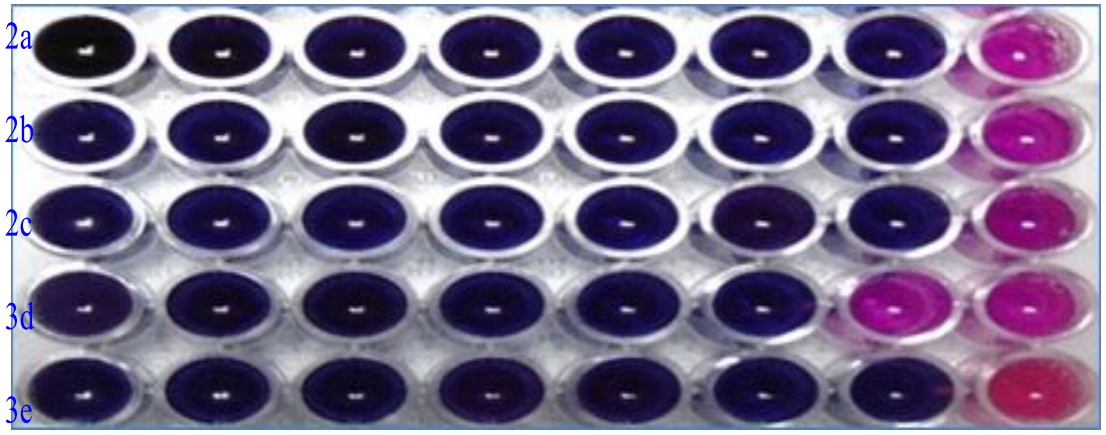


Figure 1: Photograph of Anti-tuberculosis assessment of hydrazones

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

In Silico Prediction of Chemical Admet Properties:

The in silico prediction of chemical ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties [9] for compounds has yielded promising results. Specifically, the predictions [10] for absorption have shown good accuracy, including human intestinal absorption and human oral bioavailability. In terms of distribution, the predictions for blood-brain barrier permeability, P-glycoprotein inhibition, and P-glycoprotein substrate activity have also been successful. Regarding metabolism, the compounds have demonstrated favourable properties shown in table 3 such as CYP1A2 inhibition, CYP2C9 inhibition, CYP2C9 substrate, CYP2C19 inhibition, CYP2D6 inhibition, CYP2D6 substrate, CYP3A4 substrate, and CYP inhibitory promiscuity. Furthermore, the toxicity profile of the compounds has revealed minimal or no toxicity, with low risks of carcinogenicity, eye corrosion, eye irritation, and acute oral toxicity. Overall, the in silico predictions suggest that the compounds exhibit good chemical ADMET properties, indicating their potential for safe and effective use.

Table 3: In-silico calculations of metabolism and toxicity profile of oxadiazoles and Pyrazolones

Entry/ Properties	2a	2b	2c	3a	3b
	Oxadiazole			Pyrazolone	
Ames mutagenesis	Non Toxic	Non Toxic	Non Toxic	Non Toxic	Non Toxic
Blood Brain Barrier	Barrier	Barrier	Barrier	Barrier	Barrier
Carcinogenicity	Non-carcinogenic	Non-carcinogenic	Non-carcinogenic	Non-carcinogenic	Non-carcinogenic
CYP1A2 inhibition	Inhibition	Inhibition	Inhibition	Non-Inhibitor	Non-Inhibitor
CYP2C19 inhibition	Inhibition	Inhibition	Inhibition	Inhibition	Inhibition
CYP2C9 inhibition	Inhibition	Inhibition	Inhibition	Inhibition	Inhibition
CYP2C9 substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
CYP2D6 inhibition	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor
CYP2D6 substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
CYP3A4 inhibition	Inhibitor	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor	Non-Inhibitor
CYP3A4 substrate	Substrate	Substrate	Substrate	Substrate	Substrate
Eye irritation	No	No	No	No	No
Human Intestinal Absorption	Absorption	Absorption	Absorption	Absorption	Absorption
Acute Oral Toxicity	1.632	1.705	1.840	1.734	1.694
P-glycoprotein inhibitor	Non-Inhibitor	Inhibitor	Inhibitor	Non-Inhibitor	Non-Inhibitor

3. Conclusion

This study successfully synthesized and characterized novel oxadiazole and pyrazolone derivatives using spectroscopic techniques. The anti-mycobacterial activity screening demonstrated significant potential for these compounds as anti-tuberculosis agents. Furthermore, in silico ADMET predictions confirmed favorable pharmacokinetic and toxicity profiles. These findings suggest that oxadiazole and pyrazolone derivatives warrant further biological investigations for potential therapeutic applications.

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