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Synthesis And Anti-Fungal Activity of *N'*-(3-Bromophenyl)-2-{[5-(4-Methylpyridine-3-Yl)-1,3,4-Oxadiazol-2-Yl] Sulfanyl} Acetohydrazides Derivatives

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A B S T R A C T

A series of Pyridine derivatives were prepared and evaluated for, antibacterial and antifungal activities. The title compounds were prepared by condensation of substituted aromatic aldehydes with ***N'*-(3-bromophenyl)-2-{[5-(4-methylpyridine-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides**. The structures of all these compounds were confirmed by their spectral studies. Among synthesized compounds (DK-IB, DK-IC, DK-IG, and DK-IH) have shown good anti-fungal activity and Anti-Microbial Activity (500 µg mL-1) when compared to reference drugs Ketoconazole (25µg mL-1) and Chloramphenicol (25 µg mL-1). In this study, few derivatives showed a broad spectrum of antimicrobial activity at low concentrations. The MICs (Minimum inhibitory concentration) of some compounds are 8-16µg mL-1.

Key word: Chloramphenicol, Anti-Microbial Activity, Ketoconazole, Antifungal Activity

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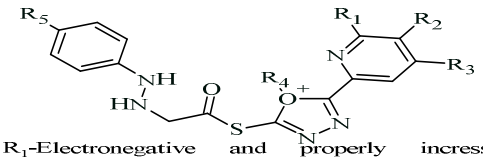
INTRODUCTION

Pyridine has the chemical formula C_5H_5N and is a fundamental heterocyclic organic molecule. It shares a structural resemblance with benzene but has a nitrogen atom in place of one of the methine groups (=CH-).Pyridine compounds are well defined by the presence of a six-membered heterocyclic ring with the chemical formula C5 H5 N, comprising of five carbon atoms and one nitrogen atom. In many aspects, it can be correlated to a well-recognized and fundamental aromatic benzene molecule, with one C-H group changed by a nitrogen atom. It was first isolated from bone oil and coal tar and characterized by Anderson in 1846. The cyclic nature of pyridine was identified by Dewar and Korner in 1869**.**

It was determined that pyridine originated from benzene and that its structure could be created by swapping a nitrogen atom for a (=CH-) moiety. In 1876, William Ramsay produced this chemical by mixing acetylene and hydrogen cyanide in a red-hot iron-tube furnace. It was the very first synthesis of a hetero-aromatic molecule. Pyridine became an interesting target in 1930 due to the role of niacin in the treatment of dermatitis and dementia[1-2].Nitrogen-containing heterocyclic chemicals are most common in the form of hormones, vitamins, and antibiotics[2]. Pyridine, like benzene, has a conjugated system of six -electrons delocalized around the heterocyclic ring. The molecule is planar in structure and meets the Hückel criterion for aromaticity[3]. As a base, pyridine can be employed as the Karl Fischer reagent, however, it is frequently substituted by alternatives with a more pleasant odour, such as imidazole.

Relationship between pyridine derivative structural activity[4].Biological activity of novel pyridine derivatives SAR study,



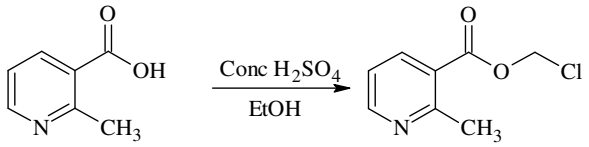
R_1-Electronegative and properly incressing substituent PPAR Activities and maintaining AT1R Antagonistic Activites
R_2-No substitution for Dual Activities
R_3-H or Optimal methyle
R4-Ethyle or propyle for dual activities larger substituentsunworkable
R_5-Tetrazole ring or Carboxilic acid

Pyridine can affect you when breathed in and by passing through your skin.

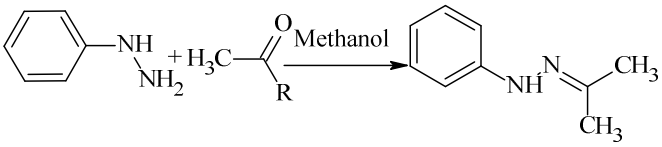
1. Contact can irritate and burn the skin and eyes.
2. Breathing Pyridine can irritate the nose and throat causing coughing and wheezing.
3. Pyridine can cause nausea, vomiting, diarrheal, and abdominal pain.

REVIEW OF LITERATURE

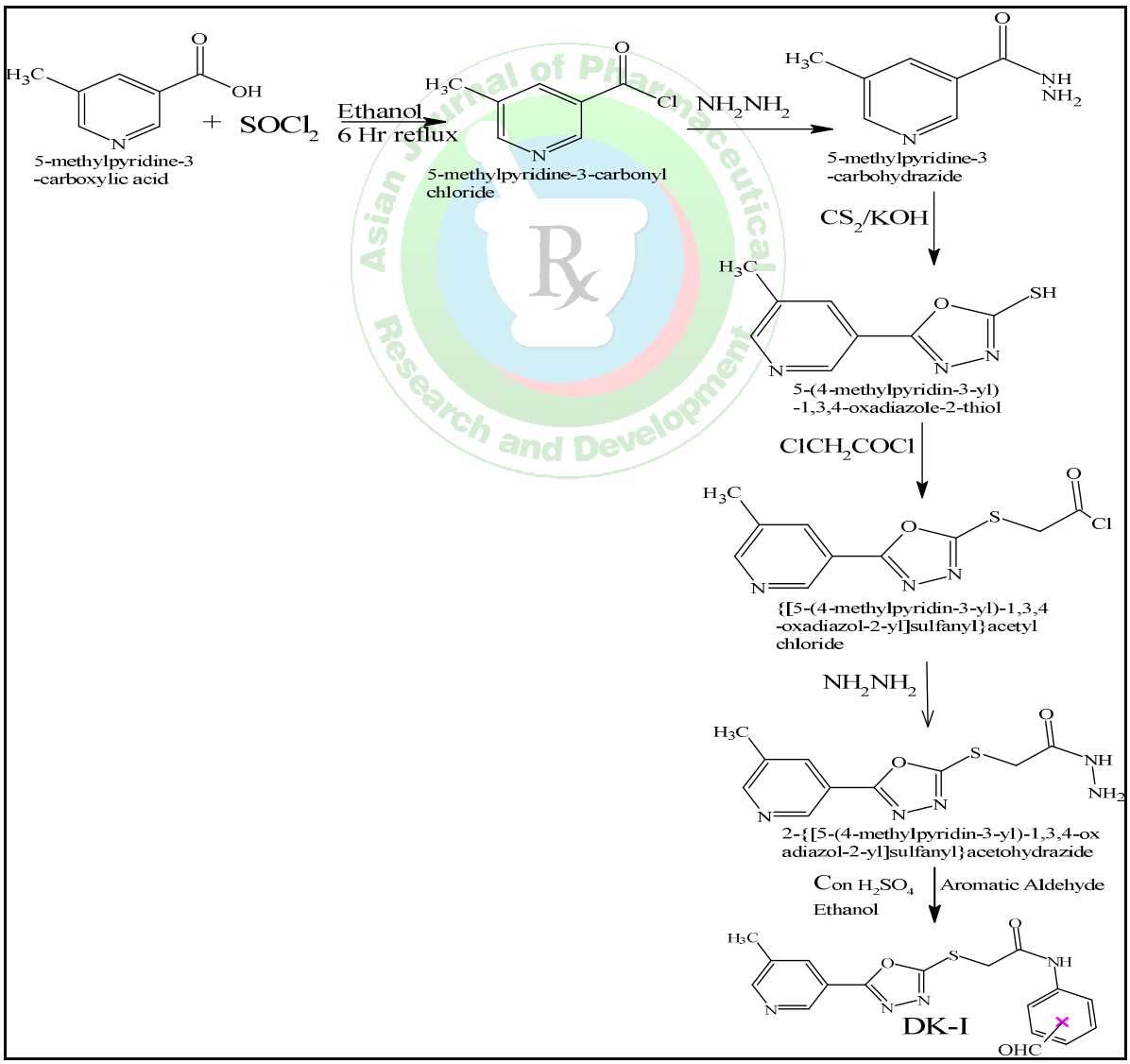
1. Vinayak Adimule et al (2014) were reported Novel Substituted Phenoxy Derivatives of 2-Chloro-N-{5-[2-(4-MethoxyPhenyl)-Pyridin-3-yl]- [1, 3, 4] Thiadiazol-2-yl}-Acetamides: Synthesis, Characterization and invitro Anticancer Properties.



2. K. C. Parmar ET al (2014) were reported Synthesis, spectral and microbial studies of some novel Schiff base derivatives of 2-amino pyridine.



SCHEME



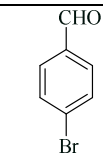
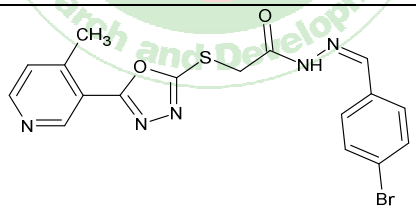
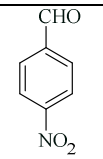
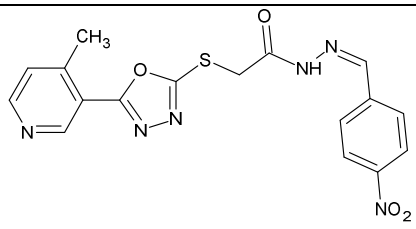
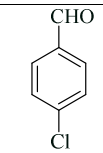
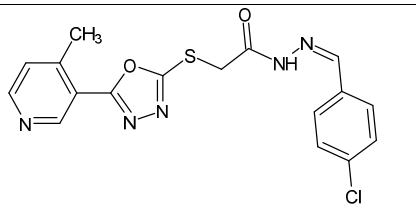
METHODOLOGY

1. **Synthesis of 5-Methylepyridine-3-carbonyl chloride**

   A mixture of 6 gm of 1 mol methylepyridine-3-carboxylic acid in 25 ml ethanol and 3.3 ml of 0.5 mol thionyl chloride was refluxed on water bath for 6 hrs. Excessof thionyl chloride was removed by distillation under reduced pressure or by adding formic acid dropwise as required and the residue so collected was used for the next step

2. **Synthesis of 5-Methylepyridine-3-carbohydrazide**
   The solution of 7 gm 5-Methylepyridine-3-carbonyl chloride in 15 ml of methanol 99% of 1.94 ml hydrazine hydrate was added and mixture was refluxed with on water bath 4 hrs. After cooling the precipitate was filtered washed with water dried under vaccum 60^0c to obtain title of compound. The crude product was recrystalized from 50% aqueous ethanol.
3. **Synthesis of 5-(4-methylpyridin-3-yl)-1,3,4-oxadiazole-2-thiol**
   A mixture of 5 gm 5-Methylepyridine-3-carbohydrazide 10 ml and carbon disulphide 0.6 ml added a solution of potassium hydroxide 0.56 gm in 50ml H_2O 50 ml ethanol was refluxed on water bath for 3 hrs then the reaction mixture was acidified with concentrated HCl. The solid product was filtered and washed with water and dried under vaccum 50^0c to obtain the compound. The crude product was recrystalized from 50% aqueous ethanol
4. **Synthesis of {[5-(4-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetyl chloride**
   Suspension of 5-(4-methylpyridin-3-yl)-1,3,4-oxadiazole-2-thiol in glacial acetic acid 30 ml and chloroacetyl chloride was drop wise with constant stirring the reaction mixture was refluxed gently at 120^0c for 5 hours and poured on crushed ice and filtered of washed with water and dried under vaccum 60^0c to obtain title compound. The crude product was recrystalised from 50% aqueous ethanol
5. **Synthesis of 2-{[5-(4-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetohydrazide**
   The {[5-(4-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetyl chloridein 15 ml of methanol 99% 1.94 ml hydrazine hydrate was added and mixture was refluxed with on water bath for 4 hours After cooling the precipitate was filtered and washed with water. Dried under vaccum 60^0c to obtain titleof compound. The crude product was recrystalized from 50% aqueous ethanol
6. **SynthesisofDerivatives*N*'-(3-bromophenyl)-2-{[5-(4-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides**
   A mixture of 2-{-5(pyridine-3-yl)-1,3,4 oxadiazole -2-yl}, sulfonylAcetohydrazides 0.01 mole and 0.1 mole Aromatic aldehyde and ethanol30ml refluxed for 5 hours the residue was stirred with ice cold water 50 ml and filtered and dried under vacuum to obtain title compound. The crude product was recrystallized from aqueous ethanol.

Table: 1 **DERIVATIVES OF *N*'-(3-BROMOPHENYL)-2-{[5-(4-METHYLPYRIDIN-3-YL)-1,3,4-OXADIAZOL-2-YL] SULFANYL} ACETOHYDRAZIDES [DK-IA TO DK-IH]**

Compound Code	Aromatic Aldehydes	Aromatic Aldehyde With Compound DK-IA TO DK-IH	Molecular Name
DK-IA	 4-bromobenzaldehyde		*N*'-(3-bromophenyl)-2-{[5-(4-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides
DK-IB	 4-nitrobenzaldehyde		*N*'-(4-nitrophenyl)-2-{[5-(4-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides
DK-IC	 4-chlorobenzaldehyde		*N*'-(4-chlorophenyl)-2-{[5-(4-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides

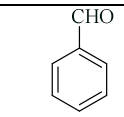
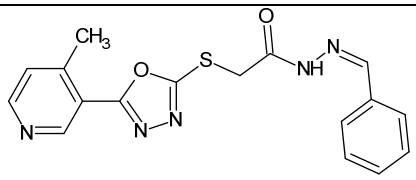
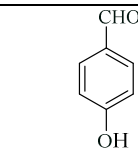
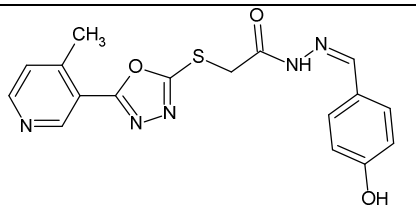
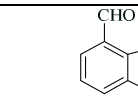
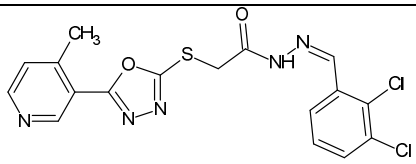
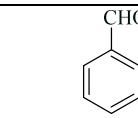
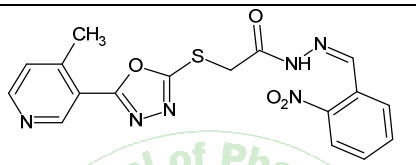
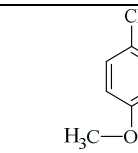
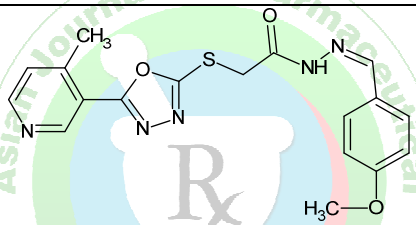
DK-ID	 benzaldehyde		*N*'-[(*Z*)-phenylmethylidene]-2-{[5-(methylepyridin-3-yl)-1,3,4oxadiazol-2-yl] sulfanyl} acetohydrazides
DK-IE	 4-hydroxybenzaldehyd		*N*'-[(3-hydroxyphenyl) methyl]-2-{[5-(methylepyridin-3-yl)-1,3,4oxadiazol-2-yl] sulfanyl} acetohydrazides
DK-IF	 2,3-dichlorobenzaldehy		*N*'-[(*Z*)-(2,3-dichlorophenyl) methylidene]-2-{[5-(methylepyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides
DK-IG	 2-nitrobenzaldehyd		*N*'-[(*Z*)-(o-nitrophenyl) methylidene]-2-{[5-(methylepyridin-3-yl)-1,3,4 oxadiazol-2-yl] sulfanyl} acetohydrazides
DK-IH	 4-methoxybenzaldehy		*N*'-[(*Z*)-(4-methoxyphenyl) methylidene]-2-{[5-(methylepyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides

TABLE 2: Physicochemical Properties of Derivatives of Compound N'-(3- Bromophen yl)-2-{[5-(4-Methylpyridin-3-yl)-1,3,4-Oxadiazol-2-yl]Sulfanyl} Acetohydrazides **[DK-IA to DK-ID]**

Sr. No	Parameter	DK-IA	DK-IB	DK-IC	DK-ID
1	Molecular Formula	$C_{17}H_{14}BrN_5O_2S$	$C_{17}H_{14}N_6O_4S$	$C_{17}H_{14}ClN_5O_2S$	$C_{17}H_{15}N_5O_2S$
2	Molecular weight	432.29gm/mol	398.39gm/mol	388gm/mol	353.39gm/mol
3	Theoretical yield	7.04gm	5.85gm	5.56gm	4.66gm
4	Practical yield	5.80gm	4.09gm	4.5gm	3.2gm
5	% Yield	82.38%	69.91%	80.93%	68.66%
6	Melting point	84-86°C	111-113°C	119-121°C	182-184°C
7	Recrystal^{n}solvent	Ethanol	Chloroform	Ethanol	Ethanol
8	TLC (mobile phase)	Benzene: Methanol (5:0.1)	Benzene: Methanol (5:0.1)	Benzene: Methanol (5:0.1)	Benzene: Methanol (5:0.1)
9	R_f value	0.9	0.7	0.6	0.8

Table 3: Physicochemical Properties of Derivatives of Compounds N'-(3-Bromophen yl)-2-{[5-(4-Methylpyridin-3-yl)-1,3,4-Oxadiazol-2-yl]Sulfanyl} Acetohydrazides [DK-IE to DK-IH]

Sr. No	Parameter	DK-IE	DK-IF	DK-IG	DK-IH
1	Molecular Formula	$C_{17}H_{15}N_5O_3S$	$C_{17}H_{13}N_5O_2SCl_2$	$C_{17}H_{14}N_6O_4S$	$C_{18}H_{17}N_5O_3S$
2	Molecular weight	370gm/mol	422gm/mol	398.39gm/mol	383.42gm/mol
3	Theoretical yield	5.1gm	6.68gm	5.85gm	5.49gm
4	Practical yield	4.00gm	4.9gm	3.9gm	4.8gm
5	% Yield	78.43%	73.35%	66.66%	87.43%
6	Melting point	159-161°C	169-171°C	159-161°C	135-161°C
7	Recrystallization solvent	Ethanol	Ethanol/ DMF	Ethanol/ Chloroform	Ethanol/ chloroform
8	TLC (mobile phase)	Benzene: Methanol (5:0.1)	Benzene: Methanol (5:0.1)	Benzene: Methanol (5:0.1)	Benzene: Methanol (5:0.1)
9	R_f value	0.6	0.8	0.9	0.7

DATA ANALYSIS

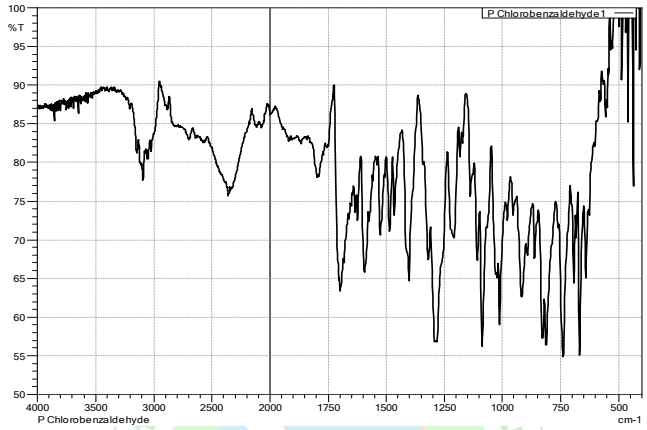


Figure 1: FT-IRSpectra *N*'-(4-chlorophenyl)-2-{[5-(4-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides [DK-IC]

Table 4: *FT-IR DataN*'-(4-chlorophenyl)-2-{[5-(4-methylpyridin-3-yl)-1,3,4oxadiazol- 2-yl] sulfanyl} acetohydrazides [DK-IC]

Sr. No	Wave number (cm^{-1})	Functional group assigned
1	3150	N – H Stretch of 2° amine
2	3050	Aromatic C-H Stretch
3	2945	Aliphatic C-H Stretch
4	1618	C = O Stretch
5	1571	C = N Strech
6	1488,1443	C =C Strech
7	954	C-O Strech
8	751	N-H bend

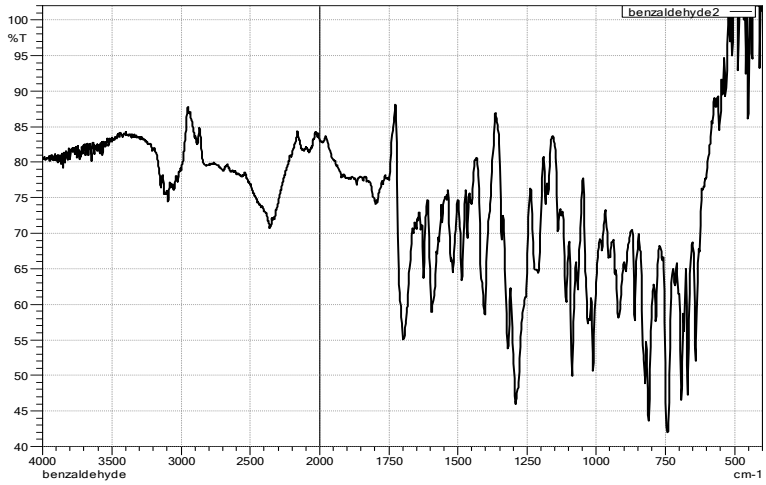
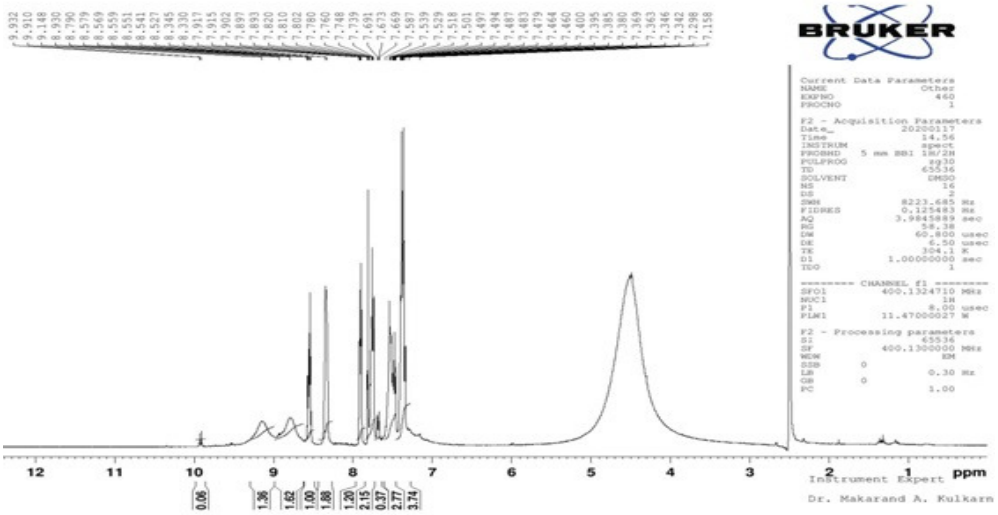


Figure 2: FT-IR Spectra *N*'-[(*Z*)-phenylmethylidene]-2-{[5-(methylepyridin-3-yl)-1,3,4oxadiazol-2-yl] sulfanyl} acetohydrazides [DK-ID]

Table 5: *FT-IR Data N'*-[(*Z*)-phenylmethylidene]-2-{[5-(methylepyridin-3-yl)-1,3,4oxadiazol-2-yl] sulfanyl} acetohydrazides [DK-ID]

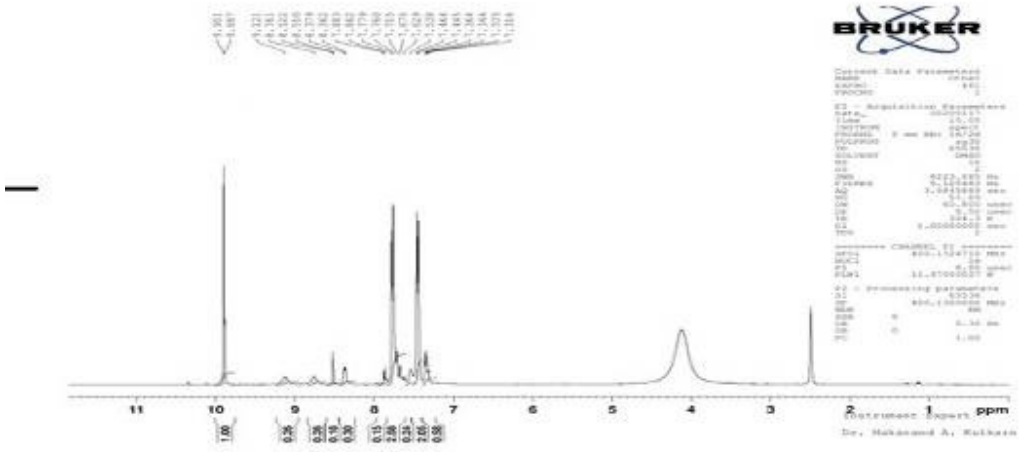
Sr. No	Wave number (cm^{-1})	Functional group assigned
1	3150	N – H Stretch of 2° amine
2	3050	Aromatic C-H Stretch
3	2945	Aliphatic C-H Stretch
4	1618	C = O Stretch
5	1571	C = N Strech
6	1488,1443	C =C Strech
7	954	C-O Strech
8	751	N-H bend

NMR-SPECTROSCOPY



[1]HNMR:δ1.04(3H, t, J=7.1Hz),2.15,2.24(3H,2.19) s,2.19s),2.70(2H, q, J=7.1Hz),6.83,7.05(3H,6.89(tt, J=8. 1,1.2Hz) dddd, J=8.3,8.1,1.4,0.5Hz),7.71,7.91(2H,7.77(dd, J=8.0,1.7Hz)7.84(dd, J=8,0,0.5Hz)) ,8.53(1H, dd, J=1.7,0.5Hz)

Figure 3: FT-IR Spectra *N'*-[(*Z*)-phenylmethylidene]-2-{[5-(methylepyridin-3-yl)-1,3,4oxadiazol-2-yl] sulfanyl} acetohydrazides [DK-ID]



[1]H NMR: δ1.04(3H, t, J=7.1Hz),2.15,2.24(3H,2.19) (s),2.19(s)),2.70(2H, q, J=7.1Hz),6.83,7.04(2H, dddd, J=8.2,2.1,0.5Hz),7.46(2H, ddd, J=8.2,1.7,0.5Hz),7.71-7.98(2H,7.77dd, J=8.0,1.7Hz),7.84(dd,J=8.0,0.5Hz)),8.53(1H, dd, J=1.7,0.5Hz)

Figure 4: FT-IR Spectra *N'*-(4-chlorophenyl)-2-{[5-(4-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides [DK-IC]

BIOLOGICAL ACTIVITY

ANTIFUNGAL ACTIVITY

The minimum inhibitory concentration (MIC) was determined by the broth dilution method (Serially diluted method). Ketoconazole has employed du6d ring the test procedures as references.MIC of the synthesized compounds ranges between 25-500µg/ml. DK-IC, DK-IG, DK-IH and were found moderate active, while DK-IA, DK-IB, DK-ID, DK-IE, DK-IF and were found to have pooractivity compared with standard. Test compounds were found to be more sensitive towards

Aspergillus niger and Candida albicans.

Table 6: Anti-Fungal activity of Compounds [DK-IA to DK-IH]

Number	Compound code	MIC µg/ml	
		C.albicans	*A. niger*
1	**DK-IA**	9	10
2	**DK-IB**	10	10
3	**DK-IC**	17	18
4	**DK-ID**	10	15
5	**DK-IE**	11	10
6	**DK-IF**	15	15
7	**DK-IG**	17	20
8	**DK-IH**	20	21
9	**Standard**	25	25
10	**Control**	-	-

[DK-IA to DK-IH] (Against Fungi)

Note: - Standard(S) = Ketoconazole Control (C) = DMF

ANTIBACTERIAL ACTIVITY

The cup plate method determined the minimum inhibitory concentration (MIC). Ciprofloxacin was employed during the test procedures as a reference. The MIC of the synthesized compounds ranges between 250-500 µg/ml.DK-IC, DK-IB, DK-IG and DK-IHwere found moderately active, while DK-IA, DK-IE,DK-ID and DK-IF were found to have an average activity compared with standard. Test compounds were found to be more sensitive toward*Staphylococcus aureus* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria).

Table 7: Anti-Bacterial activity of Compounds [DK-IA to DK-IH]

Sr No	Compound Code	*Escherichiacoli(Gram-ve)*			*S. aureus (gram+ve)*		
		Concentration of derivatives (µg/ml)			Concentration of derivatives (µg/ml)		
		250	500	750	250	500	750
		MeanzoneofInhibition (mm)					
1	DK-IA	12	13	13	11	12	15
2	DK-IB	10	11	11	11	11	12
3	DK-IC	15	19	22	13	19	21
4	DK-ID	10	11	11	11	11	12
5	DK-IE	14	22	22	12	16	20
6	DK-IF	18	18	19	12	16	20
7	DK-IG	10	11	11	11	11	12
8	DK-IH	10	11	11	11	11	12
Std	Chloramphenicol	25			25		

The minimum inhibitory concentration of synthesized compounds
[DK-IA to DK-IH] (Against Bacteria)
Note: -Standard(S) = Chloramphenicol
Control (C) = DMF (Dimethyl Formamide)

RESULT

The literature survey, reveals that pyridine has been reported for a number of pharmacological activities some molecules have shown significant activities and some compounds show moderate and good activities. Here we have synthesized some **N'-(3-bromophenyl)-2-{[5-(4-methylpyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetohydrazides [DK-IA to DK-IH] analogs** and screened them for their anti-fungal and antimicrobial activities.

The purity and homogeneity of the synthesized compounds were preliminarily checked by their physical constant and R_f value. The final compounds were found to be soluble in organic solvents. These compounds were subjected to TLC, FT-IR spectral studies, ^1H NMR studies for structural elucidation, and studies showed satisfactory results

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