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Synthesis And Anti-Microbial Activity Ofn'5-(6-Nitropyridin-3-Yl)-1,3,4-Oxadiazol-2-Yl] Sulfanyl} Acetyl Chloride Derivatives

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ABSTRACT: -
A new series of Pyridine derivatives were prepared in good yield through the reaction of **5-(6-nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetyl chloride** with a variety of **aldehydes**. The structures of the newly synthesized compounds were confirmed by Melting Point, TLC,IR, ^{1}H NMR, and mass spectral studies and elemental analysis. All the title compounds were investigated for their activity against certain strains of Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis and Streptococcus pyogenes), Gram-negative bacteria (Salmonella typhimurium, Escherichia coli and Klebsiella pneumonia) Chloramphenicol and Ampicillin were used as reference compounds. The results revealed that some of synthesized compounds displayed marked activity against all the tested microorganisms.

KEYWORD: - Anti-Microbial Activity,Chlormphenicol,Ampicillin.

I. 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.

ST-I

SAR studies of **ST-I** analogs with Aldehyde substitutions at Ring are summarized in Table No 1. A major aim of the work presented in this paper is to investigate alternative heterocycles to the 1,2triazolenalogue as novel cytotoxic agents

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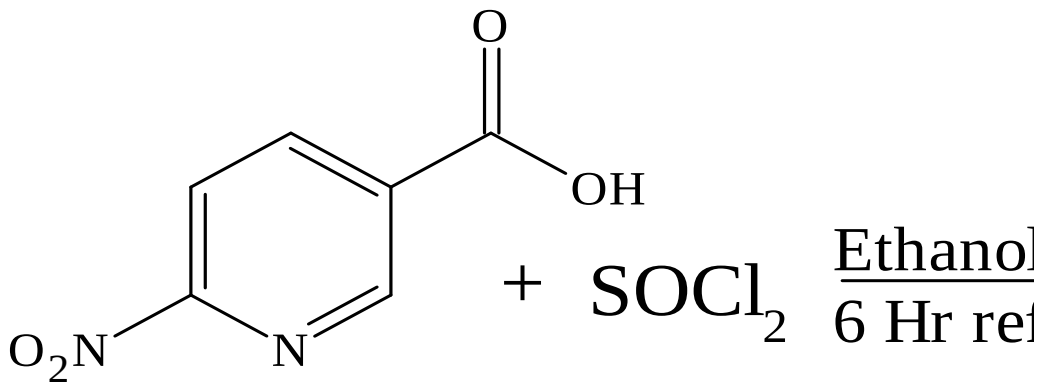
SCHEME: -



II. METHODOLOGY: -

1. Synthesis of 6-nitropyridine-3-carbonyl chloride

A mixture of 0.01 mol 6-nitropyridine-3-carboxylic acidin 25 ml ethanol and 0.01 mol thionyl chloride was refluxed on water bath for 6 hrs. Excess of thionylchloride 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 6-nitropyridine-3-carbohydrazide

The solution of 0.01 mole6-nitropyridine-3-carbonyl chloride in 15 ml of methanol 99% of 0.01 mole 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 600c to obtain title of compound. The crude product was recrystalized from 50% aqueous ethanol.

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3. Synthesis of 5-(6-nitropyridin-3-yl)-1,3,4-oxadiazole-2-thiol

A mixture of 1 mole**6-nitropyridine-3-carbohydrazide**10 ml and carbon disulphide 0.1 mole added a solution of potassium hydroxide 0.01 mole 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-(6-Nitropyridin-3-yl)-1,3,4-oxadiazol-2yl]sulfanyl}acetyl chloride**

Suspension of **5-(6-nitropyridin-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 {[5-(6-nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetyl chloride

The **5-(6-Nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetyl chloride**in 15 ml of methanol 99% 0.01 mole 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 title of compound. The crude product was recrystalized from 50% aqueous ethanol

6. **Synthesis of Derivatives N'5-(6-nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl}acetyl chloride**

A mixture of **5-(6-nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl}acetyl chloride**0.01 mole and 0.1 mole Aromatic aldehyde and ethanol 30ml 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 NO: -01 Derivatives of N'-(3-bromophenyl)-2-{[6-(4-Nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides

[ST-IA to ST-IH]

COMPOUND CODE	AROMATIC ALDEHYDEs	AROMATIC ALDEHYDE WITH COMPOUND DK-IA TO DK-IH	MOLECULAR NAME
ST-IA			N'-(3-bromophenyl)-2-{[5-(6-Nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides
ST-IB			N'-(4-nitrophenyl)-2-{[5-(6-Nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides
ST-IC			N'-(4-chlorophenyl)-2-{[5-(6-Nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2537-2544 www.ijprajournal.com ISSN: 2249-7781

ST-ID			N'-[(Z)-phenylmethylidene]-2-{[6-Nitropyridin-3-yl)-1,3,4oxadiazol-2-yl] sulfanyl} acetohydrazides
ST-IE			N'-[(3-hydroxyphenyl) methyl]-2-{[6-Nitropyridin-3-yl)-1,3,4oxadiazol-2-yl] sulfanyl} acetohydrazides
ST-IF			N'-[(Z)-(2,3-dichlorophenyl) methylidene]-2-{[6-Nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides
ST-IG			N'-[(Z)-(o-nitrophenyl) methylidene]-2-{[6-(Nitropyridin-3-yl)-1,3,4 oxadiazol-2-yl] sulfanyl} acetohydrazides
ST-IH			N'-[(Z)-(4-methoxyphenyl) methylidene]-2-{[6-(Nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides

TABLE NO: -02Physicochemical Properties of Derivatives of Compound N'-(3- Bromophen yl)-2-{[5-(6-Nitropyridin-3-yl)-1,3,4-Oxadiazol-2-yl] Sulfanyl} Acetohydrazides [ST-IA to ST-ID]

Sr. No	Parameter	ST-IA	ST-IB	ST-IC	ST-ID
1	Molecular Formula	$C_{16}H_{11}BrN_6O_4S$	$C_{16}H_{11}N_7O_6S$	$C_{16}H_{11}ClN_6O_4S$	$C_{16}H_{12}N_6O_4S$
2	Molecular weight	463.26gm/mol	429.36gm/mol	418.81gm/mol	384.36gm/mol
3	Theoretical yield	3.36gm	4.29gm	4.18gm	3.84gm
4	Practical yield	5.80gm	4.09gm	4.5gm	3.2gm

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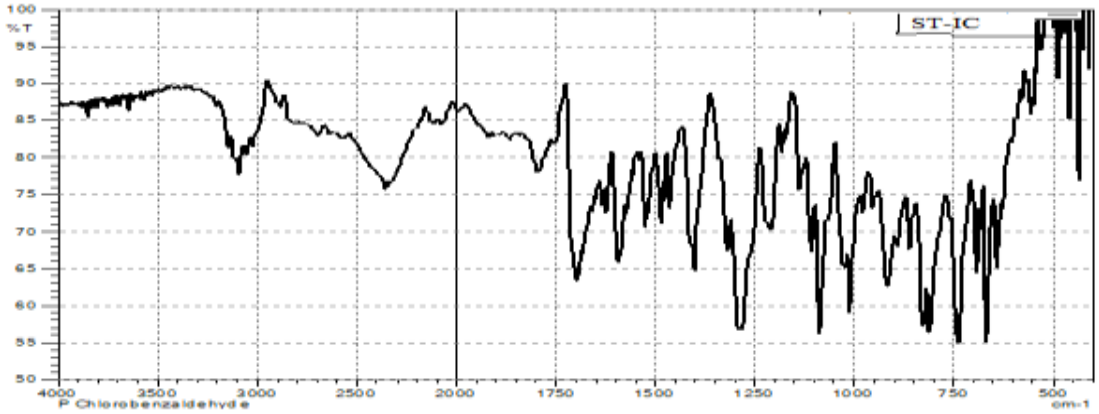
5	% Yield	57.93%	95.33%	92.88%	84.21%
6	Melting point	112-114^{o}C	120-122^{o}C	132-133^{o}C	152-154^{o}C
7	Recrystal^{n} solvent	Ethanol	Chloroform	Ethanol	Ethanol
8	TLC (mobile phase)	Benzene: Methanol (5:0.1)	Benzene: Methanol (5:0.1)	Benzene: Methanol (5:0.1)	Benzene: Methanol (5:0.1)
9	R_f value	0.9	0.7	0.6	0.8

TABLE NO: -03 Physicochemical Properties of Derivatives of Compounds N'-(3-Bromophen yl)-2-{[5-(6-Nitropyridin-3-yl)-1,3,4-Oxadiazol-2-yl] Sulfanyl} Acetohydrazides [ST-IE to ST-IH]

Sr. No	Parameter	ST-IE	ST-IF	ST-IG	ST-IH
1	Molecular Formula	$C_{16}H_{12}N_6O_5S$	$C_{16}H_{10}N_6O_4SCl_2$	$C_{16}H_{11}N_7O_6S$	$C_{17}H_{14}N_6O_5S$
2	Molecular weight	400.36gm/mol	453.25gm/mol	429.36gm/mol	419.39gm/mol
3	Theoretical yield	3.95gm	4.53gm	4.26gm	4.19gm
4	Practical yield	3.90gm	4.1gm	3.9gm	3.8gm
5	% Yield	98.73%	97.13%	91.54%	90.69%
6	Melting point	158-159^{o}C	170-171^{o}C	159-160^{o}C	130-132^{o}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: -

FIG NO: - 01 FT-IR Spectra N'-(4-chlorophenyl)-2-{[5-(6-Nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl} acetohydrazides [ST-IC]



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Sr. No	Wave number (cm^{-1})	Functional group assigned
1	3150	N – H Stretch of 2^o 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

TABLE NO: - 04 FT-IR Data N'-(4-chlorophenyl)-2-{[5-(6-Nitropyridin-3-yl)-1,3,4 oxadiazol-2-yl] sulfanyl} acetohydrazides

[ST-IC]

^{1}H NMR N'-(4-chlorophenyl)-2-{[5-(6-Nitropyridin-3-yl)-1,3,4 oxadiazol-2-yl] sulfanyl} acetohydrazides
δ 3.92 (2H, s), 6.82 (2H, ddd, J = 8.2, 1.9, 0.5 Hz), 7.13 (1H, dd, J = 7.9, 0.5 Hz), 7.46 (2H, ddd, J = 8.2, 1.7, 0.5 Hz), 8.08 (1H, dd, J = 7.9, 1.9 Hz), 8.77 (1H, dd, J = 1.9, 0.5 Hz).

FIG NO: - 02 FT-IR Spectra N'-[(Z)-phenylmethylidene]-2-{[5-(6-Nitropyridin-3-yl)-1,3,4oxadiazol-2-yl] sulfanyl} acetohydrazides [ST-ID]

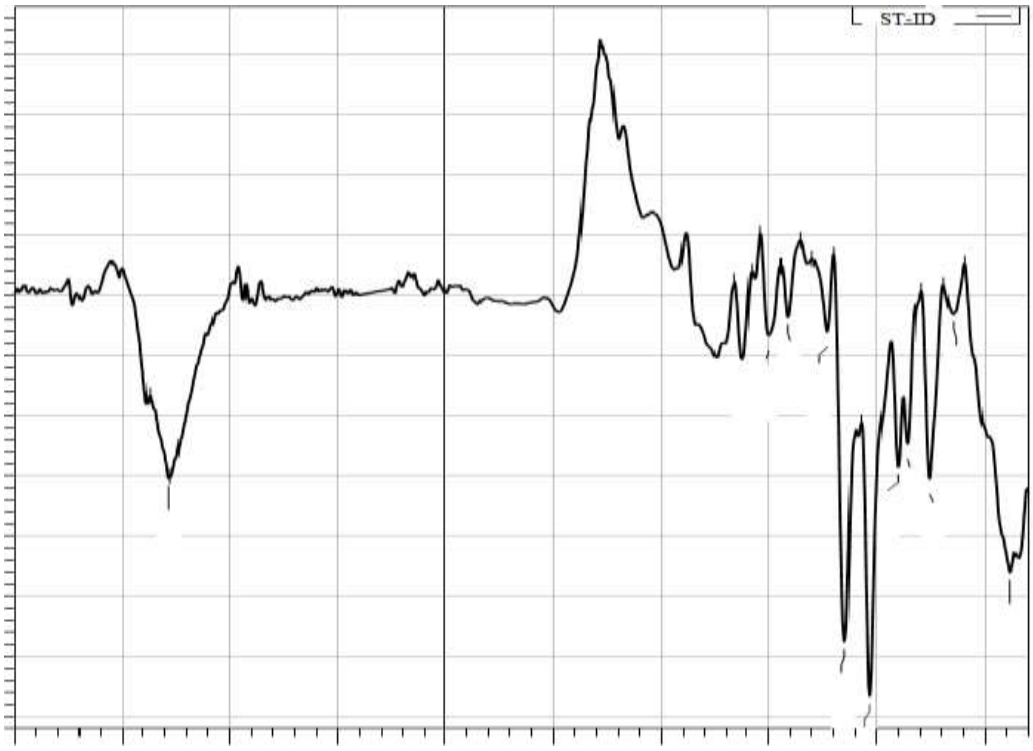

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TABLE NO: -05 FT-IR Data N'-[(Z)-phenylmethylidene]-2-{[5-(6-Nitropyridin-3-yl)-1,3,4oxadiazol-2-yl]

Sr. No	Wave number (cm^{-1})	Functional group assigned
1	3150	N – H Stretch of 2^o 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

sulfanyl} acetohydrazides [DK-ID]

^{1}H NMRN'-[(Z)-phenylmethylidene]-2-{[5-(6-Nitropyridin-3-yl)-1,3,4oxadiazol-2-yl] sulfanyl} acetohydrazides

δ 3.92 (2H, s), 6.91 (1H, tt, J = 8.1, 1.1 Hz), 6.99-7.29 (5H, 7.05 (dtd, J = 8.2, 1.2, 0.5 Hz), 7.13 (dd, J = 7.9, 0.5 Hz), 7.22 (dddd, J = 8.2, 8.1, 1.4, 0.5 Hz)), 8.08 (1H, dd, J = 7.9, 1.9 Hz), 8.77 (1H, dd, J = 1.9, 0.5 Hz).

BIOLOGICAL ACTIVITY: -

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.ST-IC, ST-IB, ST-IG and ST-IH were found moderately active, while ST-IA, ST-IE,ST-ID and ST-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 NO: - 06 Anti-Bacterial activity of Compounds

[ST-IA to ST-IH]

SrNo	CompoundCode	Escherichiacoli (Gram-ve)			S. aureus (gram+ve)		
		Concentration ofderivatives (µg/ml)			Concentration ofderivatives (µg/ml)		
		250	500	750	250	500	750
		MeanzoneofInhibition (mm)					
1	ST-IA	12	13	13	11	12	15
2	ST -IB	10	11	11	11	11	12
3	ST -IC	15	19	22	13	19	21
4	ST -ID	10	11	11	11	11	12
5	ST -IE	14	22	22	12	16	20
6	ST -IF	18	18	19	12	16	20
7	ST -IG	10	11	11	11	11	12
8	ST -IH	10	11	11	11	11	12
Std	Chloramphenicol	25			25		

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The minimum inhibitory concentration of synthesized compounds [ST-IA to ST-IH] (Against Bacteria)

Note: -Standard(S) = Chloramphenicol

Control (C) = DMF (Dimethyl Formamide)

III. 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-(6-Nitropyridin-3-yl)-1,3,4-oxadiazol-2-yl] sulfanyl}acetohydrazides [ST-IA to ST-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, ^{1}H NMR studies for structural elucidation, and studies showed satisfactory results

ACKNOWLEDGMENT

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