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STUDY ON THE CHARACTERIZATION AND SYNTHESIS OF ANTI-INFECTIVE AGENTS

Krishan kumar
Janta inter college chhajjupur dahana
District hapur 245101
Gmail id- kktomer.5k@gmail.com

ABSTRACT

Chemotherapy against fungus is dependent on biochemical differences between fungi and mammals. In contrast to bacteria, which are prokaryotes, both fungus and mammals are eukaryotes, and their biochemical distinctions are negligible. However, there are certain structural and metabolic differences, and it is these variations that serve as targets for the creation of antifungal medicines. The current standard of care for tuberculosis chemotherapy, dubbed Directly observed treatment (DOTS), is a six-month regimen consisting of a two-month cure phase with four first-line drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol. In this research, a significant number of compounds are synthesized, and the majority of the molecules examined exhibit the greatest bacteriological growth suppression at the concentrations studied. At concentrations less than 40.0µg/ml, the combinations (7e, 7g, 7h, 7i, and 7u) inhibited bacterial growth against both species. Compounds (7o) inhibited growth of both bacteria at 2.5µg/ml. additionally; all chemicals at lower concentrations must be compared to conventional Streptomycin at its MIC to determine the precise MIC of the created combinations. As a result, it can be concluded that the proposed 1, 3, 4-oxadiazole derivatives (7a-v) were effectively synthesized following the synthetic outline. Following production, the compounds were characterized using spectroscopic analysis and their biological activity was determined. All combinations shown antibacterial activity against both gramme positive and gramme negative organisms at the tested concentrations, while one of the compounds 7o showed activity at a concentration of 2.5 µg/ml. Thus, these 1, 3, 4-oxadiazole findings may be used as a starting point for developing new anti-infective drugs.

Keywords: *Detrimental, microorganism, concentration, anti-infective agents*

1. INTRODUCTION

Antibacterial agents are used to treat infectious diseases that are caused by bacteria. Antimicrobial agents are categorized into many categories. The creation of pathogenic animals resistant to all main classes of antimicrobial drugs has become a severe concern in recent years. Additionally, the emergence of multidrug-resistant strains of pathogenic organisms and the difficulties in treating immuno-compromised people have resulted in a significant increase in the prevalence of bacterial contagions. This perilous scenario necessitates the development of selective target-directed medicines with increased potency, a broader range of action, an enhanced safety profile, and effectiveness against multidrug resistant bacteria.

Thus, in light of the current trend in drug discovery, it was necessary to use a more target-based approach for the synthesis of NCEs in this study. This has necessitated the development of innovative anti-infective drugs capable of exerting wide action against both penetrating and impervious strains. One of the current trends in drug discovery and development is the investigation of novel synthetic families of compounds for their anti-infective properties. As is well known from previous synthetic chemical classes, nitrogen heterocycles including purines, pyrimidines, pyrazolines, and pyrimidinone exhibit a range of biological functions. The following is the work plan for the current study:

1. Determine the synthetic pathway for intermediates and end products.
2. Synthesis and characterization of compounds produced.
3. Evaluation of produced compounds biologically.

To begin the synthesis of planned compounds, 2-(2,4- dichlorophenoxy) aceto hydrazide is synthesized as an intermediary.

As a result, this intermediate was reacted with a substituted benzoic acid to generate the desired molecules. The suggested synthetic outlines for intermediate and final compounds are listed below.

1. Synthesis of acetohydrazide 2-(2, 4-dichlorophenoxy) The substituted phenol was reacted with ethyl chloro acetate in the presence of acetone as a solvent and K_2CO_3 in a reflux reaction. Additionally, the substituted phenoxy ester produced was reacted with hydrazine hydrate to produce the intermediate 2-(substituted phenoxy) acetohydrazide.

2. 5-((2,4-dichlorophenoxy)methyl)-1,3,4-oxadiazole-2-thiol (Scaffold-I). To synthesise the intended scaffold–I molecules, the intermediate 2-(substituted phenoxy) acetohydrazide was reacted with carbon disulphide under reflux reaction conditions in the presence of potassium hydroxide and ethanol as a solvent.

3. Scaffold-II synthetic scheme: The intermediate 2-(substituted phenoxy) acetohydrazide was treated with substituted benzoic acid in the presence of phosphoryl trichloride to get the scaffold –II molecules designed.

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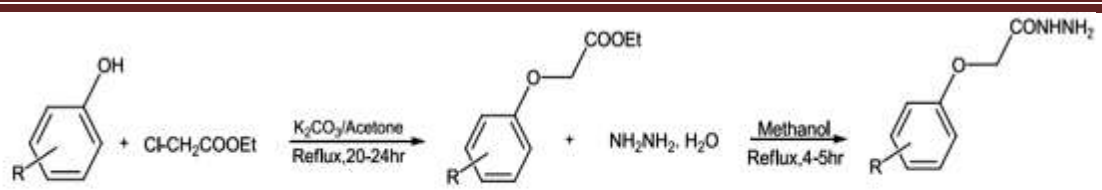
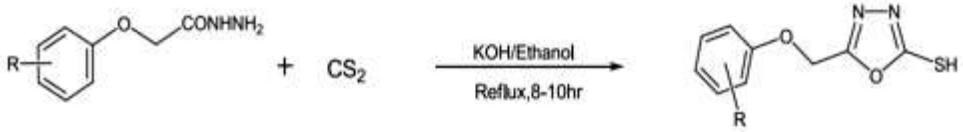
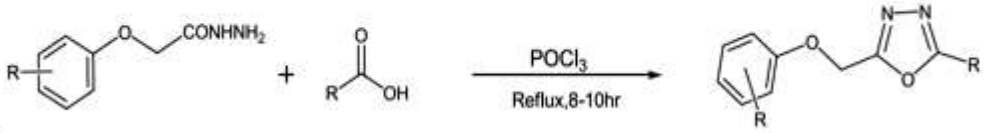


Scheme 1: General Scheme for the Synthesis of 2-(2,4-dichlorophenoxy) acetohydrazid



Scheme 2: General Scheme for the synthesis 5-((2,4-dichlorophenoxy)methyl)-1,3,4-oxadiazole-2-thiol



Scheme 3: General Scheme for the Synthesis of designed scaffold –II molecules

2. SYNTHESIS AND CHARACTERIZATION OF COMPOUNDS

1. Determination of the range of melting points
2. Analysis of T.L.C.
3. Analyses Spectral

IR, ^{1}H NMR, and mass spectroscopy will be used to characterize intermediate and final compounds synthesised.

IR Spectral Analysis: All synthesised compounds will be analyzed in the infrared spectrum to ascertain the molecule's distinctive functional group.

^{1}H NMR Spectral Analysis: A typical molecule will be characterised to ascertain the quantity and kind of hydrogen atoms contained therein.

^{13}C NMR Spectral Analysis: A typical molecule will be characterised to ascertain the quantity and kind of carbon atoms contained therein.

The Need for Novel Anti-Infective Agents:

These research focuses on synthetic compounds are pertinent to the antibacterial, and more particularly the antitubercular, class of anti-infectives. Below is a snapshot of the illness, the objectives pursued to combat it, and the current state of antitubercular medication expansion. Mycobacterium tuberculosis infection is the primary cause of death. Each year, around 9 million new instances of this illness are expected. The majority of the world's tuberculosis (TB) burden is in underdeveloped nations, which is one of the primary reasons why only 23% of prevalent active tuberculosis patients are now recognised to get appropriate antituberculosis therapy. Current treatment for communicable illnesses is constrained by the emergence of multidrug-resistant microorganisms and patients with a co-operating immune system, such as HIV/AIDS.

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The coordinated struggle of pathogens against existing anti-infective medication classes is a critical public health issue. Thus, it is necessary to enhance selective target concern with medications that have a greater potency, a broader range of action, a more favorable safety profile, and activity against multidrug resistant bacteria. The mechanisms include the following:

a) Modification of the medication's receptors
b) Compact entrance into the cell
c) Inactivation or damage to the medicine
d) Development of an alternative metabolic pathway
e) Inability of a prodrug to be metabolized

Existing classes of anti-infective agents are restricted in the following ways:

1) Act's limited scope
2) Decreased strength
3) Battle's appearance
4) Adverse circumstances
5) Selectivity

3. MATERIALS AND METHODS

Melting point, column chromatography, thin layer chromatography, infrared spectroscopy, and nuclear magnetic resonance spectroscopy were used to determine the transparency of intermediates and ready-made compounds. The melting points of the synthesised compounds were determined using the open glass capillary technique on the Janki Melting Point Apparatus and compared to the specified melting points wherever possible. The 1H- and 13C-NMR spectra of the orienting molecule were acquired using a Bruker Avance II 400 NMR spectrometer in DMSO-D6 as the solvent. Parts per million (δ, ppm) chemical changes were provided. Bruker Alpha Infra-red Spectrometer was used to identify infrared spectra. On pre-coated plates, analytical thin layer chromatography (TLC) was performed (silica gel G 254).

Chemicals used in biological testing include the following:

1) Di-methyl sulphoxide (AR Grade, CDH, Central Drug House Private Limited, New Delhi.
2) Streptomycin, a standard antimicrobial agent, was purchased from CDH.
3) For anti-bacterial tests, nutrient broth and nutrient agar were obtained from CDH, Central Drug House Pvt. Ltd., New Delhi.

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The strains utilized for testing are as follows:

- Gram-positive bacteria include Staphylococcus aureus.
- Escheria coli, Gram negative, for antimicrobial testing

Method in general

A mixture of equimolar amounts of the substituted phenol and ethyl chloroacetate was poured in a round bottom flask along with 50-60 mL acetone and anhydrous potassium carbonate (1-2gm). The mixture was refluxed over a dirt bath with gentle stirring and the reaction monitored by TLC. The reaction was maintained until all of the replacement phenol was consumed. Workup: After chilling the response mixture, it was filtered under vacuum to remove solid potassium carbonate, and the resulting filtrate was vaporised under vacuum. Under vacuum, the solvent was evaporated and the residue (liquid product) obtained was employed for the following stage.

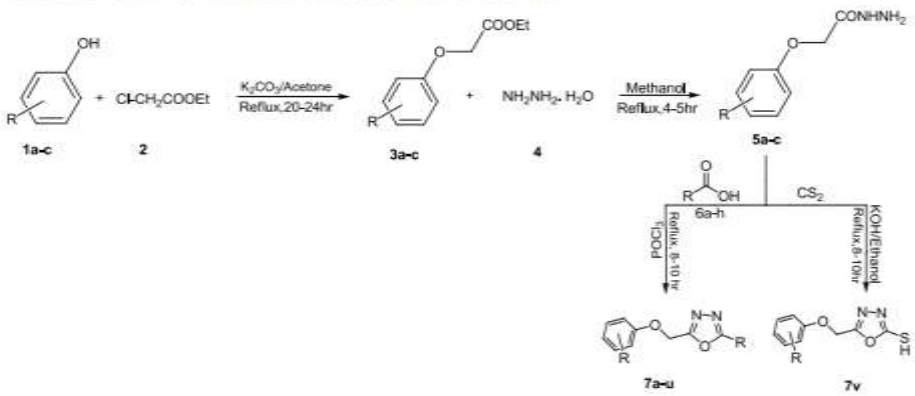
Substituted Ethyl-2- Phenoxyacetate Reaction Mechanism

Step-I: The first step of the reaction (the addition stage) involves a nucleophilic attack on the appropriately positive carbon atom of ethyl chloro acetate by one of the lone pair of electrons on the oxygen of the substituted phenol molecule, resulting in the formation of compound-I.

Step-II: The extra step (the elimination stage) involves the loss of a pair of electrons from a chloride ion, resulting in the formation of the carbon-oxygen bond.

Step-III: In the third step, the hydrogen ion is removed by the chloride ion, yielding ester and hydrogen chloride. Figure 1 illustrates the mechanics of this reaction.

General synthetic scheme for 2, 5 -disubstituted-1,3,4-oxadiazole derivatives



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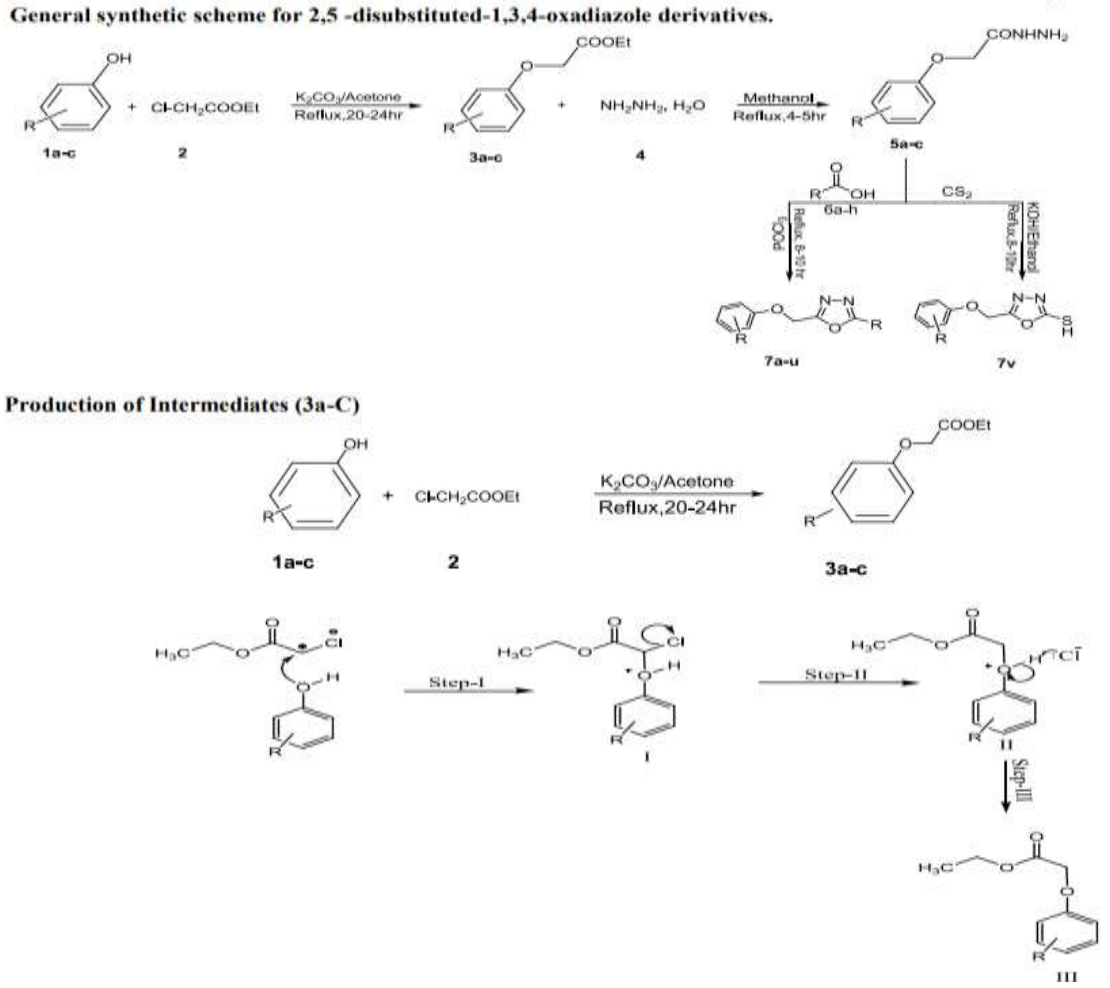
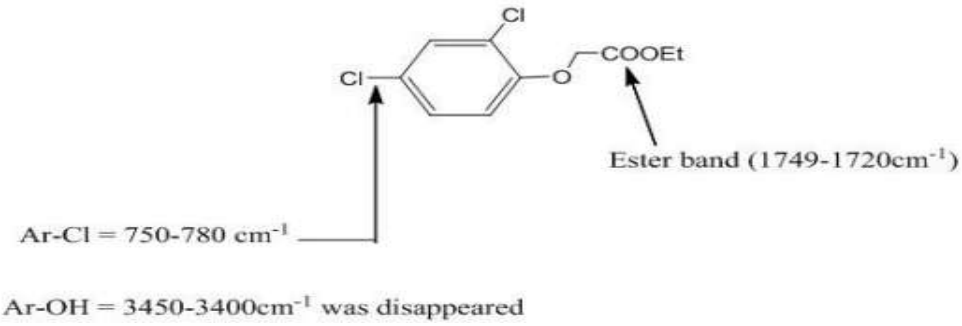


Fig 1 Mechanism of Replaced Ethyl 2-Phenoxyacetate Synthesis



Categorization of manufactured intermediate- substituted ethyl-2-phenoxyacetate

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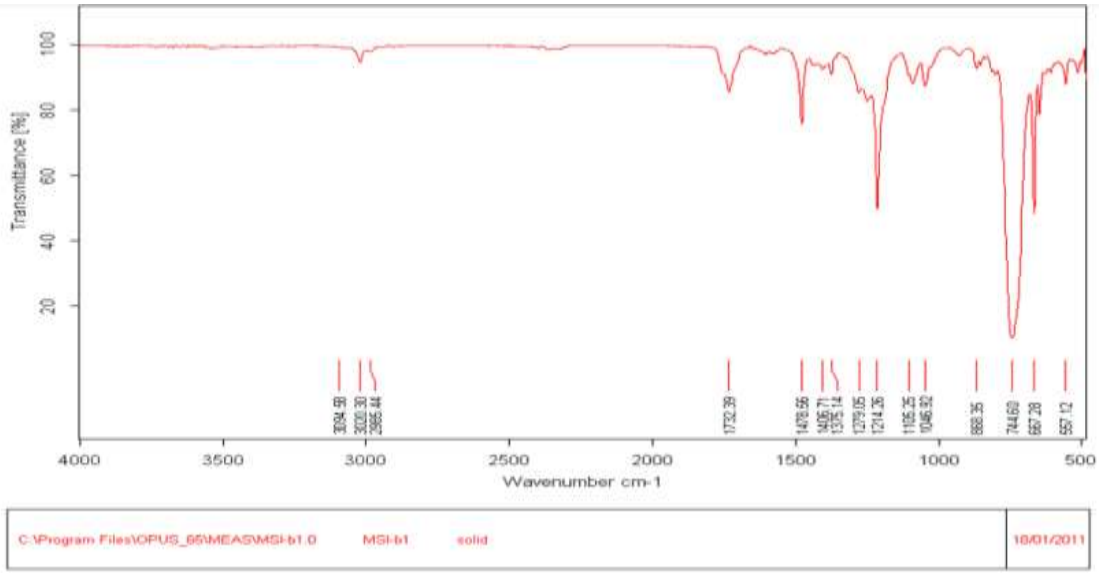
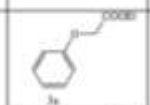
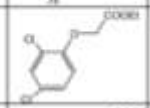
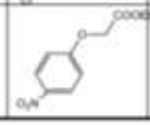
4. RESULTS AND DISCUSSIONS



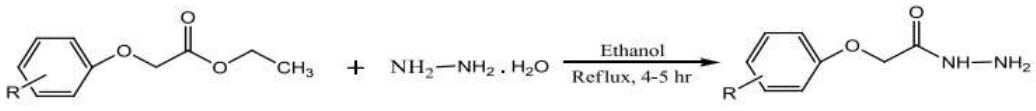
Spectrum 1 IR SPECTRUM OF SYNTHESIZED INTERMEDIATE 3b

Gradient of Manufactured Intermediates (3a-C)

Sr. No	Synthesized intermediate	Yield (%)	IR (cm^{-1})
3a		96.56	3020.32, 1732.94, 1595.22, 1497.89, 1472.39, 1374.38, 1214.69, 1090.26, 1044.69, 746.68, 696.42, 666.72
3b		92.53	3094.58, 3020.30, 2985.44, 1732.39, 1478.56, 1375.14, 1279.05, 1249.56, 1214.26, 1105.25, 1046.92, 929.20, 854.11, 744.60
3c		90.97	3062.74, 3019.59, 1749.28, 1716.97, 1592.05, 1338.83, 1213.97, 951.53, 848.51

Production of Intermediates (5a-C)

GENERAL REACTION



3a-c **4** **5a-c**

Fig 2 General synthetic scheme for substituted 2-phenoxy acetohydrazide

Production of 2,5-Disubstituted -1,3,4-Oxadiazole (7a-U)

General Reaction

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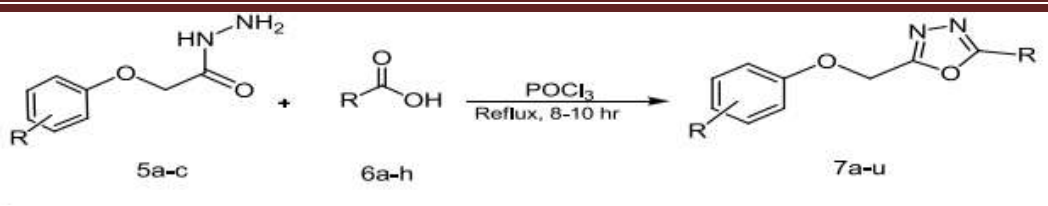


Method in general

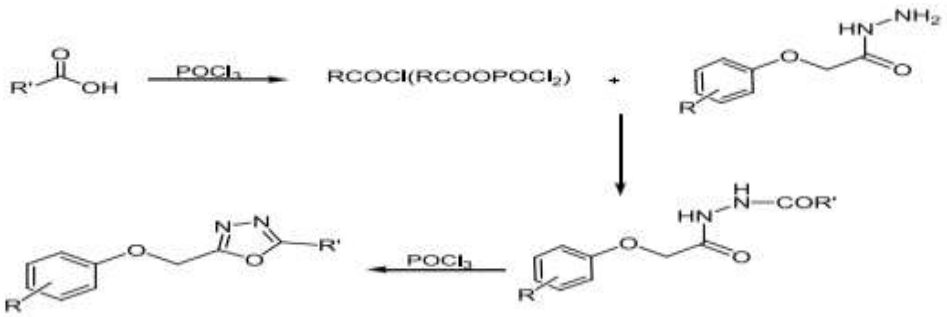
Method in general

- A mixture of equimolar amounts of replaced 2-phenoxyacetohydrazide and replaced aromatic acid was suspended in 5 ml phosphoryl tri chloride in a round bottom flask.
- The mixture was refluxed over a dirt bath with gentle stirring and the reaction was monitored using thin layer chromatography.
- The reaction was carried out indefinitely until the substituted 2-phenoxyacetohydrazide was totally depleted.

Workup:

- When cold, the reaction mixture is gently extinguished into broken ice and neutralized with solid sodium bicarbonate.
- To remove solid sodium bicarbonate, the solid was filtered under vacuum and rinsed with cold water. The strained material was then dried.

Mechanism of 2, 5-disubstituted -1,3,4-oxadiazole production:



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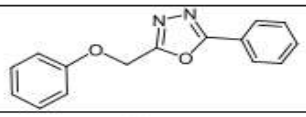
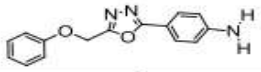
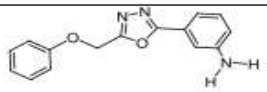
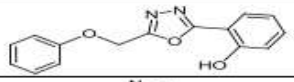
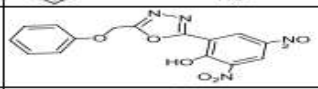
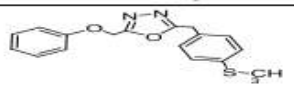
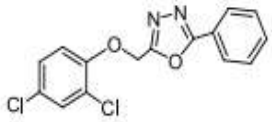
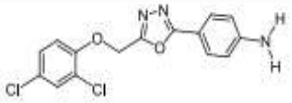
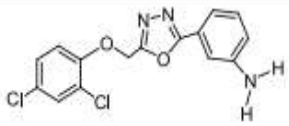
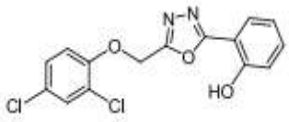
S. No	Synthesized molecule	m.p (°C)	Yield (%)	IR (cm^{-1})
7a		95-100	78.95	3011.86, 2977.55, 2966.99, 1635.48, 1597.58, 1556.61, 1436.47, 1237.48, 1175.15, 973.13, 771.21, 752.61
7b		135-140	90.68	3066.88, 3033.69, 2977.96, 1662.08, 1540.49, 1496.42, 1172.78, 995.29, 896.02, 828.55
7c		155-160	89.44	3110.94, 3077.17, 3020.98, 1669.60, 1615.92, 1418.10, 1317.71, 1219.69, 1090.33, 772.61
7d		120-125	90.06	3067.99, 3012.03, 2948.61, 2890.45, 1652.29, 1540.77, 1456.56, 1219.55, 772.51, 688.50
7e		105-110	91.66	3088.73, 3055.12, 3021.90, 1598.93, 1540.10, 1489.26, 1338.88, 1219.60, 855.69, 772.46
7f		125-130	87.76	2946.08, 2838.51, 1698.90, 1635.69, 1496.90, 1473.30, 1362.27, 1216.53, 1136.47, 843.65

Mechanism Of 2, 5-Disubstituted -1, 3,4-Oxadiazole Synthesis.

List of Synthesized Molecules

S.NO	Synthesized Molecule	M.P(°C)	Yield (%)	IR (CM^{-1})
7g		115-120	85.29	3094.58, 3020.30, 2985.44, 1732, 1478, 1375, 1279, 1249, 1105, 929, 854, 744
7h		>250	88.11	3344.56, 3274.44, 3024.34, 2922.61, 1647.19, 1558.52, 1558.52, 1473.93, 1156.29, 951.89, 798.86
7i		>250	78.32	334.31, 3139.63, 1558.60, 1520.61, 1464.99, 1295.24, 1204.84, 756.31
7j		>250	90.21	3336.78, 2925.45, 2854.17, 1652.45, 1624.40, 1540.76, 1474.58, 1435.42, 1388.64, 1289.03, 1212.89, 1157.69, 1102.84, 1072.37, 799.08

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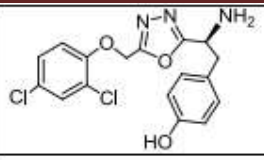
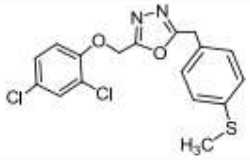
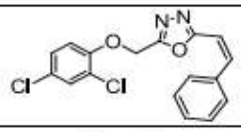
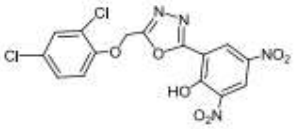
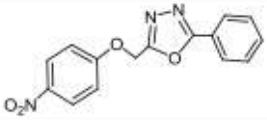
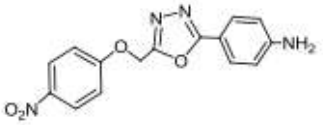
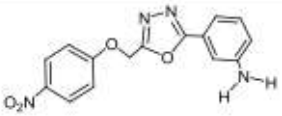
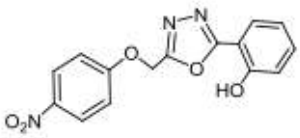
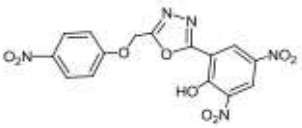
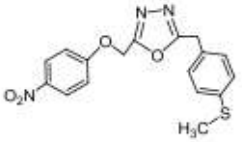
7k		110-115	90.66	3087.57, 2921.42, 2872.32, 2839.16, 1652.87, 1558.45, 1540.74, 1464.77, 1339.21, 1219.56, 883.79, 772.31, 729.42
7l		>250	79.63	3177.48, 3022.63, 2900.55, 1601.85, 1525.74, 1474.15, 1391.16, 1226.00, 991.53, 870.75, 793.81, 763.13
7m		> 250	97.30	2975.41, 2932.90, 1683.87, 1647.21, 1558.45, 1533.57, 1507.23, 1448.15, 1219.86, 773.05
7n		140-145	78.39	3446.78, 3013.35, 2976.92, 2938.40, 1662.62, 1635.81, 1558.45, 1507.23, 1473.54, 1219.90, 1084.93, 771.72

S.NO	SYNTHESIZED MOLECULE	M.P(°C)	Yield (%)	IR (CM^{-1})
7o		150-155	90.78	3065.81, 3003.83, 2946.86, 1698.96, 1669.97, 1647.22, 1558.41, 1520.83, 1473.33, 1087.92, 940.84, 689.52
7p		100-105	89.19	3333.63, 3295.67, 3136.42, 2907.44, 1635.61, 1591.39, 1508.27, 1340.76, 1251.21, 1175.91, 1111.09, 844.68, 749.56
7q		120-125	93.24	3296.10, 3241.23, 3110.94, 3077.03, 1590.12, 1507.54, 1435.99, 1339.53, 1250.66, 843.50, 797.27
7r		>250	91.89	3054.50, 2977.28, 2908.40, 1516.22, 1340.38, 1251.29, 1220.74, 1064.25, 845.02, 772.63
7s		>250	92.67	3024.44, 2984.84, 1621.48, 1539.88, 1456.63, 1374.18, 1339.92, 1286.23, 1063.36, 865.57, 772.36
7t		>250	92.90	3039.38, 2992.33, 1652.36, 1623.35, 1558.08, 1475.23, 1220.67, 1129.95, 979.82, 867.41, 772.58

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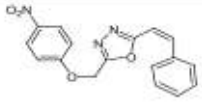
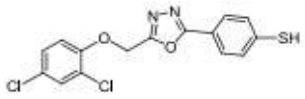
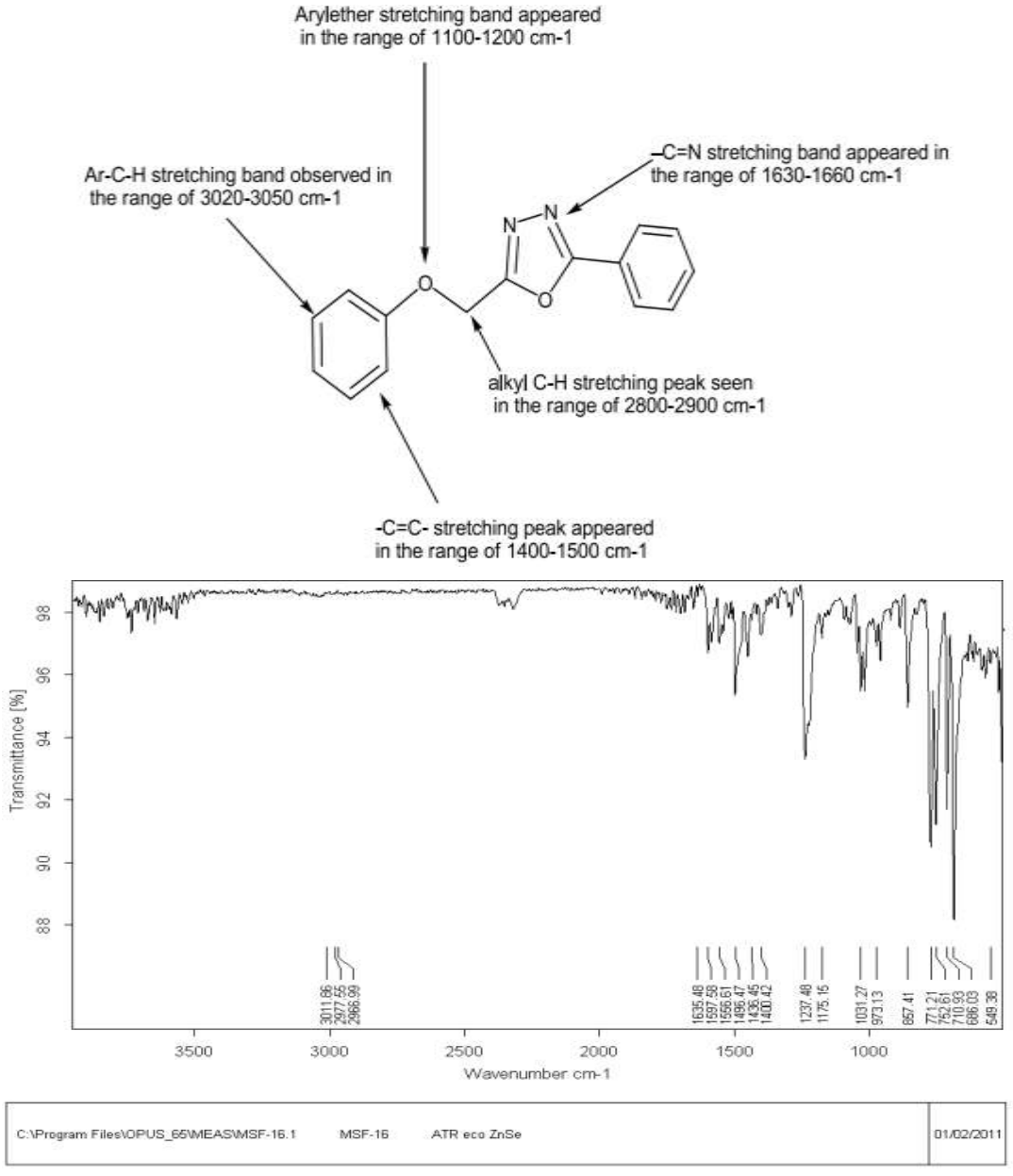
Thomson Reuters ID: L-5236-2015

7u		>250	94.12	3088.29, 3054.22, 2992.16, 1557.96, 1519.00, 1489.19, 1339.19, 1258.85, 1112.13, 844.76
7v		120-125	88.98	3229.10, 3013.16, 2946.86, 1698.96, 1669.97, 1558.41, 1520.83, 1473.33, 1087.92, 940.84, 689.52

Categorization of 2, 5-disubstituted -1,3,4-oxadiazole:



SPECTRUM 2: IR SPECTROMETER OF SYNTHESIZED COMPOUND 7a

At about 5.4, the methylene protons showed as a singlet in 1H NMR. Between δ 6.9916 - 8.1064, the aromatic protons emerged as numerous singlets. 7a is a representative case.

The 1H NMR values for chemical 7a are presented in the table below and compared to the anticipated values (Chembio office Chemdraw Ultra 11.0). (Table 1). 7a is an illustrative case (Spectrum 2)

5. CONCLUSION

This review of novel antimicrobial agents in the drug development process illustrates the rising interest in infectious illnesses and indicates that, although significant progress has been achieved, more efforts are essential to generate more promising medicines.

Hopefully, these medicines will overcome present class constraints and strike a careful balance between wide spectrum action and target specificity. Additionally, as previously said, the present trend in drug discovery and development may be summarized as follows:

1) Towards the identification of novel chemical types
2) Synthesis of analogues of well-characterized chemical classes in order to enhance their biological profile.
3) A target-based strategy to the synthesis of novel medicines capable of achieving an adequate degree of selectivity for antibacterial activity.

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