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Synthesis Characterization of 1,3,4 Oxadiazole and Its Pharmacological Activity

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ABSTRACT

We report the synthesis as well as biological assessment of 1,3,4-oxadiazole substituted 24 derivatives as novel, potential antibacterial agents. The structures of the newly synthesized derivative was established by the combined practice of UV, IR, 1H NMR, 13C NMR, as well as mass spectrometry. Further those synthesized derivative was subjected to antibacterial activity against all the selected microbial strains in comparison with amoxicillin and cefixime. The antibacterial activity of synthesized derivatives was connected with their physicochemical as well as structural properties by QSAR analysis using computer assisted multiple regression analysis and four sound predictive models were generated with good, and Fischer statistic. The derivatives with powerful antibacterial activity were subjected to molecular docking studies to investigate the interactions between the active derivatives and amino acid residues existing in the active site of peptide deformylase to estimate their antibacterial potential as peptide deformylase inhibitor.

Keywords : 1,3.4- Oxadiazole, heterocyclic compounds, alkylation, sonication

I. INTRODUCTION

Oxadiazoles are heterocyclic compound which contain two nitrogen atoms during a five membered ring possessing a diversity of a useful biological activity. Oxadiazole is taken into account furan by replacement of two methane (-CH=) groups by two nitrogen atom (-N=).

The commonly used synthetic route for 1,3,4-oxadiazoles includes reaction of acid hydrazides with acid chlorides.

From the literature survey oxadiazoles was found to be having diverse activity like anti-inflammatory, antimicrobial, antifungal, antiviral. Several methods are reported within the literature for the synthesis of 1,3,4-oxadiazoles.

The commonly used synthetic route for 1,3,4-oxadiazoles includes reactions of acid hydrazides (or hydrazine) with acid chlorides/carboxylic acids and direct cyclization of diacylhydrazines employing a kind of dehydrating agents like phosphorous oxychloride, thionyl chloride, phosphorous

pentaoxide, triflic anhydride, oxyacid and direct reaction of acid with (N-isocyanimino-) triphenylphosphorane.

We've investigate substituted 1,3,4-oxadiazole derivatives as antibacterial agents. We will distinguish several isomeric kinds of oxadiazole, which occure within the structure of many drugs, eg., anticancer zibotentan, antimicrobial furamizole, antiviral raltegravir.

The chemistry of heterocyclic compound is a remarkable interesting field of study since a protracted time. Oxadiazole plays a major role among another heterocycle. from the literature survey oxadiazole was found to be having diverse activity like anti-inflammatory, antimicrobial, antifungal, antiviral, analgesic, anti-mycobacterial, antidepressant, anticancer.

In-silico PASS Prediction is Prediction of Activity Spectra of gear i.e., Molecular Docking of drugs. Molecular docking is a lovely scaffold to grasp drug biomolecular interactions for a rational drug design and discovery, also as within the mechanistic study by placing a molecule (ligand) into the well-linked preferred binding site of the target specific region of the DNA/protein (receptor) mainly during a in a non-covalent fashion to create a stable complex of potential efficacy and more specificity. The knowledge obtained from the docking technique are often accustomed suggest the energy, free energy and stability of complexes. At present, docking technique is employed to predict the tentative binding parameters of ligandreceptor complex.

II. RELEVANCE AND MOTIVATION

Antimicrobial resistance (AMR) is one in all the most problems of recent medicine. Poor treatment of infections, over-prescription of antibiotics and their inappropriate use by patients have made a number of microorganisms insensitive to currently used drugs. This causes great difficulties in treatment because the antibiotics or other antimicrobial drugs used to date aren't any longer effective and infections become progressively difficult to treat. AMR is an increasingly serious threat to life and public health. Without effective antibiotic therapy, the value of caring for patients with drug-resistant infections increases, and there's an enormous risk during surgery and other medical procedures.

Antimicrobial resistance occurs when microorganisms develop the flexibility to defeat drugs designed to kill them. There's great diversity of microbial defence strategies. One in all ways to cater to deal with the AMR problem is that the synthesis of recent medicinal substances to which microorganisms are sensitive. Researchers round the world are performing on new molecules that will stop the event of resistance.

After studying both of this problem it is planned to synthesize a unique series of 1, 3, 4- Oxadiazole derivatives and to test their activity as Anticancer, Antimicrobial etc. Different derivatives of 1, 3, 4-Oxadiazole may give us effective anticancer drug with less side effects and effective antimicrobial drug to which microorganisms are sensitive.

Objectives: The prime objectives of this study are as follows

I. To synthesize N-Substituted 1, 3, 4-oxadiazole derivatives by Conventional and microwave method.

II. To determine Melting point, Percentage yield, Chromatographic detection and characterization of synthesized product by IR spectra.

III. To perform the Molecular Docking study and polymorphism study of synthesized compound.

IV. To perform pharmacological screening such as Anticancer, Antimicrobial activities etc. V.

V. To analyze data statistically.

III. EXPERIMENTAL WORK

Materials and methods:

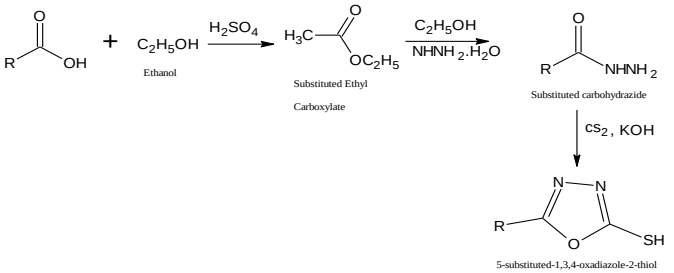
All chemicals and solvent were procured from commercial sources, purified and dried using standard procedure from literature reagents were purchased from research lab islampur. Loba Research lab (Mumbai) and issued from store department Rajarambapu college of Pharmacy, Kasegaon.

Melting point were determined by open capillary methods.

Thin layer chromatography was done using silica Gel-G plates of size 3*8cm and the final spot-on TLC plate using various solvent such as n-hexane, ethylacetate, and visualized by iodine chamber.

IR spectra were recorded using ATR on JASCO FTIR -4600. HI-NMR spectra were performed and their chemicals shifts are reported in sigma units with respects to TMS as internal

Methods – By Conventional Method



Where,R -is a different substituted carboxylic acid such as Phthalic acid and Nicotinic acid

a) Step 1st: Synthesis of substituted Dithiocarbazane

Step 2:

Synthesis of 3-(4amino -5 sulfonyl -4H-1,2,4triazole -3-yl) substituted aroyl chloride using substituted Dithiocarbazate.

Experimental Section:

A) Synthesis of 1,2,4 triazole by conventional method:

Synthesis of substituted isothiocynate:

Step 1: A solution of substituted benzoyl chloride (10mmol) in acetone (50ml) was added dropwise to ammonium thiocynate (10mmol) in absolute acetone (30ml). The reaction mixture was heated (500C) under refluxed for 30 min. After completion of reaction checked by TLC. The reaction mixture was cooled to room temperature and the formed precipitate (NH4Cl) was filtered off. To the freshly prepared solution of aroyl isothiocynate derivative .

Step 2: Synthesis of substituted Dithicarbazate .

Substituted Dithiocarbazate was prepared by using Acetone (10ml), carbohydrazide (4gm) and resulting mixture was added stirred with reflux for 1-2 hrs .after completion of reaction checked by TLC.

Step 3: Synthesis of 3-(4 amino – 5 sulfonyl -4H -1,2,4 triazole -3-yl) substituted aroyl chloride

A solution of 3-(4amino -5 sulfonyl -4H – 1,2,4 triazole -3-yl) substituted aroyl chloride was prepared by using carbon disulphide (5ml) and acetone (10ml) and resulting mixture was stirred with reflux 20-30 min and added by hydrazine hydrate (15ml) and methanol (10ml) under reflux for 1-2 hrs. after compleation of reaction checked by TLC. The solid product was washed with water and purified by washing with ethanol absolute.

B. Synthesis of 1,2,4 triazole by microwave method:

Synthesis of substituted isothiocynate

Step 1: A solution of substituted benzoyl chloride (10mmol) in acetone (50ml) was added dropwise to ammonium thiocyanate (10mmol) in absolute acetone (30ml). The reaction mixture was heated (500^{0}C) under refluxed for 15min 340 Vatt. After completion of reaction checked by TLC. The reaction mixture was cooled to room temperature and the formed precipitate (NH4Cl) was filtered off. To the freshly prepared solution of aroyl isothiocynate derivative.

Step 2: Synthesis of substituted Dithiocarbazate

Substituted Dithiocarbazate was prepared by using Acetone (10ml), carbohydrazide (4gm) and resulting mixture was added stirred with reflux for 10-25 min 340Vatt. after completion of reaction checked by TLC.

Step 3: Synthesis of 3-(4 amino -5 sulfonyl -4H-1,2,4 triazole -3-yl) substituted aroyl chloride

A solution 3-(4 amino -5 sulfonyl -4H-1,2,4 triazole -3-yl) substituted aroyl chloride was prepared by using carbon disulphide (5ml) and acetone (10ml) and resulting mixture was stirred with reflux 20-30 min and added by hydrazine hydrate (15ml) and methanol (10ml) under reflux for 30-40 min 340 Vatt. After completion of reaction checked by TLC. The solid product was washed with water and purified by washing with ethanol absolute.

Material and Chemicals :

1. Materials- RBF, Condenser, Beakers, Measuring Cylinder, Magnetic Stirrer, Vacuum Filter, Conical flask, etc.

2. Chemicals- Nicotinic acid, Phthalic acid, Ethanol, Hydrazine hydrate, hydrochloric acid, KOH, CS2, ethyl acetate, n-hexane etc.

Procedure:

Step 1:

Take 3 gm of acid and add 25 ml Ethanol

↓

2 ml of Hydrazine Hydrate and add 2,3 drops of H_2SO_4

↓

Cool mixture and pour into crushed ice

↓

Filter the product and recrystallize from ethanol

Step2:

Product of first step and addition of cs2 Koh

↓

This all-reaction mixture add in a RBF

↓

Reflux for 4 hrs

↓

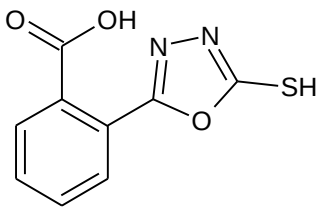
Cool mixture and pour into crushed ice

↓

Filter the product and recrystallize to get final product

1) 1st Derivative:

The acid used for 1st derivative is Phthalic acid
Final structure we got



Characterization

1.Melting point: 202^0C-204^0C 2.TLC: Mobile phase : Ethanol: cyclo hexane= 6: 4

Solvent run – 6 cm Reactant – 4. Cm Final product – 3.5 cm

Rf value = Distance travelled by solute / Distance travelled by solvent

For Reactant:

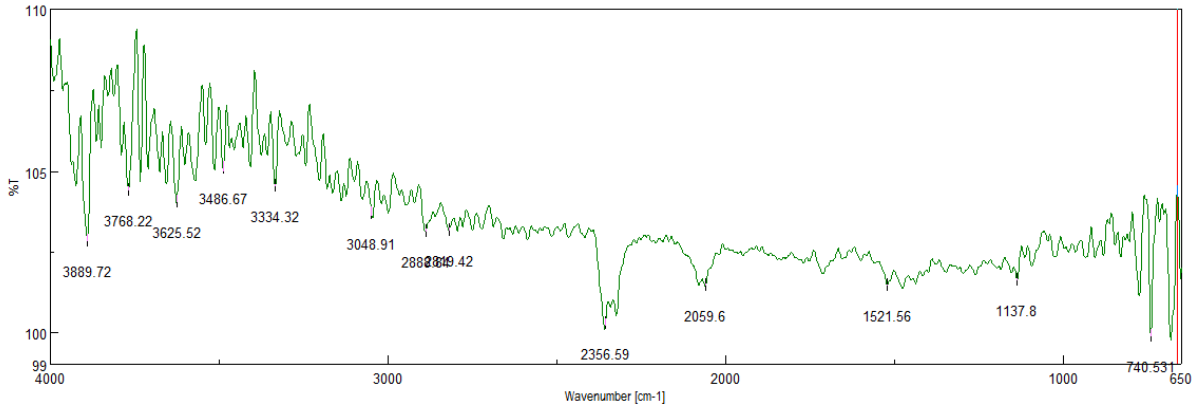
RF=4.3/6

= 0.7

For final product:

Rf =3.5/6

=0.5



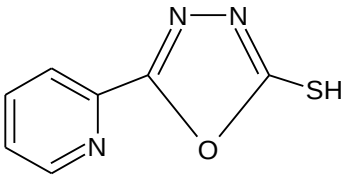
IR:

- S-H = 2600-2550
- C-O=1275-1200

2) 2nd Derivative:

The acid used in second derivative is Nicotinic acid

The structure we got :



Characterization:

1.Melting Point: 234^0C-236^0C

2. TLC: mobile Phase: ethyl acetate: n-hexane = 6ml: 4ml
Solvent run = 6 cm Reactant =4cm Final product 3.8

Rf= Distance travelled by solute/Distance travelled by solvent

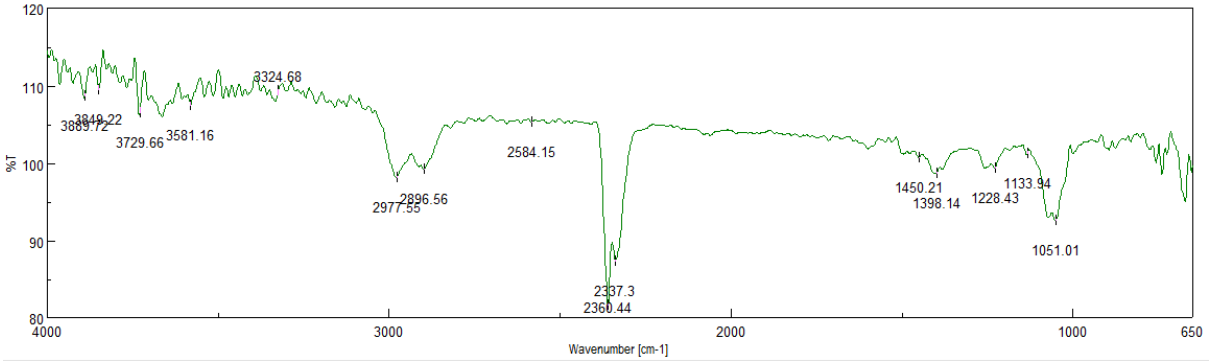
For final reactant =3.8/6

=0.6

For Reactant = 4/6

= 0.6

IR:



S-H = 2600-2550 C-O= 1275-1200 C-H = 1450

Pharmacological Activity:

Antimicrobial Activity:

- Chemicals:

All the chemicals and solvents were procured from commercial sources, purified and sterilized using standard procedures from literature required.

Nutrient agar medium

Dilution of the compound

All the synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) so on get concentration of 200 µg/ml and standard drugs Ciprofloxacin in DMSO as a level of 10 mg/ml.

Sterilization of apparatus and therefore the chemicals.

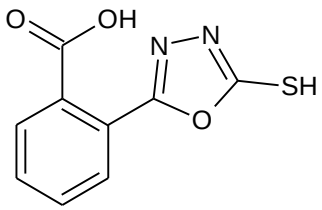
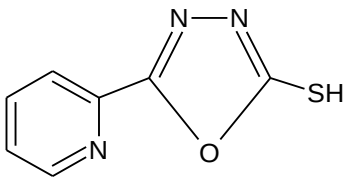
Nutrient agar medium [NO11] and normal saline were sterilized in autoclave at 15 lbs pressure [121^{0}C] for 15 min. Petri plates, Whatmann filter paper [41] disc and cotton swabs were sterilized in oven at 160^{0}C for two hrs.

- Preparation of slants :

Preparation of nutrient agar medium slants:

Nutrient agar medium 112mg and agar medium 100mg was dissolved in 4ml distilled water, boiled and then poured in the test tube then plugged with cotton and sterilized in autoclave at 15 lbs pressure [121^{0}C] for 15 min . After sterilization the tubes containing the nutrient agar medium were kept in inclined position for 30 min then on the surface of slants pure culture of bacillus Substilis , Eschrichia coli were steaked in aseptic condition and incubated at 37^{0}C for 24 hrs.

IV. RESULT

Substituted Aryl acid (R)	Molecular Formula	Molecular Weight	Melting Point	Structure
Pthalic Acid	$C_9H_6N_2O_3S$	222	202^{0}C-204^{0}C	
Nicotinic Acid	$C_7H_5N_3OS$	179	234^{0}C-236^{0}C	

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