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SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW BENZOXAZOLES FOR ANTI MICROBIAL ACTIVITY

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ABSTARCT

In the present work the effort is made to develop a convenient method for the synthesis of benzoxazoles derivative by conventional method. Understanding the importance of Benzoxazole for antimicrobial activity, some novel benzoxazole derivatives were synthesized by structural modification on benzene ring. Therefore, the present work has been aimed to achieve the following objectives. To synthesize the novel benzoxazole derivative by using reported methodology. To purify the intermediate and final compound by chromatographic techniques using suitable solvents. To characterized the synthesized compounds by the help of physical (Melting point, solubility, R f values), TLC and Spectral data (FT-IR).To identify the potent compound, for their specific activity.

KEYWORDS: Benzoxazole, biological evaluation, antimicrobial activity, chromatographic techniques, Benzaldehyde, IR spectra.

INTRODUCTION

Medicinal chemistry involves.

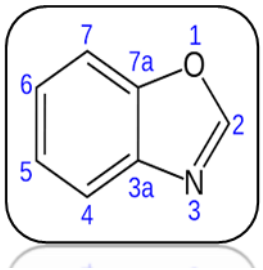
- isolation of compounds from nature or synthesis of new molecules.
- investigation of the relationships between the structure of natural and/or synthesized compounds and their biological activities.
- elucidations of their interactions with receptors of various kinds including enzymes and DNA.
- Determination of their absorption, transport, and distribution properties and studies of the metabolic transformations of these chemicals into other chemicals and their excretion.

Drug discovery research is a highly creative and stimulating work environment where people are driven to succeed by personal and scientific objectives as well as with the desire to contribute to society's well-being.

Introduction to Benzoxazoles

Pharmaceutical compounds, which are predominantly heterocyclic, have been an area of intensive research due to their applicability in the prevention and /or treatment of various disorders.

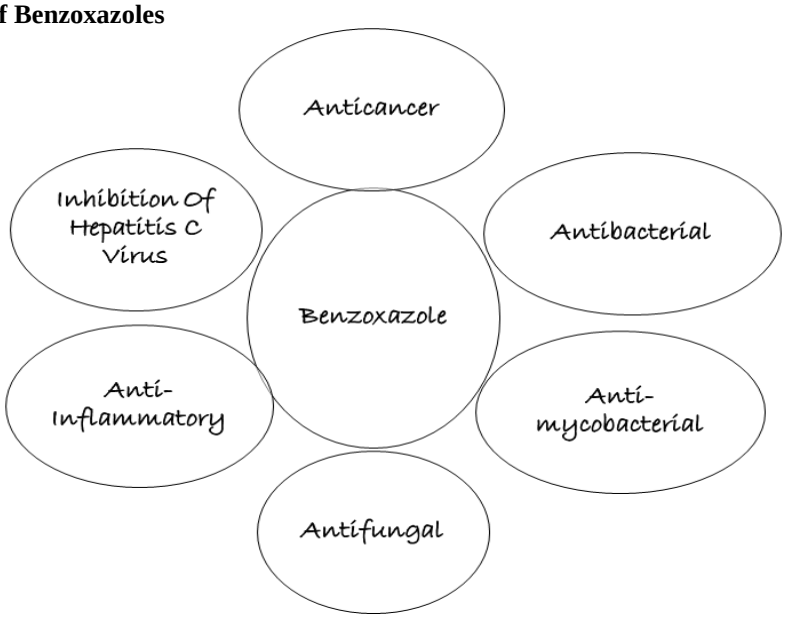
Heterocyclic compounds containing oxazole moiety plays an important role in medicinal chemistry and exhibit wide range of biological activities. Targets containing the benzoxazole moiety either isolated from plants or accessed by total synthesis have remarkable biological activities.



Molecular Formula: C_7H_5NO
Molecular Weight : 119.123

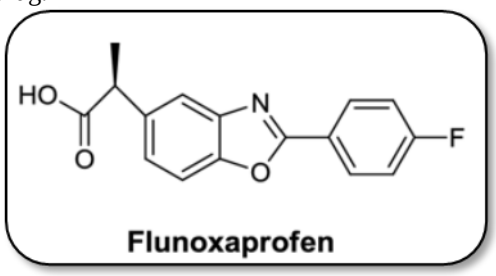
Many substituted benzoxazoles have the ability to inhibit the microbial growth, inflammation, and also has activities such as CNS, hypoglycemic, anti tubercular, anticancer, anti fungal, protein kinase inhibition and steroid sulfatase inhibition. Benzoxazole finds use in research as a starting material for the synthesis of larger bioactive structures.Biologically active benzoxazole derivatives have been known as the isosteres of cyclic nucleotides as they easily interact with the biopolymers of the organisms. The substituted benzoxazoles have been shown to exhibit various biological activities[1] like antimicrobial[2,3], anti-inflammatory[4,5], anticancer[6], antihelminthic[7], antifungal[8], cox-2 inhibition[9], antihistaminic[10], antiparasitic[11], herbicidal[12], antitubercular[13], anticonvulsant[14], hypoglycemic activities.[15]

Biological Activities of Benzoxazoles

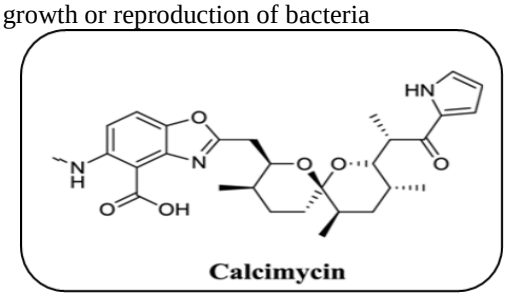


Marketed drugs of bezoxazoles

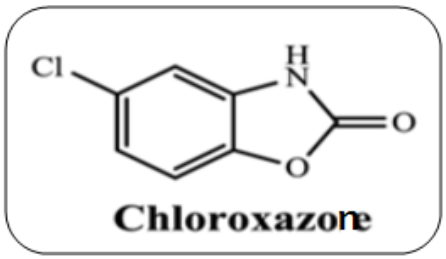
- Flunoxaprofen (INN) is a benzoxazole derivative, developed as an non-steroidal anti-inflammatory drug.



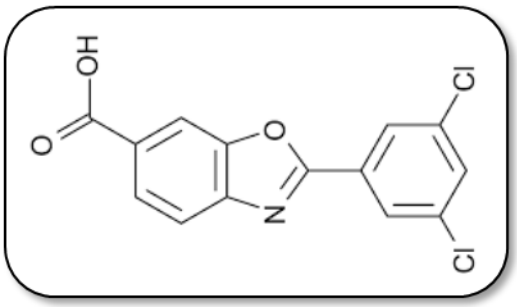
- Calcimycin a benoxazole derivative that inhibit the growth or reproduction of bacteria



- **Chlorzoxazone** (INN) is a centrally acting muscle relaxant used to treat muscle spasm and the resulting pain or discomfort.



- **Tafamidis** (trade name **Vyndaqel**) is a drug used to delay loss of peripheral nerve function in adults with familial amyloid polyneuropathy (FAP), an orphan.
- disease.



MATERIALS AND METHODS USED

All the chemicals and solvents used were of synthetic grade from SD fine chemicals Ltd., (Mumbai, India), and Avra Chemicals (Hyderabad, India). Completion of the reactions was monitored by analytical thin layer chromatography (TLC) using E-Merck 0.25 mm silica gel plates. Visualization was accomplished with UV light (256nm) and iodine chamber. Synthesized compounds were purified by re-crystallization process. The purity of the compounds was checked by a single spot in TLC and solvent system for TLC was determined on trial and error basis. Melting points were determined in open capillary tubes using ANALAB melting point apparatus and were uncorrected.

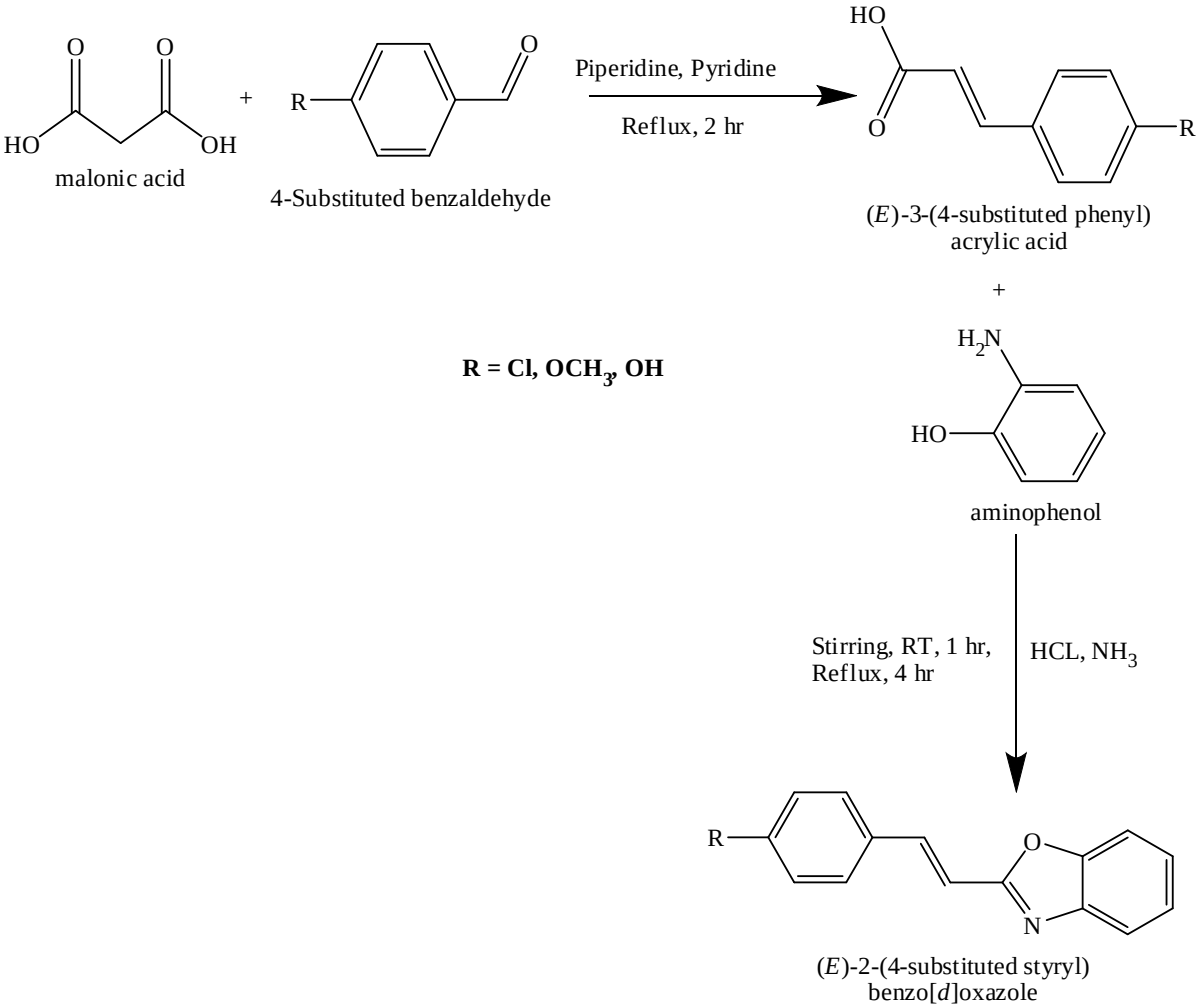
The FT-IR spectra were recorded on Schimadzu FT-IR spectrophotometer by using 1% potassium bromide discs.

List of chemicals used

Table No. 1.1 List of Chemicals.

S.NO	CHEMICALS	GRADE	COMPANY
1	Benzaldehyde	AR	AVRA
2	Chloro-benzaldehyde	AR	AVRA
3	Hydroxy benzaldehyde	AR	AVRA
4	Methoxy benzaldehyde	AR	AVRA
5	Pyridine	AR	AVRA
6	Piperidine	AR	AVRA
7	Malonic acid	AR	AVRA
8	Hydrochloric acid	AR	AVRA
9	o-Amino phenol	AR	AVRA

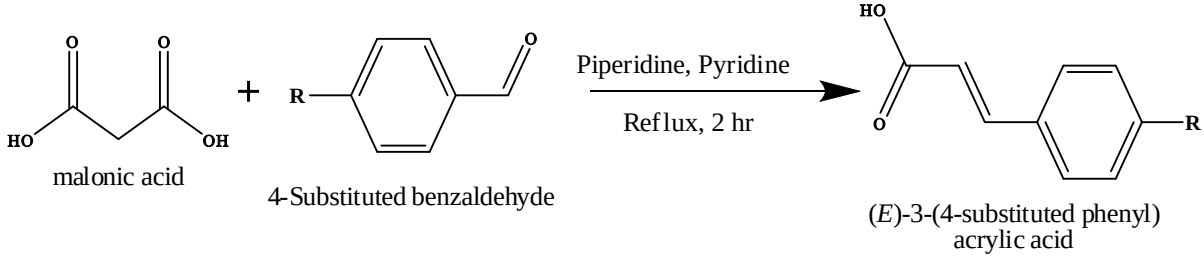
SCHEME



Synthetic procedure

STEP-1

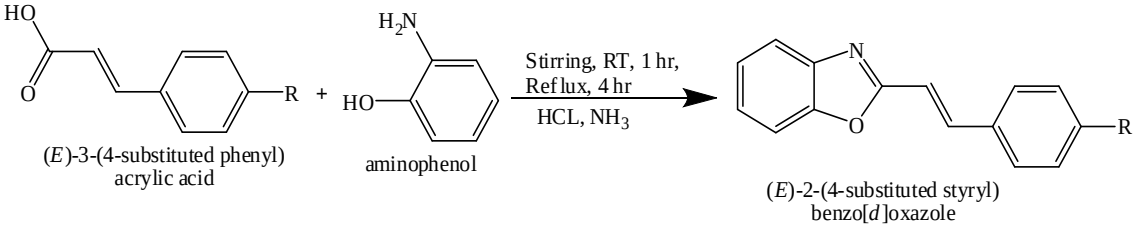
Synthesis of (E)-3-(4-substituted phenyl) acrylic acid by Knoevenagel Condensation



In a 250 ml RBF, was placed accurately measured 4 ml of Benzaldehyde and 3 g of Malonic acid. The mixture was mixed well and to the contents of flask, 4-5 drops of piperidine and pyridine were added. A porcelain chip was added to the reaction mixture in RBF to avoid bumping of the contents of flask. The flask was then connected to the reflux condenser and refluxed for 2 hrs. Yield: 75%

STEP-2

Synthesis of (E)-2-(4-Substituted Styryl) benzo [d] oxazole



(*E*)-3-(4-substituted phenyl) acrylic acid

aminophenol

(*E*)-2-(4-substituted styryl) benzo[*d*]oxazole

Weigh accurately *O*-Amino phenol followed by addition of 4 N HCl in a beaker and stir continuously using a magnetic stirrer. To this mixture, the above synthesised intermediate was added and the stirring is continued at room temperature for 1 hr. The solution is transferred to a RBF and refluxed for 2 – 6 hours.

The obtained mixture was neutralized by adding dil. ammonia drop wise. Neutralized mixture is the filtered and the precipitate is washed with water and collected. Precipitate is then crystallized using alcohol to obtain pure crystals of the solid compound.

The obtained product is confirmed by running TLC.

Fig.No:1 Reflux condenser.

Biological Evaluation (Antimicrobial Activity)

Benzoxazole derivatives possess diverse variety of pharmacological activities. Due to this benzoxazole have occupied unique place in field of medicinal chemistry. Benzoxazole ring system is present occasionally in nature. Benzoxazole finds use in research as a starting material for synthesis of larger, usually bioactive structure. It is structurally similar with nucleic bases as well as isosteres of naturally occurring cyclic nucleotide such as adenine and guanine that is why it probably interacts with biopolymers in living systems and show diverse biological activities like antimicrobial, anti inflammatory, analgesic, antifungal, anticonvulsants, antitumor, anticancer, CNS activities, anti tubercular, anti-HIV agents anthelmintic, and other anticipated activities.

Principle

Antimicrobial activity

The number of life threatening infections caused by multidrug resistant gram positive pathogens has reached an alarming level in hospitals and the community. The

infections caused by these organisms pose a serious challenge to serious challenge to the specific community and the need for an effective therapy has led to search for novel antimicrobial agents. Anti-microbial drugs are effective in treatment of infection because of their selective toxicity that is they have the ability to injure or kill an invading microorganism without harming the host. It is evident from literature that benzoxazole derivatives are known to be associated with broad spectrum of biological activities like antibacterial, antifungal etc.

Preparation of Antibiotic solution

- Prepare different concentrations of antibiotic solution (i.e.)10 mg/ml, 20, 30, 40, solutions
- Take 10 mg of antibiotic and dissolve in solvent and make up to 10 ml to get 1 mg/ml or 1000 mg/ml solution
- From the above solution take 0.1, 0.2, 0.3, and 0.4 and make up to 10 ml respectively to get 10, 20, 30, 40 mg/ml

Experimental procedure (By Cup Plate method)

- Prepare nutrient media and transfer 20ml into boiling tube, plug and sterile them
- After cooling, inoculate each boiling tube with 0.1 ml of test organism (*Bacillus subtills or E.coli*)
- The inoculated agar media is poured into petri plate and solidified
- Make holes in the solidified media at the centre by using sterile borer
- Add 0.1 ml of prepared antibiotic solution of various concentrations into the holes
- Incubate the petri plate for 37degreeC for 24hrs.

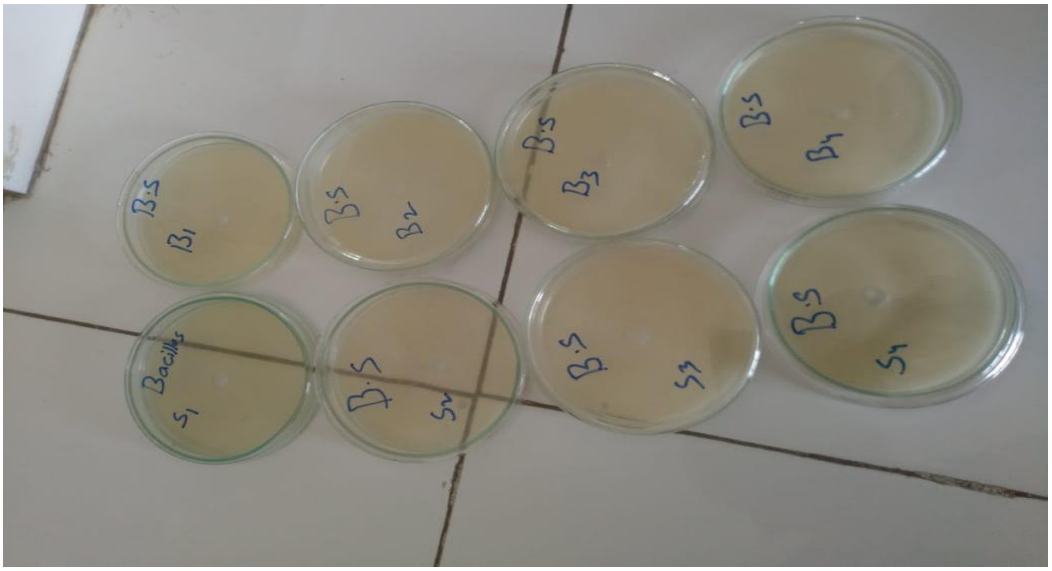


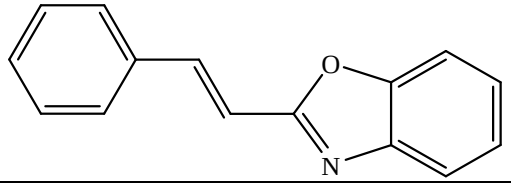
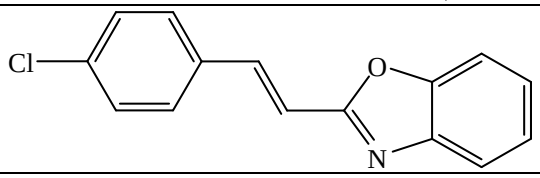
Fig.No:2: Biological Evaluation.

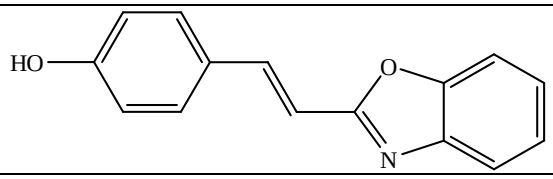
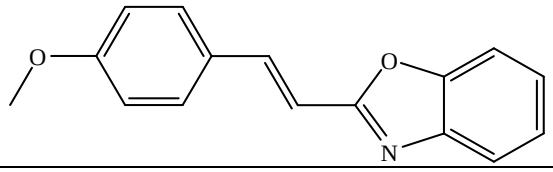
RESULTS AND DISCUSSION

Synthetic -Procedure

The present study was aimed at synthesis of Benzoxazole and its derivatives by a new synthetic procedure using benzaldehyde and malonic acid as starting compounds. The resulting intermediate of these reactants were reacted with o-aminophenol in presence of hydrochloric acid resulting in generation of Benzoxazoles. The final compounds were confirmed by FT-IR studies and TLC.

Table No 1.2: IUPAC Name of Synthesized Compounds.

S.No	Structure	IUPAC Name Of Synthesized Compounds
1		(E)-2-styrylbenzo[d]oxazole
2		(E)-2-(4-chlorostyryl)benzo[d]oxazole

3		(E)-4-(2-(benzo[d]oxazol-2-yl)vinyl)phenol
4		(E)-2-(4-methoxystyryl)benzo[d]oxazole

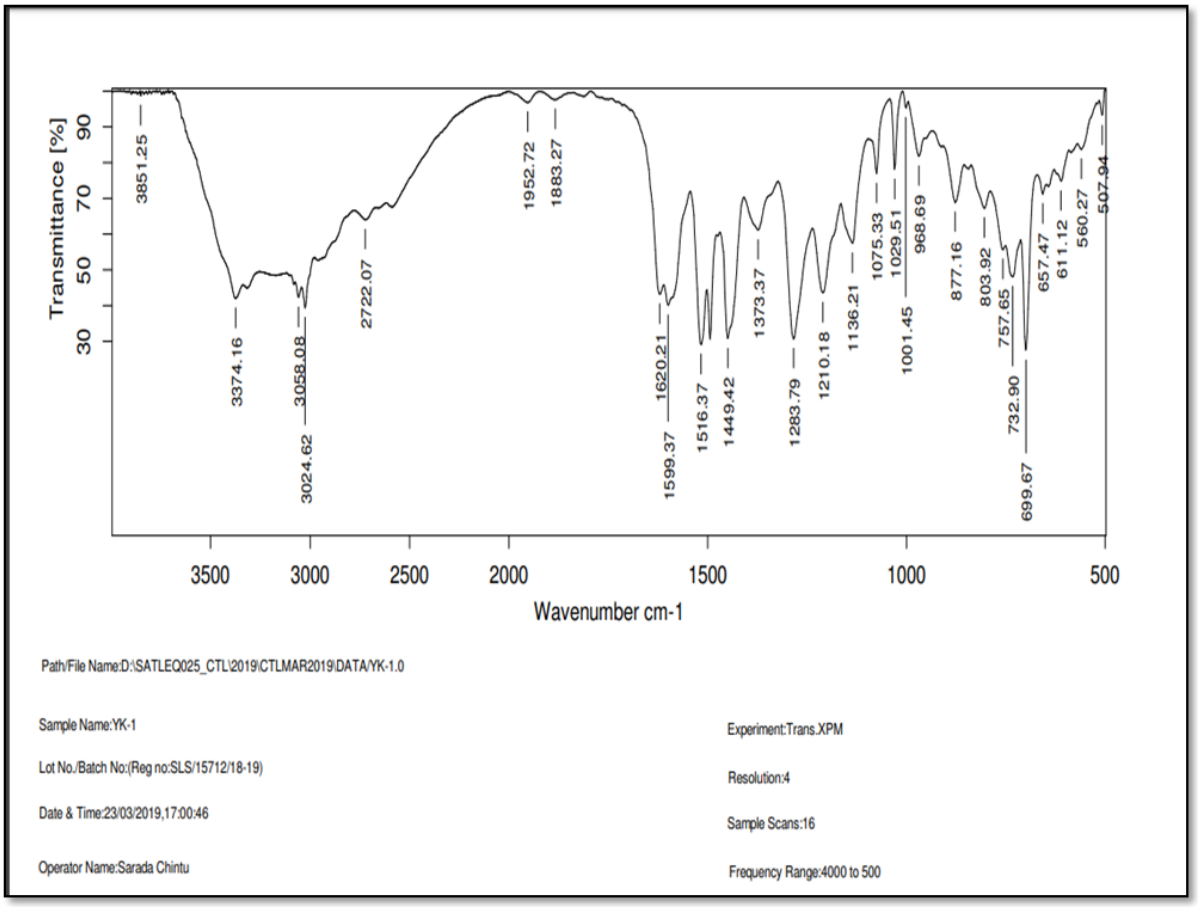


Fig No. 3: Ir Spectra of Synthesized (E)-2-Styryl Benzo[D]Oxazole.

RESULTS: Calculation

Table No 1.3: Zone of inhibition of standard (cephalosporin) against *B.Subtillis.*

Concentrations (mg/ml)	Diameter(cm)	Radius(cm)	Zone of inhibition(cm)	Zone of inhibition (mm)
10	2	1	6.28	6.28
20	3	1.5	9.42	94.2
30	3.5	1.75	10.99	109.9
40	3.5	1.75	10.99	109.9

Table No 1.4: Zone of inhibition of synthesized compound against *B. subtilils.*

Concentrations (mg/ml)	Diameter(cm)	Radius(cm)	Zone of inhibition(cm)	Zone of inhibition (mm)
10	2	1	6.28	6.28
20	3	1.5	9.42	94.2
30	3.5	1.75	10.99	109.9
40	4	2	12.56	125.6

CONCLUSION

The present study was aimed for the synthesis of benzoxazole and its derivatives and evaluation of anti – microbial activity. Three derivatives of benzoxazole were synthesized and screened for Antimicrobial activity. The study was mainly focused on the development of a new procedure for the synthesis of benzoxazoles.

In the study following steps were performed

- Synthesis of benzoxazole derivatives were carried out by new synthetic procedure in order to obtain desired products in acceptable yield.
- Products formed were confirmed by TLC and characterised by FT-IR
- The compounds were tested for antimicrobial activity.

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