Section A-Research paper

SYNTHESIS AND BIOLOGICAL EVALUATION OF BENZOXAZOLES FOR ANTI MICROBIAL ACTIVITY

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ASBSTRACT:

The sincere effort of man to control and cure diseases has implied in the search of new drugs. The synthesis of derivatives has been an important part of research in medicinal chemistry. Medicinal chemistry is the science that deals with the discovery and design of new therapeutic chemicals and their development into useful medicines to treat diseases. 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. In the past, most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery for the creation of new synthetic drug compounds. Medicinal chemistry is almost always geared towards drug discovery and development. A new approach has been developed to understand how disease and infection are controlled at the molecular and physiological level and to target specific entities based on this knowledge. The first step of drug discovery involves the identification of new active compounds, often called "hits", which are typically found by screening many compounds for the desired biological properties. These can come from natural sources, such as plants, animals or fungi. More often the hits can come from synthetic sources, such as historical

compound collections and combinatorial chemistry. The second step of drug discovery involves the synthetic modification of hits in order to improve the biological properties of the compound pharmacophore. The quantitative structure activity relationship of the pharmacophore play an important part in finding "lead compounds", which exhibit the most potency , the most selectivity and the least toxicity. Once a compound has shown its value in these tests, it will begin the process of drug development prior to clinical trials.

KEYWORDS: Pharmacophore, Drug discovery, lead compounds, combinatorial chemistry

INTRODUCTION

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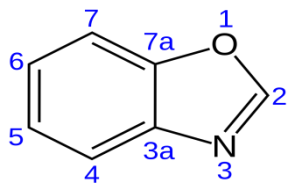
important part in finding “lead compounds”, which exhibit the most potency , the most selectivity and the least toxicity. Once a compound has shown its value in these tests, it will begin the process of drug development prior to clinical trials. The final step involves the rendering the “lead compounds” suitable for use in clinical trials. This involves the optimisation of the synthetic route for bulk production, and the preparation of suitable drug formulation. Despite advances in technology and understanding of biological systems, drug discovery is still a long process with low rate of new therapeutic discovery. Information on the human genome, its sequence what it encodes has been hailed as a potential wind fall for drug discovery , promising, to virtually eliminate the bottle neck in therapeutic targets that has been one limiting factor on the rate of therapeutic discovery It is very unlikely that a perfect drug candidate will emerge from these early screening runs. It is more often observed that several compounds are found to have some degree of activity, and if these compounds share common chemicalfeatures, one or more pharmacophores can be developed. Atthis point medicinal chemists will attempt to use structure activity relationships (SAR) to improve certain features of the lead molecules. ¬ Increase activity against the chosen target ¬ Reduce activity against unrelated targets ¬ Improve the “drug like” or ADME properties of the molecule This process will require several iterative screening runs, during which, it is hoped, the properties of the new molecular entities will improve, and allow the favoured compounds to go forward invitro and invivo testing for activity in the disease model of choice

1.1 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.

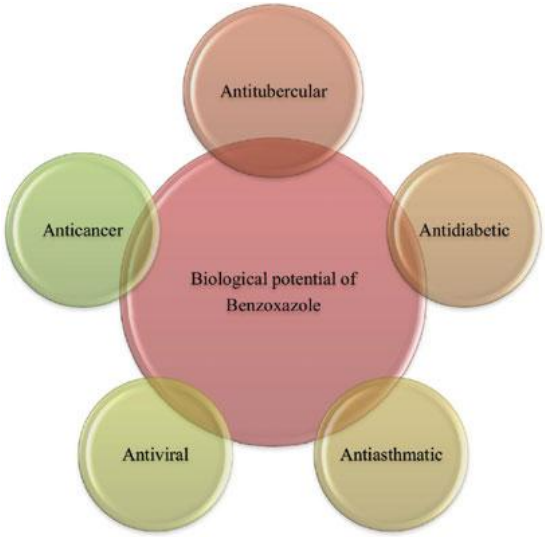


Molecular Formula : C7H5NO

Molecular Weight : 119.123

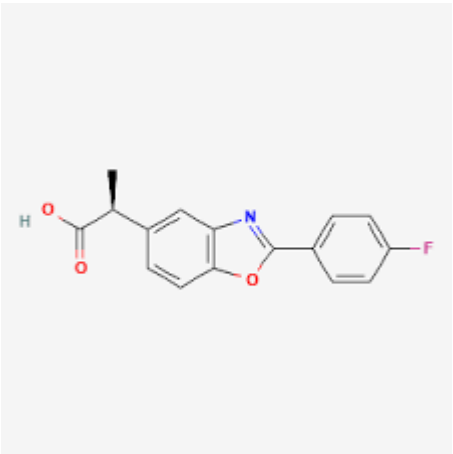
Many substituted benzoxazoles have the ability to inhibit the microbial growth, inflammation, and also has activities such as CNS, hypoglycemic, anti tubercular, anticancer, anti fungal, protein kinase inhibition and steroid sulfatase inhibition. Benzoxazole finds use in research as a starting material 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], antiinflammatory[4,5], anticancer[6], antihelminthic[7], antifungal[8], cox-2 inhibition[9], antihistaminic[10], antiparasitic[11], herbicidal[l2], antitubercular[13], anticonvulsant[14], hypoglycemic activities.[15]

Biological Activities of Benzoxazoles

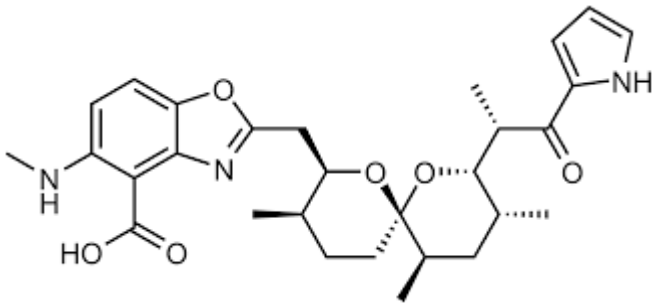


1.2.2 Marketed drugs of bezoxazoles ¬ Flunoxaprofen (INN) is a benzoxazole derivative,

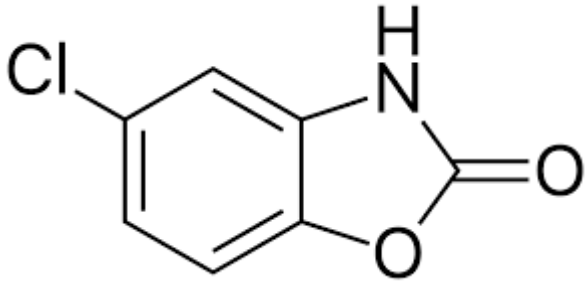
developed as an non-steroidal antiinflammatory drug



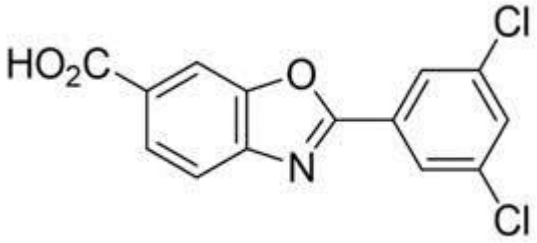
- Calcimycin a benoxazole derivative that inhibit the growth or reproduction of bacteria



- 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.



3. EXPERIMENTAL WORK

3.1 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.

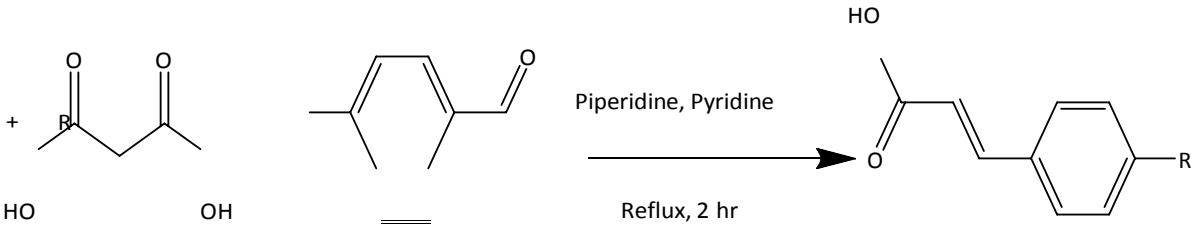
The FT-IR spectra were recorded on Schimadzu FT-IR spectrophotometer by using 1% potassium bromide discs.

3.1.1 List of chemicals used

Table 3.1.1

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



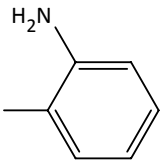
malonic acid

4-Substituted benzaldehyde

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

+

R = Cl, OCH_3, OH

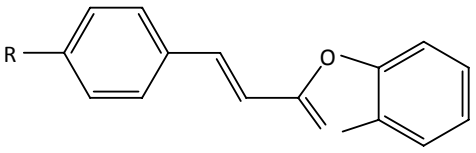


HO

aminophenol

Stirring, RT, 1 hr, Reflux, 4 hr

HCL, NH_3



N

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

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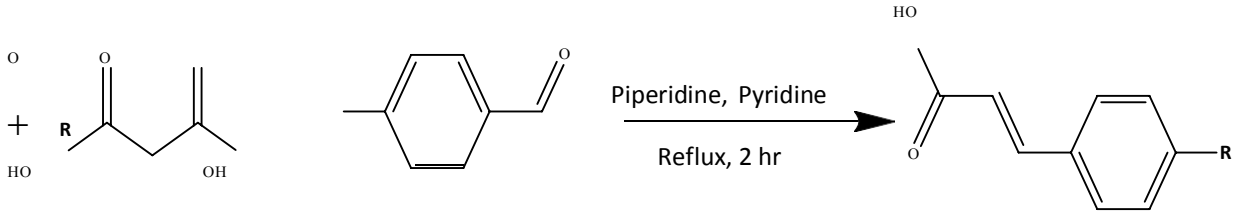
3.2 Synthetic procedure

STEP-1

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



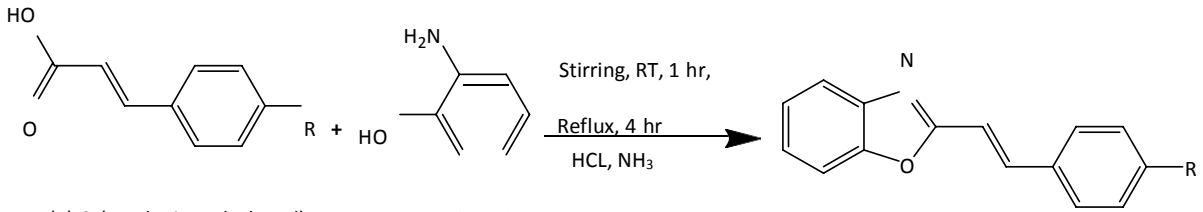
malonic acid — 4-Substituted benzaldehyde — (*E*)-3-(4-substituted phenyl) acrylic acid

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 istransferred 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

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 or1000 mg/ml solution
- From the above solution take 0.1, 0.2, 0.3, and 0.4 and make up to 10 ml respectively toget 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*)

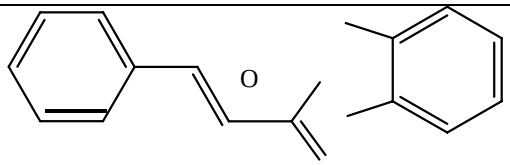
- The inoculated agar media is poured into petri plate and solidified
- Make holes in the solidified media at the centre by using sterile borer
- Add 0.1 ml of prepared antibiotic solution of various concentrations into the holes
- Incubate the petri plate for 37degreeC FOR 24hrs

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.

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

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Experimental procedure (By Cup Plate method):

- Prepare nutrient media and transfer 20ml into boiling tube, plug and sterile them

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- 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 petriplate for 37degree° C for 24hrs

Results:

Calculation:

Zone of inhibition of standard (cephalosporin) against B.Subtills

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

Zone of inhibition of synthesized compound against B. subtills

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 synthesizedand 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 inorder 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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