Review Article

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A Brief Review on Isoxazole Derivatives as Antibacterial Agents

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ABSTRACT

Isoxazole compounds exhibit a wide spectrum of targets and broad biological activities. Isoxazole derivatives are still popular scaffolds for the development of new agents with variable biological activities such as antimicrobial, antiviral, anticancer, anti-inflammatory, immunomodulatory, anticonvulsant or antidiabetic properties. The key feature of these heterocycles is that they possess the typical properties of an aromatic system but contain a weak nitrogen-oxygen bond which under certain reaction conditions like reducing or basic conditions is a potential site of ring cleavage. Thus, isoxazoles are very useful intermediates since the ring system stability allows the manipulation of substituents to give functionally complex derivatives, yet it is easily cleaved when necessary. In this review we have focused on the FDA approved antibacterial agents, clinically used drugs containing isoxazole moiety, Antibacterial agents with isoxazole moiety under preclinical trial, Isoxazole derivatives as antibacterial agents, FDA approved antibacterial agents with isoxazole ring, Mechanism of action of isoxazole derivatives, synthesis and screening of isoxazole derivatives as antibacterial agents

Key Words: Isoxazole, Antibacterial activity, FDA approval, Chalcone

INTRODUCTION

Heterocyclic compounds are those having five or six membered rings with heteroatoms of nitrogen, oxygen or sulphur. Azoles are a class of five membered heterocyclic compounds containing a nitrogen atom and at least one other non carbon atom as part of the ring. The parent compounds are aromatic and have two double bonds. Only one lone pair of electrons from each heteroatom in the ring is part of the aromatic bonding in an azole. The numbering of ring atoms in azoles starts with the heteroatom that is not part of a double bond and then proceeds towards the other heteroatom(1). Isoxazole is an azole with an oxygen atom next to the nitrogen. It is found in some natural products like ibotenic acid and muscimol. The partially saturated analogs of isoxazole are called isoxazolines and completely saturated analog is named as isoxazolidine.(2)

Isoxazoles play key role as medicinal agents due to their numerous therapeutic activities. Due to its relatively easy synthesis, isoxazole ring has been as an object of interest for chemists and pharmacologists from research groups all over the world. Its chemical modifications include both connection of isoxazole with other aromatic, heteroaromatic or non aromatic rings and substitution with different alkyl groups. Their usually low cytotoxicity, isoxazole derivatives are still popular scaffolds for the development of new agents with variable biological activities such as antimicrobial, antiviral, anticancer, anti-inflammatory, immunomodulatory, anticonvulsant or antidiabetic properties. Isoxazole is the core ring in the structure of several bioactive compounds, drugs and agrochemicals[3].

Isoxazole compounds exhibit a wide spectrum of targets and broad biological activities. The integration of isoxazole ring can offer improved physicochemical properties. Isoxazole have also been used as dyes, electric insulating oils, high temperature lubricants and polyisoxazoles have applications as semiconductors. The key feature of these heterocycles is that they possess the typical properties of an aromatic system but contain a weak nitrogen-oxygen bond which under certain reaction conditions like reducing or basic conditions is a potential site of ring cleavage. Thus, isoxazoles are very useful intermediates since the ring system stability allows the manipulation of substituents to give functionally complex derivatives, yet it is easily cleaved when necessary[4].

Chalcones are natural or synthetic compounds which belong to the flavonoid family. Chalcones are the α,β- unsaturated ketones which are chemically known as 1,3-diarylprop-2-en-1-ones. These are reported as intermediates or precursors for synthesising various heterocyclic compounds having therapeutic value. Moreover, chalcones are extensively studied for their broad spectrum of pharmacological action, such as antibacterial, antiparasitic, anticancer, anti-inflammatory, antileishmanial, antitubercular and antifungal activities. The pharmaceutical properties of chalcones are due to the presence of reactive α,β- unsaturated carbonyl group and aromatic ring[5]..

Chalcones are precursor compounds for flavonoid biosynthesis in plants and they can also be synthesised in laboratory. Chalcones possess a broad spectrum of biological activities. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new medicinal agents having improved potency and lesser toxicity. Nowadays, several chalcones are used for treatment of viral disorders, cardiovascular diseases, parasitic infections, pain, gastritis and stomach cancer as well as food additives and cosmetic ingredients.

The above informations regarding biological activity of isoxazole and chalcones encouraged us to carry out the preparation of isoxazole derivatives via chalcone in order to look for some new compounds. The general synthetic strategy for the preparation of chalcone is based on Claisen-Schmidt condensation. Then preparation of various substituted isoxazoles is made by reacting chalcones with hydroxylamine hydrochloride in the presence of sodium acetate.[6]

1.1 BACTERIA

Bacteria are single celled microbes. The cell structure is simpler than that of other organisms as there is no nucleus or membrane bound organelles. They constitute a large domain of procaryotic microorganisms. Typically, bacteria have a few millimeter lengths and a number of shapes. They are first life forms appear on earth. Bacteria can live in soil, water, acid hot springs and earth's crust. Bacteria are important in many stages of the nutrient cycle. In human and majority of animals the largest number of bacteria lives in the intestine. Most of the bacteria in our body are harmless. However a large number of species cause diseases like cholera, leprosy, syphilis etc.

Typically, the length of a bacteria is 0.5 – 5.0 micromrters. Most are either spherical called cocci or rod shaped called bacilli. In addition to this, some bacteria are comma shaped called vibrio, spiral shaped called spirilla or tightly coiled called spirochetes. They can exist as single cells, in pairs, chains or clusters. The genetic information is contained in a single loop of DNA. Some bacteria have an extra genetic material called a plasmid. The plasmid often contains genes that give the bacterium some advantage over other bacteria.

Bacteria reproduced by binary fission. Binary fission begins when the DNA of the bacterium divides into two. The bacterial cell then elongates and splits into two daughter cells each with identical DNA to the parent cell. Each daughter cell is a clone of the parent cell. Some bacteria can form endospores. These are dormant structures, which are extremely resistant to hostile physical and chemical conditions such as heat, UV light and disinfectants(7)..

1.2 ANTIBACTERIAL AGENTS

Infectious diseases are the major cause of human sickness and death. To overcome such health care issues, antibiotics proved to be promising agents. Antibactrials are a subclass of antibiotics. These agents are a group of materials that fight against pathogenic bacteria. We can classify antibacterial agents into five groups: type of action, source, spectrum of activity, chemical structure and function.

Antibacterials can be classified into two on the basis of type of action bacteriostatic and bactericidal. Antibacterials which destroy bacteria by targeting the cell wall or cell membrane of the bacteria are called bactericidal and those that slow or inhibit the growth of bacteria are referred to as bacteriostatic. The inhibition phenomenon of bacteriostatic agents involves inhibition of protein synthesis or some bacterial metabolic pathways. As bacteriostatic agents just prevent the growth of the pathogenic bacteria, sometimes it is not able to mark a clear boundary between bacteriostatic and bactericidal. When high concentrations of some bacteriostatic agents are used they may work as bactericidal.

Examples of bacteriostatic antibacterial agents:

Sulphonamides, Streptomycin, Trimethoprim, Chloramphenicol, Erythromycin, Doxycycline.

Examples of bactericidal antibacterial agents:

Penicillins, Carbapenems, Gentamicin, Quinolones, Fluoroquinolones, Vancomycin

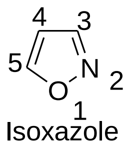
Antibacterials can be naturally obtained from fungal sources, semisynthetic members are chemically altered natural product or synthetic. Based on their target specification they may be either narrow or broad spectrum. On structural basis, antibacterials are classified into group A and group B. Group A include β-lactams and Group B include aminoglycosides [8].

1.3 CHEMISTRY OF ISOXAZOLE

Heterocyclic chemistry is a branch which is inseparable from mankind because human is totally dependent on the drugs derives from heterocyclic rings. Much attention has paid to the synthesis of nitrogen containing heterocyclic compounds like isoxazole due to their broad spectrum of biological and pharmacological activities. Derivatives of isoxazole have played a crucial role in the history of heterocyclic chemistry and been used extensively important pharmacophores in the field of organic chemistry.

Isoxazole is a five membered heterocyclic compound with various pharmacological actions, which is found in some natural products like ibotenic acid. It is used in the formation of the basis for a number of drugs like COX-2 inhibitor valdecoxib and anti-inflammatory drugs. Isoxazoles are largely applied in the area of pharmaceuticals and therapeutics including insecticidal, antibacterial, antibiotic, antitumour, antifungal, antituberculosis, anticancer and ulcerogenic. Besides, it has a great effect on reducing blood glucose, eliminating pain, resisting inflammation, killing harmful bacteria, controlling and reducing the risk of HIV. The isoxazole is an essential pharmacophore in modern drug discovery. Some beta lactamase resistant antibiotics contain an isoxazole group including cloxacillin, dicloxacillin, flucloxacillin and the isoxazole group is also found in some steroid drug.

Substituted isoxazoles are important compounds of many drugs and drug candidates. It is one of the most fundamental objectives of organic and medicinal chemistry is the design and synthesis of molecules having value human therapeutic agents. The diversity of biological activities and pharmaceutical uses has been attributed to them such as isoxazole is a part of many active molecule possessing activities

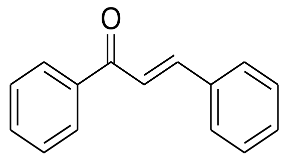


Isoxazole
Fig.1

1.4 CHEMISTRY OF CHALCONE

Chalcone is a generic term given to compounds bearing 1,3-diaryl-2-propen-1-one framework. Chalcone is a simple chemical scaffold found in many naturally occurring compounds and has a widespread distribution in vegetables, fruits, teas and other plants. The word "chalcone" is derived from the Greek word "chalcos" meaning "bronze", which results from the colors of most natural chalcones. Chalcone compounds have a common chemical scaffold of 1,3-diaryl-2-propen-1-one, also known as chalconoid, that exists as trans and cis isomers, with the trans isomer being thermodynamically more stable. Chalcones are also known as phenyl styryl ketones, benzal acetophenones, benzylidine acetophenones or alternatively called β-phenyl acrylophenone. They contain reactive keto-ethylinic group.

Many chalcone derivatives have also been prepared due to their convenient synthesis. These natural products and synthetic compounds have shown numerous interesting biological activities with clinical potentials against various diseases. Therapeutic applications of chalcones trace back thousands of years through the use of plants and herbs for the treatment of different medical disorders, such as cancer, inflammation and diabetes. Many chalcones are found to have medicinal and pharmaceutical applications ranging from antitumour, antispasmodic, antiulcer, anthelmintics, antibacterial, antiallergic, antiviral, fungicidal, germicidal and insecticidal. Several chalcone based compounds have been approved for clinical use.

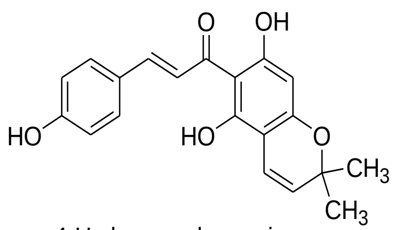


1,3-Diphenyl-propenone

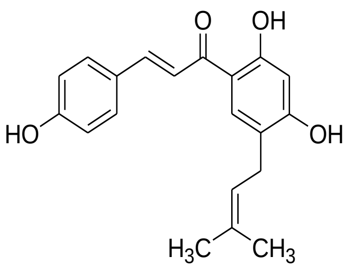
(CHALCONE)

Fig.2

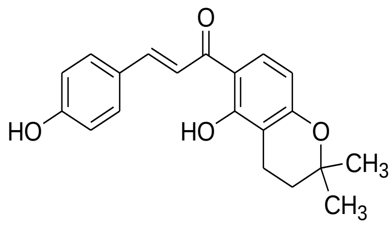
Flavonoids, a group of polyphenolic secondary metabolites have been reported to display a large panel of biochemical properties including antioxidant activity, inhibition of tyrosine kinase, cAMP phosphodiesterases and induction of phase II metabolizing enzyme both *in vitro* and *in vivo.* Flavonoids like 4-hydroxyonchocarpin (Fig.3A) have been reported to be a good chemopreventive molecule against ovarian cancer cell growth. Isobavachalcone (Fig.3B) and dorsmanin (Fig.3C) exhibited inhibitory effect on skin carcinogenesis test.



4-Hydroxyonchocarpin



Isobavachalcone



Dorsmannin

Fig.3A **Fig.3B** **Fig.3C**

The term chalcone refers generically to chemicals with an α,β-unsaturated ketone system. Chalcones are generally prepared by condensation reactions via base or acid catalysis. The Claisen-Schmidt reaction is a process in which a benzaldehyde and a methyl ketone are condensed in the presence of catalysts. The catalysts are either strong bases or acids. In the case of base catalysis, the chalcone is generated from the aldol product via dehydration in an enolate mechanism, while in the case of acid catalysis, it is generated via an enol mechanism. The classical Claisen-Schmidt condensation is base catalysed with sodium hydroxide, potassium hydroxide in methanol or ethanol at room temperature.

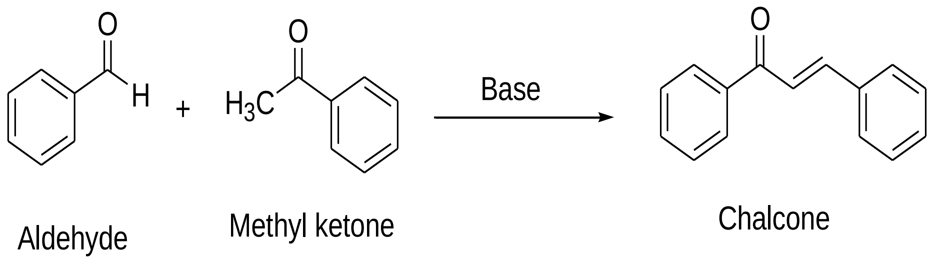


Fig.4

Chalcones have close relationship with flavones, aurones, tetralones and aziridines. Chalcones and their derivatives find application as artificial sweeteners, scintillator, polymerization catalyst, fluorescent whitening agent, organic brightening agent, stabilizer against heat, visible light, ultraviolet light and aging. They contain a keto ethylenic group and are therefore reactive towards several reagents. The chalcones have been found useful in elucidating structure of natural products[9].

1.5 MEDICINAL ASPECTS OF CHALCONES

Chalcones exhibit a broad spectrum of biological activities, probably due to their small structures. The biological activities of chalcones include anticancer activity, antibacterial activity, antituberculosis activity, antidiabetic activity, antioxidant activity, antimicrobial activity, antimalarial activity, neuroprotective effects and others. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new medicinal agents having improved potency and lesser toxicity and good pharmacological actions.[10]

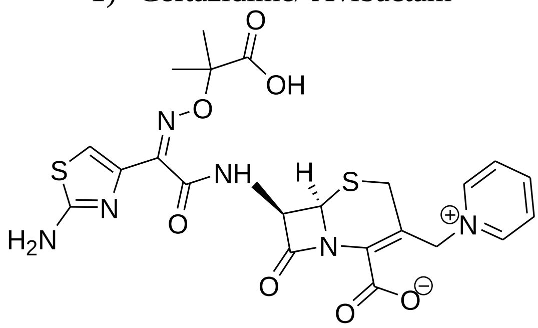
REVIEW OF LITERATURE

2.1 FDA approved antibacterial agents

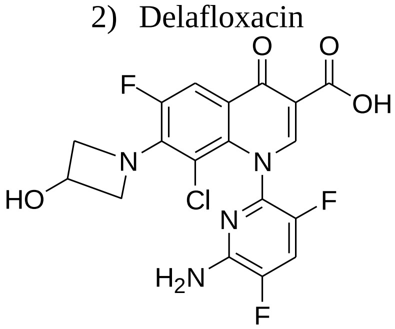
Antibiotics discovery and clinical use is one of the milestones of modern medicine. There is a continuous competition between new antibacterial drug research and the ability of bacteria to develop resistance. In 2017, the 3 approved antibacterial drugs represented 6.5% of the total of 46 new drugs. 2016 brought 2 new drugs, respectively 9% of the 22 approved molecules. In 2015, only one antibacterial agent was approved by FDA, which is2.2% from a total of 45[11].

6 novel FDA approved antibacterial drugs:

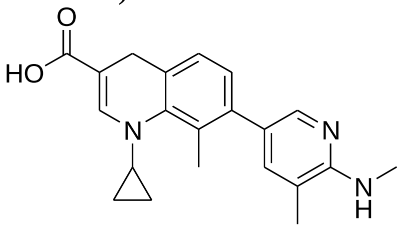
1) Ceftazidime/ Avibactam



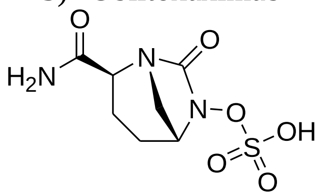
2) Delafloxacin



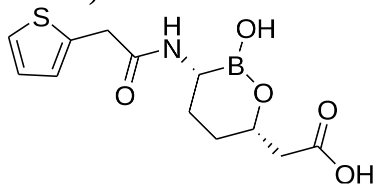
3) Ozenoxacin



5) Obiltoxaximab



6) Bezlotoxumab



4) Meropenem/Vaborbactam – Vabomere

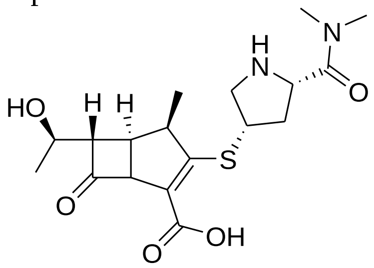


Fig.5

2.1.1 Clinically used drugs containing isoxazole moiety

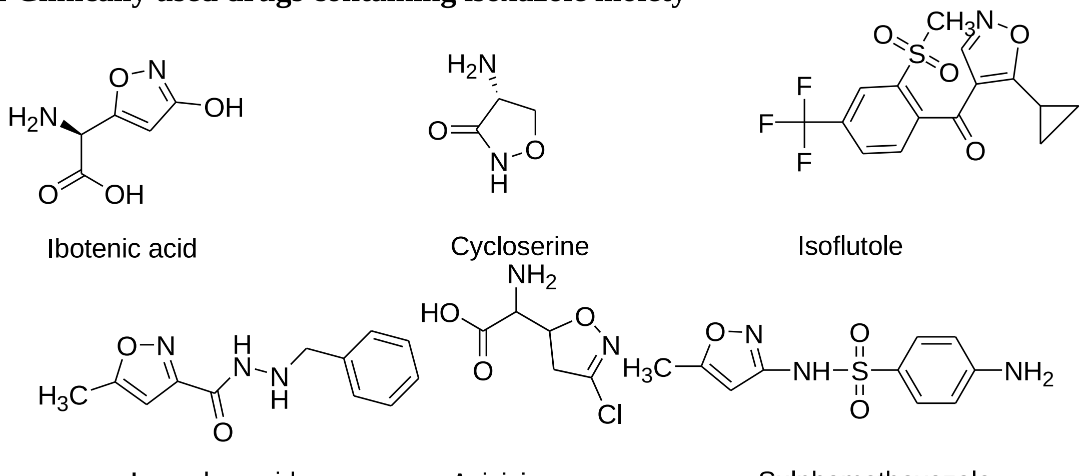
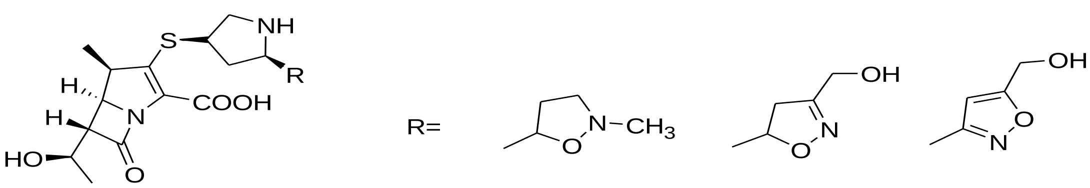


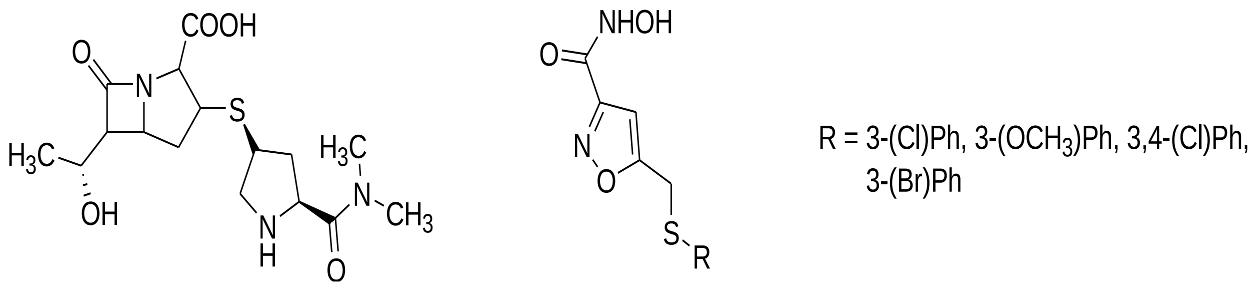
Fig. 6

2.1.2 Antibacterial agents with isoxazole moiety under preclinical trial

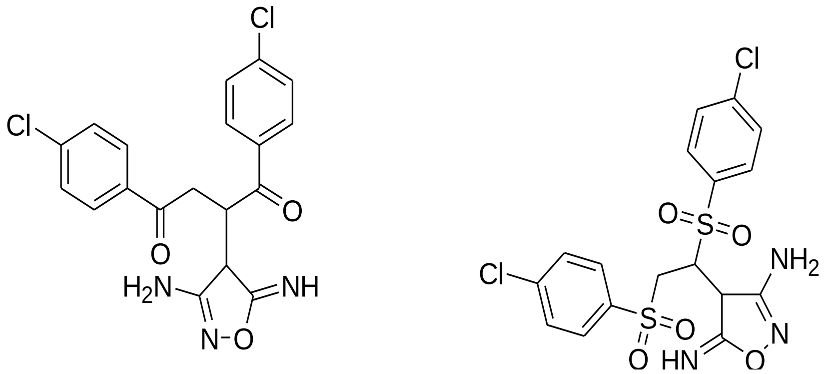
A series of new 1_{β}-methylcarbapenems with 5'-isoxazolopyrrolidin-3'ylthio moiety in C2 position possess potent antibacterial activity. The synthesised isoxazolidine, isoxazoline, isoxazole derivatives showed a similarly potent antibacterial properties against different Gram positive and Gram negative organisms. The most isoxazole derivative displayed comparable activity to meropenam against most of the bacteria except P. aeruginosa. Furthermore, the compounds featured high, comparable to that of meropenem, stability ti dehydropeptidase-I, a renal enzyme responsible for degradation of carbapenems [12].



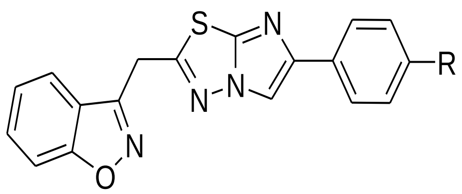
1_{β}-methylcarbapenems with isoxazolidine, isoxazoline and isoxazole moiety



Meropenem reference drug, R = isoxazole-3-hydroxamic acids as bacterial deformylase inhibitors.



Aminoiminoisoxazoles



R = Cl, Br

Ethylene bridged benzisoxazolyl imidazothiadiazoles

Fig. 7

2.2 Problems associated with antibacterial agents

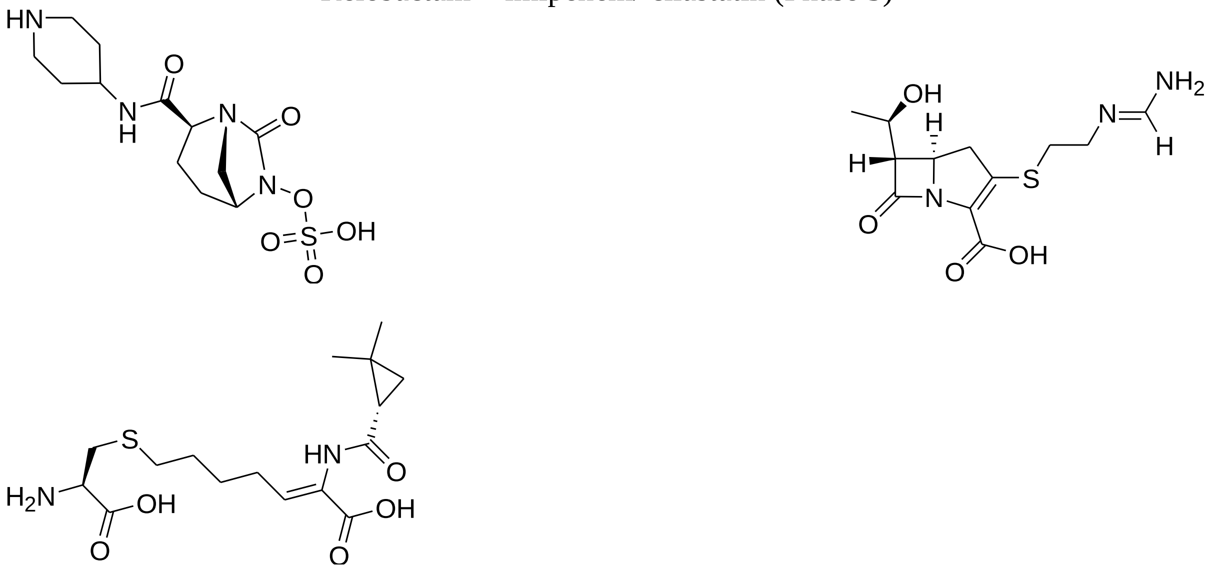
Antibacterial resistance is a major problem with the antibacterial agents. Drug resistant strains initially appeared in hospitals. Resistance to multiple drugs was first detected among enteric bacteria. Increased antimicrobial uses boost up the resistance. The re-emergence of tuberculosis has enhanced by human immunodeficiency virus infection. The severity and difficulty in treating MDR strains necessitates the use of several drugs [(13)]

Multiply resistant organisms render therapy more costly. The resistance problem has two main components: the drug which inhibits susceptible organisms and the genetic resistance in microorganisms selected by the antimicrobial drug. Drug resistance emerges only when these two components come together in an environment or host. Drug resistance is mobile – the genes for resistance traits can be transferred among bacteria of different taxonomic and ecological groups by means of mobile genetic elements such as bacteriophages, plasmids, naked DNA or transposons. In the absence of plasmids and transposons a step wise progression from low level to high level resistance occurs in bacteria through sequential mutations in chromosomes [(14)]

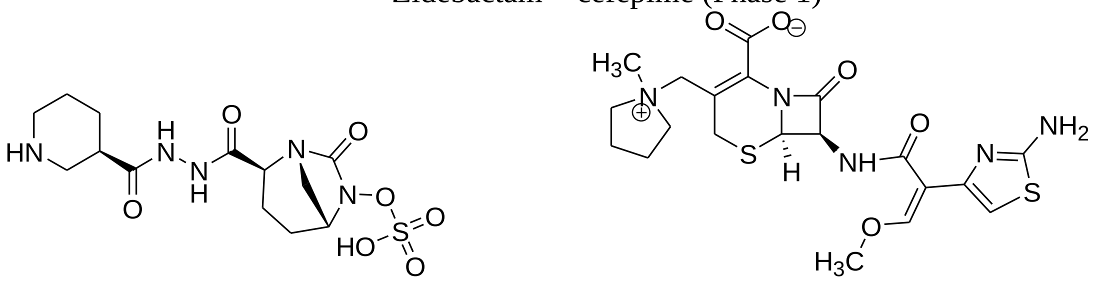
2.3 Antibacterial agents under clinical trial

- β-Lactams

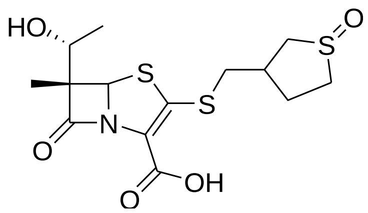
Relebactam + imipenem/ cilastatin (Phase 3)



Zidebactam + cefepime (Phase 1)

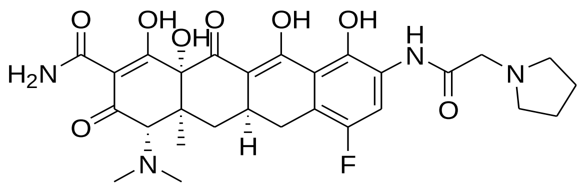


Sulopenem (Phase 2)

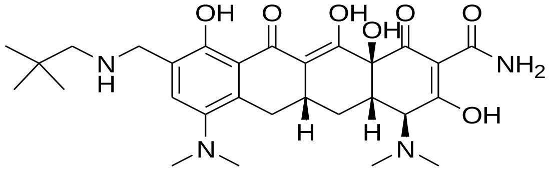


- Tetracyclines

Eravacycline (Phase 3)

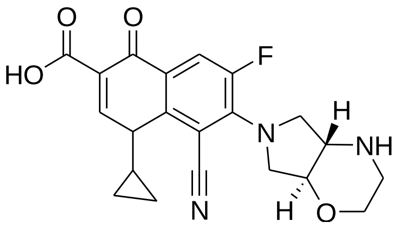


Omadacycline (Phase 3)

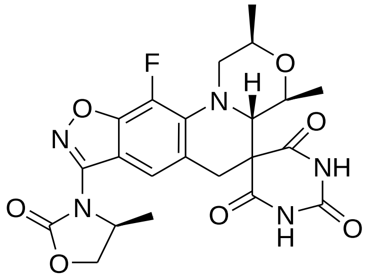


- Topoisomerase inhibitors

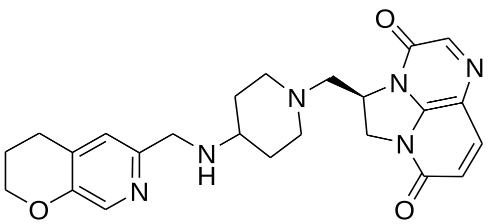
Finafloxacin (Phase 2)



Zoliflodacin (Phase 2)



Gepotidacin (Phase 2)



- Aminoglycosides

Plazomcin (Phase 3)(Organization 2017).

Fig. 8

2.4 Isoxazole derivatives as antibacterial agents

A series of novel 1,2,3- triazole/ isoxazole functionalized pyrido[2,3-d] pyrimidine derivatives were prepared in series of synthetic steps. All the compounds also screened for antibacterial activity using Rifampicin and Ciprofloxacin as standards and identified promising compounds with minimum inhibitory concentration.

A series of isoxazole-3-hydroxamic acid derivatives has been identified as a new class of small, nonpeptidic inhibitors of peptide deformylase. The synthesis, enzyme inhibition and preliminary investigation of the binding mode of these potential antibacterial compounds are reported (15).

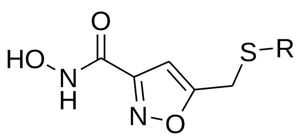


Fig. 9

A new class of heterocycles, substituted pyrazoles, isoxazoles, pyrimidines, thioxopyrimidines were prepared from Michael adducts, 2-(1,2-diaroylethyl) malononitrile and 2-(1,2-diarylsulphonylethyl) malononitrile by cyclocondensation with appropriate nucleophiles. The lead compounds were screened for the antimicrobial and antioxidant activities [16].

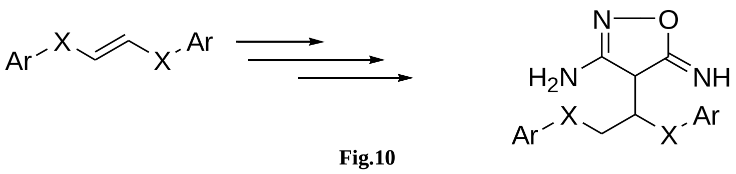
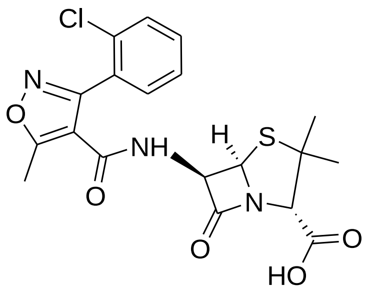


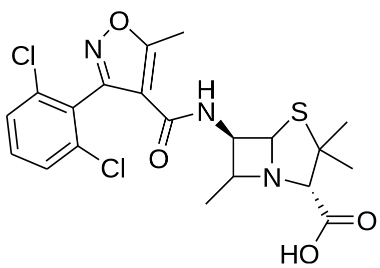
Fig.10

2.5 FDA approved antibacterial agents with isoxazole ring

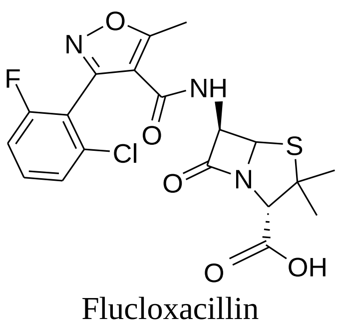
Many antibacterial agents contain isoxazole ring. Beta lactamase resistant antibiotics like cloxacillin, dicloxacillin and flucloxacillin.



Cloxacillin



Dicloxacillin



Flucloxacillin

Fig. 11

2.6 Mechanism of action of isoxazole derivatives

Leflunomide is an isoxazole derivative prodrug that is converted to an active derivative teriflunomide. Teriflunomide inhibits dihydro orotate dehydrogenase, a key mitochondrial enzyme in the de novo synthesis of the pyrimidine ribonucleotide uridine monophosphate (rUMP). Activated lymphocytes require at least eight fold increases in their pyrimidine pool to proliferate. Inadequate supply of rUMP increases the expression of the tumor suppressor molecule p53 which translocates to the cell cycle in the G_1 phase[17].

Cloxacillin is used against staphylococci that produce beta lactamase due to its large R chain which do not allow the beta lactamase to bind. Cloxacillin exerts bactericidal activity via inhibition of bacterial cell wall synthesis by binding one or more of the penicillin binding proteins. It also exerts bacterial autolytic effect by inhibition of certain penicillin binding proteins related to the activation of a bacterial autolytic process [18].

Flucloxacillin is a narrow spectrum beta lactam antibiotic. It acts by inhibiting the synthesis of bacterial cell walls. It inhibits cross linkage between the linear peptidoglycan polymer chains that make up a major component of the cell wall of Gram positive bacteria. It is very similar to dicloxacillin and they are considered interchangeable [19].

2.7 Synthesis of chalcones

Equimolar quantities of 3,4,5-trimethoxy benzaldehyde and acetophenone were dissolved in ethanol. Potassium hydroxide solution was added slowly and the mixture was stirred for 2 hours. The stirring can be provided with the help of a magnetic stirrer. Stirring was continued until the entire mixture became very sticky and cloudy. Then the mixture was poured slowly into water with constant stirring to get the precipitate. It was filtered, washed with water and dried followed by recrystallisation with ethanol. TLC was monitored to check the completion of the reaction.

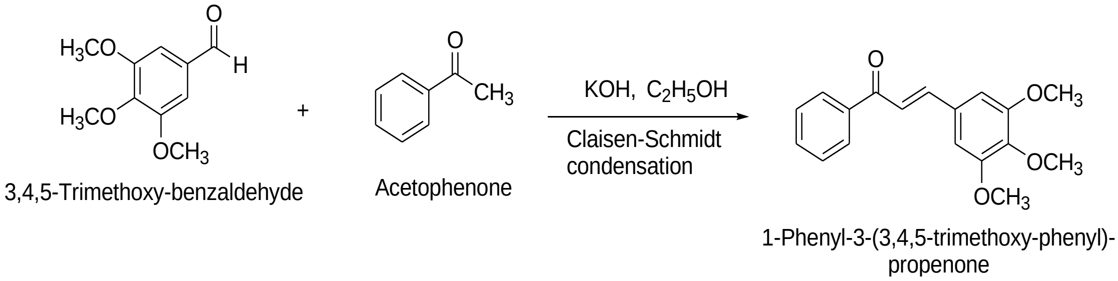


Fig. 12

2.8 Synthesis of isoxazole derivatives

2.8.1 Conventional synthesis

A mixture of chalcone, hydroxylamine hydrochloride and sodium acetate in ethanol was refluxed for 6-8 hours. TLC was monitored to check the completion of the reaction. The reaction mixture was poured into ice cold water. The precipitates thus obtained were filtered, washed and recrystallized from ethanol.[20]

2.8.2 Microwave assisted synthesis

A mixture of chalcone, hydroxylamine hydrochloride and sodium acetate in ethanol was subjected to microwave irradiation at 210W, for 10-15 min at 90-100°C. TLC was monitored to check the completion of the reaction. The reaction mixture was transferred into ice cold water to get the precipitate. It was filtered, washed and recrystallised from ethanol.[21]

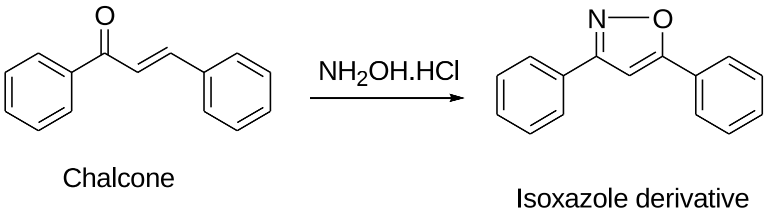
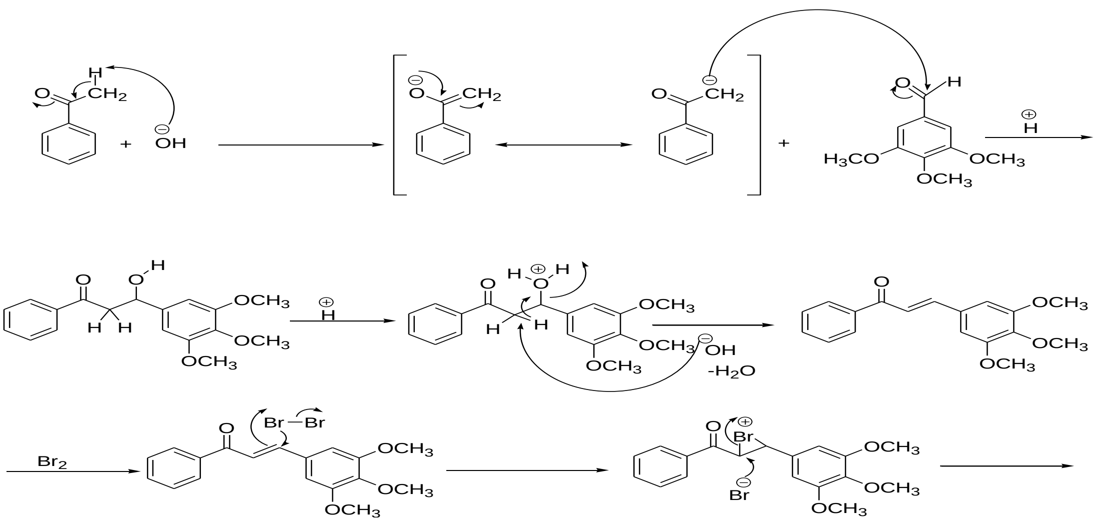


Fig. 6

2.8.3 Mechanism of reaction



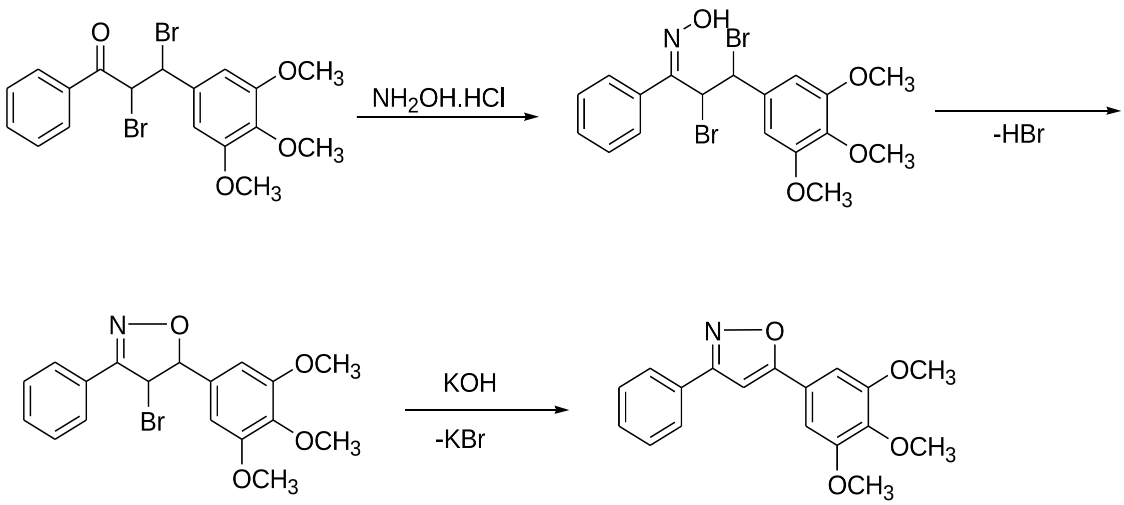


Fig. 13

2.9 In vitro antimicrobial screening

The synthesised compounds were subjected to antimicrobial screening against bacterial and fungal strains. The zone of inhibition was calculated in millimeters and compared with the standard drugs. These were evaluated *in vitro* for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* using cup plate method. The compounds were prepared in the concentration of 100µg/ml using DMSO and they were tested by using nutrient agar as the medium. After 24 hour of incubation at 37°C, the zones of inhibitions were measured. Similarly, antifungal activity was carried out against various fungal stains such as *Candida albicans* and *Aspergillus niger*. Ampicillin and Ketoconazole were used as standard drugs for antibacterial and antifungal activities respectively. The solvent DMSO was used as control [22]

CONCLUSION

Isoxazole derivatives are potentially pharmacologically active. They have antimicrobial, antioxidant, antitubercular and anticancer activities. Chalcone derivatives are also pharmacologically active. They have anticancer, anti-inflammatory, antimicrobial antitubercular and antileishmanial activities. The synthesis of chalcone can be done with an aldehyde and a ketone. From the chalcone isoxazole derivative can be synthesised by using hydroxylamine hydrochloride. Both these isoxazole and chalcone are naturally occuring. Their synthetic derivatives are also pharmacologically active. Currently many compounds containing isoxazole ring are using clinically. In addition to this many derivatives are under pre clinical and clinical trials. The pharmacological activity of the compound can be determined by using cup plate method using various strains of bacteria. The chemical properties can be determined and confirmed by using various analytical techniques like mass spectroscopy, IR spectroscopy and NMR spectroscopy.

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